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Genetic variants and the risk of gestational diabetes mellitus: a systematic review

Cuilin Zhang[1,*†], Wei Bao[1,*†], Ying Rong[2], Huixia Yang[3], Katherine Bowers[1], Edwina Yeung[1], and Michele Kiely[1]

[1]Epidemiology Branch, Division of Epidemiology, Statistics and Prevention Research, Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, 6100 Executive Blvd, Rockville, MD 20852, USA [2]Department of Nutrition and Food Hygiene, Hubei Key Laboratory of Food Nutrition and Safety, School of Public Health, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, China [3]Department of Obstetrics and Gynecology, Peking University First Hospital, Beijing 100034, China

*Correspondence address. Tel: +1-301-435-6917; Fax: +1-301-435-6917; Email: zhangcu@mail.nih.gov; wei.bao@nih.gov

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BACKGROUND: Several studies have examined associations between genetic variants and the risk of gestational diabetes mellitus (GDM). However, inferences from these studies were often hindered by limited statistical power and conflicting results. We aimed to systematically review and quantitatively summarize the association of commonly studied single nucleotide polymorphisms (SNPs) with GDM risk and to identify important gaps that remain for consideration in future studies.

METHODS: Genetic association studies of GDM published through 1 October 2012 were searched using the HuGE Navigator and PubMed databases. A SNP was included if the SNP–GDM associations were assessed in three or more independent studies. Two reviewers independently evaluated the eligibility for inclusion and extracted the data. The allele-specific odds ratios (ORs) and 95% confidence intervals (CIs) were pooled using random effects models accounting for heterogeneity.

RESULTS: Overall, 29 eligible articles capturing associations of 12 SNPs from 10 genes were included for the systematic review. The minor alleles of rs7903146 (*TCF7L2*), rs12255372 (*TCF7L2*), rs1799884 (−30G/A, *GCK*), rs5219 (E23K, *KCNJ11*), rs7754840 (*CDKAL1*), rs4402960 (*IGF2BP2*), rs10830963 (*MTNR1B*), rs1387153 (*MTNR1B*) and rs1801278 (Gly972Arg, *IRS1*) were significantly associated with a higher risk of GDM. Among them, genetic variants in *TCF7L2* showed the strongest association with GDM risk, with ORs (95% CIs) of 1.44 (1.29–1.60, $P < 0.001$) per T allele of rs7903146 and 1.46 (1.15–1.84, $P = 0.002$) per T allele of rs12255372.

CONCLUSIONS: In this systematic review, we found significant associations of GDM risk with nine SNPs in seven genes, most of which have been related to the regulation of insulin secretion.

Key words: gestational diabetes mellitus / single nucleotide polymorphism / gene / genetic factors

† The authors contributed equally to this work.

Introduction

Gestational diabetes mellitus (GDM), defined as glucose intolerance with onset or first recognition during pregnancy, is a growing health concern (Reece *et al*., 2009). The prevalence of GDM varies in different populations or ethnic groups. In the USA, ~7% (ranging from 1 to 14%) of all pregnancies are complicated by GDM (American Diabetes Association, 2004). Native American, Asian, Hispanic and African-American women are at higher risk for GDM than non-Hispanic white women (Ferrara, 2007). GDM increases risk of adverse pregnancy outcomes and has substantial long-term adverse health impacts on both mothers and their offspring, including a predisposition to obesity, metabolic syndrome and type 2 diabetes mellitus (T2DM) in later life (American Diabetes Association, 2004; Bellamy *et al*., 2009; Reece *et al*., 2009).

Well-documented risk factors for GDM include pre-pregnancy overweight and obesity, family history of diabetes and advanced maternal age (Ben-Haroush *et al*., 2004; Zhang and Ning, 2011). In the past decade, accumulating evidence has indicated that poor diet and low physical activity before or during pregnancy may also represent risk factors of GDM (Zhang and Ning, 2011). In addition, interesting, though limited, data have shown that a history of subfertility or infertility may be related to an elevated risk of GDM (Jaques *et al*., 2010; Reyes-Munoz *et al*., 2012). Moreover, polycystic ovarian syndrome, a contributor to ovulatory disorder fertility, has been repeatedly linked to an increased GDM risk (Boomsma *et al*., 2006; Bals-Pratsch *et al*., 2011; Reyes-Munoz *et al*., 2012).

There are relatively few published studies of the genetic susceptibility to GDM (Watanabe, 2011); although available data suggest that pregnancy complications have a familial tendency (Martin *et al*., 1985; Solomon *et al*., 1997). Moreover, GDM recurs in at least 30% (range 30–84%) of women with a history of GDM (Kim *et al*., 2007), potentially suggesting that there is a subgroup of women who may be genetically predisposed to develop GDM. Defects in both insulin secretion and insulin action are crucial in the pathogenesis of GDM (Buchanan and Xiang, 2005). A study among Danish twins showed major genetic components in both traits; more than 75% of the variation of the insulin secretion trait and at least 53% of peripheral insulin sensitivity can be explained by genetic components (Poulsen *et al*., 2005). Taken together, the evidence supports a genetic component in the etiology of GDM. Over the past few decades, genetic loci in several genes, responsible for insulin secretion, insulin resistance, lipid and glucose metabolism and other pathways, have been associated with GDM risk. However, inferences have been hindered by inconsistent findings across studies, partly owing to small sample size, moderate gene effects and insufficient statistical power (Robitaille and Grant, 2008).

In this study, we aimed to systematically review the current evidence regarding the genetic associations of GDM to quantitatively summarize the effect size of replicated single nucleotide polymorphisms (SNPs) on GDM risk, and to identify important gaps that remain for consideration in future studies.

Methods

We adhered to the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines (Stroup *et al*., 2000) when undertaking this study.

Literature search and data extraction

Genetic association studies of GDM published through 1 October 2012 were searched mainly using the HuGE Navigator (Yu *et al*., 2008), an integrated database of genetic associations and human genome epidemiology studies. The HuGE Navigator has been found to be equally sensitive, but more specific than PubMed in a previous validation study (Palomaki *et al*., 2010). The search term 'gestational diabetes [Text MesH]' was used for the Huge Navigator search. As the HuGE Navigator only retrieves articles published since 2001, an additional PubMed search was conducted to identify publications through 31 December 2001. For the PubMed search, the following search terms were used: ('Diabetes, Gestational/genetics'[Mesh] or 'Diabetes, Gestational/epidemiology'[Mesh] or 'Gestational diabetes'[tiab]) and ('Polymorphism, Single Nucleotide'[Mesh] or polymorphism*[tiab]) not (review[pt] or editorial[pt]). In addition, the references listed in relevant original papers and review articles were screened. No restriction was applied on language or geographical location in the literature search process.

Two reviewers (W.B. and Y.R.) independently evaluated the eligibility of inclusion and extracted the data, and disagreements were resolved by consensus. Articles were included if they reported original data about testing for SNP main effects on GDM risk. An SNP was included if the SNP–GDM associations were assessed in three or more independent studies. Cross-sectional, case–control and cohort studies were eligible for inclusion. Several types of articles were excluded: reviews or editorials, non-human studies (cell culture or animal studies), family-based studies, studies that did not include GDM as the primary outcome, studies that did not evaluate genetic associations of GDM and pharmacogenetics studies for anti-diabetic medication. In addition, other exclusions included studies that did not include a healthy control group, studies that did not report sufficient data for effect estimates of the genetic associations and studies that did not separately report association measures for GDM.

The following data were extracted from each published article: the first author's name, year of publication, sample size, number of GDM cases, ethnicity, mean age, study design (case–control, cross-sectional or cohort study), genetic variants, genotyping method, crude genotype and allele distribution by GDM status, odds ratios (ORs) and 95% confidence intervals (CIs). If ORs were available but the genotype and allele distributions according to GDM status were not reported in the original article, the corresponding authors were contacted by email.

Data synthesis and statistical analysis

The ORs of individual studies were recalculated from the available genotype distributions according to an allelic model, pooled using random effect models (DerSimonian and Laird, 1986) and visualized by forest plots. Hardy–Weinberg equilibrium (HWE) was assessed for each study by use of Fisher's exact test instead of the χ^2 test reported in the individual studies as it yields increased statistical power (Bauer *et al*., 2011). HWE was tested in the whole population for cohort studies and in the control group for case–control studies. Heterogeneity across all eligible comparisons was assessed using the χ^2-based Cochran's Q statistic and the I^2 metric (I^2 value of 25, 50 and 75% were considered as low, medium, and high heterogeneity, respectively; Higgins *et al*., 2003). The potential sources of identified heterogeneity among studies were investigated by stratification analyses. A formal meta-regression was not performed because the number of studies for some SNPs was small. Sensitivity analyses were performed by omitting one study at a time and computing the pooled ORs of the remaining studies to evaluate whether the results were affected markedly by a single study. The possibility of publication bias was statistically assessed using Egger regression asymmetry test (Egger *et al*., 1997).

All statistical analyses were performed using Stata software version 11.0 (Stata Corp, College Station, TX, USA). All *P*-values presented are two-tailed with a significance level of 0.05, except the Cochran's *Q* statistic in heterogeneity test in which the significance level was 0.10 (Higgins *et al*., 2003).

Results

Description of the included studies

The initial literature search yielded 89 articles from HuGE Navigator (2001–2012) and 23 articles from PubMed (1950–2001). After applying the inclusion and exclusion criteria, 29 articles capturing 12 SNPs from 10 genes were ultimately included in the systematic review and meta-analysis (Fig. 1). Of the 10 genes, six were related to insulin secretion, two to insulin resistance, one to energy metabolism and one to an inflammatory pathway (Table I). The study characteristics and the genotype and allele distributions of SNPs in the included studies are shown in Tables II and III, respectively.

Genes and genetic variants related to insulin secretion

Transcription factor 7-like 2 (TCF7L2)

The rs7903146 variant in the *TCF7L2* gene was the most widely studied variant in association with GDM, and showed a consistent and strong association across different populations. A meta-analysis of nine studies (Shaat *et al*., 2007; Cho *et al*., 2009; Lauenborg *et al*., 2009; Freathy *et al*., 2010; Pappa *et al*., 2011; Papadopoulou *et al*., 2011; Kwak *et al*., 2012; Vcelak *et al*., 2012) showed that the T allele of rs7903146 was associated with an increased risk of GDM [pooled OR 1.44 (95% CI 1.29–1.60), $P < 0.001$; Table IV, Fig. 2A]. The observed heterogeneity across studies for rs7903146 resulted from differences in the study populations in a stratification analysis by race/ethnicity; no significant heterogeneity was observed in Asians ($I^2 = 0.0\%$; *P* for the *Q* statistic = 0.916), although there was still a significant heterogeneity among Caucasians ($I^2 = 68.4\%$; *P* for the *Q* statistic = 0.007).

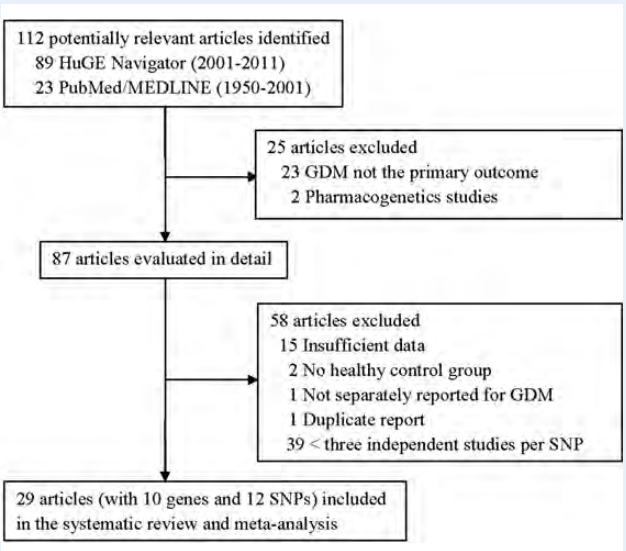

Figure 1 Flow chart for study selection.

In addition, a similar association was found in a meta-analysis of four studies (Watanabe *et al*., 2007; Cho *et al*., 2009; Papadopoulou *et al*., 2011; Vcelak *et al*., 2012) regarding the T allele of rs12255372 and GDM risk; the pooled OR was 1.46 (95% CI 1.15–1.84, $P = 0.002$), without significant heterogeneity across studies ($I^2 = 48.3\%$; *P* for the *Q* statistic = 0.122; Table IV, Fig. 2B). The similar effect sizes between associations of GDM risk with rs12255372 and rs7903146 were expected given the strong correlation between these two variants ($r^2 = 1$ in the HapMap CEU population; Povel *et al*., 2011).

No indication of publication bias was observed for either variant ($P = 0.148$ for rs7903146 and $P = 0.259$ for rs12255372 in the Egger's test). Deviations from the HWE were observed in two studies with rs7903146 (Lauenborg *et al*., 2009; Papadopoulou *et al*., 2011) and one with rs12255372 (Papadopoulou *et al*., 2011). In sensitivity analyses by omitting these studies, the pooled ORs were not changed materially and remained significant.

Glucokinase (GCK)

The association between the rs1799884 (also known as −30G/A) variant in the *GCK* gene and GDM risk has been widely investigated, but the results are conflicting (Chiu *et al*., 1994; Zaidi *et al*., 1997; Shaat *et al*., 2006; Freathy *et al*., 2010; Santos *et al*., 2010). Although early studies (Chiu *et al*., 1994; Zaidi *et al*., 1997) found no significant association between rs1799884 and GDM risk, subsequent studies with larger sample sizes found a significant association (Shaat *et al*., 2006; Freathy *et al*., 2010). A meta-analysis of these studies showed that the T allele of rs1799884 was associated with an increased risk of GDM [pooled OR 1.29 (95% CI 1.17–1.42), $P < 0.001$; Table IV, Fig. 2C]. No indication of significant heterogeneity across studies ($I^2 = 0.0\%$; *P* for the *Q* statistic = 0.878) or publication bias ($P = 0.467$ in the Egger's test) was observed.

Potassium inwardly rectifying channel, subfamily J, member 11 (KCNJ11)

The association between rs5219 (also known as E23K) and GDM was modest (ranging from 1.12–1.17) in the included studies (Shaat *et al*., 2005; Cho *et al*., 2009; Lauenborg *et al*., 2009; Pappa *et al*., 2011). Our meta-analysis showed that the T allele of rs5219 was associated with an increased risk of GDM [pooled OR 1.15 (95% CI 1.06–1.26), $P = 0.002$; Table IV, Fig. 2D]. No indication of significant heterogeneity across studies ($I^2 = 0.0\%$; *P* for the *Q* statistic = 0.976) or publication bias ($P = 0.750$ in the Egger's test) was observed.

CDK5 regulatory subunit associated protein 1-like 1 (CDKAL1)

The association between rs7754840 in *CDKAL1* and GDM risk has been examined in three studies, all of which were conducted among Asian populations (Cho *et al*., 2009; Wang *et al*., 2011; Kwak *et al*., 2012). Our meta-analysis indicated that the C allele of rs7754840 was significantly associated with risk of GDM [pooled OR 1.40 (95% CI 1.13–1.72), $P = 0.002$; Table IV, Fig. 2E]. The observed heterogeneity across these studies resulted from differences in the study populations; two studies in Korean women showed strong associations between rs7754840 and GDM risk (Cho *et al*., 2009; Kwak *et al*., 2012), whereas a study in Chinese women found no significant

Table I Genes and genetic variants included in the systematic review and their pathways

Gene	Chromosome location	Description	Variants	Insulin secretion	Insulin resistance	Other pathways
TCF7L2	10q25.3	Transcription factor 7-like 2	rs7903146 (IVS3C>T); rs12255372	Yes		
GCK	7p15.3–p15.1	Glucokinase	rs1799884 (−30G/A)	Yes		
KCNJ11	11p15.1	Potassium inwardly rectifying channel, subfamily J, member 11	rs5219 (E23K)	Yes		
CDKAL1	6p22.3	CDK5 regulatory subunit associated protein 1-like 1	rs7754840	Yes		
IGF2BP2	3q27.2	Insulin-like growth factor 2 mRNA-binding protein 2	rs4402960	Yes		
MTNR1B	11q21–q22	Melatonin receptor 1B	rs10830963; rs1387153	Yes		
PPARG	3p25	Peroxisome proliferator-activated receptor gamma	rs1801282 (Pro12Ala)		Yes	
IRS1	2q36	Insulin receptor substrate 1	rs1801278 (Gly972Arg)		Yes	
ADRB3	8p12	Adrenoceptor beta 3	rs4994 (Trp64Arg)			Energy metabolism
TNF	6p21.3	Tumor necrosis factor	rs1800629 (−308G/A)			Inflammation

association (Wang *et al.*, 2011). No indication of publication bias ($P = 0.703$ in the Egger's test) was observed.

Insulin-like growth factor 2 mRNA-binding protein 2 (IGF2BP2)

The association between rs4402960 and GDM risk showed similar effect sizes in Asian and Caucasian populations (Cho *et al.*, 2009; Lauenborg *et al.*, 2009; Wang *et al.*, 2011). A meta-analysis of these studies showed that the T allele of rs4402960 was significantly associated with an increased risk of GDM [pooled OR 1.21 (95% CI 1.10–1.33), $P < 0.001$; Table IV, Fig. 2F]. No indication of significant heterogeneity across studies ($I^2 = 0.0\%$; P for the Q statistic = 0.842) or publication bias ($P = 0.550$ in the Egger's test) was observed.

Melatonin receptor 1B (MTNR1B)

Kim *et al.* (2011) first found a significant association of GDM risk with two variants in the MTNR1B locus, rs10830963 and rs1387153, which are in tight linkage disequilibrium (LD) with each other ($|D'| = 0.89$). The association between rs10830963 and GDM risk was replicated in a subsequent study of a Greek population (Vlassi *et al.*, 2012). Our meta-analyses showed that the T allele of rs1387153 and G allele of rs10830963 were associated with an increased risk of GDM; the pooled ORs were 1.30 (95% CI 1.18–1.43, $P < 0.001$) and 1.28 (95% CI 1.05–1.55, $P = 0.016$), respectively (Table IV, Fig. 2G and H). There was no indication of significant heterogeneity across studies regarding rs1387153 and GDM risk ($I^2 = 0.0\%$; P for the Q statistic = 0.691). The observed heterogeneity across studies for rs10830963 resulted from differences in the study populations; the study in Greek women found a strong and significant association (Vlassi *et al.*, 2012), in Korean women, a weak but significant association (Kim *et al.*, 2011), while in Chinese women there was no significant association (Wang *et al.*, 2011). No indication of publication bias was observed for either variant ($P = 0.744$ for rs1387153 and $P = 0.567$ for rs10830963 in the Egger's test).

Genes and genetic variants related to insulin resistance

Peroxisome proliferator-activated receptor gamma (PPARG)

The association between rs1801282 and GDM risk has been examined in eight studies among several populations (Shaat *et al.*, 2004; Tok *et al.*, 2006b; Shaat *et al.*, 2007; Cho *et al.*, 2009; Lauenborg *et al.*, 2009; Cheng *et al.*, 2010; Heude *et al.*, 2011; Pappa *et al.*, 2011); however, none of these found a significant association. A meta-analysis of these studies showed that the G allele of rs1801282 was not significantly associated with GDM risk [pooled OR 0.94 (95% CI 0.82–1.07), $P = 0.322$; Table IV, Fig. 3A]. No indication of significant heterogeneity across studies ($I^2 = 0.0\%$; P for the Q statistic = 0.450) or publication bias ($P = 0.061$ in the Egger's test) was observed.

Insulin receptor substrate 1 (IRS1)

The association between rs1801278 (also known as Gly972Arg) and GDM has been examined in four studies (Shaat *et al.*, 2005; Fallucca *et al.*, 2006; Tok *et al.*, 2006a; Pappa *et al.*, 2011), all among Caucasians. Our meta-analysis of these studies showed that the T allele of rs1801278 was significantly associated with an increased risk of GDM [pooled OR 1.39 (95% CI 1.04–1.85), $P = 0.027$; Table IV, Fig. 3B). No indication of significant heterogeneity across studies ($I^2 = 34.5\%$; P for the Q statistic = 0.205) or publication bias ($P = 0.602$ in the Egger's test) was observed.

Genes and genetic variants related to other pathways

Adrenoceptor beta 3 (β3-adrenergic receptor, ADRB3)

Five small studies examined the association between rs4994 (also known as Trp64Arg) and GDM with inconsistent results (Festa *et al.*, 1999; Alevizaki *et al.*, 2000; Tsai *et al.*, 2004; Fallucca *et al.*, 2006; Shaat *et al.*, 2007). Festa *et al.* (1999) found that the A/G genotype was more frequent in women with GDM ($n = 70$) than in those with normal glucose tolerance ($n = 109$; 26 versus 11%; $P = 0.01$).

Table II Characteristics of the included studies regarding the association between genetic variants and GDM risk

Author, year (reference)	Study design	Ethnicity	Country	Number of cases	Number of controls	Mean age (cases/controls)	GDM criteria	Genotyping method
Chiu *et al.* (1994)	Case–control	African-American	USA	97	99	28.2/22.1	O'Sullivan and Mahan criteria	PCR–SSCP
Zaidi *et al.* (1997)	Case–control	Caucasian	UK	47	45	NA	OGTT 2 h glucose > 7.8 mmol/l	RFLP–PCR
Festa *et al.* (1999)	Case–control	Caucasian	Austria	70	109	NA	OGTT 1 h glucose ≥ 8.9 mmol/l or OGTT 2 h glucose ≥ 7.8 mmol/l	RFLP–PCR
Alevizaki *et al.* (2000)	Case–control	Caucasian	Greek	180	131	NA	ADA criteria	RFLP–PCR
Shaat *et al.* (2004)[a]	Case–control	Arabian	Sweden	100	122	31.9/NA	NA	RFLP–PCR
Tsai *et al.* (2004)	Case–control	Asian	China	41	258	NA	OGTT (not specified)	RFLP–PCR
Chang *et al.* (2005)	Case–control	Asian	China	35	35	30/28	OGTT (not specified)	RFLP–PCR
Shaat *et al.* (2005)	Case–control	Caucasian	Sweden	588	1189	32.2/30.5	EASD-DPSG criteria	TaqMan allelic discrimination assay
Fallucca *et al.* (2006)	Case–control	Caucasian	Italy	309	277	34.1/32.7	Carpenter and Coustan criteria	RFLP–PCR
Shaat *et al.* (2006)	Case–control	Caucasian	Sweden	642	1229	32.3/30.5	EASD-DPSG criteria	RFLP–PCR
Tok *et al.* (2006a)	Case–control	Caucasian	Turkey	62	100	NA	NDDG criteria	RFLP–PCR
Tok *et al.* (2006b)	Case–control	Caucasian	Turkey	62	100	NA	NDDG criteria	RFLP–PCR
Shaat *et al.* (2007)	Case–control	Caucasian	Sweden	649	1232	32.3/30.5	EASD-DPSG criteria	TaqMan allelic discrimination assay
Watanabe *et al.* (2007)	Case–control	Mexican-American	USA	94	58	35.0/33.4	OGTT (not specified)	TaqMan allelic discrimination assay
Cho *et al.* (2009)	Case–control	Asian	Korea	869	632	32/64.7	Third IWCGDM criteria	TaqMan allelic discrimination assay
Lauenborg *et al.* (2009)	Case–control	Caucasian	Denmark	283	2446	43.1/45.2	WHO criteria 1999	TaqMan allelic discrimination assay
Cheng *et al.* (2010)	Case–control	Asian	China	55	173	27/29.6	OGTT (not specified)	PCR–denaturing HPLC
Freathy *et al.* (2010) (Caucasians)	Case–control	Caucasian	Australia and UK	614	3811	NA	IADPSG 2010 criteria	TaqMan allelic discrimination assay
Freathy *et al.* (2010) (Asians)	Case–control	Asian	Thailand	384	1706	NA	IADPSG 2010 criteria	TaqMan allelic discrimination assay
Montazeri *et al.* (2010)	Case–control	Asian	Malaysia	110	102	NA	WHO criteria 1999	RFLP–PCR
Santos *et al.* (2010)	Case–control	Caucasian	Brazil	150	600	NA	ADA 2009 criteria	RFLP–PCR
Heude *et al.* (2011)	Cohort	Caucasian	France	109	1587	NA	50-g glucose load	RFLP–PCR or TaqMan allelic discrimination assay
Kim *et al.* (2011)	Case–control	Asian	Korea	928	990	33.17/32.24	Carpenter and Coustan criteria	TaqMan allelic discrimination assay
Papadopoulou *et al.* (2011)	Case–control	Caucasian	Sweden	826	1185	NA	EASD-DPSG criteria	TaqMan allelic discrimination assay
Pappa *et al.* (2011)	Case–control	Caucasian	Greece	148	107	32.5/26.67	Fourth IWCGDM criteria	RFLP–PCR
Wang *et al.* (2011)	Case–control	Asian	China	725	1039	32.0/30.0	ADA criteria	TaqMan allelic discrimination assay
Gueuvoghlanian-Silva *et al.* (2012)	Case–control	Mixed	Brazil	79	168	31.3/29.1	WHO criteria	RFLP–PCR
Kwak *et al.* (2012)	Case–control	Asian	Korea	1399	2025	31.5/59.1; 32.5/66.1	Third IWCGDM criteria	SNP array
Vcelak *et al.* (2012)	Case–control	Caucasian	Czech Republic	260	376	32.8/NA	Gestational diabetics meeting the 0.5–1 year interval after childbirth without other pathologies	TaqMan allelic discrimination assay

	Case–control	Caucasian	Greece	77	98	35.45/31.39	ADA criteria	RFLP–PCR
Vlassi *et al.* (2012)								

[a]The data of Caucasians were updated by Shaat *et al.* (2007) and therefore they were not included here.
ADA, American Diabetes Association; EASD-DPSG, the Diabetes and Pregnancy Study Groups of the European Association for the Study of Diabetes; GDM, gestational diabetes mellitus; HPLC, high-performance liquid chromatography; IADPSG, the International Association of Diabetes and Pregnancy Study Groups; IWCGDM, International Workshop-Conference on Gestational Diabetes Mellitus; NDDG, National Diabetes Data Group; OGTT, oral glucose tolerance test; RFLP, restriction fragment length polymorphism; PCR, polymerase chain reaction; SSCP, single-strand conformation polymorphism; WHO, World Health Organization.

However, this positive association was not confirmed in subsequent studies (Alevizaki *et al.*, 2000; Tsai *et al.*, 2004; Fallucca *et al.*, 2006; Shaat *et al.*, 2007). Our meta-analysis of these five studies showed no significant association between the G allele of rs4994 and GDM risk [pooled OR 1.20 (95% CI 0.88–1.65), $P = 0.252$; Table IV, Fig. 4A]. No indication of significant heterogeneity across studies ($I^2 = 38.8\%$; P for the Q statistic $= 0.163$) or publication bias ($P = 0.916$ in the Egger's test) was observed.

Tumor necrosis factor (TNF)

A meta-analysis of three studies (Chang *et al.*, 2005; Montazeri *et al.*, 2010; Gueuvoghlanian-Silva *et al.*, 2012) showed no significant association between rs1800629 and GDM [pooled OR 1.64 (95% CI 0.73–3.69), $P = 0.228$; Table IV, Fig. 4B]. The observed heterogeneity across these studies resulted from differences in the study populations; a significant and strong association between rs1800629 and GDM was found in a Chinese population (Chang *et al.*, 2005), but the positive genetic association was not replicated in Malaysians (Montazeri *et al.*, 2010) or Brazilians (Gueuvoghlanian-Silva *et al.*, 2012). No indication of significant publication bias ($P = 0.987$ in the Egger's test) was observed. It should be noted that the sample size in the included studies was small (in total 224 cases and 305 controls) and deviations from the HWE were observed in two studies (Chang *et al.*, 2005; Montazeri *et al.*, 2010); therefore the association between rs1800629 and GDM needs to be confirmed in more studies.

Discussion

In this study, we investigated relatively frequently studied genetic variants in association with GDM risk. Several previous reviews have mainly focused on the evidence regarding T2DM-associated common variants and GDM susceptibility (Watanabe *et al.*, 2007; Robitaille and Grant, 2008; Konig and Shuldiner, 2012; Mao *et al.*, 2012). Our systematic review provided a more comprehensive summary of the currently available evidence regarding GDM genetic variants. Overall, we observed significant associations of GDM with SNPs in the *TCF7L2*, *GCK*, *KCNJ11*, *CDKAL1*, *IGF2BP2*, *MTNR1B* and *IRS1* genes.

Although pregnancy is a condition characterized by progressive insulin resistance (Buchanan and Xiang, 2005; Watanabe, 2011), GDM develops in only a small proportion of pregnant women (American Diabetes Association, 2004). The insulin resistance that develops during pregnancy may result from a combination of increased maternal adiposity and the insulin-desensitizing effects of placental products such as human placental lactogen, estrogen and prolactin (Di Cianni *et al.*, 2003). Normally, the increased insulin resistance during pregnancy is compensated by the increase in insulin secretion by pancreatic islet β cells. As a result, the changes in circulating glucose levels over the course of pregnancy are quite small, compared with the large changes in insulin sensitivity (Buchanan and Xiang, 2005).

GDM could develop when a genetic predisposition of pancreatic islet β-cell impairment is unmasked by the increased insulin resistance during pregnancy (Lambrinoudaki *et al.*, 2010). Among the most widely studied genes of GDM included in the present systematic review, six genes (*TCF7L2*, *GCK*, *KCNJ11*, *CDKAL1*, *IGF2BP2* and *MTNR1B*) are thought to modulate pancreatic islet β-cell function (Petrie *et al.*, 2011; Schafer *et al.*, 2011), and all of them were significantly associated with GDM risk (ORs ranging from 1.15 to 1.46). In

Table III Genotype and allele distribution among GDM cases and controls in the included studies

Author, year	Gene	Variants	Minor allele	Number of participants		Genotypes in GDM cases[a]			Genotypes in controls[a]			Minor allele frequency (%)		HWE (*P*-value)
				Cases	Controls	AA	AB	BB	AA	AB	BB	Cases	Controls	
Chiu *et al.* (1994)	*GCK*	rs1799884	T	97	99	4	37	56	2	34	63	23.2	19.2	0.51
Zaidi *et al.* (1997)	*GCK*	rs1799884	T	47	45	2	20	25	1	22	22	25.5	26.7	0.14
Festa *et al.* (1999)	*ADRB3*	rs4994	G	70	109	0	18	52	0	12	97	12.9	5.5	1.00
Alevizaki *et al.* (2000)	*ADRB3*	rs4994	G	180	131	0	12	168	0	9	122	3.3	3.4	1.00
Shaat *et al.* (2004)[d]	*PPARG*	rs1801282	G	100	122	0	9	91	1	15	106	4.5	7.0	0.45
Tsai *et al.* (2004)	*ADRB3*	rs4994	G	41	258	1	6	34	6	63	189	9.8	14.5	0.80
Chang *et al.* (2005)	*TNF*	rs1800629	A	35	35	18	7	10	8	5	22	61.4	30.0	0.0002
Shaat *et al.* (2005)	*IRS1*	rs1801278	T	587	1189	4	49	534	0	111	1078	4.9	4.7	0.11
	KCNJ11	rs5219	T	588	1180	93	310	185	164	576	440	42.2	38.3	0.27
Fallucca *et al.* (2006)	*IRS1*	rs1801278	T	309	277	4	34	271	0	22	255	6.8	4.0	1.00
	ADRB3	rs4994	G	309	277	2	35	272	0	29	248	6.3	5.2	1.00
Shaat *et al.* (2006)	*GCK*	rs1799884	T	642	1229	26	181	435	24	316	889	18.1	14.8	0.57
Tok *et al.* (2006a)	*IRS1*	rs1801278	T	62	100	0	9	53	0	11	89	7.3	5.5	1.00
Tok *et al.* (2006b)	*PPARG*	rs1801282	G	62	100	0	12	50	0	16	84	9.7	8.0	1.00
Shaat *et al.* (2007)	*PPARG*	rs1801282	G	637	1232	11	158	468	16	298	918	14.1	13.4	0.17
	TCF7L2	rs7903146	T	585	1111	59	255	271	69	392	650	31.9	23.9	0.36
	ADRB3	rs4994	G	639	1227	5	100	534	9	158	1060	8.6	7.2	0.28
Watanabe *et al.* (2007)	*TCF7L2*	rs12255372	T	94	58	—	—	—	—	—	—	39.4	20.7	NA[b]
Cho *et al.* (2009)	*CDKAL1*	rs7754840	C	863	630	303	389	171	133	319	178	57.6	46.4	0.69
	IGF2BP2	rs4402960	T	857	627	103	365	389	57	257	313	33.3	29.6	0.70
	KCNJ11	rs5219	T	846	629	141	407	298	102	273	254	40.7	37.9	0.05
	PPARG	rs1801282	G	865	632	1	71	793	2	63	567	4.2	5.3	0.69
	TCF7L2	rs7903146	T	868	627	2	63	803	0	31	596	3.9	2.5	1.00
	TCF7L2	rs12255372	T	867	630	0	7	860	0	2	628	0.4	0.2	1.00
Lauenborg *et al.* (2009)	*IGF2BP2*	rs4402960	T	274	2334	27	132	115	224	972	1138	33.9	30.4	0.43
	KCNJ11	rs5219	T	255	2411	40	124	91	325	1101	985	40.0	36.3	0.54
	PPARG	rs1801282	G	265	2383	4	60	201	51	542	1790	12.8	13.5	0.19
	TCF7L2	rs7903146	T	276	2353	33	125	118	198	863	1292	34.6	26.8	0.002
Cheng *et al.* (2010)	*PPARG*	rs1801282	G	55	173	0	3	52	0	16	157	2.7	4.6	1.00
Freathy *et al.* (2010) (Caucasians)	*GCK*	rs1799884	T	614	3197	32	194	388	90	920	2187	21.0	17.2	0.62
	TCF7L2	rs7903146	T	614	3197	75	246	293	295	1311	1591	32.2	29.7	0.29
Freathy *et al.* (2010) (Asians)	*GCK*	rs1799884	T	384	1322	5	91	288	15	220	1087	13.2	9.5	0.33
	TCF7L2	rs7903146	T	384	1322	0	46	338	3	108	1211	6.0	4.3	0.73
Montazeri *et al.* (2010)	*TNF*	rs1800629	A	110	102	3	4	103	2	6	94	4.5	4.9	0.01
Santos *et al.* (2010)	*GCK*	rs1799884	T	150	600	8	56	86	27	186	387	24.0	20.0	0.44
Heude *et al.* (2011)	*PPARG*	rs1801282	G	109	1587	0	17	92	17	305	1265	7.8	10.7	0.80[c]
Kim *et al.* (2011)	*MTNR1B*	rs1387153	T	909	972	241	433	235	204	455	313	50.3	44.4	0.10
	MTNR1B	rs10830963	G	908	966	256	435	217	203	469	294	52.1	45.3	0.56

Papadopoulou *et al.* (2011)	*TCF7L2*	rs7903146	T	803	1110	88	352	363	82	384	644	32.9	24.7	0.02
	TCF7L2	rs12255372	T	801	1102	81	333	387	84	385	633	30.9	25.1	0.02
Pappa *et al.* (2011)	*IRS1*	rs1801278	T	148	107	17	73	58	7	40	60	36.1	25.2	1.00
	KCNJ11	rs5219	T	148	107	10	42	96	4	33	70	20.9	19.2	1.00
	PPARG	rs1801282	G	148	107	0	5	143	0	7	100	1.7	3.3	1.00
	TCF7L2	rs7903146	T	148	107	18	81	49	7	38	62	39.5	24.3	0.79
Wang *et al.* (2011)	*CDKAL1*	rs7754840	C	697	1020	159	339	199	197	512	311	47.1	44.4	0.61
	IGF2BP2	rs4402960	T	705	1025	56	278	371	59	361	605	27.7	23.4	0.60
	MTNR1B	rs10830963	G	700	1029	137	364	199	191	509	329	45.6	43.3	0.85
Gueuvoghlanian-Silva *et al.* (2012)	*TNF*	rs1800629	A	79	168	2	18	59	4	31	133	13.9	11.6	0.24
Kwak *et al.* (2012)	*CDKAL1*	rs7754840	C	1399	2025	—	—	—	—	—	—	56.2	45.4	NA[b]
	MTNR1B	rs1387153	T	468	1242	—	—	—	—	—	—	51.1	43.3	NA[b]
	TCF7L2	rs7903146	T	468	1242	—	—	—	—	—	—	4.1	2.7	NA[b]
Vcelak *et al.* (2012)	*TCF7L2*	rs7903146	T	260	376	24	128	108	24	147	205	33.8	25.9	0.79
	TCF7L2	rs12255372	T	260	376	22	115	123	23	147	206	30.6	25.7	0.69
Vlassi *et al.* (2012)	*MTNR1B*	rs1387153	T	77	98	12	26	39	11	35	52	32.5	29.1	0.22
	MTNR1B	rs10830963	G	77	98	16	31	30	12	30	56	40.9	27.6	0.02

[a]Allele A indicates the minor allele.
[b]No available data for the calculation of HWE test.
[c]*P*-value for the HWE test of the whole cohort.
[d]The data of Caucasians were updated by Shaat *et al.* (2007) and therefore they were not included here.

Table IV Associations between genetic variants and GDM risk in the systematic review and meta-analyses

Gene	Variant	Minor allele	Number of studies	Sample size (cases/controls)	OR (95% CI)[a]	*P*-value	Heterogeneity
TCF7L2	rs7903146	T	9[b]	4406/11 445	1.44 (1.29–1.60)	<0.001	$I^2 = 51.3\%$; $P_{Het} = 0.037$
TCF7L2	rs12255372	T	4	2022/2166	1.46 (1.15–1.84)	0.002	$I^2 = 48.3\%$; $P_{Het} = 0.122$
GCK	rs1799884	T	6[b]	1934/6492	1.29 (1.17–1.42)	<0.001	$I^2 = 0.0\%$; $P_{Het} = 0.878$
KCNJ11	rs5219	T	4	1837/4327	1.15 (1.06–1.26)	0.002	$I^2 = 0.0\%$; $P_{Het} = 0.976$
CDKAL1	rs7754840	C	3	2959/3675	1.40 (1.13–1.72)	0.002	$I^2 = 88.1\%$; $P_{Het} < 0.001$
IGF2BP2	rs4402960	T	3	1836/3986	1.21 (1.10–1.33)	<0.001	$I^2 = 0.0\%$; $P_{Het} = 0.842$
MTNR1B	rs1387153	T	3	1454/2312	1.30 (1.18–1.43)	<0.001	$I^2 = 0.0\%$; $P_{Het} = 0.691$
MTNR1B	rs10830963	G	3	1685/2093	1.28 (1.05–1.55)	0.016	$I^2 = 70.2\%$; $P_{Het} = 0.035$
PPARG	rs1801282	G	8	2241/6336	0.94 (0.82–1.07)	0.322	$I^2 = 0.0\%$; $P_{Het} = 0.450$
IRS1	rs1801278	T	4	1106/1673	1.39 (1.04–1.85)	0.027	$I^2 = 34.5\%$; $P_{Het} = 0.205$
ADRB3	rs4994	G	5	1239/2002	1.20 (0.88–1.65)	0.252	$I^2 = 38.8\%$; $P_{Het} = 0.163$
TNF	rs1800629	A	3	224/305	1.64 (0.73–3.69)	0.228	$I^2 = 74.3\%$; $P_{Het} = 0.020$

[a]ORs were calculated based on allelic model.
[b]The study by Freathy *et al.* included two independent study populations.

contrast, only two genes (*PPARG* and *IRS1*) are relevant to insulin resistance (Petrie *et al.*, 2011), and only the *IRS1* variant is significantly associated with GDM risk. These findings suggest that inherited abnormalities of pancreatic islet β-cell function and/or β-cell mass may be implicated in the etiology of GDM.

All genetic loci associated with GDM risk (i.e. *TCF7L2*, *GCK*, *KCNJ11*, *CDKAL1*, *IGF2BP2* and *MTNR1B*) in our systematic review have been previously related to the risk of T2DM (Frayling, 2007; McCarthy, 2010). The effect size of the associations between these SNPs and GDM was similar to those in the studies of T2DM. Moreover, in a recent genome-wide association study of GDM (Kwak *et al.*, 2012), among the 11 variants significantly associated with GDM risk, five SNPs were located in or near the known T2DM loci. In addition, two variants that reached the genome-wide significance level ($P < 5 \times 10^{-8}$), rs7754840 in CDKAL1 and rs10830962 near MTNR1B, were identical or in strong LD with known T2DM variants (Kwak *et al.*, 2012). These findings suggest an at least partly shared genetic basis between GDM and T2DM, which is not surprising given that both insulin resistance and defects in insulin secretion play key roles in the etiology of both GDM and T2DM. In addition, women with a history of GDM have a more than 7-fold risk of developing T2DM later in life (Bellamy *et al.*, 2009).

It should be noted that not all women who have a history of GDM develop T2DM. Different from T2DM, GDM as a pregnancy complication may be influenced by not only the maternal genome but also the paternal and fetal genomes. Indeed, emerging data suggest both fetal and paternal genotypes may affect glucose metabolism in pregnancy. For example, Wangler *et al.* (2005) observed that mothers carrying offspring with Beckwith–Wiedemann syndrome, in which probands have abnormally increased *IGF2* expression, showed a trend toward an increased risk of GDM. Also, in an animal study by Petry *et al.* (2010), maternal glucose concentrations in pregnant mice were elevated among women carrying pups with targeted disruption of maternally transmitted fetal $H19^{\Delta 13}$, which implied that variable fetal *IGF2* expression could affect risk for GDM. Moreover, in an epidemiological study among 1160 mother/partner/offspring trios from the UK, Petry *et al.* found that polymorphic variations in the paternally transmitted fetal *IGF2* genotype, but not the maternal or maternally transmitted fetal *IGF2* genotypes, were associated with increased maternal glucose concentrations in pregnancy, which could potentially alter the risk of maternal GDM (Petry *et al.*, 2011). These studies highlighted a potential role of the paternal and fetal genomes, in addition to the maternal genome itself, in maternal glucose homeostasis during pregnancy. Future genetic studies of GDM considering fetal and/or paternal genome are warranted.

Gene–gene and gene–environment interactions may further help illustrate the biological basis for complex diseases and provide important clues for personalized interventions or clinical therapeutics (Collins *et al.*, 2003). These interactions contribute to β-cell function (Nesher *et al.*, 1999; Li *et al.*, 2009), insulin sensitivity (Black *et al.*, 2008) and T2DM risk (Cornelis and Hu, 2012). Further, a number of environmental factors, such as diet and lifestyle factors, have been significantly associated with GDM risk (Zhang and Ning, 2011). However, so far little has been done to investigate gene–environmental interactions in relation to GDM susceptibility. Watanabe *et al.* (2007) found that the *TCF7L2* rs12255372 variant interacts with adiposity to alter insulin secretion in 132 Mexican-American families of a proband with previous GDM. In a recent study of 826 GDM cases and 1185 healthy controls, Papadopoulou *et al.* (2011) examined the interaction between *TCF7L2* and *HLA-DQB1*0602* variants in association with GDM risk in Swedish women, but observed no interaction between them. Future studies with larger sample sizes are warranted to better understand these complex interactions in the pathogenesis of GDM.

The strength of the present study is the systematic way in which we have summarized results of the available studies on SNP–GDM associations. However, our analysis has several limitations. First, although the pooled sample size for some SNPs (e.g. rs7903146 in *TCF7L2*) was relatively large, for others it was small (e.g. for rs1800629 in *TNF*, 224 cases and 305 controls). Secondly, we focused on the

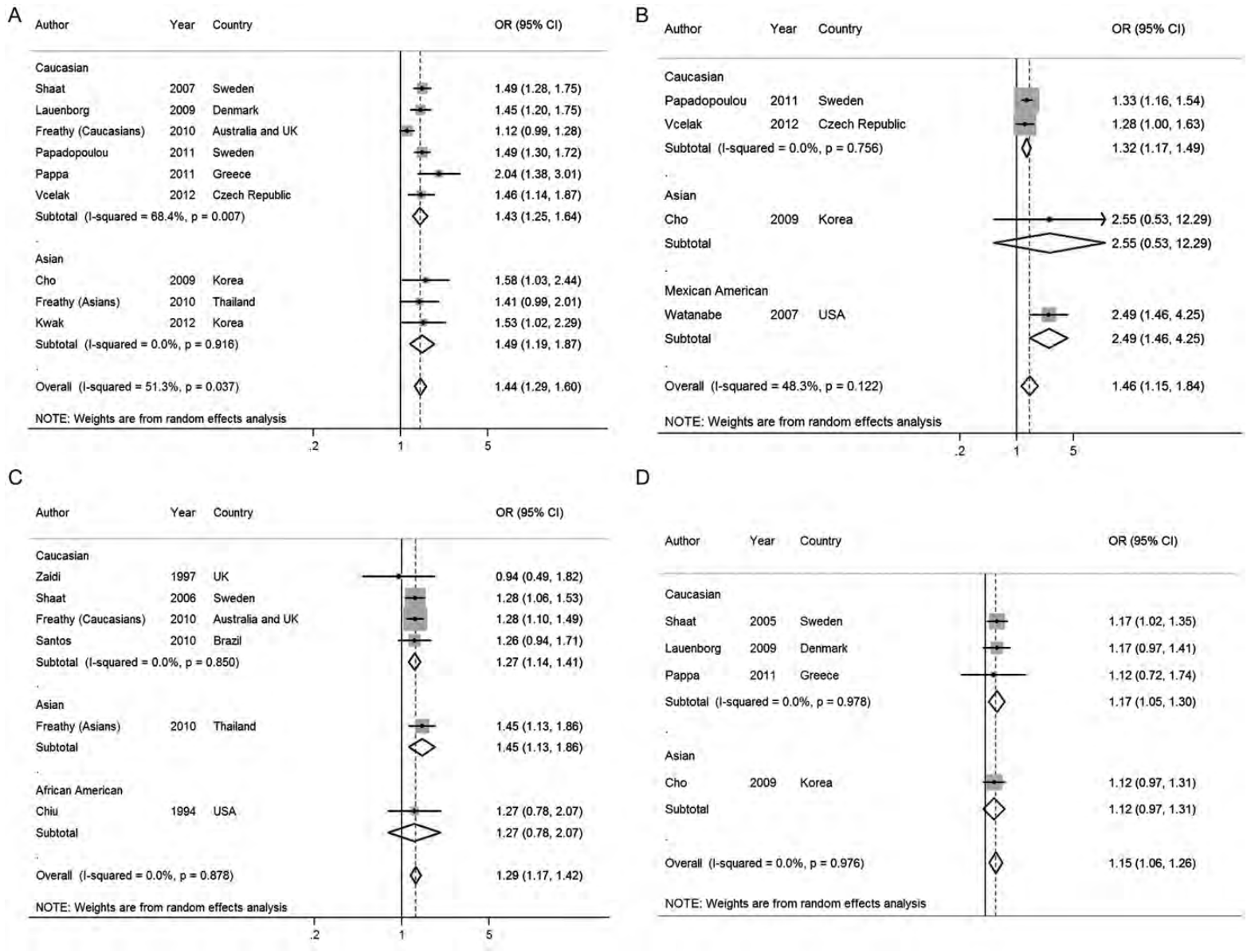

Figure 2 (**A**–**H**) The risk of GDM in association with genetic variants related to insulin secretion. (A) TCF7L2 rs7903146, (B) TCF7L2 rs12255372, (C) GCK rs1799884, (D) KCNJ11 rs5219, (E) CDAKL1 rs7754840 (all Asians), (F) IGF2BP2 rs4402960, (G) MTNR1B rs1387153 and (H) MTNR1B rs10830963. The shadowed squares and their lateral tips indicate the ORs and the corresponding 95% CIs in individual studies, with the sizes of squares proportional to weights used in the meta-analyses. The central lines and lateral tips of the diamonds indicate the pooled ORs and the corresponding 95% CIs. The solid vertical lines indicate no effect.

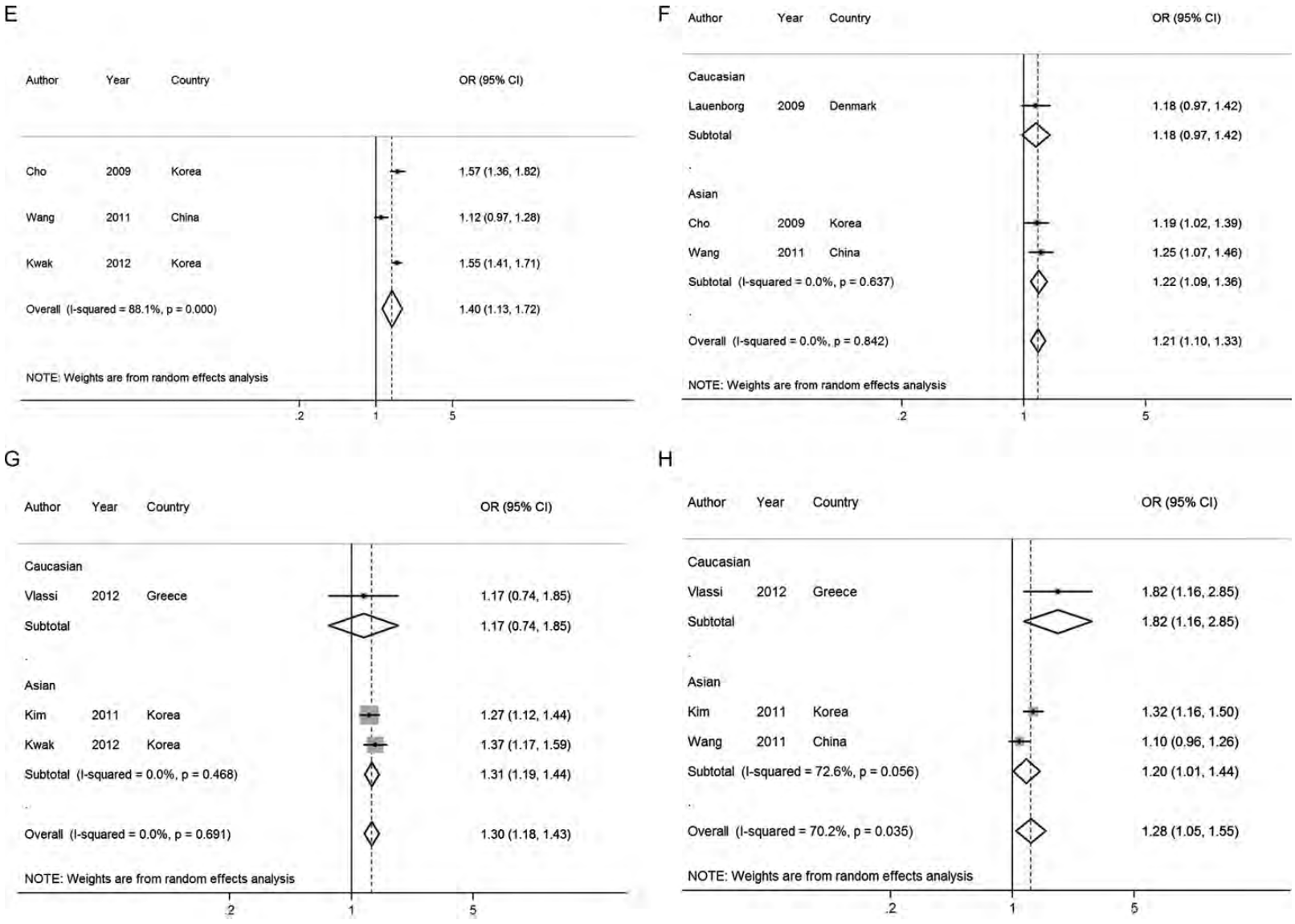

Figure 2 *Continued*

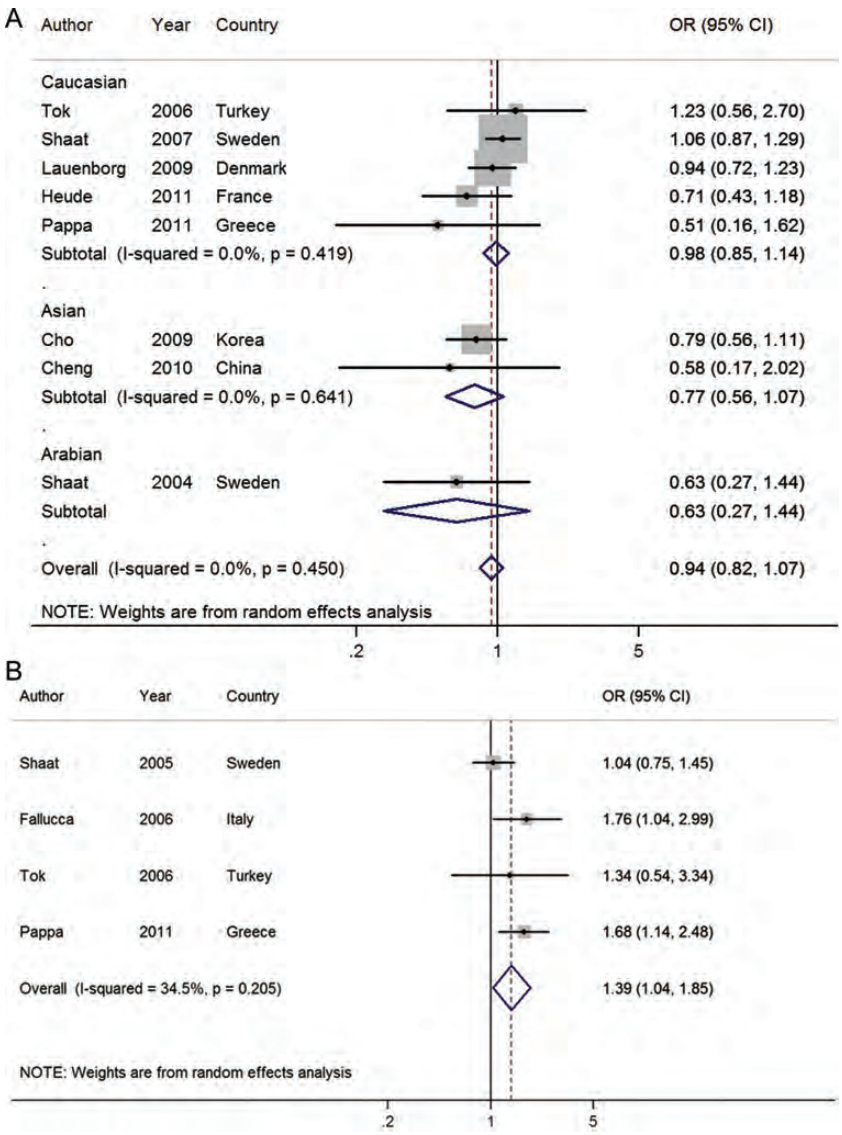

Figure 3 (**A** and **B**) The risk of GDM in association with genetic variants related to insulin resistance. (A) PPARG rs1801282 and (B) IRS1 rs1801278 (all Caucasians). The shadowed squares and their lateral tips indicate the ORs and the corresponding 95% CIs in individual studies, with the sizes of squares proportional to weights used in the meta-analyses. The central lines and lateral tips of the diamonds indicate the pooled ORs and the corresponding 95% CIs. The solid vertical lines indicate no effect.

commonly studied SNP–GDM associations (those investigated in at least three independent studies), which allowed us to conduct a meta-analysis and systematic review. However, we may have missed loci with two or less published results for a specific variant, such as the type 2 diabetes-associated common genetic variants (e.g. *FTO*, *SLC30A8*, *HHEX/IDE*, etc.) and type 1 diabetes-associated genetic variants (e.g. *HLA*, etc.). Their associations with GDM risk warrant further evaluation when more evidence becomes available. Thirdly, although the statistical test showed no indication of publication bias for any SNPs included in the meta-analysis, we cannot rule out the possibility of publication bias due to the small number of studies. Fourthly, potential confounding effects from other major risk factors of GDM, such as BMI, on the observed SNP-GDM association was not explicitly investigated in the present review due to the fact that not all eligible studies adjusted for these risk factors and we intended to maximize the number of eligible studies that can be included in the systematic review. Nevertheless, as none of the genetic variants investigated in the review is consistently associated with BMI, the effect of BMI on the association of the selected genetic variants and GDM risk is likely to be minor. In addition, Asian, Hispanic and Native American women, when compared with non-Hispanic White women, have an increased risk of GDM (Ben-Haroush *et al.*, 2004). However, genetic studies of GDM among these high-risk populations are sparse, which limited the capacity of exploring the gene-GDM association by race/ethnicity groups. Future studies among non-Caucasian populations are warranted. It should also be noted that

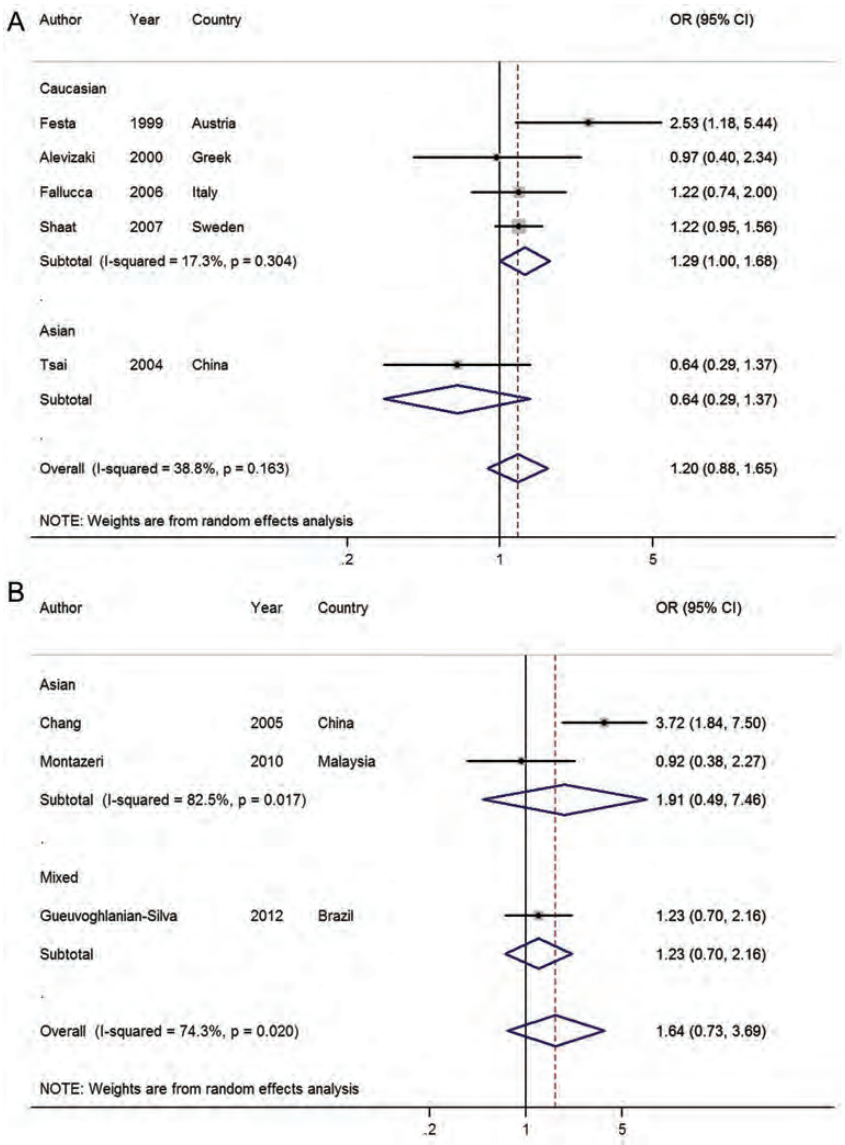

Figure 4 (**A** and **B**) The risk of GDM in association with genetic variants related to other pathways. (A) ADRB3 rs4994 (energy metabolism) and (B) TNF rs1800629 (inflammation). The shadowed squares and their lateral tips indicate the ORs and the corresponding 95% CIs in individual studies, with the sizes of squares proportional to weights used in the meta-analyses. The central lines and lateral tips of the diamonds indicate the pooled ORs and the corresponding 95% CIs. The solid vertical lines indicate no effect.

current definition of GDM does not reach consensus and the diagnosis criteria for GDM in the included studies were different. In general, the trend of the diagnosis criteria for GDM becomes less stringent.

In summary, in this systematic review, we observed evidence for significant associations of GDM with nine SNPs from seven genes. Among the seven genes, six were related to insulin secretion and one was related to insulin resistance, which supports an important role of pancreatic islet β-cell compensation in the pathogenesis of GDM. Genetic studies of GDM considering fetal and/or paternal genome, and gene–gene and gene–environmental interactions and among non-Caucasian populations are sparse. Future studies in these regards are warranted for better understanding the etiology of GDM.

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Authors' roles

W.B.: study concept and design, acquisition of data, data analysis, interpretation of data, drafting the manuscript, final approval of the manuscript. Y.R.: acquisition of data, data analysis, critically reviewing the manuscript, final approval of the manuscript. K.B., E.Y., H.Y. and M.K.: interpretation of data, critically reviewing the manuscript, final approval of the manuscript. C.Z.: study concept and design,

supervision of data acquisition and analysis, interpretation of data, drafting the manuscript, critically reviewing the manuscript, final approval of the manuscript.

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Conflict of interest

The authors declared no conflict of interest.

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