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# The in cis T251I and P587L POLG1 base changes: Description of a new family and literature review

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**Abstract**

Mutations in the polymerase gamma-1 (POLG1) gene, encoding the catalytic subunit of the mtDNA-specific polymerase-γ, compromise the stability of mitochondrial DNA (mtDNA) and are responsible for numerous clinical presentations as autosomal dominant or recessive progressive external ophthalmoplegia (PEO), sensory ataxia, neuropathy, dysarthria and ophthalmoparesis (SANDO), spinocerebellar ataxia with epilepsy (SCAE) and Alpers syndrome.

POLG1 mutations result in extremely heterogeneous phenotypes which often have overlapping clinical findings, making it difficult to categorize patients into syndromes, and genotype–phenotype correlations are still unclear.

We describe a new family with a particular spectrum of clinical signs, that carried the c.752C>T mutation in exon 3 (T251I) and the c.1760C>T in exon 10 (P587L) in cis. These mutations were associated in the proband and in her brother with the new probably pathogenic mutation c.347C>A in exon 2 (P116Q).

The proband presented a progressive cognitive impairment, mild myopathy, dilated cardiac right atrium and posterior white matter mild signal alteration, while her brother had migraine, mild myopathy, palpebral ptosis and posterior white matter mild signal alteration. Their mother and their sister carried the in cis T251I and the P587L mutations. The first presented neurosensorial hypoacusia, fatigue, heart block and a cerebral arteriovenous malformation nidus, while the latter had borderline intellectual functioning and signs of muscular involvement. Their father, with the P116Q mutation, had diabetes and myopathy.

The complexity of the genotype–phenotype correlations associated with POLG1 mutations is reinforced in this work as evidenced by the presence of different clinic features in patients carrying the same mutations.


*Keywords:* Gene mutation; Mental retardation; Mitochondrial disease; Polymerase gamma

## 1. Introduction

Disorders of nuclear–mitochondrial intergenomic cross talk are the most common form of mitochondrial disorders (MDs), especially with regard to mutations of the polymerase gamma-1 (POLG1) gene [1], that may account for about 25% of MDs [2].

The POLG1 gene on chromosome 15q25 encodes the α subunit of polymerase γ [3], a nuclear-encoded protein involved in replication and repair of mitochondrial DNA (mtDNA) in the eukaryotic cell [4]. POLG1 mutations have been found in patients with autosomal dominant or recessive progressive external ophthalmoplegia (PEO), often complicated by other clinical signs [5] and in ataxic and hepatocerebral syndromes [2].

However POLG1 mutations are associated with a wide spectrum of clinical symptoms and genotype–phenotype correlations are still unclear, as identical POLG1 mutations can give rise to distinct disease phenotypes, with a wide variation in

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age of onset, electron transport activities and either recessive or dominant pattern of inheritance [6].

In this work we describe a family with an unusual association of clinical signs, variably distributed between the family members, that carried the c.752C>T mutation in exon 3 (T251I) and the c.1760C>T in exon 10 (P587L) in cis, associated, in two of the siblings, with the new probably pathogenic mutation c.347C>A in exon 2 (P116Q). We report in detail the clinical characteristics and do an extensive revision of literature data about the T251I+P587L mutations.

Our work confirms the complexity of genotype–phenotype correlations of POLG1 mutations.

## 2. Case report

We examined 6 members (I-4, II-9, II-10, III-1, III-2, III-3) of an Italian non-consanguineous family, in 5 of whom we identified POLG1 gene mutations. Extensive clinical examinations, that included neurological, ophthalmological and cardiological examinations, hearing tests, EEG, EMG, brain MRI or CT, were carried out. Informed written consent was obtained. The family tree is shown in Fig. 1.

The proband (III-3), an 8 year-old girl, was born at term after an uneventful pregnancy. During delivery, a programmed caesarean section, the mother had sudden cardiac arrest. In the neonatal period the child was hypotonic and had a weak cry and later on delayed psychomotor development became a prominent feature.

At age 3, neurological examination showed muscular hypotonia, joint laxity, absent deep tendon reflexes, broad-based gait, scapular winging, accentuation of lumbar lordosis and flat feet. Cardiological examination and behavioral audiometry were normal. EEG showed diffuse slow rhythms. Blood CK and lactic acid were normal. When she came back to our observation at age 8, a slight gait improvement was observed, but she had fatigue and echocardiogram showed dilated right atrium and ventricle tricuspid regurgitation. Brain MRI showed mild white matter signal alteration in the posterior periventricular regions. EMG examination showed motor unit potentials (MUPs) of low amplitude and clearly polyphasic morphology, mixed with MUPs of slightly increased amplitude suggesting a slow rearrangement of the motor unit. Electroneurography was normal. The first neuropsychological investigations showed mild intellectual disability (ID), gradually switching on moderate ID, during the following longitudinal assessments. She also presented a poor expressive language, usually using unintelligible word-phrase sentences.

The brother (III-1), 14 years old, was born at term by normal delivery and after an uneventful pregnancy. His psychomotor development was normal. He presented migraine by age 7 and complained of fatigue during exercise by age 12. On neurological examination he had mild diffuse muscle hypotonia and flat feet. At age 14 left eyelid ptosis was observed. Cardiological examination, EEG, audiometric examination, blood CK and lactic acid were normal. Brain MRI showed mild white matter hyperintensity in the posterior periventricular regions. EMG examination showed slight increase in percentage of polyphasic potentials. Electroneurography was normal. The neuropsychological assessment, at the age of 12 years old, showed a normal cognitive and adaptive functioning.

The sister (III-2), 10 years old, was born at term by normal delivery and after an uneventful pregnancy. She complained of leg pain after physical activity. Neurological examination showed mild diffuse muscle hypotonia, hypotrophy, mild diffuse muscle weakness, joint laxity, scapular winging and increase of lumbar lordosis. Laboratory investigations revealed increased lactic acid (46.90 mg%; n.v. 4.55–19.80 mg%). Cardiological examination, EEG, ECG, audiometric examination and brain MRI were normal. EMG showed no evidence of peripheral neuromuscular injury. Muscular biopsy was not performed. The neuropsychological investigation showed a borderline intellectual functioning. Concerning the expressive language, she also presented a restricted vocabulary.

The father (II-9) was a 42 year old man. By age 38 he complained fatigue. At the age of 40 he presented diabetes mellitus. Deep tendon reflexes were absent on neurological examination. Brain TC was normal. EMG examination showed MUPs of low amplitude and clearly polyphasic. Electroneurography was normal. The neuropsychological assessment showed a normal cognitive and adaptive functioning.

The mother (II-10), 37 years old, presented deafness from childhood. At age 29, during her latter labor, she had sudden

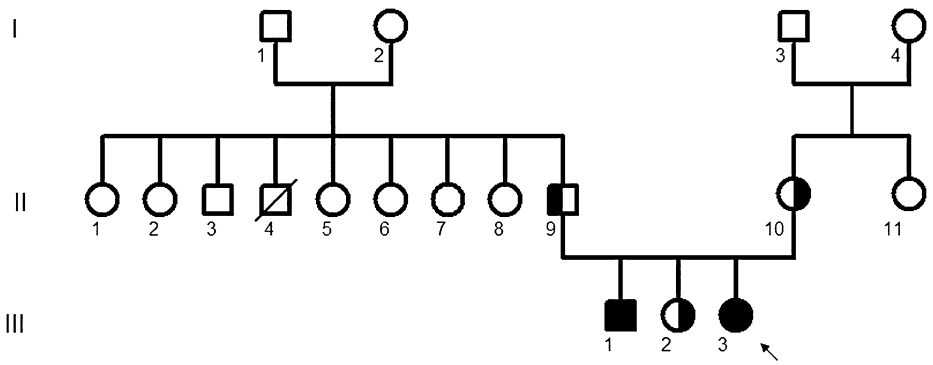


Fig. 1. Pedigree of the studied family. Arrow indicates the proband. Filled symbols represent affected individuals, semifilled symbols indicate heterozygote carriers and slash marks, deceased individuals.