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META-ANALYSIS OF THE GENETIC FACTORS THAT PREDISPOSED ASIAN WOMEN TO GESTATIONAL DIABETES MELLITUS

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ABSTRACT

A meta-analysis was conducted to determine the significant risk alleles which increase the risks of gestational diabetes mellitus (GDM) in Asian to help in decision-making for genotyping of women at risk. PubMed, Science Direct and HuGE navigator were used to identify relevant studies from January 2000 to November 2018. Data extraction was done by five reviewers. Using Review Manager 5.3, association between 11 SNPs and risks of GDM was determined. Odds ratios (ORs) with 95% confidence intervals (95% CI), test of heterogeneity and publication bias were calculated. The result was considered significant if p-value ≤ 0.05. Twenty-one studies were identified based on the inclusion and exclusion criteria. From 11 genetic variants studied, 9 were found to have significant association with GDM susceptibility with different heterogeneity. Allelic, dominant and recessive genetic models show MTNR1B (rs138753, rs10830963) and CDKAL1 (rs7754840) are significantly associated with GDM. IGF2BP2 (rs4402960) was found to have significant association with GDM using allelic and recessive models. For TCF7L2 (rs7903146), significant association was found using allelic, dominant and over dominant models. KCNQ1 (rs2237892) showed association with GDM in dominant model only. Strong associations with increased susceptibility for GDM were also found for GSTM1 (deletion), GSTT1 (deletion) and GSTP1 (rs1695). However, MTNR1B (rs10830962) and PPARγ2 are lack of association with GDM risk in Asian population. Nine genetic variants were associated with increased GDM risk in Asian population. Screening of these polymorphisms to identify pregnant women at risk is recommended for prevention and personalised intervention.

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Keywords: Gestational diabetes mellitus, Single nucleotide polymorphism, Odds ratio, Confidence interval, Meta-analysis

INTRODUCTION

Gestational diabetes mellitus (GDM) is commonly known as hyperglycaemia during pregnancy. Malaysia reported a prevalence of 18.3%, one of the countries in the South East Asia with the highest prevalence of GDM (Zhu and Zhang, 2016). A local study by Logakodie *et al*. (2017) reported an alarming rate of GDM at 27.9% in 2017, compared to 9%–12% in 2007 (Tan, Ling and Omar 2007).

Diagnosis of GDM mainly follows the guidelines by American Diabetes Association (ADA) or International Association of Diabetes and Pregnancy Study Groups (IADPSG), using oral glucose tolerance test (OGTT) at around 24–28 weeks of gestation or as early as possible in women with high risk of GDM. The risk factors for GDM include age ≥ 25 years old, body mass index (BMI) ≥ 27 kg/m^2, first degree relative with diabetes mellitus (DM), history of macrosomia, bad obstetric history and persistent glycosuria. Although OGTT is the cornerstone for the diagnosis of GDM, few studies had challenged its use for GDM diagnosis. Some researchers suggested the use of other tests or parameters for the diagnosis and identification of risks for GDM, such as haemoglobin A1c (HbA1c), other biomarkers and genetic tests (Rodrigo and Glastras 2018). Rapid advances and cost reductions of sequencing technologies, coupled with the completion of Human Genome Project, had made possible to identify regions of the genome harbouring susceptibility genes (Watanabe *et al*. 2007).

Single nucleotide polymorphisms (SNPs) which have been identified to increase the risks of developing diabetes mellitus type 2 (DM2) include MTNR1B, TCF7L2, HHEX/IDE, FTO and NOTCH2 (Beer and Mccarthy 2014). Due to the similar underlying mechanisms of DM2 and GDM, researchers hypothesise that DM2 and GDM shared the genetic variants that increase the susceptibility (Lauenborg *et al*. 2009; Stuebe *et al*. 2014). However, most of the studies were conducted on the European and Caucasian population (Lowe *et al*. 2016). Up to date, only one genome-wide association study (GWAS) have been done in Asians (Kwak *et al*. 2012). Other studies involving Asian were done in smaller sample size and fewer genetic variants. Hence, this meta-analysis was done by combining these studies of small sample size to determine the genetic factors that predisposed Asian women to GDM.

METHODS

Literature Search Strategy

A comprehensive literature search was carried out for related articles available in PubMed, Science Direct and HuGE navigator databases, which were published from January 2000 to November 2018. The search strategy consisted of queries of multiple combination ‘gestational diabetes mellitus’, ‘GDM’ and ‘genetic polymorphisms’, with names of specific genes combined with the search term ‘gestational diabetes mellitus’. The search was focused on studies that had been conducted in the Asian women. Only articles in English language were included.

Eligible Studies and Selection Criteria

The candidate studies were based on these major inclusion criteria: a) original case-control study, b) population must be pregnant Asian women, c) identification of GDM using the criteria of ADA, Implementation of the IADPSG or other standard diagnostic criteria, d) associations between the genetic polymorphisms and GDM which were assessed in two or more independent studies, e) the subjects were in 24 to 28 gestational periods, and f) the age of the GDM subjects were above 18 years old and below 50 years old. The major reasons for exclusion of studies were: a) duplicates, b) studies with insufficient data, c) meta-analysis or review articles and d) family-based studies.

Data Extraction

Five independent reviewers screened the titles and abstracts of all the articles identified from the literature search. Irrelevant articles were eliminated. The reviewers also assessed the articles for the inclusion and exclusion criteria. Discrepancies and inconsistencies of results during the assessment were resolved through consensus. The following information were independently extracted by the reviewers: author, year of publication, ethnicity, study design, mean age for cases and controls, the numbers of case and control group for each genotype, genotyping method and the criteria whereby GDM is confirmed. Control groups generally follows the criteria of case group. However, three studies included in this meta-analysis used general population to represent control group, with strict criteria: age ≥ 50 years old with no history of DM2, no first degree relative with DM2, with fasting plasma glucose level < 6.1 mmol/L and HbA1c level < 6.0%. Thus, the control group was expected to have a low risk for DM2.

Statistical Analysis

Statistical analysis was carried out with Mantel-Haenszel statistics using Review Manager (RevMan) 5.3 statistical software (Cochrane Collaboration, Oxford, England). The allele frequency for each single nucleotide polymorphism (SNP) or the genotype frequency for each case and control groups was used for calculation of odds ratios (OR) and their corresponding 95% confidence interval (CI). OR ≥ 1 shows association of the allele or genotype with the increased risk for GDM. The *Z* test ($p < 0.05$) was used to determine the significance of the pooled OR. Heterogeneity across individual studies was assessed by I^2 and Cochrane Q statistics to ensure that each group of studies was suitable for meta-analysis. Heterogeneity describes the percentage of variation across studies that is due to heterogeneity rather than chance. For this meta-analysis, $I^2 < 50\%$ shows that the heterogeneity of the studies is acceptable, while $I^2 > 50\%$ shows serious heterogeneity and thus, the results obtained must be interpreted with caution. Fixed effect model was used for $I^2 < 50\%$, while random effect model was used for $I^2 > 50\%$. Meanwhile, the genetic models used in this study include dominant, recessive, over-dominant, and allelic models. Supposed that the alleles of the gene of interest are A and B, whereby A is the 'variant' or 'risk' allele and B is wild-type allele, the dichotomisation of the SNP genotypes are as follows: Dominant (AA + AB versus BB); Recessive (AA versus AB + BB); Over Dominant (AB versus AA + BB) and Allelic (A versus B). The best model was selected to represent the result of association of the SNPs with increased risk for GDM. Genetic variant with

significant association to increased risk of GDM but with high heterogeneity was subjected to subgroup analysis. Funnel plots were used to assess the potential publication bias and sensitivity test was done to assess the robustness of the results.

RESULTS

Characteristics of Studies

We initially identified 41 eligible studies based on the inclusion and exclusion criteria outlined. However, many SNP candidates were present in only one study, rendering the data insufficient and cannot be compared. Thus, twenty studies were further excluded. Finally, 21 studies with a total of 19,577 GDM cases and 24,788 controls, involving 11 SNPs were included. The flow of study selection is shown in Figure 1. In the control groups of the population studies, the polymorphisms of these genetic variants were consistent with Hardy-Weinberg equilibrium. The characteristics of the studies are shown in Table 1. Results of analysis with respect to genetic models are listed in Table 2. Figure 2 shows the forest plots of the genetic association studies.

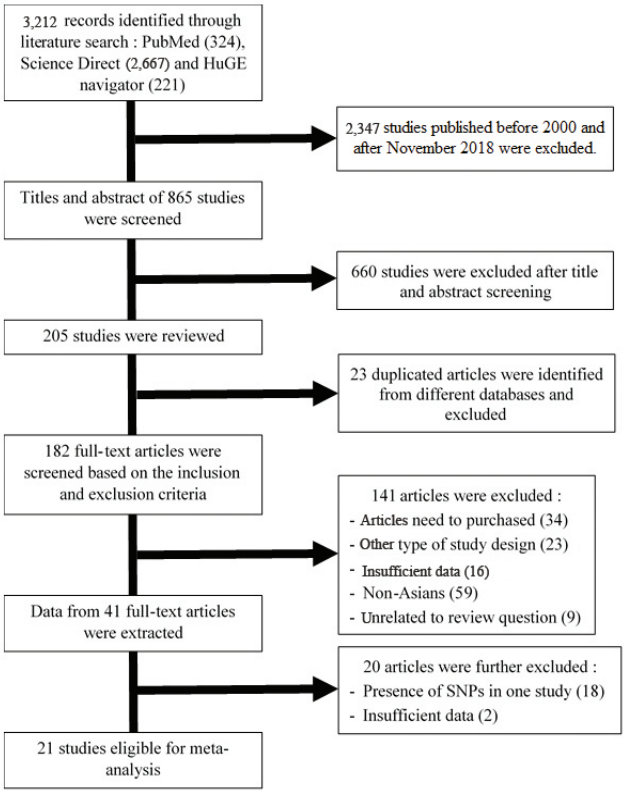

Figure 1: Selection process for the studies included in meta-analysis.

Table 1: Characteristics of the study included in the meta-analysis.

Study/Year	Ethnicity	Mean age (Case/ Control)	GDM criteria	Genotyping method	Gene	Genotype					
						Case			Control		
						AA	Aa	aa	AA	Aa	aa
Kasuga *et al*. (2017)	Japanese	36.1/36.6	OGTT, IADPSG	Sequenom, MassARRAY™	MTNR1B (rs1387153)	45	85	41	39	63	26
					MTNR1B (rs10830963)	46	85	40	36	64	28
					CDKAL1 (rs7754840)	52	85	34	40	63	25
					KCNQ1 (rs2237892)	23	80	68	14	57	57
					IGF2BP2 (rs4402960)	79	74	18	61	55	12
Cho *et al*. (2008)	Korean	32.0/64.7	GCT, OGTT; follows 3rd International Conference on GDM	TaqMan®	CDKAL1 (rs7754840)	171	389	303	178	319	133
					PPARγ2 (rs1801282)	1	71	793	2	63	567
					IGF2BP2 (rs4402960)	389	365	103	313	257	57
					TCF7L2 (rs7903146)	803	63	2	956	31	0
Kanthimathi *et al*. (2015)	Indian	28.1/26.3	OGTT, IADPSG	Sequenom, MassARRAY™	MTNR1B (rs1387153)	199	244	75	387	413	110
					MTNR1B (rs10830963)	158	256	104	307	443	160
					CDKAL1 (rs7754840)	274	172	49	558	306	46
					IGF2BP2 (rs4402960)	126	259	133	258	453	199
Wang *et al*. (2011)	Chinese	32.0/30.0	GCT, OGTT	TaqMan®	MTNR1B (rs10830963)	199	364	137	329	509	191
					CDKAL1 (rs7754840)	199	339	159	311	512	197
					IGF2BP2 (rs4402960)	371	278	56	605	361	59
Kwak *et al*. (2012)	Korean	31.5/59.1	GCT, OGTT; follows 3rd International Conference on GDM	Affymetrix Genome-Wide SNP Array 5.0	MTNR1B (rs10830962)	104	233	131	403	609	230
					CDKAL1 (rs7754840)	84	229	155	383	613	246
					TCF7L2 (rs7903146)	430	37	1	1176	65	1

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Table 1: (*continued*)

Study/Year	Ethnicity	Mean age (Case/ Control)	GDM criteria	Genotyping method	Gene	Genotype					
						Case			Control		
						AA	Aa	aa	AA	Aa	aa
Kim *et al*. (2011)	Korean	33.2/32.2	GCT, OGTT	TaqMan®	MTNR1B (rs1397153)	235	433	241	313	455	204
					MTNR1B (rs10830963)	217	435	256	294	469	203
Liao *et al*. (2012)	Chinese	29.7/28.1	GCT, OGTT	ABI PRISM 3100 Genetic Analyzer	MTNR1B (rs1397153)	210	399	153	439	577	179
					MTNR1B (rs10830963)	195	402	171	475	569	158
Chon *et al*. (2013)	Korean	32.3/32.6	GCT, OGTT	PCR, AGE	PPARγ2 (rs1801282)	0	5	89	0	7	34
					IGF2BP2 (rs4402960)	57	30	7	15	24	2
Li *et al*. (2013)	Chinese	32.4/32.0	OGTT	PCR, direct DNA sequencing	MTNR1B (rs10830962)	120	162	68	145	236	99
					MTNR1B (rs10830963)	113	158	79	172	233	75
Liu *et al*. (2016)	Chinese	NA/NA	OGTT	ABI TaqMan SNP Genotyping Assays	MTNR1B (rs1397153)	341	228	105	367	246	77
					MTNR1B (rs10830963)	162	334	178	195	362	117
Shaat *et al*. (2004)	Arabians in Sweden	31.9/NA	2-h capillary glucose concentration	PCR-RFLP	PPARγ2 (rs1801282)	0	9	91	1	15	106
Tok *et al*. (2006)	Turkish	33.7/31.5	GTT, OGTT	PCR-PAGE	PPARγ2 (rs1801282)	0	12	50	0	16	84
Zhou *et al*. (2009)	Chinese	32.5/30.7	GCT, OGTT	PCR-RFLP	KCNQ1 (rs2237892)	40	227	253	94	404	418
Kwak *et al*. (2010)	Korean	32.0/64.7	GCT, OGTT	TaqMan®	KCNQ1 (rs2237892)	96	390	367	100	289	235
Rizk (2011)	Arabian	NA/NA	NA	TaqMan®	TCF7L2 (rs7903146)	16	20	4	30	32	12
Ao *et al*. (2015)	Chinese	30.2/29.5	OGTT, IADPSG	Sequenom, MassARRAY™	KCNQ1 (rs2237892)	33	206	323	50	201	202

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Table 1: (*continued*)

Study/Year	Ethnicity	Mean age (Case/ Control)	GDM criteria	Genotyping method	Gene	Genotype					
						Case			Control		
						AA	Aa	aa	AA	Aa	aa
Li *et al*. (2015)	Chinese	32.2/27.6	OGTT, ADA	PCR-RFLP	GSTP1 (Ile105Val)	145	142	33	178	152	28
Qiu, Xu and Zhang (2016)	Chinese	31.5/28.2	OGTT, ADA	PCR-RFLP	GSTP1 (Ile105Val)	95	99	29	128	109	28
Hasan *et al*. (2016)	Bangladeshi	26.2/26.2	OGTT, WHO 2013	PCR (GoTaq®) Promega	TCF7L2 (rs7903146)	28	20	2	35	13	2
Li *et al*. (2019)	Chinese	31.4/30.9	OGTT, IADPSG	PCR-RFLP	MTNR1B (rs10830963)	54	102	59	87	121	35
Orhan *et al*. (2014)	Turkish	32.2/28.6	OGTT, ADA	PCR-AGE	GSTM1	30	20		27	23	
					GSTT1	11	39		10	40	
Li *et al*. (2015)	Chinese	32.2/27.6	OGTT, ADA	PCR-RFLP	GSTM1	149	171		121	237	
					GSTT1	142	178		102	256	
Qiu, Xu and Zhang (2016)	Chinese	31.5/28.2	OGTT, ADA	PCR-RFLP	GSTM1	106	117		87	178	
					GSTT1	75	148		78	187	

Notes: PCR = polymerase chain reaction; PCR-RFLP = polymerase chain reaction-restriction fragment length polymorphism; OGTT = oral glucose tolerance test; GCT = glucose challenge test; GTT = glucose tolerance test; IADPSG = Implementation of the International Association of Diabetes and Pregnancy Study Groups; WHO = World Health Organization; ADA = American Diabetes Association; AA = homozygous wild type; AB = heterozygous genotype; BB = homozygous variant; N/A = Not applicable.

Table 2: Result summary of genetic association studies of SNPs and their selected genetic model.

SNP	Number of studies	Sample size case/ Control	Allele (Wild type/ Variant)	Total allele (Wild type/ Variant)	Genetic model	OR (95% CI), $p < 0.05$	Heterogeneity		Meta-analysis model
							Q	I^2	
MTNR1B (rs1387153)	5	3034/3895	C/T	8293/**5565**	Allelic	1.24 [1.16, 1.33]; $p <$ **0.00001**	P = 0.59	0%	Fixed
					Dominant	1.30 [1.17, 1.43]; $p <$ **0.00001**	P = 0.23	28%	Fixed
					Recessive	1.37 [1.20, 1.55]; $p <$ **0.00001**	P = 0.93	0%	Fixed
MTNR1B (rs10830962)	2	818/1722	C/G	2784/**2296**	Allelic	1.16 [0.71, 1.90]; $p = 0.55$	P < 0.0001	94%	Random
					Dominant	1.19 [0.59, 2.37]; $p = 0.63$	P = 0.0003	92%	Random
					Recessive	1.28 [0.70, 2.32]; $p = 0.43$	P = 0.005	87%	Random
MTNR1B (rs10830963)	8	4304/5632	C/G	10984/**8888**	Allelic	1.29 [1.15, 1.44]; $p <$ **0.00001**	P = 0.0009	71%	Random
					Dominant	1.35 [1.16, 1.56]; $p <$ **0.0001**	P = 0.01	61%	Random
					Recessive	1.48 [1.24, 1.76]; $p <$ **0.0001**	P = 0.008	63%	Random
CDKAL1 (rs7754840)	5	2694/3930	G/C	7527/**5721**	Allelic	1.35 [1.12, 1.62]; $p =$ **0.001**	P = 0.0002	82%	Random
					Dominant	1.39 [1.10, 1.76]; $p =$ **0.006**	P = 0.003	75%	Random
					Recessive	1.66 [1.28, 2.15]; $p =$ **0.0002**	P = 0.005	73%	Random
IGF2BP2 (rs4402960)	5	2345/2731	G/T	6704/**3448**	Allelic	1.18 [1.08, 1.28]; $p =$ **0.0002**	P = 0.15	40%	Fixed
					Dominant	1.13 [0.92, 1.39]; $p = 0.26$	P = 0.04	60%	Random
					Recessive	1.30 [1.10, 1.55]; $p =$ **0.003**	P = 0.96	0%	Fixed

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Table 2: (*continued*)

SNP	Number of studies	Sample size case/ Control	Allele (Wild type/ Variant)	Total allele (Wild type/ Variant)	Genetic model	OR (95% CI), $p < 0.05$	Heterogeneity		Meta-analysis model
							Q	I^2	
TCF7L2 (rs7903146)	4	1426/1993	C/T	6509/**329**	Allelic	1.41 [1.10, 1.80]; p = **0.006**	P = 0.36	6%	Fixed
					Dominant	1.51 [1.16, 1.98]; p = **0.002**	P = 0.75	0%	Fixed
					Over dominant	1.53 [1.17, 2.01]; p = **0.002**	P = 0.94	0%	Fixed
KCNQ1 (rs2237892)	4	2106/2121	T/C	**2754**/5700	Allelic	1.21 [1.00, 1.46]; p = 0.05	P = 0.01	73%	Random
					Dominant	1.47 [1.20, 1.79]; p = **0.0002**	P = 0.19	37%	Fixed
					Recessive	1.23 [0.98, 1.55]; p = 0.08	P = 0.03	68%	Random
PPARγ2 (rs1801282)	4	1121/895	G (Ala)/ C(Pro)	**206**/3826	Allelic	1.30 [0.98, 1.73]; p = 0.07	P = 0.24	29%	Fixed
					Recessive	1.29 [0.97, 1.74]; p = 0.08	P = 0.23	31%	Fixed
GSTP1 (ILE105VAL)	2	543/623	A (Ile)/ G(Val)	1594/**738**	Allelic	1.19 [1.00, 1.41]; p = **0.05**	P = 0.90	0%	Fixed
					Dominant	1.22 [0.97, 1.54]; p = 0.09	P = 0.82	0%	Fixed
GSTM1	3	593/673	Present/ Null	746/**520**	Null vs Present	1.72 [1.37, 2.16]; p < **0.00001**	P = 0.70	0%	Fixed
GSTT1	3	593/673	Present/ Null	848/**418**	Null vs Present	1.51 [1.01, 2.26]; p = **0.04**	P = 0.11	54%	Random

Notes: **Bold** font in the Allele column indicates minor allele. **Bold** font in OR column indicates significant association.

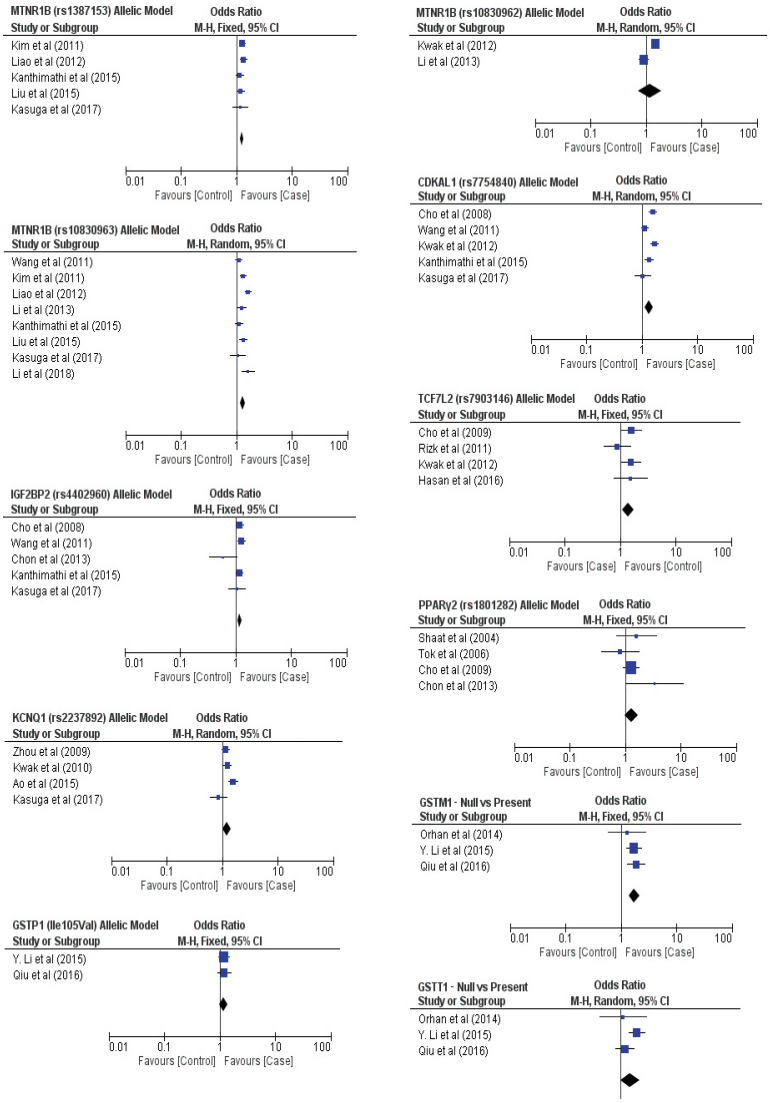

Figure 2A: Forest plot for genetic association of GDM using different genetic models (Allelic model).

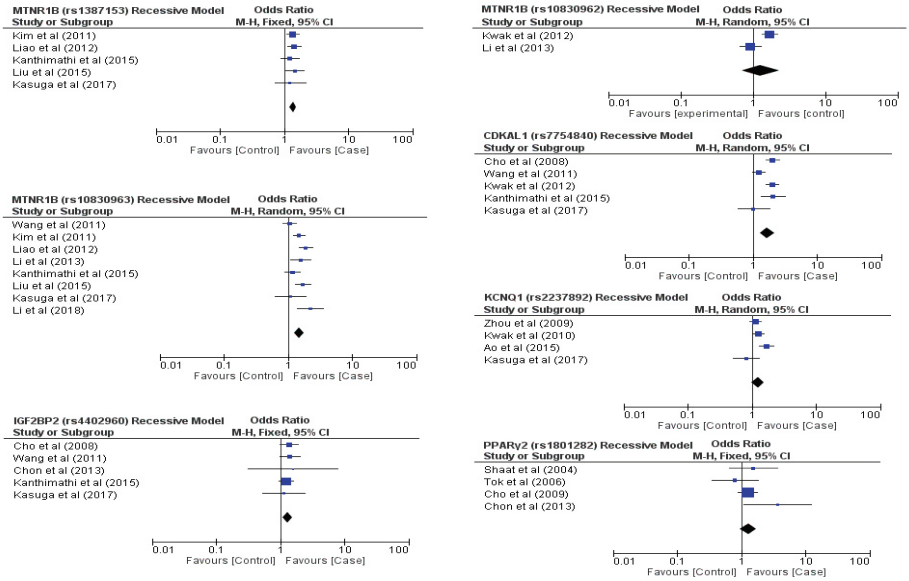

Figure 2B: Forest plot for genetic association of GDM using different genetic models (Recessive model).

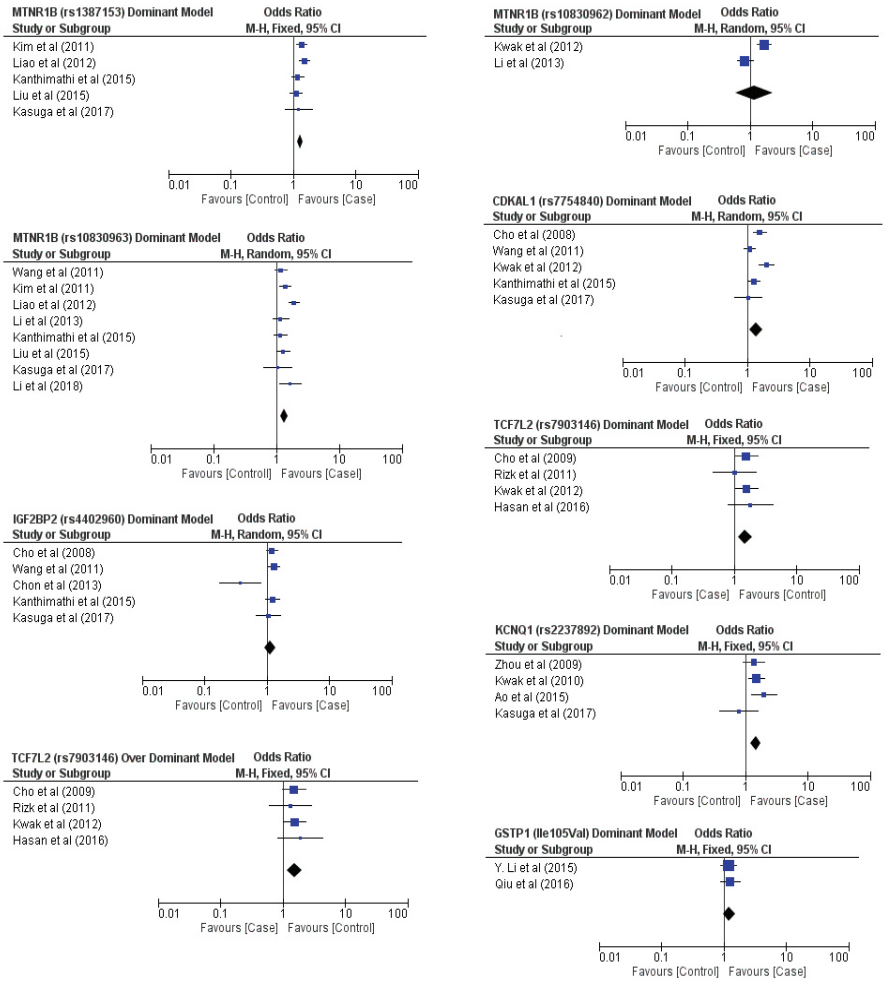

Figure 2C: Forest plot for genetic association of GDM using different genetic models (Dominant model).

Genetic Variants Involved in β-Cell Function

Melatonin receptor 1B (MTNR1B)

Three genetic variants for MTNR1B were analysed. For rs1387153, calculated pooled effects from five studies (Kanthimathi *et al*. 2015; Kasuga *et al*. 2017; Kim *et al*. 2011; Liao *et al*. 2012; Liu *et al*. 2016) showed significant association with increased risk of GDM in the allelic genetic model (Figure 2A, OR = 1.24 [95% CI: 1.16, 1.33]; $p < 0.00001$; recessive model (Figure 2B, OR = 1.37 [95% CI: 1.20, 1.55]; $p < 0.00001$); dominant model (Figure 2C, OR = 1.30 [95% CI: 1.17, 1.43]; $p < 0.00001$). The I^2 value suggests low heterogeneity and small variation across the studies. Analysis for rs10830962 demonstrated

insignificant association with increased risk of GDM, as shown by the allelic model (Figure 2A, G versus C) with OR = 1.16 [95% CI: 0.71, 1.90]; p = 0.55, recessive model (Figure 2B, OR = 1.28 [95% CI: 0.82, 2.37]; p = 0.43) and dominant model (Figure 2C, OR = 1.19 [95% CI: 0.59, 2.37]; p = 0.63). In addition, the heterogeneity for the two studies (Kwak *et al*. 2012; Li *et al*. 2013) used in the analysis of this genetic variant is significant (I^2 > 50%) and thus, random effect model was used. MTNR1B (rs10830963) is the most extensively studied polymorphism for GDM in Asian population, with eight studies (Kanthimathi *et al*. 2015; Kasuga *et al*. 2017; Kim *et al*. 2011; Li *et al*. 2013; Li *et al.* 2019; Liao *et al*. 2012; Liu *et al*. 2016; Wang *et al*. 2011) included in this meta-analysis. It shows significant association with increased risk of GDM in allelic (Figure 2A, OR = 1.29 [95% CI: 1.15, 1.44]; p < 0.00001), recessive genetic models (Figure 2B, OR = 1.48 [95% CI: 1.24, 1.76]; p < 0.0001) and dominant (Figure 2C, OR = 1.35 [95% CI: 1.16, 1.56]; p < 0. 0001) with high heterogeneity. Random effect model was used.

CDK5 regulatory subunit associated protein-like 1 (CDKAL1)

The association between CDKAL1 (rs7754840) and GDM was investigated in five studies (Cho *et al*. 2008; Kanthimathi *et al*. 2015; Kasuga *et al.* 2017; Kwak *et al.* 2012; Wang *et al*. 2011). Our meta-analysis demonstrated that the risk allele C of this SNP is significantly associated with increased risk of GDM (Figure 2A, OR = 1.35 [95% CI: 1.12, 1.62]; p = 0.001). The homozygous variant genotype CC showed an even stronger, significant association with GDM in recessive model (Figure 2B, OR = 1.66 [95% CI: 1.28, 2.15]; p = 0.0002). Dominant genetic model for this SNP also demonstrated significant association with increased GDM risk (Figure 2C, OR = 1.39 [95% CI: 1.10, 1.76]; p = 0.006). The heterogeneity is significant. Hence, we used random effect model.

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

Five studies (Cho *et al*. 2008; Chon *et al.* 2013; Kanthimathi *et al*. 2015; Kasuga *et al*. 2017; Wang *et al*. 2011) were analysed for the association of rs4402960 with increased GDM risks. Allelic model (Figure 2A, T versus G) and recessive model (Figure 2B, TT versus GG + GT) both showed significant association to GDM with low heterogeneity. The pooled effects for the allelic and recessive models for this polymorphism are OR = 1.18 [95% CI: 1.08, 1.28]; p = 0.0002 and OR = 1.30 [95% CI: 1.10, 1.55]; p = 0.003, respectively. As for dominant model (Figure 2C, TT + GT versus GG), the heterogeneity across the study is significant (I^2 = 60%). Thus, random effect model was used, resulting in insignificant association with GDM (OR = 1.13 [95% CI: 0.92, 1.39]; p = 0.26).

Transcription factor-7 like 2 (TCF7L2)

The association of TCF7L2 (rs7903146) polymorphism with increased risk of GDM was analysed by extracting genotype frequencies data from four studies (Cho *et al.* 2008; Hasan *et al.* 2016; Kwak *et al*. 2012; Rizk 2011). This polymorphism consistently showed strong association with GDM in allelic model T versus C (Figure 2A, OR = 1.41 [95% CI: 1.10, 1.80]; p = 0.006) and dominant model (Figure 2C, 1.51 [95% CI: 1.16, 1.98]; p = 0.002). In addition, the heterogeneity across these studies is very low (I^2 < 10%).

Potassium voltage-gated channel, KQT-like subfamily, member 1 (KCNQ1)

The pooled OR effects from four studies (Ao *et al*. 2015; Kasuga *et al*. 2017; Kwak *et al.* 2010; Zhou *et al*. 2009) on KNCQ1 (rs2237892) polymorphism revealed insignificant association of this genetic variant with increased susceptibility to GDM. This can be seen in allelic (Figure 2A, C versus T) and recessive model (Figure 2B, with OR = 1.21 [95% CI: 1.00, 1.46]; p = 0.05 and OR = 1.23 [95% CI: 0.98, 1.55]; p = 0.08), respectively. These models also demonstrated high heterogeneity. On the contrary, dominant model, with low heterogeneity, showed significant association towards GDM risk (Figure 2C, OR = 1.47 [95% CI: 1.20, 1.79]; p = 0.0002).

Genetic Variants Involved in Insulin Resistance

Peroxisome proliferator-activated receptor gamma 2 (PPARγ2)

Collective data from four studies (Cho *et al*. 2008; Chon *et al.* 2013; Shaat *et al*. 2004; Tok *et al*. 2006) on PPARγ2 (r1801282) showed that the wild type allele, instead of risk allele is the minor allele in Asian population. Based on allelic genetic model (Figure 2A, Pro versus Ala) and recessive genetic model (Figure 2B), moderate association to increased risk of GDM is shown by OR = 1.30 [95% CI: 0.98, 1.73]; p = 0.07 and OR = 1.29 [95% CI: 0.97, 1.74]; p = 0.08, respectively. However, the p-value for both odds ratios is more than 0.05, rendering it insignificant.

Genetic Variants Involved in Oxidative Stress

Glutathione S-transferase (GST)

Two studies (Tok *et al*. 2006; Li *et al*. 2015) on GSTP1 (rs1695) and three studies (Li *et al*. 2015; Orhan *et al*. 2014; Qiu, Xu and Zhang 2016) on GSTM1 and GSTT1 were analysed in our study. GSTP1 (rs1695) demonstrated significant association with GDM only in allelic genetic model (Figure 2A, OR = 1.19 [95% CI: 1.10, 1.41]; p = 0.05) with zero heterogeneity, whereas the dominant genetic model shows insignificant association with increased risk of GDM (Figure 2C, OR = 1.22 [95% CI: 0.97, 1.54]; p = 0.09). As for GSTM1 and GSTT1 polymorphism, the deletion of these genes are strongly and significantly associated with GDM, as depicted by Figure 2A, OR = 1.72 [95% CI: 1.37, 2.16; p < 0.00001 and Figure 2A, OR = 1.51 [95% CI: 1.01, 2.26]; p = 0.04, respectively. However, only GSTM1 showed zero heterogeneity across the studies, whereas GSTT1 has substantial heterogeneity (I^2 = 54%).

Publication Bias and Sensitivity Test

Funnel plot was used to identify potential publication biases of the studies. The shapes of the funnel plots appeared to be symmetrical, suggesting that no obvious publication bias is present. Sensitivity analysis was done by omitting one study at a time to determine the consistency of the results.

DISCUSSION

In this meta-analysis, 11 genetic variants were investigated to find their association with increased GDM susceptibility in the Asian population. Out of the 21 studies analysed, 20 studies were conducted based on candidate gene approach; one was a GWAS by Kwak *et al*. (2012). Overall, this meta-analysis found significant association of increased risk to GDM susceptibility with nine genetic variants: rs1387153 and rs10830963 from MTNR1B, rs7754840 (CDKAL1), rs4402960 (IGF2BP2), rs2237892 (KCNQ1), rs7903146 (TCF7L2), GSTM1, GSTT1 and GSTP1 (rs1695) under different combination of genetic models. However, only rs1387153, 4402960, rs2237892, rs7903146, GSTM1 and GSTP1 (rs1695) have low heterogeneity across the studies. Other SNPs with significant association but high heterogeneity (I^2 > 50%) were analysed using random effect model. The remaining SNPs in this analysis, MTNR1B (rs108309062) and PPARγ2 (rs1801282) have insignificant associations with GDM in Asian populations.

GDM and DM2 are believed to share the same pathogenesis such as insulin resistance, impaired β-cell function, abnormal glucose utilisation and oxidative stress (Lauenborg *et al*. 2009). Insulin resistance is caused by insulin-desensitising placental hormones and hormonal changes due to increased maternal adiposity such as cortisol, human placental lactogen, prolactin and oestrogen. Predisposition to chronic low-grade inflammation will increase the concentration of reactive oxygen species (ROS), deteriorating β-cell insufficiency, and by extension, glucose tolerance impairment (Law and Zhang 2017).

Melatonin is a hormone secreted mainly from pineal glands and primarily functions to maintain circadian rhythm. Melatonin inhibits cyclic adenosine monophosphate (cAMP) pathway that stimulates secretion of insulin, which are mediated through G-protein coupled Melatonin receptor 1B (Zhang *et al*. 2014). Secretion of melatonin peaks during the night, while secretion of insulin is reduced, to compensate the lack of glucose in the body during overnight fasting. Overexpression of MTNR1B exaggerates the inhibition of insulin release (Tuomi *et al*. 2016). During pregnancy, MTNR1B is likely to be involved in the regulation of glucose homeostasis.

Individuals with the risk allele T of rs1387153 showed 24% increased risk for GDM compared to those who do not possess it. TT genotype further emphasis this finding with OR that suggest strong association to increased GDM risk. This conforms to the findings by Zhang *et al*. (2014) and Gao et al. (2016) among the Caucasian and Asian populations. As for rs10830962, the result for this analysis is not considered to be representative for the Asian population. Women with allele G and GG genotype of rs10830963 for MTNR1B recorded 29% and 48% increased risk for GDM, respectively. Dominant genetic model also showed significant association to GDM. Our finding correlates with the study by Zhang *et al*. (2014) and Gao *et al*. (2016) that also found significant, positive association of this genetic variant to increased GDM susceptibility. Meanwhile, wild type allele C has protective effect against GDM.

Animal studies showed that in obese mice, CDKAL1 mRNA levels were reduced and the mitochondrial functions were impaired, leading to inefficient energy expenditure by the cells. In this meta-analysis, SNP rs7754840 was replicated in five studies (Cho *et al*. 2008; Kanthimathi *et al*. 2015; Kasuga *et al*. 2017; Kwak *et al*. 2012; Wang *et al*. 2011) in Asian populations. Pooled effects showed that risk allele C and genotype CC show significant positive association to GDM. Meanwhile, G allele and GG genotype do not show association to GDM and hence, are deemed as protective. Dominant genetic model (CC + CG versus GG) shows significant association to increased GDM risk with high heterogeneity. A meta-analysis by Gao *et al*. (2016) and a cohort study by Aris

et al. (2011) also support significant association of this genetic variant with increased risk to GDM susceptibility. However, a study by Noury *et al*. (2018) on pregnant women in Egypt revealed insignificant association to GDM.

For risk allele T of rs4402960, four out of the five studies that we analysed showed that it has association with increased risk for GDM. Only study by Chon *et al*. (2013) showed negative association of this allele. Pooled effects obtained from allelic and recessive genetic models, however, showed significant positive associations to GDM susceptibility. As for dominant model, due to high heterogeneity, the analysis was done under random effect, resulting in insignificant association towards increased risk of GDM. Subgroup analysis revealed that there was no difference in terms of association to GDM across populations. Meta-analysis by Mao, Li and Gao (2012) which comprised of both Asian and Caucasian populations supports our finding with significant positive association of this genetic variant to increased risk for GDM under allelic model. Meanwhile, a study in Danish population (Lauenborg *et al*. 2009) found insignificant association.

TCF7L2 (rs7903146) is a transcriptional regulator that is involved in stimulating the hyperplasia of pancreatic B-cells and the production of incretin hormone glucagon-like peptide-1 in enterocytes. This polymorphism modifies the sensitivity of pancreatic B-cells to incretin and subsequently insulin secretion. The risk T-allele was reported to have association with increased TCF7L2 expression, causing reduction of insulin production and secretion. It showed a consistent and strong association with impaired glucose tolerance and β-cell function across different populations, such as the Caucasians and African-American descendants. In our meta-analysis, the pooled effects of four studies showed strong, significant association of this SNP to increased risk of GDM susceptibility in allelic, dominant and over-dominant genetic models. These models demonstrated low heterogeneity, indicating that the results are highly reliable. Our findings correlate with the studies by Lauenborg *et al*. (2009), Wu *et al.* (2016) and Lin *et al*. (2016).

KCNQ1 is involved in coding the pore-forming subunit of a K+ voltage-gated channel, mainly in cardiac muscle that is responsible for the repolarisation of the action potential. Its mutation is associated with long QT interval and familial atrial fibrillation. KCNQ1 is also expressed in tissues including brain, adipose and pancreas. The risk allele will cause impaired insulin secretion, and therefore is associated in higher risk of developing type-2 diabetes and GDM. In this meta-analysis, KNCQ1 (rs2237892) found insignificant association of this genetic variant to increased GDM risk, under allelic (C versus T) and recessive models. On the other hand, dominant genetic model (CC + CT versus TT) showed significant positive association with GDM. A genetic association study by Shin *et al.* (2010) in 930 Korean females with GDM revealed that rs2237892 might represent genetic risk factors for GDM. A study in the Mexican women by Huerta-Chagoya *et al*. (2015) also found negative association of wild-type T allele with GDM, suggesting protective effect. It is worth noting that while T allele is protective, the risk allele C is the major allele for this SNP, making it a prevalent gene associated with GDM in the population.

Activation of PPARγ2 helps to improve insulin action (Cho *et al*. 2008; Tok *et al.* 2006). In this study, the major allele C is also a risk allele, as evidenced by the OR value in allelic and recessive genetic model. However, the *p*-value is more than 0.05, rendering it insignificant. The studies on Scandinavian populations (Lauenborg *et al*. 2009) and a meta-analysis by Mao, Li and Gao (2012) also showed insignificant association of this genetic variant with GDM. We found no association of minor allele G with susceptibility of GDM. The meta-analysis by Wu *et al*. (2016) supports this finding.

GST is an enzyme encoded by GST gene family that primarily functions as antioxidants. It functions are to: a) detoxify environmental toxicants and ROS mediated cell injury in the body, b) catalyse neutralisation of the harmful compounds and c) prevent DNA

damage (Li *et al*. 2015). Complete GST family comprised of 16 genes in six subfamilies. In this study, we studied the association of increased risk of GDM to three subfamilies of this gene which are pi (GSTP), mu (GSTM) and theta (GSTT).

GSTP1 enzyme plays an important role in biotransformation and bioactivation of certain environmental pollutants and other diol epoxides of polycyclic aromatic hydrocarbons. It provides protection against oxidative stress by catalysing the detoxification of base propanols that arise from DNA oxidation. The GSTP1 (rs1695) polymorphism at codon 105 (exon 5) results in an amino acid substitution of isoleucine by valine.

Similar to our study, Li *et al.* (2015) and Qiu, Xu and Zhang (2016) found that GSTP1 (rs1695) polymorphism influences the risk of GDM. The risk allele (G; Val) was also found to be associated with an increased risk for GDM in our study and in Egypt (Amer *et al.* 2012). Another study also showed significant association, suggesting this polymorphism to be screened in the North Indian population to determine diabetic risk (Bid *et al*. 2010).

GSTM1 and GSTT1 are involved in catalysing the conjugation of glutathione to a variety of hydrophobic and electrophilic substrates and carcinogens (Li *et al*. 2015). Several studies had reported that subjects who have GSTM1 NULL genotype and GSTT1 NULL genotype are susceptible to gestational diabetes mellitus (Li *et al.* 2015; Orhan *et al*. 2014; Qiu, Xu and Zhang 2016). For GSTM1 NULL genotype, our result was consistent with the findings from the Chinese (Li *et al*. 2015; Qiu, Xu and Zhang 2016) but different from the Turkish population (30). As for GSTT1 NULL genotype, our finding is only supported by the study by Li *et al*. (2015), whereby the other two studies (Orhan *et al*. 2014; Qiu, Xu and Zhang 2016) found insignificant association of null GSTT1 to increased risk of GDM.

Homozygous deletion of either GSTM1 or GSTT1 locus was found to cause loss of function on enzymatic activity of GST. In turn, it may impair the capacity of defence against oxidative stress (Yalin *et al*. 2007), aggravating the damage caused by ROS to pancreatic β-cells, causing reduction of insulin production. Polymorphism of these genes, whether alone or as combination, influence the increased risk of DM2 in North Indian population (Bhandari 2014). In addition, GSTM1 may be a useful marker for DM prediction in Turkish population (Bhandari 2014). However, Zaki *et al*. (2015) found no significant association of GSTM1 and GSTT1 null genotypes for the diabetic Egyptian. The discrepancies on studies about these genes can be attributed to the small number of studies focusing on diabetes condition among the Asians.

Potential publication bias of the 21 journals used in this meta-analysis were assessed using Funnel plot. We found that there is no obvious publication bias, based on the symmetrical shape of the plots. Egger's test is another tool used to assess publication bias but we were unable to carry it out because RevMan 5.3 package does not offer such test. Subgroup analysis based on ethnicity and genotyping method was done for CDKAL1 (rs7754840), MTNR1B (rs10830963) and GTTT1. CDKAL1 (rs7754840) showed subgroup effect for ethnicity but not on genotyping method. MTNR1B (rs10830963) showed no subgroup effect with moderate unexplained heterogeneity and uneven covariate distribution. GTT1 showed no subgroup effect at all.

The major limitation of this meta-analysis was the insufficient number of studies in some of the SNPs in Asian population. Two of the genetic variants in this analysis were only discussed in two studies and another two SNPs in three studies. It is hard to draw conclusion based on a few studies, especially when the studies show contradicting results due to different ethnicity. Other than that, small sample size affects the *p*-value and heterogeneity of the results, thus making the analysis lack reliability and credibility to represent the population. To confirm the relationship of the genes with GDM, more studies on the association of the genes with GDM in Asian population, with larger sample size are required. Furthermore, in this meta-analysis, we did not consider confounding factors

such as maternal age, BMI, history of diabetes, lifestyle during pregnancy. Finally, as there were not many studies done in Asian population, there were lack of data, hence it cannot represent for the whole Asian population. Further studies including subjects at other parts of Asia, such as the Southeast Asia, where GDM prevalence is reported to be high should be carried out to better understand the association of these genetic variants with susceptibility of GDM.

CONCLUSION

Nine genetic variants were found to have significant association with increased susceptibility for GDM in Asian population. Identification of these genetic risk variants can be used to tailor personalised preventive measures and therapeutic intervention. This could enable physicians to provide better healthcare plan and help the patients to avoid pathological conditions that could be detrimental at their later stage of life.

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