Progressive Neuromuscular Syndromes Linked to Dynamin-2 Mutations

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Abstract

Mutations in dynamin-2 are associated with several neuromuscular disorders, including two forms of Charcot-Marie-Tooth disease, axonal CMT2M and intermediate CMTDIB, Centronuclear myopathy ADCNM, Lethal congenital contractures syndrome type 5 LCCS5, and Hereditary spastic paraplegia SPG. Each disorder manifests with muscle weakness and atrophy, however the cause of weakness is due to damage to peripheral nerves in CMT2M and CMTDIB, skeletal muscle degeneration in ADCNM, and disturbances in the upper motor neurons and/or corticospinal tracts in SPG. Pathogenic effects of mutations may result from domain-specific structural and functional disruptions. ADCNM-causing mutations cluster at the interface between the Stalk and Pleckstrin homology domains, whereas CMT-related mutations occur in the part of the Pleckstrin homology domain adjoining the C-terminal Proline/arginine-rich domain. The SPG-associated p.Arg719Trp mutation is uniquely located at the highly conserved hinge region of the Bundle-signaling element, potentially preventing normal assembly of the helical polymer.

Keywords: Charcot-marie-tooth disease; Centronuclear myopathy; Spastic paraplegia; Dynamin-2, DNM2; Endocytosis

Introduction

Dynamin-2 gene (DNM2) maps to 19p13.2-p12 on chromosome 19 and contains 22 exons of which 20 are coding. The gene is expressed in all tissues examined, with highest expression in heart and skeletal muscle. Dynamin-2 protein is a highly conserved multi-domain and multifunctional GTPase best known for its essential role in clathrin-mediated endocytosis: the protein participates in converting the nascent invaginated clathrin-coated pit into a fully formed vesicle and detaching the vesicle from the plasma membrane [1]. Clathrin-mediated endocytosis plays a specialized role at neuronal synapses [2]. Dynamin-2 is found ubiquitously and is involved in several other cellular processes, such as regulation of neuronal morphology, axonal growth and formation of growth cones, centrosome cohesion, and actin- and microtubule dynamics [2-5].

Dynamin-2 is a 100 kDa protein composed of five distinct domains: i) N-terminal GTPase domain mediating nucleotide binding and hydrolysis; ii) Bundle signaling domain (BSE); iii) Stalk domain; iv) Pleckstrin homology domain (PH), critical for the interaction with membrane phosphoinositides; and v) a C-terminal proline-rich domain (PRD) mediating interactions with scaffolding proteins [6]. To accomplish vesicle scission, a dynamin tetramer assembles via the stalks into a helical array surrounding the neck of invaginating clathrin-coated pits, followed by helix constriction and GTP hydrolysis [1].

To date, 37 disease-causing DNM2 mutations have been identified and associated with distinct human disease phenotypes. The destructive effects of some of these mutations on clathrin-mediated endocytosis have been shown in cell culture models [7,8].

Phenotypic spectrum of disorders caused by dynamin-2 mutations

DNM2-associated autosomal dominant motor and sensory peripheral neuropathies CMT2M (MIM# 606482) and CMTDIB (MIM# 606482) are characterized by slowly progressive distal muscle weakness and atrophy, predominantly in the lower extremities; steppage/foot drop gait; decreased or absent tendon reflexes, impairment of pain, temperature, vibration and position sense in the distal limbs. Skeletal malformations including pes cavus, hammer-toes and scoliosis are also frequently present (Table 1) [9-11]. Muscle weakness and atrophy of upper limbs usually appear in the late phases of illness and are mild [12-14]. Moderately to severely reduced nerve conduction velocities and axonal degeneration on sural nerve biopsy have been observed in some families [11]. Needle electromyography (EMG) shows a chronic neurogenic pattern [9]. The two forms of DNM2-associated CMTs include axonal CMT2M, in which median nerve conduction velocities are normal and the intermediate CMTDIB form with moderately reduced nerve conduction velocities due to a combination of axonal and demyelinating features [9-15].

DNM2-associated Centronuclear myopathy ADCNM (MIM# 160150) is a congenital myopathy characterized by delayed motor milestones, slowly progressive muscle weakness involving mainly limb girdle, trunk, and neck muscles, difficulty walking, loss of deep tendon reflexes, and in some cases elongated face, facial weakness, ptosis and ophthalmoplegia, weakness of the paraspinal muscles, pes cavus, scoliosis, and contractures [13,16-28]. ADCNM demonstrates a wide spectrum of phenotypes ranging from a severe neonatal form with generalized muscle weakness, hypotonia, and contracture ures to milder late-onset forms [16-28]. Some patients show clinical overlap of myopathy with mild axonal involvement in peripheral nerves [17]. EMG indicates myopathic changes. Skeletal muscle biopsies reveal hypotrophy of type 1 myofibers, abnormal nuclear centralization and internalization, and radial arrangement of sarcoplasmic strands around central nuclei [16,17,22].

The Lethal congenital contractures syndrome LCCS5 (MIM#...
The neuromuscular manifestations of dynamin-2 associated disorders are compared in the Table 1. The phenotypes vary significantly by the type of neuromuscular involvement. CMT2M and CMTDIB are characterized primarily by paretic syndromes with steppe walking and hyporeflexive reflexes, whereas SPG results in spasticity with hyperreflexia and spastic gait. Nerve conduction slowing and diminished hypoactive reflexes, whereas SPG resulting in spasticity with hyperactive characterizes primarily by paretic syndromes with steppage walking and

<table>
<thead>
<tr>
<th>Disease</th>
<th>Age of onset (range, years)</th>
<th>Muscle weakness (muscle group)</th>
<th>Hyper- or hypo-reflexia</th>
<th>Gait</th>
<th>Skeletal abnormality</th>
<th>Loss of vibration sense in LL</th>
<th>EMG pattern</th>
<th>Median NCV</th>
<th>Nerve biopsy</th>
<th>Muscle biopsy</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMT2M</td>
<td>19-40</td>
<td>Distal LL</td>
<td>Hypo</td>
<td>Steppage/foot drop</td>
<td>Pes cavus</td>
<td>+</td>
<td>Diffuse denervation</td>
<td>Normal or mildly reduced</td>
<td>Loss of large myelinated fibers</td>
<td>Normal</td>
<td>[9-11]</td>
</tr>
<tr>
<td>CMTDIB</td>
<td>2-50</td>
<td>Distal LL</td>
<td>Hypo</td>
<td>Steppage</td>
<td>Pes cavus</td>
<td>+</td>
<td>Neurogenic</td>
<td>Reduced</td>
<td>Centrally located nuclei, type 1 fiber hypotrophy, radial arrangement of sarcoplasmic strands around central nuclei</td>
<td>[11-14]</td>
<td></td>
</tr>
<tr>
<td>ADCNM</td>
<td>Childhood-adulthood</td>
<td>Distal LL and UL</td>
<td>Hypo</td>
<td>Falls</td>
<td>Pes cavus</td>
<td>Nr</td>
<td>Myopathic</td>
<td>Nr</td>
<td>Centrally located nuclei, type 1 fiber hypotrophy</td>
<td>[16-27]</td>
<td></td>
</tr>
<tr>
<td>Sporadic neonatal CNM</td>
<td>Infant-childhood</td>
<td>Generalized weakness, hypotonia, contractures</td>
<td>Hypo</td>
<td>Nr</td>
<td>Nr</td>
<td>Nr</td>
<td>Myopathic</td>
<td>Normal</td>
<td>Nr</td>
<td>Centrally located nuclei, type 1 fiber hypotrophy</td>
<td>[28]</td>
</tr>
<tr>
<td>LCCS5</td>
<td>Infant</td>
<td>Hypotonia, respiratory weakness, contractures</td>
<td>Hypo</td>
<td>-</td>
<td>Thin bones</td>
<td>Nr</td>
<td>Myopathic</td>
<td>Nr</td>
<td>Rounded atrophic fibers</td>
<td>[29]</td>
<td></td>
</tr>
<tr>
<td>SPG</td>
<td>10-37</td>
<td>Distal LL weakness, contractures</td>
<td>Hyper-reflexia, clonus</td>
<td>Spastic</td>
<td>Pes cavus</td>
<td>+</td>
<td>Normal, tibial and peroneal reduced</td>
<td>Nr</td>
<td>Nr</td>
<td>[8]</td>
<td></td>
</tr>
</tbody>
</table>

| LL–Lower Limbs, UL–Upper Limbs | EMG–Electromyography | NCV–Nerve Conduction Velocity | Nr–Not Reported |

615368) is characterized by severe hypotonia, akinesia, respiratory insufficiency necessitating ventilation and nasogastric feeding, lack of reflexes, joint contractures, skeletal abnormalities, and brain and retinal hemorrhages [29]. These clinical findings are based on observations of three consanguineous patients with a homozygous missense dynamin-2 p.Phe379Val mutation [29]. The children's heterozygous parents had impaired reflexes, and analysis of a muscle biopsy revealed fiber size variation and centralized nuclei characteristic of ADCNM.

Sambuughin et al. [8] recently reported a large Siberian family with nine affected individuals showing features of Autosomal dominant hereditary spastic paraplegia (HSP or SPG) linked to a dynamin-2 p.Arg719Trp mutation. The phenotype is characterized by a slowly progressive bilateral spasticity, primarily in the lower extremities, with muscle weakness, hyperreflexia, and spastic gait. Some patients also show wasting of the lower leg muscles, pes cavus, decreased vibratory sense in the ankles, and urinary urgency as late features of illness [8]. The disease primarily affects the upper motor neurons and the corticospinal tracts. Nerve conduction studies in patients with advanced disease indicate mild motor and sensory axonal neuropathy in the lower extremities.

The phenotypic features of neuromuscular disorders linked to DNM2 mutations are summarized in Table 1. The phenotypes vary significantly by the type of neuromuscular involvement. CMT2M and CMTDIB are characterized primarily by paretic syndromes with steppe walking and hyporeflexive reflexes, whereas SPG results in spasticity with hyperreflexive reflexes and spastic gait. Nerve conduction slowing and diminished hypoactive reflexes are present in CMTDIB and to a much milder degree in ADCNM and SPG. ADCNM and LCCS5 differ from ADCMT by significant abnormalities found in muscle biopsy. Muscle weakness is shared by each disorder, however it results from damage to distinct tissues - peripheral nerves in CMT2M and CMTDIB, skeletal muscle in ADCNM and LCCS5, and upper motor neurons or corticospinal tracts in SPG.

Variable pathogenic potentials of dynamin-2 mutations

It is not clear why specific mutations in the ubiquitously expressed dynamin-2 affect skeletal muscle in one type of disease, peripheral nerves in another, and corticospinal tracts in the third. Existing hypotheses invoke distinct roles of dynamin-2 domains in different tissues. The known CMT2M and CMTDIB mutations are located within the PH and PRD domains, whereas the ADCNM mutations are concentrated in hot spot regions at the interface between the Stalk and PH protein domains [11,22] (Figure 1). It has recently been shown that CMT- and ADCNM-associated mutations have distinct effects on membrane fission activity in that CMT mutants do not impair clathrin-mediated endocytosis in myoblasts, whereas hyperactive ADCNM mutant's exhibit enhanced membrane fission activity leading to T-tubule disorganization in skeletal muscle [30]. These effects may occur through hetero-oligomerization with wild type dynamin to alter its activity and/or localization.

The pathomechanistic significance of mutations in specific dynamin-2 domains is further underlined by recent evidence that the SPG mutation, p.Arg719Trp, is uniquely located in the BSE domain, which is structurally and functionally different from the stalk and PH domains in which CMT and ADCNM mutations are located [8] (Figure 1). A mutation in the BSE domain may cause a conformational change to the helical element and affect dynamin assembly. Moreover, this mutation results in fewer hydrogen bonds between the BSE and the stalk [8]. The BSE undergoes conformational change upon GTP hydrolysis that has been described as the power stroke of dynamin [31-33]. The weaker connection potentially uncouples the power stroke from the rest of the molecule, a step likely perturbing endocytosis [31]. A mutation in this region predicts a defect in propagating the

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BSE conformational change to the rest of the molecule. In addition, the mutation is located near a hinge between the BSE and the stalk and may be capable of disrupting the connection between these domains [8].

Conclusion

Mutations in a ubiquitously expressed dynamin-2 cause several neuromuscular disorders with distinct clinical and pathological characteristics. Depending on the type and location, dynamin-2 mutations incur damage either to skeletal muscle, peripheral nerves, or corticospinal tracts. Each disorder manifests with muscle weakness, however the pathomechanisms leading to weakness are different. Existing hypotheses emphasize distinct roles of dynamin-2 domains in different tissues, suggesting that pathogenic effects of mutations may result from domain-specific structural and functional disruptions in dynamin-2.

Authors’ Contribution

NMR, LGG, and FAP contributed to the study concept and design and writing the manuscript; NS, JH, and CT carried out analysis and interpretation of data, and writing the manuscript. Each author read and approved the final version of the manuscript.

Competing Interests

The authors declare that they have no competing interests.

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References


Figure 1: Monomer structure of dynamin-2 based on the crystal structure of dynamin-1 that is about 73% identical to dynamin-2 on protein level [33]. The GTPase, BSE, stalk, and PH domains and disease-associated mutations are color coded. The ADCNM-causing mutations (magenta dots) cluster at the interface between the stalk and PH domains, whereas mutations implicated in CMT2M and CMTDIB (light-green dots) occur within the PH domain, but outside of this interface [20]. The p.R719W mutation associated with SPG (blue dot) is the only one located at the highly conserved hinge region of the BSE element.


