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Brief report

Polymorphism of circadian clock genes and temperamental dimensions of the TEMPS-A in bipolar disorder

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ABSTRACT

Background: Previously, we found correlations between lithium efficacy in bipolar disorder and temperamental dimensions of the TEMPS-A and also genes involved in the regulation of biological rhythms ("clock" genes). Here, were attempted to investigate an association between multiple, single nucleotide polymorphisms (SNPs) of four clock genes (*CLOCK, ARNTL, TIM, PER3*) and temperamental dimensions of the TEMPS-A, in bipolar patients.

Methods: The study included 70 patients with bipolar disorder (20 males, 50 females), with a mean age of 59 ± 12 years. The TEMPS-A questionnaire, 110 questions version, was used assessing five temperament domains: depressive, cyclothymic, hyperthymic, irritable and anxious. Genotyping was done for 9 SNPs of the *CLOCK* gene, 18 SNPs of the *ARNTL* gene, 6 SNPs of the *TIM* gene and 5 SNPs of the *PER3* gene.

Results: An association with hyperthymic temperament was found for three, and with anxious temperament for four SNPs of the *ARTL* gene. An association of cyclothymic temperament was found with two SNPs of the *TIM* gene and of depressive temperament with one SNP of the *PER3* gene. No association was observed with SNPs of the *CLOCK* gene.

Limitations: Relatively small number of patients studied and insufficient correction for multiple testing.

Conclusions: These results may suggest that the *ARNTL, TIM* and *PER3* genes may be associated with temperamental dimensions measured by the TEMPS-A, each of this gene being specific to given temperamental dimension. Of special interest may be the polymorphisms of *ARNTL* gene also connected with predisposition to bipolar mood disorder and/or lithium response.

1. Introduction

The TEMPS-A (Temperament Scale of Memphis, Pisa, Paris and San Diego—Autoquestionnaire) has been introduced by Akiskal et al. (2005). This scale is measuring five temperaments: depressive, cyclothymic, hyperthymic, irritable and anxious. The tool has been verified in 32 language versions and has been widely used in a number of epidemiological and clinical studies with psychiatric patients and healthy subjects. In Poland, the scale has been validated in a group of 521 Polish college students (Borkowska et al., 2010). In our study performed on 71 patients with bipolar mood disorder (21 males, 50 females), aged 31–82 years, which have been treated with lithium carbonate for at least five years (mean 15 years), significant correlations between affective temperaments an lithium response was found. The response to lithium correlated significantly positively with hyperthymic temperament score and negatively with anxious, cyclothymic and depressive temperaments scores (Rybakowski et al., 2013a, 2013b).

In recent years, some studies on the molecular-genetic underpinnings of the TEMPS-A temperaments have been performed. Savitz et al. (2008) in a large group ($n=241$) of bipolar patients found a connection between hyperthymic temperament and the Met allele of Val66Met polymorphism of the brain-derived neurotrophic factor (BDNF) gene. However, Japanese researchers (Tsutsumi et al., 2011) studying 44 healthy persons did not find any association between TEMPS-A temperament and this BDNF gene polymorphism. Hungarian investigators found an association between allele s of the 5-HTTLPR polymorphism of serotonin transporter gene and cyclothymic temperament, and to a lesser degree, with depressive, irritable and anxious temperaments, in

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139 healthy women (Gonda et al., 2006). However, a relationship between this polymorphism and temperaments of the TEMPS-A was not confirmed by Norwegian authors studying a large group of healthy subjects (287 males, 404 females) (Landaas et al., 2011).

Recently, Greenwood et al. (2012, 2013) attempted to define the TEMPS-A temperaments in the context of the genome-wide association studies (GWAS). They found highest heritability for irritable temperament (52%), and lowest for hyperthymic temperament (21%). As to hyperthymic temperament, a possible linkage with chromosome loci 1q44, 2p16, 6q16 and 14q23 has been suggested as well as chromosome loci 3p21 and 13q34 for depressive temperament and 6q24 for irritable temperament.

In our recent study we investigated multiple single nucleotide polymorphisms (SNPs) of circadian clock genes: circadian locomotor output cycle kaput (CLOCK), aryl hydrocarbon receptor nuclear translocator-like (ARNTL), timeless circadian clock (TIM), and period circadian clock 3 (PER3), in relation to prophylactic lithium response. We found an association with the degree of lithium prophylaxis for six SNPs and three haplotype blocks of the *ARNTL* gene and for two SNPs and one haplotype block of the *TIM* gene (Rybakowski et al., 2013a, 2013b). Therefore, in view of our previous association between lithium response and temperamental dimensions of the TEMPS-A, we hypothesized that these dimensions may be also associated with polymorphisms of circadian clock genes.

The aim of this study was to investigate an association between multiple, single nucleotide polymorphisms (SNPs) of four clock genes (*CLOCK, ARNTL, TIM, PER3*) and temperamental dimensions of TEMPS-A, in bipolar patients.

2. Subjects and methods

2.1. Patients

The study was performed on 70 patients with bipolar mood disorder (20 males, 50 females), with a mean age of 59 ± 12 years recruited from the outpatients in Department of Psychiatry, University of Medical Sciences in Poznan. Consensus diagnosis by at least two psychiatrists was made for each patient, according to DSM-IV criteria (SCID) (First et al., 1996).

The TEMPS-A questionnaire 110 questions version has been used. The evaluation of five temperament domains: depressive (items 1–21), cyclothymic (items 22–42), hyperthymic (items 43–63), irritable (items 64–84) and anxious (items 85–110) was performed. The scoring for each scale was calculated using the mathematical rule:

Table 1
Description of polymorphisms analyzed.

Gene	SNP ID	Chromosomal position	Custom name	MAF	Alleles	TaqMan assay ID	Function
CLOCK	rs1801260	55996126	3111C/T	0.275	A:G	C___8746719_20	3′UTR
	rs3805148	56001567		0.367	A:C	C__27519005_10	Intron
	rs6849474	56013219		0.325	G:A	C__11821338_10	Intron
	rs11932595	56018354		0.433	A:G	C____296556_10	Intron
	rs12648271	56062879		0.292	G:C	C____251897_10	Intron
	rs6850524	56076754		0.450	G:C	C__11821294_10	Intron
	rs12649507	56380484		0.331	A:G	C__1836992_10	Intron
	rs4340844	56023613		0.375	A:C	C__31137420_10	Intron
	rs534654	55984977		0.140	A:G	C____769781_10	Intron
ARNTL	rs1481892	13258497		0.258	G:C	Custom assay	Intron
	rs4146388	13263181		0.233	C:T	C___1870648_10	Intron
	rs10766075	13275163		0.233	C:T	C___1870671_10	Intron
	rs4757142	13282271		0.317	A:G	C___1870681_10	Intron
	rs7396943	13285555		0.292	G:C	C___1870682_10	Intron
	rs11824092	13302870		0.283	C:T	C___2160476_10	Intron
	rs7947951	13312606		0.275	G:A	C___2160488_10	Intron
	rs7937060	13319391		0.392	T:C	C__29136982_10	Intron
	rs1562438	13320776		0.305	C:T	C___2160492_10	Intron
	rs3816360	13324326		0.333	C:T	C__25813227_10	Intron
	rs7126303	13327111		0.408	T:C	C___2160497_10	Intron
	rs3789327	13341892		0.467	A:G	C___2160503_20	Intron
	rs11022778	13347436		0.358	T:G	C__31248681_10	Intron
	rs11600996	13352742		0.483	T:C	C___2160507_10	Intron
	rs11022779	13353386		0.208	G:A	C___2160509_10	Intron
	rs11022780	13353485		0.492	T:C	C___2160510_10	Intron
	rs7107287	13269545		0.233	G:T	C___1870658_10	Intron
	rs1982350	13306707		0.430	A:G	C___2160480_10	Intron
TIMELESS	rs2291739	55100920	Pro1018Leu	0.467	A:G	C__15966257_10	exon 25
	rs2291738	55101548		0.396	T:C	C___3134217_1_	Intron
	rs7302060	55115359		0.439	T:C	C___2690225_10	Intron
	rs10876890	55120018		0.492	A:T	C___2690213_10	Intron
	rs11171856	55128086		0.457	C:T	C__31820742_10	Intron
	rs2279665	55113961	Leu38Leu	0.483	C:G	C__15968332_10	exon 3
PER3	rs836755	7769114		0.425	A:C	C___2510236_20	Intron
	rs228727	7770423		0.450	C:T	C__11673507_10	Intron
	rs10864315	7772668		0.317	C:T	Custom assay	Intron
	rs4908694	7773485		0.200	C:T	Custom assay	Intron
	rs228682	7778933		0.392	T:C	C___8881633_20	Intron
	rs228642	7785880		0.475	T:C	C___2510264_10	Intron
	rs2172563	7796630		0.242	G:A	Custom assay	intron
	rs2640909	7812704	Met1028Thr	0.186	T:C	Custom assay	exon 18
	rs10462021	7819720	His1149Arg	0.151	A:G	Custom assay	exon 20

ARNTL=aryl hydrocarbon receptor nuclear translocator-like; CLOCK=circadian locomotor output cycle kaput; ID=identification; MAF=minor allele frequency; PER 3=period circadian clock 3; SNP=single nucleotide polymorphism; TIMELESS=timeless circadian clock; UTR=untranslated region.