GENEReviews

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Spinal Muscular Atrophy

[*Includes: Arthrogryposis Multiplex Congenita-Spinal Muscular Atrophy (AMC-SMA); Spinal Muscular Atrophy I (Werdnig-Hoffmann Disease, SMA1); Spinal Muscular Atrophy II (SMA II); Spinal Muscular Atrophy III (Kugelberg-Welander Disease, SMA III); Spinal Muscular Atrophy IV (SMA IV)*]

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Summary

Disease characteristics. Spinal muscular atrophy (SMA) is characterized by progressive muscle weakness resulting from degeneration and loss of the anterior horn cells (i.e., lower motor neurons) in the spinal cord and the brain stem nuclei. Onset ranges from before birth to adolescence or young adulthood. Poor weight gain, sleep difficulties, pneumonia, scoliosis, and joint contractures are common complications. Before the genetic basis of SMA was understood, it was classified into clinical subtypes; however, it is now apparent that the phenotype of SMA associated with disease-causing mutations of the *SMN1* gene spans a continuum without clear delineation of subtypes. Nonetheless, classification by age of onset and maximum function achieved is useful for prognosis and management; subtypes include: SMA O (proposed), with prenatal onset and severe joint contractures, facial diplegia, and respiratory failure; SMA I, with onset before six months of age; SMA II, with onset between six and 12 months; SMA III, with onset in childhood after 12 months; and SMA IV, with adult onset.

Diagnosis/testing. The diagnosis of SMA is based on molecular genetic testing. The two genes associated with SMA are *SMN1* and *SMN2*. The *SMN1* (survival motor neuron 1) gene is believed to be the primary disease-causing gene. About 95-98% of individuals with SMA are homozygous for the absence of exons 7 and 8 of *SMN1* and about 2-5% are compound heterozygotes for absence of exons 7 and 8 of *SMN1* and a point mutation in *SMN1*.

Carrier detection relies upon determining the number of exon 7-containing *SMN1* gene copies present in an individual. SMA carrier testing, a PCR-based dosage assay available on a limited clinical basis, allows determination of the number of *SMN1* gene copies. SMA carrier testing results can be difficult to interpret because some carriers have the normal number of *SMN1* gene copies caused by the presence either of two *SMN1* gene copies in cis configuration on one chromosome or of a *SMN1* point mutation. Furthermore, 2% of individuals with SMA have one *de novo* mutation, meaning that only one parent is a carrier. Because of these difficulties in SMA carrier test interpretation, SMA carrier testing should be provided in the context of formal genetic counseling.

Management. When nutrition is a concern in SMA, placement of a gastrostomy tube is appropriate. As respiratory function deteriorates, tracheotomy or non-invasive respiratory support is offered. Sleep disorder breathing can be treated with nighttime use of continuous positive airway pressure. Surgery for scoliosis in individuals with SMA II and SMA III can be carried out safely if the forced vital capacity is greater than 40%. A power chair and other equipment may improve quality of life. Surveillance includes evaluation every six months or more frequently for children who are weak to assess nutritional state, respiratory function, and orthopedic status (spine, hips, and joint range of motion).

Genetic counseling. SMA is inherited in an autosomal recessive manner. Each pregnancy of a couple who have had a child with SMA has an approximately 25% chance of producing an affected child, an approximately 50% chance of producing an asymptomatic carrier, and an approximately 25% chance of producing an unaffected child who is not a carrier. These recurrence risks deviate slightly from the norm for autosomal recessive inheritance because in about 2% of cases, the affected individual has a *de novoSMN1* mutation on one allele; because only one parent is a carrier of a *SMN1* mutation, the sibs are not at increased risk for SMA. Prenatal testing is available.

Diagnosis

Clinical Diagnosis

The diagnosis of spinal muscular atrophy (SMA) is established in individuals with the following:

- Evidence of degeneration and loss of anterior horn cells (i.e., lower motor neurons) in the spinal cord and brainstem
- A history of motor difficulties
- Evidence of motor unit disease on physical examination
- Diagnostic changes in the *SMN1* gene

The following classification of SMA is based on age of onset and maximum function attained.

Prenatal

- Arthrogryposis multiplex congenita (i.e., congenital joint contractures involving at least two regions of the body) [Bingham et al 1997]
- Weakness at birth
- Facial weakness: minimal

SMA I

- Onset 0-6 months
- Poor muscle tone
- Muscle weakness
- Lack of motor development; never achieves ability to sit without support
- Facial weakness: minimal or absent
- Fasciculation of the tongue: seen in most but not all affected individuals [Byers & Banker 1961, Iannaccone et al 1993]
- Postural tremor of the fingers: seen occasionally [Spiro 1970, Fredericks & Russman 1979]

- Mild contractures: often at the knees, rarely at the elbows
- Absence of tendon reflexes
- No sensory loss
- Alert appearance
- Normal cerebral function including intellect

SMA II

- Onset of muscle weakness usually after six months of age; achieves ability to sit independently when placed in a sitting position
- Finger trembling: almost invariably present
- Low muscle tone (flaccidity) [Moosa & Dubowitz 1973, Fredericks & Russman 1979]
- Absence of tendon reflexes in approximately 70% of individuals [Iannaccone et al 1993]
- Average intellectual skills during the formative years and above average by adolescence [von Gontard et al 2002]

SMA III

- Onset usually after ten months of age but in some cases earlier; achieves ability to walk at least 25 meters
- Weakness manifest as frequent falls or trouble walking up and down stairs at age two to three years
- Proximal limb weakness; the legs more severely affected than the arms

SMA IV. "Adult" onset of muscle weakness

Testing

The following testing has been used in the past to establish the diagnosis of SMA but currently has little role in the diagnosis of most individuals with SMA and is used primarily if molecular genetic testing of the *SMN1* gene is normal.

Electromyography (EMG). EMG reveals denervation and diminished motor action potential amplitude. The EMG regular spontaneous motor unit activity, a unique feature in SMA, is seen most commonly in SMA I and occasionally in SMA II, but not in SMA III [Buchthal & Olsen 1970, Hausmanowa-Petrusewicz & Karwanska 1986]. A reduced interference pattern is seen with maximal effort; polyphasic waves, positive sharp waves, and fibrillations are present in all individuals with SMA.

Nerve conduction velocities (NCV). Motor and sensory NCVs are normal.

Muscle histology. Muscle biopsy reveals group atrophy of type 1 and type 2 muscle fibers as opposed to the normal checkerboard pattern. Rare angulated and large type 1 fibers are scattered throughout (Dubowitz muscle biopsy).

Nerve histology. Hypomyelination of the peripheral nerve is observed in the prenatal form; otherwise, the nerves show normal histology [Korinthenberg et al 1997, MacLeod et al 1999, Hergersberg et al 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.

Molecular Genetic Testing—Genes. The two genes associated with SMA are *SMN1* and *SMN2*. The two genes are adjacent to each other. The *SMN2* gene copy number (arranged in tandem in cis configuration on each chromosome) is variable, ranging from zero to five.

SMN1 and *SMN2* differ by five base pairs; none of these differences change the amino acids encoded by the genes.

- ***SMN1*.** The *SMN1* (survival motor neuron) gene is believed to be the primary SMA disease-causing gene.
- ***SMN2***The presence of three or more copies of *SMN2* is correlated with a milder phenotype [Prior et al 2004, Yamashita et al 2004, Soler-Botija et al 2005, Swoboda et al 2005]. See Genotype-Phenotype Correlations.

Molecular genetic testing: Clinical uses

- Diagnostic testing
- Prognostication (See Genotype-Phenotype Correlations)
- Carrier testing
- Prenatal diagnosis

Molecular genetic testing: Clinical methods

- ***SMN1* targeted mutation analysis.** Targeted mutation analysis is used to detect deletion of exons 7 and 8 of *SMN1*.
  - Approximately 95-98% of individuals with a clinical diagnosis of SMA lack exon 7 in both copies of *SMN1* (i.e., they are homozygous for the deletion) [Bussaglia et al 1995, Lefebvre et al 1995, Parsons et al 1996, Hahnen et al 1997, McAndrew et al 1997, Talbot et al 1997, Parsons et al 1998, Ogino & Wilson 2002].
  - Approximately 2-5% of individuals with a clinical diagnosis of SMA are compound heterozygotes for deletion of *SMN1* exon 7 and an intragenic mutation of *SMN1*.
- ***SMN1* sequence analysis.** Sequence analysis of all *SMN1* exons and intron/exon borders may be used to identify the intragenic *SMN1* mutations present in the 2-5% of individuals who are compound heterozygotes. The *SMN1* and *SMN2* genes are very large and exonic regions must be individually amplified; therefore, sequence analysis does not detect exonic deletions or duplications.
- **Duplication analysis to determine *SMN2* copy number.** The number of copies of the *SMN2* gene ranges from zero to five. Quantitative PCR is currently used for the accurate determination of *SMN2* copy number [Anhuf et al 2003].
- **SMA carrier testing: gene dosage analysis.** Targeted mutation analysis is not reliable for carrier detection as it does not quantitate the number of *SMN1* gene copies. A PCR-based dosage assay, called "SMA carrier testing" or *"SMN* gene dosage

analysis," can determine the number of *SMN1* gene copies, thus permitting highly accurate carrier detection.

- **Linkage analysis.** Linkage analysis is available for families in which direct DNA testing (mutation analysis and/or sequence analysis) is not informative. It may be used for confirmation of carrier testing and prenatal testing results.

Table 1 summarizes molecular genetic testing for this disorder.

Table 1. Molecular Genetic Testing Used in Spinal Muscular Atrophy

Test Method	Mutations Detected	Mutation Detection Rate [1]		Test Availability
		Homozygotes	Compound Heterozygotes	
Targeted mutation analysis	Deletion of exon 7 of *SMN1*	~95-98%	~2-5%	Clinical Testing
Sequence analysis	Intragenic *SMN1* mutation	0%		
Deletion/duplication analysis	*SMN2* copy number	NA	NA	

1. Mailman et al 2002

Interpretation of test results

- For issues to consider in interpretation of sequence analysis results, click here.
- Sequence analysis cannot determine whether a point mutation is in the *SMN1* gene or the *SMN2* gene (unless one of these genes is absent); therefore, finding a mutation does not signify that the mutation is in *SMN1*. However, several point mutations have now been described in more than one person. Identification of a previously reported point mutation provides evidence that the mutation is in *SMN1*.
- Failure to identify a mutation by sequence analysis is sufficient evidence to conclude that an intragenic mutation is not present in the *SMN1* gene.

Interpretation of negative carrier test results is problematic in the following cases:

- The finding of two *SMN1* genes on a single chromosome, which occurs in about 4% of the general population [McAndrew et al 1997]. The presence of two *SMN1* genes on a single chromosome has serious counseling implications because a carrier with two *SMN1* genes on one chromosome is misdiagnosed as a non-carrier by the SMA dosage carrier test.
- *De novo* mutations occur in 2% of individuals with SMA and signify that only one parent is a carrier

See also Genetic Counseling, Carrier Detection [McAndrew et al 1997].

Genetically Related (Allelic) Disorders

No other phenotypes are associated with mutation of *SMN1*.

Clinical Description

Natural History

SMA phenotypes. SMA is characterized by muscle weakness and atrophy resulting from progressive degeneration and loss of the anterior horn cells in the spinal cord (i.e., lower motor neurons) and the brainstem nuclei. The onset of weakness ranges from before birth to adolescence or young adulthood. The weakness is almost always symmetric and progressive. Before the advent of molecular diagnosis, attempts were made to classify SMA into discrete subtypes; however, it is now apparent that the phenotype of SMA associated with disease-

causing mutations of the *SMN* gene spans a broad continuum without clear delineation of subtypes. Nonetheless, the existing classification system (Table 2) based on age of onset and maximum function attained is useful for prognosis and management.

Table 2. Spectrum of SMA Phenotypes

Phenotype	Age of Onset	Life Span	Motor Milestones	Other Findings
SMA 0 (Prenatal)	Prenatal	2-6 months	None achieved	
Congenital axonal neuropathy (CAN)	Prenatal	Days	None achieved	• Joint contractures • No movement • Facial diplegia • Ophthalmoplegia
Arthrogryposis multiplex congenita	Prenatal	Unclear	May progress to standing	• Joint contractures • Normal to mildly abnormal facial movements
SMA I	Before six months	Most often two years or less, but may live longer	Sit with support only	• Mild joint contractures • Normal or minimal facial weakness • Variable suck and swallow difficulties
SMA II	6-18 months	70% alive at 25 years old	Independent sitting when placed	• Postural tremor of fingers
SMA III	After 12 months	Normal	Independent ambulation	
SMA IV	Adulthood	Normal	Normal	

Congenital axonal neuropathy. Congenital axonal neuropathy manifests as severe weakness of prenatal onset, joint contractures, facial diplegia, ophthalmoplegia, and respiratory failure at birth requiring immediate endotracheal intubation and ventilation. Decreased fetal movement and polyhydramnios are common [Korinthenberg et al 1997].

AMC-SMA association (arthrogryposis multiplex congenita-spinal muscular atrophy). AMC-SMA manifests as severe weakness of prenatal onset and AMC (i.e., congenital joint contractures involving at least two regions of the body). Decreased fetal movement, polyhydramnios, and breech presentation are common. Typically, affected infants have absence of movement except for extraocular and facial movement. Death usually occurs from respiratory failure before one month of age [Banker 1985, Burglen et al 1996, Bingham et al 1997]. However, one report describes a child who is not ventilator-dependent at five years of age [Falsaperla et al 2001].

SMA I (acute spinal muscular atrophy; Werdnig-Hoffmann disease). SMA I manifests as severe weakness before age six months. Affected children are not able to sit without support at any time. Proximal, symmetric muscle weakness, lack of motor development, and poor muscle tone are the major clinical manifestations. Mild contractures are often noted at the knees and, rarely, at the elbows. In the neonatal period or during the first few months, the infants with the gravest prognosis have problems sucking or swallowing and often show abdominal breathing. The muscles of the face are relatively spared; the diaphragm is not involved until late in the course of disease. The heart is normal. Of note, a peculiar tremor of the

electrocardiographic baseline has been attributed to fasciculation of limb and chest wall muscles [Russman & Fredericks 1979, Coletta et al 1989].

Fasciculation of the tongue is seen in most but not all individuals [Byers & Banker 1961, Iannaccone et al 1993]. A postural tremor of the fingers is seen only occasionally in SMA I [Spiro 1970, Fredericks & Russman 1979]. Most individuals die before age two years [Ignatius 1994, Thomas & Dubowitz 1994]. However, on occasion, individuals whose weakness was thought to have started before age six months are still sitting in adolescence or adulthood [Iannaccone et al 1993, Zerres & Rudnik-Schoneborn 1995].

Those individuals who have chosen to receive respiratory support may live longer than age two years [Bach et al 2002].

SMA II (chronic spinal muscular atrophy; Dubowitz disease). SMA II manifests as onset usually between six and 12 months of age. Maximum motor milestone attained is the ability to sit independently when placed. Although poor muscle tone may be evident at birth or within the first few months of life, individuals with SMA II may gain motor milestones slowly [Iannaccone et al 1993]. Often concerns are not raised until a child is not sitting independently by age nine to 12 months or is not standing by age one year. Finger trembling and general flaccidity are common [Moosa & Dubowitz 1973, Fredericks & Russman 1979]. Affected individuals on average lose the ability to sit independently by the mid-teens [Russman et al 1996].

SMA III (juvenile spinal muscular atrophy; Kugelberg-Welander disease). SMA III manifests after one year of age. Individuals with SMA III walk independently but may fall frequently or have trouble walking up and down stairs at age two to three years. The legs are more severely affected than the arms. Prognosis generally correlates with the maximum motor function attained [Russman et al 1983]. Individuals with SMA III who have never climbed stairs without using a rail lose walking ability by the mid-teens [Russman et al 1996]. Individuals who develop normal walking skills prior to the onset of weakness can maintain this ability until the third or fourth decade of life.

SMA IV. The onset of muscle weakness is usually in the second or third decade of life. The findings are similar to those described for SMA III [Brahe et al 1995, Clermont et al 1995, Zerres et al 1995].

Complications of SMA. Poor weight gain, sleep difficulties, pneumonia, scoliosis, and joint contractures are common complications of SMA.

An unexplained potential complication of SMA is severe metabolic acidosis with dicarboxylic aciduria and low serum carnitine levels during periods of intercurrent illness or fasting [Kelley & Sladky 1986, Crisp et al 1989]. Whether these metabolic abnormalities are primary or secondary to the underlying defect in SMA is unknown. Some investigators have suggested that underweight individuals with SMA with minimum muscle mass are at risk for recurrent hypoglycemia or ketosis [Bruce et al 1995, Tein et al 1995]. The problem is self-limiting; individuals typically recover in two to four days.

Life expectancy and prognosis of SMA. Whether the loss of function observed in all individuals with SMA is caused by loss of motor units or other factors such as scoliosis, progressive contractures, and pulmonary insufficiency is difficult to determine [Hausmanowa-Petrusewicz et al 1992]. Of the individuals studied by Russman et al (1992) over a period of 18 months, none lost strength in the individual muscle groups studied, but four lost functional abilities. In a cross-sectional study of 120 individuals with SMA, Merlini et al (2004) noted that individuals no longer ambulant were weaker than those who were still ambulant,

concluding that loss of muscle strength correlated with loss of function. Given the study design these conclusions need be considered tentative.

In a physiological outcome study, Swoboda et al (2005) showed a correlation between motor unit number estimation (MUNE) and disease severity. In addition to MUNE, the measurement of compound motor action potential can be used to determine outcome.

A review of life expectancy of 569 individuals with SMA II and SMA III from Germany and Poland found that 68% of individuals with SMA II were alive at 25 years of age and that life expectancy of individuals with SMA III was not different from that of the general population [Zerres et al 1997].

Pregnancy. Women with SMA may experience exacerbation of muscle weakness during pregnancy [Rudnik-Schoneborn et al 1992]. Complications of pregnancy in ten of 12 women with SMA included premature labor in four, prolonged labor in three, and delayed post-partum recovery in six. No deleterious effects were observed in the offspring.

Neuropathology. Studies reveal a decreased number of motor neurons (and varying stages of chromatolysis and acute degeneration of anterior horn cells) and gliosis in the anterior horns of the spinal cord as well as a decreased number of lower cranial motor neurons.

Genotype-Phenotype Correlations

SMN1 produces a full-length survival motor neuron (fl SMN) protein necessary for lower motor neuron function [Lefebvre et al 1995]. *SMN2* mostly encodes a protein that is lacking in exon 7, thereby producing a less stable protein.

No correlation exists between the loss of *SMN1* exons 7 and 8 and the severity of disease.

Accumulating data indicate that the presence of three or more copies of *SMN2* is correlated with a milder phenotype [Velasco et al 1996, McAndrew et al 1997, Parsons et al 1998, Mailman et al 2002]. The most recent data [Mailman et al 2002] are summarized in Table 3. Of note, three unrelated individuals homozygous for the *SMN1* deletion who had five copies of *SMN2* were asymptomatic [Prior et al 2004]. These cases demonstrate that expression levels consistent with five copies of the *SMN2* gene may compensate for the absence of the *SMN1* gene.

Those with the phenotype of SMA I have as little as 9% of the normal amount of full-length SMN (fl SMN), those with SMA II have 14%, and those with SMA III, about 18%. Once full-length protein levels approach 23% of normal levels, motor neuron function appears normal. Carriers usually have 45-55% full-length SMN protein.

Table 3. *SMN2* Copy Number in SMA I vs. SMA III

SMN2 Copy Number	Normal	SMA I	SMA III	Total (SMA I + SMA III)
0	14.4%	0	0	
1	32%	7 (13.5%)	0 (0%)	7 (4.9%)
2	51%	43 (82.7%)	0 (0%)	43 (30.3%)
3	4%	2 (3.9%)	70 (77.8%)	72 (50.7%)
4		0 (0%)	20 (22.2%)	20 (14.1%)
Total		**52**	**90**	**142**

Adapted from Mailman et al 2002

Nomenclature

Severe SMA or SMA I is still called Werdnig-Hoffmann disease by many [Werdnig 1891, Hoffmann 1892].

SMA II was called chronic SMA prior to the current classification.

SMA III has had the eponym juvenile SMA or Kugelberg-Welander disease [Kugelberg & Welander 1956].

Prevalence (Table 4)

Table 4. Incidence of SMA and Estimated Carrier Frequency

Country	Disease Incidence per 100,000 Livebirths	Carrier Frequency	Reference
England	4	1/90	Pearn 1978
Italy	7.8 (all SMA)	1/57	Mostacciulo et al 1992
	4.1 (SMA I)		
Germany, USA	10	1/50	Thieme et al 1993, Mailman et al 2002

Differential Diagnosis

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

Arthrogryposis multiplex congenita (AMC). Although some individuals with AMC have *SMN* mutations [Burglen et al 1996, Bingham et al 1997], other infants with various types of AMC do not.

Congenital axonal neuropathy. Korinthenberg et al (1997) indicated that three siblings with *SMN* disease-causing mutations reported by them were the same infants reported by others to have congenital hypomyelination neuropathy or axonopathy [Vital et al 1989, Boylan & Cornblath 1992].

Infants with perinatal respiratory distress with diaphragmatic and intercostal muscle weakness who have evidence of denervation on electromyogram and group atrophy on muscle biopsy were described prior to the availability of molecular testing [Schapira & Swash 1985, Bove & Iannaccone 1988]. This entity has been linked to chromosome 11q13-q21 and shown to share common functions for anterior horn cell maintenance with survival motor neuron gene [Grohmann et al 2001]. An autosomal recessive form without respiratory distress has recently been described, linkage being established in the same region as the diaphragmatic form [De Angelis et al 2002].

For SMA I and SMA III, the differential includes other causes of the "floppy infant":

- **Central nervous system abnormalities.** Cranial imaging may be helpful in identifying these.
- **Chromosomal abnormalities** and specifically Prader-Willi syndrome need to be considered. High-resolution chromosome analysis and, for Prader-Willi syndrome, methylation analysis can distinguish these.
- **Peroxisome biogenesis disorders, Zellweger syndrome spectrum** are suspected if the child has lost skills previously acquired or if hepatosplenomegaly is present. Measurement of plasma very-long-chain fatty acid (VLCFA) levels shows elevation

of C26:0 and C26:1 and the ratios C24/C22 and C26/C22. Mutations in twelve different *PEX* genes are causative; molecular genetic testing is available for some.

- **Infantile acid maltase deficiency** (Pompe disease; glycogen storage disease type II) is suspected when cardiomegaly is present. Biochemical and molecular testing is available.
- **Primary diseases of muscle** need to be considered. Among these are nemaline myopathy, central core disease, X-linked myotubular myopathy, congenital myotonic dystrophy type 1, and congenital muscular dystrophy. The diagnosis of a specific type of muscle disease rests on the presence of the specific ultrastructural changes on muscle biopsy and/or genetic testing.
- **Congenital myasthenia gravis** (see Congenital Myasthenic Syndromes) may be recognized by abnormal EMG responses to repetitive nerve stimulation and in some cases genetic testing.

Other disorders to consider are trauma of the cervical spinal cord, especially with breech delivery, spinal muscular atrophy with infantile cerebellar atrophy, and spinal muscular atrophy associated with brain atrophy [Chou et al 1990, Yohannan et al 1991].

Peripheral neuropathies (see Charcot-Marie-Tooth Hereditary Neuropathy Overview) including the Guillain-Barre syndrome are part of the differential diagnosis.

Regression of motor skills associated with intact or exaggerated deep tendon reflexes suggest cerebral white matter diseases such as X-linked adrenoleukodystrophy.

SMA III is considered in the differential diagnosis of Duchenne muscular dystrophy (DMD), which is suspected when serum creatine kinase concentration is ten to 20 times greater than normal. DMD is confirmed by molecular genetic studies of the *DMD* gene or muscle biopsy.

Congenital myopathies may also present with a clumsy gait and difficulty walking up and down stairs. Metabolic myopathies, including glycogen storage diseases and lipid myopathies, need to be considered.

Other disorders with motor neuron disease may be confused with SMA: X-linked spinal and bulbar muscular atrophy (SBMA), also known as Kennedy disease, is a gradually progressive neuromuscular disorder in adult men in which degeneration of lower motor neurons results in proximal muscle weakness, muscle atrophy, and fasciculations beginning between ages 20 and 50 years. Individuals with SBMA often show gynecomastia, testicular atrophy, and reduced fertility as a result of androgen insensitivity. Identification of a CAG trinucleotide repeat expansion in the androgen receptor gene is diagnostic.

Hexosaminidase A deficiency results in lysosomal storage of the specific glycosphingolipid, GM2 ganglioside. The juvenile, chronic, and adult-onset variants have onset after infancy, slow progression, and variable neurologic findings, including progressive dystonia, spinocerebellar degeneration, and lower motor neuron disease. Diagnosis is by enzyme deficiency or molecular testing.

"Monomelic muscular atrophy" is predominantly a cervical form of spinal muscular atrophy. Rarely, the tongue may be affected; other cranial nerves are spared [Goutieres et al 1991, Hageman et al 1993].

Fazio-Londe disease is a motor neuron disease limited to the lower cranial nerves, which starts in the second decade of life and progresses to death in one to five years.

Distal spinal muscular atrophy is characterized by initial weakness and wasting of distal muscles, followed by weakness of other muscle groups. A fascioscapuloperoneal distribution of spinal muscular atrophy, a bulbospinal muscular atrophy in adults, and spinal muscular atrophy with initial involvement of the proximal muscles have also been described.

A congenital form of lower extremity SMA has been described; it is unclear whether the distal muscles are weaker than the proximal muscles. If so, this would be included under the rubric of distal spinal muscular atrophy [Mercuri et al 2004].

Amyotrophic lateral sclerosis (ALS), a progressive neurodegenerative disease involving both the upper motor neurons (UMN) and lower motor neurons (LMN), may begin with pure lower motor neuron signs. Molecular genetic testing is available for at least three genes associated with ALS: *SOD1*, *ALS2*, and *VAPB*.

Management

Evaluations at Initial Diagnosis to Establish the Extent of Disease

The following issues need to be addressed independent of SMA type:

- **Nutrition/feeding assessment**
  - Time required to complete a feeding
  - Evidence of fatigue during a feeding/meal
  - Weight plotted on standard growth curves
- **Respiratory function assessment**
  - Normal breathing pattern versus abdominal breathing pattern
  - Forced vital capacity (FVC); in children over the age four years, the hand-held spirometer is accurate. When FVC is above 40%, decompensation during respiratory infection is less likely than when FVC is less than 40%.
- **Sleep asssessment.** Consideration of a sleep study if the child snores during sleep or awakes fatigued in the morning
- **Activities of daily living.** Assessment of equipment needed for independence, such as a power-chair and other equipment in the home to improve the quality of life for the affected individual and the caregiver
- **Orthopedic evaluation.** Attention to the development of contractures, scoliosis, and hip dislocation

Treatment of Manifestations

Nutrition/feeding. When there are concerns, a feeding gastrostomy is appropriate and can be removed if oral intake becomes adequate.

Respiratory function. Inevitably, the respiratory function deteriorates [Samaha et al 1994]. Some children with SMA I can survive beyond two years of age when offered tracheotomy or non-invasive respiratory support [Bach et al 2002].

Options for management including "do not attempt to resuscitate" status should be discussed before respiratory failure occurs [Samaha et al 1994]. This discussion should be initiated when abdominal breathing is noted and/or the forced vital capacity is less than 30%.

Children relying on non-invasive respiratory support have fewer hospitalizations after age five years, may be free from daytime ventilator use, and are able to express themselves verbally. Non-invasive respiratory support is labor intensive, demands commitment, and depends upon the availability of facilities. Bush and colleagues (2005) argue that nighttime nasal intermittent positive pressure (NIPPV) and occasional daytime NIPPV are reasonable; they do not currently recommend full-time NIPPV. Miske et al (2004) use the mechanical in-exsufflator (MI-E) in treatment of neuromuscular conditions. MI-E delivers a positive pressure insufflation followed by an expulsive exsufflation, simulating a normal cough and is helpful in the management of respiratory infections in individuals with SMA.

Sleep disorders. In a study of seven persons with SMA, Mellies et al (2004) noted that sleep disorder breathing developed prior to respiratory failure. Puruckherr et al (2004) described a 46-year-old man with SMA III whose increasing daytime fatigue caused by snoring and apnea at night resolved with nighttime use of continuous positive airway pressure with a nasal mask.

Orthopedic. Children with SMA I rarely require orthopedic intervention because they do not live long enough to develop spinal deformity, hip dislocation, or contractures.

Scoliosis is a major problem in SMA II and in half of those with SMA III [Brown et al 1989, Merlini et al 1989, Rodillo et al 1989]. Before age ten years, approximately 50% of children with SMA, especially those who are non-ambulatory, develop spinal curvatures of more than 50 degrees, the threshold for surgery. Scoliosis repair can be carried out safely if the forced vital capacity is greater than 40%. The use of an orthosis does not prevent scoliosis, but does allow the affected individual to be upright rather than recumbent. Although individuals lose some upper extremity function following operative intervention, the advantages of a stable trunk and the opportunity to sit upright unassisted outweigh the disadvantages. Whether scoliosis repair prevents further deterioration of pulmonary function is unclear.

A retrospective review of a large series concluded that surgery is not needed for asymptomatic hip dislocation [Sporer & Smith 2003].

Surveillance

Individuals are evaluated at least every six months; weaker children are evaluated more frequently.

Nutritional state, respiratory function and orthopedic status (spine, hips, and joint range of motion) are assessed at each visit.

Therapies Under Investigation

Pre-clinical evaluation of drugs and other interventions is underway [Escolar et al 2001, Iannaccone & Hynan 2003, Swoboda et al 2005].

Increasing the activity of the *SMN2* gene is one of the major strategies under consideration. The following are some medications/chemicals under investigation:

- Histone deacetylase (HDAC) inhibitors can increase the level of fl-SMN [Kernochan et al 2005].
- Valproic acid [Brichta et al 2003, Sumner et al 2003] increases SMN protein in skin fibroblasts.
- Phenylbutyrate, a drug used in the treatment of urea acid cycle disorders, increased full-length SMN2 transcripts in skin fibroblasts [Andreassi et al 2004]. Oral phenylbutyrate increased SMN expression in white blood cells [Brahe et al 2005]. In

a pilot trial phenylbutyrate improved function in the short term in ten persons with SMA [Mercuri et al 2004].

- Hydroxyurea, a medication that enhances the expression of human fetal hemoglobin [Stevens 1999] also modifies gene expression and increases SMN levels in skin fibroblasts from individuals with SMA [Grzeschik et al 2005].
- Indoprofen, a non-steroidal anti-inflammatory drug (NSAID), increases SMN2 levels in fibroblasts of individuals with SMA [Lunn et al 2004].
- An open-label pilot trial of Rilutek (Riluzole) in infants with SMA is currently under way at ten participating centers. The Phase 1 trial showed it to be safe, but the power was insufficient to show benefit [Russman et al 2003].
- A multicenter randomized, double-blind study of the effect of gabapentin in individuals with SMA II and III showed benefit to muscle strength but no improvement in motor or respiratory function [Miller et al 2001, Merlini et al 2003]. However, a double-blind one-year study showed that gabapentin was not beneficial in SMA [Miller et al 2001].

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions.

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

Spinal muscular atrophy is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- Approximately 98% of parents of an affected child are heterozygotes and, therefore, carry a disease-causing mutation in the *SMN1* gene.
- About 2% of parents are not carriers of a *SMN1* mutation as their affected child has a *de novo* disease-causing mutation [Wirth et al 1997]. The majority of *de novo* mutations are paternal in origin [Wirth et al 1997].
- Heterozygotes 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.
- Even if a child with SMA appears to have inherited one disease-causing allele from a carrier parent and to have a *de novo* mutation resulting in the other disease-causing mutation, germline mosaicism in the parent without an identifiable mutation needs to

be considered [Campbell et al 1998]; therefore, it is reasonable to consider sibs of such an individual to be at risk for SMA.

- Once an at-risk sib is known to be unaffected, the risk of his/her being a carrier is 2/3.

Offspring of a proband

- Only individuals with the milder forms of SMA are likely to reproduce. All of their offspring are carriers.
- The unrelated reproductive partner of an individual with a mild form of SMA should be offered carrier testing. If the partner shows at least two *SMN1* copies, the partner has a one in 670 probability of being a carrier (taking into consideration the 2% frequency of two *SMN1* copies on the same chromosome and the small risk of an intragenic *SMN1* mutation). Thus, the risk to such a couple of having an affected child is one in 1340.

Other family members. Each sib of an obligate heterozygote is at a 50% risk of being a carrier.

Carrier Detection

Carrier detection may be considered for the following individuals:

- **Parents of a single affected child with SMA in whom the diagnosis has been confirmed with direct DNA testing.** Carrier detection for such parents has three limitations:
  - A *de novo* mutation in the *SMN* gene, occurring in approximately 2% of individuals [Wirth et al 1995]. This is a high rate when compared to most autosomal recessive disorders.
  - The finding of two *SMN1* genes on a single chromosome, which occurs in about 4% of the general population [McAndrew et al 1997]. The presence of two *SMN1* genes on a single chromosome has serious counseling implications because a carrier with two *SMN1* genes on one chromosome is misdiagnosed as a non-carrier by the SMA dosage carrier test.
  - Carriers with one normal allele and one intragenic *SMN1* gene mutation

Because of *de novo* mutational events and the presence of two *SMN1* genes on a single chromosome, approximately 6% of parents of a single child affected with SMA have normal results of *SMN* dosage testing. Thus, the finding of normal *SMN1* dosage in a parent significantly reduces, but does not eliminate, the risk of the parent being a carrier for SMA. Further study by linkage analysis including other family members may allow clarification of these two situations, since documentation of a *de novo* mutation in the child reduces the couple's risk of having additional affected children.

- **Parents of an affected deceased child with SMA on whom no molecular testing of *SMN* was performed.** Tissue, such as muscle biopsies and paraffin tissue samples, available from deceased individuals can **often** provide enough DNA for genetic testing; however, if DNA is not available, both parents could be offered SMA carrier (dosage) testing. Issues with test result interpretation include the following:
  - If both parents are found to be carriers, the diagnosis of SMA in the proband is most likely and prenatal testing can be offered.
  - If only one parent is Δ7 *SMN1* heterozygous, testing of additional family members of the parent with two *SMN1* gene copies may be informative.

- If both parents show at least two *SMN1* copies, it is extremely unlikely that the affected child had SMA caused by mutations at the *SMN* locus.

- **At-risk relatives of an individual with SMA who is homozygous for Δ7 *SMN1*.** In this instance, the risk that the dosage test will produce a false negative or uncertain result because of the presence of two *SMN1* copies on one chromosome is 4%.

- **Unrelated reproductive partners of an individual known to be heterozygous for a familial disease-causing mutation in *SMN1*or an individual at risk of being heterozygous for a *SMN*disease-causing mutation.** These unrelated reproductive partners are individuals who are at no known increased risk of being heterozygous for a *SMN* disease-causing mutation. A reproductive partner showing at least two *SMN1* copies has an approximately one-in-670 probability of being a carrier (taking into consideration the 2% frequency of two *SMN1* copies on the same chromosome and the small risk of intragenic mutations).

Related Genetic Counseling Issues

Family planning. The optimal time for determination of genetic risk, clarification of carrier status, and discussion of availability of prenatal testing is before pregnancy.

DNA banking. Because of the complex nature of the *SMN* mutations causing SMA, the difficulty in performing molecular genetic testing now, and the likelihood that testing methods will improve in the future, consideration should be given to banking the DNA of any individual known or suspected of having SMA. In this manner, a DNA sample would be available to family members who seek genetic counseling and testing in the future. See DNA Banking for a list of laboratories offering this service.

Prenatal Testing

High-risk pregnancy. Prenatal diagnosis is possible for fetuses at 25% risk when the disease-causing *SMN* mutations in both parents are known or when linkage has been established in the family. Analysis of fetal DNA obtained either through chorionic villus sampling (CVS) at about 10-12 weeks' gestation or amniocentesis usually performed at about 15-18 weeks' gestation is possible for the known parental *SMN1* gene mutations or for the previously identified linked markers. The situations in which prenatal testing is likely to occur and the issues in test result interpretation are the following:

- **The couple are the parents of a child with SMA.** It would be predicted that a fetus with the same genotype (i.e., molecular genetic test result) as a previously affected sib would have similar clinical findings.

- **One or both parents are heterozygous for *SMN*disease-causing mutations detected during testing of relatives and their partners.** In this instance, interpretation of test results may be difficult and should be done in the context of formal genetic counseling.

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

Low-risk pregnancy. For the fetus with reduced fetal movement at no known increased risk for SMA, SMA needs to be considered, as do the disorders discussed in Differential Diagnosis [Macleod et al 1999].

Preimplantation genetic diagnosis (PGD) may be available for families in which the disease-causing mutations have been identified in an affected family member in a research or clinical

laboratory [Moutou et al 2003, Malcov et al 2004]. 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 Spinal Muscular Atrophy

Gene Symbol	Chromosomal Locus	Protein Name
SMN1	5q12.2-q13.3	Survival motor neuron protein
SMN2	5q12.2-q13.3	Survival motor neuron protein

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 Spinal Muscular Atrophy

208100	ARTHROGRYPOSIS MULTIPLEX CONGENITA, NEUROGENIC TYPE; AMCN
253300	SPINAL MUSCULAR ATROPHY, TYPE I; SMA1
253400	SPINAL MUSCULAR ATROPHY, TYPE III; SMA3
253550	SPINAL MUSCULAR ATROPHY, TYPE II; SMA2
271150	SPINAL MUSCULAR ATROPHY, TYPE IV; SMA4
600354	SURVIVAL OF MOTOR NEURON 1, TELOMERIC; SMN1
601627	SURVIVAL OF MOTOR NEURON 2, CENTROMERIC; SMN2
602595	SMN-INTERACTING PROTEIN 1; SIP1
603519	SURVIVAL OF MOTOR NEURON-RELATED PROTEIN

Table C. Genomic Databases for Spinal Muscular Atrophy

Gene Symbol	Entrez Gene	HGMD
SMN1	6606 (MIM No. 600354)	SMN1
SMN2	6607 (MIM No. 601627)	SMN2

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

Molecular Genetic Pathogenesis

SMA may be the result of a genetic defect in the biogenesis and trafficking of the spliceosomal snRNP complexes. The SMN protein interacts with proteins known to be involved in the small nuclear ribonucleoprotein particle complex as well as with the survival motor neuron-interacting protein SIP. Consequently, the motor neurons of individuals with SMA are impaired in their capacity to produce specific mRNAs and as a result become deficient in proteins that are necessary for the growth and function of these cells. Thus, SMA may be a disorder affecting splicing; however, the reasons for specific motor neuron death as a consequence of *SMN1* mutations are not yet known. The SMN protein has also been reported to influence several other cellular activities such as transcription, ribosomal assembly, and apoptosis [Strasswimmer et al 1999, Lefebvre et al 2002, Vyas et al 2002].

Despite the few differences in the coding regions between *SMN1* and *SMN2*, the two genes do not encode identical proteins. *SMN1* produces full-length transcripts and *SMN2* primarily produces transcripts lacking exon 7 because the C-to-T transition in *SMN2* exon 7 disrupts an

exon-splicing enhancer sequence [Lorson et al 1999]. Therefore, SMA arises because the *SMN2* gene cannot fully compensate for the lack of expression of mutated *SMN1*. However, when the *SMN2* copy number is increased, the small amount of full-length transcript generated by *SMN2* is often able to produce a milder type II or III phenotype.

Normal allelic variants: The *SMN* region on chromosome 5q12.2-q13.3 is unusually complex, with repetitive sequences, pseudogenes, retrotransposable elements, deletions, and inverted duplications [Biros & Forrest 1999]. Unaffected individuals have two copies of the *SMN* gene arranged in tandem on each chromosome; these are referred to as *SMN1* (telomeric copy) and *SMN2* (centromeric copy). Other terms that have been used to identify *SMN1* are *telSMN*, *SMNt*, and *SMNT*; other terms that have been used to identify *SMN2* are *cenSMN*, *SMNc*, ^{c}*BCD541*, and *SMNC*. Both *SMN1* and *SMN2* contain nine exons and differ only in eight nucleotides (five are intronic and three are exonic, located within exons 6, 7, and 8) [Biros & Forrest 1999].

The presence of a SMA carrier with two *SMN1* copies on one chromosome was definitively proven utilizing hybrids monosomal for human chromosome 5 [Mailman et al 2001].

Pathologic allelic variants: It is the loss of the telomeric copy of the *SMN(SMN1*) gene that leads to development of SMA. Individuals with SMA are either homozygous for a deletion of exon 7 of *SMN1* (Δ7 *SMN1*) or are compound heterozygotes for Δ7 *SMN1* and a intragenic mutation of *SMN1*. Deletions of the *SMN1* gene appear to be directly involved in SMA, since exon 7 — or exons 7 and 8 — of *SMN1* are undetectable in more than 95% of individuals irrespective of their clinical type, either as a result of homozygous deletions, or because of conversion of sequences of *SMN1* into those of the *SMN2* gene.

Normal gene product: Evidence supports a role for SMN in snRNP (small nuclear ribonuclearprotein) biogenesis and function [Fischer et al 1997, Liu et al 1997, Pellizzoni et al 1998]. SMN has been shown to be required for pre-mRNA splicing. Immunofluorescence studies using a monoclonal antibody to the SMN protein have revealed that the SMN protein is localized to novel nuclear structures called 'gems;' gems appear similar to and possibly interact with coiled bodies, which are thought to play a role in the processing and metabolism of small nuclear RNAs [Liu & Dreyfuss 1996]. SnRNPs and possibly other splicing components require regeneration from inactivated to activated functional forms. The function of SMN is in the reassembly and regeneration of these splicing components [Pellizzoni et al 1998].

Abnormal gene product: Mutant SMN, such as that found in individuals with SMA, lacks the splicing-regeneration activity of wild-type SMN.

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*  *for the most up-to-date Resources information.*—ED.

Families of SMA
PO Box 196
Libertyville, IL 60048-0196
Phone: 800-886-1762
Fax: 847-367-7623

Email: sma@fsma.org
www.fsma.org

Medline Plus
Spinal Muscular Atrophy

National Library of Medicine Genetics Home Reference
Spinal muscular atrophy

NCBI Genes and Disease
Spinal muscular atrophy

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

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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

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