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REVIEW ARTICLE

# Possible Correlations between KCNJ11 and Risk of Diabetes Mellitus: Review Article

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## ABSTRACT

**Background:** The prevalence of diabetes mellitus (DM), a serious health concern on a global scale, has been growing at an alarming rate during the past century. Problems with insulin secretion, insulin action, or both might produce hyperglycemia, the main symptom. Type 2 diabetes is the most common form of the disease. The insulin secretion process is complex and involves multiple genes and the connections between them. Pancreatic beta cells secrete insulin via an ATP-sensitive potassium (KATP) channel. The KATP channel pore is formed by four inward-rectifier potassium ion channel (Kir6.2) tetramers, and the channel is surrounded by sulfonylurea receptor one subunit. The channel is heteromeric in nature. The KCNJ11 gene, which is a member of the potassium channel family, codifies Kir6.2. The present evidence regarding the role of common KCNJ11 genetic variations in the development of DM is summarized in this review.

**Conclusions:** The role of interactions between KCNJ11 single nucleotide polymorphisms and diabetes mellitus susceptibility has been documented in a large body of research. The literature suggests that various forms of diabetes are linked to variations in the KCNJ11 gene. This begs the question, in terms of their relative importance, which KCNJ11 polymorphisms and combinations contribute most to the onset of DM?

**Keywords:** KCNJ11, Diabetes Mellitus, Risk

## INTRODUCTION

Hyperglycemia and glucose intolerance are hallmarks of type 2 diabetes mellitus (T2DM), a condition that develops when the body's insulin response is inadequate. This leads to an increase in insulin production, which in turn leads to an insulin shortage [1].

The majority of the world's 800 million diabetics will have type 2 diabetes mellitus, which affects over 500 million adults today and is projected to reach 800 million by 2045 [2].

Also, by 2050, one out of every three Americans will have diabetes, and that number is forecast to keep climbing. These worrisome predictions highlight the critical need for new approaches to the prevention and treatment of type 2 diabetes to be developed and put into action immediately to reverse the global epidemic. Hyperglycemia, both while fasting and after food consumption, is a hallmark of type 2 diabetes and a major risk factor for a host of serious consequences and co-morbidities [3].

Diabetes mellitus type 2 is characterized by insulin resistance, decreased insulin production, and dysregulated glucose homeostasis. Retinopathy, neuropathy, nephropathy, and cardiovascular diseases are among the micro and macrovascular consequences that can develop in individuals with poorly controlled type 2 diabetes. Type 2 diabetes (T2D) risk factors include unhealthy eating habits, lack of physical activity, and inherited susceptibility, all of which interact with one another to make disease prevention and treatment more difficult [2].

More than 700 T2D risk loci have been found to be linked to T2D, which has improved our

understanding of its genetic composition [4].On the other hand, there is some evidence that the genetic variables found in GWAS increase the risk of type 2 diabetes, although only to a small degree. To better manage healthcare individually, it is necessary to identify biomarkers for screening and predicting type 2 diabetes and its consequences. Furthermore, it can provide insights into the underlying mechanisms implicated in the evolution of T2D [2].

Diabetes mellitus is the ninth leading cause of mortality worldwide, and its prevalence has quadrupled in the last 30 years. Diabetes mellitus affects around 10% of adults globally, with 90% of those cases being type 2 [5].

The International Diabetes Federation reports that as of early 2020, the prevalence of diabetes in Egypt was 15.2%, with 8,850,400 adult diabetic individuals, placing the country eighth globally. Despite how high these figures seem, between 40 and 50% of people who have diabetes or pre-diabetes go undiagnosed. This figure is projected to reach 13.1 million by 2035 [6].

If current trends continue, Egypt will have the ninth-highest prevalence of diabetes among adults (20-79 years old) in 2030 and the seventh-highest prevalence in 2045. In 2019, Egypt had the third-highest diabetes prevalence rate in the Eastern Mediterranean Region (EMR), reaching 17.2% [7].

Some of these vulnerable loci include KCNJ11, which encodes the islet ATP-sensitive potassium channel Kir6.2, and TCF7L2, which controls the production of the proglucagon gene and makes glucagon-like peptide 1 [8]; the action of insulin is influenced by IRS1 [9]; Melatonin, an endogenous ligand that regulates metabolism and governs the circadian rhythm, is associated with MTNR1B [10]; The gene PPARG2 codes for an adipocyte-differentiating transcription factor, while the gene IGF2BP2 is involved in insulin action stimulation, pancreatic development, and growth [11]; HHEX influences the maturation of β cells, while FTO increases the risk of diabetes by influencing body mass index (BMI) [12]. At the same time, a number of these loci are therapeutic targets for the most common types of type 2 diabetes medications. For instance, the thiazolidinedione family of medications targets PPARG2, whereas the sulphonylurea class targets KCNJ11 [13]. However, numerous unidentified loci for type 2 diabetes etiology remain. So, to fully comprehend and manage type 2 diabetes, we must increase our present biological understanding.

The secretion of insulin is regulated by a complex network of genes and the connections between them. The ATP-sensitive potassium (K-ATP) channel is a key component in pancreatic beta cells that facilitate insulin secretion. This channel is a heteromeric protein that is made up of sulfonylurea receptor one subunit around the pore and four inward-rectifier potassium ion channel (Kir6.2) tetramers that make up the K-ATP channel pore. The Kir6.2 gene is located among the potassium channel-regulating genes and is encoded by the KCNJ11 gene. Extensive research has linked the KCNJ11 gene and its associated single nucleotide polymorphisms to diabetes mellitus type 1 risk. [14].

## GENETIC FACTORS AND THE PROGRESSION OF DIABETES MELLITUS

Compared to unrelated individuals, those with a family history of type 1 diabetes or type 2 diabetes are six times and three times more likely to develop these diseases, respectively. Diabetes Mellitus (DM) is controlled by a complex network of genes. A few of these genes have been the focus of extensive research and analysis: PPARG, KCNJ11, and ATP-binding cassette transporter subfamily C member 8. The majority of these genes have some role in glucose metabolism, insulin action, pancreatic beta cell function, or other metabolic processes (such as energy intake/expenditure or lipid metabolism). Permanent neonatal DM has been linked to mutations in genes, including KCNJ11 and ABCC8, which can interfere with the KATP channel's potentiation function [15].

There is no intron in the potassium channel gene KCNJ11, which is located at 11p15.1. This gene encodes an inward-rectifier potassium ion channel (Kir6.2). Potassium ion channels with inward rectifiers are encoded by this gene (Kir6.2). Kir6.2 and SUR1, or high-affinity sulfonylurea receptor 1, are the two proteins that make up the KATP channel. Next to the KCNJ11 gene is the ABCC8 gene, which encodes SUR1. The Kir6.2 protein has an N- and C-terminal located within the cell and has three hundred amino acids. The protein has two transmembrane domains, M1 and M2. Pancreatic beta cells' plasma membranes have a KATP channel with four high-affinity SUR1 subunits encircling the pore and four Kir6.2 tetramers forming the pore itself. Through glucose metabolism, this channel regulates insulin secretion and synthesis. The method by which pancreatic beta cells secrete insulin through the KATP channel. Plasma insulin secretion is regulated by the KATP channel's Kir6.2

and SUR1 proteins. When glucose levels rise, potassium ions can enter the cell through the KATP channel. Free calcium ions (Ca2+) within cells are increased when there is an increase in intracellular potassium ions, which depolarizes the cell membrane and triggers calcium channels to open. Granules located at or close to the plasma membrane are released when other parts of the insulin secretion pathway are activated by calcium ions (Figures 1 and 2) [14].

Recent genome-wide association studies have shown over sixty-five hundred and sixty-five loci for type 1 diabetes, type 2 diabetes, and gestational diabetes mellitus, respectively. In humans, the most prevalent form of genetic variation can be found either within or outside of gene regions, and these variations are known as single neoclutide polymorphisms (SNPs). Less than 1% of the genome is occupied by SNPs, and about 54% of these polymorphisms do not cause harm. When present alone or as part of a linkage disequilibrium in a single gene or a cluster of genes, SNPs can alter the likelihood of disease incidence. For example, multiple studies have established a link between DM and the widely-recognized Pro12Ala, Glu23Lys, and Ser1369Ala polymorphisms in the PPARG, KCNJ11, and ABCC8 genes, respectively [16].

## LINK BETWEEN THE KCNJ11 GENE AND DIABETES RISK

The KCNJ11 gene has garnered considerable interest as a potential gene for type 2 diabetes (T2D) due to its role in glucose-stimulated insulin production; it produces Kir6.2 subunits of the ATP-sensitive potassium channel that plays a role in the glucose-mediated metabolic signalling pathway. The association between the KCNJ11 polymorphisms and type 2 diabetes has been the subject of several case-control studies within the last ten years [17].

### The structure of the KCNJ11 gene and its product

Belonging to the potassium channel gene family, the KCNJ11 gene is intron-free and situated at 11p15.1. Potassium ion channels with inward rectifiers are encoded by this gene (Kir6.2). Kir6.2 and SUR1, or high-affinity sulfonylurea receptor 1, are the two proteins that make up the KATP channel. The ABCC8 gene, which is next to the KCNJ11 gene, encodes SUR1. Kir6.2 is a 390 amino acid protein that has an N- and C-terminal located within the cell and two transmembrane domains (M1 and M2). Pancreatic beta cell plasma membrane KATP channels are structurally composed of Kir6.2 tetramers that create the pore and four high-affinity SUR1 subunits that encircle the pore. Through glucose metabolism, this channel regulates insulin secretion and synthesis [18].

### Function of Kir6.2 in the Secretion of Insulin

Interactions between the Kir6.2 and SUR1 proteins in the K-ATP channel facilitate insulin secretion. Involvement of this channel involves numerous physiological reactions. Glucose causes an increase in the amount of potassium that can enter cells through the K-ATP channel. In the presence of magnesium (Mg), ADP can be converted to ATP. This ATP binds to Kir6.2, closing the K-ATP channel and increasing the intracellular potassium ion concentration. This depolarizes the cell membrane and activates the Ca2+ channel. In order to close the voltage-dependent calcium channels, these channels direct the voltage-dependent potassium channels to repolarize the cell membrane. When free calcium levels inside cells rise, various parts of the insulin secretion pathway are triggered to release granules at or near the plasma membrane [19].

Because ATP has a diminished capacity to inhibit K-ATP channel activity and Mg-ATP has an enhanced ability to boost this channel's function concurrently, DM can result from mutations in the KCNJ11 gene. This is linked to insulin secretion issues, which can lead to diabetes mellitus [14].

## DIABETES-RELATED KCNJ11 POLYMORPHISMS

Of the 219 SNPs found in KCNJ11, the link between diabetes has recently brought additional focus to six of them. The coding regions contain three of these six frequent SNPs, while the noncoding sections contain the other three (Table 1). The rs5219, rs5215, rs5210, rs5218, rs886288, and rs2285676 SNPs are part of this set [20].

### *KCNJ11 rs5219*

This site is situated in exon 1 of the KCNJ11 gene; a shift from lysine to glutamine (Lys23Gln) at Kir6.2's NH2-terminal tail is brought about by the substitution of A for C (AAGCAG). The epsilon-amino group on lysine is positively charged, while glutamine remains unchanged in all biological contexts. The structure and function of the KCNJ11 protein are unaffected by this amino acid alteration. According to research, the rs5219 mutation can potentially change the ATP-binding region's charge and reduce the channel's ATP sensitivity [14]. The rs5219 polymorphism is strongly associated with type 2 diabetes risk, according to twenty-four

association studies and a new meta-analysis [21]. However, this result was not confirmed by other research [22].

The A allele of the rs5219 polymorphism reduces the ATP sensitivity of the KATP channel, leading to overactivity of the channel and inhibition of insulin secretion. This means that the rs5219 polymorphism possesses the potential to influence the insulin secretion pathway. Carriers of the AA genotype are more affected by this effect on insulin secretion than carriers of the GA genotype. Lower serum insulin levels were also observed in a postoral glucose tolerance test that was related to this genotype [23].

Blood pressure and hemoglobin A1c levels in type 2 diabetes are significantly impacted by the rs5219 polymorphism. Compared to G allele carriers, A allele carriers of rs5219 exhibited greater increases in HbA1c levels and blood pressure [24]. It has been proposed that there is a link between the A allele and higher hepatitis insulin sensitivity in type 2 diabetes [25]. Research in pharmacogenomics has shown that gliclazide is more effective in treating type 2 diabetes in patients who carry the A allele of the rs5219 polymorphism, as opposed to the G allele. Among patients with the A allele, those taking glimepiride or glibenclamide had a greater decrease in HbA1c than those taking gliclazide [26]. Both medications have inhibitory activity on KATP channels because their ring-fused pyrrole moiety binds to the A allele [27]. Another factor that affects repaglinide's effectiveness is the rs5219 polymorphism. Researchers also discovered that sulfonylurea treatment had less of an effect on people who carried the C allele [28].

***KCNJ11 rs5215***

Exon 1 of the KCNJ11 gene is where the rs5215 polymorphism is located. The transition from valine to isoleucine at residue 250 is brought about by a non synonymous mutation known as GTC→ATC, which is generated by a substitution of G for A. Isoleucine is one of three amino acids with branched hydrocarbon side chains; valine is hydrophobic. The other two have unbranched hydrocarbon chains. In proteins, isoleucine can stand in for leucine and, on rare occasions, valine. Three out of thirteen DM studies found a strong relationship between this variation and type 2 diabetes, while the other studies found no association with type 2 diabetes, type 1 diabetes, or gestational diabetes [29]. Another study found that people with type 2 diabetes who had the rs5215 polymorphism also had higher blood pressure [24].

***KCNJ11 RS5210***

The KCNJ11 gene's three ′ untranslated region (UTR) is a well-conserved location for the rs5210 polymorphism. A conceivable function in the development of type 2 diabetes was detected in two of the four papers that were relevant to this topic; however, the other investigations did not find any evidence of a relationship between the two [30]. According to research, this variation enhances gliclazide's therapeutic effectiveness in type 2 diabetic patients. Although this locus is a target of miR-1910, the exact way this miRNA contributes to the onset of DM remains a mystery. In both healthy and unhealthy states, microRNAs—which consist of 17–25 nucleotides—posttranscriptionally control the expression of thousands of genes across many different kinds of organisms. Insulin exocytosis control by microRNAs is an important component of blood glucose homeostasis, which relies on the proper insulin release from pancreatic beta cells. In beta cells, microRNAs regulate insulin production and secretion. While the G allele may be miR-1910's target, the A allele prevents miR-1910 from attaching to this specific area [31]. More research into the function of miR-1910 in DM may be forthcoming.

***KCNJ11 rs5218***

The KCNJ11 gene contains the rs5218 polymorphism in its 3′-untranslated region. This variant, which is identical to the original but has the letter G changed to the letter A (GCC→GCT), encodes a hydrophobic and ambivalent amino acid at position 103 in place of alanine. A single report of this DM locus did not indicate any risk of type 2 diabetes [24].

***KCNJ11 rs886288 and rs2285676***

There is a genetic variation at rs886288 in the five ′ flank close to the gene and another at rs2285676 in the 3′-UTR. Two investigations found that the rs886288 and rs2285676 polymorphisms are associated with type 2 diabetes [24].

***Interaction of the KCNJ11 Gene with Other Genes***

The KCNJ11 gene interacts with other genes that control insulin production in beta cells of the pancreas. Out of all the genes that KCNJ11 interacts with, the top ten are as follows. Through interacting with ABCC8, KCNJ11 generates the potassium ion transporter K-ATP channel. At the molecular and intracellular levels, the KCNJ11 and ABCC8 genes communicate with three sets of gene products [24].

**INTERACTIONS AT THE CELL MEMBRANE LEVEL**

In beta cells of the pancreas, the genes KCNJ11 encodes Kir6.2 and ABCC8 encodes Sur1. Rather than potassium leaving the cell, this protein pair forms a compartment in the KATP channel that G proteins use to govern potassium entry [19]. The long-lasting (L), neural (N), Purkinje (P/Q), residual (R), and transient (T) VSCCs are among those with which the KATP channel interacts (transient). In their most basic form, calcium channels consist of four subunits .The pore-forming subunit impedes calcium ion entry into excitable cells, whereas the auxiliary subunits regulate trafficking and the biophysical characteristics of the subunit, therefore controlling the calcium channel's activity. The genes that code for the various isoforms of the subunit are CACNA1A, CACNA1B, CACNA1C, CACNA1D, CACNA1E, and CACNA1G, in that order. P/Q, N, L, R, and T are the types of calcium channels produced by the A–E subunits, respectively. These channels are classified as either high-voltage activated (HVA) or low-voltage activated (LVA), with the former four categories being L, N, P/Q, and R. Several calcium-dependent processes, including the release of neurotransmitters or hormones, muscular contraction, cellular motility, gene expression, cell division, and cell death, include both the HVA and LVA group [32]. Last but not least, skeletal, vascular, nonvascular, and cardiac smooth muscle can generate an additional type of KATP channel with Kir2 and ABCC9. An extrapancreatic KATP channel subunit that binds drugs and modulates channel activity is what the ABCC9 protein appears to do according to its structure [33].

## INTERACTIONS AT THE INTRACELLULAR LEVEL

The PRKACG gene encodes a protein that interacts with the KATP channels. Involved in exocytosis through several mechanisms, including calcium- and hormone-mediated signaling, this protein is the gamma-catalytic subunit of protein kinase. Additionally, this protein triggers intracellular protein kinase and other cellular activities [34]. Proteins encoded by the RAPGEF4, FOXA2, and ENSA genes and the ABCC9 gene interact with Kir6.2. One example of an exchange protein is RAPGEF4, which cAMP can activate. Genes including alpha-fetoprotein, albumin, and tyrosine aminotransferase are activated when FOXA2 is present. A naturally occurring ligand for SUR1, ENSA promotes insulin secretion [35]. Another possible outcome of KCNJ11 gene defects is autosomal-dominant type 2 diabetes mellitus (T2DM), temporary neonatal DM type 3, or permanent neonatal DM [36].

In a novel study, authors in Iraq evaluated the role possible role of KCNJ11 SNP, among T2DM patients and they revealed that rs5219 SNP was associated with T2DM [37].

**Table 1:** Susceptibility loci associated with T2DM discovered with GWAS. [20].

| Gene | Gene Region | SNPs | Population | P-Value |
|---|---|---|---|---|
| KCNQ1 | 11p15.4 | rs2237897 | Japanese | $6.8\times10^{-13}$ |
| | 11p15.4 | rs2237895 | Chinese | $9.7\times10^{-10}$ |
| | 11p15.4 | rs231362 | European | $2.8\times10^{-13}$ |
| | 11p15.4 | rs2237892 | Japanese | $1.7\times10^{-42}$ |
| TCF7L2 | 10q25.2 | rs7903146 | European | $2.0\times10^{-31}$ |
| KCNJ11 | 11p15.1 | rs5219 | European | $6.7\times10^{-11}$ |
| | 11p15.1 | rs5215 | UK | $5.0\times10^{-11}$ |
| IRS1 | 2q36.3 | rs7578326 | European | $5.4\times10^{-20}$ |
| MTNR1B | 11q14.3 | rs1387153 | European | $7.8\times10^{-15}$ |
| IGF2BP2 | 3q27.2 | rs4402960 | European | $8.9\times10^{-16}$ |
| | 3q27.2 | rs6769511 | European | $9.0\times10^{-16}$ |

| Gene | Gene Region | SNPs | Population | P-Value |
|---|---|---|---|---|
| CDKN2A/B | 9p21.3 | rs564398 | UK | $1.3\times10^{-6}$ |
| | 9p21.3 | rs2383208 | Japanese | $1.6\times10^{-7}$ |
| | 9p21.3 | rs10811661 | European | $7.8\times10^{-15}$ |
| HHEX | 10q23.33 | rs1111875 | European | $5.7\times10^{-10}$ |
| | 10q23.33 | rs5015480 | European | $1.0\times10^{-15}$ |
| PPARG2 | 3p25.2 | rs1801282 | European | $1.7\times10^{-6}$ |
| | 3p25.2 | rs17036101 | European | $7.5\times10^{-6}$ |

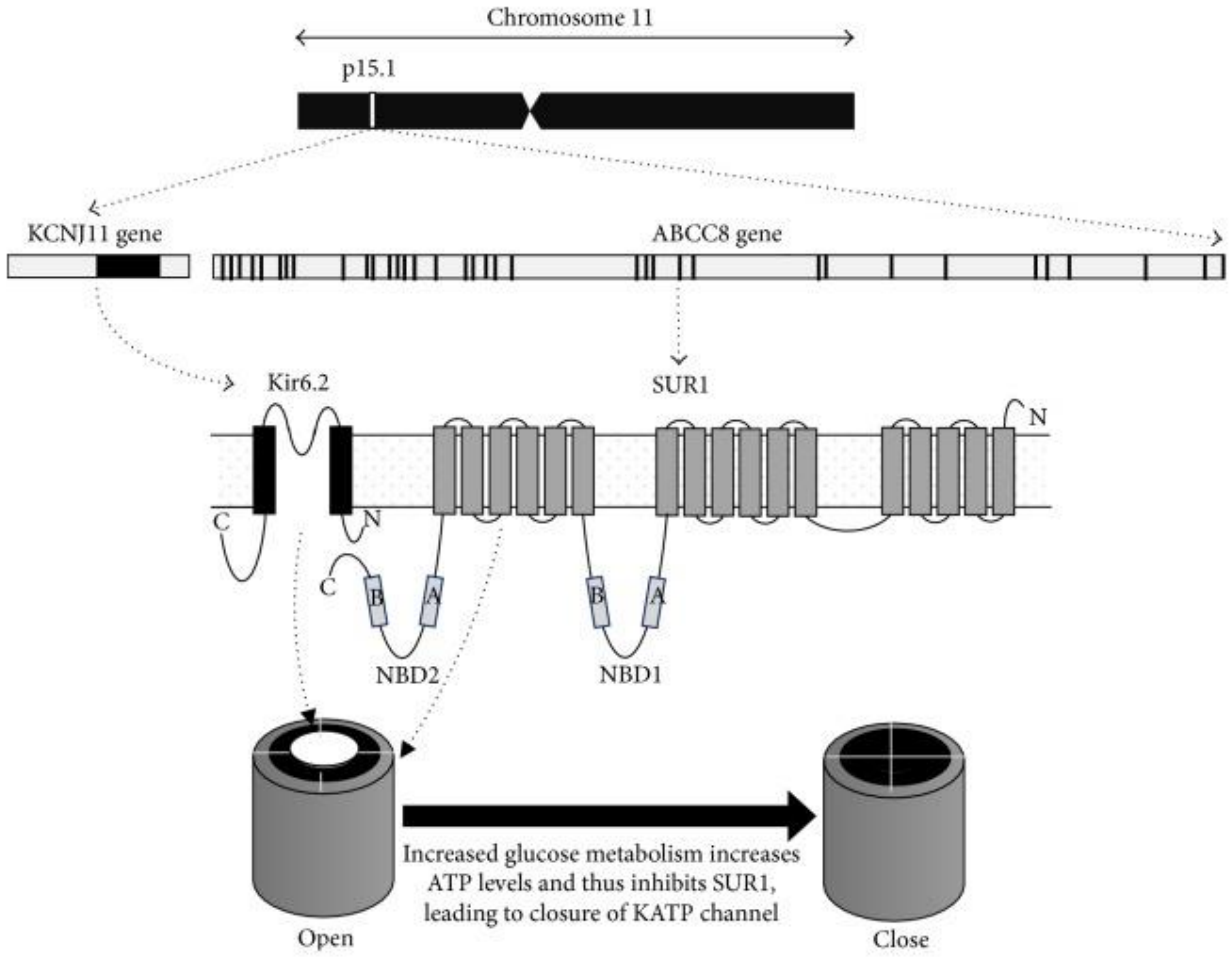


**Figure 1**: KNJ11 genes and their encoded proteins and functions [14].
ABCC8: ATP-binding cassette transporter subfamily C member 8; KCNJ11: potassium inwardly-rectifying channel, subfamily J, member 11; Kir6.2: inward-rectifier potassium ion channel; SUR1: sulfonylurea receptor 1; NBD1: nucleotide-binding domain 1; NBD2: nucleotide-binding domain 2; N: NH2 terminal of protein; C: COOH terminal of protein; A: Walker A motif; B: Walker B motif; cAMP: cyclic adenosine monophosphate; ATP: adenosine triphosphate.

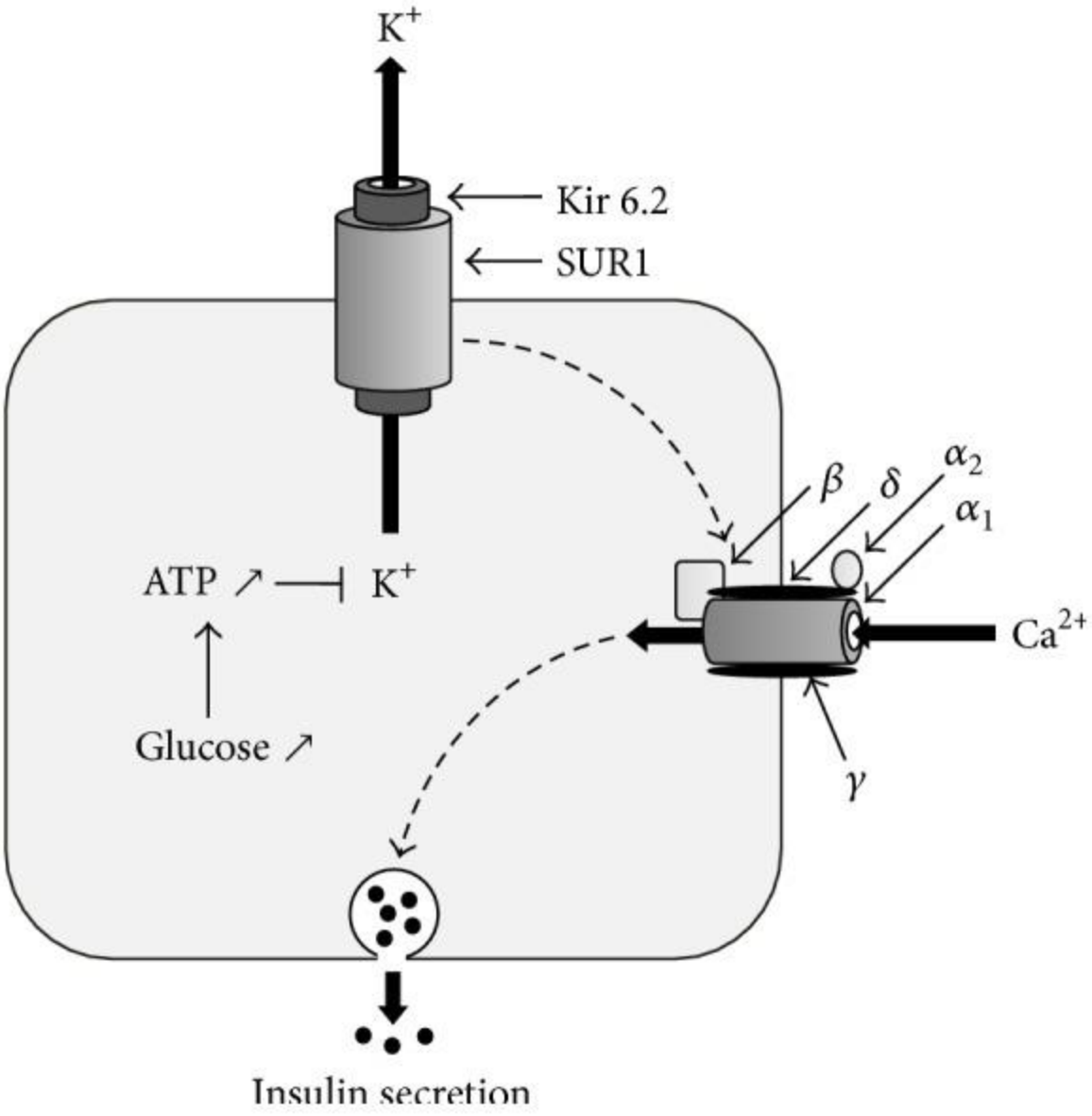


**Figure 2:** Mechanism of insulin secretion by the KATP channel in pancreatic beta cells [14].
KATP: ATP-sensitive potassium channel; Kir6.2: inward-rectifier potassium ion channel; SUR1: sulfonylurea receptor 1; ATP: adenosine triphosphate; $K^+$: potassium ion; $Ca^{2+}$: calcium ion. The calcium channel is composed of $\alpha_1$, $\alpha_2$, $\beta$, $\gamma$, and $\delta$ subunits.

## CONCLUSION

The role of interactions between KCNJ11 single nucleotide polymorphisms and diabetes mellitus susceptibility has been documented in a large body of research. The literature suggests that various forms of diabetes are linked to variations in the KCNJ11 gene. This leads to the question, in terms of their relative importance, which KCNJ11 polymorphisms and combinations contribute most to the onset of DM?

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