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POLG1 Arg953Cys MUTATION: EXPANDED PHENOTYPE AND RECESSIVE INHERITANCE IN A BRAZILIAN FAMILY

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Polymerase γ (POLG) is a nuclear DNA-encoded enzyme responsible for mitochondrial DNA (mtDNA) replication. A heterodimer composed of one alpha (140 kDa) encoded by *POLG1* and two beta (41 kDa) subunits encoded by *POLG2*, POLG resides in the inner mitochondrial membrane. The alpha subunit is catalytic and contains both polymerase and exonuclease activities, whereas the beta subunit facilitates DNA binding and promotes DNA synthesis.¹

The first pathogenic mutation of *POLG1* was described in 2001 in families with autosomal dominant or recessive chronic progressive external ophthalmoplegia (PEO) and multiple deletions of mtDNA in muscle.² Subsequent reports expanded the clinical spectrum associated with *POLG1* mutations. Autosomal dominant mutations usually cause PEO with or without parkinsonism, whereas autosomal recessive mutations have been associated with Alpers syndrome (hep-atopathy, psychomotor regression, and refractory seizures), SANDO (sensory ataxia, neuropathy, dysarthria, ophthalmoplegia), male infertility, premature menopause, cataracts, or early-onset parkinsonism and neuropathy.^{3–8}

In 2004, Luoma et al. described a heterozygous c.C2857T mutation, which changes an arginine to a cysteine at amino acid position 953 (p.Arg953Cys), in a patient with PEO, muscle weakness, ataxia, asthma, and hypothyroidism.⁷

We describe a family with 3 affected siblings. The index case was a 33-year-old man with PEO, parkinsonism, neuropathy, and cardiomyopathy who harbored the p.Arg953Cys mutation, as described by Luoma et al., in a homozygous state. He initially presented with gait abnormalities and PEO at 20 years of age. At age 30, he began to have cognitive impairment and depressive and psychotic symptoms. His oldest brother had similar symptoms and died at 30 years of age during abdominal surgery. An older sister had PEO and depression, and she committed suicide at age 29. The other 3 younger siblings were asymptomatic and had normal neurological examinations. The parents were first cousins, but neither had neurological problems. At age 33, a neurological evaluation of the index patient revealed masked face, bradykinesia, action tremor, stooped posture, rigidity, complete ophthalmoplegia, and mild proximal limb weakness. Parkinsonism improved with pra-

mipexole 3 mg/day. Electromyography and nerve conduction studies showed a myopathic pattern and a sensory polyneuropathy. Brain MRI showed diffuse cortical atrophy, and echocardiography revealed a moderate cardiomyopathy. Muscle biopsy showed numerous ragged-red fibers, which were COX-negative, and succinate dehydrogenase (SDH)-hyperreactive fibers (“ragged blue” fibers). Multiple mtDNA deletions in muscle were detected by Southern blot analysis. Direct sequencing of *POLG1* showed the p.Arg953Cys mutation in homozygosity. The mutation was heterozygous in the 2 asymptomatic brothers and absent in the asymptomatic younger sister (Fig. 1).

In 2004, Luoma et al. reported an apparently sporadic patient with isolated PEO associated with the p.Arg953Cys mutation. It was not stated whether the mutation was homozygous or heterozygous.⁸ Also, they were unable to study the parents of the patient and there were insufficient data to define the mode of inheritance. Based on this description, it was assumed that the p.Arg953Cys mutation causes autosomal dominant PEO, until now (see <http://dir-apps.niehs.nih.gov/polg/>).⁹

This study has clearly shown that p.Arg953Cys is an autosomal recessive mutation in our family and co-segregates with a more complex clinical phenotype: ophthalmoplegia; gait abnormalities; parkinsonism; sensory neuropathy; cardiomyopathy; and depression.

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FIGURE 1.

Family pedigree and POLG gene sequencing: (A) Patient (index case): homozygous for the C2857T mutation. (B, C) Asymptomatic siblings: heterozygous for the C2857T mutation. (D) Asymptomatic sibling: absence of the mutation. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]