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Nemaline Myopathy

[*Nemaline Rod Myopathy*]

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Summary

Disease 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 six forms of NM, classified by onset and severity of motor and respiratory involvement, are: severe congenital (neonatal) form (16% of all individuals with NM); Amish NM, intermediate congenital form (20%); typical congenital form (46%); childhood-onset form (13%); and adult-onset (late-onset) form (4%). Considerable overlap occurs among the forms. Significant differences exist 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.

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. Disease-causing mutations have been identified in five different genes, all of which encode protein components of the muscle thin filament. Molecular genetic testing for mutations in the *ACTA1* gene is available on a clinical basis.

Management. Treatment may include monitoring of nutritional status, special feeding techniques, aggressive treatment of lower respiratory tract infections ventilator use, physical and speech therapy, and standard care for gastroesophageal reflux. Surveillance includes routine assessment for scoliosis, joint contractures, respiratory function, and the need for assistive devices.

Genetic counseling. NM is inherited in an autosomal dominant or autosomal recessive manner. In one series, about 20% of cases were autosomal recessive, about 30% autosomal dominant, and about 50% simplex (i.e., single occurrences in a family) representing heterozygosity for *de novo* dominant mutations or homozygosity for autosomal recessive

mutations. 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. Prenatal molecular genetic testing is available to families with the exon 55 deletion in the *NEB* gene or with known *ACTA1* mutations.

Diagnosis

Clinical Diagnosis

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

The diagnosis of NM rests on the following **clinical findings**:

- Weakness that is predominantly proximal, diffuse, or selective (scapuloperoneal, scapulohumeral, or distal), with or without facial weakness
- Onset in infancy, childhood, or adulthood
- 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 mutation [North et al 1997])

Electrophysiologic studies that may suggest a myopathic process but are of limited help 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** are generally normal, although low-amplitude motor responses may be seen in those with marked loss of muscle bulk.

Muscle imaging studies

- **Muscle ultrasonography** may demonstrate increased echogenicity resulting from increased fibrous content — changes useful in distinguishing between neurogenic and myogenic disorders.
- **Computed tomography (CT)** reveals low density of muscle with preservation of volume (in contrast to neuropathies, in which atrophy is more marked).
- **Magnetic resonance imaging (MRI)** commonly reveals patchy, fatty degeneration of muscle tissue and variable involvement of different muscle groups [Oishi & Mochizuki 1998, Wallgren-Pettersson & Laing 2001].

Serum creatine kinase concentration is usually normal or minimally elevated.

Muscle histology. 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].

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, the 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.

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 actin mutations.

Muscle electron microscopy. Nemaline bodies are electron dense and measure 1-7µm in length and 0.3-2µm 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 [Goebel, Piirsoo et al 1997]. 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 six 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* mutation 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 [Goebel, Piirsoo et al 1997], and marked sarcomeric disruption have been observed in individuals with *ACTA1* mutations [Ilkovski et al 2001, Ryan et al 2003].
- In the Amish form of NM, complete loss of troponin T, slow skeletal muscle causes selective atrophy of type 1 fibers [Jin et al 2003].
- Nebulin immunocytochemistry is normal in the majority of individuals with *NEB* mutations. Abnormal staining in a small proportion of individuals can serve as a guide for molecular genetic testing [Wallgren-Pettersson & Laing 2000].

Molecular Genetic Testing

GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory *by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.*—ED.

Genes. Mutations in five genes, encoding components of the sarcomeric thin filaments, have been identified in NM (Table 2). It is too early to determine the frequency of each of the genetic subgroups of NM, the proportion of *de novo* mutations, and the incidence of germline mosaicism.

- ***ACTA1.*** *ACTA1* mutations account for 15%-25% of all individuals with NM [Nowak et al 1999, Strickland et al 2000, Ilkovski et al 2001, Ryan et al 2001]. Of note, *ACTA1* mutations may account for up to 50% of severe lethal congenital-onset forms of NM [Agrawal et al 2004].
- ***NEB.*** Results of linkage study data suggest that *NEB* mutations are likely to be a relatively common cause of NM; however, mutation detection is hampered by the large size of the gene and the large number of repeat sequences [Pelin et al 1999, Wallgren-Pettersson et al 1999]. The only known mutation hotspot is a 2,502 base pair in-frame deletion of exon 55 that was observed in five families of Ashkenazi Jewish ancestry [Anderson et al 2004]. The carrier frequency of this mutation in the Ashkenazi Jewish population is estimated to be 1/108. Its incidence in other populations is unknown.
- ***TPM3.*** *TPM3* mutations are a rare cause of NM, accounting for only 2%-3% of affected individuals (3/117 individuals screened) [Ryan et al 2001, Wallgren-Pettersson & Laing 2003].
- ***TPM2.*** Donner et al (2002) identified dominant *TPM2* mutations in two individuals (from 54 families) with typical congenital-onset NM.
- ***TNNT1.*** Mutations in *TNNT1* have been identified only in a genetically isolated group of Old Order Amish individuals with NM [Johnston et al 2000, Jin et al 2003].

Other loci

- In addition, autosomal dominant NM in a Dutch kindred with peculiarly slow voluntary movements and relative sparing of the facial and respiratory muscles has been linked to chromosome15q21-q24 [Gommans et al 2002, Gommans et al 2003, Pauw-Gommans et al 2006]. The *TPM1* gene, known to be involved in familial

hypertrophic cardiomyopathy, is located within 15q21-q24 and is regarded as a candidate gene; however, mutations in the coding region have not been identified.

- Additional individuals with NM do not link to any of the five identified loci, suggesting further genetic heterogeneity [Wallgren-Pettersson et al 1999, Wallgren-Pettersson & Laing 2003].

Clinical uses

- Confirmatory diagnostic testing
- Prenatal diagnosis

Clinical testing

- **Sequence analysis.** Sequence analysis of the *ACTA1* gene is available on a clinical basis.
- **Deletion/duplication analysis.** The deletion in exon 55 of the *NEB* gene may be a common cause of NM in the Ashkenazi Jewish population; its frequency in other populations is unknown.

Research testing. Molecular genetic testing of *NEB*, *TPM3*, *TPM2*, and *TNNT1* is available on a research basis with confirmation in a clinical laboratory.

Table 1 summarizes molecular genetic testing for this disorder.

Table 1. Molecular Genetic Testing Used in Nemaline Myopathy

Test Method	Mutations Detected	Proportion of NM Caused by Mutations in the Gene	Mutation Detection Frequency [1]	Test Availability
Sequence analysis	*ACTA1* sequence variants	15%-25%	>90%	Clinical Testing
Deletion/duplication analysis	Exon 55 in *NEB*	Unknown	Unknown	
Direct DNA [2]	*TPM3* sequence variants	2%-3%	Unknown	Research only [3]
	TPM2 sequence variants	<1%	Unknown	
	TNNT1 sequence variants	<%	Unknown	

1. Proportion of affected individuals with a mutation(s) as classified by gene and test method
2. Direct DNA methods may include mutation analysis, mutation scanning, sequence analysis, or other means of molecular genetic testing to detect a genetic alteration associated with NM.
3. No laboratories offering molecular genetic testing for *NEB*, *TPM3*, *TPM2*, or *TNNT1* on a clinical basis are listed in the GeneTests Laboratory Directory. However, testing may be available for families in which the disease-causing mutations have been identified in an affected family member in a research laboratory. For laboratories offering custom testing, see Testing.

Interpretation of test results. For issues to consider in interpretation of sequence analysis results, click here.

Testing Strategy

Creatine kinase is generally checked 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 but may be mildly elevated [Ryan et al 2001].

Neurophysiologic testing in persons with suspected lower motor neuron disorders excludes neuropathy and may demonstrate 'myopathic' abnormalities (small, short-duration action potentials).

Electromyography is nonspecific, showing similar abnormalities in all congenital myopathies.

Muscle imaging is useful in distinguishing between neuropathic and myopathic processes, and can be used to identify an appropriate muscle to biopsy. Muscle MRI 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].

- NM secondary to mutations in the nebulin *(NEB*) gene is reported to show a consistent pattern of selective muscle involvement corresponding to clinical severity. In mild cases, there may be complete sparing of thigh muscles and selective involvement of tibialis anterior and soleus. In moderate cases, there is predominant involvement of rectus femoris, vastus lateralis, and hamstring muscles and diffuse involvement of anterior compartment and soleus.
- NM secondary to mutations in the skeletal muscle alpha-actin *(ACTA1*) gene may show diffuse involvement of thigh and leg muscles with relative sparing of the gastrocnemii.

Muscle biopsy demonstrating nemaline rods is necessary for definitive diagnosis.

Genetically Related (Allelic) Disorders

ACTA1. Goebel, Anderson et al (1997) reported three individuals with congenital myopathy and excess accumulation of thin filaments that stained positive for skeletal muscleα-actin. Two of these individuals also had nemaline bodies. Mutations were subsequently identified in *ACTA1* [Nowak et al 1999]. Therefore, mutations 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 missense mutations 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* mutations had severe congenital weakness and respiratory failure without ophthalmoplegia, and were clinically indistinguishable from individuals with *ACTA1* mutations and severe congenital-onset NM [Laing et al 2004].

Jungbluth et al (2001) recently described an individual with mild NM and sleep hypoventilation in whom an *ACTA1* mutation 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 mutation 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].

Clinical Description

Natural History

The cardinal features of nemaline myopathy (NM) are weakness, hypotonia, and depressed or absent deep tendon reflexes [North et al 1997]; 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 elongated and expressionless, with a tent-shaped mouth, high-arched palate, and retrognathia. Gross motor milestones are delayed, but most affected individuals are otherwise developmentally normal.

Dysarthria and feeding difficulties are common; approximately 25% of individuals 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 individuals 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.

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 [North et al 1997, 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 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) NP 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 [Lammens et al 1997]. Uncommon findings include dilated cardiomyopathy and arthrogryposis multiplex congenita (i.e., multiple joint contractures) [Ryan et al 2001, Wallgren-Petterson & 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]. 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 present 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 [North et al 1997, 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.

Van Engelen and colleagues reported [Pauw-Gommans et al 2006] 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].

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 and cardiac involvement are uncommon but, when present, often occur in association with increasing weakness and physical disability.

Inflammatory changes on biopsy are not uncommon in adult-onset NM [Gyure et al 1997]. 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 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 individuals 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 arthogryposis 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.

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 or fetal distress [Ryan et al 2001].

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.

NM related to *NEB* (nebulin) mutations is more commonly associated with 'typical congenital' NM, and invariably inherited in an autosomal recessive fashion, while NM related to *ACTA1* (actin) mutations is associated with variable presentations ranging from severe neonatal to adult onset.

Neonatal presentation of NM has been reported in those with autosomal recessive inheritance of mutations in *NEB* [Pelin et al 1999], *TPM3* [Tan et al 1999], *TNNT1* [Johnston et al 2000, Jin et al 2003], and *ACTA1* [Sparrow et al 2003], and those with autosomal dominant inheritance of mutations in actin [Nowak et al 1999].

'Childhood-onset' disease has been seen with autosomal dominant inheritance of mutations in *TPM3* and *ACTA1* [Nowak et al 1999, Ilkovski et al 2001].

Rare, distinctive phenotypes associated with NM include the Amish form of the disease [Johnston et al 2000, Jin et al 2003] and the form associated with peculiarly slow voluntary movements and relative sparing of the facial and respiratory muscles [Gommans et al 2002, Gommans et al 2003].

Genetic subtypes of nemaline myopathy. See Table 2.

Table 2. Phenotype Correlations with Mutated Genes

Mutated Gene	Mode of Inheritance	Phenotype
TPM3	AD / AR	Severe congenital (AR) Intermediate congenital Childhood onset (AD)
NEB	AR	Typical congenital (majority) All other phenotypes (occasional)
ACTA1	AD / AR	Range from severe congenital to childhood onset
TNNT1		Amish NM
TPM2		Typical congenital

TPM3. *TPM3* mutations may be inherited in a dominant or recessive manner [Tan et al 1999, Ryan et al 2001] and to date have been associated with severe- and intermediate-congenital as well as childhood-onset NM [Wattanasirichaigoon et al 1998, Tan et al 1999, Durling et al 2002].

NEB. All *NEB* mutations identified to date have been inherited in an autosomal recessive manner [Pelin et al 1999]. The majority of individuals with NM have the typical congenital form of NM, although recent follow-up studies have identified *NEB* mutations in individuals with wide-ranging phenotypes [Wallgren-Pettersson & Laing 2003].

ACTA1. *ACTA1* mutations have now been identified in individuals with NM with varying clinical presentations and inheritance patterns [Nowak et al 1999, Strickland et al 2000, Ilkovski et al 2001, Ryan et al 2001]. The majority of individuals with NM have no family history (*de novo* dominant mutations). However, one family exhibited autosomal recessive inheritance with two affected children who were compound heterozygotes for mutations inherited from each parent. At least two families with autosomal dominant inheritance have now been reported [Nowak et al 1999, Wallgren-Pettersson & Laing 2000]. Individuals with *ACTA1* mutations exhibit marked clinical variability 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]. Marked 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].

Penetrance

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

Anticipation

No convincing evidence of anticipation has been documented.

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.

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

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 arched palate, elongated facies). 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 such as X-linked myotubular myopathy and other neuromuscular disorders including congenital muscular dystrophy, the limb-girdle muscular dystrophies, dystrophinopathies, metabolic myopathies, and spinal muscular atrophy.

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 mutations in the C-terminal of the ryanodine receptor gene *(RYR1)* 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) [Monnier et al 1997, Scacheri et al 2000]. A second locus for core-rod myopathy has already been identified at 15q21-q23 [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 siblings 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 upon both the finding of rod bodies on muscle biopsy and an appropriate clinical scenario.

Management

Evaluations Following Initial Diagnosis

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

- 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 in those with the severe congenital form

Treatment of Manifestations

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

- Assurance of adequate caloric intake and appropriate nutritional status, including special feeding techniques and high-calorie formulas and foods, if indicated
- 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
- 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
- Standard treatment of gastroesophageal reflux, if present
- Assessment of cardiac status because of the risk (albeit low) of cardiomyopathy or cor pulmonale

Prevention of Secondary Complications

Patient mobility and physical therapy help to control the development of joint contractures from disuse related to weakness.

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 four individuals and fundoplication in one), necessitating prolonged ventilation in three individuals and resulting in the death of another. Preoperative assessment of pulmonary function is essential to ensure optimal timing of surgical procedures and to minimize anesthetic risk.

Surveillance

- Routine assessment for scoliosis and joint contractures
- Regular formal assessment of respiratory function, including monitoring of sleep studies when significant respiratory impairment is identified

- 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 recent description of core-rod myopathies linking to genes for ryanodine receptor mutations [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].

Medications should not affect the course of NM.

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 on 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. An international clinical trial was recently discontinued because of difficulties with participant recruitment and drug licensing, but subjective benefits from dietary supplementation with tyrosine have been reported [Wallgren-Pettersson & Laing 2003].

Search ClinicalTrials.gov 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).

Genetics clinics, staffed by genetics professionals, provide information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as information about available consumer-oriented resources. See the GeneTests Clinic Directory.

Support groups have been established for individuals and families to provide information, support, and contact with other affected individuals. The Resources section may include disease-specific and/or umbrella support organizations.

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Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, 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. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

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

Risk to Family Members — Autosomal Dominant Inheritance

Parents of a proband

- Some individuals diagnosed with NM have an affected parent.
- However, a proband with NM may have the disorder as the result of a new gene mutation.
- Most cases of *ACTA1*-related NM are simplex, but autosomal dominant and recessive inheritance are also seen, and two families with mosaicism for dominant mutations have been reported [Ryan et al 2003, Wallgren-Pettersson et al 2004].
- If a proband has an identified *ACTA1* mutation, the parents should be offered molecular genetic testing.
- 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. The interpretation of abnormal muscle biopsy findings, however, can be difficult; therefore, biopsy should not be undertaken until other means of diagnosis (i.e., testing for *ACTA1* mutations) have been attempted.

Sibs of a proband

- The risk to the sibs of the proband depends upon the genetic status of the parents.
- If a parent is affected or has an *ACTA1* mutation, the risk 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.
- While no instances have been reported, germline mosaicism remains a possibility.

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

Other family members. The risk to other family members depends upon the genetic status of the proband's parents. If a parent is found to be affected or to have an *ACTA1* mutation, his or her family members are at risk.

Risk to Family Members — Autosomal Recessive Inheritance

Parents of a proband

- The parents of an affected individual are obligate heterozygotes and therefore carry one mutant allele.
- 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.

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

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

Carrier Detection

Carrier testing for at-risk family members is available on a clinical basis if the mutations have been identified in the proband.

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 mutations or homozygosity for autosomal recessive mutations. In their review of 143 individuals from 110 kindreds, Ryan et al (2001) found that inheritance was autosomal recessive in 29 (20%) individuals from 15 kindreds, autosomal dominant in 41 (29%) individuals from 22 kindreds, 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 whether they 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 mutation or *de novo* mutation in a proband with an *ACTA1* mutation.
- In some families, both clinically healthy parents have shown abnormalities on muscle biopsy, suggesting a manifesting heterozygous state for a recessive gene mutation. 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 gene mutation.
- 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 mutation (the proportion of which remains to be determined) in the child, germline mosaicism in one of the parents (the role 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 disease-causing mutations can be identified, correlations can be made between the gene involved and the mode of inheritance.

Considerations in families with an apparent *de novo* mutation. When neither parent of a proband with an autosomal dominant condition has the disease-causing mutation or clinical evidence of the disorder, it is likely that the proband has a *de novo* mutation. However, possible non-medical explanations including alternate paternity 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.

DNA banking. 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, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. DNA banking is particularly relevant in situations in which molecular genetic testing is available on a research basis only or in which the sensitivity of currently available testing is less than 100%. See DNA Banking for a list of laboratories offering this service.

Prenatal Testing

Prenatal diagnosis for pregnancies at increased risk for *ACTA1* mutations or the exon 55 deletion in *NEB* is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at about 15-18 weeks' gestation or chorionic villus sampling (CVS) at about ten to 12 weeks' gestation. The disease-causing mutation of an affected family member must be identified before prenatal testing can be performed.

Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

No laboratories offering molecular genetic testing for prenatal diagnosis of NM caused by mutations in genes other than *ACTA1* and the exon 55 deletion in *NEB* are listed in the GeneTests Laboratory Directory. However, prenatal testing may be available for families in which the disease-causing mutations have been identified in an affected family member. For laboratories offering custom prenatal testing, see Testing.

Preimplantation genetic diagnosis (PGD) may be available for families in which the disease-causing mutation(s) has/have been identified in an affected family member. For laboratories offering PGD, see Testing.

Molecular Genetics

Information in the Molecular Genetics tables is current as of initial posting or most recent update. —ED.

Table A. Molecular Genetics of Nemaline Myopathy

Gene Symbol	Chromosomal Locus	Protein Name
ACTA1	1q42.1	Actin, alpha skeletal muscle
NEB	2q22	Nebulin
TNNT1	19q13.4	Troponin T, slow skeletal muscle
TPM2	9p13.2-p13.1	Tropomyosin beta chain
TPM3	1q22-q23	Tropomyosin alpha-3 chain

Data are compiled from the following standard references: Gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot.

Table B. OMIM Entries for Nemaline Myopathy

102610	ACTIN, ALPHA, SKELETAL MUSCLE 1; ACTA1
161650	NEBULIN; NEB
161800	NEMALINE MYOPATHY 3; NEM3
190990	TROPOMYOSIN 2; TPM2
191030	TROPOMYOSIN 3; TPM3
191041	TROPONIN T1, SKELETAL, SLOW; TNNT1
256030	NEMALINE MYOPATHY 2; NEM2
605355	NEMALINE MYOPATHY 5; NEM5
609284	NEMALINE MYOPATHY 1; NEM1
609285	NEMALINE MYOPATHY 4; NEM4

Table C. Genomic Databases for Nemaline Myopathy

Gene Symbol	Entrez Gene	HGMD
ACTA1	58 (MIM No. 102610)	ACTA1
NEB	4703 (MIM No. 161650)	NEB
TNNT1	7138 (MIM No. 191041)	TNNT1
TPM2	7169 (MIM No. 190990)	TPM2
TPM3	7170 (MIM No. 191030)	TPM3

For a description of the genomic databases listed, click here.

Note: HGMD requires registration.

Molecular Genetic Pathogenesis

Nemaline myopathy (NM) is a disorder of thin filament proteins, and thus it is necessary to understand the normal interactions of these proteins to understand the pathogenic mechanisms underlying 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. At over 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 [Schiaffino & Reggiani 1996].

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, binding to TN-C and releasing the inhibitory effect of TN-I. Tropomyosin moves into the groove between actin helices, unmasking the myosin binding sites and triggering the contraction cycle.

Mutations 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 disease-causing mutations in *ACTA1* suggest that mutant actin has a dominant-negative effect on thin filament assembly and function and results in abnormal folding, altered polymerization, and aggregation of mutant actin isoforms [Ilkovski et al 2004]. Some of these effects are mutation-specific, and likely result in variations in the severity of muscle weakness seen in 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 *TPM3* p.Met9Arg mutation, associated with autosomal dominant childhood-onset NM, has now been studied extensively in vitro and in vivo, providing initial insights into the pathogenesis of NM. This mutation occurs in the N-terminal structure ofα-tropomyosin $_{SLOW}$, which is implicated in binding actin, troponin T, and tropomodulin, and in head-tail interactions leading to the coiled-coil dimeric structure of tropomyosin. When expressed in rat adult cardiac myocytes, the mutant protein was incorporated into sarcomeres and the contractile response to Ca^{2+} was diminished; however, there was no rod formation [Michele et al 1999]. When expressed in *Escherichia coli*, the p.Met9Arg mutant had a 30- to 100-fold reduced affinity for actin binding and reduced activation of actomyosin S1 ATPase [Moraczewska et al 2000]. When the p.Met9Arg mutation was introduced into a transgenic mouse line, rod formation occurred in all muscles, with onset of weakness at age five to six months, mimicking late-childhood onset in humans [Corbett et al 2001]. The percentage of rods varied significantly between different muscle groups despite uniform expression of the mutant transgene, reflecting the same variability of muscle involvement as seen in humans with NM. The mutant *TPM3* is expressed, suggesting a dominant negative effect; an imbalance in other specific *TPM* isoform levels within NM muscle may contribute to disease pathogenesis [Corbett et al 2005]. Fiber-typing abnormalities in the mouse model appear to be related to a disruption in the developmental maturation of different muscle fiber types. Interestingly the *TPM3* nemaline mouse has compensatory hypertrophy of muscle fibers compared to wild type that may contribute to delayed onset of muscle weakness [Corbett et al 2001, Nair-Shalliker et al 2004]. Fiber hypertrophy occurs occasionally in individuals with NM and tends to correlate with a milder phenotype [North, unpublished observations], raising the possibility that exercise and hypertrophic agents may influence the course of the disease.

ACTA1

Normal allelic variants: The *ACTA1* gene consists of seven exons.

Pathologic allelic variants: Approximately 60 mutations have now been identified in the *ACTA1* gene. These comprise 55 missense mutations, one nonsense mutation, one frameshift mutation, one splice-site mutation, and one in-frame two-amino-acid duplication.

Normal gene product: Actin, alpha skeletal muscle 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 Genetic Pathogenesis.

Abnormal gene product: See Molecular Genetic Pathogenesis.

Both hemizygous and homozygous null animals 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].

NEB

Normal allelic variants: The *NEB* gene contains 183 exons in a 249-kb genomic region.

Pathologic allelic variants: At least 19 mutations have been identified in *NEB*. Pelin et al (1999) and Pelin et al (2002) have identified 18 different recessive mutations in *NEB*, most of which were frameshifts caused by small deletions or insertions or point mutations causing premature stop codons or abnormal splicing. A 2,502-bp deletion in *NEB* appears to be a common cause of NM in Ashkenazi Jewish families [Anderson et al 2004].

Normal gene product: Nebulin is a giant protein component of the cytoskeletal matrix.

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

TPM3

Normal allelic variants: The *TPM3* gene contains 13 exons.

Pathologic allelic variants: 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 point mutation and splice site mutation. A further example of recessive *TPM3*-related NM was documented by Tan et al (1999), who identified a homozygous Gln31-to-ter (p.Gln31X) substitution in an infant with extremely delayed motor development.

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 mutation in *TPM3* identified by Laing et al (1995). This mutation 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 mutant *TPM3* exerts a dominant-negative effect and alters the Ca^{2+}-activated force production, hastening relaxation of mutant tropomyosin and shifting the force-frequency relationship in skeletal muscle [Michele et al 1999, Michele et al 2002]. In addition, the p.Met9Arg mutation reduced the affinity of the mutant tropomyosin for actin, destabilized the tropomyosin coiled-coil, and would be expected to impair end-to-end association between tropomyosins in the thin filament [Moraczewska et al 2000].

Recently, the p.Met9Arg mutation was introduced into a transgenic mouse line, resulting in rod formation in all muscles and a late-onset (age five to six months) skeletal muscle weakness

[Corbett et al 2001]. The percentage of rods varied significantly among different muscle groups despite uniform expression of the mutant transgene, reflecting the variability of muscle involvement seen in humans with NM. Preliminary studies in the mouse confirm that the mutant *TPM3* is expressed and that there is an imbalance in other specific *TPM* isoform levels within NM muscle that may contribute to disease pathogenesis. 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

Normal allelic variants: The *TPM2* gene contains ten exons.

Pathologic allelic variants: Donner et al (2002) identified two different heterozygous missense mutations in *TPM2*.

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: The two missense mutations identified to date in *TPM2* are speculated to affect the actin-binding properties of tropomyosin beta chain.

TNNT1

Normal allelic variants: The gene encoding troponin T, slow skeletal muscle consists of 14 exons.

Pathologic allelic variants: Johnston et al (2000) identified a homozygous stop codon in exon 11, predicted to truncate the protein at amino acid 179, in infants with the Amish form of NM.

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 nonsense mutation in *TNNT1* at codon Glu180, 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.

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current as of initial posting or most recent update of the GeneReview. Search GeneTests*for this disorder and select* Resources *for the most up-to-date Resources information.*—ED.

Muscular Dystrophy Association (MDA)
3300 East Sunrise Drive
Tucson AZ 85718-3208

Phone: 800-FIGHT-MD (800-344-4863); 520-529-2000
Fax: 520-529-5300
Email: mda@mdausa.org
www.mdausa.org

Muscular Dystrophy Campaign
7-11 Prescott Place
SW4 6BS
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Fax: (+44) 0 020 7498 0670
Email: info@muscular-dystrophy.org
www.muscular-dystrophy.org

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Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

Published Statements and Policies Regarding Genetic Testing

No specific guidelines regarding genetic testing for this disorder have been developed.

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Chapter Notes

Author Notes

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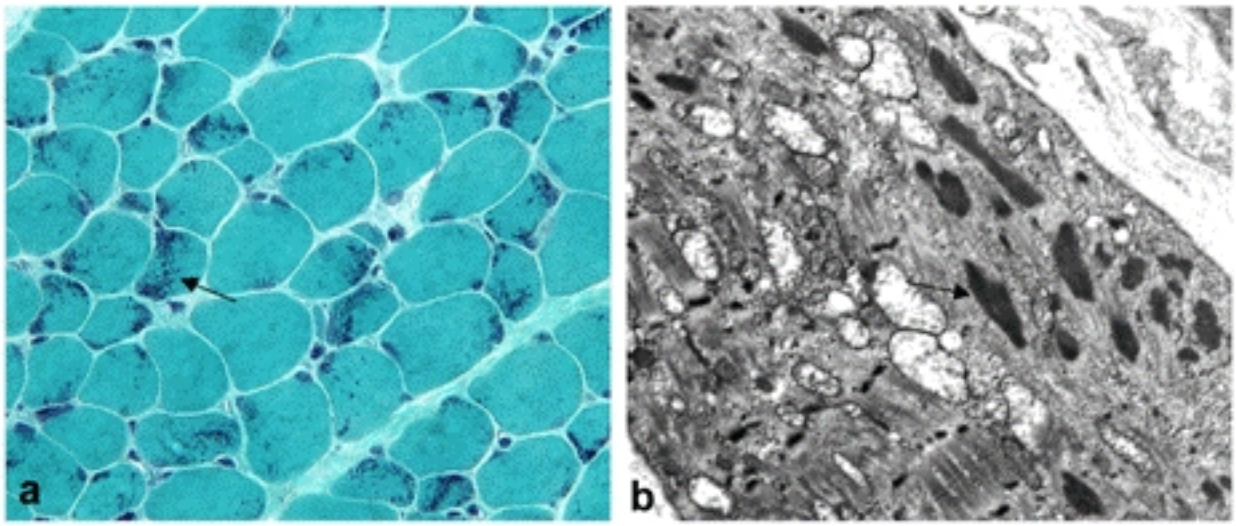

Figure 1. Pathology of nemaline myopathy. Gomori trichrome staining of frozen muscle from an affected individual shows the nemaline bodies (rods) as dark blue/purple structures scattered throughout the muscle fibers (**a**: arrow, 60x magnification). The rods appear as electron-dense structures at the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