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Deciphering the missing links between Friedreich ataxia and multiple sclerosis for targeted drug development

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Neurodegenerative diseases (NDDs), such as Friedreich ataxia (FA) and multiple sclerosis (MS), are marked by progressive neurodegeneration and heterogeneous pathologies. Despite distinct aetiologies, FA and MS appear to share some overlapping molecular mechanisms, including iron and lipid dysregulation, mitochondrial dysfunction, oxidative stress, and neuroinflammation. Recent research, including comparative transcriptomic analyses, offers valuable insights into shared disease pathways, with implications for potential biomarkers and therapeutic targets. In this review, we explore the shared pathological features and disease mechanisms in FA and MS, highlighting how delineating these shared pathways could inform early diagnostic strategies and support the development of targeted, mechanism-based interventions, including opportunities for drug repurposing.

Keywords: drug repurposing; Friedreich ataxia; inflammation; mitochondrial dysfunction multiple sclerosis; oxidative stress; targeted therapy

Introduction

NDDs are characterised by the progressive loss of neurons, accompanied by the gradual impediment of neuronal function and subsequent manifestation of symptoms causing various disabilities.(p1) Some NDDs result mainly from inherited gene mutations, whereas others are influenced by a combination of genetic and environmental factors, exemplified by FA and MS, respectively. Although each condition has its own unique molecular mechanisms, they share common pathways that trigger neuronal death.(p2) The complex pathogenesis of each NDD and their heterogenous nature make it challenging to design targeted therapies that would prevent the onset of symptoms and/or benefit patients at different clinical stages. Consequently, NDDs remain incurable and the limited therapies currently available are aimed at retarding disease progression or alleviating the worsening of symptoms. This has raised an urgent need for accurate and sensitive biomarkers that can inform early diagnosis and reliable prognosis.

The identification of common and distinctive molecular pathology (e.g., mitochondrial dysfunction, ferroptosis, oxidative stress, and neuroinflammation) and corresponding biomarkers remains the first crucial step in novel drug target identification for NDDs.(p3) Driven by the efforts to connect different NDDs, researchers investigated the transcriptional changes of nuclear-encoded mitochondrial genes in FA and compared the outcome with other NDDs, including MS.(p2) This forms a strong conceptual framework given that mitochondrial dysfunction is a common hallmark across different NDDs. A total of 19 genes detected in patients with FA and MS were demonstrated to have pairwise intersections. The expression of key genes implicated in cell metabolism [e.g., encoding alcohol dehydrogenase 5 (class III), chi polypeptide (*ADH5*) and lactate dehydrogenase B (*LDHB*)], mitochondrial genome maintenance [e.g., solute carrier family 25 member 36 (*SLC25A36*)], mitochondrial oxidative phosphorylation (e.g., ubiquinol-cytochrome *c* reductase binding protein (*UQCRB*)], mitochondrial protein

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function [e.g., DnaJ heat shock protein family (Hsp40) member C19 (*DNAJC19*) and mitochondrial ribosomal protein L1 (*MRPL1*)], lipid metabolism [e.g., sterol carrier protein 2 (*SCP2*)], and cell signalling functions, including proliferation, differentiation, and apoptosis [e.g., mitogen-activated protein kinase 9 (*MAPK9*)] is downregulated in both FA and MS. This information enables the establishment of a mechanistic map to inform the design of new therapies that could benefit both FA and MS. In addition. the gene expression levels of the inflammatory marker, heat shock protein family A (Hsp70) member 1A (*HSPA1A*), increased in both conditions, whereas that of the DNA repair/synthesis gene, poly(ADP-ribose) glycohydrolase (*PARG*), was upregulated in patients with FA but downregulated in those with MS, indicating the presence of distinct disease pathways.[(p2)] Although it is unclear how these gene expression changes impact disease phenotype, the outcome of this study provides a good starting point, revealing potential biomarkers and drug targets that could offer new candidate genes for testing in patients to confirm molecular hallmarks of NDDs at a personalised level.

In this review, we identify the commonalities between FA and MS and consider how these might facilitate the development of novel drugs or repurposing of existing therapies to target the overlapping symptom profiles of different NDDs. FA and MS have been chosen for this investigation for several reasons. First, these conditions are significant causes of morbidity and mortality, with FA being the most common form of hereditary ataxia and MS prevalence increasing in every world region between 2013 and 2020.[(p4)],[(p5)] Second, both conditions demonstrate variability in symptom onset, severity, and prognosis. Third, diagnostic delays are known to impact treatment options and outcomes, with difficulties in predicting disease progression impacting the efficacy of therapeutic interventions.[(p6)] Finally, while FA and MS share common pathogenesis, pathologies and symptoms, misdiagnosis of both conditions is often a result of the lack of understanding of the underlying mechanisms driving disease progression or the common symptoms that affect motor function experienced by patients with either disease. In addition, MS-approved drugs, such as dimethyl fumarate, are now being considered in FA trials. We also discuss the shared pathogenesis and therapeutic links between FA and MS (Figure 1) and explore targeted drug development, focussing on agents that can address iron/lipid dysregulation mitochondrial dysfunction, oxidative stress and inflammation and repurposing those that are being trialled or are used in NDDs (Tables 1 and 2).

Friedreich ataxia: emerging therapeutic horizons and key considerations

FA is an inherited and chronic debilitating disease that is more prevalent in Caucasian populations, with one in 29 000 individuals affected and a carrier rate of one in 85.[(p7)] The first symptoms typically present at the age of 5–25 years and become progressively worse. Within 10 years from diagnosis, patients usually become wheelchair bound because of the degeneration of sensory neurons in the dorsal root ganglion of the spinal cord.[(p8)] Approximately 59% of patients experience an early death as a result of cardiac complications.[(p9)] This autosomal recessive disease is characterised by the accumulation of more than 43 guanine–adenine–adenine (GAA) repeats in the gene encoding frataxin (*FXN*) (most patients have 600–900 repeats, whereas others can have as many as 1700 repeats), abnormal epigenetic changes that regulate gene expression without DNA alterations, *FXN* suppression and subsequent iron accumulation, oxidative stress and inflammation in vital organs.[(p10)] Eventually, FA becomes a multisystemic disease because cells of any organ that depend on FXN to regulate mitochondrial function and iron metabolism gradually succumb to apoptosis.[(p10)]

There is no cure for FA and treatment efficacy is challenged by the genetic heterogeneity and onset of the condition. The first and only approved treatment, omaveloxolone (Omav; Skyclarys), has only been available to patients over the age of 16 in the USA, Canada, Brazil, UK and countries within the European Union since 2023.[(p11)] In July 2025, Omav was clinically approved by Therapeutic Goods Administration for patients in Australia and eligible individuals can express their interest to join the Access Program.[(p11)],[(p12)] Omav was not designed to target the genetic cause of FA, that is, to increase *FXN* gene or protein levels, and it primarily activates the nuclear factor, erythroid derived 2, like 2 (Nrf2) redox pathway, reducing oxidative stress and inflammation.[(p13)],[(p14)] However, this drug was investigated in adults carrying only 620–740 GAA repeats, which is a narrow subset of the genetic heterogeneity of FA, and it is not available for patients younger than the age of 16 because of certain adverse effects (e.g. upper respiratory infections and elevated liver enzyme levels indicating organ inflammation or damage) observed in adult patients.[(p10)],[(p11)],[(p15)] Therefore, the trial outcomes raise concerns about complications resulting from long-term use of Omav and generalising its efficacy in all patients with FA, including those with shorter or longer repeat lengths than that of the trial participants. Ongoing clinical studies are aiming to determine the safety and efficacy of Omav in patients with FA younger than 16 years of age but there is still a need to expand the clinical menu of drugs to address disease heterogeneity and multiple pathological processes driving the symptoms of this condition.[(p16)]

Another Nrf2 activator, dimethyl fumarate (DMF; Tecfidera), is clinically approved for the treatment of MS and has been repurposed in a Phase II trial involving patients with FA.[(p17)],[(p18)],[(p19)] Preclinical data using FA models showing increased *FXN* levels and Nrf2 induction initiated this trial, which offers promise for clinical translation.[(p17)],[(p20)] The trial will evaluate the efficacy of DMF in regulating gene and protein expression of FXN, and biomarkers of the Nrf2 pathway and mitochondrial biogenesis, safety and tolerability, changes in cardiopulmonary exercise outputs, echocardiographic measures, Scale for the Rating and assessment of Ataxia (SARA), modified Friedreich Ataxia Rating Scale (m-FARS), 9-hole pegboard test (9HPT), EQ-5D, and Activities of Daily Living (ADL)/Instrumental Activities of Daily Living Scale (IADL).[(p18)] This multidimensional evaluation aims to enhance the ability to detect mechanistic, functional, and clinical benefits. However, the outcomes of the study have yet to be reported.

Coenzyme Q10 (CoQ10) is an endogenous lipophilic antioxidant present in the membranes of mammalian and plant cells and organelles, such as mitochondria.[(p21)] It is an essential

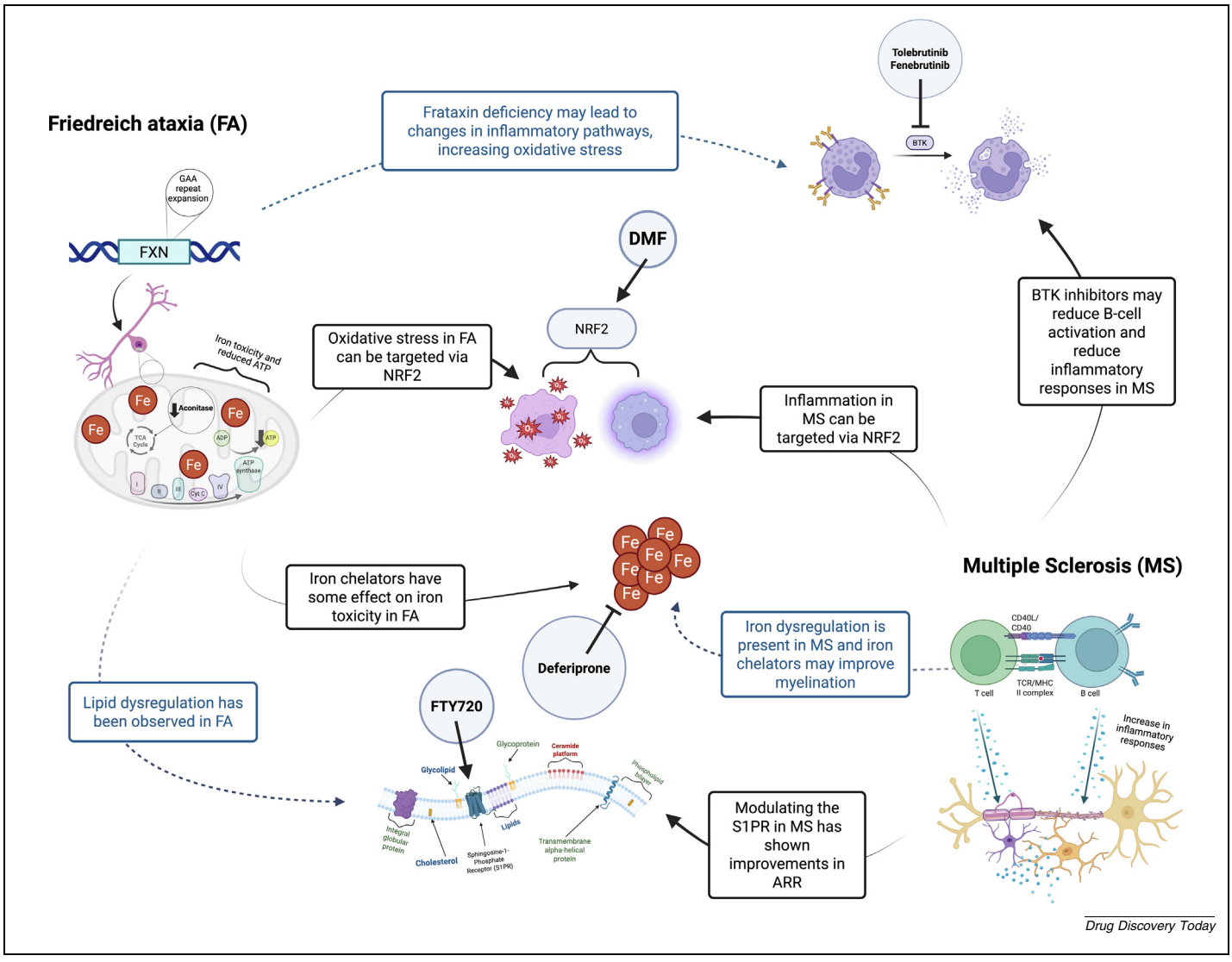

FIGURE 1

Potential links between FA and MS. Oxidative stress, iron dysregulation, and metabolic disturbance have been shown to be involved mechanisms in both FA and MS. DMF, which acts on the antioxidant modulator, NRF2, has been explored in both FA and MS, with positive results, indicating potential similarities in metabolic dysfunction in both diseases. Additionally, deferiprone has shown modest improvements in FA but may be repurposed in MS treatment, showcasing positive results in remyelination in vivo. Since the approval of fingolimod, an S1PR modulator, for MS treatment, lipid alteration has been identified in *in vitro* and *in vivo* FA models, identifying another potential similarity in disease progression. Despite no direct links currently identified between the inflammatory responses in MS and the mechanisms in FA, enzymes such as COX2 have been shown to be altered in FA and could suggest a larger role for inflammation pathways in the disease. Abbreviations: ADP: Adenosine diphosphate; ATP: Adenosine triphosphate; ARR: Annualised Relapse Rate BTK: Bruton's tyrosine kinase; CD: Cluster of differentiation; COX2: cyclooxygenase-2; DMF: dimethyl fumarate; FA: Friedreich ataxia; Fe: iron; GAA: guanine-adenine-adenine; MHC: Major histocompatibility complex; MS: Multiple sclerosis; NRF2: Nuclear factor erythroid 2-related factor 2; S1PR: sphingosine-1-phosphate receptor; TCR: T cell receptor.

component of the mitochondrial electron transport chain, which facilitates the generation of ATP and protects cells from toxic free radicals. As such, CoQ10 has been regarded as a prospective drug candidate to address the mitochondrial dysfunction and oxidative stress observed in FA. Clinical trials involving patients with FA have produced conflicting results, with longitudinal studies presenting improved cardiac and skeletal muscle mitochondrial energy synthesis, but minimal neurological benefits, despite symptoms appearing to be stabilised, as determined by the International Cooperative Ataxia Ratings Scale (ICARS).[p22],[p23] This discrepancy raises questions about the ability of CoQ10 to cross the blood–brain barrier (BBB) effectively or achieve therapeutic concentrations in neural tissue. Future research could focus on improved drug delivery platforms and combination strategies rather than on monotherapy. Comprehensive reviews of the therapeutic potential of CoQ10 for treatment of other NDDs, including MS, have been published previously.[p21],[p24],[p25],[p26]

Other antioxidants have also been investigated in the context of FA, such as lipoic acid (LA/ALA), which is involved in the scavenging of ROS and facilitating the activation of Nrf2.[p27],[p28] ALA has been shown to be effective at improving FXN and Nrf2 expression in cellular models, which should be further investigated *in vivo*.[p27] Defective cerebral iron dysregulation

TABLE 1

FA therapeutic agents clinically approved or being investigated in MS

Target	Current therapeutics	Role in FA	Potential use in MS	Refs
NRF2 activators	Omaveloxolone (Omav, SKYCLARYS)	Activate *NRF2*, a key modulator of oxidative stress Targeting *NRF2* using Omav improved mROS *in vitro* and improved mFARS scores in MOXIe trial	*NRF2* is involved in regulating anti-inflammatory genes *NRF2* has already been established as a therapeutic target via delayed-release DMF	(p13), (p14), (p66)
Mitochondria activators	Lipoic acid (LA/ ALA)	ALA has a role in scavenging ROS, improving mitochondrial biogenesis, and activating transcription factors, such as *NRF2* ALA improved *FXN* and *NRF2* expression in FA cellular models	Phase II clinical trial was recently published, investigating LA in MS. Although mobility was not improved, there were improvements in whole-brain atrophy. However, this was also accompanied by LA-associated proteinuria	(p27), (p28)
Iron chelators	Deferiprone (Ferriprox)	Iron accumulation is an established consequence of frataxin deficiency Dentate nuclei iron deposits improved following treatment with deferiprone in a 6-month trial but did not improve ICARS or FARS scores	Iron levels are dysregulated in MS *In vitro* investigations showed improvements in CD4+ and CD8+ cell proliferation *In vivo* investigations using mouse models reported improvements in myelination	(p30), (p31), (p32), (p34)
Electron transport chain	CoQ10	Dysregulated mitochondrial function and oxidative stress are hallmarks of FA Pilot study investigating CoQ10/vitamin E administration showcased improved cardiac and skeletal muscle bioenergetics, with limited improvement in ICARS scores	Oxidative stress and inflammation are hallmarks of MS Retrospective analysis of MS patient data found reduced ROS following CoQ10 treatment *In vivo* investigations in mouse models showed CoQ10 administration improved CPZ-induced demyelination	(p22), (p24), (p25), (p26)

Abbreviations: ALA: Alpha lipoic acid; CD: Cluster of differentiation; CoQ10: Coenzyme Q10; CPZ: Cuprizone; DMF: dimethyl fumarate; FA: Friedreich ataxia; FARS: Friedreich ataxia rating scale; FXN: frataxin; LA: ICARS: International cooperative ataxia rating scale; Lipoic acid; mROS: mitochondrial reactive oxygen species; MS: multiple sclerosis; NRF2: Nuclear factor erythroid 2-related factor 2; ROS: reactive oxygen species.

appears to be a common feature of NDDs, including FA and MS. Hence, iron chelation therapies are under investigation to reduce excessive iron deposits that are responsible for the degenerative changes.[p29] An attractive feature of iron chelators (e.g., deferiprone) is their ability to penetrate the BBB, and magnetic resonance imaging has demonstrated the effective reduction of cerebral iron levels following treatment.[p30],[p31],[p32] A small clinical trial involving nine patients with FA determined that 6 months of treatment with 20 mg/kg/day or 30 mg/kg/day deferiprone effectively reduced iron accumulation in the dentate nuclei; although speech, hand dexterity and gait improved, this was determined to be only a 10% improvement according to ICARS.[p33] Low (20 mg/kg/day) doses of deferiprone appeared to minimise FA progression in patients with mild symptoms but higher doses (40 mg/kg/day and 60 mg/kg/day) resulted in adverse effects and worsening of ataxic symptoms, respectively.[p34] Iron chelation therapy in FA is biologically plausible and supported by preliminary evidence, but current data are limited, safety concerns remain, and clinical benefits appear to be modest. Nevertheless, a growing body of preclinical and clinical evidence to support the benefit of iron chelators in attenuating cardiac pathology, improving motor function and increasing FXN levels has maintained research interests in using them for FA treatment.[p35],[p36],[p37],[p38]

The regenerative capacity of stem cells has made them an attractive option to cure and/or treat NDDs. Although the clinical application of stem cell therapy is restricted by the risk of tumour formation because of residual undifferentiated cells post transplantation, this has not deterred research investigating the possibility of using allogeneic transplantation of bone marrow cells carrying copies of wild-type *FXN*, to replace FA-affected sensory neurons in the dorsal root ganglia in animal models.[p39] This research had yielded promising neuroprotective effects and improved motor function in the animals that received the transplant.[p40] These positive findings were reflected in other studies in which bone marrow-derived mesenchymal stem cells from wild-type (allogeneic transplantation) or YG8 FA (autologous transplantation) mice were injected into the latter group of animals, or transplanted human umbilical mesenchymal stem cells were injected into an cytosine arabinoside-induced FA mouse model, significantly delaying neurodegeneration in the dorsal root ganglion and cerebellum, respectively.[p41],[p42] Stem cell therapy for FA is conceptually promising but remains experimental. Despite encouraging animal data, significant hurdles remain for clinical translation, including the need for robust long-term evaluation of its safety, mechanistic clarity, and feasibility.

The potential of complementary therapeutic strategies, such as dietary and lifestyle interventions, in FA has been comprehensively reviewed elsewhere.[p43] Sourced from foods such as meat, fish, and nuts, Vitamin B_1 (thiamine) and a vitamin B_3-derivative (nicotinamide) have dominated dietary research in FA. Collectively, these studies showed improved FXN protein levels and increased interventricular septum thickness and deep tendon reflexes although no neurological improvements were observed.[p44],[p45] Increased movement (e.g., walking activity) monitored by wearable sensors was correlated with decreased clinical impairment scores.[p46] These strategies appear adjunctive rather than serving as primary therapies, offering modest systemic benefits but limited neurological impact. Thus, larger, controlled trials are needed to confirm efficacy.

The clinical impact of the above interventions in FA is often challenged because of the limited number of trials and the small participant cohort size, which often necessitate the inclusion of

TABLE 2

MS therapeutic agents clinically approved or being investigated in FA[a]

Target	Current therapeutics	Role in MS	Potential use in FA	Refs
NRF2 activators	DMF (BG-12, Tecfidera)	DMF is approved disease-modifying therapy for treatment of MS, acting through *NRF2* modulation Treatment with DMF showed reductions in new and enlarging T2 lesions in DEFINE/CONFIRM trial ENDORSE trial conducted 5 years post-DEFINE/CONFIRM indicated improved T1 and T2 lesions	*In vitro* investigations of DMF showed improvements in frataxin expression DMF-FA-201 is a Phase II clinical trial aiming to determine safety and efficacy of DMF in patients with FA	(p18),(p19),(p57),(p58),(p65)
BTK inhibitors	Tolebrutinib	BTK is a tyrosine kinase involved in B cell and myeloid cell development B cell activation leads to secretion of proinflammatory cytokines (e.g., TNFα and IL-6) Treatment with tolebrutinib showed reductions in new and enlarging T2 lesions in a Phase III clinical trial	Although primary cause of FA is not via inflammation, the latter still be a relevant pathway because it contributes to ROS production In addition, COX2, which is involved in promoting inflammatory response, is increased in *in vitro* and *in vivo* FA models	(p49),(p50),(p94),(p95)
	Fenebrutinib	Phase II clinical trial (FENopta) is investigating efficacy of fenebrutinib in MS		
Lipid metabolism	Fingolimod (FTY720; Gilenya)	Fingolimod is an approved disease-modifying therapy for treatment of MS, acting through S1PR modulation FREEDOMS clinical trial showcased improvements in annualised relapse rate following treatment with fingolimod	Lipids are involved oxidative stress and apoptosis Lipid profile is altered in FA and could contribute to iron toxicity and neurodegeneration	(p56),(p63),(p64)
	Lipoic acid (LA/ALA)	ALA has a role in scavenging ROS, improving mitochondrial biogenesis, and activating transcription factors, such as *NRF2* Phase II clinical trial on LA was published in 2026, which did not showcase improvements in MS mobility and found LA-associated proteinuria, although did find improvements in whole-brain atrophy	ALA improved *FXN* and *NRF2* expression in FA cellular models	(p27),(p28)

[a] Abbreviations: ALA: Alpha lipoic acid; BTK: Bruton's tyrosine kinase; COX2: cyclooxygenase-2; DMF: dimethyl fumarate; FA: Friedreich ataxia; FXN: frataxin; IL-6: interleukin-6; LA: Lipoic acid; MS: multiple sclerosis; NRF2: Nuclear factor erythroid 2-related factor 2; ROS: reactive oxygen species; S1PR: Sphingosine-1-phosphate receptors; TNF-α: tumour necrosis factor alpha.

patients with various types of hereditary ataxia. Although studies of such therapeutic strategies have yielded promising findings, the pursuit of a treatment that can address the inherited cause of the disease and multiple pathological processes, and benefit patients with FA regardless of their genetic profile and age, continues.

Multiple sclerosis: navigating challenges and unlocking future therapies

MS is an insidious, chronic progressive neurodegenerative disease that affects ~3 million people around the world.[p47] The average age of MS disease onset is 30 years (~75% of whom are women), a time that is decisive for work and family planning; 25 years after diagnosis, ~50% of patients require permanent use of a wheelchair.[p48] The disease is also on the rise. For example, in Australia, a 30% increase in prevalence was detected from 2017 to 2021.[p47] In 2021, MS costs Australia AD$2.45 billion in total, ~AD$74 000 per year per patient with MS.[p47] Thus, MS incurs serious and life-long health impacts and represents a massive socioeconomic burden globally.

MS involves a complex interaction between the immune system and the central nervous system (CNS), which led to the development of Bruton's tyrosine kinase (BTK) inhibitors to suppress the inflammation seen in the condition.[p49],[p50] Although the initiating insult remains unknown, it is clear that MS lesions are caused by peripheral immune cell infiltration across the BBB, which promotes inflammation and demyelination in the CNS. Although MS lesions remyelinate relatively efficiently early in the disease, many lesions remain chronically demyelinated, leading to irreversible neurodegeneration that drives neurological deficits in later stages.[p48],[p51]

The treatment of MS is complicated by its evolving symptoms and clinical classifications: relapsing-remitting, secondary progressive, and primary progressive, which have guided research, clinical, and regulatory decisions. Growing evidence supports MS as a highly heterogeneous disease, shaped by evolving pathophysiological processes that vary among individuals and over time, and overlaps with symptoms delineated in other neurological, neuromuscular or neuropsychological diseases, such as FA and major depression.[p52],[p53],[p54] Given that MS is a spectrum of clinical features, this highlights the need for treatment strategies that address both inflammatory and neurodegenerative mechanisms throughout the clinical course.[p55]

Advances in understanding the mechanisms underpinning MS pathology and progression are crucial for improving treatment outcomes and informing regulatory frameworks. Over the past decade, significant progress has been made in identifying a broad spectrum of immunosuppressive drugs, including the first oral drug, fingolimod (Gilenya), which offers new hope for treating relapse-remitting forms of MS.[p56] Fingolimod and its derivatives act by partially modulating sphingosine-1-phosphate receptor 1 (S1PR) and regulating the downstream signalling of sphingolipid metabolites, such as S1P.[p56] DMF is another immunomodulatory drug used to treat MS.[p57],[p58] Although its therapeutic mechanism remains unclear, it is believed that DMF targets the glycolytic enzyme glyceraldehyde 3-phosphate dehydrogenase, thereby suppressing the activity of myeloid and lymphoid cells to exert anti-inflammatory effects.[p59] In addition, LA has been investigated in the context of MS for its potential therapeutic benefits.[p28] A Phase II clinical trial conducted in North America found improvements in whole-brain atrophy in the LA-treated group, although there were no significant improvements in mobility and, in some cases, LA-associated proteinuria was reported,[p28] This highlights the need for further understanding of the mechanisms that can be targeted in MS.

Thus, current therapies for MS are only partially effective in reducing the frequency of relapses, but not progressive disabilities driven by ongoing neuroinflammatory, demyelination and incomplete repair.[p48],[p55] Unfortunately, no proven therapy exists for MS that can stall demyelination and promote myelin repair in the highly aggressive inflammatory microenvironment.[p48] Therefore, there is an ongoing need to identify new strategies that can effectively combat inflammatory demyelination and promote repair within the lesion microenvironment to stop or reverse neurological decline.

Identifying links between FA and MS for the development of unified and targeted therapeutic approaches

Both FA and MS are distinct neurological diseases but share converging pathogenic mechanisms that drive neurodegeneration and overlapping clinical features, such as ataxia, spasticity, dysarthria, fatigue, and gait impairment.[p60] Both conditions exhibit lipid peroxidation and iron accumulation, which amplify oxidative stress and damage neuronal membranes. Mitochondrial dysfunction is central in FA because of frataxin deficiency, whereas, in MS, it arises from chronic inflammation and demyelination, leading to impaired energy metabolism in neurons. Pathologically, the decreased FXN levels relate to altered iron homeostasis, metabolic disturbance, and oxidative stress in patients with FA, processes that are also observed in MS lesions. Moreover, inflammasome activation further exacerbates neuroinflammation in both diseases, creating a vicious cycle of oxidative stress and immune-mediated damage. Transcriptomic analyses reveal overlapping signatures involving dysregulated oxidative stress pathways, mitochondrial genes, and inflammatory mediators, highlighting a common molecular landscape that links FA and MS despite their distinct aetiologies.[p61] These shared phenotypes, particularly in motor and speech domains, support the development of common diagnostic tools, such as acoustic speech analysis. In such analysis, participants repeat certain syllables in an alternating fashion as many times as possible within 10 s per breath, and parameters, such as speech rate, speech frequency, and sound quality,are measured.[p62] This study showed that the FA group exhibited globally reduced acoustic energy, greater spectral instability, and longer utterances, consistent with a slower and more diffuse speech profile. By contrast, the MS group was defined by altered spectral shaping; specifically, a steeper, more variable spectral decline with duration and spectral spread falling between the control and FA groups.[p62]

Therapeutically, there is growing interest in shared drug targets (Tables 1 and 2, Figure 1). Intriguingly, the profile of sphingolipid and its metabolites is altered in both MS and FA, contributing to iron toxicity and neurodegeneration observed in the latter,[p63],[p64]

raising a new question as to whether the signalling of S1P could be a missing link between MS and FA that is worthy of investigation. Several studies report that drugs used in MS, such as DMF, can increase FXN levels in FA models, suggesting therapeutic convergence. *In vitro* and *in vivo* studies demonstrated that Nrf2 pathway activation, a key mechanism of DMF, enhances mitochondrial function and reduces oxidative stress in FA.[p17],[p18],[p65],[p66] Moreover, combination therapy with antioxidants, such as L-ascorbic acid (LAA) and *N*-acetylcysteine (NAC), has been shown to further boost efficacy.[p65] Treatments with LAA, NAC, and DMF led to reductions in mitochondrial and cellular reactive oxygen species (ROS), increased *FXN* and *NRF2* expression, enhanced *NRF2* nuclear translocation and improved biomarkers of mitochondrial function, including aconitase/citrate synthase activity, GSH/GSSG ratios, and mitochondrial membrane potential.[p65] The completion of a Phase II DMF trial involving patients with FA supports the repurposing of MS therapies for FA and highlights opportunities for shared diagnostic and therapeutic strategies across NDDs.[p67]

Mitochondrial dysfunction is a shared pathological hallmark in both FA and MS. In FA, frataxin deficiency disrupts mitochondrial iron regulation, leading to oxidative stress, impaired energy production, and progressive neurodegeneration.[p68] Neurodegeneration in progressive forms of MS is driven by a complex interplay between the above-mentioned pathological processes.[p69] In MS, chronic inflammation and demyelination impairs mitochondrial respiratory function in neurons and oligodendrocytes, contributing to axonal degeneration and energy failure.[p70] These converging mitochondrial impairments highlight the potential for shared therapeutic strategies targeting energy metabolism. One key focus is the restoration of NAD^+ levels, essential for mitochondrial ATP production and potentially overcoming the impediment to remyelination.[p71] Inflammatory processes in MS, and mitochondrial defects in FA, both result in NAD^+ depletion, exacerbating neurodegeneration. Supporting neuronal energy supply through NAD^+ restoration has shown therapeutic promise in preclinical studies, improving cardiac and neurological function in disease models.[p72],[p73] Another important pathway involves mitochondrial biogenesis and oxidative metabolism, regulated by transcriptional coactivators, such as peroxisome proliferator-activated receptor-γ coactivator-1α (PGC-1α). Reduced activity of this pathway has been linked to neurodegeneration and myelin deficits in both FA and MS.[p74] Compounds that enhance mitochondrial function or promote myelin repair through activation of the PGC-1α pathway have shown therapeutic potential in both FA and MS models.[p75],[p76]

Oxidative stress is a core pathogenic mechanism in both FA and MS, leading to a cascade of mitochondrial dysfunction, cellular damage, and altered gene expression. In MS lesions, oxidative stress can be induced by oxidative burst in microglia and macrophages, amplified by mitochondrial damage and altered iron homeostasis within lesions, as discussed above.[p77] Excessive generation of ROS and reactive nitrogen species (RNS) resulting from impaired mitochondrial respiration and disrupted iron homeostasis, triggers a toxic cycle of lipid peroxidation, DNA oxidation, protein nitration, and apoptosis.[p78],[p79] Beyond direct structural damage, oxidative stress induces chronic alterations in transcriptional networks and intracellular signaling pathways, which amplify neurodegeneration and hinder cellular repair mechanisms. However, from a preclinical perspective, no current animal models of inflammatory demyelination resemble the same pattern or the extent of oxidative stress seen in the MS brain.[p77] This presents a significant challenge in therapeutic development and mechanistic studies. Nevertheless, remediating oxidative stress resulting from iron deposition and mitochondrial dysfunction is a proposed therapeutic strategy to prevent the progression of MS.[p69]

One of the key regulatory pathways affected by oxidative stress is modulated by the interaction between Nrf2, Kelch-like ECH-associated protein 1 (Keap1), and interaction with the antioxidant response element (ARE). Deficiencies or dysregulation in the Nrf2 pathway have been reported in multiple *in vitro* and *in vivo* models of both FA and MS.[p80],[p81] In addition, the nuclear factor kappa B (NF-κB) pathway, a key upstream regulator of Nrf2 expression and a redox-sensitive transcription factor, is also disrupted in both diseases.[p82],[p83] Aberrant NF-κB signalling contributes to neuroinflammation and oxidative damage, and pharmacological inhibition of NF-κB has shown therapeutic benefit in preclinical models of FA and MS.[p82],[p83]

Another crucial component of the antioxidant defence system altered in FA and MS is the glutathione (GSH) synthesis pathway. GSH is a major intracellular antioxidant that directly neutralises ROS, including singlet oxygen and hydroxyl radicals, thereby preventing oxidative damage and cell death via apoptosis or necrosis. GSH depletion has been consistently observed in both disorders, highlighting its potential as a disease biomarker.[p84],[p85] Furthermore, the activity of several GSH-dependent enzymes, such as glutathione peroxidase (GPX) and glutathione *S*-transferase (GST), is also impaired, contributing to the accumulation of oxidative damage.[p86],[p87]

Disruption of iron homeostasis is also a notable pathological feature shared by both FA and MS. In MS brains, MRI and histopathological stains indicate iron accumulation at the edge of chronic active white matter lesions and in the deep grey matter structures, including the basal ganglia and thalamus.[p88] Iron is vital for numerous cellular processes, including neurotransmitter synthesis, mitochondrial respiration, and myelin production. Oligodendrocytes, the myelinating cells of the CNS, require iron to maintain energy metabolism and support myelin integrity. It is believed that iron is released from the dying oligodendrocytes, resulting in extracellular accumulation and its uptake within activated microglia and macrophages at the edge of active MS lesions, as well as in astrocytes in inactive lesions, thereby propagating neurodegeneration by enhancing oxidative stress chronically.[p89] Iron overload promotes oxidative stress and tissue damage, particularly in demyelinating lesions, whereas iron deficiency can impair oligodendrocyte function and hinder remyelination.[p90] Genetic variants in key iron-regulatory genes, such as homeostatic iron regulator (*HFE*), transferrin (*TF*), transmembrane serine protease 6 (*TMPRSS6*), cubilin (*CUBN*), and solute carrier family 25 member 37 (*SLC25A37*), have been associated with altered iron transport, storage and absorption in patients with MS patients.[p91] However, in the absence of longitudinal studies, it remains unclear whether iron accumulation is a trigger of MS expansion in MS or merely a biomarker of disease progression following the ongoing death of myelin-forming

oligodendrocytes. In FA, iron dysregulation primarily results from FXN deficiency, which is essential for the biosynthesis of iron–sulfur clusters (ISCs). These clusters serve as crucial cofactors for several mitochondrial enzymes, including aconitase and respiratory chain complexes I-III. Impaired ISC assembly leads to dysfunction of these enzymes and contributes to mitochondrial iron accumulation. Altered expression and function of iron-handling proteins, such as transferrin receptor 1 (TFR1), ferritins (FRTs), and ferroportin (FPN), have been also reported in FA, further exacerbating cellular iron mismanagement and neurodegeneration.[p92] Although the role of iron accumulation in the progression of FA remains unclear, iron deposits or accumulation have been observed in frataxin-deficient models, primarily linking to mitochondrial abnormalities. Interestingly, immunohistochemistry indicates a strong expression of tissue iron within oligodendrocytes of the dentate nucleus white matter, a region that is commonly damaged in FA.[p92]

Neuroinflammation is another common feature between MS and FA. Neuroinflammation in MS is primarily immune driven and is initiated by the infiltration of autoreactive T cells across the BBB, targeting myelin and oligodendrocytes.[p93] In FA, neuroinflammation is secondary and largely driven by mitochondrial dysfunction and oxidative stress resulting from frataxin deficiency.[p94] Unlike MS, FA lacks a primary autoimmune component, but the sustained oxidative injury and mitochondrial dysfunction create a self-perpetuating inflammatory cycle, which likely contributes to disease progression. However, common immune mechanisms that are responsible for ROS generation associated with oxidative stress in MS and FA render BTK inhibitors as an attractive drug candidate for both conditions.[p50],[p95]

Together, a combination of therapeutic strategies that target iron and lipid dysregulation, mitochondrial dysfunction, oxidative stress, and inflammation could inform the design of new treatments for both MS and FA (Tables 1 and 2).

Concluding remarks

Here, we have reviewed the commonalities seen across FA and MS and considered how developing a detailed profile of their overlapping mechanisms could serve to identify new potential drug targets. The implications for treatment of focussing on these shared mechanisms include reducing the time taken for novel drug development and testing, increasing the population of patients that could stand to benefit from research trials involving these shared mechanisms, and advancing knowledge of both FA and MS disease progression. Given that large clinical trials are time and resource intensive, maximising the potential benefits and extending beyond a single disease population promotes logistical and ethical feasibility when such activities are necessary.

In addition to dietary and lifestyle changes, novel or repurposed drugs and future stem cell therapies for FA and MS could meaningfully improve quality of life for those with these and other NDDs. In terms of stem cell therapies, autologous haemopoietic stem cell transplants are being explored in both diseases as a method of reducing inflammation; however, in MS, the protocol is used in much the same way as chemotherapy for blood cancers (eliminating the immune system and then rebuilding it from the patient's stem cells), whereas for FA, a 'first-in-kind' trial was recently approved that would take blood cell-forming stem cells and remove the genetic flaw using CRISPR-Cas-9 gene editing before returning them to the patient.[p96] As noted throughout this review, a better understanding of the overlapping processes involved in iron-mediated neurotoxicity, mitochondrial dysfunction, oxidative stress, and subsequent neuroinflammation in both FA and MS could yield useful knowledge for future therapeutic interventions and symptom management that could benefit both patient groups.

In terms of future research directions, in both FA and MS, early diagnosis and symptom management are both associated with better outcomes; however, a lack of awareness among physicians and the variability of presenting symptoms are common causes of diagnostic delay.[p97],[p98] In the case of FA, genetic testing has reduced the time to diagnosis from an average of 4 years to 2; nevertheless, when patients present with non-neurological symptoms (e.g., scoliosis or cardiomyopathy), the average time to diagnosis has been reported at 6.7 years, and 3 years for patients with late-onset symptoms.[p97] For MS, diagnostic delays are often associated with early misdiagnosis and greater severity of presenting symptoms.[p99] This not only indicates an educational opportunity for healthcare professionals with the potential to vastly improve patient outcomes, but also highlights the need for further tools that can rapidly differentiate between different NDDs. Genetic testing could greatly improve diagnostic times but would introduce various practical and financial barriers.

Genetic testing is valuable not only as a diagnostic tool, but also for precision medicine. In MS, Chitnis and Prat noted that the aims of precision medicine are to identify specific biomarkers and target 'underlying biology' rather than 'clinical phenotypes', requiring that drug companies demonstrate not only that their interventions can moderate disease symptoms, but that they also have a 'clear placement within a systems biology organisational model of specific diseases'.[p100] These authors further relate the key components of precision medicine as predictive, preventive, pharmacotherapeutic, and participatory. Although all four components can be expected to have significant quality of life enhancing potential for patients with FA and MS, it remains the case that precision medicine presents various technical and socioethical challenges. Perhaps the most apparent is the substantial costs involved, leading to inequitable access. This is already a problem for many other therapeutic options for these conditions, with the price of omaveloxolone, for example, costing ~Can $399 180 per patient per year.[p101] With various therapies for FA being classified as orphan drugs, the costs are likely to remain prohibitively high unless they can also be repurposed for other conditions. This again suggests that focussing drug discovery research on the intersection of pathways and symptoms in FA and MS would promote both scientific and economic efficiencies.

Beyond securing equity of access to pharmaceutical and other interventions, there are several other ethical considerations affecting research in this area. Given space limitation, these cannot all be addressed here, but it is worth noting that broad societal concerns regarding stem cell research, animal and embryonic experimentation relevant to much of biomedical laboratory research would particularly apply to various NDD studies, given the current trajectory

of the research, including an increasing focus on emerging stem cell therapies. Similarly, concerns about data security and privacy when utilising machine learning in health research also apply here, especially when introducing precision medicine applications. Furthermore, there are also several current controversies regarding FA and MS treatment specifically that are partly attributable to the age at which symptoms typically manifest. To provide one example, the use of medical cannabis as a neuroprotective therapeutic agent for various neuropathologies shows some strong evidence, but studies have been limited in size.[p102] A 2024 systematic review of over 250 neuropathologies, including MS and FA, found that 80% had either no reports (48%) or fewer than 10 reports (32%) addressing the impact of medical cannabis on symptoms.[p103] Given the limited treatment options available for FA and MS, and the fact that some of the overlapping symptoms are known to be affected by cannabis treatments, there is an urgent need to conduct large-scale studies to explore the efficacy of this intervention.

This demonstrates another benefit of pooling efforts across FA and MS research, given that the available participants with MS are far more numerous than those with FA. However, from an ethical standpoint, it also potentially introduces equity concerns if the burdens of research end up being disproportionately borne by the MS community, whereas the benefits are conferred more diffusely across NDD populations. An added complexity for conducting such trials, especially in MS but to a lesser degree also FA, is the typical age of affected individuals and the co-occurrence of other life stages, such as pregnancy.[p104] This also presents a practical and ethical challenge for other pharmaceutical trials, because the risk of causing foetal damage often means that pregnant women are excluded from participation in research studies, thereby limiting the relevance of results to this patient population.

Despite the challenges that lie ahead in the search for ways to prevent and treat FA and MS, the rapid discovery of joint disease pathways offers unprecedented opportunities to repurpose clinically approved drugs and accelerate the development of unified and targeted therapies for these NDDs.

Declaration of interests

None declared by authors.

CRediT authorship contribution statement

Faith A.A. Kwa: Writing – review & editing, Writing – original draft, Conceptualization. **Sara Anjomani-Virmouni:** Writing – review & editing, Writing – original draft. **Zenouska Ramchunder:** Writing – review & editing, Writing – original draft. **Evie Kendal:** Writing – review & editing, Writing – original draft, Conceptualization. **Junhua Xiao:** Writing – review & editing, Writing – original draft, Conceptualization.

Data availability

No data was used for the research described in the article.

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