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Variants and Combined Genotypes Frequencies of GCKR rs780094 and KCNQ1 rs2237892 in Type 2 Diabetes Patients in Indonesia Urban Area

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Abstract: Introduction: Type 2 Diabetes (T2D) is chronic metabolic disorder that has genetic component. Single Nucleotide Polymorphism (SNP) is the variation single position in DNA sequence among individuals. Glucokinase Regulatory Protein (GCKR) and Potassium Voltage-Gated Channel Subfamily Q (KCNQ1) are SNP genes. The risk or cytosine (C) allele in gene variant GCKR rs780094 and KCNQ1 rs2237892 were associated with incidence of T2D in Asian-Caucasian populations. The aim of this study was to determine frequency of those gene variants and combined genotype in T2D patients in urban area in South Tangerang, Indonesia. Methods: Fifty-four T2D subjects were identified SNP genes using real time Polymerase Chain Reaction techniques. Results: Frequency C allele in GCKR rs780094 was 54.63% and the most common genotype was heterozygous (CT) 46.3%. Frequency of non-risk (T) allele in KCNQ1 rs223792 was 62.03% with the highest homozygous non-risk (TT) genotype 50%. The most common genotype in GCKR and KCNQ1 control group were CT 55%. The highest frequency of combined genotype was CT/TT 25.92%. Conclusion: Gene variant GCKR rs 780094 had more risk allele (C) in T2D patients in urban area in South Tangerang, Indonesia with the most common genotype CT while KCNQ1 rs2237892 had more non-risk alleles (T) with most common genotype TT. The most abundant genotype for GCKR rs780094 and KCNQ1 rs2237892 in control group were CT and the highest frequency of combined genotype was CT/TT.

Keywords: Type 2 Diabetes Mellitus, Variant Gene, Combined Genotype, GCKR rs 780094, KCNQ1 rs223782

1. Introduction

Type 2 Diabetes (T2D) is a chronic metabolic disorder characterized by high blood sugar levels due to insulin resistance [1]. Patients usually have classic symptoms including polyuria, polydipsia, polyphagia, and unexplained weight loss [2]. This condition is occurs due to interaction between environmental factors, lifestyle, epigenetics, and genetic predisposition [3]. Genetics, as an unmodifiable aspect of this disease, is an important component of the prevalence of T2D. This disorder increases by about 70 to 90% in identical twins. Likewise individual with a parental history have an increased risk of developing diabetes by 40%. However, T2D does not consist of a single gene defect, as supported by the unrecognized inheritance Mendelian pattern [3]. A gene is specific sequence consisting of a combination of four nucleotide bases that encodes information at a chromosomal locus and becomes a specific characteristic that is passed down from parents to children [4].

Alleles are a pair of alternative forms of a gene at a locus, and each individual has a pair for each gene from both parents [5]. Meanwhile, the genetic variation of single position in a DNA sequences at a specific genome among individuals is known as Single Nucleotide Polymorphism (SNP). When a gene has SNP variations, this implies that it has more than one type of allele. Certain alleles at specific gene locations are associated with the incidence of type 2 DM [6, 7].

The Glucokinase Regulatory Protein (GCKR) and Potassium Voltage-Gated Channel Subfamily Q Member 1 or KCNQ1 are two SNP genes that have a risk allele, namely cytosine (C) and a non-risk allele, thymine (T) and there are 3 genotypes (CC, CT, TT).

Previous studies showed that variant gene GCKR rs780094 and KCNQ1 rs2237892 have consistently been associated with the incidence of type 2 DM in various populations [4-14]. The GCKR (glucoinase regulatory protein) gene encodes a protein belonging to the SIS (Sugar Isomerase) subfamily and also regulates the activity of glucokinase (GCK), an enzyme that plays an important role in insulin secretion. The product of this gene is a regulatory protein that inhibits the glucokinase enzyme in liver cells and pancreatic islet cells of Langerhans which binds non-covalently to form an inactive complex with this enzyme [8, 9, 14, 15]. The process of insulin secretion begins when glucose enters pancreatic beta cells through GLUT 2, a glucose transporter, and then phosphorylated by glucokinase (GCK). After the phosphorylation, further metabolism occurs including glycolysis, Krebs cycle, and oxidative phosphorylation in mitochondria which causes an increase in ATP in the cytoplasm. This leads to the closure of ATP-gated K+ (ATP-dependent potassium channel), thereby causing accumulation of positive charge inside the cell and the depolarization of the cell membrane. Furthermore, voltage-dependent calcium channels open, allowing calcium to enter the cell and stimulate insulin release through exocytosis [11-13].

The inactivation of the glucokinase enzyme by GCKR inhibits aerobic metabolism which aims to produce ATP for beta-cell depolarization. Consequently, the calcium channels are not opened and insulin secretion is inhibited. The C allele in GCKR rs790094 is assumed to elevate the expression of GCKR protein which potentially interferes with insulin secretion, hence, this gene polymorphism is considered to increase the susceptibility to the incidence of type 2 DM in various populations [13]. Details of the GCKR mechanism in insulin secretion are shown in Figure 1.

Another protein that regulates the depolarization of pancreatic beta cells is the K+ ion channel. Beta cells have various types of potassium ion (K+) channels, an example is Kv7.1 (Kv LQT1) which distributed in various tissues in the body and have an important role in the physiological functions of the body's organs, including assisting the K+ ATPase channel in depolarizing beta cells. Most of the channel subunits are encoded by the Potassium Voltage-Gated Channel Subfamily Q Member 1 (KCNQ1) gene. Polymorphisms in this gene, particularly in rs2237892 are presumably associated with increased expression of Kv7.1. This potentially causes premature repolarization of beta cells and interfere with insulin secretion [16, 17].

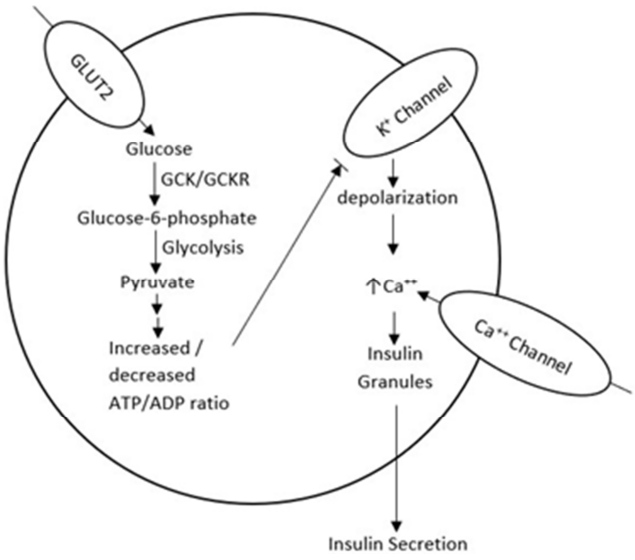

Figure 1. *The GCKR Mechanism in Insulin Secretion.*

Based on the role of gene polymorphisms to increase the incidence of T2D, this study aims to determine the frequency of GCKR rs780094 and KCNQ1 rs2237892 genes and those combined genotype in T2D patients in the South Tangerang, one of urban area Indonesia.

2. Method

This study used a cross-sectional design and the data were presented in a descriptive form. The inclusion criteria were T2D patients medically examined at the South Tangerang Health Center in collaboration with the Faculty of Medicine, Universitas Islam Negeri (UIN) Syarif Hidayatullah Jakarta, and willing to participate as subjects. In contrast, the exclusion criteria include patients who did not fast before the examination. The diagnostic criteria based on the Guidelines for the Management and Prevention of type 2 DM for Adults 2019 (PERKENI 2019) are: (1) fasting blood sugar with no minimum calorie intake for 8 hours of 126 mg/dL, (2) random blood sugar of 200 mg/dL with classic DM symptoms such as polyuria, polydipsia, polyphagia, and unexplained weight loss, (3) blood sugar of 200 mg/dL after 2 hours of Oral Sugar Tolerance Test (OGTT) according to the WHO standard with an anhydrous glucose load of 75 grams dissolved in water, and (4) examination of HbA1c 6.5% using the standard method by the National Glycohaemoglobin Standardization Program (NGSP).

For the examination of Single Nucleotide Polymorphism (SNP) GCKR and KCNQ1, DNA samples were obtained by taking 5 ml of blood placed in an ethylenediaminetetraacetic (EDTA) tube. The sample was isolated and DNA extraction was performed using Tissue/Blood DNA Mini Kit (GS100, GS300) DNA Extraction/Genomic DNA Purification from

Geneaid. Furthermore, the isolates were tested for purity and concentration using a Nano-spectrophotometer, while the purity and concentration results of the DNA extract were stored in a -20°C freezer until polymerase chain reaction (PCR) and genotyping were carried out. Meanwhile, to detect the presence of SNPs in the sample, the LightCycler II 480 Roche Instrument real time PCR was used. The GCKR and KCNQ1 genotypes were examined with the Rhamp-SNP Genotyping IDT Kit for rs780094 and rs2237892.

All patients received a detailed explanation of the study and obtained informed consent according to the format provided by the Ethics Committee. This study was approved by the Research Ethics Committee, Faculty of Medicine, Universitas Islam Negeri (UIN) Syarif Hidayatullah Jakarta number B-030/F12/KEPK/TL.00/9/2020.

3. Result and Discussion

From a total of 54 subjects, the average age was 43 ± 16 years, while 90.7% were female and 9.3% were male. The patients' characteristics are shown in Table 1.

Table 1. *Characteristics of the patients.*

Variable	Frequency (n=54)	Percentage (%)
Age		
27-37	3	5.5
38-48	34	63
49-59	17	31.5
Sex		
Male	5	9.3
Female	49	90.7

Referring to Table 2, the results showed that most of the subjects had the risk or C allele in the GCKR rs780094 gene, which was 54.63% while the majority in the KCNQ1 rs12237892 gene had the the non-risk or T allele at 62.03%.

Table 2. *Allele Frequency of GCKR rs780094 and KCNQ1 rs2237892 in T2D patients.*

	C n (%)	T n (%)
GCKR	59 (54.63)	49 (45.37)
KCNQ1	41 (37.96)	67 (62.03)

* C = Cytosine; T= Thymine; GCKR= Glucokinase Regulator Gene; KCNQ1= Potassium Voltage-Gated Channel Subfamily Q Member 1.

Table 3. *Genotype Frequency of GCKR rs780094 and KCNQ1 rs2237892 in T2D patients and controls.*

	T2D n (%)	Control n (%)
GCKR		
CC	17 (31.5)	4 (20)
CT	25 (46.3)	11 (55)
TT	12 (22.2)	5 (25)
KCNQ1		
CC	14 (25.9)	5 (25)
CT	13 (24.1)	11 (55)
TT	27 (50)	4 (20)

* CC = Homozygous risk allele; CT = Heterozygous; TT = Homozygous nonrisk allele; GCKR = Glucokinase Regulator Gene; KCNQ1 = Potassium Voltage-Gated Channel Subfamily Q Member 1.

Table 3 showed the genotype frequencies for each gene, the most common genotype in the GCKR rs780094 gene in patients with diabetes was heterozygous CT at 46.3%, while homozygous non-risk (TT) was the most common genotype for KCNQ1 rs2237892 gene at 50%, although the homozygous risk allele (CC) also had a fairly high frequency at 25,9%.

In control group, the most common genotype in the GCKR rs780094 was heterozigous (CT) at 55%, remaining 25% for TT homozygous non risk alleles and 20% for homozygous risk allele (CC). Meanwhile, the most common genotype for KCNQ1rs2237892 was homozygous non-risk (CT) at 55%, remaining 25% for CC and 20% for TT alleles. The main combination genotype or the most common in the GCKR rs780094 and KCNQ1 rs2237892 genes was CT/TT at 25.92% as shown in Table 4.

Table 4. *Combined Genotype GCKR rs780094/KCNQ1 rs2237892 Frequency in T2D Patients.*

GCKR	KCNQ1	n (%)
CC	CC	5 (9.26)
	CT	6 (11.11)
	TT	6 (11.11)
CT	CC	4 (7.41)
	CT	7 (12.96)
	TT	14 (25.92)
TT	CC	5 (9.26)
	CT	0 (0)
	TT	7 (12.96)

* CC = Homozygous risk allele; CT = Heterozygous; TT = Homozygous nonrisk allele; GCKR = Glucokinase Regulator Gene; KCNQ1 = Potassium Voltage-Gated Channel Subfamily Q Member 1.

Based on this results, the GCKR rs780094 gene variant were consistently associated with the occurrence of T2D patients in South Tangerang one of urban area in Indonesia. Previous studies showed a significant association between GCKR rs780094 gene variant and the occurrence of T2D in Chinese population such as Zhou et al. in Luoyang ($p<0.04$), Ling Y, et al. in Southern Han ($p<0.002$), and Hu C, et al. in Shanghai. Furthermore, Jamalpour S, et al. also found a significant association of T2D in a population in Kuala Lumpur, Malaysia ($p<0.006$) [13, 14]. These previous studies were similar with the results of this study which found that the gene variant GCKR rs780094 had more C or risk alleles than T or non-risk alleles in T2D patients.

Meanwhile, there was a moderate association in KCNQ1 rs2237892 gene with the incidence of T2D with in the Malaysian population (p 0.017) [12]. Other studies conducted on Chinese, Indian, and the Thai populations showed a significant association between the risk or C allele KCNQ1 rs223792 with T2D [18, 19]. Similarly, study in Korea also showed that the C allele had a significant association with the incidence of T2D ($p<0.003$) [20]. In contrast to the South and East Asian population, a study carried out in Iran did not show a significant association between the C allele and T2D. Similarly, studies conducted in Turkey, Saudi Arabia, and Azerbaijan, found no significant association between the C allele of the KCNQ1 rs2237892 variant and the incidence of T2D [21-24].

The results of this study showed the non-risk or T allele KCNQ1 rs2237892 was more commonly found in the subjects compared to C allele, as reported in Turkey, Iran, Saudi Arabia and Azerbaijan. However, there has been no meta-analysis specifically conducted to investigate the correlation between the variation of rs2237892 with aspects of ethnicity. The results showed with heterozygote variant, we were analysing sequence to re-check the position and accuracy of variant of Rhamp SNP Genotyping kit. In here we found double nucleotide C/T for GCKR rs780094 and T/A for KCNQ1 rs2237892. According to a study carried out in Japan in the form of the Genome-Wide Association Study (GWAS), an approach used in genetic studies to associate specific genetic variation with particular diseases, 41 different locus genes were associated with the incidence of T2D, but the GCKR rs780094 and KCNQ1 rs2237892 gene variants were strongly correlated with the condition in the Japanese population. Both have variations in introns with odds ratio (95% CI) GCKR rs780094 of 1.06 (1.04-1.08), and KCNQ1 rs2237892 of 1.43 (1.34-1.52). Other studies reported the effect of nucleotide changes in rs 780094 on the GCKR expression process. It is thought that mutation affects an imbalance or disequilibrium with other genes responsible for glucose or tri-glyceraldehyde levels in cells [25, 26]. Similar with rs2237892 for KCNQ1, the mutation that occurred was an intragenic substitution in the KCNQ1 gene. This gene, part of KCNQ, is responsible for calcium channel protein synthesis. Similar with intron mutations in GCKR, these changes have an effect on transcriptional initiation, and have no direct effect in calcium channel protein synthesis. Intron mutations will play a direct role in the transcription process and also an important position in the transcription process or the splicing between exons. This condition also shown in mutation occurs in the globin gene in thalassemia patients. Introns will affect the quantity of synthesized globin protein in thalassemia mutations [27].

Considering that KCNQ1 rs2237892 has a weak correlation with the incidence of T2DM in European populations, ethnicity could be another factor that affects genetic variation [28]. The pattern of inheritance of DM2 is still unclear, whether it is inherited in an autosomal dominant or autosomal recessive manner. Generally, individuals with DM2 have at least one close family member, whether their parents or siblings. However, the risk of developing DM2 will increase with the number of family members suffering from the same disease. This increase is not only caused by mutations in the same gene, but also by the same lifestyle by members of the same family.

In this study, the highest genotype for the GCKR rs780094 gene was heterozygous CT while the most common for the KCNQ1 rs2237892 was homozygous non-risk (TT), although the homozygous risk allele (CC) genotype also had a fairly high frequency at 25.9%. The most abundant genotype for gene variant GCKR rs780094 and KCNQ1 rs2237892 in control group was heterozygous (CT) allele at 55%, while homozygous risk allele (CC) was 20% in gene variant GCKR rs780094 and 25% in gene variant KCNQ1 rs2237892. This study also showed the most common genotype in gene variant GCKR rs780094 in T2D patients was heterozygous (CT) but lower than control, meanwhile most common genotip in gene variant KCNQ1 rs2237892 was homozygous non risk (TT) allele but higher than control.

The most common combined genotype of GCKR rs780094 and KCNQ1 rs2237892 was CT/TT at 25,92%, followed by genotype combination of CT/CT (12,96%), TT/TT (12,96%), CC/CT (11.11%), CC/TT (11.11%), TT/CC (9.26%), CC/CC (9.26%), and CT/CC (7.41%).

Type 2 diabetes is affected by various factors such as lifestyle, environment, and associated with multiple gene or polygenic, therefore, individual susceptibility to this condition is presumably influenced by different gene polymorphisms. In this study, the GCKR rs 780094 gene had the highest frequency of risk or C allele in subjects with T2D compared to the KCNQ1 rs2237892 gene that had more non-risk or T alleles.

From the results of our research, it is recommended to carry out the same study in a larger population and several different areas for better understanding of variants and combined genotypes frequencies of GCKR rs780094 and KCNQ1 rs2237892 in T2D patients considering that the number of T2D patients in Indonesia are quite high. In addition, it is necessary to consider about variants of other genes that are also probably interrelated in TD2M patients in Indonesia, for example, GCKR rs8179206, GCKR rs2293572, KCNQ rs2237895 and KCNQ rs2237897, as some studies showed that these genes have correlation to KCNQ1 and GCKR in TD2M patients in China [7, 18]. As Indonesia still has close genetic pattern with China, it is possible to have the same correlation between these genes, although this issue will require another scientific evidence the future.

4. Conclusion

Gene variant GCKR rs780094 had more C or risk alleles while KCNQ1 rs2237892 had more T or non-risk alleles in T2D patients in urban area South Tangerang, Indonesia. The most abundant genotype in the GCKR rs780094 was heterozygous (CT) allele, and the most common genotype in KCNQ1 rs2237892 was homozygous non-risk (TT) allele, while in the control group the most abundant genotype for GCKR rs780094 and KCNQ1 rs2237892 were heterozygous (CT) allele, which had higher frequency than T2D patients in gene variant GCKR rs780094 but had lower frequency than T2D patients in gene variant KCNQ1 rs2237892. The highest combined genotype of GCKR/KCNQ1 was CT/TT. From the results of our research, it is recommended future study in expressing the relationship between rs780094 and rs2237892 with T2D in larger population. However, this study can provide information in the relationship between gene and T2D in Indonesia. In addition, it is necessary to consider and think about the existence of other genes that are also interrelated with the possibility of the occurrence of T2D in Indonesia.

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Biography

Hari Hendarto is an Internist and Consultant in Endocrinology, Metabolic and Diabetes at the community teaching hospital. He is also a Clinical Lecturer and Researcher at the Faculty of Medicine, UIN Syarif Hidayatullah Jakarta. He earned his Ph.D degree from Kyushu university, graduate School of Medical Sciences, Fukuoka, Japan. He was trained in endocrinology at National University Hospital (NUH), Singapore. He has special interest in the research area of Diabetes, thyroid diseases, metabolic disease etc.

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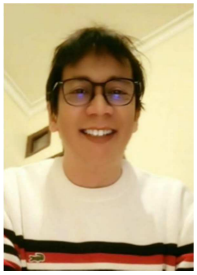

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