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Meta-analysis of the association between SNPs in *TCF7L2* and type 2 diabetes in East Asian population

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ABSTRACT

Aims: To evaluate the effect of *TCF7L2* on genetic susceptibility of type 2 diabetes (T2DM) in East Asian population by using the meta-analysis.
Methods: Search all the publications about the association between *TCF7L2* and T2DM in East Asian population from PubMed, CNKI and abstracts of major diabetes conferences. Perform the meta-analysis of all the validated studies and evaluate the association between rs7903146 T allele, rs12255372 T allele, rs11196205 C allele, rs290487 C allele and rs11196218 G allele of *TCF7L2* and the risk of T2DM.
Results: Eleven studies from nine eligible papers and one unpublished study of ours were included in the meta-analysis. Ten eligible studies were analyzed for rs7903146, five were analyzed for rs12255372 and rs11196205, and three were analyzed for rs290487 and rs11196218. We found that four SNPs (rs7903146, rs12255372, rs11196205, rs290487) in *TCF7L2* were significantly associated with T2DM in East Asian populations. The rs11196218 also showed a marginal association. The estimated population-attributable risk (PAR) associated with analyzed SNPs ranged from 2% to 7%.
Conclusions: SNPs in *TCF7L2* were strongly associated with the risk of T2DM in East Asian population. But the contribution of its genetic variants to the epidemic of type 2 diabetes in East Asian was relatively low.

1. Introduction

Recently, a common microsatellite in the *TCF7L2* gene region (DG10S478) was found to be associated with type 2 diabetes and this finding was convincingly replicated by using non-coding SNPs rs7903146, rs12255372 and rs11196205 that were in strong linkage disequilibrium with DG10S478 [1].

After the initial finding, many other research groups had found the consistently association between *TCF7L2* variants and type 2 diabetes in populations of different ethnic descent [2–8] including Europeans derived population, Africans, Americans and Asian Indians. The estimated population-attributable risk (PAR) was around 17–28%. In facts, the *TCF7L2* gene was regarded, so far, as the most influential gene in determining the genetic susceptibility for type 2 diabetes in human beings.

However, as summarized in Table 1, the replication studies in East Asian population including Japanese, Chinese and Korean did not show such a consistent result for rs7903146, rs12255372 and rs11196205 [9–17]. The major reason for the inconsistency might due to the fact that the risk allele frequencies of rs7903146 (0.01–0.03 in Chinese; 0.03–0.04 in Japanese; and 0.02–0.03 in Korean), rs12255372 (0.004–0.01 in Chinese; 0.02 in Japanese) and rs11196205 (0.01–0.03 in Chinese; 0.05 in Japanese) were very low in

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Table 1 – The association study results between five SNPs in TCF7L2 and type 2 diabetes from 12 eligible studies into meta-analysis.

Year	Author	rs7903146			rs12255372			rs11196205			rs290487			rs11196218		
		OR	95% CI	MAF	OR	95% CI	MAF	OR	95% CI	MAF	OR	95% CI	MAF	OR	95% CI	MAF
2008	Ren et al.	1.98	1.13–3.49	0.031	0.64	0.22–1.89	0.009				1.24	0.98–1.56	0.35			
2008	Luo et al.							1.10	0.64–1.90	0.030				1.04	0.85–1.29	0.26
2007	Lou et al.			0.023												
2007	Zeng et al.			0.013												
2007	Chang et al.	0.81	0.50–1.31	0.029	1.51	0.48–5.16	0.004				1.26	1.09–1.47	0.36			
2007	Ng et al.							2.11	1.04–4.26	0.013				0.70	0.56–0.88	0.29
2007	Hayashi et al.	1.30	1.00–1.68	0.042	1.70	1.20–2.41	0.022	1.37	1.08–1.73	0.052						
2007	Horikoshi et al.	1.69	1.21–2.36	0.030	1.21	0.82–1.81	0.020	1.21	0.92–1.56	0.050						
2008	Miyake et al.	1.48	1.20–1.84	0.038	1.70	1.30–2.22	0.022	1.39	1.16–1.67	0.053	1.04	0.95–1.14	0.36	0.94	0.85–1.05	0.22
2008	Ng et al.	1.30	0.95–1.76	0.023												
2008	Ng et al.	1.53	0.98–2.39	0.025												
2008	Ng et al.	1.29	0.90–1.87	0.024												

OR: odds ratio; 95% CI: 95% confidence interval; MAF: minor allele frequency in control group.

Japanese, Chinese and Korean. Due to the same reason, the effect size associated with these markers varied in a very wide range. Other two common SNPs, rs290487 and rs11196218, that were evaluated in four studies [9,12,13,16] in East Asian population also associated with varied effect sizes. The discrepancies also existed among studies carried out in the same ethnic groups [9,12,13,16]. Therefore, the current status of information regarding the association of SNPs in the *TCF7L2* region and type 2 diabetes made it hard to evaluate the impact of this gene on the genetic susceptibility of type 2 diabetes in East Asian populations. Studies with larger samples size with sufficient power was needed to clear this issue appropriately.

Previously, we had evaluated rs7903146, rs12255372, rs3814573, rs290487 and c.1637C>A of *TCF7L2* [9]. In the present report, we firstly examined rs11196205 and rs11196218 of *TCF7L2* in a case–control study in Chinese. Then, we systematically reviewed the association of these two polymorphisms and other polymorphisms that we had previously studied with risk of type 2 diabetes in a meta-analysis by combining our data with those from previous studies carried out in East Asian population.

2. Research design and methods

2.1. *Association study of rs11196205 and rs11196218*

Rs11196205 and rs11196218 were genotyped in five hundred diabetic patients and five hundred non-diabetic controls. Genotyping were conducted by ABI SNaPshot® Multiplex System operated at Chinese National Human Genome Center at Shanghai.

The clinical characteristics of study subjects were described in our previous publication [9].

2.2. *Identification and selection of studies included to meta-analysis*

We searched PubMed and CNKI (National Knowledge Infrastructure) database which was a Chinese database comprehensively collecting information on scientific publications (http://www.edu.cnki.net) as well as the abstracts published on the proceeding of scientific meetings of American Diabetes Association (ADA), European Association for the Study of Diabetes (EASD), International Diabetes Federation (IDF) and Chinese Diabetes Society (CDS) from March 2006 to July 2008. We extended the searching language to both English and Chinese. The key words of our search included *TCF7L2*, diabetes, Asian, Chinese, Japanese, Korean, Singaporean, and East Asian. All the studies included should be case–control study and in which the participants should be East Asian population (mainly from East-Asia and Southeast-Asia). We excluded studies without detailed data that prevent us from performing the meta-analysis.

2.3. *Statistical analysis*

We used the STATA 10.0 software to perform the meta-analysis. A fixed model was used if there was no heterogeneity