Charcot-Marie-Tooth neuropathy type 4 (CMT4) comprises a large group of genetically heterogeneous progressive sensory motor neuropathies characterized by autosomal recessive inheritance. Among these, CMT4B includes 3 forms related to genes of the myotubularin family, namely CMT4B1 (MTMR2), CMT4B2 (MTMR13/SBF2), and CMT4B3 (MTMR5/SBF1).

Only 2 CMT4B3 families have been reported to date. In the original Korean family, 3 siblings showed a homogeneous phenotype of pure sensory motor demyelinating neuropathy with focally folded myelin sheaths, closely resembling CMT4B1 and CMT4B2. All patients had onset of distal atrophy and weakness in upper and lower limbs, decreased vibration and proprioception, touch, and temperature sensations, areflexia, and pes planus in the first decade, with a slow progression to loss of ambulation in the fifth decade of life. None had cognitive impairment, dysmorphic features, or obvious extraneurologic syndromic manifestations.

In the second SBF1-mutated family, from Saudi Arabia, the 3 affected siblings presented a more complex syndromic phenotype. Sensory motor polyneuropathy was associated with progressive microcephaly, intellectual disability, syndactyly, and multiple cranial nerve involvement, which resulted in ophthalmoparesis, absence of pupil reactivity to light, mild facial weakness, swallowing difficulties, and dysarthria. There was distal muscle wasting and weakness but no pes cavus. Brain MRI showed unspecific diffuse brain atrophy.

We further expand the phenotypic spectrum of SBF1-associated CMT to include “fork and bracket” syndrome, a peculiar condition that we previously described in a Syrian family. The 2 affected siblings from this family were recently reassessed, and whole-exome sequencing was performed in the proband. Only the SBF1 homozygous p.L335P mutation survived the filtering pipeline (e-Methods and figure e-1 at Neurology.org/ng). The 2 siblings shared relevant features with the Saudi Arabian family, including early-onset progressive microcephaly, multiple cranial nerve neuropathies, and moderate to severe intellectual disability. Moreover, the sister recently developed a severe oromandibular dystonia that impaired mouth closure, making it difficult to eat and speak. In contrast to CMT4B1, CMT4B2, and the pure neuropathic form of CMT4B3, which are all characterized by demyelinating neuropathy with focally folded myelin sheaths, both families presented a predominantly axonal sensory motor neuropathy with evidence of denervation, markedly reduced amplitude of action potentials, and relatively preserved nerve conduction velocities (table e-1). However, there were also clinical differences, as proprioception, touch, and temperature sensations were largely spared in the 2 Syrian siblings and they both had joint laxity and thumb sign but no syndactyly. Furthermore, their brain MRI showed peculiar anomalies at the pontine and mesencephalic level described as the “fork and bracket sign” (figure e-2), presumably related to the presence of degenerated fiber bundles of oculomotor and facial nerves, which were not reported in the Saudi Arabian family (see table e-2 for a detailed phenotypic comparison among the 3 families).

There seem to be relevant genotype–phenotype correlations in CMT4B3, as the Korean patients with pure demyelinating neuropathy were compound heterozygous for 2 missense variants, both predicted as benign or tolerated by most prediction software, suggesting a mild impact on the protein. On the contrary, the 2 families with severe syndromic presentation carried missense mutations that were consistently predicted to be deleterious for the protein structure or function (figure 1A).

SBF1 is part of the myotubularin family, a large and highly conserved group of ubiquitously expressed phosphatidylinositol 3-phosphatases encompassing catalytically active (including MTMR2) and inactive (including SBF1 and SBF2) enzymes that share a core of protein domains. Most MTMR2 mutations are truncating or missense changes that drastically reduce phosphatase activity, suggesting loss of function of the protein as the key mechanism leading to CMT4B1. Both SBF1 and SBF2 proteins interact
directly with MTMR2 in the cytosol, markedly increasing its enzymatic activity; the impairment of this interaction, possibly related to protein absence, subcellular mislocalization, or functional changes of the interacting C-terminus domains, is a likely mechanism to explain the polyneuropathy associated with mutations in both genes. However, the severe syndromic phenotype shown by 2 SBF1-mutated families calls for additional explanations.

Of note, both mutations causative of syndromic CMT4B3 fall within the DENN domain (figure 1B), shared only by SBF1 and SBF2 among myotubularins. This domain was implicated in membrane trafficking and endosome function as well as in regulation of the proteins’ subcellular localization, which suggests that it may confer additional functions to SBF1 and SBF2 besides interaction with MTMR2. However, an SBF2 deletion abolishing the whole D-DENN module caused nonsyndromic demyelinating neuropathy in a Turkish family. This phenotypic variability may relate to yet unknown differences between SBF1 and SBF2 in their function and/or tissue expression pattern or to a more deleterious impact of missense mutations on the protein structure and function.

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