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Review

The Role of *TMEM230* Gene in Parkinson's Disease

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Abstract. Parkinson's disease (PD) is a common neurodegenerative disease whose pathogenesis remains unknown. *TMEM230* gene, encoding a transmembrane protein in secretory and recycling vesicle, has been recently identified as a novel disease-causing gene of autosomal dominant PD with Lewy pathology and typical clinical symptoms. Although its mutation and variants seem to be rare in PD patients, functional studies have indicated that TMEM230 protein probably plays an important role in secretory and recycling pathway and may be involved in Lewy pathological mechanism. Here we summarize current genetic and functional reports about *TMEM230* and focus on its relation with PD.

Keywords: Genetics, Lewy bodies, Parkinson's disease, *TMEM230*

INTRODUCTION

Parkinson's disease (PD) (OMIM 168600) is the second most common neurodegenerative disease after Alzheimer's disease (AD), with incidence rate of 0.014% per year in total population and 0.16% per year in people over the age of 65 in high-income countries [1]. The typical clinical symptoms of PD include progressive bradykinesia in combination with rest tremor, rigidity, postural instability, and numerous non-motor symptoms [2, 3]. The loss of dopaminergic neurons in the substantia nigra pars compacta (SNpc) and the Lewy pathology including Lewy bodies and Lewy neurites have been identified as pathological features of PD [2]. PD was once thought to be a nongenetic disease and mainly caused by environmental factors, but as a result of advances in genetic research, this notion has gradually changed and there is growing recognition of genetic mechanisms in the pathogenesis of the disease [4]. To date, at least 23 disease-causing loci and 19 genes have been reported in monogenic PD pedigree, though the list of risk-associated genes is steadily growing [3, 5]. PD is now viewed as a complex neurodegenerative disorder resulting from genetic, environmental and other, yet unknown factors [4].

Unlike sporadic PD which accounts for about 90% of total PD cases, a considerable number of patients with monogenic form of PD have been found to have young-onset of symptoms, atypical clinical features, and lack Lewy pathology [1, 6, 7]. Only a few of PD causing mutations had been reported to be related to clinically typical PD with Lewy pathology [6].

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Recently, Deng et al. reported that transmembrane protein 230 gene (*TMEM230*), may play a pathogenic role in a rare autosomal dominant PD (ADPD) with typical motor features and Lewy body pathology [8]. This finding provides new insights into the pathogenesis of PD-related neurodegeneration. The primary aim of this article is to review current genetic and functional data about *TMEM230* and suggest how the discovery of this disease-causing gene can lead to pathogenesis-targeted therapy for PD.

PARK21 AND THE *TMEM230* GENE

In 2014, a large Canadian Mennonite family with a PD phenotype was reported with c.2564A > G (p.N855S) variant in the *DNAJC13* gene, located on chromosome 3q22 [9]. But this variant did not fully cosegregate with the disease as demonstrated by its presence in one unaffected individual died at the age of 87 years and absence in two PD cases and one parkinsonism case with progressive supranuclear palsy pathology, who belong to different branches and couldn't be explained as sporadic cases because extremely low possibility ($<10^{-3}$) [8]. The causal gene locus was termed as *PARK21* (OMIM 616361) in Online Mendelian Inheritance in Man (OMIM) according to the chronology of identification of the disease-causing gene loci. However, in 2016, Deng and colleagues proposed that *TMEM230* c.422G > T (p.R141L) mutation, mapped to chromosome 20p13-p12.3, was the pathogenic mutation of PD in the same family with 13 available patients [8]. Though a *TMEM230* mutation–freed patient with atypical parkinsonism phenotype which was still mild after 23 years of disease progression was evidenced, the *TMEM230* mutation was the best genetic explanation for PD in this family under current known data, which may be explained by other conditions such as environmental or inconsistent genetic factors [10, 11]. The Canadian Mennonite family of mixed European ancestry included 14 enrolled family members with ADPD, mean age at onset of 67.0 years, and typical presentation of late-onset, levodopa-responsive PD [8, 12]. These patients had rigidity, bradykinesia, and rest tremor (in 57% patients), and dementia was present in 21% of cases [13]. Additionally, neuronal loss in substantia nigra and nucleus basalis, and Lewy bodies were found in brainstem at autopsies including α-synuclein stains, performed in three of cases [10, 13].

The *TMEM230* gene, also called as chromosome 20 open reading frame 30 (*C20orf30)*, covers a genomic region of about 13.2 kb with five exons [14]. *TMEM230* mRNA expression is high in many tissues, including several regions of nervous system, such as midbrain, cerebellum, neocortex and spinal cord [8, 15]. Its four mRNA transcriptional variants encode two protein isoforms: the isoform-1 of 183 amino acids and the isoform-2 of 120 amino acids [8]. The isoform-2 accounts for more than 95% of total protein isoforms in humans, and presents alone in species spanning zebrafish to most mammals [8]. The highly conserved amino acid sequence of isoform-2 contains two transmembrane segments, with N-terminal and C-terminal regions exposing to the cytosol [8]. There is no other known protein with sequence identical or similar to TMEM230.

TMEM230 VARIANTS IDENTIFIED IN PD

Three other PD-associated *TMEM230* variants, including two variants (p.Y92C and p.*184Wext*5) which were found through analyzing 832 North American PD cases and one variant (p.*184PGext*5) which were detected by 9 PD cases of 7 families from China were reported in original Deng et al.'s study [8]. The asymptomatic carriers with p.Y92C and p.*184PGext*5 variants suggested incomplete penetrance, similar to *LRRK2* p.G2019S variant [8, 16].

Subsequently, two novel variants p.G16W and p.M64V, and six known missense variants including p.Y106H (rs746223968), p.I162V (rs368707598), p.R68H (rs780460399), p.Y165C (rs758033952), p.M1? (rs768390203) and p.A110T were detected only in PD patients [17–22], though many other studies failed to find PD-related pathogenic variant in *TMEM230* gene (Table 1) [23–31]. Because of these variants only observed in PD patients, and the incompletion of population genetic databases (e.g., ExAC and gnomAD) caused by the age-dependent and incomplete penetrance of the disorder, these variants probably exert a disease-causing or susceptibility role of PD. In 15 studies published, approximately 0.28% PD patients were found to harbor potential PD-related variants with full detection information of coding regions of the *TMEM230* gene (Table 1) [8, 17–30]. Interestingly, most of the PD-related mutations and variants of *TMEM230* gene detected to date were in the highly conserved sequence of isoform-2, and about half of

Table 1
Mutation/variants associated with PD detected in coding region of the *TMEM230* gene

Report	Geographic distribution/ Ethnic background	Number of patients with PD [controls]	Detection region	Nucleotide change detected	Location	Amino acid change	Zygosity	Frequency in cases	MAF (ExAC)	MAF (gnomAD)
Deng et al. 2016 [8]	Canada	1 PD family	Exome	c.422G>T	Exon 5	p.R141L	Het	12/13	–	8.963×10^{-6} (European Non-Finnish)
	Northern America	433 FPD and 399 SPD [1238]	Coding regions	c.551A>G	Exon 5	p.*184Wext*5	Het	1/433 in FPD	–	–
	China	225 FPD and 349 SPD [528]	Coding regions	c.550_552del TAGins CCCGGG	Exon 5	p.*184PGext*5	5 Hom and 4 Het	9/225 in FPD	–	–
Giri et al. 2017 [17]	Caucasian	1450 PD [2267]	Exome	c.316T>C	Exon 4	p.Y106H	Het	1/1450	1.501×10^{-5} (European Non-Finnish)	1.798×10^{-5} (European Non-Finnish)
				c.484A>G	Exon 5	p.I162V	Het	1/1450	–	1.578×10^{-5} (European Non-Finnish)
	Caucasian	86 FPD [10]	Exome	–	–	–	–	–	–	–
Baumann et al. 2017 [18]	Europe	53 PD cases	Exome	c.203G>A	Exon 3	p.R68H	Het	1/53	4.548×10^{-5} (European Non-Finnish)	5.541×10^{-5} (European Non-Finnish)
Quadri et al. 2017 [19]	Taiwan	98 FPD and 717 SPD [417]	Exon 5	c.494A>G	Exon 5	p.Y165C	Het	1/717 in SPD	1.156×10^{-4} (East Asian)	2.319×10^{-4} (East Asian)
	Dutch	31 FPD and 59 SPD	Exon 5	–	–	–	–	–	–	–
	Caucasian	266 PD probands	Coding regions	c.1A>G	Exon 1	p.M1?	Het	1/226	7.06×10^{-5} (Total)	1.056×10^{-4} (European Non-Finnish)
Yang et al. 2017 [20]	Southwestern China	11 FPD and 355 SPD	Exons and exon-intron boundaries	c.46G>T	Exon 1	p.G16W	Het	1/355 in SPD	–	–
				c.328G>A	Exon 4	p.A110T	Het	2/355 in SPD	–	1.444×10^{-5} (Total)
Wei et al. 2018 [21]	Southwestern China	120 FPD [650]	Exons and exon-intron boundaries	c.46G>T	Exon 1	p.G16W	Het	1/120	–	–
Tejera-Parrado et al. 2018 [22]	Southern Spanish	148 FPD and 555 SPD [695]	Exons and exon-intron boundaries	c.190A>G	Exon 3	p.M64V	–	1/703	–	–

(*Continued*)

Table 1
(*Continued*)

Report	Geographic distribution/ Ethnic background	Number of patients with PD [controls]	Detection region	Nucleotide change detected	Location	Amino acid change	Zygosity	Frequency in cases	MAF (ExAC)	MAF (gnomAD)
Yan et al. 2017 [23]	China	192 FPD and 1043 SPD [1252]	Exons and exon-intron boundaries	–	–	–	–	0/1235	–	–
Wu et al. 2017 [24]	Eastern China	122 PD probands	Coding regions	–	–	–	–	0/122	–	–
Fan et al. 2017 [25]	Taiwan	180 FPD	Exons and exon-intron boundaries	–	–	–	–	0/180	–	–
		500 SPD [992]	c.68G>A, c.275A>G, c.422G>T and c.551A>G	–	–	–	–	0/500	–	–
He et al. 2017 [26]	China	207 FPD and 207 SPD [400]	Stop codon region	–	–	–	–	0/414	–	–
Shi et al. 2017 [27]	China	550 SPD [560]	Coding regions and exon-intron boundaries	–	–	–	–	0/550	–	–
Ma et al. 2017 [28]	Singapore	99 PD [99]	Coding regions	–	–	–	–	0/99	–	–
Buongarzone et al. 2017 [29]	Italy	86 FPD	Exons	–	–	–	–	0/86	–	–
Conedera et al. 2018 [30]	Japan	182 PD	Coding regions and exon-intron boundaries	–	–	–	–	0/182	–	–
Combined	All world	6904 PD [7299]	Coding regions	Missense mutation/ variants only in PD	Coding regions	Missense mutation/ variants only in PD	All	19/6115 (2.752×10^{-3})	–	–

FPD, familial PD; SPD, sporadic PD; Het, heterozygous; Hom, homozygous; MAF, minor allele frequency; ExAC, Exome Aggregation Consortium database; gnomAD, Genome Aggregation Database. Data in reference 31 was not extracted due to the lack of detailed information [31].

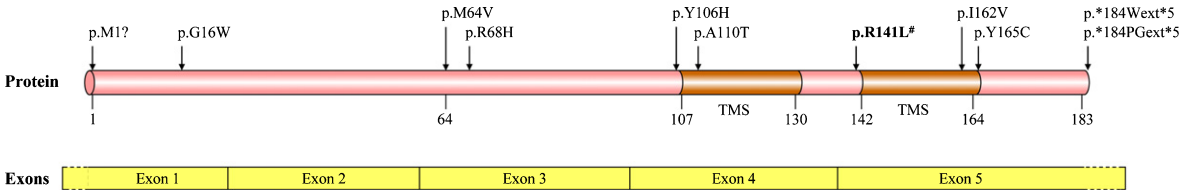

Fig. 1. Missense mutation and variants associated with PD detected in *TMEM230* coding regions. #The initial mutation detected in a large family with autosomal dominant and Lewy pathology confirmed PD. TMS, transmembrane segment.

these were in the regions around two transmembrane segments of this protein. This suggests that abnormal function of transmembrane segments in TMEM230 protein plays an important role in neurodegeneration (Fig. 1). Additionally, non-coding variants c.*746G > A (rs45610034), c.68 + 182G > A (rs149865687) and c.*161C > T were reported to be associated with PD risk or age at onset, though none of them passed the Bonferroni correction test and a large sample size will be needed to confirm the association [27, 31].

THE POTENTIAL PATHOLOGICAL MECHANISM OF *TMEM230* IN PD

The TMEM230 protein is localized to vesicle structures in human SH-SY5Y cells, and the mouse ortholog distributes to the same subcelluar structures in brain neurons including dopaminergic neurons in the substantia nigra [8]. These vesicle structures predominantly co-localize with STX6, a protein mainly enriched in the *trans*-Golgi network (TGN), and with vesicular monoamine transporter type 2 (VMAT2), vacuolar protein sorting-35 (VPS35), Rab5a and Rab11a proteins, suggesting that TMEM230-positive vesicles are involved in the function of synaptic vesicles and recycling of endosomes [8]. Thus, TMEM230 appears to play an important role in many cellular functions, including synaptic vesicles trafficking, retromer trafficking, secretory autophagy and Golgi-derived vesicle secretion. As such, it shares in pathogenic pathways implicated other PD-causing genes, such as the *SNCA*, *LRRK2*, *VPS35* and *PINK1* [32].

Interaction with SNCA

Mutations in synuclein alpha (*SNCA*) gene, which encodes α-synuclein protein, the key component of Lewy body inclusions, have resulted in ADPD [6, 33]. As the first PD-related gene identified and labeled *PARK1*, the typical PD clinical phenotype of patients was also associated with characteristic Lewy body pathology [6, 33]. Although the physiological function of α-synuclein protein remains enigmatic, mounting evidence suggests a regulatory function in synapse, such as vesicle trafficking, synaptic vesicle pool maintenance and neurotransmitter release [33]. TMEM230 protein was detected in α-synuclein-positive Lewy bodies and Lewy neurites both in sporadic PD and dementia with Lewy bodies (DLB) cases [8]. Similar to α-synuclein, the TMEM230 protein was observed in the synaptic vesicle pool region in the rat brain neuron presynapse [8, 34]. Expression of PD-related *TMEM230* variants resulted in significantly slower movement of synaptic vesicles and increased α-synuclein protein level compared to wild-type protein possibly due to impairment of autophagy-mediated clearance [8, 32]. In addition, the Rab8a protein whose function is connected with TMEM230, also interacts with α-synuclein, and its overexpression reduces α-synuclein-induced toxicity *in vitro* and improves α-synuclein-induced behavioral defects in fruit flies [32, 35]. Intriguingly, *tmem230a*, the zebrafish ortholog of human *TMEM230*, could affect angiogenic blood vessel growth though Delta/Notch signaling pathway [36], which may be involved in neurodegenerative disease and reduced by overexpressive or mutant α-synuclein protein [37, 38].

Interaction with LRRK2

Leucine-rich repeat kinase 2 (*LRRK2*) mutations represent the most common genetic cause of ADPD and nearly half of *LRRK2*-related PD cases had Lewy bodies [6, 39]. LRRK2 protein has been found to phosphorylate several members of Rab family which plays a key role in all forms of intracellular vesicular trafficking [40]. The Rab8a protein is one of substrates of LRRK2, and its phosphorylation may be increased 2-3 fold by *LRRK2* p.G2019S mutation

[40]. Thus LRRK2 kinase activity-dependent phosphorylation may lead to deficits in cell polarization, neurite outgrowth and directed migration [41]. The Rab8a-mediated secretory vesicle and retromer trafficking were impaired when TMEM230 lost function, similar to lack of LRRK2 protein [32]. This suggests that TMEM230 and LRRK2 may share Rab8a-mediated vesicle trafficking pathway in development of PD and Lewy pathology. Additionally, Notch signaling pathway which may be associated with TMEM230 was also regulated by LRRK2 through endosomal pathway [36, 42].

Interaction with VPS35

VPS35, a causal gene linked to ADPD, encodes a subunit of retromer complex [43]. The TMEM230 protein partially co-localizes with VPS35 protein and both regulate retromer trafficking function [8]. The expression of *TMEM230*-R141L mutant protein changed VPS35 and itself from perinuclear to punctate cytoplasmic distribution [32]. However, only one *VPS35*-PD autopsy report showed no immunostaining for α-synuclein and there was no neuronal loss or intraneuronal inclusions in the cortex and basal ganglia; the substantia nigra tissue was not available [44]. Further studies are warranted to clarify the similarities and differences between *TMEM230* and *VPS35* in pathogenesis of PD.

Interaction with PINK1

Many mutations of phosphatase and tensin homolog-induced putative kinase 1 (*PINK1*) gene have been identified in different families with autosomal recessive PD [45]. One early-onset PD patient with two compound heterozygous *PINK1* mutations was reported to have neuronal loss and Lewy pathology in the SNpc [46]. This gene encodes PINK1 protein, a serine/threonine protein kinase whose activation caused phosphorylation of Rab8a at residue of serine 111 and significantly impaired Rab8a activation [47]. Further studies of Rab8a-involved pathway may help to elucidate the association between *TMEM230* and *PINK1* in pathogenesis of PD.

In summary, there is a growing body of evidence that TMEM230 protein and its interaction with Rab8a, SNCA, LRRK2 and PINK1 may lead to PD-related neurodegeneration (Fig. 2).

THE POTENTIAL ROLE OF *TMEM230* IN OTHER DISEASES

The *TMEM230* gene may be potentially related with other neurodegenerative diseases with Lewy pathology such as DLB and AD, multiple system atrophy (MSA) [48, 49]. In AD patients, the TMEM230 protein was increased in hippocampal neurons and aggregated in granulovacuolar and dystrophic neurites, two prominent pathological features of AD [50]. No MSA-risk variants have been found in the *TMEM230* gene in 110 cases of MSA [51]. Furthermore, He et al. did not find stop codon variants in the *TMEM230* gene in 200 Chinese patients with essential tremor [26].

CONCLUSION

Even after exciting acceleration of PD research during the past 50 years since the discovery of levodopa, the pathogenesis of this complex disorder remains enigmatic [2]. Notable discoveries, especially the advances in genetics of PD in recent 20 years have greatly changed our understanding on etiology and pathogenesis of PD [1]. It seems increasingly clear that PD is a highly complex neurological disease with heterogeneous clinical presentation, variable pathological features, and multifactorial causes [52]. Reveal of the association of phenotype-genotype, especially analysis of protein interaction network involving in Lewy body-confirmed PD-related genes, which highly mimics idiopathic PD, will help to understand the main underlying pathogenic mechanism of this complex disorder [52]. But only a few of PD-related mutations have been associated to PD with Lewy body pathology which remains a core feature of most PD cases, without precise mechanism known [1, 6].

Only a few PD-related *TMEM230* variants could not cover up its significance in discovering pathogenesis of PD. Copy number variations including duplication and triplication in the *TMEM230* gene, perhaps share a similar mechanism resulting in PD with dementia as the *SNCA* gene [53], as well as its epigenetic or non-coding regulatory factors, cannot be ignored in future studies. The application of quantitative PCR, digital PCR, whole genome sequencing and epigenetic strategies may help to identify more pathogenic mechanisms involving *TMEM230* in PD, especially phenotype with dementia and other neurodegenerative disorders. Future research should

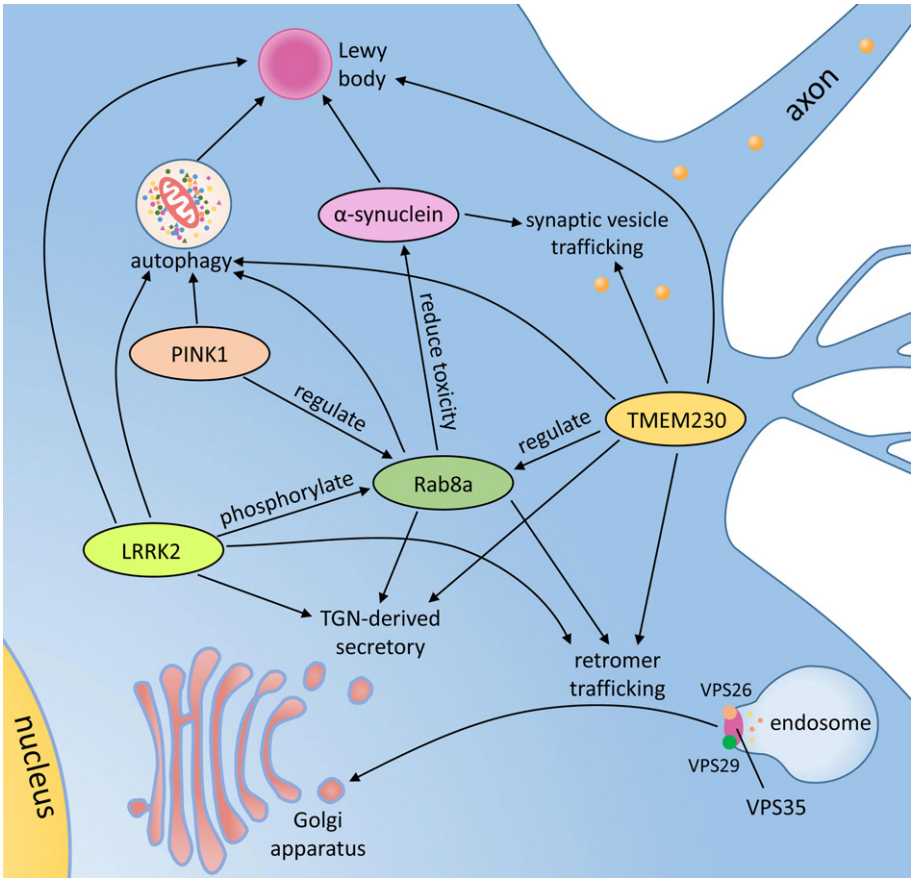

Fig. 2. The potential pathological mechanisms and associated proteins of TMEM230. TGN, *trans*-Golgi network; TMEM230, transmembrane protein 230; PINK1, phosphatase and tensin homolog-induced putative kinase 1; LRRK2, leucine-rich repeat kinase 2; VPS35, vacuolar protein sorting-35.

focus on development of *TMEM230* genetic animal models to better understand the role of *TMEM230* in pathogenesis of neurodegeneration. These studies may also provide insight into potential treatment and prevention of PD and related disorders.

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CONFLICT OF INTEREST

The authors have no conflict of interest to report.

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