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## Potassium Inwardly Rectifying Channel Subfamily J Member 11 (KCNJ11) RS5219 Gene Polymorphism as a Risk Factor for Type 2 Diabetes Mellitus in Indonesia: A Case Control Study

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### ABSTRACT

**Background:** Diabetes Mellitus (DM) is a chronic metabolic disease caused by the failure of the pancreas to produce the hormone insulin or ineffective use of the hormone insulin. It is estimated that 537 million adults aged 20-79 years worldwide suffer from DM. Genetics is one of the risk factors involved in the pathophysiology of type 2 DM. The KCNJ11 gene encodes the Kir6.2 protein that is responsible for adenosine triphosphate-sensitive potassium ion channels (kATP) synthesis in pancreatic beta cells plasma membrane.

**Aims:** This study aims to examine the KCNJ11 rs5219 gene polymorphism as a risk factor for type 2 diabetes mellitus in Cirebon population.

**Methods:** This case control study involved 29 cases of type 2 diabetes mellitus and 29 healthy controls with purposive sampling technique. Sample data was obtained through the examination of blood sugar, DNA extraction, PCR-RFLP with Eco24I restriction enzyme, then visualization of the results with Gel Electrophoresis.

**Results:** The frequency of G allele was found more in the case group (70%) while the frequency of A allele was found more in the control group (38%). The frequency of heterozygous GA genotype was found more in the control group (48.3%) and the frequency of homozygous mutant AA genotype was more in the case group (17.2%) compared to the control group (13.8%). Chi-Square Test results obtained p-value 0.115, OR value 2.318.

**Conclusion:** This study showed no significant association between Potassium Inwardly Rectifying Channel Subfamily J Member 11 (KCNJ11) rs5219 gene polymorphism and the incidence of Type 2 Diabetes Mellitus in Cirebon population.

**Keywords:** *KCNJ11 gene; rs5219 polymorphism; Type 2 diabetes mellitus.*

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## 1. Introduction

Type 2 Diabetes Mellitus (T2DM) is one of the most prevalent chronic diseases worldwide, characterized by insulin resistance, impaired insulin secretion, and hyperglycemia. In recent decades, T2DM has emerged as a major public health challenge in many countries, including Indonesia, where the disease burden has significantly increased. According to the International Diabetes Federation (IDF), the prevalence of diabetes in Indonesia continues to rise, driven by factors such as an aging population, urbanization, sedentary lifestyles, and dietary changes. Despite the clear association with lifestyle and environmental factors, it is now well-established that genetic predisposition plays a crucial role in the development of T2DM. Genetic factors, specifically gene polymorphisms, have been identified as potential contributors to the susceptibility and pathophysiology of T2DM. Among these genetic determinants, the KCNJ11 gene polymorphism, particularly the RS5219 variant, has gained attention for its potential involvement in the onset and progression of T2DM. The KCNJ11 gene encodes for the inwardly rectifying potassium channel subfamily J member 11 (KATP channel), which plays a critical role in the regulation of insulin secretion from pancreatic beta cells. The functional importance of KCNJ11 lies in its ability to mediate potassium ion flow across cell membranes, contributing to the regulation of electrical activity and the maintenance of cellular excitability in response to glucose stimulation. Mutations or polymorphisms within the KCNJ11 gene, such as the RS5219 variant, may alter the function of the KATP channel, leading to dysregulated insulin release and ultimately promoting hyperglycemia and the development of T2DM. The RS5219 polymorphism has been implicated in the pathogenesis of T2DM in various populations, with studies suggesting that individuals carrying this variant may have an increased risk of developing the disease. However, the association between KCNJ11 RS5219 and T2DM risk varies across different ethnicities and populations, highlighting the need for population-specific studies.

In Indonesia, where genetic studies on T2DM remain relatively limited, investigating the role of KCNJ11 RS5219 gene polymorphism as a potential risk factor for T2DM is essential. Indonesia is a diverse country with a rich tapestry of ethnic groups, each with distinct genetic backgrounds. Understanding the genetic predispositions to T2DM in the Indonesian population could provide valuable insights into the disease's epidemiology and contribute to more effective prevention and treatment strategies. To date, only a few studies have explored the association between KCNJ11 polymorphisms and T2DM in Southeast Asian populations, and even fewer have specifically focused on Indonesia. Therefore, conducting a case-control study to examine the relationship between KCNJ11 RS5219 gene polymorphism and the risk of T2DM in Indonesia is of paramount importance. Previous research in other populations has shown inconsistent results regarding the role of the KCNJ11 RS5219 polymorphism in T2DM susceptibility. Some studies have reported a significant association between the RS5219 variant and increased T2DM risk, while others have found no such correlation. These discrepancies may be attributed to differences in study design, sample size, and population characteristics. Additionally, gene-environment interactions, such as dietary habits, physical activity, and metabolic profiles, may further modulate the influence of KCNJ11 polymorphisms on T2DM risk. Given the complex interplay between genetic and environmental factors in T2DM, it is crucial to explore these relationships in diverse populations, including those in Indonesia, to better understand the genetic underpinnings of the disease.

Moreover, identifying genetic risk factors such as the KCNJ11 RS5219 polymorphism could have significant implications for clinical practice and public health interventions. Genetic screening for T2DM susceptibility may enable the early identification of high-risk individuals, allowing for targeted prevention efforts and personalized treatment strategies. For instance, individuals with the RS5219 polymorphism may benefit from more intensive lifestyle interventions, such as dietary modifications and increased physical activity, to reduce their risk of developing T2DM. Furthermore, pharmacogenomic studies have suggested that certain KCNJ11 polymorphisms may influence an individual's response to specific antidiabetic medications, such as sulfonylureas. Therefore, understanding the genetic landscape of T2DM in Indonesia could pave the way for more effective, tailored treatment approaches that consider a patient's genetic makeup. Despite the potential significance of the KCNJ11 RS5219 polymorphism in T2DM, several challenges remain in elucidating its exact role in disease pathogenesis. The complex nature of T2DM, which involves the interaction of multiple genes and environmental factors, makes it difficult to establish a clear-cut relationship between any single genetic variant and disease risk.

Furthermore, the genetic diversity of the Indonesian population adds an additional layer of complexity to studying gene-disease associations.

Therefore, the KCNJ11 RS5219 gene polymorphism represents a promising candidate for investigating the genetic predisposition to T2DM in Indonesia. While the role of this polymorphism in T2DM has been studied in various populations, its association with the disease in the Indonesian population remains largely unexplored. The focus of this study was specifically to understand how genetic factor, specifically the KCNJ11 RS5219 gene, influence T2DM. the aims of this study was to examine the association between the KCNJ11 RS5219 gene polymorphism as a risk factor T2DM in the Indonesia population.

## 2. Methods

### 2.1 Patient Selection

This study employed a case-control observational analytic design to investigate the association between the KCNJ11 RS5219 gene polymorphism and the risk of Type 2 Diabetes Mellitus (T2DM) in an Indonesian population. A total of 58 participants were recruited for the study, consisting of 29 case subjects diagnosed with T2DM and 29 control subjects without T2DM. The case subjects were selected based on a clinical diagnosis of T2DM, confirmed through medical records and a review of laboratory results indicating elevated fasting blood glucose levels and HbA1c values. The control group was matched to the case group by age and sex but did not have a history of diabetes or other major metabolic disorders. Inclusion criteria for both groups required participants to be of Indonesian descent and aged between 30 to 65 years to ensure a relevant study cohort. Written informed consent was obtained from all participants, and the study was approved by the relevant ethical review board.

Genomic DNA was extracted from peripheral blood samples collected from all participants using a standardized extraction method. The RS5219 polymorphism in the KCNJ11 gene was genotyped using polymerase chain reaction (PCR) and restriction fragment length polymorphism (RFLP) analysis. The genotyping procedure involved amplifying the target gene region, followed by digestion with specific restriction enzymes to identify the presence of the polymorphic variants. Data on demographic characteristics, medical history, and lifestyle factors were collected through structured questionnaires and medical interviews. Statistical analyses were performed to compare the frequency of the RS5219 polymorphism between case and control groups. Odds ratios with 95% confidence intervals were calculated to assess the association between the KCNJ11 polymorphism and T2DM risk. Additionally, potential confounders such as age, sex, body mass index, and family history of diabetes were controlled for in the analyses to ensure robust and accurate results.

### 2.2 Nucleic Acid Extraction

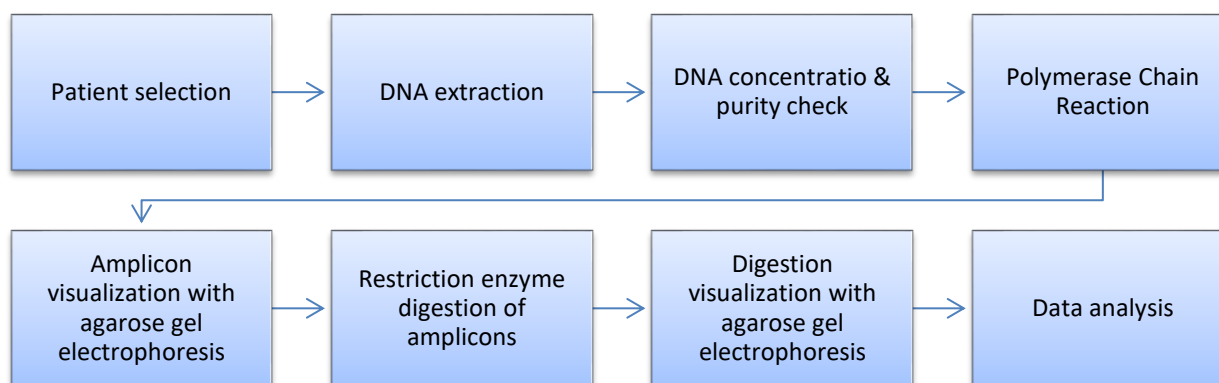
After screening medical records and obtaining consent for sample collection, 3 ml of peripheral blood was drawn in EDTA for genetic analysis. The extraction kit used for blood extraction was TianGen DNA/RNA Extraction Kit. DNA concentration was assessed using a Maestrogen MaestroNano Pro Spectrophotometer. Then, the extracted DNA was stored at -20°C.

### 2.3 Genetic Analysis

DNA amplification was performed using a BioRad T100 thermal cycler with forward primer: 5'-GAC TCT GCA GTG AGG CCC TA-3' and reverse primer: 5'-ACG TTG CAG TTG CCT TTC TT-3'. The amplification protocol included denaturation at 95° for 5 minutes, 35 cycles consisting of 95° for 30 seconds, 60° for 30 seconds, 72° for 30 seconds, 72° for 9 minutes, and ending with 25° for infinity hold. A 1.5% gel electrophoresis confirmed the 178 bp PCR product using a BioRad GelDoc EZ Imager, to ensure that the DNA had been amplified. After amplification, the product was cut with BanII restriction enzyme. The restriction results were analyzed with a 1.5% agarose gel to observe RFLP. The expected results on the agarose gel were genotypes GG (Homozygous Wildtype) cut to 28bp and 150bp, GA (Heterozygous Mutant) cut to 28bp, 150bp, and 178bp, and AA (Homozygous Mutant) cut to 178bp.

## 2.4 Data Analysis

The frequency of each genotype and allele was calculated and presented as a percentage. To determine the association between independent and dependent variables, univariate analysis was used to look at the distribution of genotypes and alleles in the KCNJ11 SNP rs5219 gene. The polymorphism at rs5219 G/A with type 2 DM was evaluated using contingency test with 2x2 table to obtain odds ratio and p-value.



**Gambar 1** Ilustrasi skema alur kerja penelitian

## 3. Results

### 3.1 Respondent characteristics

Table 1 provides a comprehensive breakdown of the characteristics of study participants by sex, presence of Type 2 Diabetes Mellitus (T2DM), age group, and duration of T2DM. In the case group, there were 4 male participants and 25 female participants, making up 13.8% and 86.2% of the group, respectively. This indicates a predominantly female sample among those diagnosed with T2DM in the study. Conversely, the control group comprised 17 males and 12 females, constituting 58.6% and 41.4% of the control subjects. The significant disparity between the sex distribution of the case and control groups suggests that the study might need to account for sex-related differences in T2DM prevalence and its impact on the study outcomes. The table clearly distinguishes between case and control subjects based on the presence of T2DM. In the case group, all 29 participants were diagnosed with T2DM, representing 100% of this group. This aligns with the study's objective to analyze genetic factors specifically in individuals with T2DM. On the other hand, all 29 participants in the control group did not have T2DM, also representing 100% of this group. The complete segregation of T2DM status between the two groups ensures that any observed associations with the KCNJ11 RS5219 polymorphism are specific to the disease group, providing clarity and focus to the analysis.

Age distribution in both case and control groups shows notable differences. Among the case subjects, 5 participants (17.2%) were aged 30-44 years, 15 participants (51.7%) were aged 45-59 years, and 9 participants (31%) were aged 60-74 years. This distribution suggests a higher concentration of T2DM cases in the middle-aged to older age groups, which is consistent with the known epidemiology of T2DM, where the risk increases with age. In contrast, the control group had 9 participants (31%) in the 30-44 year age range, 16 participants (55.2%) in the 45-59 year range, and 4 participants (13.8%) in the 60-74 year range. The higher proportion of younger individuals in the control group compared to the case group may reflect age-related differences in disease onset and prevalence. The duration of T2DM disease among the case subjects was categorized into two ranges: 1-10 years and 11-20 years. Out of the 29 case participants, 22 (75.9%) had been diagnosed with T2DM for 1-10 years, while 7 (24.1%) had the disease for 11-20 years. This indicates a predominance of relatively shorter disease

duration among the case subjects, which may have implications for understanding the disease progression and its association with genetic factors. For the control group, there was no data provided on the duration of T2DM, as expected, since these participants did not have the disease.

When comparing the characteristics between the case and control groups, several patterns emerge. The case group is notably older on average and has a higher proportion of females compared to the control group. This reflects the epidemiological trends of T2DM, where the disease is more prevalent in older adults and potentially more common among females in the studied population. The absence of data on the duration of T2DM disease in the control group emphasizes the focus on individuals with established T2DM for the genetic analysis. The observed differences in age, sex, and disease duration between the case and control groups are crucial for interpreting the study's findings. The age and sex distribution may affect the generalizability of the results and highlight the need for considering these factors in the analysis of genetic polymorphisms. The predominance of females in the case group and the older age range suggest that these variables might interact with genetic risk factors in influencing the development of T2DM.

It is important to recognize potential biases in the study based on the characteristics of the participants. The imbalance in sex distribution between the case and control groups could introduce bias if sex is an influential factor in the risk of T2DM. Additionally, the higher average age of the case group may reflect a longer exposure to risk factors associated with T2DM, which could affect the interpretation of the genetic associations studied. Future research should consider addressing the limitations identified in this table, such as balancing the sex distribution and including a more diverse age range. Additional studies with larger sample sizes and more detailed demographic information will help to confirm the associations between KCNJ11 polymorphisms and T2DM risk and provide a more comprehensive understanding of how these factors interact.

In summary, Table 1 provides a detailed overview of the demographic and clinical characteristics of the study participants, highlighting significant differences between case and control groups. These differences underscore the importance of carefully considering participant characteristics in genetic research and offer valuable insights for interpreting the study's findings. (Table 1).

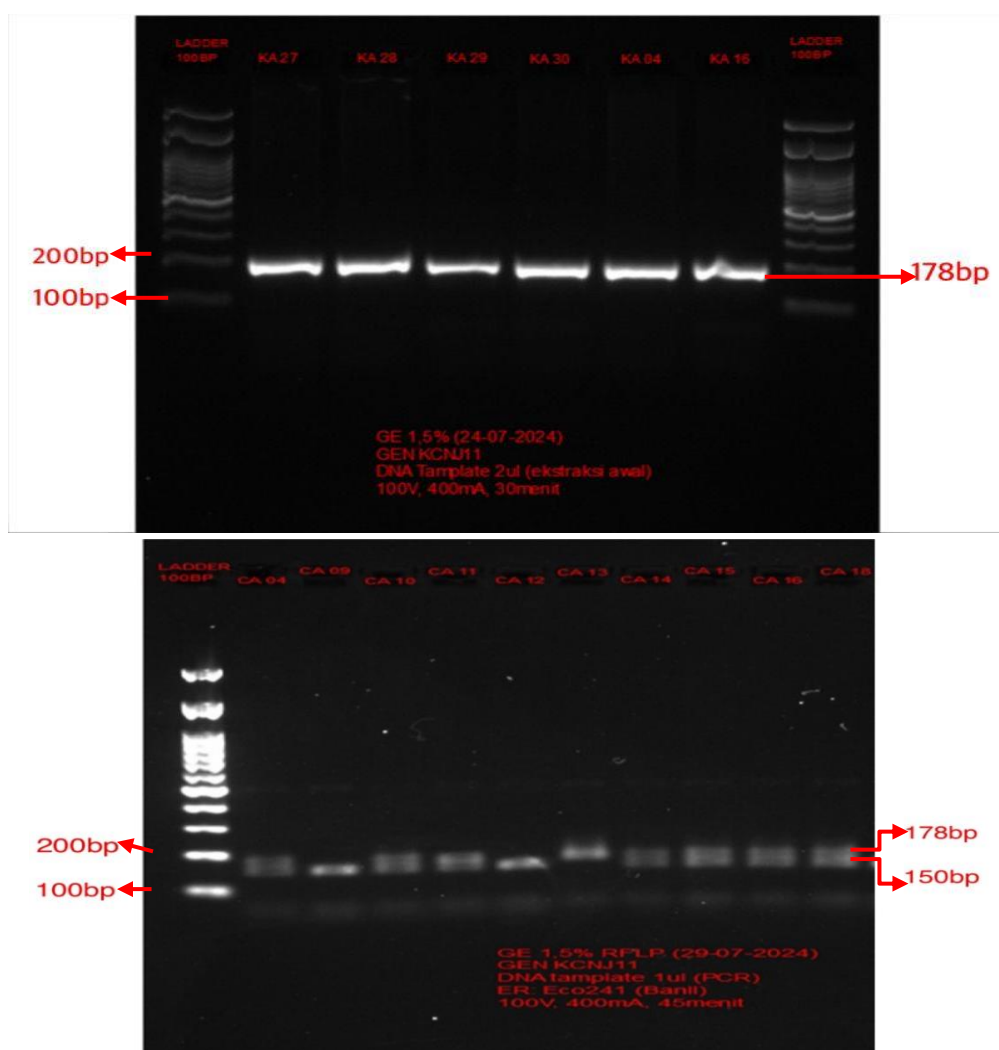
**Table 1** Subject Characteristics based on age, sex, T2DM Disease, and Duration of T2DM Disease

	Case		Control	
	n	%	n	n
<b>Sex</b>				
<b>Male</b>	4	13,8%	17	58,6%
<b>Female</b>	25	86,2%	12	41,4%
<b>Total</b>	29	100%	29	100%
<b>T2DM Disease</b>				
<b>Yes</b>	29	100%	-	-
<b>No</b>	-	-	29	100%
<b>Total</b>	29	100%	29	100%
<b>Age</b>				
<b>30-44</b>	5	17,2%	9	31%
<b>45-59</b>	15	51,7%	16	55,2%
<b>60-74</b>	9	31%	4	13,8%
<b>Total</b>	29	100%	29	100%
<b>Duration of T2DM Disease</b>				
<b>1-10 year</b>	22	75,9%	-	-
<b>11-20 year</b>	7	24,1%	-	-
<b>Total</b>	29	100%	29	100%

### 3.2 Genotypic Data

The PCR amplification results are presented in Figure 2(a), which shows a band at 178bp from KA 27-29, KA 04 and KA 16, which corresponds to control samples 27-29, control 04 and 06, respectively. The restriction enzyme results are shown in Figure 2(b). Furthermore, the uncut bands at 150bp and 28bp indicate the presence of the G allele, while the cut band at 178bp indicates the presence of the A allele. In Figure 2(b), subject CA 04 has bands at 178bp, 150bp and 28bp, indicating the GA genotype.

The genetic factors behind type 2 DM are believed to be multiple and complex. The KCNJ11 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. Kir6.2 protein is a 390 amino acid protein with two transmembrane domains (M1 and M2) and intracellular N and C terminals. Structurally, the Kir6.2 tetramer forms a pore and four high-affinity SUR1 subunits surround the pore of the KATP channel located in the plasma membrane of pancreatic beta cells. This channel modulates insulin production and secretion through glucose metabolism. (Haghvirdizadeh et al., 2015)



**Figure 2.** (a) PCR amplification results and (b) restriction enzyme digestion results. Line ladder: 100bp DNA ladder. Figure 2(a) shows the PCR amplification result of 178bp before restriction enzyme (KA27, KA28, KA29, KA30, KA04, KA06). Figure 2(b) shows line code CA: PCR-RFLP samples No.4,9-16,18. Line CA 09 & 12: genotype GG (wildtype homozygote). Line CA 13: genotype AA (homozygote mutant). Line CA 04,10,11,14-16,18: genotype GA (heterozygote mutant).

The KCNJ11 gene SNPs that have been detected include rs5219, which has received more attention due to its association with diabetes. The KCNJ11 gene polymorphism rs5219 is caused by a guanine to adenine substitution at codon 23, which changes the amino acid glutamate to the amino acid lysine at codon 23 (Glu23Lys) at the end of the Kir6.2 protein and thus inhibits glucose-induced insulin secretion. These changes reduce the sensitivity of potassium channels to ATP molecules, resulting in excessive channel activity and further inhibiting insulin secretion. (Makhzoom et al., 2019) This study aims to serve as a knowledge base in Indonesia by investigating the relationship between the KCNJ11 rs5219 gene and type 2 DM through blood glucose levels.

The results showed that the control group had more rs5219 G/A polymorphisms (38%), while the case group had less at 30%, as presented in Table 2. Examination of the frequency of rs5219 G/A SNP genotypes in the case group showed 17 (58.6%) GG genotypes, 7 (24.1%) GA, and 5 (17.2%) AA genotypes. Meanwhile, the control group had 11 (37.9%) GG genotypes, 14 (48.3%) GA, and 4 (13.8%) AA genotypes, as presented in Table 3. It was also found that the control group had a lower frequency of the GG genotype than the cases, accompanied by a higher frequency of the GA genotype.

**Table 2.** Allele frequency distribution

Allele	Case		Control	
	n	%	n	%
<b>G</b>	41	70%	36	62%
<b>A</b>	17	30%	22	38%
<b>Total</b>	58	100%	58	100%

**Table 3.** Genotype frequency distribution

Genotype	Case		Control	
	n	%	n	%
<b>GG</b>	17	58,6%	11	37,9%
<b>GA</b>	7	24,1%	14	48,3%
<b>AA</b>	5	17,2%	4	13,8%
<b>Total</b>	29	100%	29	100%

### 3.3 Association of KCNJ11 rs5219 gene polymorphism and type 2 diabetes mellitus

The results of bivariate analysis in Table 4 show that the case group has fewer rs5219 polymorphisms, namely 12 subjects (41.4%) and 17 subjects (58.6%) who do not have polymorphisms. Whereas in the control group, there were 18 subjects (62.1%) who had polymorphisms and 11 subjects (37.9%) who did not have polymorphisms. The Chi-Square Test results obtained a p-value of 0.115 which means there is no significant relationship. The results of further analysis obtained an OR value of 2.318 and a CI value of 0.809-6.644 in this study.

**Table 4.** Association of KCNJ11 rs5219 gene polymorphism and type 2 DM

Polymorphism	Case		Control		P	OR	CI (95%)
	n	%	n	%			
<b>+</b>	12	41,4%	18	62,1%	0,115	2,318	0,809-6,644
<b>-</b>	17	58,6%	11	37,9%			
<b>Total</b>	29	100%	29	100%			

## 4. Discussion

Type 2 diabetes mellitus (T2DM) accounts for approximately 85-95% of all diabetes cases, making it a major health problem worldwide and leaving a heavy burden on the global economy. Type 2 DM is a progressive hyperglycemic disease initially characterized by decreased sensitivity of peripheral tissues to plasma insulin, accompanied by gradual failure of pancreatic  $\beta$ -cells to maintain glucose homeostasis. (Li et al., 2020) Various environmental factors, advanced age, high body mass index (BMI), diet, lack of exercise, smoking, abnormal serum levels, genetics and their complex interactions are involved in the development of type 2 DM. (Alqadri, 2022)

Genome-wide association studies (GWAS) have recently identified more than 100 susceptibility loci for type 2 DM and identified various genetic markers significantly associated with type 2 DM. (Aka et al., 2021) One of the polymorphisms in the KCNJ11 gene that affects genetic expression is SNP rs5219. Several studies have observed the association between the KCNJ11 rs5219 gene polymorphism and the risk of type 2 DM. However, there are inconsistent results in previous studies in Asian populations. (Keshavarz et al., 2014)

The results obtained in this study were an odds ratio (OR) of 2.318, meaning that someone who has the KCNJ11 rs5219 gene polymorphism has a risk factor for the incidence of type 2 DM as much as 2.318 times greater than people who do not have the KCNJ11 rs5219 gene polymorphism, although statistically the results of the Chi-Square Test obtained a p-value of 0.115 concluded that there was no significant relationship between the KCNJ11 rs5219 gene polymorphism and the incidence of type 2 DM, accompanied by a confidence interval (CI 95% = 0.809-6.644) between the KCNJ11 rs5219 gene polymorphism and type 2 DM disease.

The results of this study are in line with studies conducted in the population of Northeast Mexico and South India, where no association was found between the KCNJ11 rs5219 gene polymorphism and type 2 DM, with a p-value >0.05. (Gallardo-Blanco et al., 2017; Phani et al., 2014) However, this is in contrast to a case-control study in the Syrian population and a meta-analysis in the American, East Asian, European, and Greater Middle Eastern populations that showed rs5219 in the KCNJ11 gene was involved in the risk of type 2 DM with a p-value of 0.035. (Makhzoom et al., 2019; Moazzam-Jazi et al., 2022)

It is known that type 2 DM is a complex disorder caused by the interaction of several environmental factors and genetic factors, and the influence of the same genetic factors on the development of type 2 DM disease is not the same in humans, due to differences in environment and lifestyle. So variations from previous studies can occur. (Makhzoom et al., 2019) Therefore, it is recommended that future studies be conducted using larger samples and different populations in Indonesia. This study also has limitations, namely not assessing other risk factors that can affect type 2 DM such as BMI, family history of DM, and lifestyle factors. In addition, this study did not calculate the Hardy-Weinberg balance, and did not report the genotype distribution model due to sample limitations.

## 5. Conclusion

In conclusion, approximately 62.1% of participants in this study who did not have type 2 DM had the KCNJ11 rs5219 G/A gene polymorphism. In the case group, the distribution of rs5219 G/A SNP genotypes was 17 (58.6%), 7 (24.1%), and 5 (17.2%) with GG, GA, and AA genotypes, respectively. In the control group, the breakdown was 11 (37.9%), 14 (48.3%), and 4 (13.8%) for the GG, GA, and AA genotypes regarding the rs5219 G/A SNP genotype. Statistical analysis showed an insignificant association between the KCNJ11 rs5219 G/T gene polymorphism and type 2 DM. However, the odds ratio value showed that individuals with the KCNJ11 rs5219 G/A gene polymorphism were 2.3 times more likely to develop type 2 DM. To present a more comprehensive understanding of the risk that is likely to occur in the Indonesian population, future studies should include more subjects in this demographic to accurately determine allele frequencies.



## Recommendation

Based on the results of this study, several important recommendations are proposed to strengthen the analysis of the association between KCNJ11 gene polymorphisms and the risk of Type 2 Diabetes Mellitus (T2DM). First, an increase in sample size is necessary to improve the statistical power and reliability of the results. Larger samples will produce more representative data, strengthen the validity of conclusions, and allow more accurate detection of genetic variation and other factors that influence T2DM risk. Second, balancing the sex distribution between case and control groups is a crucial aspect to reduce potential bias in the analysis of genetic risk factors. Third, future studies are recommended to consider confounding variables in more detail, including lifestyle factors and family history, to provide a more comprehensive understanding of the interaction between genetics and environment in the development of T2DM. Finally, the implementation of longitudinal studies may provide greater insight into the role of the KCNJ11 gene polymorphism in the progression of T2DM over time, allowing observation of changes in genetic, physiological, and lifestyle factors that influence the course of the disease. By adopting these recommendations, future research is expected to yield a more comprehensive understanding and more reliable findings regarding the relationship between KCNJ11 gene polymorphisms and T2DM, which in turn may contribute to the development of more effective preventive and therapeutic strategies.

## Conflict of Interest

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