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Melatonin Receptor 1B Gene Polymorphisms, Haplotypes and Susceptibility to Schizophrenia

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Abstract

Melatonin has an important role in the regulation of human sleep circadian rhythms. Sleep disturbances commonly exist in schizophrenia (SCZ) patients. To begin its performance, melatonin must interact to its receptor. In the present study, Single Nucleotide Polymorphisms (SNPs) of melatonin receptor gene 1 B (MTN1B) with SCZ development in Iranian population were investigated. The current case-control study was performed on 92 SCZ patients and 92 healthy control (HC) subjects. NESTED-PCR and ARMS-PCR modified methods (combination) and ARMS-PCR method were used on the genotype. The impact of MTN1B rs3781637 (T/C) and rs10830963(C/G) polymorphism variants on the risk SCZ in the sample of Iranian population was investigated. The findings showed significant association between MTN1B rs10830963(C/G) variant and SCZ (OR=2.78, 95%CI=1.25-6.25, P=0.012, GG vs. CC, OR=1.66, 95%CI=1.09-2.51, P=0.021 G vs. C, OR=3.85 95%CI=.89-8.33, P<0.0001, GG vs. CC+CG). There was no association between MTN1B rs3781637 (T/C) and SCZ risk. In addition, haplotype analysis revealed that TG and CC haplotype of rs3781637 (T/C) and rs10830963 (C/G) polymorphisms were associated with SCZ risk (P=0.039) and protective (P<0.0001) effects, respectively. The findings revealed that MTN1B rs10830963 (C/G) polymorphism was associated with the risk of SCZ; while another SNP rs3781637 (T/C) MTN1B gene did not show any risk/protection association with SCZ. Further studies with larger sample sizes and different ethnicities are required to approve the results.

Keywords: *Schizophrenia, Melatonin Receptor 1 B, Single Nucleotide Polymorphism, Case-Control Study.*

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Introduction

Schizophrenia (SCZ) is a disabling group of mental illnesses characterized by paranoia, hallucinations, delusions, poor planning, disorganized communication, blunted effect, and reduced motivation affecting about 1% of the world population. Although the etiology of SCZ is entirely unknown, there is much evidence

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that genetic factors play important roles in pathogenesis and the development of SCZ (1-5).

Melatonin, also known as N-acetyl 1-5-methnxytryptamine, is a neuro hormone synthesized and secreted by the pineal gland of the mammalian brain to regulate the circadian rhythm, and affects other physiological functions with peaks during night time (6). This hormone for beginning its performance must interact with receptors, MT1 (Mel_{1a} encoded by *MTNR1A*) and MT2 (Mel_{1b}, encoded by *MTNR1B*), which are two membrane receptors isoforms to transmit the action and effects of melatonin by G-protein coupled 7-transmembrane receptors mechanism. In addition, MT3 (Mel_{1c}) cloned from Zebrafish, Xenops, and Chicken has high affinity binding site for melatonin; orphan receptor GPR50 is a mammalian orthologous of MT3; however, its biological function remains unknown in humans and does not bind to melatonin (7, 8).

In previous studies, night time peak in melatonin was observed as slacken in SCZ patients compared with healthy individuals, and this continues after treatment with antipsychotic drugs (9, 10). In another research on SCZ and melatonin in 2010, Afonso et al. (11) reported that SCZ was characterized by neuroendocrine disturbance with diminished melatonin secretion, thus, they proposed that cure for this disorder should consider the correlation of sleep disruptions and low melatonin secretion and sleep efficiency in SCZ patients with low sleep quality improved with melatonin. It is assumed that melatonin expression and signaling may play a role in the development and pathogenesis of SCZ as regards melatonin. Signaling effect is basically mediated through its specific receptors like MTN1B related to SCZ and sleep distribution. In the present study, the association of gene polymorphisms between SCZ and *MTN1B* in a sample of Iranian SCZ patients was investigated through an analysis of two single nucleotide polymorphisms (SNPs) of the *melatonin receptor* gene.

Materials and Methods

Ninety-two Iranian SCZ patients admitted to Baharan Hospital of Zahedan, Sistan and Baluchestan province, Iran between Jun, 2015 to Jun, 2016 (mean age±standard deviation 35.97±11.51 years, male/female=54/38) and 92 Iranian healthy controls (HCs) (36.16±11.23 years, male/female=54.38) were enrolled. The diagnostic and statistical manual of mental disorders –IV (DSM-IV) (American Psychiatry Association, 1994) was considered by well-trained psychiatrists in diagnosing all SCZ patients. The clinical and demographic characteristics of both groups are summarized in **Table 1.** The volunteers visiting the laboratory (Razmjoo Moghadam Clinic, Zahedan city, Sistan and Baluchestan province, Iran) for routine health checkup were used as HC. HCs did not have any history of systemic and psychiatric illnesses.

The study was approved by the local ethics committee of the Medical University of

Table 1. Demographic characteristics of SCZ patients and controls

	SCZ (n=92)	Controls (n=92)	P-value
Age (Mean±SD)	35.97±11.51	36.16±11.23	0.809
Sex (female/male)	38/54	38/54	1.000
Level of Education (illiterate/literate)	18/74	19/73	0.854
Place of residence (urban and rural)	59/33	57/35	0.760
No. family members (Mean±SD)	6.38±2.11	6.19±2.29	0.597

Zahedan, Iran; written informed consents were obtained from both groups. Blood samples were collected from both groups in tubes containing anti-coagulant (EDTA), and salt-outing method (12) was used for extracting genomic DNA.

SNP selection and Genotyping

Two SNPs were selected from *MTN1B* in the Medline data (rs10830963(C/G) and rs3781637(T/C)); these SNPs were strongly associated with different diseases for which sleep disturbances and sleep problems are risk factors, such as coronary heart disease and type2 diabetes (13-16); however, the association between these SNPs and SCZ had not been described in previous studies. Therefore, the aim of the present study was to investigate the relation between *MTN1B* polymorphisms, rs10830963(C/G) and rs3781637(T/C), and SCZ risk.

Genotyping of *MTN1B* rs10830963(C/G) variant was performed using Polymerase Chain Reaction-Amplification Refractory Mutation System (PCR-ARMS) and NESTED-PCR, and ARMS-PCR modified methods (combination) (Nested-ARMS-PCR) were used for *MTN1B* rs3781637(T/C) variant genotyping. In fact, these methods were modified because the location of *MTN1B* rs3781637 (T/C) variant is very challenging for ARMS-PCR. As an advantage, this method prevents production of non-specific products and protection of SNP position for the next step of the process. The list of the primers used is available in **Table 2**.

rs10830963(C/G) polymorphism of MTN1B

To amplify the region of *MTN1B* gene in (20 µL volume), 1 µL template DNA (~80-100 ng/µL), 1 µL of each primer (10 pmol/µL), 10 µL mastermix (Ampliqon Taq 2x mastermix, Denmark), and 7 µL DNase-free water were added at the following condition: an initial denaturation 96 °C for 6 min and following that 30 cycles with this condition: denaturation 96°C for 30 s, annealing 49°C for 30 s, extension 72°C for 29 s, and the final extension was 72°C for 6 min. The product Size of this SNP was 312bp verified on 1.5% Agarose gel staining Ethidium Bromide by Electrophoresis after the PCR product was observed under UV light.

rs3781637(T/C) Polymorphism MTN1B

Nested-ARMS-PCR method was set up for the evaluation of polymorphism between SCZ and

Table 2. Polymerase Chain Reaction Primers sequences

Primer 5'-3'	Product	Method
rs3781637(T/C)	514bp	NESTED
F:GAATTGCATTTTGCAGCTGGAC		
R:GGAACTGCTCACACTATGAG		
	320bp	ARMS
F:GAATTGCATTTTGCAGCTGGAC		
Rw:TTCCTGAGGCTCTCTCTGCT		
Rm:TTCCTGAGACTCTCTCTGCC		
rs10830963(C/G)	312bp	ARMS
Fm:ATGCTAAGAATTCACACCATCCG		
Fw:ATGCTAAGAATTCAATTCACACC		
R:TGGTAGGATAGAAGCCTTGA		

Table 3. Genotypic and allelic frequencies of MTNR1B polymorphisms in SCZ patients and control subjects

MTNR1B Polymorphisms	SCZ n (%)	Control n (%)	OR (95%CI)	P-value
rs3781637(T/C)				
Codominant				
TT	92(100%)	90(97.8%)	1.00	-
TC	0(0%)	2(2.2%)	0	0.497
CC	0(0%)	0(0%)	0	
Allele				
T	184(100%)	182(98.9%)	1.00	-
C	0(0%)	2(1.1%)	0	0.499
rs10830963(C/G)				
Codominant				
CC	33(35.9%)	33(35.9%)	1.00	-
CG	23(25%)	46(50%)	0.500(0.25-1.01)	0.051
GG	36(39.1%)	13(14.1%)	2.78(1.25-6.25)	0.012
Allele				
C	89(48.4%)	112(60.9%)	1.00	-
G	95(51.6%)	72(39.1%)	1.66(1.09-2.51)	0.021
Dominant				
CC	33(35.9%)	33(35.9%)	1.00	-
CG+GG	59(64.1%)	59(64.1%)	1.00(0.55-1.83)	1.000
Recessive				
CC+CG	56(60.9%)	79(85.9%)	1.00	-
GG	36(39.1%)	13(14.1%)	3.85(1.89-8.33)	0.0001>

HC. In the first phase (NESTED-PCR stage), for amplification of *MTN1B* rs3781637 (T/C) (514 bp) product in (20 µL volume), 1 µL template DNA (~80-100 ng/µL), 1.5 µL of each forward and reverse primer (10 pmol/µL), 10 µL mastermix (Ampliqon Taq 2x mastermix, Denmark), and 6 µL DNase-free water were added. The PCR conditions were set as follows: 96°C for 6 min, 30 cycles of 96°C for 30 s, 60°C for 30 s and 72 °C for 30 s, and the final extension at 72 °C for 6 min. In the second phase of the method (ARMS-PCR stage), the PCR product resulting from the NESTED stage was used as the template. According to this template, an amount of 1:20 was diluted (1 volume PCR product in 19-volume DNase-free water). Then, ARMS-PCR was used to detect SNP. PCR was performed for 20 µL volume: 2 µL template (1:20 dilution), 1 µL of each primer (10-pmol/µL), 10 µL mastermix, and 6 µL DNase-free water were added. The PCR conditions were set as follows: 96 °C for 6 min, 30 cycles of 96°C for 30 s, 50°C for 30 s, 72 °C for 30 s, and a final extension at 72 °C for 6 min. PCR products were detected by

Table 4. Haplotype association between MTN1B gene polymorphism and SCZ risk

rs3781637 (T/C)	rs10830963 (C/G)	Total	SCZ	HC	OR (95%CI)	P-value
T	C	0.5408	0.4837	0.5978	1.00	-
T	G	0.4538	0.5163	0.3913	1.49(1.02-2.17)	0.039
C	C	0.0054	0	0.0109	0	0.0001>
C	G	0	0	0	0	0

electrophoresis on a 1.5% Agarose gel staining by Ethidium Bromide (320bp product).

Statistical analysis

The statistical package SPSS version 22 (SPSS Inc, Chicago, IL) was used for statistical analyses. Binary logistic regression test was used for determining odds ratio (OR) and 95% confidence intervals (95% CI) of each variant. Association and frequencies of haplotype with SCZ were analyzed using SNPStats online software. The Pearson's X^2 was used for comparison of the categorical data. $P<0.05$ was considered statistically significant. The Hardy–Weinberg equilibrium (HWE) was examined using $\chi 2$ for each SNP.

Results

HWE was estimated separately for SCZ and HCs. The HC group in rs3781637 (T/C) and rs10830963 (C/G) polymorphisms were in HWE ($P=0.916$, $\chi 2 = 0.01$ and $P=0.586$, $\chi 2 =0.23$, respectively), while the SCZ group were not in HWE in both SNPs ($P<0.05$).

The genotype and allelic frequencies of *MTN1B* polymorphisms are listed in **Table 3**. The results indicated that *MTN1B* rs10830963(C/G) variant increased the risk of SCZ in codominant (OR=2.78. 95%CI=1.25-6.25, P=0.012. GG vs. CC) and recessive (OR=3.85, 95%CI=1.89-8.33, P<0.0001, GG vs. CC+GG). In heritance models, the G allele increased the risk of SCZ (OR=1.66, 95%CI=1.09-2.51, P=0.021) compared with C allele. It was found that the genotype and allele frequencies of *MTN1B* rs3781637 (T/C) variant all codaminant, and allele status were not associated with the risk or protection of SCZ in the study population. In addition, the haplotype analyses indicated that the TG haplotype of rs3781637 (T/C) and rs10830963 (C/G) polymorphisms could increase the risk of SCZ (OR=1.49, 95%CI=1.02-2.17, P=0.039) (**Table 4**). Also, the CC haplotype of rs3781637 (T/C) and rs10830963 (C/G) polymorphisms were different between case and HC individuals (P=0.0001).

The association between clinical and demographic characteristics of SCZ patients with *MTN1B* rs10830963(C/G) polymorphism in the dominant model is shown in **Table 5**. There is no significant difference between clinical and demographic characteristics of SCZ patients and this variant in the dominant model (P>0.05).
There was no significant difference between the groups concerning gender and age (P=1.000, and P=0.809, respectively).

Discussion

The influences of melatonin as neuro hormone on sleep and circadian phase are mainly mediated by activation of its two especial receptors. Melatonin receptor 1 A (MT1) is encoded by *MTN1A* and melatonin receptor 1 B (MT2) is encoded by *MTN1B* (17). Previous studies showed decrease of melatonin secretion in SCZ patients compared to HCs, moreover, SCZ patients usually have sleep disturbances

Table 5. Association between MTNR1B polymorphisms with clinical demographic and characteristics of SCZ patients

Genotype	Age(year)	Sex(Male/ Female)	Hallucination (Yes/No)	Delusions (Yes/No)
rs10830963(C/G)				
CC	39.03±11.83	21/12	28/5	27/6
CG+GG	34.27±11.06	33/26	42/17	49/10
P-value	0.057	0.472	0.141	0.998

(9, 18). In treatment of SCZ patients, the correction of sleep distributions associated with low melatonin secretion should be considered (18); consequently, the effectiveness of MTN1B hormone might be involved in SCZ development.

SCZ is a multifactorial disease with highly heritable mental disorder, and factors such as urbanity, migration, sex, season of birth, pregnancy, and birth complications are possibly involved in the pathogenesis of the disease (19).

The present study investigated the potential impact of *MTN1B* gene polymorphisms on the susceptibility and clinical pathological features of SCZ in an Iranian population in the southeast of Iran. The findings proposed that *MTN1B* rs10830963 (C/G) variant significantly increased the risk of SCZ. The results did not support an association between rs3781637 (T/C) variant of *MTN1B* gene and SCZ risk although TG and CC haplotypes of rs3781637 (T/C) and rs10830963 (C/G) genes were associated with developing SCZ.

A stratified analysis was performed by clinical and demographic characteristics of SCZ patients, and the findings proposed that patients with rs10830963 (C/G) did not show difference regarding CG+GG vs. CC variants.

There was not any study regarding relationship between *MTN1B* (rs3781637(T/C) and rs10830963(C/G) variants and SCZ risk, so the current results could not be compared with similar studies; however, Hae Jeong Park et al. investigated the association of Korean SCZ patients and *MTN1B* rs4753426; they found that this SNP was not correlated with SCZ in the codominant, dominant, and recessive models (9). Another study was done on the association between *MTN1B* and occurrence of delusions (a sign of SCZ) by A de Jonghe et al., showing that neither rs10830962 nor rs3781638 polymorphisms were associated with the occurrence of delusions (20).

These two SNPs were investigated with various diseases such as systemic lupus erythematous (SLE) (21), breast cancer (22), polycystic ovary especially (23), type II diabetes (24), and gestational diabetes (6, 25). Tanev investigated the impact of *MTN1B* rs1562444, rs10830962, and rs10830963 polymorphisms on SLE on 109 SLE females and 101 healthy women; they found that CC genotype of rs10830963 polymorphism significantly increased the risk of SLE when compared with CG and GG genotypes (21). No significant association was reported between the CG genotype of rs10830963 variant and breast cancer in Egyptian women; however, the GG of this SNP was associated with the risk of breast cancer (22).

In a meta-analysis performed by Qing Xia et al., a significant association was revealed between *MTN1B* rs10830963 polymorphism and increase risk of type 2 diabetes (T2D) compared with alleles (G Vs. C, P=0.01) and recessive genetic model (P=0.001); subgroup analyses

showed that the allele (G Vs. C) of *MTN1B* rs10830906 variant was associated with the risk of T2D in East Asia but not in South Asia and Caucasus (24).

The results of a case-control study on Han Chinese individuals indicated that rs3781637 was associated with T2D in additive model and recessive model as a risk concerning T2D (26).

The deviation from HWE is not clear in the present study population; its probable reasons are: small sample size, emigration, immigration, or consanguineous marriages that are common in this region of Iran (Zahedan, southeast Iran).

The current study has several limitations. Firstly, based on the published and Medline data several *MTN1B* polymorphisms have been identified in humans, while we investigated only two polymorphisms. Secondly, we did not consider differences by specific schizophrenia subtypes. Thirdly, small sample size (although Zahedan-city has almost one million population, we found just 92 patient with SCZ in this one-year period).

In conclusion, the present study was the first attempt to demonstrate the feasible association between *MTN1B* SNPs and probability of SCZ risk in Iranian population, taking the *MTN1B* rs3781637 (T/C) and rs10830963(C/G) variants into account; rs10830963(C/G) was associated with the risk of SCZ development. Further studies are necessary with larger sample size and different ethnic groups to confirm the results.

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Conflict of Interests

The authors declare that there is no conflict of interests to disclose.

Abbreviations

SCZ	= Schizophrenia
HC	= Healthy control
MTNR1A	= Melatonin Receptor 1 A
MTNR1B	= Melatonin Receptor 1 B
SNP	= Single Nucleotide Polymorphism
DSM-IV	= Diagnostic and statistical manual of mental disorders –IV
EDTA	= Ethylenediaminetetraacetic acid
PCR	= Polymerase Chain Reaction
ARMS	= Amplification Refractory Mutation System
bp	= Base Pair
CI	= Confidence Intervals
OR	= Odds Ratio
HWE	= Hardy–Weinberg equilibrium
T2D	= Type 2 Diabetes
SLE	= Systematic Lupus Erythematous

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