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Shared genetic origin of asthma, hay fever and eczema elucidates allergic disease biology

<u>MAIN TEXT</u>

Manuel A Ferreira1*, Judith M Vonk2*, Hansjörg Baurecht3*, Ingo Marenholz4,5*, Chao Tian6*, Joshua D Hoffman7*, Quinta Helmer8*, Annika Tillander9*, Vilhelmina Ullemar9*, Jenny van Dongen8*, Yi Lu9*, Franz Rüschendorf 4*, Jorge Esparza-Gordillo4,5,10, Chris W Medway11, Edward Mountjoy11, Kimberley Burrows11, Oliver Hummel4, Sarah Grosche4,5, Ben M Brumpton11,12,13, John S Witte14, Jouke-Jan Hottenga8, Gonneke Willemsen8, Jie Zheng11, Elke Rodríguez3, Melanie Hotze3, Andre Franke15, Joana A Revez1, Jonathan Beesley1, Melanie C Matheson16, Shyamali C Dharmage16, Lisa M Bain1, Lars G Fritsche12, Maiken E Gabrielsen12, Brunilda Balliu17, the 23andMe Research Team6,18, AAGC collaborators19, BIOS collaborators20, LifeLines Cohort Study21, Jonas B Nielsen22,23, Wei Zhou23, Kristian Hveem12, Arnulf Langhammer24, Oddgeir L Holmen12, Mari Løset12,25, Gonçalo R Abecasis26,12, Cristen J Willer26,12,23,22, Andreas Arnold27, Georg Homuth28, Carsten O Schmidt29, Philip J Thompson30, Nicholas G Martin1, David L Duffy1, Natalija Novak31, Holger Schulz32,33, Stefan Karrasch32,34, Christian Gieger35, Konstantin Strauch36, Ronald B Melles37, David A Hinds6, Norbert Hübner4§, Stephan Weidinger3§, Patrik KE Magnusson9§, Rick Jansen38§, Eric Jorgenson37§, Young-Ae Lee4,5§, Dorret I Boomsma8§, Catarina Almqvist 9,39§, Robert Karlsson9§, Gerard H Koppelman40§ and Lavinia Paternoster11§

* These authors contributed equally to this work.

§ These authors jointly supervised this work.

Affiliations

1 Genetics and Computational Biology, QIMR Berghofer Medical Research Institute, Brisbane, Australia

2 Epidemiology, University of Groningen, University Medical Center Groningen, Groningen Research Institute for Asthma and COPD, Groningen, the Netherlands

3 Department of Dermatology, Allergology and Venereology, University Hospital Schleswig-Holstein, Campus Kiel, Kiel, Germany

4 Max Delbrück Center (MDC) for Molecular Medicine, Berlin, Germany

5 Clinic for Pediatric Allergy, Experimental and Clinical Research Center of Charité Universitätsmedizin Berlin and Max Delbrück Center, Berlin, Germany

6 Research, 23andMe, Mountain View, California, USA

7 Department of Epidemiology and Biostatistics, University of Calfornia San Francisco, San Francisco, California, USA

8 Department Biological Psychology, Netherlands Twin Register , Vrije University, Amsterdam, The Netherlands

9 Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden

10 Current address: GlaxoSmithKline, Stevenage, UK

11 MRC Integrative Epidemiology Unit, School of Social and Community Medicine, University of Bristol, Bristol, UK

12 K.G. Jebsen Center for Genetic Epidemiology, Department of Public Health and Nursing, NTNU, Norwegian University of Science and Technology, Trondheim, Norway

13 Department of Thoracic Medicine, St. Olavs Hospital, Trondheim University Hospital, Trondheim, Norway

47 14 Epidemiology and Biostatistics, University of Calfornia San Francisco, San Francisco, California,

48 USA

49 15 Institute of Clinical Molecular Biology, Christian Albrechts University of Kiel, Kiel, Germany

50 16 Melbourne School of Population and Global Health, University of Melbourne, Melbourne, Australia

51 17 Department of Pathology, Stanford University School of Medicine, Stanford, USA

52 18 the 23andMe Research Team is listed in Supplementary Information section 2

53 19 AAGC collaborators are listed in Supplementary Information section 3

54 20 BIOS Consortium is listed in Supplementary Information section 4

55 21 LifeLines Cohort Study is listed in Supplementary Information section 5

56 22 Department of Human Genetics, University of Michigan, Ann Arbor, USA

57 23 Department of Internal Medicine, University of Michigan, Ann Arbor, USA

58 24 The HUNT Research Centre, Department of Public Health and Nursing, NTNU, Norwegian

59 University of Science and Technology, Trondheim, Norway

60 25 Department of Dermatology, St. Olavs Hospital, Trondheim University Hospital, Trondheim,

61 Norway

62 26 Center for Statistical Genetics, University of Michigan, Ann Arbor, USA

63 27 Clinic and Polyclinic of Dermatology, University Medicine Greifswald, Greifswald, Germany

64 28 Department of Functional Genomics, Interfaculty Institute for Genetics and Functional Genomics,

65 University Medicine and Ernst-Moritz-Arndt-University Greifswald, Greifswald, Germany

66 29 Institute for Community Medicine, Study of Health in Pomerania/KEF, University Medicine

67 Greifswald, Greifswald, Germany

68 30 Institute for Respiratory Health, Harry Perkins Institute of Medical Research, University of Western

69 Australia, Nedlands, Australia

70   31 Department of Dermatology and Allergology, University-Hospital Bonn, Bonn, Germany

71   32 Institute of Epidemiology I, Helmholtz Zentrum Munchen - German Research Center for

72   Environmental Health , Neuherberg, Germany

73   33 Comprehensive Pneumology Center Munich (CPC-M), Member of the German Center for Lung

74   Research, Munich, Germany

75   34 Institute and Outpatient Clinic for Occupational, Social and Environmental Medicine, Ludwig-

76   Maximilians-Universität, Munich, Germany

77   35 Research Unit of Molecular Epidemiology and Institute of Epidemiology II,, Helmholtz Zentrum

78   Munchen - German Research Center for Environmental Health , Neuherberg, Germany

79   36 Institute of Genetic Epidemiology , Helmholtz Zentrum Munchen - German Research Center for

80   Environmental Health , Neuherberg, Germany

81   37 Division of Research, Kaiser Permanente Northern California, Oakland, California, USA

82   38 Department of Psychiatry, VU University Medical Center, Amsterdam, The Netherlands

83   39 Pediatric Allergy and Pulmonology Unit at Astrid Lindgren Children's Hospital, Karolinska

84   University Hospital, Stockholm, Sweden

85   40 Pediatric Pulmonology and Pediatric Allergology, Beatrix Children's Hospital, University of

86   Groningen, University Medical Center Groningen, Groningen Research Institute for Asthma and

87   COPD, Groningen, the Netherlands

88   **Corresponding author:**

89   Manuel A R Ferreira, PhD

90   QIMR Berghofer Medical Research Institute

91   Locked Bag 2000, Royal Brisbane Hospital,

92   Herston QLD 4029, Australia

93   Phone: +61 7 3845 3552

94   Fax: +61 7 3362 0101

95   Email: manuel.ferreira@qimrberghofer.edu.au

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107 **INTRODUCTORY PARAGRAPH**

108 Asthma, hay fever (or allergic rhinitis) and eczema (or atopic dermatitis) often coexist in the same

109 individuals[1], partly because of a shared genetic origin[2-4]. To identify shared risk variants, we performed

110 a genome-wide association study (GWAS, n=360,838) of a broad allergic disease phenotype that

111 considers the presence of any one of these three diseases. We identified 136 independent risk variants

112 (P<3x10^{-8}), including 88 not previously reported, which implicate 132 nearby genes in allergic disease

113 pathophysiology. Disease-specific effects were detected for only six variants, confirming that most

114 represent shared risk factors. Tissue-specific heritability and biological process enrichment analyses

115 suggest that shared risk variants influence lymphocyte-mediated immunity. Six target genes provide an

116 opportunity for drug repositioning, while for 36 genes CpG methylation was found to influence

117 transcription independently of genetic effects. Asthma, hay fever and eczema partly coexist because

118 they share many genetic risk variants that dysregulate the expression of immune-related genes.

MAIN TEXT

The analytical approach used is summarized in **Supplementary Fig. 1**. We tested for association with allergic disease 8,307,659 genetic variants that passed quality control filters (**Supplementary Table 1**), comparing 180,129 cases who reported having suffered from asthma and/or hay fever and/or eczema, and 180,709 controls who reported not suffering from any of these diseases (**Supplementary Table 2**), all of European ancestry. Meta-analysis of results from the 13 contributing studies (**Supplementary Fig. 2**) identified 99 genomic regions (*i.e.* loci) located >1 Mb apart containing at least one genetic variant associated with allergic disease at a genome-wide significance threshold of 3×10^{-8} (**Fig. 1** and **Supplementary Table 3**). Based on approximate conditional analysis[5], 136 genetic variants in these 99 loci had a statistically independent association with disease risk (**Table 1**). Henceforth, we refer to these as "sentinel risk variants", which either represent, or are in linkage disequilibrium (LD) with, a causal functional variant. These included 69 (in 35 loci) located <1 Mb from risk variants reported in previous GWAS of allergic disease (**Supplementary Table 4**). Of note, 21/69 sentinel variants were in low linkage disequilibrium (LD, $r^2<0.05$) with the previously reported risk variants, indicating that they represent novel associations in these loci. The remaining 67 sentinel variants (in 64 loci) were located >1Mb from previously reported associations (**Supplementary Table 5**), of which 23 were in low LD with nearby variants reported for other diseases or traits (**Supplementary Table 6**). Eighteen loci had multiple independent association signals (**Supplementary Table 3**). Altogether, we identified 88 (67+21) genetic associations with allergic disease that are new, a substantial increment over the 75 associations reported previously (**Supplementary Fig. 3 and Supplementary Table 7**).

As expected from a study design that maximized power to identify shared risk variants[6], we found that 130 of the 136 sentinel variants had similar allele frequencies in case-only association analyses that

142　compared three non-overlapping groups of adults: those who reported suffering from asthma only

143　(*n*=12,268), hay fever only (*n*=33,305) or eczema only (*n*=6,276) (**Supplementary Table 8**). There was

144　thus no evidence that these 130 variants have differential effects on the three individual diseases. The

145　six variants with evidence for stronger effects in one allergic disease when compared to the other two

146　were located in five known allergy risk loci (*e.g. FLG* and *GSDMB*, **Fig. 2**). On the other hand, many

147　sentinel variants (26 or 19%) were also associated with the age at which symptoms of any allergic

148　disease first developed (*n*=35,972, **Supplementary Table 9**), the allele associated with a higher disease

149　risk being always associated with earlier age-of-onset (**Supplementary Fig. 4**). For 18 of those 26

150　variants, the effect on age-of-onset was not significantly different between individual diseases

151　(**Supplementary Table 9**), suggesting that they influence the age at which symptoms first develop for

152　all three diseases.

153

154　We then used LD-score regression analysis[7] (see Methods) to quantify the liability-scale heritability of

155　the three individual diseases that was collectively explained by the 136 top associations in the Nord-

156　Trøndelag Health Study (HUNT, up to *n*=20,350), which was not part of the discovery meta-analysis.

157　This was found to be 3.2% for asthma, 3.8% for hay fever and 1.2% for eczema, respectively

158　representing about a fifth, a sixth and a tenth of the overall heritability of each disease that is explained

159　by common single nucleotide polymorphisms (SNPs; **Supplementary Table 10**). Therefore, the

160　inheritance of risk alleles at these loci partly explains why these three conditions coexist.

161

162　To understand the biological consequences of allergy risk variants, we then identified plausible target

163　genes of the 136 sentinel variants. There were 5,739 transcripts annotated near (+/- 1 Mb) sentinel

164　variants, including 2,569 protein-coding genes. For 132 of these transcripts, the nearby sentinel variant

165 was in high LD ($r^2 \geq 0.8$) with either a non-synonymous SNP (22 genes; **Supplementary Table 11**) or a

166 sentinel expression quantitative trait locus (eQTL) identified in relevant tissues or cell types (additional

167 110 genes; **Supplementary Tables 12** and **13**). We refer to these 132 transcripts as plausible target

168 genes, which were located in 54 of the 99 risk loci (**Fig. 1** and **Supplementary Table 14**). Studies that

169 confirm the target gene predictions and identify the underlying functional variants are warranted; genes

170 that could be prioritized for functional follow-up include 78 identified using a more conservative LD

171 threshold ($r^2 \geq 0.95$; **Supplementary Table 14**) or 61 predicted to be the likely targets based on

172 independent evidence from publicly available functional data (**Supplementary Tables 15** and **16**; see

173 Methods for details). Of note, 77 (58%) of the 132 plausible target genes have not previously been

174 implicated in allergic disease (**Supplementary Tables 14**), and so potentially represent novel key

175 contributors to disease pathophysiology (examples in **Table 2**).

176

177 Next, based on data from the GTEx consortium[8], we identified broad tissue types in which the plausible

178 target genes were disproportionally expressed, using the Tissue Specific Expression Analysis (TSEA)

179 approach described previously[9]. We excluded genes located in the major histocompatibility complex

180 (MHC) or not present in the TSEA GTEx database, leaving 112 plausible target genes for analysis.

181 When compared to the remaining 17,671 non-MHC genes in the genome, we found that the list of

182 plausible targets was enriched for genes specifically expressed in whole-blood and lung (**Fig. 2A**). Both

183 associations remained significant (**Supplementary Fig. 5**) after restricting the background gene list to

184 the subset of 12,804 non-MHC genes with eQTLs reported in the same studies used to identify the

185 plausible target genes (**Supplementary Tables 12**). These results indicate that the plausible targets are

186 enriched for genes preferentially expressed in whole-blood and lung, and that this is unlikely to arise

187 because the plausible targets were also enriched for genes with eQTLs in those tissues.

188

189 The enrichment in whole-blood and lung expression could be a general feature of arbitrary genes

190 located near the sentinel risk variants. To address this possibility, we determined how often the

191 enrichment observed with the plausible target genes was exceeded when analyzing 1,000 lists of

192 random genes. When genes were randomly selected from the same 98 non-MHC allergy risk loci

193 identified in the meta-analysis, matching on the number of plausible target genes identified per locus

194 (range 0 to 11) and in total (*i.e.* 112), the enrichment observed in whole-blood was not exceeded in any

195 of the 1,000 random lists when considering results for all 25 tissues tested (**Fig. 3A** and

196 **Supplementary Table 17**). Similar results were observed for lung. For comparison, arbitrary genes

197 were also selected from 2 Mb loci drawn at random from the genome, or simply from all genes in the

198 genome, and results were very similar (**Fig. 3A** and **Supplementary Table 17**). Randomly selecting

199 genes from the subset with eQTLs also had no impact on the results (**Supplementary Fig. 5**).

200 Therefore, we conclude that the enrichment in expression observed in whole-blood and lung was

201 specific to the genes identified as plausible targets of sentinel risk variants.

202

203 To identify specific cell types that were likely to contribute to the enrichment in whole-blood, we used

204 an orthogonal approach[10] that quantifies tissue-specific enrichments in SNP heritability rather than in

205 gene expression. Specifically, this approach quantifies the trait heritability that is explained by SNPs

206 that overlap cell type-specific regulatory annotations measured by the ENCODE project in 100

207 different cell types. In this analysis, the strongest enrichment in SNP heritability was observed for

208 regulatory annotations measured in helper T cells (including Th17, Th1 and Th2), regulatory T cells,

209 CD4$^+$ and CD8$^+$ memory T cells, CD56$^+$ NK cells and CD19$^+$ B cells (**Fig. 3B and Supplementary**

210 **Table 18**). These results are consistent with previous findings[11] and the widely documented

211 contribution of these T cell subsets to allergic responses. Similar results were obtained after removing

212 the 136 top associations from our GWAS results (**Supplementary Fig. 6 and Supplementary Table**

213 **18**), indicating that the observed enrichments extend beyond genome-wide significant SNPs. These

214 results demonstrate that genetic risk variants shared between asthma, hay fever and eczema, including

215 but not limited to the ones that reached genome-wide significance, operate to a large extent by

216 modulating gene expression in cells of the immune system.

217

218 To help understand how the sentinel variants might influence immune cell function, we then identified

219 biological processes over-represented amongst the plausible target genes when compared to the rest of

220 the genes in the genome (MHC excluded), using GeneNetwork[12]. As for the analysis of tissue-specific

221 enrichment in gene expression, for each specific biological process, we compared the enrichment

222 observed with the list of plausible target genes with that observed with 1,000 gene lists randomly

223 drawn from the same allergy risk loci. After correcting for the 3,770 biological processes tested, we

224 found 35 pathways for which the enrichment observed with the plausible target genes was exceeded in

225 <5% of the random gene lists (**Fig. 3C** and **Supplementary Table 19**). These included biological

226 processes related to T and B cell activation, B cell proliferation and isotype switching, interleukin (IL-)

227 2 and IL-4 production, confirming a key role for the sentinel variants and the likely target genes on

228 lymphocyte-mediated immunity. Other noteworthy enrichments were observed for pathways related to

229 induction of cell death, lipid phosphorylation and NK cell differentiation.

230

231 Consistent with a widespread effect of allergy risk variants on immune cell function, many sentinel risk

232 variants have been reported to associate with other immune-related traits, notably blood cell counts

233 (**Supplementary Table 20**) and auto-immune diseases (**Supplementary Table 21**). The genetic

234 overlap with auto-immune diseases was not restricted to sentinel variants, as evidenced by significant

235 positive genetic correlations with celiac disease, Crohn's disease and inflammatory bowel disease

236 obtained after excluding the 136 top associations from our GWAS results (**Supplementary Table 22**).

237 Other significant genetic correlations were observed for obesity- and depression-related traits, both

238 previously suggested by twin studies[13]. The former provides support for a role of allergy risk variants in

239 the regulation of metabolic homeostasis.

240

241 We then investigated whether any of the plausible target genes identified could potentially represent a

242 new opportunity for drug repositioning, as shown by others[14]. We found that 29 genes have been or are

243 being considered as drug targets, including nine for the treatment of allergic diseases (**Supplementary**

244 **Table 23**), four for auto-immune diseases (**Supplementary Table 24**) and 16 for other diseases

245 (**Supplementary Table 25**), mostly cancer. Therefore, for 20 genes, drugs currently in development for

246 other indications might influence biological mechanisms underlying allergic disease. For six of these

247 genes, the effect on gene expression of the allergy protective allele (**Supplementary Table 26**) and the

248 existing drug matched (**Table 3**), suggesting that the latter might attenuate (and not exacerbate) allergy

249 symptoms, and so could be prioritized for pre-clinical testing.

250

251 Finally, based on data from the BIOS consortium[15] (n=2,101), we found that a substantial fraction of

252 target genes (36 or 27%) had a nearby CpG site for which methylation levels were significantly

253 correlated with mRNA levels in blood, independently of SNP effects (**Supplementary Table 27**). This

254 observation raises the possibility that environmental effects on the methylation state of these CpGs

255 might influence target gene expression and, by extension, allergic disease risk. Well powered studies

256 that address this possibility are warranted. In exploratory analyses, we tested the association between

257   five established risk factors for allergic disease (see Methods) and the methylation state of expression-

258   associated CpGs for those 36 genes (*n*=1,211). We observed only one significant association, between

259   smoking and the methylation state of *PITPNM2* (**Supplementary Table 28**), which was reported in a

260   previous study[16]. These results indicate that smoking might influence the risk of allergic disease partly

261   by modulating the methylation state of expression-associated CpGs for *PITPNM2*, a PYK2-binding

262   protein[17] potentially involved in granulocyte function[18,19].

263

264   In conclusion, we doubled the number of risk variants for allergic disease through a large GWAS of a

265   multi-disease phenotype defined based on information from three genetically correlated diseases,

266   asthma, hay fever and eczema. With a few exceptions, the variants identified had similar effects on the

267   individual disease entities. The risk variants, and their likely target genes, are predicted to influence

268   overwhelmingly the function of immune cells. Novel drugs for allergy are proposed based on

269   genomics-guided drug repositioning. Finally, our results raise the possibility that environmental factors

270   such as smoking might influence allergic disease risk through modulation of target gene methylation.

271 **ONLINE METHODS**

272 Methods for this paper are provided in a separate file.

274
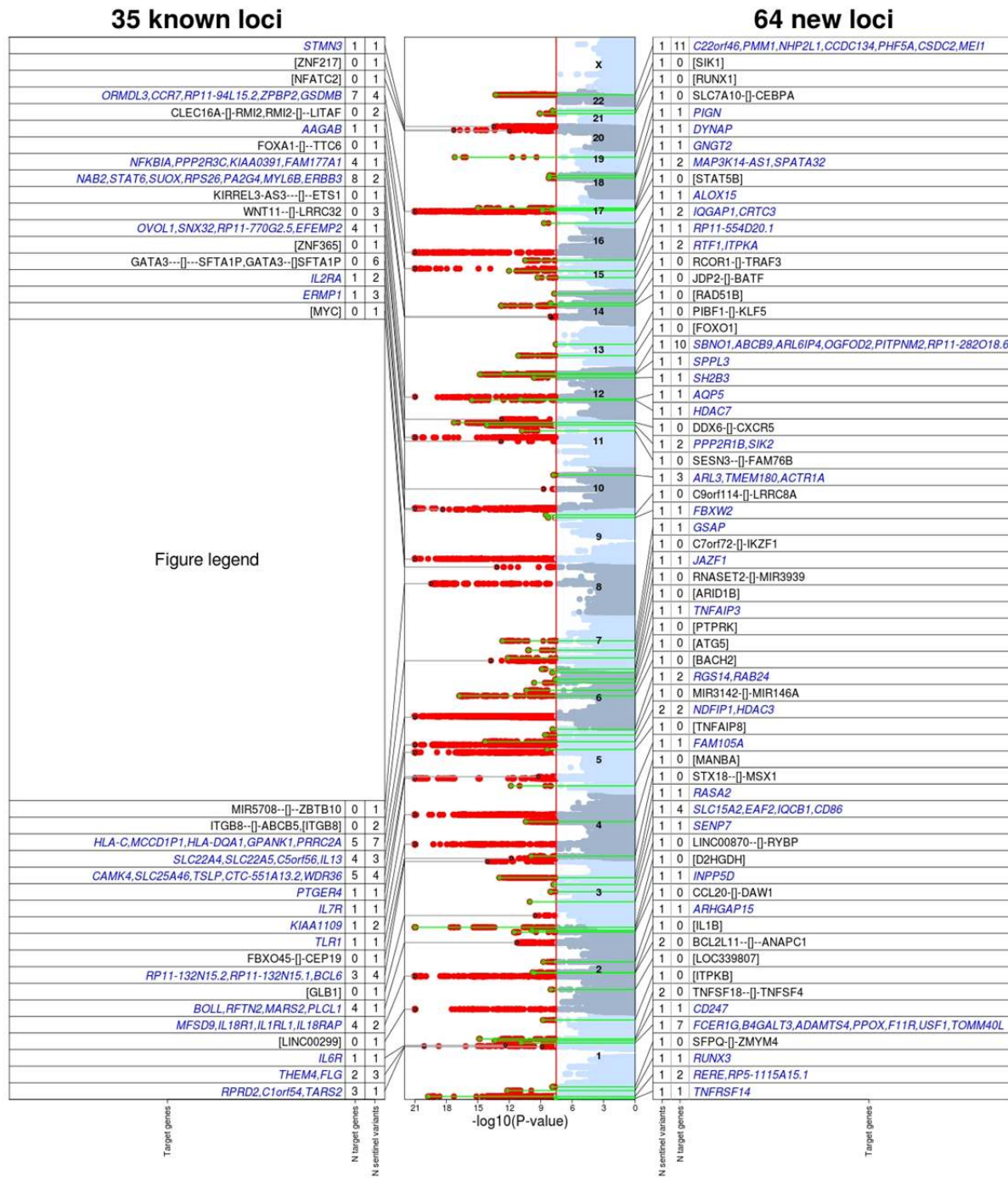
Figure 1. GWAS meta-analysis identifies 99 loci containing 136 genetic risk variants independently associated with the risk of allergic disease at $P<3\times10^{-8}$. The 136 sentinel risk variants were located in 35 previously reported (69 variants) and 64 novel (67 variants) risk loci. The numbers

278   of plausible target genes of sentinel risk variants identified for each locus are shown, with target gene

279   names listed in blue font. For loci with many target genes, only a selection is listed. When no target

280   gene was identified, the nearest gene(s) to the sentinel variants are instead shown in black font. Red

281   vertical line in Manhattan plot shows genome-wide significance threshold used ($P=3 \times 10^{-8}$).

282
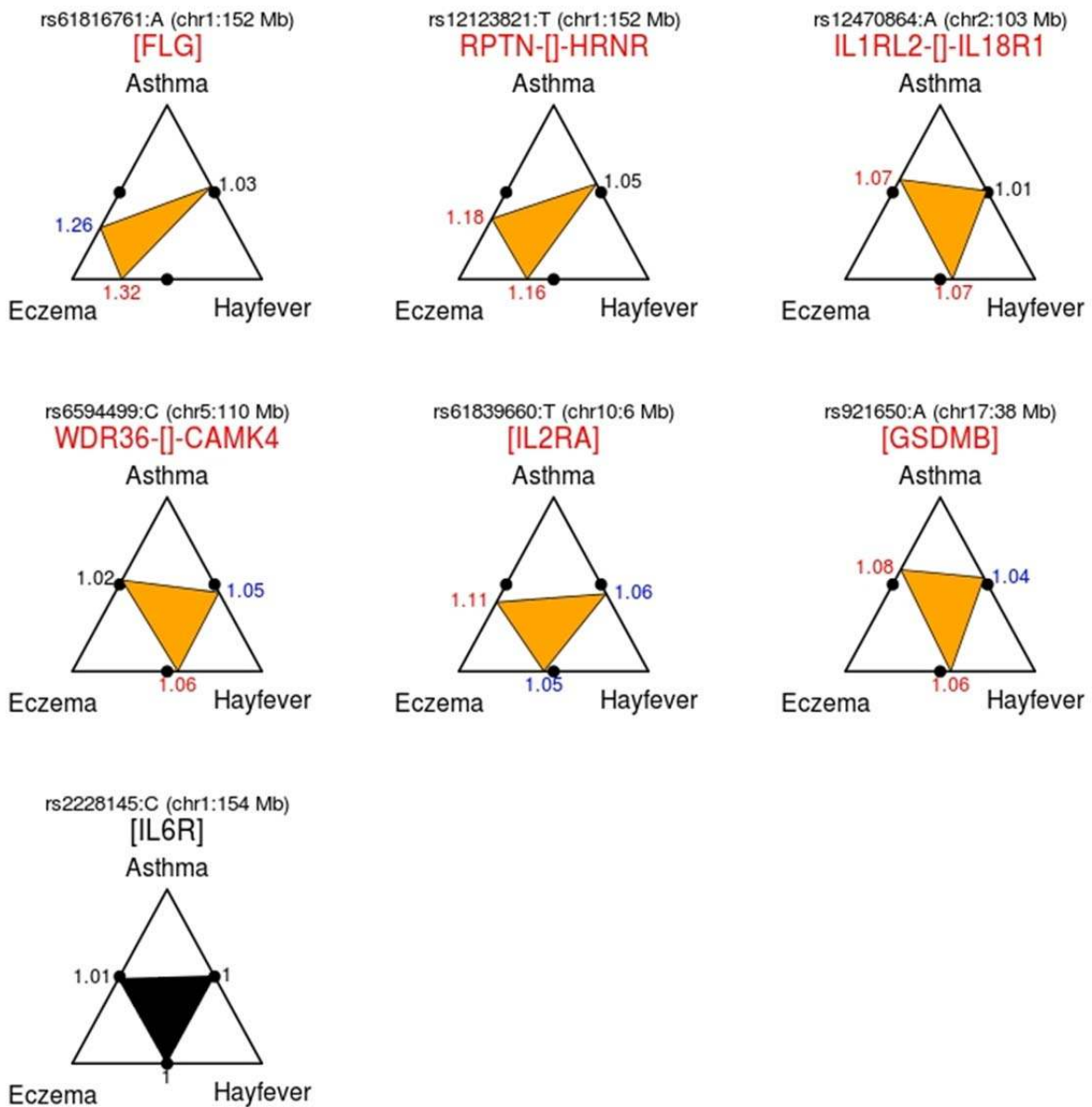
283
284 **Figure 2. Six of the 136 sentinel variants had significant allele-frequency differences in pairwise**

285 **case-only association analyses contrasting individuals suffering from a single allergic disease.** For

286 each sentinel variant, we performed three case-only association analyses, comparing asthma-only cases

287 (*n*=12,268) against hay fever-only cases (*n*=33,305); asthma-only cases against eczema-only cases

288 (*n*=6,276); and hay fever-only cases against eczema-only cases. After accounting for multiple testing,

289 significant associations for at least one of these analyses were only observed for six of the 136 sentinel

290   variants, which are shown in the first two rows of the figure. For a given variant, the vertices of the

291   inner triangle point to the position along the edges of the outer triangle that corresponds to the allele

292   frequency difference observed between pairs of single-disease cases. For example, the rs61816761:A

293   allele, which is located in the Fillagrin gene, was 1.32-fold more common in individuals suffering only

294   from eczema when compared to individuals suffering only from hay fever ($P=7.2 \times 10^{-8}$), consistent with

295   this SNP being a stronger risk factor for eczema than for hay fever. A similar result (OR = 1.26,

296    $P=0.0004$) was observed for this variant when contrasting eczema-only cases against asthma-only

297   cases. For comparison, a variant with no allele frequency differences in all three pairwise single-disease

298   association analyses is also shown (rs2228145, in the *IL6R* gene). In this case, the three estimated odds

299   ratios were approximately equal to 1. The color of the OR font reflects the significance of the

300   association: red for $P<1.2 \times 10^{-4}$ (correction for multiple testing), blue for $P<0.05$ and black for $P>0.05$.

301

302

303

304 **(A)**

Enrichment in tissue-specific gene expression
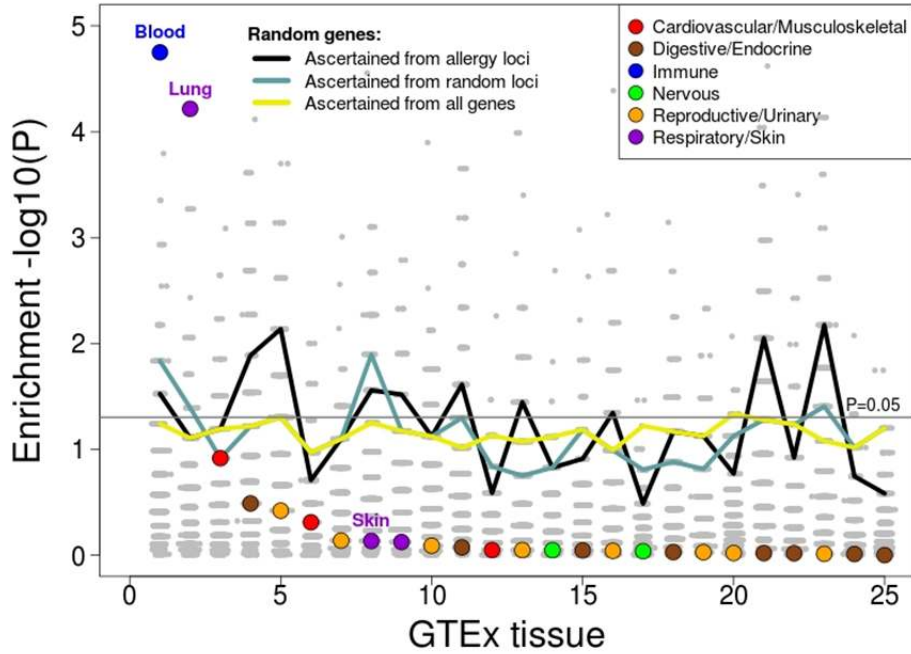
305

306 **(B)**

Enrichment in tissue-specific SNP heritability

307

308

19

309   **(C)**

Biological process enrichment

1. GO:0008624 induction_of_apoptosis_by_extracellular_signals
2. GO:0012502 induction_of_programmed_cell_death
3. GO:0006917 induction_of_apoptosis
4. GO:0045086 positive_regulation_of_interleukin-2_biosynthetic_process
5. GO:0031294 lymphocyte_costimulation
6. GO:0031295 T_cell_costimulation
7. GO:0030888 regulation_of_B_cell_proliferation
8. GO:0002695 negative_regulation_of_leukocyte_activation
9. GO:0042100 B_cell_proliferation
10. GO:0016311 dephosphorylation

Random genes:
Ascertained from allergy loci
Ascertained from random loci
Ascertained from all genes

P=0.05

y-axis: Enrichment -log10(P)
x-axis: Gene ontology biological process category (0, 1000, 2000, 3000, 3770)

310

311

312   **Figure 3. Tissues and biological processes influenced by allergy risk variants.**

313

314   **(A) Enrichment of tissue-specific gene expression in 25 broad tissues studied by the GTEx**

315   **consortium.** We used the TSEA approach[9] to test if genes specifically expressed in a given tissue were

316   enriched amongst the list of plausible target genes when compared to other genes in the genome. The

317   enrichment (*y*-axis) is shown as the -log10 of the Fisher's exact test *P*-value. For comparison, we

318   analyzed 1,000 lists of random genes instead of the plausible target genes. We selected genes at random

319   using three strategies (see Methods for details). First, genes were randomly drawn from the 98 non-

320   MHC allergy risk loci identified in our GWAS, matching on the number selected per locus and in total.

321   The enrichment *P*-value for each of the 1,000 random gene lists is shown by a grey circle. The black-

322   solid line shows the *P*-value for the 50th most significant random list (*i.e.* corresponding to the 5th

20

323   percentile): under the null hypothesis of no enrichment, this *P*-value should be close to 0.05 (horizontal

324   grey line). Second, genes were drawn at random from 2 Mb loci selected at random from the genome,

325   matching on the number of genes selected (and available for selection) per locus and in total. Third,

326   genes were drawn at random from all 18,300 genes available for analysis. For the latter two strategies,

327   the *P*-value for the 50th most significant random gene list is shown by the blue and yellow lines,

328   respectively; enrichment results for each individual random dataset are not shown. Similar results were

329   obtained after restricting the random genes and the background gene list to the subset of genes with

330   eQTLs (**Supplementary Fig. 6**). Genes in the MHC were excluded from these analyses.

331   .

332   **(B) Enrichment of SNP-based heritability in 220 individual cell type-specific regulatory**

333   **annotations.** We used stratified LD score regression analysis [10] to quantify the contribution of SNPs

334   that overlap cell type-specific regulatory annotations to the SNP-based disease heritability. Annotations

335   with an enrichment in SNP heritability (-log10 of the *P*-value of the regression coefficient, *y*-axis) that

336   was significant after correcting for multiple testing (*P*<0.0002) are shown in black circles (top 10 listed

337   in blue font; all results in **Supplementary Table 18**). SNPs in the MHC were excluded from these

338   analyses.

339

340   **(C) Biological processes enriched amongst the list of plausible target genes**. We used

341   GeneNetwork[12] to test if the plausible target genes as a group were more likely to be part of a specific

342   biological process category when compared to the rest of the genes in the genome. The enrichment (*y*-

343   axis) is shown as the –log10 of the Wilcoxon rank-sum test *P*-value (see Methods for details). The top

344   10 pathways are listed in blue font. For comparison, we analyzed 1,000 random gene lists generated

345   using the same three strategies described above. For each of these strategies, the *P*-value for the 50th

346   most significant random gene list is shown by the black (random genes from allergy loci), blue

347   (random genes from random loci) and yellow (random genes selected from all available genes) lines.

348   Similar results were obtained after restricting the random genes and the background gene list to the

349   subset of genes with eQTLs (not shown). Genes in the MHC were excluded from these analyses.

350

TABLES

Table 1. Main association results for the 136 variants independently associated with the risk of allergic disease at $P<3x10^{-8}$.

Locus	Index in locus	Chr	Bp	SNP	EA	OA	OR	SE	P-value	P-value in conditional analyses[a]	Freq	Gene context	Novelty status
1	1	1	2510755	rs10910095	G	A	1.042	0.0073	2.70E-08	NA	0.84	TNFRSF14-[]-FAM213B	NewLocus
2	1	1	8482078	rs301806	T	C	1.048	0.0050	1.77E-20	NA	0.54	[RERE]	NewLocus
3	1	1	25251923	rs760805	T	A	1.038	0.0051	6.39E-13	NA	0.58	[RUNX3]	NewLocus
4	1	1	35681738	rs76167968	T	C	1.056	0.0093	1.26E-08	NA	0.93	SFPQ-[]-ZMYM4	NewLocus
5	1	1	150265704	rs7512552	C	T	1.031	0.0049	1.43E-09	NA	0.52	C1orf54-[]-MRPS21	KnownLocus-KnownVariant
6	1	1	152285861	rs61816761	A	G	1.224	0.0211	7.38E-21	NA	0.01	[FLG]	KnownLocus-KnownVariant
6	2	1	152179152	rs12123821	T	C	1.111	0.0124	6.81E-17	4.41E-018	0.05	RPTN-[]-HRNR	KnownLocus-KnownVariant
6	3	1	151796742	rs11204896	C	G	1.063	0.0085	2.36E-12	1.18E-010	0.90	[RORC]	KnownLocus-NewVariant
7	1	1	154426970	rs2228145	C	A	1.038	0.0050	4.30E-13	NA	0.35	[IL6R]	KnownLocus-KnownVariant
8	1	1	161185058	rs2070901	T	G	1.039	0.0056	1.31E-11	NA	0.26	NDUFS2-[]-FCER1G	NewLocus
9	1	1	167431352	rs2988277	C	T	1.040	0.0051	4.00E-14	NA	0.66	[CD247]	NewLocus
10	1	1	173146921	rs4090390	A	C	1.048	0.0058	1.32E-15	NA	0.22	TNFSF18--[]-TNFSF4	NewLocus
10	2	1	172700868	rs1102705	G	A	1.058	0.0088	3.07E-10	4.20E-011	0.11	FASLG-[]--TNFSF18	NewLocus
11	1	1	226914734	rs697852	A	G	1.041	0.0066	1.58E-09	NA	0.85	[ITPKB]	NewLocus
12	1	2	8442248	rs10174949	G	A	1.066	0.0054	7.34E-31	NA	0.68	[LINC00299]	KnownLocus-KnownVariant
13	1	2	64836267	rs4671601	C	T	1.039	0.0064	8.79E-09	NA	0.83	[LOC339807]	NewLocus
14	1	2	102941311	rs10865050	G	A	1.130	0.0073	6.98E-61	NA	0.85	[IL18R1]	KnownLocus-KnownVariant
14	2	2	102926362	rs12470864	A	G	1.057	0.0051	4.23E-26	3.63E-010	0.35	IL1RL2-[]-	KnownLocus-

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												IL18R1	KnownVariant
15	1	2	112388538	rs4848612	A	G	1.038	0.0058	2.33E-10	NA	0.76	BCL2L11--[]--ANAPC1	NewLocus
15	2	2	112269127	rs13403656	A	T	1.045	0.0077	2.18E-08	2.84E-008	0.16	BCL2L11--[]--ANAPC1	NewLocus
16	1	2	113590467	rs1143633	C	T	1.034	0.0052	1.65E-10	NA	0.70	[IL1B]	NewLocus
17	1	2	143831599	rs74847330	A	G	1.048	0.0076	1.76E-09	NA	0.88	KYNU-[]-ARHGAP15	NewLocus
18	1	2	198950240	rs1064213	G	A	1.035	0.0049	5.37E-12	NA	0.47	[PLCL1]	KnownLocus-KnownVariant
19	1	2	228707862	rs13384448	T	C	1.042	0.0058	2.82E-12	NA	0.76	CCL20-[]-DAW1	NewLocus
20	1	2	234115629	rs1057258	C	T	1.045	0.0067	1.39E-10	NA	0.80	[INPP5D]	NewLocus
21	1	2	242698640	rs34290285	G	A	1.082	0.0064	4.05E-33	NA	0.73	[D2HGDH]	NewLocus
22	1	3	33069091	rs6776757	G	A	1.033	0.0050	3.14E-10	NA	0.47	[GLB1]	KnownLocus-KnownVariant
23	1	3	72394852	rs61192126	T	C	1.037	0.0055	8.85E-11	NA	0.69	LINC00870--[]-RYBP	NewLocus
24	1	3	101242751	rs13088318	A	G	1.031	0.0053	8.63E-09	NA	0.62	FAM172BP-[]-TRMT10C	NewLocus
25	1	3	121652141	rs75557865	G	A	1.029	0.0050	1.63E-08	NA	0.57	[SLC15A2]	NewLocus
26	1	3	141321836	rs10663129	ACT	A	1.042	0.0054	1.12E-13	NA	0.33	[RASA2]	NewLocus
27	1	3	188133336	rs60946162	T	C	1.041	0.0051	8.57E-15	NA	0.42	[LPP]	KnownLocus-KnownVariant
27	2	3	188402586	rs17607589	C	T	1.053	0.0066	1.83E-14	2.50E-015	0.84	[LPP]	KnownLocus-NewVariant
27	3	3	187633268	rs519973	A	G	1.034	0.0052	4.50E-10	2.57E-011	0.35	BCL6--[]--LPP-AS2	KnownLocus-NewVariant
27	4	3	187793833	rs2030030	T	C	1.041	0.0068	1.01E-08	9.55E-009	0.86	BCL6--[]-LPP-AS2	KnownLocus-NewVariant
28	1	3	196372546	rs80064395	C	T	1.070	0.0094	1.55E-12	NA	0.94	FBXO45-[]-CEP19	KnownLocus-NewVariant
29	1	4	4775401	rs10033073	G	A	1.040	0.0059	1.19E-10	NA	0.35	STX18--[]-MSX1	NewLocus
30	1	4	38798648	rs5743618	C	A	1.100	0.0058	3.29E-58	NA	0.70	[TLR1]	KnownLocus-KnownVariant
31	1	4	103593898	rs227275	C	A	1.034	0.0050	3.69E-11	NA	0.56	[MANBA]	NewLocus
32	1	4	123316076	rs4145717	T	G	1.059	0.0052	9.18E-27	NA	0.34	[ADAD1]	KnownLocus-

												KnownVariant
32	2	4	123454110	rs150254607	AT AT	A	1.078	0.0097	4.63E-14	2.08E-024	0.07	IL2-[]-IL21	KnownLocus-NewVariant
33	1	5	14610309	rs16903574	G	C	1.071	0.0095	1.40E-12	NA	0.08	[FAM105A]	NewLocus
34	1	5	35862841	rs7717955	C	T	1.073	0.0055	9.13E-36	NA	0.71	[IL7R]	KnownLocus-KnownVariant
35	1	5	40492655	rs7714574	T	C	1.032	0.0050	5.94E-10	NA	0.53	DAB2---[]--PTGER4	KnownLocus-KnownVariant
36	1	5	110470137	rs6594499	C	A	1.075	0.0050	4.64E-46	NA	0.48	WDR36-[]-CAMK4	KnownLocus-KnownVariant
36	2	5	110166083	rs6869502	T	A	1.079	0.0066	6.38E-29	4.46E-029	0.18	SLC25A46-[]--TSLP	KnownLocus-KnownVariant
36	3	5	110401872	rs1837253	C	T	1.070	0.0056	1.63E-31	7.28E-020	0.78	SLC25A46--[]-TSLP	KnownLocus-KnownVariant
36	4	5	110159879	rs1814576	C	T	1.121	0.0114	1.41E-22	2.05E-012	0.09	SLC25A46-[]--TSLP	KnownLocus-KnownVariant
37	1	5	118684297	rs250308	T	C	1.031	0.0051	3.95E-09	NA	0.37	[TNFAIP8]	NewLocus
38	1	5	131996500	rs848	A	C	1.068	0.0063	1.52E-24	NA	0.24	[IL13]	KnownLocus-KnownVariant
38	2	5	131799626	rs3749833	C	T	1.039	0.0056	3.30E-11	2.67E-009	0.30	[C5orf56]	KnownLocus-NewVariant
38	3	5	131989136	rs3091307	G	A	1.062	0.0062	3.64E-21	4.40E-010	0.20	RAD50-[]-IL13	KnownLocus-KnownVariant
39	1	5	141494934	rs10068717	T	C	1.042	0.0052	4.80E-15	NA	0.62	[NDFIP1]	NewLocus
39	2	5	140925362	rs740474	C	T	1.034	0.0051	5.62E-11	6.73E-011	0.42	[DIAPH1]	NewLocus
40	1	5	159909345	rs2910162	G	A	1.033	0.0053	2.55E-09	NA	0.68	MIR3142-[]-MIR146A	NewLocus
41	1	5	176782218	rs13153019	C	T	1.035	0.0059	1.33E-08	NA	0.26	LMAN2-[]-RGS14	NewLocus
42	1	6	32626403	rs34004019	A	G	1.101	0.0062	3.78E-52	NA	0.70	HLA-DQA1-[]-HLA-DQB1	KnownLocus-KnownVariant
42	2	6	31323012	rs2854001	A	G	1.059	0.0062	1.18E-19	5.46E-019	0.18	[HLA-B]	KnownLocus-KnownVariant
42	3	6	31351664	rs2507978	G	A	1.035	0.0052	1.23E-10	2.43E-015	0.41	HLA-B-[]-MICA	KnownLocus-NewVariant
42	4	6	33647058	rs10947428	C	T	1.046	0.0061	3.54E-13	6.45E-015	0.19	[ITPR3]	KnownLocus-KnownVariant
42	5	6	29893575	rs9259819	G	T	1.036	0.0058	2.44E-09	3.45E-010	0.50	[HLA-J]	KnownLocus-

													NewVariant
42	6	6	31574525	rs28895016	C	T	1.097	0.0113	9.36E-16	2.48E-009	0.91	NCR3-[]-AIF1	KnownLocus-KnownVariant
42	7	6	33046752	rs3097670	G	C	1.064	0.0089	7.73E-12	2.02E-008	0.88	[HLA-DPA1]	KnownLocus-NewVariant
43	1	6	90987512	rs2134814	C	G	1.046	0.0052	1.65E-17	NA	0.65	[BACH2]	NewLocus
44	1	6	106667535	rs9372120	G	T	1.042	0.0062	4.23E-11	NA	0.18	[ATG5]	NewLocus
45	1	6	128294709	rs35469349	A	T	1.037	0.0056	2.32E-10	NA	0.26	[PTPRK]	NewLocus
46	1	6	138195151	rs5029937	G	T	1.081	0.0136	2.37E-08	NA	0.97	[TNFAIP3]	NewLocus
47	1	6	157419508	rs9383820	C	T	1.037	0.0063	1.24E-08	NA	0.76	[ARID1B]	NewLocus
48	1	6	167390671	rs72033857	C	CCTTT	1.057	0.0090	1.25E-09	NA	0.11	RNASET2-[]-MIR3939	NewLocus
49	1	7	20560996	rs6461503	T	C	1.039	0.0049	1.75E-14	NA	0.53	ITGB8--[]-ABCB5	KnownLocus-NewVariant
49	2	7	20376018	rs10486391	A	G	1.030	0.0050	6.82E-09	1.46E-009	0.53	[ITGB8]	KnownLocus-NewVariant
50	1	7	28156887	rs6977955	T	C	1.046	0.0061	7.12E-13	NA	0.21	[JAZF1]	NewLocus
51	1	7	50253897	rs17664743	A	G	1.042	0.0061	6.22E-11	NA	0.20	C7orf72-[]-IKZF1	NewLocus
52	1	7	77018542	rs4296977	C	T	1.055	0.0071	2.14E-13	NA	0.16	[GSAP]	NewLocus
53	1	8	81292599	rs7824394	A	C	1.050	0.0052	3.47E-20	NA	0.37	MIR5708--[]--ZBTB10	KnownLocus-KnownVariant
54	1	8	128814091	rs6990534	A	G	1.042	0.0054	6.35E-14	NA	0.36	[MYC]	KnownLocus-KnownVariant
55	1	9	6208030	rs144829310	T	G	1.090	0.0068	1.19E-35	NA	0.16	RANBP6--[]-IL33	KnownLocus-KnownVariant
55	2	9	6051399	rs343478	G	A	1.033	0.0050	2.59E-10	8.68E-015	0.52	RANBP6-[]--IL33	KnownLocus-NewVariant
55	3	9	5064193	rs16922576	C	T	1.036	0.0056	3.22E-10	3.90E-011	0.32	[JAK2]	KnownLocus-NewVariant
56	1	9	123650534	rs10760123	T	G	1.032	0.0053	5.23E-09	NA	0.38	PHF19-[]-TRAF1	NewLocus
57	1	9	131613191	rs12551834	G	A	1.058	0.0093	3.02E-09	NA	0.92	C9orf114-[]-LRRC8A	NewLocus
58	1	10	6094697	rs61839660	T	C	1.080	0.0085	4.42E-19	NA	0.07	[IL2RA]	KnownLocus-KnownVariant
58	2	10	6074451	rs4747846	C	G	1.036	0.0051	1.00E-11	3.69E-009	0.52	[IL2RA]	KnownLocus-KnownVariant

59	1	10	9049253	rs12413578	C	T	1.095	0.0082	1.30E-27	NA	0.90	GATA3---[]---SFTA1P	KnownLocus-KnownVariant
59	2	10	9064361	rs1444789	C	T	1.066	0.0064	1.48E-22	5.05E-018	0.20	GATA3---[]---SFTA1P	KnownLocus-KnownVariant
59	3	10	8605553	rs11255753	T	G	1.041	0.0056	2.02E-12	6.97E-014	0.26	GATA3--[]SFTA1P	KnownLocus-NewVariant
59	4	10	9032555	rs72782676	C	G	1.303	0.0390	3.16E-11	6.29E-012	0.98	GATA3---[]---SFTA1P	KnownLocus-NewVariant
59	5	10	8841669	rs2025758	T	C	1.041	0.0050	4.68E-15	9.41E-012	0.58	GATA3---[]---SFTA1P	KnownLocus-NewVariant
59	6	10	8936162	rs11255968	C	T	1.090	0.0147	7.74E-09	2.92E-010	0.96	GATA3---[]---SFTA1P	KnownLocus-KnownVariant
60	1	10	64382359	rs2893907	C	A	1.031	0.0050	1.84E-09	NA	0.58	[ZNF365]	KnownLocus-KnownVariant
61	1	10	104225832	rs10883723	C	T	1.030	0.0052	1.58E-08	NA	0.31	C10orf95-[]-ACTR1A	NewLocus
62	1	11	65551957	rs479844	G	A	1.038	0.0050	1.60E-13	NA	0.57	AP5B1-[]-OVOL1	KnownLocus-KnownVariant
63	1	11	76293758	rs7936323	A	G	1.088	0.0049	2.24E-63	NA	0.46	WNT11--[]-LRRC32	KnownLocus-KnownVariant
63	2	11	76299431	rs55646091	A	G	1.179	0.0122	2.26E-40	4.20E-023	0.05	WNT11--[]-LRRC32	KnownLocus-KnownVariant
63	3	11	76343428	rs11236814	A	T	1.068	0.0085	3.98E-14	9.81E-012	0.91	WNT11--[]-LRRC32	KnownLocus-NewVariant
64	1	11	95425526	rs59593577	C	T	1.053	0.0075	1.58E-11	NA	0.87	SESN3--[]-FAM76B	NewLocus
65	1	11	111470567	rs7130753	C	T	1.045	0.0056	7.05E-15	NA	0.69	LAYN-[]-SIK2	NewLocus
66	1	11	118743286	rs12365699	G	A	1.061	0.0067	5.15E-18	NA	0.85	DDX6-[]-CXCR5	NewLocus
67	1	11	128158189	rs56129466	A	G	1.047	0.0061	1.92E-13	NA	0.79	KIRREL3-AS3---[]--ETS1	KnownLocus-KnownVariant
68	1	12	48196982	rs55726902	G	A	1.051	0.0060	2.59E-16	NA	0.80	[HDAC7]	NewLocus
69	1	12	50345671	rs11169225	A	T	1.045	0.0064	1.23E-11	NA	0.18	[AQP2]	NewLocus
70	1	12	57489709	rs1059513	T	C	1.084	0.0081	1.05E-22	NA	0.89	[STAT6]	KnownLocus-KnownVariant
70	2	12	56401085	rs10876864	G	A	1.047	0.0050	1.42E-19	1.99E-019	0.39	SUOX-[]-IKZF4	KnownLocus-KnownVariant

71	1	12	111932800	rs7137828	T	C	1.033	0.0050	2.22E-10	NA	0.54	[ATXN2]	NewLocus
72	1	12	121363724	rs6489785	T	C	1.043	0.0051	1.55E-15	NA	0.37	SPPL3-[]-HNF1A-AS1	NewLocus
73	1	12	123742692	rs63406760	T	TG	1.047	0.0062	2.95E-13	NA	0.77	C12orf65-[]-CDK2AP1	NewLocus
74	1	13	41173408	rs4943794	C	G	1.043	0.0061	7.18E-12	NA	0.23	[FOXO1]	NewLocus
75	1	13	73627275	rs9573092	A	G	1.030	0.0052	2.67E-08	NA	0.70	PIBF1-[]-KLF5	NewLocus
76	1	14	35761675	rs1048990	G	C	1.039	0.0066	1.04E-08	NA	0.16	[PSMA6]	KnownLocus-KnownVariant
77	1	14	38097001	rs111914382	TG	T	1.036	0.0059	8.09E-09	NA	0.27	FOXA1-[]--TTC6	KnownLocus-KnownVariant
78	1	14	68754417	rs2104047	T	C	1.042	0.0054	1.64E-13	NA	0.36	[RAD51B]	NewLocus
79	1	14	75968608	rs9323612	A	G	1.032	0.0053	8.58E-09	NA	0.70	JDP2-[]-BATF	NewLocus
80	1	14	103235012	rs9989163	A	G	1.029	0.0050	1.92E-08	NA	0.49	RCOR1-[]-TRAF3	NewLocus
81	1	15	41782684	rs12440045	C	A	1.033	0.0051	4.89E-10	NA	0.55	RTF1-[]-ITPKA	NewLocus
82	1	15	61068347	rs10519067	G	A	1.055	0.0073	9.32E-13	NA	0.86	[RORA]	NewLocus
83	1	15	67448363	rs56375023	A	G	1.073	0.0059	8.24E-32	NA	0.21	[SMAD3]	KnownLocus-KnownVariant
84	1	15	91045408	rs3540	G	A	1.036	0.0053	3.32E-11	NA	0.65	[IQGAP1]	NewLocus
85	1	16	11277358	rs11644510	C	T	1.072	0.0053	6.11E-38	NA	0.64	CLEC16A-[]-RMI2	KnownLocus-KnownVariant
85	2	16	11491007	rs12596613	C	G	1.032	0.0054	6.06E-09	2.53E-009	0.67	RMI2-[]--LITAF	KnownLocus-KnownVariant
86	1	17	4521473	rs71368508	C	A	1.124	0.0191	2.02E-09	NA	0.99	SMTNL2-[]-ALOX15	NewLocus
87	1	17	38069076	rs921650	A	G	1.059	0.0049	5.67E-30	NA	0.48	[GSDMB]	KnownLocus-KnownVariant
87	2	17	38764524	rs112401631	A	T	1.260	0.0213	2.20E-26	3.74E-026	0.01	CCR7-[]-SMARCE1	KnownLocus-NewVariant
87	3	17	38770641	rs11464691	TA	T	1.052	0.0052	1.37E-21	3.05E-020	0.57	CCR7-[]-SMARCE1	KnownLocus-NewVariant
87	4	17	38149033	rs11652139	A	G	1.051	0.0051	7.54E-22	1.70E-008	0.59	[PSMD3]	KnownLocus-KnownVariant
88	1	17	40414862	rs7207591	A	G	1.038	0.0060	1.43E-09	NA	0.76	[STAT5B]	NewLocus
89	1	17	43430696	rs7214661	G	A	1.032	0.0054	1.20E-08	NA	0.32	MAP3K14-[]-	NewLocus

													ARHGAP27
90	1	17	47398070	rs9889262	A	T	1.043	0.0051	9.65E-16	NA	0.35	[ZNF652]	NewLocus
91	1	18	52336175	rs4801001	T	C	1.031	0.0051	5.91E-09	NA	0.42	DYNAP-[]--RAB27B	NewLocus
92	1	18	60009814	rs4574025	T	C	1.030	0.0050	6.79E-09	NA	0.56	[TNFRSF11A]	NewLocus
93	1	19	33721455	rs10414065	C	T	1.098	0.0106	6.10E-18	NA	0.92	SLC7A10-[]-CEBPA	NewLocus
94	1	20	50157837	rs3787184	A	G	1.049	0.0066	1.06E-12	NA	0.78	[NFATC2]	KnownLocus-KnownVariant
95	1	20	52208356	rs2766678	G	A	1.057	0.0063	5.04E-18	NA	0.21	[ZNF217]	KnownLocus-NewVariant
96	1	20	62322699	rs6011033	G	A	1.047	0.0060	3.50E-14	NA	0.78	[RTEL1]	KnownLocus-KnownVariant
97	1	21	36467830	rs73205303	A	G	1.044	0.0069	7.90E-10	NA	0.13	[RUNX1]	NewLocus
98	1	21	44846426	rs76081789	T	C	1.065	0.0108	1.34E-08	NA	0.94	[SIK1]	NewLocus
99	1	22	41816652	rs5758343	A	T	1.048	0.0061	4.75E-14	NA	0.22	TEF-[]-TOB2	NewLocus

EA: effect allele. OA: other allele. Freq: Effect allele frequency in Europeans populations of the 1000 Genomes Project.

[a] Eighteen loci were found to have multiple independent associations in approximate conditional analyses. We studied these 18 loci in greater detail using data from the UK Biobank (132,702 unrelated individuals of European descent) to confirm these results. Specifically, for each of these 18 loci, we tested if the independent variants identified in the GWAS meta-analysis were associated with disease risk when included simultaneously in a logistic regression model, using R (*e.g.* glm(disease ~ rs61816761 + rs12123821 + rs11204896 + covariates)). For 17 of the 18 loci, all sentinel SNPs were independently associated with disease risk at $P<0.05$ (not shown). The exception was locus #36, for which one of the 4 sentinel SNPs (rs6594499) had a $P=0.12$. Therefore, despite the reduced sample size, results from this analysis in the UK Biobank study confirm that all but one of the independent variants identified by approximate conditional analysis in these 18 loci have a statistically independent association with disease risk.

Table 2. Selected examples of plausible target genes not previously implicated in the pathophysiology of allergic disease.

Gene	Summary	Possible role(s) in allergic disease[a]
RERE	Nuclear receptor coregulator that positively regulates retinoic acid signaling	Positive regulation of B cell differentiation, eosinophil survival and migration
PPP2R3C	Sub-unit of protein phosphatase 2A (PP2A) that regulates immune cell function	Th2 differentiation, Treg function, response to viral infection
RASA2	GTPase-activating protein of Ras that regulates receptor signal transduction	Unknown. RASA3: hematopoiesis. RASA4: macrophage phagocytosis.
SIK2	Salt-inducible kinase	Regulation of macrophage inflammatory phenotype, metabolic homeostasis
RTF1	Component of the PAF complex, that is involved in transcriptional regulation	Anti-viral response, regulation of TNF expression
SMARCE1	Sub-unit of the BAF chromatin remodeling complex	Repressor of CD4 differentiation
DYNAP	Dynactin-associated protein that activates protein kinase B	Cytokine signaling, T cell function
THEM4	Mithocondrial thioesterase that is a negative regulator of protein kinase B	Vitamin D-dependent macrophage-mediated inflammation
ARHGAP15	Rho GTPase activating protein that down-regulates RAC1	Rac1-dependent inflammatory response
SENP7	Sentrin/small ubiquitin-like modifier (SUMO)-specific protease	Susceptibility to viral infection
SLC15A2	Peptide transporter expressed in skin, nasal and lung epithelial cells	Bacterial peptide recognition and immune activation

[a] References that support the possible role(s) listed are cited in the Supplementary Information.

Table 3. Plausible target genes with drugs in development for indications other than allergic diseases, for which the effect on gene expression of the allergy protective allele and the existing drug matched.

Plausible target gene	Effect of allergy protective allele on gene expression	Drug Action	Drug Status	Drug Name	Originator Company	Active Indications
CD86	Increased	Agonist	Discovery	BR-02001	Boryung_Pharm_Co_Ltd	Autoimmune_disease
CCR7	Decreased	Antagonist	Discovery	anti-CCR7_chimeric_IgG1_antibodies	North_Coast_Biologics_LLC	Unidentified_indication
CCR7	Decreased	Antagonist	Discovery	anti-CCR7_monoclonal_antibody	Pepscan_Systems_BV	Cancer
CCR7	Decreased	Antagonist	Discovery	CCR7-targeting_antibody	Abilita_Bio_Inc	Metastatic_breast_cancer
CCR7	Decreased	Antagonist	NA	chemokine_antagonists	Neurocrine_Biosciences_Inc	NA
CCR7	Decreased	Antagonist	NA	chemokine_receptor_inhibitors	Sosei_Group_Corp	NA
F11R	Decreased	Antagonist	Discovery	F11R_inhibitors	Provid_Pharmaceuticals_Inc	Cardiovascular_disease
F11R	Decreased	Antagonist	Discovery	F-50073	Pierre_Fabre_SA	Cancer
PHF5A	Decreased	Antagonist	Discovery	PHF5A_inhibitors	Fred_Hutchinson_Cancer_Research_Center	Glioblastoma
RGS14	Decreased	Antagonist	NA	regulator_of_G-protein_signaling_14_inhibitor	University_of_Malaga	Memory loss
TARS2	Decreased	Antagonist	Discovery	borrelidin	Scripps_Research_Institute	Infectious_disease

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AUTHOR CONTRIBUTIONS

Data collection and analysis in the contributing studies. AAGC study: M.A.F., M.C.M., S.C.D., L.M.B., P.J.T., N.G.M., D.L.D.; LifeLines study: J.M.V., G.H.K.; GENEVA study: H.B., E.R., M.H., A.F., N.N., H.S.,S.K., C.G., K.S., S.W.; GENUFAD studies: I.M., F.R., J.E-G., S.G., A.A., G.H., C.O.S., N.H., Y-A,L.; 23andMe study: C.T., D.A.H.; GERA study: J.D.H., J.S.W., R.B.M, E.J.; NTR study: Q.H., J-J,H., G.W., D.I.B.; CATSS, TWINGENE and SALTY studies: A.T., V.U., Y.L., P.K.E.M., C.A., R.K.; ALSPAC study: L.P.; HUNT study: B.M.B., L.F., M.E.G., J.B.N., W.Z., K.H., A.L., O.L.H., M.L., G.A., C.W.; UK Biobank study: L.P., M.A.F.

Methylation analysis: J.vD., D.I.B., R.J.

Biological and drug annotation: M.A.F., C.W.M., E.M., K.B., O.H., J.Z., J.A.R., J.B., B.B.

Quality control, meta-analysis, tables and figures: M.A.F.

Writing group: M.A.F., J.M.V., I.M., C.T., J.D.H., Q.H., A.T., V.U., J.vD., Y.L., J.E-G., B.M.B., J.B., S.C.D., S.W., P.K.E.M., R.J., E.J., Y-A.L., D.I.B., C.A., R.K., G.H.K., L.P.

Study design and management: M.A.F., D.A.H., B.M.B., S.W., P.K.E.M., R.J., E.J., Y-A.L., D.I.B., C.A., R.K., G.H. K., L.P.

COMPETING FINANCIAL INTERESTS

The authors declare no competing financial interests.

1   **Shared genetic origin of asthma, hay fever and eczema**

2   **elucidates allergic disease biology**

3

4   **<u>ONLINE METHODS</u>**

List of risk variants reported to be associated with allergic disease in previous GWAS

We downloaded the full NHGRI-EBI GWAS catalog database [1] on January 19, 2017 (v1.0.1). We then identified SNP associations with a $P \leq 5 \times 10^{-8}$ and that were reported for an allergic condition, specifically for which the "MAPPED_TRAIT" variable included the terms "allergic rhinitis", "allergic sensitization", "allergy", "asthma", "eczema" and "atopic march". Excluded associations were inspected to ensure that no relevant variants were missed by this filtering approach. After excluding two variants without a reference SNP (rs) ID (both in the MHC), there were 169 associations, including 144 unique rs IDs. We then used the --clump procedure in PLINK [2] and genotype data from individuals of European descent from the 1000 Genomes Project [3] (n=294, release 20130502_v5a) to reduce this list of 144 SNPs to variants in low linkage disequilibrium (LD) with each other (r^2<0.05), which are likely to represent statistically independent associations with allergic disease. After excluding five variants that were not polymorphic in Europeans (rs7212938, rs62176107, rs17218161, rs10056340, rs9273349), we identified 75 variants in low LD with each other. We then identified the earliest GWAS to report an association with each of these 75 variants (or with a SNP with r^2>0.05 with it) and used the year of publication to generate **Supplementary Fig. 2**.

Meta-analysis of allergic disease GWAS results conducted in 13 studies (n=360,838)

In each of 13 participating studies (**Supplementary Tables 1 and 2**), a GWAS was performed using an additive genetic model in individuals of European descent that reported suffering from asthma and/or hay fever and/or eczema (case-group, total n=180,129), against those who never reported suffering from any of these three conditions (control group, total n=180,709). A detailed description of the procedures used to identify cases and controls, as well as for SNP genotyping, imputation and association testing, is provided for each study in the **Supplementary Information**.

28   Prior to the meta-analysis, standard quality control (QC) filters were applied to results from

29   individual studies (**Supplementary Table 1**). After QC, and restricting the analysis to SNPs present in

30   at least the two largest studies (UK Biobank and 23andMe, combined n=256,623), results were

31   available for 8,307,659 variants, of which most (89%) were available in >95% of the overall sample

32   size. Intercept estimates from LD score regression analysis [4], which reflect inflation of test statistics

33   that are likely due to technical biases, ranged between 1.00 and 1.16 (**Supplementary Table 1**). Results

34   from individual studies were adjusted for the observed inflation by multiplying the square of the

35   standard error of each genetic effect estimate by the respective LD score regression intercept. We then

36   used METAL [5] to combine association results across studies using an inverse-variance-weighted, fixed-

37   effects meta-analysis. P-values from the meta-analysis were further adjusted for the meta-analysis LD

38   score regression intercept of 1.04. The genome-wide significance threshold was set at 3×10^{-8}, as

39   suggested previously for GWAS analyzing variants with MAF$\geq$1% [6].

40

41   **Identification of independent associations through approximate conditional analyses**

42   For each chromosome, we identified all SNPs with a $P \leq 3 \times 10^{-8}$, sorted these based on base pair

43   position, and then grouped variants into the same locus if the distance between consecutive variants

44   was <1Mb. Variants located >1 Mb from the previous genome-wide significant variant were assigned

45   to a new locus. Next, for each of these loci, we identified statistically independent associations using

46   approximate conditional analyses, as implemented in GCTA [7]. We refer to these as sentinel risk

47   variants. In these analyses, LD calculations were based on a subset of 5,000 individuals from the

48   UKBiobank study. Briefly, for each locus, we (1) identified the most significantly-associated SNP [i];

49   (2) adjusted the summary statistics of all SNPs in that locus by the effect of that top SNP; (3) identified

50   the most significantly-associated SNP [j] that remained genome-wide significant in that locus; (4)

51 adjusted the summary statistics of all SNPs in that locus by the effects of SNPs *i* and *j*. We repeated this

52 process until there were no SNPs associated with allergic disease at $P \leq 3 \times 10^{-8}$ after adjusting for the

53 effect of other, more strongly independently associated variants in that locus. Lastly, we estimated the

54 LD between sentinel variants located in different risk loci (*i.e.* >1 Mb apart) and confirmed that the r^2

55 was always close to 0 (no pairs of sentinel variants with $r^2 > 0.02$).

56

57 **Determining the novelty status of independent SNP associations with allergic disease**

58 Previous GWAS identified 144 SNPs associated with the risk of various allergic conditions, which we

59 grouped into 75 independent associations based on the LD between variants (see above). We used that

60 information to classify each of our independent SNP associations into two major groups: located in

61 known (<1Mb from any of those 144 previously reported associations; "KnownLocus") or new (>1Mb

62 from those variants; "NewLocus") allergy risk loci. For the first group, we then estimated the LD

63 between each sentinel variant identified in our study and all variant(s) reported in previous GWAS. If

64 all reported variants had an $r^2 < 0.05$ with our sentinel variant, then our association was considered to

65 represent a new risk variant in a known risk locus ("KnownLocus-NewVariant"). Alternatively, when at

66 least one reported variant had an $r^2 \geq 0.05$, our association was considered to be a known risk variant in

67 a known risk locus ("KnownLocus-KnownVariant"). The second major group of variants were located

68 in new allergy risk loci. Within this group, we used the same approach just described to determine if

69 our associations were novel when considering any disease or trait with genome-wide significant

70 associations reported in the NHGRI-EBI GWAS catalog.

71

72 **Comparison of risk allele frequencies between individuals suffering from a single allergic disease**

73 By combining information from asthma, hay fever and eczema in the case-control definition used in

74 our GWAS, we expected our study design to improve power to identify risk variants shared between,

75 but not specific to any of, the three diseases [8]. To understand if the associations discovered in our

76 GWAS were indeed likely to represent risk factors shared across allergic diseases, we took advantage

77 of the observation that not all affected individuals report allergic co-morbidities [9-11], and compared

78 allele frequencies between three groups of adults: asthma-only cases (n=12,268), hay fever-only cases

79 (n=33,305) and eczema-only cases (n=6,276). The studies that contributed to this analysis are indicated

80 in **Supplementary Table 1** and described in detail in the **Supplementary Information**. We performed

81 three sets of association analyses contrasting three non-overlapping groups of individuals: asthma-only

82 (g1) vs. hay fever-only (g2); asthma-only (g1) vs. eczema-only (g3); and hay fever-only (g2) vs.

83 eczema-only (g3). These analyses are statistically independent from the case-control analysis carried

84 out as part of the GWAS, which facilitates interpretation of the results. For a given sentinel SNP, results

85 from these analyses indicate if the risk allele is more (odds ratio [OR] >1) or less (OR<1) common in

86 e.g. group 1 (g1) when compared to group 2 (g2). For example, if a SNP contributed similarly to the

87 risks of asthma and hay fever but not eczema, then one would expect an OR~1 in the asthma-only vs.

88 hay fever-only comparison, but an OR>1 in the asthma vs. eczema and hay fever vs. eczema analyses.

89 The significance threshold for these analyses was set at 1.2×10^{-4}, which corresponds to a Bonferroni

90 correction for the 136 SNPs and three sets of analyses performed (i.e. P<0.05/(136x3)).

91

92 **Association between sentinel risk variants and variation in allergy age-of-onset**

93 There is considerable variation in the age allergic diseases are first reported, and this has been shown to

94 be influenced by genetic risk factors [12]. We therefore studied the association between the sentinel

95 variants identified in our GWAS and age-of-onset observed in the UK Biobank study (n=35,972). For

96 each individual, we first considered the earliest age of any allergic disease (asthma or hay

97   fever/eczema; the latter two were covered by the same question, and so could not be differentiated)

98   being reported. SNPs were tested for association with this phenotype, with sex and a SNP array

99   variable included as covariates. The significance threshold used for this analysis was 3.6×10^{-4} (i.e.

100   $P < 0.05/136$). Because significant SNP associations with this broad age-of-onset phenotype could be

101   driven by different risk allele frequencies amongst cases suffering from different individual conditions

102   (for example, a FLG variant might be associated with earliest age-of-onset because it is more prevalent

103   in eczema cases, which tends to precede the development of asthma and hay fever [13]), we repeated the

104   analysis by considering individuals who had reported suffering only from a single disease: asthma-only

105   ($n=7,445$), hay fever-only ($n=4,232$) and eczema-only ($n=1,225$). For a given SNP, differences in effect

106   size (beta) between groups were quantified using the formula z = sigma / SE_sigma, where sigma =

107   beta_groupA – beta_groupB, and SE_sigma = sqrt(SE_beta_groupA^2 + SE_beta_groupB^2), which

108   follows a normal distribution.

109

110   **Estimating the contribution of the sentinel variants to the heritability of asthma, hay fever and**

111   **eczema**

112   Five steps were involved. First, we performed a GWAS of the individual diseases in the HUNT study,

113   which was not included in the discovery meta-analysis. The HUNT study is described in greater detail

114   in the **Supplementary Information**. Briefly, based on self-reported questionnaire information, we

115   identified 1,875 cases and 16,463 controls for the asthma GWAS; 6,939 cases and 12,844 controls for

116   the hay fever GWAS; and 2,630 cases and 16,131 controls for the eczema GWAS. After quality control

117   filters, we analyzed 7.6 million common variants (genotyped and imputed) for association with each

118   individual phenotype. The genomic inflation factor (i.e. lambda) for these analyses were 1.049 for

119   asthma, 1.078 for hay fever, and 1.041 for eczema. Second, for each of the three diseases, we

120 quantified the overall SNP-based heritabilities with LD score regression [4] using a subset of 1.2 million

121 HapMap SNPs. To obtain a heritability estimate on the liability scale, we set the population prevalence

122 to be the same as the sample prevalence, given that this was a population-based study. Third, we

123 removed the 136 sentinel variants (and all correlated variants, $r^2>0.05$) from the individual disease

124 GWAS results. Fourth, we re-estimated SNP-based heritabilities as described for step two, but now

125 using the GWAS results without the 136 top associations. In the fifth and final step, the contribution of

126 the 136 sentinel variants towards the heritability of each disease was calculated as the difference

127 between the SNP-based heritability estimated in steps two (all SNPs) and four (without 136 top

128 associations).

129

130 **Identification of plausible target genes of sentinel risk variants**

131 Two independent strategies were used to identify plausible target genes underlying the observed

132 associations. By 'target gene' we mean a gene for which protein sequence and/or variation in

133 transcription is associated with a sentinel risk variant or one of its proxies ($r^2>0.8$).

134   First, we used wANNOVAR [14] to identify genes containing non-synonymous SNPs amongst all

135 variants in LD ($r^2>0.8$) with any sentinel risk variant. SNPs in LD with sentinel risk variants were

136 identified using genotype data from individuals of European descent from the 1000 Genomes Project [3]

137 (n=294, release 20130502_v5a).

138   Second, to identify genes with transcription levels associated with a sentinel risk variant or one

139 of its proxies ($r^2>0.8$), we queried publicly available results from 39 published expression quantitative

140 trait loci (eQTL) studies conducted in 19 tissues or cell types relevant to allergic disease

141 (**Supplementary Table 12**). We used a conservative significance threshold to identify significant SNP-

142 gene expression associations, specifically a $P<2.3 \times 10^{-9}$ for *cis* effects (<1 Mb). We selected this

143   threshold based on a Bonferroni correction that considers the total number of protein-coding genes (G)

144   and the number of SNPs likely to have been tested per gene (M): $P<0.05/(GxM)$. G was set at 21,742,

145   based on the GeneCards database[15], queried on October 19th, 2016. We approximate M to be 1,000, as

146   indicated by others [16-18], and so the threshold becomes $P=0.05/(21,472$ genes x 1,000 SNPs per

147   gene)$=2.3 \times 10^{-9}$. We did not use information from *trans* eQTLs to identify plausible target genes of

148   sentinel risk variants, because often these are thought to involve indirect effects[19] (*e.g.* sentinel SNP

149   influences the expression of a transcript in *cis*, which in turn affects the expression of many other genes

150   in *trans*).

151   For each eQTL study, and within each study for each tissue, we created a list of SNPs associated

152   with gene expression in cis at a $P<2.3 \times 10^{-9}$. Then, for each gene in that study-tissue dataset, we used

153   the --clump procedure in PLINK to reduced the list of expression-associated SNPs (which often

154   included many correlated SNPs) to a set of 'sentinel eQTLs', defined as the SNPs with strongest

155   association with gene expression and in low LD ($r^2<0.05$, LD window of 2 Mb) with each other. This

156   procedure was repeated for each of the 94 study-tissue datasets listed in **Supplementary Table 12**.

157   Finally, we identified as a likely target of a sentinel allergy risk variant any gene for which a sentinel

158   eQTL in any of the 94 study-tissue datasets had an LD $r^2>0.8$ with the sentinel risk variant. That is, we

159   only considered genes for which there was strong LD between a sentinel variant and a sentinel eQTL,

160   which reduces the chance of spurious co-localization. We did not use statistical approaches developed

161   to distinguish co-localization from shared genetic effects because these have very limited resolution at

162   high LD levels ($r^2>0.8$) [20].

163   To help prioritize plausible target genes for functional validation in subsequent studies, we

164   identified genes for which publicly available functional data supported not just the presence of

165   chromatin interactions between an enhancer and a gene promoter (based on 5C[21], promoter capture Hi-

166 C[22], ChIA-PET[23] or *in situ* Hi-C[24] data), but also an association between variation in enhancer

167 epigenetic marks and variation in gene transcription levels (based on PreSTIGE[25], H3K27ac enhancer

168 and super-enhancer annotation [26], IM-PET[27] or FANTOM5[28] analyses). We considered data from

169 immune cell types, lung and skin (**Supplementary Table 15**) and putative enhancers that overlapped a

170 sentinel risk variant (or one of its strongly correlated proxies, $r^2 > 0.95$).

171   To identify genes that were unlikely to have been previously implicated in the pathophysiology

172 of allergic disease, we performed the following PubMed query on May 19th, 2017: (asthma OR rhinitis

173 OR eczema OR atopic OR dermatitis OR allergy OR allergi* OR hayfever OR "hay fever") AND

174 (gene1 OR gene2 OR … OR gene244). The gene symbols approved by the HUGO Gene Nomenclature

175 Committee (HGNC) for each of the target genes were inserted into the second part of that query. The

176 search results were downloaded as an .xml file and the number of unique articles (based on PMID)

177 listing a given gene symbol was counted using in-house scripts (results in **Supplementary Table 14**).

178 To identify genes likely to have been implicated in immune-related processes, we repeated this

179 approach but replaced the first part of the PubMed query with (immune OR immuni* OR immunol*).

180

181 **Enrichment in tissue-specific gene expression**

182 We used the TSEA approach [29] to identify tissues that were likely to be affected functionally by the

183 biological effects of the sentinel risk variants. We implemented this approach locally using custom

184 scripts. Specifically, for each of 25 broad tissue types studied by the GTEx consortium, we tested if

185 genes with tissue-specific expression (based on a Specificity Index threshold [29] [pSI] of 0.05; listed in

186 file   TableS3_NAR_Dougherty_Tissue_gene_pSI_v3-1.txt,   downloaded   from

187 http://genetics.wustl.edu/jdlab/psi_package/) were enriched amongst the list of plausible target genes,

188 when compared to the rest of the genes in the genome. After excluding genes without a pSI value and

9

189   in the MHC, there were 112 plausible target genes and 17,671 background genes available for analysis.

190   To test if the plausible target genes were enriched for genes with specific expression in a given tissue,

191   we used Fisher's exact test (one-sided). To rule out the possibility that a significant enrichment could

192   arise because the list of plausible targets was enriched for genes with eQTLs, we repeated the analysis

193   after restricting the background gene list to a subset of 12,804 genes that were found to have eQTLs in

194   the same eQTL studies that were used to identify plausible target genes of sentinel variants.

195   We also tested if a significant enrichment in tissue-specific expression could be a general

196   feature of genes near sentinel risk variants, and not specific to the list of genes identified as plausible

197   targets. To address this possibility, we generated 1,000 arbitrary gene lists, each containing 112 random

198   genes instead of the plausible target genes. We selected genes at random from the 17,783 with an

199   available pSI value and not in the MHC, using three strategies. First, genes were randomly drawn from

200   allergy risk loci (+/- 1 Mb of a sentinel variant). To generate each list of random genes, for each non-

201   MHC allergy risk locus L, we randomly selected a locus R from the subset of non-MHC allergy risk

202   loci for which the number of genes available for selection was the same or greater than the actual

203   number of plausible target genes (T) selected for that locus L. Then, for that locus R, we selected T

204   genes at random from the available genes in that locus. This procedure was repeated for all non-MHC

205   allergy risk loci, ensuring that the same locus was not selected twice in a given random dataset.

206   In the second strategy, genes were randomly drawn from 2 Mb loci selected at random from the

207   genome. In this case, to generate each list of random genes, we first partitioned the autosomes

208   (excluding the MHC) into 1,430 consecutive 2 Mb loci, and counted how many genes with an available

209   pSI value were present in each of these loci. Then, for each non-MHC allergy risk locus L, we

210   randomly selected a locus R from the subset of 2 Mb loci for which the number of genes available for

211   selection satisfied the following criteria: (1) was the same or greater than the actual number of plausible

212   target genes (*T*) selected for that locus *L*; and (2) matched (within 10%) the number of genes available

213   for selection for that locus *L*. This was important to ensure that the randomly selected locus *R* was

214   comparable to the allergy risk locus *L* in terms of the number of genes available for selection. Then, for

215   that locus *R*, we selected *T* genes at random from the available genes in that locus.

216   In the third and final strategy, we simply selected genes at random from all 17,783 non-MHC

217   genes with an available pSI value, ignoring where the genes were located in the genome. As a result,

218   for a given random list, the genes selected could only be in close proximity to other genes in that same

219   list by chance alone.

220   The same approach used to test the enrichment in tissue-specific expression for the plausible

221   target genes was then used to analyze each of the 1,000 lists of random genes. For each of these lists,

222   the smallest *P*-value observed across all 25 tissues tested was retained (P_{min}). The proportion of random

223   gene lists (out of 1,000) with a P_{min} that was the same or lower than the enrichment *P*-value observed

224   with the plausible target genes (P_{obs}) was then calculated. This corresponds to the probability of

225   exceeding that enrichment when analyzing the random gene lists, after correcting for the 25 tissues

226   tested. As we did for the analysis of the plausible target genes, we repeated the generation and analysis

227   of random gene lists after restricting the genes available for selection (and the background gene list) to

228   the subset of genes with a known eQTL.

229

230   **Enrichment in tissue-specific SNP heritability**

231   Finucane et al. [30] developed an approach to identify tissues likely affected by the functional effects of

232   disease risk variants, called stratified LD score regression. This approach quantifies the contribution of

233   SNPs located in tissue-specific regulatory annotations to the overall disease heritability. As such, it

234   does not require the identification of likely target genes of allergy risk variant and considers all SNPs in

235   the genome, not just those with a genome-wide significant association with disease risk. Specifically,

236   up to four histone marks (H3K4e1, H3K4me3, H3K9ac and H3K27ac) measured by the ENCODE

237   project are used to define regulatory annotations (*e.g.* enhancers) in 100 different cell types. SNPs that

238   overlap these regulatory annotations are then identified and their contribution as a group to the disease

239   heritability quantified. As recommended by Finucane et al. [30], we ranked cell types based on the *P*-

240   value of the regression coefficient, rather than the *P*-value of total enrichment. To ensure that

241   significant SNP heritability enrichments were not explained by the effects of sentinel variants, we

242   removed the top SNPs (and any variants with $r^2>0.05$ with these) from the meta-analysis GWAS results

243   and repeated the LD score regression analysis.

244

245   **Enrichment of biological processes**

246   To identify biological processes enriched amongst the non-MHC target genes, we used GeneNetwork

247   [31]. With this approach, gene sets originally included in a given GO biological process (BP) were

248   expanded to include other genes based on a 'guilt-by-association' procedure [31]. After excluding BPs

249   with <10 or >500 genes, 3,770 BPs were available for analysis. For each BP, we tested its enrichment

250   amongst the list of plausible target genes as follows. First, we downloaded a gene set file containing *z*-

251   scores   for   each   of   19,976   unique   genes   in   the   genome   from

252   http://129.125.135.180:8080/GeneNetwork/resources/ontology?ontology=GO_BP&term=[pathway],

253   where 'pathway' was replaced with the actual name of the BP being tested (*e.g.* "GO:0000002"). The *z*-

254   score for gene X in that file reflects the probability that gene X is part of that BP. Second, we compared

255   the distribution of z-scores between the list of plausible target genes (107 non-MHC genes were in the

256   GeneNetwork gene set files, and so were available for analysis) and a background gene list of 18,193

257   genes (obtained after excluding MHC genes, the 107 plausible target genes and genes not listed in

258 GENCODE release 19), using a one-sided Wilcoxon rank-sum test. The *P*-value from this test

259 represents the probability that genes in that BP are enriched amongst the list of plausible target genes,

260 when compared to the background gene list.

261   As for the enrichment analysis of tissue-specific expression, we estimated how often a BP

262 enrichment observed with the list of plausible target genes would be expected had we sampled genes at

263 random from the allergy risk loci or from random loci. This analysis addresses the possibility that an

264 observed enrichment might not be a specific feature of the plausible target genes identified but instead

265 a general feature of genes located near sentinel allergy risk variants, or simply in close proximity to

266 each other. We used the same three strategies described above to generate 1,000 random gene lists,

267 sampling from the 18,300 non-MHC with an available z-score and in GENCODE release 19. To

268 determine if using eQTL information to identify plausible target genes could have biased the

269 enrichment analysis, we generated and analysed random gene lists after restricting the genes available

270 for selection to the subset with known eQTLs (12,913), but found very similar results (not shown).

271

272 **Common traits and diseases associated with allergic disease risk variants**

273 We first identified all variants in LD (r^2>0.8) with a sentinel risk variant using data from Europeans of

274 the 1000 Genomes Project [3] (*n*=294, release 20130502_v5a), and extracted any associations with these

275 reported in the NHGRI-EBI GWAS catalog database [1] (queried on December 13, 2016) or by Astle et

276 al. [32], a large GWAS of blood cell counts (*n*=173,480). To complement this analysis, we estimated the

277 SNP-based genetic correlation between our GWAS and results reported for 229 common traits or

278 diseases, using LD Hub [33]. In these analyses, results from our meta-analysis were not corrected for the

279 LD score intercept, either at the study level or after the meta-analysis.

280

281 **Identification of target genes with drugs considered as drug targets for human diseases**

282 To identify genes that encode transcripts that are targets of drugs considered for clinical development,

283 we queried the Thomson Reuters Cortellis^{TM} Drug database between November 7 and 15, 2016, which

284 included 63,417 drugs. The drug search was carried out individually for each gene. First, a search query

285 was built based on the following format: HGNC approved gene name OR alias_1 OR … OR alias_N.

286 Gene name aliases were obtained from the Bioconductor annotation package org.Hs.eg.db. For

287 example, to find drugs that target *IL6R*, the search query used was: "CD126" OR "IL-6R-1" OR "IL-

288 6RA" OR "IL6Q" OR "IL6RA" OR "IL6RQ" OR "gp80" OR "IL6R" OR "interleukin 6 receptor".

289 Second, after running the search query, results were filtered based on the ascribed "Target-based

290 Actions", keeping only entries that corresponded to the gene name or an alias. For example, of the 65

291 results obtained with the *IL6R* query above, only for 20 did the target-based action mention *IL6R* or an

292 alias. Third, drug results were downloaded, and the gene and respective drug allocated to one of three

293 groups: (1) gene with at least one drug considered for the treatment of allergic diseases (15 genes); (2)

294 gene considered for the treatment of immune-related conditions, but not allergic diseases specifically (8

295 genes); and (3) gene considered for the treatment of other conditions (26 genes).

296

297 **Directional effect of the allergy protective allele on target gene expression**

298 In an attempt to predict if existing drugs would be expected to attenuate or exacerbate allergic

299 symptoms, we compared the effect on gene expression between the allergy protective allele and the

300 existing drug. We acknowledge that this is a simplistic comparison, because it assumes that the

301 directional effect of the protective allele is not tissue- or context-dependent, which is true for most but

302 not all expression-associated SNPs [34-36].

303   To determine if the allergy protective allele of a sentinel variant was associated with higher or

304   lower target gene expression, we focused on the subset of target genes identified via an eQTL (see

305   above). This was straightforward to assess when the sentinel SNP and the expression-associated SNP

306   were the same variant: for example, if the allergy-protective allele had a negative effect (e.g. beta or z-

307   score) on gene expression in the published eQTL study, then that allele was associated with lower gene

308   expression. On the other hand, when the two SNPs did not correspond to the same variant, but were in

309   high LD (r^2>0.8) with each other, we first determined which allele of the expression-associated SNP

310   was on the same haplotype as the allergy-risk allele. Then we used that allele to infer the direction of

311   effect of the allergy-risk allele on gene expression.

312

313   **Modulation of target gene methylation by environmental risk factors**

314   We first tested if variation in DNA CpG methylation was associated with variation in target gene

315   expression, independently of SNP effects, using data from the Biobank-based Integrative Omics Study

316   (BIOS) consortium that is described in detail elsewhere [37,38]. Methylation and expression levels in

317   whole-blood   samples   (n=2,101)   were   quantified   respectively   with   Illumina   Infinium

318   HumanMethylation450 BeadChip Kit arrays and RNA-seq (2x50bp paired-end, Hiseq2000, >15M read

319   pairs per sample). For each target gene, we identified CpG sites in *cis* (<250 Kb from gene) for which

320   methylation levels were significantly associated with gene expression levels (FDR<5%), after adjusting

321   the methylation levels for methyation-associated SNPs and expression levels for expression-associated

322   SNPs. Such CpG sites, called *cis*-eQTMs, were identified in a previous study [37] and downloaded from

323   http://genenetwork.nl/biosqtlbrowser. For most genes, there were multiple *cis*-eQTMs, and so we

324   selected the CpG site most strongly associated with variation in gene expression for downstream

325   analyses.

326   Next, we tested the association between methylation levels at these sentinel CpGs with five

327   established risk factors for allergic disease using data from unrelated individuals of the Netherlands

328   Twin Register (NTR) study, which was included in the BIOS consortium studies [37,38]. The risk factors

329   tested were current smoking (n=1,221), maternal smoking (n=637), BMI (n=1,214), birth weight

330   (n=1,015) and number of older siblings (n=775). Information on BMI and current smoking was

331   collected as part of the NTR biobank project [39] at blood draw. Birth weight was obtained in multiple

332   NTR surveys as previously described [40]. Maternal smoking during pregnancy was measured in NTR

333   Survey 10 (data collection in 2013) with the following question: Did your mother ever smoke during

334   pregnancy? with answer categories: no, yes, I don't know. Information on the number of older siblings

335   was obtained through self-report in NTR surveys 2, 3 and 6. For twin pairs, the answers were checked

336   for consistency and missing data for one twin were supplemented with data from the co-twin where

337   possible. Linear or logistic regression was used to test the association between methylation (β-value)

338   and individual risk factors, with the following variables included as covariates: sex, age at blood

339   sampling, methylation array row, bisulphite plate and white blood cell percentages (% neutrophils, %

340   monocytes, and % eosinophils). The association with maternal smoking was tested while also adjusting

341   for smoking status.

342

343   **Data availability**

344   Summary statistics of the meta-analysis without the 23andMe study will be made publicly available at

345   the time of publication. The full GWAS summary statistics for the 23andMe discovery data set will be

346   made available through 23andMe to qualified researchers under an agreement with 23andMe that

347   protects the privacy of the 23andMe participants. Please contact David Hinds (dhinds@23andme.com)

348   for more information and to apply to access the data.

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450

35 known loci

Target genes	N target genes	N sentinel variants
STMN3	1	1
[ZNF217]	0	1
[NFATC2]	0	1
ORMDL3,CCR7,RP11-94L15.2,ZPBP2,GSDMB	7	4
CLEC16A-[]-RMI2,RMI2-[]--LITAF	0	2
AAGAB	1	1
FOXA1-[]--TTC6	0	1
NFKBIA,PPP2R3C,KIAA0391,FAM177A1	4	1
NAB2,STAT6,SUOX,RPS26,PA2G4,MYL6B,ERBB3	8	2
KIRREL3-AS3---[]--ETS1	0	1
WNT11--[]-LRRC32	0	3
OVOL1,SNX32,RP11-770G2.5,EFEMP2	4	1
[ZNF365]	0	1
GATA3---[]---SFTA1P,GATA3--[]SFTA1P	0	6
IL2RA	1	2
ERMP1	1	3
[MYC]	0	1
MIR5708--[]--ZBTB10	0	1
ITGB8--[]-ABCB5,[ITGB8]	0	2
HLA-C,MCCD1P1,HLA-DQA1,GPANK1,PRRC2A	5	7
SLC22A4,SLC22A5,C5orf56,IL13	4	3
CAMK4,SLC25A46,TSLP,CTC-551A13.2,WDR36	5	4
PTGER4	1	1
IL7R	1	1
KIAA1109	1	2
TLR1	1	1
FBXO45-[]-CEP19	0	1
RP11-132N15.2,RP11-132N15.1,BCL6	3	4
[GLB1]	0	1
BOLL,RFTN2,MARS2,PLCL1	4	1
MFSD9,IL18R1,IL1RL1,IL18RAP	4	2
[LINC00299]	0	1
IL6R	1	1
THEM4,FLG	2	3
RPRD2,C1orf54,TARS2	3	1

64 new loci
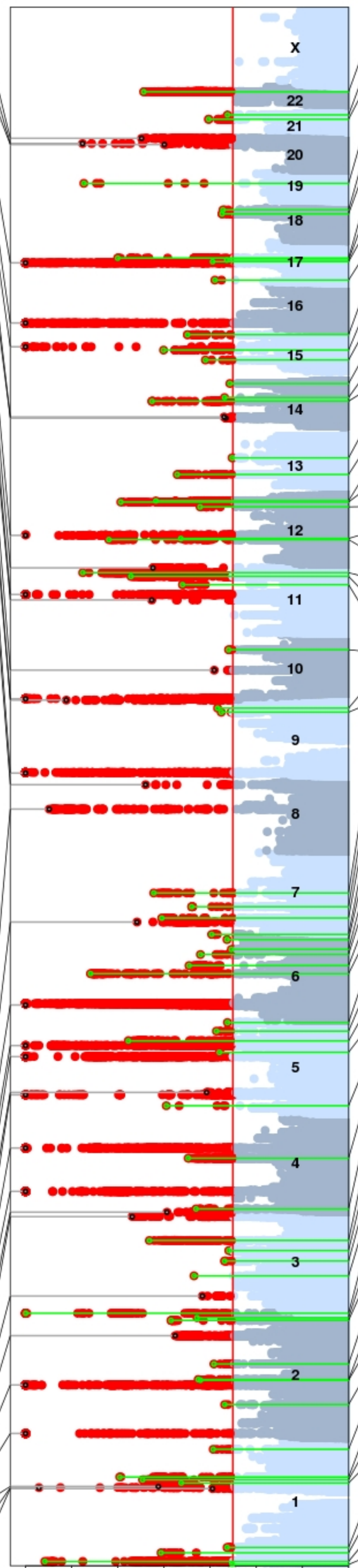
N sentinel variants	N target genes	Target genes
1	11	*C22orf46,PMM1,NHP2L1,CCDC134,PHF5A,CSDC2,MEI1*
1	0	[SIK1]
1	0	[RUNX1]
1	0	SLC7A10-[]-CEBPA
1	1	*PIGN*
1	1	*DYNAP*
1	1	*GNGT2*
1	2	*MAP3K14-AS1,SPATA32*
1	0	[STAT5B]
1	1	*ALOX15*
1	2	*IQGAP1,CRTC3*
1	1	*RP11-554D20.1*
1	2	*RTF1,ITPKA*
1	0	RCOR1-[]-TRAF3
1	0	JDP2-[]-BATF
1	0	[RAD51B]
1	0	PIBF1-[]-KLF5
1	0	[FOXO1]
1	10	*SBNO1,ABCB9,ARL6IP4,OGFOD2,PITPNM2,RP11-282O18.6*
1	1	*SPPL3*
1	1	*SH2B3*
1	1	*AQP5*
1	1	*HDAC7*
1	0	DDX6-[]-CXCR5
1	2	*PPP2R1B,SIK2*
1	0	SESN3--[]-FAM76B
1	3	*ARL3,TMEM180,ACTR1A*
1	0	C9orf114-[]-LRRC8A
1	1	*FBXW2*
1	1	*GSAP*
1	0	C7orf72-[]-IKZF1
1	1	*JAZF1*
1	0	RNASET2-[]-MIR3939
1	0	[ARID1B]
1	1	*TNFAIP3*
1	0	[PTPRK]
1	0	[ATG5]
1	0	[BACH2]
1	2	*RGS14,RAB24*
1	0	MIR3142-[]-MIR146A
2	2	*NDFIP1,HDAC3*
1	0	[TNFAIP8]
1	1	*FAM105A*
1	0	[MANBA]
1	0	STX18-[]-MSX1
1	1	*RASA2*
1	4	*SLC15A2,EAF2,IQCB1,CD86*
1	1	*SENP7*
1	0	LINC00870--[]-RYBP
1	0	[D2HGDH]
1	1	*INPP5D*
1	0	CCL20-[]-DAW1
1	1	*ARHGAP15*
1	0	[IL1B]
2	0	BCL2L11--[]--ANAPC1
1	0	[LOC339807]
1	0	[ITPKB]
2	0	TNFSF18--[]-TNFSF4
1	1	*CD247*
1	7	*FCER1G,B4GALT3,ADAMTS4,PPOX,F11R,USF1,TOMM40L*
1	0	SFPQ-[]-ZMYM4
1	1	*RUNX3*
1	2	*RERE,RP5-1115A15.1*
1	1	*TNFRSF14*

rs61816761:A (chr1:152 Mb)
[FLG]
Asthma
1.03
1.26
1.32
Eczema   Hayfever
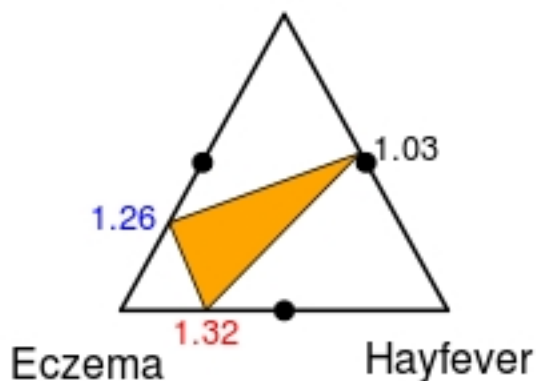
rs12123821:T (chr1:152 Mb)
RPTN-[]-HRNR
Asthma
1.05
1.18
1.16
Eczema   Hayfever
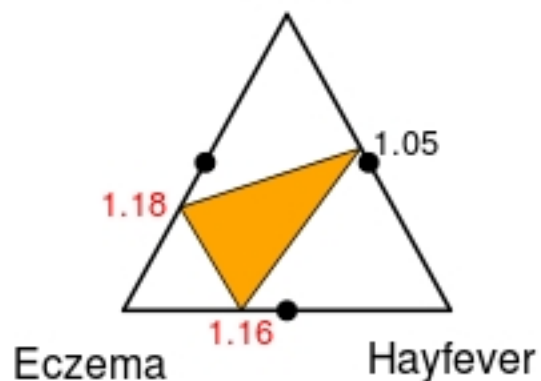
rs12470864:A (chr2:103 Mb)
IL1RL2-[]-IL18R1
Asthma
1.07
1.01
1.07
Eczema   Hayfever

rs6594499:C (chr5:110 Mb)
WDR36-[]-CAMK4
Asthma
1.02
1.05
1.06
Eczema   Hayfever
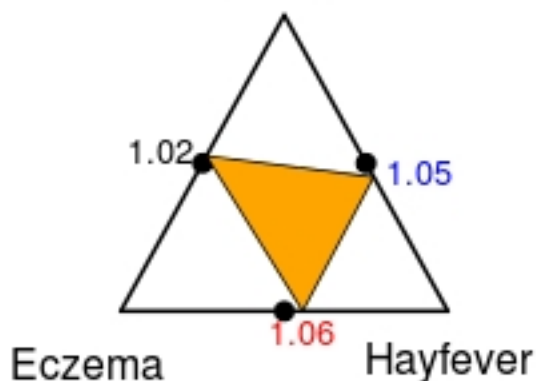
rs61839660:T (chr10:6 Mb)
[IL2RA]
Asthma
1.11
1.06
1.05
Eczema   Hayfever
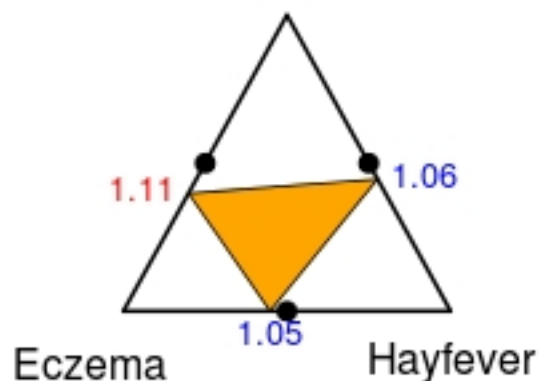
rs921650:A (chr17:38 Mb)
[GSDMB]
Asthma
1.08
1.04
1.06
Eczema   Hayfever

rs2228145:C (chr1:154 Mb)
[IL6R]
Asthma
1.01
1
1
Eczema   Hayfever
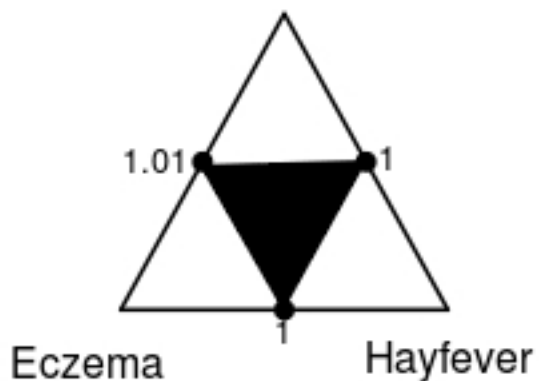
Enrichment in tissue-specific gene expression

Enrichment in tissue-specific SNP heritability

Legend:
- Cardiovascular/Musculoskeletal
- Digestive/Endocrine
- Immune
- Nervous
- Reproductive/Urinary
- Respiratory/Skin

Y-axis: Enrichment -log10(P)

P=0.0002

P=0.05

Tissues with strongest enrichment in SNP heritability:
1. CD4+_CD25-_IL17+_PMA_Ionomycin_stim_Th17_primary:H3K4me1
2. CD4_memory_primary:H3K4me1
3. CD4+_CD25-_IL17-_PMA_Ionomycin_stim_MACS_Th_primary:H3K4me1
4. CD4+_CD25-_CD45R0+_memory_primary:H3K4me1
5. CD4+_CD25-_Th_primary:H3K4me1
6. CD4+_CD25+_CD127-_Treg_primary:H3K4me1
7. CD8_memory_primary:H3K4me1
8. Th1:H3K27ac
9. CD4_naive_primary:H3K4me1
10. Th0:H3K27ac

X-axis: ENCODE tissue-specific regulatory annotation

Biological process enrichment

1. GO:0008624 induction_of_apoptosis_by_extracellular_signals
2. GO:0012502 induction_of_programmed_cell_death
3. GO:0006917 induction_of_apoptosis
4. GO:0045086 positive_regulation_of_interleukin-2_biosynthetic_process
5. GO:0031294 lymphocyte_costimulation
6. GO:0031295 T_cell_costimulation
7. GO:0030888 regulation_of_B_cell_proliferation
8. GO:0002695 negative_regulation_of_leukocyte_activation
9. GO:0042100 B_cell_proliferation
10. GO:0016311 dephosphorylation

Random genes:
— Ascertained from allergy loci
— Ascertained from random loci
— Ascertained from all genes

P=0.05