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CASE REPORT

Loss-of-Function Variant in the *SMPD1* Gene in Progressive Supranuclear Palsy-Richardson Syndrome Patients of Chinese Ancestry

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ABSTRACT

Lysosomal dysfunction plays an important role in neurodegenerative diseases, including Parkinson's disease (PD) and possibly Parkinson-plus syndromes such as progressive supranuclear palsy (PSP). This role is exemplified by the involvement of variants in the *GBA1* gene, which results in a deficiency of the lysosomal enzyme glucocerebrosidase and is the most frequently identified genetic factor underlying PD worldwide. Pathogenic variants in the *SMPD1* gene are a recessive cause of Niemann–Pick disease types A and B. Here, we provide the first report on an association between a loss-of-function variant in the *SMPD1* gene present in a heterozygous state (p.Pro332Arg/p.P332R, which is known to result in reduced lysosomal acid sphingomyelinase activity), with PSP-Richardson syndrome in three unrelated patients of Chinese ancestry.

Keywords Progressive supranuclear palsy; *SMPD1*; Genetics; *GBA1*; Lysosomal; Sphingolipid; Acid sphingomyelinase.

INTRODUCTION

Progressive supranuclear palsy (PSP) is a phenotypically diverse clinicopathologic entity that is classically characterized clinically by the early onset of postural instability, supranuclear vertical gaze palsy, dysarthria, dysphagia, and a "subcortical"

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pattern of cognitive impairment.[1,2] PSP has several clinical subtypes, with Richardson syndrome (PSP-RS) being the most common and having the highest specificity for PSP pathology.[1,2]

Although PSP is generally regarded as sporadic, there have long been reports of familial clustering with other cases of parkinsonism,[3] and there is increasing evidence implicating a role of genetic factors in both the sporadic and familial forms of PSP.[1,2,4,5] To date, more than 10 genes have been reported to be potentially associated with PSP, with some genetic overlap observed, particularly between PSP and frontotemporal dementia (FTD) and Parkinson's disease (PD).[1,2,4,5] These shared genes include *MAPT*,[1,2,6] *LRRK2*,[1,2,7] and possibly *GBA1*.[4,5,8] Heterozygous *GBA1* variants are the most common genetic risk factor for PD worldwide, with increased odds ratios (ORs, ~1.4–30×) for the disease;[9] moreover, there are emerging reports suggesting their involvement in PSP.[4,5,8]

Similar to *GBA1*, which encodes the lysosomal enzyme glucocerebrosidase, homozygous loss-of-function variants in *SMPD1* resulting in deficiency of the lysosomal enzyme acid sphingomyelinase (ASMase) also cause recessive lysosomal lipid storage disorders (Gaucher's disease and Niemann–Pick disease type A/B).[9] Niemann–Pick disease type C, another closely related autosomal recessive lipid storage disorder, presents with adult-onset neurological manifestations, including parkinsonism, supranuclear gaze palsy, and cognitive-behavioral deficits and is recognized as a PSP mimic.[10]

An association between heterozygous *SMPD1* variants and PD was first recognized a decade ago[9] due to the founder mutation p.Leu302Pro/p.L302P (also known as p.Leu304Pro/p.L304P) present in ~1% of Ashkenazi Jewish patients.[11] A large East Asian (Chinese and Korean) study subsequently identified *SMPD1* as one of only two genes with exome-wide significance for association with PD (the other gene was *GBA1*).[12] In both *GBA1*- and *SMPD1*-related PD, reduced enzyme activity leads to substrate accumulation, dysfunction of lysosomes (the main organelles responsible for α-synuclein degradation), and aggregation of α-synuclein (one of the main pathological hallmarks of PD) in cellular models.[11]

Recently, investigators have also reported reduced ASMase activity in patients with multiple system atrophy (MSA) and dementia with Lewy bodies (DLB), two Parkinson-plus syndromes.[13] Here, we report classic cases of PSP in Chinese patients found to harbor a deleterious loss-of-function *SMPD1* variant, p.Pro332Arg/p.P332R. To our knowledge, this is the first report linking *SMPD1* with PSP.

CASE REPORT

A woman of Chinese ancestry aged 67 years was first seen at the University of Malaya in July 2017. The patient presented with left limb "weakness" for six months. Prior to seeing us, she had consulted an outside neurologist who diagnosed PD and prescribed low-dose levodopa, which showed no clear benefit. She had been previously well and was a homemaker with no history of unusual environmental exposures, as per the Mini Environmental Risk Questionnaire for PD Patients Baseline questionnaire. On examination, mild left-sided parkinsonian features (bradykinesia and rigidity) were observed. Brain magnetic resonance imaging (MRI) showed moderate generalized cerebral atrophy with no hummingbird sign.

One year later, the patient exhibited imbalance with a tendency to fall. A "staring" appearance was observed, with slowing of vertical eye movements, slurring of speech, and a "gunslinger" pose of the left arm when walking. The patient remained ambulatory and walked several kilometers daily for exercise. She had a significant fall in May 2019, requiring stitches to her face. A subjective symptomatic benefit (improved strength) was reported with an increase in the levodopa dosage and the addition of amantadine. Her PSP Clinical Deficits Scale score was 5/21.[2,5]

In March 2021, another serious fall while getting out of bed due to loss of balance resulted in a shoulder injury requiring surgery. The patient exhibited a moderate restriction of downgaze. Repeated brain MRI revealed a mild hummingbird sign (Supplementary Figure 1 in the online-only Data Supplement). In April 2022, both upward and downward gazes were restricted, overcome with the doll's head maneuver, with a preserved horizontal gaze. Rigidity was severe in the neck and mild in the upper limbs. The applause sign was positive. In 2023, her swallowing worsened with coughing when drinking, and the majority of her words were unintelligible. Right eye abduction also became limited. She scored 29/124 on the Cortical Basal Ganglia Functional Scale (26/56 for Part A, 3/68 for Part B).[2]

The levodopa dosage was gradually increased to 750 mg (combined with benserazide) with 300 mg amantadine in three divided doses daily. The patient and her husband were very enthusiastic to try all available treatments and even self-purchased ambroxol. Opicapone 50 mg/d and safinamide 50 mg/d were administered off-label without clear benefit. The patient never developed any levodopa-induced dyskinesias or visual or auditory hallucinations. During the most recent review in September 2023 (Supplementary Video 1 in the online-only Data Supplement), the husband reported that she would "dream, and joke and laugh in her sleep" without aggressive movements; it was unclear whether these symptoms represented rapid eye movement sleep behavior disorder symptoms. Her cognition was

Table 1. Clinicodemographic features of progressive supranuclear palsy (PSP) cases with the *SMPD1* variant p.P332R

	Case 1	Case 2	Case 3
Diagnostic classification	PSP-RS*	PSP-RS*	PSP-RS†
Age at symptom onset (yr)	67	60	57
Ancestry; sex	Chinese (Malaysia); female	Chinese (Malaysia); female	Chinese (Singapore); male
Family history	Negative (note: patient was a single child)	Negative	Negative
Main clinical features	Recurrent falls due to imbalance, starting from ~1.5 y after symptom onset; slurred speech; vertical > horizontal supranuclear gaze palsy; mildly impaired cognition	Recurrent falls due to imbalance within 1st year of symptom onset; dragging speech; slowing of up-saccades; cognitive including memory dysfunction; depressive symptoms; insomnia (but no RBD symptoms)	Typical features presenting with recurrent falls (further records N/A as already deceased)
Brain MRI features	Cerebral atrophy; mild hummingbird sign	Unremarkable (but mid-sagittal image not available)	Generalized cerebral atrophy

Case 1 is reported in detail within the text. Diagnosed by *S.Y.L. or †E.K.T., applying the Movement Disorder Society clinical diagnostic criteria for progressive supranuclear palsy.[1,2]
N/A, not available; PSP-RS, progressive supranuclear palsy, Richardson syndrome subtype; RBD, rapid eye movement sleep behavior disorder; MRI, magnetic resonance imaging.

mildly impaired, as indicated by a Montreal Cognitive Assessment score of 24/30 and a Frontal Assessment Battery score of 13/18.

The patient's DNA was analyzed as previously described,[12] and the patient was found to harbor a heterozygous NM_000543.5:c.995C>G p.P332R variant in *SMPD1*. This variant was detected in two additional, unrelated patients of Chinese ancestry (Table 1) in our Malaysian-Singaporean Asian PSP genetics cohort, 177 of whom (126 Chinese) underwent next-generation sequencing (166 whole-exome sequencing; 9 whole-genome sequencing; 2 targeted exome sequencing), yielding a frequency of 2.4%. No other pathogenic/likely pathogenic non-synonymous variants were identified in genes related to other neurodegenerative diseases (including PSP and FTD) (Supplementary Material in the online-only Data Supplement). The minor allele frequency for p.P332R (rs202081954) in gnomAD v4.0.0 (https://gnomad.broadinstitute.org) is 0.003209 in East Asians and rarer in other populations, including Europeans, Africans and South Asians, with an average global allele frequency of 0.0001382. Thus, using the gnomAD East Asian dataset for background population frequency, this variant had an OR for PSP of 3.8 (95% confidence interval: 1.2−12.0, $p = 0.012$).

According to prior in vitro assays with the *SMPD1* variant expressed in a plasmid, the p.P332R variant has been classified as "damaging" with an ~70% reduction in ASMase activity compared to the normal copy.[12]

DISCUSSION

In this study, we report on the potential link between a deleterious *SMPD1* variant, p.P332R, and classic PSP-RS in Chinese patients.

The p.P332R missense variant was by far the most common *SMPD1* variant in the study by Chew et al.,[12] accounting for the majority (69/99 = 69.7%) of East Asian *SMPD1*-related PD cases with rare deleterious variants. The p.P332R variant was observed in a heterozygous state in 69/4,298 (1.6%) PD patients vs. 48/5,512 (0.87%) controls, a frequency that is comparable to that of our (albeit much smaller) PSP cohort (2.4%); additionally, functional studies demonstrated an associated 70% loss of ASMase activity.[12] Chew et al.[12] also showed a strong and highly significant association between *SMPD1* variants with ≥ 56% loss of enzymatic activity and PD risk (OR 2.24, $p = 1.25 \times 10^{-15}$). Notably, the previously reported p.L302P variant, which confers a markedly elevated PD risk among Ashkenazi Jewish patients with an OR of 9.0,[11] was associated with > 90% loss of enzyme activity[12] and resulted in failure of ASMase trafficking to the lysosome.[11]

Moreover, other investigators have recently found associations between reduced ASMase activity and MSA and DLB,[13] which further supports the relevance of our genetic findings. While PD, DLB, and MSA are synucleinopathies and PSP is a tauopathy, clinical, genetic, mechanistic, and neuropathological overlaps between these conditions are now widely recognized.[1,2,5,7,8,14]

Dysfunction of autophagy-lysosomal pathways has been documented in various neurodegenerative disorders, including PSP,[1,5,8,11-13,15] and we postulate that *SMPD1* could contribute to this dysfunction, at least in some cases. However, we acknowledge that the involvement of genes in sphingolipid metabolism in PSP, as suggested in previous studies[4,5,8] and the present study, requires confirmation in larger cohorts supported by functional studies, including biological experiments and in silico analysis.[11] A limitation of this report is the lack of premortem tau PET im-

aging or postmortem brain pathology confirming the diagnosis of PSP; however, clinically diagnosed probable PSP-RS (which was the PSP subtype in all three patients who were diagnosed by experienced movement disorder neurologists) has been demonstrated to have high predictive value for PSP pathology.[1,2]

Since *SMPD1* variants have ancestry-specific effects (e.g., p.L302P is found in Jewish PD patients but is undetected in East Asian or French/Canadian/American patients, and p.P332R has been observed only in East Asians to date),[11,12] further genetic correlation studies should be carried out in PD and Parkinson-plus populations of diverse ancestries. Global efforts are currently underway to characterize the genetic underpinnings of PD and related disorders, for example, the Global Parkinson's Genetics Program, which has recently expanded beyond the investigation of PD genetics to include Parkinson-plus syndromes (https://gp2.org). The analysis of these large datasets, with a specific focus on underrepresented populations, will further our understanding of genotype–phenotype correlations and hopefully reveal potential biomarkers or therapeutic targets for these debilitating conditions.

Ethics Statement

The study was approved by the ethics committees of the respective institutions (University of Malaya Medical Research Ethics Committee/MREC ID NO: 20191010-7917; and Singapore Health Services Centralised Institutional Review Board, CIRB NO: 2017/2602, 2015/2218, 2017/2137, and 2019/2330). The patient whose video is shown provided written informed consent for publication of the case details and video.

Supplementary Video Legends

Video 1. The patient is alert and cooperative. There is a very obvious "staring" appearance and facial masking. There is prominent axial (neck) rigidity, and rigidity in the upper limbs is less prominent (not shown). Repetitive upper limb movements are moderately bradykinetic and worse on the left side. There is supranuclear vertical gaze palsy (downgaze more restricted than upgaze, overcome with doll's head maneuver), with relative preservation of horizontal eye movements. Assistance is needed to stand up from her wheelchair and to walk a very short distance (several feet). There is spontaneous retropulsion even without being pulled (the patient has to be supported from behind). Speech is mild to moderately slurred, with a dragging quality and the voice sometimes trailing off. The applause sign is positive.

Supplementary Materials

The online-only Data Supplement is available with this article at https://doi.org/10.14802/jmd.24009.

Conflicts of Interest

The authors have no financial conflicts of interest.

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