Genetic analysis of the *TMEM230* gene in Chinese patients with familial Parkinson disease

Hongwei Wu, MD, ^{1*} Xiaosheng Zheng, MD, ^{1*} Zhidong Cen, MD, ¹ Fei Xie, MD, ^{1,3}
You Chen, MD, ¹ Xingjiao Lu, MD, ^{1,2} Wei Luo, MD, PhD, ^{1*}

1. Department of Neurology, Second Affiliated Hospital, School of Medicine, Zhejiang University, 88 Jiefang Road, Hangzhou Zhejiang Province, China, 310009

2. Department of Neurology, Zhejiang Hospital, 12 Lingyin Road, Hangzhou Zhejiang Province, China, 310013

3. Department of Neurology, Sir Run Run Shaw Hospital, School of Medicine, Zhejiang University, 3 East Qingchun Road, Hangzhou Zhejiang Province, China, 310016

*Hongwei Wu and Xiaosheng Zheng contributed equally to this work and should be considered co-first authors.

*Corresponding author: Wei Luo

Tel: 00-86-571-87783777

E-Mail: luoweirock@126.com

Fax: 00-86-571-87784556

Department of Neurology, Second Affiliated Hospital, School of Medicine, Zhejiang University, 88 Jiefang Road, Hangzhou Zhejiang Province, China, 310009

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Parkinson disease (PD) is a common movement disorder characterized by the cardinal features of resting tremor, rigidity, and slowness of movements with a prevalence of 1–2% in general population over 60 years of age [1]. About 5–10% of the patients show an autosomal dominant or recessive mode of inheritance, which indicated that genetic factors play an important role in the pathogenesis of PD [2].

Recently, Deng et al. [3] identified *TMEM230* as a novel causative gene of PD. A highly prevalent *TMEM230* mutation encoding p.*184ProGlyext*5, was found in seven Chinese familial PD pedigrees. In order to obtain the further prevalence of *TMEM230* mutations in familial PD patients, we sequenced *TMEM230* gene in 122 probands from familial PD pedigrees.

The study comprised 122 probands (age 62.6 ± 9.3 years, onset 56.9 ± 13.3 years) from familial PD pedigrees (95 pedigrees have 2 or more PD patients in at least 2 consecutive generations and 27 pedigrees had at least 2 siblings with PD). All patients and controls were collected at the Neurology Department of the Second Affiliated Hospital, School of Medicine, Zhejiang University. PD was diagnosed using MDS Clinical Diagnostic Criteria [4] by two experienced neurologists. Informed consent was obtained from each participant. The study was approved by the medical ethics committee of the Second Affiliated Hospital, Zhejiang University School of Medicine (Hangzhou, China).

Genomic DNA was isolated from peripheral blood of patients by standard

protocols. The primers used for PCR amplification cover all coding regions of the *TMEM230* gene [3]. PCR products were directly sequenced on an ABI 3100 automated sequencer (Applied Biosystems, Foster City, CA). DNASTar was used for sequence alignment and analysis (DNASTar, Inc., Madison, WI) by two analysts independently.

By sequencing the entire coding region of *TMEM230* gene in 122 probands from familial PD pedigrees, no pathogenic mutation was found, suggesting that *TMEM230* mutations may be rare in Chinese patients with familial PD. What's more, two single nucleotide polymorphisms (c.46G>A, c.174+11C>T) were identified. The c.46G>A was carried by the patient and his healthy father, but was not carried by his mother with PD. The c.174+11C>T was identified in 7 of 122 familial PD patients, which was reported in the ExAC database (East Asian, MAF 0.033).

TMEM230 encodes a multi-pass membrane protein, which belongs to the TMEM134/TMEM230 family. Deng et al. [3] identified it as a novel causative gene of familial PD and found that TMEM230 is a trafficking protein of secretory/recycling vesicles, and that dysfunction of synaptic vesicles, such as impaired trafficking and recycling, underlies the pathogenesis of PD linked to *TMEM230* mutation [3].

Deng et al. [3] also screened *TMEM230* gene in Chinese cohort and only one highly prevalent *TMEM230* mutation encoding p.*184ProGlyext*5, was found in seven familial PD pedigrees. No founder effect was proved by haplotype analysis with three SNPs. The role of *TMEM230* gene in Chinese familial PD needs further studies.

No pathogenic mutation was found in 122 probands from familial PD pedigrees in our study, suggesting that *TMEM230* mutations may be rare in Chinese patients with familial PD. We considered the novel variant c.46G>A was not a pathogenic mutation, for it predicted to be polymorphism by Mutation Taster [5], and was carried by the patient and his healthy father, but was not carried by his mother with PD. Nevertheless, we didn't exclude known PD gene mutations in our 122 familial PD patients and our cohorts were relatively small. Most of our patients were from east China, which could explain the different result comparing with the original study. Rearrangement mutation was not tested was a limitation in our study and may miss some mutations.

In summary, we conducted comprehensive screening of the *TMEM230* mutations in 122 probands from familial PD pedigrees. To the best of our knowledge, this is the first survey in East China to show that *TMEM230* mutations may be rare in Chinese patients with familial PD. Larger-scale genetic studies in multiple ethnic populations are needed to clarify the pathogenic role of *TMEM230* in familial PD.

Disclosure statement

The authors have no actual or potential conflicts of interest to report.

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References

- [1] L.M.L. de Lau, M.M.B. Breteler, Epidemiology of Parkinson's disease, *The Lancet Neurology* 5(6) (2006) 525-535.
- [2] C.M. Lill, J.T. Roehr, M.B. McQueen, F.K. Kavvoura, S. Bagade, B.M. Schjeide, L.M. Schjeide, E. Meissner, U. Zauft, N.C. Allen, T. Liu, M. Schilling, K.J. Anderson, G. Beecham, D. Berg, J.M. Biernacka, A. Brice, A.L. DeStefano, C.B. Do, N. Eriksson, S.A. Factor, M.J. Farrer, T. Foroud, T. Gasser, T. Hamza, J.A. Hardy, P. Heutink, E.M. Hill-Burns, C. Klein, J.C. Latourelle, D.M. Maraganore, E.R. Martin, M. Martinez, R.H. Myers, M.A. Nalls, N. Pankratz, H. Payami, W. Satake, W.K. Scott, M. Sharma, A.B. Singleton, K. Stefansson, T. Toda, J.Y. Tung, J. Vance, N.W. Wood, C.P. Zabetian, C. and Me Genetic Epidemiology of Parkinson's Disease, C. International Parkinson's Disease Genomics, G.C. Parkinson's Disease, C. Wellcome Trust Case Control, P. Young, R.E. Tanzi, M.J. Khoury, F. Zipp, H. Lehrach, J.P. Ioannidis, L. Bertram, Comprehensive research synopsis and systematic meta-analyses in Parkinson's disease genetics: The PDGene database, *PLoS genetics* 8(3) (2012) e1002548.
- [3] H.-X. Deng, Y. Shi, Y. Yang, K.B. Ahmeti, N. Miller, C. Huang, L. Cheng, H. Zhai, S. Deng, K. Nuytemans, N.J. Corbett, M.J. Kim, H. Deng, B. Tang, Z. Yang, Y. Xu, P. Chan, B. Huang, X.-P. Gao, Z. Song, Z. Liu, F. Fecto, N. Siddique, T. Foroud, J. Jankovic, B. Ghetti, D.A. Nicholson, D. Krainc, O. Melen, J.M. Vance, M.A. Pericak-Vance, Y.-C. Ma, A.H. Rajput, T. Siddique, Identification of TMEM230 mutations in familial Parkinson's disease, *Nature Genetics* (2016).
- [4] R.B. Postuma, D. Berg, M. Stern, W. Poewe, C.W. Olanow, W. Oertel, J. Obeso, K. Marek, I. Litvan, A.E. Lang, G. Halliday, C.G. Goetz, T. Gasser, B. Dubois, P. Chan, B.R. Bloem, C.H. Adler, G. Deuschl, MDS

clinical diagnostic criteria for Parkinson's disease, *Movement disorders : official journal of the Movement Disorder Society* 30(12) (2015) 1591-601.

[5] J.M. Schwarz, C. Rodelsperger, M. Schuelke, D. Seelow, MutationTaster evaluates disease-causing potential of sequence alterations, *Nature methods* 7(8) (2010) 575-6.