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ORIGINAL ARTICLE **Epidemiology of Allergic Disease**

A multi-centre study of candidate genes for wheeze and allergy: the International Study of Asthma and Allergies in Childhood Phase 2

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Summary

Background Common polymorphisms have been identified in genes suspected to play a role in asthma. We investigated their associations with wheeze and allergy in a case–control sample from Phase 2 of the International Study of Asthma and Allergies in Childhood.

Methods We compared 1105 wheezing and 3137 non-wheezing children aged 8–12 years from 17 study centres in 13 countries. Genotyping of 55 candidate single nucleotide polymorphisms (SNPs) in 14 genes was performed using the Sequenom System. Logistic regression models were fitted separately for each centre and each SNP. A combined per allele odds ratio and measures of heterogeneity between centres were derived by random effects meta-analysis.

Results Significant associations with wheeze in the past year were detected in only four genes (*IL4R, TLR4, MS4A2, TLR9*, $P<0.05$), with per allele odds ratios generally <1.3. Variants in *IL4R* and *TLR4* were also related to allergen-specific IgE, while polymorphisms in *FCER1B (MS4A2)* and *TLR9* were not. There were also highly significant associations ($P<0.001$) between *SPINK5* variants and visible eczema (but not IgE levels) and between *IL13* variants and total IgE. Heterogeneity of effects across centres was rare, despite differences in allele frequencies.

Conclusions Despite the biological plausibility of IgE-related mechanisms in asthma, very few of the tested candidates showed evidence of association with both wheeze and increased IgE levels. We were unable to confirm associations of the positional candidates *DPP10* and *PHF11* with wheeze, although our study had ample power to detect the expected associations of *IL13* variants with IgE and *SPINK5* variants with eczema.

Keywords allergy, asthma, candidate genes, multi-centre study
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Introduction

Like other complex diseases, asthma is influenced by both genetic and environmental factors. Twin studies suggest

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*Deceased

that approximately 60% of asthma susceptibility is due to genetic factors, with allergic indices such as serum IgE levels also demonstrating heritability [1]. Environmental factors also play a large role in asthma susceptibility and are likely to underlie the increases that have occurred in the recent decades [2].

Common polymorphisms have been identified in genes suspected to play a role in asthma and allergy by their link to biological mechanisms underlying innate or IgE-mediated immune responses [3]. More recently, data from positional cloning studies have suggested that allergic diseases may also result from an impairment of the epithelial barrier in affected tissues [4].

Well over 100 genes have been associated with asthma- or atopy-related phenotypes and $<50\%$ have been replicated in two or more independent samples [5]. Whole-genome association studies are thought to deliver new insights, and the first one for asthma has identified a region and a gene previously not implicated in asthma [6]. However, sufficiently large candidate gene studies are still warranted to replicate previous reports and deepen the understanding of possible disease pathways.

With the aim of characterizing the genetic influences on childhood asthma and allergies, we identified 55 polymorphisms in 14 candidate genes for asthma and related traits from the literature up to 2002 and the website http://innateimmunity.net at that time [7–19]. We investigated their genetic associations with wheeze and allergy in a case–control sample of children recruited from a worldwide panel of centres with widely varying prevalences of childhood asthma symptoms.

Methods

Study design and population

We compared 1105 wheezing and 3137 non-wheezing children aged 8–12 years from 17 study centres in 13 countries participating in Phase 2 of the International Study of Asthma and Allergies in Childhood (ISAAC) between 1995 and 2002 (Table 1).

The design and survey methods for this international multi-centre study have been described elsewhere [20]. In brief, participating centres randomly selected at least 10 schools from a complete sampling frame of all schools in a defined geographical area in order to obtain data on at least 1000 children. Then, either by simple random sampling (Munich and Dresden) or by stratified random sampling of individuals (all other centres), a nested case–control study of wheezers (defined as having had wheeze in the past 12 months) and non-wheezers was formed in each centre. The study modules comprised, among others, a parental questionnaire, a blood withdrawal, skin prick tests (SPT) and a physical examination for eczema.

Table 1. Prevalence of wheeze per participating ISAAC Phase 2 centre

			Genotyped	
Centre	Total (*N*)	Wheezers, *n* (%)	Wheezers (*n*)	Non-wheezers (*n*)
Northwest				
Germany, Munich*	3235	267 (8.3)	72	780
Norway, Tromso	3431	481 (14.0)	77	71
Sweden, Linkoeping	906	72 (7.9)	54	108
Sweden, Oestersund	1191	122 (10.2)	106	160
UK, West Sussex	1044	169 (16.2)	61	114
Northeast				
Estonia, Tallinn	961	81 (8.4)	40	131
Germany, Dresden*	2975	234 (7.9)	49	558
Southwest				
Italy, Rome	1324	105 (7.9)	30	61
Spain, Almeria	1412	168 (11.9)	82	96
Spain, Cartagena	1102	171 (15.5)	91	113
Spain, Valencia	1338	122 (9.1)	48	163
Southeast				
Georgia, Tbilisi	973	90 (9.2)	54	117
Palestine, Ramallah	2285	200 (8.8)	26	74
Turkey, Ankara	2951	322 (10.9)	99	100
Other				
China, Hong Kong	3011	165 (5.5)	101	124
Ecuador, Pichincha	892	7 (0.8)	5	256
New Zealand, Hastings	1320	289 (21.9)	110	111
Total			1105	3137
Total with skin prick test			993	3035
Total with IgE measurement			863	2550

*Random sampling (as opposed to stratified sampling in other centres).

Informed consent from at least one of the parents was documented and approval was obtained by local ethical committees.

DNA extraction and genotyping

Samples were received as either already-extracted DNA or as blood samples in the form of whole bloods, buffy coats or dried blood spots. Whole blood and buffy coat samples were extracted using the Promega Wizard Genomic DNA Purification Kit (Promega UK Ltd, Southampton, Hampshire, UK), and dried blood spots were extracted using the Qiagen Midi Kit (Qiagen UK Ltd, West Sussex, UK). Samples were processed through a whole-genome amplification step using primer extension pre-amplification in order to increase the amount of available DNA for experimental use. Genotyping was performed in 2002 with the Sequenom System assay of primer extension with detection by MALDI-TOF (www.sequenom.com).

Genes and single nucleotide polymorphisms (SNPs) were chosen based on their observed association with asthma and related traits and a minor allele frequency of at least 20% (Table 2). Previous knowledge was assembled from publications in peer-reviewed journals and the

Table 2. List of genotyped polymorphisms and their characteristics

SNP	rs number	Ref./risk allele		Call rate [% (range)]	HWE $P<0.05$ (no. of centres)
		dbSNP	Tables		
CD14 (Chr. 5)					
CD14 −4189	rs5744441	C/T	T/C	97.0 (92.5–99.3)	1
CD14 −651	rs5744455	C/T	C/T	96.1 (91.2–99.5)	0
CD14 −260	rs2569190	A/G	C/T	96.6 (92.4–99.3)	1
Dipeptidyl-peptidase 10 (*DPP10*) (Chr. 2)					
543WTC 21P	rs7568000	C/T	C/T	90.3 (23.3–98.9)	3
543WTC 122P	rs1430090	T/G	C/A	97.7 (95.9–99.4)	1
543WTC 124P	rs17763180	C/T	T/C	97.8 (92.1–99.6)	2
FCε receptor I β (*MS4A2*) (Chr. 11)					
FCER1B −211	rs1441586	T/C	C/T	98.1 (94.9–99.6)	0
FCER1B +1343	rs2583476	C/T	A/G	97.9 (94.3–99.6)	4
FCER1B +3332	rs2847666	A/G	A/G	97.3 (94.4–99.4)	4
FCER1B +3934	rs502581	C/A	G/T	98.1 (94.0–99.4)	1
FCER1B +5565	rs2583471	C/T	G/A	97.8 (94.1–99.4)	2
FCER1B +5734	rs2070970	C/T	T/C	96.7 (91.9–99.4)	3
FCER1B +10062	rs2855017	C/T	C/T	94.4 (75.0–99.4)	2
FCER1B +11664	rs574704	T/C	A/G	97.8 (95.2–99.5)	1
FCER1B +12841	rs580817	T/C	A/G	96.2 (83.0–99.4)	5
FCER1B +13948	rs521952	T/G	A/C	97.0 (91.0–99.6)	2
Interleukin 4 receptor α chain (*IL4R*) (Chr. 16)					
IL4R +148	rs1805010	A/G	A/G	96.6 (92.8–99.5)	0
IL4R +1124*	rs1805011	A/C	A/C	96.9 (92.0–99.6)	1
IL4R +1232†	rs1805013	C/T	C/T	96.9 (89.0–99.5)	2
IL4R +1431	rs1805015	T/C	T/C	97.8 (95.0–99.6)	1
IL4R +1651‡	rs1801275	A/G	G/A	96.9 (93.0–99.4)	2
Interleukin 13 (*IL13*) (Chr. 5)					
IL13 −1111	rs1800925	C/T	C/T	97.1 (89.3–99.6)	2
IL13 +389§	rs20541	T/C	A/G	96.9 (90.5–99.4)	3
IL13 +870	rs1295685	T/C	G/A	96.9 (93.0–99.6)	3
IL13 +925	rs848	T/G	C/A	96.1 (88.4–99.4)	2
PHD finger protein 11 (*PHF11*) (Chr. 13)					
185752 B4.2	rs3765526	A/G	A/G	96.2 (91.6–99.4)	2
185752 B5.2	rs9526569	C/T	C/T	96.3 (85.0–99.6)	10
185752 B5.3	rs1046295	G/A	A/G	96.9 (92.9–99.6)	3
RCBTB1¶ (Chr. 13)					
4321017 B38_1	rs9535302	A/G	C/T	93.3 (74.0–99.6)	2
SET domain, bifurcated 2 (*SETDB2*) (Chr. 13)					
185316 B1.1	rs11619265	A/G	A/G	93.5 (81.0–99.4)	3
Serine peptidase inhibitor, Kazal type 5 (*SPINK5*) (Chr. 5)					
SPINK5 1258‖	rs2303067	A/G	A/G	96.7 (90.0–99.4)	5
SPINK5 1557	rs880687	G/T	A/C	97.4 (92.4–99.3)	3
SPINK5 1659	rs2303071	G/A	T/C	97.5 (91.0–99.3)	3
SPINK5 1888-54	rs3815735	C/T	A/G	96.4 (92.4–99.4)	0
SPINK5 475-86	rs4529181	G/C	C/G	96.9 (91.8–99.6)	0
SPINK5 56-125	rs2287772	T/C	A/G	96.5 (92.2–99.6)	0
SPINK5 82-31	rs1423001	T/C	A/G	96.2 (91.9–99.6)	0
SPINK5 F2_1	rs3756688	C/T	A/G	97.3 (90.0–99.4)	0
Transforming growth factor β 1 (*TGFB1*) (Chr. 19)					
TGFB1 −509	rs1800469	T/C	C/T	95.9 (76.0–99.3)	0
Toll-like receptor 2 (*TLR2*) (Chr. 4)					
TLR2 −15606	rs1898830	A/G	A/G	95.5 (90.0–99.3)	2
Toll-like receptor 4 (*TLR4*) (Chr. 9)					
TLR4 −6142	rs1927914	C/T	G/A	96.9 (93.7–99.4)	0
TLR4 +50017	rs11536891	T/C	T/C	96.7 (91.4–99.4)	0

Table 2. continued

SNP	rs number	Ref./risk allele		Call rate [% (range)]	HWE $P<0.05$ (no. of centres)
		dbSNP	Tables		
TLR4 +50414	rs11536896	T/C	T/C	95.7 (86.0–99.4)	5
TLR4 +50890	rs11536898	C/A	C/A	96.1 (79.0–99.5)	0
Toll-like receptor 9 isoform A precursor (*TLR9*) (Chr. 3)					
TLR9 −1486	rs187084	C/T	T/C	94.1 (75.4–99.5)	0
TLR9 +1173	rs352139	G/A	G/A	92.4 (78.4–99.4)	1
TLR9 +2848	rs352140	T/C	G/A	96.6 (91.2–99.4)	1
Tumor necrosis factor (*TNF*) (Chr. 6)					
TNF −857	rs1799724	C/T	T/C	98.0 (93.4–99.6)	3
TNF −308	rs1800629	G/A	G/A	97.2 (93.9–99.6)	4
TNF −238	rs673	G/A	G/A	98.1 (93.4–99.6)	1
TNF +846	rs3093662	A/G	G/A	97.4 (92.8–99.5)	3
TNF +1299	rs3093664	A/G	G/A	97.6 (92.0–99.5)	1

Amino acid change:
*Gln375Ala.
†Ser411Leu.
‡Gln576Arg.
§Arg130Gln.
¶Regulator of chromosome condensation (RCC1) and BTB (POZ) domain containing protein 1.
‖Glu420Lys.
Grey, tagged due to substantial (at least 5 of 17) number of centres with deviation from HWE in non-wheezers; HWE, Hardy–Weinberg equilibrium; SNP, single nucleotide polymorphism.

website http://innateimmunity.net. Risk alleles were defined mainly according to the first publications of the variants [8–19]; however, the reference alleles according to dbSNP BUILD 129 are also given in Table 2.

Phenotypes

Information on the prevalence of symptoms of asthma (including severity markers), rhinitis, rhinoconjunctivitis and eczaema in the past 12 months was collected by standardized parental questionnaires. Trained fieldworkers examined each child for flexural dermatitis and performed SPTs according to a detailed protocol with extracts of six common aeroallergens (*Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, cat dander, *Alternaria tenuis*, mixed tree pollen and mixed grass pollen) produced by A. L. K. (Horsholm, Denmark) [20]. A positive skin reaction was defined as at least one weal size of 3 mm or greater, after subtraction of the negative control.

Total serum IgE levels were measured by the Insulite System (DPC Biermann, Bad Nauheim, Germany; both German centres) and CAP-RAST™ (Phadia AB, Uppsala, Sweden; all other centres). Serum levels of specific-IgE antibodies to a mix of common inhalant allergens (*D. pteronyssinus*, *D. farinae*, birch, timothy, mugwort, cat, dog, horse, *Cladosporium*, olive pollen and *Parietaria*) were measured by Phadiatop™ (Phadia AB). Measurements were performed in two central laboratories (Free University of Berlin, Germany, for both German centres and Karolinska Sjukhuset, Stockholm, Sweden, for all other centres) [20].

Statistical analyses

Levels of allergen-specific IgE antibodies were dichotomized for statistical analyses at two cut-off values: $\geqslant 0.35$ and $\geqslant 0.7$ kU/L. Levels of total IgE antibodies were log-transformed to approximate a normal distribution and modelled as a continuous trait.

Three SNPs had a callrate below 90% and were excluded from the analyses [SPINK5 2965-46; TGFB1 +912; TLR2 −16933 (rs4696480)]. Hardy–Weinberg equilibrium (HWE) was tested per centre in non-wheezers. Four SNPs had a statistically significant deviation from HWE at $P<0.05$ in at least five centres and are shaded grey in the displayed tables.

Measures of linkage disequilibrium (LD) were estimated among the control group for each of the phenotypes, except total serum IgE levels, being a quantitative trait. The extent of LD in terms of r^2 and D' is given in the text where appropriate.

The effect of each polymorphism was assumed to be additive, i.e. a linear increase in log-odds per allele. However, the deviation from additivity was tested in pooled fixed-effects models adjusting for centre using a χ^2-test statistic for binary outcomes and an F-test statistic for total IgE. At $P<0.05$, there were only three SNPs with deviation from additivity for wheeze in the past year and

one for SPT positivity. None of these four SNPs showed deviation from additivity at $P<0.01$. Hence, only the results from additive models are displayed throughout the paper.

Wheeze in the past 12 months was used as the primary outcome variable. Crude odds ratios with 95% confidence intervals are calculated for wheeze and wheeze severity outcomes with non-weighted logistic regression per centre. For additional binary outcomes, a weighted logistic regression per centre was performed to account for the stratified random sampling [21]. The weights were the inverse of the sampling fractions among wheezers and non-wheezers and were determined per centre per model. For Munich and Dresden, the weight was set to one due to the applied simple random sampling. A weighted log-linear regression was performed per centre to estimate the relative per allele increase in the geometric mean of the total IgE serum levels.

A combined odds ratio and measures of heterogeneity between centres were derived by random effects meta-analysis using the 'Dersimonian–Laird'-method. The *P*-value from the χ^2-test for heterogeneity and the value for I^2 and its confidence interval are displayed [22].

In selection of the threshold for statistical significance, multiple testing was not taken into account because each gene was considered as a prior hypothesis justified on previously published evidence and biological plausibility or evidence of linkage within families.

All statistical computations were performed using SAS 9.2 (Cary, NC, USA).

Results

Table 3 shows the variation of frequencies for the risk alleles across centres, and Tables 4a–e show the association of the risk alleles with various disease outcomes. Most polymorphisms were not significantly ($P<0.05$) associated with the primary outcome (wheeze in the last year) or other allergic conditions (full data shown in Supporting Information). Significant associations with wheeze in the past year were detected in only four genes (*IL4R, TLR4, MS4A2, TLR9*, $P<0.05$), with per allele odds ratios generally <1.3 (Table 4a). Variants in *IL4R* and *TLR4* were also related to positive skin reactions and allergen-specific IgE, while polymorphisms in *FCER1B* (*MS4A2*) and *TLR9* were not (Tables 4b and c).

The *IL13* variants showed no association with the primary outcome or with reported or examined eczema. However, there were strong associations of *IL13* SNPs with more severe asthma symptoms (sleep-disturbing or speech-limiting wheeze), symptoms of rhinitis and rhinoconjunctivits, positive skin reactions and increased levels of total serum IgE. The latter were the most significant associations detected throughout the analyses with $P=4.4\times10^{-9}$ for IL13 +925. While the promoter polymorphism IL13 −1111 was not in LD with the other three *IL13* variants, the other three were closely intercorrelated among controls for the various phenotypes ($0.85<r^2<0.94$, $0.94<D'<0.99$).

For *TLR2*, there was a significant association with more frequent wheeze (more than three attacks in the past 12 months) (TLR2 −15606: 1.23 (1.03; 1.48), $P=0.0208$). Three polymorphisms in *TNF* that were not in close LD (r^2 between 0.28 and 0.65, D' between 0.63 and 0.99) showed somewhat stronger effects on more frequent wheeze (all $P<0.01$). A fourth *TNF* variant (TNF −875; LD with the aforementioned *TNF* SNPs: $r^2=0.01$, $D'=1.00$) was associated with speech-limiting wheeze and reported symptoms of rhinitis, rhinoconjunctivitis and eczema. None of the five *TNF* variants were significantly associated with objective markers of allergic disease.

There were highly significant associations between five *SPINK5* variants and examined eczema but none of the other phenotypes (Table 4e). These five polymorphisms were in LD among controls without examined eczema ($0.73<r^2<0.97$, $D'>0.96$), and for the three showing the strongest effects, there was evidence of heterogeneity between the centre-specific estimates.

The tested variants in *CD14* also associated only with examined eczema (Table 4e). However, there was some indication of heterogeneity of effects across centres and the two polymorphisms were in strong LD among controls without examined eczema ($r^2=0.97$, $D'=0.99$).

Furthermore, for the positional candidates *DPP10* and a candidate region on chromosome 13q14 (*PHF11*, *SETDB2* and *RCBTB1*) there were only significant associations only for *DPP10* with reported and examined eczema. Finally, for *TGFB1*, there was no significant association with any of the analysed phenotypes.

Discussion

This multi-centre study demonstrates that measures of genetic associations with asthma symptoms and allergy can be reliably pooled from diverse populations, increasing the power to detect modest effect sizes that may be expected for common variants and complex diseases. Although the selection of the studied polymorphisms does not provide a comprehensive coverage of each gene, it includes specific SNPs for which there are at least one but often several published associations with asthma or allergy. The investigated genes and polymorphisms were all strong candidates at the time they were selected and genotyped for this study and most have been replicated thereafter [3]. However, for all selected genes, negative reports have also been published [5, 23].

Given that over 4200 children were investigated in this study, of whom more than 1100 reported wheeze, the size of our study population exceeds that of most of the published population-based candidate gene association studies on childhood wheeze or asthma. The application of common field work protocols and the centralized analyses

Table 3. Risk allele frequencies (% (range)) overall and per region

SNP	Risk allele	Overall	Northwest	Northeast	Southwest	Southeast	Other
CD14 (Chr. 5)							
CD14 −4189	C	76.5 (69.7–83.8)	73.9 (69.7–78.2)	75.8 (75.3–76.2)	78.9 (75.4–82.2)	81.1 (79.7–83.8)	74.3 (70.0–78.5)
CD14 −651	T	22.8 (15.9–30.5)	25.6 (22.3–30.5)	24.2 (23.9–24.4)	19.4 (16.3–22.7)	18.8 (15.9–20.2)	25.2 (20.7–29.5)
CD14 −260	T	47.7 (31.5–58.9)	41.7 (32.5–49.4)	37.2 (31.5–42.9)	50.5 (46.5–55.7)	55.5 (51.6–58.9)	51.8 (48.3–58.6)
Dipeptidyl-peptidase 10 (*DPP10*) (Chr. 2)							
543WTC 21P	T	31.8 (15.3–40.8)	37.5 (34.5–40.8)	36.9 (33.4–40.4)	31.4 (29.0–35.0)	20.1 (15.3–24.7)	34.5 (33.3–36.0)
543WTC 122P	A	69.3 (55.4–87.2)	67.7 (65.6–69.3)	67.4 (66.5–68.2)	72.1 (70.0–73.6)	66.9 (63.7–72.9)	70.9 (55.4–87.2)
543WTC 124P	C	70.0 (57.0–88.3)	69.4 (65.3–74.6)	71.3 (66.4–76.2)	59.9 (58.1–62.1)	70.5 (67.6–76.0)	81.8 (72.6–88.3)
$F_C\varepsilon$ receptor I β (*MS4A2*) (Chr. 11)							
FCER1B −211	T	53.8 (39.0–73.2)	59.2 (56.0–62.3)	60.4 (60.2–60.6)	46.8 (39.0–51.0)	44.1 (42.1–45.7)	62.1 (50.5–73.2)
FCER1B +1343	G	58.1 (45.3–83.5)	60.8 (57.8–65.3)	63.8 (63.4–64.1)	50.5 (46.2–52.3)	48.5 (45.3–52.1)	71.5 (52.1–83.5)
FCER1B +3332	G	41.6 (4.8–54.5)	41.0 (35.5–46.1)	38.1 (37.4–38.8)	49.4 (47.2–54.5)	51.2 (48.5–53.2)	22.0 (4.8–38.8)
FCER1B +3934	T	46.7 (25.1–61.1)	41.4 (38.8–44.9)	40.3 (40.0–40.6)	53.9 (51.0–61.1)	57.0 (55.6–58.5)	37.3 (25.1–49.8)
FCER1B +5565	A	42.8 (16.3–55.3)	39.7 (35.3–42.8)	38.7 (38.5–38.8)	49.9 (48.0–54.4)	52.6 (49.5–55.3)	28.4 (16.3–47.9)
FCER1B +5734	C	57.0 (44.7–83.6)	60.2 (57.5–64.2)	61.1 (61.0–61.2)	49.5 (45.6–51.2)	47.6 (44.7–51.1)	71.4 (52.0–83.6)
FCER1B +10062	T	43.2 (16.5–56.7)	39.9 (36.8–42.8)	39.4 (38.4–40.4)	50.2 (48.0–55.1)	55.6 (54.2–56.7)	28.5 (16.5–47.9)
FCER1B +11664	G	45.9 (24.9–60.4)	40.9 (38.3–44.4)	39.8 (39.4–40.2)	53.3 (50.3–60.4)	55.5 (54.7–56.5)	37.3 (24.9–50.0)
FCER1B +12841	G	50.0 (34.5–62.9)	47.2 (39.8–62.9)	47.8 (39.6–56.0)	55.2 (51.5–62.2)	56.8 (56.1–57.7)	41.2 (34.5–51.2)
FCER1B +13948	C	48.1 (29.6–63.8)	42.4 (39.6–46.3)	40.7 (40.5–40.8)	54.8 (52.0–60.6)	57.7 (56.5–59.3)	40.1 (29.6–50.9)
Interleukin 4 receptor α chain (*IL4R*) (Chr. 16)							
IL4R +148	G	45.4 (39.2–56.2)	45.5 (43.6–50.3)	42.8 (41.3–44.3)	43.8 (39.7–50.0)	47.8 (39.2–56.2)	47.6 (47.1–48.0)
IL4R +1124	C	11.1 (2.8–22.7)	13.4 (11.7–14.4)	11.5 (11.5–11.5)	11.0 (5.6–13.4)	5.1 (2.8–9.6)	13.7 (7.0–22.7)
IL4R +1232	T	5.2 (1.3–24.1)	4.6 (2.6–5.8)	3.5 (2.8–4.2)	4.2 (3.7–4.9)	5.7 (4.7–6.7)	2.3 (1.3–3.2)
IL4R +1431	C	14.5 (6.7–20.1)	17.7 (15.1–19.8)	15.7 (15.0–16.4)	13.9 (7.9–17.2)	11.4 (9.9–13.7)	13.9 (6.7–20.1)
IL4R +1651	A	78.9 (63.1–87.7)	76.9 (73.8–78.3)	78.8 (78.8–78.8)	80.1 (76.2–87.1)	84.0 (79.6–87.7)	76.0 (63.1–83.8)
Interleukin 13 (*IL13*) (Chr. 5)							
IL13 −1111	T	21.5 (17.1–28.2)	19.4 (17.1–21.5)	25.6 (22.9–28.2)	21.4 (19.2–26.7)	22.7 (19.2–27.1)	21.4 (17.4–26.2)
IL13 +389	G	76.4 (47.3–88.2)	77.1 (73.3–80.9)	75.4 (71.8–79.1)	85.4 (80.3–88.2)	78.1 (77.1–79.4)	63.7 (47.3–79.5)
IL13 +870	A	23.4 (11.4–49.8)	22.6 (18.2–26.7)	24.2 (20.9–27.6)	14.2 (11.4–18.0)	22.3 (21.0–23.1)	35.7 (21.2–49.8)
IL13 +925	A	24.5 (13.4–55.8)	22.8 (18.2–27.1)	24.4 (20.3–28.4)	17.5 (13.4–22.1)	23.5 (19.7–26.6)	37.1 (21.7–55.8)
PHD finger protein 11 (*PHF11*) (Chr. 13)							
185752 B4.2	G	50.2 (27.8–55.6)	54.4 (52.6–55.6)	52.2 (50.6–53.7)	50.3 (47.5–52.2)	46.3 (45.3–48.0)	53.0 (51.2–54.6)
185752 B5.2	T	68.1 (59.3–78.9)	68.2 (67.0–70.8)	67.3 (67.2–67.4)	63.8 (59.3–68.0)	68.5 (64.5–72.4)	73.9 (69.7–78.9)
185752 B5.3	G	49.0 (44.9–72.0)	46.3 (45.5–47.2)	48.7 (46.8–50.6)	48.7 (44.9–51.7)	47.2 (46.0–48.2)	48.3 (45.9–50.2)
*RCBTB** (Chr. 13)							
4321017 B38_1	T	72.4 (59.2–91.0)	68.7 (65.6–71.5)	69.6 (66.8–72.5)	73.3 (71.2–75.1)	72.8 (72.6–73.0)	74.9 (59.2–91.0)
SET domain, bifurcated 2 (*SETDB2*) (Chr. 13)							
185316 B1.1	G	47.4 (40.0–61.7)	45.7 (43.1–47.4)	44.3 (44.0–44.6)	47.3 (40.0–51.7)	50.5 (44.4–53.6)	45.4 (43.7–46.8)
Serine peptidase inhibitor, Kazal type 5 (*SPINK5*) (Chr. 5)							
SPINK5 1258	G	52.7 (43.2–68.6)	51.9 (50.5–54.0)	50.1 (50.0–50.3)	53.0 (48.5–56.2)	52.1 (50.3–54.6)	58.5 (53.4–68.6)
SPINK5 1557	C	47.3 (32.1–51.5)	49.0 (46.2–51.5)	49.7 (49.4–50.0)	47.7 (44.0–51.0)	47.3 (43.9–49.1)	41.5 (32.1–46.5)
SPINK5 1659	C	45.9 (23.0–51.9)	48.8 (45.7–51.9)	49.9 (49.7–50.0)	45.4 (43.2–49.3)	46.0 (39.6–50.0)	38.6 (23.0–46.4)

SPINK5 1888-54	G	30.0 (7.6–39.5)	36.7 (34.8–38.6)	37.5 (35.4–39.5)	32.8 (31.3–35.1)	28.7 (25.5–31.4)	19.0 (7.6–35.9)
SPINK5 475-86	G	35.4 (15.9–44.6)	42.1 (40.6–44.6)	43.3 (43.2–43.4)	36.3 (35.1–38.9)	32.4 (30.6–33.8)	26.0 (15.9–39.5)
SPINK5 56-125	G	63.8 (55.6–83.5)	58.2 (55.6–60.4)	56.9 (56.6–57.3)	62.3 (59.6–64.5)	66.8 (66.1–67.9)	72.4 (60.4–83.5)
SPINK5 82-31	G	69.6 (59.7–91.7)	62.3 (59.7–64.8)	61.6 (59.8–63.5)	67.3 (64.9–69.4)	71.2 (68.2–74.2)	80.8 (63.3–91.7)
SPINK5 F2_1	G	30.9 (8.1–40.8)	38.2 (36.0–40.5)	38.9 (37.1–40.8)	33.9 (30.3–36.0)	28.9 (25.6–32.8)	19.0 (8.1–37.0)
Transforming growth factor β 1 (*TGFB1*) (Chr. 19)							
TGFB1 −509	T	36.9 (29.6–56.3)	31.4 (29.6–32.9)	32.6 (32.1–33.1)	36.6 (30.6–44.8)	40.4 (36.2–46.1)	47.9 (38.9–56.3)
Toll-like receptor 2 (*TLR2*) (Chr. 4)							
TLR2 −15606	G	38.0 (27.6–62.6)	34.1 (27.6–40.9)	37.4 (36.7–38.0)	31.8 (28.5–36.4)	40.4 (32.2–45.9)	43.6 (35.0–58.4)
Toll-like receptor 4 (*TLR4*) (Chr. 9)							
TLR4 −6142	A	67.5 (58.5–71.7)	68.1 (65.8–69.5)	67.7 (67.5–67.9)	68.8 (66.3–71.2)	66.9 (58.5–71.7)	63.8 (62.7–65.2)
TLR4 +50017	C	13.6 (6.7–21.3)	13.8 (11.7–15.2)	14.9 (14.5–15.3)	13.7 (12.4–15.3)	16.1 (13.5–17.6)	13.2 (7.1–21.3)
TLR4 +50414	C	12.5 (5.6–19.7)	13.0 (11.8–14.1)	13.5 (11.9–15.1)	12.4 (9.6–15.6)	14.6 (12.7–16.9)	12.3 (7.1–19.7)
TLR4 +50890	A	11.8 (5.6–19.8)	12.2 (11.2–13.8)	13.5 (12.8–14.1)	11.8 (9.9–14.6)	13.4 (11.9–16.3)	12.0 (6.2–19.8)
Toll-like receptor 9 isoform A precursor (*TLR9*) (Chr. 3)							
TLR9 −1486	C	39.5 (31.3–46.9)	39.8 (37.4–42.2)	41.1 (37.9–44.3)	39.4 (38.3–40.1)	40.5 (37.2–43.0)	40.7 (37.0–46.9)
TLR9 +1173	A	50.1 (42.7–65.2)	48.6 (42.7–53.0)	48.7 (43.0–54.5)	49.3 (45.8–51.9)	47.4 (45.2–50.3)	52.7 (44.0–63.5)
TLR9 +2848	A	51.4 (38.1–58.7)	53.5 (49.3–56.7)	53.6 (51.2–55.9)	51.8 (49.3–55.1)	54.3 (49.7–58.7)	46.7 (38.1–52.8)
Tumor necrosis factor (*TNF*) (Chr. 6)							
TNF −857	C	87.5 (70.8–93.9)	92.0 (88.5–93.9)	89.4 (88.0–90.9)	88.6 (86.8–89.9)	81.4 (77.2–89.3)	83.6 (70.8–90.4)
TNF −308	A	12.6 (5.1–19.2)	17.3 (15.5–19.2)	15.1 (14.0–16.2)	12.2 (11.5–12.6)	8.1 (5.9–10.5)	9.6 (5.1–12.9)
TNF −238	A	5.7 (2.1–10.0)	3.7 (3.1–4.3)	3.6 (2.4–4.8)	8.8 (7.1–10.0)	4.4 (2.1–8.5)	6.8 (4.2–9.4)
TNF +846	A	91.6 (82.3–97.1)	95.0 (94.0–96.5)	95.8 (94.5–97.1)	87.7 (86.5–89.4)	87.8 (82.3–90.9)	92.0 (89.1–95.5)
TNF +1299	A	92.4 (85.8–96.6)	93.0 (91.7–94.1)	95.1 (93.5–96.6)	91.8 (85.8–95.5)	89.0 (85.9–91.4)	91.9 (90.1–95.0)

*Regulator of chromosome condensation (RCC1) and BTB (POZ) domain containing protein 1.

Grey, tagged due to substantial (at least 5 of 17) number of centres with deviation of HWE; HWE, Hardy–Weinberg equilibrium; SNP, single nucleotide polymorphism.

Table 4a. Crude associations of genotyped polymorphisms with the prevalence of wheeze in the past 12 months (estimates from random effects meta-analyses with measures of heterogeneity)

SNP	$n_{centres}$	OR	95% CI	P	$P_{heterogeneity}$	I^2	95% CI
$F_C\varepsilon$ receptor I β (*MS4A2*) (Chr. 11)							
FCER1B −211	17	0.95	(0.86–1.06)	0.3934	0.6896	0%	(0–51%)
FCER1B +1343	17	0.92	(0.83–1.03)	0.1424	0.8965	0%	(0–51%)
FCER1B +3332	17	**1.13**	**(1.01–1.27)**	**0.0383**	0.6764	0%	(0–51%)
FCER1B +3934	17	1.05	(0.94–1.17)	0.3558	0.6484	0%	(0–51%)
FCER1B +5565	17	1.07	(0.96–1.19)	0.2473	0.7429	0%	(0–51%)
FCER1B +5734	17	0.94	(0.84–1.05)	0.2755	0.7200	0%	(0–51%)
FCER1B +10062	17	1.07	(0.95–1.19)	0.2511	0.7830	0%	(0–51%)
FCER1B +11664	17	1.05	(0.94–1.17)	0.3558	0.7596	0%	(0–51%)
FCER1B +12841	17	1.03	(0.93–1.14)	0.6147	0.7248	0%	(0–51%)
FCER1B +13948	17	1.05	(0.94–1.18)	0.3451	0.8189	0%	(0–51%)
Interleukin 4 receptor α chain (*IL4R*) (Chr. 16)							
IL4R +148	17	0.97	(0.87–1.08)	0.6315	0.9763	0%	(0–51%)
IL4R +1124	17	0.86	(0.72–1.03)	0.0918	0.7571	0%	(0–51%)
IL4R +1232	14	0.79	(0.59–1.06)	0.1091	0.9714	0%	(0–55%)
IL4R +1431	17	**0.78**	**(0.67–0.91)**	**0.0020**	0.9954	0%	(0–51%)
IL4R +1651	17	**1.22**	**(1.06–1.39)**	**0.0051**	0.9797	0%	(0–51%)
Interleukin 13 (*IL13*) (Chr. 5)							
IL13 −1111	17	1.10	(0.95–1.27)	0.2063	0.3321	10%	(0–47%)
IL13 +389	17	0.89	(0.77–1.03)	0.1314	0.2369	19%	(0–54%)
IL13 +870	17	1.14	(0.98–1.34)	0.0911	0.1539	26%	(0–59%)
IL13 +925	17	1.15	(1.00–1.32)	0.0532	0.2855	14%	(0–51%)
Toll-like receptor 4 (*TLR4*) (Chr. 9)							
TLR4 −6142	17	0.92	(0.81–1.04)	0.1729	0.3063	13%	(0–49%)
TLR4 +50017	17	**1.17**	**(1.00–1.36)**	**0.0479**	0.4243	3%	(0–52%)
TLR4 +50414	17	**1.21**	**(1.01–1.44)**	**0.0388**	0.3494	9%	(0–45%)
TLR4 +50890	17	**1.24**	**(1.04–1.48)**	**0.0187**	0.2532	17%	(0–53%)
Toll-like receptor 9* (Chr. 3)							
TLR9 −1486	17	**1.13**	**(1.01–1.26)**	**0.0393**	0.5286	0%	(0–51%)
TLR9 +1173	17	1.02	(0.92–1.14)	0.6752	0.7434	0%	(0–51%)
TLR9 +2848	17	0.94	(0.85–1.05)	0.2826	0.9288	0%	(0–51%)

*Regulator of chromosome condensation (RCC1) and BTB (POZ) domain containing protein 1.

Grey, tagged due to substantial (at least 5 of 17) number of centres with deviation of HWE; Bold, statistically significantly associated SNP; HWE, Hardy–Weinberg equilibrium; SNP, single nucleotide polymorphism; CI, confidence interval.

Table 4b. Crude associations of genotyped polymorphisms with the prevalence of skin prick test positivity (estimates from random effects meta-analyses with measures of heterogeneity)

SNP	$n_{centres}$	OR	95% CI	P	$P_{heterogeneity}$	I^2	95% CI
$F_C\varepsilon$ receptor I β (*MS4A2*) (Chr. 11)							
FCER1B −211	17	0.96	(0.87; 1.06)	0.4014	0.8934	0%	(0%; 51%)
FCER1B +1343	17	0.97	(0.87; 1.07)	0.5129	0.9751	0%	(0%; 51%)
FCER1B +3332	17	1.08	(0.97; 1.20)	0.1858	0.9131	0%	(0%; 51%)
FCER1B +3934	17	1.03	(0.93; 1.14)	0.6131	0.8923	0%	(0%; 51%)
FCER1B +5565	17	1.05	(0.95; 1.16)	0.3623	0.9804	0%	(0%; 51%)
FCER1B +5734	17	0.96	(0.87; 1.07)	0.4683	0.9732	0%	(0%; 51%)
FCER1B +10062	17	1.05	(0.95; 1.16)	0.3505	0.9496	0%	(0%; 51%)
FCER1B +11664	17	1.04	(0.94; 1.15)	0.4729	0.9487	0%	(0%; 51%)
FCER1B +12841	17	1.03	(0.94; 1.13)	0.5448	0.7826	0%	(0%; 51%)
FCER1B +13948	17	1.05	(0.94; 1.16)	0.3856	0.7033	0%	(0%; 51%)
Interleukin 4 receptor α chain (*IL4R*) (Chr. 16)							
IL4R +148	17	1.08	(0.98; 1.20)	0.1142	0.9435	0%	(0%; 51%)
IL4R +1124	16	0.87	(0.73; 1.03)	0.1031	0.3534	9%	(0%; 45%)
IL4R +1232	13	0.96	(0.75; 1.25)	0.7833	0.8164	0%	(0%; 57%)

Table 4b. continued

SNP	$n_{centres}$	OR	95% CI	P	$P_{heterogeneity}$	I^2	95% CI
IL4R +1431	17	**0.83**	**(0.72; 0.95)**	**0.0090**	0.4061	4%	(0%; 53%)
IL4R +1651	17	1.13	(1.00; 1.27)	0.0566	0.8707	0%	(0%; 51%)
Interleukin 13 (*IL13*) (Chr. 5)							
IL13 −1111	17	1.06	(0.93; 1.20)	0.3740	0.4046	4%	(0%; 53%)
IL13 +389	17	**0.88**	**(0.78; 0.99)**	**0.0349**	0.9305	0%	(0%; 51%)
IL13 +870	17	**1.18**	**(1.05; 1.32)**	**0.0068**	0.9746	0%	(0%; 51%)
IL13 +925	17	**1.14**	**(1.02; 1.29)**	**0.0268**	0.9775	0%	(0%; 51%)
Toll-like receptor 4 (*TLR4*) (Chr. 9)							
TLR4 −6142	17	0.90	(0.81; 1.00)	0.0586	0.7576	0%	(0%; 51%)
TLR4 +50017	17	1.14	(0.98; 1.33)	0.0920	0.3232	11%	(0%; 48%)
TLR4 +50414	17	**1.22**	**(1.04; 1.43)**	**0.0153**	0.5242	0%	(0%; 51%)
TLR4 +50890	17	1.18	(0.99; 1.41)	0.0703	0.2026	22%	(0%; 56%)
Toll-like receptor 9 isoform A precursor (*TLR9*) (Chr. 3)							
TLR9 −1486	17	0.95	(0.85; 1.07)	0.4214	0.3299	11%	(0%; 47%)
TLR9 +1173	17	1.08	(0.98; 1.19)	0.1290	0.6494	0%	(0%; 51%)
TLR9 +2848	17	0.91	(0.82; 1.01)	0.0705	0.5513	0%	(0%; 51%)

*Regulator of chromosome condensation (RCC1) and BTB (POZ) domain containing protein 1.
Grey, tagged due to substantial (at least 5 of 17) number of centres with deviation of HWE; Bold, statistically significantly associated SNP; HWE, Hardy–Weinberg equilibrium; SNP, single nucleotide polymorphism; CI, confidence interval.

Table 4c. Crude associations of genotyped polymorphisms with the prevalence of specific IgE > 0.70 kU/L (estimates from random effects meta-analyses with measures of heterogeneity)

SNP	$n_{centres}$	OR	95% CI	P	$P_{heterogeneity}$	I^2	95% CI
$F_C\varepsilon$ receptor I β (*MS4A2*) (Chr. 11)							
FCER1B −211	12	1.01	(0.91; 1.12)	0.8776	0.7868	0%	(0%; 58%)
FCER1B +1343	12	0.98	(0.88; 1.09)	0.6884	0.9222	0%	(0%; 58%)
FCER1B +3332	12	1.05	(0.94; 1.17)	0.4238	0.6325	0%	(0%; 58%)
FCER1B +3934	12	0.98	(0.88; 1.09)	0.7395	0.8455	0%	(0%; 58%)
FCER1B +5565	12	1.02	(0.92; 1.14)	0.6578	0.8023	0%	(0%; 58%)
FCER1B +5734	12	0.99	(0.89; 1.10)	0.8037	0.8891	0%	(0%; 58%)
FCER1B +10062	12	1.03	(0.92; 1.14)	0.6446	0.5120	0%	(0%; 58%)
FCER1B +11664	12	0.99	(0.89; 1.10)	0.8546	0.8242	0%	(0%; 58%)
FCER1B +12841	12	0.99	(0.89; 1.10)	0.8328	0.6430	0%	(0%; 58%)
FCER1B +13948	12	1.00	(0.89; 1.11)	0.9547	0.7285	0%	(0%; 58%)
Interleukin 4 receptor α chain (*IL4R*) (Chr. 16)							
IL4R +148	12	1.02	(0.89; 1.16)	0.8057	0.1689	28%	(0%; 64%)
IL4R +1124	12	0.86	(0.70; 1.06)	0.1544	0.2677	18%	(0%; 57%)
IL4R +1232	12	0.89	(0.69; 1.14)	0.3468	0.6454	0%	(0%; 58%)
IL4R +1431	12	**0.79**	**(0.66; 0.95)**	**0.0123**	0.2007	25%	(0%; 62%)
IL4R +1651	12	1.15	(1.00; 1.33)	0.0541	0.3477	10%	(0%; 49%)
Interleukin 13 (*IL13*) (Chr. 5)							
IL13 −1111	12	1.08	(0.94; 1.24)	0.2993	0.3587	9%	(0%; 47%)
IL13 +389	12	0.94	(0.83; 1.08)	0.3907	0.4556	0%	(0%; 58%)
IL13 +870	12	1.13	(0.97; 1.32)	0.1258	0.2642	18%	(0%; 57%)
IL13 +925	12	1.09	(0.94; 1.27)	0.2540	0.2806	17%	(0%; 56%)
Toll-like receptor 4 (*TLR4*) (Chr. 9)							
TLR4 −6142	12	0.90	(0.81; 1.01)	0.0838	0.6034	0%	(0%; 58%)
TLR4 +50017	12	**1.18**	**(1.02; 1.37)**	**0.0276**	0.6039	0%	(0%; 58%)
TLR4 +50414	12	**1.25**	**(1.04; 1.50)**	**0.0154**	0.3437	10%	(0%; 50%)
TLR4 +50890	12	**1.17**	**(1.00; 1.37)**	**0.0445**	0.5818	0%	(0%; 58%)
Toll-like receptor 9 isoform A precursor (*TLR9*) (Chr. 3)							
TLR9 −1486	12	0.91	(0.76; 1.10)	0.3426	0.0092	56%	(16%; 77%)
TLR9 +1173	12	1.09	(0.93; 1.28)	0.2837	0.0405	46%	(0%; 72%)

Table 4c. continued

SNP	$n_{centres}$	OR	95% CI	P	$P_{heterogeneity}$	I^2	95% CI
TLR9 +2848	12	0.90	(0.75; 1.09)	0.2867	0.0036	60%	(25%; 79%)

*Regulator of chromosome condensation (RCC1) and BTB (POZ) domain containing protein 1.
Grey, tagged due to substantial (at least 5 of 17) number of centres with deviation of HWE; Bold: statistically significantly associated SNP; HWE, Hardy–Weinberg equilibrium; SNP, single nucleotide polymorphism; CI, confidence interval.

Table 4d. Geometric mean ratio (GMR) of total serum IgE levels per risk allele (estimates from random effects meta-analyses with measures of heterogeneity)

SNP	$n_{centres}$	GMR	95% CI	P	$P_{heterogeneity}$	I^2	95% CI
$F_c\varepsilon$ receptor I β (*MS4A2*) (Chr. 11)							
FCER1B −211	13	0.94	(0.87; 1.01)	0.1072	0.3818	6%	(0%; 59%)
FCER1B +1343	13	0.94	(0.87; 1.01)	0.0777	0.4946	0%	(0%; 57%)
FCER1B +3332	13	1.05	(0.97; 1.15)	0.2186	0.2864	16%	(0%; 55%)
FCER1B +3934	13	1.05	(0.97; 1.12)	0.2153	0.4675	0%	(0%; 57%)
FCER1B +5565	13	1.07	(0.99; 1.15)	0.0937	0.4099	4%	(0%; 58%)
FCER1B +5734	13	0.94	(0.88; 1.01)	0.1065	0.4298	2%	(0%; 57%)
FCER1B +10062	13	1.06	(0.98; 1.15)	0.1546	0.2986	14%	(0%; 54%)
FCER1B +11664	13	1.05	(0.98; 1.13)	0.1630	0.5292	0%	(0%; 57%)
FCER1B +12841	13	1.03	(0.96; 1.11)	0.4299	0.3893	6%	(0%; 59%)
FCER1B +13948	13	1.05	(0.98; 1.13)	0.1907	0.4819	0%	(0%; 57%)
Interleukin 4 receptor α chain (*IL4R*) (Chr. 16)							
IL4R +148	13	1.03	(0.96; 1.10)	0.4733	0.4932	0%	(0%; 57%)
IL4R +1124	13	**0.77**	**(0.69; 0.86)**	**<0.0001**	0.6011	0%	(0%; 57%)
IL4R +1232	13	0.90	(0.71; 1.15)	0.3884	0.0554	42%	(0%; 70%)
IL4R +1431	13	**0.80**	**(0.73; 0.88)**	**<0.0001**	0.7654	0%	(0%; 57%)
IL4R +1651	13	**1.19**	**(1.09; 1.30)**	**<0.0001**	0.9282	0%	(0%; 57%)
Interleukin 13 (*IL13*) (Chr. 5)							
IL13 −1111	13	**1.16**	**(1.04; 1.29)**	**0.0056**	0.1940	25%	(0%; 61%)
IL13 +389	13	**0.81**	**(0.74; 0.88)**	**<0.0001**	0.4773	0%	(0%; 57%)
IL13 +870	13	**1.27**	**(1.16; 1.38)**	**<0.0001**	0.6760	0%	(0%; 57%)
IL13 +925	13	**1.29**	**(1.19; 1.41)**	**<0.0001**	0.7123	0%	(0%; 57%)
Toll-like receptor 4 (*TLR4*) (Chr. 9)							
TLR4 −6142	13	0.97	(0.90; 1.05)	0.4389	0.4984	0%	(0%; 57%)
TLR4 +50017	13	1.03	(0.92; 1.16)	0.5695	0.2795	16%	(0%; 55%)
TLR4 +50414	13	1.07	(0.93; 1.24)	0.3392	0.1339	31%	(0%; 64%)
TLR4 +50890	13	1.06	(0.92; 1.23)	0.4266	0.0643	40%	(0%; 69%)
Toll-like receptor 9 isoform A precursor (*TLR9*) (Chr. 3)							
TLR9 −1486	13	0.92	(0.83; 1.03)	0.1635	0.0282	48%	(1%; 72%)
TLR9 +1173	13	1.06	(0.96; 1.17)	0.2902	0.0533	42%	(0%; 70%)
TLR9 +2848	13	0.95	(0.86; 1.06)	0.3464	0.0241	49%	(3%; 73%)

*Regulator of chromosome condensation (RCC1) and BTB (POZ) domain containing protein 1.
Grey, tagged due to substantial (at least 5 of 17) number of centres with deviation of HWE; Bold: statistically significantly associated SNP; HWE, Hardy–Weinberg equilibrium; SNP, single nucleotide polymorphism; CI, confidence interval.

Table 4e. Crude associations of genotyped polymorphisms with the prevalence of examined eczema (estimates from random effects meta-analyses with measures of heterogeneity)

SNP	$n_{centres}$	OR	95% CI	P	$P_{heterogeneity}$	I^2	95% CI
CD14 (Chr. 5)							
CD14 −4189	16	**0.76**	**(0.58; 0.98)**	**0.0363**	0.0894	34%	(0%; 64%)
CD14 −651	16	**1.34**	**(1.01; 1.77)**	**0.0405**	0.0681	37%	(0%; 65%)
CD14 −260	16	0.97	(0.84; 1.11)	0.6348	0.9746	0%	(0%; 52%)

Table 4e. continued

SNP	$n_{centres}$	OR	95% CI	P	$P_{heterogeneity}$	I^2	95% CI
Dipeptidyl-peptidase 10 (*DPP10*) (Chr. 2)							
543WTC 21P	16	1.33	(0.98; 1.82)	0.0703	0.0005	62%	(35%; 78%)
543WTC 122P	16	**0.70**	**(0.59; 0.83)**	**<0.0001**	0.4438	1%	(0%; 53%)
543WTC 124P	16	0.79	(0.59; 1.05)	0.0987	0.0010	60%	(31%; 77%)
$F_C\varepsilon$ receptor I β (*MS4A2*) (Chr. 11)							
FCER1B −211	16	0.87	(0.70; 1.07)	0.1870	0.0804	35%	(0%; 64%)
FCER1B +1343	16	0.83	(0.66; 1.04)	0.0993	0.0522	40%	(0%; 67%)
FCER1B +3332	16	**1.22**	**(1.01; 1.46)**	**0.0358**	0.2770	15%	(0%; 52%)
FCER1B +3934	16	1.14	(0.93; 1.40)	0.2042	0.1252	30%	(0%; 62%)
FCER1B +5565	16	1.21	(0.98; 1.49)	0.0729	0.0999	33%	(0%; 63%)
FCER1B +5734	16	0.84	(0.68; 1.03)	0.0934	0.1143	31%	(0%; 62%)
FCER1B +10062	16	1.19	(0.96; 1.46)	0.1111	0.1156	31%	(0%; 62%)
FCER1B+11664	16	1.15	(0.95; 1.40)	0.1493	0.1618	26%	(0%; 59%)
FCER1B +12841	16	1.14	(0.92; 1.41)	0.2274	0.0695	37%	(0%; 65%)
FCER1B +13948	16	1.12	(0.91; 1.37)	0.2828	0.1376	28%	(0%; 61%)
Interleukin 4 receptor α chain (*IL4R*) (Chr. 16)							
IL4R +148	16	**1.30**	**(1.08; 1.57)**	**0.0061**	0.9527	0%	(0%; 52%)
IL4R +1124	13	0.98	(0.72; 1.32)	0.8702	0.9707	0%	(0%; 57%)
IL4R +1232	8	**1.67**	**(1.09; 2.57)**	**0.0188**	0.6886	0%	(0%; 68%)
IL4R +1431	12	1.09	(0.85; 1.40)	0.5119	0.8761	0%	(0%; 58%)
IL4R +1651	13	0.96	(0.76; 1.21)	0.7354	0.4506	0%	(0%; 57%)
Interleukin 13 (*IL13*) (Chr. 5)							
IL13 −1111	16	1.02	(0.73; 1.42)	0.9207	0.0075	52%	(16%; 73%)
IL13 +389	15	0.85	(0.60; 1.21)	0.3685	0.0030	57%	(24%; 76%)
IL13 +870	15	1.14	(0.79; 1.64)	0.4953	0.0011	61%	(32%; 78%)
IL13 +925	16	1.18	(0.84; 1.64)	0.3398	0.0047	55%	(20%; 74%)
Serine peptidase inhibitor, Kazal type 5 (*SPINK5*) (Chr. 5)							
SPINK5 1258	17	0.94	(0.80; 1.10)	0.4582	0.6742	0%	(0%; 51%)
SPINK5 1557	17	1.06	(0.90; 1.24)	0.4996	0.6592	0%	(0%; 51%)
SPINK5 1659	17	1.12	(0.95; 1.32)	0.1772	0.7094	0%	(0%; 51%)
SPINK5 1888-54	15	**1.28**	**(1.05; 1.56)**	**0.0155**	0.3295	11%	(0%; 49%)
SPINK5 475-86	16	**1.29**	**(1.07; 1.57)**	**0.0092**	0.1792	24%	(0%; 58%)
SPINK5 56-125	16	**0.73**	**(0.62; 0.87)**	**0.0005**	0.1335	29%	(0%; 61%)
SPINK5 82-31	15	**0.73**	**(0.58; 0.93)**	**0.0096**	0.0385	43%	(0%; 69%)
SPINK5 F2_1	15	**1.45**	**(1.17; 1.79)**	**0.0006**	0.0341	44%	(0%; 70%)
Toll-like receptor 4 (*TLR4*) (Chr. 9)							
TLR4 −6142	14	1.03	(0.85; 1.25)	0.7724	0.4508	0%	(0%; 55%)
TLR4 +50017	12	1.11	(0.84; 1.45)	0.4627	0.4330	1%	(0%; 59%)
TLR4 +50414	11	1.12	(0.82; 1.53)	0.4927	0.4487	0%	(0%; 60%)
TLR4 +50890	11	1.20	(0.91; 1.59)	0.1863	0.4736	0%	(0%; 60%)
Toll-like receptor 9 isoform A precursor (*TLR9*) (Chr. 3)							
TLR9 −1486	16	0.96	(0.75; 1.22)	0.7225	0.0410	42%	(0%; 68%)
TLR9 +1173	16	1.10	(0.96; 1.27)	0.1753	0.3644	8%	(0%; 44%)
TLR9 +2848	17	0.89	(0.77; 1.02)	0.1012	0.2788	15%	(0%; 51%)

*Regulator of chromosome condensation (RCC1) and BTB (POZ) domain containing protein 1.

Grey, tagged due to substantial (at least 5 of 17) number of centres with deviation of HWE; Bold, statistically significantly associated SNP; HWE, Hardy–Weinberg equilibrium; SNP, single nucleotide polymorphism; CI, confidence interval.

of biological samples allowed us to compare and pool the results from diverse populations.

Despite differences in allele frequencies and differing prevalences of phenotypes across centres, heterogeneity of genetic effects on asthma symptoms and allergy was rarely found [24–26]. Furthermore, it seems unlikely that these small variations in allele frequency explain the larger variation of prevalence of wheeze across centres. The heterogeneity that was detected might be due to different measurement errors across centres for the questionnaire-based outcomes. An alternative explanation is effect modification by one or more genes, one or more

environmental factors or a combination of both with differing prevalences across the centres.

All comparisons between cases and controls were performed within centres, which minimizes the concern about population stratification. Data on the country of birth were available for 80% of the children and indicated that only 3% of the children contributing to this analysis were not born in their study country. Data on the country of birth were available for 45% of the parents of participating children. These data indicate that for 6.7% or 9.3% of the children, both or one of the parents, respectively, were not born in their study country. In another large multi-centre study with cases and controls from each centre, no effect of population stratification was detected using genomic control [27]. Furthermore, we detected little evidence for heterogeneity of effects across centres, which might be expected if estimates from one or two centres were subject to bias due to ethnic confounding. We therefore believe that uncontrolled population stratification does not affect our results.

In common with many epidemiologic studies of genetic effects, we have tested inter-correlated outcomes together with inter-correlated exposures. We have presented our findings based on $P<0.05$ as an inclusive threshold; however, this significance level has to be interpreted with caution. Certainly, if we introduced a Bonferroni-type correction to our *P*-values, decreasing the probability of falsely rejecting the null hypothesis, this would lead to even fewer 'significant' replications of previously published associations than we report here.

Although our study had substantial power to detect the expected associations of *IL13* variants with IgE and *SPINK5* variants with eczema, we were unable to replicate some other previously documented findings. However, our study shows evidence for consistent associations between SNPs in four of the tested 14 genes and wheeze. Despite the biological plausibility of IgE-related mechanisms in asthma, very few of the tested candidates showed evidence of an association with both asthma symptoms and increased IgE levels. Interestingly, for *FCER1B (MS4A2)*, there is evidence for an association with total and specific-IgE levels as well as SPT positivity from many smaller studies but we were unable to confirm these associations [5].

For the positional candidate regions containing *DPP10* and *PHF11*, the association with wheeze could not be confirmed with our data. The only significant association for these regions was detected between *DPP10* and examined eczema. Recent publications on these positional candidates also failed to confirm consistent associations with childhood asthma and related phenotypes [23, 28].

This large multi-centre study of children in diverse settings world-wide suggests that neither the biological nor the positional candidate gene variants studied are strong determinants of asthma symptoms in the general population. Ongoing studies using genome-wide technologies may provide further insight into unsuspected biological pathways or chromosomal regions deserving more detailed investigation.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Crude associations of genotyped polymorphisms with the prevalence of wheeze in the past 12 months (estimates from random effects meta-analyses with measures of heterogeneity).

Table S2. Crude associations of genotyped polymorphisms with the prevalence of more than 3 attacks of wheeze in the past 12 months (estimates from random effects meta-analyses with measures of heterogeneity).

Table S3. Crude associations of genotyped polymorphisms with the prevalence of sleep disturbing wheeze in the past 12 months (estimates from random effects meta-analyses with measures of heterogeneity).

Table S4. Crude associations of genotyped polymorphisms with the prevalence of speech limiting wheeze in the past 12 months (estimates from random effects meta-analyses with measures of heterogeneity).

Table S5. Crude associations of genotyped polymorphisms with the prevalence of skin prick test positivity (estimates from random effects meta-analyses with measures of heterogeneity).

Table S6. Crude associations of genotyped polymorphisms with the prevalence of specific IgE >0.35 kU/L (estimates from random effects meta-analyses with measures of heterogeneity).

Table S7. Crude associations of genotyped polymorphisms with the prevalence of specific IgE >0.70 kU/L (estimates from random effects meta-analyses with measures of heterogeneity).

Table S8. Geometric mean ratio (GMR) of total serum IgE levels per risk allele (estimates from random effects meta-analyses with measures of heterogeneity).

Table S9. Crude associations of genotyped polymorphisms with the prevalence of rhinitis in the past 12 months (estimates from random effects meta-analyses with measures of heterogeneity).

Table S10. Crude associations of genotyped polymorphisms with the prevalence of rhinoconjunctivitis in the past 12 months (estimates from random effects meta-analyses with measures of heterogeneity).

Table S11. Crude associations of genotyped polymorphisms with the prevalence of reported eczema in the past 12 months (estimates from random effects meta-analyses with measures of heterogeneity).

Table S12. Crude associations of genotyped polymorphisms with the prevalence of examined eczema (estimates from random effects meta-analyses with measures of heterogeneity).