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CONTENTS

Association of rs290487 Polymorphisms in TCF7L2 Gene with Type 2 Diabetes in Ethnic Minangkabau

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Abstract

Variants in the Transcription Factor 7-Like 2 (TCF7L2) gene have been found associated with type 2 diabetes mellitus (T2DM) in several ethnic group.Some tribes in the world already has Genbank for type 2 Diabetes Mellitus such as: Caucasian, Danish, USA, France and India. By analyzing gene, patients with T2DM can be diagnosed more quickly and accurately. One of the TCF7L2 gene variants were allegedly associated with type-2 diabetes mellitus is a rs290487 AGTACAAATCATGGTGACACCA [C/T] GCAAAATTGAAAATGAGAAAGG **The presence of the T allele in rs290487 is an indication of increased susceptibility to T2DM. The aim of this research is to confirm the association between SNP in rs290487 with T2DM in ethnic Minangkabau. In the other hand, it is also useful for development of an early warning system in T2DM based on molecular techniques, rapid and accurate.**

Analysis was performed on 66 subject/patients with DM and 66 subject as control, and then collection EDTA blood from all subjects for DNA extraction which will be used as a sample for testing SNP. DNA was obtained amplified using the Amplification Refractory Mutation System - Polymerase Chain Reaction (ARMS-PCR) method to detect polymorphisms in TCF7L2 gene variant rs290487.

We found no significant association between SNP rs290487 with the possibility of T2DM in Ethnic Minangkabau. It is seen from the P^{value} = 1,00 (not significant) and OR = 1,067. The results are relatively similar to some previous studies that have been reported by several researchers on ethnic Chinese and Japanese.

Keywords: TCF7L2 gene, rs290487, T2DM, Minangkabau

1. Introduction

Diabetes mellitus (DM) is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both[1]. Indonesian Society of Endocrinology (PERKENI) defines diabetes mellitus as a chronic disease with a set of symptoms in a person who caused an increase in blood sugar levels due to insulin deficiency[2]. Number of deaths attributable to diabetes mellitus worldwide more than HIV/AIDS. Estimated number of people died because of diabetes mellitus in 2000 at 6% (3.2 million people). One in ten people in the world died at the age of 35-64 years with a history of diabetes mellitus[3].

Patients with diabetes mellitus in the world each year has increased, including in Indonesia and West Sumatra. The prevalence of diabetes mellitus in the world in 2000 at 2.8% (171 million people) and in 2030 was estimated at 4.4% (366 million people). The estimated number of people with diabetes mellitus in Indonesia in 2000 at 4.1% (8.4 million Indonesian population of 205 132 000 people) and projections 2030 increased at 7.8% (21.3 million of 273 219 200 people). Estimates of diabetes mellitus in Indonesia ranks fourth after India, China and USA[2,4,5].

The prevalence of diabetes mellitus in West Sumatra at 5.2%[6], more than expected prevalence of the world in 2030. Based on this data can be known that the population of West Sumatra (Ethnic Minangkabau) has a high potential for suffering diabetes mellitus. Ethnic Minangkabau have a diet with high in carbohydrates, high in saturated fat and low in fruits and vegetables[7]. Matriakat lineage system that allows "pulang ka bako" (cosanguinitas/mating with close relatives) increase the chances of developing diabetes mellitus in ethnic Minangkabau.

Type 2 diabetes mellitus (T2DM) is influenced by several factors: family history of diabetes, obese, risky lifestyles, lack of rest, and stress. T2DM will appear on a person's with genetic disability after a genetic change in a long time. Acceleration and deceleration processes of genetic change is dependent on environmental factors that influence it. If the genetic factors do not develop in the direction of improvement due to environmental factors, then theoretically the person will not suffer DM. Abnormalities or genetic disorders at an early stage without any symptoms that are clinically difficult to recognize[8]. Genetic markers developed in the direction of improvement, but not cause impaired glucose tolerance (IGT) can be determined through DNA analysis. To perform DNA analysis needed a genetic data from associated genes with type-2 diabetes mellitus. Through the analysis of genes, candidate genetic disabled people with type 2 diabetes mellitus can be diagnosed more quickly and accurately[9].

Among the genes that are strongly associated with type-2 diabetes mellitus is a "transcription factor 7 like 2 (TCF7L2)" gene on chromosome 10q[10]. TCF7L2 gene strongly associated with type-2 diabetes mellitus in ethnic Danish, Caucasian, Indian, and in several

ethnic in Asia[9,11]. TCF7L2 gene contribute to the risk T2DM and diabetic nephropathy (DN) in the Taiwanese population[12].

TCF7L2 gene in humans consists of 224 429 bp DNA. This gene encodes a high mobility group box (HMG) which is a transcription factor that plays a key role in the wnt pathway. protein produced from transcription TCF7L2 gene have implications on blood glucose homeostasis. Genetic variants of this gene are associated with increased risk T2DM[13]. TCF7L2 gene variants can be used as a potential genetic marker of patients with type 2 diabetes mellitus in ethnic Minangkabau. Appropriate markers or haplotypes will be able to give an indication of increased susceptibility of person to type 2 diabetes mellitus.

One of the TCF7L2 gene variants were allegedly associated with type-2 diabetes mellitus is a rs290487. rs290487 sequence is:

AGTACAAATCATGGTGACACCA [C/T] GCAAAATTGAAAATGAGAAAGG

The presence of the T allele in rs290487 is an indication of increased susceptibility to type-2 diabetes mellitus[9, 14, 15].

The aim of this research is to confirm the association between snp in rs290487 with T2DM in ethnic Minangkabau. In the other hand, it is also useful for development of an early warning system in T2DM based on molecular techniques, rapid and accurate. So that it can be used to help the prevention and treatment of type-2 diabetes mellitus in ethnic Minangkabau.

2. Research Methods

This research is a cros-sectional study, by analyzing snp rs290487 of TCF7L2 gene as a genetic marker T2DM and then compared with healthy individuals without T2DM in the ethnic Minangkabau. The study population is ethnic Minangkabau communities with T2DM who come for treatment to the clinic Metabolic Endocrinology Dr. M. Djamil hospital (66 subject). For comparison used a control group who take from the ethnic Minangkabau communities who do not have type 2 diabetes mellitus (66 subject).

Early stages of research that preceded the primer design will recognize the snp rs290487. We describe the results of the primer design and confirmation of the ability of the primer amplifying the target regions as well as the ability to detect the snp rs290487. This research conducted in the biomedical laboratory Faculty of Medicine, Andalas University.

In this study used DNA derived from human peripheral blood (vena cubiti). These isolates is needed to test whether primers designed can amplify the target DNA fragment. Data were analyzed qualitatively, the data analyzed were the result of the primer design and primer capabilities amplify the target region (detecting snp rs290487 at TCF7L2 gene).

2.1. Design Primer

The primer design is done by utilizing the sequence TCF7L2 gene in *Homo sapiens* as reference (NCBI)[13]. Designing primer process performed using computer software "primer designer". Primer result of this design will be identify and detects the snp at rs290487. Before primer is used on clinical samples, primer specificity was tested by computerized to see the possibility of mispriming primer with other regions in the genome of *Homo sapiens* apart from the area to be amplified. If not found possibility of mispriming, the results of the primer design is ready to be synthesized as oligonucleotide primers.

2.2 Detection of snp rs290487

To know the ability of primers designed to detect snp in the TCF7L2 gene (rs290487), then performed tests with the following step: Isolation of genomic DNA using a kit from Invitrogen. DNA was obtained and primer have been designed, amplified using Amplification Refractory Mutation System - Polymerase Chain Reaction (ARMS-PCR) method to detect polymorphisms in TCF7L2 gene variant rs290487. PCR reaction mix was made by PCR RTG. PCR amplification results were analyzed using the technique of gel electrophoresis on agarose 1.5%[16].

If the sample used is not having snp, on agarose will appear two fragments in different size. otherwise, if there is only one fragment it means there is a mutation/snp. Selected samples were sequenced for verification and confirmation of the results of ARMS-PCR method. Sequencing or process of determining the DNA sequence amplification performed by a commercial laboratory (Macrogen, Korea). DNA sequences were obtained, analyzed to know the level of similarity with data in GenBank and then characterized using several bioinformatics programs.

To determine the significance association of the snp rs290487 TCF7L2 gene with the T2DM in Ethnic Minangkabau performed data analysis using chi-square test. Chi-square test was used because the independent variables of patients with a diagnosis of T2DM and control/people without T2DM form of nominal data (category). The dependent variable in the type of presence or absence of Thymin on snp rs290487 variant TCF7L2 gene is also a nominal data (categories).

3. Result

In this research, we made three primer desingn: forward primer RS29C, forward primer RS29F and reverse primer RS29R. Primer RS29F and RS29R used to amplify DNA that includes the region ± 415 bp (external primer). Primer RS29C and RS29R used to

Table 1. Result of primer design RS29C, RS29F dan RS29R

Sequence RS29C	5'-ACAAGTCATGGTGACACCAC-3'						
Sequence RS29F	5'-GGATGGTACATTGGACTGC-3'						
Sequence RS29R	5'-CTCCTCTCATGCTGCTCATT-3' (Complementary strand)						
Criteria	Setting of criteria	Results			Within set criteria		
		A*	B†	C‡	A*	B†	C‡
% GC	Min 50, Max 60	50	52	50	YES	YES	YES
Tm C	Min 55, Max 80	66	66	68	YES	YES	YES
No Hairpins	Energy cutoff 0.0 kcal	-	-	-	YES	YES	YES
No 3' Dimers	Reject >= 3 matches at 3' end	3	2	1	NO	YES	YES
No Dimers	Reject >= 7 homol base	5	4	4	YES	YES	YES
No Runs	Reject >= 3 base runs	2	2	2	YES	YES	YES
No 3'GC runs	Reject >= 3 G atau C at 3' end	1	2	0	YES	YES	YES

Note: * Primer RS29C
† Primer RS29F
‡ Primer RS29R

amplify the region will recognize immediately snp rs290487 (internal primer, the size fragment ± 193 bp). The results of the three primer design can be seen in Table 1.

One of the three primer is specific primer for region contained snp. The 3' end of this primer excactly on the sequence that have been snp. If the sample used is that instead of having a mutation/snp it will produce two fragments in different size. In the other hand, if there is only one fragment in PCR product its means the sample have polimorfisme/snp at rs290487. Based on the electrophoresis result from whole sample T2DM, founded 25 samples (38 %) with polymorphism/snp at rs290487. While in the samples do not have type-2 diabetes mellitus (control) there were 24 (36 %) subjetc had polymorphism (table 2).

4. Discussion

The success of an ARMS-PCR reaction to detect the mutation/snp is very dependent on the specificity of the primers designed. Selection of appropriate primer will ease in knowing and analyzing the presence/absence of snps in a sample. Inaccuracy in choosing the primer will result different regions were amplified so it will affect to the quality test result. If the selected primer is not specific to a particular region or snp the detection process will cannot be done. Therefore, the primer design is the first step and very crucial in detecting mutations/snps in a gene.

Function of the primer as initiation of DNA polymerization in vitro reaction. Appropriate primer will give the correct annealing process and is a necessary condition for the Taq DNA polymerase enzyme to be able to begin the task. Without the proper primer, taq DNA polymerase enzyme is not possible to start the process for the synthesis of complementary strands of the DNA template. In addition the primer also serves to limit the areas which will be amplified in the PCR reaction[17].

Table 2. Association of snp rs290487 TCF7L2 gene in 66 subjects with type 2 diabetes mellitus (T2DM) and 66 subjects not T2DM in ethnic Minangkabau.

Polimorphisme	type-2 Diabetes melitus				Total		OR	*P-value*
	Yes		No					
	n	%	n	%	n	%		
SNPrs290487	25	51,0	24	49	49	100	1, 067	1,000
Wild tipe	41	49,4	42	50,6	83	100	0,527-2,162	
Total	66		66		132	100		

Some things to consider in designing primer is a primer size, GC base content and TM of the primer[17]. Size of the oligonucleotides used as primers are generally 18-28 nucleotides and has a G + C content of 50-60%[18]. In this range the primer could work specifically and more easily recognize the template DNA to be amplified. Primer size is too short will reduce the specificity of the primer, otherwise primer is too long also causes the PCR reaction was not effective[17].

From the result of primer design RS29F, RS29R and RS29C can be seen that all three of the primer has been in ideal condition. The content of GC and TM of primer is quite good, there is no possibility haipins and dimmer. Run of the three primer also in good criteria. Although there is still a possibility of self-dimer at primer RS29C, but the possibility of primer-dimers is very small. Based on the primer analysis of computerized (Table 1) it can be seen that the three primer design is ideal for use in a multiplex PCR reaction.

To determine the ability of design primer in detecting snp in the TCF7L2 gene particular rs290487, then be tested by ARMS-PCR. The principle of ARMS-PCR method used to detect a snp is multiplex PCR reaction. Three or more primer used to amplify a region of DNA simultaneously. One of the three primer is specific primers to identify strains that have a snp/mutation. The occurrence of snps in a particular area can be determined by designing primers that specifically recognize the position of having snp. This can be done by positioning the 3 'end of this primer exactly on which nucleotide has a snp/point mutation[17]. Visualization testing ARMS-PCR using primers RS29C, RS29F and RS29R can be seen in Figure 1.

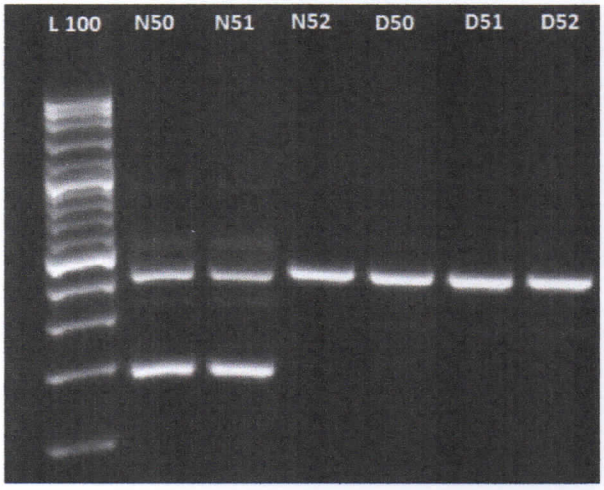

Figure 1. DNA electropherogram ARMS-PCR result of snp rs290487 TCF7L2 gene. D50: DM sample; N50: control sample; L DNA ladder 100 bp

Confirmation of ARMS-PCR test result is based on the presence or absence of PCR products in the target area (polymorphism). This is what will be used as reference to indicate the presence of snps in a gene. From Figure 1 it will be seen that the DNA samples taken from the normal (control) subject, PCR reaction that has been carried out produce two band/fragment. Both bands are expected to be the position of ± 415 bp and ± 193 bp. Otherwise, the result of PCR reaction used sample from patient with type-2 diabetes mellitus only produce one band.

The data indicates that in the sample produced only one band (± 415 bp) has occurred polymorphism/snp. snp or a single nucleotide change in the target (at 3 'end of primer) make primer cannot recognize the area. With the presence of the snp, primer pairs RS29R and RS29C could not anneal (work) and make the process of amplification because it has a different sequence in DNA template (has undergone a change) with design primer. So in this case primer annealed only at primer pairs RS29F and RS29R hence that is why only one band is appear. While the DNA sample that has not undergone a change, all primers can still recognize the area and make the process of amplification. From the results ARMS-PCR can be concluded primers designed that is able to identify snps in the TCF7L2 gene (rs290487).

After testing on the entire sample T2DM found 25 samples (38%) occurring polymorphism/snp at rs290487. The data were then analyzed using the chi-square test to determine the significance of association of snp rs290487 in the gene TCF7L2. The result data analysis of association snp rs290487 TCF7L2 gen Minangkabau T2DM can be seen in Table 2.

Table 2 shows no significant association (P^{value} > 0,005) between the snp rs290487 in the TCF7L2 gene with the possibility of T2DM on ethnic Minangkabau. This can be known froms is not too different allele frequency in DNA samples taken from diabetic patients with DNA taken from normal individuals (controls).

Several studies on the association of SNP rs290487 variant in the various ethnicities showed a positive association between TCF7L2 variants with the T2DM. Among them is a study conducted by Luo et al in East Asian ethnicity[19], in ethnic Chinese[20, 21, 22] and in northeastern chinese population[23]. However, in some other studies not found a significant association between rs290487 variant with the possibility of T2DM. This can be seen from the studies conducted in ethnic Japanese[24], in ethnic Chinese[25] and the in Chinese population[26]. Causes of differences in the effects that occur from this variant to T2DM can not be explained in detail. until now there is no fix mechanism that could explain why the SNP variants in the TCF7L2 gene may have different effects on different ethnicities. This SNP (rs290487) likely not affect to the incidence T2DM in ethnic Minangkabau. Chi-square test results for rs290487 showed the P^{value} = 1.00 (not significant) and OR = 1.067. However the effect of the other snp variant in TCF7L2 gene are not necessarily the same

(still have a chance). Therefore, further research is needed on several other SNP variants to determine the possibility of T2DM in ethnic Minangkabau.

Conclusion

We have successfully designed three pieces of primer: forward primer RS29C, forward primer RS29F and reverse primer RS29R. All primers were designed to be able to identify snp rs290487 TCF7L2 gene with ARMS-PCR method. In this study, not found significant association between rs290487 variant in TCF7L2 gene with the possibility of T2DM in ethnic Minangkabau.

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