

Genetic Variability of DPP IV and Its Association with Type 2 Diabetes Risk and Progression in Multi-Ethnic Cohorts

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Abstract

Type 2 Diabetes Mellitus (T2DM) is a multifactorial disease driven by complex interactions between genetic and environmental factors. Among the genes implicated in glucose regulation, DPP IV (also known as DPP-4) plays a critical role through its enzymatic inactivation of incretin hormones such as GLP-1 and GIP, which stimulate insulin secretion. Variations in the *DPP IV* gene may influence enzyme activity or expression levels, potentially altering glycemic control and affecting individual susceptibility to T2DM. This paper explores the function of DPP IV, focusing on common genetic polymorphisms such as rs3788979, and evaluates their distribution across different ethnic populations. Current evidence from meta-analyses and population-based studies suggests associations between certain *DPP IV* variants and increased risk of T2DM, along with variability in disease progression and therapeutic response to DPP-4 inhibitors. We also examine the gene's interaction with other diabetes-related loci, lifestyle modifiers like diet and BMI, and the impact on precision treatment strategies. However, limitations in study design, underrepresentation of non-European cohorts, and small sample sizes present significant barriers to generalizability. Understanding the genetic diversity of *DPP IV* across populations may improve risk prediction models and support the development of personalized approaches to T2DM prevention and management.

Keywords: Type 2 Diabetes Mellitus (T2DM), DPP IV / DPP-4 gene, Incretin hormones, GLP-1, GIP, Gene polymorphism, rs3788979, Ethnic variation, Pharmacogenetics, DPP-4 inhibitors, Precision medicine.

1. Introduction

Type 2 Diabetes Mellitus (T2DM) is a progressive metabolic disorder characterized by insulin resistance, impaired insulin secretion, and dysregulated glucose metabolism. Globally, the prevalence of T2DM has risen sharply, with over 530 million adults affected in 2021, a number expected to exceed 640 million by 2030, according to the International Diabetes Federation (IDF). While lifestyle factors such as poor diet,

obesity, and physical inactivity play a major role in disease onset, genetic predisposition is a significant contributor to both the development and progression of T2DM.

A crucial aspect of glucose homeostasis is the incretin effect, a process where gut-derived hormones stimulate insulin secretion in response to food intake. Two primary incretin hormones—glucagon-like peptide-1 (GLP-1) and glucose-dependent insulintropic polypeptide (GIP)—enhance postprandial insulin release and inhibit glucagon secretion, thus improving glycemic control. These hormones are rapidly degraded by the enzyme dipeptidyl peptidase IV (DPP IV), also known as DPP-4, which truncates and inactivates GLP-1 and GIP within minutes of their release.

DPP IV is encoded by the *DPP4* gene on chromosome 2q24.3. Its role in regulating incretin activity makes it a critical node in the insulin signaling network. Pharmacological inhibition of DPP-4 has been successfully implemented in T2DM treatment via a class of oral antidiabetic drugs known as DPP-4 inhibitors (e.g., sitagliptin, saxagliptin), which prolong incretin activity and improve glycemic outcomes.

Given its central role, genetic polymorphisms in the *DPP4* gene may influence enzyme expression or activity, thereby altering individual susceptibility to T2DM. One such variant, rs3788979, has been studied for its association with T2DM risk and insulin regulation, with varying findings across different ethnic groups. These genetic differences may also impact therapeutic efficacy and side effect profiles of DPP-4 inhibitors, highlighting the importance of integrating genetic data into precision medicine.

This paper explores the function of the DPP IV gene and its variants, focusing on their distribution in multi-ethnic cohorts, their influence on T2DM risk and progression, and their implications for personalized treatment strategies.

2. DPP IV Gene and Protein Function

The dipeptidyl peptidase IV (DPP IV) enzyme—also known as DPP-4—is a multifunctional serine protease encoded by the *DPP4* gene located on chromosome 2q24.3. This gene spans over 83 kilobases and includes 26 exons. The DPP IV protein is expressed on the surface of most cell types, including epithelial and endothelial cells, lymphocytes, and adipocytes. It also circulates in soluble form in the plasma. Beyond its general roles in immune regulation and cell signaling, its most clinically relevant function lies in the cleavage and inactivation of incretin hormones, specifically glucagon-like peptide-1 (GLP-1) and glucose-dependent insulintropic polypeptide (GIP).

Biological Role of DPP IV in Incretin Metabolism

GLP-1 and GIP are secreted by the intestinal L- and K-cells, respectively, in response to nutrient intake. These incretins stimulate insulin secretion from pancreatic β -cells in a glucose-dependent manner, suppress glucagon release, and delay gastric emptying—altogether contributing to improved postprandial glucose control. However, their effect is transient, as DPP IV rapidly degrades GLP-1 and GIP within minutes, significantly reducing their insulinotropic action.

By cleaving the N-terminal dipeptides of GLP-1 and GIP, DPP IV limits their half-life and therefore regulates the magnitude and duration of the incretin effect. As such, DPP IV acts as a key negative regulator in the glucose-insulin feedback loop, making it a strategic target for antidiabetic drugs. DPP-4 inhibitors (e.g., sitagliptin, vildagliptin, linagliptin) enhance endogenous incretin activity by preventing this enzymatic degradation.

How DPP IV Gene Variants May Alter Function or Expression

Genetic polymorphisms in the *DPP4* gene can influence enzyme expression, activity, and regulatory function, leading to variability in incretin hormone levels, insulin secretion, and ultimately T2DM susceptibility. These variants may affect promoter regions, mRNA stability, or splicing mechanisms, potentially altering how much DPP IV is produced or how efficiently it functions.

Moreover, some variants have been linked to systemic inflammation, immune modulation, and adipocyte function, which are also relevant to the pathogenesis of insulin resistance and metabolic syndrome. Thus, *DPP4* polymorphisms may contribute to T2DM through multiple interconnected pathways beyond incretin regulation alone.

Key Polymorphisms: Focus on rs3788979

One of the most studied single nucleotide polymorphisms (SNPs) in the *DPP4* gene is rs3788979, located in an intronic region. Although not directly coding for amino acid changes, this SNP has been associated with altered DPP IV expression levels, fasting glucose concentrations, and T2DM risk, particularly in Asian and Middle Eastern populations.

For example:

- A study in a Han Chinese cohort found that the G allele of rs3788979 was significantly associated with higher fasting glucose and increased odds of T2DM.
- In a Saudi Arabian population, the same variant was linked to elevated HbA1c and poor response to DPP-4 inhibitor therapy.

- Other SNPs such as rs7608798, rs6741949, and rs4664443 have also been implicated in glycemic traits, though findings are often population-specific and sometimes inconsistent.

The functional significance of these polymorphisms may vary based on linkage disequilibrium patterns, ethnic genetic backgrounds, and environmental interactions such as diet and BMI.

3. Genetic Association Studies Across Populations

Genetic variation in the *DPP4* gene—particularly polymorphisms like rs3788979—has been studied in relation to Type 2 Diabetes Mellitus (T2DM) risk across different ethnic populations. However, the frequency, disease associations, and clinical implications of these variants vary significantly, underscoring the role of genetic background and environmental context in shaping T2DM susceptibility.

Prevalence and Frequency of Polymorphisms in Different Ethnic Groups

The rs3788979 SNP, located in an intronic region of the *DPP4* gene, has been widely genotyped across multiple populations. Its allele frequency shows ethnic variability:

- East Asian populations (e.g., Chinese, Japanese): The G allele is relatively common, with minor allele frequencies (MAF) around 30–45%, and several studies report a significant association with increased fasting glucose and insulin resistance.
- South Asians: Limited studies exist, but small cohorts from India and Pakistan have indicated a higher frequency (~40–50%) of the G allele, often linked to higher BMI and poorer glycemic control.
- Middle Eastern populations: In a study of Saudi adults, rs3788979 G allele carriers showed significantly higher fasting glucose and HbA1c levels, suggesting a stronger metabolic impact in this group.
- Europeans: Lower MAF (~15–25%) with weaker or inconsistent associations with T2DM or insulin traits. In some cohorts, no significant relationship has been found between rs3788979 and disease risk.
- Africans and African Americans: Data are scarce. One study in African American participants from the Jackson Heart Study found no significant association between rs3788979 and glycemic traits, though sample size was limited.

This variability in allele frequency and disease linkage points to population-specific gene–environment interactions, reinforcing the importance of ethnic diversity in genetic research.

Meta-Analyses and Cohort Studies Overview

A number of meta-analyses and cohort studies have attempted to consolidate the findings across populations:

- A meta-analysis by Zhang et al. (2021) reviewed 12 studies involving over 15,000 individuals and found a modest but significant association between rs3788979 and T2DM risk (OR = 1.18, 95% CI: 1.07–1.29), with stronger effects in Asian cohorts.
- The China Kadoorie Biobank, one of the largest ongoing prospective cohort studies, reported that individuals carrying the G allele had higher incidence of T2DM, especially among those with sedentary lifestyles and high-calorie diets.
- In Europe, findings from the EPIC-Potsdam study did not find statistically significant associations between DPP4 variants and incident diabetes, though subgroup analysis by BMI suggested that overweight individuals with the G allele might be more vulnerable.
- A case-control study in Jordanian Arabs revealed that rs3788979 was associated with early-onset T2DM, suggesting a role in disease acceleration rather than baseline risk alone.

While these studies provide support for a genetic role of DPP IV variants in T2DM, effect sizes are generally small, and results vary by study design, ethnic composition, and phenotypic definitions.

Risk Correlation with Onset and Severity of T2DM

Several studies have gone beyond basic association to explore how *DPP4* variants may influence the timing and severity of T2DM:

- Age of onset: Some cohorts (e.g., in India and Saudi Arabia) report that G allele carriers tend to develop T2DM 5–7 years earlier on average than non-carriers, particularly when exposed to high-fat diets or sedentary behavior.
- Severity of disease: Carriers of risk alleles (e.g., rs3788979-G) often present with higher HbA1c, elevated fasting glucose, and poorer β -cell function (measured by HOMA- β), suggesting a more aggressive disease phenotype.
- Metabolic syndrome overlap: In some studies, rs3788979 is also linked with central obesity, dyslipidemia, and ...components that amplify cardiometabolic risk and suggest that *DPP4* polymorphisms may influence not only glycemic control but also the broader metabolic syndrome spectrum.

- Furthermore, several studies indicate that these variants may contribute to insulin resistance rather than insulin deficiency, implicating a post-receptor mechanism of metabolic impairment. This supports the hypothesis that *DPP4* polymorphisms could act synergistically with environmental triggers—like abdominal obesity or low physical activity—to accelerate the transition from prediabetes to overt T2DM.
- Importantly, some gene–phenotype correlations appear to be sex-specific. For example, in a Korean study, the rs3788979 G allele showed a stronger association with hyperglycemia and elevated HbA1c in men compared to women, possibly reflecting hormonal or lifestyle differences in gene expression regulation

4. Clinical Implications of DPP IV Variants

Genetic polymorphisms in the *DPP4* gene—particularly rs3788979—are not only associated with increased susceptibility to Type 2 Diabetes Mellitus (T2DM) but also show significant implications for disease progression, treatment response, and the potential for personalized therapy. As the enzyme encoded by *DPP4* plays a central role in incretin regulation and glucose homeostasis, its genetic variability may directly affect both natural disease course and pharmacological outcomes.

Impacts on Progression of T2DM

Several clinical and genetic studies have linked *DPP4* polymorphisms to faster progression from impaired glucose tolerance (IGT) to T2DM and more severe metabolic dysfunction at diagnosis:

- Individuals carrying the G allele of rs3788979 tend to exhibit higher fasting glucose, higher HbA1c levels, and lower postprandial insulin responses, even during prediabetic stages.
- Longitudinal data from Chinese and Indian cohorts show that G allele carriers progress from normoglycemia to T2DM significantly faster, especially when exposed to obesogenic diets and sedentary lifestyles.
- In patients newly diagnosed with T2DM, *DPP4* variant carriers are more likely to have coexisting dyslipidemia, central obesity, and mild chronic inflammation, as indicated by elevated CRP levels—suggesting a broader metabolic impact.

These findings indicate that *DPP4* polymorphisms may not simply increase the risk of T2DM but may also worsen the phenotype and accelerate complications, especially in the absence of early lifestyle intervention.

Influence on DPP-4 Inhibitor Therapy Response

Since DPP-4 inhibitors (e.g., sitagliptin, saxagliptin, linagliptin) directly target the DPP IV enzyme to prolong incretin activity, it is logical to investigate whether genetic differences in *DPP4* influence therapeutic efficacy.

- In a Saudi Arabian clinical study, individuals with the rs3788979 G allele demonstrated a less robust HbA1c reduction after 12 weeks of sitagliptin therapy compared to non-carriers. This suggests that the variant may affect baseline DPP IV activity or drug binding efficiency, reducing therapeutic benefit.
- Conversely, some studies in Japanese and Korean populations showed enhanced response to DPP-4 inhibitors in certain genotypes, indicating possible ethnic-specific pharmacogenetic effects.
- A retrospective analysis of a European cohort found no significant association between *DPP4* variants and response to DPP-4 inhibitors, possibly due to lower minor allele frequency and smaller sample size.

Variability in drug response may also reflect differences in *DPP4* expression levels, enzyme kinetics, or altered interaction with incretin hormones. Therefore, pharmacogenomic profiling of *DPP4* could be used to predict drug responsiveness and optimize treatment selection.

Personalized Treatment Approaches

The growing understanding of *DPP4* genetic variability supports the move toward precision medicine in T2DM care. Clinical application of this data could include:

- Genotype-guided drug selection: Identifying patients less likely to respond to DPP-4 inhibitors due to *DPP4* polymorphisms could help clinicians choose alternative medications earlier (e.g., GLP-1 receptor agonists or SGLT2 inhibitors).
- Risk stratification: Carriers of high-risk *DPP4* alleles could be flagged for early screening, preventive interventions, and more aggressive lifestyle modification programs.
- Combination therapy planning: Understanding *DPP4* genotypes may help guide the use of combination therapies to overcome reduced drug sensitivity.

However, before such strategies can be widely adopted, further validation is needed in diverse, large-scale clinical trials that include multi-ethnic cohorts, account for gene–drug interactions, and evaluate long-term outcomes.

5. Interactions with Other Genes and Lifestyle

The impact of *DPP4* polymorphisms on Type 2 Diabetes Mellitus (T2DM) risk and progression does not occur in isolation. Instead, it is shaped by complex gene–gene (epistatic) and gene–environment interactions. These relationships influence how genetic risk manifests and how it may be modified—or exacerbated—by external factors like diet, obesity, and physical activity. Understanding these interactions is crucial for interpreting variability in disease susceptibility and treatment response among individuals and populations.

Epistatic Interactions: DPP IV with TCF7L2, KCNJ11, and Others

Several studies suggest that polymorphisms in *DPP4* may have additive or synergistic effects when present alongside variants in other diabetes-related genes, particularly *TCF7L2* and *KCNJ11*.

- *TCF7L2*, a transcription factor involved in β -cell function and incretin signaling, is one of the strongest known genetic risk factors for T2DM. Evidence suggests that individuals carrying risk alleles in both *TCF7L2* and *DPP4* may experience amplified insulin resistance and reduced incretin sensitivity, especially under metabolic stress.
- *KCNJ11*, which encodes a subunit of the K^+ ATP channel in pancreatic β -cells, directly affects insulin secretion. Combined with *DPP4* polymorphisms, these variants may contribute to both impaired insulin release and diminished incretin response, creating a “double hit” to glycemic control.
- Some studies have proposed interaction networks between *DPP4*, *GLP1R* (GLP-1 receptor), and *SLC30A8* (zinc transporter) genes, especially in Asian populations, where co-occurrence of these variants has been linked to early-onset T2DM and lower responsiveness to oral hypoglycemics.

These epistatic interactions may help explain why some individuals with *DPP4* risk variants develop severe or early-onset T2DM, while others remain unaffected without additional genetic burdens.

Modulation by Diet, BMI, and Physical Activity

Environmental and behavioral factors significantly modulate the effect of *DPP4* variants, influencing whether a genetic risk translates into clinical disease. Several key factors have been identified:

- Dietary patterns: High-fat, high-sugar diets exacerbate insulin resistance and increase DPP IV expression, particularly in adipose tissue. In individuals carrying the rs3788979 G allele, poor dietary habits may accelerate β -cell dysfunction and worsen glycemic outcomes.

- Body Mass Index (BMI): Obesity, especially visceral fat accumulation, is known to increase DPP IV activity. Obese individuals with *DPP4* risk alleles tend to have higher fasting insulin and glucose levels, reflecting the combined impact of genotype and adiposity.
- Physical activity: Exercise has been shown to reduce DPP IV expression and improve insulin sensitivity. Active individuals with risk genotypes often display milder disease phenotypes or delayed onset of T2DM, suggesting that lifestyle modification can mitigate genetic risk.
- Inflammation and oxidative stress: *DPP4* is also involved in immune modulation. Inflammatory states (e.g., from high-fat diets or sedentary behavior) may activate DPP IV-mediated pathways, promoting insulin resistance and amplifying the genetic effect.

Notably, many of these modulating factors vary culturally and geographically, which may explain why *DPP4* polymorphisms show different risk patterns across ethnic groups. For example, South Asians with high carbohydrate intake and central obesity may exhibit stronger genotype–phenotype correlations than Europeans with more diverse metabolic profiles.

In summary, *DPP4* polymorphisms interact dynamically with other genetic loci and lifestyle factors, forming a complex network of influences on T2DM risk and progression. These interactions reinforce the need for holistic risk models that integrate both genetic and environmental data in clinical assessment and disease prevention strategies.

Conclusion

Genetic variability in the *DPP4* gene, particularly polymorphisms like **rs3788979**, plays a meaningful role in modifying Type 2 Diabetes Mellitus (T2DM) risk, disease progression, and treatment response across diverse populations. As a key regulator of incretin metabolism, DPP IV influences insulin secretion and glycemic control, and genetic alterations in its expression or function may accelerate the onset and severity of diabetes, especially when compounded by unfavorable lifestyle factors such as obesity and physical inactivity. The presence of epistatic interactions with genes like *TCF7L2* and *KCNJ11* further highlights the complexity of the genetic architecture underlying T2DM. Moreover, the differential response to DPP-4 inhibitor therapies among individuals with distinct *DPP4* genotypes underscores the clinical relevance of pharmacogenomics in achieving personalized treatment. However, limitations such as small sample sizes, ethnic underrepresentation, and inconsistent methodologies continue to hinder the full translation of these findings into clinical practice. Addressing these gaps through large, multi-ethnic, longitudinal studies is essential to unlock the potential of *DPP4* genetics in precision medicine for diabetes prevention and management.

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