©IDOSR PUBLICATIONS International Digital Organization for Scientific Research

IDOSR JOURNAL OF APPLIED SCIENCES 11(1):135-140, 2026 ISSN: 2550-7931

https://doi.org/10.59298/IDOSRJAS/2026/111135140 IDOSRJAS11106

Genetics of Diabetes Susceptibility

Nalongo Bina K.

Faculty of Medicine Kampala International University Uganda

ABSTRACT

Diabetes mellitus is a complex and heterogeneous metabolic disorder resulting from the interplay between genetic susceptibility and environmental factors. Advances in genetic research have significantly improved understanding of the molecular mechanisms underlying diabetes risk, particularly for type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM). T1DM is primarily an autoimmune condition characterized by immune-mediated destruction of pancreatic β-cells, while T2DM is a multifactorial disease driven by insulin resistance and impaired insulin secretion. Genome-wide association studies (GWAS) have identified numerous genetic loci associated with conditions, highlighting their polygenic nature and revealing pathways involved in β-cell function, insulin signaling, immune regulation, and metabolic homeostasis. In addition to polygenic risk, monogenic forms of diabetes, such as maturity-onset diabetes of the young (MODY) and permanent neonatal diabetes, demonstrate the impact of high-penetrance variants on disease development and therapeutic response. Gene–environment interactions, ethnic diversity in genetic risk, and functional genomic insights further refine current models of diabetes susceptibility. This review synthesizes evidence on the genetic architecture of diabetes, explores translational applications in genetic risk prediction and precision medicine, and addresses ethical, legal, and social considerations. Understanding the genetic basis of diabetes offers critical opportunities for early risk identification, targeted prevention, and personalized therapeutic strategies aimed at reducing the global burden of diabetes.

Keywords: Diabetes mellitus, Genetic susceptibility, Genome-wide association studies (GWAS), Polygenic risk, and Precision medicine.

INTRODUCTION

Diabetes represents one of the most widespread globally shared health obstacles. The emergence of diabetes can be related to both genetic and environmental factors [2]. Genetic susceptibility denotes the capacity of an individual to develop the disease when subjected to environmental factors, such as changes in diet or lifestyle. Diabetes is a heterogeneous disease with multiple subtypes, but the two most common types are Type 1 Diabetes Mellitus (T1DM) and Type 2 Diabetes Mellitus (T2DM)[7]. The genetic factors associated with TOD and T2D are considerably distinct; T1DM is an autoimmune disorder leading to the destruction of pancreatic beta-cells, while T2DM is a multifactorial disorder relying on metabolic and genetic factors. A number of known genetic associations have been identified for each of the two diabetes types, and family and twin studies provide solid evidence that genetic factors are important [8]. Type 1 diabetes (T1D) was first described in 1869 in a 4-year-old child. Insulin deficiency is mainly the causal factor for T1D; the disease is intricately connected to immune system dysfunction. T1D is a polygenic disease; more than 100 genetic loci believed to impact T1D susceptibility have been identified [8]. Most of these loci are discovered through genome-wide association studies (GWASs), which require large sample sizes. In T1D, the diagnosis is often made shortly after the onset of symptoms, leading to little opportunity for preventive measures before the initial immune attack [5]. For such conditions, the generation of a genetic risk score (GRS) would be an effective tool for predicting the occurrence of T1D after the birth of an at-risk child [4]. Type 2 diabetes (T2D) was first recognized in 1674 by Thomas Willis; the disease

became popularly known as "sugar diabetes" in the 18th century due to the sweet taste of the urine. T2D is characterized by two primary features: insulin resistance and inadequate insulin secretion; its onset is usually in adulthood [3]. T2D is also a polygenic disorder; the human genome is estimated to contain 50,000–100,000 protein-coding genes. The knowledge gained in studying T2D genetics promotes a better understanding of the disease mechanism [1, 2].

Overview of Diabetes Types and Genetic Architecture

Diabetes represents an important public health concern worldwide. Understanding the genetic susceptibility to type 1 and type 2 diabetes is central to elucidating the pathophysiological mechanisms involved in these multifactorial diseases and generating predictive models to facilitate early diagnosis and targeted prevention strategies [3]. Type 1 diabetes is a T-cell-mediated autoimmune destruction of insulin-producing β-cells of the pancreas, whereas type 2 diabetes stems primarily from β-cell dysfunction and insulin resistance [4]. The contrast in age of onset and biological causation has warranted the classification of diabetes mellitus into distinct types. Despite the differences in etiology and clinical presentation, type 1 and type 2 diabetes are often colloquially combined into a single "diabetes" category [5]. Classification is further complicated by the emergence of additional diabetes forms, characterized by either monogenic or polygenic mutations and defects that confer high or low penetrance of additional diabetes risk [2]. Approximately 50 loci that contribute to polygenic type 1 or type 2 diabetes susceptibility have been identified through large-scale genome-wide association studies (GWAS) and candidate gene approaches [4]. Polygenic inheritance is further complicated by specific regulatory variants in the enhancer regions of individual diabetes-susceptibility genes. Type 1 diabetes shows Barker-style multivariate latent inheritance attributes, whereas type 2 diabetes has been proposed to follow a diluted quaternary multifactorial inheritance model [6].

Polygenic Risk and Genome-Wide Association Studies

Several diabetes genome-wide association studies (GWAS) have identified common genetic variants associated with type 2 diabetes (T2D) and other metabolic traits; many of the loci discovered influence β-cell function and insulin resistance[14].313–316 At some of the early loci, such as TCF7L2 and FTO, associations have been found at the protein level throughout development and differentiation in a variety of tissues, suggesting a long-term influence on metabolic homeostasis[15]' Fine-mapping and extension with rare variant detection have since improved understanding of the genetic architecture of T2D and highlighted population-specific aspects of genetic risk.317–320 As detailed below, large-scale GWAS and metaanalyses have been crucial not only in understanding the genetic basis of T2D but also in refining genotyping platforms to increase transferability of risk alleles across cohorts and populations [5]. The most enlightening studies have employed a two-stage design, deploying large discovery cohorts to identify common variants followed by independent replications [5]. Risk estimates are typically low (odds ratios ~1.2) but, as with other multifactorial diseases, the cumulative effect remains clinically relevant. A genetic risk score based on 20 T2D-associated variants detected in genome-wide scans predicts future incidence of the disease in non-diabetic individuals 6; analogous findings exist for type 1 diabetes [7].

Monogenic Forms of diabetes and High-Penetrance Variants

Diabetes is often used as a universal term to describe a complex disorder characterized by hyperglycemia, but this disorder comprises multiple distinct pathologies for which the Latin term "diabetes" is short[5]. Such pathologies may share similar metabolic mayhem yet have very dissimilar aetiologies. Monogenic forms of diabetes are characterized by a single gene mutation that can cause diabetes regardless of any environmental influence, and a significant number of these mutations can lead to permanent neonatal diabetes (PNDM), which becomes obvious within the first six months after birth [7]. Genetic variants in such genes with a major causal role and gene pathways receiving much attention serve as ideal reference points and experimental pathways [4]. Genetic testing to precisely identify patients with a high-penetrance form of monogenic diabetes enables highly efficient therapy. Diabetes mellitus affects more than 10% of the world population and has become one of the fastest-growing global health threats, since the hyperglycemic state associated with this disease imposes chronic damage on multiple organs, including the eyes, kidneys, nerves, heart, and blood vessels [5]. At the same time, diabetes also poses another epidemic of diabetes caused by overweight and obesity [2]. The unifying method for classifying the different types of diabetes is based on their underlying pathophysiologies, and the aetiological classification of diabetes mellitus emphasizes the observation over the last several decades that diabetes mellitus consists of a wide spectrum of diseases, insulin resistance develops at different rates, and the aetiological classification assists clinical intervention [8].

Gene-Environment Interactions in Diabetes Susceptibility

The relationship between environmental exposure and diabetes is complex [1]. On the one hand, an increase in the number of people affected by diabetes worldwide cannot be attributed solely to genetic changes, since genome-

wide assessments of polymorphisms associated with diabetes show that the frequency of risk alleles has not changed significantly over the last fifty years across human populations [9]. On the other hand, the prevailing view within the field is that environmental factors predominantly determine the likelihood of developing diabetes and that congenitally acquired environmental exposure interacts with the exposition of founded genetic risk to shape the future of the majority of individuals possessing risk alleles added throughout human evolution [10]. This interaction between the environment and genetic risk is sometimes modeled as competing or complementary; that is, whether the risk added to the population susceptible to diabetes by a newly introduced environmental trigger prevents the acquisition of additional genetic risk or whether the acquisition of novel environmental risk takes place independently of the pre-existing genetic level of risk is unknown [13]. As yet, evidence favoring the view that genetic risk mitigates the deleterious consequences of later exposure to additional environmental factors that may give rise to diabetes is lacking [13]. Nevertheless, such an effect is plausible in theory. For instance, exposure to alcohol, particularly during stressful periods in life, is known to precipitate diabetes after the establishment of some genetic risk, but this does not exclude the existence of still unknown genetic factors which could delay the onset or lessen the consequences of such exposure [11]. This line of reasoning can be further generalized, leading to the speculative perspective that the number of individual environmental factors affecting the diabetic state of a population is currently on the increase, which, when coupled with rising levels of genetic predisposition, could explain gauges of sweetness and population-wide increases in glycosylated hemoglobin levels and average fat mass[19]. Furthermore, the known interaction of some environmental triggers with sleep length, together with longitudinal population increases in the daily number of hours that individuals dedicate to sleeping, points to the setting of additional environmental variables capable of influencing insulin resistance, food consumption, and accumulation of abdominal fat along the same lines [13].

Ethnic Diversity and Population-Specific Genetic Risk

Diverse ethnic backgrounds are inherently associated with particular genetic variations that confer population-specific susceptibilities to various diseases, including diabetes [5]. Numerous associations with increased type 2 diabetes risk have been uncovered since large-scale genetic studies began, yet many of the identified genetic variants were discovered in populations of European or East Asian ancestry[10]. Population-specific variants have been documented, but their effect sizes tend to be smaller than those of the European ancestry variants [7]. Thus, genetic studies based exclusively on European or East Asian populations may overlook significant determinants of type 2 diabetes risk in individuals with other ethnic backgrounds [12]. Such biases could expand existing healthcare disparities, as individuals of certain ethnicities may remain underserved by effective prevention, detection, and management strategies [13]. Self-reported ethnicity often serves as a rough proxy for genetic ancestry, but this approach may be confounded by socioeconomic, cultural, or cohort factors and fails to capture substantial genetic heterogeneity within groups [14]. Extending genetic investigations to diverse populations can facilitate the identification of previously undiscovered risk-altering variants and contribute to precision medicine across a broader veterinary (or human) spectrum. Identifying further risk variants uniformly in multiple populations could also generate usable insights into the underlying biology of type 2 diabetes [15].

Functional Genomics and Pathways Implicated in Diabetes

Genome-wide association studies (GWAS) have identified multiple genetic variants associated with type 1 and type 2 diabetes and gestational diabetes [2]. These have been linked to various molecular processes and biological pathways that are relevant to the pathophysiology of diabetes, such as signal transduction pathways that regulate beta-cell function, insulin signaling, and the inflammatory response [5]. The metabolic pathway involves a range of biological processes in the accumulation of homocysteine and a defect in the transsulfuration leading to cellular toxicity and damage, and plays a major role in orchestrating type 2 diabetes. At around 80 loci associated with type 2 diabetes, oligo- and poly-gene variants (even for monogenic ones) have been identified [3]. Taking GWAS further, different techniques have been employed to explore the link between variants and functional genes (e.g., distantly located but functionally) through expression quantitative trait loci (eQTLs), assays of chromatin accessibility, or CRISPR perturbation analyses [20]. Priority is being given to the identification of candidate genes according to chromatin accessibility, expression patterns (relevant to type 1 and type 2 diabetes) in specific tissues [5]. A number of pathways and processes that are relevant to the etiology of diabetes type 2 diabetes have been implicated through the analysis of -omic data at GWAS signals [9]. These pathways map onto diverse biological processes with minimal overlap of the set of associated enzymes between individual loci [6]. The pathway containing the TCF7L2 locus was found to have a dominant contribution to regulatory elements linked to insulin secretion, and this was concluded to be a secondary point of contact between regulatory and coding elements [15].

Translational Applications: Genetic Risk Prediction and Precision Medicine

Genetic risk prediction and precision medicine hold the potential to identify high-risk individuals and deliver health care tailored to their genetic profiles [3]. Genotype-based risk prediction is advantageous when population prevalence is low and when sufficient evidence to warrant preventive intervention is available [12]. Clinical laboratories estimate 4–6% lifetime risk for coronary heart disease, but ongoing risk factor accumulation across the life course may postpone preventive measures. A similar situation arises for stratification towards diabetes prevention or screening interventions guided by the projected age of onset [16].Monogenic mutations responsible for permanent neonatal diabetes or maturity-onset diabetes of the young (MODY) confer high penetrance that is observable in a health-care context, and pharmacogenomic data readily support risk prediction for specific therapies [17]. Therapeutic pathways thus become actionable candidates for precision medicine in diabetes during adulthood. In these models, genetic contributions are net rather than interactive; population structure, ancestry, and environment shape the pathways involved but do not change their identity. Nonetheless, the degree of spatial aggregation remains distinct, and shape-based approaches to modelling variation continue to operate [13].

Ethical, Legal, and Social Implications of Genetic Risk in Diabetes

Genetic risk testing for diabetes has ethical, legal, and social implications about privacy, discrimination, sharing of data, informed consent, and return of results [18]. Large-scale studies show that genetic risk perceptions shape decisions about testing and attitudes toward follow-up interventions [19]. The development of precise governance frameworks can guide the management of genetic information and address such ethical considerations [20]. There is a clear need for patient-centered communication strategies to convey genetic risk information effectively and appropriately [12]. Type 2 diabetes remains a major global public health issue, and genetics offers a powerful tool to gain better insight into the mechanisms of disease susceptibility [21]. Ongoing research will contribute significantly to resolving remaining knowledge gaps and to developing better models for evaluating genetic risk, while ultimately improving prevention strategies and health outcomes [20].

Future Directions and Gaps in Knowledge

Diabetes remains a major public health challenge; it is estimated that the number of people with diabetes will increase to about 528 million by 2030 and to about 783 million by 2045[6]. The growing prevalence of diabetes, especially type 2 diabetes (T2D), raises great concerns about global epidemics of diabetic disorders and their complications. Nevertheless, prevention of diabetes is possible, particularly T2D and gestational diabetes mellitus, through early intervention on risk factors [7]. Many environmental factors, the leading among which are obesity and a sedentary lifestyle, contribute to the development of diabetes. Understanding the genetic basis of diabetes is highly desirable, due to the potential for early identification of high-risk individuals and the targeting of lifestyle interventions for prevention of disease progression [8]. Although environmental factors have much stronger effects on diabetes susceptibility, genetic factors play important roles in the large variations in susceptibility to diabetes seen in clinical practice [8]. Diabetes represents a complex clinical condition due to a mixture of genetic and environmental etiology. Knowledge discovery in the genetic basis of diabetes has been advancing rapidly, especially in the past two decades. Similar approaches could be adopted to discover environmental risk factors potentially contributing to the occurrence of diabetes [21-28].

CONCLUSION

Genetic susceptibility plays a fundamental role in the development of diabetes mellitus, acting in concert with environmental and lifestyle factors to determine individual and population-level risk. Both type 1 and type 2 diabetes are polygenic disorders, with numerous genetic loci influencing immune regulation, β-cell function, insulin secretion, and insulin sensitivity. In contrast, monogenic forms of diabetes highlight the profound clinical relevance of high-penetrance variants and underscore the value of genetic testing for accurate diagnosis and targeted therapy. Despite substantial progress achieved through GWAS and functional genomic studies, important challenges remain. Genetic risk variants often confer modest individual effects, their distribution varies across ethnic populations, and gene–environment interactions are incompletely understood. Moreover, the underrepresentation of diverse populations in genetic studies limits the generalizability of current findings and risks exacerbating health inequities. Future research should prioritize inclusive, multi-ethnic genomic studies, longitudinal designs to clarify causal mechanisms, and integration of genetic data with environmental, behavioral, and clinical information. Translating genetic insights into effective risk prediction, prevention strategies, and precision medicine approaches while addressing ethical, legal, and social concerns will be essential. Strengthening this evidence base has the potential to improve early detection, optimize individualized care, and ultimately reduce the growing global burden of diabetes.

REFERENCES

1. Bawatneh A, Darwish A, Eideh H, Darwish HM. Identification of gene mutations associated with type 1 diabetes by next-generation sequencing in affected Palestinian families. Frontiers in Genetics. 2024 Jan 11;14:1292073.

2. Park KS. The search for genetic risk factors of type 2 diabetes mellitus. Diabetes & metabolism journal. 2011 Feb 28;35(1):12-22.
3. Sun X, Yu W, Hu C. Genetics of type 2 diabetes: insights into the pathogenesis and its clinical application. BioMed research international. 2014;2014(1):926713.
4. Ugwu OP, Ogenyi FC, Ugwu CN, Basajja M, Okon MB. Mitochondrial stress bridge: Could muscle-derived extracellular vesicles be the missing link between sarcopenia, insulin resistance, and chemotherapy-induced cardiotoxicity?. Biomedicine & Pharmacotherapy. 2025 Dec 1;193:118814.
5. Bakay M, Pandey R, Hakonarson H. Genes involved in type 1 diabetes: an update. Genes. 2013 Sep 16;4(3):499-521.
6. Padilla-Martínez F, Collin F, Kwasniewski M, Kretowski A. Systematic review of polygenic risk scores for type 1 and type 2 diabetes. International journal of molecular sciences. 2020 Mar 2;21(5):1703.
7. Yang J, Zhao J. Cumulative effect of common genetic variants predicts incident type 2 diabetes: A study of 21,183 subjects from three large prospective cohorts. Epidemiology (Sunnyvale, Calif.). 2011 Nov 16;1(3):108.
8. Paul-Chima UO, Nneoma UC, Bulhan S. Metabolic immunobridge: Could adipose-derived extracellular vesicles be the missing link between obesity, autoimmunity, and drug-induced hepatotoxicity?. Medical Hypotheses. 2025 Sep 28:111776.
9. Yaghootkar H, Frayling TM. Recent progress in the use of genetics to understand links between type 2 diabetes and related metabolic traits. Genome biology. 2013 Mar 28;14(3):203.
10. Sun HY, Lin XY. Genetic perspectives on childhood monogenic diabetes: Diagnosis, management, and future directions. World Journal of Diabetes. 2023 Dec 15;14(12):1738.
11. Asahara SI, Inoue H, Kido Y. Regulation of pancreatic β-cell mass by gene-environment interaction. Diabetes Metab J. 2022 Jan 27;46(46):38-48.
12. Zhu H, Ding G, Liu X, Huang H. Developmental origins of diabetes mellitus: Environmental epigenomics and emerging patterns. Journal of diabetes. 2023 Jul;15(7):569-82.
13. Song C, Gong W, Ding C, Wang R, Fang H, Liu A. Gene–Environment Interaction on Type 2 Diabetes Risk among Chinese Adults Born in Early 1960s. Genes. 2022 Apr 5;13(4):645.
14. Barroso I. The importance of increasing population diversity in genetic studies of type 2 diabetes and related glycaemic traits. Diabetologia. 2021 Dec;64(12):2653-64.
15. Ugwu OP, Ogenyi FC, Ugwu CN, Ugwu MN. Gut microbiota-derived metabolites as early biomarkers for childhood obesity: A policy commentary from urban African populations. Obesity Medicine. 2025 Sep 1;57:100641.
16. Chen R, Corona E, Sikora M, Dudley JT, Morgan AA, Moreno-Estrada A, Nilsen GB, Ruau D, Lincoln SE, Bustamante CD, Butte AJ. Type 2 diabetes risk alleles demonstrate extreme directional differentiation among human populations, compared to other diseases. PLoS genetics. 2012 Apr 12;8(4):e1002621.
17. Haiman CA, Fesinmeyer MD, Spencer KL, Bůžková P, Voruganti VS, Wan P, Haessler J, Franceschini N, Monroe KR, Howard BV, Jackson RD. Consistent directions of effect for established type 2 diabetes risk variants across populations: the population architecture using Genomics and Epidemiology (PAGE) Consortium. Diabetes. 2012 Jun 1;61(6):1642-7.
18. Ugwu OP, Okon MB, Alum EU, Ugwu CN, Anyanwu EG, Mariam B, Ogenyi FC, Eze VH, Anyanwu CN, Ezeonwumelu JO, Egba SI. Unveiling the therapeutic potential of the gut microbiota–brain axis: Novel insights and clinical applications in neurological disorders. Medicine. 2025 Jul 25;104(30):e43542.
19. Perry JR, McCarthy MI, Hattersley AT, Zeggini E, Wellcome Trust Case Control Consortium, Weedon MN, Frayling TM. Interrogating type 2 diabetes genome-wide association data using a biological pathway-based approach. Diabetes. 2009 Jun 1;58(6):1463-7.
20. Talmud PJ, Hingorani AD, Cooper JA, Marmot MG, Brunner EJ, Kumari M, Kivimäki M, Humphries SE. Utility of genetic and non-genetic risk factors in prediction of type 2 diabetes: Whitehall II prospective cohort study. Bmj. 2010 Jan 15;340.
21. Ugwu CN, Ugwu OP, Alum EU, Eze VH, Basajja M, Ugwu JN, Ogenyi FC, Ejemot-Nwadiaro RI, Okon MB, Egba SI, Uti DE. Sustainable development goals (SDGs) and resilient healthcare systems: Addressing medicine and public health challenges in conflict zones. Medicine. 2025 Feb 14;104(7):e41535.
22. Thomsen SK, Gloyn AL. Human genetics as a model for target validation: finding new therapies for diabetes. Diabetologia. 2017 Jun;60(6):960-70.
23. Wessel J, Gupta J, de Groot M. Factors motivating individuals to consider genetic testing for type 2 diabetes risk prediction. PLoS One. 2016 Jan 20;11(1):e0147071.

24. Carmichael AG, Hulswit BB, Moe EJ, Jayaratne TE, Yashar BM. A qualitative study of anticipated decision making around type 2 diabetes genetic testing: the role of scientifically concordant and discordant expectations. Journal of genetic counseling. 2017 Jun;26(3):469-79.
25. Ongesa TN, Ugwu OP, Ugwu CN, Alum EU, Eze VH, Basajja M, Ugwu JN, Ogenyi FC, Okon MB, Ejemot-Nwadiaro RI. Optimizing emergency response systems in urban health crises: A project management approach to public health preparedness and response. Medicine. 2025 Jan 17;104(3):e41279.
26. van Esch SC, Cornel MC, Snoek FJ. " I am pregnant and my husband has diabetes. Is there a risk for my child?" A qualitative study of questions asked by email about the role of genetic susceptibility to diabetes. BMC Public Health. 2010 Nov 10;10(1):688.
27. Lawlor N, Stitzel ML. (Epi) genomic heterogeneity of pancreatic islet function and failure in type 2 diabetes. Molecular metabolism. 2019 Sep 1;27:S15-24.
28. Grant SF. The TCF7L2 locus: a genetic window into the pathogenesis of type 1 and type 2 diabetes. Diabetes care. 2019 Sep 1;42(9):1624-9.

CITE AS: Nalongo Bina K.. (2026). Genetics of Diabetes Susceptibility. IDOSR JOURNAL OF APPLIED SCIENCES 11(1):135-140. https://doi.org/10.59298/IDOSRJAS/2026/111135140