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Case Report

# MORC2 Associated Neurological Disease: Beyond Peripheral Neuropathy

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## Abstract

Missense variants in the Microrchidia CW-type zinc finger protein 2 (MORC2) gene were initially identified as a cause of Charcot-Marie-Tooth disease type 2Z (CMT2Z), a hereditary peripheral neuropathy. Subsequent reports revealed that MORC2-related disease has a much wider clinical spectrum, frequently involving the central nervous system through neurodevelopmental disorders, growth impairment and craniofacial dysmorphism. We describe the first reported Greek patient with MORC2-associated disease, a 29-year-old woman found to harbor the recurrent hotspot variant c.754C>T (p.R252W) in the ATPase domain of MORC2. She presented with childhood-onset gait difficulties, mild skeletal deformities, short stature, dysmorphic facial features, learning difficulties diagnosed as attention deficit hyperactivity disorder and dyslexia, and a length-dependent sensorimotor axonal polyneuropathy confirmed by nerve conduction studies. Although the p.R252W variant is most commonly associated with a pure CMT2Z phenotype, our patient displayed overlapping features with the broader neurodevelopmental phenotype known as DIGFAN (developmental delay, impaired growth, dysmorphic facies and axonal neuropathy), a combination reported only a handful of times previously. This case illustrates the pleiotropic nature of MORC2-related disease and supports current evidence indicating that CMT2Z and DIGFAN likely represent different points along a single disease continuum rather than distinct entities, sharing a common pathomechanism related to abnormal DNA methylation and downstream gene repression. Increased clinical awareness of this phenotypic overlap is essential, since patients with apparently isolated peripheral neuropathy may harbor additional systemic or neurodevelopmental features that warrant further evaluation. Recognition of the full clinical spectrum of MORC2-related disorders can help guide genetic counselling, anticipate associated comorbidities and inform future studies aiming to correlate genotype with the variable phenotypic expression of this disease.

***Keywords:*** *Microrchidia CW-Type Zinc Finger Protein 2 (MORC2) Gene; Charcot-Marie-Tooth Disease Type 2Z (CMT2Z); Missense Variants; Peripheral Neuropathy*

## Introduction

Missense variants located in Microrchidia CW-type zinc finger protein 2 (MORC2) gene were initially identified from a Spanish case series in 2016 as a cause of Charcot-Marie-Tooth disease type 2Z (CMT2Z) [1]. Thereafter, it was realized that the disease features a global distribution across the world and, most importantly, that it may frequently manifest CNS involvement, mainly in the form of various neurodevelopmental disorders [2]. Herein, we report the first MORC2 associated Greek case harboring the hotspot c.754C>T (p.R252W)

mutation and, prompted by this case, we emphasize the pleiotropy observed in MORC 2-related disorders in the light of recent literature data.

## Case Presentation

We report the case of a 29-year-old female patient that presented to the outpatient clinic of our hospital with gait impairment and mild skeletal deformities since childhood. Her parents reported difficulty in running from the age of seven, that was initially attributed to a tibial fracture at this age and a consequent leg length discrepancy. Furthermore, they reported growth impairment in the following years, as well as learning difficulties. The patient was assessed by a child psychologist and was diagnosed with attention deficit hyperactivity disorder (ADHD) and dyslexia, whereas her gait difficulties became more prominent in the subsequent years.

Clinical examination of the patient revealed short stature, slightly dysmorphic face, scapular winging, pes cavus (Figure 1), steppage gait and mild cognitive impairment. Neurological examination showed diffuse areflexia, distal amyotrophy along with symmetrical muscle paresis in her arms (MRC scale of 4/5) and legs (MRC scale of 3/5) distally and moderately impaired proprioception.

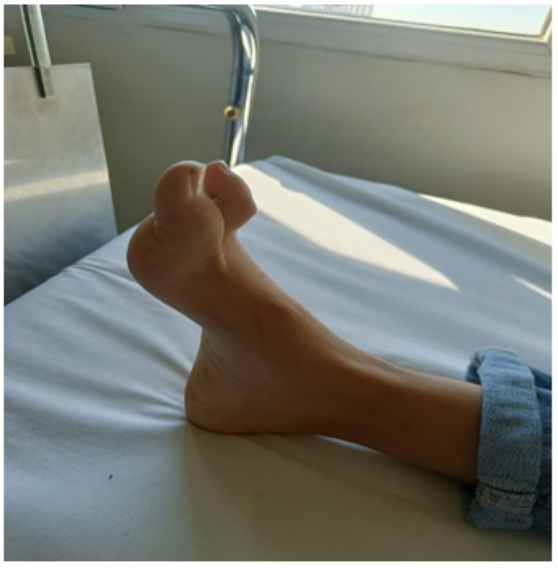

***Figure 1:*** *Pes cavus deformity observed in the patient's lower limb.*

The patient's medical and family history was unremarkable and she was not taking any medications. Nerve conduction studies were consistent with a length-dependent sensorimotor axonal polyneuropathy of moderate severity (Table 1). The patient was then referred to a geneticist and a targeted next-generation sequencing panel for hereditary neuropathies identified the heterozygous change c.754C>T in the MORC2 gene leading to p.R252W amino acid substitution. This variant, localized in the ATPase domain of the protein, has been repeatedly reported in patients with MORC2-related disorders and is considered pathogenic according to functional assays and in silico analysis [1,2]. The patient's parents have not yet undergone genetic testing to determine whether the variant has been inherited or has occurred *de novo*.

| | Normal Values | Right | Left |
|---|---|---|---|
| **Motor nerve conduction**<br><br>**DML (ms)** | | | |
| Median | < 3.9 | 3.5 | |
| Peroneal | < 5.5 | 4.8 | 5.3 |
| Tibial | < 5.5 | 3.6 | |
| F (median) | < 32 | 20 | |
| F (tibial) | <58 | 42 | |
| **Distal CMAP (mV)** | | | |
| Median | > 5 | 7.7 | |
| Peroneal | >2.5 | **0.7** | **2.3** |
| Tibial | >5 | **3.2** | |
| **MCV (m/s)** | | | |
| Median | >49 | 56.3 | |
| Ulnar | >49 | | |
| Peroneal | >40 | 38.5 | 42 |
| Tibial | >40 | **35** | |
| **Sensory nerve conduction** | | | |
| **SNAP (antidromic) (µV)** | | | |
| Median | > 16 | **4** | |
| Ulnar | > 13 | **2** | |
| Radial | > 10 | **6** | |
| Sural | > 5 | Absent | Absent |

***Table 1:*** *Neurophysiological assessment with nerve conduction studies.*

*CMAP: Compound Muscle Action Potential; DML: Distal Motor Latency; MCV: Motor Conduction Velocity; SNAP: Sensory Nerve Action Potential.*

*Bold value indicates the findings of abnormal values, or values close to normal limits.*

## Discussion

CMT2Z phenotype consists of infantile onset typically exhibiting SMA-like features, whereas childhood or early adulthood cases show either a classical axonal sensorimotor neuropathy, albeit with asymmetric progression to overt limb-girdle involvement, or a characteristic scapuloperoneal distribution of muscle paresis [1,4].

The phenotypic spectrum of MORC2-related disorders has steadily been expanded since the original descriptions made almost simultaneously by Sevilla., *et al*. and Albulym., *et al* [1,3]. Isolated case reports or case series emphasized that peripheral nerve involvement may occasionally coexist with hearing impairment, pyramidal signs, pigmentary retinopathy and mostly neurodevelopmental problems of varying severity [3,5-7].

In a landmark study, Sacoto., *et al*. described this neurodevelopmental phenotype, consisting of gross motor delay, short stature, microcephaly, intellectual disabilities and craniofacial dysmorphisms [2]. The authors proposed the term DIGFAN (developmental delay, impaired growth, dysmorphic facies, axonal neuropathy) to encompass all MORC2 related disorders apart from pure CMT2Z. Interestingly, a substantial minority of their patients showed neuroimaging features compatible with Leigh syndrome, whereas no clinical or neurophysiological evidence of peripheral neuropathy could be detected in 40% of them [2]. Notably, Stafki., *et al*. were able to identify pathogenic MORC2 variants in genetically unsolved individuals clinically diagnosed with Cockayne syndrome [8].

MORC 2 protein is a DNA-dependent chromatin remodeler, considered essential for gene silencing and DNA repair processes [2]. Mechanistically it is thought that pathogenic variants in the ATPase module of MORC2 cause increased activity of the protein resulting in down-regulation of target genes [2,9]. Recently, Peymani., *et al*. using a multiomics approach identified a specific epigenetic DNA methylation pattern in promoter regions of various target genes leading to their repression [9]. This episignature was consistent across all MORC2 related phenotypes, thus raising the hypothesis that the variability in target genes and the level of their down-regulation amongst affected individuals could potentially explain the pleiotropy of the disorder [9].

The p.R252W variant harbored by our patient is located within the GHKL-type ATPase domain of the protein [1,4]. It is the most frequently cited pathogenic variant of the disease and is generally associated with CMT2Z [4]. Interestingly, our patient showed overlapping features with DIGFAN. To our knowledge, the co-occurrence of CMT2Z and components of DIGFAN in the context of p.R252W mutation has already been reported 4 times in the literature [3,5,6,10]. Overall, our report further indicates the phenotypic variability of MORC2 causing variants and is in line with the concept that MORC2 related disorders should merge into a single disease spectrum with a shared pathomechanism, as formulated by Peymani., *et al*.

## Conclusion

This is the first reported Greek case of a patient with a p.R252W mutation of the MORC-2 gene and the unique phenotype accompanying it, with overlapping features of CMT2Z neuropathy and DIGFAN. Furthermore, a review of the relevant literature highlights the phenotypic variety of MORC2-related disorders. As such, increased clinical awareness is warranted when evaluating patients with suspected axonal genetic polyneuropathy and neurodevelopmental abnormalities, to facilitate genetic testing and thus earlier diagnosis and subsequent genetic counselling.

## Conflict of Interest

The authors declare that they have no conflict of interest.

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