Review

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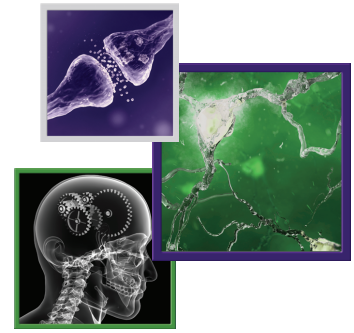
Neurodegenerative Disease Management



Friedreich ataxia: clinical features and new developments

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Practice points

- Clinical features
  - Friedreich's ataxia (FRDA) is a progressive neurodegenerative disease with features outside the nervous system;
  - Cardiac disease is the most common cause of death in FRDA;
  - Bone health including osteopenia is a new area of clinical care in FRDA.
- Clinical care requires the integration of care across many pathophysiological systems.
  - Clinical guidelines exist for essentially all aspects of medical care in FRDA;
  - Such guidelines generally do not reveal FRDA-specific treatments, but instead reinforce the need for high-quality standard medical care in FRDA.
- Clinical trials are investigating agents that ameliorate mitochondrial dysfunction in FRDA or raise frataxin levels.
  - Two new areas of treatment include the enhancement of the NRF2 pathway, which mediates the mitochondrial reaction to oxidant damage;
  - and restoration of deficient frataxin, which potentially reverses the primary cause of FRDA.
- New scientific advances continue to influence clinical understanding of FRDA.
  - A new explanation of epigenetic silencing in FRDA stresses a variegated silencing mechanism, which explains many clinical phenomena in FRDA such as the overlap in frataxin levels between carriers and patients;
  - Assessment of the neuroanatomic features of FRDA clarifies the targets of new therapies and helps understand the new perspectives on the developmental aspects of the disease.

Friedreich's ataxia (FRDA), a neurodegenerative disease characterized by ataxia and other neurological features, affects 1 in 50,000–100,000 individuals in the USA. However, FRDA also includes cardiac, orthopedic and endocrine dysfunction, giving rise to many secondary disease characteristics. The multifaceted approach for clinical care has necessitated the development of disease-specific clinical care guidelines. New developments in FRDA include the advancement of clinical drug trials targeting the NRF2 pathway and frataxin restoration. Additionally, a novel understanding of gene silencing in FRDA, reflecting a variegated silencing pattern, will have applications to current and future therapeutic interventions. Finally, new perspectives on the neuroanatomy of FRDA and its developmental features will refine the time course and anatomical targeting of novel approaches.

Plain language summary: Friedreich's ataxia (FRDA), mainly referred to as a disorder of balance, is characterized by loss of coordination (ataxia) in the arms and legs and other neurological features, affecting about 1 in 50,000 people in the USA. FRDA also includes serious heart disease, aggressive scoliosis, diabetes and many other disease characteristics. Due to various clinical care needs, disease-specific clinical care guidelines have been created. New developments in FRDA include the advancement of clinical drug trials targeting cell signaling pathways and restoration of the deficient protein found in individuals with FRDA. Additionally, a new understanding of the role of the various genetic factors that contribute to the development of FRDA could affect current and future therapies. Finally, new perspectives on the early developmental features of FRDA will help refine the time course and accelerate new treatments.

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Table 1. Comparison of the frequency of clinical features of Friedreich's ataxia between two major natural history studies, the Friedreich Ataxia Clinical Outcome Measure Study and the European Friedreich Ataxia Consortium for Translational Studies.

Feature	FACOMS	EFACTS
Neurologic dysfunction	100	100
Cardiomyopathy	51	40
Scoliosis	76	74
Diabetes	5-8	7.1
Visual loss	50	37
Hearing loss	16	NA
Depression	NA	14
Age at onset (years)	13.1	15.7
Age at baseline (years)	25.1	33.9

EFACTS: European Friedreich Ataxia Consortium for Translational Studies; FACOMS: Friedreich Ataxia Clinical Outcome Measure Study; NA: Not applicable.

Background

Friedreich's ataxia (FRDA), a progressive neurodegenerative disease, affects 1 in every 50,000-100,000 individuals in the USA, making FRDA the most commonly inherited autosomal recessive ataxia [1–5]. Typically, onset of FRDA occurs between the ages of 5 and 20 years of age but it can present outside this range with some patients presenting as late as their 60s [6,7]. FRDA most commonly results from homozygous inheritance of *FXN* alleles that contain a trinucleotide GAA repeat expansion in intron 1 [1–5]. Normal alleles have fewer than 33 GAA repeats; 96% of patients with FRDA are homozygous for abnormal GAA expansions of 66–1500 repeats. The remaining 4% of patients carry a point mutation or deletion in one *FXN* allele and an expanded GAA repeat on the other [1–5]. The trinucleotide expansion disrupts transcription of *FXN* leading to deficiency of the protein frataxin in those with FRDA. The clinical severity of FRDA correlates with the length of the GAA expansion (particularly on the shorter of the two alleles) as assessed by age of onset, rate of progression, or amount of residual frataxin [1–5,8–10].

Frataxin, a nuclear-encoded mitochondrial protein, plays a crucial role in mitochondrial iron metabolism and iron homeostasis [1–5], particularly in the maintenance of iron-sulfur clusters for enzymes involved in oxidative phosphorylation, the Krebs Cycle, and other cellular events [11–13]. Frataxin deficient cells exhibit oxidative stress *in vitro*, mitochondrial iron accumulation, decreased ATP production, and cellular dysfunction [14]. While frataxin deficiency is ubiquitous across tissues in FRDA, cells most affected clinically in FRDA include large sensory neurons of dorsal root ganglia (DRG), the dentate nucleus of the cerebellum, upper motor neurons giving rise to the corticospinal tract, cardiomyocytes, pancreatic islet cells and other selected cells of the brain and retina [15]. In the present review, we briefly summarize the clinical features of the disorder (including novel aspects such as bone health) and the availability and rationale behind clinical care guidelines. We subsequently update the status of clinical trials and discuss the details of the present approaches as well as novel basic science understanding that shapes future investigation of FRDA.

Clinical features & care

Multisystem nature of FRDA

Traditionally classified as a neurodegenerative disease with ataxia as the most common presentation, modern viewpoints approach FRDA as a multisystem disorder with diverse manifestations that require a variety of clinical therapies and comprehensive care distinct from other neurological disorders [5]. In addition to ataxia and neurological dysfunction, patients with FRDA often develop cardiomyopathy, diabetes, scoliosis and hearing and vision loss [1–5,10,16] (Table 1)

Neurological

Limb and gait ataxia is the most common presentation in FRDA patients [10,16]. Other neurological features include dysarthria, absent reflexes, and loss of vibration and proprioception sensation [17]. The three major neuroanatomical systems affected by FRDA include the proprioceptive system, the dentate nucleus of the cerebellum and the corticospinal tracts [15]. Degeneration of these systems accounts for limb ataxia, spasticity, dysarthria, lower

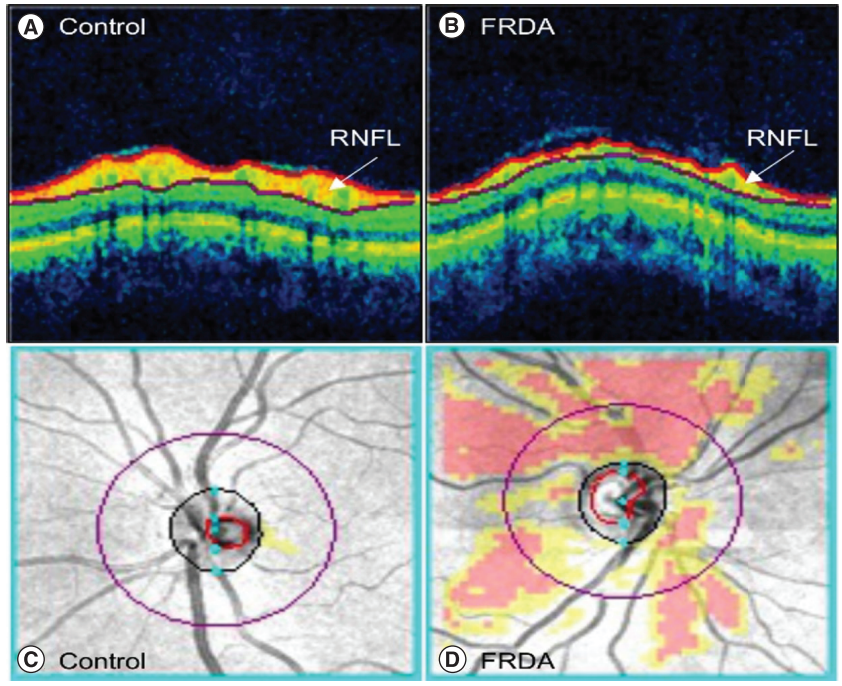

Figure 1. Retinal nerve fiber layer pathology in Friedreich's ataxia. Optical coherence tomography scans of the retina in **(A)** a healthy control subject (age and sex matched) and **(B)** a subject with FRDA. The RNFL (white arrows) is outlined in red. Overlay of RNFL thickness deviation map on fundus images of the optic disk in **(C)**the same healthy control and **(D)** the same subject with FRDA. Red and yellow regions reveal areas of the retina that deviate in thickness compared with the normal distribution. Yellow: <5th percentile, red: <1st percentile.
FRDA: Friedreich's ataxia; RNFL: Retinal nerve fiber layer.

extremity weakness and loss of proprioceptive sensation and deep tendon reflexes [15]. There is no symptomatic pharmacological treatment for the ataxia.

Visual, auditory and nonproprioceptive sensory systems are also affected in FRDA, giving rise to other neurological characteristics. These include vision loss (caused largely by optic atrophy and reduced retinal nerve fiber layer thickness related to retinal ganglion cell death), hearing loss (without loss of primary tone, reflecting auditory neuropathy), urinary urgency and neuropathic pain (reflecting sensory nerve loss). Neuropathy and spasticity can be treated symptomatically with agents for neuropathic pain (gabapentin, duloxetine, etc.) or spasticity (baclofen, tizanidine), though dosing changes over the course of FRDA as the disease evolves.

Vision

While most FRDA patients have some neuroophthalmological findings, significant afferent visual impairment is rare until later in the disease [18,19]. Early findings are diverse in FRDA including efferent abnormalities such as saccadic movements and fixation instability, abnormal neurophysiological findings in visual evoked potential tests, progressively decreasing low contrast visual acuity, impaired spatial perception, visual field abnormalities and reduced retinal nerve fiber layer (RNFL) on optical coherence tomography (OCT) scans [18–26]. Severity in all of these findings ranges from minimally abnormal to severe and typically correlates with GAA repeat length and age.

The most common cause of afferent visual dysfunction in FRDA is progressive optic neuropathy, beginning early in disease and continuing through the course of FRDA. This can either present as a slowly progressive event or as a rapid decline in vision similar to what is seen in Leber's hereditary optic neuropathy [20]. Optic neuropathy is most severe in patients with a presentation before age 10, with long GAA repeats or with point mutations including G130V [25]. The optic neuropathy of FRDA is characterized by loss of peripheral fields with later loss of central fields. Contrast letter acuity is also lost early. In the most severely affected patients vision progresses to levels worse than 20/800, a highly disabling situation. The optic neuropathy can be assessed using optical coherence tomography (OCT) which reveals moderate to severe thinning of the retinal nerve fiber layer RNFL (Figure 1) [18].

Surprisingly, when compared with MS patients with similar visual acuity, FRDA patients have thinner RNFLs, suggesting a slower progression with greater compensatory abilities of the visual system in FRDA [18].

Hearing

There is a wide phenotypic spectrum of auditory sensitivity and processing impairment among individuals with FRDA. The severity of auditory impairment shows a correlation, with GAA1 repeat length >500 increasing the likelihood of auditory and spatial processing difficulty in an individual [27,28]. Only 8–13% of individuals with FRDA develop with sensorineural hearing loss based on pure tone audiometry [27]. However, 90% manifest other types of hearing impairment associated with difficulty understanding speech when background noise is present and impairments in selective attention on a singular voice based on location. This type of hearing loss has been termed 'auditory neuropathy', showing preserved cochlear structures with axonopathy of the eighth nerve and auditory brainstem [28,29]. Abnormal brainstem auditory evoked responses (BAERs) have been identified in FRDA, associated with significant hearing loss [30]. Speech perception is greatly affected in FRDA, particularly when presented with a competing signal. Typically, FRDA individuals are only able to access about 50% of information available compared with their peers [31,32]. Because pure tones are affected to a minor degree, typical hearing aids are of little value. More sophisticated directional aids can help, though they are usually expensive [32].

Cardiac

Cardiac dysfunction is the leading cause of death for individuals with FRDA, accounting for about 60% of mortality [33]. Most people with FRDA show some form of cardiac abnormality on ECG or echocardiograms, including T-wave repolarization abnormalities seen in about 85% of individuals with FRDA [34–37]. FRDA patients also develop concentric left ventricular hypertrophy, with later appearance of fibrosis [38–40]. Whether hypertrophy and later fibrosis are obligately connected is unclear. Arrhythmias are also common in patients with FRDA, particularly atrial arrhythmias. Though atrial arrhythmias are not usually fatal in isolation, they can contribute to overall mortality in combination with other cardiac issues [38]. About 30% of FRDA patients die from heart failure, the most common cause of death for FRDA patients [34,38].

The direct clinical implications of structural heart disease are difficult to evaluate in individuals with FRDA. Due to progressive ataxia, individuals are often limited in their physical activity, making the assessment of cardiac dysfunction difficult to quantify [38,39]. However, clinically significant cardiac dysfunction can appear late in the disease as well as earlier, particularly during times of physiological stress. Diastolic dysfunction becomes discernable during times of volume overload or volume depletion, such as in the context of excess administration of i.v. fluids or during gastrointestinal illnesses associated with diarrhea or vomiting, respectively [39]. Monitoring FRDA cardiomyopathy is also complicated. Echocardiograms change slowly over time, and most parameters identified on echo have little prognostic significance. Assessment of cardiac strain has been useful in cross-sectional studies, but longitudinal analysis has not been useful [40–43]. Few FRDA-specific biomarkers exist, and assessment of classical cardiac biomarkers can be paradoxical. For example, serum troponin I values, usually a marker of cardiac damage in the setting of myocardial infarction, are elevated in individuals with FRDA even in the absence of symptomatology or structural heart disease [43,44]. While this may track with hypertrophy to some degree, the correlation is insufficient to connect troponin levels with cardiac changes in acute situations, and cardiac troponin I levels in FRDA individuals always require comparison to a baseline value for any interpretation.

Orthopedic – scoliosis & *pes cavus*

Scoliosis occurs in most patients with FRDA. Ninety percent of individuals with early onset of FRDA symptoms develop intermediate to severe scoliosis, while those who present later (>14 years old) are more likely to develop mild scoliosis or no scoliosis at all [45]. In FRDA, scoliosis is not always progressive. The main predictors of progression are symptom onset before the age of 10 years and presence of scoliosis before the age of 15 years [46–49]. In most cases, bracing appears to provide some slowing of progression, but curvature angles greater than approximately 45 degrees normally require surgery (spinal fusion).

Pes cavus is also common in individuals with FRDA. Occurring in 55–75% of FRDA patients, *pes cavus* results in an abnormally high foot arch that does not flatten with pressure [14]. Although *pes cavus* does not commonly contribute to morbidity, it may play a role in decreased functionality of the foot [1–5].

Endocrine – diabetes mellitus I (type 1) & II (type 2)

Around 10% of FRDA patients develop diabetes. Diabetes has a wide range of features among individuals with FRDA with the greatest determinant of prevalence and pathogenic mechanism being age [50–54]. Diabetes in FRDA can present as nonimmune 'type 1' (insulin-requiring) or insulin-resistant 'type 2', but more commonly presents as an intermediate between the two types [55,56]. Those FRDA patients who present with diabetes at an early age more closely resemble type 1 diabetes requiring insulin to prevent diabetic ketoacidosis [56], while individuals with later-onset FRDA can develop type 2 diabetes, with age and increasing adiposity being cofounding factors in the disease [54]. Early-onset diabetes is also associated with a greater genetic severity, and presence of diabetes is an independent risk factor for more affected neurological function in FRDA.

Other features of FRDA

Sleep apnea

Obstructive sleep apnea (OSS) has been documented in FRDA, though it remains understudied [57]. Posture, duration of disease and reduced strength in respiratory muscles have all been linked to OSS in FRDA, and the prevalence correlates with disease duration [57]. Scoliosis and deficits in chest wall mechanics are linked to the impaired airways that cause OSS, perhaps providing an explanation for its occurrence in FRDA [58]. In later disease, atrophy can appear in the brainstem in FRDA where the major respiratory neurons are localized, suggesting a neuroanatomical basis for OSS [58]. When severe, sleep apnea is generally treated through continuous positive airway pressure to prevent further cardiopulmonary and neurologic complications [5].

Bone density

Bone density in individuals with FRDA can become compromised as a result of multiple risk factors. Firstly, bone density in adults with FRDA is below the expected range, with 20% of adults with FRDA presenting with low areal bone mineral density (BMD) by dual-energy x-ray absorptiometry scanning [59]. Additionally, early onset of FRDA can diminish peak bone mass in children leading to later development of adult osteoporosis [60]. While there is no significant difference between the blood calcium levels of FRDA individuals and healthy controls, other pathophysiological reasonings for overall decreased BMD have been proposed. Early difficulty with ambulation and mobility may play a role in bone health and density, with less ambulatory individuals bearing little to no weight on their bones. Weight bearing exercises promote an increase and maintenance of BMD in children to accelerate bone growth. The use of wheelchairs at a young age creates effects on the BMD of children and young adults [61]. Additionally, FRDA may have implications in developmental or acquired deficits in skeletal muscle leading to a decreased BMD [62,63]. Despite these increased risks of decreased bone health, recommended dietary allowance values for bone health important nutrients are currently being met by less than 50% of adult individuals with FRDA [61]. However, 60.5% of individuals reported supplementation of either calcium, vitamin D3 or a multivitamin for bone health purposes [61].

Urination

A large number of people with FRDA report urinary dysfunction, usually a sense of urgency rather than true incontinence. This presumptively reflects abnormalities related to neuronal innervation of the bladder and other components of the parasympathetic nervous system, anticholinergic therapy can minimize symptomatology but is not curative.

Depression & mental illness

Another distinct under-recognized and understudied feature of FRDA is depression [64–70], with 92% of FRDA patients reporting symptoms of depression in some series. Depression uniformly affects quality-of-life, whether such depression is an endogenous disease-related feature or a reaction to disease-specific events [5]. The exact pattern of symptomatology can also vary between case series. In either case, no singular disease-specific therapy has been identified for treatment of depression in FRDA, though pharmacological interventions including selective serotonin uptake inhibitors are generally useful [5].

Care guidelines

The field of clinical FRDA research has seen a proliferation in studies aimed at exploring such factors as frataxin levels, disease progression, and disease-modifying agents, all of which potentially impact clinical care [71]. Unfortunately,

tangible improvements in clinical care in recent years are less well defined. There is at present no approved therapy that significantly alters disease symptomatology or progression; thus, providing care in FRDA remains challenging [71]. The multisystem nature of FRDA creates the necessity for both disease-specific guidelines for clinician care and a multidisciplinary approach to care treatment. In addition, the complexity and variation of FRDA symptoms onset create clinical challenges that are specific to FRDA [5,71]. In particular, the broad age differential (ages 5–90) of FRDA patients requires clinical approaches over the lifetime of patients.

The creation of clinical management guidelines has aided in resolving such challenges in several ways. Such guidelines provide a consistent framework to aid in healthcare decisions between patient and practitioner [71], particularly in situations in which the clinician is not well versed in FRDA. Clinical care guidelines simultaneously highlight the breaches in the evidence while providing a roadmap for the ongoing research that will one day underscore future revisions, which are expected in the upcoming year [71].

The current guidelines on clinical care management in patients with FRDA were developed by thirty-nine expert clinicians in the disease field from across the globe, with representation from the USA, Australia, Europe and Canada [71]. Each recommendation was assigned a grading (A–D) to specify the strength of evidence underlying the recommendation and to discern whether improved health outcomes were likely to arise through its application (consensus clin care guidelines). Those recommendations designated grade A were defined by evidence that could reliably guide practice [71], while assignments of grade D signified weak evidence backing the recommendation and that caution should be taken in its application [71]. In cases where no definitive grading level evidence was obtainable, good practice points were appointed, each formulated upon clinical experience and expert opinion [71].

Unfortunately, few controlled studies have at present identified guidelines or treatments with grade A or B evidence, highlighting the inherent gaps and difficulty in identifying effective interventions for FRDA patients. Consequently, most approaches to treatment of FRDA rely on good practice or expert observations [71]; thus, the major impetus of present guidelines is not directing clinicians toward novel therapies, but instead overcoming the hesitancy in prescribing standard of care symptomatic therapies to patients with FRDA. Essentially all pharmacological guidelines in FRDA reflect interventions based on symptoms or structural abnormalities (i.e., heart failure or hypertrophy) rather than disease-specific pathophysiology (such as frataxin deficiency mediated cardiac biology). Thus, all of the medications discussed in the present guidelines are derived from approaches to analogous situations in other diseases, including medications for neuropathic pain, spasticity or heart failure. Thus, as there are many manners to treat syndromes such as these, the guidelines put forward are truly guidelines, to be interpreted in the context of comorbidities, therapeutic urgency, patient preferences and abilities, and practicalities of healthcare systems including accessibility to treatments and health insurance. Judgement and medical art remain important aspects of the treatment of FRDA.

Interestingly, there are no identified medicines that are relatively contraindicated (even in chemotherapy) in a manner specific to FRDA, contrasting with disorders like type I Charcot Marie tooth [72–74]. One could argue that varenicline should be contraindicated based on its clinical trial being stopped due to progression of ataxia in some subjects, but the absence of discoveries of available medications specifically altering FRDA in a negative manner remains surprising. One possibility is that such discoveries would most likely be made during the presymptomatic period, as after diagnosis individuals become more reluctant to try novel approaches. Even new agents like SGLT2 inhibitors for low ejection frataxin heart failure have acquired little data in FRDA. These deficiencies illustrate that further studies of existing drugs through studies like large case series, and systematic trials of new agents (either through formal clinical trials or off-label use in justifiable situations) are needed to advance treatment, even as other research investigates the disease-specific pathophysiology of FRDA and gives rise to clinical trials of novel approaches.

Clinical trials

While FRDA currently has no approved treatment, widespread use of non-prescription antioxidants such as Vitamin E and coenzyme Q10 remains common among FRDA patients (Supplementary Table 1). While there may be suggested benefits in cardiac and skeletal energy metabolism from these supplements [75,76], they have not succeeded in blinded clinical trials for efficacy [75,76]. In those situations where supplements or antioxidants have been tested and shown modest benefit in open label studies (such as idebenone), they have failed to reach a registration level end points [77–85]. The recent failure of RT001 even suggests that reactive oxygen species (ROS) production, which provides the rationale for antioxidant use, may not be a large part of the pathophysiology of FRDA *in vivo* [86,87]. A variety of repurposed agents that raise frataxin levels to some degree (such as erythropoietin

and gamma interferon) have also shown no clear benefit in systematic trials [88–103]. Finally, with the exception of omaveloxolone, downstream modulators have not reached end points in registration level trials, though some open-label or biomarker-based studies have suggested the potential for benefit. Further work is needed on these agents such as deferiprone, PTC743, steroid therapy, letiriglitozone and related compounds [104–116].

New developments in FRDA

Omaveloxolone: NRF2 as a downstream target

FRDA can be treated in two ways: reversal of frataxin deficiency (gene therapy, protein replacement, epigenetic therapy, reversal of *FXN* silencing) or amelioration of pathogenic downstream events. While initial approaches were directed at downstream ROS production, such ROS production may be less important in FRDA than other downstream events. In particular, the lack of antioxidant reserve associated with abnormalities of activation of the transcription factor NRF2 appears to play a more important role than direct ROS production *in vivo* [116–118]. NRF2 binds to antioxidant response elements in DNA to activate genes protecting cells from oxidative damage. NRF2 is tonically degraded by the ubiquitin ligase Keap1. Cells and tissue from FRDA patients show deficiencies in NRF2 activation in response to oxidants, with low basal levels of enzymes (particularly heme oxygenase-1 [HO-1], NAD(P)H quinone oxidoreductase 1 [NQO1], Cu/Zn and Mn-superoxide dismutases) induced in response to oxidant stress. Specifically, in FRDA, NRF2 appears mislocalized and fails to enter the nucleus in FRDA cells; consequently, little activation of these enzymes occurs even in the presence of oxidant stress. Elevated levels of KEAP1 have also been found in FRDA models, which would shut off NRF2 [116–123]. Augmentation of NRF2 levels and activation should reverse these events. Restoration of NRF2 with EPI743 or sulforaphane in FRDA cells models has also been shown to block ferroptosis, an iron-based cell death mechanism in FRDA [124].

NRF2 activation thus offers a target for downstream pharmacological intervention in FRDA. Several agents such as omaveloxolone and dimethyl fumarate can increase levels of NRF2 by blocking its binding to Keap1 and thus preventing its degradation [125–128]. DMF and omaveloxolone appear beneficial in cell models, while omaveloxolone has proceeded to clinical trials. A phase II dose-finding study in FRDA reveals a benefit on neurological exam scores in FRDA as well as benefit in correcting abnormal lipid metabolism; it also reverses intrinsic biomarkers of FRDA such as decreased ferritin levels [125]. In a pivotal study at 160 mg per day, omaveloxolone led to a clinically significant improvement in neurological exam scores and a tendency toward improvement in activities of daily living and a variety of secondary outcome measures [127]. Benefit was maintained over 2–3 years as revealed by analysis of open-label extension data showing that the rate of progression over 2–3 years dropped substantially from natural history controls. Adverse events were relatively limited, suggesting that omaveloxolone may provide a safe, efficacious therapy for FRDA.

Frataxin restoration

A second major therapeutic advance in FRDA may arise from a set of interventions referred to as frataxin restoration. The primary cause of FRDA is congenital deficiency of active frataxin leading to mitochondrial dysfunction and other downstream events [1–5]. In theory, sustained restoration of frataxin, if done to a sufficient degree and at an early enough time and in sufficient numbers of cells, should provide an ideal treatment if it is free of adverse events. Experimental data supports this as removal of the GAA repeat or transfection of frataxin cDNA in cell culture restores cellular properties [129]. One way to restore frataxin is via epigenetic approaches to reactivate the gene. In FRDA mouse models, epigenetic activation of *FXN* with HDAC inhibitors increases frataxin levels and reverses behavioral deficits [130–134]. A separate approach is to restore frataxin directly with protein or gene replacement therapy. Protein replacement therapy restores cellular function *in vitro* and reverses cardiomyopathy in FRDA mouse models [135–137]. Gene therapy ameliorates disease in virtually all tissues it reaches in FRDA mouse models [138–141]. At a scientific level, the concept that frataxin restoration may be highly efficacious certainly holds; frataxin replacement appears to be ideal for treatment of FRDA subject to the constraints of finding the correct dosage, determining when to intervene, maintaining a critical duration of efficacy and providing ability to penetrate affected tissues.

The difficulties in frataxin replacement via protein replacement or gene therapy are mainly pragmatic issues. For protein replacement specifically, the large size and need for broad distribution of frataxin make it difficult for administration of cell-permeable forms of frataxin to reach all relevant cells. In a phase I study, CT1601(tat frataxin), increased functional frataxin in skin, buccal cells and blood [142]. However, its ability to alter downstream

targets and disease related tissues is unknown, and its potential to readily cross the blood–brain barrier may be incomplete. At present, CT1601 is on hold reflecting preclinical issues in primates.

Frataxin gene therapy in humans also may be limited by distribution issues. Most gene therapy paradigms at present utilize different serotypes of AAV vector to deliver the *FXN* gene, each targeting different cells, and few readily target brain without intraparenchymal administration [143,144]. This leaves cardiac tissue as an achievable target with little penetration into brain. Another challenge is that the development of immunity to AAVs associated with initial treatment likely prevents repeat administration [145]. The need to transduce large numbers of cells leads to a different problem: overexpression of frataxin in some cells, leading to toxicity [146]. The interplay between transduction of insufficient numbers of cells and excessive levels of frataxin can be difficult to navigate. Conceptually, gene therapy should couple a vector and delivery mechanism that transduces a large number of cells but produces only the minimum necessary amount of frataxin once introduced. This can be difficult to achieve and may require more optimization. Although use of gene editing methods may alleviate the toxicity from overexpression, the difficulty in delivery of these agents is more pronounced. Although scientifically sound, gene therapy and gene editing as treatments for FRDA may await improved delivery approaches.

Attempts to reactivate *FXN* expression have shown some promise in trials, but also have encountered obstacles. HDAC inhibition with RPG-2833 reached clinical trials and showed evidence of reactivation in short phase I study, but the potential for toxic metabolites appeared [134]. In addition, tissue selectivity in penetration and/or efficacy confound this therapeutic approach. Novel agents such as GeneTac may overcome many of these issues [147]. GeneTac, (DT216) designed as a selective agent to overcome *FXN* silencing by binding to the GAA repeat and recruiting transcription factors, shows wide tissue distributed in animals, making it an excellent candidate if no unexpected adverse events appear.

Still, the approaches of frataxin restoration so far have not truly had to address some of the limits of this type of therapy, in particular the questions of when must frataxin be restored, where must it be restored and how much is the minimum amount of restoration needed for efficacy. Knowing these answers may be needed to optimize therapy. New understanding of the mechanism of *FXN* silencing and of the exact neuroanatomical locations of neurodegeneration and its exact timing are now beginning to answer such questions.

Advancements in the understanding of FRDA: application to therapeutic interventions

It is widely agreed upon that the GAA repeat expansion leads to epigenetic silencing of the *FXN* gene in FRDA [148–159]. Because the GAA repeat expansion is present in every cell in FRDA, it has been historically presumed that the *FXN* gene is silenced to the same degree in every cell, resulting in all cells equally expressing 5–30% of non-FRDA frataxin levels based on GAA repeat expansion length. The first indication that an alternative model of gene silencing in FRDA should be considered emerged from studying an FRDA cell model that contained a transgene with ~200 GAA triplets upstream of a fluorescent reporter [151]. The GAA expansion acted as a source of spreading repressive chromatin that resulted in epigenetic silencing of the transgene, but not in every cell. The resulting phenotype was a stochastic pattern of gene silencing within a population of cells where some cells, although they too contained the GAA repeat expansion, escaped silencing. This variegated pattern of expression is analogous to position effect variegation (PEV), a phenomenon that was originally described in *Drosophila* [160]. In PEV, a gene is located abnormally close to a source of repressive chromatin, perhaps due to an inversion, resulting in epigenetic silencing of the gene, but only in a proportion of cells. The subsequent phenotype in *Drosophila* is a mosaic compound eye. Two recent studies, one in patient-derived cells and the other in a large clinical dataset, further support that the mechanism of *FXN* silencing in FRDA is analogous to PEV [148,161]. These studies showed that patients with shorter GAA repeat expansions retain a population of cells that escapes *FXN* silencing even while containing a GAA repeat expansion. The proportion of escaped cells reaches a minimum when GAA repeat length approaches 500–700 triplets, producing a ceiling effect on everything downstream (including clinical severity; Figure 2)

Shifting the view of *FXN* gene silencing to the PEV model has revealed a subpopulation of patients, those with >700 GAA triplets, that is relatively homogenous in their disease progression. This has important implications for pre-clinical and clinical data analysis and reveals that the severity (or presence) of disease features in FRDA is not dictated by relative frataxin deficiency alone, but rather the relative proportion of cells/*FXN* genes that escape GAA repeat-mediated silencing. Refinement of this model will allow better understanding of the selection and stratification of subjects for clinical trials as well as interpretation of the results of such trials.

Perhaps more importantly, the concept of variegated silencing leads to a reevaluation of the quantification of frataxin levels and their restoration in disease. Disease severity reflects the number of cells that are maximally

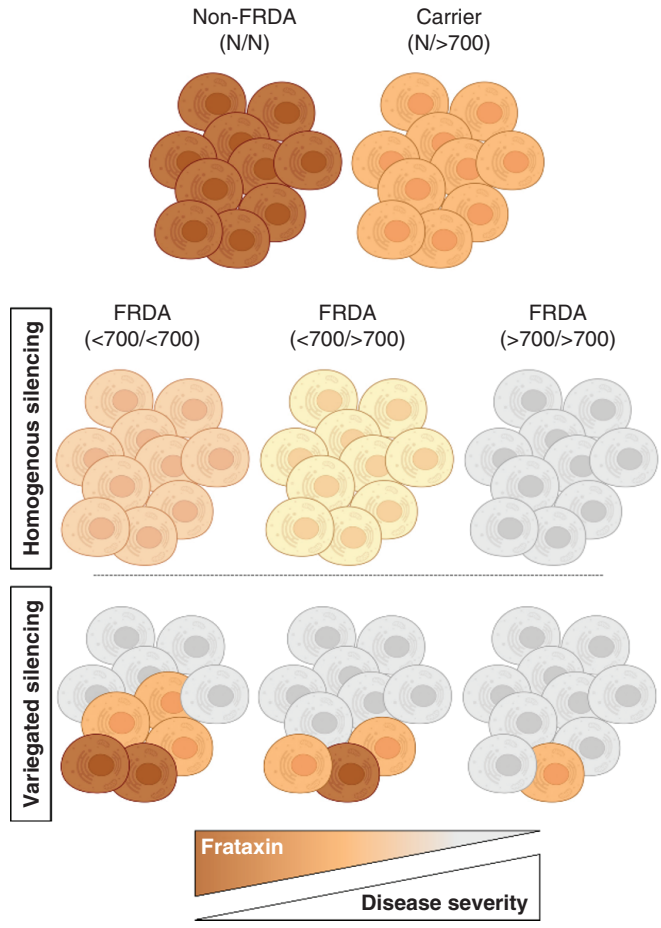

Figure 2. A model of variegated silencing in Friedreich's ataxia. Each cluster of 10 cells represents a theoretical person who does not have FRDA (non-FRDA), is a carrier of one GAA repeat expansion (carrier) or is one of three people who have FRDA with various GAA repeat lengths. Parentheses indicate the GAA repeat lengths: N = normal length GAA; >700 = more than 700 triplets; <700 = fewer than 700 triplets. The relative color saturation of cells represents the relative amount of frataxin (darker color = more frataxin). Homogenous silencing (top set of FRDA subjects) shows the same amount of frataxin in every cell, and less frataxin in each cell as the GAA repeat length increases. Variegated silencing (bottom set of FRDA subjects) shows how most cells in people with FRDA have very little frataxin (gray/no color), and few cells have escaped silencing, a proportion that increases with decreasing GAA repeat length. Protein/RNA assays would give the same result in either silencing model for a given repeat length i.e. shorter repeat patients would have ~30% residual frataxin. Recent studies however support the variegated silencing model in FRDA.
FRDA: Friedreich's ataxia.

silenced, not the absolute frataxin level. This explains why carriers who have the lowest levels manifest no symptoms: they still have one functioning *FXN* allele in almost all cells. This also suggests why the carriers with lower levels of frataxin differ from the patients with a short, expanded allele. They have similar frataxin levels, but the mechanism by which they got such levels differs. Thus, the benchmark of restoring levels of frataxin to carrier levels is flawed. In terms of restoration of frataxin level, variegated silencing emphasizes the importance of reaching many cells (particularly affected ones) more than raising the level astronomically in a few cells. In other recessive diseases, the amount of protein needed to prevent the appearance of a phenotype is frequently less than 10% of normal. New studies will need to determine the amount of frataxin needed at an individual cell level in order to better inform future approaches.

The developmental component & neuroanatomy of FRDA

Although classically viewed as a neurodegenerative disorder, many clues suggest a major developmental component to FRDA, particularly in the loss of peripheral nerve components [162]. Deep tendon reflexes are lost before clinical presentation in most individuals, and many patients recall never having reflexes even from young age. Intrinsic hand muscle atrophy and *pes cavus* also develop before presentation, suggesting long-standing loss. In addition, spine size is small in FRDA and MRI scans reveal dorsal column atrophy at the earliest scans [163].

In recent years, systematic scientific examination reveals the loss of proprioceptive input and dorsal column function may be near-complete by presentation. First, autopsy studies suggest that many of the dorsal roots fail to enter the spinal cord, consistent with a longstanding developmental injury [163]. In addition, somatosensory evoked potentials and sensory nerve action potentials are absent at presentation and, if retained, fail to progress over time [164–166]. Using MEG, a more sensitive manner to detect such potentials, somatosensory response can be identified at presentation but are of extremely low amplitude and are delayed in reaching the cortex. In addition, the size of such potentials correlates with genetic severity (GAA repeat length) but not disease duration [167–170]. All of these suggest an early origin to somatosensory dysfunction, with significant CNS remodeling before clinical

presentation. Such dysfunction depends on early genetic events rather than disease duration and changes the 'textbook' anatomy of FRDA, suggesting that while proprioceptive loss provides an early mechanism in disease causation, it does not contribute to progressive disease and may not represent a target for restorative therapies.

Where are the appropriate sites of active neurodegeneration during the progression of FRDA? Most likely the dentate nucleus of the cerebellum and the motor cortex provide the major, specific sites of degeneration, with other areas such as the retina playing roles in specific disease features [3]. In addition, sites such as the Purkinje cells may not die but appear to remodel or repair over the course of time, suggesting pathological involvement [171]. Understanding this issue is crucial to the advancement in new therapies that require specific neuroanatomic targeting, such as gene therapy. Even still, many of the neurophysiological features of FRDA may reflect age of onset more than disease duration [66–164,172], emphasizing the degree of abnormality that precedes symptomatic presentation.

The importance of developmental influences also provides a rationale for questioning the detailed relevance of animal models in FRDA. Models in which frataxin levels are knocked down after birth or later may not provide evidence of developmental events. Consequently, results from such models may not readily extrapolate to predictions on drug response in human diseases. Thus, interpretation of the role of animals and their utility is important for consideration in therapeutic development programs. This will require understanding of the specific ways that animal models match neuroanatomically selective biomarkers in human FRDA.

Conclusion

FRDA is a progressive, neurodegenerative disease that affects both children and adults. Disease specific clinical care guidelines have been adapted to urge physicians to treat each FRDA symptom individually using standard of care therapies. There have been advances in areas of drug development such as NRF2 activation and frataxin restoration, which could have implications on novel, effective therapies in the future. Likewise, new perspectives on variegated gene silencing in FRDA could have implications on how future therapies approach the application of frataxin restoration, as well as lead to better stratification of subjects in clinical trials and improve pre-clinical/clinical trial data analysis. Lastly, evidence suggested a developmental component of FRDA could play a large role in determining target areas for novel therapies.

Future perspective

The past 25 years have seen enormous growth in research on FRDA leading to a better understanding of the disease at all levels. This includes refinement of the clinical phenotype, improved clinical care through collaboration and systematic observation, and Basic and clinical research leading to clinical trials delivering at least one agent to the doorstep of approval. Still, further work is needed to translate the present findings to optimal clinical response in patients, particularly in regard to crucial questions:

- How long can the benefits of downstream agents like omaveloxolone last? While present data does not show any wearing off, homeostatic mechanisms at some point will likely blunt the effect of drug acting downstream from frataxin deficiency. At that point new agents will certainly be necessary acting either on other components of the pathophysiology or on frataxin deficiency itself;
- How much do deficiencies in understating of the detail of frataxin restoration prevent success in clinical trials? New information from concepts like variegated silencing and new findings on the developmental pathology and anatomy in FRDA can refine approaches to restoration of frataxin. That may be enough for success, but developments outside the FRDA field such as development of new delivery systems and understanding of general toxicities of gene therapy and protein restoration may also prove important.

Overall, such questions lead to a situation in which further knowledge is still needed for optimization of therapy in FRDA.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/suppl/10.2217/nmt-2022-0011

Author contributions

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