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Association study of clock gene (*CLOCK*) and schizophrenia and mood disorders in the Japanese population

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Abstract Recently the clock genes have been reported to play some roles in neural transmitter systems, including the dopamine system, as well as to regulate circadian rhythms. Abnormalities in both of these mechanisms are thought to be involved in the pathophysiology of major mental illness such as schizophrenia and mood disorders including bipolar disorder (BP) and major depressive disorder (MDD). Recent genetic studies have reported that *CLOCK*, one of the clock genes, is associated with these psychiatric disorders. Therefore, we investigated the association between the six tagging SNPs in *CLOCK* and the risk of these psychiatric disorders in Japanese patients

diagnosed with schizophrenia (733 patients), BP (149) and MDD (324), plus 795 Japanese controls. Only one association, with schizophrenia in females, was detected in the haplotype analysis ($P = 0.0362$). However, this significance did not remain after Bonferroni correction ($P = 0.0724$). No significant association was found with BP and MDD. In conclusion, we suggest that *CLOCK* may not play a major role in the pathophysiology of Japanese schizophrenia, BP and MDD patients. However, it will be important to replicate and confirm these findings in other independent studies using large samples.

Key words schizophrenia · bipolar disorder · major depressive disorder · *CLOCK* · tagging SNP

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Introduction

Sleep disturbances are commonly observed in psychiatric disorders, and sleep manipulations can influence clinical status. Abnormalities in circadian rhythms have been reported to be involved in the pathophysiology of major mental illness such as schizophrenia and mood disorders [2, 24, 26, 27]. Also, because all psychotropic drugs have actions on the systems of neurotransmitters such as dopamine and serotonin in the brain, altered neural transmission is hypothesized to be a susceptibility factor for major mental illness [21, 29]. Recently these neurotransmitter systems have been reported to have reciprocal interactions with circadian rhythms [3, 40].

Clock genes were also discussed to regulate not only circadian rhythms but dopamine neural transmission [25]. Recently, *Per2*, one of the circadian clock genes, was shown to alter dopamine levels in the caudate putamen and the nucleus accumbens, mediated by reduced expression and activity of monoamine oxidase A, and its mutant mice showed

behaviors that resembled human mood disorders [16]. Abnormalities in dopamine neural transmission are known to be involved in the pathophysiology of schizophrenia [19], bipolar disorder (BP) [7] and major depressive disorder (MDD) [31]. A recent study has reported that plasma cortisol levels are elevated in schizophrenia and BP patients compared with controls [14]. Adrenal steroid hormones levels change based on circadian rhythms, it has been suggested and this mechanism may be involved in the development of insomnia and psychiatric disorders [10]. In addition, some genetic studies showed significant associations between schizophrenia/schizo-affective disorder and timeless homolog gene (*TIMELESS*) or period homolog 3 gene (*PER3*), between BP and *Bmal1* gene (*ARNTL*) or *TIMELESS* or *PER3* [22, 32]. These facts suggest a crucial relationship between circadian rhythms and psychiatric disorders, and so genes associated with the molecular clock mechanism are good candidates for the etiology of psychiatric disorders. We thought these psychiatric disorders may have some shared mechanisms as to circadian rhythms and considered that it was reasonable to assess all these disorders.

Recent genetic studies showed significant associations of a SNP (T3111C: rs1801260) in *CLOCK*, one of the clock genes, with Japanese schizophrenia [39] and clinical features of BP such as a high recurrence rate [5, 6, 35]. In an animal study using *CLOCK* mutant mice that showed mania-like behavior, this behavior was reversed by lithium treatment [34]. In addition, *CLOCK* mutant mice showed altered regulation of dopamine release in the ventral tegmental area mediated tyrosine hydroxylase regulated by circadian rhythms [28, 41]. Therefore, *CLOCK* would seem to be a good candidate gene for the pathophysiology of psychiatric disorders.

The *CLOCK* gene (OMIM *601851, 25 exons in this genomic region spanning 115.138 kb) is located on 4q12. This genomic region was shown to be closely related to susceptibility for schizophrenia [17, 38], BP [8, 15, 23] and MDD [11, 12]. Therefore, in this study, we aim to examine the genetic association between *CLOCK* and schizophrenia, BP and MDD in the Japanese population. To do this, we applied the recently recommended strategy of 'gene-based' association analysis [30]. We conducted a case-control association analysis using relatively large samples by selecting 'tagging SNPs' from the HapMap database.

Materials and methods

Subjects

The subjects in the association analysis were 733 schizophrenia patients [393 males and 340 females; mean age $\pm$ standard deviation (SD) 36.3 ± 18.4 years], 149 with BP (79 males and 70 females; 95 patients with bipolar I disorder and 54 patients with bipolar II

disorder; 47.8 ± 14.6 years), 324 with MDD (159 males and 165 females; 47.5 ± 16.1 years) and 795 healthy controls (347 males and 448 females; 37.6 ± 14.3 years). Patients were grouped according to the following DSM-IV subtypes of schizophrenia: Paranoid Type ($n = 216$), Disorganized Type ($n = 221$), Catatonic Type ($n = 29$), Residual Type ($n = 142$), Undifferentiated Type ($n = 125$). The patients were diagnosed according to DSM-IV criteria with the consensus of at least two experienced psychiatrists on the basis of unstructured interviews and a review of medical records. All healthy control subjects were also psychiatrically screened based on unstructured interviews. None had severe medical complications such as cirrhosis, renal failure, heart failure or other Axis-I disorders according to DSM-IV. No structured methods were used to assess psychiatric symptoms in the controls, who included hospital staff, their families and medical students. None of the subjects were known to be related to each other, and all were ethnically Japanese. Written informed consent was obtained from each subject. This study was approved by the ethics committees at Fujita Health University and Nagoya University Graduate School of Medicine.

SNP selection and linkage disequilibrium evaluation

We first consulted the HapMap database (release#23.a.phase2, Mar 2008, <http://www.hapmap.org>, population: Japanese Tokyo: minor allele frequencies (MAFs) of more than 0.1) and included 106 SNPs covering *CLOCK* (5'-flanking regions including about 2 kb from the initial exon and about 5 kb downstream (3') from the last exon: HapMap database contig number chr4: 55990340.. 56108588). Then six 'tagging (tag) SNPs' including rs1801260: T3111C (called SNP5 in this study) associated with Japanese schizophrenia [39] were selected with the criteria of an r^2 threshold greater than 0.8 in 'pairwise tagging only' mode using the 'Tagger' program (Paul de Bakker, <http://www.broad.mit.edu/mpg/tagger/>) of the HAPLOVIEW software [4], in the following association analysis.

SNP genotyping

We used TaqMan assays (Applied Biosystems, Foster City, CA, USA) for all SNPs. Detailed information is available on request.

Statistical analysis

Genotype deviation from the Hardy-Weinberg equilibrium (HWE) was evaluated by chi-square test (SAS/Genetics, release 8.2, SAS Japan Inc., Tokyo, Japan). Marker-trait association analysis was used to evaluate allele- and genotype-wise association with the chi-square test (SAS/Genetics, release 8.2, SAS Japan Inc., Tokyo, Japan), and haplotype-wise association analysis was evaluated by a likelihood ratio test using the COCAPHASE2.403 program [13]. Bonferroni's correction was used to control inflation of the type I error rate. Power calculation was performed using genetic power calculator [33]. The significance level for statistical tests was 0.05.

Results

Genotype frequencies were in HWE for this SNP. Linkage disequilibrium structures from the HapMap database can be seen in Fig. 1. The LD structures of schizophrenia, BP, MDD and control samples were almost the same (Fig. 1). In addition, LD from SNP1 to SNP4 was very tight in our control samples (r^2 more than 0.9), although we selected tag SNPs from HapMap database with the criteria of r^2 more than

Fig. 1 LD evaluation and tagging SNPs in *CLOCK*. Black bars represent exons of *CLOCK*. Tagging SNPs selected from HapMap database are represented by black boxes. The color scheme is based on r^2 value. LD structure of *CLOCK* is very tight and roughly one block. The color scheme is based on r^2 value. Other information can be seen at the HAPLOVIEW website

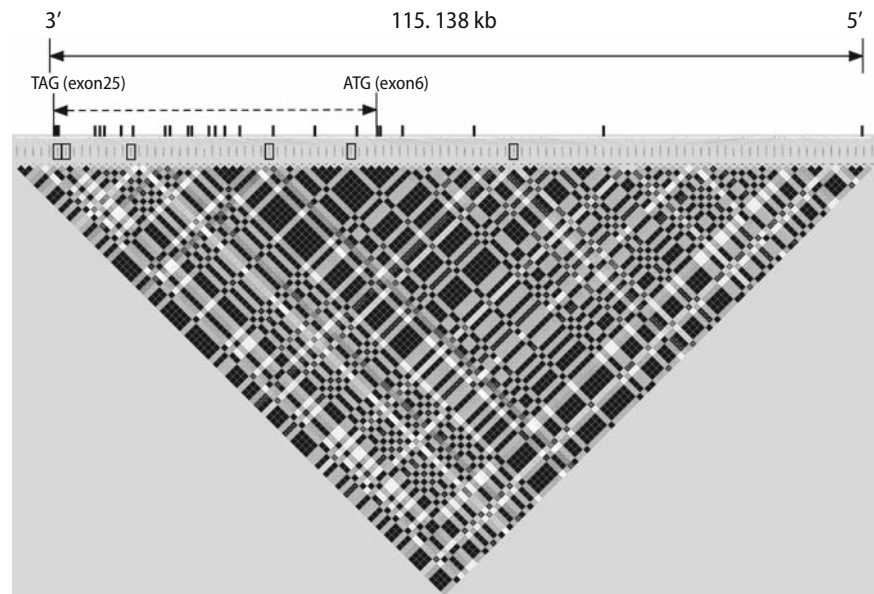


Table 1 Association analysis of tagging SNPs in *CLOCK*

SNP ID ^a	Phenotype	MAF	n	Genotype distribution			P value		
				M/M	M/m	m/m	HWE	Genotype	Allele
SNP1	rs11939815 G > T	Control	795	490	266	39	0.708		
		SCZ	733	460	243	30	0.767		0.724
		MDD	324	192	121	11	0.123	0.513	0.302
		BP	149	88	54	7	0.724	0.694	0.406
SNP2	rs11931061 A > G	Control	795	485	268	42	0.532		
		SCZ	733	454	247	32	0.827	0.536	0.699
		MDD	324	190	123	11	0.0948	0.902	0.208
		BP	149	88	54	7	0.724	0.795	0.821
SNP3	rs11133385 A > G	Control	795	485	270	40	0.760		
		SCZ	733	452	236	45	0.0615	0.881	0.541
		MDD	324	193	119	12	0.222	0.977	0.482
		BP	149	88	52	9	0.723	0.574	0.837
SNP4	rs3736544 G > A	Control	795	487	266	42	0.472		
		SCZ	733	460	246	27	0.402	0.296	0.317
		MDD	324	192	120	12	0.199	0.914	0.334
		BP	149	88	53	8	0.996	0.663	0.875
SNP5	rs1801260 T > C	Control	795	563	208	24	0.373		
		SCZ	733	532	185	16	0.986	0.321	0.519
		MDD	324	231	84	9	0.684	0.833	0.972
		BP	149	106	39	4	0.856	0.887	0.976
SNP6	rs3749474 T > C	Control	795	311	364	120	0.427		
		SCZ	733	301	338	94	0.953	0.228	0.412
		MDD	324	119	160	45	0.450	0.793	0.547
		BP	149	58	70	21	0.987	0.895	0.940

^aMajor allele > minor allele

SCZ schizophrenia, MDD major depressive disorder, BP bipolar disorder, MAF minor allele frequency, M major allele, m minor allele, HWE Hardy–Weinberg equilibrium

0.8. We did not find an association between these tag SNPs and Japanese schizophrenia, BP or MDD in any of the analyses (Tables 1, 2). It is known that there are sex differences in not only the pathophysiology of schizophrenia [18] but also in circadian rhythms [20], and we detected slight gender differences in LD structures constructed of tag SNPs of both schizophrenia samples in this study (Supplementary Figure 1). To further investigation of these associations,

we performed an explorative single marker and haplotype-wise analysis of subjects divided by sex. Only one association was detected, with schizophrenia females, in the haplotype-wise analysis ($P = 0.0362$) (Supplementary Table 4). However, this significance did not remain after Bonferroni correction ($P = 0.0724$) (Supplementary Table 4). Also, no association was detected in either sex in MDD or BP (Supplementary Tables 1, 2, 3, 4). In the power analysis, we

Table 2 Haplotype-wise analysis of tagging SNPs in *CLOCK*

Haplotype	Phenotype	Individual haplotype frequency	Individual P value	Phenotype	Global P value
GAAGTT	Control	0.625			
	SCZ	0.651	0.190	SCZ	0.340
	MDD	0.617	0.672	MDD	0.883
	BP	0.629	0.948	BP	0.957
GAAGCC	Control	0.158			
	SCZ	0.139	0.202		
	MDD	0.165	0.648		
	BP	0.150	0.782		
TGGATC	Control	0.217			
	SCZ	0.210	0.671		
	MDD	0.218	0.926		
	BP	0.220	0.867		

SCZ schizophrenia, MDD major depressive disorder, BP bipolar disorder

obtained more than 80% power for the detection of association when we set the genotype relative risk for *CLOCK* at 1.25–1.52 in schizophrenia, 1.76–1.85 in BP and 1.58–1.95 in MDD, under a multiplicative model of disease risk.

Discussion

In this study, only one association with schizophrenia in females was detected in the haplotype analysis ($P = 0.0362$), but this significance did not remain after Bonferroni correction ($P = 0.0724$). Also, we could not replicate the association between SNP5 (rs1801260: T3111C) and schizophrenia found in an earlier study [39], using larger Japanese schizophrenia and control samples. At this SNP, Takao et al. [39] showed higher MAFs of schizophrenia (MAFs: 0.224) compared with those of controls (MAFs: 0.141), although our study did not detect a significant difference with MAFs in schizophrenia or any specific gender subgroup compared with control. Also, there has been opened MAFs: 0.198 in Japanese HapMap database. In addition, LD from SNP1 to SNP4 was very tight in our control samples (r^2 more than 0.9), despite our selection of tag SNPs from HapMap database with the criteria of r^2 more than 0.8 (Minimum r^2 from SNP1 to SNP4 was 0.754 according to the database). So the differences of MAFs and r^2 in the Takao's study and the HapMap database with this study might be influenced by the sample size of each studies [39].

Similar to our study, several other investigations have found no association between *CLOCK* and BP or MDD using case-control samples and family based samples [1, 22, 32, 35, 36].

A few points of caution should be noted in interpreting our results. First, the lack of association may be due to biased samples, such as small sample sizes, especially BP and MDD samples or unmatched age- or gender-samples. Because our BP and MDD samples

are small, there are possibilities of type I errors in the results of association analysis for mood disorders statistically. Also, although we included subgroup analyses divided by gender, careful interpretation is needed with respect to the association of schizophrenia itself. On average, the controls are much younger than the patients. This means that a number of young controls may go on to develop one these disorders, most likely MDD, since the incidence of major depression is as high as 5% or more. Our subjects did not undergo structured interviews. MDD patients who are not diagnosed by structured interview may develop BP in the future [9, 37]. In addition, female schizophrenia has possibility to develop in the menopause. However, in this study patients were carefully diagnosed according to DSM-IV criteria with consensus of at least two experienced psychiatrists on the basis of a review of medical records. In addition, when we found a misdiagnosis of a patient, we promptly excluded the misdiagnosed case in consideration of the precision of our sample. Second, we did not include a mutation scan to detect rare variants with functional effects. However, it is difficult to evaluate the association of such extremely rare variants (e.g. MAFs < 0.01) from the viewpoint of power.

In conclusion, we suggest that *CLOCK* may not play a major role in the pathophysiology of schizophrenia, BP and MDD in the Japanese population. However, it will be important to replicate and confirm these findings in other independent studies using larger samples.

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