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Polymorphism Genes Sulfonylurea Receptpr-1 and Potassium Inwardly-Rectifying Channel Subfamily J Member 11 as a Risk Factor for Type 2 Diabetes Mellitus in Ethnic of Ternate

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Abstract

Background: Sulfonylurea Receptor-1 (SUR1) and Potassium Inwardly-Rectifying Channel Sub Family J Member 11 (KCNJ11) is the gene at canal its activity of ATP sensitive potassium (K_{ATP}). Canal K_{ATP} ATP acts as a sensor on the settings of the secretion of insulin. Polymorphism R1273R E23K genes SUR1 and KCNJ11 cause interference with the activity of the Canal K_{ATP}, affect the secretion of insulin causing hyperglycemia and Impaired Glucose Tolerance (IGT) are at risk of type 2 DM occurs.

Purpose: Examine the interconnectedness of Polymorphism R1273R E23K genes SUR1 and KCNJ11 as risk factors of type 2 DM on Ternate Ethnic.

Methods: The case-control Design to the subject research of sufferers of type 2 DM (n=52) as Group cases and subject to the Non-DM (n=52) as a control group. Genotyping gene is done by the method of PCR-RFLP. Compare the subject case and control groups with the test t-test are not paired. Test of chi-square and the odds ratio (OR) to analyze the relationship of polymorphism R1273R E23K genes SUR1 and KCNJ11 with risk of incident type 2 DM.

Results: The frequency of Genotype GA genes SUR1 group cases (9.6%) while genotype GA in the control group (3.8%) (p=0.256; Or=2.660). Combination genotype GG genes SUR1 and genotype GA genes KCNJ11 compared to genotype GG genes SUR1 and KCNJ11 is a protective factor for DM (p=0.000; Or=0.083). Genotype GG genes SUR1 and AA genotype genes KCNJ11 compared to genotype GG genes SUR1 and KCNJ11 (p=0.975; Or=1.031).

Conclusion: The individual carrier genotype GA polymorphism R1273R genes SUR1 statistically not different but has a significant risk of developing type 2 DM. Genotype GA E23K genes KCNJ11 polymorphism as protective factors in type 2 DM on Ternate ethnic.

Keywords: Polymorphism R1273R genes SUR1; KCNJ11 genes E23K polymorphism; Type 2 DM; Ternate ethnic

Background

Diabetes mellitus (DM) is a metabolic disorder characterized by hyperglycemia Chronicle with disorders of carbohydrate, FAT and protein is caused by impaired secretion of insulin, work to insulin, or both [1]. Diabetes mellitus are classified into 4 types but the DM type 2 is a disease of DM with a relatively high frequency [2]. Diabetes mellitus type 2 (DMT2) is a disease of the multifactorial the existence of an interaction between genetic factors with environmental as well as changing style life as a predisposing illness [3].

In the year 2011 it is estimated there are 366 million sufferers of DM and on the map increased to 552 million in the year 2030. Most sufferers DM live in low-income and médium [4]. In Indonesia the number of sufferers DM 2000 years as many as 8.4 million and is expected to rise as much as 21.3 million in 2030 [5]. A sufferer of DM in Ternate city is estimated to be as much as 19.8% of the population.

One of the causes of the disruption caused by the secretion DMT2 insulin [6]. Sulfonylurea Receptor-1 (SUR1) and Potassium Inwardly-Rectifying Channel Subfamily J Member 11 (KCNJ11) are both working on potassium channel in pancreatic β cells [7]. Genes SUR1 serves as a regulator of the Canal potassium and release insulin while genes KCNJ11 serves to regulate the secretion of insulin [8]. Genes SUR1 polymorphism can potentially affect the function of genes KCNJ11 so change activity on the Canal potassium, this is because the position of the two mutually adjacent genes. Polymorphism on genes KCNJ11 potassium sensitive channel resulting in decreased against the ATP so that the channel remains open and insulin secretion decline cause Impaired Glucose Tolerance (IGT) which eventually became type 2 DM [9].

Polymorphism on genes SUR1 and KCNJ11 in touch with DM type 2, several variants of genesis has been linked to impaired insulin secretion. The change of Single Nucleotide Polymorphism (SNPs) (AGG→AGA: Arg1273Arg/R1273R) resulted in changes in K_{ATP} channel activity that causes disruption of insulin secretion [10]. Polymorphism R1273R may be able to cause an increase in the activity of the Canal's opening in the SUR1 stimulate K_{ATP} so that insulin

cannot secreted. Disorders of insulin secretion resulted in hyperglycemia which culminate in type 2 DM [11]. SNPs change GAG→àAG caused the substitution of the amino acid glutamate into lysine that occur in the tail of the NH_2 terminal on Kir 6.2 and is the region of the binding of ATP. Disruption on one of the binding region would result in the closure of K_{ATP} channel disorders so that insulin secretion did not occur resulting in hyperglycemia and may lead to the occurrence of type 2 DM [12].

Subjects and Methods

The subject in this study amounted to 104 people, groups of cases amounted to 52 people recruited from sufferers of type 2 DM in medical treatment UNIT for the Diabetes Center and the Provincial Hospital Dr. H Chasan Boeosoirie Ternate and the control group amounted to 52 people who were recruited from the community around him [13].

The isolation of DNA using DNA isolation kit (Gene Aid). Polymorphism R1273R E23K genes genes SUR1 and KCNJ11 analyzed with polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP). Amplification of DNA fragments at codon position R1273R genes SUR1 with primer: forward primers 5'-GGT CAG GAA GTA CCT PM GC-3' and a reverse primer 5'-TGT CTC CAG TGA CGA AGG TG-3' [14].

Amplification of DNA fragments genes KCNJ11 at position 23 codon with primer: forward primers 5'-TCT GAC GCA PM AGG CCC TA-3' and a reverse primer 5'-TTG TTG CAG ACG CCT TTC TT-3' [15]. PCR cycle temperature conditions: (1) the initial Denaturation for 5 minutes at a temperature of 94°C; (2) next the denaturation temperature 94°C for 60 seconds; (3) annealing at temperatures 60°C for 60 seconds; (4) Extension at a temperature of 72°C for 60 seconds; (5) the final extension for 7 minutes at a temperature of 72°C; (6) cooling to 4°C. PCR running for 2 hours 15 minutes [16]. Cutting with restriction enzyme PCR products (RFLP) to genes SUR1 uses enzymes BslI (Thermo) [17].

Restriction enzyme (RFLP) to genes KCNJ11 using enzyme BanII (Thermo). Reaction mixture are incubated for 16 hours at a temperature of 37°C in an incubator, the result of a reaction with agarose gel electrophoresis was performed 3% and divisualisasi with ethidium bromid [15].

The results of digestion genes SUR1 IE GG Genotype (wild type) at position 132 bp, 65 bp, 52 bp and 1 bp, Genotype GA position 198 bp, 132 bp, 65 bp, 52 bp and 1 bp and Genotype AA 198 at the position, and 52 bp [14]. The results of digestion genes KCNJ11 IE GG Genotype (wild type) have 4 ribbons (150 bp, 65 bp, 32 bp and 28 bp (not visible), Genotype GA has 5 ribbons (178 bp, 150 bp, 65 bp, 32 bp and 28 bp (not visible) and AA Genotype have 2 ribbons (178 bp and 32 bp).

The analysis of the results of research conducted test t-test to compare the data pair is not the subject of the case and control groups. Test of chi-square to compare allele frequencies and genotype. Risk factors analysis of the polymorphism R1273R E23K genes genes SUR1 and KCNJ11 against DM type 2 used test Odd Ratio [18].

Results and Discussion

Several variables including age, TB, W, IMT in case and control groups did not differ significantly (p>0.05), the only variable when blood glucose (GDS) between the control and case groups statistically significant different (p=0.000) (Table 1).

Genotype on genes SUR1 in this research is genotype GG and GA while the AA genotype is not found. The length of the fragment at genotype GG can be seen in Figure 1.

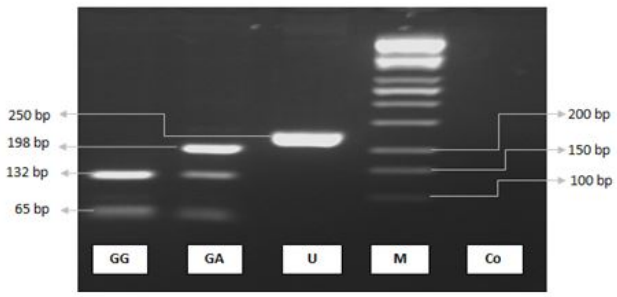

Figure 1: Genotype on genes SUR1.

Variable	Cases (n=52)	Control (n=52)	P
Gender (L/P)	14/38	16/36	0.665*
Age (Years)	50.84+8.43	50.38+9.62	0.806*
TB (cm)	163.51+5.25	163.32+5.14	0.855*
W (kg)	64.42+7.27	60.69+14.24	0.119*
IMT (kg/m^2)	24.15+2.90	22.82+5.48	0.167*
GDS (mg/dL)	292.73+85.50	111.51+23.69	0.000*
*Independent t-test			

Table 1: The characteristics of the subject.

Genotype on genes KCNJ11 in this research is genotype GG, genotype GA and genotype AA, the length of the fragment can be seen in Figure 2.

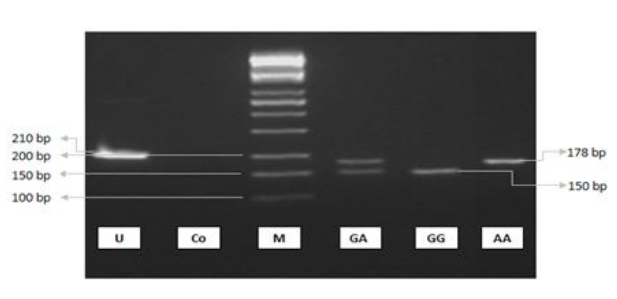

Figure 2: Genotype on genes KCNJ11.

Frequency distribution genotype genes SUR1 group case GG (90.4%) and GA (9.6%), while the control group GG (96.2%) and GA (3.8%). Statistically there is a relationship of Polymorphism with genes SUR1 disease type 2 DM (Or=2.660; 95% CI 0.492-14.377), individual carriers of genotype GA compared to genotype GG have risk 2.66

times to experience the DM type 2 but not statistically significant (Table 2). The change of Single Nucleotide Polymorphism (SNPs) (AGG→AGA: Arg1273Arg/R1273R) resulted in changes in K_{ATP} channel activity that causes disruption of insulin secretion. R1273R polymorphism can potentially lead to increased activity stimulates opening of the Canal in the SUR1 K_{ATP} so that insulin cannot secreted. Disorders of insulin secretion resulted in hyperglycemia which culminate in type 2 DM [19].

	n	%	Case (%)	Control (%)	P	Or	95% CI
Genotype							
GG	97	93.3	47 (90.4)	50 (96.2)			
GA	7	6.7	5 (9.6)	2 (3.8)	0.256	2.66	(0.492-14.377)*
Allele							
G		96.6	99 (95.2)	102 (98.1)			
A		3.4	5 (4.8)	2 (1.9)	0.265	2.576	(0.488-13.587)*
*Chi-square test							

Table 2: Frequency distribution genotype (GG and GA) and allele (G and A) genes SUR1 in people with DM and Non-DM.

Group case have genotype GG (32.7%), GA (46.2%) and AA (21.2%), while the control group had genotype GG (5.8%), GA (90.4%) and AA (3.8%). In contrast to previous studies because there genotype GA in most of the control group.

The difference in frequency between the individual carrier GA genotype compared to genotype GG (p=0.000; Or=0.088; 95% CI (0.24-0.331). Individuals who carry the AA genotype compared to genotype GG does not have a risk of developing type 2 DM (p=0.586; Or=1.941; 95% CI (0.178-21.119) (Table 3).

	n	%	Case (%)	Control (%)	P	Or	95% CI
Genotype							
GG	20	19.2	17 (32.7)	3 (5.8)			
GA	71	68.3	24 (46.2)	47 (90.4)	0	0.088	(0.24-0.331)*
AA	13	12.5	11 (21.2)	2 (3.8)	0.586	1.941	(0.178-21.119)*
Allele							
G		53.4	58 (55.8)	53 (51.0)			
A		46.6	46 (44.2)	51 (49.0)	0.676	0.89	(0.516-1.537)*
*Chi-square test							

Table 3: Frequency distribution genotype (GG, GA and AA) and allele (G and A) genes KCNJ11 in people with DM and Non-DM.

Gene E23K KCNJ11 Variants on this research shows individuals who carry genotype GA compared to genotype GG is protective factors of type 2 DM on Ternate ethnic (p=0.000; Or=0.088; 95% CI (0.24-0.331). Although the change of SNPs GAG became AAG cause substitution of amino acid glutamate into lysine that occur in the tail of the NH_2 terminal on Kir 6.2 and is the region of the binding of ATP. Disruption on one of the binding region would result in the closure of K_{ATP} channel disorders so that insulin secretion did not occur resulting in hyperglycemia and may lead to the occurrence of type 2 DM [12]. Diabetes mellitus type 2, which occurs at Ternate ethnic likely caused by factors other than polymorphism on gene K_{ATP} channel which encodes as factors of age and obesity [20,21].

Combination genotype genes SUR1 and KCNJ11 suggests that individuals who carry genotype GG genes SUR1 and genotype GA genes KCNJ11 compared with individuals who carry genotype GG on genes SUR1 and KCNJ11 differ significantly (p = 0.000; Or=0.083; 95% CI (0.022-0.319) (Table 4). Individual carrier genotype GG genes SUR1 and AA genotype genes KCNJ11 are statistically no different meaning (p=0.975; Or=1.031; 95% CI (0.147-7.226) compared with individuals who carry genotype GG on genes SUR1 and KCNJ11. Individuals who carry genotype GA on genes SUR1 and KCNJ11 statistically not different (p=0.360; Or=0.375; 95% CI (0.046-3.056)) compared with individuals who carry genotype GG genes SUR1 and KCNJ11. Individuals who carry genotype GA genes SUR1 and genotype GG genes KCNJ11 showed no significant difference (p=0.850; Or=0.842; 95% CI (0.693-1.023) compared with individuals who carry genotype GG on genes SUR1 and KCNJ11 (Table 4).

Genotype	n	%	Case (%)	Control (%)	P	Or	95% CI
SUR1+KCNJ11							
GG+GG	19	18.3	16 (30.8)	3 (5.8)			
GG+GA	65	62.5	20 (38.5)	45 (86.5)	0	0.083	(0.022-0.319)*
GG+AA	13	12.5	11 (21.2)	2 (3.8)	0.975	1.031	(0.147-7.226)*
GA+GA	6	5.8	4 (7.7)	2 (3.8)	0.36	0.375	(0.046-3.056)*
GA+GG	1	1	1 (1.9)	0	0.85	0.842	(0.693-1.023)**
*Chi-square test; **Fisher Exact test							

Table 4: Analysis of combination genotype genes SUR1 and KCNJ11.

Change of SNPs on genes SUR1 has a risk of developing type 2 DM but SNPs on not associated with KCNJ11 genes DM type 2, the result of a combination of genotype between the SUR1 and genes KCNJ11 also shows has no relationship with the risk the occurrence of type 2 DM on Ternate ethnic. Polymorphism genes SUR1 likely affect the function of genes KCNJ11 so potassium channel activity changes because second place genes. The tendency of insulin secretion disorders directly occur on polymorphism compared with KCNJ11 genes SUR1 so although the results of this research show the SNPs on genes SUR1 have risk of DM type 2 but genes SNPs change KCNJ11 has no risk of DM type 2 causes the risk of type 2 DM on Ternate ethnic due to polymorphism on genes K_{ATP} channel which encodes into small [9].

Conclusion

Individuals who carry genotype GA have a risk of developing type 2 DM in genes SUR1 but statistically insignificant. Individuals who carry genotype GA genes KCNJ11 as protective factors in type 2 DM on Ternate ethnic.

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