Shared genetic variants suggest common pathways in allergy and autoimmune diseases

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Abstract

Background

The relationship between allergy and autoimmune disorders is complex and poorly understood.

Objective

To investigate commonalities in genetic loci and pathways between allergy and autoimmune diseases to elucidate shared disease mechanisms.

Methods

We meta-analyzed two GWAS on self-reported allergy and sensitization comprising a total of 62,330 individuals. These results were used to calculate enrichment for SNPs previously associated with autoimmune diseases. Furthermore, we probed for enrichment within genetic pathways and of transcription factor binding sites, and characterized commonalities in the variant burden on tissue-specific regulatory sites by calculating the enrichment of allergy SNPs falling in gene regulatory regions in various cells using Encode Roadmap DHS data, and compared the allergy data with all known diseases.

Results

Among 290 loci previously associated with 16 autoimmune diseases, we found a significant enrichment of loci also associated with allergy ($p=1.4e-17$) encompassing 29 loci at a false discovery rate<0.05. Such enrichment seemed to be a general characteristic for all

autoimmune diseases. Among the common loci, 48% had the same direction of effect for allergy and autoimmune diseases. Additionally, we observed an enrichment of allergy SNPs falling within immune pathways and regions of chromatin accessible in immune cells that was also represented in autoimmune diseases, but not in other diseases.

Conclusion

We identified shared susceptibility loci and commonalities in pathways between allergy and autoimmune diseases, suggesting shared diseases mechanisms. Further studies of these shared genetic mechanisms might help understanding the complex relationship between these diseases, including the parallel increase in disease prevalence.

Capsule Summary

We identified shared susceptibility loci and commonalities in pathways between allergy and autoimmune diseases. Further studies of these loci and related mechanisms might help understanding the complex relationship between allergy and autoimmunity.

Key messages

- Allergy and autoimmune diseases share genetic susceptibility loci.
- These results indicate commonalities in gene regulation and genetic pathways between allergy and autoimmune diseases.
- Further studies of common genetic loci and the related mechanisms might help understanding the complex relationship between allergy and autoimmunity.

Key words

Allergy, Single Nucleotide Polymorphism, Autoimmune Disease, Autoimmunity, Genetic Association Studies

Abbreviations

DEPICT: Data-driven Expression Prioritized Integration for Complex Traits gene set enrichment method

DHS: DNase Hypersensitive Sites

GWA(S): Genome Wide Association (Studies)

PCA: Principal Component Analysis

SNP: Single Nucleotide Polymorphism

Introduction

There has been a parallel increase in allergic and autoimmune disorders in recent decades in "westernized" countries[1] suggesting that these diseases may share disease mechanisms and etiologies. In line with this, allergy and autoimmune disorders seem to share environmental risk factors including birth by caesarian section[2]. This observation is in apparent contrast to the understanding of allergy and autoimmune diseases as representatives of distinct immunological disorders with counteracting underlying immune mechanisms. Autoimmune diseases are in general thought to act through a Th1/Th17-driven cell mediated immune response,[3] while allergy and asthma encompass a Th2-mediated response[4]. Counteracting immune mechanisms have been supported by some epidemiological studies of comorbidity suggesting a lower incidence of allergy among patients with autoimmune diseases, including rheumatoid arthritis[5,6] and multiples sclerosis[7], although the evidence of such inverse relationship is conflicting.[8]

Both allergy and autoimmune diseases are highly heritable diseases and an increasing number of susceptibility loci have been discovered.[9–11] We hypothesized that studying commonalities in the genetic architecture could provide a key to understanding the complex relationship between these diseases by pinpointing possible common disease mechanisms. In a wider perspective, this might help to explain the mechanisms and aetiologies responsible for the contemporaneous, dramatic increase in incidence of allergic and autoimmune disorders[1].

We studied commonalities between allergy and autoimmune disease in terms of susceptibility loci, genetic pathways and regulatory mechanisms. We meta-analyzed two

GWAS on allergic sensitization and allergic symptoms representing the largest GWAS on allergy to date. These data were then combined with publically available GWAS data on autoimmune diseases, as well as public data on molecular pathways, transcription factor binding sites and regulatory DNA regions. The primary analyses used a methodological approach that was agnostic to the direction of effect (including loci where the risk-allele was the same for allergy and autoimmune disease as well as loci where the risk allele for one disease was protective for the other). We hypothesized that loci with same direction of effect for different diseases might be involved in shared mechanisms and thereby help understanding the parallel epidemics of diseases, while loci with opposite direction of effect might help understanding counteracting (diverging) disease mechanisms. In analogue, gene variants in beta-adrenoreceptors are likely to show diverging effects with respect to risk of cardiac and respiratory diseases but still pinpoint an essential mechanism for both diseases. For allergy and autoimmune diseases such loci might be involved in “polarization” of the immune response. We therefore chose an approach that would capture common genetic loci with both same and opposite direction of effect since we believe that both might confer important information and thereby help to elucidate the complex mechanistic relationship between these diseases.

Methods

Study group

To obtain the largest possible GWAS data set for allergy, we meta-analyzed results from two recent GWAS on self-reported allergy[9] and sensitization[10], including ~2.2 million directly genotyped and imputed single nucleotide polymorphisms (SNPs), using a fixed effects model. The self-reported allergy dataset comprised 23,335 individuals with self-reported allergy for cat-, dust-mite and/or pollen-allergy and 26,311 control subjects without symptoms. The allergic sensitization dataset included 5,809 subjects with allergic sensitization defined by either skin prick test or specific IgE measurement and 9,875 control subjects without allergic sensitization with data from the following cohorts: AAGC, ALSPAC, B58C, COPSAC2000, LISA, MAAS, NFBC 1966, RAINE and PIAMA (**Supplementary Methods**).

Common genetic loci

To identify common genetic loci, we identified all SNPs previously shown to be associated with autoimmune diseases from the NHGRI GWAS catalog[12]. From each locus defined by genetic distance (**Supplementary Methods**) the most significant SNP associated with autoimmune diseases (the index disease, one of 16 different diseases) was chosen, leaving 290 candidate SNPs which where subsequently extracted from the allergy meta-analysis results (**Supplementary Methods, Supplementary Table 1 and Supplementary Figure 1**). For each SNP, the direction of effect of the risk allele for allergy was compared with the direction of effect for the index autoimmune disease as well as for other autoimmune diseases with reported loci in high LD.

Among these autoimmune disease-associated SNPs (loci) we calculated an enrichment of significant SNPs in relation to allergy ($P<0.05$) as compared to expected under the null hypothesis. Enrichment was only calculated for diseases with at least ten loci associated with the index disease and therefore not calculated for systemic sclerosis, sarcoidosis, primary sclerosing cholangitis and myasthenia gravis. As a methodological negative control, SNPs related to two non-inflammatory phenotypes with reasonable GWA study sizes, migraine and the combination of bipolar disorder and schizophrenia from the GWAS catalog, were analyzed similarly.

Commonalities in genetic pathways

To investigate commonalities in functional origins, the Data-driven Expression Prioritized Integration for Complex Traits (DEPICT) gene set enrichment method[13] was applied to 123 diseases and traits in the GWAS catalog, as well as the current association data set on allergy, by analyzing gene set enrichments for 14,416 reconstituted gene sets capturing a wide spectrum of molecular pathways, functional annotations and mouse phenotypes. For visualization purposes the resulting enrichment matrix was reduced to fewer dimensions by principal component analysis (**Figure 1**, **Supplementary Methods**). Similarly, this approach was applied to the common loci between allergy and autoimmune diseases (**Figure 2**), and to allergy and Crohn's disease separately to identify common and disease specific networks (**Figure 3**, **Supplementary Methods**). Crohn's disease was used as a representative of autoimmune diseases as this represents the largest, with respect to sample size, public available GWAS dataset to date of an autoimmune disease[14]. Also, we consider this a good

representative of autoimmune diseases since it is considered to be Th1 driven immune like most autoimmune diseases.

The enrichment of transcription factor (TF) binding sites in loci common between allergy and autoimmune diseases was calculated using ENCODE data by assessing the overlap between loci and binding sites for 161 TFs compared to random expectations (**Supplementary Methods**).

Common disease-implicated cell types

To identify and visualize common disease-implicated cell types, the tendency of disease associated loci to fall in cell-type specific regulatory DNase Hypersensitive Sites (DHS) (a proxy for accessible and/or regulatory DNA) was calculated for all diseases in the GWAS catalog, as well as allergy based upon the current association data-set. This enrichment was computed for 168 cell types and cell lines (hereafter described as cells) from the ENCODE Roadmap repository[15]. Duplicates and directly redundant cell types were removed before analyses. As with pathway enrichments, the resulting enrichment matrix was reduced to fewer dimensions by PCA for visualization (**Supplementary Methods**). For allergy this was also compared for the full range of p-values within the allergy meta-analysis in bins of decreasing p-value thresholds, essentially as done by Maurano and colleagues[16]. This was similarly done for Crohn's disease for comparison[14] using data from a GWAS metanalysis[14] including data from 6 studies of European descent with in total 6,333 cases and 15,056 controls in the discovery imputed with Hapmap III or II with in total of 953,242 autosomal SNPs. To validate specific findings, the DHS enrichment was re-calculated for enhancer regions in data from the more conservative FANTOM5 set[17].

Results

Allergy meta-analysis

By use of the joint meta-analysis on combined data from allergic sensitization and self reported allergy we increased the number of allergy-associated SNPs compared to the previous GWAS (**Supplementary Figure 2**) resulting in a total number of 19 genome-wide significant loci (**Supplementary Figure 3**). One of these; rs11122898 near *ANAPC1/MERKT* (p=1.9e-8) has not previously been associated with allergy or any related trait. In addition there were 5 novel suggestive loci (p<e-5): rs7612543 near *ZBTB38* (p=1.0e-7); rs9790601 near *NFKB1* (P=7.4e-8); rs7072398 near *IL2RA* (p=5.2e-7); rs12365699 near *CXCR5* (p=6.5e-7) and rs12900122 near *RORA* (p=3.5e-7) (**Supplementary Figure 4 and Supplementary Table 2**). Notably, all of these suggestive loci have previously been described in relation to autoimmune disorders[11,18–30].

Commonalities in genetic loci, pathways and disease implicated cell types between allergy and autoimmune diseases

There was a significant enrichment of autoimmune-associated loci with low p-values among the allergy loci from the current meta-analysis compared with expected (enrichment OR=4.36 [3.2-5.9], p=1.4e-17) (**Figure 1A, Table 1 and supplementary table 3**). A similar enrichment was seen for the two allergy phenotypes separately (self reported allergy: OR=4.1 [3.0-5.5] p=1.1e-15, and allergic sensitization: OR=2.7 [1.6-4.0] p=1.8e-5) (**Supplementary Figure 5**). This enrichment was also seen for the individual autoimmune diseases (**Figure 1A and Supplementary Figure 6**), although not statistically significant for

Systemic Lupus Erythematosus and Ankylosing Spondylitis and for Psoriasis and Graves Disease after adjusting for multiple testing (**Table 1**). We a priori chose a P-value threshold for the calculations of enrichment of <0.05. Using lower thresholds (P <0.01 or 0.001) generally resulted in higher enrichment and significant enrichment for all autoimmune diseases.

As a methodological negative control, SNPs related to two non-inflammatory phenotypes with a large number of known genome-wide significant loci, migraine and the combination of bipolar disorder and schizophrenia from the GWAS catalog were extracted from the allergy meta-analysis. These showed no significant overlap with allergy loci (**Supplementary Figures 7 and 8**).

Using DEPICT to identify significantly enriched reconstituted gene sets for allergy (**Supplementary Table 4**) and all diseases in the GWAS catalog, we identified a strong separation of autoimmune diseases, allergy and asthma from other traits on the first PCA component (Wilcoxon rank sum test p_{PC1}=8.142e-08, Wilcoxon rank sum test) (**Figure 1B and Supplementary Figures 9 and 10**). Notably, no other disease groups seemed to cluster strongly together (**Supplementary Figures 9 and 10**).

Analysis of all published SNP-to-trait associations and the tendency of these SNPs to fall within regions of open chromatin (represented by DHS) in specific cell types[31] likewise revealed that autoimmune diseases, allergy and asthma clustered together, and differentiated from other non-immune diseases on the first two PCA components (**Supplementary Figures 11 and 12**, p_{PC1}=0.0035, p_{PC2}=3.856e-07, Wilcoxon rank sum test). Loadings indicated that immune cells are responsible for this partitioning (**Supplementary**

Figure 13). Hierarchical clustering of the DHS sites within immune cells similarly showed the tendency of co-clustering of autoimmune diseases with allergy and asthma (**Supplementary Figure 14**). Specific DHS-analyses of allergy and Crohn's disease showed similar enrichment in variants falling within DHS regions of immune cells (**Supplementary Figure 15**). For allergy, these findings were validated in the FANTOM5 high confidence enhancer data set, which showed comparable enrichment among immune cells (**Supplementary Figure 16**)"

The specific common genetic loci

Out of the 290 autoimmune disease SNPs investigated, 29 were significantly associated with allergy at a FDR <0.05 (**Table 2**). Eleven of these common loci (*C11ORF30*, *LPP*, *PLCL1*, *HLA-B*, *SMAD3*, *IKZF3*, *MYC*, *CLEC16A, NDFIP1, BACH2* and *IL2RA/IL15RA*) were already reported to be associated with allergy[9,10,32,33] (**Table 2 and Supplementary Table 5 and 6**). The remaining 18 overlapping loci included the mapped genes: *NFKB1*, *SH2B3*, *AKAP11/TNFSF11*, *ABO*, *C12ORF30*, *CD247*, *RADSNB*, *EP300*, *RORC*, *PSMG1*, *HDAC7/VDR*, *HLA-DPB2*, *BACH2*, *TNFAIP3*, *KIF1B*, *RPS6KA4*, *ERBB3*, *THADA*, and *GLB1/CCR4*. Look up of the 29 common loci in the separate results from the 2 different allergy-phenotypes (allergic symptoms and allergic sensitization) generally showed similar results, including same direction of effect for the two allergy-phenotypes for 28 out of 29 loci (**Supplementary Table 5**). For the majority of loci the effect size was higher for allergic sensitization compared to allergic symptoms, as would be expected due to the more homogenous phenotype, and for the majority of loci with evidence of heterogeneity between phenotypes, heterogeneity was due to this. The NDFIP1 locus seemed only to be associated with self reported allergy.

Comparison of the direction of effect between allergy and autoimmune disease was possible for 27 of the 29 common loci compared with the index autoimmune disease. For 13 of these (48%), we found the same direction of effect meaning that the allele increasing the risk of allergy also increases the risk of the autoimmune disease (**Table 2**). For the remaining 14 loci (52%), we found opposite direction of effect with the risk allele for allergy being associated with reduced risk of the index autoimmune disease (**Table 2 and Supplementary Table 5**). The majority of autoimmune diseases showed examples of both same and opposite direction of effect compared to allergy. For some of the common loci where several autoimmune diseases have reported association, the different autoimmune diseases showed differences in direction of effect relative to allergy (*HLA-B*, *BACH2* and *RPS6KA4*). After gene set enrichment analyses of these 29 common loci, the resulting significant hits were all ontological terms relating to immune function, including immunoglobulin diversification and production, T-and B-cell activation, signaling by nuclear receptors and abnormal immune cell physiology. (**Figure 2**, **Supplementary Figure 17 and Supplementary Table 7**). Coloring for loci with same vs. opposite direction of effect for allergy and autoimmune diseases showed no clear systematic differences (Figure 2).

To investigate the potential enrichment for certain transcription factors in mediating the effect at common loci, public transcription factor binding data from ENCODE were analyzed for overlap within loci common between allergy and autoimmune diseases. This revealed significant enrichment for several immune related transcription factors (**Supplementary Figure 18**).

In order to investigate if the common loci seem to tag the same genetic variant, we performed regional association plots showing that, for almost all loci, the autoimmune disease tagging SNP is also within the LD-block with strongest regional association with allergy (**Supplementary Figure 19**). Tagging of the same genetic variation at common loci was further supported by paired comparison of regional association plots for Crohn's disease[14] and allergy, respectively, for the most statistically significant common loci (**Supplementary Figure 20**).

Shared and differential genetic pathways for Allergy and Crohn's disease

A direct comparison of pathways targeted by allergy-related loci vs. Crohn's disease loci revealed that a large proportion of shared as well as disease-specific pathways, with a strong predominance of T cell signaling modules within the shared grouping (**Figure 3**).

Discussion

Our study demonstrated substantial commonalities between allergy and autoimmune diseases in terms of susceptibility loci, genetic pathways and genomic regulatory sites (DHS). This overlap in genetic mechanisms seemed to be a general phenomenon for allergy autoimmune diseases and distinct from other diseases. Our study identifies a substantial number of novel overlapping loci for allergy and autoimmune diseases suggesting both shared (increasing risk of both autoimmune and allergic disease) as well as diverging genetic mechanisms.

Strengths and limitations

By combining two GWAS on allergic sensitization and allergic symptoms respectively, we were able to obtain the most powerful GWAS dataset on allergy to date, which allowed a systematic analysis of the genetic commonalities of allergy and autoimmune diseases. The clinical phenotypes are not identical, with allergic sensitization often being present without symptoms and vice versa, which can also be seen as a limitation of the study. However, the phenotypes are closely correlated genetically as suggested from the initial publications of the individual GWAS' showing highly consistent mutual replication of top-SNPs between studies[9,10]. The improved number of significant SNPs and a higher number of genome-wide significant loci in the combined meta-analysis performed here compared with the individual GWAS results also underscores the validity of the combined meta-analysis approach. Furthermore, the common loci between allergy and autoimmunity generally showed similar results for the two allergy-related phenotypes (**Supplementary Table 5**), and

the enrichment of autoimmune loci was also similar for both phenotypes (**Supplementary Figure 5**), strongly suggesting that the conclusions of this study is not affected by the combination of allergy-related phenotypes.

In the primary analyses we combined GWAS loci from several autoimmune diseases. This was done in order to assess commonalities between allergy and autoimmune diseases in general and to obtain enough autoimmune loci and thereby statistical power to perform more systematic analyses. However, it should be noted that autoimmune diseases represent a heterogenous group of diseases, and the genetic architecture of autoimmune genes seem to include shared, but also differential and opposing genetic mechanisms[34-36]. We therefore also performed separate enrichment analyses for the different autoimmune diseases showing that enrichment for allergy-related loci seem to be the case for the majority of autoimmune diseases (**Supplementary table 8**).

It is a limitation that we did not have access to GWAS data for all autoimmune diseases. For the regional analyses of shared loci, a publicly available GWAS dataset on Crohn's disease was therefore used as a representative of autoimmune disease. It is a limitation of the analyses based on GWAS-catalog markers, that genotype chips and imputation panels and procedures differ between studies, adding marker coverage heterogeneity.

Our study is also limited by differences in study size of GWAS on autoimmune diseases, meaning that the diseases where the largest GWAS have been performed, and most loci have been discovered, will have a relatively larger impact on the results of the analysis combining all autoimmune diseases. The number of reported loci for each autoimmune disease is shown in Table 1.

Interpretation

We found substantial overlap of susceptibility loci for allergy and autoimmune diseases suggesting commonalities in the genetic background and hence the possibility of shared pathogenetic mechanisms. The possible common etiology of allergy and autoimmune diseases was further supported by co-clustering of autoimmune diseases, asthma and allergy in terms of genetic pathways and regulatory sites implying shared disease pathways beyond overlap of associated SNPs.

To our knowledge, no previous study has had sufficient statistical power to systematically explore commonalities in the genetic architecture between allergy and autoimmunity. One previous study found no association between susceptibility loci for type 1 diabetes and total IgE levels[37] arguing against a shared genetic background. However, that study had much lower statistical power than the present study, and the genetics of total IgE has been shown to be different from the genetics of allergen-specific IgE[10]. Another study compared results from a GWAS on asthma with published GWAS results on autoimmune diseases and found evidence of 7 overlapping susceptibility loci, both showing examples of opposite and same direction of effect for asthma and autoimmune diseases[38].

Importantly, our study demonstrates common loci with both the same and opposite direction of effects, potentially pointing towards both converging (shared) and diverging (counteracting) mechanisms, either increasing the risk of both allergy and autoimmune diseases, or increasing the risk for one of the diseases while protecting against the other. Our study thereby provides further understanding of the complex genetic relationship between allergy and autoimmune diseases. We hypothesize that the common loci with same

394 direction of effect may be involved in the mechanisms causing the contemporaneous
395 epidemics of allergy and autoimmune diseases[39] by increasing the susceptibility to immune
396 disorders in general, probably by mechanisms involving gene-environment interaction.
397 Complementarily, common loci with opposite direction of effect may be involved in
398 mechanisms determining the type of immune disorder developing in the individual, resulting
399 in the inverse relationship observed between allergy and some autoimmune diseases[5–7].
400 Understanding the mechanisms of these common genetic loci may improve understanding
401 of the epidemics of allergy and autoimmune diseases. It may also help predict how targeting
402 specific disease mechanisms could have the unintended consequence of increasing the risk
403 of other diseases. We expect the loci with *same direction of effect* to be of particular
404 importance in the search for common mechanisms driving the parallel increases in disease
405 incidence. Of specific interest are the loci at *C11orf30*, *PLCL1* and *SMAD3,* which were
406 strongly associated with allergy as well as several autoimmune diseases. Of these, *C11orf30*
407 and *SMAD3* were also identified in a previous study comparing asthma and autoimmune
408 diseases[38]. Some of the loci with same direction of effect were linked to immune-related
409 transcription factors (*RORC*, *SMAD3*), transcriptional co-factors (*EP300*), cell-cycle regulators
410 (*THADA*) or regulators of transcription (*C11ORF30*, *PLCL1*, *AKAP11*, *NDFIP1*). Several are
411 directly implicated in regulation of regulatory T cells (Treg, *SMAD3*[40], *EP300*[41]) and Th17 cells
412 (*RORC*[42], *SMAD3*[40]), or regulation of immune activity *(IL2RA*). This supports a commonality of
413 autoimmune and allergic diseases based on defects in immune suppressive functions. Other
414 loci with same direction of effect included *CLEC16A*, *TNFSF11*, *CCR4* and *GLB1*, all involved in
415 immune function by different means.

Loci with *opposite direction of effect* might be involved in "polarization" of the immune response. Since allergy is acknowledged to involve Th2-mediated pathology, while most autoimmune diseases involve Th1 cells as well as pathogenic Th17 cells, any genetic factors that perturb Th differentiation ability or the immunosuppressive Treg function could potentially influence the risk of specific disease development. The loci with opposite direction of effect included *LPP*, *NFKB1, TNFAIP3,* all involved in immune cell signaling and activation/deactivation processes. Several of the other loci with opposite direction of effect function as possible regulators of immune cell differentiation (*HDAC7*/*VDR*[43,44], *IKZF3*[45], *SH2B3*, *BACH2*, *RPS6KA4* (*MSK2*)[46]) and cell-cycle regulation (*RAD51L1*), while the remaining loci (*C12ORF30*, *PSMG1*, *HLA-DPB2*, *KIF1B*) are more general regulators of cellular function. It should however be noted that given the complexity of genetic regulation and the fact that the causal genetic variant is unknown for most susceptibility loci, the finding of common genetic loci with apparent opposite direction of effect should be interpreted with caution. It is possible that this is the result of different underlying causal variants in the region, although comparison of regional association plots suggested that the association signals for allergy and autoimmune disease did tag the same genetic variation. Potential polarizing mechanisms associated with these loci should be addressed in future studies, e.g. by demonstrating opposite disease relationships on the level of gene expression and/or protein levels.

Gene set enrichment analyses of the 29 shared loci (**Figure 2**, **Supplementary Figure 17 and Supplementary Table 7**) indicate that immune functioning and activation status specifically within T cells represents a shared focal point for allergy and autoimmune diseases.

Involvement of shared immunological paths was further supported based on the type of transcription factors found to be enriched within the common loci where generic immune regulatory transcription factors including MTA3, WRNIP1 and IKZF1 (Ikaros) turned out as central players (**Supplementary Figure 18**). MTA3 has been shown to be involved in B-cell and T helper cell differentiation[47,48] and WRNIP1 has been reported to regulate expression of transcription factors involved in Treg functioning[49]. IKZF1 activates extensive transcriptional programs involving especially regulation of T, B and NK cells with effects on differentiation, proliferation and apoptotic programs in these cell types[50]. Moreover, several other directly immune-related transcription factors were identified amongst the top 10 hits, including NFATC1, STAT2, MEF2C, RELA, SP2 and ZEB1[51–56].

The comparative pathway analysis between allergy and Crohn's disease highlights that the common pathways of these diseases are founded on (de)regulation of adaptive immune signaling, involving TCR, CD28, IL2/3/5/6, IFNg, GM-CSF, JAK/STAT and IL receptor signaling as well as of apoptosis and IgA production. The Crohn's disease-specific network primarily included pathways associated with innate immune activation involving TLR and NOD signaling, while allergy-specific pathways were associated with signaling from receptor tyrosine kinases such as EGFR. (**Figure 3**)

A strong co-clustering and separation of allergy, asthma and autoimmune diseases in terms of enrichment of SNPs in cell type specific DHS sites, points towards common immune modulatory mechanisms facilitated by the effect of the genetic SNP burden in immune cell-specific regulatory regions (**Supplementary Figures 11 and 13**). For Allergy and Crohn's disease, these related primarily to T and B cell functions (**Supplementary Figure 15**). In

accordance with our findings of coinciding immune cell involvement in several immune-mediated diseases, one previous study on Multiple Sclerosis reported several genetic markers in relevant DHS sites in immune cells.[57] Accordingly and in line with our findings a recent paper focusing on autoimmune disease variants show how these immune mediated diseases are correlated and cluster in tendency for associated variants to be enriched in specifically immune cell enhancers.[58] Moreover, the enrichment of immune-cell specific DHS sites specifically within promoter regions (**Supplementary Methods, Supplementary Figure 21**) may be a result of the adaptability and immediate early gene response requirements of the immune system, and since their positioning is essential for gene expression levels this might also explain why the identified specific SNP variants pose increased risk for disease penetrance.

In addition to pinpointing common loci between allergy and autoimmune diseases, our identification of common loci also suggests a large number of novel allergy loci; 18 of the 29 common loci have not previously been associated with allergy (**Table 2**). Our study suggests that these are all susceptibility loci for allergy that did not reach the criteria for genome-wide significance and was therefore not discovered in previous GWAS.

Furthermore, our combined meta-analysis on allergy and allergic symptoms identified suggestive allergy loci with several previously related to immune function (*NFKB1*[59] and *CXCR5*[60], **Supplementary Table 2**). One novel suggestive allergy locus was discovered at rs11122898 and reached the genome-wide significance threshold. This locus is close to *ANAPC1* but is most likely affecting the upstream *MERKT* gene (**Supplementary Figure 22**), which is involved in regulation of dendritic cells via B-cell activating factor (BAFF)[61]. One

484 additional suggestive locus was at *ZBTB38*, and genes within this family have been shown to
485 have important function in naive B-cell differentiation[62], and have been associated to
486 eczema[63] and asthma with hay fever[33] although it has not been shown that these genes are
487 the causal genes within these loci.
488
489 In conclusion, we performed the first large study on commonalities in the genetic origins of
490 allergy and autoimmune diseases and documented substantial genetic overlap between
491 these diseases. The recent availability of a vast array of genomics data from the ENCODE and
492 other consortia provides a solid foundation for systems biology analysis in disease settings.
493 Exploiting this approach, we identified common molecular pathways between allergy and
494 autoimmune diseases, identical patterns of overlaps with open chromatin specifically within
495 immune cell-specific regulatory regions, and overlap in transcription factor binding sites,
496 emphasizing common characteristics in gene regulation. Further investigation of these
497 commonalities in genetic mechanisms might improve understanding of important biological
498 pathways that increases the risk of allergy and autoimmune diseases as well as mechanisms
499 differentiating these diverse diseases. Understanding of potential shared genetic origins of
500 allergy and autoimmune diseases, maybe particularly related to the loci with the same
501 direction of effect, could point to vulnerable “hot” points in immune system pathways that
502 may also be affected by other modifiers such as epigenetics and environmental exposures.
503 This insight might provide important clues for understanding the parallel epidemics of these
504 diseases and thereby enforce future disease prevention.
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Please see supplement.

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Competing financial interests

D.H. and J.Y.T. are employees of 23andMe. The remaining authors declared no competing interests of relevance to this paper.

Figure Legends

Figure 1. Commonalities in susceptibility loci and genetic pathways between allergy and autoimmune diseases

A) Autoimmune disease-associated loci and their association with allergy. Quantile-quantile plots representing the observed vs. expected p-values in the combined allergy GWAS for all 290 candidate autoimmune disease-associated loci (large panel), and separately for selected autoimmune diseases (smaller panels). Solid line reflects the p-value distribution under the null, while the dashed line is the distribution of all SNPs from the allergy meta-analysis. T1D: Type 1 diabetes.

B) Commonalities in genetic pathways. Principal component analysis of DEPICT gene set enrichment results based on trait- associated variants for 123 traits from the GWAS Catalog and allergy. The blue area represents the shared minimal ellipsoid area of allergy and autoimmune diseases.

Figure 2. Pathway-based analysis of common loci

Principal component analysis of DEPICT gene set enrichment results based on the 29 common loci between allergy and autoimmune diseases, with each dot representing a single enriched gene set. Loadings for the index genes are illustrated by arrows. Genes denoted in blue and orange represent same and opposite direction of effect for allergy, respectively, a*s compared to index autoimmune disease*. For genes denoted in gray, index autoimmune disease did not report effect allele. The blue areas represent cohesive clusters of gene sets

549 with similar immune function. The individual gene set names are shown in **Supplementary**

550 **Figure 15.**

551

552 **Figure 3. Common and disease-specific genetic pathways**

553 DEPICT gene-set enrichment map of common (blue), allergy-specific (red) and Crohn's

554 Disease-specific (green) pathways. The correlation between pathways is depicted by the line

555 width. Sets with a correlation < 0.4 and singletons are not shown.

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559 **Table 1 – Enrichment of significant allergy loci among autoimmune disease-associated loci**

Phenotype	# Loci	# Sig. Loci*	Proportion Sig.	eOR	CI	P
All Autoimmune Loci	290	57	0.20	4.36	[3.20-5.85]	**1.40E-17§**
Inflammatory Bowel Disease	178	42	0.24	5.51	[3.80-7.84]	**2.60E-16§**
Crohn's Disease	97	26	0.27	6.53	[4.00-10.36]	**5.00E-12§**
Ulcerative Colitis	60	16	0.27	6.48	[3.41-11.72]	**6.40E-08§**
Multiple Sclerosis	54	12	0.22	5.09	[2.44-9.86]	**2.10E-05§**
Type 1 Diabetes	43	8	0.19	4.07	[1.63-8.94]	**1.70E-03§**
Arthritis	40	9	0.23	5.18	[2.17-11.14]	**2.00E-04§**
Celiac Disease	36	11	0.31	7.85	[3.48-16.53]	**1.70E-06§**
Systemic Lupus Erythematosus	27	4	0.15	3.10	[0.78-9.07]	5.30E-02
Primary Biliary Cirrosis	23	7	0.30	7.80	[2.71-20.03]	**1.40E-04§**
Psoriasis	19	4	0.21	4.75	[1.15-14.93]	**1.62E-02**
Graves Disease	15	3	0.20	4.46	[0.81-16.52]	**4.20E-02**
Ankylosing Spondylitis	11	2	0.18	3.96	[0.42-19.14]	1.10E-01

* With P<0.05 to allergy

Bold: Nominal significant. §: Significant at Bonferroni (0.05/13)

eOR: enrichment Odds-Ratio calculated for autoimmune diseases with at least 10 loci

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563 **Table 2 – Common loci between allergy and autoimmune diseases**

Chr:BP	Gene	SNP	MAF*	Beta	P, FDR	Het. P**	Traits§	Direction £	Known allergy Locus	Other genes in LD > 0.5
11:75976842	*C11ORF30*	rs2155219[T]	0.47	0.12	6.10E-23	5.20E-03	CrD(+), **IBD(+)**, UC(+)	Same	Yes$	-
3:189595248	*LPP*	rs1464510[A]	0.48	-0.07	4.20E-07	1.40E-01	**CeD(-)**	Opposite	Yes$	-
2:198605140	*PLCL1*	rs6738825[A]	0.48	0.06	9.20E-07	1.90E-01	**CrD**(+)	Same	Yes$	ANKRD44, BOLL, COQ10B, HSPD1, HSPE1, MARS2, MOB4,, RFTN2, SF3B1
6:31444079	*HLA-B*	rs7743761[A]	0.26	-0.07	1.90E-06	4.00E-01	**AS(na)**, GD(-), SLE(+), UC(+)	na	Yes$	-
15:65229650	*SMAD3*	rs17293632[T]	0.27	0.07	2.00E-06	1.90E-01	**CrD(+)**, IBD(+)	Same	Yes$	-
17:35175785	*IKZF3*	rs907092[A]	0.49	-0.06	4.10E-05	8.30E-01	CrD(-), **IBD(-)**, PBC(-), T1D(-), UC(-)	Opposite	Yes$	GSDMB, ORMDL3, ZPBP2
8:128884211	*MYC*	rs4410871[T]	0.28	0.06	4.10E-05	8.60E-04	**MS(-)**	Opposite	Yes$	-
12:110368991	*SH2B3*	rs3184504[T]	0.45	-0.06	5.30E-05	7.50E-02	A(-), CeD(-), **T1D(-)**	Opposite	Novel	ACAD10, ADAM1, ALDH2, ATXN2, BRAP, C12orf47, C12orf51, ERP29, MAPKAP5, NAA25, TMEM116, TRAFD1
13:41950880	*AKAP11, TNFSF11*	rs2062305[A]	0.43	-0.05	2.00E-03	8.50E-01	**CrD(+)**	Same	Novel	-
16:11087374	*CLEC16A*	rs12708716[A]	0.35	0.05	2.00E-03	8.60E-02	MS(+), PBC(+), **T1D(+)**	Same	Yes$	-
9:135139050	*ABO*	rs505922[T]	0.37	-0.05	2.00E-03	2.90E-01	**GD(+)**	Opposite	Novel	-
12:110971201	*C12ORF30*	rs17696736[A]	0.42	0.05	2.20E-03	1.50E-01	**T1D(-)**	Opposite	Novel	-
4:103770651	*NFKB1€*	rs7665090[A]	0.49	0.04	2.70E-03	7.00E-01	**PBC(-)**	Opposite	Novel	MANBA
1:165678008	*CD247*	rs864537[A]	0.38	0.04	4.80E-03	6.10E-01	**A(+)**, CeD(+), SC(+)	Same	Novel	-
14:67823346	*RADSNB*	rs911263[T]	0.29	-0.04	6.40E-03	1.80E-02	**PBC(-)**	Opposite	Novel	-
22:39761288	*EP300*	rs4820425[A]	0.29	0.05	6.60E-03	8.60E-01	**CrD**(+)	Same	Novel	CHADL, DNAJB7, L3MBTL2, RANGAP1, ST13, XPNPEP3, ZC3H7B
1:150068	*RORC*	rs484560	0.14	-0.06	7.50E-03	7.40E-01	**IBD(+)**	Same	Novel	-

304		4[A]								
10:61095 67	*IL2RA, IL15RA*	rs127225 63[A]	0.12	0.06	7.50E-03	1.00E+00	**T1D(na)**	na	Yes$$	-
21:39387 404	*PSMG1*	rs283687 8[A]	0.26	0.05	7.50E-03	3.10E-01	AS(-), **IBD(-)**, UC(-)	Opposite	Novel	-
12:46494 635	*HDAC7, VDR*	rs111682 49[T]	0.48	0.04	8.70E-03	4.60E-01	**IBD(-)**	Opposite	Novel	-
6:331680 96	*HLA-DPB2*	rs228138 8[A]	0.02	-0.13	8.80E-03	3.10E-01	**GD(-)**	Opposite	Novel	-
6:910149 52	*BACH2*	rs117555 27[C]	0.42	0.04	8.80E-03	3.90E-02	CrD(+), **T1D(-)**	Opposite	Yes$$$	-
6:138048 197	*TNFAIP3*	rs692022 0[A]	0.22	-0.05	1.00E-02	3.20E-01	A(-), CeD(-), **IBD(-)**, UC(-)	Opposite	Novel	-
5:141493 388	*NDFIP1*	rs686341 1[A]	0.37	-0.04	1.00E-02	4.90E-02	**IBD(+)**	Same	Yes$$$	-
1:102756 99	*KIF1B*	rs104929 72[T]	0.34	0.04	1.40E-02	5.00E-01	**MS(-)**	Opposite	Novel	PGD, UBE4B
11:63864 311	*RPS6KA4*	rs663743[A]	0.36	0.04	2.50E-02	2.40E-01	CrD(-), **S(+)**	Same	Novel	CCDC88B, ESRRA, GPR137, PRDX5, TRMT112
12:56482 180	*ERBB3*	rs229223 9[T]	0.32	0.04	2.50E-02	2.10E-01	**T1D(+)**	Same	Novel	IKZF4, SUOX
2:436604 22	*THADA*	rs104959 03[T]	0.12	0.05	3.40E-02	5.50E-01	**CrD(+)**, IBD(+)	Same	Novel	-
3:329904 73	*GLB1, CCR4*	rs133149 93[T]	0.43	-0.03	4.70E-02	8.00E-02	**CeD(+)**	Same	Novel	-

** As reported by Bønnelykke et al.[5]*

*** Test for heterogeneity within the allergy meta-analysis*

§ Reported traits associated with locus (autoimmune trait marker LD with allergy marker > 0.6 and allergy marker p < 0.05) A: Arthritis, AS: Ankylosing Spondylitis, CeD: Celiac Disease, CrD: Crohn's Disease, GD: Graves Disease, IBD: Inflammatory Bowel Disease, MS: Multiple Sclerosis, P:Psoriasis, PBC: Primary Biliary Cirrhosis, SLE: Systemic lupus erythematosus, SS: Systemic Sclerosis UC: Ulcerative Colitis, T1D: Type 1 Diabetes. The index disease used in the comparison of effect direction marked by bold and underlined. +/- denotes direction of effect for the autoimmune disease compared to the direction allergy.

£ As compared to index autoimmune disease (underlined and bold in the "Traits" column)-SNP effect direction. Na: Some diseases have not reported the effect allele

$ Genome-wide significant association to allergy/allergic sesnsitization reported by Hinds et al, and/or Bønnelykke et al.[4,5]

$$ Suggestive association to asthma with hayfever reported by Ferreira et al.[33]

$$$ Suggestive association to asthma reported by Ferreira et al.[32]

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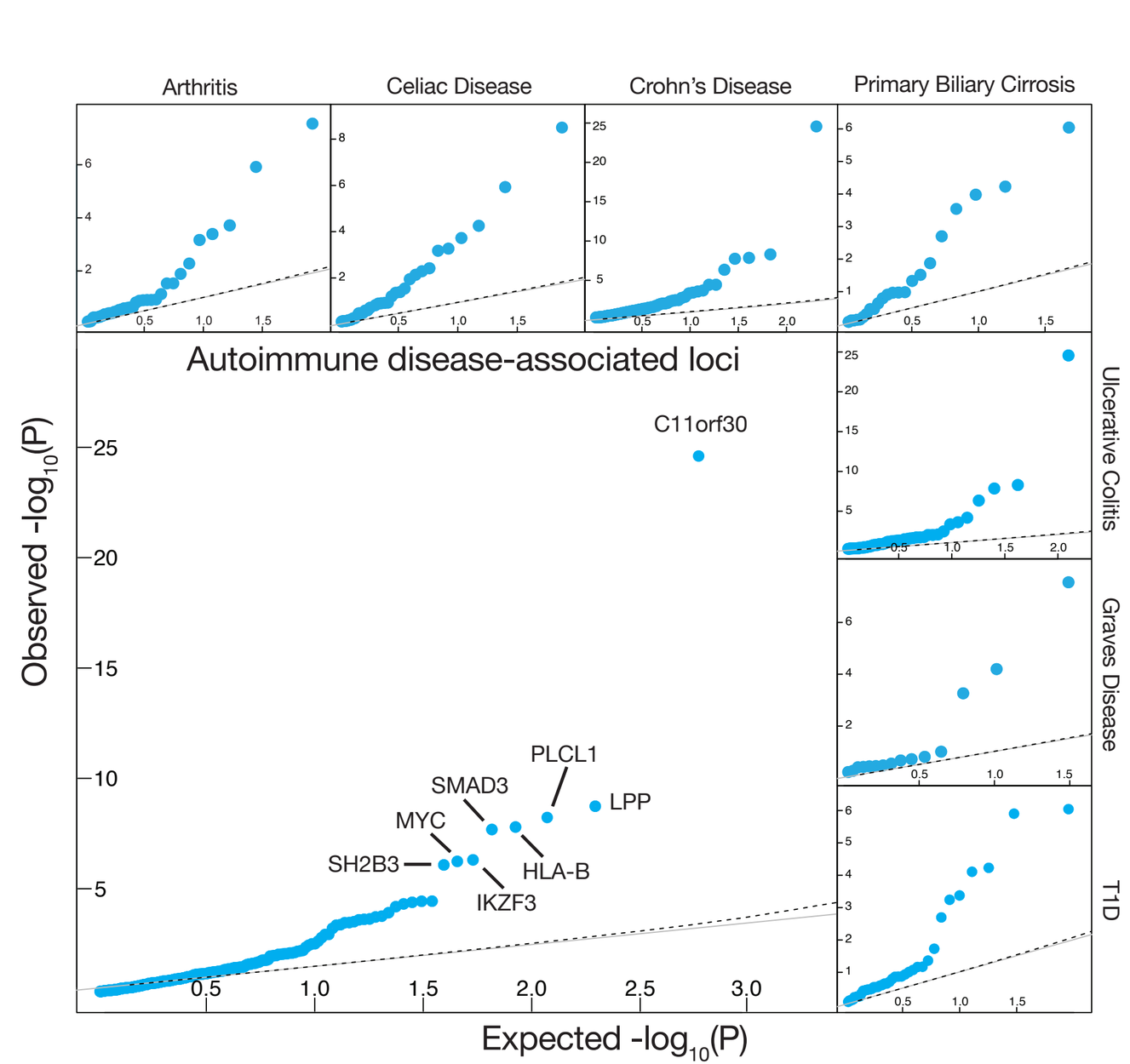
Arthritis
Celiac Disease
Crohn's Disease
Primary Biliary Cirrosis
Autoimmune disease-associated loci
Observed -log10(P)
Expected -log10(P)
C11orf30
PLCL1
SMAD3
LPP
MYC
SH2B3
HLA-B
IKZF3
Ulcerative Colitis
Graves Disease
T1D

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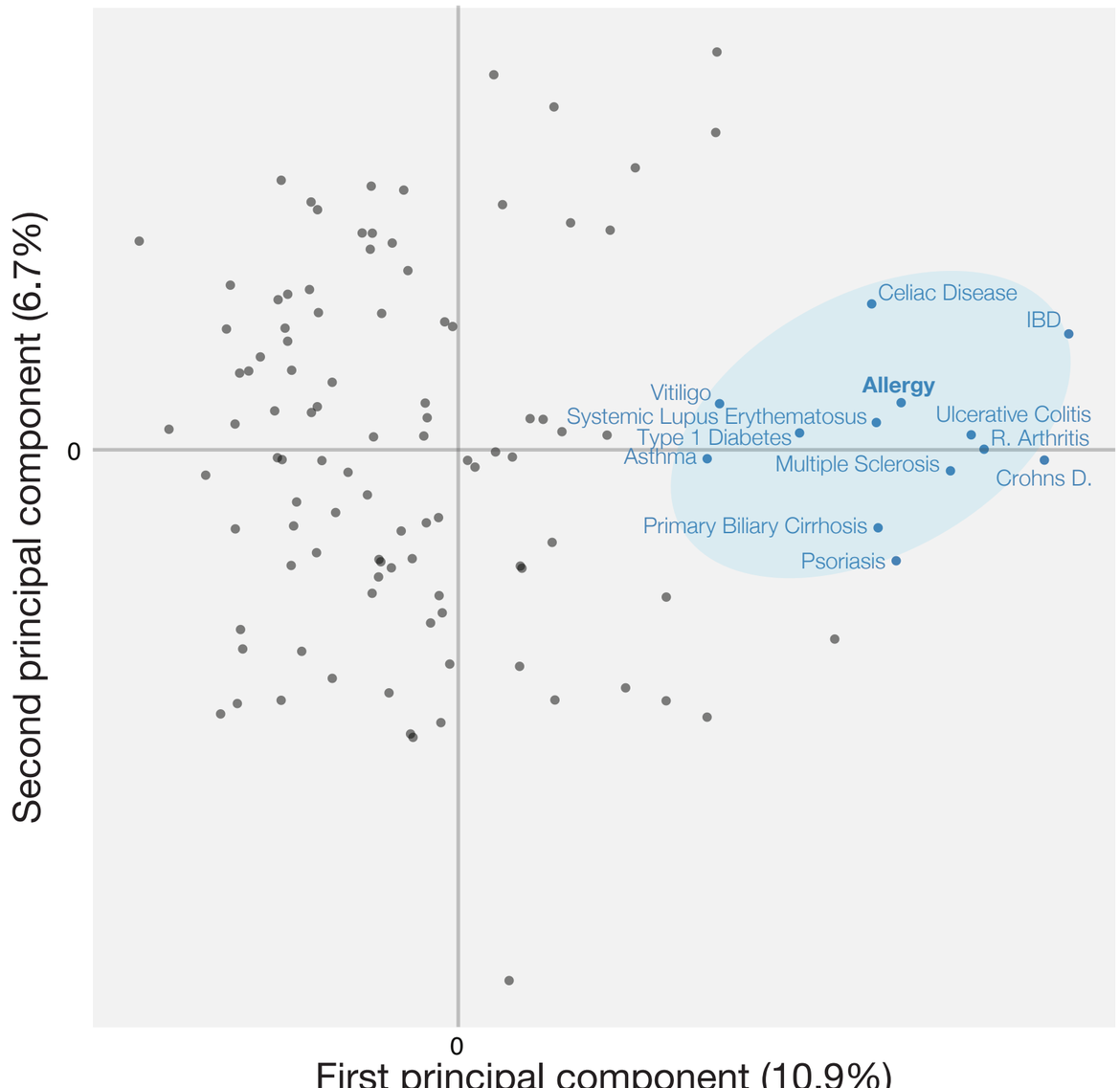
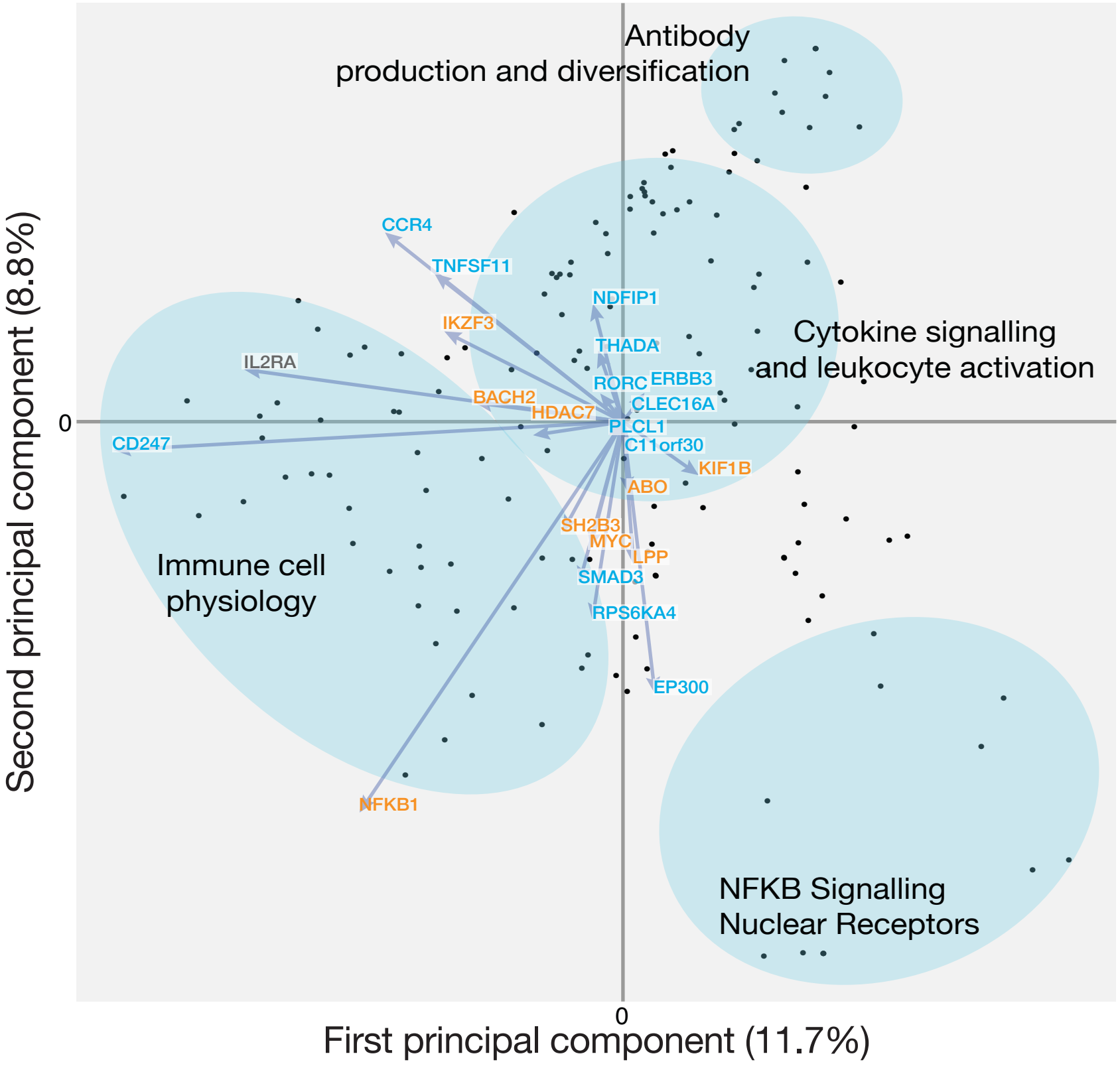
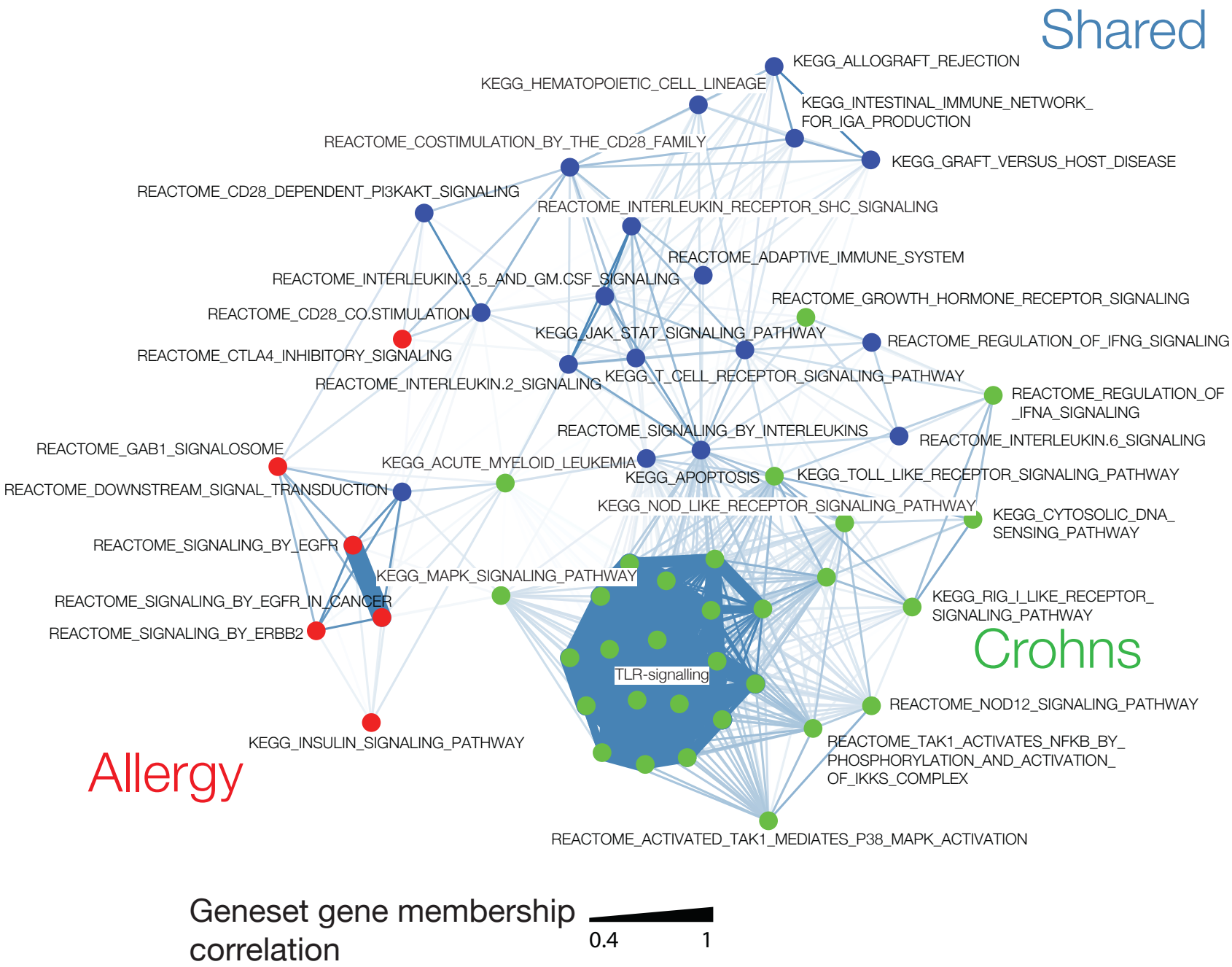

Second principal component (6.7%)
First principal component (10.9%)
0
0
Celiac Disease
IBD
Allergy
Vitiligo
Systemic Lupus Erythematosus
Ulcerative Colitis
Type 1 Diabetes
R. Arthritis
Asthma
Multiple Sclerosis
Crohns D.
Primary Biliary Cirrhosis
Psoriasis


Antibody
production and diversification
Cytokine signalling
and leukocyte activation
Immune cell
physiology
NFKB Signalling
Nuclear Receptors
CCR4
TNFSF11
NDFIP1
IKZF3
THADA
IL2RA
RORC
ERBB3
BACH2
HDAC7
CLEC16A
PLCL1
CD247
C11orf30
KIF1B
ABO
SH2B3
MYC
LPP
SMAD3
RPS6KA4
EP300
NFKB1
0
0
Second principal component (8.8%)
First principal component (11.7%)


Shared
KEGG_ALLOGRAFT_REJECTION
KEGG_HEMATOPOIETIC_CELL_LINEAGE
KEGG_INTESTINAL_IMMUNE_NETWORK_
FOR_IGA_PRODUCTION
REACTOME_COSTIMULATION_BY_THE_CD28_FAMILY
KEGG_GRAFT_VERSUS_HOST_DISEASE
REACTOME_CD28_DEPENDENT_PI3KAKT_SIGNALING
REACTOME_INTERLEUKIN_RECEPTOR_SHC_SIGNALING
REACTOME_ADAPTIVE_IMMUNE_SYSTEM
REACTOME_INTERLEUKIN.3_5_AND_GM.CSF_SIGNALING
REACTOME_GROWTH_HORMONE_RECEPTOR_SIGNALING
REACTOME_CD28_CO.STIMULATION
KEGG_JAK_STAT_SIGNALING_PATHWAY
REACTOME_REGULATION_OF_IFNG_SIGNALING
REACTOME_CTLA4_INHIBITORY_SIGNALING
REACTOME_INTERLEUKIN.2_SIGNALING
KEGG_T_CELL_RECEPTOR_SIGNALING_PATHWAY
REACTOME_REGULATION_OF
_IFNA_SIGNALING
REACTOME_SIGNALING_BY_INTERLEUKINS
REACTOME_INTERLEUKIN.6_SIGNALING
REACTOME_GAB1_SIGNALOSOME
KEGG_ACUTE_MYELOID_LEUKEMIA
KEGG_APOPTOSIS
KEGG_TOLL_LIKE_RECEPTOR_SIGNALING_PATHWAY
REACTOME_DOWNSTREAM_SIGNAL_TRANSDUCTION
KEGG_NOD_LIKE_RECEPTOR_SIGNALING_PATHWAY
KEGG_CYTOSOLIC_DNA_
SENSING_PATHWAY
REACTOME_SIGNALING_BY_EGFR
KEGG_MAPK_SIGNALING_PATHWAY
REACTOME_SIGNALING_BY_EGFR_IN_CANCER
KEGG_RIG_I_LIKE_RECEPTOR_
SIGNALING_PATHWAY
REACTOME_SIGNALING_BY_ERBB2
Crohns
TLR-signalling
REACTOME_NOD12_SIGNALING_PATHWAY
KEGG_INSULIN_SIGNALING_PATHWAY
REACTOME_TAK1_ACTIVATES_NFKB_BY_
PHOSPHORYLATION_AND_ACTIVATION_
OF_IKKS_COMPLEX
Allergy
REACTOME_ACTIVATED_TAK1_MEDIATES_P38_MAPK_ACTIVATION
Geneset gene membership
correlation
0.4
1