The correlation between polymorphism of TCF7L2 gene and the incidence of type 2 Diabetes in Asian: a meta analysis

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Abstract. Transcription Factor7-like2 (TCF7L2) gene plays a role in the control of proglucagon production which is the precursor of the glucagon-like peptide-1 (GLP-1) hormone. GLP-1 protein plays a role in the homeostasis of blood sugar levels by increasing insulin secretion. The presence of this gene variant in beta cells of the pancreas shows impaired insulin secretion in vivo and in vitro studies. The objective of this study was to strengthen some research results related to the role of TCF7L2 gene polymorphisms in lowering insulin secretion and its correlation to the incidence of type 2 diabetes mellitus (T2DM) through an analysis. This study is a quantitative study based on a literature study (meta-analysis). The framework of the meta-analysis concept was based on the determination of odds ratio (OR), standard error (SE), determination of 95% Confidence Interval from ln (OR) and 95% for OR. Furthermore, the calculation of meta-analysis was performed. The analysis was conducted on 27 research results about TCF7L2 gene polymorphism which have been disclosed by 87 researchers in various research. Based on the results of data analysis, the correlation value was 2.6 and was in the acceptance of 95% confidence interval. Genetic and functional data indicate that the TCF7L2 gene plays an important role in insulin secretion and the intermediate phenotypes are associated with adipocytes. The TCF7L2 gene can activate special proteins that affect insulin secretion and sensitivity. The TCF7L2 protein is a transcription factor that regulates the proglucagon gene. Proglucagon is a precursor of the Glucagon-like peptide-1 (GLP-1) hormone, an insulinotropic hormone produced by enteroendocrine cells. TCF7L2 gene polymorphism plays an important role to decrease the secretion of GLP-1 and ultimately leads to decreased insulin secretion. Based on the correlation value, it can be concluded that there is a relationship between TCF7L2 gene polymorphism and the incidence of T2DM.

1. Introduction
Diabetes Melitus (DM) is a non-infectious diseases characterized by chronic hyperglycemia caused by an disturbance of insulin secretion [1]. Type 2 DM is characterized by insulin deficiency due to inadequate insulin secretion or the inability of the body to respond insulin, thus causing insulin resistance [1]. Diabetes mellitus (DM) is a metabolic disease characterized by high blood glucose levels (hyperglycemia) that result from the impaired insulin secretion by pancreatic β cells [2]. Patients with DM that are not managed properly can experience acute and chronic complications. Acute complications can be hyperosmolar hyperglycemia status, while chronic complications are like kidney failure, blindness, cardiovascular disease, stroke and others [3]. Decreasing of insulin secretion causes an increasing of hepatic sugar production and a decreasing of glucose use by tissues, resulting in chronic hyperglycemia. Prolonged chronic hyperglycemia causes fatigue of pancreatic β cells resulting in type 2 DM [4].
One of the genetic factors related to type 2 DM susceptibility is the TCF7L2 gene [5]. The TCF7L2 gene is a transcription factor that has function to increase the sensitivity of a group of functional receptors to the insulin hormone. Polymorphism (variation) in T allele frequency of all people in the world is different, because it can be influenced by genetic diversity factors between different ethnic groups [5].

Polymorphism is a variant of DNA sequences that can cause changes in the function of proteins in the body. This polymorphism can be caused by environmental exposure and mutagen. The impact of polymorphism causes the vulnerability of a population to an illness. Polymorphism will continue to be inherited so the frequency of polymorphisms in each ethnicity is different [6]. TCF7L2 gene polymorphism occurs when cytosine is replaced with thymine in the intron 3 position in wild-type due to alternative splicing [7].

Transcription Factor 7 Like 2 (TCF7L2) was originally called T-cell transcription factor 4, symbolized by TCF4. The TCF7L2 gene codes for the TCF7L2 protein, a DNA-binding protein that is a member of the T-cell factor (TCF) group and the nuclear interaction pair of β-catenin which forms an essential function in Wnt-signaling growth factor. The TCF7L2 gene has a size of 1791 bp, consisting of 17 exons and 13 introns. The TCF7L2 gene is located in long arm of chromosome 10 (10q25.3) [3].

The TCF7L2 gene is a gene that is indicated as a genetic factor in the susceptibility of type 2 DM in several ethnic groups. TCF7L2 is a transcription factor in the Wnt signaling pathway and can express on some tissues containing fat, liver and islets of Langerhans in pancreas. TCF7L2 gene plays an important role in Wnt signaling [8].

The TCF7L2 gene genotype in type 2 and non-DM subjects in the populations of Brazil, Denmark, United States, and India are CC, CT and TT genotypes [2, 9]. Assmann et al. (2014) stated that TCF7L2 gene polymorphism is associated with the incidence of type 2 DM in the Brazilian population seen from the high frequency of genotypes, consists of CC (40.1%), CT (43.1%) and TT genotype (16.4%) for subjects with type 2 diabetes mellitus, while non-DM subjects consists of CC (48.8%), CT (40.22%) and TT genotype (11%) [2]. Other studies with similar results also occur in the population of Hyderabad (India) [9]. Different results are shown in Samodro's study (2015), that the genotype of the TCF7L2 gene in obese type 2 DM subjects and non-obese DM in Javanese population was only two, namely CC and CT genotypes, whereas TT genotype was not found [3].

In this paper we presented the relationship between TCF7L2 gene polymorphism and the risk of diabetes mellitus in meta analysis. The TCF7L2 gene is strongly associated with type 2 diabetes mellitus in European and Asian ethnics. TCF7L2 gene polymorphism can be used as a prospective genetic marker in patient with type 2 diabetes mellitus [10].

2. Methods
A meta-analysis study of 27 articles from 87 researchers on the role of TCF7L2 gene polymorphism in Type 2 Diabetes Mellitus (DMT-2) susceptibility. This study used coding sheets as the instrument. Coding sheet is a table, with columns to write down some information and variables from the analyzed articles. The information and variables that were collected, namely: (a) the main researcher name, (b) year of publication, (c) population, (d) Asian ethnicity, (e) case-control research design, (f) the result of evaluation at the relationship between TCF7L2 gene polymorphism, (g) the using of Odd Ratio (OR) value, (h) 95% Confidence Interval value, and (i) control group based on the Hardy-Weinberg Equilibrium (HWE) calculation (p> 0.05). The data tabulation steps are: (1) identification of research variables which after being found, are categorized in the appropriate variable column, (2) identification of mean and standard deviation from the case and control group data for each subject or sub-study, (3) calculation of effect size by using the Glass[6] Formula based on the mean and standard deviation. The calculation results then written down into the appropriate column. To compare the case and control groups, the effect size is calculated by subtracting the mean scores of the control group to the
dependent variable and the average case group then divided by the standard deviation of the control group.

Table 1. The conceptual framework of meta analysis based on OR values

| CAPN-10 gene with polymorphism | DMT-2 Case | Control (healthy) |
|-------------------------------|------------|-------------------|
| (a)                           | (b)        |                   |
| CAPN-10 gene with no polymorphism | (c)        | (d)               |

Determination of ODDS Ratio (OR) = (a).(d) / (b).(c)

Determination of Log OR Variant, Var (ln(OR)) = 1/(a) + 1/(b) + 1/(c) + 1/(d)

Determination of Standard Error (SE), SE = \sqrt{\text{var}(ln(OR))}

Determination of 95% Confidence Interval from ln(OR), 95% CI from ln(OR) = ln(OR) ± 1.96 x (SE)

Determination of 95% for OR, 95% CI from OR = Exp. ln(OR) + 1.96 x (SE) s/d Exp.ln(OR)-1.96x(SE)

Effect Unification (τ) from the experimental group is defined as:

$$\tau = \frac{\sum_{i=1}^{k} W_i \cdot T_i}{\sum_{i=1}^{k} W_i}$$

Figure 1. The formula of effect unification

where:
τ : effect unification (OR-pooled)
W_i : Weight
T_i : OR
Weight Equation (W_i) is:

$$\frac{1}{\text{Var ln(OR)}}$$

Figure 2. The formula of weight equation

If (τ) assumed to have a normal distribution, then 95% Confidence Interval (CI) of all research results is: τ ± 1.96 x SE ln(τ).

Equation of SE ln(OR-pooled):

$$\sqrt{\frac{1}{\sum_{i=1}^{k} W_i}}$$

Figure 3. The formula of equation of SE ln

TCF7L2 polymorphism has two alleles: C and T. The analysis of the relationship between the TCF7L2 gene and the case of type 2 DM using dominant TT + CT and CC alleles, TT receptor and CC + CT.
3. Result and Discussion
The search for relationship between TCF7L2 gene and type 2 diabetes mellitus was resulted in 27 journals that stated there was a relationship between TCF7L2 gene and Type 2 Diabetes Mellitus. Twenty seven journals were used as the primer data for this study. After calculated the effect size for all research results, then the Odd Ratio (OR), Var ln (OR), Standard Error (SE), 95% Confidence Interval of ln (OR) and 95% Confidence Interval for OR were determined. Some of the studies that will be analyzed are presented in table 1.

Table 2. Characteristics of included studies of association between TCF7L2 polymorphism and T2DM risk

| No | Study                  | Years | Ethnic    | OR       | 95% CI         |
|----|------------------------|-------|-----------|----------|----------------|
| 1  | Yao et al [18]         | 2015  | Chinese   | 1.475    | (1.080-2.013) |
| 2  | Zhuang et al [19]      | 2018  | Chinese   | 2.63     | (1.31-5.25)   |
| 3  | Ngwa et al [20]        | 2015  | Chamerone | 0.69     | (1.33-1.94)   |
| 4  | Miyake et al [21]      | 2008  | Japanese  | 0.61     | (1.45-3.60)   |
| 5  | Hasibe[22]             | 2017  | Turkish   | 0.88     | (1.49-1.33)   |
| 6  | Buraczynska et al [23] | 2011  | Polish    | 1.70     | (1.36-2.11)   |
| 7  | NgMc et al [24]        | 2007  | Chinese   | 1.27     | (0.70-2.29)   |
| 8  | Ren et al [25]         | 2008  | Chinese   | 1.56     | (0.97-2.49)   |
| 9  | Lou et al [26]         | 2009  | Chinese   | 1.61     | (0.98-2.62)   |
| 10 | Lin et al [27]         | 2010  | Chinese   | 1.54     | (1.21-1.95)   |
| 11 | Wen et al [28]         | 2010  | Chinese   | 2.95     | (2.19-3.97)   |
| 12 | Zhao et al [29]        | 2011  | Chinese   | 3.29     | (1.03-10.52)  |
| 13 | Zheng et al [30]       | 2011  | Chinese   | 1.36     | (0.60-2.68)   |
| 14 | Chen et al [31]        | 2011  | Chinese   | 1.8      | (1.21-2.71)   |
| 15 | Feng et al [32]        | 2012  | Chinese   | 0.73     | (0.70-2.29)   |
| 16 | Liu et al [33]         | 2012  | Chinese   | 0.59     | (0.54-1.30)   |
| 17 | Qiao et al [34]        | 2012  | Chinese   | 0.54     | (0.75-17.16)  |
| 18 | Zhang et al [14]       | 2012  | Chinese   | 2.54     | (1.28-5.05)   |
| 19 | Wang et al [11]        | 2017  | Chinese   | 1.92     | (1.06-1.91)   |
| 20 | Ereqat et al [35]      | 2009  | Palestine | 0.41     | (1.04-1.83)   |
| 21 | Bodhini et al. [36]    | 2007  | Indian    | 0.53     | (0.75-1.44)   |
| 22 | Chandak et al [37]     | 2007  | Indian    | 0.72     | (1.07-3.47)   |
| 23 | Gupta et al. [38]      | 2010  | Indian    | 0.65     | (0.60-2.89)   |
| 24 | Jyothi et al [39]      | 2013  | Indian    | 1.89     | (1.57-2.26)   |
| 25 | Hussain et al [7]      | 2014  | Indian    | 0.35     | (1.04-1.84)   |
| 26 | Tangjittipokin et al. [40] | 2012 | Thailand | 0.64     | (1.58-9.10)   |
| 27 | Samodro [3]            | 2015  | Javanese  | 0.649    | (0.11-4.06)   |

TCF7L2 gene polymorphism genetically is a risk factor for type 2 diabetes mellitus with an OR value (2.60; 95% CI, 1.38-2.83; p < 0.005). The meta-analysis result showed that 18,373 T2DM Asian ethnic patients and 36,567 control subject, and demonstrated that TCF7L2 polymorphism was associated with an elevated risk for T2DM under the allelic, heterozygous, homozygous, dominant, and recessive models, which agrees with the original findings. The pooled OR for T2DM risk was 2.15 for allelic comparison (T vs C, 95%CI =2.15-2.42, p = 0.000, I² = 24.3%, p = 0.121), 2.23 for heterozygous comparison (CT vs CC, 95%CI = 2.36-2.23, p = 0.000, I² heterogeneity = 38.8%, comparison (TT vs CC, 95%CI = 2.33-1.82, p = 0.000, I² heterogeneity = 0.001), 1.74 for homozygous = 18.2%, P = 0.197), 1.60 for dominant comparison (TT+CT vs CC, 95%CI = 1.97-1.86, p = 0.000, I² heterogeneity = 14.88%, p = 0.218), 1.72 for recessive comparison (TT vs CT+CC, 95%CI = 1.72-1.96, p = 0.000, I² = 20.2%, p = 0.150).
An increase in the case of TCF7L2 genes is associated with elevated risk of T2DM in all ethnic groups around the world [10-12]. Non-consistent results were reported due to the limitness of sample size and ethnic heterogeneity. So, it can be said that the TCF7L2 gene polymorphism genetically is related to the susceptibility of T2DM. But the mechanism of the TCF7L2 relationship with the T2DM is still unclear. Loos et al. (2017) showed that TCF7L2 polymorphism increased the risk of T2DM through the malfunction of β cells and modulation of proinsulin levels in the British population [13]. TCFL2 encodes a basic helix-loop-helix transcription factor 4 (TCF-4), which is a nuclear receptor for the Wnt / β-catenin pathway, and binds to Wnt-responsive elements in β-catenin induced genes. As it is known that β-catenin / TCF-4 complex participates in various biological events. Particularly, the complex has been found to have a critical role in pancreatic and islet development, and thus contributes to T2DM initiation and progression. In addition, Wnt signaling may utilize β-catenin/TCF-4 to mediate the expression of many target genes such as tumor necrosis factor-α, interleukin-1β, fibroblast growth factor, and vascular endothelial growth factor [14]. Moreover, high levels of tumor necrosis factor-α were correlated with impaired glucose tolerance, defective gluco regulation, and glycated hemoglobin, as well as hyperglycemia and whole-body insulin resistance in T2DM [15-16]. Individuals with T2DM have significantly increased levels of interleukin-1β compared with healthy individuals [17].

4. Conclusion
From the result of the research and discussion above, it can be concluded that the TCF7L2 gene polymorphism played a role or as a risk factor for type 2 diabetes mellitus susceptibility. Based on the result of this meta-analysis, it is advisable for health care practitioners to analyze TCF7L2 gene polymorphism in people with degenerative disease, besides blood biochemical examination. Furthermore, given the benefits obtained through meta-analysis research, it is necessary to conduct similar studies for other fields and use more experimental research samples.

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