Shared and Distinct Genetic Risk Factors for Childhood Onset and Adult Onset Asthma

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Background

Childhood and adult onset asthma differ with respect to severity and co-morbidities. Whether they also differ with respect to genetic risk factors has not been previously investigated.

Methods

We used data from the UK Biobank to conduct genome-wide association studies (GWASs) in 9,433 childhood onset asthma (onset before age 12) and 21,564 adult onset asthma (onset between ages 26 and 65) cases, each compared to 318,237 non-asthmatic controls (older than age 38), and for age of onset in 37,846 asthma cases. Enrichment studies determined the tissues in which genes at GWAS loci were most highly expressed, and PrediXcan, a transcriptome-wide gene-based test, was used to identify candidate risk genes.

Findings

We detected 61 independent asthma loci: 23 were childhood onset specific, one was adult onset specific, and 37 were shared. Nineteen loci were associated with age of asthma onset. Genes at the childhood onset loci were most highly expressed in skin, blood and small intestine; genes at the adult onset loci were most highly expressed in lung, blood, small intestine and spleen. PrediXcan identified 113 unique candidate genes at 22 of the 61 GWAS loci.

Interpretation

Genetic risk factors for adult onset asthma are largely a subset of the genetic risk for childhood onset asthma but with overall smaller effects, suggesting a greater role for non-genetic risk factors in adult onset asthma. In contrast, the onset of disease in childhood is associated with additional genes with relatively large effect sizes. Combined with gene expression and tissue enrichment patterns, we suggest that the establishment of disease in children is driven more by allergy and epithelial barrier dysfunction whereas the etiology of adult onset asthma is more lung-centered, with immune mediated pathways driving disease progression in both children and adults.

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Key Words: asthma GWAS, adult onset asthma, childhood onset asthma, transcriptome, UK Biobank

Introduction

Asthma is the most prevalent chronic respiratory disease worldwide[1]. Its diagnosis is based on the presence of reversible airflow obstruction and clinical symptoms that include wheeze, cough, and shortness of breath. Despite these shared features, asthma is likely many different conditions. In particular, childhood onset asthma and adult onset asthma differ with respect to sex ratios, triggers of exacerbation, associated co-morbidities, severity[2,3], and potentially also for genetic risk factors[4,5]. For example, the most replicated and significant genome-wide association study (GWAS) single nucleotide polymorphisms (SNPs) at the 17q12-21 locus are specific to asthma with onset of symptoms in early life[6]. Only one asthma GWAS to date was performed in adult onset cases. The GABRIEL Consortium included 1,947 cases with adult onset asthma (defined as 16 years of age or older) and 3,669 adult controls[7]. Overall, genome-wide significant variants in the combined sample of 10,365 cases and 16,110 controls revealed larger odds ratios (ORs) in the childhood onset group compared to the adult onset group, but no loci reached significance in the adult onset cases, likely due to low power. It remains unknown, therefore, whether loci other than 17q12-21 contribute specifically to childhood onset or adult onset asthma. Delineating genetic risk factors affecting age of onset from those that are shared between childhood and adult onset asthma could provide insights into the molecular mechanisms contributing to different clinical manifestations of asthma that is diagnosed at different ages.

To address this question and directly compare genetic risk architectures of adult onset and childhood onset asthma, we leveraged the U.K. Biobank (UKB), a large-scale prospective study collecting demographic, clinical, medical history, and genetic data for

79 nearly 500,000 participants[8]. We performed asthma GWASs in 9,433 adults with a
80 diagnosis of asthma before age 12 years (childhood onset cases) and 21,564 adults
81 with a diagnosis of asthma between age 26 and 65 years (adult onset cases), each
82 compared to 318,237 adults (>38 years) who did not have a diagnosis of asthma or
83 chronic obstructive lung disease (COPD) (controls). In addition, we conducted an age of
84 onset GWAS in 37,846 asthma cases. Our goals were to identify shared and distinct
85 genetic risk loci for childhood and adult onset asthma, and to identify genes that may
86 mediate the effects of associations at age of onset specific loci and those shared
87 between childhood and adult onset asthma.
88

89 **Methods**

90 Sample composition and case definitions

91 Data for 376,358 British white individuals from the UKB data release July 2017 were
92 used[8]. We extracted disease status (asthma, allergic rhinitis, atopic dermatitis (AD),
93 food allergy, COPD, emphysema, chronic bronchitis), age of onset of asthma, and sex
94 from self-reported questionnaires and hospital records (ICD10 codes) by querying our
95 in-house protected UKB database server. See our 'reproducible research' and other
96 details in the appendix (pp. 3-12).

97 We defined childhood and adult onset asthma using strict age of onset criteria
98 that would minimize the likelihood of misclassification, and considered asthma cases
99 with onset < 12 years of age as childhood onset cases (n=9,433) and with onset > 25
100 and before 66 years of age as adult onset cases (n=21,564). UKB participants without
101 an asthma diagnosis were included as controls (n=318,237). Individuals with COPD,

102 emphysema or chronic bronchitis were excluded from adult onset cases and controls.
103 For the age of onset GWAS, we included an additional 6,849 asthmatics with onset
104 between the ages of 12 and 25 years of age. Characteristics of the sample are shown in
105 Table 1. After genotype quality control, 10,894,596 variants were available for analyses.
106 See appendix (pp. 4-5) for additional details on genotype QC and phenotype definitions.
107
108 Genome-wide association studies
109 We conducted a childhood onset and adult onset GWAS by logistic regression and an
110 age of onset GWAS by linear regression, both using the allele dosages under an
111 additive genetic model, as implemented in Hail (https://github.com/hail-is/hail). In all
112 three GWASs, we included sex and the first 10 genetic principal components as
113 covariates and used a genome-wide significance threshold of $5x10^{-8}$. FUMA[9], an
114 integrative post-GWAS annotation web-based tool, was used to define independent risk
115 loci and identify enriched tissues. FUMA defines independent loci using linkage
116 disequilibrium (LD) information from the 1000 Genomes project[10]. We specified an r^2
117 threshold >0.6 between genome-wide significant SNPs to represent a single locus.
118 Tissue enrichments were calculated in FUMA using a hypergeometric test to determine
119 overrepresentation of genes mapped to risk loci (by physical distance) among highly
120 expressed genes in each tissue in GTEx relative to all others.
121 Childhood onset and adult onset specific loci were defined as those that were
122 genome-wide significant in either the childhood onset or adult onset GWAS but were not
123 associated with asthma at $p<0.05$ in other group, and the 95% confidence intervals

124 (CIs) of the respective ORs did not overlap. All other GWAS loci that were genome-wide
125 signficant in at least one of the two GWASs were considered to be shared.
126
127 Sensitivity analysis to adult onset misclassification
128 We performed sensitivity analysis to assess the effects of potential poor recall of age of
129 onset among the adult onset asthmatics. In particular, to assure that the adult onset
130 cases did not include a significant proportion of childhood onset asthma in which
131 symptoms remitted in early life but then relapsed in adulthood. To this end, we replaced
132 adult onset cases with increasing proportions of randomly selected childhood onset
133 cases, and then tested for association at the two most significant childhood onset
134 specific loci. This procedure was repeated 20 times for each proportion to quantify the
135 sampling variability (appendix pp. 8-10).
136
137 Predicted transcriptome association test
138 We used the PrediXcan[11] framework to identify genes that may mediate associations
139 between genetic variants and asthma risk. PrediXcan is a software tool that estimates
140 tissue-specific gene expression profiles from an individual's SNP genotype profile using
141 prediction models trained in large references databases of genotypes and tissue-
142 specific gene expression profiles. Using these genotype-imputed expression profiles,
143 PrediXcan can perform gene-based association tests that correlate predicted
144 expression levels with phenotypes (e.g., asthma) to identify candidate causal genes
145 from GWAS data. We used a summary version of PrediXcan, which has high
146 concordance with the individual level version (R^2 >0.99)[12]. For predictions, we

147 downloaded elastic net models trained with reference transcriptome data from the GTEx
148 consortium[13] (http://predictdb.org) for 49 tissues (appendix Table 1).
149 PrediXcan was run separately in the childhood onset and adult onset cases,
150 each with the same controls. Significance was determined using a Bonferroni correction
151 for the 38,608 genes ($p<1.29x10^{-6}$) that were expressed in the five tissues determined
152 by FUMA to be enriched (skin, lung tissue, whole blood, small intestine and spleen; see
153 Results). We defined childhood onset specific genes as those whose predicted
154 expression is significantly associated with childhood onset asthma and the variants that
155 predict their expression are within childhood onset specific loci. Adult onset specific
156 genes were similarly defined. Because SNPs at shared loci may predict the expression
157 of genes that are be associated only in childhood onset or adult onset cases, we also
158 considered genes to be age of onset specific if they were significantly associated with
159 asthma at $p<1.29x10^{-6}$ in one age group and not associated with asthma at $p<0.05$ in
160 the other. All other genes were considered shared.
161

162 ## Results

163 Genome-wide association studies of asthma

164 We first conducted GWASs of childhood onset and adult onset asthma. These studies
165 revealed 61 independent loci associated with asthma, 52 were significant in the
166 childhood onset asthma GWAS and 19 were significant in the adult onset asthma
167 GWAS ($p<5x10^{-8}$) (Figure 1). Thirty-one of the 61 loci, in 30 chromosomal regions, were
168 not previously reported in the GWAS catalog or in a recent large GWAS of asthma[14,15].
169 Among the 31 new loci, 17 were significant in the childhood onset GWAS, one was

170 significant in the adult onset GWAS, and 13 were significant in both (Table 1). Some of
171 these loci contained genes that have been associated with asthma in candidate gene
172 studies (e.g., *TLR10*[16] and *TLR6*[17,18] in the childhood onset GWAS; *FADS2*[19],
173 *MUC5AC*[20,21] and *TBX21*[22] in both GWASs), which provide independent validation of
174 our GWAS findings.

175 As in previous GWASs comprised largely of children, the most significant locus in
176 the childhood onset GWAS is at 17q12[23], with the lead SNP in the *GSDMB* gene
177 (Figure 1A). However, the estimated ORs for the lead SNPs at three other loci were
178 similar to or larger than the lead SNP at the 17q locus. The lead SNPs in *IL1RL1* at
179 2q12.1 and in *EMSY* at 11q13.5 had effect sizes on childhood onset asthma similar to
180 the lead SNP in *GSDMB* on 17q (Table 1). Both loci have been prominent in previous
181 asthma GWAS. The lead SNP at the 1q21.3 locus, corresponding to a nonsense
182 mutation (R501X) in the filaggrin (*FLG*) gene at 1q21.3, had the largest OR overall.
183 Variants in *FLG* have been robustly associated with food allergies[24-26] and AD[27-29], but
184 previous associations with asthma have been in the context of other allergic
185 conditions[15,30]. Whether variants in *FLG* are associated with risk for childhood onset
186 asthma independent of its effects on early life allergic disease is yet unknown.

187 To address this possibility, we repeated the childhood onset GWAS after
188 excluding 3,205 childhood onset cases and 5,785 controls who reported having a
189 history of allergic rhinitis, AD or food allergy. As expected in a smaller sample the p-
190 values were overall larger, but the ORs were strikingly similar (appendix Figure 1 and
191 Table 2). Even though the OR at the *FLG* locus on 1q21.3 decreased from 1.97 (95% CI
192 1.82, 2.13) to 1.61 (95% CI 1.49, 1.74), it remained both highly significant ($p=2.45x10^{-}$

193 [19]) and the largest OR for childhood onset. These results suggest both a critical role for
194 the allergic diasthesis in the development of asthma in childhood and a shared
195 architecture between allergic disease and childhood onset asthma, as previously
196 discussed[30,31].

197 The most significant association in the adult onset GWAS was in the HLA region,
198 with independent associations at the HLA-C/B (6p21.33) and HLA-DR/DQ (6p21.32) loci
199 (Figure 1B). Compared to the childhood onset GWAS, effect sizes were quite small in
200 adult onset cases, with ORs reaching 1.1 at only five loci (2q12.1, 6p21.33, 6p21.32,
201 9p24.1, 10p14) (Table 2).

202 Among the 61 asthma loci, 23 were specific to childhood onset asthma and one
203 was specific to adult onset asthma (Table 2A-B). Regional association plots for the 23
204 loci with childhood or adult onset specific effects are shown in appendix Figure 2.
205 Among the remaining 38 shared loci (Table 2C), mean ORs were larger in the childhood
206 onset cases at all but six loci (permutation test $p<10^{-4}$; appendix p.10-11), indicating that
207 both more loci contribute to childhood onset asthma and even among shared loci, effect
208 sizes are larger in childhood onset asthma cases (Figure 2).

209 Finally, to directly test for loci associated with asthma age of onset, we
210 conducted a third GWAS including all asthma cases in UKB who met our inclusion
211 criteria (n=37,846). In this analysis, 19 loci were associated with age of onset ($p<5x10^{-8}$)
212 (appendix Figure 3 and Table 3). Age of onset loci overlapped with both the childhood
213 and adult onset specific and shared loci, and asthma risk alleles were nearly all
214 associated with earlier age of onset (Table 2; Figure 2). SNPs a the 1q21.3 locus (*FLG*)
215 had the largest effect on age of onset, with each copy of the asthma risk allele

216 (rs61816761) associated on average with 4.57 (SE 0.43) years earlier onset compared
217 to individuals without the risk allele ($p=8.15x10^{-27}$). At the 17q12 locus (rs4795399) each
218 copy of the risk allele was associated on average with 2.29 (SE 0.13) years earlier
219 onset compared to individuals without the risk allele ($p=6.76x10^{-65}$). Examples of
220 significant age of onset effects at these and other loci are shown in Figure 3. Overall,
221 both childhood onset specific and shared asthma risk loci were associated with younger
222 ages of onset, and alleles at loci associated with younger ages of onset had larger
223 effects compared to alleles at loci associated with later ages of onset.
224
225 Tissue-specific expression of genes at associated loci
226 Using an unbiased approach, we asked whether the tissue-specific expression of genes
227 that map to the 52 childhood onset loci differed from the tissue-specific expression of
228 genes mapped to the 19 adult onset loci. Genes at childhood onset loci (Figure 1A)
229 were most highly expressed in skin, whole blood, and small intestine (lower ileum)
230 compared to all other tissues, whereas genes at adult onset loci (Figure 1B) were most
231 highly expression in lung, whole blood, small intestine (lower ileum), and spleen
232 (enrichment for higher expression, $p<10x10^{-3}$) (appendix Figure 4 and Table 4). These
233 patterns suggest both overlapping and distinct underlying pathways and mechanisms
234 associated with asthma that begins in childhood and asthma with onset in adulthood.
235
236 Predicted transcriptome-wide association test
237 To better understand molecular pathways and to narrow the list of candidate causal
238 genes at associated loci, we focused on the five tissues that most highly expressed the

239 genes at childhood onset or adult onset loci: skin, lung tissue, whole blood, small
240 intestine, and spleen. We used PrediXcan[11] to identify genes whose expression is
241 predicted by variants associated with asthma in the childhood onset or adult onset
242 GWAS and potentially mediate the effects of associated SNPs on asthma risk.
243 This analysis identified 113 unique, candidate causal genes at 22 of the 61
244 GWAS loci ($p<1.4x10^{-6}$) (Figures 4-5) (appendix Figures 5-6 and Table 5). These
245 included 39 genes associated with childhood onset asthma at eight of the childhood
246 onset specific loci and 76 genes associated with childhood and/or adult onset asthma at
247 13 of the shared loci. Variants at the one adult onset specific locus at 2q22.3 did not
248 predict the expression of any genes in the five tissues.
249 The predicted genes most significantly associated with childhood onset asthma
250 were at the 17q12 locus (Z score >10) in skin (*ORMDL3*, *ERBB2*, *PGAP3*, *GSDMA*, 2
251 long noncoding RNAs), lung (*ORMDL3*, *GSDMB*, *GSDMA*, *PGAP3*, *PNMT*), blood
252 (*ORMDL3*, *GSDMB*, *IKZF3*, *MED24*), small intestine (*GSDMA*, *GSDMB*, *PGAP3*), and
253 spleen (*ORMDL3*, *GSDMB*, *ZPBP2*, *MED24*). Some genes were predicted to be more
254 highly expressed in asthmatics (e.g., *ORMDL3*, *GSDMB*, *PGAP3*, *ERBB2*), while others
255 were predicted to be less expressed in asthmatics (e.g., *GSDMA*, *MED24*, *IKZF3*)
256 (Figure 4A).This pattern of expression reflects the broad regulatory effects of SNPs and
257 tissue specificifity of gene expression at this locus[23]. The childhood onset asthma locus
258 at 1q21.3 includes genes essential for epidermal differentiation and maintaining
259 essential barrier function. The predicted expression of nine genes at this locus were
260 associated with childhood onset asthma. Higher predicted expression of *CRNN*, *CRCT1*
261 and *THEM5* in skin, of *PSDM4* in lung and blood, and of *LINGO4* in skin, lung, and

262 blood were associated with increased asthma risk. Lower predicted expression of
263 *SPRR2D* in skin, of *S100A12* in lung and blood, of *FLG* in skin, lung and spleen, and of
264 *TDRKH* in skin, lung, blood and spleen were associated with increased asthma risk.
265 *S100A12* has been previously implicated in asthma[32] and *FLG* variants have been
266 associated with AD and food allergies, and asthma in the context of other allergic
267 diseases[15,24-30]. Other childhood onset specific genes previously implicated in asthma
268 but not previously reported in asthma GWASs are *CCL20*[33] at 2q36.3 and *TLR10*[16] at
269 4p14 in whole blood, and *TLR6*[17,18] at 4p14, *AP5B1* at 11q13.1 and *SERPINB7*[34] at
270 18q21.33 in skin.

271 The 5q31.1 region had independent loci that were both childhood onset specific
272 and shared in the GWASs. Although the predicted expression of all eight asthma genes
273 at this extended locus were shared, five genes were more significantly associated with
274 childhood onset asthma: higher predicted expression of *RAD50* in skin but lower
275 predicted expression of *SEPT8* in skin and lung, *IL4* in skin, lung and blood, and *AFF4*
276 small intestine were associated with increased risk for asthma (Figure 4B). The
277 remaining three genes had similar associations with childhood and adult onset asthma,
278 with predicted lower expression of *IRF1* in skin and spleen and predicted higher
279 expression of *PDLIM4* in skin and *SLC22A5* in all five tissues associated with increased
280 asthma risk. *IL4, RAD50, SLC22A5* and *PDLIM4* have been highlighted in previous
281 asthma GWAS[35,36], and *KIF3A* was identified in a GWAS of the atopic march[37] and
282 associated with childhood onset asthma in a candidate gene study[38].

283 In contrast to all other loci, predicted expression of 44 genes at two independent
284 shared loci in the HLA region (6p21.32 and 6p21.33; referred to as the HLA region from

285 hereon in) were associated with childhood asthma only (n=1; in skin and lung), adult
286 onset asthma only (n=3; in skin only), or both (n=39; in multiple tissues). (Figure 5). The
287 shear number of genes in this region with predicted expression associated with asthma,
288 the generally broad tissue expression patterns, and three associated with asthma only
289 in adult onset cases are consistent with this locus being among the two most signficant
290 loci in nearly all asthma GWASs, and the most significant locus in a previous small
291 GWASs of adult onset asthma[7] and in adults with asthma[36,39].
292 Among the remaining 37 shared loci (Figure 2B), SNPs at 12 predicted the
293 expression of 23 unique genes, all of which were associated with both childhood onset
294 and adult onset asthma. These include *IL18R1*, *IL18RAP*, and *ILRL2* at 2q12.1 in
295 multiple tissues, *TSLP* at 5q22.1 in skin, *SMAD3* at 15q22.33 in skin and blood, *LRP1* at
296 12q13.3 in skin, *IL4R* at 16p12.1 in blood, and *CLEC16A* at 16p13.13 in lung. Loci
297 associated with *IL18R1*, *IL18RAP*, *IL18RAP, ILRL2, TSLP, SMAD3*, *LRP1*, *IL4R* and
298 *CLEC16A* were reported in previous asthma GWAS[15,35,40].
299

300 ## Discussion

301 This study is the first large GWAS of age of onset of asthma to include both childhood
302 and adult onset cases. These GWASs revealed 61 independent asthma loci, 23 specific
303 to childhood onset, one specific to adult onset, and 37 shared; with overall larger effect
304 sizes for childhood onset asthma at nearly all loci. Moreover, the predicted expression
305 of 41 of the 113 implicated genes were associated specifically with childhood onset
306 asthma, compared to the predicted expression of three genes associated specifically
307 with adult onset asthma. Our findings of more childhood onset asthma loci and

308 potentially causal genes and the larger effect sizes of risk alleles in childhood onset
309 cases are particularly striking given that there were nearly 2.5-times more adult onset
310 than childhood onset cases in this study. Thus, despite having substantially less power
311 to detect loci specific to childhood onset asthma, our analyses revealed many more
312 childhood onset asthma loci. Similarly, the asthma risk alleles at 19 loci identified in the
313 age of onset GWAS were all associated with younger age of onset. These findings are
314 consistent with decreased estimates of asthma heritability with increasing age of
315 onset[41]. Taken together, our study shows for the first time that genetic risk for adult
316 onset asthma is largely a subset of the genetic risk loci for childhood onset asthma, but
317 with overall smaller effect sizes, suggesting a larger role for environmental risk factors in
318 adult onset asthma.

319 Despite the overlap of adult onset and childhood onset loci, distinct causal
320 pathways contributing to each were suggested by tissue enrichments: childhood onset
321 loci were enriched for genes with highest expression in skin whereas adult onset loci
322 were enriched for genes with highest expression in lung and spleen; both were enriched
323 for genes highly expressed in whole blood and small intestine. The highlighting of skin
324 as a target tissue for childhood onset asthma supports the widely held idea that asthma
325 in childhood is due to impaired barrier function in the skin and other epithelial surfaces.
326 This model proposes that compromised epithelial barriers promote sensitization to food
327 and airway allergens and to wheezing illnesses in early life[31,42]. In fact, childhood onset
328 specific loci identified here have been associated with AD or food allergies, such as
329 *FLG* on 1q21.3 with the atopic march[37], AD[27-29] and food allergies[24-26], *KIF3A* on 5q31.1
330 and *AP5B1*/*OVOL1* on 11q13.1 with the the atopic march[37] and AD[43], *SERPINB7* on

331 18q21.33 with food allergies[34], and *CRNN* (cornulin) on 1q21.3 with AD concomitant
332 with asthma and reduced expression in AD-affected skin[44]. Variants at those loci were
333 all associated with earlier age of asthma onset. We further show that these loci are
334 associated with childhood onset asthma, even after exclusion of cases with a history of
335 allergic diseases. In contrast, the enrichment for genes highly expressed in lung and
336 spleen at adult onset loci suggests a more lung-centered, and potentially immune
337 mediated, etiology for asthma with onset later in life. The prominant role of the HLA
338 region in the adult onset asthma GWAS and the fact that predicted expression of three
339 HLA region genes was associated only with adult onset asthma only further highlights a
340 central role for immune processes driving asthma pathogenesis in adults. The fact that
341 both childhood onset and adult onset asthma loci were enriched for genes that are most
342 highly expressed in whole blood cells and small intestine further indicate a shared
343 immune etiology, as suggested from a large GWAS that included both children and
344 adults[35].
345 Combining GWAS with a transcriptome-wide association test that uses
346 combinations of associated SNPs to predict gene expression in different tissues
347 revealed significant complexity at the two most highly associated asthma loci. SNPs at
348 the 17q12 locus predicted expression of 18 childhood onset asthma genes and SNPs at
349 the HLA region predicted expression of 42 genes: three were associated with adult
350 onset asthma and most were not HLA genes *per se*. In this regard, it is notable that the
351 *HLA-DRB1*, *HLA-DQB1*, and *HLA-DQA1* genes, which are the most associated HLA
352 loci with autoimmune diseases, are predicted to have reduced expression in both
353 childhood onset and adult onset asthma. Instead, HLA genes with less clear functions

354 have increased predicted expression in asthma (Figure 5). These results strengthen the
355 argument that multiple genes contribute to asthma risk at the HLA and 17q12 loci and
356 probably account for the highly significant GWAS p-values observed at these loci in
357 nearly all studies. It is also likely that these genes have both tissue specific and broad
358 effects in epithelium, lung, and immune tissues.

359 The new loci identified in our study include the first adult onset asthma specific
360 association at 2q22.3. The lead SNP at 2q22.3 is intergenic between *TEX41* and
361 *ACVR2A*. The predicted expression of *ACVR2A* was not associated with asthma in our
362 study, despite it being expressed in lung, blood, small intestine and spleen. *TEX41* was
363 not expressed in any of the five tissues investigated. Interestingly, a GWAS also
364 performed in UKB subjects implicated variants near *TEX41* in heavy vs. never smoking
365 behavior[45]. However, even after removing adult onset cases and controls with reported
366 'ever smoking', the p-value for this SNP remained significant and the OR slightly
367 increased (OR 1.077 [95% CI 1.05, 1.11], $p=2.26x10^{-8}$; n=12,132 cases and 176,704
368 controls). Variants in or near this gene, which encodes a lincRNA, have been
369 associated with cardiovascular and immune mediated traits[14], making this a potentially
370 interesting candidate gene for adult onset asthma.

371 Our study had limitations. First, diagnoses of asthma and allergic disease in
372 study subjects were from self reported questionnaires and medical records (ICD10
373 codes). Thus, it is possible that diagnoses, age of onset, or both are misspecified in
374 some subjects. On the one hand, the large sample size and our ability to replicate
375 nearly all previously reported asthma loci (appendix Table 6) suggest that our analyses
376 were robust to any inaccuracies in the data. On the other hand, it is possible that the

377 adult onset asthmatics included cases with poor recall of childhood onset asthma in
378 which symptoms remitted and then relapsed later in life[46]. Our sensitivity analysis
379 suggested that if even as few as 5% of the adult onset cases were misclassified we
380 should have observed some signal of association at childhood onset loci, which we did
381 not. Second, the gene expression data used to predict candidate target genes included
382 heterogeneous tissues and were collected mostly from adults. As a result, our study
383 may have missed relevant genes whose expression is developmentally regulated or
384 environment specific. Our finding of candidate genes at only 22 of the 61 asthma loci
385 may be due in part to the importance of both in asthma pathogenesis. Moreover, all
386 inference based on gene expression is using imputed expression. It is possible,
387 therefore, that some relevant genes were more difficult to impute and not included in our
388 analysis, although a recent comparative study showed that PrediXcan is a more robust
389 method for prediction of gene expression than other related methods[47]. Third, because
390 of the ethnic composition of the UKB, this study was limited to individuals of European
391 ancestry only. As a result, we could not evaluate the genetic risk architecture or assess
392 the effects of age of onset specific loci in other populations. Lastly, although many of the
393 new loci discovered in our GWASs include genes previously implicated in asthma, the
394 new genetic associations reported here need to be replicated in other populations.
395 In the largest asthma GWAS to date, we show that genetic risk loci for adult
396 onset asthma is largely a subset of the loci associated with childhood onset asthma,
397 with overall smaller effect sizes for onset at later ages. These data suggest that
398 childhood onset specific loci and those associated with age of onset play a role in
399 disease initiation, whereas the other associated loci reflect shared pathways of disease

progression. The differences in the target tissues that most highly express the genes at associated loci and the predicted expression of genes at age specific and shared loci provides additional genetic and molecular evidence for both shared and distinct pathogenic pathways in childhood onset and adult onset asthma. It is therefore likely that the most effective treatments will also differ between these two groups, and that strategies for precision medicine should be further personalized to account for age of asthma onset.

Author's Contributions

All authors were involved in the conception and design of the study and in writing the manuscript. M. P. and N.S. conducted all analyses and prepared figures and tables, under the overall supervision of D.L.N., C.O., and H.K.I.

URLs

UK Biobank, [https://www.ukbiobank.ac.uk/]

Hail: https://github.com/hail-is/hail

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550 Table 1. Characteristics of the asthma cases and controls. NA, not applicable.

	Childhood Onset (N=9,433)	Adolescent or Young Adult Onset (N=6,849)	Adulthood Onset (N=21,564)	Controls (N=318,237)
Age at recruitment (yr)				
Mean (±SD)	55±8	52±8	57±8	57±8
Range	40 - 70	40 - 70	40 - 70	39 - 73
Age at asthma onset (yr)[a]				
Mean (±SD)	6±3	19±4	44±10	NA
Range	0 - 11	12 - 25	26 - 65	NA
Sex (% female)	40.7	57.4	63.6	53.5
Asthma medication use in the past 12 months, N (%)	1,383 (14.7)	1,124 (16.4)	4,081 (18.9)	NA
Current smokers N (%)	802 (8.5)	688 (10.0)	1,379 (6.4)	30,056 (9.4)
Allergic diseases ever				
Allergic rhinitis, N (%)	2,537 (26.9)	2,042 (29.8)	4,660 (21.6)	27,289 (8.6)
Atopic dermatitis, N (%)	1,126 (11.9)	473 (6.9)	927 (4.3)	7,168 (2.3)
Food allergy, N (%)	138 (1.5)	63 (0.9)	172 (0.8)	1,229 (0.4)
Any allergic disease, N (%)	3,205 (34.0)	2,321 (33.9)	5,306 (24.6)	33,808 (10.6)

551

Table 2. Regions with SNPs that were genome-wide significant in the childhood onset or adult onset GWAS. Information for the SNP with smallest p-value at each locus is shown.

Locus[a]	rsID	Position[b]	Nearby Genes[c]	Allele[d]	RAF[e]	Childhood Onset Asthma GWAS			Adult Onset Asthma GWAS			Age of Onset GWAS		
						OR	95% CI	p-value	OR	95% CI	p-value	Beta	SE	p-value
A. Childhood Onset Specific Loci														
1q21.3	rs61816761	1:152285861	*FLG, HRNR, FLG2*	G/A	0.024	1.970	1.823-2.129	1.88E-65	1.016	0.948-1.088	6.56E-01	-4.571	0.426	8.15E-27
1q25.1	rs7518129	1:173163568	*TNFSF4, TNSF18, PRDX6*	A/G	0.310	1.111	1.077-1.146	2.21E-11	0.997	0.977-1.019	8.17E-01	-0.849	0.145	4.89E-09
2q36.3[f]	rs10175070	2:228670575	*CCL20, SLC18A3*	A/G	0.251	1.122	1.086-1.160	4.31E-12	1.000	0.978-1.023	9.92E-01	-0.862	0.154	2.24E-08
3q28	rs12634152	3:188121019	*LPP, FLJ42393, LPP-AS1*	C/T	0.547	1.133	1.100-1.166	1.08E-16	1.007	0.987-1.027	4.98E-01	-0.968	0.136	1.21E-12
4p14	rs5743618	4:38798648	*TLR1, TLR10, TLR6*	A/C	0.774	1.249	1.203-1.295	3.19E-32	1.008	0.985-1.032	5.09E-01	-1.578	0.163	4.53E-22
5q13.2[f]	rs10036789	5:71695918	*PTCD2, ZNF366*	C/G	0.460	1.085	1.054-1.117	4.51E-08	1.016	0.996-1.036	1.12E-01	-0.511	0.137	1.95E-04
5q31.1[f]	rs2051809	5:132056874	*KIF3A, IL4, CCNI2*	C/A	0.247	1.175	1.137-1.214	3.24E-22	1.016	0.994-1.040	1.58E-01	-0.933	0.155	1.59E-09
6p25.3[f]	rs9391997	6:409119	*IRF4, DUSP22, EXOC2*	A/G	0.527	1.102	1.070-1.135	6.89E-11	0.995	0.976-1.015	6.35E-01	-0.597	0.136	1.06E-05
7p15.3[f]	rs34880821	7:2277545	*IL6, TOMM7*	G/A	0.283	1.106	1.071-1.141	4.73E-10	1.000	0.979-1.022	9.88E-01	-0.667	0.149	7.59E-06
8q24.21[f]	rs13277355	8:128777719	*MYC, TMEM75*	G/A	0.274	1.110	1.075-1.146	1.65E-10	1.013	0.991-1.036	2.46E-01	-0.660	0.151	1.20E-05
9q34.3[f]	rs117137535	9:140500443	*ARRDC1, ZMYND19, EHMT1*	G/A	0.026	1.307	1.195-1.429	4.16E-09	0.977	0.913-1.046	5.10E-01	-2.464	0.446	3.42E-08
10p15.1[f]	rs943451	10:6621773	*PRKCQ, PFKFB3, SFMBT2*	C/T	0.318	1.125	1.091-1.161	7.51E-14	1.021	1.000-1.043	5.30E-02	-0.613	0.145	2.54E-05
11q13.1[f]	rs479844	11:65551957	*AP5B1, OVOL1*	A/G	0.555	1.106	1.074-1.139	1.48E-11	1.015	0.995-1.035	1.41E-01	-0.657	0.135	1.22E-06
11q23.3[f]	rs12365699	11:118743286	*CXCR5, DDX6*	A/G	0.833	1.167	1.120-1.216	1.57E-13	1.004	0.978-1.031	7.43E-01	-1.396	0.185	4.42E-14
12q13.2[f]	rs62623446	12:55368291	*TESPA1, MUCL1, NEUROD4*	C/T	0.072	1.188	1.127-1.252	1.40E-10	1.038	0.999-1.077	5.32E-02	-1.079	0.253	1.95E-05
12q24.12[f]	rs10774625	12:111910219	*ATXN2, SH2B3, BRAP*	A/G	0.504	1.087	1.056-1.119	2.07E-08	0.997	0.978-1.017	7.92E-01	-0.713	0.135	1.43E-07
12q24.31[f]	rs1696361	12:121363823	*SPPL3, HNF1A*	C/T	0.359	1.109	1.076-1.142	1.19E-11	1.019	0.998-1.040	6.96E-02	-0.696	0.140	6.84E-07
17q12	rs4795399	17:38061439	*GSDMB, ZPBP2, ORMDL3*	C/T	0.529	1.406	1.365-1.448	1.45E-111	1.005	0.985-1.025	6.28E-01	-2.286	0.134	6.76E-65
17q21.2[f]	rs8066625	17:40390629	*STAT5B, GHDC, STAT5A*	G/A	0.100	1.151	1.098-1.206	4.90E-09	1.006	0.973-1.040	7.33E-01	-0.846	0.227	1.88E-04
17q21.32[f]	rs56308324	17:45819206	*TBX21, TBKBP1, OSBPL7*	A/T	0.132	1.132	1.086-1.180	3.47E-09	1.025	0.996-1.055	8.72E-02	-0.714	0.195	2.54E-04
18q21.33[f]	rs4574025	18:60009814	*TNFRSF11A, KIAA1468, ZCCHC2*	C/T	0.535	1.090	1.058-1.122	9.25E-09	0.986	0.967-1.006	1.69E-01	-0.871	0.136	1.61E-10
18q21.33[f]	rs12964116	18:61442619	*SERPINB7, SERPINB11, SERPINB2*	A/G	0.036	1.336	1.247-1.432	2.56E-16	1.005	0.953-1.059	8.62E-01	-1.916	0.351	4.87E-08
19p13.3[f]	rs4807630	19:1170445	*SBNO2, GPX4, STK11*	C/T	0.308	1.093	1.060-1.128	2.06E-08	1.013	0.992-1.035	2.32E-01	-0.487	0.147	9.25E-04
B. Adult Onset Specific Loci														
2q22.3[f]	rs12617922	2:146156679	*TEX41, ACVR2A*	A/G	0.518	0.983	0.955-1.012	2.36E-01	1.066	1.045-1.087	1.59E-10	0.478	0.136	4.46E-04
C. Shared Asthma Loci														
1q32.1	rs12023876	1:203093201	*ADORA1, PPFIA4*	T/G	0.668	1.102	1.068-1.137	1.11E-09	1.032	1.010-1.053	3.37E-03	-0.567	0.144	8.65E-05
2p25.1	rs13416555	2:8441735	*RNF144A, ID2*	G/C	0.705	1.130	1.094-1.167	1.94E-13	1.040	1.018-1.063	3.50E-04	-0.715	0.150	1.91E-06
2q12.1	rs72823641	2:102936159	*IL1RL1, IL1RL2, IL18R1*	A/T	0.863	1.415	1.349-1.484	3.01E-46	1.109	1.077-1.142	3.72E-12	-1.687	0.208	4.73E-16
2q37.3	rs34290285	2:242698640	*D2HGDH, ING5, GAL3ST2*	A/G	0.745	1.177	1.137-1.219	2.06E-20	1.081	1.056-1.106	2.16E-11	-0.821	0.159	2.56E-07
3p22.3[f]	rs35570272	3:33047662	*GLB1, TRIM71, TMPPE*	G/T	0.396	1.100	1.068-1.133	2.68E-10	1.046	1.025-1.067	9.84E-06	-0.454	0.138	1.03E-03
4q27	rs2069763	4:123377482	*IL2, ADAD1, IL21*	C/A	0.334	1.126	1.092-1.160	1.59E-14	1.032	1.011-1.054	2.44E-03	-0.631	0.142	8.39E-06
5p15.2[f]	rs16903574	5:14610309	*FAM105A, TRIO, OTULIN*	C/G	0.077	1.236	1.174-1.302	9.01E-16	1.052	1.013-1.091	7.75E-03	-1.055	0.250	2.51E-05
5q22.1	rs1837253	5:110401872	*SLC25A46, TSLP*	T/C	0.740	1.211	1.169-1.253	2.33E-27	1.088	1.064-1.113	2.77E-13	-0.733	0.158	3.72E-06
5q31.1	rs17622378	5:131778452	*C5orf56, SLC22A5, IRF1*	G/A	0.573	1.103	1.071-1.136	8.52E-11	1.077	1.055-1.098	3.17E-13	-0.044	0.137	7.46E-01
6p22.1[f]	rs1117490	6:30170510	*TRIM26, TRIM15, TRIM39*	T/C	0.234	1.100	1.063-1.137	2.78E-08	1.059	1.036-1.084	6.83E-07	-0.453	0.158	4.07E-03
6p21.33	rs2428494	6:31322197	*HLA-B, HLA-C, MICA*	T/A	0.477	1.157	1.124-1.191	7.94E-23	1.104	1.082-1.126	4.77E-23	-0.648	0.136	1.78E-06
6p21.32	rs28407950	6:32626348	*HLA-DQA1, HLA-DQB*	T/C	0.756	1.354	1.306-1.405	1.27E-59	1.148	1.121-1.175	7.67E-31	-1.284	0.163	4.03E-15
6q15	rs1321859	6:91011673	*BACH2, MAP3K7*	T/C	0.649	1.102	1.068-1.136	9.32E-10	1.076	1.054-1.098	5.68E-12	-0.268	0.144	6.28E-02
7p21.1[f]	rs4473914	7:20426263	*ITGB6, MACC1, ABCB5*	C/T	0.604	1.092	1.060-1.125	9.02E-09	1.035	1.014-1.056	8.44E-04	-0.338	0.139	1.51E-02
7p15.1[f]	rs917115	7:28172586	*JAZF1, TAX1BP1, CREB5*	T/C	0.208	1.112	1.074-1.152	1.73E-09	1.042	1.017-1.067	7.35E-04	-0.577	0.164	4.17E-04
8q21.13	rs4739738	8:81291645	*TPD52, ZBTB10*	A/G	0.359	1.117	1.084-1.151	3.45E-13	1.057	1.036-1.079	8.63E-08	-0.450	0.140	1.27E-03
9p24.1	rs992969	9:6209697	*RANBP6, IL33*	G/A	0.252	1.248	1.209-1.289	6.76E-42	1.100	1.076-1.125	3.14E-17	-1.026	0.152	1.35E-11
10p14[f]	rs7894791	10:8591369	*GATA3, CELF2*	A/C	0.587	1.103	1.071-1.137	9.43E-11	1.024	1.004-1.045	1.94E-02	-0.494	0.137	3.24E-04
10p14	rs1775554	10:9054340	*GATA3, CELF2*	C/A	0.577	1.117	1.084-1.150	2.85E-13	1.121	1.098-1.143	5.17E-29	-0.002	0.138	9.91E-01
11p15.5[f]	rs12788104	11:1123739	*MUC6, MUC5AC*	A/G	0.688	1.029	0.997-1.061	7.99E-02	1.064	1.041-1.087	1.41E-08	0.147	0.148	3.22E-01
11q12.2[f]	rs174621	11:61630104	*FADS2, FADS1, FADS3*	A/G	0.772	1.013	0.978-1.049	4.63E-01	1.071	1.046-1.097	1.46E-08	0.508	0.163	1.87E-03
11q13.5[g]	rs61894547	11:76248630	*EMSY, THAP12, LRRC32*	C/T	0.052	1.463	1.382-1.548	2.17E-39	1.093	1.047-1.141	5.46E-05	-2.227	0.284	4.42E-15

	rs7936312	11:76293726	*EMSY, LRRC32*	G/T	0.477	1.194	1.160-1.230	4.89E-33	1.060	1.040-1.081	4.10E-09	-0.978	0.134	3.49E-13
12q13.11	rs56389811	12:48205358	*HDAC7, SLC48A1, VDR*	T/C	0.761	1.022	0.988-1.058	2.11E-01	1.078	1.054-1.104	2.36E-10	0.485	0.161	2.55E-03
12q13.2	rs705699	12:56384804	*RAB5B, CDK2, SUOX*	G/A	0.425	1.106	1.074-1.139	1.43E-11	1.052	1.031-1.072	6.10E-07	-0.481	0.136	4.20E-04
12q13.3	rs3122929	12:57509102	*STAT6, NAB2, LRP1*	C/T	0.404	1.134	1.101-1.167	6.59E-17	1.061	1.040-1.082	5.73E-09	-0.564	0.138	4.07E-05
12q21.1 [f]	rs11178648	12:71533210	*TSPAN8, PTPRR, LGR5*	T/C	0.592	1.087	1.055-1.120	4.16E-08	1.052	1.031-1.073	6.62E-07	-0.183	0.138	1.86E-01
13q32.3	rs1887704	13:99974492	*UBAC2, DOCK9, TM9SF2*	C/G	0.681	1.124	1.089-1.161	5.48E-13	1.048	1.026-1.070	1.57E-05	-0.476	0.147	1.15E-03
14q24.1	rs1950897	14:68760141	*RAD51B, ZFYVE26, ZFF36L1*	T/C	0.287	1.096	1.062-1.131	1.38E-08	1.031	1.009-1.053	5.39E-03	-0.520	0.148	4.52E-04
15q22.2	rs11071559	15:61069988	*RORA, ANXA2, VPS13C*	T/C	0.872	1.205	1.151-1.262	2.57E-15	1.069	1.037-1.101	1.22E-05	-0.958	0.210	5.11E-06
15q22.33	rs56062135	15:67455630	*SMAD3, SMAD6, AAGAB*	C/T	0.237	1.194	1.156-1.234	2.97E-26	1.083	1.058-1.108	6.27E-12	-0.681	0.155	1.10E-05
16p13.13	rs35032408	16:11215424	*CLEC16A, CIITA, RMI2*	G/T	0.785	1.152	1.111-1.195	4.59E-14	1.073	1.048-1.100	1.10E-08	-0.568	0.169	7.91E-04
16p12.1	rs3785356	16:27349168	*IL4R, NSMCE, IL21R*	C/T	0.297	1.122	1.087-1.157	5.69E-13	1.036	1.014-1.058	1.24E-03	-0.641	0.147	1.30E-05
16q12.1	rs2066844	16:50745926	*NOD2, SNX20, CYLD*	C/T	0.048	1.194	1.121-1.272	3.52E-08	1.049	1.003-1.097	3.76E-02	-0.743	0.306	1.54E-02
17q21.33	rs28406364	17:47454507	*ZNF652, PHB*	C/T	0.377	1.108	1.076-1.142	1.39E-11	1.036	1.015-1.057	6.55E-04	-0.489	0.140	4.81E-04
19q13.11	rs10414065	19:33721455	*LRP3, CEBPA*	T/C	0.934	1.207	1.133-1.287	6.37E-09	1.108	1.064-1.155	1.01E-06	-1.078	0.291	2.12E-04
21q22.12	rs11088309	21:36464631	*RUNX1, SETD4*	C/G	0.143	1.039	0.997-1.083	6.82E-02	1.079	1.050-1.109	4.83E-08	0.063	0.189	7.38E-01

[a]Cytogenetic band. [b]SNP position, Genome Reference Consortium Build 37 (hg19). [c]The gene in which the SNP is located is indicated first, followed by the previous gene and the next gene; for intergenic SNPs, only the previous and next genes are shown. [d]Alleles are shown as non-risk/risk alleles, where the risk allele is the allele associated with increased asthma risk. [e]RAF, risk allele frequency in the UK Biobank. [f]Not reported in previous GWAS. [g]The SNP with the smallest p-value differs in the childhood onset GWAS and the adult onset GWAS at the same locus; both SNPs are shown.

Figure Legends

Figure 1. GWAS of childhood onset and adult onset asthma. Miami plot showing results for the childhood onset versus controls GWAS (blue, panel A) and adult onset versus controls GWAS (red, panel B). Each point corresponds to a SNP; the y-axes show the $-\log_{10}$p-values from the childhood onset GWAS (panel A) and adult onset GWAS (panel B). The x-axis shows the position of each SNP along the 22 autosomes.

Figure 2. Forest plot showing the odds ratios (ORs) and 95% confidence intervals from the childhood onset (blue) and adult onset (red) GWASs, and betas and standard errors (gray) from the age of onset GWAS for the 61 asthma associated loci. Left panel: Childhood onset specific loci (top) and adult onset specific locus (bottom); right panel: Shared loci. Loci within each group are sorted by OR in the childhood onset GWAS (largest to smallest).

Figure 3. Age of onset effects (ORs) for lead SNPs at three genome-wide signficant childhood onset specific loci (1q21.3, 4p14 and 17q12), and three genome-wide signficant shared loci (2q12.1, 6p21.32, and 11q13.5). The sample sizes for the age of onset bins are [0,5]: n=4,637; [6,10]: n=4,255; [11,15]: n=2,684; [16,20]: n=2,128; [21,25]: n=2,578; [26,30]: n=2,923; [31,35]: n=2,599; [36,40]: n=3,571; [41,45]: n=2,967; [46,50]: n=3,266, [51,55]: n=2,544; [56,65]: n=3,694.

Figure 4. Results of PrediXcan studies at non-HLA region loci. Genes whose predicted expression was significantly associated with asthma in either the childhood onset cases or the

adult onset cases are shown for skin (left panels), lung (middle panels) and whole blood (right panels). Values shown for skin combine both sun exposed and not sun exposed skin, showing the most significant statistic of the two. Results using gene expression in spleen and small intestine are shown in appendix Figure 5. The z-scores on the x- and y-axes are from transcriptome-wide tests of association with asthma using SNP sets that predict the expression of that gene. The diagonal dashed lines show the expected when associations are the same in the childhood onset and adult onset cases. The horizontal/vertical dashed lines correspond to z-scores ±4.84 ($p=1.29x10^{-6}$); the horizontal/vertical dotted lines correspond to z-scores ±1.96 (p=0.05). Colored backgrounds correspond to the chromosome location of each gene (see Key). Upper panels: Genes that are associated with childhood onset asthma (no genes were associated with adult onset asthma). Lower panels: Shared genes associated with both childhood onset and adult onset asthma. HLA region genes (6p21.32 and 6p21.33) are shown in Figure 5.

Figure 5. Results of PrediXcan studies of HLA region genes. Genes in the HLA region whose predicted expression was associated with childhood onset or adult onset asthma are shown for skin (left panel), lung tissue (middle panel) and whole blood (right panel). Results using gene expression in spleen and small intestine are shown in appendix Figure 6. The genes on darker shaded backgrounds correspond to shared genes; the four genes on lighter color backgrounds are age-specific. See Figure 4 for additional details.

Figure 1

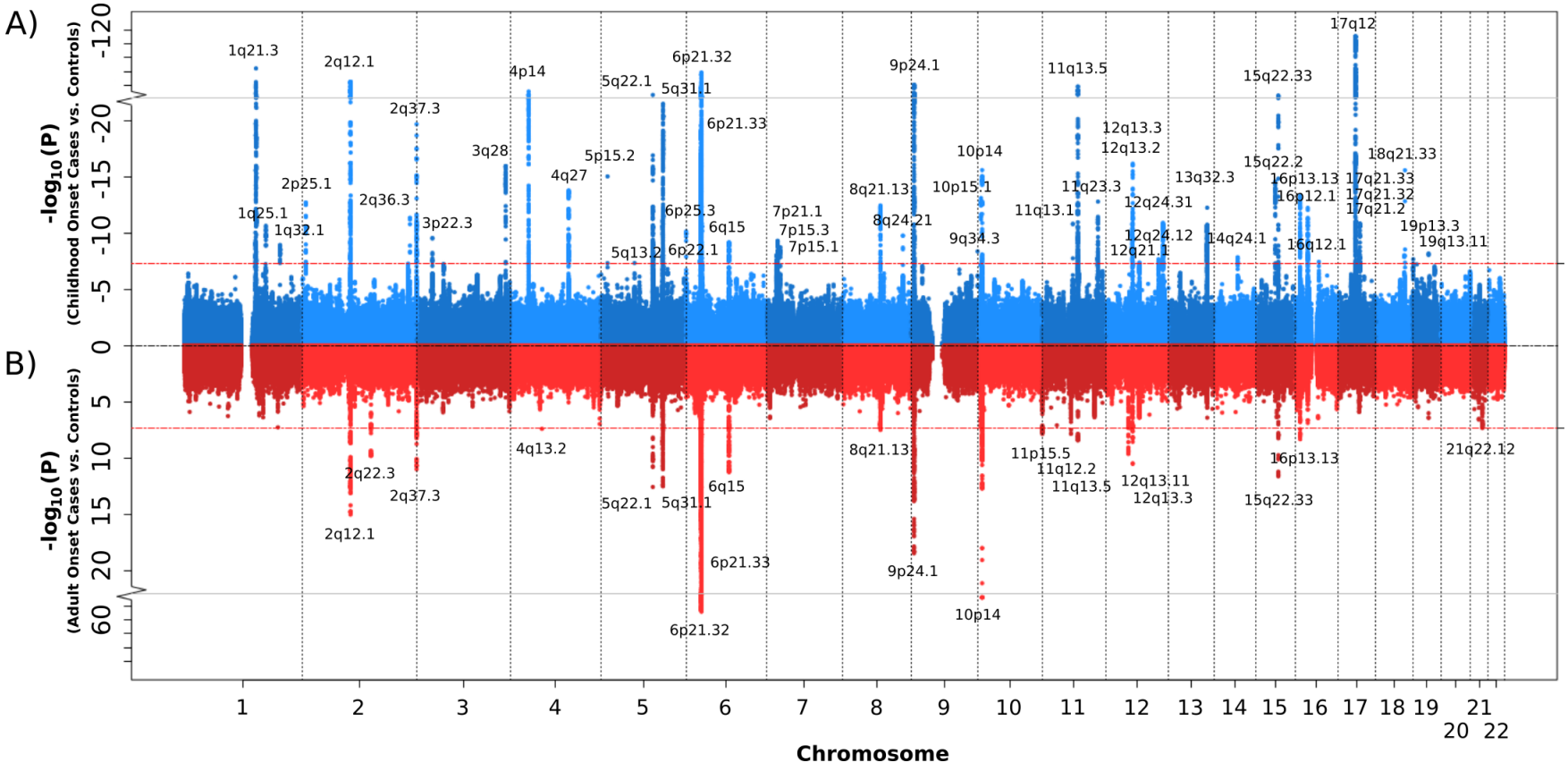

A)
B)
-log10(P)
(Childhood Onset Cases vs. Controls)
(Adult Onset Cases vs. Controls)
-120
-20
-15
-10
-5
0
5
10
15
20
60
1q21.3
2q12.1
2q37.3
4p14
5q22.1
5q31.1
6p21.32
6p21.33
9p24.1
11q13.5
15q22.33
17q12
3q28
5p15.2
4q27
2p25.1
2q36.3
1q25.1
1q32.1
3p22.3
6p25.3
6q15
5q13.2
6p22.1
7p21.1
7p15.3
7p15.1
8q21.13
8q24.21
10p14
10p15.1
9q34.3
11q13.1
11q23.3
12q13.3
12q13.2
12q24.31
12q24.12
12q21.1
13q32.3
14q24.1
15q22.2
16p13.13
16p12.1
16q12.1
17q21.33
17q21.32
17q21.2
18q21.33
19p13.3
19q13.11
4q13.2
2q22.3
2q37.3
2q12.1
5q22.1
5q31.1
6q15
6p21.33
6p21.32
8q21.13
9p24.1
10p14
11p15.5
11q12.2
11q13.5
12q13.11
12q13.3
15q22.33
16p13.13
21q22.12
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
Chromosome

Figure 2

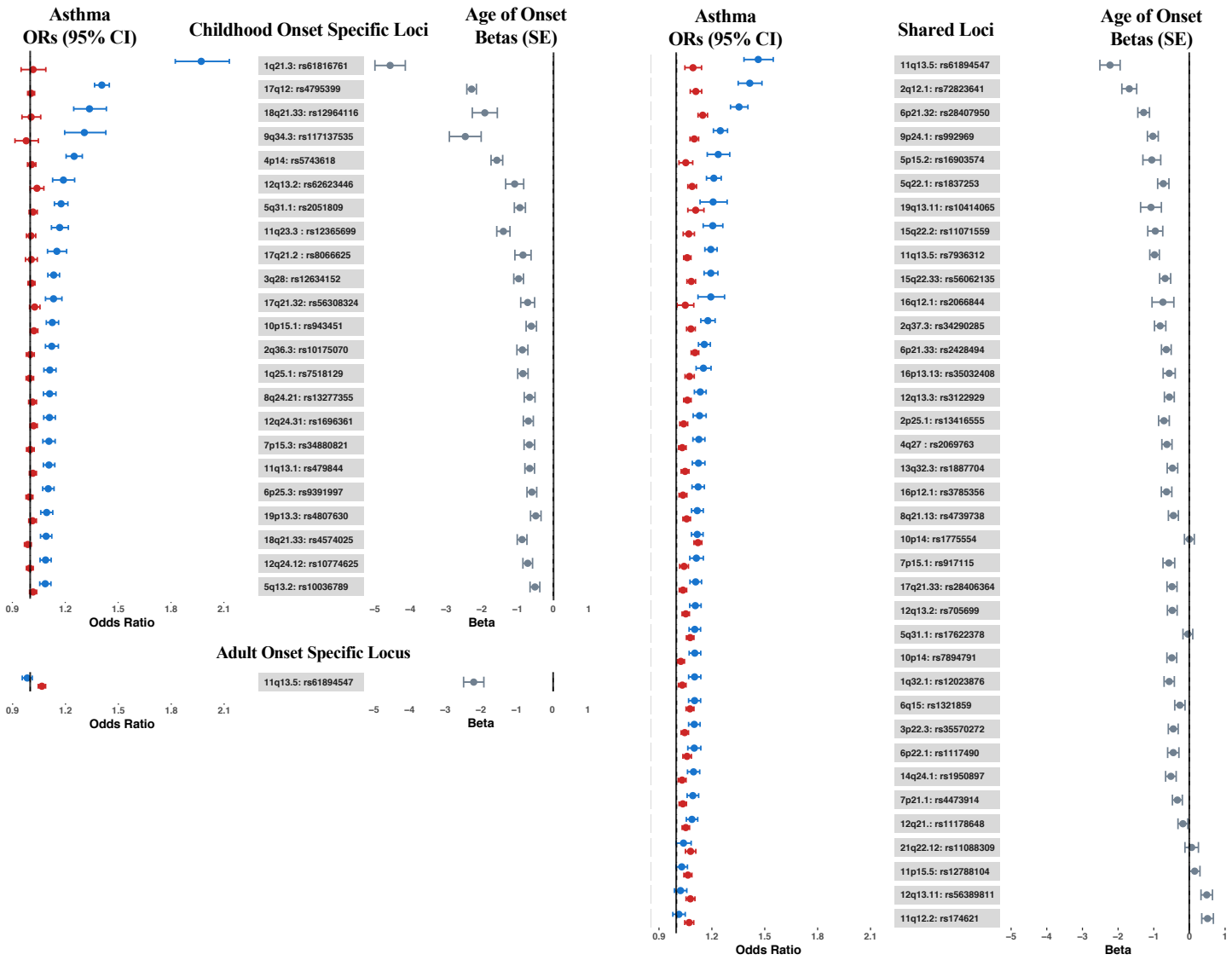

Asthma
ORs (95% CI)
Childhood Onset Specific Loci
Age of Onset
Betas (SE)
1q21.3: rs61816761
17q12: rs4795399
18q21.33: rs12964116
9q34.3: rs117137535
4p14: rs5743618
12q13.2: rs62623446
5q31.1: rs2051809
11q23.3 : rs12365699
17q21.2 : rs8066625
3q28: rs12634152
17q21.32: rs56308324
10p15.1: rs943451
2q36.3: rs10175070
1q25.1: rs7518129
8q24.21: rs13277355
12q24.31: rs1696361
7p15.3: rs34880821
11q13.1: rs479844
6p25.3: rs9391997
19p13.3: rs4807630
18q21.33: rs4574025
12q24.12: rs10774625
5q13.2: rs10036789
0.9
1.2
1.5
1.8
2.1
Odds Ratio
−5
−4
−3
−2
−1
0
1
Beta
Adult Onset Specific Locus
11q13.5: rs61894547
Asthma
ORs (95% CI)
Shared Loci
Age of Onset
Betas (SE)
11q13.5: rs61894547
2q12.1: rs72823641
6p21.32: rs28407950
9p24.1: rs992969
5p15.2: rs16903574
5q22.1: rs1837253
19q13.11: rs10414065
15q22.2: rs11071559
11q13.5: rs7936312
15q22.33: rs56062135
16q12.1: rs2066844
2q37.3: rs34290285
6p21.33: rs2428494
16p13.13: rs35032408
12q13.3: rs3122929
2p25.1: rs13416555
4q27 : rs2069763
13q32.3: rs1887704
16p12.1: rs3785356
8q21.13: rs4739738
10p14: rs1775554
7p15.1: rs917115
17q21.33: rs28406364
12q13.2: rs705699
5q31.1: rs17622378
10p14: rs7894791
1q32.1: rs12023876
6q15: rs1321859
3p22.3: rs35570272
6p22.1: rs1117490
14q24.1: rs1950897
7p21.1: rs4473914
12q21.: rs11178648
21q22.12: rs11088309
11p15.5: rs12788104
12q13.11: rs56389811
11q12.2: rs174621
0.9
1.2
1.5
1.8
2.1
Odds Ratio
−5
−4
−3
−2
−1
0
1
Beta

Figure 3

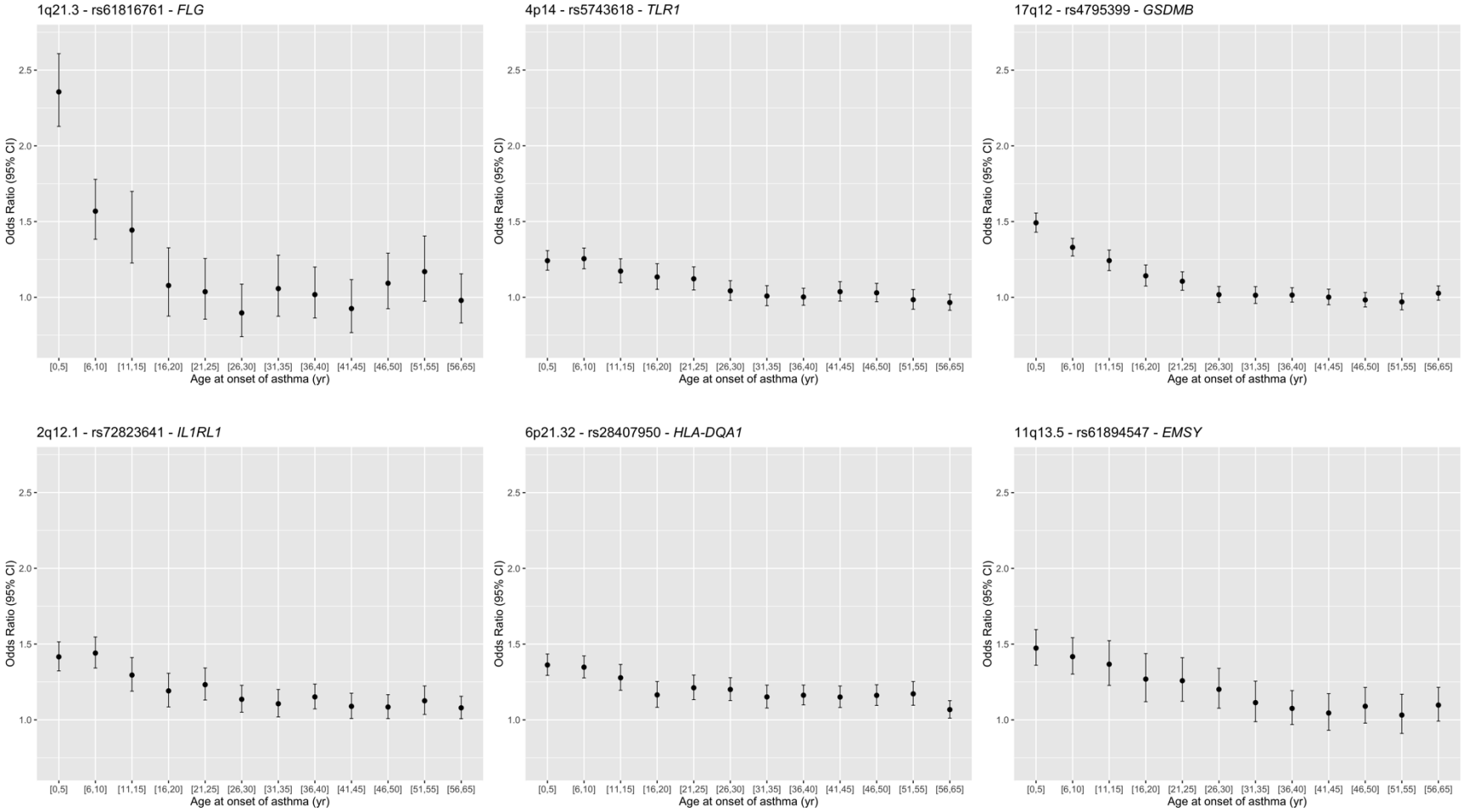

1q21.3 - rs61816761 - *FLG*
4p14 - rs5743618 - *TLR1*
17q12 - rs4795399 - *GSDMB*
2q12.1 - rs72823641 - *IL1RL1*
6p21.32 - rs28407950 - *HLA-DQA1*
11q13.5 - rs61894547 - *EMSY*
Odds Ratio (95% CI)
2.5
2.0
1.5
1.0
[0,5]
[6,10]
[11,15]
[16,20]
[21,25]
[26,30]
[31,35]
[36,40]
[41,45]
[46,50]
[51,55]
[56,65]
Age at onset of asthma (yr)

Figure 4

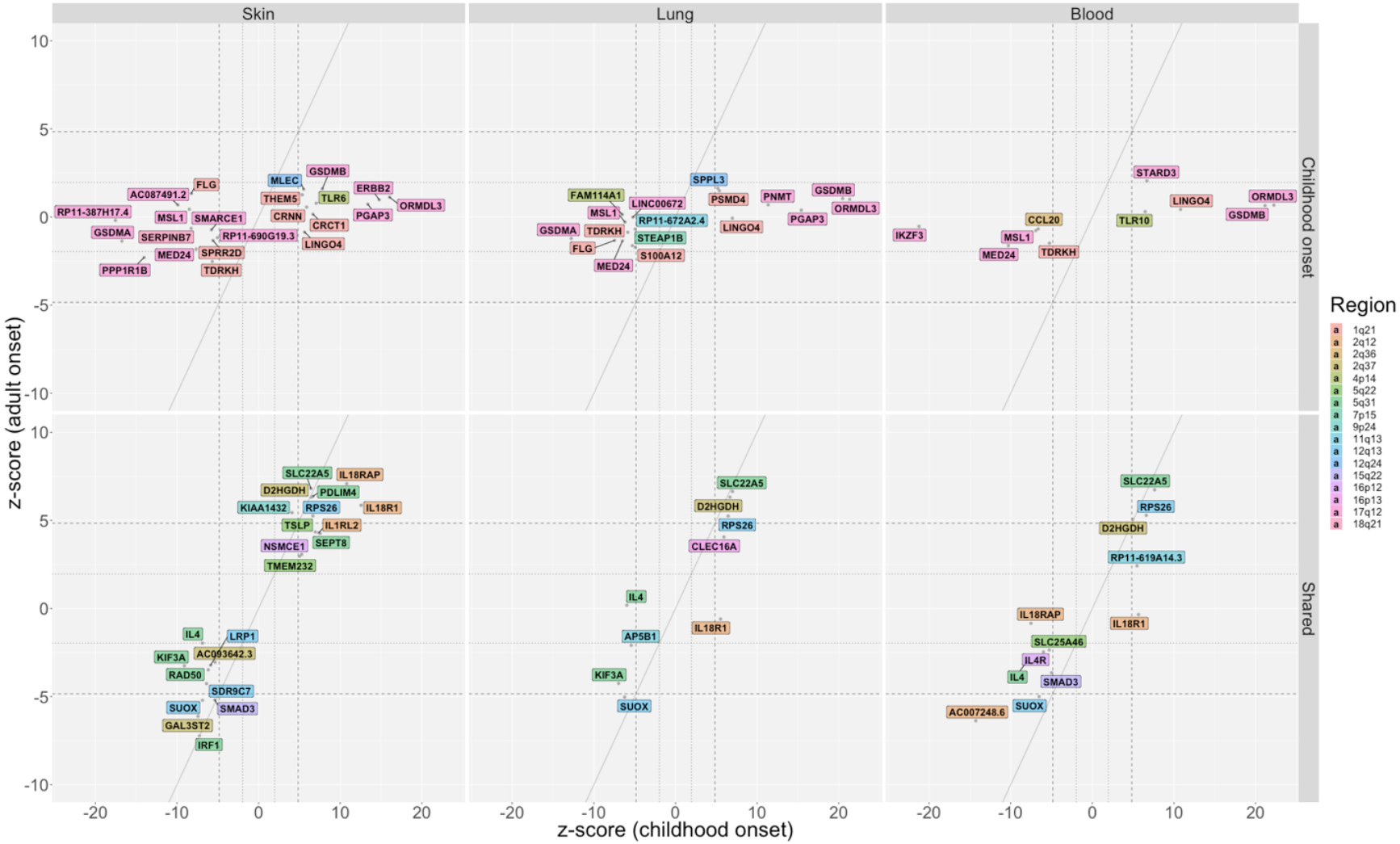
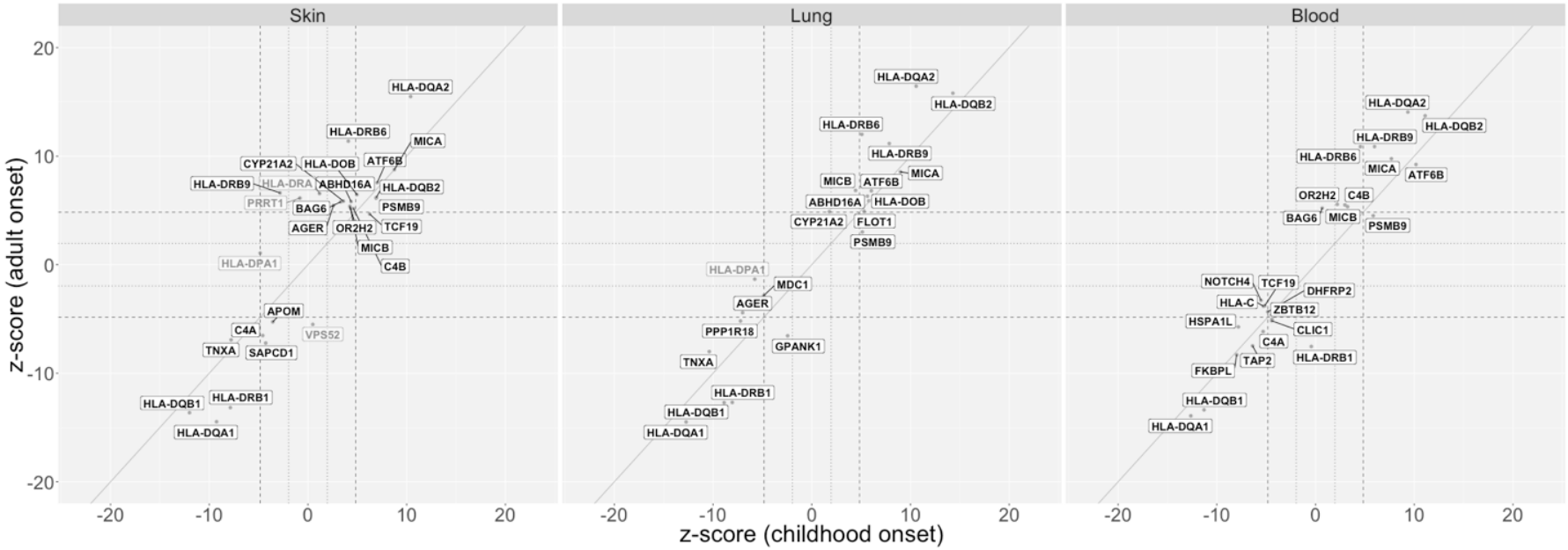

Skin
Lung
Blood
Childhood onset
Shared
z-score (adult onset)
z-score (childhood onset)
Region
1q21
2q12
2q36
2q37
4p14
5q22
5q31
7p15
9p24
11q13
12q13
12q24
15q22
16p12
16p13
17q12
18q21

Figure 5


Skin
Lung
Blood
z-score (adult onset)
z-score (childhood onset)
20
10
0
-10
-20
HLA-DQA2
HLA-DRB6
MICA
CYP21A2
HLA-DOB
ATF6B
HLA-DRB9
HLA-DRA
ABHD16A
HLA-DQB2
PRRT1
BAG6
PSMB9
AGER
OR2H2
TCF19
MICB
C4B
HLA-DPA1
APOM
C4A
VPS52
TNXA
SAPCD1
HLA-DQB1
HLA-DRB1
HLA-DQA1
HLA-DQA2
HLA-DQB2
HLA-DRB6
HLA-DRB9
MICA
MICB
ATF6B
ABHD16A
HLA-DOB
CYP21A2
FLOT1
PSMB9
HLA-DPA1
MDC1
AGER
PPP1R18
GPANK1
TNXA
HLA-DRB1
HLA-DQB1
HLA-DQA1
HLA-DQA2
HLA-DQB2
HLA-DRB9
HLA-DRB6
MICA
ATF6B
OR2H2
C4B
BAG6
MICB
PSMB9
NOTCH4
TCF19
DHFRP2
HLA-C
ZBTB12
HSPA1L
CLIC1
C4A
TAP2
HLA-DRB1
FKBPL
HLA-DQB1
HLA-DQA1