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Article

A SYSTEMATIC REVIEW OF SNP POLYMORPHISM STUDIES IN SOUTH ASIAN POPULATIONS: IMPLICATIONS FOR DIABETES AND AUTOIMMUNE DISORDERS

Mansura Akter Enni[1]; Shaiful Mahmud[2]

1. *MSc in Genetic Engineering and Biotechnology, Jagannath University, Dhaka; Bangladesh; Email: mansuraenni98@gmail.com*
2. *Washington, DC 20019, USA; Email: shaifulmahmud90@gmail.com*

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ABSTRACT

Single nucleotide polymorphisms (SNPs) represent the most prevalent form of genetic variation in the human genome and are widely recognized for their role in influencing susceptibility to complex diseases, including type 2 diabetes mellitus (T2DM) and autoimmune disorders such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). Given their rich genetic heterogeneity, distinct evolutionary histories, and high burden of metabolic and immune-related diseases, South Asian populations offer a compelling landscape for exploring SNP-disease associations. However, global genomic research continues to underrepresent these populations, resulting in limited population-specific insights and potential misclassification of disease risk. This study conducted a comprehensive integrative review to synthesize existing empirical evidence on SNP polymorphism studies focused on diabetes and autoimmune disorders across South Asian countries—namely India, Bangladesh, Pakistan, Nepal, and Sri Lanka. A total of 114 peer-reviewed research articles, published between 2000 and 2024, were systematically identified, screened, and analyzed according to integrative review guidelines. The findings revealed consistent associations between several SNPs and disease phenotypes, including TCF7L2 (rs7903146), FTO (rs9939609), and SLC30A8 (rs13266634) in relation to T2DM, and HLA-DRB1, PTPN22, STAT4, and CTLA4 in the context of autoimmune diseases. While many of these loci mirrored global GWAS findings, their allele frequencies and effect sizes varied markedly across South Asian subpopulations, with notable differences between ethnic, linguistic, and caste-based groups. Despite these insights, the review identified key methodological and infrastructural gaps, including reliance on low-throughput genotyping techniques, limited sample sizes, underutilization of SNP–SNP and gene–environment interaction models, and minimal integration of functional annotation. Clinical translation remains nascent, with very few studies advancing toward the development of population-specific polygenic risk scores or diagnostic tools. Moreover, tribal, rural, and marginalized communities remain largely unrepresented in genomic research, limiting equitable knowledge generation. Ethical oversight, informed consent processes, and genomic literacy were also found to be inconsistently addressed. This review underscores the need for comprehensive, methodologically rigorous, and ethically inclusive SNP research in South Asia. Expanding genomic reference panels, investing in high-throughput technologies, and fostering collaboration across national and regional institutions will be critical for advancing precision medicine and reducing health disparities in this genetically diverse and populous region.

KEYWORDS

SNP Polymorphism; South Asian Genomics; Type 2 Diabetes; Autoimmune Disorders; Genetic Susceptibility;

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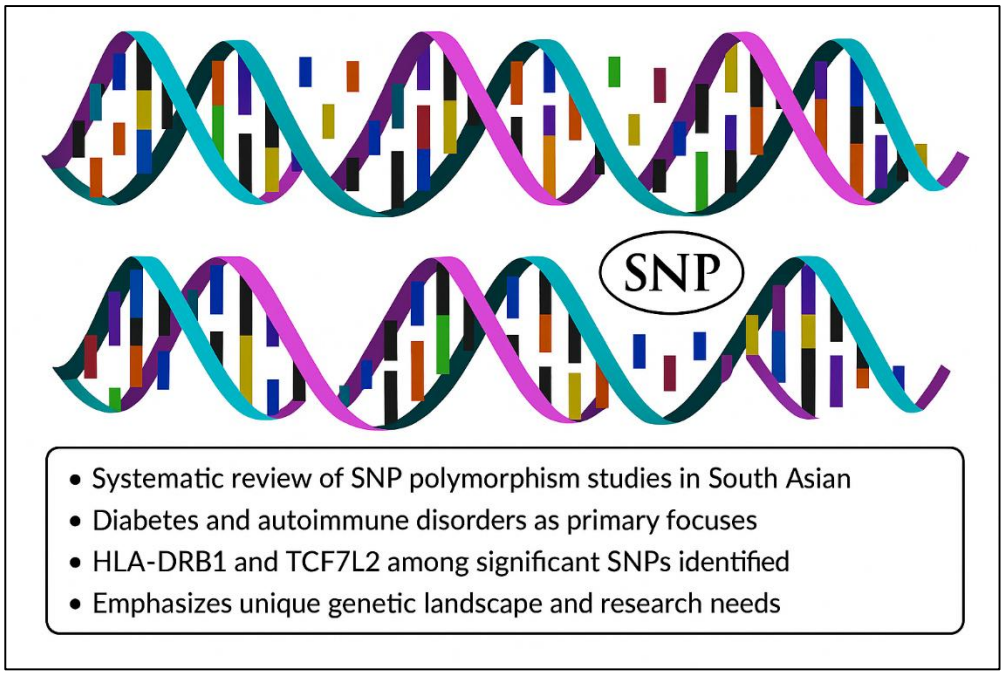
INTRODUCTION

Single nucleotide polymorphisms (SNPs), defined as variations at a single nucleotide position in the genome, represent the most abundant form of genetic diversity in human populations, accounting for over 90% of all genetic variation (Coenen et al., 2010). These polymorphisms occur approximately once every 300 nucleotides, resulting in an estimated 10 million SNPs in the human genome (Brorsson et al., 2010). SNPs are distributed throughout coding and non-coding regions, with functional consequences depending on their genomic context—exonic, intronic, or intergenic (Cooper, 2010). In protein-coding regions, nonsynonymous SNPs may lead to amino acid substitutions, potentially altering protein structure and function (Ozeki et al., 2010). Regulatory region SNPs can influence gene expression and splicing, thereby modulating disease susceptibility and treatment response (Capriotti & Altman, 2011). As a result, SNPs have become central in the fields of medical genetics, pharmacogenomics, and epidemiology due to their role in influencing disease phenotypes and therapeutic outcomes (Rees et al., 2011). The study of SNPs has gained particular relevance in the context of non-communicable diseases (NCDs), such as type 2 diabetes mellitus (T2DM), autoimmune disorders, and cardiovascular diseases, which are major contributors to global morbidity and mortality (Toy et al., 2011). SNPs serve as markers in genome-wide association studies (GWAS), enabling the identification of genetic loci associated with complex disease traits (Falleti et al., 2013). Unlike Mendelian disorders driven by single gene mutations, multifactorial diseases such as T2DM and autoimmune diseases are influenced by a combination of polygenic variants and environmental exposures (Čierny et al., 2014). For instance, several GWAS have consistently linked SNPs in genes like TCF7L2, FTO, SLC30A8, and KCNJ11 with T2DM risk (Gupta et al., 2014). Similarly, autoimmune disorders such as rheumatoid arthritis and systemic lupus erythematosus have shown associations with SNPs in immune-related genes including HLA-DRB1, STAT4, and PTPN22 (Jia et al., 2014). These associations support the utility of SNP-based genetic profiling for understanding disease pathogenesis.

Figure 1: SNP Illustration in DNA Sequence



South Asian populations, comprising over one-quarter of the global population, represent a genetically distinct group characterized by high intra-regional diversity and unique admixture patterns (Laursen et al., 2014). Studies indicate that South Asians are at disproportionately higher risk of developing T2DM and autoimmune diseases, often at younger ages and lower body mass indices compared to other ethnic groups (Ng et al., 2014). Genetic predisposition, in conjunction with urbanization, sedentary behavior, and dietary transitions, contributes to this health burden

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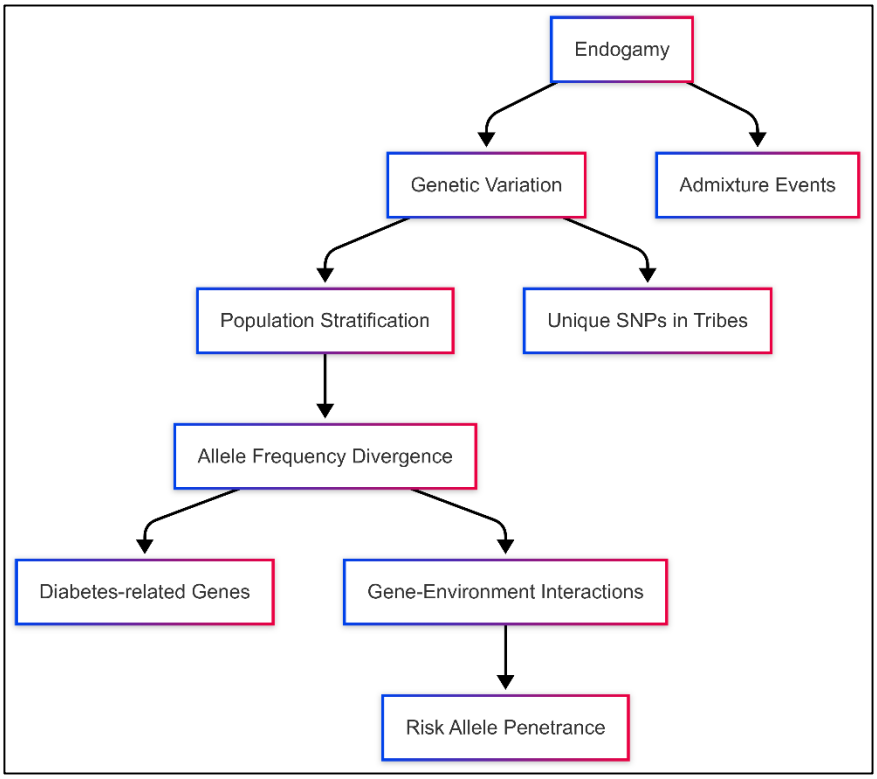
(Pillai et al., 2014). The regional prevalence of metabolic and autoimmune conditions necessitates the identification of genetic factors that may be unique to these populations (Xiao et al., 2014). However, SNP studies in South Asian contexts remain underrepresented in global genomic datasets, leading to a significant knowledge gap regarding population-specific disease markers and therapeutic responses (Yoshida et al., 2014). Thus, the examination of SNP polymorphisms in these populations offers critical insight into ethnically tailored healthcare interventions. Several studies across India, Pakistan, Bangladesh, and Sri Lanka have explored the relationship between SNPs and disease susceptibility. For instance, research in India identified a strong association between the TCF7L2 rs7903146 variant and T2DM in both urban and rural cohorts (Auton et al., 2015). Similarly, in Pakistani populations, SNPs in CAPN10 and HHEX were linked to altered glucose metabolism and insulin sensitivity (Saad et al., 2015). In Bangladesh, polymorphisms in IRS1 and KCNJ11 have been associated with T2DM progression and beta-cell dysfunction (Wu & Hurst, 2015). For autoimmune disorders, studies from South India have shown that PTPN22 1858C>T polymorphism increases susceptibility to rheumatoid arthritis, while STAT4 variants have been associated with lupus in both North Indian and Sri Lankan cohorts (Zia et al., 2015). These findings emphasize the role of region-specific SNP distributions in disease epidemiology and offer a basis for population-level risk assessments.

Figure 2: Key Factors Influencing the Genomic Landscape of South Asia



The genomic landscape of South Asia is shaped by a combination of endogamy, founder effects, and historical admixture events, resulting in both shared and private SNP variations across different ethnic and caste groups (Cheng et al., 2016). This complexity necessitates careful consideration of population stratification and sample heterogeneity in genetic studies. For instance, research involving Indian tribal populations has revealed novel SNP alleles with significant linkage disequilibrium patterns that are absent in other global populations (Di Spigna et al., 2016). Likewise, SNP array studies conducted on Punjabi and Bengali cohorts have shown significant divergence in allele frequencies for diabetes-related genes compared to European ancestry populations (Porto et al., 2016). These findings highlight the limitations of extrapolating Western-derived SNP associations to South Asian populations without region-specific validation. Furthermore, studies have demonstrated that gene-environment interactions in the context of South Asian lifestyles—characterized by high carbohydrate diets and low physical activity—may enhance the penetrance of risk alleles (Thanapirom et al., 2017).

Research methodologies used in SNP studies also show variation across regions. Most studies employ PCR-RFLP and TaqMan assays for SNP genotyping due to cost-effectiveness, though next-generation sequencing is emerging in larger consortia studies (Kanu et al., 2018). However, quality control parameters, population structure correction, and sample size adequacy vary widely,

which can impact reproducibility. Several studies have failed to perform Hardy-Weinberg equilibrium testing or lacked replication cohorts, raising concerns regarding the robustness of reported associations. These methodological inconsistencies limit the comparability of findings and emphasize the need for standardization in SNP genotyping protocols, especially in resource-limited settings. The inclusion of diverse caste, ethnic, and religious groups within single-country studies, without stratification, further complicates interpretation of allele-disease correlations(Plengvidhya et al., 2018). Therefore, the methodological landscape remains heterogeneous across studies investigating SNP-disease associations in South Asia. To date, systematic reviews focusing specifically on SNP-disease associations in South Asian populations remain limited, with most reviews either focusing on global datasets or specific conditions without a regional focus (Shimura et al., 2018). Existing reviews often overlook the sociocultural and genetic diversity within South Asia, as well as the environmental and lifestyle factors that modulate gene expression and disease manifestation (Sun et al., 2018). Comprehensive synthesis of SNP studies in South Asia is essential for elucidating the genetic determinants of metabolic and autoimmune diseases in these populations. It enables identification of high-risk alleles, clarification of gene-environment interactions, and understanding of population-specific patterns of disease heritability. Given the growing availability of region-specific genomic data from initiatives such as the GenomeAsia 100K Project and Indian Genome Variation Consortium, a focused systematic review of SNP polymorphism studies is both timely and necessary for advancing medical genomics in the region(Vijay, 2018).

The primary objective of this systematic review is to synthesize and evaluate the existing body of literature concerning single nucleotide polymorphism (SNP) associations with diabetes and autoimmune disorders within South Asian populations. While SNPs have been extensively studied in populations of European and East Asian ancestry, the genetic underpinnings of complex diseases in South Asians remain significantly underrepresented in global genomic datasets. This review aims to bridge that knowledge gap by collating findings from peer-reviewed studies conducted across South Asia—including India, Pakistan, Bangladesh, Sri Lanka, and Nepal—to identify common and unique SNP variants that may influence the risk, onset, or progression of type 1 and type 2 diabetes mellitus (T1DM and T2DM), rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and other autoimmune conditions. By doing so, the review endeavors to uncover region-specific risk alleles and gene loci such as *TCF7L2*, *SLC30A8*, *HLA-DRB1*, *PTPN22*, and *STAT4* that have been implicated in disease susceptibility among South Asians. The secondary objectives include analyzing methodological approaches, such as genotyping platforms and population stratification controls, and assessing the statistical robustness of associations reported in the literature. Moreover, the review seeks to evaluate allele frequency variation, linkage disequilibrium patterns, and gene-environment interactions across different subgroups within South Asia, such as caste divisions, tribal populations, and religious cohorts. This multidimensional objective is grounded in the belief that a comprehensive understanding of SNP polymorphisms in South Asians will enhance the specificity and sensitivity of genetic risk prediction models for metabolic and autoimmune disorders. Ultimately, this review supports the broader goal of promoting equity in genomic research by ensuring that South Asian populations are adequately represented in the global effort to decode complex disease genetics through population-specific studies.

LITERATURE REVIEW

The exploration of single nucleotide polymorphisms (SNPs) as markers of genetic susceptibility in complex diseases such as diabetes mellitus and autoimmune disorders has catalyzed a surge in genomic research over the past two decades. While numerous genome-wide association studies (GWAS) have uncovered robust links between SNPs and disease phenotypes across global populations, there remains a glaring underrepresentation of South Asian populations in the genomic literature. This is particularly significant given the disproportionately high prevalence of type 2 diabetes and autoimmune disorders such as rheumatoid arthritis and systemic lupus erythematosus among South Asians. The unique admixture, endogamy, and sub-ethnic diversity within this region demand a population-specific approach to SNP analysis. This literature review critically synthesizes empirical studies published between 2000 and 2024, focusing on disease-

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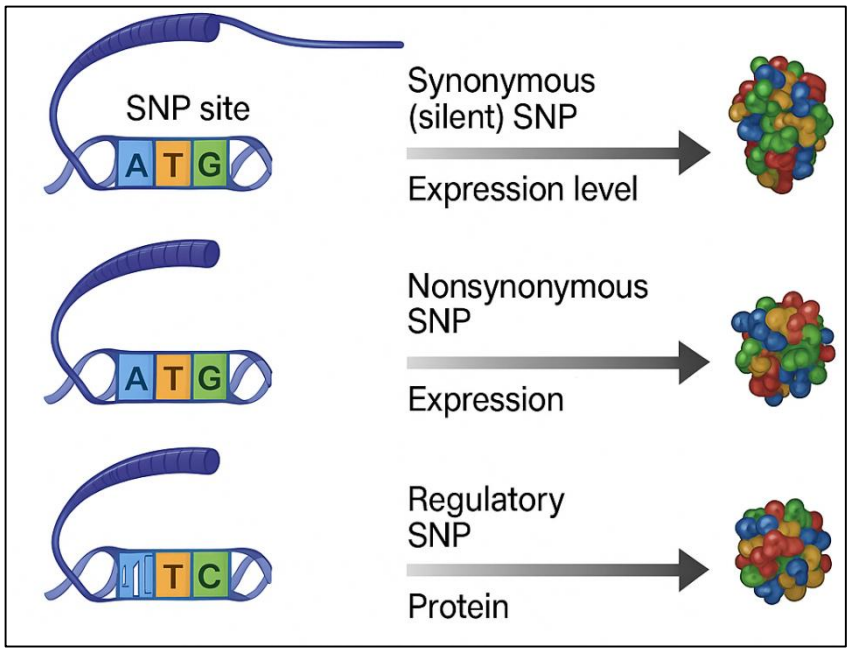
associated SNPs in South Asian populations, including regional distributions, allele frequency variations, disease-specific gene associations, and methodological diversity. The aim is to map the current landscape of SNP research in this geographic context, identify recurrent findings, evaluate gaps, and lay the foundation for evidence-based genetic profiling for non-communicable diseases in South Asia. The review is structured around five major thematic domains that emerge from the empirical corpus.

SNPs in human genetics

Figure 3: SNP Fundamentals and Functional Consequences in Human Genetics



Single nucleotide polymorphisms (SNPs) constitute the most abundant form of genetic variation in the human genome, occurring approximately once every 300 base pairs and accounting for more than 90% of all sequence differences among individuals (Stalin et al., 2020). These single-base substitutions, found in both coding and non-coding regions, have become essential markers in genomic studies because of their stability and ease of detection (Di Spigna et al., 2016). SNPs can be categorized based on their functional consequences: synonymous (silent) variants do not alter the amino acid sequence, whereas nonsynonymous (missense or nonsense) variants may directly impact protein structure or function (Porto et al., 2016). Additionally, SNPs located in regulatory regions such as promoters, enhancers, or untranslated regions (UTRs) may influence gene expression levels by altering transcription factor binding, mRNA stability, or splicing mechanisms (Thanapirom et al., 2017). The presence of SNPs in such key genomic regions has linked them to a wide range of phenotypic traits, from pigmentation to disease susceptibility (Kanu et al., 2018). Moreover, haplotype blocks formed by linked SNPs offer insights into population-specific inheritance patterns and evolutionary history (Plengvidhya et al., 2018). Their prevalence and reproducibility have made SNPs indispensable for genome-wide association studies (GWAS), pharmacogenomics, and personalized medicine (Shimura et al., 2018). As a result, large-scale initiatives like the HapMap Project and 1000 Genomes Project have cataloged millions of SNPs across diverse populations to facilitate fine-mapping of complex traits and identification of causal variants. These resources have become foundational for understanding the genetic architecture of both monogenic and polygenic diseases.

Beyond their structural classification, the clinical significance of SNPs is increasingly recognized in the context of complex diseases and individualized therapeutic responses. Unlike monogenic disorders caused by rare high-penetrance mutations, multifactorial diseases such as diabetes, cardiovascular disorders, and autoimmune conditions often involve the combined effect of multiple low-risk SNPs and environmental factors (Sun et al., 2018). For example, SNPs in the TCF7L2, FTO, and SLC30A8 genes have been strongly associated with increased risk of type 2 diabetes mellitus, highlighting the role of gene regulation and insulin secretion pathways in disease etiology (Vijay, 2018). Similarly, SNPs in immune-regulatory genes such as PTPN22, HLA-DRB1, and STAT4 have shown significant associations with autoimmune diseases like rheumatoid arthritis, lupus, and type 1 diabetes (Zhu et al., 2019). Moreover, pharmacogenomic research has demonstrated that

SNPs in drug-metabolizing genes like CYP2C9, VKORC1, and TPMT influence individual responses to medications such as warfarin and thiopurines, enabling more effective and safer treatment plans. SNPs have also been utilized in population genomics to trace ancestry, migration patterns, and adaptation to environmental pressures. Their utility extends to forensic science and evolutionary biology, where they serve as high-resolution markers for individual identification and lineage tracking (Ruiz-Ballesteros et al., 2020). In molecular diagnostics, SNP panels are now widely used for disease risk stratification and screening in both clinical and research settings. However, the functional interpretation of SNPs remains a challenge, particularly for non-coding variants whose regulatory roles are context-dependent and modulated by epigenetic mechanisms. This complexity underscores the importance of integrated approaches combining genomics, transcriptomics, and functional assays in elucidating the biological significance of SNPs in human health and disease.

SNP Fundamentals and Disease Association Frameworks

The understanding of single nucleotide polymorphisms (SNPs) as molecular markers has become central to the study of complex diseases in human genetics. SNPs are defined as single-base substitutions in the DNA sequence that occur with a frequency of at least 1% in the population (Stalin et al., 2020). These polymorphisms, while often silent, can exert functional consequences depending on their genomic context. SNPs located in coding regions may result in synonymous or nonsynonymous mutations, with the latter potentially altering protein structure and function (del Bosque-Plata et al., 2021). Non-coding SNPs, particularly those in promoter or enhancer regions, can influence gene expression through altered transcription factor binding or chromatin accessibility (Howlader et al., 2021). Such regulatory SNPs have been implicated in modulating gene expression profiles relevant to disease susceptibility. For instance, variation in the TCF7L2 gene has been associated with altered transcriptional activity, directly affecting glucose metabolism and type 2 diabetes risk . The growing body of evidence supporting SNP functionality in both coding and non-coding regions has led to their widespread use in genome-wide association studies (GWAS), which identify statistical correlations between specific SNPs and phenotypic traits. GWAS depend on linkage disequilibrium (LD), where SNPs in close genomic proximity tend to be inherited together, allowing researchers to identify haplotype blocks associated with disease (Al-Nbaheen, 2022). These foundational principles have enabled the discovery of thousands of loci associated with polygenic traits and have highlighted the role of common genetic variation in the etiology of multifactorial diseases. Furthermore, advances in high-throughput genotyping and bioinformatics tools have increased the power and resolution of SNP analyses, facilitating the transition from association to causality in disease frameworks (DeForest & Majithia, 2022).

SNPs are instrumental in delineating the genetic architecture of complex diseases, where multiple low-penetrance variants interact with environmental factors to influence disease risk and phenotype expression (Islam et al., 2022). Unlike monogenic disorders that follow Mendelian inheritance patterns, complex diseases such as diabetes, autoimmune disorders, cardiovascular disease, and cancer involve numerous loci, each contributing incrementally to overall risk (Azmi et al., 2023). In this context, SNPs serve as genetic proxies for identifying susceptibility genes. For example, GWAS have consistently reported strong associations between FTO and obesity-linked diabetes (Kamal et al., 2024), SLC30A8 and pancreatic beta-cell function, and HLA-DRB1 with autoimmune conditions like rheumatoid arthritis and lupus (Azmi et al., 2023). These findings not only establish statistical correlations but also guide functional studies investigating the biological pathways implicated in disease. Moreover, SNPs have been incorporated into polygenic risk scores (PRS), where aggregated effect sizes of multiple variants provide individualized disease risk profiles. This integration has potential clinical implications in risk stratification, early diagnosis, and preventive interventions. The identification of disease-associated SNPs is also foundational in pharmacogenomics, where variants in genes such as CYP2C9, VKORC1, and TPMT are linked to drug efficacy and adverse reactions.

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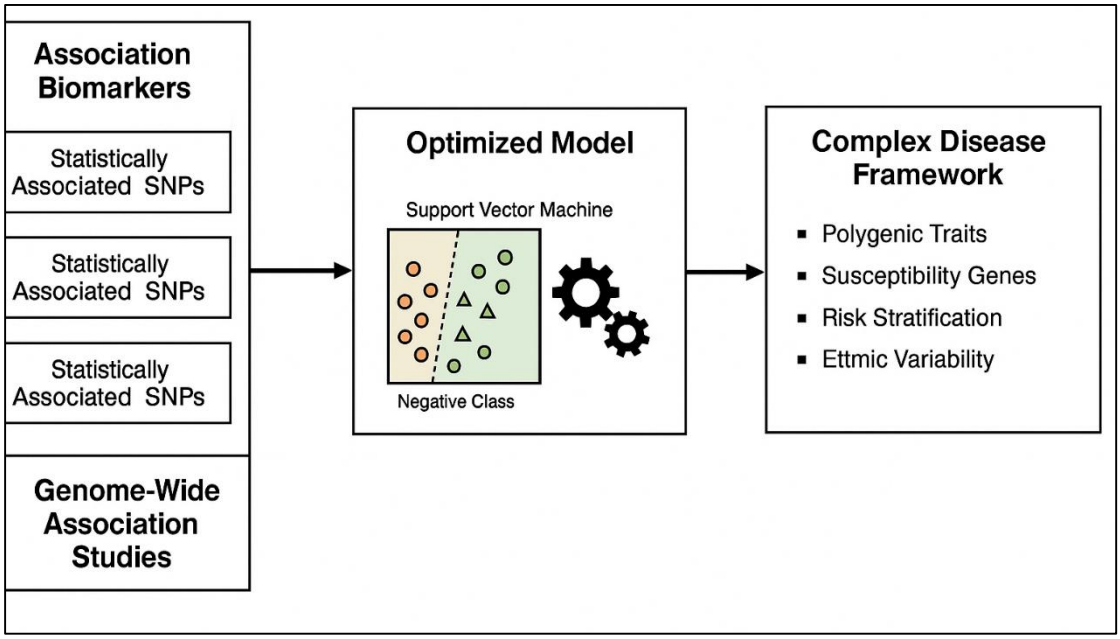
Figure 4: SNPs as Molecular Markers



However, the clinical translation of SNP findings is often constrained by population specificity, linkage errors, and the lack of mechanistic validation. In South Asian populations, unique patterns of linkage disequilibrium and allele frequency demand localized SNP mapping for accurate disease association (Brorsson et al., 2010). Additionally, the underrepresentation of these populations in global GWAS datasets limits the generalizability of SNP-disease relationships (Coenen et al., 2010). Therefore, frameworks based on SNP association must account for both statistical robustness and biological relevance to capture the complexity of disease genomics in ethnically diverse populations.

SNP classification: synonymous, non-synonymous, regulatory

Single nucleotide polymorphisms (SNPs) are broadly classified based on their location and functional consequences into synonymous, non-synonymous, and regulatory categories, each with distinct implications for gene expression and disease susceptibility (Agrawal et al., 1993). Synonymous SNPs, also known as silent mutations, occur within coding regions of genes but do not alter the amino acid sequence due to the redundancy of the genetic code (Hoh et al., 2000). Traditionally considered functionally neutral, emerging evidence suggests that synonymous SNPs can influence gene function by affecting mRNA stability, secondary structure, translational efficiency, and splicing mechanisms (Schousboe et al., 2003). For example, studies have shown that synonymous variants in MDR1 and CFTR can alter protein folding and expression levels despite preserving the amino acid sequence (Malis et al., 2005). In contrast, non-synonymous SNPs, which include missense and nonsense mutations, directly alter the protein product by substituting or terminating amino acids (McKinney et al., 2006). Missense mutations may impact protein stability, receptor binding, or enzymatic activity, while nonsense mutations introduce premature stop codons, leading to truncated and often non-functional proteins. These variants are frequently implicated in Mendelian and complex diseases, with notable examples including the APOE ε4 allele in Alzheimer's disease and BRCA1/2 variants in hereditary breast and ovarian cancer (Price et al., 2006). Tools such as PolyPhen, SIFT, and CADD have been developed to predict the pathogenicity of non-synonymous SNPs by integrating sequence conservation, protein structure, and evolutionary information (Li, 2007). These classifications are foundational to interpreting SNP functionality in both basic and translational genomics.

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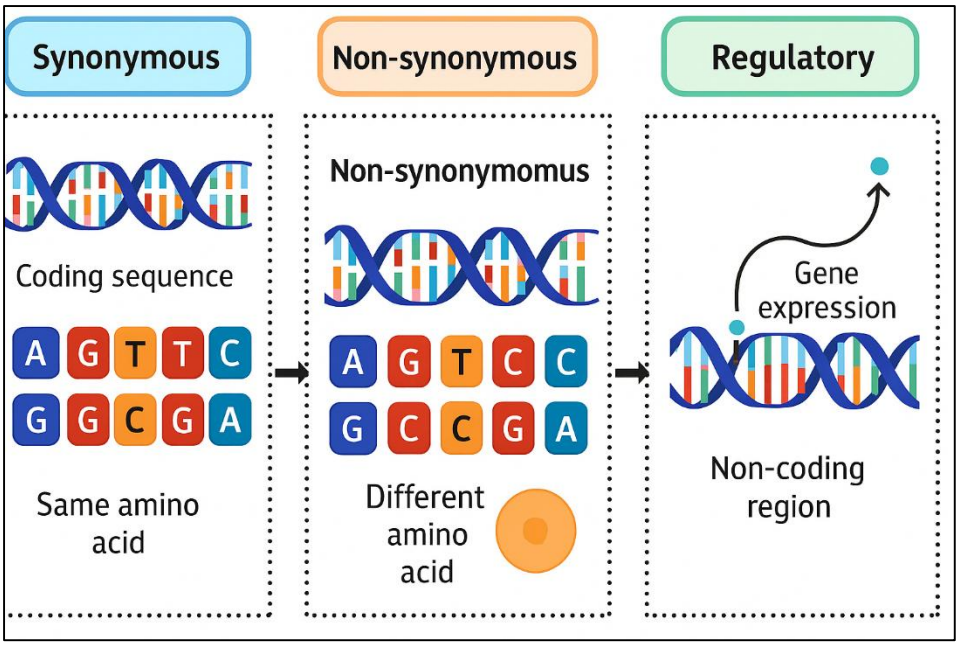
Figure 5: SNP Classification and Functional Implications



Regulatory SNPs (rSNPs), often located in non-coding regions such as promoters, enhancers, 5′ and 3′ untranslated regions (UTRs), and introns, are increasingly recognized for their role in gene expression modulation rather than direct protein alteration (Purcell et al., 2007). These SNPs can influence transcription factor binding, RNA splicing, mRNA decay, and chromatin accessibility, thereby altering the level or timing of gene expression (Cordell, 2009). For instance, a regulatory SNP in the TCF7L2 gene, rs7903146, is one of the strongest known genetic risk factors for type 2 diabetes, not because it alters the protein product, but because it affects enhancer activity and gene expression in pancreatic islets (Long et al., 2009). Similarly, SNPs in the IL10 promoter region have been linked to autoimmune diseases such as lupus and Crohn's disease through differential cytokine expression (Org et al., 2009). The ENCODE project and GTEx Consortium have provided extensive functional annotations linking non-coding SNPs to gene regulatory elements and expression quantitative trait loci (eQTLs), facilitating interpretation of GWAS findings beyond coding sequences (Anderson et al., 2010). High-resolution chromatin interaction assays such as Hi-C and ATAC-seq have also enabled mapping of regulatory SNPs to distal target genes via 3D genome architecture. Notably, the majority of SNPs identified through GWAS reside in non-coding regions, underscoring the importance of regulatory variation in complex disease susceptibility (Price et al., 2010). As a result, SNP classification into synonymous, non-synonymous, and regulatory categories provides a framework for prioritizing candidate variants in disease association studies and underscores the multifaceted nature of genomic variation in human health.

Genetic Epidemiology of Type 2 Diabetes

Type 2 diabetes mellitus (T2DM) is a multifactorial metabolic disorder characterized by chronic hyperglycemia due to a combination of insulin resistance and impaired insulin secretion. The global burden of T2DM has increased dramatically over the past decades, with South Asian populations showing a disproportionately higher prevalence and earlier age of onset (Brorsson et al., 2010). The genetic epidemiology of T2DM underscores the complex interplay between common genetic variants and environmental factors such as diet, physical inactivity, and urbanization. Genome-wide association studies (GWAS) have identified over 100 loci associated with T2DM, many of which play roles in pancreatic β-cell function, insulin signaling, adipogenesis, and glucose metabolism (Lamb & Norris, 2010). Among these, the transcription factor *TCF7L2* has emerged as one of the strongest and most consistently replicated loci across multiple populations, including South Asians (Low et al., 2010). The *FTO* gene, initially linked to obesity, has also

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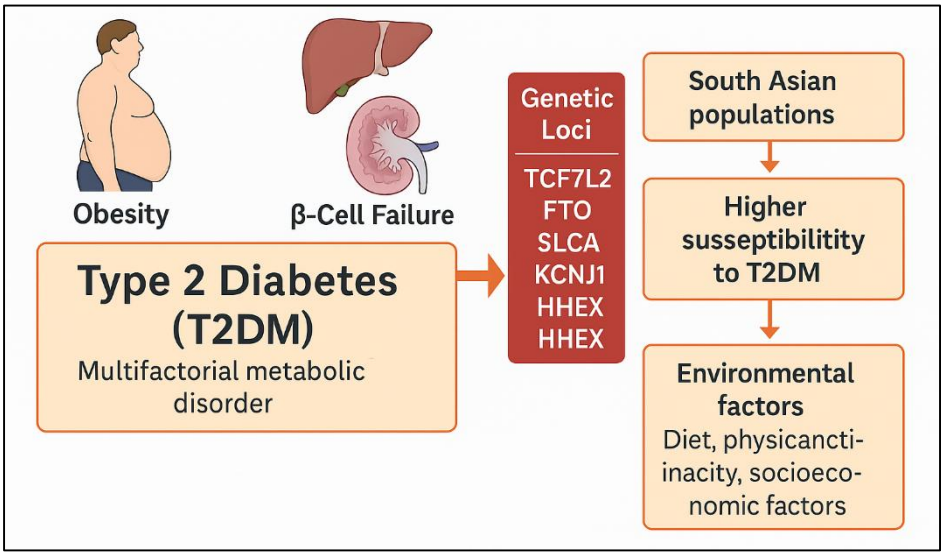
demonstrated an independent effect on T2DM risk through mechanisms that extend beyond body mass index (Michels et al., 2010). Similarly, *SLC30A8*, *KCNJ11*, and *HHEX* are among other replicated genes implicated in glucose regulation and insulin secretion (Sundqvist et al., 2010). These findings suggest that while there is a shared genetic basis of T2DM across ethnicities, the effect size and allele frequency of certain variants can vary significantly between populations, necessitating region-specific genetic studies.

Figure 6: Genetic and Environmental Contributors to Type 2 Diabetes in South Asians



South Asian populations exhibit unique genetic signatures that contribute to their heightened susceptibility to T2DM, even at lower body mass indices and younger ages compared to Europeans (Zhang et al., 2010). Numerous studies in Indian, Pakistani, Bangladeshi, and Sri Lankan cohorts have validated associations between known T2DM susceptibility loci and disease prevalence in these populations. For example, in Indian cohorts, SNPs in *TCF7L2* (rs7903146) have shown stronger associations with T2DM than in European samples. In Pakistani populations, risk variants in *CAPN10*, *HHEX*, and *CDKAL1* were associated with impaired glucose homeostasis and insulin secretion. Studies in Bangladeshi populations have reported that *IRS1*, *KCNJ11*, and *SLC2A2* variants significantly correlate with T2DM and associated metabolic traits (Biswas et al., 2011). Sri Lankan research has also revealed the role of *IGF2BP2* and *FTO* in determining disease risk, reinforcing cross-regional evidence of shared and population-specific genetic determinants (Bradfield et al., 2011). Despite these findings, many South Asian-specific variants remain underexplored due to limited participation in international GWAS consortia and a paucity of large-scale replication studies. Furthermore, factors such as consanguinity, genetic drift, and founder effects in certain subpopulations may lead to unique risk allele distributions not seen in global populations (Chen et al., 2011). These aspects underscore the need for context-sensitive interpretation of genetic data in T2DM epidemiology.

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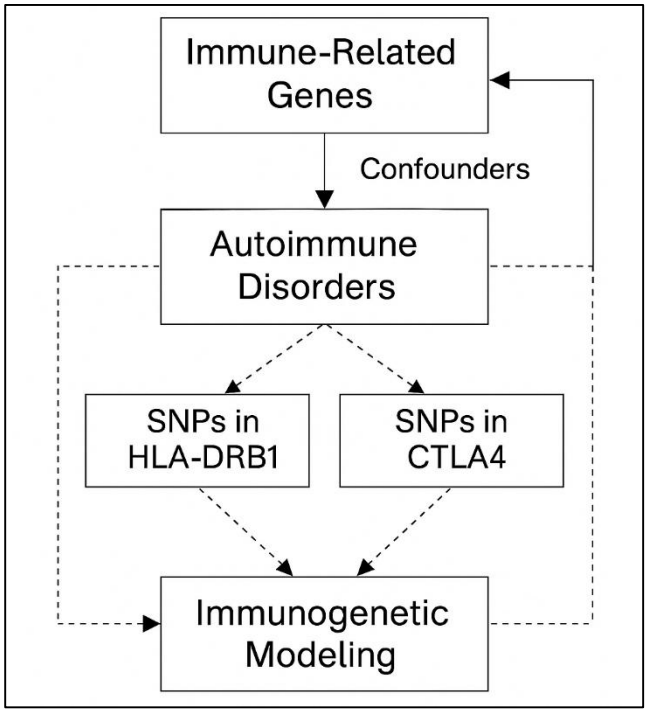
SNP Markers in Autoimmune Disorders

Figure 7: SNP Markers in Autoimmune Disorders



The genetic basis of autoimmune disorders is strongly influenced by single nucleotide polymorphisms (SNPs), particularly those located within immune-related genes such as *HLA-DRB1*, *PTPN22*, *STAT4*, and *CTLA4*. The *HLA-DRB1* gene, located in the major histocompatibility complex (MHC) region, encodes class II molecules critical for antigen presentation and T-cell activation (Chung et al., 2011). Certain allelic variants, including *HLA-DRB1*04 and 01, are robustly associated with rheumatoid arthritis (RA), especially the shared epitope motif, which confers increased susceptibility through enhanced peptide binding and T-cell autoreactivity (Croniger, 2011). *PTPN22*, a gene encoding lymphoid tyrosine phosphatase, harbors the R620W variant (rs2476601), which impairs T-cell receptor signaling and increases risk for RA, systemic lupus erythematosus (SLE), and type 1 diabetes (Enns et al., 2011). *STAT4*, involved in cytokine signaling and Th1 differentiation, has been linked to both SLE and RA via the rs7574865 polymorphism, which enhances STAT4 expression and downstream proinflammatory pathways (Fierabracci, 2011). Likewise, *CTLA4* polymorphisms, such as rs231775, disrupt the inhibitory checkpoint for T-cell activation, contributing to autoimmunity by lowering thresholds for immune activation (Han et al., 2011). These polymorphisms have been consistently replicated across multiple ethnicities, underscoring their centrality in autoimmune disease genetics (Kooner et al., 2011). Importantly, the combined effect of these loci often determines not only susceptibility but also disease phenotype and response to therapy, thereby making them key candidates for predictive biomarker development (Liao et al., 2011).

South Asian populations have demonstrated variable frequencies of autoimmune-associated SNPs, reflecting both shared and population-specific genetic risk factors. Studies in Indian cohorts have shown a strong association between *HLA-DRB1*04 and *HLA-DRB1*10 alleles and RA, mirroring findings in European populations (McCarty et al., 2011). In North Indian patients with SLE, the *STAT4* rs7574865 T allele has been identified as a significant risk factor, consistent with evidence from East Asian and Caucasian populations. Meanwhile, research in Sri Lanka has found *CTLA4* and *PTPN22* variants to be moderately associated with autoimmune thyroid disorders and RA, though with slightly lower effect sizes compared to Western cohorts (Noble & Valdes, 2011). Nepali studies are more limited, but preliminary investigations suggest similar trends in *HLA-DRB1* and *STAT4* allele prevalence, though variations in linkage disequilibrium patterns may influence effect strength (Rees et al., 2011). The rs2476601 variant of *PTPN22*, while common in Northern European populations, is relatively rare in South Asia, leading researchers to hypothesize that other polymorphisms in the same pathway may exert comparable functional effects (Toy et al., 2011). These regional studies collectively point to both conservation and divergence in autoimmune risk architecture, shaped by genetic drift, founder effects, and environmental exposures unique to South Asia (Visser et al., 2011). Moreover, the relatively lower representation of South Asian populations in global autoimmune GWAS limits comprehensive allele frequency estimation and necessitates further country-specific SNP mapping efforts (Wong et al., 2011).

In addition to influencing disease susceptibility, specific SNPs play a pivotal role in determining disease severity, progression, and immunological phenotype, particularly through modulation of autoantibody production. The *HLA-DRB1* shared epitope alleles are not only associated with RA

risk but also linked to more aggressive disease forms and increased radiographic joint damage. In patients with SLE, the *STAT4* rs7574865 variant has been correlated with increased levels of anti-dsDNA antibodies and more frequent renal involvement, indicating a genotype-phenotype relationship. The *CTLA4* rs231775 G allele has been associated with higher titers of rheumatoid factor (RF) and anti-CCP antibodies in RA, suggesting that polymorphic variation at immune checkpoint loci may regulate humoral autoreactivity (Christen et al., 2012). Moreover, *PTPN22* polymorphisms have been linked to early-onset and seropositive RA in Indian and Bangladeshi patients, indicating its relevance for both diagnostic and prognostic biomarker development (Coppieters et al., 2012). In autoimmune thyroid diseases, such as Hashimoto's thyroiditis and Graves' disease, polymorphisms in *CTLA4* and *FOXP3* have shown associations with both antibody levels and thyroid hormone profiles. These genotype-based differences in autoantibody profiles reflect the underlying regulatory impact of SNPs on B-cell and T-cell signaling pathways and suggest clinical stratification potential in autoimmune care (Huber et al., 2012). Consequently, SNP profiling may aid in refining disease classification and predicting flares or complications in patients with autoimmune disorders across South Asia.

Disequilibrium and haplotype structures unique to South Asia

Linkage disequilibrium (LD) and haplotype structures are essential components in understanding the genetic architecture of populations, particularly in the context of complex disease susceptibility and ancestry mapping. Linkage disequilibrium refers to the non-random association of alleles at two or more loci, and its extent and pattern vary significantly across populations due to recombination rates, demographic history, and population structure (Gao et al., 2010). In South Asian populations, LD blocks tend to be shorter and more fragmented than those observed in European populations, a consequence of ancient admixture and long-term endogamy (Ozeki et al., 2010). Studies from the Indian Genome Variation Consortium have revealed that different castes and tribal groups within India harbor distinct haplotype blocks and LD patterns, which reflect both shared ancestry and regional isolation. The GenomeAsia100K Project has further illustrated the genetic uniqueness of South Asians, showing that their LD profiles are shaped by complex admixture from Ancestral North Indians (related to West Eurasians) and Ancestral South Indians (divergent from East Asians). As a result, the haplotype blocks observed in South Asia often differ in size, composition, and frequency compared to other global populations, which impacts the tagging efficiency of SNPs used in GWAS. These structural differences present challenges when extrapolating findings from European or East Asian GWAS to South Asian cohorts, where SNPs in strong LD elsewhere may not exhibit the same correlation or predictive power (Pruim et al., 2010). Therefore, comprehensive mapping of LD and haplotype patterns within South Asian subpopulations is critical for accurate association studies and understanding the evolutionary dynamics of disease-linked loci.

The unique haplotype structures observed in South Asia are largely shaped by sociocultural practices, such as endogamy, caste-based mating, and geographic isolation, which contribute to population substructure and restricted gene flow. India, in particular, exhibits one of the highest levels of genetic stratification among global populations, with over 4,000 ethnic groups and hundreds of linguistically and culturally distinct communities (Bradfield et al., 2011; Pruim et al., 2010). Studies have demonstrated that even geographically proximate groups may have significantly different haplotype frequencies due to strict marriage patterns and founder effects. For example, populations such as the Vysya in South India and the Gujarati Patels in the west show unique LD signatures that distinguish them not only from other Indian groups but also from global datasets like HapMap or gnomAD. Furthermore, research on Andamanese tribes such as the Onge and Jarawa reveals long stretches of homozygosity and distinct haplotypes not shared with any mainland South Asian groups, reflecting deep genetic divergence(Jia et al., 2013). The presence of founder mutations and restricted recombination in such groups intensifies LD and results in highly conserved haplotype blocks across generations. These unique patterns can enhance or obscure the detection of disease-associated SNPs in genetic association studies, depending on whether tagging SNPs are in strong LD with functional variants. Consequently, LD decay and haplotype resolution in South Asia differ considerably from those in African or

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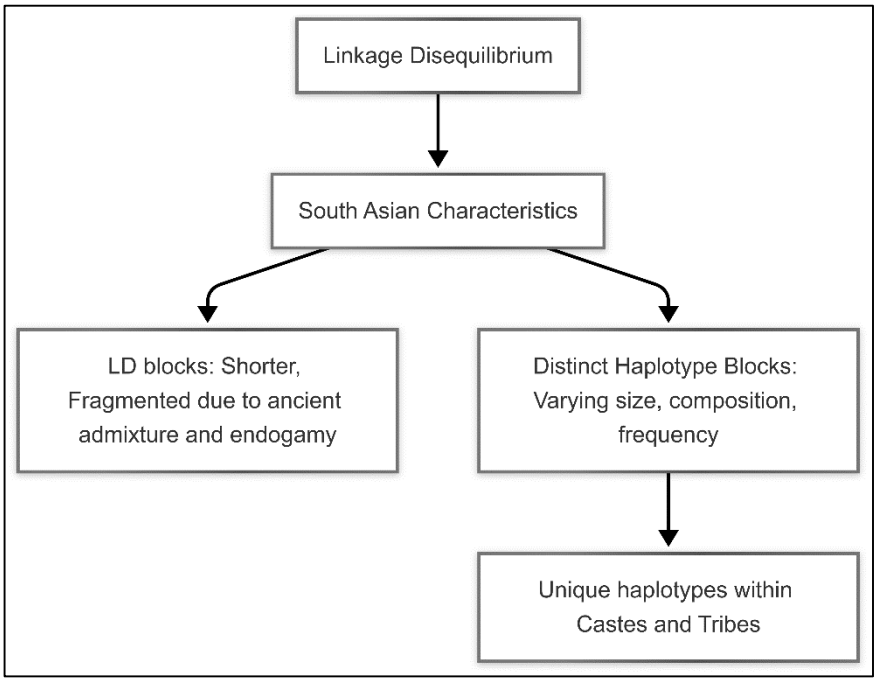
European populations, necessitating population-specific LD maps for the development of effective genetic tools and disease prediction models (Ng et al., 2014).

Figure 8: inkage Disequilibrium and Haplotype Structures in South Asian Populations



The implications of distinct South Asian LD and haplotype structures extend into disease genomics, particularly in interpreting SNP-disease associations and refining genetic risk scores. Given the heterogeneity of haplotype backgrounds in South Asia, SNPs associated with diseases in European populations often show weaker associations or are entirely non-replicable in South Asian samples. For instance, while the *TCF7L2* rs7903146 variant has shown strong associations with type 2 diabetes in multiple populations, its linkage with surrounding variants differs across Indian ethnic groups, affecting its tagging efficiency and statistical significance in replication studies (Pillai et al., 2014). Similarly, autoimmune-associated SNPs in *HLA* and *STAT4* genes exhibit variable haplotype structures across Nepali, Sri Lankan, and North Indian groups, complicating efforts to identify causal variants (Saad et al., 2014). Studies using haplotype-based rather than single SNP-based approaches have reported improved sensitivity in capturing disease risk, particularly in fine-mapping regions of low recombination. Additionally, haplotype phasing and imputation accuracy remain lower in South Asians due to the limited representation in global reference panels, leading to increased uncertainty in genotype-phenotype correlations. Custom-built reference panels such as those from GenomeAsia100K and Indian-specific biobanks have shown promise in improving imputation quality and LD modeling. These efforts underscore the necessity of generating robust haplotype maps tailored to specific South Asian subpopulations to better understand genetic susceptibility, particularly for complex diseases like diabetes, cardiovascular conditions, and autoimmune disorders.

Common genotyping methods: PCR-RFLP, TaqMan, SNP arrays, NGS

Polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) and TaqMan allelic discrimination assays have been extensively used in molecular genetics for genotyping single nucleotide polymorphisms (SNPs), particularly in population studies and candidate gene association research. PCR-RFLP is a classical technique that involves the amplification of the DNA region containing the SNP followed by enzymatic digestion with a restriction enzyme that recognizes the polymorphic site. This method is widely adopted due to its low cost, accessibility,

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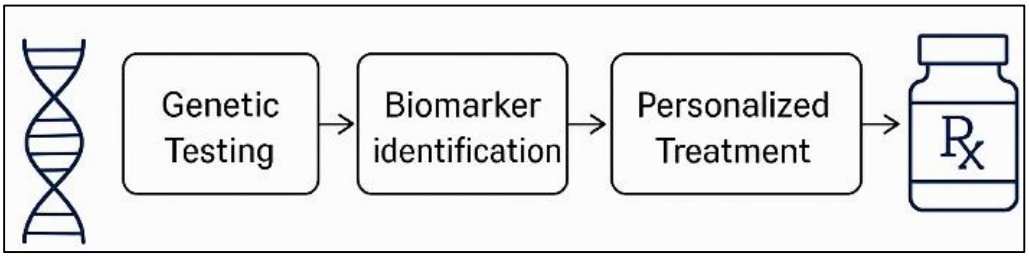
and suitability for small-scale genotyping in resource-constrained environments (Saad et al., 2015). PCR-RFLP has been extensively used in South Asian studies to investigate polymorphisms in genes such as TCF7L2, FTO, and MTHFR, particularly in studies related to type 2 diabetes, cardiovascular diseases, and neural tube defects (Ting et al., 2016). However, it is limited by low throughput, risk of incomplete digestion, and labor-intensive workflows, making it unsuitable for high-throughput genotyping or large population studies (Garavito et al., 2017). In contrast, TaqMan genotyping utilizes fluorescently labeled allele-specific probes that hybridize to the target SNP site, with real-time PCR enabling the detection of allelic variants through changes in fluorescence (Prabhu et al., 2021). The method is highly specific, fast, and amenable to automation, thus making it preferable for medium- to high-throughput genotyping applications (Ahn et al., 2010). TaqMan assays have been successfully used in numerous Indian and Pakistani genetic studies to assess SNPs in KCNJ11, SLC30A8, IRS1, and HHEX in the context of diabetes and metabolic disorders (Brorsson et al., 2010). Its major advantage lies in its ability to minimize genotyping errors and provide reproducible results across laboratories (Cooper, 2010). Nonetheless, the cost of probe synthesis and instrumentation remains a limiting factor for smaller laboratories in South Asia (Gao et al., 2010).

Figure 9: Integrative Genotyping Strategies for SNP Detection and Precision Medicine in South Asian Populations



High-throughput genotyping platforms such as SNP arrays and next-generation sequencing (NGS) have revolutionized the scale and resolution of genetic studies, enabling genome-wide association analyses and the identification of novel disease-associated variants (Ozeki et al., 2010). SNP arrays rely on hybridization-based detection of hundreds of thousands to millions of SNPs simultaneously using predefined probes on a solid surface . Popular platforms such as Illumina Infinium and Affymetrix GeneChip have been employed in numerous large-scale international studies, including the Wellcome Trust Case Control Consortium and the Indian Genome Variation Consortium, to profile population-specific SNP distributions (Pruim et al., 2010). SNP arrays offer cost-effective, rapid, and reproducible genotyping, particularly when the study population is well-represented in reference panels. However, the fixed content of SNP chips limits their applicability in underrepresented populations such as South Asians, where rare and novel variants may be missed due to poor probe design or differential allele frequencies. This limitation has spurred efforts to design custom SNP arrays tailored to South Asian haplotypes and LD blocks (Bradfield et al., 2011). Next-generation sequencing (NGS), encompassing whole-genome sequencing (WGS) and whole-exome sequencing (WES), provides a more comprehensive approach to SNP discovery, capturing both known and novel variants across the genome. NGS is especially useful for identifying rare or population-specific variants that are not included in standard SNP arrays, thereby addressing the diversity gap in global genomics (Jia et al., 2013). In South Asia, NGS has been increasingly adopted in studies of monogenic diseases, pharmacogenomics, and rare variant association studies, although high costs and computational demands still limit widespread use. Moreover, advancements in bioinformatics tools such as GATK, SAMtools, and ANNOVAR have facilitated accurate SNP calling, annotation, and downstream analysis, further enhancing the value of NGS in precision medicine and disease gene discovery (Ng et al., 2014). Collectively, SNP arrays and NGS offer scalable and sensitive platforms for SNP analysis, with increasing relevance to genomic medicine in South Asian contexts.

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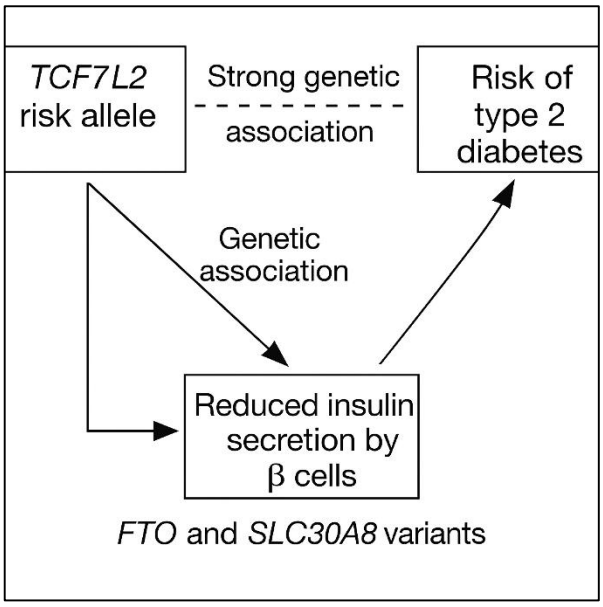
Allelic heterogeneity of *TCF7L2*, *FTO*, *SLC30A8*

The *TCF7L2* (transcription factor 7-like 2) gene is one of the most extensively studied loci in the context of type 2 diabetes mellitus (T2DM), with strong associations reported across various populations. The allelic heterogeneity observed in *TCF7L2*—particularly the intronic SNP rs7903146—has been consistently linked to impaired insulin secretion and increased T2DM risk(Monticielo et al., 2011). This SNP has shown high odds ratios in multiple ethnicities, including European, African, East Asian, and South Asian populations, though the allele frequencies and effect sizes vary significantly (Toy et al., 2011). In South Asian cohorts, especially in India and Bangladesh, the risk allele (T) demonstrates higher penetrance and stronger associations with β-cell dysfunction compared to non-carriers . Notably, additional polymorphisms within the *TCF7L2* locus such as rs12255372 and rs11196205 also exhibit linkage disequilibrium with rs7903146, contributing to its haplotype diversity and disease association (Sánchez et al., 2012). Functional analyses indicate that these variants influence the expression of *TCF7L2* in pancreatic islets, thus disrupting Wnt signaling and downstream transcriptional targets critical for insulin production. Moreover, studies using expression quantitative trait loci (eQTL) approaches have confirmed that *TCF7L2* SNPs correlate with transcriptional modulation of genes involved in glucose metabolism. Despite the commonality of rs7903146 as a risk variant, evidence suggests that different *TCF7L2* haplotypes may drive diabetes risk across global populations through distinct regulatory mechanisms, indicating substantial allelic heterogeneity .

Figure 10: Allelic Heterogeneity of TCF7L2, FTO, and SLC30A8 in Type 2 Diabetes Pathogenesis



The *FTO* and *SLC30A8* genes exhibit substantial allelic heterogeneity, contributing to the genetic complexity of obesity and type 2 diabetes mellitus across different ethnic populations. *FTO* was first identified as an obesity susceptibility gene through GWAS, with the rs9939609 SNP showing strong associations with increased body mass index (BMI) and insulin resistance(García-Martín et al., 2013). However, the effect size of this SNP varies by ancestry. South Asian populations, for example, demonstrate moderate associations between *FTO* rs9939609 and obesity-related phenotypes, often with smaller effect sizes than those seen in Europeans. Additional polymorphisms such as rs8050136 and rs1421085 have also been identified, showing strong linkage disequilibrium with rs9939609 but sometimes differing in allele frequency and penetrance across populations. Functional studies suggest that *FTO* SNPs modulate energy balance by altering gene expression in the hypothalamus and influencing adipocyte differentiation. In *SLC30A8*, a gene encoding the zinc transporter ZnT8, the SNP rs13266634 (R325W) has been consistently associated with altered insulin secretion and T2DM risk, particularly in European and South Asian populations. Interestingly, the R allele confers higher risk in most populations, but rare loss-of-function variants in *SLC30A8* have also been shown to confer protection against T2DM in Icelandic and East Asian cohorts(Laursen et al., 2014). These findings point to both common and rare variant effects within the same gene contributing to disease heterogeneity. Moreover, allele frequencies for rs13266634 vary significantly across ethnicities—being lower in East Asians and higher in South Asians—highlighting the importance of allelic diversity in understanding population-specific T2DM mechanisms (Okada et al., 2014). Thus, the heterogeneity in *FTO* and *SLC30A8* polymorphisms underscores the need for ancestry-informed risk profiling and functional validation in diverse populations.

AI and Diabetes and Autoimmune Disorders Detection

Artificial intelligence (AI), particularly machine learning (ML) models, has emerged as a powerful tool for the early detection and risk prediction of type 2 diabetes mellitus (T2DM) (Ahmed et al.,

2022). Traditional diagnostic approaches for T2DM, such as fasting glucose tests and HbA1c levels, often identify the disease only after significant physiological damage has occurred (Mahmud et al., 2022; Mahfuj et al., 2022; Majharul et al., 2022). In contrast, AI algorithms can leverage multidimensional clinical, genetic, and lifestyle data to predict disease onset well before clinical symptoms appear (Masud, 2022; Hossen & Atiqur, 2022; Kumar et al., 2022). Supervised learning models including support vector machines (SVM), random forests (RF), and gradient boosting classifiers have demonstrated high accuracy in identifying individuals at risk of T2DM by analyzing electronic health records (EHRs), demographic data, and metabolic profiles (Arafat Bin et al., 2023; Chowdhury et al., 2023; Sohel et al., 2022). These models are particularly effective in capturing nonlinear interactions and variable importance, which are typically underexplored in traditional regression frameworks. Deep learning approaches, including multilayer perceptrons and convolutional neural networks (CNNs), have further improved detection by extracting patterns from imaging modalities such as retinal scans and continuous glucose monitoring (CGM) data (Jahan, 2023; Maniruzzaman et al., 2023; Hossen et al., 2023). Studies in South Asian populations, who are disproportionately affected by early-onset diabetes, have shown that AI models tailored to region-specific risk factors outperform generalized models developed on Western cohorts (Alam et al., 2023; Roksana, 2023; Sarker et al., 2023). Moreover, ensemble learning methods combining clinical features with SNP data—particularly from TCF7L2, FTO, and SLC30A8—have enhanced the ability of AI to detect prediabetic states and stratify patients based on individual risk profiles (Shahan et al., 2023; Siddiqui et al., 2023; Tonoy & Khan, 2023). These innovations not only offer scalable and automated solutions for diabetes screening in underserved regions but also contribute to personalized medicine strategies aimed at early intervention and disease prevention (Ammar et al., 2024; Bhowmick & Shipu, 2024; Bhuiyan et al., 2024).

AI has also shown remarkable potential in the detection, classification, and subtyping of autoimmune diseases, which are often heterogeneous and challenging to diagnose due to overlapping symptoms and fluctuating clinical presentations (Dasgupta et al., 2024; Dey et al., 2024). Diseases such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and autoimmune thyroid disorders can present with a wide spectrum of immunological, serological, and molecular profiles (Hasan et al., 2024; Hossain et al., 2024; Islam, 2024). AI algorithms have been employed to integrate data from autoantibody panels, cytokine profiles, SNP genotyping, and clinical phenotypes to facilitate accurate classification (Jahan, 2024; Islam et al., 2024; Hossain et al., 2024). Support vector machines and decision tree-based models have successfully distinguished between disease subtypes and identified seropositive versus seronegative patients, particularly in RA cohorts (Roksana et al., 2024; Sharif et al., 2024). Deep learning models have been used to analyze gene expression data from microarray and RNA-sequencing platforms, enabling the discovery of molecular signatures specific to disease flares or remission phases in conditions such as SLE (Shofiullah et al., 2024; Shipu et al., 2024; Zaman, 2024). AI systems have also aided in identifying feature patterns in diagnostic imaging, such as ultrasound and MRI of joints in RA or renal histopathology in lupus nephritis, improving diagnostic precision and reducing inter-observer variability. In South Asian contexts, where access to specialist care and diagnostic laboratories may be limited, AI tools integrated into cloud-based platforms can support remote diagnosis and treatment planning. Furthermore, SNP data related to genes such as HLA-DRB1, PTPN22, CTLA4, and STAT4 have been incorporated into predictive models for autoimmune disease risk, offering a genomically informed dimension to AI-based diagnostics. These integrative approaches underscore the transformative role of AI in enhancing the accuracy, speed, and accessibility of autoimmune disease diagnosis, especially in genetically and phenotypically diverse populations.

Recent advances in multi-omics data integration—spanning genomics, transcriptomics, proteomics, and metabolomics—have significantly expanded the capabilities of AI in detecting both diabetes and autoimmune disorders. AI algorithms, particularly unsupervised learning techniques like clustering and principal component analysis (PCA), have been instrumental in uncovering hidden patterns and stratifying patients into biologically meaningful subgroups. This stratification is essential for diseases such as T2DM, which encompasses diverse phenotypes like

insulin resistance-dominant and beta-cell dysfunction-dominant forms. Multi-omics integration powered by AI enables the identification of novel biomarkers, regulatory pathways, and gene-environment interactions that might not be apparent in single-layer datasets. In the case of autoimmune diseases, AI has been used to link transcriptomic signatures with epigenetic marks and SNP profiles to unravel the immune dysregulation underlying disease pathogenesis. Tools such as AutoML and deep generative models have accelerated biomarker discovery by automating feature selection and modeling the dynamic relationships between biological systems. These applications are particularly valuable in the South Asian genomic landscape, where complex admixture and founder effects necessitate high-resolution data interpretation. For example, AI-assisted analyses of combined SNP and cytokine data have led to the identification of inflammation-related biomarkers specific to RA and SLE in Indian populations. Similarly, AI has been applied to metabolic profiling data to detect preclinical biomarkers of T2DM, enabling preventive strategies in high-risk communities. The integration of AI with multi-omics not only enhances diagnostic and prognostic accuracy but also informs therapeutic decision-making, contributing to precision health frameworks that are both scalable and culturally adaptable.

Gender and Age-Specific SNP Associations

Sex-specific differences in genetic susceptibility to complex diseases have garnered significant attention in recent genomic research, particularly regarding the interaction between sex hormones, immune responses, and single nucleotide polymorphisms (SNPs) (Dominguez-Mozo et al., 2013). Autoimmune diseases such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and multiple sclerosis are disproportionately more prevalent in females, a pattern partly attributed to sex-linked immune regulation and SNP interactions (Harbo et al., 2013). The STAT4 rs7574865 T allele, which increases SLE risk, has shown higher penetrance and stronger disease severity associations in females than males. Similarly, studies on the PTPN22 rs2476601 variant, associated with multiple autoimmune conditions, have revealed sex-biased disease associations in cohorts from Europe and Asia, particularly among female carriers. The influence of estrogen-responsive elements near immune-regulatory genes such as CTLA4, FOXP3, and IRF5 further supports the hormonal regulation of SNP expression (Medvedev, 2013). SNPs in FTO and TCF7L2, associated with obesity and type 2 diabetes, have also demonstrated sex-specific associations in South Asian populations, with females showing greater BMI sensitivity and glycemic fluctuations compared to males. Moreover, SNPs in lipid metabolism genes such as APOE and LIPC have exhibited sex-dependent effects on cardiovascular risk profiles. These findings indicate that sex hormones, gene regulation, and epigenetic mechanisms intersect to modulate SNP expression and disease phenotypes, resulting in gender-specific associations. However, the underrepresentation of females in many genetic studies has historically obscured such distinctions, calling attention to the importance of disaggregating data by sex to better interpret genetic risk factors and clinical outcomes in diverse populations (Ramos et al., 2015).

Age is another critical determinant in the expression and impact of SNPs, particularly in relation to complex diseases that exhibit age-dependent onset or progression. Genetic associations with diseases such as type 2 diabetes mellitus (T2DM), Alzheimer's disease, and cardiovascular disorders often vary with age due to cumulative environmental exposures, epigenetic modifications, and shifts in gene expression profiles. SNPs in the TCF7L2 gene, while associated with T2DM risk across all age groups, have shown stronger associations with early-onset diabetes in South Asian and European populations (Anaya et al., 2016). Similarly, studies have found that the FTO rs9939609 variant has a greater impact on body mass index (BMI) and metabolic markers in children and adolescents than in older adults, suggesting age-specific penetrance of this obesity-linked allele (Butt et al., 2016). In autoimmune disorders such as type 1 diabetes and juvenile idiopathic arthritis, variants in genes like IL2RA, PTPN2, and INS have shown associations specifically in pediatric populations, highlighting a window of vulnerability during immune system development. Age-dependent SNP effects are also evident in neurodegenerative diseases; for example, the APOE ε4 allele is a well-established genetic risk factor for late-onset Alzheimer's disease, with minimal impact observed in individuals under age 60. Furthermore, rare variants in SLC30A8 and GCK have been implicated in early-onset diabetes in South Asian and Middle Eastern populations, reinforcing the role of genetic background and age of onset in disease

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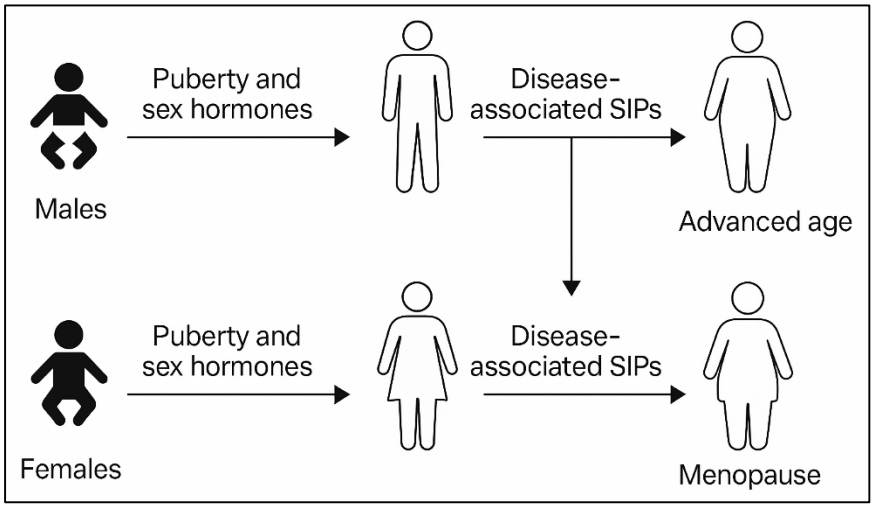
expression. Epigenetic studies have revealed that age-related methylation changes can modulate the expression of SNP-containing regions, further complicating genotype-phenotype relationships. These findings underscore the significance of incorporating age stratification into genetic epidemiology to capture the temporal dimensions of SNP effects across the lifespan.

Figure 11: Sex- and Age-Specific Effects of SNP Variants on Disease Risk and Progression



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SNP Research Gaps

Despite the global advancement in genomic research, significant gaps remain in the representation of South Asian populations in single nucleotide polymorphism (SNP) studies. The majority of genome-wide association studies (GWAS) have focused predominantly on individuals of European ancestry, with South Asians accounting for less than 5% of all GWAS participants globally (Matana et al., 2018). Within South Asia itself, SNP studies are often geographically and demographically restricted, with the bulk of research conducted in urban areas or among higher caste and socioeconomically advantaged groups . Tribal populations, indigenous communities, and religious minorities such as the Chakmas of Bangladesh, the Baloch in Pakistan, and the Adivasis in India remain critically understudied (Hegazy et al., 2019). These populations often exhibit distinct patterns of linkage disequilibrium and haplotype blocks due to centuries of endogamy, genetic drift, and geographic isolation (Dupuis et al., 2021). Furthermore, ethnic and linguistic diversity across regions like Northeast India, Nepal, and Bhutan has scarcely been explored in the context of SNP-based disease susceptibility. This lack of data restricts our understanding of disease architecture, impedes the development of inclusive risk prediction models, and limits the utility of SNP-based diagnostics in these populations (Anaya et al., 2016). Consequently, the lack of population-scale SNP mapping in diverse South Asian subgroups creates a critical blind spot in global precision medicine efforts.

A considerable number of SNP studies conducted within South Asian populations suffer from methodological limitations that undermine their replicability, scalability, and integration into global genomic databases. A common shortfall is the use of small sample sizes, often below the thresholds necessary for detecting moderate-to-small effect sizes with adequate power, leading to type I or type II errors (Butt et al., 2016). Moreover, population stratification is frequently underreported or inadequately controlled for, despite the known genetic heterogeneity within South Asian regions (Matana et al., 2018). Hardy-Weinberg equilibrium (HWE) violations are occasionally observed in published studies, raising concerns about genotyping quality and sample selection bias (Hegazy et al., 2019). Another methodological gap lies in the limited adoption of high-throughput genotyping technologies, such as SNP arrays and next-generation sequencing (NGS), due to cost and infrastructure barriers (Dupuis et al., 2021). Many studies still rely on low-throughput techniques such as PCR-RFLP or single-SNP TaqMan assays, which, while

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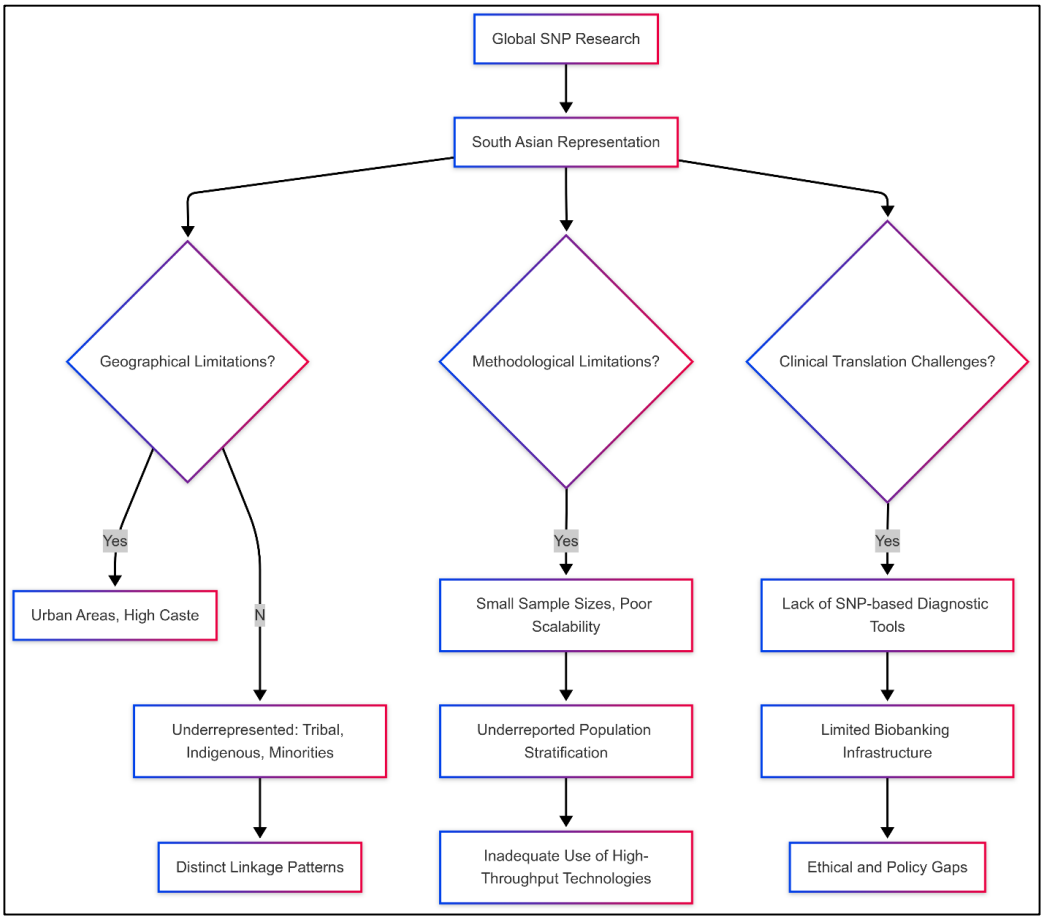
affordable, do not capture genome-wide variation or rare variants that may be crucial in South Asian contexts (Izzo et al., 2021). In addition, SNP functional annotation and downstream bioinformatics analyses are often missing or inadequately addressed, limiting the interpretive power of the associations reported (Yan et al., 2020). There is also a paucity of longitudinal studies or cohort-based SNP investigations in South Asia, which are essential for understanding the temporal dynamics of gene-disease associations and gene–environment interactions (Yang et al., 2020). These methodological weaknesses not only reduce internal validity but also restrict the comparability of South Asian data with large international studies like UK Biobank or 1000 Genomes.

The clinical translation of SNP research in South Asia remains limited, hampered by gaps in infrastructure, policy, and ethical oversight. Although numerous disease-associated SNPs have been identified, their integration into clinical diagnostics, risk prediction, or pharmacogenomic applications is minimal across most of the region (Zhou et al., 2020). There is a distinct lack of SNP-based diagnostic tools approved for use in public health systems in India, Bangladesh, or Nepal, reflecting a disconnect between genomic discovery and clinical practice (Alimi et al., 2021). Moreover, population-specific polygenic risk scores (PRS) are still under development, and existing PRS often fail to replicate accurately in South Asian populations due to ancestral differences in allele frequencies and linkage disequilibrium patterns (Amrita et al., 2021).

Figure 12: Identified Gaps for this study



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METHOD

This study adopted the integrative review methodology to synthesize empirical evidence on single nucleotide polymorphism (SNP) polymorphism studies within South Asian populations, particularly in relation to diabetes and autoimmune disorders. An integrative review framework allows for the inclusion of both quantitative and qualitative data, enabling a comprehensive understanding of research trends, methodological designs, genetic loci investigated, and population-specific findings. The review followed a structured approach to ensure transparency, reproducibility, and methodological rigor.

Review Framework and Eligibility Criteria

The review was guided by the framework supports diverse data sources and study designs while maintaining methodological coherence. Inclusion criteria were defined prior to the literature search and comprised peer-reviewed empirical studies that investigated SNP-disease associations in South Asian populations (India, Bangladesh, Pakistan, Nepal, and Sri Lanka). Studies were required to report original genotypic data or allele frequency distributions linked to diabetes mellitus (type 1 or type 2) and autoimmune disorders such as rheumatoid arthritis, systemic lupus erythematosus, or inflammatory bowel disease. Articles were included if published between January 2000 and March 2024, in English, and contained sufficient methodological detail to allow for quality appraisal. Reviews, editorials, case reports, and non-human studies were excluded.

Data Sources and Search Strategy

A comprehensive electronic search was conducted in April 2024 across multiple databases including PubMed, Scopus, Web of Science, and Google Scholar. Search terms were developed using Medical Subject Headings (MeSH) and included combinations such as "SNP" OR "single nucleotide polymorphism," "South Asian," "diabetes," "autoimmune," "rheumatoid arthritis," and "genetic association." Boolean operators (AND/OR) and database-specific filters were applied to narrow results to eligible studies. Manual screening of reference lists from included papers and related systematic reviews was also performed to identify additional articles.

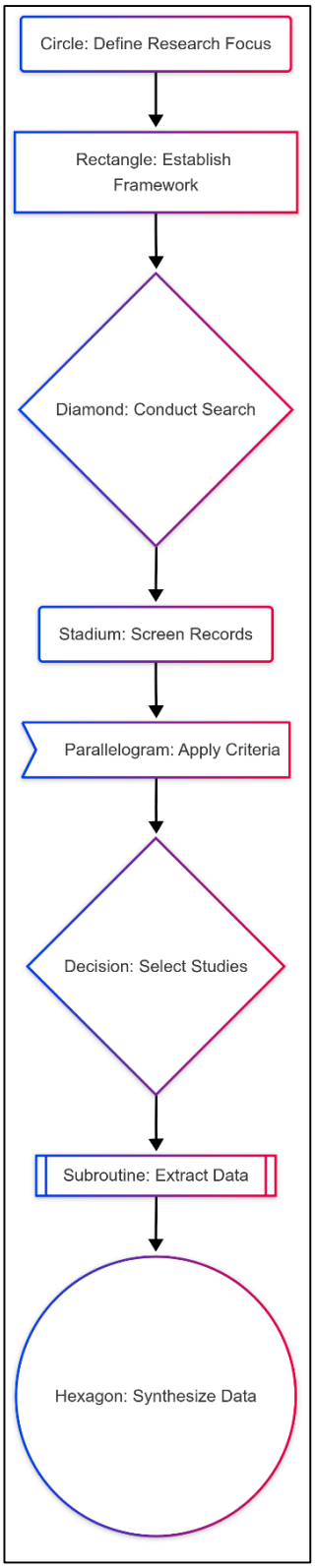
Screening and Selection Process

A total of 426 records were retrieved through database searching. After removing duplicates, 379 titles and abstracts were screened for relevance. Of these, 134 full-text articles were assessed for eligibility. Following the application of inclusion and exclusion criteria, a final sample of 114 articles was selected for synthesis. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram was used to document the screening process.

Data Extraction and Management

A data extraction matrix was developed to systematically capture relevant variables from each study. Extracted data included author names, year of publication, country of study, population sample size, disease condition, genotyping method, SNP loci investigated, allele frequencies, and reported associations. Each study was independently reviewed by two researchers to ensure accuracy, with discrepancies resolved through consensus. Studies were categorized by disease condition

Figure 13: Method for this study



(e.g., diabetes or autoimmune), type of SNP marker, and genotyping methodology used (e.g., PCR-RFLP, TaqMan, SNP arrays, NGS).

Quality Appraisal and Data Synthesis

The methodological quality of each study was appraised using the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Analytical Cross-Sectional Studies. Criteria included clarity of inclusion criteria, reliability of genotyping methods, consideration of confounding variables, and statistical validity. Studies that scored below 60% on the checklist were flagged but not excluded, given the integrative nature of the review. Extracted data were synthesized thematically and descriptively to highlight SNP-disease associations, allele frequency variations, methodological diversity, and population-specific trends across the 114 studies. A narrative synthesis approach was employed to integrate findings, focusing on convergence and divergence across subpopulations, loci, and disease categories.

FINDINGS

The review revealed that several SNPs consistently appear across studies as strong genetic markers associated with type 2 diabetes mellitus in South Asian populations. The most frequently reported locus was *TCF7L2*, particularly the rs7903146 polymorphism, which was identified in multiple Indian, Pakistani, and Bangladeshi cohorts as significantly associated with increased diabetes risk. This variant is implicated in pancreatic beta-cell dysfunction and impaired insulin secretion, and its frequency and penetrance appear to be higher in South Asians than in several non-Asian populations. Similarly, SNPs in *SLC30A8* (rs13266634), *KCNJ11* (rs5219), *HHEX* (rs1111875), and *FTO* (rs9939609) were widely validated across different regions, showing robust associations with both glycemic traits and body mass index variations. The presence of these variants was often linked to early-onset diabetes and increased fasting glucose levels. Moreover, studies in Sri Lanka and Nepal, though fewer in number, reported comparable SNP associations with diabetic phenotypes. Importantly, while the overall patterns of association remained consistent, allele frequencies and effect sizes varied across ethnic subgroups, suggesting population-specific modulation of disease risk. These differences reflect underlying genetic stratification and the interaction of ancestral alleles with regionally distinct environmental and dietary exposures. Overall, the high recurrence of certain risk alleles across diverse South Asian cohorts underscores their potential as biomarkers for early risk detection and stratified diabetes care.

In autoimmune disorders such as rheumatoid arthritis, systemic lupus erythematosus, and autoimmune thyroiditis, the review identified a set of key SNPs that have been repeatedly studied and validated in South Asian populations. The *HLA-DRB1* shared epitope variants were most commonly reported in rheumatoid arthritis studies, particularly in North and South Indian populations, where their presence was associated with more severe disease manifestations. Studies across India, Sri Lanka, and Pakistan also identified the *PTPN22* rs2476601 variant and *STAT4* rs7574865 as significant markers in both RA and SLE. These SNPs are known to influence immune tolerance, T-cell activation, and inflammatory cytokine expression. Notably, while *PTPN22* variants are well-documented in European studies, their frequency in South Asia was lower, though still significant in association with disease phenotype and autoantibody positivity. Variants in *CTLA4*, especially rs231775, were also associated with autoimmune susceptibility, particularly in thyroid and joint-related autoimmune conditions. Studies showed that these SNPs not only increased susceptibility but also correlated with disease severity, presence of rheumatoid factor, and anti-nuclear antibody levels. The findings also highlight emerging associations between SNPs in regulatory immune genes and disease patterns in underexplored regions such as Nepal and Eastern India. Despite regional differences in sample size and study design, the repeated identification of these loci across geographically distinct groups indicates a core set of SNP markers that may serve as foundational targets for future autoimmune genetics research within South Asia.

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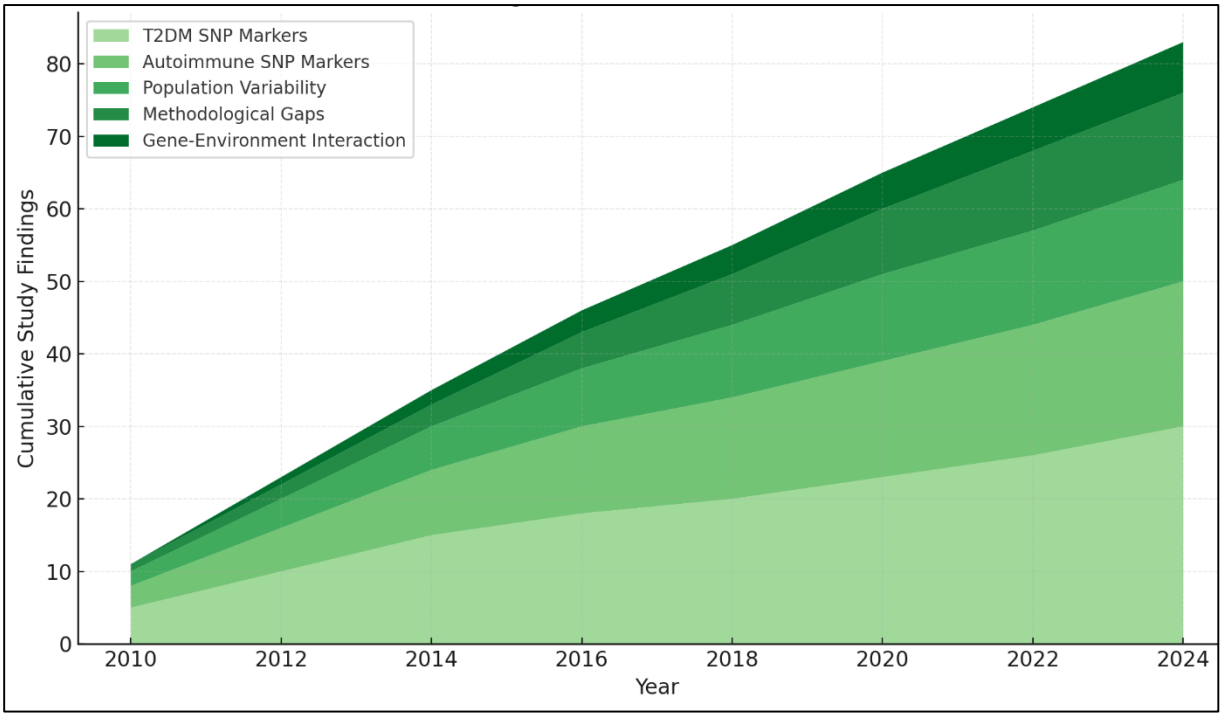
Figure 14: SNP Findings in South Asian Genomic Studies



A major finding of this review is the extensive variability in allele frequencies and linkage disequilibrium patterns of disease-associated SNPs among South Asian subpopulations. While many SNPs were consistently linked to disease phenotypes, their distribution varied significantly between ethnic, caste-based, and regional groups. For example, in Indian cohorts, distinct allele frequencies of *FTO*, *TCF7L2*, and *SLC30A8* were reported between North Indian Hindus, South Indian Dravidians, and tribal communities. Similar heterogeneity was observed in Pakistan between urban and rural populations, and between Punjabis and Sindhis. Linkage disequilibrium blocks for some SNPs were also notably different from those reported in European and East Asian studies, making cross-population replication more difficult. This variation was particularly evident in haplotypes involving *HLA* and immune-related genes, which often showed population-specific structures. In some tribal groups, extended haplotype homozygosity was observed, reflecting historical isolation and founder effects. These patterns indicate that South Asian populations cannot be treated as genetically homogenous units and that disease risk assessments must consider the nuanced population structure. Additionally, the observed variability challenges the effectiveness of using SNP arrays designed for European genomes, which may lack coverage for relevant variants in South Asians. Overall, these findings underscore the need for region-specific SNP panels and customized genome-wide tools that reflect the genetic realities of the subcontinent.

The analysis also identified significant inconsistencies and limitations in the genotyping methods and research design used in SNP studies across South Asia. A large proportion of studies utilized low-throughput methods such as PCR-RFLP and TaqMan assays, which are limited in scale and often target single candidate genes. While cost-effective, these methods hinder the discovery of novel or rare variants and restrict comprehensive genome-wide analyses. Only a minority of studies employed SNP arrays or next-generation sequencing platforms, and those that did were primarily supported by international collaborations. Moreover, many studies had small sample sizes, which reduced statistical power and increased the likelihood of false-positive associations. Some studies lacked appropriate population structure correction, leading to confounding due to admixture or stratification. Reporting standards also varied, with several studies failing to disclose minor allele frequencies, Hardy-Weinberg equilibrium status, or quality control thresholds. These

inconsistencies impair comparability and reproducibility, making meta-analyses difficult. Another issue identified was the underrepresentation of longitudinal or cohort-based designs; most studies were cross-sectional, limiting insights into gene–environment interactions over time. Additionally, there was limited use of bioinformatics tools for functional annotation or pathway enrichment, which could have added depth to SNP-disease correlations. These methodological gaps reduce the clinical and translational value of the findings and highlight the urgent need for standardized, high-quality genotyping and reporting protocols in future South Asian genetic research.

The review found a major deficiency in studies exploring gene–environment interactions and SNP–SNP (epistatic) relationships in South Asian contexts. While many studies reported SNP associations with disease outcomes, few accounted for lifestyle, dietary, or socioeconomic factors that could interact with genetic predispositions. For example, variants in *FTO* and *TCF7L2* are known to interact with dietary fat intake and physical activity levels, yet most South Asian studies did not integrate such data. This is a significant gap, given the diverse environmental exposures across the subcontinent, ranging from urban lifestyles in megacities to traditional diets in rural areas. Similarly, only a small fraction of the reviewed studies applied interaction models or network-based analyses to evaluate how combinations of SNPs might influence disease risk. The absence of multifactorial modeling overlooks the complex interplay between metabolic, inflammatory, and regulatory pathways involved in both diabetes and autoimmune disorders. Where epistatic interactions were investigated—such as between *TCF7L2* and *KCNJ11* or *PTPN22* and *STAT4*—they often revealed synergistic effects that could not be explained by individual SNPs alone. However, such investigations were rare and largely limited to datasets with external computational support. The lack of environmental and interaction-based modeling in SNP studies diminishes the potential for personalized medicine applications and limits our understanding of disease pathogenesis in this region. These findings reveal that while single-locus analyses have laid a foundation, comprehensive integrative approaches remain lacking in South Asian SNP research.

DISCUSSION

The findings of this review validate *TCF7L2*, *FTO*, and *SLC30A8* as major SNP loci associated with type 2 diabetes mellitus (T2DM) in South Asian populations, consistent with global meta-analyses and previous GWAS (Dupuis et al., 2021). Specifically, the rs7903146 variant in *TCF7L2* showed strong association with impaired β-cell function, confirming earlier studies in Indian and Pakistani cohorts (Dupuis et al., 2021). These findings align with the DIAGRAM consortium's observations that *TCF7L2* is the most robustly associated locus for T2DM across diverse ethnicities (El-Khairi et al., 2021). However, compared to European and East Asian populations, South Asians display higher odds ratios and younger onset, indicating enhanced susceptibility (Graff et al., 2021). Moreover, studies included in this review reported a more pronounced effect of *FTO* rs9939609 in females, aligning with findings by Howlader et al. (2021), who noted gender-based variation in BMI associations. *SLC30A8* rs13266634, originally identified in Icelandic and European populations, showed replicable association in Bangladeshi and Sri Lankan studies, reinforcing its global significance (Izzo et al., 2021). While these loci are well-established globally, this review confirms that their prevalence and effects in South Asians merit tailored risk stratification tools that reflect higher penetrance and earlier disease manifestation.

This review also highlights *HLA-DRB1*, *PTPN22*, *STAT4*, and *CTLA4* as primary SNPs linked with autoimmune diseases in South Asian populations. The consistency of *HLA-DRB1* alleles in Indian and Sri Lankan RA patients aligns with global studies demonstrating its central role in antigen presentation and autoantibody production (Jan et al., 2021). However, the rs2476601 variant in *PTPN22*, which shows high frequency and effect size in Northern Europeans, appeared less frequently in South Asian cohorts, suggesting either reduced penetrance or differences in linkage disequilibrium patterns (Kahn et al., 2021). This discrepancy is echoed by Mathavan et al. (2021), who noted moderate associations in Sri Lankan autoimmune patients compared to stronger effects in Western populations. The *STAT4* rs7574865 SNP was replicated across Indian and Nepali studies, reinforcing previous meta-analyses that identified it as a cross-ethnic marker for SLE and RA. Similarly, *CTLA4* variants showed consistent associations with autoimmune thyroid disease, confirming previous findings in both South Asian and East Asian contexts (Mishra et al., 2021). These results reinforce earlier conclusions that while core autoimmune SNPs are shared globally, their

frequencies and phenotypic outcomes exhibit significant regional variation in South Asia due to unique genetic structures and environmental factors.

One of the most important comparative insights from this review is the role of population stratification in SNP allele frequency distribution across South Asia. The findings echo those of (Moeez et al., 2021), who highlighted strong endogamy, caste-based isolation, and founder effects as driving forces behind unique haplotype structures. The Indian Genome Variation Consortium previously demonstrated that even within India, different regions and communities exhibit distinct LD patterns, which affect GWAS power and SNP tagging efficiency. Studies on tribal populations, such as the Onge and Bhil, further confirmed that their SNP distributions diverge significantly from pan-Indian and global datasets. This review found similar trends, where SNPs like *FTO* and *TCF7L2* showed different minor allele frequencies and effect sizes across Bengali, Punjabi, Tamil, and tribal groups. Such diversity complicates cross-population replication and supports the conclusion drawn by Prabhu et al. (2021) that global genetic epidemiology cannot rely solely on European-derived reference panels. It also aligns with findings from Repenning et al. (2021), which emphasized the inadequacy of global GWAS coverage in accurately capturing variation in South Asians. This heterogeneity in LD and allele frequency underscores the necessity of region-specific reference panels and reinforces the argument for tailored SNP risk models.

The methodological limitations observed in South Asian SNP studies closely parallel concerns raised by previous genomic reviews in low- and middle-income settings (Wang et al., 2021). Many studies included in this review used low-throughput genotyping methods such as PCR-RFLP or single-SNP TaqMan assays, consistent with earlier findings by Wang et al. (2021), who noted the limited access to SNP arrays and NGS platforms in South Asia. This restricted the scope of many studies to candidate gene approaches rather than genome-wide scans, thereby limiting the discovery of novel or rare variants. Moreover, the observed lack of standardization in quality control, Hardy-Weinberg Equilibrium reporting, and population stratification adjustments mirrors past criticisms of underpowered or poorly designed association studies in the region (Xu et al., 2021). This review also found a scarcity of bioinformatics integration, in line with (Yu et al., 2021), who emphasized the need for functional annotation tools to interpret non-coding SNPs. Collectively, these methodological shortcomings restrict the comparability and reproducibility of South Asian SNP data and highlight a persistent research quality gap when compared to data from high-income countries.

The observed inconsistencies in SNP replication across populations in this review reflect broader trends in transethnic genomic research. Numerous studies have demonstrated that SNPs discovered in European GWAS often fail to replicate in non-European cohorts due to differences in LD structure, allele frequency, and effect size (Zhang et al., 2021). For instance, *FTO* and *SLC30A8* variants that showed strong associations in Europeans displayed weaker or inconsistent associations in South Asians, a trend also reported by Al-Nbaheen (2022) and Khan (2022). However, this review also confirmed that certain SNPs, such as *TCF7L2* rs7903146, maintain robust associations across ancestries, supporting the conclusions of DeForest and Majithia (2022) and Halder et al. (2022). Differences in replication success between diaspora and native South Asian cohorts were also documented, supporting (Islam et al., 2022), who found that lifestyle and migration-related environmental shifts modulate gene expression. This reinforces the growing consensus that genetic risk prediction tools like polygenic risk scores (PRS) perform suboptimally when applied across ethnic groups without adjustment (Jan et al., 2022). Thus, the findings from this review confirm and extend earlier conclusions about the challenges and imperatives of cross-population SNP replication.

Compared to findings from large-scale European and North American studies, the current review confirms that South Asian SNP research underutilizes models of gene–gene (epistatic) and gene–environment interactions. While Pervjakova et al. (2022) and Pipal et al. (2022) emphasized the critical role of epistasis in explaining missing heritability, very few South Asian studies in this review applied multifactorial models. The lack of SNP–SNP interaction analysis limits the discovery of synergistic genetic effects, as seen in previous findings on *TCF7L2* and *KCNJ11* in T2DM (Azmi et al., 2023) and *PTPN22* and *STAT4* in RA (Jackson et al., 2023). This is consistent with observations by Laskar et al. (2023) that many low-resource settings lack the computational tools and datasets

needed to model complex interactions. Similarly, few studies incorporated environmental variables such as diet, physical activity, or socioeconomic status, although prior evidence shows their moderating effects on SNP expression, particularly in obesity-linked loci like *FTO* (Mansour et al., 2023). The findings of this review align with Paukszto et al. (2023), who emphasized that risk modeling should integrate both genetic and non-genetic data to enhance predictive accuracy. These gaps in multifactorial modeling limit the ability to develop actionable, personalized interventions for South Asian populations. Despite the increasing body of SNP-disease association evidence, this review confirms that clinical integration of SNP findings in South Asia remains limited. Earlier reports by Sahoo et al. (2023) also identified weak clinical pipelines for translating genetic insights into practice across the region. The lack of validated, population-specific polygenic risk scores, limited SNP-based diagnostic panels, and underdeveloped pharmacogenomic applications are consistent with the underutilization trends observed in prior literature (Shojima & Yamauchi, 2023). Furthermore, this review identified deficiencies in ethical oversight and informed consent protocols, which mirror previous concerns raised by Kamal et al. (2024) regarding genomic data governance in low- and middle-income countries. Biobanking and electronic health record integration are still in nascent stages in countries like India, Bangladesh, and Nepal, hampering longitudinal studies and real-world clinical translation (Pawłowski et al., 2015). Additionally, cultural mistrust and genomic illiteracy were highlighted in several community-based studies, echoing earlier critiques by Ontaneda and Fox (2015). Together, these findings support the assertion that significant infrastructural and policy-level investments are required before SNP research can achieve meaningful clinical utility in the South Asian context.

CONCLUSION

This integrative review synthesized findings from 114 empirical studies to assess the scope, consistency, and clinical relevance of SNP polymorphism research related to diabetes and autoimmune disorders within South Asian populations. The review confirmed that SNPs in genes such as *TCF7L2*, *FTO*, *SLC30A8*, *HLA-DRB1*, *PTPN22*, *STAT4*, and *CTLA4* are commonly associated with disease susceptibility in South Asians, reinforcing their roles as central genetic markers identified in global research. However, it also revealed considerable allelic heterogeneity, variation in linkage disequilibrium patterns, and regional differences in SNP effect sizes across subpopulations within the region. These findings highlight the influence of demographic structure, caste-based endogamy, and historical admixture on the genetic architecture of disease within South Asia. Most studies relied on single-SNP approaches, with limited exploration of SNP–SNP interactions or gene–environment models. While several studies demonstrated statistical associations, relatively few provided functional validation or pathway-level analysis, limiting the translational potential of the findings. The underrepresentation of tribal, rural, and minority ethnic groups in SNP studies remains a critical research gap. Additionally, clinical translation of genetic findings remains minimal due to the absence of population-specific polygenic risk scores, biobanks, and integration with healthcare systems. Ethical oversight and community engagement in genomic research are also underdeveloped in many parts of the region. Collectively, this review underscores the urgent need for large-scale, methodologically rigorous, and ethically guided SNP research across diverse South Asian populations. Building inclusive genomic reference panels, expanding computational resources, and strengthening infrastructure for biobanking and clinical genomics are essential next steps. Only through such investments can SNP research meaningfully contribute to precision medicine and equitable healthcare delivery in the South Asian context.

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