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Meta-analysis of association of common variants in the *KCNJ11-ABCC8* region with type 2 diabetes

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ABSTRACT. *KCNJ11* (potassium inwardly rectifying channel, subfamily J, member 11) and *ABCC8* (ATP-binding cassette, subfamily C (CFTR/MRP), member 8) have been studied for association with type 2 diabetes in various ethnic populations with contradictory results. We performed a comprehensive meta-analysis for *KCNJ11* rs5219, rs5210, rs5215, and *ABCC8* rs757110 to evaluate the effect of these regions on genetic susceptibility for type 2 diabetes. Forty-one case-control association studies of *KCNJ11* and *ABCC8* polymorphisms with type 2 diabetes, including 61,879 subjects, were identified and used in our meta-analysis. Combined odds ratios (OR) of associations of this disease with the rs5219 T, rs5210 G, rs5215 G, and rs757110 G alleles were 1.15 [95% confidence interval (95%CI) = 1.10-1.21, P < 0.0001], 1.16 (95%CI = 1.08-1.24, P = 0.023), 1.08 (95%CI = 1.02-1.13, P = 0.006), and 1.12 (95%CI = 1.07-1.18, P < 0.0001), respectively. The effect of allele T of rs5219 was similar (OR = 1.16) in Europeans and Japanese. However, rs5219 was not associated with type 2 diabetes in the Chinese Han population. Our meta-analysis demonstrated that *KCNJ11* and *ABCC8* polymorphisms are associated with risk for type 2 diabetes in the global population. Comparative genomics and bioinformatics

analyses revealed that rs5210 is located within a conserved 3'-UTR, and that allele A may abolish the binding site of hsa-miR-1910 that the risk allele G possesses.

Key words: *ABCC8*; *KCNJ11*; Type 2 diabetes; miRNA; Meta-analysis

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a chronic polygenic metabolic disorder that is characterized by impaired insulin secretion, insulin action, and hyperglycemia. Except for environmental factors such as obesity, diet, and physical inactivity, genetic factors play a key role in the development of T2DM. In the past two decades, a number of T2DM susceptibility genes have been identified by a candidate gene approach, family linkage studies, and gene expression profiling, including *KCNJ11* (potassium inwardly rectifying channel, subfamily J, member 11) and *ABCC8* (ATP-binding cassette, subfamily C (CFTR/MRP), member 8) (Huang et al., 2006).

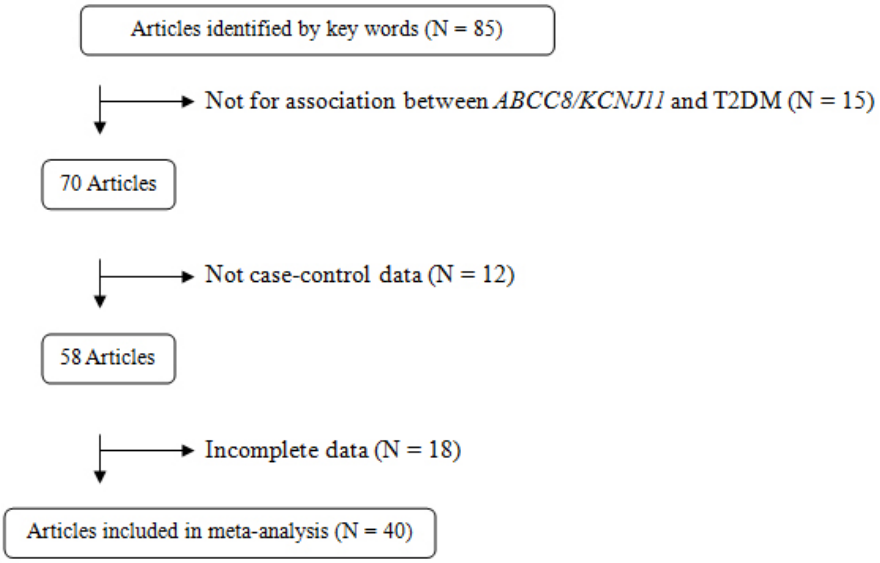
KCNJ11 and *ABCC8* are located adjacent to one another on the same locus, 11p15.1, and are only 4.5 kb apart (Inagaki et al., 1995). Mutations in these two genes have been associated with a few types of diabetes mellitus. About 30% of patients with permanent neonatal diabetes were found to be due to activating *KCNJ11* mutations (Gloyn et al., 2004). After a few years, activating mutations in the *ABCC8* gene were identified in other neonatal diabetes mellitus cases (Proks et al., 2006; Babenko et al., 2006). Functional studies have revealed that these mutations cause diabetes by reducing the sensitivity of the potassium channel K_{ATP} to adenosine triphosphate (ATP), thereby preventing insulin secretion (Remedi and Koster, 2010). A number of studies in different ethic populations have reported that multiple SNPs across *KCNJ11* and *ABCC8* were associated with the risk of T2DM (Hani et al., 1998; Gloyn et al., 2001, 2003; Chen et al., 2003; Frazer et al., 2004; van Dam et al., 2005; Hansen et al., 2005; Doi et al., 2007; Sakamoto et al., 2007; Alsmadi et al., 2008; Chistiakov et al., 2009; Hu et al., 2009; Yu, 2009; Tang, 2009). However, contradictory results were also reported in Japanese, Chinese, and European populations (John et al., 2004; Cejková et al., 2007; Vaxillaire et al., 2008; Xu et al., 2010). Moreover, results from several genome-wide association studies in a variety of populations have identified several SNPs in *KCNJ11* and *ABCC8* associated with T2DM (Florez et al., 2004; Willer et al., 2007; Tang, 2009; Chauhan et al., 2010). There is one exon in *KCNJ11* and 39 exons in *ABCC8*. Previous association studies have largely focused on rs5219 (exon 1, E23K, Chr11: 17409572), rs5215 (exon 1, Chr11: 17408630), and rs5210 (3'-UTR, Chr11: 17408251) in *KCNJ11*, and rs757110 (exon37, Chr11: 17418477) of *ABCC8*. To comprehensively assess the potential role of *KCNJ11* rs5219, rs5210, and rs5215 and *ABCC8* rs757110 in T2DM susceptibility, we performed an updated meta-analysis on eligible case-control studies worldwide, which included 61,879 individuals. Comparative genomic and bioinformatic approaches were used to explore the potential function of these SNPs in the regulation of gene expression.

MATERIAL AND METHODS

Search strategy and data collection

A PubMed search up to September 2011, using "*KCNJ11*" or "*KCNJ11* gene polymor-

phism" or "*KCNJ11* rs5219" or "*KCNJ11* rs5215" or "*KCNJ11* rs5210" or "*ABCC8*", and "diabetes" or "diabetes 2" or "type 2 diabetes" or "type 2 diabetes mellitus" or "T2D" or "T2DM" as key words, was performed. The references of all computer-identified publications were searched for additional studies. The PubMed option "Related Articles" was used to search for potentially relevant papers. Reference lists in retrieved articles were also screened. The search without any language restrictions was performed in duplicate by two independent reviewers (Y.L. and L.J.Q.). Only the studies with complete genotype data were selected. Articles with incomplete data were not included in our meta-analysis. We found 85 published articles, but only 40 articles with genotype frequency information were used in our meta-analysis (Table S1). The QUORUM flow chart is shown below:



Statistical analysis

The odds ratios (ORs) were calculated using 2 x 2 contingency tables for each study. The Stata 10.0 software was used to evaluate the heterogeneity between studies. Pooled ORs were computed by the fixed-effect model of Mantel-Haenszel (Peto's method) for data combined under no heterogeneity between studies. If there was significant heterogeneity between studies, the random-effect model of DerSimonian-Laird was then applied for combined data. Publication bias was evaluated by the Begg correlation test and the Egger linear regression test ($P < 0.05$ was considered to be significant).

Bioinformatic analysis

A comparative genomic approach was adopted to determine potential functional elements in the genomic region associated with T2DM. The chromosomal position of the region was submitted to the VISTA Genome browser. Per-computed whole-genome alignment between larger vertebrates, which had a high sensitivity in covering more than 90% of known exons, was available

on the browser with timely update upon the release of new genome assemblies (Frazer et al., 2004).

MicroRNA.org was adopted to predict common targets of the miRNAs. Target predictions of microRNA.org are based on the miRanda algorithm (John et al., 2004; Betel et al., 2008). miRanda analyzes the complementarity between a given mRNA and a set of miRNAs using a weighted dynamic programming algorithm. It computes a weighted sum of scores for matches and mismatches of base pairs. A value less than -0.1 is considered a "good" miR SVR score.

RESULTS

The characteristics of 40 published articles in our meta-analysis are summarized in Table 1. Forty association studies of *KCNJ11* and *ABCC8* with T2DM included 61,879 subjects (28,886 cases and 32,993 controls). Begg's correlation analysis indicated no publication bias for the SNP rs5219 (Figure 1).

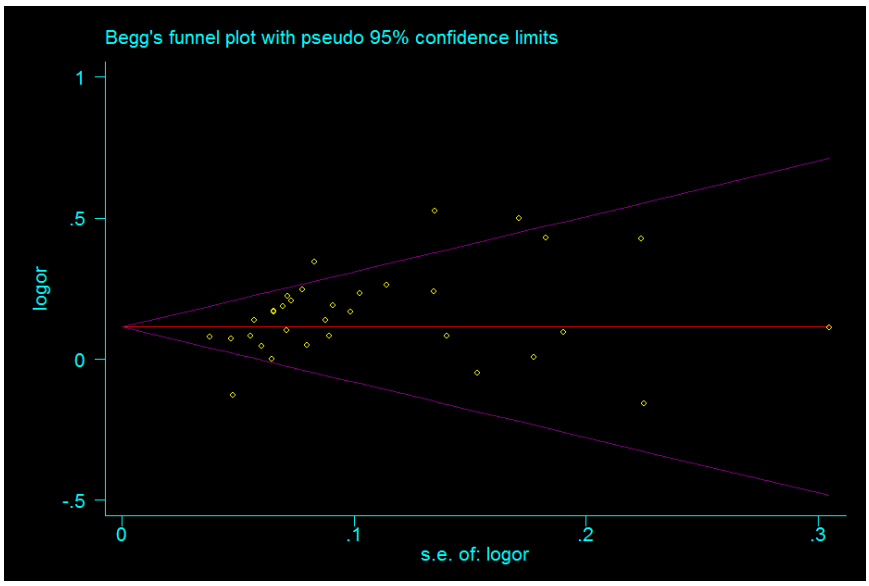


Figure 1. Egger's funnel plot for evaluation of publication bias for the SNP rs5219 (corrected z = 1.84 and corrected P = 0.065 for the Begg test, t = 2.57 and P = 0.015 for the Egger test).

KCNJ11 rs5219 and T2DM

Figure 2A presents the forest plot of risk allele OR of an individual study and meta-analysis for association between *KCNJ11* rs5219 and T2DM in a total of 23,262 T2DM patients and 27,042 control subjects from the 33 studies. Thirty studies showed a trend of elevated OR for the risk allele T. Two studies from China (Hu et al., 2009; Wang et al., 2011) and one study from Utah (Inoue et al., 1997) showed a trend in the opposite direction. Significant heterogeneity between studies was found ($P < 0.0001$, $I^2 = 58.9\%$). A random-effect model was thus performed for meta-analysis and generated a combined allelic OR = 1.15 (95%CI = 1.10-1.21, $P < 0.0001$) for the risk allele T of rs5219.

Table 1. Characteristics of case-control studies included in a meta-analysis.

Study	Ethnicity	Groups	No.	rs757110		rs5215		rs5219		rs5210	
				GG/GT/TT	MAF	AA/AG/GG	MAF	TT/TC/CC	MAF	GG/GA/AA	MAF
Sakura et al., 1996	UK	Case	100			46/56/16	0.373	17/45/38	0.395		
		Control	82			44/27/10	0.29	11/27/44	0.299		
Inoue et al., 1997	UK	Case	172			62/85/25	0.39	22/78/72	0.35		
		Control	96			25/64/7	0.41	6/52/38	0.33		
	Utah	Case	134					12/55/52	0.33		
		Control	74					3/44/21	0.37		
Hani et al., 1998	France	Case	168	25/76/52	0.412	164/23/0	0.061	51/87/53	0.495		
		Control	106	44/38/13	0.337	104/9/0	0.04	16/53/45	0.373		
Rissanen et al., 2000	Finnish	Case	40	NA	0.463						
		Control	377	NA	0.418						
Gloyn et al., 2001	UK	Case	364					66/161/133	0.407		
		Control	328					30/152/30	0.345		
Gloyn et al., 2003	UK	Case	854					134/412/308	0.398		
		Control	1182					157/534/491	0.359		
Nielsen et al., 2003	Danmark	Case	803					134/382/287	0.405		
		Control	862					124/408/330	0.381		
van Dam et al., 2005	Netherland	Case	192					34/92/66	0.417		
		Control	296					36/141/119	0.36		
Hansen et al., 2005	Danmark	Case	1187					196/568/423	0.404		
		Control	1454					206/668/580	0.371		
Cejková et al., 2007	Czech	Case	172					21/85/66	0.369	NA	0.324
		Control	113					18/47/48	0.367	NA	0.318
Willer et al., 2007[Δ]	Finnish	Case	1170							NA	0.329
		Control	983							NA	0.382
Vaxillaire et al., 2008[Δ]	France	Case	287					49/137/101	0.409		
		Control	2684					403/1287/994	0.39		
Chistiakov et al., 2009	Russia	Case	129					29/72/28	0.496		
		Control	117					12/69/36	0.397		
Chistiakov et al., 2010		Case	588					115/339/134	0.484		
		Control	597					62/352/183	0.399		
Qi et al., 2007	USA	Case	714					115/322/245	0.405		
		Control	1120					127/505/446	0.352		
Cornelis et al., 2009	USA	Case	2709					379/1275/1055	0.375		
		Control	3334					426/1536/1382	0.357		
Ezzidi et al., 2009	Tunis	Case	884					82/352/371	0.32		
		Control	513					40/213/250	0.291		
Cruz et al., 2010	Mexico	Case	519			NA	0.405			NA	0.324
		Control	547			NA	0.412			NA	0.318
Alsmadi et al., 2008	Saudi	Case	2709					22/187/341	0.21		
		Control	3344					8/75/252	0.136		
Neuman et al., 2010	Israel	Case	573					79/266/228	0.37		
		Control	843					100/404/339	0.358		
Chauhan et al., 2010	India	Case	1017					ND	0.39		
		Control	1006					ND	0.35		
Chavali et al., 2011	India	Case	1019	NA	0.42	NA	0.39	ND	0.39		
		Control	1006	NA	0.38	NA	0.35	ND	0.35		
Keiko et al., 1999	Japan	Case	31			8/10/6	0.458	7/13/11	0.435		
		Control	76			28/30/8	0.348	8/46/22	0.408		
Ohta et al., 1998	Japan	Case	100	NA	0.37						
		Control	67	NA	0.381						
Shigemoto et al., 1998	Japan	Case	236	44/115/77	0.43						
		Control	220	40/99/81	0.407						
Ishyama et al., 2006[Δ]	Japan	Case	1590	276/744/570	0.408			246/734/610	0.386		
		Control	1244	194/587/463	0.392			171/570/503	0.367		
Sakamoto et al., 2007	Japan	Case	909	151/441/310	0.412			127/446/333	0.386	213/471/213	0.5
		Control	893	126/407/357	0.37			107/396/386	0.343	188/445/253	0.463
Doi et al., 2007	Japan	Case	550					85/263/202	0.394		
		Control	1487					161/655/617	0.345		
Tabara et al ., 2009[Δ]	Japan	Case	484					83/232/169	0.411		
		Control	397					50/195/152	0.372		
Koo et al., 2007	Korean	Case	761			245/372/144	0.434	150/364/244	0.438	236/365/157	0.448

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Table 1. Continued.

Study	Ethnicity	Groups	No.	rs757110		rs5215		rs5219		rs5210	
				GG/GT/TT	MAF	AA/AG/GG	MAF	TT/TC/CC	MAF	GG/GA/AA	MAF
		Control	630			251/259/101	0.377	102/273/255	0.379	163/286/179	0.487
Chen et al., 2003	China	Case	105	25/60/20	0.476						
		Control	51	5/27/19	0.363						
Zhang et al., 2002	China	Case	502					NA	0.430		
		Control	501					NA	0.384		
Zhou et al., 2009	China	Case	1823					329/863/656	0.412		
		Control	1973					288/930/692	0.394		
Hu et al., 2009	China	Case	1849					NA	0.394		
		Control	1785					NA	0.425		
Yu, 2009	China	Case	295					27/150/118	0.346		
		Control	188					22/79/87	0.327		
Tang, 2009	China	Case	1529			NA	0.421				
		Control	1439			NA	0.405				
Xu et al., 2010	China	Case	1825			NA	0.411				
		Control	2200			NA	0.393				
Wen et al., 2010	China	Case	1165					183/587/395	0.409		
		Control	1136					193/517/425	0.398		
Liu et al., 2010	China	Case	397					86/180/131	0.443		
		Control	392					58/187/147	0.386		
Wang et al., 2011	China	Case	188					31/84/73	0.388		
		Control	170					24/88/58	0.4		

Characteristics of case-control studies included in a meta-analysis. MAF = minor allele frequency; Δ = data from GWAS; NA = not available.

In the stratified meta-analysis on the basis of ethnicity, 15 European studies including 9165 T2DM patients, and 13,300 control subjects showed a significant heterogeneity between studies (P = 0.05, I^2 = 40%). Fourteen studies showed a trend of increased OR for the risk allele T. One study from Utah (Inoue et al., 1997) showed a trend in the opposite direction. A random-effect model generated a combined allelic OR = 1.156 (95%CI = 1.11-1.20, P < 0.0001) for the risk allele T of rs5219 in the European population. Thirteen Asian studies including 13,213 T2DM patients and 13,229 control subjects showed significant heterogeneity between studies (P = 0.001, I^2 = 62.5%). Eleven studies showed a trend of high OR for the risk allele T. Two studies from China (Hu et al., 2009; Wang et al., 2011) showed a trend in the opposite direction. A random-effect model generated a combined allelic OR = 1.114 (95%CI = 1.036-1.198, P = 0.004) for the risk allele T of rs5219 in the Asian population. Seven Chinese studies including 6308 T2DM patients and 6213 control subjects showed a significant heterogeneity between studies (P = 0.004, I^2 = 68.9%). A random-effect model showed no association for allele T of rs5219 (P = 0.284) in the Chinese population. Five Japanese studies including 3561 T2DM patients and 4039 control subjects showed no significant heterogeneity between studies (P = 0.648, I^2 = 0.0%). A fixed-effect model generated a combined allelic OR = 1.157 (95%CI = 1.08-1.24, P < 0.0001) for the risk allele T of rs5219 in the Japanese population.

KCNJ11 rs5210 and T2DM

Five studies investigating the associations between rs5210 and T2DM in a total of 3863 T2DM patients and 3591 control subjects showed significant heterogeneity between studies (P = 0.029, I^2 = 62.9%). Three studies showed a trend of high OR for the risk G. One study from the Czech Republic (Cejková et al., 2007) and one study from Mexico (Cruz et al., 2010) showed a

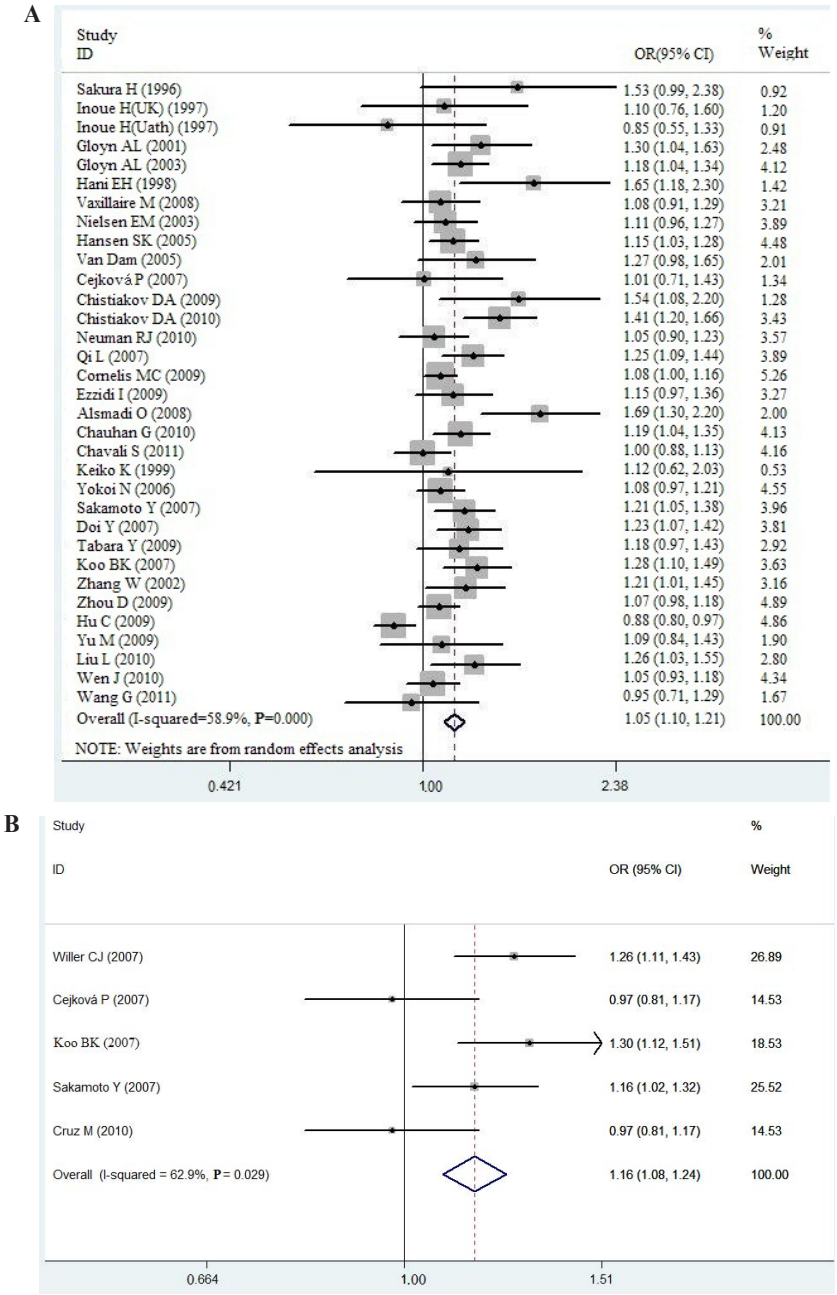

Figure 2. Forest plots of meta-analysis of the association of *KCNJ11* rs5219 (**A**), rs5210 (**B**), rs5215 (**C**), *ABCC8* rs757110 (**D**) with type 2 diabetes in 40 case-control studies. Estimations of odds ratios (OR) and 95% confidence intervals (95%CI) in each study are displayed as closed square and horizontal line, respectively. The size of the black squares reflects the weight of the study in the meta-analysis. The diamond represents the combined OR, calculated using a random- or fixed-effect model, with its 95%CI.

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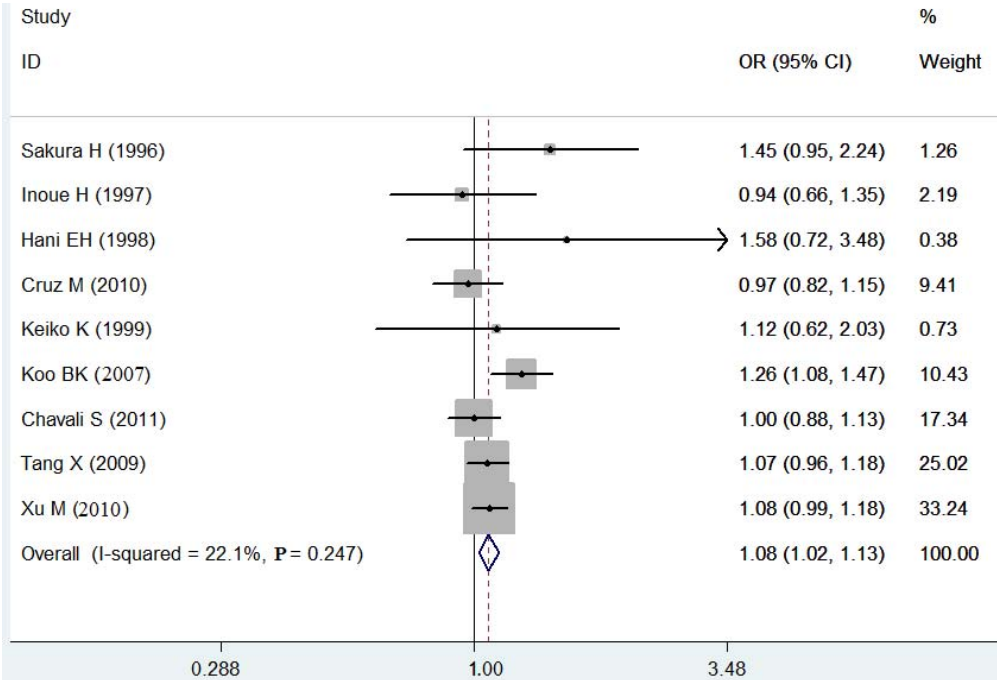
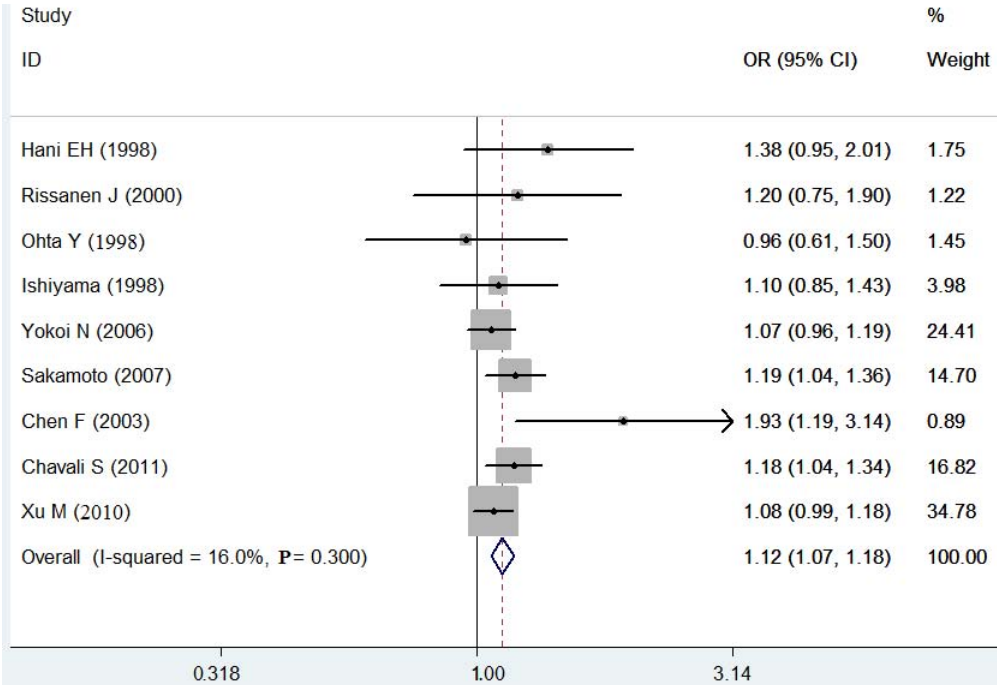
Figure 2. Continued.

C



D



trend in the opposite direction. Meta-analysis with a random-effect model generated a combined allelic OR of 1.16 (95%CI = 1.08-1.24, P = 0.023) for the risk allele G of rs5210 (Figure 2B).

KCNJ11 rs5215 and T2DM

Nine studies investigating the associations between rs5215 and T2DM in a total of 4179 T2DM patients and 4356 control subjects showed no significant heterogeneity between studies (P = 0.247, I^2 = 22.1%). Seven studies showed a trend of elevated OR for the risk G. One study from Japan (Inoue et al., 1997) and one study from Mexico (Cruz et al., 2010) showed a trend in the opposite direction. Meta-analysis with a fixed-effect model generated a combined allelic OR of 1.08 (95%CI = 1.02-1.13, P = 0.006) for the risk allele G of rs5215 (Figure 2C).

ABCC8 rs757110 and T2DM

Nine studies investigating the associations between rs757110 and T2DM in a total of 5835 T2DM patients and 5261 control subjects showed no significant heterogeneity between studies (P = 0.300, I^2 = 16.0%). Eight studies showed a trend of elevated OR for the risk allele G. One study from Japan (Ohta et al., 1998) showed a trend in the opposite direction. Meta-analysis with a fixed-effect model generated a combined allelic OR of 1.12 (95%CI = 1.07-1.18, P < 0.0001) for the risk allele G of rs757110 (Figure 2D).

Bioinformatic analysis

Since 3 SNPs genotyped within *KCNJ11* showed significant associations with T2DM in the meta-analysis, the chromosomal position of the *KCNJ11-ABCC8* region (Chr11: 17,406,795-17,498,449) was submitted to the VISTA genome browser to determine the presence of any potential conserved elements. RankVISTA for multiple alignment showed that the *KCNJ11* gene in humans is a conserved sequence in the pairwise alignments of *Mus* species (Figure 3). It is worth noting that rs5210 in the 3'-UTR of *KCNJ11* is located within a highly conserved region with an alignment P value of 1.9×10^{-41}. Prediction of potential miRNA targets with microRNA.org online revealed that the seed sequence of hsa-miR-1910 targets the *KCNJ11* 3'-UTR where rs5210 is located (miR SVR score: -0.1211; Phast Cons score: 0.6514).

DISCUSSION

To comprehensively evaluate the effect of the *KCNJ11-ABCC8* region on genetic susceptibility to T2DM, we performed an updated meta-analysis for rs5219, rs5210, and rs5215 in *KCNJ11* and rs757110 in *ABCC8*. The strongest association was observed between rs5219 and T2DM (OR = 1.15, P < 0.0001). Interestingly, our stratified meta-analysis by ethnicity suggested that the effect size for allele T of rs5219 in European and Japanese was similar (OR = 1.16), whereas no association for SNP rs5219 was observed in the Chinese Han population. It is noteworthy that the frequency of the risk T allele (40.1%) among Chinese controls was higher than that among European (36.8%) and Japanese controls (35.4%), whereas the frequency of the risk T allele was similar among Chinese, European, and Japanese patients with T2DM (40.6, 39.9, and 39.1%, respectively). In addition, significant associations were also

A

B

Human Feb. 2009(+)	017408236	GGGTGAGCCAGTCCTGAATTGGGTTGGGAGGAGCAGGGACAAAAATAACC	017408285
Chimp Mar. 2006(+)	017335043	GGGTGAGCCAGTCCTGAATTGGGGTGGGAGGAGCAGGGACAAAAATAACC	017335092
Rhesus Jan. 2006(-)	054552156	GGGTGAGGCAATCCTGAATTGGGTTGGGAGGAGCAAGGACAAAAATAACC	054552107
Marmoset Jun. 2007(+)	000062949	GGGTGAGCCAGTCCTGAATCGGGCTGGGAGGAGCAGGGACAAAAATAACT	000062998
Orangutan Jul. 2007(-)	052687124	GGGTGAGCCAGTCCTGAATTGGGTTGGGAGGAGCAGGGACAAAAATAACC	052687075

Figure 3. VISTA browser plot of the comparative analysis between human and mouse genome for the chromosomal position of *KCNJ11-ABCC8* (Chr11: 17,406,795-17,408,449 on the human Feb. 2009 genome). The red sign points to the genomic location of rs5210 in the x-axis.

observed for the rs5210 G, rs5215 G, and rs757110 G alleles in the global population. Our updated meta-analysis demonstrated that *KCNJ11* and *ABCC8* polymorphisms were associated with the risk of T2DM in the global population.

ABCC8 rs757110 and *KCNJ11* rs5219, which are in different linkage disequilibrium blocks, were found to be in strong linkage disequilibrium ($r^2 > 0.8$) in different populations. *KCNJ11* encodes the Kir6.2 subunit of the pancreatic β-cell ATP-sensitive potassium channel K_{ATP}, which operates as a high-fidelity molecular rheostat adjusting membrane potential-dependent functions to match cellular energy demands (Terzic et al., 1995; Alekseev et al., 2005). Mutations in the *KCNJ11* gene result in lower channel activity recognized in familial hyperinsulinemic hypoglycemia T2DM (Ashcroft, 2005). Recent findings indicated that *KCNJ11* rs5219 and *ABCC8* rs757110 variants display decreased ATP-inhibition, which may

contribute to the observed increased risk for T2DM (Hamming et al., 2009).

Our meta-analysis revealed significant between-study heterogeneity for SNPs rs5219 and rs5210. Between-study heterogeneity may be due to various differences. 1) Difference in the sample content. Some are thousands in a large sample size, and some only a few hundred. 2) Difference in geographical regions and race of subjects. 3) Differences in sample selection (age, gender). For example, both case and control groups are composed of females in one USA study (Qi et al., 2007). 4) Differences in diagnostic criteria for T2DM. T2DM was diagnosed based on 1985 or 1999 World Health Organization criteria in some studies (van Dam et al., 2005; Hansen et al., 2005; Alsmadi et al., 2008; Chistiakov et al., 2009), whereas according to 1998 American Diabetes Association criteria in other studies (Vaxillaire et al., 2008; Cornelis et al., 2009; Ezzidi et al., 2009). 5) Differences in genotyping methods. Some used a PCR-RFLP genotyping method and some used high-throughput SNP genotyping methods. 6) Differences in Hardy-Weinberg equilibrium (HWE), the principal law in population genetic studies. Sometimes HWE was met, but the genotype frequency was not always consistent with that of the local population. The complexity of T2DM or family history of cases may also affect the results. The factors that play a leading role across populations may be different. 7) Slightly different sources of the control groups. Some were from the general healthy population, some were patients in the hospital over the same period, and some were healthy donors. The different sources of controls may affect the representativeness of the sample.

Recent studies found that miRNA plays a key role in insulin production and secretion, pancreatic islet development, β-cell differentiation and insulin resistance, and is implicated in T2DM (Dehwah et al., 2012). Our comparative genomic analysis showed that rs5210 is located within a conserved 3'-UTR of the *KCNJ11* gene. Prediction of miRNA targets shows that the allele A at rs5210 may abolish the binding site of hsa-miR-1910 that the risk allele G possesses. The regulatory function of hsa-miR-1910 may be affected by the rs5210 A/G alleles. This theoretical prediction needs to be validated by experimental approach in the future.

In summary, our updated meta-analysis demonstrated significant associations of rs5219, rs5210, and rs5215 in *KCNJ11* and rs757110 in the *ABCC8* gene with the susceptibility of T2DM. The effect size for allele T of rs5219 was similar in European and Japanese, but no association was observed in the Chinese Han population. Comparative genomics and bioinformatic analyses revealed that rs5210 is located within a conserved 3'-UTR, and that allele A may abolish the binding site of hsa-miR-1910 that the risk allele G possesses.

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