A New Gene for the Charcot-Marie-Tooth Disorder

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Charcot-Marie-Tooth neuropathy type 2A (CMT2A) is an inherited neurologic disease characterized by a slowly progressive degeneration of the limb muscles. It was previously reported to be caused by the kinesin family member 1B-β (*KIF1B*) gene, based on a study of a single Japanese family [1]. Now a new publication by Zuchner et al. [2] casts doubt on this identification and provides strong evidence that the disease is actually caused by a completely different gene, mitofusion 2 (*MFN2*), coding for a mitochondrial membrane fusion protein.

Charcot-Marie-Tooth disease constitutes a clinically and genetically heterogeneous group of hereditary motor and sensory neuropathies. On the basis of electrophysiologic criteria, CMT1 is divided into two major types: CMT1, the demyelinating form, characterized by a slow motor median nerve conduction velocity (less than 38 m/s), and CMT2, the axonal form, with a normal or slightly reduced velocity (above 38 m/s). CMT1 and CMT2 share phenotypic symptoms characterized by progressive weakness and atrophy, initially of the peroneal muscles and later of the distal muscles of the arms [3].

For CMT1 subtypes, the major underlying molecular genetic defects have long been known, and are related to mutations in three genes [3]. In contrast, the autosomal dominant axonal form of the disease (CMT2) is currently subdivided into 12 subtypes based on genetic localization. Most of the genes associated with CMT2 have only recently been identified, while for some others no gene has yet been correlated [3]. Each gene, located in a completely different genomic region, defines a unique subtype of CMT2. In the presently covered report, Zuchner and colleagues [2] studied seven large families with CMT2A (located on chromosome 1p36.2) of diverse ethnicities (European, Italian, Russian, Turkish, and Japanese descent). Like Zhao [2] before them, they found linkage to a similar genomic region on chromosome 1, spanning 9.6 cM, including the genes *MFN2* and *KIF1B* located 1.65 Mb apart.

Careful analysis of the *KIF1B* gene in the affected individuals revealed only intronic and synonymous single-nucleotide polymorphisms distributed along the entire gene. Following these findings, 14 other candidate genes expressed in the nervous system and located in the genomic region were studied, but all were excluded as they did not carry mutations correlated to the CMT2A disorder. Yet another gene examined, mitofusin 2, rewardingly showed genetic variations in all seven CMT2A families. These missense mutations cleanly co-segregated with the disease phenotype. In addition, none of the amino acid changes was found in 250 (500 chromosomes) healthy control samples of European descent or in 70 (140 chromosomes) additional Japanese controls.

Mitofusin 2 is ubiquitously expressed in human tissues, including spinal cord and peripheral nerve. The *MFN2* gene product is localized to the outer mitochondrial membrane and regulates the mitochondrial network architecture by controlling membrane fusion [Figure 1]. Mitochondria are dynamic organelles enclosed within two lipid bilayer membranes. They undergo frequent fission and fusion as well as branching – morphologic changes that are considered crucial for cellular functions [4]. An efficient mitochondrial network is required for fundamental cell functions, such as equilibrating mitochondrial proteins to overcome acquired somatic mutation of mitochondrial DNA and establishing a uniform membrane potential at the mitochondrial double membrane for even energy supply throughout the cell.

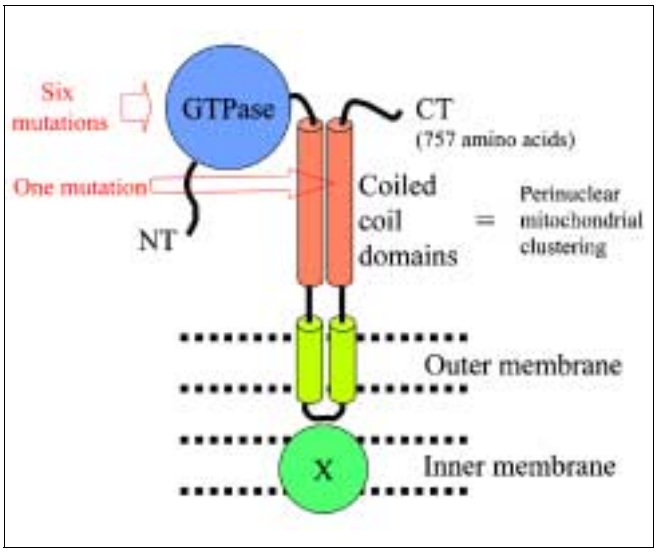

Figure 1. Putative Mfn2 domain structure and topology. The three domains indicated are of the GTPase, at the N-terminal end, the two trans-membrane domains and the two coiled coil domains responsible for perinuclear mitochondrial clustering. The trans-membrane domains are anchored in the outer membrane. The mutations' relative locations are indicated. NT = amino-terminus, CT = carboxy-terminus, X = unknown protein of the mitochondrial inner membrane [8].

It has previously been shown in mouse embryonic fibroblast cultures from *Mfn2* knockout mice that mitochondrial mobility was markedly reduced [5]. In cells with extremely long processes such as neurons, mobility and transport of mitochondria are key elements for functional health, particularly in peripheral nerves. The authors suggest that this could be a clue to a possible mechanism of action in CMT2A, and might explain the neuron-specific phenotype.

The amino acids affected by the *MFN2* mutations in the seven families with CMT2A are highly conserved in different species. Six of seven identified mutations, all missense, are within or immediately upstream of the GTPase domain of *MFN2* [Figure 1]. It was previously shown that an intact GTPase domain is essential for normal formation of mitochondrial filaments and networks [5–7]. The homolog of MFN2 in *Drosophila*, Fzo [8], is an integral membrane protein of the mitochondrial outer membrane. The intermembrane space loop is required for contact between the mitochondrial outer and inner membranes and may interact with the as yet unknown inner membrane protein X [Figure 1]. Fzo mutations show abnormal "fuzzy onion" mitochondrial membrane shapes in the fly spermatids [8].

While it may be surprising that a ubiquitously expressed gene affects particular tissues in the body, this is not the only example for such scenarios. There are other genes expressed in all tissues and yet affect specific tissues when mutated; for example, the gene *GNE* when mutated causes Hereditary Inclusion Body Myopathy, which manifests in limb muscle degeneration except for the quadriceps [9].

There is a genetic lesson to be learned from this study: a gene should be considered as correlated to a disease only when all affected individuals have mutations in it. When only a few affected individuals are studied an erroneous identification of the disease-causing gene may occur due to linkage disequilibrium. In the specific case described here it is rather unlikely, though not completely impossible, that KIF1B mutations reported earlier define a separate CMT2 subtype.

The discovery of a new disease gene does not generally imply immediate routes to therapy. For the new *CMT2A* gene, however, there is greater hope for gene therapy, since a virally transported mitofusin 2 construct introduced in an Mfn2-deficient mouse cell line has been shown to rescue the normal phenotype by correcting the fusion-fission imbalance [5].

References

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