Diabetes mellitus (DM) is a major worldwide health problem and its prevalence has been rapidly increasing in the last century. It is caused by defects in insulin secretion or insulin action or both, leading to hyperglycemia. Of the various types of DM, type 2 occurs most frequently. Multiple genes and their interactions are involved in the insulin secretion pathway. Insulin secretion is mediated through the ATP-sensitive potassium (KATP) channel in pancreatic beta cells. This channel is a heteromeric protein, composed of four inward-rectifier potassium ion channel (Kir6.2) tetramers, which form the pore of the KATP channel, as well as sulfonylurea receptor 1 subunits surrounding the pore. Kir6.2 is encoded by the potassium inwardly rectifying channel, subfamily J, member 11 (KCNJ11) gene, a member of the potassium channel genes. Numerous studies have reported the involvement of single nucleotide polymorphisms of the KCNJ11 gene and their interactions in the susceptibility to DM. This review discusses the current evidence for the contribution of common KCNJ11 genetic variants to the development of DM. Future studies should concentrate on understanding the exact role played by these risk variants in the development of DM.
hypertension, abnormal cholesterol levels, age, and smoking [8]. Pathogenic and nonpathogenic mutations in genomic DNA can also contribute to the development of diabetes. Several single nucleotide polymorphisms (SNPs), which are a type of nonpathogenic mutation, have been reported to be associated with susceptibility to different types of DM. The aim of this review is to assess the possible contribution of SNPs of the gene known as the potassium inwardly rectifying channel, subfamily J, member 11 (KCNJ11), which forms a compartment of the ATP-sensitive potassium (KATP) channel, present in beta cells of the islets, in the susceptibility to different types of DM.

2. Role of Genetics in the Development of DM

People with a family history of T1DM and T2DM are six and three times more likely, respectively, to develop these diseases than are unrelated individuals [9]. Multiple genes are involved in DM. Those that have garnered the most attention are the ATP-transporting cassette transporter subfamily C member 8 (ABCC8) gene; the KCNJ11 gene; and the peroxisome proliferator-activated receptor-gamma (PPARG) gene. Most of these genes are involved in insulin action/glucose metabolism, pancreatic beta cell function or other metabolic conditions (e.g., energy intake/expenditure, lipid metabolism) [10]. Mutations in genes such as ABCC8 and KCNJ11 can disrupt the potentiating activity of the KATP channel and have thus been associated with permanent neonatal DM [11]. The PPARG gene is implicated in adipogenesis and the development of insulin resistance. Deleterious mutations in this gene impair insulin resistance and can cause lack of response to insulin [12].

From recent genome-wide association studies, more than 60, 500, and 65 loci have been identified for susceptibility to T1DM, T2DM, and GDM, respectively [13]. SNPs are the most common type of genetic variation distributed within or outside a gene region in the human genome. The frequency of SNPs is less than 1% in the genome, and approximately 54% of these variants are not deleterious [14]. SNPs can modify the risk of occurrence of a disease, either alone or in linkage disequilibrium in one gene or in neighborhood genes. For instance, in several studies, the common Pro12Ala polymorphism in the PPARG gene, the Glu23Lys polymorphism in the KCNJ11 gene, or the Ser1369Ala polymorphism in the ABCC8 gene was confirmed to be associated with DM [15].

3. KCNJ11 Gene and Its Product

The KCNJ11 gene, a member of the potassium channel gene family, is located at 11p15.1 and has no intron (Figure 1: 17,385,237–17,389,331). This gene encodes an inward-rectifier potassium ion channel (Kir6.2). The Kir6.2 protein, together with the high-affinity sulfonylurea receptor 1 (SUR1), forms the KATP channel. SUR1 is encoded by the ABCC8 gene located next to the KCNJ11 gene. The Kir6.2 protein is a 390-amino acid protein with two transmembrane domains (M1 and M2) and intracellular N- and C-terminals. Structurally, Kir6.2 tetramers form the pore and four high-affinity SUR1 subunits surround the pore of the KATP channel located at the plasma membrane of pancreatic beta cells. This channel modulates insulin production and secretion through glucose metabolism [16].

3.1. Role of Kir6.2 in Insulin Secretion. The Kir6.2 protein, coupled with the SUR1 protein in the KATP channel, mediates insulin secretion. This channel is involved in a wide range of physiological responses. Increased glucose induces higher potassium flow into the cell through the KATP channel. ADP in the presence of magnesium (Mg) converts to ATP; the ATP then closes the KATP channel by binding to Kir6.2, increasing the intracellular potassium ion concentration, which depolarizes the cell membrane and subsequently activates calcium ion (Ca\(^{2+}\)) channel. Ca\(^{2+}\) is a ubiquitous intracellular second messenger that is critical for cellular functioning. These calcium channels influence the voltage-dependent potassium channels to repolarize the cell membrane, leading to closure of the voltage-dependent calcium channels. Increased intracellular free Ca\(^{2+}\) levels trigger other components of the insulin secretion pathway to release granules at or near the plasma membrane (Figure 2). Mutations in the KCNJ11 gene can cause DM because of the reduced ability of ATP to inhibit the activity of the KATP channel and the enhanced ability of MgATP to simultaneously stimulate the function of this channel. This is associated with defective insulin secretion, ultimately causing DM [17].

3.2. KCNJ11 Common Polymorphisms Involved in Diabetes. KCNJ11 has 219 SNPs, six of which have been receiving more attention for their association with diabetes. Among these six common SNPs, three are located in the coding regions and three in the noncoding regions (Table 1). These six SNPs include rs5219, rs5215, rs5210, rs5218, rs886288, and rs2285676.

3.2.1. KCNJ11 rs5219. This locus is located in exon 1 of the KCNJ11 gene. Substitution of A to C (AAG → CAG) changes the amino acid from lysine to glutamine (Lys23Gln) at the NH2-terminal tail of Kir6.2. Lysine has a positively charged epsilon-amino group, whereas glutamine is uncharged under all biological conditions. Despite this amino acid substitution, theoretically, it does not make a remarkable change in the structure and function of the KCNJ11 protein [18]. Studies have shown, however, that the rs5219 variant may alter the charge of the ATP-binding region and decrease channel sensitivity to ATP. Twenty-four association studies and a recent meta-analysis showed a strong relationship between the rs5219 polymorphism and susceptibility to T2DM [19–43], whereas 21 studies did not confirm this finding [44–64]. This meta-analysis showed that the rs5219 polymorphism is a risk factor for developing T2DM in Caucasians and in some Asian populations. Populations from East Asia were more prone to this disease, where the A allele frequency in some Asian populations. Populations from East Asia were more prone to this disease, where the A allele frequency in most patients was more common than in controls. Therefore, genetic background can affect susceptibility to T2DM [65].

The rs5219 polymorphism can affect the insulin secretion pathway. The A allele of this locus impairs this pathway by reducing ATP sensitivity of the KATP channel, hence
**Table 1:** Characteristics of KCNJ11 gene variants in association with diabetes mellitus.

<table>
<thead>
<tr>
<th>Number</th>
<th>SNP</th>
<th>Chromosome</th>
<th>Location</th>
<th>Gene</th>
<th>MAF</th>
<th>Allele</th>
<th>Amino acid</th>
<th>Diabetes</th>
<th>Association</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>rs2285676</td>
<td>17386478</td>
<td>3' UTR</td>
<td>—</td>
<td>0.46</td>
<td>T&gt;C</td>
<td>—</td>
<td>T2DM</td>
<td>Yes</td>
<td>[30]</td>
</tr>
<tr>
<td>2</td>
<td>rs5210</td>
<td>17386704</td>
<td>3' UTR</td>
<td>—</td>
<td>0.46</td>
<td>G&gt;A</td>
<td>—</td>
<td>T2DM</td>
<td>Yes</td>
<td>[30, 36, 76]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No</td>
<td>[72, 74]</td>
</tr>
<tr>
<td>3</td>
<td>rs5215</td>
<td>17387083</td>
<td>Exon</td>
<td>0.28</td>
<td>G&gt;A</td>
<td>Val250Ile</td>
<td>T2DM</td>
<td>Yes</td>
<td>No</td>
<td>[27, 30, 35, 36]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>T1DM</td>
<td>No</td>
<td>No</td>
<td>[49, 50, 69–72]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>GDM</td>
<td>No</td>
<td>No</td>
<td>[68]</td>
</tr>
<tr>
<td>4</td>
<td>rs5218</td>
<td>17387522</td>
<td>Exon</td>
<td>0.27</td>
<td>C&gt;T</td>
<td>Ala103Ala</td>
<td>T2DM</td>
<td>No</td>
<td>[36]</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>rs5219</td>
<td>17388025</td>
<td>Exon</td>
<td>0.27</td>
<td>G&gt;A</td>
<td>Lys23Gln</td>
<td>T1DM</td>
<td>No</td>
<td>Yes</td>
<td>[19–43]</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>T2DM</td>
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<td>No</td>
<td>[44–64]</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>GDM</td>
<td>Yes</td>
<td>No</td>
<td>[38]</td>
</tr>
<tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>[66–68]</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>rs886288</td>
<td>17389616</td>
<td>5' near gene</td>
<td>0.46</td>
<td>T&gt;C</td>
<td>—</td>
<td>T2DM</td>
<td>Yes</td>
<td>[36]</td>
<td></td>
</tr>
</tbody>
</table>

MAF: minor allele frequency; T1DM: type 1 diabetes mellitus; T2DM: type 2 diabetes mellitus; GDM: gestational diabetes mellitus; SNP: single nucleotide polymorphism; UTR: untranslated region.

**Figure 1:** ABCC8 and KCNJ11 genes and their encoded proteins and functions. The KCNJ11 and ABCC8 genes are next to each other on chromosome 11p15.1. KCNJ11 is a single exon (dark box) gene encoding the Kir6.2 protein, and ABCC8 has 35 exons (dark boxes) encoding the SUR1 protein; both are subunits of the ATP-sensitive potassium (KATP) channel. Metabolism of glucose can affect ATP levels and thereby the function of the KATP channel. 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.
The calcium channel is composed of α, β, γ, δ, and ε subunits. ATP: adenosine triphosphate; K: inward-rectifier potassium ion channel; SUR1: sulfonylurea receptor; KATP: ATP-sensitive potassium channel; Kir6.2: the insulin secretion pathway to release granules at or near the plasma membrane. Hypertension is a main complication of T2DM. The ring-fused pyrrole moiety in these two drugs binds to the A allele, underling the inhibitory potency of these drugs on KATP channels [41]. The rs5219 polymorphism also plays a role in determining the efficacy of repaglinide [33, 39]. Carriers of the C allele were also found to have a reduced response to sulfonylurea therapy [42, 43].

3.2.2. KCNJ11 rs5215. The rs5215 polymorphism is located in exon 1 of the KCNJ11 gene. It is a nonsynonymous variant caused by a substitution of G to A (GTC → ATC), which changes the amino acid from valine to isoleucine at residue 250. Valine is hydrophobic, whereas isoleucine is one of three amino acids having branched hydrocarbon side chains. Isoleucine is usually interchangeable with leucine and occasionally with valine in proteins. Of 13 studies on DM, 3 showed strong associations between this variant and T2DM [27, 30, 35], whereas the remaining studies showed no association with T2DM, T1DM, or GDM [36, 49–51, 69–74]. In another study, the rs5215 polymorphism was associated with blood pressure among subjects with T2DM [36].

3.2.3. KCNJ11 rs5210. The rs5210 polymorphism is located at a highly conserved 3′ untranslated region (UTR) of the KCNJ11 gene. Of four reports relevant to susceptibility to T2DM, two identified a plausible role in development of this disease, whereas the other studies did not confirm this relationship [30, 36, 72, 75]. A study found that this variant improves the clinical efficacy of gliclazide in patients with T2DM [76]. This locus is a target of miR-1910; however, the mechanism of action of this miRNA in the development of DM is unknown. MiRNAs control insulin synthesis and release in betacells. The G allele is a potential target for miR-1910, whereas the A allele abolishes binding of this miRNA to this region [77, 78]. Further studies may reveal the role of miR-1910 in DM.

3.2.4. KCNJ11 rs5218. The rs5218 polymorphism is located in the 3′-UTR of the KCNJ11 gene. It is a synonymous variant with a substitution of G to A (GCC → GCT), which encodes, for alanine at residue 103, a hydrophobic and ambivalent amino acid. There is only one report of this locus in DM, which showed no association with T2DM risk [36].

3.2.5. KCNJ11 rs886288 and rs2285676. The rs886288 polymorphism is located in the 5′ flank near the gene, whereas the rs2285676 polymorphism is located at the 3′-UTR region. Two studies revealed an association of the rs886288 and rs2285676 polymorphisms with T2DM [30, 36].

3.3. Interaction of the KCNJ11 Gene with Other Genes. Insulin secretion from pancreatic beta cells can be modulated by a complex cluster of proteins encoded by related genes,
including KCNJ11, ABCC8, voltage-sensitive calcium channels (VSCCs), ABCC9, protein kinase catalytic subunit G (PRKACG), rap guanine nucleotide exchange factor 4 (RAPGEF4), forkhead box A2 (FOXA2), and endosulfine alpha (ENSA). These proteins act at the cell membrane or intracellular level (Figure 3).

3.3.1. Interactions at the Cell Membrane Level. KCNJ11 and ABCC8 genes encode Kir6.2 and SUR1, respectively, in pancreatic beta cells. Both proteins form compartments in the KATP channel, which allow potassium to flow across the beta cells. The KCNJ11 and ABCC8 genes interact with three groups of gene products at the cell membrane (white) and the intracellular (dark gray) levels. KATP: ATP-sensitive potassium channel; CACNA1A: calcium channel, voltage-dependent, P/Q type, alpha 1A subunit; CACNA1B: calcium channel, voltage-dependent, N type, alpha 1B subunit; CACNA1C: calcium channel, voltage-dependent, L type, alpha 1C subunit; CACNA1D: calcium channel, voltage-dependent, L type, alpha 1D subunit; CACNA1E: calcium channel, voltage-dependent, R type, alpha 1E subunit; CACNA1G: calcium channel, voltage-dependent, T type, alpha 1G subunit; ABCC9: ATP-binding cassette transporter subfamily C member 9; Kir6.2: inwardly rectifying channel, subfamily J, member 1; ENSA: endosulfine alpha; PRKACG: protein kinase catalytic subunit G; RAPGEF4: rap guanine nucleotide exchange factor 4; FOXA2: forkhead box A2.

3.3.2. Interactions at the Intracellular Level. The KATP channels interact with the PRKACG protein encoded by the PRKACG gene. This protein is the gamma catalytic subunit of protein kinase, which is involved in exocytosis through different pathways such as calcium- and hormone-mediated signaling. This protein also activates cellular processes such as intracellular protein kinase A [81]. Kir6.2 interacts with RAPGEF4, FOXA2, and ENSA proteins, encoded by RAPGEF4, FOXA2, ENSA, and ABCC9 genes, respectively. RAPGEF4 is an exchange protein that can be activated by cAMP. FOXA2 functions as a transcription activator for genes such as alpha-fetoprotein, albumin, and tyrosine aminotransferase. ENSA is an endogenous ligand for SUR1, which stimulates insulin secretion [82–84].

4. Concluding Remarks

DM is one of the most common diseases globally, with high social and economic burdens. Kir6.2 plays a potential role in the function of the KATP channel. Some active mutations in this gene can disrupt Kir6.2 activity and consequently reduce the potential of the KATP channel, leading to DM. It is evident from the literature that several variants of the KCNJ11 gene are associated with different types of DM. This raises the question of which polymorphisms of the KCNJ11 gene and their combinations play more prominent roles in the development of DM.

Most previous studies have focused on six common polymorphisms in DM: rs5210, rs5215, rs5218, rs5219, rs886288, and rs2285676. Of these six loci, rs5219, rs5215, and rs5210 have been given most attention. No evidence yet exists in the literature for the involvement of other SNPs of the KCNJ11 gene. The rs5219 A allele plays an important role in insulin secretion through reduction of ATP sensitivity of the KATP channel and suppression of insulin secretion. However, the mechanism of action of this locus in the insulin secretion pathway is still not completely understood. The rs5210 G allele acts as a potential target for miR-1910, which is implicated in T2DM; however, the mechanism of action of this miRNA in the development of DM is unknown. MirRNAs control insulin synthesis and release from beta cells. Future studies are suggested to reveal the use of miR-1910 as a potential
biodmarkert in the diagnosis of diabetes and its plausible application for treatment of DM.

Regulation of insulin release is mediated by KCNJ11 in concert with different genes such as ABCC8, ABCC9, and CACNA1A-G. Diminished coexpression of these genes may increase the risk of DM. Nevertheless, the exact functional relationship of the network of these genes in the regulation of insulin release remains to be determined. Future studies are suggested to discover the exact role of KCNJ11 gene variants and their interaction with other genes in DM for the possible development of suitable therapies and the diagnosis of this common disease.

**Conflict of Interests**

The authors declare that there is no conflict of interests regarding the publication of this paper.

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