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Spinocerebellar Ataxia Type 13

Synonym: SCA13

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Summary

Clinical characteristics

Spinocerebellar ataxia type 13 (SCA13) is a phenotypic spectrum that includes both non-progressive infantile-onset ataxia and progressive childhood-onset and adult-onset cerebellar ataxia. Three phenotypes are seen:

- Cerebellar hypoplasia with non-progressive infantile-onset limb, truncal, and gait ataxia with mild-to-moderate intellectual disability and occasionally seizures and/or psychiatric manifestations. Cognition and motor skills improve over time.
- Childhood-onset slowly progressive cerebellar atrophy with slowly progressive cerebellar ataxia and dysarthria, delayed motor milestones, and mild-to-moderate intellectual disability
- Adult-onset progressive cerebellar atrophy with progressive ataxia and spasticity

Diagnosis/testing

The diagnosis of spinocerebellar ataxia type 13 (SCA13) is established in a proband with suggestive clinical and brain imaging findings and a heterozygous *KCNC3* pathogenic variant identified by molecular genetic testing.

Management

Treatment of manifestations: A multidisciplinary approach to management of ataxia and related neurologic manifestations is recommended including neurology, physical therapy (PT), occupational therapy (OT), speech and language pathology, and feeding team, as well as experts in educational needs and/or social/behavioral issues.

Surveillance: Regular neurologic examinations to evaluate disease progression and response to treatment; PT/OT to assess mobility and activities of daily living; feeding team re nutrition and risk for aspiration; speech and language pathology re dysarthria. Regular assessment of educational / mental health needs.

Agents/circumstances to avoid: Alcohol and sedating drugs, which can exacerbate ataxia.

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Genetic counseling

SCA13 is inherited in an autosomal dominant manner. In rare instances, an individual diagnosed with SCA13 has the disorder as the result of a *de novo* *KCNC3* pathogenic variant. Each child of an individual with SCA13 has a 50% chance of inheriting the *KCNC3* pathogenic variant. Once the *KCNC3* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

GeneReview Scope

Spinocerebellar Ataxia Type 13: Included Phenotypes [1]
• Congenital-onset non-progressive cerebellar ataxia • Childhood-onset progressive cerebellar ataxia w/delayed milestones • Adult-onset progressive cerebellar ataxia

1. For other genetic causes of these phenotypes, see Hereditary Ataxia Overview.

Diagnosis

Formal diagnostic criteria for spinocerebellar ataxia type 13 (SCA13) have not been established.

Suggestive Findings

SCA13 **should be considered** in individuals with the following age-related phenotypes.

Congenital-onset cerebellar hypoplasia with non-progressive cerebellar ataxia

- Congenital-onset non-progressive severe cerebellar hypoplasia on brain MRI [Khare et al 2017]
- Ataxia
  - Gait and/or appendicular
  - Dysarthria
- Cognitive impairment
  - Delayed motor milestones
  - Delayed speech acquisition
- Tremor/myoclonus
- Seizures
- Gradual lifetime improvement in motor and cognitive function

Childhood-onset progressive cerebellar ataxia with delayed milestones

- Cognitive impairment
- Seizures
- Delayed motor milestones
- Cerebellar atrophy on brain MRI

Adult-onset progressive spinocerebellar ataxia

- Ataxia
  - Gait and/or appendicular
  - Truncal ataxia
  - Titubation
- Hypotonia
- Dysarthria

- Impaired sound localization
- On brain MRI:
  - All affected individuals show age-related progressive mild-to-moderately severe cerebellar atrophy that is primarily midline. This has been evident as early as age three years.
  - Atrophy of the brain stem and/or cerebral cortex can be observed.

Establishing the Diagnosis

The diagnosis of SCA13 **is established** in a proband with suggestive clinical and brain imaging findings and a heterozygous *KCNC3* pathogenic (or likely pathogenic) variant identified by molecular genetic testing (see Table 1).

Note: (1) Per ACMG variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants. (2) Identification of a heterozygous *KCNC3* variant of uncertain significance does not establish or rule out the diagnosis of SCA13.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (multigene panel) and **comprehensive genomic testing** (exome sequencing or genome sequencing) depending on the phenotype.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Because the phenotypes associated with SCA13 are indistinguishable from other congenital-onset and adult-onset ataxias, affected individuals are likely to be diagnosed using a multigene panel (see Option 1), whereas those with an atypical presentation in whom the diagnosis of SCA13 has not been considered are more likely to be diagnosed using genomic testing (see Option 2). Note: Single-gene testing (sequence analysis of *KCNC3,* followed by gene-targeted deletion/duplication analysis) is rarely useful and typically NOT recommended.

Option 1

A multigene panel that includes *KCNC3* and other genes of interest (see Hereditary Ataxia Overview) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests; however, since SCA13 occurs through a dominant-negative or gain-of-function mechanism [Waters et al 2006, Figueroa et al 2010, Minassian et al 2012] and large intragenic deletions or duplications have not been reported, testing for intragenic deletions or duplications is unlikely to identify a *KCNC3* pathogenic variant.

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Option 2

Comprehensive genomic testing does not require the clinician to determine which gene(s) are likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in Spinocerebellar Ataxia Type 13

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
KCNC3	Sequence analysis [3]	All reported to date [4]
	Gene-targeted deletion/duplication analysis [5]	None reported [6]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Waters et al [2006], Figueroa et al [2010], Németh et al [2013], Duarri et al [2015], Coutelier et al [2017], Montaut et al [2017], Coutelier et al [2018]
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
6. Since SCA13 occurs through a dominant-negative or gain-of-function mechanism [Waters et al 2006, Figueroa et al 2010, Minassian et al 2012] and large intragenic deletions or duplication have not been reported, testing for intragenic deletions or duplication is unlikely to identify a disease-causing variant.

Clinical Characteristics

Clinical Description

The phenotypic spectrum of spinocerebellar ataxia type 13 (SCA13) originally clustered into two presentations: congenital-onset ataxia with little progression, typically accompanied by mild-to-moderate intellectual disability and occasionally seizures [Herman-Bert et al 2000, Figueroa et al 2011, Khare et al 2017] and adult-onset progressive ataxia [Waters et al 2005, Waters & Pulst 2008, Figueroa et al 2010]. A rapidly progressive phenotype associated with adult onset (age 30 years) with fairly rapid (10-15 years) progression was described by Khare et al [2018].

Congenital-Onset Cerebellar Hypoplasia with Non-Progressive Cerebellar Ataxia

In all affected individuals:

- Non-progressive limb, truncal, gait ataxia
- Dysarthria
- Tremor
- Delayed gross and/or fine motor milestones
- Cognitive impairment that is mild to moderate and relatively domain-specific to language
- Gradual lifetime improvement in motor and cognitive function

Variably present:

- Nystagmus
- Hyperreflexia
- Psychiatric manifestations
- Seizures

Life expectancy is unknown, but many affected individuals have been surveyed and examined at age 50 years and older [Author, personal observation].

Childhood-Onset Progressive Cerebellar Ataxia with Delayed Milestones

In the family described by Herman-Bert et al [2000], seven women and a boy age four years exhibited slowly progressive childhood-onset cerebellar gait ataxia associated with cerebellar dysarthria, moderate intellectual disability (IQ 62-76), and mild delays in motor acquisition. Nystagmus and pyramidal signs were observed in some.

Life span is not shortened and many persons live beyond age 70 years; assistance with gait may be required as the disease progresses.

Duarri et al [2015] described a proband and sib with an early-onset (age 2-3 years) slowly progressive cerebellar ataxia with mild cognitive impairment.

Adult-Onset Progressive Spinocerebellar Ataxia

The p.Arg420His variant (often referred to as R420H) causes an adult-onset autosomal dominant ataxia with isolated cerebellar signs, slow progression, mild cognitive impairment, and a paucity of cerebellar oculomotor signs. Myoclonic muscle movements have been described in some affected individuals but are not a reliable pathognomonic feature [Waters et al 2006, Minassian et al 2012, Bürk et al 2013, Subramony et al 2013, Duarri et al 2015, Montaut et al 2017].

MRI findings may include cerebellar atrophy with little change over years. Notably, imaging evidence suggests that cerebellar atrophy may significantly precede overt clinical symptomatology.

Life expectancy is unknown, but many affected individuals have been surveyed and examined at age 60 years and older [Author, personal observation].

Genotype-Phenotype Correlations

While the known pathogenic variants in *KCNC3* are associated with different phenotypes (see Table 8), data to date are too limited to make any genotype-phenotype correlations.

- The p.Arg420His variant was associated with adult-onset progressive spinocerebellar ataxia in one large pedigree [Waters et al 2005]; subsequently, multiple individuals and small pedigrees have been described [Waters et al 2006, Minassian et al 2012, Bürk et al 2013, Duarri et al 2015, Montaut et al 2017].
- The p.Arg423His variant has been associated with congenital-onset cerebellar hypoplasia, non-progressive cerebellar ataxia, mild cognitive impairment, and seizures [Figueroa et al 2010, Minassian et al 2012, Duarri et al 2015, Khare et al 2017, Montaut et al 2017].
- The p.Phe448Leu variant is associated with childhood-onset progressive ataxia with delayed milestones often intellectual disability and seizures [Herman-Bert et al 2000, Waters et al 2006, Minassian et al 2012].
- The p.Val535Met variant is associated with childhood-onset cerebellar ataxia with intellectual disability [Duarri et al 2015].
- The p.Pro583_Pro585del variant is associated with adult onset (age 30 years) with fairly rapid (10-15 years) progression [Khare et al 2018].

Penetrance

KCNC3 pathogenic variants appear to be fully penetrant in the families described. (See Table 8 for relevant publications.)

Prevalence

The prevalence of SCA13 is not known. Only one person with SCA13 was identified in a cohort of 327 probands with ataxia [Figueroa et al 2011].

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with heterozygous pathogenic variants in *KCNC3*.

Differential Diagnosis

See Hereditary Ataxia Overview.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with congenital-onset non-progressive spinocerebellar ataxia type 13 or adult-onset progressive SCA13, the multidisciplinary evaluations summarized in Table 2 and Table 3, respectively (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 2. Recommended Evaluations Following Initial Diagnosis in Individuals with Congenital-Onset Non-Progressive SCA13

System/Concern	Evaluation	Comment
Constitutional	Measure height, weight, & head circumference.	To assess for FTT
Feeding	If frequent choking or severe dysphagia: assess nutritional status & aspiration risk; evaluate for GERD.	Consider involving gastroenterologist / nutrition / feeding team.
Neurologic	Exam by neurologist for: history of known or suspected seizures, tremor, gait &/or appendicular ataxia	
	Assessment by physical medicine, OT/PT	To incl assessment of gross motor & fine motor skills, ambulation
Musculoskeletal	Assess spine & extremities, w/attn to hip joint abnormalities & range of motion.	
Motor delay / Intellectual disability	Developmental assessment	To incl motor, speech/language eval, general cognitive, & vocational skills
Psychiatric/ Behavioral	Neuropsychiatric eval	Persons age >12 mos: screen for behavioral problems incl sleep disturbances, ADHD, anxiety, &/or traits suggestive of ASD.
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of SCA13 to facilitate medical & personal decision making

Table 2. continued from previous page.

System/Concern	Evaluation	Comment
Family support/ resources	Social work	Assess: • Use of community resources & support/advocacy organizations (e.g., Parent to Parent); • Need for social work involvement for parental support.

ADHD = attention-deficit/hyperactivity disorder; FTT = failure to thrive; GERD = gastroesophageal reflux disease; MOI = mode of inheritance; OT = occupational therapy; PT = physical therapy
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Table 3. Recommended Evaluations Following Initial Diagnosis in Individuals with Adult-Onset Progressive SCA13

System/Concern	Evaluation	Comment
Neurologic	Neurologic assessment for cerebellar motor dysfunction (gait & postural ataxia, dysmetria, dysdiadochokinesis, tremor, dysarthria, nystagmus, saccades, & smooth pursuit)	Use standardized scale (SARA, ICARS, or BARS) to establish baseline for ataxia. [1]
	Physical medicine, OT/PT assessment	To incl assessment of gross motor & fine motor skills, ambulation
Speech	Speech/language eval for those w/dysarthria	If dysarthria is atypical or severe enough to cause communication problems
Feeding	If frequent choking or severe dysphagia: assess nutritional status & aspiration risk.	Consider placement of feeding tube for severe cases to ↓ risk of aspiration.
Psychiatric/ Behavioral	Neuropsychiatric eval for those w/problems in learning &/or social adaptation	No evidence that pharmacologic therapy has been required or effective in patients w/known pathogenic variants
Genetic counseling	By genetics professionals [2]	To inform patients & families re nature, MOI, & implications of SCA13 to facilitate medical & personal decision making
Family support/ resources	Social work	Assess: • Use of community resources & support/advocacy organizations (e.g., Parent to Parent); • Need for social work involvement for caregiver support.

BARS = Brief Ataxia Rating Scale; ICARS = International Co-operative Ataxia Rating Scale; MOI = mode of inheritance; OT = occupational therapy; PT = physical therapy; SARA = Scale for the Assessment and Rating of Ataxia
1. Bürk & Sival [2018], Hoche et al [2018]
2. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Treatment by a multidisciplinary team is recommended for individuals with congenital-onset non-progressive SCA13 (see Table 4) and individuals with adult-onset progressive SCA13 (see Table 5).

Table 4. Treatment of Manifestations in Individuals with Congenital-Onset Non-Progressive SCA13

Manifestation/Concern	Treatment	Considerations/Other
Ataxia	Assessment by physical medicine, OT/PT	Consider adaptive devices to maintain/improve independence in mobility, feeding.
Seizures	ASM under care of experienced neurologist	See footnote 1.

Table 4. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Tremor	None	Tremor-controlling drugs are not effective for cerebellar tremors.
Dysarthria	Speech/language therapy	Consider alternative communication methods as needed (e.g., writing pads & digital devices).
Dysphagia	Modify food consistency to ↓ aspiration risk.	Typically will gain independence through speech/ swallow therapy
Poor weight gain	Nutrition assessment	Consider vitamin/dietary supplements.
Developmental delay / Intellectual disability	See Developmental Delay / Intellectual Disability Management Issues.	Gradual lifetime improvement in motor & cognitive function

ASM = anti-seizure medication; OT = occupational therapy; PT = physical therapy
1. Education of parents regarding common seizure presentations is appropriate. For information on non-medical interventions and coping strategies for parents or caregivers of children diagnosed with epilepsy, see Epilepsy Foundation Toolbox.

Developmental Delay / Intellectual Disability Management Issues

The following information represents typical management recommendations for individuals with developmental delay / intellectual disability in the United States; standard recommendations may vary from country to country.

Ages 0-3 years. Referral to an early intervention program is recommended for access to occupational, physical, speech, and feeding therapy as well as infant mental health services, special educators and sensory impairment specialists. In the US, early intervention is a federally funded program available in all states that provides in-home services to target individual therapy needs.

Ages 3-5 years. In the US, developmental preschool through the local public school district is recommended. Before placement, an evaluation is made to determine needed services and therapies and an individualized education plan (IEP) is developed for those who qualify based on established motor, language, social, or cognitive delay. The early intervention program typically assists with this transition. Developmental preschool is center based; for children too medically unstable to attend, home-based services are provided.

All ages. Consultation with a developmental pediatrician is recommended to ensure the involvement of appropriate community, state, and educational agencies (US) and to support parents in maximizing quality of life. Some issues to consider:

- IEP services:
  - An IEP provides specially designed instruction and related services to children who qualify.
  - IEP services will be reviewed annually to determine whether any changes are needed.
  - Special education law requires that children participating in an IEP be in the least restrictive environment feasible at school and included in general education as much as possible, when and where appropriate.
  - PT, OT, and speech services will be provided in the IEP to the extent that the need affects the child's access to academic material. Beyond that, private supportive therapies based on the affected individual's needs may be considered. Specific recommendations regarding type of therapy can be made by a developmental pediatrician.
  - As a child enters the teen years, a transition plan should be discussed and incorporated in the IEP. For those receiving IEP services, the public school district is required to provide services until age 21.
- A 504 plan (Section 504: a US federal statute that prohibits discrimination based on disability) can be considered for those who require accommodations or modifications such as front-of-class seating,

assistive technology devices, classroom scribes, extra time between classes, modified assignments, and enlarged text.
- Developmental Disabilities Administration (DDA) enrollment is recommended. DDA is a US public agency that provides services and support to qualified individuals. Eligibility differs by state but is typically determined by diagnosis and/or associated cognitive/adaptive disabilities.
- Families with limited income and resources may also qualify for supplemental security income (SSI) for their child with a disability.

Motor Dysfunction

Gross motor dysfunction

- Physical therapy is recommended to maximize mobility and to reduce the risk for later-onset orthopedic complications (e.g., contractures, scoliosis, hip dislocation).
- Consider use of durable medical equipment and positioning devices as needed (e.g., wheelchairs, walkers, bath chairs, orthotics, adaptive strollers).
- For muscle tone abnormalities including hypertonia or dystonia, consider involving appropriate specialists to aid in management of baclofen, tizanidine, Botox®, anti-parkinsonian medications, or orthopedic procedures.

Fine motor dysfunction. Occupational therapy is recommended for difficulty with fine motor skills that affect adaptive function such as feeding, grooming, dressing, and writing.

Oral motor dysfunction. Oral-motor dysfunction should be assessed at each visit and clinical feeding evaluations and/or radiographic swallowing studies should be obtained for choking/gagging during feeds, poor weight gain, frequent respiratory illnesses, or feeding refusal that is not otherwise explained. Assuming that the child is safe to eat by mouth, feeding therapy (typically from an occupational or speech therapist) is recommended to help improve coordination or sensory-related feeding issues. Feeds can be thickened or chilled for safety. When feeding dysfunction is severe, an NG-tube or G-tube may be necessary.

Communication issues. Consider evaluation for alternative means of communication (e.g., augmentative and alternative communication [AAC]) for individuals who have expressive language difficulties. An AAC evaluation can be completed by a speech-language pathologist who has expertise in the area. The evaluation will consider cognitive abilities and sensory impairments to determine the most appropriate form of communication. AAC devices can range from low-tech, such as picture exchange communication, to high-tech, such as voice-generating devices. Contrary to popular belief, AAC devices do not hinder verbal development of speech, but rather support optimal speech and language development.

Table 5. Treatment of Manifestations in Individuals with Adult-Onset Progressive SCA13

Manifestation/Concern	Treatment	Considerations/Other
Ataxia	Care by physical medicine, OT/PT	• PT (balance exercises, gait training, & muscle strengthening) to maintain mobility & function [1] • OT to optimize ADL • Consider adaptive devices to maintain/improve independence in mobility (e.g., canes, walkers, ramps to accommodate motorized chairs), feeding (e.g., weighted eating utensils), dressing (e.g., dressing hooks). • Home adaptations to prevent falls (e.g., grab bars, raised toilet seats) • Weight control & physical activity to avoid obesity & related difficulties with mobility
Seizures	ASM under care of experienced neurologist	See footnote 2.

Table 5. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Tremor	None	Tremor-controlling drugs are not effective for cerebellar tremors.
Dysarthria	Speech/language therapy	Consider alternative communication methods as needed (e.g., writing pads & digital devices).
Dysphagia	Modify food consistency to ↓ aspiration risk.	Fiber-optic endoscopic exam of swallowing (FEES) can help define appropriate consistency.
Poor weight gain	Nutrition assessment	Consider nutritional & vitamin supplementation to meet dietary needs.
Social/behavioral concerns	Social work & psychology	Assist w/adaptation & compensation.

ADL = activities of daily living; ASM = anti-seizure medication; OT = occupational therapy; PT = physical therapy
1. Martineau et al [2014]
2. Education of caregivers regarding common seizure presentations is appropriate. For information on non-medical interventions and coping strategies for parents or caregivers of individuals diagnosed with epilepsy, see Epilepsy Foundation Toolbox.

Surveillance

Surveillance by a multidisciplinary team is recommended for individuals with congenital-onset non-progressive SCA13 (see Table 6) and individuals with adult-onset progressive SCA13 (see Table 7).

Table 6. Recommended Surveillance for Individuals Congenital-Onset Non-Progressive SCA13

System/Concern	Evaluation	Frequency
Neurologic	Neurologic assessment	Annually or more often for an acute exacerbation
	Physical medicine, OT/PT assessment of mobility, self-help skills	
Dysphagia	Assess aspiration risk.	As neurologic function improves consider advancing food consistency & diet.
Dysarthria	• Speech/language development • Need for alternative communication method	• Patients should receive routine care in the context of a comprehensive program if available. • Ongoing & continuous, especially for 1st several yrs
Developmental delay / Intellectual disability	Assess motor & cognitive abilities based on improving neurologic function/ cognition.	
Social/behavioral concerns	Assess age-related social/maturation issues.	

Table 7. Recommended Surveillance for Individuals with Adult-Onset Progressive SCA13

System/Concern	Evaluation	Frequency
Neurologic	Neurologic assessment	Annually or more often for an acute exacerbation
	Physical medicine, OT/PT assessment of mobility, self-help skills	
Dysarthria	Need for alternative communication method	
Dysphagia	Assess aspiration risk & feeding methods.	
Social/behavioral concerns	Social work & psychology	As needed to assist w/adaptation & compensation

Agents/Circumstances to Avoid

Avoid alcohol and sedating drugs, which can exacerbate ataxia.

Evaluation of Relatives at Risk

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

Pregnancy Management

Weight gain during pregnancy can further impair gait ataxia.

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

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 13 (SCA13) is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- Most individuals diagnosed with SCA13 have an affected parent.
- In rare instances, an individual diagnosed with SCA13 has the disorder as the result of a *de novo KCNC3* pathogenic variant [Khare et al 2017].
- Molecular genetic testing is recommended for the parents of a proband with an apparent *de novo KCNC3* pathogenic variant.
- If the *KCNC3* pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, possible theoretic explanations include a *de novo* pathogenic variant in the proband or germline mosaicism in a parent.
- The family history of some individuals diagnosed with SCA13 may appear to be negative because of failure to recognize the disorder in family members or early death of the parent before the onset of symptoms. Therefore, an apparently negative family history cannot be confirmed unless molecular genetic testing has been performed on the parents of the proband.

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

- If a parent of the proband is affected and/or is known to have the *KCNC3* pathogenic variant, the risk to the sibs of inheriting the variant is 50%. Sibs who inherit a pathogenic variant will typically have clinical manifestations of SCA13 similar to those observed in the proband.

- If the *KCNC3* pathogenic variant cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is estimated to be 1% because of the theoretic possibility of parental germline mosaicism [Rahbari et al 2016].
- If the parents have not been tested for the *KCNC3* pathogenic variant but are clinically unaffected, the risk to sibs of the proband appears to be low. However, sibs of a proband with clinically unaffected parents are still presumed to be at increased risk for SCA13 because of the theoretic possibility of parental germline mosaicism.

Offspring of a proband. Each child of an individual with SCA13 has a 50% chance of inheriting the pathogenic variant.

Other family members. The risk to other family members depends on the genetic status of the proband's parents: if a parent is affected or has a pathogenic variant, 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 the pathogenic variant identified in the proband or clinical evidence of the disorder, the pathogenic variant 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 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 or at risk.

Prenatal Testing and Preimplantation Genetic Testing

Once the *KCNC3* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing for SCA13 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.

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.

- **Ataxia UK**
  United Kingdom
  Phone: 0800 995 6037; +44 (0) 20 7582 1444 (from abroad)
  Email: help@ataxia.org.uk
  ataxia.org.uk

- **euro-ATAXIA (European Federation of Hereditary Ataxias)**
  United Kingdom
  Email: ageorgousis@ataxia.org.uk
  euroataxia.org

- **National Ataxia Foundation**
  Phone: 763-553-0020
  Email: naf@ataxia.org
  ataxia.org
- **Spanish Ataxia Federation (FEDAES)**
  Spain
  Phone: 601 037 982
  Email: info@fedaes.org
  fedaes.org
- **CoRDS Registry**
  Sanford Research
  Phone: 605-312-6300
  CoRDS Registry

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 13: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
KCNC3	19q13.33	Voltage-gated potassium channel KCNC3	KCNC3 database	KCNC3	KCNC3

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 13 (View All in OMIM)

176264	POTASSIUM CHANNEL, VOLTAGE-GATED, SHAW-RELATED SUBFAMILY, MEMBER 3; KCNC3
605259	SPINOCEREBELLAR ATAXIA 13; SCA13

Molecular Pathogenesis

KCNC3 encodes the potassium voltage-gated channel subfamily C member 3 (KCNC3), also known as Kv3.3, which has six membrane-spanning domains. KCNC3 forms a heterotetramer with KCNC1. Because this channel opens late during depolarization and is rapidly deactivated, it is important in regulation of the action potential and properties of bursting neurons [Joho & Hurlock 2009].

Mechanism of disease causation. SCA13-associated dysregulation of KCNC3 can occur through pathogenic variants that confer either a dominant-negative effect [Waters et al 2006] or a gain-of-function effect [Figueroa et al 2010, Minassian et al 2012]. Note that due to the mechanism of disease, these types of variants are the most commonly identified in affected individuals [Waters et al 2006, Figueroa et al 2010, Montaut et al 2017].

Table 8. Notable *KCNC3* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_004977.2 NP_004968.2	c.1259G>A	p.Arg420His	Nonfunctional but expressed protein; adult-onset progressive ataxia [1]
	c.1268G>A	p.Arg423His	Slow channel activation; congenital-onset cerebellar hypoplasia, cerebellar ataxia, mild cognitive impairment, & seizures [2]
	c.1344C>A	p.Phe448Leu	Slow channel closing; childhood-onset ataxia & often ID & seizures [3]
	c.1603G>A	p.Val535Met	Childhood onset; cerebellar ataxia; mild ID [Duarri et al 2015]
	c.1746_1754del	p.Pro583_Pro585del	Cerebellar ataxia; mild cognitive impairment; seizures; dysarthria/dysphagia; hyperreflexia; pasticity; onset in 30s w/progression to severe disease over several decades [Khare et al 2018]

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.
ID = intellectual disability
1. Waters et al [2005], Waters et al [2006], Minassian et al [2012], Bürk et al [2013], Duarri et al [2015], Montaut et al [2017]
2. Figueroa et al [2010], Minassian et al [2012], Duarri et al [2015], Montaut et al [2017]
3. Herman-Bert et al [2000], Minassian et al [2012], Waters et al [2006]

Chapter Notes

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