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GENOMIC INSIGHTS INTO CHRONIC DISEASE SUSCEPTIBILITY: IMPLICATIONS FOR PERSONALISED MEDICINE

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ABSTRACT

The complex interplay of genetic, metabolic and immune-related processes influences chronic diseases. Even though genomic research has found susceptibility loci to specific conditions, there have been fewer studies that combine variant-level, pathway-level, and cumulative risk using a single framework to examine chronic disease susceptibility. This study aimed to investigate genomic variation associated with susceptibility patterns and examine its implications for personalised medicine using type 2 diabetes mellitus as a model chronic disease. A secondary analysis was conducted using SNP genotype data from the GEO dataset GSE226084. Following quality control, principal component analysis was applied for dimensionality reduction, and K-means clustering was used to derive genomic susceptibility groups. Logistic regression identified associated SNPs, which were subsequently annotated, aggregated at the gene level, and evaluated through pathway enrichment analysis. A weighted genetic risk score was calculated to assess cumulative genetic burden across clusters. Two distinct genomic clusters were identified, comprising 63 and 243 individuals. Among 3,733 tested SNPs, 871 remained significant after false discovery rate correction. Key loci included *HLA-DPA1*, *ETV6*, *TRIM15*, *TRIM26*, and *TCF7L2*, with notable signal concentration on chromosome 6. Enrichment analysis revealed pathways related to immune regulation, inflammatory response, and cellular signaling. Genetic risk scores differed markedly between clusters, with one group exhibiting consistently higher cumulative genetic burden. These findings demonstrate that genomic susceptibility is organised into biologically distinct profiles defined by coordinated variant, gene, pathway, and cumulative risk signals. Integrating these layers provides a practical basis for risk stratification and supports the application of genomics in personalised medicine.

KEYWORDS: chronic disease susceptibility, genomics, type 2 diabetes mellitus, pathway enrichment, personalised medicine

1. INTRODUCTION

Chronic diseases are a significant and increasing problem to health systems worldwide, and are a significant contributor to morbidity, mortality, and health care expenditure. The rise in the incidence of such problems as diabetes, cardiovascular diseases, and metabolic syndromes is indicative of the multifaceted interplay between biological, environmental, and lifestyle factors (Hacker, 2024). These disorders tend to develop silently and end in serious complications, and it is necessary to enhance the knowledge of underlying susceptibility mechanisms. Although lifestyle interventions (physical exercise and dietary changes) are significant in the prevention of diseases, they do not explain inter-individual differences in disease risk (Anderson & Durstine, 2019). The ongoing increase of global chronic diseases further demonstrates the importance of researching intrinsic biological factors that affect predisposition and progress (Eva & Pathak, 2023). Type 2 diabetes mellitus (T2DM) is a representative model of a chronic condition, as its etiology is multifactorial, and its complications have been well reported. Long-term effects like neuropathy, nephropathy, retinopathy, and cardiovascular disease are closely linked with the condition and lead to substantial health loss (Urgiles et al., 2020). These complications do not occur consistently in the affected persons, implying that there must be an underlying genetic variation that affects disease courses. Past research has pointed to certain genetic variants linked to the issue of T2DM complications that are more likely to affect certain groups of people, which underscores the role of genetic predisposition in determining the outcomes of the disease (ElHajj Chehadeh et al., 2022). Additionally, the evolution of chronic diseases is frequently

predetermined by biological alterations through the years that strengthen each other and create a necessity for methods that would record both immediate and latent determinants of vulnerability (Sukumaran, 2021).

The field of genomics has also opened new possibilities to study disease susceptibility on a molecular level. Genetic variation, especially in the form of single-nucleotide polymorphisms (SNPs), has been extensively investigated to identify loci that are linked to risk of disease. These methods have graduated to genomic studies that are large-scale and include complex genetic architecture in populations. The interplay between the genetic background and environmental factors, including diet, has also been identified as a key determinant of chronic diseases, which further supports the importance of integrative genomic studies (Franzago et al., 2020). Moreover, genomic analyses at the population level have found that there are large amounts of diversity in disease-related variants, which highlights the significance of studying diverse groups to draw a more accurate picture of the patterns of disease susceptibility worldwide (Gurdasani et al., 2019).

In spite of these developments, there are major gaps in comprehending the translation of the genomic discoveries to meaningful information on disease susceptibility. Numerous studies are based on pre-determined clinical phenotypes, which may not be sufficient to measure underlying biological heterogeneity. The risk of disease among different individuals is frequently varied due to genetic awareness and the use of lifestyle factors, and it is thought that the susceptibility cannot be identified by only one of the dimensions (Hussain et al., 2025). Moreover, although polygenic risk scores have become some of the most promising instruments to quantify genetic risk, their usage in clinical practice still needs strong validation and incorporation with biologic interpretation (Lennon et al., 2024). Recent studies in genomic research have highlighted the importance of shifting from isolated variant associations to a more holistic picture of biological pathways and systems-level interactions that mediate chronic disease processes (Katikala et al., 2025).

The theory of personalised medicine has become a popular approach to the notion of individual differences in predisposition to disease and response to treatment. The key aspect of this approach is that it is possible to stratify people according to genetic profiles and provide specific interventions to enhance clinical outcomes. Genomic screening, risk stratification, and predictive modeling are some of the strategies that have been suggested to help in this transition, but integrating genomic data into the standard clinical practice still presents some challenges (Knoppers et al., 2021). The use of systems biology also reinforces this paradigm by allowing the combination of genetic, molecular, and functional data to gain a better understanding of disease mechanisms and find possible therapeutic targets (Angione, 2019). Moreover, pathway-based analyses have become useful to interpret genomic variation and enable researchers to connect genetic results to established biological processes and functional networks (Kanehisa et al., 2019).

In this regard, analytical frameworks that combine genomic variation, biological explanation, and risk stratification in a single framework are still required. Previous literature does not include a detailed workflow that links variant-level relationships to the higher-order biological functions and risk profiling on an individual level. This disconnect restricts the potential to convert genomic information into practical information on chronic disease susceptibility and personalised medicine.

This gap is addressed in the current study by using a multi-layered analytical framework to explore genomic variation as relates to patterns of susceptibility. The study combines dimensionality reduction and clustering-based stratification, association analysis, and pathway enrichment using SNP genotype data of individuals with T2DM to detect biologically relevant genomic signals. Furthermore, the genetic risk scoring method is used to assess the cumulative genetic burden of stratified groups. With this unified strategy, the paper will offer information about the genomic architecture of susceptibility and discuss its effects on personalised medicine in the context of chronic diseases.

2. METHODOLOGY

2.1 Research Design

The research used a secondary data analysis to examine the genomic variation related to susceptibility patterns based on SNP genotype data. A cross-sectional analytical design was followed with the combination of dimensionality reduction, unsupervised clustering, and association testing to find out genetic variants associated with stratified genomic profiles. The analytical process involved preprocessing of genotype, phenotype derivation using clustering, SNP-based association testing, and biological interpretation using gene mapping, pathway analysis and risk profiling.

2.2 Data Retrieval

The genotype data were retrieved from the Gene Expression Omnibus (GEO) with accession number GSE226084, which contains SNP array information of participants with type 2 diabetes mellitus (Mansour et al., 2023). The dataset provides the 310 human samples of an Emirati cohort and was initially named to examine the genetic loci related to the complications of diabetes, such as microvascular and macrovascular disorders. Genotyping was done on the Infinium Human Exome-12 v1.2 BeadChip platform that offers exome-wide coverage to the coding variants of importance to disease susceptibility.

2.3 Data Preprocessing and Quality Control

Raw genotype data were tabulated into a sample by SNP matrix, with genotypes tabulated as numbers according to the dosage of alleles. Data reliability was ensured by applying quality control procedures. SNPs that were missing over 5% of the samples were filtered, and then those with missingness over 5% filtered as well. To remove rare variants, minor allele frequency filtering (MAF < 1%) was used. Outliers (remaining missing values) were imputed with mean imputation at the SNP level to permit complete-case analysis in subsequent steps.

2.4 Dimensionality Reduction and Genomic Stratification

The standardised genotype matrix was subjected to principal component analysis (PCA) in order to identify the main axes of genomic variation and to minimise the dimensions of the standardised genotype. Population structure was measured using the resulting principal components. The K-means algorithm was used to perform unsupervised clustering with k = 2 to define genetically different subgroups in the cohort. These clusters were proxy susceptibility groups and were proxies of underlying genomic stratification as opposed to predefined clinical phenotypes.

2.5 SNP Association Analysis

The logistic regression analysis was performed to assess the relationship between SNPs that are individual SNPs and the formed genomic clusters. The dependent variable was cluster membership, and SNPs were all tested as independent predictors. The p-values were corrected with the false discovery rate (FDR) of Benjamini-Hochberg to take into account numerous comparisons. Statistically significant SNPs were those that had an adjusted p-value of below 0.05.

2.6 SNP Annotation and Gene Mapping

The annotation of significant SNPs was done through the annotation file of the GEO platform (GPL26511) that gives genomic coordinates and variant identifiers. Genomic locations were used to map SNPs to chromosomal locations and associate them with nearby genes. In cases where the direct annotation was not available, nearest-gene mapping was done based on the genomic coordinates to place the variants in the proximal genes.

2.7 Pathway Enrichment Analysis

Pathway enrichment analysis on the Enrichr framework through the GSEApy library was conducted to explore the biological relevance of the identified genes. The list of unique mapped genes was compared with supplemented pathway databases, such as KEGG, Gene Ontology (Biological Process) and Reactome. Adjusted p-values were used to determine significance, and overrepresentation of input genes in known biological processes was used to identify enriched pathways.

2.8 Genetic Risk Score Construction

The weighted genetic risk score (GRS) was estimated to measure the cumulative genetic burden across individuals. GRS was calculated as the aggregate of the genotype values, with weighting given to effect sizes (beta coefficients) obtained through the logistic regression analysis. To obtain the most informative genetic signals, only the top significantly associated SNPs were used in the calculation of the score. This GRS was then compared to risk distribution across genomic clusters.

2.9 Statistical Analysis

Associations between genetic variants and genomic clusters were assessed using statistical analyses. SNP-level analysis was done using logistic regression models, where the outcome variable was cluster membership. The correction of multiple testing was done with the Benjamini-Hochberg false discovery rate (FDR). The adjusted p-value <0.05 was used to determine statistical significance.

3. RESULTS

3.1 Genomic Stratification of Study Population

To investigate the underlying genomic structure of the study population, principal component analysis (PCA) was conducted to analyse the data. The initial two main constituents demonstrated that there was a clear division of the samples into two groups, which showed that there is heterogeneity in genomic variation among the people. Cluster 0 had 63 individuals (20.59%), whereas Cluster 1 had 243 individuals (79.41%) (Genetic stratification of groups was unevenly but clearly defined). The distance in Figure 1 suggests that the clustering method was successful in capturing inherent genomic variations. Cluster 1 appeared more dispersed, suggesting greater genomic variability, which implied that genetic variability was higher, but Cluster 0 was narrower, which implied that this subgroup was relatively homogenous.

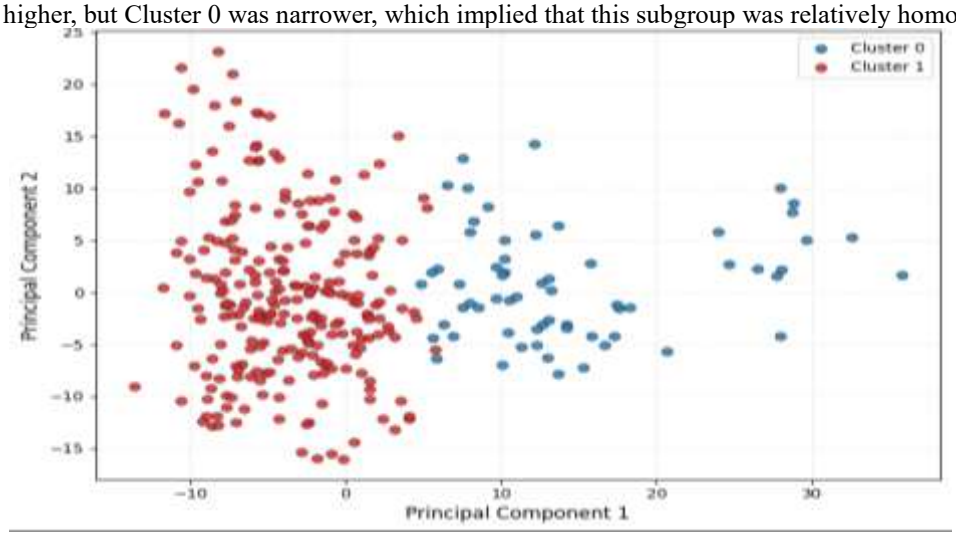

Figure 1. Principal Component Analysis of Genomic Variation Across Samples

3.2 Genome-wide SNP Association Analysis

There were 3,733 SNPs that were tested in a logistic regression analysis to identify the association between the SNP and the inferred genomic clusters. Following the process of multiple testing with the Benjamini-Hochberg false discovery rate, 871 SNPs were found to be statistically significant (FDR < 0.05). The distribution of the association signals is depicted in the general plot in the form of a Manhattan plot, and a few loci are above the significance level, which points to regions of strong genomic association (Figure 2). Table 1 summarises the most important SNPs.

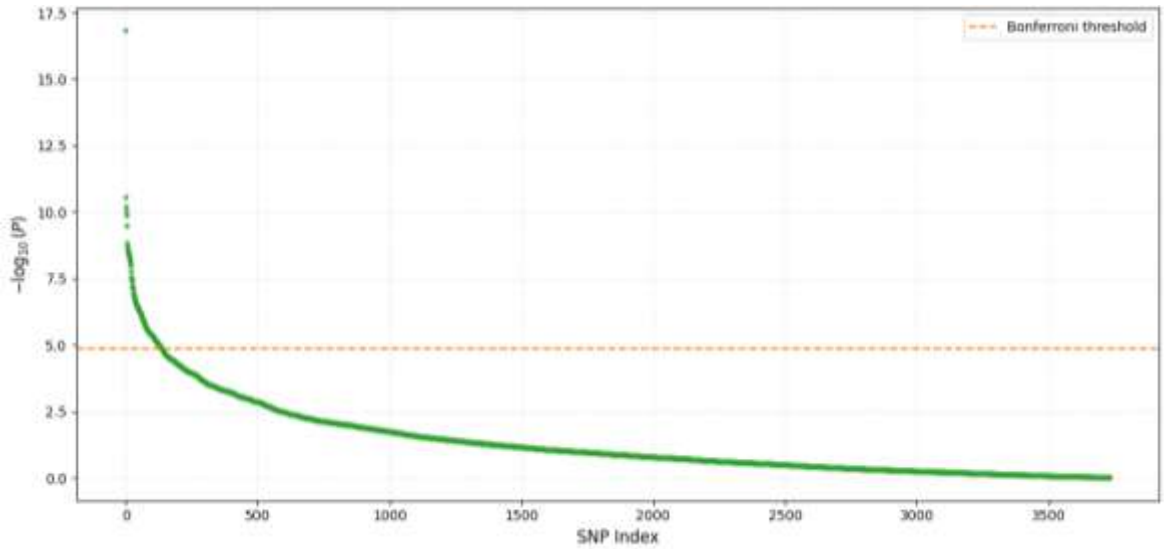

Figure 2. Genome-wide SNP Association Profile

Table 1. Top Significantly Associated SNPs

SNP ID	Effect size (Beta)	Adjusted P-value
exm-rs11965763	-3.2887	5.503e-14
exm-rs2066808	-2.0800	5.284e-08
exm-rs1490384	-1.5322	8.027e-08
exm-IND10-27476467	2.6648	9.033e-08
exm-rs10484548	-2.4352	1.003e-07
exm-rs1117324	-1.8774	2.114e-07
exm-rs1490388	-1.3925	8.070e-07
exm-rs2856321	-1.3615	9.319e-07
exm-rs1480380	2.4263	9.594e-07
exm-rs2284168	1.9141	9.594e-07

There were both positive and negative effect sizes, which reflect the difference in the association of SNPs with the two genomic clusters. Some variants, including rs11965763, were statistically significant with a large effect size, indicating a possible significant role in genomic susceptibility.

3.3 Gene-level Interpretation of Associated Loci

In order to increase the biological interpretability, significant SNPs were projected to genes that they were nearest to, and an aggregation of genes was done to define loci with multiple correlated variants. Figure 3 depicts the most important genes, ordered by adjusted p-values. Table 2 below provides a brief overview of some of the most important genes that were found during the analysis.

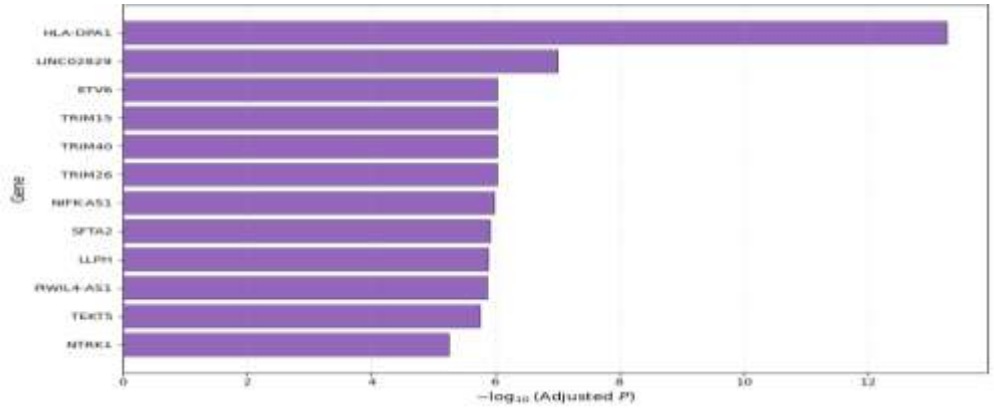

Figure 3. Top Genes Associated with Genomic Susceptibility

Table 2. Gene-level Summary of Key Loci

Gene	Number of SNPs	Best adjusted P-value
HLA-DPA1	1	5.503e-14
LINC02829	1	1.003e-07
ETV6	2	9.319e-07
TRIM15	2	9.594e-07
TRIM26	2	9.594e-07
TRIM40	1	9.594e-07
NIFK-AS1	1	1.054e-06
SFTA2	1	1.227e-06
LLPH	1	1.342e-06
PIWIL4-AS1	1	1.368e-06

Genes, including HLA-DPA1 had the best signals of association, and the role of immune-related genomic regions is important. Moreover, loci such as ETV6, TRIM15 and TRIM26 had several related SNPs indicating a localised clustering of genetic effects. In order to give a genomic context to these findings, Table 3 summarises the chromosomal locations and representative variants.

Table 3. Genomic Context of Representative Variants

Gene	Representative SNP	Chromosome	Position
HLA-DPA1	rs11965763	6	33076682
ETV6	rs2856321	12	11855773
TRIM15	rs2284168	6	30172233
TRIM26	rs1264691	6	30193874
TRIM40	rs2428504	6	30151370
LINC02829	rs10484548	6	29508273
NIFK-AS1	rs11122834	2	121701289
SFTA2	rs2844697	6	30932309
LLPH	rs2358944	12	66117558
PIWIL4-AS1	rs10831284	11	94667964

The findings indicate that protein-coding genes as well as regulatory elements are contributors to genomic susceptibility. The abundance of signals in particular areas of chromosomes 6, in particular, indicates that loci of functional interest participate in the development of the profiles of susceptibility.

3.4 Pathway Enrichment Analysis

Pathway enrichment analysis was also conducted on the mapped gene set to further explore the biological processes involved in the identified genomic associations. The analysis showed that the pathways were significantly enriched with mostly the immunological regulation, inflammatory signaling, and mechanisms of cell response (Figure 4).

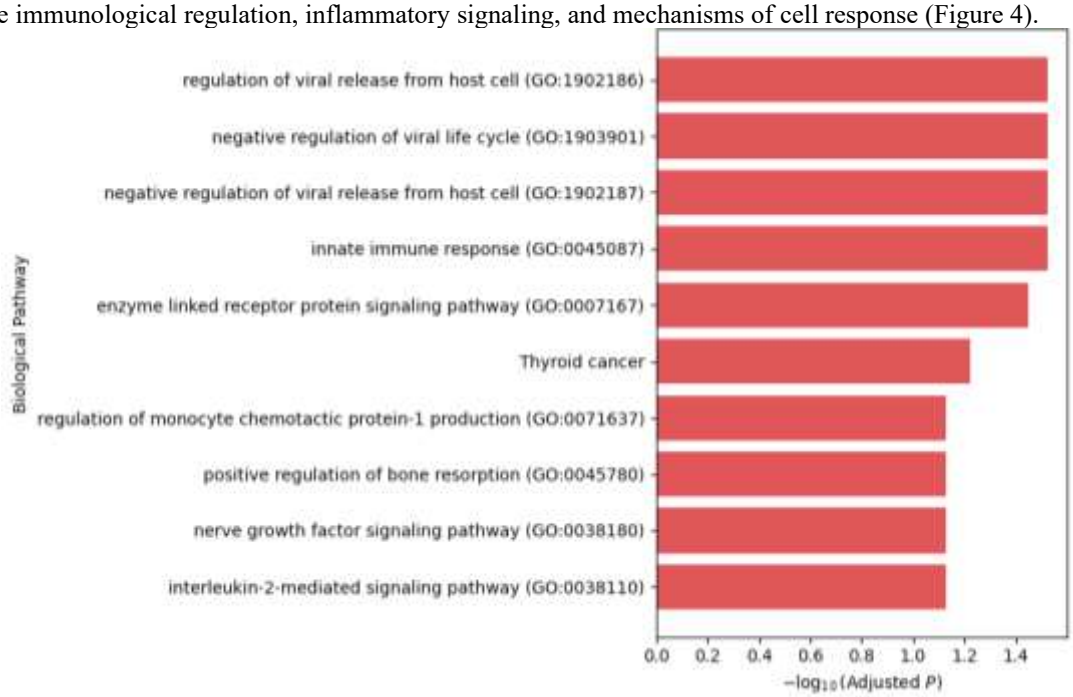

Figure 4. Top Enriched Biological Pathways Associated with Genomic Susceptibility

Pathways that were most enriched were associated with the innate immune response and the regulation of the host defence processes. Despite the fact that a number of pathways are marked in the context of viral regulation, they are fundamental elements of the cellular immune defence mechanisms, but are not pathogen-specific responses. TRIM family genes

(TRIM15, TRIM26, TRIM40) were enriched in all these pathways, indicating their established functions in intracellular immune signaling. The role of antigen presentation and immune modulation in the patterns of susceptibility is indicated by enrichment of interferon-mediated signaling pathways with HLA-DPA1. The involvement of signal transduction processes is further suggested by pathways that are linked to receptor-mediated signaling and kinase activity, which include genes like NTRK1, EPHA6, and SYK. These findings indicate that coordinated biological pathways, especially those involving immune and inflammatory responses, are the determinants of genomic susceptibility, which are relevant to chronic disease mechanisms.

3.5 Genetic Risk Profiling and Implications for Personalised Medicine

A weighted genetic risk score (GRS) of each individual was computed based on the most significantly associated variants to determine whether genomic stratification was a measure of disparity in cumulative genetic burden. The genetic risk scores between the two genomic clusters are quite different, as illustrated in Figure 5. Cluster 1 shows an apparent rightward shift with an increased median and a comparatively small range, which results in a steady high genetic load among people. Conversely, Cluster 0 shows wider distribution with less central tendency, indicating more heterogeneity and less genetic susceptibility.

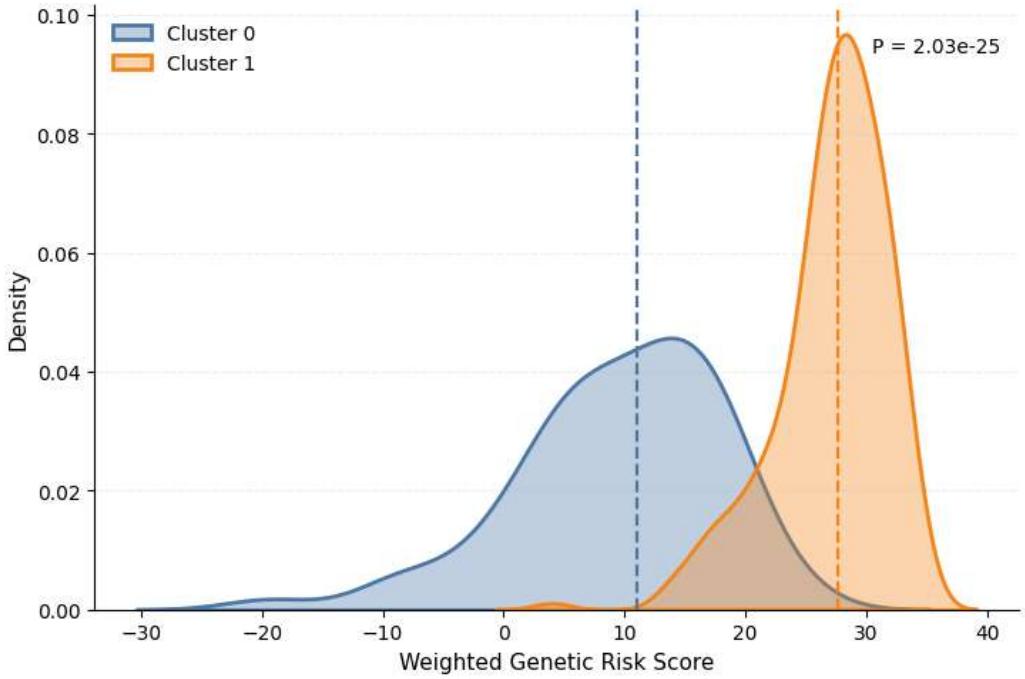

Figure 5. Distribution of Genetic Risk Scores by Genomic Cluster

A highly significant difference between the two groups ($P = 2.03 \times 10^{-25}$) was statistically compared to prove the strength of the observed separation. The small overlap of the distributions is also a sign that the clusters indicate biologically different susceptibility profiles.

Such results imply that stratification of individuals using genetic variation in aggregate can be effective in terms of underlying susceptibility, instead of using the effect of a single variant. The capacity to differentiate between high- and low-risk genomic groups demonstrates the possible power of genetic profiling in individualised medicine models. This stratification can allow better risk forecasting, precision in monitoring, and customisation of therapeutic approaches to chronic disease treatment.

4. DISCUSSION

The results suggest that genomic vulnerability among the cohort under study is organised and that it is the coordination of biological processes and not individual genetic influences. The discovery of two different genomic clusters, along with the apparent distinction in genetic risk scores, implies that people can be ranked according to cumulative genetic burden. Such stratification indicates the existence of underlying susceptibility profiles, in which a single subgroup always has a higher genomic risk. The high-quality SNPs at the variant level support a polygenic architecture, where several loci have a part in the susceptibility via an additive mechanism. The clustering variants around certain genomic regions, especially in chromosome 6, are indicative of the existence of localised susceptibility hotspots. This conclusion is further supported at the level of gene mapping, where loci that play a role in metabolic regulation, as well as in immune-related processes are identified. The results of the pathway enrichment can be used to provide further biological context by showing that related genes coalesce in immune, inflammatory, and signaling pathways. These results indicate that metabolic dysfunction is not the only factor that leads to susceptibility, but also the activity of the immune system and cellular communication processes. Improvement of interferon-related and receptor-mediated pathways suggests that immune signaling can be a key factor in regulating the susceptibility. These observations are supported by the genetic risk score analysis, which shows that cumulative genetic variation can be effectively used to distinguish people on the basis of

overall susceptibility. The sharp distinction between clusters implies that aggregated genomic data will give a stronger representation of risk than single variants. Collectively, these results suggest a multi-layered model of susceptibility, which combines variant-level relationships with higher-level biological mechanisms.

Genomic clues that were discovered in this research align with previous discoveries in the genetics of chronic diseases. The TCF7L2 and predisposition coincide with a body of literature indicating that this gene is linked to type 2 diabetes and other associated metabolic characteristics (Sen et al., 2025). Functional studies also show that TCF7L2 has an effect on the pancreatic beta-cell functions via important signaling pathways, which gives mechanistic evidence of its involvement in disease pathogenesis (Wu et al., 2019). The prevalence of immune-related loci, especially those in the HLA region, is also evident in the existing literature. HLA genes are key immune regulators and antigen presenters, and therefore are critical factors of disease susceptibility in a broad spectrum of diseases (Shiina & Kulski, 2024). The observed results of pathway enrichment in this study can be compared to the general knowledge that inflammation is a unifying process that connects a variety of chronic conditions (Libby et al., 2024). The implicated TRIM family genes further coincide with the emerging studies that have also shown the family to play a role in cellular signaling and disease pathogenesis. It has been demonstrated that these proteins control intracellular mechanisms affecting metabolic and inflammatory pathways (Sun et al., 2021). Their role in metabolic disorders has been noted to increase, too, which underlines their importance in the susceptibility mechanisms (Zhang et al., 2023). The overall trend of relationships observed here is in line with genome-wide analyses that show common genetic construction among chronic diseases. The existence of overlapping loci between type 2 diabetes and obesity and associated characteristics has been demonstrated in pleiotropic analyses, which allow a model of disease susceptibility using a network (Zeng et al., 2021). Population-based validation studies also suggest that genetic associations may differ between cohorts, and it is essential to study different populations (Jan et al., 2022). Other evidence to support the discovered loci is that ETV6 is correlated with immune dysregulations and hematopoietic processes, which are pertinent to susceptibility pathways (Zhou et al., 2022). Similar roles of immune and signaling networks in metabolic diseases have also been found by proteomic and pathway-based efforts, supporting the biological validity of the current results (Bertalan et al., 2025). Additionally, the combination of various types of genomic signals in this study is consistent with methods that apply polygenic risk models to clinical practice, indicating the increasing significance of cumulative genetic evaluation in the process of disease prognosis (Lennon et al., 2024).

The findings have significant implications for the management and understanding of chronic disease susceptibility. This capacity to classify people according to their genomic profiles underscores the possibility of genetic data to determine high-risk groups. This methodology is an improvement to the conventional risk assessment techniques that do not take into account underlying biological variation in the assessment of susceptibility. Biologically, the identification of immune and signaling pathways as being major contributors implies that there are some targets that can be used in therapeutic intervention. These pathways are common to various chronic diseases and provide areas of wider and more effective therapeutic approaches. Combined with the genomic and pathway-scale insights, this enables a systemic view of disease, which is critical to advancing precision medicine. The use of genetic risk scoring also increases the translational relevance of the results. This method allows the assessment of risks individually and the tailored design of prevention and intervention strategies through the quantification of cumulative genetic burden. These structures are the key to the adaptation of personalised medicine, where the treatment and monitoring can be personalised to an individual's susceptibility profile.

These findings have a number of limitations that have to be taken into consideration. It was analysed using only one dataset of a medium sample size, which might reduce the ability of the findings to generalise. Unsupervised clustering is used as a proxy of susceptibility, resulting in uncertainty with the groups obtained not being directly associated with clinical outcomes. Moreover, the mapping of genes was reliant on available annotation sources, and certain variants could not be conclusively attributed to particular genes. The breadth of biological interpretation may be limited by the small number of mapped genes under which pathway enrichment analysis was performed. The genetic risk score was computed using the same dataset and was not externally verified, which could have an impact on its predictive power.

These findings should be validated in future studies in independent and larger cohorts, especially on different populations. Combining genomic information with clinical, environmental, and lifestyle variables would be more informative of the susceptibility. Genomic stratification should be evaluated longitudinally to determine its predictive value in the long run. The accuracy and clinical utility of personalised medicine approaches might be improved by further refinement of genetic risk models and integration of multi-omics data.

5. CONCLUSION

Genomic variation was structured into distinct susceptibility profiles rather than occurring randomly that can be supported by clustering, SNP-levels of association, pathway enrichment and cumulative risk scoring. The findings reveal that an architecture is multi-layered, where individual variants are fused on genes and biological pathways that are associated with immune regulation, inflammatory signaling, and metabolism. The fact that the signals are concentrated in loci like the HLA region, and that there are already known metabolic genes, only adds to the biological relevance of the patterns. The apparent division in the scores of genetic risk based on genetic clusters implies that the aggregated genetic risk can offer a useful framework to stratify people based on genetic susceptibility. This substantiates the larger promise of genomics to transcend locus discovery to a risk-oriented interpretation with translational value. Combined, the results indicate that variant-level analysis, when combined with pathway and risk profiling, has the potential to provide biologically-informed understanding of chronic disease susceptibility. This could provide a viable foundation for how

personalised medicine can be developed by a better classification of risks, early detection of susceptible people and more specific preventative measures.

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