Neurosci. Bull. October, 2018, 34(5):867–869
https://doi.org/10.1007/s12264-018-0233-7

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

LETTER TO THE EDITOR

Lack of Association Between *DNMT3B* Polymorphisms and Sporadic Parkinson's Disease in a Han Chinese Population

Hong Pan[1,2] · Jun-Yi Shen[2] · Juan-Juan Du[2] · Shi-Shuang Cui[2] · Jin Liu[2] · Yi-Qi Lin[2] · Yi-Xi He[2] · Yang Fu[2] · Chao Gao[2] · Gen Li[2] · Sheng-Di Chen[2] · Jian-Fang Ma[2]

Received: 11 December 2017 / Accepted: 3 April 2018 / Published online: 14 May 2018

Dear Editor,

Recently, several single nucleotide polymorphisms (SNPs; rs34094401 on *RAD51B*, rs41309351 on *CPXM1*, rs143555311 on *MPHOSPH10*, rs141620200 on *SERPINA1*, and rs2424913 on *DNMT3B*) have been associated with Parkinson's disease (PD) in Caucasians [1–3]. Considering the genetic variance among different ethnic populations, it is essential to know whether these candidate SNPs are also associated with PD in other ethnic cohorts. Therefore, we investigated these newly-reported risk SNPs in 249 PD patients and 239 controls to test their association with PD.

There was no difference in age (P = 0.425) and gender (P = 0.718) between the PD and control groups (Table S1). Alleles and genotypes of the candidate SNPs are shown in Table S2. Hardy–Weinberg equilibrium was calculated for each SNP, and no significant deviation was found. The minor allele frequencies of rs34094401 (*RAD51B*), rs41309351 (*CPXM1*), rs143555311 (*MPHOSPH10*), and rs141620200 (*SERPINA1*) were all zero in both the PD and control groups. Two adjacent SNPs, rs9941620 *MPHOSPH10* and rs75826787 *DNMT3B*, were not associated with PD risk in either of the models. As rs75826787 and rs2424913 are on the same chromosome, linkage disequilibrium was analyzed, and none was found between them (Table S3).

Notably, for rs2424913 on *DNMT3B*, the frequency of the minor allele "C" in the control group (0.84%) was more than twice the minor allele frequency in the PD group (0.40%), and the odds ratio (OR) was 0.48. However, this difference was not statistically significant, either in allelic association (P = 0.443), the dominant model (P = 0.443), or the additive model (P = 0.394) (Table S2). Interestingly, the "C" allele of rs2424913 showed an even lower odds ratio in females (OR 0.31) under subgroup analysis based on gender (Table 1), though this association was not statistically significant (P = 0.356).

Two studies [3, 4] have investigated the association between rs2424913 and PD risk in a Brazilian population of European ancestry and a South Chinese Han population. The latter was included in our meta-analysis. In total, 736 PD patients and 724 controls were included. The fixed effect model was applied since there was no heterogeneity (I^2 = 0%). The results showed that rs2424913 was not significantly associated with PD in the Han Chinese population (P = 0.42 for allelic association, and P = 0.64 for the dominant model). In addition, the result of subgroup analysis based on gender in meta-analysis was similar to the results in our cohort (Table S4, Fig. S1).

To our knowledge, this is the first study on the association of rs75826787 (*DNMT3B*), rs34094401

Hong Pan and Jun-Yi Shen have contributed equally to this work.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s12264-018-0233-7) contains supplementary material, which is available to authorized users.

✉ Sheng-Di Chen
ruijincsd@126.com

✉ Jian-Fang Ma
majifa@hotmail.com

[1] Laboratory of Neurodegenerative Diseases, Institute of Health Sciences, Shanghai Institutes for Biological Sciences, Chinese Academy of Sciences, University of Chinese Academy of Sciences, Shanghai 200031, China

[2] Department of Neurology and Collaborative Innovation Center for Brain Science, Ruijin Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai 200025, China

Table 1 Subgroup analysis stratified by gender

GENE	SNP_ID	Gender	Power	Allele			Additive model			Dominant model			Recessive model		
				P	OR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI
MPHOSPH10	rs9941620	Female	0.27	0.180	0.74	0.48–1.14	0.164	0.753	0.50–1.12	0.121	0.67	0.39–1.14	0.812	0.82	0.28–2.35
		Male	0.05	0.695	0.92	0.61–1.37	0.656	0.917	0.63–1.34	0.899	0.95	0.56–1.61	0.520	0.74	0.28–1.92
DNMT3B	rs2424913	Female	0.12	0.356	0.31	0.01–3.85	0.305	0.304	0.03–2.96	0.354	0.305	0.01–3.86	1.000	0.00	–
		Male	0.05	1.000	0.99	0.01–78.13	0.995	0.992	0.06–16.04	1.000	0.99	0.01–78.44	1.000	0.00	–
	rs75826787	Female	0.12	0.688	1.25	0.52–3.08	0.531	1.301	0.57–2.96	0.678	1.30	0.53–3.29	1.000	0.00	–
		Male	0.06	0.835	0.91	0.35–2.29	0.811	0.901	0.38–2.13	0.899	0.95	0.56–1.61	1.000	0.00	–

OR odds ratio, *95% CI* 95% confidence interval

(*RAD51B*), rs41309351 (*CPXM1*), rs141620200 (*SERPINA1*), rs143555311 (*MPHOSPH10*), and rs9941620 (*MPHOSPH10*) with the risk of PD in an Asian population. In this study, we did not find any significant association between rs2424913 (*DNMT3B*) and PD risk in a Han Chinese population, although rs2424913 was first reported to be associated with PD risk by Pezzi *et al*. in a Brazilian population of European ancestry [3]. As the sample size of our cohort was small, a meta-analysis was further performed by including the recently published study of Chen *et al*. [4] in a Han Chinese population, together with our study, and no significant risk of PD was found for rs2424913 *DNMT3B*. The difference in results between Brazilian and Chinese cohorts may be attributable to ethnic diversity. However, two other SNPs, rs2424932 and rs998382 on *DNMT3B*, have been reported to be significantly associated with PD in a Han Chinese population [4], particularly in the female PD subgroup. As our study did not investigate these two SNPs, we cannot exclude the possibility of an association between *DNMT3B* and the risk of PD. Further validation studies, especially those in non-Asian populations, are warranted.

In the study of Pezzi *et al*. [3], the T allele of rs2424913 on *DNMT3B* was associated with PD risk, and they raised the hypothesis that this allele may up-regulate the expression of DNMT3B, and would presumably enhance the methylation on many PD-related genes like *SNCA* [5–7]. However, according to the UCSC genome browser, rs2424913 is located on the intron, rather than on the promoter of *DNMT3B* as reported by Coppedè *et al*. [8, 9], as the histone marker of the promoter on rs2424913 locus was faint. We speculate that rather than regulating the transcription of *DNMT3B*, the rs2424913 locus might affect the regulation of mRNA splicing, because it is close to the intron–exon junction, which usually contains a splicing code.

In conclusion, our study found no significant association of the SNPs on *RAD51B, CPXM1, MPHOSPH10, SERPINA1,* and *DNMT3B* with PD risk in a Han Chinese population. Still, there was the possibility that the risks of these candidate SNPs are specific to certain ethnic groups, or that the sample size in our study was not big enough to discover the risk. Therefore, more studies are needed in Chinese or Asian populations to increase the sample size and reveal the links between these SNPs and PD. Also, different PD-associated polymorphisms on the 5 corresponding genes, and even expression or functional problems of these genes might exist, from which new fascinating mechanisms in PD remain to be explored.

Acknowledgements We are grateful to the participants in this study. This work was supported by the National Natural Science Foundation

of China (81430022, 91332107, and 81371407), and the National Key R&D Program of China (2016YFC1306000).

Compliance with Ethical Standards

Conflict of interest The authors have no conflict of interest to report.

References

1. Sandor C, Honti F, Haerty W, Szewczyk-Krolikowski K, Tomlinson P, Evetts S, *et al*. Whole-exome sequencing of 228 patients with sporadic Parkinson's disease. Sci Rep 2017, 7: 41188.
2. Siitonen A, Nalls MA, Hernandez D, Gibbs JR, Ding J, Ylikotila P, *et al*. Genetics of early-onset Parkinson's disease in Finland: exome sequencing and genome-wide association study. Neurobiol Aging 2017, 53: 195.e7–195.e10.
3. Pezzi JC, de Bem CM, da Rocha TJ, Schumacher-Schuh AF, Chaves ML, Rieder CR, *et al*. Association between DNA methyltransferase gene polymorphism and Parkinson's disease. Neurosci Lett 2017, 639: 146–150.
4. Chen X, Xiao Y, Wei L, Wu Y, Lu J, Guo W, *et al*. Association of DNMT3b gene variants with sporadic Parkinson's disease in a Chinese Han population. J Gene Med 2017, 19: 360–365.
5. Jowaed A, Schmitt I, Kaut O, Wullner U. Methylation regulates alpha-synuclein expression and is decreased in Parkinson's disease patients' brains. J Neurosci 2010, 30: 6355–6359.
6. Song Y, Ding H, Yang J, Lin Q, Xue J, Zhang Y, *et al*. Pyrosequencing analysis of SNCA methylation levels in leukocytes from Parkinson's disease patients. Neurosci Lett 2014, 569: 85–88.
7. Tan YY, Wu L, Zhao ZB, Wang Y, Xiao Q, Liu J, *et al*. Methylation of alpha-synuclein and leucine-rich repeat kinase 2 in leukocyte DNA of Parkinson's disease patients. Parkinsonism Relat Disord 2014, 20: 308–313.
8. Coppedè F, Bosco P, Tannorella P, Romano C, Antonucci I, Stuppia L, *et al*. DNMT3B promoter polymorphisms and maternal risk of birth of a child with Down syndrome. Hum Reprod 2013, 28: 545–550.
9. Xiao Y, Word B, Hammons G, Lyn-Cook B. Transcriptional activity of DNMT3B in pancreatic cancer cells: effects of -149 (C→T) promoter polymorphism. Biochem Biophys Res Commun 2011, 415: 220–223.