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Differential associations of allergic disease genetic variants with developmental profiles of eczema, wheeze and rhinitis

Hannah Clark^{1*} BSc (Hons), Raquel Granell^{1*} PhD, John A Curtin² PhD, Danielle Belgrave³ PhD, Angela Simpson² MD PhD, Clare Murray² MD, A John Henderson¹ MD, Adnan Custovic³ MD PhD FAAAI, Lavinia Paternoster¹ PhD

* Joint first authors

¹ MRC Integrative Epidemiology Unit (IEU), Population Health Sciences, Bristol Medical School, University of Bristol, Bristol, UK

² Division of Infection, Immunity and Respiratory Medicine, School of Biological Sciences, The University of Manchester, Manchester Academic Health Science Centre, and Manchester University NHS Foundation Trust, UK

³ Section of Paediatrics, Department of Medicine, Imperial College London, UK

Corresponding author:

Dr Raquel Granell, MRC Integrative Epidemiology Unit (IEU), Population Health Sciences, Bristol Medical School, University of Bristol Email: Raquel.Granell@bristol.ac.uk Tel: +44 (0)117 10105

Short running tile: Genetic markers and latent profiles of allergic disease

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Abstract

Background

Allergic diseases (eczema, wheeze and rhinitis) in children often present as heterogeneous phenotypes. Understanding genetic associations of specific patterns of symptoms might facilitate understanding of the underlying biological mechanisms.

Objective

To examine associations between allergic disease-related variants identified in a recent genome-wide association study and latent classes of allergic diseases (LCADs) in two population-based birth cohorts.

Methods

Eight previously defined LCADs between 1 and 11 years: 'No disease', 'Atopic march', 'Persistent eczema and wheeze', 'Persistent eczema with later-onset rhinitis', 'Persistent wheeze with later-onset rhinitis', 'Transient wheeze', 'Eczema only' and 'Rhinitis only' were used as the study outcome.

Weighted multinomial logistic regression was used to estimate associations between 135 SNPs (and a polygenic risk score, PRS) and LCADs among 6,345 individuals from The Avon Longitudinal Study of Parents and Children (ALSPAC). Heterogeneity across LCADs was assessed before and after Bonferroni correction. Results were replicated in Manchester Asthma and Allergy Study (MAAS) (n=896) and pooled in a meta-analysis.

Results

We found strong evidence for differential genetic associations across the LCADs; pooled PRS heterogeneity $p\text{-value}=3.3\times 10^{-14}$, excluding 'no disease' class. The associations between the PRS and LCADs in MAAS were remarkably similar to ALSPAC. Two SNPs (a protein truncating variant in *FLG* and a SNP within an intron of *GSDMB*) had evidence for differential association (pooled $p\text{-values}\leq 0.006$). The *FLG* locus was differentially associated across LCADs that included eczema, with stronger associations for LCADs with comorbid wheeze and rhinitis. The *GSDMB* locus in contrast was equally associated across LCADs that included wheeze.

Conclusions & Clinical Relevance

We have shown complex, but distinct patterns of genetic associations with LCADs, suggesting that heterogeneous mechanisms underlie individual disease trajectories. Establishing the combination of allergic diseases with which each genetic variant is associated may inform therapeutic development and/or predictive modelling.

Abbreviations

ALSPAC	Avon Longitudinal Study of Parents and Children
CI	Confidence interval
<i>FLG</i>	Filaggrin
<i>GSDMB</i>	Gasdermin B
GWAS	Genome-wide association study
INFO	Imputation quality score
LCADs	Latent classes of Allergic Diseases (eczema, wheeze and rhinitis)
LO	Later-onset
MAAS	Manchester Asthma and Allergy Study
ND	No disease
PRS	Polygenic risk score
RA	Risk allele
RAF	Risk allele frequency
RRR	Relative risk ratio
SNP	Single Nucleotide Polymorphism

Introduction

Although asthma, eczema (atopic dermatitis) and allergic rhinitis (AR) are diagnosed clinically as distinct conditions, their co-occurrence is well acknowledged (1). Twin heritability estimates vary vastly, the range has been reported to be between 35- 95% for asthma, 33-91% for AR and 71-84%

for eczema (2), and estimates of the genetic correlation between them are also high: 0.55 between asthma and eczema, 0.47 between asthma and rhinitis and 0.62 between eczema and rhinitis (3).

This supports shared genetic factors between all three conditions, but also genetic factors that are specific to each. Although we are starting to uncover both shared and specific genetic risk factors, understanding more precisely which loci predispose individuals to particular patterns of symptoms should translate into clinical benefits, such as personalised approaches to disease management and identification of novel therapeutic targets (4).

Children often present with broad and heterogeneous phenotypes of allergic diseases (5, 6). For example, some cases have mild symptoms affecting a single organ/system, but others have more severe symptoms encompassing multiple organs (e.g. skin, upper and lower airways). The term 'atopic march' has been proposed for a specific pattern of progression from childhood eczema to subsequent asthma and AR (7). We have previously used Bayesian machine learning methods to model the developmental profiles of eczema, wheeze and rhinitis during childhood in two population-based birth cohorts: the Avon Longitudinal Study of Parent and Children (ALSPAC) and the Manchester Asthma and Allergy Study (MAAS) (8). Eight latent classes were identified, each characterised by unique patterns of diseases over time: 'No disease' (51.3% of the children), 'Atopic march' (3.1%), 'Persistent eczema and wheeze' (2.7%), 'Persistent eczema with later-onset rhinitis' (4.7%), 'Persistent wheeze with later-onset rhinitis' (5.7%), 'Transient wheeze' (7.7%), 'Eczema only' (15.3%) and 'Rhinitis only' (9.6%).

A recent genome wide association study (GWAS) (9) identified 136 independent risk variants ($P < 3 \times 10^{-8}$) for asthma, eczema and AR, including 73 novel variants, and went on to link the pathophysiology of allergic diseases to 132 neighbouring genes. Although this study was designed to detect risk variants shared across allergic diseases, six SNPs in five established risk loci (rs61816761, rs921650, rs115288876, rs12470864, rs6594499 and rs61839660) were identified as having some

disease-specific effects. In this study, we aimed to examine the associations between these 136 genetic variants associated with allergic diseases (9) and the developmental profiles of eczema, wheeze, and rhinitis (“Latent Classes of Allergic Diseases”, LCADs) we previously described (8) to better understand the genetic heterogeneity between the allergic disease class profiles.

Methods

Study populations

ALSPAC is a population-based birth cohort which recruited 14,541 pregnant women with expected delivery dates between 1st April 1991 and 31st December 1992. The study protocol was described previously (10, 11). Ethical approval was obtained from the ALSPAC Ethics and Law Committee and local research ethics committees. The study website contains details of all the data that is available through a fully searchable data dictionary: <http://www.bris.ac.uk/alspac/researchers/data-access/data-dictionary/>.

MAAS is an unselected birth cohort established in 1995 in Manchester (12). It included 1,184 children born between February 1996 and April 1998. Participants were recruited prenatally and followed prospectively (13). The study was approved by the Local Research Ethics Committee.

Latent Classes of Allergic Diseases (LCADs)

Eight LCADs were previously identified using a latent disease profile model in a Bayesian machine learning modelling framework applied to longitudinal individual reports of eczema, wheezing and rhinitis collected at multiple time points between ages 1 and 11 years using joint ALSPAC and MAAS data (8, 14): ‘No disease’, ‘Atopic march’, ‘Persistent eczema and wheeze’, ‘Persistent eczema with later-onset rhinitis’, ‘Persistent wheeze with later-onset rhinitis’, ‘Transient wheeze’, ‘Eczema only’, ‘Rhinitis only’; these are described in more detail in the **Supplemental Material**. Posterior probabilities of class membership (mean probabilities between 0.76 and 0.94 in joint ALSPAC and MAAS data), were used as the outcome in this study (Table S2 in Belgrave et al. (8)).

Genotyping

In ALSPAC, we used the Illumina HumanHap550 quad chip and imputed against the Dec 2013 Version 1 Phase 3 release of 1000 Genomes reference haplotypes (15) using IMPUTE2 (16). Participants with genetic evidence of non-European ancestry were excluded before imputation. Further details describing the QC and imputation procedure of the ALSPAC genetic data can be found here (17). In MAAS, DNA samples were genotyped using Illumina 610 quad and imputed using the 1,000 Genomes Phase 3 integrated variant set reference (18).

Genetic Risk Score

Per-allele SNP dosages were extracted in ALSPAC for the 136 SNPs identified in previous GWAS (9), and proxies were identified for SNPs with imputation quality <0.80 (**Table S1**). All 136 relevant SNPs were available; SNP rs34290285 was excluded due to poor imputation quality and lack of adequate proxy. All 135 SNPs included in the ALSPAC score were available in MAAS; SNP rs10305290 was monomorphic and hence excluded from the MAAS score (see **Supplemental Material**). A weighted polygenic risk score (PRS) including 135 SNPs with $\text{INFO} \geq 0.77$ was derived, weighted according to the overall effect sizes observed in (9). The standardised PRS represented a per 1-standard deviation increase in the weighted risk score (details in **Supplemental Material**). Individual SNPs were also analysed separately, where each SNP was coded as the dosage of the risk allele. Following investigation of individual SNPs, a modified PRS, which excluded any SNPs with evidence for differential association, was generated to test for any residual effects amongst the remaining SNPs.

Association analysis

For the PRS and each SNP, a multinomial logistic regression was conducted, and relative risk ratios (RRR; also known as multinomial odd ratio) with corresponding 95% confidence intervals (Cis) for associations of the PRS or SNP dosages with the LCADs were reported. All regressions were weighted by posterior membership probabilities (the probabilities that a child belongs to each class)

to account for uncertainty in class membership. 'No disease' class was used as the baseline group.

Heterogeneity p-values from chi-square tests excluding (degrees of freedom=6) and including (degrees of freedom=7) the 'No disease' class were generated (using post-estimation *test* command) to test for both associations with any latent class and differential associations across LCADs. To further assess heterogeneity, pairwise tests among disease latent classes were performed when omnibus test for differential associations provided nominal evidence for overall heterogeneity.

In the single SNP analysis, a Bonferroni-corrected p value threshold was calculated ($p=0.05/135=3.7\times10^{-4}$) to control for type 1 error. For six SNPs reported as disease-specific in GWAS (rs61816761, rs921650, rs115288876, rs12470864, rs6594499 and rs61839660) (9), a less stringent p-value threshold of 8.3×10^{-3} ($0.05/6$) was also used.

To assess the level of power in the analysis of ALSPAC data, power calculations were conducted for associations with individual phenotypes (details in the **Supplemental Material** and **Table S2**).

The associations of the nominal SNPs ($p<0.05$) identified in ALSPAC, the disease-specific SNPs reported in Ferreira's GWAS (9) and the genetic risk scores (original and modified versions) with LCADs were then tested in MAAS. Pooled estimates and overall test for heterogeneity between subgroups (including and excluding 'No disease' class) were derived. All statistical analysis was conducted with Stata 15.0 (19).

Results

Characteristics of the study populations

A total of 6,345 participants in ALSPAC and 896 in MAAS had both genetic and outcome data.

Characteristics of the study populations are presented in **Table 1**.

Similar proportions of males (51.1%, 53.8%), lower social class (43.9%, 36.9%) and lower maternal educational level (57.5%, 55.3%) were reported in ALSPAC and MAAS respectively (for more details see **Supplemental Material**). Parents of participants excluded from the study because of missing data tended to be from the lower social class ($p=3.54\times 10^{-29}$) and lower maternal educational level ($p=1.31\times 10^{-62}$) in ALSPAC, as seen before (20). Marginal evidence for lower social class among the excluded individual was observed in MAAS ($p=0.10$), but not for lower maternal educational level ($p=0.39$). No differences were found between proportions of LCADs in the study populations vs. the excluded samples in either cohort (**Table 1**).

Discovery population (ALSPAC)

Standardised Genetic Score (original)

There was strong evidence for an association between the standardised PRS and the LCADs (het. p -value= 3.2×10^{-30} including 'No disease' class) and strong evidence for differential association with the PRS across the latent classes (het p -value = 3.3×10^{-13} excluding 'No disease' class), with stronger associations observed for classes with more than one disease (**Figure 1** and **Table S3**). Pairwise tests provide further evidence for differential associations between multiple-disease and single-disease classes: p -values $\leq 9.68\times 10^{-10}$ for 'atopic march' vs 'transient wheeze', 'eczema only' and 'rhinitis only' (**Table S4**).

Individual SNP associations

Table S5 reports individual associations for all 135 individual SNPs with LCADs. Two SNPs, rs61816761 (a protein truncating variant in *FLG*) and rs921650 (within an intron of *GSDMB*), showed strong evidence for differential association between the LCADs (p -values 0.002 and 1.42×10^{-5} respectively, excluding 'No disease' class) (**Table S5** and **Figures 2 & 3**). Pairwise tests provide further evidence of these differential associations: p -values $\leq 8.8\times 10^{-3}$ for 'transient wheeze' vs. 'persistent eczema LO rhinitis', 'eczema only' and 'rhinitis only' in the association between rs921650 (*GSDMB*)

and the LCADs; p-values $\leq 3.0 \times 10^{-3}$ for 'atopic march' vs. 'persistent wheeze LO rhinitis', 'transient wheeze' and 'rhinitis only' in the associations between rs61816761 (*FLG*) and the LCADs (**Table S6**).

A modified PRS which excluded these two SNPs still showed strong evidence for differential association (heterogeneity p-value = 9.6×10^{-12} , **Table S3, Figure 4**), suggesting that there are additional differential associations amongst the SNPs which did not meet our significance threshold. Four additional SNPs (rs11652139, rs479844, rs6990534, rs5743618) showed nominal evidence of differential association across the LCADs (heterogeneity p-values < 0.05 , **Table S5**). Pairwise tests provide further evidence of these differential associations. For example: p-values $\leq 6.8 \times 10^{-3}$ for 'eczema only' vs. 'atopic march', 'persistent wheeze LO rhinitis' and 'transient wheeze' in the association between rs11652139 and the LCADs; p-values ≤ 0.007 for 'atopic march' vs. 'transient wheeze' and 'eczema only' in the association between rs6990534 and the LCADs (**Table S6**).

Replication in MAAS and Pooled Estimates

Standardised Genetic Scores (original and modified)

The associations between the PRS and LCADs in MAAS were remarkably similar to ALSPAC (**Table S7** and **Figure 1**). In the pooled analysis, there was strong evidence for differential association across LCADs (excluding the baseline class; p-value = 3.27×10^{-14}). To investigate the nature of these differences we compared ORs and CIs across the 7 classes. There was evidence for a large effect on 'Atopic march' (pooled RRR = 1.99, 95% CI 1.74-2.29), 'Persistent eczema with late-onset rhinitis' (1.51, 1.35 to 1.68), 'Persistent wheeze with late-onset rhinitis' (1.44, 1.30 to 1.60) and 'Persistent eczema and wheeze' (1.39, 1.22 to 1.60), per 1-SD increase in the per-risk-allele standardised PRS compared to 'No disease'. A modest increased risk was observed for LCADs affecting single organ/system: 'Transient wheeze' (1.11, 1.02 to 1.21), 'Eczema only' (1.16, 1.08 to 1.24) and 'Rhinitis only' (1.21, 1.12 to 1.31), per unit increase in the PRS compared to 'No disease' class (**Table 2, Figure 1**).

Omitting SNPs rs61816761 (a protein truncating variant in *FLG*) and rs921650 (within an intron of *GSDMB*) from original standardised PRS slightly attenuated the associations across LCADs (pooled het. p-value = 3.83×10^{-12} including 'No disease', 1.07×10^{-12} excluding 'No disease' class) (**Table 2, Figure 4**).

Individual SNP associations

We tested six nominally associated individual SNPs from ALSPAC ($p < 0.05$) in MAAS (**Table S8**).

Pooled results are shown in **Table 3**. We found moderate evidence for differential associations across LCADs (excluding the baseline class) for SNPs rs61816761, rs921650 and rs11652139 (pooled heterogeneity p-values ≤ 0.006). To investigate the nature of these differences we compared ORs and CIs across the 7 LCADs. There was evidence for a large effect on 'Atopic march' (pooled RRR=3.01, 95%CI 1.79 to 5.08), 'Persistent eczema and wheeze' (1.87, 1.01 to 3.48), 'Persistent eczema with late-onset rhinitis' (2.30, 1.45 to 3.65) and 'Eczema only' (1.63, 1.15 to 2.30), per increased A-allele of rs61816761 (a protein truncating variant in *FLG*) (**Table 3, Figure 2**). Little or no evidence of association was seen for other LCADs. We found evidence for a large effect on 'Atopic march' (pooled RRR=1.36, 95%CI 1.13 to 1.65), 'Persistent eczema and wheeze' (1.37, 1.13 to 1.66), 'Persistent wheeze with late-onset rhinitis' (1.36, 1.18 to 1.57) and 'Transient wheeze' (1.24, 1.10 to 1.40), per increased A-allele of rs921650 (within an intron of *GSDMB*), compared to 'No disease' (**Table 3, Figure 3**). Little or no evidence of association was seen for other LCADs.

The pattern of associations for SNP rs11652139 was very similar to SNP rs921650 (within an intron of *GSDMB*) (**Table 3, Figure S1**). For SNP rs479844, we found evidence for a moderate effect on 'Persistent eczema with late-onset rhinitis' (pooled RRR 1.21, 95% CI 1.04 to 1.41) and 'Eczema only' (1.14, 1.03 to 1.26) per increased G-allele, when compared to 'No disease' class (**Figure S2**). We observed evidence for a moderate effect on 'Atopic march' per increased A-allele of SNP rs6990534 (1.33, 1.09 to 1.62) (**Figure S3**) and per increased C-allele of SNP rs5743618 (1.31, 1.04 to 1.67); SNP rs5743618 showed evidence for a moderate effect on 'Rhinitis only' (1.19, 1.04 to 1.36) (**Figure S4**).

Discussion

We examined the associations between 135 independent risk variants for allergic diseases identified in a recent GWAS (9) and LCADs which we previously described in two independent birth cohorts (8). SNP rs61816761 (a protein truncating variant in *FLG* gene) and SNP rs921650 (within an intron of *GSDMB*) which were previously identified as having disease-specific effects (9), were differentially associated with distinct LCADs. The *FLG* locus was associated with all LCADs that included eczema, with stronger associations seen for those classes with comorbid wheeze and/or rhinitis. In contrast, the strength of the association for *GSDMB* locus was equal for all LCADs which included wheeze, with no additional risk for co-morbid eczema and/or rhinitis. An allergic disease polygenic risk score (including all 135 SNPs and after excluding SNPs rs61816761 and rs921650) showed strong evidence of heterogeneity across the LCADs, suggesting there are further individual SNPs with differential association.

rs61816761 (*FLG*)

rs61816761 (also known as R501X) has long been linked with eczema (21). In Ferreira's GWAS (9), the risk allele [A] for SNP rs61816761, which is located on chromosome 1 in the *FLG* gene, was 1.32-fold more common in individuals experiencing eczema-only symptoms compared with individuals experiencing only AR. Similarly, a 1.26-fold difference was observed when comparing individuals experiencing only eczema with individuals with only asthma. This indicated that this SNP predisposes to eczema more strongly than to either of the other two conditions. In the present study, we found evidence for a large effect on each of the four latent classes including eczema, but no association with classes which did not include eczema. We observed the strongest association with 'Atopic march' (pooled RRR 3.01). This is in line with a recent meta-analysis which found that the two *FLG* mutations combined (R501X and *FLG* 2282del4) were associated with Atopic march (22).

It is tempting to speculate that genotyping patients with eczema for *FLG* mutations could help to identify individuals who may benefit from interventions targeted at prevention of progression to the atopic march (23). However, the difference in odds between the 'Atopic march' versus 'Eczema only' classes is of insufficient magnitude to be of a clinical predictive value. It is also important to note that whilst *FLG* mutations (including R501X), play a role in predisposing individuals of Caucasian ancestry to eczema, such mutations have not been seen in other ethnic groups (24).

rs921650 (*GSDMB*)

In Ferreira's GWAS (9), the risk allele [A] for SNP rs921650 on chromosome 17q21.1, was 1.08-fold more common in asthma-only compared with eczema-only cases. It was also 1.04-fold more common in asthma-only compared with AR-only cases, thus representing a stronger risk factor for asthma compared with both eczema and AR. In the present study, we found evidence for a large effect on all four wheeze-related classes per increased A-allele of rs921650. However, unlike for associations with *FLG* locus, where we observed increasing odds for classes with comorbid wheeze and rhinitis (ORs from 1.87 to 3.01) when compared to 'Eczema only' class (OR 1.63), for associations with *GSDMB* locus we did not observe increasing odds for classes with comorbid eczema and rhinitis (ORs from 1.36 to 1.37), when compared to 'Transient wheeze' class (OR 1.24). These results suggest that there is no additional risk of co-morbid conditions compared to wheeze alone in association with *GSDMB*.

rs921650 is located within an intron of *GSDMB* (gasdermin B) gene (also known as *GSDML*) (25, 26), likely affecting the expression of genes in the 17q21 locus. SNPs in the 17q21 locus have been associated with childhood asthma, and there is evidence that common SNPs in this region are associated with persistent wheeze (27). Results of our analysis are consistent with this evidence, with the increased risk of three classes characterised by wheeze persistence ('Persistent wheeze with late-onset rhinitis', 'Persistent eczema and wheeze' and 'Atopic march') per increased A-allele

of rs921650. However, our study has also shown the evidence for an association of rs921650 with transient wheeze, which has not been observed in previous studies (27). Given that transient wheeze in the absence of other allergic symptoms (such as eczema) is mostly virus-induced, our results are in agreement with observations from recent studies which provided evidence that polymorphisms on chromosome 17q21 regulate ICAM1 expression and thus may affect the frequency and severity of rhinovirus infection and early childhood wheezing illness (28), that impaired anti-virus immunity is associated with early-life wheezing (29), and that early-life antibiotic use (a proxy for impaired innate anti-virus immunity) is associated with 17q21 polymorphisms (30). Given this mechanistic (28, 31) and epidemiological evidence (32), the association of rs921650 with transient wheezing is not unexpected. One reason why previous studies have not observed such association may be because more homogeneous disease subtypes with clearer genetic association can be discovered when using more holistic information about multiple symptoms (which was the approach taken in the current study (8)), compared to studies which focus on wheeze as a single symptom (which was the approach taken in most previous latent class analyses (27, 33)).

Interpretation of the Polygenic Risk Score (PRS)

We report strong evidence of heterogeneity of associations across the LCADs (pooled het. p-value=3.3x10⁻¹⁴ excluding 'No disease' class). The strongest association was seen for 'Atopic march' (pooled RRR 1.99, 1.74 to 2.29). Our results suggest that although the presence of multiple risk alleles increases the risk of all latent classes, this is strongest for the 'Atopic march', and weakest for the classes characterised by the presence of single symptoms. This may indicate that the greater the standardised per-allele weighted PRS, the greater the likelihood of developing multiple comorbidities. After excluding SNPs rs61816761 and rs921650 this effect was still observed (pooled het. p-value=1.1x10⁻¹²). As none of these 133 individual SNPs showed good evidence for differential association, we can assume that there are some unidentified differential single SNP associations, which we did not have power to detect. Therefore, studies of larger sample sizes should be designed to investigate this further.

Strengths and Limitations

The prevalence of rhinitis-related classes was higher in MAAS compared to ALSPAC (8). However, in the original study, similar latent profiles were identified in MAAS and ALSPAC, suggesting consistent patterns across the two populations (8). Furthermore, we have used latent classes derived from joint modelling, which accounted for these differences and increased the resolution of the identified latent classes (8).

The restricted sample (after removal of individuals who had missing genetic and/or outcome data) resulted in a loss of participants from lower social class and maternal educational level. Selection bias can be introduced if the individuals from a lower social class had missing data because of factors related to the outcome. Issues such as this can also impact on the generalisability of the results.

However, despite the loss of individuals from lower social class, there was still a good representation in the included study samples (43.9% in ALSPAC and 36.9% in MAAS).

ALSPAC was part of the meta-analysis by Ferreira et al. that was used to identify the 136 SNPs; this could have led to some overfitting in our ALSPAC analysis. However, our sample only makes up 0.6% of the sample used by Ferreira et al. and our main analysis focuses on the comparison between case (disease) groups, rather than the comparison of combined cases versus controls (from which the beta values were taken) so any overfitting is likely to be negligible.

It is likely that combining the SNPs in a composite score increased the power sufficiently to detect an overall effect, even when individual SNPs showed little evidence of association. However, grouping together variants which may individually have different effects might act to attenuate or obscure individual effects.

Whilst understanding more about the role that the 135 genetic variants identified to date by Ferreira et al. play in allergic disease profiles is beneficial, a limitation of the Ferreira approach is that it is better powered to detect homogenous as opposed to heterogeneous effects and so there may be additional SNPs with interesting heterogeneous effects that have yet to be identified. However, our results are a good proof of principle of the latent disease profile method as a good way to characterise heterogeneous effects across the allergic disease classes. As carefully phenotyped GWAS sample sizes increase it may be possible to undertake such latent disease profile analyses in a GWAS context with better power to detect novel loci with heterogeneous effects.

Conclusions

We found strong evidence for differential genetic associations across different developmental profiles of eczema, wheeze and rhinitis, which were remarkably consistent across two cohorts. Two polymorphisms (a protein truncating variant in *FLG* and a SNP within an intron of *GSDMB*) had evidence for distinct patterns of association. The *FLG* locus was associated with all profiles that included eczema, but with stronger associations for those with comorbid wheeze and rhinitis. The *GSDMB* locus in contrast was associated with all profiles which included wheeze (including transient wheezing), but with no additional risk of co-morbid conditions. This emphasises the likely complex and heterogeneous mechanisms underlying within-individual disease trajectories and demonstrates the need for future studies to take account of the complex nature of these associations. Our analysis using a PRS also demonstrates that there is likely to be additional heterogeneity amongst other SNPs, that this study did not have power to detect. This approach to disentangling the complex nature of multi-trait aetiology might be a promising one that should be used in future larger studies.

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TABLES

Table 1. Characteristics of the study populations in ALSPAC and MAAS cohorts

	Study sample §		Excluded sample (no data on outcome and/or genetics)		
Characteristics	N with characteristic (%)	Total N	N with characteristic (%)	Total N	P-value ‡
ALSPAC					
Gender (male)	3244 (51.1)	6345	4375 (51.6)	8479	0.575
Lower combined social class *	2617 (43.9)	5957	3017 (54.4)	5547	3.54E-29
Lower maternal educational level †	3577 (57.5)	6220	4466 (71.8)	6218	1.31E-62
Allergic diseases latent classes II					
No Disease	3175 (50.0)		1150 (49.8)		(reference)
Atopic March	175 (2.8)		59 (2.5)		0.621
Persistent eczema and wheeze	181 (2.9)		72 (3.1)		0.508
Persistent eczema with late-onset rhinitis	307 (4.8)	6345	111 (4.8)	2309	0.991
Persistent wheeze with late-onset rhinitis	348 (5.5)		149 (6.5)		0.107
Transient wheeze	534 (8.4)		195 (8.4)		0.939
Eczema only	948 (15.0)		323 (14.0)		0.394
Rhinitis only	677 (10.7)		250 (10.8)		0.820
MAAS					
Gender (male)	482 (53.8)	896	186 (55.7)	287	0.305
Lower combined social class *	225 (36.9)	610	60 (43.2)	139	0.101
Lower maternal educational level †	359 (55.3)	649	45 (57.7)	78	0.392
Allergic diseases latent classes II					
No Disease	322 (35.9)		87 (38.9)		(reference)
Atopic March	55 (6.1)		11 (5.1)		0.471
Persistent eczema and wheeze	46 (5.1)		10 (4.6)		0.611
Persistent eczema with late-onset rhinitis	73 (8.1)	896	18 (7.9)	223	0.710
Persistent wheeze with late-onset rhinitis	81 (9.0)		18 (8.2)		0.557
Transient wheeze	65 (7.3)		15 (6.8)		0.644
Eczema only	141 (15.7)		34 (15.3)		0.634
Rhinitis only	114 (12.8)		29 (13.1)		0.836

* Mother and partner level of occupation (manual vs non-manual) in ALSPAC, combined socio-economic status (not working, routine, intermediate vs managerial) in MAAS

† In ALSPAC, mother educated to the General Certificate of Education level (school-leaving certificate) or lower; In MAAS, mother not educated to UK A or As level (data from follow-up questionnaire at 13-16 years).

‡ P-values are from chi-squared test for binary variables and logistic regression for latent variables (baseline group is 'no disease' class), comparing 'included' vs. 'excluded' individuals

§ Participants with SNP data and outcome data available

II Proportions were weighted by posterior membership probabilities

Table 2. ALSPAC-MAAS pooled estimates of the associations between standardised genetic scores and profile latent classes before and after excluding SNPs rs61816761 (*FLG*) and rs921650 (*GSDMB*).

ALSPAC-MAAS Pooled Multinomial Odds Ratio (95% CI)		
Allergic diseases latent classes	Stand. Score	Stand. Score excluding <i>FLG</i> and <i>GSDMB</i> SNPs
Atopic March	1.99 (1.74,2.29)	1.90 (1.66,2.18)
Persistent eczema and wheeze	1.39 (1.22,1.60)	1.35 (1.17,1.54)
Persistent eczema with late-onset rhinitis	1.51 (1.35,1.68)	1.49 (1.34,1.66)
Persistent wheeze with late-onset rhinitis	1.44 (1.30,1.60)	1.42 (1.28,1.57)
Transient wheeze	1.11 (1.02,1.21)	1.09 (1.00,1.19)
Eczema only	1.16 (1.08,1.24)	1.15 (1.07,1.23)
Rhinitis only	1.21 (1.12,1.31)	1.21 (1.12,1.31)
P-value for differential association*	3.27E-14	1.07E-12
P-value for any association†	1.22E-13	3.83E-12

* Overall test for heterogeneity between classes excluding the baseline class of 'no disease'

† Overall test for heterogeneity between classes including the baseline class of 'no disease' (Pooled multinomial Odds Ratio =1)

Table 3. ALSPAC-MAAS pooled estimates of the associations between the top six nominal SNPs (heterogeneity p-value excluding the baseline ‘no disease’ class <0.05) and allergic diseases latent classes.

ALSPAC-MAAS Pooled Multinomial Odds Ratio (95% CI)							
SNP[RA]	rs61816761[A]	rs921650[A]	rs11652139[A]	rs479844[G]	rs6990534[A]	rs5743618[C]	
Nearby Gene	<i>FLG</i>	<i>GSDMB</i>					
Allergic diseases latent classes							
Atopic March	3.01 (1.79,5.08)	1.36 (1.13,1.65)	1.47 (1.20,1.80)	1.12 (0.92,1.36)	1.33 (1.09,1.62)	1.31 (1.04,1.67)	
Persistent eczema and wheeze	1.87 (1.01,3.48)	1.37 (1.13,1.66)	1.22 (1.00,1.49)	1.19 (0.98,1.44)	0.92 (0.74,1.14)	0.98 (0.78,1.22)	
Persistent eczema with late-onset rhinitis	2.30 (1.45,3.65)	0.95 (0.82,1.11)	1.06 (0.91,1.24)	1.21 (1.04,1.41)	1.08 (0.91,1.27)	1.06 (0.89, 1.26)	
Persistent wheeze with late-onset rhinitis	0.87 (0.47,1.62)	1.36 (1.18,1.57)	1.22 (1.05,1.42)	0.95 (0.82,1.10)	1.03(0.88,1.21)	1.13 (0.96,1.35)	
Transient wheeze	1.00 (0.60,1.66)	1.24 (1.10,1.40)	1.15 (1.02,1.31)	1.02 (0.90,1.16)	0.93 (0.81,1.07)	0.97 (0.84, 1.13)	
Eczema only	1.63 (1.15,2.30)	0.99 (0.90,1.09)	0.98 (0.88,1.08)	1.14 (1.03,1.26)	0.96 (0.86,1.07)	0.99 (0.89, 1.11)	
Rhinitis only	1.08 (0.69,1.68)	1.00 (0.90,1.12)	1.04 (0.93,1.17)	0.95 (0.85,1.06)	1.10 (0.98,1.24)	1.19 (1.04, 1.36)	
P-value for differential association*	0.006	1.71E-05	0.006	0.044	0.055	0.138	
P-value for any association†	0.011	4.26E-05	0.011	0.074	0.091	0.207	

RA=risk allele;

* Overall test for heterogeneity between classes excluding the baseline class of ‘no disease’

† Overall test for heterogeneity between classes including the baseline class of ‘no disease’ (Pooled multinomial Odds Ratio =1)

FIGURE LEGENDS

Figure 1 Forest plot of the associations between the standardised genetic score and allergic disease latent classes in ALSPAC and MAAS cohorts.

Figure 2. Forest plot of the associations between SNP rs61816761[A] near *Filaggrin* gene and allergic disease latent classes in ALSPAC and MAAS cohorts.

Figure 3. Forest plot of the associations between SNP rs921650[A] near *GSDMB* gene and allergic disease latent classes in ALSPAC and MAAS cohorts.

Figure 4. Forest plot of the associations between the modified standardised genetic score (excluding SNPs rs61816761 and rs921650) and allergic disease latent classes in ALSPAC and MAAS cohorts.

FIGURES

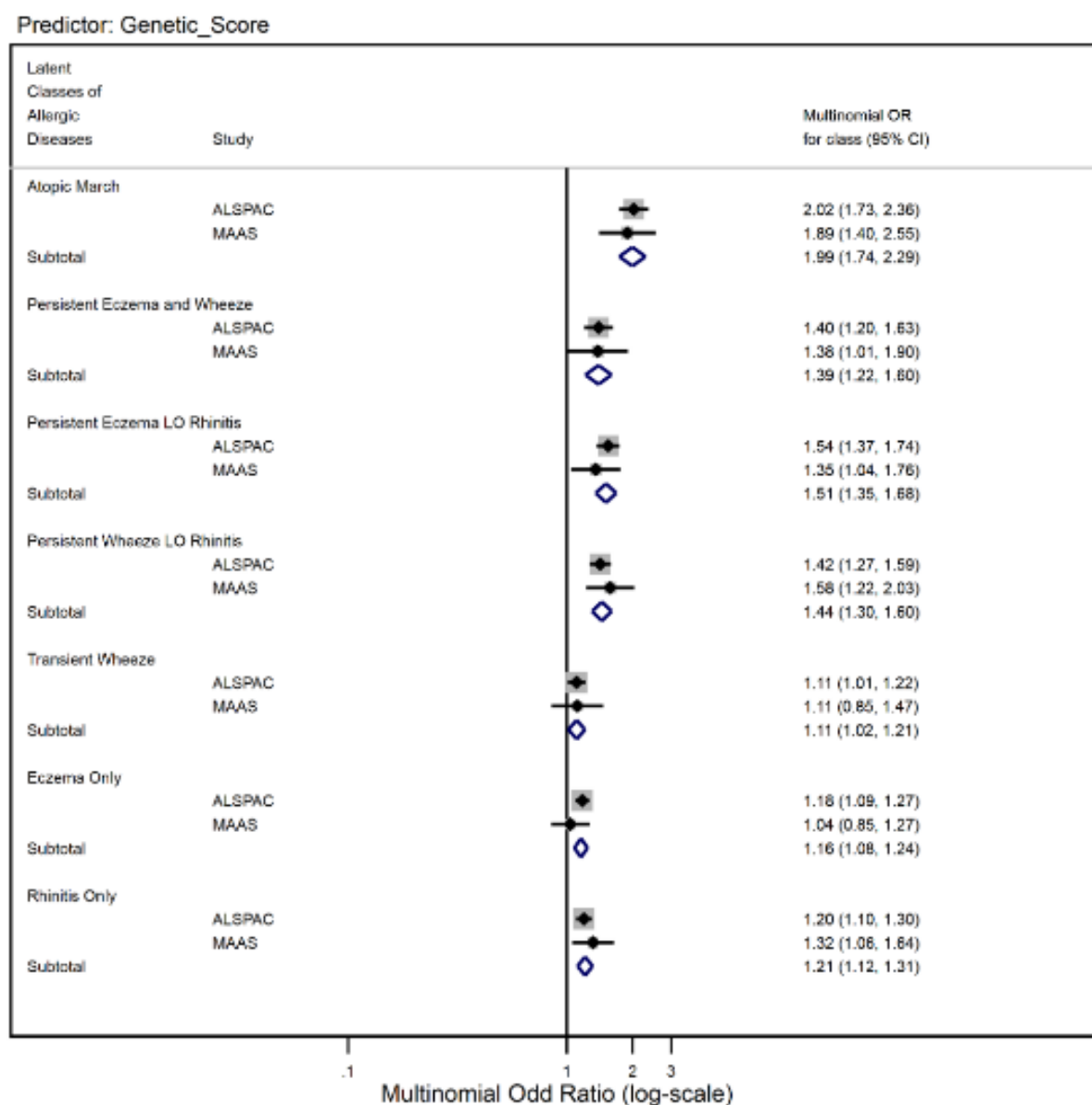


Figure 1 Forest plot of the associations between the standardised genetic score and allergic disease latent classes in ALSPAC and MAAS cohorts.

Predictor: rs61816761 (FLG)

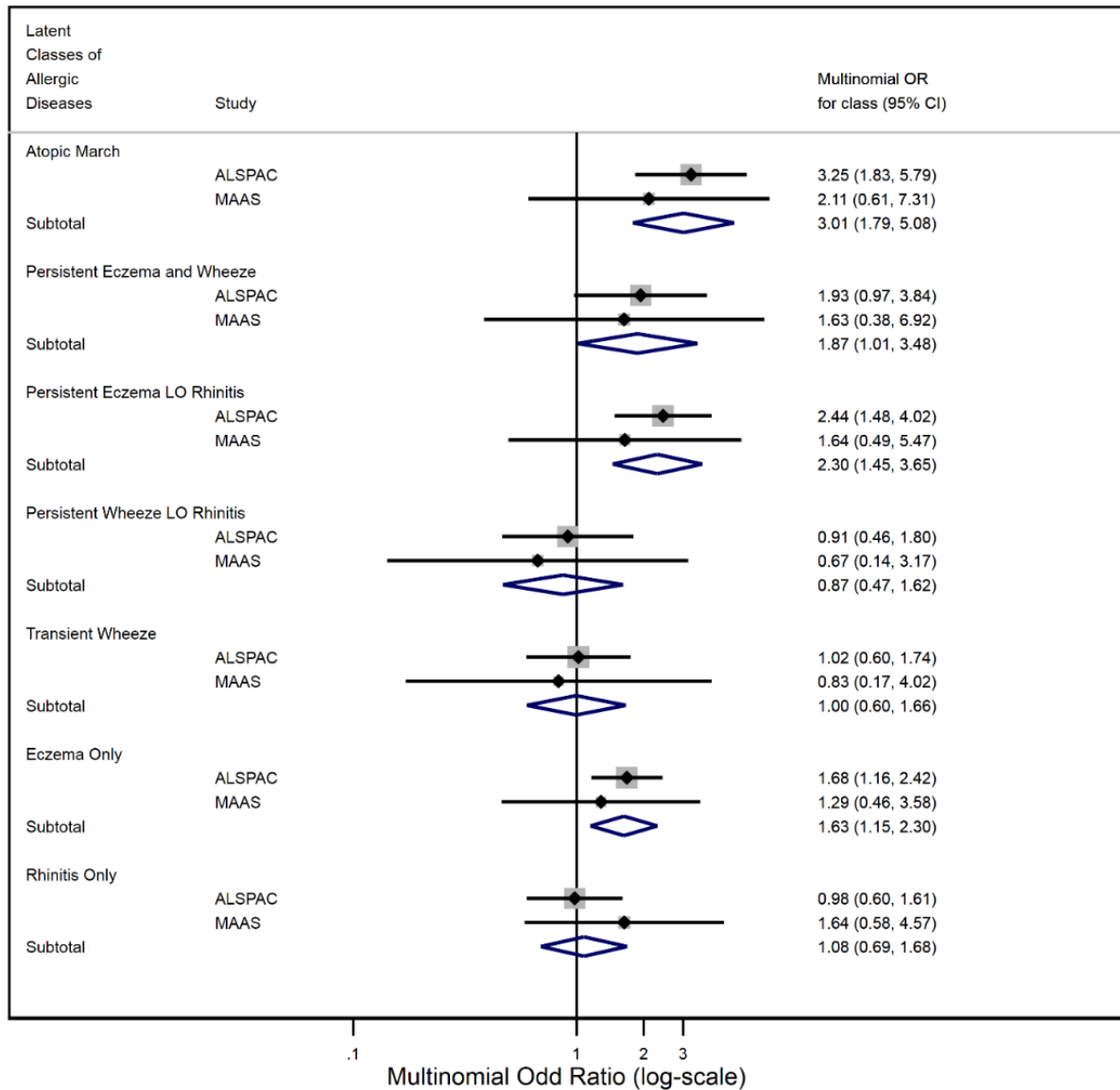


Figure 2. Forest plot of the associations between SNP rs61816761[A] near *Filaggrin* gene and allergic disease latent classes in ALSPAC and MAAS cohorts.

Predictor: rs921650 (GSDMB)

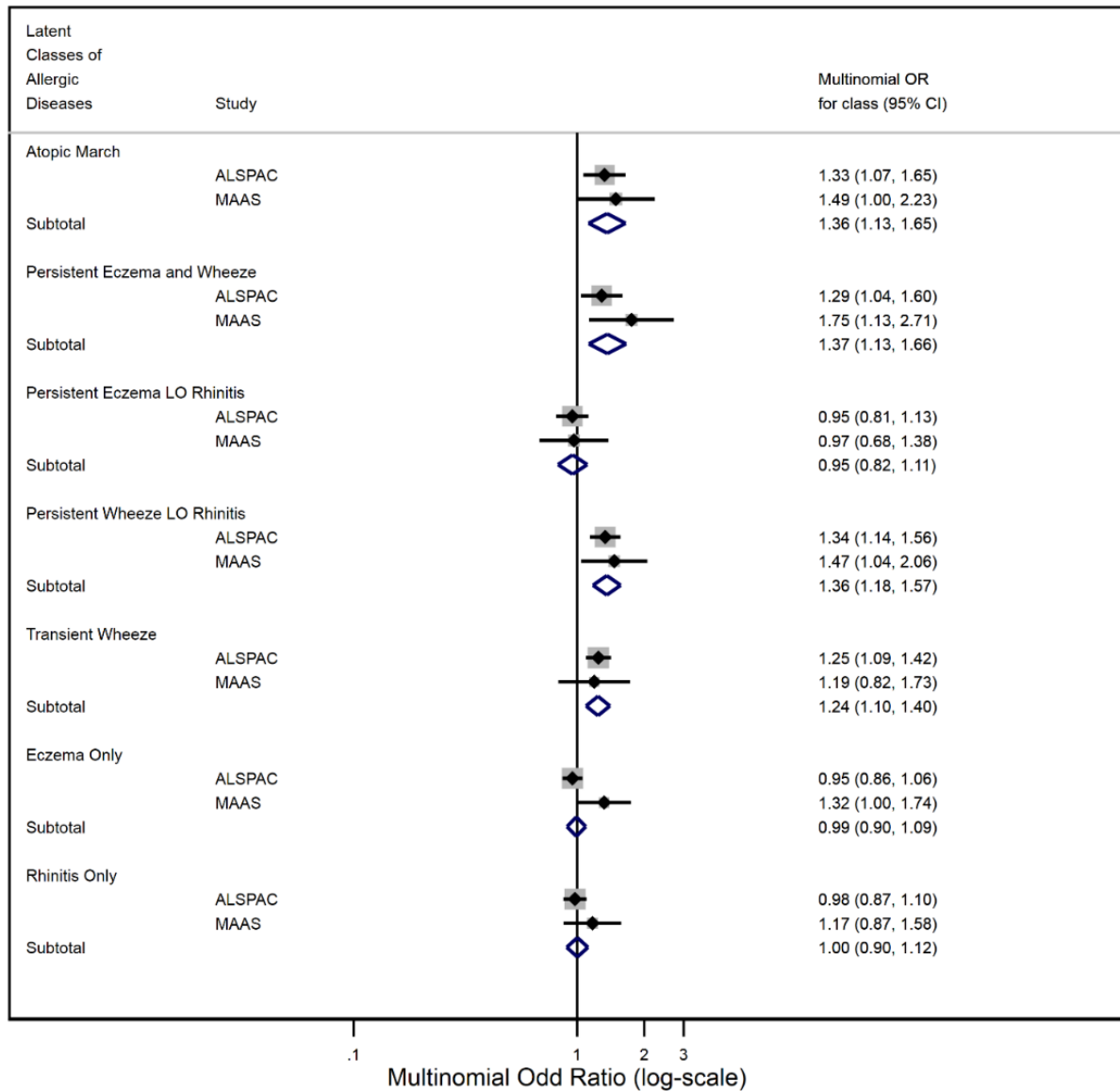


Figure 3. Forest plot of the associations between SNP rs921650[A] near *GSDMB* gene and allergic disease latent classes in ALSPAC and MAAS cohorts.

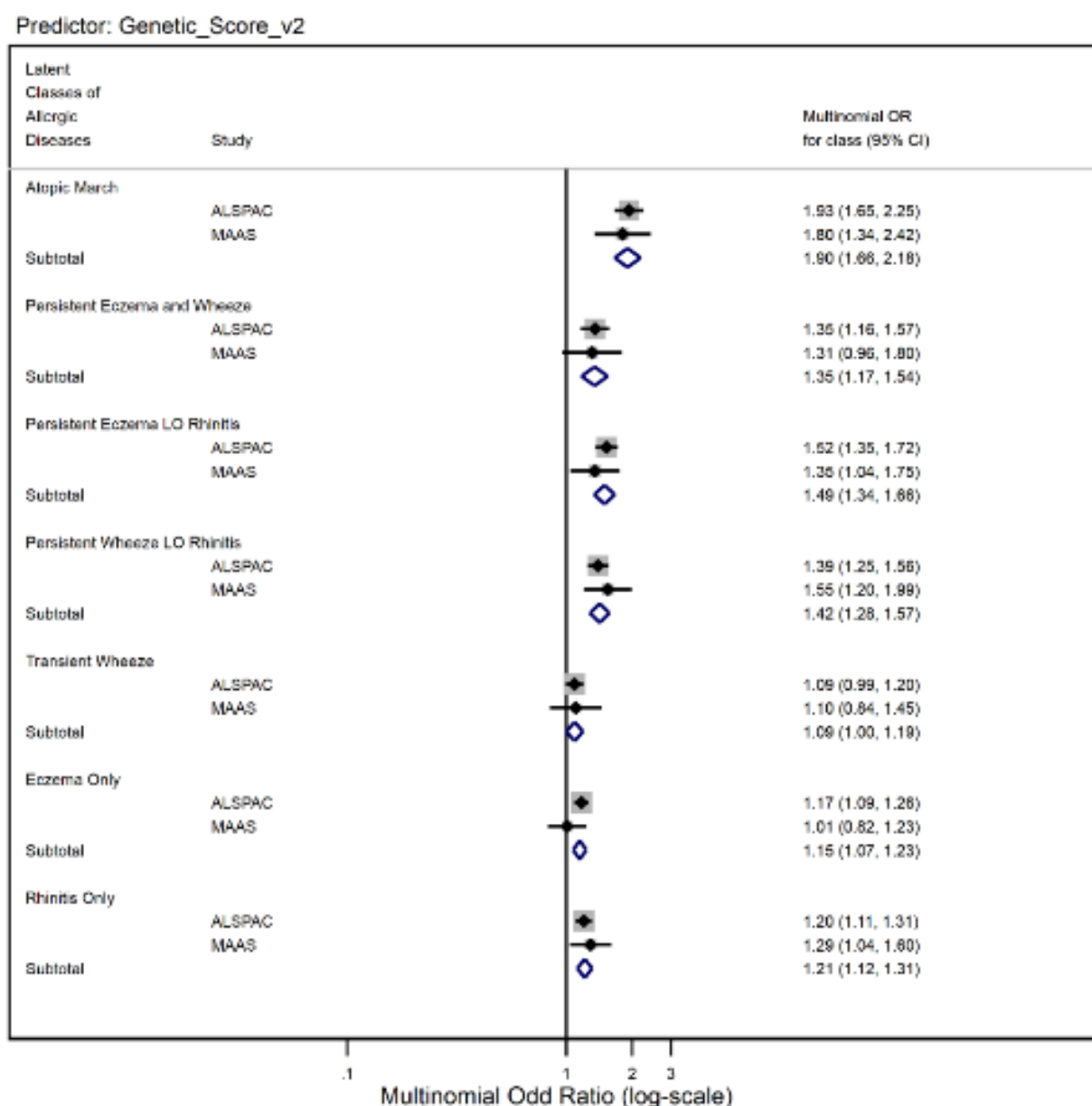


Figure 4. Forest plot of the associations between the modified standardised genetic score (excluding SNPs rs61816761 and rs921650) and allergic disease latent classes in ALSPAC and MAAS cohorts.

Differential associations of allergic disease genetic variants with developmental profiles of eczema, wheeze and rhinitis

Supplemental Material

1 Methods

2 ALSPAC

3 Pregnant women resident in Avon, UK with expected dates of delivery 1st April 1991 to 31st December 1992
4 were invited to take part in the study. The initial number of pregnancies enrolled is 14,541 (for these at least
5 one questionnaire has been returned or a “Children in Focus” clinic had been attended by 19/07/99). Of these
6 initial pregnancies, there was a total of 14,676 fetuses, resulting in 14,062 live births and 13,988 children who
7 were alive at 1 year of age.

8 When the oldest children were approximately 7 years of age, an attempt was made to bolster the initial
9 sample with eligible cases who had failed to join the study originally. As a result, when considering variables
10 collected from the age of seven onwards (and potentially abstracted from obstetric notes) there are data
11 available for more than the 14,541 pregnancies mentioned above.

12 The number of new pregnancies not in the initial sample (known as Phase I enrolment) that are currently
13 represented on the built files and reflecting enrolment status at the age of 24 is 904 (452, 254 and 198
14 recruited during Phases II, III and IV respectively), resulting in an additional 811 children being enrolled. The
15 phases of enrolment are described in more detail in the cohort profile paper (see footnote 4 below). Please
16 note that phase 4 enrolment (age 18-24) is not currently included in the cohort profile.

17 The total sample size for analyses using any data collected after the age of seven is therefore 15,247
18 pregnancies, resulting in 15,458 fetuses. Of this total sample of 15,656 fetuses, 14,973 were live births and
19 14,899 were alive at 1 year of age.

20 A 10% sample of the ALSPAC cohort, known as the Children in Focus (CiF) group, attended clinics at the
21 University of Bristol at various time intervals between 4 to 61 months of age. The CiF group were chosen at
22 random from the last 6 months of ALSPAC births (1432 families attended at least one clinic). Excluded were
23 those mothers who had moved out of the area or were lost to follow-up, and those partaking in another study
24 of infant development in Avon.

25 Maternal educational attainment in the two cohorts

26 In ALSPAC, we obtained details of maternal educational attainment (lower level defined as educated to school
27 leaving certificate at 16 years or lower), and joint parental social class (manual vs non-manual derived from

28 occupation categorisation using the OPCS job codes) from questionnaires sent to the mother during
 29 pregnancy.

30 In MAAS, details on gender and socio-economic status (lower social class defined as not working, routine or
 31 intermediate; higher social class defined as managerial) were obtained from questionnaire data at
 32 recruitment. Maternal educational level was obtained from followed up questionnaires at age 13-16 years.
 33 Lower maternal education level was defined as not educated to UK A or As level.

34 Imputation quality and frequency checks

35 The imputation quality of each SNP was assessed, and four SNPs (rs12123821, rs34290285, rs16903574,
 36 rs112401631) with imputation quality of <0.80 were investigated for potential SNP proxies with higher
 37 imputation quality. Proxies were identified using the LDproxy tool (LDlink) ([1](#)) and selected based on highest
 38 INFO score and $R^2 > 0.40$ and $D' \text{ values} > 0.60$ (for LD). The LDproxy tool was then used to identify the risk
 39 alleles for the proxies, so that the odds ratios (ORs) used for the proxy SNPs were the same as the top SNP
 40 (extracted from the GWAS paper ([2](#))). Details on suitable proxies were found for three of the four SNPs and
 41 substituted into the dataset. No suitable proxy for rs34290285 was identified in ALSPAC, so this SNP was
 42 excluded from the dataset, leaving 135 SNPs in the ALSPAC analyses. All 135 SNPs were available in MAAS,
 43 however, SNP rs10305290 was monomorphic and hence excluded from the MAAS score.

44 In the dataset, the alleles for each SNP were coded as B1 and B2. The per-B2-allele dosages were extracted
 45 and checks were made to ensure that the SNP dosages were coded as expected before any further analysis
 46 took place, by comparing observed risk allele frequencies to those reported for 1000 Genome phase 3 in the
 47 Database of Single Nucleotide Polymorphisms (dbSNP) ([3](#)). The formula used to calculate the allele frequencies
 48 in ALSPAC was:

$$\frac{\sum D_i}{n \times 2}$$

49 Where D_i was the per-B2-allele dosage for each SNP and n was the number of individuals (8802). The
 50 comparison of ALSPAC and dbSNP frequencies showed that SNP dosages had been coded correctly. Per-allele
 51 SNP dosages were then flipped if necessary so that the dosages were coded as per risk-allele.

52 Polygenic risk score (PRS)

53 A weighted polygenic risk score (PRS) was calculated for 8,802 individuals from ALSPAC with complete data on
54 all 135 SNPs.

55 The following formula was used to calculate the PRS for each individual:

$$\frac{\sum(\beta_i \times D_i)}{n}$$

56 Where β_i is the beta value for each SNP (i.e. its effect size as reported by Ferreira et al. (2) , converted by
57 $\beta = \log(OR)$). D_i is the per risk-allele dosage of each SNP and n is the total number of SNPs (135). The units of
58 the derived risk score are per risk-allele weighted by effect size. A histogram was created to visualise the
59 distribution of the score. A standardised version of the PRS was then calculated using the following formula:

$$\frac{\left(\frac{\sum(\beta_i \times D_i)}{n} \right) - \bar{x}}{\sigma}$$

60 The standardised PRS represents a per 1-standard deviation increase in the per risk-allele weighted score. A
61 histogram was also created for the standardised PRS. Information on the 135 SNPs used to generate the risk
62 score (including their weight/beta values) can be found in **Table S1**.

63 Allergic Diseases Latent Classes

64 The eight latent classes of allergic diseases were defined as described previously (4):

- 65 1. No disease: children in this class had a low probability of eczema, wheeze and rhinitis
- 66 2. Atopic March: high probability of eczema from infancy to age 11 years with increased probability of
67 wheeze over time. For rhinitis, the probability increased from zero at age 1 year to almost 100% by 8
68 years. Eczema developed first, followed by wheeze, and then rhinitis;
- 69 3. Persistent eczema and wheeze: similar probability of wheeze and eczema throughout childhood, likely
70 as co-morbidities, with a low probability of rhinitis throughout childhood.
- 71 4. Persistent eczema with later-onset rhinitis ('Persistent eczema later-onset rhinitis'): increased eczema
72 prevalence from ~70% in early life to 95% at age 5 years, with little resolution at 11 years. The
73 probability of rhinitis increased to almost 100% by age 8 years with low probability of wheeze
74 throughout childhood.

5. Persistent wheeze with later-onset rhinitis ('Persistent wheeze later-onset rhinitis'): high probability of wheeze throughout childhood, with increasing probability of rhinitis to almost 100% by age 11 years. Probability of eczema was low, declining steadily at age 11 years.
6. Transient wheeze: high probability of wheeze within the first 5 years, with remission by age 8 years, and a very low probability of eczema and rhinitis throughout childhood.
7. Eczema only: high probability of eczema throughout life, peaking at ~80% at age 5 years, then declining steadily to a 50% probability at age 11 years.
8. Rhinitis only: increasing probability of rhinitis from age 5 to 11 years, but no wheeze or eczema.

While in ALSPAC the 'no disease' class had a proportion of 50.0%, in MAAS this was only 36.5%. In both cohorts the largest disease latent classes were 'eczema only' (15.3% in ALSPAC vs. 15.6% in MAAS) and 'rhinitis only' (9.5% in ALSPAC vs. 12.8% in MAAS). 'Atopic march' (2.7% vs. 5.9%), 'persistent eczema and wheeze' (2.4% vs. 5.0%), 'persistent eczema later-onset rhinitis' (4.4% vs. 8.1%) and 'persistent wheeze later-onset rhinitis' (5.2% vs. 8.9%) were less prevalent in ALSPAC compared to MAAS. The proportion of 'transient wheeze' class was similar in both cohorts (7.7% vs. 7.2%).

Power calculations in ALSPAC

To assess the level of power in the individual SNP analysis (the probability of detecting an effect given that the effect is real), power calculations were conducted for associations with individual phenotypes. Power calculations were performed using the GAS online power calculator ([5](#)). The calculations assumed an additive genetic model, with the following input parameters for each disease class: number of cases and controls, the significance level, prevalence, risk allele frequency and relative risk. The input 'prevalence' was taken from the previous publication ([4](#)) on the latent disease classes, and the significance level was that of the Bonferroni corrected threshold. Calculations were made for various values of risk allele frequency (0.05, 0.15, 0.25, 0.45) and relative risk (1.1, 1.3, 1.5).

Results for the power calculations are displayed in **Table S2**. Generally, the power to detect associations for single SNPs in ALSPAC was low, especially for 'Atopic march' (n=173, power≤0.35), 'Persistent eczema and wheeze' (n=154, power≤0.28) and 'Persistent eczema with late-onset rhinitis' (n=279, power≤0.70), where the sample size of each class was lower. As the effect size (RRR) increased and the risk allele frequency (RAF) increased, the power to detect associations also increased. Statistical power was >0.80 for detecting

103 associations in 'Persistent wheeze with late-onset rhinitis' class (n=328) for minimum RRR 1.50 and minimum
104 RAF 0.45. For 'Transient wheeze' (n=491) and 'Rhinitis only' (n=602) classes, power to detect associations
105 above a level of 0.80 was reached at a minimum RRR 1.50 and minimum RAF 0.15. For 'Eczema only' class
106 (n=971), the largest of the disease latent classes in terms of number of cases, power to detect associations
107 above a level of 0.80 was reached at a minimum RRR 1.30 and minimum RAF 0.25.

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119

120 Tables

121 ALSPAC Results

122 **Table S1.** Information on the 135 SNPs used to generate the standardised genetic score in ALSPAC cohort.

Chr	Position b37	SNP	Gene context	Risk allele	Other allele	Risk allele frequency	Info*	Weight†	Proxy for	Merged into‡
1	2510755	rs10910095	<i>TNFRSF14</i> -[]- <i>FAM213B</i>	G	A	0.865	0.983	0.041	rs12123821	
1	8482078	rs301806	[<i>RERE</i>]	T	C	0.581	0.997	0.047		
1	25251923	rs760805	[<i>RUNX3</i>]	T	A	0.57	0.986	0.037		
1	35681738	rs76167968	<i>SFPQ</i> -[]- <i>ZMYM4</i>	T	C	0.919	0.994	0.054		
1	150265704	rs7512552	<i>C1orf54</i> -[]- <i>MRPS21</i>	C	T	0.513	0.998	0.031		
1	151796742	rs11204896	[<i>RORC</i>]	C	G	0.899	0.974	0.061		
1	152000117	rs115288876	<i>RPTN</i> -[]- <i>HRNR</i>	A	G	0.053	0.765	0.105		
1	152285861	rs61816761	[<i>FLG</i>]	A	G	0.021	0.803	0.202		
1	154426970	rs2228145	[<i>IL6R</i>]	C	A	0.416	0.999	0.037		
1	161185058	rs2070901	<i>NDUFS2</i> -[]- <i>FCER1G</i>	T	G	0.263	0.996	0.038		
1	167431352	rs2988277	[<i>CD247</i>]	C	T	0.607	0.991	0.039		
1	172700868	rs1102705	<i>FASLG</i> -[]- <i>TNFSF18</i>	G	A	0.101	0.954	0.056		
1	173146921	rs4090390	<i>TNFSF18</i> --[]- <i>TNFSF4</i>	A	C	0.239	0.952	0.047		
1	226914734	rs697852	[<i>ITPKB</i>]	A	G	0.819	0.974	0.040		
2	8442248	rs10174949	[<i>LINC00299</i>]	G	A	0.707	1	0.064		
2	64836267	rs4671601	[<i>LOC339807</i>]	C	T	0.806	0.966	0.038		
2	102926362	rs12470864	<i>IL1RL2</i> -[]- <i>IL18R1</i>	A	G	0.385	0.997	0.055		
2	102941311	rs10865050	[<i>IL18R1</i>]	G	A	0.866	0.996	0.122		
2	112269127	rs13403656	<i>BCL2L11</i> --[]- <i>ANAPC1</i>	A	T	0.173	0.827	0.044		
2	112388538	rs4848612	<i>BCL2L11</i> --[]- <i>ANAPC1</i>	A	G	0.773	0.996	0.037		
2	113590467	rs1143633	[<i>IL1B</i>]	C	T	0.644	0.96	0.033		
2	143831599	rs74847330	<i>KYNU</i> -[]- <i>ARHGAP15</i>	A	G	0.879	0.942	0.047		
2	198950240	rs1064213	[<i>PLCL1</i>]	G	A	0.517	1	0.034		

2	228707862	rs13384448	<i>CCL20</i> -[]- <i>DAW1</i>	T	C	0.755	0.986	0.041	
2	234115629	rs1057258	[<i>INPP5D</i>]	C	T	0.815	0.969	0.044	
3	33069091	rs6776757	[<i>GLB1</i>]	G	A	0.507	0.995	0.032	
3	72394852	rs61192126	<i>LINC00870</i> --[]- <i>RYBP</i>	T	C	0.702	0.946	0.036	
3	101242751	rs13088318	<i>FAM172BP</i> -[]- <i>TRMT10C</i>	A	G	0.663	0.992	0.031	
3	121652141	rs75557865	[<i>SLC15A2</i>]	G	A	0.528	1	0.029	
3	141321836	rs10663129	[<i>RASA2</i>]	ACT	A	0.337	0.993	0.041	
3	187633268	rs519973	<i>BCL6</i> --[]- <i>LPP-AS2</i>	A	G	0.339	0.987	0.033	
3	187793833	rs2030030	<i>BCL6</i> --[]- <i>LPP-AS2</i>	T	C	0.844	0.979	0.040	
3	188133336	rs60946162	[<i>LPP</i>]	T	C	0.458	0.96	0.040	
3	188402586	rs17607589	[<i>LPP</i>]	C	T	0.832	0.998	0.052	
3	196372546	rs80064395	<i>FBXO45</i> -[]- <i>CEP19</i>	C	T	0.932	0.826	0.068	
4	4775401	rs76991385	<i>STX18</i> --[]- <i>MSX1</i>	G	A	0.36	0.979	0.039	rs10033073
4	38798648	rs5743618	[<i>TLR1</i>]	C	A	0.748	0.935	0.095	
4	103593898	rs227275	[<i>MANBA</i>]	C	A	0.534	0.984	0.033	
4	123316076	rs4145717	[<i>ADAD1</i>]	T	G	0.333	1	0.057	
4	123454110	rs150254607	<i>IL2</i> -[]- <i>IL21</i>	ATAT	A	0.075	0.988	0.075	
5	14690667	rs78486128	[<i>FAM105A</i>]	G	A	0.935	0.815	0.069	rs16903574
5	35862841	rs7717955	[<i>IL7R</i>]	C	T	0.724	0.997	0.070	
5	40492655	rs7714574	<i>DAB2</i> ---[]- <i>PTGER4</i>	T	C	0.604	0.989	0.031	
5	110159879	rs1814576	<i>SLC25A46</i> -[]- <i>TSLP</i>	C	T	0.065	0.95	0.114	
5	110166083	rs6869502	<i>SLC25A46</i> -[]- <i>TSLP</i>	T	A	0.149	0.995	0.076	
5	110401872	rs1837253	<i>SLC25A46</i> --[]- <i>TSLP</i>	C	T	0.742	1	0.068	
5	110470137	rs6594499	<i>WDR36</i> -[]- <i>CAMK4</i>	C	A	0.515	0.985	0.072	
5	118684297	rs250308	[<i>TNFAIP8</i>]	T	C	0.389	0.999	0.031	
5	131799626	rs3749833	[<i>C5orf56</i>]	C	T	0.258	0.996	0.038	
5	131989136	rs3091307	<i>RAD50</i> -[]- <i>IL13</i>	G	A	0.197	0.966	0.060	
5	131996500	rs848	[<i>IL13</i>]	A	C	0.184	0.982	0.066	
5	140925362	rs740474	[<i>DIAPH1</i>]	C	T	0.398	0.999	0.033	
5	141494934	rs10068717	[<i>NDFIP1</i>]	T	C	0.615	1	0.041	
5	159909345	rs2910162	<i>MIR3142</i> -[]- <i>MIR146A</i>	G	A	0.674	0.989	0.032	
5	176782218	rs13153019	<i>LMAN2</i> -[]- <i>RGS14</i>	C	T	0.25	0.956	0.034	

6	29893575	rs9259819	[HLA-J]	G	T	0.519	0.927	0.035	
6	31323012	rs2854001	[HLA-B]	A	G	0.24	0.986	0.057	
6	31351664	rs114333358	HLA-B-[]-MICA	G	A	0.422	0.998	0.034	rs2507978
6	31574525	rs149130795	NCR3-[]-AIF1	C	T	0.939	0.998	0.093	rs28895016
6	32626403	rs113453523	HLA-DQA1-[]-HLA-DQB1	A	G	0.761	0.971	0.096	rs34004019
6	33046752	rs114305667	[HLA-DPA1]	G	C	0.883	0.986	0.062	rs3097670
6	33647058	rs10947428	[ITPR3]	C	T	0.215	0.964	0.045	
6	90987512	rs2134814	[BACH2]	C	G	0.645	0.996	0.045	
6	106667535	rs9372120	[ATG5]	G	T	0.215	0.998	0.041	
6	128294709	rs35469349	[PTPRK]	A	T	0.278	0.941	0.036	
6	138195151	rs5029937	[TNFAIP3]	G	T	0.969	0.998	0.078	
6	157419508	rs9383820	[ARID1B]	C	T	0.792	1	0.036	
6	167390671	rs72033857	RNASET2-[]-MIR3939	C	CCTTT	0.109	0.96	0.055	
7	20376018	rs10486391	[ITGB8]	A	G	0.584	1	0.030	
7	20560996	rs6461503	ITGB8-[]-ABCB5	T	C	0.482	1	0.038	
7	28156887	rs6977955	[JAZF1]	T	C	0.202	0.996	0.045	
7	50253897	rs17664743	C7orf72-[]-IKZF1	A	G	0.201	0.985	0.041	
7	77018542	rs4296977	[GSAP]	C	T	0.14	0.998	0.054	
8	81292599	rs7824394	MIR5708-[]-ZBTB10	A	C	0.358	0.998	0.049	
8	128814091	rs6990534	[MYC]	A	G	0.296	0.993	0.041	
9	5064193	rs16922576	[JAK2]	C	T	0.278	0.978	0.035	
9	6051399	rs343478	RANBP6-[]-IL33	G	A	0.544	0.977	0.032	
9	6208030	rs144829310	RANBP6-[]-IL33	T	G	0.17	0.999	0.086	
9	123650534	rs10760123	PHF19-[]-TRAF1	T	G	0.397	0.928	0.031	
9	131613191	rs12551834	C9orf114-[]-LRRC8A	G	A	0.912	0.881	0.056	
10	6074451	rs4747846	[IL2RA]	C	G	0.479	0.972	0.035	
10	6094697	rs61839660	[IL2RA]	T	C	0.1	0.982	0.077	
10	8605553	rs11255753	GATA3-[]-SFTA1P	T	G	0.278	1	0.040	
10	8841669	rs2025758	GATA3-[]-SFTA1P	T	C	0.553	1	0.040	
10	8936162	rs11255968	GATA3-[]-SFTA1P	C	T	0.971	0.987	0.086	
10	9032555	rs72782676	GATA3-[]-SFTA1P	C	G	0.993	0.839	0.265	

10	9049253	rs12413578	<i>GATA3</i> ---[]--- <i>SFTA1P</i>	C	T	0.894	0.929	0.091
10	9064361	rs1444789	<i>GATA3</i> ---[]--- <i>SFTA1P</i>	C	T	0.189	0.981	0.064
10	64382359	rs2893907	[<i>ZNF365</i>]	C	A	0.533	0.985	0.031
10	104225832	rs10883723	<i>C10orf95</i> -[]- <i>ACTR1A</i>	C	T	0.355	0.996	0.030
11	65551957	rs479844	<i>AP5B1</i> -[]- <i>OVOL1</i>	G	A	0.556	1	0.037
11	76293758	rs7936323	<i>WNT11</i> --[]- <i>LRRC32</i>	A	G	0.485	0.982	0.084
11	76299431	rs55646091	<i>WNT11</i> --[]- <i>LRRC32</i>	A	G	0.053	0.922	0.165
11	76343428	rs11236814	<i>WNT11</i> --[]- <i>LRRC32</i>	A	T	0.91	0.875	0.066
11	95425526	rs59593577	<i>SESN3</i> --[]- <i>FAM76B</i>	C	T	0.874	0.806	0.052
11	111470567	rs7130753	<i>LAYN</i> -[]- <i>SIK2</i>	C	T	0.729	0.992	0.044
11	118743286	rs12365699	<i>DDX6</i> -[]- <i>CXCR5</i>	G	A	0.841	1	0.059
11	128158189	rs56129466	<i>KIRREL3-AS3</i> ---[]-- <i>ETS1</i>	A	G	0.794	0.972	0.046
12	48196982	rs55726902	[<i>HDAC7</i>]	G	A	0.765	0.977	0.050
12	50345671	rs11169225	[<i>AQP2</i>]	A	T	0.198	0.992	0.044
12	56401085	rs10876864	<i>SUOX</i> -[]- <i>IKZF4</i>	G	A	0.419	1	0.046
12	57489709	rs1059513	[<i>STAT6</i>]	T	C	0.893	1	0.081
12	111932800	rs7137828	[<i>ATXN2</i>]	T	C	0.521	0.999	0.032
12	121363724	rs6489785	<i>SPPL3</i> -[]- <i>HNF1A-AS1</i>	T	C	0.392	0.986	0.042
12	123742692	rs63406760	<i>C12orf65</i> -[]- <i>CDK2AP1</i>	T	TG	0.786	0.991	0.046
13	41173408	rs4943794	[<i>FOXO1</i>]	C	G	0.213	1	0.042
13	73627275	rs9573092	<i>PIBF1</i> -[]- <i>KLF5</i>	A	G	0.645	0.987	0.030
14	35761675	rs1048990	[<i>PSMA6</i>]	G	C	0.176	0.992	0.038
14	38097001	rs111914382	<i>FOXA1</i> -[]-- <i>TTC6</i>	TG	T	0.24	0.991	0.035
14	68754417	rs2104047	[<i>RAD51B</i>]	T	C	0.279	0.998	0.041
14	75968608	rs9323612	<i>JDP2</i> -[]- <i>BATF</i>	A	G	0.67	0.992	0.031
14	103235012	rs9989163	<i>RCOR1</i> -[]- <i>TRAF3</i>	A	G	0.467	0.986	0.029
15	41782684	rs12440045	<i>RTF1</i> -[]- <i>ITPKA</i>	C	A	0.52	0.94	0.032
15	61068347	rs10519067	[<i>RORA</i>]	G	A	0.874	0.997	0.054
15	67448363	rs56375023	[<i>SMAD3</i>]	A	G	0.246	0.994	0.070
15	91045408	rs3540	[<i>IQGAP1</i>]	G	A	0.682	0.999	0.035
16	11277358	rs11644510	<i>CLEC16A</i> -[]- <i>RMI2</i>	C	T	0.638	0.952	0.070
16	11491007	rs12596613	<i>RMI2</i> -[]-- <i>LITAF</i>	C	G	0.66	0.937	0.031

17	4521473	rs71368508	<i>SMTNL2-[]-ALOX15</i>	C	A	0.979	0.845	0.117	
17	38069076	rs921650	<i>[GSDMB]</i>	A	G	0.478	1	0.057	
17	38149033	rs11652139	<i>[PSMD3]</i>	A	G	0.563	0.98	0.050	
17	38604546	rs10305290	<i>CCR7-[]-SMARCE1</i>	T	C	0.014	0.904	0.231	rs112401631
17	38770641	rs11464691	<i>CCR7-[]-SMARCE1</i>	TA	T	0.632	0.995	0.051	
17	40414862	rs7207591	<i>[STAT5B]</i>	A	G	0.754	0.869	0.037	
17	43430696	rs116053081	<i>MAP3K14-[]-ARHGAP27</i>	G	A	0.353	1	0.031	rs7214661
17	47398070	rs9889262	<i>[ZNF652]</i>	A	T	0.371	0.997	0.042	
18	52336175	rs4801001	<i>DYNAP-[]-RAB27B</i>	T	C	0.469	0.922	0.031	
18	60009814	rs4574025	<i>[TNFRSF11A]</i>	T	C	0.545	0.947	0.030	
19	33721455	rs10414065	<i>SLC7A10-[]-CEBPA</i>	C	T	0.936	0.851	0.093	
20	50157837	rs3787184	<i>[NFATC2]</i>	A	G	0.82	0.88	0.048	
20	52208356	rs2766678	<i>[ZNF217]</i>	G	A	0.218	0.941	0.055	
20	62322699	rs6011033	<i>[RTEL1]</i>	G	A	0.772	0.956	0.046	
21	36467830	rs73205303	<i>[RUNX1]</i>	A	G	0.158	0.997	0.043	
21	44846426	rs76081789	<i>[SIK1]</i>	T	C	0.944	0.987	0.063	
22	41816652	rs5758343	<i>TEF-[]-TOB2</i>	A	T	0.204	0.997	0.047	

123 * Imputation quality measure

124 † Beta from regression Ferreira et al ([2](#))

125 ‡ Duplicate SNPs as in dbSNP records ([3](#))

126 **Table S2.** Power calculations for associations with individual latent classes based on ALSPAC data.

Allergic diseases latent classes	N cases	Prev.*	RRR [†]	Risk allele frequency (RAF)			
				0.05	0.15	0.25	0.45
Atopic March	173	0.031	1.10	0.001	0.002	0.002	0.003
			1.30	0.006	0.030	0.058	0.082
			1.50	0.027	0.159	0.282	0.351
Persistent eczema and wheeze	154	0.027	1.10	0.001	0.001	0.002	0.003
			1.30	0.005	0.024	0.045	0.064
			1.50	0.021	0.123	0.223	0.281
Persistent eczema later-onset rhinitis	279	0.047	1.10	0.001	0.003	0.005	0.007
			1.30	0.014	0.082	0.158	0.221
			1.50	0.073	0.398	0.611	0.699
Persistent wheeze later-onset rhinitis	328	0.057	1.10	0.001	0.004	0.006	0.009
			1.30	0.019	0.116	0.221	0.302
			1.50	0.103	0.517	0.736	0.813
Transient wheeze	491	0.077	1.10	0.002	0.006	0.011	0.017
			1.30	0.041	0.252	0.440	0.558
			1.50	0.229	0.803	0.941	0.969
Eczema only	971	0.153	1.10	0.005	0.022	0.044	0.070
			1.30	0.185	0.747	0.920	0.964
			1.50	0.725	0.998	1.000	1.000
Rhinitis only	602	0.096	1.10	0.002	0.009	0.016	0.025
			1.30	0.063	0.371	0.596	0.716
			1.50	0.343	0.915	0.985	0.993

127 * Prevalence of each class

128 † Relative risk ratio (Multinomial odds ratio)

129 Highlighted values indicate where statistical power > 0.80 (which is generally considered a standard for power
130 adequacy).

131

Table S3. Associations between genetic scores and profile latent classes (weighted by membership probabilities) before and after excluding SNPs rs61816761 (*FLG*) and rs921650 (*GSDMB*) in ALSPAC cohort.

Multinomial Odds Ratio (95% CI)		
Allergic diseases latent classes	Stand. Score	Stand. Score excluding <i>FLG</i> and <i>GSDMB</i>
Atopic March	2.021 (1.731,2.360)	1.931 (1.654,2.254)
Persistent eczema and wheeze	1.397 (1.200,1.626)	1.353 (1.163,1.575)
Persistent eczema later-onset rhinitis	1.543 (1.370,1.739)	1.525 (1.354,1.717)
Persistent wheeze later-onset rhinitis	1.420 (1.269,1.589)	1.395 (1.247,1.560)
Transient wheeze	1.108 (1.009,1.216)	1.089 (0.992,1.195)
Eczema only	1.177 (1.093,1.267)	1.171 (1.088,1.260)
Rhinitis only	1.196 (1.099,1.301)	1.202 (1.105,1.307)
P-value for differential association*	3.28E-13	9.56E-12
P-value for any association†	3.19E-30	2.43E-27

Bonferroni corrected significance threshold is 0.000370 (0.05/135)

* Heterogeneity p value from chi-square test excluding the baseline class of 'no disease'

† Heterogeneity p value from chi-square test including the baseline class of 'no disease' (Multinomial Odds Ratio =1)

Table S4 Pairwise tests among disease latent classes from associations between genetic scores and profile latent classes (Table S3) in ALSPAC.

		Atopic March	Persistent eczema and wheeze	Persistent eczema LO rhinitis	Persistent wheeze LO rhinitis	Transient wheeze	Eczema only	Rhinitis only
		standard genetic score						
Atopic March	standard genetic score excluding <i>FLG</i> and <i>GSDMB</i>		5.51E-04	4.64E-03	1.56E-04	1.00E-11	8.10E-11	9.68E-10
Persistent eczema and wheeze		8.99E-04		0.29	0.86	7.85E-03	0.04	0.07
Persistent eczema LO rhinitis		0.013	0.21		0.29	5.06E-06	4.44E-05	2.52E-04
Persistent wheeze LO rhinitis		5.03E-04	0.74	0.26		3.77E-04	2.98E-03	0.010
Transient wheeze		8.73E-11	0.012	3.51E-06	3.72E-04		0.28	0.19
Eczema only		1.81E-09	0.08	6.86E-05	5.45E-03	0.19		0.75
Rhinitis only		3.12E-08	0.16	6.10E-04	2.44E-02	0.09	0.61	

141 **Table S5.** Individual SNP associations with profile latent classes in ALSPAC (analysis weighted by class membership probabilities)

Multinomial Odds Ratio (95% CI) for each AD latent class									
SNP	Atopic March	Persistent eczema and wheeze	Persistent eczema later-onset rhinitis	Persistent wheeze later-onset rhinitis	Transient wheeze	Eczema only	Rhinitis only	P-value differential association*	P-value any association
Nominal SNPs									
rs921650 (GSDMB)	1.327 (1.068,1.648)	1.289 (1.041,1.596)	0.952 (0.805,1.125)	1.336 (1.141,1.565)	1.246 (1.093,1.420)	0.953 (0.860,1.057)	0.978 (0.869,1.101)	1.42E-05	5.32E-06
rs61816761 (FLG)	3.254 (1.830,5.789)	1.934 (0.975,3.838)	2.440 (1.479,4.024)	0.913 (0.464,1.796)	1.019 (0.595,1.744)	1.680 (1.165,2.422)	0.981 (0.599,1.606)	0.0019	3.60E-05
rs11652139	1.446 (1.153,1.812)	1.131 (0.910,1.405)	1.086 (0.917,1.286)	1.267 (1.078,1.490)	1.190 (1.042,1.360)	0.961 (0.866,1.067)	1.048 (0.930,1.181)	0.003	0.0006
rs479844	1.133 (0.909,1.414)	1.207 (0.970,1.503)	1.233 (1.038,1.463)	0.951 (0.811,1.115)	1.057 (0.925,1.206)	1.132 (1.019,1.257)	0.939 (0.834,1.058)	0.0336	0.0189
rs6990534	1.350 (1.076,1.693)	0.949 (0.748,1.203)	1.069 (0.892,1.282)	1.037 (0.873,1.232)	0.944 (0.817,1.092)	0.947 (0.844,1.062)	1.132 (0.997,1.286)	0.0382	0.0541
rs5743618	1.491 (1.126,1.974)	1.033 (0.802,1.329)	1.076 (0.882,1.313)	1.179 (0.973,1.427)	0.950 (0.816,1.105)	1.020 (0.904,1.152)	1.188 (1.030,1.372)	0.0487	0.0253
Disease-Specific SNPs									
rs115288876 (LOC105371442)	1.774 (1.134,2.775)	1.163 (0.695,1.946)	1.024 (0.671,1.563)	0.733 (0.466,1.151)	0.829 (0.580,1.184)	1.138 (0.883,1.466)	1.059 (0.788,1.425)	0.0902	0.1218
rs12470864 (IL1RL1)	0.867 (0.690,1.091)	1.059 (0.849,1.320)	1.011 (0.850,1.202)	1.053 (0.895,1.239)	1.089 (0.952,1.246)	0.960 (0.862,1.069)	1.096 (0.971,1.238)	0.3626	0.4266
rs61839660 (IL2RA)	1.033 (0.724,1.474)	1.032 (0.727,1.464)	1.222 (0.944,1.582)	0.978 (0.752,1.273)	0.953 (0.765,1.188)	1.076 (0.910,1.272)	0.903 (0.737,1.106)	0.5685	0.6706
rs6594499 (WDR36 and CAMK4)	1.089 (0.877,1.353)	1.055 (0.852,1.307)	1.082 (0.916,1.279)	1.183 (1.010,1.385)	1.032 (0.905,1.176)	1.094 (0.986,1.213)	1.051 (0.934,1.183)	0.8866	0.4412
Other SNPs									
rs2104047	1.226 (0.974,1.544)	1.258 (1.004,1.577)	1.150 (0.961,1.376)	1.100 (0.927,1.305)	0.928 (0.802,1.075)	0.980 (0.874,1.099)	0.978 (0.858,1.115)	0.0714	0.0961
rs7512552	1.179 (0.950,1.463)	1.142 (0.923,1.412)	1.112 (0.942,1.313)	0.952 (0.815,1.113)	0.874 (0.768,0.995)	1.005 (0.907,1.113)	1.029 (0.915,1.156)	0.0852	0.1329
rs6776757	1.122 (0.904,1.393)	1.084 (0.876,1.341)	0.942 (0.798,1.113)	1.159 (0.990,1.357)	1.092 (0.959,1.244)	0.945 (0.852,1.047)	0.949 (0.843,1.067)	0.1087	0.1645
rs7936323	1.412 (1.137,1.752)	0.976 (0.790,1.206)	1.029 (0.872,1.213)	0.986 (0.843,1.152)	1.043 (0.917,1.187)	1.060 (0.957,1.174)	1.033 (0.919,1.161)	0.174	0.1392
rs7824394	1.279 (1.028,1.591)	1.218 (0.981,1.512)	1.025 (0.863,1.217)	1.074 (0.914,1.262)	1.028 (0.898,1.176)	0.979 (0.879,1.089)	0.980 (0.867,1.107)	0.1951	0.2317
rs343478	1.105 (0.886,1.378)	1.018 (0.820,1.264)	0.865 (0.731,1.023)	1.112 (0.947,1.305)	0.935 (0.819,1.067)	0.987 (0.889,1.096)	0.908 (0.806,1.023)	0.1987	0.2267

rs1059513	1.432 (0.969,2.118)	1.453 (0.986,2.140)	1.223 (0.921,1.622)	1.196 (0.918,1.559)	1.097 (0.887,1.357)	1.190 (1.002,1.414)	0.946 (0.787,1.137)	0.1995	0.0679
rs3091307	1.113 (0.847,1.463)	1.239 (0.954,1.609)	1.339 (1.094,1.637)	1.112 (0.911,1.356)	1.093 (0.926,1.290)	1.032 (0.903,1.179)	0.986 (0.845,1.150)	0.2158	0.1124
rs2766678	0.959 (0.732,1.258)	0.961 (0.736,1.254)	1.065 (0.869,1.305)	0.848 (0.692,1.039)	0.885 (0.750,1.045)	1.086 (0.957,1.231)	0.962 (0.830,1.115)	0.2422	0.3254
rs12365699	1.241 (0.906,1.700)	1.078 (0.802,1.447)	1.190 (0.938,1.510)	0.931 (0.757,1.146)	0.935 (0.787,1.110)	0.951 (0.829,1.091)	1.109 (0.941,1.307)	0.2447	0.3329
rs4574025	1.383 (1.103,1.735)	1.101 (0.885,1.370)	1.022 (0.862,1.212)	1.167 (0.993,1.373)	1.028 (0.900,1.175)	1.055 (0.949,1.172)	1.025 (0.908,1.156)	0.2456	0.1254
rs12440045	1.249 (0.997,1.564)	1.015 (0.815,1.264)	0.964 (0.812,1.144)	1.109 (0.943,1.305)	0.973 (0.851,1.112)	1.028 (0.925,1.144)	0.940 (0.833,1.062)	0.2825	0.3761
rs7207591	0.967 (0.741,1.262)	1.127 (0.859,1.479)	1.279 (1.028,1.592)	0.996 (0.819,1.210)	0.921 (0.786,1.080)	1.033 (0.909,1.175)	0.992 (0.858,1.148)	0.2934	0.38
rs1057258	1.220 (0.900,1.654)	0.872 (0.664,1.145)	1.124 (0.894,1.412)	0.959 (0.780,1.179)	0.974 (0.821,1.157)	0.883 (0.773,1.009)	0.973 (0.833,1.137)	0.3158	0.3449
rs114333358	0.854 (0.685,1.066)	0.959 (0.773,1.189)	1.015 (0.859,1.200)	1.143 (0.977,1.337)	0.996 (0.874,1.135)	0.995 (0.897,1.103)	1.086 (0.965,1.222)	0.3252	0.3984
rs2228145	1.350 (1.089,1.673)	1.112 (0.899,1.376)	1.108 (0.938,1.309)	1.013 (0.865,1.187)	1.157 (1.015,1.317)	1.050 (0.946,1.164)	1.057 (0.939,1.190)	0.3294	0.0836
rs848	1.423 (1.097,1.846)	1.354 (1.045,1.755)	1.264 (1.027,1.555)	1.130 (0.923,1.382)	1.118 (0.945,1.322)	1.093 (0.956,1.249)	1.087 (0.933,1.267)	0.3398	0.0264
rs4943794	1.210 (0.941,1.555)	1.193 (0.931,1.530)	1.199 (0.987,1.456)	1.070 (0.886,1.292)	1.026 (0.876,1.202)	1.002 (0.884,1.136)	0.969 (0.838,1.120)	0.3604	0.3535
rs4848612	1.370 (1.039,1.807)	1.095 (0.848,1.414)	1.109 (0.908,1.355)	1.010 (0.840,1.215)	0.967 (0.831,1.126)	1.058 (0.936,1.195)	1.134 (0.984,1.307)	0.3607	0.2395
rs144829310	1.201 (0.913,1.579)	1.224 (0.936,1.600)	1.157 (0.935,1.433)	1.229 (1.008,1.498)	1.097 (0.925,1.300)	1.001 (0.872,1.149)	0.997 (0.852,1.168)	0.3681	0.2347
rs3540	1.123 (0.889,1.417)	1.254 (0.992,1.586)	1.021 (0.856,1.218)	1.199 (1.010,1.423)	1.069 (0.930,1.228)	0.999 (0.896,1.114)	1.103 (0.972,1.251)	0.3789	0.192
rs10174949	1.294 (1.009,1.660)	1.239 (0.972,1.579)	1.051 (0.876,1.262)	1.042 (0.877,1.237)	0.967 (0.841,1.114)	1.084 (0.968,1.214)	1.075 (0.944,1.224)	0.3844	0.2292
rs2854001	1.241 (0.977,1.576)	0.956 (0.745,1.228)	1.110 (0.919,1.341)	0.936 (0.778,1.127)	0.928 (0.795,1.082)	0.999 (0.886,1.126)	1.006 (0.878,1.154)	0.386	0.4998
rs1102705	1.050 (0.732,1.507)	0.887 (0.608,1.294)	1.299 (1.002,1.684)	1.137 (0.880,1.468)	0.944 (0.753,1.182)	0.966 (0.809,1.153)	1.065 (0.875,1.296)	0.407	0.4814
rs17664743	0.793 (0.595,1.056)	1.135 (0.880,1.465)	1.057 (0.863,1.295)	0.898 (0.735,1.097)	0.909 (0.770,1.072)	0.990 (0.871,1.125)	0.930 (0.802,1.079)	0.4267	0.4384
rs9323612	1.103 (0.873,1.393)	1.116 (0.886,1.406)	1.103 (0.922,1.321)	1.144 (0.964,1.357)	0.951 (0.829,1.092)	1.124 (1.005,1.256)	1.016 (0.896,1.152)	0.4273	0.2681
rs1048990	1.322 (1.014,1.724)	1.077 (0.817,1.419)	1.150 (0.930,1.422)	1.051 (0.856,1.291)	0.948 (0.796,1.130)	1.102 (0.965,1.260)	1.026 (0.878,1.198)	0.4403	0.3366
rs13403656	1.159 (0.858,1.567)	1.138 (0.844,1.534)	1.056 (0.832,1.341)	1.001 (0.797,1.258)	0.966 (0.798,1.170)	1.164 (1.008,1.346)	0.957 (0.804,1.138)	0.4612	0.4454
rs2070901	1.235 (0.975,1.564)	0.928 (0.725,1.188)	1.110 (0.922,1.337)	1.090 (0.914,1.300)	0.988 (0.852,1.147)	0.977 (0.868,1.099)	1.039 (0.909,1.188)	0.4663	0.5267

rs2025758	1.150 (0.922,1.436)	1.110 (0.892,1.379)	1.089 (0.919,1.291)	1.165 (0.991,1.368)	1.101 (0.964,1.258)	0.982 (0.884,1.090)	1.027 (0.911,1.158)	0.4671	0.3427
rs55646091	1.283 (0.800,2.058)	0.900 (0.527,1.537)	1.512 (1.071,2.134)	0.941 (0.639,1.386)	1.136 (0.842,1.533)	1.147 (0.904,1.454)	1.037 (0.783,1.372)	0.4751	0.3506
rs10305290	2.207 (1.073,4.540)	1.147 (0.454,2.897)	0.997 (0.462,2.150)	0.897 (0.421,1.913)	1.070 (0.596,1.921)	1.081 (0.681,1.717)	1.502 (0.939,2.404)	0.4901	0.4087
rs7714574	1.124 (0.898,1.407)	1.060 (0.852,1.321)	0.984 (0.830,1.167)	1.110 (0.943,1.306)	1.117 (0.976,1.278)	0.968 (0.871,1.076)	1.061 (0.940,1.198)	0.5029	0.4779
rs6461503	1.225 (0.985,1.525)	1.027 (0.828,1.272)	0.971 (0.821,1.149)	1.004 (0.857,1.177)	0.990 (0.868,1.129)	0.940 (0.847,1.043)	1.001 (0.889,1.127)	0.5031	0.612
rs60946162	0.917 (0.737,1.142)	1.025 (0.826,1.270)	0.985 (0.833,1.165)	1.080 (0.922,1.265)	0.898 (0.787,1.025)	1.018 (0.918,1.130)	0.942 (0.836,1.061)	0.5094	0.5836
rs11644510	1.055 (0.838,1.327)	0.971 (0.776,1.215)	1.017 (0.853,1.213)	0.955 (0.809,1.126)	1.103 (0.960,1.268)	0.946 (0.849,1.054)	1.060 (0.935,1.202)	0.533	0.6424
rs13384448	1.097 (0.848,1.419)	1.053 (0.819,1.353)	1.130 (0.925,1.379)	1.040 (0.864,1.251)	0.941 (0.810,1.093)	1.136 (1.005,1.285)	1.089 (0.947,1.252)	0.5407	0.364
rs61192126	1.262 (0.981,1.624)	1.210 (0.946,1.547)	1.110 (0.919,1.340)	1.107 (0.926,1.322)	0.989 (0.856,1.143)	1.066 (0.950,1.197)	1.022 (0.896,1.166)	0.5512	0.3693
rs150254607	1.406 (0.988,2.001)	1.163 (0.799,1.692)	1.094 (0.809,1.478)	0.892 (0.655,1.215)	1.000 (0.784,1.277)	1.090 (0.904,1.316)	1.012 (0.813,1.262)	0.5673	0.5796
rs11464691	1.165 (0.927,1.463)	1.130 (0.904,1.413)	0.898 (0.758,1.064)	0.996 (0.847,1.172)	0.999 (0.874,1.143)	1.015 (0.913,1.129)	0.992 (0.878,1.120)	0.5734	0.6843
rs227275	1.107 (0.891,1.374)	1.070 (0.865,1.324)	1.040 (0.881,1.228)	0.997 (0.853,1.166)	0.956 (0.840,1.088)	1.002 (0.904,1.110)	1.110 (0.987,1.249)	0.6096	0.645
rs740474	1.005 (0.806,1.253)	0.965 (0.776,1.200)	0.882 (0.743,1.048)	0.887 (0.754,1.043)	1.014 (0.888,1.158)	1.019 (0.918,1.132)	0.954 (0.845,1.076)	0.6253	0.6612
rs6489785	0.940 (0.752,1.176)	1.030 (0.828,1.282)	0.934 (0.786,1.110)	1.087 (0.926,1.276)	0.927 (0.810,1.060)	0.958 (0.861,1.065)	1.032 (0.915,1.165)	0.6358	0.717
rs13153019	1.166 (0.909,1.495)	1.040 (0.809,1.336)	0.985 (0.808,1.201)	0.922 (0.762,1.115)	0.978 (0.837,1.142)	0.949 (0.838,1.073)	1.062 (0.925,1.219)	0.6364	0.7435
rs3787184	1.239 (0.901,1.702)	0.911 (0.684,1.214)	1.075 (0.850,1.359)	1.062 (0.852,1.324)	0.951 (0.796,1.136)	1.016 (0.881,1.172)	1.111 (0.940,1.314)	0.6489	0.6934
rs10519067	1.059 (0.761,1.475)	1.064 (0.768,1.475)	1.131 (0.872,1.467)	1.318 (1.017,1.708)	1.083 (0.886,1.323)	0.992 (0.850,1.157)	1.104 (0.920,1.325)	0.649	0.5207
rs9383820	1.141 (0.867,1.501)	1.191 (0.906,1.566)	1.071 (0.870,1.317)	1.175 (0.961,1.436)	1.016 (0.866,1.192)	0.988 (0.872,1.121)	1.009 (0.874,1.166)	0.6492	0.6554
rs3749833	1.257 (0.993,1.591)	0.936 (0.731,1.198)	0.993 (0.821,1.201)	1.014 (0.848,1.212)	1.027 (0.886,1.191)	0.997 (0.886,1.121)	0.989 (0.864,1.131)	0.653	0.7486
rs9989163	1.220 (0.980,1.519)	0.916 (0.737,1.138)	1.003 (0.847,1.188)	1.074 (0.916,1.260)	1.017 (0.891,1.160)	1.023 (0.922,1.136)	1.018 (0.903,1.147)	0.6617	0.6966
rs4671601	1.265 (0.941,1.701)	1.332 (0.990,1.792)	1.199 (0.959,1.500)	1.087 (0.885,1.334)	1.138 (0.958,1.351)	1.065 (0.932,1.217)	1.053 (0.904,1.226)	0.679	0.2467
rs10414065	1.227 (0.740,2.034)	1.349 (0.804,2.262)	1.266 (0.855,1.876)	1.136 (0.796,1.622)	1.018 (0.766,1.351)	0.958 (0.769,1.193)	1.183 (0.903,1.550)	0.6794	0.6555
rs71368508	0.799 (0.372,1.716)	1.478 (0.557,3.918)	1.039 (0.539,2.001)	1.205 (0.625,2.325)	0.753 (0.478,1.187)	0.907 (0.616,1.335)	1.201 (0.736,1.958)	0.6808	0.7745

rs17607589	1.062 (0.795,1.419)	0.918 (0.698,1.205)	1.135 (0.904,1.425)	1.238 (0.992,1.544)	1.122 (0.940,1.340)	1.041 (0.908,1.194)	1.054 (0.900,1.233)	0.6845	0.5011
rs149130795	1.152 (0.716,1.853)	1.119 (0.705,1.777)	1.119 (0.780,1.605)	0.919 (0.670,1.260)	0.899 (0.693,1.166)	1.166 (0.931,1.461)	1.039 (0.811,1.331)	0.7044	0.7655
rs1143633	1.001 (0.795,1.259)	1.225 (0.970,1.547)	1.011 (0.847,1.207)	1.082 (0.914,1.281)	1.025 (0.892,1.178)	0.991 (0.889,1.106)	0.985 (0.869,1.116)	0.7084	0.7782
rs1444789	1.159 (0.889,1.513)	1.223 (0.944,1.583)	1.029 (0.833,1.272)	1.100 (0.904,1.339)	1.077 (0.914,1.269)	0.980 (0.858,1.119)	1.055 (0.909,1.225)	0.7169	0.6516
rs2893907	1.178 (0.948,1.465)	0.924 (0.748,1.143)	0.963 (0.816,1.137)	1.036 (0.885,1.212)	0.969 (0.851,1.103)	0.980 (0.885,1.086)	1.006 (0.894,1.131)	0.7174	0.8111
rs760805	1.076 (0.864,1.341)	0.924 (0.745,1.146)	1.143 (0.964,1.355)	1.109 (0.944,1.301)	1.027 (0.900,1.172)	1.037 (0.934,1.152)	1.007 (0.894,1.135)	0.7201	0.6683
rs111914382	0.958 (0.740,1.241)	0.921 (0.712,1.191)	1.014 (0.833,1.233)	0.933 (0.772,1.127)	0.951 (0.814,1.112)	1.070 (0.949,1.207)	1.051 (0.916,1.207)	0.7218	0.81
rs11255753	1.199 (0.949,1.516)	1.006 (0.793,1.277)	1.069 (0.889,1.285)	1.117 (0.940,1.328)	1.036 (0.896,1.198)	0.985 (0.878,1.106)	1.015 (0.889,1.158)	0.724	0.7311
rs10910095	1.214 (0.867,1.700)	0.912 (0.675,1.233)	0.980 (0.770,1.247)	1.056 (0.836,1.333)	1.020 (0.843,1.234)	1.124 (0.963,1.313)	1.139 (0.952,1.361)	0.7305	0.6033
rs519973	0.988 (0.787,1.240)	0.960 (0.767,1.202)	1.028 (0.863,1.223)	0.975 (0.826,1.150)	0.905 (0.788,1.040)	1.009 (0.906,1.124)	0.907 (0.800,1.028)	0.7394	0.7185
rs116053081	0.932 (0.741,1.173)	1.023 (0.818,1.278)	0.962 (0.807,1.147)	1.061 (0.901,1.250)	1.029 (0.898,1.179)	0.991 (0.889,1.104)	1.101 (0.974,1.245)	0.74	0.788
rs5029937	1.701 (0.782,3.698)	0.892 (0.505,1.573)	1.012 (0.633,1.620)	0.857 (0.567,1.296)	1.096 (0.750,1.602)	0.913 (0.690,1.208)	1.057 (0.754,1.483)	0.7418	0.8319
rs56375023	1.039 (0.814,1.327)	1.009 (0.792,1.287)	1.121 (0.932,1.349)	1.033 (0.865,1.235)	0.934 (0.803,1.086)	0.957 (0.850,1.078)	1.016 (0.888,1.162)	0.743	0.8341
rs10760123	1.119 (0.892,1.403)	1.072 (0.857,1.342)	1.129 (0.949,1.344)	1.031 (0.873,1.217)	0.960 (0.836,1.103)	1.001 (0.898,1.116)	1.045 (0.923,1.183)	0.7563	0.7822
rs10876864	0.991 (0.796,1.235)	0.913 (0.734,1.136)	1.024 (0.865,1.212)	1.137 (0.970,1.332)	1.068 (0.936,1.218)	1.018 (0.917,1.131)	1.033 (0.917,1.164)	0.7599	0.7463
rs2134814	1.004 (0.802,1.256)	0.896 (0.720,1.114)	1.042 (0.875,1.239)	1.077 (0.913,1.270)	1.008 (0.881,1.154)	1.049 (0.942,1.168)	0.962 (0.851,1.086)	0.7626	0.8377
rs11204896	1.401 (0.939,2.090)	1.129 (0.786,1.622)	1.340 (0.991,1.812)	1.105 (0.848,1.440)	1.047 (0.844,1.299)	1.128 (0.948,1.342)	1.081 (0.888,1.316)	0.7703	0.3914
rs12596613	1.090 (0.859,1.382)	1.077 (0.852,1.361)	1.096 (0.912,1.316)	1.055 (0.888,1.253)	0.953 (0.828,1.096)	1.041 (0.930,1.165)	0.972 (0.856,1.105)	0.7813	0.8351
rs11255968	0.971 (0.519,1.815)	1.156 (0.593,2.253)	1.327 (0.763,2.308)	1.055 (0.658,1.691)	0.872 (0.608,1.252)	1.159 (0.842,1.595)	1.249 (0.855,1.822)	0.7827	0.7889
rs10883723	0.949 (0.755,1.192)	0.961 (0.767,1.202)	0.953 (0.800,1.136)	1.016 (0.862,1.198)	0.989 (0.863,1.134)	0.991 (0.889,1.104)	1.094 (0.968,1.236)	0.785	0.8636
rs113453523	1.069 (0.826,1.383)	1.242 (0.954,1.618)	1.196 (0.975,1.466)	1.209 (0.997,1.466)	1.046 (0.896,1.220)	1.078 (0.953,1.219)	1.124 (0.976,1.296)	0.7865	0.213
rs4090390	1.000 (0.769,1.300)	1.104 (0.857,1.422)	1.133 (0.930,1.379)	1.024 (0.847,1.238)	0.962 (0.820,1.128)	1.050 (0.928,1.189)	0.966 (0.836,1.115)	0.7876	0.8422
rs12413578	1.176 (0.807,1.714)	1.292 (0.879,1.897)	1.230 (0.917,1.651)	1.015 (0.783,1.316)	1.155 (0.923,1.445)	1.097 (0.921,1.305)	1.001 (0.825,1.215)	0.7904	0.593

rs55726902	0.934 (0.725,1.202)	1.061 (0.821,1.371)	0.891 (0.735,1.081)	0.991 (0.823,1.194)	1.061 (0.907,1.241)	0.971 (0.860,1.097)	1.030 (0.895,1.186)	0.7954	0.8728
rs250308	1.119 (0.901,1.390)	1.061 (0.856,1.315)	1.092 (0.924,1.291)	0.953 (0.812,1.119)	0.967 (0.847,1.104)	1.019 (0.918,1.131)	1.027 (0.911,1.157)	0.7974	0.8493
rs9889262	1.062 (0.852,1.323)	0.994 (0.799,1.237)	1.079 (0.911,1.279)	0.967 (0.822,1.137)	1.037 (0.908,1.185)	0.984 (0.885,1.094)	1.089 (0.966,1.228)	0.7974	0.8227
rs697852	1.113 (0.831,1.491)	1.199 (0.893,1.609)	1.170 (0.932,1.470)	1.138 (0.919,1.409)	1.089 (0.914,1.296)	1.086 (0.946,1.246)	0.983 (0.842,1.147)	0.7984	0.5584
rs75557865	1.066 (0.861,1.318)	0.948 (0.770,1.169)	1.054 (0.895,1.241)	1.134 (0.971,1.324)	1.012 (0.891,1.150)	1.012 (0.914,1.119)	0.994 (0.885,1.115)	0.7985	0.8326
rs72782676	1.148 (0.273,4.822)	0.779 (0.237,2.565)	1.264 (0.401,3.990)	1.352 (0.443,4.125)	0.704 (0.346,1.430)	1.379 (0.668,2.846)	1.298 (0.574,2.933)	0.8027	0.8711
rs4296977	0.976 (0.712,1.338)	0.999 (0.734,1.360)	1.063 (0.840,1.347)	1.012 (0.807,1.269)	1.100 (0.916,1.321)	0.962 (0.828,1.119)	0.915 (0.768,1.090)	0.804	0.8803
rs1814576	1.133 (0.733,1.750)	0.877 (0.545,1.410)	1.224 (0.883,1.695)	1.126 (0.820,1.547)	0.938 (0.708,1.244)	1.139 (0.924,1.403)	1.129 (0.889,1.433)	0.8047	0.7072
rs74847330	1.099 (0.775,1.558)	0.893 (0.648,1.230)	1.058 (0.812,1.379)	1.249 (0.959,1.627)	1.063 (0.864,1.307)	1.053 (0.894,1.239)	1.110 (0.918,1.342)	0.811	0.7029
rs5758343	1.044 (0.800,1.364)	1.104 (0.852,1.429)	0.986 (0.800,1.214)	1.051 (0.866,1.275)	1.137 (0.971,1.331)	1.129 (0.996,1.279)	1.014 (0.876,1.174)	0.813	0.5603
rs11236814	1.025 (0.688,1.527)	1.086 (0.727,1.624)	1.112 (0.811,1.526)	1.296 (0.945,1.777)	0.996 (0.785,1.263)	0.980 (0.813,1.182)	1.025 (0.825,1.274)	0.8155	0.8575
rs6011033	1.206 (0.919,1.581)	1.003 (0.778,1.294)	1.174 (0.955,1.444)	1.007 (0.835,1.215)	1.042 (0.891,1.219)	1.119 (0.987,1.270)	1.073 (0.930,1.238)	0.8213	0.4894
rs10068717	1.117 (0.890,1.402)	0.972 (0.780,1.212)	1.040 (0.874,1.237)	1.037 (0.880,1.221)	0.976 (0.852,1.116)	1.072 (0.963,1.194)	0.982 (0.869,1.110)	0.8222	0.8525
rs9372120	1.203 (0.934,1.549)	1.038 (0.801,1.345)	1.015 (0.828,1.244)	1.068 (0.883,1.291)	1.082 (0.925,1.265)	0.983 (0.866,1.116)	1.014 (0.878,1.171)	0.8258	0.8401
rs6869502	1.039 (0.768,1.406)	0.885 (0.646,1.213)	1.092 (0.868,1.373)	1.170 (0.947,1.447)	1.079 (0.901,1.293)	1.015 (0.878,1.174)	1.036 (0.878,1.223)	0.8278	0.8051
rs10947428	1.020 (0.782,1.331)	0.990 (0.760,1.290)	1.103 (0.902,1.349)	1.040 (0.858,1.261)	0.929 (0.788,1.095)	1.063 (0.937,1.205)	1.011 (0.874,1.169)	0.8433	0.8839
rs9573092	0.915 (0.731,1.146)	1.147 (0.913,1.441)	0.980 (0.823,1.167)	0.967 (0.820,1.140)	1.035 (0.902,1.188)	0.998 (0.896,1.113)	0.981 (0.867,1.110)	0.8453	0.9109
rs7137828	0.976 (0.787,1.211)	1.140 (0.921,1.411)	1.075 (0.910,1.270)	1.146 (0.979,1.341)	1.085 (0.952,1.236)	1.028 (0.928,1.140)	1.072 (0.953,1.206)	0.8485	0.5413
rs10486391	0.974 (0.783,1.211)	1.087 (0.876,1.350)	0.922 (0.780,1.090)	1.061 (0.905,1.245)	0.982 (0.861,1.119)	0.974 (0.878,1.081)	1.013 (0.899,1.141)	0.8518	0.9131
rs4145717	1.008 (0.798,1.272)	1.203 (0.961,1.505)	1.131 (0.948,1.349)	1.100 (0.931,1.301)	1.034 (0.899,1.190)	1.125 (1.008,1.256)	1.134 (1.000,1.285)	0.855	0.2062
rs35469349	1.101 (0.863,1.403)	1.059 (0.832,1.348)	1.090 (0.903,1.314)	1.105 (0.926,1.318)	0.951 (0.818,1.106)	1.053 (0.936,1.183)	1.042 (0.911,1.191)	0.8573	0.8037
rs10865050	1.010 (0.742,1.375)	1.027 (0.757,1.394)	1.266 (0.980,1.636)	1.203 (0.949,1.526)	1.164 (0.958,1.413)	1.162 (0.997,1.354)	1.084 (0.913,1.286)	0.8634	0.2654
rs9259819	1.051 (0.839,1.315)	0.973 (0.780,1.214)	1.099 (0.924,1.306)	1.053 (0.894,1.240)	1.085 (0.948,1.242)	1.134 (1.019,1.263)	1.047 (0.926,1.183)	0.8736	0.4527

rs72033857	0.900 (0.622,1.303)	0.754 (0.511,1.112)	1.036 (0.790,1.359)	1.005 (0.776,1.301)	0.988 (0.797,1.226)	0.947 (0.797,1.126)	0.996 (0.820,1.209)	0.8808	0.9106
rs2988277	1.011 (0.809,1.262)	0.968 (0.778,1.204)	1.032 (0.869,1.225)	1.030 (0.876,1.210)	0.931 (0.815,1.063)	1.041 (0.936,1.158)	0.997 (0.884,1.125)	0.8812	0.9347
rs4801001	1.076 (0.860,1.346)	1.186 (0.952,1.479)	1.157 (0.974,1.374)	1.081 (0.919,1.273)	1.066 (0.932,1.220)	1.073 (0.965,1.194)	1.026 (0.908,1.160)	0.8932	0.5079
rs16922576	0.991 (0.778,1.263)	1.024 (0.808,1.299)	0.999 (0.829,1.203)	0.910 (0.761,1.089)	0.934 (0.806,1.083)	1.021 (0.910,1.145)	0.950 (0.832,1.086)	0.8957	0.9167
rs76081789	0.990 (0.619,1.584)	0.903 (0.579,1.410)	0.915 (0.645,1.300)	0.867 (0.627,1.199)	0.947 (0.717,1.251)	0.969 (0.775,1.210)	1.128 (0.861,1.476)	0.8996	0.9375
rs13088318	1.069 (0.850,1.344)	1.149 (0.915,1.444)	1.187 (0.992,1.420)	1.055 (0.893,1.245)	1.030 (0.898,1.181)	1.062 (0.952,1.184)	1.081 (0.954,1.225)	0.9017	0.5464
rs78486128	1.059 (0.640,1.753)	0.710 (0.462,1.091)	0.919 (0.636,1.329)	0.883 (0.626,1.244)	0.987 (0.734,1.327)	0.904 (0.719,1.135)	0.941 (0.722,1.224)	0.9022	0.8446
rs76167968	0.911 (0.616,1.348)	0.883 (0.603,1.293)	1.143 (0.823,1.588)	1.094 (0.806,1.484)	0.974 (0.764,1.240)	0.946 (0.783,1.144)	0.962 (0.774,1.197)	0.9091	0.9462
rs301806	1.003 (0.808,1.247)	1.066 (0.860,1.322)	0.967 (0.818,1.142)	1.033 (0.882,1.210)	1.017 (0.893,1.160)	0.953 (0.859,1.056)	1.025 (0.910,1.154)	0.9121	0.955
rs73205303	0.928 (0.687,1.253)	0.841 (0.619,1.141)	0.851 (0.671,1.080)	0.991 (0.801,1.227)	0.857 (0.713,1.031)	0.937 (0.813,1.080)	0.929 (0.789,1.094)	0.9173	0.6136
rs7717955	1.151 (0.898,1.476)	0.993 (0.784,1.259)	1.055 (0.874,1.273)	1.019 (0.855,1.215)	1.088 (0.939,1.262)	0.999 (0.890,1.120)	1.052 (0.921,1.201)	0.921	0.8925
rs114305667	1.060 (0.749,1.498)	0.964 (0.693,1.340)	0.895 (0.696,1.152)	1.040 (0.810,1.336)	0.973 (0.795,1.192)	1.032 (0.877,1.215)	0.925 (0.772,1.108)	0.9212	0.9539
rs63406760	0.912 (0.705,1.178)	1.026 (0.790,1.332)	1.029 (0.839,1.263)	1.126 (0.924,1.371)	1.024 (0.873,1.201)	1.005 (0.887,1.139)	1.042 (0.901,1.204)	0.9213	0.9401
rs56129466	1.007 (0.772,1.315)	1.017 (0.782,1.324)	1.100 (0.891,1.357)	0.996 (0.821,1.209)	1.031 (0.877,1.212)	1.117 (0.981,1.272)	1.027 (0.887,1.188)	0.9248	0.8477
rs12551834	1.148 (0.747,1.762)	1.251 (0.809,1.935)	1.007 (0.735,1.380)	0.948 (0.708,1.268)	1.001 (0.783,1.280)	0.969 (0.799,1.175)	0.959 (0.770,1.194)	0.9275	0.964
rs10663129	1.119 (0.891,1.404)	1.097 (0.877,1.373)	1.078 (0.904,1.285)	1.047 (0.887,1.237)	1.028 (0.895,1.181)	1.005 (0.901,1.122)	0.991 (0.874,1.124)	0.9314	0.9321
rs1064213	0.934 (0.753,1.159)	0.969 (0.783,1.198)	0.951 (0.805,1.123)	0.984 (0.841,1.152)	0.957 (0.840,1.090)	0.939 (0.847,1.041)	1.027 (0.913,1.156)	0.9328	0.9113
rs2030030	0.946 (0.706,1.268)	1.018 (0.758,1.368)	1.187 (0.932,1.512)	1.049 (0.842,1.307)	1.044 (0.870,1.251)	1.043 (0.904,1.204)	1.040 (0.883,1.226)	0.9486	0.9241
rs7130753	0.949 (0.749,1.203)	1.055 (0.831,1.340)	1.035 (0.860,1.247)	1.003 (0.843,1.195)	1.054 (0.911,1.220)	1.077 (0.960,1.210)	1.003 (0.880,1.143)	0.9499	0.9332
rs2910162	1.051 (0.833,1.326)	0.997 (0.795,1.252)	1.046 (0.875,1.251)	1.086 (0.916,1.286)	1.040 (0.904,1.196)	0.978 (0.876,1.091)	1.030 (0.908,1.169)	0.9511	0.9627
rs11169225	1.098 (0.841,1.434)	0.985 (0.751,1.292)	1.027 (0.833,1.266)	1.071 (0.881,1.302)	1.111 (0.946,1.305)	1.111 (0.978,1.263)	1.044 (0.901,1.211)	0.968	0.7693
rs6977955	1.169 (0.903,1.515)	1.015 (0.779,1.323)	1.102 (0.900,1.350)	1.028 (0.846,1.249)	1.015 (0.863,1.193)	1.046 (0.921,1.189)	1.048 (0.906,1.212)	0.9734	0.9287
rs59593577	1.102 (0.764,1.591)	0.986 (0.696,1.397)	0.980 (0.747,1.286)	1.058 (0.813,1.376)	1.022 (0.824,1.268)	1.076 (0.905,1.279)	0.972 (0.802,1.179)	0.9806	0.9875

rs1837253	1.056 (0.823,1.356)	1.026 (0.804,1.310)	1.065 (0.878,1.290)	1.023 (0.854,1.224)	1.005 (0.866,1.166)	0.973 (0.866,1.093)	1.030 (0.900,1.179)	0.9816	0.9915
rs80064395	1.014 (0.631,1.628)	0.919 (0.585,1.442)	1.021 (0.709,1.472)	1.123 (0.786,1.604)	1.014 (0.762,1.348)	0.942 (0.756,1.175)	0.977 (0.757,1.260)	0.9867	0.9949
rs4747846	1.021 (0.822,1.269)	1.014 (0.819,1.256)	1.060 (0.897,1.253)	1.002 (0.856,1.174)	1.053 (0.924,1.201)	1.021 (0.921,1.133)	1.010 (0.897,1.137)	0.9973	0.9944
rs76991385	1.049 (0.838,1.314)	0.969 (0.774,1.212)	1.011 (0.849,1.203)	0.993 (0.842,1.171)	1.011 (0.882,1.159)	0.993 (0.892,1.107)	1.004 (0.888,1.136)	0.9993	0.9998

142 * heterogeneity p value from chi-square test excluding the baseline class of 'no disease'

143 † heterogeneity p value from chi-square test including the baseline class of 'no disease'

144 Bonferroni corrected p value threshold is 0.0004 (0.05/135). For the six SNPs reported as disease-specific (rs61816761, rs921650, rs115288876, rs12470864, rs6594499 and

145 rs61839660) (9), a less stringent p-value threshold of 0.008 (0.05/6) was also used.

146

Table S6 Pairwise tests among disease latent classes from associations between individual nominal SNPs and profile latent classes in ALSPAC cohort (Table S5).

		Atopic March	Persistent eczema and wheeze	Persistent eczema LO rhinitis	Persistent wheeze LO rhinitis	Transient wheeze	Eczema only	Rhinitis only
		SNP rs61816761 (<i>FLG</i>)						
Atopic March	SNP rs921650 (<i>GSDMB</i>)		0.23	0.42	3.00E-03	1.88E-03	0.04	7.92E-04
Persistent eczema and wheeze		0.84		0.57	0.11	0.13	0.70	0.09
Persistent eczema LO rhinitis		0.014	0.024		0.015	0.011	0.18	5.25E-03
Persistent wheeze LO rhinitis		0.97	0.79	2.60E-03		0.79	0.09	0.86
Transient wheeze		0.61	0.78	8.84E-03	0.48		0.09	0.91
Eczema only		4.94E-03	9.50E-03	0.99	1.79E-04	5.61E-04		0.05
Rhinitis only		0.012	0.022	0.78	1.01E-03	3.58E-03	0.72	
		SNP rs11652139						
Atopic March	SNP rs479844		0.11	0.041	0.33	0.13	8.25E-04	0.010
Persistent eczema and wheeze		0.69		0.78	0.40	0.68	0.17	0.54
Persistent eczema LO rhinitis		0.54	0.87		0.18	0.39	0.20	0.72
Persistent wheeze LO rhinitis		0.19	0.07	0.021		0.54	2.75E-03	0.05
Transient wheeze		0.57	0.29	0.14	0.29		6.86E-03	0.13
Eczema only		0.99	0.59	0.37	0.05	0.37		0.23
Rhinitis only		0.13	0.04	0.007	0.92	0.17	0.010	
		SNP rs6990534						
Atopic March	SNP rs5743618		0.031	0.10	0.06	0.007	4.09E-03	0.17
Persistent eczema and wheeze		0.05		0.42	0.53	0.97	0.98	0.18
Persistent eczema LO rhinitis		0.06	0.80		0.81	0.27	0.23	0.59
Persistent wheeze LO rhinitis		0.16	0.39	0.49		0.38	0.34	0.40
Transient wheeze		4.21E-03	0.56	0.30	0.07		0.99	0.05
Eczema only		0.012	0.92	0.63	0.18	0.43		0.022
Rhinitis only		0.14	0.33	0.40	0.95	0.023	0.08	

151 MAAS Results

152 **Table S7.** Associations between genetic scores and profile latent classes (weighted by membership probabilities)
 153 before and after excluding SNPs rs61816761 (*FLG*) and rs921650 (*GSDMB*) in MAAS cohort.

Multinomial Odds Ratio (95% CI)		
Allergic diseases latent classes	Stand. Score	Stand. Score excluding <i>FLG</i> and <i>GSDMB</i>
Atopic March	1.889 (1.401,2.546)	1.804 (1.344,2.422)
Persistent eczema and wheeze	1.384 (1.007,1.902)	1.311 (0.957,1.797)
Persistent eczema later-onset rhinitis	1.354 (1.042,1.759)	1.349 (1.041,1.749)
Persistent wheeze later-onset rhinitis	1.576 (1.224 2.030)	1.546 (1.203,1.985)
Transient wheeze	1.115 (0.848,1.465)	1.104 (0.841,1.449)
Eczema only	1.037 (0.847,1.271)	1.008 (0.823,1.234)
Rhinitis only	1.316 (1.056,1.604)	1.290 (1.037,1.604)
P-value for differential association*	0.006	0.007
P-value for any association†	8.06E-05	0.0002

154 Bonferroni corrected significance threshold is 0.000370 (0.05/135)

155 * Heterogeneity p value from chi-square test excluding the baseline class of 'no disease'

156 † Heterogeneity p value from chi-square test including the baseline class of 'no disease' (Multinomial Odds Ratio =1)

157

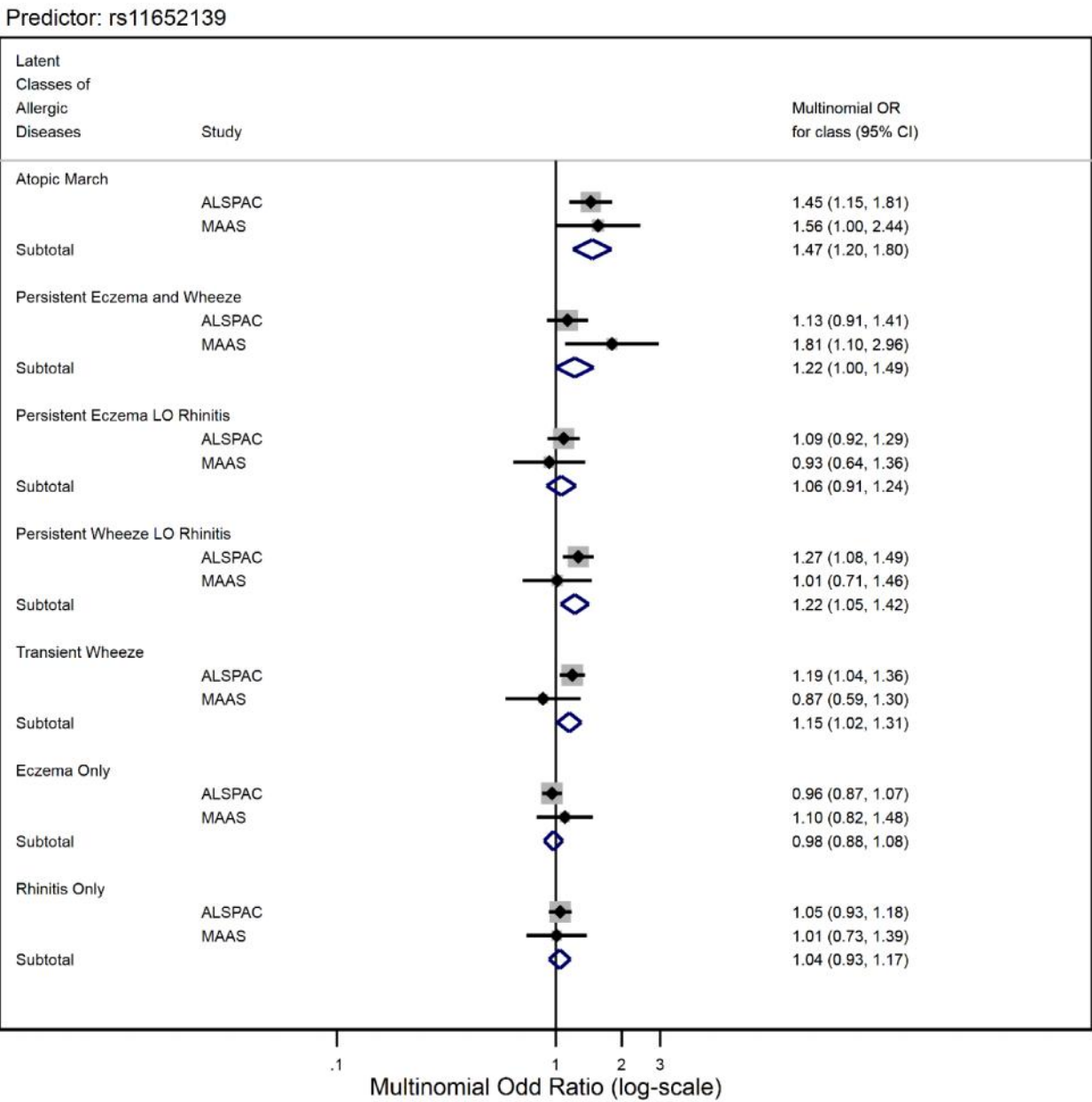
Table S8. Associations between the top six nominal SNPs (heterogeneity p-value excluding the baseline ‘no disease’ class <0.05 in ALSPAC) and allergic diseases latent classes (weighted by membership probabilities) in MAAS cohort.

SNP[RA]	Multinomial Odds Ratio (95% CI)					
	rs921650[A]	rs61816761[A]	rs11652139[A]	rs479844[G]	rs6990534[A]	rs5743618[C]
Nearby Gene	<i>GSDMB</i>	<i>FLG</i>				
MAAS						
Allergic diseases latent classes						
Atopic March	1.491 (0.999, 2.225)	2.107 (0.607, 7.312)	1.560 (0.999,2.437)	1.064 (0.713,1.589)	1.254 (0.812,1.936)	0.948 (0.604,1.490)
Persistent eczema and wheeze	1.753 (1.132, 2.713)	1.632 (0.384, 6.924)	1.806 (1.104,2.955)	1.110 (0.719,1.712)	0.805 (0.486,1.334)	0.808 (0.505,1.291)
Persistent eczema later-onset rhinitis	0.969 (0.679, 1.382)	1.644 (0.495, 5.469)	0.934 (0.640,1.363)	1.108 (0.776,1.581)	1.121 (0.758,1.657)	0.984 (0.657,1.475)
Persistent wheeze later-onset rhinitis	1.467 (1.043, 2.062)	0.670 (0.142, 3.166)	1.015 (0.705,1.461)	0.944 (0.672,1.325)	1.015 (0.694,1.486)	0.972 (0.660,1.431)
Transient wheeze	1.193 (0.824, 1.727)	0.830 (0.171, 4.015)	0.874 (0.589,1.298)	0.783 (0.540,1.135)	0.823 (0.535,1.268)	1.223 (0.780,1.917)
Eczema only	1.322 (1.004, 1.742)	1.285 (0.462, 3.578)	1.101 (0.818,1.481)	1.196 (0.905,1.580)	1.071 (0.788,1.456)	0.845 (0.622,1.147)
Rhinitis only	1.171 (0.871, 1.576)	1.635 (0.585, 4.572)	1.009 (0.734,1.387)	0.996 (0.740,1.341)	0.896 (0.638,1.258)	1.206 (0.844,1.723)
P-value for differential association*	0.298	0.883	0.122	0.567	0.655	0.554
P-value for any association†	0.054	0.861	0.153	0.668	0.761	0.664

RA=risk allele,, Bonferroni corrected significance threshold is 0.00037 (0.05/135)

* Heterogeneity p value from chi-square test excluding the baseline class of ‘no disease’

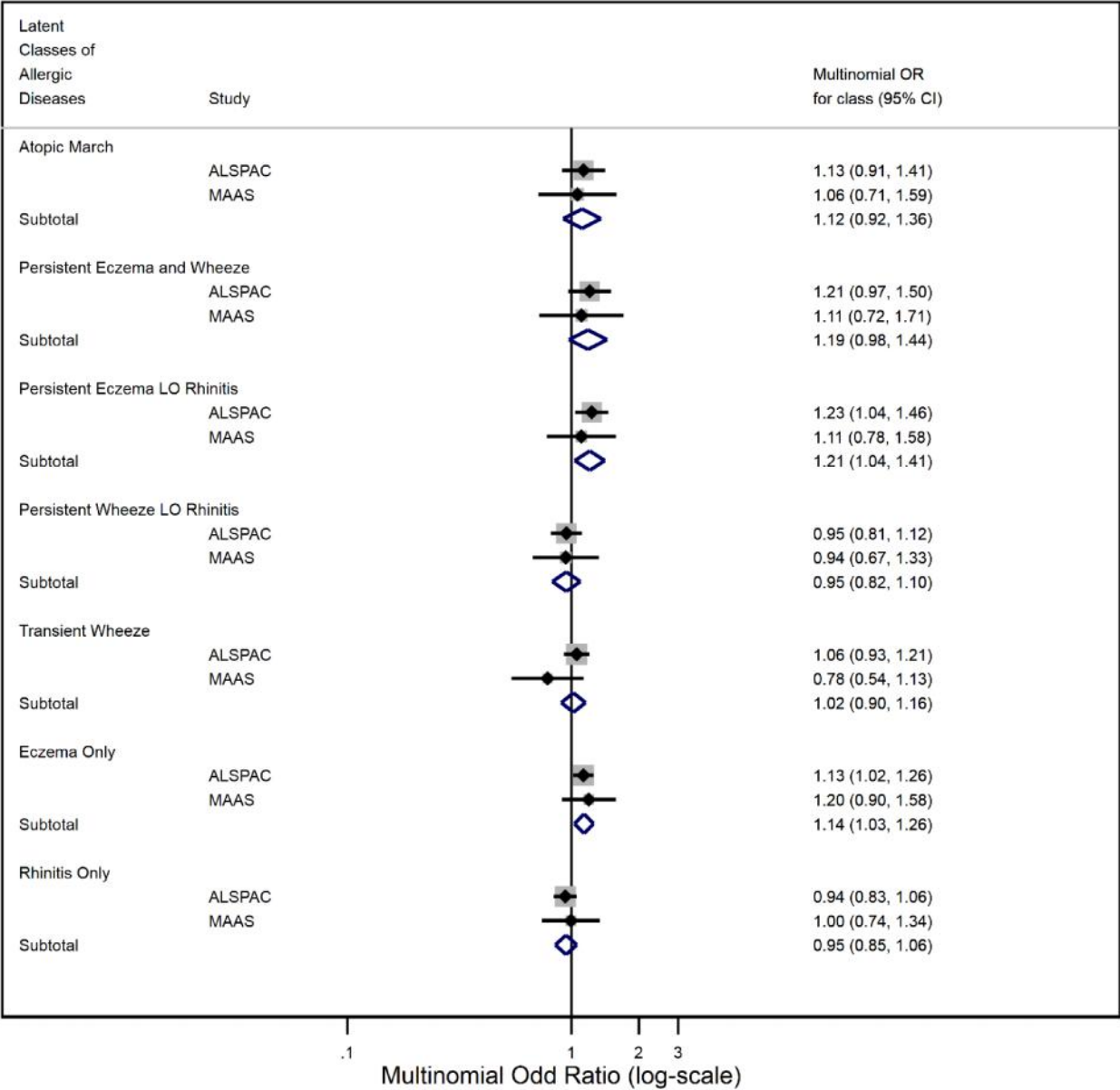
† Heterogeneity p value from chi-square test including the baseline class of ‘no disease’ (Multinomial Odds Ratio =1)



165

166 **Figure S1.** Forest plot of the associations between top nominal SNP rs11652139 [A] and allergic disease latent
167 classes in ALSPAC and MAAS cohorts.

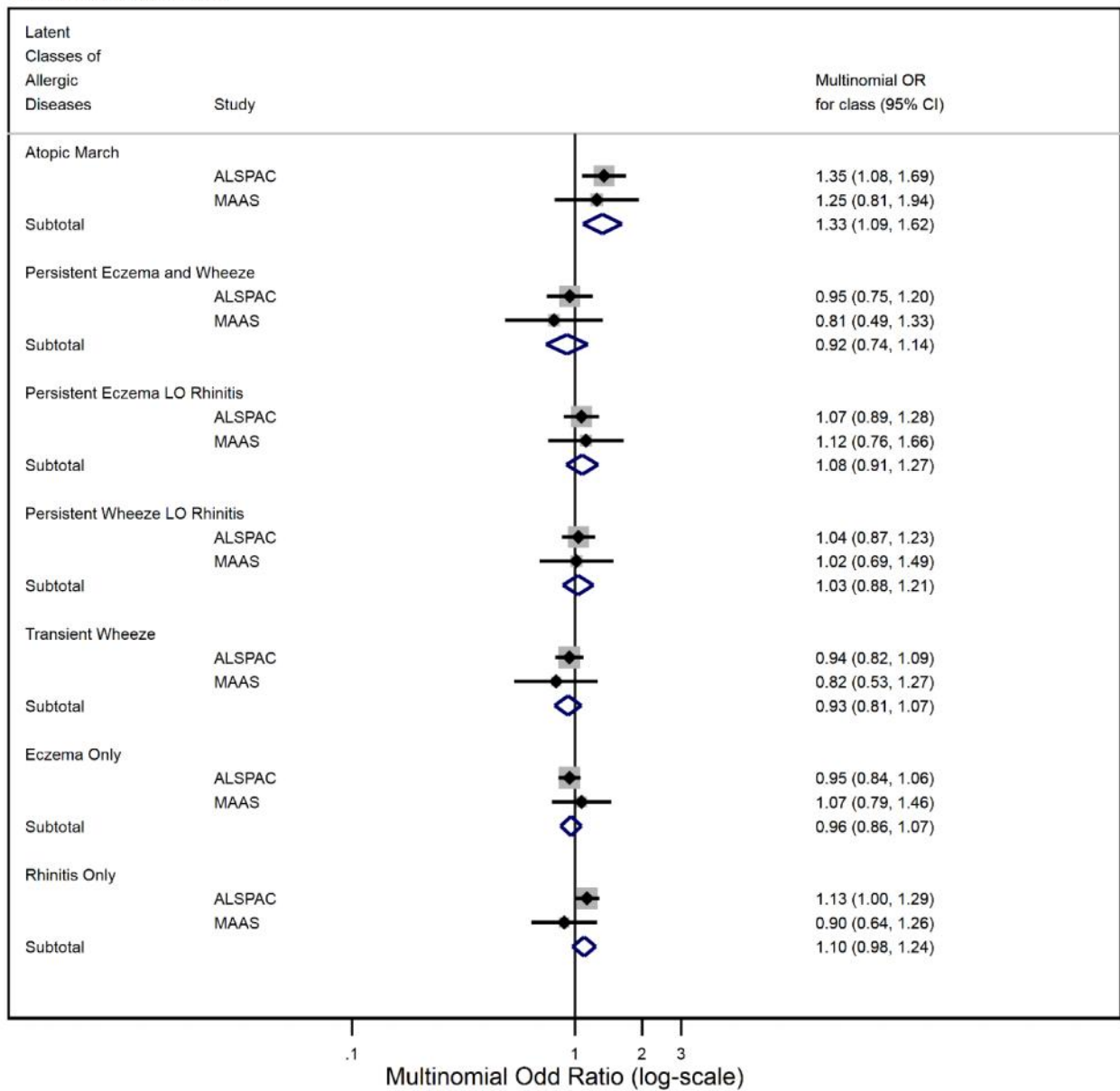
Predictor: rs479844



168

169 **Figure S2.** Forest plot of the associations between top nominal SNP rs479844 [G] and allergic disease latent
170 classes in ALSPAC and MAAS cohorts.

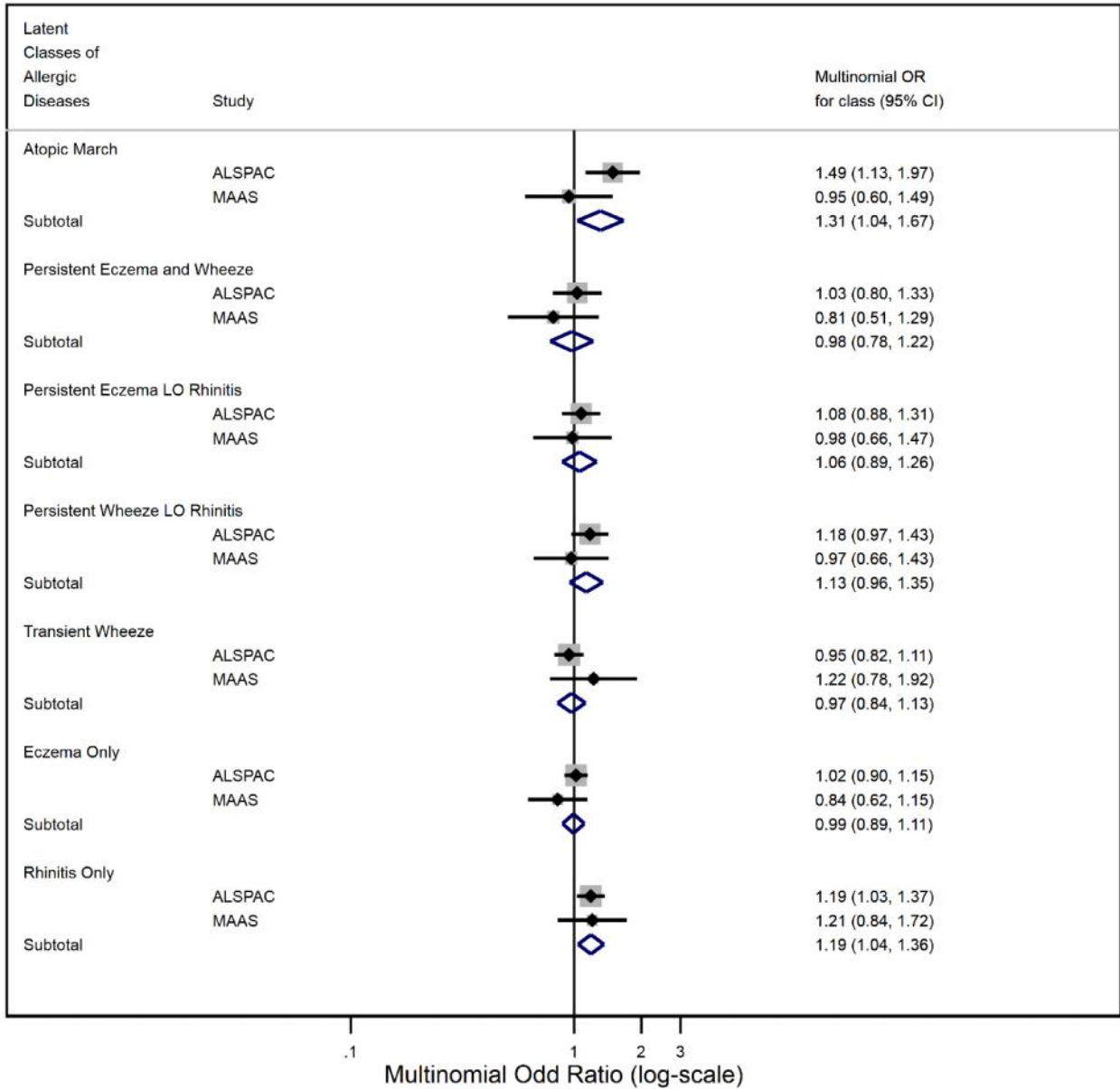
Predictor: rs6990534



171

172 **Figure S3.** Forest plot of the associations between top nominal SNP rs6990534 [A] and allergic disease latent
 173 classes in ALSPAC and MAAS cohorts.

Predictor: rs5743618



174

175 **Figure S4.** Forest plot of the associations between top nominal SNP rs5743618 [C] and allergic disease latent
176 classes in ALSPAC and MAAS cohorts.