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Clinical and Molecular Features of POLG‑Related Sensory Ataxic Neuropathy with Dysarthria and Ophthalmoparesis

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### Abstract

Sensory ataxic neuropathy, dysarthria, and ophthalmoparesis (SANDO) is a rare mitochondrial disorder associated with mutations in the *POLG* gene, which encodes the DNA polymerase gamma catalytic subunit. A few POLG-related SANDO cases have been reported, but the genotype–phenotype correlation remains unclear. Here, we report a patient with SANDO carrying two novel missense variants (c.2543G>C, p.G848A and c.452 T>C, p.L151P) in *POLG.* We also reviewed previously reported cases to systematically evaluate the clinical and genetic features of POLG-related SANDO. A total of 35 distinct variants in the coding region of *POLG* were identified in 63 patients with SANDO. The most frequent variant was the p.A467T variant, followed by the p.W748S variant. The clinical spectrum of SANDO is heterogeneous. No clear correlation has been observed between the mutation types and clinical phenotypes. Our findings expand the mutational spectrum of *POLG* and contribute to clinical management and genetic counseling for POLG-related SANDO.

**Keywords** Sensory ataxic neuropathy · Dysarthria · Ophthalmoparesis · *POLG* · Mutation · Phenotype

# Introduction

Sensory ataxic neuropathy, dysarthria, and ophthalmopa- resis (SANDO) is a rare inherited mitochondrial disorder associated with multiple mitochondrial DNA (mtDNA) deletions. It was first described in 1997 (Fadic et al. [1997](#_bookmark8)). Since then, relatively few cases have been reported. Clas- sically, the disorder presents with the triad of sensory ataxic neuropathy, dysarthria, and ophthalmoparesis. Mutations in the DNA polymerase gamma (*POLG*) gene, which encodes the DNA polymerase gamma catalytic subunit, have been identified as the major genetic cause of SANDO.

However, diseases related to *POLG* mutations are het- erogeneous, consisting of a wide spectrum of disorders involving multiple organs, with variable age at onset

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and varying degrees of severity. Apart from SANDO, POLG-related disorders include Alpers syndrome; auto- somal dominant and recessive forms of chronic progres- sive external ophthalmoplegia; spinocerebellar ataxia with epilepsy; mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS); and mito- chondrial neurogastrointestinal encephalomyopathy syn- drome (Da Pozzo et al. [2017](#_bookmark6); Rouzier et al. [2014](#_bookmark23); Tang et al. [2011](#_bookmark24)). Although *POLG* variants have been found throughout the region from exon 2 to exon 21, no clear correlation has been identified between the phenotype and genotype.

The diagnosis of SANDO is best made with genetic testing coupled with clinical findings. To date, the clinical phenotype and *POLG* mutational spectrum of SANDO patients have not yet been systematically evalu- ated. In this study, we report a case of SANDO associ- ated with two novel heterozygous variants (c.2543G>C, p.G848A and c.452 T>C, p.L151P) in *POLG.* We also searched the literature on POLG-related SANDO and reviewed previously reported cases to summarize the clinical and genetic features of this disorder.

# Materials and Methods

## Subjects

The patient was recruited from the Neurological Department of Tongji Hospital, Tongji University School of Medicine in 2019. The patient and his parents signed written informed consent forms in accordance with the ethical protocol approved by the Ethics Board of Tongji Hospital, Tongji University School of Medicine.

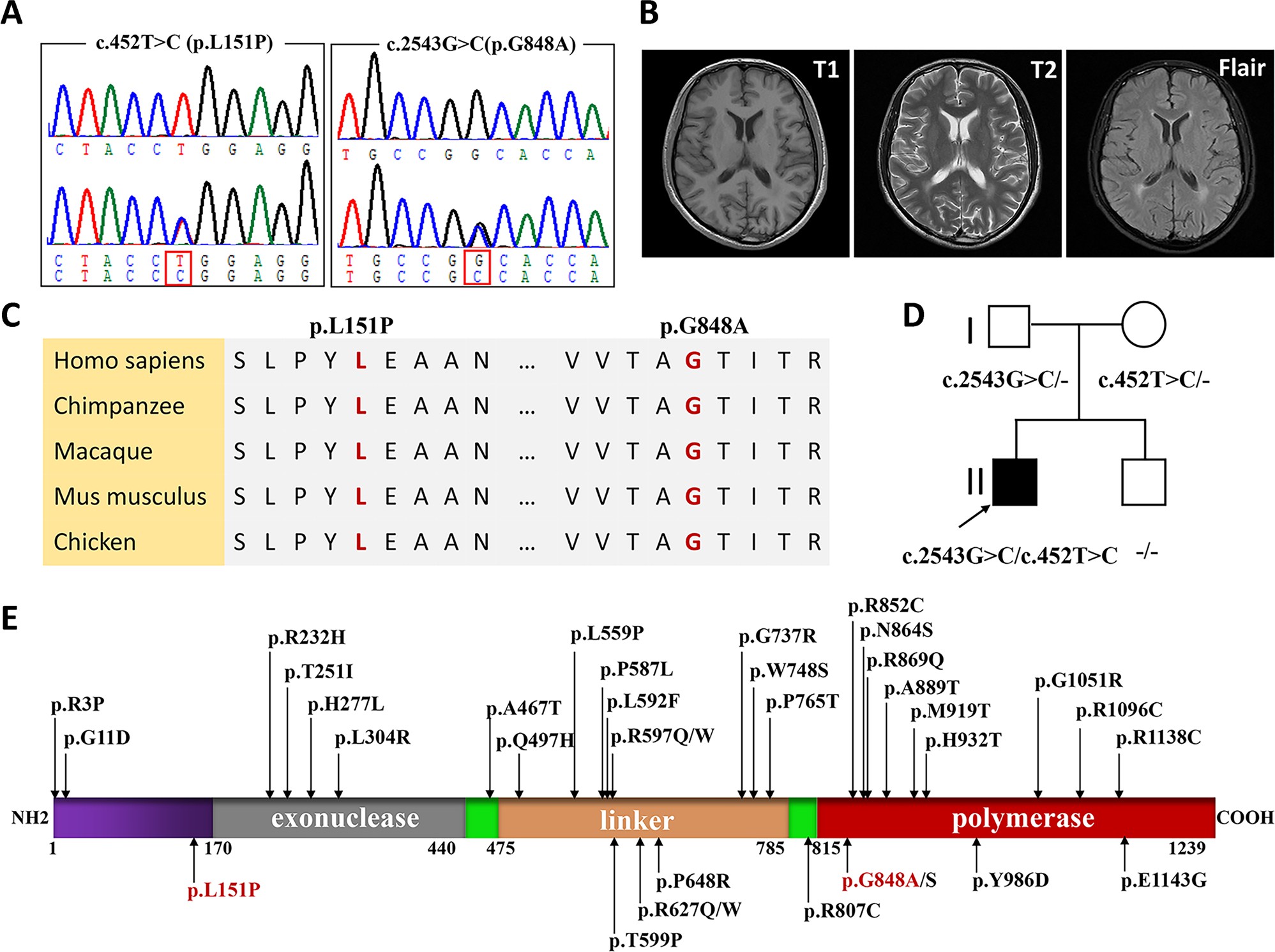
## Genetic Analysis

Genomic DNA was extracted from peripheral blood samples. Whole-exome sequencing of the proband was performed on the Illumina NovaSeq 6000 platform using methods reported

previously (Dong et al. [2020](#_bookmark7)). Sanger sequencing was car- ried out to verify the potential variants and co-segregation of the pedigree.

## Literature Review

The PubMed (<https://pubmed.ncbi.nlm.nih.gov/>)*,* CNKI (<https://www.cnki.net/>), and Wanfang ([http://www.](http://www.wanfangdata.com.cn/) [wanfangdata.com.cn/](http://www.wanfangdata.com.cn/)) databases were used to search for previously reported cases associated with POLG-related SANDO. Patients with homozygous or compound het- erozygous variants in the *POLG* gene were included in this study. The clinical history, genetic variants, brain magnetic resonance imaging (MRI), and electrophysi- ological and histological findings of these cases were reviewed (Supplementary Table 1).



**Fig. 1** A SANDO family carrying biallelic *POLG* variants. **a** Chro- matograms of c.2543G>C (p.G848A) and c.452 T>C (p.L151P) vari- ants. The upper chromatograms represent normal sequences, and the lower chromatograms represent mutant sequences. **b** Brain MRI find- ings of the proband. **c** Conservation analysis of amino acid sequences

on the p.L151P and p.G848S variant sites. **d** The pedigree shows seg- regation of variants verified by Sanger sequencing. The arrow indi- cates the proband. **e** POLG protein structure and the identified vari- ants reported in SANDO patients. The red characters represent the variants reported in this study

**Table 1** Clinical features of patients with POLG-related SANDO

|  |  |
| --- | --- |
|  | All patients |
| Number of patients | 63 |
| Male | 27/49 (55.1%) |
| Age at onset (years) | 32.2 (5–73) |
| First disabling symptom |  |
| Ataxia | 25/41 (61.0%) |
| Ptosis | 10/41 (24.4%) |
| Paresthesia | 4/41 (9.8%) |
| Epileptic seizure | 3/41 (7.3%) |
| Limb weakness | 1/41 (2.4%) |
| Symptoms in addition to SANDO |  |
| Proximal muscle weakness | 18/63 (28.6%) |
| Dysphagia | 18/63 (28.6%) |
| Cognitive deficits | 14/63 (22.2%) |
| Movement disorders | 13/63 (20.6%) |
| Psychiatric disorders | 12/63 (19.0%) |
| Hearing/visual symptoms | 9/63 (14.4%) |
| Epilepsy | 6/63 (9.5%) |
| Headache | 6/63 (9.5%) |
| Gastrointestinal symptoms | 5/63 (7.9%) |
| Heart symptoms | 4/63 (6.3%) |
| Endocrine symptoms | 4/63 (6.3%) |
| Autonomic dysfunction | 4/63 (6.3%) |
| Brain MRI findings |  |
| Normal | 12/36 (33.3%) |
| Cerebellar atrophy | 9/36 (25.0%) |
| Cerebellar lesions | 6/36 (16.7%) |
| Thalamic lesions | 5/36 (13.9%) |
| Cortical atrophy | 4/36 (11.1%) |
| White matter lesions | 3/36 (8.3%) |
| Olivary hypertrophy | 3/36 (8.3%) |
| Electrophysiological findings |  |
| Axonal >Demyelinating | 47/51 (92.2%) |
| Axonal =Demyelinating | 3/51 (5.9%) |
| Axonal <Demyelinating | 1/51 (1.9%) |
| Muscle biopsy |  |
| COX-negative fibers | 23/30 (76.7%) |
| Ragged-red fibers | 18/25 (72.0%) |
| Multiple mtDNA deletions | 21/22 (95.5%) |

# Results

## Clinical Presentation

The patient was a 37-year-old man. He said he was a poor runner and was unable to keep up with his peers during childhood. He complained of fatigue after exercise. At the age of 35, he suffered from bilateral eyelid drooping. At age 36, he experienced numbness in both feet that was notice- able when standing or walking and diminished when lying

down. At the same time, a hand tremor, particularly in the right hand, was observed. The tremor appeared in the resting state but disappeared when he actively used the hand. Three months before visiting our department, he exhibited a more severe hand tremor and developed slurred speech.

On examination, he was 164 cm tall and weighed only 45 kg. Neurological examinations showed normal cogni- tion. He had a moderate nasal, flaccid dysarthria. There was bilateral ptosis with moderate horizontal ophthalmoparesis without double vision. This symptom was more severe in the right eye. His muscle power was reduced in neck flexors to 3/5 grade strength (Medical Research Council Muscle Scale). He also had bilateral sternocleidomastoid muscular atrophy. Fasciculation was observed in the bilateral pectoralis major and left bicep. Excessive sweating of the palms and soles was also observed. Deep tendon reflexes were absent in all limbs. Absent vibratory sensations in the lower extremities and impaired joint position sense in the toes were observed. The finger-to-nose test was normal. His heel-knee-tibia test and Romberg sign were positive. A static tremor was evident in his right hand.

Chemical laboratory investigations revealed slightly ele- vated levels of lactic acid up to 3.0 mmol/L (reference range 0.7–2.1 mmol/L), while his creatine kinase, glucose, vitamin B12, thyroid function, and autoantibody levels were all within normal ranges. His electrocardiogram (ECG) test was normal, showing no arrhythmia. Nerve conduction studies revealed absent right sural and peroneal sensory nerve action poten- tials (SNAP), along with moderately reduced radial, median, and ulnar SNAP, consistent with sensory axonopathy. Motor studies demonstrated reduced compound muscle action potentials (CMAP) in the lower limbs. His F-wave latencies were normal. A needle electromyographic (EMG) study of his right arm and leg showed some high-amplitude, long- duration motor unit action potentials, with fibrillation poten- tials and positive sharp waves. Lower limb somatosensory evoked potentials were absent. No noticeable abnormalities were seen on MRI of the spinal cord. Periventricular white matter hyperintensities were observed on T2-weighted/fluid attenuated inversion recovery (T2/FLAIR) brain MRI (Fig. [1](#_bookmark0)).

## Genetic Findings

Whole-exome sequencing was performed to screen for possible causative genes for these symptoms. Two novel heterozygous missense variants in compound heterozygosity, c.2543G>C (p.G848A) and c.452 T>C (p.L151P) in *POLG* (NM\_002693.2)

were identified as candidate disease-causing variants after veri- fication by Sanger sequencing. Family co-segregation analysis demonstrated that these variants were inherited from his asymp- tomatic mother and father (Fig. [1](#_bookmark0)). The variant p.G848A affects

**Table 2** *POLG* variants identified in SANDO patients

Nucleotide variant Amino acid alteration Exon Domain Frequency

No. of patients

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | | | | of MU (%) | MU/MU | WT/MU |
| c.8G >C | p.R3P | 2 | N-terminus | 1.44 | 0 | 2 |
| c.32G >A | p.G11D | 2 | N-terminus | 0.72 | 0 | 1 |
| c.452 T >C | p.L151P | 2 | N-terminus | 0.72 | 0 | 1 |
| c.695G >A | p.R232H | 3 | exonuclease | 1.44 | 0 | 2 |
| c.752C >T | p.T251I | 3 | exonuclease | 4.32 | 0 | 6 |
| c.830A >T | p.H277L | 3 | exonuclease | 1.44 | 0 | 2 |
| c.911 T >G | p.L304R | 4 | exonuclease | 2.16 | 1 | 1 |
| c.1399G >A | p.A467T | 7 | thumb | 30.94 | 8 | 27 |
| c.1491G >T | p.Q497H | 8 | linker | 0.72 | 0 | 1 |
| c.1676 T >C | p.L559P | 9 | linker | 0.72 | 0 | 1 |
| c.1760C >T | p.P587L | 10 | linker | 3.60 | 0 | 5 |
| c.1774C >T | p.L592F | 10 | linker | 0.72 | 0 | 1 |
| c.1789C >T | p.R597W | 10 | linker | 0.72 | 0 | 1 |
| c.1790G >A | p.R597Q | 10 | linker | 0.72 | 0 | 1 |
| c.1795A >C | p.T599P | 10 | linker | 1.44 | 1 | 0 |
| c.1879C >T | p.R627W | 10 | linker | 1.44 | 0 | 2 |
| c.1880G >A | p.R627Q | 10 | linker | 3.60 | 0 | 5 |
| c.1943C >G | p.P648R | 10 | linker | 2.16 | 1 | 1 |
| c.2209G >C | p.G737R | 13 | linker | 0.72 | 0 | 1 |
| c.2243G >C | p.W748S | 13 | linker | 20.86 | 6 | 17 |
| c.2293C >A | p.P765T | 14 | linker | 1.44 | 1 | 0 |
| c.2419C >T | p.R807C | 14 | thumb | 0.72 | 0 | 1 |
| c.2542G >A | p.G848S | 16 | polymerase | 2.16 | 0 | 3 |
| c.2543G >C | p.G848A | 16 | polymerase | 0.72 | 0 | 1 |
| c.2554C >T | p.R852C | 16 | polymerase | 0.72 | 0 | 1 |
| c.2591A >G | p.N864S | 16 | polymerase | 0.72 | 0 | 1 |
| c.2606G >A | p.R869Q | 17 | polymerase | 0.72 | 0 | 1 |
| c.2665G >A | p.A889T | 17 | polymerase | 0.72 | 0 | 1 |
| c.2756 T >C | p.M919T | 18 | polymerase | 0.72 | 0 | 1 |
| c.2794C >T | p.H932T | 18 | polymerase | 1.44 | 0 | 2 |
| c.2956 T >G | p.Y986D | 18 | polymerase | 0.72 | 0 | 1 |
| c.3151G >C | p.G1051R | 20 | polymerase | 1.44 | 0 | 2 |
| c.3286C >T | p.R1096C | 21 | polymerase | 0.72 | 0 | 1 |
| c.3412C >T | p.R1138C | 21 | polymerase | 1.44 | 0 | 2 |
| c.3428A >G | p.E1143G | 21 | polymerase | 5.04 | 2 | 3 |

*MU* mutant, *WT* wild type

the same amino acid as a previously reported mutation (p.G848S) (Weiss and Saneto [2010](#_bookmark27)). These two novel variants were found at a low frequency in the public database and were predicted to be damaging by PolyPhen-2 [Polymorphism Phenotyping v2] and CADD [Combined Annotation Dependent Depletion] software programs. Moreover, both variant sites are conserved throughout vertebrate species (Supplementary Table 2).

## Literature Review

Overall, 63 SANDO patients carrying homozygous or com- pound heterozygous variants in *POLG* were included in this

study. Their clinical and molecular data are summarized in Supplementary Table 1. The mean age at onset of POLG- related SANDO was 32.2 years (range, 5–73 years), with 96.7% of patients developing symptoms before the age of 50. Most patients were prompted to seek medical advice because of gait ataxia and progressive ptosis. Multiple organs were affected in SANDO patients. Common additional symptoms included proximal muscle weakness, dysphagia, cognitive def- icits, movement disorders, and psychiatric disorders (Table [1](#_bookmark1)). Except for one SANDO patient carrying a homozygous p.A889T variant, who presented with demyelinating neuropa- thy, all of the patients were characterized by axonal neuropathy.

Muscle histological analysis revealed that a majority of patients had a histological pattern of mitochondrial myopathy with rag- ged-red fibers (RRFs, 18/25) and cytochrome c oxidase (COX)- negative fibers (23/30). Multiple mtDNA deletions were present in the muscle specimens of all but one patient (21/22). In addi- tion, brain MRI anomalies were identified in some patients. Major brain MRI features included cerebellar atrophy (9/36) and cerebellar lesions (6/36).

A total of 35 distinct variants in the coding region of the *POLG* gene have been identified so far in SANDO patients (Table [2](#_bookmark2)). These variants are distributed throughout the coding region of *POLG* and are mainly concentrated in the linker region and the polymerase domain (Fig. [1](#_bookmark0)). The bio- informatic characterization of these variants is presented in Supplementary Table 2. The most frequently detected *POLG* variant associated with SANDO is the p.A467T variant (30.9% of alleles) followed by the p.W748S variant (20.9% of alleles).

# Discussion

In this report, we describe two novel variants in the *POLG* gene in a patient with SANDO, hand tremors, and exercise intolerance. These two variants, p.L151P and p.G848A, are located in the N-terminal and polymerase domains of POLG, respectively. Based on the clinical manifestation and genetic analysis, this patient was diagnosed with SANDO.

To date, 35 distinct variants throughout the coding region of the *POLG* gene have been detected in SANDO patients (Bereau et al. [2016](#_bookmark3); Hanisch et al. [2015](#_bookmark11); Horvath et al. [2006](#_bookmark13); Hou Yue et al. [2018](#_bookmark15); Posada et al. [2010](#_bookmark20); Rajakulendran et al. [2016](#_bookmark21); Van Goethem et al. [2003](#_bookmark26); Winterthun et al. [2005](#_bookmark28)). The *POLG* gene encodes the DNA polymerase gamma catalytic subunit, which forms a heterotrimeric DNA polymerase gamma with the accessory subunit encoded by DNA poly- merase subunit gamma-2, mitochondrial (*POLG2*). DNA polymerase gamma is involved in mtDNA maintenance. Mutations in *POLG* reduce the activity of DNA polymerase gamma, leading to mtDNA deletions. Mitochondrial dys- function impairs cellular metabolism. Among these variants in *POLG* identified in SANDO patients, the p.A467T variant is the most common. However, this variant is not specific to SANDO (Kurt et al. [2010](#_bookmark16)).

Classically, SANDO presents with the aforementioned triad of sensory ataxic neuropathy, dysarthria, and ophthal- moparesis. However, there is wide phenotypical variation among SANDO patients. Patients with the disease can dis- play additional symptoms of multiple organ involvement, including cerebellar ataxia (Milone et al. [2008](#_bookmark19)), dyspha- gia (Bereau et al. [2016](#_bookmark3)), parkinsonism (Batla et al. [2015](#_bookmark4)), chorea (Bereau et al. [2016](#_bookmark3)), cognitive deficits (Lovan et al. [2013](#_bookmark17)), diabetes (Horvath et al. [2006](#_bookmark13)), constipation (Gati

et al. [2011](#_bookmark9)), and cardiomyopathy (Horvath et al. [2006](#_bookmark13)). In addition, muscle biopsy indicated that some patients did not show RRFs or COX-negative fibers (Hanisch et al. [2015](#_bookmark11); Milone et al. [2008](#_bookmark19); Rouzier et al. [2014](#_bookmark23)). This wide variation in patient presentation often makes diagnosis difficult. Sup- port for the diagnosis of SANDO comes from the patient’s clinical history, electrophysiology, histology, and genetic testing.

In our patient, a resting tremor was observed in his right hand. According to a literature review, symptoms of movement disorders such as chorea, tremors, and parkin- sonism were reported in 13 SANDO patients harboring 12 distinct *POLG* mutations (Bereau et al. [2016](#_bookmark3); Habek et al. [2012](#_bookmark12); Van Goethem et al. [2004](#_bookmark25)). However, the exact pathogenesis is not clear. It has been reported that mito- chondrial dysfunction is related to the occurrence of par- kinsonism (Batla et al. [2015](#_bookmark4)). Among the POLG-related SANDO patients, a majority (24/35) also exhibited brain MRI anomalies, including cerebellar lesions, thalamic lesions, white matter lesions, cerebellar atrophy, cortical atrophy, and hypertrophic olivary degeneration (Bostan et al. [2012](#_bookmark5); Gebus et al. [2018](#_bookmark10); Henao et al. [2016](#_bookmark14); Richter et al. [2018](#_bookmark22)). Recent studies have shown that the levels of dopamine transporters were reduced in the bilateral striata of SANDO patients with parkinsonism (Batla et al. [2015](#_bookmark4); Miguel et al. [2014](#_bookmark18)). In addition, histological examination revealed degenerative changes in the substantia nigra, den- tate nucleus, and red nuclei, as well as striking bilateral hypertrophy of the inferior olive in a patient with POLG- related SANDO. These pathological findings are in line with prior brain MRI findings and may partially explain the occurrence of movement disorders in SANDO patients. In conclusion, this study reported two novel *POLG* vari- ants in a patient with SANDO. POLG-related SANDO is a rare heterogeneous mitochondrial disorder with multiple organ involvement. Our findings expand the mutational spectrum of *POLG* and will be useful in clinical man- agement and genetic counseling for patients with POLG-

related SANDO.

**Supplementary Information** The online version contains supplemen- tary material available at <https://doi.org/10.1007/s12031-021-01831-9>.

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**Availability of Data and Materials** The data and materials are available.

## Declarations

**Ethics Approval and Consent to Participate** This study was approved by the Ethics Board of Tongji Hospital, Tongji University School of Medicine. The patient and his parents signed written informed consent agreements.

**Consent for Publication** All authors agree to publish this study.

**Competing Interests** All authors declare no conflict of interest.

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