Spinal-Bulbar Muscular Atrophy (SBMA): Updates in Diagnosis, Management, and Research

A Resource for Clinicians

Background

- SBMA, also known as Kennedy disease, is an X-linked inherited motor neuron disease.
- The diagnostic odyssey can last several years for people with SBMA.
- Clinical management involves symptom management and multi-disciplinary care; best-practicing sharing can help optimize care.
- This document captures highlights from an MDA webinar with a SBMA expert.
- View the companion webinar here.

Overview

Description[1,2]

- Affects males (androgen-dependent)
- Caused by a CAG repeat expansion in exon 1 of the androgen receptor gene
  - Occurs when it **exceeds 37 repeats**
- Characterized by slowly progressive lower motor neuron loss, muscle weakness, and other non-neuromuscular symptoms

Epidemiology[2,3]

- Prevalence: 1 in 40,000
- Reported in as many as 1 in 7,000 males

Onset and Prognosis[1,4]

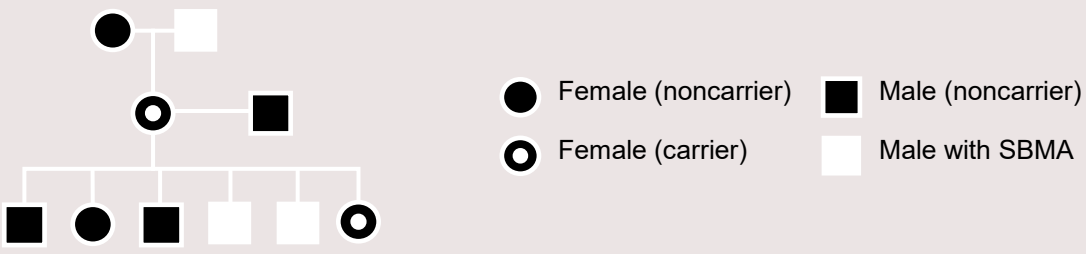
- Age of onset: mid-40s
- Disease progresses slowly (~2% decline per year)
  - Patients may become wheelchair-dependent 20-30 years after onset
- Majority of patients have normal life expectancy

CAG, cytosine-adenine-guanine.
1. Rhodes LE, et al. *Brain.* 2009:132;3242-3251. 2. Zanovello M, et al. *Brain*. 2023:146(7);2723-2729. 3. Grunseich C, et al. *Oral Dis*. 2014;20(1):6-9. 4. Arnold FJ, Merry DE. *Neurotherapeutics*. 2019;16(4):928-947.

Genetic Etiology

SBMA is caused by a CAG repeat expansion in exon 1 of the androgen receptor (AR) gene and is inherited in an X-linked recessive pattern

SBMA inheritance pattern[1]



AR, androgen receptor; CAG, cytosine-adenine-guanine; SBMA, spinal-bulbar muscular atrophy. 1. La Spada A. Spinal and bulbar muscular atrophy. In: *GeneReviews® [Internet]*. Seattle, WA: University of Washington, Seattle; 1993-2024.

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Clinical Manifestations

Neuromuscular dysfunctions[1,2]

- Loss of lower motor neurons from brainstem and spinal cord
- Proximal + distal muscle atrophy and weakness

Other manifestations[1]

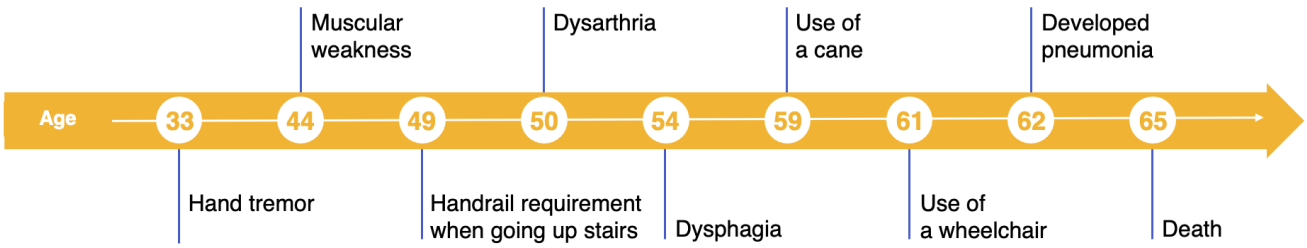
- Androgen insensitivity (gynecomastia, infertility, testicular atrophy)
- Elevated CK
- Altered metabolism (nonalcoholic fatty liver disease, insulin resistance, cholesterol, and triglycerides)
- Sensory neuropathy
- Brugada syndrome

CK, creatine kinase.
1. Arnold FJ, Merry DE. *Neurotherapeutics*. 2019;16(4):928-947. 2. Grunseich C, et al. *Oral Dis*. 2014;20(1):6-9.

Slow Disease Progression

Age distribution of ADL milestones (median)[1]

Based on 223 patients with SBMA and a mean of 46.6 CAG repeats (range 40-57)



SBMA progresses slowly, with a **2% decrease in muscle strength per year[2]**

ADL, activities of daily living; CAG, cytosine-adenine-guanine; SBMA, spinal-bulbar muscular atrophy.
1. Atsuta N, et al. *Brain.* 2006;129:446-1455. 2. Rhodes LE, et al. *Brain.* 2009;132:3242-3251.

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Diagnosis of SBMA

Diagnostic odyssey can last **several years**

- Importance of family history and presentation examination

Involvement of a **genetic counselor** should be considered

- Elevated CK (~2-5x >ULN)
- Evidence of denervation on EMG/NCS
- Genetic testing (blood or saliva)

  >37 CAG repeats in androgen receptor gene

CAG, cytosine-adenine-guanine; CK, creatine kinase; EMG, electromyogram; NCS, nerve conduction study; SBMA, spinal-bulbar muscular atrophy; ULN, upper limit of normal. 1. Grunseich C, zet al. *Oral Dis*. 2014;20(1):6-9.

Multidisciplinary Team

SPEECH THERAPIST[1,2]
- Preserve oral communication

NEUROLOGIST[1,2]
- Establish diagnosis
- Ensure coordination of care

DIETICIAN[1,2]
- Advice on dietary adaptation to bulbar function
- Food supplements
- Formal swallowing evaluation

PHYSICAL THERAPIST[1,2]
- Support adapted exercise
- Prevent painful musculoskeletal complications of poor mobility

OCCUPATIONAL THERAPIST[1,2]
- Support necessary adaptation to physical disability (provide adapted environment and assistive device)

PULMONOLOGIST[1,2]
- Monitor respiratory function and prevent infections
- Evaluate need for respiratory support (cough assist/ noninvasive ventilation)

SOCIAL WORKER[1]
- Educate patients on genetic risks and financial resources available

ENDOCRINOLOGIST[1,2]
- Monitor metabolic parameters, including cholesterol and insulin resistance

PSYCHOLOGIST[1]
- Provide psychological support to patients and caregivers

CARDIOLOGIST[1]
- Monitor cardiac function and arrhythmias (Brugada syndrome)

1. Pradat PF, et al. *Orphanet J Rare Dis*. 2020;15(1):90. 2. La Spada A. Spinal and bulbar muscular atrophy. In: *GeneReviews® [Internet]*. Seattle, WA: University of Washington, Seattle; 1993-2024.

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SBMA Research

No effective or disease-modifying treatments are currently available

AKT, protein kinase B; AR, androgen receptor; ASO, antisense oligonucleotide; BDNF, brain-derived neurotrophic factor; DHT, dihydrotestosterone; IGF1, insulin-like growth factor 1; PACAP, pituitary adenylate-cyclase-activating polypeptide; PI3K, phosphatidylinositol-3-kinase; SBMA, spinal-bulbar muscular atrophy; UPS, ubiquitin-proteasome system
Marchioretti C, et al. *Curr Opin Pharmacol.* 2023;71:102394.

Pathogenetic pathways and therapeutic targets in SBMA

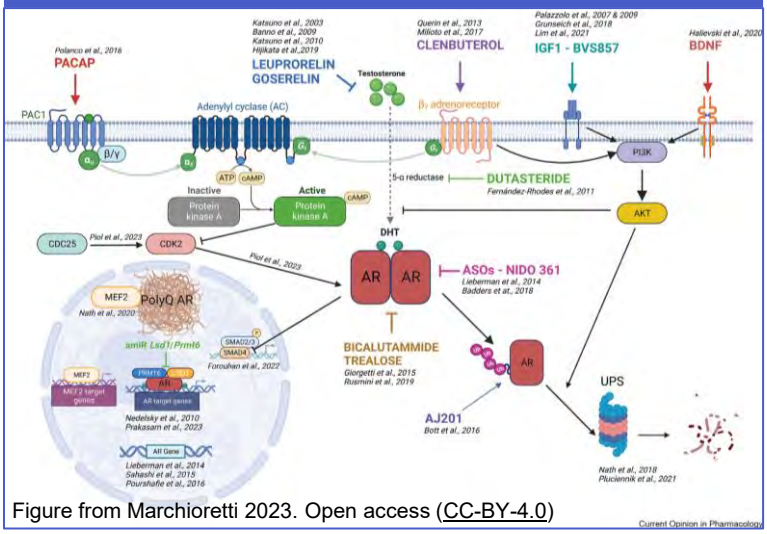

Figure from Marchioretti 2023. Open access (CC-BY-4.0)

Therapies for SBMA in Pipeline

	PRECLINICAL	PHASE 1/2	PHASE 3
AJ201 activation of Nrf2 (US)		Phase 1/2a randomized, double-blind study to evaluate safety, tolerability, pharmacokinetics, and pharmacodynamics of AJ201 in patients with SBMA (NCT05517603)[1,2]	
Clenbuterol Beta-2 agonist (Italy)		Phase 2 placebo-controlled study of clenbuterol in patients with SBMA (BetaSBMA - NCT06169046)[3]	
NIDO-361 Androgen receptor allosteric modulator (Denmark, Italy, Republic of Korea, UK)		Phase 2 randomized, double-blind, placebo-controlled study of NIDO-361 in patients with SBMA (PIONEER KD - NCT06411912)[4,5]	

Nrf2, nuclear factor erythroid 2-related factor 2; SBMA, spinal-bulbar muscular atrophy. 1. Product pipeline. AnnJi Pharmaceuticals website. https://www.ajpharm.com/product-pipeline/. 2. A study to evaluate safety, tolerability, pharmacokinetics, and pharmacodynamics of AJ201 in patients. ClinicalTrials.gov website. https://clinicaltrials.gov/study/NCT05517603. 3. A placebo-controlled study of clenbuterol in spinal and bulbar muscular atrophy (BetaSBMA). ClinicalTrial.gov website. https://clinicaltrials.gov/study/NCT06169046. 4. Pushing the boundaries of neuroscience. NIDO Biosciences website. https://nidobio.com/. 5. A Study of NIDO-361 in Patients With SBMA (PIONEER KD). ClinicalTrial.gov website. https://clinicaltrials.gov/study/NCT06411912.

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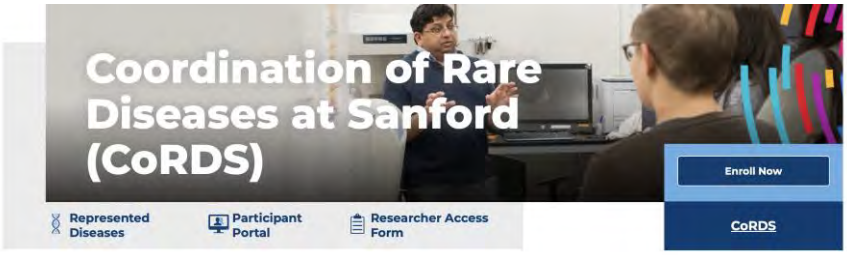
SBMA Patient Registry



https://research.sanfordhealth.org/rare-disease-registry

- Help to facilitate enrollment into future clinical studies
- Planning and design of future clinical studies
- Information shared with qualified research teams

Image from Sanford Research. https://research.sanfordhealth.org/rare-disease-registry

SBMA Clinical Resources

Clinical Management


Pradat et al. Orphanet Journal of Rare Diseases (2020) 15:90
https://doi.org/10.1186/s13023-020-01366-z

Orphanet Journal of Rare Diseases

RESEARCH Open Access

The French national protocol for Kennedy's disease (SBMA): consensus diagnostic and management recommendations

Pierre-François Pradat[1*], Emilien Bernard[2], Philippe Corcia[3], Philippe Couratier[4], Christel Jublanc[5], Giorgia Querin[1], Capucine Morélot Panzini[6,7], François Salachas[8], Christophe Vial[9], Karim Wahbi[10], Peter Bede[1,11], Claude Desnuelle[12] and on behalf of the French Kennedy's Disease Writing Group

Pradat, PF., *et al. Orphanet J Rare Dis* 2020;15:90. https://doi.org/10.1186/s13023-020-01366-z

Associations

Kennedy's Disease Association

https://kennedysdisease.org/welcome.html

MDA Muscular Dystrophy Association

www.mda.org/disease/spinal-bulbar-muscular-atrophy

Access companion MDA webinar here

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