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Nemaline Myopathy – RETIRED CHAPTER, FOR HISTORICAL REFERENCE ONLY

Synonym: Nemaline Rod Myopathy

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Summary

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Clinical characteristics

Nemaline myopathy (referred to in this entry as NM) is characterized by weakness, hypotonia, and depressed or absent deep tendon reflexes. Muscle weakness is usually most severe in the face, the neck flexors, and the proximal limb muscles. The clinical classification defines six forms of NM, which are classified by onset and severity of motor and respiratory involvement:

- Severe congenital (neonatal) (16% of all individuals with NM)
- Amish NM
- Intermediate congenital (20%)
- Typical congenital (46%)
- Childhood-onset (13%)
- Adult-onset (late-onset) (4%)

Considerable overlap occurs among the forms. There are significant differences in survival between individuals classified as having severe, intermediate, and typical congenital NM. Severe neonatal respiratory disease and the presence of arthrogryposis multiplex congenita are associated with death in the first year of life. Independent ambulation before age 18 months is predictive of survival. Most children with typical congenital NM are eventually able to walk.

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Diagnosis/testing

Diagnosis is based on clinical findings and the observation of characteristic rod-shaped structures (nemaline bodies) on muscle biopsy stained with Gomori trichrome. Pathogenic variants have been identified in ten different genes, six of which encode protein components of the muscle thin filament, while three appear to be involved in the protein turnover in the muscle sarcomere via the ubiquitin proteosome pathway.

Management

Treatment of manifestations: Aggressive treatment of lower respiratory tract infections, ventilator use for nocturnal hypoxia, preoperative assessment of pulmonary function to ensure optimal timing of surgical procedures and to minimize anesthetic risk, monitoring of nutritional status, special feeding techniques, standard care for gastroesophageal reflux, mobility and physical therapy to help prevent joint contractures, speech therapy, and assessment of cardiac status.

Surveillance: Routine assessment for respiratory function, scoliosis, joint contractures, and the need for assistive devices.

Agents/circumstances to avoid: Neuromuscular blocking agents, because of possible association with malignant hyperthermia susceptibility.

Genetic counseling

NM is inherited in an autosomal dominant or autosomal recessive manner. In one series, approximately 20% of cases were autosomal recessive, approximately 30% autosomal dominant, and approximately 50% simplex (i.e., single occurrences in a family) representing heterozygosity for a *de novo* dominant pathogenic variant or biallelic autosomal recessive pathogenic variant. Accurate recurrence risk information requires determination of the mode of inheritance, if possible, through pedigree analysis and a combination of clinical evaluation, molecular genetic testing, and muscle biopsy of the parents. Carrier testing for at-risk relatives in families with autosomal recessive NM is possible if the pathogenic variants in the family are known. Prenatal molecular genetic testing is possible for pregnancies at increased risk for autosomal dominant and autosomal recessive NM if the pathogenic variant(s) in the family are known.

Diagnosis

The term "nemaline myopathy" (NM) refers to a group of genetically distinct disorders linked by common morphologic features observed on muscle histology.

Suggestive Findings

Nemaline myopathy **should be suspected** in individuals with the following [North et al 2014]:

- Weakness that is predominantly proximal and generalized with or without facial weakness. Distal weakness may occur in a subset of individuals.
- Hypotonia and depressed deep tendon reflexes, with preserved sensation and normal cognition
- Feeding difficulties related to facial and bulbar weakness, respiratory difficulties, recurrent infections or a weak cough related to restrictive lung disease from weakness of the respiratory muscles. Cardiac function is usually normal.
- Onset in infancy, childhood, or adulthood. In infancy weakness is usually proximally predominant or generalized, while in later forms weakness may be proximally (or – less commonly – distally) predominant.

- Family history consistent with autosomal recessive or autosomal dominant inheritance, although many affected individuals represent simplex cases (i.e., a single occurrence in a family) attributable to autosomal recessive inheritance or a *de novo* dominant pathogenic variant [North et al 2014].

Preliminary Testing

Creatine kinase concentration is generally measured early in the evaluation of individuals with suspected muscle weakness and is useful for distinguishing myopathies from muscular dystrophies. Muscle enzymes are usually normal in NM or may be mildly elevated [Ryan et al 2001].

Electrophysiologic studies that may suggest a myopathic process but are of limited utility in making a specific diagnosis include the following:

- **Electromyography (EMG)** may be normal in young individuals with NM and those who are mildly affected, but is usually myopathic in older individuals with NM. It shows polyphasia, small motor unit potentials with normal fiber density, and a full interference pattern with effort. In those with distal disease, "neurogenic" abnormalities (large motor potentials with increased fiber density, discrete patterns on effort, and increased jitter on single-fiber EMG) are occasionally apparent.
- **Nerve conduction studies (NCV)** are generally normal, although low-amplitude motor responses may be seen in those with marked loss of muscle bulk.

Muscle imaging is useful in distinguishing between neuropathic and myopathic processes, and can be used to identify an appropriate muscle to biopsy. Muscle MRI in the congenital myopathies commonly reveals patchy, fatty degeneration of muscle tissue and variable involvement of different muscle groups [Oishi & Mochizuki 1998, Wallgren-Pettersson & Laing 2001]. These patterns of selective muscle involvement may guide genetic testing once the diagnosis of NM is made based on the pathologic findings [Jungbluth et al 2004], although characteristic neuroimaging changes are defined for only a subset of genetic forms of NM:

- NM secondary to pathogenic variants of *NEB* (encoding nebulin) shows a consistent pattern of selective muscle involvement corresponding to clinical severity. In mild cases, there may be relative sparing of thigh muscles and selective involvement of tibialis anterior and soleus muscles. Severe cases show diffuse involvement of the lower limbs with sparing of the gastrocnemius [Jungbluth et al 2004].
- *TPM2*-associated NM is commonly associated with involvement of the masticator (temporal) muscles and distal lower leg muscles [Jarraya et al 2012].

Establishing the Diagnosis

The diagnosis of nemaline myopathy **is established** in a proband with a muscle biopsy demonstrating nemaline rods and/or molecular genetic testing that detects pathogenic variant(s) in one of the ten genes known to be associated with nemaline myopathy (see Table 1).

Muscle Biopsy

A clinically affected muscle should be biopsied. Muscles with "end-stage" weakness should be avoided. Consideration should be given to biopsying more than one muscle, as findings can vary in different muscle groups/limbs [Ryan et al 2003].

Muscle histology. The diagnostic hallmark of NM is the presence of distinct rod-like inclusions (nemaline bodies) in the sarcoplasm of skeletal muscle fibers (see Figure 1).

The rods are often not visible on hematoxylin and eosin (H & E) staining, but appear as red or purple structures against the blue-green myofibrillar background with the modified Gomori trichrome stain. The distribution of rods within myofibers may be random, but they show a tendency to cluster under the sarcolemma and around nuclei. The proportion of fibers containing rods varies from one individual to another and from muscle to

muscle. Although the number of rods appears to increase with age, no definitive correlation exists between number of rods and severity or age of onset of the myopathy [Ilkovski et al 2001, Ryan et al 2003]. In some individuals with NM, rods are not identified in the first muscle biopsy as a result of sampling; thus, diagnosis is delayed until biopsy is repeated.

Pathologic changes of NM are much the same irrespective of the severity of the clinical manifestations or the age of onset, but the finding of rod bodies within muscle nuclei (intranuclear rods) is often associated with a more severe clinical course. Very numerous nemaline bodies, glycogen accumulation, and marked sarcomeric disruption are more common in nemaline myopathy associated with pathogenic variants in skeletal alpha-actin, while NM caused by pathogenic variants in slow alpha-tropomyosin is characterized by preferential rod formation in, and atrophy of, type 1 fibers [Ryan et al 2003].

Note: (1) Nemaline rods are not pathognomonic for NM. Nemaline rods observed on muscle biopsy in other neuromuscular disorders and unrelated conditions are considered a reflection of "secondary" NM (see Differential Diagnosis). (2) Nemaline bodies are not usually present in heart muscle; however, rods have occasionally been observed in muscle of the diaphragm and heart [Ryan et al 2001]. (3) Whereas nemaline bodies typically occur in the sarcoplasm of the muscle fiber, intranuclear rods have been observed in muscle biopsies from those with severe neonatal myopathy, the "typical" congenital-onset form of NM [Sparrow et al 2003, Hutchinson et al 2006], and in some with adult-onset progressive myopathy. Intranuclear rods may be more common in individuals with NM related to *ACTA1* (actin) pathogenic variants.

Muscle electron microscopy. Nemaline bodies are electron dense and measure 1-7 µm in length and 0.3-2 µm in width. The nemaline bodies are in structural continuity with Z-disks; their ultrastructure resembles the lattice pattern of the Z-disk. Focal disruption of the myofibrillar pattern and accumulation of thin filaments in areas devoid of sarcomeric structure are often observed. Rods are often associated with marked sarcomeric disorganization and loss of normal sarcomeric registration [Ilkovski et al 2001, Ryan et al 2003]. Not infrequently, however, areas of complete sarcomeric disarray abut relatively normal sarcomeres, a phenomenon that is poorly understood.

Rod composition. Consistent with their appearance as extensions of Z-lines, rods are largely made up of α-actinin. In addition, rods contain several other Z-line proteins including telethonin, filamin, myotilin, myozenin, and myopallidin. Although rods likely contain thin filament proteins such as tropomyosin and nebulin, antibodies to these proteins do not reveal any increase in fluorescence at the site of rods, presumably because their epitopes are inaccessible to staining.

Fiber typing. Predominance of type 1 fibers is a common feature of NM. In extreme cases, fiber typing by the ATPase reaction reveals a uniform reactivity of a pure population of type 1 fibers. Rods may be found equally in all fiber types or preferentially in either type 1 or type 2 fibers. Rod-containing fibers are often but not always hypotrophic. Fiber type 1 predominance and atrophy tend to become more prominent with age and are associated with abnormally high expression of fetal myosin (usually not expressed after age 6 months) and coexpression of fast and slow myosin in some muscle fibers [Ilkovski et al 2001, Ryan et al 2003]. Two studies have documented progressive conversion of type 2 to type 1 fibers [Gurgel-Giannetti et al 2003, Ryan et al 2003].

No definitive pathologic markers exist for the various genetic forms of NM. Detailed pathologic studies may provide morphologic clues to guide molecular genetic testing; however, the number of individuals with NM studied in detail is still too small to draw conclusions about the specificity of these findings:

- *TPM3* is expressed only in type 1 (slow) fibers, and fiber atrophy and nemaline bodies in individuals with the *TPM3* pathogenic variant occur preferentially in type 1 fibers [Wallgren-Pettersson et al 1998, Tan et al 1999, Ryan et al 2003].

- Very numerous rods, abnormal accumulation of glycogen and actin filaments, marked sarcomeric disruption, and (rarely) zebra bodies have been observed in individuals with *ACTA1* pathogenic variants [Ilkovski et al 2001, Ryan et al 2003].
- In the Amish form of NM, associated with complete loss of troponin T, slow skeletal muscle causes selective atrophy of type 1 fibers [Jin et al 2003, van der Pol 2014].
- Nebulin immunocytochemistry is normal in the majority of individuals with *NEB* pathogenic variants. Abnormal staining in a small proportion of individuals can serve as a guide for molecular genetic testing [Wallgren-Pettersson & Laing 2000].
- The NM associated with pathogenic variants in *KBTBD13* is characterized by relative predominance and hypertrophy of type 1 fibers with atrophy of type 2 fibers [Sambuughin et al 2010].
- The severe nemaline myopathy associated with *KLHL40* pathogenic variants is associated on muscle biopsy with very numerous small nemaline bodies, sometimes only visible by electron microscopy, frequently with virtually no normal myofibrils remaining ("miliary NEM") [Ravenscroft et al 2013].
- In NM associated with *LMOD3*, nemaline bodies have a distinctive ultrastructural appearance on EM and may appear as thickened Z-discs, in pairs interconnected by thin filaments or surrounded by a short thin filament "fringe" [Yuen et al 2015].

Molecular Genetic Testing

Genes. Pathogenic variants in ten genes have been identified as causative of nemaline myopathy (NM) (Table 1). Seven of these genes encode components of the sarcomeric thin filament (*NEB*, *ACTA1*, *TPM2*, *TPM3*, *TNNT1*, *CFL2*, *LMOD3*). Three additional genes, *KBTBD13*, *KLHL40*, and *KLHL41*, belong to the BTB-BACK-kelch (BBK) protein family and are involved in the ubiquitin proteosome pathway. LMOD3 and NEB bind to KLHL40, suggesting a common pathway for the pathogenesis of the different genetic forms of NM.

It is too early to determine the precise frequency of each of the genetic subgroups of NM, the proportion of *de novo* pathogenic variants, and the incidence of germline mosaicism, but trends are becoming apparent (see Table 1).

Multigene panel. Because of the number of genes responsible for NM, a good strategy for molecular diagnosis of a proband suspected of having NM is use of a multigene panel that includes the genes known to be associated with NM (see Table 1) and other genes of interest (see Differential Diagnosis).

Sequence analysis is performed first, followed by deletion/duplication analysis where relevant (see Table 1) if no pathogenic variant is found.

Note: (1) The genes included in a multigene panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*; thus, clinicians need to determine which multigene panel is most likely to identify the genetic cause of the condition at the most reasonable cost while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician.

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Single-gene testing. Where a multigene panel is not available or not preferred, molecular genetic testing should be prioritized based on clinical features – presentation and presumed mode of inheritance – and findings on muscle pathology and imaging (see Table 2).

- Mutation of *ACTA1* (encoding alpha-skeletal actin) causes 20%-25% of all nemaline myopathy, but 50% of severe nemaline myopathy.

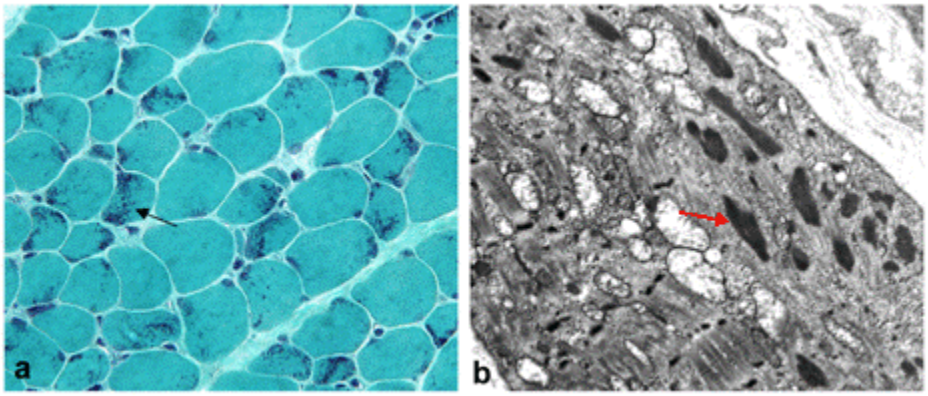

Figure 1. Pathology of nemaline myopathy. Gomori trichrome staining of frozen muscle from an affected individual shows the nemaline bodies (rods) as dark blue/purple structures scattered throughout the muscle fibers (a: arrow, 60x magnification). The rods appear as electron-dense structures at the electron microscopy level (b: arrow, 15,000x magnification).

- Mutation of *NEB* (encoding nebulin) accounts for about 50% of NM. The associated phenotype is usually "typical congenital"; less commonly, *NEB* pathogenic variants are associated with a severe neonatal presentation or in older patents with predominantly distal weakness.
- Mutation of *TPM3* (encoding slow α-tropomyosin) should be considered particularly if nemaline rods are restricted to type 1 slow muscle fibers, or if fiber type disproportion is the only feature.
- Mutation of *TPM2* (encoding beta-tropomyosin) should be especially considered for mild dominant disease.
- Mutation of *TNNT1* (encoding low troponin T) has been described almost exclusively in the Old Order Amish population, but likely occurs rarely in other populations [van der Pol 2014].
- Mutation of *CFL2* (encoding muscle-specific cofilin) is a rare cause of nemaline myopathy, having been described in only three families to date [Agrawal et al 2007, Ockeloen et al 2012, Ong et al 2014].
- Mutation of *KBTBD13* is associated with peculiarly slow voluntary movements and relative sparing of the facial and respiratory muscles.
- Mutation of *KHLH40* has been identified in a small number of individuals with a very severe neonatal phenotype, often in association with congenital contractures, respiratory failure, and swallowing difficulties [Ravenscroft et al 2013].
- Mutation of *KHL41* has been associated with a variable NM phenotype. Pathogenic frameshift variants resulted in a severe phenotype with neonatal death, whereas missense changes resulted in impaired motor function with survival into late childhood and/or early adulthood [Gupta et al 2013].
- Mutation of *LMOD3* (encoding leiomodin 3) has been identified in a small number of individuals, the majority of whom have severe congenital NM associated with nonsense or frameshift variants. Two sibs with typical congenital NM have also been described. [Yuen et al 2015]

Table 1. Molecular Genetic Testing Used in Nemaline Myopathy

Gene [1]	Proportion of Nemaline Myopathy Attributed to Mutation of Gene	Method
NEB	Up to 50% [2]	Targeted analysis for pathogenic variants [3, 4]
		Sequence analysis [5]
		Deletion/duplication analysis [6, 7]

Table 1. continued from previous page.

Gene [1]	Proportion of Nemaline Myopathy Attributed to Mutation of Gene	Method
ACTA1	15%-25% [8]	Sequence analysis [5]
		Deletion/duplication analysis [6]
TPM3	2%-3% [9]	Sequence analysis [5]
		Deletion/duplication analysis [6]
TPM2	<1% [10]	Sequence analysis [5]
		Deletion/duplication analysis [6]
TNNT1	Almost exclusively in Old Amish [11]	Sequence analysis [5]
		Deletion/duplication analysis [6]
CFL2	Rare [12]	Sequence analysis [5]
KBTBD13	Unknown	Sequence analysis [5]
KLHL40	Unknown	Sequence analysis [5]
KLHL41	Unknown	Sequence analysis [5]
LMOD3	Unknown [13]	Sequence analysis [5]
Unknown [14]	NA	NA

1. See Table A. Genes and Databases for chromosome locus and protein. See Molecular Genetics for information on allelic variants.
2. It is likely that more than half of nemaline myopathy cases are caused by *NEB* pathogenic variants; the exact proportion has yet to be conclusively determined.
3. Note: Pathogenic variants included in a panel may vary by laboratory.
4. Testing that employs a method to detect the specific 2,502-nucleotide deletion spanning exon 55 (see Table 3). The only known *NEB* mutational hot spot is a 2,502-bp in-frame deletion of exon 55 observed in five families of Ashkenazi Jewish ancestry [Anderson et al 2004]. This pathogenic variant may be a common cause of NM in the Ashkenazi Jewish population; its frequency in other populations is unknown.
5. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Pathogenic variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
6. Testing that identifies exon or whole-gene deletions/duplications not detectable by sequence analysis of the coding and flanking intronic regions of genomic DNA. Methods used may include quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and chromosomal microarray (CMA) that includes this gene/chromosome segment.
7. Deletion/duplication analysis of *NEB* may employ any of a variety of techniques to detect not only deletion of exon 55, but also other deletions of an exon(s) or of the whole gene. Two such novel deletions have been reported [Lunkka-Hytonen et al 2008] (see Table A. Genes and Databases, **HGMD**).
8. Mutation of *ACTA1* accounts for 15%-25% of all individuals with NM [Nowak et al 1999, Ilkovski et al 2001, Ryan et al 2001]. Of note, mutation of *ACTA1* may account for up to 50% of severe lethal congenital-onset forms of NM [Agrawal et al 2004].
9. 3/117 individuals screened [Ryan et al 2001, Wallgren-Pettersson & Laing 2003]
10. Dominant *TPM2* pathogenic variants in 2/54 families with typical congenital-onset NM [Donner et al 2002]
11. Identified only in a genetically isolated group of Old Order Amish individuals with NM [Johnston et al 2000, Jin et al 2003], and a single Dutch case [van der Pol 2014]
12. Mutation of *CFL2* has been described in three families to date [Agrawal et al 2007, Ockeloen et al 2012, Ong et al 2014].
13. Yuen et al [2015]
14. Additional individuals with NM do not link to any of the identified loci suggesting further genetic heterogeneity [Pelin & Wallgren-Pettersson 2008].

Clinical Characteristics

Clinical Description

The cardinal features of nemaline myopathy (NM) are weakness, hypotonia, and depressed or absent deep tendon reflexes; intrafamilial variation in course and outcome is considerable.

Muscle weakness is usually most severe in the face, the neck flexors, and the proximal limb muscles. In some individuals with NM, the distal muscles are involved. In congenital forms of NM, the face is often long and expressionless, with a tented vermilion border of the upper lip, high palate, and retrognathia. Gross motor milestones are delayed, but most affected individuals are otherwise developmentally normal.

Dysphagia and feeding difficulties are common; approximately 25% of children with congenital-onset NM require gavage feeding or gastrostomy during the first few years of life.

Respiratory problems secondary to involvement of the diaphragm and intercostal muscles are common in congenital NM. The degree of skeletal muscle weakness does not necessarily reflect the degree of respiratory muscle involvement, particularly in older children and adults [Ryan et al 2001].

Many children with NM have hypermobility of joints in infancy and early childhood; contractures and deformities of the joints, including scoliosis, commonly develop with time.

The extraocular muscles are usually spared.

Cardiac contractility is usually normal but occasional cases of dilated cardiomyopathy are seen in NM [Gatayama et al 2013].

Classification

The existing classification of NM into six forms is based on age of onset and severity of motor and respiratory involvement and includes the severe congenital (neonatal) form, Amish NM, intermediate congenital form, typical congenital form, childhood-onset form, and adult-onset (late-onset) form [Wallgren-Pettersson et al 1998].

Overlap among these groups is significant. It is also important to note that adults are sometimes diagnosed with NM in the course of investigation of other family members. Individuals in whom muscle involvement is relatively mild, despite onset in infancy or childhood, may be misclassified as having the adult-onset form.

In a review of 143 individuals with NM from Australia and North America, Ryan et al [2001] found that 23 (16%) had severe congenital NM, 29 (20%) had intermediate congenital NM, 66 (46%) had typical congenital NM, 19 (13%) had childhood-onset NM, and six (4%) had adult-onset NM. Children who crawled before age 12 months and walked before age 18 months were classified as having typical congenital NM. The distinction between the intermediate congenital and typical congenital forms of NM can often be made only in retrospect as no single parameter in infancy distinguishes between the two phenotypes.

Severe congenital (neonatal) NM presents at birth with severe hypotonia and muscle weakness, little spontaneous movement, difficulties with sucking and swallowing, gastroesophageal reflux, and respiratory insufficiency. Decreased fetal movements and polyhydramnios may complicate the pregnancy [Ryan et al 2001], and death in utero associated with fetal akinesia has been described. Uncommon findings include dilated cardiomyopathy and arthrogryposis multiplex congenita (i.e., multiple joint contractures) [Ryan et al 2001, Wallgren-Pettersson & Laing 2003]. Early mortality is common, usually resulting from respiratory insufficiency or aspiration pneumonia. However, occasional individuals with severe generalized weakness and inadequate respiration at birth survive long-term.

Amish NM is a clinically distinct autosomal recessive form with neonatal onset and early childhood lethality. To date, it has been described in only a single genetic isolate of related Old Order Amish families [Johnston et al 2000], and a single recent Dutch case [van der Pol 2014]. It presents at birth with hypotonia, contractures, and, remarkably, tremors that typically subside over the first two to three months of life. Progressive weakness associated with severe pectus carinatum, muscle atrophy, and contractures often leads to death resulting from respiratory insufficiency in the second year of life.

Intermediate congenital NM lies between the severe congenital form and typical congenital form in terms of disease severity at birth and long-term outcome. The early development of joint contractures is characteristic of this form of NM. Although individuals with this form of NM have anti-gravity movement and independent respiration at delivery, they are included in this subgroup if weakness prevents achievement of motor milestones or necessitates use of a wheelchair and/or ventilatory support by age 11 years. Distinction between intermediate congenital and typical congenital NM may therefore be possible only with increasing age.

Typical (mild) congenital NM usually presents in the neonatal period or first year of life with hypotonia, weakness, and feeding difficulties. The severity of muscle involvement is less than that seen in the severe congenital and intermediate congenital forms. Spontaneous anti-gravity movements are present and respiratory involvement is less prominent. Some weakness of the respiratory musculature is usual but may be subclinical, manifesting as insidious nocturnal hypoventilation or frequent lower respiratory tract infections. A minority of children presents after age one year with delay of gross motor milestones, an abnormal waddling gait, or bulbar weakness manifesting as hypernasal speech or swallowing difficulties. Weakness is usually proximal at presentation, but late distal involvement evolves in a minority of individuals. Occasionally, individuals have both proximal and distal weakness early in life. Weakness is usually static or very slowly progressive and most individuals are able to lead independent, active lives [Wallgren-Pettersson et al 1998]. Cardiac involvement is rare.

Childhood-onset NM was first described by Laing et al [1992] in a large Australian kindred in which it was inherited in an autosomal dominant manner. Early motor development is normal. In the late first or early second decade, children experience the onset of symmetric weakness of ankle dorsiflexion with foot drop reminiscent of a peripheral neuropathy. Weakness is slowly progressive with eventual involvement of all ankle movement and more proximal limb musculature. Two older family members were wheelchair bound by age 40 years.

This form of NM is caused by mutation of *TPM3*.

Van Engelen and colleagues [Pauw-Gommans et al 2006] reported a new phenotype in a Dutch pedigree with autosomal dominant NM and proximal muscle weakness with onset in childhood [Wallgren-Pettersson & Laing 2001, Gommans et al 2003]. Facial, respiratory, and cardiac muscles are normal. The remarkable feature is the complaint of muscle "slowness"; individuals move in "slow motion" and are unable to jump or run. Physiologic studies confirm slowing of muscle speed (as measured by force oscillation amplitude and maximal rate of force rise) and muscle relaxation time [Pauw-Gommans et al 2006]. This form of NM is caused by mutation of *KBTBD13* [Sambuughin et al 2010].

Adult-onset (late-onset) NM varies in clinical presentation and disease progression. Most individuals with this phenotype develop generalized weakness between age 20 and 50 years without antecedent symptoms or family history. Myalgia may be prominent, and weakness may progress rapidly. Occasionally, individuals present with cardiomyopathy or the "dropped head" syndrome, with severe weakness of neck extension with or without neck flexor weakness [Lomen-Hoerth et al 1999]. Respiratory or cardiac involvement is uncommon but, when present, often occurs in association with increasing weakness and physical disability.

Inflammatory changes on biopsy are not uncommon in adult-onset NM. A small number of affected individuals have developed a monoclonal gammopathy and paresthesiae in association with their myopathy. Comorbid monoclonal gammopathy may be a marker of poor prognosis in individuals with late-onset NM [Chahin et al

2005]. Based on the presence of additional and "atypical" features on muscle biopsy in many individuals, the progressive nature of the weakness, and the absence of family history in the majority of individuals, the adult-onset variant of NM (sporadic late-onset nemaline myopathy, SLONM) is likely to represent a different clinical entity from childhood NM.

Prognosis

In a review of 14 individuals with NM seen in London and 85 individuals with NM from the literature, Martinez & Lake [1987] identified neonatal hypotonia as the single most important prognostic sign in NM. However, their classification of children into severe congenital and mild congenital forms was retrospective and few details were given regarding the basis of their grouping.

In the 143 affected individuals reported by Ryan et al [2001], analysis of cumulative survival probabilities revealed significant differences in survival among those classified as having severe, intermediate, and typical congenital NM. In this series, hypotonia and severe weakness in infancy were not predictive of early mortality; however, very severe neonatal respiratory disease and the presence of arthrogryposis multiplex congenita were associated with death in the first year of life in all but one individual. Independent ambulation before age 18 months was predictive of survival. Seventeen of 23 children with severe congenital NM and 8/29 children with intermediate congenital NM died of respiratory failure, compared to 4/66 with typical congenital, 1/19 with childhood-onset, and 0/6 with adult-onset NM. In many individuals, a stormy early course with frequent respiratory tract infections was followed by clinical stabilization. Most children with typical congenital NM were eventually able to walk.

Genotype-Phenotype Correlations

Genotype-phenotype correlation remains poorly defined in NM, largely because of the significant clinical overlap between differing forms of the disease (Table 2) and the significant proportion of cases for which the genetic basis remains unknown.

Neonatal presentation of NM has been reported in those with autosomal recessive inheritance of pathogenic variants in *NEB* [Pelin et al 1999], *TPM3* [Tan et al 1999], *TNNT1* [Johnston et al 2000, Jin et al 2003], *ACTA1* [Sparrow et al 2003], *KLHL40* [Ravenscroft et al 2013], *KLHL41* [Gupta et al 2013], and *LMOD3* [Yuen et al 2015] and in those with autosomal dominant inheritance of pathogenic variants in *ACTA1* [Nowak et al 1999].

"Childhood-onset" disease has been seen with autosomal dominant inheritance of pathogenic variants in *TPM3*, *ACTA1*, and *KBTBD13* [Nowak et al 1999, Ilkovski et al 2001, Sambuughin et al 2010].

Marked clinical variability is noted in individuals with *ACTA1* pathogenic variants ranging from severe congenital weakness with death from respiratory failure in the first year of life to childhood-onset myopathy with survival into adulthood [Ryan et al 2001]. Wide variation in age of onset and clinical severity was observed in three affected members of the same family, suggesting that the *ACTA1* genotype is not the sole determinant of phenotype [Ryan et al 2003].

Genetic subtypes of nemaline myopathy. See Table 2.

Table 2. Phenotype Correlations with Mutated Genes

Mutated Gene [1]	MOI	Phenotype
NEB	AR	• Typical congenital (majority) • All other phenotypes (occasional)

Table 2. continued from previous page.

Mutated Gene [1]	MOI	Phenotype
ACTA1	AD/AR	• Range from severe congenital to childhood onset • Causes 50% of severe lethal NM • Rare cases with cardiac involvement
TPM3	AD/AR	• Severe congenital (AR) • Intermediate congenital • Childhood onset (AD)
TPM2	AD	Typical congenital
TNNT1	AR	Amish NM
CFL2	AR	• Typical congenital • Only 2 families reported to date
KBTBD13	AD	• Childhood onset, slowly progressive weakness w/characteristic slowness of movements • Unstructured cores present on muscle biopsy, in addition to rods
KLHL40	AR	• Severe congenital lethal • Fetal akinesia
KLHL41	AR	• Severe congenital • Intermediate congenital • Typical congenital
LMOD3	AR	• Severe congenital • Typical congenital

AD = autosomal dominant; AR = autosomal recessive; MOI = mode of inheritance
1. Where known, in descending order by the proportion of nemaline myopathy attributed to pathogenic variants in the gene (see Table 1)

Penetrance

Data are insufficient to draw conclusions about penetrance in dominant *(ACTA1*-, *TPM3*-, *TPM2*-, and *KBTBD13*-related) forms of NM.

Nomenclature

Nemaline myopathy was first described in 1963 by investigators from the United States and Canada, and defined by a particular ultrastructural change on muscle biopsy: the finding of thread-shaped structures in muscle fibers, which are known as nemaline bodies, or rods (from the Greek *nema*, meaning thread). Prior to the identification of discrete forms of congenital myopathy, persons with these disorders were generally labeled as having "amyotonia congenita," or benign congenital hypotonia.

Prevalence

NM is a rare disorder with an estimated incidence of 1:50,000 live births in one Finnish study and a more recent study in an American Ashkenazi Jewish population [Anderson et al 2004].

NM may be more common in some populations; Johnston et al [2000] suggested an incidence of 1:500 in the Amish community.

Overall, NM represents about 17% of all congenital myopathies [Maggi et al 2013].

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with mutation of *NEB*, *TNNT1*, *CFL2*, *KLHL40*, *KLHL41*, or *LMOD3*.

ACTA1. Goebel et al [1997] reported three individuals with congenital myopathy and excess accumulation of thin filaments that stained positive for skeletal muscle α-actin. Two of these individuals also had nemaline bodies. Pathogenic variants were subsequently identified in *ACTA1* [Nowak et al 1999]. Therefore, pathogenic variants in this gene may present with the pathologic finding of accumulation of thin filaments in the absence of nemaline bodies [Wallgren-Pettersson & Laing 2003].

Heterozygous pathogenic missense variants in *ACTA1* have also been identified in individuals with the histologic picture of congenital fiber-type disproportion (CFTD), characterized by selective hypotrophy of type 1 fibers in the absence of other abnormalities on light or electron microscopy. All three individuals with CFTD with *ACTA1* pathogenic variants had severe congenital weakness and respiratory failure without ophthalmoplegia, and were clinically indistinguishable from individuals with *ACTA1* pathogenic variants and severe congenital-onset NM [Laing et al 2004].

Jungbluth et al [2001] described an individual with mild NM and sleep hypoventilation in whom an *ACTA1* pathogenic variant was identified. Cores were also noted in the muscle biopsy, suggesting that cores may also occur as a secondary feature in primary NM. The cores were predominantly in type 2 fibers, as distinct from typical central core disease (CCD) and the core-rod myopathy found in the family described by Scacheri et al [2000], in which the cores occurred predominantly in type 1 fibers. The identification of a novel ryanodine receptor gene pathogenic variant causing a form of central core disease with associated rod formation suggests that core-rod myopathy may exist as a separate disease entity [Monnier et al 2000, Scacheri et al 2000].

A single case of cap disease caused by an *ACTA1* pathogenic variant has been reported [Hung et al 2010]. Cap disease is a congenital myopathy defined by the finding on muscle biopsy of enlarged Z-discs and cap-like structures containing disorganized thin filaments at the periphery of muscle fibers.

O'Grady et al [2015] describe two brothers with congenital muscular dystrophy with rigid spine caused by a homozygous missense variant in *ACTA1*. This is the first description of disease caused by recessive variants in *ACTA1* associated with expression of skeletal α-actin.

TPM3. Pathogenic variants in *TPM3* have been associated with congenital fiber type disproportion [Clarke et al 2008] and cap disease [Waddell et al 2010].

TPM2. Pathogenic variants in *TPM2* have been associated with distal arthrogryposis multiplex congenita type I (Escobar syndrome), congenital fiber-type disproportion [Clarke et al 2012], and cap disease [Tajsharghi et al 2007].

KBTBD13. Pathogenic variants in *KBTBD13* can be associated with core-rod myopathy as well as nemaline myopathy. The cores are unstructured and differ from the classic sharply demarcated cores observed in central core or core-rod disease associated with mutation of *RYR1* [Sambuughin et al 2010].

Differential Diagnosis

All congenital myopathies have a number of common clinical features: generalized weakness, hypotonia and hyporeflexia, poor muscle bulk, and dysmorphic features secondary to muscle weakness (e.g., pectus carinatum, scoliosis, foot deformities, a high palate, long face). Therefore, the diagnosis of nemaline myopathy (NM) rests on the presence of the specific ultrastructural changes on muscle biopsy. In addition, marked clinical overlap exists between congenital myopathies including centronuclear myopathies, core myopathies, and congenital

fiber-type disproportion; and other neuromuscular disorders including the muscular dystrophies, congenital myasthenic syndromes, metabolic myopathies including Pompe disease, and spinal muscular atrophy, as well as Prader-Willi syndrome, which can present with marked hypotonia in the newborn period.

In some individuals with congenital myopathy, cores and rods coexist (so-called "core-rod" myopathy). Monnier et al [1997] and Scacheri et al [2000] reported different pathogenic variants in the C-terminal of *RYR1* (encoding the ryanodine receptor*)* in two large families with core-rod myopathy, suggesting that the rods are a secondary feature of some cases of primary central core disease (CCD) [Scacheri et al 2000, von der Hagen et al 2008]. Core-rod myopathy is also associated with pathogenic variants in skeletal muscle isoforms of the genes encoding tropomyosin [Marttila et al 2014] and *KBTBD13* [Gommans et al 2003] and further genetic heterogeneity is likely.

Another form of inherited myopathy with hyaline and nemaline bodies, for which no genetic locus has yet been identified, has been reported [Selcen et al 2002]. The affected sibs in this kindred had adult-onset muscle weakness that was greater distally than proximally, as well as respiratory insufficiency, cardiomyopathy, and cervical spine anomalies.

Secondary NM. Nemaline rods are not pathognomonic for NM. In humans, nemaline bodies have been seen on muscle biopsy in numerous other neuromuscular and unrelated conditions including mitochondrial myopathy [Lamont et al 2004], dermatomyositis, myotonic dystrophy type 1, and Hodgkin's disease, and in normal human extraocular muscle [Skyllouriotis et al 1999, Portlock et al 2003]. In NM secondary to other disease processes, clinical presentation and examination findings are usually consistent with the primary disease process. For example, in HIV myopathy, presentation is with a polymyositis-like illness characterized by progressive, painless proximal weakness possibly associated with dysphagia, muscle cramps, and paresthesia. Thus, rod formation likely represents a common pathophysiologic response of skeletal muscle to certain pathologic situations, and the diagnosis of "primary" NM rests on both the finding of rod bodies on muscle biopsy and an appropriate clinical scenario.

In sporadic late-onset NM, progressive weakness is often associated with a monoclonal gammopathy, which may be a marker of poor prognosis [Chahin et al 2005], and which may support this being a primarily immunologic, rather than genetic, condition.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with nemaline myopathy (NM), the following evaluations are recommended:

- Thorough assessment of respiratory status, including pulmonary function studies and assessment for nocturnal hypoxia
- For early-onset forms, assessment of feeding abilities (sucking, swallowing, gastroesophageal reflux) and growth parameters to determine the need for feeding interventions such as gavage feeding or gastrostomy insertion
- Physical examination to evaluate for joint contractures
- Physical examination to evaluate for scoliosis, followed by spinal x-ray if scoliosis is suspected
- Physical and occupational therapy evaluations relevant to the degree of weakness
- Speech therapy evaluation if dysarthria and/or hypernasal speech is present
- Orthodontic evaluation if palatal anomalies are present
- Evaluation for the presence of dilated cardiomyopathy (rare association)
- Clinical genetics consultation

Treatment of Manifestations

Consensus for management of congenital myopathies have been published [Wang et al 2012].

A multidisciplinary approach to the clinical management of the affected individual greatly improves quality of life and can influence survival:

- Aggressive treatment of lower respiratory tract infections
- Evaluation at an early stage of the need for intermittent or permanent use of a mechanical ventilator to prevent insidious nocturnal hypoxia
- Assurance of adequate caloric intake and appropriate nutritional status, including special feeding techniques and high-calorie formulas and foods, if indicated
- Standard treatment of gastroesophageal reflux, if present
- Referral to an orthopedist for management of scoliosis and joint contractures, as in the general population
- Physical therapy for maintenance/improvement of function and joint mobility
- Speech therapy if dysarthria and/or hypernasal speech is present
- Assessment of cardiac status because of the risk (albeit low) of cardiomyopathy or cor pulmonale

Prevention of Secondary Complications

Preoperative assessment of pulmonary function is essential to ensure optimal timing of surgical procedures and to minimize anesthetic risk.

Anesthetics are generally well tolerated in individuals with NM. Ryan et al [2001] reviewed the outcome of 130 affected individuals who underwent one or more surgical procedures. None developed malignant hyperthermia. However, five developed unexpected postoperative respiratory failure (following scoliosis repair in 4 individuals and fundoplication in 1), necessitating prolonged ventilation in three individuals and resulting in the death of another.

Surveillance

The following are appropriate:

- Regular formal assessment of respiratory function, including monitoring of sleep studies when significant respiratory impairment is identified
- Routine assessment for scoliosis and joint contractures
- Routine assessment of physical function and the need for mechanical assistance, such as a wheelchair

Agents/Circumstances to Avoid

Malignant hyperthermia is a risk in congenital myopathies such as central core disease and in some muscular dystrophies. NM has not been definitively associated with malignant hyperthermia to date, although bradycardia and slight hyperthermia have been reported during cardiac surgery. It is advisable to avoid neuromuscular blocking agents when possible, especially given the reports of core-rod myopathies linking to genes for ryanodine receptor pathogenic variants [Monnier et al 2000, Scacheri et al 2000].

Prolonged periods of immobilization should be avoided after illness or surgery, as immobility may markedly exacerbate muscle weakness [Ryan et al 2001].

Evaluation of Relatives at Risk

It is appropriate to evaluate the older and younger sibs of a proband in order to identify as early as possible those who would benefit from medical surveillance and preventive measures.

- If the pathogenic variant(s) in the family are known, molecular genetic testing can be used to clarify the genetic status of at-risk sibs.
- If the pathogenic variant(s) in the family are not known, a targeted clinical examination, with or without neurophysiologic testing, can clarify whether a muscle biopsy should be considered.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Pregnancy Management

Pregnancy and delivery are relatively well tolerated by women with NM [Ryan et al 2001].

A high frequency of obstetric complications is associated with an affected fetus, including polyhydramnios, decreased fetal movements, and abnormal presentation and/or fetal distress [Ryan et al 2001].

Therapies Under Investigation

L-tyrosine has been proposed as a potential therapy. A precursor of the neurotransmitters dopamine, norepinephrine, and epinephrine, L-tyrosine has been shown after oral administration in rats to increase catecholamine production and release, and to improve reaction and attention time and tolerance of physical stress.

Two reports have shown subjectively improved muscle strength and clearance of oral secretions after oral tyrosine supplementation in individuals with NM. Subjective benefits from dietary supplementation with tyrosine have been reported in a small series of individuals with nemaline myopathy. L-tyrosine may be particularly effective in improving bulbar dysfunction and exercise tolerance in this condition [Ryan et al 2008].

L-tyrosine was shown to improve muscle strength in a mouse model of severe *ACTA1* nemaline myopathy [Nguyen et al 2011].

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions.

Other

In a mouse model, endurance exercise programs may overcome the increase in muscle weakness that follows prolonged periods of immobilization [Nair-Shalliker et al 2004]. Human data are lacking; however, the authors have cared for some individuals with typical congenital-onset NM who have demonstrated clinical improvement after a program of regular low-impact exercise (cycling and swimming) [Authors, personal observation].

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Nemaline myopathy (NM) is inherited in an autosomal dominant or autosomal recessive manner.

Autosomal Dominant Inheritance – Risk to Family Members

Parents of a proband

- Some individuals diagnosed with NM have an affected parent.
- A proband with NM may have the disorder as the result of a *de novo* pathogenic variant.
- Most cases of *ACTA1*-related NM are simplex (i.e., a single occurrence in a family), but autosomal dominant and recessive inheritance are also seen, and two families with mosaicism for dominant pathogenic variants has been reported [Ryan et al 2003, Wallgren-Pettersson et al 2004].
- The family history of some individuals diagnosed with nemaline myopathy may appear to be negative because of failure to recognize the disorder in family members, early death of the parent before the onset of symptoms, or late onset of the disease in the affected parent. Therefore, an apparently negative family history cannot be confirmed unless appropriate evaluations have been performed on the parents of the proband.
- Recommendations for the evaluation of parents of an individual with no known family history of NM include evaluation of both parents for evidence of minor muscle weakness and possible muscle biopsy. If a proband has an identified *ACTA1*, *TPM3*, *TPM2*, or *KBTBD13* pathogenic variant, the parents should be offered molecular genetic testing to determine if the pathogenic variant is *de novo*. The interpretation of abnormal muscle biopsy findings can be difficult; therefore, biopsy should not be undertaken until other means of diagnosis (i.e., testing for familial pathogenic variants) have been attempted.

Note: If the parent is the individual in whom the pathogenic variant first occurred, s/he may have somatic mosaicism for the variant and may be mildly/minimally affected.

Sibs of a proband

- The risk to the sibs of the proband depends on the genetic status of the parents:
  - If a parent is affected and has a family history suggestive of AD inheritance or has a pathogenic variant in *ACTA1*, *TPM3*, *TPM2*, or *KBTBD13*, the risk to each sib of inheriting NM is 50%.
  - If the parents are clinically unaffected and show no abnormality on muscle biopsy, the risk to the sibs of a proband appears to be low unless the disorder is inherited in an autosomal recessive manner.
- To date, germline mosaicism has been reported only in association with *ACTA1* pathogenic variants but remains a possibility for other dominantly inherited forms of NM.

Offspring of a proband. Every child of an individual with autosomal dominant NM has a 50% chance of inheriting the pathogenic variant.

Other family members of a proband. The risk to other family members depends on the genetic status of the proband's parents: if a parent is clinically affected or known to have an *ACTA1*, *TPM3*, *TPM2*, *or KBTBD13* pathogenic variant, his or her family members are at risk.

Autosomal Recessive Inheritance

Risk to Family Members

Parents of a proband

- Each parent is a carrier for one pathogenic variant.
- Heterozygotes (carriers) are asymptomatic.

Sibs of a proband

- At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Once an at-risk sib is known to be unaffected, the risk of his/her being a carrier is 2/3.
- Heterozygotes (carriers) are asymptomatic.

- Even if the sibs of a proband are asymptomatic, molecular genetic testing to determine their genetic status should be considered for the purpose of early diagnosis and treatment of those who have inherited both pathogenic variants (see Management, Evaluation of Relatives at Risk).

Offspring of a proband. The offspring of an individual with autosomal recessive NM are obligate heterozygotes (carriers) for a pathogenic variant causing NM.

Other family members of a proband. Each sib of the proband's parents is at a 50% risk of being a carrier.

Carrier (Heterozygote) Detection

Carrier testing for at-risk family members is possible if the pathogenic variants have been identified in the family.

Related Genetic Counseling Issues

Simplex cases. The majority of individuals with NM represent simplex cases (i.e., a single occurrence in a family), with heterozygosity for *de novo* dominant pathogenic variants or biallelic autosomal recessive pathogenic variants. In their review of 143 individuals from 110 kindreds, Ryan et al [2001] found that inheritance was autosomal recessive in 29 individuals from 15 kindreds (20%), autosomal dominant in 41 individuals from 22 kindreds (29%), and indeterminate in 73 individuals (50%).

Disease severity. Substantial variation in disease severity was observed within families with autosomal dominant inheritance and families with autosomal recessive inheritance, despite presumed genotypic homogeneity. To further complicate genetic counseling, asymptomatic parents can have pathologic changes of NM on muscle biopsy. It is unclear whether such individuals are manifesting heterozygotes of autosomal recessive NM or are subclinically affected with autosomal dominant NM.

Determination of inheritance pattern. When only one person in a family is affected by NM, determining the mode of inheritance can be problematic:

- Inheritance is usually autosomal dominant as the result of either an inherited pathogenic variant or a *de novo* pathogenic variant in a proband with an *ACTA1*, *TPM3*, *TPM2*, or *KBTBD13* pathogenic variant.
- In some families, both clinically healthy parents have shown abnormalities on muscle biopsy, suggesting a manifesting heterozygous state for a recessive allelic variant. Thus, if only one parent were to undergo muscle biopsy and show abnormalities, it cannot be determined if those changes are manifestations of a dominant allelic variant.
- If one parent shows overt disease clinically and typical histologic abnormalities on muscle biopsy, and the other parent is healthy and shows normal findings on muscle biopsy, the likely mode of inheritance is autosomal dominant.
- If both parents are clinically healthy and show no abnormality on muscle biopsy, dominant transmission from one of the parents is unlikely, leaving the possibility of a *de novo* dominant pathogenic variant (the proportion of which remains to be determined) in the child, germline mosaicism in one of the parents (the frequency of which has yet to be determined), or recessive inheritance.
- As the molecular genetics of NM are clarified, some of these genetic counseling issues may be resolved.
- In research studies in which pathogenic variants can be identified, correlations can be made between the gene involved and the mode of inheritance.

Considerations in families with an apparent *de novo* pathogenic variant. When neither parent of a proband with an autosomal dominant condition has the pathogenic variant or clinical evidence of the disorder, it is likely that the proband has a *de novo* pathogenic variant. However, possible non-medical explanations including alternate paternity or maternity (e.g., with assisted reproduction) or undisclosed adoption could also be explored.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected, are carriers, or are at risk.

DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals.

Prenatal Testing and Preimplantation Genetic Diagnosis

Once the pathogenic variant(s) have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic diagnosis for nemaline myopathy are possible.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **Muscular Dystrophy Association - USA (MDA)**

  222 South Riverside Plaza

  Suite 1500

  Chicago IL 60606

  Phone: 800-572-1717

  Email: mda@mdausa.org

  www.mda.org

- **Muscular Dystrophy UK**

  61A Great Suffolk Street

  London SE1 0BU

  United Kingdom

  Phone: 0800 652 6352 (toll-free); 020 7803 4800

  Email: info@musculardystrophyuk.org

  www.musculardystrophyuk.org

- **Congenital Muscle Disease International Registry (CMDIR)**

  The CMDIR is a patient self-report registry with the goal to register the global congenital muscle disease population including persons with congenital myopathy, congenital muscular dystrophy, and congenital myasthenic syndrome. The CMDIR registers affected individuals of all ages with symptoms from birth through late onset (limb-girdle). Registrants will receive educational information and connections to others in the CMD community, and will be contacted about potential participation in clinical trials for their CMD subtype.

  19401 South Vermont Avenue

  Suite J100

Torrance CA 90502

Phone: 323-250-2399

Fax: 310-684-2023

Email: counselor@cmdir.org; sarah.foye@cmdir.org

www.cmdir.org

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Nemaline Myopathy: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
ACTA1	1q42.13	Actin, alpha skeletal muscle	ACTA1 homepage - Leiden Muscular Dystrophy pages	ACTA1	ACTA1
CFL2	14q13.1	Cofilin-2	CFL2 homepage - Leiden Muscular Dystrophy pages	CFL2	CFL2
KBTBD13	15q22.31	Kelch repeat and BTB domain-containing protein 13	KBTBD13 homepage - Leiden Muscular Dystrophy pages	KBTBD13	KBTBD13
KLHL40	3p22.1	Kelch-like protein 40	KLHL40 homepage - Leiden Muscular Dystrophy pages	KLHL40	KLHL40
KLHL41	2q31.1	Kelch-like protein 41		KLHL41	KLHL41
LMOD3	3p14.1	Leiomodin-3		LMOD3	LMOD3
NEB	2q23.3	Nebulin	NEB homepage - Leiden Muscular Dystrophy pages	NEB	NEB
TNNT1	19q13.42	Troponin T, slow skeletal muscle	Leiden Muscular Dystrophy pages (TNNT1)	TNNT1	TNNT1
TPM2	9p13.3	Tropomyosin beta chain	TPM2 homepage - Leiden Muscular Dystrophy pages	TPM2	TPM2
TPM3	1q21.3	Tropomyosin alpha-3 chain	TPM3 homepage - Leiden Muscular Dystrophy pages	TPM3	TPM3

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Nemaline Myopathy (View All in OMIM)

102610	ACTIN, ALPHA, SKELETAL MUSCLE 1; ACTA1
161650	NEBULIN; NEB
161800	NEMALINE MYOPATHY 3; NEM3

Table B. continued from previous page.

190990	TROPOMYOSIN 2; TPM2
191030	TROPOMYOSIN 3; TPM3
191041	TROPONIN T1, SKELETAL, SLOW; TNNT1
256030	NEMALINE MYOPATHY 2; NEM2
601443	COFILIN 2; CFL2
605355	NEMALINE MYOPATHY 5; NEM5
607701	KELCH-LIKE 41; KLHL41
609273	NEMALINE MYOPATHY 6; NEM6
609284	NEMALINE MYOPATHY 1; NEM1
609285	NEMALINE MYOPATHY 4; NEM4
610687	NEMALINE MYOPATHY 7; NEM7
613727	KELCH REPEAT- AND BTB/POZ DOMAIN-CONTAINING PROTEIN 13; KBTBD13
615340	KELCH-LIKE 40: KLHL40
615348	NEMALINE MYOPATHY 8; NEM8
615731	NEMALINE MYOPATHY 9; NEM9
616112	LEIOMODIN 3; LMOD3
616165	NEMALINE MYOPATHY 10; NEM10

Molecular Pathogenesis

Nemaline myopathy (NM) is a disorder of thin filament proteins and proteins of the ubiquitin proteosome pathway. Interruption of the normal function and interaction of these proteins is thought to underpin the abnormal muscle contraction causing muscle weakness in NM.

Alpha-actinin, the major protein component of nemaline bodies, forms diagonal cross-connections between the thin filaments, which are anchored via a network of interactions between α-actinin, actin, nebulin, and other proteins. The myosin-containing thick filaments interdigitate with the thin filaments, which are made up of a double-stranded helix of globular actin monomers (e.g., F actin) associated with a single molecule of nebulin. More than 770 kd in size, nebulin ranks as one of the largest known proteins. The central portion contains up to 185 tandem repeats of 35 residues, each of which likely binds a single actin monomer. The carboxy terminus is unique and is embedded in the Z-lines. Along the length of the thin filaments, the tropomyosins and troponins together form a complex of proteins responsible for control of contraction by regulating the interactions of actin and myosin.

At rest, tropomyosin dimers lie along the actin filament in a potential myosin-binding site, sterically inhibiting myosin-actin interactions. Tropomyosin position and movement are controlled by the troponin complex consisting of three subunits: TN-I (inhibitory), TN-T (tropomyosin-binding), and TN-C (calcium-binding). When muscle is stimulated, intracellular calcium levels increase to a critical level and bind to TN-C. This releases the inhibitory effect of TN-I, so that tropomyosin moves into the groove between actin helices, unmasking the myosin binding sites and triggering the contraction cycle.

Pathogenic variants in the genes encoding various components of the thin filament likely disrupt the orderly assembly of sarcomeric proteins and the functional interaction between the thin and thick filament during muscle contraction. Tissue culture studies of pathogenic variants in *ACTA1* suggest that mutated actin has a dominant-negative effect on thin filament assembly and function and results in abnormal folding, altered

polymerization, and aggregation of mutated actin isoforms [Ilkovski et al 2004]. Some of these effects are variant-specific and likely result in variations in the severity of muscle weakness seen in affected individuals. A combination of these effects contributes to the common pathologic hallmarks of NM, namely intranuclear and cytoplasmic rod formation, accumulation of thin filaments, and myofibrillar disorganization.

The Kelch-like (KLHL) gene family encodes a group of proteins that generally possess a BTB/POZ domain, a BACK domain, and five to six Kelch motifs.

- BTB domains facilitate protein binding and dimerization.
- The BACK domain has no known function, but appears to be of functional importance, since pathogenic variants in this domain are associated with disease.
- Kelch domains form a tertiary structure of β-propellers that have a role in extracellular functions, morphology, and binding to other proteins.
- Three members of the Kelch-like protein family – *KBTBD13*, *KLHL40*, and *KLHL41* – are now implicated in NM, in which extensive skeletal muscle disorganization likely reflects abnormal surveillance and degradation of aberrant thin-filament proteins.

Interaction between thin filament proteins and the kelch protein family has been demonstrated; KLHL40 is a binding partner of both LMOD3 and NEB, suggesting a common pathogenesis of different genetic forms of NM.

See Table A, **Gene** for a detailed summary of gene and protein information for the following genes.

NEB

Gene structure. *NEB* contains 183 exons in a 249-kb genomic region. Exon numbering varies in the literature because some exons are differentially expressed.

Pathogenic variants. See Table 3. To date, 64 different pathogenic variants in 55 families have been identified in *NEB* [Pelin et al 1999, Pelin et al 2002, Lehtokari et al 2006].

The majority of pathogenic variants are frameshifts caused by small deletions or insertions or single nucleotide variants causing premature stop codons or abnormal splicing. In addition, a 2,502-bp deletion in *NEB* appears to be a common cause of NM in Ashkenazi Jewish families, with a carrier frequency of approximately 1:100 [Anderson et al 2004].

Table 3. Selected *NEB* Pathogenic Variants

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.7622-2025_7727+372del2502 (exon 55 deletion)	p.Arg2478_Asp2512del	NM_004543.3 NP_004534.2

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

Normal gene product. Nebulin is a giant protein (600-900 kd) component of the cytoskeletal matrix.

Abnormal gene product. Most *NEB* pathogenic variants are predicted to result in truncated or internally deleted proteins. See Molecular Pathogenesis.

ACTA1

Gene structure. *ACTA1* consists of seven exons.

Pathogenic variants. More than 195 different pathogenic variants have now been identified in *ACTA1* and are listed in the *ACTA1* locus-specific database. The vast majority of these pathogenic variants are missense (see Table A, **Locus Specific**, *ACTA1*).

Normal gene product. Skeletal muscle actin has vital roles in cell integrity, structure, and motility. Muscle contraction results from the force generated between the thin filament protein actin and the thick filament protein myosin. See Molecular Pathogenesis.

Abnormal gene product. See Molecular Pathogenesis. Both hemizygous and homozygous null mice show an increase in cardiac and vascular *ACTA1* mRNA in skeletal muscle. No skeletal *ACTA1* mRNA is present in null mice [Crawford et al 2002].

TPM3

Gene structure. *TPM3* contains 13 exons. Multiple transcript variants encoding different isoforms have been found for this gene.

Pathogenic variants. See Table 4. Laing et al [1995] identified a p.Met9Arg substitution in the N-terminal end of tropomyosin$_{SLOW}$ in a kindred with dominantly inherited NM. Wattanasirichaigoon et al [2002] reported a person who was compound heterozygous for a single nucleotide variant and splice site pathogenic variant. A further example of recessive *TPM3*-related NM was documented by Tan et al [1999], who identified a homozygous p.Gln32Ter pathogenic nonsense variant in an infant with extremely delayed motor development.

Table 4. Selected *TPM3* Pathogenic Variants

DNA Nucleotide Change	Predicted Protein Change (Alias [1])	Reference Sequences
c.26T>G	p.Met9Arg	NM_152263.2 NP_689476.2
c.94C>T	p.Gln32Ter (Gln31Ter)	

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
1. Variant designation that does not conform to current naming conventions

Normal gene product. Tropomyosin alpha-3 chain is expressed mostly in slow, type 1 muscle fibers. Tropomyosin isoforms are components of the thin filaments of the sarcomere, acting to mediate the effect of calcium on actin-myosin interaction.

Abnormal gene product. In terms of understanding disease pathogenesis in NM, the best characterized is tropomyosin NM. Tissue culture and animal models have been developed for the p.Met9Arg pathogenic variant in *TPM3* identified by Laing et al [1995]. This pathogenic variant was predicted to affect the N-terminal structure of the α-tropomyosin, which is implicated in binding actin and troponin T and for head-tail interactions leading to the coiled-coil dimeric structure of tropomyosin, which polymerizes along the entire length of the thin filament. In vitro studies suggest that the mutated *TPM3* exerts a dominant-negative effect and alters the Ca^{2+}-activated force production, hastening relaxation of mutated tropomyosin and shifting the force-frequency relationship in skeletal muscle [Michele et al 1999, Michele et al 2002]. Fiber typing abnormalities in the mouse model appear to be related to a disruption in the developmental progression of the different muscle fiber types.

TPM2

Gene structure. *TPM2* contains ten exons.

Pathogenic variants. Donner et al [2002] identified two different heterozygous pathogenic missense variants in *TPM2*. Thirty distinct pathogenic variants in *TPM2* have been identified to date, causing a variety of phenotypes including NM, cap disease, core-rod myopathy, congenital fiber-type disproportion, and distal arthrogryposis [Tajsharghi et al 2012, Marttila et al 2014].

Normal gene product. Tropomyosins are actin-filament-binding proteins expressed in skeletal, cardiac, and smooth muscle that act to regulate the calcium-sensitive interaction of actin and myosin during muscle contraction.

Abnormal gene product. Identified *TPM2* pathogenic variants are thought to affect tropomyosin-actin association or tropomyosis head-to-tail binding [Marttila et al 2014].

TNNT1

Gene structure. The gene encoding troponin T, slow skeletal muscle consists of 14 exons.

Pathogenic variants. See Table 5. Johnston et al [2000] identified a homozygous stop codon pathogenic variant, predicted to truncate the protein at amino acid 180, in infants with the Amish form of NM.

Table 5. Selected *TNNT1* Pathogenic Variants

DNA Nucleotide Change	Predicted Protein Change	Reference Sequence
c.538G>T	p.Glu180Ter	NM_003283.4

Note on variant classification: Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
Note on nomenclature: *GeneReviews* follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

Normal gene product. The tropomyosin-troponin complex regulates the calcium sensitivity of the contractile apparatus of the sarcomere, linking excitation to contraction in skeletal muscle. The troponin T part of the troponin complex regulates its binding to tropomyosin.

Abnormal gene product. In the Amish form of NM, which is caused by a homozygous p.Glu180Ter pathogenic nonsense variant in *TNNT1*, troponin T (TnT), slow skeletal muscle, slow TnT is completely absent from slow fibers. Slow TnT confers greater calcium sensitivity than does fast TnT in single fiber contractility assays. Despite the lack of slow TnT, individuals with Amish NM have normal muscle strength at birth. The postnatal onset and infantile progression of Amish NM correspond to a down-regulation of cardiac and embryonic splice variants of fast TnT in normal developing human skeletal muscle, suggesting that the fetal TnT isoforms complement slow TnT.

CFL2

Gene structure. CFL2 consists of five exons [Thirion et al 2001].

Pathogenic variants. See Table 6. *CFL2* has been directly implicated in human disease in only three families to date [Agrawal et al 2007, Ockeloen et al 2012, Ong et al 2014].

A homozygous missense change (c.103C>A) was found in two sisters from a consanguineous family of Middle Eastern origin. Both children had typical clinical features of a congenital myopathy that included congenital hypotonia, delayed early milestones, frequent falls, and inability to run. Nemaline bodies were seen on muscle

biopsy at age two years in one child, together with occasional minicore lesions and actin filament accumulations. A muscle biopsy of the older child at age four years showed nonspecific abnormalities [Agrawal et al 2007].

A subsequent report described two sibs from a consanguineous Iraqi Kurdish family with predominant axial and limb girdle weakness. Muscle biopsies showed features of both nemaline myopathy and myofibrillar myopathy. Sequencing showed a novel homozygous pathogenic missense variant in exon 2 of *CFL2* (c.19G>A, p.Val7Met) in in both sibs [Ockeloen et al 2012].

More severe weakness was described in a third kindred with a confirmed case and two probably affected cousins, all of whom were ventilator-dependent from early infancy. Exome sequencing identified a novel homozygous null variant in *CFL2*, which was inferred to shift the reading frame, introducing a premature stop codon in exon 2 [Ong et al 2014].

Agrawal et al [2007] directly sequenced *CFL2* in 113 unrelated individuals with nemaline myopathy of unknown genetic basis and 58 patients with other muscle pathologies. They found pathogenic variants in only the initial family reported above and concluded that *CFL2* is a rare cause of nemaline myopathy, accounting for fewer than 1% of patients.

Table 6. Selected *CFL2* Pathogenic Variants

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.103C>A	p.Ala35Thr	NM_021914.6 NP_068733.1

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

Normal gene product. The cofilins, together with actin depolymerization factor (ADF), form a group of proteins that catalyze the depolymerization of actin filaments in a pH-dependent manner. *CFL2* encodes the muscle isoform of cofilin. *CFL2* was considered a good candidate for nemaline myopathy because of its role in actin filament turnover in muscle.

Abnormal gene product. The c.103C>A change is predicted to substitute threonine in place of a highly conserved alanine 35 residue. In addition the mutated protein tended to precipitate abnormally when expressed in bacterial cells, suggesting that the pathogenic variant causes protein misfolding. Molecular modeling has suggested that the pathogenic variant may disrupt a beta sheet directly adjacent to the nuclear localization signal.

KBTBD13

Gene structure. *KBTBD13* has a single exon and the predicted open reading frame comprises 1,374 nucleotides.

Pathogenic variants. Three identified pathogenic variants (p.Arg248Ser, p.Lys390Asn, and p.Arg408Cys) (see Table 7) are located in conserved domains of Kelch repeats [Sambuughin et al 2010].

Table 7. Selected *KBTBD13* Pathogenic Variants

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.742C>A	p.Arg248Ser	NM_001101362.2 NP_001094832.1
c.1170G>C	p.Lys390Asn	
c.1222C>T	p.Arg408Cys	

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

Normal gene product. The gene encodes a protein, KBTBD13, of 458 amino acids with a molecular mass of 49 kd. The KBTBD13 protein contains a BTB/POZ domain and five Kelch repeats and is expressed primarily in skeletal and cardiac muscle. Previously identified BTB/POZ/Kelch domain-containing proteins have been implicated in a broad variety of biologic processes, including cytoskeleton modulation, regulation of gene transcription, ubiquitination, and myofibril assembly. The functional role of the KBTBD13 protein in skeletal muscle is not yet known.

Abnormal gene product. The identified pathogenic variants are predicted to disrupt the molecule's structure (beta-propeller blades); the effects on protein function are not yet known.

KLHL40

Gene structure. The *KLHL40* transcript has six exons (NM_152393.3).

Normal gene product. The KLH40 protein product has 621 amino acids (NP_689606.2). KLHL40 is a striated muscle-specific protein that localizes to the sarcomere. It has been shown to bind to and promote stability of NEB and LMOD3.

KLHL41

Gene structure. The *KLHL41* transcript has six exons (NM_006063.2).

Normal gene product. The *KLHL41* protein product is 606 amino acids in length (NP_006054.2).

LMOD3

Gene structure. The *LMOD3* transcript has three exons (NM_198271.3).

Normal gene product. The *LMOD3* protein product has 560 amino acids and a molecular mass of 65-kDA (NP_938012.2). The LMOD3 protein contains three actin-binding domains and one tropomyosin-binding helix. It has a proline-rich region, Glu-rich region, and basic region, the functions of which are unknown. LMOD3 localizes close to the pointed ends of actin thin filaments, is a strong actin filament nucleator, and is thought to be important for embryonic myofibrillogenesis and for the organization of sarcomeric thin filaments in skeletal muscle. LMOD3 is a binding partner of KLHL40.

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Chapter Notes

Author Notes

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Revision History

- 7 November 2019 (ma) Chapter retired: histologic diagnosis without strong genetic correlation
- 11 June 2015 (aa) Revision: *LMOD3* added
- 18 September 2014 (me) Comprehensive update posted live
- 15 March 2012 (me) Comprehensive update posted live
- 21 October 2010 (cd) Revision: deletion/duplication analysis for *NEB* gene available
- 17 August 2010 (me) Comprehensive update posted live
- 2 April 2009 (me) Comprehensive update posted live
- 16 October 2006 (me) Comprehensive update posted live
- 17 June 2004 (me) Comprehensive update posted live
- 25 November 2002 (kn) Revisions
- 19 June 2002 (me) Review posted live
- 24 February 2002 (kn) Original submission

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