Meta-analysis of the association between the rs7903146 polymorphism at the *TCF7L2* locus and type 2 diabetes mellitus susceptibility

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Genet. Mol. Res. 14 (4): 16856-16862 (2015)
Received June 5, 2015
Accepted September 26, 2015
Published December 14, 2015
DOI http://dx.doi.org/10.4238/2015.December.14.12

ABSTRACT. Type 2 diabetes mellitus (T2DM) is a chronic disease caused by genetic and environmental factors. T2DM has been associated with specific polymorphisms in the *TCF7L2* gene. This study evaluates the relationship between the rs7903146 locus polymorphism of the *TCF7L2* gene and T2DM susceptibility through meta-analysis; the overall aim is to provide a basis for evidence-based medicinal treatment of T2DM. Cohort and case-control studies from Medline, PubMed, EMBASE, CBM, CNKI, and academic conferences/dissertations that examined the correlation between T2DM and rs7903146 polymorphisms were evaluated. We determined whether the TCF7L2 rs7903146 locus was associated with T2DM susceptibility by comparing alleles and genotypes. The Stata 11.0 software was applied for meta-analysis, and a random-effects model was adopted for heterogeneity testing and odds ratio (OR) calculation. A fixed-effect model was used for quantitative analysis of the heterogeneity between different studies, and for calculating the percentage of variability

I^2. A total of 10 studies related to the rs7903146 loci and T2DM susceptibility were enrolled; this included 3404 cases of T2DM patients and 6473 control cases. Meta-analysis showed that the T allele of rs7903146 was significantly correlated with the risk of T2DM, with both a dominant fixed-effect model (OR = 1.653, 95%CI = 1.416-1.653) and a co-dominant-fixed effect model (OR = 1.525, 95%CI = 1.350-1.723). Meta-analysis revealed that the T allele of rs7903146 was also correlated with T2DM susceptibility.

Key words: T2DM; rs7903146; TCF7L2; Polymorphism; Meta-analysis

INTRODUCTION

Type 2 diabetes is a disease with multifactorial etiology that is characterized by high blood glucose and associated metabolic disorders. Patients are at increased risk of cardiovascular and cerebrovascular disease, kidney disease, and nerve ending lesions; these complaints can seriously influence the quality of life of affected individuals. Global T2DM morbidity has increased significantly in recent years, and is a manifestation of combined environmental and genetic factors. Indeed, genome-wide association studies have implicated many genetic loci in the onset, prognosis, or severity of T2DM (Grant et al., 2006). Long-term studies are required for the identification of susceptibility genes in T2DM; this hampers progress in the field, as underscored by the discovery of only a handful of susceptibility genes by 2005. Furthermore, the penetrance of some of these genes with respect to T2DM onset or severity remains questionable (Coustan and Carpenter, 1998). The situation is also made more complex due to ethnic and socioeconomic factors (Buchanan, 2001). Here, we evaluated the relationship between *TCF7L2* rs7903146 locus polymorphisms and T2DM. This was performed by meta-analysis of cohort and case-control studies from Medline, PubMed, EMBASE, CBM, CNKI, and academic conferences/dissertations. The overall motivation for our study was to provide evidence-based rationale for screening and treatment of T2DM patients based on their genotype.

MATERIAL AND METHODS

Data source

Cohort and case-control studies between January of 2005 and November of 2014 that investigated the correlation between T2DM and TCF7L2 rs7903146 polymorphisms were searched from Medline, PubMed, EMBASE, CBM, CNKI, and academic conferences/dissertations. Keywords for searching include transcriptionfactor7-like2, TCF7L2 gene polymorphism, TCF7L2, rs7903146, type 2 diabetes, type 2, diabetes 2, and T2DM.

Inclusion and exclusion criteria

Inclusion criteria (Lapolla et al., 2009): 1) T2DM diagnosis as defined by the diagnostic criteria published by the World Health Organization (WHO) in 1999; 2) data in the enrolled cohort and case-control studies were original instead of cited; 3) all of the data related to genotypes are complete and can be used for further statistical calculations; 4) single data from the same race at

the same research period (time); 5) patients were randomly selected and the general data (such as the age, sex, occupation etc.) had no strict limits; 6) literature must have been published within the year limits described above; 7) and a sufficient level of data must have been available for calculation of the OR value and the 95%CI calculation.

Exclusion criteria: 1) data on T2DM was confounded by concomitant study of other diseases; 2) cohort study did not provide case detail; 3) single data from different ethnic groups and periods; 4) insufficient sample size (excluding the study of less than 50 samples).

Statistical analysis

Two researchers independently screened studies that met the above mentioned criteria. A third researcher was enlisted when these two researchers could not reach a consensus. Stata 11.0 was applied for statistical analysis. The D-L random-effect model was applied when the heterogeneity test showed P < 0.1, while the M-H-fixed-effect model was used when the heterogeneity test showed P > 0.1. The I^2 value was used to demonstrate the degree of heterogeneity between different studies. I^2 > 75% indicates high heterogeneity; I^2 > 56% suggests significant heterogeneity; I^2 between 31 and 56% represents moderate heterogeneity; and I^2 < 25% was interpreted as low heterogeneity.

RESULTS

General characteristics

As shown in Table 1, a total of 10 studies of rs7903146 and T2DM were enrolled (Shaat et al., 2007; Cho et al., 2009; Lauenborg et al., 2009; Ekelund et al., 2010; Aris, 2011; Papadopoulou et al., 2011; Pappa et al., 2011; Rizk et al., 2011; Klein et al., 2012; Vcelak et al., 2012). All 10 were case-control studies, providing a total of 3404 cases in the observation group and 6473 cases in the control group.

Table 1. Genotype distribution of the TCF7L2 rs7903146 gene polymorphism.

Author	Country	Sample size		CC/CT/TT genotype		T allele frequency (%)		P	OR
		T2DM	Control	T2DM	Control	T2DM	Control		
Ekelund (2012)	Switzerland	125	476	49/56/20	239/194/42	38.4	58.9	0.825	1.564
Papadbouolou (2011)	Switzerland	803	1110	363/352/88	644/384/82	32.9	24.7	0.024	1.675
Lauenborg (2009)	Denmark	276	2353	118/125/33	1292/863/198	34.6	59.2	0.002	1.631
Pappa (2011)	Greece	148	107	49/81/18	62/38/7	32.3	24.2	0.792	2.784
Shaat (2007)	Switzerland	585	1111	271/255/59	650/392/69	31.9	23.9	0.363	1.634
Cho (2009)	Korea	868	627	803/63/2	596/31/10	24.3	4.9	1	4.556
Vcelak (2012)	Czekh	261	376	142/102/17	156/185/35	26.1	33.9	0.067	0.594
Rizk (2011)	Qatar	40	74	16/18/6	29/37/8	37.5	35.8	0.613	0.967
Aris (2011)	Malaysia	173	114	1/43/129	0/15/99	86.7	93.4	1	0.502
Klein (2012)	Thailand	125	125	8/112/5	10/107/8	48.8	49.2	0	0.747

Meta-analysis

Meta-analysis showed that the T allele of rs7903146 was significantly correlated with T2DM risk. The co-dominance module yielded OR = 1.232, 95%CI = 1.002-1.232, while the recessive

module gave OR = 1.246, 95%CI = 0.912-1.703. Together, these data indicate that the T allele of rs7903146 is a T2DM susceptibility gene (P = 0.000). Heterogeneity and sensitivity analysis of the source are shown in Table 2. Single-variable multiple regression analysis, correction of publishing years, age and race, covariates showed no significant statistical difference. The heterogeneity and homogeneity tests were able to exclude that the differences were not due to substantial differences between the way each separate study was carried out.The sensitivity of T allele polymorphism in rs7903146 of TCF7L2 with T2DM yielded OR = 1.653, 95%CI = 1.416-1.930 in the dominant fixed-effect model and OR = 1.525, 95%CI = 1.350-1.7232 in the co-dominant fixed-effect model (Table 2).

Table 2. Meta-analysis of the relationship between the T allele polymorphism in rs7903146 of TCF7L2 and T2DM.

Data	Genetic module	Cases		OR (95%CI)		P	I^2
		T2DM	Control	FEM	REM		
Related literature	Dominant	3404	6473	1.477 (1.336-1.633)	1.384 (1.062-1.804)	0.016	79.60
	Recessive	3404	6474	1.360 (1.149-1.610)	1.246 (0.912-1.703)	0.168	61.40
	Co-dominant	3405	6475	1.341 (1.243-1.447)	1.232 (1.002-1.515)	0.048	83.10
Sensitivity analysis	Dominant	1936	2509	1.653 (1.416-1.930)	1.660 (1.350-2.040)	0.000	22.10
	Recessive	2027	2771	1.497 (1.161-1.930)	1.465 (0.992-2.165)	0.055	42.10
	Co-dominant	1766	2395	1.525 (1.350-1.723)	1.525 (1.350-1.723)	0.000	0.000

Dominant model: TT + TC *vs* CC; Recessive model: TT *vs* TC + CC; Co-dominant model: T *vs* C; FEM = fixed-effect model; REM = random-effect model.

Forest map analysis of the relationship between the TCF7L2 polymorphism and T2DM susceptibility

The D-L random-effect model was applied for data combination. Literature that did not conform to HWE genetic balance was excluded from the sensitivity analysis (Lauenborg et al., 2009; Papadopoulou et al., 2011; Klein et al., 2012). The heterogeneity between key factors is represented as a forest map (Figure 1).

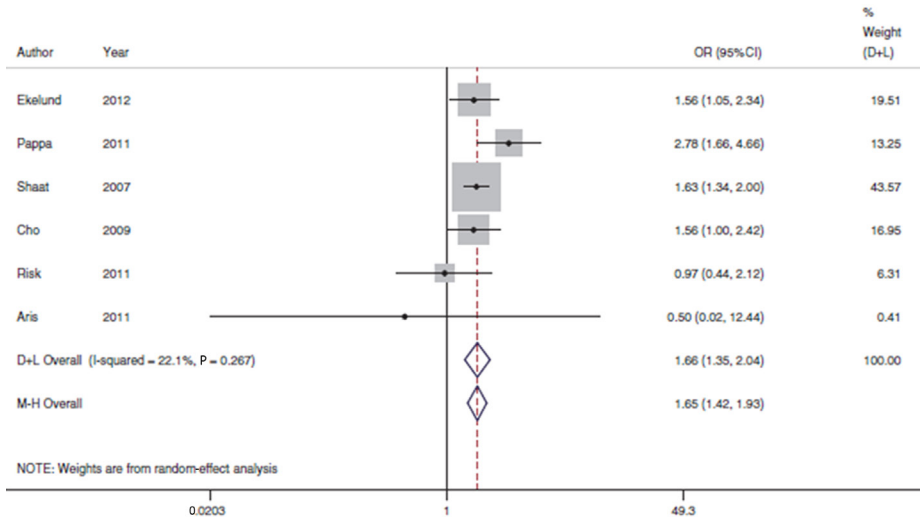

Figure 1. Forest map of the TCF7L2 rs7903146 polymorphism and T2DM susceptibility analysis.

DISCUSSION

Many studies indicate that T2DM prevalence varies greatly between different races, and also has a trend of family history (Duval et al., 2000). Technological developments such as next generation sequencing have increased our understanding of T2DM pathogenesis, and of genotype-phenotype relationships in this disease. With additional molecular profiling and further screening of large patient cohorts, it is hoped that a substantial breakthrough in T2DM management can be achieved (Florez et al., 2006).

Research into the combined effects of alterations at multiple genetic loci may help elucidate the molecular mechanism(s) that underlie disease pathology. Each genetic variation has a discrete effect on disease risk, and the cumulative effect across many genes can trigger disease onset (Saxena et al., 2006). In recent years, with the development of the gene chip technology, massively parallel sequencing has helped unearth several susceptibility genes that influence T2DM onset. Targeting some of these genes may provide the basis for gene therapy (Saxena et al., 2006). Among all genes studied, TCF7L2 has perhaps the greatest influence on T2DM susceptibility (Damcott et al., 2006).

TCF7L2, also known as lymphatic factor-4 (TCF4), is a gene located at 10q25.3 with 216.86 kbp in length. It highly expressed in fat cells and pancreatic cells, while its levels are low in bone cells and muscle cells. This distribution pattern is consistent with its proposed role in insulin secretion. TCF7L2 is an important component of the Wnt signaling pathway, which is most studied in the context of embryonic cellular development (Cauchi et al., 2006). In recent years, a growing number of studies have found that the Wnt signaling pathway is closely related to insulin secretion (Patsopoulos et al., 2008). Reflective of this convergence, it is now clear that TCF7L2 regulates insulin and glucagon gene secretion through the Wnt signaling pathway. Furthermore, several major genes in the Wnt signaling pathway can improve the function of beta cells in pancreatic islets, thereby regulating insulin secretion. They showed a two-way effect (regulation of insulin secretion in the body and the secretion of glucagon gene) in blood glucose regulation (Higgins et al., 2003).

Scholars conducted a linkage disequilibrium analysis on TCF7L2 gene variants with T2DM risk. They found that one of the segments of the chromosome has a close connection with T2DM pathogenesis by comparing the chromosome gene in T2DM patients and healthy subjects. Further gene chip positioning technology revealed that the TCF7L2 rs7903146 locus was the most relevant to T2DM. It is located in a linkage disequilibrium area that contains the TCF7L2 introns and exons (Williams et al., 2003). Further allele analysis demonstrated that T2DM patients generally inherit or acquire a T allele at the rs7903146 locus. In vivo experiments confirmed that this allelotype engenders the expression of metabolism-related markers and increases susceptibility to T2DM. Multiple prospective studies found patients carrying such polymorphisms have significant different insulin and blood glucose levels when compared with non-affected people. The main physiological basis for these differences is an altered secretion of glucose and arginine, which leads to reduced insulin secretion. In healthy individuals, the T allele of rs7903146 loci of TCF7L2 gene is negatively correlated with fasting insulin and cleaved proinsulin. The gene expression of women during pregnancy can be increased, which will also result in reduced insulin secretion and lead to gestational diabetes. In the elderly, the C/T allele of rs7903146 is also associated with reduced insulin levels and increased diabetes risk. TCF7L2 gene loci. Additionally, the C/T allele of rs7903146 and the G/T allele of rs12255372 are closely associated with the incidence of T2DM. Another study found that rs7903146 polymorphisms were associated with waistline reduction, BMI

reduction, and T2DM diagnosis; this correlation was stronger in younger subjects (Ben-Haroush et al., 2004). However, the risk of metabolic disease in patients with rs7903146 C/T alleles has not been fully explored.

With the improvements in genetic testing technology and increased focus on T2DM, there is now a large body of clinical data on the genetics of diabetes. Systematic analysis of the data may provide an evidence-based method for the identification of susceptibility genes. Scientists found that TCF7L2 polymorphisms are highly correlated with T2DM through multiple datasets (Munafo and Flint, 2004). Though racial differences exist in disease genotypes, several large-scale multi-center clinical studies, such as ones in Europe, America, Japan, Australia, China, Taiwan, and Hong Kong confirm that rs7903146 polymorphisms are closely correlated to T2DM (Yu et al., 2010). In the present study, we confirmed that the T allele of rs7903146 is associated with T2DM. However, there was considerable heterogeneity in the number of cases and the proportion of individuals from different ethnic groups across the ten studies we analyzed. Therefore, this could have biased the results somewhat, and future analyses will be designed to control better for this type of systematic error.

Conflicts of interest

The authors declare no conflict of interest.

ACKNOWLEDGMENTS

We thank the anonymous reviewers for reviewing this manuscript.

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