Postprint: The Interaction Between Sleep Quality During Pregnancy and MTNR1B Polymorphism on Gestational Hypertension

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Abstract

Background In recent years, with increasing social pressure and lifestyle changes, the incidence of sleep problems during pregnancy has risen significantly. Studies have found that circadian rhythm disruption can participate in blood pressure regulation through mechanisms such as activating the hypothalamic-pituitary-adrenal axis and triggering inflammatory responses; however, the interaction mechanism between environmental factors and genetic susceptibility remains unclear. Melatonin receptor 1B gene (MTNR1B), as a key regulatory factor in the melatonin signaling pathway, encodes a protein that not only participates in circadian rhythm regulation but also plays a crucial role in maintaining placental vascular endothelial function. MTNR1B gene polymorphisms are significantly associated with type 2 diabetes and insulin resistance, yet the regulatory effect of this gene polymorphism on susceptibility to gestational hypertension remains unclear.

Objective To investigate whether sleep status during pregnancy combined with peripheral blood MTNR1B gene polymorphisms exerts a synergistic effect on the onset of gestational hypertension (GH).

Methods A total of 235 pregnant women in their second trimester who underwent prenatal examinations at a provincial hospital in Gansu from March 2021 to December 2021 were enrolled as study subjects, and 235 healthy pregnant women with normal pregnancy outcomes at the same hospital during the same period were selected as the control group. The Pittsburgh Sleep Quality Index, Hospital Anxiety and Depression Scale, and Pregnancy Sleep-related Health Factors Questionnaire were administered. Peripheral venous blood was collected from both the control and case groups before delivery, and genotyping of three single nucleotide polymorphism loci (rs3781638, rs10830963, rs3781637)

of the MTNR1B gene was performed using improved liquid chip detection technology (im-LDR). Multivariate logistic regression analysis was used to explore the association between late-pregnancy sleep, MTNR1B gene polymorphisms, and GH onset, and a multiplicative interaction model was established to explore the effect of sleep-gene interactions on GH.

Results Comparisons of genotypes, allele types, dominant and overdominant genotypes of the MTNR1B gene rs3781638 locus between the case and control groups showed statistically significant differences (P<0.05). Comparisons of the MTNR1B gene rs10830963 and rs3781637 loci between the two groups showed no statistically significant differences (P>0.05). Multivariate logistic regression analysis results showed that carrying the GT genotype (OR=1.88, 95%CI=1.24~2.84), the T allele (OR=1.28, 95%CI=1.02~1.71), the dominant genotype GG+GT (OR=1.93, 95%CI=1.29~2.89), and the overdominant genotype GT (OR=1.84, 95%CI=1.22~2.72) were independent risk factors for GH. Interaction analysis results showed that pregnant women with the TT genotype and coughing/snoring 1-2 times per week during night sleep (OR=2.82, 95%CI=1.36~5.84) and those coughing/snoring $ $3 times per week (OR=2.21, 95%CI=1.09~4.48) had 2.82 and 2.21 times higher risk of developing GH, respectively, compared to those with the TT genotype and no coughing/snoring during night sleep. Compared to those with the TT genotype and no coughing/snoring during night sleep, carrying the GT+GG genotype, regardless of whether there was coughing/snoring during night sleep, increased the risk of developing GH, with the highest risk observed in those with coughing/snoring $ $3 times per week during night sleep (OR=4.90, 95%CI=2.24~10.75).

Conclusion The MTNR1B gene rs3781638 (G>T) locus may be a susceptibility gene for GH, and there exists a synergistic effect with night sleep snoring on the occurrence and development of GH.

Full Text

Study of the Interaction between Sleep Quality and MTNR1B Gene Polymorphism on Gestational Hypertension

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Abstract

Background In recent years, the incidence of sleep problems during pregnancy has increased significantly due to rising social pressures and lifestyle changes. Research has shown that circadian rhythm disruption can participate in blood pressure regulation through mechanisms such as activation of the hypothalamic-pituitary-adrenal axis and induction of inflammatory responses, yet the interaction mechanisms between environmental factors and genetic susceptibility remain unclear. The melatonin receptor gene 1B (MTNR1B), a key regulator of the melatonin signaling pathway, encodes the melatonin receptor 1B protein which not only participates in circadian rhythm regulation but also plays a critical role in maintaining placental vascular endothelial function. MTNR1B gene polymorphisms show clear associations with type 2 diabetes and insulin resistance, but their modulatory effect on susceptibility to gestational hypertension remains undefined.

Objective To investigate whether a synergistic effect exists between maternal sleep status during pregnancy and peripheral blood MTNR1B gene polymorphisms on the development of gestational hypertension (GH).

Methods A total of 235 pregnant women in their second trimester who received prenatal care at a provincial hospital in Gansu from March 2021 to December 2021 were enrolled as study subjects, with 235 healthy pregnant women with normal pregnancy outcomes from the same hospital selected as the control group. The Pittsburgh Sleep Quality Index, Hospital Anxiety and Depression Scale, and a pregnancy sleep-related health factors questionnaire were used for investigation. Peripheral venous blood was collected from both groups before delivery, and an improved liquid chip detection technology (im-LDR) was used for genotyping three single nucleotide polymorphism sites (rs3781638, rs10830963, rs3781637) of the MTNR1B gene. Multivariate logistic regression analysis was used to explore the association between late-pregnancy sleep and MTNR1B gene polymorphisms with GH onset, and a multiplicative interaction model was established to examine the impact of sleep-gene interactions on GH.

Results Significant differences were observed between the case and control groups in the genotype, allele type, dominant genotype, and overdominant genotype of the MTNR1B gene rs3781638 locus ($P<0.05$). No significant differences were found between the two groups for the MTNR1B gene rs10830963 and rs3781637 loci ($P>0.05$). Multivariate logistic regression analysis revealed that carrying the GT genotype (OR=1.88, 95%CI=1.24~2.84), T allele (OR=1.28, 95%CI=1.02~1.71), dominant genotype GG+GT (OR=1.93, 95%CI=1.29~2.89), and overdominant genotype GT (OR=1.84, 95%CI=1.22~2.72) were independent risk factors for GH. Interaction analysis showed that the risk of developing GH in individuals carrying the TT genotype with nighttime coughing/snoring 1-2 times/week (OR=2.82, 95%CI=1.36~5.84)

and $ $3 times/week (OR=2.21, 95%CI=1.09~4.48) was 2.82 and 2.21 times higher, respectively, compared to those carrying the TT genotype without nighttime coughing/snoring. Compared to TT genotype carriers without nighttime coughing/snoring, those carrying the GT+GG genotype had increased GH risk regardless of nighttime coughing/snoring status, with the highest risk observed in those with nighttime coughing/snoring $ $3 times/week (OR=4.90, 95%CI=2.24~10.75).

Conclusion The MTNR1B gene rs3781638 (G>T) locus may be a susceptibility gene for GH and exhibits a synergistic effect with nighttime snoring on the occurrence and development of GH.

Keywords Gestational hypertension; MTNR1B gene; Single nucleotide polymorphism; Pregnancy sleep; Interaction

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1. Methods

1.1 Study Design and Participants

This study employed a nested case-control design. Pregnant women with regular prenatal check-ups in the second and third trimesters who planned to deliver at the hospital from March 2021 to December 2021 were enrolled as study subjects and followed up for pregnancy outcomes. A total of 235 pregnant women diagnosed with GH were included in the case group. Concurrently, 235 healthy pregnant women were matched as controls based on maternal body mass index (BMI) and gestational week at a 1:1 ratio. The study protocol was reviewed and approved by the Medical Ethics Committee of Gansu Maternal and Child Health Hospital (Approval No.: [2017] Hospital Ethics Review Research No. (13)), and all participants provided informed consent.

1.1.1 Diagnostic Criteria Gestational hypertension disorders were defined as pregnancy-specific diseases occurring after 20 weeks of gestation with systolic blood pressure $ $140 mmHg (1 mmHg=0.133 kPa) and/or diastolic blood pressure $ $90 mmHg, including gestational hypertension, preeclampsia, eclampsia, chronic hypertension with superimposed preeclampsia, and chronic hypertension in pregnancy. Among these, gestational hypertension, preeclampsia, and eclampsia were collectively referred to as gestational hypertension disease (GHD) [6].

1.1.2 Inclusion Criteria **Case group:** (1) Pregnant women aged 19-40 years; (2) Singleton pregnancy; (3) Met the above GHD diagnostic criteria; (4) Regular prenatal care with complete clinical data. **Control group:** (1) Age-matched ($\pm 3 years$); (2) $BMI-matched(\pm 1.5 kg/m\hat{}\{2\})$; (3) $Gestational week-matched(\pm$$1 week); (4) No history of GHD or chronic hypertension; (5) Normal blood pressure: systolic <140 mmHg and diastolic <90 mmHg.

1.1.3 Exclusion Criteria

(1) Pregnancy complicated by primary/secondary hypertension, metabolic syndrome, HELLP syndrome, or other serious medical diseases; (2) Multiple pregnancy; (3) Important organ insufficiency; (4) Mental disorders or poor compliance preventing cooperation with the study.

1.2 Data Collection

1.2.1 Pregnancy Sleep-Related Health Factors Questionnaire The questionnaire included items on age, ethnicity, residence, housing type, family size, education level, monthly household income, reproductive history, smoking exposure, diet, exercise, and depression/anxiety screening.

1.2.2 Pittsburgh Sleep Quality Index (PSQI) The PSQI was used to assess sleep quality during the past month of pregnancy. The scale consists of 18 items evaluating seven sleep components: sleep quality, sleep latency, habitual sleep duration, sleep efficiency (calculated as sleep time/bedtime, with >85% considered normal threshold), sleep disturbances, use of sleep medication, and daytime dysfunction. The cumulative component scores yield a total PSQI score ranging from 0-21, where 0-5 indicates good sleep quality, 6-10 mild impairment, 11-15 moderate impairment, and 16-21 severe impairment [7].

1.2.3 Hospital Anxiety and Depression Scale (HADS) The HADS was used to screen for anxiety and depression during pregnancy to exclude confounding effects of psychological factors on sleep quality. The HADS comprises 14 items divided into two subscales: anxiety (HADS-A) and depression (HADS-D), each with 7 items. Each item uses a 4-point scale from 0-3, with total subscale scores ranging from 0-21 [7].

1.2.4 MTNR1B Gene Polymorphism Detection Peripheral venous blood (2 ml) was collected from both control and case groups before delivery and stored at -80°C. DNA was extracted using the SSNP-2000B automatic nucleic acid purification system and 配套试剂盒 from Shanghai Shengshi Biological Technology Co., Ltd. DNA concentration and purity were measured using the NanoDrop micro nucleic acid protein detector from Thermo Fisher Scientific, with 260/280=1.8-2.0 indicating successful extraction. The im-LDR technique was used to detect SNPs at three MTNR1B gene loci (rs10830963, rs3781637, rs3781638). PCR amplification was performed on the ABI 2720 thermal cycler from Applied Biosystems, followed by SNaPshot multiplex single-base extension reaction and sequencing on the ABI3730XL sequencer from Tianjin Jinside Biotechnology Co., Ltd. Raw data were analyzed using GeneMapper 4.1.

1.2.5 Quality Control of Questionnaires Survey personnel were trained medical postgraduate students who obtained full informed consent before ad-

ministration. Uniform instructions and face-to-face guidance were provided for completing and submitting questionnaires via WeChat Questionnaire Star (copyright by Changsha Ranxing Information Technology Co., Ltd.). After testing, data were organized and analyzed for timely error correction. Correction standards included: completeness check (valid questionnaires had $ $2 missing items, with trend-based imputation for missing reverse-scored items), logical contradiction screening (contradictory scores within subscales or total scores $ $15 requiring diagnostic review), and outlier determination (single item scores >3 or abnormal total scores). Correction methods involved both manual verification and system detection, with double-checking for data consistency, marking discrepancies, and reviewing original records. Contradictory or abnormal questionnaires were subject to backtracking investigation or secondary confirmation, with logical jumps and required fields set on the platform. Finally, Excel or SPSS 26.0 software was used to filter unqualified questionnaires.

1.3 Statistical Analysis

SPSS 26.0 statistical software was used for data analysis. Normally distributed measurement data were expressed as ($\bar{x}\pm s$) and compared between groups using independent samples t-test. Count data were expressed as constituent ratios and compared between groups using ^{2} test, which was also used for Hardy-Weinberg genetic equilibrium testing. Unconditional logistic regression analysis was used to examine the relationship between MTNR1B gene SNP loci and pregnancy sleep factors with GH. A multiplicative interaction model was used to explore the impact of sleep-gene interactions on GH. $P<0.05$ was considered statistically significant.

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2. Results

2.1 Comparison of General Characteristics Between Case and Control Groups

A total of 470 study subjects were included, with 235 cases (50%) and 235 controls (50%). Significant differences were found between the two groups in age, education level, exercise amount, and dietary regularity ($P<0.05$). No significant differences were observed in ethnicity, residence, family size, monthly household income, reproductive history, passive smoking, or depression/anxiety screening ($P>0.05$), see .

2.2 Comparison of Pregnancy Sleep Quality Between Case and Control Groups

Pregnancy sleep quality survey results showed significant differences between the two groups in frequency of sleep coughing/snoring, family member snoring frequency, nightmares, pain/discomfort during sleep, sleep apnea, and PSQI

scores (P<0.05). No significant differences were found in sleep latency or sleep efficiency (P>0.05), see .

2.3 Comparison of MTNR1B Gene Polymorphisms Between Case and Control Groups

Hardy-Weinberg equilibrium test results showed that the genotype distributions of MTNR1B gene rs10830963, rs3781637, and rs3781638 loci in both case and control groups were in accordance with Hardy-Weinberg genetic equilibrium (rs10830963: ^{2}=0.155, P=0.694; rs3781637: ^{2}=2.926, P=0.087). Statistical analysis revealed no significant differences between the two groups in genotype or allele type for MTNR1B gene rs10830963 and rs3781637 loci (P>0.05), see Supplementary Tables 1 and 2 (scan the QR code on the front page for details). However, significant differences were found in genotype, allele type, dominant genotype, and overdominant genotype of MTNR1B gene rs3781638 locus between the GH group and control group (P<0.05), see and .

2.4 Multivariate Logistic Regression Analysis of Association Between MTNR1B rs3781638 Gene Polymorphism and GH

Using GH as the dependent variable (assignment: normal=0, onset=1) and MTNR1B rs3781638 gene polymorphism as the independent variable, logistic regression analysis was performed without adjusting for any variables (Model 1). Results showed that carrying the GT genotype (OR=1.87, 95%CI=1.27~2.76), T allele (OR=1.31, 95%CI=1.07~1.60), dominant genotype GG+GT (OR=1.79, 95%CI=1.25~2.60), and overdominant genotype GT (OR=1.78, 95%CI=1.22~2.59) were risk factors for GH.

After adjusting for confounding factors including age (assignment: <25 years=2, 25-30 years=1, >30-35 years=3, $ $35 years=4), education level (assignment: master' s and above=2, bachelor' s=1, high school=3, junior high school and below=4), exercise amount (assignment: regular exercise=1, almost no activity=2), and dietary regularity (assignment: basically regular=1, irregular=2) (Model 2), results showed that carrying the GT genotype (OR=1.88, 95%CI=1.24~2.84), T allele (OR=1.28, 95%CI=1.02~1.71), dominant genotype GG+GT (OR=1.93, 95%CI=1.29~2.89), and overdominant genotype GT (OR=1.84, 95%CI=1.22~2.72) were independent risk factors for GH, see .

2.5 Interaction Effect of MTNR1B Gene rs3781638 Locus Dominant Genotype and Pregnancy Snoring on GH

Analysis of the interaction between MTNR1B gene rs3781638 locus dominant genotype and pregnancy snoring showed that the risk of developing GH in individuals carrying the TT genotype with nighttime coughing/snoring 1-2 times/week (OR=2.82, 95%CI=1.36~5.84) and $ $3 times/week (OR=2.21, 95%CI=1.09~4.48) was 2.82 and 2.21 times higher, respectively, compared to TT genotype carriers without nighttime coughing/snoring. Compared to

TT genotype carriers without nighttime coughing/snoring, those carrying the GT+GG genotype had increased GH risk regardless of nighttime coughing/snoring status, with the highest risk observed in those with nighttime coughing/snoring $ $3 times/week (OR=4.90, 95%CI=2.24~10.75), see .

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3. Discussion

Gestational hypertension disease (GHD) is a critical risk factor for adverse maternal and neonatal outcomes during the perinatal period, with pathogenesis involving interactions between genetic and environmental factors. Studies have shown that sleep disorders (such as snoring and apnea) may participate in GH development through pathways including sympathetic activation and oxidative stress, while melatonin signaling pathway-related gene polymorphisms are also considered potential genetic markers. However, the combined effect of pregnancy sleep problems and MTNR1B gene polymorphisms on GH remains unclear. This study employed a nested case-control design to investigate the interaction between MTNR1B gene polymorphisms and sleep factors on GH, providing a basis for high-risk population screening and personalized intervention.

This study found that the incidence of poor sleep quality (PSQI $ $11) was significantly higher in the GH group than in the control group, and GH patients had higher rates of nighttime coughing/snoring, family member snoring, nightmares, pain/discomfort, and sleep apnea. These results are consistent with reports by Meers et al. [8], Querejeta et al. [9], and Wilson et al. [10], suggesting that sleep-disordered breathing may elevate blood pressure by inducing vascular endothelial damage through intermittent hypoxia. However, no significant differences were found between the GH and control groups in sleep latency or sleep efficiency (P>0.05), indicating that GH-related sleep problems are more concentrated in respiratory disorders and subjective discomfort rather than simple sleep structural changes.

Through detection of MTNR1B gene rs10830963, rs3781637, and rs3781638 loci polymorphisms and analysis with GH, we found that MTNR1B gene rs3781638 (G>T) genotype, allele type, GG+GT genotype, and overdominant GT genotype all increased GH risk. No domestic literature has reported on the relationship between MTNR1B gene rs3781638 polymorphism and GH. Huber et al. [11] suggested that rs3781638 (G>T) polymorphism is significantly positively correlated with cardiac ejection fraction, and that melatonin and melatonin signaling may be effective intermediaries transmitting environmental information to central blood pressure regulation.

This study found that the MTNR1B gene rs3781638 (G>T) locus dominant model (GT+GG) significantly increased GH risk (OR=1.93, 95%CI=1.22~3.06), partially consistent with Staiger et al. [12] who found this locus associated with increased insulin sensitivity. Li et al. [13] reported that MTNR1B rs3781638 is

associated with osteoporosis in Chinese elderly cohorts, and the genetic direction of MTNR1B rs3781638 polymorphism points to the influence of melatonin signaling pathways on blood pressure and left ventricular function, which may support the melatonin system as a potential therapeutic target. The mechanism by which rs3781638 polymorphism affects GH requires further research; rs3781638 is located in the MTNR1B gene promoter region and may affect blood pressure rhythm by regulating melatonin receptor expression. Previous studies have extensively reported on MTNR1B gene rs10830963 polymorphism affecting blood glucose and lipids, and a recent Meta-analysis published in the journal *Gene* again confirmed that rs10830963 locus polymorphism is an independent risk factor for gestational diabetes [14]. Kolomeichuk et al. [15] found that MTNR1B gene rs10830963 polymorphism is associated with elevated low-density lipoprotein and triglycerides, as well as individual differences in vascular wall elastic properties. Few studies have reported on MTNR1B gene rs3781637 A/G locus polymorphism, and rs10830963 and rs3781637 loci showed no significant association in this study (P>0.05) (negative results not shown in figures due to space limitations), showing phenotypic heterogeneity with Ling et al. [16] regarding their association with glucose and lipid metabolism, suggesting that different MTNR1B loci may participate in disease occurrence through independent pathways. Although MTNR1B gene rs10830963 and rs3781637 loci have been reported to be associated with glucose and lipid metabolism in previous studies, this study found no significant association with GH risk (P>0.05). This result may be related to ethnicity, gene-environment interaction effects, and insufficient sample size. The rs10830963 (C/G) has been confirmed to be associated with gestational diabetes mellitus (GDM) in European populations (OR=1.15~1.25), but its risk allele frequency (e.g., G allele frequency is 12% in Asian populations vs. 30% in European populations) and linkage disequilibrium patterns (LD Block) may vary by population, diluting the association with GH. Pregnant women included in this study from Gansu region may be exposed to unique dietary structures (such as high-salt, high-carbohydrate intake) or environmental factors (such as altitude affecting hypoxia sensitivity) that mask the main gene effect. In summary, the relationship between MTNR1B gene rs10830963 and rs3781637 polymorphisms and blood pressure requires further research confirmation.

This study found a significant synergistic effect between rs3781638 GT+GG genotype and nighttime snoring ($ $3 times/week), with combined exposure increasing GH risk by 4.9-fold (OR=4.90, 95%CI=2.24~10.75), consistent with conclusions from a Michigan pregnant women cohort study [17] that snoring increases GH risk. This suggests that genetic susceptibility may amplify the pathological effects of sleep-disordered breathing. The potential mechanism may involve melatonin secretion rhythm disorders exacerbating hypoxia-induced vasoconstriction and gene-environment interactions activating the renin-angiotensin system. Therefore, for pregnant women carrying rs3781638 GT/GG genotype with snoring and apnea, enhanced blood pressure monitoring is recommended; sleep assessment (e.g., PSQI scale) and genetic testing during

the second trimester can enable early identification of GHD risk; melatonin receptor agonists or continuous positive airway pressure (CPAP) therapy may be trialed in high-risk populations. For pregnant women carrying the MTNR1B gene rs3781638 GT+GG genotype who also have nighttime snoring problems, their risk of developing GH increases significantly. Clinically, more attention should be paid to pregnant women with poor nighttime sleep, with timely intervention and guidance to promote good maternal and neonatal outcomes.

This study has certain limitations. Due to the difficulty in collecting clinical information and samples for GH, the sample size is relatively small. Future research should expand the sample size and conduct multi-center cooperation to carry out in-depth molecular epidemiological studies, refine phenotype stratification, explore mechanisms by which sleep factors may affect GHD through oxidative stress, inflammatory responses, and sympathetic activity, and find appropriate intervention strategies to improve pregnant women' s snoring and other sleep problems and reduce GHD risk.

Author Contributions: ZHOU XiaoYa was responsible for data collection, organization, and manuscript writing; WANG WeiKai was responsible for data organization and assisted with editing and revision; LIU Qian assisted with statistical analysis; LI JianHua was responsible for SNP experiments; SUN Bo provided conceptual guidance; WANG YanXia was responsible for project management, resource provision, and supervision and review of the article.

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Note: Figure translations are in progress. See original paper for figures.