Multi-ancestry genome-wide association study of 21,000 cases and 95,000 controls identifies new risk loci for atopic dermatitis

Genetic association studies have identified 21 loci associated with atopic dermatitis risk predominantly in populations of European ancestry. To identify further susceptibility loci for this common, complex skin disease, we performed a meta-analysis of >15 million genetic variants in 21,399 cases and 95,464 controls from populations of European, African, Japanese and Latino ancestry, followed by replication in 32,059 cases and 228,628 controls from 18 studies. We identified ten new risk loci, bringing the total number of known atopic dermatitis risk loci to 31 (with new secondary signals at four of these loci). Notably, the new loci include candidate genes with roles in the regulation of innate host defenses and T cell function, underscoring the important contribution of (auto)immune mechanisms to atopic dermatitis pathogenesis.

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Atopic dermatitis (eczema) is a common inflammatory skin disease affecting 15–30% of children and 5–10% of adults[1]. Its pathogenesis involves skin barrier abnormalities and T cell–driven cutaneous inflammation. Atopic dermatitis has considerable genetic contributions, with heritability estimates of up to 90% in Europeans[2]. The strongest known risk factors are null mutations of the *FLG* gene (encoding filaggrin), resulting in epidermal barrier deficiency[3–5]. Genome-wide association studies (GWAS) have identified 20 additional loci (ten in European, eight in Japanese and two in Chinese populations), mostly implicated in immune dysregulation[6–12]. Genetic modeling suggests that further loci may be identified with well-powered GWAS[13]. We therefore carried out a multi-ancestry meta-analysis of 26 studies comprising 21,399 cases and 95,464 controls imputed to the 1000 Genomes Project Phase 1 reference panel (**Supplementary Table 1** and **Supplementary Note**). We analyzed 15,539,996 variants with minor allele frequency (MAF) ≥1%.

A fixed-effects meta-analysis of the 22 European studies identified 21 genome-wide significant ($P < 5 \times 10^{-8}$) loci (**Fig. 1**, **Table 1** and **Supplementary Figs. 1–4**), and a multi-ancestry meta-analysis identified an additional six loci with $\log_{10}$ (Bayes factor) > 6.1, four of which (10q21.2, 6p21.33, 11p13 and 2p13.3) also showed nominal association in the European analysis (**Table 1**). These 27 loci included all 11 loci previously associated with atopic dermatitis in Europeans and five loci originally reported in Japanese. Three loci identified in Japanese (6p21.33, 10q21.2 and 2q12.1) were also strongly associated in the European analysis, whereas two (3q13.2 and 11p15.4) might represent Japanese-specific signals (**Supplementary Figs. 1** and **2**), with the European confidence intervals ruling out all but very small effects (odds ratio (OR) < 1.03; **Table 1**). Furthermore, a locus originally reported in a Chinese GWAS (20q13.33) showed association in Europeans. We identified 11 new loci for atopic dermatitis. Four (11q24.3, 10p15.1, 8q21.13 and 2p25.1) were previously associated with self-reported allergy[14], and another (8q21.13) was associated with asthma[15]. Two newly identified variants (5p13.2 and 2p25.1) showed statistically significant evidence of heterogeneity between European and non-European studies (Cochran's Q test P ~0.01; **Supplementary Table 2**). Both variants showed little evidence for association in non-Europeans (particularly Japanese; **Supplementary Fig. 2**). The confidence intervals also overlapped for all variants when comparing pediatric studies (defined by disease onset by 6 years of age) with studies considering any age of onset (**Supplementary Fig. 3**). For Europeans, there was some evidence of heterogeneity in effect sizes between studies for known variants (for example, 11q13.5: $I^2 = 62.9\%$, $P < 0.0001$; 11p13: $I^2 = 55.6\%$, $P = 0.0011$) but little evidence of heterogeneity for new variants (I^2 range = 0–40%, all $P > 0.02$; **Supplementary Fig. 2**). Nevertheless, studies with phenotype definition based on a dermatological exam tended to report larger effect sizes than studies using self-reporting (**Supplementary Fig. 4**), which is to be expected, assuming a moderate degree of phenotypic misclassification in the latter. The inclusion of studies using self-reporting is therefore likely to bias estimates of effect size toward the null, and this should be borne in mind when interpreting the odds ratios from our study. Given that the primary aim of GWAS is the discovery of new loci, the increase in sample size achieved by including these studies is so large that any potential detrimental effect on statistical power is more than outweighed, and the expected direction of bias means that there is unlikely to be an issue of spurious findings (corroborated by **Supplementary Fig. 4**).

Seven of the 21 established loci for asthma[15–20], seven of the ten loci for allergic sensitization[21] and six of 14 loci for self-reported allergy[14] showed association with atopic dermatitis ($P < 0.05$), all with consistent directions of effect, supporting the notion of common atopic mechanisms in atopic dermatitis and allergy (**Supplementary Table 3**). However, several studies used here have contributed to multiple GWAS, which may have biased the observed overlap upward. Nevertheless, a substantial proportion of the loci associated with other atopic conditions appeared not to be strongly associated with atopic dermatitis.

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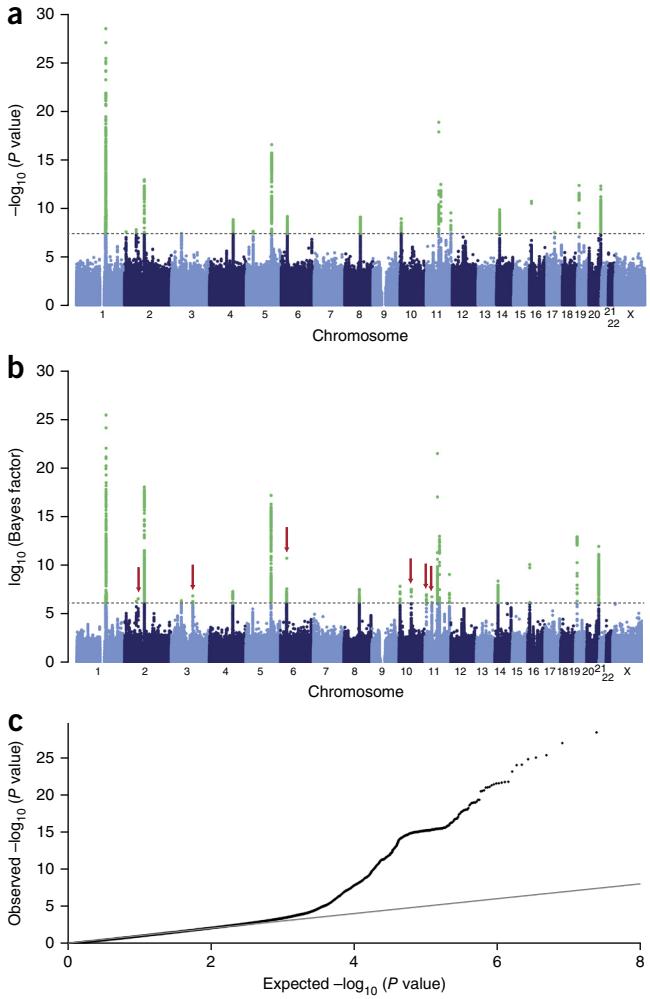


Figure 1 Atopic dermatitis GWAS meta-analysis results. (**a**) Manhattan plot of European fixed-effects meta-analysis. (**b**) Manhattan plot of the multi-ancestry MANTRA meta-analysis of all studies. Arrows mark variants not associated in the European-only analysis. (**c**) Quantile-quantile plot of the European analysis; λ (genomic inflation) = 1.054.

Twenty-one of the 27 atopic dermatitis–associated loci have previously been implicated in other immune-mediated traits (**Supplementary Table 4**), most notably inflammatory bowel disease (IBD) and psoriasis. We therefore compared significant results from GWAS of IBD[22], psoriasis[23], ankylosing spondylitis[24], multiple sclerosis[25], rheumatoid arthritis[26] and type 1 diabetes[27] with the results from our present study of atopic dermatitis. Of 163 established IBD risk variants, 39 reached $P < 0.05$ for atopic dermatitis (8.1 expected, $P = 2.4 \times 10^{-16}$; **Supplementary Table 5**), with 35 showing the same direction of effect (sign-test $P < 0.0001$), consistent with the observational association between the two diseases[28–30]. Of the 36 known psoriasis-associated variants, 15 reached $P < 0.05$ for atopic dermatitis (1.8 expected, $P = 6 \times 10^{-11}$; **Supplementary Table 6**), with ten showing the same direction of effect (sign-test $P = 0.30$). However, these two conditions rarely co-occur clinically[31], and the most strongly associated genetic variants show opposite directions of effect[32]. Therefore, our results, suggesting a more complex genetic relationship, might warrant further investigation. SNPs robustly associated with other autoimmune diseases were also more likely to be nominally associated with atopic dermatitis than expected by chance, but there was little evidence of any consistency in direction of effect (**Supplementary Tables 7–10**). These findings did not appear to be affected by contamination from the use of common controls across studies. Analyses performed excluding common cohorts yielded similar results (data not shown).

Conditional analysis showed evidence for secondary independent signals at four known atopic dermatitis loci (2q12.1, 4q27, 11p13 and 5q31.1; **Supplementary Table 11**), one of which (5q31.1) has been previously reported[9]. In the epidermal differentiation complex (1q21.2-3; where *FLG* is located), the signals near *MRPS21* (rs7512552) and *IL6R* (rs12730935 or the known functional mutation rs2228145) were independent from *FLG*, whereas the top signal near *LCE3E* (rs61813875) appeared to be partially tagging the *FLG* variant encoding p.Arg501* ($r^2 = 0.49$) and showed no significant residual association ($P > 0.05$) after conditioning on the four most prevalent *FLG* variants (**Supplementary Tables 12** and **13**).

To identify additional variants of biological relevance not reaching genome-wide significance, we applied gene set enrichment analysis using Meta-Analysis Gene Set Enrichment of Variant Associations (MAGENTA)[33] (**Supplementary Table 14**). A significant enrichment of 22 partially overlapping gene sets (false discovery rate (FDR) ≤ 0.01) related to innate immune signaling and T cell polarization was observed (**Supplementary Fig. 5**).

For replication, we selected the lead SNPs from the 11 new loci, nine candidate SNPs from the MAGENTA analysis (with $P < 1 \times 10^{-5}$ mapping to gene sets with FDR < 0.05) and three SNPs representing potentially new secondary signals. These SNPs were investigated in 18 studies (32,059 cases and 228,628 controls; **Supplementary Table 1**). In the European studies, 11 of the 20 new loci reached a Bonferroni-corrected significance threshold ($\alpha = 0.0025$) with one-sided tests in a fixed-effects analysis (**Table 2**). However, one of these loci showed evidence of heterogeneity (10p15.1, $P = 0.041$) and was not significantly associated in a random-effects analysis ($P = 0.019$; **Supplementary Table 15**). Two of the SNPs selected by gene set enrichment analysis reached genome-wide significance in the combined analysis (representing the 2q37.1 and 12q15 loci). A random-effects analysis of all the replication cohorts (European and other ancestries) gave broadly consistent results (although only six SNPs reached genome-wide significance), with no clear population-specific effects (**Supplementary Fig. 6** and **Supplementary Table 16**).

All three secondary signals showed significant association in the replication phase conditional analysis (**Supplementary Table 11**).

As a preliminary step toward understanding the functional underpinnings of the atopic dermatitis genetic associations, we established a 'credible set' of SNPs (all with strong association) for each locus (as described in the Online Methods[34]). We reviewed the functional annotations of these SNPs in Encyclopedia of DNA Elements (ENCODE) Consortium and Roadmap Epigenomics Consortium data, evaluated expression quantitative trait locus (eQTL) effects in MuTHER[35], reviewed evidence of differential expression and surveyed relevant mouse mutants (**Supplementary Tables 17–21** and **Supplementary Note**). Regions of DNase I hypersensitivity from the ENCODE and Roadmap Epigenomics data[36,37] were strongly enriched for atopic dermatitis association in comparison to the rest of the genome (**Supplementary Fig. 7** and **Supplementary Table 22**), particularly in immune cells (naive (T_H0) T cells and helper T cells type 1 (T_H1) and type 17 (T_H17); $P < 0.0001$); this enrichment was observed well below the genome-wide significance threshold, indicating the presence of additional undetected risk variants. We observed multiple *cis* eQTLs (Bonferroni-corrected $P < 7 \times 10^{-4}$) in lymphoblastoid cell lines (LCLs) or skin (**Supplementary Tables 17** and **19**).

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Table 1 Discovery results

Variant	Locus	Nearest gene[a]	EA/OA	European, fixed effects				All cohorts, MANTRA		Known atopy loci?	
				n (studies)	EAF	OR (95% CI)	*P*	*n* (studies)	$\log_{10}$ (BF)	Trait	Reference
Known loci											
rs61813875	1q21.3	*CRCT1*/***LCE3E*** (*FLG*)[b]	G/C	93,326 (18)	0.02	1.61 (1.48–1.75)	**5.6×10^{-29}**	96,419 (20)	**25.53**	AD	3–5
rs10791824	11q13.1	*OVOL1*	G/A	102,761 (21)	0.57	1.12 (1.09–1.15)	**2.1×10^{-19}**	116,556 (25)	**21.56**	AD	9
rs12188917	5q31.1	*RAD50*/***IL13***	C/T	102,761 (21)	0.21	1.14 (1.10–1.17)	**4.0×10^{-17}**	116,554 (25)	**17.24**	AD, A, IgE	9,18,58
rs6419573	2q12.1	*IL18R1*/***IL18RAP***	T/C	102,760 (21)	0.26	1.11 (1.08–1.14)	**1.5×10^{-13}**	116,557 (25)	**18.10**	AD, A, AS, SRA	8,14,18,21
rs2212434	11q13.5	***C11orf30***/*LRRC32*	T/C	102,761 (21)	0.45	1.09 (1.07–1.12)	**4.6×10^{-13}**	116,557 (25)	**13.02**	AD, AS, SRA, AR, A	11,14,15, 21,59
rs4809219	20q13.33	***RTEL1***/***TNFRSF6B***	C/A	102,760 (21)	0.27	0.90 (0.87–0.93)	**7.0×10^{-13}**	116,555 (25)	**11.98**	AD	7,10
rs2918307	19p13.2	*ADAMTS10*/***ACTL9***	G/A	100,707 (20)	0.16	1.12 (1.08–1.16)	**4.6×10^{-12}**	114,504 (24)	**12.98**	AD	9
rs2041733	16p13.13	*CLEC16A*	C/T	103,066 (22)	0.55	0.92 (0.90–0.94)	**2.5×10^{-11}**	116,862 (26)	**10.11**	AD, A+HF	7,53
rs12730935[c]	1q21.3	*IL6R*	A/G	102,760 (21)	0.39	1.08 (1.05–1.11)	**6.1×10^{-11}**	116,556 (25)	**7.15**	AD, A	12,15
4:123243592[d]	4q27	*KIAA1109* (*IL2*)[b]	R/I	102,761 (21)	0.37	1.08 (1.05–1.10)	**4.2×10^{-9}**	107,119 (24)	**7.32**	AD, AS, SRA	7,14,21
rs4713555	6p21.32	***HLA-DRB1***/*HLA-DQA1*	T/G	91,217 (15)	0.27	0.91 (0.89–0.94)	**5.4×10^{-9}**	105,014 (19)	**10.76**	AD, AS, SRA, A	6,8,14,18,21
rs2944542	10q21.2	*ZNF365*	C/G	102,762 (21)	0.41	0.94 (0.92–0.96)	1.2×10^{-6}	116,559 (25)	**7.56**	AD	8,10
rs145809981	6p21.33	*MICB*	T/C	97,697 (19)	0.14	0.91 (0.88–0.95)	1.5×10^{-6}	110,228 (22)	**7.33**	AD, AS, SRA	8,14,21
rs4312054	11p15.4	*OR10A3*/***NLRP10***	G/T	102,760 (21)	0.41	1.00 (0.97–1.02)	0.744	116,556 (25)	**7.00**	AD	8
rs1249910	3q13.2	***CCDC80***/*CD200R1L*	A/G	99,164 (20)	0.34	0.98 (0.96–1.01)	0.137	112,960 (24)	**6.86**	AD	8
rs2592555	11p13	*PRR5L*	C/T	102,760 (21)	0.27	0.93 (0.90–0.96)	8.7×10^{-7}	116,551 (25)	**6.78**	AD	7
New loci											
rs2038255	14q13.2	*PPP2R3C*	T/C	102,760 (21)	0.18	1.11 (1.07–1.14)	**1.8×10^{-10}**	116,557 (25)	**8.40**		
rs7127307	11q24.3	–/***ETS1***	C/T	103,066 (22)	0.47	0.93 (0.90–0.95)	**3.9×10^{-10}**	116,855 (26)	**9.08**	SRA	14
rs7512552	1q21.2	*C1orf51*/***MRPS21***	T/C	102,762 (21)	0.49	0.93 (0.91–0.95)	**9.1×10^{-10}**	116,544 (25)	**6.91**		
rs6473227	8q21.13	*MIR5708*/***ZBTB10***	A/C	102,761 (21)	0.61	0.93 (0.91–0.95)	**1.4×10^{-9}**	116,557 (25)	**7.54**	(AD), SRA, A+HF	9,14,53
rs6602364	10p15.1	*IL15RA*/***IL2RA***	G/C	103,065 (22)	0.45	1.08 (1.05–1.10)	**1.5×10^{-9}**	116,855 (26)	**7.86**	(SRA)	14
rs10214237	5p13.2	***IL7R***/*CAPSL*	C/T	102,761 (21)	0.27	0.93 (0.90–0.95)	**2.9×10^{-8}**	116,554 (25)	4.79		
rs10199605	2p25.1	*LINC00299*/–	A/G	102,760 (21)	0.30	0.93 (0.90–0.95)	**3.4×10^{-8}**	116,557 (25)	4.67	(SRA)	14
rs4643526	2p16.1	*PUS10*	A/G	103,066 (22)	0.19	1.09 (1.06–1.12)	**3.5×10^{-8}**	107,425 (25)	**6.31**		
rs12951971	17q21.2	*STAT3*	G/T	102,761 (21)	0.09	1.13 (1.08–1.17)	**4.1×10^{-8}**	107,120 (24)	5.33		
rs7625909	3p21.1	***SFMBT1***/*RFT1*	T/C	102,761 (21)	0.32	1.07 (1.05–1.10)	**4.9×10^{-8}**	116,558 (25)	5.83		
rs112111458	2p13.3	*CD207*/***VAX2***	G/A	102,760 (21)	0.13	0.91 (0.87–0.94)	1.4×10^{-7}	116,553 (25)	**6.57**		

The table shows the index variant for loci associated with $P < 5 \times 10^{-8}$ in the European analysis or $\log_{10}$ (Bayes factor) > 6.1 in the multi-ancestry MANTRA analysis. Previous atopy trait associations with these loci are also listed. *P* values and $-\log_{10}$ (Bayes factor) values in bold indicate genome-wide significant results. AD, atopic dermatitis; A, asthma; AS, allergic sensitization; SRA, self-reported allergy; AR, allergic rhinitis; A+HF, asthma and hay fever combined; EA/OA, effect allele/other allele; EAF, effect allele frequency; OR, odds ratio; CI, confidence interval; *n*, sample size; BF, Bayes factor. Traits in parentheses did not reach genome-wide significance in the previous studies but were reported as suggestively associated. [a]Nearest genes are the two flanking genes if the variant is intergenic (with the closer gene in bold; a minus sign indicates no gene within 250 kb); single genes denote that the variant is intronic. [b]At 1q21.2, the variant is closest to *LCE3A*, but the previous association with *FLG* is within 250 kb; at 4q27, the variant is within an intron of *KIAA1109*, but the previous association with *IL2* is within 150 kb. [c]In LD with the known functional variant rs2228145 ($r^2 = 0.86$). [d]A nearby SNP (rs6827756; at 123,184,411 bp) in LD ($r^2 = 0.97$ in the 1000 Genomes Project) showed similar association ($\log_{10}$ (Bayes factor) = 7.21, European fixed-effects $P = 3 \times 10^{-9}$).

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The most significant were two variants from the credible set at 2p13.3, which were strong eQTLs for *CD207* (langerin) in skin (rs4852714, $P = 1.23 \times 10^{-10}$; rs6723629, $P = 1.67 \times 10^{-10}$; linkage disequilibrium (LD) with the lead SNP: $r^2 = 0.56$, $D' = 0.96$ and $r^2 = 0.53$, $D' = 0.93$, respectively; 99% posterior probability that the atopic dermatitis and eQTL signals colocalized). rs4852714 is also in an open chromatin region with histone marks indicative of promoter or enhancer activity in LCLs (**Supplementary Fig. 8** and **Supplementary Tables 18** and **19**). *CD207* encodes an intracellular pattern recognition receptor expressed in subpopulations of dendritic cells, in particular epidermal Langerhans cells, which have a vital role in the induction of tolerance and direction of adaptive immune responses[38]. CD207 binds to carbohydrates present, for example, on microorganisms and exerts antiviral and antifungal defense mechanisms[39]. Of note, atopic dermatitis is characterized by increased susceptibility to skin infection with pathogens such as *Staphylococcus aureus*, herpes simplex virus and *Malassezia* species[40], and differences in langerin function might contribute to this dysregulated cutaneous immunity.

There is longstanding evidence that skin barrier defects and inappropriate immune responses to environmental antigens[1] contribute to atopic dermatitis. However, evidence for autoimmune mechanisms, in particular in the context of progression to the chronic phase, has only recently emerged[41]. Interestingly, the majority of our new susceptibility loci harbor candidate genes with functional annotations related to autoimmunity. At 14q13.2, the lead SNP (rs2038255) is intronic to *PPP2R3C* (a protein phosphatase component regulating B cell maturation and survival), the dysregulation of which has been associated with autoimmunity in mice[42], and the signal colocalizes with a strong eQTL signal for *KIAA0391* (**Supplementary Table 19**). The lead variant at 5p13.2 (rs10214237) is located 4 kb downstream of the gene encoding the α chain of the interleukin-7 receptor (IL-7R), which is a key mediator in T cell–driven autoimmunity and inflammation[43]. Of interest, the credible set contained an *IL7R* missense variant (rs6897932, $P = 1.6 \times 10^{-7}$, $r^2 = 0.94$ with the lead SNP) that displayed the same direction of effect in multiple sclerosis[44,45]. The risk allele leads to enhanced IL-7 bioavailability[46], which in mice causes severe dermatitis with intense pruritus and high IgE levels, that is, atopic dermatitis–like features[47]. Likewise, as part of the autosomal dominant hyper-IgE syndrome, rare dominant-negative mutations in the *STAT3* gene (in which our lead 17q21.2 variant is intronic) cause severe dermatitis and high serum IgE levels, as well as recurrent *S. aureus* skin infections, which may be driven by impaired T_H17 cell differentiation and effector function[48,49]. *STAT3* might

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Table 2 Replication results for the new genome-wide significant loci and loci identified in the MAGENTA gene set enrichment analysis

Variant	Locus	Nearest gene	EA/OA	EAF	Discovery European			Replication European			Overall European, fixed effects			Het	Random-effects *P*	
					n (studies)	OR (95% CI)	*P*	*n* (studies)	OR (95% CI)	*P*[a]	*n*	OR (95% CI)	*P*	*P*	European	All studies
New genome-wide significant loci																
rs7512552	1q21.2	*C1orf51*/*MRPS21*	T/C	0.49	102,762 (21)	0.93 (0.91–0.95)	9.1×10^{-10}	257,019 (15)	0.98 (0.96–0.99)	0.0048	359,781	0.96 (0.94–0.97)	**5.4×10^{-9}**	**0.002**	1.5×10^{-7}	1.3×10^{-7}
rs10199605	2p25.1	*LINC00299*/–	A/G	0.30	102,760 (21)	0.93 (0.90–0.95)	3.4×10^{-8}	256,958 (15)	0.97 (0.95–0.99)	0.0045	359,718	0.96 (0.94–0.97)	**4.0×10^{-8}**	**0.024**	4.1×10^{-6}	1.5×10^{-5}
rs4643526	2p16.1	*PUS10*	A/G	0.19	103,066 (22)	1.09 (1.06–1.12)	3.5×10^{-8}	257,050 (14)	1.03 (1.01–1.05)	0.0058	360,116	1.05 (1.03–1.07)	5.9×10^{-8}	0.249	3.8×10^{-6}	1.1×10^{-5}
rs112111458	2p13.3	*CD207*/*VAX2*	G/A	0.13	102,760 (21)	0.91 (0.87–0.94)	1.4×10^{-7}	257,019 (15)	0.95 (0.93–0.98)	**8.0×10^{-4}**	359,779	0.94 (0.92–0.96)	**9.4×10^{-9}**	0.076	4.4×10^{-6}	1.6×10^{-7}
rs11923593[b]	3p21.1	*SFMBT1*/*RFT1*	G/A	0.32	102,761 (21)	1.07 (1.04–1.10)	9.7×10^{-8}	257,002 (15)	1.01 (0.99–1.03)	0.2600	359,763	1.03 (1.01–1.05)	1.3×10^{-4}	0.081	8.7×10^{-5}	1.7×10^{-5}
rs10214237	5p13.2	*IL7R*/*CAPSL*	C/T	0.27	102,761 (21)	0.93 (0.90–0.95)	2.9×10^{-8}	257,010 (15)	0.94 (0.93–0.96)	**6.7×10^{-8}**	359,771	0.94 (0.92–0.95)	**2.9×10^{-14}**	0.773	**2.9×10^{-14}**	**1.5×10^{-10}**
rs6473227	8q21.13	*MIR5708*/*ZBTB10*	A/C	0.61	102,761 (21)	0.93 (0.91–0.95)	1.4×10^{-9}	257,006 (15)	0.95 (0.93–0.97)	**4.5×10^{-9}**	359,767	0.94 (0.93–0.95)	**2.2×10^{-16}**	0.622	**2.2×10^{-16}**	**5.3×10^{-18}**
rs6602364	10p15.1	*IL15RA*/*IL2RA*	G/C	0.45	103,065 (22)	1.08 (1.05–1.10)	1.5×10^{-9}	256,993 (15)	1.03 (1.01–1.05)	**3.9×10^{-4}**	360,058	1.05 (1.03–1.06)	**1.3×10^{-10}**	**0.041**	3.6×10^{-6}	1.6×10^{-6}
rs7127307	11q24.3	–/*ETS1*	C/T	0.47	103,066 (22)	0.93 (0.90–0.95)	3.9×10^{-9}	257,034 (15)	0.94 (0.93–0.96)	**2.5×10^{-10}**	360,100	0.94 (0.92–0.95)	**1.5×10^{-18}**	0.935	**1.5×10^{-18}**	**1.0×10^{-20}**
rs2143950[b]	14q13.2	*PPP2R3C*	T/C	0.17	102,762 (21)	1.10 (1.07–1.14)	6.8×10^{-10}	249,940 (12)	1.07 (1.04–1.09)	**9.9×10^{-8}**	352,702	1.08 (1.06–1.10)	**1.8×10^{-15}**	0.092	4.8×10^{-7}	**8.6×10^{-10}**
rs17881320[b]	17q21.2	*STAT3*	T/G	0.08	96,796 (19)	1.12 (1.07–1.17)	2.0×10^{-6}	249,949 (12)	1.05 (1.02–1.09)	**1.5×10^{-3}**	346,745	1.08 (1.05–1.11)	1.4×10^{-7}	0.405	6.2×10^{-7}	2.6×10^{-6}
MAGENTA gene set enrichment analysis loci																
rs1057258	2q37.1	*INPP5D*	T/C	0.18	101,012 (21)	0.94 (0.91–0.97)	6.6×10^{-5}	257,030 (15)	0.94 (0.92–0.96)	**3.8×10^{-7}**	358,042	0.94 (0.92–0.96)	**1.7×10^{-10}**	0.811	**1.7×10^{-10}**	**4.1×10^{-13}**
rs6872156	5q35.1	*DUSP1*	A/G	0.24	103,066 (22)	0.93 (0.91–0.96)	2.4×10^{-6}	257,047 (15)	0.97 (0.95–0.99)	0.0055	360,113	0.96 (0.94–0.97)	8.1×10^{-7}	0.340	1.8×10^{-6}	2.7×10^{-7}
rs7016497	8q24.3	*PTK2*	T/C	0.21	103,066 (22)	0.94 (0.91–0.97)	1.1×10^{-4}	257,040 (15)	0.98 (0.95–1.00)	0.0290	360,106	0.96 (0.95–0.98)	9.4×10^{-5}	0.757	9.4×10^{-5}	1.4×10^{-6}
rs2905493	11q12.2	*CD6*/*CD5*	T/C	0.01	89,617 (15)	0.78 (0.68–0.89)	2.6×10^{-4}	254,992 (13)	1.01 (0.94–1.08)	0.6040	344,609	0.95 (0.90–1.02)	0.1432	0.150	0.419	0.098
rs1799986	12q13.3	*LRP1* (*STAT6*)[c]	T/C	0.15	99,165 (20)	0.91 (0.88–0.94)	1.1×10^{-7}	257,022 (15)	0.98 (0.96–1.01)	0.1140	356,187	0.96 (0.94–0.98)	2.9×10^{-5}	0.182	1.1×10^{-4}	1.6×10^{-3}
rs2227483	12q15	*IL22* (and *IFNG*)[c]	A/T	0.44	102,762 (21)	0.94 (0.92–0.97)	2.3×10^{-6}	253,446 (14)	0.94 (0.92–0.96)	**3.6×10^{-11}**	356,208	0.94 (0.93–0.96)	**6.7×10^{-16}**	0.664	**6.7×10^{-16}**	**1.2×10^{-17}**
rs7146581	14q32.32	*TRAF3*	T/C	0.24	102,760 (21)	0.95 (0.92–0.97)	1.4×10^{-4}	256,971 (15)	0.96 (0.94–0.98)	**5.7×10^{-5}**	359,731	0.95 (0.94–0.97)	6.2×10^{-8}	0.219	1.2×10^{-4}	4.1×10^{-6}
rs11657987	17q25.3	*PGS1* (*SOCS3*)[c]	T/G	0.49	100,695 (21)	1.06 (1.04–1.09)	1.1×10^{-6}	257,019 (15)	1.03 (1.01–1.05)	**1.0×10^{-3}**	357,714	1.04 (1.03–1.06)	5.1×10^{-8}	0.235	9.7×10^{-5}	6.0×10^{-5}
rs77714197	19q13.11	*CEBPA*	T/C	0.02	87,690 (14)	1.35 (1.19–1.54)	3.3×10^{-6}	256,447 (14)	0.98 (0.89–1.08)	0.6540	344,137	1.10 (1.02–1.18)	0.0139	**0.048**	0.102	0.116

[a]Replication *P* values for a one-sided test. [b]rs11923593 replaces rs7625909 ($r^2 = 0.98$), rs2143950 replaces rs2038255 ($r^2 = 0.94$) and rs17881320 replaces rs12951971 ($r^2 = 0.75$) in the replication analysis. [c]rs1799986 is within *LRP1* but was selected in the MAGENTA analysis because of its proximity to *STAT6*; rs2227483 is within *IL22* but was selected because of its proximity to both *IL22* and *IFNG*; rs11657987 is within *PGS1* but was selected because of its proximity to *SOCS3*. Replication *P* values in bold were considered significant ($P < 0.0025$). Overall *P* values in bold are genome-wide significant. Heterogeneity *P* values <0.05 appear in bold. EA/OA, effect allele/other allele; EAF, effect allele frequency; OR, odds ratio; CI, confidence interval; *n*, sample size; het, heterogeneity.

thus represent an example of a risk gene or pathway shared by a complex trait and a related Mendelian condition[50,51], harboring highly penetrant, severe-effect rare mutations and common variants of milder effect. At 8q21.13, the closest candidate gene was *ZBTB10*, which encodes a zinc-finger protein that is a putative repressor of the Sp1, Sp3 and Sp4 transcription factors[52]. Variants in moderate LD ($r^2 > 0.7$) with the lead variant for atopic dermatitis were previously associated with self-reported allergy[14] and a combined asthma and hay fever phenotype[53]. However, although not excluding *ZBTB10* as the causal gene, the credible SNP set comprises a 47-kb interval on the other side of a recombination peak (60 cM/Mb). The variant most likely to be regulatory among this set, deletion rs5892724 ($r^2 = 0.82$ with the lead SNP), is located in open chromatin in several cell types, including $CD4^+$ helper T cells, and affects a STAT3-binding site[49,54]. At 11q24.3, the most plausible candidate gene is *ETS1*, which encodes a transcription factor with a range of immune functions, including roles in T_H17 and B cell differentiation and function; ETS1-deficient mice display autoimmune features[55]. ETS1 appears to be additionally involved in keratinocyte differentiation and the formation of the cornified envelope[56]. Additional variants identified through the gene set approach implicate genes with cytokine signaling functions (*INPP5D*, *TRAF3*, *SOCS3* and a cytokine cluster at 12q15).

In conclusion, we have identified ten new loci robustly associated with atopic dermatitis in Europeans (six of which also reach genome-wide significance in random-effects analysis across studies of all ancestry groups), bringing the total number of susceptibility loci to 31 (24 in Europeans), with evidence of secondary signals at four of these loci. Altogether, in the subset of European studies with clinically defined cases, the previously established and newly identified variants explain approximately 12.3% and 2.6% of the variance in liability, respectively (**Supplementary Table 23**). All newly identified susceptibility loci are related to (auto)immune regulation, in particular innate immune signaling and T cell activation and specification, and there appears to be a substantial genetic overlap with other inflammatory and autoimmune diseases. Although not detracting from the importance of maintaining the skin barrier in the prevention and treatment of atopic dermatitis, our findings lend support to new therapeutic approaches targeted at immune modulation[57].

URLs. Gene Expression Omnibus, http://www.ncbi.nlm.nih.gov/geoprofiles; Mouse Genome Informatics (MGI) database, http://www.informatics.jax.org/.

METHODS

Methods and any associated references are available in the online version of the paper.

Accession codes. Genome-wide results are available on request through the corresponding author, on condition of signing any Data Transfer Agreements required according to the institutional review board (IRB)-approved protocols of contributing studies.

Note: Any Supplementary Information and Source Data files are available in the online version of the paper.

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AAGC provided results for the discovery analysis.

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The authors declare competing financial interests: details are available in the online version of the paper.

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ONLINE METHODS

GWAS meta-analysis. We carried out genome-wide association analysis for atopic dermatitis case-control status in 26 individual studies (**Supplementary Table 1**), comprising a total of 21,399 cases and 95,464 controls. The majority of these studies included individuals of only European ancestry (22 studies; 18,900 cases, 84,166 controls). We also included one study of Japanese individuals (RIKEN; 1,472 cases, 7,966 controls), one study of African-American individuals (SAPPHIRE; 422 cases, 844 controls), one study of Latin American individuals (GALA II; 300 cases, 1,592 controls) and one study with individuals of mixed non-European ancestry (Generation R; 305 cases, 896 controls). Details on informed consent and ethical approval procedures for the individual studies are included in the **Supplementary Note**.

Each cohort separately imputed their genetic data to the 1000 Genomes Project Phase 1 reference panel (with the majority using the March 2012 release; **Supplementary Table 1**) and carried out genome-wide association analysis across all imputed variants. Before meta-analysis, we restricted each study to only variants with MAF >1% and a moderate imputation quality score (Rsq >0.3 for variants imputed in MACH and proper info >0.4 for variants imputed in IMPUTE). For some cohorts, additional quality control filters were applied (the full methods for each study are available in the **Supplementary Note**).

Meta-analysis was conducted for Europeans only in GWAMA (using a fixed-effects model) and for all ancestry groups combined in MANTRA[60]. Rather than imposing a fixed- or random-effects model, MANTRA accounts for the heterogeneity of effects between ancestry groups by allowing the studies to cluster according to allele frequency profile (and, hence, population genetic similarity). To prevent very small European studies (with less precise estimates of allele frequencies) from having undue weight in our analysis, we fixed the Europeans to cluster together using the European fixed-effects results in the MANTRA analysis. Variants with $P < 5 \times 10^{-8}$ in the European analysis were considered to be associated, as were any additional variants with $\log_{10}$ (Bayes factor) > 6.1 (equivalent to $P < 5 \times 10^{-8}$) (ref. 61) in the MANTRA analysis. Each locus is represented in the corresponding results table by the variant with the strongest evidence for association. Heterogeneity was assessed using the I^2 statistic and Cochrane's Q test. Meta-analysis results were also stratified according to ancestry, method of case definition and age of onset to explore sources of heterogeneity.

For the epidermal differentiation complex region (where the *FLG* gene is located and which has previously shown complex association results), we repeated the association tests (across the region from 150.2 to 154.5 Mb on chromosome 1) conditioning on the four most common *FLG* variants (p.Arg501*, c.2282del4, p.Arg2447* and p.Ser3247*) in the individual studies where these data were available (ten studies, 20,384 individuals; **Supplementary Table 12**). These samples were subjected to meta-analysis to determine whether there were any remaining independent association signals in this region.

Identification of independent secondary signals at associated loci. To identify secondary independent signals at each of the other associated loci, we carried out conditional analysis of the European meta-analysis results using GCTA[62], with ALSPAC 1000 Genomes Project imputation (restricted to variants with MAF >1% and imputation quality proper info score >0.8) serving as the reference. The regions tested were within 250 kb up- or downstream of the top hit at each locus. Locus-specific significance thresholds were estimated by first calculating the effective number of tests in each 500-kb region using Nyholt's procedure[63] and the 1000 Genomes Project reference data (European). For each locus, we estimated the new threshold for a locus-wide error rate of 5% by dividing α (0.05) by the corresponding number of effective tests in that region (α values are shown in **Supplementary Table 11**). For 4q27, we defined the region as lying within 500 kb of the top hit because a known hit was just less than 500 kb from the top SNP in our analysis. We conditioned each region on the top hit from our meta-analysis. Any variant that surpassed the locus-specific significance threshold was considered an independent secondary signal.

MAGENTA gene set enrichment analysis. We tested our meta-analysis results for enriched gene sets using MAGENTA[33]. This method assigns SNPs to genes on the basis of genomic distance (SNPs are assigned if within 110 kb upstream or 40 kb downstream of each gene) and generates gene-based summary P values. Subsequently, genes are assigned to gene sets (using curated repositories including GO-data, Biocarta, PANTHER, KEGG, etc.), and each gene set is assigned a P value by comparing gene summary P values to a null model where SNPs are drawn randomly 10,000 times (normalizing for the number of SNPs genotyped in each gene) and controlling for FDR at $\alpha = 0.05$. Approximately 10,000 gene sets were tested. As MAGENTA requires a P value as input and to take account of the differing effects between populations, we reanalyzed our meta-analysis of all studies using a random-effects model, to generate results to serve as input for the MAGENTA analysis. All genes in the human leukocyte antigen (HLA) region (chr. 6: 29,710,331–33,150,000) were removed from the analysis. To identify additional variants of interest to take forward to replication, we examined any pathway with FDR <0.05. From these gene sets, we took forward to replication any additional locus with a genetic variant associated at $P < 1 \times 10^{-5}$.

Cross-phenotype comparisons. The National Human Genome Research Institute (NHGRI) GWAS catalog[64] was mined for traits with reported associations at each of our genome-wide significant loci. To further investigate the genetic overlap between atopic dermatitis and autoimmune diseases, we took the genome-wide significant loci from recent GWAS of IBD[22], psoriasis[23], ankylosing spondylitis[24], multiple sclerosis[25], rheumatoid arthritis[26] and type 1 diabetes[27] and extracted the atopic dermatitis results for these variants from our European discovery GWAS, noting whether each variant was associated ($P < 0.05$) with atopic dermatitis (testing the enrichment of overlap using a two-sided binomial exact test) and carried the same or opposite directions of effect for the two traits (tested using a sign test).

Replication. The top SNPs from the 11 newly associated regions ($\log_{10}$ (Bayes factor) > 6.1 or $P < 5 \times 10^{-8}$) were taken forward to replication, along with nine suggestively associated SNPs ($P < 1 \times 10^{-5}$) that were in genes highlighted in the MAGENTA analysis as good candidates. In addition, we included any variant with evidence of being a secondary independent signal in the associated loci. Replication consisted of 18 studies (32,059 cases and 228,628 controls) with genome-wide imputed data available or custom genotyping (**Supplementary Table 1**). The studies of European ancestry were combined in fixed-effects meta-analyses in GWAMA. We also carried out random-effects meta-analysis for the European studies to assess association for variants that showed evidence of heterogeneity ($P < 0.05$). Significant association in the replication phase was defined by a one-sided P value meeting a Bonferroni-corrected threshold ($\alpha = 0.05/20 = 0.0025$). Random-effects meta-analyses of replication studies of all ancestry groups were also carried out, and forest plots were examined for evidence of population-specific effects. For replication of the three secondary signals, the secondary SNPs were tested for association after conditioning on the top SNP in each of the European cohorts. These results were then combined in fixed-effects meta-analyses.

Credible sets. To assemble a sensible list of variants at each locus for functional look-ups, we constructed credible sets[34] that represented the SNPs most likely to be causal on the basis of statistical evidence from the MANTRA analysis (or from the European analysis for the three variants that appeared to be European specific). The European-only GWAS was repeated in MANTRA to generate the Bayes factors required for credible set analysis. Bayes factors were used to calculate posterior probabilities for all SNPs in each region (±1 Mb from the top SNP); the minimum set of SNPs that had a cumulative posterior probability of at least 95% made up each credible set. These sets can be interpreted similarly to confidence intervals, assuming that the association signal at a locus can be attributed to a single causal variant (and that the true causal variant is included in the analysis and has been well imputed); there is a 95% probability that the 95% credible set contains that causal variant. Given that analysis based on 1000 Genomes Project imputation may not include the true causal variant or that each association may be driven by more than one causal variant, we do not expect these credible sets to necessarily contain the causal variants at the suggested probability of 95%. Nevertheless, they demonstrate which neighboring variants, in addition to the top SNP, also show strong association with atopic dermatitis, and we find them useful in

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assessing the size of the regions of interest and for defining a set of variants to follow up. As the posterior probabilities for the MAGENTA-identified credible sets were extremely large (owing to the weaker signals at these loci), we instead carried out functional look-ups for all variants with $r^2 \geq 0.8$ with the top hit for these loci.

Functional look-ups. For variants identified as part of a credible set, we carried out look-ups in functional data resources as follows: (i) RegulomeDB and HaploReg were mined for evidence of coding or regulatory function (these resources collate annotations (for example, coding variation, regulatory chromatin marks, DNase I hypersensitivity, protein binding and motif alteration) from the ENCODE Consortium, the US National Institutes of Health Roadmap Epigenomics Mapping Consortium and the literature over a wide range of tissues); (ii) *cis* eQTLs in skin or LCLs were identified in data from the MuTHER Consortium[35] (with variants considered to be eQTLs if the association with any transcript within 1 Mb had $P < 7 \times 10^{-4}$, corresponding to significance with Bonferroni correction for 36 loci and two tissues); (iii) implicated genes were identified with differential expression reported between uninvolved skin from cases and skin from controls[65] and between lesional and non-lesional skin in patients with atopic dermatitis in a study deposited in the Gene Expression Omnibus (GDS4444) (ref. 66) and (iv) mouse mutants of implicated genes were examined in the Mouse Genome Informatics (MGI) database.

Colocalization of atopic dermatitis GWAS signals and eQTLs in the MuTHER data was investigated using the R package coloc[67]. All SNPs within 100 kb of the lead atopic dermatitis SNP were included in the analysis, and we report the posterior probability of each pair of signals colocalizing in **Supplementary Table 19**.

To identify and visualize cell types implicated in atopic dermatitis pathogenesis, the tendency of disease-associated loci to fall in cell type–specific regulatory DNase I–hypersensitive sites (DHSs; a proxy for accessible and/or regulatory DNA) was calculated for the full range of *P* values, essentially as described[68]. Enrichment was computed for 168 cell types and cell lines in the ENCODE and Roadmap repositories[36]. Duplicates and directly redundant cell types were removed before analysis. One-sided *P* values for enrichment were calculated from an empirical null distribution of locus overlap for DHS regions, generated by 10,000 random permutations with overlap of an identical number of randomly selected loci as found at $P \leq 1 \times 10^{-10}$ with all DHS regions for all cell and tissue types.

Variance in liability explained. We estimated the proportion of variance in atopic dermatitis liability explained by the established and new variants in a subset of studies that had clinically diagnosed cases (GENEVA/KORAF4/POPGEN, NCRC-ADC, GENUFADex-SHIP1, GENUFAD-SHIP2, GENEVA (replication) and CECCS) using the method of So *et al.*[69].

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Supplementary Note

1. Individual Study Methods

23andMe

Recruitment

All individuals included in the analyses provided informed consent and answered surveys online according to our human subjects protocol, which was reviewed and approved by Ethical & Independent Review Services, a private institutional review board (http://www.eandireview.com). Samples were drawn from 23andMe research participants who reported via web-based questionnaires whether they had been diagnosed with 'Eczema'.

Case/Control definition

23andMe participants were able to fill out web-based questionnaires whenever they logged into their 23andMe accounts.

For GWAS (v2 and v3):

Eczema information used in GWAS was derived from "Your Medical History" survey and the "Roots into the future" survey.

Survey: Your Medical History

Q1. Have you ever been diagnosed by a doctor with any of the following autoimmune conditions? (Eczema) [cases: "Yes" ; controls: "No" ; NAs: "I'm not sure"]

Survey: Roots into the future

Q2. Has a doctor ever told you that you have any of these skin conditions? Please check all that apply. (Eczema) [cases: "Yes" ; controls: "No" ; NAs: "I'm not sure"]

A combined "eczema" phenotype is first assigned based on the unambiguous response from the question in "Your Medical History" survey, and then for individuals who were not classified, the responses from the question in the "Roots into the future" survey were used.

For replication analysis:

Eczema information used in the replication analysis was derived from **additional data** collected from the "Your Medical History" survey and the "Roots into the future" survey. In addition, we also combined information from the "Allergies and Asthma" survey, "Asthma" survey, "Allergies" Survey, a question on research snippet and the "Your Profile and Health History" Survey.

Survey: Your Medical History

Q1. Have you ever been diagnosed by a doctor with any of the following autoimmune conditions? (Eczema) [cases: "Yes" ; controls: "No" ; NAs: "I'm not sure"]

Survey: Roots into the future

Q2. Has a doctor ever told you that you have any of these skin conditions? (Eczema) [cases: "Yes" ; controls: "No" ; NAs: "I'm not sure"]

Survey: Allergies and Asthma

Q3. Did you have any of the following problems as a child (age 17 or younger)? Eczema (atopic dermatitis) [cases: "Yes" ; controls: "No" ; NAs: "I'm not sure"]

Survey: Asthma

Q4. Have you ever had any of the following? Atopic dermatitis/Eczema (chronic itchy and scaly skin rashes caused by allergies) [cases: "Yes" ; controls: "No" ; NAs: "I'm not sure"]

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Survey: Allergies

Q5. Did you have any of these problems before you were 18 years old? Eczema (atopic dermatitis) [cases: "Yes" ; controls: "No" ; NAs: "I'm not sure"]

Survey: Research Snippet

Q6.1. Have you ever been diagnosed with eczema? [cases: "Yes" ; controls: "No" ; NAs: "I'm not sure"]

Survey: Your Profile and Health History

Q6.2. Have you ever been diagnosed with or treated for any of the following conditions? Eczema [cases: "Yes" ; controls: "No" ; NAs: "I'm not sure"]

Q7.1. Have you ever been diagnosed or treated for any of the following conditions? (An autoimmune disease (a disease in which your immune system attacks part of your body) [cases: "Yes" ; controls: "No" ; NAs: "I'm not sure"]

Q7.2. What autoimmune diseases have you been diagnosed with? Eczema [cases: "Yes" ; controls: "No" ; NAs: "I'm not sure"]

Q8.1. Have you ever been diagnosed or treated for any of the following conditions? A skin condition [cases: "Yes" ; controls: "No" ; NAs: "I'm not sure"]

Q8.2. What skin conditions have you had? Eczema [cases: "Yes" ; controls: "No" ; NAs: "I'm not sure"]

1. Q6.1 and Q6.2 were first merged into one source by taking the most recent response from them. A combined phenotype is assigned based on the first unambiguous response from the questions in sources 1 to 6: cases and controls are first assigned based on the question in ``Your Medical History'', then for individuals who were not classified, the subsequent questions in sources 2 to 6 are used in the given order.

2. Another phenotype is assigned based on the two questions Q7.1 and Q7.2: cases answered "yes" to Q7.2 and controls answered "no" to either Q7.1 or Q7.2.

3. A third phenotype is assigned based on the two questions Q8.1 and Q8.2: cases answered "yes" to Q8.2 and controls answered "no" to either Q8.1 or Q8.2.

The final 'eczema' cases are defined as being "case" in at least one of the above three derived phenotypes, controls are defined as being "control" in at least one of the above three derived phenotypes. When discordant, we assume the 'case' answer is correct.

Genotyping and imputation

DNA extraction and genotyping were performed on saliva samples by National Genetics Institute (NGI), a CLIA licensed clinical laboratory and a subsidiary of Laboratory Corporation of America. Samples have been genotyped on one of four genotyping platforms. The V1 and V2 platforms were variants of the Illumina HumanHap550+ BeadChip, including about 25,000 custom SNPs selected by 23andMe, with a total of about 560,000 SNPs. The V3 platform was based on the Illumina OmniExpress+ BeadChip, with custom content to improve the overlap with our V2 array, with a total of about 950,000 SNPs. The V4 platform in current use is a fully custom array, including a lower redundancy subset of V2 and V3 SNPs with additional coverage of lower-frequency coding variation, and about 570,000 SNPs. Samples that failed to reach 98.5% call rate was re-analyzed. Individuals whose analyses failed repeatedly were re-contacted by 23andMe customer service to provide additional samples, as is done for all 23andMe customers.

GWAS V2: samples are from V1 and V2 platforms, but the majority are genotyped on V2 platform.
GWAS V3: samples are solely from V3 platform.

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Replication: samples are combined from V1, V2, V3 and V4 platforms, but the majority are genotyped on V3 and V4 platform.

For our standard GWAS, we restrict participants to a set of individuals who have >97% European ancestry, as determined through an analysis of local ancestry[1]. Briefly, our algorithm first partitions phased genomic data into short windows of about 100 SNPs. Within each window, we use a support vector machine (SVM) to classify individual haplotypes into one of 31 reference populations. The SVM classifications are then fed into a hidden Markov model (HMM) that accounts for switch errors and incorrect assignments, and gives probabilities for each reference population in each window. Finally, we used simulated admixed individuals to recalibrate the HMM probabilities so that the reported assignments are consistent with the simulated admixture proportions. The reference population data is derived from public datasets (the Human Genome Diversity Project, HapMap, and 1000 Genomes), as well as 23andMe research participants who have reported having four grandparents from the same country.

A maximal set of unrelated individuals was chosen for each analysis using a segmental identity-by-descent (IBD) estimation algorithm[2]. Individuals were defined as related if they shared more than 700cM IBD, including regions where the two individuals share either one or both genomic segments identical-by-descent. This level of relatedness (roughly 20% of the genome) corresponds approximately to the minimal expected sharing between first cousins in an outbred population.

Participant genotype data were imputed against the March 2012 "v3" release of 1000 Genomes reference haplotypes[3]. We phased and imputed data for each genotyping platform separately. First, we used Beagle[4] (version 3.3.1) to phase batches of 8000-9000 individuals across chromosomal segments of no more than 10,000 genotyped SNPs, with overlaps of 200 SNPs. We excluded SNPs with Hardy-Weinberg equilibrium $P<10^{-20}$, call rate < 95%, or with large allele frequency discrepancies compared to European 1000 Genomes reference data. Frequency discrepancies were identified by computing a 2x2 table of allele counts for European 1000 Genomes samples and 2000 randomly sampled 23andMe research participants with European ancestry, and identifying SNPs with a chi squared $P<10^{-15}$. We imputed each phased segment against all-ethnicity 1000 Genomes haplotypes (excluding monomorphic and singleton sites) using Minimac2[5], using 5 rounds and 200 states for parameter estimation. We excluded SNPs from the reference panel if they failed to impute to a minimum quality threshold ($r^2<0.3$) in one batch of research participants data.

For the non-pseudoautosomal region of the X chromosome, males and females were phased together in segments, treating the males as already phased; the pseudoautosomal regions were phased separately. We then imputed males and females together using Minimac2, as with the autosomes, treating males as homozygous pseudo-diploids for the non-pseudoautosomal region.

Statistical Analysis

We computed association test results by logistic regression assuming additive allelic effects. For tests using imputed data, we use the imputed dosages rather than best-guess genotypes. We included covariates for age, gender, and the top five principal components to account for residual population structure. Results for the X chromosome are computed similarly, with male genotypes coded as if they were homozygous diploid for the observed allele.

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Australian Asthma Genetic Consortium (AAGC)

Recruitment and case/control definition

As part of the AAGC, we performed a GWAS of eczema in 7,197 unrelated individuals of European ancestry ascertained from the Australian population as described in detail elsewhere[6]. For this analysis, we selected 3,035 individuals (56% females, mean age 36 years, range 3 to 89), including 934 who reported having had atopic dermatitis at any point in their lifetime and 2,101 atopic dermatitis-free controls. These individuals participated in one of five studies: QIMR (N=1849), CAPS (N=53), LIWA (N=637), MESCA (N=127) or TAHS (N=369). Participants provided informed consent to participate in this study, which was approved by the respective ethics committees

Genotyping and imputation

Genotyping was performed with Illumina 610K and stringent quality control filters applied as described previously[6]. Imputation to 1000 Genomes Project (release v3.20101123) SNPs was performed with Impute2[7].

Statistical Analysis

Logistic regression was used to test the association between SNP allelic dosage and disease status with SNPTEST[8], with sex and age included as a covariate.

Acknowledgements and Funding

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ALSPAC

Recruitment

ALSPAC recruited 15,247 pregnant women resident in Avon, UK with expected dates of delivery 1st April 1991 to 31st December 1992, resulting in 14,775 live births and 14,701 children who were alive at 1 year of age. Enrolment is described in more detail in the cohort profile paper[9] and via the website http://www.bris.ac.uk/alspac/researchers/data-access/data-dictionary/. Biological samples including DNA have been collected for 10,121 of the children from this cohort. Ethical approval for the study was obtained from the ALSPAC Ethics and Law Committee and the Local Research Ethics Committees and written and informed consent was provided by the parents.

Case/Control definition

The children have been followed up with regular questionnaires and clinic visits. For the current study data collected from the questionnaires was used to classify children as eczema cases or controls. When the children were approximately 81, 91, 103 months, 10, 13 and 14 years, parents were asked the following questions [possible answers]:

1. Has your child in the past 12 months had eczema? [yes, saw a Dr; Yes, but did not see a Dr; No, did not have]
2. Has a doctor ever actually said that your child has eczema? (10 & 14 years only) [yes; no]

We defined cases as the children of parents who answered 'Yes, and saw a Dr' to Q1 or 'yes' to Q2. We defined controls as the children who were not cases and whose parent answered 'no' to Q2 at age 14 years.

Genotyping and imputation

GWAS data was generated by Sample Logistics and Genotyping Facilities at the Wellcome Trust Sanger Institute and LabCorp (Laboratory Corporation of America) using support from 23andMe. 975 individuals were genotyped at the WTSI and 9382 were genotyped at LabCorp, both on the Illumina 550K Custom chip. All individuals of non-European ancestry, ambiguous sex, extreme heterozygosity (<0.32 or >0.345 in the WTSI set and <0.31 or >0.33 in the LabCorp set), cryptic relatedness (>10% IBD) and high missingness (>3%) were removed. SNPs with low genotyping rate (<95%), with low minor allele frequency (<1%), out of Hardy Weinberg equilibrium ($p<5x10^{-7}$) or from the pseudo-autosomal region of the X chromosome were excluded. 8365 individuals typed on 464,311 probes remained. Phasing of the SNPs was carried out using MaCH 1.0 Markov Chain Haplotyping software[10] and imputation was carried out using Minimac[11] using phase 1 1000 Genomes reference panel (v3.20101123, ALL populations, no monomorphic/singletons). The final imputed dataset consisted of 8365 individuals and 31,337,615 variants.
Four filaggrin mutations (R501X, 2282del4, R2447X and S3247X) were genotyped to enable the association signal identified in this region to be tested for independence from the four most common atopic dermatitis-risk filaggrin mutations. Genotyping was undertaken by LGC Genomics using KASP™ genotyping technology.

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Statistical Analysis

Genome-wide association analysis was carried out using mach2dat.v1.0.23[12] for the 1712 cases and 3719 controls with genetic and phenotypic data. Summary statistics were available for 30,005,032 variants that were successfully analyzed.

Acknowledgements and Funding

We are extremely grateful to all the families who took part in this study, the midwives for their help in recruiting them, and the whole ALSPAC team, which includes interviewers, computer and laboratory technicians, clerical workers, research scientists, volunteers, managers, receptionists and nurses. The UK Medical Research Council and the Wellcome Trust (Grant ref: 102215/2/13/2) and the University of Bristol provide core support for ALSPAC. GWAS data was generated by Sample Logistics and Genotyping Facilities at the Wellcome Trust Sanger Institute and LabCorp (Laboratory Corporation of America) using support from 23andMe. FLG genotyping was funded by an MRC centenary award (awarded to L Paternoster).

1958 Birth Cohort (B58C)

Recruitment

The British 1958 birth cohort is an ongoing follow-up of all persons born in England, Scotland and Wales during one week in 1958. At ages 7, 11 and 16 years, a history of eczematous rashes was obtained by interview with a parent, and the presence of visible eczema on skin examination was recorded by a school medical officer[13]. At the age of 44-45 years, the cohort were followed up with a biomedical examination and blood sampling[14], from which a DNA collection was established as a nationally representative reference panel.

Case/Control definition

For the purpose of this meta-analysis, cases were defined by a positive parental or self-report of eczema up to age 16, or eczema recorded on skin examination at ages 7, 11 and/or 16. The cases included 305 ascertained by medical examination, of which 245 were also reported by parents; 467 additional cases reported by parents, but without eczema when examined at school; plus 146 cohort members who self-reported a history of eczema starting before age 17 years, when interviewed as adults. Controls (N=4560) were defined as cohort members with no parentally reported or self-reported history of eczema by age 16, and no record of eczema on skin examination at ages 7, 11 or 16 years.

Genotyping and imputation

Three non-overlapping subsets of the DNA collection from cohort members of white European ethnicity contributed to the genome-wide dataset:

(i) 3027 specimens selected as nationally representative controls for use by the Wellcome Trust Case-Control Consortium (WTCCC)[15] – 1430 from WTCCC1 and 1597 from WTCCC2;
(ii) 2592 specimens selected as nationally representative controls for the Type 1 Diabetes Genetics Consortium (T1DGC)[16]; and
(iii) 872 specimens selected by the GABRIEL consortium[17], including equal numbers of asthmatics and non-asthmatics.

Genotyping was performed using the Illumina 550K array (WTCCC1 and T1DGC), the Illumina 610K array (GABRIEL) or the Illumina 1M array (WTCCC2). A set of SNPs common to these arrays were used for imputation against the March 2012 (phase 1, version 3) release of the 1000-genomes reference haplotypes for all ancestries.

Pre-imputation phasing was performed using MACH v1.0.18[10] and imputation was performed using Minimac[11] (version dated 16 November 2012). SNPs were excluded from inputs to the imputation step if one or more of the following applied:

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- SNP-wise call-rate <95% (>=5% missing genotypes)
- Minor allele frequency <1%
- Inconsistency of allele frequencies across the deposits (p<0.0001 for any of the pairwise comparisons)
- Departure from Hardy-Weinberg equilibrium (p<0.0001). (HWE on chrX was tested in females only)
- Inconsistency of allele frequencies in males and females (p<0.0001) for chrX SNPs.
- Inconsistency of allele frequencies with 1000-genomes European ancestry haplotypes.

Additionally, for this eczema analysis, four filaggrin mutations (R501X, 2282del4, R2447X and S3247X) were genotyped directly by LGC Genomics using KASP™ genotyping technology, as described for the ALSPAC samples.

Statistical Analysis

Within-cohort logistic regression analyses for eczema were performed in ProbABEL v0.1-9e from the GenABEL suite of programs[18], using the imputed allele dosage for each SNP as the explanatory variable. Imputed allele dosages were not replaced with original genotypes for the directly genotyped SNPs. Thus, there were no missing data for any of the imputed variants. Analyses of the four filaggrin mutations were restricted to those with valid genotypes: 809 cases (155 of whom had one or more null mutations) and 3918 controls (383 of whom had a null mutation).

Acknowledgements and Funding

We acknowledge use of phenotype and genotype data from the British 1958 Birth Cohort DNA collection, funded by the Medical Research Council grant G0000934 and the Wellcome Trust grant 068545/Z/02. Genotyping for the B58C-WTCCC subset was funded by the Wellcome Trust grant 076113/B/04/Z. The B58C-T1DGC genotyping utilized resources provided by the Type 1 Diabetes Genetics Consortium, a collaborative clinical study sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Institute of Allergy and Infectious Diseases (NIAID), National Human Genome Research Institute (NHGRI), National Institute of Child Health and Human Development (NICHD), and Juvenile Diabetes Research Foundation International (JDRF) and supported by U01 DK062418. B58C-T1DGC GWAS data were deposited by the Diabetes and Inflammation Laboratory, Cambridge Institute for Medical Research (CIMR), University of Cambridge, which is funded by Juvenile Diabetes Research Foundation International, the Wellcome Trust and the National Institute for Health Research Cambridge Biomedical Research Centre; the CIMR is in receipt of a Wellcome Trust Strategic Award (079895). The B58C-GABRIEL genotyping was supported by a contract from the European Commission Framework Programme 6 (018996) and grants from the French Ministry of Research. FLG genotyping was funded by an MRC centenary award (awarded to L Paternoster).

BAMSE

Recruitment

BAMSE is a Swedish birth cohort study. A total number of 4,089 newborn infants were recruited between 1994 and 1996 in the Stockholm area[19]. The first questionnaire data, dealing with parental allergic diseases, socio-economic status and residential characteristics, was obtained when the children were about 2 months. Similar questionnaires, with a focus on the children's symptoms related to asthma and allergic diseases including eczema, were answered by the parents when the children were approximately 1, 2, 4, 8 and 12 years old. At 8 years of age, all children were invited to clinical testing, and blood samples were obtained from 2,480 children (~60%). DNA was extracted from 2,033 samples after exclusion of samples with too little blood, lack of questionnaire data, or if

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parental consent to genetic analysis of the sample was not obtained. From these samples, all children with a doctor's diagnosis of asthma (up to 8 years) and children with no history of eczema or other allergic diseases (controls) underwent GWAS genotyping[17] (n_total=505). After QC, a total of 469 subjects of European descent remained for analyses in this study (117 eczema cases and 352 non-eczema controls).

Case/Control definition

Case: Doctor's diagnosis of eczema (ever) up to 12 years of age (n=117). Controls: No diagnosis of eczema up to 12 years of age (n=352).

Genotyping and imputation

Genotyping in the BAMSE cohort was done on the Illumina Human610 Quad platform at the Centre National de Génotypage in Evry, France through the GABRIEL framework[17].
For imputation, the genotyped SNPs were filtered at - call rate >95%, Hardy Weinberg p-value > $1x10^{-6}$ and MAF > 0.01; and sample call rate > 95%. 515,445 SNPs remained after quality control. These were imputed using Minimac[11] RELEASE STAMP 2012-11-16 and the GIANT ALL reference panel, phase 1 v3.20101123 onto n=30,061,897 variants.

Statistical Analysis

Statistical analysis was done using mach2dat 1.0.23[12] software. For genome-wide analysis, logistic regression on the eczema phenotype adjusting for sex and principal components capturing inner European ancestry was performed.

Acknowledgements and Funding

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Children's Hospital of Philadelphia (CHOP)

Recruitment

The Center for Applied Genomics (CAG) has recruited ~80K pediatric patients from CHOP. Enrolment into the study is random and therefore encompasses all of the major common pediatric disorders including atopic dermatitis. Upon enrollment, CAG is authorized to extract the patients' medical history from their electronic medical record (EMR) and store the information in a de-identified database. Approximately 90% of enrollees consent to a yearly EMR update. Biological samples including DNA have been collected from all patients. The study was approved by the CHOP Institutional Review Board (IRB). Written informed consent for participation in the study was obtained from all participants and their parents or guardians.

Case/Control definition

Cases were defined from the electronic medical record according to one of the following two criteria. 1) Individuals 60 days old or older with relevant ICD9 code for Atopic Dermatitis (691.8) in two or more in person visits to the hospital, on separate calendar days. Plus, two or more prescriptions for Atopic Dermatitis-related medications; or 2) Individuals 60 days old or older with relevant ICD9 code for Atopic Dermatitis (691.8) in three or more in person visits, on separate calendar days. Individuals with ICD9 codes for Scabies, Wiskott-Aldrich Syndrome, Allergic Purpura or Ichtyosis congenita were excluded from the study.

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Controls were defined as individuals 60 days or older with two or more in person visits to the hospital over the preceding 5 years, no diagnosis codes for atopic dermatitis (691.8), no history of relevant medications and no exclusionary ICD 9 codes. Exclusionary codes included a comprehensive list of skin diseases and allergic conditions.

Genotyping and imputation

Samples were genotyped on either the Illumina HumanHap550 or the HH610 at CAG, following the manufacturers' instructions. Standard quality control parameters were applied to the dataset, samples with chip-wide genotyping failure rate < 5% were excluded; SNPs with minor allele frequencies of < 1%; genotyping failure rates of greater that 2% or Hardy-Weinberg P-Values less that $1x10^{-6}$ were excluded from further analysis.

Imputation of untyped markers (~39M) was carried out using IMPUTE2[7] after prephasing with SHAPEIT[20]. Each chromosome was prephased separately. Reference phased cosmopolitan haplotypes and recombination rates were obtained from the 1000 genomes project (1000 Genomes Phase I integrated release 3). Imputation was carried out in 5Mb intervals using an effective population size of 20,000 as recommended. As a measure of the overall imputation accuracy we compared the concordance between the imputed and known genotypes in the subset of SNPs for which genotyping data was available. At a call threshold of 0.9, over 99% of the imputed genotypes were called and over 96% of those were concordant with the known genotypes

Statistical Analysis

Statistical tests for association were carried out using the SNPTESTv2 package[8] for the 673 cases and 1839 controls.

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COPSAC2000

Recruitment

The COPSAC2000 birth cohort study is a prospective clinical study of a birth cohort of 411 infants born to mothers with a history of asthma. The newborns were enrolled at the age of 1 month, the recruitment of which was previously described in detail[21]. The study was approved by the Ethics Committee for Copenhagen (KF 01- 289/96) and The Danish Data Protection Agency (2008-41-1754) and informed consent was obtained from both parents

Case/Control definition

The families used doctors employed at the clinical research unit, and not the family practitioner, for diagnosis and treatment of atopic dermatitis and other skin-related symptoms. Skin lesions were described at both scheduled visits at 6-monthly intervals and acute visits with skin symptoms according to pre-defined morphology and localization; atopic dermatitis was defined based on the Hanifin-Rajka criteria.

Genotyping and imputation

High throughput genome-wide SNP genotyping were performed using the Illumina Infinium™ II HumanHap550 v1 and v3 platform (Illumina, San Diego), at the Children's Hospital of Philadelphia's Center for Applied Genomics. Phasing of the SNPs was carried out using MaCH 1.0 Markov Chain

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Haplotyping software[22] and imputation was carried out using Minimac[11] using phase 1 1000 Genomes admixed reference panel.
Genotyping of Filaggrin variants R501X, 2282del4, R2447X and S3247X was performed as previously described[23].

Statistical Analysis
Genome-wide analysis was carried out using mach2dat 1.0.21[12] and using sex as covariate.

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Danish National Birth Cohort (DNBC)

Recruitment
The Danish National Birth Cohort (DNBC) is a population-based cohort of more than 100,000 pregnancies, recruited in the years 1996-2002[24]. Extensive phenotype information was collected by computer-assisted telephone interviews twice during pregnancy as well as 6 and 18 months after delivery. Additional questionnaire-based follow-up surveys are conducted at regular intervals. The DNBC mothers provided written informed consent on behalf of themselves and their children. The study protocol was approved by the Danish Scientific Ethical Committee and the Danish Data Protection Agency.

Case/Control definition
Cases with early onset eczema were identified from the 18 months telephone interview data using an algorithm specifically developed for this purpose[25]. In addition, children with a positive response to both of the following two questions from the 7 year survey were included in the case group: 1) "Has a doctor ever said that your child had eczema, also known as allergic rash?" and 2) "Has your child ever had an itchy *rash which was coming and going for at least 6 months?*". Finally, children with ICD10 diagnosis code L20 in the Danish Hospital Discharge Register were also included in the case group. Controls were required not to have any eczema or eczema symptoms recorded in interview, questionnaire, or register data.

Genotyping and imputation
GWAS data were generated for 3,840 individuals from the DNBC (mothers and their children) in a study of prematurity and its complications within the Gene Environment Association Studies (GENEVA) consortium. Genotyping was performed using the Illumina Human660W-Quad BeadChip. Prior to imputation, we required participants to have a genotype call rate >97%, and we excluded SNPs based on a missing rate >2%, deviation from Hardy-Weinberg equilibrium in controls ($P<10^{-3}$), minor allele frequency <0.5%. We also converted the genotype data from NCBI build 36 to NCBI build 37 and aligned all genotypes to the forward strand. Finally, we excluded SNPs that did not match known variant positions in the 1000 Genomes project reference data. The remaining 529128 SNPs were used for imputation.
We used a two-step procedure to impute unobserved genotypes using phased haplotypes from the integrated Phase I release of the 1000 Genomes Project[3] (v3.20101123, ALL populations, no monomorphic/singletons). In a first prephasing step, we used SHAPEIT[20] to estimate the haplotypes for our study samples. In a second step, we imputed the missing alleles for additional SNPs directly

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onto these phased haplotypes using IMPUTE2[7]. Eczema information and genome-wide genotype and imputed data were available for 1,631 children.
Four filaggrin mutations (R501X, 2282del4, R2447X and S3247X) were genotyped by LGC Genomics using KASP™ genotyping technology, as described for ALSPAC.

Statistical Analysis
Genome-wide association analysis was carried out using SNPTEST[8] for the 224 cases and 1407 controls with genetic and phenotypic data. Summary statistics were available for 30,071,690 variants that were successfully analyzed.

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The Genes-environments & Admixture in Latino Americans (GALA II) study

Recruitment
The genes-environments & Admixture in Latino Americans (GALA II) study is an ongoing case-control study of asthma in Latinos involving five recruitment centers throughout the U.S. (Chicago, Illinois; Bronx, New York; Houston, Texas; San Francisco Bay Area, California; and San Juan, Puerto Rico) coordinated from the University of California, San Francisco[26]. Participants were eligible if they were aged between 8 to 21 years, had <10 pack-years of smoking history and self-identified all four grandparents as Latino. Subjects were excluded if they reported any of the following: (1) 10 or more pack-years of smoking; (2) any smoking within one year of recruitment date; (3) pregnancy in the third trimester; or (4) history of one of the following conditions: sickle cell disease, cystic fibrosis, sarcoidosis, cerebral palsy, or history of heart or chest surgery. Both children with physician-diagnosed asthma and non-allergic, non-asthmatic controls were recruited. For the purposes of this study only asthma cases were included as controls were ineligible for recruitment if they had history of eczema or atopic dermatitis. All local institutional review boards approved the study and all subjects/parents provided written assent/consent, respectively.

Case/Control definition
Among asthma cases, subjects were considered to have atopic dermatitis if they self-reported having a physician diagnosis of eczema or atopic dermatitis. A total of 300 asthma cases had atopic dermatitis and 1592 did not have atopic dermatitis.

Genotyping and imputation
GALA II subjects were genotyped with the Axiom LAT1 array (World Array 4, Affymetrix, Santa Clara, CA) [27-29], and quality control of the genotyping data was performed as described elsewhere. Briefly, SNPs that did not pass quality control procedures were removed from the analyses using the following criteria: failing Axiom quality controls, <95% call rate, or deviation from Hardy-Weinberg equilibrium ($p<10^{-6}$) within controls of each defined Latino group (Puerto Rican, Mexican, and other Latino). Subjects were filtered based on 97% call rates, discrepancy between genetic sex and

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reported gender, cryptic relatedness (identity by descent>0.3), and standard Affymetrix Axiom manufacturer's recommendations. SNPs passing quality control criteria were used for imputation of variants from the 1000 Genomes project. For that, genotyped SNPs were phased using SHAPEIT[20] and then imputation was performed using IMPUTE2[7] considering all populations from the 1000 Genomes Project Phase I v3 as a reference[3].

Statistical Analysis

Genome-wide association testing was carried using PLINK[30] using logistic regression models and adjusting by sex and also by ethnicity and genetic ancestry to avoid the confounding effect of population stratification in this admixed population.

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Generation R

Recruitment

The Generation R Study is a population-based prospective cohort study of pregnant women and their children from fetal life onwards in Rotterdam, The Netherlands[31,32]. All children were born between April 2002 and January 2006, and currently followed until young adulthood. Of all eligible children in the study area, 61% were participating in the study at birth. Cord blood samples including DNA have been collected at birth. The study protocol was approved by the Medical Ethical Committee of the Erasmus Medical Centre, Rotterdam (MEC 217.595/2002/20). Written informed consent was obtained from parents of all participants.

Case/Control definition

Information about ever physician diagnosed eczema (no; yes) and doctor-attendance for eczema in the past 12 months (no; yes) was collected by a questionnaire at age 6 years. Response rates for this questionnaire was 68%. Cases were defined as ever physician diagnosed eczema with doctor attendance in the last 12 months. We defined controls as the individuals who responded with "no" to either of these two questions.

Genotyping and imputation

Samples were genotyped using Illumina Infinium II HumanHap610 Quad Arrays following standard manufacturer's protocols. Intensity files were analyzed using the Beadstudio Genotyping Module software v.3.2.32 and genotype calling based on default cluster files. Any sample displaying call rates below 97.5%, excess of autosomal heterozygosity (F<mean-4SD), and mismatch between called and phenotypic gender were excluded. In addition, individuals identified as genetic outliers by the IBS

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clustering analysis (>3 standard deviations away from the HapMap CEU population mean) were excluded from the analysis. Genotypes were imputed for all polymorphic SNPs from phased haplotypes in autosomal chromosomes using the 1000 Genomes GIANTv3 panel in minimac[11]. Twins were excluded from the analyses. Ethnicity was grouped into Caucasians and non-Caucasians, based on genetic ancestry. Ancestry determination analysis included the genomic data of all Generation R individuals merged with the three reference panels of the HapMap Project Phase II (YRI, CEU and CHB/JPT).
FLG null mutations (R501X, 2282del4, R2447X and S3247X) were genotyped by modified Taqman allelic discrimination assays[23,33], using previously described primers[34].

Statistical Analysis
The sample of 3,282 individuals from the Generation R study used for the analysis included a majority of individuals with Caucasian ancestry (63.4%). Caucasians and non-Caucasians were subsequently analyzed seperately. Numbers with genetic and phenotypic data were, Caucasians: 332 cases and 1749 controls, non-Caucasians: 305 cases and 896 controls.
Association between atopic dermatitis phenotype and GWAS SNPs was performed using a regression framework adjusting for population stratification in the Generation R cohort using mach2dat[12] as implemented in GRIMP[35]. Since Generation R is a population-based study of unrelated individuals of different ethnic background, 4 principal components were used for the Caucasian subpopulation and 4 were used for the non-Caucasian subpopulation, both analyses had a Genomic Inflation Factor of 1.

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GENEVA/KORAF4/PopGen

Recruitment
Atopic dermatitis patients were recruited from tertiary dermatology clinics based at three centers (Technische Universität Munich, as part of the GENEVA study, University of Kiel, University of Bonn). German controls were obtained from the population-representative PopGen biorepository[36] and the population-based KORA study[37]

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Case/Control definition

Atopic dermatitis was diagnosed on the basis of a skin examination by experienced dermatologists according to standard criteria, which included the presence of chronic or chronically relapsing pruritic dermatitis with the typical morphology and distribution.[38]

Genotyping and imputation

Prior imputation we excluded samples with extensive missing data rate (>5%), excess of heterozygosity or homozygosity and ambiguous sex. We examined IBS and excluded close related samples with PI_HAT>0.1875 (halfway between expected IBD for third- and second degree relatives) as well as outliers of unusual ancestry by MDS analysis. SNPs with low genotyping rate (<95%), low minor allele frequency (<1%), strong deviation from Hardy-Weinberg equilibrium ($p<10^{-8}$) and differential call rate between cases and controls were excluded.
Cases and controls with high quality SNPs were matched and imputed by array type. Pre-phasing was carried out with SHAPEIT[20] and imputation with IMPUTE2[7] using phase I 1000 Genomes reference panel (integrated variant set of all populations, release March 2012). Post imputation SNPs with low imputation quality (info score<0.4), call rate<95%, deviation from Hardy-Weinberg equilibrium ($p<10^{-8}$) or minor allele frequency<5% were excluded. 1046 cases and 2551 controls with 4,169,995 overlapping SNPs were carried forward to analysis.

Filaggrin variants (R501X, 2282del4, R2447X and S3247X) were obtained from data generated for previous studies[39,40].

Statistical Analysis

Genome-wide association analysis was carried out using SNPTEST[8] using a frequentist approach with allele dosages (option –method expected) to account for imputation uncertainty.

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GENUFAD – SHIP-2

Recruitment

All atopic dermatitis patients were recruited at Charité Universitätsmedizin Berlin for the GENUFAD study (GEnetic analysis of NUclear Families with Atopic Dermatitis) and have been previously described in a previous GWAS[41] (Set 2 in original study). 270 German families were recruited through two affected siblings with an age of onset below two years of age and moderate to severe disease expression. One affected child was selected from each family and 262 atopic dermatitis patients were included in the present study.
All controls originated from the population-based Study of Health in Pomerania (SHIP)[42], which recruited individuals in the North-Eastern part of Germany. The SHIP set was split for two case-control studies by a random function. 1792 unrelated individuals were included in SHIP-2

Case/Control definition

All cases had an early onset (< 2years) physician’s diagnosis of atopic dermatitis made according to standard criteria[43]. Controls were unrelated individuals from the population-based SHIP cohort.

Genotyping and imputation

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All cases were genotyped with Affymetrix 500K arrays and only samples with high call rate (> 0.95) were used for the analysis. Controls were genotyped with Affymetrix Genome-Wide Human SNP Array 6.0 and were excluded when call rate < 0.96. For both case and control groups, samples were excluded when the gender estimated from X-chromosome heterozygosity did not match the clinical records. SNPs from the 500K array were filtered as previously described[41] according to the following criteria: i) low call rate (< 0.95), ii) low allele frequency (MAF < 0.01), iii) Mendelian errors in 5 or more families, iv) unlikely genotypes in more than 5 families (double recombinants as detected by Merlin[44]), v) founder genotypes out of Hardy-Weinberg equilibrium ($p < 0.00001$). Additionally, SNPs with a call rate < 0.99 were excluded if having MAF < 0.05 or if they were out of Hardy-Weinberg equilibrium ($p < 0.001$). SNPs on the Human SNP Array 6.0 were excluded if having: i) low call rate (< 0.97), ii) low allele frequency (MAF < 0.01), iii) founder genotypes out of Hardy-Weinberg equilibrium ($p < 0.0005$). Additionally SNPs with a call rate < 0.99 were excluded if having MAF < 0.05 or if they were out of Hardy-Weinberg equilibrium ($p < 0.001$). Only SNPs fulfilling the above mentioned QC on both arrays were used in subsequent steps, and the rest of non-overlapping SNPs were excluded. Genotypes of cases and controls were recoded to the "+" using the –flip command from PLINK[30] and merged. Additionally, markers were excluded if: i) 3 alleles were detected, ii) the allele frequencies in the SHIP control population differed by more than 0.1 compared to the 379 Europeans available from the 1000 Genomes project. After filtering, 345407 SNPs remained in the analysis. All samples were imputed together with Mach1[10] using the 1000Genome/GIANT reference panel. Principal component (PC) analysis was performed with EIGENSTRAT (SMARTPCA)[45]. 1 Case and 6 Controls were identified as outliers.

Statistical Analysis

Association between SNP dosage and disease status was calculated with mach2dat v1.0.23[12] using gender and the first 2 PCs as co-variables.

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GENUFAD extended – SHIP-1 (GENUFADex-SHIP1)

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Recruitment

Atopic dermatitis patients were recruited at Charité Universitätsmedizin Berlin, Germany for the extended GENUFAD study (GEnetic analysis of NUclear Families with Atopic Dermatitis) and have been described previously[41,46] (Berlin cases of set 1). Children of the extended GENUFAD study were unrelated individuals recruited based on moderate to severe atopic dermatitis and an age of onset below two years. A total of 417 unrelated atopic dermatitis patients were included in the present study. All controls originated from the population-based Study of Health in Pomerania (SHIP)[42], which included individuals in the North-Eastern part of Germany. The SHIP set was split for two case-control studies by a random function. 1667 unrelated individuals were included in SHIP-1

Case/Control definition

All cases had early onset eczema (< 2years) diagnosed by a physician according to standard criteria[43]. Controls were unrelated individuals from the population-based SHIP cohort.

Genotyping and imputation

All cases and controls were genotyped with Affymetrix Genome-Wide Human SNP Array 6.0. Individuals with a call rate < 0.95 were excluded from the study. In addition, samples were excluded when the gender estimated from X-chromosome heterozygosity did not match the clinical records. SNPs were filtered according to the following criteria: i) low call rate (< 0.95 in cases or controls), ii) low allele frequency (MAF < 0.01 in cases or controls), iii) genotypes out of Hardy-Weinberg equilibrium ($p < 0.00001$ in cases or $p < 0.0005$ in controls). Additionally, SNPs with a call rate < 0.99 were excluded if having MAF < 0.05 or if they were out of Hardy-Weinberg equilibrium ($p < 0.001$). Only SNPs fulfilling the above mentioned QC were used in subsequent steps. Genotypes of cases and controls were recoded to the "+" using the –flip command from PLINK[30]. In addition, markers were excluded if: i) 3 alleles were detected, ii) the allele frequency in the SHIP control population differed by more than 0.1 compared with the frequency in 379 Europeans available from the 1000 Genomes project. After filtering, 643539 SNPs remained in the analysis. All samples were imputed together with Mach1[10] using the 1000Genome/GIANT reference panel. Principal component (PC) analysis was performed with EIGENSTRAT (SMARTPCA)[45]. 3 Case and 9 Controls were removed as outliers.

Statistical Analysis

Association between SNP dosage and disease status was calculated with mach2dat v1.0.23[10] using gender and the first 2 PCs as co-variables. For the X-chromosome, above analysis was performed for males and females separately, including PC1 and PC2 as co-variables. The study on females included 164 cases and 833 controls, the study on males 253 cases and 834 controls.

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GINI/LISA

Recruitment

The influence of Life-style factors on the development of the Immune System and Allergies in East and West Germany PLUS the influence of traffic emissions and genetics (LISAplus) Study is a population based birth cohort study. A total of 3094 healthy, full-term neonates were recruited between 1997 and 1999 in Munich, Leipzig, Wesel and Bad Honnef. The participants were not pre-selected based on family history of allergic diseases[47].

A total of 5991 mothers and their newborns were recruited into the German Infant study on the influence of Nutrition Intervention PLUS environmental and genetic influences on allergy development (GINIplus) between September 1995 and June 1998 in Munich and Wesel. Infants with at least one allergic parent and/or sibling were allocated to the interventional study arm investigating the effect of different hydrolysed formulas for allergy prevention in the first year of life[48]. All children without a family history of allergic diseases and children whose parents did not give consent for the intervention were allocated to the non-interventional arm. Detailed descriptions of the LISAplus and GINIplus studies have been published elsewhere[47,48]. DNA was collected at the age 6 and 10 years. For both studies, approval by the local Ethics Committees and written consent from participant's families were obtained.

Case/Control definition

Information on ever having physician-diagnosed atopic dermatitis was collected using self-administered questionnaires completed by the parents. The questionnaires were completed at 6, 12, 18 and 24 months and 4, 5, 6, 10 years of age in the LISAplus study and 1, 2, 3, 4, 6 and 10 years in the GINIplus study asking for each year of age since the previous follow-up. Cases were defined as subjects who reported having a diagnosis at any time point, and controls were defined as those reporting no diagnosis at every time point.

Genotyping and imputation

1511 children from Munich from both studies were included (835 (55%) children from the GINIplus study and 676 (45%) children from the LISAplus study). 1423 individuals (835 from the GINIplus study and 588 from the LISA study) were analyzed using the Affymetrix Human SNP Array 5.0 and 88 individuals from the LISAplus study were analyzed using Affymetrix Human SNP Array 6.0. Genotypes were called using BRLMM-P algorithm (5.0), respectively BIRDSEED V2 algorithm (6.0). In each of the two data sets, criteria for exclusion of individuals were: a call rate below 95%, a heterozygosity outside mean +/- 4sd, a failure of the sex check or a failure of the similarity quality control using MDS analysis based on IBS. Criteria for exclusion of variants were: a call rate below 95%, a MAF < 0.01 and a HWE p-value < 0.00001. The filtered data sets were prephased using SHAPEIT V2[20] and imputation was done using IMPUTE2.3[7] considering the haplotypes from the 1000 Genomes Project Phase I v3 as a reference (March 2012 release, updated version from 26 Aug 2012, all ancestries, limited to variants with more than one minor allele copy).

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Genotyping for the two most common variants of the filaggrin gene (FLG), R501X and 2282del4, was performed as described previously[49,50]. Participants with at least one FLG mutation were classified as having the FLG loss-of-function mutation. Participants with missing data for a particular variant were excluded if the remaining variant was wild-type.

Statistical Analysis

Genome-wide association analysis of atopic dermatitis was carried out in SNPTEST V2.4[8] (https://mathgen.stats.ox.ac.uk/genetics_software/snptest/snptest.html) regressing expected allelic dosage on case-control status, including sex as a covariate. SNPTEST allows for a combination of the results from the two genotyping chips.

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INMA

Recruitment

Population-based birth cohorts were established as part of the INMA – INfancia y Medio Ambiente [Environment and Childhood] Project in several regions of Spain following a common protocol. This analysis uses the INMA cohorts of Menorca, Valencia, Sabadell established between 1997 and 2006. This project aims to study the associations between pre- and postnatal environmental exposures and growth, health, and development from early fetal life until adolescence and has been described previously in detail[51]. Pregnant women were enrolled during the 1st trimester of pregnancy at public primary health care centers or public hospitals. Detailed measurements were performed using ultrasound and physical examinations and biological samples were collected. Informed consent was obtained from all participants and the study was approved by the Hospital Ethics Committees in each participating region.

Case/Control definition

Children from the subcohorts of INMA Sabadell, Valencia and Menorca were included in the present study. Atopic eczema (Sabadell and Valencia) and doctor atopic eczema (Menorca) was assessed by questionnaire at the ages of 1, 2 and 4y. Atopic eczema cases were those children that had had eczema at least in one of the three visits. Control children were those that had never had eczema.

Genotyping and imputation

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DNA was obtained from cord blood, whole blood collected at 4y or saliva using the Chemagen protocol at the Spanish National Genotyping Centre (CEGEN). Children whose parents reported to be white and to be born in Spain or in European countries and that were not lost during the follow-up were selected for genotyping. Genome-wide genotyping was performed using the HumanOmni1-Quad Beadchip (Illumina) at CEGEN. Genotype calling was done using the GeneTrain2.0 algorithm based on HapMap clusters implemented in the GenomeStudio software. Quality control was done using PLINK[30] and following standard criteria. First of all, SNPs were flipped to the human genome + strand. We applied the following initial quality control thresholds: sample call rate>98% and/or LRR SD<0.3. Then, we checked sex, relatedness, heterozygosity and population stratification. Genetic variants were filtered for SNP call rate>95%, MAF>1% and HWE p value>1.10E-6. Imputation was done using IMPUTE2[7] and a cosmopolitan panel from the 1000 GENOME project (release March 2012, downloaded from http://mathgen.stats.ox.ac.uk/impute/ALL_1000G_phase1integrated_v3_impute.tgz) as a reference. Additionally, four filaggrin mutations (R501X, 2282del4, R2447X and S3247X) were genotyped directly by LGC Genomics using KASP™ genotyping technology, as described for the ALSPAC samples.

Statistical Analysis

Genome-wide association analysis was carried out using SNPTEST[8] program for the 414 cases and 443 controls with genetic and phenotypic data. Summary statistics were available for approximately 30M variants that were successfully analyzed.

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MAAS

Recruitment

The Manchester Asthma and Allergy Study is an unselected (i.e. population-based), birth cohort study[52-56]. The setting is the maternity catchment area of Wythenshawe and Stepping Hill Hospitals, comprising of 50 square miles of South Manchester and Cheshire, UK, a stable mixed urban-rural population. Study was approved by the Local Research Ethics Committee. Informed consent was obtained from all parents.

Screening & Recruitment

All pregnant women were screened for eligibility at antenatal visits (8th-10th week of pregnancy). The study was explained to the parents, and informed consent for initial questionnaires and skin prick testing was obtained. Both parents completed a questionnaire about their and their partner's history of asthma and allergic diseases and smoking habits. If the pregnant woman's partner was not

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present at the antenatal clinic visit, an invitation was sent for him to attend an open-access evening clinic for skin prick testing and questionnaire. Once both parents had completed questionnaires and skin prick testing, a full explanation of the proposed future follow-up for the child was given. Of the 1499 couples who met the inclusion criteria (<10 weeks of pregnancy, maternal age >18 years, questionnaire and skin test data available for both parents), 288 declined to take part in the study. A total of 1185 participants had at least some evaluable data.

Follow-up

The children have been followed prospectively, and attended review clinics at ages 1, 3, 5, 8 and 11 years.

Case/Control definition

Cases were defined as a doctor diagnosis of atopic dermatitis on the day that the child came to the follow-up clinic, at any timepoint (1y, 3y, 5y, 8y)

Controls were a Parental report of “no” at all timepoints (1y, 3y, 5y, 8y) to the question "Has your child ever suffered from atopic dermatitis", ‘No’

Genotyping and imputation

DNA samples were genotyping on an Illumina 610 quad chip. The Illumina genotypes were called using the Illumina GenCall application following the manufacturer’s instructions. Quality control criteria for samples included: 97% call rate, exclusion of samples with an outlier autosomal heterozygosity (scree-plot visualization) gender validation and sequenome genotype concordance. Quality control criteria for SNPs included a 95% call rate, HWE > 5.9×10^{-7}, minor allele frequency > 0.005. Genotypes were prephased with SHAPEIT[20] shapeit.v2.644 and imputed with IMPUTE2[7] version 2.2.2 using the March2012 release of the 1000 genomes Phase I integrated variant set release (v3; updated 26 Aug 2012) reference genotypes.

FLG genotyping was carried out as previously described in Bisgaard et al.[57] and Sandilands et al.[23]. Briefly genotyping The R501X[57], R2447X and S3247X[23] mutations was performed using a TAQMAN-based allelic discrimination assay (Applied Biosystems). The 2282del4 Mutation was genotyped on an Applied Biosystems 3100 or 3730 DNA sequencer[57].

Statistical Analysis

Association analysis was carried out using SNPTEST[8] version 2.4.1 using frequentist with the score method.

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MAS-HNR

Recruitment

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The Multicentre Allergy Study (MAS) is a German birth cohort which has been described in detail previously[58,59]. Briefly, in 1990, the MAS cohort recruited 1314 newborns, who were regularly followed-up. Data were collected from examinations and questionnaires at birth, at 1, 3, 6, 12, and 18 months, and yearly from age 2 to age 13. All MAS samples included in this study participated in the GWAS on asthma of the GABRIEL consortium[17]. German controls are from the population-based Heinz Nixdorf RECALL (HNR) study which randomly selected 4200 individuals in the Western part of Germany in order to study atherosclerotic disease[60].

Case/Control definition

Eczema was defined based on a parental report of a doctor's diagnosis of eczema up to the age of 13 years. Controls were unrelated individuals from the population-based HNR study.

Genotyping and imputation

MAS samples were genotyped with the Illumina Human610 array, HNR samples with the Illumina Human550v3 array. Individuals with a call rate < 0.95 or with high heterozygosity (> 0.35) were excluded. SNPs were filtered according to the following criteria: i) low call rate (< 0.95 in cases or controls), ii) low allele frequency (MAF < 0.01 in cases or controls), iii) genotypes out of Hardy-Weinberg equilibrium ($p < 0.00001$ in cases or $p < 0.0005$ in controls). Additionally, SNPs with a call rate < 0.99 were excluded if having a MAF < 0.05 or if they were out of Hardy-Weinberg equilibrium ($p < 0.001$). Only SNPs fulfilling the above mentioned QC were used in subsequent steps. Genotypes of cases and controls were recoded to the "+" using the –flip command from PLINK[30]. Additionally, markers were deleted if: i) 3 alleles were detected, ii) the allele frequencies in the HNR control population differed by more than 0.15 compared with the frequency in 379 Europeans available from the 1000 Genomes project. After filtering, 514680 SNPs remained in the analysis. All samples were imputed together with Mach1[10] using the 1000Genome/GIANT reference panel. Principal component (PC) analysis was performed with EIGENSTRAT (SMARTPCA[45]).

Statistical Analysis

Association between SNP dosage and disease status was calculated with mach2dat v1.0.23[12] using gender and the first two PC's as co-variable. For the autosomes 104 cases and 379 controls were analyzed. For the X-chromosome, above analysis was performed for males and females separately. The study on females included 39 cases and 198 controls, the study on males 65 cases and 181 controls.

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MoBa (The Norwegian Mother and Child Cohort Study)

Recruitment

This study includes data from the Norwegian Mother and Child Cohort Study (MoBa) conducted by the Norwegian Institute of Public Health[61]. MoBa is a prospective population-based pregnancy cohort. Participants were recruited from all over Norway from 1999-2008, and 38.7% of invited women consented to participate. The cohort includes 109000 children, 91000 mothers and 71700 fathers. Blood samples were obtained from both parents during pregnancy and from mothers and children (umbilical cord) at birth. Follow-up is conducted by questionnaires at regular intervals and by linkage to national health registries. The current study is based on version 6 of the quality-assured data files released for research on May 11, 2011. MoBa has obtained a license from the Norwegian Data Inspectorate. Researchers are required to follow the terms of an Assistance Agreement containing a number of clauses designed to ensure protection of privacy and compliance with relevant laws.

The genotyped samples used are from the sub-study on preterm delivery in which singleton live-born spontaneous pregnancies with mothers in the age group of 20-34 years were selected. Pregnancies involving pre-existing medical conditions, pregnancies with complications as well as pregnancies conceived by in vitro fertilization, were excluded. Random sampling was done from two gestational age ranges 154-258 days (preterm births) and 273-286 days (term births). In total 3120 mothers and children were genotyped. Only the children whose mothers answered questionnaire Q5 and/or Q6 were selected for the current eczema GWAS meta-analysis.

Case/Control definition

Eczema cases were defined as children whose mothers reported atopic eczema in any of the two relevant questionnaires – one filled when a child was approximately 18 months old (questionnaire Q5), another when a child was approximately 36 months old (questionnaire Q6). Controls were the children whose mothers reported no atopic eczema in both of these two questionnaires. The total number of cases was 206, the number of controls was 413 individuals.

Questionnaire Q5 had a question “Does your child have or has she/he had any of the following health problems?” with one of the health problems described as “Atopic eczema (childhood eczema)" and multiple tick boxes as answer choices (“No”, "Yes, has now", "Yes, had previously"). Any of the positive answers (2 and/or 3) was considered as an indication of eczema phenotype, and a negative answer (1) was a candidate for eczema control group. Questionnaire Q6 had a question “Has your child suffered any long-term illness or health problems since the age of 18 months?” with the similar answer options as in Q5.

Genotyping and imputation

Genotyping was carried out using Illumina Human660W-Quad genotyping BeadChip. Genotyping quality control excluded SNPs with the call rate lower than 98%, SNPs with HWE p-value <10E-5, ambiguous SNPs (A/T, C/G), monomorphic SNPs, SNPs that “changed chromosome” (when comparing genotyping manifest file and 1000G reference), X chromosome SNPs located in pseudo-autosomal regions, SNPs with 1000G-incompatable alleles (e.g., genotyped A/C vs 1000G A/G). Genotyping quality control excluded samples with more than 3% missing genotypes, samples with X chromosome heterozygosity problems (male F<0.8, female F>0.2), individuals with the fraction of heterozygous genotypes being 2SD from the group’s mean, sample duplicates, one sample (with a higher missingness rate) from each of related sample-pairs (PI_HAT>0.1875), non-Europeans (PCA, visual exclusion). Haplotypes from 1000 Genomes Project (phase1, version3, release date March 2012) were used as a reference panel. Software SHAPEIT2[20] (v2.644) was used to phase the genotypes, software IMPUTE2[7] (v2.3.0) was use to impute genotypes.

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Statistical Analysis

For statistical analyses software SNPTEST2[8] (v2.4.1) was used. Additive genetic model with a risk allele dosage was used (option "-frequentist 1"). Inbuilt option "expected" was used as the parameter for the statistical method (option "-method expected"). Reference panel SNPs that were located in larger than 10MB ungenotyped chromosome regions were not used. SNPTEST2 by default skipped SNPs with low genotyping probabilities.

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National Children's Research Centre – Atopic Dermatitis Collection (NCRC – ADC)

Recruitment

631 atopic dermatitis cases were recruited from secondary/tertiary clinics in Our Lady's Children's Hospital Crumlin, Dublin and clinics in Glasgow, Dundee and Edinburgh.

Case/Control definition

All patients all had early onset disease (<2 years; mean age at recruitment 2.8 years) with a mean atopic dermatitis severity score (Nottingham Eczema Severity Score; NESS) of 10.23 (SD 3.11). The Irish controls comprised 996 subjects with no history of atopic dermatitis from a collection of 1237 blood donor volunteers of the Trinity Biobank.

Genotyping and imputation

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Genome-wide genotyping was performed on bar-coded LIMS (Laboratory Information Management System) tracked samples using the Illumina Human 610-Quad BeadChip (Illumina, San Diego) for AD cases and Affymetrix genome-wide SNP array 6.0 (Affymetrix, Santa Clara) for Trinity controls. BeadChips were processed within an automated BeadLab as per the respective manufacturer's instructions. Samples were subject to strict quality control criteria including assessment of concentration, fragmentation and response to PCR. A total of 20 µl of DNA aliquoted to a concentration of 50 ng/µl was used for each array. Replication phase genotyping was performed using matrix-assisted laser desorption/ionization time-of flight (MALDI-TOF) mass spectrometry (http://www.sequenom.com), or Applied Biosystems TaqMan probes (http://www.appliedbiosystems.com/).
Prior to imputation we excluded samples with extensive missing data rate (>5%), excess of heterozygosity or homozygosity and ambiguous sex. We examined IBS and excluded close related samples with PI_HAT>0.1875 (halfway between expected IBD for third- and second degree relatives) as well as outliers of unusual ancestry by MDS analysis. SNPs with low genotyping rate (<95%), low minor allele frequency (<1%), strong deviation from Hardy-Weinberg equilibrium (p<10-8) and differential call rate between cases and controls were excluded. Cases and controls with high quality SNPs of the overlapping SNP-set were matched and carried forward to imputation. Pre-phasing was carried out with SHAPEIT[20] and imputation with IMPUTE2[7] using phase I 1000 Genomes reference panel (integrated variant set of all populations, release March 2012). Post imputation SNPs with low imputation quality (info score<0.4), call rate<95%, deviation from Hardy-Weinberg equilibrium (p<10-8) or minor allele frequency<5% were excluded. 572 cases and 1797 controls with 5,262,635 overlapping SNPs were carried forward to analysis.
Genotyping of Filaggrin variants R501X, 2282del4, R2447X and S3247X was performed as previously described[23].

Statistical Analysis
Genome-wide association analysis was carried out using SNPTEST[8] using a frequentist approach with allele dosages (option –method expected) to account for imputation uncertainty.

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NFBC66

Recruitment
The Northern Finland Birth Cohort 1966 is a prospective follow-up study of children from the two northernmost provinces of Finland[62]. Women with expected delivery dates in 1966 were recruited through maternity health centers[63]. Cohort members living in northern Finland or in the capital area were invited to a clinical examination as well as questionnaire at age 31 years. DNA was extracted from blood samples given at the clinical examination[64]. Informed consent for the use of the data including DNA was obtained from all subjects. The study was approved by the ethics committees in Oulu (Finland) and Oxford (UK) universities in accordance with the Declaration of Helsinki.

Case/Control definition
For the purpose of this meta-analysis, we included data from the following questions:

1. Have you had eczema (infantile, atopic or allergic)?
2. If yes, have you ever been treated by a doctor

Individuals who answered yes to both questions were defined as cases (1200). Individuals that answered no to the first question were defined as controls (2270).

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Genotyping and imputation

Genotyping was completed at the Broad Institute Biological Sample Repository in participants with available DNA using Illumina HumanCNV370DUO Analysis BeadChip array for 339,629 SNPs. We excluded 3,345 SNPs from analysis because HWE was not met at a level p <0.0001, 55 because of low call rate (<95%) and 7,681 because the MAF was <1% as well as SNPs with duplicates concordance < 99% leaving 309, 948 SNPs for the association analysis. Individuals with IBS pairwise sharing>0.20, that withdrew consent, with gender mismatch, that are heterozygosity outliers 0.29<F<0.35, and MDS outliers were also removed. Imputation was conducted using the algorithm implemented in IMPUTE v2.3.0[7] using 1000G panel of March 2012 phase1 integrated v3.

Statistical Analysis

Genome-wide association analysis was conducted using SNPTEST[8] and complemented with R.

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Netherlands Twin Registry (NTR)

Recruitment

In the Young Netherlands Twin Register (YNTR), twins are followed from birth onwards. Around every two to three years, a survey is sent out inquiring about physical and mental health. At ages 1, 2, 3, 5, 7, 10 and 12 years, the surveys are completed by the parents and/or teachers, from age 14 onward, twins and their non-twin siblings are asked to complete the surveys by themselves.

Case/Control definition

Data on eczema were available from an YNTR survey that is sent out to the parents of twins at age 5 years[65]. Parents were asked to indicate for each child separately whether a doctor had ever diagnosed the child with eczema. A similar question concerned doctor diagnosed baby eczema. Children were considered cases if their parents answered yes to any of the two questions and controls if they answered no to both questions. For MZ pairs, if both twins were cases or controls, this defined the phenotype. Discordant pairs received a case phenotype. MZ pairs were included as one case or control. For dizygotic twin pairs, both twins were included in the analysis (taking their relatedness into account in the analyses). After exclusion of subjects from non-Western European ancestry, data from 1,466 individuals were available for analysis.

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Genotyping and imputation

In recent years, blood and buccal DNA samples were collected for various projects within the NTR [66,67]. From these samples, high molecular weight genomic DNA was extracted using the QIAamp DNA Blood Maxi kit (QIAGEN; Dusseldorf, Germany) following the manufacturers' protocol; DNA from buccal epithelial cells was extracted following a previous protocol[68]. Genotyping for the 1466 subjects was done on the Affymetrix 6.0 array and genotype calls were made with the Affymetrix GCT 4.0 software[69].

Genotypes were aligned to the GIANT 1000 Phase I Integrated release version 3 All panel. SNPs that were not mapped at all, SNPs that had ambiguous locations, and SNPs that did not have matching - or strand opposite alleles were removed. SNPs were also removed if they still had mismatching alleles with this imputation reference set, if the allele frequencies differed more than 0.20 with the reference set, if the MAF was < 1%, if the HWE p-value was < 0.00001 or if the call rate was <95%. Lastly, SNPs with C/G and A/T allele combinations were removed if the MAF was between 0.35 and 0.50 to avoid wrong strand alignment for these SNPs. Samples were excluded from the data if their expected sex did not match their genotyped sex, if the genotype missing rate was above 10%, if the sample did not match the expected IBD sharing between relatives, or if the Plink F inbreeding value was either > 0.10 or < -0.10 (heterozygosity). Phasing was done in chromosomal chunks with the Mach program[10]. Then imputation of the reference panel haplotypes was performed with the minimac program[7] following the GIANT imputation protocols (http://genome.sph.umich.edu/wiki/Minimac:_1000_Genomes_Imputation_Cookbook).

Statistical Analysis

A logistic regression was performed in Plink[30] in which eczema status was regressed on genome-wide SNP data, sex of the child and 5 additional covariates (3 Dutch PCs, one covariate for array effects and one for blood/ buccal) The analysis was corrected for familial clustering with the --family option in Plink.

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RIKEN

Recruitment

We recruited a total of 9,438 subjects. This research project was approved by the ethical committees at the Institute of Medical Science, the University of Tokyo and RIKEN Yokohama Institute.

Case/Control definition

A total of 1,472 cases were recruited from several medical institutes through the BioBank Japan project[70]. All subjects with atopic dermatitis were diagnosed by physicians according to the criteria of Hanifin and Rajka. Controls consisted of 6,042 cases who did not have atopic dermatitis and bronchial asthma in BioBank Japan, 1,018 healthy volunteers from members of the Rotary Club of Osaka-Midosuji District 2660 Rotary International in Japan, and 906 healthy subjects from the PharmaSNP Consortium[70]. All individuals were Japanese and gave written informed consent to participate in the study.

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Genotyping and imputation

We genotyped all subjects using the Illumina HumanOmniExpress BeadChip. We performed principal component analysis (PCA) and QC control as described[70]. Genotype imputation within the GWAS was performed using minimac[11]. We used data from the 1000 Genomes Project (phased JPN, CHB and Han Chinese South (CHS) data, phase1 v3 release). We included SNPs with $P \geq 1 \times 10^{-6}$ for the Hardy-Weinberg equilibrium test and with MAF ≥ 0.01 in the reference panel. We excluded SNPs whose MAF were large difference between GWAS and the reference panel.

Statistical Analysis

The association test was performed with mach2dat[12] using the fractional dosages output of minimac. We used the *P* value of likelihood ratio test.

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SAPALDIA

Recruitment

SAPALDIA is a population-based cohort from Switzerland that recruited subjects aged 18 to 60 from population registries in eight communities, representing the three largest language groups (German, French, Italian) as well as different levels of air pollution and degrees of urbanization[71,72]**.** Subjects underwent spirometry as well as a detailed interview on respiratory health and allergies, smoking history, lifestyle factors and anthropometry in the baseline (year 1991) and follow-up (year 2002) examination. 6,055 subjects participated in both examinations and agreed to provide blood for genetic analysis. From all subjects that were part of a nested asthma case-control sample subjected for genomewide genotyping in the context of the GABRIEL genome-wide association study on asthma[17], all non-asthmatic participants and a random-sample of the asthma cases formed the basis of the current study (n=976 in total). The asthmatic participants were thereby sampled randomly to have the same proportion in the analysis sample as in the whole study population.

Case/Control definition

Subjects were considered to have atopic dermatitis if they self-reported to ever have had skin eczema. There were 533 cases of atopic dermatitis and 443 controls.

Genotyping and imputation

Genotyping in the SAPALDIA cohort was done on the Illumina Human610 Quad platform at the Centre National de Génotypage in Evry, France on 663 asthmatic and a random sample of 997 non-asthmatic participants in the framework of the GABRIEL study. The genotyped SNPs were subjected to the following quality control criteria: subject call rate >95%, SNP call rate >95%, Hardy Weinberg p-value > $1x10^{-6}$ and minor allele frequency > 0.01. 545'131 SNPs remained after quality control. These were imputed using minimac[11] release 2012-05-29 and the GIANT ALL reference panel, phase 1 v3.20101123 onto n=30'061'897 variants

Statistical Analysis

Statistical analysis was done using routine 'palogist' in ProbABEL v. 0.3.0.from the GenABEL suite of programs[18]. For genome-wide analysis, logistic regression of atopic dermatitis on sex and principal components capturing inner European ancestry was performed.

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SAPPHIRE

Recruitment
The Study of Asthma Phenotypes and Pharmacogenomic Interactions by Race-ethnicity (SAPPHIRE) is an ongoing study that was approved by the Institutional Review Board of Henry Ford Health System. Study individuals included in the current study were members of a large health system, which serves southeast Michigan and all of the Detroit metropolitan statistical area. Individuals were 12-56 years of age and no prior diagnosis of congestive heart failure or chronic obstructive pulmonary disease. Patient recruitment included patients with and without a clinical diagnosis of asthma. Written informed consent was required at the time of enrolment as a condition for study participation. The exam at the time of enrolment included both a staff-administered questionnaire and lung function testing.

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Case/Control definition

For the current analysis we used patient responses to the staff-administered questionnaire to define cases and controls. Patients were considered to be a case if they answered in the affirmative to the question, "Have you ever had eczema or any kind of skin allergy?"

Genotyping and imputation

DNA was isolated from whole blood samples. Genome wide genotyping was performed using the Axiom® AFR array (Affymetrix Inc., Santa Clara, CA. To be included in the analysis, an individual's array results had to have a dish quality control measure ≥0.82, an overall call rate ≥97%, and no discordance between patient-reported sex and the measured X-heterozygosity. We removed SNPs from the analysis which had an overall SNP call rate <95%, Fisher's linear discriminant <3.6, Het strength offset <-0.1, minor allele frequency (MAF) <5%, and Hardy-Weinberg equilibrium p-value $<10^{-5}$. We imputed missing genotypes using the SNPs that passed quality control and data from the March 2012 release of the 1000 Genomes Project. The software program, IMPUTE2[7], performed the imputation.

Statistical Analysis

An additive logistic regression model was used to evaluate the association between individual SNP variant dosage and atopic dermatitis status. Models were adjusted for sex. Variants on the X chromosome were evaluated separately for females and males, since SNP dosage varied from 0-2 in the former and from 0-1 in the latter.

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REPLICATION STUDIES

Anhui Medical University (AMU)

Recruitment

All samples from 1,012 atopic dermatitis cases and 1,362 controls were obtained from doctors through collaboration with multiple hospitals in southern China. All participants provided written informed consent. The study was approved by the Institutional Ethical Committee of each hospital and was conducted according to the Declaration of Helsinki principles.

Case/Control definition

All the cases with atopic dermatitis were diagnosed according to Hanifin and Rajka criteria. Clinical information was collected from the affected individuals through a full clinical checkup by physician specialists. Additional demographic information was collected from cases and controls through a structured questionnaire. All controls were clinically assessed to be without atopic dermatitis, other atopic diseases, systemic disorders or family history of atopic diseases (including first-, second- and third-degree relatives).

Genotyping and imputation

The genome-wide genotyping analysis was conducted using Illumina Human610-Quad BeadChips array. SNPs were analyzed if they showed a call rate ≥90% in cases and controls, a MAF ≥1% in the population and significant deviation from Hardy-Weinberg equilibrium (HWE) in the controls (P>10−7). SNPs passing quality control criteria were used for imputation of variants from the 1000

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Genomes project. The imputation of 27 SNPs was performed using IMPUTE2[7] considering all populations from the 1000 Genomes Project Phase v3 as a reference.

Statistical Analysis

Genome-wide association analysis was performed using PLINK1.07[30] for 1012 cases and 1362 controls. The 1000 Genomes cosmopolitan reference panel (released 21 May 2011, V3) was used for imputation. We first phased the study data with the SHAPEIT2 haplotype estimation tool[20] following "best practices" guidelines in the IMPUTE2 documentation[7] (Impute2, 2.3.0). And the association analysis of imputation result was performed using PLINK1.07.

Acknowledgements and Funding

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CAG/CSGA/SARP

Recruitment

Subjects were from the Chicago Asthma Genetics Study (CAG), the NHLBI Collaborative Studies on the Genetics of Asthma (CSGA), and the Severe Asthma Research Program (SARP) and are described previously[73].

CAG included subjects recruited from a) families ascertained through asthma affected sib pairs, b) asthma affected children, c) adults and children with severe persistent asthma, and d) non-asthma controls over 18 years of age. Asthma was defined as 1) a physicals diagnosis, 2) the presence of at least two self-reported symptoms, 3) current use of medications, and 4) bronchial hyperresponsiveness to methacholine or reversibility to inhaled bronchodilator. Controls had no self-reported personal or family history (1st degree relatives) of asthma.

SARP and CSGA subjects were recruited from the NHLBI funded Severe Asthma Research Program (SARP) centers and the NHLBI Collaborative Studies on the Genetics of Asthma (CSGA). CSGA cases were recruited and diagnosed as described above for CAG. The SARP asthma cases met the American Thoracic Society definition of severe persistent asthma, and controls from the same medical centers were individuals with no self-reported personal or family history (1st degree relatives) of asthma.

Case/Control definition

Asthma cases who self-reported with atopic dermatitis were considered cases, and asthma cases self-reported no atopic dermatitis were controls. A subset of the non-asthmatic control subjects had self-reported atopic dermatitis status and were also included as atopic dermatitis cases or controls.

Genotyping and imputation

Subjects were genotyped on the Illumina 1Mv1 platform with individual genotypes called using the BeadStudio software by Illumina. SNP-wise quality control included call rates > 95%, HWE p values > 10-5, consistency with HapMap allele frequencies (chisq test p value > 10-5), and < 5 heterozygous calls for X-linked markers in male subjects. Subjects with call rates > 95%, matching genetic and reported sex, and consistent between self-reported ethnicity and PCA (Eigenstrat) inferred ancestry, were retained. Subjects with unexpected pairwise relatedness or genetic identify were reduced to 1 subject per pair. SNPs and subjects passing quality control were first phased using SHAPEIT[20] and 1000 Genomes project (phase 1v3) variants were imputed using IMPUTE2[7].

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Statistical Analysis

Replication statistical analysis was completed using allelic dosages estimated from IMPUTE2 genotype probabilities and logistic regression in R (http://www.r-project.org/). Analysis was completed separately for African Americans and European Americans and both analyses included 5 covariates, sex and 4 principle components to control for population structure.

Acknowledgements and Funding

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CAMP

Recruitment

The Childhood Asthma Management Program (CAMP) population is composed of non-Hispanic white subjects from a multicenter clinical trial that followed 1,041 children with asthma for four years and 84% of the original participants for 12 years[74]. Stringent inclusion criteria ensured that participants had mild to moderate asthma, which was assessed as having asthma symptoms at least twice per week, using asthma medication daily, or using an inhaled bronchodilator twice per week for six or more months of the year prior to recruitment. CAMP subjects had increased airway responsiveness, as established by a bronchoprovocation test of up to 12.5mg/dl of methacholine resulting in 20% or greater forced expiratory volume in one second (FEV1) reduction.

Case/Control definition

581 subjects with genome-wide SNP genotype data were used for this analysis. Subjects were considered to have atopic dermatitis if they self-reported having seen a physician for eczema or atopic dermatitis at the baseline visit. A total of 143 subjects had atopic dermatitis and 438 did not have atopic dermatitis.

Genotyping and imputation

Genome-wide SNP genotyping of 581 CAMP subjects was performed on Illumina's HumanHap550v3 and 610 Genotyping BeadChips (Illumina, Inc., San Diego, CA). We included SNPs that satisfy minor allele frequency ≥5%, a minimum of 95% genotyping rate, and the Hardy Weinberg equilibrium (HWE) test at the 0.001 threshold. Details of the quality control (QC) criteria used to screen the genome-wide SNP data have been provided previously[75].

SNPs passing quality control criteria were used for imputation of variants from the 1000 Genomes project. This imputation was done using MaCH[10], version 1.0.16, and was imputed against "1000Genomes 0908" (http://www.sph.umich.edu/csg/abecasis/MACH/download/1000G-Sanger-0908.html). Results were lifted over to hg19 format for the analysis.

Statistical Analysis

We tested for the association of SNPs with atopic dermatitis using an additive logistic regression model, where SNP was coded as allele dose. Models were implemented in PLINK[30] and controlled for age.

Acknowledgements and Funding

We thank all CAMP subjects for their ongoing participation in this study. We acknowledge the CAMP investigators and research team, supported by NHLBI, for collection of CAMP Genetic Ancillary Study data. All work on data collected from the CAMP Genetic Ancillary Study was conducted at the Channing Laboratory of the Brigham and Women's Hospital under appropriate CAMP policies and human subject's protections. The CAMP Genetics Ancillary Study is supported by U01 HL075419, U01

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Central European Case Control Study (CECCS)

Recruitment

This study consisted of 2116 atopic dermatitis cases and 2180 geographically matched controls from Germany, the Czech Republic and Poland, and has a large overlap with the replication set previously described in a GWAS for atopic dermatitis[41] (set 4 in original study). All German cases (N=1336) were diagnosed and recruited at Charité Universitätsmedizin Berlin. German controls (N=1369) originated from blood donation programs in Bonn (N=979) or were individuals free of allergic symptoms (N=390) selected from the previously described population-based Multicentre Allergy Study (MAS)[58,59].

The Polish (N=456) and Czech (N=324) atopic dermatitis cases had a positive family history of atopy and were recruited for the EPAAC (Early Prevention of Asthma in Atopic Children) and ETAC (Early Treatment of the Atopic Child) trials, two similar randomized, double-blind, placebo-controlled studies on the efficacy of levocetirizine or cetirizine, respectively, in the prevention of asthma[76,77]. The Czech (N=374) and Polish (N=437) controls were obtained from blood donation programs in Prague and Szczecin, as previously described.

Case/Control definition

All cases had an early onset (< 2years) physician's diagnosis of atopic dermatitis made according to standard criteria[43]. All controls, except those originating from the MAS study, were population-based individuals with unknown clinical status. Individuals from the MAS study were selected by negative parental reports of atopic dermatitis.

Genotyping and imputation

Genotyping of selected SNPs was performed using KASP™ at LGC Genomics (Hoddesdon, UK). Genotyping cluster plots were examined with SNPViewer for each SNP and for each plate. In some cases specific genotypes from selected samples were manually edited when the automatic calling algorithm had made a clear error. Samples with a call rate lower than 95% were excluded from subsequent analysis (57 samples excluded). All SNPs had a call rate higher than 99%. All SNPs, except rs6473227 (p=0.02), were in Hardy-Weinberg equilibrium as assessed by PLINK[30] using all unaffected individuals.

Statistical Analysis

All SNPs were switched to the "+" genome strand. Association with atopic dermatitis was assessed using logistic regression and including age as covariate with mach2dat[12].

Acknowledgements and Funding

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COPSAC2010

Recruitment

The $COPSAC_{2010}$ birth cohort is a population based longitudinal clinical study of 800 pregnant women and their offspring. The families are monitored closely from week 24 of mothers' pregnancy till age 3 year of the offspring with 10 scheduled visits to the research center and additional visits at onset of any skin or wheezy symptoms.

Case/Control definition

The families used doctors employed at the clinical research unit, and not the family practitioner, for diagnosis and treatment of atopic dermatitis and other skin-related symptoms. Skin lesions were described at both scheduled visits at 6-monthly intervals and acute visits with skin symptoms according to pre-defined morphology and localization; atopic dermatitis was defined based on the Hanifin-Rajka criteria.

Genotyping and imputation

Genotyping of 951,117 genetic markers were carried on the Illumina Infinium HumanOmniExpressExome Bead chip at the AROS Applied Biotechnology AS center, in Aarhus, Denmark. Genotypes were called with Illumina's Genome Studio software. All individuals underwent quality control (QC) filters, where individuals with Hardy-Weinberg equilibria p values >10-6, minor allele frequency (MAF>0.01), individual genotyping call rate > 0.95, and SNP genotyping call rate > 0.95 were retained. We excluded individuals with gender mismatches, genetic duplicates, outlying heterozygosity > 0.27 and < 0.037, and those individuals not clustering with the CEU individuals (Utah residents with ancestry from northern and Western Europe) through a multi-dimensional clustering analyses (MDS) seeded with individuals from the International Hap Map Phase 3. Imputation to 1000 Genomes reference panel using SHAPEIT2[20] and IMPUTE2[7] was carried out at Barcelona Supercomputing Center (www.bsc.es) after doing the appropriate post-imputation QC (MAF>0.01, HWE_controls>5e-6, info>0.882) and successfully imputed ~7.2 million SNPs.

Statistical Analysis

Genome-wide analysis was carried out using SNPTEST[8] v.2.5 using the –score method, frequentist statistics, assuming and additive model, and using sex and the first five population principal components as covariates.

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ECRHS

Recruitment

Details of the methods of ECRHS I and ECRHS II, a multicenter international cohort study, have been published elsewhere[78,79]. Participants within the ECRHS were eligible for inclusion in this analysis if they were identified by random sampling of those who fulfilled the following criteria 1) lived in centers that took part in genome-wide genotyping initiative under the auspices of GABRIEL[17] AND 2)

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were initially selected to take part in the ECRHS clinical measurements as part of the random sample (i.e. not specifically selected for inclusion because of any pre-existing disease). Each participating center obtained ethical permission from the appropriate local committee.

Case/Control definition

Cases were those answering positively to the questions 'Have you ever had an itchy rash that was coming and going for at least 6 months?' AND yes to 'Have you had this itchy rash in the last 12 months?' during ECRHS II (aged 27-58). Further information on the distribution of eczema within the cohort is available[80].

Genotyping and imputation

Subjects were genotyped with the Human 610 Quad Chip (ILLUMINA). Genotypes were called using BeadStudio. Criteria for exclusion of variants were: a call rate below 95%, a MAF < 0.01 and a HWE p-value < 0.0001. Other QC criteria applied were: exclusion of males with high X heterozygosity, sex discrepancies, IBS analysis for relatedness and ancestry analysis using PCA. Imputation was done using IMPUTE2[7] considering the haplotypes from the 1000 Genomes Project Phase I version v3.20101123 as a reference.

Statistical Analysis

Genome-wide association analysis of atopic dermatitis was carried out in SNPTEST V2.4[8] (https://mathgen.stats.ox.ac.uk/genetics_software/snptest/snptest.html) regressing expected allelic dosage on case-control status, adjusted for sex and the first two principal components informative of European ancestry.

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GENEVA

Recruitment

Atopic dermatitis patients were recruited from tertiary dermatology clinics based at three centers (Technische Universität Munich, as part of the GENEVA study, University of Kiel, University of Bonn). German controls were obtained from the population-representative PopGen biorepository[36].

Case/Control definition

Atopic dermatitis was diagnosed on the basis of a skin examination by experienced dermatologists according to standard criteria, which included the presence of chronic or chronically relapsing pruritic dermatitis with the typical morphology and distribution[38].

Genotyping

De novo genotyping of the 11 lead SNPs of novel loci and 9 candidate SNPs from MAGENTA analysis was carried out using Sequenom MassARRAY and TaqMan. Individuals with ambiguous sex and extensive missing data rate (≥40%, ≥8 SNPs) were excluded. SNPs with low genotyping rate (<95%), low minor allele frequency (<1%) and strong deviation from Hardy-Weinberg equilibrium ($p<0.01$) were discarded.

Statistical Analysis

1362 cases and 2205 controls were analyzed using logistic regression and an additive genetic model (allele counts) adjusted for sex.

Acknowledgements and Funding

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HEALTH2006

Recruitment

The Health2006 study took place during 2006-2008 and consisted of a random sample of 7,931 Danish (Danish nationality and born in Denmark) men and women aged 18-69 years invited to participate in a health examination[81]. A total of 3,471 (43.8%) persons participated. Potential participants living in the Copenhagen area were identified in the central Danish Civil Registration System, and then recruited by invitation. The aim was to investigate the prevalence and risk factors of chronic diseases such as mental health, asthma, allergies, CVD, and diabetes. Informed written consent was obtained from all participants. The Health2006 was approved by the Ethical Committee of Copenhagen (KA-20060011) and the Danish Data Protection Agency.

Case/Control definition

All participants were mailed a standard invitation letter and a questionnaire about health, lifestyle, and socioeconomic factors. Atopic dermatitis was defined by the U.K. Working Party's diagnostic criteria for atopic dermatitis as a history of an itchy skin condition plus a minimum of two of four minor criteria.

Genotyping and imputation

Blood samples were taken from all participants as part of their health examination. The buffy coat was frozen for DNA extraction, and later genomic DNA was extracted using a QiagenAutoPure LS system. Genotyping of 27 SNPs was performed using KASP™ by LGC Genomics (Hoddesdon, UK). Three SNPs (rs2038255, rs12951971, rs142185235) failed genotyping. The call rate of the remaining 24 SNPs was>99 % for all SNPs. No errors were observed in 370 samples genotyped in duplicate.

Statistical Analysis

Statistical analyses were performed using SAS, version 9.3 (SAS Institute Inc., Cary, NC, USA). Replication analysis was performed for the 335-338 cases and 2934-2957 controls with genetic and phenotypic data. Associations between SNPs and atopic dermatitis were examined in additive logistic regression models adjusted for sex. Moreover, SNP's identified in the conditional GWAS were adjusted for the top SNP in an additional analysis.

Acknowledgements and Funding

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Isle of Wight (IoW)

Recruitment

A whole-population birth cohort was established on the Isle of Wight (IoW) in 1989 to prospectively study the natural history of asthma and allergic conditions (*n* = 1,536 subjects). After exclusion of adoptions, perinatal deaths and refusal for follow-up, 1,456 children (95%) were enrolled. The local

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research ethics committee approved the study and informed written parental or participant consent was obtained for all participants at recruitment and subsequently at follow-ups, which were conducted at ages 1, 2, 4, 10, and 18 years of age. The IoW birth cohort has been described in detail elsewhere [82].

Case/Control definition

Cases were defined as subjects who were recorded at ages 4, 10 or 18 as having ever had eczema. Eczema was defined as chronic or chronically relapsing, itchy dermatitis lasting more than 6 weeks with characteristic morphology and distribution, following Hanifin and Rajka criteria[43,83].

Genotyping and imputation

DNA from peripheral blood samples was extracted using a salting-out method. Target SNPs were genotyped using KASP™ by LGC Genomics (Hoddesdon, UK).

Statistical Analysis

Genome-wide association analysis was carried out using SPSS v21.0 for the 173-176 cases and 541-552 controls with phenotypic data and genetic data at each locus.

Acknowledgements and Funding

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KORAF3

Recruitment

The KORA study is a series of independent population-based epidemiological surveys of participants living in the region of Augsburg, Southern Germany. All survey participants are residents of German nationality identified through the registration office and were examined 2004/05 (KORA F3). 3,006 subjects participated in KORA F4 which is a 10-year follow-up examination of KORA survey S3 (1994/95). Individuals for genotyping in KORA F3 were randomly selected. The age range of the participants was 25 to 74 years of recruitment. Informed consent has been given by all participants. The study has been approved by the local ethics committee.

Case/Control definition

Among cases, subjects were considered to have atopic dermatitis if they self-reported having a physician diagnosis of atopic eczema.

Genotyping and imputation

In the F3 population, genotyping was performed with the Illumina HumanOmniExpress BeadChip and the Illumina 2.5 BeadChip. Only SNPs that were genotyped with good quality on both chips were used for analysis. In addition, SNPs that did not pass the following quality control criteria were removed: <98% call rate, deviation from Hardy-Weinberg equilibrium ($p<5x10^{-6}$) or MAF <0.01. The genotyped SNPs were phased using SHAPEIT v2[20], and the following imputation was performed with IMPUTE v2.3.0[7] using the 1000g phase1 reference panel (ALL_1000G_phase1integrated_v3_impute_mac1).

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Statistical Analysis
Genome-wide association analysis was performed using SNPTEST 2.4.1[8] for 74 cases and 2532 controls with genetic and phenotypic data.

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North Cumbria Community Genetics Project (NCCGP)

Recruitment
The North Cumbria Community Genetics Project (NCCGP) is a population-based birth cohort comprising 7737 babies delivered in one hospital in the Northwest of England between 1996 and 2003. Children aged between 7 and 9 years in 2008 were invited to participate in an eczema genetic study; 805 were enrolled with DNA samples from cord blood or saliva collection and were requested to complete a questionnaire and undergo skin examination[84]. DNA samples and clinical data were available for 756 individuals for the purposes of this study.

Case/Control definition
Cases of atopic dermatitis were defined using the UK diagnostic criteria for 12-month period prevalence and each child was examined by an experienced dermatologist, for flexural dermatitis and point prevalence of eczema. Controls were those children who were not defined as having atopic dermatitis by the criteria above.

Genotyping and imputation
SNP genotyping was performed using KASP™ technology, by LGC Genomics (Hoddesdon, UK).

Statistical Analysis
Statistical analyses were performed using R(v3.0.1). Each of the SNPs were tested for association using additive logistic regression models adjusted for sex. Additionally, potential secondary hits identified in the discovery phase were tested for independent association using additive logistic regression models adjusted for sex and the top SNP at each locus.

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Prevention and incidence of asthma and mite allergy birth cohort study - (PIAMA)

Recruitment

PIAMA is a birth cohort study consisting of two parts: a placebo controlled intervention study in which the effect of mite impermeable mattress covers on the development of asthma and allergy was studied and a natural history study in which no intervention took place. Details of the study design have been published previously[85]. Recruitment took place in 1996-1997 through prenatal clinics. A screening questionnaire was distributed to pregnant women visiting one of 52 prenatal clinics at three regions in the Netherlands. A total of 10,232 pregnant women completed a validated screening questionnaire. Mothers reporting a history of asthma, current hay fever or allergy to pets or house dust mite were defined as allergic. Based on this screening, 7,862 women were invited to participate, of whom 4,146 women (1,327 allergic and 2,819 non-allergic) gave written informed consent. Follow-up of the children took place at 3 months of age and yearly from 1 to 8 years of age. The Medical Ethical Committees of the participating institutes approved the study, and all participants gave written informed consent.

Case/Control definition

Questionnaire information on eczema was obtained at ages 3m,1y,2y,3y,4y,5y,6y, 7y,8y. Cases were defined as a positive response to one or more of these three questions:
1. Has your child ever had atopic dermatitis? 2. Did a doctor ever diagnose atopic dermatitis in your child? And did your child have atopic dermatitis during the past 12 months?
Controls were defined a negative response to these questions at ages 2 – 8 years.

Genotyping and imputation

DNA was collected from 2,162 children. Genome-wide genotyping was performed in three phases. The first phase was performed within the framework of the GABRIEL Consortium using an Illumina Human 610K quad array37. Genotypes were available from 172 children with asthma and from 187 controls after quality control. A second group of 268 children who were more extensively examined during follow up was genotyped with an Illumina HumanOmniExpress array. A final group of 1377 children was genotyped with the Illumina Human Omni Express Exome Array. SNPs were harmonized by base pair position annotated to genome build 37, name and annotation of strand for each platform. Discordant or duplicate SNPs or SNPs that showed large differences in allele frequencies (> 15 %) were removed. After quality control, a total of 1968 individuals remained and imputation was performed per platform using IMPUTE 2.0[7] against the reference data set of the CEU panel of the 1000 Genomes project (version March 2012). SNPs of high quality (info-score IMPUTE ≥ 0.7) were merged into one dataset using GTOOL and used for further analysis. Dosages of imputed SNPs were predicted based on the following assumptions; 0 is the first homozygote, 0.5 is a heterozygote and 1 is the other homozygote. The info scores of the imputed SNPs were all ≥0.99 which provided reliable dosages estimates. The current replication analysis was restricted to Caucasian individuals with genome-wide data and phenotype information (n= 1703 children).

Statistical Analysis

The SNP association analysis for replication was carried out in R 3.0.1 for the 808 cases and 895 controls with genetic and phenotypic data. R function glm is used to fit logistic regression models between phenotype and SNPs, with the correction of gender effect.

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Institute for Public Health and the Environment, Bilthoven (A.H. Wijga), Department of Pediatrics, Division of Respiratory Medicine, Erasmus MC -Sophia, Rotterdam (J.C. de Jongste), Pulmonology (D.S. Postma) and Pediatric Pulmonology and Pediatric Allergology (G.H. Koppelman) of the University Medical Center Groningen and the Department of Immunopathology, Sanquin Research, Amsterdam (R.C. Aalberse), The Netherlands. The study team gratefully acknowledges the participants in the PIAMA birth cohort study, and all coworkers who helped conducting the medical examinations, field work and data management. We specifically thank O. Savenije, I. Nolte and P. van der Vlies for their support.
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RAINE

Recruitment

The Western Australian Pregnancy Cohort (Raine) Study[86] is a prospective pregnancy cohort where 2900 were recruited from King Edward Memorial Hospital between 1989 and 1991. Data were collected throughout pregnancy and the children have been followed-up at ages 1, 2, 3, 5, 8, 10, 14, 17, 18, 20, and 23. Ethics approval for this study was obtained from King Edward Memorial Hospital and Princess Margaret Hospital. Participants were consented to being involved in this study prior to each follow-up.

Case/Control definition

The children have been followed up with regular questionnaires and clinic visits. For the current study data collected from the questionnaires was used to classify children as eczema cases or controls. When the children were approximately 5, 13 and 16 years, parents were asked the following questions:

1. Has anyone ever told you that your child has eczema? If yes, who told you your child has eczema?

We defined cases as the children of parents who answered 'Yes and was diagnosed by a doctor or pediatrician' at any one of the follow-ups. Controls were defined as children of parents who answered no at all 3 follow-ups.

Genotyping and imputation

The GWAS data was genotyped in two separate lots (dependent on when the subjects DNA was processed and ready to genotype) using the Illumina Human660W Quad Array at the Centre for Applied Genomics (Toronto, Ontario, Canada). The first round of genotyping was completed on 1,259 Raine children (including 63 replicates and a plate control on each plate) and the second on 334 children (including 18 replicates and a plate control on each plate). The 660W Quad Array includes 657,366 genetic variants including ~560,000 single nucleotide polymorphisms (SNPs) and ~95,000 copy number variants (CNV's).
All individuals of non-European ancestry, ambiguous sex, extreme heterozygosity (<0.3), cryptic relatedness (π>0.1875) and high missingness (>3%) were removed. SNPs with low genotyping rate (<95%), with low minor allele frequency (<1%), out of Hardy Weinberg equilibrium ($p<5x10^{-7}$) were excluded. 1494 individuals typed on 535,632 probes remained. Phasing of the SNPs was carried out

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using MaCH 1.0 Markov Chain Haplotyping software[10] and imputation was carried out using minimac[11] using phase 1 1000 Genomes reference panel (v3.20101123, ALL populations, no monomorphic/singletons). The final imputed dataset consisted of 1494 individuals and 31,337,617 variants.

Statistical Analysis

Genome-wide association analysis was carried out using ProbABEL from the Gen ABEL suite of programs[11] for the 404 cases and 972 controls with genetic and phenotypic data. Summary statistics were available for 30,061,897 autosomal variants and 1,204,531 Chr X variants.

Acknowledgements and Funding

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Study of African Americans, Asthma, Genes & Environments (SAGE II)

Recruitment

The Study of African Americans, Asthma, Genes & Environments (SAGE II) is an ongoing study of asthma in children and young adults coordinated from the University of California San Francisco. Recruitment protocols were similar to GALA II with the only differences being that the recruitment was restricted to San Francisco Bay Area and participants self-identified all four grandparents as African American[26].

Case/Control definition

As for GALA II. A total of 875 asthma cases had genotyping data: 365 had atopic dermatitis and 510 were used as controls.

Genotyping and imputation

Subjects were genotyped with the Axiom LAT1 array (World Array 4, Affymetrix) and quality control procedures and imputation were performed similarly to GALA II, as described above.

Statistical Analysis

Association testing of SNPs selected for replication was carried out carried using logistic regression models in PLINK[30], which were adjusted by sex and also genetic ancestry to avoid the confounding effect of population stratification in African Americans.

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Southampton Women's Survey (SWS)

Recruitment

Between 1998 and 2002 the Southampton Women's Survey team interviewed 12,583 Southampton women aged 20 to 34 years. Those who became pregnant after interview were invited to take part in the pregnancy phase of the survey. Enrolment is described in more detail in the cohort profile paper[87] and via the website http://www.mrc.soton.ac.uk/sws/. There were 3,158 babies born to women in the study between 1998 and 2007. The survey has followed up these children with home visits at six months, one year, two and three years. A sample of over 1,000 children was seen at 4 years of age; more than 2,000 children have been seen so far at ages 6-7 years. Biological samples including DNA have been collected for 2,000 of the children from this cohort. The study was conducted according to the guidelines in the Declaration of Helsinki, and the Southampton and South West Hampshire Research Ethics Committee approved all procedures (276/97, 307/97, 340/97). Written informed consent was obtained from all participating women and by parents or guardians with parental responsibility on behalf of their children.

Case/Control definition

The children have been followed up with regular questionnaires and clinic visits. For the current study, data collected from the questionnaires was used to classify children as eczema cases or controls. When the children were approximately 6 months, 1, 3 and 6 years, parents were asked about skin conditions in the child. The case definition validated by Williams et al.[38] to qualify for a case of atopic dermatitis was used to classify eczema cases and controls, omitting a history of asthma or hay fever as a criterion given the young age of the infants/children. Cases were thus defined as: (A) must have a history of an itchy skin condition plus (B) 3 or more of the following:

1. History of flexural involvement
2. History of asthma/hay fever
3. History of generalized dry skin
4. Onset of rash under the age of 2
5. Visible flexural dermatitis identified by trained research nurses.

Genotyping

The Southampton Women's Survey children's samples were genotyped using KASP™ by LGC Genomics (Hoddesdon, UK). The call rate was >99% for each genotyped SNP, all SNPs were found to be in Hardy Weinberg equilibrium and 5% duplicates were included with no errors.

Statistical Analysis

Association analysis was carried out using STATA 13.1 (Statacorp USA) for the 247 cases and 1122 controls with genetic and phenotypic data. Summary statistics were available for 20 variants that were successfully genotyped.

Acknowledgements and Funding

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TwinsUK

Recruitment

The St Thomas's UK Adult Twin Registry includes 12,000 mainly female twins from throughout the United Kingdom recruited by means of media campaigns without specifying the diseases for study. Pairs were invited to attend the Twin Research Unit, St Thomas's Hospital, London, for a full day of clinical tests, including a self-completed questionnaire relating to allergic diseases. The study was approved by the Local Research Ethics Committee of St Thomas's Hospital, and subjects gave full informed consent.

Case/Control definition

Questions on eczema, hay fever and allergic rhinitis, were derived from the International Study of Asthma and Allergies in Childhood. Respondents were asked, "Have you ever had eczema?" on three occasions 1999, 2004 and 2008. Cases were determined from those people who had consistently answered at all three time points. In addition volunteers were asked about suffering from eczema in the previous 12 months and about family history of eczema and atopy which was not used in this analysis.

Genotyping and imputation

Genotyping of the TwinsUK dataset was done with a combination of Illumina arrays (HumanHap300, HumanHap610Q, 1M-Duo and 1.2MDuo 1M). Intensity data for each of the three arrays were pooled separately (with 1M-Duo and 1.2MDuo 1M pooled together) and genotypes were assigned using the Illuminus calling algorithm. We applied similar quality control criteria to each dataset and merged them. Pre-phasing was done with SHAPEIT[20] software and imputation was performed using IMPUTE2[7] using 1000 Genomes haplotypes-Phase I integrated variant set release (v3) in NCBI build 37 (hg) coordinates.

Statistical Analysis

In order to avoid issues due to family structure, one twin was selected from each pair and used for further analysis. We analyzed a total of 418 cases and 968 controls with SNPTEST v2[8](https://mathgen.stats.ox.ac.uk/genetics_software/snptest/snptest.html).

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2. Notes on the credible sets of variants for each locus (summarising Supplementary Tables 17-21)

NB - In all cases, given the caveats with the credible set approach, we cannot be sure that the causal variant is included in the credible set (and so we may have missed some important causal variants). In addition, even if the correct causal regulatory element is identified, without further experimental work it cannot be determined which gene it regulates (even if the regulatory element falls within a gene). eQTL data (where available) can provide some additional evidence as to which gene the variant is acting on. Despite this caveat, we believe that this type of mining of the regulatory resources can uncover some potential good starting-points for taking these findings forward to identify the causal variants and/or genes.

Known loci

1q21.3. rs61813875. *FLG* - 1.5kb of 3' of LCE3E. Known[33]

After conditioning on the 4 *FLG* mutations there is no residual signal at this locus, indicating that this signal is caused by the known functional mutations (R501X, 2282del4, R2447X, S3247X).

1q21.3. rs12730935. *IL6R* – intronic. Known[88]

The credible set contains 23 variants spanning 23kb within *IL6R*. One of the variants in the credible set is a missense mutation (rs2228145), which is the variant previously reported to be associated with AD[88]. This mutation encodes an aspartic acid to alanine exchange (Asp358Ala) and is known to affect IL6R signalling[89]. It is likely that this is the causal SNP at this locus.

2q12.1. rs6419573. *IL18R1/IL18RAP* – intergenic. Known[90]

NB -There is evidence for multiple signals at this locus and therefore the credible set approach may not be suitable.

From the credible set of 59 variants identified in our meta-analysis spans 115kb including the *IL18R1* and *IL18RAP* genes. No variant is protein coding and the variant most likely to have a regulatory function is rs3755267 (in an intron of *IL18RAP*). This position has chromatin markers indicative of a strong or weak enhancer (leukemia and B-LCLs, respectively), is in a region of open chromatin in primary Th1 T cells and B-LCLs and binds several TFs according to ENCODE data. The GATA-4 motif binding affinity is greatly increased in the presence of the atopic dermatitis risk allele at this position. This variant (along with 18 others in the credible set) is associated with expression of *IL18R1* (p=0.0013) in the MuTHER skin expression data[91], with the atopic dermatitis risk allele (T) associated with an increase in IL18R1 expression (Supplementary Table 19). However, the posterior probability that the atopic dermatitis and skin *IL18R1* signals colocalize is only 26%. *IL18RAP* shows some evidence for increased expression in lesional versus non-lesional skin in GEO (p=0.042), but no difference between the two cell types for *IL18R1* (very small sample sizes)[92]. This locus is also associated with IBD (same direction of effect)[93]. IL18R1, IL18RAP and IL1RL1 are all members of the IL-1 cytokine family that drives production of CD4+ T cell cytokines and induces inflammation.

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3q13.2. rs1249910. *CCDC80/CD200R1L* – 23 kb 5' *of CCDC80*. Known[90]

The credible set contains 30 variants spanning 33.5kb between *CCDC80* and *CD200R1L*. No variant in this set is coding. One variant, rs12637953 (27kb 5' of *CCDC80*) is listed by regulomeDB as 'likely to affect binding'. This variant is at a position with chromatin marks indicative of a strong enhancer in several relevant tissue types (including epidermal keratinocytes) and a weak enhancer in B-LCLs. It is in a region of open chromatin for 102 cell types and 46 proteins are thought to bind here, including NFKB. The affinity of several binding motifs (such as NF-E2, Nrf and TCF11) is thought to be greatly compromised by the atopic dermatitis risk allele at this locus. This SNP was not analysed in the MuTHER expression analysis[91] but 8 others in the credible set were. 6 show nominal association with *CD200R1L* expression, with the atopic dermatitis risk alleles associated with a decrease in expression. Two other alleles within the credible set show nominal association with expression of *BTLA* (p=0.019) and *WDR52* (p=0.022). None are associated with *CCDC80* expression. *BTLA* encodes a B and T lymphocyte attenuator and BTLA-deficient mice have been found to be resistant to the peripheral T cell tolerance induction[94].

4q27. rs6827756. *KIAA109* – intronic. Known[39]

NB - There is evidence for multiple signals at this locus and therefore the credible set approach may not be suitable.
The credible set contains 31 variants, spans 377kb and three genes (*KIAA1109, ADAD1* and *IL2*). Ellinghaus et al. had previously suggested that the signal in this region could implicate *IL2* as the target gene, given its known role in control of proliferation and survival of regulatory T-cells[39]. No variant in our credible set was coding. The two variants with the best evidence for a regulatory function were rs55904957 (in an intron of *KIAA1109*) and rs11727369 (2.3kb 3' of *KIAA1109*). Both are sites of TF binding and open chromatin. 8 of the 31 variants are included in the MuTHER skin expression analysis[91]. Of these, 5 are nominally associated with *FGF2* expression (lowest p=0.019) and one is associated with *SPRY1* expression (p=0.031). The two SNPs listed above were not analysed and neither was the *IL2* transcript. *FGF2* expression is lower in lesional versus non-lesional skin in atopic dermatitis patients (p=0.0143)[92].

5q31.1. rs12188917. *RAD50/IL13* – intergenic. Known[95]

NB - There is evidence for multiple signals at this locus and therefore the credible set approach may not be suitable.
The credible set of 38 variants identified in our meta-analysis spans 109kb including *IL5* and *RAD50*. No variant is protein coding and the variant most likely to have a regulatory function is rs12653750 (within an intron of *RAD50*). This position has chromatin marks indicative of a strong enhancer in B-LCLs, binds NFKB and GATA1 proteins and the atopic dermatitis risk allele at this SNP (T) decreases the affinity of the Pax2 binding motif. This SNP (along with 15 others in the credible set) was nominally associated with the expression of *IL5* (p=0.0011) in the MuTHER skin expression data[91], with the atopic dermatitis risk allele associated with an increase in IL5 expression (Supplementary Table 19). These SNPs were also associated with *RAD50* expression in LCLs (lowest $p=3x10^{-6}$). However, the posterior probability of the atopic dermatitis and *RAD50* signals colocalizing is <1%. IL5 is a Th2 cytokine that mediates eosinophil activation. Multiple independent associations for atopic dermatitis have previously been reported in this cytokine rich region and multiple genes probably have a role.

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6p21.32. rs4713555. *HLA-DRB1* – 18kb 5' *of HLA-DRB1*. Known[90]

When this region was previously identified as being associated with atopic dermatitis in a Japanese population, the top signal was reported to be within C6orf10. Weidinger et al. have since shown that the signal in this region may be explained by classical HLA allele HLA-DRB1*0701[40].
The HLA-DRB1*0701 allele has been associated with a range of T-cell mediated inflammatory diseases.

6p21.33. rs145809981. *MICB* – intronic. Known[90]

Weidinger et al have previously shown that the signal in this region may be explained by the classical HLA allele, HLA-B*4402[40]. Our top signal is in the first intron of the MICB gene and the credible set (27 SNPs) spans the promoter of this gene. In ENCODE data several SNPs show chromatin marks indicative of an active promoter in multiple cell types (including B-LCLs, epidermal keratinocytes and lung fibroblasts), they also show open chromatin state and evidence of binding to RNA polymerase machinery and multiple transcription factor binding sites. 2 SNPs (rs2253051 and rs2534670) affect the affinity of several binding motifs. 7 variants in the credible set are eQTLs for *MICB* (strongest rs2904785 $p=3x10^{-10}$) in the MuTHER skin data (though the posterior probability for colocalization of the atopic dermatitis and *MICB* signals is only 3%) and *MICB* expression is higher in lesional versus non-lesional skin in atopic dermatitis patients[92].

10q21.2. rs2944542. *ZNF365* – intronic. Known[90,96]

The credible set contains 7 variants spanning 26.5Kb within *ZNF365*. No variant in this set is coding or has good regulatory evidence in regulomeDB. Variants in this gene have been previously found to be associated with AD[70,96] and IgE levels[28]. The IgE study was able to refine this association to intron 1 of transcript variant D of *ZNF365*[28]. The credible set in our atopic dermatitis analysis spans 26Kb of the same intron.

11p13. rs2592555. *PRR5L* – intronic. Known[39]

NB - There is evidence for multiple signals at this locus and therefore the credible set approach may not be suitable.
The credible set contains 20 variants spanning 85kb within *PRR5L*. No variant is coding. The three variants with the best prediction of regulatory function in regulomeDB are rs2592555, and rs10501149. rs2592555 has chromatin marks indicative of a weak enhancer in umbilical vein endothelial cells, is in open chromatin in promyelocytic leukemia cells and the mutation at this position is predicted to have some effect on the affinity of several binding motifs. rs10501149 has chromatin marks indicative of a strong enhancer in epidermal keratinocytes, mammary epithelial cells and skeletal muscle myoblasts and a weak enhancer in B-LCLs. It is in open chromatin in B-LCLs and primary Th2 T cells, binds several TFs, including NFKB, BATF, IRF4, EBF1, JUND. Both of these variants (along with another 8 in the credible set) are nominally associated with *PRR5L* expression (*FLJ14213*) in the MuTHER skin eQTL data. The atopic dermatitis risk alleles are associated with a decrease in *PRR5L* expression (p=0.002 for both). These variants show even stronger association in LCLs ($p=1x10^{-10}$ and $p=4x10^{-10}$, respectively), but no association in adipose

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tissue. However, the posterior probability for the colocalization of the atopic dermatitis and *PRR5L* signals is only 2%.

11p15.4. rs4312054. *OR10A3/NLRP10* – 3.8kb 3' of *NLRP10*. Known[90]

The credible set contains 8 variants and spans 10kb between *OR10A3* and *NLRP10*. No variant in this set is coding or has good regulatory evidence in regulomeDB. Hirota et al. previously suggested that the target gene in this region may be *NLRP10* given its anti-inflammatory role in NFKB activation[70]. Of the 8 variants only rs907203 is associated with a transcript (*C11orf17*, p=0.028) in the region in the MuTHER skin data and none were associated with *NLRP10* expression.

11q13.1. rs10791824. *OVOL1* – intronic. Known[95]

This locus was identified in the previous EAGLE atopic dermatitis GWAS[95]. The top hit in that paper was rs479844 (<3kb upstream of *OVOL1*). The new top hit is in high LD with the previous SNP (r2=0.91), but the BF credible SNP analysis estimates the posterior probability of rs10791824 being the causal SNP in this region to be >99%. ENCODE data shows this SNP to be at a position with chromatin marks indicative of a strong enhancer in mammary epithelial cells and B-LCLs and a weak enhancer in epidermal keratinocytes and to have high DNAse I hypersensitivity (indicative of open chromatin) in many relevant cell types (e.g. B-LCLs, epidermal keratinocytes and dermal fibroblasts). This position has also been shown (using ENDOCE ChIP-seq data) to be a binding site for RNA polymerase and several transcription factor proteins, including some that are lymphocyte-specific (BATF and IRF4). The atopic dermatitis risk allele at this locus increases the affinity of the RREB-1_2 and decreases the affinity of the NF-I_1 binding motifs. Disruption of Ovol1 in mice leads to keratinocyte hyper-proliferation, hair shaft abnormalities, kidney cysts and defective spermatogenesis[97,98] and in one strain leads to perinatal death accompanied by kidney cyst formation and delayed epithelial barrier formation[99]. rs10791824 is not analysed in the MuTHER skin eQTL data[91].

11q13.5. rs2212434. *C11orf30/LRRC32* – intergenic. Known[41]

Our meta-analysis results, suggest a tight credible set of 10 SNPs, spanning 18kb between *C11orf30* and *LRRC32*. The variant most likely to have a regulatory function is rs11236797. This position has chromatin marks indicative of a strong enhancer in umbilical vein endothelial cells and a weak enhancer in lung fibroblasts and leukemia cells. This position is in open chromatin in a range of cell types including CD4+ T helper cells. Several TFs bind at this site, including ELF1, a TF known to be involved in T cell development and function[100]. Previously, Esparza-Gordillo et al. reported no cis-regulatory effect of their top SNP (rs7927894) in eQTL data[41]. Only one of the credible set (rs2155219) was analysed in the MuTHER skin expression analysis[91]. This SNP showed no association (i.e. p>0.05) with all transcripts in the region, including *LRRC32* and *C11orf30*. This locus is also associated with IBD (with the same direction of effect)[93].

16p13.13. rs2041733. *CLEC16A* – intronic. Known[39]

The credible set contains only 2 variants and spans 6kb in an intron of *CLEC16A*. RegulomeDB suggests the most likely functional SNP to be the top hit (rs2041733). This position has chromatin marks indicative of a weak enhancer in mammary epithelial cells, epidermal keratinocytes and lung fibroblasts, open chromatin in mammary epithelial cells (amongst others) and TF binding, including STAT3, known to mediate cellular response to interleukins. The atopic dermatitis risk

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allele (T) at this SNP is nominally associated with increased *PRM3* expression in skin in the MuTHER data (p=0.0092), but is not associated with expression of *CLEC16A* (p=0.120). Several SNPs in *CLEC16A* have been associated with immune-mediated diseases such as MS [101], T1D[102] and alopecia areata[103].

19p13.2. rs2918307. *ADAMTS10/ACTL9* – 18kb 3' of *ACTL9*. Known[95]

The credible set of 21 variants identified in our meta-analysis spans 4.5Kb, 18kb 3' of *ACTL9*. No variant in this set has good evidence of regulatory function from ENCODE data. However three have high DNAse I hypersensitivity in epidermal melanoctye cells only and the 8 that were analysed in the MuTHER skin expression analysis[91] showed nominal association with *RAB11B* expression in skin tissue, but no association in the LCL or adipose tissue, suggesting that any regulatory function might be cell-type specific. The atopic dermatitis risk allele (A) of the SNP showing the strongest expression association (rs2164983, p=0.0015) is associated with a decrease in *RAB11B* expression. This SNP showed no association with expression of either *ADAMTS10* or *ACTL9* (MGC33407) in MuTHER (data not shown).

20q13.33. rs4809219. *RTEL-1-TNFRSF6B* –intronic. Known[39,96]

The credible set of 25 variants identified in our meta-analysis spans 71Kb including *RTEL1-TNFRSF6B, ARFRP1, ZGPAT, LIME1* and *SLC2A4RG*. It contains 1 SNP in the 3'UTR of *LIME1* (rs1056441) and 2 *RTEL1* synonymous SNPs (rs2236506 & rs3208007). RegulomeDB labels two SNPs from the credible set as 'likely to affect binding'. One is in an intron of *RTEL1* (rs2236507) and the other is in an intron of *SLC2A4RG* (rs4809221). At rs2236507 there are chromatin marks indicative of a weak enhancer in mammary epithelial cells, epidermal keratinocytes and skeletal muscle myoblasts, open chromatin in several cell types (including B-LCLs and induced pleuripotent stem cells derived from skin fibroblasts) and evidence of RNA polymerase binding. At rs4809221 there are chromatin marks indicative of an active promoter in lung fibroblast cells and a weak promoter in B-lymphocyte lymphoblastoid, umbilical vein epithelial and mammary epithelial cells. This position is in open chromatin in several cell types (including dermal fibroblasts, amniotic epithelial cells and B-LCLs). Many TFs bind at this site and a large number of motifs have their binding affinity affected by this mutation. Ellinghaus et al. previously reported a slight over-expression of DcR3 (coded by *TNFRSF6B*) in serum from atopic dermatitis patients[39], suggesting this could be the target gene of the causal mutation. Of the four SNPs in the credible set for which there is MuTHER expression data available[91], for three (rs6010620, rs2297440 and rs2236507) the atopic dermatitis risk alleles were associated with increased *TNFRSF6B* expression in skin (lowest $p=2x10^{-4}$, with colocalization posterior probability=33%) and for the other (rs6062509) the atopic dermatitis risk allele was nominally associated with decreased *LIME1* expression ($p=7x10^{-4}$) (Supplementary Table 19). This locus is also associated with IBD also (with the same direction of effect)[93].

Novel loci

1q21.2. rs7512552. 584bp 5' of *MRPS21*. Novel.

The credible set contains 184 variants, spans 955kb and includes 33 genes, including *C1orf51, MRPS21, PRPF3, RPRD2, TARS2, ECM1, GABPB2* and *PIP5K1A*. One variant (rs13294 in exon 8 of *ECM1*) is missense. ECM1 is known to contribute to skin integrity and homeostasis and may be the causal gene in this region. Loss-of-function mutations in this gene cause a rare autosomal

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recessive disorder, lipoid proteinosis (LP), characterised by generalized thickening of the skin, mucosae and certain viscera[104]. rs13294 is predicted by PolyPhen to be benign. In MuTHER skin expression data rs13294 is actually associated ($p=2x10^{-4}$) with *MRPS21* expression. rs13294 and another *ECM1* variant (rs3737240) have previously been associated with ulcerative colitis[105]. There are also several variants in the credible set for which there is evidence of regulatory functions. One variant is in the 3'UTR for *RPRD2* (rs45595332) and another is in the 3'UTR for *MRPS21* (rs8006). The two variants from the credible set most likely to have regulatory functions according to the regulomeDB score are rs10888578 (1.5kb 3' of C1orf51), which is an eQTL for *MRPS21* and rs578353 (6kb 5' PRPF3), which is an eQTL for *MRPS21* and *C1orf51*. In the MuTHER skin expression data 40 credible variants are eQTLs for *MRPS21* (p~10-4). These all have even stronger associations in the MuTHER LCL data (p~10-8) and posterior probability that the atopic dermatitis and *MRPS21* signals colocalize of between 89% (skin) and 97% (LCLs). *MRPS21* encodes a protein that forms part of a mitochondrial ribosome and *C1orf51* (CIART) is thought to be a negative-modulator of circadian rhythms. It is unclear if this association is driven by coding changes to *ECM1* or through regulation of *MRPS21* expression.

2p13.3. rs112111458. 28kb 5' of *VAX2*. Novel.

The credible set contains 7 variants, spans 32kb between *CD207* and *VAX2*. The variant from the set with the best regulomeDB score is rs4852714. This variant has chromatin marks indicative of a strong enhancer in B-LCLs and the atopic dermatitis risk allele (A) decreases the affinity of Ik-2 and SIX5 binding. Ikaros is a TF known to play a role in the development of lymphocytes, B-cells and T-cells. In the MuTHER skin expression data, this variant (and another, rs6723629) show association with *CD207* expression ($p=1x10^{-10}$, with no association seen in LCL or adipose tissue), where the atopic dermatitis risk allele (A) increases the expression. The posterior probability of the atopic dermatitis and *CD207* signals colocalizing is 99%. There was no association with *VAX2* expression. *CD207* codes the protein langerin, selectively expressed in Langerhan cells of the epidermis. Langerin is involved in the uptake and processing of antigens in these specialised dendritic cells. A role for *CD207* in initiating the allergic response in atopic dermatitis has been posited before[106], but this is the first time that a genetic role in dendritic cell function has been seen.

2p16.1. rs4643526. *PUS10* –intron. Novel.

The credible set contains 24 variants, spans 148kb and includes *LINC01185(FLJ16341), REL* and *PUS10*. The variant from the set with the best regulomeDB score is the top SNP (rs4643526). This variants is an eQTL for *AHSA2* (~200kb away) in monocytes[107]. *AHSA2* acts as a co-chaperone of Hsp90 in activating ATPase activity. Three other variants (rs6545835, rs10208155 and rs12713428) in the credible set that cluster in the first intron of *REL* have chromatin marks indicative of active or weak promoter in B-LCLs and for one (rs654835), marks indicative of a strong enhancer in epidermal keratinocytes and a weak enhancer in mammary epithelial cells. These three variants also disrupted the affinity of several binding motifs. Of interest is the HIF1 motif, whose binding affinity is greatly reduced by the atopic dermatitis risk allele at rs6545835. This is a hypoxia-induced TF involved in oxygen homeostasis that is thought to have an important role in the hypoxic environment of the epidermis (due to atmospheric oxygen uptake)[108]. Many HIF-1α target genes are important in skin physiology and HIF1a has been found to be upregulated in psoriasis, indicating that *REL* could be the atopic dermatitis causal gene in this region. REL is a component of the NF-KB complex, a transcription factor with a key role in regulating the immune response. No credible SNPs were eQTLs in the MuTHER data (*AHSA2* is not included in the MuTHER data, but *REL* is). There is some evidence that *REL* expression is higher in lesional versus non-lesional atopic dermatitis patient skin (p=0.029)[92]. Genetic variants in this region have also been found to be associated with several other immune-mediated disease, such as IBD[93],

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psoriasis[109] and rheumatoid arthritis[110]. *REL* codes the proto-oncogene c-Rel protein. This is a member of the NF-κB family of transcription factors and has an important role in B-cell survival and proliferation. It is expressed in the epidermis and hair follicles in normal mouse embryos with mice lacking both c-Rel and RelA displaying multiple epidermal defects, including this epidermis[111].

2p25.1. rs10199605. 26.5kb 5' *LINC00299*. Novel.

The credible set contains 20 variants, spans 25.4kb just upstream of *LINC00299*. The variant with the best regulomeDB score is rs13419662 (2kb 5' of *LINC00299*). This variant has chromatin marks indicative of a weak enhancer in the H1 cell line and binds several TFs. This variant is not included in the MuTHER data. But two other SNPs from the credible seta showed nominal association with *ASAP2* (*DDEF2*) expression in the MuTHER skin expression data (p=0.022 and p=0.033), with the atopic dermatitis risk alleles associated with decreased expression[91]. This locus has previously been suggestively associated with self-reported allergy[112] and IgE levels[113].

3p21.1. rs7625909/rs11923593. 8.7kb 5' of *SFMBT1*. Novel.

The credible set contains 24 variants, spans 123kb including the *SFMBT1* gene. The variant from the set with the best regulomeDB score is rs2581790. This variant has chromatin marks indicative of a weak enhancer in leukaemia cells, is in open chromatin in several cell types, binds ZNF263 and the atopic dermatitis risk allele (C) affects the affinity of several binding motifs, including decreasing the affinity of the SPI-B (a lymphoid-specific enhancer, involved in B-cell development) motif . This variant is an eQTL for *PPM1M* in lymphoblastoids[114]. *PPM1M*, 817kb away from rs2581790 is thought to be involved in manganese dependent CTD phosphatise activity and has previously been implicated in bipolar disorder[115]. In the MuTHER skin expression data this variant (along with 4 others) is nominally associated with *CACNA1D* expression (p=0.010, but not in LCLs or adipose tissue). In LCLs this variant (along with 4 others) is associated with *GNL3* expression, with the posterior probability of colocalization of the atopic dermatitis and *GNL3* signals estimated to be 93%. Another variant in the credible set (rs7613013) has chromatin marks indicative of a weak promoter in B-LCLs and a weak enhancer in mammary epithelial cells. It is in open chromatin in several cell types and the atopic dermatitis risk allele (G) decreases the affinity of the TATA binding motif. A variant in *SFMBT1* has previously been associated with ulcerative colitis[93]. This association did not replicate.

5p13.2. rs10214237. 4kb 3' of *IL7R*. Novel.

The credible set contains 18 variants, spans 38.5kb, including the *IL7R* gene. One variant in the set (rs6897932) is a missense mutation (T244I) in *IL7R*. This variant has also been associated with multiple sclerosis and type 1 Diabetes. PolyPhen predicts this mutation to be benign. The more common C allele is the risk allele for MS, T1D and AD. It has been shown that this variant disrupts an alternative splice site, thereby affecting the inclusion of exon 6 in the transcript[116]. Transcripts containing exon 6 are membrane-bound, whereas when exon 6 is skipped (as in C-allele carriers), a soluble form of the protein is produced[117]. Therefore, the increase in the soluble form of IL7Ra, affecting IL7 signalling, could be the mechanism by which atopic dermatitis (and the other diseases) are influenced. Consistent with this, *IL7R* expression is higher in lesional versus non-lesional skin of atopic dermatitis patients (p=0.0201)[92]. This locus had previously been associated with several autoimmune diseases, including UC[118]. The IL7 pathway has an important role in B and T cell development[119].

8q21.13. rs6473227. 32kb 5' of *RNU6-1213P*. Novel

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The credible set contains 70 variants, spans 47kb including *RP11-775E10.1* (*ZBTB10* is ~700kb away). The credible set contains no coding variants. The variant most likely to be regulatory amongst this set according to regulomeDB is rs5892724 (12kb 3' of *RP11-941H19.3* and 135kb 5' of *ZBTB10*). This position is in open chromatin in several cell types (including primary Th1 and Th2 T-cells and mammary epithelial cells), binds STAT3 (a transcription activator known to mediate cellular response to interleukins)[120,121] and the atopic dermatitis risk allele (G insertion) increases the affinity of glucocorticoid receptor biding motifs (a known regulator of other TFs, such as NF-kB and STAT, that modulates immune response through suppression of chemokine and cytokine production). This locus was previously found to be associated with AD, but was not replicated[95]. Hinds et al found this locus to be associated with self-reported allergy[112] and Ferreira et al found this locus to be associated with a combined asthma and hay fever phenotype[122]. The top hit in the Ferreira analysis was rs7009110, which was part of our credible set. They note in that paper that ZBTB10 is a putative repressor of the Sp1 transcription factor (which regulates multiple immune-related genes) and so this gene represents the current best causal candidate in this region. The region containing the credible set lies on the other side of a recombination peak (60cM/Mb) from *ZBTB10*. However, it is possible that this region contains an enhancer that acts on the *ZBTB10* gene. *ZBTB10* is not included in the MuTHER eQTL analysis. However, eight variants from the credible set are nominally associated with *ZNF704* expression (p~0.045) in the MuTHER skin expression analysis*. ZNF704* showed lower expression in lesional versus non-lesional skin of atopic dermatitis patients[92]. In Cole et al. *ZBTB10* or *ZNF704* showed no differences, but *RPSAP47* showed increased expression in uninvolved skin from atopic dermatitis patients versus skin from controls ($p=3x10^{-6}$)[123].

10p15.1. rs6602364. 14kb 3' of *IL2RA*. Novel.

NB - There is evidence for multiple signals at this locus and therefore the credible set approach may not be suitable.

The credible set contains 7 variants, spans 85kb which encompasses *IL2RA*. 1. One variant (rs1570538) is within the 3'-UTR region of the gene and affects the affinity of several binding motifs (including glucocorticoid receptor, known to up-regulate the expression of anti-inflammatory proteins). According to regulomeDB the variant in the set most likely to affect gene regulation is rs10795733. This variant is in a location with chromatin marks indicative of a weak enhancer in leukemia cells, it is in a region of open chromatin in chorion cells, binds GATA1 and affects the affinity of several binding motifs. In the MuTHER skin expression data the atopic dermatitis risk allele (T) at this SNP is nominally associated with an increase in *IL15RA* expression (p=0.022), whereas this SNP show no association with *IL2RA* expression. There is a recombination peak (55cM/Mb) between the credible set and *IL15RA*, but this expression data could indicate that an enhancer is acting across the recombination peak and potentially implicates *IL15RA* (rather than the closer *IL2RA*) as the causal gene*. IL15RA* expression is increased in lesional versus non-lesional skin in atopic dermatitis patients (p=0.012)[92], but no difference was seen for *IL2RA*. Hinds et al. found a suggestive association between this locus and self-reported allergy[112]. This locus has also previously been associated with several autoimmune diseases including rheumatoid arthritis[124] inflammatory bowel disease[93], but the signals look to be independent. IL-15 expression has previously been implicated in AD[125].

11q24.3. rs7127307. 141kb 3' of *ETS1*. Novel

The credible set contains only 1 variant (rs7127307) 141kb 3' of *ETS1*. RegulomeDB gives this variant a score of 5. This location has chromatin marks indicative of a weak enhancer in B-LCLs (ENCODE) and the atopic dermatitis risk allele at this locus affects the affinity of several binding

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proteins, including increasing the affinity of foxp3, known to play a role in the differentiation of T-cells into induced regulatory T-cells. The closest gene to rs7127307 is *ETS1*, a transcription factor with a wide range of immune functions including Th17 and B-cell differentiation. Hinds et al. previously reported an association between this locus and self-reported allergy[112]. This locus has also previously been associated with systemic lupus erythematosus and suggestively associated with rheumatoid arthritis[126]. In the SLE study, they report that the SLE risk allele (rs1128334) was associated with a significantly lower expression of *ETS1*. This SNP is not associated in our atopic dermatitis analysis p=0.296). In the MuTHER data there is no evidence for an association with either of these SNP and expression of any transcript in the region (in LCL, adipose or skin). Ets-1 deficient mice have been shown to have altered B cell differentiation and evidence of autoimmune disease[127,128] and ETS1 appears to be additionally involved in keratinocyte differentiation and formation of the cornified envelope[129]. In addition, a recent study of *ETS1* expression in humans found an almost two-fold increase in uninvolved skin from atopic dermatitis patients versus skin from controls ($p=4x10^{-10}$)[123].

14q13.2. rs2038255/rs2143950. *PPP2R3C* – intronic. Novel.

The credible set contains 47 variants and spans 148kb, including *FAM177A1, PPP2R3C* and *KIAA0391*. The credible set includes two variants with chromatin marks indicative of active promoters (in B-LCLs, mammary epithelial cells, epidermal keratinocytes and lung fibroblasts amongst others) within genes *PPP2R3C* (rs28365850) and *KIAA0391* (rs941653). rs28365850 is a synonymous coding variant and rs941653 is in the 5'UTR. Both are in open chromatin in a range of relevant cell types (such as B-LCLs, primary Th1 T-cells, adult dermal fibroblasts and abdominal skin fibroblasts). Both are protein binding sites for a range of transcription factors. rs28365850 in particular affects the affinity of the Sp1 binding motif. Sp1 is a TF known to be involved in a variety of processes including immune response (via the JAK-STAT pathway). rs28365850 is not included in the MuTHER expression data, but rs941653 (and 8 other variants in the credible set) shows association with expression on *KIAA0391* ($p=4x10^{-12}$) in skin, with the atopic dermatitis risk allele (G) associated with increased expression. The posterior probability for the colocalization of the atopic dermatitis and *KIAA0391* signals is >99%. A Mouse knockout for *PPP2R3C* shows abnormal C cell activation[130]. This locus has previously been associated with psoriasis with the same direction of effect[131].

17q21.2. rs12951971/rs17881320. *STAT3* – intronic. Novel.

The credible set contains 15 variants, spans 230kb and includes genes *GHDC, STAT5A, STAT5B* and *STAT3*. No variants are coding. The variants in this set with the best regulomeDB score are rs9912773 and rs4796793 (linkage disequilibrium with lead SNP 0.24 and 0.23, respectively), which are both eQTLs for *MLX* ~200kb away (regulomeDB). *MLX* encodes a TF involved in glucose-responsive gene regulation. There is also nominal evidence of association with STAT3 expression in skin for these variants (Supplementary Table 19). Both variants have chromatin marks indicative of strong enhancers in B-LCLs. Both of these variants (along with 2 other variants from the credible set) are nominally associated with *STAT3* expression in the MuTHER skin data (p~0.01), with the atopic dermatitis risk alleles associated with a decrease in expression. Another variant in the region given a good score in regulomeDB is rs17881320. This variant in an intron of *STAT3* is a strong enhancer in B-LCLs, is in open chromatin in B-LCLs, CD4+ cells and primary Th1T-cells. It binds several TFs including NF-kB and effects the affinity of the ERR-a motif. ERR-a regulates the metabolic pathway critical for effector T-cell differentiation[132]. This variant is not included in the MuTHER data. Though no differences were seen for *STAT3*, the nearby *STAT5B* expression is lower in lesional verses non-lesional skin in atopic dermatitis patients (p=0.048)[92] and in uninvolved atopic skin versus controls (p=0.0023)[123]. STAT3 and STAT5B are part of the JAK-

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STAT pathway that activates target genes in response to cytokine-binding. Rare mutations in *STAT3* cause hyper-IgE recurrent infection syndrome[133]. Interestingly Crohn's disease is associated with excess TH17 activation, whereas deficient TH17 activation owing to mutations in *STAT3* leads to hyper-IgE syndrome. The direction of effect in atopic dermatitis is opposite to what is found in Crohn's disease consistent with this.

MAGENTA gene-set replicated associations

2q37.1 rs1057258. *INPP5D* –within gene. Novel

INPP5D is involved in the cytokine and chemokine mediated signalling pathway that had an FDR=0.002 in the MAGENTA analysis. INPP5D down-regulates cytokine receptor signalling[134]. A variant in high LD with the top hit (rs9247, r2>0.8) is in a region of open chromatin in Th1 cells and immortalised cell lines. Knockout mice of this gene show poor allogenic T cell response[135]

12q15. rs2227483. *IFNG/IL22* – 788bp 5' IL22, 100kb from IFNG. Novel

rs2227483 is located in a cytokine cluster on 12q15, which includes *IL22* and interferon-gamma (*IFNG*). *IFNG* is involved in a number of pathways with FDR<0.05 in the MAGENTA analysis.

14q32.32. rs7146581. *TRAF3* – intronic. Novel

TRAF3 is involved in a number of pathways with FDR<0.05 in the MAGENTA analysis. TRAF3 is a signalling protein which mediates certain innate immune receptor and cytokine receptor signals[136]. *TRAF3* expression is higher in lesional versus nonlesional skin of atopic dermatitis patients (p=0.015)[92], TRAF3 deficient mice show abnormal B- and T-cell morphology[137] and an atopic-like skin disease with increased IgE phenotype in mice has been attributed to the mouse homologue of a TRAF3 interacting protein (TRAFIP3)[138].

17q25.3. rs11657987. 32kb from *SOCS3*. Novel

SOCS3 is involved in the JAK-STAT pathway that had an FDR=0.0001 in the MAGENTA analysis. SOCS3 binds to JAK2 kinase and inhibits STAT3 activity in a negative feedback regulation of cytokine signalling[139]. *SOCS3* showed increased expression in skin from atopic patients compared to that of controls and a haplotype of *SOCS3* SNPs has previously show suggestive evidence of association with AD[140]. In atopic dermatitis patients there is increased *SOCS3* expression in lesional versus non-lesional skin (p=0.00044)[92].

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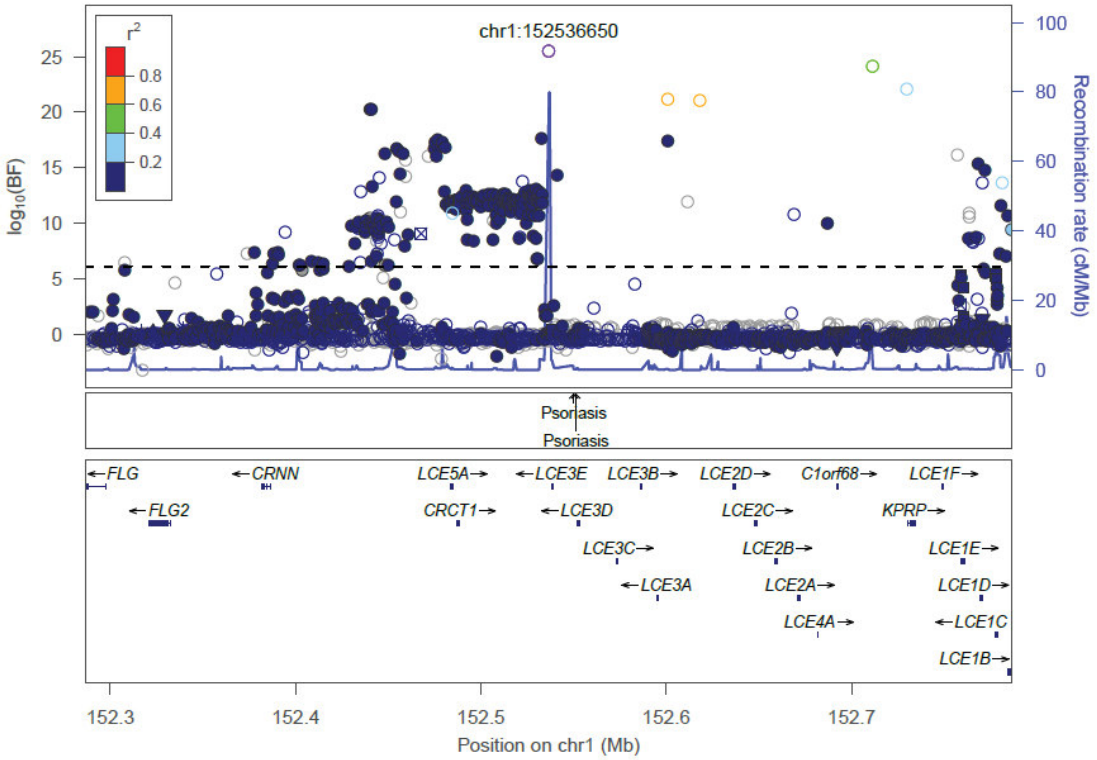
Supplementary Figures

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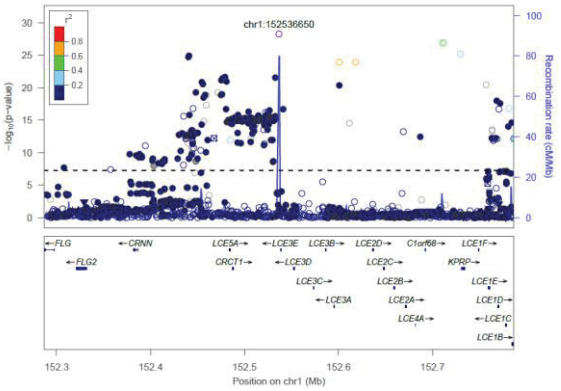
Supplementary Figure 1. Regional association plots for the 27 loci p<5x10-8(a-aa). The MANTRA results for all studies are displayed (i), as well as the ethnic-specific results for European, Japanese, African American and Latino (ii-v respectively).

a. 1q21.3 - rs61813875 (FLG)

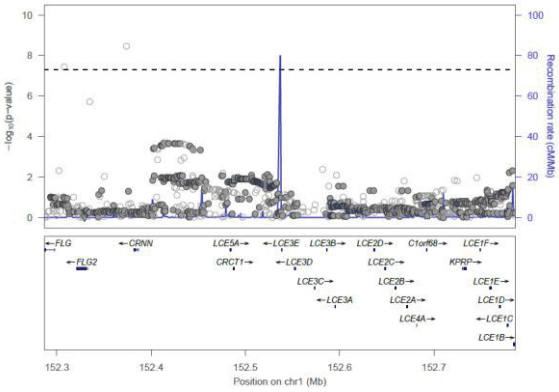
i. All studies (MANTRA)



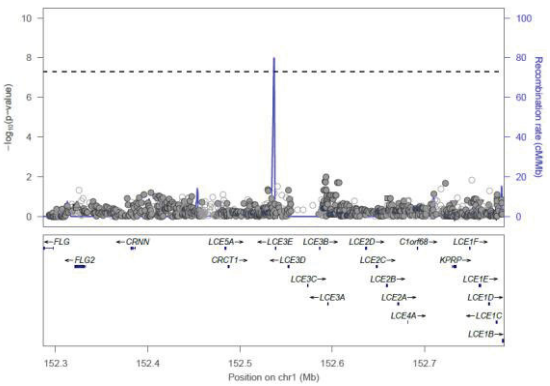
ii. European



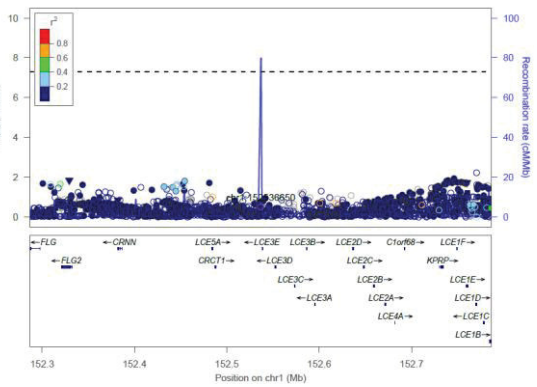
iii. East Asian (RIKEN)



iv. African American (SAPPHIRE)

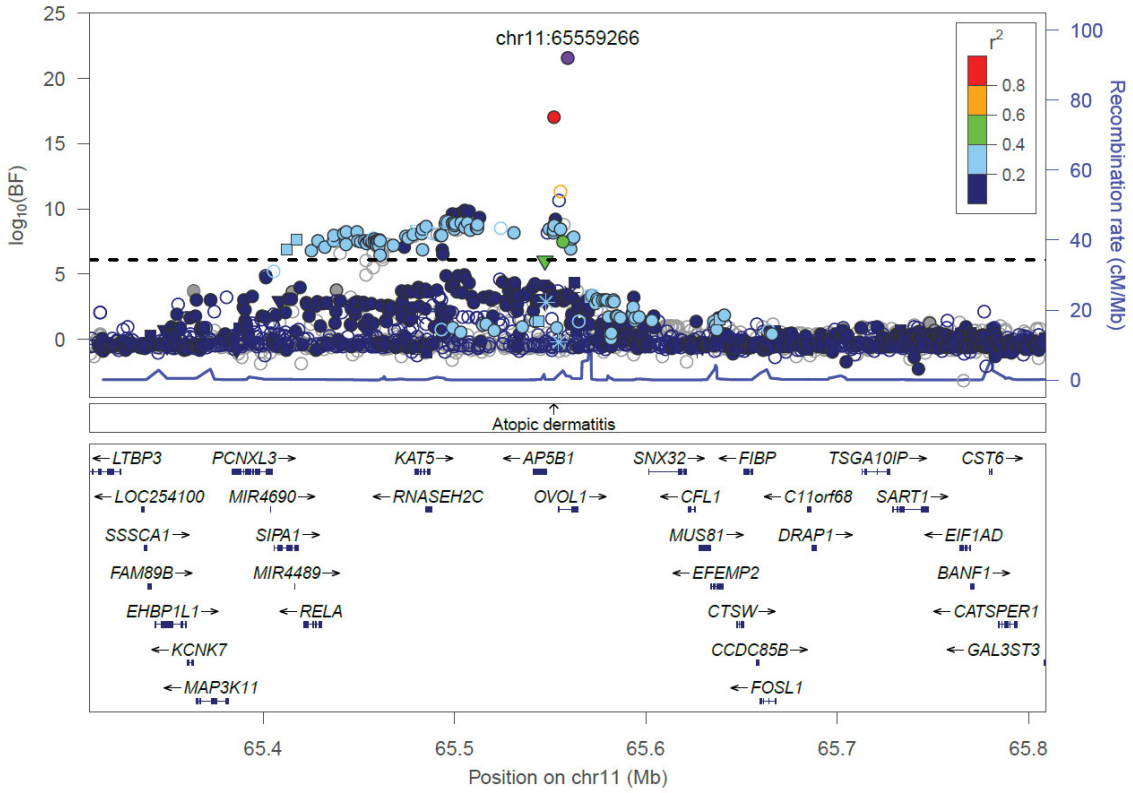


v. Latino (GALA II)

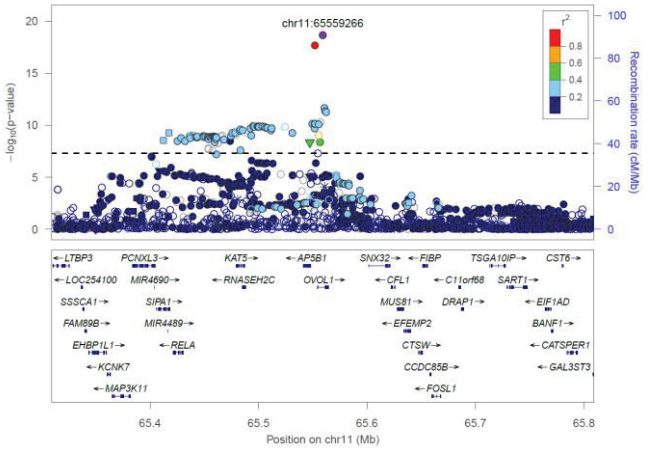


b. 11q13.1 - rs10791824 (OVOL1)

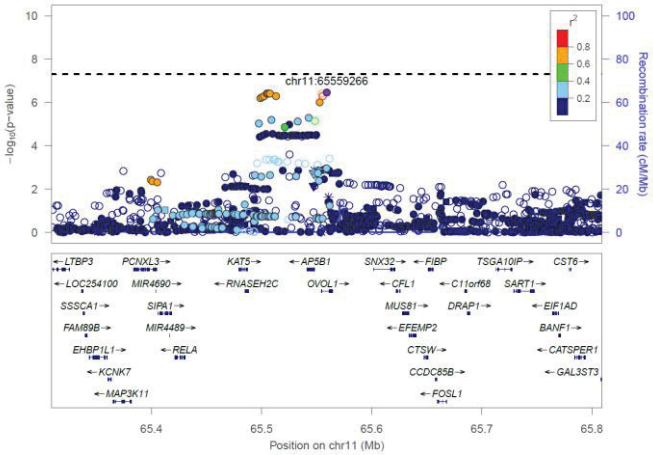
i. All studies (MANTRA)



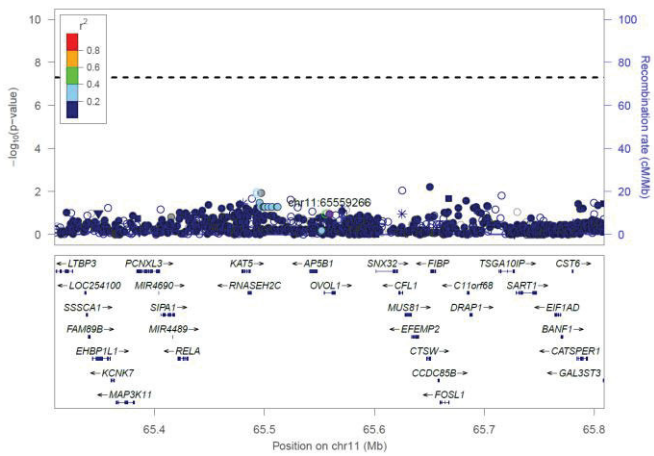
ii. European



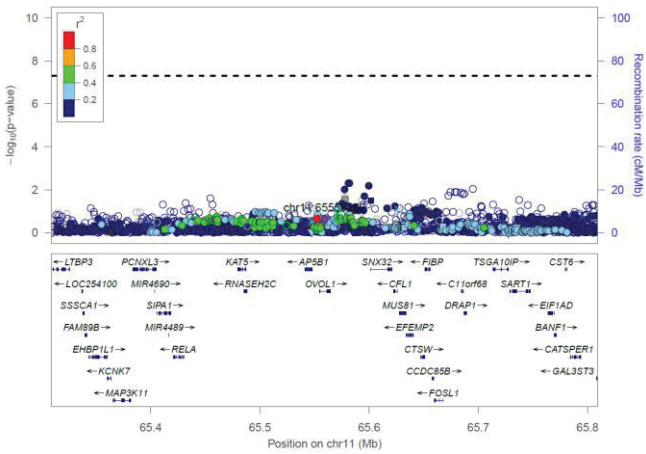
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iv. African American (SAPPHIRE)

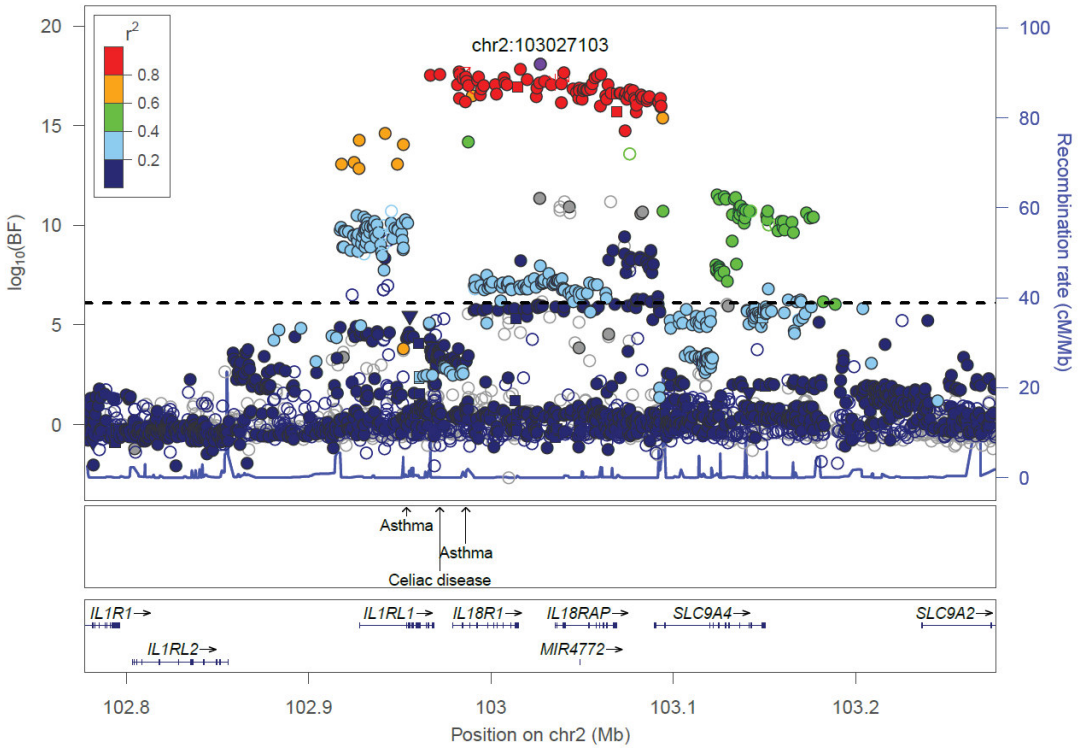


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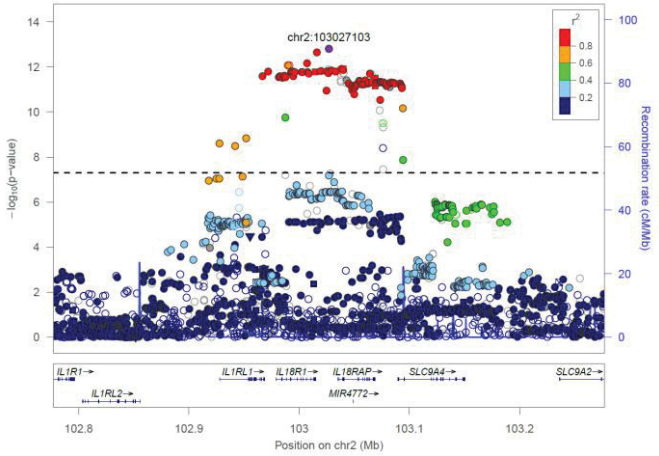


c. 2q12.1 - rs6419573 (IL18RAP)

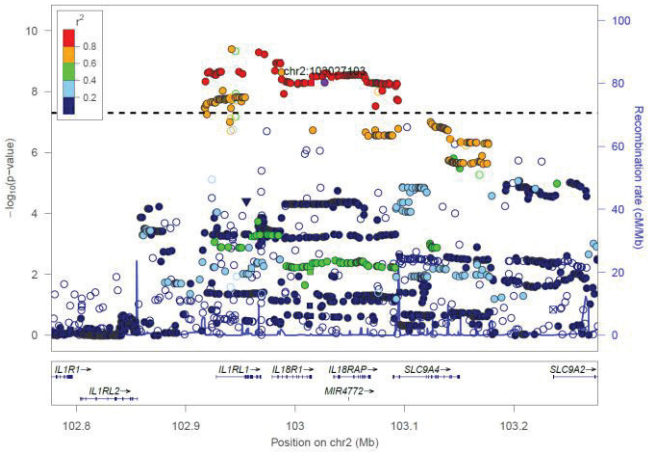
i. All studies (MANTRA)



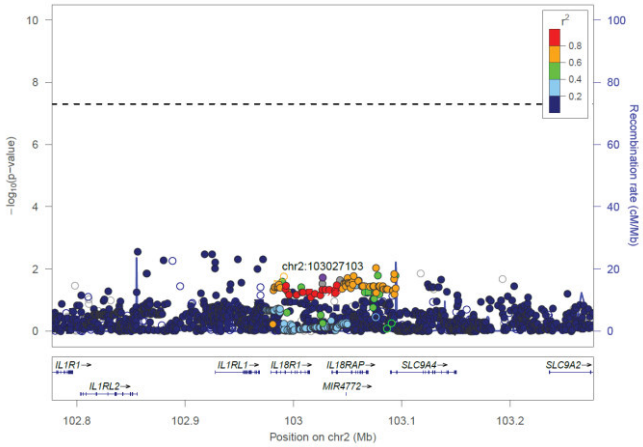
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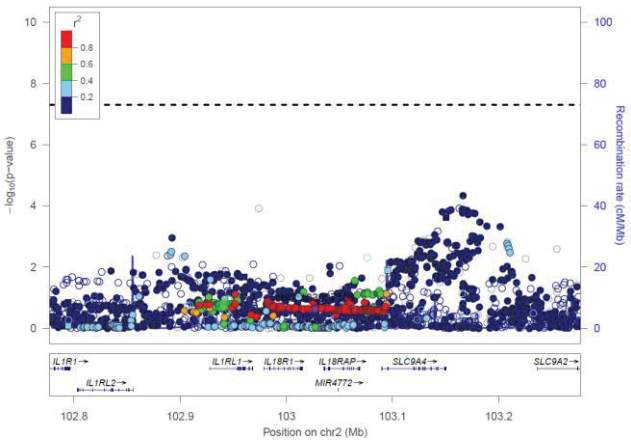
iii. East Asian (RIKEN)



iv. African American (SAPPHIRE)

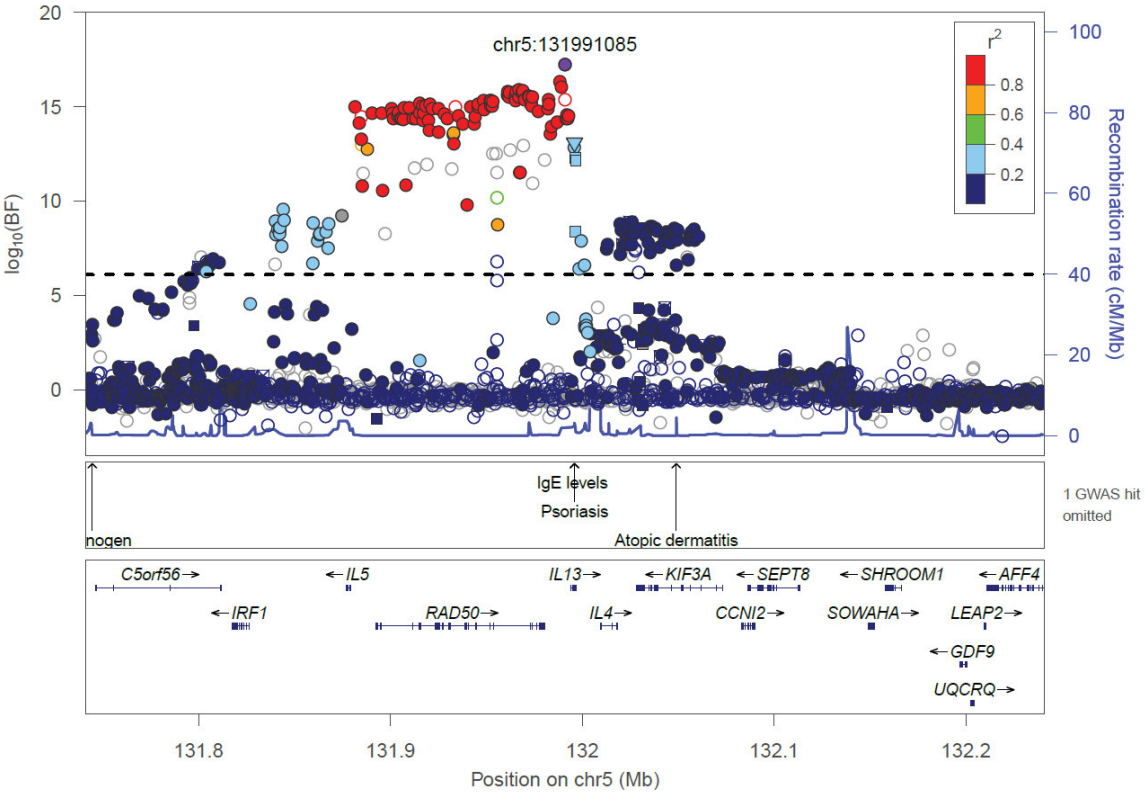


v. Latino (GALA II)

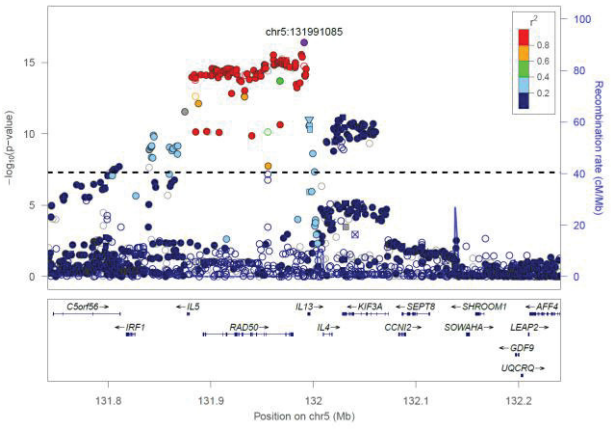


d. 5q31.1 - rs12188917 (IIL13)

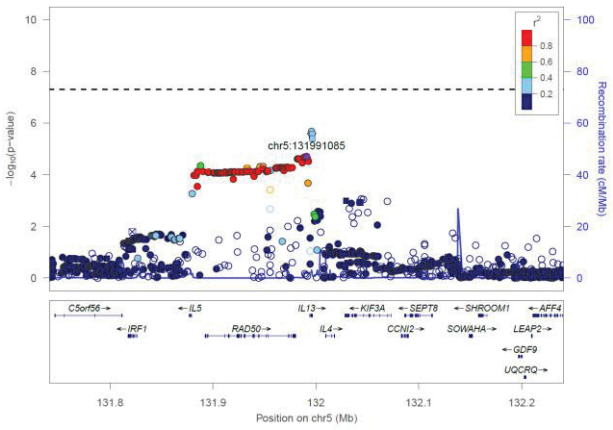
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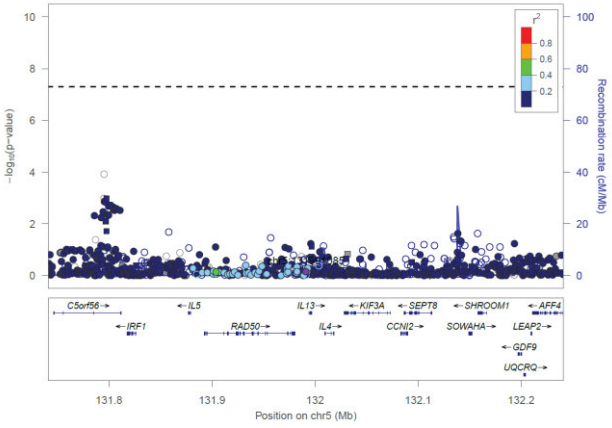
ii. European



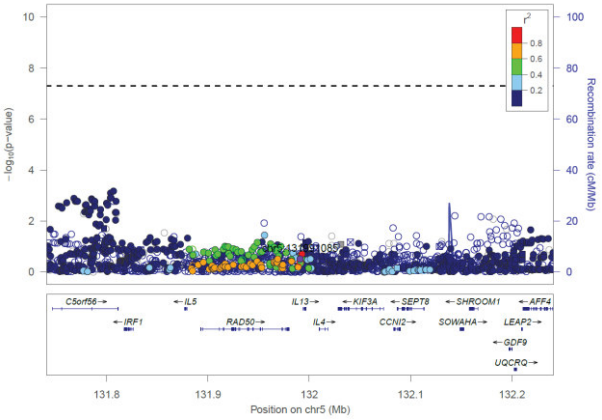
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iv. African American (SAPPHIRE)

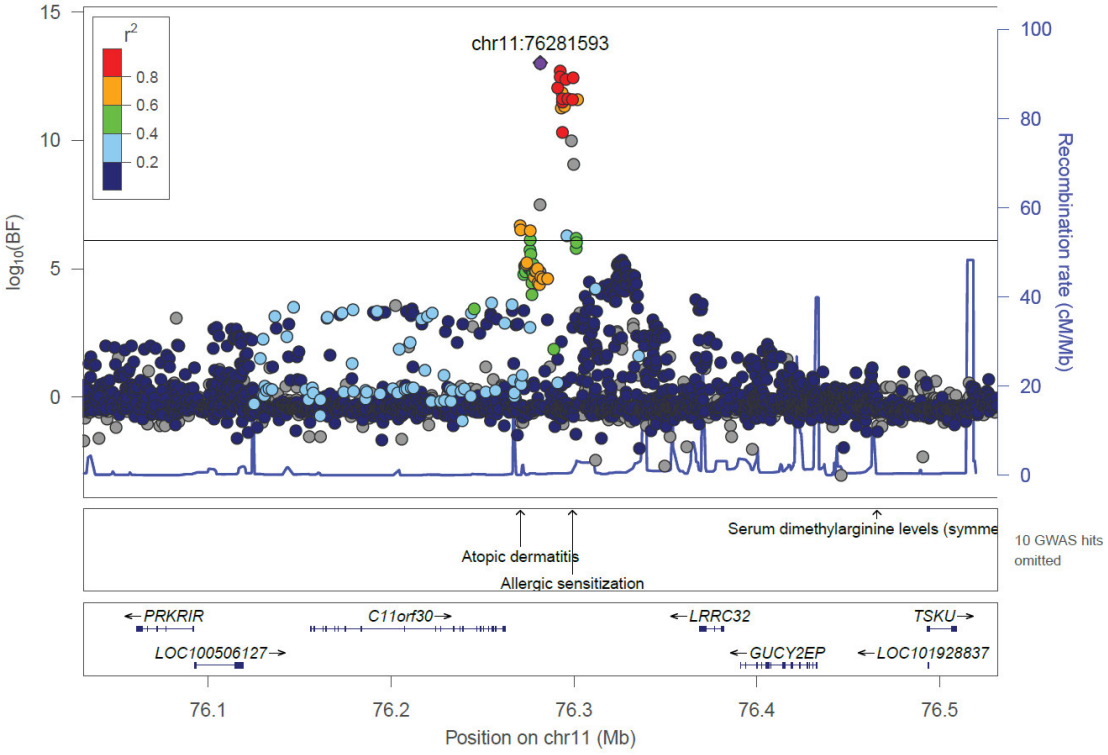


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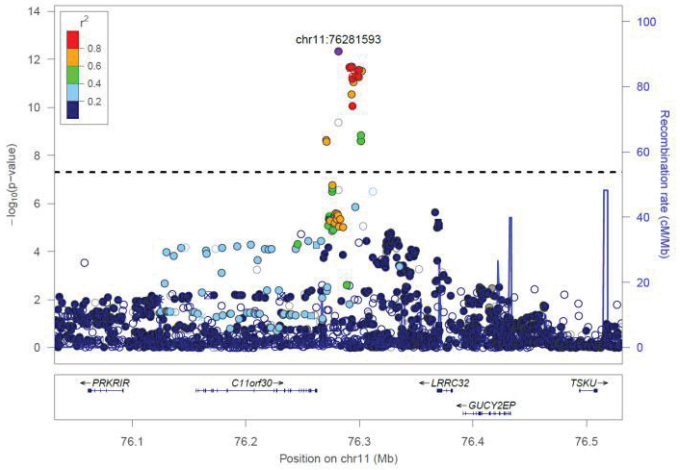


e. 11q13.5 - rs2212434 (C11orf30)

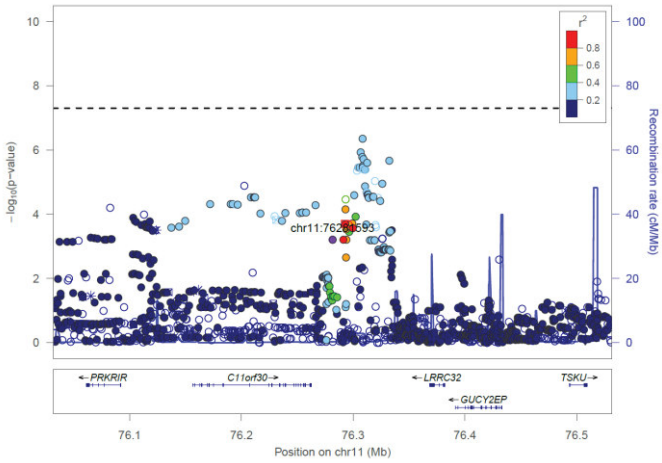
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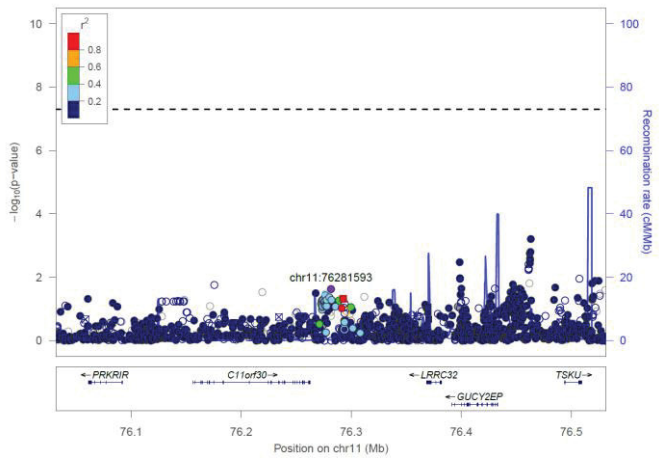
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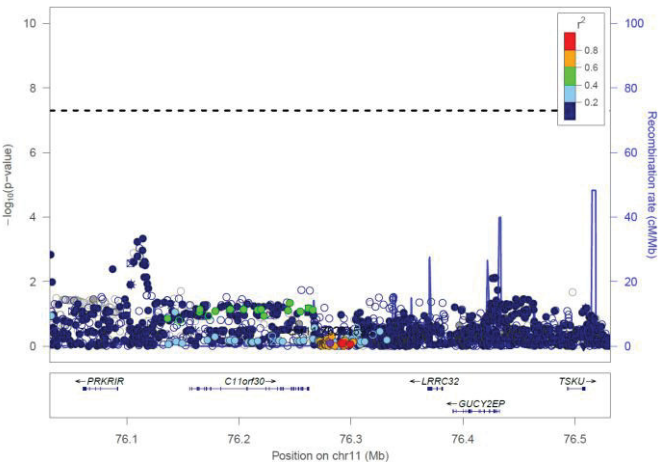
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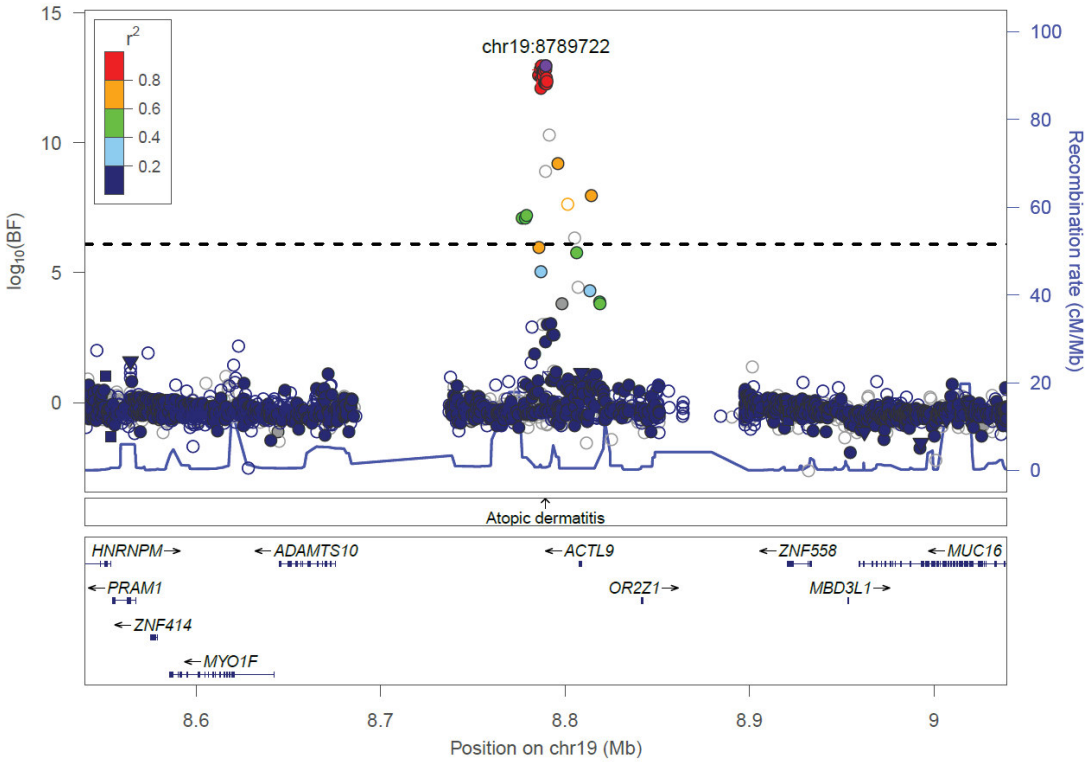


v. Latino (GALA II)

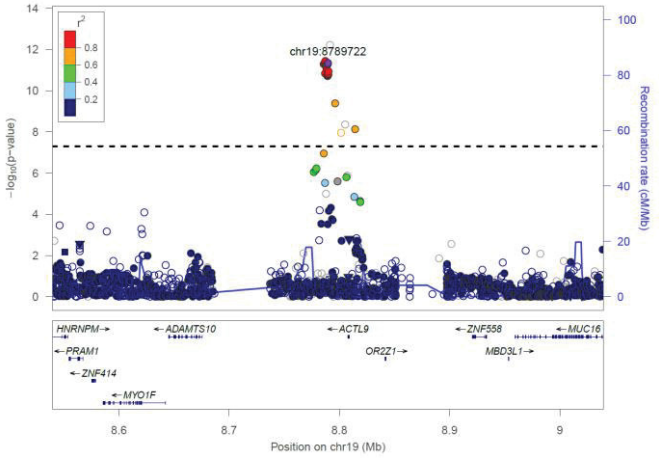


f. 19p13.2 - rs2918307 (ACTL9)

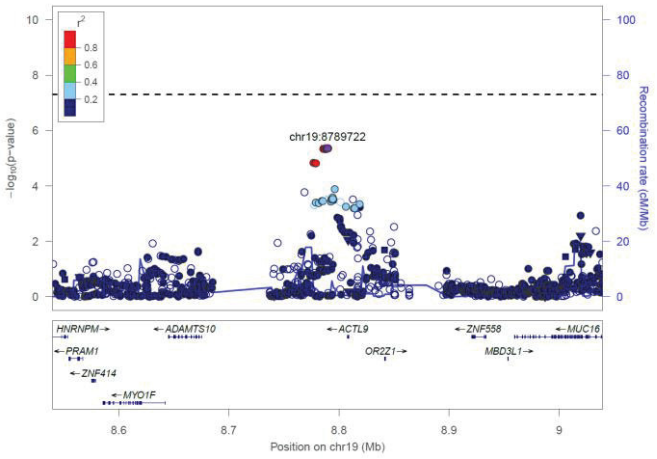
i. All studies (MANTRA)



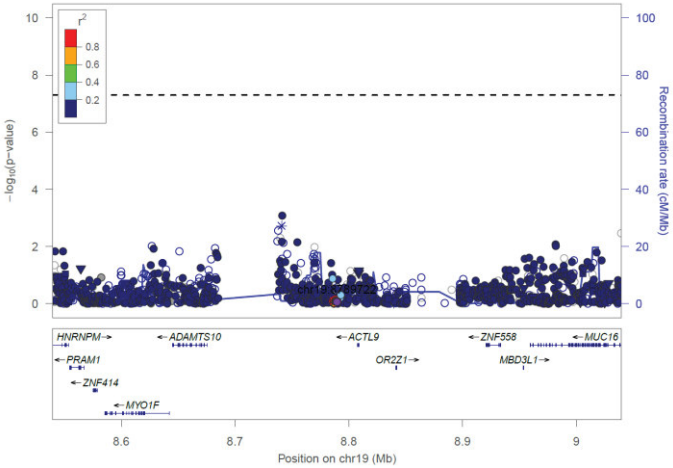
ii. European



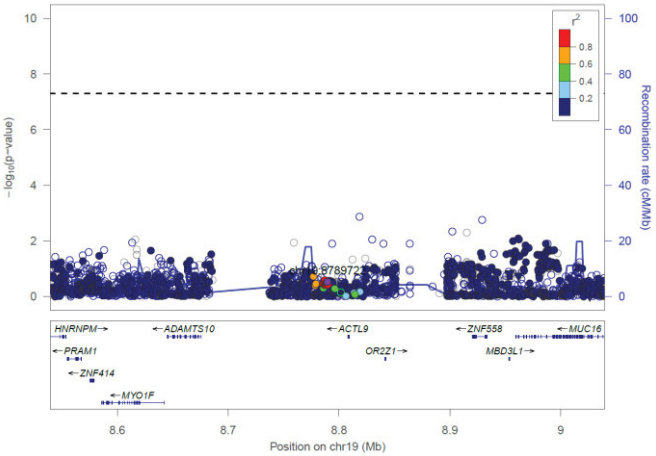
iii. East Asian (RIKEN)



iv. African American (SAPPHIRE)

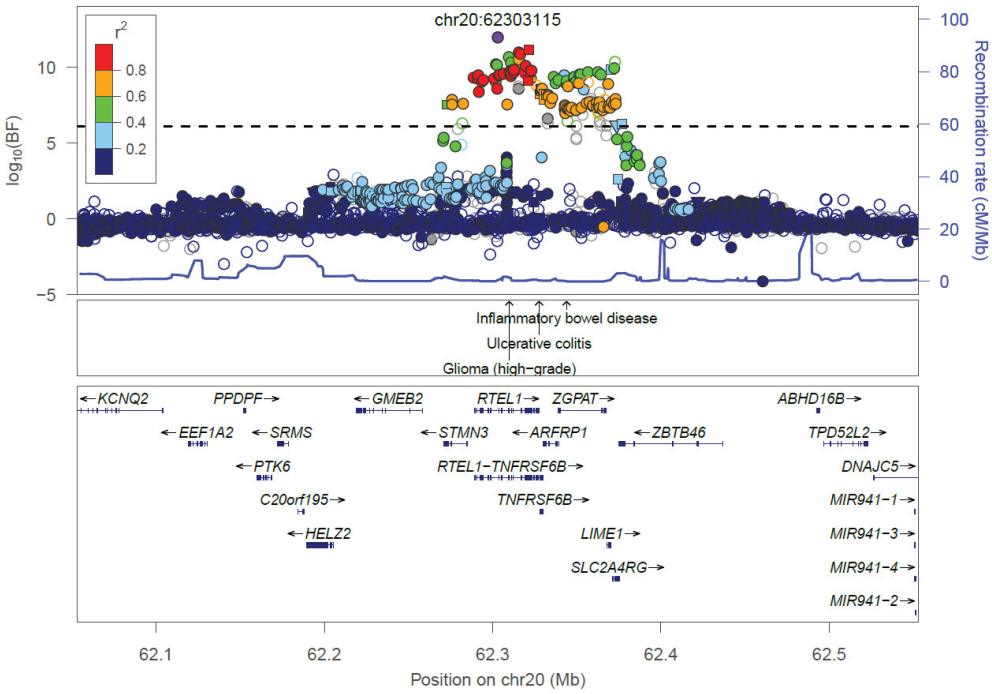


v. Latino (GALA II)

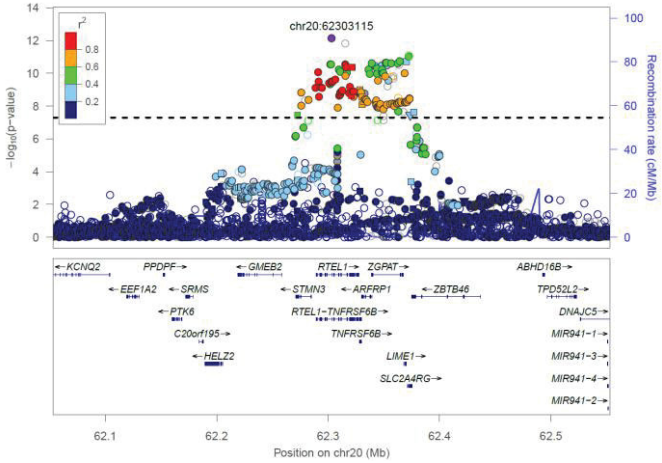


g. 20q13.33 - rs4809219 (RTEL1-TNFRSF6B)

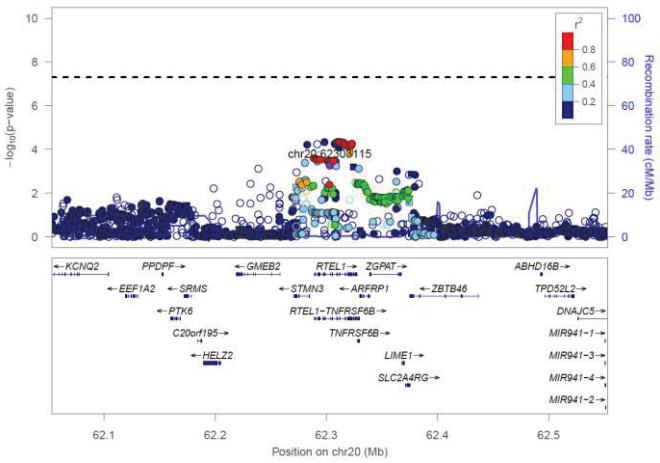
i. All studies (MANTRA)



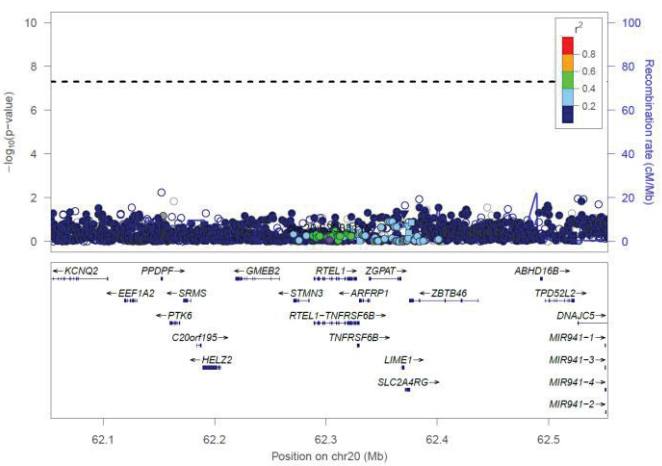
ii. European



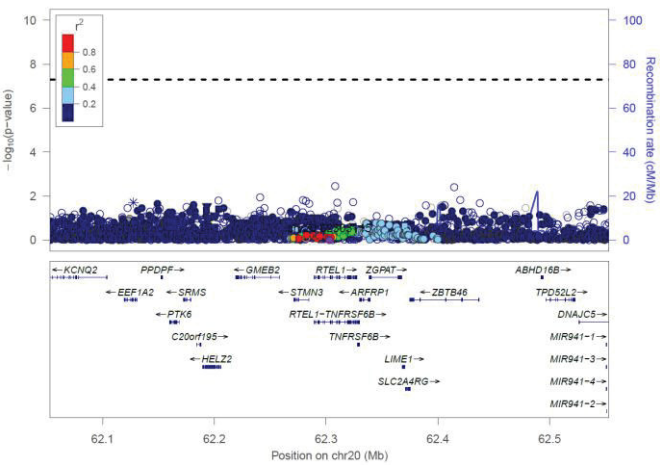
iii. East Asian (RIKEN)



iv. African American (SAPPHIRE)

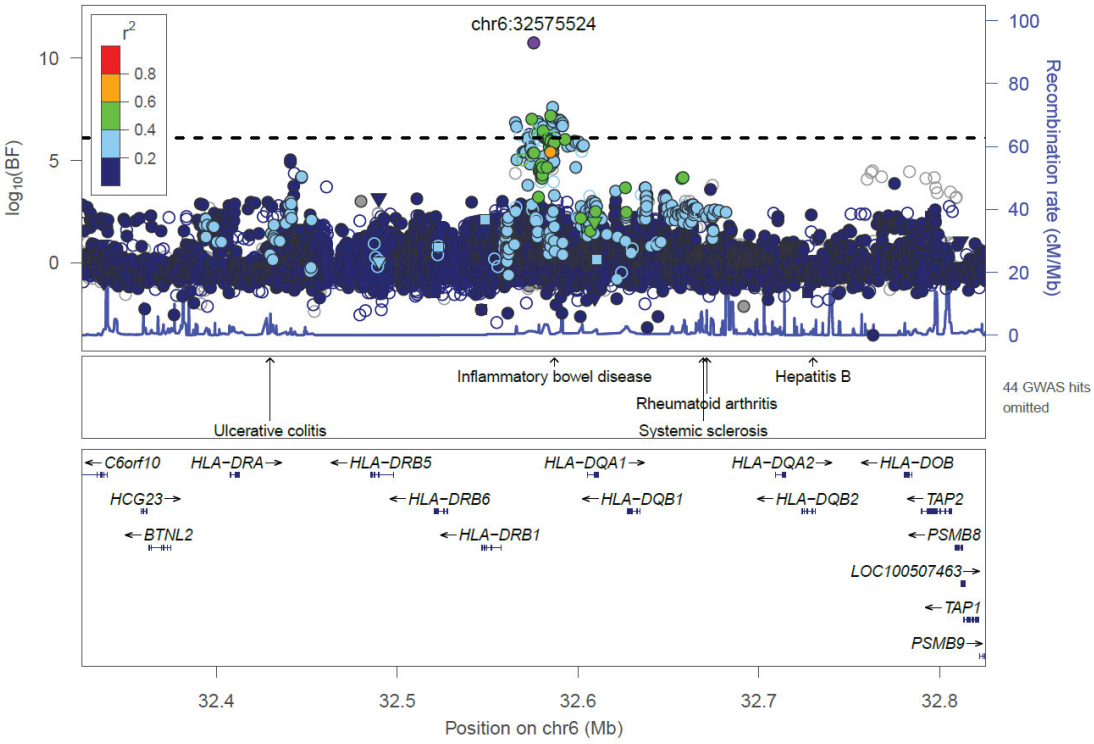


v. Latino (GALA II)

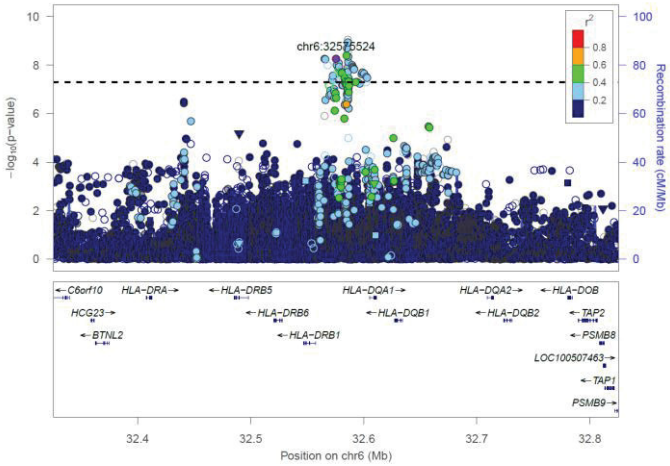


h. 6p21.32 - rs4713555 (HLA-DRB1)

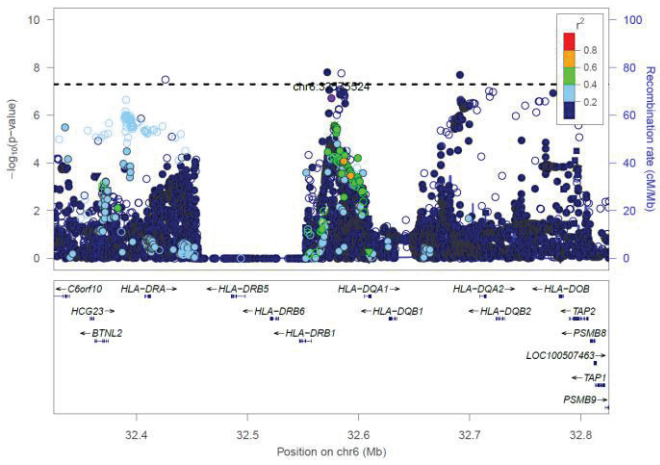
i. All studies (MANTRA)



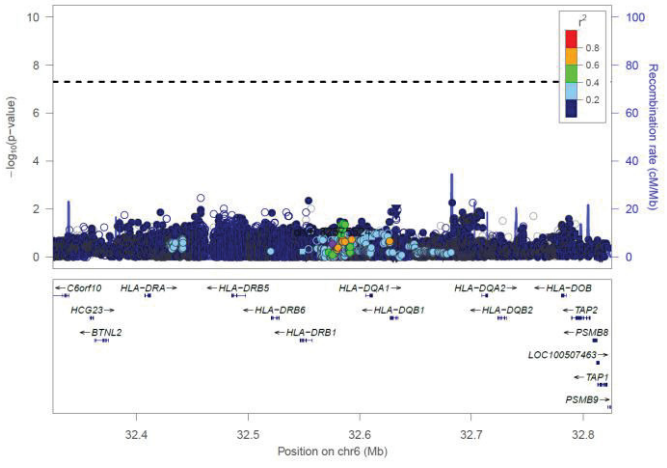
ii. European



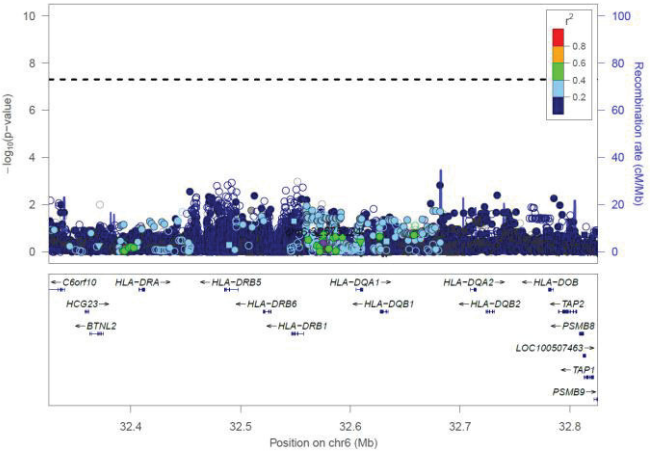
iii. East Asian (RIKEN)



iv. African American (SAPPHIRE)

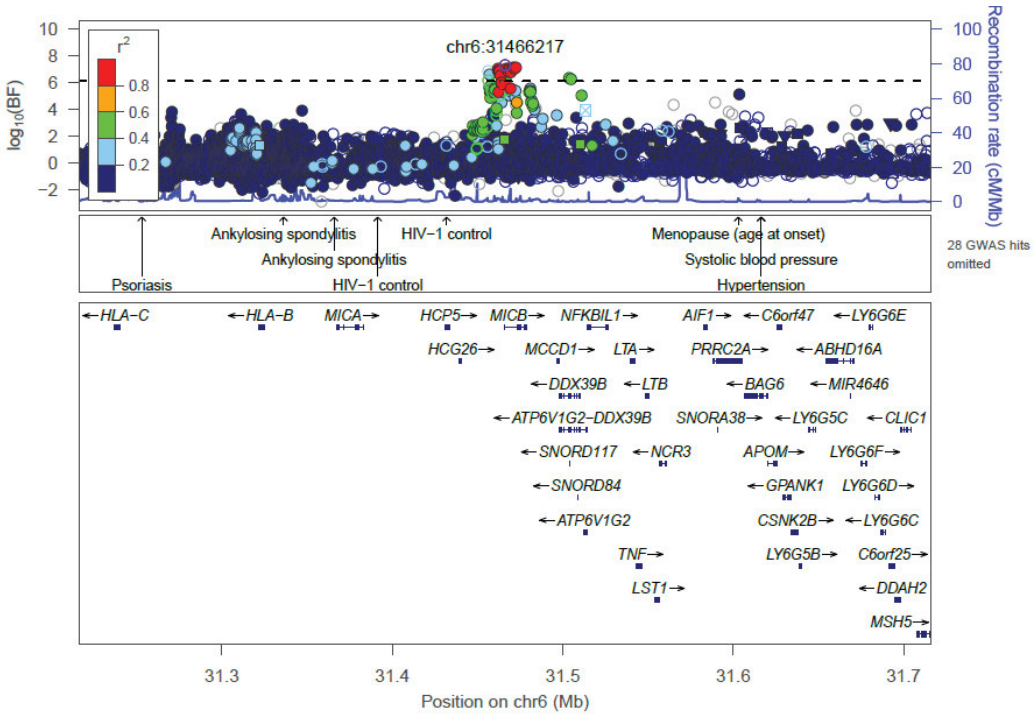


v. Latino (GALA II)

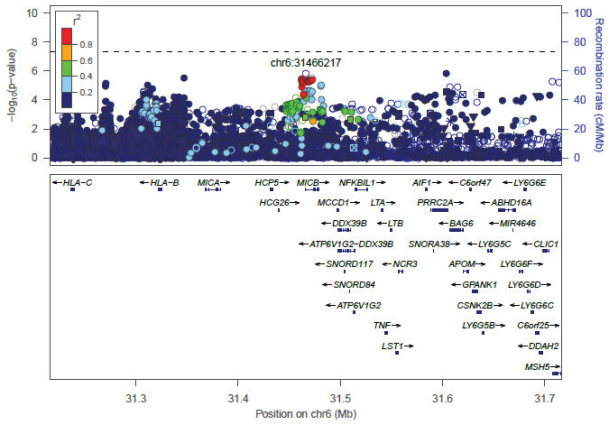


i. 6p21.33 - rs145809981 (MICB)

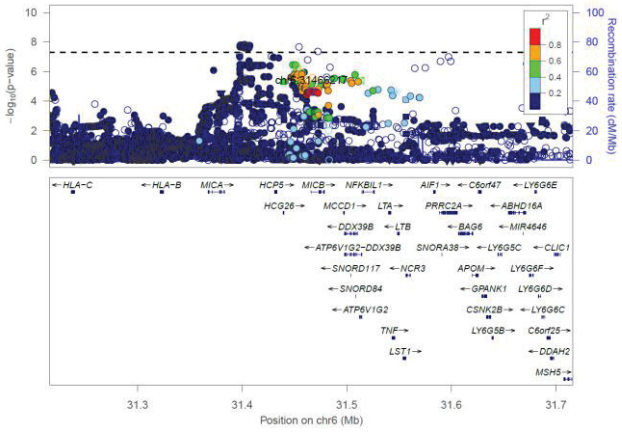
i. All studies (MANTRA)



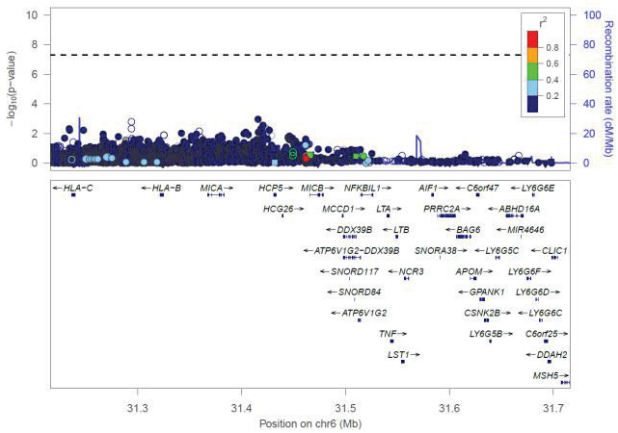
ii. European



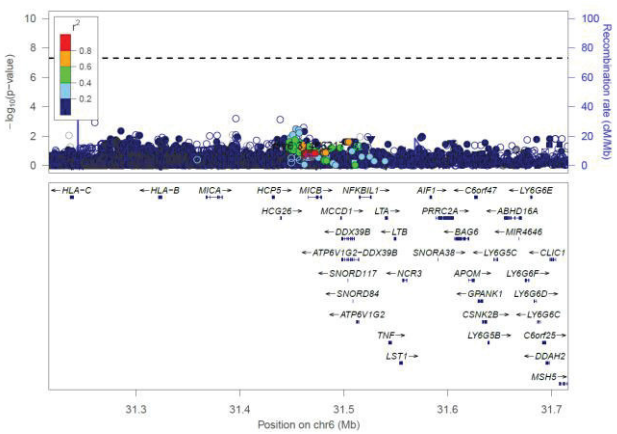
iii. East Asian (RIKEN)



iv. African American (SAPPHIRE)

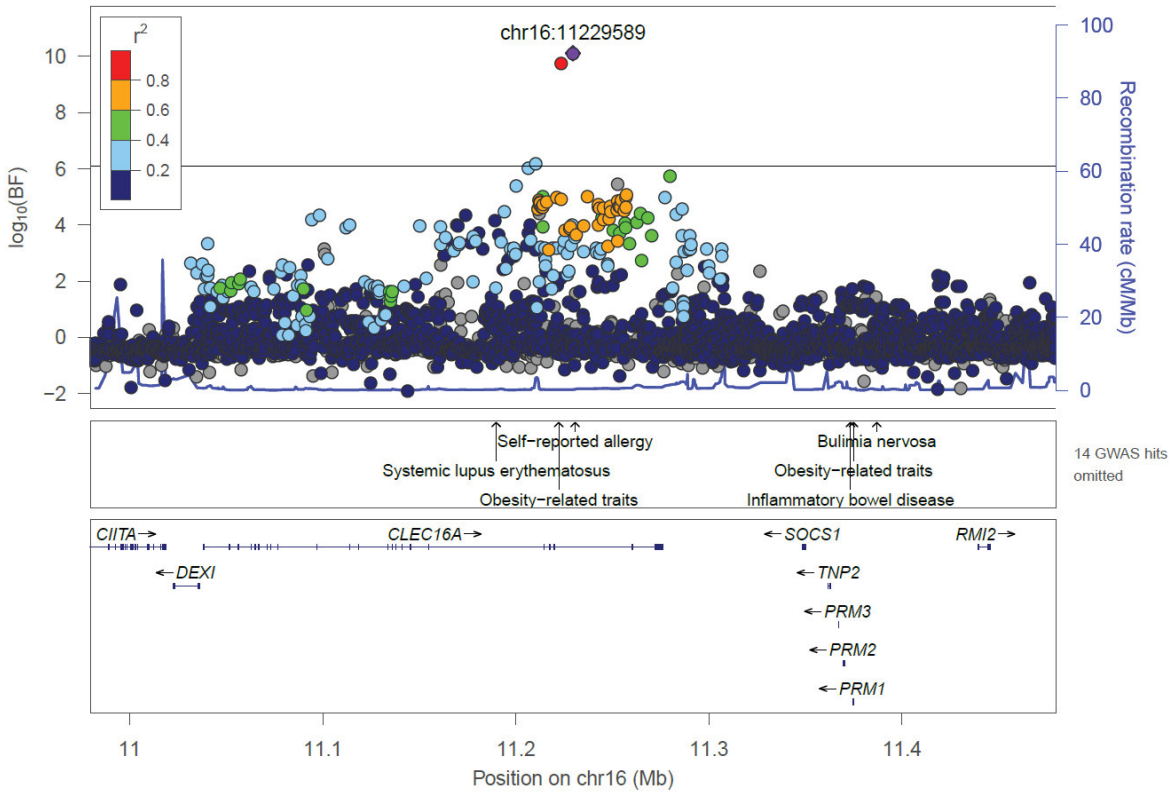


v. Latino (GALA II)

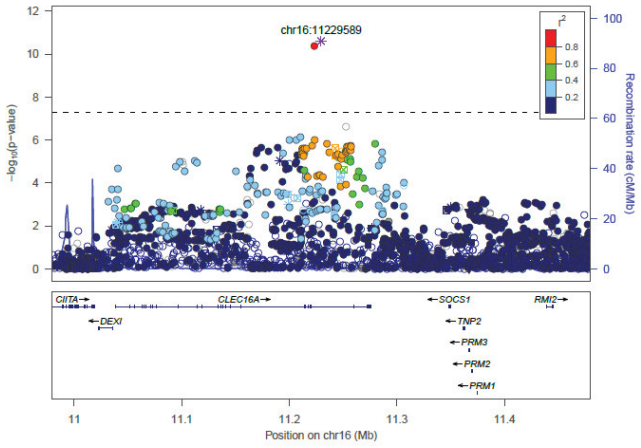


j. 16p13.13 - rs2041733 (CLEC16A)

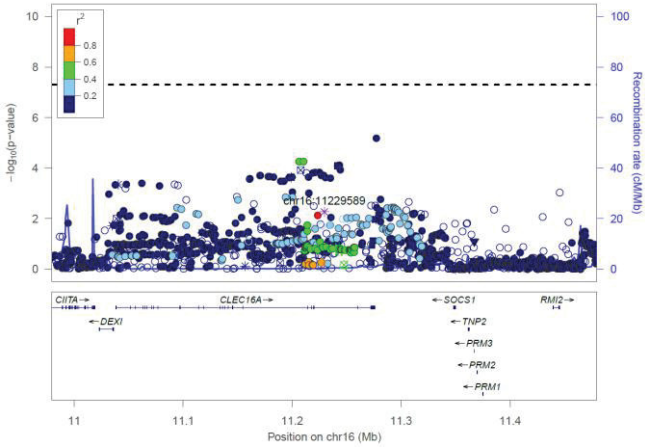
i. All studies (MANTRA)



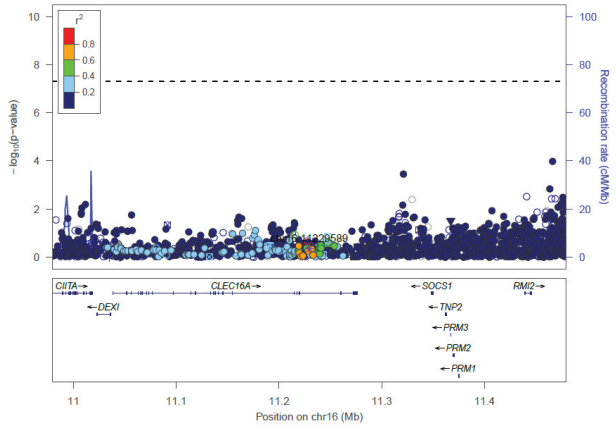
ii. European



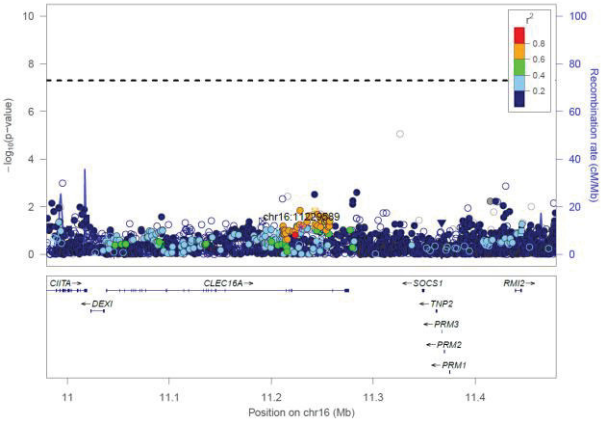
iii. East Asian (RIKEN)



iv. African American (SAPPHIRE)

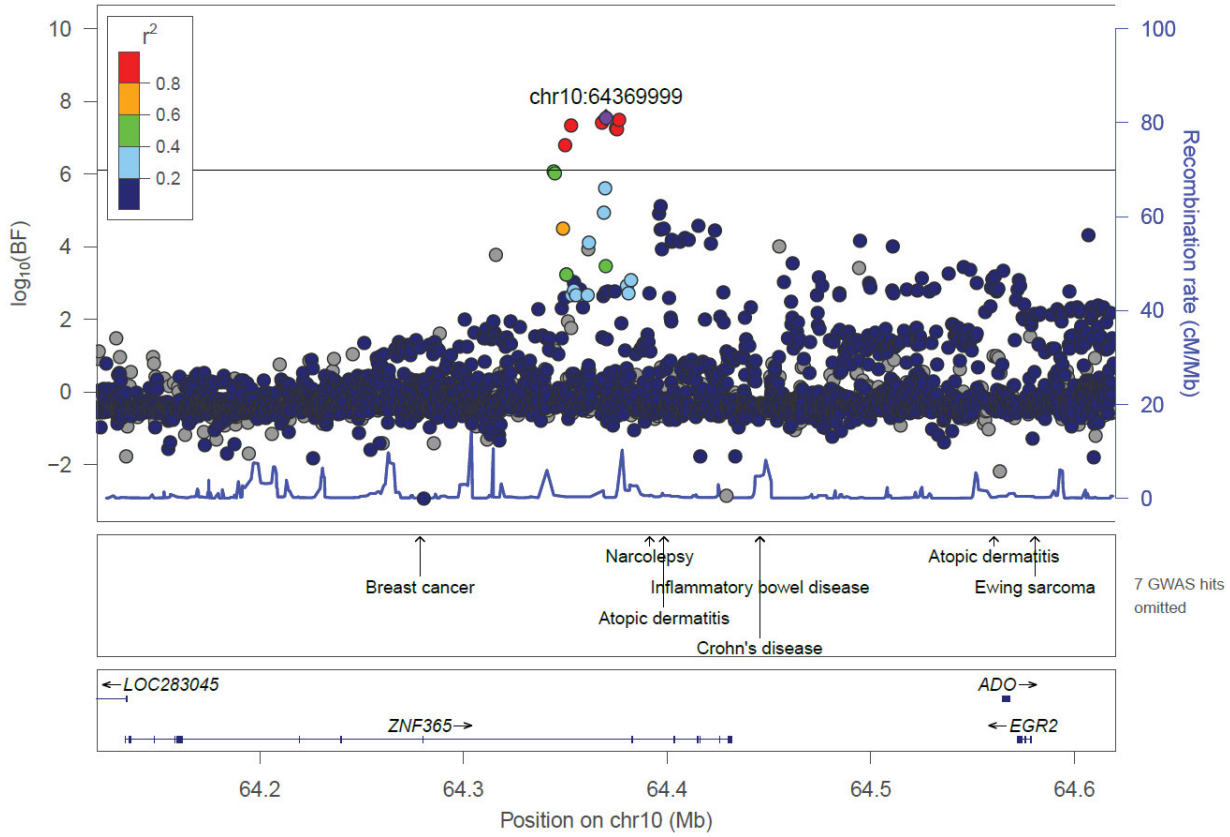


v. Latino (GALA II)

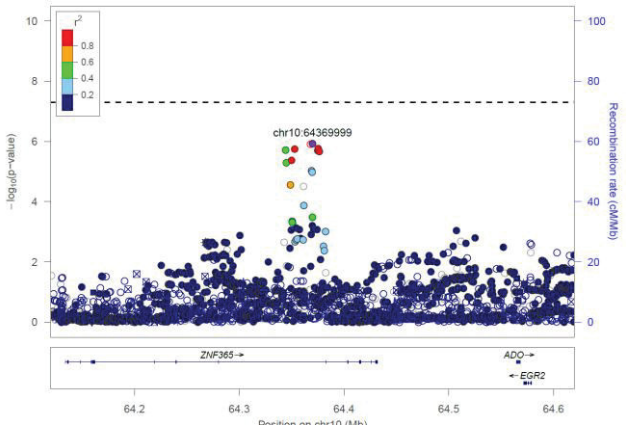


k. 10q21.2 - rs2944542 (ZNF365)

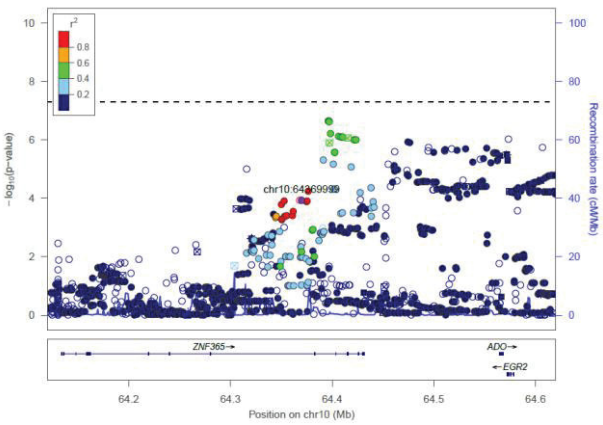
i. All studies (MANTRA)



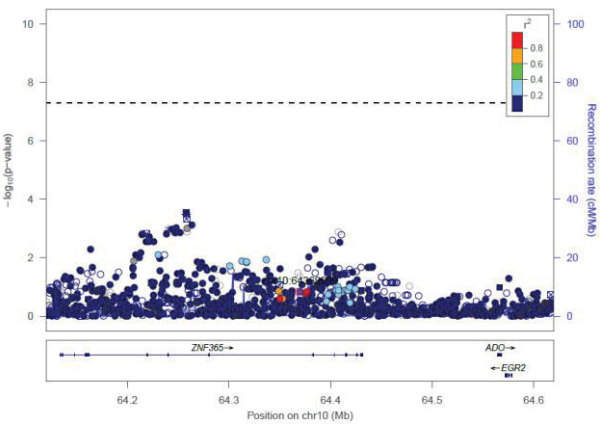
ii. European



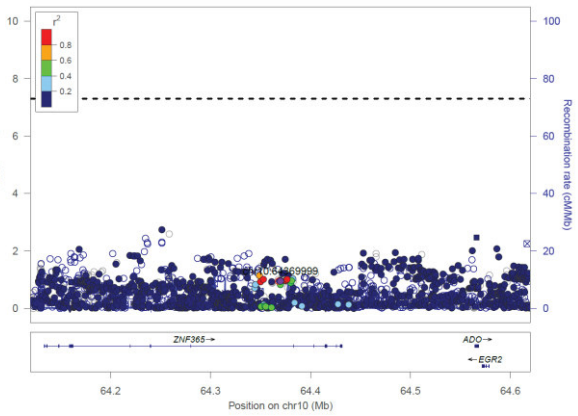
iii. East Asian (RIKEN)



iv. African American (SAPPHIRE)

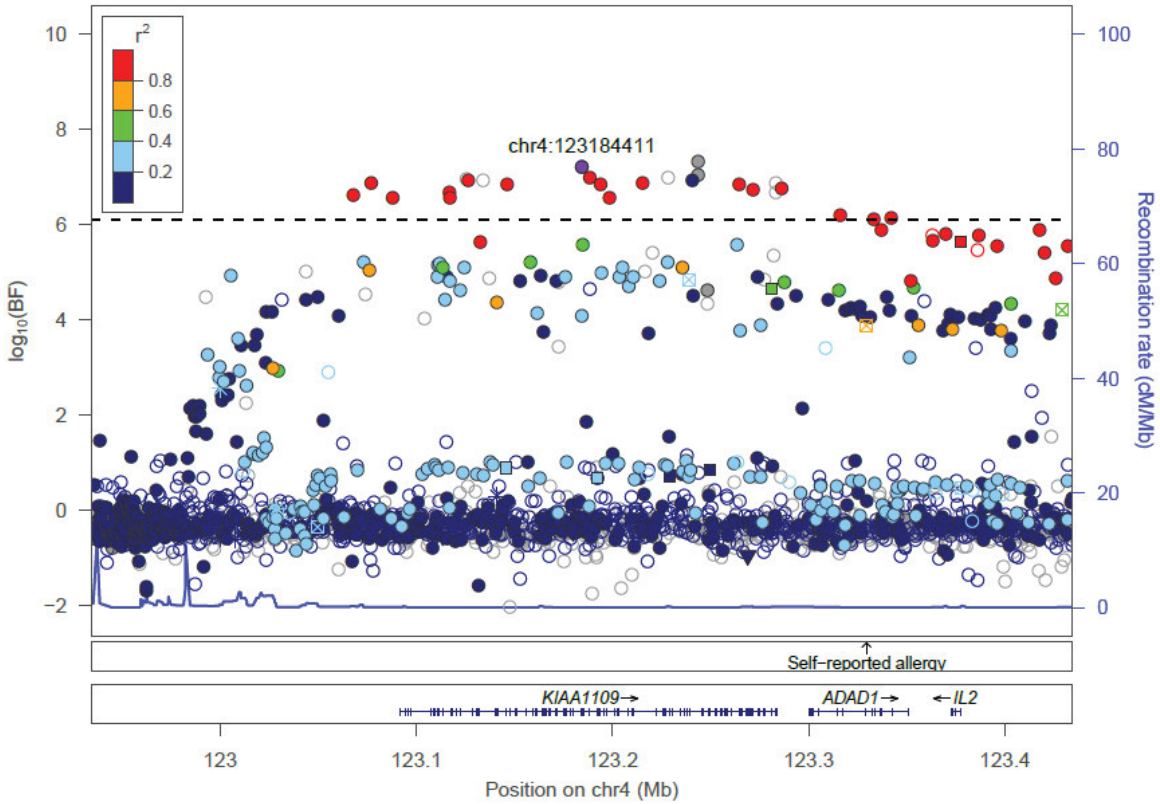


v. Latino (GALA II)

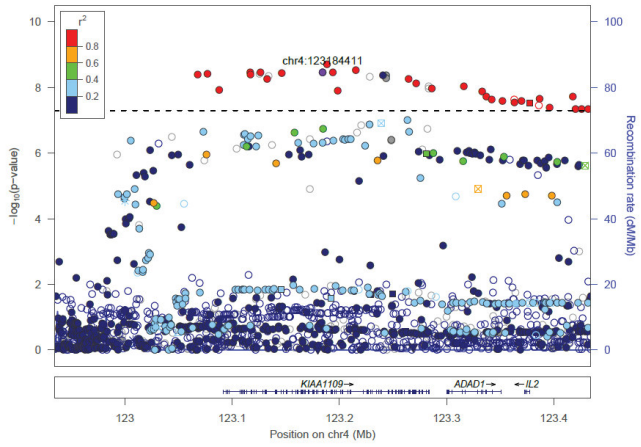


I. 4q27 - rs6827756 (KIAA109)

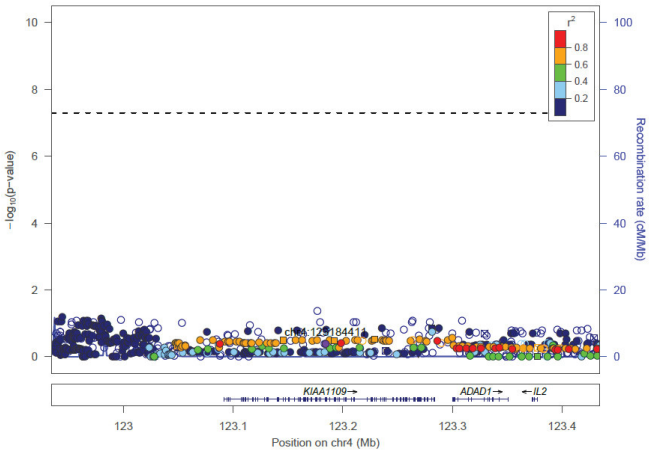
i. All studies (MANTRA)



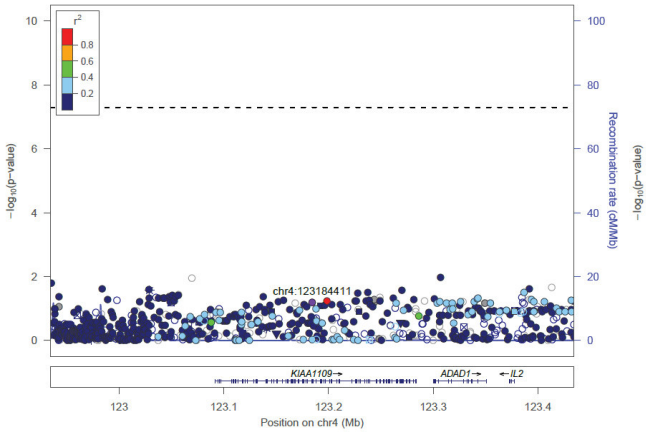
ii. European



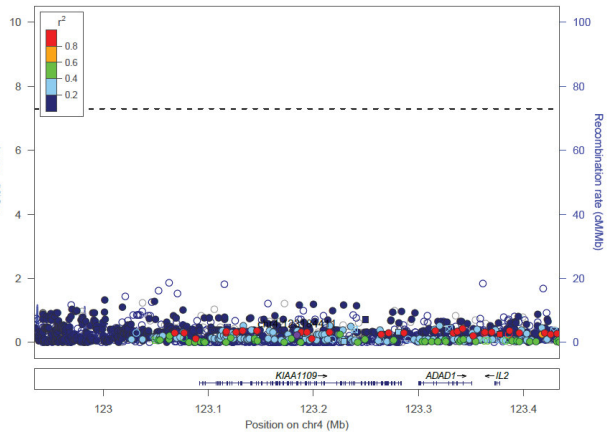
iii. East Asian (RIKEN)



iv. African American (SAPPHIRE)

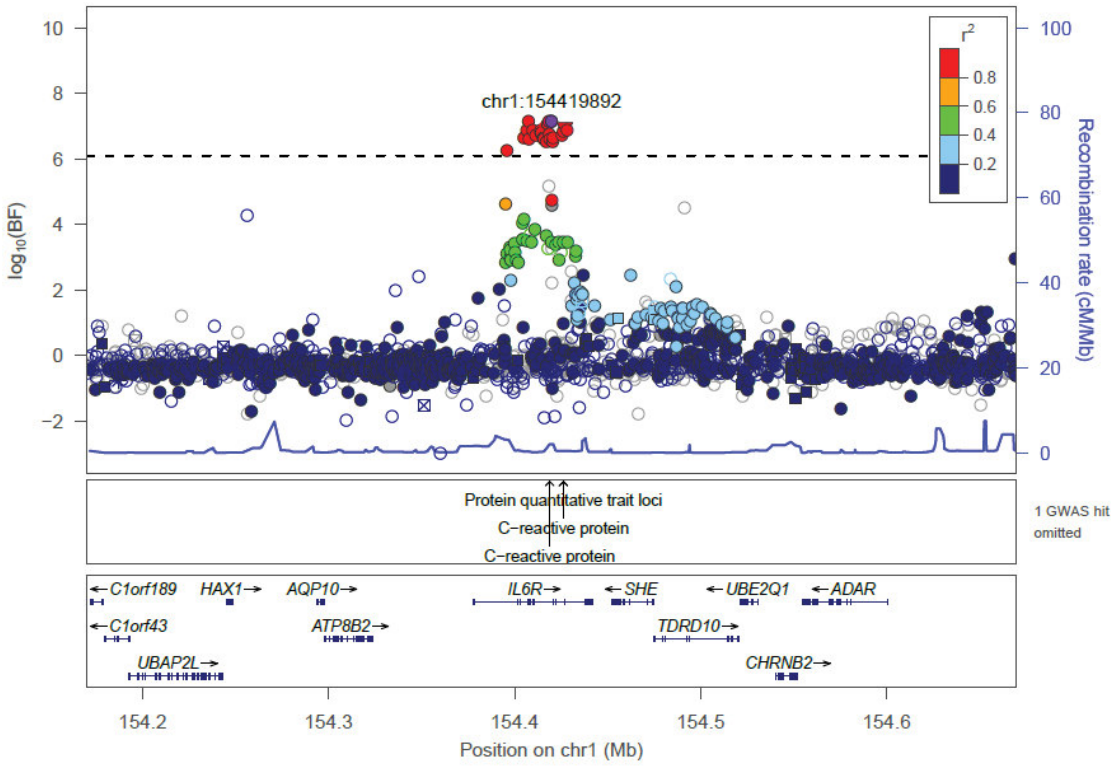


v. Latino (GALA II)

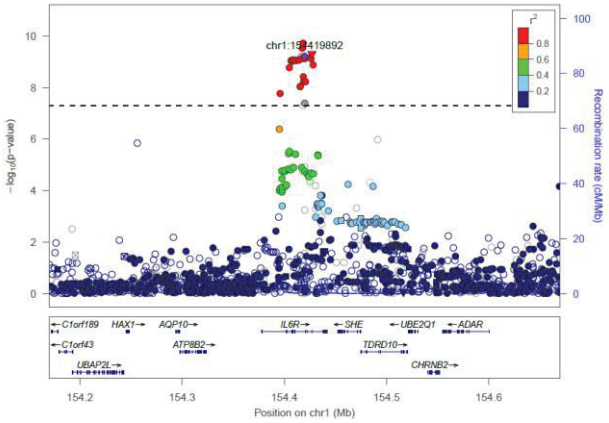


m. 1q21.3 - rs12730935 (IL6R)

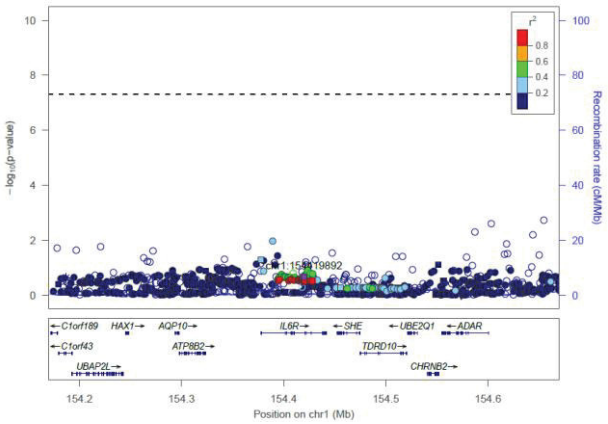
i. All studies (MANTRA)



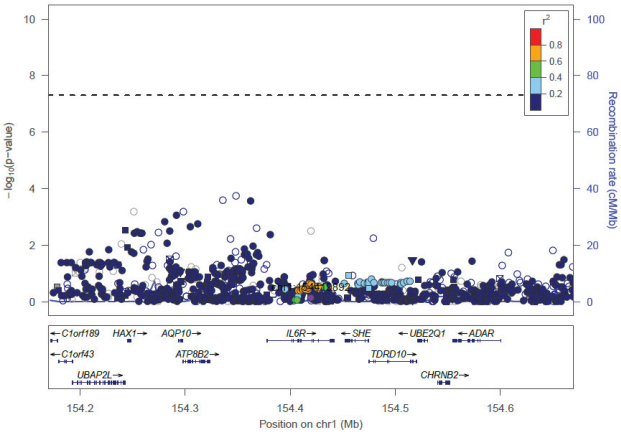
ii. European



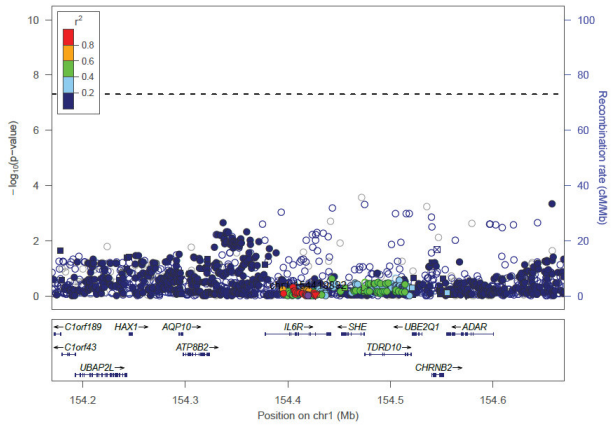
iii. East Asian (RIKEN)



iv. African American (SAPPHIRE)

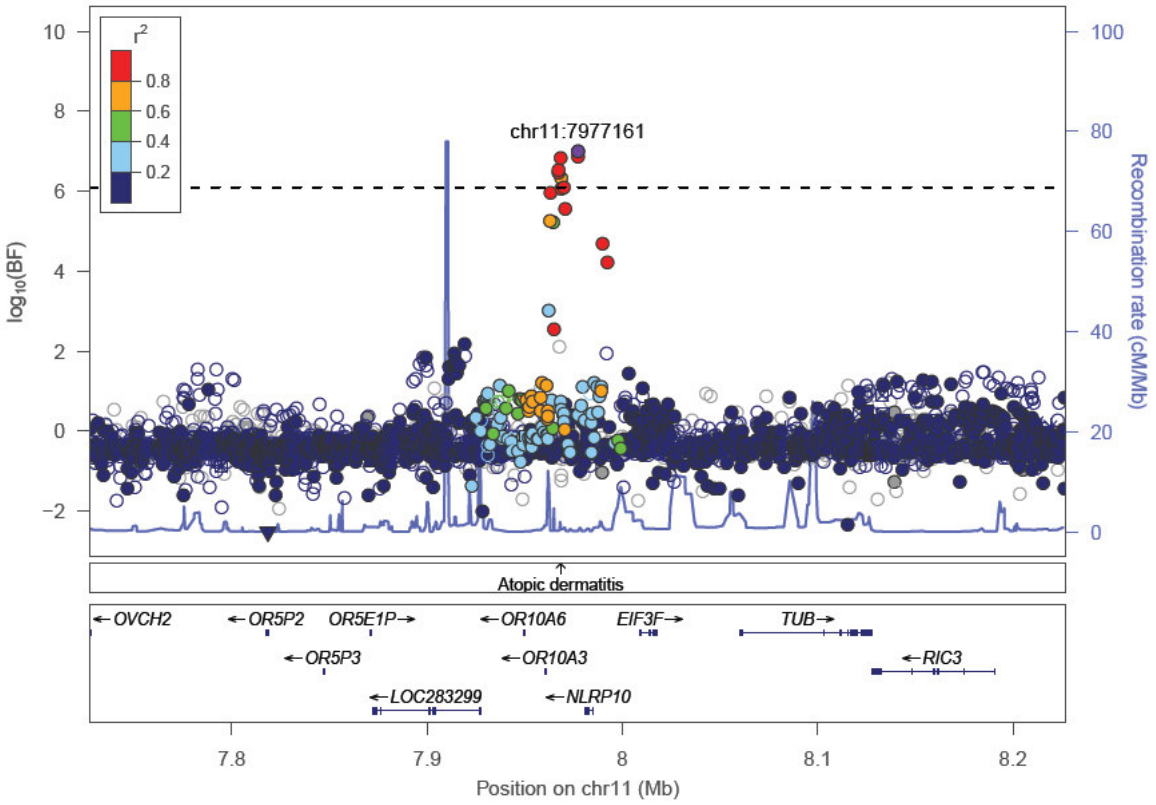


v. Latino (GALA II)

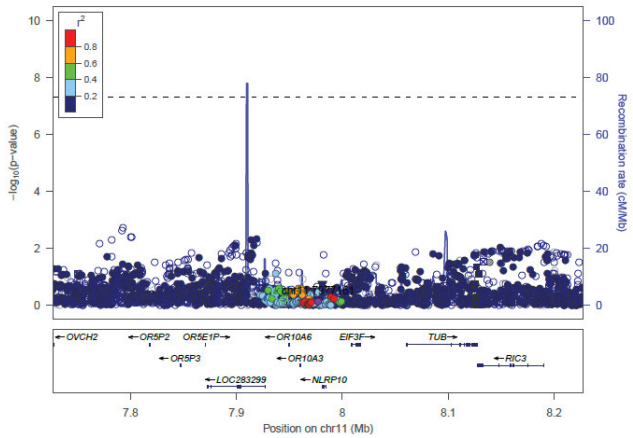


n. 11p15.4 - rs4312054 (NLRP10)

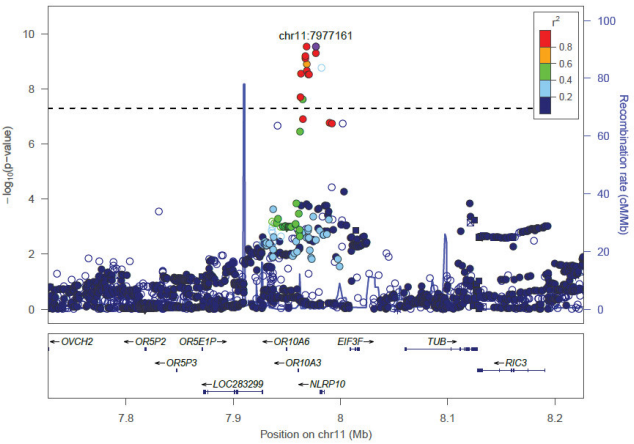
i. All studies (MANTRA)



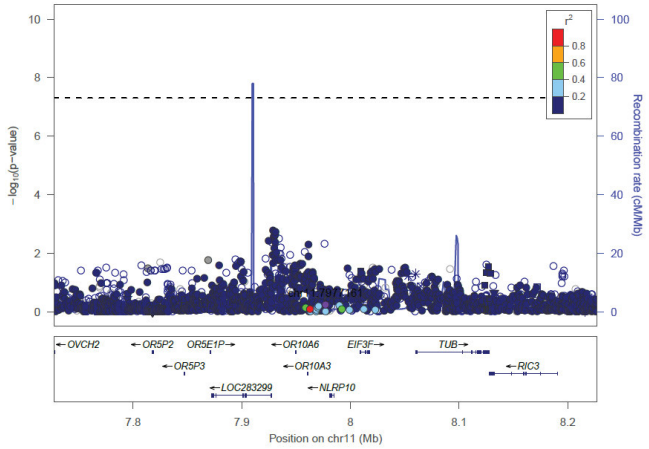
ii. European



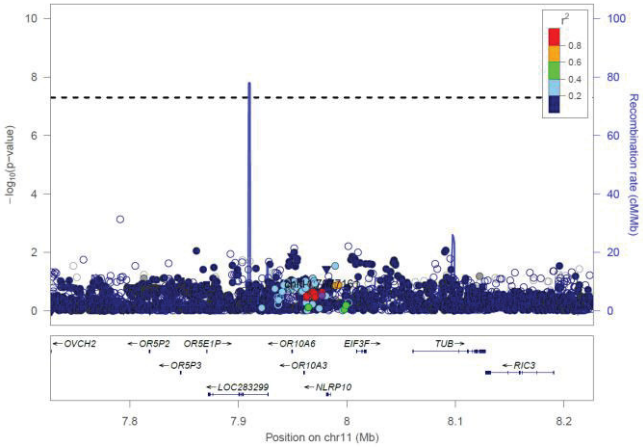
iii. East Asian (RIKEN)



iv. African American (SAPPHIRE)

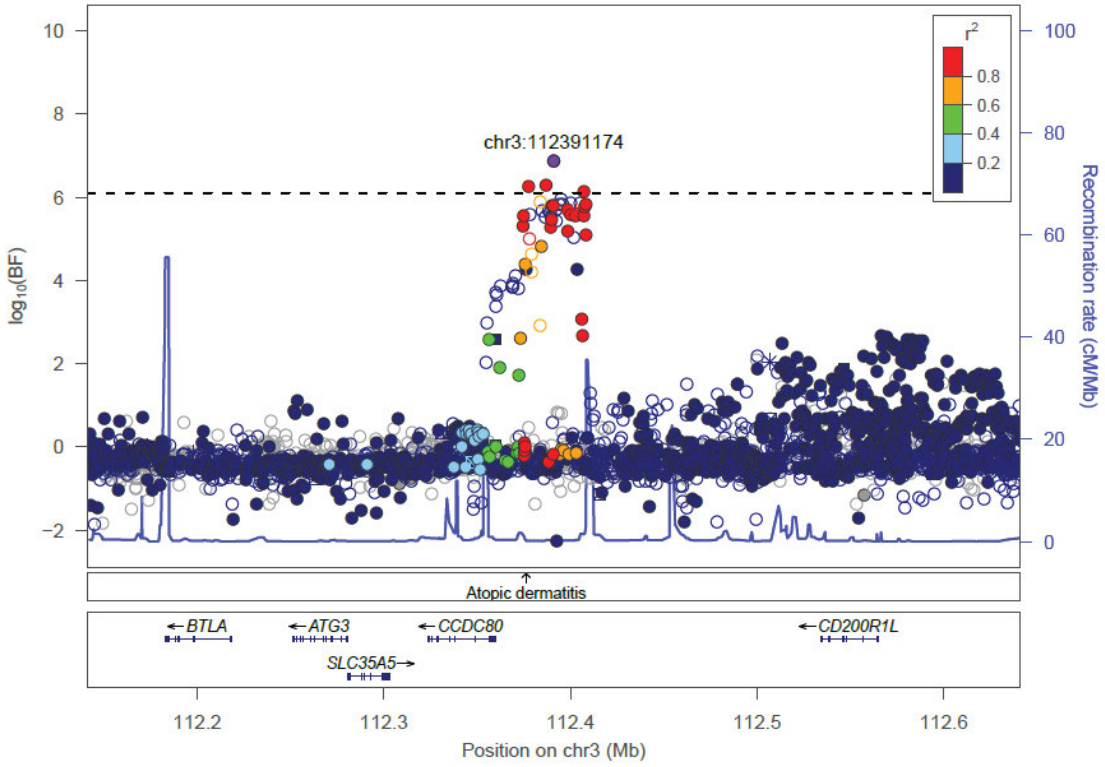


v. Latino (GALA II)

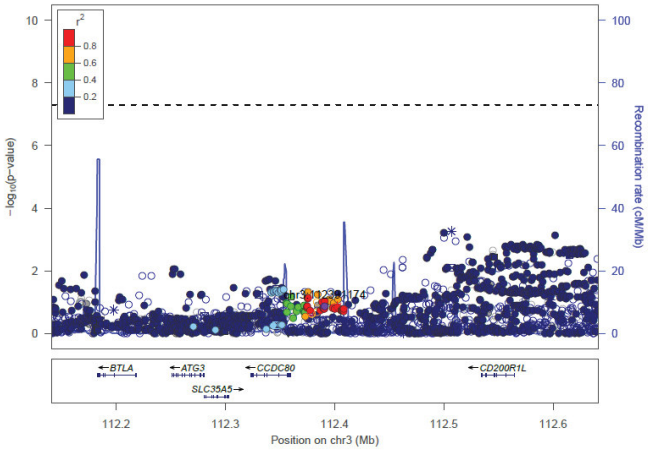


o. 3q13.2 - rs1249910 (CCDC80)

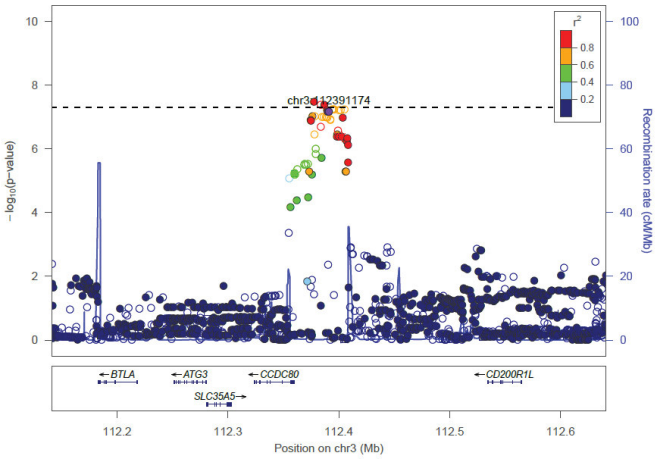
i. All studies (MANTRA)



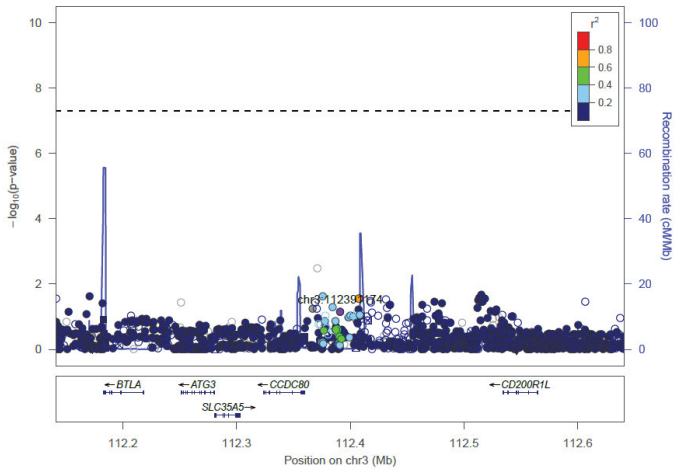
ii. European



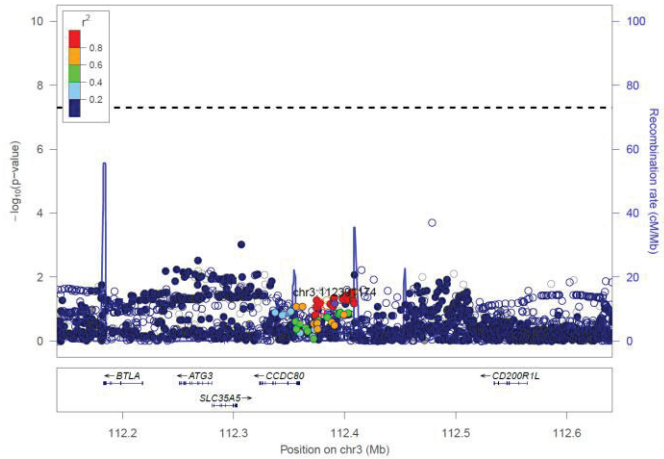
iii. East Asian (RIKEN)



iv. African American (SAPPHIRE)

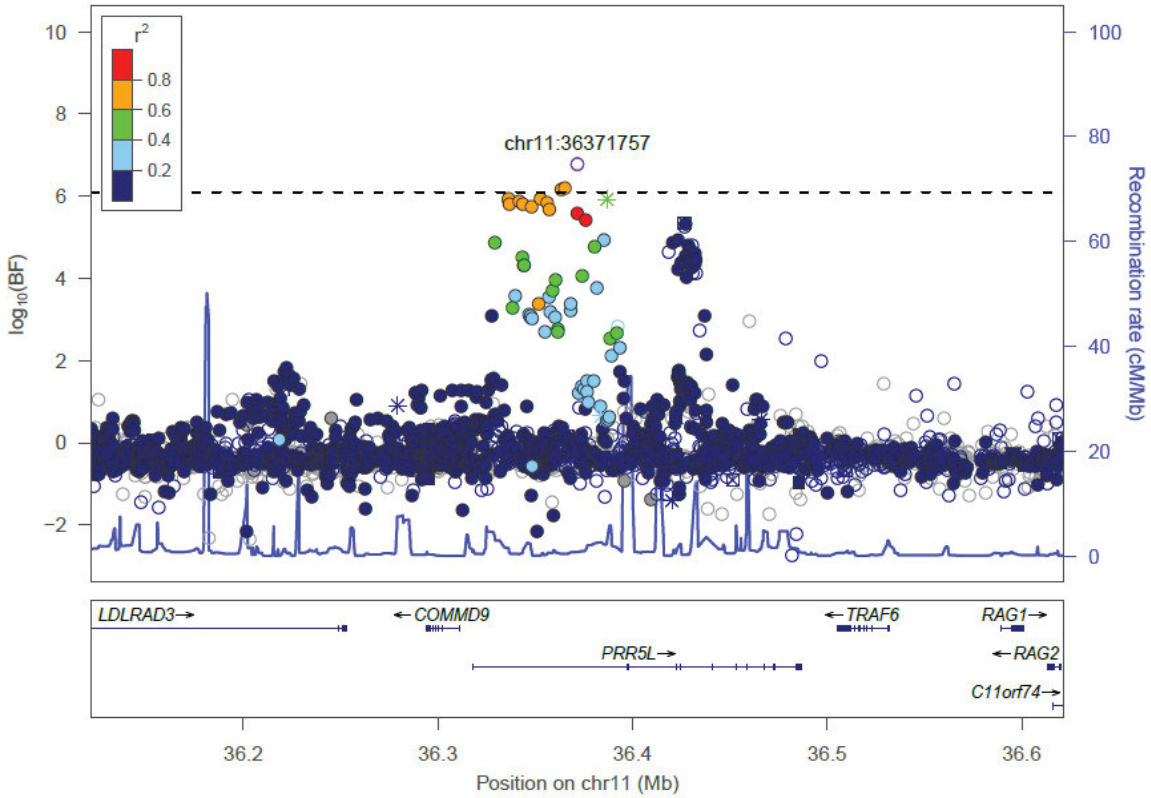


v. Latino (GALA II)

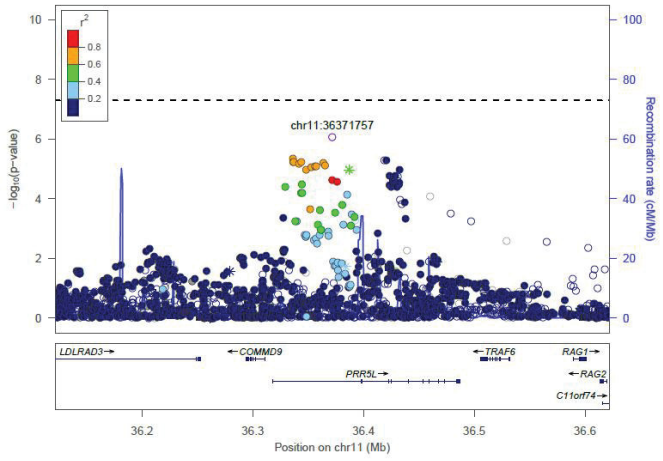


p. 11p13 - rs2592555 (PRR5L)

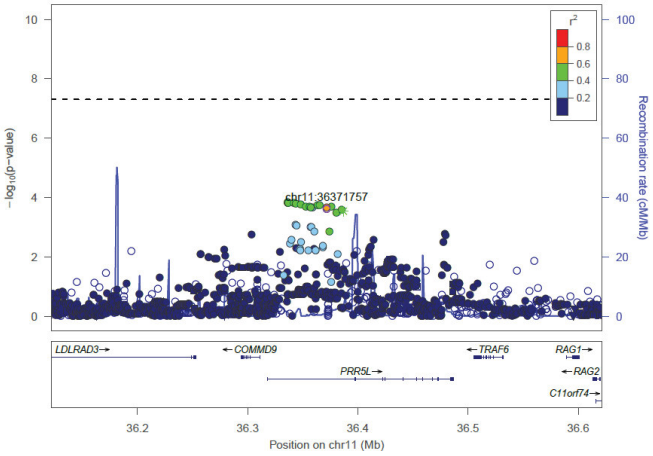
i. All studies (MANTRA)



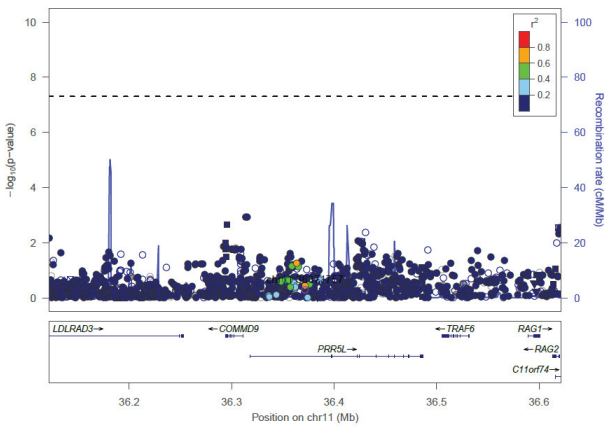
ii. European



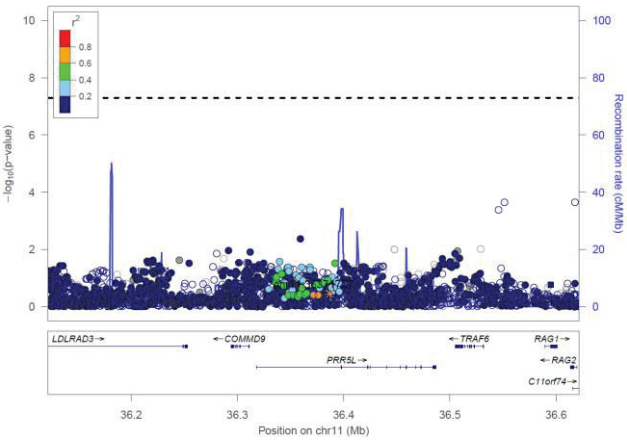
iii. East Asian (RIKEN)



iv. African American (SAPPHIRE)

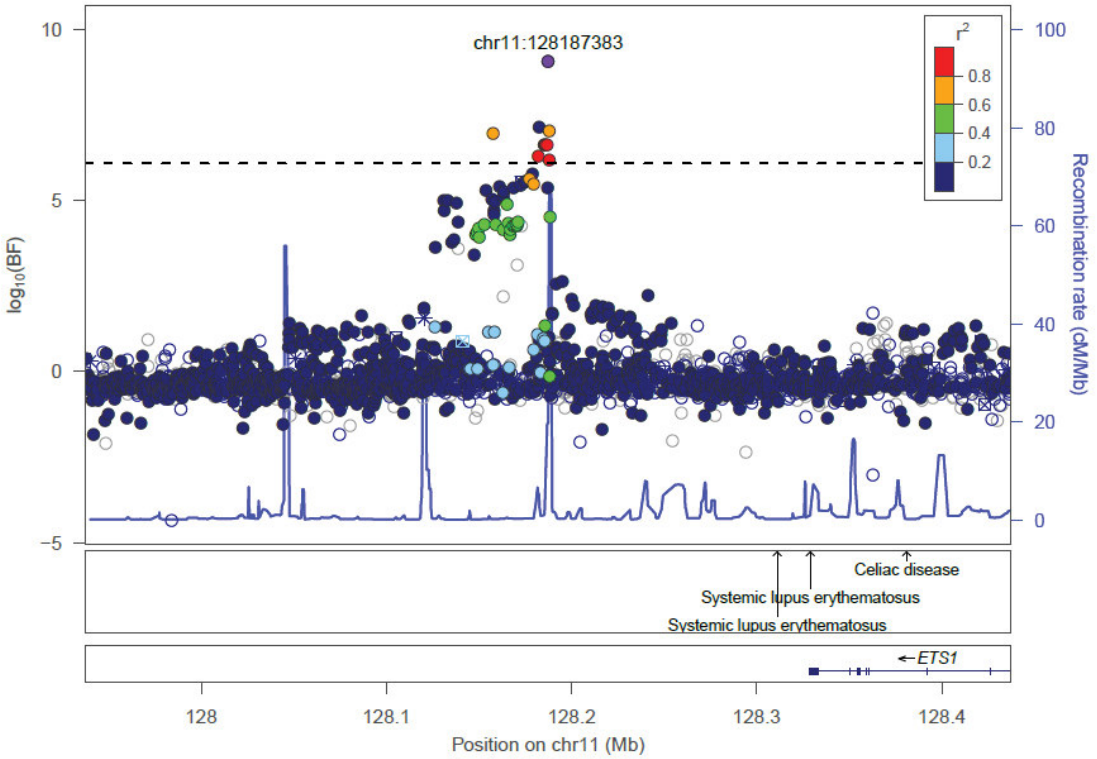


v. Latino (GALA II)

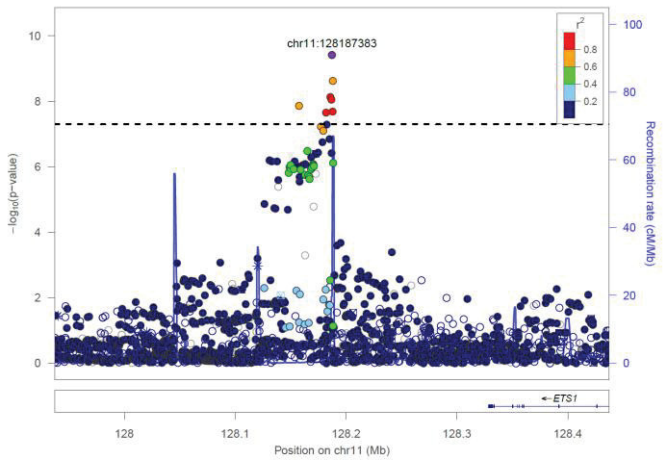


q. 11q24.3 - rs7127307 (ETS1) - NOVEL

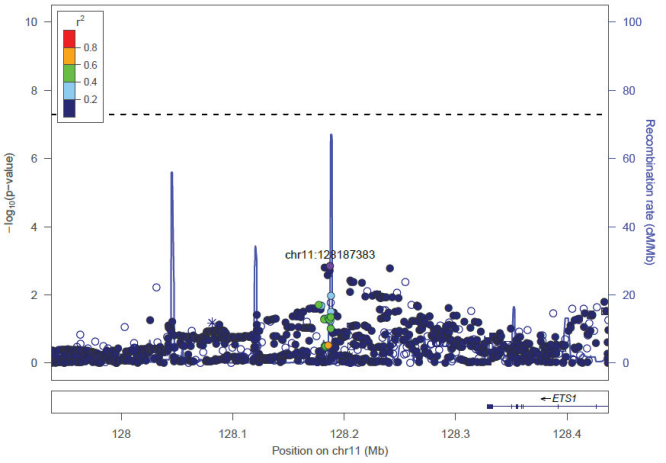
i. All studies (MANTRA)



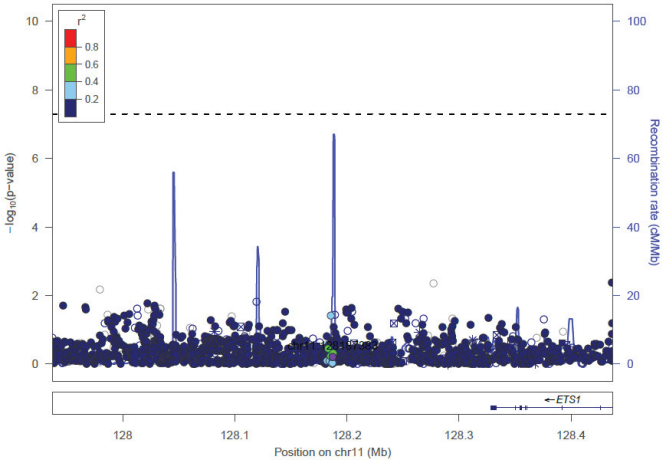
ii. European



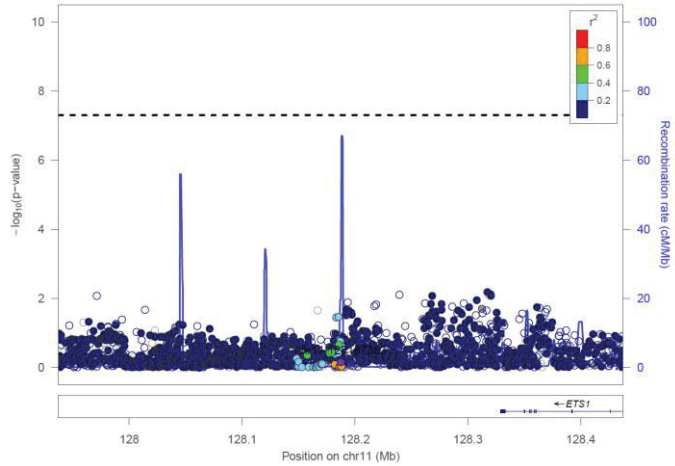
iii. East Asian (RIKEN)



iv. African American (SAPPHIRE)

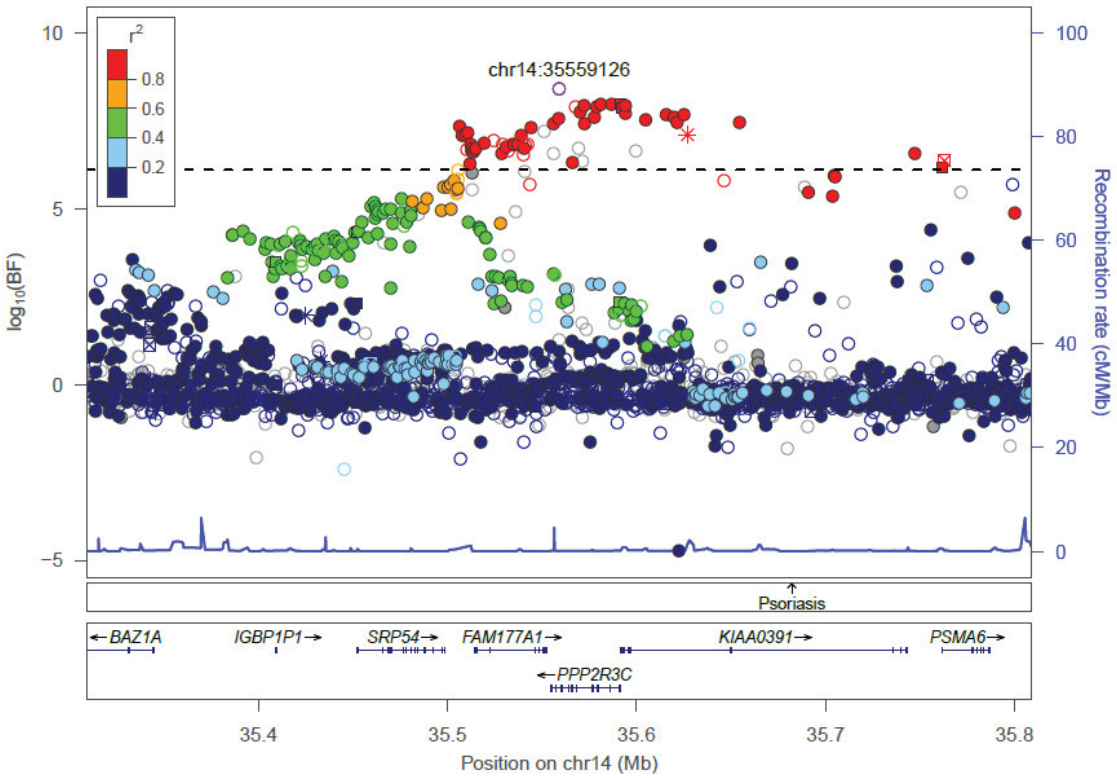


v. Latino (GALA II)

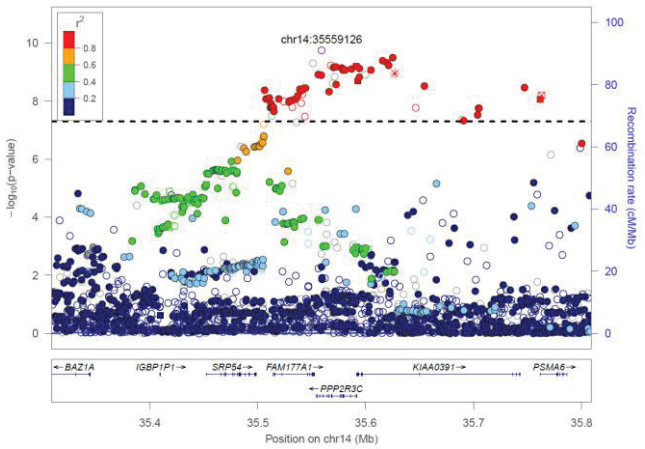


r. 14q13.2 - rs2038255 (PPP2R3C) - NOVEL

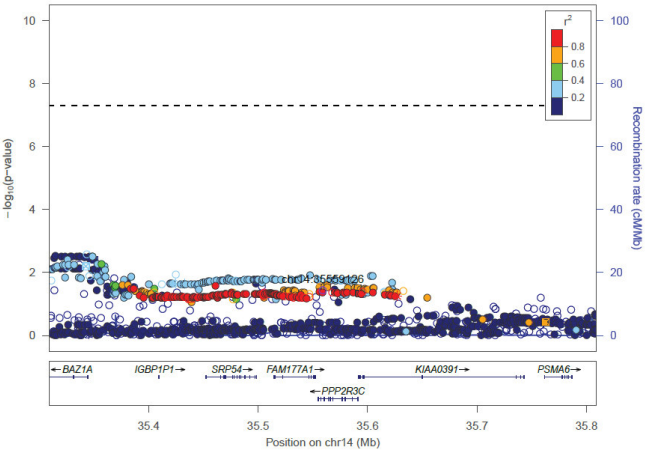
i. All studies (MANTRA)



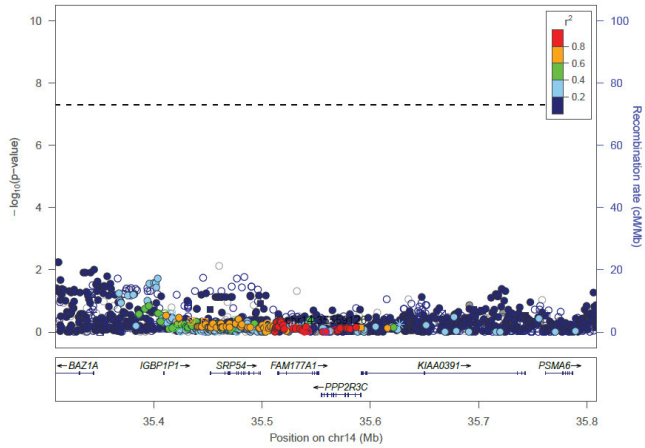
ii. European



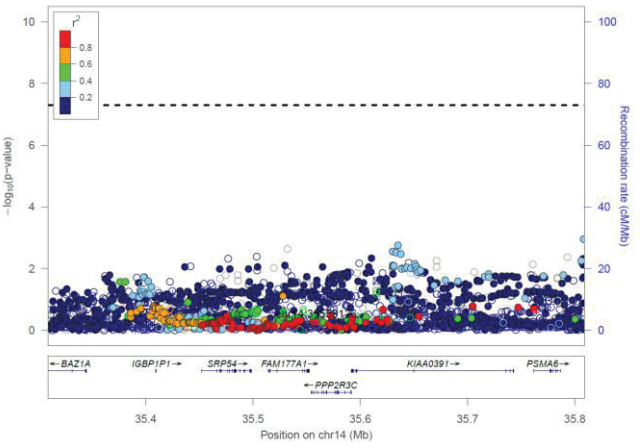
iii. East Asian (RIKEN)



iv. African American (SAPPHIRE)

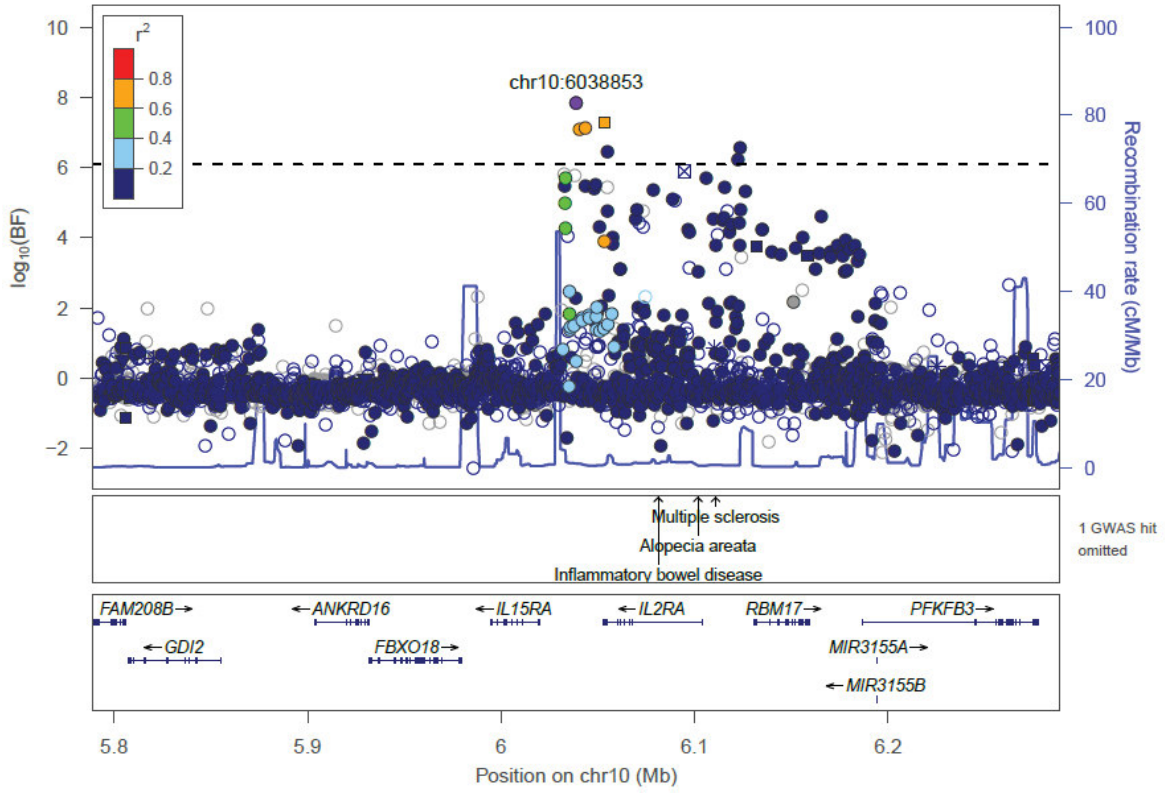


v. Latino (GALA II)

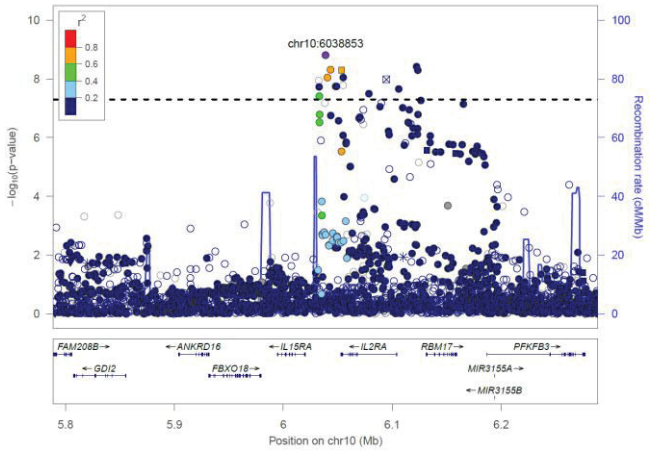


s. 10p15.1 - rs6602364 (IL2RA) - NOVEL

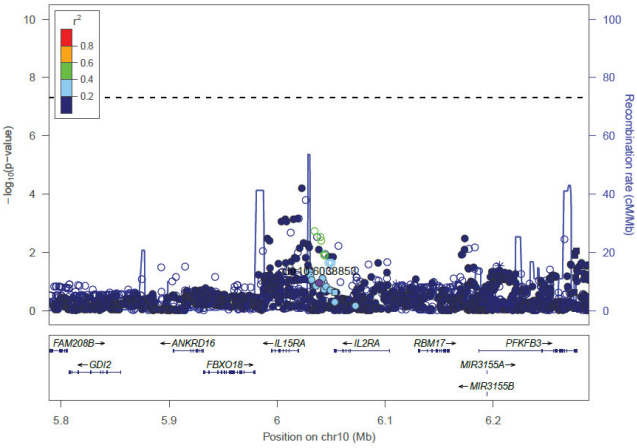
i. All studies (MANTRA)



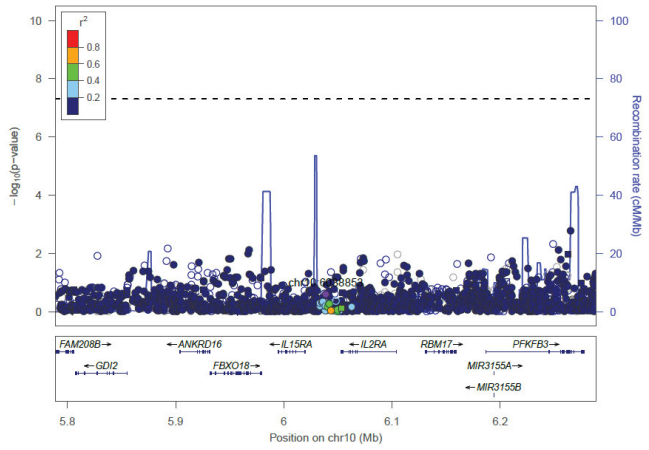
ii. European



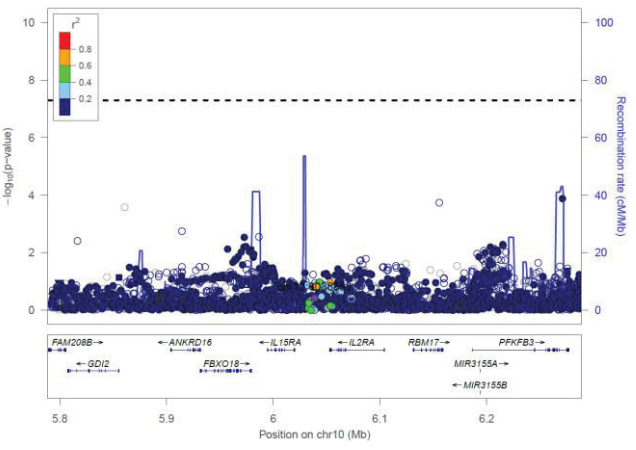
iii. East Asian (RIKEN)



iv. African American (SAPPHIRE)

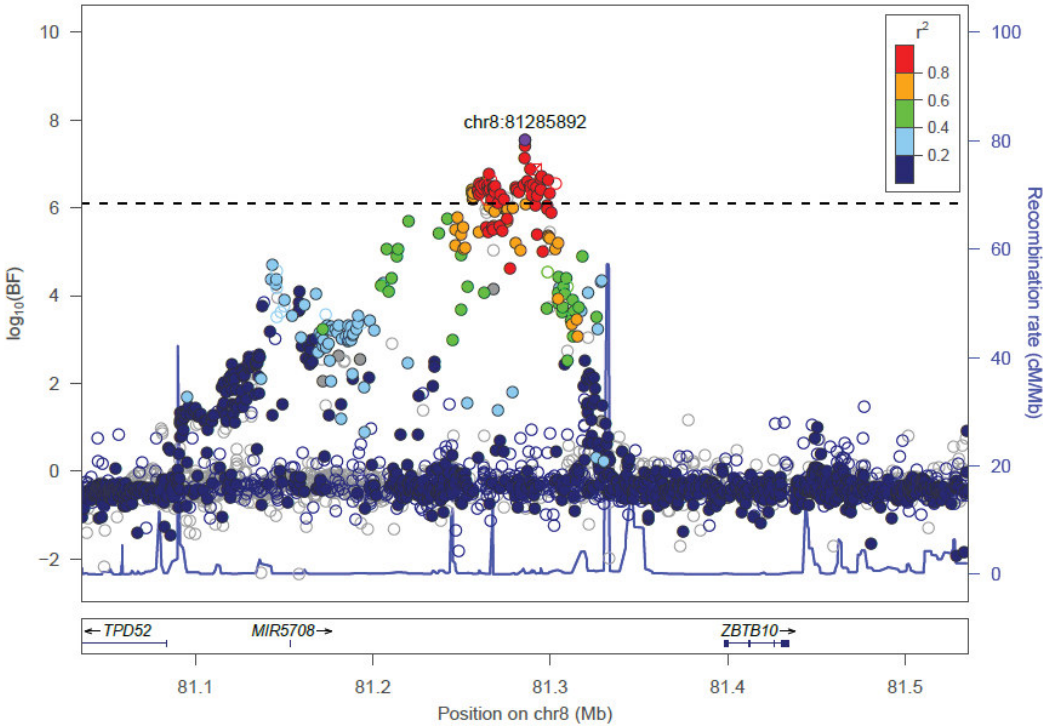


v. Latino (GALA II)

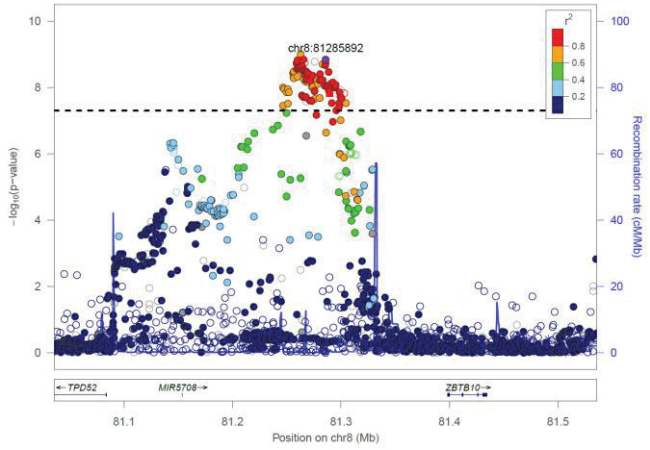


t. 8q21.13 - rs6473227 (ZBTB10) - NOVEL

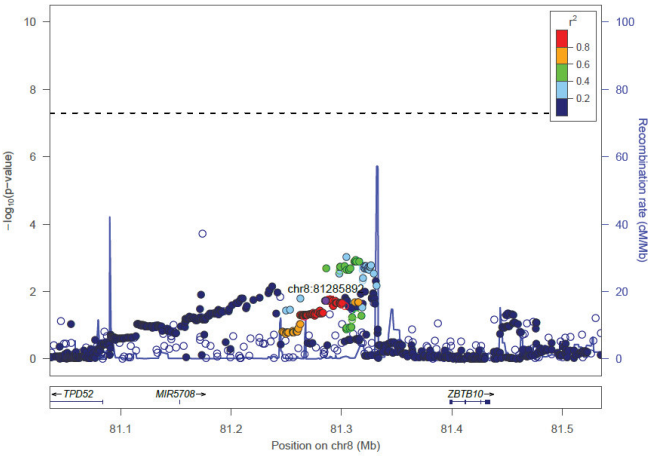
i. All studies (MANTRA)



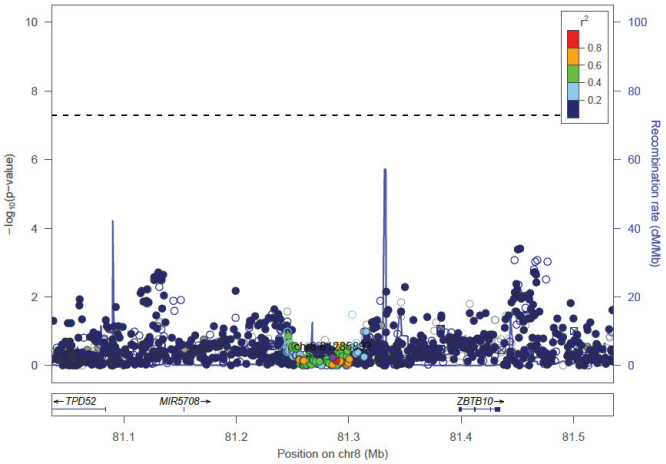
ii. European



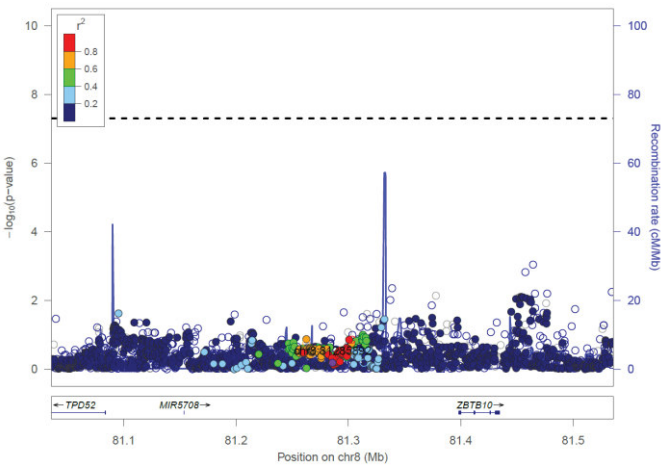
iii. East Asian (RIKEN)



iv. African American (SAPPHIRE)

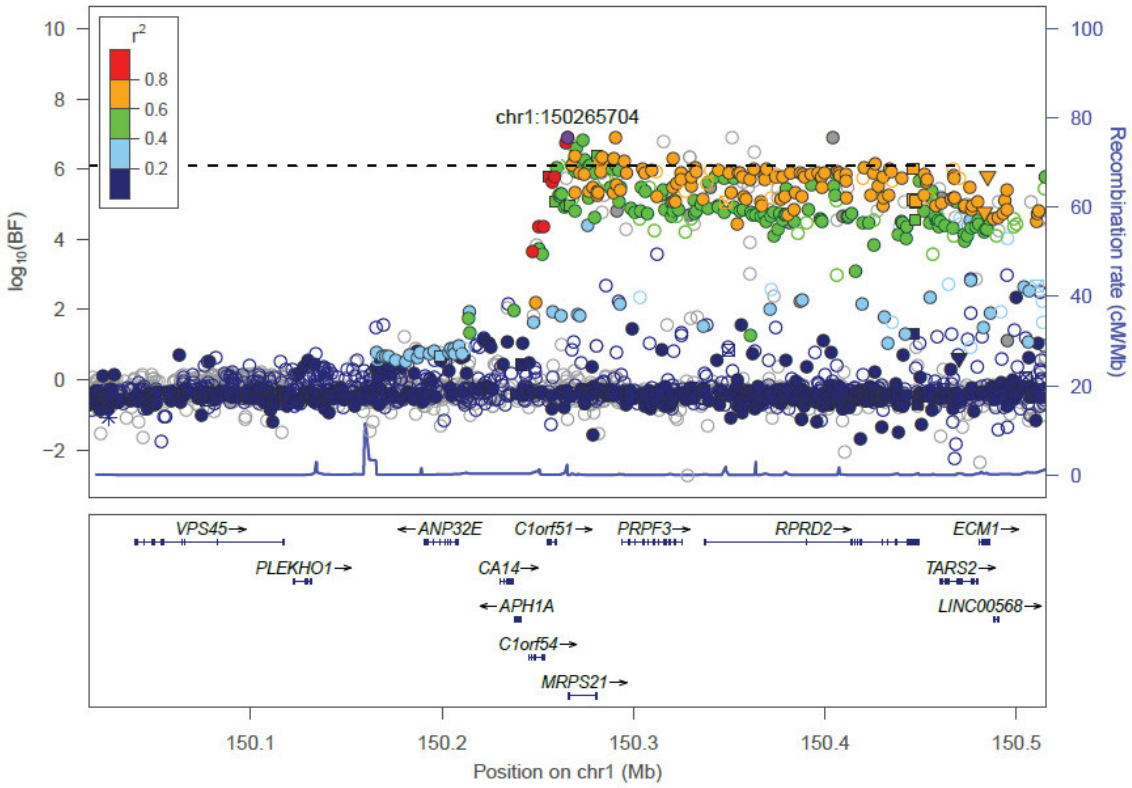


v. Latino (GALA II)

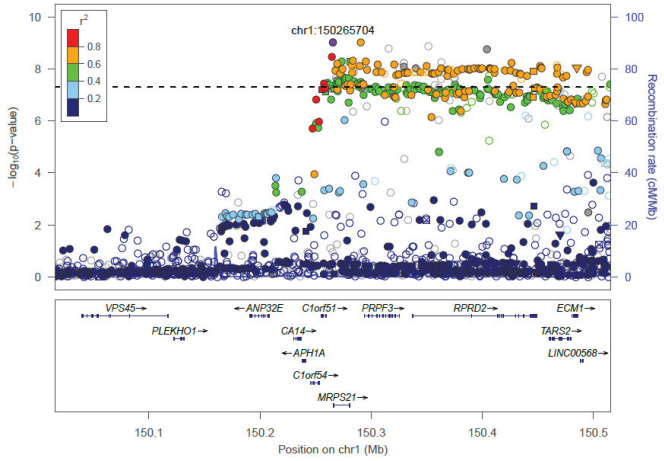


u. 1q21.2 - rs7512552 (MRPS21) - NOVEL

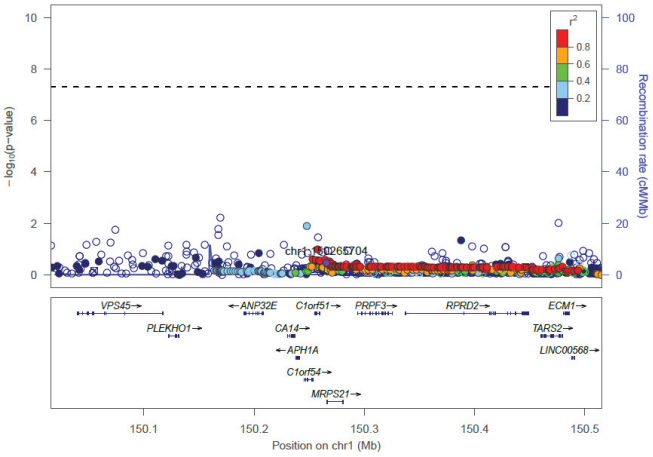
i. All studies (MANTRA)



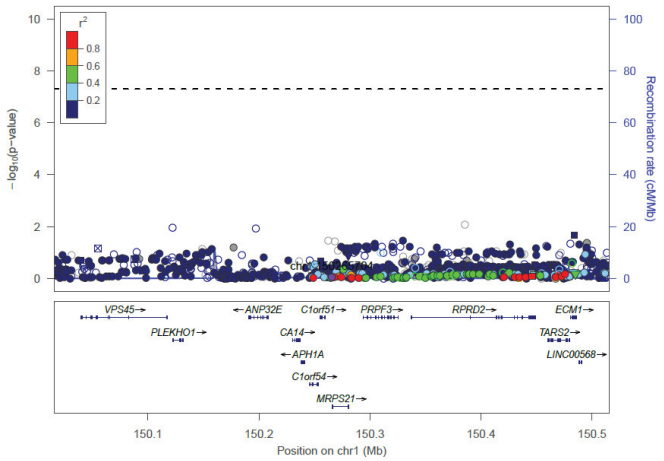
ii. European



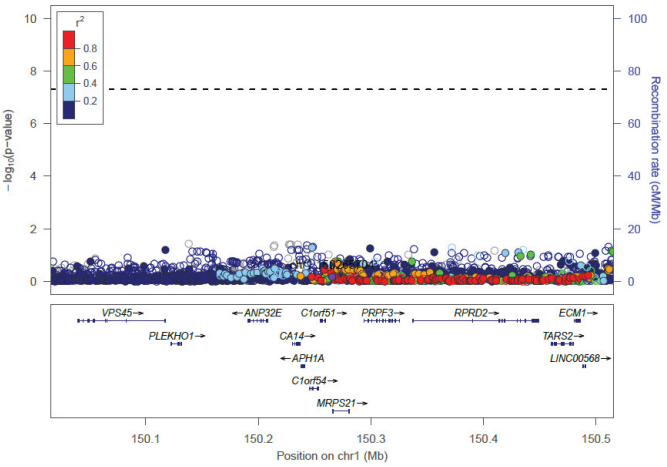
iii. East Asian (RIKEN)



iv. African American (SAPPHIRE)

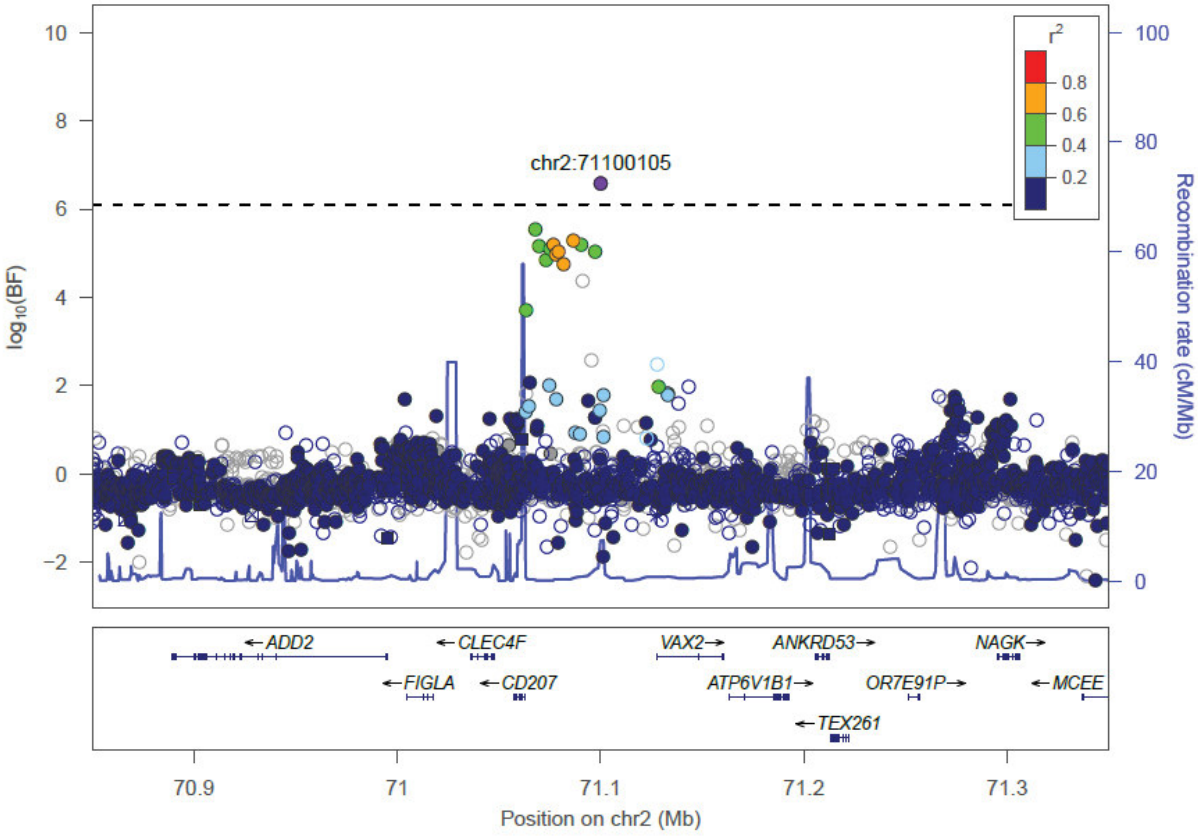


v. Latino (GALA II)

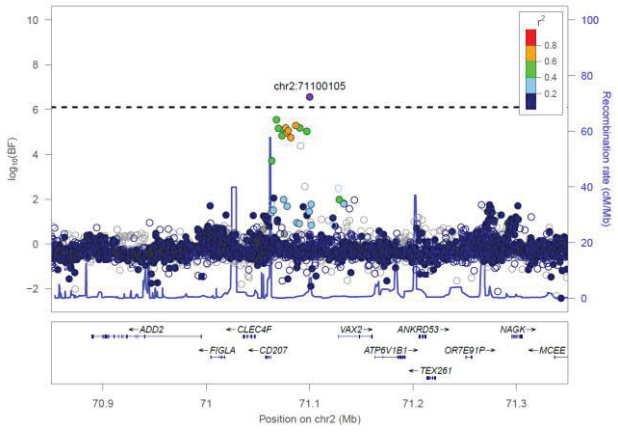


v. 2p13.3 - rs112111458 (VAX2) - NOVEL

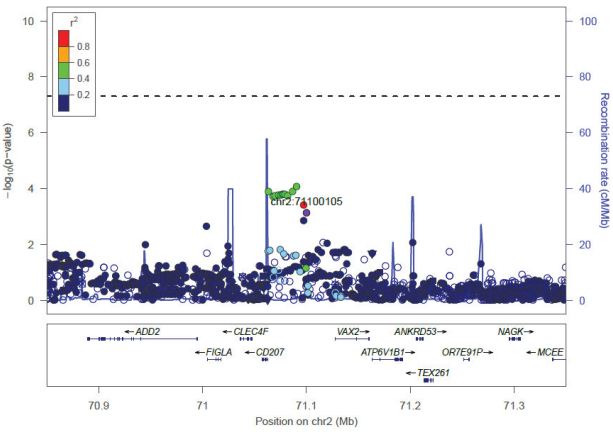
i. All studies (MANTRA)



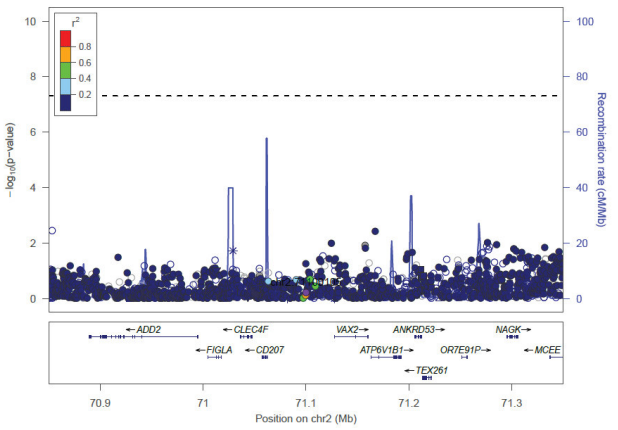
ii. European



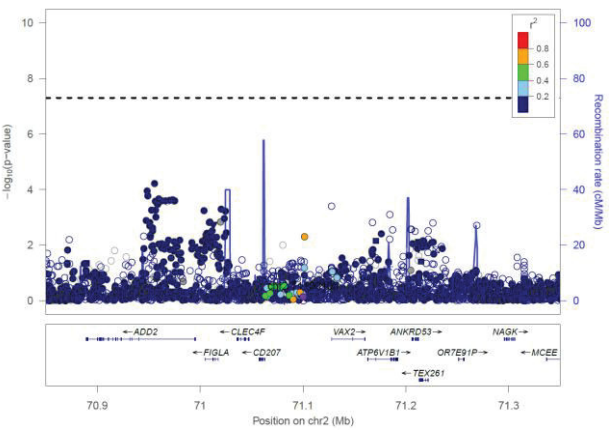
iii. East Asian (RIKEN)



iv. African American (SAPPHIRE)

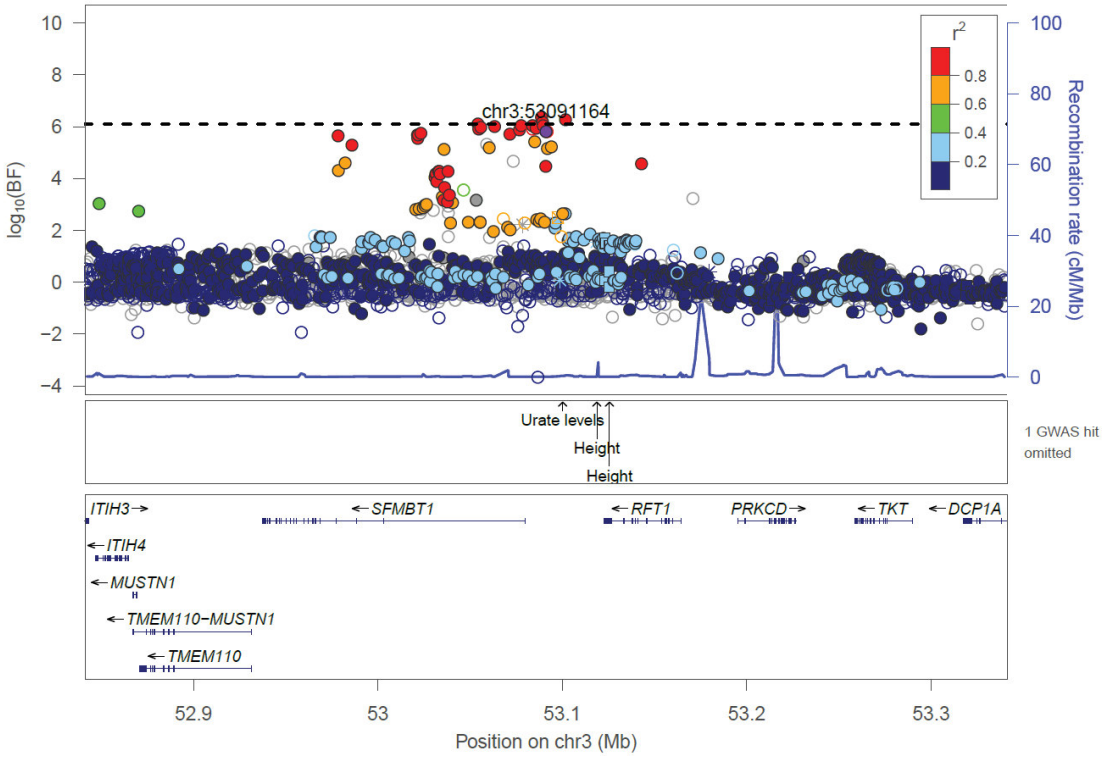


v. Latino (GALA II)

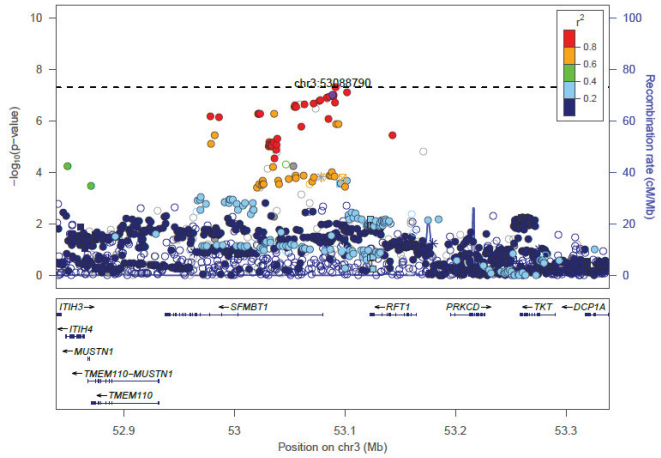


w. 3p21.1 - rs7625909 (SFMBT1) - NOVEL

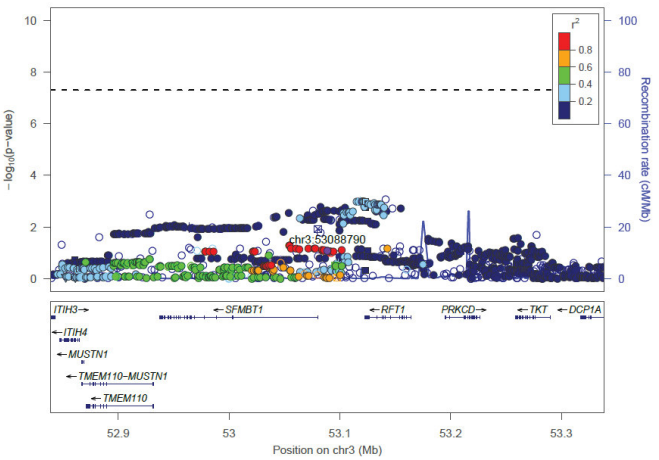
i. All studies (MANTRA)



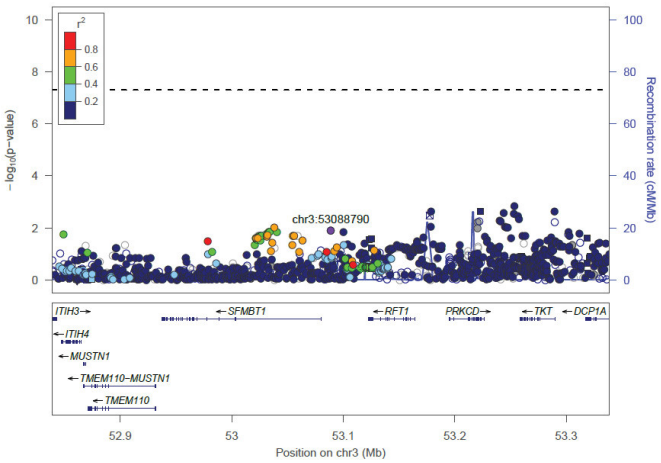
ii. European



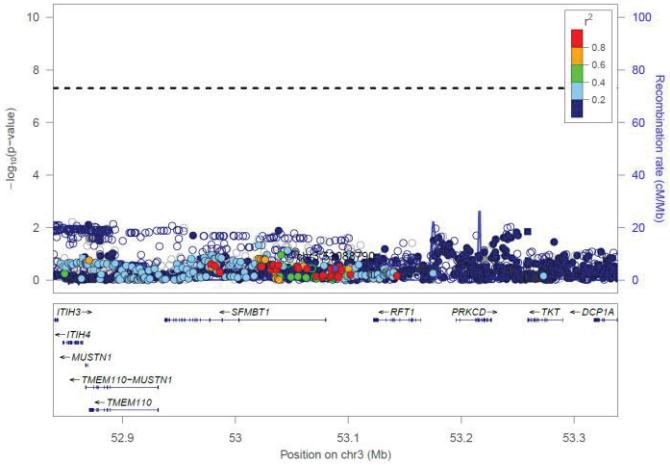
iii. East Asian (RIKEN)



iv. African American (SAPPHIRE)

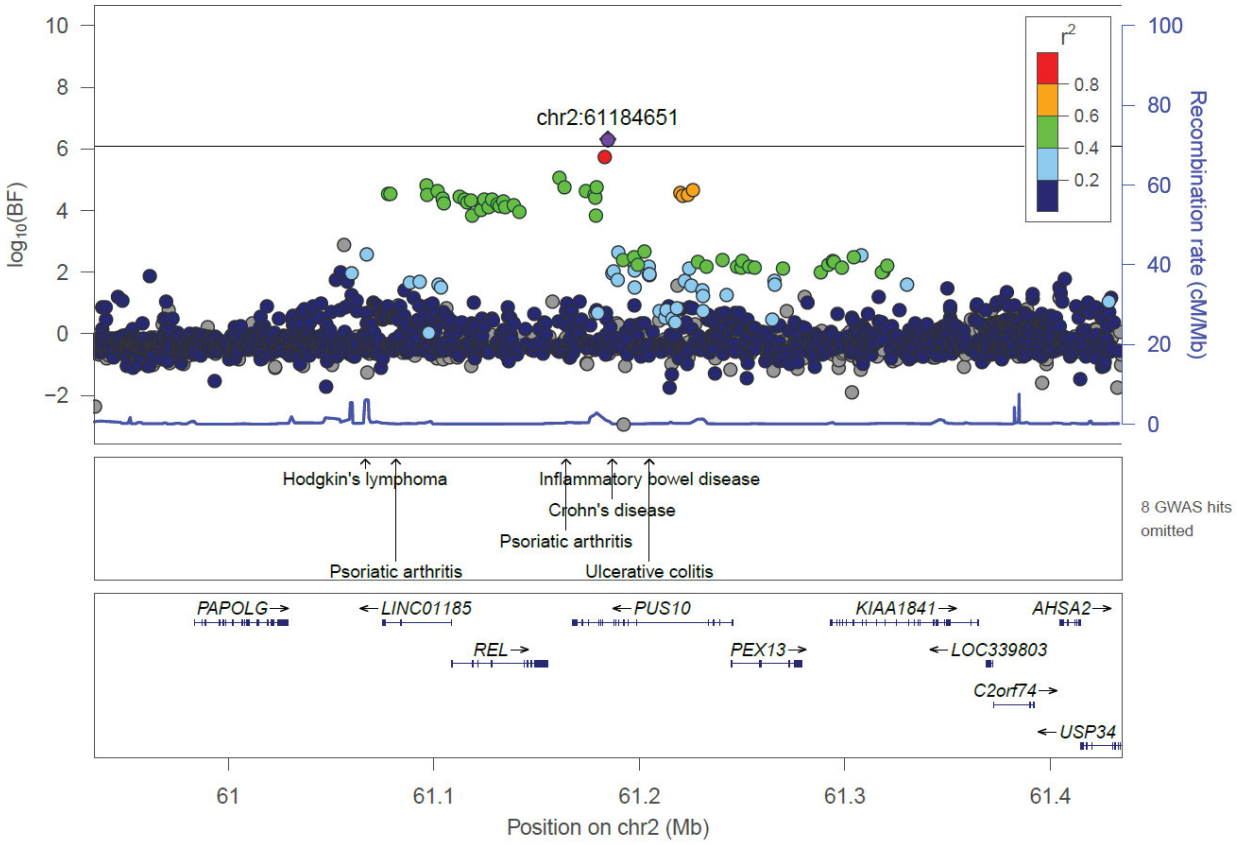


v. Latino (GALA II)

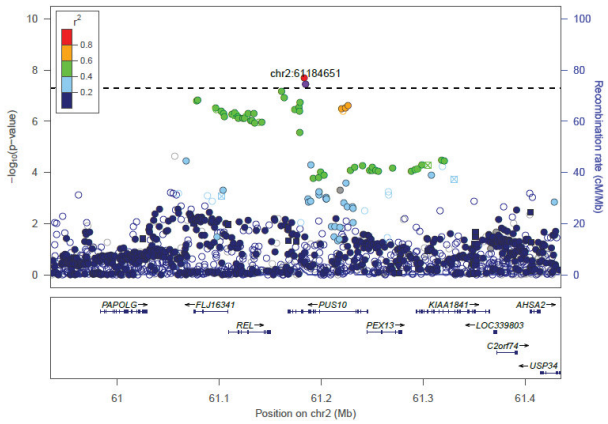


x. 2p16.1 - rs4643526 (PUS10) - NOVEL

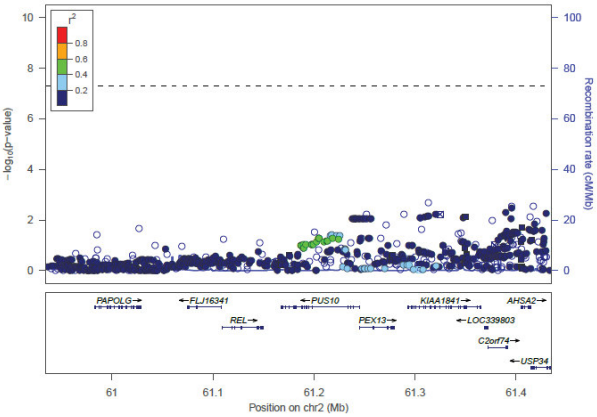
i. All studies (MANTRA)



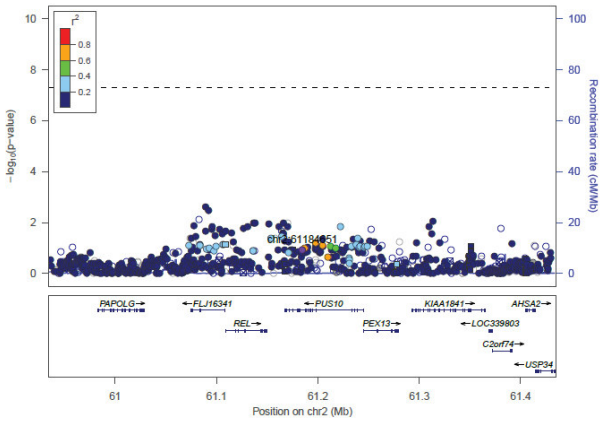
ii. European



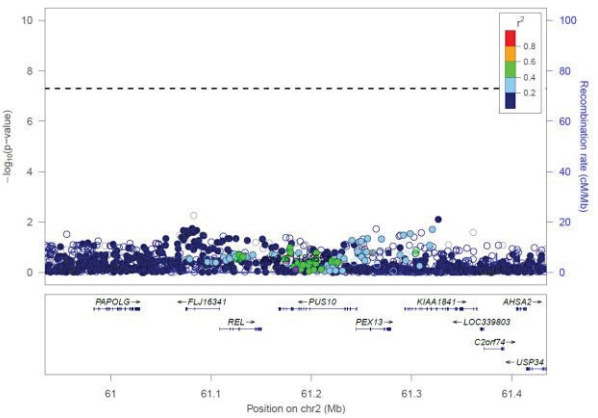
iii. East Asian (RIKEN)



iv. African American (SAPPHIRE)

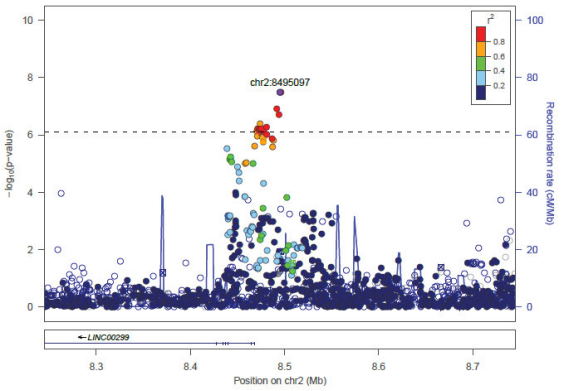


v. Latino (GALA II)

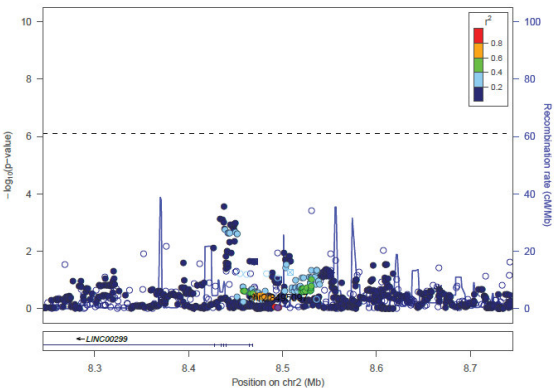


y. 2p25.1 - rs10199605 (LINC00299) – NOVEL – European-only

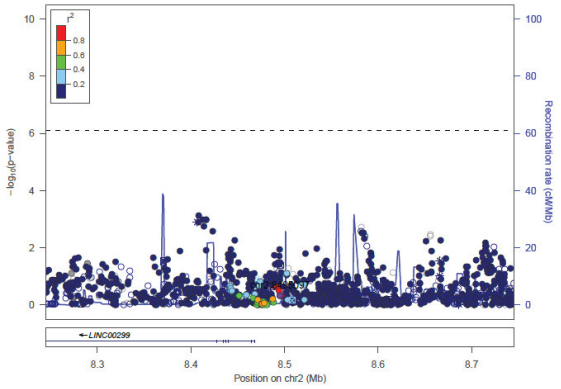
ii. European



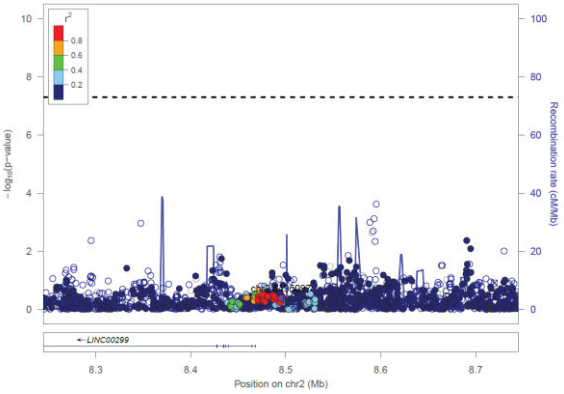
iii. East Asian (RIKEN)



iv. African American (SAPPHIRE)

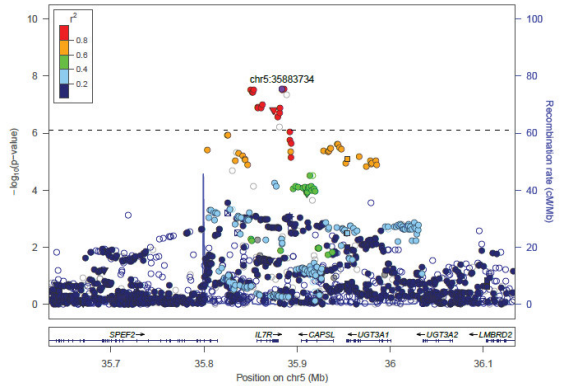


v. Latino American (GALA II)

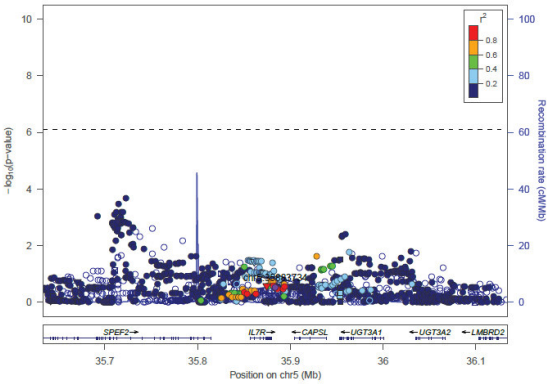


z. 5p13.2 - rs10214237 (IL7R) – NOVEL – European-only

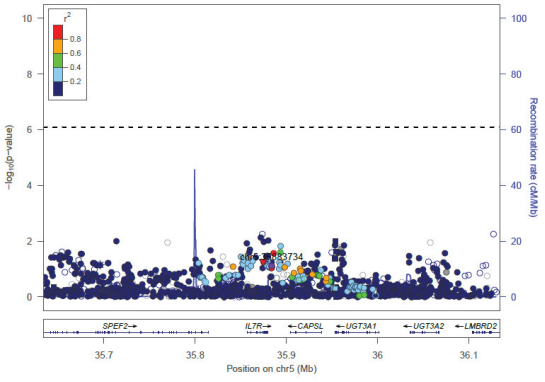
ii. European



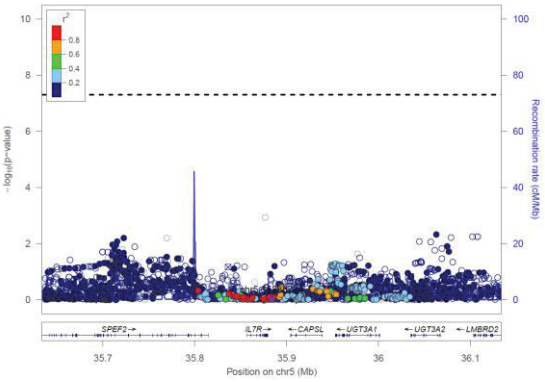
iii. East Asian (RIKEN)



iv. African American (SAPPHIRE)

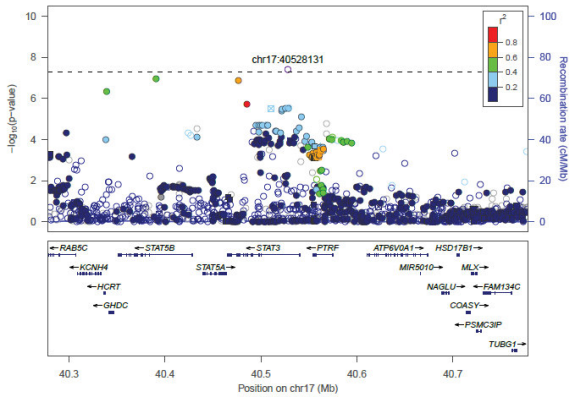


v. Latino American (GALA II)

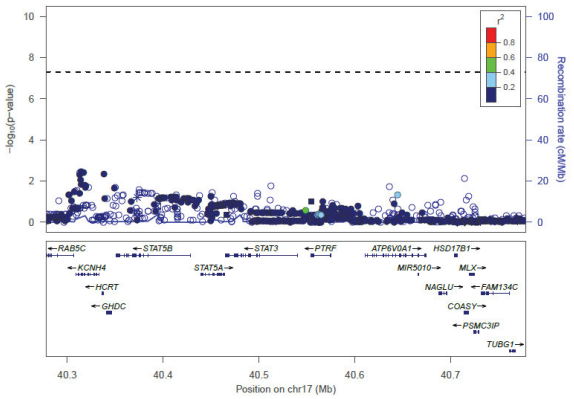


aa. 17q21.2 - rs12951971 (STAT3) – NOVEL – European-only

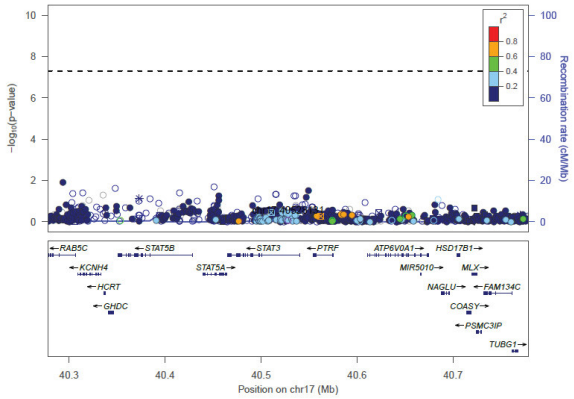
ii. European



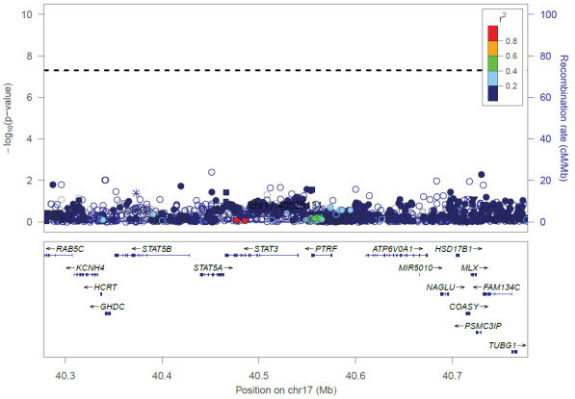
iii. East Asian (RIKEN)



iv. African American (SAPPHIRE)

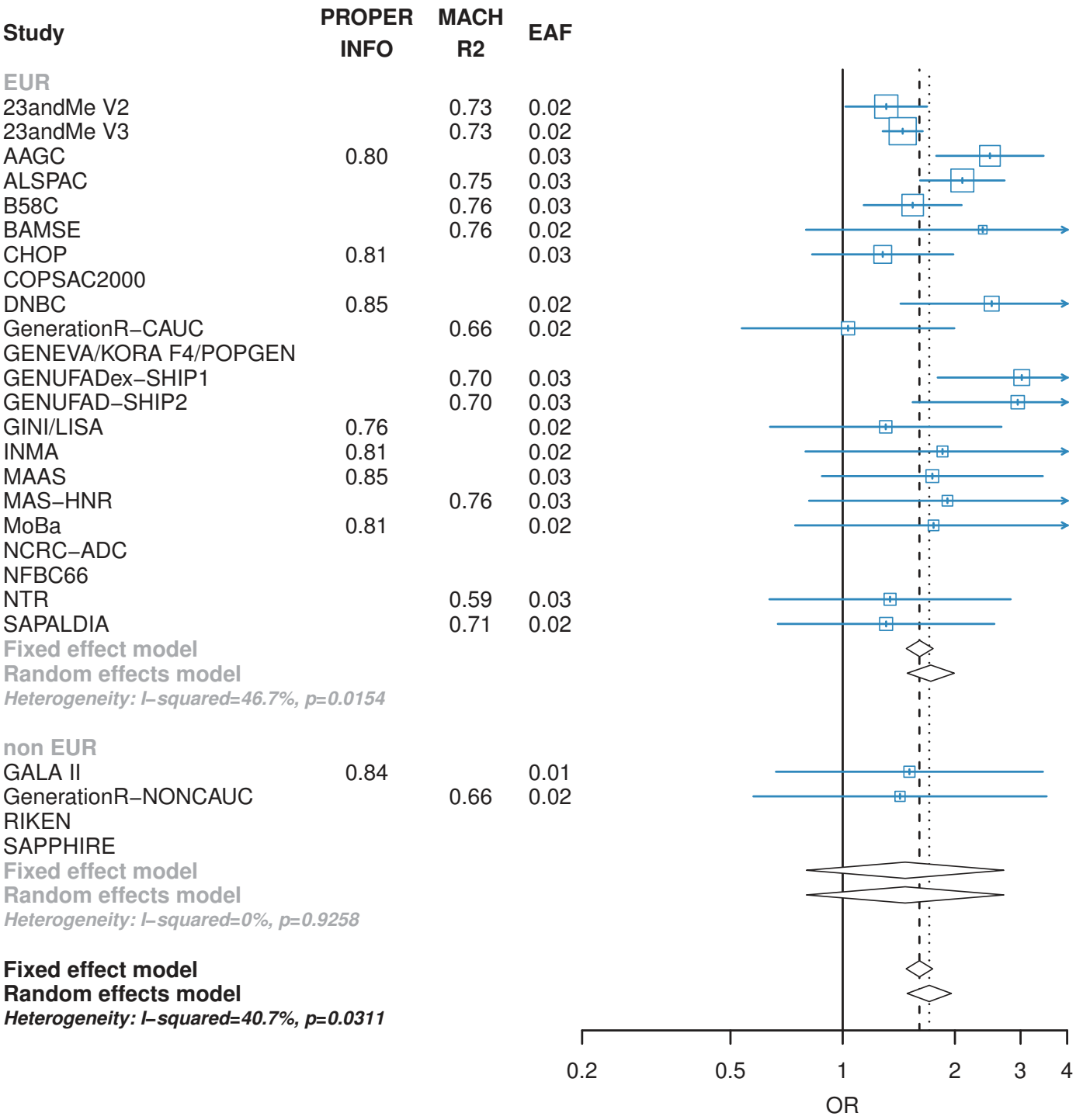


v. Latino American (GALA II)



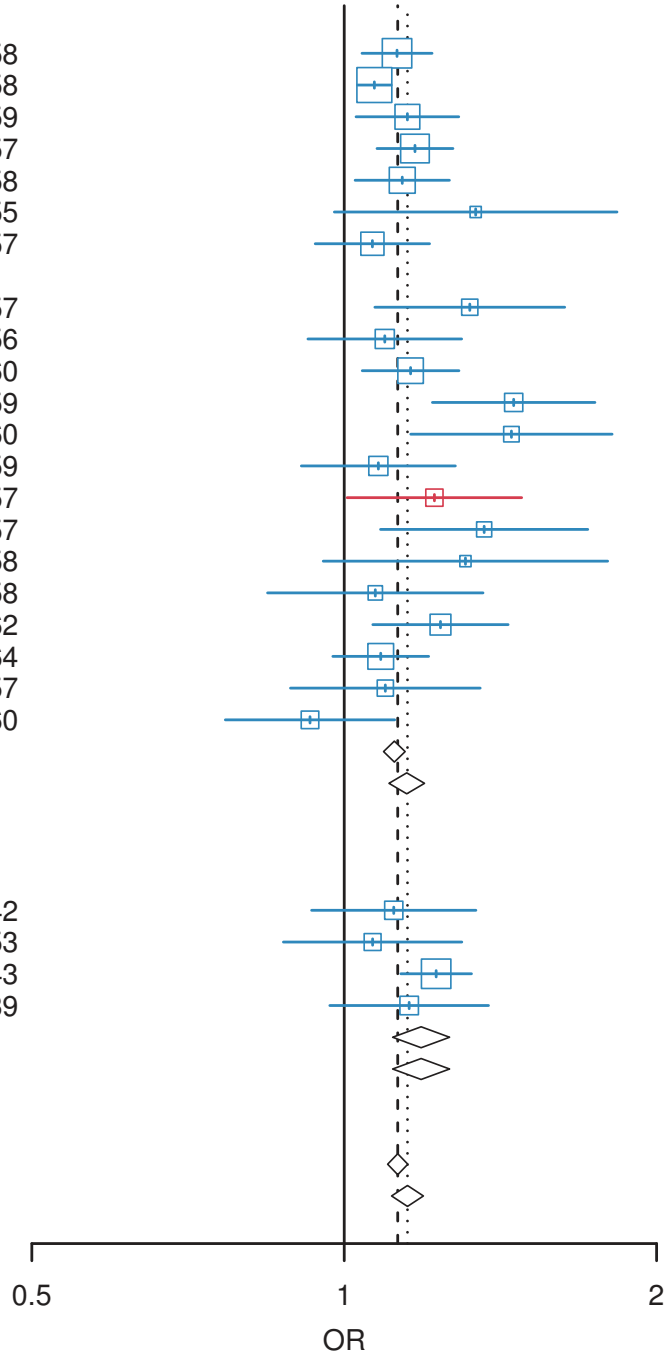
Supplementary Figure 2. Forest plots for the 27 loci p<5x10−8(a−aa). Studies are stratified into European ancestry and non−European ancestry. The non−European ancestry studies include GALAII (Latino), Generation R−NONCAUC (non−European ancestry), RIKEN (Japanese) and SAPPHIRE (African American). Fixed and random effects meta−analysis results are shown. For each study the imputation quality (PROPER INFO or MACH R2) and effect allele frequency (EAF) are shown. Blue=imputed genotypes, red=genotyped.

a. rs61813875 (1q21.3, CRCT1/LCE3E (FLG)), effect allele=G



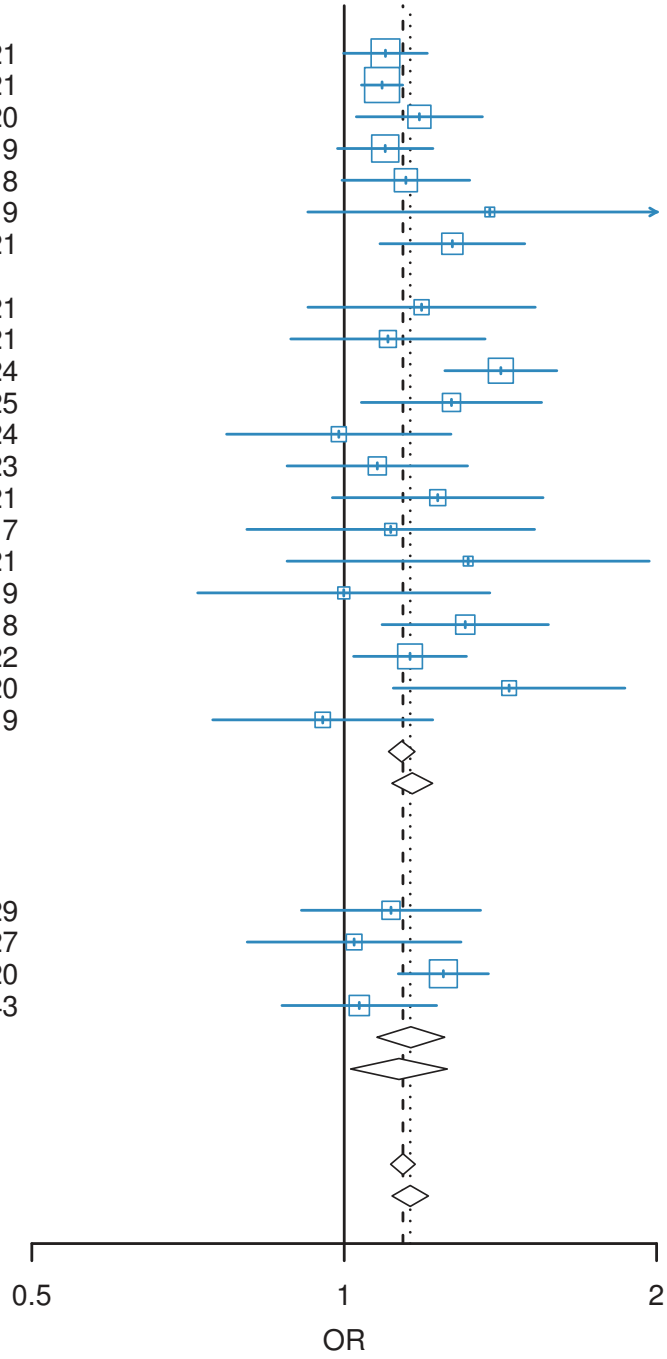
b. rs10791824 (11q13.1, OVOL1), effect allele=G

Study	PROPER INFO	MACH R2	EAF
EUR			
23andMe V2		0.96	0.58
23andMe V3		1.00	0.58
AAGC	0.95		0.59
ALSPAC		0.96	0.57
B58C		0.96	0.58
BAMSE		0.97	0.55
CHOP	0.96		0.57
COPSAC2000			
DNBC	0.97		0.57
GenerationR–CAUC		0.94	0.56
GENEVA/KORA F4/POPGEN	0.95		0.60
GENUFADex–SHIP1		0.95	0.59
GENUFAD–SHIP2		0.89	0.60
GINI/LISA	0.95		0.59
INMA	1.00		0.57
MAAS	0.96		0.57
MAS–HNR		0.96	0.58
MoBa	0.97		0.58
NCRC–ADC	0.87		0.62
NFBC66	0.97		0.64
NTR		0.91	0.57
SAPALDIA		0.95	0.60
Fixed effect model			
Random effects model			
Heterogeneity: I–squared=44.4%, p=0.0154			
non EUR			
GALA II	0.96		0.42
GenerationR–NONCAUC		0.94	0.53
RIKEN		1.00	0.43
SAPPHIRE	0.90		0.39
Fixed effect model			
Random effects model			
Heterogeneity: I–squared=0%, p=0.504			
Fixed effect model			
Random effects model			
Heterogeneity: I–squared=41.9%, p=0.0154			



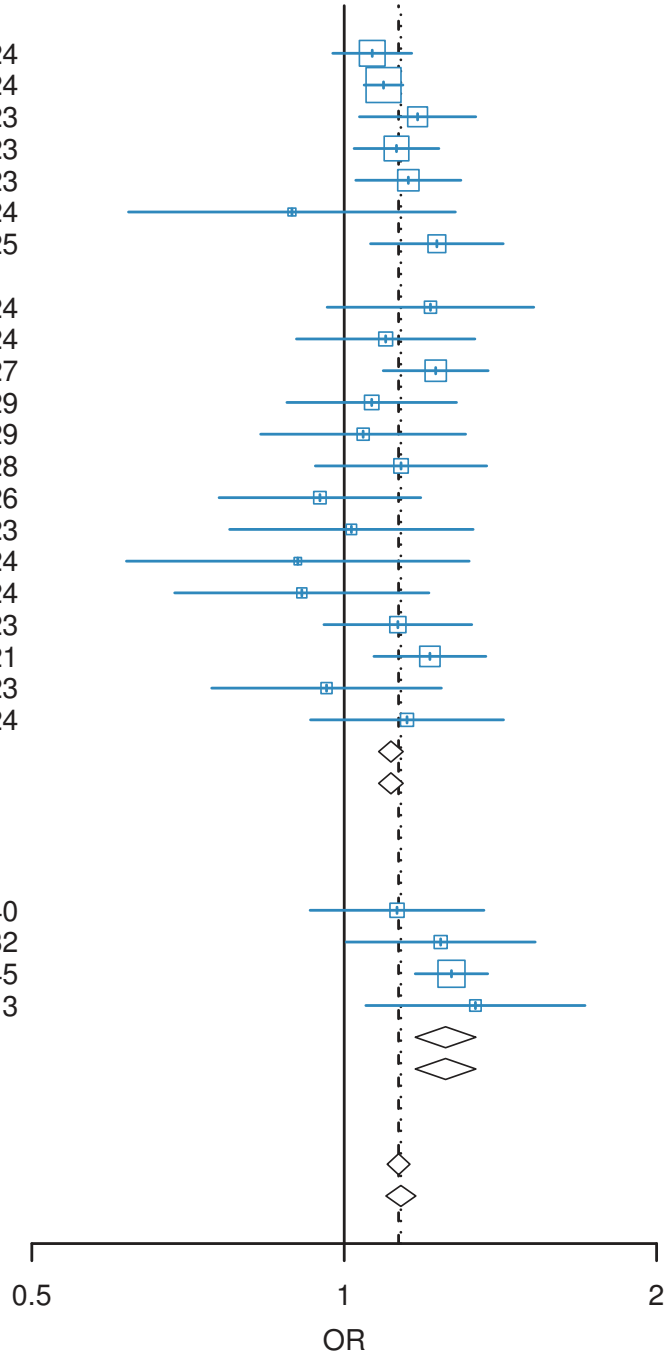
c. rs12188917 (5q31.1, RAD50/IL13), effect allele=C

Study	PROPER INFO	MACH R2	EAF
EUR			
23andMe V2		0.97	0.21
23andMe V3		0.98	0.21
AAGC	0.91		0.20
ALSPAC		0.97	0.19
B58C		0.84	0.18
BAMSE		0.85	0.19
CHOP	0.91		0.21
COPSAC2000			
DNBC	0.93		0.21
GenerationR–CAUC		0.84	0.21
GENEVA/KORA F4/POPGEN	0.93		0.24
GENUFADex–SHIP1		0.91	0.25
GENUFAD–SHIP2		0.87	0.24
GINI/LISA	0.92		0.23
INMA	0.96		0.21
MAAS	0.91		0.17
MAS–HNR		0.85	0.21
MoBa	0.93		0.19
NCRC–ADC	0.85		0.18
NFBC66	0.95		0.22
NTR		0.79	0.20
SAPALDIA		0.86	0.19
Fixed effect model			
Random effects model			
Heterogeneity: I–squared=37%, p=0.0462			
non EUR			
GALA II	0.98		0.29
GenerationR–NONCAUC		0.84	0.27
RIKEN		0.90	0.20
SAPPHIRE	0.89		0.43
Fixed effect model			
Random effects model			
Heterogeneity: I–squared=39.8%, p=0.1733			
Fixed effect model			
Random effects model			
Heterogeneity: I–squared=35.1%, p=0.0442			



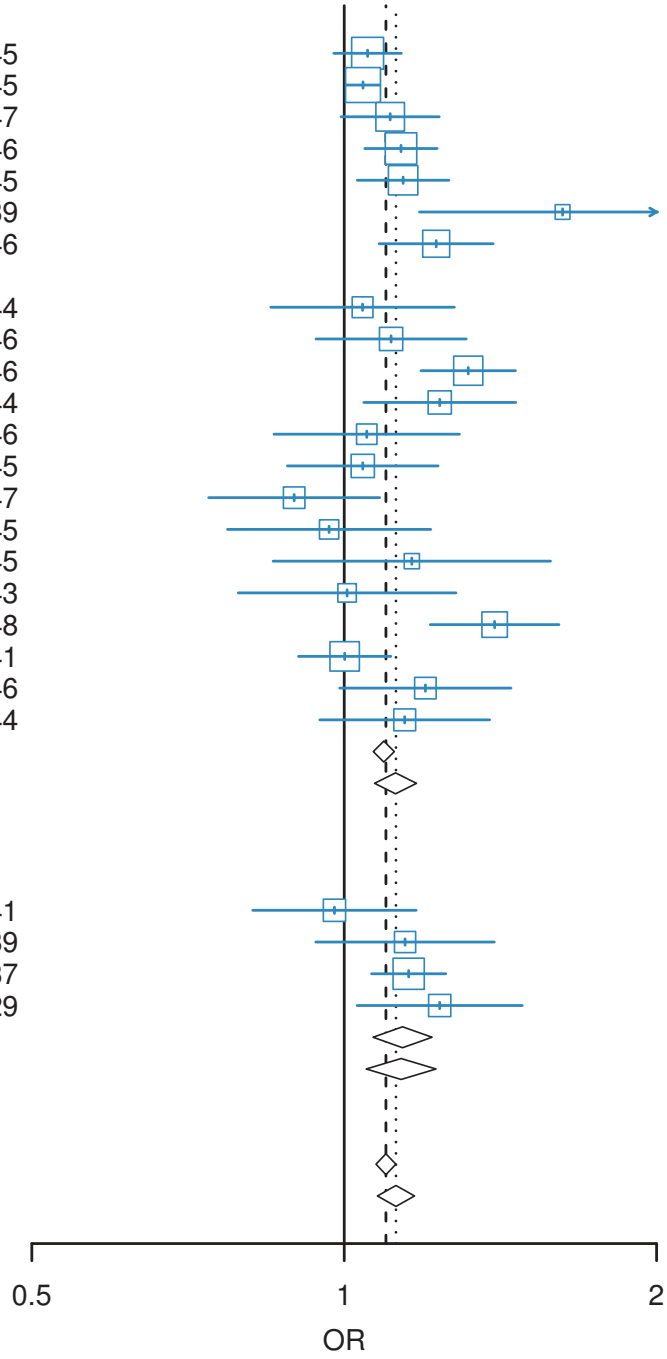
d. rs6419573 (2q12.1, IL18R1/IL18RAP), effect allele=T

Study	PROPER INFO	MACH R2	EAF
EUR			
23andMe V2		0.98	0.24
23andMe V3		0.98	0.24
AAGC	0.99		0.23
ALSPAC		0.98	0.23
B58C		0.98	0.23
BAMSE		0.98	0.24
CHOP	0.99		0.25
COPSAC2000			
DNBC	0.99		0.24
GenerationR–CAUC		0.98	0.24
GENEVA/KORA F4/POPGEN	0.97		0.27
GENUFADex–SHIP1		0.95	0.29
GENUFAD–SHIP2		0.94	0.29
GINI/LISA	0.97		0.28
INMA	0.99		0.26
MAAS	0.99		0.23
MAS–HNR		0.98	0.24
MoBa	0.99		0.24
NCRC–ADC	0.89		0.23
NFBC66	0.99		0.21
NTR		0.97	0.23
SAPALDIA		0.98	0.24
Fixed effect model			
Random effects model			
Heterogeneity: I–squared=0%, p=0.5597			
non EUR			
GALA II	0.98		0.40
GenerationR–NONCAUC		0.98	0.32
RIKEN		0.98	0.45
SAPPHIRE	0.97		0.13
Fixed effect model			
Random effects model			
Heterogeneity: I–squared=0%, p=0.6601			
Fixed effect model			
Random effects model			
Heterogeneity: I–squared=22%, p=0.1604			

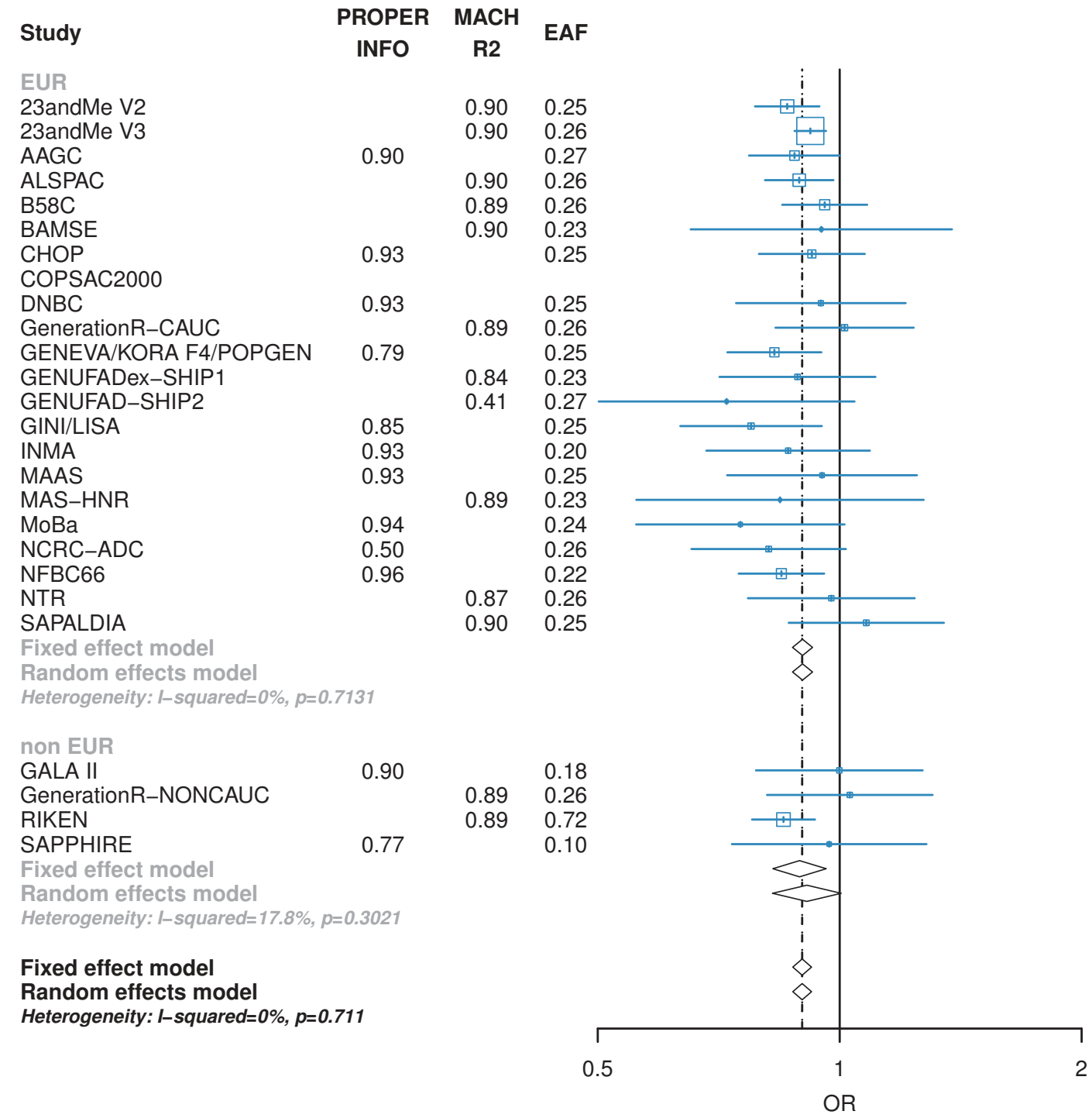


e. rs2212434 (11q13.5, C11orf30/LRRC32), effect allele=T

Study	PROPER INFO	MACH R2	EAF
EUR			
23andMe V2		0.99	0.45
23andMe V3		0.99	0.45
AAGC	0.99		0.47
ALSPAC		0.99	0.46
B58C		0.99	0.45
BAMSE		0.99	0.39
CHOP	0.99		0.46
COPSAC2000			
DNBC	0.99		0.44
GenerationR–CAUC		0.98	0.46
GENEVA/KORA F4/POPGEN	0.99		0.46
GENUFADex–SHIP1		0.98	0.44
GENUFAD–SHIP2		0.97	0.46
GINI/LISA	0.97		0.45
INMA	0.99		0.47
MAAS	0.99		0.45
MAS–HNR		0.99	0.45
MoBa	1.00		0.43
NCRC–ADC	0.92		0.48
NFBC66	1.00		0.41
NTR		0.99	0.46
SAPALDIA		0.99	0.44
Fixed effect model			
Random effects model			
Heterogeneity: I–squared=62.9%, p<0.0001			
non EUR			
GALA II	0.99		0.41
GenerationR–NONCAUC		0.98	0.39
RIKEN		0.94	0.37
SAPPHIRE	0.95		0.29
Fixed effect model			
Random effects model			
Heterogeneity: I–squared=15.6%, p=0.3139			
Fixed effect model			
Random effects model			
Heterogeneity: I–squared=59.2%, p<0.0001			

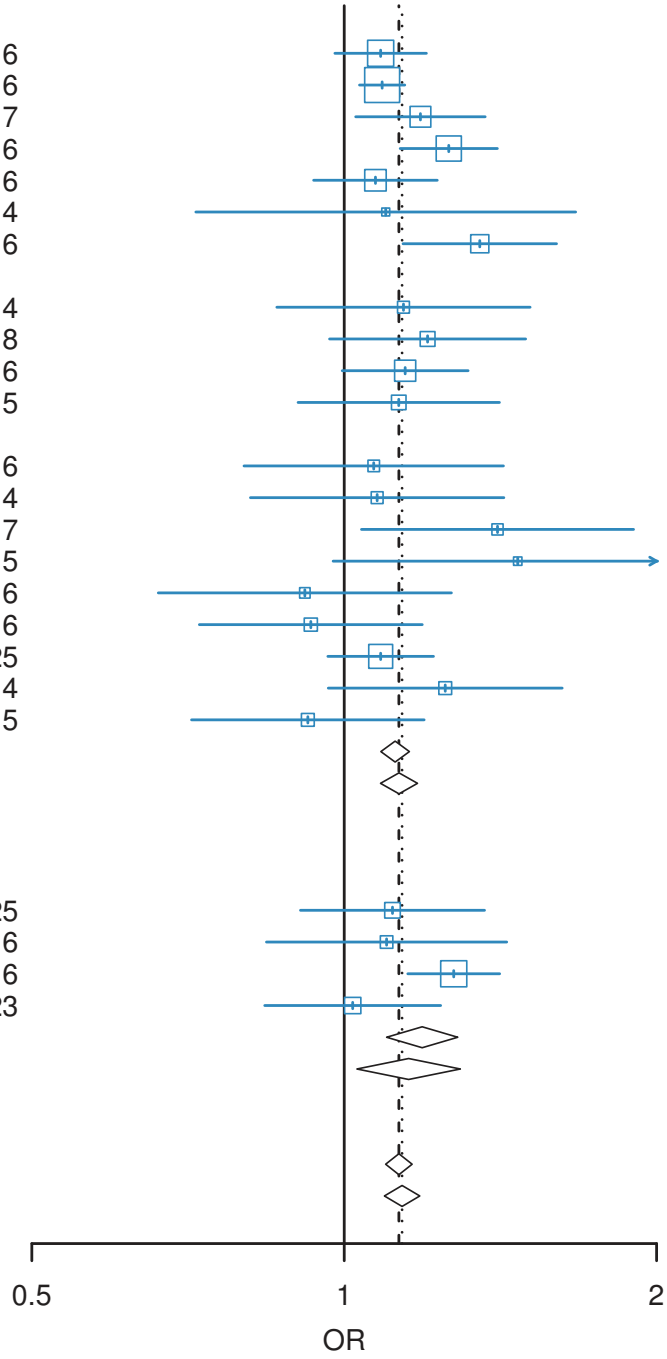


f. rs4809219 (20q13.33, RTEL1−TNFRSF6B), effect allele=C



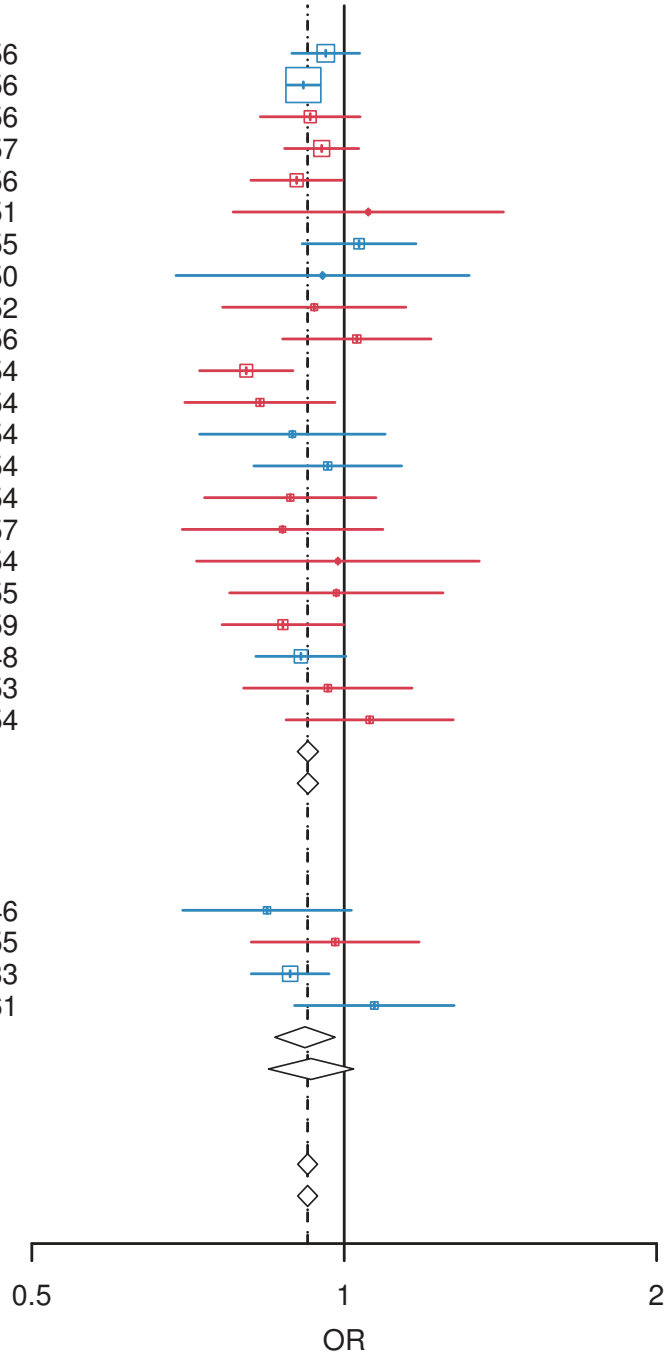
g. rs2918307 (19p13.2, ADAMTS10/ACTL9), effect allele=G

Study	PROPER INFO	MACH R2	EAF
EUR			
23andMe V2		0.99	0.16
23andMe V3		1.00	0.16
AAGC	1.00		0.17
ALSPAC		0.99	0.16
B58C		0.99	0.16
BAMSE		0.99	0.14
CHOP	0.99		0.16
COPSAC2000			
DNBC	1.00		0.14
GenerationR–CAUC		0.99	0.18
GENEVA/KORA F4/POPGEN	0.99		0.16
GENUFADex–SHIP1		0.98	0.15
GENUFAD–SHIP2			
GINI/LISA	0.62		0.16
INMA	1.00		0.14
MAAS	1.00		0.17
MAS–HNR		0.99	0.15
MoBa	0.99		0.16
NCRC–ADC	0.54		0.16
NFBC66	1.00		0.25
NTR		0.99	0.14
SAPALDIA		0.99	0.15
Fixed effect model			
Random effects model			
Heterogeneity: I–squared=18.8%, p=0.2203			
non EUR			
GALA II	0.98		0.25
GenerationR–NONCAUC		0.99	0.16
RIKEN		1.00	0.16
SAPPHIRE	0.95		0.23
Fixed effect model			
Random effects model			
Heterogeneity: I–squared=39.3%, p=0.1758			
Fixed effect model			
Random effects model			
Heterogeneity: I–squared=24%, p=0.1422			



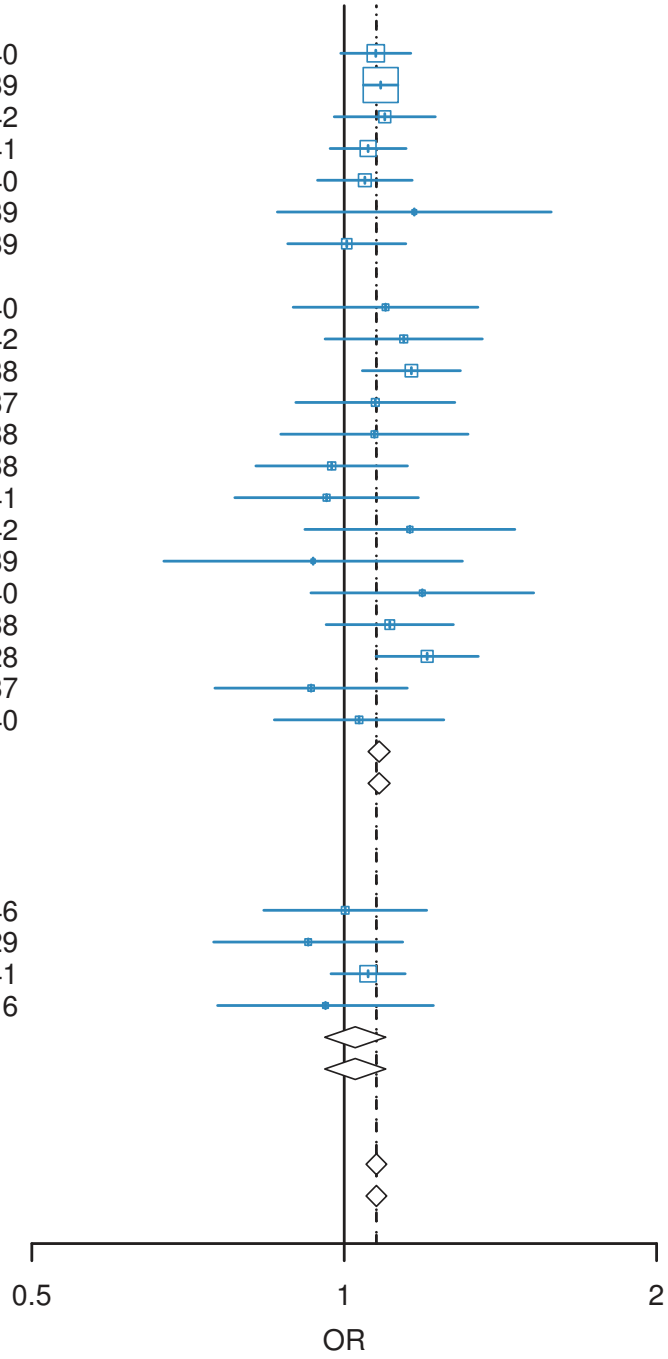
h. rs2041733 (16p13.13, CLEC16A), effect allele=C

Study	PROPER INFO	MACH R2	EAF
EUR			
23andMe V2		1.00	0.56
23andMe V3		1.00	0.56
AAGC	1.00		0.56
ALSPAC		1.00	0.57
B58C		1.00	0.56
BAMSE		0.99	0.51
CHOP	1.00		0.55
COPSAC2000		1.00	0.50
DNBC	1.00		0.52
GenerationR−CAUC		1.00	0.56
GENEVA/KORA F4/POPGEN	1.00		0.54
GENUFADex−SHIP1		1.00	0.54
GENUFAD−SHIP2		0.95	0.54
GINI/LISA	0.97		0.54
INMA	1.00		0.54
MAAS	1.00		0.57
MAS−HNR		1.00	0.54
MoBa	1.00		0.55
NCRC−ADC	1.00		0.59
NFBC66	1.00		0.48
NTR		1.00	0.53
SAPALDIA		1.00	0.54
Fixed effect model			
Random effects model			
Heterogeneity: I−squared=0%, p=0.5046			
non EUR			
GALA II	0.98		0.46
GenerationR−NONCAUC		1.00	0.55
RIKEN		0.99	0.33
SAPPHIRE	0.95		0.61
Fixed effect model			
Random effects model			
Heterogeneity: I−squared=36.7%, p=0.1919			
Fixed effect model			
Random effects model			
Heterogeneity: I−squared=0.1%, p=0.4604			



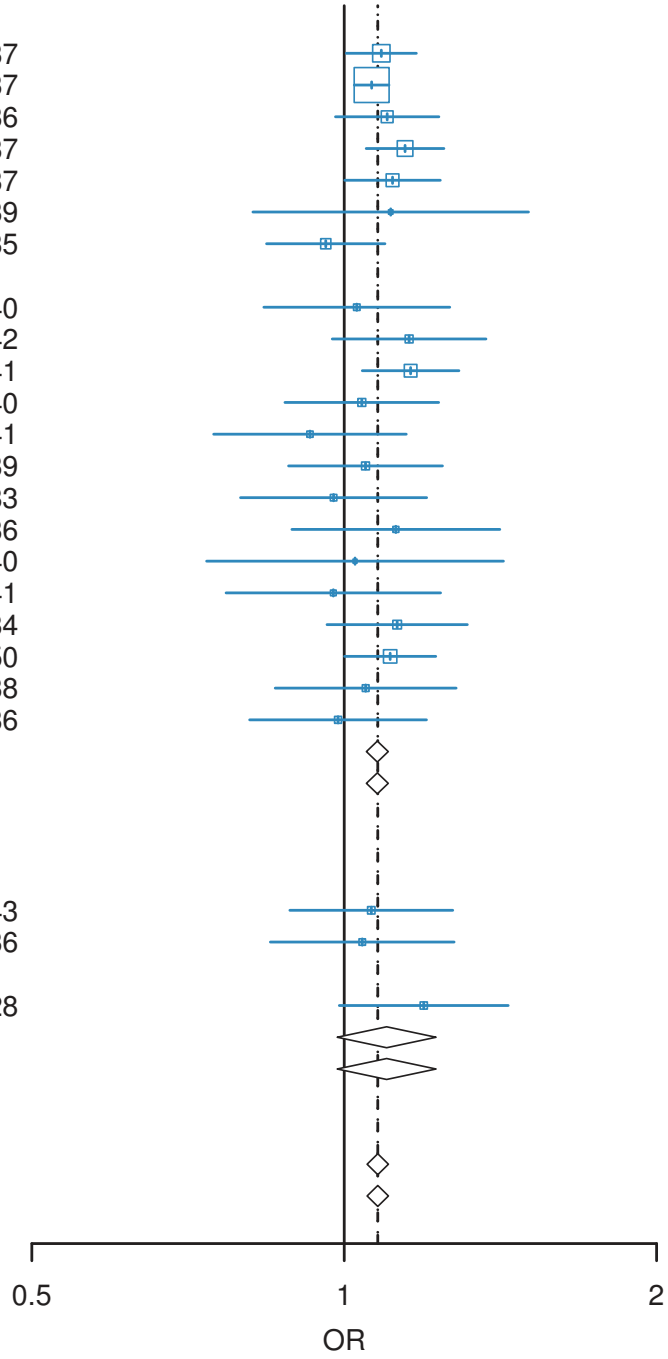
i. rs12730935 (1q21.3, IL6R), effect allele=A

Study	PROPER INFO	MACH R2	EAF
EUR			
23andMe V2		0.96	0.40
23andMe V3		0.96	0.39
AAGC	0.96		0.42
ALSPAC		0.96	0.41
B58C		0.96	0.40
BAMSE		0.96	0.39
CHOP	0.98		0.39
COPSAC2000			
DNBC	0.98		0.40
GenerationR–CAUC		0.95	0.42
GENEVA/KORA F4/POPGEN	0.97		0.38
GENUFADex–SHIP1		0.94	0.37
GENUFAD–SHIP2		0.92	0.38
GINI/LISA	0.96		0.38
INMA	0.96		0.41
MAAS	0.97		0.42
MAS–HNR		0.97	0.39
MoBa	0.97		0.40
NCRC–ADC	0.92		0.38
NFBC66	0.97		0.28
NTR		0.90	0.37
SAPALDIA		0.96	0.40
Fixed effect model			
Random effects model			
Heterogeneity: I–squared=0%, p=0.8135			
non EUR			
GALA II	0.98		0.46
GenerationR–NONCAUC		0.95	0.29
RIKEN		0.94	0.41
SAPPHIRE	0.90		0.16
Fixed effect model			
Random effects model			
Heterogeneity: I–squared=0%, p=0.6225			
Fixed effect model			
Random effects model			
Heterogeneity: I–squared=0%, p=0.7942			

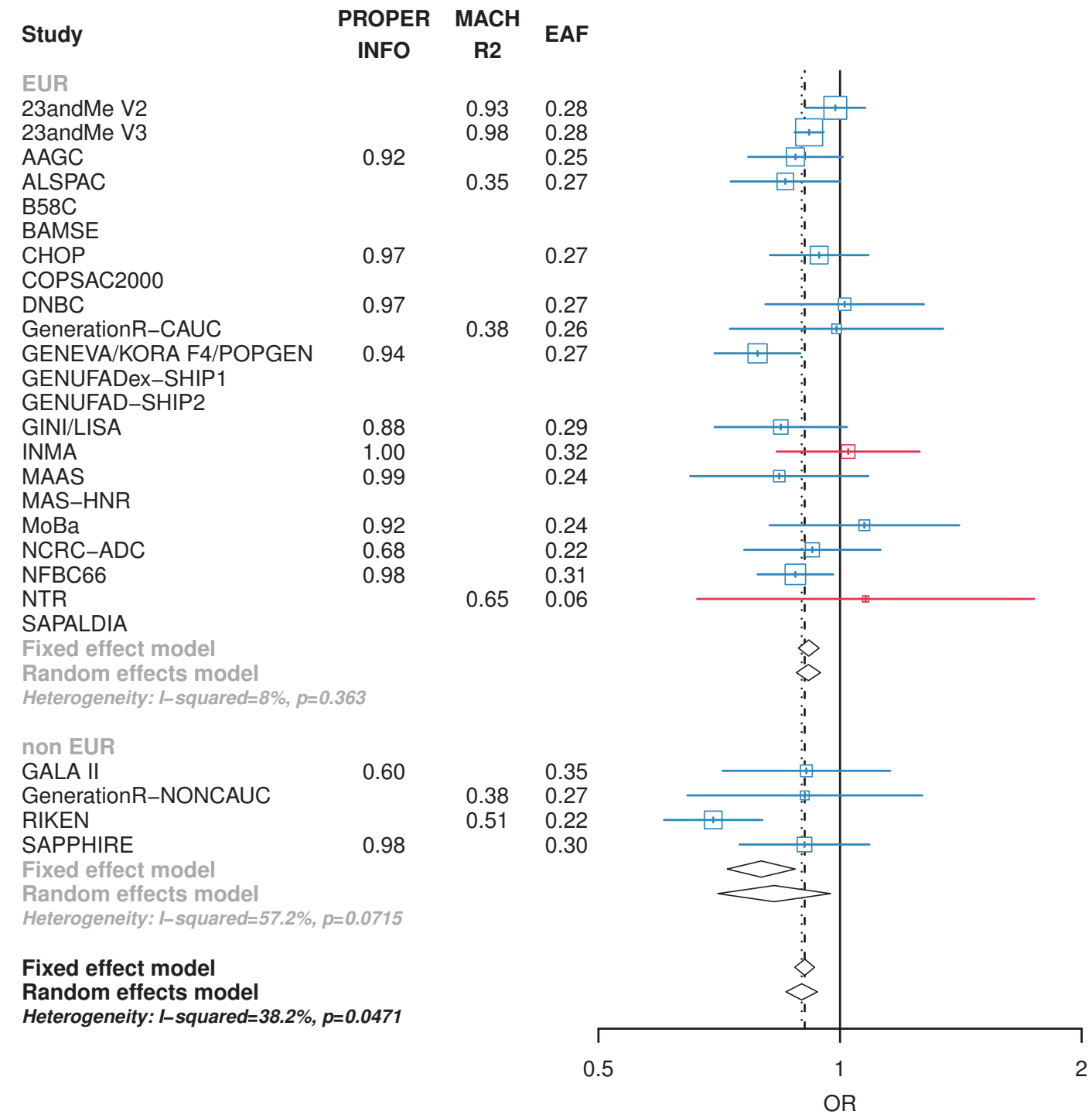


j. 4:123243592:INDEL (4q27, KIAA109 (IL2)), effect allele=R

Study	PROPER INFO	MACH R2	EAF
EUR			
23andMe V2		0.97	0.37
23andMe V3		0.98	0.37
AAGC	0.98		0.36
ALSPAC		0.97	0.37
B58C		0.97	0.37
BAMSE		0.98	0.39
CHOP	0.98		0.35
COPSAC2000			
DNBC	0.98		0.40
GenerationR–CAUC		0.97	0.42
GENEVA/KORA F4/POPGEN	0.98		0.41
GENUFADex–SHIP1		0.97	0.40
GENUFAD–SHIP2		0.89	0.41
GINI/LISA	0.97		0.39
INMA	0.99		0.33
MAAS	0.99		0.36
MAS–HNR		0.97	0.40
MoBa	0.99		0.41
NCRC–ADC	0.80		0.34
NFBC66	0.99		0.50
NTR		0.97	0.38
SAPALDIA		0.97	0.36
Fixed effect model			
Random effects model			
Heterogeneity: I–squared=0%, p=0.839			
non EUR			
GALA II	0.99		0.43
GenerationR–NONCAUC		0.97	0.36
RIKEN			
SAPPHIRE	0.98		0.28
Fixed effect model			
Random effects model			
Heterogeneity: I–squared=0%, p=0.5629			
Fixed effect model			
Random effects model			
Heterogeneity: I–squared=0%, p=0.8907			

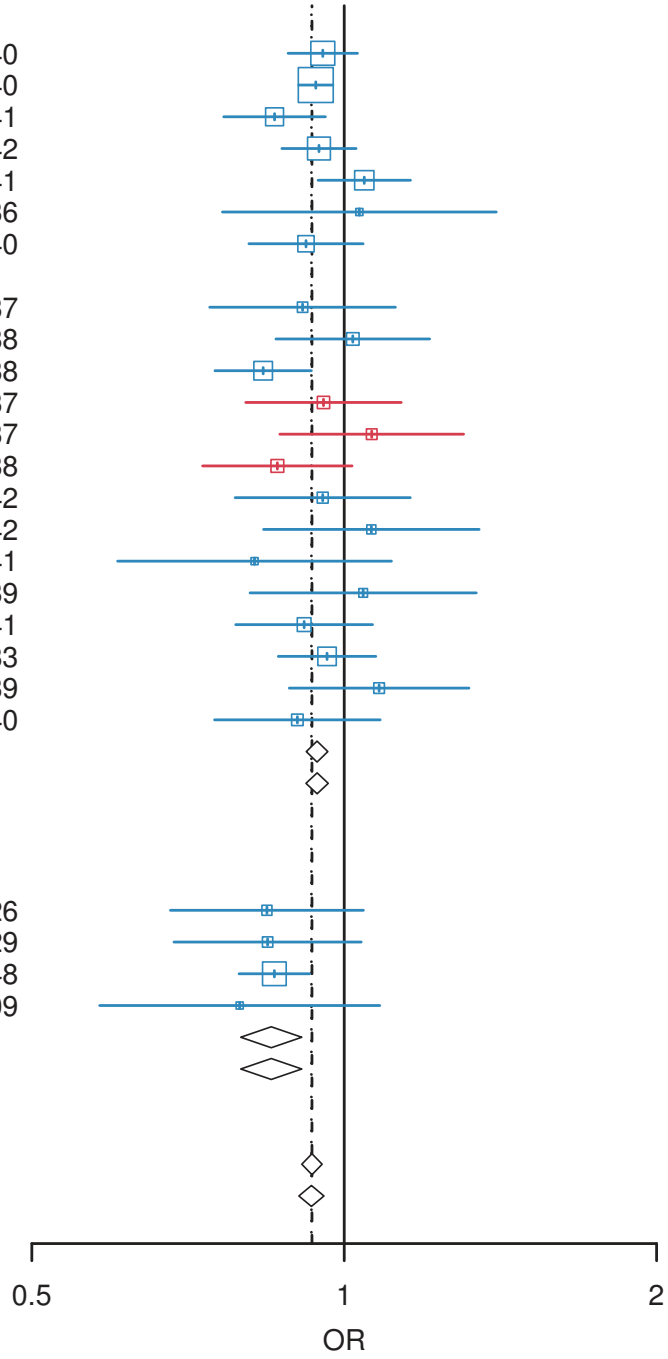


k. rs4713555 (6p21.32, HLA−DRB/HLA−DQA1), effect allele=T

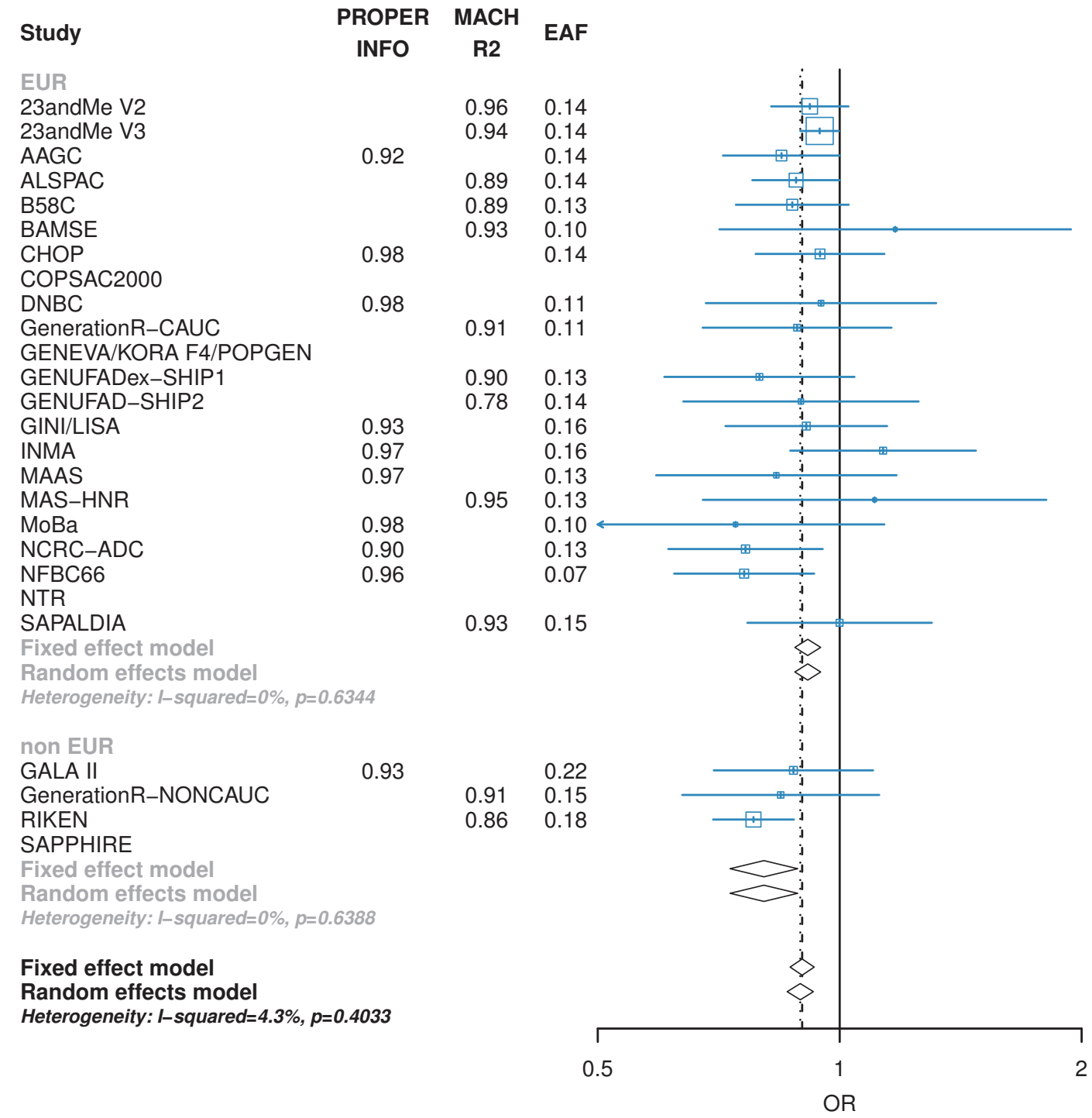


I. rs2944542 (10q21.2, ZNF365), effect allele=C

Study	PROPER INFO	MACH R2	EAF
EUR			
23andMe V2		1.00	0.40
23andMe V3		1.00	0.40
AAGC	1.00		0.41
ALSPAC		1.00	0.42
B58C		1.00	0.41
BAMSE		1.00	0.36
CHOP	1.00		0.40
COPSAC2000			
DNBC	1.00		0.37
GenerationR–CAUC		0.97	0.38
GENEVA/KORA F4/POPGEN	0.99		0.38
GENUFADex–SHIP1		1.00	0.37
GENUFAD–SHIP2		1.00	0.37
GINI/LISA	1.00		0.38
INMA	1.00		0.42
MAAS	1.00		0.42
MAS–HNR		1.00	0.41
MoBa	1.00		0.39
NCRC–ADC	0.79		0.41
NFBC66	0.99		0.33
NTR		1.00	0.39
SAPALDIA		1.00	0.40
Fixed effect model			
Random effects model			
Heterogeneity: I–squared=1.5%, p=0.4385			
non EUR			
GALA II	1.00		0.26
GenerationR–NONCAUC		0.97	0.29
RIKEN		1.00	0.48
SAPPHIRE	0.97		0.09
Fixed effect model			
Random effects model			
Heterogeneity: I–squared=0%, p=0.9712			
Fixed effect model			
Random effects model			
Heterogeneity: I–squared=15%, p=0.25			

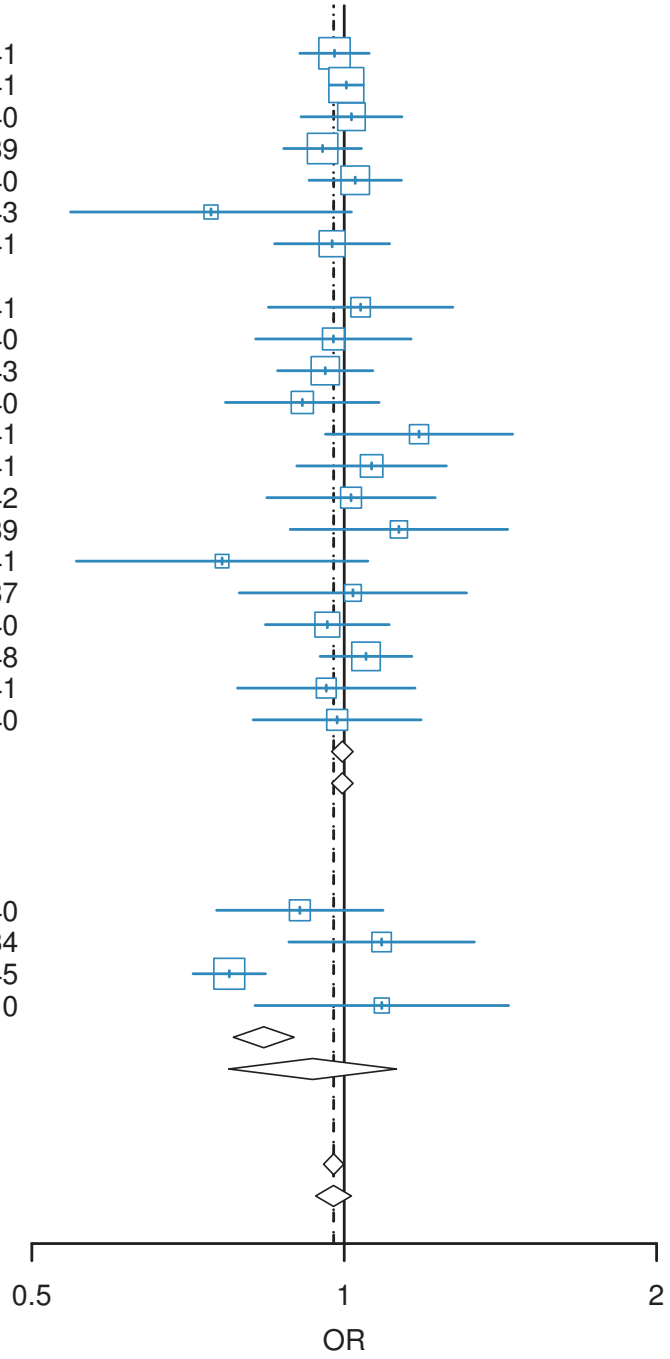


m. rs145809981 (6p21.33, MICB), effect allele=T



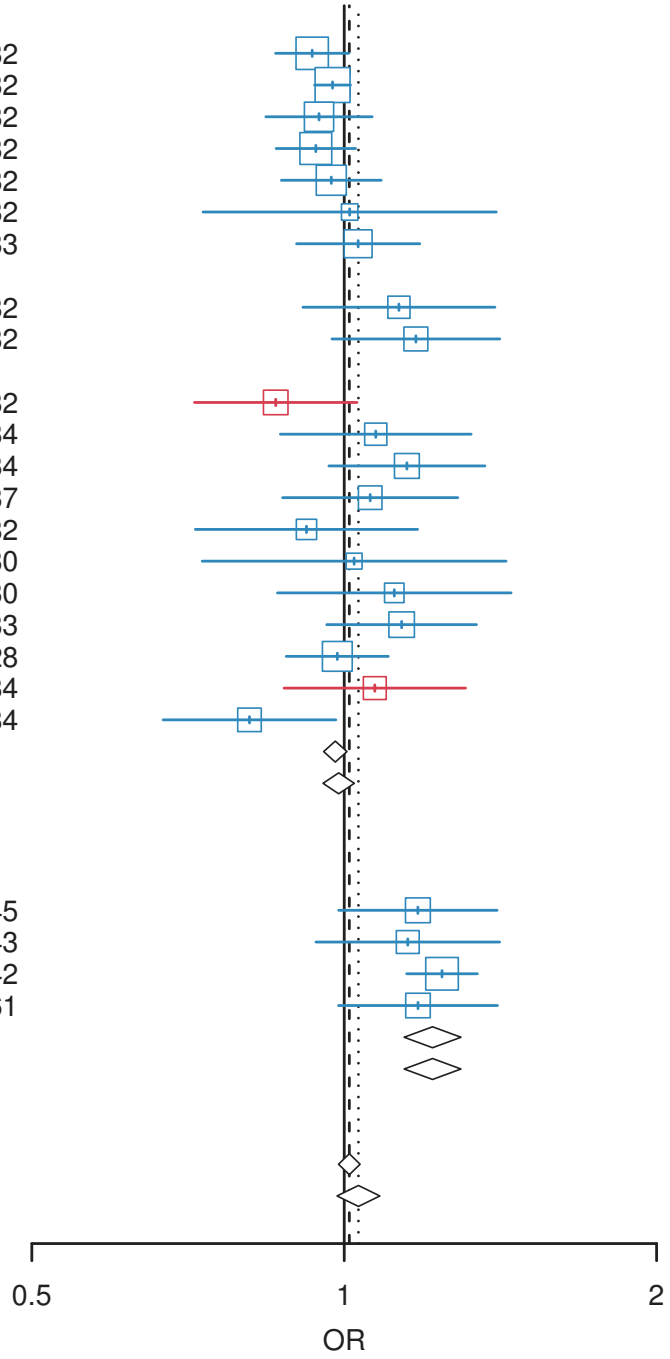
n. rs4312054 (11p15.4, OR10A3/NLRP10), effect allele=G

Study	PROPER INFO	MACH R2	EAF
EUR			
23andMe V2		0.97	0.41
23andMe V3		1.00	0.41
AAGC	0.98		0.40
ALSPAC		0.97	0.39
B58C		0.97	0.40
BAMSE		0.97	0.43
CHOP	0.98		0.41
COPSAC2000			
DNBC	0.98		0.41
GenerationR–CAUC		0.97	0.40
GENEVA/KORA F4/POPGEN	0.98		0.43
GENUFADex–SHIP1		0.97	0.40
GENUFAD–SHIP2		0.95	0.41
GINI/LISA	0.97		0.41
INMA	1.00		0.42
MAAS	0.98		0.39
MAS–HNR		0.97	0.41
MoBa	0.99		0.37
NCRC–ADC	0.98		0.40
NFBC66	0.98		0.48
NTR		0.98	0.41
SAPALDIA		0.97	0.40
Fixed effect model			
Random effects model			
Heterogeneity: I–squared=0%, p=0.7574			
non EUR			
GALA II	0.98		0.40
GenerationR–NONCAUC		0.97	0.34
RIKEN		0.99	0.45
SAPPHIRE	0.88		0.10
Fixed effect model			
Random effects model			
Heterogeneity: I–squared=78.2%, p=0.0033			
Fixed effect model			
Random effects model			
Heterogeneity: I–squared=53.8%, p=0.0008			



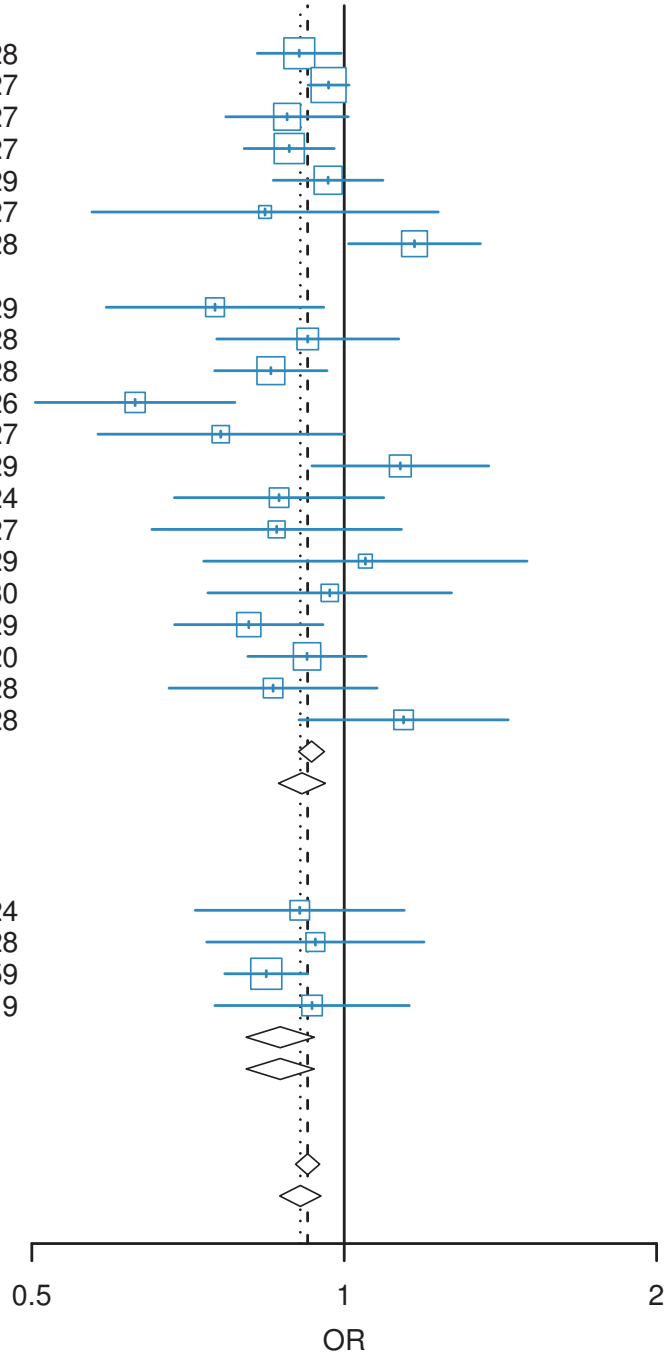
o. rs1249910 (3q13.2, CCDC80/CD200R1L), effect allele=A

Study	PROPER INFO	MACH R2	EAF
EUR			
23andMe V2		0.97	0.32
23andMe V3		0.99	0.32
AAGC	0.97		0.32
ALSPAC		0.96	0.32
B58C		0.95	0.32
BAMSE		0.98	0.32
CHOP	0.97		0.33
COPSAC2000			
DNBC	0.98		0.32
GenerationR–CAUC		0.96	0.32
GENEVA/KORA F4/POPGEN			
GENUFADex–SHIP1		1.00	0.32
GENUFAD–SHIP2		0.99	0.34
GINI/LISA	1.00		0.34
INMA	0.99		0.37
MAAS	0.98		0.32
MAS–HNR		0.97	0.30
MoBa	0.98		0.30
NCRC–ADC	0.71		0.33
NFBC66	0.97		0.28
NTR		1.00	0.34
SAPALDIA		0.97	0.34
Fixed effect model			
Random effects model			
Heterogeneity: I–squared=21.4%, p=0.1899			
non EUR			
GALA II	1.00		0.45
GenerationR–NONCAUC		0.96	0.43
RIKEN		1.00	0.42
SAPPHIRE	0.97		0.61
Fixed effect model			
Random effects model			
Heterogeneity: I–squared=0%, p=0.8457			
Fixed effect model			
Random effects model			
Heterogeneity: I–squared=63.8%, p<0.0001			

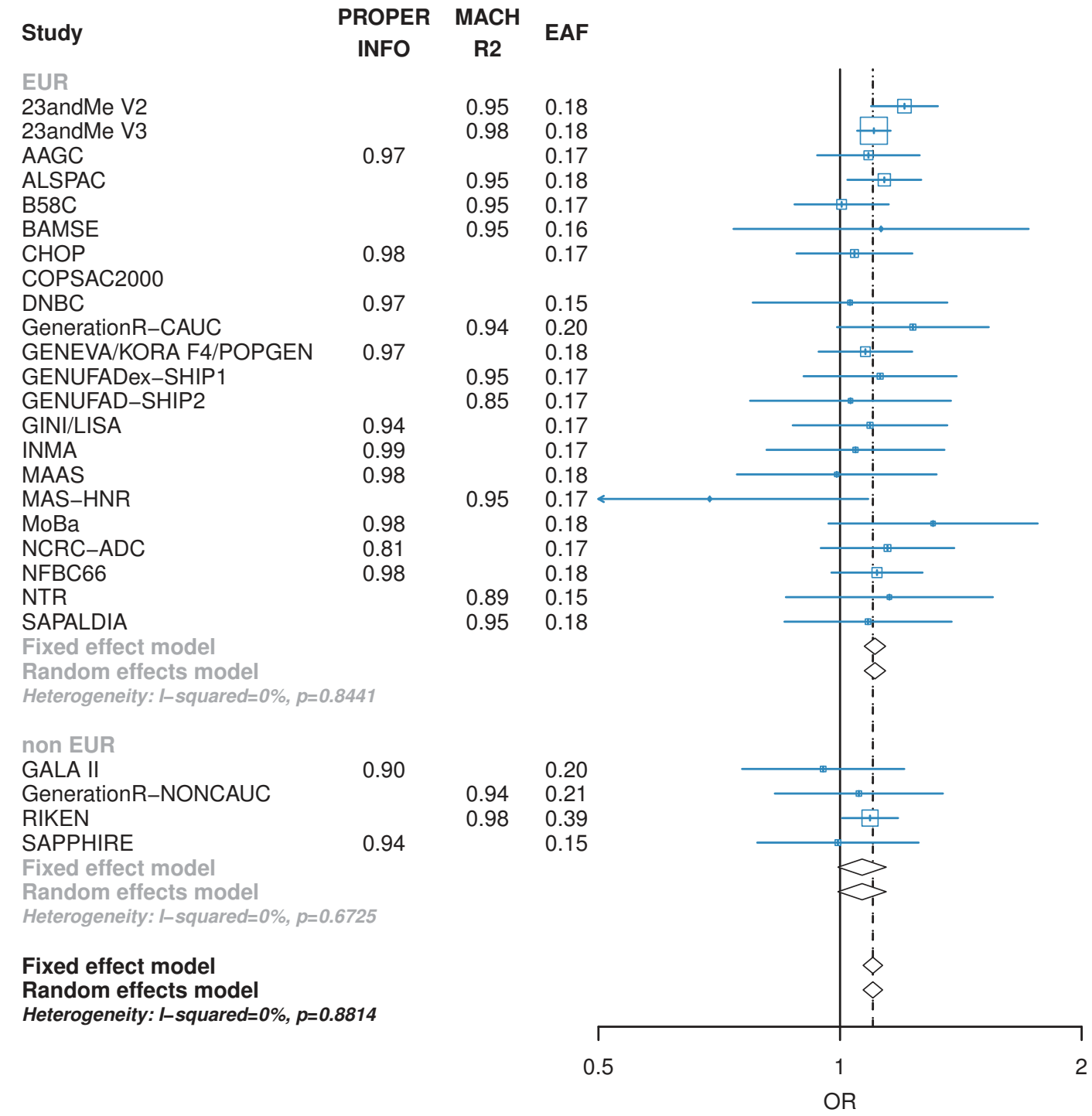


p. rs2592555 (11p13, PRR5L), effect allele=C

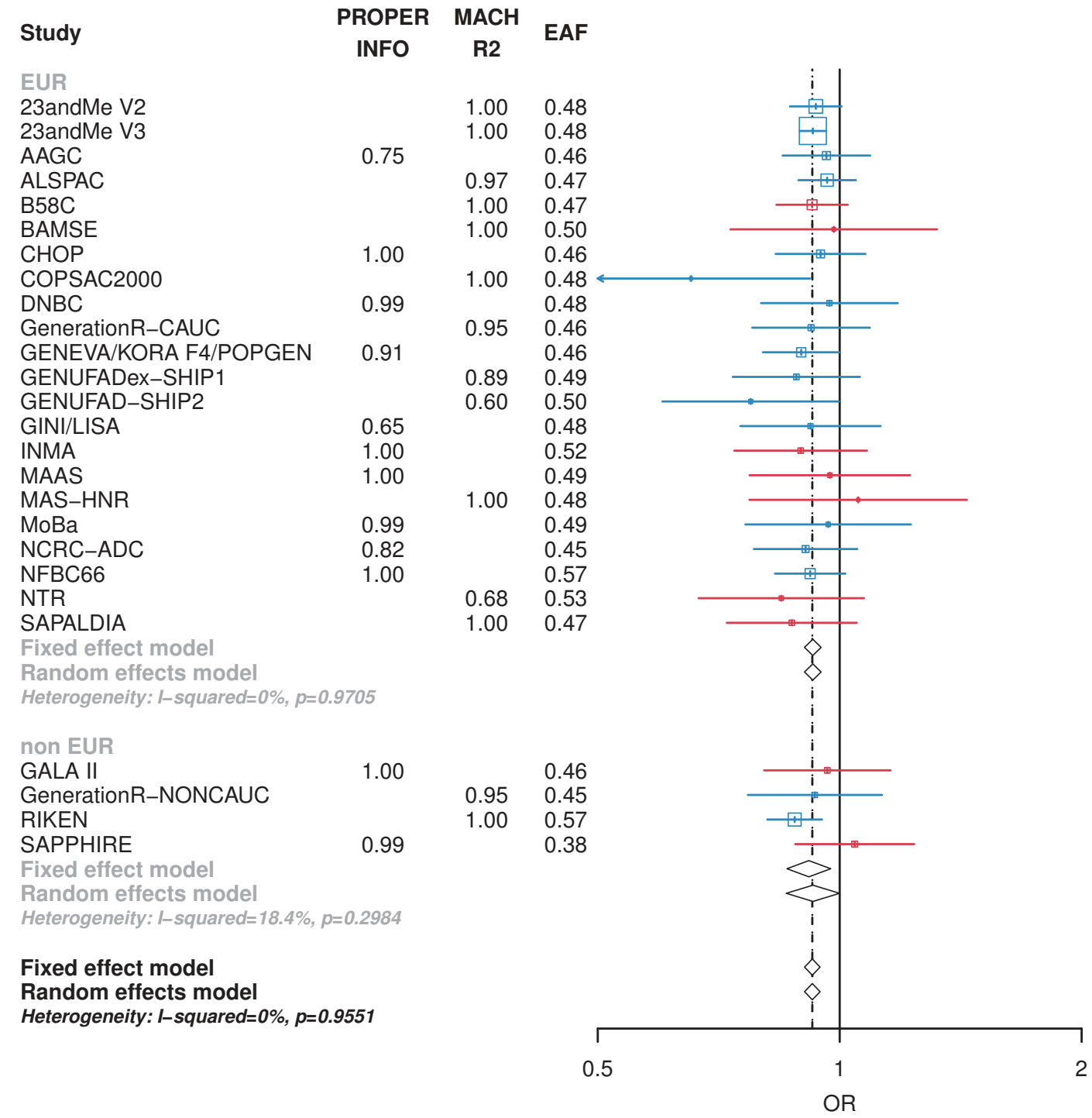
Study	PROPER INFO	MACH R2	EAF
EUR			
23andMe V2		0.84	0.28
23andMe V3		0.84	0.27
AAGC	0.85		0.27
ALSPAC		0.84	0.27
B58C		0.83	0.29
BAMSE		0.86	0.27
CHOP	0.89		0.28
COPSAC2000			
DNBC	0.91		0.29
GenerationR–CAUC		0.82	0.28
GENEVA/KORA F4/POPGEN	0.88		0.28
GENUFADex–SHIP1		0.84	0.26
GENUFAD–SHIP2		0.72	0.27
GINI/LISA	0.86		0.29
INMA	0.87		0.24
MAAS	0.89		0.27
MAS–HNR		0.84	0.29
MoBa	0.92		0.30
NCRC–ADC	0.85		0.29
NFBC66	0.90		0.20
NTR		0.79	0.28
SAPALDIA		0.83	0.28
Fixed effect model			
Random effects model			
Heterogeneity: I–squared=55.6%, p=0.0011			
non EUR			
GALA II	0.84		0.24
GenerationR–NONCAUC		0.82	0.28
RIKEN		0.73	0.59
SAPPHIRE	0.82		0.19
Fixed effect model			
Random effects model			
Heterogeneity: I–squared=0%, p=0.7095			
Fixed effect model			
Random effects model			
Heterogeneity: I–squared=51.2%, p=0.0018			



q. rs2038255 (14q13.2, PPP2R3C), effect allele=T

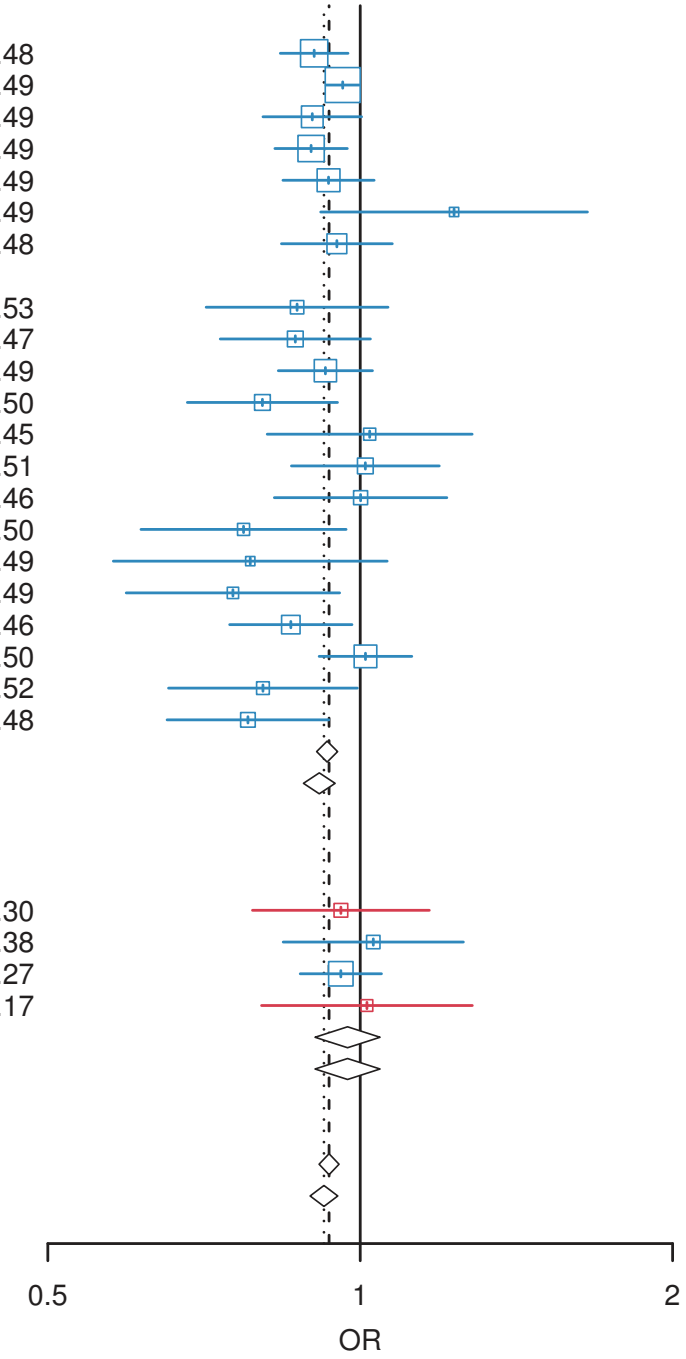


r. rs7127307 (11q24.3, –/ETS1), effect allele=C



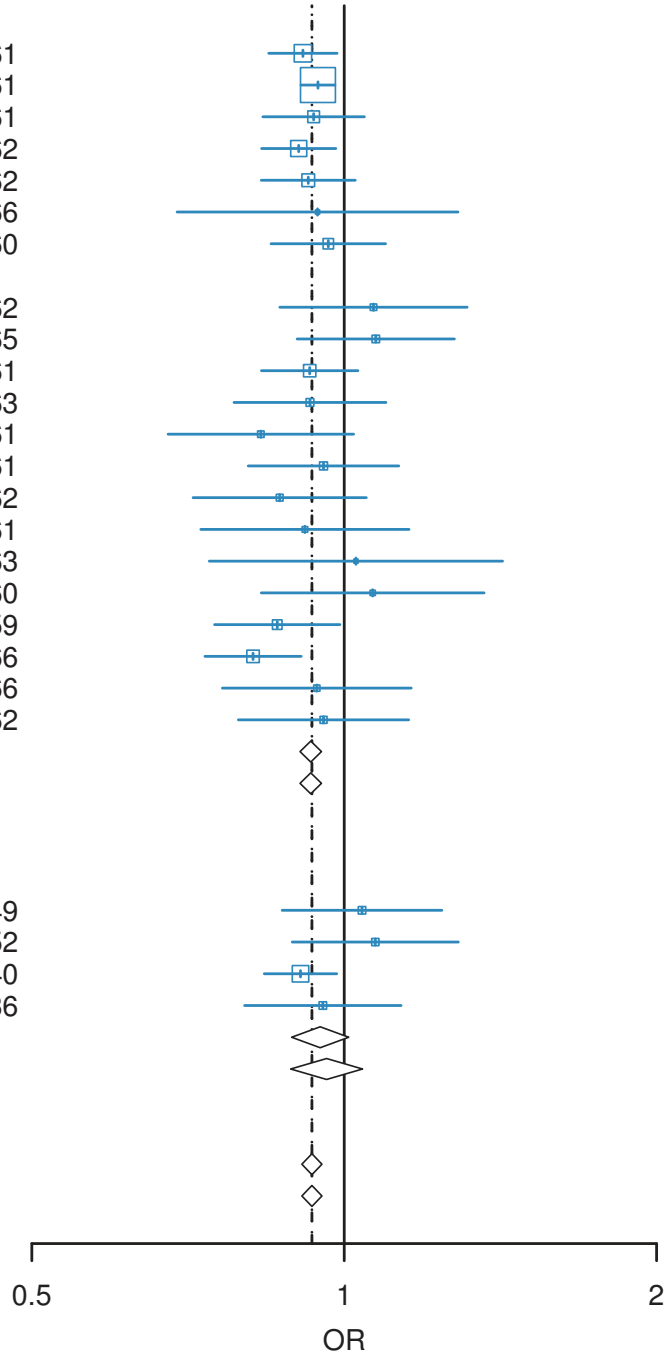
s. rs7512552 (1q21.2, C1orf51/MRPS21), effect allele=T

Study	PROPER INFO	MACH R2	EAF
EUR			
23andMe V2		0.99	0.48
23andMe V3		1.00	0.49
AAGC	0.99		0.49
ALSPAC		0.99	0.49
B58C		0.99	0.49
BAMSE		0.99	0.49
CHOP	1.00		0.48
COPSAC2000			
DNBC	1.00		0.53
GenerationR–CAUC		0.99	0.47
GENEVA/KORA F4/POPGEN	0.98		0.49
GENUFADex–SHIP1		0.99	0.50
GENUFAD–SHIP2		0.78	0.45
GINI/LISA	0.97		0.51
INMA	1.00		0.46
MAAS	0.99		0.50
MAS–HNR		0.99	0.49
MoBa	0.99		0.49
NCRC–ADC	0.96		0.46
NFBC66	0.99		0.50
NTR		0.90	0.52
SAPALDIA		0.99	0.48
Fixed effect model			
Random effects model			
Heterogeneity: I–squared=35.6%, p=0.0544			
non EUR			
GALA II	1.00		0.30
GenerationR–NONCAUC		0.99	0.38
RIKEN		0.99	0.27
SAPPHIRE	0.97		0.17
Fixed effect model			
Random effects model			
Heterogeneity: I–squared=0%, p=0.9033			
Fixed effect model			
Random effects model			
Heterogeneity: I–squared=27.3%, p=0.104			



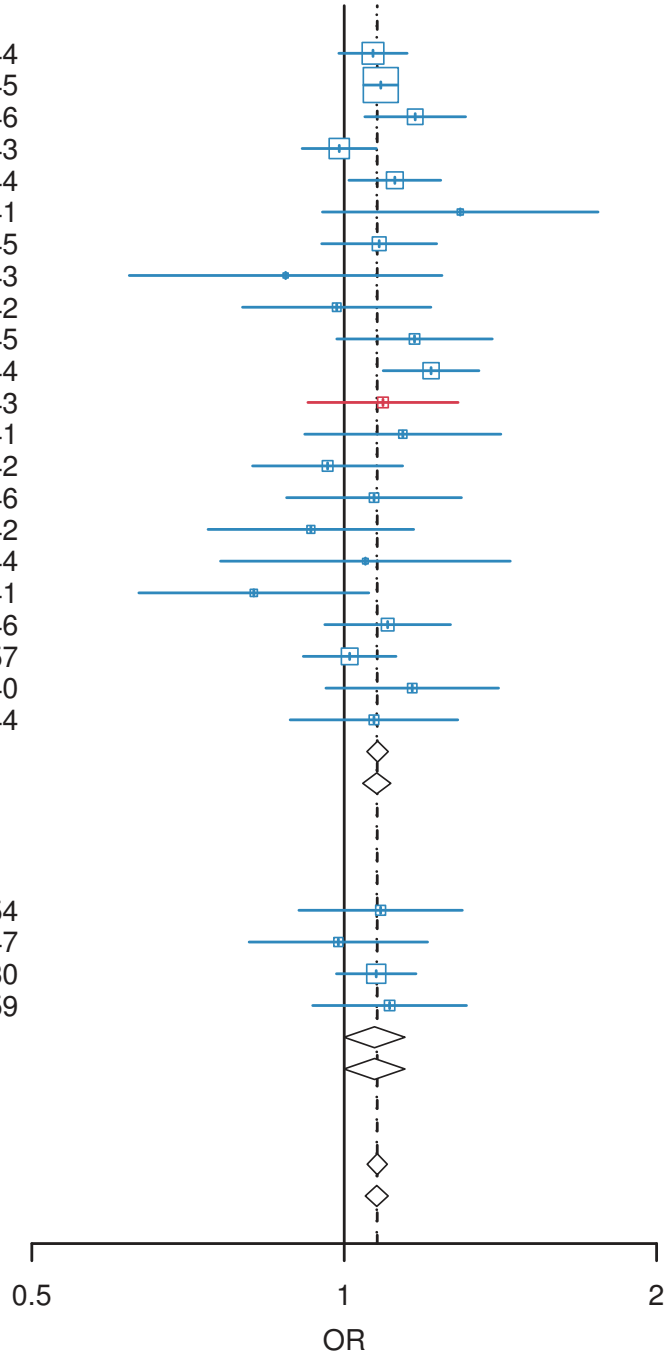
t. rs6473227 (8q21.13, MIR5708/ZBTB10), effect allele=A

Study	PROPER INFO	MACH R2	EAF
EUR			
23andMe V2		1.00	0.61
23andMe V3		1.00	0.61
AAGC	1.00		0.61
ALSPAC		1.00	0.62
B58C		1.00	0.62
BAMSE		0.99	0.66
CHOP	1.00		0.60
COPSAC2000			
DNBC	1.00		0.62
GenerationR–CAUC		1.00	0.65
GENEVA/KORA F4/POPGEN	0.99		0.61
GENUFADex–SHIP1		0.99	0.63
GENUFAD–SHIP2		0.98	0.61
GINI/LISA	0.98		0.61
INMA	1.00		0.62
MAAS	1.00		0.61
MAS–HNR		1.00	0.63
MoBa	1.00		0.60
NCRC–ADC	0.96		0.59
NFBC66	1.00		0.66
NTR		0.99	0.66
SAPALDIA		1.00	0.62
Fixed effect model			
Random effects model			
Heterogeneity: I–squared=0%, p=0.7137			
non EUR			
GALA II	0.98		0.49
GenerationR–NONCAUC		1.00	0.52
RIKEN		1.00	0.40
SAPPHIRE	0.95		0.36
Fixed effect model			
Random effects model			
Heterogeneity: I–squared=22.8%, p=0.274			
Fixed effect model			
Random effects model			
Heterogeneity: I–squared=0%, p=0.6795			

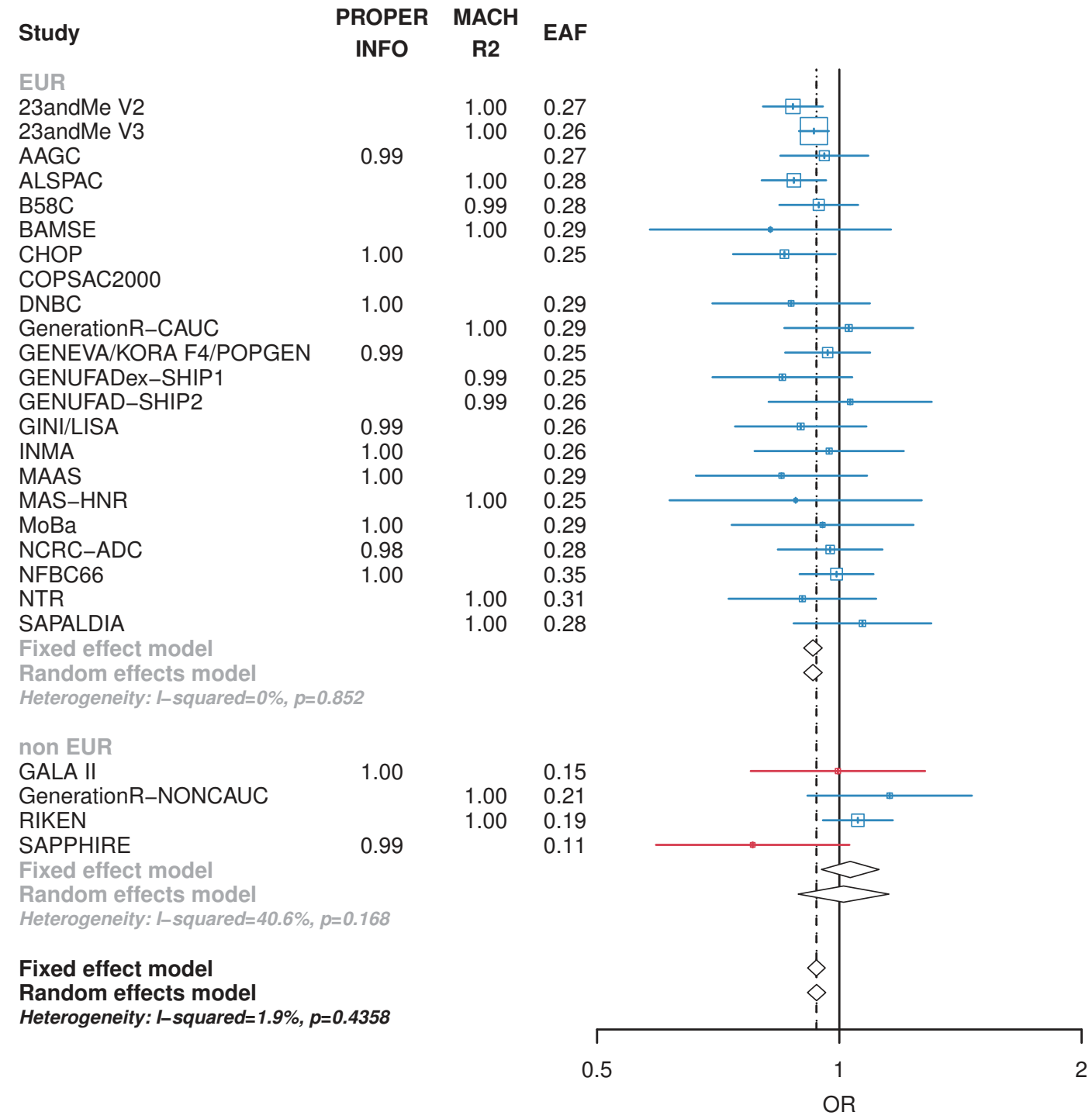


u. rs6602364 (10p15.1, IL15RA/IL2RA), effect allele=G

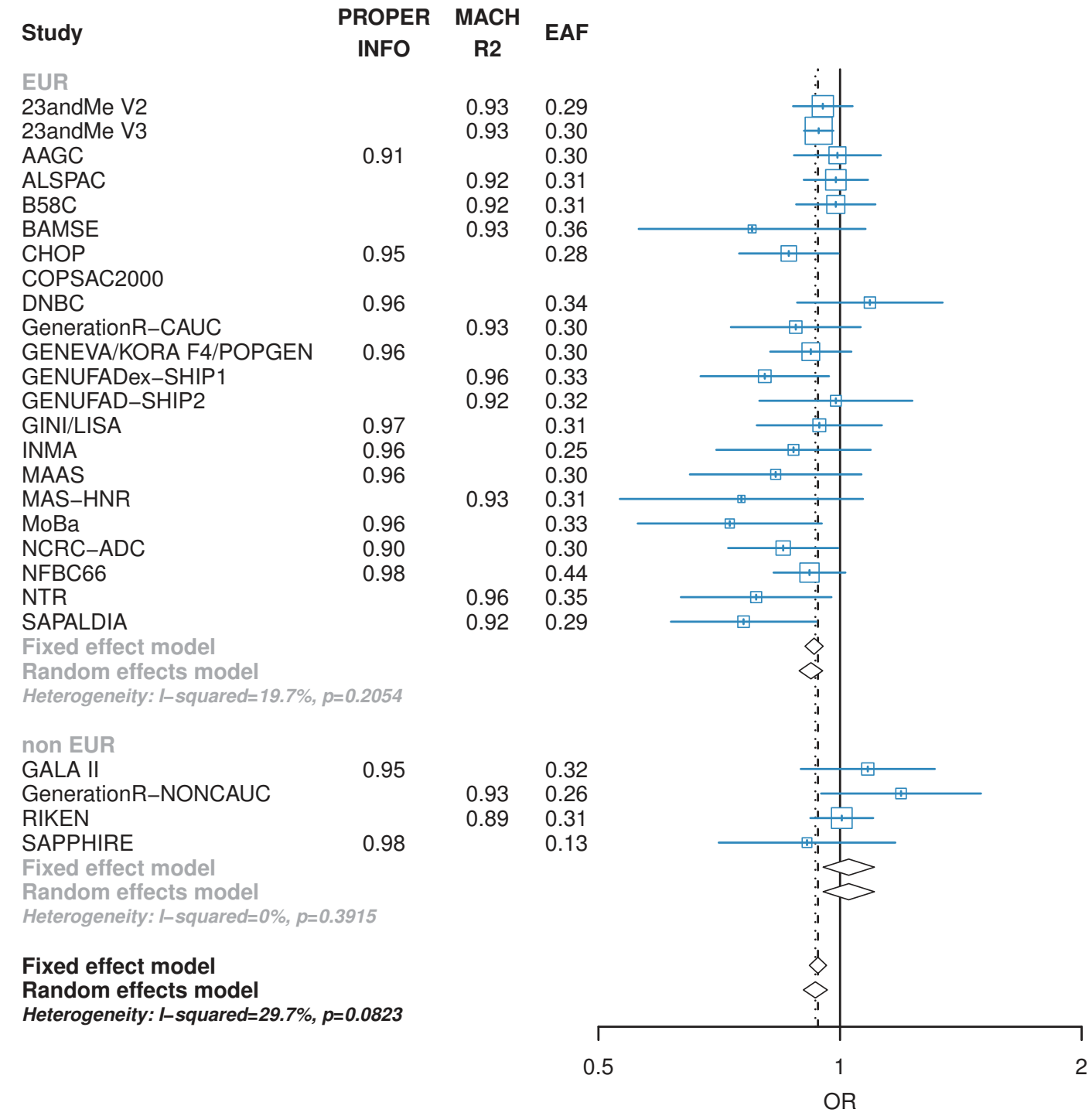
Study	PROPER INFO	MACH R2	EAF
EUR			
23andMe V2		0.97	0.44
23andMe V3		0.97	0.45
AAGC	0.96		0.46
ALSPAC		0.97	0.43
B58C		0.97	0.44
BAMSE		0.97	0.41
CHOP	0.97		0.45
COPSAC2000		0.95	0.43
DNBC	0.98		0.42
GenerationR–CAUC		0.95	0.45
GENEVA/KORA F4/POPGEN	0.95		0.44
GENUFADex–SHIP1		1.00	0.43
GENUFAD–SHIP2		0.86	0.41
GINI/LISA	0.93		0.42
INMA	0.98		0.46
MAAS	0.98		0.42
MAS–HNR		0.96	0.44
MoBa	0.98		0.41
NCRC–ADC	0.89		0.46
NFBC66	0.98		0.57
NTR		0.94	0.40
SAPALDIA		0.97	0.44
Fixed effect model			
Random effects model			
Heterogeneity: I–squared=20.2%, p=0.1952			
non EUR			
GALA II	0.96		0.54
GenerationR–NONCAUC		0.95	0.47
RIKEN		0.93	0.30
SAPPHIRE	0.86		0.59
Fixed effect model			
Random effects model			
Heterogeneity: I–squared=0%, p=0.8477			
Fixed effect model			
Random effects model			
Heterogeneity: I–squared=7.9%, p=0.3488			



v. rs10214237 (5p13.2, IL7R/CAPSL), effect allele=C

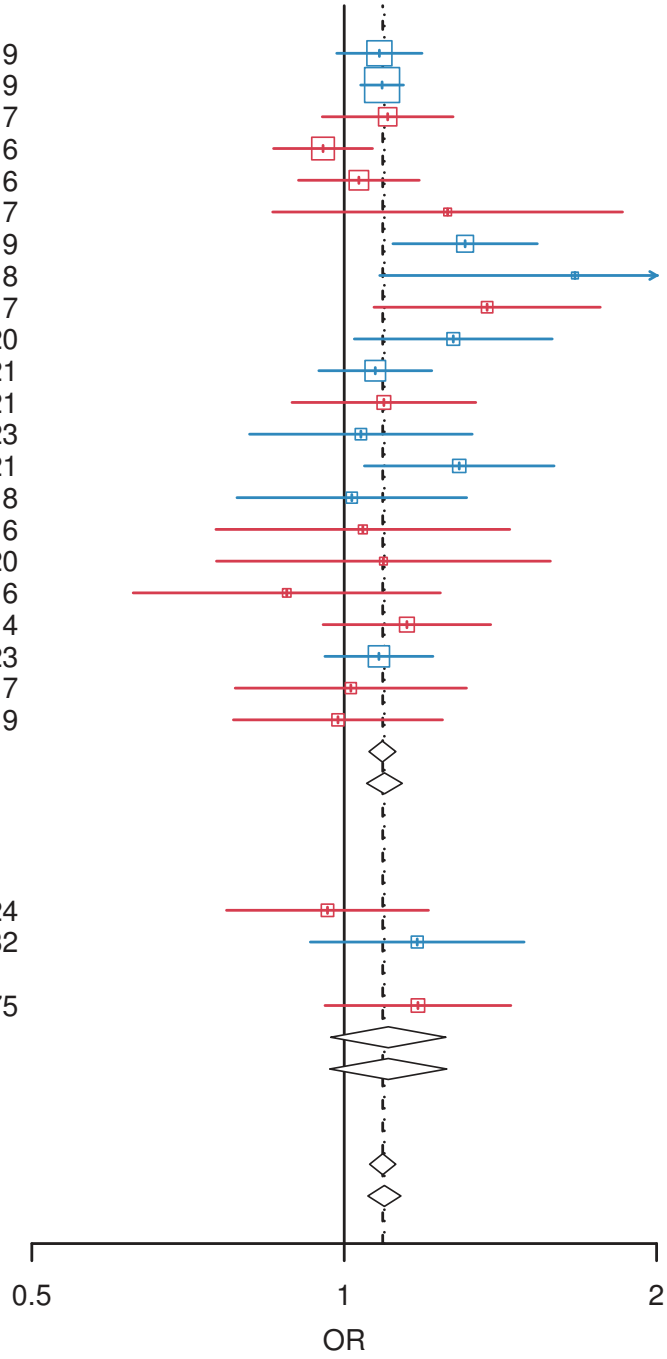


w. rs10199605 (2p25.1, LINC00299/–), effect allele=A

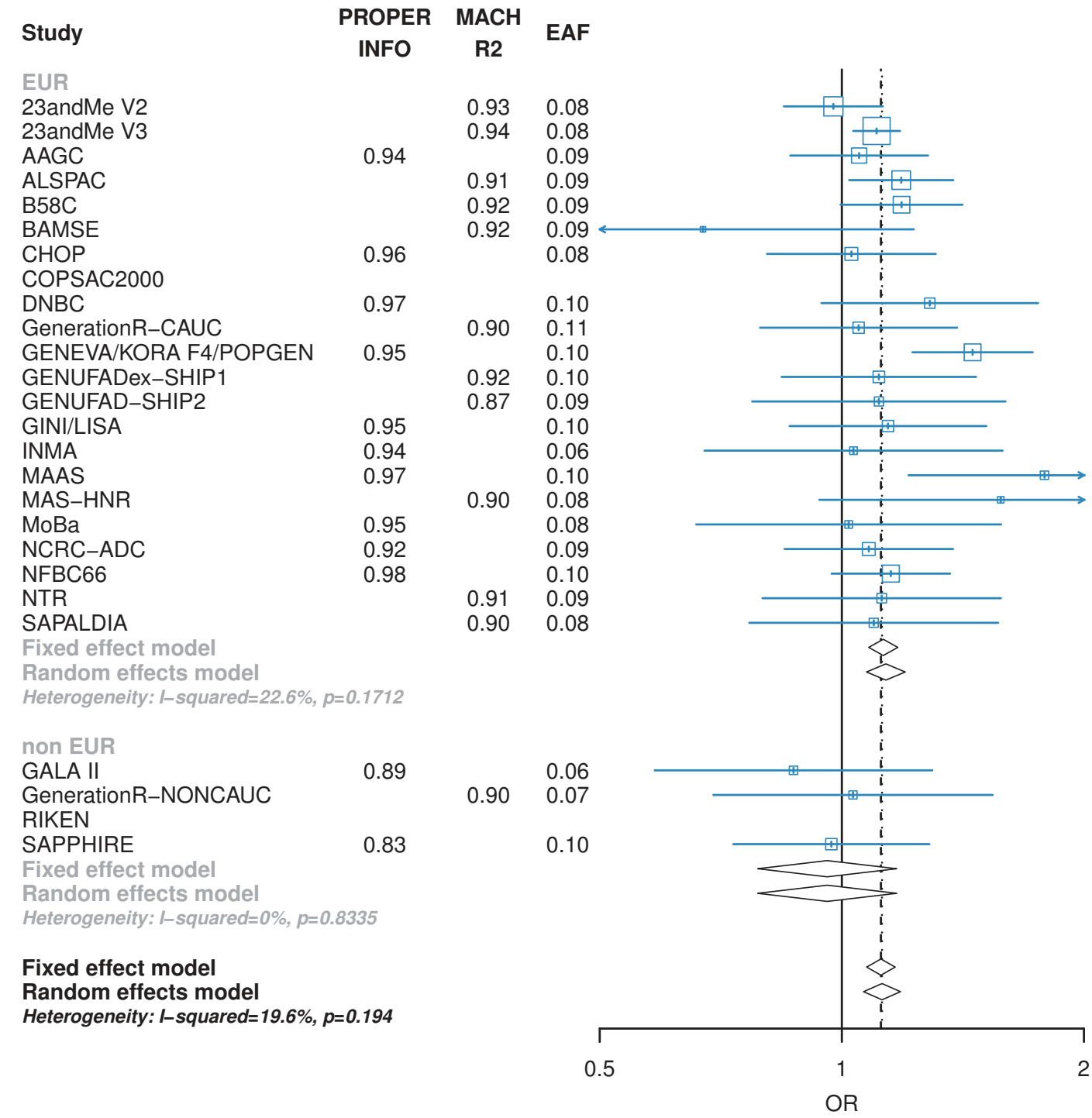


x. rs4643526 (2p16.1, PUS10), effect allele=A

Study	PROPER INFO	MACH R2	EAF
EUR			
23andMe V2		1.00	0.19
23andMe V3		1.00	0.19
AAGC	1.00		0.17
ALSPAC		1.00	0.16
B58C		1.00	0.16
BAMSE		1.00	0.17
CHOP	1.00		0.19
COPSAC2000		1.00	0.18
DNBC	1.00		0.17
GenerationR–CAUC		0.93	0.20
GENEVA/KORA F4/POPGEN	1.00		0.21
GENUFADex–SHIP1		1.00	0.21
GENUFAD–SHIP2		0.88	0.23
GINI/LISA	0.93		0.21
INMA	0.98		0.18
MAAS	1.00		0.16
MAS–HNR		1.00	0.20
MoBa	1.00		0.16
NCRC–ADC	1.00		0.14
NFBC66	1.00		0.23
NTR		1.00	0.17
SAPALDIA		1.00	0.19
Fixed effect model			
Random effects model			
Heterogeneity: I–squared=21.1%, p=0.1838			
non EUR			
GALA II	1.00		0.24
GenerationR–NONCAUC		0.93	0.32
RIKEN			
SAPPHIRE	1.00		0.75
Fixed effect model			
Random effects model			
Heterogeneity: I–squared=3.2%, p=0.356			
Fixed effect model			
Random effects model			
Heterogeneity: I–squared=16.4%, p=0.2307			

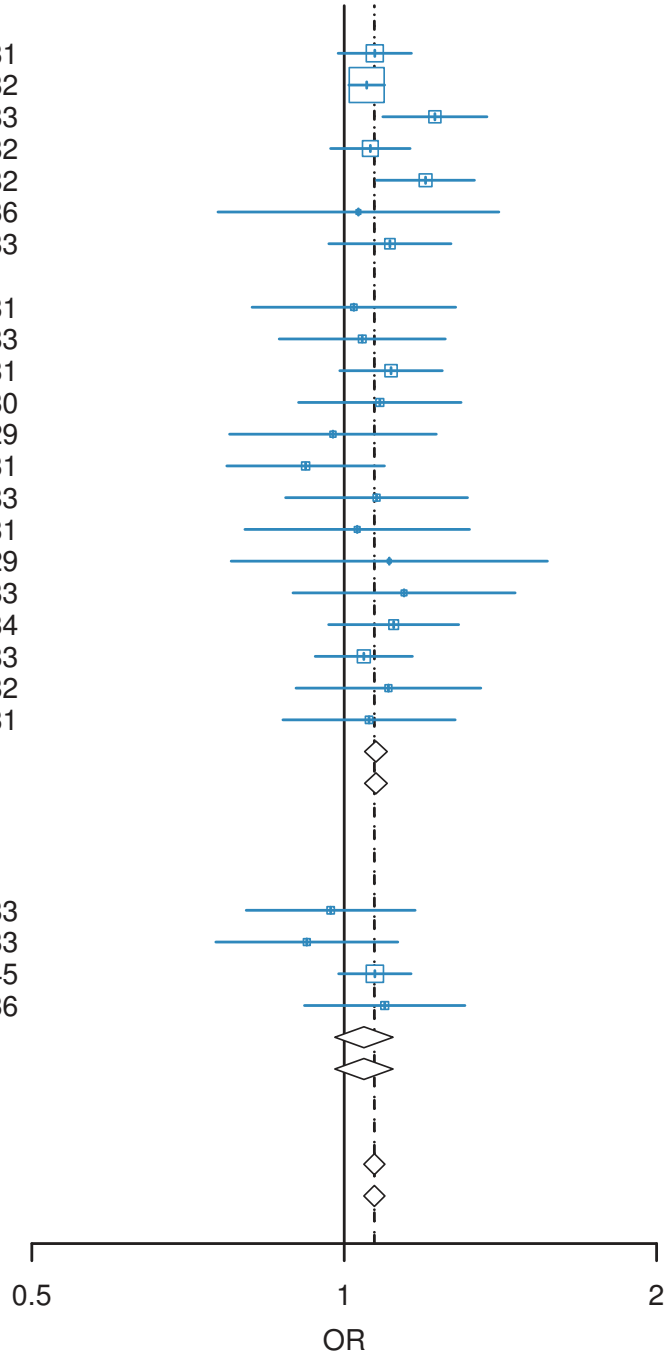


y. rs12951971 (17q21.2, STAT3), effect allele=G

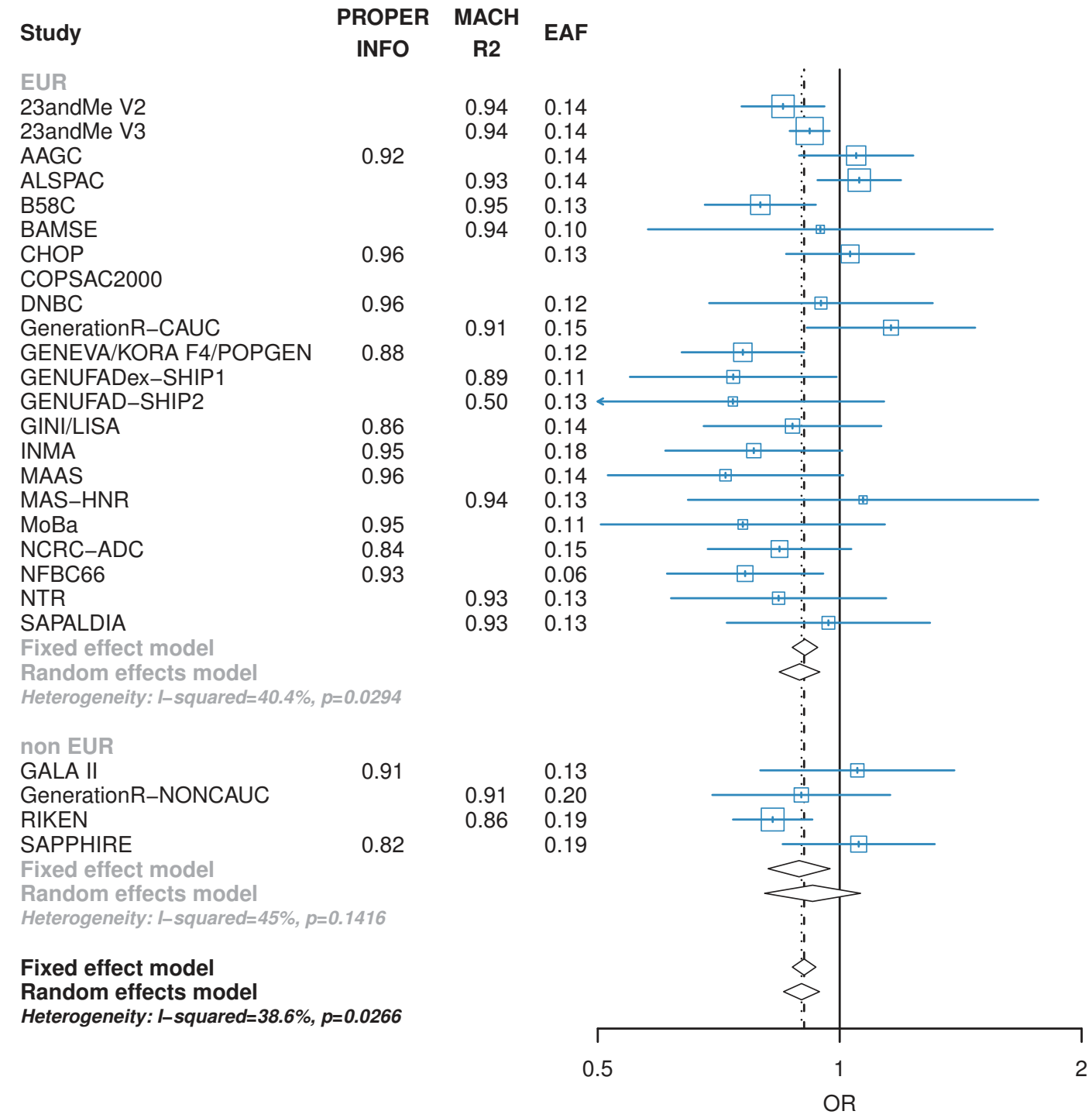


z. rs7625909 (3p21.1, SFMBT1/RFT1), effect allele=T

Study	PROPER INFO	MACH R2	EAF
EUR			
23andMe V2		0.96	0.31
23andMe V3		0.99	0.32
AAGC	0.99		0.33
ALSPAC		0.95	0.32
B58C		0.95	0.32
BAMSE		0.99	0.36
CHOP	0.97		0.33
COPSAC2000			
DNBC	0.97		0.31
GenerationR–CAUC		0.95	0.33
GENEVA/KORA F4/POPGEN	0.97		0.31
GENUFADex–SHIP1		0.98	0.30
GENUFAD–SHIP2		0.95	0.29
GINI/LISA	0.99		0.31
INMA	0.99		0.33
MAAS	0.99		0.31
MAS–HNR		0.95	0.29
MoBa	0.98		0.33
NCRC–ADC	0.94		0.34
NFBC66	0.99		0.33
NTR		0.98	0.32
SAPALDIA		0.99	0.31
Fixed effect model			
Random effects model			
Heterogeneity: I–squared=0%, p=0.7413			
non EUR			
GALA II	0.97		0.33
GenerationR–NONCAUC		0.95	0.33
RIKEN		0.97	0.45
SAPPHIRE	0.93		0.36
Fixed effect model			
Random effects model			
Heterogeneity: I–squared=0%, p=0.4372			
Fixed effect model			
Random effects model			
Heterogeneity: I–squared=0%, p=0.7582			

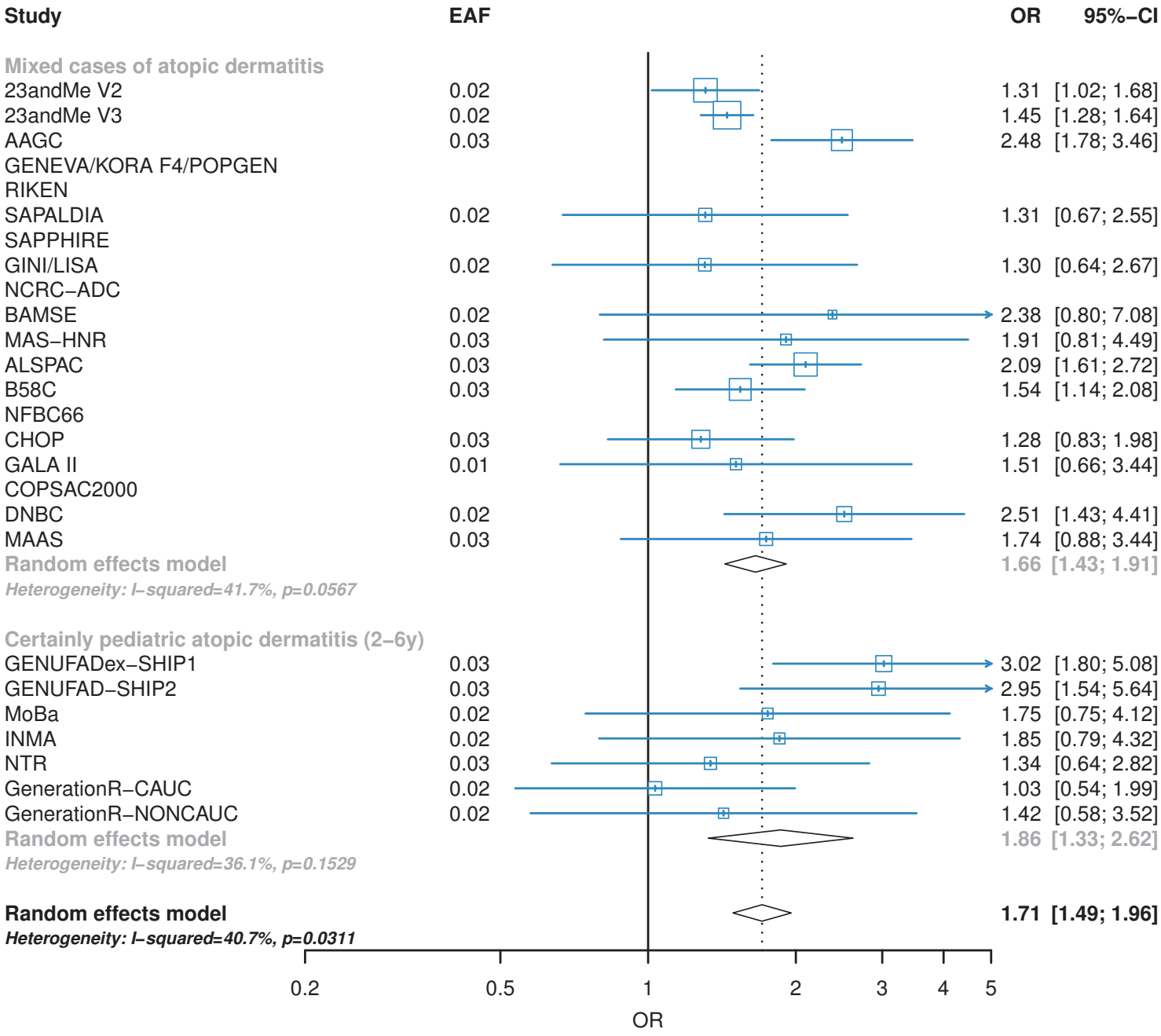


aa. rs112111458 (2p13.3, CD207/VAX2), effect allele=G

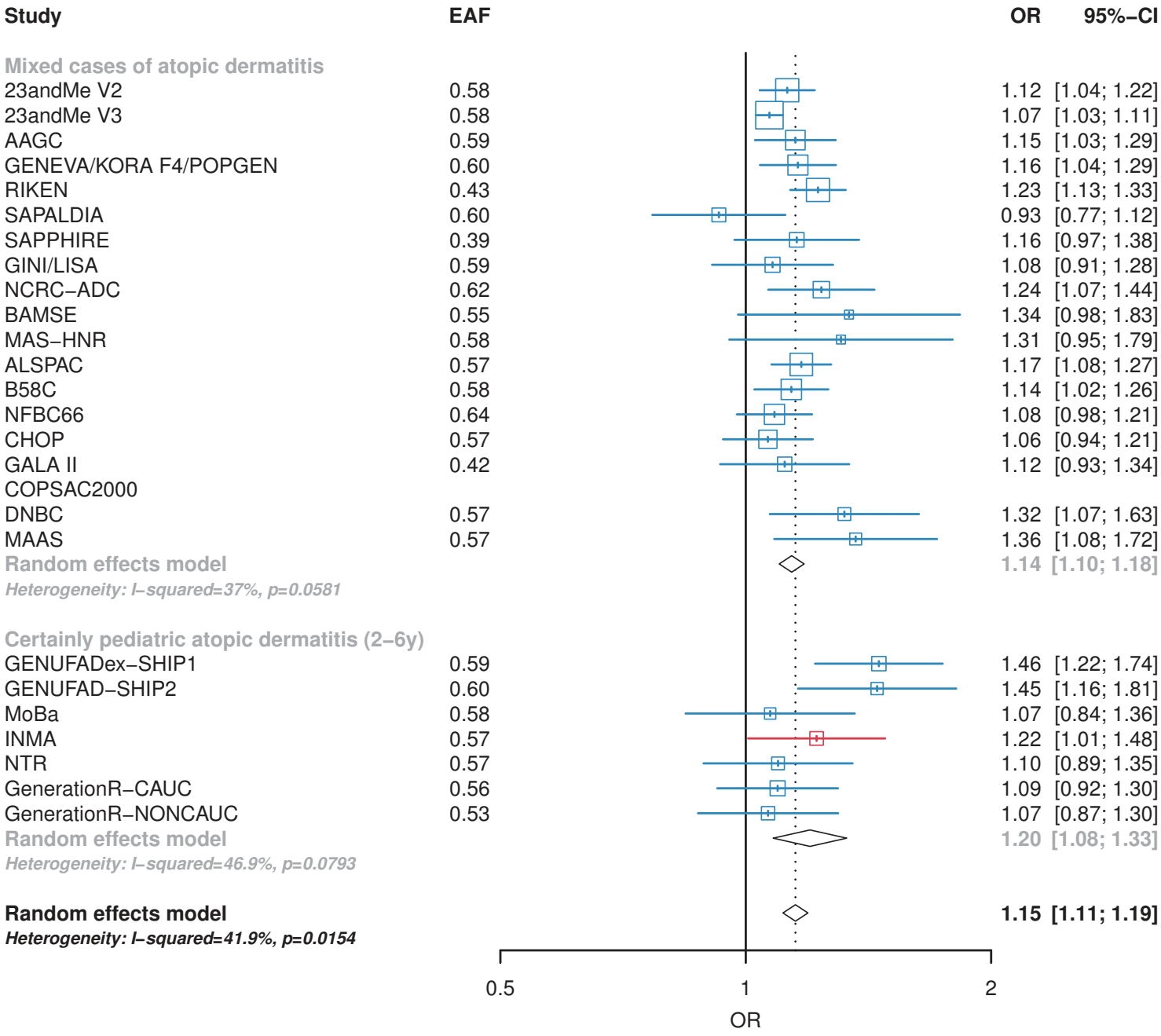


Supplementary Figure 3. Forest plots for the 27 loci p<5x10−8(a−aa). Studies are grouped by reported age of onset to compare cohorts that exclusively involve cases of pediatric onset (by age 6) with cohorts where age of onset is either uncertain or pediatric. Summary random effects meta−analysis results per diagnosis group are shown. The studies of non−European ancestry are marked *. Blue=imputed genotypes, red=genotyped. EAF=effect allele frequency.

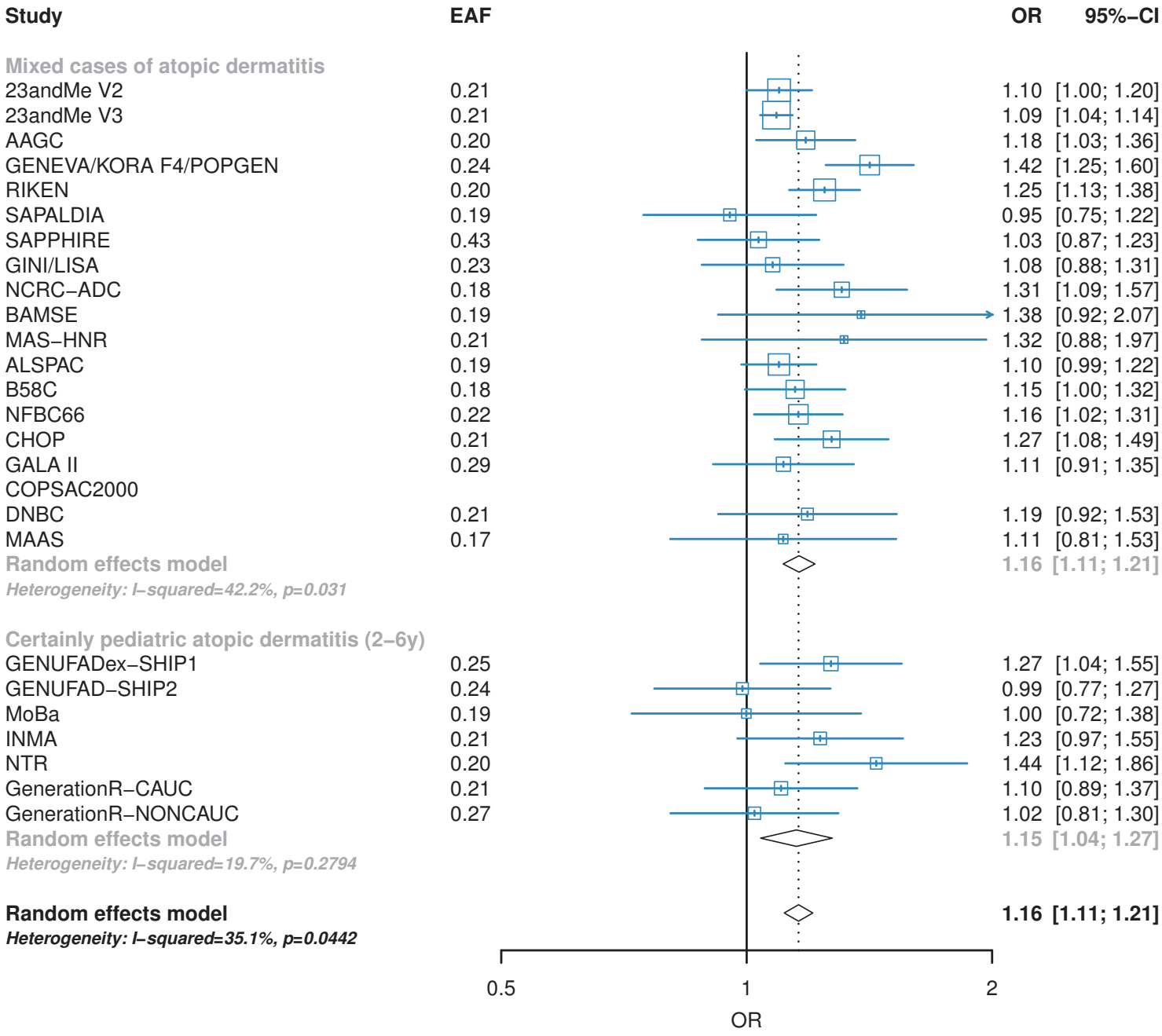
a. rs61813875 (1q21.3, CRCT1/LCE3E (FLG)), effect allele=G



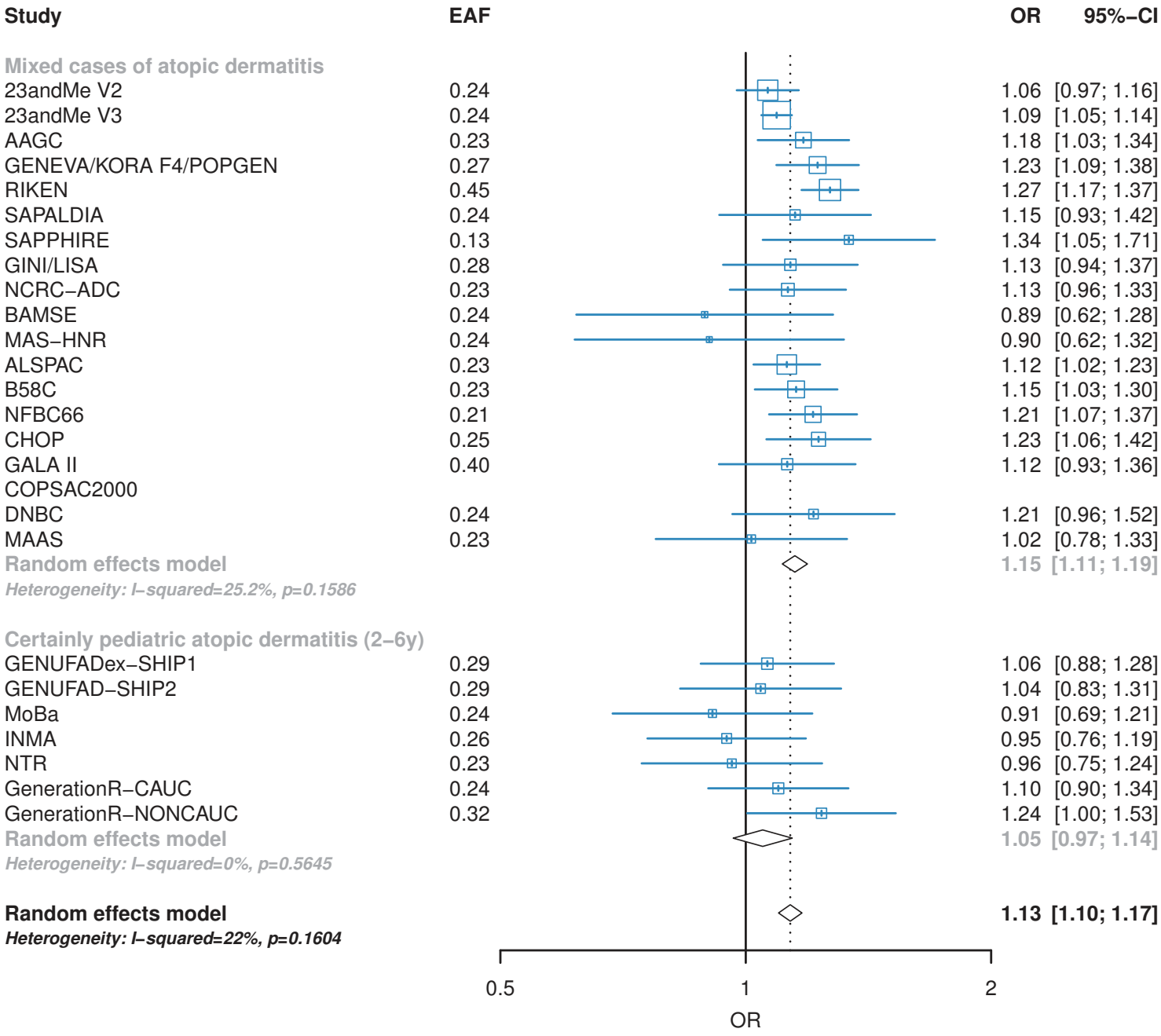
b. rs10791824 (11q13.1, OVOL1), effect allele=G



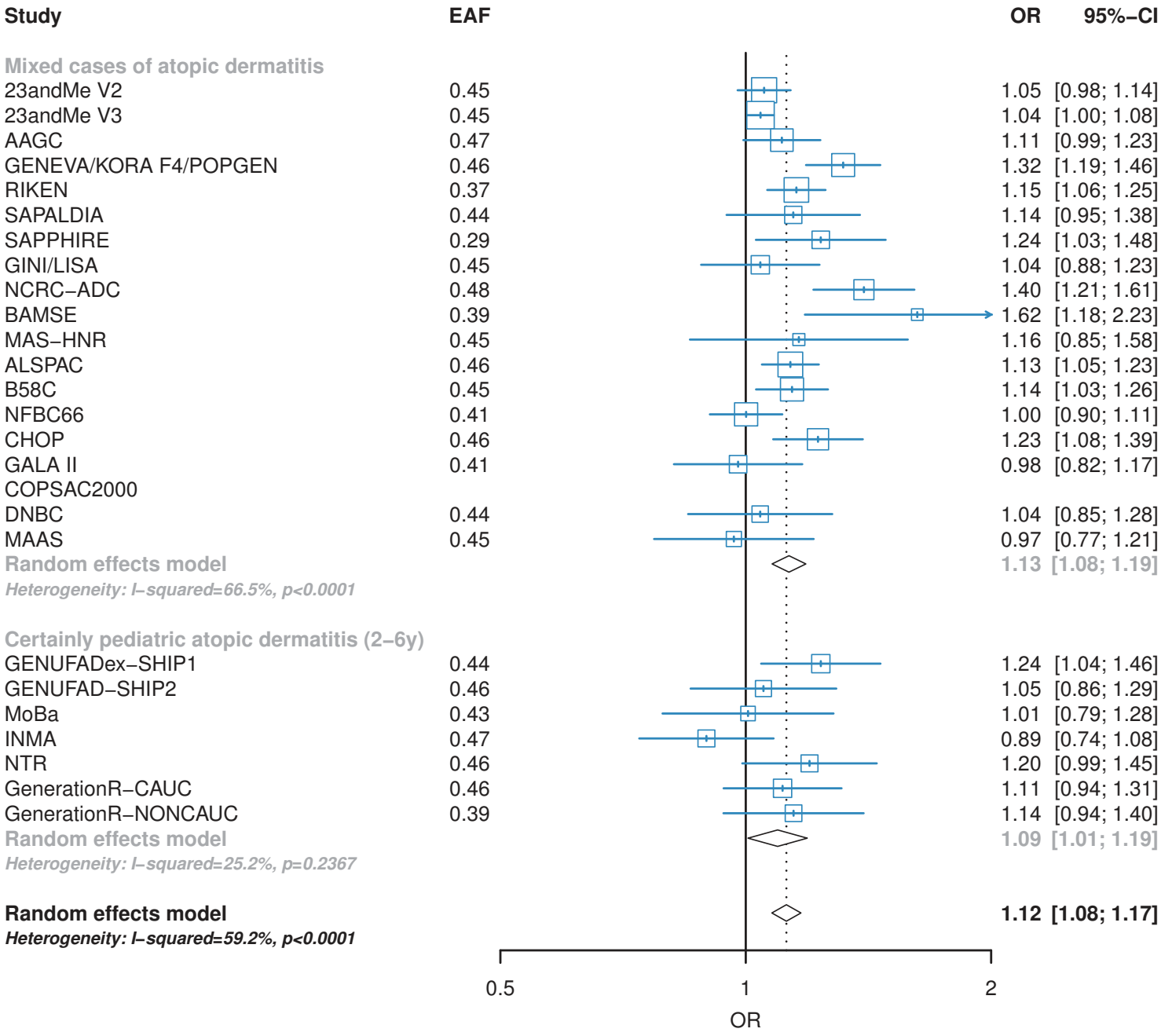
c. rs12188917 (5q31.1, RAD50/IL13), effect allele=C



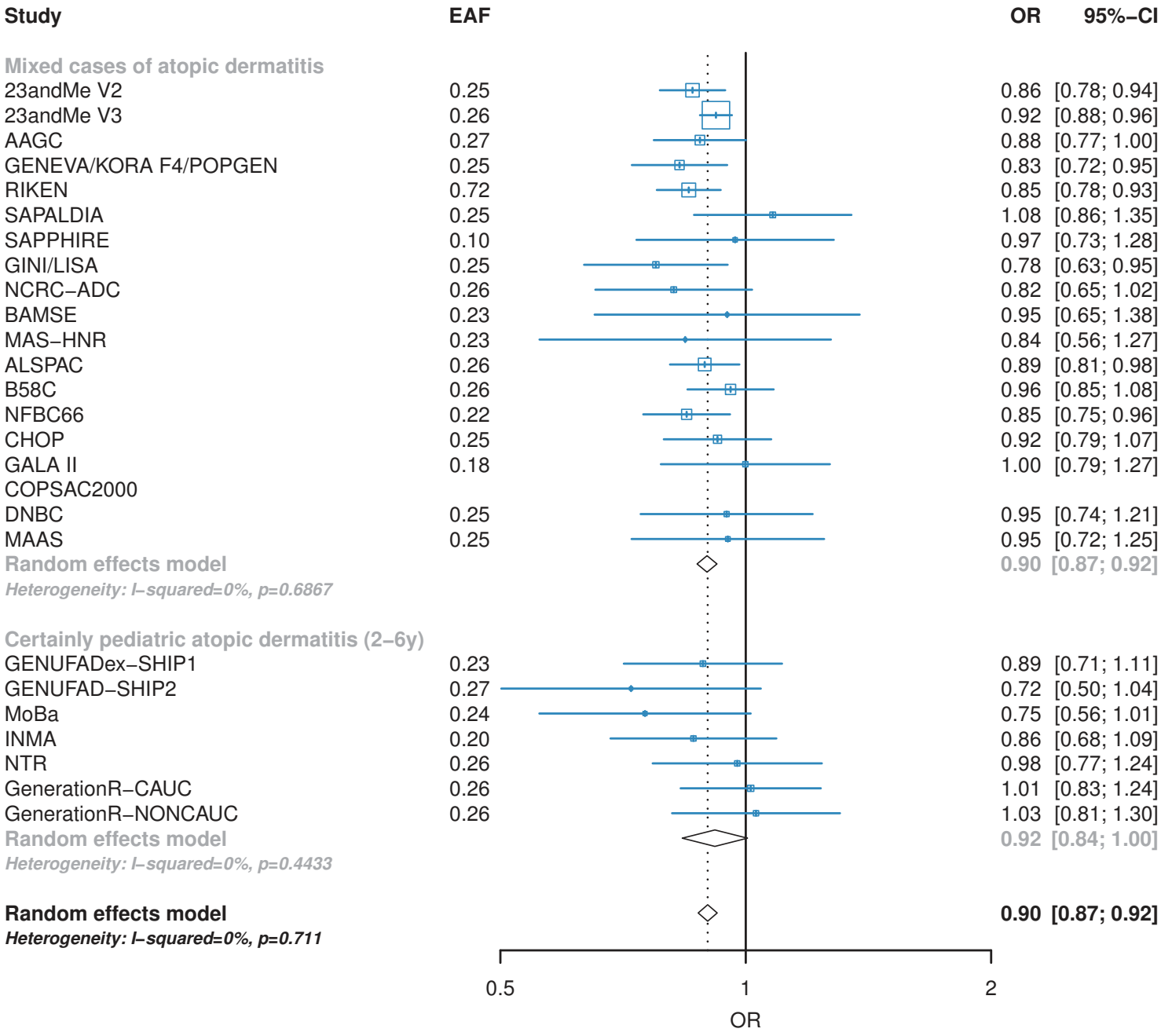
d. rs6419573 (2q12.1, IL18R1/IL18RAP), effect allele=T



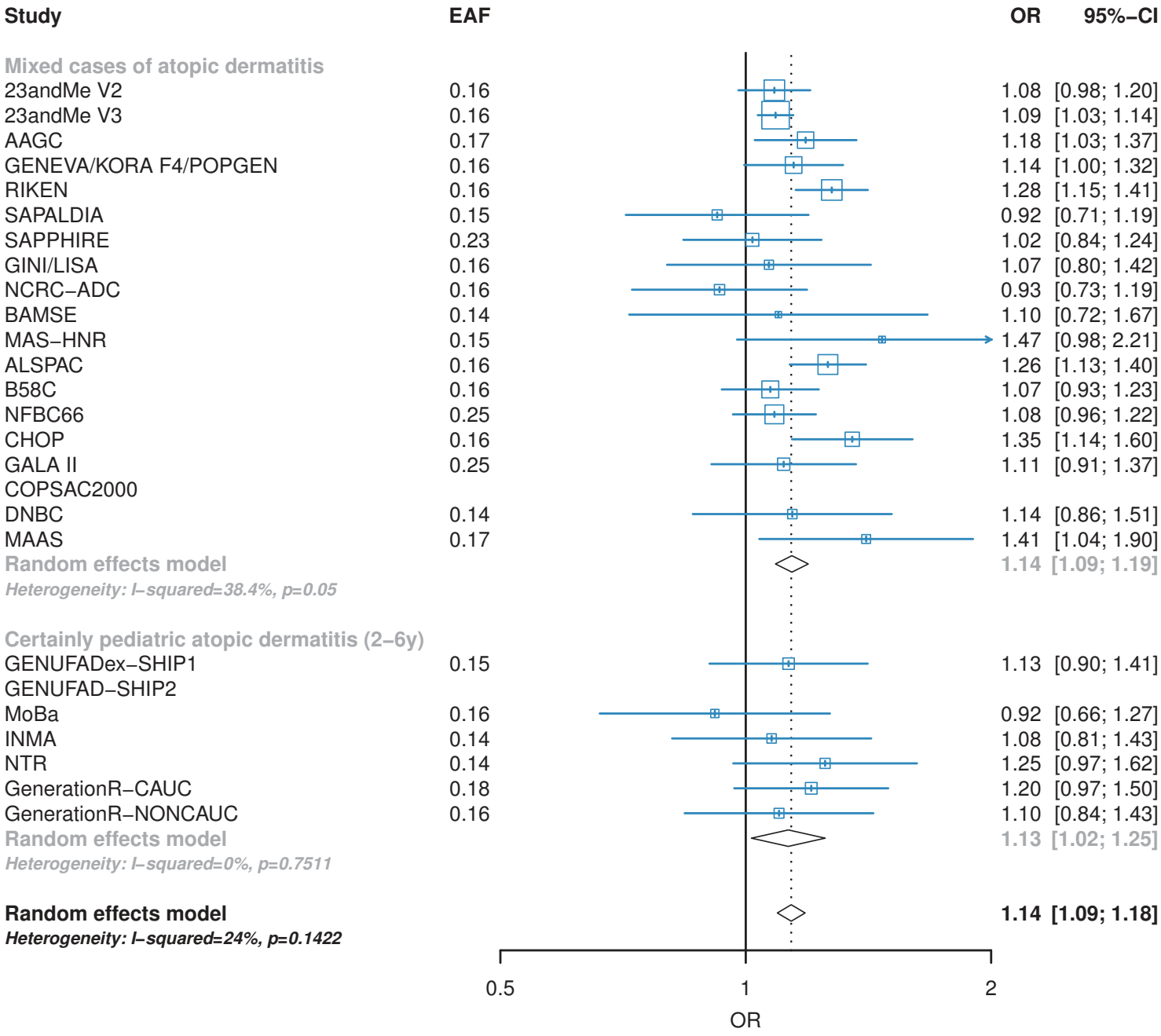
e. rs2212434 (11q13.5, C11orf30/LRRC32), effect allele=T



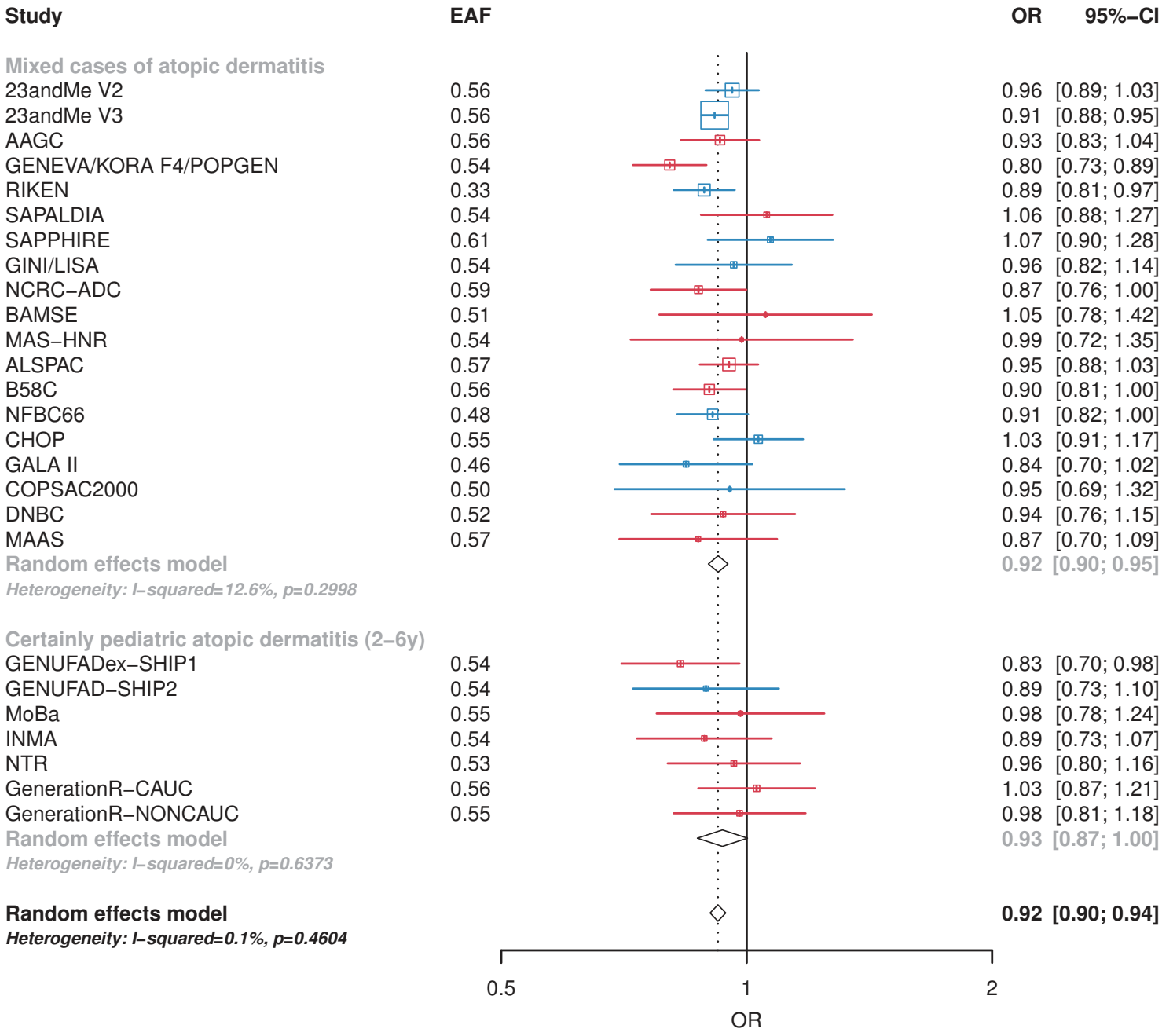
f. rs4809219 (20q13.33, RTEL1–TNFRSF6B), effect allele=C



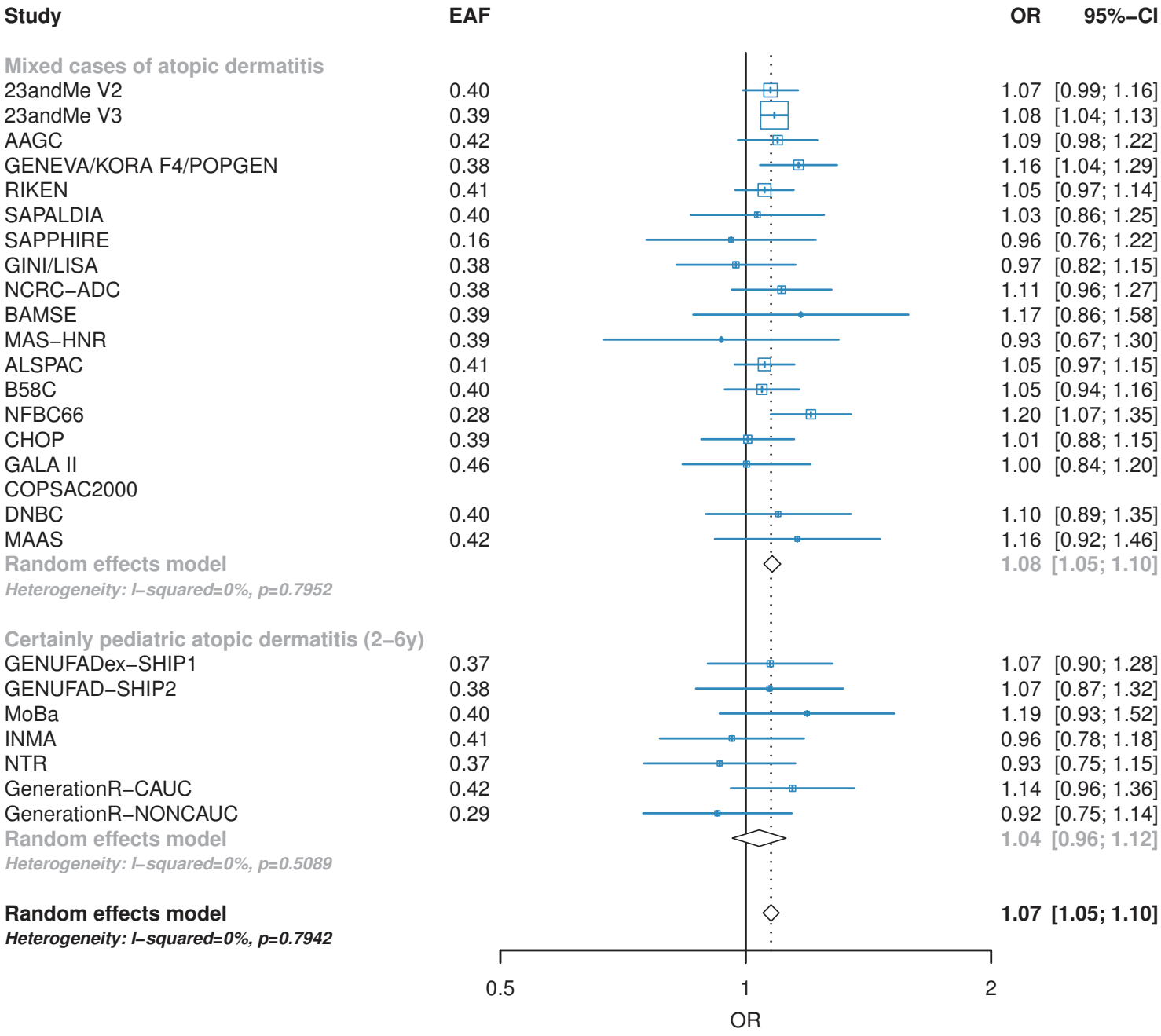
g. rs2918307 (19p13.2, ADAMTS10/ACTL9), effect allele=G



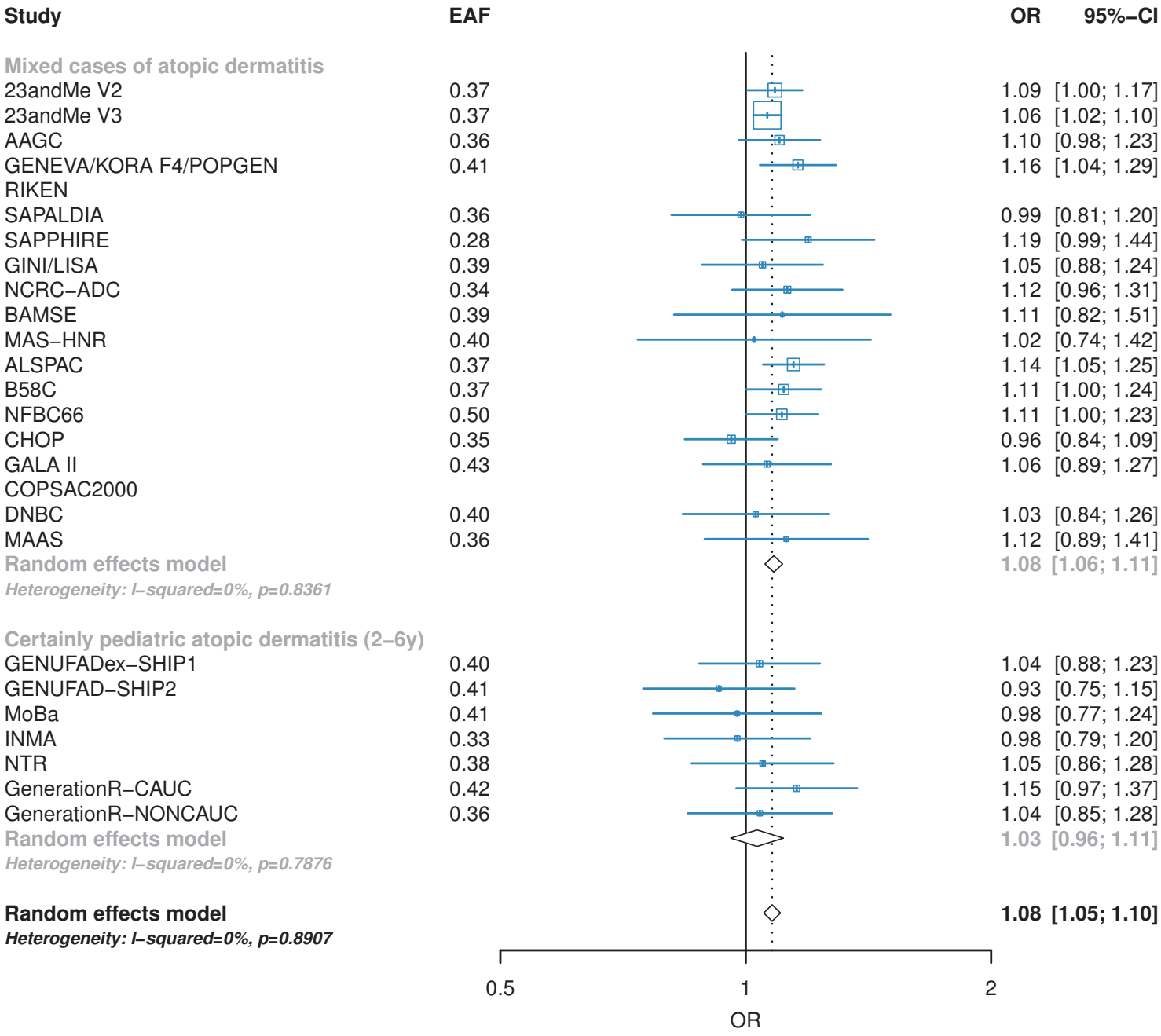
h. rs2041733 (16p13.13, CLEC16A), effect allele=C



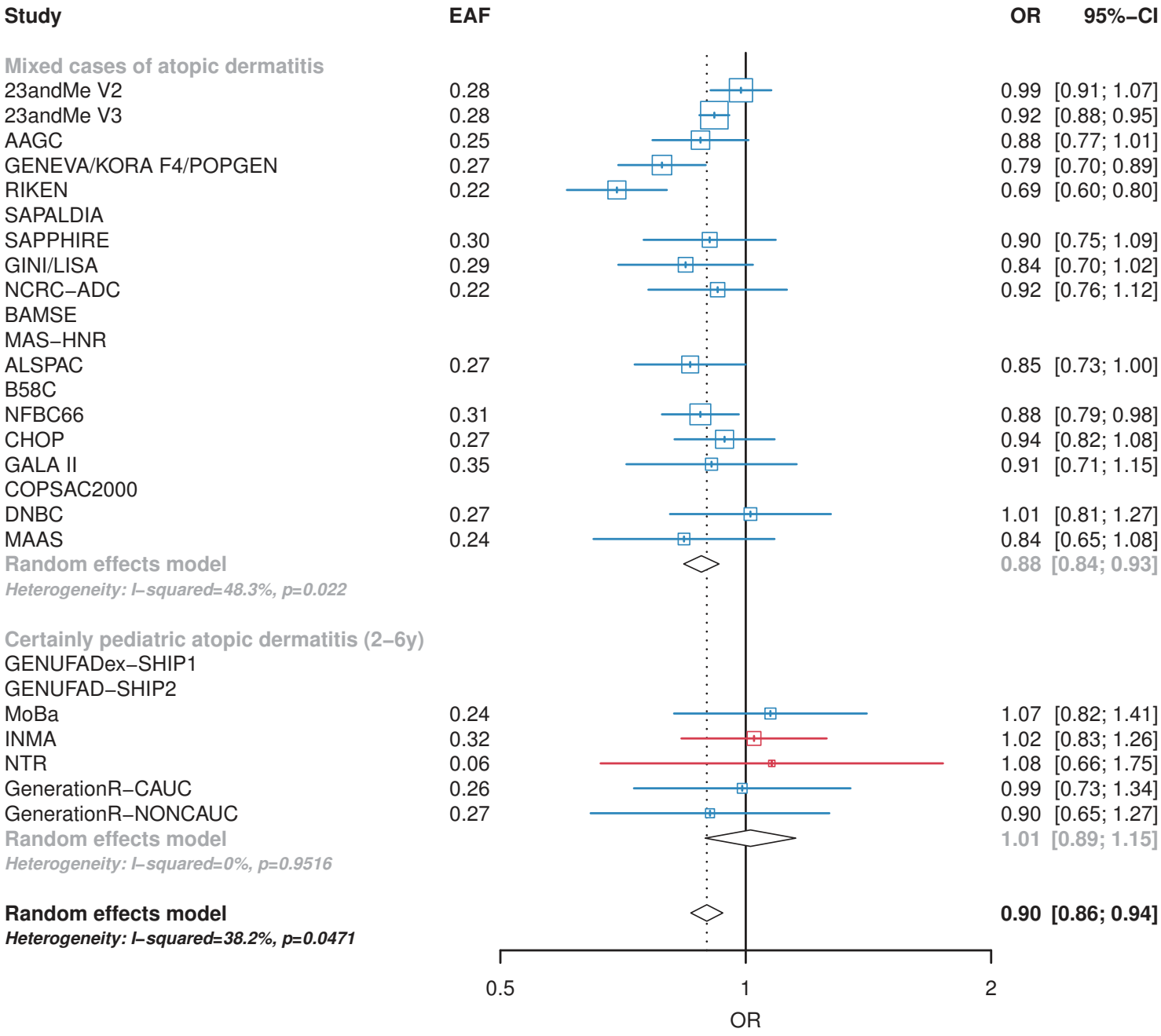
i. rs12730935 (1q21.3, IL6R), effect allele=A



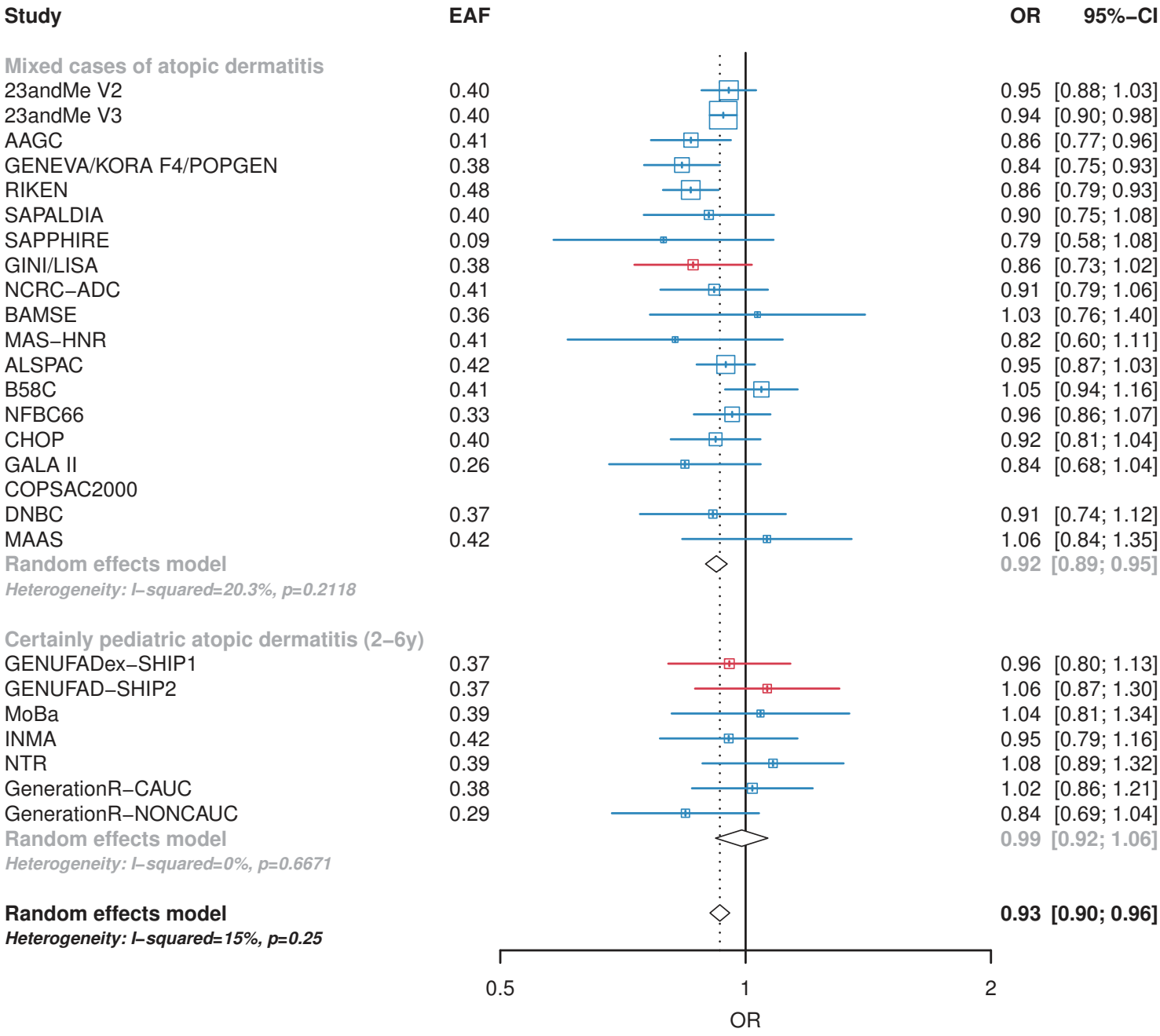
j. 4:123243592:INDEL (4q27, KIAA109 (IL2)), effect allele=R



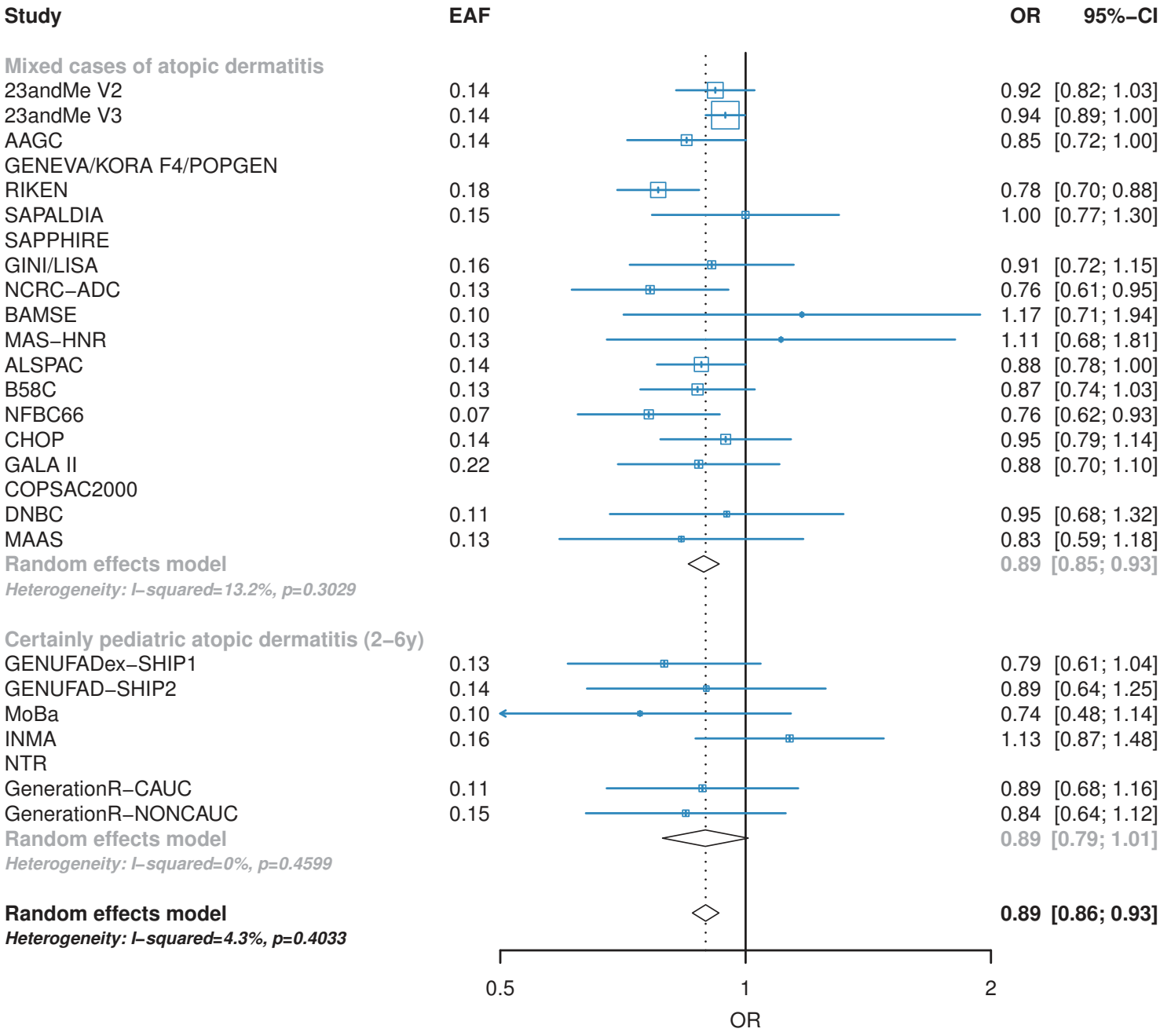
k. rs4713555 (6p21.32, HLA−DRB/HLA−DQA1), effect allele=T



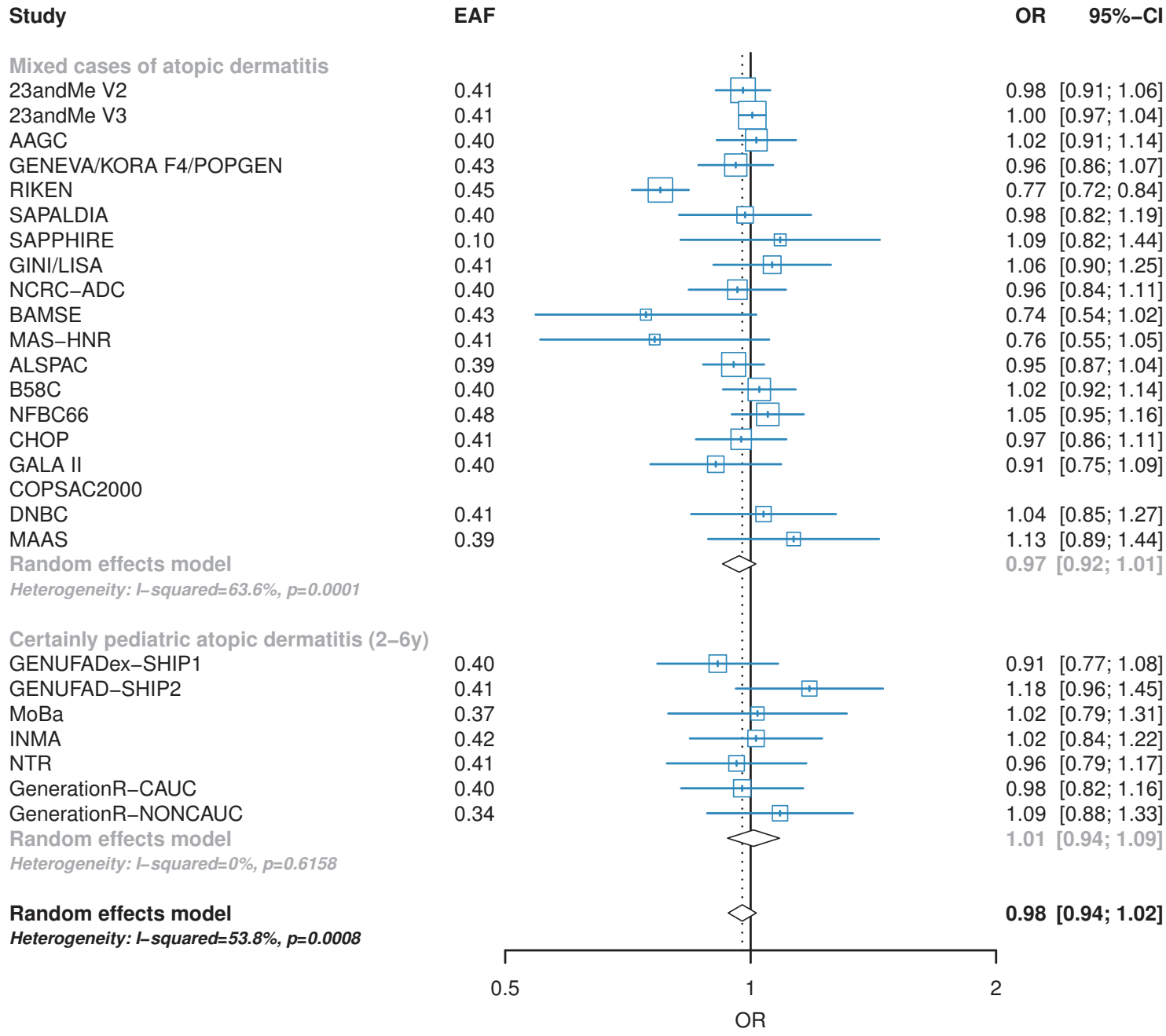
I. rs2944542 (10q21.2, ZNF365), effect allele=C



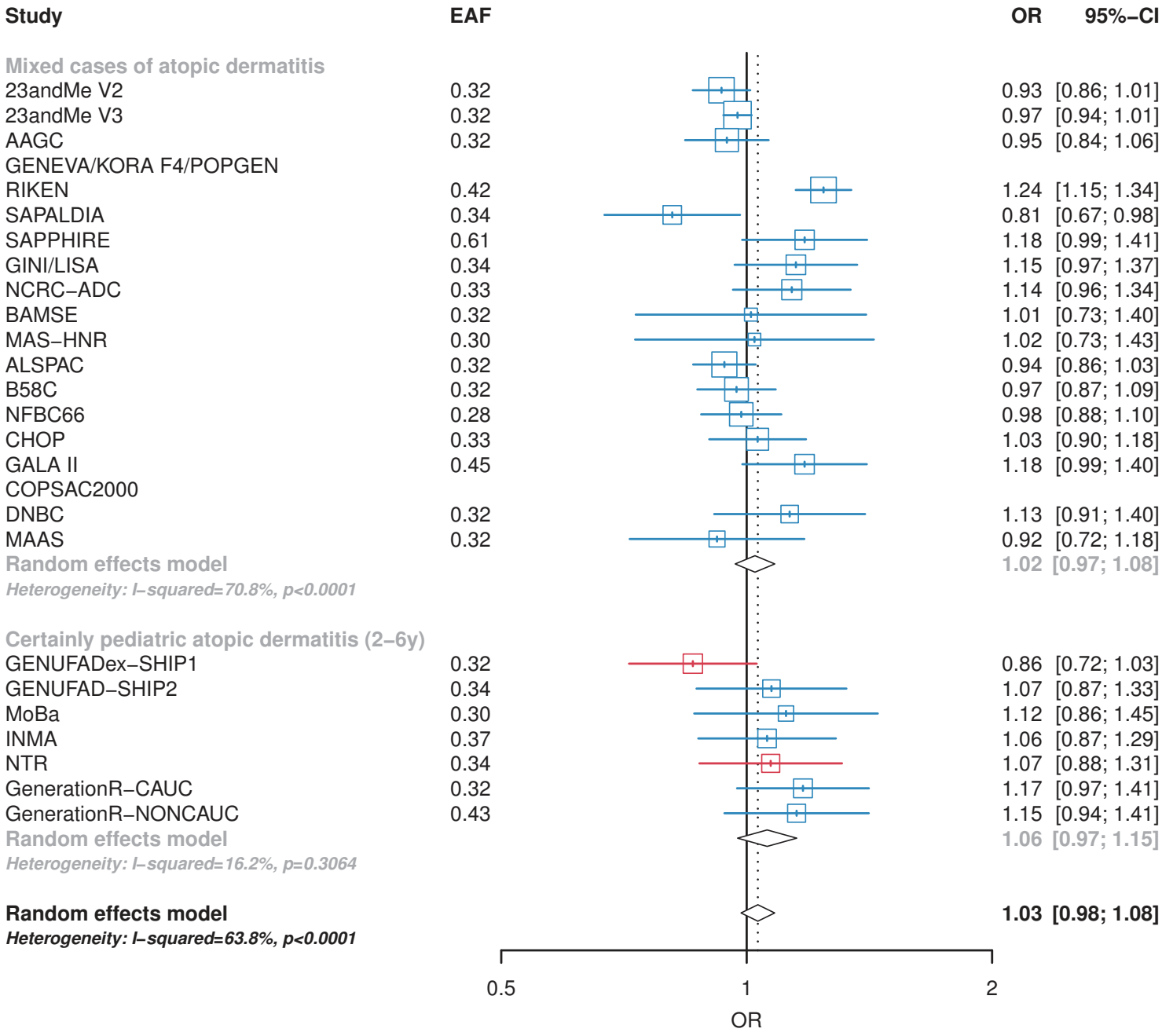
m. rs145809981 (6p21.33, MICB), effect allele=T



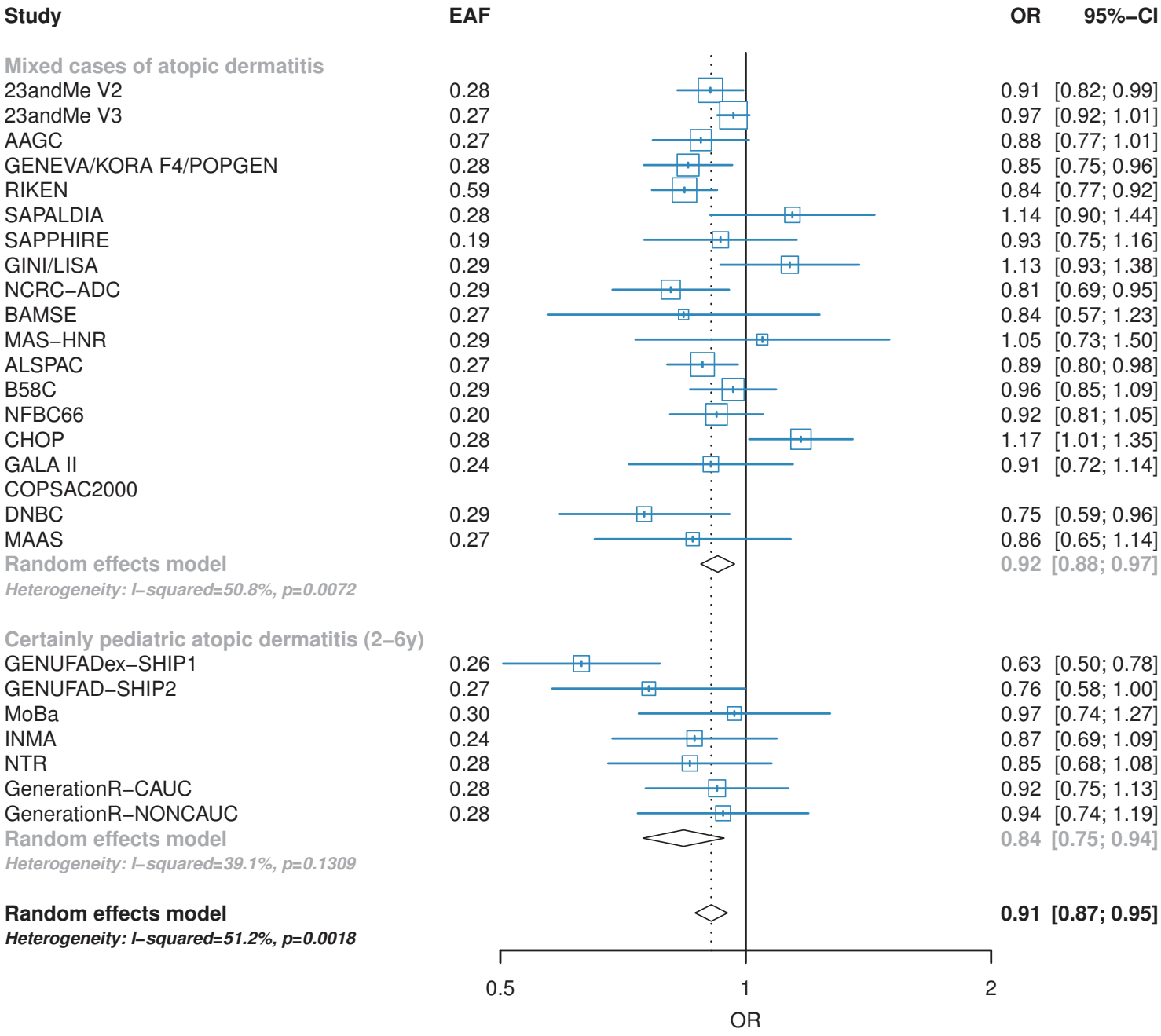
n. rs4312054 (11p15.4, OR10A3/NLRP10), effect allele=G



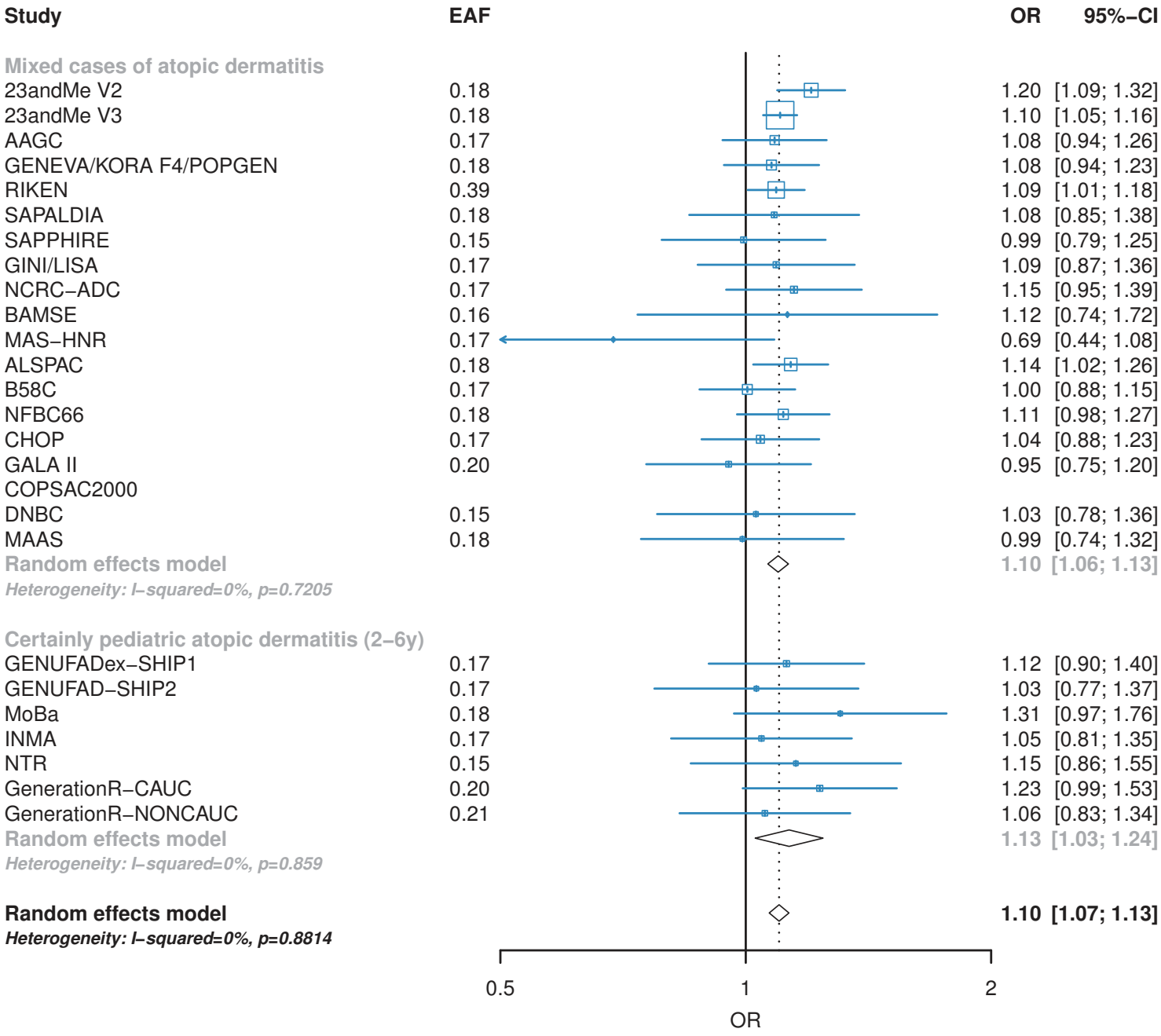
o. rs1249910 (3q13.2, CCDC80/CD200R1L), effect allele=A



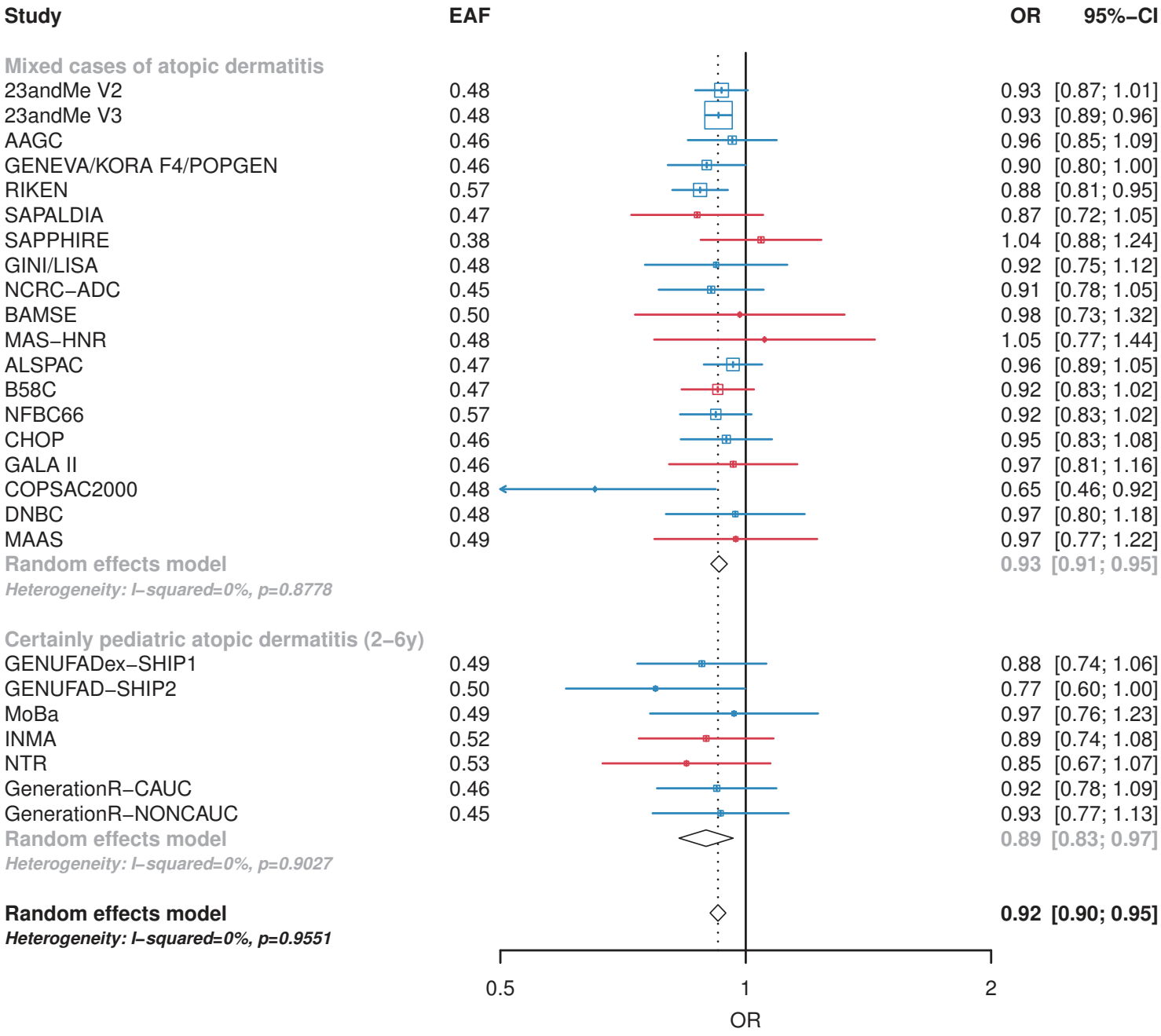
p. rs2592555 (11p13, PRR5L), effect allele=C



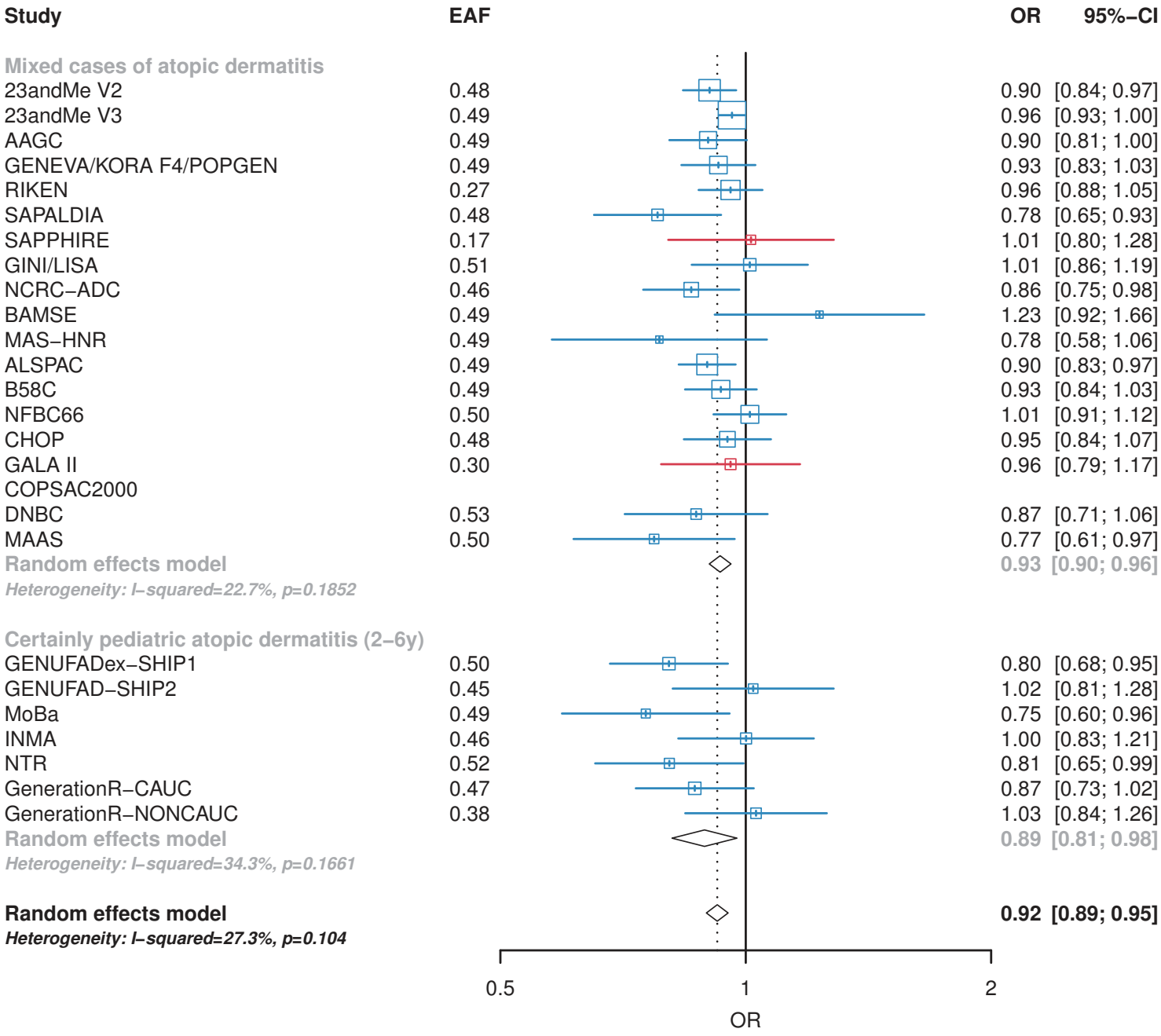
q. rs2038255 (14q13.2, PPP2R3C), effect allele=T



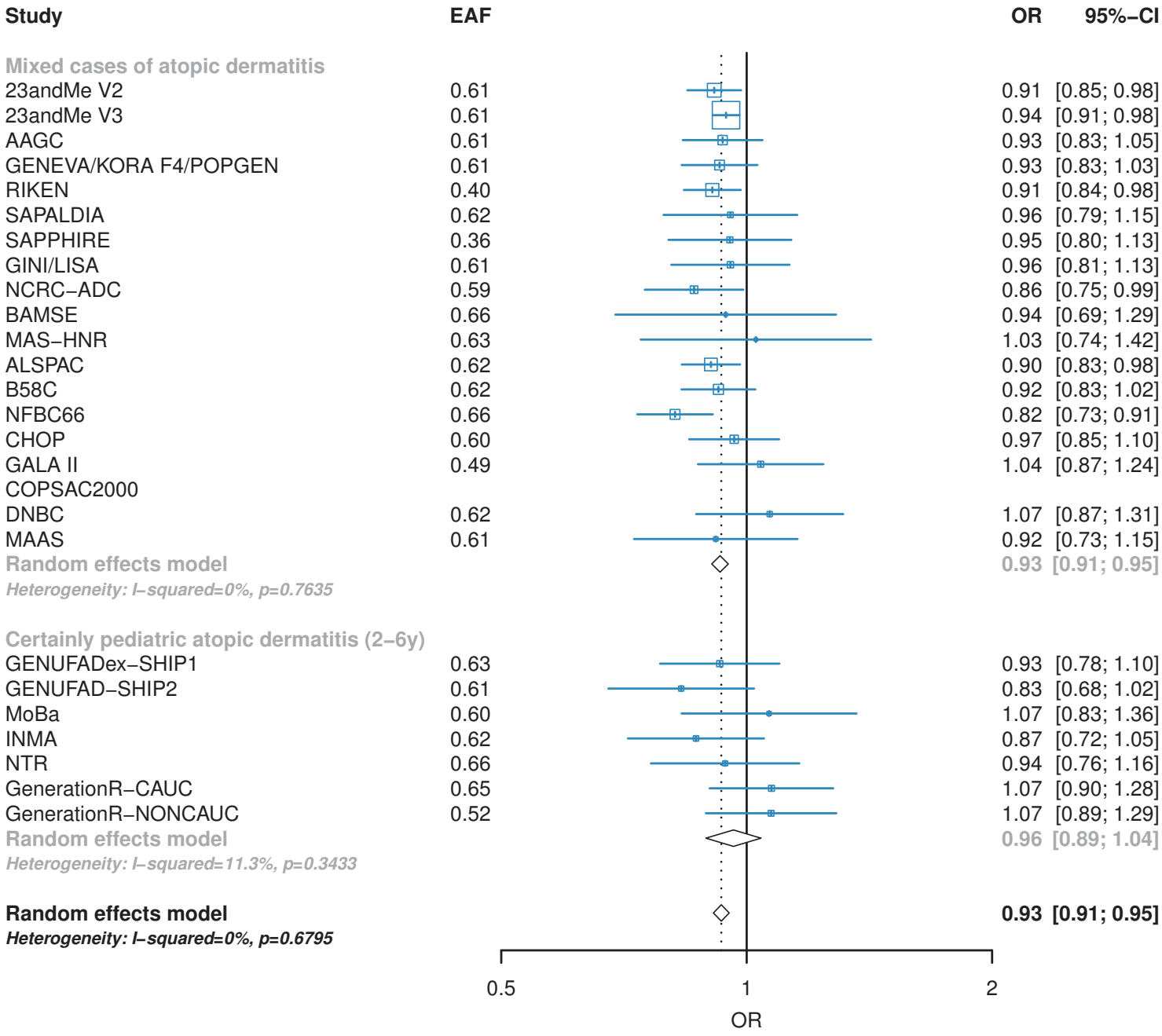
r. rs7127307 (11q24.3, –/ETS1), effect allele=C



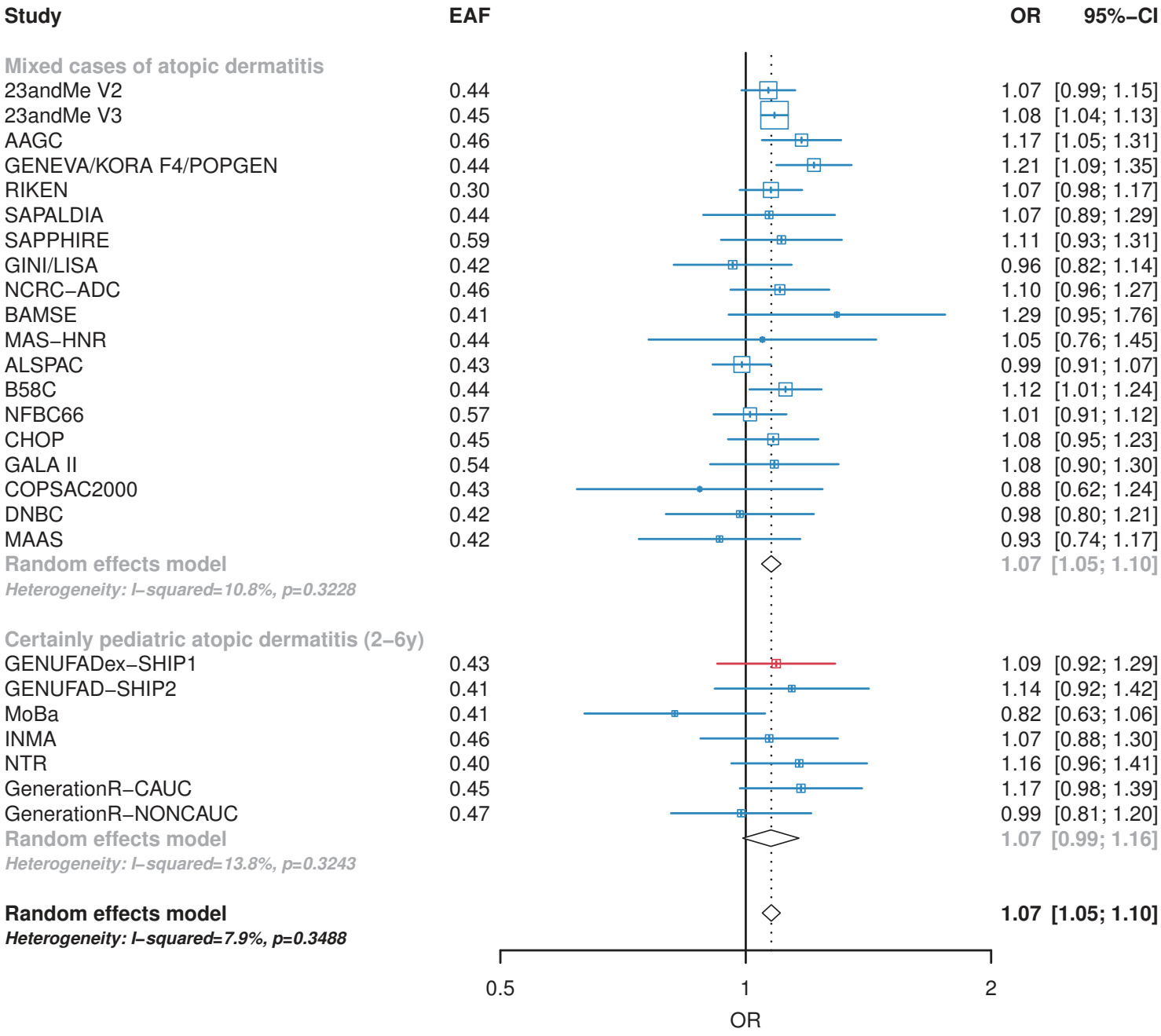
s. rs7512552 (1q21.2, C1orf51/MRPS21), effect allele=T



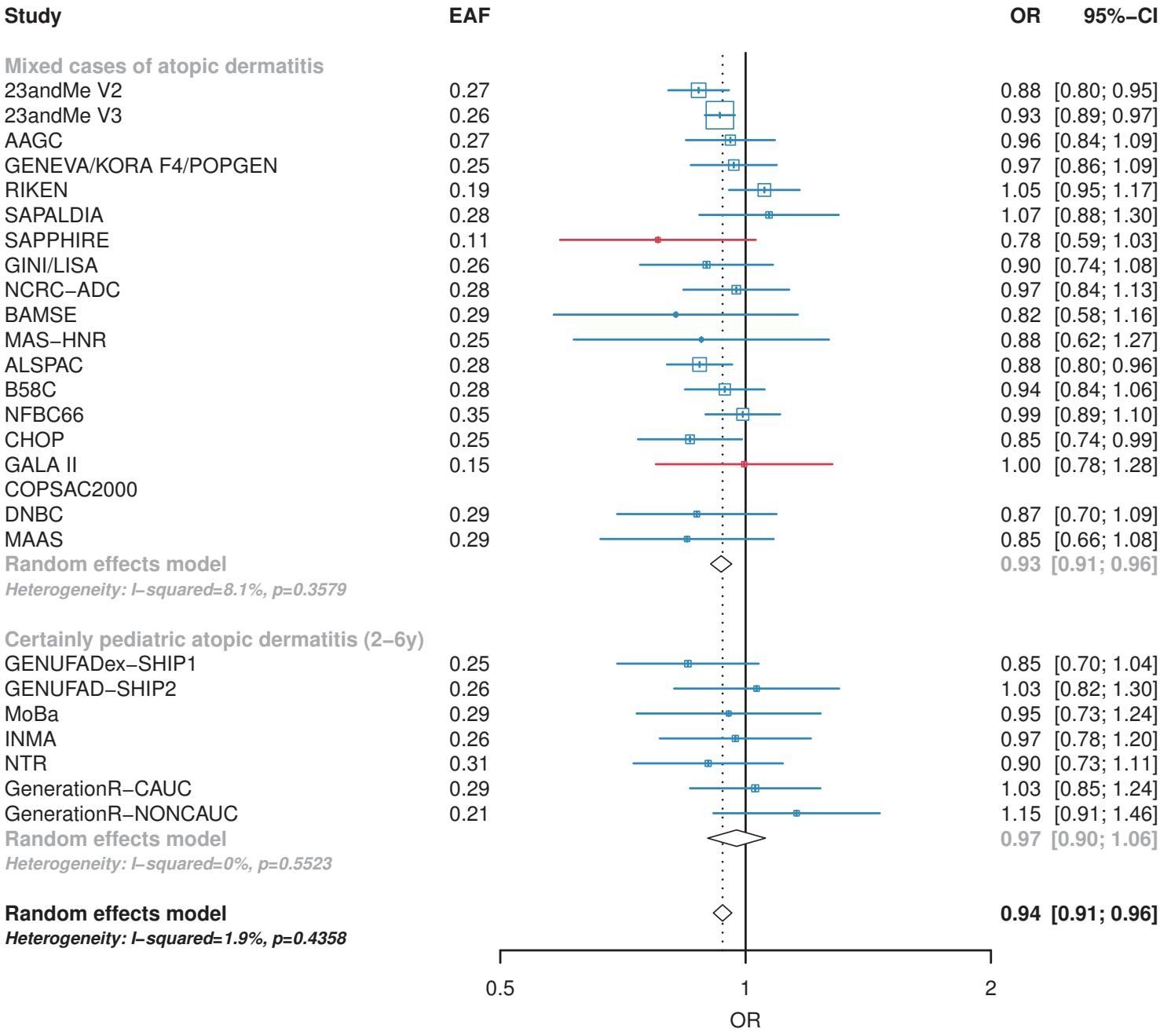
t. rs6473227 (8q21.13, MIR5708/ZBTB10), effect allele=A



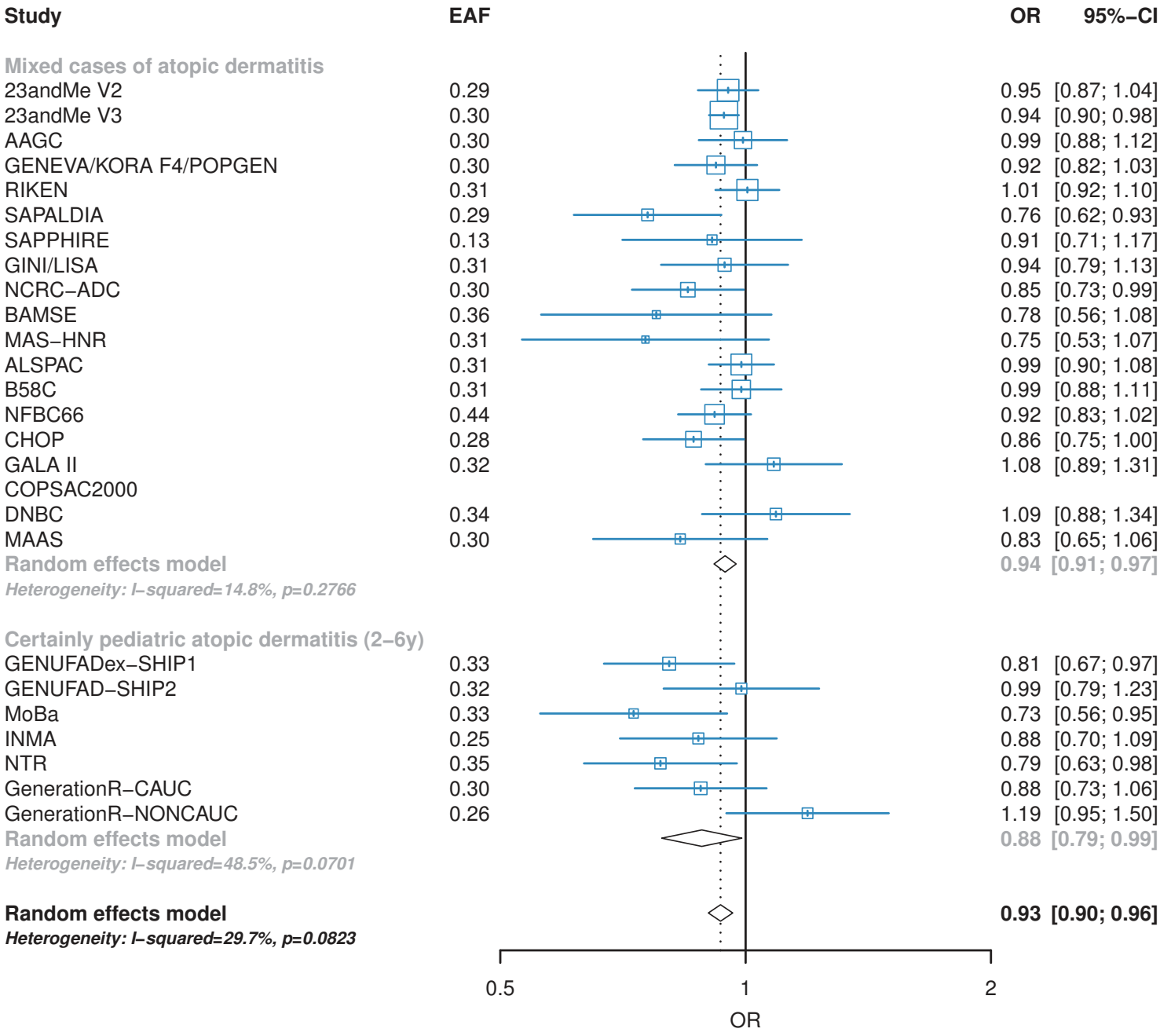
u. rs6602364 (10p15.1, IL15RA/IL2RA), effect allele=G



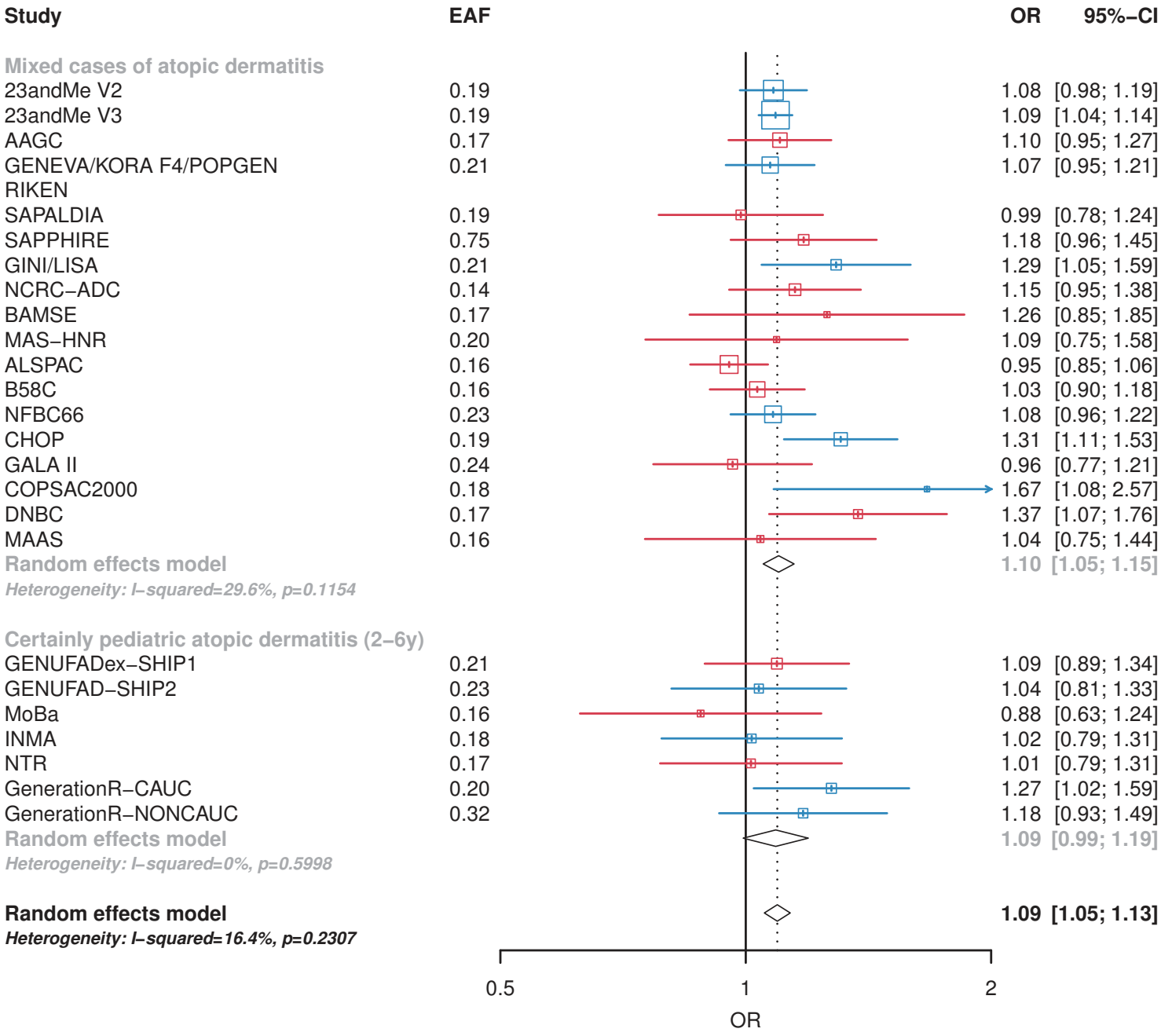
v. rs10214237 (5p13.2, IL7R/CAPSL), effect allele=C



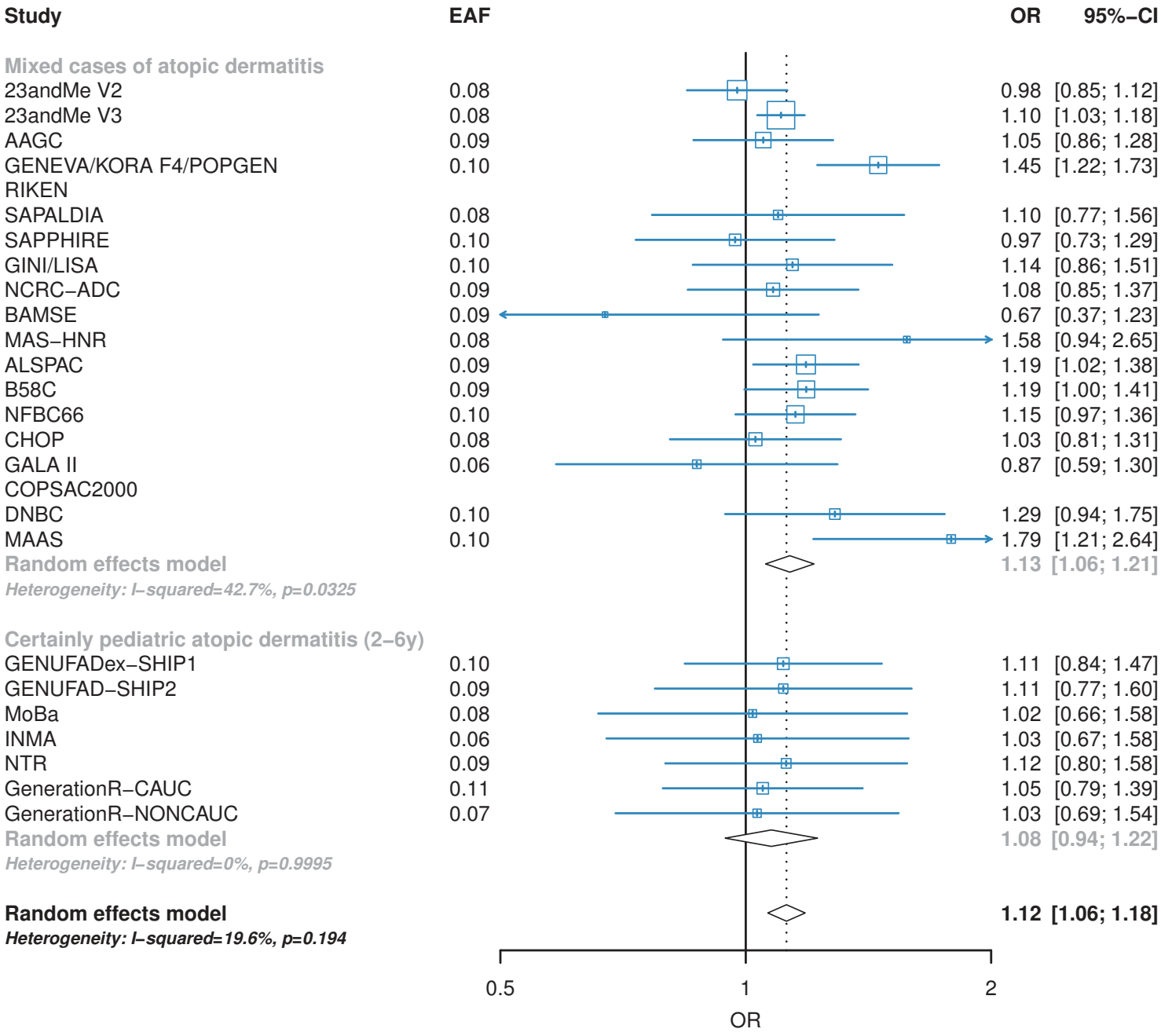
w. rs10199605 (2p25.1, LINC00299/–), effect allele=A



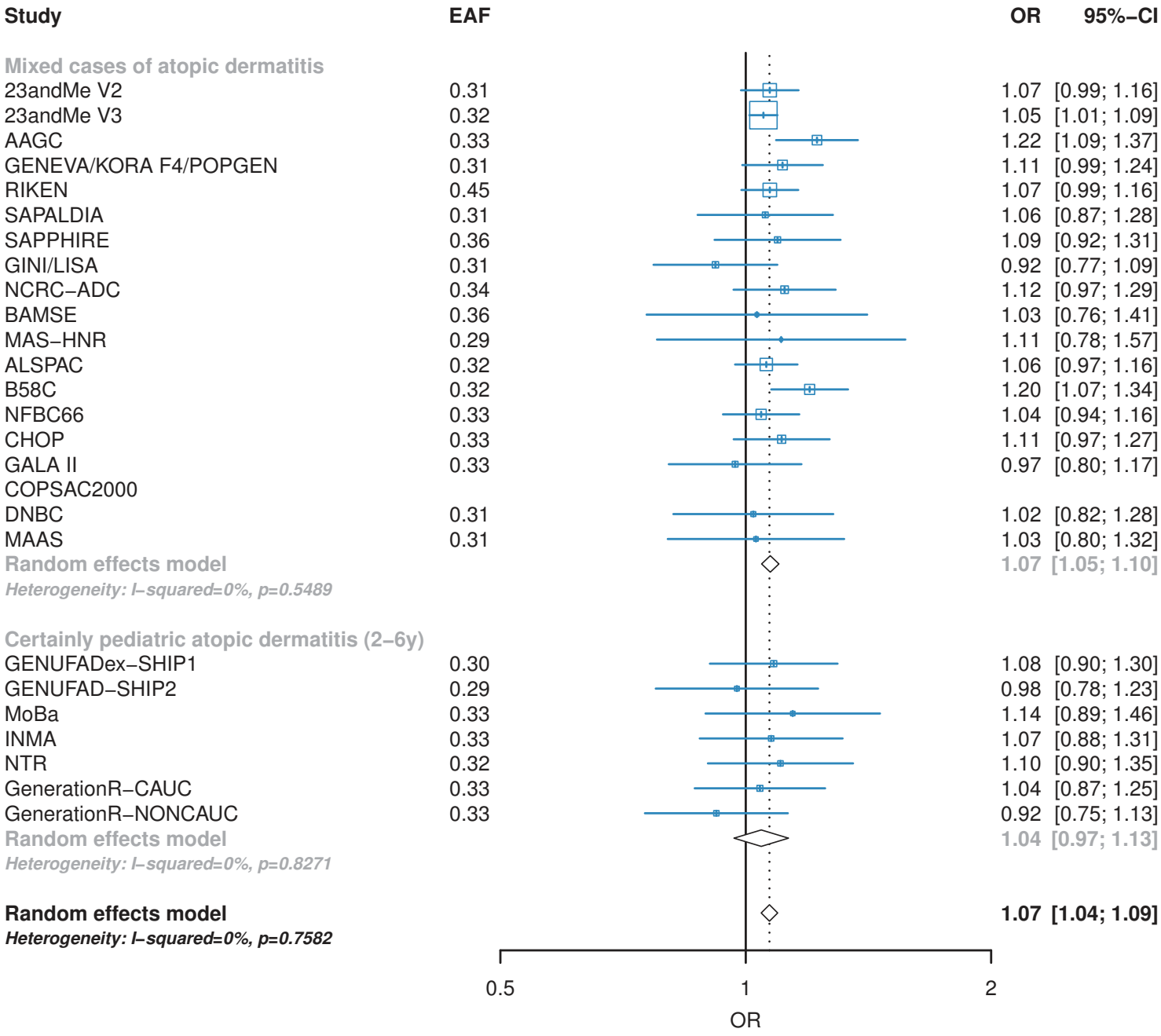
x. rs4643526 (2p16.1, PUS10), effect allele=A



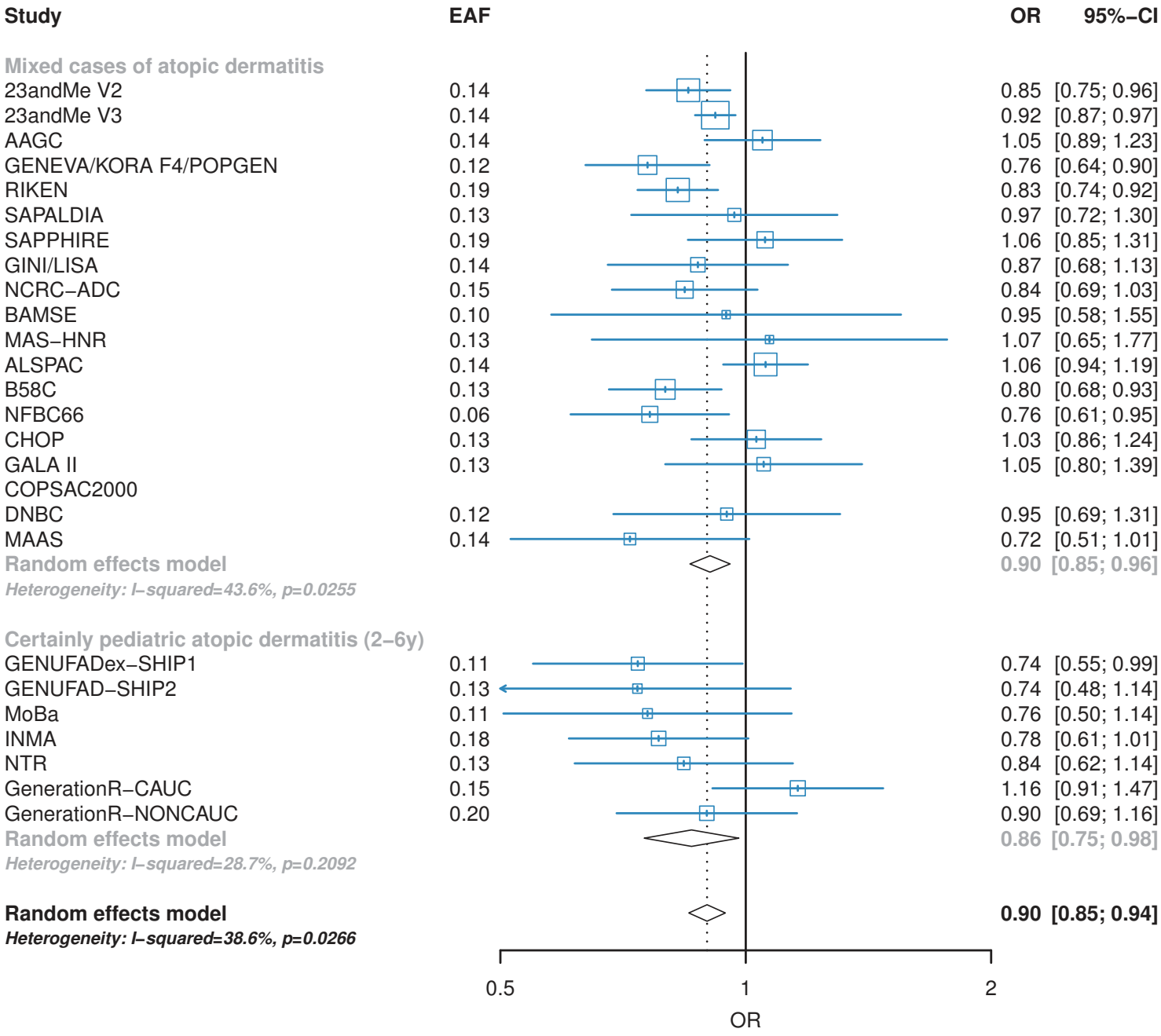
y. rs12951971 (17q21.2, STAT3), effect allele=G



z. rs7625909 (3p21.1, SFMBT1/RFT1), effect allele=T

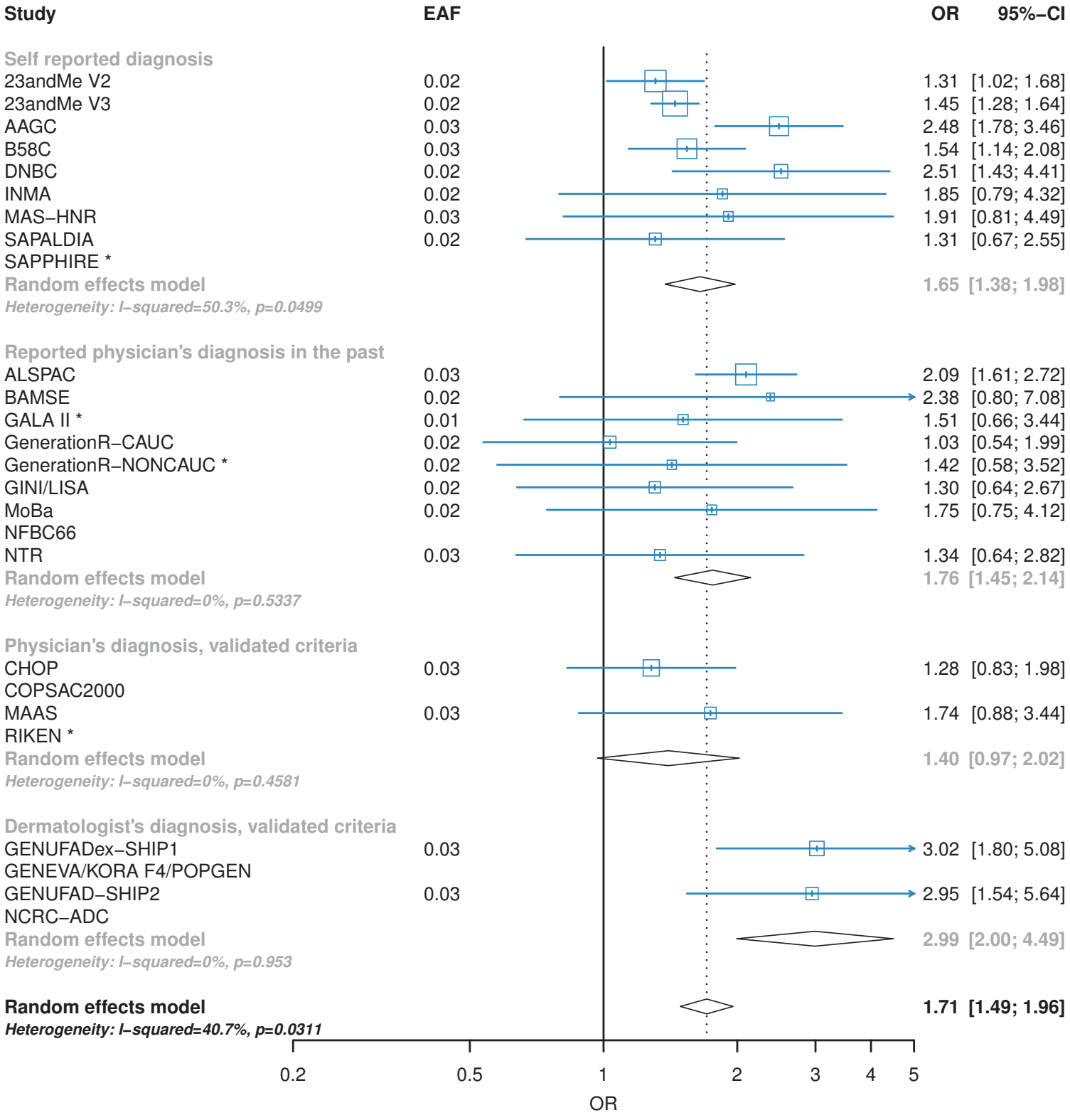


aa. rs112111458 (2p13.3, CD207/VAX2), effect allele=G

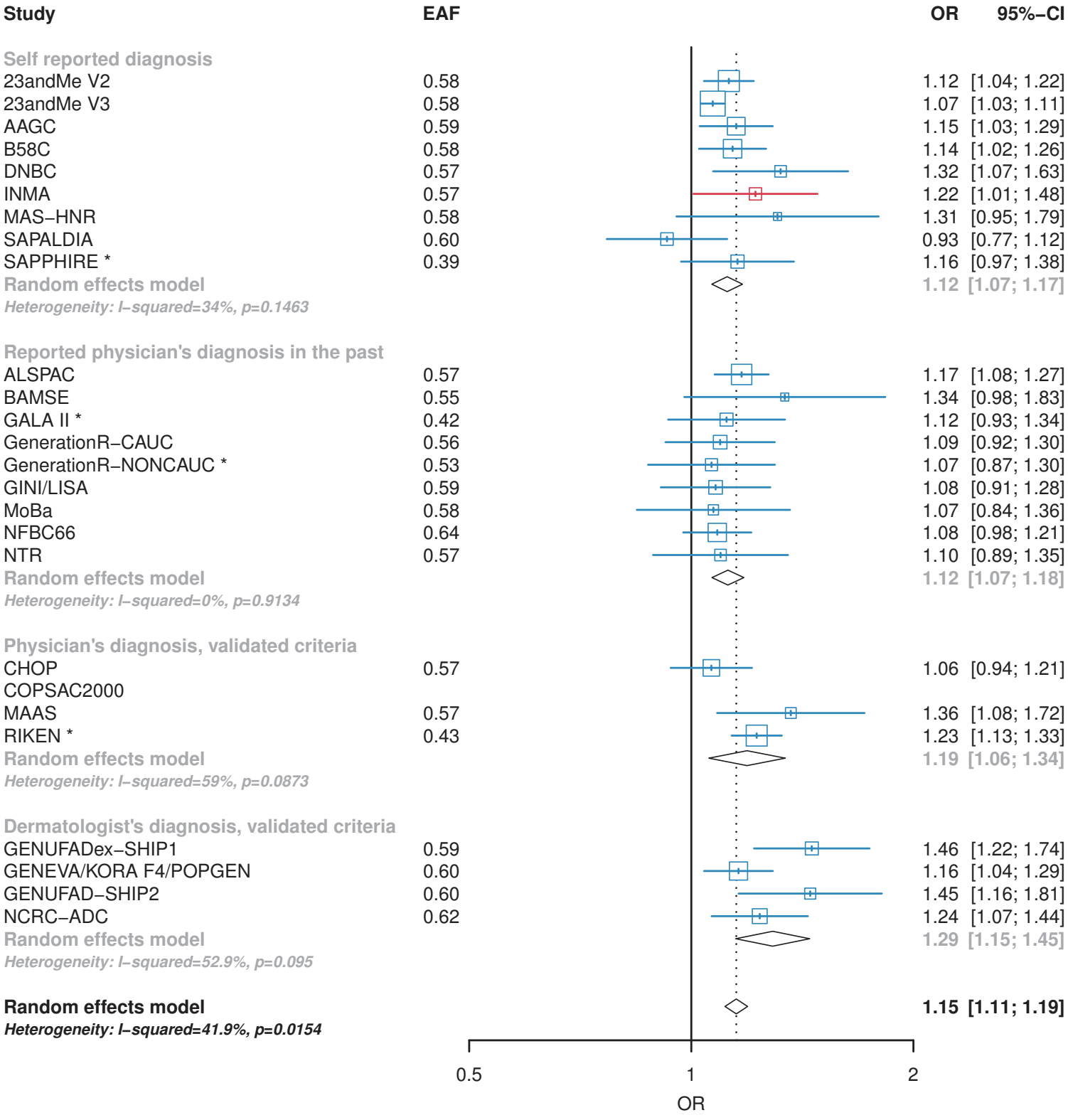


Supplementary Figure 4. Forest plots for the 27 loci p<5x10−8(a−aa). Studies are grouped by diagnosis quality to reflect association strength. Summary random effects meta−analysis results per diagnosis group are shown. The studies of non−European ancestry are marked *. Blue=imputed genotypes, red=genotyped. EAF=effect allele frequency.

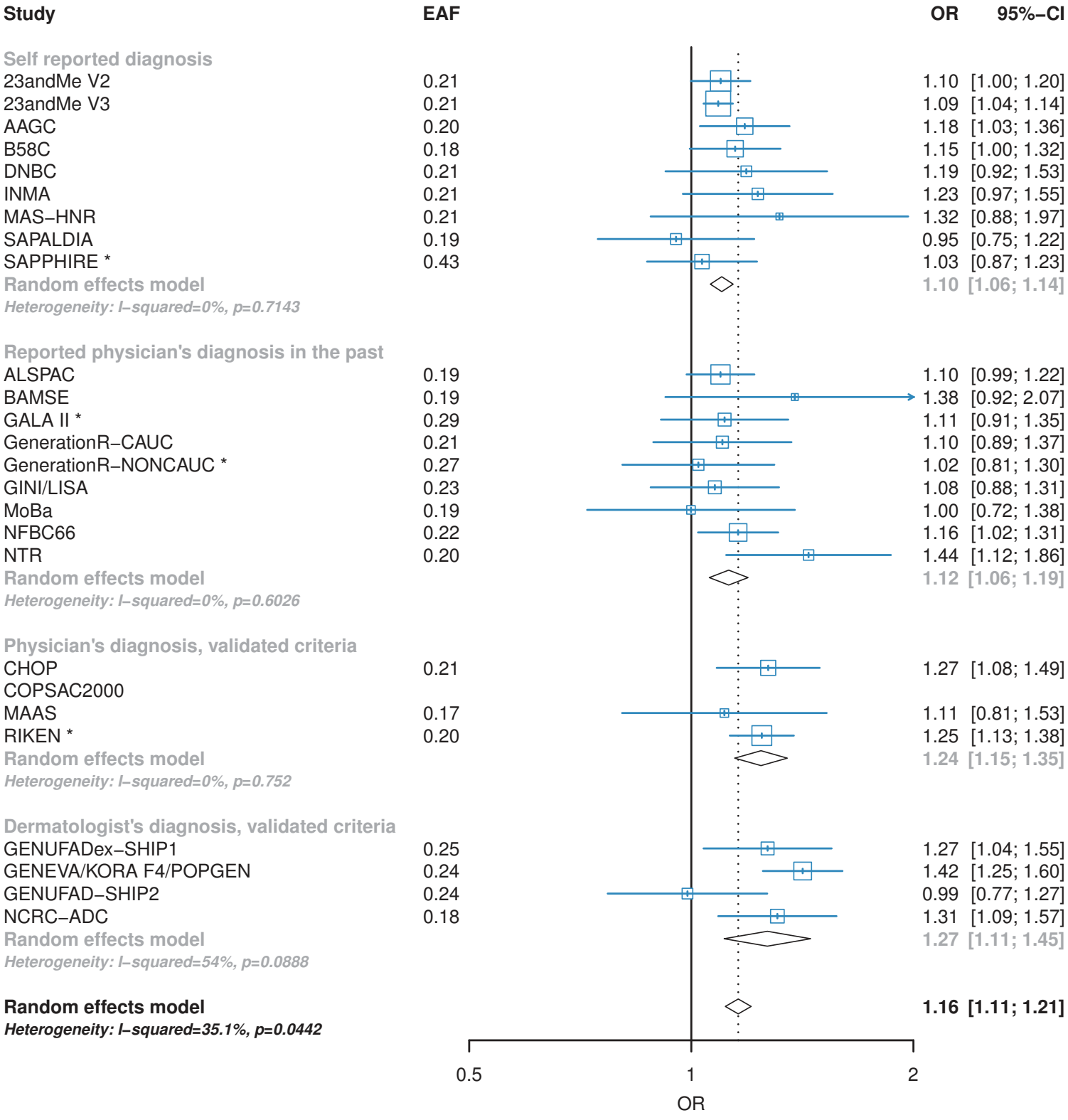
a. rs61813875 (1q21.3, CRCT1/LCE3E (FLG)), effect allele=G



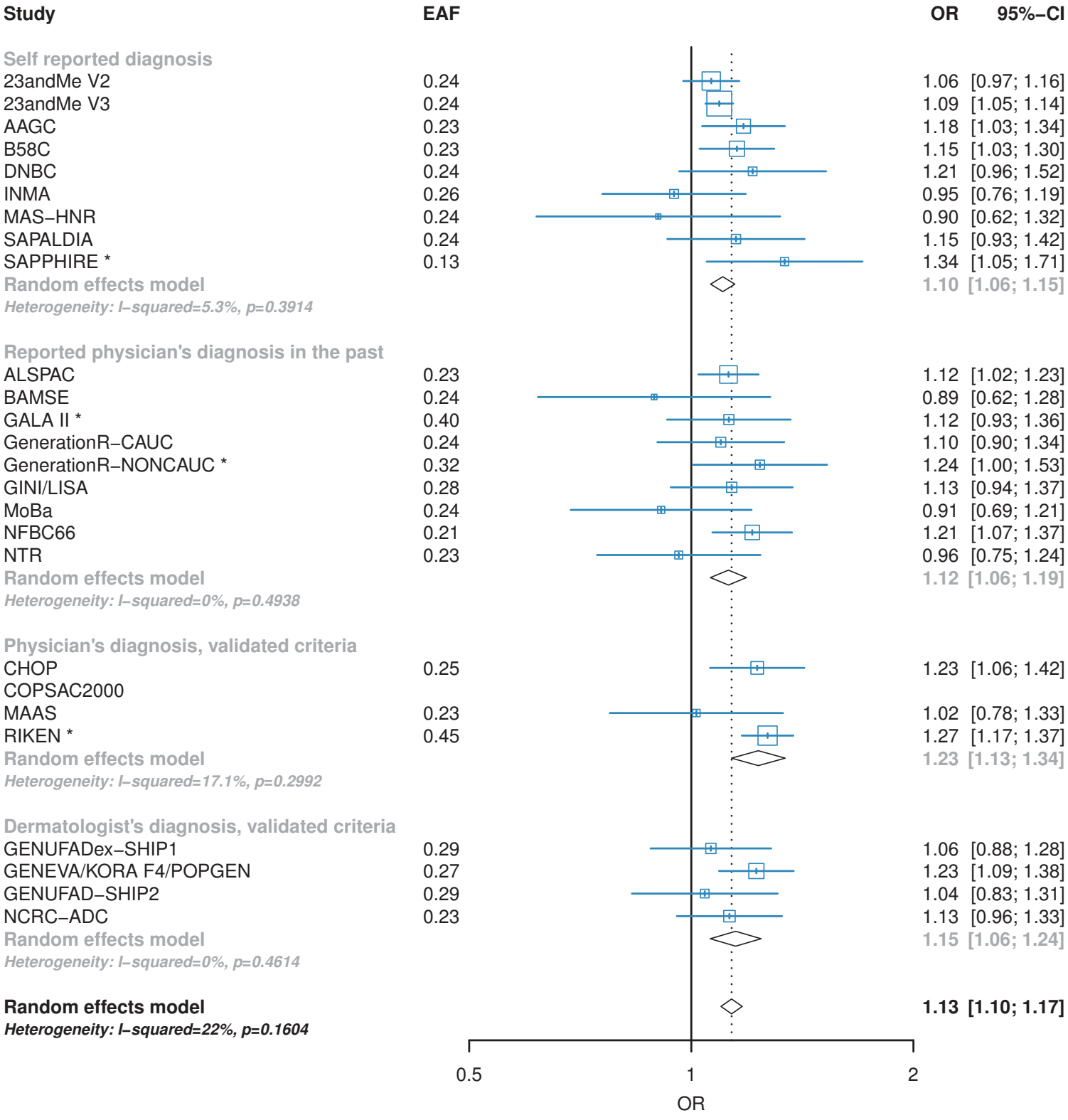
b. rs10791824 (11q13.1, OVOL1), effect allele=G



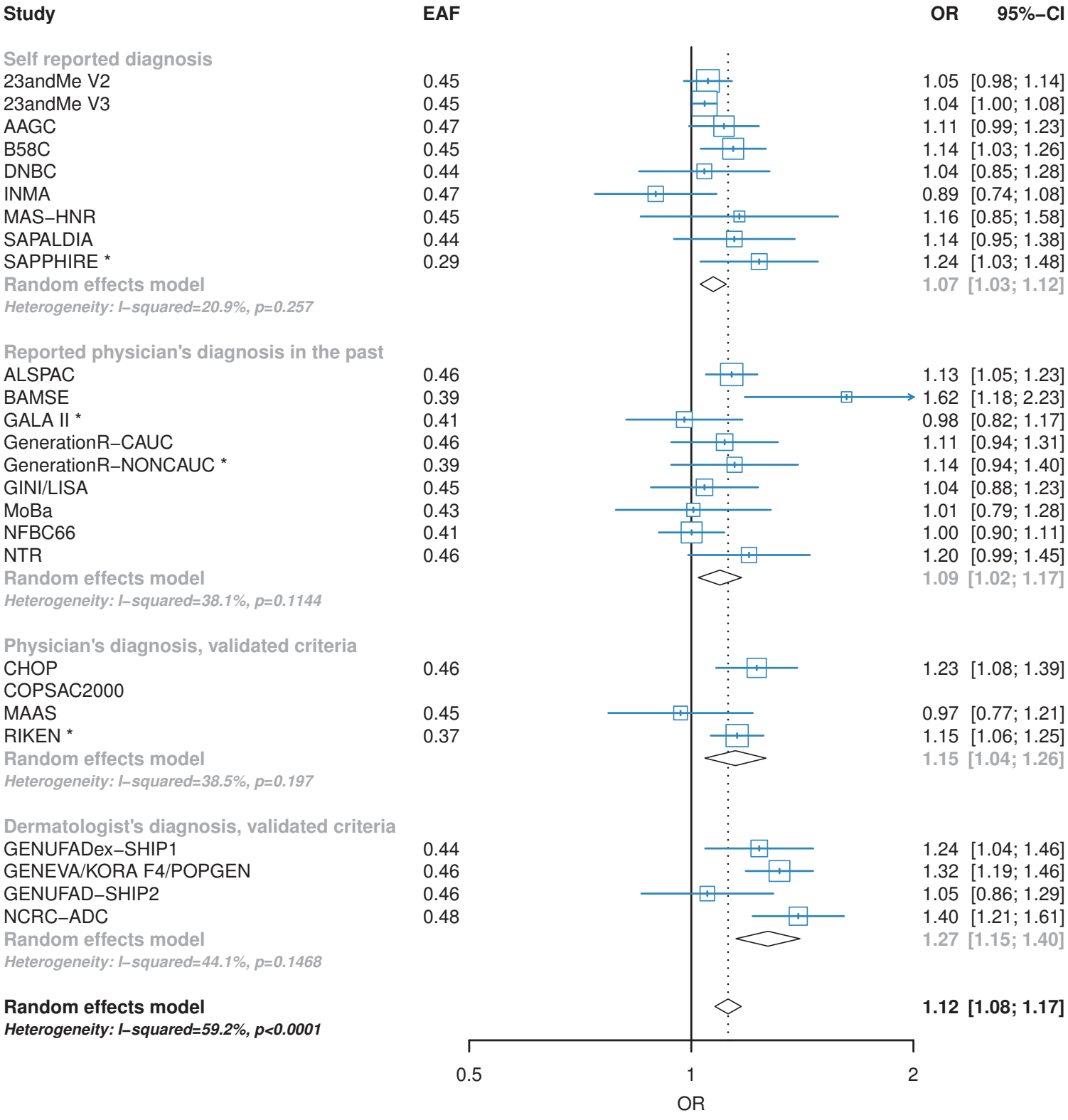
c. rs12188917 (5q31.1, RAD50/IL13), effect allele=C



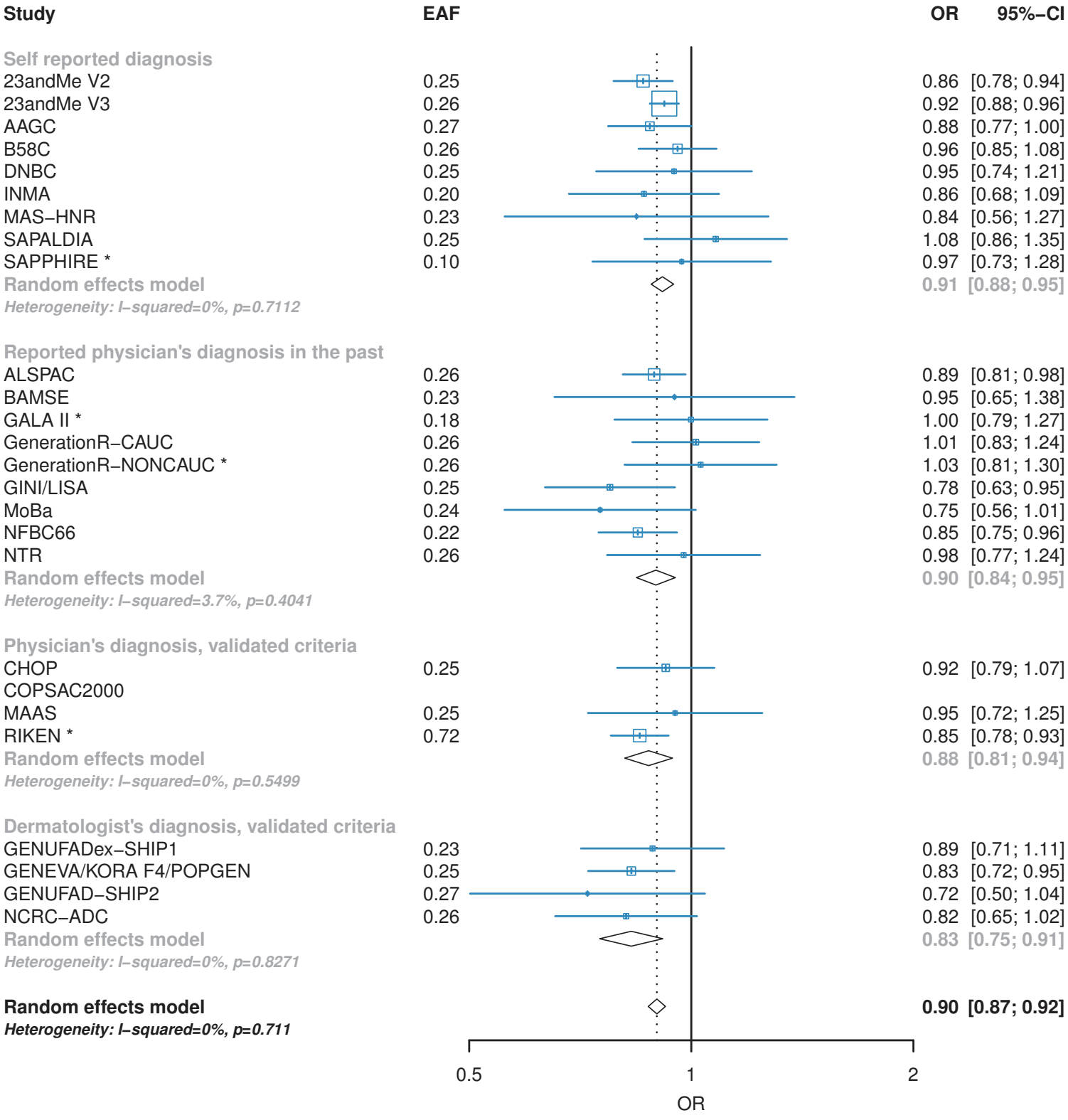
d. rs6419573 (2q12.1, IL18R1/IL18RAP), effect allele=T



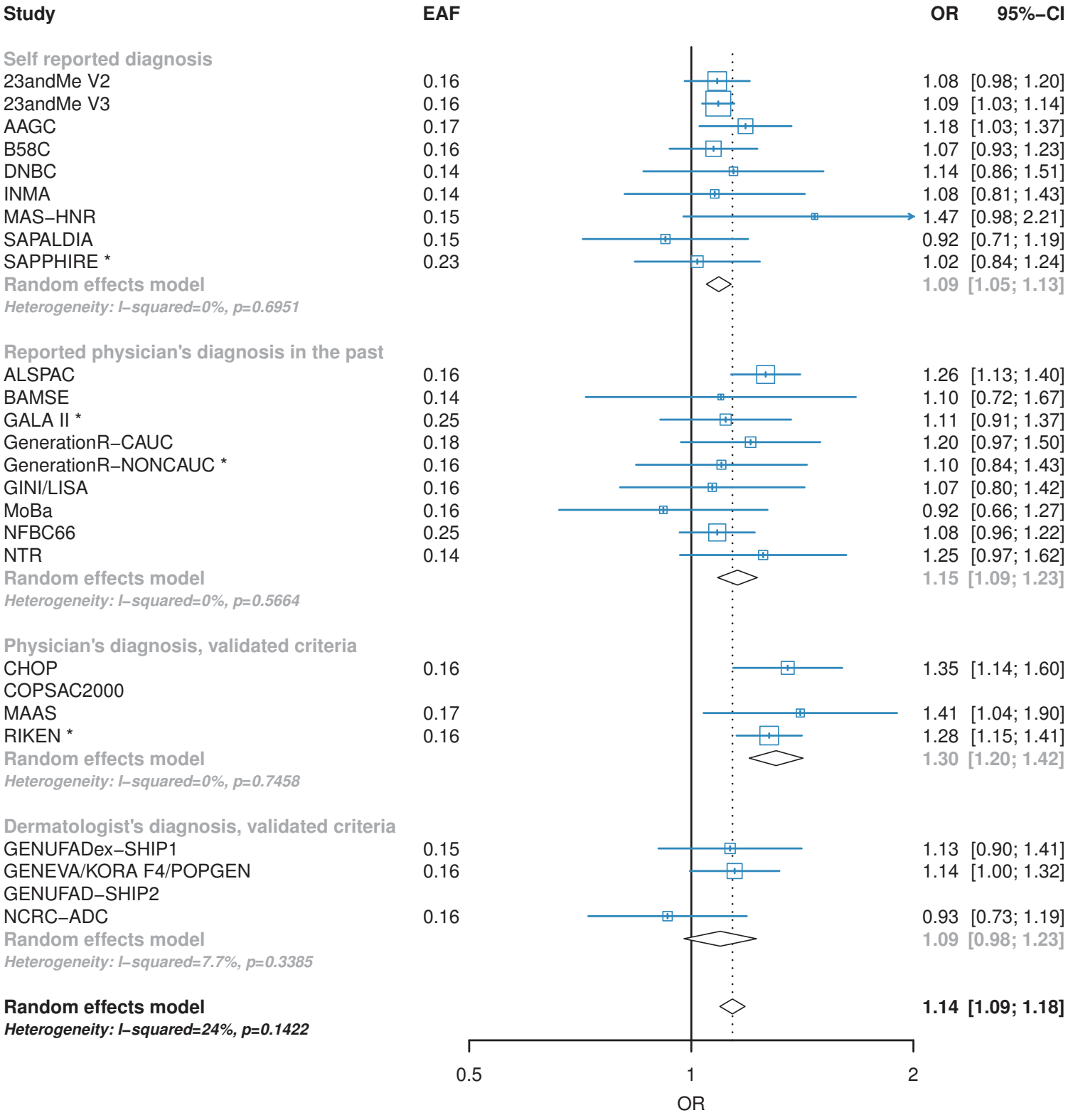
e. rs2212434 (11q13.5, C11orf30/LRRC32), effect allele=T



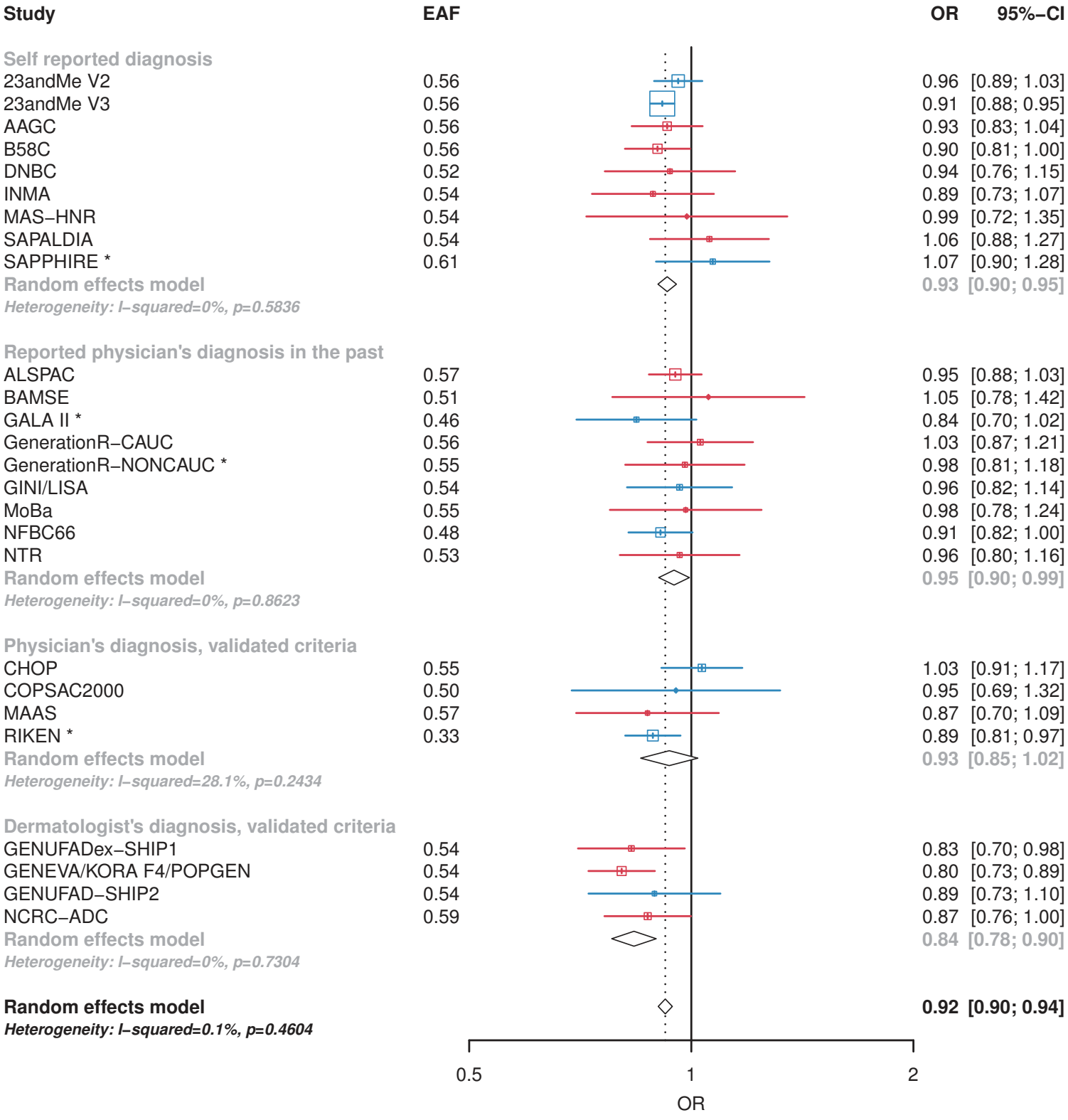
f. rs4809219 (20q13.33, RTEL1–TNFRSF6B), effect allele=C



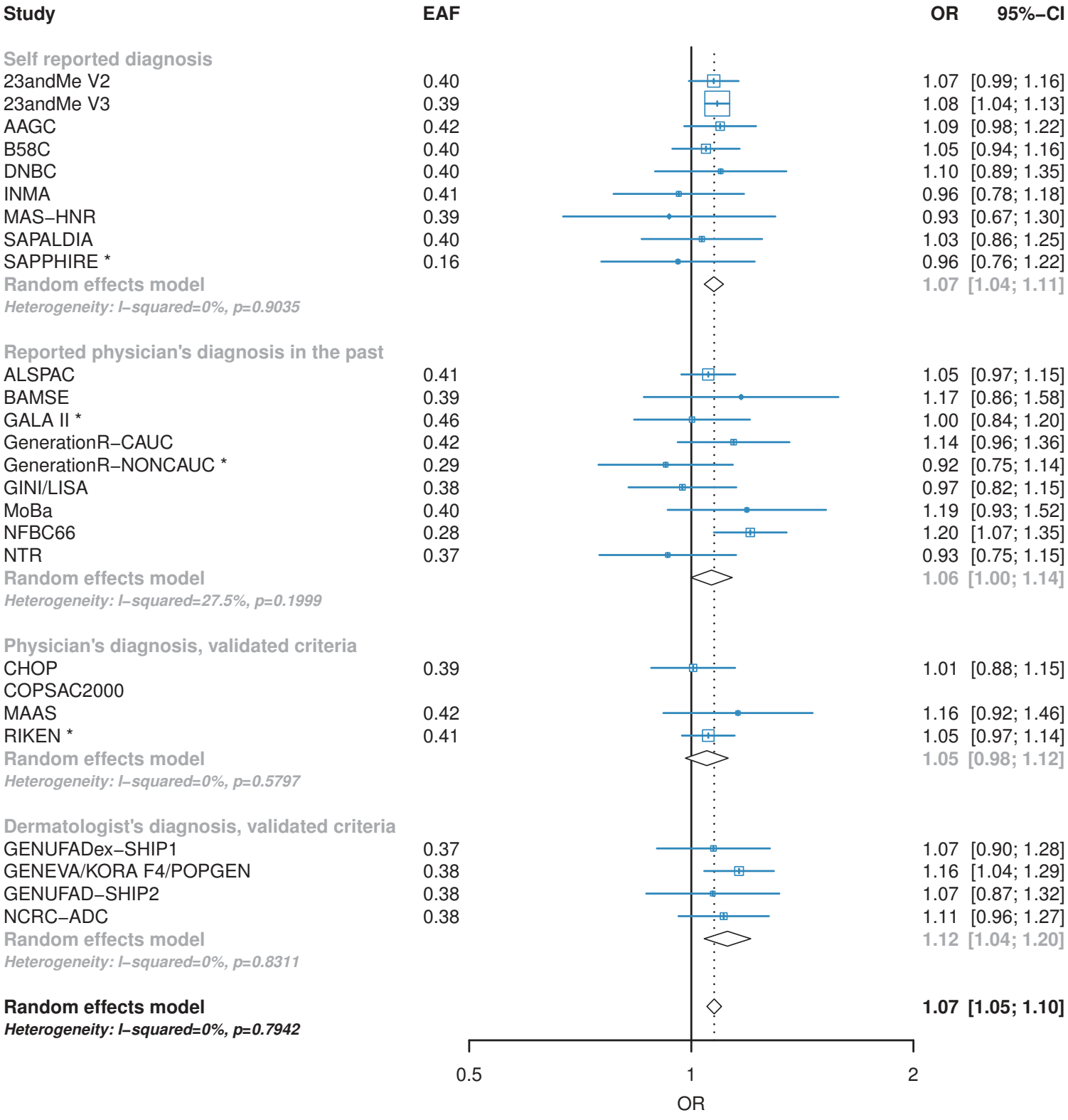
g. rs2918307 (19p13.2, ADAMTS10/ACTL9), effect allele=G



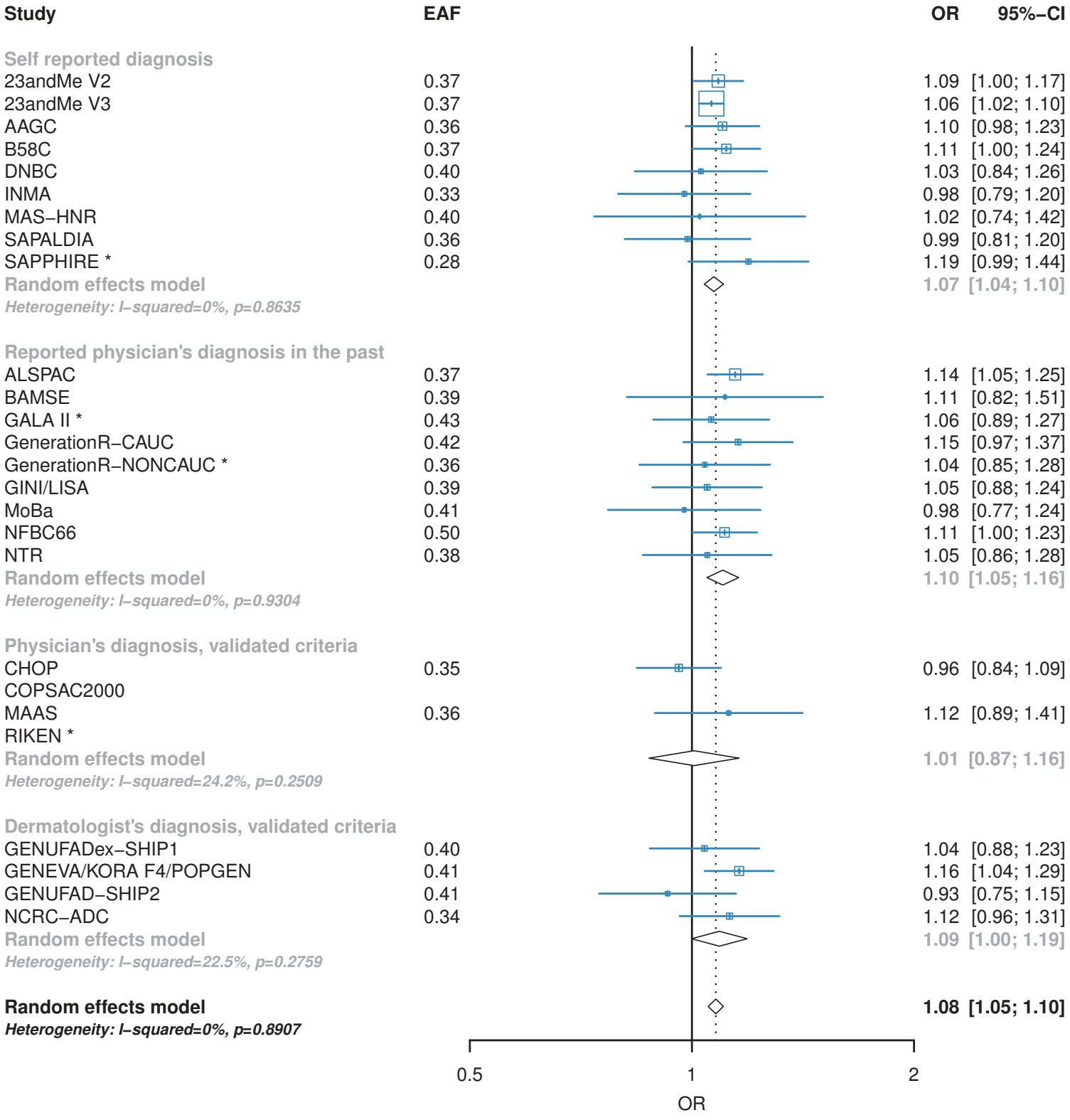
h. rs2041733 (16p13.13, CLEC16A), effect allele=C



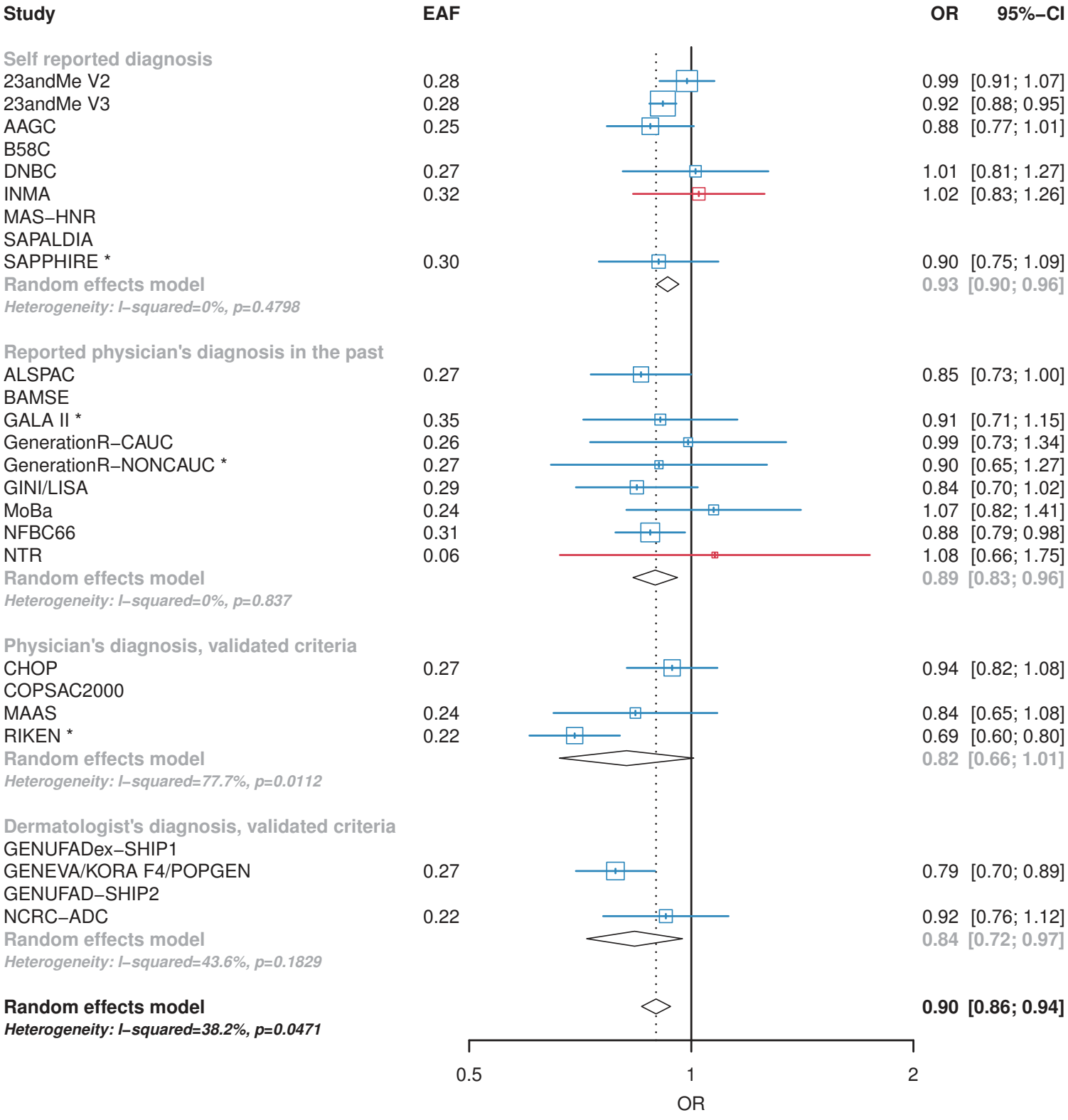
i. rs12730935 (1q21.3, IL6R), effect allele=A



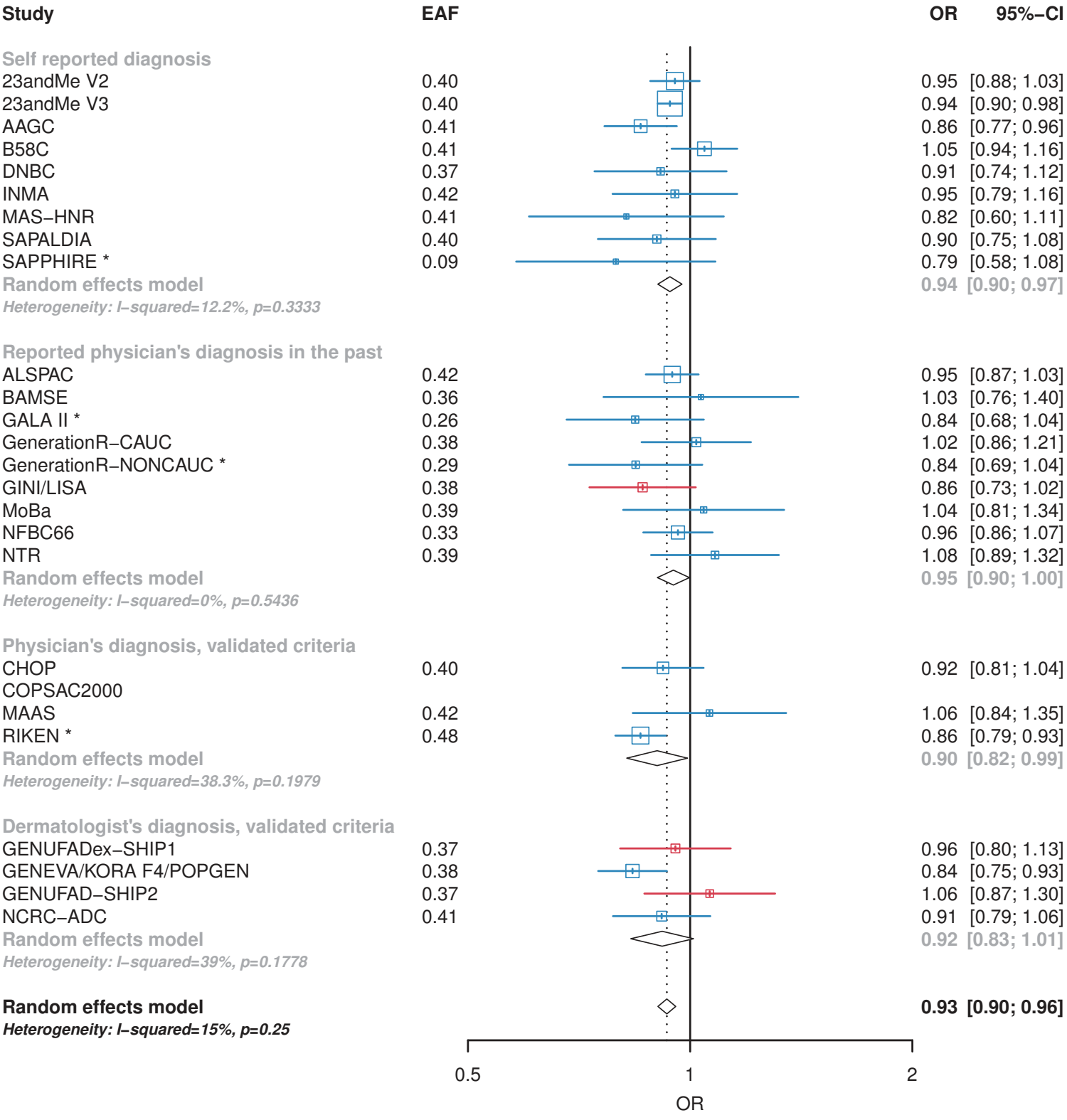
j. 4:123243592:INDEL (4q27, KIAA109 (IL2)), effect allele=R



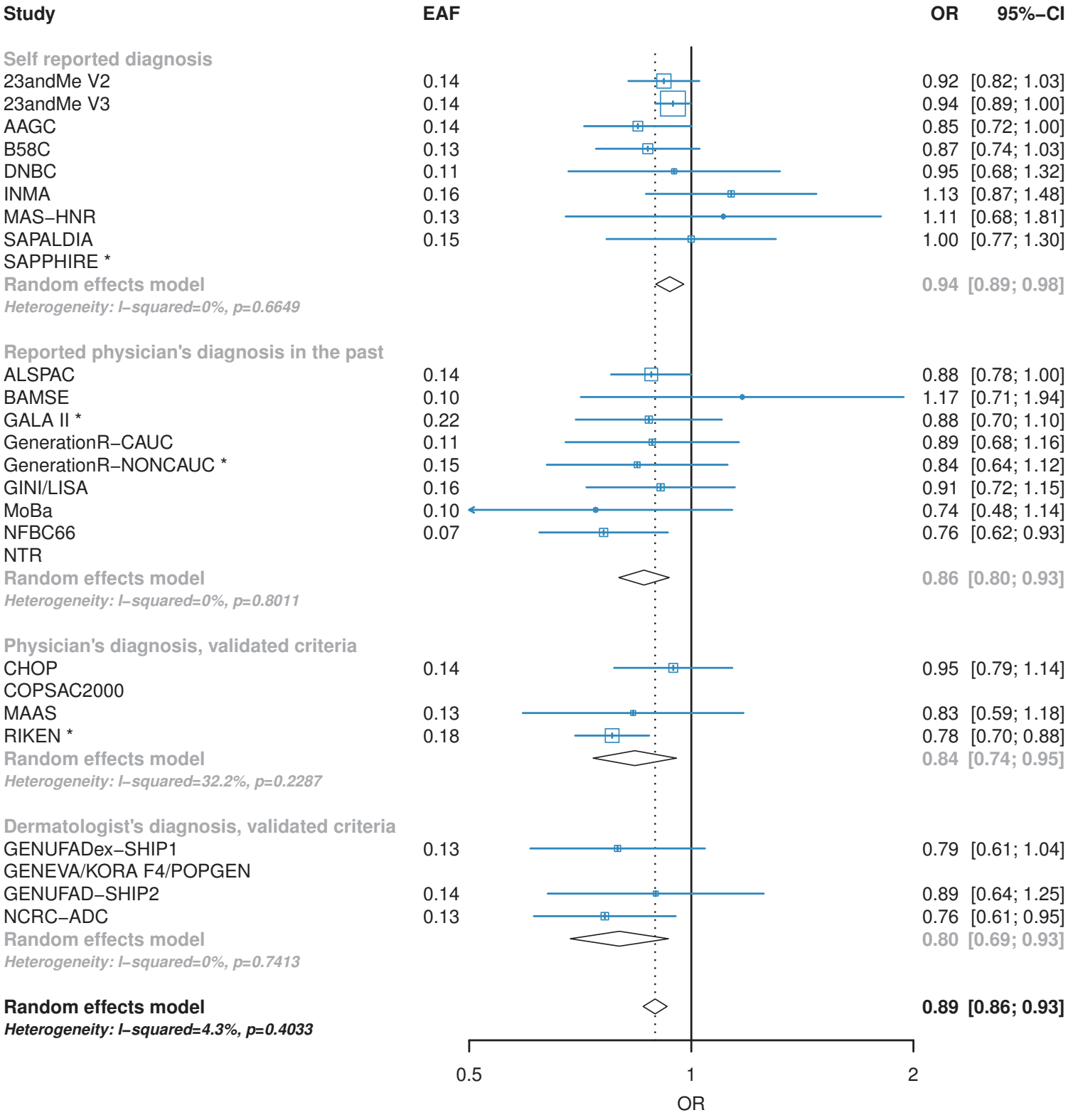
k. rs4713555 (6p21.32, HLA−DRB/HLA−DQA1), effect allele=T



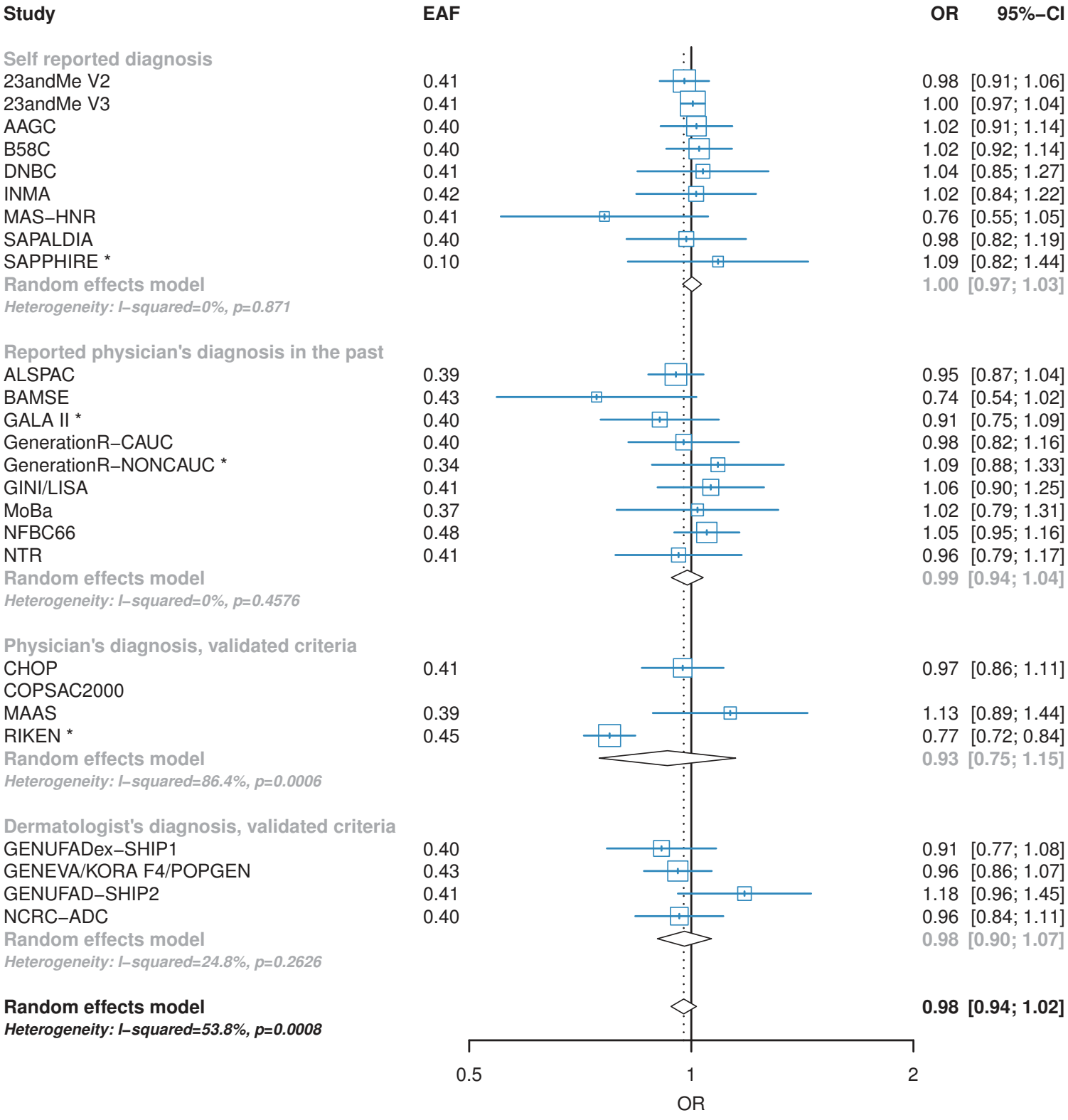
I. rs2944542 (10q21.2, ZNF365), effect allele=C



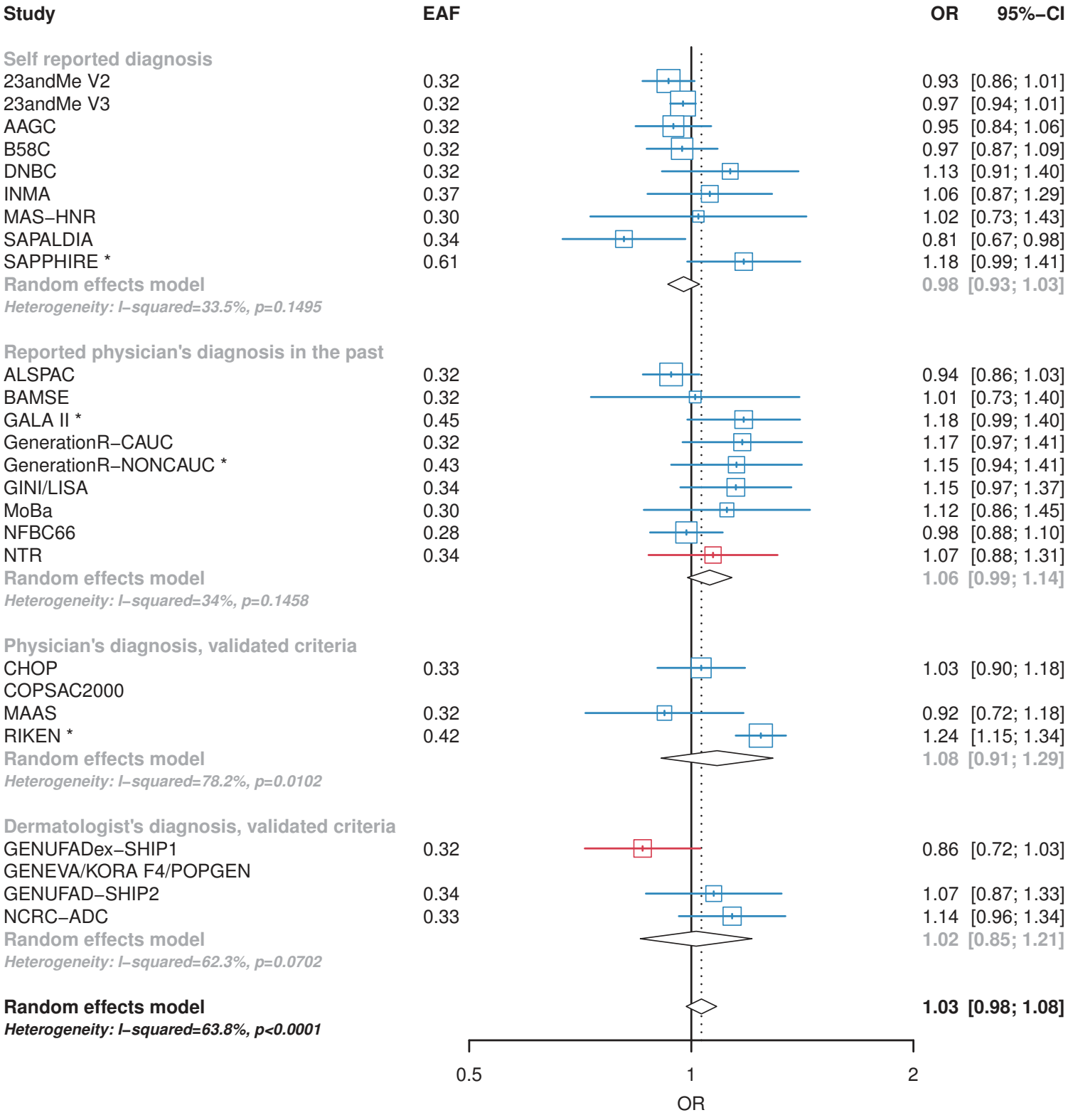
m. rs145809981 (6p21.33, MICB), effect allele=T



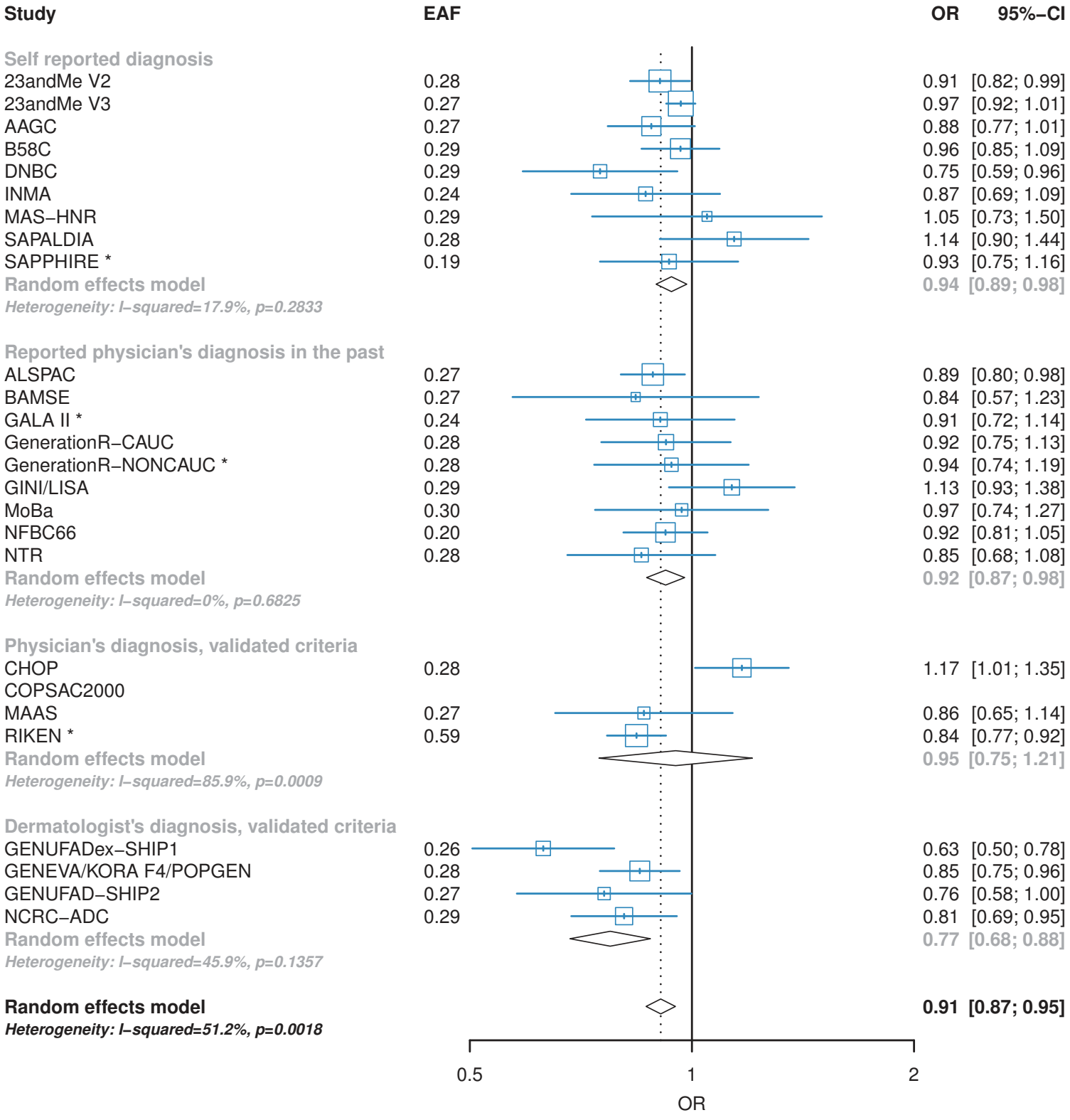
n. rs4312054 (11p15.4, OR10A3/NLRP10), effect allele=G



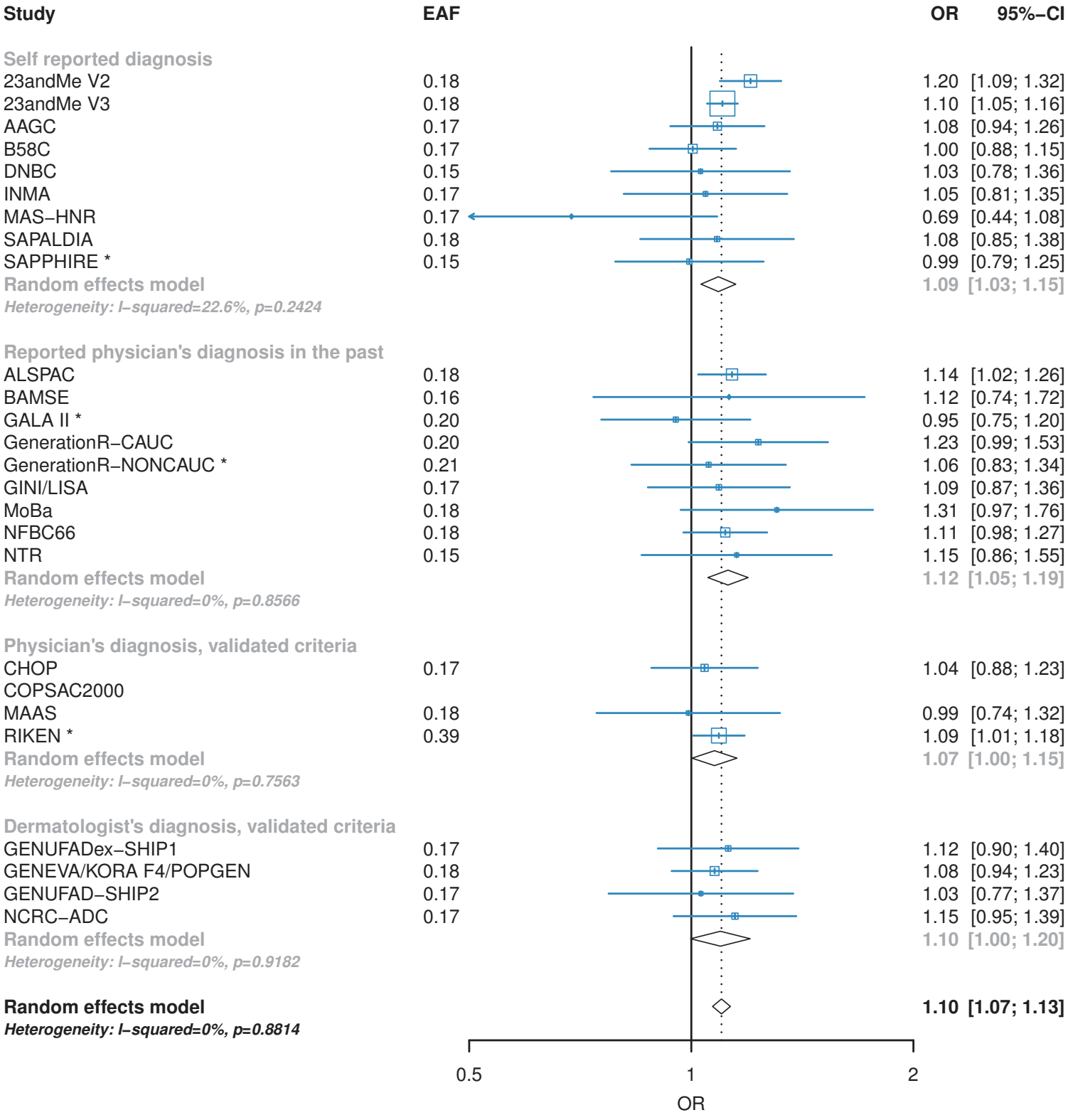
o. rs1249910 (3q13.2, CCDC80/CD200R1L), effect allele=A



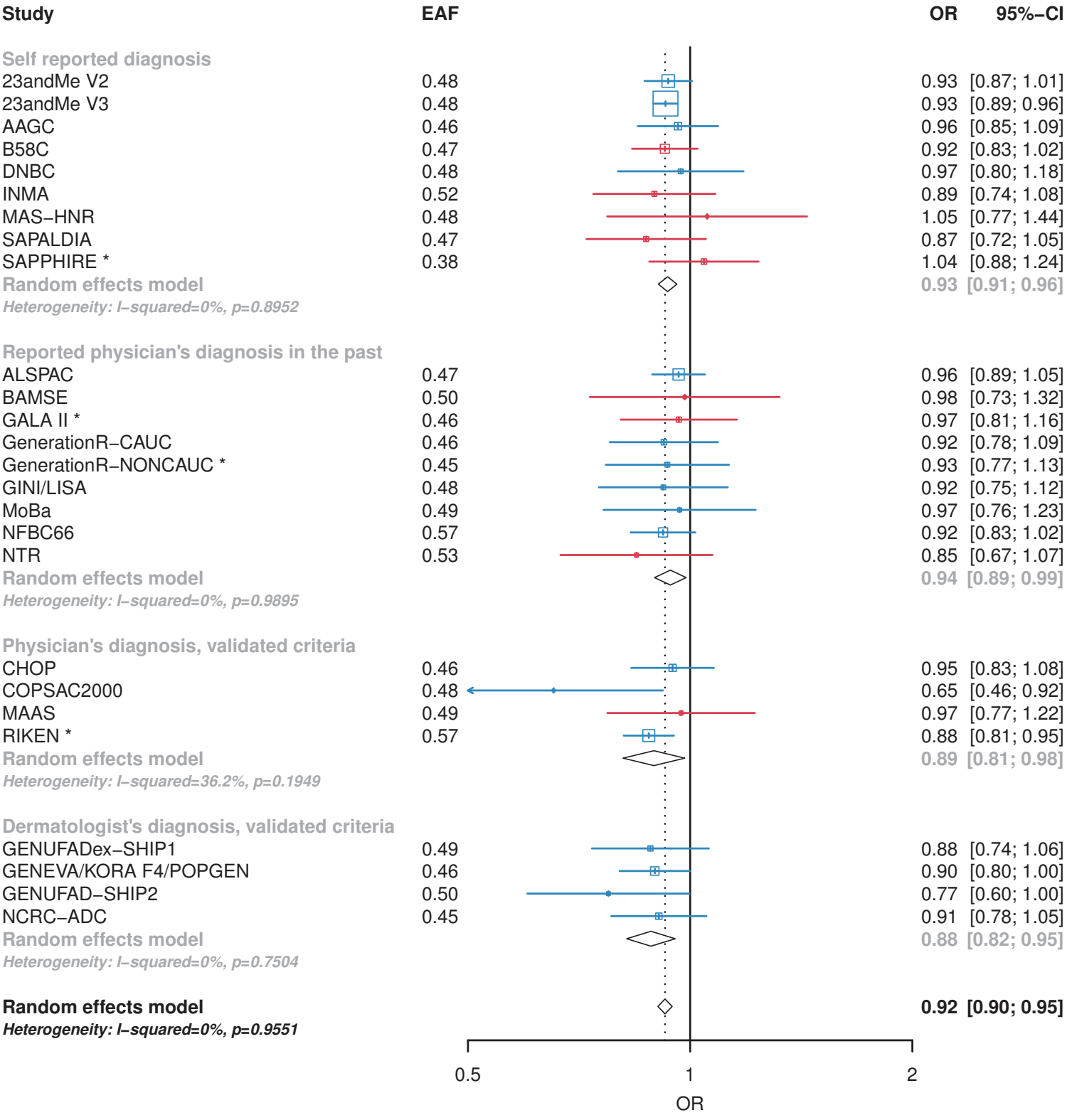
p. rs2592555 (11p13, PRR5L), effect allele=C



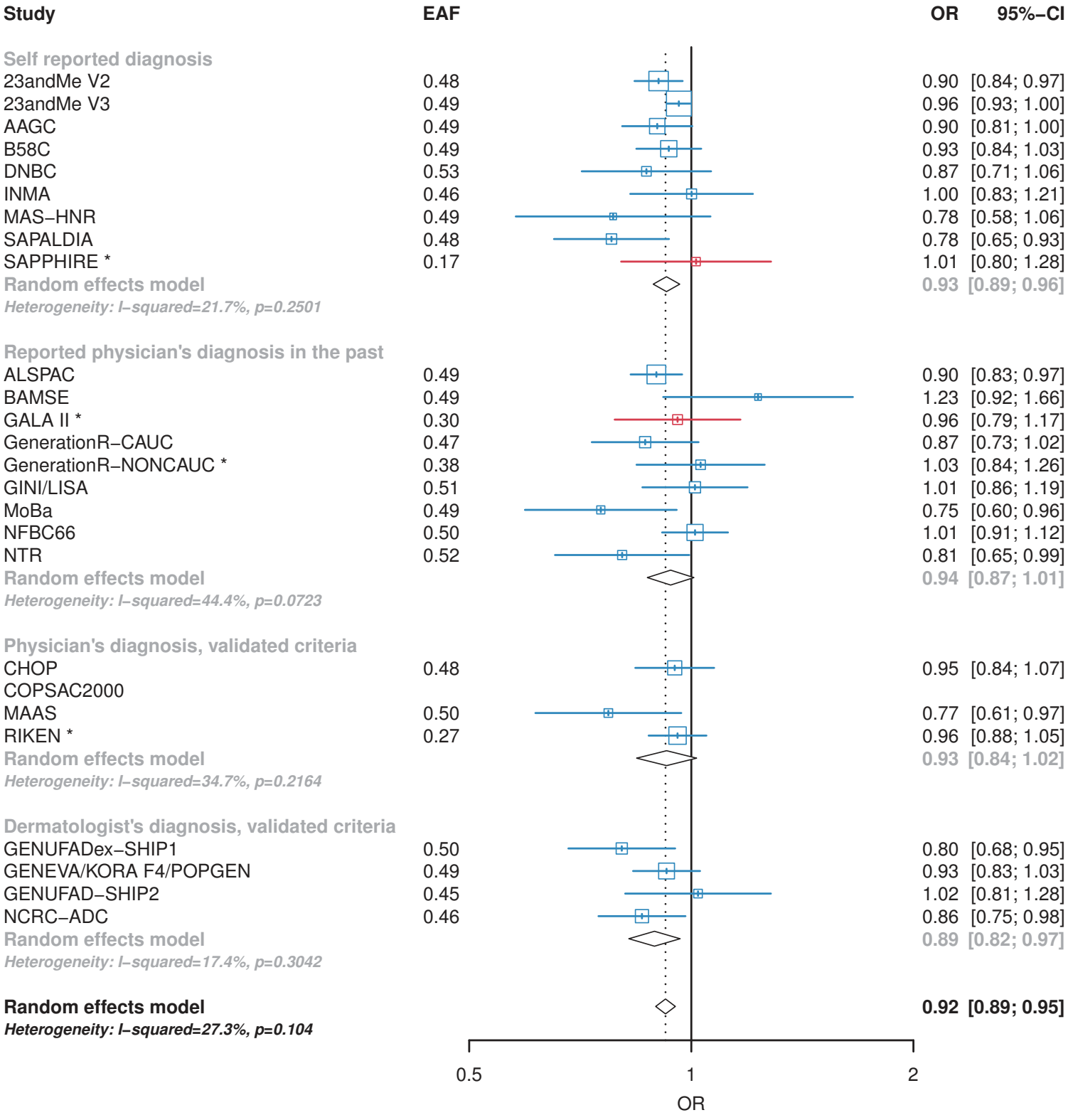
q. rs2038255 (14q13.2, PPP2R3C), effect allele=T



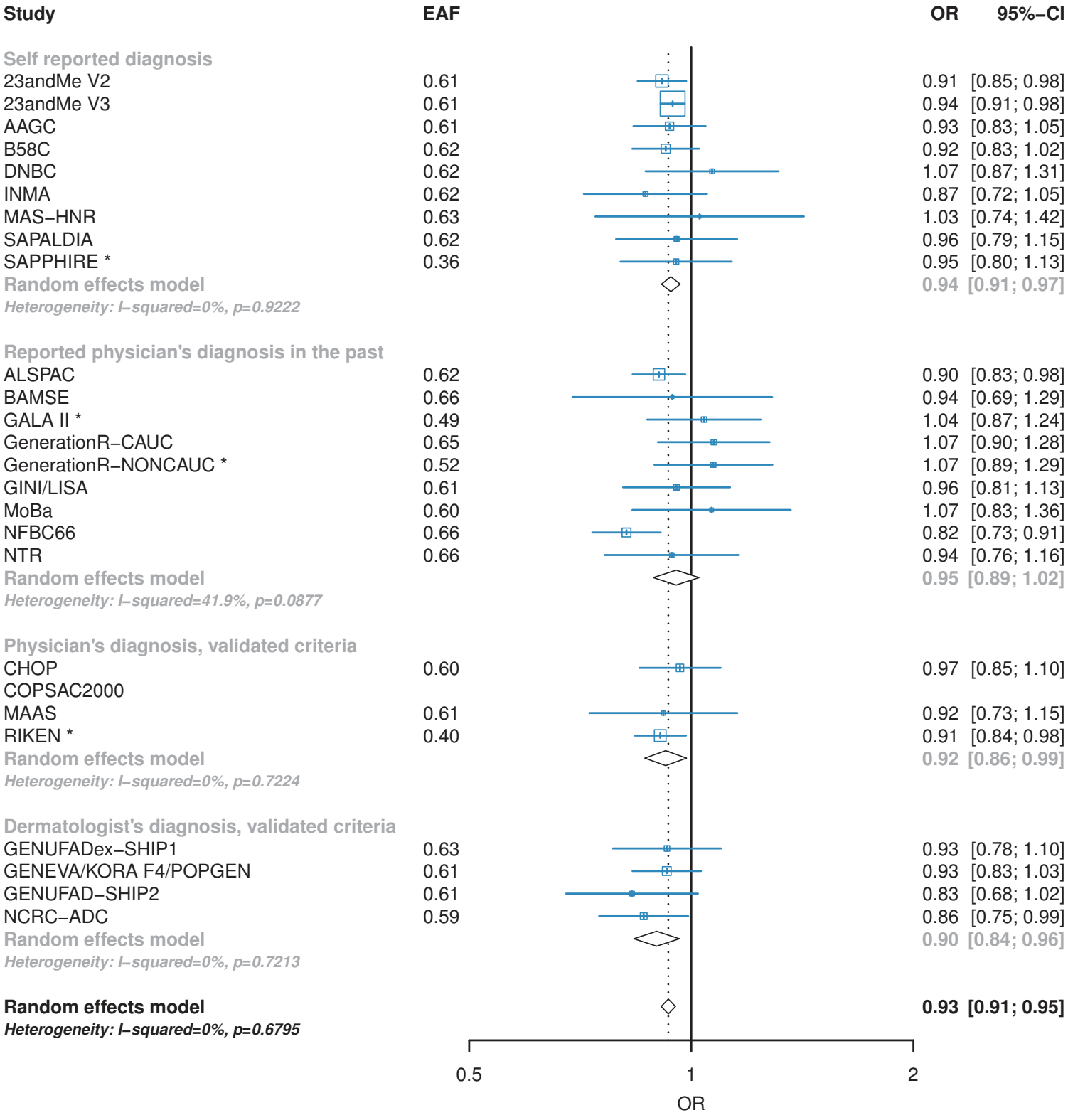
r. rs7127307 (11q24.3, –/ETS1), effect allele=C



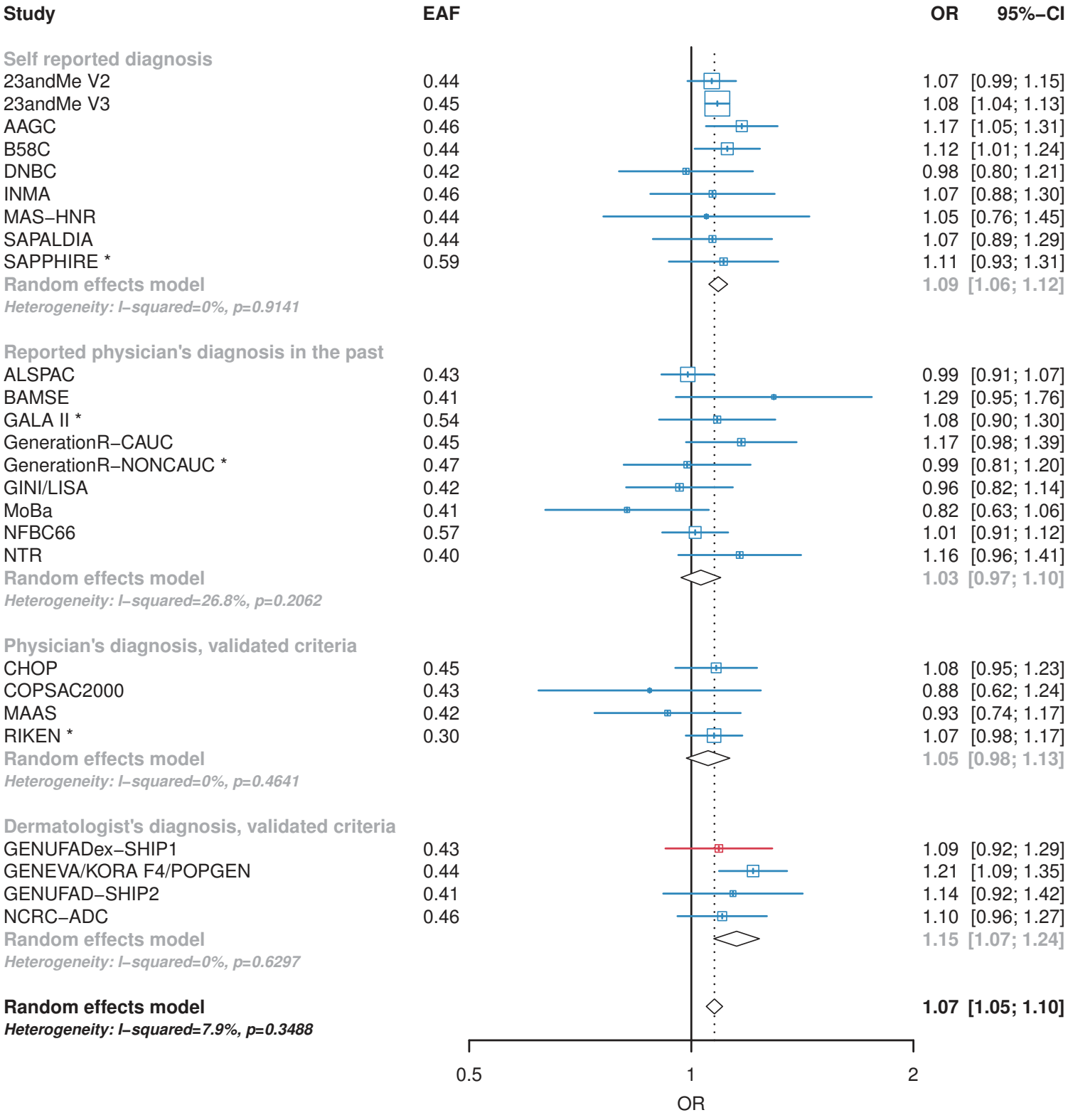
s. rs7512552 (1q21.2, C1orf51/MRPS21), effect allele=T



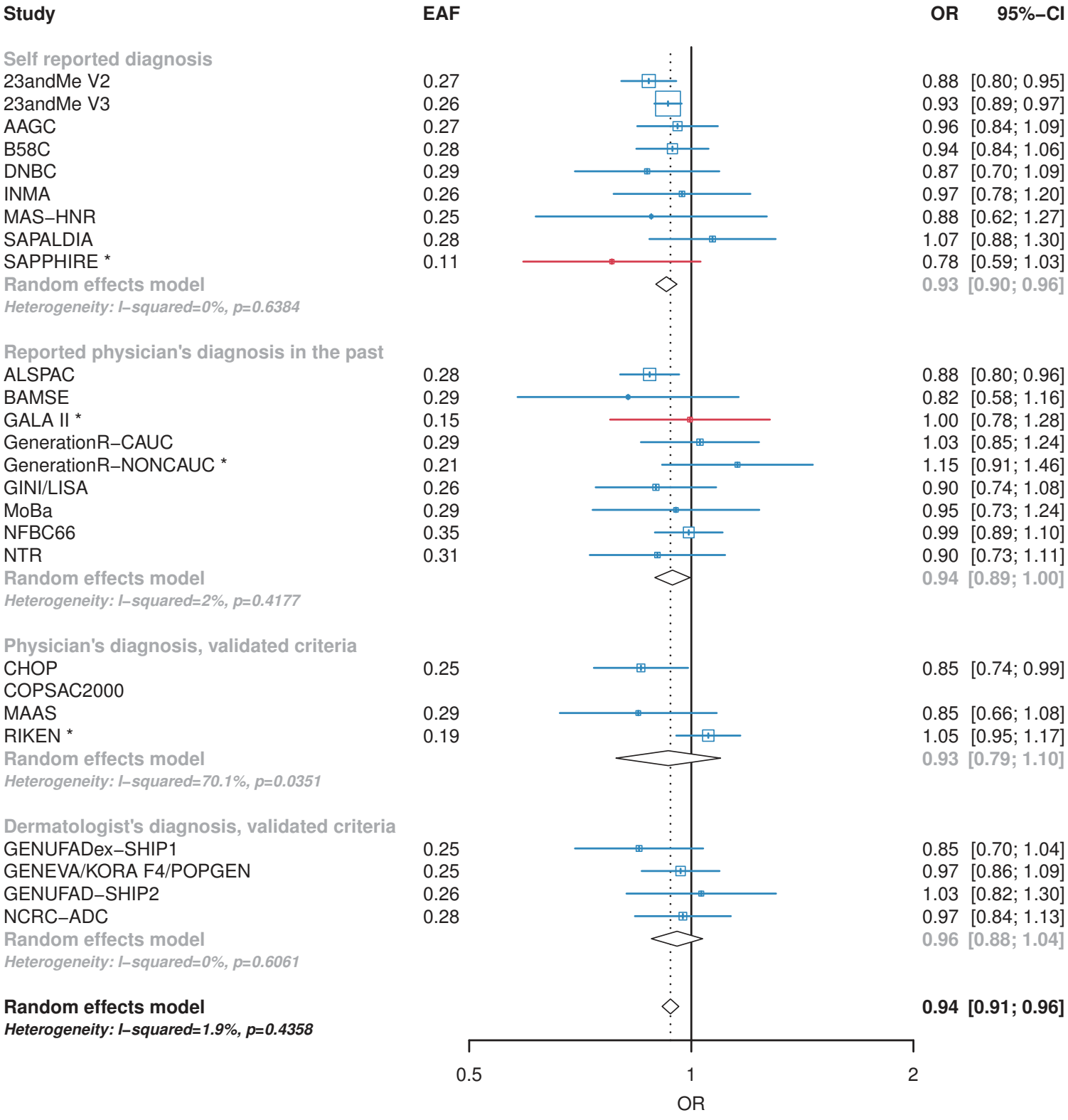
t. rs6473227 (8q21.13, MIR5708/ZBTB10), effect allele=A



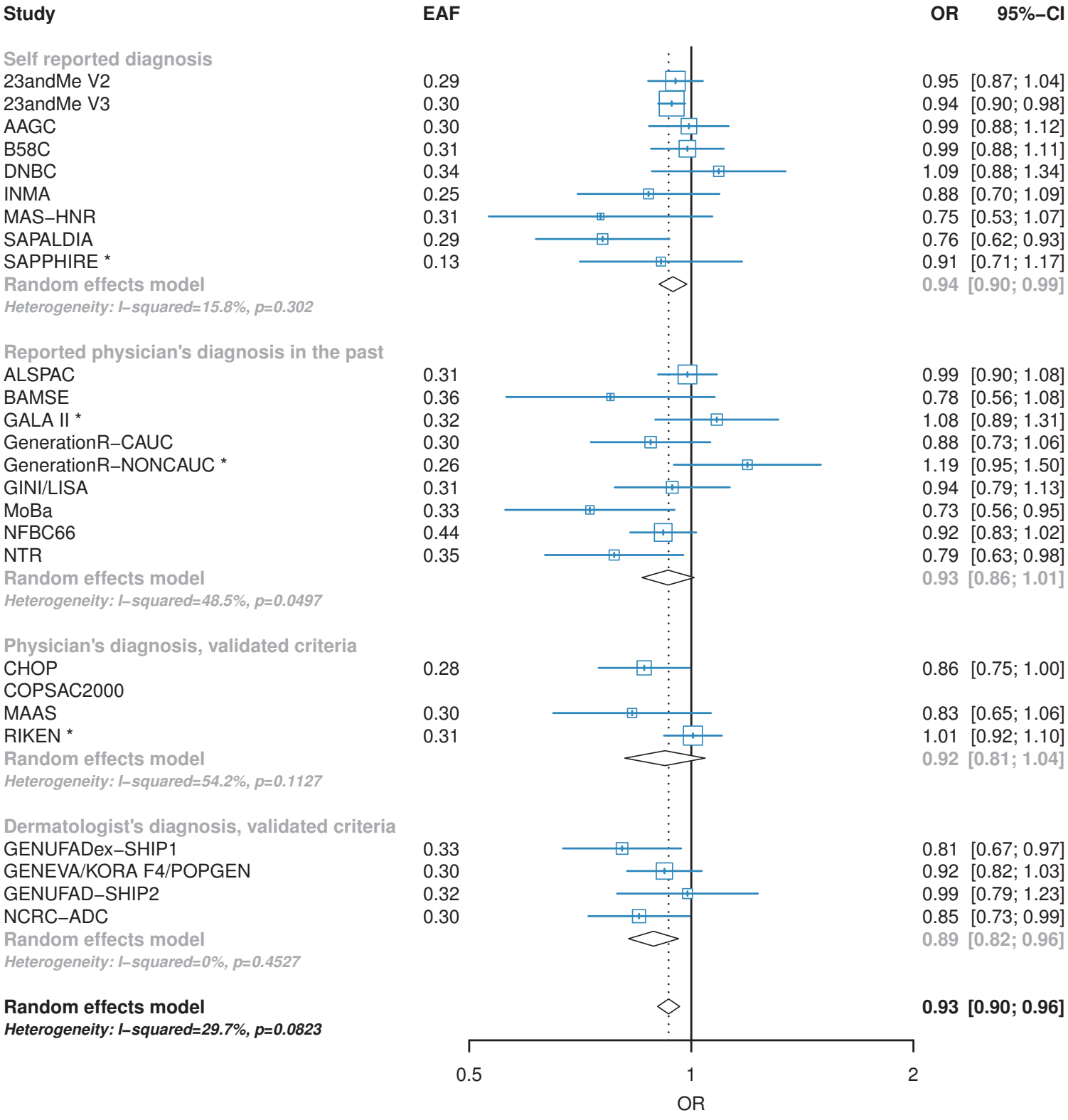
u. rs6602364 (10p15.1, IL15RA/IL2RA), effect allele=G



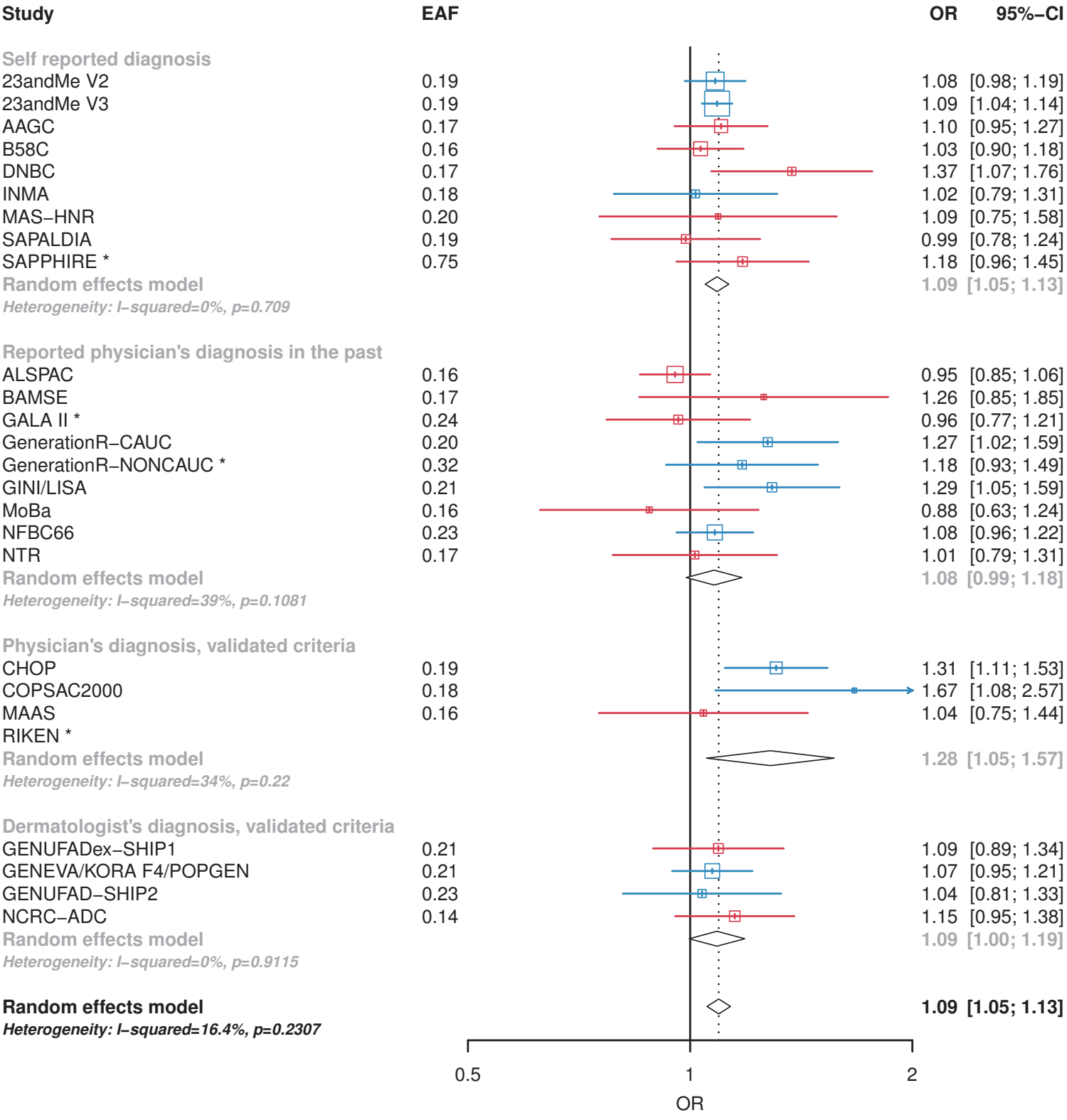
v. rs10214237 (5p13.2, IL7R/CAPSL), effect allele=C



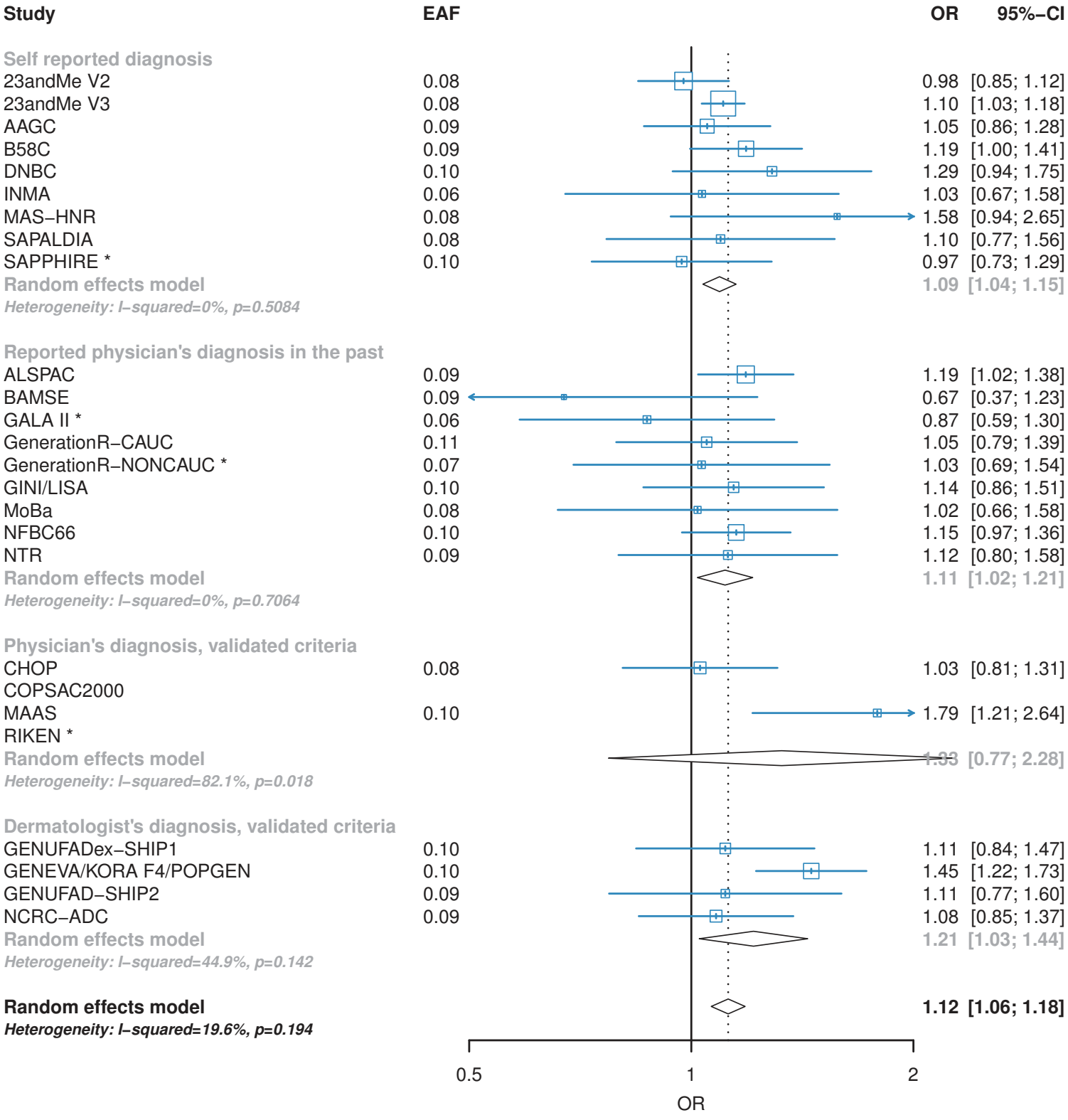
w. rs10199605 (2p25.1, LINC00299/–), effect allele=A



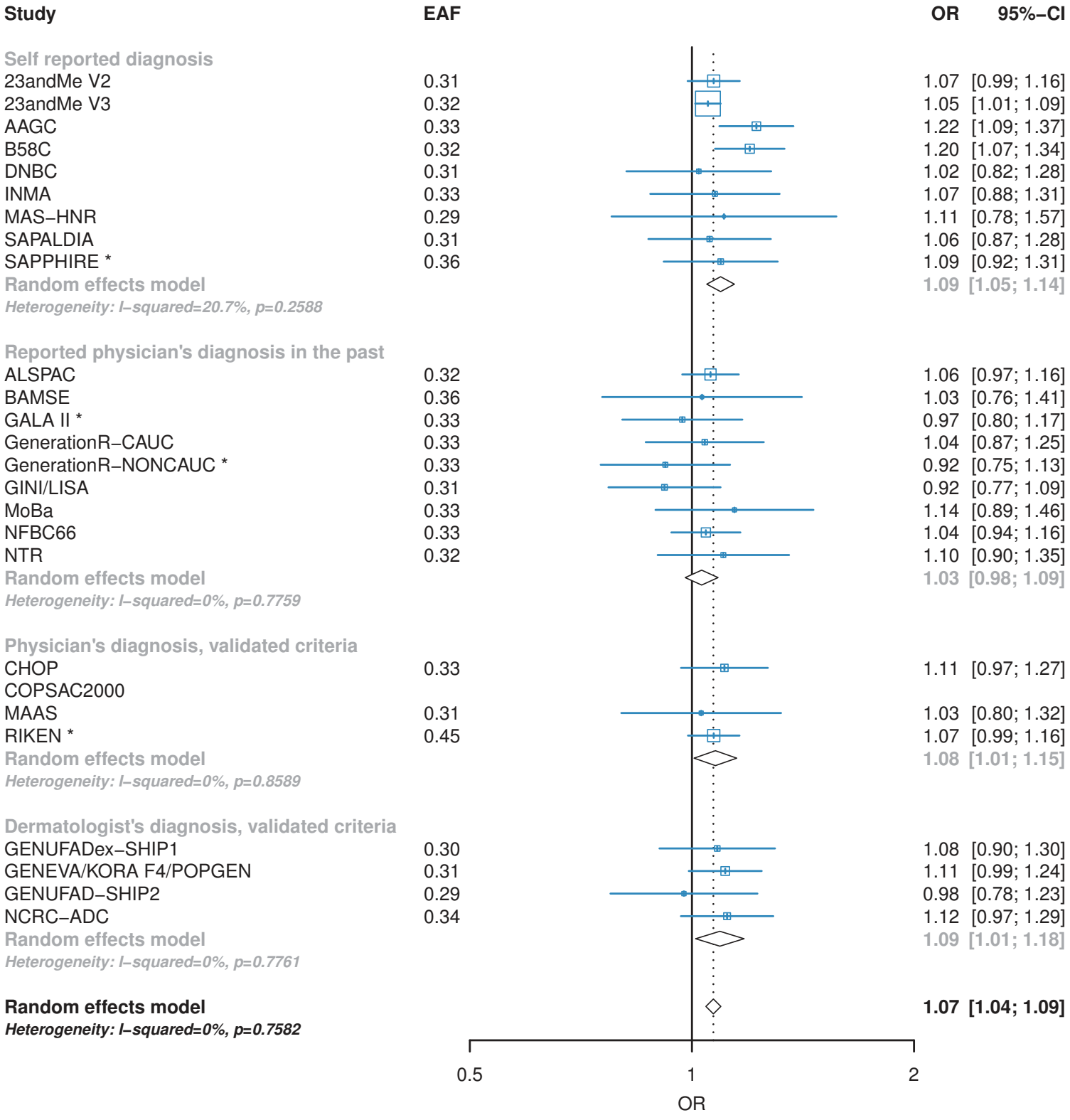
x. rs4643526 (2p16.1, PUS10), effect allele=A



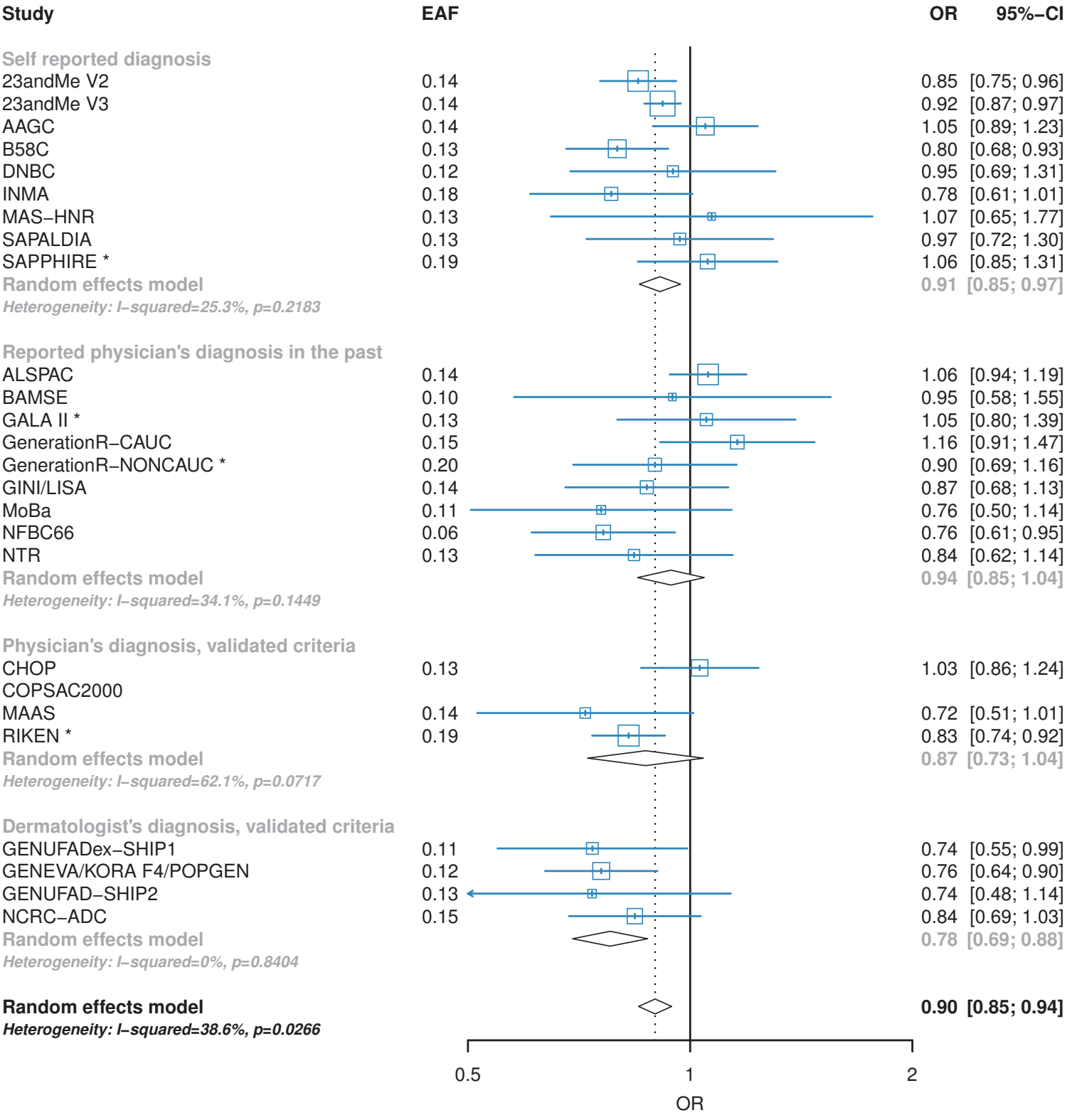
y. rs12951971 (17q21.2, STAT3), effect allele=G



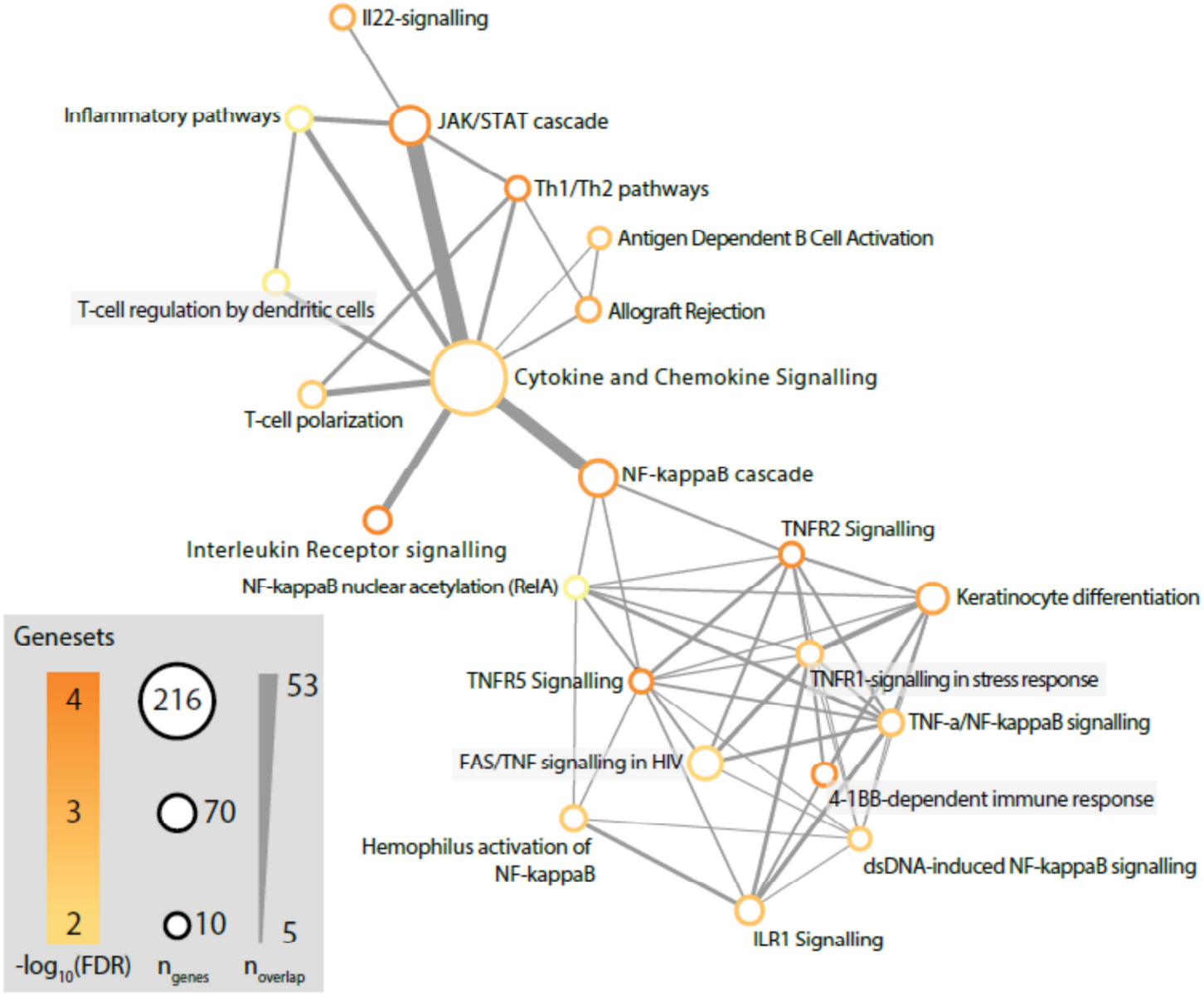
z. rs7625909 (3p21.1, SFMBT1/RFT1), effect allele=T



aa. rs112111458 (2p13.3, CD207/VAX2), effect allele=G

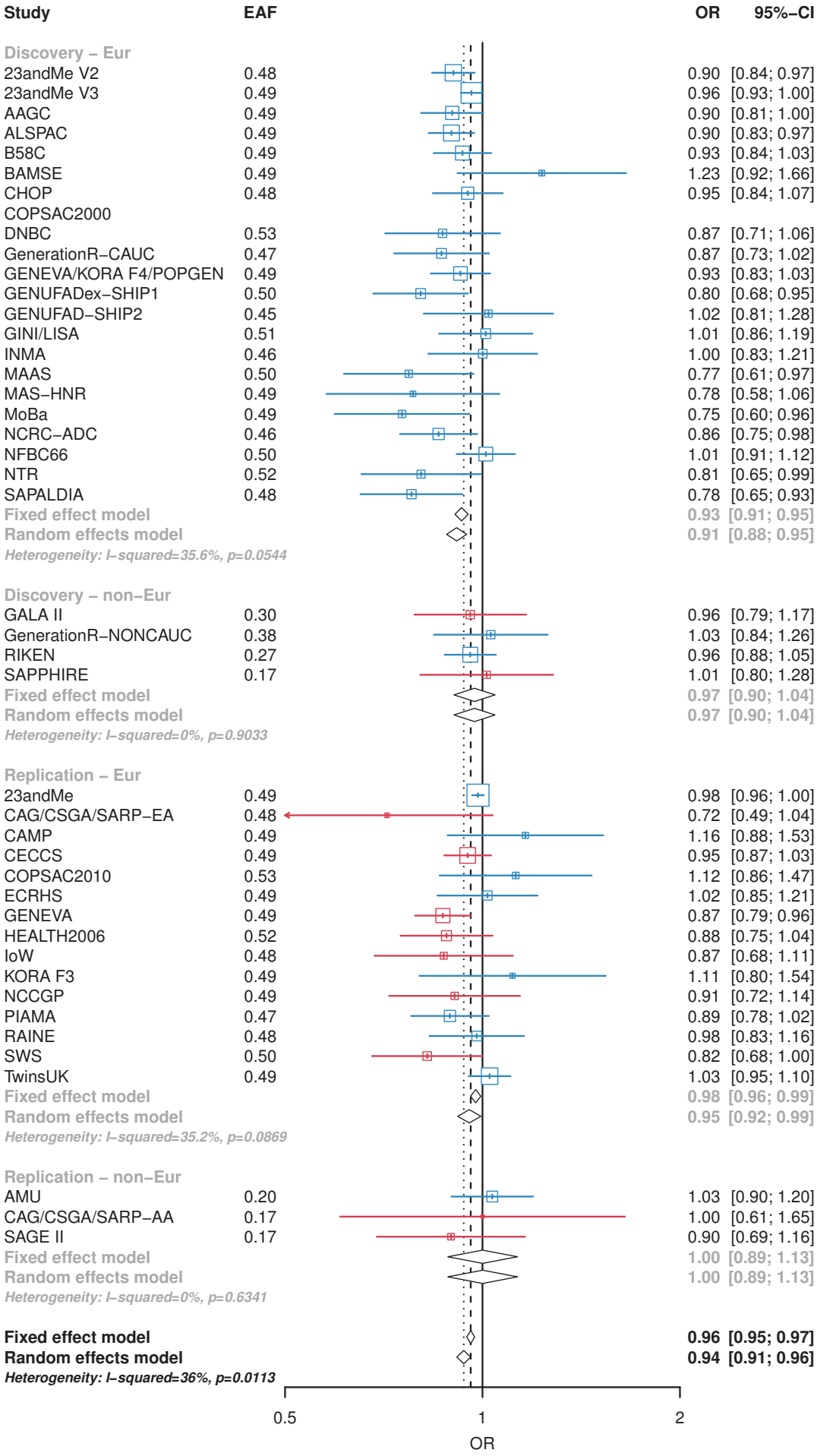


Supplementary Figure 5. Overlap graph of gene-sets enriched in atopic dermatitis with FDR <= 0.01, as reported by MAGENTA. The color of each node represents FDR-value, the size of each node represents gene-set size, and the connecting line thicknesses represent the number of common genes between gene-sets. Edges with <50% overlap and unconnected gene-sets are not shown.

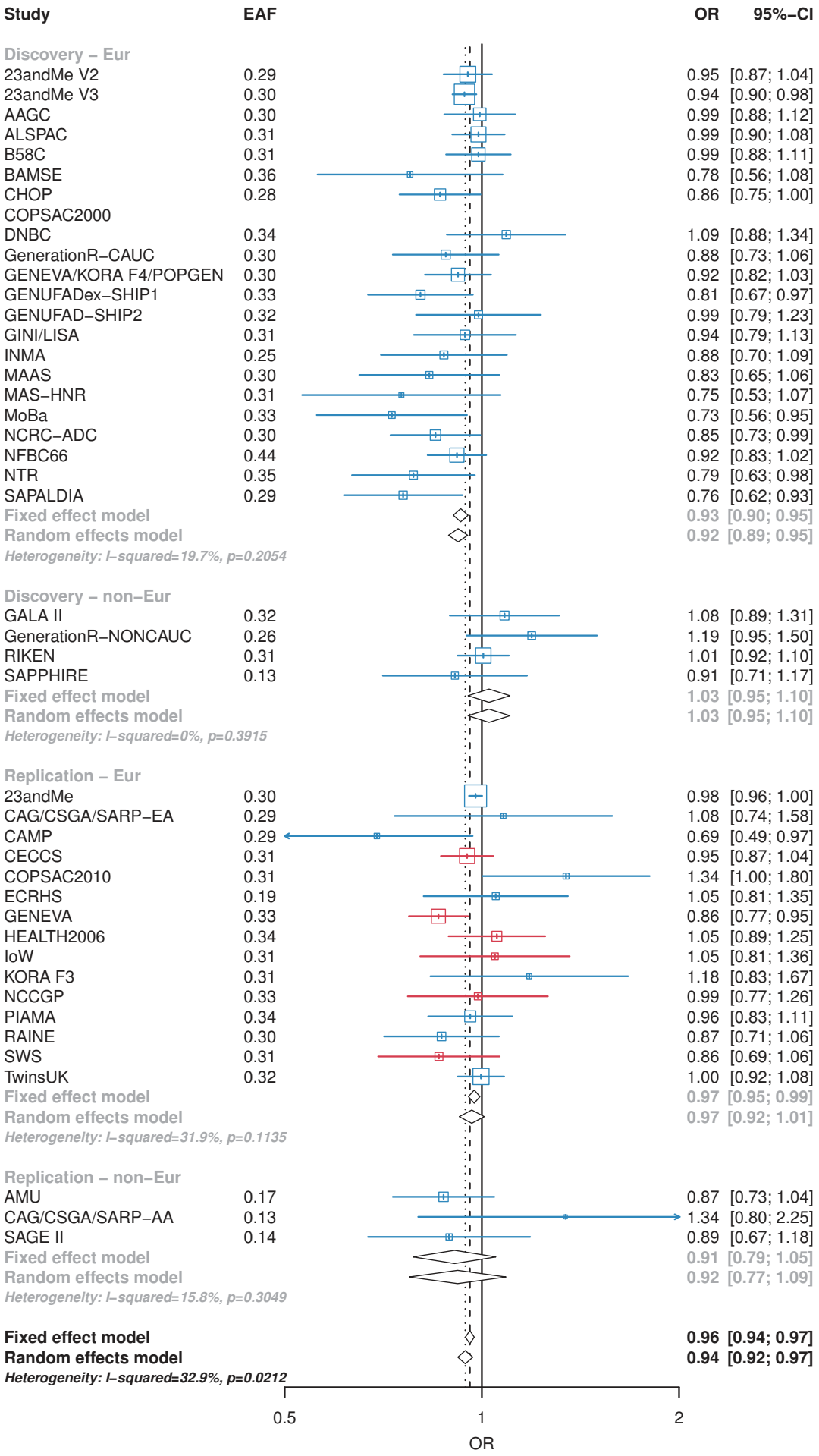


Nature Genetics: doi:10.1038/ng.3424

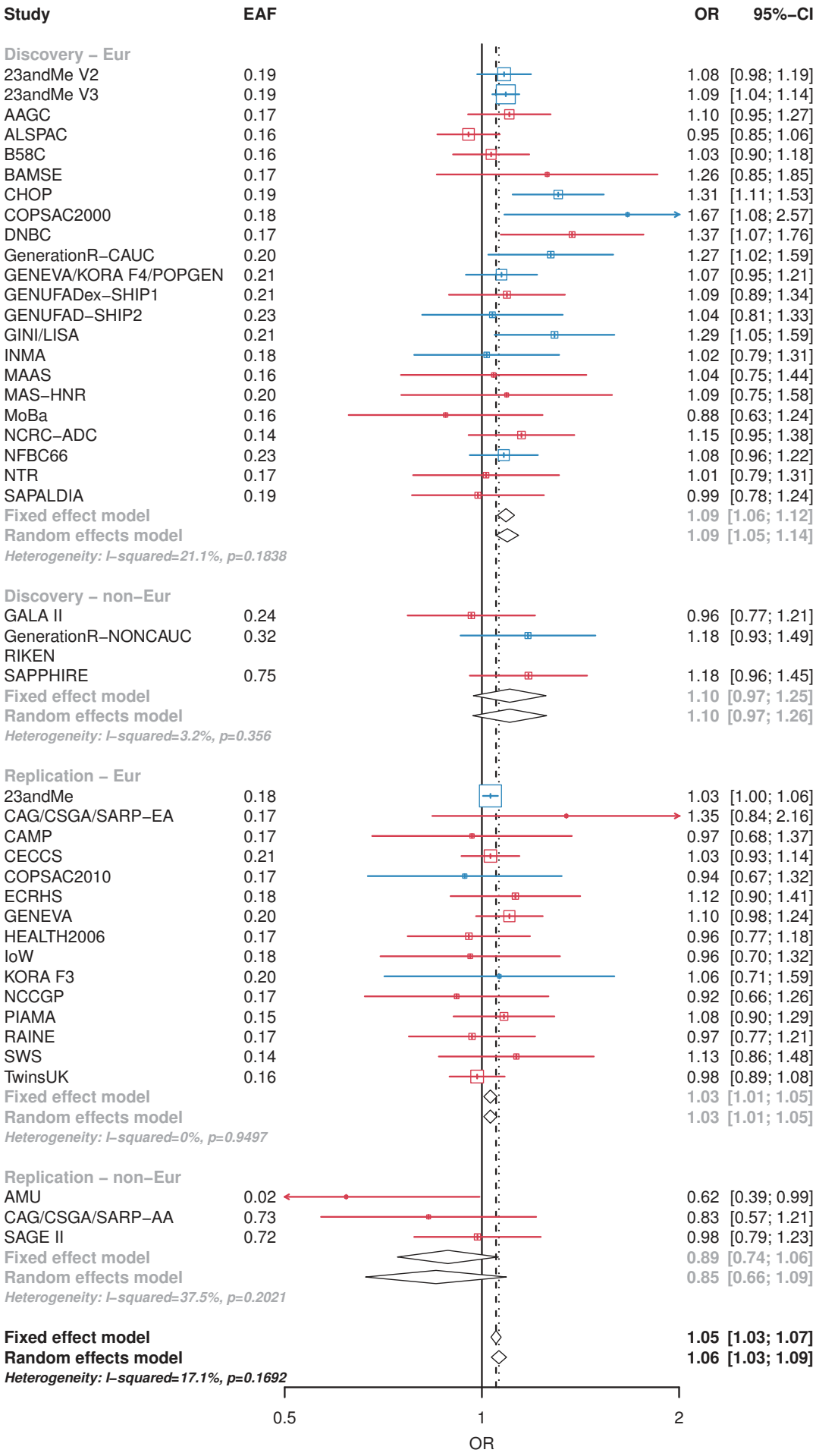
Supplementary Figure 6. Forest plots for discovery and replication results of the SNPs taken forward to replication. Summary random effects meta–analysis results of all studies are shown.
Blue=imputed genotypes, red=genotyped.
EAF=effect allele frequency.
a. rs7512552 (1q21.2, C1orf51/MRPS21), effect allele=T



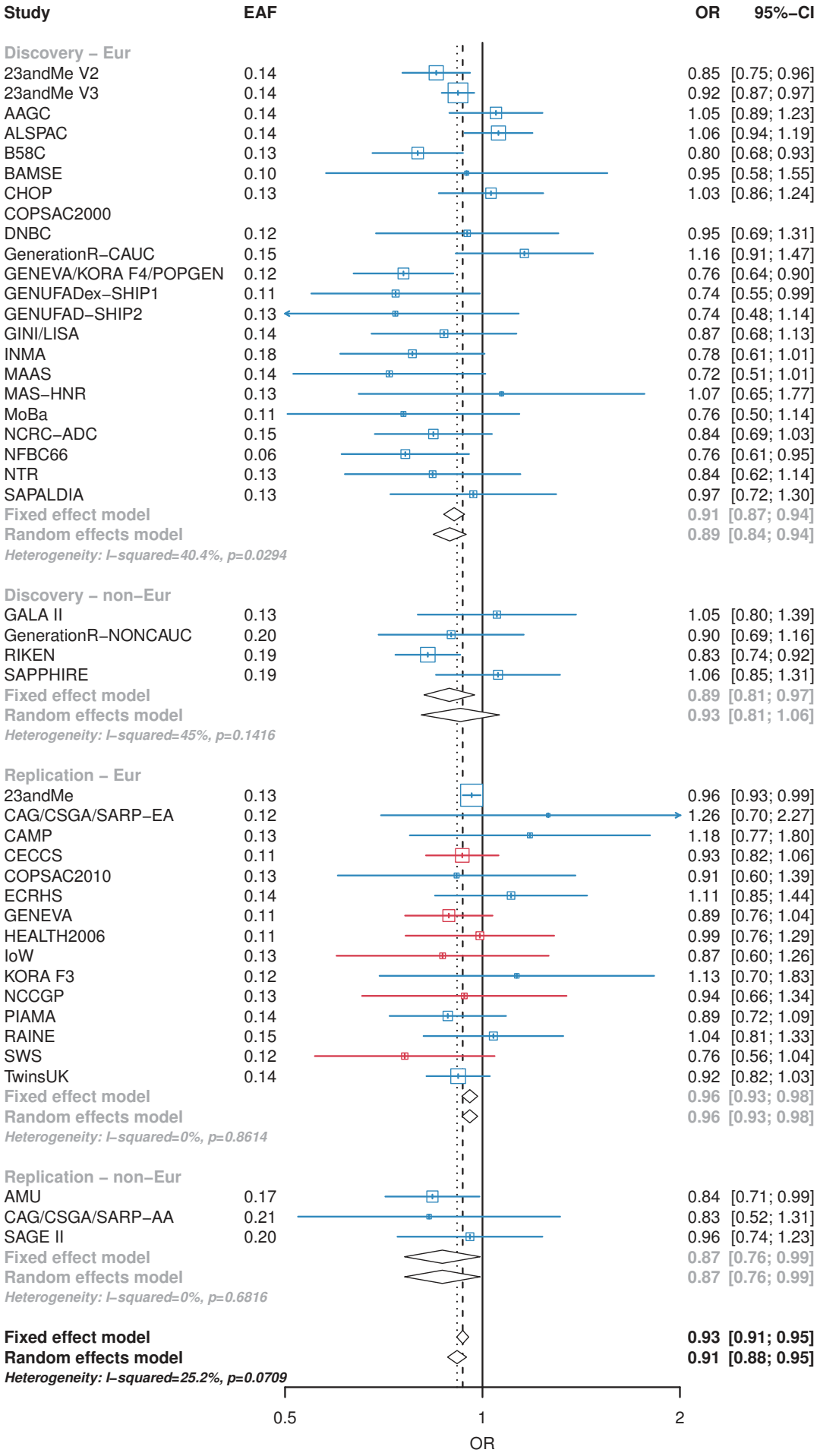
b. rs10199605 (2p25.1, LINC00299/–), effect allele=A



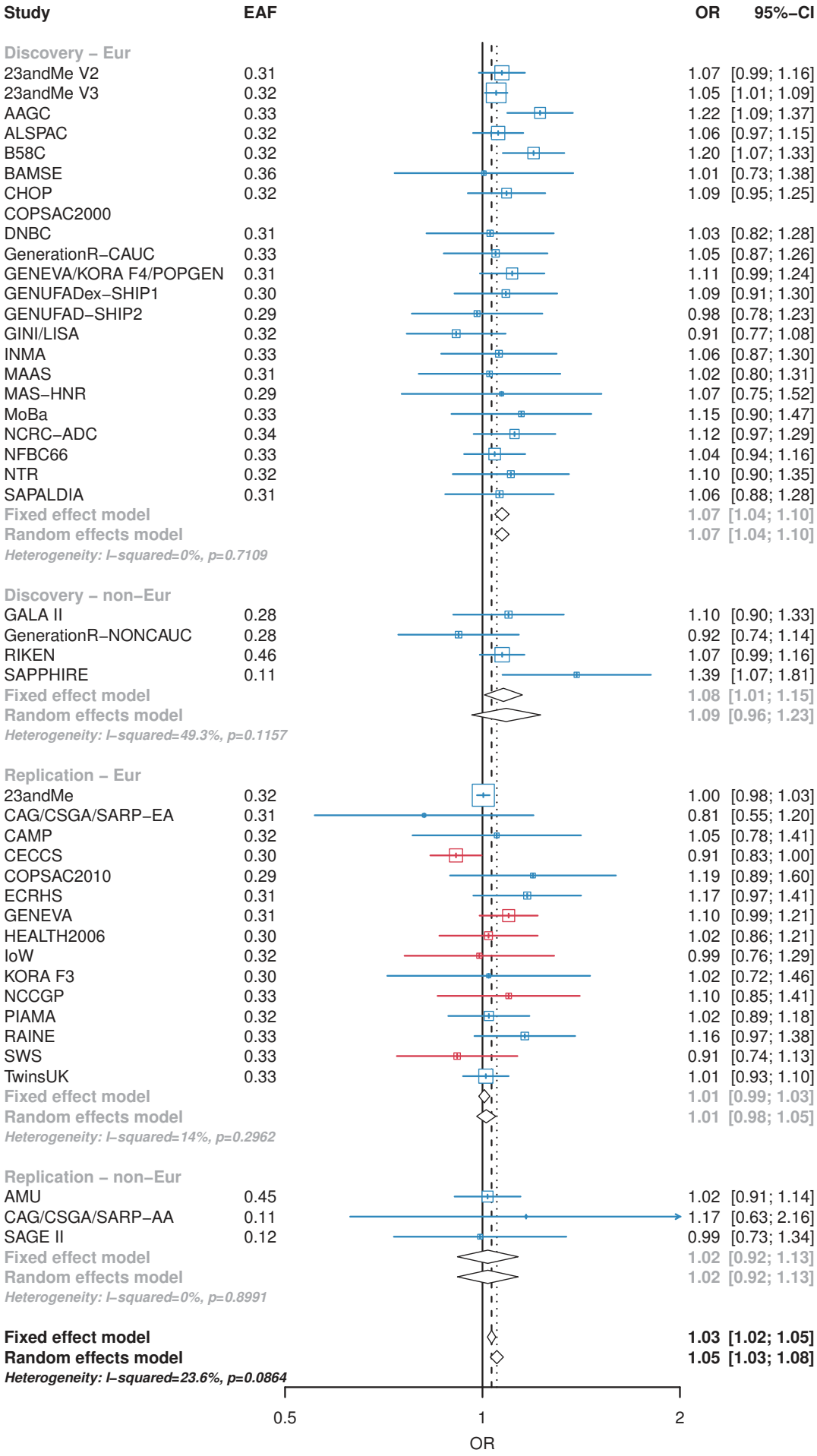
c. rs4643526 (2p16.1, PUS10), effect allele=A



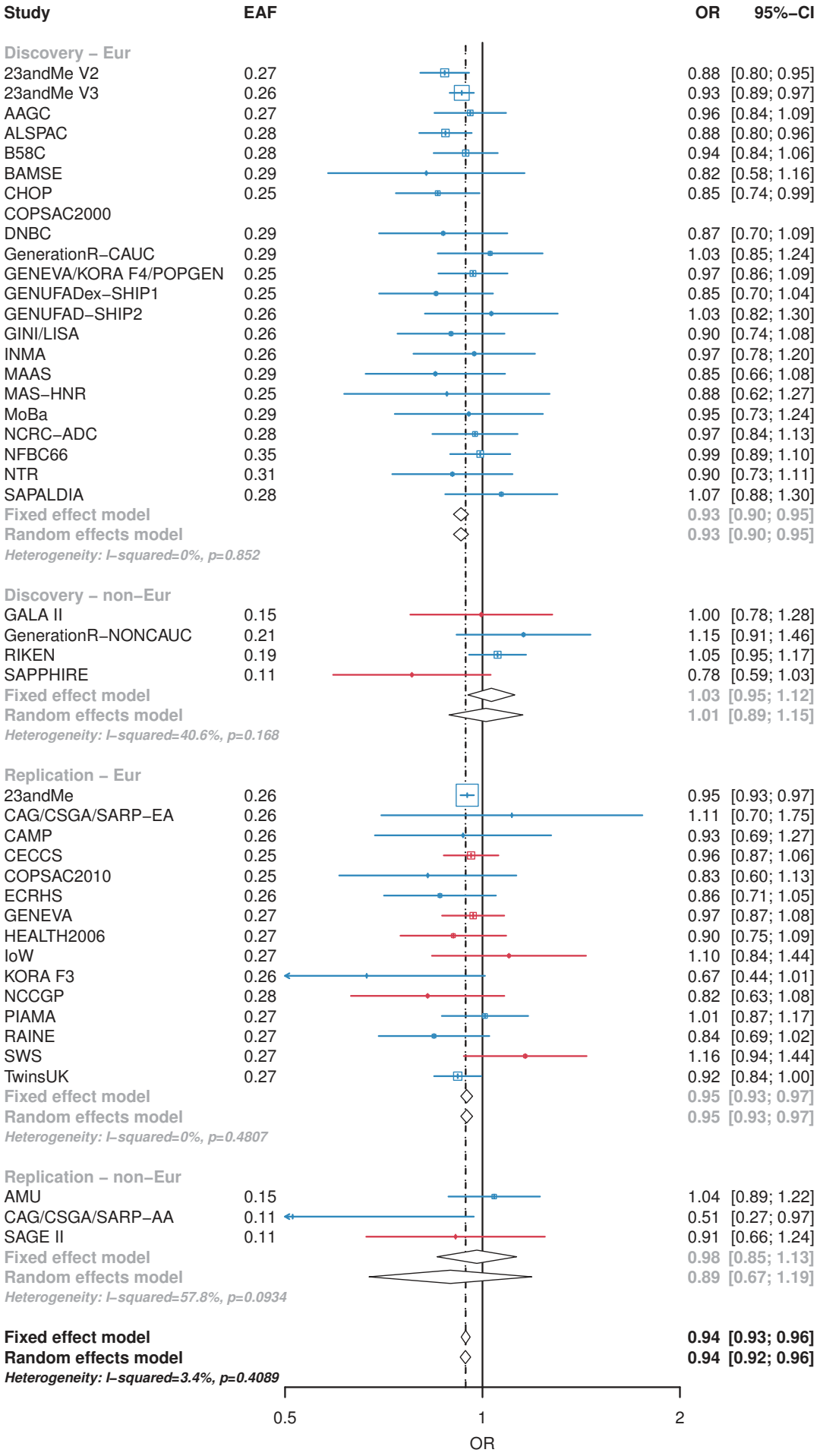
d. rs112111458 (2p13.3, CD207/VAX2), effect allele=G



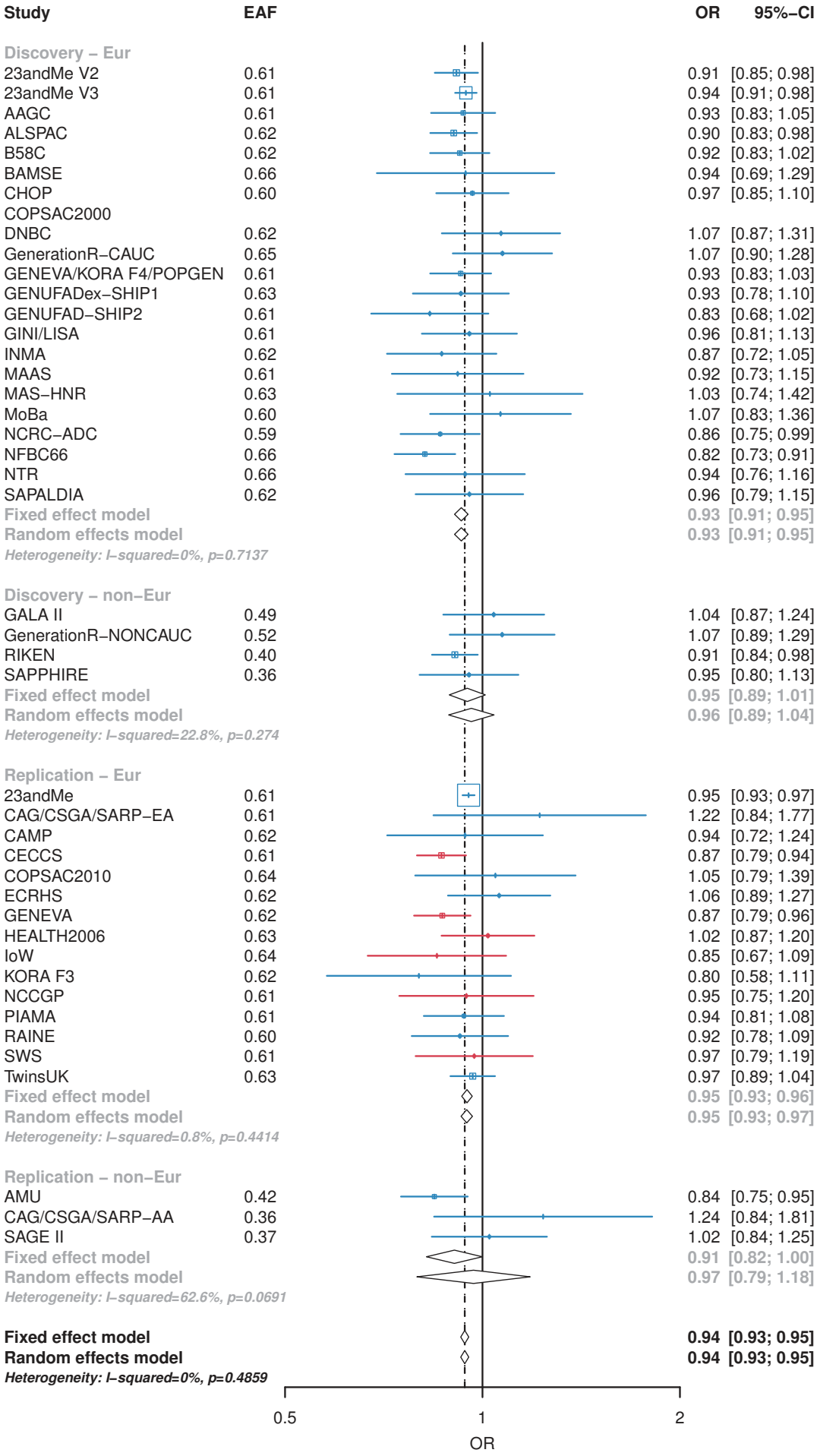
e. rs11923593 (3p21.1, SFMBT1/RFT1), effect allele=G



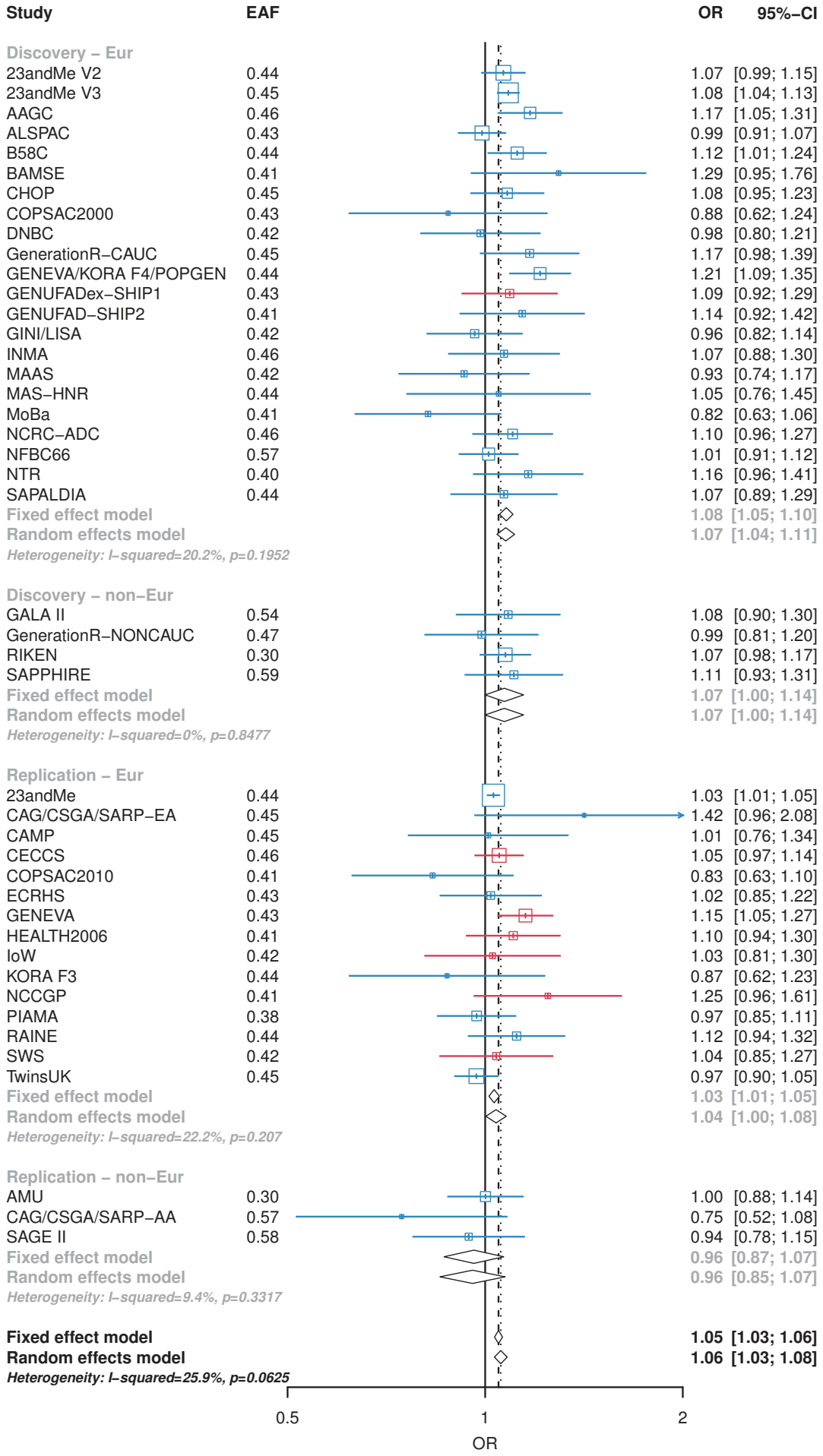
f. rs10214237 (5p13.2, IL7R/CAPSL), effect allele=C



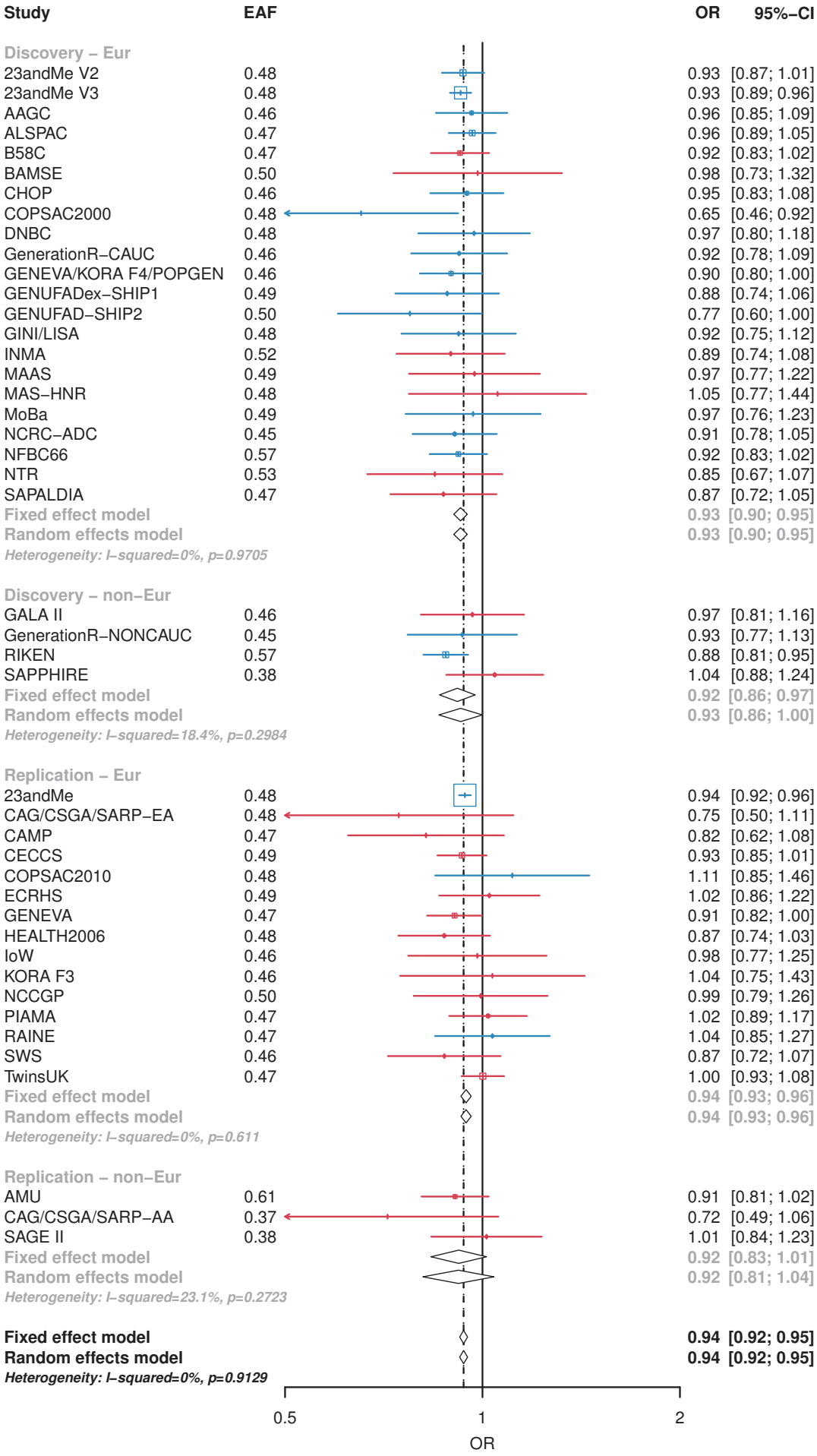
g. rs6473227 (8q21.13, MIR5708/ZBTB10), effect allele=A



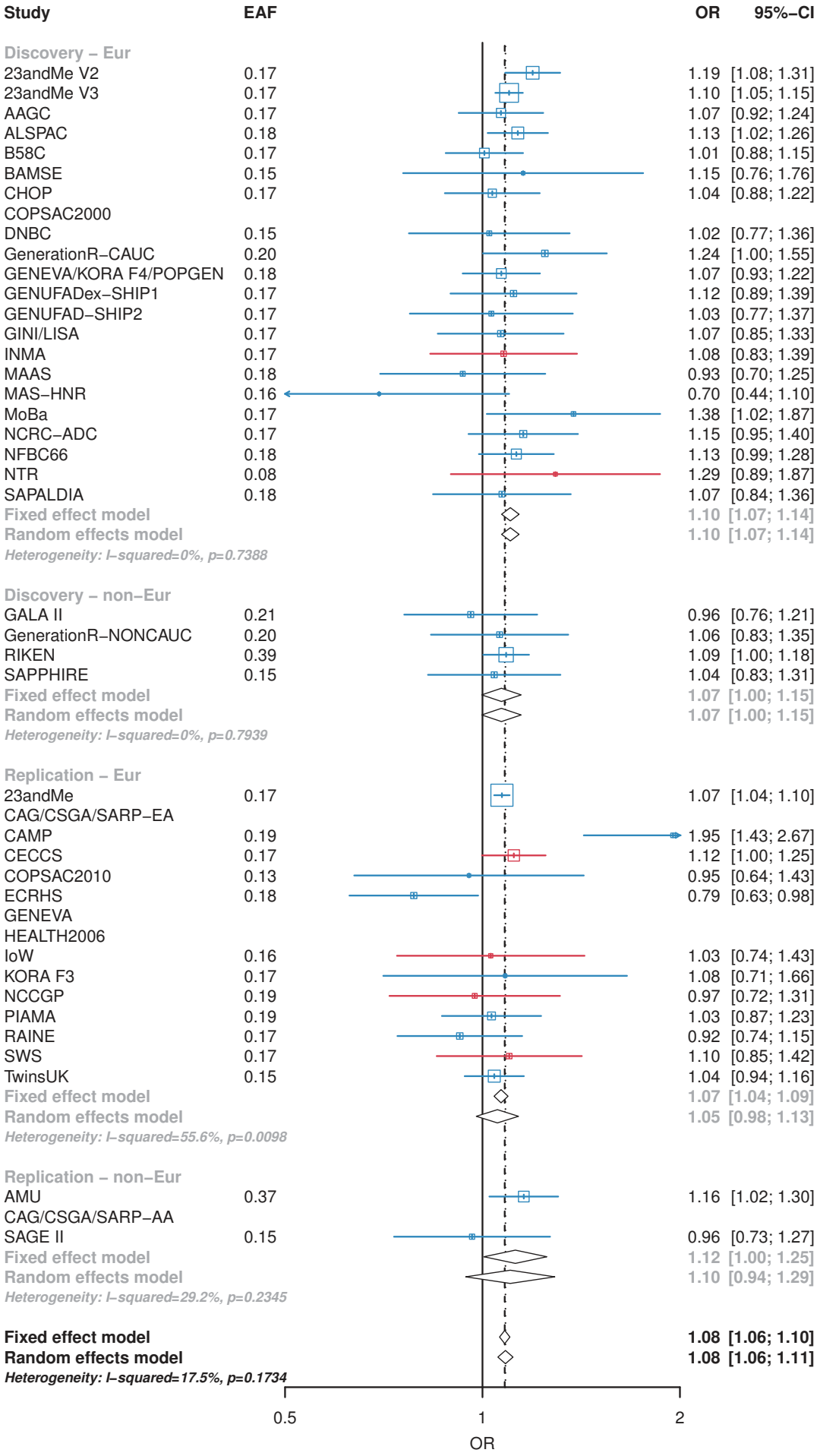
h. rs6602364 (10p15.1, IL15RA/IL2RA), effect allele=G



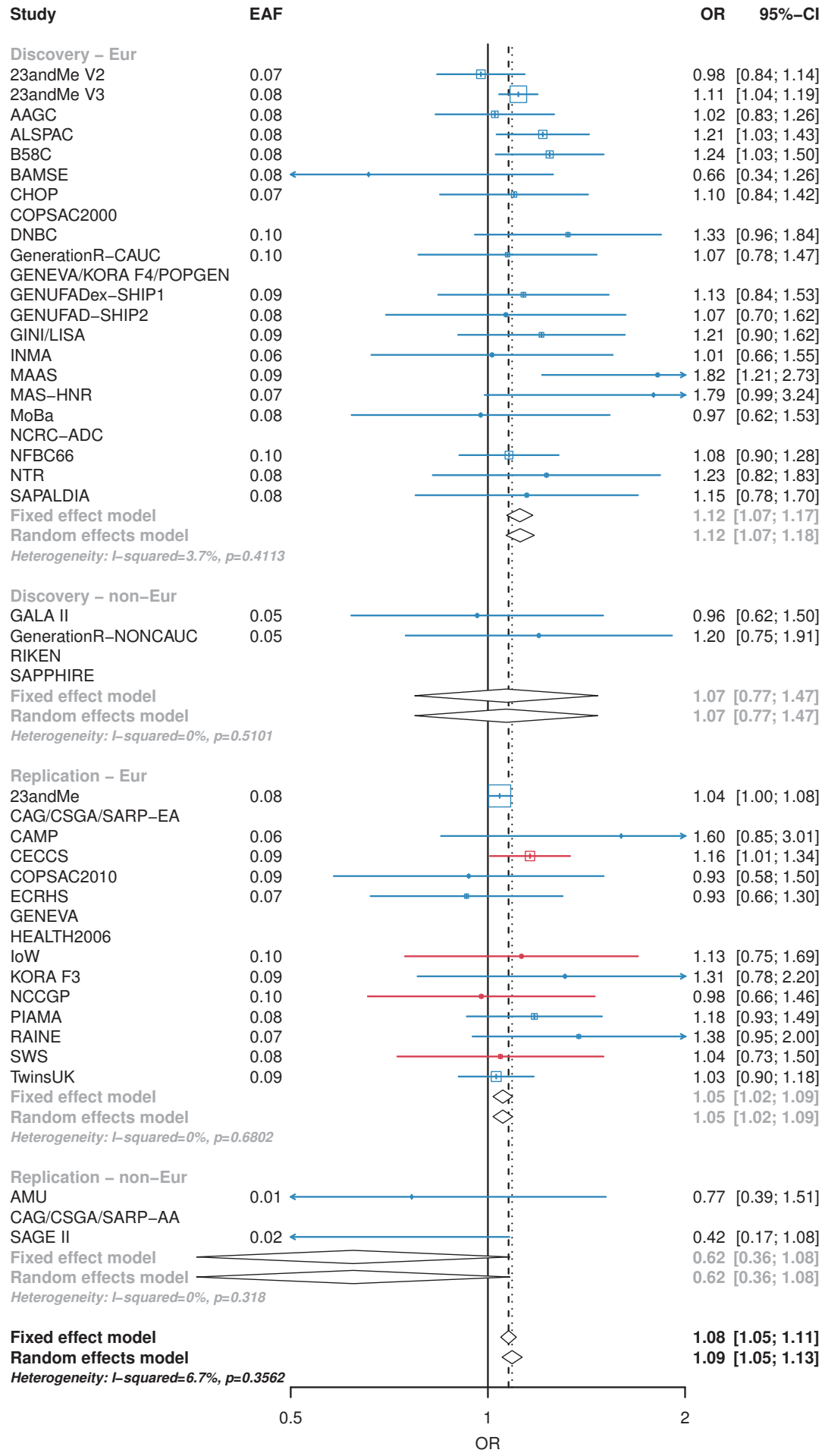
i. rs7127307 (11q24.3, –/ETS1), effect allele=C



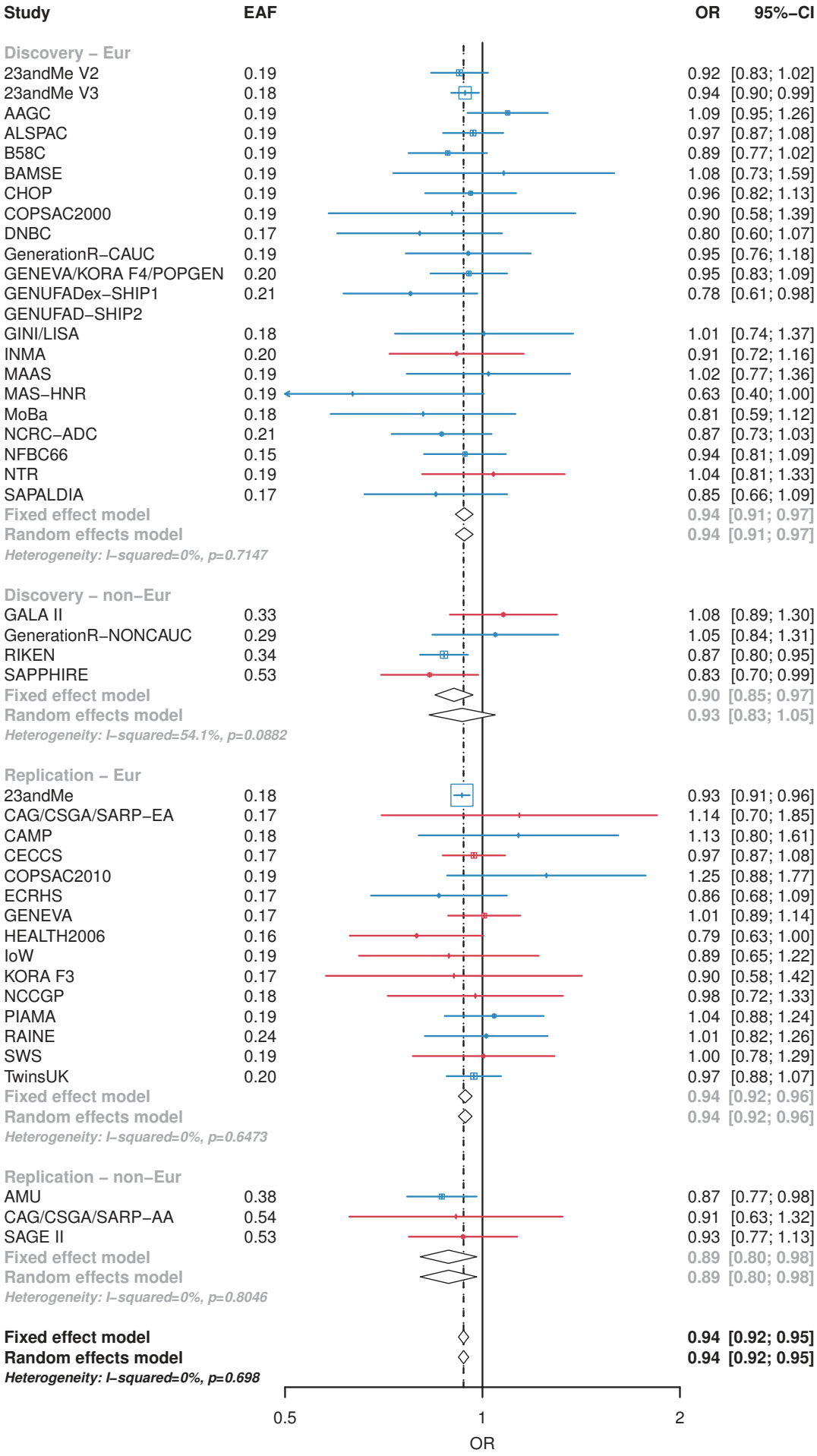
j. rs2143950 (14q13.2, PPP2R3C), effect allele=T



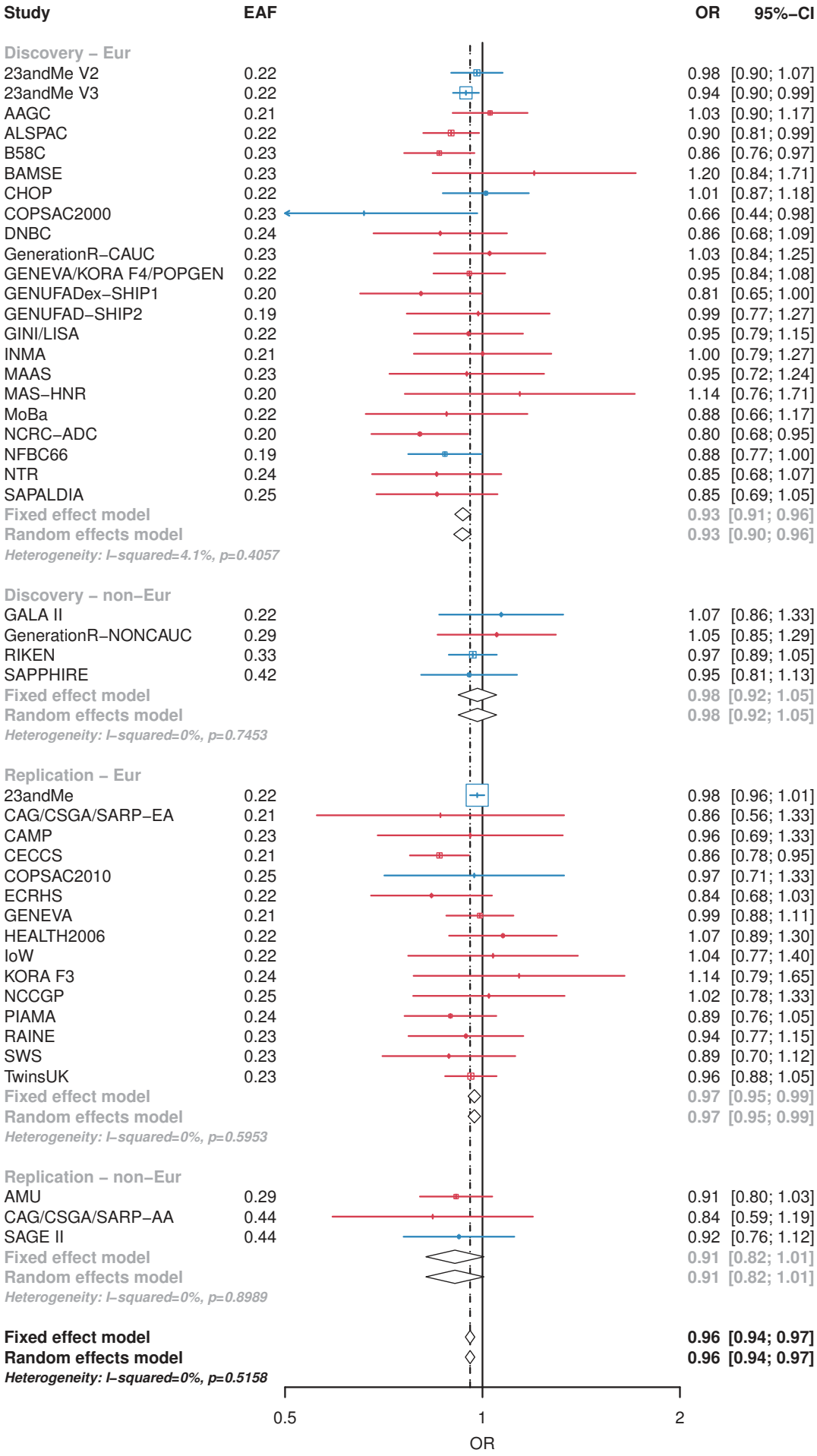
k. rs17881320 (17q21.2, STAT3), effect allele=T



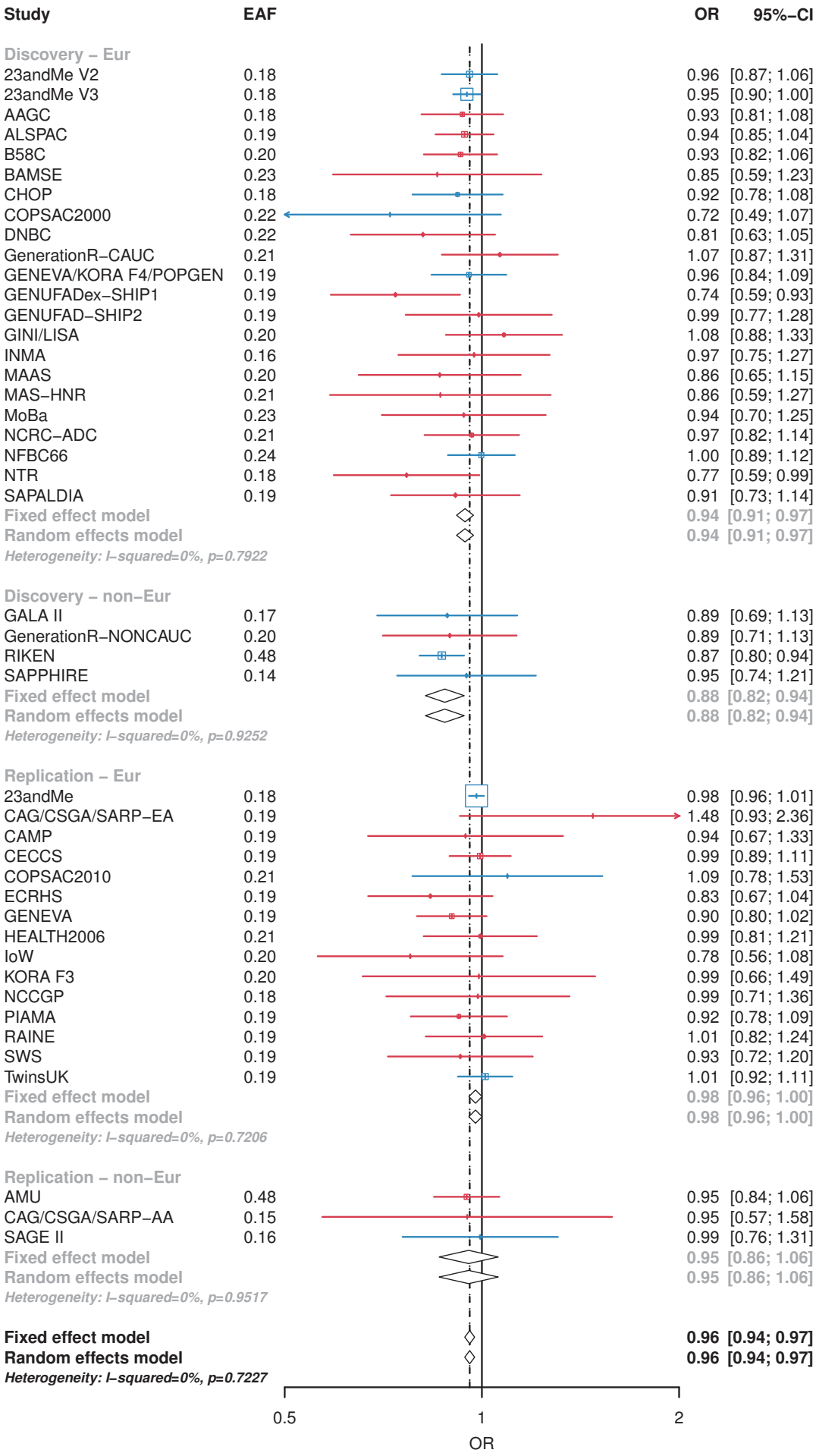
I. rs1057258 (2q37.1, INPP5D), effect allele=T



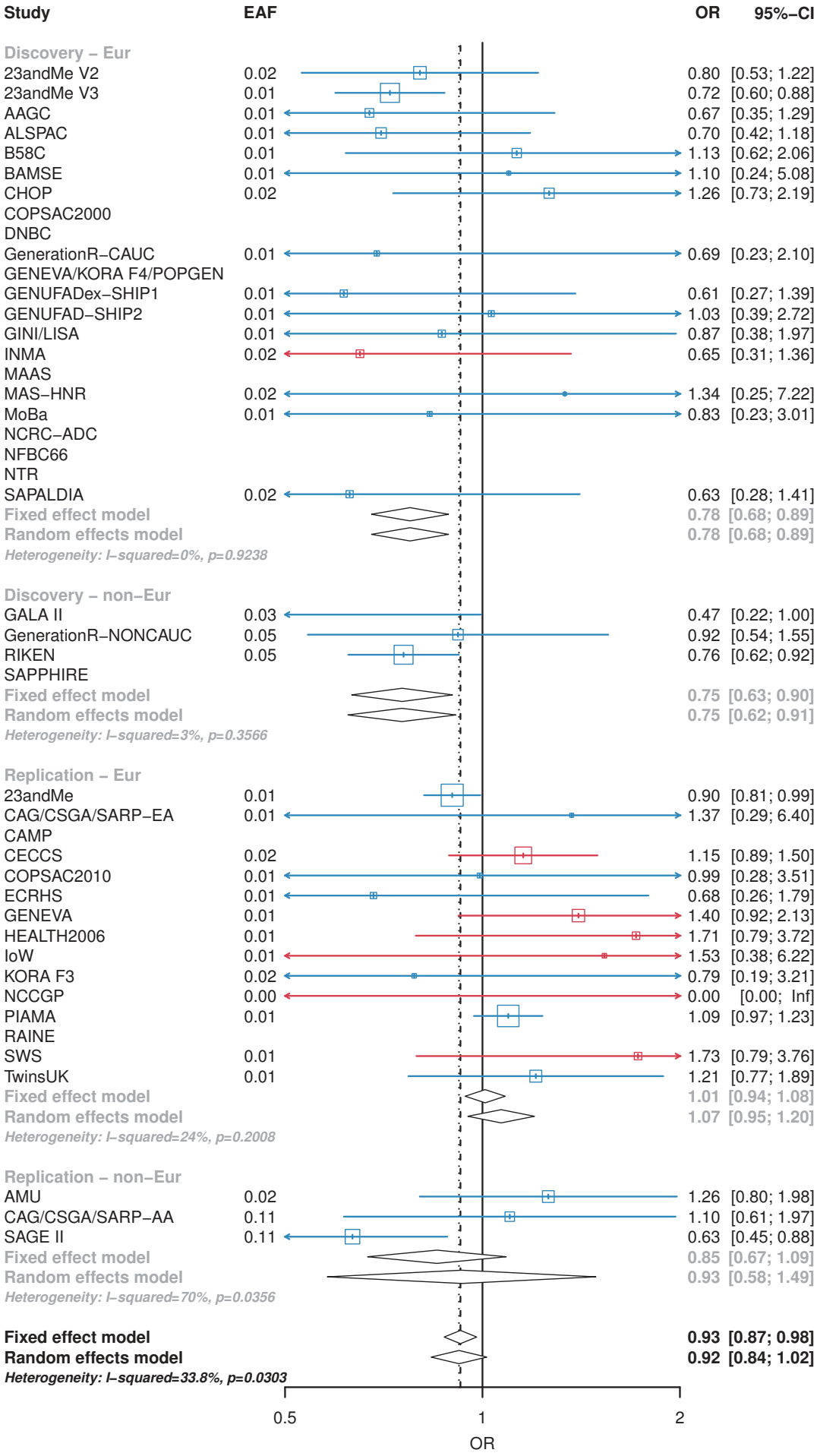
m. rs6872156 (5q35.1, DUSP1), effect allele=A



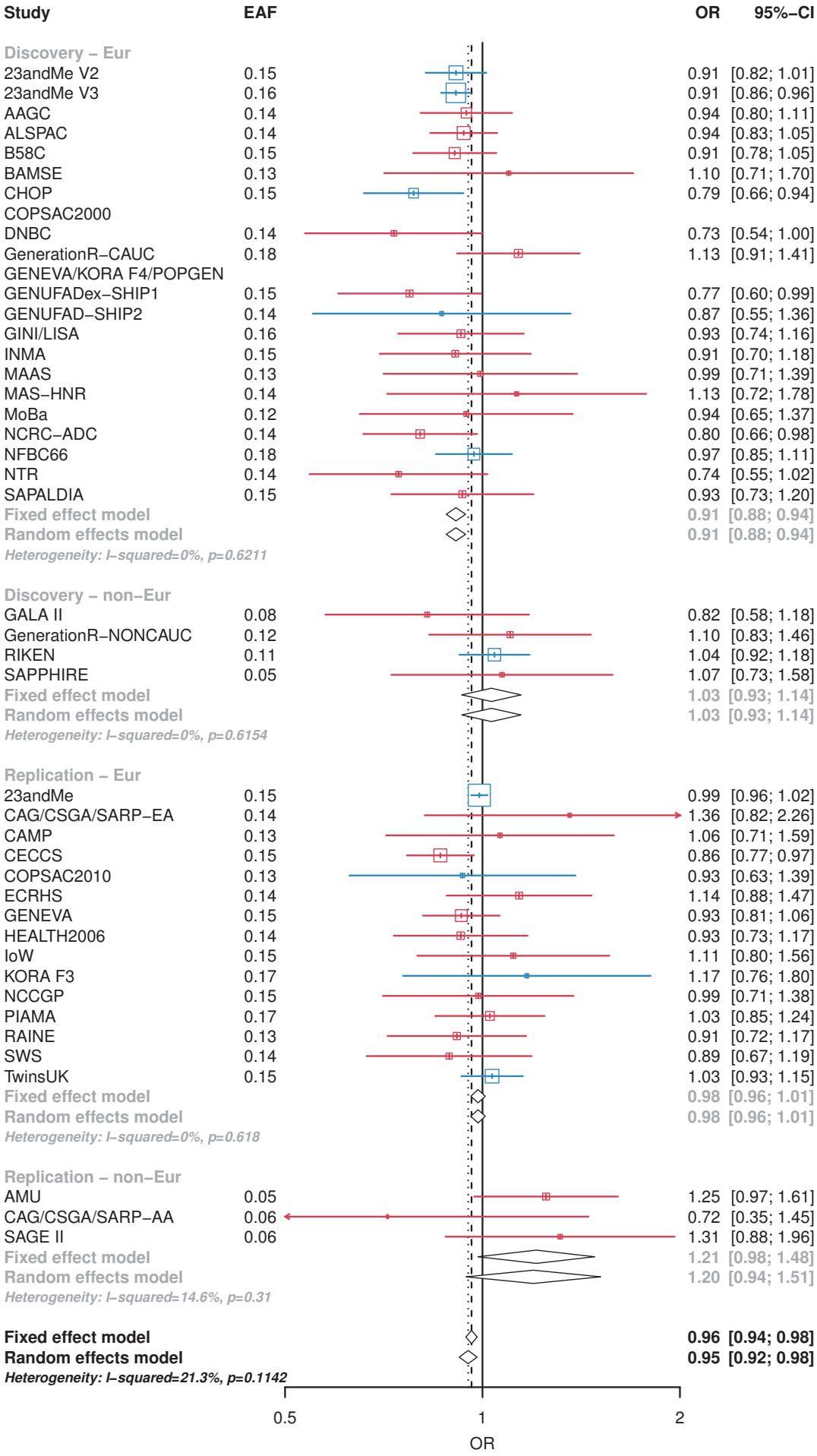
n. rs7016497 (8q24.3, PTK2), effect allele=T



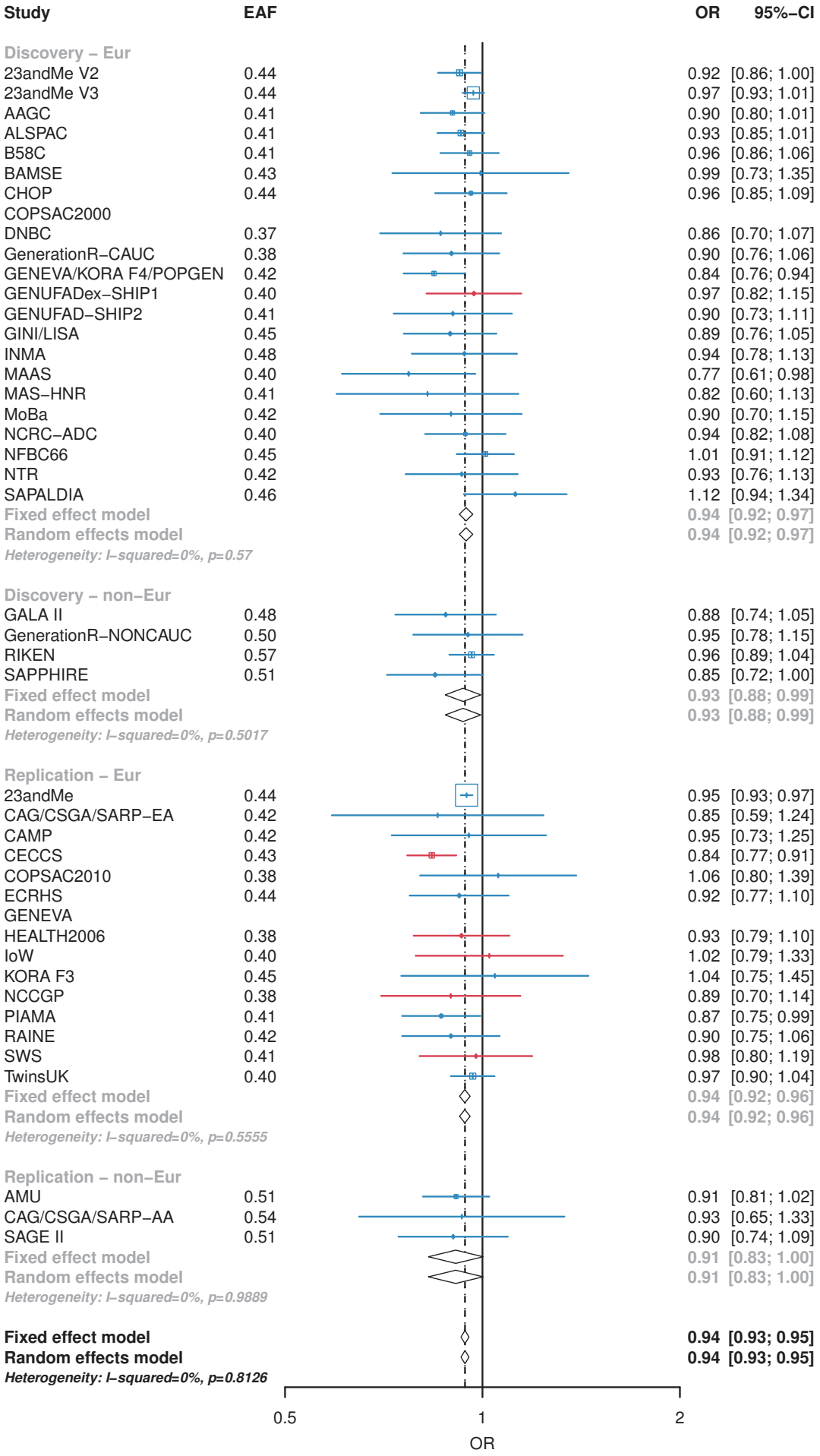
o. rs2905493 (11q12.2, CD6/CD5), effect allele=T



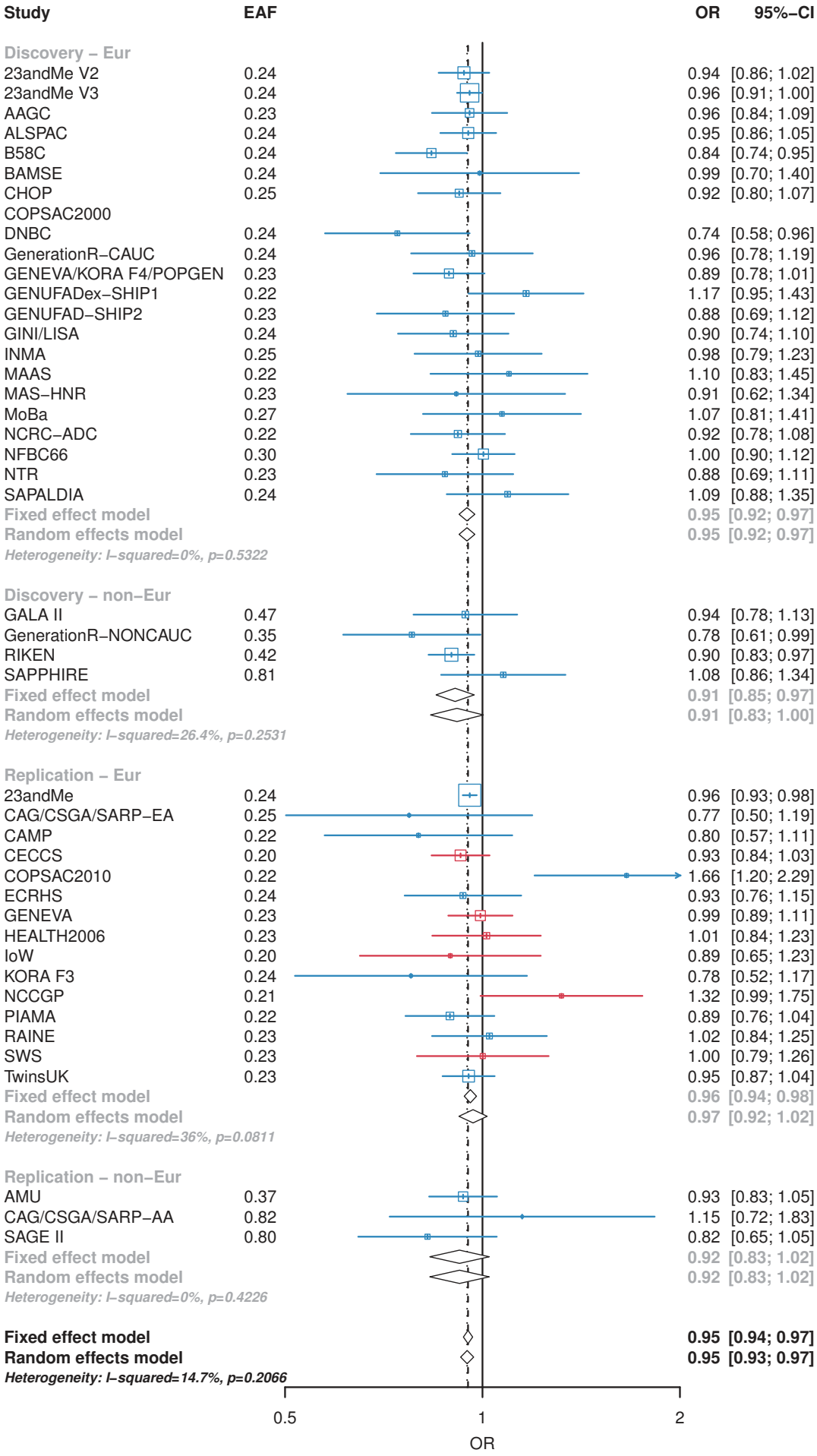
p. rs1799986 (12q13.3, LRP1(STAT6).), effect allele=T



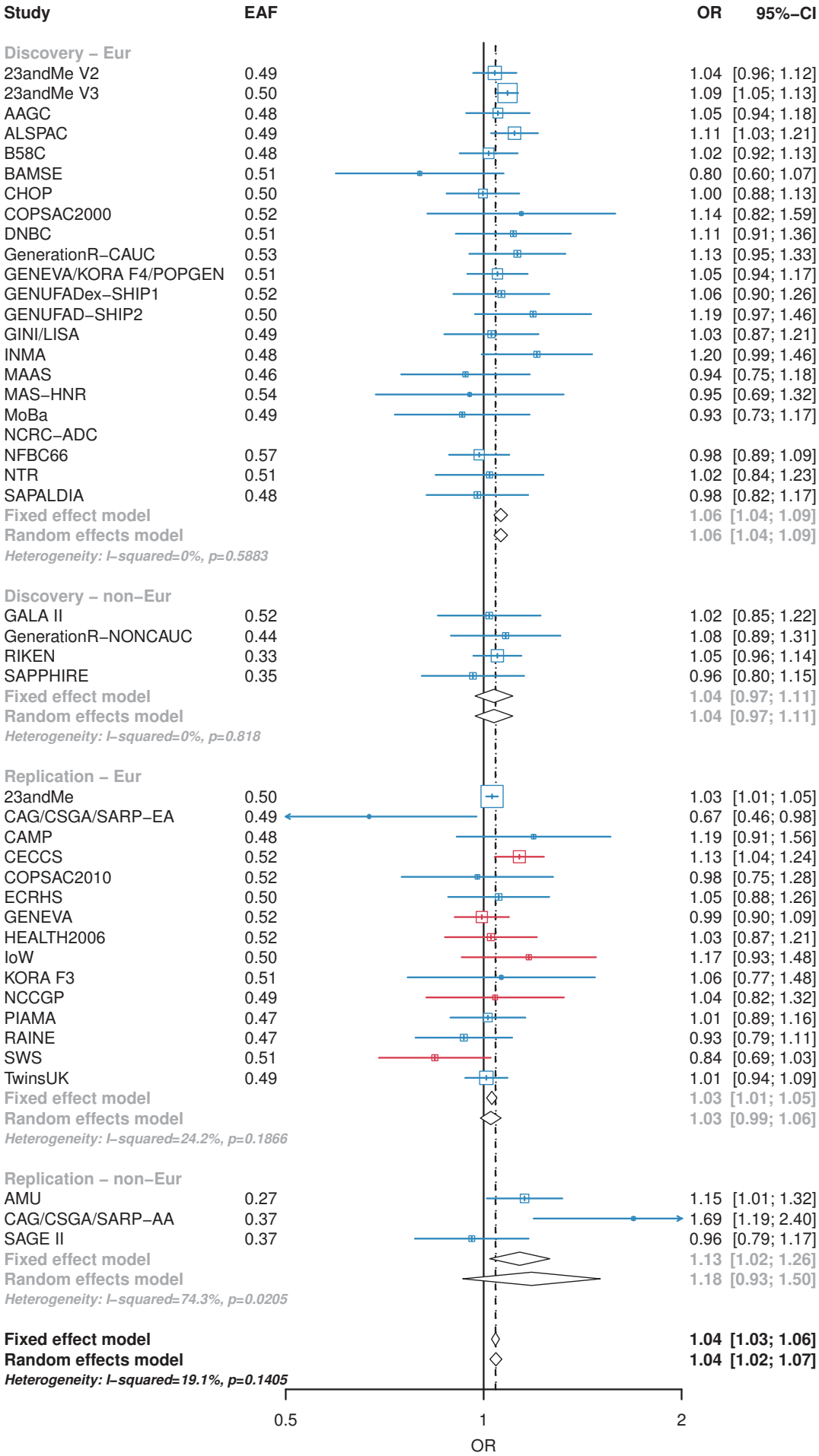
q. rs2227483 (12q15, IL22(& IFNG).), effect allele=A



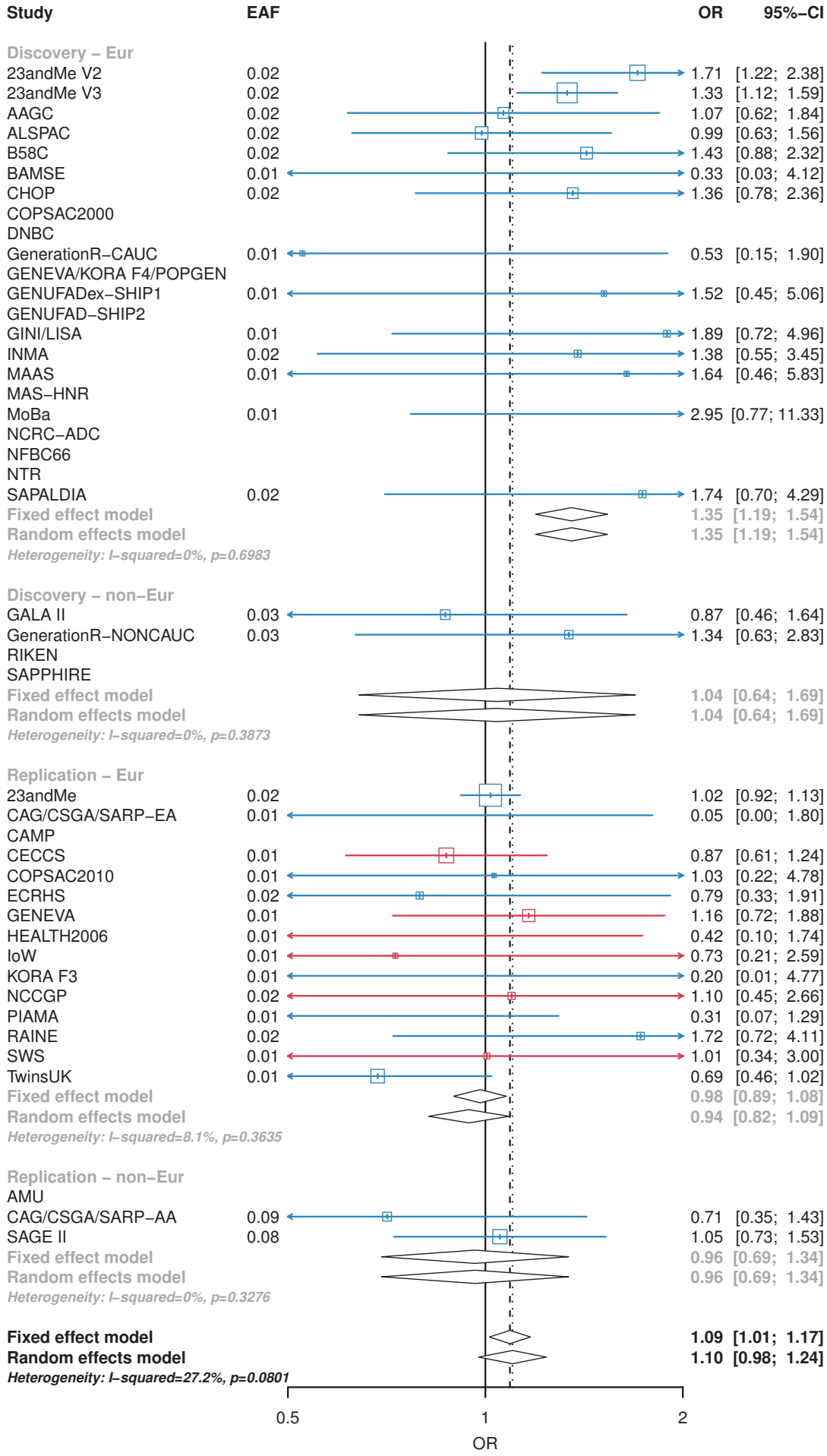
r. rs7146581 (14q32.32, TRAF3), effect allele=T



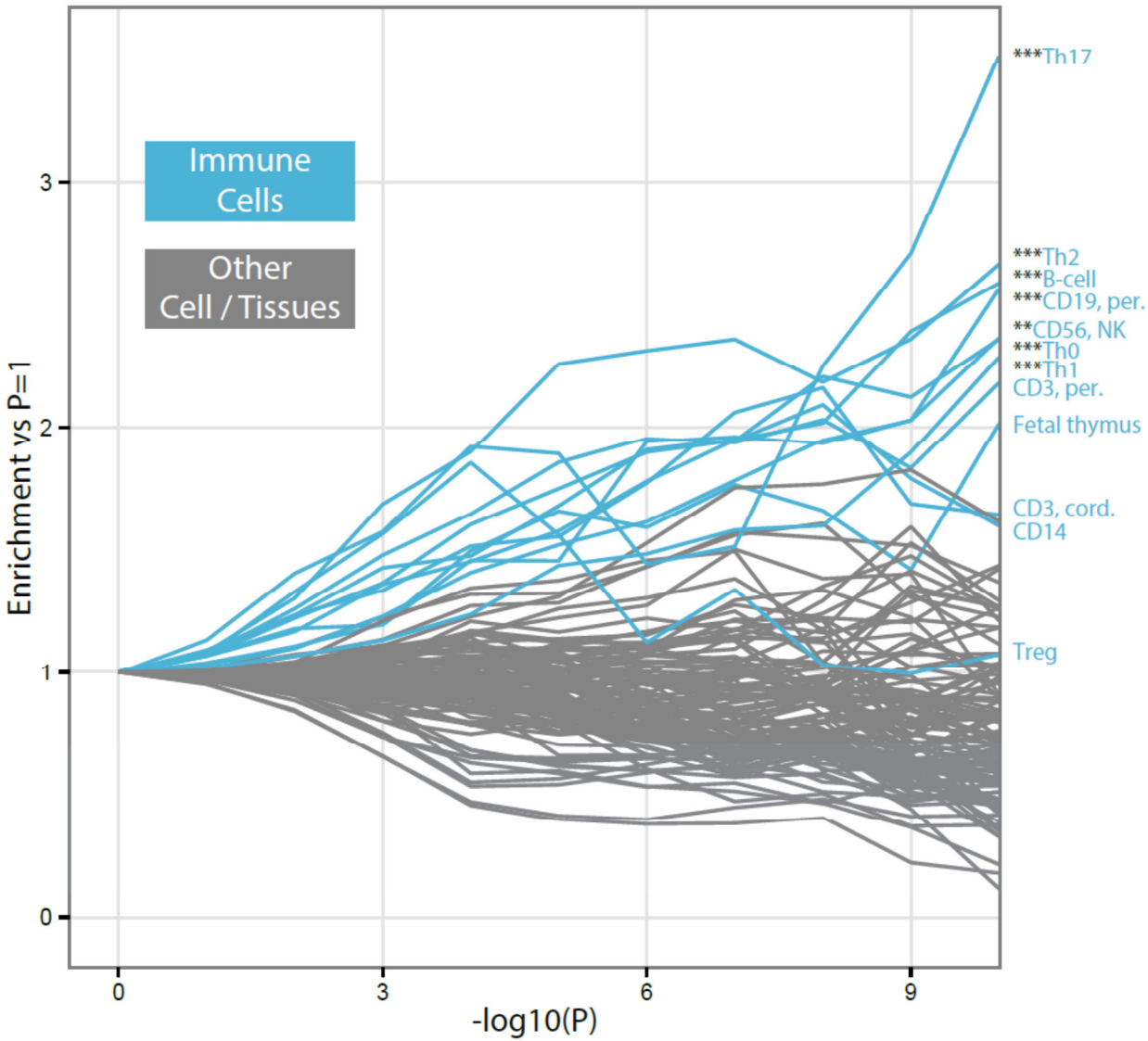
s. rs11657987 (17q25.3, PGS1(SOCS3).), effect allele=T



t. rs77714197 (19q13.11, CEBPA), effect allele=T

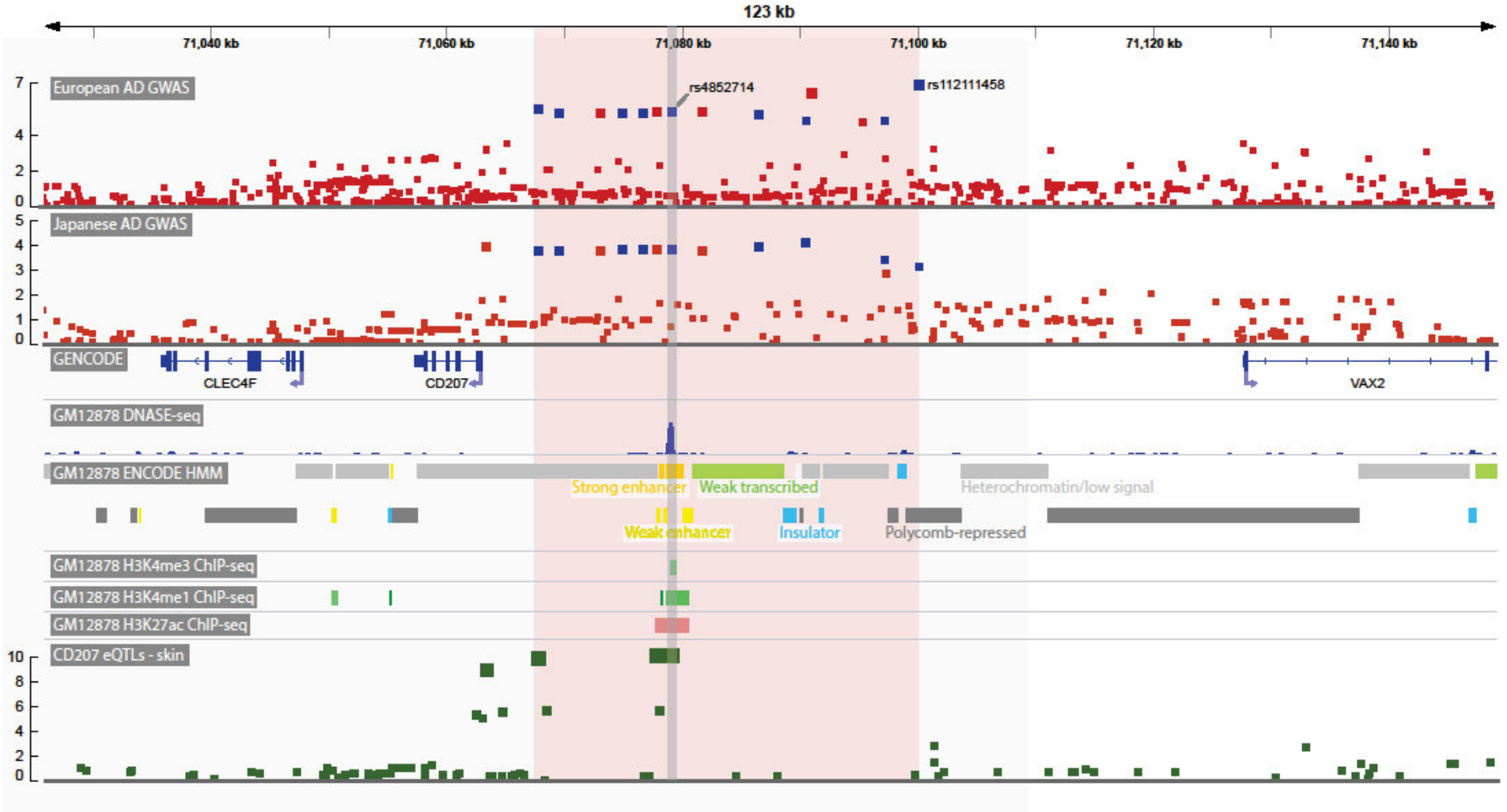


Supplementary Figure 7. Enrichment of atopic dermatitis-associated SNPs within open chromatic (DHS-sites) as reported by ChIP-seq in ENCODE/Roadmap projects. For each integer on the x-axis the proportion of SNPs with association p-values<-log10(x) that are in DHSs is compared to the proportion of all SNPs that are in DHSs(fold-enrichment). Each plotted line represents a specific cell- or tissue types (blue for immune, grey for other cells/tissues). **/*** represent cell-types with 1-sided enrichment p-values<0.01/0.001 resepctively when considering only the markers which reach an association $p<10^{-10}$(i.e. a test for enrichment at the most right-hand side of the plot). Enrichment p-values for all-tissue types are displayed in Supplementary Table 22 (page 204).



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Supplementary Figure 8. Functional investigation of 2p13.3 locus shows one of the credible SNPs (rs4852714) at this locus to be a strong eQTL for *CD207* in skin, in a region of chromatin with high DNAse sensitivity and with histone marks indicative of a poised and active enhancer. The location of a nearby insulator modification mark suggests the enhancer is acting in the CD207 direction. We highlight this locus as an example where the functional investigations converge, implicating *CD207* as the likely causal gene and a particular SNP (rs4852714) worthy of further functional work to establish whether it might be the causal variant. The top two plots show the discovery GWAS European and Japanese association results (respectively), credible SNPs (all highly associated with AD) are marked in blue (y-axis=-log10 p-values). ENCODE data for GM12878 (LCLs) show regions of open chromatin (DNASE-seq) and histone modification marks (HMMs), including enhancer markers, H3K4me3 (active/poised), H3K4me1 (active/poised) and H3K27ac (active). Final plot displays eQTL data for *CD207* expression in skin from the MuTHER consortium (y-axis=-log10 p-values). In this data the atopic dermatitis risk allele (A) at rs4852714 is associated with increased *CD207* expression in skin (also see Supplementary Table 19). LD between index SNP (rs112111458) and rs4852714 is r^2=0.56, D'=-0.96.



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Supplementary Tables

Supplementary Table 1. Study characteristics for (a) discovery studies, (b) in silico replication studies and (c) de novo replication studies.

a. Discovery studies

Study	Ancestry	Case definition	Age of onset	N cases	N controls	1000 genomes release	Imputation software	#variants passed filters*	filtered lambda
23andMe_v2	European	self-report	any age	1592	11813	phase 1 v3 - March 2012 rel	minimac2	9,201,574	1.01
23andMe_v3	European	self-report	any age	6520	42306	phase 1 v3 - March 2012 rel	minimac2	9,355,562	1.03
AAGC	European	self-report	any age	934	2101	phase 1 v3 - March 2012 rel	impute2	9,051,993	1.01
ALSPAC	European	Dr ever diagnosed	by 14 years	1712	3719	phase 1 v3 - March 2012 rel	minimac	9,011,418	1.01
B58C	European	self-report	by 16 years	918	4560	phase 1 v3 - March 2012 rel	minimac	9,052,437	1.01
BAMSE	European	Dr diagnosed	by 12 years	117	352	phase 1 v3 - March 2012 rel	minimac	9,267,805	1.02
CHOP	European	ICD9 code	by 17 years	673	1839	phase 1 v3 - March 2012 rel	impute2	9,732,004	1.04
COPSAC2000	European	Hanifin and Rajka criteria	by 7 years	155	149	phase 1 v3 - March 2012 rel	minimac	3,006,163†	1.03
DNBC	European	self-report	by 7 years	224	1407	phase 1 v3 - March 2012 rel	impute2	9,523,603	1.01
GALAII	Latino	Dr diagnosed	by 21 years	300	1592	phase 1 v3 - March 2012 rel	impute2	12,216,106	1.01
GenerationR_caucasian	European	Dr diagnosed	by 6 years	332	1749	phase 1 v3 - March 2012 rel	mach	8,808,123	1.00
GenrationR_non-caucasian	Non-European	Dr diagnosed	by 6 years	305	896	phase 1 v3 - March 2012 rel	mach	11,811,682	1.02
GENEVA/KORAF4/POPGEN	European	tertiary care cases	any age	1046	2551	phase 1 v3 - March 2012 rel	impute2	4,322,598†	1.07
GENUFAD-SHIP2	European	diagnosed moderate/severe AD	by 2 years	262	1792	phase 1 v3 - March 2012 rel	mach1	8,258,241	1.04
GENUFADex-SHIP1	European	diagnosed moderate/severe AD	by 2 years	417	1667	phase 1 v3 - March 2012 rel	mach1	9,021,682	1.02
GINI/LISA	European	Dr diagnosed	by 10 years	442	865	phase 1 v3 - March 2012 rel	impute2	9,496,869	1.00
INMA	European	self-report	by 4 years	414	443	phase 1 v3 - March 2012 rel	impute2	9,738,802	1.00
MAAS	European	Dr examination	by 8 years	257	355	phase 1 v3 - March 2012 rel	impute2	9,505,872	1.00
MAS-HNR	European	Dr diagnosed	by 13 years	104	379	phase 1 v3 - March 2012 rel	mach1	9,125,330	1.03
MoBa	European	Dr diagnosed	by 3 years	206	413	phase 1 v3 - March 2012 rel	impute2	9,644,675	1.03
NCRC-ADC	European	tertiary care cases	by 2 years	572	1797	phase 1 v3 - March 2012 rel	impute2	5,408,143†	1.04
NFBC66	European	Dr diagnosed	any age	1200	2270	phase 1 v3 - March 2012 rel	impute2	9,587,816	1.01
NTR	European	Dr diagnosed	by 5 years	270	1196	phase 1 v3 - March 2012 rel	minimac	8,554,104	1.02
RIKEN	Japanese	Hanifin and Rajka criteria	any age	1472	7966	phase 1 v3 - March 2012 rel	minimac	6,831,096†	1.06
SAPALDIA	European	self-report	any age	533	443	phase 1 v3 - March 2012 rel	minimac	9,170,364	1.01
SAPPHIRE	African American	self-report	any age	422	844	phase 1 v3 - March 2012 rel	impute2	7,724,177	1.00
			Total discovery	**21399**	**95464**			**15,539,996**	

*filters were MAF>1%, PROPER_INFO>0.4, Rsq>0.3

†some studies have a lower number of variants that pass filters due to additional exclusion criteria being applied in those cohorts (COPSAC low # due to small sample size, hence fewer rare variants observed) additional exclusions: RIKEN(indels), GENEVA and NCRC (call rate<95%, HWE p<10-8, MAF<5%). Full details of QC procedures are in the individual studies methods description (Supplementary Note 1).

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b. in silico replication studies

Study	Ancestry	Case definition	Age of onset	N cases	N controls	1000 genomes release	Imputation software
23andMe	European	self-report	any age	23761	208703	phase 1 v3 - March 2012 rel	minimac2
AMU	Chinese	Hanifin and Rajka criteria	any age	1012	1362	phase 1 v3 - March 2012 rel	impute2
CAG/CSGA/SARP-E	European	self-report	any age	97	161	phase 1 v3 - March 2012 rel	impute2
CAG/CSGA/SARP-AA	African American	self-report	any age	94	219	phase 1 v3 - March 2012 rel	impute2
CAMP	European	self-report of Dr. visit for AD	by 5-12 years	143	438	pilot - Aug 1009 rel	mach1
COPSAC2010	European	Hanifin and Rajka criteria	by 3 years	154	387	phase 1 v3 - March 2012 rel	impute2
ECRHS	European	self-report	any age	300	1895	phase 1 v3 - March 2012 rel	impute2
KORAF3	European	Dr diagnosed	any age	74	2532	phase 1 v3 - March 2012 rel	impute2
PIAMA	European	self-report	any age	808	895	phase 1 v3 - March 2012 rel	impute2
RAINE	European	Dr diagnosed	by 16 years	404	972	phase 1 v3 - March 2012 rel	minimac
SAGEII	African American	Dr diagnosed	by 21 years	365	510	phase 1 v3 - March 2012 rel	impute2
TwinsUK	European	self-report	any age	418	968	phase 1 v3 - March 2012 rel	impute2
				27630	**219042**		

c. de novo genotyping studies

Study	Ancestry	Case definition	Age of onset	N cases	N controls	genotyping method
CECCS	European	diagnosed moderate/severe AD	by 2 years	2116	2180	KASP
GENEVA/PopGen	European	tertiary care cases	any age	1362	2205	Sequenom MassARRAY/TaqMan
Health2006	European	self-report	any age	338	2957	KASP
IoW	European	Hanifin and Rajka criteria	by 18 years	176	552	KASP
NCCGP	European	UK diagnostic criteria	7-9 years	190	570	KASP
SWS	European	UK diagnostic criteria	by 6 years	247	1122	KASP
				4429	**9586**	
			Total replication	**32059**	**228628**	

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Supplementary Table 2. Comparison of European and nonEuropean association results. European and non-European summary statistics are from fixed effects meta-analyses. Cochran's Q test p-values are presented for the difference between two strata.

Genetic variant	Locus	Nearest Gene	European OR (95% CI)	non-European OR (95% CI)	P-value diff
KNOWN LOCI					
rs61813875	1q21.3	CRCT1/LCE3E (FLG)§	1.61(1.48-1.75)	1.47(0.80-2.71)	0.775
rs10791824	11q13.1	OVOL1	1.12(1.09-1.15)	1.19(1.11-1.26)	0.085
rs12188917	5q31.1	RAD50/IL13	1.14(1.10-1.17)	1.16(1.08-1.25)	0.625
rs6419573	2q12.1	IL18R1/IL18RAP	**1.11(1.08-1.14)**	**1.25(1.17-1.34)**	**0.001**
rs2212434	11q13.5	C11orf30/LRRC32	1.09(1.07-1.12)	1.14(1.07-1.22)	0.241
rs4809219	20q13.33	RTEL1-TNFRSF6B	0.90(0.87-0.93)	0.89(0.83-0.96)	0.837
rs2918307	19p13.2	ADAMTS10/ACTL9	1.12(1.08-1.16)	1.19(1.10-1.29)	0.166
rs2041733	16p13.13	CLEC16A	0.92(0.90-0.94)	0.92(0.86-0.98)	0.858
rs12730935	1q21.3	IL6R	1.08(1.05-1.11)	1.02(0.96-1.10)	0.149
4:123243592	4q27	KIAA109 (IL2)§	1.08(1.05-1.10)	1.10(0.98-1.23)	0.719
rs4713555	6p21.32	HLA-DRB1/HLA-DQA1	**0.91(0.89-0.94)**	**0.80(0.72-0.88)**	**0.009**
rs2944542	10q21.2	ZNF365	**0.94(0.92-0.96)**	**0.85(0.79-0.91)**	**0.006**
rs145809981	6p21.33	MICB	**0.91(0.88-0.95)**	**0.80(0.73-0.89)**	**0.018**
rs4312054	11p15.4	OR10A3/NLRP10	**1.00(0.97-1.02)**	**0.84(0.78-0.89)**	**2E-06**
rs1249910	3q13.2	CCDC80/CD200R1L	**0.98(0.96-1.01)**	**1.22(1.14-1.30)**	**6E-10**
rs2592555	11p13	PRR5L	0.93(0.90-0.96)	0.87(0.80-0.94)	0.092
NOVEL LOCI					
rs2038255	14q13.2	PPP2R3C	1.11(1.07-1.14)	1.07(0.99-1.14)	0.339
rs7127307	11q24.3	-/ETS1	0.93(0.90-0.95)	0.92(0.86-0.97)	0.740
rs7512552	1q21.2	C1orf51/MRPS21	0.93(0.91-0.95)	0.97(0.90-1.04)	0.241
rs6473227	8q21.13	MIR5708/ZBTB10	0.93(0.91-0.95)	0.95(0.89-1.01)	0.544
rs6602364	10p15.1	IL15RA/IL2RA	1.08(1.05-1.10)	1.07(1.00-1.14)	0.852
rs10214237	5p13.2	IL7R/CAPSL	**0.93(0.90-0.95)**	**1.03(0.95-1.12)**	**0.016**
rs10199605	2p25.1	LINC00299/-	**0.93(0.90-0.95)**	**1.03(0.95-1.10)**	**0.013**
rs4643526	2p16.1	PUS10	1.09(1.06-1.12)	1.10(0.97-1.25)	0.845
rs12951971	17q21.2	STAT3	1.13(1.08-1.17)	0.96(0.79-1.17)	0.122
rs7625909	3p21.1	SFMBT1/RFT1	1.07(1.05-1.10)	1.04(0.98-1.11)	0.451
rs112111458	2p13.3	CD207/VAX2	0.91(0.87-0.94)	0.89(0.81-0.97)	0.731

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Supplementary Table 3. Known atopy SNP look-ups

TRAIT	Paper	Chr	Pos	SNP*	GENE / position	Effect allele*	Original study result			European fixed effect MA			MANTRA
							OR	(95%-CI)	p-value	OR	(95%-CI)	p-value	log10 BF
Atopic Dermatitis	Ellinghaus, 2013	16	11229589	rs2041733	CLEC16A,DEXI/ 16p13.13	T (A)	1.23	(1.17–1.29)	3.4E-15	1.08	(1.06-1.11)	**2.5E-11**	10.11
Atopic Dermatitis	Ellinghaus, 2013	11	36432024	rs12295535	PRR5L/ 11p13	T (A)	1.68	(1.46–1.93)	8.0E-13	1.16	(1.08-1.25)	**3.3E-05**	4.50
Atopic Dermatitis	Ellinghaus, 2013	17	47440466	rs16948048	ZNF652/ 17q21.32	G	1.17	(1.11–1.23)	2.9E-09	1.05	(1.03-1.08)	**1.7E-05**	4.04
Atopic Dermatitis	Ellinghaus, 2013	4	123497697	rs17389644	IL2,IL21/4q27	A	1.19	(1.12–1.26)	1.4E-08	1.07	(1.04-1.10)	**4.0E-06**	3.99
Atopic Dermatitis	Esparza-Gordillo, 2009	11	76301316	rs7927894	C11orf30 / 11q13.5	T (A)	1.22	(1.15–1.30)	7.6E-10	1.08	(1.05-1.10)	**2.5E-09**	5.81
Atopic Dermatitis	Hirota, 2012	11	7968359	rs878860	OR10A3,NLRP10/ 11p15.4	C (G)	1.31	1.24–1.38	1.5E-22	1.00	(0.98-1.02)	9.4E-01	6.85
Atopic Dermatitis	Hirota, 2012	10	64398466	rs10995251	ZNF365/ 10q21.2	C	1.28	1.22–1.36	5.9E-20	1.02	(1.00-1.05)	9.8E-02	4.51
Atopic Dermatitis	Hirota, 2012	6	32158319	rs114764276 (rs176095)	GPSM3/ 6p21.32	A (T)	1.40	1.30–1.51	8.4E-20	1.06	(1.03-1.10)	**2.2E-04**	2.34
Atopic Dermatitis	Hirota, 2012	3	112376308	rs12634229	CCDC80/ 3q13.2	C (G)	1.29	1.22–1.37	1.6E-19	1.01	(0.96-1.06)	7.2E-01	4.26
Atopic Dermatitis	Hirota, 2012	2	102971865	rs13015714	IL1RL1,IL18RAP/2q12	G	1.27	1.20–1.34	8.4E-18	1.10	(1.07-1.14)	**1.6E-12**	17.61
Atopic Dermatitis	Hirota, 2012	3	33087200	rs6780220	GLB1/ 3p21.33	C (G)	1.25	1.19–1.32	2.8E-16	1.01	(0.98-1.05)	4.0E-01	2.43
Atopic Dermatitis	Hirota, 2012	7	3128789	rs4722404	CARD11/ 7p22	C (G)	1.18	1.12–1.25	7.8E-09	1.00	(0.98-1.03)	8.1E-01	1.54
Atopic Dermatitis	Hirota, 2012	20	52807221	rs16999165	CYP24A1,PFDN4/ 20q13	A (T)	1.19	1.12–1.26	1.7E-08	0.94	(0.88-1.00)	6.5E-02	2.73
Atopic Dermatitis	Paternoster, 2011	11	65551957	rs479844	OVOL1 / 11q13.1	A	0.88	(0.85–0.91)	1.1E-13	0.90	(0.88-0.92)	**2.0E-18**	17.08
Atopic Dermatitis	Paternoster, 2011	19	8789381	rs2164983	ACTL9 / 19p13.2	A	1.16	(1.10–1.22)	7.1E-09	1.12	(1.08-1.15)	**1.9E-11**	12.33
Atopic Dermatitis	Paternoster, 2011	5	132049027	rs2897442	KIF3A / 5q31	C	1.11	(1.07–1.15)	3.8E-08	1.09	(1.06-1.12)	**1.4E-10**	6.62
Atopic Dermatitis	Sun, 2011	5	109858821	rs7701890	TMEM232 /5q22.1	G	1.24	NA	3.2E-09	1.02	(0.98-1.06)	3.6E-01	0.37
Atopic Dermatitis	Sun, 2011	20	62309839	rs6010620	TNFRSF6B / 20q13.33	G	1.17	NA	3.0E-08	1.09	(1.06-1.13)	**2.2E-09**	9.69
Atopic Dermatitis	Weidinger, 2013	6	32074804	rs12153855	TNXB / 6p21.33	T	1.58	(1.41–1.78)	3.0E-14	1.10	(1.05-1.14)	**1.0E-05**	3.10
Atopic Dermatitis	Esparza-Gordillo, 2013	1	154426970	rs2228145	IL6R / 1q21.3	C	1.15	(1.09-1.21)	5.4E-09	1.08	(1.05-1.11)	**4.9E-10**	6.96
Allergy	Hinds, 2013	4	38811551	rs2101521	TLR1-6/ 4p14	G	1.15	(1.11–1.18)	5.3E-21	1.04	(1.01-1.07)	**6.1E-03**	1.21
Allergy	Hinds, 2013	5	110467499	rs1438673	WDR36,CAMK4/ 5q22.1	C	1.12	(1.09–1.14)	2.3E-20	1.03	(1.00-1.05)	**2.1E-02**	1.46
Allergy	Hinds, 2013	2	102879464	rs10189629	IL1RL2,IL1RL1/ 2q12.1	C	1.16	(1.12–1.20)	1.8E-16	1.05	(1.02-1.09)	**4.0E-03**	2.74
Allergy	Hinds, 2013	6	31352113	rs115002418 (rs9266772)	HLA-C,MICA/ 6p21.33	C	1.11	(1.08–1.14)	3.2E-12	1.04	(1.01-1.08)	**1.8E-02**	0.81
Allergy	Hinds, 2013	5	40486896	rs7720838	PTGER4/ 5p13.1	T	1.08	(1.06–1.11)	8.2E-11	1.02	(0.99-1.04)	1.4E-01	-0.24
Allergy	Hinds, 2013	2	198914072	rs10497813	PLCL1/ 2q33,1	G	1.08	(1.05–1.10)	6.1E-10	1.01	(0.99-1.03)	3.8E-01	-0.35
Allergy	Hinds, 2013	3	188128979	rs9860547	LPP/ 3q28	A	1.08	(1.05–1.10)	1.2E-09	1.04	(1.02-1.07)	**1.2E-03**	1.13
Allergy	Hinds, 2013	9	6172380	rs7032572	RANBP6,IL33/ 9p24.1	G	1.12	(1.08–1.16)	1.7E-09	1.02	(0.99-1.06)	1.7E-01	-0.26
Allergy	Hinds, 2013	20	50141264	rs6021270	NFATC2/ 20q13.2	T	1.16	(1.11–1.23)	6.9E-09	1.03	(0.98-1.09)	2.2E-01	-0.18
Allergy	Hinds, 2013	17	38074031	rs9303280	GSDMB / 17q12	C	1.07	(1.05–1.10)	8.9E-09	1.02	(0.99-1.04)	1.5E-01	-0.21
Allergy	Hinds, 2013	15	67450305	rs17228058	SMAD3 / 15q22.33	G	1.08	(1.05–1.11)	1.2E-08	1.02	(0.99-1.05)	1.6E-01	-0.04
Allergy	Hinds, 2013	10	9053132	rs962993	GATA3/ 10p14	C	1.07	(1.05–1.10)	1.5E-08	1.01	(0.99-1.04)	3.6E-01	-0.56
Allergy	Hinds, 2013	4	123329362	rs17388568	ADAD1/ 4q27	A	1.08	(1.05–1.10)	3.9E-08	1.06	(1.03-1.09)	**1.2E-05**	3.88
Allergy	Hinds, 2013	14	38077148	rs1998359	FOXA1,TTC6/ 14q21.1	G	1.08	(1.05–1.12)	4.8E-08	0.99	(0.96-1.02)	5.3E-01	-0.25
Asthma	Ferreira, 2011	11	76270683	rs7130588	/ 11q13.5	G	1.09	(1.06–1.13)	1.8E-08	1.08	(1.05-1.10)	**2.3E-09**	6.67
Asthma	Ferreira, 2011	1	154426264	rs4129267	IL6R / 1q21.3	T	1.09	(1.06–1.12)	2.3E-08	1.08	(1.05-1.10)	**7.4E-10**	6.84

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Asthma	Himes, 2009	5	59369794	rs1588265	PDE4D / 5q12.1	G	0.85	(0.77–0.93)	4.3E-07	1.01	(0.98-1.04)	4.6E-01	-0.32
Asthma	Hirota, 2011	6	32184345	rs115718626 (rs404860)	/ 6p21	T (A)	1.21	(1.16–1.25)	4.1E-23	1.00	(0.96-1.03)	8.0E-01	-0.20
Asthma	Hirota, 2011	5	110401872	rs1837253	/ 5q22	C	1.17	(1.13–1.22)	1.2E-16	1.00	(0.98-1.03)	8.8E-01	-0.29
Asthma	Hirota, 2011	10	8972018	rs10508372	/ 10p14	G (C)	1.16	(1.12–1.21)	1.8E-15	1.03	(0.99-1.08)	1.5E-01	-0.10
Asthma	Hirota, 2011	12	56412487	rs1701704	/ 12q13	G	1.19	(1.14–1.25)	2.3E-13	1.03	(1.01-1.06)	**7.4E-03**	0.94
Asthma	Hirota, 2011	4	144003159	rs7686660	/ 4q31	T	1.16	(1.11–1.21)	1.9E-12	0.99	(0.96-1.01)	3.2E-01	-0.65
Asthma	Moffat, 2010	6	32625869	rs9273349*	HLA-DQB1 / 6p21.32	C (G)	1.18	(1.13–1.24)	7.0E-14	1.03	(0.94-1.13)	4.8E-01	-0.28
Asthma	Moffat, 2010	2	102986222	rs3771166	IL18R1 / 2q12.1	A	0.87	(0.83–0.91)	3.5E-12	0.96	(0.94-0.99)	**3.7E-03**	3.17
Asthma	Moffat, 2010	9	6190076	rs1342326	IL33 / 9p24.1	C	1.20	(1.13–1.28)	8.7E-12	1.02	(0.99-1.05)	2.5E-01	-0.48
Asthma	Moffat, 2010	15	67446785	rs744910	SMAD3 / 15q22.33	A	0.89	(0.86–0.92)	3.9E-09	0.99	(0.97-1.02)	5.7E-01	-0.33
Asthma	Moffat, 2010	17	38121993	rs3894194	GSDM1 / 17q21.1	A	1.17	(1.11–1.23)	4.6E-09	1.03	(1.01-1.06)	**1.1E-02**	0.05
Asthma	Moffat, 2010	22	37534034	rs2284033	IL2RB / 22q12.3	A	0.89	(0.86–0.93)	1.2E-08	1.01	(0.99-1.04)	3.1E-01	-0.38
Asthma	Moffat, 2010	5	131995843	rs1295686	IL13 / 5q31.1	C	0.87	(0.83–0.92)	1.4E-08	0.91	(0.88-0.93)	**2.6E-11**	12.83
Asthma	Moffat, 2010	17	38062196	rs2305480	GSDMB / 17q12	A	0.85	(0.81–0.90)	9.6E-08	0.98	(0.96-1.01)	1.6E-01	-1.05
Asthma	Moffat, 2010	15	61069988	rs11071559	RORA /15q22.2	T	0.85	(0.80–0.90)	1.1E-07	1.00	(0.97-1.03)	9.9E-01	0.65
Asthma	Moffat, 2010	5	131723288	rs2073643	SLC22A5 / 5q31.1	C	0.90	(0.87–0.94)	2.2E-07	0.96	(0.94-0.98)	**1.4E-03**	2.27
Asthma	Noguchi, 2011	8	118025645	rs3019885	SLC30A8 / 8q24.11	G	1.34	(1.24–1.45)	5.0E-13	1.00	(0.98-1.03)	7.6E-01	-0.49
Asthma	Noguchi, 2011	6	33042880	rs115505532 (rs987870)	HLA-DPB1 / 6p21.32	G (C)	1.40	(1.26–1.55)	2.3E-10	1.02	(0.98-1.06)	4.3E-01	-0.47
Asthma	Sleiman, 2010	1	197325908	rs2786098	DENND1B / 1q31.3	A	0.70	NA	9.3E-11	0.98	(0.96-1.01)	3.0E-01	-0.16
IgE	Moffat, 2010	6	32581582	rs113013369	HLA-DRB1 / 6p21.32	G	NA	NA	8.3E-15	0.98	(0.95-1.01)	1.6E-01	-0.04
IgE	Moffat, 2010	12	57503775	rs167769	STAT6 / 12q13.3	T	NA	NA	8.5E-07	1.05	(1.03-1.08)	**3.2E-05**	3.00
IgE	Moffat, 2010	5	131995964	rs20541	IL13 / 5q31.1	A	NA	NA	1.0E-06	1.11	(1.07-1.14)	**1.0E-11**	13.08
IgE	Moffat, 2010	16	27397998	rs1859308	IL4,IL21R / 16p12.1	A	NA	NA	8.2E-06	0.99	(0.96-1.03)	6.6E-01	-0.37
IgE	Moffat, 2010	1	159276153	rs2252226	FCER1A /1q23.2	C	NA	NA	6.6E-05	0.99	(0.97-1.02)	4.9E-01	0.06
Sensitisation	Bonnelyke, 2013	11	76299194	rs2155219	C11orf30 / 11q13.5	T	1.18	(1.13–1.22)	1.4E-18	1.09	(1.06-1.11)	**5.5E-12**	11.61
Sensitisation	Bonnelyke, 2013	12	57489709	rs1059513	STAT6 / 12q13.3	T	1.30	(1.21–1.39)	1.0E-14	1.09	(1.05-1.14)	**1.8E-05**	3.31
Sensitisation	Bonnelyke, 2013	5	110190052	rs10056340	SLC25A46 / 5q22.1	T	0.83	(0.78–0.87)	5.2E-14	0.96	(0.93-0.99)	**7.8E-03**	1.11
Sensitisation	Bonnelyke, 2013	6	32626311	rs112935615 (rs6906021)	HLA-DQB1 /6p21.32	T	0.87	(0.83–0.90)	2.2E-12	1.02	(0.99-1.05)	1.5E-01	-0.14
Sensitisation	Bonnelyke, 2013	2	102960210	rs3771175	IL1RL1,IL18R1 / 2q12.1	A	0.83	(0.78–0.88)	4.9E-11	0.94	(0.91-0.98)	**9.7E-04**	4.07
Sensitisation	Bonnelyke, 2013	4	38812876	rs17616434	TLR1,6,10 / 4p14	T	1.23	(1.18–1.29)	5.2E-11	1.03	(1.00-1.06)	**2.8E-02**	0.11
Sensitisation	Bonnelyke, 2013	3	188072513	rs9865818	LPP / 3q28	A	0.89	(0.86–0.92)	2.7E-10	0.97	(0.95-0.99)	**1.4E-02**	0.37
Sensitisation	Bonnelyke, 2013	8	128815029	rs4410871	MYC,PVT1 / 8q24.21	T	1.14	(1.09–1.19)	5.4E-10	1.00	(0.97-1.02)	7.5E-01	-0.28
Sensitisation	Bonnelyke, 2013	4	123353432	rs17454584	IL2,ADAD1 / 4q27	A	0.87	(0.83–0.91)	5.5E-10	0.93	(0.90-0.96)	**1.3E-06**	4.67
Sensitisation	Bonnelyke, 2013	6	31354182	rs116832676 (rs6932730)	HLA-B,MICA / 6p21.33	T	1.14	(1.09–1.20)	4.2E-08	1.03	(0.99-1.07)	1.1E-01	-0.16

* SNP and effect allele reported for 1000 genomes. If annotation has changed since publication, the SNP/effect allele as reported in the paper is given in brackets.

P-values that reach p<0.05 in our European-only fixed effects meta-analysis are shown in **bold.** Genome build=GRCh37

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Supplementary Table 4. atopic dermatitis-associated loci overlapping with GWAS catalog. For each locus (+/-250kb of top hit) we list traits in NHGRI GWAS catalog (7/8/14) or Immunobase with p<5x10-8. If GWAS catalog SNP is in LD (r2>0.6 and p<10-5) with our associated SNPs we tested for consistency of direction of effect: * same direction of effect for AD, † opposite direction of effect for AD. Also listed are mendelian traits of interest in each region from OMIM.

Genetic variant	Locus	Nearest Gene	b38 region	NHGRI hits in region	Immunobase	OMIM Mendelian traits (ID)
KNOWN LOCI						
rs61813875	1q21.3	CRCT1/LCE3E (FLG)	1:152314174-152814174	AD, Psor, curly hair	Psor	IV (146700)
rs12730935	1q21.3	IL6R	1:154197416-154697416	Asth*, RA†, CRP*, Fib*, IL6R	AS†, JIA, RA†	AG (615010)
rs6419573	2q12.1	IL18R1/IL18RAP	2:102160643-102660644	AD, Asth, Asth&HF, AlS, SRA, IBD*, CD*, sST2, Cel*, EC	CD*, Cel*	
rs1249910	3q13.2	CCDC80/CD200R1L	3:112422327-112922327	AD	none	
rs6827756	4q27	KIAA109 (IL2)	4:122072437-122572437	AlS, SRA, IBD, CD*, T1D	Cel*, CD*, JIA*, RA*, T1D, UC*	severe immunodeficiency
rs12188917	5q31.1	RAD50/IL13	5:132405393-132905393	AD, Fib, IBD, HL, IgE, PlC, CRP, EC, Psor†, CD	CD, JIA, Psor, UC	Eosinophilia (131400)
rs145809981	6p21.33	MICB	6:31248440-31748440	72 hits incl. AD, AlS, SRA & autoimmune traits	all	
rs4713555	6p21.32	HLA-DRB/HLA-DQA1	6:32357747-32857747	152 hits incl. Asth, AlS, SRA & autoimmune traits	all	ALDD (256040)
rs2944542	10q21.2	ZNF365	10:62360240-62860239	AD, BC, IBD, CD, Narc, BS, ES, MD	CD, UC	
rs4312054	11p15.4	OR10A3/NLRP10	11:7705614-8205614	AD*	none	
rs2592555	11p13	PRR5L	11:36100207-36600207	none	JIA*	severe immunodeficiency (601457)
rs10791824	11q13.1	OVOL1	11:65541795-66041795	AD*, ht, urate, HDL, BC, IBD	CD	AG (610329)
rs2212434	11q13.5	C11orf30/LRRC32	11:76320549-76820549	AD, AlS, SRA, AR, Asth, UC, IBD*, IgE, CD	CD*, UC*	
rs2041733	16p13.13	CLEC16A	16:10885732-11385732	Asth&HF, IBD, CD, T1D, MS, PBC, Cel	Cel, CD, JIA, MS, Psor, T1D, PBC	
rs2918307	19p13.2	ADAMTS10/ACTL9	19:8474838-8929046	AD*, ht	none	
rs4809219	20q13.33	RTEL1-TNFRSF6B	20:63421762-63921762	PC, IBD, UC*, CD, Glioma*	CD, MS, UC	
NOVEL LOCI						
rs7512552	1q21.2	C1orf51/MRPS21	1:150043732-150543228	none	none	curly hair (139450)
rs10199605	2p25.1	LINC00299/-	2:8104967-8604967	none	none	
rs4643526	2p16.1	PUS10	2:60707516-61207516	IBD, CD, UC, PA, Cel, RA†, HL	Cel, CD, MS, Psor, RA, UC	
rs112111458	2p13.3	CD207/VAX2	2:70622973-71122975	none	none	Birbeck granule deficiency (613393)
rs11923593	3p21.1	SFMBT1/RFT1	3:52804774-53304760	ht, urate, UC*, IL2	UC*, CD*	immunodeficiency (615559)
rs10214237	5p13.2	IL7R/CAPSL	5:35633632-36133632	PBC*, MS*, UC*	MS*, PBC*, UC, CD	severe immunodeficiency (608971)
rs6473227	8q21.13	MIR5708/ZBTB10	8:80123657-80623657	Asth&HF*, RA, SHBG	RA	
rs6602364	10p15.1	IL15RA/IL2RA	10:5746890-6246890	RA, MS, IBD, CD, T1D, Inflamm, Alo, Vit	ATD, CD, JIA, MS, RA, T1D†, Vit, Alo	IL2RA deficiency (606367)
rs7127307	11q24.3	-/ETS1	11:128067488-128567488	SLE, Cel	Cel, Psor	
rs2038255	14q13.2	PPP2R3C	14:34839920-35339920	Psor	none	
rs12951971	17q21.2	STAT3	17:42126113-42626113	IBD, CD, MS	CD, MS, Psor, UC	HIES (147060)

Trait acronyms: AD=atopic dermatitis, AGS=Aicardi-Goutieres syndrome, Alo=alopecia areata, AlS=allergic sensitisation, AR=allergic rhinitis, AS=ankylosing spondylitiis, Asth=asthma, Asth&HF=asthma with hayfever, ATD=autoimmune thyroid disease, BC=breast cancer, BS=breast size, CD=Crohn's disease, CDR=Vertical cup-disc ratio (opthalmology), Cel=celiac disease, CRP=C-reactive protein, EC=eosinophil counts, ES=Ewing sarcoma, Fib=Fibrinogen, HDL=HDL cholesterol, HIES=Hyper-IgE recurrent infection syndrome, HL=Hodgkin's lymphoma, ht=height, IBD= inflammatory bowel disease, IL2= IL2 immune response to smallpox, Inflamm=Inflammatory biomarkers, IV=ichthyosis vulgaris, Juvenile idiopathic arthritis, MD=mammographic density, MS=multiple sclerosis, Narc=Narcolepsy, PA=psoriatic arthritis, PBC=primary biliary cirrhosis, PC=prostate cancer, PlC=platelet counts, Psor=Psoriasis, RA=rheumatoid arthritis, SHBG=sexhormone-binding globulin, SRA=self-reported allergy, sST2=soluble ST2 protein, T1D=type 1 diabetes, UC=ulcerative colitis, Vit=Vitiligo

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Supplementary Table 11. Conditional analysis of secondary independent signals

Region	primary SNP	secondary SNP	secondary α-value*	Chr	Pos	EA	EAF	Crude association† OR(95%CI)	Crude association† P	Conditional association‡ OR(95%CI)	Conditional association‡ P	secondary signal known/ novel	Replication OR(95%CI)	Replication 1-sided P-value
2q12.1 (IL18RAP)	rs6419573	rs3917265	9.29E-05	2	102778461	C	0.53	1.03(1.01-1.06)	0.0100	1.06(1.03-1.08)	9.3E-07	novel	1.04(1.02-1.06)	**1.96E-04**
4q27 (KIAA109)	rs6827756	rs13152362	1.30E-04	4	123240619	A	0.21	0.91(0.89-0.94)	4.2E-09	0.95(0.92-0.97)	9.0E-05	novel	0.96(0.94-0.98)	**7.57E-04**
5q31.1 (IL13)	rs12188917	rs4705962	0.00012	5	132028858	T	0.28	1.10(1.07-1.13)	7.0E-12	1.07(1.04-1.10)	5.3E-07	known	NA	NA
11p13 (PRR5L)§	rs12295535	rs2218565	8.43E-05	11	36336263	T	0.34	0.94(0.92-0.97)	4.4E-06	0.94(0.92-0.97)	4.6E-06	novel	0.96(0.94-0.98)	**1.02E-05**

* secondary α-value is the locus-specific significance threshold, a bonferroni-corrected threshold for the number of effective tests +/-250kb of top hit (using the Nyholt procedure)

† crude association is the association of the secondary SNP unadjusted for the top SNP

‡ conditional association is the association of the secondary SNP adjusted for the top SNP

§ rs12295535 was previously associated with atopic dermatitis in Ellinghaus et.al. 2013, and hence is classified as the primary SNP. The top hit in the current GWAS (rs2592555) failed genotyping in replication, but is in LD (r^2=0.65) with the secondary signal reported here (rs2218565).

Genome build=GRCh37

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Supplementary Table 12. Studies contributing to FLG conditional analysis

Study	FLG variants adjusted for	Cases	Controls
ALSPAC	R501X, 2282del4, R2447X, S3247X	1712	3719
B58C	R501X, 2282del4, R2447X, S3247X	803	3907
COPSAC2000	R501X, 2282del4, R2447X, S3247X	155	149
DNBC	R501X, 2282del4, R2447X, S3247X	206	1288
GenerationR	R501X, 2282del4, R2447X, (S3247X n=2, so excluded)	295	1519
GENEVA/KORAF4/POPGEN	R501X, 2282del4, R2447X, S3247X	1004	757
GINI/LISA	R501X, 2282del4	442	865
INMA	R501X, 2282del4, R2447X, S3247X	374	397
MAAS	R501X, 2282del4, R2447X, S3247X	224	314
NCRC-ADC	R501X, 2282del4, R2447X, S3247X	556	1698
	Totals	**5771**	**14613**

Supplementary Table 13. FLG conditional analysis. Results for the three independent SNPs associated with atopic dermatitis from the EDC region. 'All-European' shows the results from the GWAS meta-analysis of all European studies, results are then shown for the subset of studies with FLG available (Supp Table 12). Results are shown for this subset before (unconditional) and after (conditional) conditioning on the 4 FLG mutations.

			All -European		Subset - unconditional		Subset - conditional	
rs number	position	EA	Beta (SE)	P-value	Beta (SE)	P-value	Beta (SE)	P-value
rs7512552	150265704	T	-0.07 (0.01)	9.10E-10	-0.12 (0.03)	1.50E-06	-0.10 (0.03)	2.00E-04
rs61813875	152536650	G	0.48 (0.04)	5.60E-29	0.62 (0.09)	1.10E-11	0.23 (0.13)	7.20E-02
rs12730935	154419892	A	0.08 (0.01)	6.10E-10	0.05 (0.03)	5.60E-02	0.06 (0.03)	3.10E-02

NB - Though the p-values in the conditional analysis for all variants are attenuated compared to the GWAS results, this attenuation is small for rs7512552 and rs12730935 when considering the unconditioned results from the subset and beta values are only marginally affected. The rs61813875 result is greatly attenuated and this signal is likely driven by the known FLG mutations. The other SNPs however, are considered independent.

Genome build=GRCh37

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Supplementary Table 14. MAGENTA results. The gene-sets with false discovery rate (FDR)<0.05 are listed, along with any variants from those gene-sets that reach p<10-5 in the random effects analysis of all cohorts. Variants denoted by chr:position. Genome build=GRCh37

Rows are shaded dark grey for established atopic dermatitis loci, light grey for loci genome-wide significant in the current discovery GWAS and unshaded for additional MAGENTA-identified variants with p<10-5. The final column lists the variants that represent each of these loci in our analysis.

Database	Gene_Set	FDR	Gene	Gene p	Best_variant	SNP p	Representing SNP
BIOCARTA	41BB_PATHWAY	0.0001	IL4	0	5:131907190:SNP	6.4E-17	rs12188917
BIOCARTA	41BB_PATHWAY	0.0001	RELA	6.7E-14	11:65505289:SNP	3.7E-12	rs10791824
BIOCARTA	41BB_PATHWAY	0.0001	IL2	2.5E-07	4:123445039:INDEL	1.5E-08	rs6827756
BIOCARTA	41BB_PATHWAY	0.0001	IFNG	1.5E-05	12:68648315:INDEL	9.6E-08	rs2227483
BIOCARTA	ASBCELL_PATHWAY	0.0058	IL4	0	5:131907190:SNP	6.4E-17	rs12188917
BIOCARTA	ASBCELL_PATHWAY	0.0058	IL2	2.5E-07	4:123445039:INDEL	1.5E-08	rs6827756
BIOCARTA	CD40_PATHWAY	0.0007	RELA	6.7E-14	11:65505289:SNP	3.7E-12	rs10791824
BIOCARTA	CD40_PATHWAY	0.0007	TRAF3	2.5E-03	14:103301072:SNP	4.0E-06	rs7146581
BIOCARTA	CD40_PATHWAY	0.0007	DUSP1	5.2E-03	5:172179584:SNP	7.5E-06	rs6872156
BIOCARTA	CDMAC_PATHWAY	0.0158	RELA	6.7E-14	11:65505289:SNP	3.7E-12	rs10791824
GOTERM	cornified envelope	<0.0001	IVL	0	1:152859811:SNP	1.4E-15	rs61813875
GOTERM	cornified envelope	<0.0001	SPRR1A	0	1:152859811:SNP	1.4E-15	rs61813875
GOTERM	cornified envelope	<0.0001	SPRR2A	0	1:153094297:SNP	4.5E-15	rs61813875
GOTERM	cornified envelope	<0.0001	SPRR2B	0	1:153094297:SNP	4.5E-15	rs61813875
GOTERM	cornified envelope	<0.0001	SPRR2D	0	1:153094297:SNP	4.5E-15	rs61813875
GOTERM	cornified envelope	<0.0001	SPRR2E	0	1:153094297:SNP	4.5E-15	rs61813875
GOTERM	cornified envelope	<0.0001	SPRR2F	0	1:153094297:SNP	4.5E-15	rs61813875
GOTERM	cornified envelope	<0.0001	SPRR2G	0	1:153094297:SNP	4.5E-15	rs61813875
GOTERM	cornified envelope	<0.0001	SPRR1B	0	1:152893891:SNP	1.6E-14	rs61813875
GOTERM	cornified envelope	<0.0001	FLG	1.5E-12	1:152394261:SNP	8.8E-12	rs61813875
GOTERM	cornified envelope	<0.0001	LOR	2.7E-09	1:153160673:SNP	3.0E-10	rs61813875
GOTERM	cornified envelope	<0.0001	RPTN	5.8E-09	1:152098428:SNP	1.2E-09	rs61813875
PANTHER_BIOL	Cytokine_&_chemokine_mediated_sig_pathway	0.0020	IL4	0	5:131907190:SNP	6.4E-17	rs12188917
PANTHER_BIOL	Cytokine_&_chemokine_mediated_sig_pathway	0.0020	IL13	0	5:131907190:SNP	6.4E-17	rs12188917
PANTHER_BIOL	Cytokine_&_chemokine_mediated_sig_pathway	0.0020	IL5	0	5:131907190:SNP	6.4E-17	rs12188917
PANTHER_BIOL	Cytokine_&_chemokine_mediated_sig_pathway	0.0020	IL18R1	4.6E-13	2:103016044:SNP	3.4E-12	rs6419573
PANTHER_BIOL	Cytokine_&_chemokine_mediated_sig_pathway	0.0020	IL1RL1	1.2E-10	2:103007220:SNP	5.7E-11	rs6419573
PANTHER_BIOL	Cytokine_&_chemokine_mediated_sig_pathway	0.0020	IL6R	6.3E-09	1:154418415:SNP	8.0E-10	rs12730935
PANTHER_BIOL	Cytokine_&_chemokine_mediated_sig_pathway	0.0020	IL2	2.5E-07	4:123445039:INDEL	1.5E-08	rs6827756
PANTHER_BIOL	Cytokine_&_chemokine_mediated_sig_pathway	0.0020	IL2RA	8.2E-06	10:6043478:SNP	3.3E-08	rs6602364
PANTHER_BIOL	Cytokine_&_chemokine_mediated_sig_pathway	0.0020	IFNG	1.5E-05	12:68648315:INDEL	9.6E-08	rs2227483
PANTHER_BIOL	Cytokine_&_chemokine_mediated_sig_pathway	0.0020	IL1RL2	4.4E-04	2:102883618:SNP	8.7E-07	rs6419573
PANTHER_BIOL	Cytokine_&_chemokine_mediated_sig_pathway	0.0020	INPP5D	9.4E-04	2:234115629:SNP	1.4E-06	rs1057258
PANTHER_BIOL	Cytokine_&_chemokine_mediated_sig_pathway	0.0020	TRAF3	2.5E-03	14:103301072:SNP	4.0E-06	rs7146581
BIOCARTA	CYTOKINE_PATHWAY	0.0073	IL4	0	5:131907190:SNP	6.4E-17	rs12188917
BIOCARTA	CYTOKINE_PATHWAY	0.0073	IL5	0	5:131907190:SNP	6.4E-17	rs12188917
BIOCARTA	CYTOKINE_PATHWAY	0.0073	IL13	0	5:131907190:SNP	6.4E-17	rs12188917
BIOCARTA	CYTOKINE_PATHWAY	0.0073	IL2	2.5E-07	4:123445039:INDEL	1.5E-08	rs6827756
BIOCARTA	CYTOKINE_PATHWAY	0.0073	IFNG	1.5E-05	12:68648315:INDEL	9.6E-08	rs2227483
BIOCARTA	DC_PATHWAY	0.0087	IL4	0	5:131907190:SNP	6.4E-17	rs12188917
BIOCARTA	DC_PATHWAY	0.0087	IL5	0	5:131907190:SNP	6.4E-17	rs12188917
BIOCARTA	DC_PATHWAY	0.0087	IL13	0	5:131907190:SNP	6.4E-17	rs12188917
BIOCARTA	DC_PATHWAY	0.0087	IFNG	1.5E-05	12:68648315:INDEL	9.6E-08	rs2227483
BIOCARTA	DC_PATHWAY	0.0087	CD5	8.3E-04	11:60830025:SNP	1.9E-06	rs2905493
BIOCARTA	EPONFKB_PATHWAY	0.0077	RELA	6.7E-14	11:65505289:SNP	3.7E-12	rs10791824
PANTHER_BIOL	Extracellular_transport_and_import	0.0023	SLC22A5	5.8E-05	5:131769174:SNP	3.2E-07	rs12188917
PANTHER_BIOL	Extracellular_transport_and_import	0.0023	SLC22A4	1.9E-03	5:131707537:SNP	3.6E-06	rs12188917
PANTHER_BIOL	Extracellular_transport_and_import	0.0023	SLC6A13	2.8E-03	12:296223:SNP	4.5E-06	*
PANTHER_BIOL	Extracellular_transport_and_import	0.0023	SLC6A12	3.5E-03	12:296223:SNP	4.5E-06	*
BIOCARTA	GATA3_PATHWAY	0.0123	IL4	0	5:131907190:SNP	6.4E-17	rs12188917
BIOCARTA	GATA3_PATHWAY	0.0123	IL5	0	5:131907190:SNP	6.4E-17	rs12188917
BIOCARTA	GATA3_PATHWAY	0.0123	IL13	0	5:131907190:SNP	6.4E-17	rs12188917
BIOCARTA	HIVNEF_PATHWAY	0.0081	RELA	6.7E-14	11:65505289:SNP	3.7E-12	rs10791824
BIOCARTA	HIVNEF_PATHWAY	0.0081	PRKCD	3.5E-07	3:53088790:SNP	9.4E-09	rs7625909
BIOCARTA	HIVNEF_PATHWAY	0.0081	PTK2	4.4E-04	8:141677324:SNP	6.2E-07	rs7016497
BIOCARTA	IL1R_PATHWAY	0.0057	RELA	6.7E-14	11:65505289:SNP	3.7E-12	rs10791824
BIOCARTA	IL22BP_PATHWAY	0.0041	IL22	1.1E-05	12:68648315:INDEL	9.6E-08	rs2227483
BIOCARTA	IL22BP_PATHWAY	0.0041	SOCS3	4.8E-04	17:76387363:SNP	7.4E-07	rs11657987
BIOCARTA	IL22BP_PATHWAY	0.0041	STAT5A	3.5E-04	17:40485239:SNP	1.3E-06	rs12951971
BIOCARTA	IL22BP_PATHWAY	0.0041	STAT5B	3.9E-04	17:40485239:SNP	1.3E-06	rs12951971
BIOCARTA	IL22BP_PATHWAY	0.0041	STAT3	4.2E-04	17:40485239:SNP	1.3E-06	rs12951971
BIOCARTA	IL22BP_PATHWAY	0.0041	STAT6	3.5E-04	12:57535266:SNP	1.5E-06	rs1799986
BIOCARTA	IL2_PATHWAY	0.0084	IL2	2.5E-07	4:123445039:INDEL	1.5E-08	rs6827756
BIOCARTA	IL2_PATHWAY	0.0084	IL2RA	8.2E-06	10:6043478:SNP	3.3E-08	rs6602364
BIOCARTA	IL2_PATHWAY	0.0084	STAT5A	3.5E-04	17:40485239:SNP	1.3E-06	rs12951971
BIOCARTA	IL2_PATHWAY	0.0084	STAT5B	3.9E-04	17:40485239:SNP	1.3E-06	rs12951971
BIOCARTA	IL3_PATHWAY	0.0094	STAT5A	3.5E-04	17:40485239:SNP	1.3E-06	rs12951971
BIOCARTA	IL3_PATHWAY	0.0094	STAT5B	3.9E-04	17:40485239:SNP	1.3E-06	rs12951971
BIOCARTA	INFLAM_PATHWAY	0.0124	IL4	0	5:131907190:SNP	6.4E-17	rs12188917
BIOCARTA	INFLAM_PATHWAY	0.0124	IL5	0	5:131907190:SNP	6.4E-17	rs12188917
BIOCARTA	INFLAM_PATHWAY	0.0124	IL13	0	5:131907190:SNP	6.4E-17	rs12188917

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BIOCARTA	INFLAM_PATHWAY	0.0124	IL2	2.5E-07	4:123445039:INDEL	1.5E-08	rs6827756
BIOCARTA	INFLAM_PATHWAY	0.0124	IFNG	1.5E-05	12:68648315:INDEL	9.6E-08	rs2227483
PANTHER_BIOL	Inhibition_of_apoptosis	0.0018	IL5	0	5:131907190:SNP	6.4E-17	rs12188917
PANTHER_BIOL	Inhibition_of_apoptosis	0.0018	IL4	0	5:131907190:SNP	6.4E-17	rs12188917
PANTHER_BIOL	Inhibition_of_apoptosis	0.0018	IL13	0	5:131907190:SNP	6.4E-17	rs12188917
PANTHER_BIOL	Inhibition_of_apoptosis	0.0018	TNFRSF6B	0	20:62303115:SNP	9.4E-15	rs4809219
PANTHER_BIOL	Inhibition_of_apoptosis	0.0018	RELA	6.7E-14	11:65505289:SNP	3.7E-12	rs10791824
PANTHER_BIOL	Inhibition_of_apoptosis	0.0018	IFNG	1.5E-05	12:68648315:INDEL	9.6E-08	rs2227483
PANTHER_BIOL	Inhibition_of_apoptosis	0.0018	REL	1.2E-04	2:61183228:SNP	5.5E-07	rs10791824
PANTHER_BIOL	Inhibition_of_apoptosis	0.0018	SOCS3	4.8E-04	17:76387363:SNP	7.4E-07	rs11657987
PANTHER_BIOL	Inhibition_of_apoptosis	0.0018	STAT5A	3.5E-04	17:40485239:SNP	1.3E-06	rs12951971
PANTHER_BIOL	Inhibition_of_apoptosis	0.0018	STAT5B	3.9E-04	17:40485239:SNP	1.3E-06	rs12951971
PANTHER_BIOL	Inhibition_of_apoptosis	0.0018	STAT3	4.2E-04	17:40485239:SNP	1.3E-06	rs12951971
PANTHER_BIOL	Inhibition_of_apoptosis	0.0018	MCL1	2.4E-03	1:150571938:SNP	5.8E-06	rs7512552
PANTHER_MOL	Interleukin_receptor	<0.0001	IL18R1	4.6E-13	2:103016044:SNP	3.4E-12	rs6419573
PANTHER_MOL	Interleukin_receptor	<0.0001	IL18RAP	7.0E-13	2:103016044:SNP	3.4E-12	rs6419573
PANTHER_MOL	Interleukin_receptor	<0.0001	IL1RL1	1.2E-10	2:103007220:SNP	5.7E-11	rs6419573
PANTHER_MOL	Interleukin_receptor	<0.0001	IL6R	6.3E-09	1:154418415:SNP	8.0E-10	rs12730935
PANTHER_MOL	Interleukin_receptor	<0.0001	IL2RA	8.2E-06	10:6043478:SNP	3.3E-08	rs6602364
PANTHER_MOL	Interleukin_receptor	<0.0001	IL1RL2	4.4E-04	2:102883618:SNP	8.7E-07	rs6419573
PANTHER_BIOL	JAK-STAT_cascade	0.0001	IL5	0	5:131907190:SNP	6.4E-17	rs12188917
PANTHER_BIOL	JAK-STAT_cascade	0.0001	IL4	0	5:131907190:SNP	6.4E-17	rs12188917
PANTHER_BIOL	JAK-STAT_cascade	0.0001	IL13	0	5:131907190:SNP	6.4E-17	rs12188917
PANTHER_BIOL	JAK-STAT_cascade	0.0001	IL6R	6.3E-09	1:154418415:SNP	8.0E-10	rs12730935
PANTHER_BIOL	JAK-STAT_cascade	0.0001	IL2	2.5E-07	4:123445039:INDEL	1.5E-08	rs6827756
PANTHER_BIOL	JAK-STAT_cascade	0.0001	IL2RA	8.2E-06	10:6043478:SNP	3.3E-08	rs6602364
PANTHER_BIOL	JAK-STAT_cascade	0.0001	IFNG	1.5E-05	12:68648315:INDEL	9.6E-08	rs2227483
PANTHER_BIOL	JAK-STAT_cascade	0.0001	SOCS3	4.8E-04	17:76387363:SNP	7.4E-07	rs11657987
PANTHER_BIOL	JAK-STAT_cascade	0.0001	STAT5A	3.5E-04	17:40485239:SNP	1.3E-06	rs12951971
PANTHER_BIOL	JAK-STAT_cascade	0.0001	STAT5B	3.9E-04	17:40485239:SNP	1.3E-06	rs12951971
PANTHER_BIOL	JAK-STAT_cascade	0.0001	STAT3	4.2E-04	17:40485239:SNP	1.3E-06	rs12951971
PANTHER_BIOL	JAK-STAT_cascade	0.0001	STAT6	3.5E-04	12:57535266:SNP	1.5E-06	rs1799986
KEGG	KEGG_ALLOGRAFT_REJECTION	0.0049	IL4	0	5:131907190:SNP	6.4E-17	rs12188917
KEGG	KEGG_ALLOGRAFT_REJECTION	0.0049	IL5	0	5:131907190:SNP	6.4E-17	rs12188917
KEGG	KEGG_ALLOGRAFT_REJECTION	0.0049	IL2	2.5E-07	4:123445039:INDEL	1.5E-08	rs6827756
KEGG	KEGG_ALLOGRAFT_REJECTION	0.0049	IFNG	1.5E-05	12:68648315:INDEL	9.6E-08	rs2227483
BIOCARTA	KERATINOCYTE_PATHWAY	0.0033	RELA	6.7E-14	11:65505289:SNP	3.7E-12	rs10791824
BIOCARTA	KERATINOCYTE_PATHWAY	0.0033	PRKCD	3.5E-07	3:53088790:SNP	9.4E-09	rs7625909
BIOCARTA	KERATINOCYTE_PATHWAY	0.0033	CEBPA	5.7E-03	19:33777109:SNP	6.9E-06	rs77714197
PANTHER_BIOL	mRNA_transcription_termination	0.0026	PTRF	3.2E-03	17:40528131:SNP	8.4E-06	rs12951971
PANTHER_BIOL	Neuromuscular_synaptic_transmission	0.0020	P2RX2	7.5E-03	12:133137841:SNP	9.4E-06	*
PANTHER_BIOL	NF-kappaB_cascade	0.0024	RELA	6.7E-14	11:65505289:SNP	3.7E-12	rs10791824
PANTHER_BIOL	NF-kappaB_cascade	0.0024	IFNG	1.5E-05	12:68648315:INDEL	9.6E-08	rs2227483
PANTHER_BIOL	NF-kappaB_cascade	0.0024	REL	1.2E-04	2:61183228:SNP	5.5E-07	rs10791824
PANTHER_BIOL	NF-kappaB_cascade	0.0024	TRAF3	2.5E-03	14:103301072:SNP	4.0E-06	rs7146581
BIOCARTA	NFKB_PATHWAY	0.0048	RELA	6.7E-14	11:65505289:SNP	3.7E-12	rs10791824
BIOCARTA	NKT_PATHWAY	0.0068	IL4	0	5:131907190:SNP	6.4E-17	rs12188917
BIOCARTA	NKT_PATHWAY	0.0068	IL5	0	5:131907190:SNP	6.4E-17	rs12188917
BIOCARTA	NKT_PATHWAY	0.0068	IL18R1	4.6E-13	2:103016044:SNP	3.4E-12	rs6419573
BIOCARTA	NKT_PATHWAY	0.0068	IL2	2.5E-07	4:123445039:INDEL	1.5E-08	rs6827756
BIOCARTA	NKT_PATHWAY	0.0068	IFNG	1.5E-05	12:68648315:INDEL	9.6E-08	rs2227483
BIOCARTA	NTHI_PATHWAY	0.0060	RELA	6.7E-14	11:65505289:SNP	3.7E-12	rs10791824
BIOCARTA	NTHI_PATHWAY	0.0060	DUSP1	5.2E-03	5:172179584:SNP	7.5E-06	rs6872156
BIOCARTA	PPARA_PATHWAY	0.0084	RELA	6.7E-14	11:65505289:SNP	3.7E-12	rs10791824
BIOCARTA	PPARA_PATHWAY	0.0084	STAT5A	3.5E-04	17:40485239:SNP	1.3E-06	rs12951971
BIOCARTA	PPARA_PATHWAY	0.0084	STAT5B	3.9E-04	17:40485239:SNP	1.3E-06	rs12951971
BIOCARTA	PPARA_PATHWAY	0.0084	DUSP1	5.2E-03	5:172179584:SNP	7.5E-06	rs6872156
BIOCARTA	RELA_PATHWAY	0.0135	RELA	6.7E-14	11:65505289:SNP	3.7E-12	rs10791824
BIOCARTA	RNA_PATHWAY	0.0065	RELA	6.7E-14	11:65505289:SNP	3.7E-12	rs10791824
BIOCARTA	STRESS_PATHWAY	0.0060	RELA	6.7E-14	11:65505289:SNP	3.7E-12	rs10791824
BIOCARTA	TALL1_PATHWAY	0.0062	RELA	6.7E-14	11:65505289:SNP	3.7E-12	rs10791824
BIOCARTA	TALL1_PATHWAY	0.0062	TRAF3	2.5E-03	14:103301072:SNP	4.0E-06	rs7146581
BIOCARTA	TH1TH2_PATHWAY	0.0003	IL4	0	5:131907190:SNP	6.4E-17	rs12188917
BIOCARTA	TH1TH2_PATHWAY	0.0003	IL18R1	4.6E-13	2:103016044:SNP	3.4E-12	rs6419573
BIOCARTA	TH1TH2_PATHWAY	0.0003	IL2	2.5E-07	4:123445039:INDEL	1.5E-08	rs6827756
BIOCARTA	TH1TH2_PATHWAY	0.0003	IL2RA	8.2E-06	10:6043478:SNP	3.3E-08	rs6602364
BIOCARTA	TH1TH2_PATHWAY	0.0003	IFNG	1.5E-05	12:68648315:INDEL	9.6E-08	rs2227483
BIOCARTA	TNFR2_PATHWAY	0.0001	RELA	6.7E-14	11:65505289:SNP	3.7E-12	rs10791824
BIOCARTA	TNFR2_PATHWAY	0.0001	TRAF3	2.5E-03	14:103301072:SNP	4.0E-06	rs7146581
BIOCARTA	TNFR2_PATHWAY	0.0001	DUSP1	5.2E-03	5:172179584:SNP	7.5E-06	rs6872156
BIOCARTA	TOB1_PATHWAY	0.0035	IL4	0	5:131907190:SNP	6.4E-17	rs12188917
BIOCARTA	TOB1_PATHWAY	0.0035	IL2	2.5E-07	4:123445039:INDEL	1.5E-08	rs6827756
BIOCARTA	TOB1_PATHWAY	0.0035	IL2RA	8.2E-06	10:6043478:SNP	3.3E-08	rs12951971
BIOCARTA	TOB1_PATHWAY	0.0035	IFNG	1.5E-05	12:68648315:INDEL	9.6E-08	rs2227483
BIOCARTA	VEGF_PATHWAY	0.0081	PTK2	4.4E-04	8:141677324:SNP	6.2E-07	rs7016497

*two loci were excluded from further analysis because in most discovery cohorts these SNPs were poorly imputed and had very low minor allele frequencies.

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Supplementary Table 15. European-only replication results random effects analysis.

					Discovery European random effects			Replication European random effects			Overall European - random effects		
SNP	Locus	Nearest Gene	EA/OA	EAF	N	OR (95% CI)	P-value	N	OR (95% CI)	P-value‡	N	OR (95% CI)	P-value
NOVEL GENOMEWIDE SIGNIFICANT LOCI													
rs7512552	1q21.2	C1orf51/MRPS21	T/C	0.49	102762	0.91(0.88-0.95)	4.06E-07	257019	0.95(0.92-0.99)	0.0130	359781	0.93(0.90-0.95)	1.47E-07
rs10199605	2p25.1	LINC00299/-	A/G	0.30	102760	0.92(0.89-0.95)	1.26E-06	256958	0.97(0.92-1.01)	0.0567	359718	0.94(0.91-0.96)	4.05E-06
rs4643526	2p16.1	PUS10	A/G	0.19	103066	1.09(1.05-1.14)	9.62E-06	257050	1.03(1.01-1.05)	0.0058	360116	1.06(1.04-1.09)	3.78E-06
rs112111458	2p13.3	CD207/VAX2	G/A	0.13	102760	0.89(0.84-0.94)	0.0001	257019	0.96(0.93-0.98)	**0.0008**	359779	0.92(0.89-0.95)	4.42E-06
rs11923593*	3p21.1	SFMBT1/RFT1	G/A	0.32	102761	1.07(1.04-1.10)	6.99E-08	257002	1.01(0.98-1.05)	0.2202	359763	1.05(1.03-1.08)	8.68E-05
rs10214237	5p13.2	IL7R/CAPSL	C/T	0.27	102761	0.93(0.90-0.95)	2.11E-08	257010	0.95(0.93-0.97)	**6.71E-08**	359771	0.94(0.92-0.95)	**2.86E-14**
rs6473227	8q21.13	MIR5708/ZBTB10	A/C	0.61	102761	0.93(0.91-0.95)	9.76E-10	257006	0.95(0.93-0.97)	**3.23E-08**	359767	0.94(0.93-0.95)	**2.22E-16**
rs6602364	10p15.1	IL15RA/IL2RA	G/C	0.45	103065	1.07(1.04-1.11)	5.22E-06	256993	1.04(1.00-1.08)	0.0185	360058	1.06(1.03-1.09)	3.55E-06
rs7127307	11q24.3	-/ETS1	C/T	0.47	103066	0.93(0.90-0.95)	2.26E-10	257034	0.94(0.93-0.96)	**2.51E-10**	360100	0.94(0.92-0.95)	**1.48E-18**
rs2143950*	14q13.2	PPP2R3C	T/C	0.17	102762	1.10(1.07-1.14)	4.53E-10	249940	1.05(0.98-1.13)	0.0831	352702	1.08(1.05-1.12)	4.82E-07
rs17881320*	17q21.2	STAT3	T/G	0.08	96796	1.12(1.07-1.18)	8.34E-06	249949	1.05(1.02-1.09)	**0.0015**	346745	1.09(1.05-1.12)	6.20E-07
MAGENTA GENE-SET ENRICHMENT ANALYSIS LOCI													
rs1057258	2q37.1	INPP5D	T/C	0.18	101012	0.94(0.91-0.97)	5.33E-05	257030	0.94(0.92-0.96)	**3.79E-07**	358042	0.94(0.92-0.96)	**1.72E-10**
rs6872156	5q35.1	DUSP1	A/G	0.24	103066	0.93(0.90-0.96)	6.75E-06	257047	0.97(0.95-0.99)	0.0055	360113	0.95(0.93-0.97)	1.75E-06
rs7016497	8q24.3	PTK2	T/C	0.21	103066	0.94(0.91-0.97)	9.05E-05	257040	0.98(0.96-1.00)	0.0290	360106	0.96(0.95-0.98)	9.37E-05
rs2905493	11q12.2	CD6/CD5	T/C	0.01	89617	0.78(0.68-0.89)	0.0002	254992	1.07(0.95-1.20)	0.8640	344609	0.96(0.87-1.06)	0.4185
rs1799986	12q13.3	LRP1(STAT6)†	T/C	0.15	99165	0.91(0.88-0.94)	7.52E-08	257022	0.98(0.96-1.01)	0.1142	356187	0.94(0.91-0.97)	0.0001
rs2227483	12q15	IL22(& IFNG)†	A/T	0.44	102762	0.94(0.92-0.97)	1.69E-06	253446	0.94(0.92-0.96)	**3.55E-11**	356208	0.94(0.93-0.96)	**6.66E-16**
rs7146581	14q32.32	TRAF3	T/C	0.24	102760	0.95(0.92-0.97)	0.0001	256971	0.97(0.92-1.02)	0.0946	359731	0.95(0.93-0.98)	0.0001
rs11657987	17q25.3	PGS1(SOCS3)†	T/G	0.49	100695	1.06(1.04-1.09)	7.72E-07	257019	1.03(0.99-1.06)	0.0901	357714	1.04(1.02-1.06)	9.74E-05
rs77714197	19q13.11	CEBPA	T/C	0.02	87690	1.35(1.19-1.54)	2.60E-06	256447	0.94(0.82-1.09)	0.7887	344137	1.12(0.98-1.28)	0.1024

*rs11923593 replaces rs7625909 (r2=0.98), rs2143950 replaces rs2038255 (r2=0.94), rs17881320 replaces rs12951971 (r2=0.75) in the replication analysis

†rs1799986 is within LRP1, but was selected in the MAGENTA analysis due to its proximity to STAT6. rs2227483 is with IL22, but was selected due to its proximity to both IL22 and IFNG.
rs11657987 is within PGS1, but was selected due to its proximity to SOCS3

‡ Replication p-values for a 1-sided test

Replication p-values in **bold** were considered significant (p<0.0025), overall p-values in **bold** are genome-wide significant

EA/OA= effect allele/other allele, EAF=effect allele frequency

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Supplementary Table 16. All studies replication results random effects analysis.

Genetic variant	Locus	Nearest Gene	EA/ OA	EAF	Discovery random effects			Replication random effects			Overall random effects		
					N	OR (95% CI)	P-value	N	OR (95% CI)	1-sided P-value	N	OR (95% CI)	P-value
NOVEL GENOMEWIDE SIGNIFICANT LOCI													
rs7512552	1q21.2	C1orf51/MRPS21	T/C	0.462	116544	0.92(0.89-0.95)	3.02E-07	260581	0.96(0.93-1.00)	0.0134	377125	0.94(0.91-0.96)	1.28E-07
rs10199605	2p25.1	LINC00299/-	A/G	0.304	116557	0.93(0.9-0.96)	6.07E-05	260520	0.96(0.92-1.00)	0.0323	377077	0.94(0.92-0.97)	1.51E-05
rs4643526	2p16.1	PUS10	A/G	0.195	107425	1.09(1.05-1.13)	1.88E-06	260612	1.03(1.00-1.05)	0.0098	368037	1.06(1.03-1.09)	1.13E-05
rs112111458	2p13.3	CD207/VAX2	G/A	0.138	116553	0.9(0.85-0.94)	3.67E-05	260581	0.95(0.93-0.98)	**2.19E-04**	377134	0.91(0.88-0.95)	1.56E-07
rs11923593*	3p21.1	SFMBT1/RFT1	G/A	0.326	116558	1.07(1.05-1.1)	9.42E-09	260564	1.01(0.99-1.03)	0.2440	377122	1.05(1.03-1.08)	1.71E-05
rs10214237	5p13.2	IL7R/CAPSL	C/T	0.259	116554	0.94(0.91-0.96)	3.92E-07	260572	0.95(0.92-0.98)	**0.0003**	377126	0.94(0.92-0.96)	**1.54E-10**
rs6473227	8q21.13	MIR5708/ZBTB10	A/C	0.584	116557	0.93(0.91-0.95)	4.83E-10	260568	0.94(0.91-0.97)	**3.26E-05**	377125	0.94(0.93-0.95)	**5.33E-18**
rs6602364	10p15.1	IL15RA/IL2RA	G/C	0.438	116855	1.07(1.05-1.1)	1.65E-08	260555	1.03(1.00-1.07)	0.0423	377410	1.06(1.03-1.08)	1.63E-06
rs7127307	11q24.3	-/ETS1	C/T	0.480	116855	0.92(0.9-0.95)	1.04E-11	260596	0.94(0.93-0.96)	**6.80E-11**	377451	0.94(0.92-0.95)	**1.04E-20**
rs2143950*	14q13.2	PPP2R3C	T/C	0.17	116558	1.10(1.07-1.14)	1.71E-10	253189	1.06(1.00-1.13)	0.0344	369747	1.08(1.06-1.11)	**8.59E-10**
rs17881320*	17q21.2	STAT3	T/G	0.08	99889	1.12(1.07-1.17)	1.92E-06	253198	1.05(1.02-1.09)	**0.0021**	353087	1.09(1.05-1.13)	2.61E-06
MAGENTA GENE-SET ENRICHMENT ANALYSIS LOCI													
rs1057258	2q37.1	INPP5D	T/C	0.203	114790	0.93(0.91-0.96)	1.44E-06	260592	0.94(0.92-0.96)	**4.18E-08**	375382	0.94(0.92-0.95)	**4.09E-13**
rs6872156	5q35.1	DUSP1	A/G	0.248	116863	0.94(0.92-0.97)	5.40E-06	260609	0.97(0.95-0.99)	**0.0020**	377472	0.96(0.94-0.97)	2.69E-07
rs7016497	8q24.3	PTK2	T/C	0.228	116863	0.93(0.91-0.96)	5.93E-07	260602	0.98(0.95-1.00)	0.0206	377465	0.96(0.94-0.97)	1.43E-06
rs2905493	11q12.2	CD6/CD5	T/C	0.018	102148	0.77(0.69-0.86)	2.01E-06	258554	1.05(0.92-1.19)	0.7635	360702	0.92(0.84-1.02)	0.098
rs1799986	12q13.3	LRP1(STAT6)†	T/C	0.147	112946	0.92(0.89-0.95)	1.11E-06	260584	0.99(0.95-1.02)	0.2395	373530	0.95(0.92-0.98)	1.62E-03
rs2227483	12q15	IL22(& IFNG)†	A/T	0.449	116559	0.94(0.92-0.96)	2.29E-07	257008	0.94(0.92-0.96)	**6.75E-12**	373567	0.94(0.93-0.95)	**1.24E-17**
rs7146581	14q32.32	TRAF3	T/C	0.268	116557	0.94(0.92-0.97)	5.23E-06	260533	0.96(0.92-1.00)	0.0345	377090	0.95(0.93-0.97)	4.05E-06
rs11657987	17q25.3	PGS1(SOCS3)†	T/G	0.477	114492	1.06(1.04-1.08)	7.70E-07	260581	1.03(0.99-1.08)	0.0555	375073	1.04(1.02-1.07)	6.02E-05
rs77714197	19q13.11	CEBPA	T/C	0.018	90783	1.33(1.18-1.51)	5.61E-06	257635	0.98(0.89-1.07)	0.6935	348418	1.10(0.98-1.24)	0.116

*rs11923593 replaces rs7625909 (r2=0.98), rs2143950 replaces rs2038255 (r2=0.94), rs17881320 replaces rs12951971 (r2=0.75) in the replication analysis

†rs1799986 is within LRP1, but was selected in the MAGENTA analysis due to its proximity to STAT6. rs2227483 is with IL22, but was selected due to its proximity to both IL22 and IFNG. rs11657987 is within PGS1, but was selected due to its proximity to SOCS3

Replication p-values in **bold** were considered significant (p<0.0025), overall p-values in **bold** are genome-wide significant

EA/OA= effect allele/other allele, EAF = effect allele frequency

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Supplementary Table 22. P-values for enrichment of atopic dermatitis SNPs within DHS-sites for all cell- or tissue types. Blue=immune cells, Grey=other cells/tissues.

Overlaps at $P<=10^{-10}$	ENCODE Cell Type	1-sided p-value	Figure name
33	Th0	<0.0001	Th0
49	Th1	<0.0001	Th1
4	Th17	<0.0001	Th17
16	Th2	2.00E-04	Th2
14	CD19_Primary_Cells_Peripheral_UW	3.00E-04	"CD19, per."
16	GM06990	4.00E-04	B-cell
13	CD56_Primary_Cells	0.0059	"CD56, NK"
11	CD3_Primary_Cells_Peripheral_UW	0.0625	"CD3, per."
14	Fetal_Thymus	0.1306	Fetal thymus
9	CD3_Primary_Cells_Cord_BI	0.7923	"CD3, cord."
12	Mobilized_CD34_Primary_Cells_Male	0.8297	
11	CD14_Primary_Cells	0.8544	CD14
2	Treg	0.9969	Treg
16	Myometr	0.9971	
15	CD34Mobilized	0.9979	
19	iPS	0.9985	
12	HPDE6E6E7	0.9995	
33	HMEC	0.9996	
11	Mobilized_CD34_Primary_Cells_Female	0.9997	
12	Gastric	0.9998	
11	AG04449	1	
8	AG04450	1	
6	AG09309	1	
5	AG09319	1	
6	AoAF	1	
9	AoSMC	1	
5	BJ	1	
11	Breast_vHMEC	1	
15	Chorion	1	
6	Fetal_Adrenal_Gland	1	
2	Fetal_Brain_Female	1	
5	Fetal_Brain_Male	1	
4	Fetal_Heart	1	
3	Fetal_Intestine_Large	1	
8	Fetal_Intestine_Small	1	
5	Fetal_Kidney	1	
9	Fetal_Lung	1	
7	Fetal_Muscle_Leg	1	
8	Fetal_Muscle_Trunk	1	
13	Fetal_Placenta	1	
8	Fetal_Stomach	1	
13	FibroP	1	
20	Fibrobl	1	

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9	H1_BMP4_Derived_Mesendoderm_Cultured_Cells	1
4	H1_BMP4_Derived_Trophoblast_Cultured_Cells	1
8	H1_Cell_Line	1
6	H1_Derived_Mesenchymal_Stem_Cells	1
4	H1_Derived_Neuronal_Progenitor_Cultured_Cells	1
23	H1hESC	1
4	H7hESC	1
9	H9ES	1
6	H9_Cell_Line	1
13	HAEpiC	1
7	HAc	1
5	HAh	1
10	HAsp	1
8	HBMEC	1
9	HCF	1
6	HCFaa	1
12	HCM	1
8	HCPEpiC	1
7	HConF	1
11	HEEpiC	1
10	HFF	1
13	HFFMyc	1
5	HGF	1
10	HIPEpiC	1
8	HMF	1
7	HMVECLBl	1
4	HMVECLLy	1
6	HMVECdAd	1
5	HMVECdBlAd	1
9	HMVECdBlNeo	1
3	HMVECdLyAd	1
7	HMVECdLyNeo	1
4	HMVECdNeo	1
7	HNPCEpiC	1
8	HPAEC	1
9	HPAF	1
7	HPF	1
6	HPdLF	1
11	HRCEpiC	1
11	HRE	1
5	HRGEC	1
7	HRPEpiC	1
20	HSMM	1
8	HSMMemb	1
27	HSMMtube	1
3	HTR8svn	1
15	HUVEC	1

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5	HVMF	1
7	HeLaS3IFNa4h	1
13	Hepatocytes	1
9	IMR90_Cell_Line	1
7	NHA	1
12	NHDFAd	1
10	NHDFneo	1
18	NHEK	1
8	NHLF	1
26	Osteobl	1
6	Ovary	1
12	PanIsletD	1
9	PanIslets	1
1	Pancreas	1
9	Penis_Foreskin_Fibroblast_Primary_Cells_skin01	1
7	Penis_Foreskin_Fibroblast_Primary_Cells_skin02	1
13	Penis_Foreskin_Keratinocyte_Primary_Cells_skin02	1
7	Penis_Foreskin_Melanocyte_Primary_Cells_skin01	1
9	PrEC	1
6	Psoas_Muscle	1
5	RPTEC	1
11	RWPE1	1
9	SAEC	1
5	SKMC	1
10	Small_Intestine	1
11	Stellate	1
9	Urothelia	1
8	UrotheliaUT189	1
6	WI38	1
9	WI38TamoxifenTamoxifen	1
22	pHTE	1

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Supplementary Table 23. Variance in atopic dermatitis-liability explained by known and novel variants.
Calculated assuming a population prevalence of 0.15

Category	Locus	Nearest gene	variant	variance explained	subtotals
Filaggrin	1q21.3	*FLG*	4 FLG mutations	7.96%	7.96%
known	1q21.3	*IL6R*	rs2228145	0.24%	
known	10q21.2	*ZNF365*	rs10995251	0.05%	
known	11p12	*PRR5L*	rs12295535	0.10%	
known	11q13.1	*OVOL1*	rs479844	0.78%	
known	11q13.5	*C11orf30*	rs7927894	0.72%	
known	16p13.13	*CLEC16A*	rs2041733	0.65%	
known	17q21.33	*ZNF652*	rs16948048	0.09%	
known	19p13.2	*ACTL9*	rs2164983	0.09%	
known	2q12.1	*IL18R1*	rs13015714	0.20%	
known	20q13.33	*RTEL1-TNFRSF6B*	rs6010620	0.49%	
known	4q27	*KIAA109*	rs17389644	0.02%	
known	5q31.1	*KIF3A*	rs2897442	0.59%	
known	6p21.32	*TNXB*	rs12153855	0.33%	4.37%
novel	11q24.3	*ETS1*	rs7127307	0.21%	
novel	12q15	*IL22*	rs2227483	0.24%	
novel	14q13.2	*PPP2R3C*	rs2143950	0.09%	
novel	14q32.32	*TRAF3*	rs7146581	0.04%	
novel	17q21.2	*STAT3*	rs17881320	0.07%	
novel	17q25.3	*PGS1(SOCS3)*	rs11657987	0.10%	
novel	2p13.3	*CD207*	rs112111458	0.22%	
novel	2q37.1	*INPP5D*	rs1057258	0.16%	
novel	5p13.2	*IL7R*	rs10214237	0.03%	
novel	8q21.13	*ZBTB10*	rs6473227	0.32%	1.45%
novel-secondary	11p13	*PRR5L*	rs2218565	0.95%	
novel-secondary	2q12.1	*IL1R1*	rs3917265	0.08%	
novel-secondary	4q27	*KIAA109*	rs13152362	0.12%	1.14%
				known	**12.32%**
				novel	**2.59%**
				total	**14.91%**

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