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Spinocerebellar Ataxia Type 20

Synonym: SCA20

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Summary

Clinical characteristics

Spinocerebellar ataxia type 20 (SCA20) is characterized by a slowly progressive ataxia and dysarthria. Approximately two thirds of those affected also display palatal tremor ("myoclonus") and/or abnormal phonation clinically resembling spasmodic adductor dysphonia. Dysarthria, which may be abrupt in onset, precedes the onset of ataxia in about two thirds of affected individuals, sometimes by a number of years. Hypermetric horizontal saccades (without nystagmus or disturbance of vestibulo-ocular reflex gain) are seen in about half of affected persons. Although minor pyramidal signs (brisk knee jerks, crossed adductor spread) may be seen, spasticity and extensor plantar responses are not. Cognition is normal. Clinical information is based on the findings in 16 personally examined affected members of a single Australian family of Anglo-Celtic descent.

Diagnosis/testing

The diagnosis of SCA20 is based on clinical findings and neuroimaging. Within five years of disease onset CT scan shows pronounced dentate calcification, typically without concomitant pallidal calcification. In addition to evidence of dentate calcification, MRI shows mild-to-moderate pan cerebellar atrophy and normal cerebrum and brain stem (except for increased inferior olivary T_2 signal in those with palatal tremor). The locus for SCA20 lies within the pericentromeric region of chromosome 11; the gene is unknown. A 260-kb duplication of 11q12.2-11q12.3 has been proposed as the probable cause of SCA20 in the index family.

Management

Treatment of manifestations: Physical and occupational therapy; guidance from a speech pathologist expert in the management of neurogenic dysphagia.

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Prevention of secondary complications: Prevention of falls by using appropriate gait aids and home modifications; personal alarm system.

Genetic counseling

SCA20 is inherited in an autosomal dominant manner. Each child of an affected individual has a 50% chance of inheriting the pathogenic variant.

Diagnosis

Suggestive Findings

Spinocerebellar ataxia type 20 (SCA20) **should be considered** in individuals with a slowly progressive ataxia without sensory features who have the following findings:

- Onset with dysarthria (rather than with gait ataxia) that may be abrupt in onset (seen in ~66%)
- Palatal tremor (in ~66%)
- Family history consistent with autosomal dominant inheritance

Additional findings may include the following:

- Hypermetric horizontal saccades (without nystagmus or disturbance of vestibuloocular reflex gain) in about half
- Mild hyperreflexia (typically without spasticity or extensor plantar responses) in a minority
- Postural tremor of arms with or without involvement of the head (seen in a minority; may be the first symptom)

Neuroimaging

- CT scan (Figure 1) shows pronounced dentate calcification, typically without concomitant pallidal calcification, at an early stage of the illness (≤3 years from onset).
- MRI (Figure 2) shows mild-to-moderate pan cerebellar atrophy, with low dentate signal on T_1- and T_2-weighted sequences (consistent with calcification) and normal cerebrum and brain stem (apart from increased inferior olivary T_2 signal in some, as a correlate of palatal tremor).

Neurophysiology. Nerve conduction studies are normal.

Laboratory features. Indices of calcium metabolism (serum concentrations of calcium, phosphate, magnesium, alkaline phosphatase, parathyroid hormone, 25-hydroxy vitamin D) are normal.

Establishing the Diagnosis

The diagnosis of SCA20 **is established** in a proband with the above Suggestive Findings and the following characteristic radiographic features:

- **Brain CT.** Pronounced dentate calcification, typically without concomitant pallidal calcification
- **Brain MRI.** Mild-to-moderate pan cerebellar atrophy and normal cerebrum and brain stem (except for increased inferior olivary T_2 signal in those with palatal tremor)

Note: The candidate region for SCA20 lies within the pericentromeric region of chromosome 11, encompassing chr11:44,045,910-69,634,192 (loci D11S903-FGF3). Although the candidate region includes *SPTBN2* (pathogenic variants in which are responsible for SCA5), *SPTBN2* pathogenic variants were excluded as the cause of SCA20 [Lorenzo et al 2006]. Knight et al [2008] reported a 260-kb heterozygous duplication within the candidate region, at 11q12.2-11q12.3 (chr11:61,453,940-61,746,019), cosegregating with SCA20 in the index

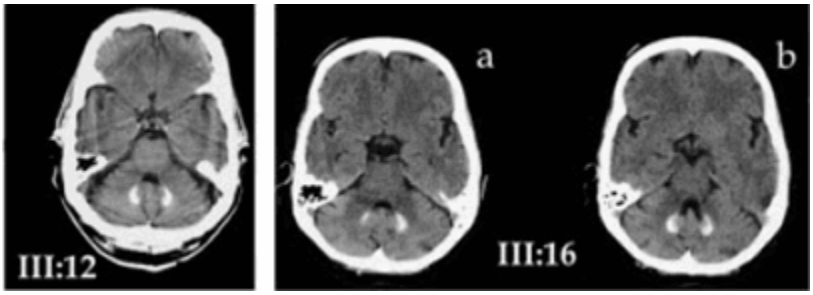

Figure 1. III:12. CT scan showing heavy dentate calcification and pan cerebellar atrophy in an individual age 62 years with mild ataxia, three years after symptom onset

III:16. CT scan slices at two levels of the dentate showing heavy dentate calcification and mild cerebellar atrophy in an individual age 56 years with very mild ataxia; one year after symptom onset

Note: Roman:arabic numeral combinations refer to pedigree numbers in Knight et al [2004].

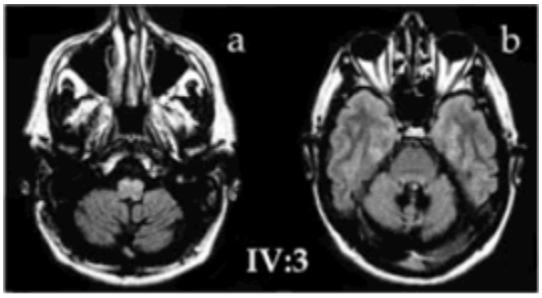

Figure 2. MRI axial proton density images showing (a) inferior olivary hypertrophy and (b) low dentate signal consistent with dentate calcification in an individual age 54 years; 16 years after onset

Note: Roman:arabic numeral combinations refer to pedigree numbers in Knight et al [2004].

family. It remains unknown whether this cosegregating duplication contains a locus or loci that are pathogenic in the duplicated state, or the duplication is merely in linkage disequilibrium with a closely linked locus that is the actual basis of the cerebellar phenotype (or whether there is another more complex genetic explanation).

Molecular genetic testing approaches can include a combination of **chromosomal microarray analysis** or **exome array**.

Chromosomal microarray analysis (CMA) uses oligonucleotide or SNP arrays to detect genome-wide large deletions/duplications that cannot be detected by sequence analysis.

Table 1. Genomic Testing Used in Spinocerebellar Ataxia Type 20

Duplication [1]	Method	Proportion of Probands with a Pathogenic Variant Detectable by Method
Heterozygous duplication at 11q12.2-11q12.3 [2]	CMA [3]	100%
	Targeted duplication analysis [4]	100%

1. See Molecular Genetics for details of the duplication and genes of interest in the region.
2. For this *GeneReview*, the 11q12.2-11q12.3 recurrent duplication, observed in all reported individuals with SCA20, is defined as a 260-kb duplication at the 11q12 region of chromosome 11.
3. Chromosomal microarray analysis (CMA) using oligonucleotide arrays or SNP arrays. CMA designs in current clinical use target the 11q12.2-11q12.3 region.
4. Targeted duplication analysis methods can include FISH, quantitative PCR (qPCR), and multiplex ligation-dependent probe amplification (MLPA), as well as other targeted quantitative methods.

Clinical Characteristics

Clinical Description

Clinical information on spinocerebellar ataxia type 20 (SCA20) is based on the index pedigree, an Australian family of Anglo-Celtic descent that is the only family with SCA20 reported to date [Knight et al 2004, Storey et al 2005, Storey & Gardner 2012].

The 16 affected family members had onset between age 19 and 64 years (mean 47).

SCA20 presents with dysarthria without ataxia in a majority (10/16); the dysarthria may be of abrupt (2/16) or subacute (1/16) onset. It often combines the clinical appearance of spasmodic adductor dysphonia with cerebellar dysarthria. Other initial symptoms were dysarthria with simultaneous gait ataxia (2/16), gait ataxia alone (2/16), upper-limb kinetic and isometric tremor (1/16), and episodic vertigo (1/16).

Progression of SCA20, as judged by cross-sectional data, appears to be relatively slow; all affected members of this family were able to walk with or without gait aids except one, who became wheelchair dependent after 40 years of symptoms. Another required a feeding gastrostomy after 15 years of symptoms.

The clinical picture usually includes palatal tremor ("myoclonus") without ear click (10/16), although this finding can be subtle. Gaze-evoked nystagmus is unusual (3/16). In two it was impersistent; in another affected individual persistent downbeating nystagmus was evident. Saccades are typically hypermetric into downgaze (10/16) and horizontally (8/16). The vestibulo-ocular reflex gain, as judged by dynamic vs static visual acuity, is normal, correlating with absence of movement-induced oscillopsia. Minor pyramidal signs (brisk knee jerks, crossed adductor spread) are seen in a minority (5/16), but none have spastic tone or extensor plantar responses. Postural and kinetic tremor of the upper limbs, the presenting feature in one individual, was evident in only one other family member. Only one displayed intention tremor (as distinct from dysmetria and dyssynergia) on the finger/nose test.

Other extrapyramidal features (apart from slowing of repetitive movements without movement decay) are absent. None had a history of cognitive decline.

Penetrance

The penetrance is unknown, as the involved gene has not been identified.

Anticipation

Only four parent-child pairs could be documented by self-report regarding age of onset, which was younger by an average of 12 years in the offspring. This information is inadequate to confirm or refute anticipation. Large CAG/CTG and ATTCT/AGAAT repeats have been excluded in the region of interest [Knight et al 2004].

Prevalence

The prevalence of SCA20 is unknown; it is assumed to be very rare, given that no further individuals have been reported since the publication of the original family in 2008.

Genetically Related (Allelic) Disorders

No genetically related disorders are known.

Differential Diagnosis

The differential diagnosis of spinocerebellar ataxia type 20 (SCA20) is essentially that of its component features, as the constellation of progressive, dominantly inherited ataxia, early dentate calcification, and (often) palatal tremor is distinctive.

Inherited ataxia. See Hereditary Ataxia Overview.

Dentate calcification appears early in SCA20; it was seen in five affected individuals who had been symptomatic for five years or less.

- While dentate calcification is common in the general population with increasing age, affecting 0.7% of those older than age 65 years in one study [Harrington et al 1981], it rarely occurs in the absence of basal ganglia calcification (as it did in 9/11 individuals in the family with SCA20).
- Hyperparathyroidism and pseudohypoparathyroidism (see Disorders of GNAS Inactivation) with basal ganglia (and dentate) calcification may be dominantly inherited, and can be excluded on biochemical testing.
- Dentatorubral-pallidoluysian atrophy (DRPLA) can include pallidal microcalcification in the Haw River phenotype.
- Dominant "familial idiopathic brain calcification" (see Primary Familial Brain Calcification) has been reported in several families, but basal ganglia calcification dominates, and the clinical presentation includes cognitive decline and parkinsonism rather than ataxia.

Palatal tremor ("myoclonus") may be seen in the following situations, while dentate calcification is not:

- In conjunction with progressive ataxia in sporadic (i.e., not inherited) cases, possibly representing a unique degenerative syndrome [Sperling & Herrmann 1985]
- Rarely, in multiple-system atrophy, cerebellar type
- In early adult-onset Alexander disease, in which bulbar palsy and spastic tetraparesis are also seen. Inheritance is autosomal dominant.
- In a dominant branchial myoclonus syndrome with ataxia (OMIM 113610) [de Yebenes et al 1988], which may be a phenotypic variant of adult-onset Alexander disease

Dysphonia (which is apparent in SCA20 rather than confirmed on formal voice analysis) may also be seen with ataxia and motor neuropathy (OMIM 606183) [Barbieri et al 2001]; this latter syndrome appears to be inherited in an autosomal recessive manner. The presence of motor neuropathy and the absence of dentate calcification and palatal tremor also serve to distinguish this syndrome from SCA20.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with spinocerebellar ataxia type 20 (SCA20), the evaluations summarized in this section (if not performed as part of the evaluation that led to the diagnosis) are recommended:

- Careful clinical and neurologic evaluation
- Speech assessment
- Consultation with a clinical geneticist and/or genetic counselor

Treatment of Manifestations

Affected persons should be followed by a neurologist with consultation from physiatrists and physical and occupational therapists.

Although neither exercise nor physical therapy has been shown to stem the progression of incoordination or muscle weakness, individuals should maintain activity.

Canes and walkers help prevent falls. Modification of the home with such conveniences as grab bars, raised toilet seats, and ramps to accommodate motorized chairs may be necessary.

Speech therapy and communication devices such as writing pads and computer-based devices may benefit those with dysarthria or dysphonia.

Weighted eating utensils and dressing hooks help maintain a sense of independence.

Weight control is important because obesity can exacerbate difficulties with ambulation and mobility.

When dysphagia becomes troublesome, videofluoroscopic swallow evaluation can identify the consistency of food least likely to trigger aspiration.

Prevention of Secondary Complications

Secondary complications are unlikely in the early years of the disease.

Later, prevention of falls via appropriate gait aids and home modifications, and (if falls are frequent) a personal alarm system may be required. To limit the likelihood of fractures resulting from falls, bone density should be estimated and osteoporosis treated if present.

Vitamin supplements are recommended, particularly if caloric intake is reduced.

Weight control is important because obesity can exacerbate difficulties with ambulation and mobility.

Surveillance

The following are appropriate:

- Periodic speech assessment if dysphagia becomes a problem
- Routine follow up with a neurologist about every two years or as needed

Agents/Circumstances to Avoid

Affected individuals should avoid alcohol as well as medications known to cause nerve damage (e.g., isoniazid).

Therapies Under Investigation

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. Note: There may not be clinical trials for this disorder.

Other

Tremor-controlling drugs do not work well for cerebellar tremors.

Education for affected individuals and their families is the cornerstone of management.

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

Spinocerebellar ataxia type 20 (SCA20) is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- Almost all individuals diagnosed with SCA20 have an affected parent.
- A proband with SCA20 may have the disorder as the result of a *de novo* pathogenic variant. The proportion of cases caused by *de novo* pathogenic variants is unknown.
- Recommendations for the evaluation of parents of a proband with an apparent *de novo* pathogenic variant include neurologic assessment and CT scan of brain.
- Although almost all individuals diagnosed with SCA20 have an affected parent, the family history may appear to be negative because of failure to recognize the disorder in family members, early death of the parent before the onset of symptoms, or late onset of the disease in the affected parent. Therefore, an apparently negative family history cannot be confirmed unless appropriate clinical evaluation has been performed on the parents of the proband.

Sibs of a proband. The risk to the sibs of the proband depends on the clinical/genetic status of the proband's parents:

- If a parent of the proband is affected, the risk to the sibs is 50%.
- If the parents are clinically unaffected, the risk to the sibs of a proband is likely to be low.

Offspring of a proband. The risk to offspring of an individual with SCA20 is 50%.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent is affected, the parent's family members are at risk.

Related Genetic Counseling Issues

Considerations in families with an apparent *de novo* pathogenic variant. When neither parent of a proband with an autosomal dominant condition has clinical evidence of the disorder, the causative genetic alteration is

likely *de novo*. However, non-medical explanations including alternate paternity or maternity (e.g., with assisted reproduction) and undisclosed adoption could also be explored.

Family planning

- The optimal time for determination of genetic risk 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 or at risk.

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown). For more information, see Huang et al [2022].

Prenatal Testing

Because the gene in which pathogenic variants are responsible for SCA20 has not been identified, prenatal testing is not possible.

Resources

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

- **NCBI Genes and Disease**
  Spinocerebellar ataxia
- **Ataxia UK**
  United Kingdom
  Phone: 0800 995 6037; +44 (0) 20 7582 1444 (from abroad)
  Email: help@ataxia.org.uk
  www.ataxia.org.uk
- **euro-ATAXIA (European Federation of Hereditary Ataxias)**
  United Kingdom
  Email: lporter@ataxia.org.uk
  www.euroataxia.org
- **Spanish Ataxia Federation (FEDAES)**
  Spain
  Phone: 601 037 982
  Email: info@fedaes.org
  fedaes.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. Spinocerebellar Ataxia Type 20: Genes and Databases

Gene	Chromosome Locus	Protein	ClinVar

Table A. continued from previous page.

Unknown	11p13-q11	Unknown	

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 Spinocerebellar Ataxia Type 20 (View All in OMIM)

608687	SPINOCEREBELLAR ATAXIA 20; SCA20

Molecular Pathogenesis

Introduction. The 260-kb duplicated segment reported by Knight et al [2008] includes ten known and two unknown genes. It was not found in 1,129 control samples, suggesting that it is not merely a copy number variant.

Mechanism of disease causation is unknown, but suspected to be a dosage effect of one or more genes in the 11q12.2-12.3 region.

Genes of interest in this region. One of the known genes in the duplicated region, *DAGLA*, is potentially an attractive candidate as it is highly expressed in murine Purkinje cells.

Chapter Notes

Revision History

- 18 April 2019 (sw) Comprehensive update posted live
- 7 June 2012 (me) Comprehensive update posted live
- 6 January 2009 (es) Revision: 260-kb duplication of 11q12.2-11q12.3 identified as suspected cause of SCA20
- 27 February 2007 (me) Review posted live
- 6 February 2007 (es) Original submission

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