Supplement - Shared genetic variants suggest common pathways in allergy and autoimmune diseases
Supplementary Methods

Discovery and meta-analysis

Discovery results from an allergic sensitization GWAS was included as one of the datasets comprising results from 5,809 with allergic sensitization and 9,875 controls with data from the following cohorts: AAGC, ALSPAC, B58C, COPSAC2000, LISA, MAAS, NFBC 1966, RAINE and PIAMA. Please see discovery paper for ethical statements, cohort profiles and numbers. Sensitization status was assessed objectively by either elevated levels of allergen-specific IgE (sIgE) in blood or by a positive skin reaction after skin prick test (SPT) against common food and inhalant allergens. The SPT cut off level was 3 mm larger than the negative control for cases, and below 1 mm for controls. For sIgE, cases were defined as levels at or above 3.5 IU/mL and for controls below 0.35 IU/mL. Imputation was independently conducted for each study with reference to HapMap phase 2 or 3 CEU genotypes (Central European ancestry). Study level association analysis was performed using logistic regression models based on an expected additive allelic dosage model for SNPs, adjusting for ancestry-informative principal components as necessary. SNPs with MAF <1% and/or poor imputation quality (MACH r^2 <0.3 or IMPUTE proper info <0.4) were excluded. After genomic control at the level of the individual studies, the summary statistics were meta-analyzed using a fixed effects model and inverse variance as weights in METAL (2010-08-01). In total 2,400,129 SNPs were available in three or more cohorts.

GWAS results from the 23andMe study were included in the present study involving 10,509 individuals with self-reported cat-allergy, 9,815 with Dust-mite allergy, 16,133 with Pollen allergy (grasses, trees or weeds) and 26,311 without symptoms in a total of 46,646 individuals. Allergy was defined as those individuals who reported a positive allergy test, difficulty in swallowing or speaking, hives, itchy mouth, itchy eyes, itchy nose or asthma in response to a particular allergen. The second part of the study sample on self-reported allergy (mothers from the Alspac cohort) was not included in the present study as these individuals are related to individuals in the GWA on sensitization.
Imputation was performed in the 23andMe study using the 1000 Genomes reference (August 2010 release) in batches. SNPs with an imputed $r^2 > 0.5$ averaged across all batches and $r^2 > 0.3$ in every batch were used. SNPs were remapped to B36. A generalized estimating equation (GEE) model was applied to assess the shared genetic effects on all three phenotypes taking into account the correlations between these phenotypes.

The meta-analysis was performed using a fixed effects model using inverse variance as weights in METAL (2010-08-01)\textsuperscript{4} after a second genomic control for the meta-analysis of the dataset on self reported allergy and sensitization.

**Enrichment of autoimmune disease-associated loci and allergy**

Candidate loci were chosen from the GWA’s catalog\textsuperscript{5} accessed 25th of November 2013 using autoimmune and inflammatory traits of interest (Supplementary Table E1). These reported traits were collapsed into 16 overall autoimmune disease traits. All SNP-trait associations with P$<5e$-8 were used. We collapsed close SNPs into loci (+/-250kb)\textsuperscript{6} and used for each locus the SNP with lowest reported P as index SNP (Supplementary Figure 1). For common loci (listed in table 2), all original publications were checked for effect allele, and any discrepancies with the GWA’S catalog was corrected. After the extraction of SNP-associations, the enrichment Odds Ratio was calculated as the number of observed extracted SNPs with P$<0.05$ out of total extracted SNPs as compared to total number of independent SNPs with P$<0.05$ within the GWA discovery results using a Fisher’s exact test. For this we used Hapmap, CEU panel, to define independent loci. This was performed using PLINK (-- indep-pairwise 200 5 0.5) with a sliding window on 200 SNPs at steps on 5 SNPs pruning the datasets to contain only one of 2 correlated SNPs with a r^2$>0.5$. To plot enrichment, we equally plotted observed P-values against expected under the null hypothesis (QQ plots). Enrichment and QQ plots were plotted overall for all 290 loci and separately for each of the 16 autoimmune diseases, however only for those diseases with more than 10 loci reported in the GWA catalogue. For extracted SNPs a False Discovery Rate corrected P-value $< 0.05$ was considered significant. Analysis were performed in Plink\textsuperscript{7} and R project (3.0.1)\textsuperscript{8}. 
Functional evaluation

Enrichment of SNPs falling in DHS sites:
DHS sites were downloaded from the ENCODE project and from the Epigenomics Roadmap selecting only cell types (or cell lines, herefrom “cell types”) with duplicates, removing transformed cell types, and removing redundant cell lines, based on manual curation. Huh7 was an outlier in all analyses, and was removed. DHS sites were set to a fixed width of 150bp from center of region for all cell types. Allergy and Crohn’s Disease SNPs were split in bins of increasing p-value cutoff, starting at 1 (including all SNPs and setting baseline for enrichment) and decreasing one decimal digit per each bin (1, 0.1, 0.001 etc). Each bin was overlapped with DHS regions using bedtools v2.19.0, and enrichment for each bin was calculated for each cell type as compared to p =1. For GWAS Catalogue SNPs, SNPs were selected for traits with > 30 reported associated SNPs. For identical SNPs for the same trait, the SNP with the lowest p-value was chosen. SNPs were then overlapped with DHS regions using bedtools v2.19.0, and ratio of overlapping SNPs was calculated. To filter out non-informative cell-types, only cell-types with the highest quartile of overlap ratios was included. For immune cell hierarchical clustering the manhattan distance of square root transformed ratios were used. For PCA, log10 transformed ratios were used.

Enrichment of SNPs falling in FANTOM enhancers:
FANTOM cell specific enhancers were downloaded from ‘http://enhancer.binf.ku.dk/’ and were set to a fixed width of 150bp from center of region for all cell types. The ratio between overlaps of all SNPs (p <= 1) and SNPs at p<= 1e-5 was calculated, and a p-value for this ratio calculated using a binomial test with the genomic overlap frequency as null frequency, calculated as the number of total enhancers per cell type times enhancer length (150bp), divided by the total number of base pairs shown to be bound by transcription factors in the human genome across cell types in the ENCODE project (231mb). FDR values were calculated adjusting p-values with the Benjamini-Hochberg method.
Data-driven Enrichment-Prioritized Integration for Complex Traits (DEPICT):

For details of this method please refer to Pers et al.\textsuperscript{11}. DEPICT facilitates gene set enrichment analysis by testing whether genes in associated regions enrich for reconstituted versions of known pathways, gene sets, as well as protein complexes. The gene-set enrichment analyses in DEPICT contains three steps: first a scoring step; second a bias correcting step taking into account gene density that possibly could inflate results due to gene length and finally estimating experiment-wide FDR’s.

Gene set reconstitution is accomplished by identifying genes that are co-expressed with genes in a given gene set based on a panel of 77,840 gene expression microarrays; genes that co-express with genes from a given gene set are likely to be part of that gene set.\textsuperscript{12} In DEPICT, several types of gene sets were reconstituted: 5,984 protein complexes that were derived from 169,810 high-confidence experimentally-derived protein-protein interactions\textsuperscript{13}; 2,473 phenotypic gene sets derived from 211,882 gene-phenotype pairs from the Mouse Genetics Initiative\textsuperscript{14}; 737 Reactome database pathways\textsuperscript{15}; 184 KEGG database pathways\textsuperscript{16}; and 5,083 Gene Ontology database terms\textsuperscript{17}. In addition, the DEPICT also facilitates tissue and cell type enrichment analysis, by testing whether genes in associated regions are highly expressed in any of 209 Medical Subject Heading annotations of 37,427 microarrays from the Affymetrix U133 Plus 2.0 Array platform. We used DEPICT to test enrichment in a total of 14,461 reconstituted gene sets and enrichment of 209 tissue and cell type annotations. For the allergy meta-analysis, and Crohn’s disease, DEPICT was performed on all loci $P<10^{-5}$. For PCA GWAS catalogue data, DEPICT was performed on all traits with more than 30 reported associated SNPs. For identical SNPs for the same trait, the SNP with the lowest $p$-value was chosen.

Pathway analysis and visualization for allergy and Crohn’s disease:

To account for difference in GWAS study sizes, a linear model was fitted between logged $p$-values of DEPICT results for allergy and Chron’s disease, and the estimator was used to adjust the $p$-value thresholds for the largest study, Crohn’s disease. The inflation estimate for Crohn’s disease was 1.21. Shared pathways were set at $p_{allergy}$ and $p_{crohns\_adjusted} < 0.001$, allergy specific pathways were set at $p_{allergy} < 0.001$ and $p_{crohns\_adjusted} > 0.05$ and Crohn’s disease specific pathways were set at $p_{allergy} > 0.05$ and $p_{crohns\_adjusted} < 0.001$. 
DHS genomic location:

Genomic regions for 186 cell types, of which 14 cell types (CD14_Primary_Cells, CD19_Primary_Cells_Peripheral_UW, CD20, CD3_Primary_Cells_Cord_BI, CD3_Primary_Cells_Peripheral_UW, CD34Mobilized, CD56_Primary_Cells, Th0, Th1, Th17, Th2, Treg, GM12864, and Fetal_Thymus) were annotated as immune cells, were downloaded from the ROADMAP and ENCODE tracks (June 2014) in the UCSC Genome Browser and processed by bedtools, ensuring no redundancy between exons, introns, promoters (defined as 5000 bases upstream and 200 bases downstream of transcription start sites), and intergenic sites. DHS sites were overlapped with genomic regions, requiring 1bp of overlap. Enrichment of markers in DHS regions was calculated for GWAS catalog traits with 30 or more reported variants, and was normalized by trait SNP count and cell type specific DNAse sequence lengths.

The uneven distribution of cell types within the Roadmap ENCODE dataset could possibly contribute to the separation of immune-mediated diseases from other diseases. However, repeated iterative removal of ¼ of cell types continuously produced a statistical significant separation of autoimmune diseases, allergy and asthma vs. other traits (results not shown), hence supporting the finding of common SNPs and cell types to congregate in allergy and autoimmune diseases. In addition, hierarchical clustering was performed on the full ENCODE Roadmap set to investigate if this clustering was facilitated by similar DHS-profiles in different immune cells, basically representing a single “immune-system-footprint”, but this was not the case, as different immune cell types also separated internally, comparable to other non-immune cell types (Supplementary Figure 18).

A further cluster analysis of the cell-type specific genomic DHS location in all cells (intronic, exonic, intergenic, promoter) was performed revealing that the DHS sites in immune cells tend to fall within promoter and exonic regions (Supplementary Figure 19).
Transcription factor binding sites:

Transcription factor binding sites for 161 transcription sites were downloaded in BED format from ENCODE for the hg19 build, and were intersected with 28 independent shared loci, expanded to included markers with r2>= 0.5 in the 1000g CEU panel, using BedTools. Enrichment and one-sided p-values were calculated in relation to an empirical null distribution of loci overlap for each TF, generated by 10,000 random permutations of random genomic loci with the same length characteristics as the 28 LD-expanded shared loci. Random locus LD-structure was assumed to have no effect on TF-binding probability as a function of locus length.
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Supplementary Figure 1

Flowchart of the selected known autoimmune disease associated SNPs/loci for lookup in the allergy GWAS identified within the GWA’s catalog (accessed 25th of November 2013). Please also see methods section here in the supplement. A detailed description for each step in the flow chart:

1) The GWA’s catalog\(^5\) were accessed 25th of November 2013.

2) All autoimmune diseases and associations to SNPs were selected with p<5*10^-8. The chosen traits were collapsed into 16 overall autoimmune disease categories (see supplemental table 1)

3) We collapsed close SNPs into loci (+/-250kb)\(^6\) and used for each locus only the SNP with lowest reported P as index SNP and as representative for the specific locus.

4) For several of the SNPs we had to use a proxy SNP as the index SNP were not present within the allergy GWAS. Proxy SNPs were chosen on highest r\(^2\) to index SNP and if two or more proxies had the same r\(^2\) the SNP closest in physical distance to the index SNP were chosen. In total 290 SNPs were available for look up/extraction within the allergy GWAS.
Supplementary Figure 2
QQ plot of the meta-analysed 2,284,215 SNPs and association to 1) Sensitization
2) Self-reported allergy 3) These two data-sets meta-analysed and 4) Without reported known loci
Supplementary Figure 3
Manhattan plot of the meta-analysed 2,284,215 SNPs and association to allergy. Red dots indicate novel loci not described in the discovery papers (grey)\(^2,3\), with \(p<5\times10^{-6}\). Dashed line: 10e-6. Solid line: 5e-8.
Supplementary Figure 4
LocusZoom plots of the suggestive novel loci from the allergy meta-analyses
Plotted SNPs

rs7612543

Position on chr3 (Mb)

Recombination rate (cM/Mb)

log_{10}(p-value)

0.2 0.4 0.6 0.8

r^2

SPSB4 ACPL2 ZBTB38 RASA2 RNF7

GRK7

142.4 142.6 142.8 143
Supplementary Figure 5

QQ plots of the autoimmune disease associated loci within the combined allergy meta-analysis as well as allergic sensitization and self-reported allergy separately. The numbers in the figures show enrichment Odds Ratio and P-value for enrichment.
Supplementary Figure 6
Separate QQ plots of the autoimmune disease associated loci within the allergy meta-analysis with printed calculated enrichment Odds Ratio and P-value for enrichment. Only plotted for autoimmune diseases with at least 10 loci associated. Solid line reflects the P-value distribution under the null while the dashed is the distribution of all SNPs from the allergy meta-analysis.

Ankylosing Spondylitis:

OR=3.96, P=1.1e−01
Arthritis:

OR = 5.18, P = 2e-04
Celiac Disease:

OR=7.85, P=1.7e-06
Primary Biliary Cirrhosis:

OR=7.8, P=1.4e−04
Ulcerative colitis:

OR=6.48, P=6.4e−08
Crohn's Disease:

OR=6.53, P=5e−12
Graves Disease:

OR=4.46, P=4.2e−02
Inflammatory Bowel Disease:

OR=5.51, P=2.6e−16
Systemic Lupus Erythematosus:

\[ \text{OR} = 3.1, \quad P = 5.3 \times 10^{-02} \]
Multiple Sclerosis:

OR=5.09, P=2.1e-05
Type-1 Diabetes:

OR=4.07, \text{P}=1.7\times10^{-03}
Supplementary Figure 7
QQ plot of 57 Migraine loci extracted from the allergy meta-analysis results.

Migraine:
Supplementary Figure 8

QQ plot of 77 loci associated with the combined phenotype of schizophrenia and bipolar disorder extracted from the allergy meta-analysis results.

Bipolar disorder and schizophrenia:
Supplementary Figure 9
Principal component plot of GWAS Catalogue SNPs’ perturbation of gene networks, based on the DEPICT tool, PC1 vs PC3

(PLEASE SEE SEPARATE FILE)
Supplementary Figure 10
Principal component plot of GWAS Catalogue SNPs’ perturbation of gene networks, based on the DEPICT tool, PC1 vs PC2, all trait names.

(PLEASE SEE SEPARATE FILE)
**Supplementary Figure 11**

Allergy related loci and their resemblance to autoimmune disease and other types of disease loci were assessed by principal component analysis by analyzing the tendency of each trait-locus to fall in DHS sites in specific cell lines. This plot shows PC1 vs. PC2 and has the outlier “lipid metabolism phenotypes” omitted, and only names for autoimmune diseases, asthma and allergy are printed. The blue area represents the shared minimal ellipsoid area of immune-mediated diseases.

(PLEASE SEE SEPARATE FILE)
Supplementary Figure 12

Allergy related loci and their resemblance to autoimmune disease and other types of disease loci were assessed by principal component analysis by analyzing the tendency of each trait-locus to fall in DHS sites in specific cell lines. This plot shows PC1 vs. PC2 for the full data set.

(PLEASE SEE SEPARATE FILE)
Supplementary Figure 13
Allergy related loci and their resemblance to autoimmune disease and other types of disease loci were assessed by principal component analysis by analyzing the tendency of each trait-locus to fall in DHS sites in specific cell lines. This plot shows PC1 vs. PC2 overlayed with cell- and tissue type loadings.

(PLEASE SEE SEPARATE FILE)
**Supplementary Figure 14**
Hierarchical clustering of all NHRGI GWAS catalog diseases’ associated SNPs’ tendency to fall within DHS sites for immune cell types within the Encode data set.

(PLEASE SEE SEPARATE FILE)
Supplementary Figure 15
Enrichment of DHS sites in SNPs associated to allergy and Crohn’s disease.
X-axis denominates all SNPs associated to the given trait at −log10(p) \( \leq x \), and \( y \) gives the enrichment of DHS sites for a given cell/tissue-type for those SNPs, as compared to all SNPs (x=0). Immune cells are indicated in blue.

(PLEASE SEE SEPARATE FILE)
Supplementary Figure 16
Enrichment of SNPs falling in FANTOM enhancers

(PLEASE SEE SEPARATE FILE)
Supplementary Figure 17
PCA plot of DEPICT pathway perturbation analysis, showing names for all gene sets.

(PLEASE SEE SEPARATE FILE)
Supplementary Figure 18
Enrichment of shared loci with ENCODE ChIP-seq based transcription factor binding sites. Green line indicates FDR < 0.05. Transcription factors in blue have FDR < 0.05 and enrichment >= 3.

(PLEASE SEE SEPARATE FILE)
Supplementary Figure 19
LocusZoom plots of the autoimmune disease associated loci within the allergy meta-analysis. Each dot represents the association between allergy and the particular SNP. The purple SNP is the index SNP for which the remaining SNPs are colored with respect to the r2 value to the index SNP. The position on the Y-axis represents the P-value (left handside Y-axis). The blue line represents recombination rates (right handside Y-axis).
rs12708716

Plotted SNPs: TEKT5, NUBP1, C16orf75, FAM18A, CIITA, CLEC16A, SOCS1, C16orf75, TNP2, PRM3, PRM2, PRM1

- log10(p-value) vs Recombination rate (cM/Mb)

<table>
<thead>
<tr>
<th>Gene</th>
<th>Position on chr16 (Mb)</th>
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<tbody>
<tr>
<td>TEKT5</td>
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<tr>
<td>NUBP1</td>
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<td>PRM2</td>
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<td>PRM1</td>
<td></td>
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</tbody>
</table>
Plotted SNPs:

- rs505922

Position on chr9 (Mb):

1 gene omitted
Plotted SNPs

rs4845604
Plotted SNPs

- log10(p-value)

- Recombination rate (cM/Mb)

- rs6863411

- PCDH1
- PCDH12
- NDFIP1
- SPRY4
- LOC729080
- GNPDA1
- KIAA0141
- RNF14
- NDFIP1
- SPRY4

Position on chr5 (Mb)
**Supplementary Figure 20**

Paired LocusZoom plots within a Crohn’s data\textsuperscript{17} meta-analysis (top panel) and the allergy meta-analysis (bottom panel) for the 5 most significant shared loci.
Supplementary Figure 21

ENCODER Roadmap DHS region overlap with genomic features. DHS regions for each cell type (vertical lines) were overlapped with genomic features (exons, introns, promoters, and intergenic (remaining)) (horizontal lines). Overlaps were z-scaled within each feature, and a heatmap was generated after hierarchical clustering. Immune cells are marked in red at bottom.
Supplementary Figure 22
Association plot for rs11122898 with added enhancer regions for four cell types, as well as enhancer-to-gene regulatory associations, from the FANTOM5 data repository.19
Supplement references