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RFC1 CANVAS / Spectrum Disorder

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Summary

Clinical characteristics

The phenotypic spectrum associated with biallelic *RFC1* AAGGG repeat expansion encompasses a range including (1) typical *c*erebellar *a*taxia, *n*europathy, *v*estibular *a*reflexia *s*yndrome (CANVAS); (2) cerebellar, sensory, and vestibular impairment; (3) more limited phenotypes involving predominantly or exclusively one of the systems involved in balance control; (4) autonomic dysfunction; and (5) cough. Onset begins after age 35 years. In a retrospective study of 100 affected individuals after ten years of disease duration, two thirds had clinical features of CANVAS; 16 had a complex sensory ataxia with cerebellar or vestibular involvement; and 15 had a sensory neuropathy as the only clinically detectable manifestation.

Diagnosis/testing

The diagnosis of *RFC1* CANVAS / spectrum disorder is established in a proband with suggestive findings and biallelic intronic AAGGG pentanucleotide expansions in *RFC1* identified by molecular genetic testing that is targeted to detect these expansions. Note that pathogenic *RFC1* AAGGG repeat expansions cannot be detected by sequence-based multigene panels or exome sequencing. However, they can be suspected by genome sequencing.

Management

Treatment of manifestations: The goals of treatment are to maximize function and reduce complications. Depending on the clinical manifestations, each affected individual should be managed by a multidisciplinary team of relevant specialists such as neurologists, occupational therapists, physical therapists, physiatrists, and (depending on individual needs) speech therapists, respiratory therapists, nutritionists, and gastroenterologists.

Surveillance: Routine follow up by multidisciplinary specialists to assess: progression of neurologic findings; mobility, self-help skills; need for alternative communication methods; and aspiration risk and feeding methods.

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Agents/circumstances to avoid: Medications of known toxicity for peripheral nerves (e.g., neurotoxic chemotherapy agents, pyridoxine), the cerebellum (e.g., phenytoin), or the vestibular system (e.g., aminoglycosides); chronic alcohol consumption.

Genetic counseling

RFC1 CANVAS / spectrum disorder is inherited in an autosomal recessive manner. If both parents are known to be heterozygous for an *RFC1* AAGGG repeat expansion, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. Once biallelic *RFC1* AAGGG repeat expansions have been identified in an affected family member, carrier testing for at-risk relatives, prenatal testing for a pregnancy at increased risk, and preimplantation genetic testing are possible.

GeneReview Scope

The phenotypic spectrum associated with biallelic intronic AAGGG pentanucleotide expansions in *RFC1* ranges from typical *c*erebellar *a*taxia, *n*europathy, *v*estibular *a*reflexia *s*yndrome (CANVAS) – encompassing cerebellar, sensory, and vestibular impairment – to more limited phenotypes involving predominantly or exclusively one of the systems involved in balance control. The title, *RFC1* CANVAS / spectrum disorder, emphasizes that clinicians need to evaluate an individual with biallelic *RFC1* pathogenic variants for medically actionable manifestations in the entire phenotypic spectrum (regardless of clinical findings that prompted molecular genetic testing) and to counsel individuals and families that the finding of biallelic *RFC1* AAGGG repeat expansions is not equivalent to a diagnosis of CANVAS syndrome.

Diagnosis

Formal diagnostic criteria for *RFC1* CANVAS / spectrum disorder have not been established.

Suggestive Findings

RFC1 CANVAS / spectrum disorder **should be suspected** in individuals with onset after age 35 years of one or more the following clinical findings (with supportive electrodiagnostic, vestibular, and imaging findings and family history).

Clinical Findings

Complex impairment of balance and coordination of peripheral, vestibular, and cerebellar origin

- Symptoms include unsteadiness (imbalance, dizziness), falls, clumsiness of hands.
- Examination reveals progressive ataxia of gait and limb dysmetria.

Sensory neuropathy or neuronopathy

- Symptoms include unsteadiness, loss of feeling, pins and needles, pain and cramps.
- On examination:
  - Altered sensation (pinprick, vibration, position sense) in all limbs in either a length-dependent (distal extremities worse) or non-length-dependent pattern
  - Reflexes can be normal, decreased/abolished, or brisk.
  - Positive Romberg and dysmetria worsened by eye closure
  - Normal muscle bulk, strength, and tone
  - Flexor plantar responses

Bilateral vestibular areflexia

- Symptoms include oscillopsia.
- Examination reveals bilateral vestibular hypofunction:
  - Absent/reduced vestibulo-ocular reflex at bedside on head impulse test
  - Impaired visually enhanced vestibulo-ocular reflexes (indicating the coexistence of vestibular and cerebellar pathology)

  Note: Vertigo, defined as an abnormal sensation of motion in which the individual or the individual's surroundings seem to whirl dizzily, stemming from a subacute/acute imbalance of vestibular inputs, **is not** a symptom suggestive of *RFC1* CANVAS / spectrum disorder.

Cerebellar dysfunction

- Symptoms include dysarthria, dysphagia.
- Examination reveals abnormal eye movements (downbeat, horizontal, rotatory gaze-evoked nystagmus, broken pursuits, dysmetric saccades), dysdiadokokinesia, normal/reduced muscle tone.

Chronic cough (with or without associated gastroesophageal reflux disease)

Autonomic dysfunction (mild and rarely disabling)

- Symptoms include postural hypotension; erectile dysfunction; urinary dysfunction; chronic constipation and/or diarrhea; nausea, vomiting or bloating after a small meal; anhidrosis or increased sweating; dry mouth/eyes.
- Examination includes autonomic testing (in some cases) for sympathetic dysfunction (measuring blood pressure response to change in posture and handgrip and sympathetic skin response) and/or parasympathetic dysfunction (ECG monitoring of heart rate variation during Valsalva maneuver, deep breathing and standing).

Supportive Findings

Electrodiagnostic findings. Nerve conduction studies are consistent with sensory neuropathy or neuronopathy:

- Reduced or absent sensory action potential (SAP). When the individual already has a clear ataxic gait, SAPs are often absent throughout.
- Usually normal motor study
- Abnormal blink reflex (trigeminal neuronopathy), preserved H–reflex (Hoffmann reflex)

Electromyography is usually normal.

Vestibular testing

- Bilaterally abnormal video head impulse test
- Bilaterally reduced caloric response
- Vestibulo-ocular reflex gain tested using a rotatory chair

Imaging

- Brain MRI shows cerebellar atrophy (vermian atrophy, crus I atrophy).
- Spine MRI shows cord atrophy and T_2-weighted hyperintensity in the posterior columns.
- Nerve ultrasound shows reduced cross-sectional area of upper and lower limb nerves (reported by 1 group) [Pelosi et al 2018].

Autonomic testing shows sympathetic and/or parasympathetic dysfunction.

Family history

- Consistent with autosomal recessive inheritance (e.g., affected sibs and/or parental consanguinity)
- Family history may alternatively be consistent with pseudodominant inheritance (i.e., the occurrence of an autosomal recessive disorder in two generations of a family without consanguinity) due to the high heterozygote carrier frequency of *RFC1* AAGGG repeat expansions (see Prevalence).
- Absence of a known family history does not preclude the diagnosis.

Establishing the Diagnosis

The diagnosis of *RFC1* CANVAS / spectrum disorder **is established** in a proband with suggestive findings and biallelic intronic AAGGG pentanucleotide expansions in *RFC1* identified by molecular genetic testing (see Table 1).

Note: Pathogenic AAGGG repeat expansions in *RFC1* **cannot be detected** by sequence-based multigene panels or exome sequencing. However, they can be suspected based on genome sequencing.

Repeat Sizes

Normal

- $AAAAG_{11}$ repeats (allele frequency = 0.75)
- $AAAAG_{12\text{-}200}$ (allele frequency = 0.13)
- $AAAGG_{40\text{-}1000}$ (allele frequency = 0.08)

Pathogenic (full-penetrance)

- Most commonly AAGGG repeat expansion, most frequently ranging from 400 to more than 2000 repeats (maximum number of repeats in Authors' series = 2750) (allele frequency = 0.01-0.04)
- Additional pathogenic repeat expansions recently identified in specific populations:
  - ACAGG repeat expansion (~1000 repeats) in two Asia-Pacific families and one Japanese individual [Scriba et al 2020, Tsuchiya et al 2020]
  - $(AAAGG)_{10\text{-}25}(AAGGG)_{exp}$ $(AAAGG)_{4\text{-}6}$ repeat expansion (990-1940 repeats), identified in 13 affected individuals of New Zealand Māori and Cook Island ancestry [Beecroft et al 2020]

  Note: Expansions of additional likely non-pathogenic repeat configuration including AAGAG and AGAGG, and repeat interruptions of slightly expanded AAAAG alleles by AGAAG and AAGAG motifs were identified in the heterozygous state in individuals with ataxia and in healthy controls [Akçimen et al 2019, Gisatulin et al 2020].

Molecular genetic testing relies on targeted analysis to establish the presence and characterize the number of *RFC1* AAGGG pentanucleotide repeats (see Molecular Genetics).

Table 1. Molecular Genetic Testing Used in *RFC1* CANVAS / Spectrum Disorder

Gene [1]	Method [2, 3]	Proportion of Pathogenic Variants Detectable by Method
RFC1	Targeted analysis for AAGGG pentanucleotide expansions [4]	100%

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for specific methods to characterize the number of *RFC1* AAGGG pentanucleotide repeats.
3. **Note:** Sequence-based multigene panels and exome sequencing cannot detect pathogenic repeat expansions in this gene. However, they can be suspected on the basis of genome sequencing.
4. After exclusion of biallelic AAGGG expansions, targeted analysis for ACAGG repeats can also be advised in typical CANVAS cases of Asian and Asian Pacific origin, based on current and evolving knowledge.

Clinical Characteristics

Clinical Description

The phenotypic spectrum associated with biallelic *RFC1* AAGGG repeat expansions ranges from typical cerebellar ataxia, neuropathy, vestibular areflexia syndrome (CANVAS), to cerebellar, sensory and vestibular impairment, to more limited phenotypes involving predominantly or exclusively one of the systems involved in balance control.

Before its molecular basis was known, CANVAS was characterized as cerebellar dysfunction with predominant vermian atrophy, spinal and cranial sensory neuronopathy, and bilateral vestibular areflexia [Bronstein et al 1991, Migliaccio et al 2004, Szmulewicz et al 2011, Cazzato et al 2016, Szmulewicz et al 2016, Rust et al 2017, Burke & Halmagyi 2018, Infante et al 2018, Pelosi et al 2018, Taki et al 2018]. Following the discovery of the causative biallelic *RFC1* repeat expansions, this genetic alteration was also identified in individuals with a progressive disorder of balance, but not full CANVAS, thus expanding the phenotypic spectrum to include phenotypes involving predominantly or exclusively one of the systems involved in balance control, as well as autonomic dysfunction [Wu et al 2014] and cough.

To date, more than 200 individuals – either simplex cases (i.e., a single occurrence in a family) or having a family history consistent with autosomal recessive inheritance – have been identified with biallelic AAGGG repeat expansions in *RFC1* [Akçimen et al 2019, Cortese et al 2019, Rafehi et al 2019, Aboud Syriani et al 2020, Cortese et al 2020b, Gisatulin et al 2020]. The clinical features of 100 individuals with *RFC1* CANVAS / spectrum disorder were recently evaluated in a retrospective study [Cortese et al 2020b] and are summarized in Table 2 and detailed in the text that follows.

After ten years of disease duration:

- Clinical features of CANVAS were seen in two thirds of affected individuals;
- A complex sensory ataxia with cerebellar or vestibular involvement was identified in 16 and six individuals, respectively;
- A sensory neuropathy was the only clinically detectable diasease manifestation in 15 individuals.

Table 2. *RFC1* CANVAS / Spectrum Disorder: Frequency of Select Features

Feature	Frequency
Sensory neuropathy	100%
Bilateral vestibular impairment	69% (93% of those tested)
Cough	64%
CANVAS	63%
Cerebellar syndrome	63%
Dysautonomia	32% (50% of those undergoing specific investigations)

Based on 100 individuals with *RFC1* disorder [Cortese et al 2020b]
CANVAS = *c*erebellar *a*taxia, *n*europathy, *v*estibular *a*reflexia *s*yndrome

In the series of Cortese et al [2020b], the mean age of onset of neurologic manifestations was 52 years (range 19-76 years) and mean age at the time of the study (and at diagnosis) was 72 years. However, symptoms can present as early as the third decade and it is expected that in the future more affected individuals will be diagnosed at a younger age.

Sensory neuropathy. More than two thirds of individuals complain of sensory symptoms, including loss of feeling, pins and needles, and neuropathic pain – in many cases since the onset of disease. Neurologic

examination shows impaired sensation to pinprick, vibration and joint position, more typically in a length-dependent distribution. Reflexes can be either reduced/abolished, retained, or brisk. Motor nerves are usually unaffected.

Imbalance. Progressive imbalance is the most common complaint and is the presenting symptom in half of the cases. Imbalance is often worse in the dark, indicating a prominent peripheral component. Upper-limb coordination and hand dexterity are better preserved than gait.

Vestibular dysfunction. Oscillopsia, defined as a visual disturbance in which objects appear to oscillate during head movements, is a common sequela of a bilaterally impaired vestibulo-ocular reflex; it is reported by one third of affected individuals and can be the presenting complaint in some. Vertigo and hearing loss are not part of the syndrome but (as they are common in the general population) can independently occur. Bedside head impulse test reveals bilateral vestibular function in up to 90% of individuals.

Cough. Notably, a chronic spasmodic dry cough is frequently associated and can be reported as early as the second decade of life, up to three decades before any neurologic symptoms develop. Gastroesophageal reflux may coexist.

Cerebellar dysfunction. Dysarthria and dysphagia, which are attributed to cerebellar dysfunction, frequently complicate the disease course in later stages. Abnormal eye movements of putative cerebellar origin, including gaze-evoked, downbeat, and horizontal nystagmus, saccadic pursuits, and dysmetric saccades, are common and can be observed earlier in the disease course.

Dysautonomia. Symptoms of autonomic dysfunction including postural hypotension, erectile dysfunction, chronic constipation, urinary dysfunction, and altered sweating are not infrequent but rarely disabling. Autonomic testing confirms the presence of a parasympathetic and/or sympathetic dysfunction in half of individuals undergoing specific investigations.

Disease course. Current data support a pattern of spatial progression from the early involvement of sensory neurons to the later appearance of vestibular and cerebellar dysfunction. The disease has a slowly progressive course. Half of individuals need a cane after ten years of disease duration and one fourth are wheelchair dependent five years later. Life expectancy does not appear to be affected.

Genotype-Phenotype Correlations

No genotype-phenotype correlations have been identified.

Prevalence

The heterozygote carrier frequency of *RFC1* AAGGG repeat expansions ranges from 0.7% to 4% in populations of predominantly northern European origin [Akçimen et al 2019, Cortese et al 2019, Rafehi et al 2019]. A similar allele frequency (2.24%) was found in the Chinese Han population [Fan et al 2020].

Therefore, the estimated prevalence of *RFC1* CANVAS / spectrum disorder ranges from 1:20,000 to 1:625.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *RFC1*.

Differential Diagnosis

AAGGG expansions in *RFC1* were identified in 82%-97% of individuals with clinical features consistent with the full CANVAS phenotype [Cortese et al 2019, Rafehi et al 2019], suggesting that locus heterogeneity for the full CANVAS phenotype (albeit limited) is possible.

AAGGG expansions in *RFC1* represent one of the more common causes of hereditary adult-onset ataxia (see Hereditary Ataxia Overview). In individuals with adult-onset ataxia, *RFC1* AAGGG expansions were identified in 14%-22% of individuals [Cortese et al 2019, Cortese et al 2020b].

Given the multisystem involvement of *RFC1* CANVAS / spectrum disorder and the possible asynchronous involvement of different systems during disease progression, the differential diagnosis is broad and includes:

- Genetic causes of inherited ataxia (see Hereditary Ataxia Overview);
- Genetic causes of inherited neuropathy (see Charcot-Marie-Tooth Hereditary Neuropathy Overview);
- Mitochondrial disorders that can manifest with ataxia, neuropathy and (more occasionally) bilateral vestibular areflexia (see Mitochondrial Disorders Overview).

Selected genes and disorders of interest are summarized in Table 3 [Pandolfo 2008, Valdmanis et al 2011, Paulson 2012, Mead et al 2013, Cook & Giunti 2017, Paul et al 2017, Peng et al 2017, Rahman & Copeland 2019, Cortese et al 2020a].

Table 3. Genes of Interest in the Differential Diagnosis of *RFC1* CANVAS / Spectrum Disorder

Gene	DiffDx Disorder	MOI	Clinical Features of DiffDx Disorder	
			Overlapping w/*RFC1* CANVAS	Distinguishing from *RFC1* CANVAS
ATXN3	SCA3 (MJD)	AD	• Progressive cerebellar ataxia • Sensory loss • Bilateral vestibular areflexia • Because MJD is a late-onset disorder (5th-7th decade) & pyramidal/ extrapyramidal signs may be absent, MJD may mimic *RFC1*-CANVAS.	• Frequent assoc of dystonic-rigid extrapyramidal syndrome &/or peripheral amyotrophy • Sensorimotor neuropathy (vs pure sensory neuropathy typical of *RFC1* CANVAS) • In some, addl clinical signs incl PEO, dystonia, action-induced facial & lingual fasciculation-like movements, & bulging eyes
FXN	Friedreich ataxia (FRDA)	AR	• Sensory neuronopathy • Cerebellar dysfunction • Bilateral vestibular areflexia is possible. • Late-onset FRDA can be clinically indistinguishable from *RFC1*-CANVAS.	• Typical age of onset: <25 yrs • Frequent muscle weakness, pyramidal involvement (Babinski signs) & skeletal deformities (pes cavus, scoliosis) • Assoc cardiomyopathy & diabetes • Vision & hearing loss
MT-ATP6 *MT-TL1* [1] mtDNA deletion	NARP; MIDD/MELAS; Kearns-Sayre syndrome (See mtDNA Deletion Syndromes.)	Mat	• Ataxia • Neuropathy • Bilateral vestibular areflexia (reported in assoc w/ m.3243A>G)	• Earlier onset • Chronic PEO • Hearing & vision loss • Weakness • Extraneurologic involvement

Table 3. continued from previous page.

Gene	DiffDx Disorder	MOI	Clinical Features of DiffDx Disorder	
			Overlapping w/*RFC1* CANVAS	Distinguishing from *RFC1* CANVAS
POLG	SANDO (See *POLG* Disorders, Ataxia Neuropathy Spectrum.)	AR	• Sensory neuronopathy • Cerebellar dysfunction	• Onset 2nd-4th decade • Chronic PEO • Multisystem involvement
PRNP	Gerstmann-Sträussler-Scheinker disease (diarrhea & autonomic neuropathy) [2] (See Genetic Prion Disease.)	AD	• Neuropathy • Ataxia • Autonomic failure	• Dementia • More rapid decline
RNF170	AD sensory ataxia; sensory ataxia neuropathy w/ vestibular areflexia	AD	• Sensory neuronopathy • Bilateral vestibular areflexia • Adult onset	• Normal cerebellar function • SAPs can be normal.

AD = autosomal dominant; AR = autosomal recessive; CANVAS = cerebellar ataxia, neuropathy, vestibular areflexia syndrome; DiffDx = differential diagnosis; Mat = maternal transmission; MELAS = mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes; MIDD = maternally inherited diabetes and deafness; MJD = Machado-Joseph disease; MOI = mode of inheritance; NARP = neuropathy, ataxia, and retinitis pigmentosa; PEO = progressive external ophthalmoplegia; SANDO = sensory ataxic neuropathy, dysarthria, and ophthalmoparesis; SAP = sensory action potential; SCA = spinocerebellar ataxia

1. m.8993T>G or m.8993T>C in MT-ATP6; m.3243A>G in MT-TL1

2. Mead et al [2013]

Sensory Neuronopathy

As sensory neuronopathy was identified in all individuals with genetically confirmed diagnoses and tends to appear early in the disease course, the differential diagnosis should initially encompass causes of acquired sensory neuronopathy including:

- Paraneoplastic syndrome
- Sjogren syndrome
- Acute and chronic immune-mediated disorders
- Metabolic disorders (diabetes mellitus, vitamin B_{12} deficiency, copper deficiency)
- Toxins (alcohol, pyridoxine, platinum derivatives, pyridoxine intoxication)

Late-Onset Cerebellar Ataxia

Multisystem atrophy (MSA), a rapidly progressive neurodegenerative disease, is the main differential diagnosis in an individual with late-onset cerebellar ataxia [Fan et al 2020, Sullivan et al 2020, Wan et al 2020]. The following clinical characteristics distinguish MSA from *RFC1* CANVAS / spectrum disorder.

- The average time from first manifestations to death in MSA is 9.3 years, while disease progression in *RFC1* CANVAS / spectrum disorder is very slow and life expectancy does not appear to be reduced [Fanciulli & Wenning 2015].
- Unlike *RFC1* CANVAS / spectrum disorder, sensory neuropathy and vestibular dysfunction do not occur in MSA, or, if coexisting, are most likely unrelated.
- Autonomic dysfunction, a common and highly debilitating feature of MSA, is usually mild in *RFC1* CANVAS / spectrum disorder.
- Presence of additional features that favor an MSA diagnosis include rapid eye movement sleep behavior disorder, parkinsonism, and MRI pattern (putaminal, pontine, and middle cerebellar peduncle atrophy and "hot cross-bun" sign cruciform T_2-weighted hyperintensity in the pons) [Chelban et al 2019].

Additional causes of progressive cerebellar impairment to consider include: paraneoplastic syndromes; toxic, nutritional, vascular, and inflammatory conditions; and idiopathic (i.e., idiopathic late-onset cerebellar) ataxia.

Wernicke's disease due to vitamin B_1 deficiency typically presents with mental status change, cerebellar ataxia, and altered eye movements as well as vestibular areflexia and chronic neuropathy. Exposure to chronic alcohol intake, the acute course, and the presence of delirium help distinguish this potentially reversible condition from *RFC1* CANVAS / spectrum disorder.

Bilateral Vestibular Areflexia

The differential diagnosis of bilateral vestibular areflexia includes (among other conditions) aminoglycoside ototoxicity, Meniere's disease, bilateral vestibular neuritis, tumors compressing both vestibular nerves (e.g., bilateral schwannomas in neurofibromatosis 2), and infectious and/or inflammatory systemic disorders.

Bilateral vestibular hypofunction can be observed in several hereditary neurodegenerative conditions including spinocerebellar ataxia (SCA3 as well as SCA1, SCA2, and SCA6), Friedreich ataxia, Gaucher disease, and Charcot-Marie-Tooth (CMT) hereditary neuropathy. Although vestibular dysfunction is probably more common than previously thought in CMT, nerve conduction study, typically showing an alteration of motor and sensory conductions, can help in the differential diagnosis [Poretti et al 2013, Pérez-Garrigues et al 2014, Akdal et al 2020].

When bilateral vestibular hypofunction occurs with hearing and visual loss, Usher syndrome type I and Usher syndrome type II should also be considered.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *RFC1* CANVAS / spectrum disorder, 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 *RFC1* CANVAS / Spectrum Disorder

System/Concern	Evaluation	Comment
Neurologic	Assessment by neurologist for gait & postural ataxia	No validated clinical scale for *RFC1* CANVAS / spectrum disorder exists; consider use of validated scales for eval of cerebellar disorder (e.g., SARA) & neuropathy (e.g., CMTNS). [1]
	Assess sensory neuropathy (sensory impairment, ↓/↑ reflexes, dysmetria) to evaluate for pain.	Electrophysiologic studies (EMG & NCS) to establish presence of sensory neuropathy
	Cerebellar dysfunction (dysmetria, dysdiadochokinesis, tremor, dysarthria, nystagmus, saccades & smooth pursuit)	Brain MRI to assess presence/severity of cerebellar atrophy
	Bilateral vestibular dysfunction (head impulse test & visually enhanced vestibular ocular reflex)	Vestibular testing (video head impulse test, caloric response, vestibulo-ocular reflex gain tested using a rotatory chair) to assess vestibular hypofunction
	Clinical assessment of symptoms of autonomic dysfunction	Consider autonomic testing in symptomatic persons.
PT/OT / Rehabilitation	Assess gross motor & fine motor skills & ambulation.	• Prevention of falls • Adaptive devices (cane, walker, wheelchair) • PT

Table 4. continued from previous page.

System/Concern	Evaluation	Comment
Speech	For those w/dysarthria: speech/language eval	
Feeding	For those w/frequent choking or severe dysphagia, assess: • Nutritional status; • Aspiration risk.	Consider involving a gastroenterologist & nutritionist.
Respiratory	For those w/disabling cough or respiratory symptoms: consider referring to pulmonary specialist.	Consider: • Respiratory function testing, esp in non-ambulant individuals; • A sleep study if sleep apnea is suspected.
Genetic counseling	By genetics professionals [2]	To inform patients & their families re nature, MOI, & implications of *RFC1* CANVAS / spectrum disorder in order to facilitate medical & personal decision making
Family support/ resources	Assess: • Use of community or online resources; • Need for social work involvement for caregiver support.	

CMTNS = Charcot-Marie-Tooth Neuropathy Score; EMG = electromyogram; MOI = mode of inheritance; NCS = nerve conduction study; OT = occupational therapy; PT = physical therapy; SARA = Scale for the Assessment and Rating of Ataxia

1. Murphy et al [2011], Bürk & Sival [2018]

2. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

The goals of treatment are to maximize function and reduce complications. Depending on the clinical manifestations, each affected individual should be managed by a multidisciplinary team of relevant specialists including neurologists, occupational therapists, physical therapists, physiatrists, and (depending on individual needs) speech therapists, respiratory therapists, nutritionists, and gastroenterologists.

Table 5. Treatment of Manifestations in Individuals with *RFC1* CANVAS / Spectrum Disorder

Manifestation/ Concern	Treatment	Considerations/Other
Ataxia (multifactorial)	Care by neurorehabilitation specialist, physiatrist, OT/PT	• Consider adaptive devices to maintain/improve mobility (e.g., canes, walkers, ramps to accommodate motorized chairs), feeding (e.g., weighted eating utensils), dressing (e.g., dressing hooks). • PT (balance exercises, gait training, muscle strengthening) to maintain mobility & function [1] • OT to optimize ADL • Inpatient rehab w/OT/PT may improve ataxia & functional abilities in patients w/degenerative ataxias. [2, 3] • Consider vestibular rehab. • Home adaptations to prevent falls (e.g., grab bars, raised toilet seats) • Exercise w/in patient's capability • Weight control to avoid obesity
Sensory neuropathy	Neurologist, physiatrist	• Advice on injury avoidance • Consider pain treatment (rarely required).

Table 5. continued from previous page.

Manifestation/ Concern	Treatment	Considerations/Other
Vestibular dysfunction	Neurorehabilitation specialist, ENT specialist	Consider vestibular rehab. [4]
Autonomic dysfunction	Care by neurologist, neurorehabilitation specialist, physiatrist	Consider treatment for erectile dysfunction, urinary incontinence/ retention, constipation/diarrhea, dry eyes/mouth.
Dysarthria	Speech & language therapy	Consider alternative communication methods as needed (e.g., writing pads & digital devices; rarely required).
Dysphagia	Modify food consistency to ↓ aspiration risk.	Video esophagram may help define best consistency.
Cough	Respiratory specialist / ENT specialist / gastroenterologist	Proton pump inhibitor if gastroesophageal reflux is present

ADL = activities of daily living; OT = occupational therapy/therapist; PT = physical therapy/therapist
1. Martineau et al [2014]
2. Zesiewicz et al [2018]
3. van de Warrenburg et al [2014]
4. While 4-aminopyridine (used for the treatment of episodic ataxia type 2, ataxia-telangiectasia, and downbeat nystagmus) may be considered in individuals with *RFC1* CANVAS / spectrum disorder, currently there are no data supporting this use.

Surveillance

Table 6. Recommended Surveillance for Individuals with *RFC1* CANVAS / Spectrum Disorder

System/ Concern	Evaluation	Frequency
Neurologic	Neurologic assessment for progression of ataxia; sensory impairment; vestibular dysfunction; dysautonomia No validated clinical scale exists for *RFC1* CANVAS / spectrum disorder; consider monitoring disease w/validated scales for cerebellar disorder (e.g., SARA) and neuropathy (e.g., CMTNS). [1]	Annually; more often for an acute exacerbation
	Physiatry, OT/PT assessment of mobility, self-help skills	
Dysarthria	Need for alternative communication method or speech therapy (rarely required)	Per symptom progression
Dysphagia	Assess aspiration risk & feeding methods.	

CMTNS = Charcot-Marie-Tooth Neuropathy Score; OT = occupational therapy; PT = physical therapy; SARA = Scale for the Assessment and Rating of Ataxia
1. Murphy et al [2011], Bürk & Sival [2018]

Agents/Circumstances to Avoid

Medications of known toxicity for peripheral nerves (e.g., neurotoxic chemotherapy agents, pyridoxine), the cerebellum (e.g., phenytoin), or the vestibular system (e.g., aminoglycosides) as well as chronic alcohol consumption may worsen the condition.

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

RFC1 CANVAS / spectrum disorder is inherited in an autosomal recessive manner.

Pseudodominance (the occurrence of an autosomal recessive disorder in two generations of a family without consanguinity) may be observed in *RFC1* CANVAS / spectrum disorder due to the high heterozygote carrier frequency of *RFC1* AAGGG repeat expansions (see Prevalence).

Parents of a proband

- The parents of an affected individual are obligate heterozygotes (i.e., presumed to be carriers of one *RFC1* AAGGG repeat expansion based on family history).
- Molecular genetic testing of the parents can be used to confirm that both parents are heterozygous for an *RFC1* AAGGG repeat expansion and to facilitate reliable recurrence risk assessment; however, given the mean age of onset of *RFC1* CANVAS / spectrum disorder, molecular genetic testing of the parents is often not possible.
- To date, all reported heterozygotes (carriers) are asymptomatic and are presumed not to be at risk of developing the disorder (additional long-term testing is needed to confirm this observation).

Sibs of a proband

- If both parents are known to be heterozygous for an *RFC1* AAGGG repeat expansion, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- To date, all reported heterozygotes (carriers) are asymptomatic and are presumed not to be at risk of developing the disorder (additional long-term testing is needed to confirm this observation).

Offspring of a proband. Unless an individual with *RFC1* CANVAS / spectrum disorder has children with an affected individual or a carrier, his/her offspring will be obligate heterozygotes (carriers) for an *RFC1* AAGGG repeat expansion.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of an *RFC1* AAGGG repeat expansion.

Carrier Detection

Once biallelic *RFC1* AAGGG repeat expansions have been identified in an affected family member, carrier testing for at-risk relatives is possible.

Related Genetic Counseling Issues

Family planning

- The optimal time for determination of genetic risk, clarification of carrier status, 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, are carriers, or are at risk of being carriers.

DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals.

Prenatal Testing and Preimplantation Genetic Testing

Once biallelic *RFC1* AAGGG repeat expansions have 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. 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.

- **ACMT-Rete per la Charcot-Marie-Tooth**
  Italy
  acmt-rete.it
- **American Hearing Research Foundation**
  Phone: 630-617-5079
  Email: info@american-hearing.org
  american-hearing.org
- **Associazione Malati Menière Insieme ODV**
  Italy
  ammi-italia.it
- **Ataxia UK**
  United Kingdom
  Phone: 0800 995 6037; +44 (0) 20 7582 1444 (from abroad)
  Email: help@ataxia.org.uk
  ataxia.org.uk
- **Charcot Marie Tooth UK**
  United Kingdom
  Phone: 0300 323 6316
  Email: enquiries@cmt.org.uk
  cmt.org.uk

- **Charcot-Marie-Tooth Association (CMTA)**
  Phone: 800-606-2682
  Email: info@cmtausa.org
  cmtausa.org
- **euro-ATAXIA (European Federation of Hereditary Ataxias)**
  United Kingdom
  Email: ageorgousis@ataxia.org.uk
  euroataxia.org
- **Ménière's Society**
  United Kingdom
  Phone: 01306 876883
  Email: info@menieres.org.uk
  menieres.org.uk
- **Multiple System Atrophy Trust**
  United Kingdom
  Phone: 0333 323 4591
  Email: support@msatrust.org.uk
  msatrust.org.uk
- **Muscular Dystrophy UK**
  United Kingdom
  Phone: 0800 652 6352
  musculardystrophyuk.org
- **National Ataxia Foundation**
  Phone: 763-553-0020
  Email: naf@ataxia.org
  ataxia.org

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. RFC1 CANVAS / Spectrum Disorder: Genes and Databases

Gene	Chromosome Locus	Protein	HGMD	ClinVar
RFC1	4p14	Replication factor C subunit 1	RFC1	RFC1

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 RFC1 CANVAS / Spectrum Disorder (View All in OMIM)

102579	REPLICATION FACTOR C, SUBUNIT 1; RFC1
614575	CEREBELLAR ATAXIA, NEUROPATHY, AND VESTIBULAR AREFLEXIA SYNDROME; CANVAS

Molecular Pathogenesis

Mechanism of disease causation. The mechanism underlying neurodegeneration in *RFC1* CANVAS / spectrum disorder is unknown. *RFC1* is a gene implicated in DNA replication and repair. Notably, preliminary studies

have not shown reduced expression or overt loss of function of RFC1 protein, which is unexpected given the autosomal recessive pattern of inheritance [Cortese et al 2019].

Table 7. *RFC1* Technical Considerations

Technical Issue	Comment [Reference]
Sequence of repeat	AAAAG (normal) & AAGGG (expanded pathogenic). However, expansions may be AAAAG, AAAGG, AAGAG, AGAGG, ACAGG or AAGGG; imperfect repeats w/interruptions are also possible.
Methods to detect expanded allele	Conventional PCR, repeat-primed PCR (RP-PCR) [Cortese et al 2019, Akçimen et al 2019], & Southern blotting [Cortese et al 2019] have been described. The presence of biallelic AAGGG pentanucleotide expansions is suggested by the following: • Absence of PCR amplifiable product on flanking PCR • Presence of a saw-tooth decremental pattern on repeat-primed PCR (RP-PCR) for the pathogenic AAGGG pentanucleotide expansion • Optional: Absence of a saw-tooth decremental pattern on repeat-primed PCR for non-pathogenic repeat expansions of (e.g.,) AAAAG, AAAGG, and other possible configurations [Akçimen et al 2019] These expansions can be large enough to prevent amplification of a PCR product on standard flanking PCR conditions. Given the large size of the AAGGG pentanucleotide repeat expansions, sizing can be obtained only by Southern blotting, which is the only available method to confirm the presence of biallelic expansions, showing either 2 discreet bands or 1 band corresponding to 2 expanded alleles of similar size.
Somatic instability	Data not available
Germline instability	Data not available

PCR = polymerase chain reaction

***RFC1*-specific laboratory technical considerations.** Detection of an AAGGG pentanucleotide repeat expansion may be done by conventional PCR and RP-PCR, followed by confirmation of the presence of biallelic expansions and their size by Southern blotting. However, the presence of non-pathogenic expansions of different repeated units (e.g., AAAAG, AAAGG), interruptions, or insertions of different repeated units inside the expanded microsatellite cannot be ruled out.

Recently, biallelic ACAGG repeat expansions were identified in one Japanese individual with typical CANVAS who did not have the common AAGGG repeat expansion [Tsuchiya et al 2020].The size of the ACAGG expansion was in the same range as pathogenic AAGGG expansions, indicating that ACAGG repeat expansion could also cause CANVAS.

Other techniques, including long-read sequencing [Nakamura et al 2020], may have the potential to reliably assess the presence, size, and sequence of repeat expansions in *RFC1*.

Table 8. Notable *RFC1* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Repeat Range
NM_001204747.1	c.132+2923_2927AAAAG[11]	--	Normal
	c.132+2923_2927AAAAG[12_200]	--	Normal
	c.132+2923_2927AAAGG[40_~1000]	--	Normal
	c.132+2923_2927ACAGG [1]		Uncertain significance
	c.132+2923_2927AAGGG[~400_~2000] [2]		Pathogenic (full-penetrance)

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. Not available, but reported to be in the same range as AAGGG expansions [Author, personal observation]
2. In 13 affected individuals of New Zealand Māori and Cook Island ancestry, the core AAGGG expansion was identified to be flanked by short AAAGG expansion arms, resulting in the configuration (AAAGG)10-25(AAGGG)exp (AAAGG)4-6 [Beecroft et al 2020].

Chapter Notes

Author Notes

Andrea Cortese's work focuses on genetic discovery, functional modeling, and treatment of neuromuscular diseases and other hereditary neurodegenerative conditions. A major area of his research focuses on understanding how *RFC1* pathogenic AAGGG repeat expansions lead to neurodegeneration and how this can be therapeutically reversed.

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References

Literature Cited

Aboud Syriani D, Wong D, Andani S, De Gusmao CM, Mao Y, Sanyoura M, Glotzer G, Lockhart PJ, Hassin-Baer S, Khurana V, Gomez CM, Perlman S, Das S, Fogel BL. Prevalence of RFC1-mediated spinocerebellar ataxia in a North American ataxia cohort. Neurol Genet. 2020;6:e440. PubMed PMID: 32582864.

Akçimen F, Ross JP, Cynthia V., Bourassa CV, Liao C, Rochefort D, Gama MTD, Dicaire MJ, Barsottini OG, Brais B, Pedroso JL, Dion PA, Rouleau GA. Investigation of the pathogenic RFC1 repeat expansion in a Canadian and a Brazilian ataxia cohort: identification of novel conformations. Front Genet. 2019;10:1219. PubMed PMID: 31824583.

Akdal G, Koçoğlu K, Tanrıverdizade T, Bora E, Bademkıran F, Yüceyar AN, Ekmekçi Ö, Şengün İŞ, Karasoy H. Vestibular Impairment in Charcot-Marie-Tooth disease. J Neurol. 2020. Epub ahead of print. PubMed PMID: 32862243.

Beecroft SJ, Cortese A, Sullivan R, Yau WY, Dyer Z, Wu TY, Mulroy E, Pelosi L, Rodrigues M, Taylor R, Mossman S, Leadbetter R, Cleland J, Anderson T, Ravenscroft G, Laing NG, Houlden H, Reilly MM, Roxburgh RH. A Māori-specific RFC1 pathogenic repeat configuration in CANVAS, likely due to a founder allele. Brain. 2020;143:2673–80. PubMed PMID: 32851396.

Bronstein AM, Mossman S, Luxon LM. The neck-eye reflex in patients with reduced vestibular and optokinetic function. Brain. 1991;114:1–11. PubMed PMID: 1998877.

Bürk K, Sival DA. Scales for the clinical evaluation of cerebellar disorders. Handb Clin Neurol. 2018;154:329–39. PubMed PMID: 29903450.

Burke D, Halmagyi GM. Normal tendon reflexes despite absent sensory nerve action potentials in CANVAS: a neurophysiological study. J Neurol Sci. 2018;387:75–79. PubMed PMID: 29571876.

Cazzato D, Dalla Bella E, Dacci P, Mariotti C, Lauria G. Cerebellar ataxia, neuropathy, and vestibular areflexia syndrome: a slowly progressive disorder with stereotypical presentation. J Neurol. 2016;263:245–9. PubMed PMID: 26566912.

Chelban V, Bocchetta M, Hassanein S, Haridy NA, Houlden H, Rohrer JD. An update on advances in magnetic resonance imaging of multiple system atrophy. J Neurol. 2019;266:1036–45. PubMed PMID: 30460448.

Cook A, Giunti P. Friedreich's ataxia: clinical features, pathogenesis and management. Br Med Bull. 2017;124:19–30. PubMed PMID: 29053830.

Cortese A, Callegari I, Currò R, Vegezzi E, Colnaghi S, Versino M, Alfonsi E, Cosentino G, Valente E, Gana S, Tassorelli C, Pichiecchio A, Rossor AM, Bugiardini E, Biroli A, Di Capua D, Houlden H, Reilly MM. Mutation in RNF170 causes sensory ataxic neuropathy with vestibular areflexia: a CANVAS mimic. J Neurol Neurosurg Psychiatry. 2020a;91:1237–8. PubMed PMID: 32943585.

Cortese A, Simone R, Sullivan R, Vandrovcova J, Tariq H, Yau WY, Humphrey J, Jaunmuktane Z, Sivakumar P, Polke J, Ilyas M, Tribollet E, Tomaselli PJ, Devigili G, Callegari I, Versino M, Salpietro V, Efthymiou S, Kaski D, Wood NW, Andrade NS, Buglo E, Rebelo A, Rossor AM, Bronstein A, Fratta P, Marques WJ, Züchner S, Reilly MM, Houlden H. Biallelic expansion of an intronic repeat in RFC1 is a common cause of late-onset ataxia. Nat Genet. 2019;51:649–58. PubMed PMID: 30926972.

Cortese A, Tozza S, Yau WY, Rossi S, Beecroft SJ, Jaunmuktane Z, Dyer Z, Ravenscroft G, Lamont PJ, Mossman S, Chancellor A, Maisonobe T, Pereon Y, Cauquil C, Colnaghi S, Mallucci G, Curro R, Tomaselli PJ, Thomas-Black G, Sullivan R, Efthymiou S, Rossor AM, Laurá M, Pipis M, Horga A, Polke J, Kaski D, Horvath R, Chinnery PF, Marques W, Tassorelli C, Devigili G, Leonardis L, Wood NW, Bronstein A, Giunti P, Züchner S, Stojkovic T, Laing N, Roxburgh RH, Houlden H, Reilly MM. Cerebellar ataxia, neuropathy, vestibular areflexia syndrome due to RFC1 repeat expansion. Brain. 2020b;143:480–90. PubMed PMID: 32040566.

Fan Y, Zhang S, Yang J, Mao CY, Yang ZH, Hu ZW, Wang YL, Liu YT, Liu H, Yuan YP, Shi CH, Xu YM. No biallelic intronic AAGGG repeat expansion in RFC1 was found in patients with late-onset ataxia and MSA. Parkinsonism Relat Disord. 2020;73:1–2. PubMed PMID: 32151945.

Fanciulli A, Wenning GK. Multiple-system atrophy. N Engl J Med. 2015;372:249–63. PubMed PMID: 25587949.

Gisatulin M, Dobricic V, Zühlke C, Hellenbroich Y, Tadic V, Münchau A, Isenhardt K, Bürk K, Bahlo M, Lockhart PJ, Lohmann K, Helmchen C, Brüggemann N. Clinical spectrum of the pentanucleotide repeat expansion in the RFC1 gene in ataxia syndromes. Neurology. 2020;95:e2912–e2923. PubMed PMID: 32873692.

Infante J, García A, Serrano-Cárdenas KM, González-Aguado R, Gazulla J, de Lucas EM, Berciano J. Cerebellar ataxia, neuropathy, vestibular areflexia syndrome (CANVAS) with chronic cough and preserved muscle

stretch reflexes: evidence for selective sparing of afferent Ia fibres. J Neurol. 2018;265:1454–62. PubMed PMID: 29696497.

Martineau L, Noreau A, Dupré N. Therapies for ataxias. Curr Treat Options Neurol. 2014;16:300. PubMed PMID: 24832479.

Mead S, Gandhi S, Beck J, Caine D, Gajulapalli D, Carswell C, Hyare H, Joiner S, Ayling H, Lashley T, Linehan JM, Al-Doujaily H, Sharps B, Revesz T, Sandberg MK, Reilly MM, Koltzenburg M, Forbes A, Rudge P, Brandner S, Warren JD, Wadsworth JDF, Wood NW, Holton JL, Collinge J. A novel prion disease associated with diarrhea and autonomic neuropathy. N Engl J Med. 2013;369:1904–14. PubMed PMID: 24224623.

Migliaccio AA, Halmagyi GM, McGarvie LA, Cremer PD. Cerebellar ataxia with bilateral vestibulopathy: description of a syndrome and its characteristic clinical sign. Brain. 2004;127:280–93. PubMed PMID: 14607788.

Murphy SM, Herrmann DN, McDermott MP, Scherer SS, Shy ME, Reilly MM, Pareyson D. Reliability of the CMT neuropathy score (second version) in Charcot-Marie-Tooth disease. J Peripher Nerv Syst. 2011;16:191–8. PubMed PMID: 22003934.

Nakamura H, Doi H, Mitsuhashi S, Miyatake S, Katoh K, Frith MC, Asano T, Kudo Y, Ikeda T, Kubota S, Kunii M, Kitazawa Y, Tada M, Okamoto M, Joki H, Takeuchi H, Matsumoto N, Tanaka F. Long-read sequencing identifies the pathogenic nucleotide repeat expansion in RFC1 in a Japanese case of CANVAS. J Hum Genet. 2020;65:475–80. PubMed PMID: 32066831.

Pandolfo M. Friedreich ataxia. Arch Neurol. 2008;65:1296–303. PubMed PMID: 18852343.

Paul A, Drecourt A, Petit F, Deguine DD, Vasnier C, Oufadem M, Masson C, Bonnet C, Masmoudi S, Mosnier I, Mahieu L, Bouccara D, Kaplan J, Challe G, Domange C, Mochel F, Sterkers O, Gerber S, Nitschke P, Bole-Feysot C, Jonard L, Gherbi S, Mercati O, Ben Aissa I, Lyonnet S, Rötig A, Delahodde A, Marlin S. FDXR mutations cause sensorial neuropathies and expand the spectrum of mitochondrial Fe-S-synthesis diseases. Am J Hum Genet. 2017;101:630–7. PubMed PMID: 28965846.

Paulson H. Machado-Joseph disease/spinocerebellar ataxia type 3. Handb Clin Neurol. 2012;103:437–49. PubMed PMID: 21827905.

Pelosi L, Mulroy E, Leadbetter R, Kilfoyle D, Chancellor AM, Mossman S, Wing L, Wu TY, Roxburgh RH. Peripheral nerves are pathologically small in cerebellar ataxia neuropathy vestibular areflexia syndrome: a controlled ultrasound study. Eur J Neurol. 2018;25:659–65. PubMed PMID: 29316033.

Peng Y, Shinde DN, Valencia CA, Mo J-S, Rosenfeld J, Cho MT, Chamberlin A, Li Z, Liu J, Gui B, Brockhage R, Basinger A, Alvarez-Leon B, Heydemann P, Magoulas PL, Lewis AM, Scaglia F, Gril S, Chong SC, Bower M, Monaghan KG, Willaert R, Plona MR, Dineen R, Milan F, Hoganson G, Powis Z, Helbig KL, Keller-Ramey J, Harris B, Anderson LC, Green T, Sukoff Rizzo SJ, Kaylor J, Chen J, Guan MX, Sellars E, Sparagana SP, Gibson JB, Reinholdt LG, Tang S, Huang T. Biallelic mutations in the ferredoxin reductase gene cause novel mitochondriopathy with optic atrophy. Hum Mol Genet. 2017;26:4937–50. PubMed PMID: 29040572.

Pérez-Garrigues H, Sivera R, Vílchez JJ, Espinós C, Palau F, Sevilla T. Vestibular impairment in Charcot-Marie-Tooth disease type 4C. J Neurol Neurosurg Psychiatry. 2014;85:824–7. PubMed PMID: 24614092.

Poretti A, Palla A, Tarnutzer AA, Petersen JA, Weber KP, Straumann D, Jung HH. Vestibular impairment in patients with Charcot-Marie-Tooth disease. Neurology. 2013;80:2099–105. PubMed PMID: 23658384.

Rafehi H, Szmulewicz DJ, Bennett MF, Sobreira NLM, Pope K, Smith KR, Gillies G, Diakumis P, Dolzhenko E, Eberle MA, Barcina MG, Breen DP, Chancellor AM, Cremer PD, Delatycki MB, Fogel BL, Hackett A, Halmagyi GM, Kapetanovic S, Lang A, Mossman S, Mu W, Patrikios P, Perlman SL, Rosemergy I, Storey E, Watson SRD, Wilson MA, Zee DS, Valle D, Amor DJ, Bahlo M, Lockhart PJ. Bioinformatics-based identification of expanded repeats: a non-reference intronic pentamer expansion in RFC1 causes CANVAS. Am J Hum Genet. 2019;105:151–65. PubMed PMID: 31230722.

Rahman S, Copeland WC. POLG-related disorders and their neurological manifestations. Nat Rev Neurol. 2019;15:40–52. PubMed PMID: 30451971.

Rust H, Peters N, Allum JHJ, Wagner B, Honegger F, Baumann T. VEMPs in a patient with cerebellar ataxia, neuropathy and vestibular areflexia (CANVAS). J Neurol Sci. 2017;378:9–11. PubMed PMID: 28566187.

Scriba CK, Beecroft SJ, Clayton JS, Cortese A, Sullivan R, Yau WY, Dominik N, Rodrigues M, Walker E, Dyer Z, Wu TY, Davis MR, Chandler DC, Weisburd B, Houlden H, Reilly MM, Laing NG, Lamont PJ, Roxburgh RH, Ravenscroft G. A novel RFC1 repeat motif (ACAGG) in two Asia-Pacific CANVAS families. Brain. 2020;143:2904–10. PubMed PMID: 33103729.

Sullivan R, Yau WY, Chelban V, Rossi S, O'Connor E, Wood NW, Cortese A, Houlden H. RFC1 intronic repeat expansions absent in pathologically confirmed multiple systems atrophy. Mov Disord. 2020;35:1277–9. PubMed PMID: 32333430.

Szmulewicz DJ, Roberts L, McLean CA, MacDougall HG, Halmagyi GM, Storey E. Proposed diagnostic criteria for cerebellar ataxia with neuropathy and vestibular areflexia syndrome (CANVAS). Neurol Clin Pract. 2016;6:61–8. PubMed PMID: 26918204.

Szmulewicz DJ, Waterston JA, MacDougall HG, Mossman S, Chancellor AM, McLean CA, Merchant S, Patrikios P, Halmagyi GM, Storey E. Cerebellar ataxia, neuropathy, vestibular areflexia syndrome (CANVAS): a review of the clinical features and video-oculographic diagnosis. Ann NY Acad Sci. 2011;1233:139–47. PubMed PMID: 21950986.

Taki M, Nakamura T, Matsuura H, Hasegawa T, Sakaguchi H, Morita K, Ishii R, Mizuta I, Kasai T, Mizuno T, Hirano S. Cerebellar ataxia with neuropathy and vestibular areflexia syndrome (CANVAS). Auris Nasus Larynx. 2018;45:866–70. PubMed PMID: 29089158.

Tsuchiya M, Nan H, Koh K, Ichinose Y, Gao L, Shimozono K, Hata T, Kim YJ, Ohtsuka T, Cortese A, Takiyama Y. RFC1 repeat expansion in Japanese patients with late-onset cerebellar ataxia. J Hum Genet. 2020;65:1143–7. PubMed PMID: 32694621.

Valdmanis PN, Dupré N, Lachance M, Stochmanski SJ, Belzil VV, Dion PA, Thiffault I, Brais B, Weston L, Saint-Amant L, Samuels ME, Rouleau GA. A mutation in the RNF170 gene causes autosomal dominant sensory ataxia. Brain. 2011;134:602–7. PubMed PMID: 21115467.

van de Warrenburg BP, van Gaalen J, Boesch S, Burgunder JM, Dürr A, Giunti P, Klockgether T, Mariotti C, Pandolfo M, Riess O. EFNS/ENS Consensus on the diagnosis and management of chronic ataxias in adulthood. Eur J Neurol. 2014;21:552–62. PubMed PMID: 24418350.

Wan L, Chen Z, Wan N, Liu M, Xue J, Chen H, Zhang Y, Peng Y, Tang Z, Gong Y, Yuan H, Wang S, Deng Q, Hou X, Wang C, Peng H, Shi Y, Peng L, Lei L, Duan R, Xia K, Qiu R, Shen L, Tang B, Ashizawa T, Jiang H. Biallelic intronic AAGGG expansion of RFC1 is related to multiple system atrophy. Ann Neurol. 2020;88:1132–43. PubMed PMID: 32939785.

Wu TY, Taylor JM, Kilfoyle DH, Smith AD, McGuinness BJ, Simpson MP, Walker EB, Bergin PS, Cleland JC, Hutchinson DO, Anderson NE, Snow BJ, Anderson TJ, Paermentier LA, Cutfield NJ, Chancellor AM, Mossman SS, Roxburgh RH. Autonomic dysfunction is a major feature of cerebellar ataxia, neuropathy, vestibular areflexia 'CANVAS' syndrome. Brain. 2014;137:2649–56. PubMed PMID: 25070514.

Zesiewicz TA, Wilmot G, Kuo SH, Perlman S, Greenstein PE, Ying SH, Ashizawa T, Subramony SH, Schmahmann JD, Figueroa KP, Mizusawa H, Schöls L, Shaw JD, Dubinsky RM, Armstrong MJ, Gronseth GS, Sullivan KL. Comprehensive systematic review summary: Treatment of cerebellar motor dysfunction and ataxia: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. Neurology. 2018;90:464–71. PubMed PMID: 29440566.

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