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Maria Liguori
Antonella La Russa
Ida Manna
Virginia Andreoli
Manuela Caracciolo
Patrizia Spadafora
Rita Cittadella
Aldo Quattrone

A phenotypic variation of dominant optic atrophy and deafness (ADOAD) due to a novel OPA1 mutation

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Sirs: Autosomal Dominant Optic Atrophy (ADOA or Kier's disease, OMIM #165500) is one of the most frequent forms of inherited optic atrophy [1], often presenting in the first decade of life with progressive impairment of visual acuity, variably combined with dyschromatopsia and optic nerve pallor [2]. More than 90 mutations spanning throughout the Optic Atrophy 1 (OPA1) gene were disease-associated with most cases of ADOA (http://lbbma.univ-angers.fr/eOPA1/) [3]; the gene encodes a dynamin-related GTPase involved in mitochondrial biogenesis [4].

M. Liguori · A. La Russa · I. Manna · V. Andreoli · M. Caracciolo · P. Spadafora · R. Cittadella · A. Quattrone
Institute of Neurological Sciences
National Research Council
Mangone (CS), Italy

A. Quattrone
Institute of Neurology
University "Magna Graecia"
Catanzaro, Italy

Dr. M. Liguori (✉)
Institute of Neurological Sciences, CNR
Contrada Burga
87050 Pianolago di Mangone (CS), Italy
Tel.: +39-0984-9801272
Fax: +39-0984-969306
E-Mail: m.liguori@isn.cnr.it

Genotype-phenotype comparisons have been inconclusive except for ADOA complicated with a rare sensorineural deafness (ADOAD); some authors reported that only the R445H mutation could be linked to ADOAD, as hearing loss has never been associated to other OPA1 mutations [5, 6].

Here we present a family with an unusual phenotype of ADOAD and peripheral polineuropathy associated with a novel OPA1 mutation. The proband (IV.13) (pedigree reported in Fig. 1) was a 38-year-old man from Southern Italy, who complained of bilateral and progressive reduction of visual acuity since the age of 7 years. In the second decade of his life, he experienced progressive deafness followed by development of an ataxic gait.

At the time of the evaluation, he was legally blind (bilateral visual acuity less than 0.3) and almost deaf (loss of hearing more than 90 dB); on neurological examination he presented bilateral ophthalmoplegia, mild ataxia, distal weakness and severe reduction of proprioception. The auditory brainstem responses (ABRs) were suggestive of bilateral neurosensorial deafness; the electrodiagnostic study of his legs showed decreased amplitude of sensory potentials and motor responses which were consistent with a peripheral axonal neuropathy. Brain and spinal cord MRI were normal.

Complete clinical, ophthalmological and audiological examinations were performed on the living family members (Fig. 1a). They were negative except for the proband's daughter (V.14), a 6-year-old child who was showing modest but progressive difficulties in visual acuity and hearing abilities during the last year. The ophthalmologic examination revealed mild bilateral optic pallor and the ABRs were bilaterally impaired (hearing loss < 40 dB); brain MRI and peripheral nerves electrophysiology were normal.

After informed consent, genomic DNA was obtained from the proband and his relatives (the proband's father, his daughter and wife, the 7 siblings and their spouses). The entire coding region and the intron-exon junctions of OPA1 were sequenced by ABI-PRISM 3130xl Genetic Analyzer (Applied Biosystems – Foster City, CA), as described elsewhere [7].

A novel missense 1316 G > T mutation was found in exon 14 of the proband and his daughter (Fig. 1b–c). This base change causes the amino acid substitution of a highly conserved Glycine to Valine at codon 439 (G439V) in the GTPase domain of OPA1 gene. No other family members harbored the same DNA mutation.

For confirmation, 100 gender, age and ethnicity matched chromosomes controls were analyzed with the same procedure; no one carried the novel OPA1 mutation.

OPA1 is believed to play a key role in mitochondrial morphology and function, by promoting its fusion (with the interaction of Mitofusin-1,2) and regulating mitochondrial apoptosis. Frezza et al. [8] demonstrated that oligomerization of OPA1 regulates mitochondrial apoptosis by maintaining the tightness of cristae junctions. Experimental data suggested that the pathogenesis of ADOA may result from haploinsufficiency, with most of the OPA1 mutations causing loss of function of the mutant allele [7, 9]. Recently, the authors reported that OPA1 mutations spanning the GTP-binding pocket disorganize the mitochondrial pathway by abolishing GTPase activity or affecting the self-assembly of OPA1 proteins. These mechanisms could impair the energy supply in the highly energy-demanding compartments,

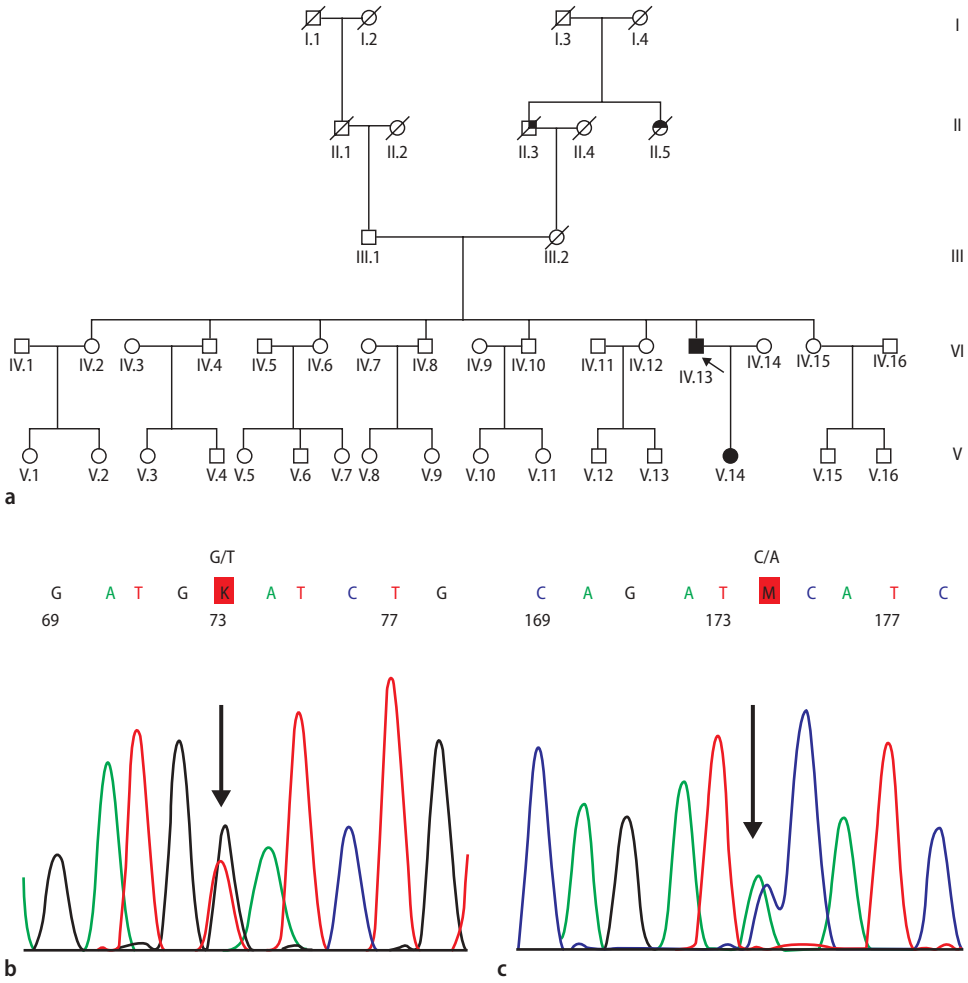

Fig. 1 **a** Pedigree of the study family; the affected members are differently represented by symptoms through the generations (II.3 mild hearing loss with onset at young unspecified age, unknown reason of death; II.5 deficit of visual acuity started at her 20s, unknown reason of death; IV.13 proband; V.14 proband's daughter). No clinical data were available about the proband's mother (III.2) who died at age 32 years presumably for a myocardial infarction. The OPA1 mutation screening analysis was carried out in the proband's father, his daughter and wife, the 7 siblings and their spouses. Sequence chromatograms of the proband – forward (**b**) and reverse (**c**) DNA strands; the arrows indicate the nucleotide changes of the heterozygous missense mutation 1316 G > T. The daughter has the same mutation

i. e. the nerve cell axons of retinal ganglion cells, skeletal muscles, or peripheral nerves [4, 5].

In summary, we identified a novel OPA1 heterozygous mutation (G439V) consegregating with both optic atrophy and sensorineural deafness; based on these data, we conclude that a missense mutation other than the previously described R445H may be associated with ADOAD. It is intriguing to note that both the G439V and R445H mutations are located adjacent to each other in the same functional GTPase domain of the gene [4, 5]; we can speculate that they share the same pathogenic mechanism of mitochondrial network fragmentation leading to a significant impairment of oxidative phosphorylation [5].

We also found that only the proband showed ADOAD complicated with axonal neuropathy and ophthalmoplegia. This already described phenotypic intra-familial heterogeneity [6, 10] might be due to the particular nature of the mutation within the GTPase active site of OPA1 gene; thus we cannot exclude that the proband's daughter might exhibit these signs later in her life.

However, the present report expands the phenotypic spectrum of ADOA-associated symptoms [6], since the peripheral axonal polyneuropathy has never been described.

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