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REVIEW ARTICLE **OPEN ACCESS**

A Review on Genetic Variants and Risk of Diabetes Mellitus

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ABSTRACT
Diabetes mellitus is a major health problem, which affects large population size. Most prevalent type of diabetes is type 2 diabetes that is caused by both environmental and genetic factors. Major problem that is associated with pathogenesis of diabetes mellitus is abnormal function of K_{ATP} channel that leads towards failure of insulin release. This channel is encoded by KCNJ11 and ABCC8 gene. In TCF7L2 gene the normal function of beta cell is due to Wnt signaling pathway. Disturbance in Wnt signaling pathway disturb the insulin release mechanism and glucagon peptide. Previous studies revealed that genetic variants and type 2 diabetes mellitus show positive relationship.
Key words: *Diabetes mellitus, Genetic Variants, K_{ATP} channel, TCF7L2, Wnt signaling*

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INTRODUCTION

Diabetes Mellitus is acute disease in which level of blood glucose enhance because pancreatic β-cells do not produce enough insulin or body cells cannot response properly to insulin[1] It was estimated that in 2011, almost 366 million people had suffer with this chronic disease and it is expected that in 2030, this ratio increase to 522 million people[2] Diabetes mellitus has many complications which are classified into early stage and late stage. Early stage complications are increase of appetite, excessive thirst, increase level of blood glucose and blurred vision. These early stage complications can leads to late stage complications such as nephropathy, stroke, vascular disease, neuropathy and heart disease[3].

Diabetes Mellitus is categorized into many types and among the various types of diabetes, Type 1 Diabetes Mellitus, Type 2 Diabetes Mellitus and Gestational Diabetes Mellitus gained more attention[4] The most prevalent is type 2 diabetes mellitus. About 90% of diabetic patients have type 2 diabetes mellitus and 5 to 10% people with diabetes mellitus suffer from type 1 diabetes mellitus[5] Type 1 diabetes mellitus is insulin dependent diabetes which is due to destruction of pancreatic β-cell that function is to produce insulin and this type is most prevalent in children[6] Type 2 diabetes mellitus is insulin dependent and it is metabolic disorder which results from insulin resistance. Mostly this type is common in older people[7] 3 to 10% of population is affected with gestational diabetes. In gestational diabetes, the level of blood glucose enhance during pregnancy due to improper functioning of insulin receptors[8].

INSULIN ROLE IN DIABETES MELLITUS

Insulin is a hormone that is synthesized by pancreatic β-cell and plays a major role in metabolism of body. It consists of 51 amino acids[9] Insulin helps to control the level of blood glucose. Glucose is converted into energy and this energy is provided to all the body cells with the help of insulin[10] Due to abnormalities in the function of pancreatic β-cell, insulin is not produced in sufficient amount that leads to hyperglycemia and result in pathogenesis of diabetes mellitus[11]

Factors affecting the Diabetes Mellitus

Both environmental and genetic factors contribute to the dysfunctioning of the pancreatic β-cell from this secretion of insulin is disturbed and results in insulin resistance which leads to development of diabetes mellitus[12].

Environmental factors

The etiopathogenesis of diabetes include the following environmental factors which are polluted air, soil, water, unhealthy diet, stress, and physical inactivity, lack of vitamin D and damage of the immune system due to the exposure of viruses. Unhealthy food that cause the obesity and DM which are rich in saturated

fatty acid, sugar and have the refined amount of carbohydrates. Three major cereal grains which are refined flour, Omega-6 industrial seed oil and fructose are the dietary toxins that trigger the diabesity and also cause the inflammation. Excessive use of fructose causes the nonalcoholic fatty liver diseases. About 25% dietary calories conversion from glucose to fructose increases the abdominal fat, impaired glucose tolerance, high blood pressure and high cholesterol level. Aerated soft drinks and overcooked foods have the low protein cause the malnutrition due to which dysfunction of β-cells. Exposure of viruses in host dysfunction the β-cells functions and leads to the inflammatory cytokines. Chemicals agent like afloxan and streptozotocin and drugs like cyclosporine, pentamidine also induce the DM. Lack of physical activity use of automobiles even for a short distances and long time sitting work on computers in offices increases the fat in body which cause the obesity and DM.

ROLE OF GENETICS IN DIABETES MELLITUS

Genetic basis of diabetes mellitus is still unclear. It is reported that mutation in *ABCC8* gene, *KCNJ11* gene and *TCF7L2* cause diabetes mellitus[13] When insulin binds with insulin receptor alpha subunit then it starts the insulin signaling pathway and this pathway exerts many biological effects in numerous tissues. To stimulate the transport of glucose is significant effect of insulin. Mutation in insulin signaling pathway is associated with development of type 2 diabetes mellitus. Skeletal muscles cannot uptake the sufficient glucose because of insulin resistance that is caused by polymorphism in those genes that play role in proteins expression[14] *TCF7L2* increases the chance of diabetes mellitus by 1.5 times due to genetic variation[15] Diabetes is also occurring due to positive family history. If one parent is diagnosed with diabetes then there is 38% chance that offspring would be affected and this chance will be 60% if both parents are affected with diabetes mellitus[16].

ATP dependent potassium channels

Blood glucose level is maintained and insulin is released by the help of normal potassium channels. These ATP sensitive potassium channels are present in pancreatic β-cell, brain and muscle. K_{ATP} channels consist of eight subunits of protein[17] Four are sulphonylurea receptor (SUR1) subunits and four subunits from potassium inward rectifying potassium channel (Kir6.2) subunits. When Kir6.2 combines with SUR1 then it form K_{ATP} channel [18].

***KCNJ11* Gene**

KCNJ11 gene (Potassium inward rectifying channel, subfamily J, member 11) is present in the chromosome 11p15.1 and consists of 4084bp. *KCNJ11* encodes the protein Kir6.2[19] *KCNJ11* gene comprises 1 exon and this exon encodes protein of 390 amino acids and no non-coding region[20]

***ABCC8* Gene**

ABCC8 gene (ATP-binding cassette, subfamily C, member 8) is present in the chromosome 11p15.1 and consists of 83,961bp. *ABCC8* gene encodes the SUR1 protein[21] *ABCC8* gene comprises 39 exons and encodes 1581 amino acids protein[22].

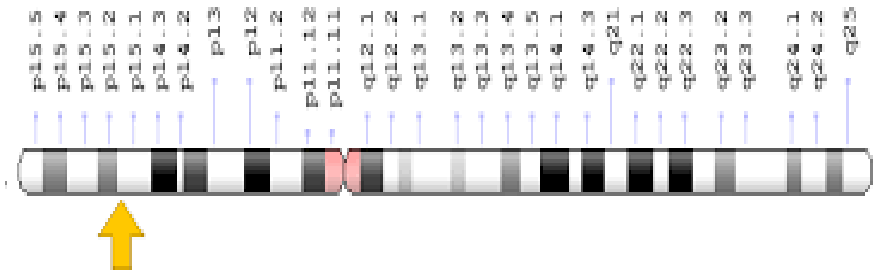

Figure-1 Location of *KCNJ11* and *ABCC8* gene on human chromosomes Adopted from (ncbi.nlm.nih.gov)

Role of K_{ATP} in insulin secretion

K_{ATP} cannel promotes the secretion of insulin. Through different mechanism these K_{ATP} channels open and close [23] Glucose metabolism generates the ATP and ADP molecules that control the activity of K_{ATP}. By activation of glycolysis, the intracellular ATP/ADP ratio increases which result in the closing of K_{ATP} channel and membrane become depolarized and lead to activation of voltage gated calcium channels. Calcium ions move inside the cell. The increase of intracellular level of calcium ions results in insulin secretion[24]

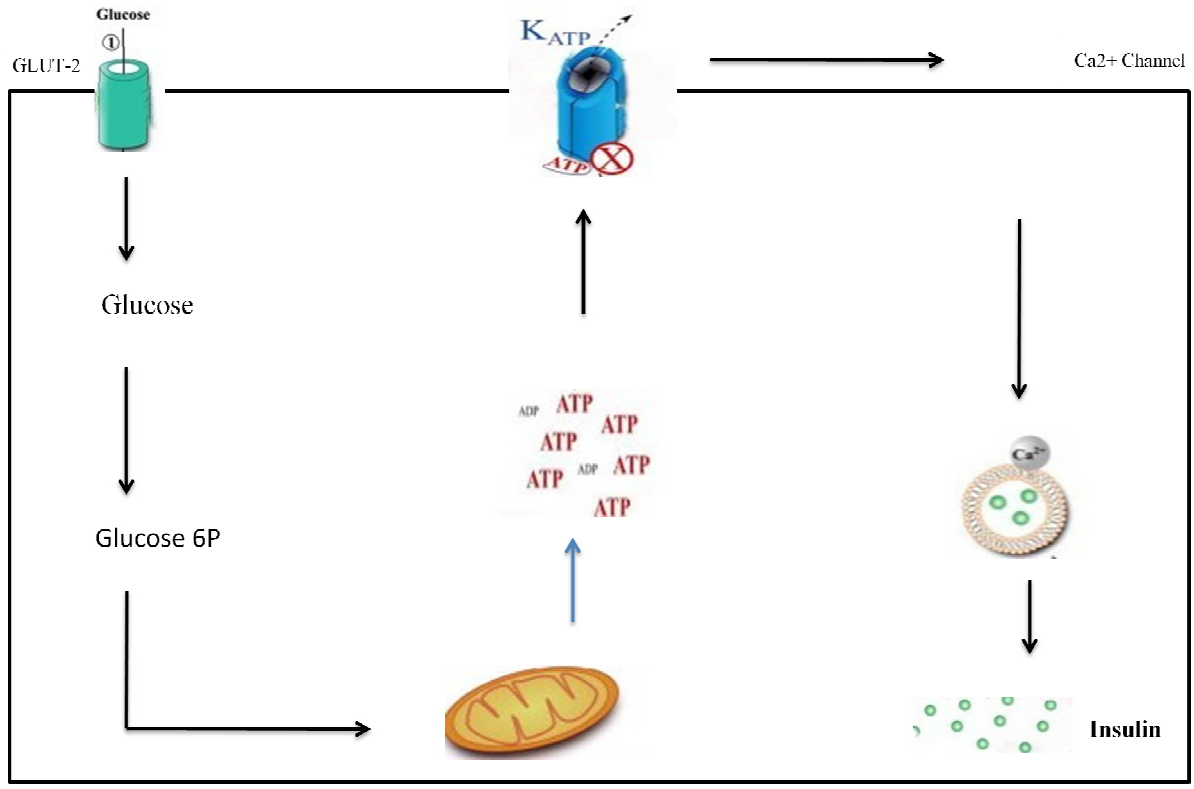

Figure-2 Schematic representation of insulin release mechanism by K_{ATP} channel. Through glucose transporter (GLUT-2), pancreatic beta cell takes the blood glucose. This glucose is phosphorylated with the help of glucokinase and converted into glucose 6-phospahte. In glycolysis, high ATP/ADP ratio results in closure of K*ATP* channel and cell membrane depolarization. The depolarization activates the voltage gated calcium channels (VGCC) leads to influx of calcium ions into cell. These calcium ions trigger the vesicles moment that contain insulin granules for the release of insulin into blood circulation. Modified from[5]

K_{ATP} polymorphism and Type 2 Diabetes Mellitus

It is widely studied that abnormalities in many genes may be linked with dysfunction of β-cells. In same gene, different polymorphisms may have different effects on its function. Mutation in *KCNJ11*, *ABCC8* and *TCF7L2* gene cause insulin resistance and lead to development of diabetes mellitus[25] Because due to mutation, Voltage gated calcium channel become close, and potassium channel activated so it result in suppression of insulin[26] K_{ATP} play a significant role in release of insulin. So, glucose homeostasis is changed due to single nucleotide polymorphism in these genes. 219 SNPs have been identified for *KCNJ11* gene, among these 219 SNPs, more attention is given to 6 SNPs which are given in Table 1[5] rs5219 (E23K) SNP show more association with the development of type 2 diabetes mellitus[27] It has been reported that two Polymorphism, (*KCNJ11* E23K and *ABCC8* rs1799854) were more associated with type 2 diabetes mellitus[28] Many Studies showed the positive association between E23K and type 2 diabetes mellitus. E23K polymorphism is caused due to substitution of glutamic acid to lysine at codon 23[29] It is reported that, in different population's lysine variant affect the properties of potassium channel[30]

***TCF7L2* gene**

Transcription factor 7-like 2 (*TCF7L2*) is a gene that involved in Wnt signaling pathway. Wnt contain the some transcription factor that is encoded by this gene. This gene is a member of T-cell factor (TCF) that regulates the cell elongation and cell differentiation[31] When *TCF7L2* bind to the β-catenin it initiate the transcription of many genes and also involving the intestinal proglucagon. The size of this gene is 215.9 kb and the position of this gene on chromosomes is 10q25. The intron 3 of this gene have the microsatellite marker (DG10S478) and five other related single nucleotide variants(rs12255372, rs11196205, rs7903146, rs7901695, rs7895340) were identified that have the strong linkage with type 2 diabetes[32]

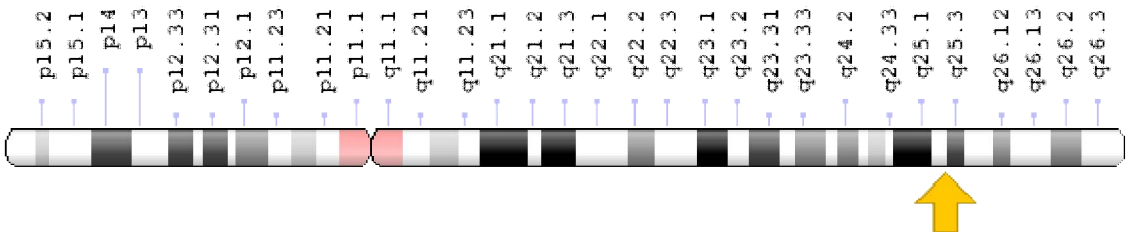

Figure-3 Location of TCF7L2 gene on human Chromosome. Adopted from (ncbi.nlm.nih.gov)

Role of Wnt signaling pathway in TCF7L2 gene

Wnt is a very complex process that is important for the normal cell function, communication of cell, tissue and organ development. Wnt protein have conserved domain of 300 amino acid which are also called the cell secreted glycoprotein ligands. Activation of Wnt signaling is done by the frizzled and LRP receptors and these receptors secreted by Wnt protein. When these receptors are bind to Wnt molecules, the β-catenin level is high than this β catenin join with nuclear TCF7L2 receptor and release the Groucho receptor[33] β catenin play the important role in the Wnt signaling because it activated the some genes, in which encoding GLP-1and intracellular cAMP are included that increases the beta cell function[31]

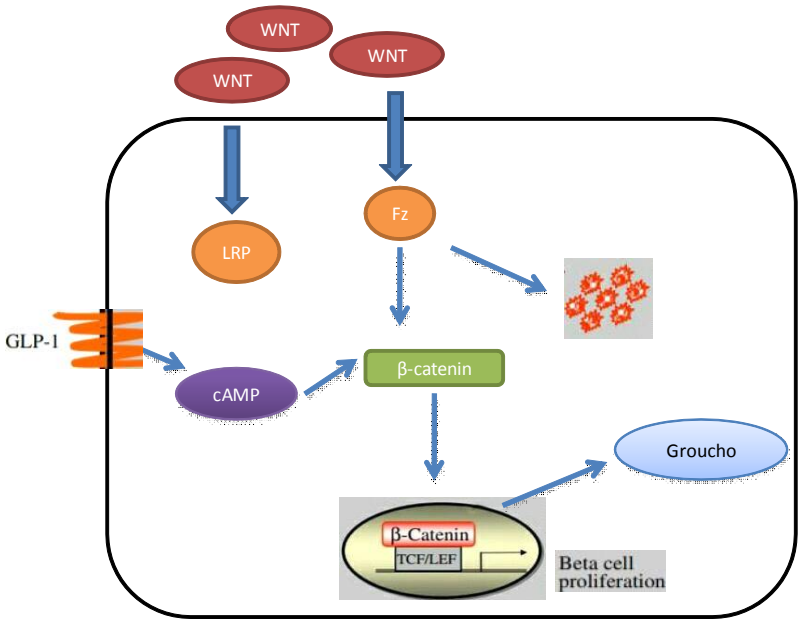

Figure-4 Role of Wnt signaling in the initiation of β-cell proliferation. Wnt molecules bind to the both receptors LRP and Fz that initiate the beta catenin level and GLP-1 then this beta catenin bind to the nuclear TCF7L2 and enhance the beta cell proliferation[31]

TCF7L2 risk genotypes

Single nucleotide polymorphism in *TCF7L2* gene associated with the impaired secretion of insulin and GLP-1that cause the diabetes mellitus. According to the recent report the stimulating effect of GLP-1on the beta cell is due to both the *TCF7L2* and β catenin.GLP-1 is important key factor for the activation of beta cell growth in Wnt pathway. While the transcription of *TCF7L2,* insulin and glucagon secretion influence due to the risk genotype[34]

Table-1 Location and Genetic Variants of different genes

Serial No.	Gene	SNP	Location	Allele	References
1	KCNJ11	rs5210	3'UTR	G>A	[35]
2	KCNJ11	rs5215	Exon	G>A	[36]
3	KCNJ11	rs2285676	3'UTR	T>C	[5]
4	KCNJ11	rs5218	Exon	C>T	[35]
5	KCNJ11	rs5219	Exon	G>A	[37]
6	KCNJ11	rs886288	5'near gene	T>C	[35]
7	ABCC8	rs1048099	Exon 2	A>G	[38]
8	ABCC8	rs1799854	Intron 15	T>C	[39]
9	ABCC8	rs757110	Exon 33	T>G	[40]
10	ABCC8	rs1799857	Exon 12	C>T	[41]
11	TCF7L2	rs7901695	Intron 3	T>C	[33]
12	TCF7L2	rs7903146	Intron 3	C>T	[34]
13	TCF7L2	rs11196205	Intron 4	C>G	[31]
14	TCF7L2	rs12255372	Intron 4	G>T	[31]
15	TCF7L2	rs7895340	Intron 4	A>G	[34]

CONCLUSION

Diabetes mellitus is chronic disease worldwide. Kir6.2 and SUR1 play a significant role in K_{ATP} channel function. Mutation in the *KCNJ11* and *ABCC8* gene can disrupt the activity of K_{ATP} channel and cause diabetes mellitus. According to previous studies, Polymorphisms in *TCF7L2* gene can cause diabetes mellitus. Many genetic variants of *KCNJ11*, *ABCC8* and *TCF7L2* have been linked with diabetes mellitus. Among many genetic variants, rs5219 and rs1799854, rs11196205, rs12255372 seems to be strong genetic variant that are associated with development of diabetes mellitus in many populations worldwide.

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