Acta Scientific MEDICAL SCIENCES (ISSN: 2582-0931)

Volume 8 Issue 6 June 2024

Short Communication

Role of Genes in Diabetes mellitus

Dr. Anusha Sunder*

Doctorate in Lifescience/Human Nutrition, Accredited Certification in Nutrigenetics, Lead Scientist and Nutrigenetic Expert, Xcode Life Sciences, Pvt. Ltd. Chennai, India

***Corresponding Author:** Dr. Anusha Sunder, Doctorate in Lifescience/Human Nutrition, Accredited Certification in Nutrigenetics, Lead Scientist and Nutrigenetic Expert, Xcode Life Sciences, Pvt. Ltd. Chennai, India.

DOI: 10.31080/ASMS.2024.08.1835

Received: May 09, 2024

Published: May 27, 2024

The latest edition of the International Diabetes Federation (IDF), the Diabetes Atlas displays the diabetes count in adults as nearly 463 million, with an additional 1.1 million children and adolescents having type 1 diabetes. The year 2010 projected global diabetes numbers to be 438 million in 2025. With a year still to go, that prediction has already been surpassed by 25 million [1].

Diabetes is rising worldwide... and is set to rise even further [2].

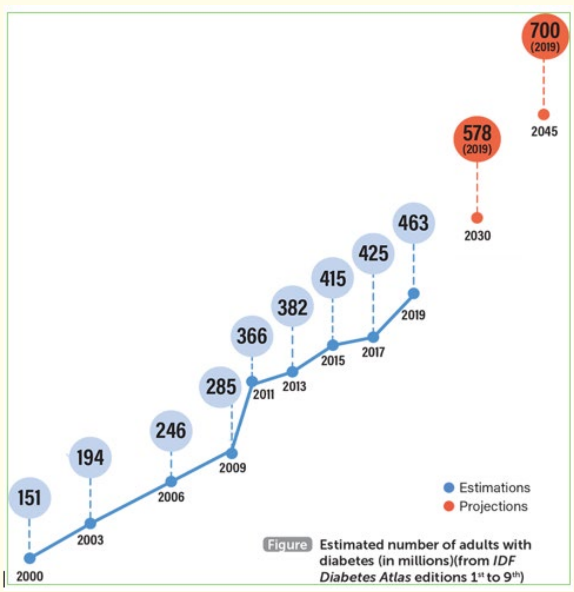

Figure 1

Genes and diabetes [3-5]

Diabetes (especially type 1 and 2) is caused by a combination of genetic and environmental risk factors. Type 1, 2 and gestational diabetes are polygenic, meaning they are related to a change, or defect, in multiple genes. This includes variations in important genes which have a role in glucose metabolism (regulation of fasting and postprandial blood glucose levels), insulin function (mainly insulin resistance) and triglyceride metabolism. Environmental factors have a crucial role in the development of polygenic forms of diabetes, for instance obesity predisposes to type 2 diabetes. Nevertheless, some rare forms of monogenic diabetes are caused by mutation(s) in a single gene and are directly inherited. These include Maturity Onset Diabetes in the Young (MODY), and Neonatal diabetes (ND).

Type 1 diabetes (T1D) is caused by an autoimmune reaction in which the body's immune system attacks the insulin-producing beta cells of the pancreas, resulting in less or nil insulin production.

Example(s) signifying role of genes in Type 1 Diabetes [6-13]

Type 2 diabetes (T2D), the commonest from of the disease is characterized by hyperglycaemia (high blood glucose levels) resulting from the inability of the body cells to respond fully to insulin, a situation termed 'insulin resistance'.

Gene	Gene Function	Effect of genetic variation
HLA class II genes (major histocompatibility complex/MHC or HLA molecules)	Initiate immune response. Probable role in autoimmune destruction of pancreatic beta cells	Children with the highest-risk HLA genotype (DR3/DR4-DQB1*03:02) have a risk of approximately 1 in 20 for a diagnosis of T1D by the age of 15 years. If the child has the high-risk genotype and has a sibling who has T1D, the risk is even higher (~ 55%)

Table 1

Estimates for the heritability of T2D range from 20%-80%, and the evidence for the same is attained in varied population through family- and twin-based studies. The lifetime risk of developing T2D is 40% for individuals who have one parent with T2D and 70% if both parents are affected. The risk of developing T2D in a 'first degree relative' of an individual with T2D is thrice as much as those without a positive family history of the disease.

Example(s) signifying role of genes in Type 2 Diabetes [14-17].

Gene	Gene Function	Effect of genetic variation
TCF7L2	encodes a transcription factor that is a member of the Wnt signaling pathway and is known to be active in the beta cells.	Risk alleles increase the level of TCF7L2 protein in beta cells, relating with impaired insulin secretion, & enhanced rate of hepatic glucose production. TCF7L2 expression in human islets was increased 5-fold in T2D, particularly in homozygotes and overexpression of TCF7L2 in human islets reduced glucose-stimulated insulin secretion. TCF7L2 probably plays a role in causation of T2D by decreasing insulin secretion from beta cells, perhaps by altering the action of incretins that modulate the insulin response to meals
PPARγ (peroxisome proliferator-activated receptor gamma)	PPAR-γ activation induces the expression of genes involved in the insulin signaling cascade. importance in adipocyte and lipid metabolism.	PPARG is a target for the hypoglycemic drugs known as thiazolidinediones. Proline to arginine change at position 12 in the PPARG gene (rsl801282) might lead to a 20% increase in the risk of diabetes due to decreased insulin sensitivity.

Table 2

Maturity-onset diabetes of the young (MODY) denotes monogenic disorders with autosomal dominant inheritance for non-insulin dependent diabetes whereby hyperglycemia usually becomes evident during adolescence or early adulthood (before the age of 25 years). Being a rare form, MODY accounts for just 1% of all cases and is often misdiagnosed as T1D or T2D. Genetic insight can lead to optimal treatment of the individual alongside allowing early diagnosis of their asymptomatic family members.

Example(s) signifying role of genes in Maturity-onset diabetes of the young [18,19].

Gene	Gene Function	Effect of genetic variation
Glucokinase/GCK In pancreas, this enzyme plays a role in glucose-stimulated insulin secretion, while in liver, this enzyme is important in glucose uptake and conversion to glycogen.	It acts as the "glucose sensor" for pancreas, increasing insulin production when blood glucose rises. Normal gene function ensures blood glucose control	GCK mutations cause a mild non-progressive hyperglycemia since birth. Mostly characterized as asymptomatic, and stable fasting hyperglycemia usually requiring no specific treatment.

HNF1A (hepatocyte nuclear factor-1 homeobox A) and HNF4A (hepatocyte nuclear factor-4 homeobox A)	Regulation of gene activity by the HNF-1A protein is critical for the growth and development of beta cells in pancreas which produce and release insulin. In pancreatic beta cells HNF4A directly activates insulin gene expression	Mutations in HNF1A and HNF4A predispose to MODY 3 and MODY 1, causing a progressive pancreatic β-cell dysfunction and hyperglycemia that can result in microvascular complications.
HNF1B (hepatocyte nuclear factor-4 homeobox B)	Encodes a transcription factor critical for the development of kidney and pancreas.	HNF1B mutations predispose to MODY 5, and is associated with pancreatic agenesis, renal abnormalities, genital tract malformations, and liver dysfunction

Table 3

Gestational diabetes (GDM) typifies as hyperglycaemia during pregnancy. Though it might occur any time during pregnancy, it is usually seen after 24 weeks and generally disappears after pregnancy. Globally, GDM accounts for 2%-5% of pregnancy complications, and its prevalence has significantly ascended over the last decade. It is believed to be a result of interactions between genetic, epigenetic, and environmental factors (such as late pregnancy, obesity and high fat diet). Women with mutations in MODY genes often present with GDM. Multiple common variants in candidate genes such as KCNJ11, GCK, or HNF1A have been found to increase the disease risk [20,21].

Neonatal Diabetes (ND) diabetes occurring under 6 months of age usually appears to be predominantly monogenic. Neonatal diabetes can either be transient or permanent. In a transient form, it may be so mild without requiring treatment or may spontaneously remit, often showing relapse during adolescence. While the permanent form requires lifelong treatment.

Variations in the KCNJ11 gene, and genes encoding insulin are the most common causes of permanent neonatal diabetes. The overexpression of paternally imprinted genes at chromosome 6q24 or a maternal methylation defect might predispose to transient neonatal diabetes with severe intrauterine growth restriction, often diagnosed within days of life. In neonatal diabetes, the transient forms may also originate from mildly activating mutations of ABCC8 and KCNJ11 genes. However, in such cases, there is low predictability of clinical course with relapsing or remitting diabetes requiring intermittent treatment throughout childhood.

Example(s) signifying role of genes in Neonatal Diabetes [22,23].

Gene	Gene Function	Effect of genetic variation
KCNJ11 and ABCC8 (SUR) genes (potassium channel, inwardly rectifying subfamily J, member 11 and ATP binding cassette, subfamily C, member 8)U	They encode the high-affinity sulfonylurea receptor (SUR1) subunit. Both genes are part of the ATP-sensitive potassium channel, which plays a key role in regulating the release of hormones, such as insulin and glucagon, in the beta cell. Mutations in either gene can affect the potassium channel's activity and insulin secretion	Activating mutations in KCNJ11 gene are a well-established cause of neonatal diabetes. Sulfonylurea treatment in potassium channel-linked ND have marked impact on endogenous insulin secretion and is now considered the treatment of choice

Table 4

Diabetes is regarded as one of the most serious public health challenges of the 21st century. Genetic insights can help in accurately classifying an individual by determining the type of diabetes that he/she is suffering from. This consequently aids in deciding customized and effective treatment modalities [24].

Bibliography

1. International Diabetes Federation (IDF); Diabetes Atlas, 9th Edition, (2019).

2. International Diabetes Federation (IDF); Diabetes Atlas, 9th Edition. Worldwide toll of Diabetes (2019).

3. Alberti KG and Zimmet PZ. "Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation". *Diabetic Medicine* 15.7 (1998): 539-553.

4. https://www.who.int/genomics/about/Diabetis-fin.pdf

5. Mohan V., *et al*. "From Individualized to Personalized Medicine in Diabetes: An Expert Overview". *Journal of the Association of Physicians of India* 67.9 (2019): 78-82.

6. Noble JA and Valdes AM. "Genetics of the HLA region in the prediction of type 1 diabetes". *Current Diabetes Reports* 11.6 (2011): 533-542.

7. Eisenbarth GS. "Banting Lecture2009: An unfinished journey: molecular pathogenesis to prevention of type 1A diabetes". *Diabetes* 59 (2010): 759-774.

8. Concannon P., *et al*. "Genetics of type 1A diabetes". *The New England Journal of Medicine* 360 (2009): 1646-1654.

9. Noble JA., *et al*. "The role of HLA class II genes in insulin-dependent diabetes mellitus: molecular analysis of 180 Caucasian, multiplex families". *American Journal of Human Genetics* 59 (1996): 1134-1148.

10. Lambert AP., *et al*. "Absolute risk of childhood-onset type 1 diabetes defined by human leukocyte antigen class II genotype: a population-based study in the United Kingdom". *The Journal of Clinical Endocrinology and Metabolism* 89 (2004): 4037-4043.

11. Horton R., *et al*. "Gene map of the extended human MHC". *Nature Review Genetics* 5 (2004): 889-899.

12. Aly TA., *et al*. "Genetic prediction of autoimmunity: initial oligogenic prediction of anti-islet autoimmunity amongst DR3/DR4-DQ8 relatives of patients with type 1A diabetes". *Journal of Autoimmune* 25 (2005): 40-45.

13. Aly TA., *et al*. "Extreme genetic risk for type 1A diabetes". *Proceedings of the National Academy of Sciences of the United States of America* 103 (2006): 14074-14079.

14. Chung WK., *et al*. "Precision medicine in diabetes: a Consensus Report from the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)". *Diabetologia* 63.9 (2020): 1671-1693.

15. Xue Sun., *et al*. "Genetics of Type 2 Diabetes: Insights into the Pathogenesis and Its Clinical Application". *BioMed Research International* (2014).

16. Ali O. "Genetics of type 2 diabetes". *World Journal of Diabetes* 4.4 (2013): 114-123.

17. Florez JC., *et al*. "The inherited basis of diabetes mellitus: implications for the genetic analysis of complex traits". *Annual Review of Genomics and Human Genetics* 4 (2003): 257-291.

18. Anık A., *et al*. "Maturity-onset diabetes of the young (MODY): an update". *Journal of Pediatric Endocrinology and Metabolism* 28.3-4 (2015): 251-263.

19. Peixoto-Barbosa R., *et al*. "Update on clinical screening of maturity-onset diabetes of the young (MODY)". *Diabetology and Metabolic Syndrome* 12 (2020): 50.

20. Rosik J., *et al*. "The role of genetics and epigenetics in the pathogenesis of gestational diabetes mellitus". *Annals of Human Genetics* 84.2 (2020): 114-124.

21. Shaat N and Groop L. "Genetics of gestational diabetes mellitus". *Current Medicinal Chemistry* 14.5 (2007): 569-583.

22. Greeley SA., *et al*. "Neonatal diabetes: an expanding list of genes allows for improved diagnosis and treatment". *Current Diabetes Reports* 11.6 (2011): 519-532.

23. Lemelman MB., *et al*. "Neonatal Diabetes Mellitus: An Update on Diagnosis and Management". *Clinical Perinatology* 45.1 (2018): 41-59.

24. Viswanathan Mohan and Ranjit Unnikrishnan. "Precision diabetes: Where do we stand today?" *Indian Journal of Medical Research* 148.5 (2018): 472-475.