**Genome-wide association analysis identifies 26 novel loci for asthma, hay fever and eczema.**

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**Introductory paragraph**

Heritability estimates has indicated that a large part of the variation of risk of asthma, hay fever and eczema are attributable to genetic variation. With this large GWAS, including 443,068 Caucasian participants, we discovered and validated 26 novel GWAS loci, as well as replicate many previously reported loci, for self-reported asthma, the combined phenotype hay fever/eczema, or the combined phenotype asthma/hay fever/eczema. Many genes, especially those encoding Interleukins, overlapped between diseases, while others are more disease specific. Interestingly, for the *HLA* and *FLG* regions, we identified multiple independent associations to be associated with all phenotypes. Pinpointing candidate genes for common diseases are of importance for further studies that wants to prioritize candidate genes for developing novel therapeutic strategies.

Asthma, hay fever and eczema are common complex diseases, with an underlying architecture that include both environmental and genetic risk factors. However, the major cause of these diseases is believed to be the genetic factors. Family and twin studies have estimated the heritability of asthma to 35-95%[1,2,3], hay fever to 33-91%[2,3], and eczema to 90% in Europeans[4].

Previous genome wide association studies (GWAS) have identified many genetic variants to be associated to asthma, hay fever and eczema. GWAS loci previously reported for asthma includes *IL33, IL1RL1, HLA-DQB1* and *RAD50*[5]. Genetic variants within *HLA-DRB4*, *LRRC32* and *TMEM232* have been associated with hay fever[6]. The strongest known risk factors for developing eczema are the deleterious mutations of the *FLG* gene (encoding filaggrin), resulting in epidermal barrier deficiency[7.8], and a locus, including *FLG*, has also been associated to eczema in previous GWA studies[9,10,11,12,13,14,15,16]. Previous studies have shown a genetic overlap between asthma, hay fever and eczema[17,18], and genetic variants have been identified when analyzing asthma and hay fever together, as a combined phenotype[19].

In this study, we investigated self-reported asthma, hay fever/eczema combined and asthma/hay fever/eczema combined using data from the UK Biobank (UKBB). Hay fever and eczema could not be separated for most of the participants, since they had primarily answered (yes or no) on whether they have either hay fever or eczema. Most previous GWAS for asthma, hay fever and eczema have been conducted in relatively small cohorts that later was meta-analyzed to increase power[20]. Using a large homogenous cohort like UKBB will increase the power to find novel associations and reduce the bias of heterogeneity in disease definition. Even though the phenotypes in the UKBB database are self-reported, the questions are well defined and identical for all participants.

The UKBB database includes 502,682 participants with self-reported medical conditions, diet and lifestyle factors, as well as 820,967 genotyped SNPs and up to 90 million imputed variants. Participants were recruited from all across the UK and aged 37 to 73 years at the time of recruitment between 2006 and 2010. Disease prevalence in UKBB was 11.7% for asthma and 23.2% for hay fever/eczema. Baseline characteristics of UKBB participants included in this study can be found in Table 1.

We first performed a GWAS including the interim release from UKBB (including 116,137 unrelated Caucasian participants and 22,438,073 SNPs) as the discovery cohort. We selected the most significant SNP from each locus for replication. As replication cohort we used 246,360 unrelated Caucasians from the second UKBB release, and a Bonferroni-correction for the number of SNPs selected for each disease was used as replication threshold. For all SNPs that replicated we meta-analyzed the discovery and replication cohort to generate a combined P-value ($P_{meta}$). QC and the final number of included participants in respective analyses are summarized in Table 1, Figure 1 and in the online version of the paper.

We identified 6,337 SNPs at 52 loci (Supplementary Table 1, Supplementary Figure1A-B, $\lambda$=1.33) to be associated with self-reported asthma ($P<1x10^{-6}$). A total 33 loci replicated (Table 2), of which nine were novel GWAS asthma loci. The most significant loci for asthma were found on chromosome 6 (the *HLA* locus), including 3,126 SNPs, with the leading SNP rs28407950 ($P_{meta}$= $5.45x10^{-102}$). Several genes within this region have previously been reported to be associated with asthma (i.e. *MHC, HLA-DQB1, HLA-G* and *HLA-DRB1*)[19,3]. In the novel loci, not previously reported to be associated with asthma, we found i.e. *BACH2, MYOG, LPP, RAD15B, FAM105A, NDFIP1, ABCB5, UBAC2* and *STAT5B. STAT5B* is biologically interesting since it is a transcription factor that previously have been shown to be involved with asthma in rats[21], but to our knowledge, an association has not been reported in humans. STAT5B protein mediates the signal transduction triggered by IL-2, IL-4, CSF1 and different growth hormones[22]. *BACH2* is also functionally interesting since protein encoded by this gene has been shown to stabilize immunoregulatory capacity and repress the differentiation programs in $CD4^+$ T cells[23].

Many loci, previously reported to be associated with asthma, were replicated in our study[3], including: *RAD50, SMAD3, STAT6, IL33, LRRC32, IL1RL1, FLG* and *IL1RL2* (Table 2*)*. In addition, *BACH2* and *LPP* have previously been associated with self reported allergies and other immune diseases[24,25], but to our knowledge not previously with asthma (Table 2). Neither of these loci was genome-wide significantly associated to hay fever/eczema in our discovery cohort, even though the P-values for the most significant SNPs were nominally associated with P = 0.00073

and P =9.33x$10^{-6}$ for rs186060766 (*LPP*) and rs564184433 (*BACH2*) respectively (Supplementary Table 4).

We identified 5,078 SNPs at 48 loci (Supplementary Table 2, Supplementary Figure 2A-B, $\lambda$=1.27) to be associated with self-reported hay fever/eczema. A total of, 42 loci replicated (Table 3) including 14 novel hay fever/eczema loci. The most significant SNP (rs11236797, $P_{meta}$= 7.5x$10^{-76}$) is intergenic with one of the closest genes being *FAM114A1*. This region has previously been reported to be associated with allergy[18]. Within the 14 novel hay fever/eczema loci we found genes including; *DQ658414, ZBTB38, TNFRSF8, CD200R1, ZDHHC12, CXCR5, GLB1, PTPRK, ABCB5, TMEM180, EXD1, IQGAP1, DYNAP* and *EYA2*. Especially, *ZBTB38* is biologically interesting since this gene has previously been shown to be involved in lung function in asthmatics[26], but to our knowledge not previously reported for hay fever or eczema. The top SNP in the *ZBTB38* locus (rs13077048) was nominally significantly associated to asthma in UKBB (P=0.00072). Another interesting candidate is the *CXCR5* locus that we identified to be associated with hay fever/eczema for the first time ($P_{meta}$=2.59x$10^{-11}$). *CXCR5* has previously been reported to be nominally associated with eczema in a previous study (P=5.45x$10^{-6}$)[14], which further strengthen our results. A SNP close to the *CXCR5* promoter has previously been associated with multiple sclerosis probably by influencing the autoimmune response[27]. We also replicated many loci previously reported to be associated with hay fever, eczema or allergy, for example: *FAM114A1, TLR10, TLR1, TLR6, STAT6, NAB2, IL2, ADAD1, KIAA1109, IL21, GATA3, RANBP6* and *IL33*[18, 17, 6, 28] (Table 3).

For the combined analysis asthma/hay fever/eczema we identified 6,512 SNPs at 60 loci, of which 44 replicated (Table 4, Supplementary Table 3, Supplementary Figure 3A-B, $\lambda$=1.30). Out of these 44 loci, four were GWAS novel loci not significantly associated to asthma or hay fever/eczema independently and close to: *AK056081, HIST1H2BD, ZNF365* and *NDUFAF1* (Figure 2). A previous study has shown an increased expression of *HIST1H2BD* in B cells of patients with allergic asthma[29], but to our knowledge, a genetic association has not previously been reported. The most significant SNP in the combined analysis, rs72823641 ($P_{meta}$= 2.988x$10^{-84}$), located within the gene *ILRL1*, was also statistically significant for both asthma ($P_{meta}$=

$1.39x10^{-50}$) and hay fever / eczema ($P_{meta}=4.82x10^{-68}$), with the same direction of effect (Table 2 and 3, Figure 2). Interestingly, many genes seem to overlap between asthma and hay fever/eczema, while others seem to be disease specific (Figure 2). Many regions overlapping for asthma and hay fever/eczema are annotated to Interleukins, a type of cytokine signaling molecule in the immune system, for example *ILRL1, IL2, IL2RA* and *IL4* (Figure 2).

For the discovery cohort, we conditioned on the most significant SNP within each locus with a P-value $<5x10^{-8}$. Interestingly, when conditioning on the most significant SNP within the *HLA* and the *FLG* region, a secondary signal were identified for all phenotypes, indicating that there are more than one independent association within the these loci. The *HLA* region association with immune diseases are particularly complex, and it has been suggested that the HLA region includes many independent regulatory factors[30]. We also found secondary signals for previously reported asthma loci including the genes *TMEM232, STAT6, HLA-DRB1, IL1RL1, IL1RL2, IL18R1* and *IL18RAP.* A secondary signal was also identified for the novel asthma locus, close to the gene *ABCB5.* A locus on chromosome 5, including the gene *TMEM232* and another region including the *STAT6* gene reported a second locus for hay fever/eczema. We identified the same secondary signals reported for asthma and hay fever/eczema when conditioning on the most significant SNPs in the combined analysis.

To investigate how much of the heritability that can be explained by genotyped SNPs we also estimated the array heritability for each disease using GCTA[31]. 730,616 autosomal genotyped SNPs, in a subsample of 116,137 unrelated Caucasians in the discovery cohort, was included in the analysis. The SNP heritability was estimated to 0.38 (0.35-0.41 95% CI) for asthma and 0.30 (0.26-0.32 95% CI) for hay fever/eczema. Compared to the very high estimates for the heritability (33-95%) from family and twin studies[3,1,4], this suggests that a major contribution to the genetic risk for asthma, hay fever and eczema might not be targeted using common genetic variants.

Using information from the Drug Gene Interaction database (DGIdb), we show that at least three of our novel GWAS loci interacts with druggable proteins, i.e. *STAT5B*, *TNFRSF8* and *NDUFAF1*[32].

In summary, we describe 26 novel GWAS loci for asthma, hay fever and eczema, of which at least three interacts with druggable proteins, in the largest GWAS published so far. We also highlight a large amount of shared genetic contribution to these diseases, which indicates that the comorbidity between asthma, hay fever and eczema is at least partly due to shared genetic factors. Pinpointing candidate genes for common diseases are of importance for further studies that wants to prioritize candidate genes for developing novel therapeutic strategies.

**URLs.**

UK Biobank, http://www.ukbiobank.ac.uk/; Drug Gene Interaction Database, http://www.dgidb.org/; GWAS Catalog, https://www.ebi.ac.uk/gwas/; PhenoScanner, (http://www.phenoscanner.medschl.cam.ac.uk/phenoscanner).

**METHODS**

Methods and any associated references are available in the online version of the paper.

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**Author contributions**

Planned the study (WEE and ÅJ), analyzed the data (WEE and ÅJ), literature search (WEE), Figures (WEE), data interpretation (WEE, ÅJ, TK, MRA), writing of manuscript (WEE, ÅJ, TK, MRA).

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**Table 1. Baseline characteristics of participants in the UK Biobank database. The total number of Caucasian s are N= 443,068**

| | Asthma | Hay fever/eczema | Asthma/hay fever/eczema Combined* | Controls** |
|---|---|---|---|---|
| **N Caucasians (prior to QC)** | 51,645 | 102,862 | 130,865 | 294,477 |
| **N total included after QC** | 41,934 | 84,050 | 106,772 | 239,773 |
| **N (%) males after QC** | 21,730 (51.8%) | 42,639 (57.8%) | 55,124 (51.6%) | 138,666 (57.8%)) |
| **N in discovery after QC** | 14,396 | 26,382 | 34,426 | 76,414 |
| **N in replication after QC** | 27,538 | 57,668 | 72,346 | 163,359 |
| **Age year span (mean)** | 38-70 (56.1) | 39-72 (55.4) | 38-72 (55.7) | 39-73 (57.2) |
| **Townsend deprivation index range (mean)** | -6.3-10.6 (-1.3) | -6.3-10.6 (-1.6) | -6.3-10.6 (-1.5) | -6.3-10.9 (1.5) |
| **% Ever smoked (N yes / N no)** | 60.4% (31,040 / 20,390) | 58.5% (59,983 / 42,616) | 59.3% (77,335/53,121) | 60.4% (177,212/116,275) |

* Asthma and hay fever/eczema combined

****** the same controls were used in all analyses

**Table 2. Results for self-reported asthma in the discovery cohort, replication cohort and when meta-analyzing both cohorts. Novel loci are marked as bold and the shaded area indicates where the original SNP was missing in the replication and if substituted for a proxy SNP. N is the number of SNPs within each locus and the annotated gene is the gene/genes within the locus. More details can be found in Supplementary Table 1 and 4.**

| | | | | | **Discovery (14,396 cases/76,414 controls)** | | | | **Replication (27,538 cases/163,359 controls)** | | | | **Meta-analysis (41,934 cases /239,773 controls)** | | **Annotated Gene** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **SNP** | **CHR** | **BP locus (hg19)** | **N** | | **A1** | **OR** | **P** | | **A1** | **OR** | **P** | | **P** | **OR** | |
| rs301806 | 1 | 8476428-8505058 | 11 | | C | 0.93 (0.91-0.96) | $6.49x10^{-8}$ | | C | 0.96 (0.95-0.98) | $7.23x10^{-5}$ | | $1.86x10^{-10}$ | 0.95 | *RERE* [α] |
| rs61813920 | 1 | 152000117-153094297 | 23 | | T | 1.27 (1.17-1.37) | $2.36x10^{-9}$ | | T | 1.18 (1.11-1.24) | $1.317x10^{-8}$ | | $6.66x10^{-16}$ | 1.21 | *FLG, LCE1E, LCE20, LCE2B, KPRP, LCE1B LCE5A, CRCT1* |
| rs3108155* | 1 | 167417884-167436300 | 22 | | G | 0.93 (0.91-0.96) | $1.37x10^{-7}$ | | | | | | | | |
| rs1214598 | 1 | r2=0.85 D'=1.0 | | | A | 0.93 (0.91-0.96) | $1.66x10^{-7}$ | | A | 0.94 (0.91-0.95) | $3.573x10^{-12}$ | | $3.30x10^{-18}$ | 0.93 | *CD247* |
| **rs6702345** | **1** | **203065729-203084158** | **4** | | **A** | **0.93 (0.91-0.96)** | **$6.70x10^{-7}$** | | **A** | **0.95 (0.94-0.97)** | **$3.12x10^{-6}$** | | **$2.50x10^{-11}$** | **0.95** | ***MYOG, ADORA1*** [α] |
| rs891058 | 2 | 8438693-8474038 | 19 | | A | 0.92 (0.90-0.95) | $9.55x10^{-9}$ | | A | 0.93 (0.91-0.95) | $8.897x10^{-13}$ | | $5.61x10^{-20}$ | 0.93 | *LINC00299* |
| rs950880 | 2 | 102734380-103207959 | 427 | | A | 1.13 (1.10-1.16) | $3.31x10^{-19}$ | | A | 1.12 (1.10-1.14) | $6.45x10^{-33}$ | | $1.39x10^{-50}$ | 1.12 | *IL1RL1, IL1RL2 IL18R1, IL18RAP* |
| rs34290285 | 2 | 242690675-242711282 | 24 | | A | 0.90 (0.87-0.93) | $2.56x10^{-12}$ | | A | 0.87 (0.85-0.89) | $6.47x10^{-38}$ | | $6.33x10^{-48}$ | 0.88 | *D2HGDH GAL3ST2* |
| **rs60946162** | **3** | **188077586-188133336** | **46** | | **T** | **1.08 (1.05-1.10)** | **$3.08x10^{-8}$** | | **T** | **1.06 (1.04-1.08)** | **$1.476x10^{-9}$** | | **$4.33x10^{-16}$** | **1.06** | ***LPP*** |

| | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| rs80064395 | 3 | 196343817-196377051 | 14 | | T | 0.88 (0.84-0.92) | $9.87x10^{-8}$ | | T | 0.94 (0.91-0.97) | 0.00028 | | $1.62x10^{-9}$ | 0.92 | *LRRC33* |
| rs11464936;rs371468470* | 4 | 38736550-38906951 | 212 | | GT | 0.88 (0.85-0.92) | $1.41x10^{-11}$ | | | | | | | | *FAM114A1 TLR10, TLR1 TLR6, KLF3 MIR574* |
| rs10013453 | 4 | | | | G | 0.91 (0.88-0.94) | $4.51x10^{-9}$ | | G | 0.91 (0.89-0.93) | $1.52x10^{-15}$ | | $4.14x10^{-23}$ | 0.91 | |
| rs4380538 | 4 | 123024769-123501086 | 191 | | T | 1.09 (1.06-1.12) | $6.72x10^{-10}$ | | T | 1.07 (1.05-1.10) | $1.81x10^{-13}$ | | $1.56x10^{-21}$ | 1.08 | *IL2, ADAD1, KIAA1109, IL21* |
| **rs16903574** | **5** | **14610309-14610309** | **1** | | **G** | **1.13 (1.08-1.18)** | **$3.48x10^{-7}$** | | **G** | **1.10 (1.07-1.14)** | **$2.75x10^{-8}$** | | **$7.28x10^{-14}$** | **1.11** | ***FAM105A*** |
| **rs568737902*** | **5** | **141540017-141549536** | **8** | | **AT TT** | **0.93 (0.90-0.95)** | **$2.60x10^{-7}$** | | | | | | | | |
| **rs2338819** | **5** | **r2=1.0 D'=1.0** | | | **T** | **0.93 (0.90-0.95)** | **$2.77x10^{-7}$** | | **T** | **0.95 (0.93-0.97)** | **$1.488x10^{-7}$** | | **$3.83x10^{-13}$** | **0.94** | ***NDFIP1*** [α] |
| rs1837253 | 5 | 109992267-110558882 | 135 | | T | 0.87 (0.85-0.90) | $4.87x10^{-19}$ | | T | 0.89 (0.87-0.90) | $1.64x10^{-29}$ | | $8.86x10^{-47}$ | 0.88 | *TMEM232 SLCA25A46 TSLP SLC25A46, WDR36 CAMK4* |
| rs11741255 | 5 | 131511729-132128644 | 367 | | A | 0.91 (0.89-0.94) | $1.31x10^{-11}$ | | A | 0.93 (0.91-0.95) | $4.37x10^{-14}$ | | $6.73x10^{-24}$ | 0.93 | *SLC22A4 FLJ44796 IL3, IRF1 SLC22A5 IL5, RAD50 IL13 IL4, KIF3A* |
| rs9273410* | 6 | 30163955-33000686 | 3126 | | C | 0.85 (0.83-0.87) | $1.66x10^{-35}$ | | | | | | | | *MHC, TRIM26 PSORS1C1 PSORS1C2, MICA, HLA-B, MICB HCP5, 3.8-1 HCG26, SKIV2L* |

| | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | | | | | *HLA-DRB1 NR, BTNL2 HLA-DRA, DQB1HLA-DQA1 HLADRB1, HLA-C LOC642072 HLA HLA-DRB5 HLA-HLA-DQB, HLA-DQA/B, HLA-* |
| rs28407950 | 6 | | | | C | 0.85 (0.83-0.87) | $1.66x10^{-35}$ | | T | 0.82 (0.80-0.84) | $4.24x10^{-69}$ | | $5.45x10^{-102}$ | 0.83 | |
| **rs148639908*** | **6** | **90850164-91011673** | **54** | | **AT** | **0.93 (0.90-0.95)** | **$2.46x10^{-8}$** | | | | | | | | ***BACH2*** |
| **rs969577** | **6** | r2=1.0 D'=1.0 | | | **AT** | **0.93 (0.90-0.95)** | **$2.46x10^{-8}$** | | **C** | **0.91 (0.90-0.93)** | **$6.25x10^{-20}$** | | **$1.30x10^{-26}$** | **0.92** | |
| **rs6461503** | **7** | **20376018-20581949** | **98** | | **T** | **1.08 (1.05-1.11)** | **$1.06x10^{-8}$** | | **T** | **1.05 (1.03-1.07)** | **$1.47x10^{-6}$** | | **$3.11x10^{-13}$** | **1.06** | ***ABCB5*** [α] |
| rs36100905* | 8 | 81246659-81315490 | 108 | | C | 1.09 (1.06-1.12) | $1.22x10^{-10}$ | | | | | | | | *MIR5708, ZBTB10* [**] |
| rs2136016 | 8 | r2=0.81 D'=0.95 | | | G | 1.09 (1.06-1.12) | $2.60x10^{-10}$ | | G | 1.07 (1.05-1.09) | $4.01x10^{-12}$ | | $8.54x10^{-21}$ | 1.07 | |
| rs9775039* | 9 | 5903101-6548270 | 329 | | A | 1.18 (1.14-1.22) | $3.99x10^{-22}$ | | | | | | | | *RANBP6 IL33* |
| rs13298116 | 9 | r2=0.60 D'=0.97 | | | T | 1.11 (1.08-1.14) | $8.91x10^{-12}$ | | T | 1.12 (1.09-1.14) | $5.03x10^{-24}$ | | $3.26x10^{-34}$ | 1.11 | |
| rs12244238 | 10 | 6083239-6083239 | 1 | | G | 1.07 (1.04-1.10) | $8.67x10^{-7}$ | | G | 1.04 (1.02-1.06) | $1.56x10^{-5}$ | | $2.22x10^{-10}$ | 1.05 | *IL2RA* |
| rs1444782 | 10 | 8605553-9208204 | 126 | | A | 0.91 (0.88-0.93) | $4.77x10^{-14}$ | | A | 0.89 (0.88-0.91) | $9.05x10^{-33}$ | | $4.81x10^{-45}$ | 0.90 | *GATA3* [α] |

| | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| rs61893460 | 11 | 76057946-76303195 | 113 | | A | 1.13 (1.10-1.16) | $9.90x10^{-22}$ | | A | 1.13 (1.11-1.16) | $4.90x10^{-42}$ | | $5.24x10^{-62}$ | 1.13 | *C11orf30 LRRC32*[α] |
| rs10876864 | 12 | 56368078-57520255 | 80 | | G | 1.10 (1.07-1.13) | $1.51x10^{-12}$ | | G | 1.06 (1.05-1.08) | $3.20x10^{-11}$ | | $1.84x10^{-21}$ | 1.07 | *RAB5B, SUOX MEL, DGKA CDK2, NAB2 ZNFN1A4, PA2G4 RPS26 ERBB3 IKZF4, STAT6*[α] |
| **rs1923897** | **13** | **99836033-100040979** | **53** | | **T** | **093 (0.90-0.95)** | **$3.20x10^{-8}$** | | **T** | **0.94 (0.92-0.96)** | **$5.60x10^{-10}$** | | **$1.47x10^{-16}$** | **0.94** | ***UBAC2*** |
| **rs2208397** | **14** | **68752643-68753593** | **3** | | **T** | **1.07 (1.04-1.10)** | **$5.56x10^{-7}$** | | **T** | **1.06 (1.03-1.08)** | **$1.52x10^{-7}$** | | **$7.46x10^{-13}$** | **1.06** | ***RAD15B*** |
| rs36045143 | 16 | 11031741-11285678 | 118 | | G | 0.88 (0.85-0.91) | $4.95x10^{-17}$ | | G | 0.91 (0.89-0.93) | $9.38x10^{-20}$ | | $1.33x10^{-34}$ | 0.90 | *KIAA0350 CLEC16A, DEXI* |
| rs3024655* | 16 | 27355849-27384383 | 11 | | A | 0.85 (0.80-0.90) | $1.63x10^{-8}$ | | | | | | | | *IL4R* |
| rs3024664 | 16 | | | | T | 0.85 (0.80-0.90) | $2.35x10^{-8}$ | | T | 0.87 (0.84-0.91) | $3.48x10^{-11}$ | | $5.92x10^{-18}$ | 0.87 | |
| **rs9909628*** | **17** | **40414877-40427147** | **3** | | **T** | **0.93 (0.91-0.96)** | **$7.24x10^{-7}$** | | | | | | | | ***STAT5B*** |
| **rs8080122** | **17** | | | | **A** | **0.93 (0.91-0.96)** | **$9.43x10^{-7}$** | | **A** | **0.96 (0.95-0.98)** | **0.0003305** | | **$8.02x10^{-9}$** | **0.95** | |
| rs9889262 | 17 | 47398070-47450057 | 4 | | A | 1.07 (1.04-1.10) | $3.71x10^{-7}$ | | A | 1.08 (1.06-1.10) | $3.35x10^{-14}$ | | $1.04x10^{-19}$ | 1.07 | *ZNF652* |
| rs10414065 | 19 | 33721455-33726578 | 4 | | T | 0.85 (0.80-0.89) | $1.18x10^{-9}$ | | T | 0.85 (0.82-0.88) | $5.97x10^{-16}$ | | $4.52x10^{-24}$ | 0.85 | *SLC7A10*[α] |

A1 is the reference allele

* SNP was missing in the replication and a proxy was selected, i.e. the second most significant SNP in discovery with an R2 <0.6

[α] The leading SNP is intergenic and the closest gene/genes are reported

**Table 3. Results for self-reported hay fever and/or eczema (hay fever/eczema) in the discovery cohort, replication cohort and when meta-analyzing both cohorts. Novel loci are marked as bold and the shaded area indicates where the original SNP was missing in the replication and if substituted for a proxy SNP. N is the number of SNPs within each locus and the annotated gene is the gene/genes within the locus. More details can be found in Supplementary Table 2 and 4.**

| | | | | **Discovery (26,382 cases / 76,414 controls)** | | | | **Replication (57,668 cases / 163,359 controls)** | | | | **Meta-analysis (84,050 cases / 239,773 controls)** | | **Annotated gene** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **SNP** | **CHR** | **BP Locus (hg19)** | **N** | | **A1** | **OR** | **P** | | **A1** | **OR** | **P** | | **P** | **OR** | |
| rs301802 | 1 | 8476428-8505058 | 11 | | T | 0.95 (0.93-0.96) | $7.53x10^{-8}$ | | T | 0.96 (0.95-0.98) | $1.32x10^{-7}$ | | $1.57x10^{-13}$ | 0.96 | *RERE* |
| **rs113102463*** | **1** | **11916095-12106036** | **7** | | **C** | **0.91 (0.87-0.94)** | **$2.68x10^{-7}$** | | | | | | | | ***MIIP, TNFRSF8*** [α] |
| **rs34286591** | **1** | **r2=0.79 D'=0.99** | | | **C** | **0.91 (0.87-0.94)** | **$3.68x10^{-7}$** | | **C** | **0.95 (0.93-0.98)** | **0.00013** | | **$2.01x10^{-9}$** | **0.94** | |
| rs7518125 | 1 | 25249252-25262022 | 20 | | C | 0.95 (0.93-0.97) | $2.40x10^{-7}$ | | C | 0.96 (0.95-0.98) | $2.69x10^{-8}$ | | $6.47x10^{-14}$ | 0.96 | *RUNX3* |
| rs61815559 | 1 | 151664878-153094297 | 33 | | T | 1.20 (1.14-1.27) | $4.60x10^{-11}$ | | T | 1.15 (1.11-1.20) | $5.64x10^{-13}$ | | $3.34x10^{-22}$ | 1.17 | *FLG, FLG-AS1, LCE1E, LCE20, KPRP, LCE1B LCE5A, CRCT1* |
| rs4845373 | 1 | 154405024-154428283 | 29 | | T | 1.06 (1.04-1.08) | $5.68x10^{-8}$ | | T | 1.03 (1.02-1.05) | $1.66x10^{-6}$ | | $2.51x10^{-12}$ | 1.04 | *IL6R, TDRD10, SHE, UBE2Q1, ADAR* |
| rs1214598 | 1 | 167417884-167436320 | 25 | | A | 0.94 (0.92-0.96) | $4.77x10^{-9}$ | | A | 0.95 (0.93-0.96) | $8.21x10^{-15}$ | | $2.57x10^{-22}$ | 0.94 | *CD247* |

| | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| rs10174949 | 2 | 8438693-8481299 | 52 | | A | 0.91 (0.89-0.93) | $9.11x10^{-16}$ | | A | 0.94 (0.93-0.95) | $6.98x10^{-16}$ | | $4.80x10^{-29}$ | 0.93 | *LINC00299* |
| rs202011557* | 2 | 102579017-103 277 862 | 439 | | AAAAC | 0.85 (0.83-0.88) | $6.70x20^{-24}$ | | | | | | | | *IL1RL1, IL1RL2, IL18R1, IL18RAP* |
| rs72823641 | 2 | r2=0.96 D'=0.99 | | | A | 0.86 (0.83-0.88) | $8.15x10^{-24}$ | | A | 0.86 (0.85-0.88) | $5.72x10^{-46}$ | | $4.82x10^{-68}$ | 0.86 | |
| rs34290285 | 2 | 242675847-242740090 | 101 | | A | 0.90 (0.88-0.92) | $4.11x10^{-18}$ | | A | 0.90 (0.89-0.92) | $6.51x10^{-39}$ | | $2.47x10^{-55}$ | 0.90 | *D2HGDH, GAL3ST2* |
| **rs4274702** | **3** | **33068055-33159266** | **12** | | **T** | **1.06 (1.04-1.08)** | **$3.63x10^{-8}$** | | **T** | **1.04 (1.02-1.05)** | **$1.82x10^{-6}$** | | **$1.76x10^{-12}$** | **1.04** | ***GLB1*** |
| **rs62263759** | **3** | **112640302-112693753** | **4** | | **T** | **1.06 (1.04-1.08)** | **$1.04x10^{-7}$** | | **T** | **1.03 (1.02-1.05)** | **$7.59x10^{-5}$** | | **$3.20x10^{-10}$** | **1.04** | ***CD200R1*** |
| **rs13077048** | **3** | **141093285-141147414** | **22** | | **T** | **1.06 (1.04-1.08)** | **$7.82x10^{-8}$** | | **T** | **1.03 (1.02-1.05)** | **$9.31x10^{-6}$** | | **$2.60x10^{-11}$** | **1.04** | ***ZBTB38*** |
| rs763342 | 3 | 187639375-187639375 | 1 | | C | 1.06 (1.03-1.08) | $5.18x10^{-7}$ | | C | 1.05 (1.04-1.07) | $8.41x10^{-12}$ | | $1.98x10^{-17}$ | 1.05 | *BCL6*[α] |
| rs4916533 | 3 | 196372546-196373582 | 2 | | T | 0.91 (0.87-0.94) | $3.02x10^{-7}$ | | T | 0.95 (0.92-0.97) | $1.10x10^{-5}$ | | $7.59x10^{-11}$ | 0.93 | *LRRC33* |
| rs28393318 | 4 | 38708403-38933726 | 263 | | G | 0.87 (0.85-0.90) | $2.83x10^{-25}$ | | G | 0.87 (0.86-0.89) | $2.42x10^{-52}$ | | $7.50x10^{-76}$ | 0.87 | *FAM114A1, TLR10, TLR1, TLR6, KLF3, MIR574*[α] |
| rs34834002* | 4 | 123024769-123559707 | 457 | | T | 1.07 (1.05-1.09) | $2.36x10^{-10}$ | | | | | | | | *IL2, ADAD1, KIAA1109, IL21* |
| rs12499753 | 4 | r2=0.89 D'=0.96 | | | C | 1.07 (1.05-1.09) | $7.67x10^{-10}$ | | C | 1.08 (1.06-1.09) | $1.83x10^{-24}$ | | $8.21x10^{-33}$ | 1.07 | |
| rs6881270 | 5 | 35803577-36029754 | 77 | | T | 0.91 (0.89-0.93) | $1.30x10^{-16}$ | | T | 0.91 (0.89-0.92) | $3.84x10^{-37}$ | | $4.47x10^{-52}$ | 0.91 | *IL7R, CAPSL* |
| rs1438673 | 5 | 109800443-110606055 | 580 | | T | 0.90 (0.89-0.92) | $8.99x10^{-23}$ | | T | 0.91 (0.90-0.92) | $1.05x10^{-42}$ | | $9.47x10^{-64}$ | 0.91 | *TMEM232, SLCA25A46, SLC25A46, WDR36, CAMK4*[α] |

| | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| rs20541 | 5 | 131885240-131996669 | 53 | | A | 1.07 (1.05-1.10) | $1.16x10^{-7}$ | | A | 1.05 (1.03-1.07) | $6.64x10^{-8}$ | | $1.17x10^{-13}$ | 1.06 | *IL13, SLC22A4 FLJ44796 IL3, IRF1 SLC22A5 IL5, RAD50, IL4, KIF3A* |
| **rs62390337** | **5** | **159903134-159922209** | **16** | | **T** | **0.94 (0.91-0.96)** | **$4.26x10^{-8}$** | | **T** | **0.95 (0.93-0.96)** | **$1.61x10^{-11}$** | | **$5.44x10^{-18}$** | **0.94** | ***DQ658414*** |
| rs28407950 | 6 | 29628367-33465482 | 1571 | | T | 0.89 (0.87-0.91) | $5.78x10^{-21}$ | | T | 0.91 (0.90-0.93) | $6.16x10^{-30}$ | | $1.03x10^{-48}$ | 0.91 | *MHC, TRIM26 PSORS1C1 PSORS1C2, MICA, HLA-C, DRA HLA-B, MICB HCP5, 3.8-1 HCG26, SKIV2L HLA-DRB1 NR, BTNL2 HLA- HLA-DQA1 HLADRB1 LOC642072 HLA HLA-DRB5 HLA-DQB1 HLA-DQB, HLA-DQA/B* |
| **rs41285280** | **6** | **128291649-128291649** | **1** | | **T** | **1.06 (1.04-1.09)** | **$8.81x10^{-8}$** | | **T** | **1.04 (1.02-1.05)** | **$1.84x10^{-5}$** | | **$3.54x10^{-10}$** | **1.04** | ***PTPRK*** |
| rs6461503 | 7 | 20534004-20560996 | 4 | | T | 1.06 (1.04-1.08) | $8.40x10^{-8}$ | | T | 1.05 (1.04-1.07) | $1.91x10^{-13}$ | | $1.07x10^{-19}$ | 1.05 | ***ABCB5*** [α] |
| rs13277355 | 8 | 128777719-128777766 | 2 | | A | 1.06 (1.04-1.08) | $3.70x10^{-7}$ | | A | 1.04 (1.02-1.06) | $9.38x10^{-7}$ | | $4.17x10^{-12}$ | 1.05 | *MYC* [α] |
| rs12339348 | 9 | 5632583-6535500 | 70 | | T | 1.07 (1.05-1.10) | $1.55x10^{-8}$ | | T | 1.07 (1.05-1.09) | $6.54x10^{-17}$ | | $6.90x10^{-24}$ | 1.07 | *IL33 RANBP6* |

| | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| rs34823362** | 9 | 123708286-<br>123 708 286 | 1 | | CA | 1.06<br>(1.03-1.08) | $7.34x10^{-7}$ | | | | | | | | *C5* [α] |
| **rs11539209** | **9** | **131483551-<br>131483551** | **1** | | **A** | **0.91<br>(0.88-0.94)** | **$5.09x10^{-7}$** | | **A** | **0.93<br>(0.91-0.95)** | **$2.57x10^{-8}$** | | **$1.11x10^{-13}$** | **0.92** | ***ZDHHC12*** |
| rs61839660 | 10 | 6061499-<br>6185344 | 66 | | T | 1.13<br>(1.09-1.16) | $1.42x10^{-12}$ | | T | 1.12<br>(1.10-1.15) | $1.38x10^{-24}$ | | $1.92x10^{-35}$ | 1.12 | *IL2RA* |
| **rs10883723** | **10** | **104225832-<br>104272789** | **4** | | **C** | **1.05<br>(1.03-1.08)** | **$5.76x10^{-7}$** | | **C** | **1.04<br>(1.02-1.05)** | **$1.02x10^{-6}$** | | **$6.24x10^{-12}$** | **1.04** | ***TMEM180*** |
| rs71040008* | 11 | 76038068-<br>76 302 073 | 124 | | GT | 1.11<br>(1.09-1.13) | $1.84x10^{-24}$ | | | | | | | | *C11orf30*<br>*LRRC32* [α] |
| rs11236797 | 11 | r2=0.99<br>D'=1 | | | A | 1.12<br>(1.09-1.13) | $1.23x10^{-23}$ | | A | 1.11<br>(1.09-1.12) | $5.85x10^{-50}$ | | $2.57x10^{-71}$ | 1.11 | |
| rs4616071 | 11 | 111417779-<br>111594077 | 150 | | G | 0.93<br>(0.91-0.95) | $2.80x10^{-9}$ | | G | 0.96<br>(0.94-0.97) | $2.21x10^{-8}$ | | $1.74x10^{-15}$ | 0.95 | *ALG9, BTG4*<br>*C11orf1*<br>*C11orf88,*<br>*FDXACB1*<br>*LAYN, SIK2*<br>*MIR34B*<br>*MIR34C,*<br>*PPP2R1B* |
| **rs12365699** | **11** | **118743286-<br>118743286** | **1** | | **A** | **0.93<br>(0.91-0.96)** | **$9.47x10^{-7}$** | | **A** | **0.96<br>(0.94-0.97)** | **$1.91x10^{-6}$** | | **$2.59x10^{-11}$** | **0.95** | ***CXCR5*** |
| rs533495047** | 11 | 128163162-<br>128163162 | 1 | | AG | 0.94<br>(0.92-0.96) | $8.56x10^{-7}$ | | | | | | | | *ETS1* [α] |
| rs181074992** | 12 | 51425765-<br>51425765 | 1 | | T | 3.77<br>(2.29.6.19) | $1.64x10^{-7}$ | | | | | | | | *SLC11A2* |
| rs11171739 | 12 | 56364321-<br>57493727 | 84 | | C | 1.07<br>(1.05-1.09) | $7.20x10^{-11}$ | | C | 1.05<br>(1.03-1.06) | $1.19x10^{-10}$ | | $2.09x10^{-19}$ | 1.05 | *RAB5B, SUOX*<br>*MEL, DGKA*<br>*CDK2, NAB2*<br>*ZNFN1A4, PA2G4*<br>*RPS26 ERBB3*<br>*IKZF4, STAT6* [α] |

| | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| rs147149967** | 12 | 78054477-78 069 911 | 2 | | C | 2.10 (1.57-2.82) | $7.49x10^{-7}$ | | | | | | | | *NAV3*[α] |
| rs4943794 | 13 | 41154792-41210878 | 11 | | C | 1.07 (1.04-1.09) | $2.85x10^{-7}$ | | C | 1.05 (1.03-1.06) | $6.54x10^{-8}$ | | $2.44x10^{-13}$ | 1.05 | *FOXO1* |
| **rs8043253** | **15** | **41503730-41774423** | **8** | | **T** | **1.05 (1.03-1.08)** | **$2.99x10^{-7}$** | | **T** | **1.04 (1.03-1.06)** | **$7.86x10^{-9}$** | | **$2.46x10^{-14}$** | **1.05** | ***EXD1*** |
| rs10152544 | 15 | 67441750-67466599 | 25 | | C | 1.07 (1.05-1.09) | $1.64x10^{-10}$ | | C | 1.05 (1.03-1.06) | $3.45x10^{-11}$ | | $1.08x10^{-19}$ | 1.05 | *SMAD3* |
| **rs2074585** | **15** | **90936225-91056428** | **34** | | **G** | **1.06 (1.04-1.08)** | **$8.58x10^{-9}$** | | **G** | **1.05 (1.04-1.06)** | **$1.74x10^{-12}$** | | **$1.20^{-19}$** | **1.05** | ***IQGAP1*** |
| rs12935657 | 16 | 11031741-11297273 | 259 | | A | 0.90 (0.88-0.93) | $6.15x10^{-17}$ | | A | 0.92 (0.90-0.93) | $1.62x10^{-26}$ | | $1.45x10^{-41}$ | 0.91 | *KIAA0350 CLEC16A, DEXI* |
| rs564046070** | 17 | 3798709-3798709 | 1 | | T | 2.55 (1.75-3.71) | $9.64x10^{-7}$ | | | | | | | | *P2RX1*[α] |
| rs112401631 | 17 | 38706103-38876409 | 139 | | A | 1.41 (1.31-1.52) | $3.08x10^{-19}$ | | A | 1.33 (1.26-1.39) | $6.11x10^{-31}$ | | $3.75x10^{-48}$ | 1.35 | *CCR7, KRT222 SMARCE1*[α] |
| **rs8092019** | **18** | **52265785-52323618** | **7** | | **A** | **1.06 (1.03-1.08)** | **$2.05x10^{-7}$** | | **A** | **1.02 (1.01-1.04)** | **0.00056** | | **$8.80x10^{-9}$** | **1.03** | ***DYNAP***[α] |
| rs10414065 | 19 | 33721455-33721455 | 1 | | T | 0.90 (0.86-0.94) | $6.89x10^{-7}$ | | NA | 0.90 (0.88-0.93) | $3.95x10^{-12}$ | | $1.47x10^{-17}$ | 0.90 | *SLC7A10*[α] |
| rs533128189** | 19 | 50842964-50842964 | 1 | | T | 3.17 (2.00-5.02) | $8.69x10^{-7}$ | | | | | | | | *NR1H2* |
| **rs8125525** | **20** | **45678917-45686453** | **5** | | **T** | **0.94 (0.92-0.96)** | **$4.75x10^{-7}$** | | **T** | **0.95 (0.93-0.96)** | **$9.07x10^{-11}$** | | **$2.69x10^{-16}$** | **0.95** | ***EYA2*** |
| rs2766664 | 20 | 52168159-62322699 | 20 | | A | 1.09 (1.06-1.11) | $1.24x10^{-12}$ | | A | 1.04 (1.02-1.05) | $1.89x10^{-05}$ | | $5.27x10^{-14}$ | 1.05 | *ZNF217*[α] |

A1 is the reference allele

* SNP was missing in the replication and a proxy was selected, i.e. the second most significant SNP in discovery with an R2 <0.6

** No proxy was found in the replication

[α] The leading SNP is intergenic and the closest gene/genes are reported

**Table 4. Results for self-reported asthma and hay fever/eczema analyzed as the same disease, in the discovery cohort, replication cohort and when meta-analyzing both cohorts. Novel loci are marked as bold and the shaded area indicates where the original SNP was missing in the replication and if substituted for a proxy SNP. N is the number of SNPs within each locus and the annotated gene is the gene/genes within the locus. More details can be found in Supplementary Table 3 and 4.**

| | | | | | **Discovery (34,426 cases / 76,414 controls)** | | | | **Replication (72,346 cases / 163,359 controls)** | | | | **Meta-analysis (106,772 cases / 239,773 controls)** | | **Annotated gene** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **SNP** | **CHR** | **BP Locus (hg19)** | **N** | | **A1** | **OR** | **P** | | **A1** | **OR** | **P** | | **OR** | **P** | |
| rs301802 | 1 | 8476428-8663821 | 24 | | T | 0.94 (0.92-0.96) | $4.94x10^{-10}$ | | T | 0.96 (0.95-0.98) | $4.097x10^{-8}$ | | 0.96 | $8.89x10^{-16}$ | *RERE* |
| **rs2230624** | **1** | **12175658-12175658** | **1** | | **A** | **0.81 (0.75-0.87)** | **$6.24x10^{-8}$** | | **A** | **0.91 (0.86-0.96)** | **0.00026** | | **0.88** | **$1.50x10^{-9}$** | ***TNFRSF8/CD30*** |
| rs61816766 | 1 | 151792984-153094297 | 45 | | C | 1.18 (1.12-1.24) | $1.66x10^{-10}$ | | C | 1.13 (1.091.17) | $8.17x10^{-11}$ | | 1.15 | $1.99x10^{-19}$ | *FLG, FLG-AS1, LCE1E, LCE20, LCE2B, KPRP, LCE1B LCE5A, CRCT1* |
| rs12753254 | 1 | 154405024-154426970 | 16 | | A | 1.05 (1.03-1.07) | $4.79x10^{-7}$ | | A | 1.03 (1.02-1.05) | $4.99x10^{-7}$ | | 1.04 | $2.25x10^{-12}$ | *IL6R* |
| rs1214598 | 1 | 167408670-167436320 | 33 | | A | 0.94 (0.92-0.96) | $4.86x10^{-11}$ | | A | 0.95 (0.93-0.96) | $4.81x10^{-17}$ | | 0.94 | $2.01x10^{-26}$ | *CD247* |
| rs10174949 | 2 | 8438693-8488143 | 58 | | A | 0.92 (0.90-0.94) | $3.30x10^{-16}$ | | A | 0.94 (0.93-0.96) | $5.52x10^{-17}$ | | 0.94 | $1.05x10^{-30}$ | *LINC00299* |
| rs72823641 | 2 | 102579017-103277862 | 473 | | A | 0.87 (0.84-0.89) | $1.76x10^{-25}$ | | A | 0.86 (0.84-0.87) | $1.19x10^{-60}$ | | 0.86 | $2.99x10^{-84}$ | *IL1RL1* |
| rs34290285 | 2 | 242675847-242740090 | 101 | | A | 0.91 (0.89-0.93) | $6.92x10^{-19}$ | | A | 0.90 (0.89-0.91) | $1.15x10^{-45}$ | | 0.90 | $9.90x10^{-63}$ | *D2HGDH, GAL3ST2* |
| **rs6800001** | **3** | **33068055-33126972** | **8** | | **A** | **1.05 (1.03-1.07)** | **$7.10x10^{-8}$** | | **A** | **1.04 (1.02-1.05)** | **$1.54x10^{-7}$** | | **1.04** | **$2.26x10^{-13}$** | ***TMPEE/GLB1*** |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **rs62263759** | **3** | **112646699-112693753** | **3** | | **T** | **1.05 (1.03-1.07)** | **$2.22x10^{-7}$** | | **T** | **1.03 (1.01-1.04)** | **$9.4x10^{-5}$** | | **1.04** | **$7.29x10^{-10}$** | ***CD200R1*** |
| **rs13077048** | **3** | **141106954-141106954** | **1** | | **T** | **1.05 (1.03-1.07)** | **$5.12x10^{-7}$** | | **T** | **1.03 (1.01-1.04)** | **$1.14x10^{-5}$** | | **1.04** | **$1.24x10^{-10}$** | ***ZBTB38*** |
| rs567713 | 3 | 187661983-187681712 | 5 | | T | 0.91 (0.88-0.94) | $1.07x10^{-7}$ | | T | 0.95 (0.92-0.97) | $1.52x10^{-6}$ | | 0.93 | $3.19x10^{-12}$ | *BCL6*[α] |
| rs80064395 | 3 | 196327220-196377051 | 36 | | T | 0.90 (0.87-0.93) | $1.44x10^{-9}$ | | T | 0.95 (0.93-0.98) | $3.66x10^{-5}$ | | 0.94 | $9.61x10^{-12}$ | *LRRC33* |
| **rs56075897** | **4** | **4762315-4775137** | **13** | | **G** | **1.05 (1.03-1.07)** | **$8.32x10^{-8}$** | | **G** | **1.02 (1.01-1.04)** | **0.00032** | | **1.03** | **$2.69x10^{-9}$** | ***AK056081*** |
| rs28393318 | 4 | 38708403-3892258 | 319 | | G | 0.89 (0.87-0.91) | $1.56x10^{-23}$ | | G | 0.90 (0.88-0.91) | $1.05x10^{-45}$ | | 0.89 | $1.70x10^{-67}$ | *FAM114A1 TLR10, TLR1 TLR6, KLF3 MIR574*[α] |
| rs936607 | 4 | 123024769-123561869 | 520 | | G | 0.93 (0.91-0.95) | $1.08x10^{-11}$ | | G | 0.94 (0.93-0.95) | $4.13x10^{-19}$ | | 0.94 | $3.51x10^{-29}$ | *IL2, ADAD1, KIAA1109, IL21* |
| rs11567694 | 5 | 35803577-35985395 | 55 | | G | 0.92 (0.90-0.94) | $1.75x10^{-14}$ | | G | 0.92 (0.90-0.93) | $3.48x10^{-34}$ | | 0.92 | $6.40x10^{-47}$ | *IL7R* |
| rs1438673 | 5 | 109800443-110709125 | 603 | | T | 0.91 (0.89-0.93) | $4.87x10^{-24}$ | | T | 0.91 (0.90-0.93) | $2.80x10^{-45}$ | | 0.91 | $1.35x10^{-67}$ | *TMEM232 SLCA25A46 TSLP SLC25A46, WDR36 CAMK4*[α] |
| rs2301713 | 5 | 131677047-132105698 | 162 | | C | 1.08 (1.05-1.10) | $6.61x10^{-10}$ | | C | 1.06 (1.04-1.07) | $2.00x10^{-11}$ | | 1.06 | $1.15x10^{-19}$ | *RAD50, SLC22A4 FLJ44796 IL3, IRF1 SLC22A5 IL5, IL1, IL4, KIF3A* |
| **rs62390337** | **5** | **159899745-** | **21** | | **T** | **0.94** | **$6.21x10^{-9}$** | | **T** | **0.95** | **$1.58x10^{-11}$** | | **0.95** | **$9.68x10^{-19}$** | ***DQ658411*** |

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| | | **159929015** | | | | **(0.92-0.96)** | | | | **(0.94-0.96)** | | | | | |
| **rs9379828** | **6** | **26167951-26167951** | **1** | | **G** | **1.05 (1.03-1.07)** | **$9.67x10^{-7}$** | | **G** | **1.03 (1.01-1.04)** | **$3.63x10^{-5}$** | | **1.03** | **$9.03x10^{-10}$** | ***HIST1H2BD*** |
| rs568483267* | 6 | 29772244-33 261 871 | 2188 | | C | 0.88 (0.86-0.90) | $1.73x10^{-29}$ | | | | | | | | |
| rs28407950 | 6 | r2=0.99 D'=1.0 | | | T | 0.88 (0.86-0.90) | $1.81x10^{-29}$ | | T | 0.90 (0.88-0.91) | | | 0.89 | $1.20x10^{-75}$ | *MHC, TRIM26 PSORS1C1 PSORS1C2, MICA, HLA-C, DRA HLA-B, MICB HCP5, 3.8-1 HCG26, SKIV2L HLA-DRB1 NR, BTNL2 HLA- HLA-DQA1 HLADRB1 LOC642072 HLA HLA-DRB5 HLA-DQB1 HLA-DQB, HLA-DQA/B* |
| **rs148639908*** | **6** | **90963614-90987512** | **23** | | **AT** | **0.95 (0.93-0.97)** | **$2.70x10^{-7}$** | | | | | | | | |
| **rs969577** | **6** | **r2=0.99 D'=1.0** | | | **C** | **0.95 (0.93-0.97)** | **$3.70x10^{-7}$** | | **C** | **0.94 (0.93-0.96)** | | | **0.95** | **$7.83x10^{-24}$** | ***BACH2*** $^{\alpha}$ |
| **rs6461503** | **7** | **20376018-20581949** | **94** | | **T** | **1.06 (1.04-1.08)** | **$8.59x10^{-10}$** | | **T** | **1.05 (1.04-1.06)** | **$9.77x10^{-14}$** | | **1.05** | **$4.34x10^{-22}$** | ***ABCB5*** $^{\alpha}$ |
| rs4739738 | 8 | 81256041-81303039 | 95 | | G | 1.06 (1.04-1.08) | $8.53x10^{-9}$ | | G | 1.04 (1.03-1.05) | 4.05x10-9 | | 1.05 | $3.98x10^{-16}$ | *MIR5708, ZBTB10* $^{\alpha}$ |
| rs13277355 | 8 | 128777719-128814091 | 3 | | A | 1.06 (1.03-1.08) | $1.93x10^{-7}$ | | A | 1.04 (1.03-1.06) | $3.02x10^{-8}$ | | 1.05 | $6.98x10^{-14}$ | *MYC* $^{\alpha}$ |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| rs12339348 | 9 | 5632583-6548270 | 165 | | T | 1.09 (1.06-1.11) | $8.54x10^{-14}$ | | T | 1.08 (1.06-1.09) | $2.98x10^{-22}$ | | 1.08 | $2.21x10^{-34}$ | *IL33, RANBP6* |
| **rs11539209** | **9** | **131455796-131613191** | **6** | | **A** | **0.91 (0.88-0.95)** | **$1.58x10^{-7}$** | | **A** | **0.94 (0.91-0.96)** | **$1.76x10^{-8}$** | | **0.93** | **$2.50x10^{-14}$** | ***ZDHHC12*** |
| rs12244238 | 10 | 5917072-6185344 | 68 | | G | 1.07 (1.05-1.09) | $9.56x10^{-13}$ | | G | 1.05 (1.04-1.06) | $7.58x10^{-14}$ | | 1.06 | $4.16x10^{-24}$ | *IL2RA* |
| rs12413578 | 10 | 8565990-9148600 | 90 | | T | 0.89 (0.86-0.92) | $3.51x10^{-14}$ | | T | 0.92 (0.90-0.93) | $3.02x10^{-17}$ | | 0.91 | $2.60x10^{-29}$ | *GATA3*[α] |
| **rs10995245** | **10** | **64391375-64438271** | **3** | | **A** | **1.05 (1.03-1.07)** | **$1.52x10^{-7}$** | | **A** | **1.03 (1.01-1.04)** | **0.00012** | | **1.03** | **$8.69x10^{-10}$** | ***ZNF365*** |
| rs61893460 | 11 | 76038068-76302073 | 120 | | A | 1.11 (1.09-1.13) | $5.03x10^{-27}$ | | A | 1.10 (1.09-1.12) | $8.66x10^{-55}$ | | 1.10 | $1.22x10^{-79}$ | *C11orf30 LRRC32*[α] |
| rs4616071 | 11 | 111417779-111543916 | 116 | | G | 0.94 (0.92-0.96) | $1.44x10^{-9}$ | | G | 0.95 (0.94-0.94) | $3.37x10^{-11}$ | | 0.95 | $6.28x10^{-19}$ | *ALG9, BTG4 C11orf1 C11orf88, FDXACB1 LAYN, SIK2 MIR34B MIR34C, PPP2R1B*[α] |
| rs181074992** | 12 | 51425765-51425765 | 1 | | T | 3.40 (2.10-5.48) | $5.73x10^{-7}$ | | | | | | | | *SLC11A2*[α] |
| rs10876864 | 12 | 56364321-57493727 | 83 | | G | 1.07 (1.05-1.09) | $1.46x10^{-12}$ | | G | 1.05 (1.03-1.06) | $1.23x10^{-12}$ | | 1.05 | $3.90x10^{-23}$ | *RAB5B, SUOX MEL, DGKA CDK2, NAB2 ZNFN1A4, PA2G4 RPS26 ERBB3 IKZF4, STAT6*[α] |
| rs4943794 | 13 | 41154792-41204015 | 7 | | C | 1.06 (1.04-1.08) | $3.66x10^{-7}$ | | C | 1.04 (1.03-1.06) | $2.72x10^{-7}$ | | 1.05 | $8.18x10^{-13}$ | *FOXO1* |
| **rs7169278** | **15** | **41602866-** | **9** | | **A** | **0.95** | **$7.34x10^{-8}$** | | **A** | **0.97** | **$5.26x10^{-7}$** | | **0.96** | **$6.49x10^{-13}$** | ***NDUFAF1***[α] |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | **41774423** | | | | **(0.93-0.97)** | | | | **(0.96-0.98)** | | | | | |
| rs56062135 | 15 | 67439023-67466599 | 27 | | T | 1.09 (1.07-1.12) | $1.69x10^{-16}$ | | T | 1.08 (1.06-1.10) | $1.11x10^{-24}$ | | 1.08 | $2.82x10^{-39}$ | *SMAD3* |
| **rs2074585** | **15** | **91009484-91009484** | **1** | | **G** | **1.05 (1.03-1.07)** | **$4.37x10^{-7}$** | | **G** | **1.04 (1.03-1.05)** | **$6.80x10^{-9}$** | | **1.04** | **$3.09x10^{-14}$** | ***IQGAP1*** |
| rs36045143 | 16 | 11031741-11297273 | 257 | | G | 0.91 (0.89-0.92) | $2.80x10^{-20}$ | | G | 0.92 (0.91-0.93) | $4.02x10^{-29}$ | | 0.92 | $2.21x10^{-47}$ | *KIAA0350 CLEC16A, DEXI* |
| rs9911533 | 17 | 37903731-38876409 | 237 | | C | 0.92 (0.90-0.94) | $3.02x10^{-17}$ | | C | 0.96 (0.94-0.97) | $2.66x10^{-11}$ | | 0.95 | $9.97x10^{-25}$ | *SMARCE1, CCR7, KRT222* |
| rs9889262 | 17 | 47338083-47448346 | 19 | | A | 1.05 (1.03-1.07) | $1.14x10^{-7}$ | | A | 1.04 (1.03-1.06) | $5.02x10^{-11}$ | | 1.05 | $6.20x10^{-17}$ | *ZNF652* |
| **rs8092019** | **18** | **52230660-52391095** | **155** | | **A** | **1.05 (1.03-1.07)** | **$3.59x10^{-8}$** | | **A** | **1.02 (1.01-1.04)** | **0.00039** | | **1.03** | **$1.25x10^{-9}$** | ***DYNAP*** |
| rs10414065 | 19 | 33721455-33726578 | 3 | | T | 0.89 (0.86-0.93) | $6.55x10^{-9}$ | | T | 0.89 (0.87-0.92) | $3.59x10^{-17}$ | | 0.89 | $1.41x10^{-24}$ | *SLC7A10*[α] |
| rs2766667 | 20 | 52170783-52186784 | 15 | | T | 1.07 (1.05-1.09) | $4.38x10^{-10}$ | | T | 1.03 (1.02-1.05) | $3.17x10^{-5}$ | | 1.04 | $2.88x10^{-12}$ | *ZNF217*[α] |
| rs6011033 | 20 | 62288752-62323006 | 19 | | A | 0.94 (0.92-0.96) | $7.48x10^{-8}$ | | A | 0.96 (0.95-0.98) | $2.80x10^{-7}$ | | 0.96 | $3.42x10^{-13}$ | *RTEL1* |

A1 is the reference allele

* SNP was missing in the replication and a proxy was selected, i.e. the second most significant SNP in discovery with an R2 <0.6

** No proxy was found in the replication

[α] The leading SNP is intergenic and the closest gene/genes are reported

**Figure 1. Flow chart of included UKBB participants in discovery, replication and meta-analysis**

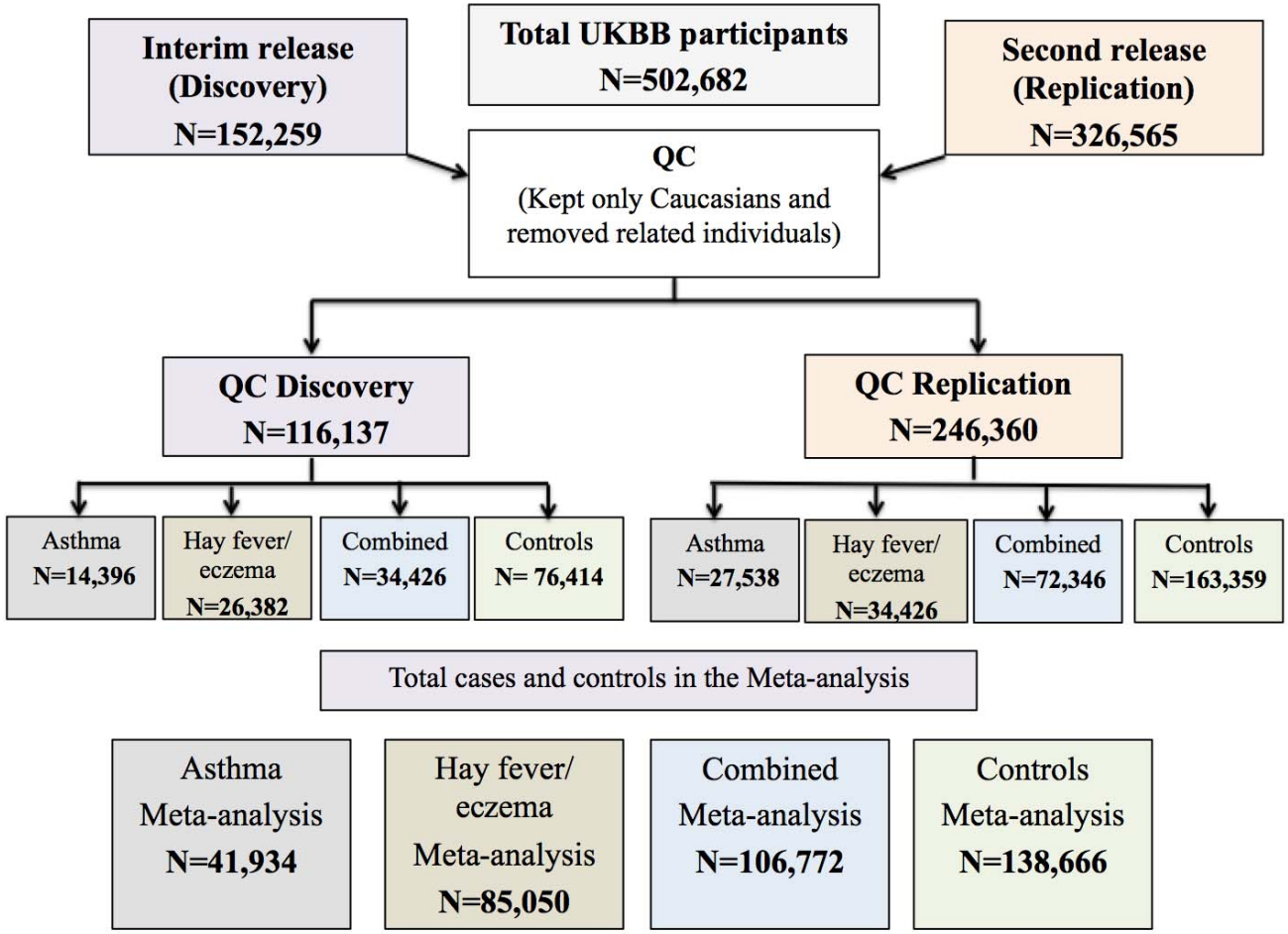
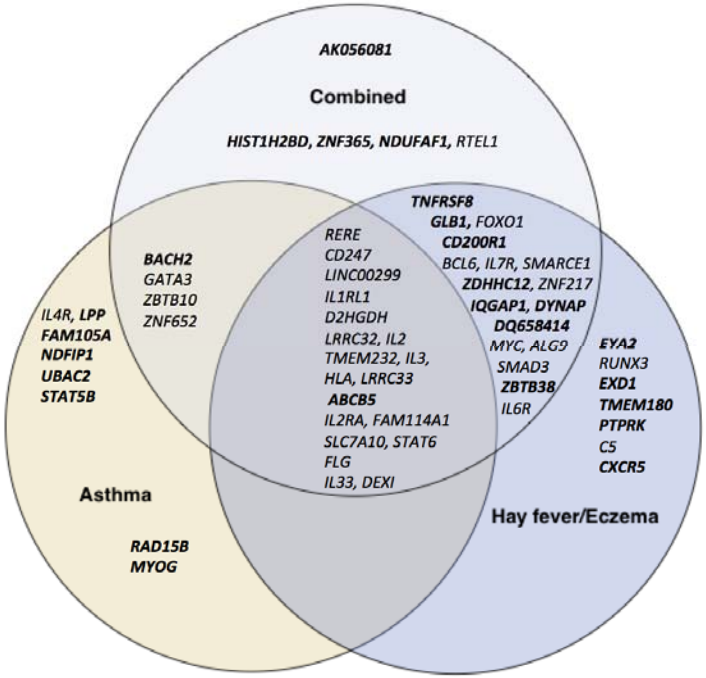
**Figure 2. Venn diagram of the discovered and validated loci from our study. This diagram shows concordance of significant association across self-reported asthma and hay fever/eczema, as well as the disease phenotype where we combined asthma and hay fever/eczema as one disease. The locus names labeled within the diagram correspond to the closest gene. The locus names in bold highlights the GWAS loci that are reported for the first time in our study.**