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Association of common variant in the MTNR1B gene and risk of type 2 diabetes: Asian meta-analysis

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Abstract: **MTNR1B gene encodes one of two high affinity forms of a receptor for melatonin that expressed in many tissues, including pancreatic islets β-cells. Several large-scale genome-wide association studies and meta-analysis have shown that common variants (rs10830963, rs1387153) in MTNR1B gene are significantly associated with type 2 diabetes (T2D) in European populations. However, the replication studies in various populations showed an inconsistent result. The aim of the present meta-analysis is to investigate this inconsistency, especially in Asian populations. A systemic literature search inclusive to November 2018 yielded a total of 19 potentially relevant articles with the eligible studies concerning the association of MTNR1B rs10830963 and /or rs1387153 gene variants with T2D in Asian populations. We performed the final meta-analysis of 18 studies (26,289 T2D cases and 24,881controls) for rs10830963 and 12 studies (11,085 T2D cases and 10,520 controls) for rs1387153 with T2D in Asian populations. In the overall estimates, a significant association with T2D was detected only for the risk allele G of the rs10830963 with T2D in Asian populations with a combined allelic OR=1.04 (95%CI 1.01 - 1.07, P=0.003) under fixed effects model. In the stratified meta-analysis on the basis of ethnicity, the significant association of rs10830963 was only in the East Asian population (OR = 1.05, 95%CI 1.02 - 1.08, P=0.001). However, no association for rs1387153 with T2D in East or South Asian. The present meta-analysis confirmed that the MTNR1B rs10830963 gene variant was significantly associated with increased risk for T2D in Asian populations, particularly in East Asian descent.**

Keywords: **MTNR1B; Gene polymorphism; Type 2 diabetes; Meta-analysis.**

I. INTRODUCTION

Type 2 diabetes (T2D) is a complex, multifactorial disorder, characterized by High fasting plasma glucose (FPG) levels, impaired insulin sensitivity and pancreatic β-cell dysfunction; and is involved in complicated interactions between genetic variants and environmental factors such as physical inactivity, obesity and aging, trigger the disease in genetically susceptible individuals (Prasad and Groop, 2015). Association studies of genetic variants in the susceptibility to T2D, especially Genome-wide association studies (GWASs) have identified more than 100 genetic variants associated with T2D in various populations (Prasad and Groop, 2015; Visscher et al., 2012), including a common diabetogenic (rs10830963 and rs1387153) variants in or near the MTNR1B gene, which have been associated with increased risk of T2D and its related metabolic traits, such as increased FPG levels and impaired insulin secretion in populations of European descent (Bouatia-Naji *et al.*, 2009; Prokopenko *et al.*, 2009; Sabatti *et al.*, 2009; Lyssenko *et al.*, 2009). After that, a number of replication studies concerning the association between this variants and T2D have been conducted in various ethnic populations (Rönn *et al.*, 2009; Reiling *et al.*, 2009; Tam *et al.*, 2010; Hu *et al.*, 2010; Liu *et al.*, 2010; Xu *et al.*, 2010; Kan *et al.*, 2010; Ohshige *et al.*, 2011; Ling *et al.*, 2011; Cho *et al.*, 2011; Rees *et al.*, 2011; Been *et al.*, 2012; Liu *et al.*, 2012; Fujita *et al.*, 2012; Bai *et al.*, 2015; Kong *et al.*, 2015; Qian *et al.*, 2015; Salman *et al.*, 2015; Gao *et al.*, 2016; Plengvidhya *et al.*, 2018; Patel *et al.*, 2018; Tabara *et al.*, 2011; Sparsø *et al.*, 2009; Langenberg *et al.*, 2009; Reinehr *et al.*, 2011; Dupuis *et al.*, 2010; Chambers *et al.*, 2009; Takeuchi *et al.*, 2010; Voight *et al.*, 2010; Bonnefond *et*

al., 2012; Jonsson *et al.*, 2013; Renström *et al.*, 2015; Florez *et al.*, 2012; Dietrich *et al.*, 2011; Mussig *et al.*, 2010; Stancakova *et al.*, 2009; Wang *et al.*, 2013; Xia *et al.*, 2012; Andersson *et al.*, 2010; Heshmat *et al.*, 2014; Semiz *et al.*, 2014; Olsson *et al.*, 2011). However, the results from different studies were inconsistent. Therefore, we conducted a meta-analysis to assess the contributions of the two common genetic variants (rs10830963 and rs1387153) in the MTNR1B to the risk of T2D, and achieve a more comprehensive result in Asian populations.

II. MATERIALS AND METHODS

A. SEARCH STRATEGY

We searched the worldwide literature published in MEDLINE via PubMed, EMBASE, Cochrane CENTRAL, Chinese databases (CNKI, CQVIP, Wanfang databases), and Google Scholar for articles of case-control association studies of the rs10830963, and/or rs1387153 variants in MTNR1B gene with T2D, published up to 2018. The following search terms keywords were used: melatonin receptor 1B' or ''MTNR1B'' ''Gene polymorphism'', ''Genetic variant'', ''Genetic variation'', ''genotype'', in combination with words related to ''Type 2 diabetes''/''Type 2 diabetes mellitus'' or ''T2D/T2DM''. The research subjects were limited to human studies published in English or Chinese languages were retrieved. The reference lists of main reports and review articles were also searched in order to identify any additional relevant articles.

B. INCLUSION CRITERIA

Studies were selected based on the following inclusion criteria: case-control or cohort studies; studies that examining the association of the MTNR1B rs10830963 and/or rs1387153 gene variants with the risk of T2D; and both cases and controls reporting genotype and/or allele frequencies; controls group accord with Hardy-Weinberg equilibrium. The exclusion criteria were: studies that did not fit within the selected conditions; studies with repetitive data.

C. DATA EXTRACTION

Data were drawn out according to a standard protocol. Repeated publications and studies violating the inclusion criteria or providing insufficient data were excluded. Same data from different studies were only adopted once. The extracted information from all eligible articles included: first author's surname, publication year, characteristics of study population, including country, ethnicity, sex, age, BMI, sample size "cases /controls" and number of genotypes and/or alleles frequency in case and control groups. Hardy–Weinberg equilibrium (HWE) test for the controls were included as quality assessment indicator. If the reported data were incomplete, the corresponding author was contacted to obtain complete data.

D. STATISTICAL ANALYSIS

In the current meta-analysis, an allele-contrast model was used to investigate the associations of the rs10830963 and/or rs1387153 gene variants with the risk of T2D. The strength of the association of each gene variant and the risk of T2D was determined by using odds ratios (ORs) and their corresponding 95% confidence intervals (CIs). The pooled ORs were obtained only for allele contrast model (G vs. C) of rs10830963 gene variant and (T vs. C) of rs1387153 gene variant because some studies lack the information for genotypes. The statistical significance of pooled ORs was determined by using the Z test, with the significance level set at $P<0.05$.

The heterogeneity between studies was analyzed by using the chi-square test based on the Q statistic, with the significance level set at $P<0.1$ (Cochran, 1968) and/or heterogeneity index (I^2, 0–100) (Higgins *et al.*, 2003). The heterogeneity was quantified by the I^2 value (Higgins *et al.*, 2003), if no heterogeneity between the individual studies was existed, the pooled ORs were computed by using the fixed–effects method of Mantel–Haenszel (Petos method) (Mantel and Haenszel, 1959). If the significant heterogeneity between the individual studies was existed, the pooled OR was estimated using random-effects model of DerSimonian–Laird (D–L method) (DerSimonian and Laird, 1986).

The potential publication bias was estimated using the funnel plot (Mutshinda and Sillanpaa, 2012). The funnel plot asymmetry was quantified using Egger's regression approach (Egger *et al.*, 1997), on the natural logarithmic scale of the OR, with the significance level set a $P<0.05$, which considered to indicate significant asymmetry and the existing of significant publication bias. The population-attributable risk (PAR) was calculated on the basis of estimated ORs and risk allele frequencies in cases group to get a comprehensive view of the impact of the two genetic variants on T2D at

population level, using the following formula: (OR-1)/OR * risk allele frequency (Cugino *et al.*, 2012). The statistical analyses were performed by STATA 11.0 software (StataCorp, College Station, TX, USA).

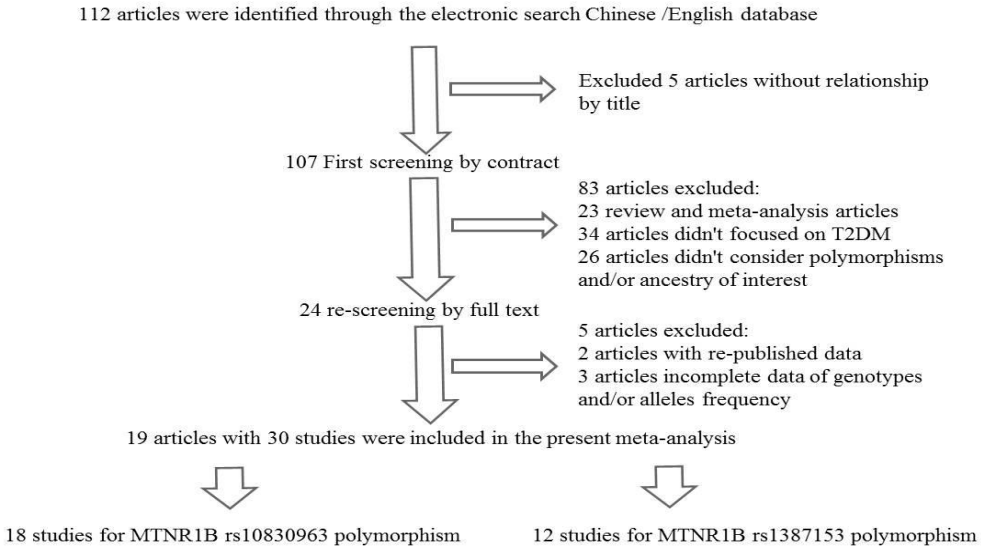

Figure 1: Flow chart of search strategy for eligible studies

Table 1: The characteristics of the eligible studies included in the present meta–analysis

Study	Population	Groups	Sex (M/F%)	Age	BMI (kg/m²)	Sample size	rs10830963				rs1387153			
							GG/GC/CC	G/C F	RAF	HWE-p	TT/TC/CC	T/ C F	RAF%	HWE-p
Rönn et al. 2009	1. Chinese	case	39.1/60.9	60.3±10.9	25.2±3.4	1165	239/548/367	1026/1282	0.445					
		control	31.6/68.4	59.4±7.7	24.1±3.0	1105	171/553/370	895/1293	0.409	0.31				
Tam et al. 2010	2. Chinese	case	41.0/59.0	50.5±13.7	25.0±4.0	1342	261/633/448	1155/1529	0.430					
		control	45.0/54.0			1644	332/789/523	1453/1835	0.442					
Hu et al. 2010	3. Chinese	case	54.7/45.3	60.3±12.5	24.38±3.51	3410		2770/3686	0.429					
		control	40.0/60.0	50.1±14.3	23.46±3.25	3412		2815/3809	0.425					
Xu et al. 2010	4. Chinese	case	43.9/56.1	63.3±69.7	26.3±63.8	1825		1475/1956	0.430			1458/1973	0.425	
		control	38.4/61.6	59.3±69.6	24.3±63.3	2200		1741/2395	0.421			1708/2428	0.413	0.48
Kan et al. 2010	5. Chinese	case	41.1/58.9	63.9±9.5	25.3±3.48	1912	356/931/568	1643/2067	0.443		345/940/570	1630/2080	0.439	
		control	31.1/68.9	58.1±9.4	24.5±3.24	2041	345/972/663	1662/2298	0.420		296/996/688	1659/2301	0.419	
Ohshige et al. 2011	6. Japanese	case	60.0/40.0	61.5±11.6	23.7±3.9	1630	299/776/537	1374/1850	0.426	0.088	262/773/561	1297/1895	0.406	0.47
		control	64.9/35.1	44.3±9.9	22.9±3.1	716	107/327/237	541/801	0.403	0.21	102/312/253	516/818	0.387	0.57
	7.Japanese	case	62.3/37.7	64.9±11.1	24.5±3.9	724	146/344/227	636/798	0.444		125/344/249	594/842	0.414	0.947
		control	47.1/52.9	72.5±9.0	22.7±3.3	763	134/387/235	655/857	0.433		117/387/253	621/893	0.410	0.298
	8.East asian	case	59.4/40.6	64.2±11.5	24.9±4.6	485	103/215/163	421/541	0.438		90/212/169	392/550	0.416	
		control	29.1/70.9	35.6±10.3	21.6±3.0	646	101/317/221	519/759	0.406		95/299/246	489/791	0.382	
Ling et al. 2011	9. Chinese	case	44.6/55.4	60.2±0.37	24.4±0.11	1118	174/527/395	875/1317	0.40					
		control	42.7/57.3	56.5±0.32	23.5±0.09	1161	164/578/396	906/1370	0.40	0.13				
Rees et al. 2011	10.Pakistani GP	case	52.4/47.6			821	138/367/311	643/989	0.39					
		control	52.9/47.1			1167	200/513/444	913/1401	0.39	> 0.05				
	11.Pakistani KADS	case	45.3/54.7			857	145/386/320	676/1026	0.40					
		control	52.0/48.0			417	71/201/139	343/479	0.42	> 0.05				
Been et al. 2012	12. Indians	case	52.3/47.7			1169	174/560/435	908/1430	0.39		17/558/459	852/1476	0.37	
		control	52.4/47.6			1001	163/445/393	771/1231	0.39		131/479/363	741/1205	0.38	
Liu et al. 2012	13. Chinese	case	154/141		27.65±4.06	295					0/150/105	230/360	0.39	
		control	119/120		26.34±3.77	239					8/84	192/286	0.40	
Fujita et al.2012	14. Japanese	case		64.1		2632		1089/1503	0.42					
		control		69.7		2050		847/1170	0.42	>0.05				
Bai et al. 2015	15. Chinese Mongolian	case	43.1/56.9	54.3±10.1	26.1±4.0	511						417/577	0.420	
		control	35.8/64.2	40.5±15.8	24.0±4.8	475						336/602	0.358	
Kong et al 2015	16. Chinese	case				5166		4331/5765	0.429	0.710				
		control				4560		3681/5231	0.413	0.592				
Qian et al. 2015	17. Chinese	case	39.8/60.2	57.4±9.8	24.92±3.42	1200						997/1371	0. 421	
		control	39.8/60.2	56.4±8.0	22.64±2.87	1200						1006/1362	0.425	> 0.05
Salman et al. 2015	18.India	case	59.25/40.7	55.21±11.8	25.42±4.1	346		402/290	0.419			441/251	0.363	
		control	50.7/49.3	45.22±15.4	21.56±2.65	341		389/293	0.430	0.510		423/259	0.380	0.305
Gao et al. 2016	19. Chinese	case	57.9/42.1	52.50	28.58	721	134/347/243	615/833	0.425					
		control	42.2/57.8	47.0	23.50	757	129 /350/280	608/910	0.40	0.274				
Plengvidhya et al. 2018	20. Thai	case	32.8/67.2	57.2±12.2	27.3±5.0	500					104/232/164	440/560	0.44	
		control	28.8/71.2	53.0±8.4	24.1±3.3	500					95/231/174	421/579	0.42	
Patel et al. 2018	21. India	case	44.5/55.5	55.1±10.42	27.04±5.1	434	35/266/133	336/532	0.39					
		control	50/50	39.64±16.3	24.24±5.2	489	61/259/169	381/597	0.39					
Tabara et al. 2011	22. Japan	case				488	77/230/181	384/592			73/226/196	372/618		
		control				398	72/192/134	336/460	0.406		65/195/139	325/473	0.390	

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III. RESULTS

A. CHARACTERISTICS OF INCLUDED STUDIES

A total of nineteen potentially relevant articles withe twenty-two eligible studies were included in the present meta-analysis (Fig. 1) describing an association of the two genetic variants in MTNR1B and T2D. Eighteen studies (26,289 cases and 24,881controls) concerning the association between MTNR1B rs10830963 and T2D (Rönn *et al.*, 2009; Tam *et al.*, 2010; Hu *et al.*, 2010; Xu *et al.*, 2010; Kan *etal.*, 2010; Ohshige *et al.*, 2011; Ling *et al.*, 2011; Rees *et al.*, 2011; Been *et al.*, 2012; Fujita *et al.*, 2012;Kong *et al.*, 2015; Salman *et al.*, 2015; Gao *et al.*, 2016; Patel *et al.*, 2018; Tabara *et al.*, 2011) and twelve studies (11,085 cases and 10,520 controls) concerning the association between MTNR1B rs1387153 and T2D (Xu *et al.*, 2010; Kan *et al.*, 2010; Ohshige *et al.*, 2011; Been *et al.*, 2012; Liu *et al.*, 2012; Bai *et al.*, 2015; Qian *et al.*, 2015; Salman *et al.*, 2015; Plengvidhya *et al.*, 2018; Tabara *et al.*, 2011). Table 1 lists the main characteristics of the nineteen eligible articles for our meta-analysis. No study was excluded for deviating from the Hardy-Weinberg equilibrium (HWE).

Egger regression analysis indicated no publication bias for the MTNR1B rs10830963 and rs1387153 gene variants which indicated reliability of the pooled results (t=-0.92, P=0. 0.371, 95%CI –2.024~0.798, t=-0.03, P=0.976, 95%CI –2.69~2.62, respectively) (data not shown).

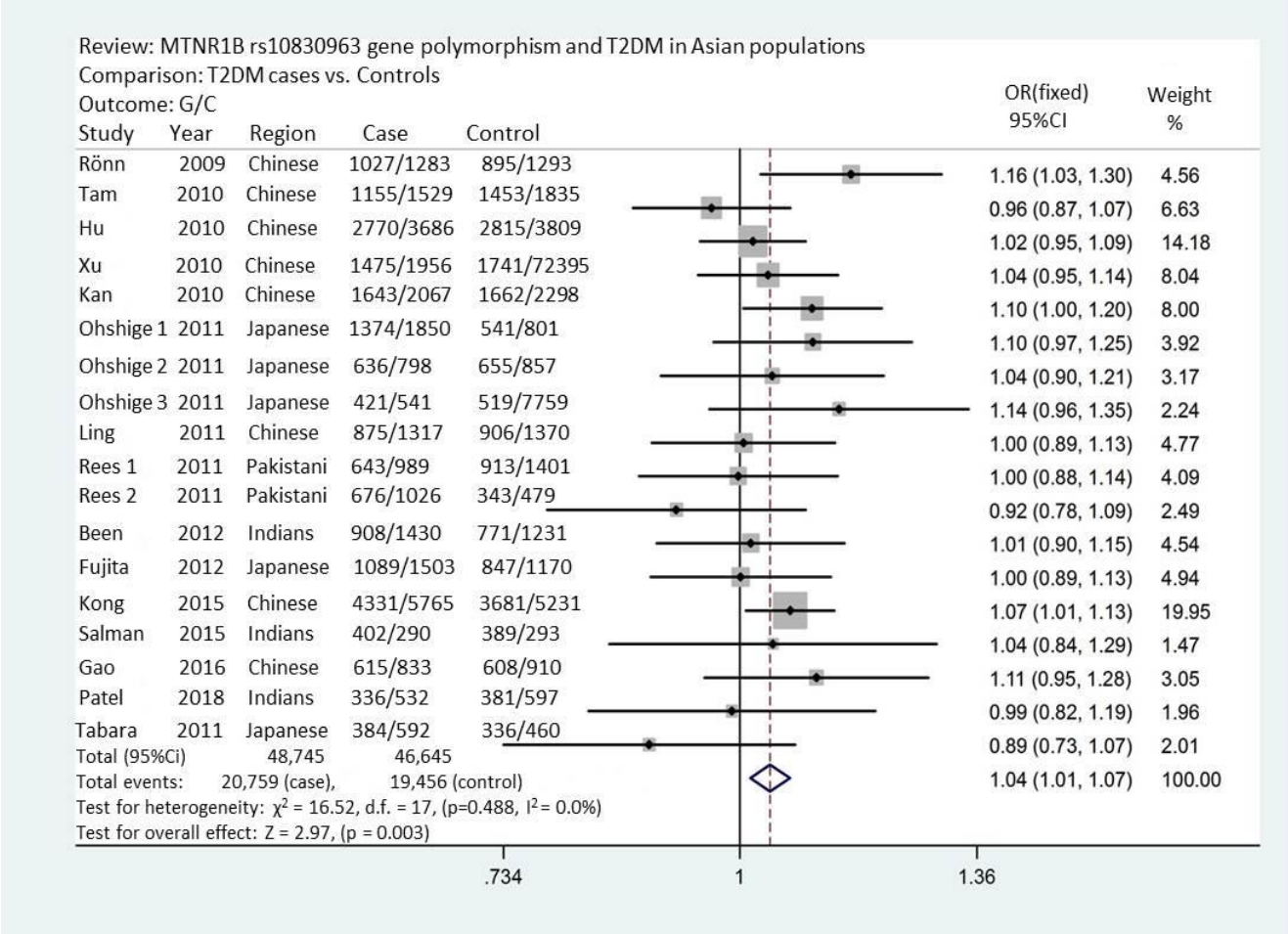

Figure 2 Forest plot of association between MTNR1B rs10830963gene polymorphism and risk of T2D in Asian populations under allele contrast model comparison. For each study, the estimate of OR and its 95% CI is plotted with a closed square and horizontal line. The size of the black squares is proportional to the weight that the study has in calculating the summary effect estimate (diamond). The center of the diamond indicates the pooled OR and the ends of the diamond correspond to the 95% CI. A dashed line is plotted vertically through the combined odds ratio. This line crosses the horizontal lines of all individual studies.

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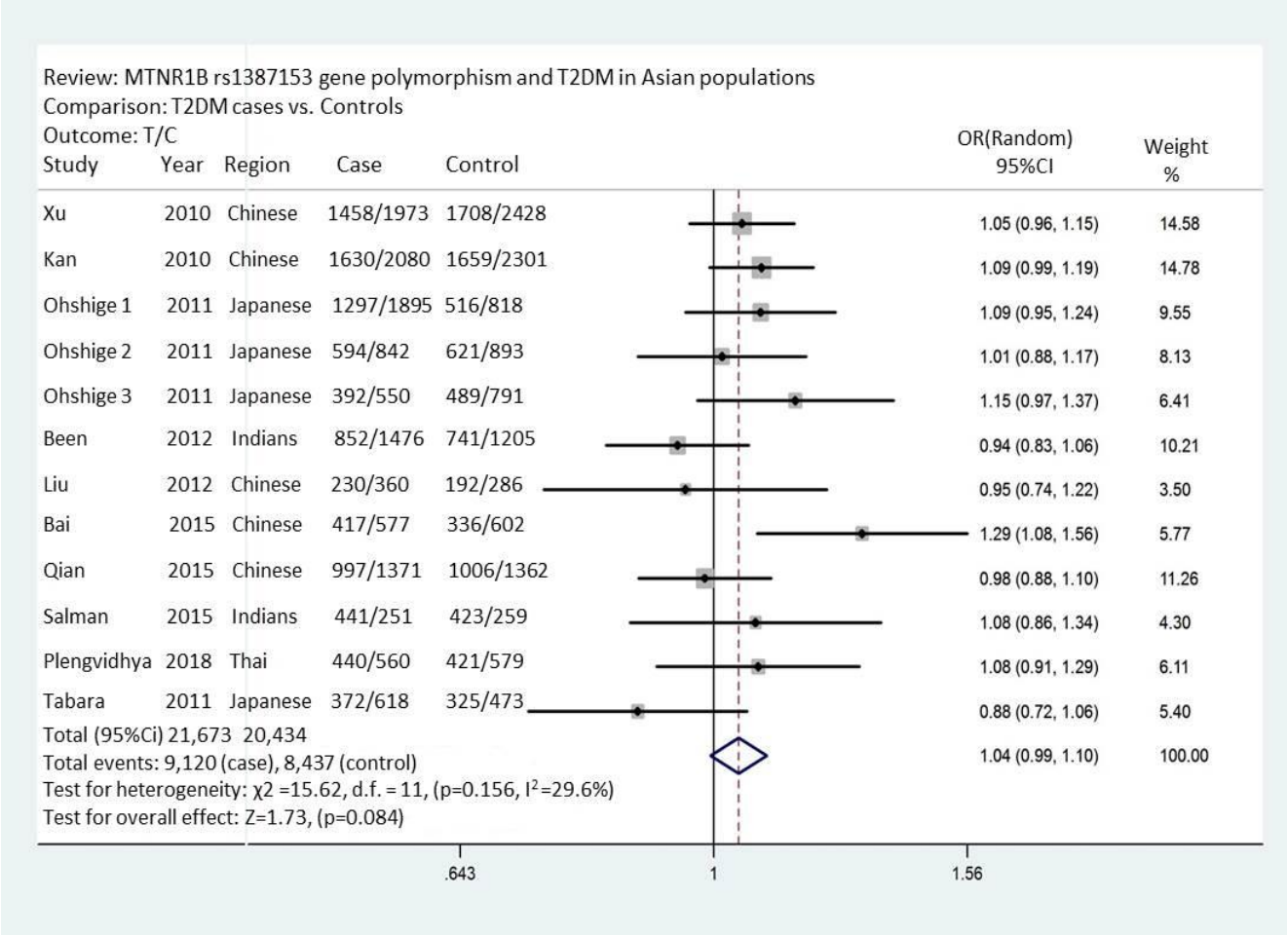

Figure 3 Forest plot of the association between MTNR1B rs1387153gene polymorphism and risk of T2D in Asian populations under allele contrast model comparison.

B. MTNR1B rs10830963 AND TYPE 2 DIABETES

Figure 2 represents the forest plot of risk allele OR of an individual studies and meta–analysis for association between MTNR1B rs10830963 gene variant and T2D in a total of 26,289 T2D patients and 24,881 control subjects from the eighteen studies. Twelve studies showed a trend of elevated OR forthe risk allele G of MTNR1B rs10830963. Three studies, Chinese (Ling *et al.*, 2011), Pakistani DGP (Rees *et al.*, 2011) and Japanese (Fujita *et al.*, 2012) showed no association. Four studies, Chinese (Tam *et al.*, 2010), Pakistan UKADS (Rees et *al.*, 2011), Indian (Patel *et al.*, 2018) and Japanese (Tabara *et al.*, 2011) showed a trend in the opposite direction. The overall frequency of the risk allele G was to 42.4% in cases and 41.7% in controls. No heterogeneity was detected between studies (P=0.488, I^2=0.0%). A fixed effect model was performed and generated a combined allelic OR of 1.04 (95%CI 1.01 - 1.07, P=0.003) for the G allele of MTNR1B rs10830963 in Asian populations.

The population attributable risk (PAR) of T2D related to this variant was 1.64%.

In the stratified meta-analysis on the basis of ethnicity, threaten East Asian studies including 22,618 T2D patients and 21,453 control subjects were enrolled. Nine studies showed a trend of elevatedOR for the risk allele G. Two studies, Chinese (Tam *et al.*, 2010) and Japanese (Tabara *et al.*, 2011) showed a trend in the opposite direction. Two studies, Chinese (Ling *et al.*, 2011) and Japanese (Fujita *et al.*, 2012), showed no association. The overall frequency of the risk allele G was to 42.9% in cases and 41.2% in controls. No significant heterogeneity was detected between studies (P = 0. 0.342, I^2 = 10.3%). A fixed effect model was performed and generated a combined allelic OR of 1.05 (95%CI 1.02 - 1.08, P=0.001) for the risk allele G of MTNR1B rs10830963 in the East Asian populations.

Five south Asian studies including 3,671 T2D patients and 3,428 control subjects were enrolled. Two studies from India (Been *et al.*, 2012; Salman *et al.*, 2015) showed a trend of elevated OR for the risk allele G. One study from Pakistan DGP (Rees *et al.*, 2011) showed no association. Two studies, Pakistani UKADS (Rees *et al.*, 2011) and Indian (Patel *et al.*, 2018), showed a trend in the opposite direction. The overall frequency of the risk allele G was to 40.6% in cases and 41.14% in controls. No heterogeneity was detected between studies (P =0.893, I^2 = 0.0%). A fixed effect model was performed and generated a combined allelic OR of 0.99 (95%CI 0.93 - 1.00, P=0.842) for the risk allele G of MTNR1B rs10830963 in the south Asian populations (data not shown).

C. MTNR1B rs1387153 AND TYPE 2 DIABETES

Figure 3 represents the forest plot of risk allele OR of an individual study and meta–analysis for association between MTNR1B rs1387153 gene variant and T2D in a total of 11,085 T2D patients and 10,520 control subjects from the twelve studies. Eight studies showed a trend of elevated OR for the risk allele G. Four studies, Indians (Been *et al.*, 2012), Chinese (Liu *et al.*, 2012; Qian *et al.*, 2015) and Japanese (Tabara *et al.*, 2011) showed a trend in the opposite direction. The overall frequency of the risk allele T was to 42.1% in cases and 41.3% in controls. A week between-study heterogeneity was observed (P= 0.156, I^2=29.6%). A random effect model was performed and generated a combined allelic OR of 1.04 (95%CI 0.99 - 1.10, p=0.084) for the risk allele T of MTNR1B rs1387153 in the Asian populations. The population attributable risk (PAR) of T2D related to this variant was 1.6%.

In the stratified meta-analysis on the basis of ethnicity, nine East Asian studies including 9,070 T2D patients and 8,678 control subjects enrolled. Six studies showed a trend of elevated OR for the risk allele T. Three studies Chinese (Liu *et al.*, 2012; Qian *et al.*, 2015) and Japanese (Tabara *et al.*, 2011) showed a trend in the opposite direction. The overall frequency of the risk allele T was to 41.8% in cases and 40.8% in controls. A week between-study heterogeneity was observed (P = 0.135, I^2 = 35.4%). A random effect model was performed and generated a combined allelic OR of 1.05 (95%CI 1.00 - 1.12, P=0.071) for the risk allele T of MTNR1B rs1387153 in the East Asian populations.

Three south Asian studies including 2,015 T2D patients and 1,842 control subjects were enrolled. Two studies from Indian and Thailand (Salman *et al.*, 2015; Plengvidhya *et al.*, 2018), showed a trend of elevated OR for the risk allele T. One study from India (Been *et al.*, 2012) showed a trend in the opposite direction. The overall frequency of the risk allele T was to 43.1% in cases and 43.7% in controls. No significant heterogeneity between studies was observed (P =0.340, I^2 = 7.3%). A fixed effect model was performed and generated a combined allelic OR of 1.00 (95%CI 0.91 - 1.10, P=0.987) for the risk allele T of MTNR1B rs1387153 in the south Asian populations.

IV. DISCUSSION

Several large genome wide association studies (GWAS) and large-scale meta-analysis have indicated a consistent and significant association of the minor allele of the two common variants (rs10830963, rs1387153) in MTNR1B gene with the a higher risk of T2D in populations of European descent (Bouatia-Naji *et al.*, 2009; Prokopenko *et al.*, 2009; Lyssenko *et al.*, 2009). MTNR1B gene (13.16 kb) comprises of two exons, one intron, and 5′- and 3′-flanking regions (Li *et al.*, 2010). The rs10830963, was found to be located in the middle of the single intron (11.5 kb) of MTNR1B at chromosome 11q21-q22, where it's G allele was associated with decreased pancreatic β-cell function, increased FPG, hepatic insulin resistance and T2D (Prokopenko *et al.*, 2009; Lyssenko *et al.*, 2009; Sparsø *et al.*, 2009; Langenberg *et al.*, 2009; Staiger *et al.*, 2008; Song *et al.*, 2011), while the rs1387153, was found to be located 28 kb upstream of the 5 region of MTNR1B, where it's T allele was associated with both increased FPG levels and T2D in the genome-wide association study of European populations (Bouatia-Naji *et al.*, 2009). This association was also later widely replicated in other independent studies from same or different ethnicities; however, inconsistent results were reported. Therefore, we conducted the present meta-analysis to investigate this inconsistency, especially in Asian populations.

Our meta-analyses provided the most comprehensive evaluation of the associations between common variants in the MTNR1B (rs10830963, rs1387153) and the risk of T2D in Asian populations.

In the overall estimates, different associations for the MTNR1B rs10830963 and the MTNR1B rs1387153 gene variants with T2D in Asian populations were observed. Significant association for the MTNR1B rs10830963 gene variant with the increased risk of T2D was detected, a combined allelic OR of 1.04 (95%CI 1.01 - 1.07, P=0.003) for the risk allele G of MTNR1B rs10830963 and no association for the MTNR1B rs1387153 gene variant with increased risk of T2D was

detected, a combined allelic OR of 1.04 (95%CI 0.99 - 1.10, P=0.084) for the risk allele T of MTNR1B rs1387153 in the Asian populations, under fixed and random effects model, respectively.

Our result for the MTNR1B rs10830963 gene variant is consistent with the previous reported results in European populations (Prokopenko *et al.*, 2009; Lyssenko *et al.*, 2009; Reiling *et al.*, 2009; Sparsø *et al.*, 2009; Langenberg *et al.*, 2009), Egyptian population (Heshmat *et al.*, 2014), Norwegian population (Olsson *et al.*, 2011). However, the effect sizes in our combined sample of Asians ancestry was smaller than that in European populations (1.04 vs. 1.09) for the risk allele G of MTNR1B rs10830963 gene variant (Prokopenko *et al.*, 2009), but inconsistent with the previous reported results in European populations for MTNR1B rs1387153 gene variant (Bouatia-Naji *et al.*, 2009), also with smaller effect sizes than that in European populations (1.04 vs. 1.15) for the risk allele T of MTNR1B rs1387153 (Bouatia-Naji *et al.*, 2009). Notably, the risk alleles G of the MTNR1B rs10830963 variant and the risk allele T of MTNR1B rs1387153 gene variants in Asian and European studies is the minor alleles, and the intronic variant, MTNR1B rs10830963 is in substantial linkage disequilibrium (LD) with MTNR1B rs1387153 ($r^2 = 0.7$) (Prokopenko *et al.*, 2009).

In the stratified meta-analysis on the basis of ethnicity, different associations for the MTNR1B rs10830963 gene variant with T2D in East and South Asian populations were observed. Significant association for the risk allele G of MTNR1B rs10830963 gene variant with the T2D risk was detected in East Asian population, a combined allelic OR = 1.05 (95%CI 1.02 - 1.08, P=0.001), but not in south Asian population, a combined allelic OR = 0.99 (95%CI 0.93 - 1.00, P=0.842). However, no association for the risk allele T of MTNR1B rs1387153 gene variant with the T2D risk was detected in East or South Asian populations was detected, the combined allelic OR for the risk allele T in East or South Asian were 1.05 (95%CI 1.00 - 1.12, P=0.071), and 1.00 (95%CI 0.91 - 1.10, P=0.987), respectively), suggesting variability in the contribution of these variants to the risk of T2D among different ethnic groups.

There are several possible reasons may explain the differences across the East and South Asian for association of MTNR1B rs10830963 gene variant with T2D. Firstly, such different results could also be explained by the sample size. The combined sample size differ from 22,618 and 21,453 control for East Asian studies to 3,671 case and 3,428 control for south Asian studies, concerning the MTNR1B rs10830963 variant. Naturally, the power of genetic association studies is always limited by sample size especially when the effect of a genetic variant is small. Thus, absence of association with T2D in South Asian could be due to insufficient power to detect positive association with a small effect. Thus, additional association studies with much larger sample size will be required in the future to detect the association of MTNR1B rs10830963 gene variant with T2D risk in south Asian population. Secondly, there may be population-specific genetic effects as a result of gene-gene and gene-environment interactions (Hunter, 2005; Yang *et al.*, 1999). All the above-mentioned factors might have contributed to the heterogeneous association results across ethnic groups.

Although the present meta-analysis limited to Asian populations, albeit this meta-analysis still revealed a weak between-study heterogeneity for the MTNR1B rs1387153 variant (P=0.156, I^2=29.6%) in all Asian populations and (P= 0.135, I^2 = 35.4%) in East Asian population. Between-study heterogeneity may be due to: 1) Difference in the sample size. Some are thousands in a large sample size, and some only a few hundred. The power of genetic association studies is always limited by sample size especially when the effect of a genetic variant is small; 2) Ethnicity difference. Studies were conducted in different geographical regions and ethnic, and the factors that play a leading role across populations may be different and might have contributed to the heterogeneous association results across ethnic groups; 3) Differences in sample selection (age, gender); 4) Differences in diagnostic criteria for T2D. T2D was diagnosed based on 1998, 1999 or 2003 World

Health Organization criteria in some studies (Kan *et al.*, 2010; Ohshige *et al.*, 2011; Bai *et al.*, 2015), whereas other studies (Been *et al.*, 2012; Liu *et al.*, 2012; Plengvidhya *et al.*, 2018) were based on 2003, 2004 or 2005 American Diabetes Association criteria; 5) Hardy-Weinberg equilibrium is the principal law in population genetic studies. Generally, meeting Hardy-Weinberg equilibrium suggests that samples have representation. The genotypic distributions of this variant were in Hardy-Weinberg equilibrium in both T2D patients and control groups in all selected studies for our meta-analysis. Sometimes Hardy-Weinberg equilibrium was met, but the genotype frequency was not always consistent to that of the local population. The complexity of T2D or family history of cases may also affect the results. The factors that play a leading role across populations may be different.

The melatonin receptor 1B (MTNR1B) gene is located on human chromosome 11q21–q22 and was found to be expressed in human retina, brain and, more specifically, in the diencephalon, including the hypothalamus and the suprachiasmatic

nucleus (SCN) and the circadian rhythm control center (Peschke, 2008). It is also expressed in human pancreatic islets β-cells (Bouatia-Naji *et al.*, 2009; Lyssenko *et al.*, 2009; Ramracheya e*t al.*, 2008), suggesting a putative direct role of melatonin on β-cell function (Staiger *et al.*, 2008).

MTNR1B encodes melatonin receptor 2 (MT2) which is one of the two high-affinity G-protein-coupled receptors for melatonin, neurohormone primarily secreted by the pineal gland in response to the loss of light exposure to the retina (Mulder *et al.*, 2009, Peschke and Mu¨hlbauer, 2010) and is mainly involved in the regulation of circadian rhythm and sleep cycles (Peschke, 2008).

Plasma melatonin follows an opposite circadian rhythm to plasma insulin and glucose, rising by night and falling by day and the melatonin receptor 2 (MT2) was found to be indirectly regulate glucose levels and insulin secretion through the brain control center of the circadian clock (Bouatia-Naji *et al.*, 2009). MT2 is predominantly expressed in β-cells and upregulated in pancreatic islets of T2D patients (Lyssenko *et al.*, 2009; Peschke, 2008; Ramracheya *et al.*, 2008), and the defective MTNR1B G-protein-coupled receptor signaling on human β-cells decreased glucose sensitivity and impaired insulin secretion (Peschke *et al.*, 2013), suggesting that MT2 receptor may play a role in insulin secretion and T2D.

Genetic association studies of the T2D susceptibility variants, especially Genome-wide association studies (GWASs) provided a link between MTNR1B gene and T2D risk and/or FPG levels, the common genetic variants, rs10830963 and rs1387153 (r^2= 0.7 in Europeans) in the MTNR1B were associated with higher levels of FPG, dicreased insulin secretion and increased risk to T2D in European population (Bouatia-Naji *et al.*, 2009; Prokopenko *et al.*, 2009; Lyssenko *et al.*, 2009), and some of the variants of MTNR1B have been suggested to be the proper causal variants in functional studies (Gaulton *et al.*, 2015). In Addition, candidate gene based studies reported that rare loss-of function variants of MTNR1B were associated with the highest incidence of T2D (Bonnefond *et al.*, 2012).

Melatonin has an inhibitory effect on insulin secretion in clonal β-cells (Lyssenko *et al.*, 2009; Ramracheya *et al.*, 2008) thereby explaining the association between the MTNR1B locus and FPG as well as T2D (Mulder *et al.*, 2009). Suggesting that common genetic variants of the MTNR1B gene may contribute to the increased risk of impaired FPG and T2D through impaired insulin secretion.

V. CONCLUSIONS

To the best of our knowledge, the present meta-analysis is the first largest study reported to date on the association of the common genetic variants (rs10830963, rs1387153) in MTNR1B gene and T2D in Asian populations. Its strength was based on the accumulation of published data giving greater information to detect significant differences. The present meta-analysis confirmed significant associations of the MTNR1B rs10830963 gene variant with T2D in the all Asian populations, and especially in the East Asian population. Population based whole genome screening studies and larger studies with detailed phenotypic data in patients with T2D are needed to address the clinical significance of this finding.

Author contributions

Mustafa Abdo Saif Dehwa designed the study, searched the literature, analysed the data, prepared the manuscript;

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