## ORIGINAL ARTICLE

# Effects of *MTNR1B* genetic variants on the risk of type 2 diabetes mellitus: A meta-analysis

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## Abstract

**Background:** Whether melatonin receptor 1B (*MTNR1B*) variants are associated with type 2 diabetes mellitus (T2DM) remains unclear. Therefore, we performed this meta-analysis to better explore correlations between *MTNR1B* variants and T2DM. **Methods:** Literature research was performed in PubMed, Medline, and Embase.

Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated.

**Results:** Totally 21 studies were enrolled to analyses. Pooled overall analyses showed that *MTNR1B* rs10830963 variant was significantly correlated with the susceptibility to T2DM (allele model: p = 0.02, OR = 0.97, 95% CI 0.95–1.00). Further subgroup analyses by ethnicity of participants revealed that rs10830963 variant was significantly correlated with the susceptibility to T2DM in South Asians, but not in Caucasians or East Asians. No any other positive results were found in overall and subgroup analyses.

**Conclusions:** Our findings indicated that *MTNR1B* rs10830963 variant might serve as a genetic biomarker of T2DM, especially in South Asians.

## **KEYWORDS**

genetic variants, melatonin receptor 1B (MTNR1B), meta-analysis, type 2 diabetes mellitus (T2DM)

# **1** | INTRODUCTION

Type 2 diabetes mellitus (T2DM), characterized by chronic hyperglycemia resulted from resistance against insulin, is the most prevalent metabolic disorder worldwide, and it currently affects over 300 million people all over the world (American Diabetes Association, 2014; Zheng, Ley, & Hu, 2018). To date, the exact underlying pathogenic mechanism of T2DM is still unclear. Nevertheless, accumulating evidence support that genetic predisposition factors may play a crucial part in its pathogenesis. First, it was proved that positive family history is a strong independent risk factor of T2DM (Papazafiropoulou, Papanas, Melidonis, & Maltezos, 2017). Second, over one hundred genetic loci were found to be correlated with an increased risk of T2DM by past genome-wide association studies (Gaulton, 2017). Overall, these findings jointly supported that genetic factors are crucial for the occurrence and development of T2DM.

Melatonin—a pineal gland hormone that is responsible for regulating circadian rhythm— can also impact glucose metabolism by affecting circadian (Claustrat & Leston, 2015). Previous experimental studies found that melatonin receptor (MTNR) was abundantly expressed in pancreatic islet, and plasma melatonin level was reversely correlated with insulin level (Espino, Pariente, & Rodríguez, 2011; Lardone, Alvarez-Sanchez, Guerrero, & Carrillo-Vico, 2014; Singh & Jadhav, 2014). Consequently, it is rational to believe that genetic variants of *MTNR* might influence melatonin function and impact individual susceptibility to T2DM.

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So far, several studies already investigated potential roles of *MTNR1B* in T2DM. But the results of these studies were inconsistent (Hu & Jia, 2016; She, Laudon, & Yin, 2014). Therefore, we performed the present meta-analysis to better evaluate potential associations between *MTNR1B* genetic variants and T2DM.

# 2 | MATERIALS AND METHODS

## 2.1 | Literature search and inclusion criteria

This meta-analysis adhered to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guideline (Moher, Liberati, Tetzlaff, & Altman; PRISMA Group, 2009). Potentially relevant literatures that were published before November 2018 were retrieved from PubMed, Medline, and Embase using the following searching strategy: (melatonin receptor type 1B OR MTNR1B) AND (polymorphism OR variant OR mutation OR genotype OR allele) AND (type 2 diabetes mellitus OR T2DM). We also screened the references of retrieved articles to identify other potentially relevant studies.

To test the research hypothesis of this meta-analysis, included studies must meet all the following criteria: (a) case–control study on correlations between *MTNR1B* genetic variants and T2DM; (b) provide genotypic and/or allelic frequency of investigated variants in cases and controls; (c) full text in English available. Studies were excluded if one of the following criteria was fulfilled: (a) not relevant to *MTNR1B* genetic variants and T2DM; (b) case reports or case series; (c) abstracts, reviews, comments, letters, and conference presentations. For duplicate publications, we only included the study with the largest sample size for analyses.



**FIGURE 1** Flowchart of study selection for the present study

|                    |                       |   |   |   |  |   |  |  |  
   
   
   |  |  |  |   | | | | | | |
  |  |  | oiec   | ulai  | Gen   | enca  |   | Jenc  | JIIIC   | IVIEC  |  
   |   | W   | IL  | ΕY   |  
   |  |  |
|--------------------|-----------------------|---|---|---|--|---|--|--
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---|---|---|---|---|---|--|--
---|---|---|--|--
--|--|
|                    | NOS score             |   | 7   | 8   | 2  | 7   | 7  | 7  | 7  
   
   
   | 8  |  | 8  | 7   |  
  | 7  | 7  |  | 8   | ∞   | 7   | 7   | 7   | 7   | ~ • • •  |  
   | 7   | L   | 8   | ∞  | 7  
   | (Continues)  |  |
|                    | -Value for HWE        |   | IA  | .171  | IA   | .915  | IA   | IA   | IA   
   
   
   | .807   |  | .037   | .230  |  
  | .406   | IA   |  | .052  | .573  | IA  | .274  | [A  | 707.  | .039   | IA   
   | IA  | .012  | .040  | .275   | .139   
   |  |  |
| ion                | Controls 1            |   | NA NA   | 363/479/131 0   | NA   | 688/996/357 (   | NA   | NA   | NA N   
   
   
   | 139/195/65 (   |  | 208/439/173 0  | 134/252/95 (  |  
  | 122/226/122 (  | NA   |  | 393/445/163 0   | 439/327/55 0  | NA  | 280/350/129 0   | NA  | 675/989/350 0   | 404/590/167 0  | NA   
   | NA  | 169/259/61 (  | 583/714/271 0   | 1,111/764/115 0  | 374/558/173 0  
   |  |  |
| Genotype distribut | Cases                 | CC/CT/TT  | NA  | 459/558/147   | NA   | 587/969/356   | NA   | NA   | NA   
   
   
   | 196/226/73   | TT/TC/CC   | 28/47/25   | 123/201/102   | GG/GC/CC   
  | 114/205/98   | NA   | CC/CG/GG   | 435/560/174   | 56/44/3   | NA  | 243/347/134   | NA  | 585/960/367   | 403/538/177  | NA   
   | NA  | 133/266/35  | 631/753/283   | 1,343/1,011/183  | 371/553/241  
   |  |  |
|                    | Sample size           |   | 497/469   | 1,164/973   | 4,366/3,848  | 1,912/2,041   | 2,839/2,125  | 1,180/1,186  | 346/341  
   
   
   | 495/399  |  | 100/820  | 426/481   |  
  | 417/470  | 346/341  |  | 1,169/1,001   | 103/821   | 2,592/2017  | 724/759   | 3,410/3,412   | 1,912/2,041   | 1,118/1,161  | 2,201/16,630   
   | 2,839/2,125   | 434/489   | 1,667/1,568   | 2,537/1,990  | 1,165/1,105  
   |  |  |
|                    | Type of disease       |   | T2DM  | T2DM  | T2DM   | T2DM  | T2DM   | T2DM   | T2DM   
   
   
   | T2DM   |  | T2DM   | T2DM  |  
  | T2DM   | T2DM   |  | T2DM  | T2DM  | T2DM  | T2DM  | T2DM  | T2DM  | T2DM   | T2DM   
   | T2DM  | T2DM  | T2DM  | T2DM   | T2DM   
   |  |  |
|                    | Sthnicity             |   | East Asian  | Aixed   | Aixed  | East Asian  | East Asian   | East Asian   | south Asian  
   
   
   | East Asian   |  | Caucasian  | South Asian   |  
  | south Asian  | outh Asian   |  | Aixed   | Caucasian   | East Asian  | East Asian  | East Asian  | East Asian  | East Asian   | Caucasian  
   | East Asian  | outh Asian  | Caucasian   | Caucasian  | Caucasian  
   |  |  |
|                    | Country               |   | China   | USA N   | Mexico   | China   | Japan I  | China  | India  
   
   
   | Japan  |  | Germany  | India   |  
  | India  | India  |  | USA N   | Germany (   | Japan I   | China   | China   | China   | China  | Sweden   
   | Japan I   | India   | UK  | The Netherlands (  | Sweden   
   |  |  |
|                    | First author, year    | rs1387153   | Bai, 2015   | Been, 2012  | Huerta-Chagoya,<br>2015  | Kan, 2010   | Ohshige, 2011  | Qian, 2015   | Salman, 2015   
   
   
   | Tabara, 2011   | rs4753426  | Dietrich, 2011   | Patel, 2018   | rs10830962   
  | Patel, 2018  | Salman, 2015   | rs10830963   | Been, 2012  | Dietrich, 2011  | Fujita, 2012  | Gao, 2016   | Hu, 2010  | Kan, 2010   | Ling, 2011   | Lyssenko, 2009   
   | Ohshige, 2011   | Patel, 2018   | Rees, 2011  | Reiling, 2009  | Rönn, 2009   
   |  |  |
|                    | Genotype distribution | First author, year     Country     Ethnicity     Type of disease     Sample size     Cases     Controls     P-Value for HWE     NOS score | Eist author, year   Country   Ethnicity   Type of disease   Sample size   Cases   Controls   P-Value for HWE   NOS score     rs1387153   CC/CT/TT   CC/CT/TT   CC/CT/TT   CC/CT/TT   CC/CT/TT | First author, year Contype distribution   rs1387153 Ethnicity   rs1387153 Ethnicity   rs1387153 C/CT/TT   rs1387153 C/CT/TT | First author, yearComtoryGenotype distributionFirst author, yearCountryEthnicityType of diseaseSample sizeControlsP-Value for HWENOS scorers1387153 $C(CT)TT$ $C(CT)TT$ $C(CT)TT$ $C(CT)TT$ $C(CT)TT$ $C(CT)TT$ $C(CT)TT$ $C(CT)TT$ Bai, 2015USAMixedT2DM $1,04,973$ $459,558,147$ $363,479,131$ $0.171$ $8$ | First author, yearGenotype distributionFirst author, yearCountryEthnicityrs1387153EthnicityType of diseaseSample sizeControlsP-Value FHWENOS 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					Genotype distribu	ution		
First author, year	Country	Ethnicity	Type of disease	Sample size	Cases	Controls	<b>P-Value for HWE</b>	NOS score
Salman, 2015	India	South Asian	T2DM	341/346	NA	NA	NA	7
Semiz, 2014	Bosnia and Herzegovina	Caucasian	T2DM	162/106	96/58/8	51/47/8	0.527	L
Sparsø, 2009	Denmark	Caucasian	T2DM	6,055/1,948	3,228/2,360/467	1,002/776/170	0.260	7
Tabara, 2011	Japan	East Asian	T2DM	488/398	181/230/77	134/192/72	0.824	8
Tam, 2010	China	East Asian	T2DM	1,342/1,644	448/633/261	523/789/332	0.273	8
<i>Note</i> . HWE: Hardy–Weinber HWE assumes that allele and	g equilibrium; NOS: Ne l genotype frequencies ir	wcastle-Ottawa scale; NA: not n a population will remain con	t available. stant from generation to genera	ttion in the absence of	other evolutionary inf	luences. Consider a po	pulation of monoecious dip	loids, where each

(Continued)

TABLE 1

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#### 2.2 Data extraction and quality assessment

The following data were extracted from included studies: (a) name of the first author; (b) publication time; (c) country and ethnicity; (d) sample size; and (e) genotypic distributions of MTNR1B variants in cases and controls. The probability value (P-value) of Hardy-Weinberg equilibrium (HWE) was also calculated. When necessary, we wrote to the corresponding authors for raw data. We used the Newcastle-Ottawa scale (NOS) to assess the quality of eligible studies (Stang, 2010). This scale has a score range of 0 to 9, and studies with a score of more than seven were thought to be of high quality. Two experienced reviewers conducted data extraction and quality assessment independently. Any disagreement between two reviewers was solved by discussion until a consensus was reached.

#### 2.3 Statistical analyses

All statistical analyses were conducted with Review Manager Version 5.3.3 (The Cochrane Collaboration, Software Update, Oxford, United Kingdom). Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to estimate strength of associations between MTNR1B and T2DM in all possible genetic models, and *P*-values  $\leq 0.05$  were considered to be statistically significant. Between-study heterogeneities were evaluated by  $I^2$  statistic. If  $I^2$  was greater than 50%, random effect models (REMs) would be used to pool the data. Otherwise, fixed effect models (FEMs) would be employed for synthetic analyses. Subgroup analyses by ethnicity of participants were subsequently performed. Sensitivity analyses were conducted to examine the stability of synthetic results. Funnel plots were used to evaluate possible publication biases.

#### 3 RESULTS

#### 3.1 **Characteristics of included studies**

We found 370 potential relevant articles. Among these articles, a total of 21 eligible studies were finally included for synthetic analyses (see Figure 1). The NOS score of eligible articles ranged from 7 to 8, which indicated that all included studies were of high quality. Baseline characteristics of included studies were shown in Table 1.

#### 3.2 **Overall and subgroup analyses**

To investigate potential correlations between MTNR1B genetic variants and T2DM, eight studies about rs1387153 variant (12,799 cases and 11,382 controls), two studies about rs4753426 variant (526 cases and 1,301 controls), two studies about rs10830962 variant (763 cases and 811 controls), and eighteen studies about rs10830963 variant (30,259 cases and 39,561 controls) were enrolled to analyses. A significant

					HEN AP
uo	Additive co	mparison	Allele co	omparison	ND JIN
5% CI)	P value	OR (95% CI)	<i>P</i> value	OR (95% CI)	
.91-1.13)	0.92	1.00 (0.92-1.08)	0.48	0.98 (0.92–1.04)	
.92-1.17)	0.83	1.01 (0.92–1.11)	0.22	0.95 (0.87–1.03)	

81-1.11)

81-1.08)

81 - 1.08

95-1.00)

.89-1.06)

94-1.01)

85-1.13)

			Dominant c	omparison	Recessive c	omparison	Additive co	omparison	Allele co	mpariso
Polymorphisms	Population	Sample size (cases/controls)	<i>P</i> -value	OR (95% CI)	<i>P</i> -value	OR (95% CI)	P value	OR (95% CI)	<i>P</i> value	OR (95
rs1387153	Overall	12,799/11,382	0.73	0.97 (0.85–1.12)	0.79	1.02 (0.91–1.13)	0.92	1.00 (0.92–1.08)	0.48	0.98 (0
	East Asian	6,923/6,220	0.93	0.99 (0.83-1.19)	0.57	1.04 (0.92–1.17)	0.83	1.01 (0.92–1.11)	0.22	0.95 (0
rs4753426	Overall	526/1,301	0.56	0.93 (0.72–1.19)	0.08	1.27 (0.97–1.65)	0.05	0.80 (0.64–1.00)	0.51	0.95 (0
rs10830962	Overall	763/811	0.40	0.88 (0.65–1.19)	0.64	1.07 (0.80–1.45)	0.75	1.04 (0.80–1.36)	0.31	0.97 (0
	South Asian	763/811	0.40	0.88 (0.65–1.19)	0.64	1.07 (0.80–1.45)	0.75	1.04(0.80 - 1.36)	0.31	0.97 (0
rs10830963	Overall	30,259/39,561	0.44	0.98 (0.94–1.03)	0.81	1.01 (0.91–1.13)	0.84	1.00 (0.96–1.05)	0.02	0.97 (0
	Caucasian	13,890/24,168	0.99	1.00 (0.90–1.11)	0.68	1.05 (0.84–1.30)	0.36	0.97 (0.91–1.03)	0.53	0.97 (0
	East Asian	14,425/13,557	0.68	0.98 (0.91–1.06)	0.25	1.06 (0.96–1.16)	1.00	1.00 (0.93-1.08)	0.18	0.98 (0
	South Asian	775/835	0.21	0.84 (0.63–1.10)	0.03	0.62 (0.40 - 0.95)	0.01	1.41 (1.08-1.83)	0.72	0.97 (0
Vota OB · odds ratio: CI	confidence interval	NA - not available								

The values in bold represent there is statistically significant differences between cases and controls

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association with the susceptibility to T2DM was detected for rs10830963 variant (allele model: p = 0.02, OR = 0.97, 95% CI 0.95–1.00) in overall analyses. Further subgroup analyses according to ethnicity of participants revealed that rs10830963 variant was significantly correlated with the susceptibility to T2DM in South Asians, but not in East Asians or Caucasians. No any other positive results were found in overall and subgroup analyses (see Table 2 and Supplementary Figure 1).

#### 3.3 Sensitivity analyses

We performed sensitivity analyses by excluding studies that deviated from HWE. No alterations of results were detected in sensitivity analyses, which suggested that our findings were statistically reliable.

#### 3.4 **Publication biases**

Publication biases were evaluated with funnel plots. We did not find obvious asymmetry of funnel plots in any comparisons, which indicated that our findings were unlikely to be impacted by severe publication biases.

#### 4 DISCUSSION

To the best of our knowledge, this is so far the most comprehensive meta-analysis on correlations between MTNR1B genetic variants and T2DM, and our pooled analyses demonstrated that rs10830963 variant may be correlated with susceptibility to T2DM, especially in South Asians.

There are several points that need to be addressed about this meta-analysis. Firstly, previous experimental studies showed that mutant allele of rs10830963 variants was correlated with altered glucose level and B-cell function, which may partially explain our positive finding (Li et al., 2018; Staiger et al., 2008). Secondly, the pathogenic mechanism of T2DM is highly complex, and hence it is unlikely that a single genetic variant could significantly contribute to its development. As a result, to better illustrate potential correlations of certain genetic variants with T2DM, we strongly recommend further studies to perform haplotype analyses and explore potential gene-gene interactions.

Like all meta-analyses, this study certainly has some limitations. First, our results were derived from unadjusted analyses due to lack of raw data, and lack of further adjusted analyses for potential confounding factors may impact the reliability of our findings (Xie, Shi, & Liu, 2017; Xie, Shi, Xun, & Rao, 2017). Second, obvious heterogeneities were found in several subgroups, which indicated that the controversial results of included studies could not be fully explained by differences in ethnic background, and other baseline characteristics of participants may also contribute to between-study

Overall and subgroup analyses for MTNRIB genetic variants and T2DM

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TABLE

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heterogeneities (Shi, Xie, Jia, & Li, 2016). Third, associations between *MTNR1B* genetic variants and T2DM may also be modified by gene–gene and gene–environmental interactions. However, most eligible studies ignore these potential interactions, which impeded us to perform relevant analyses accordingly. To sum up, our findings should be cautiously interpreted on account of above mentioned limitations.

In conclusion, our meta-analysis suggested that *MTNR1B* rs10830963 variant might serve as a genetic biomarker of T2DM, especially in South Asians. However, further well-designed studies are still warranted to confirm our findings.

## ETHICAL APPROVAL

This article does not contain any studies with human participants or animals performed by any of the authors.

## **CONFLICT OF INTEREST**

The authors declare that they have no conflict of interest.

## **AUTHORS' CONTRIBUTIONS**

Ling-long Shen and Yin Jin conceived the study, participated in its design, conducted the systematic literature review, performed data analyses, and drafted the manuscript. All the authors gave final approval and agreed to be accountable for all aspects of work ensuring integrity and accuracy.

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## REFERENCES

- American Diabetes Association. (2014). Diagnosis and classification of diabetes mellitus. *Diabetes Care*, 37(Suppl 1), S81–S90. https://doi. org/10.2337/dc14-S081
- Claustrat, B., & Leston, J. (2015). Melatonin: Physiological effects in humans. *Neuro-Chirurgie*, 61, 77–84. https://doi.org/10.1016/j. neuchi.2015.03.002
- Espino, J., Pariente, J. A., & Rodríguez, A. B. (2011). Role of melatonin on diabetes-related metabolic disorders. *World Journal of Diabetes*, 2, 82–91. https://doi.org/10.4239/wjd.v2.i6.82
- Gaulton, K. J. (2017). Mechanisms of type 2 diabetes risk loci. Current Diabetes Reports, 17, 72. https://doi.org/10.1007/s11892-017-0908-x
- Hu, C., & Jia, W. (2016). Linking MTNR1B variants to diabetes: The role of circadian rhythms. *Diabetes*, 65, 1490–1492. https://doi. org/10.2337/dbi16-0012
- Lardone, P. J., Alvarez-Sanchez, S. N., Guerrero, J. M., & Carrillo-Vico, A. (2014). Melatonin and glucose metabolism: Clinical relevance. *Current Pharmaceutical Design*, 20, 4841–4853.
- Li, Y., Wu, H., Liu, N., Cao, X., Yang, Z., Lu, B., ... Wen, J. (2018). Melatonin exerts an inhibitory effect on insulin gene transcription

via MTNR1B and the downstream Raf-1/ERK signaling pathway. *International Journal of Molecular Medicine*, *41*, 955–961. https://doi.org/10.3892/ijmm.2017.3305

- Moher, D., Liberati, A., Tetzlaff, J., & Altman, D. G.; PRISMA Group. (2009). Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *Annals of Internal Medicine*, 151, 264– 269. https://doi.org/10.7326/0003-4819-151-4-200908180-00135
- Papazafiropoulou, A. K., Papanas, N., Melidonis, A., & Maltezos, E. (2017). Family history of type 2 diabetes: Does having a diabetic parent increase the risk? *Current Diabetes Review*, 13, 19–25. https://doi.org/10.2174/1573399812666151022143502
- She, M., Laudon, M., & Yin, W. (2014). Melatonin receptors in diabetes: A potential new therapeutical target? *European Journal of Pharmacology*, 744, 220–223. https://doi.org/10.1016/j.ejphar.2014.08.012
- Shi, X., Xie, X., Jia, Y., & Li, S. (2016). Associations of insulin receptor and insulin receptor substrates genetic polymorphisms with polycystic ovary syndrome: A systematic review and meta-analysis. *Journal of Obstetrics* and Gynaecology Research, 42, 844–854. https://doi.org/10.1111/ jog.13002
- Singh, M., & Jadhav, H. R. (2014). Melatonin: Functions and ligands. Drug Discovery Today, 19, 1410–1418. https://doi.org/10.1016/j. drudis.2014.04.014
- Staiger, H., Machicao, F., Schäfer, S. A., Kirchhoff, K., Kantartzis, K., Guthoff, M., ... Fritsche, A. (2008). Polymorphisms within the novel type 2 diabetes risk locus MTNR1B determine beta-cell function. *PLoS ONE*, *3*, e3962. https://doi.org/10.1371/journal. pone.0003962
- Stang, A. (2010). Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in metaanalyses. *European Journal of Epidemiology*, 25, 603–605. https:// doi.org/10.1007/s10654-010-9491-z
- Xie, X., Shi, X., & Liu, M. (2017). The roles of TLR gene polymorphisms in atherosclerosis: A systematic review and meta-analysis of 35,317 subjects. *Scandinavian Journal of Immunology*, 86, 50–58. https://doi.org/10.1111/sji.12560
- Xie, X., Shi, X., Xun, X., & Rao, L. (2017). Endothelial nitric oxide synthase gene single nucleotide polymorphisms and the risk of hypertension: A meta-analysis involving 63,258 subjects. *Clinical and Experimental Hypertension*, 39, 175–182. https://doi.org/10.1080/1 0641963.2016.1235177
- Zheng, Y., Ley, S. H., & Hu, F. B. (2018). Global aetiology and epidemiology of type 2 diabetes mellitus and its complications. *Nature Reviews Endocrinology*, 14, 88–98. https://doi.org/10.1038/nrendo.2017.151

## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

How to cite this article: Shen L-L, Jin Y. Effects of *MTNR1B* genetic variants on the risk of type 2 diabetes mellitus: A meta-analysis. *Mol Genet Genomic Med.* 2019;7:e611. <u>https://doi.org/10.1002/mgg3.611</u>