Friedreich's ataxia—a rare multisystem disease

Kathrin Reetz, Stella A Lischewski, Imis Dogan, Claire Didszun, Miguel Pishnamaz, Kerstin Konrad, Katharina Marx-Schütt, Jennifer Farmer, David R Lynch, Louise A Corben, Massimo Pandolfo, Jörg B Schulz, on behalf of the FACROSS study group

Lancet Neurol 2025; 24: 614–24

Department of Neurology, RWTH Aachen University, Aachen, Germany (Prof K Reetz MD, S A Lischewski MD, I Dogan PhD, C Didszun PhD, Prof J B Schulz MD); **JARA-BRAIN Institute Molecular Neuroscience and Neuroimaging, Research Centre Juelich GmbH, Aachen, Germany** (Prof K Reetz, S A Lischewski, I Dogan, C Didszun, Prof J B Schulz); **Department for Orthopaedics, Trauma and Reconstructive Surgery, University Hospital, RWTH Aachen, Germany** (M Pishnamaz MD); **Section Child Neuropsychology, Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy, University Hospital, RWTH Aachen, Germany** (Prof K Konrad PhD); **Department of Internal Medicine I, Cardiology, RWTH Aachen University, Aachen, Germany** (K Marx-Schütt MD); **Friedreich's Ataxia Research Alliance, Downingtown, PA, USA** (J Farmer MS); **Departments of Neurology and Pediatrics, Children's Hospital of Philadelphia, University of Pennsylvania, Philadelphia, PA, USA** (Prof D R Lynch MD); **Bruce Lefroy Centre for Genetic Health Research, Murdoch Children's Research Institute, Parkville, VIC, Australia** (L A Corben PhD); **Department of Paediatrics, University of Melbourne, Melbourne, VIC, Australia** (L A Corben); **Turner Institute for Brain and Mental Health, Monash University, Clayton, VIC, Australia** (L A Corben); **McGill University, Montreal, QC, Canada** (Prof M Pandolfo MD)

Correspondence to: Prof Kathrin Reetz, Department of Neurology, RWTH Aachen University, Aachen 52074, Germany
kreetz@ukaachen.de

Friedreich's ataxia is a rare autosomal recessive neurodegenerative disease. Most patients have a homozygous GAA repeat expansion in the *FXN* gene, resulting in a deficiency of the mitochondrial protein frataxin. Disease onset occurs typically in adolescence but can vary widely, ranging from early childhood to late adulthood. Friedreich's ataxia is increasingly recognised as a multisystem disorder, affecting not only the nervous system, but also the heart and musculoskeletal system, and metabolism. Common extraneural manifestations include cardiomyopathy, which is the most common cause of mortality, and also scoliosis and diabetes. Despite research advances, the phenotypical heterogeneity of patients with Friedreich's ataxia remains inadequately explained by current knowledge of the underlying genetics. The approval of omaveloxolone by the US Food and Drug Administration and the European Medicines Agency has been a pharmacological milestone; however, further research addressing complex interorgan interactions is crucial for a better understanding of the multisystem nature of Friedreich's ataxia and the development of targeted treatment approaches.

Introduction

Friedreich's ataxia is a rare neurodegenerative disease, primarily caused by a homozygous GAA repeat expansion in the *FXN* gene, leading to a deficiency in the mitochondrial protein frataxin.[1] The clinical hallmark is ataxia, a progressive loss of balance and coordination, and natural history studies have described the heterogeneity of the progression of neurological symptoms;[2,3] however, patients can have non-neurological comorbidities, including cardiomyopathy, musculoskeletal deformities, and metabolic dysfunction. Increasing evidence indicates that Friedreich's ataxia is a complex disease with diverse symptoms that our current understanding of the underlying genetic mutation fails to fully explain. This need for better understanding and the absence of validated outcome measures for non-neurological features are major roadblocks towards therapeutic development. The approval of omaveloxolone for the treatment of patients with Friederich's ataxia represents a milestone[4–7] but an urgent need remains for further trials to develop disease-modifying therapies.

In this Review, we aim to integrate evidence on basic science and clinical research to provide an overview of the current understanding of the multisystem manifestations of Friederich's ataxia and their treatment. Based on the findings of natural history studies, we evaluate outcome measures and potential biomarkers. We also cover findings from clinical trials, including advances in mitochondrial and frataxin modulation, and novel perspectives on gene therapy and gene editing.

Genetics and epidemiology

Friedreich's ataxia is caused by pathogenic mutations in the *FXN* gene, located on chromosome 9, leading to a reduced amount of frataxin.[1] Approximately 96% of patients with Friedreich's ataxia are homozygous for a GAA repeat expansion in intron 1 of the *FXN* gene, whereas the remainder are compound heterozygous, with a GAA expansion in one allele and another inactivating mutation (eg, a missense or splice mutation) in the other allele.[8] Disease-causing repeats can range from 66 to 1700,[9] but mutations with fewer than 100 repeats rarely cause disease, particularly if interrupted by non-GAA sequences, which stabilise against expansion.[10] Conversely, uninterrupted repeats can expand to beyond 300 repeats in a generation, resulting in somatic instability. Post-mortem analyses reveal substantial variation in the length of the GAA repeat expansion among different tissues—notably, the cerebellum, brainstem, and spinal cord.[11] Whether the GAA expansions are stable over the lifespan of a mutation carrier remains unclear. Overall, the GAA repeat size on the shorter allele (GAA1) accounts for only 36–50% of the variability in age of onset;[12,13] the remaining variability might reflect other unknown genetic and epigenetic modifiers.

The *FXN* gene encodes frataxin,[14] a mitochondrial protein with an integral role in iron homoeostasis, iron–sulphur cluster biogenesis, cellular redox reaction, and haem synthesis.[15]Consequently, frataxin deficiency results in reduced mitochondrial ATP production, perturbed iron metabolism, and an impaired oxidative stress response (figure 1),[16]culminating in iron accumulation within the mitochondria, generation of free radicals, and, ultimately, cell death.[17] Tissues affected by frataxin deficiency tend to be dependent on mitochondrial oxidative phosphorylation and, in healthy individuals, display high amounts of frataxin expression.[16,18] Pathologically, the nervous system is predominantly affected in the dorsal columns and nuclei dorsalis, corticospinal tracts, spinocerebellar tracts, dentate nuclei of the cerebellum, dorsal root ganglia, and sensory peripheral nerves.[19,20] High amounts of wild type frataxin expression are also found in the heart, pancreatic β-cells, liver, skeletal muscle, thymus, skin, teeth, and brown fat.[14] Tissue vulnerability and pathological involvement probably commence during embryonic development[21] and continue throughout life, with a combination of developmental delays and atrophy.[18]

Friedreich's ataxia is the most prevalent inherited ataxia, with an average global prevalence of 0·5 cases per 100 000 people.[22] Prevalence varies considerably across

continents and countries (figure 2; Friedreich's ataxia is more common in populations with predominantly Caucasian or Indian ancestry, with a prevalence of approximately 1 case per 30 000 people in Australia, India, and several parts of Europe.[22,23] The prevalence seems somewhat lower in North America (1–3 cases per 100 000 people) and even lower in Mexico and central America and South America (<1 case per 100 000 people).[22,24,25] Conversely, Friedreich's ataxia appears to be extremely rare in sub-Saharan Africa, China, Japan, and southeast Asia.[23] In Europe, notable regional disparities in prevalence exist, with a prevalence gradient from 1 case per 20 000 people in the southwest to 1 case per 250 000 people in the north and east.[23]

Multisystem signs and symptoms

Friedreich's ataxia usually manifests before age 25 years, most often between the ages of 8 years and 15 years, although onset can range from early childhood to late adulthood, with higher GAA1 repeat expansions linked to earlier onset.[12,26] Diagnosis is based on clinical presentation and genetic testing. The most common first symptoms are gait instability (in about 77% of patients), scoliosis (23%), and falls (20%).[27] Friedreich's ataxia is a slowly progressive and usually life-limiting condition. Patients are frequently wheelchair-dependent by early adulthood[28]. Mean life expectancy is 35–40 years, although prognosis is highly variable, with some patients surviving into their seventh or eighth decade.[29] Early onset, large GAA repeat size, and the presence of diabetes and cardiomyopathy confer a prognostic disadvantage.[2,12,26,30–32] Mortality results primarily from heart disease (in about 62% of cases), particularly congestive heart failure and arrhythmias, with non-cardiac causes, such as dysphagia-related bronchopneumonia (28%), accounting for a smaller proportion of deaths.[30–32] The clinical hallmark is ataxia, leading to a progressive loss of balance and coordination (appendix p 3). Patients can have many other signs and symptoms, including dysphagia, neuropathy, spasticity, depression, sleep disturbances, restless leg syndrome, urinary disturbances, and pain, as well as comorbidities, such as cardiomyopathy, musculoskeletal deformities involving the spine (scoliosis) and feet, diabetes, and vision or hearing impairments.[27]

Late-onset ataxia, defined as symptom onset after age 25 years, and very-late-onset ataxia, defined as symptom onset after age 40 years, account for approximately 17% of cases.[13] Patients with late-onset and very late onset ataxia frequently present with milder and more slowly progressive symptoms and lower prevalence of cardiomyopathy and skeletal abnormalities than patients with typical onset.[33] Retained deep tendon reflexes and prominent spasticity are common, sometimes leading to diagnostic delays.

Charcot-Marie-Tooth disease, ataxia telangiectasia, ataxia with oculomotor apraxia, ataxia with vitamin E deficiency, and abetalipoproteinaemia can clinically mimic Friedreich's ataxia. These are differential diagnoses that can be distinguished by specific clinical symptoms (ocular movements, ocular telangiectasia, and spasticity), blood tests, electrophysiology, and genetic testing.

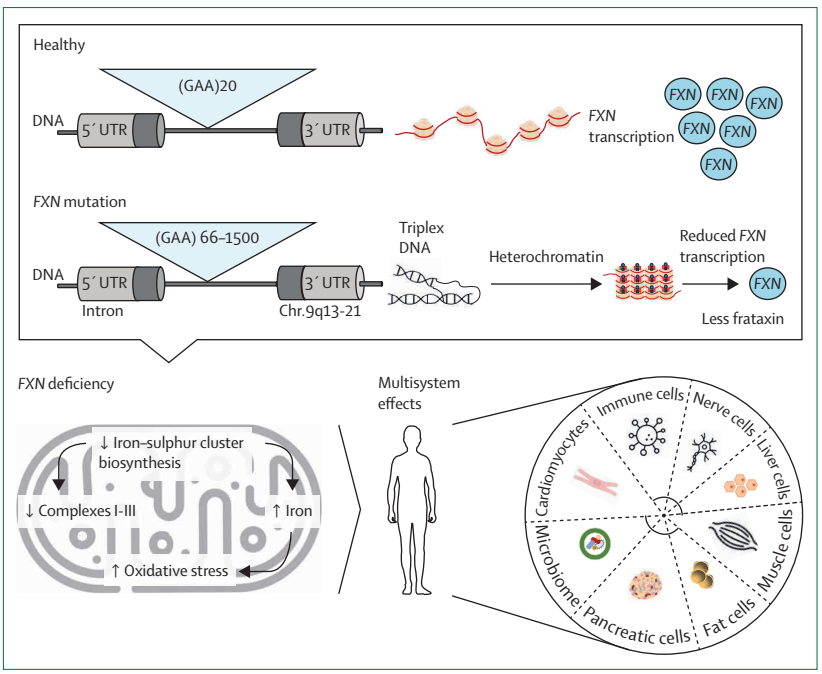

Figure 1: **Pathological mechanisms in Friedreich's ataxia**
The intron between exons 1 and 2 of the *FTX* gene contains a GAA triplet, which is typically shorter than 20 copies in length, but in patients with Friedreich's ataxia this triplet can expand to over a thousand repeats (66–1500). The expansion of the intronic GAA repeat leads to the formation of abnormal DNA structures that arrest RNA polymerase II, and to histone modifications that cause heterochromatin-mediated silencing of *FXN* and production of too little of the protein frataxin. Amounts of *FXN* mRNA and protein are reduced. Reduction of frataxin protein results in defective iron–sulphur clusters, leading to iron accumulation in mitochondria, and to deficiencies of cytosolic aconitase and complexes I, II, and III of the mitochondrial electron transport chain. Consequently, energy production and biogenesis in mitochondria decrease, and susceptibility to oxidative stress increases. In addition to the effects in neurons, mutations in *FXN* also affect other cells, such as cardiomyocytes, liver cells, muscle cells, fat cells, pancreatic cells, and the microbiome, and the interplay between these cells (ie, crosstalk) is altered.

See Online for appendix

Neurological and psychiatric symptoms

Axial and appendicular ataxia is a universal symptom in all patients, and is aetiologically ascribed to cerebellar pathology and dysfunction of the posterior column, dorsal roots, and peripheral nerves, leading to loss of position sense. Dysarthria can heavily affect quality of life due to communication difficulties and might confound cognitive assessments of verbal fluency.[33] Dysphagia is very common, occurring in 69–98% of cases,[27,34] and aspiration pneumonia might be the second most common cause of death after cardiac causes.[30] Spasticity occurs more frequently in people with advanced disease and in the late-onset form. In people with late-onset Friedreich's ataxia, spasticity can manifest as the primary presenting feature. Prevalence estimates classically range between 12% and 15% in people with

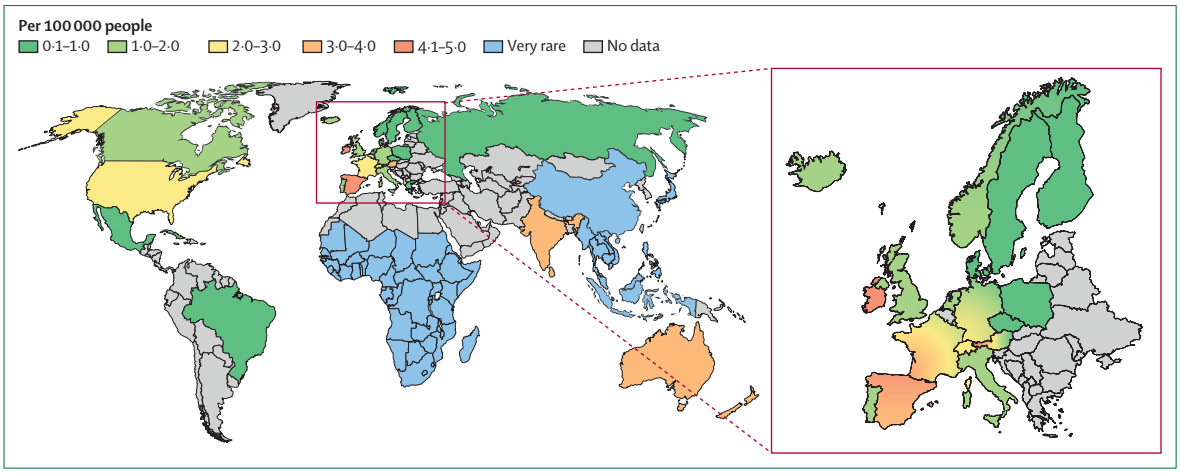

Figure 2: **The global prevalence of Friedreich's ataxia**
In the inset map depicting European countries, prevalence gradients are shown for countries where data are available. The highest estimated prevalence has been reported in western Europe (west Austria, southwest France, Ireland, and northern Spain). Whereas the prevalence in the USA is about 1 in 50 000 people; prevalence decreases in Mexico and central America, Canada, and in South America. Friedreich's ataxia appears to be extremely rare or inexistent in sub-Saharan Africa, China, Japan, and southeast Asia. Owing to the scarcity of systematic studies, data for some regions are rare or non-existent.

typical onset and 33% and 40% in people with late onset.[35,36]

Sensory peripheral neuropathy almost invariably occurs in patients with Friedreich's ataxia and predominantly affects the lower limbs, leading to sensory ataxia and, often, neuropathic pain. Electrophysiological testing commonly reveals unobtainable or low-in-amplitude sensory nerve action potentials, with motor-conduction studies being regular or only mildly abnormal. Urinary disturbances, especially urgency and frequent urination, occur in 23–80% of patients.[27,37,38]

Affective disorders such as depression and anxiety have been reported not only in individuals with Friedreich's ataxia, but also in their families, highlighting the wide-ranging effect of this neurological disease on their emotional and social wellbeing. Estimates range from 14% to 36% of patients with Friedreich's ataxia for major depression[27,39,40] to 50% to 92% for minimal mood disturbances.[39,41] Cognitive function is largely preserved, and patients do not usually have significant cognitive impairment.[42] However, lower cognitive performance compared with healthy control participants in some domains, such as executive function, attention, visuospatial abilities, or social cognition, have been reported.[43] The specific cognitive profile of patients with Friedreich's ataxia remains to be fully understood, in particular the extent to which timed assessments of cognitive abilities might be confounded by physical disability, in particular limb ataxia and dysarthria.[100,33]

Cardiac symptoms

Heart disease occurs in 40–85% of patients with Friedreich's ataxia.[31,44] The cardiac hallmark feature, cardiomyopathy, is characterised by concentric and increased ventricular wall thickness associated with either a normal or a small left ventricular cavity.[45,46] In the early stages, left ventricular ejection fraction is typically preserved but can decline as the disease progresses.[47] Predictors of mortality and heart failure progression include higher GAA1 repeat expansions, a lower left ventricular ejection fraction, and a higher left ventricular mass index.[48] Notably, cardiac measures appear unrelated to ataxia severity, suggesting a disparity between the gradual advancement of neurodegeneration and the occurrence of cardiac disease.[91] Diagnostic evaluations include electrocardiogram, which typically shows early abnormal repolarisation with T-wave inversion, and echocardiography to identify thickening of the ventricular septum and left ventricular wall. Complementing these diagnostic evaluations, cardiac MRI with gadolinium can detect concentric left ventricular remodelling, as indicated by the mass–volume ratio, and focal myocardial fibrosis. Late gadolinum enhancement, which can be lateral subepicardial or transmural, is indicative of dense replacement fibrosis.[49] Overall, evidence suggest a progressive continuum of cardiac involvement, from early electrical abnormalities to later occurrence of cardiac hypertrophy and dense fibrosis, finally leading to cardiac dysfunction.

Musculoskeletal symptoms

Progressive muscle weakness typically starts distally, and frequently leads to exacerbation of the ataxia-related immobility. Scoliosis, the most common non-neurological symptom, occurs in 63–90% of patients,[27,50–53] and is often apparent before the onset of neurological symptoms.[50,52] Scoliosis is mainly a consequence of neuromuscular weakness and is often characterised by a left-sided thoracic curve and hyperkyphosis.[52,53] A large retrospective analysis of data from the Friedreich's Ataxia Clinical Outcome Measures (FACOMS) registry found that longer GAA1 repeat expansions were associated with earlier age

of scoliosis surgery.[51] Foot deformities are common, with a prevalence of 59% of patients,[27] pes cavus being the most common, characterised by an abnormally elevated plantar arch.

Metabolic symptoms

The risk of diabetes is increased in patients with Friedreich's ataxia compared with the general population, although its prevalence is low compared with that of other multiorgan manifestations. Although approximately 30% of patients with Friedreich's ataxia have impaired glucose tolerance,[53,55] only 7–9% develop diabetes,[27,54] contrasting with earlier estimates of up to 18% of patients.[56] The earlier study[56] did not mandate genetic testing for inclusion, and included only patients with onset before 20 years with evidence of cardiomyopathy (ie, a much more severely affected group of patients). The prevailing hypothesis implicates mitochondrial dysfunction induced by frataxin deficiency as a primary contributor to pancreatic β-cell dysfunction and higher sensitivity to metabolic and endoplasmic reticulum stress-induced β-cell death. This hypothesis is supported by findings indicating that neither body composition nor BMI are associated with insulin resistance and type 2 diabetes in these patients.[55] Nonetheless, the pathophysiological mechanisms underlying diabetes in patients with Friedreich's ataxia remain elusive.

Growth is altered in patients with Friedreich's ataxia,[57] as underweight is characteristic in children with any mitochondrial disorder,[58] and BMI correlates with ATP production in children with a mitochondrial disorder, as mitochondrial energy production is known to correlate with age-related BMI in children with underlying mitochondrial disorders.[59] Paediatric patients are often short in height, with boys having a delayed growth spurt and girls having a slower peak height velocity compared with a healthy paediatric reference population,[57] which might indicate altered pubertal maturation. In contrast to patients with other neurodegenerative disorders, such as amyotrophic lateral sclerosis, spinocerebellar ataxia, and Huntington's disease, in whom underweight is common,[60,61] adults with Friedreich's ataxia are frequently overweight.[62] A putative mechanism for their obesity constitutes frataxin deficiency in white adipose cells, which can lead to increase in adipocyte size, hypovascularisation, production of pro-inflammatory adipokines, immune cell recruitment, and fibrosis, as observed in *FXN* knockout mice.[63] A tight crosstalk has been described in the mouse model between white adipose tissue and gut microbiota that synergistically maintains metabolic homoeostasis. In mice, an obesogenic diet was found to aggravate the metabolic dysfunction caused by frataxin deficiency.[64] Inflammation might play an important, yet underinvestigated, role as patients with Friedreich's ataxia might have a low-grade subclinical inflammation.[65] Studies using PET [18F]-FEMPA and analysing blood inflammatory cytokines as markers of glial activation have provided the first evidence of neuroinflammation in patients with Friedreich's ataxia.[66] One study using single-cell RNA in a Friedreich's ataxia mouse model showed that frataxin-deficient microglia had heightened reactions to inflammatory stimuli (lipopolysaccharide) characterised by increased expression of M1-like markers (proinflammatory markers, eg, CD86+), reduced expression of M2-like markers (anti-inflammatory markers, eg, CD206), and increased production of proinflammatory cytokines. Conversely, butyrate treatment can counteract these immunometabolic changes, initiating an antioxidant response via the itaconate-Nrf2-GSH pathway, and dampening inflammation.[67] Generally, little is known about the complex interplay between inflammation, immune activation, metabolism, the gut microbiome, and the occurrence of diabetes in people with Friedreich's ataxia. However, preliminary studies suggest that a better understanding of the immunometabolic mechanisms might lead to the identification of therapeutic targets for

Panel 1: **Natural history studies and research priorities**

Clinician-reported outcome measures

Frequently used standardised clinical rating scales to quantify neurological function include the Scale for the Assessment and Rating of Ataxia (SARA) and the modified Friedreich's Ataxia Rating Scale (mFARS). Although both scales have similar psychometric properties, the SARA incorporates fewer items and enables faster and clinically more practicable assessment than the mFARS. The mFARS is more granular and potentially more sensitive at early stages.[69] Natural history data from EFACTS and FACOMS have described stage-dependent annual progression rates of SARA (EFACTS) and mFARS (FACOMS), showing greater decline in ambulatory patients and in those with earlier onset, as well as differential worsening in subscales related to gait and balance versus upper or lower limb functions.[2,3] The Inventory of Non-Ataxia Signs (INAS) measures severity of non-ataxic symptoms and signs.[70] The 4-year EFACTS study (N=602) showed that the number of non-ataxic neurological signs assessed with the INAS increased only marginally over time.[2]

Activities of daily living

The activities of daily living (ADL) refer to an individual's daily self-care activities, reflecting functional status and capturing how individuals engage and participate in life, and is best assessed in a structured interview. In the EFACTS 4-year natural history study, the ADL worsened by 0·93 points per year in the entire cohort. Progression rates were similar between ambulatory (0·94) and non-ambulatory (0·91) patients.[2] In most cases, especially in early-onset patients, the ADL showed even higher sensitivity to change than the SARA.

Performance outcome measures

The Spinocerebellar Ataxia Functional Index (SCAFI) consists of three timed performance-based tests, including an 8 m walk at maximum speed, the 9-hole peg test (9HPT), and the rate of repeating the syllables "pata" within 10 s.[71] Overall, the SCAFI has low-to-moderate sensitivity to change over time, with better responsiveness in ambulatory patients, given that the 8 m walk test is not suitable after loss of ambulation.[2] The 9HPT is a measure of dexterity and upper limb coordination, with good sensitivity to change in wheelchair users.[2] Given ongoing disease progression, and that scales measuring gait and lower limb function can reach ceiling effects, the assessment of upper limb extremities and speech might serve as a sensitive measure.

	Location	Mechanism of action	Primary outcome	Participants	Duration	Administration	Phase	Status or results
Vatiquinone (NCT05515536; EudraCT 2022-002668-65)	USA, Australia, Brazil Canada, France, Germany, Italy, New Zealand, Spain	Small molecule that inhibits 15-lipoxygenase	Long-term safety (adverse events)	N=130 (actual);* age <7 years	Open-label extension up to 5 years	Oral	3 (open-label extension)	Ongoing (2022–27)†
Resveratrol (NCT03933163)	Australia	Wide-ranging health benefits, including antioxidant, anticarcinogenic, antidiabetic, and neuroprotective properties	Improvement on the mFARS scale	N=25 (actual), N=40 (estimated); aged ≥16 years	24 weeks	Oral (capsules)	2	Completed (2019–24)†
Vatiquinone (NCT05485987; PTC743-NEU-005-FA)[79]	USA	Small molecule that inhibits 15-lipoxygenase	Pharmacokinetics and safety (adverse events)	N=5; age <7 years	72 weeks	Oral (solution)	2	Ongoing (2022–24)†
Nomlabofusp (NCT05579691;[80] CLIN-1601-200)	USA	Recombinant fusion protein intended to deliver human frataxin	Safety and treatment-emergent adverse events	N=28; age ≥18 years	93 days	Subcutaneous	2	Completed (2022–23)†
Nomlabofusp (NCT06447025;[80] CLIN-1601-201)	USA	Recombinant fusion protein intended to deliver human frataxin	Safety and treatment-emergent adverse events	N=75; age ≥18 years	Open-label extension up to 24 months	Subcutaneous	2 (open-label extension)	Ongoing (2024–27)†
Dimethyl fumarate and monomethyl fumarate	Italy	Nrf2 activator that can rescue deficits related to frataxin deficiency	*FXN* gene expression and frataxin protein concentration	N=40 ; age ≥12 years	12 weeks (core phase)	Oral	2	Ongoing (not applicable)
Etravirine (NCT04273165; EudraCT 2019-002618-38)	Italy	Diarylpyrimidine acting as a non-nucleoside reverse transcriptase inhibitor and found to upregulate frataxin protein	Adverse events	N=30; age 10–40 years	4 months	Oral (tablets)	2	Completed (2020–24)
Artesunate (NCT04921930; C20-54)	France	Regulation of iron homoeostasis and TfR1 in peripheral blood mononuclear cells	Efficacy and toxicity maximal tolerated and effective dose of oral artesunate	N=20; age 16–65 years (male)	4 weeks	Oral	1/2	Completed (2022–24)†
Elamipretide (NCT05168774)	USA	Tetrapeptide that increases mitochondrial respiration and ATP production	Change in high contrast visual acuity	N=20; age ≥16 years	52 weeks	Subcutaneous	1/2	Completed (2022–24)†
LX2006 (AAVrh.10hFXN; NCT05445323;[81] LX2006-01)	USA	Up to 3 (low, mid, and high) doses of a single administration of LX2006, adeno-associated virus gene therapy designed to intravenously deliver the human *FXN* to cardiac cells	Treatment-emergent adverse events and treatment-emergent serious events	N=8; age 18–50 years (Friedreich's ataxia and cardiomyopathy)	52 weeks open-label extension, long-term 5 years	Intravenous injection	1/2	Ongoing (2022–29)†
DT-216-P2[82] and DTX-216P2 (NCT06874010)	Australia	Transcription activation of *FXN* and restoration of frataxin protein	Frequency of treatment-emergent adverse events	N=20; age 18–55 years	12 weeks	Intravenous injection and subcutaneous	1/2	Ongoing (2025–27)†
NAD+ and exercise (NCT04192136)	USA	Aerobic capacity (skeletal muscle mitochondrial oxidative phosphorylation and mass)	Maximal oxygen consumption	N=80; age 10–40 years	12 weeks	Oral (capsules) exercise	Interventional	Ongoing (2020–25)†
Omaveloxolone (NCT06054893; 408-C-2001)	USA	Activation of Nrf2	Pharmacokinetics and safety	N=20; age ≥2 to <16 years	Maximum of up to 240 weeks	Oral (capsules)	1	Ongoing (2024–30)†
AAVrh.10hFXN (and prednisolone; NCT05302271; 20-01021274; R61HL151355)	USA	AAVrh.10hFXN (a serotype rh.10 adeno-associated virus gene transfer vector coding for *FXN*)	Safety and treatment-emergent adverse events	N=25; age 18–50 years (Friedreich's ataxia and cardiomyopathy)	5 years	Intravenous injection	1	Ongoing (2022–29)†

FARA=Friedreich's Ataxia Research Alliance. mFARS=modified Friedreich Ataxia Rating Scale. Nrf2=nuclear factor (erythroid-derived 2)-like 2. PPAR=peroxisome proliferator-activated receptor. TfR1=transferrin 1 receptor. *From previous vatiquinone studies. †Estimated study completion.

Table: **Ongoing clinical trials in Friedreich's ataxia**

this rare disease. Although reduced frataxin is widely accepted as the underlying cause of Friedreich's ataxia, whether organ-specific involvement is solely due to frataxin deficiency or also influenced by interorgan communication has not been established yet.

Treatment

Omaveloxolone is the first available medication for the treatment of patients older than age 16 years, and was approved by the US Food and Drug Administration in 2023,[68] and by the European Comission, on behalf of the

European Medicines Agency, in 2024. Omaveloxolone is an activator of the nuclear factor (erythroid-derived 2)-like 2 (Nrf2) pathway, which regulates antioxidant genes (eg, *NQO1*, *SRXN1*, and *TXNRD1*) and mitochondrial activity to neutralise oxidative stress. Pharmacodynamics, safety, and efficacy were evaluated in a two-part study (MOXIe; a multicentre trial in 11 clinical institutions in the USA, Europe, and Australia). The initial dose ranging study (part 1) established 160 mg/day as the optimal dose.[4] The phase 2 trial (part 2) showed its beneficial effects with respect to the primary outcome, with a 1·55 point improvement in modified Friedreich Ataxia Rating Scale (mFARS) scores (panel 1) at 48 weeks in the omaveloxolone group (n=51), compared with a 0·85 point deterioration in the placebo group (n=52).[72] Patients who completed part 2 were offered participation in an open-label extension study for up to an additional 144 weeks. The initial treatment assignment was kept blinded, so that a delayed-start design was applied in the analysis of data from 73 participants.[6] Between the end of part 2 and the enrolment into the open-label extension, there was a 4 week washout period.[4] During this period, the mFARS scores of patients treated with omaveloxolone worsened from the 48 weeks of treatment.[4] In the open-label extension study, patients initially treated with omaveloxolone maintained their benefit for most time points compared with those initially treated with placebo (–2·91 points mFARS ±1·437), in comparison with the patients who initially received placebo. Additionally, a propensity-match analysis of data from the MOXIe study and data from the FACOMS natural history registry[5] showed that patients treated with omaveloxolone had persistent benefits over a 3 year period, compared with untreated individuals, with a smaller change from baseline in mFARS at each year.[5]

A common adverse effect of omaveloxolone is elevation of aminotransferases, occurring in 19 (37%) out of 51 participants in the MOXIe part 2 study; first results of clinical treatment showed that, over the first year, 56·6% of patients had at least one transamnianse value above the upper limit of normal.[73] However, elevation of aminotransferase concentrations usually occur soon after start of treatment and reverse within 12 weeks of treatment, and appear to be related to Nrf2 activation rather than liver injury. Increase in cholesterol concentrations are also commonly observed.[73] The size of the improvements seen with omaveloxolone treatment is comparable with the amount of functional decline that patients with Friedreich's ataxia typically experience over the course of 2 years, based on data from similar patients in the FACOMS natural history study.[72] However, the relatively small number of participants and the fact that elevation of aminotransferases could have led to unblinding represent important limitations in the trial. Given the early onset of Friedreich's ataxia, prioritising paediatric clinical trials seems crucial.

Non-invasive brain stimulation

The evidence on the use of non-invasive brain stimulation in the treatment of patients with Friedreich's ataxia is limited, but some studies have shown potential therapeutic benefit. A randomised, sham-controlled trial using anodal cerebellar transcranial direct current stimulation over 5 days in 24 patients showed improved ataxia and cognitive symptoms.[74] Larger randomised controlled trials are needed to determine optimal stimulation protocols and their efficacy in patients with Friedreich's ataxia.

Rehabilitation and palliative care

The clinical management of patients with Friedreich's ataxia remains largely symptomatic and focuses on supporting the maintenance of function. Most symptoms are best managed by a multidisciplinary approach, including rehabilitation and pharmacological treatment according to guidelines (appendix p 2).[75] Management includes physiotherapy, occupational therapy, and speech therapy. Physiotherapy should target gait, balance, coordination, posture, and muscle strength. Physical activity is encouraged throughout life,[75] as rehabilitation[76] and physiotherapy[77] can benefit individuals with Friedreich's ataxia at any age or disease stages, and help to delay or improve functional decline. A meta-analysis suggested that therapeutic exercise might reduce ataxia

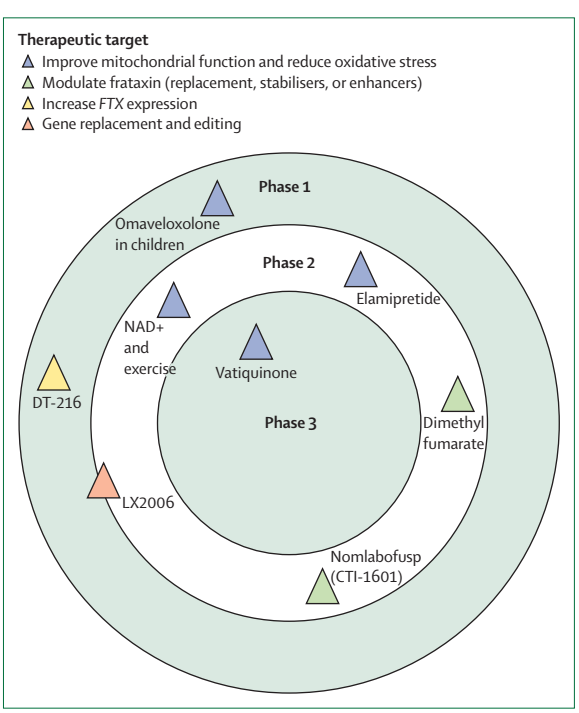

Figure 3: **Clinical trials in people with Friedreich's ataxia**
Agents being investigated in clinical trials of Friedreich's ataxia (data extracted from Clinical Trials.gov as of Sept 28, 2024). The internal ring displays agents investigated in phase 3 trials, the middle ring shows those in phase 2 trials, and the external ring shows agents that are being investigated in phase 1 studies.

Panel 2: Natural history studies and research priorities

Ongoing unification of the European Friedreich's Ataxia Consortium for Translational Studies and Clinical Outcome Measures in Friedreich's Ataxia

Natural history studies are crucial for understanding disease evolution. To date, there have been two large multicentric natural history studies: the European Friedreich's Ataxia Consortium for Translational Studies (EFACTS) in Europe (NCT02069509) and the Clinical Outcome Measures in Friedreich's Ataxia in Australia, Canada, India, New Zealand, and the USA (FACOMS; NCT03090789). Joining forces globally, a harmonised Friedreich's Ataxia Global Clinical Consortium UNIFIED Natural History Study (NCT06016946) was recently initiated by the Friedreich's Ataxia Global Clinical Consortium. UNIFAI was designed to provide a deeper understanding of the natural history of Friedreich's ataxia, to develop sensitive outcome measures and to improve clinical research infrastructure.

Fluid biomarkers

Frataxin shows promise as a biomarker. However, its measurement remains difficult due to the existence of two isoforms of the protein: mitochondrial (frataxin-M) and extra-mitochondrial frataxin, found in erythrocytes (frataxin-E).[90] Frataxin-M can be measured in blood cells that contain mitochondria. Frataxin concentrations are associated with age of onset and inversely with the length of the GAA repeat expansion, with stronger associations for frataxin-E than frataxin-M.[91] Neurofilament light chain, a cytoskeletal protein widely investigated in various neurodegenerative disorders[92,93] has also been proposed as a potential biomarker in Friedreich's ataxia. However, evidence remains inconclusive. Several studies showed that serum concentrations were not associated with age[94–97] or disease progression, and did not change over 2 years.[94] Therefore, further longitudinal studies including individuals at early disease stage are required.[98]

Neuroimaging

In patients with Friederich's ataxia, routine MRI of the spine–brain axis often reveals spinal cord thinning and mild cerebellar atrophy, but brain atrophy can be absent on visual inspection. Quantitative MRI and spectroscopy studies have provided insights into the macrostructure and microstructure of the spinal cord and brain alterations, neurochemical changes, and functional network dynamics.[99–102] Nevertheless, current monocentric efforts in this field usually do not have a sample size sufficient for cohort stratification, and only few longitudinal imaging studies have been done. A longitudinal quantification of spinal cord alterations provided evidence of degenerative change, showing an annual decrease of about 2·4% in the cervical cross-sectional area.[103] Longitudinal brain-imaging studies have indicated progressive white matter abnormalities over time, especially in the superior cerebellar peduncles, and increase of iron accumulation in the dentate nucleus.[104–108] The ENIGMA-Ataxia multinational initiative retrospectively aggregated structural MRI data, enabling investigations into cervical spinal cord and brain damage in about 250 individuals with Friedreich's ataxia.[109,110] These analyses showed volume reductions in the brainstem, dentate nucleus, and cerebellar peduncles as early features,[110] and pronounced reductions of the cervical spinal cord suggested both developmental thinning of dorsal columns, as well as corticospinal tract damage that can progress during the disease course.[109] A worldwide natural history study (TRACK-FA) was initiated in 2020 to track brain and spinal cord changes, with a particular focus on early disease stages and paediatric patients.[111] This global effort will enable a better understanding of the extent of hypoplasia and degenerative patterns of pathology, and will validate sensitive, clinical-trial-ready neuroimaging markers.

severity, but the studies that were included in the meta-analysis have yielded conflicting results.[78] Early palliative care and advance care planning are also highly recommended.[75]

Ongoing clinical trials

Designing sufficiently powered trials for a multisystem, slowly progressive and heterogenous rare disease is challenging. Efforts are further hampered by the inconsistent genotype–phenotype correlations and scarcity of biomarkers. Nonetheless, several clinical trials are investigating diverse treatment approaches. These treatment approaches include improving mitochondrial function and reducing oxidative stress; modulation of frataxin controlled metabolic pathways; frataxin replacement, stabilisers, or enhancers of frataxin concentrations; increasing *FXN* gene expression; and, finally, gene replacement and editing (table, figure 3).

The first clinical trial testing omaveloxolone was successfully completed; however, future trials need to investigate its long-term safety and efficacy in children. A post-authorisation safety (phase 4) study is planned in all patients receiving the drug, with a separate clinical trial planned for children, and a phase 1 study (NCT06054893) to evaluate pharmacokinetics in three paediatric cohorts has been initiated.

Vatiquinone (PTC-743) is a small molecule that is orally administered and inhibits 15-lipoxygenase, a crucial enzyme involved in regulating oxidative stress, ferroptosis, and inflammation pathways.[83] The phase 3 MOVE-FA study that investigated vatiquinone did not meet its primary endpoint, a change in the mFARS score over 72 weeks. However, in the long-term extension study, after 36 months, the treatment group had a 3·75-point increase in mFARS compared with a 7·48-point increase in the placebo group. Vatiquinone resulted in a 3·7-point benefit (p>0·001, n=70), corresponding to a 50% slowing of disease progression.[84] A phase 2 trial (NCT05485987) in young children (aged <7 years) is ongoing.

Elamipretide is a peptide that localises to the inner mitochondrial membrane, where it binds to cardiolipin and modulates mitochondrial function. In experimental studies, it increased mitochondrial respiration and ATP production, and reduced the formation of pathogenic reactive oxygen species concentrations.[85] A phase 1/2 clinical trial (NCT05168774) with elamipretide comparing different dosage regimens in individuals with Friederich's ataxia and vision loss or advanced cardiac disease has recently been completed, and the results are anticipated.

An interventional study (NCT04192136) is investigating the combined effect of exercise and 300 mg nicotinamide riboside on maximum rate of oxygen consumption in patients with Friedreich's ataxia,[86] to test the hypothesis that the intervention will enhance mitochondrial oxidative phosphorylation in skeletal muscle and will increase muscle mass.

A monocentric phase 2 study in Italy (EudraCT 2021-006274-23) is investigating whether dimethyl-fumarate increases frataxin concentrations in lymphocytes of patients with Friedreich's ataxia.[87]

Nomlabofusp (CTI-1601) is a subcutaneously administered frataxin replacement therapy. This recombinant fusion protein includes a cell-penetrant peptide that facilitates the delivery of human frataxin into mitochondria and increases mitochondrial frataxin concentrations.[88] Phase 1 and 2a studies of nomlabofusp showed dose-dependent increases of frataxins measured in peripheral tissues.[88] An open-label extension is ongoing, and paediatric and phase 3 efficacy studies are being planned.

DT-216 uses *FXN* gene-targeted chimera small molecules targeting the *FXN* GAA repeat expansion to modulate the cell's native transcriptional processes and restore production of frataxin. This drug is administered intravenously. A phase 1a (NCT05573698) randomised, double-blind, placebo-controlled, single ascending dose study found that DT-216 was well tolerated and led to a dose-related increase in frataxin mRNA concentrations in skeletal muscle biopsies. A phase 1/2 open-label study (NCT06874010) to assess a second-generation drug with improved pharmacokinetics, DT-216P2, has been initiated.

LX2006 is an adeno-associated virus (AAV)-based gene therapy designed to restore frataxin concentrations in a single intravenous infusion. Two phase 1 dose-ascending trials in patients with Friedreich's ataxia and cardiomyopathy, the SUNRISE-FA and the Weill Cornell Medicine investigator-initiated trial, reported a 25% reduction in left ventricular mass index in 75% of patients with elevated left ventricular mass index at baseline by 12 months; clinically meaningful improvements in cardiac biomarkers, functional measures, and frataxin expression in all patients; and no serious adverse events.[89] A registrational trial is now planned.

Conclusions and future directions

Friedreich's ataxia is characterised by considerable variability in age of onset, prognosis, and extent of system involvement, which, to date, remains insufficiently explained by our knowledge of the underlying genetic mutation. Symptomatic treatment, including rehabilitation, continues to be the foundation of care; however, the recent approval of omaveloxolone, targeting metabolic pathways to reduce oxidative stress, represents a crucial milestone. An urgent need remains for novel disease-modifying therapies. Several clinical trials are underway to investigate promising therapies and compounds designed to increase frataxin concentrations, targeting the core pathogenesis of the disease. To enhance the success of future trials, it is crucial to develop biomarkers and outcome measures that address the multisystem nature of the disease (panel 2), capturing its slow progression and reflecting meaningful changes in patients' lives. One key challenge to be tackled in future research is the accurate and cost-effective measurement of frataxin in blood; furthermore, advances in neuroimaging and digital phenotyping research will contribute to better trial endpoints. These advances will rely on a holistic understanding of the pathophysiology, including the interplay between neurodevelopment and neurodegeneration.

Search strategy and selection criteria

We searched PubMed, Google Scholar, and Embase for articles in English on Friedreich's ataxia published between Jan 1, 2014, and April 1, 2025, using the main search terms "Friedreich ataxia" AND "multisystem" OR "heart" OR "cardiomyopathy" OR "diabetes" OR "metabolism" OR "scoliosis" OR "neuromuscular deformities" AND "biomarker", "genetic", "treatment", and "clinical trial", and by cross-referencing. The final reference list was generated on the basis of the quality of the studies and relevance to the covered topics. For clinical trials, we searched https://www.clinicaltrials.gov, using the search term "Friedreich ataxia".

FACROSS study group members

Ana Sofia Costa, Sandro Romanzetti, Ravi Dadsena (Department of Neurology, University Hospital RWTH Aachen, Germany); Maximillian Praster (Department for Orthopaedics, Trauma and Reconstructive Surgery, University Hospital RWTH Aachen, Germany); Thomas Clavel (Functional Microbiome Research Group, Institute of Medical Microbiology, University Hospital RWTH Aachen, Germany); Vera Jankowski, Joachim Jankowski (Institute for Molecular Cardiovascular Research, University Hospital RWTH Aachen, Germany); Oliver Pabst (Institute of Molecular Medicine, University Hospital RWTH Aachen, Germany); Nikolaus Marx, Julia Möllmann, Malte Jacobsen (Department of Internal Medicine I, Cardiology, University Hospital RWTH Aachen, Germany); Juergen Dukart, Simon Eickhoff (Institute of Neuroscience and Medicine, Brain and Behaviour [INM-7], Research Centre Jülich, Germany); and Ralf-Dieter Hilgers (Department of Medical Statistics, University Hospital RWTH Aachen, Germany).

Contributors

KR, SAL, ID, and JBS conceptualised the manuscript and searched for and selected the references. All authors wrote sections of the manuscript, reviewed and commented on several preliminary drafts by KR, and approved the final version of the Review.

Declaration of interests

KR has received grants from the German Research Foundation, Friedreich's Ataxia Research Alliance (FARA), the Interdisciplinary Center for Clinical Research within the Faculty of Medicine at the RWTH Aachen University, Germany (OC2), German Federal Ministry of Education and Research (BMBF KP22-106E); and honoraria for presentations or advisory boards from Biogen, Eisai, Eli Lilly, and Roche. ID received grants from FARA and the Interdisciplinary Center for Clinical Research within the faculty of Medicine at the RWTH Aachen University, Germany (OC2). JBS received grants from the German Research Foundation, Interdisciplinary Center for Clinical Research within the Faculty of Medicine at the RWTH Aachen University, Germany, Biogen, and Eisai; and for presentations or advisory boards from Biogen, Reata, Eisai, Eli Lilly, Roche, and NovoNordisk. KM-S is supported by the Deutsche Forschungsgemeinschaft (German Research Foundation; TRR 219; Project-ID 322900939 [C07]); has received personal fees for lectures from Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Eli Lilly, Merck Sharp & Dohme, Novo Nordisk, Novartis, and OmniaMed; and served as an advisor for Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, and Novo Nordisk. DRL receives grants from FARA, the National Institutes of Health, the US Food and Drug Administration, Reata, Biogen, and PTC therapeutics. LAC receives grant funding from the Friedreich's Ataxia Research Alliance FARA; and provides paid

consultancy and advisory services to Biogen. MPi received consulting fees from Stryker. KK received payment from the Max Planck Society, grants from German Research Foundation and Federal Ministry of Research & Education. MPa received consulting fees from Biogen, Biomarin, Design Therapeutics, Larimar, and Solid Bio. JF received consulting fees from UCB, Biogen, Larimar Therapeutics, and Lexeo Therapeutics; and honoraria from the Chan Zuckerberg Initiative. All other authors declare no competing interests.

Acknowledgments

We thank our patients and families who have willingly and with interest participated in research studies and clinical trials, and have shown incredible endurance, helping us to advance our medical knowledge of this rare complex disease. We thank all clinicians and researchers dedicated to this rare disease, especially those who have been involved in European Friedreich's Ataxia Consortium for Translational Studies (EFACTS) and Friedreich Ataxia Clinical Outcome Measures Study (known as FACOMS). A special thanks to Claire Didszun for her long and thorough commitment to EFACTS and help with the demographic data. We express our gratitude to Laura Bell from the Audiovisual Media Centre of the Medical Faculty at RWTH Aachen University for creating an illustration (appendix figure 1 [p 3]). Our work is supported by a grant from the Interdisciplinary Center for Clinical Research within the Faculty of Medicine at the RWTH Aachen University, Germany (OC2).

References

1 Campuzano V, Montermini L, Moltò MD, et al. Friedreich's ataxia: autosomal recessive disease caused by an intronic GAA triplet repeat expansion. *Science* 1996; **271:** 1423–27.
2 Reetz K, Dogan I, Hilgers R-D, et al, and the EFACTS study group. Progression characteristics of the European Friedreich's Ataxia Consortium for Translational Studies (EFACTS): a 4-year cohort study. *Lancet Neurol* 2021; **20:** 362–72.
3 Rummey C, Corben LA, Delatycki M, et al. Natural history of Friedreich ataxia: heterogeneity of neurologic progression and consequences for clinical trial design. *Neurology* 2022; **99:** e1499–510.
4 Lynch DR, Farmer J, Hauser L, et al. Safety, pharmacodynamics, and potential benefit of omaveloxolone in Friedreich ataxia. *Ann Clin Transl Neurol* 2018; **6:** 15–26.
5 Lynch DR, Goldsberry A, Rummey C, et al. Propensity matched comparison of omaveloxolone treatment to Friedreich ataxia natural history data. *Ann Clin Transl Neurol* 2024; **11:** 4–16.
6 Lynch DR, Chin MP, Boesch S, et al. Efficacy of omaveloxolone in Friedreich's ataxia: delayed-start analysis of the MOXIe extension. *Mov Disord* 2023; **38:** 313–20.
7 Lynch DR, Chin MP, Delatycki M, et al. Safety and efficacy of omaveloxolone in Friedreich's ataxia (MOXIe Study): a multicentre, randomised, double-blind, placebo-controlled trial. *Ann Neurol* 2021; **89:** 212–25.
8 Galea CA, Huq A, Lockhart PJ, et al. Compound heterozygous FXN mutations and clinical outcome in friedreich ataxia. *Ann Neurol* 2016; **79:** 485–95.
9 Delatycki MB, Williamson R, Forrest SM. Friedreich ataxia: an overview. *J Med Genet* 2000; **37:** 1–8.
10 McDaniel DO, Keats B, Vedanarayanan VV, Subramony SH. Sequence variation in GAA repeat expansions may cause differential phenotype display in Friedreich's ataxia. *Mov Disord* 2001; **16:** 1153–58.
11 Montermini L, Kish SJ, Jiralerspong S, Lamarche JB, Pandolfo M. Somatic mosaicism for Friedreich's ataxia GAA triplet repeat expansions in the central nervous system. *Neurology* 1997; **49:** 606–10.
12 Reetz K, Dogan I, Costa AS, 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* 2015; **14:** 174–82.
13 Filla A, De Michele G, Cavalcanti F, et al. The relationship between trinucleotide (GAA) repeat length and clinical features in Friedreich ataxia. *Am J Hum Genet* 1996; **59:** 554–60.
14 Campuzano V, Montermini L, Lutz Y, et al. Frataxin is reduced in Friedreich ataxia patients and is associated with mitochondrial membranes. *Hum Mol Genet* 1997; **6:** 1771–80.
15 Adamec J, Rusnak F, Owen WG, et al. Iron-dependent self-assembly of recombinant yeast frataxin: implications for Friedreich ataxia. *Am J Hum Genet* 2000; **67:** 549–62.
16 González-Cabo P, Palau F. Mitochondrial pathophysiology in Friedreich's ataxia. *J Neurochem* 2013; **126** (suppl 1)**:** 53–64.
17 Palau F. Friedreich's ataxia and frataxin: molecular genetics, evolution and pathogenesis (Review). *Int J Mol Med* 2001; **7:** 581–89.
18 Koeppen AH. Friedreich's ataxia: pathology, pathogenesis, and molecular genetics. *J Neurol Sci* 2011; **303:** 1–12.
19 Koutnikova H, Campuzano V, Foury F, Dollé P, Cazzalini O, Koenig M. Studies of human, mouse and yeast homologues indicate a mitochondrial function for frataxin. *Nat Genet* 1997; **16:** 345–51.
20 Jiralerspong S, Liu Y, Montermini L, Stifani S, Pandolfo M. Frataxin shows developmentally regulated tissue-specific expression in the mouse embryo. *Neurobiol Dis* 1997; **4:** 103–13.
21 Koeppen AH, Becker AB, Qian J, Feustel PJ. Friedreich ataxia: hypoplasia of spinal cord and dorsal root ganglia. *J Neuropathol Exp Neurol* 2017; **76:** 101–08.
22 Buesch K, Zhang R. A systematic review of disease prevalence, health-related quality of life, and economic outcomes associated with Friedreich's ataxia. *Curr Med Res Opin* 2022; **38:** 1739–49.
23 Vankan P. Prevalence gradients of Friedreich's ataxia and R1b haplotype in Europe co-localize, suggesting a common Palaeolithic origin in the Franco-Cantabrian ice age refuge. *J Neurochem* 2013; **126** (suppl 1)**:** 11–20.
24 Mariño TC, Zaldivar YG, Mesa JML, et al. Low predisposition to instability of the Friedreich ataxia gene in Cuban population. *Clin Genet* 2010; **77:** 598–600.
25 Fussiger H, Saraiva-Pereira ML, Leistner-Segal S, Jardim LB. Friedreich ataxia: diagnostic yield and minimal frequency in south Brazil. *Cerebellum* 2019; **18:** 147–51.
26 Reetz K, Dogan I, Hilgers R-D, et al, and the EFACTS Study Group. Progression characteristics of the European Friedreich's Ataxia Consortium for Translational Studies (EFACTS): a 2 year cohort study. *Lancet Neurol* 2016; **15:** 1346–54.
27 Reetz K, Dogan I, Hohenfeld C, et al, and the EFACTS Study Group. Nonataxia symptoms in Friedreich Ataxia: report from the Registry of the European Friedreich's Ataxia Consortium for Translational Studies (EFACTS). *Neurology* 2018; **91:** e917–30.
28 Rummey C, Farmer JM, Lynch DR. Predictors of loss of ambulation in Friedreich's ataxia. *EClinicalMedicine* 2020; **18:** 100213.
29 Schulz JB, Boesch S, Bürk K, et al. Diagnosis and treatment of Friedreich ataxia: a European perspective. *Nat Rev Neurol* 2009; **5:** 222–34.
30 Tsou AY, Paulsen EK, Lagedrost SJ, et al. Mortality in Friedreich ataxia. *J Neurol Sci* 2011; **307:** 46–49.
31 Pousset F, Legrand L, Monin M-L, et al. A 22-year follow-up study of long-term cardiac outcome and predictors of survival in Friedreich ataxia. *JAMA Neurol* 2015; **72:** 1334–41.
32 Legrand L, Weinsaft JW, Pousset F, et al. Characterizing cardiac phenotype in Friedreich's ataxia: the CARFA study. *Arch Cardiovasc Dis* 2022; **115:** 17–28.
33 Corben LA, Blomfield E, Tai G, et al. The role of verbal fluency in the cerebellar cognitive affective syndrome scale in Friedreich ataxia. *Cerebellum* 2024; **23:** 1975–80.
34 Keage MJ, Delatycki MB, Gupta I, Corben LA, Vogel AP. Dysphagia in Friedreich ataxia. *Dysphagia* 2017; **32:** 626–35.
35 Klockgether T, Chamberlain S, Wüllner U, et al. Late-onset Friedreich's ataxia. Molecular genetics, clinical neurophysiology, and magnetic resonance imaging. *Arch Neurol* 1993; **50:** 803–06.
36 Harding AE. Friedreich's ataxia: a clinical and genetic study of 90 families with an analysis of early diagnostic criteria and intrafamilial clustering of clinical features. *Brain* 1981; **104:** 589–620.
37 Lad M, Parkinson MH, Rai M, et al. Urinary, bowel and sexual symptoms in a cohort of patients with Friedreich's ataxia. *Orphanet J Rare Dis* 2017; **12:** 158.
38 Dürr A, Cossee M, Agid Y, et al. Clinical and genetic abnormalities in patients with Friedreich's ataxia. *N Engl J Med* 1996; **335:** 1169–75.
39 Pérez-Flores J, Hernández-Torres A, Montón F, Nieto A. Health-related quality of life and depressive symptoms in Friedreich ataxia. *Qual Life Res* 2020; **29:** 413–20.
40 Nieto A, Hernández-Torres A, Pérez-Flores J, Montón F. Depressive symptoms in Friedreich ataxia. *Int J Clin Health Psychol* 2018; **18:** 18–26.

41 Flood MK, Perlman SL. The mental status of patients with Friedreich's ataxia. *J Neurosci Nurs* 1987; **19:** 251–55.

42 Bürk K. Friedreich ataxia: current status and future prospects. *Cerebellum Ataxias* 2017; **4:** 4.

43 Naeije G, Schulz JB, Corben LA. The cognitive profile of Friedreich ataxia: a systematic review and meta-analysis. *BMC Neurol* 2022; **22:** 97.

44 Norrish G, Rance T, Montanes E, et al. Friedreich's ataxia-associated childhood hypertrophic cardiomyopathy: a national cohort study. *Arch Dis Child* 2022; **107:** 450–55.

45 Weidemann F, Störk S, Liu D, et al. Cardiomyopathy of Friedreich ataxia. *J Neurochem* 2013; **126** (suppl 1)**:** 88–93.

46 Peverill RE, Romanelli G, Donelan L, Hassam R, Corben LA, Delatycki MB. Left ventricular structural and functional changes in Friedreich ataxia - relationship with body size, sex, age and genetic severity. *PLoS One* 2019; **14:** e0225147.

47 Casazza F, Ferrari F, Piccone U, Maggiolini S, Capozi A, Morpurgo M. Progression of cardiopathology in Friedreich ataxia: clinico-instrumental study. *Cardiologia* 1990; **35:** 423–31.

48 Legrand L, Heuze C, Diallo A, et al. Prognostic value of longitudinal strain and ejection fraction in Friedreich's ataxia. *Int J Cardiol* 2021; **330:** 259–65.

49 Peverill RE, Lin KY, Fogel MA, et al. Insights into the effects of Friedreich ataxia on the left ventricle using T1 mapping and late gadolinium enhancement. *PLoS One* 2024; **19:** e0303969.

50 Indelicato E, Nachbauer W, Eigentler A, et al, and the EFACTS (European Friedreich's Ataxia Consortium for Translational Studies). Onset features and time to diagnosis in Friedreich's Ataxia. *Orphanet J Rare Dis* 2020; **15:** 198.

51 Rummey C, Flynn JM, Corben LA, et al. Scoliosis in Friedreich's ataxia: longitudinal characterization in a large heterogeneous cohort. *Ann Clin Transl Neurol* 2021; **8:** 1239–50.

52 Simon AL, Meyblum J, Roche B, et al. Scoliosis in patients with Friedreich ataxia: results of a consecutive prospective series. *Spine Deform* 2019; **7:** 812–21.

53 Milbrandt TA, Kunes JR, Karol LA. Friedreich's ataxia and scoliosis: the experience at two institutions. *J Pediatr Orthop* 2008; **28:** 234–38.

54 Tamaroff J, DeDio A, Wade K, et al. Friedreich's ataxia-related Diabetes: epidemiology and management practices. *Diabetes Res Clin Pract* 2022; **186:** 109828.

55 Cnop M, Igoillo-Esteve M, Rai M, et al. Central role and mechanisms of β-cell dysfunction and death in friedreich ataxia-associated diabetes. *Ann Neurol* 2012; **72:** 971–82.

56 Filla A, DeMichele G, Caruso G, Marconi R, Campanella G. Genetic data and natural history of Friedreich's disease: a study of 80 Italian patients. *J Neurol* 1990; **237:** 345–51.

57 Patel M, McCormick A, Tamaroff J, et al. Body mass index and height in the Friedreich ataxia clinical outcome measures study. *Neurol Genet* 2021; **7:** e638.

58 Wolny S, McFarland R, Chinnery P, Cheetham T. Abnormal growth in mitochondrial disease. *Acta Paediatr* 2009; **98:** 553–54.

59 Wortmann SB, Zweers-van Essen H, Rodenburg RJT, et al. Mitochondrial energy production correlates with the age-related BMI. *Pediatr Res* 2009; **65:** 103–08.

60 Diallo A, Jacobi H, Schmitz-Hübsch T, et al. Body mass index decline is related to spinocerebellar ataxia disease progression. *Mov Disord Clin Pract* 2017; **4:** 689–97.

61 van der Burg JMM, Gardiner SL, Ludolph AC, Landwehrmeyer GB, Roos RAC, Aziz NA. Body weight is a robust predictor of clinical progression in Huntington disease. *Ann Neurol* 2017; **82:** 479–83.

62 Shinnick JE, Schadt K, Strawser C, et al. Comorbid medical conditions in Friedreich ataxia: association with inflammatory bowel disease and growth hormone deficiency. *J Child Neurol* 2016; **31:** 1161–65.

63 Turchi R, Sciarretta F, Ceci V, et al. Butyrate prevents visceral adipose tissue inflammation and metabolic alterations in a Friedreich's ataxia mouse model. *iScience* 2023; **26:** 107713.

64 Pomplun D, Voigt A, Schulz TJ, Thierbach R, Pfeiffer AF, Ristow M. Reduced expression of mitochondrial frataxin in mice exacerbates diet-induced obesity. *Proc Natl Acad Sci USA* 2007; **104:** 6377–81.

65 Nachun D, Gao F, Isaacs C, et al. Peripheral blood gene expression reveals an inflammatory transcriptomic signature in Friedreich's ataxia patients. *Hum Mol Genet* 2018; **27:** 2965–77.

66 Khan W, Corben LA, Bilal H, et al. Neuroinflammation in the cerebellum and brainstem in Friedreich ataxia: an [18F]-FEMPA PET study. *Mov Disord* 2022; **37:** 218–24.

67 Sciarretta F, Zaccaria F, Ninni A, et al. Frataxin deficiency drives a shift from mitochondrial metabolism to glucose catabolism, triggering an inflammatory phenotype in microglia. *Life Sci Alliance* 2024; **7:** e202402609.

68 Lee A. Omaveloxolone: first approval. *Drugs* 2023; **83:** 725–29.

69 Rummey C, Harding IH, Delatycki MB, Tai G, Rezende T, Corben LA. Harmonizing results of ataxia rating scales: mFARS, SARA, and ICARS. *Ann Clin Transl Neurol* 2022; **9:** 2041–46.

70 Jacobi H, Rakowicz M, Rola R, et al. Inventory of Non-Ataxia Signs (INAS): validation of a new clinical assessment instrument. *Cerebellum* 2013; **12:** 418–28.

71 Schmitz-Hübsch T, Giunti P, Stephenson DA, et al. SCA Functional Index: a useful compound performance measure for spinocerebellar ataxia. *Neurology* 2008; **71:** 486–92.

72 Lynch DR, Chin MP, Delatycki MB, et al. Safety and efficacy of omaveloxolone in Friedreich ataxia (MOXIe study). *Ann Neurol* 2021; **89:** 212–25.

73 Gunther K, Profeta V, Keita M, et al. Safety Monitoring of omaveloxolone in Friedreich ataxia: results from one year of clinical treatment. *Neurol Ther* 2025; **14:** 1105–114.

74 Naeije G, Rovai A, Destrebecq V, Trotta N, De Tiège X. Anodal cerebellar transcranial direct current stimulation reduces motor and cognitive symptoms in Friedreich's ataxia: a randomized, sham-controlled trial. *Mov Disord* 2023; **38:** 1443–50.

75 Corben LA, Collins V, Milne S, et al, and the Clinical Management Guidelines Writing Group. Clinical management guidelines for Friedreich ataxia: best practice in rare diseases. *Orphanet J Rare Dis* 2022; **17:** 415.

76 Milne SC, Campagna EJ, Corben LA, et al. Retrospective study of the effects of inpatient rehabilitation on improving and maintaining functional independence in people with Friedreich ataxia. *Arch Phys Med Rehabil* 2012; **93:** 1860–63.

77 Maring JR, Croarkin E. Presentation and progression of Friedreich ataxia and implications for physical therapist examination. *Phys Ther* 2007; **87:** 1687–96.

78 Winser S, Chan HK, Chen WK, et al. Effects of therapeutic exercise on disease severity, balance, and functional Independence among individuals with cerebellar ataxia: a systematic review with meta-analysis. *Physiother Theory Pract* 2023; **39:** 1355–75.

79 Klein MB. PIVOT-HD topline results. 2025. https://ir.ptcbio.com/static-files/c0babb34-ab5f-442b-8a92-8733a00efebf (accessed May 24, 2025).

80 Larimar Therapeutics. Larimar Therapeutics announces positive initial data from ongoing long-term open label extension study & progress across nomlabofusp program for Friedreich's ataxia. 2024. https://investors.larimartx.com/news-releases/news-release-details/larimar-therapeutics-announces-positive-initial-data-ongoing (accessed May 24, 2025).

81 Lexeo Therapuetics. Lexeo Therapeutics announces positive interim phase 1/2 data for LX2006 in Friedreich ataxia cardiomyopathy supporting advancement to registrational study. 2025. https://ir.lexeotx.com/news-releases/news-release-details/lexeo-therapeutics-announces-positive-interim-phase-12-data (accessed May 24, 2025).

82 Design Therapeutics. Design Therapeutics highlights progress across lead GeneTAC programs and reports fourth quarter and full year 2024 financial results. 2025. https://investors.designtx.com/news-releases/news-release-details/design-therapeutics-highlights-progress-across-lead-genetacr (accessed May 24, 2025).

83 Zesiewicz T, Salemi JL, Perlman S, et al. Double-blind, randomized and controlled trial of EPI-743 in Friedreich's ataxia. *Neurodegener Dis Manag* 2018; **8:** 233–42.

84 PTC Therapuetics. PTC Therapeutics announces positive results from long-term treatment studies and updates on regulatory progress for vatiquinone Friedreich ataxia program. 2024. https://ir.ptcbio.com/news-releases/news-release-details/ptc-therapeutics-announces-positive-results-long-term-treatment (accessed May 24, 2025).

85 Chatfield KC, Sparagna GC, Chau S, et al. Elamipretide improves mitochondrial function in the failing human heart. *JACC Basic Transl Sci* 2019; **4:** 147–57.

86 Perry CE, Halawani SM, Mukherjee S, et al. NAD+ precursors prolong survival and improve cardiac phenotypes in a mouse model of Friedreich's Ataxia. *JCI Insight* 2024; **9:** e177152.

87 Pane C, Marra AM, Aliberti L, et al. Rationale and protocol of a double-blind, randomized, placebo-controlled trial to test the efficacy, safety, and tolerability of dimethyl fumarate in Friedreich ataxia (DMF-FA-201). *Front Neurosci* 2023; **17:** 1260977.

88 Clayton R, Galas T, Scherer N, et al. Safety, pharmacokinetics, and pharmacodynamics of nomlabofusp (CTI-1601) in Friedreich's ataxia. *Ann Clin Transl Neurol* 2024; **11:** 540–53.

89 Lexeo Therapuetics. Lexeo Therapeutics provides update on cardiac portfolio and reports third quarter 2024 financial results. 2024. https://ir.lexeotx.com/news-releases/news-release-details/lexeo-therapeutics-provides-update-cardiac-portfolio-and-reports (accessed May 24, 2025).

90 Guo L, Wang Q, Weng L, et al. Characterization of a new N-terminally acetylated extra-mitochondrial isoform of frataxin in human erythrocytes. *Sci Rep* 2018; **8:** 17043.

91 Rojsajjakul T, Wu L, Grady CB, et al. Liquid chromatography-mass spectrometry analysis of frataxin proteoforms in whole blood as biomarkers of the genetic disease Friedreich's ataxia. *Anal Chem* 2023; **95:** 4251–60.

92 Khalil M, Teunissen CE, Otto M, et al. Neurofilaments as biomarkers in neurological disorders. *Nat Rev Neurol* 2018; **14:** 577–89.

93 Khalil M, Teunissen CE, Lehmann S, et al. Neurofilaments as biomarkers in neurological disorders - towards clinical application. *Nat Rev Neurol* 2024; **20:** 269–87.

94 Hayer SN, Liepelt I, Barro C, et al, and the EFACTS study group. NfL and pNfH are increased in Friedreich's ataxia. *J Neurol* 2020; **267:** 1420–30.

95 Johnsson M, Zetterberg H, Blennow K, Lindberg C. Clinical stage and plasma neurofilament concentration in adults with Friedreich ataxia. *Heliyon* 2023; **10:** e23347.

96 Zeitlberger AM, Thomas-Black G, Garcia-Moreno H, et al. Plasma markers of neurodegeneration are raised in Friedreich's ataxia. *Front Cell Neurosci* 2018; **12:** 366.

97 Clay A, Obrochta KM, Soon RK Jr, Russell CB, Lynch DR. Neurofilament light chain as a potential biomarker of disease status in Friedreich ataxia. *J Neurol* 2020; **267:** 2594–98.

98 Frempong B, Wilson RB, Schadt K, Lynch DR. The role of serum levels of neurofilament light (NfL) chain as a biomarker in Friedreich ataxia. *Front Neurosci* 2021; **15:** 653241.

99 Dogan I, Romanzetti S, Didszun C, et al. Structural characteristics of the central nervous system in Friedreich ataxia: an in vivo spinal cord and brain MRI study. *J Neurol Neurosurg Psychiatry* 2019; **90:** 615–17.

100 Dogan I, Tinnemann E, Romanzetti S, et al. Cognition in Friedreich's ataxia: a behavioral and multimodal imaging study. *Ann Clin Transl Neurol* 2016; **3:** 572–87.

101 Öz G, Harding IH, Krahe J, Reetz K. MR imaging and spectroscopy in degenerative ataxias: toward multimodal, multisite, multistage monitoring of neurodegeneration. *Curr Opin Neurol* 2020; **33:** 451–61.

102 Krahe J, Dogan I, Didszun C, et al. Increased brain tissue sodium concentration in Friedreich ataxia: a multimodal MR imaging study. *Neuroimage Clin* 2022; **34:** 103025.

103 Joers JM, Adanyeguh IM, Deelchand DK, et al. Spinal cord magnetic resonance imaging and spectroscopy detect early-stage alterations and disease progression in Friedreich ataxia. *Brain Commun* 2022; **4:** fcac246.

104 Rezende TJR, Silva CB, Yassuda CL, et al. Longitudinal magnetic resonance imaging study shows progressive pyramidal and callosal damage in Friedreich's ataxia. *Mov Disord* 2016; **31:** 70–78.

105 Mascalchi M, Toschi N, Giannelli M, et al. Regional cerebral disease progression in Friedreich's ataxia: a longitudinal diffusion tensor imaging study. *J Neuroimaging* 2016; **26:** 197–200.

106 Ward PGD, Harding IH, Close TG, et al. Longitudinal evaluation of iron concentration and atrophy in the dentate nuclei in friedreich ataxia. *Mov Disord* 2019; **34:** 335–43.

107 Selvadurai LP, Georgiou-Karistianis N, Shishegar R, et al. Longitudinal structural brain changes in Friedreich ataxia depend on disease severity: the IMAGE-FRDA study. *J Neurol* 2021; **268:** 4178–89.

108 Adanyeguh IM, Joers JM, Deelchand DK, et al. Brain MRI detects early-stage alterations and disease progression in Friedreich ataxia. *Brain Commun* 2023; **5:** fcad196.

109 Rezende TJR, Adanyeguh IM, Arrigoni F, et al. Progressive spinal cord degeneration in Friedreich's ataxia: results from ENIGMA-Ataxia. *Mov Disord* 2023; **38:** 45–56.

110 Harding IH, Chopra S, Arrigoni F, et al. Brain structure and degeneration staging in Friedreich ataxia: magnetic resonance imaging volumetrics from the ENIGMA-Ataxia working group. *Ann Neurol* 2021; **90:** 570–83.

111 Georgiou-Karistianis N, Corben LA, Reetz K, et al. A natural history study to track brain and spinal cord changes in individuals with Friedreich's ataxia: TRACK-FA study protocol. *PLoS One* 2022; **17:** e0269649.