PLOS ONE

RESEARCH ARTICLE

Transcription Factor 7-Like 2 (TCF7L2) rs7903146 Polymorphism as a Risk Factor for Gestational Diabetes Mellitus: A Meta-Analysis

Pei-Chao Lin[1], Wei-Ting Lin[1], Yao-Hsien Yeh[2,3], Shu-Fen Wung[4]*

1 College of Nursing, Kaohsiung Medical University, Kaoshiung, Taiwan, **2** Department of Occupational and Environmental Medicine, National Cheng Kung University Hospital, Tainan, Taiwan, **3** Department of Environmental and Occupational Health, College of Medicine, National Cheng Kung University, Tainan, Taiwan, **4** College of Nursing, The University of Arizona, Tucson, Arizona, United States of America

* wung@arizona.edu

Citation: Lin P-C, Lin W-T, Yeh Y-H, Wung S-F (2016) Transcription Factor 7-Like 2 (TCF7L2) rs7903146 Polymorphism as a Risk Factor for Gestational Diabetes Mellitus: A Meta-Analysis. PLoS ONE 11(4): e0153044. doi:10.1371/journal.pone.0153044

Editor: Marta Letizia Hribal, University of Catanzaro Magna Graecia, ITALY

Received: November 19, 2015

Accepted: March 22, 2016

Published: April 8, 2016

Data Availability Statement: All relevant data are within the paper (figures and tables). Supporting Information files are attached.

Funding: This meta-analysis was supported by a grant from the Kaohsiung Medical University Research Foundation (KMU-Q105009). The University of Arizona Open Access Publishing Fund provides full support of the publication fee.

Competing Interests: The authors have declared that no competing interests exist.

Abstract

Background

There are racial and ethnic differences in the prevalence of gestational diabetes mellitus (GDM). Prior meta-analyses included small samples and very limited non-Caucasian populations. Studies to determine the relationship between transcription factor 7 like-2 (*TCF7L2)* rs7903146 polymorphism and risk of GDM in Hispanics/Latinos are recently available. The present meta-analysis was to estimate the impact of allele variants of *TCF7L2* rs7903146 polymorphism on GDM susceptibility in overall population and racial/ethnic subgroups.

Methods

Literature was searched in multiple databases including PubMed, Web of Science, EMBASE (Ovid SP), Airiti Library, Medline Complete, and ProQuest up to July 2015. Allelic frequency for *TCF7L2* rs7903146 polymorphism in GDM and control subjects was extracted and statistical analysis was performed using Comprehensive Meta-Analysis (CMA) 2.0 statistical software. The association between *TCF7L2* rs7903146 polymorphism and GDM risk was assessed by pooled odd ratios (ORs) using five gene models (dominant, recessive, homozygote, heterozygote, and allele). Stratified analysis based on race/ethnicity was also conducted. The between-study heterogeneity and contribution of each single study to the final result was tested by Cochran Q test and sensitivity analyses, respectively. Publication bias was evaluated using Egger's linear regression test.

Results

A total of 16 studies involving 4,853 cases and 10,631 controls were included in this meta-analysis. Significant association between the T-allele of rs7903146 and GDM risk was observed under all genetic models, dominant model (OR = 1.44, 95% CI = 1.19–1.74),

recessive model (OR = 1.35, 95% CI = 1.08–1.70), heterozygous model (OR = 1.31, 95% CI = 1.12–1.53), homozygous model (OR = 1.67, 95% CI = 1.31–2.12), and allele model (OR = 1.31, 95% CI = 1.12–1.53). Stratified analysis by race/ethnicity showed a statistically significant association between rs7903146 polymorphism and susceptibility to GDM under homozygous genetic model (TT versus CC) among whites, Hispanics/Latinos and Asians. Sensitivity analysis showed that the overall findings were robust to potentially influential decisions of the 16 studies included. No significant evidence for publication bias was observed in this meta-analysis for overall studies and subgroup studies.

Conclusions

This meta-analysis showed that the T allele of *TCF7L2* rs7903146 polymorphism was associated with susceptibility of GDM in overall population in white, Hispanic/Latino and Asian sub-groups. Asians with homozygous TT allele of rs7903146 polymorphism have highest risk of GDM (OR = 2.08) followed by Hispanics/Latinos (OR = 1.80) and whites (OR = 1.51). The highest and lowest frequency of T allele of rs7903146 was found in Malaysia and South Korea, respectively. Future studies are needed to profile genetic risk for GDM among high risk Asian and Pacific Islander subgroups.

Introduction

Gestational diabetes mellitus (GDM) is a glucose tolerance disorder leading to hyperglycemia, diagnosed for the first time in pregnancy [1]. GDM is a global public health concern and its prevalence is increasing yearly. The prevalence of GDM ranges from 1.8% to 25.1% of all pregnancies, depending on the population studied and diagnostic tests used [2]. GDM has short- and long-term adverse outcomes both in women and their offspring, resulting in an increase in medical costs [3]. Women with a history of GDM are at over seven-fold higher risk of developing type 2 diabetes mellitus (T2DM) later in life than those without [4], however data on the risk of progression from GDM to T2DM are still limited [2]. Although the exact pathophysiology of GDM is still unclear, it is generally believed that GDM and T2DM share the same underlying pathologic mechanisms, including insulin resistance and β-cell dysfunction leading to metabolic changes [5]. In addition, T2DM is a multifactorial disease and GDM may share genetic risk factors with T2DM [6].

There are racial and ethnic differences in the prevalence of GDM. As reported by some studies [7, 8], Asian/Pacific Islander women have a higher prevalence of GDM than non-Hispanic white, Black, or Hispanic women. A contemporary estimate of global prevalence of GDM shows great regional and social economic variations [2]. Developing and low-to-middle income countries suffer from escalating burden of GDM and T2DM [2]. The prevalence of GDM is higher among Middle East and North Africa, South Asia, and Western Pacific regions and the prevalence is lowest in Europe [2]. Because of racial and regional differences of GDM prevalence, several studies have focused on exploring relationship of susceptible T2DM genes in women with GDM of different racial background [9–13].

Among common genetic variants associated with T2DM identified thus far, single nucleotide polymorphism rs7903146 of the transcription factor 7 like-2 (*TCF7L2*) gene produces the strongest susceptibility for T2DM [14,15] and this relationship is reproducibly shown in various ethnic groups [16]. *TCF7L2* is a commonly investigated gene in women with GDM [6]. It

is located at chromosome 10q25.3 and its product is a high mobility group (HMG) box-containing transcription factor that is implicated in blood glucose homeostasis [17] in the morphogenic wingless-type MMTV integration site family (Wnt) signaling pathway [18]. This pathway plays an essential role in regulation of pancreatic β-cell proliferation and synthesis of incretin hormones, glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP), in the enteroendocrine cells [19, 20]. Evidence suggests that TCF7L2 is a major regulator of insulin production and processing in pancreatic islet [21]. TCF7L2 plays a central role in coordinating the expression and subsequent processing of proinsulin to form mature insulin via several TCF7L2-target genes and the downstream regulatory network [21]. In addition, TCF7L2 may also influence hepatic clearance of insulin [21] as well as peripheral or whole body insulin sensitivity [22, 23].

The risk T allele of rs7903146 in the *TCF7L2* gene is strongly associated with an increased risk of T2DM and this effect is additive. Approximately 10% of population has two copies of the risk T allele and these individuals are twice as likely to develop T2DM as compared with individuals with no risk alleles [24]. A meta-analysis of 27 different studies confirms the association of the *TCF7L2* rs7903146 risk T allele with T2DM with a resulting global odd ratio (OR) of 1.46 [1.42–1.51] [16]. Such reproducible results among studies is indicative of a universal contribution of this gene to T2DM, thus, the population-attributable risk of diabetes is driven by the prevalence of the at risk T allele in a specific ethnic group [16]. The exact mechanisms of *TCF7L2* in the development of diabetes have not been fully determined but it is suggested that diabetes arises as a consequence of reduced pancreatic islet mass and/or impaired function [25]. The risk T allele is associated with impaired insulin secretion and incretin effects as well as enhanced rate of hepatic glucose production [17, 21]. In a longitudinal cohort with up to 22 years of follow-up, carriers of the risk T-allele had a lower insulin response to an initial oral glucose tolerance test (OGTT) and a higher risk of future T2DM than those with CC homozygotes [17]. In addition, among patients converted to T2DM after the initial screening, those carrying the risk T-allele had more severe progressive deterioration in insulin secretion as compared to those with the CC genotype [17]. The rs7903146 in *TCF7L2* gene is shown to be associated with GDM in different populations, including Korean, European Caucasian, and Mexican-American [9,26–29]. As reported in two meta-analyses, the risk variants in the *TCF7L2* gene increase risk of GDM with an effect size similar to that reported in T2DM [13, 30]. These prior meta-analyses included small samples of women with GDM and very limited non-Caucasian populations. The lack of racial/ethnic diversity in these two meta-analyses has limited the investigation of association between *TCF7L2* gene rs7903146 polymorphism and GDM in racial/ethnic subgroups. In addition, studies to determine the relationship between *TCF7L2* rs7903146 polymorphism and risk of GDM in Hispanics/Latinos were not available until recently [29, 31, 32]. Understanding genetic contributions to GDM may help to identify targets for pharmacological and non-pharmacological personalized prevention and treatment strategies.

Materials and Methods

Search Strategy

A broad search was performed for reports on *TCF7L2* rs7903146 polymorphism and GDM in PubMed, Web of Science, EMBASE (Ovid SP), Airiti Library, Medline Complete, and ProQuest. The keywords used for searching were "gestational diabetes" in combination with "*TCF7L2*" and the search was not limited to English language. All articles published up to June of 2015 were included. To further identify eligible studies, reference lists from the retrieved articles were also examined.

Inclusion and exclusion criteria

Published studies meeting the following criteria were selected: (1) study subjects must be humans; (2) study design conformed to case-control; (3) study was published as an original article or a conference abstract with original data including allelic frequencies and their distributions in cases and controls; and (4) study investigated the relationship between *TCF7L2* gene and GDM. If an article did not include information on genotypic frequencies in cases and controls, the researcher contacted the study authors by mail to request specific additional data. Studies were excluded if they met any of the following criteria: (1) overlapping and insufficient data; (2) family-based studies or case only design; (3) review articles; (4) rs7903146 polymorphism was not investigated.

Data extraction

The studies were reviewed by two independent reviewers who extracted the following information: name of the first author, year of publication, country of study setting, race/ethnicity of study subjects, sample size, mean age of cases and controls, allelic frequencies and their distributions in cases and controls, adjusted OR and 95% confidence intervals (CI), and p value for Hardy-Weinberg Equilibrium (HWE) test. Disagreements concerning inclusion/exclusion of studies or risk estimates were resolved by consensus.

Statistical analysis

The meta-analysis was performed using Comprehensive Meta-Analysis (CMA) 2.0 statistical software (Biostat Inc., Englewood, New Jersey, USA). The strength of association between rs7903146 polymorphism and GDM risk was assessed by calculating the logarithm of OR with 95% CI. We calculated the OR by genotype and allele model comparisons of rs7903146 polymorphism between cases and controls. Stratified analysis was performed for race/ethnicity. I2 statistical test was performed to calculate the degree of inconsistency. I2 is the ratio of true heterogeneity to total variation in observed effects, representing a signal to noise ratio [33]. I2 values were calculated and used to quantify the percentages of total variation across studies that were due to heterogeneity rather than chance, with I2 $>$ 25%, 50%, and 75% indicating low, moderate, and high heterogeneity, respectively [34]. I2 is preferable to a test for heterogeneity in judging consistency of evidence and its use is not inherently dependent on the number of studies in the meta-analysis [34]. When moderate or high between-study variation was found, a random- effect model was used to estimate the pooled ORs with their corresponding 95% CIs [35]. Two-sided *p* values less than 0.05 were considered statistically significant [36].

HWE deviation was assessed in controls of each study by chi-square test. Publication bias was examined in funnel plots and with the Egger's regression test [37] and a p value of $<$ 0.1 was considered statistically significant for asymmetry [37,38]. Sensitivity analysis based on the leave-one-out method was performed to evaluate the influence of each individual study on the overall results [39]. Furthermore, JMP Statistical Discovery software (Version 12 SAS institute Inc., Cary, NC) was used to create global maps to demonstrate variations in the geographical distributions of the risk allele frequency.

Results

Literature selection and characteristics of eligible studies

Our meta-analysis was performed according to the "Preferred Reporting Items for Systematic Reviews and Meta-analyses" (PRISMA) (S1 Table) and the "Meta-analysis on Genetic Association Studies" (S2 Table). Literature search and selection process flow chart is shown in Fig 1.

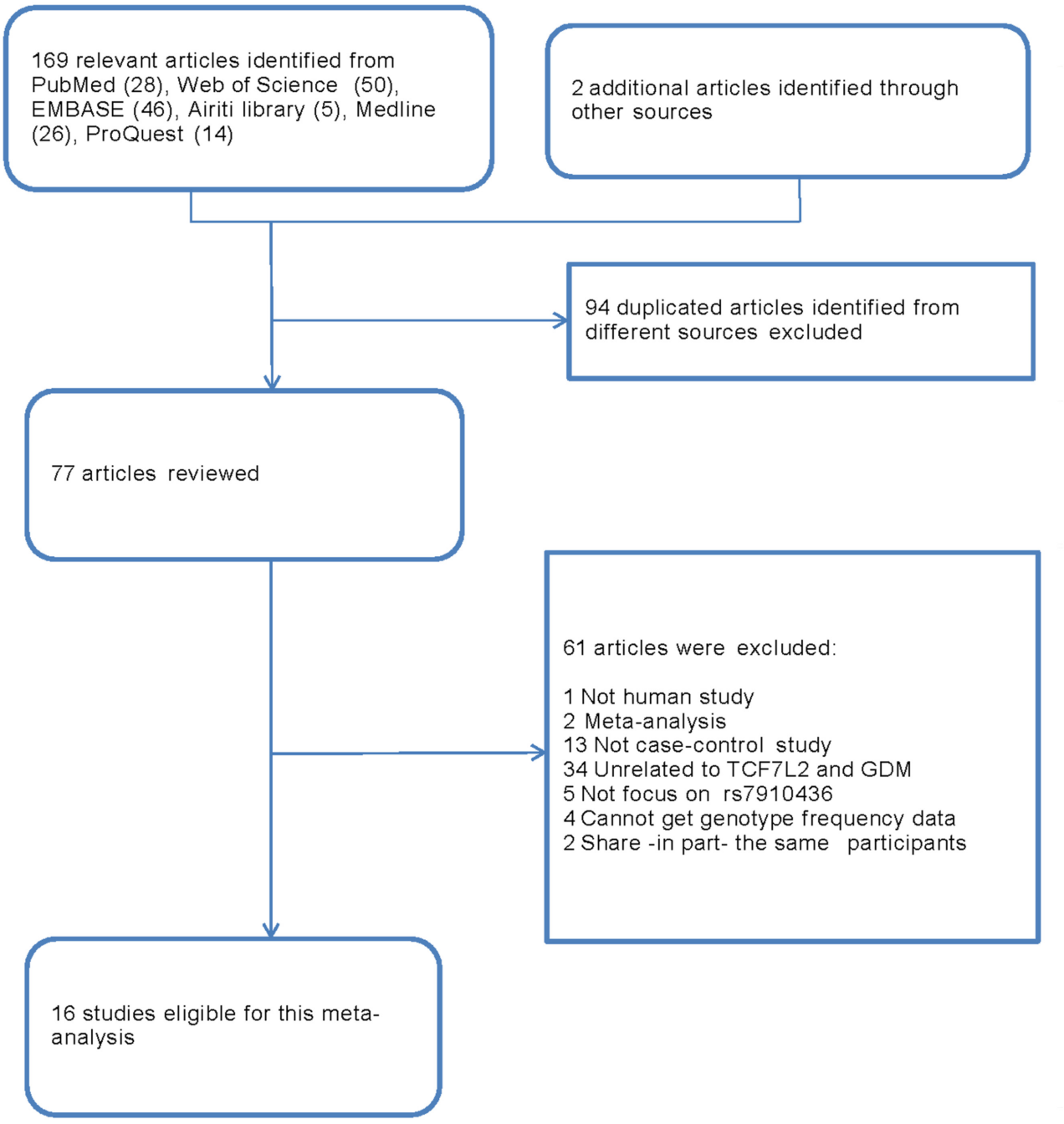

Fig 1. Selection of studies for inclusion in meta-analysis.

doi:10.1371/journal.pone.0153044.g001

One hundred and seventy-one articles were initially identified through literature search. These included 28 from PubMed, 50 from Web of Science, 46 from EMBASE (Ovid SP), 5 from Airiti Library, 26 from Medline Complete, 14 from ProQuest, and one article identified through google website search [40] and another article identified through reference list of a meta-analysis [41]. Same articles (n = 94) identified from different databases were initially excluded. Subsequently, additional 61 articles were excluded for the following reasons: (1) one article on non-human model of GDM [42]; (2) two meta-analyses on association between *TCF7L2*

polymorphism and GDM; (3) 13 non case-control studies; (4) 34 studies unrelated to *TCF7L2* gene and GDM; (5) five studies not focus on rs7903146 polymorphism; (6) four articles lacking genotype frequency data in the text or from corresponding authors [43–46]; (7) two abstracts [47–48] sharing -in part- the same participants with other articles [46, 49]. Hence, 16 studies published between 2007 and 2015 were ultimately retained in this meta-analysis [9, 10, 26–29, 31, 32, 40, 41, 49–54] (S1 Text).

Characteristics of 4,853 GDM cases and 10,631 controls included in this meta-analysis are displayed in Table 1. Study countries, racial/ethnic categories, sample sizes, as well as genotype frequencies of *TCF7L2* rs7903146 polymorphism are detailed in Table 2.

Association between TCF7L2 rs7903146 polymorphism and GDM risk

Association between *TCF7L2* rs7903146 polymorphism and GDM risk is shown in Table 3. Significant associations between the at risk T-allele of rs7903146 and GDM risk were observed under all gene models: the dominant model (TT + CT versus CC; OR = 1.44, 95% CI = 1.19–1.74, $p < 0.001$), the recessive model (TT versus CT + CC: OR = 1.37, 95% CI = 1.19–1.57, $p < 0.001$), the heterozygote model (TT versus CT: OR = 1.17, 95% CI = 1.01–1.35, $p = 0.035$), the homozygous model (TT versus CC: OR = 1.63, 95% CI = 1.31–1.89, $p < 0.001$), and the allele model (T-allele versus C-allele: OR = 1.31, 95% CI = 1.12–1.53, $p = 0.001$).

Stratified analysis by race/ethnicity showed significant association between rs7903146 polymorphism and GDM risk under homozygous models (TT versus CC) in whites (OR = 1.51, 95% CI = 1.12–2.05, $p = 0.007$), Hispanics/Latinos (OR = 1.80, 95% CI = 1.01–2.94, $p = 0.020$) and Asians (OR = 2.08, 95% CI = 1.53–6.18, $p = 0.002$) (Table 3). Under allele model, presence of T allele as compared to the C allele had increased GDM risk in whites and Hispanics/Latinos but not in Asians. Under recessive and heterozygote models, significant associations between rs7903146 polymorphism and GDM risk were only observed in whites. Fig 2 depicts the forest plot summarizing the effect of T-allele versus C-allele of the rs7903146 polymorphism and risk of GDM under fixed effect model in overall sample and sub-racial groups.

Allele frequencies of rs7903146 polymorphism by study countries are showed in Table 4. The highest frequency of T allele was found in Malaysia (89.5%) and the lowest frequency of T allele was found in South Korea (3.3%). Geographic distributions of risk T and TT alleles of rs7903146 polymorphism among subjects included in this meta-analysis stratified by study country are presented in Figs 3 and 4, respectively.

Sensitivity analysis

To evaluate the robustness of the association results, leave-one-out sensitivity analysis was conducted by removing one study at a time and recalculating the summary ORs. The summary ORs remained stable (Table 5), indicating that our results were not driven by any single study.

Publication bias analysis

Publication bias was determined using Egger's test. No statistically significant evidence of publication bias was observed for studies included in the overall and subgroup analyses (all p values for Egger's test were > 0.1) (Table 3).

Discussion

The result of this meta-analysis indicates that the at risk T allele of *TCF7L2* rs7903146 polymorphism was significantly associated with the risk of GDM in overall sample as well as in racial/ethnic subgroups, Whites, Hispanics/Latinos and Asians. The T allele of *TCF7L2*

Table 1. Characteristics of 4,853 GDM cases and 10,631 controls included in this meta-analysis.

Author	Year	GDM Mean age ± SD	Control Mean age ± SD	Controls source	GDM criteria
Aris	2012	29.7 ± 4.7	28.5 ± 3.6	Pregnant women with NGT	ADA [55]
Cho	2009	32.0 ± 3.9	Women 64.4 ± 3.3 Men 64.9 ± 3.8	Age ≥ 60 years, no history of T2DM, no first-degree relatives with T2DM, fasting plasma glucose level < 6.1 mmol/L and HbA1C level < 5.8%	NDDG [56]
de Melo	2015	33.0 ± 6.4	24.9 ± 4.0	Pregnant women with NGT	ADA [57]
Freathy	2010	NA	NA	Pregnant women with NGT	IADPSG [58]
Huerta-Chagoya	2015	28	35	Pregnant women with NGT	Carpenter and Coustan (1982) [59]
Klein	2012	30.1 ± 3.4	28.2 ± 4.8	Pregnant women with NGT	IADPSG [58]
Lauenborg	2009	43.1	45.2	Middle-aged women with NGT	50-g OGTT (year 1978–1985) [60], 75-g OGTT (year 1987–1996) [61]
Pagán	2014	31.2 ± 0.95	34.31 ± 0.63	Pregnant women with NGT	NDDG [56]
Papadppoulou	2011	31 (Median)	30 (Median)	Pregnant women with NGT	Lind et al. [58]
Pappa	2011	32.5 ± 4.5	26.67 ± 3.87	Pregnant women with NGT	ADA [62]
Reyes-López	2014	31 ± 7	29 ± 8	Pregnant women with NGT	ADA [57]
Rizk	2011	NA	NA	NA	NA
Shaat	2007	32.3 ± 0.2	30.5 ± 0.1	Pregnant women with NGT	Lind et al. (1991) [58]
Shi	2014	30 ± 5	29 ± 4	Pregnant women with NGT	IADPSG [63]
Thomas	2014	NA	NA	Pregnant women with NGT	NA
Vcelak	2012	32.8 ± 4.9	Women 29.9 ± 10.8 Men 29.4 ± 7.8	Healthy controls without family history of T2DM, PCOS, and GDM	NA

ADA, American Diabetes Association; GDM, gestation diabetes mellitus; HbA1C, hemoglobin A1C; IADPSG, International Association of Diabetes and Pregnancy Study Groups; OGTT, oral glucose tolerance test; NDDG, National Diabetes Data Group; NGT, normal glucose tolerance; PCOS, polycystic ovary syndrome; T2DM, type 2 diabetes mellitus

doi:10.1371/journal.pone.0153044.t001

rs7903146 polymorphism was associated with a reduced compensation of insulin secretion for insulin resistance induced by 9 days of bed rest [64].

Mao and colleagues [13] performed a meta-analysis to determine the relationship between multiple polymorphisms in seven genes and GDM. Of the six studies included (four studies on Caucasians and two on East Asians), they reported that the risk T allele of TCFL2 rs7903146 polymorphism is associated with GDM for East Asians and Caucasians. Subsequently, Kang and associates [30] included 10 studies (3,404 cases and 6,473 controls) in a meta-analysis and showed a significant association between *TCF7L2* rs7903146 polymorphism and risk of GDM in the dominant and co-dominant models (ORs of 1.653 and 1.525, respectively). Of the 10 studies considered, all included Caucasians except for three studies (one study from South Korea, one from Qatar, and another from Malaysia). Due to small sample sizes with limited racial/ethnic subgroups, evaluating the relationship between *TCF7L2* rs7903146 polymorphism and the risk of GDM among racial/ethnic subgroups was limited. Our meta-analysis included an extensive dataset from 16 distinct studies with 4,853 GDM cases and 10,631 controls and showed a significant association between *TCF7L2* rs7903146 polymorphism and risk of GDM. The odd ratios in our meta- analysis are similar to the two existing meta-analyses when data are pooled disregard racial/ethnic subgroups. However, studies to determine the relationship between *TCF7L2* rs7903146 polymorphism and risk of GDM in Hispanics/Latinos were not available until recently [29, 31, 32]. In our meta-analysis, we were not only able to incorporate

Table 2. Study countries, racial/ethnic categories, sample sizes, and genotype frequencies of TCF7L2 rs7903146 polymorphism of studies included.

Author	Year	Country	Race/ Ethnicity	GDM (n)	Control (n)	GDMCC	Control CC	GDMCT	ControlCT	GDMTT	ControlTT	p for HWE test
Aris	2012	Malaysia	Asian	173	114	1	0	43	15	129	99	0.452
Cho	2009	South Korea	Asian	868	627	803	596	63	31	2	0	0.526
de Melo	2015	Brazil	Hispanic/ Latino	200	200	76	98	104	86	20	16	0.633
Freathy	2010	United Kingdom	White	614	3811	293	1884	246	1557	75	370	0.066
Huerta-Chagoya	2015	Mexico	Hispanic/ Latino	408	342	265	265	124	67	19	10	0.030*
Klein	2012	Australia	White	125	125	10	11	110	106	5	8	0.000*
Lauenborg	2009	Denmark	White	276	2353	118	1292	125	863	33	198	0.002*
Pagán	2014	Spain	White	45	24	19	10	18	12	8	2	0.540
Papadppoulou	2011	Sweden	White	803	1110	363	644	352	384	88	82	0.020*
Pappa	2011	Greece	White	148	107	49	62	81	38	18	7	0.720
Reyes-López	2014	Mexico	Hispanic/ Latino	90	108	55	81	29	23	6	4	0.165
Rizk	2011	Qatar	White	40	74	16	29	18	37	6	8	0.451
Shaat	2007	Sweden	White	585	1111	271	650	255	392	59	69	0.339
Shi	2014	China	Asian	100	100	40	55	36	38	24	7	0.901
Thomas	2014	India	Asian	117	49	55	27	46	18	16	4	0.686
Vcelak	2012	Czech Republic	White	261	376	142	156	102	185	17	35	0.058

* p value < 0.05

GDM, gestational diabetes mellitus; HWE, Hardy-Weinberg Equilibrium

doi:10.1371/journal.pone.0153044.t002

these recent Hispanics/Latinos studies but also one study from China [53] and another from India [40] to perform analyses in racial/ethnic subgroups.

Of racial/ethnic groups in the United States, Asian and Pacific Islander women were found to have a higher age-adjusted prevalence of GDM than whites, blacks, or Hispanics [7, 8, 65]. These racial/ethnic differences cannot be fully explained by differences in pre-pregnancy body mass index or obesity [66] as many Asian women with GDM do not have any historical or clinical GDM risk factors, especially excessive body weight [66]. Therefore, factors other than obesity, such genetics and lifestyle, should be explored. Asian women with TT genotype of rs7903146 polymorphism are three times as likely to have GDM as women with CC genotype.

In a genome wide association study conducted in South Korea [67] including 1,399 women with GDM and 2,025 controls, although genome-wide association between the T allele of *TCF7L2* rs7903146 polymorphism and GDM did not reach statistical significance (odd ratio of 1.499; p = 0.051), this level of association is similar to results from our overall pooled data and in Asian subgroup. In our analysis, the association between *TCF7L2* rs7903146 polymorphism and GDM in Asians is strongest under homozygous genetic model (TT vs. CC; OR 3.08; p = 0.002); however, only allele model (T vs. C allele) was used in the genome-wide association study by Kwak et al. [67].

Interestingly, we found that the at-risk T allele in Asian population varied greatly, with the most frequent percentage of 89.5% reported by a study from Malaysia [41] and the least frequent percentage of 3.3% by a study from South Korea [26], suggesting heterogeneous genetic background between Asians. It has been reported that the prevalence of GDM varies

Table 3. Association between TCF7L2 rs7903146 polymorphisms and risk of gestational diabetes mellitus in overall sample and in sub-racial groups.

Genotype (number of studies)	Type of Model	Test of Heterogeneity	Statistical Model	Test of Association		Test of Publication Bias
		I^2 (%)		Odd Ratio (95% CI)	*p*	Egger's *p*
TT+ CT vs. CC (16)	Dominant	74.5	Random	1.44 (1.19–1.74)	< 0.001	0.938
TT vs. CC+CT (16)	Recessive	48.7	Fixed	1.37 (1.19–1.57)	< 0.001	0.851
TT vs. CT (16)	Heterozygous	17.7	Fixed	1.17 (1.01–1.35)	0.035	0.868
TT vs. CC (16)	Homozygous	45.3	Fixed	1.63 (1.31–1.89)	< 0.001	0.781
T vs. C allele (16)	Allele	56.5	Random	1.31 (1.12–1.53)	0.001	0.952
Subgroups						
White						
TT+ CT vs. CC (9)	Dominant	84.7	Random	1.31 (1.00–1.71)	0.053	0.801
TT vs. CC+CT (9)	Recessive	22.8	Fixed	1.39 (1.19–1.62)	< 0.001	0.684
TT vs. CT (9)	Heterozygous	0	Fixed	1.20 (1.03–1.41)	0.022	0.763
TT vs. CC (9)	Homozygous	61.6	Random	1.51 (1.12–2.05)	0.007	0.764
T vs. C allele (9)	Allele	66.5	Random	1.24 (1.02–1.51)	0.028	0.729
Hispanic/Latino						
TT+ CT vs. CC (3)	Dominant	0	Fixed	1.76 (1.40–2.22)	< 0.001	0.960
TT vs. CC+CT (3)	Recessive	0	Fixed	1.47 (0.91–2.38)	0.114	0.420
TT vs. CT (3)	Heterozygous	0	Fixed	1.05 (0.64–1.74)	0.848	0.185
TT vs. CC (3)	Homozygous	0	Fixed	1.80 (1.01–2.94)	0.020	0.377
T vs. C allele (3)	Allele	0	Fixed	1.55 (1.19–2.03)	0.001	0.775
Asian						
TT+ CT vs. CC (4)	Dominant	0	Fixed	1.58 (1.16–2.14)	0.004	0.264
TT vs. CC+CT (4)	Recessive	82.9	Random	1.62 (0.43–6.13)	0.480	0.480
TT vs. CT (4)	Heterozygous	77.8	Random	1.41 (0.41–4.79)	0.585	0.456
TT vs. CC (4)	Homozygous	0	Fixed	3.08 (1.53–6.18)	0.002	0.397
T vs. C allele (4)	Allele	62.0	Random	1.28 (0.73–2.25)	0.384	0.077

dominant model: TT + CT versus CC; recessive model: TT versus CC+CT; heterozygote model: TT versus CT; homozygous model: TT versus CC; allele model: T allele versus C allele. Note: When I^2 was greater than 50%, indicating moderate or high between-study variations, a random-effect statistical model was used to estimate the pooled odds ratios with their corresponding 95% confidence intervals (CIs).

doi:10.1371/journal.pone.0153044.t003

significantly among Asian and Pacific Islander subgroups, from 8.0% among Asian Indian women to 3.5% among Japanese women and 3.9% among Korean women [7]. Therefore, whenever possible, Asian and Pacific Islander subgroups should be evaluated separately in genetic health research. Interpreting genetic data from all Asian and Pacific Islanders as a group can mask important differences between many ethnic groups within this population and result in incorrect understanding of the risk for GDM in individual Asian and Pacific Islanders subgroups. The four studies included in this meta-analysis were conducted in China, South Korea, India, and Malaysia. No replicated study was conducted in the same population making more refined ethnic group analysis difficult. Future studies are needed to profile genetic risk for GDM among high risk Asian and Pacific Islander subgroups.

Result of this meta-analysis suggests the Hispanic/Latino women with TT genotype of rs7903146 polymorphism are 1.8 times more likely to have GDM than women with CC genotype. Huerta-Chagoya and associates [29] performed an association study in 750 Mexican women (408 GDM and 342 controls) and reported an association between GDM and *TCF7L2*

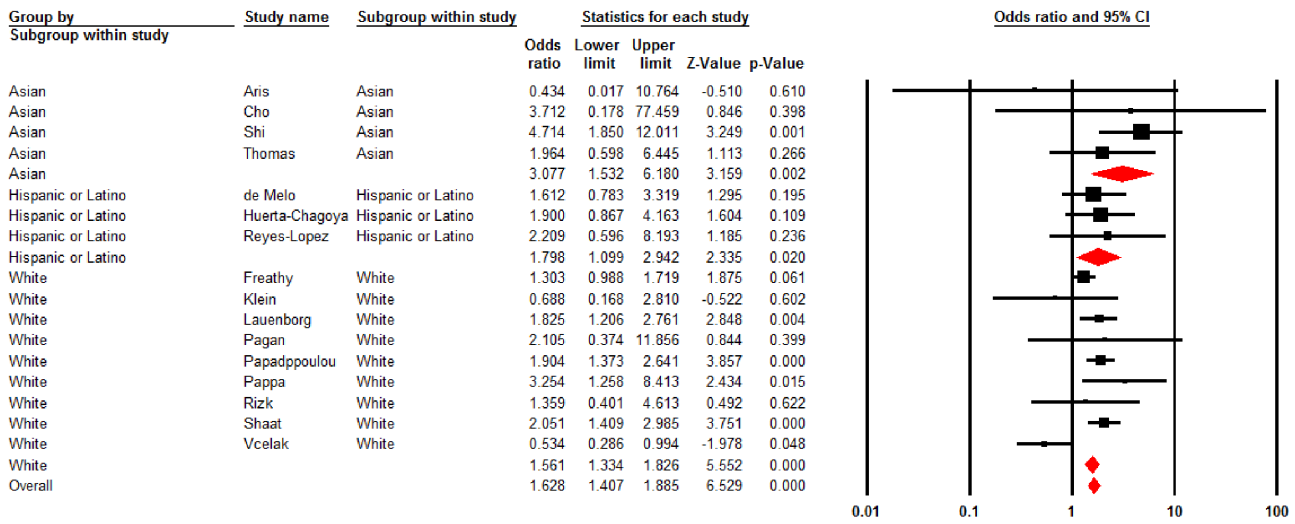

Fig 2. Forest plot of TCF7L2 rs7903146 polymorphism (TT versus CC) and GDM risk under fixed effect model in overall sample and sub-racial groups. The squares and horizontal lines correspond to the study specific odds ratios (ORs) and 95% confidence intervals (CI) respectively. The diamond represents the pooled ORs and 95% CI.

doi:10.1371/journal.pone.0153044.g002

risk haplotype (CTTC of rs7901695, rs4506565, rs7903146, rs12243326; OR 2.95, p = 2.16 x 10–06). In addition, the *TCF7L2* risk haplotype was also associated with metabolic quantitative traits, including higher levels of fasting glycemia (p = 0.0128), and 60 and 120 minutes of OGTT glycemia (p = 2.82 x 10–05, p = 0.00028, respectively). In our meta-analysis, we have included one study from Brazil [31] and two studies from Mexico [29, 32] in the Hispanic/Latino subgroup. The association between the risk T allele of rs7903146 and GDM appears to be stronger in two studies in Mexicans than the study in Euro-Brazilians, suggesting genetic differences and GDM among Hispanic/Latino subgroups require further investigation.

Characteristics of controls varied greatly between studies. For example, Cho and colleagues [26] recruited older men and women without personal or family history of T2DM as controls,

Table 4. The allele frequencies of rs7903146 polymorphism by country.

Country	Author	Race/Ethnicity	Total (n)	CC (%)	CT (%)	TT (%)	C allele (%)	TT allele (%)
Australia	Klein	White	250	8.4	86.4	5.2	51.6	48.4
Brazil	de Melo	Hispanic/ Latino	400	43.5	47.5	9.0	67.3	32.8
China	Shi	Asian	200	47.5	37.0	15.5	66.0	34.0
Czech Republic	Vcelak	White	637	46.8	45.0	8.2	69.3	30.7
Denmark	Lauenborg	White	2629	53.6	37.6	8.8	72.4	27.6
Greece	Pappa	White	255	43.5	46.7	9.8	66.9	33.1
India	Thomas	Asian	166	49.4	38.6	12.0	68.7	31.3
South Korea	Cho	Asian	1495	93.6	6.3	0.1	96.7	3.3
Malaysia	Aris	Asian	287	0.4	20.2	79.4	10.5	89.5
Mexico	Reyes-Lopez & Huerta-Chagoya	Hispanic/Latino	948	70.3	25.6	4.1	83.1	16.9
Qatar	Rizk	White	114	39.5	48.2	12.3	63.6	36.4
Spain	Pagan	White	69	42.0	43.5	14.5	63.8	36.2
Sweden	Papadppoulou & Shaat	White	3609	53.4	38.3	8.3	72.6	27.4
United Kingdom	Freathy	White	4425	49.2	40.7	10.1	69.6	30.4

doi:10.1371/journal.pone.0153044.t004

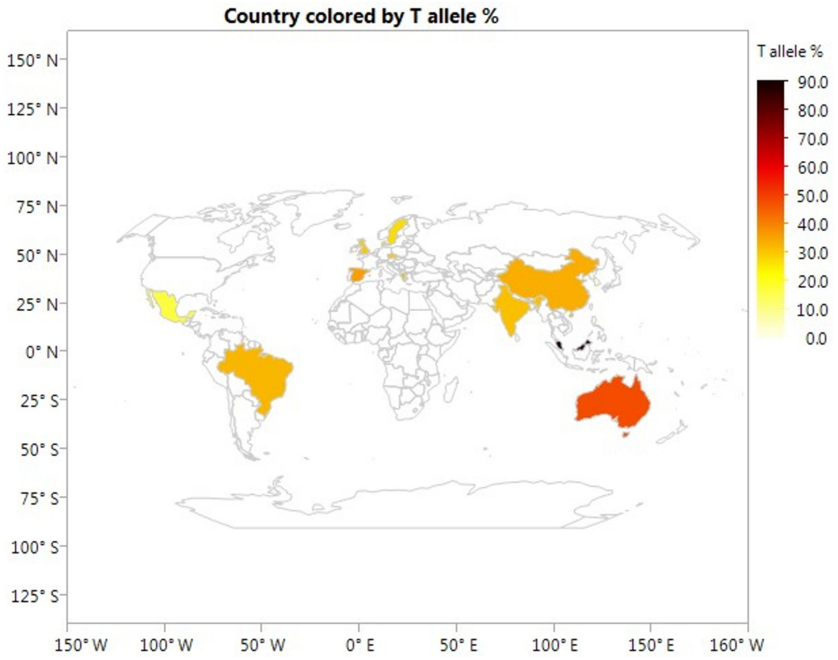

Fig 3. Geographic distribution of risk T allele of rs7903146 polymorphism stratified by study country. The color bar on the right corresponds to the respective allele frequency map (10% interval). This global map showing geographical distributions of the risk T allele frequency was generated using JMP Statistical Discovery software (Version 12 SAS institute Inc., Cary, NC).

doi:10.1371/journal.pone.0153044.g003

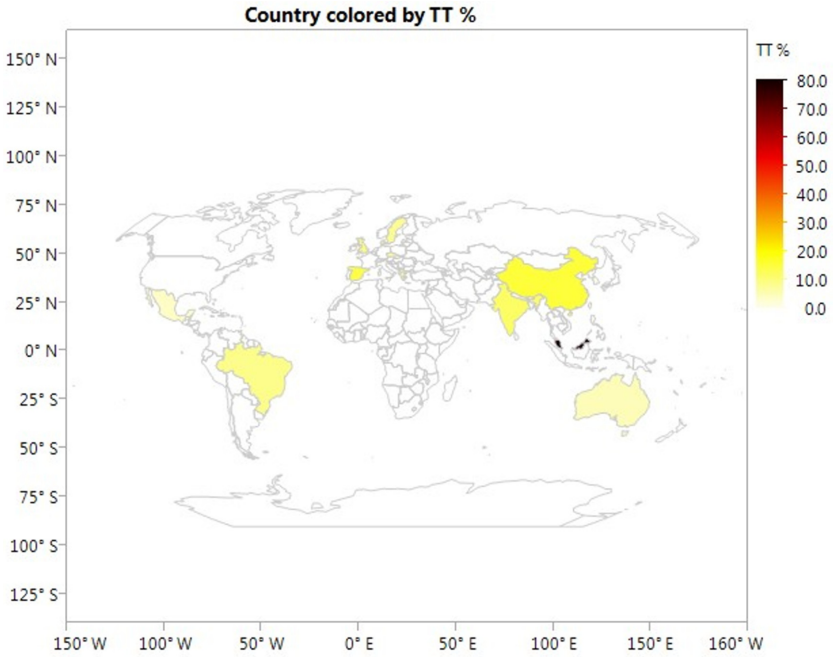

Fig 4. Geographic distribution of risk TT allele of rs7903146 polymorphism stratified by study country. The color bar on the right corresponds to the respective allele frequency map (10% interval). This global map showing geographical distributions of the risk T allele frequency was generated using JMP Statistical Discovery software (Version 12 SAS institute Inc., Cary, NC).

doi:10.1371/journal.pone.0153044.g004

Table 5. Leave-one-out sensitivity analyses: Meta-analysis fixed-effects estimates when a study is omitted at a time.

Study Excluded	TT+CT vs. CC			TT vs. CC+CT			TT vs. CT			TT vs. CC			T allele vs. C allele		
	p	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p	OR	95% CI
Aris	< 0.001	1.44	1.19–1.74	< 0.001	1.45	1.25–1.73	0.006	1.23	1.06–1.43	< 0.001	1.68	1.31–2.15	< 0.001	1.34	1.16–1.55
Cho	0.001	1.43	1.17–1.74	0.012	1.35	1.07–1.70	0.037	1.17	1.01–1.35	< 0.001	1.66	1.30–2.12	0.002	1.30	1.10–1.52
de Melo	0.001	1.43	1.16–1.74	0.014	1.36	1.06–1.74	0.032	1.18	1.01–1.36	< 0.001	1.67	1.29–2.17	0.002	1.31	1.11–1.54
Freathy	< 0.001	1.48	1.22–1.80	0.024	1.37	1.04–1.79	0.153	1.13	0.96–1.34	< 0.001	1.74	1.33–2.28	0.001	1.34	1.13–1.58
Huerta-Chagoya	0.001	1.40	1.15–1.71	0.018	1.34	1.05–1.70	0.033	1.17	1.01–1.36	< 0.001	1.65	1.28–2.14	0.003	1.28	1.09–1.51
Klein	< 0.001	1.45	1.19–1.76	0.005	1.30	1.10–1.75	0.025	1.18	1.02–1.37	< 0.001	1.71	1.34–2.18	< 0.001	1.33	1.13–1.57
Lauenborg	0.001	1.42	1.15–1.74	0.026	1.34	1.04–1.73	0.045	1.17	1.00–1.37	< 0.001	1.65	1.26–2.17	0.003	1.29	1.09–1.54
Pagán	< 0.001	1.45	1.19–1.76	0.014	1.34	1.06–1.69	0.043	1.16	1.01–1.34	< 0.001	1.66	1.29–2.13	0.001	1.31	1.12–1.54
Papadppoulou	0.001	1.41	1.14–1.74	0.032	1.33	1.03–1.73	0.057	1.17	1.00–1.37	0.001	1.64	1.24–2.17	0.004	1.29	1.08–1.53
Pappa	0.001	1.38	1.14–1.66	0.019	1.33	1.05–1.68	0.038	1.17	1.01–1.35	< 0.001	1.61	1.26–2.06	0.002	1.28	1.09–1.50
Reyes-López	0.001	1.41	1.16–1.72	0.015	1.34	1.06–1.70	0.036	1.17	1.01–1.35	< 0.001	1.65	1.29–2.13	0.002	1.29	1.10–1.52
Rizk	< 0.001	1.46	1.20–1.77	0.014	1.35	1.06–1.71	0.041	1.16	1.01–1.35	< 0.001	1.68	1.31–2.16	0.001	1.32	1.12–1.55
Shaat	0.001	1.42	1.15–1.75	0.034	1.32	1.02–1.69	0.087	1.15	0.98–1.34	< 0.001	1.62	1.24–2.12	0.004	1.29	1.08–1.53
Shi	0.001	1.41	1.16–1.72	0.019	1.29	1.04–1.59	0.082	1.14	0.98–1.32	< 0.001	1.58	1.26–1.98	0.002	1.28	1.09–1.50
Thomas	< 0.001	1.44	1.18–1.75	0.016	1.34	1.06–1.70	0.041	1.16	1.01–1.35	< 0.001	1.66	1.29–2.14	0.001	1.31	1.11–1.53
Vcelak	< 0.001	1.55	1.34–1.80	0.001	1.43	1.15–1.78	0.023	1.19	1.02–1.38	< 0.001	1.75	1.50–2.05	< 0.001	1.38	1.22–1.57

CI, confidence interval; OR, odds ratio

doi:10.1371/journal.pone.0153044.t005

however, history of GDM among non-diabetic controls were not provided. Vcelak and colleagues [49] included healthy men without family history of T2DM as controls. Even with the diverse controls, all included studies in this meta- analysis satisfied sensitivity and publication bias analyses, supporting the *TCF7L2* rs7903146 polymorphism as a risk factor for GDM.

Some limitations exist in this meta-analysis. First, we were unable to obtain detailed genotype frequency data from four published studies [43, 44, 46, 68]. Second, the statistical power of this meta- analysis is relatively small, especially for stratification analysis by ethnic subgroups. Third, our meta- analysis was to evaluate the relationship between *TCF7L2* rs7903146 polymorphism and the risk of GDM. Other factors that can affect risk of GDM, such as obesity, family history of T2DM were not included.

Fourth, geographic distribution of risk T or TT alleles of rs7903146 polymorphism can only be stratified when specific genotype data are available by study country. For example, the study by Freathy and colleagues [50] was excluded from such analysis because study subjects were from the United Kingdom and Australia, however, specific allelic frequency was not provided by country.

Conclusion

In summary, our meta-analysis provides evidence that the T allele of the *TCF7L2* rs7903146 polymorphism is associated with GDM risk in whites, Hispanics/Latinos and Asians. Asians with homozygous TT allele of rs7903146 polymorphism have highest risk of GDM (OR = 2.08) followed by Hispanics/Latinos (OR = 1.80) and whites (OR = 1.51). The highest and lowest frequency of T allele of rs7903146 was found in Malaysia and South Korea, respectively. Future studies are needed to profile genetic risk for GDM among high risk Asian and Pacific Islander subgroups.

Supporting Information

S1 Table. PRISMA 2009 Checklist.
(DOC)

S2 Table. Meta-analysis on Genetic Association Studies Checklist.
(DOCX)

S1 Text. A List of Excluded Studies.
(DOCX)

Acknowledgments

We are grateful to the researchers who provided their data for these analyses and for subjects who participated in the original studies.

Author Contributions

Conceived and designed the experiments: PCL. Performed the experiments: PCL WTL YHY. Analyzed the data: PCL YHY SFW. Contributed reagents/materials/analysis tools: PCL. Wrote the paper: PCL SFW.

References

1. Metzger BE, Coustan DR. Summary and recommendations of the Fourth International Workshop- Conference on Gestational Diabetes Mellitus. The Organizing Committee. Diabetes Care. 1998; 21 Suppl 2:B161–7. PMID: 9704245
2. Zhu Y, Zhang C. Prevalence of Gestational Diabetes and Risk of Progression to Type 2 Diabetes: a Global Perspective. Current diabetes reports. 2016; 16(1):7. doi: 10.1007/s11892-015-0699-x PMID: 26742932
3. Chen Y, Quick WW, Yang W, Zhang Y, Baldwin A, Moran J, et al. Cost of gestational diabetes mellitus in the United States in 2007. Popul Health Manag. 2009; 12(3):165–74. doi: 10.1089/pop.2009.12303 PMID: 19534581
4. Bellamy L, Casas JP, Hingorani AD, Williams D. Type 2 diabetes mellitus after gestational diabetes: a systematic review and meta-analysis. Lancet. 2009; 373(9677):1773–9. doi: 10.1016/S0140-6736(09)60731-5 PMID: 19465232
5. Harlev A, Wiznitzer A. New insights on glucose pathophysiology in gestational diabetes and insulin resistance. Current diabetes reports. 2010; 10(3):242–7. doi: 10.1007/s11892-010-0113-7 PMID: 20425589
6. Wung SF, Lin PC. Shared genomics of type 2 and gestational diabetes mellitus. Annu Rev Nurs Res. 2011; 29:227–60. PMID: 22891507
7. Chu SY, Abe K, Hall LR, Kim SY, Njoroge T, Qin C. Gestational diabetes mellitus: all Asians are not alike. Prev Med. 2009; 49(2–3):265–8. doi: 10.1016/j.ypmed.2009.07.001 PMID: 19596364
8. Kim SY, England L, Sappenfield W, Wilson HG, Bish CL, Salihu HM, et al. Racial/ethnic differences in the percentage of gestational diabetes mellitus cases attributable to overweight and obesity, Florida, 2004–2007. Prev Chronic Dis. 2012; 9:E88. PMID: 22515970
9. Pappa KI, Gazouli M, Economou K, Daskalakis G, Anastasiou E, Anagnou NP, et al. Gestational diabetes mellitus shares polymorphisms of genes associated with insulin resistance and type 2 diabetes in the Greek population. Gynecological Endocrinology: The Official Journal of The International Society of Gynecological Endocrinology. 2011; 27(4):267–72.
10. Pagan A, Sabater-Molina M, Olza J, Prieto-Sanchez MT, Blanco-Carnero JE, Parrilla JJ, et al. A gene variant in the transcription factor 7-like 2 (TCF7L2) is associated with an increased risk of gestational diabetes mellitus. European Journal of Obstetrics Gynecology and Reproductive Biology. 2014; 180 (1):77–82.
11. Ao D, Wang HJ, Wang LF, Song JY, Yang HX, Wang Y. The rs2237892 Polymorphism in KCNQ1 Influences Gestational Diabetes Mellitus and Glucose Levels: A Case-Control Study and Meta-Analysis. PLoS One. 2015; 10(6):e0128901. doi: 10.1371/journal.pone.0128901 PMID: 26039078

12. Han X, Cui H, Chen X, Xie W, Chang Y. Association of the glucokinase gene promoter polymorphism—30G > A (rs1799884) with gestational diabetes mellitus susceptibility: a case-control study and meta-analysis. Arch Gynecol Obstet. 2015; 292(2):291–8. doi: 10.1007/s00404-015-3635-z PMID: 25633883
13. Mao H, Li Q, Gao S. Meta-Analysis of the Relationship between Common Type 2 Diabetes Risk Gene Variants with Gestational Diabetes Mellitus. PLoS ONE. 2012; 7(9).
14. Yaghootkar H, Frayling TM. Recent progress in the use of genetics to understand links between type 2 diabetes and related metabolic traits. Genome biology. 2013; 14(3):203. doi: 10.1186/gb-2013-14-3-203 PMID: 23548046
15. Grant SF, Thorleifsson G, Reynisdottir I, Benediktsson R, Manolescu A, Sainz J, et al. Variant of transcription factor 7-like 2 (TCF7L2) gene confers risk of type 2 diabetes. Nat Genet. 2006; 38(3):320–3. PMID: 16415884
16. Cauchi S, El Achhab Y, Choquet H, Dina C, Krempler F, Weitgasser R, et al. TCF7L2 is reproducibly associated with type 2 diabetes in various ethnic groups: a global meta-analysis. Journal of molecular medicine. 2007; 85(7):777–82. PMID: 17476472
17. Lyssenko V, Lupi R, Marchetti P, Del Guerra S, Orho-Melander M, Almgren P, et al. Mechanisms by which common variants in the TCF7L2 gene increase risk of type 2 diabetes. J Clin Invest. 2007; 117 (8):2155–63. PMID: 17671651
18. Florez JC. The new type 2 diabetes gene TCF7L2. Current opinion in clinical nutrition and metabolic care. 2007; 10(4):391–6. PMID: 17563454
19. Rulifson IC, Karnik SK, Heiser PW, ten Berge D, Chen H, Gu X, et al. Wnt signaling regulates pancreatic beta cell proliferation. Proceedings of the National Academy of Sciences of the United States of America. 2007; 104(15):6247–52. PMID: 17404238
20. Yi F, Brubaker PL, Jin T. TCF-4 mediates cell type-specific regulation of proglucagon gene expression by beta-catenin and glycogen synthase kinase-3beta. The Journal of biological chemistry. 2005; 280 (2):1457–64. PMID: 15525634
21. Zhou Y, Park SY, Su J, Bailey K, Ottosson-Laakso E, Shcherbina L, et al. TCF7L2 is a master regulator of insulin production and processing. Human molecular genetics. 2014; 23(24):6419–31. doi: 10.1093/hmg/ddu359 PMID: 25015099
22. Elbein SC, Chu WS, Das SK, Yao-Borengasser A, Hasstedt SJ, Wang H, et al. Transcription factor 7-like 2 polymorphisms and type 2 diabetes, glucose homeostasis traits and gene expression in US participants of European and African descent. Diabetologia. 2007; 50(8):1621–30. PMID: 17579832
23. Damcott CM, Pollin TI, Reinhart LJ, Ott SH, Shen H, Silver KD, et al. Polymorphisms in the transcription factor 7-like 2 (TCF7L2) gene are associated with type 2 diabetes in the Amish: replication and evidence for a role in both insulin secretion and insulin resistance. Diabetes. 2006; 55(9):2654–9. PMID: 16936218
24. Weedon MN. The importance of TCF7L2. Diabetic medicine: a journal of the British Diabetic Association. 2007; 24(10):1062–6.
25. Hansson O, Zhou Y, Renstrom E, Osmark P (2010) Molecular function of TCF7L2: Consequences of TCF7L2 splicing for molecular function and risk for type 2 diabetes. Curr Diab Rep 10: 444–451. doi: 10.1007/s11892-010-0149-8 PMID: 20878273
26. Cho YM, Kim TH, Lim S, Choi SH, Shin HD, Lee HK, et al. Type 2 diabetes-associated genetic variants discovered in the recent genome-wide association studies are related to gestational diabetes mellitus in the Korean population. Diabetologia. 2009; 52(2):253–61. doi: 10.1007/s00125-008-1196-4 PMID: 19002430
27. Lauenborg J, Grarup N, Damm P, Borch-Johnsen K, Jorgensen T, Pedersen O, et al. Common type 2 diabetes risk gene variants associate with gestational diabetes. Journal of Clinical Endocrinology and Metabolism. 2009; 94(1):145–50. doi: 10.1210/jc.2008-1336 PMID: 18984664
28. Shaat N, Lernmark Å, Karlsson E, Ivarsson S, Parikh H, Berntorp K, et al. A variant in the transcription factor 7-like 2 (TCF7L2) gene is associated with an increased risk of gestational diabetes mellitus. Diabetologia. 2007; 50(5):972–9. PMID: 17342473
29. Huerta-Chagoya A, Vázquez-Cárdenas P, Moreno-Macías H, Tapia-Maruri L, Rodríguez-Guillén R, López-Vite E, et al. Genetic determinants for gestational diabetes mellitus and related metabolic traits in mexican women. Plos One. 2015; 10(5):e0126408–e. doi: 10.1371/journal.pone.0126408 PMID: 25973943
30. Kang S, Xie Z, Zhang D. Association of the rs7903146 polymorphism in transcription factor 7-like 2 (TCF7L2) gene with gestational diabetes mellitus: a meta-analysis. Gynecological Endocrinology: The Official Journal Of The International Society Of Gynecological Endocrinology. 2013; 29(10):873–7.

31. de Melo SF, Frigeri HR, Dos Santos-Weiss ICR, Réa RR, de Souza EM, Alberton D, et al. Polymorphisms in FTO and TCF7L2 genes of Euro-Brazilian women with gestational diabetes. Clinical Biochemistry. 2015.
32. Reyes-López R, Pérez-Luque E, Malacara JM. Metabolic, hormonal characteristics and genetic variants of TCF7L2 associated with development of gestational diabetes mellitus in Mexican women. Diabetes/Metabolism Research And Reviews. 2014; 30(8):701–6. doi: 10.1002/dmrr.2538 PMID: 24639413
33. Borenstein M, Hedges L, Higgins J, Rothstein H. Introduction to Meta-Analysis: John Wiley & Sons; 2009.
34. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003; 327(7414):557–60. PMID: 12958120
35. Jackson D, White IR, Riley RD. Quantifying the impact of between-study heterogeneity in multivariate meta-analyses. Stat Med. 2012; 31(29):3805–20. doi: 10.1002/sim.5453 PMID: 22763950
36. McDonald JH. Handbook of biological statistics. 3rd ed: Sparky House Publishing Baltimore, Maryland; 2014. 16–23 p.
37. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997; 315(7109):629–34. PMID: 9310563
38. Egger M, Smith GD, Altman D. Systematic reviews in health care: meta-analysis in context: John Wiley & Sons; 2008.
39. Patsopoulos NA, Evangelou E, Ioannidis JP. Sensitivity of between-study heterogeneity in meta- analysis: proposed metrics and empirical evaluation. Int J Epidemiol. 2008; 37(5):1148–57. doi: 10.1093/ije/dyn065 PMID: 18424475
40. Thomas N, Mahesh DM, Chapla A, Paul J, Shwetha N, Christina F, et al. Does TCF7L2 polymorphisms increase the risk of gestational diabetes mellitus in South Indian population? Endocrine Abstracts. 2014; 34:270.
41. Aris NKM, Ismail NAM, Mahdy ZA, Ahmad S, Naim NM, Siraj HHH, et al. An Analysis of Targeted Single Nucleotide Polymorphisms for the Risk Prediction of Gestational Diabetes Mellitus in a Cohort of Malaysian Patients. Asia-Pacific Journal of Molecular Medicine. 2011; 1(1):1–8.
42. Pasek RC, Gannon M. Advancements and challenges in generating accurate animal models of gestational diabetes mellitus. American Journal of Physiology-Endocrinology and Metabolism. 2013; 305 (11):E1327–E38. doi: 10.1152/ajpendo.00425.2013 PMID: 24085033
43. Huopio H, Cederberg H, Vangipurapu J, Hakkarainen H, Pääkkönen M, Kuulasmaa T, et al. Association of risk variants for type 2 diabetes and hyperglycemia with gestational diabetes. European Journal Of Endocrinology / European Federation Of Endocrine Societies. 2013; 169(3):291–7. doi: 10.1530/EJE-13-0286 PMID: 23761423
44. Katsarou A, Lynch K, Shaat N, Hakansson R, Nilsson A, Lernmark B, et al. Gestational diabetes is associated with a common variant of the transcription factor 7 like 2 (TCF7L2) gene. Diabetologia. 2007; 50:S138–S.
45. Khder A, Al-Khinji M, Saleh R, Rooshenas AA, Rizk NM. Association between carriers of TCF7L2 polymorphisms, insulin and glucagon-like peptide-1 among Arab pregnant women. Endocrine Reviews. 2013; 34.
46. Potasso L, Perakakis N, Lamprinou A, Polyzou E, Kassanos D, Peter A, et al. The type 2 diabetes genetic risk variant TCF7L2 rs7903146 is differentially associated with gestational diabetes: differences between central and Mediterranean Europeans. Diabetologia. 2012; 55:S443–S444.
47. Vejrazkova D, Lukasova P, Vankova M, Bradnova O, Halkova T, Vcelak J, et al. Genetic background of gestational diabetes mellitus in the Czech population. Diabetologia. 2013; 56:S511.
48. Potasso L, Perakakis N, Lamprinou A, Polyzou E, Kassanos D, Peter A, et al. Type 2 diabetes mellitus genetic risk variant T in TCF7L2 rs 7903146 in women is associated with an increased probability of insulin therapy in gestational diabetes mellitus. Diabetologia. 2014; 57:S450.
49. Vcelak J, Vejrazkova D, Vankova M, Lukasova P, Bradnova O, Halkova T, et al. T2D risk haplotypes of the TCF7L2 gene in the Czech population sample: The association with free fatty acids composition. Physiological Research. 2012; 61(3):229–40. PMID: 22480428
50. Freathy RM, Hayes MG, Urbanek M, Lowe LP, Lee H, Ackerman C, et al. Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study: Common genetic variants in GCK and TCF7L2 are associated with fasting and postchallenge glucose levels in pregnancy and with the new consensus definition of gestational diabetes mellitus from the International Association of Diabetes and Pregnancy Study Groups. Diabetes. 2010; 59(10):2682–9. doi: 10.2337/db10-0177 PMID: 20682688
51. Klein K, Haslinger P, Bancher-Todesca D, Leipold H, Knöfler M, Handisurya A, et al. Transcription factor 7-like 2 gene polymorphisms and gestational diabetes mellitus. The Journal Of Maternal-Fetal &

Neonatal Medicine: The Official Journal Of The European Association Of Perinatal Medicine, The Federation Of Asia And Oceania Perinatal Societies, The International Society Of Perinatal Obstetricians. 2012; 25(9):1783–6.

52. Rizk NM, Rooshenas AA, Rooshenas FA, Fouladi EA, Alali KA, Khedr AM. The Rs12255372 variant of transcription like factor 7-like 2 [TCF7L2] is associated with an increased risk of gestational diabetes mellitus in Arab women. Diabetes. 2011; 60:A643.
53. Shi X, Cai Q, Zou M, Shen Y. Correlation between TCF7L2 gene polymorphism and genetic susceptibility in women with gestational diabetes mellitus. Chin J Obstet Gynecol. 2014; 49:588–93.
54. Papadopoulou A, Lynch KF, Shaat N, Håkansson R, Ivarsson SA, Berntorp K, et al. Gestational diabetes mellitus is associated with TCF7L2 gene polymorphisms independent of HLA-DQB1*0602 genotypes and islet cell autoantibodies. Diabetic Medicine: A Journal Of The British Diabetic Association. 2011; 28(9):1018–27.
55. American Diabetes Association. Gestational diabetes mellitus. Diabetes Care. 2004; 27 Suppl 1:S88–90. PMID: 14693936
56. National Diabetes Data Group. Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. National Diabetes Data Group. Diabetes. 1979; 28(12):1039–57. PMID: 510803
57. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care. 2010; 33 Suppl 1:S62–9. doi: 10.2337/dc10-S062 PMID: 20042775
58. Lind T, Phillips PR. Influence of pregnancy on the 75-g OGTT. A prospective multicenter study. The Diabetic Pregnancy Study Group of the European Association for the Study of Diabetes. Diabetes. 1991; 40 Suppl 2:8–13. PMID: 1748272
59. Carpenter MW, Coustan DR. Criteria for screening tests for gestational diabetes. Am J Obstet Gynecol. 1982; 144(7):768–73. PMID: 7148898
60. Kuhl C. Glucose metabolism during and after pregnancy in normal and gestational diabetic women. 1. Influence of normal pregnancy on serum glucose and insulin concentration during basal fasting conditions and after a challenge with glucose. Acta Endocrinol (Copenh). 1975; 79(4):709–19.
61. Damm P, Handberg A, Kuhl C, Beck-Nielsen H, Molsted-Pedersen L. Insulin receptor binding and tyrosine kinase activity in skeletal muscle from normal pregnant women and women with gestational diabetes. Obstet Gynecol. 1993; 82(2):251–9. PMID: 8336874
62. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care. 2004; 27 Suppl 1:S5–S10. PMID: 14693921
63. International Association of Diabetes and Pregnancy Study Groups Consesus Panel. International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. Diabetes Care. 2010; 33(3):676–82. doi: 10.2337/dc09-1848 PMID: 20190296
64. Alibegovic AC, Sonne MP, Hojbjerre L, Hansen T, Pedersen O, et al. (2010) The T-allele of TCF7L2 rs7903146 associates with a reduced compensation of insulin secretion for insulin resistance induced by 9 days of bed rest. Diabetes 59: 836–843. doi: 10.2337/db09-0918 PMID: 20107109
65. Savitz DA, Janevic TM, Engel SM, Kaufman JS, Herring AH. Ethnicity and gestational diabetes in New York City, 1995–2003. Bjog. 2008; 115(8):969–78. doi: 10.1111/j.1471-0528.2008.01763.x PMID: 18651880
66. Shelley-Jones DC, Wein P, Nolan C, Beischer NA. Why do Asian-born women have a higher incidence of gestational diabetes? An analysis of racial differences in body habitus, lipid metabolism and the serum insulin response to an oral glucose load. Aust N Z J Obstet Gynaecol. 1993; 33(2):114–8. PMID: 8216104
67. Kwak SH, Kim SH, Cho YM, Go MJ, Cho YS, Choi SH, et al. A genome-wide association study of gestational diabetes mellitus in Korean women. Diabetes. 2012; 61(2):531–41. doi: 10.2337/db11-1034 PMID: 22233651
68. Lopez-Reyes R, Malacara JM, Perez-Luque EL. Association of rs7901695 and rs12255372 of TCF7L2 gene with gestational diabetes mellitus and its relationship with metabolic and hormonal characteristics in Mexican women. Endocrine Reviews. 2013; 34(3).