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Mapping the genetic landscape of immune-mediated disorders: potential implications for classification and therapeutic strategies

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Objectives: Based on clinical, biomarker, and genetic data, McGonagle and McDermott suggested that autoimmune and autoinflammatory disorders can be classified as a disease continuum from purely autoimmune to autoinflammatory with mixed diseases in between. However, the genetic architecture of this spectrum has not been systematically described. Here, we investigate the continuum of polygenic immune-mediated disorders using genome-wide association studies (GWAS) and statistical genetics methods.

Methods: We mapped the genetic landscape of 15 immune-mediated disorders using GWAS summary statistics and methods including genomic structural equation modeling (genomic SEM), linkage disequilibrium score regression, Local Analysis of [co]Variant Association, and Gaussian causal mixture modeling (MiXeR). We performed enrichment analyses of tissues and biological gene sets using MAGMA.

Results: Genomic SEM suggested a continuum structure with four underlying latent factors from autoimmune diseases at one end to autoinflammatory on the opposite end. Across disorders, we observed a balanced mixture of negative and positive local genetic correlations within the major histocompatibility complex, while outside this region, local genetic correlations were predominantly positive. MiXeR analysis showed large genetic overlap in accordance with the continuum landscape. MAGMA analysis implicated genes associated with known monogenic immune diseases for prominent autoimmune and autoinflammatory component.

Conclusions: Our findings support a polygenic continuum across immunemediated disorders, with four genetic clusters. The "polygenic autoimmune" and "polygenic autoinflammatory" clusters reside on margins of this continuum. These findings provide insights and lead us to hypothesize that the identified clusters could inform future therapeutical strategies, with patients in the same clusters potentially responding similarly to specific therapies.

KEYWORDS

autoimmunity, inflammation, autoimmune diseases, genome-wide association studies, polygenicity, classification

1 Introduction

During the last 20 years, autoimmune and autoinflammatory disorders have garnered attention in the fields of neurology and rheumatology particularly regarding nosology and treatment. Various new diseases have been described, including autoimmune encephalitis (1), myelin oligodendrocyte glycoprotein-associated diseases, and monogenic autoinflammatory diseases (interferonopathies and adenosine deaminase 2 deficiency) (2–4). The global rise in the prevalence of immune-mediated diseases, as highlighted by epidemiological studies (5, 6), has sparked a need for urgent innovation in the development of classification, curation approaches, and treatment strategies.

The release of new therapeutic options for neuromyelitis optica (7), myasthenia gravis (8), and monogenic immune diseases (9) brings to the fore the importance of clinical conception and classification of immune diseases and their underlying genetics. The current understanding of immune-mediated diseases relies on immunological concepts, which define autoinflammation as a dysregulated activation of innate immune cells, driven by an imbalance of pro- and anti-inflammatory cytokines, which leads to damage of host tissues without a break in immune tolerance (10, 11). Conversely, autoimmunity is characterized by the loss of immune tolerance, the recognition of self-antigens, and the activation of T and B cells, followed by the production of specific autoantibodies and the damage of multiple organs owing to a dysregulated adaptive immune response (12–14).

The conceptualization of autoimmune and autoinflammatory diseases as a continuum began with proof-of-concept publications suggesting the classification of immunological diseases based on clinical and laboratory data [(12) updated by (15) and (10)]. This classification described a continuum with five main classes (monogenic autoinflammatory, polygenic autoinflammatory, mixed pattern, polygenic autoimmune, and monogenic autoimmune diseases) highlighting the importance of genetic factors for the classification (Figure 1). This classification has become standard practice in rheumatology, where systemic lupus erythematosus (SLE) represents the prototype of systemic autoimmunity with production of multiple autoantibodies. There is still no consensus on the precise classification of some diseases such as rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA), and ankylosing spondylitis (AS) (17), since they exhibit overlapping features of both autoimmunity and autoinflammation (11). In neurology, some immune-mediated diseases are easier to place on the continuum: for example, myasthenia gravis and anti-LGi1-positive autoimmune encephalitis are classical autoimmune diseases (18, 19). However, for conditions like central nervous system vasculitis and acute encephalomyelitis (20, 21), their placement remains unclear. Since autoimmune and autoinflammatory diseases are widely spread across different medical specialities (neurology, rheumatology, endocrinology, gastroenterology, etc.), current categorization efforts based on clinical features and qualitative markers lead to competing classifications with different hierarchical structures (22, 23). This highlights a need for new methods and data-driven approaches to improve classification.

Immune-mediated diseases have a high degree of comorbidity within families (24, 25), twins (26), and individuals, suggesting shared genetic risk factors across different immune pathologies (27, 28). The idea of genetic-based disease classification has been used previously in cross-disorder genetic analyses of immune diseases (29–32). Nevertheless, most of these studies have used only a limited number of disorders and focus on shared-genetic components as opposed to characterizing genetic-based clusters of disorders. Few studies have systematically evaluated the autoimmune-autoinflammatory continuum itself. A great effort was made to use the AutoCore network for the integration of a set of inborn errors of immunity (33) with predominant autoimmunity or autoinflammation into a comprehensive map of

Abbreviations: AIC, Akaike Information Criterion; AITD, autoimmune thyroiditis; EFA, exploratory factor analysis; CeD, celiac disease; CD, Crohn's disease; CFA, confirmatory factor analysis; CFI, Comparative Fit Index; CNS, central nervous system; F, factor; Genomic SEM, genomic structural equation modeling; GWAS, genome-wide association studies; IL, interleukin; JAK, Janus kinase; JIA, juvenile idiopathic arthritis; LAVA, Local Analysis of [co]Variant Association; LD, linkage disequilibrium; LDSC, linkage disequilibrium score regression; MHC, major histocompatibility complex; MS, multiple sclerosis; MiXeR, Gaussian causal mixture modeling; MG, myasthenia gravis; PBC, primary biliary cholangitis; PS, psoriasis; PSA, psoriatic arthritis; PSC, primary sclerosing cholangitis; RA, rheumatoid arthritis; SjS, primary Sjogren's syndrome; SLE, systemic lupus erythematosus; SRMR, standardized root mean square residual; SS, systemic sclerosis; T1D, type 1 diabetes; UC, ulcerative colitis.



The immunological disease landscape (initial idea taken from (10, 12, 16)). Autoimmune and autoinflammatory diseases were described by McGonagle and McDermott as a continuum with five main classes (monogenic autoinflammatory, polygenic autoinflammatory, mixed pattern, polygenic autoimmune, and monogenic autoimmune disorders) highlighting the importance of genetic factors for the classification. Methods of statistical genetics can work with polygenic disorders and can help to characterize this continuum from genetics perspectives using available GWAS data.

human immune dysregulation (34). The TransImmunome project revisits the nosology of autoimmune and autoinflammatory diseases by combining clinical and biomarkers information (35, 36). State-of-the-art methods of statistical genetics provide an additional opportunity to address this heterogeneity through diseases classification into more homogeneous subgroups based on the underlying genes and pathways that drive disease.

Here, we aim to a) evaluate the hypothesis of autoimmuneautoinflammatory continuum for polygenic disorders based on genome-wide association studies (GWAS) data and b) identify genetically driven clusters of closely related polygenic disorders and their shared genetic factors using publicly available large datasets and advanced methodology. Bridging genetically driven classification with existing clinical knowledge can deepen our understanding of disease-specific molecular mechanisms, guiding further research on classification and potential drug targets.

2 Materials and methods

2.1 Samples

We curated a collection of well-powered publicly available GWAS summary statistics of 15 polygenic immune-mediated diseases (Table 1), which belong to neurological, rheumatological, gastroenterological, and endocrine system domains. The selection procedure is described below. We emphasize that our study is focused exclusively on polygenic disorders within the immunemediated continuum. Unfortunately, we are unable to include rare monogenic disorders in our analysis, as the statistical genetics methods that we employ are specifically designed to be effective for polygenic disorders.

We started with 26 immune-linked disorders (Supplementary Table S1) with existing GWAS data. Those GWAS with an effective sample size >5,000 [based on recommendations (54, 55); N effective = 4/(1/n cases) + (1/n controls)] and >200,000 single-nucleotide polymorphisms (SNPs), which overlap with the linkage disequilibrium (LD) score regression reference panel (56) were included. We also excluded AS and narcolepsy because only ImmunoChip genetic data were available without genome-wide coverage. This resulted in the inclusion of 15 immune-mediated diseases for this study. To increase GWAS power for SLE, JIA, psoriasis (PS), and celiac disease (CeD), we performed in-house meta-analyses for each disorder across multiple publicly available GWAS datasets using METAL (Table 1; Supplementary Table S2). As well, we can highlight the need for more powerful GWAS datasets in immune-mediated neurological diseases because we can keep only two neurological diseases across whole dataset. All GWAS summary statistics were limited to participants of European ancestry. After data harmonization (conversion to GRCh37 genomic build) and preprocessing of the GWAS summary statistics with Python Convert (https://github.com/precimed/python_convert), we conducted crosstrait analyses using a variety of analytical tools as described below. The study design was shown at Figure 2

| Diseases | Abbr. | N cases | N controls | N effective | GWAS source, PMID | |
|--|------------------|---------|------------|-------------|--|--|
| Autoimmune thyroiditis | AITD | 30,234 | 725,172 | 114,296 | 32581359 (37) | |
| Celiac disease | CeD | 6,897 | 334,824 | 22,142 | 20190752 (38), 34278373 (39); for details, see Supplementary Table S2. | |
| Crohn's disease | CD | 12,194 | 34,915 | 36,151 | 28067908 (40) | |
| Juvenile idiopathic arthritis | JIA | 4,799 | 294,231 | 15,670 | FinnGen (41), 33106285 (42); for details, see Supplementary Table S2 | |
| Multiple sclerosis | MS | 14,802 | 26,703 | 38,093 | 31604244 (43) | |
| Myasthenia gravis | MG | 1,873 | 36,370 | 7,125 | 35074870 (44) | |
| Primary biliary cholangitis | PBC | 8,021 | 16,489 | 21,584 | 34033851 (45) | |
| Primary sclerosing cholangitis | PSC | 2,871 | 12,019 | 9,270 | 27992413 (46) | |
| Primary Sjogren's syndrome | SjS | 3,232 | 17,481 | 10,911 | 35896530 (47) | |
| Psoriasis (including Psoriatic arthritis) | PS (with PsA) | 17,255 | 693,100 | 64,320 | FinnGen (41), 34278373 (39), 24482804 (48); for details, see Supplementary Table S2 | |
| Rheumatoid arthritis | RA | 22,350 | 74,823 | 68,838 | 36333501 (49) | |
| Systemic lupus erythematosus | SLE | 5,595 | 361,571 | 15,096 | FinnGen (41), 26502338 (50), 29848360 (51); for details, see Supplementary Table S2 | |
| Systemic sclerosis | SS | 9,095 | 17,584 | 23,978 | 31672989 (52) | |
| Type 1 diabetes | T1D | 18,942 | 501,638 | 73,011 | 34012112 (53) | |
| Ulcerative colitis | UC | 12,366 | 34,915 | 36,527 | 28067908 (40) | |

TABLE 1 Overview of the GWAS used in the study.

2.2 Analytical tools

2.2.1 Genomic structural equation modeling

Genomic structural equation modeling (SEM) (57) can be used to model the multivariate genetic architecture across traits and reveal latent factors underlying genetic correlations and determine how those latent factors correlate with each other.

We conducted exploratory and confirmatory factor analyses (EFA and CFA, respectively) of the 15 immune-mediated diseases. First, the multivariable extension of LD score regression (LDSC) employed in genomic SEM was used to derive a genetic covariance matrix (S) and sampling covariance matrix (V). Population prevalence was taken from the literature (Supplementary Table S3). Next, EFA with promax rotation was conducted on the standardized S matrix using the R genomic SEM package (R version 4.3.2, https://github.com/GenomicSEM/, Supplementary Table S4). Results from the EFA were used to guide CFA for a one-, two-, three-, four-, and five-factor model. EFA was performed using genomic SEM, and correlated factors with standardized loadings >0.25 were retained for CFA. Model fit (Table 2; Supplementary Table S5) for each factor model was assessed using recommended fit indices: standardized root mean square residual (SRMR), model χ^2 statistic, Akaike Information Criterion (AIC), and Comparative Fit Index (CFI). Model fit was considered acceptable for CFI values \geq 0.90 and SRMR < 0.1 (57).

2.2.2 Linkage disequilibrium score regression and Gaussian causal mixture modeling (MiXeR)

For each phenotype, we estimated the SNP heritability and genome-wide genetic correlation using linkage disequilibrium score regression (LDSC) (54).

We applied MiXeR (58), (https://github.com/precimed/mixer) to pairs of phenotypes, to estimate the number of variants influencing both analyzed phenotypes (shared polygenicity) and the number of variants distinctively influencing each of the analyzed traits (traitspecific polygenicity). For MiXeR analyses, we excluded the MHC region 26–34 Mb, chromosome 6, as described (58) due to the intricate LD structure. For assessment of model robustness, delta AIC >0 and visual evaluation of log-likelihood plots were used. For the analysis of disease triplets, we used trivariate MiXeR (59), https://codeberg.org/intercm/mix3r with the possibility to access overlap between three phenotypes simultaneously.

2.2.3 Local Analysis of [co]Variant Association

For local correlation analyses, we used Local Analysis of [co] Variant Association (LAVA) version 1.3.8, following the protocol with the LD reference panel based on 1000 Genomes phase 3 genotype data for European samples and the partition of the genome into 2,495 regions with an average size of 1 Mb as described elsewhere (60). Only regions revealing significant estimated SNP heritability (p<0.05/2,495) in both diseases were used to estimate local genetic correlations



Schematic overview of the study design. The genomic structural equation model (SEM) was performed to cluster 15 immune-linked disorders on autoimmune–autoinflammatory axis. Linkage disequilibrium score regression (LDSR) was applied to study common genetic correlation between disorders. We did Local Analysis of [co]Variant Association (LAVA) to study local genetic correlations inside and outside MHC region. The causal mixture model (MiXeR), univariate, bivariate, and trivariate were applied to genetic overlap beyond global genetic correlation. Finally, MAGMA analysis was performed to reveal shared and unique gene, gene sets, and perform tissue analysis.

TABLE 2 Genomic SEM model performance criteria.

| N factors | Df | χ ² | p-value _{χ2} | AIC | CFI | SRMR |
|-----------|----|----------------|-----------------------|----------|-------|-------|
| 1 | 90 | 1,321.83 | 4.56E-218 | 1,381.83 | 0.658 | 0.124 |
| 2 | 88 | 1,073.7 | 3.08E-169 | 1,137.69 | 0.727 | 0.111 |
| 3 | 87 | 779.35 | 9.09E-112 | 845.35 | 0.808 | 0.094 |
| 4 | 56 | 215.59 | 1.42E-20 | 285.59 | 0.919 | 0.077 |
| 5 | 54 | 238.37 | 5.25E-25 | 312.37 | 0.907 | 0.083 |

 χ^2 , model chi-square, reflecting index of exact fit to observed data df; *p*-value $_{\chi^2}$, degrees of freedom and p-value for the model χ^2 ; AIC, Akaike Information Criterion; CFI, Comparative Fit Index; SRMR, standardized root mean square residual. Bold font was used for optimal 4-factor model.

between the traits. We applied Bonferroni correction to account for multiple comparisons within each pairwise correlation analysis. The statistical tests conducted were all two-sided. Then, we identified 10 regions with the greatest number of significant local genetic correlations across immune traits and created network plots displaying these associations.

2.2.4 Functional annotation

We applied MAGMA v1.08 with default parameters as implemented in FUMA v1.6.1 (61–63) to perform gene-level analysis for protein coding genes, gene-set analysis (17,023 gene sets from MsigDB v2023.1Hs), and tissue specificity analysis (54 different tissue types from GTEx eQTL v8) (61). We also analyzed genes revealed by MAGMA in each of the 15 diseases and common for all phenotypes and unique genes for diseases assigned to marginal latent factors obtained in genomic SEM analysis. Additionally, we analyzed unique gene sets from MAGMA results for genomic SEM factors. Bonferroni correction was used according to the number of comparisons. We used Cytoscape application Java 11.0.6 version 3.9.1 with default settings http://cytoscape.org, STRING app (64), and the STRING protein database (65) for protein–protein interaction visualization.

3 Results

3.1 Genomic SEM

In our investigation of the genetic basis underlying the 15 immune-mediated diseases using genomic SEM, we sought to identify latent genetic factors shared across these traits. We employed multivariate LDSC as it implemented in genomic SEM to estimate genetic correlations, which informed our EFA. During CFA, we uncovered latent factors that represent shared variance components across diseases and modelled the genetic variance-covariance matrices across traits (Figure 3). This analysis identified a model with four latent factors as optimal among one-, two-, three-, four-, and five-factor model presented in Table 2, based on model performance criteria (see Material and methods). T1D and MS loaded on multiple factors using our predefined significance threshold (<0.25, see Material and methods), indicating diffuse association patterns that compromised the CFA model fit. Consequently, T1D and MS were excluded from the final model to maintain statistical robustness, as minor loadings led to reduced model performance. Supplementary Table S4 showcases the EFA



FIGURE 3

Four groups of immune-mediated diseases identified in genomic SEM analysis. Genomic SEM model with four latent factors representing four diseases clusters. Green represents factor 1 (F1, "autoimmune"), orange factor 2 (F2, "autoimmune-mixed"), blue factor 3 (F3, "mixed pattern"), purple factor 4 (F4, "autoinflammatory"), and diseases cross-load on two factors are shown in its own color. The arrows connecting the latent variables with diseases are shown as "factor loadings" obtained from confirmatory factor analysis. The rounded and dashed arrows on the indicators (traits) are residual variances in the genetic indicators not explained by the common factor. The dashed arrows connecting factors are covariances and give an idea about the factors' mutual associations.

loadings of the four-factor model illustrating the non-specific loading patterns of T1D and MS.

Factor 1 consists of polygenic rheumatic diseases with autoimmune origin (SjS, SLE, and SS). Factor 2 consists of MG and CeD, but MG also loaded on factor 3. Factor 3 consists of AITD, JIA, and PS, which belong to a "mixed pattern" of pathologies between autoimmunity and autoinflammation. Factor 4 consists of diseases with gastrointestinal tract with inflammatory origin (CD, UC, and PSC). Several diseases cross-loaded on two factors, such as RA (equally belongs to factors 1 and 2), PBC (factors 1 and 3), and MG (factors 2 and 3; see Figure 3; Supplementary Table S6).

Here, we presented model performance criteria for the genomic SEM for a one-, two-, three-, four-, and five-factor model. The correlated factors with standardized loadings > 0.25 were retained from EFA for CFA. Model fit for each factor model was assessed using recommended fit indices: SRMR, model χ^2 statistic, AIC, and CFI. Model fit was considered acceptable for CFI values \geq 0.90 and SRMR < 0.1 (57).

3.2 LDSC and MiXeR

We ran LDSC analysis (Supplementary Figure S1) to quantify SNP heritability, observed scale (Figure 4), and univariate and bivariate MiXeR for all phenotypes to characterize polygenicity and overlap between diseases.

We quantified SNP heritability using LDSC (Supplementary Figure S1) with the observed scale values depicted in Figure 4. CD, SLE, and PBC have a higher SNP heritability compared to others (>0.45).

MiXeR results are presented in tables (Supplementary Tables S7, S8) and as a heatmap (Supplementary Figure S2) showing the proportion of trait-specific and shared trait-influencing SNPs followed by the standard deviation across 20 independent runs. Univariate MiXeR models exhibited good model fit (Supplementary Table S7). As shown in Figure 4, CD, SLE, and PBC have a higher observed scale SNP heritability compared to others (>0.45). CeD and SjS have the lowest polygenicity, and RA and AITD have the highest polygenicity. Bivariate results, for those diseases with acceptable model fit as it was evaluated by delta AIC criteria and log-likelihood profiles (58), see description in Methods) are presented in Supplementary Figure S2, Supplementary Table S8. Bivariate analysis for CeD, SjS, and PSC and as pairs of diseases including SLE-SS and RA-SS did not fulfil model robustness criteria and therefore are not presented. We run trivariate MiXeR for factor 1 and factor 4 clusters to show that diseases from the same factor have more overlap when compared to another factor. Trivariate analyses revealed that SLE/SS has less overlap with UC compared with RA (Figure 5).

3.3 LAVA across immune-mediated diseases

Local genetic correlation analyses complemented global genetic correlation between the immune-related phenotypes. This step allowed us to show which immune disorders genetic correlations are restricted to specific genomic regions and to identify the shared genetic factors located within these genomic regions. SLE, JIA, and MG were excluded, as their models failed to converge.



FIGURE 4

Genetic architecture characteristics. Left part: single-nucleotide polymorphism-based heritability, observed scale, for 15 immune-mediated diseases according to linkage disequilibrium score regression. Right part: the polygenicity value multiplied by 1000 according to Gaussian causal mixture modeling. The color of dots corresponds to color in genomic SEM figure (green factor 1, orange factor 2, blue factor 3, purple factor 4, and own color for mixed diseases).



We visualized local genetic correlation across all loci (Supplementary Figure S3). During assessment of the pattern of intercorrelations (Supplementary Figure S3), we revealed that most of all diseases display a high degree of locus correlations, except CeD, which can be linked to small power of initial GWAS.

In addition, we separately visualized the significant local genetic correlation inside MHC region (Figure 6) versus non-MHC loci. We confirmed that the local correlation and heritability were prominent in the MHC region, where strong genetic risk was shown. Among 20 regions with top significant local genetic correlation, 10 were in the MHC region with the top 1 being in HLA DRB1 gene, top 2 in HLA DQB1 (see Supplementary Table S12 with figures). The pattern of local genetic correlation in the MHC region (Figure 6) involved a mixture of concordant and discordant effects across the diseases. For example, in loci on chromosome 6 (32539568–32586784), UC was negatively correlated with PBC, PSC, PS, AITD, and RA but positively correlated with MS. In comparison, fewer diseases displayed significant correlations in loci outside the MHC, but the correlations were generally strongly positive between the diseases (for example, chromosome 2: 191051955–193033982).

3.4 Functional annotation

3.4.1 MAGMA shared results

MAGMA enrichment analyses for all 15 summary statistics revealed whole blood as the most enriched tissues for all diseases except PSC, SjS, and MG, and the spleen for all except PSC, SjS, and CeD. In addition, the small intestine terminal ileum, Cells_EBVtransformed_lymphocytes, and lung participated in 11, 9, and 8 diseases, respectively (Supplementary Table S11). We did not detect grouping of enriched tissues by factor.

We assessed the most frequently associated genes across traits: for 11 diseases follows (Supplementary Figure S4), *GABBR1* (gamma-aminobutyric acid type B receptor subunit 1), *ZKSCAN3* (Zinc Finger With KRAB And SCAN Domains 3), and *PGBD1* (PiggyBac Transposable Element-Derived 1), and for 10 diseases, *ZSCAN31* (Zinc Finger And SCAN Domain Containing 31), *SCAND3* (SCAN Domain Containing 3), and *ZSCAN23* (Zinc Finger And SCAN Domain Containing 23).

3.4.2 Factor-specific MAGMA results for nonoverlapping genes and gene sets

We also revealed genes only included in factor 1 or factor 4 (the most margin groups of autoimmune and autoinflammatory phenotypes, Supplementary Table S9). In factor 1, 22 genes were unique, and in factor 4, 159 genes were unique with some of them involved in monogenic immune diseases (see Supplementary Figure S6 and *Discussion*).

Subsequently, we assessed gene sets and revealed the uniqueness of each factor. Nine unique gene sets were revealed for factor 1 (N02-mediated IL12 pathways, PID_TCR_pathway, and leukocytes and lymphocytes signaling), 16 unique gene sets for factor 3, 41 unique gene sets for factor 4, and 19 gene sets for MS and T1D (Supplementary Table S10 and *Discussion*). There were no gene sets specific for factor 2 likely because factor 2 diseases shared many common genes with other factors.

4 Discussion

In this study of the common variant genetic architecture of diseases on the autoimmune and autoinflammatory continuum, we observed a strong convergence of shared genetic signal across different statistical genetics methods, which indicate clustering of immune-mediated disorders along the autoimmune-autoinflammatory continuum. Thus, we provide new evidence that supports recent call to action (33–36) on redefining the classification of immune-mediated diseases by integrating the genetics of polygenic immune disorders. We used state-of-the-art statistical methods to identify four clusters across the continuum from GWAS data, with strong autoimmune component in factor 1 and autoinflammatory component in factor 4. The extreme



FIGURE 6

Local Analysis of [co]Variant Association (LAVA) characteristics for MHC locus. Correlation matrix of positive and negative significant correlation and number of loci within MHC (upper triangular part), with loci outside MHC (bottom triangular part). Numbers in cells show the number of regions with significant heritability in both traits (Bonferroni corrected), where the correlation was assessed. Colour indicates the direction of effect (aquamarine, positive; green, negative) for mean across all correlation values (r_{gs}) within the regions with significant h2 for each phenotype. The correlation range is represented on the scale with a color gradient changing from -1 to 1.

positions for factor 1 and factor 4 diseases were further supported by trivariate MiXeR. A significant overlap was observed within autoimmune diseases (SS, SLE, and RA), while there was a smaller overlap between factor 1 diseases (SLE and SS) and the factor 4 diseases (UC). In addition, we revealed a "mixed pattern" in factor 3, which includes JIA, PS, and AITD inside cluster, while factor 2 consists of MG and CeD. MG and CeD diseases are confirmed to be autoimmune disorders (12), but genetically, MG also shares components with factor 3, which belongs to mixed pathology. Therefore, we proposed naming this cluster "autoimmune-mixed".

The classification of UC, CD, and PSC in the same cluster (factor 4) is consistent with a previous study (30) that utilized genomic SEM to demonstrate pathway convergence in immune disorders. While authors (30) suggest that this factor corresponds to gastric disorders, we show that other gastroenterological phenotypes (PBC and CeD) cluster with different diseases. Therefore, this grouping may not solely be due to the involvement of the gastroenterological tract but may suggest grouping based on inflammatory pathogenesis. Additionally, it is noteworthy that disorders affecting the same organ can be classified into different groups, highlighting the complexity of their immune mechanisms. Topaloudi et al. (32) also revealed four factors structure in line with a recent preprint (16). The study found that MS was grouped with PSC (32), and our study confirmed this connection using LDSC and LAVA methods. Similarly, MG was grouped with RA(32), and we were able to show that they belong partly to the same factor 2. In the Transimmunome project (36, 66), five factors were identified based on molecular immunophenotyping but with inclusion of additional diseases with monogenic inheritance or diseases lacking robust GWAS data. Furthermore, our factor 3 consists of diseases that were not studied in their project. Tchitchek et al. grouped CD and UC into the same factor (factor 4) supporting the findings on biomarkers level. In addition, RA and T1D were grouped together, which aligns with our large genetic overlap observed in MiXeR (rg 0.33, shared fraction 38%) and strong local positive correlations in some loci as indicated by LAVA.

In addition, in our study, SLE belongs to the "autoimmune" factor 1, while RA is split between factors 1 and 2, indicating distinct genetic backgrounds for RA and SLE.

SLE is regarded as a classical autoimmune disease with autoantibody production, whereas RA has both autoimmune (classical seropositive RA) and mixed/autoinflammatory features (seronegative subtypes) (11). A notable observation in our study is the grouping of MG with CeD (in factor 2), which may explain their co-occurrence in case reports, despite lacking population-level evidence (67). While MS was excluded from our genomic SEM model, it shows high correlation and overlap with factor 4 diseases and PBC using other methods. This was shown in previous studies (67, 68), which support the observation that MS has common genetic background not only with autoimmune but also with autoinflammatory clusters or, as it was suggested recently, for functionally integrated immunopathology (69).

Based on our findings and previous literature (30, 32, 70), it appears that the factor structure in the genomic SEM model depends on 1) the initial set of disorders and 2) GWAS power. By including more diseases in our analyses compared to the previous studies, we were able to differentiate more factors within the autoimmune spectrum. In summary, our results align with and expand previous findings by including a broader range of immunemediated diseases, which enabled us to define more refined clusters on the "autoimmune-autoinflammatory axis".

LAVA analysis showed a mixed pattern of correlations (positive and negative) inside the MHC region, but in loci outside, the MHC region correlations were mostly positive. The same pattern for mixed correlation in the main MHC hotspot (chromosome 6: 32539568– 32586784) was shown for immune-mediated diseases in the original LAVA paper (60). Most MHC loci with significant local correlation belong to the MHC II subgroup. In contrast, PS categorized as an MHC-1-opathy according to the European Alliance of Associations for Rheumatology classification (71, 72) generally shows a negative correlation with other diseases in top-MHC loci. Considering the development of demyelinating disorders in some MHC-I-opathies during biological treatment (28), this insight can guide research on more informed treatment choices and help prevent complications arising from impacts on various pathways.

The most frequently identified overlapping genes (Supplementary Figure S4) among the immune-mediated disorders were involved in cell signaling and interaction, which is common for all types of immune disorders and consistent with findings from a previous study (31). We also assessed the unique genes in marginal "autoimmune" and "autoinflammatory" factors. In "autoimmune" factor (factor 1), 22 genes were unique, among them neutrophil cytosolic factor 2, which is associated with autosomal recessive chronic granulomatous disease 2 (73). Mutation in Interferon Regulatory Factor 7 was described as a cause of immunoteficiency-39 (73) and as a gene, which is linked to innate immunity according to the classification of inborn errors of immunity (74). Mutation in *IKZF3* is linked to immunodeficiency-84, which is an autosomal dominant primary immunologic disease associated with low levels of B cells and impaired early B-cell development (75).

For "autoinflammatory" factor 4, 159 genes were unique, but few participated in immunological processes (Supplementary Figure S6). One immune-related example is *NOD2*, a gene involved in Blau syndrome, which is a rare autosomal dominant autoinflammatory syndrome classified as an autoinflammatory phenotype (74). These findings are in line with (34), which reports that monogenic immunemediated diseases may represent genetically determined, more severe forms of more common polygenic autoimmune and inflammatory diseases. That also enables combining results from rare and complex diseases, which can potentially inform new strategies for more precise treatment selection. Based on these findings, we can explore certain potential agents in greater depth. If these agents prove effective for Blau syndrome, there is a possibility that they could also benefit other disorders within the group (76, 77).

In the assessment of gene sets, we identified the involvement of interleukin 12 (IL12) and IL23 gene sets in factor 4 diseases. A monoclonal antibody that targets IL12/IL23 (ustekinumab) is approved for the treatment of UC and CD, and PS (78–80). In addition, IL3, IL4, IL18, IL27, T-helper, and IFN gene sets involvement in "inflammatory" factor 4 can inform the potential application of drugs that targets these interleukins and related pathways.

For "autoimmune" factor 1, both N02-mediated IL12 pathways and the IL12 pathway were involved as previously linked to SLE risk (81). In addition, TCR signaling in naive CD4+ T cells and leukocyte-associated pathways participated in factor 1 diseases. This can be important for SjS and SS where fewer IL pathwayslinked studies exist due to the lack of powerful data (82).

In factor 3 diseases, a lot of pathways were enriched that were linked to T cells, B cells, and JAK signaling, and IL17. Recent studies have shown the involvement of IL17 in JIA pathogenesis (83). This has led to the approval of secukinumab, an IL 17 blocker, for treating two JIA subtypes (juvenile psoriatic arthritis and enthesitisrelated arthritis) and for PS treatment. In addition, for MS and T1D, different IL2, IL6, and T-cell pathways were important.

Our approach offers significant advancements in understanding the intricate genetics of immune-mediated disorders, and its translational potential could be significant. The accumulated evidence from this study and previous findings can help inform further research on immunotherapy in immune-mediated disorders. Already designed drugs that suppress major pro-inflammatory signaling pathways as IL-17 and JAK inhibitors have success compared to traditional systemic therapies (84). However, there are still unaddressed medical requirements in terms of both long-term safety and overall effectiveness, as a considerable number of patients do not attain disease remission. Enhanced understanding of the genetically informed mechanisms and diversity within immune-mediated diseases would create opportunities to address these challenges, resulting in a more personalized and efficient treatment approach (85).

A limitation of our study is that it focused only on GWAS performed on populations of European ancestry. This is because genomic SEM and LD score regression require the same ancestry samples, and powerful GWAS data are lacking for non-European ancestries in most diseases. The second limitation was that only powerful GWAS datasets of polygenic diseases were included, a requirement of the employed statistical methods. In addition, cohort sample size and SNP sets are drivers of the limited resolution of genetic mapping and the ability to detect robust disease associations (86). The MHC findings could be limited by non-specialized genotyping chips in GWAS and resolution of the MHC region, and limitations of the LAVA method due to LD structure and GWAS power. An additional limitation was to focus only on genetics but not on the deep immunophenotyping due to the lack of powerful data for these phenotypes.

To summarize, the revelation of four-factor clustering can help to define the disease groups for which it is possible to use the same therapies. The shared genetic landscape of this continuum can potentially be used to update the nosological classification. Our findings should be viewed as a foundation for further investigation into personalized treatment strategies based on genetic clustering. We believe that these insights could eventually contribute to optimizing therapeutic approaches, but rigorous clinical validation is necessary before any changes to existing treatments can be recommended. Furthermore, our results can be instrumental in assembling cluster-guided multi-parametric analyses that include genetics and omics data and enable deep phenotyping of patients leading to personalized drug selection. The current study sheds light on the autoimmune-autoinflammatory continuum from a genetic perspective and can inform future studies in this field.

Data availability statement

GWAS data are publicly available at GWAS catalogue or available on request (International Multiple Sclerosis Genetic Consortium, deCODE, FinnGen). Statistical analyses were performed with Python and R using existing tools available in FUMA (https://fuma.ctglab.nl/), GitHub (https://github.com/ precimed/). Genomic SEM (https://github.com/GenomicSEM/), METAL (https://github.com/statgen/METAL), MiXeR bivariate (https://github.com/precimed/mixer), MiXeR trivariate (https:// codeberg.org/intercm/mix3r), LAVA (https://github.com/josefinwerme/LAVA), LDSC (https://github.com/bulik/ldsc), MAGMA (https://cncr.nl/research/magma/), and Python Convert (https:// github.com/precimed/python_convert).

Author contributions

VF: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Validation, Visualization, Writing - original draft, Writing - review & editing. AS: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Resources, Software, Validation, Visualization, Writing - original draft, Writing - review & editing. PJ: Conceptualization, Data curation, Investigation, Methodology, Writing - original draft, Writing - review & editing. JF: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Software, Validation, Visualization, Writing - original draft, Writing - review & editing. NP: Conceptualization, Methodology, Writing - original draft, Writing - review & editing. EW: Validation, Writing - original draft, Writing - review & editing. OF: Methodology, Resources, Software, Writing - original draft, Writing - review & editing. OS: Funding acquisition, Methodology, Validation, Writing - original draft, Writing - review & editing. HS: Conceptualization, Funding acquisition, Supervision, Writing original draft, Writing - review & editing. SD: Funding acquisition, Project administration, Resources, Supervision, Writing - original draft, Writing - review & editing. OA: Conceptualization, Funding acquisition, Project administration, Resources, Supervision, Writing original draft, Writing - review & editing.

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Conflict of interest

OA has received speaker fees from Lundbeck, Janssen, Otsuka, and Sunovion and is a consultant to Cortechs.ai. and Precision Health. OF is a consultant to Precision Health.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fimmu.2025.1543781/ full#supplementary-material

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