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Research Report

Mutation of *OPA1* gene causes deafness by affecting function of auditory nerve terminals

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ABSTRACT

Autosomal dominant optic atrophy (DOA) is a retinal neuronal degenerative disease characterized by a progressive bilateral visual loss. We report on two affected members of a family with dominantly inherited neuropathy of both optic and auditory nerves expressed by impaired visual acuity, moderate pure tone hearing loss, and marked loss of speech perception. We investigated cochlear abnormalities accompanying the hearing loss and the effects of cochlear implantation. We sequenced OPA1 gene and recorded cochlear receptor and neural potentials before cochlear implantation. Genetic analysis identified R445H mutation in OPA1 gene. Audiological studies showed preserved cochlear receptor outer hair cell activities (otoacoustic emissions) and absent or abnormally delayed auditory brainstem responses (ABRs). Trans-tympanic electrocochleography (ECochG) showed prolonged low amplitude negative potentials without auditory nerve compound action potentials. The latency of onset of the cochlear potentials was within the normal range found for inner hair cell summating receptor potentials. The duration of the negative potential was reduced to normal during rapid stimulation consistent with adaptation of neural sources generating prolonged cochlear potentials. Both subjects had cochlear implants placed with restoration of hearing thresholds, speech perception, and synchronous activity in auditory brainstem pathways. The results suggest that deafness accompanying this OPA1 mutation is due to altered function of terminal unmyelinated portions of auditory nerve. Electrical stimulation of the cochlea activated proximal myelinated portions of auditory nerve to restore hearing.

1. Introduction

Autosomal dominant optic atrophy (DOA) is characterized by a slowly progressive bilateral visual loss beginning in childhood. There is temporal pallor of the optic disc, central vision loss (centrocaecal scotomas) and impairment of color vision (tritanopia). DOA is one of the most common forms of inherited optic neuropathy with an incidence of 1:12,000 to 1:50,000 (Votruba et al., 2003) and mutation of *OPA1* is one of the most common genetic causes. OPA1 protein is a dynamin-related GTPase, encoded by the nuclear genome, but localized to the inner membrane of the mitochondria, and is ubiquitously expressed (Alexander et al., 2000; Delettre et al., 2000; Misaka et al., 2002). The protein consists of a mitochondrial target signal (MTS), a transmembrane domain (TM), a presenilin-associated rhomboid-like protease site (PARL), and a dynamin/GTPase

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domain. More than 100 mutations have been identified, including missense, nonsense, deletion/insertion and splicing mutations (http://lbbma.univ-angers.fr/lbbma.php?id=9). The majority of the mutations cause truncation of the protein, suggesting that haploinsufficiency is the mechanism causing this condition. OPA1 mutations lead to fragmentation of mitochondria, decreased ATP production and increased oxygen reactive species (Tang et al., 2009; Lodi et al., 2004).

Optic nerve degeneration in *OPA1* mutations is considered to be secondary to their effect on retinal ganglion cells and not to involve rods and cones or bipolar cells (Votruba et al., 2003). Axons of ganglion cells within the retina are unmyelinated, of small diameter, and contain numerous mitochondria that provide energy for transmitting graded neural potentials. The disorder of visual function in OPA1 mutations has been suggested to originate in disordered function of the unmyelinated axons within the retina (Delettre et al., 2000). After the nerve fibers exit the retina through the lamina cribrosa, they become myelinated and nerve conduction is saltatory and energy efficient.

Some OPA1 mutations have additional clinical features including hearing loss, ataxia, and peripheral neuropathy (Amati-Bonneau et al., 2008; Chen et al., 2007; Hudson et al., 2008; Ke et al., 2006). The hearing loss has been characterized as sensorineural and specifically as auditory neuropathy by abnormal auditory nerve and brainstem responses (ABRs) in the presence of preserved otoacoustic emissions (OAEs) (Amati-Bonneau et al., 2005; Ke et al., 2006). OPA1 proteins have been localized in both inner and outer hair cells, auditory nerve terminals, and spiral ganglion cells (Chen et al., 2007) but the site(s) of abnormal function in the cochlea are not yet known. We have identified R445H mutation of the OPA1 gene in two subjects, mother and daughter, previously described as having optic and auditory neuropathies (Santarelli et al., 2008). Fig. 1 contains their pedigree and sequence trace of R445H mutation. We now show that the OPA1 mutation affects synchrony of neural discharges in unmyelinated dendrites of the auditory nerve while receptor potentials of hair cells were normal. Moreover, the myelinated portions of auditory nerve remain capable of responding to electrical stimulation from cochlear implants to restore both hearing and neural synchrony in auditory brainstem pathways.

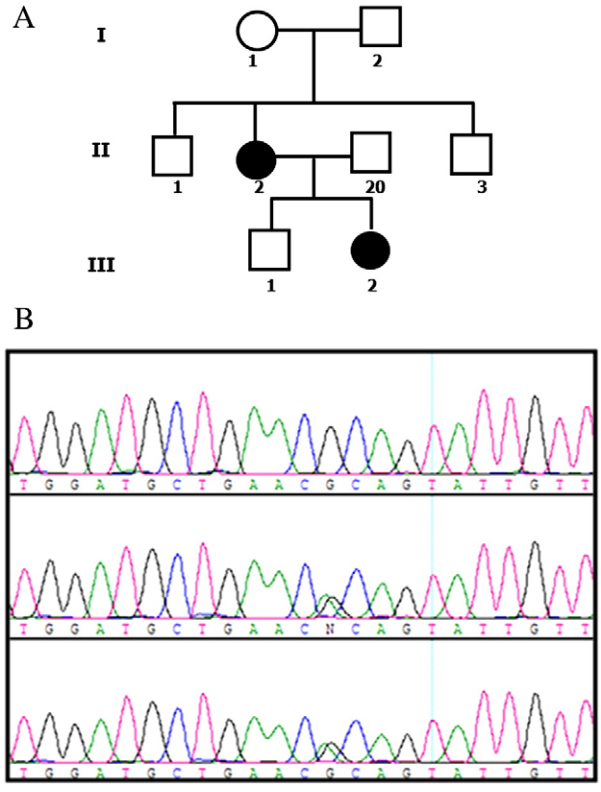

Fig. 1 – (A) Pedigree of OPA1 Family. Squares indicate males, circles indicate females, and filled symbols are the affected family members. (B) Sequence trace of R445H mutation detected in this family.

2. Results

2.1. *Audiological studies*

Pure tone thresholds were moderately elevated affecting predominantly low frequencies in the daughter (subject III-2) and high frequencies in the mother (subject II-2) (Fig. 2, Table 1). The audiogram is a measure of threshold and varies widely in AN (Sininger and Oba, 2001). In contrast, measures of auditory temporal processing such as gap detection threshold and speech perception can be related to the severity of the hearing disorder (Zeng et al., 2005). Speech recognition (vowels, words and sentences) was severely impaired (disyllabic words were not recognized, Table 1) beyond that expected for the degree of hearing loss. Acoustic but not non-acoustic middle ear reflexes were absent in both subjects. Fig. 2 shows the auditory measures. Cochlear outer hair cell receptor potentials (DPOAEs and CMs) were normal bilaterally in both subjects. In contrast auditory brain stem responses (ABRs) to high intensity clicks (125 dB p.e. SPL, 90 dB nHL) were absent unilaterally in both subjects whereas the other ear showed only low amplitude Wave V of delayed latency (7.5 ms II-2, 6.9 ms III-2, normal <6 ms). These results are consistent with abnormal synchrony of auditory nerve in the presence of normal receptor outer hair cell activities.

2.2. *Transtympanic ECochG*

Cochlear potentials recorded from a normal hearing control at 120 dB p.e. SPL and from the left ear (left ear) of both subjects with *OPA1* are in Fig. 3 as a function of stimulus intensity only in the OPA1 mutated subjects. In the control, summating potential (SP) begins at short latency after CM onset and is followed by the compound action potential (CAP) returning to baseline by 2.5 ms. In the *OPA1* subjects potentials were prolonged in duration without clear distinction between SP and CAP. Compared to control values, the cochlear potentials obtained from patients with R445H mutation in OPA1 were abnormally decreased in amplitude and prolonged in duration (Table 2).

A neural adaptation paradigm using rapid stimulus rates was performed to distinguish whether the abnormal cochlear potentials were generated by neural and/or receptor sources.