Recessive cerebellar and afferent ataxias — clinical challenges and future directions

Marie Beaudin[1,2], *Mario Manto*[3,4], *Jeremy D. Schmahmann*[5], *Massimo Pandolfo*[6] *and Nicolas Dupre*[1,2] ✉

Abstract | Cerebellar and afferent ataxias present with a characteristic gait disorder that reflects cerebellar motor dysfunction and sensory loss. These disorders are a diagnostic challenge for clinicians because of the large number of acquired and inherited diseases that cause cerebellar and sensory neuron damage. Among such conditions that are recessively inherited, Friedreich ataxia and *RFC1*-associated cerebellar ataxia, neuropathy, vestibular areflexia syndrome (CANVAS) include the characteristic clinical, neuropathological and imaging features of ganglionopathies, a distinctive non-length-dependent type of sensory involvement. In this Review, we discuss the typical and atypical phenotypes of Friedreich ataxia and CANVAS, along with the features of other recessive ataxias that present with a ganglionopathy or polyneuropathy, with an emphasis on recently described clinical features, natural history and genotype–phenotype correlations. We review the main developments in understanding the complex pathology that affects the sensory neurons and cerebellum, which seem to be most vulnerable to disorders that affect mitochondrial function and DNA repair mechanisms. Finally, we discuss disease-modifying therapeutic advances in Friedreich ataxia, highlighting the most promising candidate molecules and lessons learned from previous clinical trials.

Cerebellar ataxia can result from a large number of inherited and acquired disorders that involve cerebellar damage that produces the typical cerebellar motor phenotype of gait ataxia, dysmetria, adiadochokinesia, dysarthria and nystagmus. The presence of additional neurological and systemic manifestations can provide important diagnostic clues about the underlying aetiology. Among these manifestations are dorsal root ganglionopathy, which leads to primary degeneration of sensory neuron cell bodies in the dorsal root ganglion[1], and polyneuropathy, which cause sensory deficits. This combination leads to a typical mixed cerebellar and afferent gait disorder, in which ataxia is typically worst in the dark and the Romberg test is positive, meaning that patients cannot maintain balance with their eyes closed.

Mixed cerebellar and afferent ataxias have a wide range of aetiologies and can be acquired or inherited (BOX 1). Some acquired conditions, such as those with paraneoplastic, infectious and autoimmune causes, are treatable, thus requiring a high index of suspicion. Among the inherited causes, autosomal recessive cerebellar ataxias are characterized by complex neurological and multisystemic phenotypes associated with genetic heterogeneity. The first of these to be identified was Friedreich ataxia (also known as ATX-FXN in the International Parkinson and Movement Disorder Society nomenclature)[2], which is caused by mutation of the *FXN* gene, but at least 58 other genes have subsequently been identified as causes of recessive disorders in which ataxia is the main feature[3] and more are discovered each year. If all metabolic and multisystemic disorders that involve some degree of ataxia are included, the number of possible diagnoses is >180 (REF.[2]). Most of these disorders are individually rare but, collectively, autosomal recessive cerebellar ataxias have a pooled prevalence of 3.3 per 100,000 (REF.[4]), although this prevalence varies with geographical area and ethnic background. In 2019, the discovery of mutations in *RFC1* as the cause of the cerebellar ataxia, neuropathy and vestibular areflexia syndrome (CANVAS; also known as ATX-RFC1) brought to light substantial clinical and pathophysiological overlap between cerebellar and sensory neuron pathology in recessively inherited diseases.

In this Review, we focus on recessive cerebellar ataxias associated with a ganglionopathy — in particular, Friedreich ataxia and CANVAS — because these disorders pose a particular diagnostic challenge. They present with a complex gait disorder and the family history is

✉*e-mail:* *nicolas.dupre.med@ssss.gouv.qc.ca*

https://doi.org/10.1038/s41582-022-00634-9

Key points

- Cerebellar and afferent ataxias have a wide range of aetiologies, including paraneoplastic syndromes, infections, autoimmune disorders, drugs, toxicities, vitamin deficiencies and genetics.
- Autosomal recessive disorders that have cerebellar involvement and a dorsal root ganglionopathy include Friedreich ataxia, cerebellar ataxia, neuropathy, vestibular areflexia syndrome (CANVAS), ataxia with vitamin E deficiency, and *POLG*-related neuropathy–ataxia spectrum disorders.
- CANVAS is caused by biallelic intronic expansions in the *RFC1* gene and can present as unexplained, late-onset ataxia or idiopathic sensory neuronopathy.
- The main pathophysiological mechanisms of cerebellar and afferent ataxias are mitochondrial dysfunction and DNA break repair defects, possibly owing to the high energy demands of sensory and cerebellar neurons.
- Promising therapies in Friedreich ataxia aim to increase *FXN* transcription, increase levels of frataxin, reduce oxidative stress, reduce iron levels or replace the mutated gene.

R-loops
Three-stranded DNA–RNA hybrid structures that can occur during transcription and cause replication stress, gene silencing, chromatin alterations and genome instability.

Pes cavus
Deformation of the foot with a high plantar longitudinal arch, which can be associated with equinus deformity and clawing of the toes.

often negative. Despite these challenges, prompt recognition of these disorders is becoming essential because genetic testing for CANVAS and other recently described recessive ataxias has become commercially available and effective disease-modifying therapies are emerging for Friedreich ataxia. We provide an overview of the clinical phenomenology of the major recessive cerebellar ataxias with ganglionopathy to facilitate their recognition and identification with appropriate genetic testing. We also consider other inherited ataxias that are associated with polyneuropathy as these disorders can have similar presentations and may share underlying mechanisms. We provide an update on these mechanisms of disease, with an emphasis on shared pathways, and consider therapeutic approaches with a focus on novel advances in disease-modifying therapies for Friedreich ataxia.

Recessive ataxias with ganglionopathy

Friedreich ataxia

Genetics. Friedreich ataxia is the most common recessive ataxia in populations of European descent; the estimated prevalence is ~1 in 50,000 in these populations, and the carrier frequency is 1 in 120 (REFS[4–6]). Among patients with Friedreich ataxia, 96% are homozygous for an intronic GAA trinucleotide expansion in *FXN* and ~4% are compound heterozygotes for this expansion and a point mutation, insertion, or deletion in the other allele. Normal *FXN* alleles contain 5–33 GAA repeats at this location, whereas fully penetrant disease is caused by expansions of 66–1,300 repeats. Intermediate expansions of 34–65 repeats are referred to as premutation alleles because they are associated with a higher risk of hyper-expansion during parent-to-child transmission[5,7,8]. Premutation alleles also confer a risk of developing a late-onset, relatively mild form of the disease in individuals who harbour a full-length pathogenic mutation in the homologous *FXN* gene. This late-onset disease develops as a result of somatic instability[7]. Indeed, unstable GAA repeats continue to expand during the lifetime of patients owing to age-dependent and tissue-specific somatic instability mediated by stalled DNA replication forks and aberrant origin activation[9]. This somatic instability primarily affects the dorsal root ganglia and contributes to disease progression[10].

The GAA intronic expansion results in reduced levels of *FXN* transcripts. Consequently, levels of the protein product, frataxin, are reduced. In patients who are homozygous, frataxin levels are 5–30% of normal levels. In asymptomatic heterozygous carriers, frataxin levels can be 50–60% of normal levels[11]. Transcriptional deficiency results from a combination of epigenetic processes, including repressive histone modifications, DNA methylation, formation of R-loops and stalling of the RNA polymerase II upstream of the expansion[12]. DNA hypermethylation upstream of the expanded repeat correlates with *FXN* transcriptional deficiency and age of onset, highlighting the importance of this phenomenon in gene silencing[13].

Typical phenotype and clinical variants. The median age of onset for Friedreich ataxia is ~11 years but age at onset varies from 2 to 78 years[14,15]. Shorter GAA repeat expansions tend to be associated with later symptom onset[16]. In patients who are homozygous, age of onset correlates most strongly with the length of the shorter repeat (referred to as GAA1)[16]. A mild degree of afferent ataxia, manifesting as gait impairment with eyes closed or in low-light environments, often predates overt symptoms and is attributable to the early (possibly developmental) involvement of the posterior columns and dorsal root ganglia[17]. Symptom onset is marked by the development of ataxia despite visual input[18], and most patients present with gait instability that causes falls[19]. Deep tendon reflexes are usually absent. The cerebellar features of ataxia become evident within a few years upon the development of dysarthria, dysphagia and upper limb ataxia. Loss of pyramidal tract fibres causes weakness and atrophy, which become prominent in advanced disease. Extensor plantar responses are very common and most patients have episodic muscle spasm or clonus but only some develop constant spasticity.

Scoliosis and hypertrophic cardiomyopathy are associated with Friedreich ataxia and are the presenting symptoms in 9.3% of patients[19]. The majority of patients develop concentric cardiac hypertrophy, which is characterized by interstitial fibrosis, cardiomyocyte hypertrophy and chronic inflammation, and this can evolve into dilated cardiomyopathy[20–23]. Other associated features include pes cavus, diabetes mellitus, sensorineural hearing loss and optic neuropathy, which can cause progressive optic atrophy and linear loss of low-contrast visual acuity[24]. Example videos of typical findings in Friedreich ataxia are available elsewhere[25].

Progression of ataxia throughout the disease course is reflected by worsening scores on the Scale for the Assessment and Rating of Ataxia (SARA) and on

Author addresses

[1]Axe Neurosciences, CHU de Québec–Université Laval, Québec, QC, Canada.
[2]Department of Medicine, Faculty of Medicine, Université Laval, Quebec City, QC, Canada.
[3]Service de Neurologie, Médiathèque Jean Jacquy, CHU-Charleroi, Charleroi, Belgium.
[4]Service des Neurosciences, Université de Mons, Mons, Belgium.
[5]Ataxia Center, Laboratory for Neuroanatomy and Cerebellar Neurobiology, Department of Neurology, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA.
[6]Department of Neurology and Neurosurgery, McGill University, Montreal, QC, Canada.

the Friedreich Ataxia Rating Scale (FARS), although these scales are limited by ceiling effects once patients become non-ambulatory[14,26–28]. Patient-reported measures of function deteriorate more rapidly in patients with onset before age 25, tightly correlated with a worsening SARA score, whereas quality of life worsens very slowly regardless of age at onset[14,18,28]. Earlier onset is associated with a more severe and rapidly progressive phenotype. In parallel with the motor deterioration, patients develop typical cerebellar cognitive affective syndrome, which is characterized by executive, language and visuospatial dysfunction with altered expression of emotions and emotional recognition[29,30]. Ophthalmological biomarkers can reveal quantifiable anomalies that begin in the symptomatic ambulatory stage; for example, corneal confocal microscopy can detect reductions in corneal nerve fibre density and fibre length, the extent of which correlate with SARA and FARS scores[31].

Sensory involvement in Friedreich ataxia is caused by a dorsal root ganglionopathy, which is thought to result from hypoplasia and superimposed atrophy[32]. Neuropathological studies have revealed an overall reduction in the size of nerve cells in the dorsal ganglia, hypercellularity beneath the ganglion capsule, satellite cell proliferation and the presence of residual nodules[32]. These features are associated with anterograde degeneration of axons in the dorsal columns and spinocerebellar tracts, and with trans-synaptic atrophy in the cuneate nucleus, gracile nucleus and the dorsal nuclei of Clarke[32]. In the peripheral nerves, the number of Schwann cells is reduced and nerves lack large myelinated fibres; unmyelinated fibres are relatively preserved but show increased variability in axonal size[33]. These features are thought to result from a developmental hypomyelination with superimposed degenerative axonal disease in accordance with evidence that loss of myelinated fibres in sural nerves increases with age[33]. Accumulating evidence suggests that developmental abnormalities contribute to anomalies in the dorsal root ganglia and in the spinal cord[17,34]. Neuropathological studies have also demonstrated selective atrophy of large neurons in the dentate nuclei, Purkinje cell injury and loss of Betz cells in the corticospinal tracts, all of which are associated with clinical cerebellar and pyramidal dysfunction[32,35].

The mean age of death among patients with Friedreich ataxia is 39 years. Death usually results from cardiovascular causes, particularly progressive heart failure, arrhythmias and cardioembolic stroke attributable to atrial fibrillation[20,36]. Predictors of earlier mortality include longer GAA1 repeats, a lower left ventricular ejection fraction (LVEF) and a higher left ventricular mass index[20]. In one longitudinal study, LVEF progressively declined in 21.4% of patients and these patients had a worse cardiac prognosis. This cardiac progression was associated with shorter GAA1 and earlier age at onset but not with neurological decline[20]. Patients without cardiac complications typically survive longer but life expectancy is shortened by complications of severe neurological impairment, including pneumonia and sepsis[20,36].

Approximately 25% of patients with Friedreich ataxia have phenotypic variants. The main variant is delayed-onset Friedreich ataxia, which can be subdivided into late-onset (after 25 years of age) and very-late-onset

Box 1 | **Main acquired and inherited aetiologies of mixed cerebellar and afferent ataxias**

Paraneoplastic disorders
- Anti-Hu ganglionopathy/cerebellar degeneration
- Anti-collapsin response mediator protein 5 (CRMP5) peripheral neuropathy/cerebellar degeneration
- Anti-amphiphysin peripheral neuropathy/cerebellar degeneration
- Anti-microtubule-associated protein 1B (MAP1B; also known as PCA2) peripheral neuropathy/cerebellar degeneration

Infections
- Syphilis
- HIV
- Epstein–Barr virus

Autoimmune disorders
- Sjögren syndrome
- Gluten ataxia
- GAD65 antibody-associated cerebellar ataxia

Drug treatments
- Chemotherapies (platin derivatives, bortezomib, trastuzumab)
- Amiodarone
- Lithium
- Phenytoin
- Immune-checkpoint inhibitors

Toxicities
- Alcohol
- Mercury
- Thallium
- Lead
- Acrylamide

Vitamin and mineral deficiencies
- Vitamin E
- Vitamin B_{12}
- Copper

Autosomal recessive ataxias
- Friedreich ataxia
- Cerebellar ataxia, neuropathy, vestibular areflexia syndrome
- Ataxia with vitamin E deficiency
- *POLG*-related neuropathy–ataxia spectrum

See Supplementary Table 1 for a complete list.

Autosomal dominant spinocerebellar ataxias
- Spinocerebellar ataxia types 1, 2, 3, 4 and 7

See Supplementary Table 1 for a complete list.

Other inherited disorders
- Some X-linked ataxias
- Mitochondrial ataxias
- Subtypes of Charcot–Marie–Tooth disease
- Subtypes of complicated hereditary spastic paraparesis

See Supplementary Table 1 for a complete list.

(after 40 years of age) disease. Both subgroups are associated with shorter GAA expansions than those associated with the typical phenotype[15]. The phenotype of delayed-onset Friedreich ataxia is milder — dysarthria, areflexia, extensor plantar reflexes, amyotrophy, scoliosis and cardiomyopathy are all less common. Progression is also slower and disease duration before reliance on a wheelchair is longer[15,37]. The other main phenotypic variant is Friedreich ataxia with retained reflexes, which has a later age of onset than typical Friedreich ataxia and can be associated with spasticity[15,38].

People with compound heterozygosity for an *FXN* point mutation, insertion or deletion exhibit phenotypic differences depending on the impact of the mutation on the structure and function of frataxin[39]. Null mutations are associated with an earlier age of onset and a higher prevalence of diabetes mellitus. Cardiomyopathy is less common among people with compound heterozygosity[39]. Compound heterozygosity for a missense mutation in the amino-terminal half of the protein — particularly the Gly130Val mutation — presents with an atypical phenotype with retained reflexes and no dysarthria[40,41].

Early neuroimaging features. Upon routine brain imaging in Friedreich ataxia, cerebellar atrophy is either absent or mild, whereas a thin spinal cord is an invariable finding. Multimodal MRI has revealed substantial alterations in the cervical spinal cord, including volumetric reduction, altered diffusivity and abnormal magnetic resonance spectroscopy findings. Changes in volume and diffusivity are most pronounced in the infratentorial white matter of the brainstem, the superior and inferior cerebellar peduncles, and the dentate nuclei[42–44]. Volumetric deficits — particularly those in the superior cerebellar peduncle and the dentate region — correlate with disease duration and severity[44,45].

Involvement of cerebral white matter occurs later and is less pronounced than the changes seen in the cerebellar peduncles and dentate nuclei. Cerebral white matter volume loss is widespread but preferentially affects the corticospinal tracts, anterior thalamic radiations and occipital tracts[44]. Diffusion tensor imaging also reveals microstructural damage in the splenium of the corpus callosum that progresses over time[43,45–47]. The cerebellar cortex is not obviously atrophic, but volumetric studies have demonstrated that cerebellar grey matter volume loss can occur in all cerebellar lobules, to the greatest extent in lobules I–IV, V and VI, and more modest atrophy in the posterior lobules[44]. Patients with a long disease duration have diffuse supratentorial grey matter involvement and reductions in volume are most pronounced in the precentral gyri[44]. These macrostructural and microstructural alterations progress over time — the cerebellum and brainstem regions are involved earliest, then the supratentorial white matter and, finally, the supratentorial grey matter[44,48].

CANVAS

Genetics. The cause of CANVAS in European populations was identified in 2019 as a homozygous, intronic AAGGG repeat expansion $(AAGGG)_{exp}$ in the *RFC1* gene[49,50]. Repeat lengths in mutated alleles range from 400 to 2,000. The reference allele at this locus is $(AAAAG)_{11}$ and other benign configurations include $(AAAAG)_{exp}$ and $(AAAGG)_{exp}$ (REF.[49]). Two other pathological allelic configurations have been described in other populations: an ACAGG expansion and an AAGGG expansion preceded by a variable length of non-pathogenic AAAGG repeats[51–53]. Patients in these populations shared the core haplotype described in European populations, suggesting a common origin of the *RFC1* mutation. The nucleotide changes from AAAAG to AAAGG and AAGGG are thought to stem from a unique ancestral founder event ~25,000 years ago in Europe, which caused somatic instability and variable expansion of the pentanucleotide repeats[50].

The proportion of healthy individuals who carry an AAGGG expansion is 0.7% in European populations, 1–2.2% in China and 4% in Canada[49,54–57]. Moreover, biallelic expansions have been identified in 3.2–22% of patients in cohorts with previously unexplained familial or sporadic late-onset ataxia[49,53,58,59]. On this basis, *RFC1* mutations are thought to be responsible for many cases of late-onset ataxia with associated neuropathy, with or without vestibular areflexia[49].

The relatively high guanine and cytosine content of the AAGGG and ACAGG motifs is thought to be important in driving the formation of repeat expansions and in the pathogenicity of these expansions[49,52,60]. A_nG_m motifs cause base stacking interactions that promote the formation of expansion and prevent repair[61]. Repetitive G-rich DNA motifs promote R-loop formation in vivo and are associated with other neurological repeat expansion disorders[62].

Typical and atypical phenotypes. The typical phenotype of CANVAS is characterized by the triad of late-onset, progressive cerebellar ataxia, severe sensory neuropathy, and bilateral vestibulo-ocular dysfunction, which manifests as an abnormal head impulse test (the patient is unable to maintain focus on a specified point during rapid rotation of the head and generates a correction saccade). Chronic cough is reported by two-thirds of patients, and dysautonomic symptoms, such as postural hypotension, erectile dysfunction, urinary dysfunction, chronic constipation and anhidrosis, are common[49,63,64]. Most patients develop sensory complaints, such as hypoaesthesia, pins and needles, and neuropathic pain, and some also develop vertigo, oscillopsia, dysarthria and dysphagia[63,64]. The median age of onset of neurological symptoms is 52 years (range 6–76 years), but the chronic cough can begin up to three decades before the onset of neurological symptoms[51,63].

In the largest cohort of patients with CANVAS described to date, only 46% presented with the complete triad on the basis of clinical assessment alone[63]. When brain MRI, nerve conduction studies and formal vestibular testing were also used, this proportion increased to 63%, and sensory potentials were reduced or absent in all diagnosed patients[63]. These findings demonstrate that the disease can present as an unexplained chronic sensory polyneuropathy with subclinical or no cerebellar symptoms[65]. MRI reveals cerebellar atrophy that mainly

Crus I
A hemispheric subdivision of cerebellar lobule VII, located above the horizontal fissure.

Bergmann gliosis
A distinctive reactive histological pattern that occurs after cerebellar insult with hyperplasia of radial astrocytes following Purkinje cell loss.

H reflex
A late-response electrophysiological test performed at the soleus muscle that assesses the integrity of the Aα muscle spindles as afference and α motor neurons as efference.

affects the anterior and dorsal vermis and lateral cerebellar hemispheric atrophy that preferentially involves Crus I[63,66]. Spinal cord atrophy and T2 hyperintensity in the posterior columns have also been observed[63]. Pathological studies have demonstrated prominent cerebellar atrophy, with severe depletion of Purkinje cells and prominent Bergmann gliosis, and severe loss of neurons in the dentate nuclei and inferior olives[49,67].

Sensory involvement in CANVAS results from ganglionopathy — neuropathological studies have demonstrated severe atrophy of the dorsal root ganglia with secondary demyelination of the posterior columns, along with atrophy and a marked decrease in trigeminal ganglion cells[68]. Bilateral vestibular dysfunction is attributed to involvement of the vestibular ganglia (the ganglia of the vestibular branches of the vestibulocochlear nerves). In a series of patients with biallelic *RFC1* expansions who were initially diagnosed with chronic axonal idiopathic sensory polyneuropathy, nerve conduction studies revealed a non-length-dependent pattern suggestive of a ganglionopathy in 70%[65]. Sensory nerve fibres are not equally affected in CANVAS — Aβ, Aδ and unmyelinated C fibres are preferentially involved. Indeed, deep tendon reflexes are often normal or brisk, suggesting relative sparing of the Aα fibres that carry muscle spindle information[63]. This sparing of Aα fibres is also indicated by the fact that the H reflex is preserved in patients with CANVAS, even in the absence of sensory nerve action potentials[69]. Involvement of thinly myelinated Aδ fibres and unmyelinated C fibres is suggested by the presence of pinprick anaesthesia and chronic cough — the cough is thought to result from denervation hypersensitivity of secondary neurons in the nucleus of the tractus solitarius[70]. Ultrasound imaging has demonstrated that peripheral nerves in patients with CANVAS have small diameters, an observation that is specific for sensory neuronopathies[71]. Furthermore, sural nerve biopsy has demonstrated severe, chronic loss of large and small myelinated fibres without active axonal degeneration and little regeneration in CANVAS, observations that are also consistent with a ganglionopathy[49,63,69,72].

In rare cases, patients with CANVAS have abnormalities in motor nerve conduction as well as in sensory nerves[63,66]. For example, in two Asian–Pacific families, the typical CANVAS phenotype was associated with distal muscle wasting and weakness, fasciculations, elevated serum creatine kinase and electromyographic evidence of denervation, all of which indicate lower motor neuron involvement[52]. In one European series, upper and/or lower motor neuron signs were frequently reported, with mixed motor and sensory neuronopathy in 19% of patients[73].

In rare cases, *RCF1* expansions have been identified in patients who had initially been diagnosed with multisystem atrophy (MSA) of the cerebellar or parkinsonian types[55], suggesting that CANVAS can present with an MSA-like phenotype. Features that are similar to MSA include autonomic dysfunction, bradykinesia, REM sleep behaviour disorder, early dysphagia, brainstem atrophy, early dependence on walking aids, and rapid progression phases[64]. Indeed, in one cohort of patients with CANVAS in New Zealand, REM sleep behaviour disorder was common[51]. Nevertheless, biallelic *RFC1* expansions were not observed in a cohort of 336 patients with pathologically confirmed MSA[54]. On this basis, testing for *RFC1* expansions should be considered for patients who present with an MSA-like phenotype if some atypical features are present such as sensory involvement, chronic cough or vestibular dysfunction.

No association exists between the size of the repeat expansion and the age of onset or disease severity in CANVAS[63]. Disease progression is highly heterogeneous and can be non-linear with phases of rapid deterioration. On average, scores on SARA reduce by 1.3 points per year, indicating a more rapid progression than that of Friedreich ataxia, in which scores reduce by an average of 0.82 points per year[14,28]. Some patients die relatively early (for example, in their 60s), and earlier death is associated with severe dysphagia, cough and immobility[64].

Ataxia with vitamin E deficiency

Ataxia with vitamin E deficiency (also known as ATX-TTPA) is caused by mutations in the *TTPA* gene, which encodes the α-tocopherol transfer protein, a vitamin E transporter. The disorder is most common among people of Mediterranean origin, probably owing to a founder effect[74]. The clinical syndrome is similar to Friedreich ataxia[74] (TABLE 1) but can include extrapyramidal symptoms, head tremor and cervical dystonia[75]. Retinitis pigmentosa can occur in rare cases and has most frequently been observed in patients from Japan[76].

Nerve conduction studies have demonstrated that patients have mild-to-moderate axonal neuropathy, which can be sensorimotor, purely sensory or purely motor. This neuropathy correlates with the loss of dorsal root ganglion cells and lipopigment storage in the remaining cells[77]. Historically, patients would become wheelchair-bound in their late 20s, but supplementation with high-dose vitamin E stabilizes and, in some cases, improves neurological deficits, especially if initiated early in the disease evolution; thus, fewer patients now progress so rapidly[74,78].

POLG-related neuropathy–ataxia spectrum

Recessive *POLG* mutations cause mitochondrial DNA depletion and have been associated with diverse clinical syndromes, including mitochondrial recessive ataxia syndrome (MIRAS) and sensory ataxia, neuropathy, dysarthria and ophthalmoplegia (SANDO), both of which sit on the neuropathy–ataxia spectrum[79,80]. *POLG* mutations are associated with an axonal or mixed, sensory-predominant and occasionally painful neuropathy[81]. Patients develop areflexia with deficits in sensation of vibration and proprioception[82].

Nerve conduction studies in this condition reveal a sensory neuronopathy; motor fibre involvement can develop later in the course of the disease. The sensory neuronopathy correlates with neuronal loss in the dorsal root ganglia and severe demyelination and atrophy in the posterior columns[80]. MRI features include mild or moderate cerebellar atrophy with T2 hyperintensities

in the deep cerebellar structures[82]. Chronic progressive external ophthalmoplegia is almost ubiquitous[82]. Ptosis, myopathy, seizures, cognitive impairment, chorea, dystonia and myoclonus can all occur[82].

Other recessive ataxias with ganglionopathy

Several other recessively inherited ataxias are associated with a dorsal root ganglionopathy (TABLE 1). Infantile-onset spinocerebellar ataxia (also known as ATX-TWNK) is caused by mutations in the *TWNK* gene and is characterized clinically by ataxia, athetosis, hypotonia, areflexia and cognitive impairment with onset in infancy. The condition involves a sensory axonal neuropathy and severe degenerative changes in the dorsal root ganglia, posterior columns and posterior spinocerebellar tracts[83]. Ophthalmoplegia, optic atrophy, sensorineural hearing loss and epilepsy can develop during the course of the disease and contribute to severe functional disability.

Mitochondrial complex IV deficiency, nuclear type (also known as ATX-COX20) is caused by mutations in *COX20* and leads to early-onset cerebellar ataxia, dysarthria, dystonia, hypotonia and severe, non-length-dependent sensory neuropathy[84]. Mutations in *COX20* also cause an isolated sensory neuronopathy with afferent ataxia[85].

Cerebellar ataxias with polyneuropathy

Numerous other inherited ataxias can present with polyneuropathy, and if this polyneuropathy includes a moderate-to-severe sensory component, the resulting afferent deficit can lead to a mixed cerebellar and afferent ataxia, similar to that seen in a dorsal root ganglionopathy. A large number of conditions can present in this way (Supplementary Table 1); in the following sections, we highlight the most prevalent recessive and dominant disorders as these conditions are the most likely to be encountered by neurologists and some share pathophysiological mechanisms with cerebellar ataxias with ganglionopathy, with implications for therapeutics.

ARSACS

Autosomal recessive spastic ataxia of Charlevoix–Saguenay (ARSACS; also known as ATX/HSP-SACS) presents with a clinical triad of cerebellar ataxia, pyramidal signs, and a demyelinating or axonal sensorimotor polyneuropathy, though the full triad might not be present in all patients. The neuropathy is characterized by amyotrophy, loss of proprioception and sensation of vibration, absent Achilles deep tendon reflexes, and mild afferent ataxia in some patients[86]. Thickened retinal nerve fibres visible with fundoscopy is a pathognomonic finding. MRI features are cerebellar

Table 1 | **Autosomal recessive ataxias associated with a dorsal root ganglionopathy**

Traditional nomenclature	MDS nomenclature	OMIM	Age at onset (years)	Clinical features	Paraclinical specificities	Refs
Friedreich ataxia	ATX-FXN	229300	Median 11, range 2–78	Ataxia, loss of vibration and proprioception, areflexia, Babinski sign, amyotrophy, square-wave jerks, hypertrophic cardiomyopathy, scoliosis, pes cavus, diabetes mellitus	Early spinal cord atrophy, absence of cerebellar atrophy, reduced corneal nerve fibre density and fibre length in corneal confocal microscopy	15,16,26,31
Cerebellar ataxia, neuropathy, vestibular areflexia syndrome (CANVAS)	ATX-RFC1	614575	Median 52, range 6–76	Ataxia, loss of vibration and proprioception, pinprick hypoaesthesia, vestibular areflexia, chronic cough, dysautonomia, dysphagia, RSBD	Absent or reduced sensory evoked potentials, cerebellar and spinal cord atrophy	51,63
Ataxia with vitamin E deficiency	ATX-TTPA	227460	Mean 13, range 2–52	Ataxia, loss of vibration and proprioception, dysarthria, areflexia, Babinski sign, axonal sensorimotor neuropathy, head tremor, retinitis pigmentosa, dystonia, skeletal deformities	Reduced or undetectable vitamin E, possible cerebellar atrophy	75,76,78
POLG-related ataxia-neuropathy spectrum	POLG	607459	Mean 26, range 12–45	Ataxia, dysarthria, progressive external ophthalmoplegia, ptosis, areflexia, sensory neuronopathy, pain, dysarthria, myopathy, cognitive impairment, epilepsy, chorea, dystonia	T2 MRI hyperintensities in thalami, cerebellar white matter and inferior olivary nuclei, no or mild cerebellar atrophy	82,183
Infantile-onset spinocerebellar ataxia (MTDPS7)	ATX-TWNK	271245	Usual 1–2, range 0–48	Sensory axonal neuronopathy, loss of vibration and proprioception, hyporeflexia, athetosis, hypotonia, sensorineural deafness, optic atrophy, ophthalmoplegia, epilepsy, migraine, cognitive deficits, psychiatric symptoms	Atrophy of the brainstem, cerebellum and posterior columns of the spinal cord, hypergonadotropic hypogonadism in females, elevation of serum transaminases	83,184
Mitochondrial complex IV deficiency	COX20	619054	Usual 1–4, range 0–12	Hypotonia evolving to spasticity, dystonia, sensory neuronopathy, areflexia, dysarthria, cognitive impairment, strabismus, growth retardation	Elevation of blood lactate, cerebellar atrophy, complex IV deficiency in muscle and fibroblasts	84,185

MDS, International Parkinson and Movement Disorder Society; MTDPS7, mitochondrial DNA depletion syndrome 7; OMIM, Online Mendelian Inheritance in Man; RSBD, REM sleep behaviour disorder.

atrophy, linear T2 hypointensities in the pons, T2 and/or fluid-attenuated inversion recovery (FLAIR) hyperintensities in the lateral pons or middle cerebellar peduncle, biparietal atrophy, and thinning of the posterior corpus callosum[86,87].

Ataxia–telangiectasia

Ataxia–telangiectasia (also known as ATX-ATM) presents in early infancy with gait unsteadiness that is often static between the ages of 2 and 5 years as children acquire motor skills. At ~6 years of age, conjunctival and cutaneous telangiectasias become more prominent and patients deteriorate progressively with dysmetria, dysphagia, oculomotor apraxia and progressive gait ataxia, leading to wheelchair dependency[88]. This progression is associated with axonal sensory-predominant polyneuropathy, drooling and extrapyramidal movement disorders, including dystonia, choreoathetosis, parkinsonism, myoclonus and tremor[88]. The disorder is also associated with immunodeficiency, sensitivity to radiation and a predisposition to cancers[89].

Ataxia with oculomotor apraxia 2

Ataxia with oculomotor apraxia 2 (also known as ATX-SETX) is characterized by ataxia, an axonal sensory-predominant polyneuropathy, pyramidal signs, oculomotor apraxia and extrapyramidal involvement that manifests as head tremor and dystonia. Typical paraclinical features include elevated alphafetoprotein, cerebellar atrophy and loss of dentate nuclei hypointensity on susceptibility-weighted MRI sequences[90,91].

Dominant ataxias with a polyneuropathy

The dominantly inherited spinocerebellar ataxias (SCA) 1, 2, 3 and 7 can be associated with prominent peripheral nervous system involvement[92]. Electrophysiology, ultrasound and neuropathology data suggest that the sensory involvement results from dorsal root ganglionopathy in the majority of patients with SCA2 and in some patients with SCA1, SCA3 and SCA7 (REFS[92–95]).

Shared mechanisms of disease

Various pathophysiological mechanisms have been implicated in recessive cerebellar and afferent ataxias (FIG. 1), reviewed in detail elsewhere[2,96]. Some aspects of these diseases suggest that some mechanisms are likely to be shared. In particular, dorsal root ganglion cells and Purkinje cells are some of the largest neurons in the nervous system, meaning that they have high energy and metabolic demands that make them particularly vulnerable to defects in energy production. Similarly, many genes involved in cerebellar and afferent ataxias are involved in DNA repair, indicating that defects in this process are common to these diseases. Furthermore, oxidative damage to mitochondrial DNA is a high risk in cells with high energy demand, and therefore defects in DNA repair could exacerbate the metabolic cellular vulnerability. In the sections that follow, we discuss possible shared mechanisms in detail and consider how they could combine to underlie multiple recessive ataxias that present with a dorsal root ganglionopathy or significant neuropathy despite their different genetic aetiologies.

Mitochondrial dysfunction

One disease mechanism that has been identified in recessive afferent and cerebellar ataxias is mitochondrial dysfunction, which can result from alterations in several pathways (FIG. 1). In Friedreich ataxia, deficits in frataxin lead to reduced biosynthesis of Fe–S clusters, which are important cofactors for cellular processes such as oxidative phosphorylation and iron metabolism. In healthy cells, frataxin colocalizes with the Fe–S assembly machinery in the mitochondrial cristae, close to the respiratory chain enzymes. However, in cells from patients with Friedreich ataxia, frataxin widely redistributes to the mitochondrial matrix, which is associated with alterations in respiratory supercomplex assembly and impairments in oxidative phosphorylation[97]. Deficits in Fe–S proteins that result from low levels of frataxin also lead to reduced ATP production, which is accompanied by increased production of reactive oxygen species and greater oxidative stress. Simultaneously, endogenous antioxidants, including superoxide dismutase and glutathione, the expression of which is controlled by the transcription factor Nrf2, are depleted[98] owing to reduced Nrf2 expression (a result of frataxin deficiency) and failure of its activation following oxidative insult[99,100]. Multiple tissues are affected by this mitochondrial dysfunction, in particular the dorsal root ganglia, spinal cord, cerebellar dentate nuclei, pancreas, heart and skeletal muscles[101].

Iron metabolism is also altered in Friedreich ataxia, leading to increased cellular iron uptake. Excess iron is imported into the mitochondria, possibly as a homeostatic response to support Fe–S cluster biogenesis[102]. However, inefficient incorporation of iron into Fe–S clusters leads to its accumulation in mitochondria and consequent toxicity. Furthermore, frataxin is a key regulator of ferroptosis, a form of non-apoptotic regulated cell death that is driven by iron-dependent phospholipid peroxidation[103]. In cells from patients with Friedreich ataxia, ferroptosis inhibitors but not apoptosis inhibitors rescued cell death induced by erastin (which initiates ferroptosis), suggesting that ferroptosis is an important pathogenic mechanism in the disease[98]. Alterations in iron metabolism have long been thought to explain the preferential involvement of the dentate nuclei, which have a high iron content, but how iron metabolism relates to dorsal root ganglion and peripheral nerve damage remains unclear[32,33].

Alterations to mitochondrial DNA also contribute to mitochondrial dysfunction in some cerebellar and afferent ataxias. The mitochondrion does not encode DNA repair machinery and therefore depends on nuclear-encoded proteins to ensure mitochondrial DNA integrity. DNA polymerase-γ, which is encoded by *POLG*, is one such protein, as it is the main enzyme responsible for mitochondrial DNA replication. Mutations in *POLG* cause clonally expanded mitochondrial DNA deletions that lead to respiratory chain deficiency and alterations in the cytoplasmic distribution and density of mitochondria[80]. Similarly, Twinkle is a mitochondrial replicative helicase encoded by *TWNK* that functions closely with DNA polymerase-γ. Mutations in *TWNK* and *POLG*, which

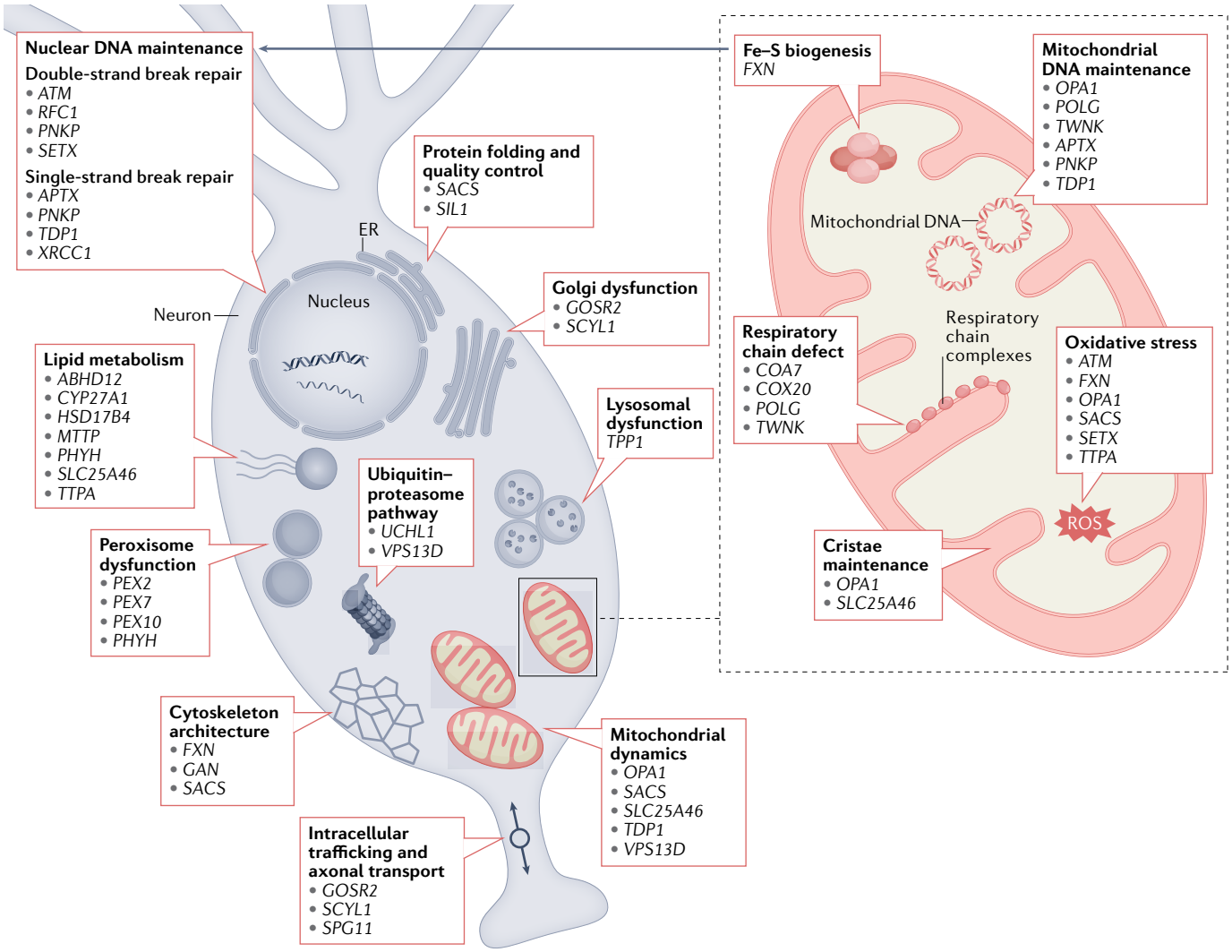

Fig. 1 | **Cellular pathways involved in recessive cerebellar and afferent ataxias.** The sites of pathways involved in the pathogenesis of cerebellar and afferent ataxias in a neuron (left). Several pathways are involved specifically in mitochondrial dysfunction (right). Gene names indicate the genes involved in each pathway that has been implicated in these diseases. ER, endoplasmic reticulum; ROS, reactive oxygen species.

are associated with infantile-onset spinocerebellar ataxia and *POLG*-related neuropathy–ataxia spectrum, respectively (TABLE 1), cause mitochondrial DNA depletion and deficiency of respiratory complexes I and IV, which is most prominent in large neurons[80,104]. Another nuclear gene involved in this pathway is *COX20*, which encodes a chaperone protein involved in the assembly of respiratory complex IV[85]. Disorders associated with mutations in these genes present with respiratory complex deficiencies and some common clinical features such as severe sensory neuronopathy, ophthalmoplegia, dystonia and cognitive deficits (TABLE 1).

Abnormalities of the mitochondrial network are also relevant to cerebellar and afferent ataxias. Frataxin deficiency is associated with excessive mitochondrial fragmentation owing to the altered function of dynamin-related protein 1 (Drp1), which is essential in mitochondrial fission[105]. Conversely, in autosomal recessive spastic ataxia of Charlevoix–Saguenay, deficiency of the protein sacsin results in a hyperfused mitochondrial network. Sacsin is a chaperone of the intermediate filament cytoskeleton and normally recruits Drp1 to the mitochondrial membrane. In sacsin-deficient cells, recruitment of Drp1 is reduced at mitochondrial fission sites, leading to an overly interconnected and functionally impaired mitochondrial network with accumulation of mitochondria in the soma and proximal dendrites of neurons[106]. These alterations result in abnormal oxidative phosphorylation and increased oxidative stress[106,107].

DNA break repair mechanisms

RFC1 encodes the large subunit of replication factor C (RFC), a protein involved in DNA replication and repair that is predominantly expressed in the brain and cerebellum[50]. RFC opens the protein ring of proliferating cell nuclear antigen (PCNA) and loads it onto DNA, thereby enabling it to recruit and coordinate

proteins involved in DNA replication and repair[108]. RFC1 is an essential isoform that interacts with DNA ligase, transcription factors and the histone chaperone ASF1 (REFS[108,109]). This isoform is crucial for nucleotide excision repair, base excision repair and mismatch repair, which involve loading of PCNA and recruitment of DNA polymerase-δ and DNA polymerase-ε[110,111]. RFC1 is also involved in homologous recombination for double-strand break (DSB) repair through its interaction with the transcriptional regulator ATRX (a chromatin remodeller) and PCNA[112]. These functions of RFC1 suggest that DNA repair mechanisms could be involved in CANVAS, though evidence to support this hypothesis has been elusive.

Analysis of cell lines from patients with CANVAS has provided no evidence that *RFC1* transcription is reduced compared with that in healthy controls[49]. Quantitative reverse transcription PCR analysis of several tissues has shown a consistent increase in retention of intron 2 in pre-mRNA but provided no evidence of aberrant splicing or reduced expression at the mature mRNA level, and levels of the RFC1 protein were not decreased[49,113]. Age at onset of CANVAS is not associated with the number of repeats, and studies of fibroblasts from patients have provided no evidence for increased susceptibility to DNA damage or impairment of damage responses[49]. Therefore, the mechanism of selective sensory neuron and Purkinje cell damage in RFC1 disease remains elusive.

ATM and *SETX*, which are mutated in ataxia–telangiectasia and ataxia with oculomotor apraxia 2, are also involved in DSB repair pathways. Indeed, the primary function of the kinase ataxia–telangiectasia mutated (ATM) is to act as a key regulator of the DNA damage response to coordinate downstream events after DSB such as cell cycle arrest, DNA repair and/or apoptosis[114]. Single-strand break (SSB) repair has also been implicated in ataxias. *APTX* (mutated in ataxia with oculomotor apraxia 1), *PNKP* (mutated in ataxia with oculomotor apraxia 4) and *TDP1* (mutated in spinocerebellar ataxia with axonal neuropathy 1) encode proteins that are all directly involved in this pathway. Tyrosyl-DNA phosphodiesterase 1 (TDP1) and polynucleotide kinase-phosphatase (PNKP) closely interact to repair SSBs linked with topoisomerase 1 (REF.[115]). PNKP is also involved in non-homologous end-joining for DSB repair.

Interplay between mechanisms

Pathophysiological overlap exists between mitochondrial dysfunction and DNA break repair mechanisms in cerebellar and afferent ataxias because the proteins affected are involved in several pathways or cause multiple downstream alterations. For example, ATM regulates several cellular pathways besides DSB repair, including oxidative stress homeostasis, epigenetic regulation of brain development and neuronal survival, insulin signalling, and synaptic transmission[114]. Accumulating evidence suggests that oxidative stress has an important role in neurodegeneration in ataxia–telangiectasia. Oxidation can activate ATM directly, independently of DSBs, in which case ATM acts as an oxidative sensor to activate downstream homeostasis pathways[116]. In cellular and mouse models of ataxia–telangiectasia, levels of oxidative stress markers, oxidative DNA damage and DNA deletions are all increased[114].

Another example is TDP1, which is involved in SSB repair but also in mitochondrial DNA repair, such that mutations in this gene lead to mitochondrial dysfunction. In model cells that express *TDP1* mutations, the protein is trapped on mitochondrial DNA, which increases mitochondrial fission rate, prevents mitochondrial transcription, alters energy production and abrogates mitobiogenesis[117]. Similarly, aprataxin (encoded by *APTX*) and PNKP primarily mediate DNA repair but are also present in the mitochondria, and their dysfunction is associated with diverse mitochondrial alterations and mitochondrial DNA damage[118,119].

Conversely, the pathogenesis of Friedreich ataxia can involve DNA repair defects in addition to mitochondrial dysfunction. Indeed, Fe–S cluster enzymes have been shown to play a critical role in DNA replication and repair — they are incorporated into DNA primase, all replicative polymerases and DNA2 nuclease/helicase, and they are also involved in nucleotide excision repair, base excision repair and telomere maintenance[120]. In Friedreich ataxia cells with low expression of *FXN*, mitochondrial DNA damage is increased and repair capacity is decreased[121]. Cellular models of Friedreich ataxia exhibit transcriptional deregulation in many genes involved in DNA repair pathways, including *APTX*[122].

In general, mutations of DNA repair genes are also likely to contribute to mitochondrial dysfunction because the mitochondrion does not encode DNA repair machinery and depends on nuclear-encoded proteins to ensure mitochondrial DNA integrity. Such mitochondrial dysfunction as a result of DNA repair defects could be a common final pathway in several cerebellar and afferent ataxias because of two combined factors: first, mitochondrial DNA is particularly vulnerable to oxidative damage by reactive oxygen species produced by oxidative phosphorylation owing to its close proximity to the respiratory chain, and second, Purkinje cells and dorsal root ganglion neurons are large cells with high energy demands that translate into high production of reactive oxygen species and consequent oxidative mitochondrial DNA damage. This combination could explain the shared vulnerability of the cerebellum and dorsal root ganglia to alterations in energy production and cumulative oxidative DNA damage.

However, if all the disorders discussed above share cerebellar and sensory neuron pathology, the reasons why other cell types with high energy demands are affected in certain disorders but not in others remain unclear. For example, Betz cells of the pyramidal tracts, cardiomyocytes and retinal pigment epithelium cells[32,123] are affected in Friedreich ataxia but not in CANVAS or in *POLG*-related neuropathy–ataxia spectrum disorders. One likely explanation is that disease-specific metabolic defects place specific cell types at higher risk depending on their metabolic requirements beyond energy demand. Future research is needed to identify

which factors are involved in this tissue specificity and why other disorders that affect these pathways lead to different phenotypes.

Other potential shared mechanisms

The fact that Friedreich ataxia and CANVAS present with overlapping neurological phenotypes and are both caused by intronic expansions suggests the possibility of a shared genetic pathogenic mechanism, although *RFC1* transcription does not seem to be reduced in CANVAS in the same way that *FXN* transcription is in Friedreich ataxia. An alternative genetically driven mechanism could be repeat-associated non-ATG translation, which occurs in other microsatellite repeat expansion disorders and leads to the formation of toxic intracellular protein inclusions[124]. This potential mechanism has not been studied in cerebellar and afferent ataxias but should be investigated in this context. Some evidence suggests that secondary inflammation contributes to the pathogenesis of some recessive cerebellar and afferent ataxias, notably Friedreich ataxia (in which it is involved in dorsal root ganglion and cardiac damage) and ataxia–telangiectasia[22,125–127]; therefore, this potentially shared mechanism also warrants further study.

Treatment

Promising therapies for Friedreich ataxia

Several potential therapeutic targets are currently under investigation in Friedreich ataxia (FIG. 2). Most therapeutic approaches are based on two general principles: increasing frataxin expression and reducing oxidative stress.

Increasing frataxin expression. One approach to increase the expression of frataxin is to target epigenetic mechanisms that alter *FXN* expression. Histone deacetylase inhibitors can remodel pathological heterochromatin in Friedreich ataxia by restoring acetylation, a modification that activates transcription, at key histone residues. Nicotinamide (also known as vitamin B_3) is a non-specific inhibitor of NAD-dependent class III histone deacetylases. In an 8-week open-label dose-escalation study, treatment with nicotinamide increased levels of *FXN* mRNA transcripts and frataxin protein to levels seen in asymptomatic carriers[128]. A 24-month randomized controlled trial of daily nicotinamide is expected to start in 2022 (REF.[129]). A phase II clinical trial to evaluate the combined effect of nicotinamide riboside and exercise on aerobic capacity is ongoing[130]. Similarly, in cellular and animal models of Friedreich

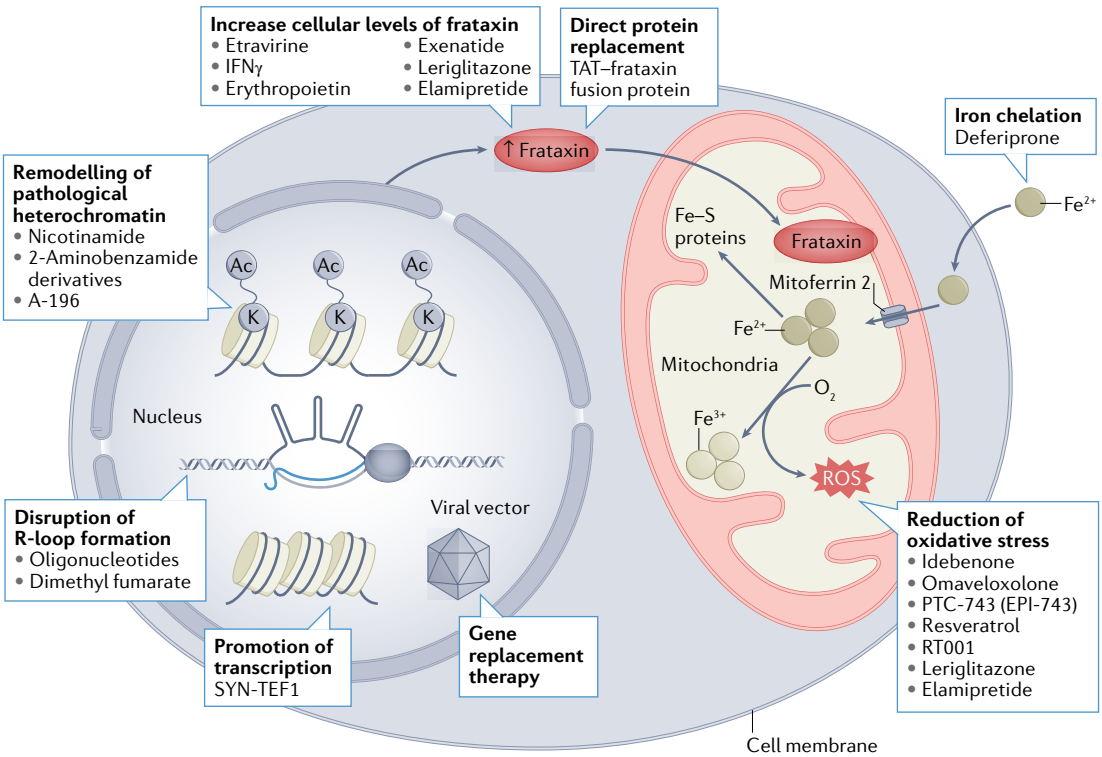

Fig. 2 | **Therapeutic targets of experimental therapies in Friedreich ataxia.** Possible therapeutic mechanisms in Friedreich ataxia are shown in the boxes, along with the names of experimental therapeutics that target each mechanism and that are currently being studied in Friedreich ataxia. Increasing transcription of the *FXN* gene to produce more frataxin is one promising approach and could be done by remodelling pathological heterochromatin, disrupting R-loop formation, promoting transcription, or with gene replacement therapy. Alternatively, frataxin protein levels can be increased through direct protein replacement or with repurposed drugs that have been found to generate a small-to-moderate increase in frataxin expression. Restoration of endogenous antioxidant mechanisms or the use of antioxidant drugs to reduce oxidative stress is another avenue, as is iron chelation to reduce excess iron accumulation and toxicity in the mitochondria. ROS, reactive oxygen species; TAT, transactivator of transcription.

ataxia, 2-aminobenzamide derivatives, which are inhibitors of class I histone deacetylases, upregulated *FXN* mRNA[131,132]. Histone methylation can also be targeted to upregulate the expression of *FXN*. In cells derived from patients with Friedreich ataxia, inhibition of the SUV4-20 methyltransferases with A-196 led to a 1.5–2-fold upregulation of *FXN* expression[133].

Disruption of R-loop formation with oligonucleotides is another epigenetic strategy to increase frataxin production. Repeat-targeted duplex RNAs and antisense oligonucleotides transfected into patient-derived cells can interfere with R-loop formation and increase the expression of frataxin to levels seen in wild-type cells[134,135]. However, this approach is still at the preclinical investigation stage. Similarly, preclinical experiments in patient-derived cells have shown that the synthetic transcription elongation factor SYN-TEF1, which was specifically designed to promote transcription across repressive chromatin at the *FXN* locus, partially restores *FXN* transcription and protein production[136].

Dimethyl fumarate, which is already approved for the treatment of multiple sclerosis and psoriasis, can increase frataxin expression by increasing initiation of *FXN* transcription and by reducing R-loop formation and transcriptional pausing[137,138]. Dimethyl fumarate can also induce mitochondrial biogenesis through activation of the Nrf2 pathway, and it rescued mitochondrial enzymatic activity in a mouse model of Friedreich ataxia[137,139,140]. A clinical trial in patients with Friedreich ataxia is still awaited.

Several compounds can produce a small-to-moderate increase in cellular levels of frataxin through pathways other than epigenetic modifications but the magnitude of the changes remain low and of uncertain clinical impact. A drug repositioning screen identified that etravirine, a currently available anti-HIV therapy, can increase frataxin levels by 50% in cultured cells via an increase in the translation of *FXN* mRNA[141]. A phase I study of etravirine in patients with Friedreich ataxia is planned. IFNγ had a similar effect in cell culture but a 6-month, double-blind placebo-controlled trial of IFNγ failed[142]. Modest stabilization of the disease in treated patients has been reported in the open-label extension of the trial[142].

Erythropoietin also increased frataxin levels in patient-derived cell lines[143]. On this basis, the drug was tested in a 48-week randomized controlled trial but no effect was seen on the primary end point of cardiopulmonary function[144]. However, performance on the nine-hole pegboard test improved with erythropoietin treatment, suggesting that it has a mild symptomatic benefit. Erythropoietin can cause erythrocytosis, and therefore small molecules that specifically target the tissue-protective erythropoietin receptor have been developed to avoid this effect. These compounds can also induce a moderate upregulation of frataxin in cultured cells and seem to have a greater impact than erythropoietin on the CNS expression of *FXN* in a mouse model[145]. However, they have not yet been tested in clinical trials. Finally, the glucagon-like peptide 1 analogue exenatide, which is approved for treatment of type 2 diabetes mellitus, induced frataxin expression, reduced oxidative stress and improved mitochondrial function in sensory neurons from patients with Friedreich ataxia[146]. In a 5-week pilot trial, exenatide modestly increased frataxin expression in platelets[146].

Levels of frataxin protein can also be increased via more direct approaches. The most direct is protein replacement therapy, which involves the administration of frataxin fused to the HIV protein transactivator of transcription (TAT), which enables penetration of biological membranes and entrance to the mitochondria. This approach is now in the early clinical phases following proof-of-principle studies in an animal model[147]. Alternatively, *FXN* mRNA can be delivered in lipid-encapsulated nanoparticles to enable the production of frataxin protein. In mouse models of Friedreich ataxia, this approach leads to the synthesis of mature frataxin[148]. Gene replacement therapy via an adeno-associated viral vector is also of considerable interest, particularly given that the efficacy of this approach has been demonstrated in cardiomyopathy[149] and in a mouse model of Friedreich ataxia[150]. However, this approach remains in preclinical development as a number of key issues are still unsolved, including capsid selection, construct design and the route of administration[151,152].

Reducing oxidative stress. Some promising therapies for Friedreich ataxia target oxidative stress. In a 48-week phase II study, omaveloxolone, which is an activator of the oxidative stress response mediated by Nrf2, led to a significant improvement in scores on the modified FARS[153]. This difference was more pronounced in post hoc analyses in which the unbalanced covariates of cardiomyopathy and GAA1 repeat length were controlled for. Adverse effects included transient elevation of aminotransferase levels, headache, nausea and fatigue. An open-label extension study is ongoing[154].

Idebenone, a synthetic analogue of coenzyme Q10, generated considerable interest after subgroup analysis of a randomized placebo-controlled trial in Friedreich ataxia suggested that the drug had efficacy in ambulatory patients who were treated with high doses[155]. However, subsequent trials of high-dose idebenone and a systematic review of long-term randomized controlled trials indicate that idebenone and coenzyme Q10 in combination with vitamin E have no significant effect on neurological or cardiac function[156,157].

In a 6-month randomized controlled trial of PTC-743 (previously known as EPI-743), which is an antioxidant and activates the respiratory chain, treatment had no effect on FARS scores but the 18-month open-label extension phase of the trial indicated a possible effect, which led to a phase III trial in children and young adults[158].

Resveratrol, a naturally occurring polyphenol, was tested in Friedreich ataxia in an open-label 12-week study. Treatment led to a dose-dependent improvement in FARS scores and a decrease in oxidative stress markers, suggesting an antioxidant effect[159]. A phase II study is currently ongoing[160].

RT001, a deuterated ethyl linoleate that inhibits lipid peroxidation, had a positive impact on cardiopulmonary function in patients with Friedreich ataxia in

a 28-day phase I/II study[161], and a phase II/III study is now nearing completion[162]. Other promising candidate therapies include leriglitazone, a pioglitazone metabolite that activates the peroxisome proliferator-activated receptor-γ (PPARγ) coactivator 1α (PGC1α), which is a transcriptional master regulator of mitochondrial function and antioxidant defence[163]. In a mouse model of Friedreich ataxia, leriglitazone increased frataxin protein levels and survival of dorsal root ganglion neurons and rescued the motor phenotype[164]. A proof-of-concept phase II study of leriglitazone has been conducted, and improvements in imaging biomarkers have been reported in a press release[165], but the publication of these results is awaited. Finally, elamipretide (SS-31) is also a mitochondrion-targeted antioxidant, and studies in cellular models have shown that it can reduce frataxin deficiency-induced oxidative stress and mitochondrial fragmentation in addition to translationally upregulating frataxin levels[105,166]. A phase I/II clinical trial to assess the effects of elamipretide on vision loss is planned[167].

In a 6-month randomized controlled trial of the Fe chelator deferiprone in Friedreich ataxia, treatment reduced cardiac hypertrophy but did not improve neurological functional status[168]. Low-dose deferiprone was associated with slower progression in patients with less severe disease but high-dose deferiprone seemed to worsen ataxia[168]. This effect could result from excessive Fe chelation that impairs Fe–S cluster biogenesis.

Riluzole. Finally, in a randomized controlled trial of patients with various genetic cerebellar ataxias, riluzole treatment significantly reduced SARA scores. The mechanism of action of riluzole is poorly understood — a pleiotropic effect is suspected. Indeed, riluzole acts as a small-conductance potassium channel opener, protects neurons against glutamatergic excitotoxicity, increases the activity of the TWIK-related potassium channel 1, and increases the expression of heat shock proteins, which are neuroprotective[169]. The clinical effects of riluzole need to be studied in a well-characterized cohort of patients with Friedreich ataxia to better determine its effects on this specific patient population.

Lessons from clinical trials

Experience from previous clinical trials has highlighted several difficulties and pitfalls in research into disease-modifying therapies for Friedreich ataxia. Many early-phase trials have produced promising results but subsequent phase III studies have failed. Though development of better potential treatments is necessary, trial design is also a key aspect. The main likely causes of failure are lack of a control group with a representative placebo effect, short trial durations and inadequate outcome measures.

In addition, given that Friedreich ataxia is a rare disease, clinical trials can involve only a limited number of patients, and therefore an efficient design is essential, particularly because of the number of treatments entering the clinical arena. Thus, it is essential to identify the patient population in which disease progression can best be detected and to select the most sensitive and robust outcome measures for this stage of the disease[170]. Two ongoing, large-scale, collaborative, prospective natural history studies have shown that clinical scales are the most sensitive measures of progression in ambulatory patients, and that the FARS and SARA scales are equally effective[14,26,28]. A smaller, single-site study confirmed that the SARA is a sensitive outcome measure in ambulatory patients with Friedreich ataxia, and showed that measurable worsening was fastest among individuals with onset before 8 years of age[18]. The FARS and SARA also have excellent test–retest reliability, although they are limited by floor and ceiling effects in specific subscales and by the potential for practice effects[170–172]. The Activities of Daily Living scale — a patient-reported measure of functional decline — is a sensitive alternative outcome in non-ambulatory patients with advanced disease[28].

None of the currently used clinical outcome scales adequately capture PNS involvement in Friedreich ataxia. The original FARS had a PNS subscale that was removed in the modified FARS to simplify the score and focus on functional, patient-relevant items[27]. The Inventory of Non-Ataxia Signs (INAS) incorporates signs and symptoms of neuropathy but is not a sensitive measure of change over time. In comparison, the SARA assesses only cerebellar tasks but does correlate well with the complete FARS neurological examination score[173]. None of the currently used outcome scales specifically assess the sensory component of the ataxia but their performance on cerebellar tasks integrates motor, sensory and cerebellar functions, which is likely to be sufficient to evaluate responses to treatment in clinical trials.

Loss of ambulation has been used as a clinical end point in trials but has important limitations because only a small proportion of unselected patients with Friedreich ataxia will lose ambulation over a 2-year follow-up period[174]. However, loss of ambulation does follow a predictable pattern of functional loss that is reflected in the upright stability subscale of the modified FARS. In one study, 44% of patients with early-onset Friedreich ataxia who lost the ability to stand with feet apart and eyes closed subsequently lost ambulation during the following 2 years[174]. Given that this measure identifies patients who are at high risk of losing ambulation, it could be used to select patients for clinical trials in which the loss of ambulation would be used as a primary outcome measure. Alternatively, the loss of other stance capacities could be used as a proxy for impending loss of ambulation in order to increase statistical power[174].

Power calculations for trials in Friedreich ataxia have typically been made on the basis of natural history data, but these data have limited value in the context of a clinical trial owing to the placebo effect and closer follow-up than in natural history studies. Nevertheless, these studies show that trials must have a duration of at least 1 year, as is also suggested by the fact that previous trials with durations of 6 months have failed to meet their primary end points but potential improvements were observed in open-label extension periods[142,158].

Other treatments

Multidisciplinary care and rehabilitation (including physical therapy, occupational therapy, speech therapy and nutritional therapy) are important parts of

the management of patients with degenerative ataxias and should be tailored to the symptoms of individual patients, taking into consideration the afferent and cerebellar contributions to the gait ataxia. However, how the afferent deficit affects the benefits of rehabilitation interventions is a question that warrants further study[175]. Consensus guidelines have been published on the multidisciplinary management of patients with degenerative ataxias, including the use of transcranial magnetic stimulation for cerebellar deficits[176–178]. More studies are under way to provide high-quality data on the efficacy of rehabilitation programmes for hereditary ataxias[179]. Specific recommendations exist for patients with Friedreich ataxia and ataxia–telangiectasia[130,180,181]. Symptomatic treatments should also be considered for positive sensory symptoms in conditions with involvement of small sensory fibres[181].

Conclusions and future research

The field of recessive cerebellar and afferent ataxias has expanded dramatically in the past few years with the identification of biallelic *RFC1* expansion in CANVAS, which has been shown to underlie a sizeable proportion of unexplained cases of ataxia and neuropathy. Clinicians should maintain a high index of suspicion for the combination of cerebellar and sensory deficits, which should prompt assessment for treatable causes, especially paraneoplastic, infectious and autoimmune aetiologies and ataxia with vitamin E deficiency. When a genetic aetiology is suspected, an adequate testing strategy is paramount because Friedreich ataxia and CANVAS are caused by intronic expansions, which are not adequately detected by short-read next-generation sequencing techniques (gene panels, whole-exome sequencing and whole-genome sequencing)[182]. Friedreich ataxia remains the most prevalent diagnosis in early-onset cases, whereas CANVAS is probably a leading cause in late-onset cases[4,49].

Sensory neurons and the cerebellum seem to be particularly vulnerable to disorders that affect mitochondrial function and DNA repair pathways, and therefore these mechanisms could be common to cerebellar ataxias with ganglionopathy or sensory polyneuropathy. An understanding of the pathophysiological mechanisms through which the *RFC1* expansion leads to cellular death will be key to developing effective disease-modifying therapies in CANVAS. In Friedreich ataxia, frataxin deficiency leads to multiple downstream alterations in cellular pathways, which are now being targeted with experimental therapies. Future clinical trials should be randomized, of sufficient duration and designed to include adequate clinical outcomes in order to draw definitive conclusions regarding efficacy and safety. Recently discovered small molecules and the advent of genetic therapy hold the promise of changing the prospects of patients with these debilitating diseases.

Published online: 24 March 2022

1. Amato, A. A. & Ropper, A. H. Sensory ganglionopathy. *N. Engl. J. Med.* **383**, 1657–1662 (2020).
A state-of-the-art review of acquired causes of sensory ganglionopathy.
2. Rossi, M. et al. The genetic nomenclature of recessive cerebellar ataxias. *Mov. Disord.* **33**, 1056–1076 (2018).
This article presents the revised nomenclature of recessive cerebellar ataxias, in which an ATX prefix is followed by the gene name.
3. Beaudin, M. et al. The classification of autosomal recessive cerebellar ataxias: a consensus statement from the society for research on the cerebellum and ataxias task force. *Cerebellum* **18**, 1098–1125 (2019).
A scoping systematic review of the literature on recessive cerebellar ataxias with a clinical classification and diagnostic approach.
4. Ruano, L., Melo, C., Silva, M. C. & Coutinho, P. The global epidemiology of hereditary ataxia and spastic paraplegia: a systematic review of prevalence studies. *Neuroepidemiology* **42**, 174–183 (2014).
5. Cossee, M. et al. Evolution of the Friedreich's ataxia trinucleotide repeat expansion: founder effect and premutations. *Proc. Natl Acad. Sci. USA* **94**, 7452–7457 (1997).
6. Campuzano, V. et al. Friedreich's ataxia: autosomal recessive disease caused by an intronic GAA triplet repeat expansion. *Science* **271**, 1423–1427 (1996).
7. Sharma, R. et al. Friedreich ataxia in carriers of unstable borderline GAA triplet-repeat alleles. *Ann. Neurol.* **56**, 898–901 (2004).
8. Montermini, L. et al. The Friedreich ataxia GAA triplet repeat: premutation and normal alleles. *Hum. Mol. Genet.* **6**, 1261–1266 (1997).
9. Gerhardt, J. et al. Stalled DNA replication forks at the endogenous GAA repeats drive repeat expansion in Friedreich's ataxia cells. *Cell Rep.* **16**, 1218–1227 (2016).
10. De Biase, I. et al. Progressive GAA expansions in dorsal root ganglia of Friedreich's ataxia patients. *Ann. Neurol.* **61**, 55–60 (2007).
11. Plasterer, H. L. et al. Development of frataxin gene expression measures for the evaluation of experimental treatments in Friedreich's ataxia. *PLoS ONE* **8**, e63958 (2013).
12. Delatycki, M. B. & Bidichandani, S. I. Friedreich ataxia — pathogenesis and implications for therapies. *Neurobiol. Dis.* **132**, 104606 (2019).
13. Rodden, L. N. et al. Methylated and unmethylated epialleles support variegated epigenetic silencing in Friedreich ataxia. *Hum. Mol. Genet.* **29**, 3818–3829 (2021).
14. Reetz, K. et al. Progression characteristics of the European Friedreich's Ataxia Consortium for Translational Studies (EFACTS): a 2 year cohort study. *Lancet Neurol.* **15**, 1346–1354 (2016).
15. Lecocq, C. et al. Delayed-onset Friedreich's ataxia revisited. *Mov. Disord.* **31**, 62–69 (2016).
16. Reetz, K. et al. Biological and clinical characteristics of the European Friedreich's Ataxia Consortium for Translational Studies (EFACTS) cohort: a cross-sectional analysis of baseline data. *Lancet Neurol.* **14**, 174–182 (2015).
17. Koeppen, A. H., Becker, A. B., Qian, J., Gelman, B. B. & Mazurkiewicz, J. E. Friedreich ataxia: developmental failure of the dorsal root entry zone. *J. Neuropathol. Exp. Neurol.* **76**, 969–977 (2017).
18. Pandolfo, M. Neurologic outcomes in Friedreich ataxia: study of a single-site cohort. *Neurol. Genet.* **6**, e415 (2020).
19. Indelicato, E. et al. Onset features and time to diagnosis in Friedreich's ataxia. *Orphanet J. Rare Dis.* **15**, 198 (2020).
20. Pousset, F. et al. A 22-year follow-up study of long-term cardiac outcome and predictors of survival in Friedreich ataxia. *JAMA Neurol.* **72**, 1334–1341 (2015).
This study demonstrates the evolution of long-term cardiac complications and predictors of survival in patients with Friedreich ataxia.
21. Takazaki, K. A. G. et al. Pre-clinical left ventricular myocardial remodeling in patients with Friedreich's ataxia: a cardiac MRI study. *PLoS ONE* **16**, e0246633 (2021).
22. Hanson, E., Sheldon, M., Pacheco, B., Alkubeysi, M. & Raizada, V. Heart disease in Friedreich's ataxia. *World J. Cardiol.* **11**, 1–12 (2019).
23. Koeppen, A. H. et al. The pathogenesis of cardiomyopathy in Friedreich ataxia. *PLoS ONE* **10**, e0116396 (2015).
24. Hamedani, A. G. et al. Longitudinal analysis of contrast acuity in Friedreich ataxia. *Neurol. Genet.* **4**, e250 (2018).
25. Pandolfo, M. & Manto, M. Cerebellar and afferent ataxias. *Continuum* **19**, 1312–1343 (2013).
26. Patel, M. et al. Progression of Friedreich ataxia: quantitative characterization over 5 years. *Ann. Clin. Transl. Neurol.* **3**, 684–694 (2016).
This article presents the 5-year longitudinal data in the FA-COMS study, a large international collaborative study on the natural history of Friedreich ataxia.
27. Rummey, C. et al. Psychometric properties of the Friedreich ataxia rating scale. *Neurol. Genet.* **5**, 371 (2019).
28. Reetz, K. et al. Progression characteristics of the European Friedreich's Ataxia Consortium for Translational Studies (EFACTS): a 4-year cohort study. *Lancet Neurol.* **20**, 362–372 (2021).
This article presents the 4-year follow-up data in the EFACTS study, a large European study of patients with Friedreich ataxia, including assessment of the sensitivity to change of different outcome scales.
29. Naeije, G. et al. Cerebellar cognitive disorder parallels cerebellar motor symptoms in Friedreich ataxia. *Ann. Clin. Transl. Neurol.* **7**, 1050–1054 (2020).
30. Argyropoulos, G. P. D. et al. The cerebellar cognitive affective/Schmahmann syndrome: a task force paper. *Cerebellum* **19**, 102–125 (2020).
31. Pagovich, O. E. et al. Corneal confocal microscopy: neurologic disease biomarker in Friedreich ataxia. *Ann. Neurol.* **84**, 893–904 (2018).
32. Koeppen, A. H. & Mazurkiewicz, J. E. Friedreich ataxia: neuropathology revised. *J. Neuropathol. Exp. Neurol.* **72**, 78–90 (2013).
33. Morral, J. A., Davis, A. N., Qian, J., Gelman, B. B. & Koeppen, A. H. Pathology and pathogenesis of sensory neuropathy in Friedreich's ataxia. *Acta Neuropathol.* **120**, 97–108 (2010).
34. Koeppen, A. H., Becker, A. B., Qian, J. & Feustel, P. J. Friedreich ataxia: hypoplasia of spinal cord and dorsal root ganglia. *J. Neuropathol. Exp. Neurol.* **76**, 101–108 (2017).
35. Kemp, K. C. et al. Purkinje cell injury, structural plasticity and fusion in patients with Friedreich's ataxia. *Acta Neuropathol. Commun.* **4**, 53 (2016).
36. Tsou, A. Y. et al. Mortality in Friedreich ataxia. *J. Neurol. Sci.* **307**, 46–49 (2011).
37. Bhidayasiri, R., Perlman, S. L., Pulst, S. M. & Geschwind, D. H. Late-onset Friedreich ataxia:

phenotypic analysis, magnetic resonance imaging findings, and review of the literature. *Arch. Neurol.* **62**, 1865–1869 (2005).
38. Coppola, G. et al. Why do some Friedreich's ataxia patients retain tendon reflexes? A clinical, neurophysiological and molecular study. *J. Neurol.* **246**, 353–357 (1999).
39. Galea, C. A. et al. Compound heterozygous FXN mutations and clinical outcome in Friedreich ataxia. *Ann. Neurol.* **79**, 485–495 (2016).
40. Delatycki, M. B. et al. G130V, a common FRDA point mutation, appears to have arisen from a common founder. *Hum. Genet.* **105**, 343–346 (1999).
41. Cossee, M. et al. Friedreich's ataxia: point mutations and clinical presentation of compound heterozygotes. *Ann. Neurol.* **45**, 200–206 (1999).
42. Rezende, T. J. R. et al. Developmental and neurodegenerative damage in Friedreich's ataxia. *Eur. J. Neurol.* **26**, 483–489 (2019).
43. Selvadurai, L. P., Harding, I. H., Corben, L. A. & Georgiou-Karistianis, N. Cerebral abnormalities in Friedreich ataxia: a review. *Neurosci. Biobehav. Rev.* **84**, 394–406 (2018).
44. Harding, I. H. et al. Brain structure and degeneration staging in Friedreich ataxia: magnetic resonance imaging volumetrics from the ENIGMA-ataxia working group. *Ann. Neurol.* **90**, 570–583 (2021).
Results of a large-scale international collaboration on imaging findings in Friedreich ataxia, covering the whole spectrum of findings according to age at onset and disease duration.
45. Selvadurai, L. P. et al. Multiple mechanisms underpin cerebral and cerebellar white matter deficits in Friedreich ataxia: the IMAGE-FRDA study. *Hum. Brain Mapp.* **41**, 1920–1933 (2020).
46. Rezende, T. J. et al. Longitudinal magnetic resonance imaging study shows progressive pyramidal and callosal damage in Friedreich's ataxia. *Mov. Disord.* **31**, 70–78 (2016).
47. Vavla, M. et al. Functional and structural brain damage in Friedreich's ataxia. *Front. Neurol.* **9**, 747 (2018).
48. Selvadurai, L. P. et al. Longitudinal structural brain changes in Friedreich ataxia depend on disease severity: the IMAGE-FRDA study. *J. Neurol.* **268**, 4178–4189 (2021).
49. Cortese, A. et al. Biallelic expansion of an intronic repeat in RFC1 is a common cause of late-onset ataxia. *Nat. Genet.* **51**, 649–658 (2019).
In this study, *RFC1* intronic expansions were identified as the underlying genetic defect in CANVAS and the clinical spectrum.
50. Rafehi, H. et al. Bioinformatics-based identification of expanded repeats: a non-reference intronic pentamer expansion in RFC1 Causes CANVAS. *Am. J. Hum. Genet.* **105**, 151–165 (2019).
51. Beecroft, S. J. et al. A Maori specific RFC1 pathogenic repeat configuration in CANVAS, likely due to a founder allele. *Brain* **143**, 2673–2680 (2020).
52. Scriba, C. K. et al. A novel RFC1 repeat motif (ACAGG) in two Asia-Pacific CANVAS families. *Brain* **143**, 2904–2910 (2020).
53. Tsuchiya, M. et al. RFC1 repeat expansion in Japanese patients with late-onset cerebellar ataxia. *J. Hum. Genet.* **65**, 1143–1147 (2020).
54. Sullivan, R. et al. RFC1 intronic repeat expansions absent in pathologically confirmed multiple systems atrophy. *Mov. Disord.* **35**, 1277–1279 (2020).
55. Wan, L. et al. Biallelic intronic AAGGG expansion of RFC1 is related to multiple system atrophy. *Ann. Neurol.* **88**, 1132–1143 (2020).
56. Akcimen, F. et al. Investigation of the RFC1 repeat expansion in a Canadian and a Brazilian ataxia cohort: identification of novel conformations. *Front. Genet.* **10**, 1219 (2019).
57. Fan, Y. et al. No biallelic intronic AAGGG repeat expansion in RFC1 was found in patients with late-onset ataxia and MSA. *Parkinsonism Relat. Disord.* **73**, 1–2 (2020).
58. Van Daele, S. H. et al. Diagnostic yield of testing for RFC1 repeat expansions in patients with unexplained adult-onset cerebellar ataxia. *J. Neurol. Neurosurg. Psychiatry* **91**, 1233–1234 (2020).
59. Aboud Syriani, D. et al. Prevalence of RFC1-mediated spinocerebellar ataxia in a North American ataxia cohort. *Neurol. Genet.* **6**, e440 (2020).
60. Kiktev, D. A., Sheng, Z., Lobachev, K. S. & Petes, T. D. GC content elevates mutation and recombination rates in the yeast Saccharomyces cerevisiae. *Proc. Natl Acad. Sci. USA* **115**, E7109–E7118 (2018).
61. Mousavi, N., Shleizer-Burko, S., Yanicky, R. & Gymrek, M. Profiling the genome-wide landscape of tandem repeat expansions. *Nucleic Acids Res.* **47**, e90 (2019).
62. Abu Diab, M. et al. The G-rich repeats in FMR1 and C9orf72 loci are hotspots for local unpairing of DNA. *Genetics* **210**, 1239–1252 (2018).
63. Cortese, A. et al. Cerebellar ataxia, neuropathy, vestibular areflexia syndrome due to RFC1 repeat expansion. *Brain* **143**, 480–490 (2020).
This article presents the largest series of patients with biallelic *RFC1* mutations published so far, with detailed clinical phenotyping.
64. Traschutz, A. et al. Natural history, phenotypic spectrum, and discriminative features of multisystemic RFC1 disease. *Neurology* **96**, e1369–e1382 (2021).
65. Curro, R. et al. RFC1 expansions are a common cause of idiopathic sensory neuropathy. *Brain* **144**, 1542–1550 (2021).
This article shows the phenotypic variability of biallelic *RFC1* mutations and details the sensory involvement.
66. Szmulewicz, D. J. et al. Sensory neuropathy as part of the cerebellar ataxia neuropathy vestibular areflexia syndrome. *Neurology* **76**, 1903–1910 (2011).
67. Montaut, S. et al. Biallelic RFC1-expansion in a French multicentric sporadic ataxia cohort. *J. Neurol.* **268**, 3337–3343 (2021).
68. Szmulewicz, D. J. et al. Dorsal root ganglionopathy is responsible for the sensory impairment in CANVAS. *Neurology* **82**, 1410–1415 (2014).
This article details the neuropathological findings of CANVAS and identifies the ganglionopathy as responsible for sensory involvement.
69. Burke, D. & Halmagyi, G. M. Normal tendon reflexes despite absent sensory nerve action potentials in CANVAS: a neurophysiological study. *J. Neurol. Sci.* **387**, 75–79 (2018).
70. Baloh, R. H., Jen, J. C., Kim, G. & Baloh, R. W. Chronic cough due to Thr124Met mutation in the peripheral myelin protein zero (MPZ gene). *Neurology* **62**, 1905–1906 (2004).
71. Pelosi, L. et al. Peripheral nerves are pathologically small in cerebellar ataxia neuropathy vestibular areflexia syndrome: a controlled ultrasound study. *Eur. J. Neurol.* **25**, 659–665 (2018).
72. Kumar, K. R. et al. RFC1 expansions can mimic hereditary sensory neuropathy with cough and Sjogren syndrome. *Brain* **143**, e82 (2020).
73. Huin, V. et al. Motor neuron pathology in CANVAS due to RFC1 expansions. *Brain* https://doi.org/10.1093/brain/awab449 (2021).
74. El Euch-Fayache, G., Bouhlal, Y., Amouri, R., Feki, M. & Hentati, F. Molecular, clinical and peripheral neuropathy study of Tunisian patients with ataxia with vitamin E deficiency. *Brain* **137**, 402–410 (2014).
75. Becker, A. E., Vargas, W. & Pearson, T. S. Ataxia with vitamin E deficiency may present with cervical dystonia. *Tremor Other Hyperkinet. Mov.* **6**, 374 (2016).
76. Yokota, T. et al. Friedreich-like ataxia with retinitis pigmentosa caused by the His101Gln mutation of the alpha-tocopherol transfer protein gene. *Ann. Neurol.* **41**, 826–832 (1997).
77. Larnaout, A. et al. Friedreich's ataxia with isolated vitamin E deficiency: a neuropathological study of a Tunisian patient. *Acta Neuropathol.* **93**, 633–637 (1997).
78. Gabsi, S. et al. Effect of vitamin E supplementation in patients with ataxia with vitamin E deficiency. *Eur. J. Neurol.* **8**, 477–481 (2001).
79. Rahman, S. & Copeland, W. C. POLG-related disorders and their neurological manifestations. *Nat. Rev. Neurol.* **15**, 40–52 (2019).
This article presents the wide spectrum of neurological manifestations associated with *POLG* mutations.
80. Lax, N. Z. et al. Sensory neuronopathy in patients harbouring recessive polymerase gamma mutations. *Brain* **135**, 62–71 (2012).
81. Mancuso, M. et al. "Mitochondrial neuropathies": a survey from the large cohort of the Italian Network. *Neuromuscul. Disord.* **26**, 272–276 (2016).
82. Synofzik, M., Srulijes, K., Godau, J., Berg, D. & Schols, L. Characterizing POLG ataxia: clinics, electrophysiology and imaging. *Cerebellum* **11**, 1002–1011 (2012).
83. Lonnqvist, T., Paetau, A., Nikali, K., von Boguslawski, K. & Pihko, H. Infantile onset spinocerebellar ataxia with sensory neuropathy (IOSCA): neuropathological features. *J. Neurol. Sci.* **161**, 57–65 (1998).
84. Otero, M. G. et al. Novel pathogenic COX20 variants causing dysarthria, ataxia, and sensory neuropathy. *Ann. Clin. Transl. Neurol.* **6**, 154–160 (2019).
85. Dong, H. L. et al. Bi-allelic loss of function variants in COX20 gene cause autosomal recessive sensory neuronopathy. *Brain* **144**, 2457–2470 (2021).
86. Synofzik, M. et al. Autosomal recessive spastic ataxia of Charlevoix Saguenay (ARSACS): expanding the genetic, clinical and imaging spectrum. *Orphanet J. Rare Dis.* **8**, 41 (2013).
87. Duquette, A., Brais, B., Bouchard, J. P. & Mathieu, J. Clinical presentation and early evolution of spastic ataxia of Charlevoix-Saguenay. *Mov. Disord.* **28**, 2011–2014 (2013).
88. Levy, A. & Lang, A. E. Ataxia-telangiectasia: a review of movement disorders, clinical features, and genotype correlations. *Mov. Disord.* **33**, 1238–1247 (2018).
89. Suarez, F. et al. Incidence, presentation, and prognosis of malignancies in ataxia-telangiectasia: a report from the French national registry of primary immune deficiencies. *J. Clin. Oncol.* **33**, 202–208 (2015).
90. Anheim, M. et al. Ataxia with oculomotor apraxia type 2: clinical, biological and genotype/phenotype correlation study of a cohort of 90 patients. *Brain* **132**, 2688–2698 (2009).
91. Ronsin, S. et al. A new MRI marker of ataxia with oculomotor apraxia. *Eur. J. Radiol.* **110**, 187–192 (2019).
92. van de Warrenburg, B. P. et al. Peripheral nerve involvement in spinocerebellar ataxias. *Arch. Neurol.* **61**, 257–261 (2004).
This study details peripheral nerve involvement in dominant spinocerebellar ataxias.
93. Pelosi, L. et al. Spinocerebellar ataxia type 2-neuronopathy or neuropathy? *Muscle Nerve* **60**, 271–278 (2019).
94. Pelosi, L., Mulroy, E., Rodrigues, M. J. & Roxburgh, R. H. Neuronopathy and neuropathy in autosomal dominant spino-cerebellar ataxia (SCA): a preliminary peripheral nerve ultrasound study. *Clin. Neurophysiol.* **128**, 2436–2437 (2017).
95. Estrada, R., Galarraga, J., Orozco, G., Nodarse, A. & Auburger, G. Spinocerebellar ataxia 2 (SCA2): morphometric analyses in 11 autopsies. *Acta Neuropathol.* **97**, 306–310 (1999).
96. Synofzik, M., Puccio, H., Mochel, F. & Schöls, L. Autosomal recessive cerebellar ataxias: paving the way toward targeted molecular therapies. *Neuron* **101**, 560–583 (2019).
An in-depth review of the pathophysiological mechanisms involved in recessive cerebellar ataxias.
97. Doni, D. et al. The displacement of frataxin from the mitochondrial cristae correlates with abnormal respiratory supercomplexes formation and bioenergetic defects in cells of Friedreich ataxia patients. *FASEB J.* **35**, e21362 (2021).
98. Lynch, D. R. & Farmer, G. Mitochondrial and metabolic dysfunction in Friedreich ataxia: update on pathophysiological relevance and clinical interventions. *Neuronal Signal.* **5**, NS20200093 (2021).
99. Shan, Y. et al. Frataxin deficiency leads to defects in expression of antioxidants and Nrf2 expression in dorsal root ganglia of the Friedreich's ataxia YG8R mouse model. *Antioxid. Redox Signal.* **19**, 1481–1493 (2013).
100. D'Oria, V. et al. Frataxin deficiency leads to reduced expression and impaired translocation of NF-E2-related factor (Nrf2) in cultured motor neurons. *Int. J. Mol. Sci.* **14**, 7853–7865 (2013).
101. Koeppen, A. H. Friedreich's ataxia: pathology, pathogenesis, and molecular genetics. *J. Neurol. Sci.* **303**, 1–12 (2011).
102. Martelli, A. et al. Iron regulatory protein 1 sustains mitochondrial iron loading and function in frataxin deficiency. *Cell Metab.* **21**, 311–323 (2015).
103. Du, J. et al. Identification of Frataxin as a regulator of ferroptosis. *Redox Biol.* **32**, 101483 (2020).
104. Hakonen, A. H. et al. Infantile-onset spinocerebellar ataxia and mitochondrial recessive ataxia syndrome are associated with neuronal complex I defect and mtDNA depletion. *Hum. Mol. Genet.* **17**, 3822–3835 (2008).
105. Johnson, J., Mercado-Ayon, E., Clark, E., Lynch, D. & Lin, H. Drp1-dependent peptide reverse mitochondrial fragmentation, a homeostatic response in Friedreich ataxia. *Pharmacol. Res. Perspect.* **9**, e00755 (2021).
106. Bradshaw, T. Y. et al. A reduction in Drp1-mediated fission compromises mitochondrial health in autosomal recessive spastic ataxia of Charlevoix Saguenay. *Hum. Mol. Genet.* **25**, 3232–3244 (2016).
107. Girard, M. et al. Mitochondrial dysfunction and Purkinje cell loss in autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS). *Proc. Natl Acad. Sci. USA* **109**, 1661–1666 (2012).

108. Shiomi, Y. & Nishitani, H. Control of genome integrity by RFC complexes; conductors of PCNA loading onto and unloading from chromatin during DNA replication. *Genes* **8**, 52 (2017).
109. Zhang, W., Feng, J. & Li, Q. The replisome guides nucleosome assembly during DNA replication. *Cell Biosci.* **10**, 37 (2020).
110. Overmeer, R. M. et al. Replication factor C recruits DNA polymerase delta to sites of nucleotide excision repair but is not required for PCNA recruitment. *Mol. Cell Biol.* **30**, 4828–4839 (2010).
111. Shivji, M. K., Podust, V. N., Hubscher, U. & Wood, R. D. Nucleotide excision repair DNA synthesis by DNA polymerase epsilon in the presence of PCNA, RFC, and RPA. *Biochemistry* **34**, 5011–5017 (1995).
112. Juhasz, S., Elbakry, A., Mathes, A. & Lobrich, M. ATRX Promotes DNA repair synthesis and sister chromatid exchange during homologous recombination. *Mol. Cell* **71**, 11–24.e7 (2018).
113. Gisatulin, M. et al. Clinical spectrum of the pentanucleotide repeat expansion in the RFC1 gene in ataxia syndromes. *Neurology* **95**, e2912–e2923 (2020).
114. Pizzamiglio, L., Focchi, E. & Antonucci, F. ATM protein kinase: old and new implications in neuronal pathways and brain circuitry. *Cells* **9**, 1969 (2020).
115. Caldecott, K. W. Single-strand break repair and genetic disease. *Nat. Rev. Genet.* **9**, 619–631 (2008).
116. Guo, Z., Kozlov, S., Lavin, M. F., Person, M. D. & Paull, T. T. ATM activation by oxidative stress. *Science* **330**, 517–521 (2010).
A landmark paper on the role of ATM in regulating oxidative stress.
117. Ghosh, A. et al. SCAN1-TDP1 trapping on mitochondrial DNA promotes mitochondrial dysfunction and mitophagy. *Sci. Adv.* **5**, eaax9778 (2019).
118. Sykora, P., Croteau, D. L., Bohr, V. A. & Wilson, D. M. 3rd Aprataxin localizes to mitochondria and preserves mitochondrial function. *Proc. Natl Acad. Sci. USA* **108**, 7437–7442 (2011).
119. Tahbaz, N., Subedi, S. & Weinfeld, M. Role of polynucleotide kinase/phosphatase in mitochondrial DNA repair. *Nucleic Acids Res.* **40**, 3484–3495 (2012).
120. Fuss, J. O., Tsai, C. L., Ishida, J. P. & Tainer, J. A. Emerging critical roles of Fe-S clusters in DNA replication and repair. *Biochim. Biophys. Acta* **1853**, 1253–1271 (2015).
121. Bhalla, A. D., Khodadadi-Jamayran, A., Li, Y., Lynch, D. R. & Napierala, M. Deep sequencing of mitochondrial genomes reveals increased mutation load in Friedreich's ataxia. *Ann. Clin. Transl. Neurol.* **3**, 523–536 (2016).
122. Moreno-Lorite, J., Perez-Luz, S., Katsu-Jimenez, Y., Oberdoerfer, D. & Diaz-Nido, J. DNA repair pathways are altered in neural cell models of frataxin deficiency. *Mol. Cell Neurosci.* **111**, 103587 (2021).
123. Rojas, P. et al. Neuro-ophthalmological findings in Friedreich's ataxia. *J. Pers. Med.* **11**, 708 (2021).
124. Castelli, L. M., Huang, W. P., Lin, Y. H., Chang, K. Y. & Hautbergue, G. M. Mechanisms of repeat-associated non-AUG translation in neurological microsatellite expansion disorders. *Biochem. Soc. Trans.* **49**, 775–792 (2021).
125. Koeppen, A. H., Ramirez, R. L., Becker, A. B. & Mazurkiewicz, J. E. Dorsal root ganglia in Friedreich ataxia: satellite cell proliferation and inflammation. *Acta Neuropathol. Commun.* **4**, 46 (2016).
126. Nachun, D. et al. Peripheral blood gene expression reveals an inflammatory transcriptomic signature in Friedreich's ataxia patients. *Hum. Mol. Genet.* **27**, 2965–2977 (2018).
127. McGrath-Morrow, S. A. et al. Inflammation and transcriptional responses of peripheral blood mononuclear cells in classic ataxia telangiectasia. *PLoS ONE* **13**, e0209496 (2018).
128. Libri, V. et al. Epigenetic and neurological effects and safety of high-dose nicotinamide in patients with Friedreich's ataxia: an exploratory, open-label, dose-escalation study. *Lancet* **384**, 504–513 (2014).
129. Reetz, K. et al. Protocol of a randomized, double-blind, placebo-controlled, parallel-group, multicentre study of the efficacy and safety of nicotinamide in patients with Friedreich ataxia (NICOFA). *Neurol. Res. Pract.* **1**, 33 (2019).
130. Lynch, D. R., Schadt, K., Kichula, E., McCormack, S. & Lin, K. Y. Friedreich ataxia: multidisciplinary clinical care. *J. Multidiscip. Healthc.* **14**, 1645–1658 (2021).
131. Rai, M. et al. HDAC inhibitors correct frataxin deficiency in a Friedreich ataxia mouse model. *PLoS ONE* **3**, e1958 (2008).
132. Soragni, E. et al. Epigenetic therapy for Friedreich ataxia. *Ann. Neurol.* **76**, 489–508 (2014).
133. Vilema-Enriquez, G. et al. Inhibition of the SUV4-20 H1 histone methyltransferase increases frataxin expression in Friedreich's ataxia patient cells. *J. Biol. Chem.* **295**, 17973–17985 (2020).
134. Li, L., Matsui, M. & Corey, D. R. Activating frataxin expression by repeat-targeted nucleic acids. *Nat. Commun.* **7**, 10606 (2016).
135. Li, L. et al. Activation of frataxin protein expression by antisense oligonucleotides targeting the mutant expanded repeat. *Nucleic Acid. Ther.* **28**, 23–33 (2018).
136. Erwin, G. S. et al. Synthetic transcription elongation factors license transcription across repressive chromatin. *Science* **358**, 1617–1622 (2017).
137. Hui, C. K., Dedkova, E. N., Montgomery, C. & Cortopassi, G. Dimethyl fumarate dose-dependently increases mitochondrial gene expression and function in muscle and brain of Friedreich's ataxia model mice. *Hum. Mol. Genet.* **29**, 3954–3965 (2021).
138. Jasoliya, M. et al. Dimethyl fumarate dosing in humans increases frataxin expression: a potential therapy for Friedreich's ataxia. *PLoS ONE* **14**, e0217776 (2019).
139. Linker, R. A. et al. Fumaric acid esters exert neuroprotective effects in neuroinflammation via activation of the Nrf2 antioxidant pathway. *Brain* **134**, 678–692 (2011).
140. Hayashi, G. et al. Dimethyl fumarate mediates Nrf2-dependent mitochondrial biogenesis in mice and humans. *Hum. Mol. Genet.* **26**, 2864–2873 (2017).
141. Alfedi, G. et al. Drug repositioning screening identifies etravirine as a potential therapeutic for Friedreich's ataxia. *Mov. Disord.* **34**, 323–334 (2019).
142. Lynch, D. R. et al. Randomized, double-blind, placebo-controlled study of interferon- γ 1b in Friedreich ataxia. *Ann. Clin. Transl. Neurol.* **6**, 546–553 (2019).
143. Acquaviva, F. et al. Recombinant human erythropoietin increases frataxin protein expression without increasing mRNA expression. *Cerebellum* **7**, 360–365 (2008).
144. Sacca, F. et al. Long-term effect of epoetin alfa on clinical and biochemical markers in friedreich ataxia. *Mov. Disord.* **31**, 734–741 (2016).
145. Miller, J. L. et al. Erythropoietin and small molecule agonists of the tissue-protective erythropoietin receptor increase FXN expression in neuronal cells in vitro and in Fxn-deficient KIKO mice in vivo. *Neuropharmacology* **123**, 34–45 (2017).
146. Igoillo-Esteve, M. et al. Exenatide induces frataxin expression and improves mitochondrial function in Friedreich ataxia. *JCI Insight* **5**, e134221 (2020).
147. Vyas, P. M. et al. A TAT-frataxin fusion protein increases lifespan and cardiac function in a conditional Friedreich's ataxia mouse model. *Hum. Mol. Genet.* **21**, 1230–1247 (2012).
148. Nabhan, J. F. et al. Intrathecal delivery of frataxin mRNA encapsulated in lipid nanoparticles to dorsal root ganglia as a potential therapeutic for Friedreich's ataxia. *Sci. Rep.* **6**, 20019 (2016).
149. Perdomini, M. et al. Prevention and reversal of severe mitochondrial cardiomyopathy by gene therapy in a mouse model of Friedreich's ataxia. *Nat. Med.* **20**, 542–547 (2014).
150. Piguet, F. et al. Rapid and complete reversal of sensory ataxia by gene therapy in a novel model of Friedreich ataxia. *Mol. Ther.* **26**, 1940–1952 (2018).
151. Gottesfeld, J. M. Molecular mechanisms and therapeutics for the GAA.TTC expansion disease Friedreich ataxia. *Neurotherapeutics* **16**, 1032–1049 (2019).
152. Ocana-Santero, G., Diaz-Nido, J. & Herranz-Martin, S. Future prospects of gene therapy for Friedreich's ataxia. *Int. J. Mol. Sci.* **22**, 1815 (2021).
153. Lynch, D. R. et al. Safety and efficacy of omaveloxolone in Friedreich ataxia (MOXIe study). *Ann. Neurol.* **89**, 212–225 (2021).
This phase II study produced promising results with respect to the efficacy of omaveloxolone, a molecule that targets oxidative stress, in patients with Friedreich ataxia.
154. US National Library of Medicine. *ClinicalTrials.gov* https://clinicaltrials.gov/ct2/show/NCT02255435 (2021).
155. Di Prospero, N. A., Baker, A., Jeffries, N. & Fischbeck, K. H. Neurological effects of high-dose idebenone in patients with Friedreich's ataxia: a randomised, placebo-controlled trial. *Lancet Neurol.* **6**, 878–886 (2007).
156. Lynch, D. R., Perlman, S. L. & Meier, T. A phase 3, double-blind, placebo-controlled trial of idebenone in friedreich ataxia. *Arch. Neurol.* **67**, 941–947 (2010).
157. Kearney, M., Orrell, R. W., Fahey, M., Brassington, R. & Pandolfo, M. Pharmacological treatments for Friedreich ataxia. *Cochrane Database Syst. Rev.* **8**, CD007791 (2016).
158. Zesiewicz, T. et al. Double-blind, randomized and controlled trial of EPI-743 in Friedreich's ataxia. *Neurodegener. Dis. Manag.* **8**, 233–242 (2018).
159. Yiu, E. M. et al. An open-label trial in Friedreich ataxia suggests clinical benefit with high-dose resveratrol, without effect on frataxin levels. *J. Neurol.* **262**, 1344–1353 (2015).
160. US National Library of Medicine. *ClinicalTrials.gov* https://ClinicalTrials.gov/show/NCT03933163 (2021).
161. Zesiewicz, T. et al. Randomized, clinical trial of RT001: early signals of efficacy in Friedreich's ataxia. *Mov. Disord.* **33**, 1000–1005 (2018).
162. US National Library of Medicine. *ClinicalTrials.gov* https://ClinicalTrials.gov/show/NCT04102501 (2021).
163. Marmolino, D. et al. PGC-1alpha down-regulation affects the antioxidant response in Friedreich's ataxia. *PLoS ONE* **5**, e10025 (2010).
164. Rodriguez-Pascau, L. et al. PPAR gamma agonist leriglitazone improves frataxin-loss impairments in cellular and animal models of Friedreich Ataxia. *Neurobiol. Dis.* **148**, 105162 (2021).
165. Minoryx Therapeutics. Minoryx's clinical candidate leriglitazone shows clinical benefit in a proof of concept phase 2 study in Friedreich's ataxia. *Minoryx* https://www.minoryx.com/media/minoryx's_clinical_candidate_leriglitazone_shows_clinical_benefit_in_a_proof_of_concept_phase_2_study_in_friedreichs_ataxia/ (2020).
166. Zhao, H. et al. Peptide SS-31 upregulates frataxin expression and improves the quality of mitochondria: implications in the treatment of Friedreich ataxia. *Sci. Rep.* **7**, 9840 (2017).
167. US National Library of Medicine. *ClinicalTrials.gov* https://ClinicalTrials.gov/show/NCT05168774 (2021).
168. Pandolfo, M. et al. Deferiprone in Friedreich ataxia: a 6-month randomized controlled trial. *Ann. Neurol.* **76**, 509–521 (2014).
169. Romano, S. et al. Riluzole in patients with hereditary cerebellar ataxia: a randomised, double-blind, placebo-controlled trial. *Lancet Neurol.* **14**, 985–991 (2015).
This study shows a positive effect of riluzole on SARA score in patients with hereditary ataxia, including some with Friedreich ataxia.
170. Rummey, C., Kichula, E. & Lynch, D. R. Clinical trial design for Friedreich ataxia — where are we now and what do we need? *Expert Opin. Orphan Drugs* **6**, 219–230 (2018).
171. Rummey, C. et al. Test-retest reliability of the Friedreich's ataxia rating scale. *Ann. Clin. Transl. Neurol.* **7**, 1708–1712 (2020).
172. Schmitz-Hubsch, T. et al. Scale for the assessment and rating of ataxia: development of a new clinical scale. *Neurology* **66**, 1717–1720 (2006).
173. Burk, K. et al. Comparison of three clinical rating scales in Friedreich ataxia (FRDA). *Mov. Disord.* **24**, 1779–1784 (2009).
174. Rummey, C., Farmer, J. M. & Lynch, D. R. Predictors of loss of ambulation in Friedreich's ataxia. *EClinicalMedicine* **18**, 100213 (2020).
175. Milne, S. C., Corben, L. A., Georgiou-Karistianis, N., Delatycki, M. B. & Yiu, E. M. Rehabilitation for individuals with genetic degenerative ataxia: a systematic review. *Neurorehabil. Neural Repair* **31**, 609–622 (2017).
176. Zesiewicz, T. A. et al. 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* **90**, 464–471 (2018).
An evidence-based guideline on the management of cerebellar ataxia.
177. van de Warrenburg, B. P. et al. EFNS/ENS Consensus on the diagnosis and management of chronic ataxias in adulthood. *Eur. J. Neurol.* **21**, 552–562 (2014).
An evidence-based guideline on the diagnosis and management of chronic ataxias in adults.
178. Ilg, W. et al. Consensus paper: management of degenerative cerebellar disorders. *Cerebellum* **13**, 248–268 (2014).
179. Milne, S. C. et al. Rehabilitation for ataxia study: protocol for a randomised controlled trial of an

outpatient and supported home-based physiotherapy programme for people with hereditary cerebellar ataxia. *BMJ Open* **10**, e040230 (2020).
180. van Os, N. J. H. et al. Ataxia-telangiectasia: recommendations for multidisciplinary treatment. *Dev. Med. Child Neurol.* **59**, 680–689 (2017).
181. Corben, L. A. et al. Consensus clinical management guidelines for Friedreich ataxia. *Orphanet J. Rare Dis.* **9**, 184 (2014).
182. Chintalaphani, S. R., Pineda, S. S., Deveson, I. W. & Kumar, K. R. An update on the neurological short tandem repeat expansion disorders and the emergence of long-read sequencing diagnostics. *Acta Neuropathol. Commun.* **9**, 98 (2021).
183. Henao, A. I. et al. Characteristic brain MRI findings in ataxia-neuropathy spectrum related to POLG mutation. *Neuroradiol. J.* **29**, 46–48 (2016).
184. Lonnqvist, T., Paetau, A., Valanne, L. & Pihko, H. Recessive twinkle mutations cause severe epileptic encephalopathy. *Brain* **132**, 1553–1562 (2009).
185. Szklarczyk, R. et al. A mutation in the FAM36A gene, the human ortholog of COX20, impairs cytochrome c oxidase assembly and is associated with ataxia and muscle hypotonia. *Hum. Mol. Genet.* **22**, 656–667 (2013).

Author contributions
M.B. wrote the manuscript. All authors researched data for the article, made substantial contributions to discussion of the content, and reviewed and edited the manuscript before submission.

Competing interests
M.P. has received grants and personal fees from Biomarin, Minoryx and Voyager Therapeutics, and has received, grants from the European Commission — 7th Framework Programme, Fonds National de la Recherche Scientifique (Belgium) and the Friedreich's Ataxia Research Alliance, and personal fees from Apopharma, Exicure, Design Therapeutics, Aavanti Bio, and UCB. He has a patent for methods to diagnose Friedreich ataxia (WO1997032996A1), royalties for which have been paid by Athena Diagnostics. None of these disclosures represent a conflict of interest that may be perceived as biasing the content of this manuscript. All other authors declare no competing interests.

Peer review information
Nature Reviews Neurology thanks L. Corben, C. Tranchant and the other, anonymous, reviewer(s) for their contribution to the peer review of this work.

Supplementary information
The online version contains supplementary material available at https://doi.org/10.1038/s41582-022-00634-9.