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Investigation of ABO Blood Group in relation to KCNJ11 E23K rs5219 Gene Polymorphisms among F1 Type 2 Diabetes Mellitus Patients of Lembak Ethnicity in Bengkulu, Indonesia

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Abstract

Consistent evidence in the literature indicates a correlation between ABO blood group and type 2 diabetes mellitus. Numerous studies have established a correlation between particular genetic variants and an elevated risk of type 2 diabetes mellitus, one of which involves a polymorphism in the KCNJ11 gene. This study aims to analyze the prevalence of KCNJ11 gene variants in relation to blood type in Bengkulu. This study is a descriptive observational research employing a cross-sectional design. The present study analyzed the link between blood groups and KCNJ11 gene polymorphisms. The correlation between variables was examined with the Chi-Square Test. This study's results indicated no significant association between ABO blood group and KNCJ11 gene polymorphisms ($p=0.232$; $p=0.825$; $p>0.05$). Blood type analysis indicated that participants with a history of F1 in T2DM patients predominantly exhibited the EE genotype in the O group (57.1%), whereas the EK+KK genotype was prevalent in the non-O group (66.7%). The group in the F1 of Non-T2DM patients was predominantly composed of EK+KK in the non-O group (54.5%). The EE genotype in individuals with blood type O may elevate the risk of diabetes.

Keywords: KCNJ11, Blood group, Type 2 diabetes, first descendants, ethnicity

1. Introduction

Diabetes Mellitus Type 2 (DMT2) is a chronic metabolic disease characterized by high blood glucose levels due to insulin resistance and insulin secretion deficiency. This disease is a global health problem that continues to increase in developed and developing countries. According to the World Health Organization (WHO), in 2019, about 463 million adults worldwide had diabetes, with the prevalence expected to continue to increase (International Diabetes Federation, 2019). In Indonesia, DMT2 is also the leading cause of morbidity and mortality, with an estimated prevalence of 8.6% in the population aged 15 years and above (Ministry of Health, 2018).

The main risk factors contributing to the development of DMT2 include unhealthy diet, lack of physical activity, obesity, and genetic factors (Wu et al., 2014). Research shows that genetic factors predispose to DMT2, where many genes regulate glucose metabolism, including the KCNJ11 gene (Malekizadeh et al., 2021). Among the genes involved, the KCNJ11 gene, which regulates potassium channels in pancreatic beta cells, is a significant research focus. Several studies have shown that variations in this gene, especially the polymorphism E23K, are strongly associated with a predisposition to DMT2 (Rizvi et al., 2016).

Many studies have identified a link between specific genetic polymorphisms and an increased risk of DMT2, one of which is polymorphism in the KCNJ11 gene. In an independent control case study, Alqadri et al. (2022) found a significant relationship between Rs5210 polymorphism in the KCNJ11 gene and DMT2 in the Saudi Arabian population. The study suggests that genetic variants can affect the prevalence of DMT2 in certain population groups, which can then be used to assess an individual's risk of developing the disease (Alqadri, 2022).

A further study by Diaz-Garcia et al. (2024) examined genetic variation in several genes, including KCNJ11, and their relationship to DMT2. The study found that the polymorphisms present in KCNJ11 may play a role in the insulin resistance mechanisms underlying the DMT2 pathophysiology. This research paves the way for a deeper understanding of how these variants affect pancreatic beta cell function and contribute to the development of the disease (Díaz-García et al., 2024). Genetic variation in KCNJ11 significantly impacts the development of DMT2, with varying influences between populations (Phani et al., 2014). Polymorphism in KCNJ11 can play a role in other mechanisms associated with metabolic disorders, such as gestational diabetes and DMT2 (Rizvi et al., 2016; Shaat et al., 2005). These two studies prove that understanding genetic variation in KCNJ11 is essential for preventing and managing metabolic diseases.

The Lembak tribe is one of the ethnic groups in Bengkulu Province, Indonesia. This society has cultural peculiarities and lifestyles that may be different from other populations in Indonesia. Research on DMT2 in certain ethnic groups has become essential to understand whether certain genetic or environmental factors increase the prevalence of this disease in those groups. This study is vital to explore how specific genetic factors, such as blood type and genetic variants in the KCNJ11 gene, are related to the risk of DMT2 in first-generation individuals in the Lembak tribe.

Blood type has long been studied as a biological factor that may be related to various health conditions, including diabetes mellitus. Some studies suggest that blood type may influence its susceptibility to metabolic diseases such as DMT2, although the scientific evidence linking it is still limited and inconsistent (Meo et al., 2016). However, genetic variations in the ABO

locus may increase the risk of diabetes (Qi et al., 2010). More in-depth research is needed to confirm whether this association is significant in a given population.

The KCNJ11 gene plays a vital role in insulin regulation and glucose metabolism. This gene is located on chromosome 11 and produces a protein that functions in the potassium ion channel, which is very influential in insulin production from the pancreas (Alqadri, 2022). Several genetic variants in KCNJ11 have been linked to an increased risk of diabetes, especially in the context of decreased pancreatic function (Muftin & Jubair, 2019). Therefore, studying the relationship between the KCNJ11 genotype and other risk factors, such as blood type in the context of DMT2 in the Lembak tribe, can provide new insights into the genetic determinants of this disease.

Understanding the relationship between genetics and T2DM is essential for designing a more personalized approach to treating and preventing this disease. More profound knowledge of KCNJ11 and its polymorphism could open the door to more effective therapies and accurate diagnoses.

2. Materials and methods

This research used a cross-sectional study design. The data presented is actual data acquired straight from the completion of a questionnaire. This research involves instruments that encompass respondent characteristics, including blood type. The research was conducted in Bengkulu, Indonesia. Primary data management will be executed by a questionnaire from January to February 2023. The study population consists of the initial generation of patients with type 2 diabetes mellitus in Bengkulu. The research sample size was established via the categorical descriptive method for unpaired categorical analysis (Yunita et al., 2024) providing a total of 54 participants. Genetic polymorphism data is obtained as secondary data from our previous studies that have been recorded (Yunita et al., 2024). The eligibility criteria for this study were: 1) being a first-generation T2DM patient of Lembak ethnicity in Bengkulu; and 2) willingness to engage as a research subject and provide informed consent. The exclusion criteria for this study encompassed: 1) individuals diagnosed with Type 1 Diabetes Mellitus (T1DM) and Type 2 Diabetes Mellitus (T2DM), smokers, those deemed obese according to WHO standards for Asian populations (BMI < 25 kg/m²), and persons with hypertension as defined by the Joint National Committee 8 (JNC 8) guidelines (SBP < 140 mmHg and DBP < 90 mmHg). The dropout criteria in this study were that the research participants either withdrew from the study or did not complete the procedure. The research topic for the original generation of type 2 diabetes mellitus (T2DM) was sourced from medical data at a Community Health Center (Pusat Kesehatan Masyarakat; PUSKESMAS) in Bengkulu. The primary descendant of non-T2DM in this investigation was obtained from the area predominantly inhabited by the Lembak ethnicity. The collected data will be analyzed using the Statistical Program for Social Science 29.0, utilizing the Chi-Square test.

3. Results and Discussions

3.1 Subjects Characteristics

Table 1 illustrates the distribution of blood groups among 30 persons with F1 diabetes (50.00%) and 30 individuals without diabetes (50.00%). The majority of research participants had blood type B (28.3%) and blood type O (28.3%) in comparison to other blood types. A majority of the participants possessed EE genotypes (48.3%) in comparison to other genotypes. Type 2 diabetes mellitus (T2DM) is among the most widespread non-communicable diseases globally

and is a significant healthcare challenge. The genetic determinants of T2DM are considered to be diverse and complicated (Kwak & Park, 2016). Consequently, it is essential to examine the genetic factors linked to the risk of T2DM. Due to the lack of genetic studies on T2DM and its correlation with ABO blood types in Bengkulu Province, we investigated the relationship between the rs5219 polymorphism of the KCNJ11 gene and ABO blood types in a sample of F1 T2DM patients. The vulnerability to numerous diseases, including cardiovascular diseases, cognitive disorders, circulatory diseases, and metabolic diseases, has been associated with ABO blood groups (Abegaz, 2021).

Table 1. Frequency Distribution of Research Subjects (Yunita et al., 2024)

	Characteristic Data	Frequency		Total
		N	%	
F1 Patients	Diabetic	30	50	60
	Non-Diabetic	30	50	
ABO Blood Group	A	15	25	60
	B	17	28,3	
	AB	11	18,3	
	O	17	28,3	
KCNJ11	EE	29	48,3	60
	KK	16	26,7	
	EK	15	25	

Table 2. Analysis of ABO Blood Group of KCNJ11 Gene Polymorphisms

Subject	ABO Blood Group	EE		KK and EK		Total n	Total %	P-value	OR(95%CI)
		n	%	n	%				
Diabetes	Non O	9	42.9	6	66.7	30	100	0.232	0.372(0.073-1.920)
	O	12	57.1	3	33.3				
	Total	21	70	9	30				
Non-diabetes	Non O	10	45.5	12	54.5	30	100	0.825	0.833(0.165-4.212)
	O	4	50	4	50				
	Total	14	56.7	16	53.5				

3.2 The Prevalence of Blood types of KCNJ11 Gene Polymorphisms

The findings indicated no statistically significant association between ABO blood types and KCNJ11 gene polymorphisms in both groups (p=0.232; p=0.825; p>0.05). The analysis of

blood type indicated that respondents with a history of F1 of T2DM patients predominantly exhibited the EE genotype in the O group (57.1%), whereas the EK+KK genotype was prevalent in the non-O group (66.7%). The cohort in the F1 of Non-T2DM patients was predominantly composed of EK+KK individuals in the non-O group (54.5%). Research indicates that ABO affects numerous metabolic endophenotypes, particularly increasing the risk of type 2 diabetes mellitus (T2DM), while KCNJ11 similarly elevates the risk of T2DM (Sharjeel et al., 2021)

Several studies have attempted to investigate a potential correlation between ABO blood types and diabetes mellitus. The results have been diverse, inconsistent, and varied among regions. Certain studies have detected a correlation between blood types and T2DM, whereas others have found no such association.

The results of this study indicate that blood type O was more likely to be associated with F1 in T2DM patients, although this difference was not statistically significant. In control groups, individuals with non-O blood types were predominant. These results align with the findings of Karagoz et al. (2015) and Zhang et al. (2015), indicating that blood type O is associated with an increased risk of T2DM (Karagoz et al., 2015; Zhang et al., 2015).

Our results differ slightly from other studies, which suggest that individuals with blood type AB are at an increased risk of diabetes, independent of geographic region, age, race, and gender (Abegaz, 2021). Meo et al. (2016) found that blood type B is linked to a higher incidence of type 2 diabetes mellitus (T2DM), while blood type O shows the least association with T2DM (Meo et al., 2016). Bener and Yousafzai et al. (2014) examined the relationship between ABO blood types and diabetes mellitus in Qatar. The study indicated that blood type B was significantly more prevalent, while blood type O was notably less prevalent among diabetic patients compared to a healthy non-diabetic population (Bener & Yousafzai, 2014).

The mechanism underlying the association between ABO blood types and the incidence of T2DM remains inadequately defined. Conflicting results concerning the association between ABO blood types and diabetes mellitus may be attributed to racial and geographical variations influencing the genetic expression of the disease.

The KCNJ11 gene is found at 11p15.1 and comprises a single exon that encodes the Kir6.2 protein. This protein constitutes the inner component of the adenosine triphosphate-sensitive potassium ion channel (KATP) in pancreatic beta cells, significantly influencing insulin secretion. Multiple SNPs in the KCNJ11 gene have been identified, particularly rs5219, which has received increased focus due to its relationship with diabetes. The KCNJ11 rs5219 polymorphism results from a guanine to adenine transition at codon 23, leading to a substitution of glutamic acid with lysine, which critically inhibits glucose-induced insulin secretion. This modification decreases the sensitivity of potassium channels to ATP molecules, leading to channel overactivity and a subsequent inhibition of insulin secretion (Haghvirdizadeh et al., 2015; Schwanstecher et al., 2002; Wang et al., 2018).

The study indicated that the EE genotype prevalence was greater in the F1 generation of diabetic patients, while the frequency of EK+KK was elevated in the F1 generation of healthy individuals. Our study differs from other studies that suggest the KK genotype is a dominant factor in increasing the risk of T2DM (Chistiakov et al., 2008; Makhzoom et al., 2019; Rastegari et al., 2015). The conflicting results result from our participants, who are primarily descendants of diabetic patients and a healthy population, rather than diabetic patients

themselves. Another possible reason is attributed to varying geographical regions and racial factors that differ from other studies. Further investigations are required to understand the influence of ABO blood type on genetic variants in diabetic patients of the Lembak ethnicity in Bengkulu, Indonesia.

4. Conclusions

This research demonstrated no correlation between ABO blood types and KCNJ11 gene polymorphism in the first descendants of diabetic patients from the Lembak Ethnicity in Bengkulu, Indonesia. The limited number of samples represented a limitation of this study. Furthermore, additional investigations are required to examine other risk factors that may contribute to the incidence of T2DM.

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