First TMEM126A missense mutation in an Italian proband with optic atrophy and deafness

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Recessively inherited optic neuropathy has been an elusive entity for a long time. Currently, a few causative genes have been described, associated with a spectrum of isolated or syndromic optic atrophy. Among these genes, TMEM126A (OPA7) was the first to be reported, with a single causative mutation found in all pedigrees identified to date of North African ancestry (c.163C>T; p.Arg55X), thus possibly belonging to the same founder mutational event.1,7,8

Case report
A 16-year-old girl was born by likely consanguineous parents (figure A). Delivery was uneventful, and psychomotor development was normal. Medical history was relevant for an isolated febrile seizure at 4 months and migraine since age 14 years. The only brother presents a mild language disorder improved by logopedic rehabilitation, and the grand-grandmother is affected by epilepsy.

Visual problems were recognized when the patient was aged 4 years with evidence of bilateral optic atrophy. We observed the patient at age 16 years. Neurologic examination was unremarkable except for the presence of sporadic postural and rest myoclonic jerks at upper and lower limbs and brisk deep tendon reflexes. Ophthalmologic evaluation showed visual acuity OD 0.16, OS 0.125, bilateral temporal pallor at fundus examination, profound color deficit, and bilateral cecocentral scotoma at automated visual fields (figure B). Optical coherence tomography showed bilateral diffuse optic atrophy (figure B).

Laboratory examinations were relevant for the presence of increased lactic acid levels after standardized exercise (35.5 mg/dL; normal values 5–22 mg/dL). Brain MRI was normal. Cardiologic examination showed only the presence of a mild mitral valve prolapse. Audiometry disclosed the presence of bilateral mild sensorineural deafness. EMG ruled out the presence of peripheral neuropathy. Pattern visual evoked potentials showed the absence of cortical responses in OD and increased latency in OS. Somatosensory evoked potentials and EEG with muscle recordings were normal and in particular did not reveal the presence of a cortical correlate of myoclonic jerks. Cognitive evaluation showed a profile within normal limits (Wechsler Intelligence Scale for Children-IV score = 88).

Genetic analysis, after informed consent and EC approval (CE AVEC 211/2018), by a custom next-generation sequencing (NGS) panel of optic atrophy-related genes revealed the presence of a homozygous mutation affecting the TMEM126A gene (c.497A>G, p.Q166R), affecting one of the transmembrane helices. According to the public database GnomAD
(gnomad.broadinstitute.org), this variant is reported in 3 alleles, but never in homozygosity, and it is predicted to be pathogenic (CADD phred 26.2). This mutation is compatible with the diagnosis of recessive optic neuropathy (figure A).

**Discussion**

The genetic landscape of inherited optic neuropathies, including the rare recessive forms, has been greatly expanding thanks to the availability of NGS techniques.\(^1\)\(^-\)\(^6\) Our case is a non-African patient carrying a recessive homozygous TMEM126A missense mutation, born from likely consanguineous Italian parents and presenting in early childhood with isolated bilateral optic atrophy. Both in silico predictions and segregation analysis were compatible with the diagnosis of recessive optic neuropathy associated with this TMEM126A missense variant. Careful clinical evaluation disclosed also a mild sensorineural deafness, which has been previously reported in association with the North African TMEM126A mutation.\(^1\)\(^,\)\(^7\)\(^,\)\(^8\) Only 6 families of African ancestry (Algeria and Morocco) have been reported to date, all carrying the c.163C>T (p.Arg55X) mutation, suggesting a founder effect.\(^1\)\(^,\)\(^7\)\(^,\)\(^8\) The patients described in these reports presented a variable phenotype, despite the association with the same mutation, ranging from isolated to syndromic optic atrophy. Extraocular features included sensorineural deafness, hypertrophic cardiomyopathy, and peripheral polyneuropathy. Moreover, a Leber's hereditary optic neuropathy–like presentation has been described in 1 patient.\(^8\)
TMEM126A is a mitochondrial protein, located in the inner mitochondrial membrane with still unknown functions, highly expressed in the brain, cerebellum, fetal brain, skeletal muscle, tests, fetal retinal pigmentary epithelium, and fetal retina of humans. Polarographic tests and spectrophotometric assays on cultured skin fibroblasts showed normal respiratory chain function, but partial deficiency of complex I in 1 patient from the original study. In our case, the abnormal lactic acid elevation after standardized effort confirms that TMEM126A is somehow involved in oxidative phosphorylation, even if its precise role remains to be defined and further functional studies are needed.

Overall, we found a second recessive mutation in the TMEM126A gene in an Italian proband, who, similarly to the previously reported cases with the same North African founder mutation, is affected by optic atrophy and mild sensorineural deafness. The phenotype recurring with recessive TMEM126A mutations is quite consistent, and we predict that more cases will be diagnosed, as NGS is now largely available in diagnostic centers.

Author contributions
C. La Morgia, L. Caporali, and V. Carelli: conception, drafting, and revision of the manuscript. F. Tagliavini and F. Palombo: genetic analysis and interpretation of results. M. Carbonelli and P. Barboni: ophthalmologic evaluation and revision of the manuscript. R. Liguori: interpretation of results and revision of the manuscript.

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Disclosure
C. La Morgia is involved in clinical trials with Santhera Pharmaceuticals (Raxone in Leber’s Hereditary Optic Neuropathy) and GenSight Biologics (gene therapy with GS10 in Leber’s Hereditary Optic Neuropathy) and received travel reimbursements from Santhera Pharmaceuticals and Omicron Pharmaceuticals. V. Carelli is involved in clinical trials with Santhera Pharmaceuticals (Raxone in Leber’s Hereditary Optic Neuropathy), GenSight Biologics (gene therapy with GS10 in Leber’s Hereditary Optic Neuropathy), and Stealth BioPharma (Elamipretide in Primary Mitochondrial Myopathy) and received speaker honoraria for educational courses and travel reimbursements from Santhera Pharmaceuticals. He is also funded for research program by Stealth Pharmaceuticals, and his research is supported by grants from the Italian Ministry of Health, Telethon, the Emilia Romagna Region, the patient’s organization MITOCON, and by private donations. Disclosures available: Neurology.org/NG.

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