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Clinical report

De novo *DNM1L* variant presenting with severe muscular atrophy, dystonia and sensory neuropathy

Natalie Keller [a], Cem Paketci [b], Pinar Edem [b], Holger Thiele [c], Uluc Yis [b], Brunhilde Wirth [a], Mert Karakaya [a,*]

[a] Institute of Human Genetics, Center for Molecular Medicine Cologne (CMMC), Institute of Genetics, and Center for Rare Diseases Cologne, University of Cologne, Cologne, Germany
[b] Dokuz Eylül University, Department of Pediatric Neurology, Izmir, Turkey
[c] Cologne Center for Genomics, University of Cologne, Cologne, Germany

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ABSTRACT

DNM1L encodes dynamin-related protein 1 (DRP1), a multi-domain GTPase essential for mitochondrial and peroxisomal division. Autosomal dominant and recessive variants in *DNM1L* cause encephalopathy due to defective mitochondrial and peroxisomal fission 1 (EMPF1), which presents as a complex and clinically heterogeneous neurological disorder of variable severity, often accompanied by seizures. Clinical features are diverse, and no clear phenotype-genotype correlations were drawn to date. *DNM1L*-related sensory neuropathy has recently been reported as a predominant feature in one case with a *de novo* variant in the GTPase domain. Herein we present a second case with *DNM1L*-related sensory neuropathy as the predominant underlying feature without motor neuron involvement, which resulted in severe muscular atrophy and generalized dystonia.

1. Introduction

DNM1L encodes dynamin-related protein 1 (DRP1), a member of the dynamin superfamily of large multi-domain GTPases that share a characteristic domain structure consisting of a GTPase domain, a middle domain and a GTPase effector domain (GED) (Praefcke and McMahon 2004). DRP1 has long been recognized as a crucial player in mitochondrial fission, with a role also in peroxisomal division (Koch et al., 2003). Recruited by receptor proteins, cytosolic DRP1 re-localizes to the mitochondrial outer membrane (MOM), assembling into large multimeric structures in a ring-like formation around the MOM, which is then constricted via GTP-dependent conformational changes (Tilokani et al., 2018). The balance of fission and fusion, known as 'mitochondrial dynamics', is essential for mitochondrial and cellular function, and pathogenic mutations causing disruption of the mitochondrial dynamics machinery have been associated with severe human disorders mainly affecting the neuromuscular and central nervous system (Tilokani et al., 2018).

Pathogenic variants in *DNM1L* can cause complex and severe autosomal dominant or recessive encephalopathy due to defective mitochondrial and peroxisomal fission 1 (EMPF1, OMIM 614388), as well as isolated autosomal dominant optic atrophy 5 (OPA5, OMIM 610708). EMPF1 is characterized by a large phenotypic variability, ranging from lethal infantile encephalopathy to hypotonia and developmental delay, presenting with or without seizures and with a highly variable set of additional features including microcephaly, brain MRI abnormalities, optic atrophy, ataxia and spasticity (Waterham et al., 2007, Chao et al., 2016, Fahrner et al., 2016, Nasca et al., 2016, Sheffer et al., 2016, Vanstone et al., 2016, Yoon et al., 2016, Zaha et al., 2016, Diez et al., 2017, Hogarth et al., 2018, Whitley et al., 2018, Assia Batzir, Bhagwat et al., 2019, Kahrizi et al., 2019, Kim et al., 2019, Tarailo-Graovac et al., 2019, Vandeleur et al., 2019, Verrigni et al., 2019, Longo et al., 2020) (Fig. 1). Investigation on patient-derived fibroblasts typically shows mitochondrial elongation, while peroxisomal morphology is only impaired in some cases (Waterham et al., 2007; Chao et al., 2016; Nasca et al., 2016; Verrigni et al., 2019; Longo et al., 2020). As a consequence, a clear genotype-phenotype correlation could not be reached due to the unique molecular profile and clinical outcome of each different *DNM1L* variant. Especially in this context, it is essential to molecularly diagnose and phenotypically characterize novel pathogenic *DNM1L* variants that can in turn shed further light upon the complexity of *DNM1L* mutations and their phenotypical consequences.

* Corresponding author. Institute of Human Genetics, University of Cologne, Kerpener Str. 34. 50931 Cologne, Germany.
E-mail address: mert.karakaya@uk-koeln.de (M. Karakaya).

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So far, *DNM1L*-related sensory neuropathy has only been reported as a predominant feature in one recent case with a *de novo* missense variant in the GTPase domain. This individual presented with severe hypotonia, developmental delay, reduced muscle bulk, ataxia due to sensory neuropathy, and an unremarkable muscle biopsy (Longo et al., 2020). In this work, we report the second case with a predominant severe axonal sensory neuropathy resulting in a severe muscle amyotrophy, developmental delay and dystonia, caused by a novel *de novo* variant in *DNM1L* in the GTPase domain.

2. Clinical report

A 10-year-old boy from a non-consanguineous family of Turkish origin was first admitted to the hospital due to muscular weakness at the age of five months. He did not gain head control or sitting without support over time. He could smile and make eye contact. He learned to use a few single words but lost this ability as the disease progressed. He developed generalized tonic-clonic seizures at the age of eight years. The initial levetiracetam therapy was changed to oxcarbazepine due to ongoing seizure activity. Clinical examination at 10 years of age showed severe developmental and growth delay and a cachectic appearance. Growth percentiles were significantly below the standards (weight: 10 kg [-9.4 sds], length: 100 cm [-6.2 sds] and head circumference: 47 cm [-4.45 sds]). Both distal and proximal muscles were weak and severely atrophic (Fig. 2A). Furthermore, he had a dystonic posture and showed intermittent opisthotonus and bilateral ulnar deviation but no contractures (Fig. 2B). He did not have any numbness or sensory loss on his feet, which could not be evaluated optimally due to his cognitive limitation. However, no chronic ulcers or pain insensitivity could be detected on sensorial examination. Deep tendon reflexes were diminished and Babinski sign was negative. There were no respiratory or feeding difficulties. Cranial nerve examination was normal. The presence of ataxia could not be assessed due to his ambulatory loss. Dysmorphic facial features included large eyes, prominent eyelashes, long face, triangular face shape, thin upper lip vermillion, broad nasal bridge and high arched palate (Fig. 2C). The cranial MRI at seven years of age was unremarkable except for a non-specific left cerebellar venous angioma. Electroencephalographic examination at the age of 10 years showed right anterior sharp-slow wave activity without any encephalopathic pattern. Electromyography showed neurogenic abnormalities. Interestingly, nerve conduction studies were consistent with a pure axonal sensory neuropathy with normal motor nerve conduction velocities and amplitudes. No stimulation could be detected on the sensory nerves of both upper and lower extremities. Echocardiography revealed grade 0–1 mitral insufficiency. Auditory tests were normal. Except for the tigroid appearance of the retina that was shown through a fundus examination, no other ophthalmologic examinations were performed. Creatine kinase levels and a large metabolic screening (including lactate, pyruvate, ammonia, plasma/urine amino acids, acylcarnitine profile, and very long chain fatty acids) were normal.

An extensive genetic testing was undertaken previously but revealed no causal genetic alterations (including karyotype, microarray, subtelomeric FISH, del15q11.2 FISH, gene panel for epileptic encephalopathies and mitochondrial depletion syndromes and single gene testing of *SMN1*, *NPC1*, *NPC2* and *PMM2* genes). We performed trio whole exome sequencing (trio WES) for the index patient and his biological parents. Informed written consent for next generation sequencing (NGS) and publication purposes (including photos depicting relevant clinical

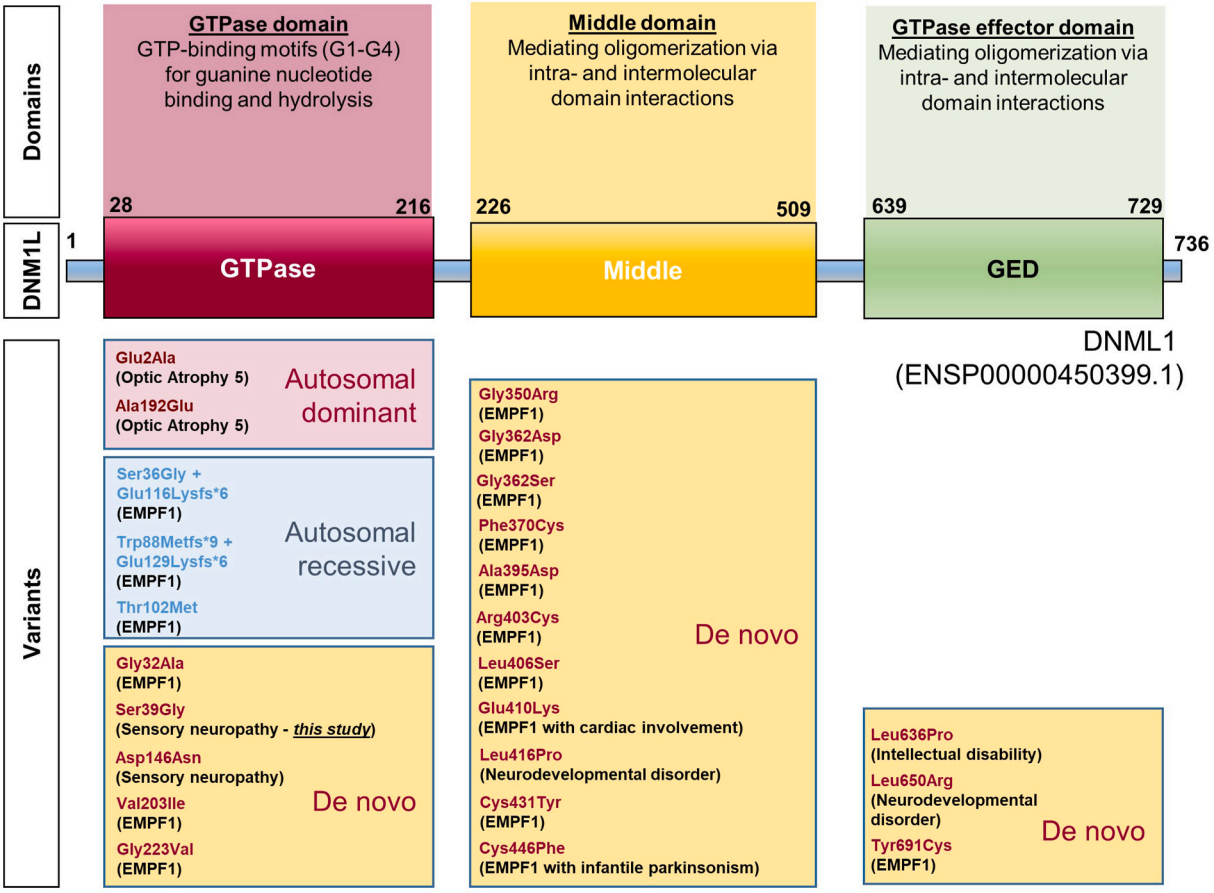

Fig. 1. Overview of the domain structure of DNM1L, the identified variants at each domain. *Upper:* Overall architecture of the GTPase domain, the middle domain and the GTPase effector (GED) domain that are essential for the oligomerization and regulation of the GTPase activity [1]. *Lower:* Identified variants and consequent phenotypes due to each reported pathogenic variant. EMPF1: Encephalopathy due to defective mitochondrial and peroxisomal fission 1.

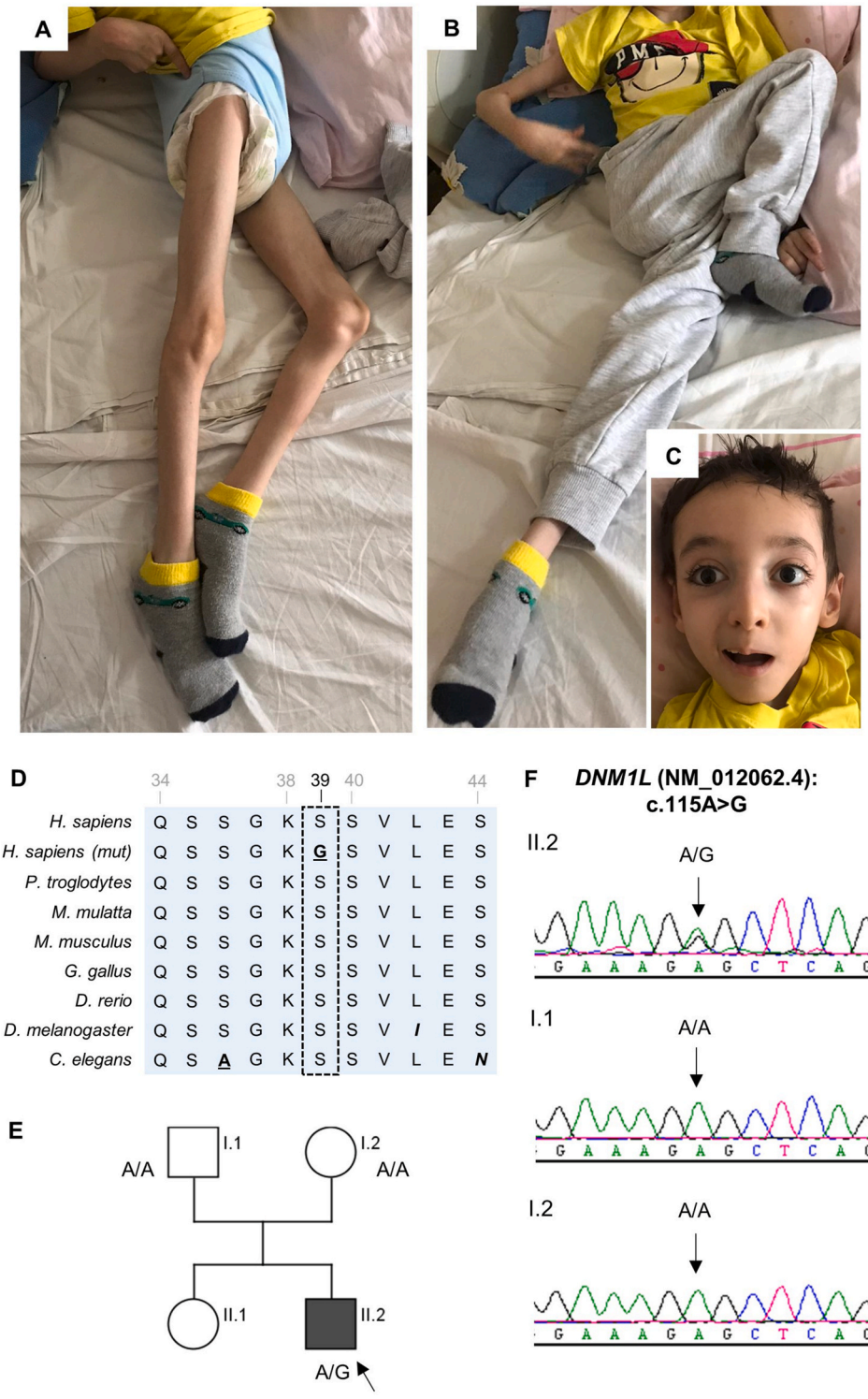

Fig. 2. Clinical findings and genetic analysis **(A)** Severe muscular atrophy of the proximal and distal lower extremities. **(B)** Dystonic posture of the trunk, and muscular atrophy of the upper extremity. **(C)** Facial features of the patient. **(D)** Conservation of Ser39 in *DNM1L* across species. Bold&underlined: amino acid changes causing a charge alteration. Bold&*italic*: amino acid changes within similar groups. **(E)** Pedigree of family. **(F)** Sanger sequencing confirmed the *de novo* c.115 A > G (NM_012062.4) variant.

features) were obtained from the parents and the affected individual in accordance with the regulations of the ethics committee of the University of Cologne. WES and bioinformatics processing of the NGS data was performed as described in the supplementary material (Supplementary Data 1).

Trio WES confirmed non-consanguinity of the parents via the overall low runs of homozygosity (ROH) sum of 41 Mb in the patient and the average allele sharing percentage between the parents of only 1%. In total, the exome analysis yielded two *de novo* and two compound-heterozygous variants (Supplementary Data 2). After variant prioritization and filtering (Supplementary Data 1), we identified a *de novo* missense variant in exon 2 of *DNM1L* (NM_012062.4: c.115 A > G) as the single putatively causative variant. The variant results in the replacement of the evolutionary conserved serine 39 residue with glycine (p.Ser39Gly) in the G1 motif (P-Loop) of the GTPase domain (Wenger et al., 2013) (Fig. 2D). The Ser39 residue in the P-Loop is involved in GTP binding, as it forms one of the four hydrogen bonds that fix the α-phosphate to the P-Loop, and enables a conformation change that putatively stabilizes a GTP transition state by rotating its side chain about 180° upon GTP binding (Wenger et al., 2013). Systematic

mutation of serine 39 to alanine was previously shown to result in complete abolishment of GTP hydrolysis (Wenger et al., 2013), highlighting the importance of the Ser39 residue and suggesting impairment of GTP binding and consequently GTPase activity as the underlying pathomechanism in our patient with a p. Ser39Gly mutation. The c.115 A > G variant was not reported in the in-house database or in gnomAD (https://gnomad.broadinstitute.org/). A median rank score of 0.9 (0 = benign; 1 = pathogenic) according to 31 different *in silico* prediction algorithms was highly indicative of pathogenicity (Supplementary Table 1). We subsequently validated the d*e novo* status via Sanger sequencing (Fig. 2E–F). The variant is submitted to Clinvar and can be accessible under the accession number: VCV000974819.1.

3. Discussion

This report constitutes a novel case of a severe neurodevelopmental disorder presenting with severe amyotrophy, dystonia and sensory neuropathy due to a heterozygous *de novo DNM1L* missense variant in the GTPase domain, and thereby provides a further step towards uncovering and understanding the complex phenotypical spectrum caused by impairment of DRP1 structure and function. All three typical dynamin-superfamily domains of DRP1 (GTPase domain, middle domain and GED) have been implied in the complex EMPF1 spectrum. Both the middle domain and GED have to date only been associated with *de novo* variants causing a complex early-onset neurological and neurodevelopmental phenotype with or without seizures through a putative dominant-negative mechanism (Fig. 1).

The GTPase domain, on the other hand, is associated with significant genetic and phenotypic variability. Inherited dominant missense variants have been reported in three large families with isolated optic atrophy due to a dominant negative effect restricted to mitochondrial fission (Gerber et al., 2017). Biallelic mutations in the GTPase domain have been detected in five individuals from three unrelated families with infantile encephalopathy through a loss-of-function effect, although the clinical spectrum ranged from rapidly lethal to slowly progressive and showed a variable set of accompanying features including cerebellar and ocular involvement, pyramidal signs and MRI abnormalities (Nasca et al., 2016; Yoon et al., 2016; Hogarth et al., 2018). Neither optic atrophy nor seizures were reported in these cases. All biallelic mutations were shown to cause defective mitochondrial fission, whereas impaired peroxisomal morphology was only detected in one family (Nasca et al., 2016; Yoon et al., 2016; Hogarth et al., 2018).

So far, *de novo* variants in the GTPase domain have only been reported in four cases. All reported variants were missense and had a dominant negative effect (Trujillano et al., 2017; Whitley et al., 2018; Verrigni et al., 2019; Longo et al., 2020), in which mitochondrial fission defects were characteristic while peroxisomal morphology abnormalities were present variably. The heterozygous p. Gly223Val mutation presented with severe early-onset epileptic encephalopathy, cerebral and cerebellar atrophy (Verrigni et al., 2019). The p. Val203Ile resulted in a complex infantile condition with global developmental delay, dystonia and unspecified peripheral neuropathy (Trujillano et al., 2017). In a 7-year-old female, the *de novo* p. Gly32Ala variant caused a developmental delay, optic atrophy, ataxia and chronic recurrent aphthous ulcers without epileptic encephalopathy. The ataxia of this patient was based on the pure sensory neuropathy (Whitley et al., 2018). The *de novo* p. Asp146Asn variant caused the only case with a severe sensory neuropathy as a predominant feature resulted in severe muscular atrophy and hypotonia, sensory ataxia, and mild spasticity (Longo et al., 2020). Generally, our patient had a similar clinical presentation compared to this individual, although ataxia could not be assessed due to his ambulation loss. However, it should be noted that clinical features possibly due to a sensory neuropathy were present in other previously reported cases with mutations both in the GTPase and in middle domain, such as pain insensitivity and areflexia (Sheffer et al., 2016; Yoon et al., 2016). Because of the severity and complexity of *DNM1L* phenotypes, it is possible that in some cases sensory neuropathy was simply not a prominent feature and therefore not specifically investigated.

To explain the facial dysmorphic features of our patient, we performed a comprehensive genetic testing including conventional chromosome analysis and microarray, however no alteration that could explain the facial features was identified. To date, there is no evidence that the facial dysmorphia could be a phenotypical outcome of the variants in *DNM1L*. In the absence of the more informative ophthalmologic methods, it is not clear yet if the tigroid appearance of the retina shown by a fundus examination belongs to the phenotypic spectrum of *DNM1L*-related disease.

As in our case, severe muscle wasting is a substantial feature in the majority of the individuals with pathogenic *DNM1L* variants. However, no clear consensus regarding the cause of the severe muscle wasting has been reached to date. Although in some patients peculiar findings in muscle biopsies suggest an abnormal mitochondria distribution (Verrigni et al., 2019), these findings were not present invariably in other affected individuals (Whitley et al., 2018; Longo et al., 2020). Lack of sensorial input due to severe sensorial defects could also contribute to this severe muscle pathology, as we and others have previously shown that disturbed proprioception could lead to aberrant muscle development and function caused by the mutations in Piezo-type mechanosensitve ion channel component 2 (*PIEZO2*) (Chesler et al., 2016; Delle Vedove, Storbeck et al., 2016).

The underlying pathomechanism of DRP1 mutations, in which peripheral sensory nerves are impaired while the motor neurons are spared, remains to be elucidated. Contrastingly, encephalopathy due to defective mitochondrial and peroxisomal fission 2 (EMPF2, OMIM 617086), which is caused by mutations in another mitochondrial fission factor (*MFF*), displays peripheral neuropathy with motor nerve involvement (Koch et al., 2016). Another remaining question is how peroxisomal abnormalities contribute to the EMPF1 phenotype, as abnormal peroxisomal morphology and/or increased very long fatty chain acids (VLFCA) were only detected in a number of individuals, without clinical links that could establish a peroxisomal defect presenting with additional or specific features.

Extreme muscle wasting is not a typical feature of sensory neuropathies, which is rather a typical feature of primary muscular disorders. However, no muscle pathology that might explain this severe muscle phenotype was reported to date. Moreover, the sole involvement of peripheral sensory nerves in the absence of motor neuron involvement remains to be elucidated. This report further highlights the complexity of the *DNM1L*-related disorder spectrum, which is yet to be completely understood. In the diagnosis of early-onset complex neurological and neurodevelopmental conditions, *DNM1L* variants should be considered as the emerging cause of a common picture of sensory neuropathy, severe muscular atrophy, dystonia and epilepsy.

Author statement

NK and MK recruited, analysed the NGS data and interpreted variants. BW and MK designed and coordinated the study. HT provided NGS platform, raw data and the software to analyze NGS data. CP, PE and UY performed the neurological and physical assessment of the patient provided clinical data and biological material from probands and family members, NK and MK wrote the manuscript, MK and BW provided main revision of the manuscript, all coauthors read and commented the manuscript.

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Declaration of competing interest

The authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejmg.2020.104134.

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