International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 5 Sept - Oct 2025, pp: 323-329 www.ijprajournal.com ISSN: 2456-4494

Understanding the High Incidence of Type 2 Diabetes in Indian Populations: A Genetic and Environmental Perspective

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Date of Submission: 10-09-2025 Date of Acceptance: 20-09-2025

ABSTRACT:
Type 2 Diabetes (T2D) poses a growing public health challenge in India, where its prevalence continues to rise at an alarming rate. Over recent decades, India has observed a sharp rise in diabetes prevalence, with national rates increasing alongside earlier age of onset. This trend not only highlights the scale of the burden but also raises important questions about the hereditary basis of Type 2 Diabetes. Understanding its development is especially important in the South Asian context, where complex interactions between genetics, environment and lifestyle create unique patterns of risk. This review explores current evidence on the drivers of T2D, with attention to how both biological and socio-cultural influences shape susceptibility.

Keywords: Type 2 Diabetes Mellitus, Genetic Risk Factors, Environmental Risk Factors, Single Nucleotide Polymorphisms.

I. INTRODUCTION

Type 2 Diabetes (T2D) Mellitus is a chronic metabolic disorder, commonly characterized by insulin resistance and persistent high levels of blood sugar. It develops when the body's cells become less responsive to insulin, and the pancreas can no longer produce enough insulin to compensate, leading to elevated blood glucose levels over time.

Type 2 diabetes has multiple acute and chronic complications. Examples of acute complications are hyperglycaemia (high levels of blood sugar) and hypoglycaemia (low levels of blood sugar) which can occur because of either an incorrect dose of medication or an insufficient dose [1,2]. Diabetic ketoacidosis, a life-threatening condition that can be characterised as severe hyperglycaemia, normally affects patients with Type 1 Diabetes, but it can also occur in people with T2D. Type 2 Diabetes is also known to increase the risk of cardiovascular diseases [3].

According to the International Diabetes Federation (IDF), approximately 580 million adults between the ages 20-79 are living with diabetes, and more than 90% of these people have T2D. Alarmingly, by the year 2050, this number is estimated to increase to 853 million cases [4].

In India, the prevalence of diabetes has been growing rapidly, positioning the country as a key contributor to the global diabetes epidemic. In 2016, the disability-adjusted life years (DALY) rate for diabetes was four times higher than in 1990, with the disease rising from the 35th to the 13th leading cause of DALYs nationally [5]. The presence of diabetes among Indians increased from 7.1% in 2009 to 8.9% in 2019. Currently, India ranks second after China in the number of individuals with diabetes, with an estimated 77 million cases, 12.1 million of whom are over the age 65. This number is projected to increase to 27.5 million by 2045 [6]. There has also been a noticeable rise in T2D among younger individuals, with many cases linked to a genetic predisposition, due to a family history of the condition. Genetic susceptibility to insulin deficiency, as well as unfavourable fat distribution, are also key factors [7, 8].The phenotypic characteristics of T2D in Indian populations differ greatly from other populations. Many Asian Indians have several unique characteristics, collectively referred to as the "Asian Indian Phenotype". This includes the "thin-fat" phenotype, which is defined as an individual who has a normal body weight but a disproportionately high body fat percentage, also known as 'metabolic obesity' [9].

Comparing South Asians with Europeans, South Asians tend to develop T2D earlier and at a lower body mass index (BMI) (even though they have a higher body fat percentage), with higher HbA1c and triglyceride levels than white Europeans [10]. HbA1c and triglyceride levels are often common features that help clinicians to identify T2D. Elevated triglyceride levels are one of the criteria to identify a patient who is at risk of T2D, usually elevated TG levels are strongly and positively associated with inadequate glycaemic control [11]. High levels of HbA1c, which is known as glycated haemoglobin, implies that there is too much sugar in the blood and the patient is

International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 5 Sept - Oct 2025, pp: 323-329 www.ijprajournal.com ISSN: 2456-4494

more likely to develop diabetes complication. An ideal HbA1c level for patients with, or at risk, of diabetes is 48 mmol/mol (6.5%) or 42 mmol/mol (6%), respectively [12].

This review aims to provide an overview of the factors that contribute to the high incidence of T2D in Indian populations, with a particular focus on both genetic and environmental contributors. We discuss the epidemiological burden and distinctive clinical characteristics of T2D in Indians, as well as key genetic risk factors, and environmental and lifestyle determinants that may interact with genetic susceptibility to exacerbate disease risk. Finally, we address the current challenges in genomics research specific to Indian populations and highlight the need for population-specific studies to improve understanding and inform precision medicine approaches.

II. GENETIC RISK FACTORS IN INDIAN POPULATION

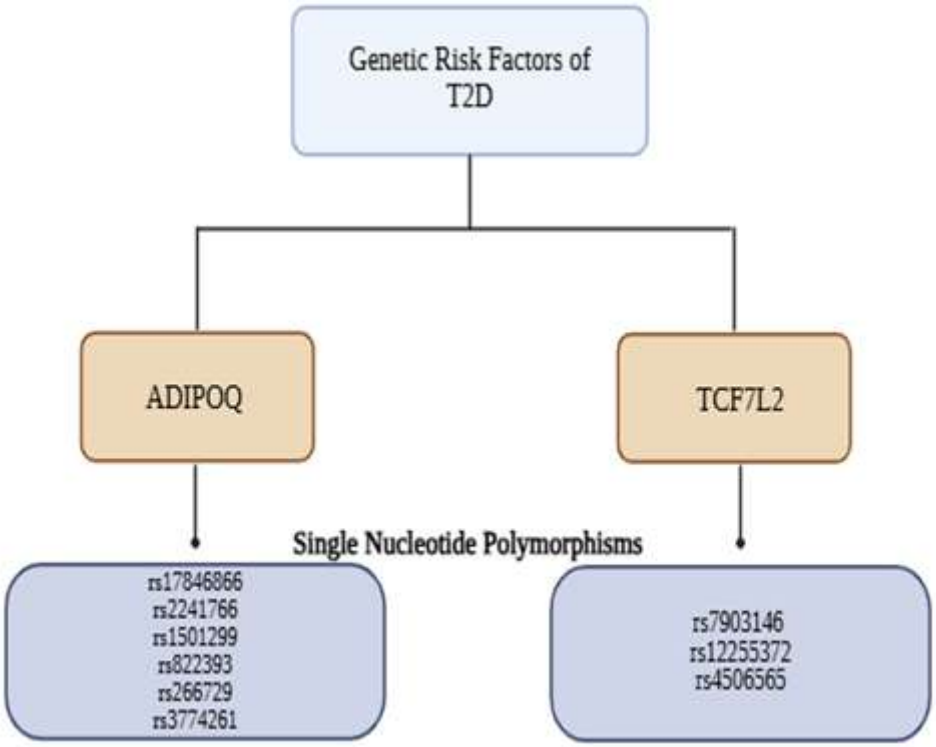

Figure 1: Overview of the genetic risk factors associated with type 2 diabetes in Indian populations

2.1. Adipokines and Metabolic Regulation

Adipokines are proteins secreted by adipose tissue, which play a significant role in regulating insulin sensitivity and the homeostasis of glucose. One such adipokine, adiponectin, has been found to have an inverse relationship with insulin resistance and T2D risk in South Asians.

Studies showed lower circulating levels of adiponectin in South Asians compared to Caucasians, which suggests a possible driver for the genetic disparity between the two populations [13].

According to Khan et al, the most studied variants of ADIPOQ – the gene that codes for adiponectin – were found to be +10211T/G (rs17846866), +45T/G (rs2241766), and +276G/T (rs1501299), which are frequently studied within Indian populations [14]. A large-scale South Indian study (CURES) identified several ADIPOQ single nucleotide polymorphisms (SNPs), including +276G/T, -4522C/T (rs822393), -11365C/G (rs266729), and +712G/A (rs3774261), as significantly associated with T2D, obesity, and hypoadiponectinemia [15]. Importantly, +45T/G (rs2241766**)** (Figure 1) has been found to confer T2D risk in Asian populations but not in Caucasians, highlighting the ethnic specificity of adiponectin-related genetic susceptibility [16].

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2.2 TCF7L2

Transcription Factor 7-Like 2 (TCF7L2) is a transcription factor that is involved in the Wnt signalling pathway.[17] The Wnt signalling pathway regulates crucial cellular processes such as cell fate determination, neural patterning, cell migration, cell polarity and organ formation during embryonic development and later development [18]. As explained by Grant et al, variants of the TCF7L2 gene have been identified as a factor of susceptibility to T2D [19]. Moreover, a study performed on a group ethnic West-Indians patients with T2D showed that three TCF7L2 SNPs (rs7903146, rs12255372, and rs4506565) were significantly associated with increased diabetes risk. The risk was particularly pronounced in individuals homozygous for the risk alleles, with the strongest association observed at rs12255372 (Figure 1). These genetic variants were associated with elevated fasting glucose, 2-hour post-load glucose, and insulin resistance in non-diabetic individuals, despite no association with BMI or waist–hip ratio [20]. This suggests that TCF7L2 contributes to T2D risk independent of obesity, due to the mechanism involving both impaired insulin secretion and increased insulin resistance.

In Indian populations, several additional genetic loci have been identified to contribute to type 2 diabetes risk, through their effects on insulin regulation and glucose metabolism. Variants in ADAM30 and CDKN2A/B have been associated with altered insulin sensitivity and ß-cell function, while NOTCH2 influences basal insulin secretion. Polymorphism in CDKAL1 and CXCR4 are linked with disturbances in fasting glucose homeostasis. Notably, the THADA locus confers diabetes risk independent of BMI, highlighting its direct role in disease predisposition [21].

These findings highlight the need for large scale genetic studies in Indian populations, to betterunderstand disease susceptibility and inform precision medicine strategies.

III. ENVIRONMENTAL RISK FACTORS IN INDIAN POPULATION

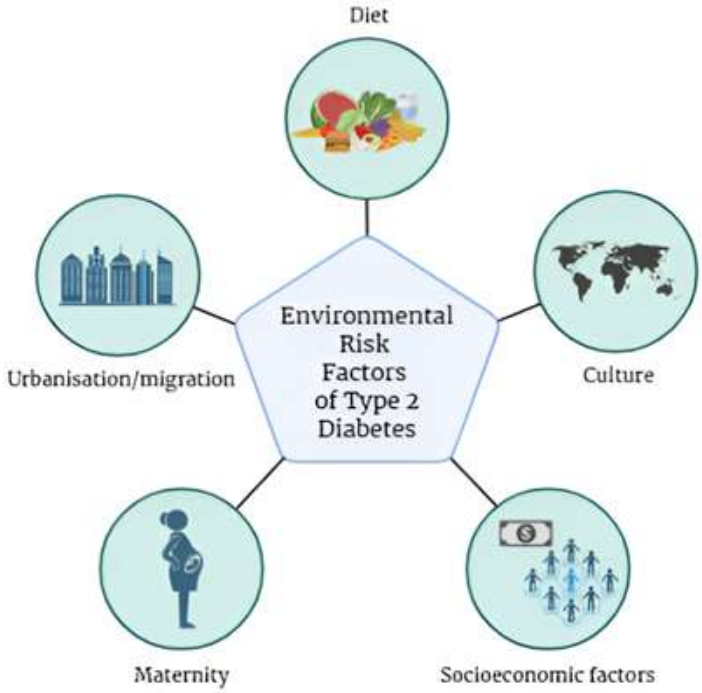

Figure 2: Overview of the Environmental Risk Factors of Type 2 Diabetes in Indian Populations [22].

While genetic predispositions play an integral part in the high burden of T2D, especially amongst the Indian population, genetics alone cannot explain the rise in T2D incidence. These inherited risk factors often interact with environmental and lifestyle conditions, compounding the overall risk. Accordingly, it is essential to examine the environmental and lifestyle determinants of T2D, which not only amplify inherent genetic risk but also play a pivotal role in shaping disease onset and progression. Figure 2 gives a summary of the environmental risk

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factors associated with the development of Type 2 Diabetes.

3.1 Dietary Patterns

Refined rice, a major part of the typical South Asian diet, contributes to the incidence of T2D due to its high glycaemic index (GI). Approximately 23.1% of T2D cases are attributed to excess consumption of refined rice. The recent rise in T2D incidence has also been linked to the intake of refined wheat, which, like white rice has a high GI and lower dietary fibre content. This trend is closely linked to urbanization, India's rising economy, and dietary transitions influenced by globalization, which has led to the popularity of wheat-based foods such as breads and pastries [23].

Overconsumption of these refined grains is associated with frequent blood sugar spikes and reduced fibre intake, both of which increase the risk of insulin resistance, leading to a higher risk of developing T2D.

3.2 Urbanisation and Effect of Migration

Evidence from a sibling-paired study conducted in India demonstrated that rural-urban migrants exhibit a higher prevalence of diabetes, as well as obesity, compared to rural non-migrants. Migration was associated with higher fat intake and reduced physical activity, factors that likely contributed to the elevated levels of diabetes observed. Additionally, higher levels of serum insulin observed in urban migrant participants suggested that urbanization may contribute to tissue-level insulin resistance [24]. According to a recent study which compared the presence of diabetes amongst Indian immigrants in the US and Indians living in India, it was shown that the prevalence of diabetes was higher in the Indian cohort compared to the immigrants that were based in the U.S.

On the other hand, pre-diabetes was more common in the U.S cohort [25]. Together, these findings highlight how different migration contexts shape diabetes outcomes, with urban transitions within India, and acculturation abroad, each exerting unique influences on metabolic risk.

3.3 Early Life and Maternal Factors

Early life factors may also contribute to T2D risk in Indian populations. Specifically, exposure to elevated maternal blood glucose levels during gestation has been associated with increased fat mass at birth, which may predispose the child to insulin resistance and impaired glucose regulation from an early age. In Indian populations, the previously discussed genetic and phenotypic traits, such as a tendency toward "Thin-fat" body composition may amplify this risk for the mother [26].

3.4 Socioeconomic Status and Health Literacy

Low literacy levels and limited community awareness, which can be observed in some cross-sections of Indian populations, can often result in poor understanding of the true prevalence of T2D, leading to a distorted perception of individual susceptibility and the seriousness of the disease. It can also lead to a delay in diagnosis, which can prove detrimental and lead to many complications for the patient in the future [27, 28]. Studies have shown that participants often lacked understanding of both biomedical and socio-spiritual causes of diabetes, and tended to dissociate their personal illness experience from general knowledge of its causative factors [29]. This may prevent individuals taking preventative measures, or seeking early diagnosis.

3.5 Cultural Factors

The South Asian cultural norms also play a contributing role in the development of T2D and often act as a barrier to healthy eating habits [28]. In South Asian communities, cultural and religious celebrations often play a central role in social life. These gatherings frequently involve the consumption of rich, calorie-dense foods that are high in refined carbohydrates, sugars, and saturated fats - all dietary patterns that have been linked to the development of T2D. Such occasions may contribute to habitual overeating,

or make adherence to recommended dietary practice more difficult, especially for individuals

at risk of or living with T2D.Gender roles in South Asian households also influence the patients' management of T2D, especially in females. The burden of overwhelming household responsibilities which may include preparing food for the entire extended family, including joint families, often makes it challenging for women to prioritise their own dietary needs. As a result, they may resort to quicker, more convenient food options that typically lack the nutritional quality necessary for effective T2D management [30].

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IV. CHALLENGES IN INDIAN GENOMICS RESEARCH FOR IDENTIFICATION OF GENETIC RISK FACTORS

South Asia represents immense genetic and environmental diversity, with over 45,000 anthropologically defined groups. However, South Asians remain underrepresented in genomic research, comprising less than 2% of global study participants, which constrains population-specific insights into disease risk and hampers efforts in precision medicine [31]. Precision medicine, though promising for tailoring interventions based on genetic, environmental and lifestyle factors, faces considerable challenges in India. These may be ethical, social or legal, and include concerns about informed consent, patient privacy, genetic discrimination, high costs, rural inaccessibility and weak regulatory framework [32]. Moreover, the principle of informed consent, central to biomedical ethics, is difficult to operationalize in India due to barriers such as illiteracy, poverty, socio-cultural resistance, paternalistic practices and inconsistent oversight, particularly among tribal and rural caste communities [33].

Given the high percentage of T2D patients in India, and the various genetic risks driving it, expanding genomic research and testing holds significant potential for early identification and intervention. However, identifying genetic risk factors for T2D that are specific to the Indian population remains challenging, primarily due to the limited availability of genotype-phenotype data tailored to this group. This shortage limits the use of genetic insights in clinical settings, such as for early detection and personalized treatment [34].

But India is ever changing, and genome sequencing is becoming more widely available, one example being the Genome India project. Since 2020, it aims to provide a detailed database of all the genetic variations within the diversity of India's population and as of January 2025, has sequenced the genomes of over 10,000 individuals across 99 ethnic groups [35].

V. CONCLUSION

The growing prevalence of T2D in India underscores the importance of addressing both genetic susceptibility and environmental influences. Expanding genomic research offers opportunities for earlier detection and tailored interventions, but meaningful progress will depend on bridging scientific advances with accessible healthcare and clear public policy. Looking ahead, the integration of genomics with lifestyle and environmental data could provide a more complete understanding of the risks, paving the way for equitable prevention and personalized treatment strategies across India's diverse population.

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