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Genotype-phenotype and OCT correlations in Autosomal Dominant Optic Atrophy related to *OPA1* gene mutations: Report of 13 Italian families

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ABSTRACT

Mutations in *OPA1* are responsible of 32–89% cases of Autosomal Dominant Optic Atrophy (ADOA). OPA1 ADOA usually presents in childhood with bilateral, progressive visual loss due to retinal ganglion cells neurodegeneration, but environmental factors are supposed to influence onset and phenotype. Sixty Italian *OPA1* mutations carriers (fifty-two symptomatic), belonging to thirteen families, underwent neuro-ophthalmologic evaluation. Visual acuity (n = 60) and Optical Coherence Tomography (OCT) (n = 12) were compared in missense mutations (OPA-M) versus haploinsufficiency-inducing mutations (OPA-H) and correlated with age. Presence of plus phenotypes was investigated. We found four known mutations, the most common being missense c.1034G > A, and a new missense mutation, c1193A > C, the latter in a 54-yrs old female with late-onset phenotype. Visual acuity, colour sensitivity, and optic disc atrophy were sensitive indicators of disease. OCT RNFL thickness was reduced in OPA1 compared to controls. OPA-M showed worst visual acuity than OPA-H, but not more frequent plus-phenotype, observed only in four OPA-H patients. In both groups, visual acuity worsened with age. Our data confirm worst vision in OPA-M, but not increased plus-phenotype. Since most patients belonged to nine families from south-eastern Sicily (a famous region for the cult of St. Lucy, patron of the blinds) local genetic and environmental factors might have accounted for the low occurrence of plus-phenotypes.

1. Introduction

Autosomal Dominant Optic Atrophy (ADOA; OMIM 605290), firstly described by Kjer [1], represents one of the most common hereditary optic neuropathies, with an estimated prevalence of 1:12,000 to 1:50,000 [2]. ADOA usually presents insidiously in childhood with bilateral visual loss, ultimately leading to optic atrophy [3,4], with selective retinal ganglion cells (RGCs) loss as its defining pathological characteristic [5,6]. However, its clinical expressivity greatly varies even within families [4]. Mutations in *OPA1*, a gene composed of 30 coding exons linked to nuclear mitochondrial disorders and mapped to chromosome 3q28–29, has been recognized as the major causative gene in a percentage ranging from 32% to 89% of families with ADOA [3,7,8]. *OPA1* encodes a dynamin-related GTPase, localized in the mitochondrial inner membrane, which is involved in multiple functions, including a key role in the fusion of mitochondria and mitochondrial network dynamics, a contribution in oxidative phosphorylation, and in apoptosis control [9–11]. So far, over 200 pathologic mutations of *OPA1* have been identified [12], including missense, nonsense, deletion/insertion and splicing mutations. In most cases, *OPA1* mutations lead to a truncated protein, likely inducing haploinsufficiency [13]. Conversely, missense mutations act through a dominant negative mechanism and have been associated with more severe phenotype [14]. Globally, *OPA1*-related ADOA has incomplete penetrance, some carriers being asymptomatic [3].

Besides the classical ADOA clinical presentation, a syndromic form

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