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NLM Citation: Chen DH, Bird TD, Raskind WH. Spinocerebellar Ataxia Type 14. 2005 Jan 28 [Updated 2020 Feb 20]. 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/

Spinocerebellar Ataxia Type 14

Synonym: SCA14

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Created: January 28, 2005; Updated: February 20, 2020.

Summary

Clinical characteristics

Spinocerebellar ataxia type 14 (SCA14) is characterized by slowly progressive cerebellar ataxia, dysarthria, and nystagmus. Axial myoclonus, cognitive impairment, tremor, and sensory loss may also be observed. Parkinsonian features including rigidity and tremor have been described in some families. Findings seen in other ataxia disorders (e.g., dysphagia, dysphonia) may also occur in SCA14. The average age of onset is in the 30s, with a range from childhood to the seventh decade. Life span is not shortened.

Diagnosis/testing

The diagnosis of SCA14 is established in a proband with a pathogenic variant in *PRKCG* identified by molecular genetic testing.

Management

Treatment of manifestations: Physical therapy to maintain mobility and function; occupational therapy to optimize activities of daily living; adaptive devices to maintain/improve independence in mobility; clonazepam or valproic acid to help improve axial myoclonus; speech therapy and communication devices for those with dysarthria; modify food consistency to reduce aspiration risk; consider nutritional and vitamin supplementation to meet dietary needs.

Surveillance: At least yearly neurologic, physical medicine, and speech and language evaluation. Periodic assessment for dysphagia and assessment of cognitive abilities.

Agents/circumstances to avoid: Alcohol and sedation may make gait and coordination worse.

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Genetic counseling

SCA14 is inherited in an autosomal dominant manner. Offspring of an affected individual have a 50% chance of inheriting the *PRKCG* pathogenic variant. Prenatal testing for pregnancies at increased risk is possible if the diagnosis has been established by molecular genetic testing in an affected family member.

Diagnosis

Formal diagnostic criteria for spinocerebellar ataxia type 14 have not been established.

Suggestive Findings

Spinocerebellar ataxia type 14 (SCA14) **should be considered** in individuals with the following clinical and imaging findings:

- Slowly progressive cerebellar ataxia
- Myoclonus, dystonia, rigidity, and tremor
- Sensory loss
- Dysarthria
- Nystagmus
- Cognitive impairment (some individuals)
- Depression (some individuals)
- Family history consistent with autosomal dominant inheritance
- Mild-to-moderately severe cerebellar atrophy that is primarily midline on brain MRI examination

Establishing the Diagnosis

The diagnosis of SCA14 **is established** in a proband with a pathogenic variant in *PRKCG* identified by molecular genetic testing (see Table 1).

Because the phenotype of SCA14 is indistinguishable from many other inherited disorders with ataxia, recommended molecular genetic testing approaches include use of a **multigene panel** or **comprehensive genomic testing**.

Note: Single-gene testing (sequence analysis of *PRKCG*, followed by gene-targeted deletion/duplication analysis) is rarely useful and typically NOT recommended.

- **An ataxia multigene panel** that includes *PRKCG* and other genes of interest (see Differential Diagnosis) 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. For this disorder, a multigene panel that also includes deletion/duplication analysis is recommended (see Table 1).

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

- **Comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are likely involved) is another good option. **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 14

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
PRKCG	Sequence analysis [3]	<100% [4]
	Gene-targeted deletion/duplication analysis [5]	Unknown [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. Data derived from the subscription-based professional view of HGMD [Stenson et al 2020]
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. One intragenic multiexon deletion of 1,717 nucleotides of genomic DNA has been reported (see Table 6).

Clinical Characteristics

To date, more than 60 individuals and/or families with a pathogenic variant in *PRKCG* have been identified [Chelban et al 2018, Shirafuji et al 2019]. The following description of the phenotypic features associated with this condition is based on these reports.

Table 2. Features of Spinocerebellar Ataxia Type 14

Feature	% of Persons w/Feature	Comment
Gait ataxia	100%	The initial symptom in most individuals
Dysarthria	70%	
Abnormal eye movements	60%	Nystagmus, saccadic pursuit, & others
Myoclonus	10%	Axial, multifocal
Tremor	15%	Rigidity can be present.
Decreased sensation	17%	Mostly vibration sense
Pyramidal signs	60%	Some w/↓ reflexes; a few w/extensor plantar responses (Babinski reflex)
Cognitive deficits	20%	Mostly mild to moderate
Depression	7 families/individuals	
Hearing deficits	4 individuals	↓ to loss
Cerebellar atrophy	100%	Mostly mild to moderate; severe in a few

Individuals with SCA14 typically present with a slowly progressive pure ataxia, but many individuals also manifest other symptoms. In a cohort study that identified 13 families carrying pathogenic variants in *PRKCG*, more than a third of individuals had a complex phenotype [Chelban et al 2018].

Onset. Accurate age of onset is often difficult to determine. The usual onset is in early adult life, typically in the 30s (age range: 3-70 years) [Yamashita et al 2000, Brkanac et al 2002, Chen et al 2003, Hiramoto et al 2006, Vlak et al 2006, Ganos et al 2014, Chelban et al 2018].

Ataxia. The initial finding is almost always subtle unsteadiness of gait that slowly worsens. Almost all persons remain ambulatory, but many fall frequently and require the assistance of stair railings and canes. Some people require a wheelchair late in life.

Dysarthria. Mild-to-moderate dysarthria is common. Findings seen in other ataxia disorders (e.g., dysphagia, dysphonia) may also occur in individuals with SCA14.

Abnormal eye movements. More than half of individuals have horizontal jerk nystagmus or saccadic intrusions.

Myoclonus. Five persons in a Japanese family with early onset had episodic axial myoclonus manifest as irregular tremulous movements of the trunk and head lasting minutes to hours [Yamashita et al 2000]. Mild persistent multifocal myoclonus has been reported in a person with early onset [Vlak et al 2006] and in a few other individuals [van de Warrenburg et al 2003, Klebe et al 2005, Foncke et al 2010, Ganos et al 2014, Chelban et al 2018]. An individual homozygous for a deletion that results in extension of the protein by 13 amino acids had early onset and developed generalized myoclonus in late teenage years [Asai et al 2009]. Identification of *PRKCG* pathogenic variants in persons with phenotypes similar to progressive myoclonic ataxia (Ramsay Hunt syndrome) [Visser et al 2007] and myoclonus-dystonia [Foncke et al 2010] suggest that SCA14 should be considered in individuals with these clinical syndromes.

Stevanin et al [2004] reported facial fasciculations and/or myokymia in several individuals in one family.

Parkinsonism. Parkinsonian features including rigidity and tremor were described in some families [Stevanin et al 2004, van de Warrenburg et al 2004, Fahey et al 2005, Klebe et al 2005, Dalski et al 2006, Vlak et al 2006, Nolte et al 2007, Visser et al 2007, Asai et al 2009, Sailer et al 2012, Chelban et al 2018].

Dystonia was described in several individuals [Nolte et al 2007, Visser et al 2007, Miura et al 2009, Foncke et al 2010] and more recently has been described as a common feature in SCA14 [Chelban et al 2018].

Sensory loss. One fifth of affected families show mild or moderate sensory loss, mostly decreased vibration sense.

Tendon reflexes vary from decreased to normal to hyperactive. Extensor plantar reflexes are present in a few individuals.

Cognitive deficits may be part of the SCA14 phenotype [Stevanin et al 2004]. Intellectual impairment, attention deficit, and deficient executive function were identified in 13 of 18 (72%) individuals in a French family [Stevanin et al 2004] and in a few families in another French study [Klebe et al 2005]. Mild cognitive deficits were found in two members with adult-onset disease in a Japanese family [Miura et al 2009]. Three affected individuals in a Norwegian family were described as having learning difficulty with IQ in the normal to low range [Koht et al 2012]. One of two affected individuals in one family and two of six affected individuals in another family had mild deficits in concentration and memory [Chelban et al 2018]. In a large cohort study of recessive cognitive disorders, different homozygous *PRKCG* variants were identified in cousins with moderate cognitive impairment and ataxia in two families [Najmabadi et al 2011]. However, a detailed neuropsychological study of Norwegian families found no significant cognitive deficit in ten individuals with SCA14 compared to intrafamilial controls – although verbal IQ, verbal executive function, and psychomotor speed tended to be slightly reduced in the affected individuals [Wedding et al 2013].

Prognosis. Life span is not shortened and many persons live beyond age 70 years.

Other

- **Memory loss** after age 70 years observed in several affected individuals may be coincidentally occurring age-related dementia [Chen et al 2005].
- **Depression** found in some families with SCA14 [Chen et al 2003, Chen et al 2005, Vlak et al 2006, Nolte et al 2007, Wieczorek et al 2007, Miura et al 2009, Ganos et al 2014] may reflect general dysfunction in progressive diseases, rather than a feature specific to SCA14.
- **Hearing impairment** was observed in four persons with SCA14 [Stevanin et al 2004, Klebe et al 2005, Coutelier et al 2017, Shirafuji et al 2019], but it is not clear if the impairment results from *PRKCG* pathogenic variants.
- **Seizures.** One person with intractable generalized tonic-clonic epilepsy was reported in a Japanese family; however, she had experienced birth asphyxia and intellectual impairment from infancy [Hiramoto et al 2006]. It is likely that her seizures were not related to SCA14.

Neuroimaging. Brain MRI in all affected persons has shown mild-to-moderately severe cerebellar atrophy that is primarily midline. Atrophy of the brain stem or cerebral cortex is not observed in young individuals with SCA14; mild cerebral atrophy reported in some elderly individuals [Dalski et al 2006] may have been age-related.

Neuropathology studies on postmortem brain tissue has been reported in two individuals with SCA14. Loss of Purkinje cells in the cerebellum and decreased staining of residual Purkinje cells for PKCγ antibody were found in one individual at age 66 years [Chen et al 2003]. Severe loss of Purkinje cells in all lobules of the neocerebellum associated with Bergmann gliosis and mislocalized PKCγ staining of the remaining Purkinje cells associated with large cytoplasmic aggregates in the soma were found in an individual at age 90 years [Wong et al 2018].

Genotype-Phenotype Correlations

No genotype-phenotype correlations have been identified.

Penetrance

Clinically unaffected individuals with *PRKCG* pathogenic variants who are older than age 60 years have been described in at least three families [Yabe et al 2003, Chen et al 2005].

Nomenclature

The term "olivopontocerebellar atrophy" (OPCA) was used to denote SCA in the past. Prior to the discovery of the genes that differentiate members of the group, the autosomal dominant cerebellar ataxias (ADCA) were divided into subgroups depending on the presence of clinical features in addition to ataxia. ADCA III, to which SCA14 would belong, referred to a pure form of late-onset cerebellar ataxia without additional features.

Prevalence

SCA14 probably accounts for fewer than 1% of all autosomal dominant ataxia diagnoses and accounts for approximately 1.5% to 6.7% of autosomal dominant cerebellar ataxia without trinucleotide repeat expansions [Chen et al 2005, Klebe et al 2005, Basri et al 2007, Chelban et al 2018]. The range in prevalence may reflect variable prevalence among individuals of different ethnic backgrounds.

A founder variant (p.Gly118Asp) has been reported in the Dutch population [van de Warrenburg et al 2003, Verbeek et al 2005]. The p.Phe643Leu variant found in two French kindreds was suggested to represent a founder variant in this population (see Molecular Genetics) [Stevanin et al 2004, Klebe et al 2005].

Genetically Related (Allelic) Disorders

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

Differential Diagnosis

Persons with spinocerebellar ataxia type 14 (SCA14) may present with ataxia that is indistinguishable from other adult-onset inherited or acquired ataxias (see Hereditary Ataxia Overview).

Note: SCA14 should particularly be considered if the proband or an affected relative displays axial myoclonus, dystonia, or cognitive impairment.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with spinocerebellar ataxia type 14 (SCA14), 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 Spinocerebellar Ataxia Type 14.

System/Concern	Evaluation	Comment
Neurologic	Neurology referral to assess for cerebellar motor dysfunction (gait ataxia, dysarthria, tremor, dystonia, nystagmus)	Use standardized scale to establish baseline for ataxia (SARA, ICARS, or BARS).
Speech	For those w/dysarthria: speech/language eval	If dysarthria is atypical or severe enough to cause communication problems
Cognition	Neuropsychiatric eval for those w/problems in learning &/or attention	For example: MMSE, MoCA, WISC & WAIS
Miscellaneous/ Other	Consultation w/clinical geneticist &/or genetic counselor	

BARS = Brief Ataxia Rating Scale; ICARS = International Co-operative Ataxia Rating Scale; MMSE= Mini-Mental State Exam; MoCA= Montreal Cognitive Assessment; SARA= Scale for the Assessment and Rating of Ataxia; WAIS = The Wechsler Adult Intelligence Scale; WISC= Wechsler Intelligence Scales for Children

Treatment of Manifestations

Table 4. Treatment of Manifestations in Individuals with Spinocerebellar Ataxia Type 14

Manifestation/ Concern	Treatment	Considerations/Other
Ataxia	Assessment & care by physical medicine, OT/PT	• PT (balance exercises, gait training, & muscle strengthening) to maintain mobility & function • OT to optimize activities of daily living • 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 w/mobility

Table 4. continued from previous page.

Manifestation/ Concern	Treatment	Considerations/Other
Axial myoclonus	Clonazepam or valproic acid	May be effective [1]
Dysarthria	Speech & language therapy	Consider alternative communication methods as needed (e.g., writing pads, digital devices).
Dysphagia	Modify food consistency to ↓ aspiration risk.	Video esophagram may help define best consistency.
Poor weight gain	Nutrition assessment	Consider nutritional & vitamin supplementation to meet dietary needs.
Intellectual disability	Assessment by educational psychologist & IEP eval	Ensure appropriate social work involvement to connect families w/local resources, respite, & support.

IEP = individualized education plan; OT = occupational therapy; PT = physical therapy
1. Yamashita et al [2000]

Surveillance

Table 5. Recommended Surveillance for Individuals with Spinocerebellar Ataxia Type 14

System/Concern	Evaluation	Frequency
Neurologic	• Neurologic assessment • Physical medicine, OT/PT assessment of mobility, self-help skills	Annually or more often for an acute exacerbation
Dysarthria	• Speech & language development • Need for alternative communication method	Annually
Dysphagia	Assess aspiration risk.	As neurologic function improves, consider advancing food consistency & diet.
Intellectual disability	Assess cognitive abilities based on improving neurologic function/cognition,	W/age, reassess changing needs for social & educational services.

OT = occupational therapy; PT = physical therapy

Agents/Circumstances to Avoid

Alcohol and sedation may worsen gait and coordination.

Evaluation of Relatives at Risk

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

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.

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 14 (SCA14) is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- Many individuals diagnosed with SCA14 have an affected parent.
- An individual diagnosed with SCA14 may have the disorder as the result of a *de novo* pathogenic variant [van Gaalen et al 2013]. However, too few unselected cases have been studied to derive a reliable estimate of the proportion of cases that result from a *de novo* variant.
- Molecular genetic testing is recommended for the parents of a proband with an apparent *de novo* pathogenic variant.
- If the pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, possible explanations include a *de novo* pathogenic variant in the proband or germline mosaicism in a parent.* Though theoretically possible, no instances of germline mosaicism have been reported.

  * Misattributed parentage can also be explored as an alternative explanation for an apparent *de novo* pathogenic variant.
- The family history of some individuals diagnosed with SCA14 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, late onset of the disease in the affected parent, or reduced penetrance. Therefore, an apparently negative family history cannot be confirmed unless appropriate 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 or has the pathogenic variant, the risk to the sibs of inheriting the variant is 50%. Intrafamilial variability in age of onset and clinical features is observed in SCA14.
- If the proband has a known SCA14-related pathogenic variant that 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 *PRKCG* pathogenic variant but are clinically unaffected, sibs of a proband are still presumed to be at increased risk for SCA14 because of the possibility of age-related penetrance in a heterozygous parent or the theoretic possibility of parental germline mosaicism.

Offspring of a proband. Each child of an individual with SCA14 has a 50% chance of inheriting the *PRKCG* pathogenic variant.

Other family members. The risk to other family members depends on the genetic status of the proband's parents: if a parent has the pathogenic variant, members of the parent's family may be at risk.

Related Genetic Counseling Issues

At-risk individuals. The age of onset, severity, specific symptoms, and progression of SCA14 are variable and cannot be predicted by the family history or results of molecular genetic testing.

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

- Predictive testing for at-risk relatives is possible once molecular genetic testing has identified the causative pathogenic variant in an affected family member.
- This testing is not useful in predicting age of onset, severity, type of symptoms, or rate of 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 SCA14, 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 or at risk.

Prenatal Testing and Preimplantation Genetic Testing

Once the *PRKCG* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing for SCA14 are possible. However, in general, age of onset, severity of disease, specific symptoms, and rate of disease progression are variable and cannot be accurately predicted by molecular genetic testing.

Note: Some reported *PRKCG* variants have been associated with functional evidence for pathogenicity, many variants are recurrent, and others have convincing cosegregation evidence. However, if the pathogenicity of a *PRKCG* variant has not been confirmed, results from molecular genetic testing should be used with extreme caution for prenatal testing at the present time.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testingis. 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
  www.ataxia.org.uk
- **euro-ATAXIA (European Federation of Hereditary Ataxias)**
  United Kingdom
  Email: lporter@ataxia.org.uk
  www.euroataxia.org
- **National Ataxia Foundation**
  Phone: 763-553-0020
  Fax: 763-553-0167
  Email: naf@ataxia.org
  www.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 14: Genes and Databases

Gene	Chromosome Locus	Protein	HGMD	ClinVar
PRKCG	19q13.42	Protein kinase C gamma type	PRKCG	PRKCG

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 14 (View All in OMIM)

176980	PROTEIN KINASE C, GAMMA; PRKCG
605361	SPINOCEREBELLAR ATAXIA 14; SCA14

Molecular Pathogenesis

The majority of pathogenic variants cluster in exon 4 encoding the regulatory C1 domain. In vitro and in vivo investigations of effects of some of these pathogenic variants on the function of the protein have been performed. Computer simulation studies on three pathogenic missense variants [Chen et al 2003] suggested that mutated gene products may be less stable than the normal protein. In vitro experiments on multiple pathogenic missense variants demonstrated cytotoxic aggregations in the cytoplasm of primary Purkinje cells and mammalian cell lines, followed by cell death [Seki et al 2005, Doran et al 2008, Seki et al 2009, Takahashi et al 2015], altered kinase activity [Seki et al 2005, Verbeek et al 2008, Chopra et al 2018], impaired ubiquitin proteasome degradation [Seki et al 2007], and altered substrate specificity [Asai et al 2009]. A transgenic mouse model of SCA14 showed that Purkinje cells have a strong reduction of their dendritic tree [Ji et al 2014, Trzesniewski et al 2019], however, there was no overt degeneration of Purkinje cells. Neuropathology of SCA14 in postmortem cerebellum and in induced pluripotent stem cells derived from affected individuals demonstrated PKCγ aggregations, mislocalization, and increased kinase activity.

Mechanism of disease causation. It is speculated that the SCA14 phenotype results from gain of function rather than haploinsufficiency because heterozygous PKCγ-null animals are neurologically normal [Chen et al 1995, Kano et al 1995]. However, from functional studies of SCA14 pathogenic variants in transfected cells and in a mouse model, there is evidence for both gain-of-function [Craig et al 2001, Seki et al 2005, Takahashi et al 2015] and loss-of-function mechanisms [Adachi et al 2008, Verbeek et al 2008]. More recently, functional investigation of nonsense variant p.Arg76Ter showed that the mutation inhibited PKC phosphorylation activity and induced more apoptosis compared to wild type PKCγ, suggesting that a dominant-negative mechanism may be at least partially responsible for the disease [Shirafuji et al 2019].

Table 6. Notable *PRKCG* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change (Alias [1])	Predicted Protein Change (Alias [1])	Comment [Reference]
NM_002739.5 NP_002730.1	c.76A>G	p.Arg26Gly	Recurrent variant
	c.197G>A	p.Cys66Tyr	Recurrent variant
	c.226C>T	p.Arg76Ter	Nonsense variant
	c.767T>C	p.Met256Thr	Homozygous variant; identified in an ADCA cohort study; no further clinical description
	c.353G>A	p.Gly118Asp	Dutch founder variant [van de Warrenburg et al 2003]
	c.301C>T	p.His101Tyr	Recurrent variant. The His101 residue is a mutational hot spot for SCA14
	c.302A>G	p.His101Arg	
	c.303C>G	p.His101Gln	
	c.383G>A	p.Gly128Asp	Recurrent variant
	c.391T>C	p.Cys131Arg	Recurrent variant
	c.392G>A	p.Cys131Tyr	Recurrent variant
	c.413T>A	p.Val138Glu	Recurrent variant
	c.530_919del [2]	p.Val177_Tyr307del	Reported in 3 homozygous sibs w/ID & ataxia [Najmabadi et al 2011]
	c.1927T>C	p.Phe643Leu	Possible French founder variant, reported in 2 French kindreds [Stevanin et al 2004, Klebe et al 2005]

Table 6. continued from previous page.

Reference Sequences	DNA Nucleotide Change (Alias [1])	Predicted Protein Change (Alias [1])	Comment [Reference]
	c.2091_*98del [3] (2089-2192del)	p.Met697_Ter698delins(76) (p.Met697_Ter698delinsXaa) (Met697Ileex) (M697I-ex13)	Homozygous variant; deletion of terminal Met codon, stop codon, & part of 3'UTR [Asai et al 2009, Najmabadi et al 2011]

Variants listed in the table have been provided by the authors. *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.
ADCA = autosomal dominant cerebellar ataxia; ID = intellectual disability
1. Variant designation that does not conform to current naming conventions.
2. Intragenic multiexon deletion of 1,717 nucleotides of genomic DNA (Chr19:59086740-59088457) (NCBI36)
3. NG_009114.1:g.29680_29781del

Table 7. Notable *PRKCG* Benign Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_002739.5 NP_002730.1	c.285C>G	p.Asp95=	Proposed as potential splice site pathogenic variant [Chen et al 2005] but now documented as benign variant, particularly in North Africans [Klebe et al 2005].

Variants listed in the table have been provided by the authors. *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.

Chapter Notes

Author Notes

Supported by funds from the NORD, the NINDS, and the Department of Veterans Affairs

Revision History

- 20 February 2020 (sw) Comprehensive update posted live
- 18 April 2013 (me) Comprehensive update posted live
- 23 March 2010 (me) Comprehensive update posted live
- 8 February 2007 (me) Comprehensive update posted live
- 21 December 2005 (dhc) Revision: prenatal diagnosis available
- 28 January 2005 (me) Review posted live
- 23 September 2004 (dhc) Original submission

References

Literature Cited

Adachi N, Kobayashi T, Takahashi H, Kawasaki T, Shirai Y, Ueyama T, Matsuda T, Seki T, Sakai N, Saito N. Enzymological analysis of mutant protein kinase Cgamma causing spinocerebellar ataxia type 14 and dysfunction in Ca2+ homeostasis. J Biol Chem. 2008;283:19854–63. PubMed PMID: 18499672.

Asai H, Hirano M, Shimada K, Kiriyama T, Furiya Y, Ikeda M, Iwamoto T, Mori T, Nishinaka K, Konishi N, Udaka F, Ueno S. Protein kinase C gamma, a protein causative for dominant ataxia, negatively regulates nuclear import of recessive-ataxia-related aprataxin. Hum Mol Genet. 2009;18:3533–43. PubMed PMID: 19561170.

Basri R, Yabe I, Soma H, Sasaki H. Spectrum and prevalence of autosomal dominant spinocerebellar ataxia in Hokkaido, the northern island of Japan: a study of 113 Japanese families. J Hum Genet. 2007;52:848–55. PubMed PMID: 17805477.

Brkanac Z, Bylenok L, Fernandez M, Matsushita M, Lipe H, Wolff J, Nochlin D, Raskind WH, Bird TD. A new dominant spinocerebellar ataxia linked to chromosome 19q13.4-qter. Arch Neurol. 2002;59:1291–5. PubMed PMID: 12164726.

Chelban V, Wiethoff S, Fabian-Jessing BK, Haridy NA, Khan A, Efthymiou S, Becker EBE, O'Connor E, Hersheson J, Newland K, Hojland AT, Gregersen PA, Lindquist SG, Petersen MB, Nielsen JE, Nielsen M, Wood NW, Giunti P, Houlden H. Genotype-phenotype correlations, dystonia and disease progression in spinocerebellar ataxia type 14. Mov Disord. 2018;33:1119–29. PubMed PMID: 29603387.

Chen DH, Brkanac Z, Verlinde CL, Tan XJ, Bylenok L, Nochlin D, Matsushita M, Lipe H, Wolff J, Fernandez M, Cimino PJ, Bird TD, Raskind WH. Missense mutations in the regulatory domain of PKC gamma: a new mechanism for dominant nonepisodic cerebellar ataxia. Am J Hum Genet. 2003;72:839–49. PubMed PMID: 12644968.

Chen DH, Cimino PJ, Ranum LP, Zoghbi HY, Yabe I, Schut L, Margolis RL, Lipe HP, Feleke A, Matsushita M, Wolff J, Morgan C, Lau D, Fernandez M, Sasaki H, Raskind WH, Bird TD. The clinical and genetic spectrum of spinocerebellar ataxia 14. Neurology. 2005;64:1258–60. PubMed PMID: 15824357.

Chen C, Kano M, Abeliovich A, Chen L, Bao S, Kim JJ, Hashimoto K, Thompson RF, Tonegawa S. Impaired motor coordination correlates with persistent multiple climbing fiber innervation in PKC gamma mutant mice. Cell. 1995;83:1233–42. PubMed PMID: 8548809.

Chopra R, Wasserman AH, Pulst SM, De Zeeuw CI, Shakkottai VG. Protein kinase C activity is a protective modifier of Purkinje neuron degeneration in cerebellar ataxia. Hum Mol Genet. 2018;27:1396–1410. PubMed PMID: 29432535.

Coutelier M, Coarelli G, Monin ML, Konop J, Davoine CS, Tesson C, Valter R, Anheim M, Behin A, Castelnovo G, Charles P, David A, Ewenczyk C, Fradin M, Goizet C, Hannequin D, Labauge P, Riant F, Sarda P, Sznajer Y, Tison F, Ullmann U, Van Maldergem L, Mochel F, Brice A, Stevanin G, Durr A, et al. A panel study on patients with dominant cerebellar ataxia highlights the frequency of channelopathies. Brain. 2017;140:1579–94. PubMed PMID: 28444220.

Craig NJ, Durán Alonso MB, Hawker KL, Shiels P, Glencorse TA, Campbell JM, Bennett NK, Canham M, Donald D, Gardiner M, Gilmore DP, MacDonald RJ, Maitland K, McCallion AS, Russell D, Payne AP, Sutcliffe RG, Davies RW. A candidate gene for human neurodegenerative disorders: a rat PKC gamma mutation causes a Parkinsonian syndrome. Nat Neurosci. 2001;4:1061–2. PubMed PMID: 11600890.

Dalski A, Mitulla B, Burk K, Schattenfroh C, Schwinger E, Zuhlke C. Mutation of the highly conserved cysteine residue 131 of the SCA14 associated PRKCG gene in a family with slow progressive cerebellar ataxia. J Neurol. 2006;253:1111–2. PubMed PMID: 16649092.

Doran G, Davies KE, Talbot K. Activation of mutant protein kinase Cgamma leads to aberrant sequestration and impairment of its cellular function. Biochem Biophys Res Commun. 2008;372:447–53. PubMed PMID: 18503760.

Fahey MC, Knight MA, Shaw JH, Gardner RJ, du Sart D, Lockhart PJ, Delatycki MB, Gates PC, Storey E. Spinocerebellar ataxia type 14: study of a family with an exon 5 mutation in the PRKCG gene. J Neurol Neurosurg Psychiatry. 2005;76:1720–2. PubMed PMID: 16291902.

Foncke EM, Beukers RJ, Tijssen CC, Koelman JH, Tijssen MA. Myoclonus-dystonia and spinocerebellar ataxia type 14 presenting with similar phenotypes: trunk tremor, myoclonus, and dystonia. Parkinsonism Relat Disord. 2010;16:288–9. PubMed PMID: 19913450.

Ganos C, Zittel S, Minnerop M, Schunke O, Heinbokel C, Gerloff C, Zühlke C, Bauer P, Klockgether T, Münchau A, Bäumer T. Clinical and neurophysiological profile of four German families with spinocerebellar ataxia type 14. Cerebellum. 2014;13:89–96. PubMed PMID: 24030789.

Hiramoto K, Kawakami H, Inoue K, Seki T, Maruyama H, Morino H, Matsumoto M, Kurisu K, Sakai N. Identification of a new family of spinocerebellar ataxia type 14 in the Japanese spinocerebellar ataxia population by the screening of PRKCG exon 4. Mov Disord. 2006;21:1355–60. PubMed PMID: 16763984.

Ji J, Hassler ML, Shimobayashi E, Paka N, Streit R, Kapfhammer JP. Increased protein kinase C gamma activity induces Purkinje cell pathology in a mouse model of spinocerebellar ataxia 14. Neurobiol Dis. 2014;70:1–11. PubMed PMID: 24937631.

Kano M, Hashimoto K, Chen C, Abeliovich A, Aiba A, Kurihara H, Watanabe M, Inoue Y, Tonegawa S. Impaired synapse elimination during cerebellar development in PKC gamma mutant mice. Cell. 1995;83:1223–31. PubMed PMID: 8548808.

Klebe S, Durr A, Rentschler A, Hahn-Barma V, Abele M, Bouslam N, Schols L, Jedynak P, Forlani S, Denis E, Dussert C, Agid Y, Bauer P, Globas C, Wullner U, Brice A, Riess O, Stevanin G. New mutations in protein kinase Cgamma associated with spinocerebellar ataxia type 14. Ann Neurol. 2005;58:720–9. PubMed PMID: 16193476.

Koht J., Stevanin G., Durr A., Mundwiller E., Brice A. Tallaksen CME. SCA14 in Norway, two families with autosomal dominant cerebellar ataxia and a novel mutation in the PRKCG gene. Acta Neurologica Scandinavica. 2012;125:116–22. PubMed PMID: 21434874.

Miura S, Nakagawara H, Kaida H, Sugita M, Noda K, Motomura K, Ohyagi Y, Ayabe M, Aizawa H, Ishibashi M, Taniwaki T. Expansion of the phenotypic spectrum of SCA14 caused by the Gly128Asp mutation in PRKCG. Clin Neurol Neurosurg. 2009;111:211–5. PubMed PMID: 18986758.

Najmabadi H, Hu H, Garshasbi M, Zemojtel T, Abedini SS, Chen W, Hosseini M, Behjati F, Haas S, Jamali P, Zecha A, Mohseni M, Püttmann L, Vahid LN, Jensen C, Moheb LA, Bienek M, Larti F, Mueller I, Weissmann R, Darvish H, Wrogemann K, Hadavi V, Lipkowitz B, Esmaeeli-Nieh S, Wieczorek D, Kariminejad R, Firouzabadi SG, Cohen M, Fattahi Z, Rost I, Mojahedi F, Hertzberg C, Dehghan A, Rajab A, Banavandi MJ, Hoffer J, Falah M, Musante L, Kalscheuer V, Ullmann R, Kuss AW, Tzschach A, Kahrizi K, Ropers HH. Deep sequencing reveals 50 novel genes for recessive cognitive disorders. Nature. 2011;478:57–63. PubMed PMID: 21937992.

Nolte D, Landendinger M, Schmitt E, Müller U. Spinocerebellar ataxia 14: novel mutation in exon 2 of PRKCG in a German family. Mov Disord. 2007;22:265–7. PubMed PMID: 17149711.

Rahbari R, Wuster A, Lindsay SJ, Hardwick RJ, Alexandrov LB, Turki SA, Dominiczak A, Morris A, Porteous D, Smith B, Stratton MR, Hurles ME, et al. Timing, rates and spectra of human germline mutation. Nat Genet. 2016;48:126–33. PubMed PMID: 26656846.

Sailer A, Scholz SW, Gibbs JR, Tucci A, Johnson JO, Wood NW, Plagnol V, Hummerich H, Ding J, Hernandez D, Hardy J, Federoff HJ, Traynor BJ, Singleton AB, Houlden H. Exome sequencing in an SCA14 family demonstrates its utility in diagnosing heterogeneous diseases. Neurology. 2012;79:127–31. PubMed PMID: 22675081.

Shirafuji T, Shimazaki H, Miyagi T, Ueyama T, Adachi N, Tanaka S, Hide I, Saito N, Sakai N. Spinocerebellar ataxia type 14 caused by a nonsense mutation in the PRKCG gene. Mol Cell Neurosci. 2019;98:46–53. PubMed PMID: 31158466.

Seki T, Adachi N, Ono Y, Mochizuki H, Hiramoto K, Amano T, Matsubayashi H, Matsumoto M, Kawakami H, Saito N, Sakai N. Mutant protein kinase Cgamma found in spinocerebellar ataxia type 14 is susceptible to aggregation and causes cell death. J Biol Chem. 2005;280:29096–106. PubMed PMID: 15964845.

Seki T, Shimahara T, Yamamoto K, Abe N, Amano T, Adachi N, Takahashi H, Kashiwagi K, Saito N, Sakai N. Mutant gammaPKC found in spinocerebellar ataxia type 14 induces aggregate-independent maldevelopment of dendrites in primary cultured Purkinje cells. Neurobiol Dis. 2009;33:260–73. PubMed PMID: 19041943.

Seki T, Takahashi H, Adachi N, Abe N, Shimahara T, Saito N, Sakai N. Aggregate formation of mutant protein kinase C gamma found in spinocerebellar ataxia type 14 impairs ubiquitin-proteasome system and induces endoplasmic reticulum stress. Eur J Neurosci. 2007;26:3126–40. PubMed PMID: 18005063.

Stenson PD, Mort M, Ball EV, Chapman M, Evans K, Azevedo L, Hayden M, Heywood S, Millar DS, Phillips AD, Cooper DN. The Human Gene Mutation Database (HGMD®): optimizing its use in a clinical diagnostic or research setting. Hum Genet. 2020;139:1197–207. PubMed PMID: 32596782.

Stevanin G, Hahn V, Lohmann E, Bouslam N, Gouttard M, Soumphonphakdy C, Welter ML, Ollagnon-Roman E, Lemainque A, Ruberg M, Brice A, Durr A. Mutation in the catalytic domain of protein kinase C gamma and extension of the phenotype associated with spinocerebellar ataxia type 14. Arch Neurol. 2004;61:1242–8. PubMed PMID: 15313841.

Takahashi H, Adachi N, Shirafuji T, Danno S, Ueyama T, Vendruscolo M, Shuvaev AN, Sugimoto T, Seki T, Hamada D, Irie K, Hirai H, Sakai N, Saito N. Identification and characterization of PKCγ, a kinase associated with SCA14, as an amyloidogenic protein. Hum Mol Genet. 2015;24:525–39. PubMed PMID: 25217572.

Trzesniewski J, Altmann S, Jäger L, Kapfhammer JP. Reduced Purkinje cell size is compatible with near normal morphology and function of the cerebellar cortex in a mouse model of spinocerebellar ataxia. Exp Neurol. 2019;311:205–12. PubMed PMID: 30312605.

van de Warrenburg BP, Notermans NC, Schelhaas HJ, van Alfen N, Sinke RJ, Knoers NV, Zwarts MJ, Kremer BP. Peripheral nerve involvement in spinocerebellar ataxias. Arch Neurol. 2004;61:257–61. PubMed PMID: 14967775.

van de Warrenburg BP, Verbeek DS, Piersma SJ, Hennekam FA, Pearson PL, Knoers NV, Kremer HP, Sinke RJ. Identification of a novel SCA14 mutation in a Dutch autosomal dominant cerebellar ataxia family. Neurology. 2003;61:1760–5. PubMed PMID: 14694043.

van Gaalen J, Vermeer S, van Veluw M, van de Warrenburg BP, Dooijes D. A de novo SCA14 mutation in an isolated case of late-onset cerebellar ataxia. Mov Disord. 2013;28:1902–3. PubMed PMID: 23853068.

Verbeek DS, Goedhart J, Bruinsma L, Sinke RJ, Reits EA. PKC gamma mutations in spinocerebellar ataxia type 14 affect C1 domain accessibility and kinase activity leading to aberrant MAPK signaling. J Cell Sci. 2008;121:2339–49. PubMed PMID: 18577575.

Verbeek DS, Warrenburg BP, Hennekam FA, Dooijes D, Ippel PF, Verschuuren-Bemelmans CC, Kremer HP, Sinke RJ. Gly118Asp is a SCA14 founder mutation in the Dutch ataxia population. Hum Genet. 2005;117:88–91. PubMed PMID: 15841389.

Visser JE, Bloem BR, van de Warrenburg BP. PRKCG mutation (SCA-14) causing a Ramsay Hunt phenotype. Mov Disord. 2007;22:1024–6. PubMed PMID: 17343273.

Vlak MH, Sinke RJ, Rabelink GM, Kremer BP, van de Warrenburg BP. Novel PRKCG/SCA14 mutation in a Dutch spinocerebellar ataxia family: expanding the phenotype. Mov Disord. 2006;21:1025–8. PubMed PMID: 16547918.

Wedding IM, Koht J, Dietrichs E, Landrø NI, Tallaksen CM. Cognition is only minimally impaired in Spinocerebellar ataxia type 14 (SCA14): a neuropsychological study of ten Norwegian subjects compared to intrafamilial controls and population norm. BMC Neurol. 2013;13:186. PubMed PMID: 24289098.

Wieczorek S, Arning L, Gizewski ER, Alheite I, Timmann D. Benign SCA14 phenotype in a German patient associated with a missense mutation in exon 3 of the PRKCG gene. Mov Disord. 2007;22:2135–6. PubMed PMID: 17708558.

Wong MMK, Hoekstra SD, Vowles J, Watson LM, Fuller G, Németh AH, Cowley SA, Ansorge O, Talbot K, Becker EBE. Neurodegeneration in SCA14 is associated with increased PKCγ kinase activity, mislocalization and aggregation. Acta Neuropathol Commun. 2018;6:99. PubMed PMID: 30249303.

Yabe I, Sasaki H, Chen DH, Raskind WH, Bird TD, Yamashita I, Tsuji S, Kikuchi S, Tashiro K. Spinocerebellar ataxia type 14 caused by a mutation in protein kinase C gamma. Arch Neurol. 2003;60:1749–51. PubMed PMID: 14676051.

Yamashita I, Sasaki H, Yabe I, Fukazawa T, Nogoshi S, Komeichi K, Takada A, Shiraishi K, Takiyama Y, Nishizawa M, Kaneko J, Tanaka H, Tsuji S, Tashiro K. A novel locus for dominant cerebellar ataxia (SCA14) maps to a 10.2-cM interval flanked by D19S206 and D19S605 on chromosome 19q13.4-qter. Ann Neurol. 2000;48:156–63. PubMed PMID: 10939565.

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