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ORIGINAL ARTICLE

# Novel *POLG* mutations and variable clinical phenotypes in 13 Italian patients

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**Abstract** *POLG* gene encodes the catalytic subunit of DNA polymerase gamma, essential for mitochondrial DNA (mtDNA) replication and repair. Mutations in *POLG* have been linked to a spectrum of clinical phenotypes, resulting in autosomal recessive or dominant mitochondrial diseases. These mutations have been associated with heterogeneous phenotypes, presenting with varying severity and at different ages of onset, ranging from the neonatal period to late adult life. We screened 13 patients for *POLG* mutations. All patients underwent a complete neurological examination, and in most of cases, muscle biopsy was performed. We detected 15 different variations in 13 unrelated Italian patients. Two mutations were novel and mapped in the *pol* domain (p.Thr989dup and p.Ala847Thr) of the enzyme. We also report new cases carrying controversial variations previously described as incompletely penetrant or a variant of unknown significance. Our study increases the range of clinical presentations associated with mutations in *POLG* gene, underlining some peculiar clinical features, such as PEO associated with corneal edema, and epilepsy, severe neuropathy with achalasia. The addition of two new substitutions, including the second report of an in-frame duplication, to the growing list of defects increases the value of *POLG* genetic diagnosis in a range of neurological presentations.

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## Introduction

Mutations associated with an extensive spectrum of clinical phenotypes are described in an increasing number of nuclear genes, which control mitochondrial DNA (mtDNA) synthesis and maintenance. These nuclear mutations, involving nearly a dozen genes discovered since 1999, can cause point mutations, deletions, or depletion in mtDNA, resulting in mitochondrial syndromes [1]. DNA polymerase gamma (polγ) is the only polymerase found in animal cell mitochondria, having a key role in the replication and repair of mtDNA [2]. In human mitochondria, polγ is a heterotrimer and consists of a catalytic subunit (p140) encoded by the *POLG* gene, as well as two smaller identical accessory subunits (p55) encoded by the *POLG2* gene. *POLG* has three functional domains: an amino-terminal exonuclease domain, a highly conserved linker domain, and a polymerase carboxyterminal domain [3]. The human *POLG* gene (Ref Seq NM_002693.2) is located on chromosome 15q25, spanning 23 exons, with the codon of the translation initiator methionine located in exon 2 [4]. Mutations in *POLG* result in aberrant replication and impaired maintenance of mtDNA. *POLG* is a major locus for mitochondrial disease, with over 200 variations described to date [5]. These mutations have been associated with heterogeneous phenotypes, presenting with varying severity and at different ages of onset, ranging from the neonatal period to late adult life [6].

In our study, we described 13 patients showing key features of mitochondrial disease and heterogeneous