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Association of Tef Polymorphism With Depression in Parkinson Disease

Ping Hua, MS[1], **Weiguo Liu, MD**[1,*], **Sheng-Han Kuo, MD**[2], **Yanyan Zhao, BS**[1], **Ling Chen, BS**[3], **Ning Zhang, BS**[3], **Chun Wang, MD**[3], **Suwan Guo, MD**[3], **Li Wang, BS**[4], **Hong Xiao, PhD**[5], **Justin Y. Kwan, MD**[6], and **Tianxia Wu, PhD**[7]

[1]Department of Neurology, Affiliated Brain Hospital of Nanjing Medical University, Nanjing, China

[2]Department of Neurology, College of Physicians and Surgeons, Columbia University, New York, New York, USA

[3]Medical Psychology, Affiliated Brain Hospital of Nanjing Medical University, Nanjing, China

[4]Clinical Laboratory, Affiliated Brain Hospital of Nanjing Medical University, Nanjing, China

[5]Institute of Scientific Research, Affiliated Brain Hospital of Nanjing Medical University, Nanjing, China

[6]Department of Neurology, University of Maryland, Baltimore, Maryland, USA

[7]National Institute of Neurological Diseases and Stroke, National Institutes of Health, Bethesda, Maryland, USA

Abstract

Background—Circadian rhythm disturbance has been implicated in depression, and polymorphisms of circadian genes *Cry1*, *Cry2*, and *Tef* are associated with depression. However, the relationship between these genes and depression symptoms in Parkinson's disease (PD) has not been established.

Methods—Four hundred eight subjects with PD participated in this study. Demographics, UPDRS, Mini–Mental Status Examination (MMSE), and Hamilton Rating Scale for Depression (HAMD) were obtained in all subjects. Frequency of polymorphisms of *Cry1* rs2287161, *Cry2* rs10838524, and *Tef* rs738499 was determined, and the association between genetic polymorphisms of circadian genes and HAMD scores in patients with PD was examined.

Results—*Tef,* but not *Cry1* or *Cry2*, is associated with HAMD scores in patients with PD in a linear regression model after adjusting for clinical variables ($P = 0.004$).

Conclusions—The polymorphism of *Tef* rs738499 is associated with depression symptoms in PD.

*Correspondence to: Dr. Weiguo Liu, Department of Neurology, Nanjing Brain Hospital Affiliated to Nanjing Medical University, Nanjing, 210029, PR China; liuweiguo1111@sina.com.

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Keywords

Parkinson's disease; depression; Tef; circadian genes

Parkinson's disease (PD) is a neurodegenerative disorder characterized by Lewy body inclusions and dopaminergic neuronal death in the substantia nigra. The cardinal clinical symptoms of PD are rest tremor, rigidity, and bradykinesia, which are usually levodopa responsive.[1] Several nonmotor symptoms can also occur in PD, such as dementia, depression, rapid eye movement behavior disorder, and constipation, and these symptoms can cause significant disability and adversely affect quality of life in PD patients.[2]

Among the nonmotor symptoms in PD, depression is the most common neuropsychiatric comorbid condition. [3] The prevalence of depression in PD (dPD) varies from 2.7% to 90% in different studies, with a mean prevalence of approximately 40%.[3,4] Several risk factors have been identified that increase the risk for dPD. Patients with early-onset PD and PD patients who carry LRRK2 mutations are more likely to be depressed.[5,6] Polymorphism in the serotonin transporter gene promoter (5-HTTLPR) were also found to be associated with dPD,[7–9] but this result was not consistently present in a subsequent study that included a larger cohort of PD patients.[10]

Genetic polymorphisms in the circadian genes, *Cry1*, *Cry2*, *Npas2*, *Sirt1*, and *Tef*, have been reported to be associated with major depression.[11–14] However, little is known about the underlying biological mechanism of this association. The circadian rhythm is tightly regulated by the circadian gene networks consisting of a series of auto-regulatory transcription-translation loops with positive and negative feedbacks to the central circadian genes and their proteins.[15] The positive feedback loop is comprised of *Clock/Npas2* and *Bmal1* genes and their proteins (CLOCK and BMAL1). CLOCK and BMAL1 form heterodimers to bind to the promoter of *Cry1*, *Cry2, Per1*, and *Per2* to activate their transcription. The protein products of these genes, CRY and PER, gradually accumulate during a 24-hour period. In the negative feedback loop, CRY and PER form heterodimers that translocate to the nucleus and inhibit their own synthesis by interacting with CLOCK/BMAL1 heterodimers. The entire cycle requires approximately 24 hours to complete, and these feedback loops are postulated to be the cellular mechanism of circadian rhythm.[15] Many other genes also modulate the circadian loops. Thyrotroph embryonic factor (TEF), a transcription factor, is of particular interest because light exposure can alter circadian rhythm by inducing *Tef* expression and, subsequently, increasing PER levels.[16] It is possible that genetic polymorphisms in these circadian genes lead to a disturbance in the circadian rhythm, resulting in neurotransmission dysfunction and a higher risk of depression.

In patients with depression, the circadian rhythms are disrupted, and this abnormality manifests clinically as alterations in core temperature, sleep length, and rhythmic hormone secretion.[17,18] Therapies to modulate circadian rhythms have been found to be effective in treating depression. Light therapy has been used to treat seasonal depression, and sleep deprivation has been used as an adjunct therapy in treating major depression.[19,20] Fluoxetine and lithium are suggested to exert their antidepressant effects by regulating circadian mechanisms.[21,22]

It is uncertain whether circadian gene polymorphisms are associated with dPD. We conducted a study to analyze single-nucleotide polymorphisms (SNPs) of clock genes (*Cry1* rs2287161, *Cry2* rs10838524, and *Tef* rs738499) in PD patients in the Han Chinese population. These SNPs were chosen based on previous studies that showed an association between these SNPs and depression and sleep disorders.[11,13,23]

Patients and Methods

Study Population

Four hundred eight unrelated PD patients were recruited from the PD Clinic at the Affiliated Brain Hospital of Nanjing Medical University (Nanjing, China) between September 2007 and October 2010. All patients were diagnosed with PD, using the Queen Square Brain Bank Criteria,[24] by two neurologists specialized in movement disorders (W.L. and Y.Z.). Depression severity in all PD patients was evaluated using the 24-item Hamilton Rating Scale for Depression (HAMD).[25] Clinical assessment of PD patients also included demographic variables, disease duration, Mini–Mental State Examination (MMSE),[26] H & Y staging,[27] UPDRS Part III (UPDRS-III) [28] and daily L-dopa equivalent dose (LED): 100 mg standard L-dopa = 140 mg controlled-release L-dopa = 50 mg ropinirole = 1 mg pramipexole = 10 mg selegiline.[29] All clinical evaluations were performed during the “on” period in PD patients. Patients who had other neurodegenerative disorders, severe medical illnesses, and a history of schizophrenia or bipolar disorders, as well as dementia determined by MMSE adjusted by age and education levels, were excluded from participation in this study.[30] All subjects gave written informed consent for the study, which was approved by the ethics committee of Nanjing Medical University.

Genetic Association Study

Genotyping was performed using methods previously described,[23,31] and the genotypes of *Cry1* rs2287161, *Cry2* rs10838524, and *Tef* rs738499 were screened by polymerase chain reaction–restriction fragment length polymorphism (PCR-RFLP) (Supporting Table 1). Statistical analysis was performed using *SPSS for Windows* software (version 13.0; SPSS, Inc., Chicago, IL) and the *SHEsis program*.[32] HAMD scores were compared between different genotypes of each SNP using Kruskal-Wallis’s H test for global comparison and Mann-Whitney’s U test for pairwise comparison. The correlation between clinical variables and HAMD scores was analyzed using Spearman’s rank correlation. A linear regression was generated to determine the extent to which the genetic polymorphisms in *Cry1*, *Cry2*, and *Tef* were associated with HAMD scores after adjusting for gender, disease duration, UPDRS-III, H & Y, and MMSE. The statistical significance threshold was set at $P < 0.05$ corrected.

Results

Mean age of the PD patients was 65.3 ± 10.2, and 61.5% were men. Mean UPDRS-III was 25.7 ± 15.1, mean H & Y was 2.0 ± 0.8, mean LED was 341.0 ± 283.7, mean MMSE score was 27.7 ± 3.3, and mean HAMD score was 14.4 ± 10.4. None of the clinical variables were normally distributed, except for age.

Distribution of the genotypes from all PD patients fitted the Hardy-Weinberg equilibrium (HWE). Higher HAMD scores were found in the TT genotype group in *Tef* rs738499 ($P < 0.01$) and the CC genotype group in *Cry1* rs2287161 ($P < 0.01$). There was no difference in HAMD score between the AA genotype and AG genotype group in *Cry2* rs10838524 (Table 1). Spearman's rank correlation showed that a higher HAMD score was associated with female gender ($P < 0.01$), longer disease duration ($P < 0.05$), higher UPDRS-III score ($P < 0.01$), higher H & Y ($P < 0.01$), lower MMSE scores ($P < 0.01$), the CC genotype in *Cry1* rs2287161 ($P < 0.01$), and the TT genotype in *Tef* rs738499 ($P < 0.01$). There was no correlation between HAMD score and age, LED, or *Cry2* rs10838524.

Stepwise linear regression adjusting for gender, disease duration, UPDRS-III, H & Y, and MMSE showed that UPDRS-III, gender, and the polymorphism in *Tef* rs738499 contributed to 20.7% of the variance, and *Tef* rs738499 accounted for 1.8% of the variance in HAMD scores ($P = 0.004$) (Table 2). *Cry1* and *Cry 2* polymorphisms did not contributed to the variance in HAMD scores.

Discussion and Conclusions

This study showed an association between *Tef* rs738499 and HAMD scores in PD patients, suggesting that the *Tef* rs738499 polymorphism may confer an increased risk for depression in this patient group. Polymorphisms in *Cry1* rs2287161 and *Cry2* rs10838524 were not associated with depression symptoms in our PD patients.

The protein product of the gene, *Tef*, belongs to the PAR bZip (proline and acidic amino-acid–rich basic leucine zipper) transcription factor family, which are important regulators of circadian rhythm.[33] *Tef* expression is induced by light exposure and can modulate *Per2* expression.[16] Interestingly, PAR bZip-deficient mice have been shown to have abnormal neurotransmitter metabolism, including a decreased brain level of 5-HT and dopamine.[34] Polymorphism in *Tef* rs738499 may be a susceptibility factor for altered circadian rhythm and dysfunctional neurotransmission and may increase the risk for depression in PD patients.

It is uncertain whether *Tef* rs738499 is associated with major depressive disorders or is specific to PD patients with depressive symptoms. Additional studies with larger sample sizes are necessary to confirm our findings. Longitudinal studies that include clinical measures of depression symptoms and severity of PD motor symptoms are warranted to further understand the complex relationships between these genetic variants and the neuropsychiatric symptoms in PD patients. In addition, the molecular mechanisms by which *Tef* rs738499 alters the risk for dPD remain obscure, and the effect of the polymorphism on the protein function or gene expression level is unknown. But, a previous study[13] reported that rs738499 had the highest linkage with rs599609, and that an SNP highly correlates with *Tef* expression.[35] Further studies to determine the effects of the genetic polymorphisms may facilitate a better understanding of the mechanisms that underlie psychiatric symptoms in neurodegenerative disorders such as PD. The association between other circadian genes, such as *Sirt1* and *Npas2*, and dPD is largely unknown and requires further examination.[12] We determined the SNPs in *Npas2* rs11123857 in 200 Chinese subjects, and no GG or AG

genotypes were found, suggesting that the G allele in *Npas2* rs11123857 is rare in the Han Chinese population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1

Comparison of HAMD scores among different genotypes

			P Value		
Gene	**Genotype (Number)**	**HAMD Scores**	**Global Test***	**Pairwise Comparison****	
Tef	TT (283)	15.7 ± 11.1	0.003	reference	
	TG (116)	11.6 ± 8.1		0.001	reference
	GG (9)	10.1 ± 8.0		0.127	0.563
Cry1	CC (289)	15.2 ± 10.7	<0.001	reference	
	CG (106)	13.3 ± 9.5		0.140	reference
	GG (13)	5.2 ± 4.7		<0.001	0.001
Cry2	AA (330)	14.9 ± 10.7	0.078		
	AG (78)	12.0 ± 8.6			

*Kruskal-Wallis's H test for global comparison of HAMD scores of different genotypes.

**Mann Whitney's U test for comparison of HAMD scores between two genotypes.

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Table 2

Contribution of genotypes to HAMD scores adjusted by gender, duration, UPDRS-III, H & Y, and MMSE

Predictor	Beta	r	r^2	Adjusted r^2	r^2 Change	t	*P* Value
UPDRS-III	0.387	0.394	0.155	0.153	0.155	8.371	0.000
Gender	0.173	0.434	0.189	0.184	0.033	3.755	0.000
Tef	−0.136	0.455	0.207	0.201	0.018	32.932	0.004

Abbreviations: Beta, standardized regression coefficients; r, multiple correlation coefficients; r^2, determination coefficient; *t*, *t* test statistics for Beta.