Parkinsonism and Related Disorders 102 (2022) 54–56

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis

Correspondence

A misleading presentation of Mohr–Tranebjaerg syndrome: What is hidden behind an axonal neuropathy?

- Mohr–Tranebjaerg syndrome can present with rare sub-phenotypes.
- Peripheral neuropathy can be an uncommon sign of Deafness Dystonia syndrome.
- Accurate pedigree collection and evaluation is needed to improve exome results analysis in patients with uncommon phenotypes.

The X-linked Mohr-Tranebjaerg syndrome (MTS) is one of the most reported sub-groups of deafness dystonia syndromes, characterised by early-onset progressive auditory neuropathy, dystonia, and optic atrophy. Cognitive and behavioural impairment are also frequent [1].

Genetic cause of MTS has been identified in *TIMM8A* gene mutations [2]. *TIMM8A* encodes Tim8A, a translocase involved both in the import of proteins from the cytoplasm into the mitochondrial inner membrane and in the maintenance of oxidative phosphorylation [3]. To date only 32 pathogenic mutations in less than 100 cases have been reported [1].

In this paper we report a 49-year-old man who came to our attention for a peripheral neuropathy associated with early onset hypoacusia. At 6 years, he presented a slowly progressive sensorineural hypoacusia. He can lip-read and presents dysarthria due to the ear impairment. At the age of 40, he presented an axonal peripheral sensory-motor neuropathy (nerve conduction study in Fig. 1D).

At 47 years, he developed a postural tremor, a kinetic tremor of the upper limbs and a cerebellar and sensorial ataxia. At the age of 52, he showed dysarthria, soft palate and uvula hypofunction and no pharyngeal reflex. At this age, neurological examination showed normal muscle trophism and strength, bilateral distal hypoesthesia, and ankle hypopallesthesia. Only the achilles reflexes were bilaterally absent. He presented broad-based gait, not possible in tandem. Positive Romberg sign was present. At the examination, the patient complained of muscles cramps in the back of the thighs.

His eldest brother, died at 56 years due to a septicaemia, came at our attention at 47 years for peripheral neuropathy. He had severe childhood hypoacusia and a diagnosis of axonal peripheral sensory-motor neuropathy at 46 years. He also developed tremor of head and limbs and progressive generalised dystonia at 54 years. He presented a trunk dystonia with hyperextension of head and a distal progression to fingers and toes in flexion. A diffuse parathonia was also described.

In both probands the common causes of axonal neuropathies such as alcoholism, diabetes or vitamins deficiency were ruled out.

The analyses of genes *GJB1, ATXN1, 2, 3, 8, FXTAS* and *POLG1* were carried out, but no pathogenic variants were found.

Due to the association of hypoacusia and axonal neuropathy, CMT-related genes NGS panel and Perrault syndrome genes direct sequencing were carried out. All analyses resulted negative.

The family was revaluated in a genetic counselling session, which ascertained the presence of a maternal uncle, not previously reported, with similar clinical phenotype (Fig. 1A). Due to the suggestive family history and the negativity of all previous results, a CNVs evaluation in the proband was carried out through CGH-array and a whole exome analysis (WES) was performed in both affected siblings and their parents, focusing on X-linked and autosomal recessive inheritance genes. Nextera rapid capture exomes kit (Illumina) was used to prepare libraries, which were sequenced on an Illumina sequencer.

After alignment against hg38 reference and annotation through Ensembl-VEP, variants of interest were selected based on allele frequency ($f<0.01\%$) with priority for those with damaging impact prediction.

The CGH-array did not show any structural rearrangements, while WES detected, in hemizygous state in the siblings and in heterozygous state in the healthy mother, the already reported variant c.133_135del (p.E45del) in exon 2 of *TIMM8A* (NM_004085.4).

The deletion was confirmed by Sanger sequencing (Fig. 1A), preceded by a selective PCR of *TIMM8A* to avoid pseudogene amplification.

Our *in-silico* analysis suggests two possible pathogenic mechanisms. The first one focuses on the E45 deletion leading to a probably break of the canonical acceptor site, according to four prediction tools (HSF, MaxEnt, Fruit Fly and SpliceAI) (Fig. 1B). Notably a transversion c.133-1G > T, involving the same acceptor site, was recently reported in ClinVar (RCV001268360).

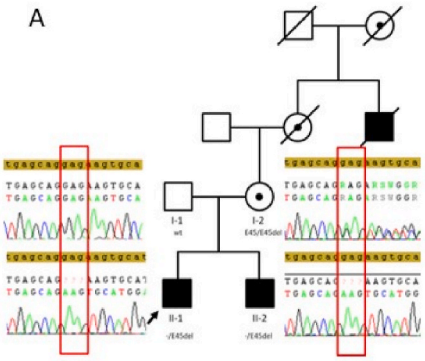
The second mechanism affects Tim8A tertiary structure characterized by a Twin CX3C motif; here two disulfide bonds C43–C66 and C47–C62 allow a zinc finger folding. An *in-silico* evaluation by *DiANNA 1.1 web server* highlights a probable loss of the C47–C62 disulfide bond due to the E45 deletion (Fig. 1C). This conformational change possibly prevents Tim8A from accomplish its role as a transporter between the two mitochondrial membranes. Based on these *in silico* evidences, we can postulate a complete loss of function due to an incorrect mRNA splicing or to a disruption of the proper protein conformation. To date loss of function mechanism is the only one described for all *TIMM8A* mutations associated with MTS.

Interestingly, also the only reported pathogenic missense variant (p.C66W) replaces one cysteine disrupting the disulfide bond [4].

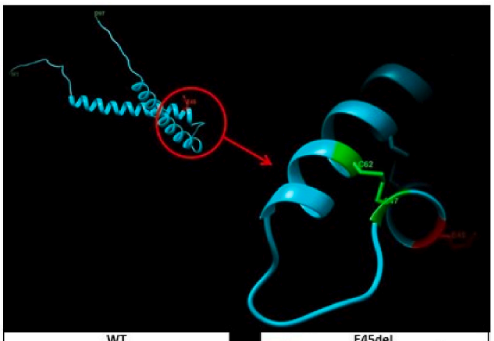
According to the American College of Medical Genetics and Association for Molecular Pathology (ACMG/AMP) guidelines, considering the

https://doi.org/10.1016/j.parkreldis.2022.07.021
Received 10 May 2022; Received in revised form 21 July 2022; Accepted 24 July 2022
Available online 5 August 2022

A



C



WT			E45del		
Cys sequence position	Distance	Score	Cys sequence position	Distance	Score
47-62	15	0,997	46-61	15	0,049

B

agggacccctgcccccaaccgtcttttttctttccaagttccctttgtgattctgtatcttgtcct
gagcagGAGAAGTGCATGGACAAGCCTGGGCCAAAGTTGGACAGTC
GGGCTGAGGCCTGTTTTGTGAACTGCGTTGAGCGCTTCATTGATACA
AGCCAGTTCATCTTGAATCGACTGGAACAGACCCAGAAATCCAAGCC
AGTTTTCTCAGAAAGCCTTTCTGACTGA

	PREDICTION			
	Donor Site	Acceptor Site	Criptic Donor Site	Criptic Acceptor Site
HSF matrix	/	Broken	Activation	Activation
MaxEnt matrix	/	Broken	/	Activation
Fruit Fly	/	Broken	/	Activation
AI splice	/	Broken	/	Activation

D

	Onset lat (ms)	Amp (mV)	Vel (m/s)
Left Median nerve Motor			
Wrist	4.0	7.2	50
Elbow	9.4	6.8	
Right Median nerve Motor			
Wrist	2.9	0.5	47
Elbow	8.4	0.3	
Left Ulnar nerve Motor			
Wrist	3.0	9.7	51
Below elbow	7.6	7.1	62
Above elbow	9.5	6.6	
Left Tibial nerve Motor			
Ankle	5.8	0.2	35
Knee	19.2	0.2	
Left Peroneal nerve Motor			
Ankle	5.5	0.2	36
Popliteal fossa	15.9	0.4	35
Fibular head	18.5	0.1	
Right Sural Nerve sensory			
Calf	Not evocable		

Fig. 1. 1A. *TIMM8A* family pedigree. An electropherogram showing c.133_135del is besides every analyzed individual. **1B**. exon 2 acceptor site in bold letters and the 3-base deletion in a box; the table summarizes splicing *in silico* predictions**. 1C.** the wild type 3d model of the mutation region. The p.E45 is red marked while the cysteine bisulfide bonds are in green. Table shows the decrease in probability of C47–C62 disulfide bond formation due to E45 deletion. **1D**. Nerve conduction study at the first visit of the youngest brother. Onset lat: onset latency; Amp: amplitude; Vel: velocity. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

congruent co-segregation resulting from WES analysis, the variant is classified Likely Pathogenic.

This variant has been described only once in a 13-year-old boy who presented bilateral hypoacusia. Due to the young age this patient cannot yet present the complete clinical picture associated with *TIMM8A* mutations [1]. The siblings we describe herein presented early onset hypoacusia and axonal peripheral neuropathy with later onset. Both were ataxic, while dystonia appeared in the sixth decade only in the older brother.

MTS male patients usually present childhood-onset bilateral hypoacusia and dystonia/ataxia with mean onset in the third decade, ranging from childhood to the sixth decade. At the best of our knowledge, a peripheral neuropathy that precedes the onset of dystonia by years was never described.

Inherited hypoacusia is not so rare and it can be transmitted in all inheritance patterns. For this reason, hypoacusia, when described in patients with other symptoms, is not always part of a syndromic picture. However, the presence of neuropathy and hypoacusia is not rare in association with several genes. Nowadays at least 36 hereditary neuropathies genes have been described in association with deafness [5]. Thus, we first investigated in our patient CMT-related and then Perrault syndrome genes, considering this diagnosis could explain the presence of ataxia.

The precise diagnosis was reached only when the collection of an accurate familial history, suggesting X-linked inheritance, and genetic technological advancements were associated. In-depth knowledge of the patients' clinical and family history can effectively guide exome analysis and filter promising variants. This once again underlines the absolute need for information sharing and collaborative patient's evaluation between clinicians and the medical genetics laboratory.

All patients signed informed consent waivers for diagnostic and research purpose in accordance with national laws and guidelines for genetic testing.

This work was developed within the framework of the DINOGMI Department of Excellence of MIUR 2018–2022 (legge 232 del 2016). Thanks to ACMT Rete for all the support.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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