

The association between melatonin receptor 1B gene polymorphisms and type 2 diabetes mellitus (T2DM) in Chinese populations: a meta-analysis

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Background: Type 2 diabetes mellitus (T2DM) is associated with a large number of genetic variants of melatonin receptor 1B (MTNR1B), but the results of studies involving different racial groups have been inconsistent. Thus, we carried out a meta-analysis to evaluate the correlation between the MTNR1B variants and T2DM in the Chinese population.

Methods: A systematic search was conducted of English-language databases including PubMed, Embase, and Medline, and Chinese-language databases including China National Knowledge Infrastructure (CNKI), Wanfang Database, and CQVIP to collect relevant articles published up to January 31, 2020. Count data were pooled using odds ratio (OR) and 95% confidence interval (CI), and the analysis was performed using the "meta" package of the R3.5.1 software.

Results: Nine articles involving 10,127 subjects in the T2DM group and 10,885 subjects in the healthy control group were entered into the final analysis. Four articles reported the rs1387153 variant of the MTNR1B gene in Chinese populations. Meta-analysis showed there to be no correlation between the C-allele and TT genotype and the occurrence of T2DM. However, a subgroup analysis based on the Hardy-Weinberg equilibrium (HWE) revealed that the frequency of the CC genotype was significantly lower in the T2DM group than in the control group (OR: 0.88; 95% CI: 0.78, 1.00; P=0.049). Seven articles reported the rs10830963 variant of the MTNR1B gene among Chinese populations. Meta-analysis discovered that the G-allele was correlated with the T2DM occurrence. The frequency of the G-allele in the T2DM group was 1.07 times that in the control group (95% CI: 1.02, 1.12). The GG genotype was associated with the occurrence of T2DM, with its frequency in the T2DM group 1.15 times that in the control group (95% CI: 1.05, 1.25) (P<0.05); however, there was no correlation between the CC genotype and T2DM.

Conclusions: There is a correlation between the CC genotype of the rs1387153 variant in the MTNR1B gene and T2DM in the Chinese population, although this finding needs to be verified in studies with large sample sizes. The G-allele and GG genotype of the rs10830963 variant in the MTNR1B gene are associated with the occurrence of T2DM.

Keywords: Type 2 diabetes mellitus (T2DM); melatonin receptor 1B (MTNR1B); gene polymorphisms; metaanalysis

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Introduction

Diabetes mellitus, a group of metabolic diseases characterized by hyperglycemia stemming from a variety of causes, is the ninth leading cause of death in the world. By 2040, there will be an estimated 642 million diabetic patients worldwide, 90% of whom will be diagnosed with type 2 diabetes mellitus (T2DM) (1).

T2DM is a progressive insulin deficiency, the core factor of which is insulin resistance. Its mechanisms are pathogenically complex, and its occurrence is attributed to a combination of genetic and environmental factors and personal lifestyle habits. The complications brought about by T2DM often affect multiple organs. With high rates of disability and mortality, it places heavy disease and economic burdens on both patients' families and society (2).

Melatonin (MLT) is a neuroendocrine hormone that binds to MLT receptors on islet cells and inhibits insulin secretion (3). Studies have revealed that multiple gene variants of melatonin receptor 1B (MTNR1B) gene are susceptibility genes in T2DM; the single-nucleotide polymorphisms (SNP) of the rs10830963 and rs1387153 variants, for instance, are associated with T2DM (4,5). However, no correlation has been found between the MTNR1B variants and T2DM (6,7). A meta-analysis by Shen and Jin (8) found that MTNR1B variant rs10830963 was correlated with T2DM, but the results depended on the race of the subjects. Moreover, their analysis did not take Chinese literature into account and thus the relationship between MTNR1B variants and T2DM in the Chinese population could not be reflected. Therefore, in the current study, we explored the relationship between MTNR1B variants and T2DM in Chinese populations, in an attempt to clarify the pathogenesis of T2DM and provide a theoretical basis for the treatment of T2DM.

We present the following article in accordance with the PRISMA reporting checklist (available at http://dx.doi. org/10.21037/apm-20-691).

Methods

Literature search

A systematic literature search of English-language databases including PubMed, Embase, and Medline, and Chineselanguage databases including China National Knowledge Infrastructure (CNKI), Wanfang Database, and CQVIP, was conducted to collect relevant articles published up to January 31, 2020. The keywords applied to search the titles and abstracts in the English-language databases included: "melatonin receptor type 1B" or "MTNR1B"; "polymorphism*" AND "variant" or "mutation" or "genotype" or "allele" AND "type 2 diabetes mellitus" or "T2DM". The corresponding Chinese keywords and the same search strategies were used to search the Chineselanguage databases. The references of the returned articles were also searched to ensure all relevant articles were identified.

Inclusion and exclusion criteria

Articles were included according to the following criteria: (I) all the subjects in the T2DM group were T2DM patients and those in the control group were healthy controls; (II) studies involving MTNR1B gene polymorphisms (at any variant); (III) case-control studies; (IV) the frequencies of each genotype in the T2DM group and the control group were available in the original articles; and (V) the study was carried out on Chinese populations. Articles that met the following criteria were excluded from the meta-analysis: (I) case reports, reviews, summaries, comments, and meeting articles; (II) studies with a Newcastle-Ottawa Scale (NOS) score below 5; (III) inadequate data. For duplicate publications, only the article with the largest sample size was included.

Literature screening and data extraction

The search results were screened sequentially by title, abstract, and full text using the pre-defined inclusion/ exclusion criteria by two independent researchers. Data extraction and quality assessment were performed using a standardized form. The basic data extracted from the literature included: name of the first author; year of publication; language of the publication; sample sizes of the T2DM and control groups; and the frequency of each variant of the MTNR1B gene. When substantial differences existed between the two reviewers, a third reviewer was appointed to resolve the dispute.

Quality evaluation of the articles

The quality of the literature was assessed according to the NOS (9), taking into account the selection of the T2DM and control groups, comparability of the study, and exposure/outcome. The NOS ranges from to nine stars, and a higher score represents higher quality of a specific study.



Figure 1 Flowchart of references retrieval.

Statistical analysis

The Hardy-Weinberg equilibrium (HWE) was checked first. The correlation between the MTNR1B gene polymorphisms and T2DM was pooled with the odds ratio (OR) and 95% confidence interval (CI). A P value of ≤ 0.05 indicated statistical significance. Before the data were pooled, the I² statistic was used to quantify the heterogeneity. When I^2 was $\leq 50\%$, a fixed effect model was used. For studies with an I^2 of >50%, subgroup analysis and sensitivity analysis were performed to check HWE; if the source of the heterogeneity could not be identified, a random effects model was used for meta-analysis. The presence of publication bias was detected using a funnel plot and assessed with Begg's rank correlation and Egger's weighted regression tests. All of the statistical analyses were performed by using the "meta" package of the R3.5.1 software.

Results

Included articles

A total of 564 Chinese- and English-language articles were

retrieved through the literature searches. After screening, 9 articles (4-7,10-14) met the inclusion criteria; the literature searching and screening flowchart is shown in *Figure 1*. These articles involved 10,127 subjects (T2DM patients) in the T2DM group and 10,885 subjects (healthy individuals) in the control group. Of the nine articles four were published in Chinese and five in English; two MTNR1B variants, rs1387153 and rs10830963, were described; two articles (5,6) considered both variants, whereas the remaining seven articles focused on one variant. Seven articles conformed to HWE (P \geq 0.05). The quality of the included articles was high, with NOS scores ranging from 7 to 8 points. The characteristics of the included literature are shown in *Table 1*.

Relationship between rs1387153 SNPs and T2DM

Four studies (3,551 T2DM cases and 3,709 controls) investigated the relationship between rs1387153 SNPs and T2DM. One of these articles did not conform to HWE.

Analysis of alleles (C vs. T)

Meta-analysis of the C-allele revealed high allelic heterogeneity

Table 1 Basic characteristics of the included articles on the relationship between variants of MTNR1B and T2DM in Chinese populations

Authors (voor		Variant		T2DM	l group			Contro	ol group		HWE test	HWE test	NOS
Authors/year	Language	Variant	CC	CT/CG*	TT/GG*	Total	СС	CT/CG*	TT/GG*	Total	χ^2 value	P value	score
Liu 2011 (10)	Chinese	rs1387153	105	150	40	295	84	118	37	239	0.176	0.674	7
Liang 2010 (5)	Chinese	rs1387153	23	51	17	91	27	49	13	89	1.482	0.223	7
Li 2012 (4)	Chinese	rs1387153	234	442	577	1253	720	90	530	1340	99.795	<0.001	8
Kan 2010 (6)	English	rs1387153	587	969	356	1912	688	996	357	2041	0.011	0.915	7
Rönn 2009 (11)	English	rs10830963	371	553	241	1165	374	558	173	1105	2.189	0.086	7
Liang 2010 (5)	Chinese	rs10830963	15	47	29	91	25	46	18	89	0.143	0.086	7
Kan 2010 (6)	English	rs10830963	585	960	367	1912	675	989	350	2014	0.142	0.707	7
Tam 2010 (12)	English	rs10830963	448	633	261	1342	523	789	332	1644	1.2	0.274	8
Ling 2011 (13)	English	rs10830963	403	538	177	1118	404	590	167	1161	4.258	0.039	8
Shi 2015 (14)	Chinese	rs10830963	80	100	44	224	144	208	52	404	2.989	0.084	7
Gao 2016 (7)	English	rs10830963	243	347	134	724	280	350	129	759	1.198	0.274	7

*, the genotypes of variant rs10830963 were CC, CG, and GG. MTNR1B, melatonin receptor 1B; T2DM, type 2 diabetes mellitus; HWE, Hardy-Weinberg equilibrium; NOS, Newcastle-Ottawa Scale.

(I² =98%). OR was estimated using a random effects model, which showed there to be no significant correlation between the C-allele and risk of T2DM; the frequency of the C-allele in the T2DM group was 0.76 times that in the control group (95% CI: 0.46, 1.24). The allelic heterogeneity was significantly reduced to 0% in the subgroups that conformed to HWE. Estimates based on a fixed effects model showed that the C-allele had no statistical correlation with the occurrence of T2DM (OR =0.93, 95% CI: 0.86, 1.01) (*Figure 2*).

Analysis of genotypes (CC vs. CT + TT)

Meta-analysis of the CC genotype revealed high heterogeneity (I^2 =98%). OR was estimated using a random effects model, which showed there to be no significant correlation between the CC genotype and risk of T2DM; the frequency of the CC genotype in the T2DM group was 0.60 times that in the control group (95% CI: 0.24, 1.53). The heterogeneity was significantly reduced to 0% in the subgroups that conformed to HWE. Estimates based on a fixed effects model showed that the CC genotype was significantly correlated with the occurrence of T2DM (OR =0.88, 95% CI: 0.78, 1.00) (*Figure 3*).

Analysis of genotypes (TT vs. CT+CC)

Meta-analysis of the TT genotype revealed low heterogeneity

($I^2 = 34\%$). OR was estimated using a fixed effects model, which showed significant correlation between the TT genotype and risk of T2DM; the frequency of the TT genotype in the T2DM group was 1.17 times that in the control group (95% CI: 1.05, 1.31). The heterogeneity was significantly reduced to 0% in the subgroups that conformed to HWE. Estimates based on a fixed effects model showed that the CC genotype had no statistical correlation with the occurrence of T2DM (OR =1.06, 95% CI: 0.91, 1.24) (*Figure 4*).

Relationship between rs10830963 SNPs and T2DM

Seven studies (3,551 T2DM cases and 3,709 controls) investigated the relationship between rs10830963 SNPs and T2DM.

Meta-analysis of alleles (G vs. C)

Meta-analysis of the G-allele revealed low allelic heterogeneity ($I^2 = 50\%$). OR was estimated using a fixed effects model, which showed significant correlation between the G allele and risk of T2DM; the frequency of the G allele in the T2DM group was 1.07 times that in the control group (95% CI: 1.02, 1.12). The heterogeneity was significantly increased to 54% in the subgroups that conformed to HWE. Estimates based on a random effects model showed

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Study	Experin Events	nental Total	Co Events	ontrol Total	Odds Ratio	OR	95%-CI	Weight (fixed)	Weight (random)
HWE = not conformed Li H 2012 Fixed effect model Random effects model Heterogeneity: not applica	910	2506 2506	1530	2680 2680	# \$	0.43 0.43 0.43	[0.38; 0.48] [0.38; 0.48] [0.38; 0.48]	44.4% 44.4% 	26.3% 26.3%
HWE = conformed Liu Y 2010 Liang SQ 2010 Kan 2010 Fixed effect model Random effects model Heterogeneity: $l^2 = 0\%$, τ^2	360 97 2143 = 0, <i>p</i> = 0	590 182 3824 4596	286 103 2372	478 178 4082 4738		1.05 0.83 0.92 0.93 0.93	[0.82; 1.34] [0.55; 1.26] [0.84; 1.00] [0.86; 1.01] [0.86; 1.01]	5.8% 2.3% 47.5% 55.6%	25.0% 22.4% 26.4% 73.7%
Fixed effect model Random effects model Heterogeneity: $I^2 = 98\%$, τ Residual heterogeneity: I^2	² = 0.237 = 0%, p =	7102 3, <i>p</i> < (= 0.52	0.01	7418	0.5 1	0.71 0.76	[0.66; 0.75] [0.46; 1.24]	100.0% 	 100.0%

Figure 2 Meta-analysis of the correlation of the C-allele in rs1387153 in the MTNR1B gene with T2DM in Chinese populations. MTNR1B, melatonin receptor 1B; T2DM, type 2 diabetes mellitus.

Study	Experin Events	nental Total	Co Events	ontrol Total		Odo	ls Rati	o	OR	95%-CI	Weight (fixed)	Weight (random)
HWE [:] = not conformed Li H 2012 Fixed effect model Random effects model Heterogeneity: not applica	234	1253 1253	720	1340 1340					0.20 0.20 0.20	[0.17; 0.24] [0.17; 0.24] [0.17; 0.24]	51.1% 51.1% 	25.8% 25.8%
HWE ⁻ = conformed Liu Y 2010 Liang SQ 2010 Kan 2010 Fixed effect model Random effects model Heterogeneity: $l^2 = 0\%$, τ^2	105 23 587 = 0, p = 0	295 91 1912 2298	84 27 688	239 89 2041 2369					1.02 0.78 0.87 0.88 0.88	[0.71; 1.46] [0.40; 1.49] [0.76; 1.00] [0.78; 1.00] [0.78; 1.00]	5.4% 1.8% 41.7% 48.9% 	25.1% 23.1% 25.9% 74.2%
Fixed effect model Random effects model Heterogeneity: $l^2 = 98\%$, τ Residual heterogeneity: l^2	² = 0.865 = 0%, <i>p</i> =	3551 0, <i>p</i> < 0 = 0.67	0.01	3709	0.2	0.5	1	1 2	0.53 0.60	[0.48; 0.59] [0.24; 1.53]	100.0% 	 100.0%

Figure 3 Meta-analysis of the correlation of the CC genotype in rs1387153 in the MTNR1B gene with T2DM in Chinese populations. MTNR1B, melatonin receptor 1B; T2DM, type 2 diabetes mellitus.

that the G allele had no significant correlation with the occurrence of T2DM (OR =1.10; 95% CI: 1.01, 1.19) (*Figure 5*).

Analysis of genotypes (CC vs. CG + GG)

Meta-analysis of the CC genotype revealed low heterogeneity ($I^2 = 36\%$). OR was estimated using a fixed effects model,

which showed no significant correlation between the CC genotype and risk of T2DM; the frequency of the CC genotype in the T2DM group was 0.95 times that in the control group (95% CI: 0.88, 1.02). The heterogeneity was slightly reduced to 34% in the subgroups that conformed to HWE. Estimates based on a fixed effects model showed that the CC genotype had no statistical correlation with

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Study	Experin Events	nental Total	Co Events	ontrol Total	C	Odds Ratio	O	R 95%-C	Weight (fixed)	Weight (random)
HWE = not conformed Li H 2012 Fixed effect model Random effects model Heterogeneity: not applica	577 ble	1253 1253	530	1340 1340			1.3 1.3 1.3	0 [1.12; 1.52] 0 [1.12; 1.52] 0 [1.12; 1.52]	45.8% 45.8% 	44.2% 44.2%
HWE = conformed Liu Y 2010 Liang SQ 2010 Kan 2010 Fixed effect model Random effects model Heterogeneity: $l^2 = 0\%$, τ^2	40 17 356 = 0, p = 0	295 91 1912 2298	37 13 357	239 89 2041 2369			0.8 	6 [0.53; 1.39] 4 [0.61; 2.96] 8 [0.92; 1.27] 6 [0.91; 1.24] 6 [0.91; 1.24]	5.9% 1.8% 46.6% 54.2%	9.4% 3.8% 42.7% 55.8%
Fixed effect model Random effects model Heterogeneity: $l^2 = 34\%$, τ Residual heterogeneity: l^2	² = 0.008 = 0%, p =	3551 3, p = (= 0.57	0.21	3709	0.5	1	1.1 1.1 2	7 [1.05; 1.31] 6 [0.99; 1.36]	100.0% 	 100.0%

Figure 4 Meta-analysis of the correlation of the TT genotype in rs1387153 in the MTNR1B gene with T2DM in Chinese populations. MTNR1B, melatonin receptor 1B; T2DM, type 2 diabetes mellitus

Study	Experir Events	nental Total	C Events	Control Total	Odds Ratio	OR	95%-CI	Weight (fixed)	Weight (random)
HWE = not conformed					ļ,				
Ling 2011	892	2236	924	2322		1.00	[0.89; 1.13]	16.9%	17.3%
Fixed effect model		2236		2322	\Leftrightarrow	1.00	[0.89; 1.13]	16.9%	
Random effects model						1.00	[0.89; 1.13]		17.3%
Heterogeneity: not applica	ble								
HWE = conformed					c c				
Ronn 2009	1035	2330	904	2210	c	1.15	[1.03; 1.30]	16.0%	17.4%
Liang SQ 2010	105	182	82	178		- 1.60	[1.05; 2.42]	1.1%	2.8%
Kan 2010	1694	3824	1689	4028		1.10	[1.01; 1.20]	28.4%	21.5%
Tam 2010	1155	2684	1453	3288		0.95	[0.86; 1.06]	23.1%	19.5%
Shi XE 2015	188	448	312	808		1.15	[0.91; 1.45]	4.0%	7.5%
Gao 2016	615	1448	608	1518		1.11	[0.95; 1.28]	10.6%	14.0%
Fixed effect model		10916		12030	\	1.08	[1.02; 1.14]	83.1%	
Random effects model					\diamond	1.10	[1.01; 1.19]		82.7%
Heterogeneity: $I^2 = 54\%$, a	$z^2 = 0.0055$	5, p = 0	.06		с с с				
Fixed effect model		13152		14352	\$	1.07	[1.02; 1.12]	100.0%	
Random effects model					<u> </u>	1.08	[1.00; 1.16]		100.0%
Heterogeneity: $I^2 = 50\%$, 1	$r^2 = 0.0048$	5, p = 0	.06		I I I				
Residual heterogeneity: I ²	= 54%, p	= 0.06			0.5 1 2				

Figure 5 Meta-analysis of the correlation of the G allele in rs10830963 in the MTNR1B gene with T2DM in Chinese populations. MTNR1B, melatonin receptor 1B; T2DM, type 2 diabetes mellitus.

the occurrence of T2DM (OR =0.93, 95% CI: 0.86, 1.01) (*Figure 6*).

Meta-analysis of genotypes (GG vs. CG + CC)

Meta-analysis of the GG genotype revealed low heterogeneity

 $(I^2 = 50\%)$. OR was estimated using a fixed effect model, which showed there was significant correlation between the GG genotype and risk of T2DM; the frequency of the GG genotype in the T2DM group was 1.15 times that in the control group (95% CI: 1.05, 1.25). The heterogeneity

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Study	Experin Events	nental Total	Co Events	ontrol Total	Odds Ratio	OR	95%-CI	Weight (fixed)	Weight (random)
HWE = not conformed									
Ling 2011	403	1118	404	1161	1	1.06	[0.89; 1.25]	16.3%	17.8%
Fixed effect model		1118		1161		1.06	[0.89; 1.25]	16.3%	
Random effects model					\Rightarrow	1.06	[0.89; 1.25]		17.8%
Heterogeneity: not applica	ble								
					1				
HWE = conformed									
Ronn 2009	371	1165	374	1105		0.91	[0.77; 1.09]	16.8%	17.4%
Liang SQ 2010	15	91	25	89	*	0.51	[0.25; 1.04]	1.4%	1.7%
Kan 2010	585	1912	675	2014		0.87	[0.76; 1.00]	29.4%	23.0%
Tam 2010	448	1342	523	1644	1 + -	1.07	[0.92; 1.25]	20.2%	20.1%
Shi XE 2015	80	224	144	404	<u>ii</u>	1.00	[0.71; 1.41]	4.3%	6.6%
Gao 2016	243	724	280	759		0.86	[0.70; 1.07]	11.7%	13.5%
Fixed effect model		5458		6015	\$	0.93	[0.86; 1.01]	83.7%	
Random effects model					4	0.93	[0.83; 1.03]		82.2%
Heterogeneity: $I^2 = 34\%$, τ	² = 0.005	5, p = (0.18						
Fixed effect model		6576		7176	\$	0.95	[0.88; 1.02]	100.0%	
Random effects model					\diamond	0.95	[0.86; 1.04]		100.0%
Heterogeneity: $I^2 = 36\%$, τ	$^{2} = 0.005$	5, $p = 0$	0.15				- · •		
Residual heterogeneity: I^2	= 34%. p	= 0.18			0.5 1 2				

Figure 6 Meta-analysis of the correlation of the CC genotype in rs10830963 in the MTNR1B gene with T2DM in Chinese populations. MTNR1B, melatonin receptor 1B; T2DM, type 2 diabetes mellitus.

was significantly increased to 58% in the subgroups that conformed to HWE. Estimates based on a random effects model showed the GG genotype was significantly correlated with the occurrence of T2DM (OR =1.20; 95% CI: 1.02, 1.42) (*Figure 7*).

Publication bias and sensitivity

Due to the small number (<10) of articles included in this meta-analysis, the statistical power was low and the funnel chart was not sufficient to identify any publication bias. Therefore, this meta-analysis did not assess publication bias.

Sensitivity analysis was performed after one-by-one removal of the articles, and the results did not change significantly.

Discussion

In our current analysis, the C-allele and TT genotype of the rs1387153 variant of the MTNR1B gene were shown to have no correlation with the occurrence of T2DM among Chinese populations. However, subgroup analysis based on the HWE revealed that the frequency of the CC genotype was significantly lower in the T2DM group than in the control group (OR: 0.88; 95% CI: 0.78, 1.00) (P=0.049). In addition, no significant correlation was found between the TT genotype and the risk of T2DM. The G-allele and GG genotype of the rs10830963 variant in the MTNR1B gene were associated with T2DM occurrence, as the frequency of the G-allele in the T2DM group was 1.07 times that in the control group (95% CI: 1.02, 1.12). An association was revealed between the GG genotype and the occurrence of T2DM, with its frequency in the T2DM group 1.15 times that in the control group (95% CI: 1.05, 1.25) (P<0.05); however, the CC genotype and T2DM were not found to be correlated.

The MTNR1B gene is located on human chromosome 11q21-q22 and comprises two exons and one intron. With a total mRNA length of 1,662 bp, it encodes a total of 362 amino acids. Its translation product is MLT receptor 2 (MT2), which binds to MLT and subsequently mediates the inhibition of insulin secretion (3). The secretion of MLT and insulin is regulated by the circadian rhythm. Circadian rhythm disorders can lead to the occurrence of metabolic diseases, including diabetes (15). Studies have discovered that MT2 is a G protein-coupled receptor which is highly expressed in the islet tissue of T2DM patients. Its binding to MLT affects the β -cell cAMP level in human islets, thereby reducing insulin secretion and increasing the risk of T2DM (16,17). To date, studies have found that SNPs

	Experin	nental	C	ontrol				Weight	Weight
Study	Events	Total	Events	Total	Odds Ratio	OR	95%-CI	(fixed)	(random)
HWE = not conformed					- 6 - 6				
Ling 2011	177	1118	167	1161	- -	1.12	[0.89; 1.41]	14.7%	16.4%
Fixed effect model		1118		1161		1.12	[0.89; 1.41]	14.7%	
Random effects model						1.12	[0.89; 1.41]		16.4%
Heterogeneity: not applica	ble								
t na e									
HWE = conformed									
Ronn 2009	241	1165	173	1105		1.41	[1.13; 1.74]	15.0%	17.4%
Liang SQ 2010	29	91	18	89		- 1.84	[0.94; 3.64]	1.3%	3.5%
Kan 2010	367	1912	350	2014	+ + -	1.13	[0.96; 1.33]	29.3%	21.5%
Tam 2010	261	1342	332	1644		0.95	[0.80; 1.14]	25.6%	20.0%
Shi XE 2015	44	224	52	404		1.65	[1.07; 2.57]	3.2%	7.2%
Gao 2016	134	724	129	759	- =	1.11	[0.85; 1.45]	10.9%	14.1%
Fixed effect model		5458		6015	\	1.15	[1.05; 1.27]	85.3%	
Random effects model						1.20	[1.02; 1.42]		83.6%
Heterogeneity: $I^2 = 58\%$, π	$^{2} = 0.021$	7, p = 0	0.03						
Fixed effect model		6576		7176	, in the second	1.15	[1.05; 1.25]	100.0%	
Random effects model					\diamond	1.18	[1.03; 1.35]		100.0%
Heterogeneity: $I^2 = 50\%$, τ	² = 0.015	1, p = 0	0.06						
Residual heterogeneity: I ²	= 58%, p	= 0.03			0.5 1 2				

Figure 7 Meta-analysis of the correlation of the TT genotype in rs10830963 in the MTNR1B gene with T2DM in Chinese populations. MTNR1B, melatonin receptor 1B; T2DM, type 2 diabetes mellitus.

of the rs1387153 and rs10830963 variants of the MTNR1B gene are associated with the pathogenesis of T2DM, although the results of these studies are inconsistent.

The rs138715 variant in the MTNR1B gene is located on chromosome 11, 28.3 kb upstream of the gene. Its SNPs include homozygous CC, heterozygous CT, and wild-type TT. In our current analysis, the C-allele and CC genotype of the rs1387153 variant in the MTNR1B gene were not revealed to be associated with the occurrence of T2DM. Notably, the heterogeneity of the four relevant articles was as high as 98%. Subgroup analysis based on HWE revealed a significant reduction in heterogeneity. Meta-analysis based on HWE found that the CC genotype of the rs1387153 variant in the MTNR1B gene is a protective factor of T2DM, and no significant change was shown in the sensitivity analysis. However, since the number of relevant articles was small, this finding needs to be further verified in studies with larger sample sizes comprising Chinese populations.

The rs10830963 variant is located in the intron of the MTNR1B gene. With reduced beta cell function or increased fasting blood glucose levels, A large study carried out in a European population revealed that the SNP of the rs10830963 variant increases the risk of T2DM (16). In our current analysis, the G-allele of the rs10830963 variant in the MTNR1B gene was associated with the occurrence of T2DM; in addition, the GG genotype was associated with the occurrence of T2DM, with a frequency significantly higher in the T2DM group than in the control group. Subgroup analysis based on HWE did not identify any decrease in the heterogeneity, indicating that the heterogeneity in this meta-analysis cannot be attributed to disequilibrium among the HWE populations. Further literature analysis showed that most of the studies were performed in Han Chinese populations, whereas the study carried out by Shi *et al.* (14) targeted the Bao'an ethnic group in Jishishan, Gansu Province, which may have caused heterogeneity. Furthermore, differences in age, gender, and T2DM history among the included studies also contributed to the heterogeneity observed in this meta-analysis.

A meta-analysis performed by Shen and Jin (8) found that no correlation existed between the SNPs of the rs1387153 variant in the MTNR1B gene and T2DM; however, the distribution of the C and G alleles of rs10830963 differed significantly, and the frequency of the C-allele in the T2DM group was 0.97 times that in the control group (95% CI: 0.95, 1.00). Their conclusions on the relationship between the SNPs of the rs1387153 variant in the MTNR1B gene and T2DM are inconsistent with the results of our current meta-analysis, mainly due to the difference in the

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included articles, thus further proving that the distribution of polymorphisms in the MTNR1B gene is race-specific. Therefore, it is of great significance that SNP analysis of different races and ethnic groups is conducted. However, due to the lack of data on the SNPs of the rs1387153 variant in the MTNR1B gene, population-based studies with large sample sizes are needed.

Our meta-analysis had the following limitations: (I) high heterogeneity existed between the studies on the SNPs of the rs1387153 variant of the MTNR1B gene. In addition to the differences in the population characteristics, the reagents and equipment used in different studies might also have contributed to the high heterogeneity. However, stratified analysis is still not possible due to limited data for relevant populations. (II) The research results might have been influenced by gene-gene and/or gene-environment interactions; however, these were not described in the included articles. (III) In this analysis, the CC genotype of the rs1387153 variant in the MTNR1B gene was investigated in studies with small sample sizes, and the relevant conclusions need to be further verified.

Since the quality of the case-control studies involving Chinese populations included in this analysis was high, the following conclusions can be drawn: (I) the C allele and TT genotypes of rs1387153 in the MTNR1B gene are not associated with the risk of T2DM in Chinese populations, whereas the CC genotype of the rs1387153 variant in the MTNR1B gene is weakly correlated with T2DM. However, these findings need to be further verified in studies with large sample sizes. The G-allele and GG genotype of the rs10830963 variant in the MTNR1B gene are associated with the occurrence of T2DM.

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Footnote

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