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Association of rs12255372 in the *TCF7L2* gene with type 2 diabetes mellitus: a meta-analysis

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Abstract

Our objective was to evaluate the association of rs12255372 in the *TCF7L2* gene with type 2 diabetes mellitus (T2DM) in the world population. We carried out a survey of the literature about the effect of rs12255372 on genetic susceptibility to T2DM by consulting PubMed, the Cochrane Library, and Embase from 2006 to 2012, and then performed a meta-analysis of all the studies in order to evaluate the association between rs12255372 and T2DM. A total of 33 articles including 42 studies (with 34,076 cases and 36,192 controls) were confirmed to be eligible and were included in the final meta-analysis: 6 studies conducted on Europeans, 14 on Caucasians, 17 on Asians, 2 on Africans, and 3 on Americans. Overall, the effect size was as follows: for the variant allele T (OR = 1.387, 95%CI = 1.351-1.424), for the TT genotype (OR = 1.933, 95%CI = 1.815-2.057), for the GT genotype (OR = 1.363, 95%CI = 1.315-1.413), for the dominant model (OR = 1.425, 95%CI = 1.344-1.510), and for the recessive model (OR = 1.659, 95%CI = 1.563-1.761). In summary, by pooling all available qualified data from genetic studies on rs12255372 and T2DM, we have confirmed that rs12255372 is significantly associated with susceptibility to T2DM in the global population.

Key words: Type 2 diabetes mellitus; rs12255372; SNPs; Meta-analysis

Introduction

Type 2 diabetes mellitus (T2DM) represents the most common major form of diabetes, which results from a defect in insulin secretion, almost always with a major contribution from insulin resistance. The incidence and prevalence of T2DM have reached epidemic proportions all over the world. It is predicted that there will be at least 350 million people in the world with T2DM by the year 2030, unless appropriate action is taken (1).

The mechanisms associated with T2DM have remained uncertain, but are considered to be due to a combination of lifestyle and genetic factors. Recently, research on genetic factors in T2DM has become more and more frequent and there is no doubt that the transcription factor 7-like 2 (*TCF7L2*) emerges as one of the strongest T2DM susceptibility genes among the possible candidate genes.

The *TCF7L2* gene spans 215.9 kb on chromosome 10q25, and rs12255372, located in the intron region of *TCF7L2*, contains a single G to T base transition at position 293. A number of epidemiological studies have evaluated the association between rs12255372 and T2DM, but the results remain conflicting rather than conclusive (2-34; see Table 1). Two meta-analyses on the association between the *TCF7L2* polymorphism rs12255372 and T2DM have been published (35,36). The first, published in 2009, detected significant associations between 4 single nucleotide polymorphisms (SNPs: rs7903146, rs12255372, rs7901695, and rs11196205) in *TCF7L2* and T2DM all over the world (35); however, only articles published before 2008 were included. The second meta-analysis published in 2009 focused on the alleles on 5 SNPs (rs7903146, rs12255372, rs11196205,

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Table 1. Distribution of genotypes of the rs12255372 polymorphism in studies of the *TCF7L2* gene and susceptibility to type 2 diabetes.

First author (Ref/year)/ethnicity	Genotype distribution										Frequency of risk allele (%)	
	Cases (n = 34,076)					Controls (n = 36,192)					Cases	Controls
	N	TT	GT	GG	P (HWE)	N	TT	GT	GG	P (HWE)		
Grant (31) 2006												
European	1086	154	476	456	0.258	795	71	316	408	0.684	36.1	28.8
European	221	29	88	104	0.331	520	43	185	292	0.216	33.0	26.1
Caucasian	344	62	144	138	0.846	509	39	186	284	0.546	39.0	25.9
Damcott (28) 2006												
Caucasian	137	24	67	46	0.963	342	47	159	136	0.961	42.0	37.0
Zhang (30) 2006												
Caucasian	1573	178	705	690	0.995	1947	140	772	1035	0.971	33.7	27.0
Scott (29) 2006												
European	1128	50	354	724	0.726	936	20	255	661	0.727	20.1	15.8
Cauchi (34) 2006												
Caucasian	2367	373	1131	858	1.000	2483	209	1031	1243	0.973	39.6	29.2
Groves (32) 2006												
Caucasian	2021	244	941	836	0.704	2491	214	1057	1220	0.782	35.4	29.8
Humphries (33) 2006												
Caucasian	1468	170	662	636	0.994	2489	188	994	1307	0.999	34.1	27.5
Asian	841	68	350	423	0.933	302	20	104	178	0.668	28.9	23.8
African	304	28	120	156	0.780	313	24	148	141	0.214	28.9	31.3
Horikoshi (17) 2007												
Asian	191	0	16	175	0.833	271	0	17	254	0.868	4.2	3.1
Asian	657	1	41	615	0.935	360	1	16	343	0.246	3.3	2.5
Asian	347	1	16	330	0.265	192	0	7	185	0.967	3.0	1.8
Kimber (25) 2007												
Caucasian	3225	359	1432	1434	0.999	3291	233	1323	1735	0.672	33.3	27.2
Marzi (26) 2007												
Caucasian	667	74	287	306	0.863	1658	107	698	853	0.0764	32.6	27.5
Mayans (20) 2007												
European	828	38	333	457	0.0651	786	28	236	522	0.979	24.7	18.6
van Vliet-Ostaptchouk (18) 2007												
Caucasian	492	59	217	216	0.924	901	84	348	469	0.256	34.0	28.6
Sale (23) 2007												
African	577	53	262	262	0.553	596	50	235	311	0.839	31.9	28.1
Guo (24) 2007												
American	1425	0	18	1407	0.972	1773	0	26	1747	0.953	2.8	1.7
Hayashi (21) 2007												
Asian	1630	3	112	1515	0.828	1043	0	45	998	0.776	3.6	2.2
Parra (27) 2007												
American	369	11	66	292	0.201	268	4	54	210	0.970	15.5	11.6
Bodhini (15) 2007												
Asian	1031	66	348	617	0.210	1038	46	305	687	0.272	23.3	19.1
Chandak (19) 2007												
Asian	955	99	377	479	0.160	399	22	134	243	0.825	30.1	22.3
Chang (16) 2007												
Asian	760	0	9	751	0.987	760	0	6	754	0.994	0.6	0.4

Continued on next page

Table 1. Continued.

First author (Ref/year)/ethnicity	Genotype distribution										Frequency of risk allele (%)	
	Cases (n = 34,076)					Controls (n = 36,192)					Cases	Controls
	N	TT	GT	GG	P (HWE)	N	TT	GT	GG	P (HWE)		
Sladek (22) 2007												
Caucasian	694	131	342	221	0.998	654	55	267	332	0.992	43.5	28.8
Miyake (14) 2008												
Asian	465	1	28	436	0.745	323	0	11	312	0.953	3.2	1.7
Asian	559	2	48	509	0.753	565	0	27	538	0.844	4.8	2.4
Asian	1146	2	76	1068	0.869	949	1	42	906	0.781	3.4	2.3
Rees (11) 2008												
Asian	817	89	346	382	0.726	435	41	153	241	0.0791	32.1	27.0
Ren (12) 2008												
Asian	500	0	9	490	0.839	500	0	9	490	0.839	0.9	0.9
Sanghera (13) 2008												
Asian	556	81	248	227	0.324	537	67	219	242	0.118	36.9	33.4
Cruz (9) 2010												
Caucasian	519	12	135	372	0.952	547	8	113	426	0.021	15.3	11.8
Gupta (10) 2010												
Asian	219	40	87	64	0.304	184	26	64	68	0.107	43.7	36.7
Martinez-Gomez (7) 2011												
Caucasian	719	10	147	562	0.912	746	10	151	585	0.942	15.6	11.4
Dabelea (8) 2011												
Caucasian	86	10	28	48	0.077	608	49	237	322	0.562	32.0	27.5
American	154	16	63	75	0.610	391	28	164	199	0.461	31.0	28.0
Turki (2) 2013												
Caucasian	900	154	430	311	0.797	875	101	353	424	0.038	41.0	34.0
Nemr (3) 2012												
Asian	691	159	345	187	0.996	919	113	418	388	0.979	48.0	35.0
Alami (4) 2012												
Asian	221	38	95	88	0.163	235	25	92	118	0.272	38.7	30.2
Kalnina (6) 2012												
European	1032	55	361	616	0.823	1079	37	322	720	0.892	22.8	18.4
Ciccacci (5) 2012												
European	154	32	70	52	0.350	182	19	80	83	0.966	44.0	32.0

HWE = Hardy-Weinberg equilibrium.

rs290487, and rs11196218) in *TCF7L2* polymorphisms and the risk for T2DM in the East-Asian population (36). However, this meta-analysis involved only 5 articles about the East Asian population published before 2008. In addition, 11 studies (2-10,13,28) examining the global population were published after the aforementioned meta-analyses. Therefore, a meta-analysis is currently needed to assess the associations between rs12255372 polymorphisms and the susceptibility to T2DM in the global population. The aim of the present study was to evaluate the association of rs12255372 with T2DM by performing a meta-analysis of 34,076 cases and 36,192 controls.

Research design and methods

Publication search

A systematic search of the US National Library of Medicine's PubMed, the Cochrane Library, and Embase databases was conducted for all genetic association studies on rs12255372 in the *TCF7L2* gene and T2DM published from 2006 [when the initial study reporting the association between rs12255372 and T2DM was published (31)] to 2012. The language was limited to English. The following search terms were used in our meta-analysis: 'rs12255372', '*TCF7L2*', 'T2DM/T2D', and 'genetic polymorphism'.

Inclusion criteria

We used the following criteria to select our literature: 1) original papers, 2) case-control studies, 3) studies that provided raw data for genotypic distribution or allele frequencies. A total of 41 papers were identified as potential candidates; 6 of them did not analyze rs12255372 and 2 did not concern the association between rs12255372 and T2DM and were excluded. Therefore, a total of 33 manuscripts were included in the final meta-analysis (2-34).

Data extraction

The following data were extracted independently from the articles by 2 of the authors (J. Wang and J. Zhang): first author's name, publication date, ethnicity, the sample size of cases and controls, allele frequencies, and numbers of each genotype.

Statistical analysis

To perform the meta-analysis, we used the METAN module within the STATA 11.0 software (USA). The strength of association between rs12255372 and the risk of T2DM was measured by odds ratios (ORs) with 95% confidence intervals (CI) via the Z-test. The heterogeneity index (I^2, 0-100) was applied to assess heterogeneity among the studies (37). If I^2 is above 50%, there is high heterogeneity between studies based on the Cochrane reviewer's handbook 4.2.2 (38). The fixed-effect model with the Mantel-Haenszel method was applied if heterogeneity was not an issue in the studies (39). Otherwise the random model using the DerSimonian and Laird method was used (40). Subgroup analyses were performed according to ethnicity (European, Caucasian, Asian, African, and American). A funnel plot was constructed to display the potential publication bias, in

Table 2. Results of meta-analysis for rs12255372 and type 2 diabetes.

Comparison	No. of studies	Odds ratio	95% confidence interval	Heterogeneity		
				Q	P	I^2 (%)
T allele *vs* G allele	42	1.387	1.351-1.424	80.11	<0.001	48.8
Europeans	6	1.386	1.290-1.488	2.43	0.787	0.0
Caucasians	14	1.401	1.346-1.448	38.50	<0.001	66.2
Asians	17	1.409	1.324-1.498	20.57	0.196	22.2
Africans	2	1.082	0.938-1.249	3.64	0.057	72.5
Americans	3	1.362	1.136-1.634	2.86	0.240	30.0
TT *vs* GG	38	1.933	1.815-2.057	63.33	0.004	41.6
Europeans	6	1.927	1.602-2.319	2.30	0.806	0.0
Caucasians	14	2.016	1.867-2.177	32.25	0.002	59.7
Asians	14	1.839	1.587-2.132	18.79	0.130	30.8
Africans	2	1.186	0.842-1.670	0.23	0.633	0.0
Americans	2	1.634	0.919-2.906	0.15	0.696	0.0
GT *vs* GG	42	1.363	1.315-1.413	69.19	0.004	40.7
Europeans	6	1.367	1.247-1.499	3.23	0.664	0.0
Caucasians	14	1.377	1.315-1.442	33.38	0.001	61.1
Asians	17	1.431	1.318-1.553	8.68	0.926	0.0
Africans	2	1.078	0.888-1.309	7.99	0.005	87.5
Americans	3	0.932	0.722-1.202	2.0	0.840	0.0
Dominant model	42	1.425	1.344-1.510	91.61	0.000	55.2
Europeans	6	1.437	1.316-1.568	2.49	0.778	73.2
Caucasians	14	1.462	1.333-1.605	48.47	<0.001	0.0
Asians	17	1.490	1.377-1.611	14.46	0.564	85.4
Africans	2	1.022	0.613-1.705	6.87	0.009	0.0
Americans	3	0.994	0.778-1.270	0.51	0.776	55.2
Recessive model	38	1.659	1.563-1.761	43.84	0.204	15.6
Europeans	6	1.700	1.421-2.033	2.70	0.746	0.0
Caucasians	14	1.711	1.590-1.841	20.78	0.077	37.5
Asians	14	1.568	1.364-1.802	13.85	0.385	6.1
Africans	2	1.143	0.822-1.589	0.08	0.777	0.0
Americans	2	1.629	1.932-2.849	0.20	0.656	0.0

which OR (in log units) was on the x-axis and the standard error of log OR was on the y-axis. If there is any publication bias, the funnel plot will support the presence of asymmetry. We assessed the funnel plot asymmetry by the Egger test. Sensitivity analysis was performed by omitting one study at a time and calculating the pooled ORs for the remaining studies.

Results

Description of the studies

The electronic search yielded 41 potentially relevant articles on the association between rs12255372 and T2DM; however, only 33 papers including 42 studies met our inclusion criteria and were included in the final meta-analysis (2-34). Table 1 lists the distribution of the rs12255372 genotypes in studies on the *TCF7L2* gene and susceptibility to T2DM. Among the 42 studies with 34,076 cases and 36,192 controls [3 studies in the paper by Grant et al. (31), 3 in the paper by Horikoshi et al. (17), 3 in the paper by Humphries et al. (33), 3 in the paper by Miyake et al. (14), and 2 in the paper by Dabelea et al. (8)], 6 studies were about Europeans, 14 about Caucasians, 17 about Asians, 2 about Africans, and 3 about Americans.

Results of the meta-analysis

Table 2 lists the main results of our meta-analysis, in which we analyzed OR for the risk allele T, the TT genotype, the GT genotype, the dominant model, and the recessive model. The heterogeneity test (I^2 >50%) revealed high heterogeneity between studies for the dominant model. A random effect model was applied and generated a combined allelic OR = 1.425 for the dominant model of 12255372 (95%CI = 1.344-1.510). Light heterogeneity was found between studies in other genetic models by I^2, and a fixed-effect model was applied for meta-analysis (for the risk allele T: OR = 1.387, 95%CI = 1.351-1.424; for TT *vs* GG: OR = 1.933, 95%CI = 1.815-2.057; for GT *vs* GG: OR = 1.363, 95%CI = 1.315-1.413; for the recessive model: OR = 1.659, 95%CI = 1.563-1.761). Figures 1 to 5 present the results of meta-analysis for rs12255372 from a pooled sample of 34,076 T2DM subjects and 36,192 control subjects from 42 studies.

Subgroup analyses

Subgroup analysis by ethnicity showed that all genotypes were significantly associated with T2DM for Europeans, Caucasians, and Asians; the risk allele T and the recessive model of rs12255372 were associated with T2DM for the American population; neither genotype contributed to T2DM among Africans (see Table 2). The difference in ethnicity contributed to the heterogeneity. The studies on Caucasians involved more heterogeneity,

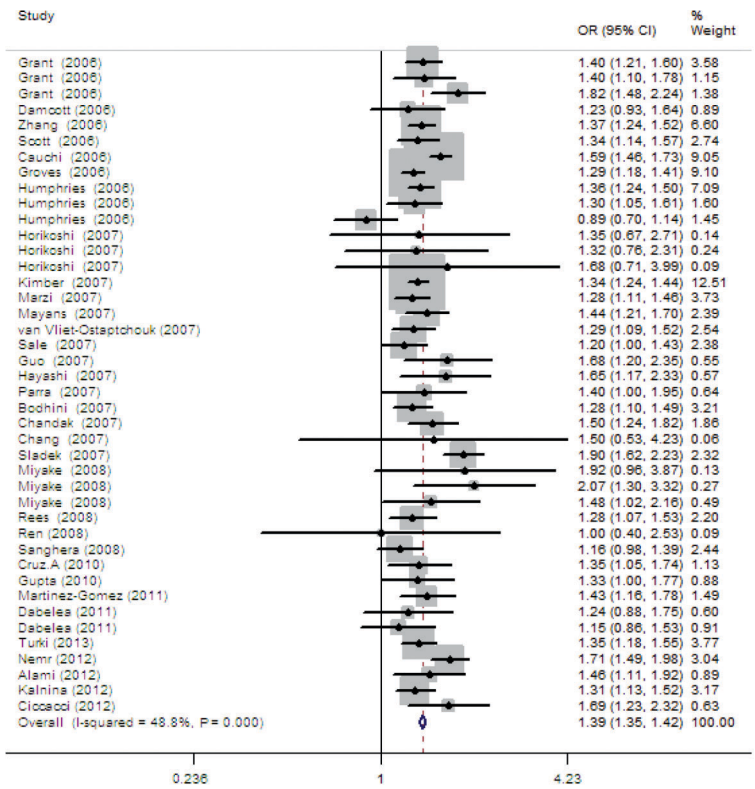

Figure 1. Meta-analysis of the association between type 2 diabetes and the risk allele T of rs12255372.

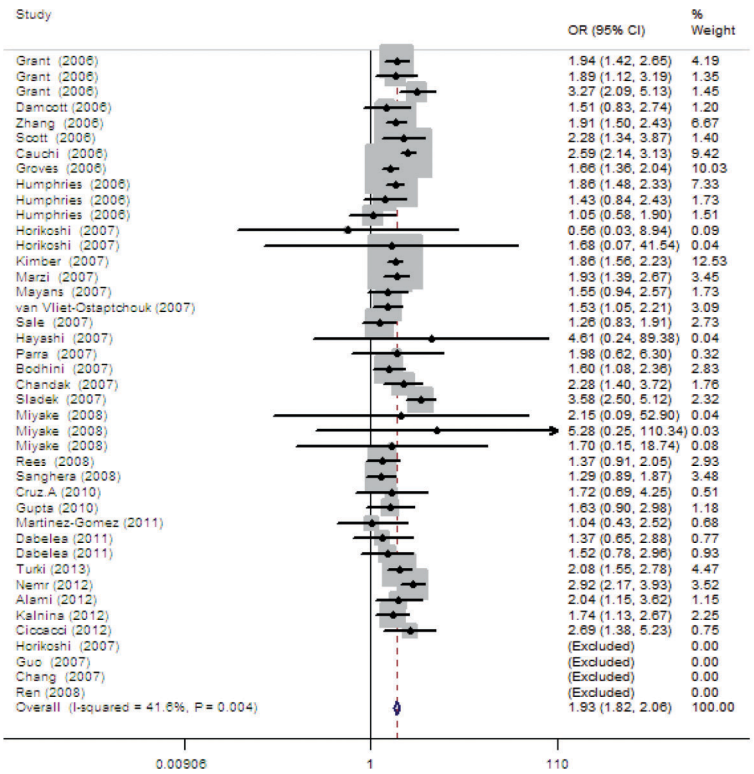

Figure 2. Meta-analysis of the association between type 2 diabetes and the TT genotype of rs12255372.

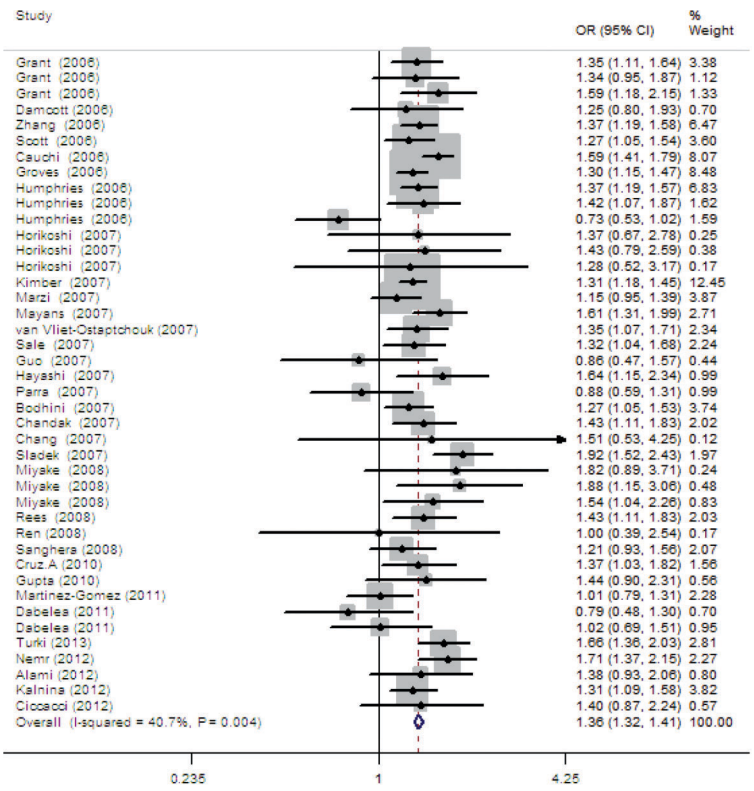

Figure 3. Meta-analysis of the association between type 2 diabetes and the GT genotype of rs12255372.

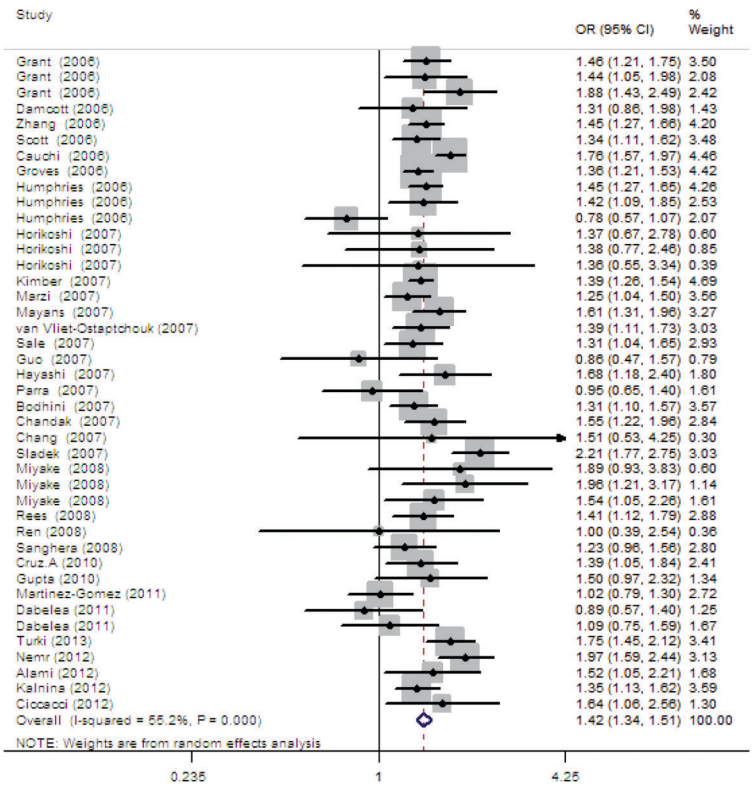

Figure 4. Meta-analysis of the association between type 2 diabetes and the dominant model of rs12255372.

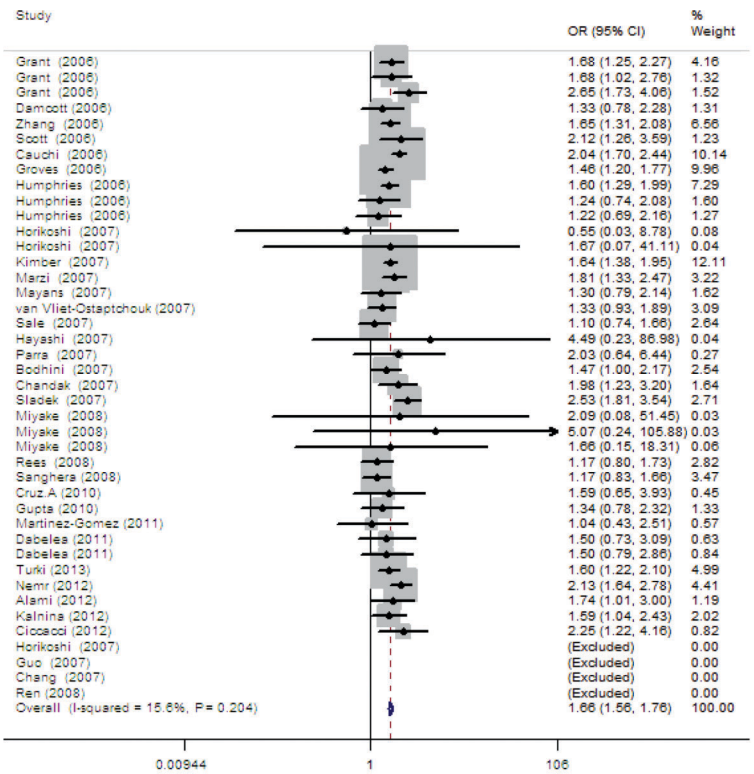

Figure 5. Meta-analysis of the association between type 2 diabetes and the recessive model of rs12255372.

Table 3. Results of the Egger test.

SNP	Genetic models	PE
rs12255372	T/G	0.610
	TT/GG	0.588
	GT/GG	0.658
	Dominant model	0.504
	Recessive model	0.912

SNP = single nucleotide polymorphism; PE = P values for publication bias from the Egger test.

with the complex compositions possibly being the main reason for this heterogeneity.

Publication bias

The funnel plot and the Egger test were performed to assess the publication bias of the literature. We displayed the funnel plot for ORs, and no evidence of obvious asymmetry was observed. All P values were higher than 0.05 according to the Egger test (see Table 3), and therefore no publication bias was found. Figure 6 presents Begg's funnel plots of publication bias.

Sensitivity analyses

We performed sensitivity analysis by omitting one study at a time and calculating the pooled ORs for the remaining studies. The results showed that none of the individual studies influenced the final conclusion. The sensitivity analysis indicated that our meta-analysis had reliable and stable results.

Discussion

TCF7L2 encodes an enteroendocrine transcription factor that controls the transcription of the proglucagon gene, which encodes both glucagon and glucagon-like peptide 1 (GLP-1). GLP-1 is a 30-amino acid peptide hormone produced by the intestinal epithelial endocrine L-cells by differential processing of proglucagon, the gene, which is expressed in these cells. The main actions of GLP-1 are to stimulate insulin secretion and to inhibit glucagon secretion, thereby contributing to limiting post-prandial glucose excursions. Therefore, it has been suggested that polymorphisms in the *TCF7L2* gene may affect the risk of T2DM by regulating the expression of GLP-1.

After a common microsatellite in the *TCF7L2* gene region (DG10S478) was found to be associated with T2DM and this finding was convincingly replicated by Grant in 2006 (31) by using non-coding SNPs rs7903146, rs12255372, and rs11196205 that were in strong linkage disequilibrium with DG10S478, many other epidemiological study groups have detected a consistent association between these SNPs and T2DM in different ethnic populations including Japanese, Chinese, Americans, and Asian Indians. However, although the association between rs12255372 and T2DM has been evaluated by many research groups, the results remain conflicting rather than conclusive. These conflicting results indicated that a meta-analysis would be essential in order to validate the association between rs12255372 and T2DM.

Our meta-analysis included 33 papers for rs12255372; the results showed that the variant allele T, the TT genotype, the GT genotype, the dominant model, and the recessive model were all strongly associated with T2DM in the global population. Because the risk allele frequency of rs12255372 differed greatly among ethnicities (about 0.000 to 0.029 for Asians, 0.217-0.500 for Europeans, and 0.267-0.274 for Sub-Saharan Africans), we performed subgroup analyses according to ethnicity. The results suggested that the role of rs12255372 in T2DM may be mediated by ethnicity. For Europeans, Caucasians, and Asians, all genotypes and the risk allele T were significantly associated with T2DM, while for Americans, only the risk allele T and the recessive model could notably increase the risk of T2DM, suggesting that, although the risk allele T may increase the risk of incidence of T2DM, both copies of the mutant allele could achieve the goal, and a copy of the wild allele could be sufficient to provide protection. In contrast, for Africans, neither genotype contributed to the risk of T2DM. First, the differences in ethnicity and region may contribute to the strong heterogeneity of the genetic phenotype of T2DM. Second, the lack of original data in the studies reviewed limited our further evaluation of potential interactions of rs12255372 and T2DM, and confounders such as gender, age, and body mass index (BMI) may have contributed to the different results. Third, since studies on Africans were relatively rare in our meta-analysis, this may have reduced the power to detect an association of rs12255372 with T2DM in Africans.

In multiple ethnicities, the differences were reflected not only in the distributions of minor allele frequency in rs12255372 but also in the linkage disequilibrium (LD) structure between rs12255372 and rs7903146. Table 4 summarizes the pairwise LD coefficients r^2 and D' between these two SNPs in different populations based on the data from HapMap (HapMap Data Rel 27 PhaseII+III, Feb09, on NCBI B36 assembly, dbSNP b126). The results showed that rs12255372 and rs7903146 are in relatively strong LD in Europeans, and therefore the effect of rs12255372 is not independent. rs7903146 is known to be the strongest SNP for the risk of T2DM, and therefore the interaction between these two SNPs may be the key point for the association with T2DM. More representative and comprehensive studies on populations of different ethnic backgrounds are needed to clarify the mechanisms and underlying genetic effects of these two SNPs for T2DM in the global population.

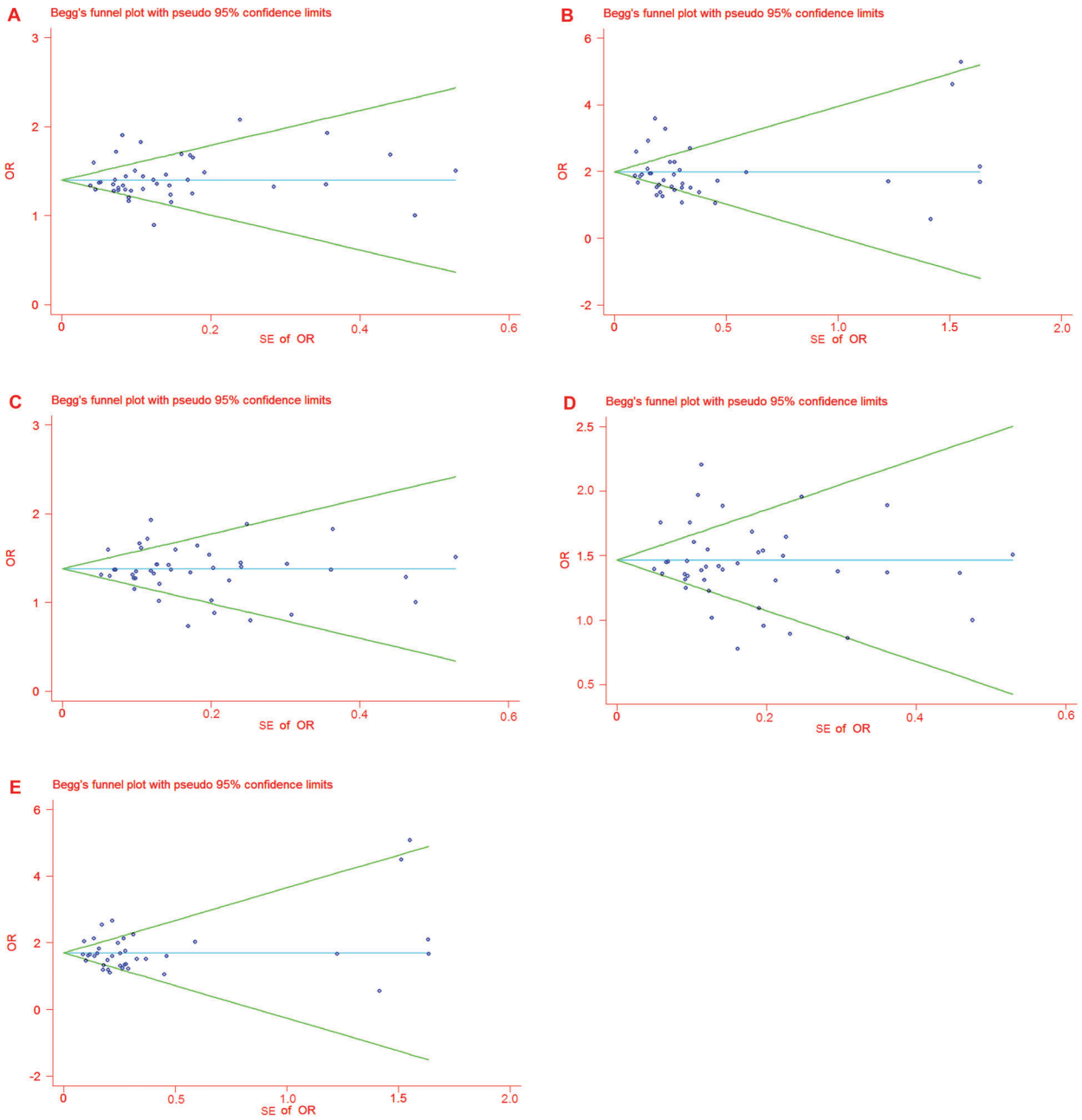

Figure 6. Funnel plot analyses for odds ratios. *Panel A*, Funnel plot analysis for odds ratios of allele T compared with allele G in the studies analyzed. *Panel B*, Funnel plot analysis for odds ratios of genotype TT compared with genotype GG in the studies analyzed. *Panel C*, Funnel plot analysis for odds ratios of genotype GT compared with genotype GG in the studies analyzed. *Panel D*, Funnel plot analysis for odds ratios of the dominant model. *Panel E*, Funnel plot analysis for odds ratios of the recessive model.

Table 4. Linkage disequilibrium (as r^2 and D') between rs12255372 and rs7903146 of the *TCF7L2* gene in multiple ethnicities.

	CEU	YRI	CHB + JPT
r^2	0.746	0.001	0.114
D'	0.948	0.075	0.479

CEU = Europeans; YRI = Sub-Saharan Africans; CHB + JPT = Chinese and Japanese.

However, due to the really weak LD structure between them, and coupled to the lower minor allele frequency, the effect of rs12255372 for the risk of T2DM in Sub-Saharan Africans and East Asians was quite small.

Hardy-Weinberg equilibrium is a principle showing how representative the samples are. Violations of Hardy-Weinberg assumptions can cause deviations from expectation. In our 33 eligible articles, the genotypes in both cases and controls almost conformed to the Hardy-Weinberg principle.

Heterogeneity is a potential problem when interpreting the results of meta-analysis. Our meta-analysis revealed high heterogeneity between studies for the dominant model (I^2 >50%). By subgroup analysis, we found that studies focusing on Caucasians exhibited more heterogeneity because of their complex composition. The differences in gender, age, and BMI among the studies, and the quality of the articles might also contribute to the heterogeneity.

Some limitations of this meta-analysis should be acknowledged. Because of the absence of detailed information about BMI, age, and gender in some studies, we did our research based on single-factor estimates without adjustment for the other risk factors mentioned above. On the other hand, our study also showed some strengths. First, the sample sizes of the studies included were relatively large, possibly reducing the influence of the low allele frequency. Second, our meta-analysis showed much better homogeneity, suggesting the uniform composition or character of our studies. Third, no publication bias was found in our meta-analysis by the funnel plot and the Egger test.

In summary, in this meta-analysis, by pooling all available qualified data of genetic studies on rs12255372 and T2DM, we confirmed that rs12255372 was significantly associated with susceptibility to T2DM in the global population, the risk allele and the genotypes could increase the risk of T2DM from 1.363- to 1.933-fold.

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