

Genome-wide association and HLA fine mapping studies identify risk loci and genetic pathways of allergic rhinitis

Johannes Waage^{1†}, Marie Stand^{2†}, John A Curtin³, Leon Jessen¹, Jonathan Thorsen¹, The 23andMe_Research_Team⁴, AAGC_collaborators⁴, Abdel Abdellaoui⁵, Tarunveer S Ahluwalia¹, Alexander Alves⁶, Andre F S Amaral⁷, Josep Maria Antó⁸, Andreas Arnold⁹, Carlos Flores^{10,30}, Hansjörg Baurecht¹¹, Toos CEM Beijsterveldt⁵, Eugene R. Bleecker¹², Silvia Bonàs-Guarch¹³, Dorret Boomsma^{5,14}, Susanne Brix¹⁵, Supinda Bunyavanich¹⁶, Esteban Burchard^{17,18}, Zhanghua Chen¹⁹, Ivan Curjurić^{20,21}, Adnan Custovic²², Martijn den Dekker^{23,24,25}, Shyamali C. Dharmage²⁶, Julia Dmitrieva²⁷, Liesbeth Duijts^{23,24,25,28}, Markus Ege²⁹, Amalia Barreto-Luis¹⁰, W. James Gauderman¹⁹, Michel Georges²⁷, Christian Gieger^{31,32}, Frank Gilliland¹⁹, Raquel Granell³³, Hongsheng Gul³⁴, Torben Hansen³⁵, Joachim Heinrich^{2,36}, John Henderson³³, Natalia Hernandez-Pacheco^{10,37}, David A. Hinds³⁸, David Hinds³⁸, Patrick Holt³⁹, Medea Imboden^{20,21}, Vincent Jaddoe^{23,24,25}, Marjo-Riita Jarvelin⁶, Deborah L Jarvis⁷, Kamilla K Jensen⁴⁰, Ingileif Jónsdóttir^{41,42}, Michael Kabesch⁴³, Jaakko Kaprio^{44,45,46}, Ashish Kumar^{47,48,49}, Young-Ae Lee^{50,51}, Albert M Levin⁵², Xingnan Li⁵³, Fabian Lorenzo-Diaz³⁷, Erik Melén^{47,54}, Josep Maria Mercader^{13,55,56}, Deborah A. Meyers¹², Rachel Myers⁵⁷, Dan L. Nicolae⁵⁷, Ellen Nohr⁵⁸, Teemu Palviainen⁴⁵, Lavinia Paternoster⁵⁹, Lavinia Paternoster⁵⁹, Craig Pennell⁶⁰, Göran Pershagen^{47,61}, Maria Pino-Yanes^{10,30,37}, Nicole M Probst-Hensch^{20,21}, Franz Rüschenhoff⁶⁰, Nathan Schoettler⁵⁷, Angela Simpson³, Kari Stefansson^{41,42}, Jordi Sunyer⁸, Gardar Sveinbjörnsson⁴¹, Elisabeth Thiering^{2,62}, Philip J. Thompson⁶³, Chao Tian³⁸, Chao Tian³⁸, Maties Torrent⁶⁴, David Torrents^{13,65}, Joyce Y. Tung³⁸, Carol Wang⁶⁰, Stephan Weidinger¹¹, Scott Weiss⁶⁶, Gonneke Willemsen⁵, L Keoki Williams^{34,67}, Carole Ober⁵⁷, Manuel A. Ferreira⁶⁸, Hans Bisgaard¹, David Strachan⁶⁹, Klaus Bønnelykke¹

Corresponding author: Hans Bisgaard¹

¹COPSAC, Copenhagen Prospective Studies on Asthma in Childhood, Herlev and Gentofte Hospital, University of Copenhagen, Copenhagen, Denmark. ²Institute of Epidemiology I, Helmholtz Zentrum München - German Research Center for Environmental Health, Neuherberg, Germany. ³Centre for Respiratory Medicine and Allergy, Institute of Inflammation and Repair, University of Manchester and University Hospital of South Manchester, Manchester Academic Health Sciences Centre, Manchester, UK. ⁴To be listed in Supplementary Information. ⁵Dept Biological Psychology, Netherlands Twin Register, VU University, Amsterdam. ⁶Department of Epidemiology and Biostatistics, School of Public Health, Imperial College, London, UK. ⁷Population Health and Occupational Disease, National Heart and Lung Institute, Imperial College London, London, UK. ⁸ISGlobal-Center for Research in Environmental Epidemiology (CREAL), Universitat Pompeu Fabra (UPF), CIBER Epidemiología y Salud Pública (CIBERESP), Barcelona, Spain. ⁹Clinic and Polyclinic of Dermatology, University Medicine Greifswald, Greifswald, Germany. ¹⁰Research Unit, Hospital Universitario N.S. de Candelaria, Universidad de La Laguna, Tenerife, Spain. ¹¹Department of Dermatology, Venereology and Allergology, University-Hospital Schleswig-Holstein, Campus Kiel, Kiel, Germany. ¹²Divisions of Pharmacogenomics and Genetics, Genomics and Precision Medicine, Department of Medicine, University of Arizona College of Medicine, Tucson, AZ, USA. ¹³Barcelona Supercomputing Center (BSC). Joint BSC-CRG-IRB Research Program in Computational Biology, Barcelona, Spain. ¹⁴EMGO Institute for Health and Care Research. ¹⁵Department of Biotechnology and Biomedicine, Technical University of Denmark, Kgs. Lyngby, Denmark. ¹⁶Department of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai, New York, NY, USA. ¹⁷Department of Medicine, University of California San Francisco, San Francisco, California, USA. ¹⁸Department of Bioengineering & Therapeutic Sciences, University of California San Francisco, San Francisco, California, USA. ¹⁹Dept of Preventive Medicine, University of Southern California, Keck School of Medicine. ²⁰University of Basel, Switzerland. ²¹Swiss Tropical and Public Health Institute, Basel, Switzerland. ²²Department of Paediatrics, Imperial College London, UK. ²³The Generation R Study Group. ²⁴Department of Pediatrics, division of Respiratory Medicine. ²⁵Department of Epidemiology, Erasmus Medical Center, Rotterdam, the Netherlands. ²⁶Melbourne School of Population and Global Health, University of Melbourne, Melbourne, Australia. ²⁷Laboratory of Animal Genomics, Unit of Medical Genomics, GIGA Institute, University of Liège, Belgium. ²⁸Department of Pediatrics, division of Neonatology. ²⁹LMU Munich, Dr von Hauner Children's Hospital, Munich and German Center for Lung Research (DZL), Munich, Germany. ³⁰CIBER de Enfermedades Respiratorias (CIBERES), Instituto de Salud Carlos III, Madrid, Spain. ³¹Research Unit of Molecular Epidemiology, Helmholtz Zentrum München–German Research Center for Environmental Health, Neuherberg, Germany. ³²Institute of Epidemiology II, Helmholtz Zentrum München–German Research Center for Environmental Health, Neuherberg, Germany. ³³School of Social and

56 Community Medicine, University of Bristol, UK. ³⁴Center for Health Policy and Health Services Research, Henry Ford
57 Health System, Detroit, MI, USA. ³⁵Novo Nordisk Foundation Center for Basic Metabolic Research, Section of
58 Metabolic Genetics, Department of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark.
59 ³⁶Institute and Outpatient Clinic for Occupational, Social and Environmental Medicine, University of Munich Medical
60 Center, Ludwig-Maximilians-Universität München, Munich, Germany. ³⁷Genomics and Health Group, Department of
61 Biochemistry, Microbiology, Cell Biology and Genetics, Universidad de La Laguna, La Laguna, Tenerife, Spain.
62 ³⁸23andMe, Inc., Mountain View, California, USA. ³⁹Telethon Kids Institute (TKI), Perth Australia. ⁴⁰Department of
63 Bioinformatics, Technical University of Denmark, Kgs. Lyngby, Denmark. ⁴¹deCODE genetics / Amgen Inc, Reykjavik,
64 Iceland. ⁴²Faculty of Medicine, University of Iceland, Reykjavik, Iceland. ⁴³Department of Pediatric Pneumology and
65 Allergy, University Children`s Hospital Regensburg (KUNO), Regensburg, Germany. ⁴⁴Department of Public Health,
66 University of Helsinki, Helsinki, Finland. ⁴⁵Institute for Molecular Medicine Finland FIMM, University of Helsinki,
67 Helsinki, Finland. ⁴⁶National Institute for Health and Welfare, Helsinki, Finland. ⁴⁷Institute of Environmental Medicine,
68 Karolinska Institutet, Stockholm, Sweden. ⁴⁸Department of Public Health Epidemiology, Unit of Chronic Disease
69 Epidemiology, Swiss Tropical and Public Health Institute, Basel, Switzerland. ⁴⁹University of Basel, Basel,
70 Switzerland. ⁵⁰Max-Delbrück-Center (MDC) for Molecular Medicine, Berlin, Germany. ⁵¹Clinic for Pediatric Allergy,
71 Experimental and Clinical Research Center, Charité Universitätsmedizin Berlin, Germany. ⁵²Department of Public
72 Health Sciences, Henry Ford Health System, Detroit, MI, USA. ⁵³Divisions of Genetics, Genomics and Precision
73 Medicine, Department of Medicine, University of Arizona College of Medicine, Tucson, AZ, USA. ⁵⁴Sachs' Children's
74 Hospital, Stockholm, Sweden. ⁵⁵Programs in Metabolism and Medical & Population Genetics, Broad Institute of
75 Harvard and MIT, Cambridge, Massachusetts, USA. ⁵⁶Diabetes Unit and Center for Genomic Medicine,
76 Massachusetts General Hospital, Boston, Massachusetts, USA. ⁵⁷Department of Human Genetics, University of
77 Chicago, Chicago IL, USA. ⁵⁸Institute of Clinical Research, University of Southern Denmark, Department of Obstetrics
78 & Gynecology, Odense University Hospital, Odense, Denmark. ⁵⁹MRC Integrative Epidemiology Unit at the University
79 of Bristol, School of Social and Community Medicine, University of Bristol, UK. ⁶⁰Division of Obstetrics and
80 Gynaecology, The University of Western Australia (UWA), Perth, Australia. ⁶¹Centre for Occupational and
81 Environmental Medicine, Stockholm County Council, Stockholm. ⁶²Ludwig-Maximilians-University of Munich, Dr. von
82 Hauner Children's Hospital, Division of Metabolic Diseases and Nutritional Medicine, Munich, Germany. ⁶³Institute for
83 Respiratory Health, Harry Perkins Institute of Medical Research, University of Western Australia, Nedlands, Australia.
84 ⁶⁴ib-salut, Area de Salut de Menorca, Menorca, Spain. ⁶⁵Institució Catalana de Recerca i Estudis Avançats (ICREA),
85 Barcelona, Spain. ⁶⁶Channing Division of Network Medicine, Brigham & Women's Hospital and Harvard Medical
86 School, Boston, MA, USA. ⁶⁷Department of Internal Medicine, Henry Ford Health System, Detroit, MI, USA. ⁶⁸QIMR
87 Berghofer Medical Research Institute, Brisbane, Queensland, Australia. ⁶⁹Population Health Research Institute, St
88 George's, University of London, London, UK.

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90 †These authors contributed equally to this work

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92 Introduction

93 Allergic rhinitis is the most common clinical presentation of allergy, affecting 400 million people
94 worldwide, and with increasing incidence in westernized countries.^{1,2} To elucidate the genetic
95 architecture and understand disease mechanisms of allergic rhinitis, we carried out a meta-
96 analysis of allergic rhinitis in 59,762 cases and 152,358 controls of European ancestry and
97 identified a total of 41 risk loci for allergic rhinitis, including 20 loci not previously associated with
98 allergic rhinitis, which were confirmed in a replication phase of 60,720 cases and 618,527
99 controls. Functional annotation implied genes involved in various immune pathways, and fine
100 mapping of the HLA region suggested amino acid variants of importance for antigen binding.
101 We further performed GWASs of allergic sensitization against inhalant allergens and non-
102 allergic rhinitis suggesting shared genetic mechanisms across rhinitis-related traits. Future
103 studies of the identified loci and genes might identify novel targets for treatment and prevention
104 of allergic rhinitis.

106 Main text

107 Allergic rhinitis (AR) is an inflammatory disorder of the nasal mucosa mediated by
108 allergic hypersensitivity responses to environmental allergens¹ with large adverse effects on
109 quality of life and health care expenditures. The underlying causes for AR are still not
110 understood and prevention of the disease is not possible. The heritability of AR is estimated to
111 be more than 65%^{3,4}. Seven loci have been associated and with allergic rhinitis in genome-wide
112 association studies (GWAS) of AR per se, while other have been suggested from GWAS
113 studies on related traits, such as self-reported allergy, asthma plus hay fever, or allergic
114 sensitization⁵⁻⁹, but only few of these have been replicated.

115 We carried out a large-scale meta-GWAS of AR including a discovery meta-analysis of
116 16,531,985 genetic markers from 18 studies comprising 59,762 cases and 152,358 controls of
117 primarily European ancestry (**Supplementary Table 1**, cohort recruitment details in
118 **Supplementary Note**). We report the genetic heritability on the liability scale of AR as at least
119 7.8% (assuming 10% disease prevalence), with a genomic inflation of 1.048 (**Supplementary**
120 **Figure 1**). We identified 42 genetic loci, with index markers below genomewide significance
121 ($p < 5e-8$), of which 21 have previously been reported in relation to AR or other inhalant allergy⁶⁻⁹
122 (**Fig. 1, Table 1, Supplementary Fig. 2, Supplementary Fig. 3**).

123 One study (23andMe) had a proportionally large weight (~80%) in the discovery phase.
124 Overall there was good agreement between 23andMe and the other studies with respect to
125 effect size and direction, and regional association patterns (**Supplementary Table 2 and**
126 **Supplementary Fig. 4+5**), and the genetic correlation was 0.80 ($p < 2e-17$). Heterogeneity
127 between 23andMe and the remaining studies was statistically significant ($p < 0.05$) for 7 of 42
128 loci, in most cases due to a smaller effect size in 23andMe. This was likely due to many non-
129 23andMe studies using a more robust phenotype definition of doctor diagnosed AR
130 (**Supplementary Table 3**), which tended to result in larger effect sizes (**Supplementary Table**
131 **4**).

132 The index markers from a total of 25 loci that had not previously been associated
133 with AR or other inhalant allergy were carried forward to the replication phase. These included
134 16 loci that showed genome-wide significant association in the discovery phase and evidence of
135 association ($p < 0.05$) in both 23andMe and non-23andMe studies (**Supplementary Table 2**),
136 and an additional 9 loci that were selected from the p-value stratum between $5e-8$ and $1e-6$
137 based on enrichment of gene sets involved in immune-signalling (**Supplementary Table 5**).
138 Replication was sought in another 10 studies with 60,720 cases and 618,527 controls. Of the 25
139 loci, 20 loci reached a Bonferroni-corrected significance threshold of 0.05 ($p < 0.0019$) in a meta-
140 analysis of replication studies (**Fig. 1 (blue), Table 1**), and all of these reached genome-wide
141 significance in the combined fixed-effect meta-analysis of discovery and replication studies
142 (**Table 1**). Evidence of heterogeneity was seen for one of these loci (rs1504215), which did not
143 reach statistical significance in the random effects model (0.95 [0.92; 0.97], $p = 2.83e-07$,
144 **Supplementary Fig. 3**).

145 A conditional analysis of top loci identified 13 additional independent variants at
146 $p < 1e-5$, with 4 of these being genome-wide significant (near *WDR36*, *HLA-DQB1*, *IL1RL1* and
147 *LPP*) (**Supplementary Table 6 and Supplementary Fig. 5**, bottom panel).

148 To gain insight into functional consequences of known and novel loci, we utilised a number of
149 data sources, including 1) 11 eQTL sets and 1 meQTL set from blood and blood subsets; 2) 2
150 eQTL sets and 1 meQTL set from lung tissue; and 3) data on enhancer-promoter interactions in
151 15 different blood subsets. Support of regulatory effects on coding genes was found for 33 out
152 of the 41 loci. Many loci showed evidence of regulatory effects across a wide range of immune
153 cell types (including B- and T-cells), while other seemed cell type-specific, like e.g. innate
154 lymphoid cells (**Table 2 and Supplementary Table 7**). Calculation of the “credible set” of
155 markers for each locus using a Bayesian approach that selects markers likely to contain the
156 causal disease-associated markers (**Supplementary Table 8**) and looking up these in the
157 Variant Effect Predictor database generated a list of 17 markers producing amino acid changes,
158 including deleterious changes in NUSAP1, SULT1A1 and PLCL, as predicted by SIFT
159 (**Supplementary Table 9**).

160 The major histocompatibility complex on chr6p harbored some of the strongest association
161 signals in the GWAS with 2 independent signals located around *HLA-DQB* and *HLA-B*,
162 respectively. The top variant at *HLA-DQB* was an eQTL for several HLA-genes, including *HLA-*
163 *DQB1*, *HLA-DQA1*, *HLA-DQA2*, and *HLA-DRB1* in immune and/or lung tissue, and the top
164 variant at *HLA-B* was an eQTL for *MICA* (**Supplementary Table 7**). In addition we found highly
165 significant associations with several well imputed amino acid variants (**Supplementary Tables**
166 **10 and 11**). Importantly, the strongest associated amino acid variants in *HLA-DQB1* and *HLA-B*,
167 respectively (**Supplementary Table 10**) were both located in the peptide binding pockets with a
168 high likelihood of affecting MHC-peptide interaction (**Figure 2**). MHC class II molecules,
169 including *HLA-DQ*, are known for their role in allergen-binding and Th2 driven immune
170 responses.¹⁰ The strong association with *HLA-DQB1 His30* ($p = 2.06e-28$, OR=0.91) in the
171 peptide binding pocket, and the moderate LD ($r^2 = 0.71$) with the GWAS top SNP rs3400401,
172 therefore suggest that the association signal at this locus involves changes in allergen binding
173 properties by *HLA-DQ* and thereby altered risk of allergen-specific immunity. We also found
174 association with several classical HLA alleles, including *HLA-DQB1*02:02*, *HLA-DQB1*03:01*,

175 HLA-DRB1*04:01, and HLA-C*04:01, which were in weak LD ($r^2 < 0.1$) with the GWAS top SNPs
176 (**Supplementary Tables 12 and 13**). These findings suggest that genetic associations in HLA-
177 MHC region both involve variants affecting gene regulation and structure, similar to what has
178 been found for autoimmune disease.^{11,12}

179 The majority of the 20 loci not previously associated with AR per se imply genes with a
180 known role in the immune system, including IL7R^{13, 14}, SH2B3¹⁵, CEBPA/CEBPG^{16, 17}, CXCR5¹⁸,
181 FCER1G, NFKB1¹⁹, BACH2^{20, 21}, TYRO3²², LTK²³, VPRBP²⁴, SPPL3²⁵, OASL²⁶, RORA²⁷, and
182 TNFSF11²⁸. Other loci imply genes with no clear function in AR pathogenesis. These include
183 one of the strongest associated loci in this meta-analysis at 12q24.31 with the top-signal located
184 between CDK2AP1 and C12orf65, harboring cis-eQTLs in blood and lung tissue for several
185 genes and evidence for enhancer-promoter interaction with DDX55 in various immune cells.
186 (Table 2 and further locus description in the Supplementary Note). Concomitantly with the
187 current study, a GWAS combining asthma, eczema and AR was conducted.²⁹ The majority
188 (15/20) of identified AR loci in our study were also suggested in the previous, more unspecific,
189 GWAS²⁹ (as indicated in Tables 1 and 2), while many suggested loci from the previous GWAS
190 were not identified in our study. Asthma, eczema and allergic rhinitis are related but distinct
191 disease entities, often with separate disease mechanisms, e.g. allergic sensitization is present
192 in only 50% of children with asthma³⁰ and 35% of children with eczema.³¹ Our results therefore
193 complement those from the less specific “atopic phenotype” GWAS²⁹ by pinpointing loci
194 specifically associated, and replicated, in relation to allergic rhinitis.

195 AR loci were significantly enriched ($p < 1e-5$) for variants reported to be associated with
196 autoimmune disorders. Reported autoimmune variants were located within a 1mb distance of 31
197 (76%) of the 41 AR loci. For 24 of these, an autoimmune top SNP was also associated with AR,
198 and for 12 of these the autoimmune top SNP was in LD ($r^2 > 0.5$) with the AR top SNP
199 (**Supplementary Table 14**). For approximately half of these, the direction of effect was the
200 same for the autoimmune and AR top SNP in line with a previous study,³² underlining the
201 complex genetic relationship between AR and autoimmunity, which might involve shared as well
202 as diverging molecular mechanisms.

203 Assessment of enrichment of AR-associated variant burden in open chromatin as defined by
204 DNase hypersensitive sites showed a clear enrichment in several blood and immune cell
205 subsets, with the largest enrichment in T-cells (CD3 expressing), B-cells (CD19 expressing),
206 and T and NK-cells (CD56-expressing) (**Fig. 3, Supplementary Table 15, Supplementary Fig.**
207 **6**). We also probed tissue enrichment by means of gene expression data from a wide number of
208 sources, showing enrichment of AR genes in blood and immune cell subsets, as well as in
209 tissues of the respiratory system, including oropharynx, respiratory and nasal mucosa
210 (**Supplementary Table 16**).

211 To explore biological connections and identify new pathways associated with AR, we combined
212 all genes suggested from eQTL/meQTL analyses, enhancer-promoter interactions and
213 localization within the top loci. The resultant prioritized gene set consisted of 255 genes, of
214 which 89 (~36%) were present in more than one set (**Supplementary Fig. 7**). Overall, the full
215 set was enriched for pathways involved in Th1 and Th2 Activation (**Fig. 4**), antigen presentation,
216 cytokine signaling, and inflammatory responses (**Supplementary Table 17**).

217 Using the 255 prioritized genes in combination with STRING to identify proteins that interact
218 with the proteins encoded by the high priority genes, we demonstrated a high degree of
219 interaction at the protein level, and several of these proteins are target of approved drugs or
220 drugs in development, including TNFSF11, NDUFAF1, PD-L1, IL-5, and IL-13 (**Fig. 4**).
221 AR is strongly correlated to allergic sensitization (presence of allergen-specific IgE), but
222 sensitization is often present without AR suggesting specific mechanisms determining
223 progression from sensitization to disease. We therefore conducted a GWAS on sensitization to
224 inhalant allergens (AS) comprising 8,040 cases and 16,441 controls from 13 studies
225 (**Supplementary Table 1**), making it the largest GWAS on allergic sensitization to date⁷. A total
226 of 10 loci reached genome-wide significance, including one novel hit near the *FASLG* gene
227 (**Supplementary Table 18**). The genetic heritability on the liability scale was 17.75% (10%
228 prevalence), considerably higher than the heritability of AR in consistency with a more
229 homogeneous phenotype. Look-up of AR top-loci in the AS GWAS demonstrated large
230 agreement with 39 of the 41 AR markers showing same direction of effect and 28 also showing
231 nominal significance for AS (**Supplementary Table 19**). This suggests that AR and AS share
232 biological mechanisms and that AS loci generally affect systemic allergic sensitization. We
233 compared genetic pathways of AR and AS using the DEPICT tool showing overlap in enriched
234 pathways but also differences among the top gene sets, with AR gene sets characterized by B-
235 cell, Th2, and parasite responses and AS gene sets characterized by a broader activation of
236 cells (**Supplementary Fig 8 and Supplementary Tables 20 and 21**).

237 Non-allergic rhinitis, defined as rhinitis symptoms without evidence of allergic sensitization, is a
238 common but poorly understood disease entity.³³ We performed the first GWAS on this
239 phenotype hypothesizing that this might reveal specific rhinitis mechanisms. The analysis
240 included 2,028 cases and 9,606 controls from 9 studies but did not identify any risk loci at the
241 genome-wide significance level. Comparison with AR results suggested some overlap in
242 susceptibility loci (**Supplementary Note and Supplementary Table 22**).

243 We estimated the proportion of AR in the general population that can be attributed to the 41
244 identified AR loci and obtained a conservative population-attributable risk fraction estimate of
245 39% (95% CI 26%-50%), considering the 10% of the population with the lowest genetic risk
246 scores to represent an 'unexposed' group. Allergic rhinitis prevalence plotted by genetic risk
247 score (**Supplementary Fig. 9**) showed approximately 2 times higher prevalence in the 7% of
248 the population with the highest risk score compared to the 7% with the lowest risk score.

249 Finally, we investigated the genetic correlation of AR with AS, asthma³⁴, and eczema³⁵ by LD
250 score regression. There was a strong correlation between AR and AS ($r^2=0.73$, $p<2e-34$),
251 moderate with asthma ($r^2=0.60$, $p<3e-14$) and weaker with eczema ($r^2=0.40$, $p<2e-07$).

252 In conclusion, we expanded the number of established susceptibility loci for AR and highlighted
253 involvement of AR susceptibility loci in diverse immune cell types and both innate and adaptive
254 IgE-related mechanisms. Future studies of novel AR loci might identify targets for treatment and
255 prevention of disease.

256
257

258 Methods:

259 Phenotype definition

260 Allergic rhinitis (AR)

261 Cases were defined as individuals ever having a diagnosis or symptoms of AR dependant on
262 available phenotype definitions in the included studies (**Supplementary Table 3** and cohort
263 recruitment details in **Supplementary Note**). To maximize numbers and optimize statistical
264 power, we did not require doctor-diagnosed AR or verification by allergic sensitization. This
265 approach was confirmed by a sensitivity analysis in 23andMe based on association with known
266 risk loci for allergic rhinitis (data not shown). Controls were defined as individuals who never had
267 a diagnosis or symptoms of AR.

268

269 Allergic sensitization (AS)

270 We considered specific IgE production against inhalant allergens without restriction by
271 assessment method or type of inhalant allergen. Cases were defined as individuals with
272 objectively measured sensitization against at least one of the inhalant allergens tested for in the
273 respective studies, and controls were defined as individuals who were not sensitized against
274 any of the allergens tested for. We included sensitization assessed by skin reaction after
275 puncture of the skin with a droplet of allergen extract (SPT) and/or by detection of the levels of
276 circulating allergen-specific IgE in the blood. The SPT wheal diameter cutoffs were 3 mm larger
277 than the negative control for cases and smaller than 1 mm for controls. To optimize case
278 specificity and the correlation between methods, we chose a high cutoff of specific IgE levels for
279 cases (0.7 IU/ml) and a low cutoff for controls (0.35 IU/ml).

280

281 Non-allergic rhinitis (NAR)

282 Case were defined as individuals with current allergic rhinitis symptoms (within the last 12
283 months) and no allergic sensitization (negative specific IgE (< 0.35 IU/mL) and/or negative skin
284 prick test (< 1 mm) for all allergens and time points tested)

285 Controls were defined as individuals never having symptoms of allergic rhinitis and no allergic
286 sensitization (negative specific IgE (< 0.35 IU/mL) and/or negative skin prick test (< 1 mm) for all
287 allergens and time points tested)

288

289 For all 3 phenotypes, we combined data from children and adults but chose a lower age limit of
290 6 years, as allergic rhinitis and sensitization status at younger ages show poorer correlation with
291 status later in life, both owing to transient symptoms/sensitization status and frequent
292 development of symptoms/sensitization during late childhood.

293 GWAS QC and cohort summary data harmonization

294 For AR, AS, and NAR, each cohort imputed their data separately using the 1000 Genomes
295 Project (1KGP) phase 1, version 3 release, and conducted the genome-wide association
296 analysis adjusted for sex and if necessary for age and principal components (Supplementary

297 Table COHORTS). All studies included individuals of European descent, except Generation R
298 and RAINE, comprising a mixed, multi-ethnic population. We utilized EasyQC v. 9.2³⁶ for quality
299 control and marker harmonization for cohort-level meta-GWAS summary files. Cohort data was
300 harmonized to genome build GRCh37 and checked against 1KGP phase 3 reference allele
301 frequencies for processing problems. GWAS summary “karyograms” were visually inspected to
302 catch cohorts with incomplete data. Distributions of estimate coefficients and errors, as well as
303 “Standard error vs. sample size”- and “p value vs. z-score” plots were inspected for each cohort
304 for systematic errors in statistical models. Ambiguous markers that were non-unique in terms of
305 both genomic position and allele coding were removed. A minimum imputation score of 0.3 (R^2)
306 or 0.4 (proper_info) was required for markers. A minimum minor allele count of 7 was required
307 for each marker in each cohort, as suggested by the GIANT consortium and EasyQC.
308

309 Meta-Analysis

310 For AR, AS, and NAR, meta-analysis for the discovery phase was conducted using GWAMA³⁷
311 with an inverse variance weighted fixed-effect model with genomic control correction of the
312 individual studies. Each locus is represented by the variant showing the strongest evidence
313 within a 1Mb buffer. Loci were inspected visually by plotting genomic neighbourhood and
314 coloring for 1KGP r^2 values. From the pool of genomewide significant markers in the discovery,
315 one locus with index marker rs193243426 without a credible LD structure was removed from
316 further analysis (**Supplementary Fig. 10**). Heterogeneity was assessed with Cochran’s Q test.
317 Meta-analysis of replication candidates from the AR discovery phase was carried out using R
318 version 3.4.0, and the *meta* package version 4.8-2 with an inverse variance weighted fixed-
319 effect model. For a subset of markers, cohorts reported suitable proxies ($r^2 > 0.85$), where
320 followed-up markers were not present or had insufficient imputation or genotyping quality
321 (**Supplementary Table 23**).

322 Gene set overrepresentation analysis, discovery phase

323 To facilitate selection of biologically relevant discovery candidates in the sub-genomewide
324 significant stratum ($5e-8 < p < 1e-6$), we employed a custom gene set overrepresentation
325 analysis algorithm implemented in R, with a scoring and permutation regime modelled after
326 MAGENTA.³⁸ Genes with lengths less than 200bp, with copies on multiple chromosomes, and
327 with multiple copies on the same chromosome more than 1Mb apart were removed from
328 analysis. Gene models (GENCODE v 19) were downloaded from the UCSC Table Browser,³⁹
329 and expanded 110 kb upstream, and 40 kb downstream, similar to MAGENTA. The HLA region
330 was excluded from analysis (chromosome 6: 29,691,116-33,054,976). Similar to MAGENTA,
331 gene scores were adjusted for number of markers per gene, gene width, recombination
332 hotspots, genetic distance, and number of independent markers per gene, all with updated data
333 from UCSC Table Browser. For the gene set overrepresentation permutation calculation, gene
334 sets from the MSigDB collections c2, c3, c5, c7, and hallmark, were included.⁴⁰ A MAGENTA-
335 style enrichment cutoff at 95% was used. Gene sets with $FDR < 0.05$ were considered.

336 Conditional analyses

337 To identify additional independent markers at each discovery genomic region, we used
338 Genome-wide Complex Trait Analysis (GCTA) v. 1.26.0.⁴¹ Within a window of +/- 1Mb of each
339 discovery phase index marker, all markers were conditioned on the index using the --cojo-cond
340 feature of GCTA with default parameters. Plink v. v1.90b3.42⁴² was used to calculate r^2 for
341 GCTA with the UK10K full genotype panel⁴³ as reference. A total of 42 of 52 markers from the
342 full discovery phase were present in UK10K. As a MAF-dependent inflation of conditional p-
343 values was observed (data not shown), only conditional markers with MAF \geq 10% were
344 selected.

345 Locus definition and credible sets for VEP annotation

346 Discovery loci were defined as index markers extended with markers in LD ($r^2 \geq 0.5$), based on
347 the 1KGP phase 3. Protein coding gene transcript models (GENCODE V24) were downloaded
348 from the UCSC Table Browser, and nearest upstream, downstream, as well as all genes within
349 the extended loci were annotated.

350 Credible sets for each locus were calculated using the method of Morris, A.P.⁴⁴.

351 LD was calculated for each discovery index variant within +/- 500 kb, and markers with $r^2 < 0.1$
352 were excluded. For the remaining markers, the Bayesian Factor (ABF) values and the posterior
353 probabilities (PostProb) were calculated, and cumulative posterior probability values were
354 generated based ranking markers on ABF. Finally, variants were included in the 99% credible
355 set until the cumulative posterior probability was greater or equal than 0.99.

356 Credible sets for each loci was annotated with information on mutation impact in coding regions
357 using the Variant effect Prediction (VeP) REST API⁴⁵, exporting only the nonsynonymous
358 substitutions.

359 GWAS catalogue lookup

360 For annotation of markers with identification in previous GWA studies, the GWAS catalog was
361 downloaded from NHGRI-EBI (v.1.0.1, 2016-11-28). For this analysis, AR loci were lifted from
362 genomic build GRCh37 to GRCh38, and extended with +/- 1Mb in each direction before being
363 overlapped with GWAS catalog annotations. Relevant GWAS catalog overlap traits were binned
364 into trait groups "Allergic Rhinitis", "Asthma", "Autoimmune", "Eczema", "Infectious Diseases",
365 "Lung-related Traits", and "Other allergy". A million random genomic intervals of the same length
366 (2Mb) were obtained to generate a background overlap distribution, and p-values were
367 calculated from this background.

368 HLA classical allele analysis

369 Analyses of imputed classical HLA-alleles were performed in the 23andMe study (AR discovery
370 population) comprising 49,180 individuals with allergic rhinitis and 124,102 controls.

371 HLA imputation was performed with HIBAG.⁴⁶ We imputed allelic dosage for HLA-A, B, C,
372 DPB1, DQA1, QB1, and DRB1 loci at four-digit resolution using the default settings of HIBAG
373 for a total of 292 classical HLA alleles.

374 Using an approach suggested by P. de Bakker,⁴⁷ we downloaded the files that map HLA alleles
375 to amino acid sequences from <https://www.broadinstitute.org/mpg/snp2hla/> and mapped our
376 imputed HLA alleles at four-digit resolution to the corresponding amino acid sequences; in this
377 way we translated the imputed HLA allelic dosages directly to amino acid dosages. We encoded
378 all amino acid variants in the 23andMe European samples as 2395 bi-allelic amino acid
379 polymorphisms as previously described.⁴⁸
380 Similar to the SNP imputation, we measured imputation quality using r^2 , which is the ratio of the
381 empirically observed variance of the allele dosage to the expected variance assuming Hardy-
382 Weinberg equilibrium.
383 To test associations between imputed HLA alleles, amino acid variants, and phenotypes, we
384 performed logistic regression using the same set of covariates used in the SNPbased GWAS.
385 We applied a forward stepwise strategy, within each type of variant, to establish statistically
386 independent signals in the HLA region. Within each variant type, we first identified the most
387 strongly associated signals (lowest p-value) and performed forward iterative conditional
388 regression to identify other independent signals. All analyses were controlled for sex and five
389 principal components of genetic ancestry. The p-values were calculated using a likelihood ratio
390 test.
391

392 Structural visualization of amino acid variants

393 Structural visualization of amino acid variants was performed for the strongest associated
394 variants in HLA-DQB1 (position 30) and HLA-B (position 116), respectively (**Supplementary**
395 **Table 10**) and were made using X-ray structures from Protein Data Bank (PDB).⁴⁹ To find the
396 best structure we used the specialized search function in the Immune Epitope Database,⁵⁰
397 selecting only X-ray crystalized structures for the specific MHC type HLA-DQB1 and HLA-B.
398 Using this criterion, we found 17 crystallized structures for HLA-DQB1 and 164 structures for
399 HLA-B. From these lists, we selected the structure with the lowest resolution and the amino
400 acids encoded by the reported top SNPs. The PDB accession code for the selected structures
401 was 4MAY⁵¹ for HLA-DQB1 and 2A83⁵² for HLA-B and both structures were visualized using
402 PyMOL (<http://www.pymol.org>). Furthermore, we used PyMOL to measure intra-molecular
403 distances from the side chain of the amino acids associated with allergic rhinitis to the C atoms
404 in the peptide. This distance measure was chosen to accommodate the possibility for different
405 amino acids in the peptide. In order for two amino acids to interact the distance should be
406 approximately 4Å or less. We measured distances of 6Å (HLA-DQB1) and 7Å (HLA-B), however
407 these distances do not include the peptide side chains which range from 1.5 Å – 8.8 Å.
408 Therefore, we estimate that physical interaction between the amino acids encoded by the top
409 SNPs and the peptide is likely.

410 Genetic heritability and genetic correlation

411 For calculating genetic heritability and genetic correlation between AR and AS, as well as
412 between clinical cohorts and 23andMe within AR, we utilized the LD score regression based
413 method as implemented by LDSC v.1.0.^{45,53} Population prevalence was set to 10% for AR and

414 AS. Genetic correlation analysis between AR, AS and published GWAS studies was carried out
415 using the LDHUB platform v1.3.1⁵⁴ against all traits, but excluding Metabolites⁵⁵.

416 eQTL sources and analysis

417 From GTEx V6p⁵⁶, all significant variant-gene cis eQTL pairs for whole blood, lung, and EBV-
418 transformed lymphocytes were downloaded from <https://gtexportal.org>, and carried forward in
419 analysis. From Westra et al.⁵⁷, both cis and trans eQTLs in whole blood were downloaded, and
420 variant-gene pairs with FDR < 0.1 were carried forward in analysis. From Fairfax et al.⁵⁸, cis
421 eQTLs from monocytes and B cells were downloaded, and variant-gene pairs with FDR < 0.1
422 were carried forward in analyses. From Bonder et al.⁵⁸, meQTLs from whole blood were
423 downloaded, and variant-probe pairs with FDR < 0.05 were carried forward in analyses. From
424 Nicodemus-Johnson et al.⁵⁹, cis eQTLs and meQTLs from lung were downloaded, and variant-
425 gene pairs with FDR < 0.1 were carried forward in analyses. From Momozawa et al. [in press,
426 personal correspondence], cis eQTLs from blood cell types CD14, CD15, CD19, CD4, and CD8
427 were downloaded, and variant-gene pairs with a weighted correlation of ≥ 0.6 were carried
428 forward to analysis. For table 2 priority genes, protein coding information was downloaded from
429 the UCSC Table Browser, using the "transcriptClass" field from the
430 "wgEncodeGencodeAttrsV24lift37" table.

431 Promoter Capture Hi-C Gene Prioritisation

432 To assess spatial promoter interactions in the discovery set, we performed a Capture Hi-C
433 Gene Prioritisation (CHIGP) as described in Javierre et al.⁶⁰ and
434 <https://github.com/ollyburren/CHIGP> using recommended settings and data sources: 0.1cM
435 recombination blocks, 1KGP EUR reference population, coding markers from the GRCh37
436 Ensembl assembly and the CHICAGO-generated⁶¹ Promoter Capture Hi-C peak matrix data
437 from 17 human primary blood cell types supplied in the original paper. The resulting protein-
438 coding prioritized genes (gene score > 0.5) were used in the downstream network analysis,
439 from cell types "Fetal thymus", "Total CD4 T cells", "Activated total CD4 T cells", "Non-activated
440 total CD4 T cells", "Naive CD4 T cells", "Total CD8 T cells", "Naive CD8 T cells", "Total B cells",
441 "Naive B cells", "Endothelial precursors", "Macrophages M0", "Macrophages M1",
442 "Macrophages M2", "Monocytes", and "Neutrophils".

443 Gene set overrepresentation analysis of known and replicating novel loci

444 All high-confidence gene symbols from eQTL and meQTL sources, PCHiC, as well as genes
445 (models extended 110kb upstream, and 40kb downstream) within each r^2 -based loci definition
446 from known and replicating novel loci were input into the pathway-based set over-representation
447 analysis module of ConsensusPathDB (CPDB) database and tools⁶² with 229 of 277 gene
448 identifiers translated. In addition, these same symbols were used for Ingenuity pathway analysis
449 (IPA; www.ingenuity.com; a curated database of the relationships between genes obtained from
450 published articles, and genetic and expression data repositories) to identify biological pathways
451 common to genes. IPA determines whether the associated genes are significantly enriched in a

452 specific biological function or network by assessing direct interactions. We assigned significance
453 if right-tailed Fisher's exact test p-value < 0.05.
454 eQTL/meQTL, PCHiC and locus gene intersections were visualized using the UpSetR
455 package⁶³.

456 Tissue overrepresentation

457 To assay the enrichment of variants associated with AR in tissue specific gene expression sets,
458 we utilized the DEPICT enrichment method⁶⁴, using a p-value threshold of 1e-5, and standard
459 settings.

460 Enrichment of regulatory regions

461 To assay the enrichment of variants associated with AR in regions of open chromatin and
462 specific histone marks, we utilized the GWAS Analysis of Regulatory or Functional Information
463 Enrichment with LD correction (GARFIELD) method⁶⁵. In essence, GARFIELD performs greedy
464 pruning of GWAS markers (LD $r^2 > 0.1$) and then annotates them based on functional
465 information overlap. Next, it quantifies Fold Enrichment (FE) at various GWAS significance
466 cutoffs and assesses them by permutation testing, while adjusting for minor allele frequency,
467 distance to nearest transcription start site and number of LD proxies ($r^2 > 0.8$). GARFIELD was
468 run with 10,000,000 permutations, and otherwise default settings.

469 PARF

470 Population-attributable risk fractions (PARFs) were estimated from B58C, a general-population
471 sample with participant ages 44-45 years also contributing to the discovery stage. The genetic
472 risk score was calculated by applying the pooled per-allele coefficients (ln(OR) values) from the
473 AR discovery set to the number of higher-risk alleles of each of the 41 established (known
474 genome-wide significant and novel replicated loci), one SNP per locus. Because there were no
475 individuals observed with zero higher-risk alleles, the prevalence of sensitization for individuals
476 in the lowest decile of the genetic risk score distribution was used to derive PARF estimates on
477 the assumption that this 10% of the population was unexposed. This method has the advantage
478 that it does not predict beyond the bounds of the data, but its results are conservative. The
479 PARF was then derived (with 95% confidence interval) by expressing the difference between
480 the observed prevalence and the predicted (unexposed) prevalence as a percentage of the
481 observed prevalence. PARFs were estimated using the 41 AR loci in relation to AR, AS and
482 NAR, respectively.

483 Protein network and drug interactions

484 In order to analyse protein-protein-drug interaction networks, STRING (V10)⁶⁶ was used. Protein
485 network data (9606.protein.links.v10.txt.gz) and protein alias data (9606.protein.aliases.v10.txt)
486 files were downloaded from the string db website [<http://string-db.org/>]. GWAS hits stratified on
487 'all', 'blood' and 'lung' were converted to Ensembl protein ids using the protein alias data. The
488 interactors were subsequently identified using the link data at a 'high confidence cutoff of >0.7'

489 as described in the STRING FAQ. The interactor Ensembl protein ids were then converted to
490 UniProt gene names and both hits and interactors were then analyzed for interactions with FDA
491 approved drugs using the ChEMBL Database⁶⁷ API via Python (v2.7.12). Lastly, stratified
492 networks consisting of GWAS hits connected to interactors and drugs connected to both GWAS
493 hits and interactors were visualised using GGraph (v1.0.0), iGraph (v1.0.1), TidyVerse (v1.1.1)
494 under R (v3.3.2).

495 Data availability

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

499

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650 **Table legends**

651 **Table 1**

652 Association results of index markers (variant with lowest p-value for each locus) from the
653 discovery phase. Column “Nearest gene” denotes nearest up- and downstream gene (for
654 intergenic variants with two genes listed), or surrounding gene (for intronic variants with one
655 gene listed), with the exception of rs5743618, an exonic missense variant within *TLR1*; and
656 rs1504215, an exonic synonymous variant within *BACH2*. Replication and combined p values
657 are for a one-sided test.

658

659 **Table 2**

660 Functional description of known and novel replicating loci. ‘Locus genes’ column denotes genes
661 overlapping with R2-extended loci (See Methods). ‘Missense variant’ column denotes variants
662 with a predicted missense coding consequences. ‘e/meQTL priority genes’ denotes genes
663 prioritized from the combined e/meQTL analysis. ‘PCHiC priority genes’ denotes genes
664 prioritized from the PCHiC chromatin capture analysis.

665 a) Overlap for rs35350651 with group “other allergy” is “eosinophil count”, b) rs11671925 =
666 eosinophilic esophagitis.

667

668

669 Figure legends

670 **Figure 1: Manhattan plot of the meta-GWAS discovery phase**

671 Circular plot of p-values of genetic marker association to allergic rhinitis from the discovery
672 phase. Only markers with $p < 1e-3$ are shown. Labels indicate nearest gene name for index
673 marker in locus (marker with lowest p-value). Green labels indicate loci previously associated
674 with allergy; blue labels indicate novel AR loci; grey labels indicate novel loci that were not
675 carried forward to the replication phase. Green line indicates level of genome wide significance
676 ($p = 5e-8$).

677

678 **Figure 2: Structural visualization of amino acid variants associated with allergic rhinitis**

679 The surface of the MHC molecules is shown in white, while the backbone of the bound peptides
680 is shown in dark gray. The amino acid variant is highlighted in red and the peptide binding
681 pockets of the MHC molecule is indicated with dashed circles. P1-P9 refers to positions in the
682 peptides counting from the N-termini. (A) Localization of the strongest associated amino acid
683 variant in HLA-DQB (MHC class II), HLA-DQB1 His30, located in the peptide binding pocket
684 close to P6 of the peptide with a distance of 6Å (excluding peptide side chain). The protective
685 amino acid variant at this location in relation to AR is His, whereas the risk variant is Ser.
686 Histidine is positively charged and has a large aromatic ring, whereas Ser is not charged and
687 not aromatic. Therefore, this mutation results in a significant change of the binding pocket
688 environment. (B) Localization of the strongest associated amino acid variation in HLA-B (MHC
689 class I), HLA-B AspHisLeu116, located close to P9 with a distance of 7Å (excluding peptide side
690 chain). The close proximity to the bound peptide for both variants indicates that they are likely to
691 affect the MHC-peptide interaction and thereby which peptides are presented.

692

693 **Figure 3: Enrichment of allergic rhinitis-associated variants in tissue-specific open 694 chromatin**

695 Enrichment of variants associated with allergic rhinitis (at $p < 1e-08$ as threshold for marker
696 association) in 189 cell types from ENCODE and Roadmap epigenomics data. Enrichment and
697 p-value was calculated empirically against a permuted genomic background using the
698 GARFIELD tool. Red labels indicate blood and blood-related cell-types, grey labels indicate
699 other cell types. Due to number of permutations = $1e7$, empirical p-values reached a minimum
700 ceiling of $1/1e7$. FDR threshold = 0.00026. For Epstein-Barr virus transformed B-lymphocyte cell
701 types (cell type "GM****"), only most enriched instance is shown ("B-Lymphocyte"). NHEK =
702 normal human epidermal keratinocytes, HMEC/vHMEC = mammary epithelial cells, HCM =
703 human cardiac myocytes, WI-38 = lung fibroblast-derived, HRGEC = human renal glomerular
704 endothelial cell, HCFaa = Human Cardiac Fibroblasts-Adult Atrial cell, HMVEC-dBI-Neo =
705 human microvascular endothelial cells, Th1 = T helper cell, type 1, Th2 = T helper cell, type 2.

706

707 **Figure 4: Interaction network between drugs and proteins from genes associated with 708 allergic rhinitis**

709 Grey nodes represent locus genes as well as genes prioritized from e/meQTL and PCHiC
710 sources. Blue nodes represent drugs from the ChEMBL drug database. Edges represent very-

711 high confidence interactions from the STRING database (for locus-locus interactions) and drug
712 target evidence (for drug-locus interactions). Red borders indicate genes with protein products
713 that were significantly enriched in the “Th1 and Th2 Activation” pathway ($-\log[p\text{-value}] > 19.1$)
714 from the IPA pathway analysis.

715

716

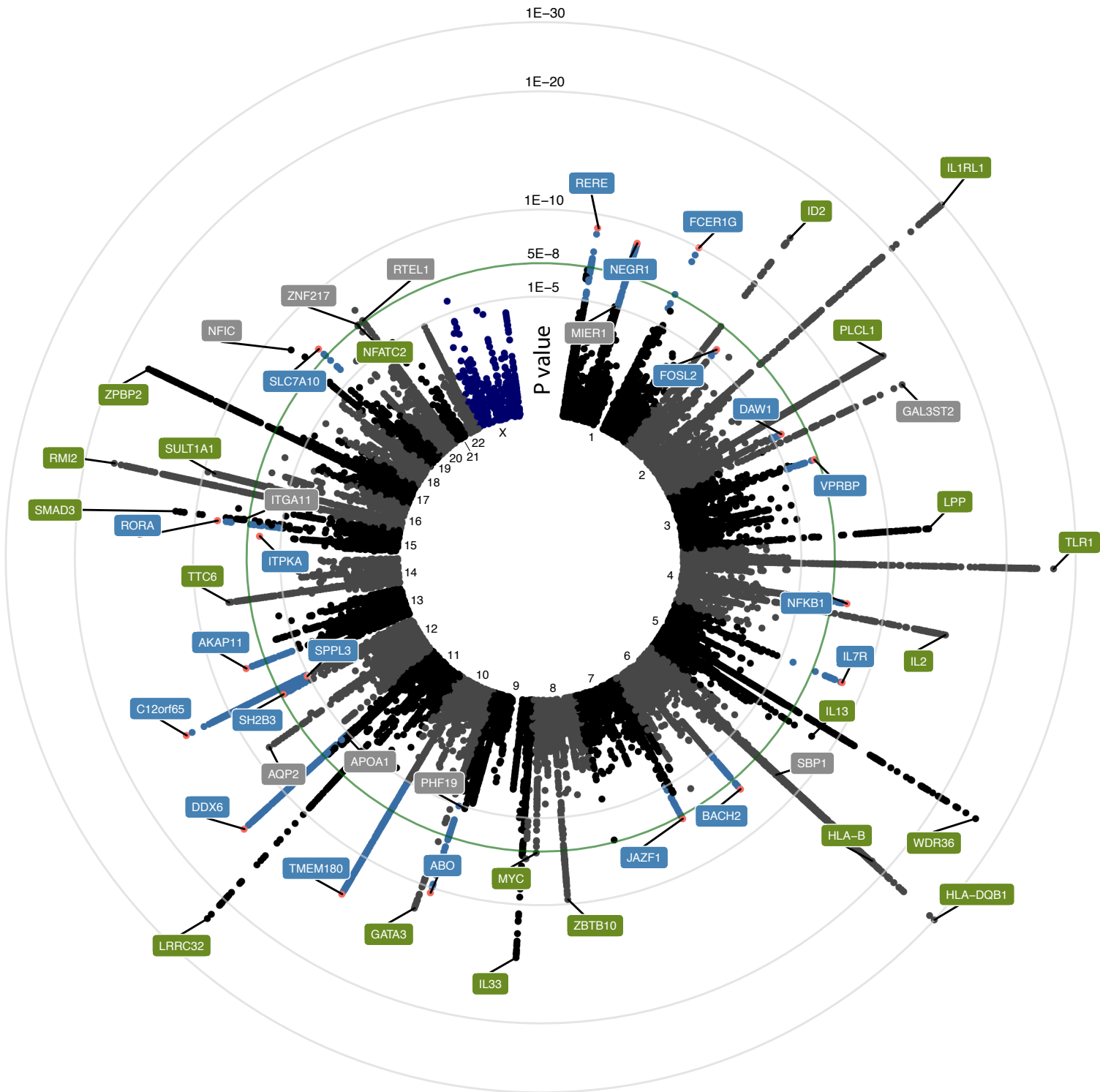
Table 1. Association results of index markers (variant with lowest p-value for each locus). Column “Nearest gene” denotes nearest up- and downstream gene (for intergenic variants with two genes listed), or surrounding gene (for intronic variants with one gene listed), with the exception of rs5743618, an exonic missense variant within *TLR1*; and rs1504215, an exonic synonymous variant within *BACH2*. Replication and combined p values are for a one-sided test. EA/OA=effect allele/other allele. P-value is calculated from the logistic regression model. Het.P=p-value for heterogeneity obtained from Cochrane’s Q test. * Variants also reported associated with a combined asthma/eczema/hay fever phenotype by Ferreira et al.²⁹ (within +/- 1Mb).

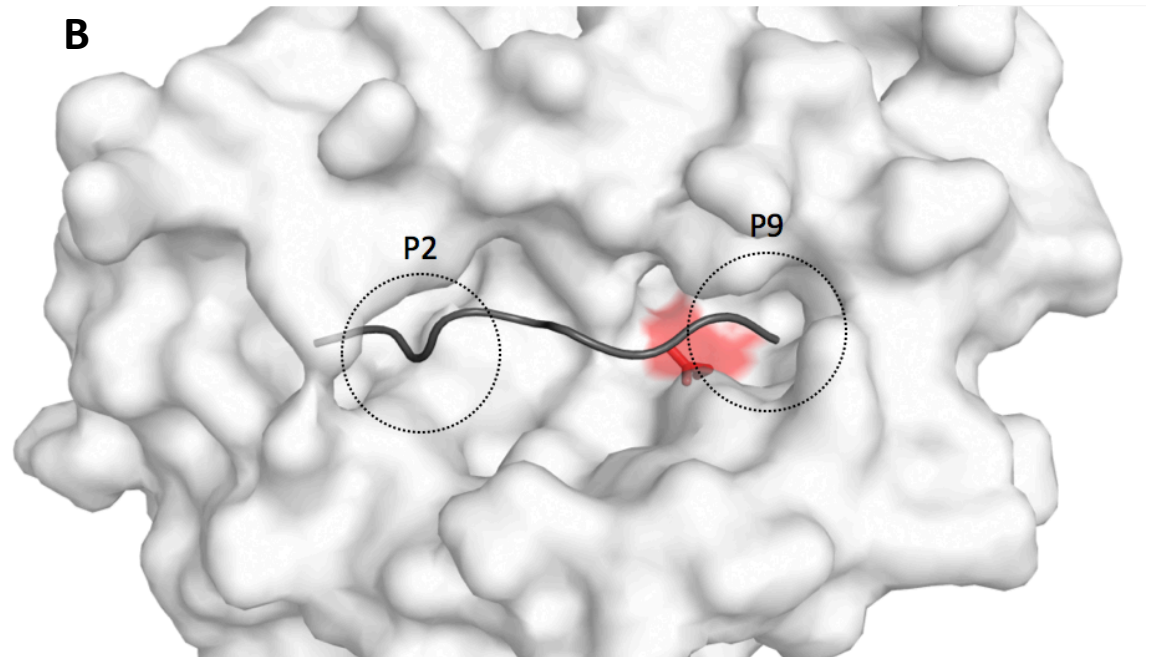
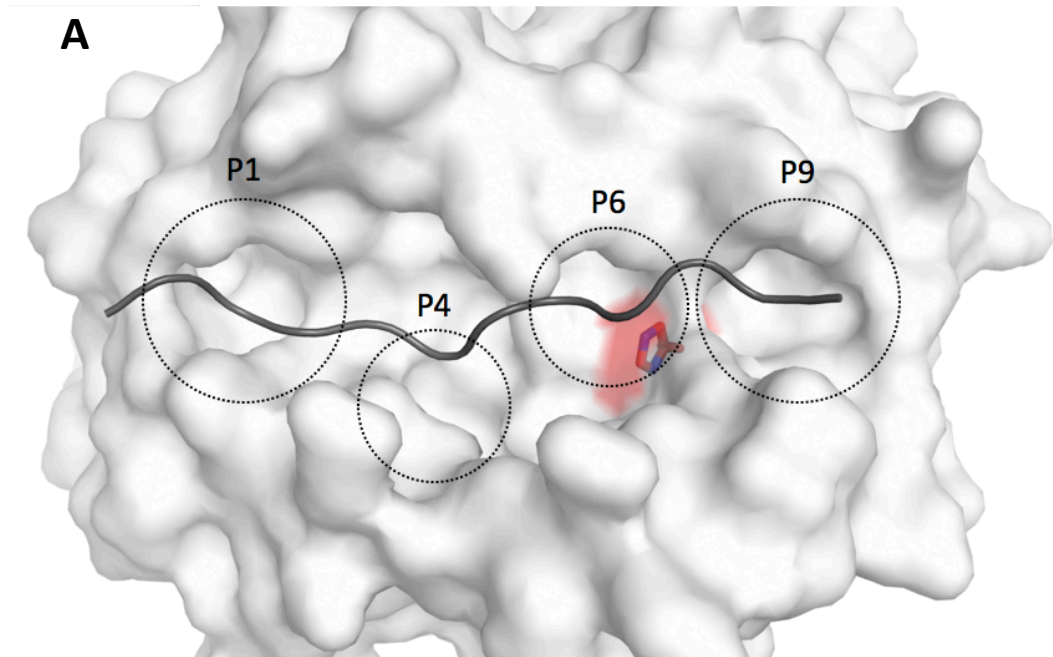
Variant	Locus	Nearest genes	EA/OA	Discovery					Het. P							
				EA/F	n (studies)	OR [95% conf.int]	P	Het. P								
Known																
rs34004019	6p21.32	HLA-DQB1;HLA-DQA1	G/A	0.27	196,951 (11)	0.89 [0.87-0.90]	1.00E-30		0.41							
rs950881	2q12.1	IL1RL1;IL1RL1	T/G	0.15	212,120 (18)	0.88 [0.87-0.90]	1.74E-30		0.91							
rs5743618	4p14	TLR1;TLR10	A/C	0.27	210,652 (17)	0.90 [0.89-0.92]	4.38E-27		0.70							
rs1438673	5q22.1	CAMK4;WDR36	C/T	0.50	212,120 (18)	1.08 [1.07-1.10]	3.15E-26		0.26							
rs7936323	11q13.5	LRR32;C11orf30	A/G	0.48	212,120 (18)	1.08 [1.06-1.09]	6.53E-24		0.0001							
rs24248494	6p21.33	HLA-B;HLA-C	A/T	0.42	195,753 (12)	1.08 [1.06-1.09]	7.01E-19		0.25							
rs11644510	16p13.13	RMI2;CLEC16A	T/C	0.37	212,120 (18)	0.93 [0.92-0.95]	1.58E-17		0.65							
rs12939457	17q12	GSDMB;ZPBP2	C/T	0.44	212,120 (18)	0.94 [0.92-0.95]	2.35E-17		0.02							
rs148505069	4q27	IL21;IL2	G/A	0.33	212,120 (18)	1.07 [1.05-1.08]	2.54E-15		0.02							
rs13395467	2p25.1	ID2;RNF144A	G/A	0.28	212,120 (18)	0.94 [0.92-0.95]	9.93E-15		0.61							
rs9775039	9p24.1	IL33;RANBP6	A/G	0.16	212,120 (18)	1.08 [1.06-1.10]	2.22E-14		0.40							
rs2164068	2q33.1	PLCL1	A/T	0.49	212,120 (18)	0.94 [0.93-0.96]	4.21E-14		0.82							
rs2030519	3q28	TPRG1;LPP	G/A	0.49	212,120 (18)	1.06 [1.04-1.07]	1.83E-13		0.12							
rs11256017	10p14	CELFG2;GATA3	T/C	0.18	212,120 (18)	1.07 [1.05-1.09]	2.72E-12		0.60							
rs17294280	15q22.33	AAGAB;SMAD3	G/A	0.25	212,120 (18)	1.07 [1.05-1.09]	5.97E-12		0.07							
rs7824993	8q21.13	ZBTB10;TPD52	A/G	0.37	212,120 (18)	1.05 [1.04-1.07]	1.86E-10		0.56							
rs9282864	16p11.2	SULT1A1;SULT1A2	C/A	0.33	208,761 (16)	0.94 [0.93-0.96]	4.69E-10		0.03							
rs9687749	5q31.1	IL13;RAD50	T/G	0.44	207,604 (16)	1.06 [1.04-1.09]	1.84E-09		0.19							
rs61977073	14q21.1	TTC6	G/A	0.22	212,120 (18)	1.06 [1.04-1.08]	5.78E-09		0.05							
rs6470578	8q24.21	TMEM75;MYC	T/A	0.28	212,120 (18)	1.05 [1.03-1.07]	4.36E-08		0.02							
rs3787184	20q13.2	NFATC2;KCNG1	G/A	0.19	207,604 (16)	0.94 [0.93-0.96]	4.76E-08		0.69							
Novel																
Replication																
Combined																
Novel	Locus	Nearest genes	EA/OA	EA/F	n (studies)	OR [95% conf.int]	P	Het. P	P	P	Het. P	Replication		Combined		
												n (studies)	OR [95% conf.int]	P	FWER	n (studies)
rs7717955*	5p13.2	CAPSL;IL7R	T/C	0.27	212,120 (18)	0.95 [0.93-0.96]	1.50E-09	0.24	679,247 (10)	0.93 [0.91-0.94]	4.09E-25	1.06E-23	891,367 (28)	0.94 [0.93-0.95]	3.78E-32	0.09
rs63406760*	12q24.31	CDK2AP1;C12orf65	G/-	0.26	210,652 (17)	0.93 [0.91-0.95]	5.12E-14	0.91	675,338 (7)	0.95 [0.93-0.96]	3.27E-12	8.51E-11	885,990 (24)	0.94 [0.93-0.95]	2.54E-24	0.89
rs1504215*	6q15	BACH2;GJA10	A/G	0.34	207,604 (16)	0.95 [0.94-0.97]	1.49E-08	0.02	679,247 (10)	0.95 [0.94-0.97]	1.99E-11	5.17E-10	886,851 (26)	0.95 [0.94-0.96]	1.54E-18	0.05
rs28361986*	11q23.3	CXCR5;DDX6	A/T	0.20	212,120 (18)	0.93 [0.91-0.95]	1.81E-14	0.87	675,919 (8)	0.94 [0.93-0.96]	7.92E-11	2.06E-09	888,039 (26)	0.94 [0.92-0.95]	2.32E-23	0.91
rs2070902*	1q23.3	AL590714.1;FCER1G	T/C	0.25	212,120 (18)	1.06 [1.04-1.08]	1.03E-10	0.18	679,247 (10)	1.05 [1.03-1.06]	7.27E-10	1.89E-08	891,367 (28)	1.05 [1.04-1.06]	6.19E-19	0.23
rs11371454*	15q15.1	ITPKA;RTF1	G/A	0.21	212,120 (18)	1.06 [1.03-1.08]	1.65E-07	0.17	675,338 (7)	1.04 [1.03-1.06]	8.47E-09	2.20E-07	887,458 (25)	1.05 [1.03-1.06]	1.28E-14	0.22
rs12509403*	4q24	MANBA;NFKB1	T/C	0.32	212,120 (18)	0.95 [0.94-0.97]	9.97E-09	0.27	679,247 (10)	0.96 [0.95-0.97]	1.86E-08	4.84E-07	891,367 (28)	0.96 [0.95-0.97]	1.17E-15	0.39
rs9648346*	7p15.1	JAZF1;TAX1BP1	G/C	0.22	207,604 (16)	1.05 [1.03-1.07]	3.62E-08	0.74	679,247 (10)	1.04 [1.03-1.06]	1.39E-07	3.63E-06	886,851 (26)	1.05 [1.03-1.06]	3.30E-14	0.48
rs35350651*	12q24.12	ATXN2;SH2B3	C/-	0.49	206,136 (15)	1.04 [1.03-1.06]	6.63E-08	0.60	672,701 (6)	1.04 [1.02-1.05]	1.41E-07	3.66E-06	878,837 (21)	1.04 [1.03-1.05]	5.82E-14	0.43
rs2519093*	9q34.2	ABO;OBP2B	T/C	0.20	212,120 (18)	1.06 [1.04-1.09]	4.96E-11	0.38	675,919 (8)	1.04 [1.03-1.06]	2.96E-07	7.68E-06	888,039 (26)	1.05 [1.04-1.07]	2.79E-16	0.61
rs62257549	3p21.2	VPRBP	A/G	0.20	212,120 (18)	0.95 [0.93-0.97]	7.13E-08	0.45	677,615 (9)	0.96 [0.94-0.97]	3.37E-07	8.76E-06	889,735 (27)	0.95 [0.94-0.97]	1.84E-13	0.53
rs11677002	2p23.2	FOSL2;RBKS	C/T	0.45	212,120 (18)	0.96 [0.95-0.98]	3.80E-07	0.21	679,247 (10)	0.97 [0.96-0.98]	3.54E-07	9.20E-06	891,367 (28)	0.97 [0.96-0.97]	7.08E-13	0.36
rs35597970*	10q24.32	ACTR1A;TMEM180	-/A	0.45	210,652 (17)	1.06 [1.04-1.07]	1.34E-13	0.96	676,970 (8)	1.03 [1.02-1.05]	4.37E-07	1.14E-05	887,622 (25)	1.04 [1.03-1.05]	5.42E-18	0.53
rs2815765	1p31.1	LRR1Q3;NEGR1	T/C	0.37	212,120 (18)	0.95 [0.94-0.97]	1.18E-09	0.59	679,247 (10)	0.97 [0.95-0.98]	6.16E-07	1.60E-05	891,367 (28)	0.96 [0.95-0.97]	9.45E-15	0.52
rs11671925*	19q13.11	CEBPA;SLC7A10	A/G	0.17	206,136 (15)	0.94 [0.92-0.96]	1.80E-08	0.97	677,551 (9)	0.96 [0.94-0.98]	2.80E-06	7.29E-05	883,687 (24)	0.95 [0.94-0.96]	5.91E-13	0.60
rs2461475*	12q24.31	SPPL3;ACADS	C/T	0.47	212,120 (18)	1.04 [1.02-1.05]	9.19E-07	0.97	677,551 (9)	1.03 [1.02-1.04]	6.52E-06	0.0002	889,671 (27)	1.03 [1.02-1.04]	3.81E-11	0.83
rs6738964*	2q36.3	SPHKAP;DAW1	G/T	0.24	212,120 (18)	0.96 [0.94-0.97]	4.51E-07	0.72	679,247 (10)	0.97 [0.96-0.98]	4.96E-05	0.0013	891,367 (28)	0.96 [0.95-0.97]	1.86E-10	0.87
rs10519067*	15q22.2	RORA	A/-	0.13	212,120 (18)	0.93 [0.91-0.96]	1.78E-09	0.37	442,354 (7)	0.93 [0.90-0.96]	7.53E-05	0.0020	654,474 (25)	0.93 [0.92-0.95]	5.53E-13	0.36
rs138050288*	1p36.23	RERE;SLC45A1	-/CA	0.29	210,652 (17)	1.05 [1.04-1.07]	5.96E-10	0.71	675,338 (7)	1.03 [1.01-1.04]	0.0002	0.0046	885,990 (24)	1.04 [1.03-1.05]	6.62E-12	0.63
rs7328203	13q14.11	TNFSF11;AKAP11	G/T	0.46	212,120 (18)	1.05 [1.03-1.06]	5.94E-09	0.90	677,551 (9)	1.02 [1.01-1.04]	0.0005	0.0134	889,671 (27)	1.03 [1.02-1.04]	1.28E-10	0.78

Table 2. Functional description of known and novel replicating loci. ‘Locus genes’ column denotes genes overlapping with R2-extended loci (See Methods). ‘Missense variant’ column denotes variants with a predicted missense coding consequences. ‘e/meQTL priority genes’ denotes genes prioritized from the combined e/meQTL analysis. ‘PCHiC priority genes’ denotes genes prioritized from the PCHiC chromatin capture analysis. * Variants also reported associated with a combined asthma/eczema/hay fever phenotype by Ferreira et al.²⁹ (within +/- 1Mb).

Variant	Locus	Locus genes	Missense variant	e/meQTL priority genes	PCHiC priority genes	Possible function
Known						
rs13395467	2p25.1				ID2	Transcription factor required for specific innate cell, T cell and B cell subsets
rs950881	2q12.1	IL1RL1 , IL18R1, IL18RAP		IL18R1, IL18RAP, IL1RL1 , MFSD9	IL1RL1	Interleukin receptor, IL33-signalling, Th2-response
rs2164068	2q33.1	PLCL1	PLCL1	COQ10B, MARS2, PLCL1 , RFTN2, SF3B1	PLCL1	Phospholipase, intracellular signalling
rs2030519	3q28	LPP				Transcription factor, Th2-differentiation
rs5743618	4p14	TLR10 , TLR1 , TLR6 , FAM114A1	TLR1	FAM114A1, TLR1 , TLR10 , TLR6		Pattern recognition receptors, innate immunity
rs148505069	4q27	IL2		IL21		Interleukin, immune regulatory effects
rs1438673	5q22.1	WDR36, CAMK4		TSLP		Th2 immune responses
rs9687749	5q31.1	IL13 , IL4, IL5, RAD50	IL13			Interleukin, IgE secretion, allergic inflammation
rs34004019	6p21.32	HLA-DRB1, HLA-DQB1, HLA-DQA2, HLA-DQA1		C4A, CYP21A2, HLA-DOB , HLA-DQA1, HLA-DQA2, HLA-DQB1, HLA-DQB2, HLA-DRA, HLA-DRB1, HLA-DRB5, LY6G5B, TAP2		Antigen presentation, self tolerance
rs2428494	6p21.33	MICA , HLA-B, HLA-C		C4A, HCG27, MICA		Stress induced ligand recognized by NK and T cells
rs7824993	8q21.13				MRPS28	Unknown
rs6470578	8q24.21			MYC		Transcription factor, B-cell proliferation and differentiation
rs9775039	9p24.1	IL33		CD274		IL33: Interleukin, Th2-signalling. CD274: Immune regulation
rs11256017	10p14					
rs7936323	11q13.5	C11orf30, LRRC32				Treg expressed, TGF-beta signalling
rs61977073	14q21.1	TTC6, FOXA1	FOXA1			Transcription factor, Treg differentiation
rs17294280	15q22.33	SMAD3 , IQCH, AAGAB		SMAD3	SMAD3	Transcriptional factor, TGF-beta signalling
rs9282864	16p11.2	EIF3C, IL27 , NPIP8, NUPR1, SGF29, SULT1A1, SULT1A2		APOBR, ATXN2L, CLN3, EIF3C, EIF3CL, IL27 , NPIP6, NPIP7, SBK1, SH2B1, SPNS1, SULT1A1, SULT1A2, TUFM		Induces naïve T cell proliferation and Th1 differentiation while suppressing Th17, Th2 and Treg responses. Induces isotype switching of B cells and has additional effects on innate immune cells.
rs11644510	16p13.13	RMI2, CLEC16A		DEXI	C16orf72, CLEC16A, DEXI , GSPT1, LITAF, NUBP1, PRM2, PRM3, RMI2, RSL1D1, SNN, SOCS1, TNP2, TXNDC11, ZC3H7A	Unknown function. Highly expressed in lung, B- and T-cells
rs12939457	17q12	GSDMA, GSDMB, IKZF3, LRRC3C, PSMD3, ZPBP2	GSDMB, ZPBP2	GSDMA, GSDMB, IKZF3, MED24, ORMDL3, PGAP3, ZPBP2	GSDMB, ORMDL3	Regulator of sphingolipid synthesis. Endoplasmic reticulum-mediated Ca(+2) signaling
rs3787184	20q13.2	NFATC2				Transcription factor, activated T-cell gene transcription

Variant	Locus	Locus genes	Missense variant	e/meQTL priority genes	PCHiC priority genes	Possible function
Novel, replicating						
rs2815765	1p31.1	NEGR1		NEGR1		Cell adhesion.
rs138050288*	1p36.23	RERE		RERE		Transcription factor associated with apoptosis.
rs2070902*	1q23.3	ADAMTS4, AL590714.1, APOA2, B4GALT3, DEDD, FCER1G , NDUFS2, NR1I3, PCP4L1, PFDN2, SDHC, TOMM40L		FCER1G , TOMM40L, USF1		Codes for the high affinity IgE receptor involved in allergic responses. Present on many cell types, including immune cells and epithelial cells.
rs11677002	2p23.2	FOSL2 , PLB1		FOSL2		Cell cycle and proliferation.
rs6738964*	2q36.3	DAW1				Dynein assembly factor.
rs62257549	3p21.2	VPRBP , RAD54L2		HYAL3, MAPKAPK3, NAT6, RBM15B		Required for optimal T cell proliferation after antigen encounter and involved in V(D)J recombination during B cell development.
rs12509403*	4q24	NFKB1 , MANBA		BDH2, MANBA, NFKB1		NFKB1: Activation of multiple inflammatory pathways, mediating signals from toll-like receptors and cytokines.
rs7717955*	5p13.2	IL7R		IL7R , LMBRD2, SPEF2, UGT3A2		Necessary for V(D)J recombination of T and B cell receptors. T cell sub-populations have different levels of IL-7R on the cell surface.
rs1504215*	6q15	BACH2	IL7R	BACH2	BACH2	Role in several immune cells, including antigen-induced formation of memory B cells and memory T cells.
rs9648346*	7p15.1	JAZF1		CREB5, JAZF1		Transcriptional repressor, associated with systemic sclerosis, type 2 diabetes and endometrial stromal tumors.
rs2519093*	9q34.2	ABO, GBGT1, OBP2B, RPL7A, STKLD1, SURF2		ABO , GBGT1, MED22, SURF1, SURF4, SURF6		Allelic variants of ABO determine blood group type.
rs35597970*	10q24.32	CUEDC2, PSD, TMEM180, ACTR1A, SUFU		ACTR1A, ARL3, AS3MT, SUFU, TMEM180, TRIM8	NFKB2	Subunit of NFKB complex which is expressed in many cell types and involved in regulating immune responses, including TLR-4 and cytokine signaling.
rs28361986*	11q23.3	DDX6, CXCR5		CXCR5 , TRAPPC4	CXCR5 , DDX6	Chemokine receptor present on B cells and involved in B cell migration to the B cell follicular zone in lymph nodes and spleen; CXCR5 is also expressed on a subset of follicular T cells.
rs35350651*	12q24.12	SH2B3 , FAM109A, ATXN2		ALDH2, SH2B3 , TMEM116		Involved in hematopoiesis as well as downstream of T cell receptor activation.
rs63406760*	12q24.31	C12orf65, CDK2AP1, MPHOSPH9, SBNO1	SH2B3 SBNO1	ABCB9, ARL6IP4, C12orf65, CDK2AP1, MPHOSPH9, OGFOD2, PITPNM2, RILPL2, SBNO1, SETD8, SNRNP35, C12orf43, OASL , RNF10, SPPL3	DDX55	DDX55: Involved in multiple nuclear processes.
rs2461475*	12q24.31	SPPL3				SPPL3: Deletion results in decreased numbers of NK cells. OASL: Involved in IFN-gamma signaling.
rs7328203	13q14.11	TNFSF11 , AKAP11		AKAP11		Enhances T cell activation by dendritic cells.
rs111371454*	15q15.1	ITPKA, NDUFAF1, RTF1, TYRO3 , LTK	NDUFAF1, NUSAP1	ITPKA, LTK , NDUFAF1, OIP5, RPAP1		TYRO3: Inhibits TLR-mediated immune signaling and activates SOCS1 (identified as potential gene in previous screen). LTK: Leukocyte tyrosine kinase that is involved in downstream T cell receptor signalling.
rs10519067*	15q22.2	RORA				Involved natural helper cell development and allergic disease.
rs11671925	19q13.11	SLC7A10, LRP3			CEBPA , CEBPG	CEBPA: Important for lung development. Associated with inflammatory bowel disease. CEBPG: Transcriptional enhancers for the immunoglobulin heavy chain.





$-\log_{10}[\text{Empirical } p\text{-value}]$



Fold enrichment

