A CASE OF PLAGIARISM

Pharmacologia editorial office received a complaint from Batoul Sadat Haerian, Pharmacogenomics Lab, Department of Pharmacology, Faculty of Medicine, University of Malaya, 50603 Kuala Lumpur, Malaysia about a plagiarism of her paper published in Pharmacologia Volume 6 Number 5: 149-159, 2015.

On the receipt of her complaint, the case forwarded to the Ethics Committee of the Pharmacologia. As per the report of the Ethics Committee, article entitled “Role of KCN11, Gene Polymorphism and Risk of Type 2 Diabetes Mellitus” authored by M. Akhtaruzzaman, M.S.Islam, M.M.R.Howlader, M.M.hossain and M.SD. Islam published in Pharmacologia Volume 6 Number 5: 149-159, 2015 contains substantial sections of text that have been taken verbatim from earlier publication without clear and unambiguous attribution. The corresponding author of this article is M.Akhtaruzzaman, Pharmacogenomics Lab., Department of Pharmacology, Faculty of Medicine, University of Malaya, 50603 Kuala Lumpur, Malaysia.

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Plagiarism is a violation of copyright and a serious breach of scientific ethics. The Editors and Publisher have agreed to officially retract this article.

Pharmacologia is highly thankful to Batoul Sadat Haerian for pointing out this plagiarism.

Detail of the article from which M. Akhtaruzzaman has copied text:

Final Decision: Ethics Committee strongly condemns the act of plagiarism committed by M.Akhtaruzzaman and suggested to retract the paper immediately and also suggested to communicate this to the higher authorities of the corresponding author for suitable action according to their rules and regulations.
Role of KCNJ11 Gene Polymorphisms and Risk of Type 2 Diabetes Mellitus


ABSTRACT

Diabetes Mellitus (DM) is a major fast growing epidemic 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. Type 2 Diabetes Mellitus (T2DM) is a genetically heterogeneous disease, with several relatively rare monogenic forms and a number of more common forms resulting from a complex interaction of genetic and environmental factors. 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 forms 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 T2DM. This review discusses the current evidence for the contribution of common KCNJ11 genetic variants to the development of T2DM. Future studies should concentrate on understanding the exact role played by these risk variants in the development of T2DM.

Key words: Type 2 diabetes mellitus, KCNJ11, polymorphism

INTRODUCTION

Diabetes Mellitus (DM) is a common lifelong health condition. Diabetes Mellitus (DM) is a chronic metabolic diseases characterized by high blood glucose levels caused by either insufficient insulin production by the pancreas or improper response of the body cells to insulin. Diabetes mellitus type 2 (formerly non-insulin-dependent diabetes mellitus (NIDDM) or adult-onset diabetes) is a metabolic disorder due to hyperglycemia in the context of insulin resistance and relative lack of insulin. This is in contrast to Type 1 Diabetes Mellitus (T1DM), in which there is an absolute lack of insulin due to the breakdown of islet cells in the pancreas.

The prevalence of T2DM is growing exponentially in Western countries and the incidence of this condition is today increasing worldwide. Approximately, 366 million people were diagnosed with DM in the world in 2011 and it will increase to 552 million by 2030. This disease has early and late-stage complications. Early complications include hyperglycemia, polyphagia, polydipsia, polyuria and blurred vision, leading to complications manifested later such as vascular disease, heart disease, stroke, peripheral neuropathy, nephropathy and predisposition to infection. The DM is classified into various types, of which type 2 (T2DM) occurs most frequently. Approximately more than 90% of patients are affected by T2DM. T2DM is contributed by a complex interaction between genetic
condition and environment. Physical inactivity, sedentary lifestyle, smoking, unhealthy diet, overweight and obesity are the most important factors contributing to development of T2DM. Obesity is thought to be the primary cause of type 2 diabetes in people who are genetically predisposed to the disease. For example, obesity is a major role in approximately 55% of all diagnosed cases of T2DM worldwide6 or young obese adults are more susceptible to T2DM7. Early detection and treatment strategies can prevent development of T2DM and allows a better surveillance of the carriers. Genetic condition in T2DM includes monogenic and polygenic mutations. Monogenic mutations in single gene can change the structure and subsequently the protein’s function. The monogenic forms of T2DM is rare occurring in 1-5% of T2DM cases, in which the body loses its ability to produce or secret insulin hormone8. In contrast, polygenic or non-pathogenic mutations are the most common form of T2DM. These genes in concert with environmental factors play an important role in development of this disease. Amongst the non-pathogenic mutations, Single Nucleotide Polymorphisms (SNPs) in the coding or non-coding regions of the genes, alone or in combination can develop various diseases, including T2DM. SNPs in the exons may change amino acids or loci in the promoter may affect the gene expression. 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 of T2DM. Finally, the role of KCNJ11 polymorphisms with particular emphasis on six common SNPs as well as interaction of this gene with other genes in development of T2DM was highlighted.

PATHOPHYSIOLOGY OF TYPE 2 DIABETES MELLITUS

Type 2 diabetes is due to insufficient insulin production from beta cells in the setting of insulin resistance. Insulin resistance which is the inability of cells to respond adequately to normal levels of insulin, occurs primarily within the muscles, liver and fat tissue11,12 and has identified alpha-cell function in the pathophysiology of T2DM13. In the liver, insulin normally suppresses glucose release (Fig. 1).

However, in the setting of insulin resistance, the liver inappropriately releases glucose into the blood14. The proportion of insulin resistance versus beta cell dysfunction differs among individuals, with some having primarily insulin resistance and only a minor defect in insulin secretion and others with slight insulin resistance and primarily a lack of insulin secretion15. Uniformly impaired genes in the hormone insulin secretion are observed in T2DM patients in every ethnic community15. At the beginning of the natural history regarding T2DM, insulin resistance is usually more developed but glucose threshold stays regularly as a result of the compensatory rise in insulin secretion. This discussion between insulin secretion and insulin resistance continues to be extensively recorded. In addition, within the regular glucose tolerant populace, around 20-25% of people tend to be severely resistant against the particular simulator impression of blood insulin on glucose uptake and the subject matter in the lowest quartile is associated with blood insulin resistance as T2DM16. The actual history associated with T2DM started with regular glucose tolerance, insulin resistance and compensatory hyperinsulinemia along with progression to Impaired Glucose Tolerance (IGT)16.

ROLE OF GENETICS IN THE DEVELOPMENT OF TYPE 2 DIABETES MELLITUS

T2DM is a multi-factorial disease influenced by both genetic and environmental factors. People with a family history of T2DM have more six and three times higher risk of developing this disease than unrelated individuals, respectively18,19. More than 70% of T2D risk has been attributed to genetics, with multiple genes involved and different combinations of genes playing roles in different subsets of individuals are involved in T2DM20. Those that have garnered the most attention are the ATP-binding 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 conditions21. Mutations in genes such as ABCC8 and KCNJ11 can disrupt the potentiation activity of the KATP channel and have thus been associated with T2DM22. 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 insulin23. From recent genome-wide association...
studies, more than 60, 500 and 65 loci have been identified for susceptibility to T2DM. 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. 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, theGlu23Lys polymorphism in the KCNJ11 gene or the Ser1369Ala polymorphism in the ABCC8 gene was confirmed to be associated with T2DM.

STRUCTURE, FUNCTION AND MECHANISM OF ACTION OF KCNJ11 GENE

The KCNJ11 (potassium inwardly-rectifying channel, subfamily J, member 11) gene, a member of the potassium channel gene family, is located at 11p15.1 and has no intron (Fig. 2).

This gene encodes an inward-rectifier potassium ion channel (Kir6.2). The encoded protein which has a greater tendency to allow potassium to flow into a cell rather than out of a cell, is controlled by G-proteins and is found to be associated with the sulfonylurea receptor SUR. 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.

ROLE OF KIR6.2 IN INSULIN SECRETION

The Kir6.2 protein, coupled with the SUR1 protein in the KATP channel, mediates insulin secretion. This
Fig. 2: ABCC8 and KCNJ11 genes and their encoded proteins and functions

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 leading to closure of the voltage-dependent calcium channels. Increased intracellular free Ca2+ levels trigger other components of the insulin secretion pathway to release granules at or near the plasma membrane (Fig. 3).

Mutations in the KCNJ11 gene can cause T2DM 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 T2DM.

KCNJ11 COMMON POLYMORPHISMS INVOLVED IN TYPE 2 DIABETES MELLITUS

KCNJ11 has 219 SNPs, six of which have been receiving more attention for their association with T2DM. 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.
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 protein29,93. 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 T2DM30-54 whereas 21 studies did not confirm this finding55-75. 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 most patients was more common than in controls. Therefore, genetic background can affect susceptibility to T2DM. 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 resulting in over activity of the channel and subsequent suppression of insulin secretion. This effect on insulin secretion is more significant in carriers of the AA genotype compared with carriers of the GA genotype41. The A allele increased the fasting plasma glucose and postprandial plasma glucose levels in these patients, whereas GA carriers had higher 2 h postprandial plasma glucose levels than did GG carriers with T2DM43,49. This allele was also associated with reduction in serum insulin levels in a postoral glucose tolerance test50. Hypertension is a main complication of T2DM. The rs5219 polymorphism plays a strong role in HbA1c and blood pressure levels in this disease44,46,47,51,52. A study found that this variant improves the clinical efficacy of gliclazide in patients with T2DM84. MiRNAs encompass 17-25 nucleotides which post transcriptionally regulate the expression of thousands of genes in a broad range of organisms in both normal physiological and disease contexts. Appropriate secretion of insulin from pancreatic beta cells is a vital factor in blood glucose homeostasis and miRNAs have been identified as being involved in the regulation of insulin exocytosis. MiRNAs control insulin synthesis and release it in beta cells. The G allele is a potential response to gliclazide than do G allele carriers. In the A allele group, HbA1c was also reduced more in patients taking glimepiride and glibenclamide than it was in patients taking gliclazide treatment61. The rs5219 polymorphism also plays a role in determining the efficacy of repaglinide44,50. Carriers of the C allele were also found to have a reduced response to sulfonylurea therapy33,34.

Rs5215: The rs5215 polymorphism is located in exon 1 of the KCNJ11 gene. It is a non-synonymous 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 T2DM47,93, whereas the remaining studies showed no association with T2DM46,51,52. In another study, the rs5215 polymorphism was associated with blood pressure among subjects with T2DM47,93.

Rs5210: The rs5210 polymorphism is located at a highly conserved 3’ untranscribed 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 relationship31,47,80,93. A study found that this variant improves the clinical efficacy of gliclazide in patients with T2DM44. MiRNAs encompass 17-25 nucleotides which post transcriptionally regulate the expression of thousands of genes in a broad range of organisms in both normal physiological and disease contexts. Appropriate secretion of insulin from pancreatic beta cells is a vital factor in blood glucose homeostasis and miRNAs have been identified as being involved in the regulation of insulin exocytosis. MiRNAs control insulin synthesis and release it in beta cells. The G allele is a potential...

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Table 1: Characteristics of the KCNJ11 gene variants in association with type 2 diabetes mellitus

<table>
<thead>
<tr>
<th>Polymorphism</th>
<th>Chromosome</th>
<th>Chromosome</th>
<th>Gene</th>
<th>MAF</th>
<th>Allele</th>
<th>Amino acid</th>
<th>Diabetes</th>
<th>Association</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs2285676</td>
<td>11p15.1</td>
<td>1738678</td>
<td>3' UTR</td>
<td>0.46</td>
<td>T&gt;C</td>
<td>-</td>
<td>T2DM</td>
<td>Yes</td>
<td>41, 93</td>
</tr>
<tr>
<td>rs5210</td>
<td>11p15.1</td>
<td>17386704</td>
<td>3' UTR</td>
<td>0.46</td>
<td>G&gt;A</td>
<td>-</td>
<td>T2DM</td>
<td>Yes</td>
<td>41, 47, 84, 93</td>
</tr>
<tr>
<td>rs5215</td>
<td>11p15.1</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>38, 41, 46, 47, 93</td>
</tr>
<tr>
<td>rs5218</td>
<td>11p15.1</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>38, 41</td>
</tr>
<tr>
<td>rs5219</td>
<td>11p15.1</td>
<td>17388025</td>
<td>Exon</td>
<td>0.27</td>
<td>G&gt;A</td>
<td>Lys23Gln</td>
<td>T2DM</td>
<td>Yes</td>
<td>38, 41, 46, 47, 93</td>
</tr>
<tr>
<td>rs886288</td>
<td>11p15.1</td>
<td>17389616</td>
<td>5' near gene</td>
<td>0.46</td>
<td>T&gt;C</td>
<td>-</td>
<td>T2DM</td>
<td>No</td>
<td>30-54, 93</td>
</tr>
</tbody>
</table>

MAF: Minor allele frequency, T2DM: Type 2 diabetes mellitus, SNP: Single nucleotide polymorphism and UTR: Untranslated region.
target for miR-1910, whereas the A allele abolishes binding of this miRNA to this region\textsuperscript{85,86}. Further studies may reveal the role of miR-1910 in T2DM.

**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 association with T2DM risk\textsuperscript{47}.

**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\textsuperscript{41,47}.

**INTERACTION OF 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 (Fig. 4).

**Gene interaction 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 channels which allow potassium to flow into the cell rather than out of it, as mediated by G proteins\textsuperscript{28}. The KATP channel interacts with different types of VSCCs, including L (long-lasting), N (neural), P/Q (purkinje), R (residual) and T (transient). Calcium channels are generally composed of four subunits: α1, α2-δ, β and γ. The function of the calcium channel is controlled by the pore-forming α1 subunit which blocks the entry of calcium ions into the excitable cells and by the auxiliary subunits which modulate trafficking and the biophysical properties of the α1 subunit. The α1 subunit isoforms include A, B, C, D, E and G, encoded by CACNA1A, CACNA1B, CACNA1C, CACNA1D, CACNA1E and CACNA1G genes, respectively. The A to E forms of the α1 subunit produce various types of calcium channels, including L/P, N, L, L, R and T, respectively. The L, N, P/Q and R types of these channels belong to the high-voltage activated (HVA) group and the T type belongs to the Low Voltage Activated (LVA) group. Both HVA and LVA groups are involved in calcium-dependent processes such as neurotransmitter or hormone release, muscle contraction, cell motility, gene expression, cell division and cell death\textsuperscript{86,87}. Finally, Kir2 and ABCC9 can form another type of KATP channel in cardiac, skeletal, vascular and nonvascular smooth muscle. The structure of the ABCC9 protein suggests a role as a drug binding, channel-modulating subunit of the extra pancreatic KATP channels\textsuperscript{88}.

**Gene interaction 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\textsuperscript{89}. 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\textsuperscript{90-92}. Defects in the KCNJ11 gene may also lead to autosomal-dominant T2DM\textsuperscript{93}.

**CONCLUSION**

DM is one of the most common disease 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 T2DM. It is evident from the literature that several variants of the KCNJ11 gene are associated with T2DM. This raises the question of which polymorphisms of the KCNJ11 gene and their combinations play more prominent roles in the development of T2DM. Most previous studies have focused on six common polymorphisms in T2DM: rs5210, rs5215, rs5218, rs5219, rs886288 and rs2285676. Of these six loci, rs5219, rs5215 and rs5210 have been given most attention. Future studies are suggested to reveal the use of miR-1910 as a potential biomarker in the diagnosis of diabetes and its plausible application for treatment of T2DM. 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 T2DM. Future studies are suggested to discover the exact role of KCNJ11 gene variants and their interaction with other genes in T2DM for the possible development of suitable therapies and the diagnosis of this common disease.

REFERENCES


