Genetic Analysis of Six Transmembrane Protein Family Genes in Parkinson’s Disease in a Large Chinese Cohort

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Objectives: Parkinson’s disease (PD) is a neurodegenerative disorder with the manifestation of motor symptoms and non-motor symptoms. Previous studies have indicated the role of several transmembrane (TMEM) protein family genes in PD pathogenesis.

Materials and Methods: In order to better investigate the genetic role of PD-related TMEM protein family genes in PD, including TMEM230, TMEM59, TMEM108, TMEM163, TMEM175, and TMEM229B, 1,917 sporadic early onset PD (sEOPD) or familial PD (FPD) patients and 1,652 healthy controls were analyzed by whole-exome sequencing (WES) while 1,962 sporadic late-onset PD (sLOPD) and 1,279 healthy controls were analyzed by whole-genome sequencing (WGS). Rare and common variants for each gene were included in the analysis.

Results: One hundred rare damaging or loss of function variants of six genes were found at the threshold of MAF < 0.1%. Three rare Dmis variants of TMEM230 were specifically identified in PD. Rare missense variants of TMEM59 were statistically significantly associated with PD in the WES cohort, indicating the role of TMEM59 in FPD and sEOPD. Rare missense variants of TMEM108 were suggestively associated with PD in the WGS cohort, indicating the potential role of TMEM108 in sLOPD. The rare variant of the other three genes and common variants of six genes were not significantly associated with PD.

Conclusion: We performed a large case-control study to systematically investigate the role of several PD-related TMEM protein family genes in PD. We identified three PD-specific variants in TMEM230, the significant association of TMEM59 with FPD, and sEOPD and the suggestive association of TMEM108 with sLOPD.

Keywords: TMEM protein family genes, genetic analysis, Parkinson’s disease, burden analysis, rare variants, common variants
INTRODUCTION

Parkinson’s disease (PD) is the second most prevalent neurodegenerative disorder characterized by different combinations of motor and non-motor symptoms, including bradykinesia, resting tremor, rigidity, postural instability, olfactory loss, sleep dysfunction, autonomic dysfunction, and cognitive impairment (Armstrong and Okun, 2020). The pathophysiology of PD is dopaminergic neuron death and α-synuclein accumulation (Bloom et al., 2021). Neuroinflammation, mitochondrial/oxidative stress pathways dysregulation, autophagy/lysosomal dysfunction, and synaptic vesicle endocytosis disruptions have been indicated in the pathogenesis of PD (Nguyen et al., 2019; Hirsch and Standaert, 2021). Genetic, epigenetic, environmental, and lifestyle risk factors contribute to PD etiology (Jankovic and Tan, 2020). Previous studies have identified more than 20 PD-causing genes through linkage analysis or homoygous mapping strategies and many PD risk loci affecting disease risk, age at onset (AAO), and progression of PD through the genome-wide association study (GWAS) (Blauwendraat et al., 2020).

Transmembrane (TMEM) proteins belong to a large protein family with the characteristic of having at least one transmembrane peptide that entirely or partially crosses the biological membrane (Marx et al., 2020). With the transmembrane property, TMEM proteins play an essential role in many cell processes, such as signal transduction, ion/small molecule transportation, and cell adhesion (Ryu et al., 2019). Especially some members of the TMEM protein family play roles in PD-related pathways, such as synaptic vesicle trafficking and lysosomal and mitochondrial function (Deng et al., 2016; Jinn et al., 2017; Wang et al., 2021a). However, many TMEM proteins are still poorly investigated (Marx et al., 2020).

Several TMEM proteins have been reported to be associated with PD, for example, TMEM230, TMEM175, TMEM163, TMEM229B, TMEM108, and TMEM59. TMEM230 mutations were reported to cause autosomal dominant PD (Deng et al., 2016). Moreover, mutant TMEM230 could impair synaptic vesicle trafficking, disrupt mitochondria transport, and induce apoptotic cell death (Deng et al., 2016; Wang et al., 2020, 2021a). A genome-wide significant locus (rs34311866) located around the TMEM175 gene was reported in a large-scale GWAS meta-analysis study (Nalls et al., 2014), and TMEM175 deficiency resulted in lysosomal and mitochondrial dysfunction and α-synuclein aggregation (Jinn et al., 2017). Another two loci located around TMEM163 or TMEM229B were also identified to be associated with PD in a large-scale meta-analysis of the GWAS study (Nalls et al., 2014). In contrast, a large longitudinal study found the rs138073281 located around TMEM108 linked to cognitive progression in PD (Zhang et al., 2021). Specifically, the association of TMEM163 with PD was further confirmed in other cohorts (Kia et al., 2021; Rudakou et al., 2021). TMEM59 was reported within the PARK10 locus indicating a possible role in PD (Beecham et al., 2015). Moreover, over-expression of TMEM59 in a Drosophila PD model ameliorated the phenotype of shortened lifespan, impaired locomotor activity, and dopaminergic neuron loss (Zhang et al., 2018). Although the above evidence indicated that those TMEM proteins family genes might be associated with PD, few studies systematically analyze whether these genes are associated with early onset or late-onset PD populations, respectively, considering that early onset and late-onset cases may have certain genetic heterogeneity.

This study analyzed rare and common variants of TMEM230, TMEM175, TMEM163, TMEM229B, TMEM108, and TMEM59 with gene-based and allele-based, respectively, through next-generation sequencing in a large Chinese PD cohort to better explore the genetic contribution of these six TMEM protein family genes in Chinese PD patients.

MATERIALS AND METHODS

Participants

Three thousand eight hundred seventy-nine unrelated PD patients and 2,931 healthy controls were enrolled in this study. Blood samples for DNA extraction and clinical data of each participant were collected. All the participants have been divided into two cohorts: 1,917 sporadic early onset PD (sEOPD) or familial PD (FPD) probands and 1,652 healthy controls were in one cohort, and 1,962 sLOPD probands and 1,279 healthy controls were in another cohort (Supplementary Table 1). PD diagnosis was made according to the Movement Disorders Society (MDS) clinical diagnostic criteria by neurologists with expertise in movement disorders at the Department of Neurology, Xiangya Hospital, and other centers from Parkinson’s Disease & Movement Disorders Multicenter Database and Collaborative Network in China (PD-MDCNC). This study conforms with the World Medical Association Declaration of Helsinki. Each participant signed the written consent. The Ethics Committee of Xiangya Hospital, Central South University, approved the study. It is worth noting that the PD patients harboring the pathogenic or likely pathogenic variants identified in sEOPD or FPD patients were ruled out in this study, according to the principle of our previous study (Zhao et al., 2020).

Gene Selection

We included six TMEM protein family genes to perform the genetic analysis in this study (Supplementary Table 2). TMEM230 was reported to cause autosomal dominant PD; TMEM175, TMEM163, and TMEM229B were found to be risk loci of PD in a large meta-analysis GWAS study; TMEM108 was associated with cognitive progression in PD; TMEM59 was functionally related to PD phenotype. To investigate the role of these six TMEM protein family genes in PD, we conducted the genetic analysis by next-generation sequencing in FPD, sEOPD, sLOPD patients, and healthy controls from a large Chinese cohort.

Sequencing and Bioinformatic Analysis

We sequenced the first cohort with 1,917 sEOPD or FPD patients and 1,652 healthy controls by whole-exome sequencing.
RESULTS

This study mined the WES or WGS data of 3,879 PD patients and 2,931 healthy controls. There were 1,917 sEOPD or FPD patients and 1,652 healthy controls in the first cohort with WES. The sEOPD or FPD patients were at the mean age of 52.22 ± 9.03 years with a mean AAO of 46.31 ± 8.40 years, and the healthy controls were at the mean age of 62.03 ± 12.59 at the time of enrollment. There were 1,962 sLOPD and 1,279 healthy controls for WGS in the second cohort. The mean age for the sLOPD patients and their healthy matching controls was 66.76 ± 7.08 years and 62.32 ± 7.11 years, respectively. In addition, the mean AAO for sLOPD at the enrollment was 61.88 ± 6.93 years (Supplementary Table 1).

A total of 118 rare missense and eight rare LoF variants were found in the WES cohort, whereas 111 rare missense and seven rare LoF variants were detected in the WGS cohort, at the threshold of MAF < 1%. Furthermore, 102 and 94 rare missense variants, and seven and six rare LoF variant were found in the WES and WGS data, respectively, at the threshold of MAF < 0.1% (Supplementary Table 3). On the other hand, for the WES cohort, there were 36 common variants of these six genes included in the single-variant logistic association analysis. In contrast, 1,444 common variants of these six genes included in the WGS cohort. However, they were not significantly associated with PD in our cohorts.

We detected nine missense variants, including six Dmis variants for TMEM230 with MAF < 1% in the WES, whereas 10 missense variants and six Dmis variants were identified in the WGS cohort. At the threshold of MAF < 0.1%, six or seven missense variants were found in the WES or WGS cohort, with four of them being Dmis variants in each cohort (Table 1; Figure 1A). Gene-based burden analysis showed no significant association of these variants with PD. However, three rare Dmis variants, including p.S174F, p.Y165C, and p.V9L were identified in four sporadic PD patients from the WGS cohort but not in control individuals of our two cohorts (Table 2).

We identified 14 rare missense variants, including 12 Dmis variants and one LoF variant for TMEM59 in the WES cohort with MAF < 1%. Gene-based burden analysis showed that the rare missense variants of TMEM59 in the WES cohort were suggestively associated with PD (P = 0.035). When the MAF was limited to less than 0.1%, the association of 13 rare missense variants of TMEM59 with PD became statistically significant (P = 0.007). At the same time, the 11 rare Dmis variants (P = 0.016) and the 12 Dmis plus LoF variants (P = 0.030) of TMEM59 both became suggestively associated with PD in the WES cohort (Table 1; Figure 1B). Furthermore, 24 PD cases carried rare Dmis or LoF variants of TMEM59, so we listed their corresponding clinical manifestations in Supplementary Table 4. All those patients showed good responses to L-dopa treatment, and 10 of 24 cases showed dyskinesia. Besides, 13 and 12 rare non-synonymous variants were identified in the WGS cohort at the threshold of MAF < 1% and 0.1%, respectively. However, the association of these variants with PD was not statistically significant (Table 1; Figure 1B).
we conducted a large case-control study in PD from the Chinese TMEM163, TMEM230, TMEM175, TMEM163, TMEM229B, TMEM108, and TMEM59, in PD, we conducted a large case-control study in PD from the Chinese population, including FPD patients, sporadic early onset, and late-onset PD patients. Moreover, we mined the WES and WGS data, including rare and common variants covering coding, intron, and 2000 bp upstream and downstream of each gene, to explore these six genes. Then we found PD patient-specific rare variants for TMEM230, the significant association of rare missense variants of TMEM59 with PD, and a suggestive association of rare missense variants of TMEM108 with PD. However, no common variant of these genes was found to be significantly associated with PD.

TABLE 1 | Analysis of rare variant burden within targeted genes in Parkinson’s disease.

| Gene       | MAF < 1% | MAF < 0.1% |
|------------|----------|------------|
|            | Missense | Dmis | LoF | LoF + Dmis | Missense | Dmis | LoF | LoF + Dmis |
| TMEM230    | WES cohort | 9 (0.147) | 6 (0.874) | - | 6 (0.874) | 6 (0.648) | 4 (0.475) | - | 4 (0.475) |
| WGS cohort | 10 (0.755) | 6 (0.355) | - | 6 (0.355) | 7 (0.829) | 4 (0.456) | - | 4 (0.456) |
| TMEM59     | WES cohort | 14 (0.035) | 12 (0.069) | 1 (0.635) | 13 (0.071) | 13 (0.007) | 11 (0.016) | 1 (0.635) | 12 (0.030) |
| WGS cohort | 12 (0.582) | 11 (0.420) | 1 (0.125) | 12 (0.191) | 11 (0.383) | 10 (0.216) | 1 (0.125) | 11 (0.071) |
| TMEM108    | WES cohort | 27 (0.259) | 17 (0.444) | - | 17 (0.444) | 24 (0.691) | 17 (0.444) | - | 17 (0.444) |
| WGS cohort | 27 (0.071) | 12 (0.526) | 1 (0.413) | 13 (0.551) | 24 (0.014) | 12 (0.526) | 1 (0.413) | 13 (0.551) |
| TMEM163    | WES cohort | 11 (0.511) | 10 (0.510) | - | 10 (0.510) | 11 (0.511) | 10 (0.510) | - | 10 (0.510) |
| WGS cohort | 8 (0.689) | 8 (0.689) | - | 8 (0.689) | 7 (0.603) | 7 (0.603) | - | 7 (0.603) |
| TMEM175    | WES cohort | 51 (0.151) | 29 (0.582) | 7 (0.618) | 36 (0.601) | 42 (0.284) | 25 (0.729) | 6 (0.492) | 31 (0.820) |
| WGS cohort | 49 (0.396) | 25 (0.646) | 4 (0.182) | 29 (0.441) | 40 (0.299) | 21 (0.630) | 3 (0.095) | 24 (0.343) |
| TMEM229B   | WES cohort | 6 (0.403) | 5 (0.442) | - | 5 (0.442) | 6 (0.403) | 5 (0.442) | - | 5 (0.442) |
| WGS cohort | 5 (0.764) | 4 (0.830) | 1 (0.582) | 5 (0.865) | 5 (0.764) | 4 (0.830) | 1 (0.582) | 5 (0.865) |

Data were show as Number of Variants (SKAT-O P-value). MAF, minor allele frequency; Dmis, damaging missense variant (predicted by CADD < 12.37); LoF, loss of function variant. Bold text indicates a statistically significant association with a p-value less than 0.05.

DISCUSSION

To systematically investigate the genetic burden of six TMEM protein family genes, including TMEM230, TMEM175, TMEM163, TMEM229B, TMEM108, and TMEM59, in PD, we conducted a large case-control study in PD from the Chinese population, including FPD patients, sporadic early onset, and late-onset PD patients. Moreover, we mined the WES and WGS data, including rare and common variants covering coding, intron, and 2000 bp upstream and downstream of each gene, to explore these six genes. Then we found PD patient-specific rare variants for TMEM230, the significant association of rare missense variants of TMEM59 with PD, and a suggestive association of rare missense variants of TMEM108 with PD. However, no common variant of these genes was found to be significantly associated with PD.

We identified several PD-specific rare non-synonymous variants for TMEM230, but no significant association was found between this gene with PD. The p.Y165C variant was previously identified in a Taiwanese sporadic PD patient, while p.S174F and p.V9L variants have not previously been reported in PD patients or healthy controls (Quadri et al., 2017). According to the American College of Medical Genetics and Genomics (ACMG) guidelines, these variants were predicted to be uncertain significance due to a lack of supporting evidence. Hence, verifications of these variants in more studies and related functional investigations are warranted to confirm their pathogenicity in the future. TMEM230 mutations were reported to cause autosomal dominant PD with the potential mechanism of impairing synaptic vesicle trafficking, disrupting mitochonaria transport, and inducing apoptotic cell death (Deng et al., 2016; Wang et al., 2020, 2021a). Of note, TMEM230 protein is present in SNCA-positive Lewy bodies and Lewy neurites, indicating its potentially vital role in PD pathogenesis (Deng et al., 2016). There have been several subsequent verifications of the pathogenicity of the TMEM230 gene in PD. However, many of them have not been verified (Yan et al., 2017; Wang et al., 2021b), which may be due to the relatively small contribution of the TMEM230 gene in PD patients. In our recent large-cohort study, we identified one pathogenic variant (c.429delT/p.P144Qfs*2) of TMEM230, supporting the pathogenic role of TMEM230 in PD (Zhao et al., 2020).
FIGURE 1 | Schematic diagram of six PD-related transmembrane (TMEM) protein family genes. Schematic diagram showing the transmembrane regions of six PD-related TMEM protein family genes and the rare damaging missense and loss-of-function variants of TMEM230 (A), TMEM59 (B), TMEM108 (C), TMEM163 (D), TMEM175 (E), and TMEM229B (F) in both cohorts.

Then, we explored the role of common and rare variants in the other five TMEM family genes located within known PD risk loci. This study is the first to report that rare variants of TMEM59 were significantly enriched in FPD and sEOPD patients, indicating TMEM59 might play an essential role in PD. TMEM59 has differentially expressed in substantia nigra pars compacta astrocytes in a PD mouse model (Khan et al., 2022). Besides, TMEM59 interacted with TREM2, which was also related to PD, and regulated microglia function (Liu et al., 2020). TMEM59 was found to mediate PD-related pathways, such as autophagy and dopamine system dysfunction (Boada-Romero et al., 2013; Liu et al., 2017); moreover, overexpression of TMEM59 in a Drosophila PD model ameliorated the phenotype of shortened lifespan, impaired locomotor activity, and loss of dopaminergic neurons by degrading a-synuclein (Zhang et al., 2018). Combining all the evidence, we supported that the rare variants of TMEM59 might predictably increase the risk of PD. Since this is the first study to report the association of TMEM59 with PD, genetic analysis studies for TMEM59 in PD from larger cohorts and different populations are warranted to verify our findings.

We also found the suggestive association of TMEM108 with PD. TMEM108 was reported to be enriched in the dentate gyrus and involved in regulating spine development and glutamatergic activity in the granule neurons of the dentate gyrus (Jiao et al., 2017). Moreover, TMEM108 was found to play a vital role in adult neurogenesis in the dentate gyrus (Yu et al., 2019). A large longitudinal study showed that TMEM108 variant rs138073281 was associated with cognitive progression in PD (Zhang et al., 2021). However, no association of the TMEM108 gene with PD was found in previous studies, and no functional study has been conducted to investigate the
TABLE 2 | Parkinson’s disease (PD) patient specific variants of TMEM230.

| Gene       | Position (hg19) | Ref  | Alt  | NM number | AAChange | Consequence | gnomAD_genome_EAS | gnomAD_exome_EAS | ExAC_EAS | CADD | WES cohort | WGS cohort |
|------------|-----------------|------|------|-----------|----------|-------------|-------------------|-------------------|-----------|------|------------|------------|
| TMEM230    | 20:5081468      | G    | A    | NM_001009923 | c.521C>T | p.S174F | Missense | –                 | –                 | 0.0001    | 21.1 | 22.7       | 31         |
| TMEM230    | 20:5081495      | T    | C    | NM_001009923 | c.494A>G | p.Y165C | Missense | 0.0002            | -                  | -         | -     | -           | -          |
| TMEM230    | 20:5093650      | C    | G    | NM_001009923 | c.25G>C | p.V9L  | Missense | –                 | –                 | 0.0002    | 22.7 | 22.7       | 22.7       |

Variants minor allele frequencies from gnomAD_genome_EAS, gnomAD_exome_EAS, and ExAC_EAS. AAChange, amino acid change.

Our study identified several rare non-synonymous TMEM175, TMEM163, and TMEM229B variants, but no association of these genes with PD was found. TMEM175 is a component of a lysosomal K⁺ channel, and its deficiency results in impaired lysosomal and mitochondrial function (Jinn et al., 2017; Pergel et al., 2021). Variants of TMEM175 have been identified to be associated with PD in a GWAS study, indicating its role in PD (Nalls et al., 2014). Further studies found that both rare and common variants of TMEM175 were correlated to PD (Hopfner et al., 2020; Rudakou et al., 2021), and different common variants of TMEM175 may have opposite influences on stress-induced damage and α-synuclein accumulation in neurons, which complicated the specific role of TMEM175 in PD (Wie et al., 2021). It may explain why we could not find the association of TMEM175 with PD at the gene level.

TMEM163 is a zinc efflux transporter and belongs to the cation diffusion facilitator (CDF) protein family (Sanchez et al., 2019; Styrpejko and Cuajungco, 2021). The mutations of CDF family member, SLC30A10, were reported to cause parkinsonism (Quadri et al., 2012). TMEM163 is highly expressed in the cortex and cerebellum, and its expression was positively associated with PD risk (Cuajungco et al., 2014; Kia et al., 2021). The loci around TMEM163 was reported to associate with PD in GWAS studies (Nalls et al., 2014; Bandrés-Ciga et al., 2016), but our study did not verify the association between TMEM163 with PD. Hence further studies with larger sample sizes and different ethnic populations are needed.

TMEM229B is a novel protein with unclear biological function. We did not find the association of TMEM229B with PD, and the association of TMEM229B locus with PD was controversial in previous studies (Nalls et al., 2014; Chang et al., 2017). So, TMEM229B may not play a vital role in PD, and functional studies for TMEM229B and its mutants are warranted to illustrate its role in PD better.

In addition, several studies investigated the gene expression profile in the human postmortem substantia nigra of PD patients, but the expression level of the six genes investigated in our study was not significantly different between PD and controls (Kelly et al., 2019; Nido et al., 2020). We also searched the six genes in BrainEXP-NPD, a website showing expression profiling in human brains for six neuropsychiatric disorders, including PD. No expression level for TMEM230 was found in any brain region on the website. No significant difference between PD and controls for other five genes regarding the expression level in different brain regions was found (Supplementary Figure 3; Supplementary Table 5).

Our study has several limitations. Firstly, the statistical power of the analysis in our study was limited, even though we had a large case-control cohort. Secondly, non-coding variants cannot be detected by WES, so these variants were not analyzed in our sEOPD and FPD patients. Finally, our findings for role of TMEM108 in PD pathogenesis. Further research for TMEM108 in PD should focus on these genetic analysis studies and functional investigations.
the association of TMEM family genes with PD were only from genetic analysis and have not been further verified by functional studies.

In conclusion, we performed a large case-control study to systematically investigate the role of PD-related TMEM protein family genes in PD using WES and WGS with gene-based and allele-based burden analysis. We found three PD patient-specific variants of TMEM230, which need further verification for pathogenicity. Moreover, we identified the significant association of TMEM59 with FPD and eEOPD, and a suggestively significant association of TMEM108 with sLOPD. However, we did not find any significant association of common variants of TMEM family genes with PD. Our study shed light on the gene burden of TMEM protein family genes in PD, and furthermore extensive genetic analysis studies and functional experiments for these genes are warranted.

DATA AVAILABILITY STATEMENT

According to national legislation/guidelines, specifically the Administrative Regulations of the China on Human Genetic Resources (http://www.gov.cn/zhengce/content/2019-06/10/content_5398829.htm, http://english.www.gov.cn/policies/latest_releases/2019/06/10/content_281476708945462.htm), no additional raw data is available at this time. Data of this project can be accessed after an approval application to the China National GeneBank (CNGB) (https://db.cngb.org/cnsa/). Please refer to https://db.cngb.org/ or email: CNGBdb@cngb.org for detailed application guidance. The accession code CNP0003134 should be included in the application.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of Xiangya Hospital of Central South University in China. The patients/participants provided their written informed consent to participate in this study.

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AUTHOR CONTRIBUTIONS

YZ: design, methodology, and writing – original draft. KZ: design, execution, and writing – original draft. HP: methodology and writing. YW: blood samples collection and DNA extraction. XZ and QX: patients enrollment. YX: blood samples collection. QS: clinical data collection. JT: DNA extraction and writing – review. XY and JG: patients enrollment and clinical data collection. JL: methodology and writing – review. BT: conception and patients enrollment. ZL: design, conception, writing – review and editing, and supervision. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2022.889057/full#supplementary-material

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