

No association between genetic ancestry and susceptibility to asthma or atopy in Canary Islanders

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Abstract Asthma is a complex respiratory disease characterized by chronic inflammation of airways and frequently associated with atopic symptoms. The population from the Canary Islands, which has resulted from a recent admixture of North African and Iberian populations, shows the highest prevalence of asthma and atopic symptoms among the Spanish populations. Although environmental particularities would account for the majority of such disparity, genetic ancestry might play a role in increasing the susceptibility of

asthma or atopy, as have been demonstrated in other recently African-admixed populations. Here, we aimed to explore whether genetic ancestry was associated with asthma or related traits in the Canary Islanders. For that, a total of 734 DNA samples from unrelated individuals of the GOA study, self-reporting at least two generations of ancestors from the Canary Islands (391 asthmatics and 343 controls), were successfully genotyped for 83 ancestry informative markers (AIMs), which allowed to precisely distinguishing

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between North African and Iberian ancestries. No association was found between genetic ancestry and asthma or related traits after adjusting by demographic variables differing among compared groups. Similarly, none of the individual AIMs was associated with asthma when results were considered in the context of the multiple comparisons performed ($0.005 \leq p \text{ value} \leq 0.042$; $0.221 \leq q \text{ value} \leq 0.443$). Our results suggest that if genetic ancestry were involved in the susceptibility to asthma or related traits among Canary Islanders, its effects would be modest. Larger studies, examining more genetic variants, would be needed to explore such possibility.

Keywords Allergy · Genetic susceptibility · North Africa · Admixture

Asthma is a complex respiratory disease characterized by chronic inflammation of airways and frequently associated with atopic symptoms (Ober 2005). Although environmental factors are involved in its pathogenesis, familiar clustering, twin studies, and genetic studies also support an important genetic contribution to disease predisposition (Holberg et al. 1999; Ober and Hoffjan 2006; Bouzigon et al. 2010; Thomsen et al. 2010). The prevalence of asthma varies widely around the world (1–18 %), and predictions for the coming years indicate that an increase is expected for Western societies (Braman 2006; Pearce et al. 2007). In Spain, the prevalence of asthma symptoms has been estimated around 5–6 %, with considerable geographic variation among regions (5–12 %) (The Spanish Group of the European Asthma Study 1995). However, the highest prevalence of asthma in adults from Spain has been found in the Canary Islands (17.2 %), based on the European Community Respiratory Health Survey (The Spanish Group of the European Asthma Study 1995; Julia Serda et al. 2005). In addition, estimates of asthma prevalence in children aged 6–7 years are twofold higher in the Canary Islands (18.4 %) than the mean for the Spanish population (9.9 %) (Sanchez-Lerma et al. 2009). Similarly, the prevalence of atopy in the Canary Islands is also elevated (40.6 %), compared to the mainland Spanish populations (Julia-Serda et al. 2011).

The Canary Islands belong politically to Spain, in spite of being located at about 1,000 km from the closest European point in Iberian Peninsula and only 100 km off the Northwest coast of Africa. These islands were inhabited by aboriginal people related to the Berber populations at the time of Spanish occupation in the fifteenth century, as pointed by historical, anthropological, archeological, and linguistic records (Navarro 1991). Genetic footprints of such Northwest African influence (as a proxy for the aborigines) in Canary Islanders have been demonstrated in contemporary inhabitants using classical (Flores et al. 2001) and autosomal

markers (Maca-Meyer et al. 2004; Fregel et al. 2005; Pino-Yanes et al. 2011), as well as with mitochondrial DNA (Rando et al. 1999) and the Y chromosome (Flores et al. 2003). Recently, we have estimated North African admixture in Canary Islanders using almost a hundred ancestry informative markers (AIMs), genetic loci showing large allele frequency differences between populations, selected from different regions of the autosomal genome (Pino-Yanes et al. 2011). Intriguingly, our results suggested that North African ancestry averaged 17 ± 25 %, but showed a wide interindividual variation ranging from 0 to 96 %, which was interpreted as a trace of the violent way the islands were conquered and colonized (Pino-Yanes et al. 2011).

Although the prevalence of asthma is generally low within countries from West Africa, individuals with West African ancestry have shown a higher prevalence of asthma and related traits when exposed to a Western style of living compared to European descent populations (NHLBI 2004). This has been explained as a consequence of gene–environment interaction by which the admixed African population would carry risk alleles for asthma and related traits because these alleles would provide them an adaptation to a higher load of parasites in their original populations that are no longer present in the new environment (Le Souef et al. 2006). As a consequence, in a recent admixed population, it is expected that genomic segments originated from the ancestral ethnic group with the higher risk will be enriched with risk alleles (Smith et al. 2004), which will be reflected in a larger proportion of ancestry from the ancestral population in affected individuals compared to the unaffected group. This hypothesis has been confirmed for African American and African Caribbean individuals, in which a larger African admixture has been associated with higher susceptibility for asthma and related traits and with lower pulmonary function measures (Tsai et al. 2006; Vergara et al. 2009; Kumar et al. 2010, 2012; Flores et al. 2012). Similar to the West African populations, the prevalence of asthma is generally low in the North African countries (NHLBI 2004), being estimated in 3–4 % for clinical diagnosed asthma in Algeria, Morocco, and Tunisia (Nafti et al. 2009). However, a trend for a markedly increase of prevalence has been found in these populations over recent decades due to the acquisition of a Western lifestyle and continued urban shifts (NHLBI 2004). In fact, for Morocco, the highest prevalence of asthma and asthma symptoms, as well as of other allergic diseases, is found in Casablanca, the largest city and the economic capital (Bouayad et al. 2006). This prevalence has been associated with an increase in urbanization and the acquisition of urban life style of living (Bouayad et al. 2006). In line with this data, the genetic expression profile in peripheral blood leukocytes has been found to be profoundly changed by an urban living style compared to a rural living style in Northwest African

populations (Idaghdour et al. 2008). Therefore, a higher risk for asthma and related traits would be expected in populations with North African genetic ancestry with Western living style.

Although the Canary Islands have particular climatic conditions that could promote the emergence of atopic symptoms, it has been suggested that the genetic background might also contribute to the high prevalence of atopic symptoms and asthma in this population (Julia Serda et al. 2005). Here, we aimed to analyze if genetic ancestry, assessed from autosomal AIMs, was associated with asthma or related traits in a case–control sample of Canary Islanders.

This study was approved by the ethics committees at participating hospitals, and written informed consent was obtained from all subjects. This study was conducted using a case–control design of 734 DNA samples from unrelated individuals reporting at least two generations of ancestors born in the Canary Islands. See Table 1 for the characteristics of subjects included in the study. Samples utilized constituted a subset of the Genetics of Asthma Study in the Spanish population, described elsewhere (Pino-Yanes et al. 2012). Briefly, cases were represented by 391 physician-diagnosed asthmatic patients aged >5 years and fulfilling the Global Initiative for Asthma guidelines for diagnosis and classification of asthma (<http://www.ginasthma.com>). These samples were collected from respiratory medicine and allergy departments from hospitals belonging to the Spanish National Health System. Only individuals, who reported having at least two generations of ancestors born in the Canary Islands, were included in this study. Demographical and clinical data

recorded included: age, sex, smoking habits, age at diagnosis of the disease, rhinitis, atopic dermatitis, basal forced expiratory volume in 1 s (FEV₁), serum total IgE levels, and the symptomatic treatment. Atopy was confirmed by a positive skin prick test (SPT, a wheal with a diameter 3 mm greater than the saline control) and/or elevated specific serum IgE levels (>0.35 UI mL⁻¹) to at least one of seven common allergens. Particularly, allergens evaluated for specific IgE were: dust mite (*Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, *Glycyphagus* spp, *Blomia tropicalis*, *Acarus siro*, *Tyrophagus putrescentiae*, *Lepidoglyphus destructor*, and *Euroglyphus maynei*), epithelium (*Felis domesticus*, *Canis familiaris*, *Equus caballus*, and *Oryctolagus cuniculus*), pollen (*Olea europaea*, *Salsola* spp, *Lolium perenne*, *Artemisia vulgaris*, *Parietaria* spp, *Platanus* spp, *Chenopodium* spp, *Plantago* spp, *Rumex* spp, and *Cupressus* spp), fungi (*Penicillium notatum*, *Alternaria alternate*, *Aspergillus fumigatus*, and *Cladosporium herbarum*), food (Cow's milk, hen's egg, peanut, soybean, wheat, fish, shrimp, crabs, lobster, clams, oysters, mussels, banana, chestnut, and kiwi), latex and cockroaches (*Blattella germanica*).

Controls consisted of 343 DNA samples from nonasthmatic unrelated adults, which were obtained from blood bank donors who did not report a personal or familiar medical history for allergic or pulmonary diseases and self-reporting at least two generations of ancestors born in the Canary Islands. A total of 93 European AIMs (from now on referred as EuroAIMs), allowing to distinguish between North African and Iberian ancestries, were genotyped in cases and controls using iPLEXTM Gold assays on MassARRAY system by the

Table 1 Relevant demographic and clinical features of samples

Variable	Cases (n=391)	Controls (n=343)	p Value
Gender (% of males)	37.4 (387)	62.6 (343)	<0.001 ^a
Age (years); mean, P ₂₅ –P ₇₅	38, 22–48 (352)	36, 31–45 (343)	0.087 ^b
Smoking habits (% of ever smokers)	20.8 (126)	79.2 (234)	<0.001 ^a
Clinical features			
Serum IgE levels (kUI mL ⁻¹); mean, P ₂₅ –P ₇₅	499.1, 89.3–425.5 (163)	NA	
Age at diagnosis (years); mean, P ₂₅ –P ₇₅	24, 10–32 (356)	NA	
FEV ₁ (% predicted); mean, P ₂₅ –P ₇₅	81, 67–95 (206)	NA	
Rhinitis (% positive)	44.9 (273)	NA	
Dermatitis (% positive)	4.0 (273)	NA	
SPT (% positive)	60.4 (240)	NA	
Specific IgE (% positive)	42.7 (225)	NA	
Atopy (% positive)	61.7 (256)	NA	
Treatment			
Inhaled corticoids (%)	86.5 (222)	NA	
Oral corticoids (%)	2.9 (279)	NA	
Long-acting β ₂ -agonists (%)	53.3 (291)	NA	
Short-acting β ₂ -agonists (%)	81.5 (205)	NA	

In parentheses, total number of subjects with available data

NA not available, P₂₅ percentile 25, P₇₅ percentile 75

^aχ² test

^bMann–Whitney U test

Spanish National Genotyping Center, Santiago de Compostela Node (CeGen, <http://www.cegen.org/>) (Pino-Yanes et al. 2011). Briefly, iPLEX™ assays were scanned by MALDI-TOF mass spectrometry, and individual SNP genotype calls were automatically generated using Sequenom Typer 3.4™ software. Samples from the Coriell Institute for Medical Research (<http://www.coriell.org>) were included to test allele calling reliability of this platform.

Departures from Hardy–Weinberg equilibrium (HWE) were evaluated separately in cases and controls using an exact test (Wigginton et al. 2005), by means of the SNPIn-foStats software (Pino-Yanes et al. 2011). Given its higher discriminatory power to detect differences among closely related populations, such as North Africans and Iberians (Maca-Meyer et al. 2004), than alternative algorithms based on the assignment of individuals to discrete populations (Heath et al. 2008; Li and Yu 2008; Price et al. 2008), principal component analysis (PCA) was utilized to derive individual ancestry estimates as scores of the first principal component as the major axis covering the Iberian–North African genetic differences (Pino-Yanes et al. 2011). For this purpose, data for the same set of EuroAIMs from individuals, self-declaring two generations of ancestors from the Iberian Peninsula ($n=889$) and Morocco in North Africa ($n=68$), were jointly analyzed with the case–control sample to serve as reference populations (Pino-Yanes et al. 2011). EIGENSOFT was used to assess PCA and to test the association of ancestry estimates with asthma and atopic traits between cases and controls by means of ANOVA statistics (Price et al. 2006). Then, in order to adjust this association, clinical and demographic variables were included as covariates along with ancestry estimates in regression models utilizing SPSS 15.0 (SPSS Inc., Chicago, IL). Given that genetic ancestry estimates represented a mean value from the genome, we also explored the possibility of having local differences in genetic ancestry that could be detected by using the individual EuroAIMs as proxies. For that, SNPAssoc (Gonzalez et al. 2007) was employed to test the association of individual EuroAIMs with asthma, adjusting for the genetic ancestry estimates by means of logistic regression models. Finally, in order to limit the expected proportion of false positives incurred in the study when a particular individual EuroAIM association test was called significant and to account for the multiple phenotypes tested for association with genetic ancestry, a false discovery rate was computed using QVALUE (Storey and Tibshirani 2003), and a threshold q value of 0.05 was established to declare significance.

Eight SNPs gave poor-quality genotype data during genotyping (rs1032143, rs1073321, rs12502036, rs1364394, rs153595, rs1854226, rs2171209, and rs7108371) and were discarded from the study. In addition, two SNPs that deviated significantly from HWE, after considering a multiple correction threshold of $p < 6 \times 10^{-4}$ (0.05/85)

at least in one study sample (rs7277342 and rs2596501), were also dropped from the analyses. Therefore, further analyses included the remaining 83 EuroAIMs, which had an average completion rate of 98.0 % (P_{25} – P_{75} =97.5–98.6 %), for a total of 734 samples (mean sample completion rate=98.0 %, P_{25} – P_{75} =98.8–100.0 %). As previous findings have showed a high correlation between individual ancestry estimates obtained with the full set of 93 EuroAIMs and with a reduced subset of as few as 65 markers (Pino-Yanes et al. 2011), the final number of EuroAIMs considered was still adequate for the purpose of the study. See Table S1 in the Online Resource for further details.

The comparison of genetic ancestries between asthmatic or atopic asthma patients with the control group did not reveal significant differences. Similarly, no association was found between genetic ancestry and a positive result neither for atopy, SPT or rhinitis (Table 2), nor with serum levels of total IgE or with pulmonary function, measured by the percentage of predicted FEV₁ (Table 2). Genetic ancestry was associated at nominal significance with a positive result for specific IgE among asthmatics ($p=0.004$) (Table 2). Although this comparison was still significant after considering all traits tested ($q=0.032$), this result was considered nonsignificant after adjusting for age as a covariate ($p=0.056$). We further explored the effect of age by subdividing the sample according to age quartiles (Q): ≤ 23 years (Q1), 24–32 years (Q2), 33–44 years (Q3), and >44 years (Q4). The results were not significant in any of the age groups, and the directionality of effects was different between subsamples, particularly between the group of individuals with ≤ 23 years versus all the rest of analyzed groups (≥ 24 years) (Table S2 in the Online Resource). In fact, genetic ancestry was significantly associated with a positive result for specific IgE among asthmatics with ≥ 24 years (p value=0.008 and $\beta=-29.82$). This result may point to a modifier effect of age in the association of genetic ancestry with a positive result for specific IgE among asthmatics. While several evidences suggest that demographic and environmental factors influence total and specific IgE, and that specific IgE levels decrease with the increasing of age (Omenaas et al. 1994; Borish et al. 2005), due to the limited power to detect association after sample was subdivided (<22 % on each subsample), future studies with larger sample sizes would be needed to determine if such effect is genuine.

Despite no evidence of association was found between genetic ancestry and asthma risk among Canary Islanders, we then determined whether any of the individual EuroAIMs was associated with asthma. Adjusting the association of each marker by ancestry differences between patients and controls, seven EuroAIMs were nominally associated ($0.005 \leq p$ value ≤ 0.042), although none of these associations was considered significant in the context of the multiple comparisons performed ($0.221 \leq q$ value ≤ 0.443) (Table S3 in the Online Resource).

Table 2 Association between genetic ancestry and asthmatic and atopic phenotypes

Clinical variable	Association <i>p</i> value (<i>q</i> value)		Beta
	Unadjusted	Adjusted	
Cases versus controls			
Asthma	0.379 (0.599)	0.667 ^a (0.889)	−3.21
Atopic asthma	0.501 (0.599)	0.861 ^a (0.958)	1.53
Asthmatic patients			
Atopy (positiveness)	0.408 (0.599)	0.473 ^b (0.889)	−5.96
SPT (positiveness)	0.363 (0.599)	0.344 ^b (0.889)	−7.99
Rhinitis (positiveness)	0.137 (0.548)	0.452 ^b (0.889)	6.51
Specific IgE (positiveness)	0.004 (0.032)	0.056 ^b (0.448)	−18.66
Total IgE levels (log scale)	0.524 (0.599)	0.958 ^c (0.958)	−0.13
FEV ₁ (%)	0.609 (0.609)	0.576 ^c (0.889)	43.95

^aLogistic regression model including gender and smoking habits as covariates

^bLogistic regression model including the age as a covariate

^cLinear regression model including the age as a covariate

In this study, we have explored for the first time whether genetic ancestry in Canary Islanders was associated with asthma and related traits. Despite the high prevalence of asthmatic and atopic symptoms estimated for this population compared to the rest of populations from Spain (Julia Serda et al. 2005), no association was found between genetic ancestry and asthma or related traits in Canary Islanders. Similarly, none of the individual EuroAIMs showed associations with asthma. These results are in agreement with previous observations based on self-reported information from grandparental place of birth, where subjects with two generations of ancestors born in the Canary Islands did not show increased asthma risk when compared with subjects with ancestors born elsewhere (Julia Serda et al. 2005).

Although the Canary Islands have particular climatic conditions, such as high humidity and stable warm temperatures that provide ideal conditions for mites and molds, which favor the emergence of atopic and asthmatic symptoms in the Canary Islands (Sanchez-Lerma et al. 2009), genetic factors are also be involved in this disease. According to the hygiene hypothesis (Strachan 1989), we speculated that genetic African ancestry in the Canary Islanders could provide a higher risk for asthma and atopy because the African ancestral population would have adapted to a pathogen-rich environment that no longer exists in the current urban society in the Canary Islands. In line with this, a recent study has shown that the pathogenic environment (mostly the exposure to helminthes) is the predominant driver of local adaptation, even stronger than climate (Fumagalli et al. 2011). In addition, allele frequencies in genes involved in immunity response have been strongly correlated with pathogenic environment (Fumagalli et al. 2011). Remarkably, it has been revealed that several genes associated at the genome-wide level with helminth diversity were also associated with susceptibility for asthma and atopy (Fumagalli et al. 2010). Under this scenario, the helminth-driven selective pressure is expected to favor individuals carrying alleles that allow a

strong Th2 response and, therefore, to promote the transmission and spread of asthma-susceptibility variants (Fumagalli et al. 2010).

Previous studies have examined the association of genetic ancestry and asthma susceptibility in recently admixed populations, observing a difference of 5–6 % in African ancestry between cases and controls in independent African descent populations from the USA and the Caribbean (Vergara et al. 2009; Flores et al. 2012). Our statistical power was adequate (≥ 80 %) to detect differences in North African admixture between cases and controls with effects even lower than the previously observed (up to 3.2 % of differences in North African admixture, i.e., a standardized effect of ≥ 0.2) (Fig. 1). However, in the hypothetical case that the genetic ancestry had a true association with susceptibility to asthma or related traits, the presence of smaller effects cannot be discarded. Similarly, it is likely that the use of a larger number of markers will allow estimating further ancestries among

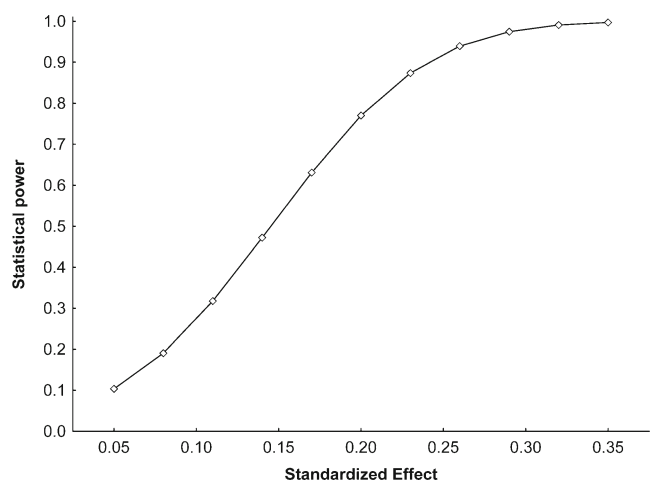


Fig. 1 Statistical power to detect differences in the genetic ancestry proportions by standardized effects for the sample size utilized (391 cases and 343 controls)

Canary Islanders. In this study, samples from different locations in Morocco were used as a proxy for the aboriginal population inhabiting the Canary Islands before the conquest. Although this is a reasonable assumption given the evidence from the historical records (Chejne 1974; Flores et al. 2001) and the numerous previous genetic studies (Rando et al. 1999; Flores et al. 2001, 2003, 2004; Alonso et al. 2005; Adams et al. 2008; Fregel et al. 2009), this obviously constitutes a simplification of the heterogeneous African influences that have affected the Canary Islands populations. Therefore, it is likely that further sampling of North African regions and the typing of additional markers might allow identifying other genetic influences in Canary Islanders, which could clarify if a true relationship between genetic ancestry and asthma exists in this population. In addition, another limitation of this study is that the socioeconomic status of individuals was not recorded, and therefore, its effects on asthma risk were not explored. Given that the Spanish National Health System guarantees free healthcare access to the whole population, not only for treatment and rehabilitation but also for the promotion of health and prevention of disease, a limited effect on asthma risk is expected.

In conclusion, no association was found between genetic ancestry and asthma or related traits among Canary Islanders. Larger studies examining more genetic variants would be needed to explore whether genetic ancestry has modest effects in increasing asthma risk in the Canary Islanders.

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Conflict of interest None.

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No association between genetic ancestry and susceptibility to asthma or atopy in Canary Islanders

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Table S1. Summary and quality control measures for the EuroAIMs successfully genotyped in this study.

rs#	Alleles	Chr.	Position ^a	CR (%) ^b	Reference allele				Hardy-Weinberg equilibrium <i>p</i> -value ^d			
					Allele	Frec. IBE	Frec. NWA	Delta ^c	IBE	NWA	Cases	Controls
rs11807062	A/C	1	3176394	97.6	C	0.16	0.38	0.22	0.133	0.118	0.526	0.293
rs495347	C/T	1	17909228	98.6	C	0.31	0.48	0.17	0.874	0.628	0.191	0.437
rs1416467	A/G	1	80470749	98.7	A	0.49	0.35	0.14	0.736	0.018	0.149	0.663
rs7552548	A/G	1	82775867	96.3	G	0.30	0.39	0.09	0.293	0.799	0.224	0.100
rs1890131	C/T	1	164329131	98.3	T	0.32	0.09	0.23	0.352	1.000	0.801	0.112
rs725974	G/T	1	167344909	96.5	G	0.18	0.43	0.25	0.817	0.452	0.486	1.000
rs2236876	A/G	1	169749143	97.1	A	0.30	0.43	0.13	0.523	0.459	0.102	0.807
rs2419063	A/G	1	186988492	97.7	G	0.09	0.18	0.09	0.422	0.440	0.149	0.343
rs1157492	C/T	1	211627299	97.8	C	0.45	0.25	0.20	0.376	0.330	0.515	0.345
rs6432110	A/T	2	10688616	98.0	T	0.44	0.39	0.05	0.029	0.128	0.353	0.428
rs4832640	C/T	2	19025771	97.0	C	0.25	0.43	0.18	0.787	0.622	0.068	0.167
rs1517407	A/G	2	63401982	98.1	G	0.48	0.36	0.12	0.013	0.292	0.040	0.912
rs6745653	C/T	2	97748515	98.8	T	0.11	0.26	0.15	1.000	0.362	1.000	0.820
rs10496610	C/G	2	123757682	99.2	G	0.24	0.07	0.17	0.314	0.020	0.881	0.045
rs3769005	C/G	2	136437098	97.9	C	0.47	0.60	0.13	0.417	0.206	0.305	0.581
rs1448314	A/G	2	223811705	98.1	A	0.08	0.20	0.12	0.504	0.276	0.570	0.119
rs2596834	C/T	3	10795067	95.0	C	0.51	0.43	0.08	0.585	0.138	0.467	0.002
rs822759	G/T	3	22948116	98.4	T	0.32	0.51	0.19	0.534	1.000	0.026	0.175
rs1879558	C/T	3	155137053	98.6	C	0.19	0.22	0.03	0.445	0.288	0.399	0.581
rs9290675	C/T	3	180489335	99.1	C	0.13	0.20	0.07	0.458	0.718	0.167	0.167
rs4686497	A/G	3	190124209	98.2	A	0.16	0.32	0.16	0.615	1.000	0.195	0.018
rs9861816	C/G	3	195649797	98.1	C	0.27	0.40	0.13	0.103	0.326	1.000	0.765
rs9328764	A/G	4	2143685	98.4	A	0.15	0.48	0.33	0.245	1.000	0.731	0.469
rs2014303	A/C	4	10262125	97.5	A	0.23	0.38	0.15	1.000	0.611	0.313	0.297
rs1873195	C/T	4	38713739	98.4	T	0.31	0.26	0.05	1.000	1.000	0.052	0.479
rs17443616	A/G	4	41063093	98.3	A	0.29	0.44	0.15	0.462	0.052	0.231	0.070
rs4555709	C/T	4	53867889	99.4	T	0.07	0.19	0.12	0.032	0.695	0.506	0.469
rs10516982	G/T	4	96963279	98.0	T	0.26	0.53	0.27	0.600	0.224	0.188	0.796
rs974020	C/T	4	117865302	98.4	C	0.31	0.22	0.09	0.050	0.485	0.447	0.779

rs1373557	G/T	4	167601812	98.8	T	0.21	0.24	0.03	0.258	0.041	0.057	0.857
rs2251432	A/G	4	191063741	97.8	A	0.21	0.28	0.07	0.609	0.763	0.612	0.393
rs16891982	C/G	5	33987450	99.2	C	0.17	0.66	0.49	0.128	0.280	0.904	0.407
rs33706	C/G	5	87540920	98.5	G	0.27	0.38	0.11	0.447	0.800	0.287	0.029
rs3822616	A/G	5	94828145	98.6	A	0.20	0.34	0.14	0.014	0.102	0.352	0.278
rs2804756	C/T	6	698586	99.1	T	0.08	0.10	0.02	0.007	0.099	0.293	0.568
rs10484547	C/G	6	29560753	99.5	C	0.06	0.15	0.09	0.765	1.000	1.000	1.000
rs2596501	C/T	6	31429190	95.8	C	0.34	0.36	0.02	6.6x10⁻⁵	0.285	0.003	0.008
rs2187684	C/T	6	32872697	97.9	C	0.37	0.33	0.04	0.168	0.174	0.635	0.068
rs756147	A/G	6	141672412	99.6	A	0.05	0.12	0.07	0.075	0.583	1.000	0.035
rs2097884	A/C	7	4125658	97.2	C	0.25	0.39	0.14	0.856	0.614	0.511	0.090
rs10486207	A/G	7	7884020	98.3	G	0.29	0.35	0.06	0.870	1.000	0.439	0.036
rs2905347	A/G	7	22393559	95.8	A	0.43	0.60	0.17	1.000	0.456	0.403	0.305
rs17864053	A/G	7	89801957	98.6	A	0.21	0.25	0.04	0.191	0.518	0.303	0.736
rs2219248	C/T	7	113965977	98.7	C	0.37	0.22	0.15	0.389	0.722	0.202	0.370
rs2367191	A/G	7	141571268	98.2	A	0.42	0.19	0.23	0.781	1.000	0.394	0.363
rs1922086	C/T	7	155515702	97.5	T	0.38	0.58	0.20	0.100	1.000	0.597	0.054
rs920590	C/T	8	19695441	98.0	C	0.35	0.48	0.13	0.303	0.811	0.504	0.216
rs10504924	C/T	8	94157437	97.6	T	0.09	0.12	0.03	0.830	0.215	0.367	0.770
rs2086085	A/C	9	1680761	99.3	C	0.10	0.16	0.06	0.065	0.343	0.015	0.417
rs1408794	A/G	9	12641340	94.6	A	0.46	0.57	0.11	0.248	0.805	0.014	0.002
rs10512122	C/G	9	81715524	98.5	C	0.15	0.35	0.20	0.796	0.586	0.489	0.201
rs10508372	A/G	10	9012024	99.6	A	0.08	0.19	0.11	0.825	0.698	0.757	0.755
rs1045873	A/C	10	25177778	98.4	C	0.31	0.19	0.12	0.814	0.684	0.899	0.005
rs7908825	C/G	10	75224547	97.4	C	0.31	0.29	0.02	0.472	0.144	0.276	0.560
rs10509384	A/G	10	78693188	97.1	G	0.31	0.12	0.19	1.000	0.194	1.000	0.092
rs379773	C/G	10	109905342	95.0	G	0.35	0.42	0.07	0.331	0.806	1.000	0.028
rs10509954	A/G	10	113658378	98.4	A	0.10	0.13	0.03	0.276	1.000	0.011	0.211
rs1560569	A/G	11	8896463	97.3	G	0.35	0.20	0.15	0.882	0.714	0.727	0.032
rs923031	A/C	11	15777602	98.2	A	0.48	0.34	0.14	0.280	0.587	0.472	0.498
rs4938377	G/T	11	116801502	98.0	G	0.06	0.04	0.02	0.107	1.000	0.037	0.136
rs2847502	C/T	11	119623708	98.9	T	0.30	0.38	0.08	0.809	1.000	0.273	0.175

rs1003306	A/T	12	2624458	97.9	A	0.32	0.49	0.17	0.282	1.000	0.064	1.000
rs7965049	A/G	12	7537044	97.3	A	0.25	0.35	0.10	0.649	0.419	0.365	0.232
rs998401	A/G	12	53641500	97.9	A	0.08	0.05	0.03	0.054	1.000	1.000	1.000
rs3809125	C/T	12	55130616	98.4	T	0.36	0.31	0.05	0.379	1.000	0.510	0.299
rs1582398	A/G	12	78624019	97.6	G	0.11	0.35	0.24	0.057	1.000	0.536	0.024
rs986642	C/G	13	56944263	98.8	G	0.25	0.11	0.14	0.478	0.171	0.023	0.124
rs7997100	C/T	13	67988075	98.3	T	0.35	0.39	0.04	0.302	0.445	0.910	0.001
rs10483853	A/G	14	72826052	98.5	G	0.22	0.47	0.25	0.145	0.633	0.113	1.000
rs1129038	C/T	15	26030454	98.4	C	0.65	0.95	0.30	0.941	0.006	0.734	1.000
rs7163907	C/T	15	73632152	98.8	C	0.29	0.34	0.05	0.628	1.000	0.219	0.319
rs10519269	A/C	15	77705433	96.3	C	0.10	0.23	0.13	0.247	0.737	0.366	0.452
rs1476162	A/G	17	8031808	98.6	G	0.12	0.31	0.19	0.434	0.779	0.308	1.000
rs1107820	C/T	17	41491195	97.2	C	0.28	0.16	0.12	0.802	0.358	0.157	0.659
rs2003092	A/G	17	59516509	97.8	G	0.26	0.41	0.15	0.484	0.618	0.240	0.526
rs959260	C/T	17	70881017	98.1	C	0.21	0.34	0.13	0.759	0.590	0.655	0.653
rs523776	C/T	18	7554299	98.2	T	0.24	0.40	0.16	0.852	0.804	0.372	0.661
rs2418844	A/G	18	26037261	97.4	G	0.48	0.41	0.07	0.787	0.618	0.682	0.180
rs959763	G/T	18	56797826	98.0	G	0.36	0.36	0.00	0.609	1.000	0.387	0.190
rs4892082	A/C	18	69051672	97.5	A	0.10	0.40	0.30	0.357	0.141	0.681	0.131
rs103294	C/T	19	59489660	98.6	T	0.17	0.06	0.11	0.636	1.000	0.540	0.650
rs202546	C/T	20	1611539	97.0	T	0.57	0.47	0.10	0.240	1.000	1.000	0.497
rs477627	A/G	20	47613465	97.5	A	0.19	0.21	0.02	0.583	1.000	0.093	0.726
rs7277342	A/C	21	29040845	95.0	A	0.32	0.48	0.16	5.4x10⁻²²	1.7 x10⁻⁴	7.8 x10⁻²⁴	1 x10⁻³⁰
rs969539	A/G	22	24942341	96.8	A	0.39	0.16	0.23	0.478	0.190	0.218	0.105

^aAccording to NCBI Build 35; ^bCompletion rate; ^cAllele frequency difference between Iberians and Northwest Africans; ^dSignificant *p*-values in boldface. IBE, Iberians; NWA, Northwest Africans.

Table S2. Regression models of association of ancestry with a positive result for specific IgE using different age cutoffs.

Age group	<i>p</i> -value	Beta
≤23 years (n=100)	0.803	4.00
24-32 years (n=77)	0.328	-16.92
33-44 years (n=79)	0.116	-36.05
>44 years (n=96)	0.131	-42.73

Table S3. Association of individual EuroAIMs with asthma.

rs	Chr.	Minor allele frequency		Association results ^a	
		Cases	Controls	<i>p</i> -value ^b	<i>q</i> -value
rs11807062	1	0.21	0.20	0.622	0.848
rs495347	1	0.31	0.30	0.642	0.848
rs1416467	1	0.45	0.49	0.091	0.545
rs7552548	1	0.31	0.37	0.014	0.258
rs1890131	1	0.28	0.25	0.240	0.623
rs725974	1	0.24	0.21	0.129	0.560
rs2236876	1	0.33	0.35	0.442	0.841
rs2419063	1	0.12	0.13	0.604	0.848
rs1157492	1	0.38	0.37	0.536	0.841
rs6432110	2	0.46	0.41	0.039	0.443
rs4832640	2	0.27	0.27	0.908	0.852
rs1517407	2	0.47	0.47	0.922	0.852
rs6745653	2	0.13	0.14	0.797	0.848
rs10496610	2	0.22	0.20	0.624	0.848
rs3769005	2	0.48	0.48	0.816	0.848
rs1448314	2	0.10	0.10	0.874	0.852
rs2596834	3	0.47	0.49	0.178	0.593
rs822759	3	0.36	0.33	0.318	0.688
rs1879558	3	0.19	0.18	0.735	0.848
rs9290675	3	0.13	0.14	0.528	0.841
rs4686497	3	0.23	0.19	0.073	0.536
rs9861816	3	0.26	0.24	0.563	0.847
rs9328764	4	0.18	0.18	0.920	0.852
rs2014303	4	0.23	0.20	0.123	0.560
rs1873195	4	0.27	0.26	0.889	0.852
rs17443616	4	0.31	0.35	0.096	0.545
rs4555709	4	0.09	0.08	0.733	0.848
rs10516982	4	0.31	0.31	0.970	0.862
rs974020	4	0.28	0.27	0.675	0.848
rs1373557	4	0.20	0.19	0.481	0.841
rs2251432	4	0.19	0.20	0.536	0.841
rs16891982	5	0.30	0.27	0.201	0.593
rs33706	5	0.31	0.31	0.778	0.848
rs3822616	5	0.21	0.18	0.258	0.634
rs2804756	6	0.08	0.11	0.080	0.536
rs10484547	6	0.09	0.09	0.810	0.848
rs2187684	6	0.31	0.34	0.303	0.688
rs756147	6	0.09	0.06	0.042	0.443
rs2097884	7	0.26	0.26	0.921	0.852
rs10486207	7	0.28	0.27	0.815	0.848
rs2905347	7	0.45	0.47	0.694	0.848
rs17864053	7	0.22	0.20	0.455	0.841
rs2219248	7	0.33	0.31	0.563	0.847

rs2367191	7	0.39	0.40	0.676	0.848
rs1922086	7	0.41	0.44	0.189	0.593
rs920590	8	0.36	0.42	0.009	0.221
rs10504924	8	0.13	0.10	0.170	0.593
rs2086085	9	0.14	0.11	0.237	0.623
rs1408794	9	0.46	0.47	0.810	0.848
rs10512122	9	0.18	0.22	0.056	0.516
rs10508372	10	0.09	0.10	0.682	0.848
rs1045873	10	0.28	0.27	0.851	0.852
rs7908825	10	0.30	0.37	0.008	0.221
rs10509384	10	0.27	0.27	0.946	0.861
rs379773	10	0.33	0.36	0.315	0.688
rs10509954	10	0.10	0.13	0.193	0.593
rs1560569	11	0.33	0.33	0.906	0.852
rs923031	11	0.46	0.42	0.146	0.567
rs4938377	11	0.08	0.08	0.749	0.848
rs2847502	11	0.30	0.33	0.160	0.590
rs1003306	12	0.38	0.38	0.924	0.852
rs7965049	12	0.28	0.24	0.138	0.565
rs998401	12	0.07	0.06	0.477	0.841
rs3809125	12	0.37	0.39	0.309	0.688
rs1582398	12	0.15	0.18	0.077	0.536
rs986642	13	0.25	0.20	0.019	0.280
rs7997100	13	0.34	0.34	0.963	0.862
rs10483853	14	0.26	0.27	0.667	0.848
rs1129038	15	0.35	0.28	0.005	0.221
rs7163907	15	0.35	0.32	0.245	0.623
rs10519269	15	0.13	0.13	0.741	0.848
rs1476162	17	0.15	0.17	0.237	0.623
rs1107820	17	0.23	0.25	0.497	0.841
rs2003092	17	0.32	0.32	0.809	0.848
rs959260	17	0.22	0.24	0.331	0.688
rs523776	18	0.22	0.25	0.121	0.560
rs2418844	18	0.49	0.48	0.507	0.841
rs959763	18	0.38	0.36	0.468	0.841
rs4892082	18	0.15	0.18	0.105	0.553
rs103294	19	0.15	0.14	0.705	0.848
rs202546	20	0.44	0.42	0.617	0.848
rs477627	20	0.21	0.20	0.456	0.841
rs969539	22	0.36	0.34	0.336	0.688

^aSignificant associations in boldface; ^bAdjusted for genetic ancestry estimates.