*Molecular Vision* 2010; 16:178-183 <http://www.molvis.org/molvis/v16/a22>
Received 12 October 2009 | Accepted 5 February 2010 | Published 10 February 2010



# Alu-element insertion in an *OPA1* intron sequence associated with autosomal dominant optic atrophy

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**Purpose:** Autosomal dominant optic atrophy (ADOA) is the most common form of hereditary optic neuropathy caused by mutations in the optic atrophy 1 (*OPA1)* gene. It is characterized by insidious onset with a selective degeneration of retinal ganglion cells, variable loss of visual acuity, temporal optic nerve pallor, tritanopia, and development of central, paracentral, or cecocentral scotomas. Here we describe the clinical and molecular findings in a large Italian family with ADOA.

**Methods:** Routine ophthalmologic examination and direct sequencing of all coding regions of the *OPA1* gene were performed. Further characterization of a new *OPA1* gene insertion was performed by reverse transcription-PCR (RT–PCR) of RNA from patients and control subjects.

**Results:** We identified an Alu-element insertion located in intron 7 of *OPA1* causing an in-frame deletion of exon 8 in 18 family members.

**Conclusions:** The predicted consequence of this mutation is the loss of the guanosine triphosphatase (GTPase) activity of OPA1. Alu insertions have been reported in the literature as causing human genetic disease. However, this is the first report of a pathogenic *OPA1* gene mutation resulting from an Alu insertion.

Autosomal dominant optic atrophy (ADOA; OMIM 165500) is the most common form of hereditary optic neuropathy, with an estimated prevalence between 1:10,000 and 1:50,000 in different populations [1]. It is characterized by insidious onset with a selective degeneration of retinal ganglion cells, variable loss of visual acuity, temporal optic nerve pallor, tritanopia, and development of central, paracentral, or cecocentral scotomas [2]. ADOA is inherited in an autosomal dominant manner with high interfamilial and intrafamilial phenotypic variability and incomplete penetrance.

Mutations in the optic atrophy 1 (*OPA1)* gene (that consists of 30 coding exons) are responsible for approximately 90% of cases. *OPA1* encodes a large guanosine triphosphatase (GTPase), implicated in the formation and maintenance of the mitochondrial network [3] and in protection against apoptosis by segregating cytochrome *c* inside the mitochondrial cristae [4]. OPA1 comprises a highly basic N-terminus, a dynamin GTPase domain, and a C-terminus. More than 200 pathogenic mutations have been reported in the literature (see the eOPA1 database). No significant correlation has been observed between degree of visual impairment and location or type of mutation [5]. Missense mutations in *OPA1*, however, leading to multiple mitochondrial DNA (mtDNA) deletions in skeletal muscle and a mosaic defect of cytochrome *c* oxidase, were recently found. In these cases the disorder presented with visual failure and optic atrophy in childhood, followed by Progressive External Ophthalmoplegia (PEO), ataxia, deafness, and sensory-motor neuropathy in adulthood. Moreover, some cases show additional neurologic symptoms, the so-called optic atrophy *plus* phenotypes [6].

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## METHODS

*Family study:* Twenty-eight individuals of a single large Italian family were recruited from the Department of Neurologic, Neurosurgical and Behavioral Sciences of Siena, the Italian Union of the Blind of Siracusa and the Department of Pediatric of Catania. There were 15 females and 13 males ranging in age from 9 to 59 years. We use the term "family" to indicate descendants of a multigenerational pedigree of related individuals (Figure 1). Autosomal dominant inheritance was indicated by multiple affected individuals in each generation. All patients underwent routine ophthalmologic examination, including visual acuity, color vision, manual visual field, slit-lamp examination, intraocular pressure (IOP), and dilated fundoscopy. Clinical neurologic examination and genetic analysis was also performed in all patients.

*Mutation analysis:* After informed consent was obtained, 5 ml of blood from the proband, his family members, and healthy controls, was drawn into an ethylenediamine tetraacetic acid