

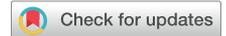


Genetic analysis of *PODXL* gene in patients with familial and young-onset Parkinson's disease in a Taiwanese population

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ABSTRACT

Mutations in the podocalyxin-like gene (*PODXL*) have been recently identified in a consanguineous Indian family with juvenile-onset Parkinson's disease (PD) and 3 unrelated patients with PD. However, the pathogenicity of *PODXL* mutations in the disease and their role in other PD populations remain unclear. The aim of this study was to investigate the *PODXL* mutations in a Taiwanese cohort with familial and young-onset PD. Among 531 participants, including 161 probands from PD pedigrees without known PD-causative gene mutations and 370 patients with early-onset PD (age of onset <50 years), all exons and exon-intron boundary junctions of *PODXL* were analyzed by Sanger sequencing. We did not find any pathogenic coding variants or previously reported mutations, indicating that *PODXL* mutations may not play a role in familial or early-onset PD in this Taiwanese population.

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1. Introduction

Parkinson disease (PD) is the second most common neurodegenerative disease arising from a complex interaction between genetic and environmental factors (Ross and Smith, 2007). Although mutations in a number of PD-causative genes have been identified in nearly 30% of familial forms of the disease and 3%–5% of sporadic patients (Klein and Westenberger, 2012), these mutations account for only a small percentage of patients with PD in most populations (Singleton and Hardy, 2016), indicating additional genes contributing to disease risk are needed to be identified.

Homozygous frameshift mutation (exon 1 c.89_90insGTCGCCCC) in the podocalyxin-like gene (*PODXL*) was recently found to be associated and co-segregated with autosomal-recessive juvenile-onset PD in a consanguineous Indian family, and 3 heterozygous missense mutations were found in another 3 unrelated PD patients with onset age ranging from 22 to 71 years (Sudhman et al., 2016). The mutant protein encoded by the homozygous frameshift mutation, c.89_90insGTCGCCCC, in exon 1 of *PODXL* was shown to cause neurite degeneration in stably transfected PC12 cells. *PODXL* is a polysialylated adhesion glycoprotein associated with neuronal development and synaptogenesis (Sudhman et al., 2016). However,

the evidence for a disease-causing pathogenicity of *PODXL* is not conclusive, and their role in other PD populations remains unclear. We previously performed a comprehensive analysis of mutations in multiple candidate genes in a cohort of PD patients from Taiwan (Lin et al., 2013, 2017; Wu et al., 2005), but the major genetic causes of our familial PD patients are still unknown. The aim of this study was to investigate the genetic contribution of *PODXL* in patients with familial and early-onset PD in our Taiwanese population.

2. Methods

We enrolled 531 participants diagnosed with PD, including 161 PD pedigrees and 370 young-onset PD with onset age less than 50 years, in the study. PD was diagnosed according to the UK PD Society Brain Bank Clinical Diagnostic Criteria (Hughes et al., 1992). Among 161 patients with familial PD, 98 had autosomal-dominant inheritance and 63 followed autosomal-recessive pattern. None of the patients were from consanguineous family. All the participants are negative for genetic mutations including *SNCA*, *GBA*, *LRRK2*, *UCHL1*, *GIGYF2*, *VPS35*, *DNAJC13*, *PARKIN*, *PINK1*, *DJ-1*, *ATP13A2*, *PLA2G6*, *FBXO7*, *SYNJ1*, *DNAJC13*, *CHCHD2*, *HtrA2*, and *Rab39B* using a targeted multigene next-generation sequencing panel, and large deletions or duplications of common PD-causative genes including *SNCA*, *Parkin*, *PINK1*, *DJ-1*, *ATP13A2*, *PLA2G6*, *FBXO7*, *DNAJC6*, and *LRRK2* were detected using the salsa multiplex ligation-dependent probe amplification kit P051-c1/P52-c1 (MRC-Holland, Amsterdam,

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The Netherlands) (Fan et al., 2016; Lin et al., 2013, 2017; Wu et al., 2005). Rare mutations of genes that may present with parkinsonism-like phenotype were not excluded in the enrolled cases in our study. Informed consent was obtained from all participants. Institutional ethics board committees of National Taiwan University Hospital approved the study.

DNA extraction was performed via venous blood by standard protocol. All the 8 exons and exon-intron boundary junctions of *PODXL* were analyzed through PCR-based Sanger sequencing analysis. Primer sequences and PCR conditions were described previously (Sudhama et al., 2016).

3. Results

The mean age of disease onset was 59.8 ± 12.7 years in patients with familial PD, and the mean age at enrollment was 67.2 ± 13.1 years. For patient with young-onset PD, the mean age of disease onset was 42.1 ± 6.5 years and the mean age at enrollment was 55.6 ± 13.8 years. None of our patients had previously reported exon 1 c.89_90insGTCGCCCC frameshift mutation or heterozygous missense mutations, including c.1285C>A (p.P429T), c.1118G>A (p.S373N), or c.881G>A (p.R294Q) in *PODXL* (Sudhama et al., 2016). However, we found several genetic polymorphisms, including an in-frame insertion or deletion in exon 1 (c.64_65insCGTCGC or c.65_70delCGTCGC, rs79759078), resulting in 2 transcripts of *PODXL*, one nonsynonymous variant in exon 2 (c.334G>A, p.G112S, rs3735035), and another synonymous variant in exon 7 (c.1314A>G, p.A438A, rs6651125) (Supplementary Table 1). All aforementioned exonic variants were also found in the exome database ($n = 1514$ exomes) from healthy controls of Taiwan Biobank (<https://taiwanview.twbiobank.org.tw/login>). Further functional studies and expression assay for the 2 transcripts of *PODXL* are needed to clarify the individual roles of these 2 transcripts in neurons.

4. Conclusions

PODXL gene mutations may not associate with familial or young-onset PD in the Taiwanese population. Validation of the role of *PODXL* in PD in other ethnic group is still needed.

Disclosure

All authors report no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.neurobiolaging.2019.08.027>.

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