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NLM Citation: Brussino A, Brusco A, Durr A, et al. Spinocerebellar Ataxia Type 28. 2011 May 17 [Updated 2018 Mar 22]. 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 28

Synonym: SCA28

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Created: May 17, 2011; Updated: March 22, 2018.

Summary

Clinical characteristics

Spinocerebellar ataxia type 28 (SCA28) is characterized by young-adult onset, very slowly progressive gait and limb ataxia resulting in coordination and balance problems, dysarthria, ptosis, nystagmus, and ophthalmoparesis. In most individuals, SCA28 presents as a loss of coordination of lower limbs (unsteadiness, gait ataxia). Less frequently, ptosis/ophthalmoplegia, dysarthria, or upper-limb incoordination may occur as the initial finding. The course of the disease is slowly progressive without impairment of functional autonomy even decades after onset.

Diagnosis/testing

Because the phenotype of SCA28 is indistinguishable from many other inherited disorders with SCA, the diagnosis of SCA28 is established in a proband with typical clinical findings by the identification of a heterozygous pathogenic variant in *AFG3L2* by molecular genetic testing.

Management

Treatment of manifestations: Ambulatory aids (crutches, canes, walkers); home adaptations as needed; physical therapy to help with tasks such as eating, dressing, walking, and bathing; stretching exercise for those with pyramidal involvement to avoid contractions and lack of comfort during sleep. Speech/ language therapy is helpful for those with dysarthria and swallowing difficulties as is surgery for severe ptosis.

Prevention of secondary complications: Psychological support; weight control to facilitate ambulation; thickened feeds or gastrostomy feedings to avoid aspiration pneumonia.

Surveillance: Annual assessment to evaluate stability or progression of the cerebellar ataxia. Monitoring of speech and swallowing.

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Agents/circumstances to avoid: Alcohol consumption and sedatives such as benzodiazepines that may worsen gait ataxia and coordination.

Genetic counseling

SCA28 is inherited in an autosomal dominant manner. Most individuals diagnosed with SCA28 have an affected parent; the proportion of cases caused by *de novo* pathogenic variants is unknown. Each child of an individual with SCA28 has a 50% risk of inheriting the pathogenic variant. Prenatal and preimplantation genetic testing are possible if the pathogenic variant in the family has been identified.

Diagnosis

Suggestive Findings

Spinocerebellar ataxia type 28 (SCA28) **should be suspected in** individuals with the following:

- Onset generally in young adulthood (but with a wide range: ages 3-76 years)
- A slowly progressive gait disorder resulting from cerebellar impairment
- Cerebellar dysarthria
- Oculomotor abnormalities including ophthalmoparesis, nystagmus and ptosis
- Hyperreflexia or brisk deep tendon reflexes
- Brain MRI showing cerebellar atrophy predominantly of the superior vermis, with sparing of the brain stem
- A family history consistent with autosomal dominant inheritance

Establishing the Diagnosis

The diagnosis of SCA28 **is established** in a proband with typical clinical findings and identification of a heterozygous pathogenic (or likely pathogenic) variant in *AFG3L2* by molecular genetic testing (see Table 1).

Note: 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.

Because the phenotype of SCA28 is indistinguishable from many other inherited disorders with SCA, recommended molecular genetic testing approaches include use of a **multigene panel** and **more comprehensive genomic testing**.

Note: Single-gene testing (sequence analysis of *AFG3L2,* followed by gene-targeted deletion/duplication analysis) is rarely useful and typically NOT recommended because of a likely gain-of-function or dominant-negative disease mechanism (see Molecular Genetics).

- **A multigene panel** that includes *AFG3L2* and other genes of interest (see Differential Diagnosis) may be considered. 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*; thus, clinicians need to determine which multigene panel 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. (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 is recommended (see Table 1). At present the role for whole-gene deletions/duplication in the pathology is not supported by available data. Partial-gene deletions, if identified, would require additional studies to determine clinical significance (see Molecular Genetics).

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

- **More comprehensive genomic testing** (when available) including exome sequencing and genome sequencing may be considered. Such testing may provide or suggest a diagnosis not previously considered (e.g., mutation of a different gene or genes that results in a similar clinical presentation).

  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 SCA28

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
AFG3L2	Sequence analysis [3]	>99% [4, 5, 6]
	Gene-targeted deletion/duplication analysis [7]	Extremely rare [8]

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. Unselected individuals, all exons analyzed [Cagnoli et al 2010, Di Bella et al 2010, Fogel et al 2014, Sawyer et al 2014, Pyle et al 2015, Coutelier et al 2017, Iqbal et al 2017]
5. Autosomal dominant cases, all exons analyzed [Jia et al 2012, Németh et al 2013, Löbbe et al 2014, Hadjivassiliou et al 2017, Szpisjak et al 2017]
6. Unselected individuals, only exons 15-16 analyzed [Edener et al 2010, Musova et al 2014]
7. 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.
8. Smets et al [2014] reported a deletion of exons 14-16, which likely truncates the protein, in two families (likely related) with autosomal dominant transmission.

Clinical Characteristics

Clinical Description

Spinocerebellar ataxia type 28 (SCA28) is characterized by young-adult onset, very slowly progressive gait and limb ataxia resulting in coordination and balance problems, dysarthria, ptosis, nystagmus, and ophthalmoparesis.

Age of onset and progression. The usual age at onset is early adulthood (26.5 ± 17.2 years); the range is from age three to 78 years. The course of the disorder is slowly progressive without impairment of functional autonomy even decades after onset.

Presentation. In most individuals, SCA28 presents as a loss of coordination of lower limbs (unsteadiness, gait ataxia). Less frequently, ptosis/ophthalmoplegia, dysarthria, or upper-limb incoordination may occur as the initial finding.

Gait and limb ataxia

- Reflexes may be increased in the lower limbs and Babinski sign is present in some.
- Decreased vibration sense at the ankles is present in some, but superficial sensation is always normal.
- Extrapyramidal signs, either parkinsonism (mainly rigidity and/or bradykinesia) or dystonia, have been observed.

Dysarthria. Severity can vary from individual to individual and changes with progression of the disorder.

- During the initial phases of the disease individuals may have impaired speech, but be easy to understand.
- Later on, speech becomes slurred so that the affected individual is difficult to understand.

Dysphagia. Mild dysphagia has been occasionally reported [Löbbe et al 2014, Zühlke et al 2015, Szpisjak et al 2017].

Ocular problems

- Ptosis
- Nystagmus
- Ophthalmoparesis with limited horizontal and vertical gaze

Intellectual disability, cognitive difficulties, and/or behavior problems have been reported [Cagnoli et al 2010, Edener et al 2010, Musova et al 2014], but are not considered hallmarks of SCA28. Some individuals have memory and attention deficits [Szpisjak et al 2017].

Electrophysiologic studies. Some neurogenic changes have been observed in two individuals [Cagnoli et al 2010], impaired vibration sense in five [Zühlke et al 2015, Svenstrup et al 2017], impaired thermo- and nociception in two [Zühlke et al2015], and metatarsal pallanesthesia in one [Löbbe et al 2014].

Imaging studies. Cerebellar atrophy can be prominent, affecting the vermis with sparing of the brain stem on brain MRI.

Genotype-Phenotype Correlations

No genotype-phenotype correlations can be proposed based on published studies, although persons with the p.Met666Arg, p.Glu700Lys, and p.Gly671Arg pathogenic variants have early-onset disease (i.e., in infancy/childhood), whereas the other pathogenic missense variants are mainly associated with onset in the second to fourth decade [Mariotti et al 2008, Cagnoli et al 2010, Edener et al 2010, Szpisjak at al 2017].

Penetrance

From the studies of SCA28 published to date, disease penetrance appears to be complete.

Prevalence

According to published data, heterozygous pathogenic variants in *AFG3L2* account for approximately 1.5% of autosomal dominant cerebellar ataxia (ADCA) in individuals of European origin [Cagnoli et al 2010, Di Bella et al 2010, Edener et al 2010], with an estimated incidence of 0.045 in 100,000.

Genetically Related (Allelic) Disorders

Spastic ataxia 5 (SPAX5) (OMIM 614487). The phenotype of two brothers from a consanguineous relationship, who were homozygous for the c.1847A>G (p.Tyr616Cys) sequence variant in *AFG3L2*, appears to be complex and severe, including spastic gait and epilepsy leading to death of one of the two affected brothers at age 13 years. Mitochondrial DNA depletion was also noted [Pierson et al 2011]. It is not clear if the phenotype results

from the sequence variant in *AFG3L2* alone or from pathogenic variants in another gene or genes as well. An additional report by Muona et al [2015] described two unrelated individuals with a different homozygous missense variant and a less severe phenotype than those reported by Pierson et al [2011]. The variants associated with SPAX5 occur outside the region common for SCA28-causing variants.

Differential Diagnosis

The ataxic gait of persons with SCA28 is indistinguishable from that seen in other adult-onset inherited or acquired ataxias. When the family history suggests autosomal dominant inheritance, all other autosomal dominant cerebellar ataxias (ADCAs) have to be considered (see Hereditary Ataxia Overview).

- The most commonly occurring SCAs, those caused by polyglutamine expansions (i.e., SCA1, SCA2, SCA3, SCA7, SCA17 and DRPLA), usually begin before age 30 years, are more rapidly progressive, and have brain stem involvement on MRI.
- SCA6 is characterized by adult-onset slowly progressive ataxia and gaze-evoked nystagmus findings that overlap with those of SCA28.
- SPG7 is characterized by adult-onset slowly progressive ataxia with increased reflexes (or even spasticity), ophthalmoparesis, and optic atrophy.
- Friedreich ataxia and ataxia with oculomotor apraxia type 1 and type 2 (AOA1 and AOA2) are autosomal recessive and more rapidly progressive than SCA28, and usually have childhood onset and severe peripheral involvement (polyneuropathy).

Mitochondrial disorders, especially those associated with external ophthalmoplegia and ptosis, should be considered as well (see Mitochondrial DNA Deletion Syndromes and Mitochondrial Disorders Overview).

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs of an individual diagnosed with spinocerebellar ataxia type 28 (SCA28) the following evaluations are recommended if they have not already been completed:

- Neurologic examination (including scales to evaluate the severity of cerebellar ataxia and to allow subjective follow up)
- Cerebral MRI

  Note: MRI is part of the routine evaluation of persons with ataxia; however, in SCA28 no association between the extent of cerebellar atrophy and disease severity or progression has been proven.
- Speech assessment and evaluation for swallowing difficulties
- Examination by an ophthalmologist
- Evaluation of cognitive abilities
- Consultation with a clinical geneticist and/or genetic counselor

Treatment of Manifestations

At present, only symptomatic treatments are available. These include the following:

- Crutches (less often canes) and walkers
- Home adaptations including grab bars for the bathtub or shower chairs and raised toilet seats as needed

- Physical therapy to ameliorate coordination difficulties, especially with tasks such as eating, dressing, walking, and bathing
- Stretching exercise for those with pyramidal involvement to avoid contractions and lack of comfort during sleep
- Speech/language therapy for dysarthria and swallowing difficulties
- Surgical intervention as needed for severe ptosis

Prevention of Secondary Complications

Psychological support helps affected individuals cope with the consequences of the disease.

Weight control can facilitate ambulation.

To avoid complications such as aspiration pneumonia, thickened feeds or gastrostomy should be considered.

Surveillance

Annual assessment of the cerebellar ataxia using SARA (Scale for the Assessment and Rating of Cerebellar Ataxia), CCFS (Composite Cerebellar Functional Severity Score), or similar scales should be performed to evaluate stability or progression of the disease.

Monitoring of speech and swallowing difficulties is recommended.

Agents/Circumstances to Avoid

Alcohol consumption and sedatives such as benzodiazepines may worsen gait ataxia and coordination difficulties.

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.

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 28 (SCA28) is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- Most individuals diagnosed with SCA28 have an affected parent.

- A proband with SCA28 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.
- 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 leukocyte DNA of either parent, two possible explanations are germline mosaicism in a parent or a *de novo* pathogenic variant in the proband. Although no instances of germline mosaicism have been reported, it remains a possibility.
- The family history of some individuals diagnosed with SCA28 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 molecular genetic testing has been performed on the parents of the proband.

Note: If the parent is the individual in whom the pathogenic variant first occurred, the parent may have somatic mosaicism for the pathogenic variant and may be mildly/minimally affected.

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, the risk to the sibs of inheriting the variant is 50%.
- If the parents have been tested for the *AFG3L2* pathogenic variant identified in the proband and:
  - A parent of the proband has the *AFG3L2* pathogenic variant, the risk to the sibs of inheriting the variant is 50%. The intrafamilial phenotypic variability reported among affected individuals is usually related to onset age or disease duration.
  - The *AFG3L2* pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, the risk to sibs is presumed to be slightly greater than that of the general population (though still <1%) because of the theoretic risk of parental germline mosaicism.
- If the parents have not been tested for the *AFG3L2* pathogenic variant but are clinically unaffected, the risk to the sibs of a proband appears to be low. The sibs of a proband with clinically unaffected parents are still at increased risk for SCA28 because of the possibility of reduced penetrance in a parent or the theoretic risk of parental germline mosaicism.

Offspring of a proband. Each child of an individual with SCA28 is at 50% risk of inheriting the pathogenic variant.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent has the *AFG3L2* pathogenic variant, the parent's family members may be 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 it is likely that the proband has the disorder as a result of a *de novo* pathogenic variant. However, possible non-medical explanations including alternate paternity or maternity (e.g., with assisted reproduction) and undisclosed adoption could also be explored.

Testing of at-risk asymptomatic adults. Testing of at-risk asymptomatic adults for SCA28 is possible using the techniques described in Molecular Genetic Testing. Such testing is not useful in accurately predicting age of onset, disease severity, type of symptoms, or rate of progression in asymptomatic individuals. When testing at-risk individuals for SCA28 an affected family member should be tested first to confirm the molecular diagnosis in the family.

Testing for the pathogenic variant in the absence of definite symptoms of the disease is predictive testing. At-risk asymptomatic adult family members may seek testing in order to make personal decisions regarding reproduction, financial matters, and career planning. Others may have different motivations including simply the "need to know." Testing of asymptomatic at-risk adult family members should involve pre-test interviews in which the motives for requesting the test, the individual's knowledge of SCA28, the possible impact of positive and negative test results, and neurologic status are assessed. Those seeking testing should be counseled about possible problems that they may encounter with regard to health, life, and disability insurance coverage, employment and educational discrimination, and changes in social and family interaction. Other issues to consider are implications for the at-risk status of other family members. Informed consent should be procured and records kept confidential. Individuals with a positive test result need arrangements for long-term follow-up and evaluations.

Molecular genetic testing of asymptomatic individuals younger than age 18 years who are at risk for adult-onset disorders for which no treatment exists is not considered appropriate, 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 also 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.

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 *AFG3L2* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are 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

- **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 28: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
AFG3L2	18p11.21	AFG3-like protein 2	AFG3L2 database	AFG3L2	AFG3L2

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 28 (View All in OMIM)

604581	AFG3-LIKE MATRIX AAA PEPTIDASE, SUBUNIT 2; AFG3L2
610246	SPINOCEREBELLAR ATAXIA 28; SCA28

Gene structure. *AFG3L2* has 17 coding exons and spans ~48 kb on chromosome 18p11.21. There is a single disease-relevant transcript encoding for a 797-amino acid protein. The 3'UTR of the gene partially overlaps the 5'UTR of a *TUBB6* mRNA isoform.

Pathogenic variants. All known pathogenic variants are missense variants or small insertion/deletion variants.

Variants predicted to be loss-of-function should be interpreted cautiously, and referred as pathogenic only if supported by functional studies. For example, a potential loss-of-function variant in one case results in a truncated protein being produced, suggesting a dominant-negative mechanism [Smets et al 2014üü]. However, in a second case a c.1958dupT variant was passed from an affected mother to her unaffected daughter, strongly suggesting that the variant is not associated with disease [Musova et al 2014].

Table 2. *AFG3L2* Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.1295A>C	p.Asn432Thr	NM_006796.2 NP_006787.2
c.1958dupT	p.Thr654AsnfsTer15	
c.1996A>G	p.Met666Val	
c.1997T>G	p.Met666Arg	
c.1997T>C	p.Met666Thr	
c.2011G>A	p.Gly671Arg	
c.2012G>A	p.Gly671Glu	
c.2062C>A	p.Pro688Thr	
c.2065T>A	p.Tyr689Asn	
c.2065T>C	p.Tyr689His	
c.2098G>A	p.Glu700Lys	

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.

Normal gene product. *AFG3L2* encodes an ATP-dependent metalloprotease belonging to the AAA-superfamily (*A*TPases *a*ssociated with a variety of cellular activities). This gene was cloned as a paralog of *SPG7* (paraplegin) [Banfi et al 1999], whose homozygous inactivation causes an autosomal recessive form of hereditary spastic paraplegia (HSP) [Casari et al 1998] (see Spastic Paraplegia 7).

Both AFG3L2 and paraplegin are mitochondrial proteins, and are highly conserved through evolution – the orthologous protein FtsH being present in *E coli* [Ito & Akiyama 2005].

The two proteins have been extensively studied in yeast models (orthologous genes are *Yta10* (*SPG7*) and *Yta12* (*AFG3L2*). Yta10p-12p constitutes a membrane-embedded complex of ~850 kd (m-AAA protease), active on the matrix side of the inner mitochondrial membrane (IMM) [Arlt et al 1996, Arlt et al 1998].

Studies in yeast assigned a dual activity to the m-AAA protease for protein degradation and activation (cleavage) [Nolden et al 2005]:

1. It conducts protein quality surveillance in the IMM and degrades non-assembled membrane proteins to peptides [Arlt et al 1996, Leonhard et al 2000];
2. It mediates protein processing and thereby activates certain mitochondrial proteins [Koppen et al 2009].

Abnormal gene product. Except for one pathogenic variant (c.1295A>C; p.Asn432Thr), all known pathogenic variants are located in the M41-protease domain of the AFG3L2 protein [Cagnoli et al 2010, Di Bella et al 2010, Edener et al 2010].

The clustering of missense variants in a narrow region of the protein suggests the presence of a critical functional domain. Several pathogenic variants occur on the same three codons: p.Met666, p.Gly671, and p.Tyr689. Data extracted from ExAC and gnomAD metrics include loss-of-function variants reported in the population (exac.broadinstitute.org; gnomad.broadinstitute.org) [Lek et al 2016]. Of note, 66 control subjects (~1:1,800) are reported in gnomAD data with frameshift/stop-gain/splicing variants/exome deletions.

Overall these data strongly indicate that haplosufficient alleles occur in the population, and that *AFG3L2* variants causative of SCA28 act through a gain-of-function or dominant-negative mechanism.

Yta10-Yta12-deficient yeast cells fail to be complemented by expression of mutated human AFG3L2 protein [Di Bella et al 2010].

Chapter Notes

Acknowledgments

Telethon Foundation support is gratefully acknowledged (grant GGP07110)

Revision History

- 22 March 2018 (ha) Comprehensive update posted live
- 7 February 2013 (cd) Revision: prenatal diagnosis available
- 17 May 2011 (me) Review posted live
- 7 February 2011 (ab) Original submission

References

Published Guidelines / Consensus Statements

Committee on Bioethics, Committee on Genetics, and American College of Medical Genetics and Genomics Social, Ethical, Legal Issues Committee. Ethical and policy issues in genetic testing and screening of children. Available online. 2013. Accessed 6-27-22.

National Society of Genetic Counselors. Position statement on genetic testing of minors for adult-onset conditions. Available online. 2018. Accessed 6-27-22.

Literature Cited

Arlt H, Steglich G, Perryman R, Guiard B, Neupert W, Langer T. The formation of respiratory chain complexes in mitochondria is under the proteolytic control of the m-AAA protease. EMBO J. 1998;17:4837–47. PubMed PMID: 9707443.

Arlt H, Tauer R, Feldmann H, Neupert W, Langer T. The YTA10-12 complex, an AAA protease with chaperone-like activity in the inner membrane of mitochondria. Cell. 1996;85:875–85. PubMed PMID: 8681382.

Banfi S, Bassi MT, Andolfi G, Marchitiello A, Zanotta S, Ballabio A, Casari G, Franco B. Identification and characterization of AFG3L2, a novel paraplegin-related gene. Genomics. 1999;59:51–8. PubMed PMID: 10395799.

Cagnoli C, Stevanin G, Brussino A, Barberis M, Mancini C, Margolis RL, Holmes SE, Nobili M, Forlani S, Padovan S, Pappi P, Zaros C, Leber I, Ribai P, Pugliese L, Assalto C, Brice A, Migone N, Dürr A, Brusco A. Missense mutations in the AFG3L2 proteolytic domain account for ~1.5% of European autosomal dominant cerebellar ataxias. Hum Mutat. 2010;31:1117–24. PubMed PMID: 20725928.

Casari G, De Fusco M, Ciarmatori S, Zeviani M, Mora M, Fernandez P, De Michele G, Filla A, Cocozza S, Marconi R, Dürr A, Fontaine B, Ballabio A. Spastic paraplegia and OXPHOS impairment caused by mutations in paraplegin, a nuclear-encoded mitochondrial metalloprotease. Cell. 1998;93:973–83. PubMed PMID: 9635427.

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. SPATAX network. A panel study on patients with dominant cerebellar ataxia highlights the frequency of channelopathies. Brain. 2017;140:1579–94. PubMed PMID: 28444220.

Di Bella D, Lazzaro F, Brusco A, Plumari M, Battaglia G, Pastore A, Finardi A, Cagnoli C, Tempia F, Frontali M, Veneziano L, Sacco T, Boda E, Brussino A, Bonn F, Castellotti B, Baratta S, Mariotti C, Gellera C, Fracasso V, Magri S, Langer T, Plevani P, Di Donato S, Muzi-Falconi M, Taroni F. Mutations in the mitochondrial protease gene AFG3L2 cause dominant hereditary ataxia SCA28. Nat Genet. 2010;42:313–21. PubMed PMID: 20208537.

Edener U, Wöllner J, Hehr U, Kohl Z, Schilling S, Kreuz F, Bauer P, Bernard V, Gillessen-Kaesbach G, Zühlke C. Early onset and slow progression of SCA28, a rare dominant ataxia in a large four-generation family with a novel AFG3L2 mutation. Eur J Hum Genet. 2010; 2010;18:965–8. PubMed PMID: 20354562.

Fogel BL, Lee H, Deignan JL, Strom SP, Kantarci S, Wang X, Quintero-Rivera F, Vilain E, Grody WW, Perlman S, Geschwind DH, Nelson SF. Exome sequencing in the clinical diagnosis of sporadic or familial cerebellar ataxia. JAMA Neurol. 2014;71:1237–46. PubMed PMID: 25133958.

Hadjivassiliou M, Martindale J, Shanmugarajah P, Grünewald RA, Sarrigiannis PG, Beauchamp N, Garrard K, Warburton R, Sanders DS, Friend D, Duty S, Taylor J, Hoggard N. Causes of progressive cerebellar ataxia: prospective evaluation of 1500 patients. J Neurol Neurosurg Psychiatry. 2017;88:301–9. PubMed PMID: 27965395.

Iqbal Z, Rydning SL, Wedding IM, Koht J, Pihlstrøm L, Rengmark AH, Henriksen SP, Tallaksen CM, Toft M. Targeted high throughput sequencing in hereditary ataxia and spastic paraplegia. PLoS One. 2017;12:e0174667. PubMed PMID: 28362824.

Ito K, Akiyama Y. Cellular functions, mechanism of action, and regulation of FtsH protease. Annu Rev Microbiol. 2005;59:211–31. PubMed PMID: 15910274.

Jia D, Tang B, Chen Z, Shi Y, Sun Z, Zhang L, Wang J, Xia K, Jiang H. Spinocerebellar ataxia type 28 (SCA28) is an uncommon cause of dominant ataxia among Chinese kindreds. Int J Neurosci. 2012;122:560–2. PubMed PMID: 22563911.

Koppen M, Bonn F, Ehses S, Langer T. Autocatalytic processing of m-AAA protease subunits in mitochondria. Mol Biol Cell. 2009;20:4216–24. PubMed PMID: 19656850.

Lek M, Karczewski KJ, Minikel EV, Samocha KE, Banks E, Fennell T, et al. Analysis of protein-coding genetic variation in 60,706 humans. Nature. 2016;536:285–91. PubMed PMID: 27535533.

Leonhard K, Guiard B, Pellecchia G, Tzagoloff A, Neupert W, Langer T. Membrane protein degradation by AAA proteases in mitochondria: extraction of substrates from either membrane surface. Mol Cell. 2000;5:629–38. PubMed PMID: 10882099.

Löbbe AM, Kang JS, Hilker R, Hackstein H, Müller U, Nolte D. A novel missense mutation in AFG3L2 associated with late onset and slow progression of spinocerebellar ataxia type 28. J Mol Neurosci. 2014;52:493–6. PubMed PMID: 24293060.

Mariotti C, Brusco A, Di Bella D, Cagnoli C, Seri M, Gellera C, Di Donato S, Taroni F. Spinocerebellar ataxia type 28: a novel autosomal dominant cerebellar ataxia characterized by slow progression and ophthalmoparesis. Cerebellum. 2008;7:184–8. PubMed PMID: 18769991.

Muona M, Berkovic SF, Dibbens LM, Oliver KL, Maljevic S, Bayly MA, Joensuu T, Canafoglia L, Franceschetti S, Michelucci R, Markkinen S, Heron SE, Hildebrand MS, Andermann E, Andermann F, Gambardella A, Tinuper P, Licchetta L, Scheffer IE, Criscuolo C, Filla A, Ferlazzo E, Ahmad J, Ahmad A, Baykan B, Said E, Topcu M, Riguzzi P, King MD, Ozkara C, Andrade DM, Engelsen BA, Crespel A, Lindenau M, Lohmann E, Saletti V, Massano J, Privitera M, Espay AJ, Kauffmann B, Duchowny M, Møller RS, Straussberg R, Afawi Z, Ben-Zeev B, Samocha KE, Daly MJ, Petrou S, Lerche H, Palotie A, Lehesjoki AE. A recurrent de novo mutation in KCNC1 causes progressive myoclonus epilepsy. Nat Genet. 2015;47:39–46. PubMed PMID: 25401298.

Musova Z, Kaiserova M, Kriegova E, Fillerova R, Vasovcak P, Santava A, Mensikova K, Zumrova A, Krepelova A, Sedlacek Z, Kanovsky P. A novel frameshift mutation in the AFG3L2 gene in a patient with spinocerebellar ataxia. Cerebellum. 2014;13:331–7. PubMed PMID: 24272953.

Németh AH, Kwasniewska AC, Lise S, Parolin Schnekenberg R, Becker EB, Bera KD, Shanks ME, Gregory L, Buck D, Zameel Cader M, Talbot K, de Silva R, Fletcher N, Hastings R, Jayawant S, Morrison PJ, Worth P, Taylor M, Tolmie J, O'Regan M; UK Ataxia Consortium. Valentine R, Packham E, Evans J, Seller A, Ragoussis J. Next generation sequencing for molecular diagnosis of neurological disorders using ataxias as a model. Brain. 2013;136:3106–18. PubMed PMID: 24030952.

Nolden M, Ehses S, Koppen M, Bernacchia A, Rugarli EI, Langer T. The m-AAA protease defective in hereditary spastic paraplegia controls ribosome assembly in mitochondria. Cell. 2005;123:277–89. PubMed PMID: 16239145.

Pierson TM, Adams D, Bonn F, Martinelli P, Cherukuri PF, Teer JK, Hansen NF, Cruz P. Mullikin For The Nisc Comparative Sequencing Program JC, Blakesley RW, Golas G, Kwan J, Sandler A, Fuentes Fajardo K, Markello T, Tifft C, Blackstone C, Rugarli EI, Langer T, Gahl WA, Toro C. Whole-exome sequencing identifies homozygous AFG3L2 mutations in a spastic ataxia-neuropathy syndrome linked to mitochondrial m-AAA proteases. PLoS Genet. 2011;7:e1002325. PubMed PMID: 22022284.

Pyle A, Smertenko T, Bargiela D, Griffin H, Duff J, Appleton M, Douroudis K, Pfeffer G, Santibanez-Koref M, Eglon G, Yu-Wai-Man P, Ramesh V, Horvath R, Chinnery PF. Exome sequencing in undiagnosed inherited and sporadic ataxias. Brain. 2015;138:276–83. PubMed PMID: 25497598.

Sawyer SL, Schwartzentruber J, Beaulieu CL, Dyment D, Smith A, Warman Chardon J, Yoon G, Rouleau GA, Suchowersky O, Siu V, Murphy L, Hegele RA, Marshall CR; FORGE Canada Consortium. Bulman DE, Majewski J, Tarnopolsky M, Boycott KM. Exome sequencing as a diagnostic tool for pediatric-onset ataxia. Hum Mutat. 2014;35:45–9. PubMed PMID: 24108619.

Smets K, Deconinck T, Baets J, Sieben A, Martin JJ, Smouts I, Wang S, Taroni F, Di Bella D, Van Hecke W, Parizel PM, Jadoul C, De Potter R, Couvreur F, Rugarli E, De Jonghe P. Partial deletion of AFG3L2 causing spinocerebellar ataxia type 28. Neurology. 2014;82:2092–100. PubMed PMID: 24814845.

Svenstrup K, Nielsen TT, Aidt F, Rostgaard N, Duno M, Wibrand F, Vinther-Jensen T, Law I, Vissing J, Roos P, Hjermind LE, Nielsen JE. SCA28: novel mutation in the AFG3L2 proteolytic domain causes a mild cerebellar syndrome with selective type-1 muscle fiber atrophy. Cerebellum. 2017;16:62–7. PubMed PMID: 26868664.

Szpisjak L, Nemeth VL, Szepfalusi N, Zadori D, Maroti Z, Kalmar T, Vecsei L, Klivenyi P. Neurocognitive characterization of an SCA28 family caused by a novel AFG3L2 gene mutation. Cerebellum. 2017;16:979–85. PubMed PMID: 28660440.

Zühlke C, Mikat B, Timmann D, Wieczorek D, Gillessen-Kaesbach G, Bürk K. Spinocerebellar ataxia 28: a novel AFG3L2 mutation in a German family with young onset, slow progression and saccadic slowing. Cerebellum Ataxias. 2015;2:19. PubMed PMID: 26677414.

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