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Parental History of Type 2 Diabetes Mellitus: A Lurking Genetic Threat

Sheh Zano[1*], Zil-a-Rubab[1], Saeeda Baig[1] and Burhanuddin Tahir[2]

[1]Department of Biochemistry, Ziauddin University, Karachi, Pakistan.
[2]Ziauddin University, Karachi, Pakistan.

Authors' contributions

This work was carried out in collaboration among all authors. Author SZ designed and wrote the first draft of the manuscript. Authors ZR and SB helped in the formation of figures, addition of some latest literature and improvement of literature and author BT managed the literature searches and final drafting. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Type-2 Diabetes Mellitus (T2DM) is presently the fastest growing disease and has been recognized to be caused by a collision between inherited parental genes and the environment. The current prevalence in Pakistan of type-2 diabetes mellitus is 26.3%. Out of them 19.2% had disease two to three decades back while 7.1% are recently diagnosed cases. Worldwide burden of disease was 415 million in 2015 and this number will increase to 642 million by 2040. Parental history of diabetes mellitus is a chief reason for the development of T2DM in children, but whether this association derives from shared genetic or environmental factors is unclear. Persistent high blood glucose levels can result in drastic outcomes like Diabetic Ketoacidosis and Hyperosmolar non ketotic syndrome. Genome-wide association analyses have uncovered multiple genomic regions associated with T2DM, but identification of the causal variants remains a challenge. This review will discuss the approach of diagnosing T2DM by analyzing the association of gene variants and family history.

**Corresponding author: E-mail: shehzano@zu.edu.pk;*

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1. INTRODUCTION

Type-2 Diabetes Mellitus (T2DM) is a prolonged metabolic illness which is described by higher blood glucose level secondary to defect either in insulin production or insulin resistance [1]. There are many risk factors of T2DM but the parental antiquity of T2DM is one of the major risk factors among them. T2DM established genetic components among relatives. Parental history is a reflection of the environment, cultural practices, and behaviors shared by family members. It is documented that there are increased chances of having T2DM if one or more first degree relatives are affected with this disease as compared to people whose relatives are without the disease [2]. Individuals with a parental history of T2DM are three times greater risk than other populations. In order to form effective T2DM preventive strategies, it is important to recognize and intervene with the families with history of T2DM. Among people who have family history of T2DM are made part of the diabetes prevention approach, the probability of detecting and enlisting these greater risk individuals need to be recognized. Up till now on the basis of intervention one review article has produced proof in involvement to reduce the threat of T2DM in people with parental history [3]. T2DM occurs around more than 400 million around the globe [4]. The rate of T2DM is increasing rapidly, especially in developing countries like Pakistan, Bhutan, Bangladesh and Nepal [5]. By the year of 2040, 1 in 10 adults affected by this disease and around 642 million will suffer from diabetes. Around 12% of the global health expenditure that is $673 billion expended on DM management. The predominant type of diabetes is T2DM and about 91 % of adults who are troubled with diabetes have T2DM.

Other factors like obesity, increased BMI, decreased exercise, poor diet, past history of gestational diabetes and elderly age also have great influence on T2DM [6]. Even though the pathophysiology of T2DM is not understood, genetic variants have a dominant part in the mechanism and causes of diabetes mellitus [7]. DM is identified as a vital common endocrine illness which is caused by dysregulation of cellular and molecular pathways. Many studies specified that numerous events including mutation, phosphorylation of serine and upregulation/downregulation of several genes could contribute to evolving and progressing of T2DM. Studies revealed that insulin opposition through targeting a sequence of molecular and cellular pathways (PPAR γ coactivator-1, PI3 kinases, microRNAs, serine/threonine Kings Akt, and serine phosphorylation) can cause diabetes. There are numerous reasons involved in the diabetes mellitus development, microRNAs, and exosomes have been occurring as actual aspects in the beginning and development of disease. Many studies showed that dysregulation of these particles could alter the activity of several kinds of cells and participate in development of Diabetes mellitus. In insulin resistance there is an involvement of signal molecule-Resistin. Various confirmation specified that resisting applies its effect on C6H12O6 metabolism, will resist to fatty acid uptake and metabolism by the disturbing variety of objects such as CD36, fatty acid transport protein1, Acetyl-CoA carboxylase, and AMP-activated protein kinase [8].

Genome wide association (GWA) studies were agreed to define the genetic origin of type 2 DM in different populations which are listed [9,10]. Transcription factor 7 like 2 *(TCF7L2)* shows the relation with type 2 diabetes in Sub-Saharan Africans [11]. Potassium voltage-gated channel subfamily Q member 1 *(KCNQ1*) gene, which belongs to voltage-gated potassium channel family found in East Azerbaijan population, Northwest of Iran or East Asians [12]. Juxtaposed with another zinc Finger gene *(JAZF1)* functions as a regulatory cofactor involved in homeostasis of glucose and lipid metabolism found in Saudi population [13]. Insulin receptor substrate 1 *(IRS1)* found in the population of Bosnia and Herzegovina [14]. Fat mass and obesity related gene *(FTO)* found in a North Indian population [15]. Kruppel like factor 14 *(KLF14)* gene is the chief controller of gene expression in adipose tissue found in Europeans [16]. Cyclin-dependent kinase inhibitor-2A/B *(CDKN2A/B*), Homeo box hematopoietic ally, expressed *(HHEX)* and solute carrier family 30 member 8 *(SLC30A8)* is commonly related to DM type 2 especially in Japan population [17].

In light of above fact we aim to review the provisional role of following genes *KCNQ1, FTO, JAZF1, PPARG, TF7L2, CDK2A/2B, HHEX, SLC30A8, IRIS and KLF14* in the development of type 2 DM in relation with family history.

2. REVIEW METHODS

This review article effort was done by going through a wide range of literature on the evolving role of various genes in T2DM. Evidence related to this article is recovered through PubMed and other search engines available. The literature was retrieved by consuming following keywords such as type 2 diabetes mellitus, family history, Genetic variant, *KCQN1, FTO, JAZF1, PPARG, TCF7L2, CDKN2A/2B, HHEX, SLC30A8, IRS1 and KLF14.* The material was assembled through epidemiological studies, systematic reviews and original research from February 2000 to August 2019.

3. DISCUSSION

3.1 Role of Specific Genes in Type 2 Diabetes Mellitus

3.1.1 *KCNQ1* (potassium voltage gated channel subfamily Q member 1k)

K+ channel have a vital role in various tissues such as heart, inner ear, stomach and colon. By potassium selective outward current, voltage is dependent by speedily initiating and gradually disabling its activity GWA studies identify over 100 susceptible loci of type 2 DM among them *KCNQ1* locus is the main epigenetic determinant that influences insulin sensitivity [18]. *KCNQ1* chiefly expressed in human kidneys where it interacts with KCNE1 (one of the subunit of potassium channel) and forms a potassium channel complex which is mainly found on the brush border of proximal tubule These observations suggested that *KCNQ1* gene also found in patients with diabetic nephropathy but larger data is necessary to establish one of the diagnostic markers for diabetic nephropathy [18]. *KCNQ1* gene is also expressed in a wide variety of human tissues such as heart, inner ear intestine, stomach and lungs. This gene is also involved in prolonged QT syndrome as well as congenital deafness [19]. Metabolic syndrome might be a significant reason for type 2 DM among Chinese women. The underlying etiology of metabolic syndrome is also insulin resistance but its association with *KCNQ1* gene has not been investigated yet. Studies confirmed the relation of metabolic syndrome with genetic as well as environmental factors. *KCNQ1* is also associated with metabolic syndrome and cardiovascular diseases in Turkish population [20].

3.1.2 *FTO* (fat mass obesity related gene)

Fat mass and obesity-associated protein has RNA demethylase which have a role in oxidative demethylation of RNA, such as mRNAs, t RNAs and Sn RNAs, and function as a controller of fat mass, adipogenesis and energy homeostasis. In eukaryotes De methylated N6-methyladenosine RNA is the most common internal modification of MRNA [21]. The frequency of overweight and obesity has been multiplied three times worldwide and in 2016 WHO approximates adults around 1.9 billion (18years/ older) were overweight and 650 million were fat [22]. This might be the fact that obesity is one of the major health threats and economic burden as well. *FTO* is directly related to obesity or adiposity and obesity is a chief reason for end stage renal disease (ESRD) [23]. FTO variant confers susceptibility to end stage renal disease through a mechanism mediated by obesity in Japanese patients [23], In South Asian population obesity linked with T2DM which confirms that variant of the *FTO* predispose to type 2 DM [24] One meta-analysis was performed to establish the relationship between *FTO* polymorphism & patients with obesity with Asian ancestry. This meta-analysis reveals rs9939609 and rs8050136 polymorphisms close to *FTO* are significantly associated with an amplified risk of obesity among Asian population [25].

3.1.3 *JAZF1* (Juxtaposed with another zinc finger protein 1)

This gene acts as a transcriptional corepressor of orphan nuclear receptor NR2C2 which inhibits expression of the gluconeogenesis enzyme PCK2 through inhibition of NR2C2 activity improves glucose metabolism and insulin sensitivity. It has a role in lipid metabolism by decreasing lipogenesis, upregulating lipolysis and in lipid accumulation [26]. *JAZF1* is involved in prostate cancer, T2DM and progression of different cancers such as endometrial stromal sarcoma. This gene encodes a protein called cysteine -2 histidine -2 zinc finger proteins that actually interact with heavy metals. This protein-protein interaction might suppress the activity of the testicular nuclear receptor (TR4). This TR4 triggers gluconeogenesis by stimulating transcription of PEPCK and enlarged weight and accumulation of fat. *JAZF1* suppresses the activity of the TR4 receptor, thereby declines the expression of PEPCK transcription, and hence reduces body weight [21].

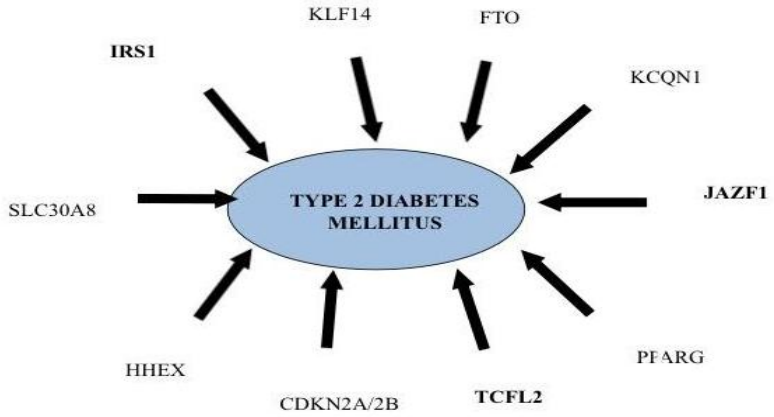

Fig. 1. Variants of type 2 diabetes mellitus

3.1.4 *PPARG* (peroxisome proliferator-activated receptor gamma 2)

It is also known as glitazone receptor or NR1C3 (nuclear receptor subfamily 1, group C, member 3) that actually senses steroid and thyroid hormones. It is mainly found in human tissues such as adipose tissue, macrophages and large intestine [25]. On the basis of amino acid sequence, these proteins have two isoforms such as *PPAR-γ1* (except muscle it is present in all tissues) and *PPAR-γ2* (adipose tissue and large intestine). This gene is mainly responsible for storage of fat as well as metabolism of glucose. There are 3 kinds of *PPAR* such as *PPAR*- alpha, *PPAR*- delta and *PPAR*- gamma. *PPAR*- gamma chiefly regulates differentiation of adipocytes. This is the reason that the PPAR-gamma gene is implicated in pathogenesis of obesity, and diabetes mellitus as well. The *PPAR* - gamma gene is activated by naturally occurring polyunsaturated fatty acids such as the 5-hydroxyeicosatetraenoic acid and 5-Oxo-eicosatetraenoic acid family. Activation of *PPAR* gene by above factors downregulates the risk of lung, prostate and gastric carcinoma [27]. Thiazolidinedione also called glitazones bind to *PPAR* gamma receptors. This leads to increased production of means of insulin dependent enzymes. The end result is increased use of glucose by cells [28].

3.1.5 *TCFL2* (transcription factor 7 like 2 t-cell specific, hmg-box)

It is involved in transcription of multiple genes, thereby exerting multiple functions within cells. This protein, mainly found in the brain, the liver, the intestine and fatty tissue. The basic mechanism of causing T2DM is not well known. *TCF7L2* regulates pancreatic islet beta cell functions and is mainly associated with gestational diabetes mellitus [29]. A mutation caused either by deleting or insertion of a number of nucleotides in DNA sequence leads to proliferation and metastases of colorectal cancer [15]. This gene is also involved in causing prostate cancer by activation of the PI3K/Akt pathway. T2DM risk is increased in schizophrenia patients. The *TCF7L2* gene is also involved in the development of schizophrenia, especially in European and Chinese populations. SNP rs12573128 is the main variant of *TCF7L2* involved in the progress of schizophrenia and also uses a diagnostic marker [29] *TCF7L2* gene also downregulates WNT/β-catenin pathway. Activation of this pathway leads demyelination in multiple sclerosis [15].

3.1.6 *CDKN2A/2B* (cyclin dependant kinase inhibitor)

It is located on chromosome 9. This gene mainly codes for two proteins such as P14 ARF and P16, which is the member of the INK4 family [30]. P16 protein is mainly linked with the cyclin dependent kinase inhibitor family, containing 33 amino acids and creates a helix-turn-helix-motif. The water phobic properties of P14 ARF protein, mainly involved in mitochondrial import sequence [31]. Both these proteins act as a tumor suppressor. P16 mainly shows a vital role in the pathogenesis of Retinoblastoma by inhibiting *CDK4* and *CDK6* [32]. On the other hand, P53 tumor suppressor gene is activated by P14 ARF. A mutation in *CDKN2A* is mainly associated with familial melanoma [33]. Most malignancies are associated with this gene because this gene is located on chromosome 9p21 locus which is renowned for one of the most common sites of

genetic deletions leading to the formation of malignant melanoma. Another notable property of this locus is that it is linked with myocardial infarction and CHD along with the development and progression of atherosclerosis [34]. Based on its chromosomal position and role in beta cell function and regeneration, this gene is also related to the development of T2DM [35]. Addition to skin malignancy such as malignant melanoma, this gene is also involved in other malignancies such as gastric carcinoma pancreatic carcinoma, oral cancer and non-small cell malignancies of lung [36].

3.1.7 *HHEX* (hematopoietically-expressed homeobox protein)

It plays a vital part in hematopoietic differentiation [37]. *HHEX* gene interacts with many signaling molecules inside multiple organs such as liver, forebrain and thyroid. Previous study suggested the role of *HHEX* gene in thyroid gland differentiation. The absence of this gene causes regression in the morphology of thyroid gland [37]. It also interacts with VEGF protein, which is involved in endothelial cell development. This gene interacts with a pro Myelocytic leukemia protein [38]. Previous study confirmed the role of *HHEX* gene in the progress of early postpartum DM ≤8 weeks [39]. It also acts as a tumor suppressor gene in early stages of breast cancer. Its nuclear action may be compromised in breast tumor cells by expanded HHEX phosphorylation and/or diminished HHEX mRNA expression and modified subcellular localization [40] The rs111875 T>C and rs7923837 A>G may contribute to an expanded colorectal carcinoma (CRC) chance in people of China. Other comprehensive studies must be performed in order to establish the effect of HHEX on CRC hazard, particularly in several populations [41]. HHEX rs1111875G/A and rs5015480C/T may contribute to the upgrade of T2D hazard in a test of the southeast Iranian population [42].

3.1.8 *SLC30A8* (solute carrier family 30 member 8)

It has an important role in the secretion of insulin. Alleles related with *SLC30A8* rise the threat of T2DM. This gene is found on chromosome 8q24.11 [43]. This gene is familiar among endocrinologists because of its relationship with T2DM. GWS reveals common polymorphism such as rs13266634 that is linked with T2DM. This polymorphism mainly lowers beta cell function and thereby causes T2DM. This variable encodes a tryptophan-to-arginine at 325 positions in protein intracellular carboxyl-terminal domain. Poorly regulated zinc levels in humans are similar in both T1DM (Type 1 diabetes mellitus) and T2DM. Therefore, identification of such variants is obligatory to expose the etiology of the disease [44]. This gene that affects insulin production and secretion is found among Russian population [45].Therefore, the quantity of ZnT8 autoantibodies is significant to diagnose type 1 diabetes mellitus. Non-European ancestry *SLC30A8* rs2466293 seems to influence the threat of having T1DM. [46,47]

3.1.9 *IRS1* (insulin receptor substrate 1)

IRS1 plays a vital role in stimulating the insulin pathway of signaling. Many experimental studies exhibit that this gene has a vital part in insulin function in adipose tissue, skeletal muscle and pancreatic beta cell and it is recognized by having an essential part in the progress of T2DM. Phosphorylation sites of *IRS1* are serine/ threonine sites which show upregulation and downregulation in IR tissue specific. GWA studies recognized FTO rs2943641 upregulation is associated with IR and risk of T2DM. [48]. In acute hyperglycemia and the estimation of insulin opposition in normal individual polymorphism (G>A) of *IRS1* play an essential role in identifying IR in T2DM. [49]. In coronary artery disease patients with underlying T2DM (G) allele *IRS1* rs13431554 are related with hyperactive platelet phenotype. [50]. Risk of polycystic ovary disease syndrome PCOS and its development is associated with polymorphism Gly 972 Arg of *IRS1* [51].

3.1.10 *KLF14* (kruppel like factor 14)

Studies confirmed that variants nearby the *KLF14* are intensely related with HDL levels, triglyceride levels, risk of T2DM, and risk of CAD. It is referred to as a “conductor of the metabolic syndrome orchestra” because of its association between *KLF14* and metabolic disorder. It is identified as a unique controller of lipid signaling and it also regulates fibroblast growth factor 2(FGF2). *KLF14* increases the expression of Apo A-I as a result of which plasma HDL-C level and lipid efflux rises. One vitro study showed that *KLF14* increases glucose uptake in Hepa1-6 cells and increases insulin sensitivity. *KLF14's role* in insulin and glucose metabolism has remained unknown while its role in regulating HDL-C levels has proved [52]. GWA studies

Table 1. Summary of genes susceptible to type 2 diabetes mellitus

S. No	Gene	Name	Chromosome	Locus	Role in diabetes	References
1.	*PPARG*	Peroxisome-proliferator activated receptor gamma gene	3	3p25.2	Act as insulin sensitizers, when TZD (antidiabetic drug) acts on its upregulate insulin sensitivity and enhanced glucose tolerance in T2DM	Safi SZ et al., 2016
2.	*TCF7L2*	Transcription factor 7 like 2	10	10q25.2	It disturbed β-cell function and Wnt signaling has an important role in decreasing glucagon-like peptide 1 and insulin secretion	Matveyenko AV et al., 2009
3.	*FTO*	Fat mass and obesity associated protein	16	16q12.2	In vivo regulation of FTO and its function are still largely unknown	Lefai E et al., 2011.
4.	*CDKN*	Cyclin dependant kinase inhibitor	9	9p21	It decreases pancreatic secretions	Mart S et al.,2019
5.	*HHEX*	Hemo poetically expressed homeobox	10	10q23.33	It is expressed in the somatostatin secreting cell, deficiency of it reduces somatostatin level, which causes disturbance in a paracrine inhibition of insulin release	McKenna LB et al., 2014
6.	*SLC30A8*	Solute carrier family 30 member 8	8	8q24.11	It is found in pancreatic B cells where it provides zinc to insulin, which helps in the maturation and storage processes of insulin.	Sun QM et al., 2011
7.	*JAZF1*	Juxtaposed with another zinc finger protein	7	7p15.2-p15.1	It causes defect in beta cell function, but its function is still largely unknown	Khan IA et al., 2015.
8.	*KCNQ1*	potassium voltage-gated channel subfamily Q member 1k	11	11p15.5-p15.4	The molecular mechanism for how KCNQ1 SNPs within the intron disturbs insulin secretion is not clear.	Senokuchi T et al., 2011
9.	*IRS1*	Insulin receptor substrate 1	2	2q36.3	It has an effect on insulin secretion and its actions	Sesti G et al.,2000
10.	*KLF14*	Kruppel like factor	7	7q32.2	Its mechanism is unknown.	Kawamura Y et al.,2005

have identified association of *KLF14* with coronary heart disease and HDL trait which is found on chromosome 7 which encodes the transcription factor *KLF14.* It acts in Trans to regulate the expression of various metabolic traits like LDL-c, HDL-c, TG and BMI. In GWA studies variants near the maternally-expressed transcription factor *KLF14* are related with both Type 2 DM and HDL-c. It is established that the T allele from maternal sites is related to the rise of *KLF14* in body fat and therefore regulated lipoprotein metabolism [53].

4. CONCLUSION

Our study concludes that all genes are associated with T2DM while the mechanism of action of some genes are clear (PPARG, TCF7L2, CDKN, HHEX, SLC30A8, IRS1) and while role of some genes is still not clear in the progression of T2DM. Improved accepting of the new mechanism and genes involved in the development of T2DM may help to advance policies and beneficial means for early detection of T2DM Further studies are required for early detection of gene variant associated with T2DM is essential in order to prevent long term complications with improved quality of life. Therefore, a thorough investigation of all genes that contributed to diabetes mellitus type 2 should be strongly emphasized.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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