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NLM Citation: La Spada A. Spinal and Bulbar Muscular Atrophy. 1999 Feb 26 [Updated 2022 Dec 15]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Spinal and Bulbar Muscular Atrophy

Synonyms: Kennedy's Disease, SBMA, X-Linked Spinal and Bulbar Muscular Atrophy

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Created: February 26, 1999; Updated: December 15, 2022.

Summary

Clinical characteristics

Spinal and bulbar muscular atrophy (SBMA) is a gradually progressive neuromuscular disorder in which degeneration of lower motor neurons results in muscle weakness, muscle atrophy, and fasciculations in affected males. Affected individuals often show gynecomastia, testicular atrophy, and reduced fertility as a result of mild androgen insensitivity.

Diagnosis/testing

The diagnosis of SBMA is established in a male proband by the identification of a hemizygous expansion of a CAG trinucleotide repeat (>35 CAGs) in *AR* by molecular genetic testing.

Management

Treatment of manifestations: Use of braces and walkers for ambulation as needed as the disease progresses; standard treatments for dysarthria and dysphagia; breast reduction surgery for gynecomastia as needed; standard treatment per cardiologist and/or endocrinologist for cardiac manifestations and metabolic syndrome; psychosocial support and education to decrease stress and burden on caregivers.

Surveillance: Annual assessment of strength, mobility, activities of daily living, speech, and feeding issues; annual assessment of pulmonary function in those with advanced disease; annual assessment of cholesterol and triglycerides, with hepatic function testing if elevated; annual assessment of cardiovascular health per cardiologist; assessment of need for family and caregiver support.

Other: Clinical trials of anti-androgen drugs (e.g., leuprorelin) did not consistently reveal significant efficacy, but leuprorelin was efficacious as a treatment for dysphagia in a follow-up clinical trial in Japan, leading to its approval in Japan but not elsewhere. Based on animal studies, administration of testosterone and its analogs may worsen motor neuron disease.

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Genetic counseling

SBMA is inherited in an X-linked manner. Affected males who are fertile pass the expanded CAG repeat to each daughter. Carrier females have a 50% chance of transmitting the CAG trinucleotide expansion to each child; males who inherit it will be affected; females who inherit it will be carriers and will usually not be affected. Carrier testing for at-risk female relatives and prenatal testing for a pregnancy at increased risk are possible if the expanded CAG repeat has been identified in an affected family member.

Diagnosis

Suggestive Findings

Spinal and bulbar muscular atrophy (SBMA) **should be suspected** in males with the following clinical features and family history.

Clinical features

- Adolescent-onset signs of androgen insensitivity (e.g., gynecomastia)
- Post-adolescent onset of:
  - Spinal lower motor neuron disease with muscle weakness of the limbs or muscle cramps
  - Bulbar lower motor neuron disease with fasciculations of the tongue, lips, or perioral region; dysarthria and difficulty swallowing
- No signs of upper motor neuron disease (e.g., hyperreflexia, spasticity)

Family history is consistent with X-linked inheritance (e.g., no male-to-male transmission). Absence of a known family history does not preclude the diagnosis.

Establishing the Diagnosis

The diagnosis of SBMA **is established** in a male proband by identification of a hemizygous expansion of a CAG trinucleotide repeat (>35 CAGs) in *AR* by molecular genetic testing (see Table 1).

Allele sizes. All individuals with SBMA have an expansion in the number of CAG trinucleotide repeats in exon 1 of *AR*.

- **Normal alleles.** 34 or fewer CAG trinucleotide repeats
- **Mutable normal alleles.** None reported to date
- **Reduced-penetrance alleles.** Kuhlenbäumer et al [2001] suggested that an allele of 37 CAG trinucleotide repeats can manifest reduced penetrance. Therefore, the clinical significance of alleles with 36-37 CAG repeats should be interpreted within the context of family history, the proband's clinical presentation, and genotype-phenotype correlations in other family members.
- **Full-penetrance alleles.** 38 or more CAG trinucleotide repeats
- **Alleles of questionable significance.** There is no consensus as to the clinical significance of alleles of 35 CAG repeats. Interpretation of alleles of this size may require consideration of the affected individual's clinical presentation and reconciliation with repeat sizes in family members.

Molecular genetic testing approaches include **targeted testing** for the CAG repeat size in *AR*.

Table 1. Molecular Genetic Testing Used in Spinal and Bulbar Muscular Atrophy

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
AR	Targeted analysis [3]	100%

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. CAG repeat number can be determined by fragment length analysis of amplicons from polymerase chain reaction (PCR) amplification of the CAG repeat region within AR.

Clinical Characteristics

Clinical Description

Spinal and bulbar muscular atrophy (SBMA) is a disorder of slowly progressive muscle weakness associated with mild androgen insensitivity.

Affected Males

Neurologic findings. Neurologic symptoms typically begin between age 30 and 50 years [Breza & Koutsis 2019]. Onset of neurologic symptoms does not usually occur in childhood or adolescence.

Early signs are difficulty with walking and a tendency to fall. Many individuals have muscle cramps, while others report an action tremor [Grunseich et al 2014b]. Deep tendon reflexes are decreased.

After one to two decades of symptoms, most affected individuals have difficulty climbing stairs. With time, atrophy of the proximal and distal musculature becomes evident. About one third of affected individuals require a wheelchair 20 years after the onset of symptoms.

Most individuals eventually show involvement of the bulbar muscles and have difficulty with speech articulation and swallowing. Severely affected individuals (many of whom are non-ambulatory) are at risk for aspiration pneumonia and ventilatory failure because of weakness of the bulbar and respiratory musculature [Hashizume et al 2017]. This complication is the main life-threatening issue in SBMA, and likely becomes a problem for only a minority of individuals. Therefore, the majority of individuals with SBMA have a normal life expectancy and do not die from direct complications of their motor neuron disease. Fifteen of 223 persons in one study died at a mean age of 65 years [Atsuta et al 2006].

Affected males may also have degeneration of the dorsal root ganglia, leading to mild-to-moderate abnormalities in sensory function in the distal extremities [Grunseich et al 2014b].

Cardiac and other systemic manifestations. Two reports have noted that some individuals with SBMA develop abnormal cardiac rhythms and may occasionally show hypertrophic cardiomyopathy-type changes [Araki et al 2014, Steinmetz et al 2022]. While the pathologic significance of these findings is unclear, there has also been a growing appreciation that most individuals with SBMA exhibit hyperlipidemia and insulin resistance, and that these metabolic changes often qualify such individuals for a diagnosis of nonalcoholic fatty liver disease [Rhodes et al 2009, Guber et al 2017, Francini-Pesenti et al 2018]. As hyperlipidemia and insulin resistance can predispose to coronary artery disease, there is growing concern that individuals with SBMA may be at elevated risk for myocardial infarction with aging, especially given a decline in physical activity and exercise as a result of ongoing neuromuscular disease. Hence, it is prudent to follow lipids, cholesterol, and blood sugars annually and refer individuals with SBMA to a cardiologist or endocrinologist for management of any metabolic or cardiac abnormalities.

Electrodiagnostic studies are consistent with diffuse denervation atrophy, anterior horn cell loss, and sensory neuronopathy [Jokela & Udd 2016].

Histopathology. Degeneration of anterior horn cells in the spinal cord of affected individuals is observed [Breza & Koutsis 2019]. Changes in muscle include evidence of myopathy [Katsuno et al 2012] in addition to neurogenic muscle atrophy. Immunohistochemistry shows inclusions of mutated androgen receptor protein [Adachi et al 2005].

Androgen insensitivity. Symptoms of androgen insensitivity typically begin in adolescence with gynecomastia, which is observed frequently in affected males [Breza & Koutsis 2019]. Variability in disease severity and progression occurs both within and between families [Finsterer 2009]. This is especially true of the androgen insensitivity signs of testicular atrophy and oligospermia/azoospermia with reduced fertility (see Androgen Insensitivity Syndrome). Males with SBMA may not be able to grow a thick beard and may have difficulty conceiving.

The androgen insensitivity can be of greater concern to affected individuals than the motor neuron disease, especially early in the course of the disorder [Fischbeck 2016].

Heterozygous Females

Neurologic findings. Females heterozygous for a full-penetrance allele of greater than 38 CAG repeats in *AR* are usually asymptomatic. While some heterozygous females experience muscle cramps or occasional tremors, heterozygous females usually do not have significant motor neuron disease [Breza & Koutsis 2019]. Females who are symptomatic may have an abnormal electromyography [Sobue et al 1993].

Androgen insensitivity. SBMA is a sex-limited disorder; females have low levels of circulating androgens, leading to lower levels of androgen receptor stimulation. As a result of X-chromosome inactivation, females have only a portion of actively transcribed full-penetrance alleles (CAG >37), but it is the low level of circulating androgen that likely accounts for limited-to-absent symptoms in heterozygous females or in females with biallelic full-penetrance *AR* alleles.

Genotype-Phenotype Correlations

Studies of the number of CAG repeats in *AR* alleles in males with SBMA have established a correlation between number of CAG repeats and disease severity. In general, CAG repeat number inversely correlates with the age of onset of muscle weakness, difficulty climbing stairs, and wheelchair dependence [La Spada et al 1992]. Thus, males with SBMA whose alleles have a larger number of CAG repeats tend to have earlier disease onset and more rapid progression [Doyu et al 1992, Igarashi et al 1992]. For example, early onset (age 8-15 years) and rapid progression have been described in a family in which affected individuals have alleles of 50-54 CAG repeats [Echaniz-Laguna et al 2005]. However, these correlations are only generalizations and exceptions have been reported. For example, while the average number of CAG repeats in affected males is 37, Kuhlenbäumer et al [2001] reported a male in a family with SBMA with *AR* alleles of 37 CAG repeats who was asymptomatic at age 46 years. The largest *AR* repeat expansion reported in a person with SBMA is 68 [Grunseich et al 2014a].

The genotype-phenotype correlation between allelic CAG repeat number and disease severity can only account for about 60% of the variability observed in clinical findings, indicating that other factors in addition to CAG repeat number determine age of disease onset and rate of disease progression. Indeed, relatives with SBMA with an identical CAG repeat number may have considerably different disease courses.

Nomenclature

SBMA has been called Kennedy's disease, named for the neurologist who published an early clinical description. In the past, SBMA has also been called X-linked spinal muscular atrophy.

Prevalence

SBMA has an estimated prevalence of 1:300,000 males. To date, SBMA has only been reported in individuals of European or Asian ethnic background; it has yet to be reported in individuals of African or Aboriginal racial background.

European populations in which SBMA has been observed include English, Belgian, French, Italian, German, Polish, Spanish, Swiss, Moroccan, and Turkish [La Spada et al 1991]. A founder effect has been reported in Scandinavia [Lund et al 2000].

Asian populations in which SBMA has been observed include Chinese, Japanese, Korean, and Vietnamese. SBMA is much more common in the Japanese population than in other population groups because of a founder effect [Tanaka et al 1996].

Genetically Related (Allelic) Disorders

Germline single-nucleotide variants in *AR* cause androgen insensitivity syndrome.

Differential Diagnosis

A number of hereditary and acquired neuromuscular disorders can produce gradually progressive muscle weakness.

The disorder with which spinal and bulbar muscular atrophy (SBMA) is most often confused is amyotrophic lateral sclerosis (ALS). Approximately one in 25 individuals diagnosed with ALS actually has SBMA [Parboosingh et al 1997]. Although occasionally individuals with SBMA are still misdiagnosed with ALS, the frequency of such misdiagnoses has decreased owing to greater familiarity with SBMA and better recognition of SBMA in the differential diagnosis of adult-onset motor neuron disease [Breza & Koutsis 2019]. Other disorders in the differential diagnosis of SBMA include adult-onset spinal muscular atrophy and Charcot-Marie-Tooth hereditary neuropathy (see Table 2).

Table 2. Genes of Interest in the Differential Diagnosis of Spinal and Bulbar Muscular Atrophy

Gene(s)	Disorder	MOI	Clinical Features	Comment
~30 genes [1] incl: *C9orf72* *SOD1* *FUS* *TARDBP*	Amyotrophic lateral sclerosis (ALS)	AD AR	Involves upper & lower motor neurons; upper motor neuron signs incl hyperreflexia & spasticity.	Differentiation of ALS from SBMA can usually be made based on history & physical exam. Persons w/ALS typically show involvement of wider range of muscle groups & more rapid disease progression. An important feature of SBMA is androgen insensitivity (often causing gynecomastia); thus, eval of males w/motor neuron disease should incl exam for gynecomastia. [2]
SMN1	Adult-onset spinal muscular atrophy (SMA IV) [3]	AR	Typically presents w/muscle weakness in 2nd or 3rd decade. Specific pattern of muscle involvement: weakness disproportionately affects deltoids, triceps, & quadriceps. Cardiac & cognitive functioning normal. If loss of ambulation occurs, may be after 5th decade.	Unlike SBMA, SMA IV is not assoc w/ gradual progression, gynecomastia, testicular atrophy, or ↓ fertility.

Table 2. continued from previous page.

Gene(s)	Disorder	MOI	Clinical Features	Comment
>80 genes incl: *GDAP1* *GJB1* *HINT1* *MFN2* *MPZ* *PMP22* *SH3TC2* *SORD*	Charcot-Marie-Tooth hereditary neuropathy (CMT)	AD AR XL	Prominent sensory findings in addition to muscle weakness	Persons w/CMT do not have lower motor neuron disease findings, esp tremors or fasciculations. Also, males w/CMT do not develop signs of androgen insensitivity.

AD = autosomal dominant; AR = autosomal recessive; MOI = mode of inheritance; SBMA = spinal and bulbar muscular atrophy; XL = X-linked

1. It is estimated that 10% of individuals with ALS have at least one family member with ALS. The identified ALS-related genes may account for at least half of ALS that occurs in families with a history of more than one affected individual. Thirty genes have been implicated in ALS; of these, *C9orf72*, *FUS*, *SOD1*, and *TARDBP* are the most commonly associated genes.

2. Breza & Koutsis [2019]

3. SMA IV is the least common form of SMA and affects fewer than 5% of individuals with SMA.

Muscle atrophy and muscle weakness from loss of motor neurons in the spinal cord are seen in other inherited neurodegenerative disorders including spinocerebellar ataxia type 3, Friedreich ataxia, Tay-Sachs disease (see *HEXA* Disorders), and the adrenomyeloneuropathy variant of X-linked adrenoleukodystrophy; however, these disorders are quite different from SBMA.

Non-genetic causes for motor neuron disease include structural lesions (e.g., spinal cord arteriovenous malformations), infections (especially poliomyelitis), toxins (chronic lead poisoning), metabolic issues (thyrotoxicosis), and paraneoplastic syndromes. Individuals with SBMA have been misdiagnosed as having chronic inflammatory neuropathy, metabolic myopathy, polymyositis, and myasthenia gravis.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs of an individual diagnosed with spinal and bulbar muscular atrophy (SBMA), the evaluations summarized in Table 3 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 3. Recommended Evaluations Following Initial Diagnosis in Individuals with Spinal and Bulbar Muscular Atrophy

System/Concern	Evaluation	Comment
Neurologic	Complete neurologic exam	Assess: • UMN involvement: spasticity, Babinski signs, hyperreflexia; • LMN involvement: weakness, amyotrophy, fasciculations, EMG.

Table 3. continued from previous page.

System/Concern	Evaluation	Comment
Musculoskeletal/ ADL	Orthopedics / physical medicine & rehab / PT eval	To incl assessment of: • Muscle tone, joint range of motion, posture, mobility, strength, coordination & endurance, pain, bedsores • Need for adaptive devices • Footwear needs • PT needs • Need for assistive walking devices (e.g., canes, walker, walker w/wheels, walker w/seat, wheelchairs)
	OT	Assess: • Fine motor function (e.g., hands, feet, face, fingers, toes); • Home adaptations for ADL & safety.
Dysarthria	For those w/dysarthria: speech/language eval	Referral for speech therapy as needed
Dysphagia	For those w/frequent choking or severe dysphagia, assess nutritional status & aspiration risk.	Consider involving a gastroenterology/nutrition/feeding team, incl formal swallowing eval.
Respiratory function	By pulmonologist	Assess respiratory function & need for respiratory support.
Endocrine	• Androgen responsiveness: male-pattern hair growth, testicular size, & fertility • Assess for gynecomastia.	Consider mastectomy if gynecomastia presents in teenage years or young adult years causing psychosocial stress to self-image / gender identity.
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of SBMA to facilitate medical & personal decision making

ADL = activities of daily living; EMG = electromyography; LMN = lower motor neuron; MOI = mode of inheritance; OT = occupational therapy; PT = physical therapy; SBMA = spinal and bulbar muscular atrophy; UMN = upper motor neuron
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Supportive care to improve quality of life, maximize function, and reduce complications is recommended. This ideally involves multidisciplinary care by specialists in relevant fields (see Table 4).

Table 4. Treatment of Manifestations in Individuals with Spinal and Bulbar Muscular Atrophy

Manifestation/Concern	Treatment	Considerations/Other
UMN & LMN involvement / ADL	Physical medicine & rehab / PT & OT	Ankle-foot braces, walkers, wheelchairs, hospital beds, toileting equipment, lifts to improve functionality
Dysarthria	Speech/language therapy	Use of augmentative communication devices
Dysphagia	Feeding eval & therapy	• Safe swallowing techniques, diet modifications, education re cutting food into small pieces for eating & avoiding items that may be difficult to chew & swallow • Gastrostomy tube as needed
Gynecomastia	Breast reduction surgery as needed	
Cardiac & other manifestations	Standard treatment per cardiologist &/or endocrinologist	Monitor blood sugar, lipids, & cholesterol for insulin resistance & nonalcoholic fatty liver disease.

Table 4. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Family/caregiver support & resources	Psychosocial support & education via caregiver & patient support groups	To ↓ stress & burden on caregivers

ADL = activities of daily living; LMN = lower motor neuron; OT = occupational therapy; PT = physical therapy; UMN = upper motor neuron

Surveillance

To monitor existing manifestations, the individual's response to supportive care, and the emergence of new manifestations, the evaluations in Table 5 are recommended.

Table 5. Recommended Surveillance for Individuals with Spinal and Bulbar Muscular Atrophy

System/Concern	Evaluation	Frequency
Mobility/ADL	• Strength assessment • Physical medicine & rehab / PT & OT assessments	Annually or as needed
Dysarthria	Speech/language therapy	
Dysphagia	Feeding eval	
Respiratory function	Pulmonary function tests	Annually in those w/advanced disease
Cardiac manifestations	• Cholesterol & triglycerides • Hepatic function testing in those w/↑ cholesterol &/or triglycerides • Any additional assessment of cardiac health per cardiologist	Annually
Family/caregiver support & resources	Assess need for additional support.	Annually or as needed

ADL = activities of daily living; OT = occupational therapy; PT = physical therapy

Agents/Circumstances to Avoid

Individuals with a tendency to fall should avoid slippery or rough walking surfaces.

Evaluation of Relatives at Risk

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

Therapies Under Investigation

High-dose testosterone. At least one clinical trial of high-dose oral testosterone has been undertaken; no significant benefit was reported for the androgen treatment group [Goldenberg & Bradley 1996]. Based on research in *Drosophila* and mouse models of SBMA, many investigators believe that androgen treatment may be harmful.

Anti-androgen therapy. There is no consensus or clear evidence as to whether anti-androgen therapy is an effective form of treatment for the neurologic complications.

- Anti-androgen therapy shows promise based on studies in *Drosophila* and mouse models as well as knowledge of the molecular basis of SBMA. For these reasons, Banno et al [2009] performed a clinical trial of leuprorelin in individuals with SBMA, who were followed over 48 weeks. Significant improvement was observed in cricopharyngeal opening duration but in no other outcome measures. In particular, there was no effect on the primary outcome measure, the ALS Functional Rating Scale (ALSFRS), in the period of randomization. Although the trial was continued as an open-label extension, and encouraging results were

reported, the conclusion was that this clinical trial did not establish efficacy for anti-androgen therapy in SBMA [Fischbeck & Bryan 2009].

- A larger subsequent study in Japan with swallow function as the primary outcome measure also did not show an overall benefit, except in post hoc analysis of subjects in whom disease duration was less than ten years [Katsuno et al 2010]. Because leuprorelin was efficacious as a treatment for dysphagia in this clinical trial, it has been approved as a treatment for individuals with SBMA in Japan but not elsewhere.
- In another anti-androgen therapy study [Fernández-Rhodes et al 2011], individuals with SBMA were randomized to placebo or dutasteride, a drug that blocks the conversion of testosterone to dihydrotestosterone (DHT). The rationale was that DHT may mediate many of the toxic effects, and this drug would permit affected individuals to retain the anabolic effects of testosterone, thereby diminishing the side effects of anti-androgen therapy. However, the study did not show a significant effect of dutasteride on the progression of muscle weakness in SBMA.

Hence, the utility of anti-androgen therapy as a treatment for SBMA remains controversial. Furthermore, it is possible that anti-androgen therapies, even if effective, would need to be administered prior to disease onset or early on in the neurodegenerative process. More importantly, the side effects of anti-androgen therapies would probably far outweigh the therapeutic benefit for most individuals, and likely should be reserved for people with SBMA who are wheelchair bound or exhibit pronounced bulbar weakness.

Creatine supplementation. Studies of amyotrophic lateral sclerosis (ALS) suggest that creatine supplementation may temporarily enhance muscle strength and exercise performance in this motor neuron disease [Mazzini et al 2001], prompting speculation that it may offer a similar benefit to individuals with SBMA; this hypothesis remains to be tested.

AJ201. AnnJi Pharmaceuticals intends to move forward with a Phase II clinical trial of AJ201, a small molecule capable of inducing Nrf1, Nrf2, and possibly Hsf1, based on encouraging results obtained in preclinical trails performed in SBMA model mice [Bott et al 2016] and acceptable safety/toxicity testing in a Phase I clinical trial. Recruitment for the Phase II clinical trial will begin in 2023.

Experimental therapies in animal models

- Other interventions shown to have benefit in mouse models of SBMA include the HSP-90 inhibitors 17-AAG and 17-DMAG, the synthetic curcumin derivative ASC-J9, and insulin-like growth factor 1 (reviewed in Fischbeck [2012]).
- Cortes et al [2014] directly examined the role of muscle expression of mutated androgen receptor (AR) in SBMA disease pathogenesis by developing a BAC transgenic mouse model featuring a floxed first exon to permit cell type-specific excision of a human *AR* transgene. They engineered the human *AR* transgene to carry 121 CAG repeats (BAC fxAR121), and found that BAC fxAR121 mice develop a male sex-restricted progressive neuromuscular phenotype characterized by weight loss, motor deficits, muscle atrophy, myopathy, and shortened life span. By terminating expression of mutated AR in the skeletal muscles of BAC fxAR121 male mice, this study revealed a crucial role for muscle expression of mutated AR in SBMA disease pathogenesis. Hence, this work predicts that muscle-directed therapies hold great promise as definitive treatments for SBMA motor neuron degeneration.
- Another study sought to ameliorate toxicity in mouse models of SBMA by suppressing polyQ-AR expression using antisense oligonucleotides (ASOs) [Lieberman et al 2014]. This investigation developed compounds to specifically target *AR* expression in the periphery and, using two mouse models, found that peripheral gene suppression of mutated AR rescues deficits in muscle weight, fiber size, and grip strength; reverses changes in muscle gene expression; and extends the life span of mutated males. Interestingly, delivery of an anti-AR ASO to the central nervous system also elicited a modest improvement in these disease readouts in an SBMA mouse model but was much less effective than peripheral delivery. Hence, this report, together with the genetic rescue study of SBMA [Cortes et al 2014], strongly suggests that

peripheral administration of therapies directed to muscle should be explored in humans with SBMA. There is interest in pursuing a clinical trial of anti-AR ASO therapy via peripheral delivery in SBMA, but this is not yet being planned.

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

Other

Administration of male hormones (testosterone and its analogs) is not effective in overcoming the androgen insensitivity.

Genetic Counseling

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

Mode of Inheritance

Spinal and bulbar muscular atrophy (SBMA) is inherited in an X-linked manner.

Risk to Family Members

Parents of a male proband

- The father of an affected male will not have the disorder, nor will he be hemizygous for a CAG trinucleotide repeat expansion in *AR*; therefore, he does not require further evaluation/testing.
- To date, all mothers of affected males who have undergone molecular genetic testing have been shown to be heterozygous for a CAG trinucleotide repeat expansion.
- In a family with more than one affected individual, the mother of an affected male is an obligate heterozygote (carrier). Note: If a woman has more than one affected child and no other affected relatives and if the CAG trinucleotide repeat expansion cannot be detected in her leukocyte DNA, she most likely has germline mosaicism.
- If a male is the only affected family member (i.e., a simplex case), the mother may be a heterozygote (carrier) or, theoretically, the affected male may have a *de novo* CAG trinucleotide repeat expansion (in which case the mother is not a carrier) or the mother may have somatic/germline mosaicism.

  The true incidence of *de novo* CAG trinucleotide repeat expansion in males with SBMA is not presently known; no *de novo* expansions have been reported thus far.
- Molecular genetic testing of the mother is recommended to confirm her genetic status and to allow reliable recurrence risk assessment. (Note: Because SBMA is a late-onset disorder, mothers may not always be available for testing.)

Sibs of a male proband. The risk to sibs depends on the genetic status of the mother.

- If the mother of the proband has a CAG trinucleotide repeat expansion, the chance of transmitting it in each pregnancy is 50%.
- Males who inherit:

  - An expansion of 38 or more CAG trinucleotide repeats will be affected;
  - A CAG trinucleotide repeat expansion in the reduced-penetrance range are at risk for SBMA. (The clinical significance of alleles with 36-37 CAG repeats should be interpreted within the context of family history and genotype-phenotype correlations in other family members; see Establishing the Diagnosis.)
- Intrafamilial clinical variability is observed in SBMA; affected male family members with identical CAG repeat numbers may have considerably different disease courses (see Genotype-Phenotype Correlations).
- Females who inherit a full-penetrance allele of 38 or more CAG repeats are usually asymptomatic or may have mild symptoms (see Clinical Description, Heterozygous Females).

Offspring of a male proband

- Affected males who are fertile transmit the CAG trinucleotide repeat expansion to all of their daughters (who will be heterozygotes and will usually not be affected) and none of their sons.
- Repeat instability with male transmission of a CAG trinucleotide repeat expansion has been described (see Related Genetic Counseling Issues, **CAG repeat instability**).

Other family members. The proband's maternal aunts may be at risk of being heterozygotes (carriers) for the CAG trinucleotide expansion, and the aunt's offspring, depending on their sex, may be at risk of being carriers or of being affected.

Heterozygote (Carrier) Detection

Identification of female heterozygotes requires prior identification of the *AR* CAG trinucleotide repeat expansion in an affected family member.

Note: Females who are heterozygous (carriers) for this X-linked disorder will usually not be affected.

Related Genetic Counseling Issues

CAG repeat instability. Pathogenic *AR* alleles with abnormally large numbers of CAG repeats have the property of genetic instability, meaning that the number of CAG repeats often changes when transmitted from parent to offspring. In SBMA, a slight tendency toward expansion (an increase in number) of CAG repeats exists, although the number of CAG repeats is relatively stable, with only small increases in repeat length and frequent small decreases in repeat number (i.e., contractions). Repeat instability with male transmission of a pathogenic allele has been described. Although a correlation exists between CAG repeat number and disease onset and severity in individuals with SBMA, prediction of disease course **cannot** be based on measured CAG repeat number.

Predictive testing (i.e., testing of asymptomatic at-risk individuals)

- Predictive testing for at-risk relatives is possible once the *AR* CAG trinucleotide expansion has been identified in an affected family member. Such testing is not useful in accurately predicting age of onset, severity, type of symptoms, or rate of disease progression in asymptomatic individuals.
- Potential consequences of such testing (including but not limited to socioeconomic changes and the need for long-term follow up and evaluation arrangements for individuals with a positive test result) as well as the capabilities and limitations of predictive testing should be discussed in the context of formal genetic counseling prior to testing.

Predictive testing in minors (i.e., testing of asymptomatic at-risk individuals age <18 years)

- For asymptomatic minors at risk for adult-onset conditions for which early treatment would have no beneficial effect on disease morbidity and mortality, predictive genetic testing is considered inappropriate, primarily because it negates the autonomy of the child with no compelling benefit. Further, concern exists

regarding the potential unhealthy adverse effects that such information may have on family dynamics, the risk of discrimination and stigmatization in the future, and the anxiety that such information may cause.
- For more information, see the National Society of Genetic Counselors position statement on genetic testing of minors for adult-onset conditions and the American Academy of Pediatrics and American College of Medical Genetics and Genomics policy statement: ethical and policy issues in genetic testing and screening of children.

In a family with an established diagnosis of SBMA, it is appropriate to consider testing of symptomatic individuals regardless of age.

Family planning

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

Prenatal Testing and Preimplantation Genetic Testing

Once an *AR* CAG trinucleotide repeat expansion has been identified in an affected family member, prenatal and preimplantation genetic testing for SBMA are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful. For more information, see the National Society of Genetic Counselors position statement on prenatal testing in adult-onset conditions.

Resources

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

- **Kennedy's Disease Association**
  Phone: 855-532-7762
  www.kennedysdisease.org
- **MedlinePlus**
  Spinal and bulbar muscular atrophy
- **Muscular Dystrophy Association (MDA) - USA**
  Phone: 833-275-6321
  Email: ResourceCenter@mdausa.org
  mda.org

Molecular Genetics

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

Table A. Spinal and Bulbar Muscular Atrophy: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar

Table A. continued from previous page.

AR	Xq12	Androgen receptor	AR @ LOVD alsod/AR genetic mutations The Androgen Receptor Gene Mutations Database	AR	AR

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

Table B. OMIM Entries for Spinal and Bulbar Muscular Atrophy (View All in OMIM)

313200	SPINAL AND BULBAR MUSCULAR ATROPHY, X-LINKED 1; SMAX1
313700	ANDROGEN RECEPTOR; AR

Molecular Pathogenesis

AR encodes a member of the steroid receptor superfamily. The androgen receptor (AR) protein is expressed in the brain, spinal cord, and muscle [Matsuura et al 1993, Ogata et al 1994]. A highly polymorphic CAG repeat starting at amino acid codon number 58 is found within the AR coding domain. Unaffected individuals have five to 34 CAG trinucleotide repeats; some may have reduced-penetrance alleles with 36-37 repeats. Expansion beyond the normal range of CAG trinucleotide repeats within the coding region of *AR* causes spinal and bulbar muscular atrophy (SBMA) [La Spada et al 1991]. CAG expansions produce an AR protein with an abnormally long polyglutamine stretch at the N-terminal end [La Spada et al 1991]. A model for how polyglutamine tract expansion in the AR protein leads to neurodegeneration in SBMA has been established over the course of the last three decades. The AR protein is in complex with co-actors and chaperones in the cytosol, and upon binding to its ligand testosterone (or metabolites thereof), the AR protein enters the nucleus, where it functions as a transcription factor. Heterozygous females do not display fulminant motor neuron disease because of their low levels of circulating testosterone, thereby preventing nuclear entry of mutated AR protein. Polyglutamine-expanded AR protein misfolds and interferes with transcription regulation. Once in the nucleus, polyglutamine-expanded AR protein may cause pathology by interfering with transcriptional coactivators such as the CREB-binding protein [McCampbell et al 2000, Sopher et al 2004].

In addition to gain-of-function polyglutamine proteotoxicity, recent research work has focused on the role of altered normal function in dictating cell type specificity in SBMA, and this work suggests that altered protein complex interactions between the AR protein and its coactivators and corepressors may underlie disease pathogenesis [Nedelsky et al 2010]. The polyglutamine tract region is also proteolytically processed and a polyglutamine-containing peptide fragment is retained in the nucleus, where it forms neuronal intranuclear inclusions (NIIs) [Young et al 2009]. NIIs have been found in spinal cord and skeletal muscle sections from deceased individuals with SBMA [Li et al 1998]. The expression of mutated AR protein in skeletal muscle appears to be a major driver of the disease process, based on the presence of myopathy in individuals with SBMA and experiments in SBMA mouse models [Cortes et al 2014].

Genetic testing of sperm of an affected male showed that 20% of the sperm had a CAG repeat number equal to that in the DNA from somatic cells, whereas 56% had further expansion of the CAG repeat number, and 24% had contraction of the CAG repeat number. Most of the allelic expansions and contractions were between one and three CAG repeats. Similar studies on oocytes have not been possible.

Mechanism of disease causation. The expanded polyglutamine tract presumably alters the conformation of the AR protein (or an N-terminal peptide fragment from the AR protein) resulting in neurodegeneration in SBMA via a gain-of-function mechanism.

***AR*-specific laboratory technical considerations.** About 98% of females have *AR* alleles with different numbers of CAG repeats on their two X chromosomes. The high degree of heterozygosity in females makes the *AR* CAG repeat a useful marker for studying X-chromosome inactivation. The most common alleles number from 18 to 25 CAG repeats. Variation in mean CAG repeat length occurs within different racial populations, with Africans having the smallest mean CAG repeat length and Asians having the largest mean CAG repeat length; the CAG repeat length in white European populations is intermediate to these two.

Table 6. Notable *AR* Variants

Reference Sequences	Variant Classification	DNA Nucleotide Change	Predicted Protein Change
NM_000044.3 NP_000035.2	**Benign**	c.172_174CAG(7_34) (CAG ?-34 repeats)	See footnote 1.
	Unknown	c.172_174CAG(35) (CAG 35 repeats)	
	Reduced-penetrance allele	c.172_174CAG(36_37) (CAG 36-37 repeats)	
	Pathogenic	c.172_174CAG(38_68) (CAG 38-? repeats)	

Variants listed in the table have been provided by the author. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
1. Each CAG repeat results in the addition of a glutamine residue to the polymorphic polyglutamine repeat.

Cancer and benign tumors. Dozens of epidemiologic and genetic association studies have examined a potential inverse relationship between *AR* CAG repeat length and the risk of developing prostate cancer. In 2013, a meta-analysis of published data up to that time concluded that "a shorter CAG repeat polymorphism may increase the risk of prostate cancer compared with the longer CAG repeat; in particular, the effect of shorter CAG repeats on the increased risk of prostate cancer was predominantly observed in Caucasians and Asians" [Sun & Lee 2013].

Chapter Notes

Author Notes

Dr La Spada is a Distinguished Professor at UC Irvine , where he maintains a research program focused on neurodegenerative proteinopathies. Spinal and bulbar muscular atrophy (SBMA) remains a major focus of his research efforts.

Acknowledgments

Dr La Spada's SBMA research is supported by a R35 award (NS122140) from the NINDS at the National Institutes of Health.

Revision History

- 15 December 2022 (sw) Comprehensive update posted live
- 26 January 2017 (ma) Comprehensive update posted live
- 3 July 2014 (me) Comprehensive update posted live
- 13 October 2011 (me) Comprehensive update posted live
- 28 December 2006 (me) Comprehensive update posted live
- 1 July 2004 (me) Comprehensive update posted live
- 29 August 2002 (me) Comprehensive update posted live

- 26 February 1999 (pb) Review posted live
- 15 December 1998 (als) Original submission

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- Committee on Bioethics, Committee on Genetics, and American College of Medical Genetics and Genomics Social, Ethical, Legal Issues Committee. Ethical and policy issues in genetic testing and screening of children. Available online. 2013. Accessed 12-6-22.
- National Society of Genetic Counselors. Position statement on genetic testing of minors for adult-onset conditions. Available online. 2019. Accessed 12-6-22.

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