Neurosci. Bull. December, 2017, 33(6):734–736
https://doi.org/10.1007/s12264-017-0167-5

www.neurosci.cn
www.springer.com/12264

LETTER TO THE EDITOR

CLOCK rs1801260 Polymorphism is Associated with Susceptibility to Parkinson's Disease in a Chinese Population

Fan Lou[1] · Ming Li[2] · Yan Ren[1] · Xiao-Guang Luo[1] · Na Liu[1] · Xiaohong Li[1]

Received: 23 February 2017 / Accepted: 17 June 2017 / Published online: 5 August 2017

Dear Editor,

Until now, over 7 genes have been involved in the pathogenesis of Parkinson's disease (PD), which is generally considered to be caused by a combination of genes and environment. Recently, the clock genes that regulate the circadian rhythm have aroused much interest, since a great deal of evidence suggests that alterations of the circadian system participate in the pathogenesis of PD [1, 2]. Among these genes, Circadian Locomotor Output Cycles Kaput (*CLOCK*) and Period2 (*PER2*) are key components of the molecular mechanism that generates circadian rhythms in the brain and periphery. The polymorphisms rs1801260 of *CLOCK* and rs2304672 of *PER2* have previously been shown to be associated with regulation of the circadian rhythm, such as psycho-behavioral control, hormone secretion, mood, and sleep [3, 4]. They both contain functional polymorphisms which have recently been reported to be associated with disorders of circadian rhythms in neurodegenerative diseases [5, 6]. Yang [7] has found that the rs1801260 C > T polymorphism of the *CLOCK* gene may increase the susceptibility to Alzheimer disease among Chinese people. However, so far, little is known about whether polymorphisms of functional clock genes are associated with the risk of PD pathogenesis.

Therefore, in order to examine the association of the above single-nucleotide polymorphisms (SNPs; rs1801260 and rs2304672) of key functional clock genes with susceptibility to PD, we recruited 646 patients with PD and 352 healthy controls in a Chinese Han population in northeastern China for a case-control study (Table S1). All the participants were genotyped for both SNPs using the Kompetitive Allele-Specific PCR (KASP) method. The genotype frequencies of *CLOCK* rs1801260 and *PER2* rs2304672 among the controls were all in agreement with the Hardy–Weinberg equilibrium (all $P > 0.05$).

As shown in Table 1, a significant difference was found for *CLOCK* rs1801260 in a dominant model. Compared with the control group, the frequencies of the TC genotype (OR = 1.818, 95% CI = 1.212–2.728, $P = 0.004$) and CC + TC genotype for rs1801260 (OR = 1.906, 95% CI = 1.296–2.805, $P = 0.001$) were significantly higher in the PD group. There was also a significantly higher frequency of the rs1801260 C allele in patients than in controls (OR = 1.868, 95% CI = 1.310–2.644, $P = 0.001$). However, no significant difference was found in the frequencies of genotypes and alleles of *PER2* rs2304672 between patients and controls (all $P > 0.05$), although the frequency of the GG + CG genotype in the PD group showed a tendency to increase. Therefore, we further performed subtype analyses of *PER2* rs2304672 by sex, and found that no significant difference remained for the genotype and allele frequencies within male or female subtypes ($P > 0.05$). Logistic regression analysis revealed that an increased incidence risk of PD was significantly associated with the CC + TC genotype of rs1801260 (OR = 1.648, 95% CI = 1.149–2.347, $P = 0.034$) when confounding risk factors were adjusted, such as age (>60 years old), family history (PD or Parkinsonism), toxic exposure (MPTP, insecticide, or weedicide), and depression (Table S2).

Electronic supplementary material The online version of this article (doi:10.1007/s12264-017-0167-5) contains supplementary material, which is available to authorized users.

✉ Yan Ren
renyan0411@163.com

[1] Department of Neurology, First Affiliated Hospital of China Medical University, Shenyang 110001, China

[2] Department of Neurology, The Fourth Affiliated Hospital of China Medical University, Shenyang 110032, China

Table 1 Genotype and allele distributions of rs1801260 in patients with PD and controls

	CLOCK rs1801260						*PER2* rs2304672				
	Case $n = 646$	Control $n = 352$	OR	95% CI	*P* value		Case $n = 646$	Control $n = 352$	OR	95% CI	*P* value
Genotype						Genotype					
TT	522 (80.8)	313 (88.8)	Reference			CC	573 (88.7)	325 (92.3)	Reference		
TC	108 (16.7)	35 (9.9)	1.818	1.212–2.728	0.004[a]	CG	69 (10.7)	26 (7.4)	1.499	0.936–2.401	0.090
CC	16 (2.5)	4 (1.1)	2.058	0.733–6.661	0.149	GG	4 (0.6)	1 (0.3)	2.187	0.243–4.642	0.474
Dominant effect						Dominant effect					
CC+TC *vs* TT	124/522	39/313	1.906	1.296–2.805	0.001[a]	GG+CG *vs* CC	73/573	27/325	1.534	0.966–2.434	0.068
Allele						Allele					
T	1152 (89.2)	661 (93.9)	Reference			C	1215 (94.0)	676 (96.0)	Reference		
C	140 (10.8)	43 (6.1)	1.868	1.310–2.644	0.001[a]	G	77 (6.0)	28 (4.0)	1.530	0.983–2.382	0.058

The Chi-square test was used to compare categorical variables.

[a] $P < 0.01$.

Circadian dysfunction involving sleep disorders, fluctuations of motor symptoms, dysfunction of the autonomic nervous system (thermoregulation disorders and circadian variation of blood pressure and heart rate) and even emotional dysregulation (usually caused to depression) coexists with PD [8]. In fact, there is much overlap in the motor and non-motor symptoms experienced by PD patients and in the consequences of circadian dysfunction. On the other hand, disruption of the circadian system is considered to have pervasive effects throughout the body and may itself lead to neurological disorders [1, 9]. To date, very few exploratory studies have examined the effects of circadian disorders on the susceptibility to neurodegeneration [5, 7]. In this study, we found that the rs1801260 polymorphism of *CLOCK* was associated with susceptibility to PD, even after we adjusted for common risk factors. To our knowledge, this is the first study investigating the possible association of *CLOCK* polymorphism with PD in a northeastern Chinese population. However, we did not find significant differences in genotypic or allelic frequencies for the rs2304672 polymorphism of the *PER2* gene between patients with PD and controls, even in the analysis of subgroups. But a tendency for increased frequencies in the GG + CG genotype and G allele was seen in PD patients. These results cannot exclude the influence of the small sample size and the specific region of participant selection.

CLOCK is the key gene that regulates the circadian rhythm and we found that the rs1801260 C > T polymorphism of *CLOCK* was associated with the risk of PD. Thus we infer that disorders of circadian rhythm are related to PD pathogenesis. Kudo and colleagues found that mice over-expressing α-synuclein have a decreased rate of neuro-humoral output from the suprachiasmatic nucleus, suggesting that a weakening of circadian output may be a core feature of PD itself [10], which may be caused by oxidative stress and mitochondrial dysfunction. Besides, PD is characterized by a deficiency of dopamine in the substantia nigra. While dopamine is a neurotransmitter of major importance at several levels of the circadian system, its metabolism and signaling activity are strongly influenced by the circadian clock. Furthermore, circadian dysfunction has been considered as a pathology of aging, causing aging damage of dopaminergic neurons in PD. All of these suggest that circadian dysfunction is not merely a typical symptom of PD, but also a factor that may promote its pathological process.

The present study confirmed that circadian dysfunction is associated with the risk of PD in a Chinese population at the genetic level and provided a potential genetic locus related to PD. However, there are still some limitations. The study was conducted in individuals from a Chinese population, and these findings may not necessarily apply to other ethnicities. Besides, other functional clock genes or loci should be considered and discussed for interaction with the *CLOCK* rs1801260 on PD incidence. The evidence available so far warrants further research into the role of clock genes in regulating the pathophysiology of basal ganglis. The mechanism by which these SNPs affect the pathology of PD also requires further functional studies.

References

1. Musiek ES. Circadian clock disruption in neurodegenerative diseases: cause and effect? Front Pharmacol 2015, 6: 29.
2. Li S, Wang Y, Wang F, Hu LF, Liu CF. A new perspective for parkinson's disease: circadian rhythm. Neurosci Bull 2017, 33: 62–72.
3. Mishima K, Tozawa T, Satoh K, Saitoh H, Mishima Y. The 3111T/C polymorphism of hClock is associated with evening

preference and delayed sleep timing in a Japanese population sample. Am J Med Genet B Neuropsychiatr Genet 2005, 133B: 101–104.
4. Forbes EE, Dahl RE, Almeida JR, Ferrell RE, Nimgaonkar VL, Mansour H, *et al.* PER2 rs2304672 polymorphism moderates circadian-relevant reward circuitry activity in adolescents. Biol Psychiatry 2012, 71: 451–457.
5. Chen HF, Huang CQ, You C, Wang ZR, Si-qing H. Polymorphism of CLOCK gene rs 4580704 C > G is associated with susceptibility of Alzheimer's disease in a Chinese population. Arch Med Res 2013, 44: 203–207.
6. Gravotta L, Gavrila AM, Hood S, Amir S. Global depletion of dopamine using intracerebroventricular 6-hydroxydopamine injection disrupts normal circadian wheel-running patterns and PERIOD2 expression in the rat forebrain. J Mol Neurosci 2011, 45: 162–171.
7. Yang YK, Peng XD, Li YH, Wang ZR, Chang-quan H, Hui W, *et al.* The polymorphism of CLOCK gene 3111T/C C > T is associated with susceptibility of Alzheimer disease in Chinese population. J Investig Med 2013, 61: 1084–1087.
8. Bruguerolle B, Simon N. Biologic rhythms and Parkinson's disease: a chronopharmacologic approach to considering fluctuations in function. Clin Neuropharmacol 2002, 25: 194–201.
9. Videnovic A, Lazar AS, Barker RA, Overeem S. 'The clocks that time us'–circadian rhythms in neurodegenerative disorders. Nat Rev Neurol 2014, 10: 683–693.
10. Kudo T, Loh DH, Truong D, Wu Y, Colwell CS. Circadian dysfunction in a mouse model of Parkinson's disease. Exp Neurol 2011, 232: 66–75.