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Original Article

The Role Of Single Nucleotide Polymorphisms (SNPS) In The Pathogenesis Of Type 2 Diabetes Mellitus

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ABSTRACT

Type 2 Diabetes Mellitus (T2D) is a complex metabolic disorder characterized by chronic hyperglycemia resulting from insulin resistance and beta-cell dysfunction. While environmental and lifestyle factors contribute significantly, genetic components—particularly single nucleotide polymorphisms (SNPs)—have emerged as key factors in disease susceptibility. Genome-wide association studies (GWAS) have identified numerous SNPs influencing insulin secretion, action, and glucose metabolism. This review discusses major T2D-associated SNPs, their molecular impact, and their implications for precision medicine and personalized treatment strategies.

Keywords: Type 2 Diabetes, SNPs, TCF7L2, Insulin Resistance, GWAS, Genetic Risk, Precision Medicine.

INTRODUCTION

Type 2 Diabetes Mellitus (T2D) is a chronic non-communicable disease affecting more than 10% of the global adult population. It is characterized by persistent hyperglycemia caused by a combination of insulin resistance and inadequate insulin secretion from pancreatic beta-cells. Over time, T2D leads to severe complications including cardiovascular diseases, nephropathy, neuropathy, and retinopathy, imposing an enormous socio-economic burden.

While lifestyle factors such as obesity, physical inactivity, high-fat diets, and stress are major contributors to T2D onset, the disease is also strongly influenced by genetic factors. Epidemiological studies, including family- and twin-based designs, estimate that the heritability of T2D ranges from 30% to 70%. The identification of genetic risk factors has become increasingly important for early diagnosis, prediction, and individualized treatment approaches.

Single nucleotide polymorphisms (SNPs), which are small-scale genetic variants, have revolutionized our understanding of genetic susceptibility to T2D. Over the last two decades, genome-wide association studies (GWAS) have uncovered hundreds of SNPs associated with T2D across diverse populations. These variants are located in or near genes that influence insulin secretion, glucose transport, lipid metabolism, inflammation, and circadian rhythm regulation. Thus, SNPs offer a valuable window into the complex biological pathways contributing to T2D.

2. OVERVIEW OF SNPs

Single nucleotide polymorphisms (SNPs) are the most common form of genetic variation, involving a change in a single base pair in the DNA sequence. They occur approximately once every 300 nucleotides, totaling more than 10 million SNPs in the human genome. While many SNPs are functionally silent, others can significantly affect gene expression, protein function, and cellular behavior.

In the context of T2D, SNPs can influence the disease process in several ways:
- Coding SNPs may lead to amino acid substitutions in proteins, thereby altering enzyme activity or receptor function.
- Non-coding SNPs, especially those in promoter or enhancer regions, can regulate gene expression levels, either enhancing or repressing transcription.
- Intronic or intergenic SNPs may influence splicing, epigenetic regulation, or chromatin structure, with downstream effects on cell function.

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Many T2D-associated SNPs are involved in the regulation of beta-cell function, insulin synthesis, and glucose uptake. For example, SNPs in the TCF7L2 gene are strongly associated with reduced insulin secretion, while variants in PPARG influence insulin sensitivity in adipose tissue. Others, like SLC30A8, affect zinc transport essential for insulin crystallization and granule formation.

Although each individual SNP contributes only modestly to disease risk, the cumulative effect of multiple SNPs—especially when interacting with environmental risk factors—can significantly elevate the likelihood of developing T2D. This polygenic nature of T2D underscores the importance of integrating SNP data into disease models and therapeutic planning.

5. Clinical and Therapeutic Context

The discovery of SNPs associated with T2D has transformed clinical approaches to disease risk prediction, diagnosis, and treatment. Although clinical utility is still evolving, there are several promising applications:

a. Genetic Risk Prediction:

Polygenic Risk Scores (PRS) aggregate the effects of numerous T2D-associated SNPs into a single quantitative measure of genetic susceptibility. These scores can identify individuals at high genetic risk, particularly useful for early intervention in younger populations or those with a family history of diabetes. For example, individuals with high PRS may benefit from early lifestyle modifications even before hyperglycemia develops.

b. Pharmacogenomics:

SNPs can influence how patients respond to anti-diabetic medications. For instance:

- Variants in KCNJ11 and ABCC8 affect response to sulfonylureas by altering pancreatic K-ATP channel function.

- CYP2C9 polymorphisms can modify the metabolism of sulfonylureas, affecting both efficacy and risk of hypoglycemia.

- SNPs near SLC22A1 impact metformin transport into hepatocytes, influencing drug absorption and efficacy.

This growing field of pharmacogenomics promises to optimize treatment regimens based on an individual's genetic profile, improving outcomes while reducing adverse effects.

c. Precision Medicine:

Personalized approaches to T2D management are increasingly possible thanks to genetic insights. By combining genomic, clinical, and environmental data, clinicians may soon tailor prevention and treatment strategies at the individual level.

d. Population-Level Screening:

In future healthcare settings, screening for common SNPs could be integrated into routine health check-ups, especially in high-risk ethnic populations. This could lead to the development of genotype-based preventive programs and dynamic risk prediction models.

3. Notable T2D-Associated SNPs and Genes

The following table summarizes key SNPs strongly associated with T2D, identified through GWAS:

Gene	SNP ID	Risk Allele	Function	Mechanism / Impact
TCF7L2	rs7903146	T	Wnt pathway transcription factor	Disrupts incretin-stimulated insulin secretion

KCNJ11	rs5219	G (E23K)	K+ channel subunit	Alters membrane polarization and insulin release
SLC30A8	rs13266634	T (R325W)	Zinc transporter in islets	Affects insulin granule formation and secretion
PPARG	rs1801282	C (Pro12Ala)	Regulator of adipogenesis	Improves insulin sensitivity; variant protective
FTO	rs9939609	A	Obesity-associated gene	Indirect effect via body mass and adiposity
CDKAL1	rs7754840	G	Insulin granule maturation	Decreases insulin synthesis in beta cells
IGF2BP2	rs4402960	T	mRNA-binding protein for IGF2	Impairs beta-cell development
MTNR1B	rs10830963	G	Melatonin receptor	Modulates circadian regulation of insulin secretion
CDKN2A/B	rs10811661	T	Cell cycle control	Inhibits beta-cell proliferation

4. Biological Mechanisms and Pathways

- Beta-cell dysfunction: SNPs like TCF7L2 and CDKAL1 interfere with insulin synthesis and secretion.

- Insulin resistance: Variants in PPARG and FTO affect adipocyte differentiation and lipid storage.

- Circadian disruption: MTNR1B variants influence sleep-wake cycles and nocturnal insulin regulation.

- Epigenetic and regulatory changes: Many SNPs lie in non-coding regions affecting enhancers, promoters, and non-coding RNAs.

6. Limitations and Future Perspectives

Despite advances, SNPs explain only a fraction of T2D heritability. Limitations include:

- Small effect sizes of individual SNPs

- Ethnic variability in SNP effects

- Gene-environment interactions not fully understood

- Need for integration of epigenomics, transcriptomics, and microbiomics in future studies

CONCLUSION

SNPs significantly contribute to the understanding of T2D pathogenesis. Their integration into risk models, therapeutic strategies, and public health interventions offers promise for personalized and preventive medicine. Ongoing research must address current limitations through multi-omics and population-specific studies.

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