Phenotypic Spectrum of DNM2-Related Centronuclear Myopathy

Leslie Hotchkiss Hayes, MD,* Morgane Perdomini, PhD,* Asli Aykanat, MD,* Casie A. Genetti, MS, Heather L. Paterson, BS, Belinda S. Cowling, PhD, Christian Freitag, MD, and Alan H. Beggs, PhD
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Abstract

Background and Objectives
Centronuclear myopathy (CNM) due to mutations in the dynamin 2 gene, DNM2, is a rare neuromuscular disease about which little is known. The objective of this study was to describe the range of clinical presentations and subsequent natural history of DNM2-related CNM.

Methods
Pediatric and adult patients with suspicion for a CNM diagnosis and confirmed heterozygous pathogenic variants in DNM2 were ascertained between December 8, 2000, and May 1, 2019. Data were collected through a retrospective review of genetic testing results, clinical records, and pathology slides combined with patient-reported clinical findings via questionnaires.

Results
Forty-two patients with DNM2-related CNM, whose ages ranged from 0.95 to 75.76 years at most recent contact, were enrolled from 34 families in North or South America and Europe. There were 8 different DNM2 pathogenic variants within the cohort. Of the 32 biopsied patients, all had histologic features of CNM. The disease onset was in infancy or childhood in 81% of the cohort, and more than half of the patients had high arched palates, indicative of weakness in utero. Ambulation was affected in nearly all (92%) the patients, and while the rapidity of progression was variable, most (67%) reported a “deteriorating course.” Ptosis, ophthalmoparesis, facial weakness, dysphagia, and respiratory insufficiency were commonly reported. One-third of the patients experienced restricted jaw mobility. Certain pathogenic variants appear to correlate with a more severe phenotype.

Discussion
DNM2-related CNM has a predominantly early-onset, often congenital, myopathy resulting in progressive difficulty with ambulation and occasionally bulbar and respiratory dysfunction. This detailed characterization of the phenotype provides important information to support clinical trial readiness for future disease-modifying therapies.
Centronuclear myopathies (CNM) are a group of congenital myopathies with common clinical features, slowly progressive, often early-onset, weakness, and muscular atrophy, that are histopathologically defined by their characteristic hallmark of centralized nuclei in the absence of ongoing myofiber regeneration.1,2

CNMs are rare, severe muscle diseases, with an estimated incidence of 1 per 41,000 births. The most reported cases are boys with X-linked myotubular myopathy (XLMTM) due to mutations of MTM1; however, a recent study in the Netherlands found DNM2 to be a more common cause of CNM in their cohort.4 Mutations of BIN1, which is an autosomal recessive CNM, are relatively rare.5 Mutations in TTN, RYR1, and SPEG can also produce a congenital myopathy with internal nuclei.6-8

Pathogenic mutations of the DNM2 gene, encoding dynamin 2, lead to an autosomal dominant (AD) phenotypic spectrum.5,10 The onset of weakness can range from neonatal to adult ages and is thought to have a milder though slowly progressive course compared with other forms of CNM. Facial weakness, ptosis, and ophthalmoplegia have been described, and muscle histology is characterized by prominent central nuclei in many myofibers without signs of degeneration. Muscle imaging demonstrates predominantly distal muscle involvement.1,1,12

In addition to CNM, DNM2 mutations are associated with Charcot-Marie-Tooth (CMT) peripheral neuropathy13 and occasionally a broader array of neuromuscular presentations such as a lethal congenital syndrome and hereditary spastic paraplegia.13-16 Our understanding of tissue-specific mechanisms causing these different phenotypes is limited but suggests that CNM is caused by a gain of function mechanism, whereas CMT generally results from a loss of function mechanism.10,16-18

DNM2 encodes the large GTPase dynamin 2 that plays a role in many cellular functions, particularly membrane trafficking.19,20 In DNM2-related CNM, most mutations cluster in the middle and pleckstrin homology (PH) domains of dynamin 2, leading to reduced inhibition of GTPase activity (Figure 1A).20 However, DNM2 mutations that cause CMT are typically in the loops of the PH domain.16 In fact, increased dynamin 2 activity appears to be the common disease pathomechanism in most CNMs.21 This is supported by studies demonstrating that the reduction of dynamin 2 activity through various mechanisms can rescue the phenotype in DNM2, MTM1, or BIN1-CNMy mouse models.22-25

There has been significant progress in understanding disease mechanisms of DNM2-related CNM resulting in proof of principle and preclinical studies for several therapeutic approaches,5,26 including antisense oligonucleotide-mediated DNM2 knockdown. However, the clinical variability and small numbers of reported patients18,27-34 pose a challenge to defining the natural history of this rare disorder. This retrospective case series study aims to further describe the phenotypic variability of DNM2-related CNM, highlight underreported clinical features, and evaluate genotype-phenotype correlation.

Methods

Forty-two patients from 34 families with DNM2-related CNM were evaluated in a retrospective natural history study. Patients were ascertained by physician or self-referral, generally prompted by a previous publication, patient advocacy group engagement, or study advertisement. Informed consent was obtained according to the Declaration of Helsinki from all participants or a parent/legal guardian. This study was approved by the Institutional Review Board of Boston Children’s Hospital. Twenty-five patients were previously reported in the literature.9,10 All the patients had a molecularly confirmed diagnosis of DNM2-related CNM due to heterozygous DNM2 variants classified as pathogenic according to the American College of Medical Genetics criteria.35 Genetic confirmation was obtained via whole-exome sequencing in 12%, neuromuscular panel testing in 14%, and single-gene testing in 74%. No other clinically relevant variants were identified in patients who had whole-exome sequencing or panel testing.

Study participants were initially enrolled between 2000 and 2019, and comprehensive clinical data were collected in the form of existing medical records and self-report clinical history questionnaires. Clinical data were collected at the time of enrollment directly from referring physicians, by medical records release procedures, and/or from the patients themselves and were updated over time when feasible. Medical records included but were not limited to neurology notes, muscle pathology reports, EMG reports, imaging reports, pulmonary function testing, sleep studies, cardiac evaluations, and inpatient hospitalization records. A systematic review of muscle pathology reports was supplemented by the manual review of slides when available, and all scoring and interpretation were performed by 1 coauthor (A.H.B.) to ensure consistency of interpretation. The self-report questionnaires focused on birth, developmental history, and current health and physical abilities and were answered by the patient or parent/guardian at 1 or more time points. In addition to these existing records, prospectively collected updated self-report data were obtained in 2021 by phone-administered questionnaire for 26 participants who were available for follow-up. Available records for each case were reviewed, and cross-sectional and longitudinal data were manually extracted and entered into a RedCap database for standardized reporting and descriptive...
analysis. Discrepancies or conflicts in patient data points, either over time or by source, were reviewed and resolved on an individual basis by a clinical expert and the data extraction team. Data were extracted between April 2020 and August 2021.

**Standard Protocol Approvals, Registrations, and Patient Consents**
Informed consent was obtained according to the Declaration of Helsinki from all participants or a parent/legal guardian. This study was approved by the Institutional Review Board of Boston Children’s Hospital.

**Data Availability**
Deidentified participant data in the RedCap database may be made available to qualified investigators on request.

**Results**

**Participants**
This study included 42 patients (52% male and 48% female) from 34 families. Patients were born between 1939 and 2017, and the median age at enrollment was 30.9 years (range 0–69.5 years) and at the last report was 39.4 years (range 0.95–75.8 years). Over the 20 years since data collection began, 7 (17%) patients died after enrollment (1 due to complications of CNM, 1 due to heart failure, 1 due to pulmonary failure, and 4 unspecified). Additional demographics are provided in eTable 1, links.lww.com/NXG/A547. Patients had one of 8 different pathogenic heterozygous missense variants in DNM2 (Figure 1A; eTable 2, links.lww.com/NXG/A547). Twenty-two participants had a family history consistent with AD inheritance, mutations were proven de novo in 7, and 13 were sporadic cases (i.e., no positive family history and parental testing unavailable).

**Onset and Diagnosis**
The self-reported age at onset was variable throughout the cohort. The disease onset was neonatal (age <2 years) in 16 patients (38%), childhood (age 2–17 years) in 18 patients (43%), early adult (age 18–49 years) in 5 patients (12%), and late adult (age ≥50 years) in 3 patients (7%). Early symptoms included reduced fetal movements (n = 10, 42% of reported), hypotonia at birth (n = 12, 43%), respiratory difficulties at
| Participant ID | Protein variant | Weak/infrequent fetal movements | Birth hypotonia | Insufficient respiration at birth | Delayed motor milestones |
|----------------|-----------------|---------------------------------|-----------------|----------------------------------|-------------------------|
| BOS1203-1      | p.Phe372Ser     | +                               | +               | +                                | +                       |
| BOS0746-1      | p.Ser619Leu     | NR                             | +               | +                                | +                       |
| BOS1158-1      |                  | +                               | +               |                                  |                         |
| BOS1504-1      |                  | +                               | +               | +                                | +                       |
| BOS1432-1      | p.Ala618Asp     | +                               | +               | +                                |                         |
| BOS1403-1      |                 |                                 |                |                                  |                         |
| BOS1831-1      | p.Glu368Lys     | −                               | +               | +                                |                         |
| BOS0839-1      |                  | +                               | +               | −                                |                         |
| BOS0848-1      |                  | −                               | +               | −                                |                         |
| BOS1353-1      |                  | +                               | +               | +                                |                         |
| BOS0848-2      |                  | +                               | +               | +                                |                         |
| BOS0593-1      | NR              | NR                             | −               |                                  | +                       |
| BOS1132-1      | +               | +                               | +               |                                  |                         |
| BOS0905-1      | −               | −                               | −               |                                  |                         |
| BOS1021-1      | p.Pro627Arg     | −                               | −               | −                                |                         |
| BOS1185-1      | NR              | NR                             | NR             | +                                |                         |
| BOS1021-2      | NR              | NR                             | NR             | +                                |                         |
| BOS0703-5      | p.Arg465Trp     | −                               | −               | −                                |                         |
| BOS1536-1      | −               | −                               | −               | +                                |                         |
| BOS1475-1      | −               | −                               | −               | +                                |                         |
| BOS1059-1      |             | NR                             | −               | −                                |                         |
| BOS0835-1      | NR              | NR                             | NR             | +                                |                         |
| BOS0601-1      | NR              | NR                             | NR             | +                                |                         |
| BOS0703-1      | NR              | NR                             | −               | −                                |                         |
| BOS0930-1      | +               | −                               | −               | −                                |                         |
| BOS1075-1      | −               | −                               | −               | −                                |                         |
| BOS0703-6      | −               | −                               | −               | −                                |                         |
| BOS1061-1      | −               | −                               | −               | −                                |                         |
| BOS0928-1      | NR              | −                               | +               | −                                |                         |
| BOS0703-7      | −               | −                               | −               | −                                |                         |
| BOS0893-1      | −               | −                               | −               | −                                |                         |
| BOS1311-1      | NR              | NR                             | NR             | −                                |                         |
| BOS1311-4      | NR              | NR                             | NR             | −                                |                         |
| BOS0393-2      | NR              | −                               | −               | −                                |                         |
| BOS1145-1      | p.Arg522His     | NR                             | NR             | NR                               | −                       |
| BOS0877-1      | −               | NR                             | −               | −                                |                         |
| BOS1218-1      | −               | −                               | −               | −                                |                         |
| BOS0909-1      | NR              | NR                             | NR             | NR                               |                         |

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birth (n = 13, 41%), and/or delayed motor milestones (n = 18, 47%) (Table 1). Six patients reported premature birth (gestational age <37 weeks), and 8 patients had low Apgar scores (reported as either "low" or <7).

The median time to CNM diagnosis decreased over time: 20.0 years for patients with disease onset prior to 1990 (n = 22), 4.0 years if disease onset was between 1990 and 2005 (n = 7), and 0.9 years if disease onset was after 2005 (n = 10) which was the year that DNM2 was identified (Figure 1B). The main reason for referral was weakness (n = 33, 80%). Ten patients (24%) were initially misdiagnosed with other neuromuscular disorders, such as CMT (n = 3), spinal muscular atrophy (n = 2), myasthenia gravis (n = 1), and limb-girdle muscular dystrophy (n = 1) (eTable 3, links.lww.com/NXG/A547). Most EMGs were interpreted as myopathic (n = 16, 73%). Ten EMGs had abnormal spontaneous activity (11 with fibrillating potentials and positive sharp waves, 3 with myotonic discharges, and 1 with complex repetitive discharges). Three reported neurogenic changes on EMG (2 with concurrent myopathic motor units), and 1 patient had mild demyelinating features of nerve conduction studies. Two patients had normal EMGs at a young age (2 weeks and 1.7 years old) and were never retested.

Muscle Pathology

Muscle biopsies were performed on 34 patients from the cohort, of whom pathology reports were obtained for 32 and slides or photomicrographic images were reviewed from 21 patients (Figure 2). Age at biopsy ranged from 0.03 to 58.3 years. The most commonly biopsied muscle was the quadriceps (N = 14), followed by the tibialis anterior (N = 7),

Table 1 Presentation at Birth and Motor Milestones (continued)

| Participant ID | Protein variant | Weak/infrequent fetal movements | Birth hypotonia | Insufficient respiration at birth | Delayed motor milestones |
|---------------|----------------|--------------------------------|-----------------|-------------------------------|-------------------------|
| BOS0898-1     | p.Arg369Trp    | NR                            | NR              | +                             | −                       |
| BOS0929-1     | NR             | NR                            | NR              | NR                            | NR                      |
| BOS0929-6     | NR             | NR                            | NR              | −                             | −                       |

+ = present; − = absent; NR = not reported.
Pathology reports, clinical records, and manual review for 32 patients listed a centronuclear or myotubular-type myopathy as the leading likely or possible histopathologic diagnosis. Of the remaining 2 biopsies, one was interpreted as "features consistent with limb girdle dystrophy" with both central and internal nuclei, severe fiber size variation, and moderately increased endomysial fibrosis. The other was a quadriceps biopsy from a 37-year-old individual whose muscle was also characterized by central nuclei in many fibers with moderate fiber size variation, disruptions of oxidative staining reminiscent of minicores, with moderate adipose replacement and a mild inflammatory infiltrate. This biopsy was interpreted as simply indicative of "marked chronic myopathy."

Specific histopathologic findings are presented in eFigure 1 and eTable 4, links.lww.com/NXG/A547. All 34 biopsies were characterized by central nuclei in many fibers (N = 31) or in a few fibers (N = 3). In addition, internal (noncentral) nuclei were present in 10 of 33 biopsies. Nemaline rods were not seen, and central cores and minicore-like structures were present in a few fibers for 6 patients. Characteristic oxidative staining abnormalities including “necklace fibers” and radial rays resembling “spokes on a wheel” were present in 10 and 14 biopsies, respectively, and largely not commented on in the rest. Ninety-seven percent reported moderate to severe fiber size variation, with fiber type 1 predominance a feature of more than half of biopsies when commented. Evidence of dystrophic processes, such as degenerating or regenerating fibers, necrosis, large-scale adipose replacement, inflammatory infiltrates, and extensive fibrosis, was largely absent as was fiber-type grouping or other evidence for underlying neurogenic processes.

Electron microscopy findings, available for 11 biopsies, confirmed the presence of centrally located nuclei, often surrounded by a cytoplasmic halo containing mitochondria...
| Participant ID | Protein variant | Age at the last report | Disease course | Proximal | Distal | Facial | Extraocular | Asymmetry |
|----------------|-----------------|------------------------|----------------|----------|--------|--------|-------------|----------|
| BOS1203-1      | p.Phe372Ser     | 1.25                   | Improving      | +        | —      | +      | +           | —        |
| BOS0746-1      | p.Ser619Leu     | 0.95                   | Stable         | +        | +      | —      | —           | —        |
| BOS1158-1      |                 | 13.59                  | Deteriorating  | —        | +      | —      | +           | —        |
| BOS1504-1      |                 | 3.71                   | Improving      | +        | +      | +      | —           | —        |
| BOS1432-1      |                 | 7.71                   | Variable       | +        | +      | +      | —           | —        |
| BOS1403-1      | p.Ala618Asp     | 18.52                  | Deteriorating  | +        | —      | —      | —           | +        |
| BOS0183-1      |                 | 30.43                  | Deteriorating  | +        | +      | —      | —           | —        |
| BOS0839-1      |                 | 30.92                  | Stable         | +        | +      | +      | +           | —        |
| BOS0848-1      |                 | 39.4                   | Deteriorating  | +        | +      | +      | —           | +        |
| BOS1353-1      |                 | 9.81                   | Improving      | —        | +      | +      | —           | +        |
| BOS0848-2      |                 | 13.93                  | Stable         | —        | +      | +      | —           | +        |
| BOS0593-1      |                 | 14.34                  | Variable       | +        | +      | —      | —           | —        |
| BOS1132-1      |                 | 39.45                  | Deteriorating  | +        | +      | —      | —           | —        |
| BOS0905-1      |                 | 20.62                  | Deteriorating  | +        | +      | —      | —           | —        |
| BOS1021-1      | p.Pro627Arg     | 52.42                  | Deteriorating  | +        | +      | +      | —           | —        |
| BOS1185-1      |                 | 27.98                  | Stable         | +        | +      | +      | —           | —        |
| BOS1021-2      |                 | 69.62                  | Deteriorating  | +        | +      | —      | —           | +        |
| BOS0703-5      | p.Arg465Trp     | 38.31                  | Deteriorating  | +        | +      | +      | +           | +        |
| BOS1536-1      |                 | 11.62                  | Deteriorating  | +        | +      | +      | —           | —        |
| BOS1475-1      |                 | 12.34                  | Stable         | +        | +      | —      | —           | —        |
| BOS1059-1      |                 | 39.41                  | Deteriorating  | +        | +      | +      | —           | —        |
| BOS0393-1      |                 | 50.33                  | Deteriorating  | +        | +      | —      | —           | —        |
| BOS0835-1      |                 | 58.85                  | Stable         | —        | +      | —      | —           | —        |
| BOS0601-1      |                 | 55.91                  | Deteriorating  | +        | +      | —      | —           | —        |
| BOS0703-1      |                 | 72.25                  | Deteriorating  | +        | +      | +      | —           | +        |
| BOS0930-1      |                 | 24.91                  | Stable         | +        | +      | —      | —           | —        |
| BOS1075-1      |                 | 43.89                  | Deteriorating  | +        | +      | —      | —           | —        |
| BOS0703-6      |                 | 47.26                  | Deteriorating  | +        | +      | +      | —           | —        |
| BOS1061-1      |                 | 48.12                  | Deteriorating  | +        | +      | —      | —           | +        |
| BOS0928-1      |                 | 17.14                  | Stable         | +        | +      | —      | +           | —        |
| BOS0703-7      |                 | 48.62                  | Stable         | +        | +      | —      | —           | —        |
| BOS0893-1      |                 | 33.04                  | Deteriorating  | +        | +      | —      | —           | —        |
| BOS1311-4      |                 | 52.48                  | Deteriorating  | +        | +      | —      | —           | +        |
| BOS1311-1      |                 | 49.85                  | Deteriorating  | —        | +      | —      | —           | +        |
| BOS0393-2      |                 | 75.76                  | Deteriorating  | +        | +      | —      | —           | —        |
| BOS1145-1      | p.Arg522His     | 60.9                   | Deteriorating  | +        | +      | —      | —           | +        |
| BOS0877-1      |                 | 17.25                  | Deteriorating  | —        | +      | —      | —           | —        |
| BOS1218-1      |                 | 64.48                  | Deteriorating  | —        | +      | —      | —           | —        |
| BOS0909-1      |                 | 73.1                   | Deteriorating  | +        | +      | —      | —           | —        |

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and other cellular organelles with no evidence of rods, cores, or other diagnostic ultrastructural elements. None of these findings appeared to correlate strongly with age at biopsy, clinical severity, or underlying mutation (eFigure 1, links.lww.com/NXG/A547), although the small numbers and retrospective nature of the analysis preclude making any firm conclusions.

**Weakness and Ambulation**

Most patients reported both proximal and distal limb weakness (n = 31, 74%). Ten percent (n = 4) reported proximal weakness only, and 17% (n = 7) reported distal weakness only. Facial weakness was reported in 27 patients (64%). In addition, ptosis (n = 20, 56%) and eye movement abnormalities (n = 14, 39%) were common (Table 2). While most patients had a symmetric distribution of weakness, over a third reported recognizable asymmetry (n = 16, 38%) (Table 3). Upon review of medical records, 14 patients were described to have a waddling gait and 8 had a Trendelenburg gait. Twenty-one patients could not heel-walk, and 17 could not toe-walk. Figure 3 illustrates the progression of ambulation loss over time in each patient. Ambulation was affected in almost all patients (n = 37/40, 92%). Of those with normal ambulation at last report (n = 3/40), 2 patients were younger than 20 years. The progression of ambulation difficulties was heterogeneous within this cohort. Of 16 patients with onset before 2 years of age, 1 was <1 year at last report and ambulation status is unknown, and 11 developed difficulties during toddlerhood or childhood. Three patients did not report difficulties until adulthood, and 1 was ambulant at last report (age 38 years).

Of the late adult-onset patients, weakness, gait difficulties, and foot drop in 1 patient were presenting symptoms. Among patients with onset during childhood or adulthood, 14 reported first ambulation difficulties between 18 and 49 years old and 9 first developed difficulties after 50 years old. One patient who died at age 3 years was never ambulant, and 7 ultimately progressed to full wheelchair dependence at a median age of 55 years (range = from 10 to 71). Most patients (74%) reported falling, and some who were nonambulant at the time of the interview reported frequent falls prior to losing ambulation. Overall, 67% of patients reported a deteriorating course of their disease (Table 3). These patients were aged 11–75 years (median age of 48 years), whereas patients reporting stable or variable courses (n = 11, 26%) were younger, ranging from age 1 to 58 years (median age of 17 years). Three of the young children were reported by their parents to be “improving,” although it is unknown whether this just reflects normal motor development. Fifty-one percent of patients reported being independent in activities of daily living, while 27% required some assistance and 20% required full-time assistance (Table 2).

**Nonmotor Manifestations**

Table 2 summarizes additional clinical features. While about half the cohort described some degree of respiratory insufficiency (n = 22, 53%), only a few patients required invasive or non-invasive respiratory support (n = 6, 15%). The 2 patients requiring tracheostomy and 24-hour ventilation developed respiratory failure at age 1 month and 1 year, respectively. Three of the 4 patients requiring nocturnal bi-level positive airway pressure or continuous positive airway pressure ventilation began using it in childhood. Ten patients had sleep studies that identified sleep apnea (n = 6) or hypoventilation (n = 1). Forty-five percent of patients reported at least 1 pneumonia in their lifetime, mostly occurring between age 5 and 64 years. Nine patients reported multiple pneumonias (eTable 5, links.lww.com/NXG/A547). Overall, the incidence of pneumonia (45%) among patients with DNM2-related CNM was higher than the general US population (2.4 cases of community-acquired pneumonia per 1,000 adults).38

Many patients reported chewing or swallowing difficulties (n = 17, 40%). Three patients, aged 0.95–3.7 years, required a gastrostomy tube beginning in infancy, and one 7.7-year-old used it occasionally for circumstances, such as extreme fatigue or illness. Most patients reported various speech abnormalities (n = 27, 84%). A high arched palate (n = 14, 47%) and restricted jaw opening (n = 10, 33%) were common. Contractures were present in half of the patients, most commonly ankle contractures (19%) (eTable 6, links.lww.com/NXG/A547). Fourteen patients reported scoliosis (12 mild, 1 moderate, and 1 severe).

No cardiac disease was reported. Of the 20 echocardiograms available for review, only common minor cardiac variations were seen. One patient had concurrent homochromatosis, but otherwise no patients reported clinically known liver disease, although liver ultrasounds were not systematically performed. Available liver function tests are provided in eTable 7, links.lww.com/NXG/A547. Alanine aminotransferase was slightly above normal in 4 patients, but only within 1.5 times the upper limit of normal (ULN). Aspartate aminotransferase was slightly above the ULN in 2 patients, up to ×1.2 ULN.
Multiple psychiatric comorbidities were reported, including depression (n = 7), anxiety (n = 2), and posttraumatic stress disorder (n = 1) independent of age. There were no clear neurocognitive manifestations.

**Treatment**

Information on therapies was available for 27 patients. Almost all patients (n = 24, 89%) reported participating in physical therapy. Occupational therapy (n = 8, 29%) and speech therapy (n = 7, 26%) were also reported. Medications and supplements used included pyridostigmine (n = 5), coenzyme Q10 (n = 5), carnitine (n = 4), and creatine (n = 3). Eight patients reported using albuterol, but the indication for use is unknown (eTable 8, links.lww.com/NXG/A547).

**Phenotype Trends by Gene**

When looking at metrics of disease severity including the age at onset, the age at which ambulation was affected, and the degree of respiratory and feeding difficulties, some DNM2 variants appear to be associated with more severe phenotypes (Figure 4). Most patients with p.Phe372Ser, p.Ser619Leu, p.Ala618Asp, or p.Glu368Lys variants have a congenital or infantile onset disease (all with a median age at onset <3 months). Of the 5 patients requiring invasive or noninvasive ventilatory support in childhood, all had p.Phe372Ser, p.Ser619Leu, or p.Ala618Asp variants. Similarly, the most severe oropharyngeal dysphagia was in patients with p.Phe372Ser and p.Ser619Leu variants. By contrast, patients with p.Arg522His and p.Arg639Trp appear to have a later age...
at onset (median age of 29 and 18 years, respectively). The most common variant, p.Arg465Trp, was associated with a wide spectrum of onset, but these patients generally still had slower progression of ambulation difficulties and minimal respiratory or feeding impairment.

**Discussion**

**DNM2**-related CNM is characterized by slowly progressive weakness with centralized nuclei on muscle histology, although the full spectrum of clinical characteristics is still being elucidated. This retrospective case series illustrates the wide variation in age at onset, progression and severity of the disease, and associated features. This detailed account of the phenotypic spectrum can help inform clinical outcome measures for future clinical trials, although the heterogeneity in presentation and severity will certainly present a challenge. Further exploration for reliable clinical outcome measures and biomarkers, such as muscle MRI, is needed.

Given this phenotypic variability, **DNM2**-related CNM is a challenging diagnosis to make. With technological advances and increasing availability of genetic testing, patients are being genotyped faster, as illustrated by the shorter times to diagnosis in patients born more recently.
However, some patients were misdiagnosed with other neuromuscular disorders, possibly due to overlapping clinical features. Of interest, multiple patients were initially thought to have neurogenic disorders (e.g., CMT or spinal muscular atrophy) (eTable 3, links.lww.com/NXG/AS47). This may be due to the frequency of distal weakness that could clinically mimic neupathy or in some cases due to electrophysiologic data suggestive of a neurogenic process. It is unknown whether the neurogenic appearing motor unit morphology reflects true neurogenic pathology or is "pseudoneurogenic" as has been reported in other chronic myopathies.39 This warrants further investigation, particularly given that DNM2 mutations can also cause CMT.

Overall, our cohort confirmed that disease onset occurs predominantly in infancy and early childhood,4,10 although DNM2-related CNM was initially identified in families showing late-onset CNM.9 This may be in part due to the nature of patient-reported retrospective data, whereby patients report symptoms years before presenting to medical care. Although this cohort was identified through research at a children’s hospital, only 7 patients were ascertained locally, suggesting this represented a minimal bias of ascertainment at most.

Our study further characterized early manifestations of DNM2-related CNM. We found that 38% of patients showed early signs of myopathy, such as decreased fetal movements, neonatal hypotonia, and early respiratory difficulties. Although 42% of the respondents indicated affected pregnancies were associated with reduced fetal movements, this may be an underestimate because many adults may not have known about their own gestational histories. In addition, congenital anomalies, such as a high arched palate, which was present in almost half of the cohort, including 1 patient with adult-onset disease, suggest early muscle weakness even if subclinical. Confounders such as prematurity should be considered when interpreting these data, although the prematurity rate of this cohort (14%) was comparable with national rates in the United States (10%).40

In addition to early onset of motor symptoms, some patients can have a severe clinical course, as illustrated in patient BOS1203-1 who had weakness and severe motor impairment and respiratory failure and died at age 3 years. While this is not the common phenotype, it is important that DNM2-related CNM can have a severe neonatal presentation similar to XLMTM.41 However, in contrast to infants with XLMTM, more than 90% of whom require respiratory support at birth,32,43 only 2 of 16 infantile-onset patients required invasive ventilation, while 3 more received noninvasive support. Despite the relatively low rate of patients requiring respiratory support, many patients reported symptoms or comorbidities suggestive of an underecognized respiratory insufficiency. Further characterization of respiratory involvement in DNM2-related CNM is needed.

Facial and bulbar weakness were frequently reported. Like respiratory involvement, few patients had severe enough oropharyngeal dysphagia to require a gastrostomy tube. However, many patients reported difficulty with chewing and swallowing. One-third of the patients described restricted jaw opening, as previously noted,44,45 which can contribute to feeding difficulties, and in some cases resulted in a significant barrier to adequate dental care. Ptosis and eye movement abnormalities were also common. Taken together, these symptoms overlap with those of neuromuscular junction disorders. This observation is of interest given recent literature illustrating the important role of dynamin-2 in the postsynaptic membrane.56 In fact, 5 patients were trialed on anticholinesterase inhibitors.47 Efficacy has not been systematically studied, but some small case series reported benefit.47,48 The clinical relevance of any potential links to deficits in neuromuscular transmission remains to be determined.

Recently, there has been increasing recognition of liver disease in XLMTM.49 In the initial trial of adenovirus associated virus-based gene therapy for XLMTM, 4 patients died with evidence of hepatobiliary disease as a contributing factor.50 Given the pathophysiologic closeness of XLMTM and DNM2-related CNM, it is imperative to investigate for possible liver disease in all CNMs, given the safety implications for future therapeutic trials and interventions. In our cohort, liver enzymes were largely normal in our small sample, but markers of cholestasis were not reported. There was no clinical history of hepatic peliosis in this population, although ultrasound imaging was not routinely performed to rule out subclinical findings.

Of the 8 different pathogenic variants in this cohort, severe phenotypes (early age at onset, faster progression of ambulation difficulties, and respiratory involvement) were predominantly seen in patients with p.Glu368Lys, p.Phe372Ser, p.Ala618Asp, and p.Ser619Leu mutations. These variants are all located at the autoinhibitory interface between the PH and middle domains (Figure 1A), where disease-causing mutations are proposed to release autoinhibition of dynamin-2 and promote protein oligomerization, supporting the “gain-of-function” mechanism suggested for DNM2-related CNM.51

This study was limited by its largely retrospective nature. Data were collected from multiple sources for comprehensive phenotyping, but this did result in some inconsistencies between patient-reported data and medical records. Due to a focus on collection of neuromuscular records and incomplete collection of medical records, especially from older patients, findings related to other organ systems may have been missed. Recall bias was also likely present in patient-reported data. While genotype-phenotype trends were highlighted, we cannot determine association due to the small numbers and rarity of the disease. Quality of life was not directly assessed but should be investigated in a subsequent study. High rates of depression and anxiety were reported, which is likely a secondary effect of this chronic disorder.

In conclusion, DNM2-related CNM is a progressive disease associated with significant disability. More than 80% of the cases presented in infancy or childhood and more than half of the patients had a high arched palate, consistent with the view that this is a true congenital myopathy. Despite wide variation...
in age at onset and degree of weakness, shared features of slowly progressive skeletal muscle weakness, often with distal involvement, and consistent pathologic findings of central nuclei, fiber size variation, and often, abnormalities on oxidative staining define the clinicopathologic presentation. Evidence for an underlying dystrophic process is lacking, as are any signs of neuropathy. Restrictive jaw mobility, bulbar weakness, and respiratory insufficiency may be underrecognized yet impactful. Most patients require ambulation assistance at some point during adulthood if not sooner. While often thought of as the “milder” cousin disease to XLMTM, DNM2-related CNM can present as a severe congenital onset myopathy. Furthermore, most patients describe their condition as “deteriorating.” Regardless of the age at onset, this is a progressive condition leading to increasing difficulty with ambulation and challenges with independent functioning. Currently, no disease-targeted therapy exists for DNM2-related CNM, but innovative therapies are on the horizon for this disabling disease.5 In preparation of clinical trials, large multicenter international natural history studies are needed.

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Appendix

| Name             | Contribution                                                                 |
|------------------|-------------------------------------------------------------------------------|
| Leslie Hotchkiss Hayes, MD | Division of Genetics and Genomics, The Manton Center for Orphan Disease Research, Boston Children's Hospital, Harvard Medical School; Department of Neurology, Boston Children's Hospital Drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data |
| Morgane Perdomini, PhD | Dynacure, Illkirch, France Drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data |
| Asli Aykanat, MD | Division of Genetics and Genomics, The Manton Center for Orphan Disease Research, Boston Children's Hospital, Harvard Medical School; Department of Neurology, Boston Children's Hospital Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data |
| Casie A. Genetti, MS | Division of Genetics and Genomics, The Manton Center for Orphan Disease Research, Boston Children’s Hospital, Harvard Medical School Drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data |
| Heather L. Paterson, BS | Division of Genetics and Genomics, The Manton Center for Orphan Disease Research, Boston Children's Hospital, Harvard Medical School Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data |
| Belinda S. Cowling, PhD | Dynacure, Illkirch, France Drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data |
| Christian Freitag, MD | Dynacure, Illkirch, France Drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data |
| Alan H. Beggs, PhD | Division of Genetics and Genomics, The Manton Center for Orphan Disease Research, Boston Children's Hospital, Harvard Medical School Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data; additional contributions: A.H.B. had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. |
