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Case report

Two novel cases of compound heterozygous mutations in mitofusin2: Finding out the inheritance

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Abstract

MFN2 is the major gene involved in the axonal form of Charcot–Marie–Tooth disease. It usually has an autosomal dominant pattern of inheritance, but a few cases of homozygous or compound heterozygous mutations have been described. These patients usually present an earlier onset, more severe phenotype and their inheritance pattern can span from autosomal recessive to semidominant.

Here we report two unrelated patients carrying two compound heterozygous *MFN2* mutations. Both present a pure axonal neuropathy without any additional features. The first patient presents a mild clinical phenotype with onset in the 2nd decade, while the second patient shows a severe, early onset phenotype with loss of independent ambulation. Only a careful clinical examination as well as neurophysiological and genetic studies allowed us to establish the role and the transmission pattern of the identified variants. We discuss practical consequences of this finding in genetic counseling.

Keywords: *MFN2*; CMT2; Compound heterozygosity; Inheritance; Genetic counseling

1. Introduction

MFN2 (*Mitofusin 2*) is the most frequently involved gene in the axonal form of Charcot–Marie–Tooth disease (CMT2), with a mutation frequency ranging from 8 to 30% [1]. *MFN2* is a nuclear gene encoding for MFN2, a mitochondrial GTPase, essential for structural integrity, morphology and motility of mitochondria together with Mitofusin 1 (MFN1), Ganglioside-induced differentiation-associated protein 1 (GDAP1) and Optic atrophy 1 (OPA1) [2]. MFN2 also plays a role in mitochondrial anterograde transport in cooperation with Miro–Milton complex [3]. It is involved in the energetic metabolism through its effects on oxidative phosphorylation [4] and it is implicated in Ca2+ uptake regulation, which promotes the endoplasmatic reticulum–mitochondria binding [5].

To date, 191 different *MFN2* variants are described in HGMD® database, mostly with an autosomal dominant (AD) inheritance. However, since 2008, rare cases of compound heterozygous or homozygous mutations have been reported [6]. This has contributed to the expansion of inheritance features of *MFN2*-related neuropathies.

Clinically, the *MFN2* related form of CMT (CMT2A) can span from a severe early onset neuropathy to mild late onset neuropathy [1]. Phenotype is often more complex than a pure form of peripheral neuropathy and additional features such as hearing loss, optical atrophy or pyramidal signs have been described [7–9].

Literature reported approximately 15 patients that are compound heterozygous or homozygous carriers of *MFN2*

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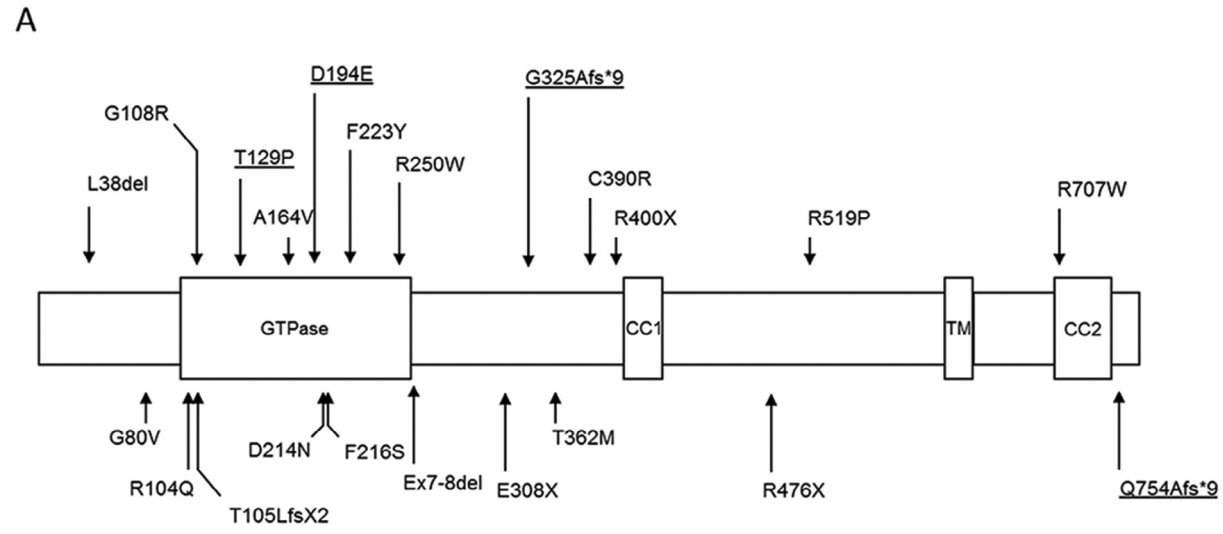

B

	748	758
wt	---F T H Q Y L Q P S R	**Stop**
	748	761
Q754Afs	---F T H Q Y L A A Q Q I V G T	**Stop**

AA Change	POLYPHEN2	SIFT
T129P	Pr. Damaging (0,979)	Damaging (0,001)

C

	325	758
wt	--- A Q G M P E G G G A L A E G F Q ..... R	**Stop**
	325	332
G325Afs	--- A Q G M P E G G A L S Q K A F K	**Stop**

AA Change	POLYPHEN2	SIFT
D194E	Pr. Damaging (0,992)	Damaging (0,002)

Fig. 1. *MFN2* "double mutations". (A) Schematic view of MFN2 protein backbone in which pointed out are all homozygous or compound heterozygous *MFN2* mutations reported in literature. MFN2 mutations described in this work are underlined. (B) MFN2 mutations impact concerning family 1. Up: Frameshift mutation effect on protein. Down: missense mutation in silico pathogenicity prediction. (C) MFN2 mutations impact concerning family 2. Up: Frameshift mutation effect on protein. Down: missense mutation in silico pathogenicity prediction.

mutations (Fig. 1A), with autosomal recessive (AR) or semi-dominant inheritance [10]. These patients usually present with a severe early onset neuropathy. Milder cases with childhood onset have also been described [10,11]. Patients with severe phenotype often become wheelchair bound within 30 years of life [6,12,13] and occurrence of additional features is quite common as in patients with autosomal dominant mutations [1,6,11–13].

The presence of rare variants without strong pathological effect, *de novo* mutations and incomplete penetrance makes *MFN2* genetic scenario even more complicated.

Here we present two unrelated patients who carry compound heterozygous *MFN2* mutations. We will also discuss practical consequences of this finding in genetic counseling.

2. Case report

2.1. Patient 1

The patient is a 17 year old woman with a mild peripheral neuropathy with onset at age 14. Family history was positive for neuromuscular disorder with the patient's mother, maternal grandfather and a younger brother showing very mild signs of peripheral neuropathy (Fig. 2A).

At neurological examination, performed at the age 14, the proband showed a mild waddling gait with upright impossible on the toe and the heels. She also showed bilateral pes cavus, mild hypotrophy and weakness of lower distal muscles and resting tremor of the hands. Nerve conduction studies (NCS), performed at the same age, showed an axonal neuropathy at lower limbs (Table 1). At last visit CMTES score was 8/28.

DNA sequencing, previously negative for mutations in *GJB1* and *MPZ* genes, identified two heterozygous variants in *MFN2* gene: a novel substitution c.385A>C p.T129P and an already described insertion c.2258dupT p.Q754Afs*9 [14] (mutations submitted to lovd – http://databases.lovd.nl/shared/genes/MFN2). The c.385A>C transversion was not reported in public databases (Exome Aggregation Consortium – Exac, Exon Variant Server – EVS, 1000genomes) and it was predicted pathogenetic by *in silico* prediction software, Polyphen2 (probably damaging: 0.979) and SIFT (damaging: 0.001) (Fig. 1B).