



Spinocerebellar Ataxia Type 11

Synonym: SCA11

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Summary

Clinical characteristics

Spinocerebellar ataxia type 11 (SCA11) is characterized by progressive cerebellar ataxia and abnormal eye signs (jerky pursuit, horizontal and vertical nystagmus). Pyramidal features are seen on occasion. Peripheral neuropathy and dystonia are rare. Six families have been reported to date, one each from the UK, Pakistan, France, Germany, Denmark, and China. Age of onset ranged from early childhood to the mid-40s. Life span is thought to be normal.

Diagnosis/testing

The diagnosis of spinocerebellar ataxia type 11 (SCA11) is established in a proband with a heterozygous pathogenic variant in *TTBK2* identified by molecular genetic testing.

Management

Treatment of manifestations: Management is supportive; there are no known disease-modifying treatments to date. Physiotherapy and assessment for assistive devices for ambulation; occupational therapy, including home adaptations; speech and language therapy for dysarthria and dysphagia; ankle-foot orthotics if required and good foot care for those with neuropathy; treatment per ophthalmologist for vision issues; prism glasses may be helpful for diplopia.

Surveillance: Annual neurologic evaluation; evaluations with physiotherapist, occupational therapist, speech and language therapist, and ophthalmologist as indicated.

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Genetic counseling

SCA11 is inherited in an autosomal dominant manner. The proportion of SCA11 caused by *de novo* mutation is unknown. Each child of an individual with SCA11 has a 50% chance of inheriting the pathogenic variant. Prenatal testing for an at-risk pregnancy is possible if the diagnosis has been established by molecular genetic testing in an affected family member.

Diagnosis

Suggestive Findings

Spinocerebellar ataxia type 11 (SCA11) **should be considered** in individuals with the following clinical features:

- Progressive cerebellar ataxia
- Abnormal eye signs (jerky pursuit, horizontal and vertical nystagmus)
- Dysarthria
- Pyramidal features (mild-to-moderate lower-extremity hyperreflexia; in very rare cases, a positive Babinski sign or other pyramidal features)
- Swallowing difficulties

Rare findings in SCA11:

- Peripheral neuropathy
- Dystonia

Establishing the Diagnosis

The diagnosis of spinocerebellar ataxia type 11 (SCA11) **is established** in a proband with a heterozygous pathogenic variant in *TTBK2* identified by molecular genetic testing (see Table 1).

Because the phenotype of SCA11 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 *TTBK2*, followed by gene-targeted deletion/duplication analysis) is rarely useful and typically NOT recommended.

- **An ataxia multigene panel** that includes *TTBK2* 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*. Of note, given the rarity of SCA11, some panels for ataxia may not include this gene. (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 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 11

Gene ¹	Method	Proportion of Probands with a Pathogenic Variant ² Detectable by Method
<i>TTBK2</i>	Sequence analysis ³	6/6 families 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. Houlden et al [2007], Bauer et al [2010], Lindquist et al [2017], Deng et al [2020]

5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include 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. No data on detection rate of gene-targeted deletion/duplication analysis are available.

Clinical Characteristics

Clinical Description

To date, 28 individuals from six families have been identified with a pathogenic variant in *TTBK2* [Houlden et al 2007, Bauer et al 2010, Lindquist et al 2017, Deng et al 2020]. The following description of the phenotypic features associated with this condition is based on these reports.

Table 2. Clinical Features of Spinocerebellar Ataxia Type 11

Feature	Number of Persons w/Feature	Comment
Cerebellar ataxia	28/28	Variable truncal &/or gait ataxia
Limb ataxia	21/28	
Dysarthria	22/28	
Jerky pursuit	18/28	
Nystagmus	20/28	
Ophthalmoplegia	2/28	
Diplopia	4/28	
Hyperreflexia	18/28	<ul style="list-style-type: none"> • Most prominent in the British family • Lower > upper limbs
Extrapyramidal features	1/28	<ul style="list-style-type: none"> • Laterocollis • "No-no" head tremor

Onset. In the six families described with spinocerebellar ataxia type 11 (SCA11), age of onset ranged from age nine years in the family of Danish origin to age 40–50 years in the families from France, Germany, and China. Most individuals present with a pure ataxia phenotype, with few additional features. Abnormal eye findings were identified in a third of individuals, a small proportion of whom presented with diplopia at onset.

Ataxia. The cerebellar ataxia was clinically similar in all six families. All individuals presented with an ataxia-predominant disorder and difficulty walking due to unsteadiness and maintaining balance. In approximately a third of individuals, limb ataxia was also present. Ataxia was usually slowly progressive. For example, in the British family described, the mean disease duration was 26.8 years [Houlden et al 2007].

Abnormal eye findings include jerky pursuit and horizontal and vertical nystagmus. All of the individuals with SCA11 from Devon had abnormal eye movements at presentation, with jerky pursuit and vertical nystagmus more prevalent than horizontal nystagmus [Houlden et al 2007]. Half of the individuals with vertical nystagmus had an upbeat nystagmus [Giunti et al 2012]. Only a very small proportion were found to be symptomatic with ophthalmoplegia and diplopia. No members of the French family had abnormal eye findings. One individual in the German family had oculomotor disturbances with jerky pursuit, gaze-evoked nystagmus, dysmetric saccades, and impaired optokinetic nystagmus on presentation, nine years after symptom onset [Bauer et al 2010]. In the Danish family, one individual presented with diplopia and nystagmus at age nine years [Lindquist et al 2017]. A sib presented at age four years with ataxia and was found to have nystagmus at age nine years [Lindquist et al 2017]. Three individuals of Chinese descent had nystagmus at the time of presentation [Deng et al 2020]. It is unclear if abnormal eye findings progress, but ocular symptoms were the only presenting feature for one individual out of 28 affected. Although abnormal eye findings may be seen at the time of presentation, they are rarely symptomatic.

Pyramidal features exist in varying degrees across the different families. In the British family, mild limb hyperreflexia more prevalent in the upper than the lower limbs (with negative Babinski sign) was found in all but one affected individual [Houlden et al 2007]. In the family from Pakistan, mild-to-moderate hyperreflexia was observed in only two of five affected individuals [Houlden et al 2007]. Only one of the three individuals affected from the Danish family had hyperreflexia [Lindquist et al 2017]. Two of the five individuals of Chinese descent had hyperreflexia [Deng et al 2020]. Reflexes and tone were, however, normal in the German and French families described [Bauer et al 2010].

No other pyramidal signs apart from hyperreflexia were observed in the 28 individuals apart from one individual with upgoing plantar reflexes. This individual from Devon presented with both extrapyramidal and pyramidal signs including spastic gait, hyperreflexia with upgoing plantar reflexes, "no-no" head tremor, and upper-limb tremor with laterocollis [Giunti et al 2012]. No extrapyramidal signs have been described in other individuals.

Bulbar symptoms. Dysarthria and swallowing difficulties are common in individuals with SCA11. Dysarthria as a result of cerebellar dysfunction was moderate to severe in almost all individuals in the families of British and Pakistani origin but was not present at diagnosis [Houlden et al 2007]. In the French family, dysarthria was an early feature [Bauer et al 2010]. Dysarthria was reported to be progressive in individuals in the family of Chinese origin [Deng et al 2020]. Liquid dysphagia was also noted in individuals with SCA11, especially in the families from Devon and China, but was not common at presentation.

Peripheral neuropathy is not a common feature of SCA11. In the British cohort, nerve conduction studies (NCS) and electromyography (EMG) were normal in eight affected subjects [Houlden et al 2007]. One other affected subject had slightly small sensory nerve action potentials at the age of 61 (disease duration 43 years) but without clinically manifesting neuropathy. In the Pakistani, Danish, French, and German families, neuropathy was not seen. In the Chinese family, EMG of the proband showed extensive neurogenic damage. Somatosensory evoked potentials of the lower limbs were abnormal. Generalized neurogenic damage was seen on NCS and EMG of two other affected Chinese individuals, but it is not apparent whether these individuals also presented with neuropathy symptoms clinically.

Other. One individual from Devon presented with laterocollis [Giunti et al 2012]. Dystonia has not been described in other individuals.

Prognosis. SCA11 is slowly progressive with severity ranging from very mild balance problems at disease onset, to severe speech and swallowing problems and ataxia requiring the use of a wheelchair. In affected individuals from the British and Pakistani families, eight of 17 persons required a wheelchair 20 to 30 years after onset. The same was reported in the French and German families, where progression of disease is slow; individuals remained active many years and required a wheelchair decades after onset [Bauer et al 2010]. Life span in individuals with SCA11 is normal; many affected individuals live beyond age 75 years. In nine individuals from the British and Pakistani families, death occurred between ages 55 and 88 years.

Neuroimaging. Brain MRI examination shows mild-to-severe atrophy in both cerebellar hemispheres and the vermis. The brain stem and cerebrum were normal in most individuals [Giunti et al 2012]. Occasionally, atrophy has also been described in the medulla but this was not associated with disease severity [Giunti et al 2012, Deng et al 2020]. In a Danish proband, an 18Ffluorodeoxyglucose positron emission tomography scan showed reduced metabolic activity in the cerebellum and pons, and repeat brain MRI four years later showed worsening cerebellar atrophy with olivopontine atrophy [Lindquist et al 2017].

Neuropathology. Neuropathologic examination of the brain of one affected individual showed marked cerebellar and brain stem loss with Purkinje cell degeneration and abnormal tau deposition in the brain stem and cortex [Houlden et al 2007].

Genotype-Phenotype Correlations

No genotype-phenotype correlations have been identified.

Penetrance

The *TTBK2* pathogenic variants in the six families described to date appear to be fully penetrant, although a number of at-risk relatives are younger than the typical age of onset. To date, no non-penetrant pathogenic variants have been identified in older individuals.

Prevalence

Prevalence is unknown but SCA11 is a rare cause of pure spinocerebellar ataxia. It accounts for less than 1% of autosomal dominant ataxia in Europe [Bauer et al 2010]. Pathogenic variants in *TTBK2* were identified in six of 238 families with spinocerebellar ataxia [Houlden et al 2007; Bauer et al 2010; Author, personal observation]. A study in Germany of 49 individuals with a family history of ataxia did not identify pathogenic variants in *TTBK2* [Edener et al 2009]. A study in China of 68 unrelated probands with autosomal dominant ataxia also did not identify pathogenic variants in *TTBK2* [Xu et al 2010].

The six families described with SCA11 are from Devon (UK), Pakistan, France, Germany, Denmark, and China.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *TTBK2*.

Differential Diagnosis

According to AE Harding's classification, spinocerebellar ataxia type 11 (SCA11) is included in the pure autosomal dominant cerebellar ataxias (ADCA III) [Worth et al 1999], the most common group of inherited ataxias. SCA11 accounts for approximately 2% of ADCA III.

Significant overlap is observed between SCA11 and SCA5, SCA6, SCA15, and SCA20, all of which may be distinguished by molecular genetic testing (see Table 3).

Table 3. Hereditary Ataxia Disorders of Interest in the Differential Diagnosis of Spinocerebellar Ataxia Type 11

Gene	Disorder	MOI	Key Clinical Features
<i>CACNA1A</i>	SCA6	AD	Pure cerebellar ataxia w/slow progression. Some described w/downbeat nystagmus, whereas 50% of British individuals w/SCA11 had an upbeat nystagmus.
<i>ITPR1</i>	SCA15 (OMIM 606658)	AD	Slowly progressive pure cerebellar ataxia w/mild tremor & mild hyperreflexia
<i>SPTBN2</i>	SCA5 (OMIM 600224)	AD	Slowly progressive pure cerebellar ataxia
Unknown ¹	SCA20	AD	Slowly progressive cerebellar ataxia w/abnormal phonation & dysarthria, & palatal tremor in 2/3s of individuals. Minor pyramidal signs may also be seen.

AD = autosomal dominant; MOI = mode of inheritance; SCA = spinocerebellar ataxia

1. The locus for SCA20 lies within the pericentromeric region of chromosome 11; the gene is unknown. A 260-kb duplication of 11q12.2-11q12.3 has been proposed as the probable cause of SCA20 in the index family.

See the [Hereditary Ataxia Overview](#) for information on other types of inherited (genetic) ataxia.

Management

Management is supportive; a multidisciplinary approach is recommended.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with spinocerebellar ataxia type 11 (SCA11), the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 4. Recommended Evaluations Following Initial Diagnosis in Individuals with Spinocerebellar Ataxia Type 11

System/Concern	Evaluation	Comment
Neurologic	Neurologic eval	Use SARA to establish baseline.
	Head MRI	Initial imaging to establish extent of cerebellar atrophy at disease presentation
	Feeding eval	To evaluate for bulbar involvement that may require intervention (e.g., adjustment to dietary consistency to improve safe swallow)
	Speech & language therapy eval	If dysarthria is atypical or severe enough to cause communication problems
	PT & OT eval	To evaluate mobility, activities of daily living, & need for adaptive devices
Peripheral nervous system	Nerve conduction studies	Nerve conduction studies recommended to exclude a coexisting neuropathy that may require further monitoring
Ophthalmologic	Ophthalmologic eval	To evaluate eye movement & for diplopia
Other	Consultation w/clinical geneticist &/or genetic counselor	

OT = occupational therapy; PT = physical therapy; SARA = Scale for the Assessment and Rating of Ataxia

Treatment of Manifestations

Management is supportive; no disease-modifying treatments are known to date.

Table 5. Treatment of Manifestations in Individuals with SCA11

Manifestation Concern	Treatment	Considerations/Other
Ataxia	<ul style="list-style-type: none"> PT eval/treatment OT eval/treatment 	Consider adaptive devices (cane &/or wheelchair) & home adaptations to maintain/improve independent mobility.
	Weight control	To facilitate ambulation
Dysarthria & dysphagia	Speech & language therapy eval/treatment	To teach strategies to improve articulation & avoid aspiration
	Modify food consistency to reduce aspiration risk	Video esophagram may help define best consistency.
Peripheral neuropathy	Ankle-foot orthotics	Ensure good foot care & foot health w/regular review by podiatrist.
Diplopia	Ophthalmologic consultation	Prism glasses can be helpful.

OT = occupational therapy; PT = physical therapy

Surveillance

Table 6. Recommended Surveillance for Individuals with SCA11

System/Concern	Evaluation	Frequency
Ataxia	Neurologic eval	Annually
	PT & OT	Ideally, in the context of a multidisciplinary setting w/more intensive follow up if needed
Dysarthria & dysphagia	Eval w/speech-language pathologist	Follow up dependent on severity & requirements
Ophthalmoplegia & diplopia	Ophthalmology	Follow up dependent on severity & requirements

OT = occupational therapy; PT = physical therapy

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](https://clinicaltrials.gov) in the US and [EU Clinical Trials Register](https://clinicaltrialsregister.eu) 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 11 (SCA11) is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- Twenty-seven of 28 of individuals diagnosed with SCA11 have an affected parent.
- A proband with SCA11 may have the disorder as the result of a *de novo* *TTBK2* pathogenic variant. The proportion of cases caused by *de novo* variants is unknown but likely small. To date, *de novo* SCA11 has been seen in one individual, from the family of Danish origin [Lindquist et al 2017].
- 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).
- The family history of some individuals diagnosed with SCA11 may appear to be negative because of failure to recognize the disorder in family members with a milder phenotypic presentation, early death of the parent before the onset of symptoms, or late onset of the disease in the affected parent. Therefore, an apparently negative family history cannot be confirmed unless appropriate molecular genetic testing has been performed on the parents of the proband.

Sibs of a proband. The risk to the sibs of a 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 pathogenic variant identified in the proband, the risk to the sibs is 50%. Age of onset may vary within a family.
- If the proband has a known SCA11-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 *TTBK2* pathogenic variant but are clinically unaffected, sibs are still presumed to be at increased risk for SCA11 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 SCA11 has a 50% chance of inheriting the *TTBK2* 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 pathogenic variant, his or her family members may be at risk.

Related Genetic Counseling Issues

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

- Predictive testing for at-risk relatives is possible once the *TTBK2* pathogenic variant has been identified in an affected family member. Such testing is not useful in accurately 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 SCA11, it is appropriate to consider testing of symptomatic individuals regardless of age.

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 *TTBK2* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis. 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](#).

- **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 11: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
<i>TTBK2</i>	15q15.2	Tau-tubulin kinase 2	TTBK2 database	TTBK2	TTBK2

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 11 ([View All in OMIM](#))

604432	SPINOCEREBELLAR ATAXIA 11; SCA11
611695	TAU TUBULIN KINASE 2; TTBK2

Molecular Pathogenesis

TTBK2 encodes tau-tubulin kinase 2 (TTBK2), which modifies targets such as tau and tubulin, to initiate ciliogenesis [Goetz et al 2012]. TTBK2 phosphorylates the tau protein to exacerbate tau toxicity as well as TDP43, driving neurodegeneration [Taylor et al 2018]. Abnormal tau deposition has been described in SCA11, further implicating the direct link between *TTBK2* and tauopathic disease [Houlden et al 2007].

Non-ciliary functions of TTBK2 within the brain include phosphorylation of synaptic vesicle protein 2A (SV2A), which is important for synaptic vesicle trafficking and regulation of neurotransmitter release [Zhang et al 2015]. TTBK2 has also been implicated in regulation of sodium-coupled transporters [Alesutan et al 2012].

Loss of TTBK2 function affects normal phosphorylation of tau, which leads to tau deposition and impaired ciliogenesis. There is evidence that TTBK2 may interact with the inositol/IP3 pathway and stabilize cells (in particular, Purkinje cells) against calcium-induced cell death [Houlden et al 2007] (see [bioRxiv](#)).

Mechanism of disease causation. Reported *TTBK2* pathogenic variants are predicted to result in premature stop codons, and individuals with SCA11-associated *TTBK2* variants were reported to have mRNA levels reduced by 50% when compared to unaffected individuals [Houlden et al 2007]. Further, treating lymphoblasts from affected individuals with cycloheximide, a known inhibitor of nonsense-mediated decay (NMD), resulted

in increased total *TTBK2* mRNA and a selective increase in the abundance of the mutated mRNA, suggesting that a proportion of the abnormal mRNA escapes NMD [Houlden et al 2007]. This means that a truncated protein could be produced, causing a dominant-negative effect on the normal allele. A recent study showed that the abnormal truncated protein can disrupt function of the residual normal protein in cilium assembly, stability, and signaling, supporting a dominant-negative effect [Bowie et al 2018].

Further supporting the dominant-negative effect is the presence of other reported heterozygous frameshift variants clustered in exon 11, leading to truncation of the *TTBK2* protein C-terminal to the kinase domain at amino acid 450 [Bauer et al 2010] and truncation at amino acid 402 [Lindquist et al 2017] – suggesting a dominant-negative effect exerted by the truncated protein. One missense variant has recently been described in the Chinese population but the mechanism for this is unclear.

No gene-dosage alterations have been detected in *TTBK2*.

Table 7. Notable *TTBK2* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change (Alias ¹)	Predicted Protein Change	Comment [Reference]
NM_173500.3 NP_775771.3	c.1205_1207delinsA	p.Thr402fs	Pathogenic variants clustered in exon 11 [Houlden et al 2007, Bauer et al 2010, Lindquist et al 2017]
	c.1287_1288delAG (1284_1285delAG)	p.Glu429AspfsTer21	
	c.1306_1307delGA	p.Asp435TyrfsTer14	
	c.1329dupA (1329insA)	p.Arg444ThrfsTer7	
	c.3290T>C	p.Val1097Ala	Missense variant identified in a 3-generation Chinese family w/5 individuals w/adult-onset ataxia [Deng et al 2020]

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.

1. Variant designation that does not conform to current naming conventions

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Chapter Notes

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