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ORIGINAL RESEARCH

Melatonin Receptor 1B Genetic Variants on Susceptibility to Gestational Diabetes Mellitus: A Hospital-Based Case–Control Study in Wuhan, Central China

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Purpose: The aim of the study was to find out the associations of Melatonin receptor 1B (*MTNR1B*) genetic variants with gestational diabetes mellitus (GDM) in Wuhan of central China.

Patients and Methods: A hospital-based case–control study that included 1679 women was carried out to explore the associations of *MTNR1B* single nucleotide polymorphisms (SNPs) with GDM risk, which were analyzed through logistic regression analysis by adjusting age, pre-pregnancy BMI and family history of diabetes. Multifactor dimensionality reduction was applied to determine gene–gene interactions between SNPs.

Results: *MTNR1B* SNPs rs10830962, rs10830963, rs1387153, rs7936247 and rs4753426 were significantly associated with GDM risk ($P<0.05$). The rs10830962/G, rs10830963/G, rs1387153/T, and rs7936247/T were risk variants, whereas rs4753426/T was protective variant for GDM development. Fasting plasma glucose (FPG) and 1h-plasma glucose (PG) were significantly different among genotypes at rs10830962 and rs10830963, whereas 2h-PG levels were not. Gene–gene interactions were not found among the five SNPs on GDM risk.

Conclusion: *MTNR1B* genetic variants have significant associations but no gene–gene interactions with GDM risk in central Chinese population. Furthermore, *MTNR1B* SNPs have significant relationships with glycemic traits.

Keywords: melatonin receptor 1B, gestational diabetes mellitus, single nucleotide polymorphisms, multifactor dimensionality reduction, gene–gene interactions

Introduction

Gestational diabetes mellitus (GDM), characterized by glucose intolerance or hyperglycemia, is one of the most common metabolic disorders in pregnant women.[1] It is reported in a meta-analysis that the total incidence of GDM in mainland China is 14.8.[2] The adverse outcomes associated with GDM for both pregnant women and their offspring are diverse. Apart from potential adverse pregnant outcomes such as macrosomia, neonatal hypoglycemia, this disorder is also associated with an increased risk of type 2 diabetes (T2D) and cardiovascular disease later in life.[3] Therefore, it is essential to identify potential risk factors for GDM.

As a pre-diabetic status, GDM is thought to be associated with hyperinsulinemia and insulin resistance, but the exact underlying pathogenic mechanism of GDM is still unclear. Nevertheless, accumulating evidences reveal that genetic

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predisposition may play a crucial role in its pathogenesis.[4,5] Recently, a genome-wide association study (GWAS) in Korean population concluded that genetic variants near melatonin receptor 1B (*MTNR1B*) gene were strongly associated with GDM.[6] Moreover, another GWAS showed that *MTNR1B* polymorphism was associated with glycemic levels in both gravid and non-gravid populations.[7]

MTNR1B, which is strongly expressed in the brain, retina and β-cells, encodes the MT_2 protein. Except for regulating circadian rhythm, melatonin can also impact insulin secretion both in vivo and in vitro.[8,9] Plasma melatonin level was reversely correlated with insulin level.[10] As a melatonin receptor, MT_2 regulates blood glucose homeostasis through the regulation of insulin release via the melatonin signaling pathway.[11] Hence, it is rational to believe that genetic variants in the *MTNR1B* might affect pancreatic glucose sensing, insulin secretion and conceivably glucose tolerance.[12] Existed studies have predominantly demonstrated the associations of *MTNR1B* gene polymorphisms with GDM risk and genetic heterogeneity has been observed across ethnic groups.[13–19] Nevertheless, these findings were not consistent in Chinese population. Li et al showed that in Chinese women rs10830963 but not rs10830962 was associated with an increased risk of developing GDM.[15] However, Xie et al concluded that rs10830962 variant was associated with a higher GDM risk.[16] In addition, other candidate single nucleotide polymorphisms (SNPs), such as rs1387153, rs7936247, rs4753426, which were confirmed to be significantly associated with glucose homeostasis, have not been fully elucidated in GDM in Chinese population to date.[20–24] Furthermore, few data are available on the associations of *MTNR1B* SNPs with GDM risk in central Chinese population until now. Thus, the present study was carried out to explore whether these SNPs contributed to GDM risk in Wuhan of central China.

Materials and Methods

Study Population and Data Collection

The pregnant women who took antenatal examination in Obstetrics and Gynecology Clinic of Maternal and Child Health Hospital of Hubei Province from January 15, 2018 to March 31, 2019 were recruited in the study. All subjects were enrolled at 24–28 weeks' gestation right after the 75g oral glucose tolerance test (OGTT). The diagnosis of GDM was based upon the criteria of International Association of Diabetes and Pregnancy Study Groups (IADPSG): fasting plasma glucose (FPG) ≥5.1 mmol/L, or 1h-plasma glucose (PG) ≥10.0 mmol/L, or 2h-PG ≥8.5 mmol/L. The non-diabetic controls were randomly selected at the same outpatient clinic matched with testing date and gestation week. Exclusion criteria: age <18 years; ethnic minorities; pre-gestational diabetes; multiple pregnancies; pregnancies complicated with endocrine diseases such as hypertension and polycystic ovary syndrome; any other medical condition that might affect glucose regulation; unable or unwilling to participate in the study. At the genotyping stage, unsuccessful samples were also excluded. After exclusion, 1679 pregnant women (818 GDM patients and 861 non-diabetic controls) were included. All the subjects were unrelated Han Chinese residing in Wuhan of Hubei Province, a central area of China. The method of data collection was reported in previous article.[25] The study protocol was approved by the institutional review board of Wuhan University of Science and Technology and was performed in accordance with the Declaration of Helsinki. All subjects provided informed consents for participation.

Selection and Genotyping of SNPs

By tracking the literature, combined with genome-wide association studies of GDM and minor allele frequency (MAF) >0.05 reported in Chinese population, we selected five SNPs in or near *MTNR1B* gene for assessment. These SNPs were rs10830963, rs10830962, rs1387153, rs7936247 and rs4753426. The method of sample collection was also reported in the previous article.[25] The aforementioned five SNPs were genotyped on the Sequenom MassARRAY platform (Sequenom Inc., San Diego, CA, USA). For quality control: (i) case and control samples were mixed on each plate; (ii) genotyping was performed blinded to case or control status; (iii) two water controls were used in each plate as blank controls; (iv) 5% of the samples were randomly selected for repeated genotyping, as blind duplicates, and the reproducibility was 100%. The call rates of rs10830963, rs10830962, rs1387153, rs7936247, rs4753426 were respectively 98%, 99%, 99%, 99%, 96%.

Statistical Analysis

We used *t*-test or analysis of variance (ANOVA) for normally distributed data and Chi-square test for non-normally distributed data. The exact Chi-square test was used to detect Hardy–Weinberg equilibrium (HWE). Logistic regression adjusted by age, pre-pregnancy BMI and family history of diabetes was performed to evaluate the associations with GDM risk. No Bonferroni correction was applied, in the case of replication studies, as it is unlikely to detect effects due to statistical fluctuation only.[26] $P<0.05$ was considered statistically significant. Post hoc power calculations were performed giving the power to detect a given effect which could be estimated. All the statistical analyses were performed through SPSS 24.0 (SPSS Inc., Chicago, IL, USA). Multifactor dimensionality reduction (MDR) method, proposed by Ritchie et al[27] as a new statistical and computational method to analyze gene–gene interactions in genetic studies and shown to have good power in case–control studies,[28] was applied to determine gene–gene interactions.

Results

Demographic and Clinical Characteristics

Table 1 presented the demographic and clinical characteristics of subjects. Differences in age, pre-pregnancy BMI, family history of diabetes, FPG, 1h-PG and 2h-PG between the case and control groups were statistically significant ($P<0.05$). There were no significant differences in gravidity and parity between the two groups.

Association of *MTNR1B* Gene SNPs with GDM

The distributions of rs10830962, rs10830963, rs1387153, rs4753426 and rs7936247 in the control group were all in HWE. Table 2 showed that the allele and genotype distributions of the five SNPs were significantly different between GDM women and controls ($P<0.05$). The rs10830962/G, rs10830963/G, rs1387153/T and rs7936247/T led to a higher risk whereas the rs4753426/T led to a lower risk for GDM. The associations of the five SNPs with GDM were all statistically significant ($P<0.05$). The *MTNR1B* rs10830962 CG genotype was significantly associated with an increased GDM risk compared with CC genotype (OR=1.423, 95% CI: 1.059–1.912), and the risk of developing GDM with GG genotype was twofold than that of the CC genotype (OR=2.056, 95% CI: 1.444–2.927). The SNPs rs10830963, rs1387153 and rs7936247 could increase the GDM risk with a similar effect as rs10830962. In contrast, rs4753426 TT genotype was significantly associated with a decreased GDM risk compared with CC genotype (OR=0.466, 95% CI: 0.283–0.769).

Table 1 Demographic and Clinical Characteristics of Subjects

	GDM (n=818)	Non-GDM (n=861)	t/χ^2	*P*
Age (year)	30.98±4.54	28.81±4.16	10.223	**<0.001**
Pre-pregnancy BMI (kg/m^2)	22.15±3.69	20.87±6.54	4.631	**<0.001**
FPG (mmol/L)	5.04±0.86	4.34±0.31	20.908	**<0.001**
1h-PG (mmol/L)	10.42±1.70	7.37±1.33	33.878	**<0.001**
2h-PG (mmol/L)	9.13±1.73	6.50±0.97	34.926	**<0.001**
Gravidity				
1	285 (35.76)	340 (40.19)	5.303	0.071
2	235 (29.49)	254 (30.02)		
≥3	277 (34.75)	252 (29.79)		
Parity				
Nulliparous	481 (58.87)	526 (61.16)	0.915	0.339
Multiparous	336 (41.13)	334 (38.84)		
Family history of diabetes				
No	569 (69.90)	748 (88.10)	83.560	**<0.001**
Yes	245 (30.10)	101 (11.90)		

Notes: Data were given as the mean ± SD or as n (%), with the significance of differences between groups evaluated using *t*-test or χ^2 test. Bold represents significant *P* values.

Abbreviations: GDM, gestational diabetes mellitus; BMI, body mass index; FPG, fasting plasma glucose; PG, plasma glucose; SD, standard deviation.

Table 2 Associations Between *MTNR1B* Gene SNPs and the Risk of GDM

	GDM (n=818)	Non-GDM (n=861)	Crude OR (95% CI)	Crude *P*	Adjusted* OR (95% CI)	Adjusted *P*
rs10830962						
Allele						
C	781	949	Ref		Ref	
G	811	745	1.727 (1.311–2.275)	<0.001	2.155 (1.494–3.108)	<0.001
Genotypes						
CC	189	272	Ref		Ref	
CG	403	405	1.432 (1.136–1.805)	0.002	1.423 (1.059–1.912)	0.019
GG	204	170	1.727 (1.311–2.275)	<0.001	2.056 (1.444–2.927)	<0.001
rs10830963						
Allele						
C	769	965	Ref		Ref	
G	813	721	1.656 (1.258–2.179)	<0.001	1.727 (1.225–2.434)	0.002
Genotypes						
CC	185	287	Ref		Ref	
CG	399	391	1.583 (1.256–1.996)	<0.001	1.626 (1.210–2.187)	0.001
GG	207	165	1.946 (1.477–2.564)	<0.001	2.328 (1.637–3.310)	<0.001
rs1387153						
Allele						
C	808	950	Ref		Ref	
T	768	736	1.447 (1.103–1.899)	0.008	1.884 (1.318–2.691)	0.001
Genotypes						
CC	208	285	Ref		Ref	
CT	392	380	1.413 (1.126–1.775)	0.003	1.401 (1.045–1.878)	0.024
TT	188	178	1.447 (1.103–1.899)	0.008	1.812 (1.280–2.565)	0.001
rs7936247						
Allele						
G	809	952	Ref		Ref	
T	779	738	1.487 (1.135–1.948)	0.004	1.928 (1.349–2.754)	<0.001
Genotypes						
GG	211	285	Ref		Ref	
GT	387	382	1.368 (1.090–1.718)	0.007	1.357 (1.013–1.817)	0.041
TT	196	178	1.487 (1.135–1.948)	0.004	1.844 (1.305–2.607)	0.001
rs4753426						
Allele						
C	1184	1191	Ref		Ref	
T	394	467	0.665 (0.452–0.979)	0.039	0.445 (0.266–0.745)	0.002
Genotypes						
CC	444	434	Ref		Ref	
CT	296	323	0.896 (0.729–1.101)	0.295	0.795 (0.611–1.034)	0.086
TT	49	72	0.665 (0.452–0.979)	0.039	0.466 (0.283–0.769)	0.003

Notes: *Adjusted by age, pre-pregnancy BMI, family history of diabetes.
Abbreviations: *MTNR1B*, melatonin receptor 1B; SNPs, single-nucleotide polymorphisms; GDM, gestational diabetes mellitus; OR, odds ratio; CI, confidence interval; Ref, reference genotype.

Relationships Between MTNR1B Gene Polymorphism and Glycemic Traits

Table 3 showed that FPG and 1h-PG levels were significantly different among genotypes at rs10830962 and rs10830963.

For rs10830962, FPG levels of GG genotype carriers were significantly higher than those of CC and CG genotype carriers, and the 1h-PG levels of CG and GG genotype carriers were significantly higher than those of CC genotype carriers.

Table 3 Relationships Between *MTNR1B* Gene Polymorphisms and Glycemic Traits

	Variables	Genotype			*F*	*P*
		AA	AB	BB		
rs10830962	FPG	4.71±0.78*	4.76±0.71*	4.88±0.92	3.773	**0.023**
	1h-PG	8.95±2.23*♦	9.29±2.07	9.52±2.24	5.532	**0.004**
	2h-PG	8.05±2.04	8.12±1.83	8.24±2.17	0.774	0.461
rs10830963	FPG	4.71±0.78*	4.77±0.71	4.87±0.92	3.473	**0.031**
	1h-PG	8.88±2.25*♦	9.33±2.06	9.54±2.22	7.856	**<0.001**
	2h-PG	8.00±2.05	8.14±1.82	8.26±2.16	1.323	0.267
rs1387153	FPG	4.72±0.77	4.81±0.85	4.76±0.65	1.566	0.209
	1h-PG	9.06±2.24	9.32±2.18	9.33±2.04	1.859	0.156
	2h-PG	8.07±1.96	8.19±2.03	8.06±1.86	0.665	0.515
rs4753426	FPG	4.80±0.80	4.78±0.76	4.69±0.09	0.853	0.427
	1h-PG	9.32±2.09	9.24±2.21	9.11±2.42	0.494	0.610
	2h-PG	8.17±1.93	8.14±1.98	8.04±2.31	0.157	0.855
rs7936247	FPG	4.72±0.77	4.82±0.85	4.76±0.66	1.909	0.149
	1h-PG	9.03±2.23	9.34±2.17	9.35±2.03	2.530	0.080
	2h-PG	8.06±1.95	8.19±2.03	8.09±1.84	0.542	0.582

Notes: AA: homozygote of major allele, AB: heterozygote, BB: homozygote of minor allele; *Compared with BB Genotype by post hoc LSD test, $P<0.05$; ♦Compared with AB Genotype by post hoc LSD test, $P<0.05$. Bold represents significant P values.
Abbreviations: *MTNR1B*, melatonin receptor 1B; FPG, fasting plasma glucose; PG, plasma glucose.

For rs10830963, FPG levels of GG genotype carriers were significantly higher than those of CC genotype carriers, and the 1h-PG levels of CG and GG genotype carriers were significantly higher than those of CC genotype carriers.

Gene–Gene Interactions to GDM

The results in Table 4 showed that both one-factor model (rs10830963) and three-factor model (rs10830963, rs1387153 and rs4753426) had good cross-validation consistency at 10/10, but the test accuracy of the one-factor model (0.5536) was higher than that of the three-factor model (0.5528). After further analysis, none of the results were statistically significant ($P>0.05$). Hence, we could infer that there were no gene–gene interactions among the five *MTNR1B* gene SNPs on the GDM risk.

Discussion

Up to now, several studies have explored associations of *MTNR1B* with GDM risk.[16,29–33] However, these studies with diverse sample sizes in different populations reported that there are controversial associations of *MTNR1B* with GDM risk. Furthermore, most analyses only examined one or two SNPs and the gene–gene interactions were commonly neglected. In the present study, we explored the associations with GDM risk and gene–gene interactions among the selected five *MTNR1B* SNPs. The results revealed that *MTNR1B* SNPs had significant associations but no gene–gene interactions with GDM risk in Wuhan of China. As far as we know, this is the first study that examines associations of several *MTNR1B* SNPs with GDM risk in genetic models as well as interactions between genetic polymorphisms in Central Chinese population.

Table 4 Analysis of Gene–Gene Interactions

Model	Training Accuracy	Test Accuracy	Cross-Validation Consistency
X2	0.5536	0.5536	10/10
X2, X3	0.5623	0.5439	9/10
X2, X3, X4	0.5708	0.5528	10/10

We found that *MTNR1B* rs10830962 GG genotype increased GDM risk compared with CC genotype, which was consistent with findings of Xie et al[16] but differed from those of Li et al.[29] Moreover, we also found that the G allele of rs10830963 lead to a higher risk for GDM. Consistent with our findings, studies in Caucasian populations[17,18] as well as in Chinese[15] and South Korean[34] populations confirmed the robust association of *MTNR1B* rs10830963/G variant with GDM. However, Wang et al observed that rs10830963 was not associated with GDM in Beijing.[35] For rs1387153, we also detected a significant association with GDM risk, which was consistent with all the previous studies.[13,26,34,36] The SNP rs10830963, maps within the single 11.5kb intron of *MTNR1B*. The association signal is bounded by recombination hot spots defining a ~60-kb interval within which all our strongly associated SNPs lie and the causal variant is likely to reside.[37] As for SNP rs1387153, it maps within a 62.1-kb linkage disequilibrium (LD) block on chromosome 11 and is located in the 5′ region of *MTNR1B*, encoding the *MTNR1B*.[20] A recent bioinformatics analysis reveals that rs10830962 is located in the functional elements of pancreatic islets and alters motif binding.[16] Thus, it is biologically plausible that these SNPs may affect the expression of genes and be involved in the pathogenesis of GDM. However, due to controversial LD analyses among *MTNR1B* SNPs,[13,23,34,36,38–40] further large-scale research is expected to analyze related molecular pathways combining multi-racial GWAS results by bioinformatics.

So far, remarkably, few studies have reported the associations between SNPs rs7936247, rs4753426 and GDM risk. Our study revealed that T allele of rs7936247 lead to a higher risk for GDM. Up to now, only one Chinese study had focused on the relationship between rs7936247 and GDM, indicating that the SNP rs7936247 was located in the region of histone modifications and regulated *small nucleolar RNA, H/ACA box 8 (SNORA8)* expression in pancreatic tissue,[16] which makes the association of this SNP with GDM risk biologically plausible. Outstandingly, we found that rs4753426/T lead to a lower risk for GDM, which was consistent with findings of Shen et al[26] but differed from those of Tarnowski et al.[17] Qiu et al in 2007 detected a potential transcription factor of SNP rs4753426 and found a nearby transcription factor-binding site for v-Myb.[41] Moreover, they also found SNP rs4753426 was located in the regulatory region of *MTNR1B* and could result in variation of *MTNR1B* expression level. Those findings suggested the *MTNR1B* SNP rs4753426 might be a susceptibility gene locus for GDM. However, functional studies are needed to confirm this.

Interestingly, FPG and 1h-PG levels were significantly different among genotypes at rs10830963 and rs10830962, whereas 2h-PG levels were not. The FPG and 1h-PG levels of GG genotype carriers were significantly higher than those of CC genotype carriers at rs10830963 and rs10830962. Numerous studies in ethnically diverse populations indicated that the G allele of rs10830963 was associated with FPG levels and impaired insulin secretion, as well as increased risk of T2D or GDM.[18,23,34,37,42–44] The risk G allele of rs10830963 in *MTNR1B* preferentially binds NEUROD1 in islet-derived cells in vitro, and increases FOXA2-bound enhancer activity in human islet and liver-derived cells.[43] In addition, the risk allele has also been associated with increased expression of *MTNR1B* in pancreatic beta cells, thereby possibly enhancing the effects of impaired early insulin secretion and elevated FPG levels.[42] With respect to postprandial PG levels, Liao S et al found the association of rs10830963 with the increased 1h-PG levels in Chinese population, while Rosta et al demonstrated the association of rs10830963/G with 2h-PG values in Caucasian population. Our study found that 1h-PG levels but not 2h-PG levels were significantly different among genotypes of rs10830963. We speculate that there might be a timing effect on the association of *MTNR1B* rs10830963 with glycemic changes. Lane et al revealed that carriers of the rs10830963 might extend the duration of endogenous melatonin secretion later to morning and that early wake time might magnify the diabetes risk caused by the risk allele.[45] They suggested that because melatonin inhibited glucose stimulated insulin secretion, it was plausible that a longer duration of melatonin production and delayed melatonin offset in the morning, in concurrence with an earlier waking, might lead to melatonin suppressing insulin secretion during times of raised glucose intake. A recent study indicated that rs10830963 variant was a marker for the initiation of antenatal insulin therapy in GDM, which also proposed clinical value of *MTNR1B* in the prevention and treatment of GDM.[31] If our speculations are confirmed in large-scale prospective cohort studies, it would be advisable in the general population to avoid concurrence of food intake with elevated melatonin levels, which is of great importance for the human to improve health. As for rs10830962, because it might have a high LD with rs10830963 and thus the effect observed for rs10830962 might be due to rs10830963,[46] the findings of rs10830962 should be dealt with cautiously and needed to be verified in large-scale genomic studies.

There were several similarities between this study and the previous research. They used similar methods to explore the associations of gene polymorphisms with GDM. The present but not the previous one found significant associations

of gene polymorphisms with GDM. In addition, they both found no interactions amongst the examined SNPs. And unfortunately, the present study has some similar limitations with the previous research. First, the information regarding environmental and lifestyle factors, recently reported to be important determinants of GDM development,[47,48] was not collected. Second, considerable controversies remain regarding the screening timing of GDM.[49] Third, the level of melatonin was not tested because of practical reasons. We will carry out further study to explore the relation of melatonin and other possible biomarkers[50] with GDM. Moreover, additional studies concerning other above-mentioned factors will be required in future to validate the findings of the study.

Nevertheless, there were still some strengths in the present study. First, MDR method was employed. The MDR method was developed for detecting and characterizing gene–gene interactions and was widely employed in genetic studies.[51–54] The main principle of MDR is to reduce multidimensional genotypes into one-dimensional binary attributes, in which multi-level genotypes of SNPs are classified into either high-risk or low-risk groups, using a ratio of cases and controls in case–control studies.[55] It was also applied in our previous study for detecting gene–gene interactions and found to be effective. Second, the interrelations of *MTNR1B* SNPs were considered and potential confounding factors including age, pre-pregnancy BMI and family history of diabetes were adjusted. Last but not least, a relatively large sample size was used in our study. Although post hoc analyses are debated and should be dealt with cautiously, the relatively large sample size might achieve adequate statistical power for the credibility.

Conclusions

In conclusion, *MTNR1B* SNPs rs10830962, rs10830963, rs1387153, rs7936247 and rs4753426 are associated with GDM risk in central Chinese population. There are no gene–gene interactions among the examined *MTNR1B* SNPs on GDM risk. FPG and 1h-PG levels but not 2h-PG levels are significantly different at *MTNR1B* SNPs rs10830962 and rs10830963, which inspire us to speculate that there might be a timing effect on the association of *MTNR1B* SNPs with glycemic changes. The findings of the study may provide a novel perspective for the prevention and treatment of GDM in the future. Additional studies are warranted to validate the findings and clarify the underlying mechanism.

Abbreviations

GDM, gestational diabetes mellitus; T2D, type 2 diabetes; GWAS, genome-wide association study; *MTNR1B*, melatonin receptor 1B; SNPs, single nucleotide polymorphisms; OGTT, oral glucose tolerance test; IADPSG, International Association of Diabetes and Pregnancy Study Groups; FPG, fasting plasma glucose; PG, plasma glucose; MAF, minor allele frequency; ANOVA, analysis of variance; HWE, Hardy–Weinberg Equilibrium; MDR, multifactor dimensionality reduction; LD, linkage disequilibrium; BMI, body mass index; SD, standard deviation; OR, odds ratio; CI, confidence interval; LSD, least significant difference.

Data Sharing Statement

The datasets of this study are available from the corresponding authors on reasonable request.

Ethics Approval and Informed Consent

The study was approved by the institutional review board of Wuhan University of Science and Technology. Informed consent was obtained from all subjects of the study.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no known competing financial interests or personal relationships or conflicts of interest that could have appeared to influence the work reported in this paper.

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