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.
So far, several studies already investigated potential roles of \textit{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 \textit{MTNR1B} genetic variants and T2DM.

\section{Materials and Methods}

\subsection{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 \textit{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 \textit{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.

\includegraphics[width=\textwidth]{flowchart.png}

\textbf{FIGURE 1} Flowchart of study selection for the present study
| First author, year | Country     | Ethnicity   | Type of disease | Sample size | Genotype distribution | Cases          | Controls         | P-Value for HWE | NOS score |
|---------------------|-------------|-------------|-----------------|-------------|-----------------------|----------------|------------------|----------------|----------|
| Bai, 2015           | China       | East Asian  | T2DM            | 497/469     | CC/CT/TT              | NA             | NA               | NA             | 7        |
| Been, 2012          | USA         | Mixed       | T2DM            | 1,164/973   | 459/558/147           | 363/479/131    | 0.171            | 8              |
| Huerta-Chagoya, 2015| Mexico      | Mixed       | T2DM            | 4,366/3,848 | NA                    | NA             | NA               | NA             | 7        |
| Kan, 2010           | China       | East Asian  | T2DM            | 1,912/2,041 | 587/969/356           | 688/996/357    | 0.915            | 7              |
| Ohshige, 2011       | Japan       | East Asian  | T2DM            | 2,839/2,125 | NA                    | NA             | NA               | NA             | 7        |
| Qian, 2015          | China       | East Asian  | T2DM            | 1,180/1,186 | NA                    | NA             | NA               | NA             | 7        |
| Salman, 2015        | India       | South Asian | T2DM            | 346/341     | NA                    | NA             | NA               | NA             | 7        |
| Tabara, 2011        | Japan       | East Asian  | T2DM            | 495/399     | 196/226/73            | 139/195/65     | 0.807            | 8              |
| Dietrich, 2011      | Germany     | Caucasian   | T2DM            | 100/820     | TT/TC/CC              | 28/47/25       | 0.037            | 8              |
| Patel, 2018         | India       | South Asian | T2DM            | 426/481     | 123/201/102           | 134/252/95     | 0.230            | 7              |
| Patel, 2018         | India       | South Asian | T2DM            | 417/470     | 114/205/98            | 122/226/122    | 0.406            | 7              |
| Salman, 2015        | India       | South Asian | T2DM            | 346/341     | NA                    | NA             | NA               | NA             | 7        |
| Been, 2012          | USA         | Mixed       | T2DM            | 1,169/1,001 | 435/560/174           | 393/445/163    | 0.052            | 8              |
| Dietrich, 2011      | Germany     | Caucasian   | T2DM            | 103/821     | 56/44/3               | 439/327/55     | 0.573            | 8              |
| Fujita, 2012        | Japan       | East Asian  | T2DM            | 2,592/2017  | NA                    | NA             | NA               | NA             | 7        |
| Gao, 2016           | China       | East Asian  | T2DM            | 724/759     | 243/347/134           | 280/350/129    | 0.274            | 7              |
| Hu, 2010            | China       | East Asian  | T2DM            | 3,410/3,412 | NA                    | NA             | NA               | NA             | 7        |
| Kan, 2010           | China       | East Asian  | T2DM            | 1,912/2,041 | 585/960/367           | 675/989/350    | 0.707            | 7              |
| Ling, 2011          | China       | East Asian  | T2DM            | 1,118/1,161 | 403/538/177           | 404/590/167    | 0.039            | 8              |
| Lyssenko, 2009      | Sweden      | Caucasian   | T2DM            | 2,201/16,630| NA                    | NA             | NA               | NA             | 7        |
| Ohshige, 2011       | Japan       | East Asian  | T2DM            | 2,839/2,125 | NA                    | NA             | NA               | NA             | 7        |
| Patel, 2018         | India       | South Asian | T2DM            | 434/489     | 133/266/35            | 169/259/61     | 0.012            | 7              |
| Rees, 2011          | UK          | Caucasian   | T2DM            | 1,667/1,568 | 631/753/283           | 583/714/271    | 0.040            | 8              |
| Reiling, 2009       | The Netherlands | Caucasian | T2DM            | 2,537/1,990 | 1,343/1,011/183      | 1,111/764/115  | 0.275            | 8              |
| Rönn, 2009          | Sweden      | Caucasian   | T2DM            | 1,165/1,105 | 371/553/241           | 374/558/173    | 0.139            | 7              |

(Continues)
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 ≤0.05 were considered to be statistically significant. Between-study heterogeneities were evaluated by I² statistic. If I² 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
Association with the susceptibility to T2DM was detected for rs10830963 variant (allele model: \( p = 0.02, \text{OR} = 0.97, 95\% \text{CI 0.95–1.00} \)) 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 differences.
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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SUPPORTING INFORMATION

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

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