Foundations & Frontiers: — Advancing Care in Friedreich's Ataxia

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Speaker disclosures

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SAB, Scientific Advisory Board; FARA, Friedreich's Ataxia Research Alliance

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After attending this session, you will be better able to:

Describe the genetics, pathophysiology, and clinical presentation of Friedreich's ataxia (FA).

Apply standardized tools and multidisciplinary strategies to diagnose and manage FA.

Discuss emerging therapies and their potential to improve patient outcomes.

FA, Friedrich ataxia

1 Foundations in Diagnosis

1

FA is an autosomal recessive multisystem progressive disease most commonly due to intronic GAA repeat expansions in the *FXN* gene

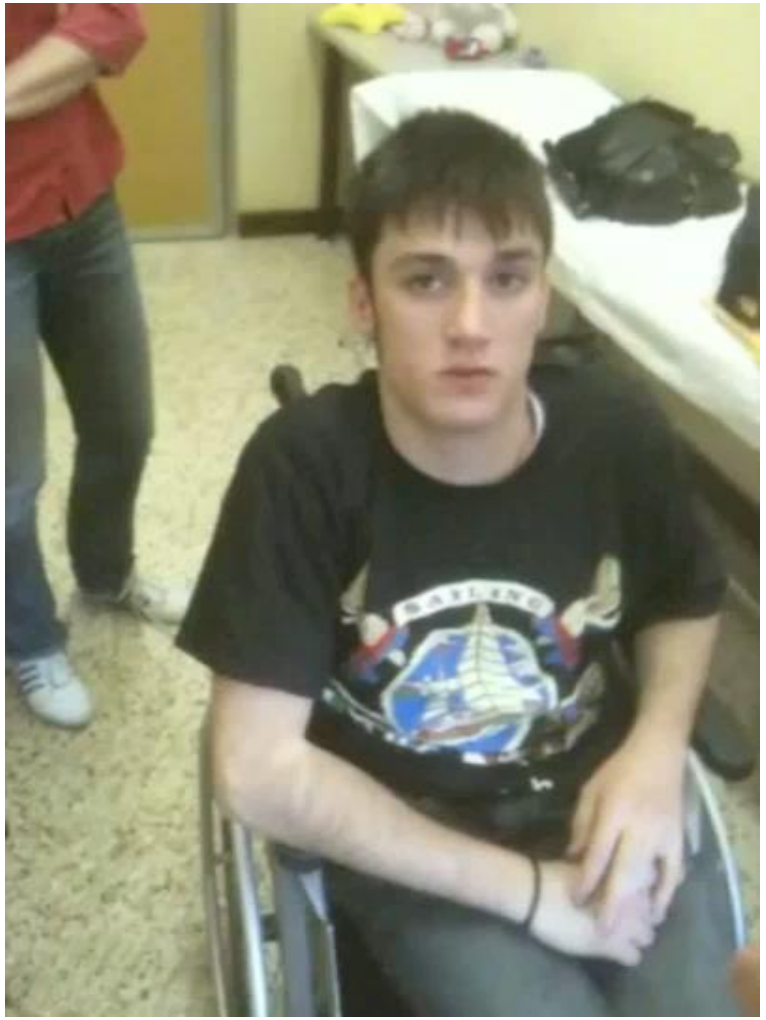
FA, Friedreich ataxia; FXN, frataxin; GAA, guanine-adenine-adenine.

Gottesfeld JM. Neurotherapeutics. 2019 Oct;16(4):1032-1049

OS

Early onset: Impact of long GAA1 and very low frataxin on patients

1



Age	22
Social history	Attends high school; mother is the main caregiver
Medical history	Pre-diabetic Hypertrophic changes in the heart with normal LVEF Scoliosis present before FA diagnosis, Foot deformity (pes cavus)
Symptoms at presentation	Onset at age 10; Ataxia and dysarthria
Referral	General neurology

FA, Friedreich ataxia; GAA, guanine-adenine-adenine
Authors personal experience

Late onset: Impact of short GAA1 and higher frataxin on patients

1

Age	72
Social history	Retired; lives with a partner who is supportive
Medical history	Mild gait/balance issues Dysarthria, instability of fixation, mild upper limb ataxia Mild hypertrophic changes in heart (no heart failure) No scoliosis, no foot deformity Preserved gait; using walker for safety
Symptoms at presentation	Onset at age 55; Ataxia
Referral	General neurology

FA Foundations

9 Authors personal experience

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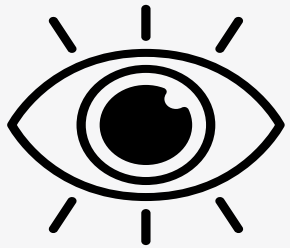
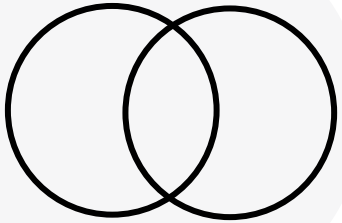
Challenges in diagnosing FA

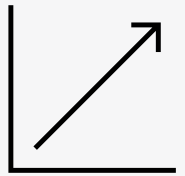
1



Lack of awareness[1,2]



Large differential diagnosis due to early symptom overlap and the need to rule out other causes of ataxia[1,2]



Misinterpreted as non-specific neurologic or orthopedic conditions[3]

Challenges in ordering genetic testing (some locations)[3]

A diagnosis of FA requires careful clinical examination of medical history and a physical exam, with genetic testing providing a conclusive diagnosis[4]

FA, Friedreich ataxia

1. Salomão, Rubens et al. Cerebellum (London, England) vol. 16,2 (2017): 599-601. 2. Trantham, Shandra J et al. Molecular therapy. Methods & clinical development vol. 32,1 101179. 18 Dec. 2023, 3. Bidichandani SI, et al. Friedreich Ataxia. 1998 Dec 18 [Updated 2024 Oct 31]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024. 4. NIH. Friedreich Ataxia. Available at: https://www.ninds.nih.gov/health-information/disorders/friedreich-ataxia (Accessed: January 2024).

What is the best test to confirm an FA diagnosis?

a) CGH microarray

b) ataxia panel through accredited lab

c) clinical exome testing

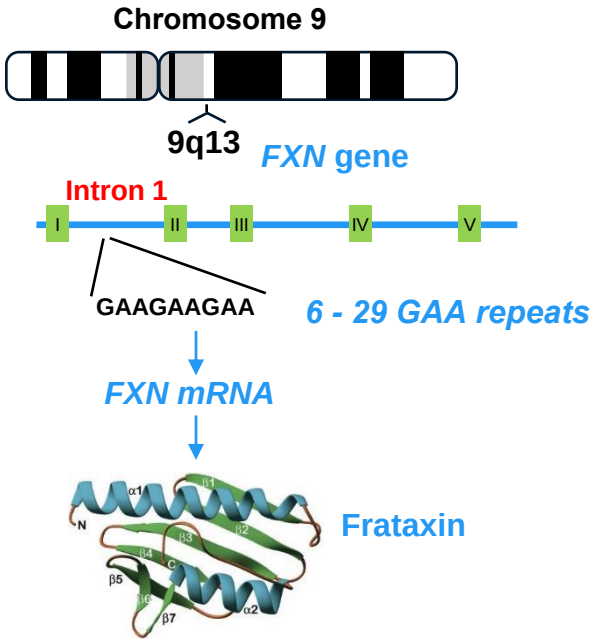
d) specific FA triplet repeat expansion testing

e) sequencing of FA gene

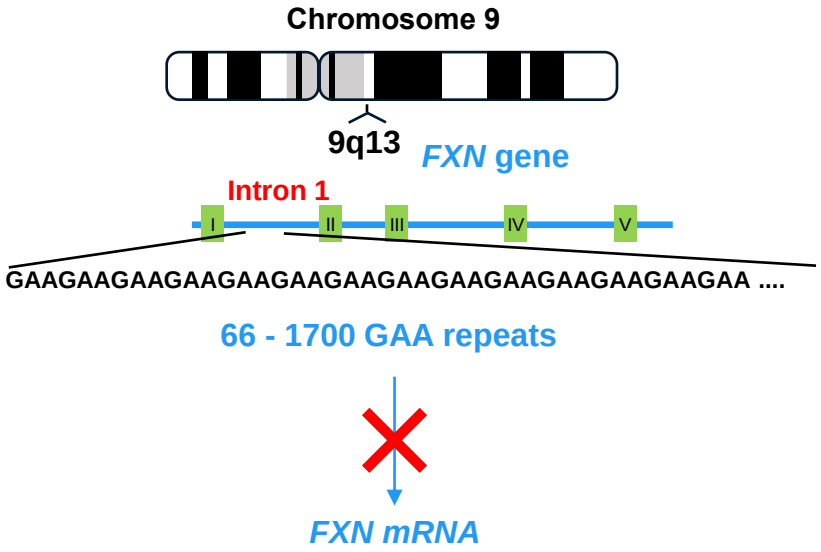
Confirming a diagnosis of FA requires accurate administration of a genetic test[1]

1

Healthy individuals



Individuals with FA



- To confirm an FA diagnosis, a **genetic test** must be ordered by the clinician to **identify a GAA trinucleotide repeat expansion** in the person's *FXN* gene[1,2]
- **Panels and exome sequencing do not test for triplet repeat disorders.**

FA, Friedreich ataxia; FXN, frataxin; GAA, guanine, adenine, adenine; mRNA, messenger ribonucleic acid

1. Schulz JB, et al. Nat Rev Neurol. 2009;5(4):222–234; 2. NAF. Ataxia Genetic Test Options. Available at: www.ataxia.org/ataxia-genetic-test-options/ (Accessed: August 2024); 3. https://labs.utsouthwestern.edu/napierala-lab

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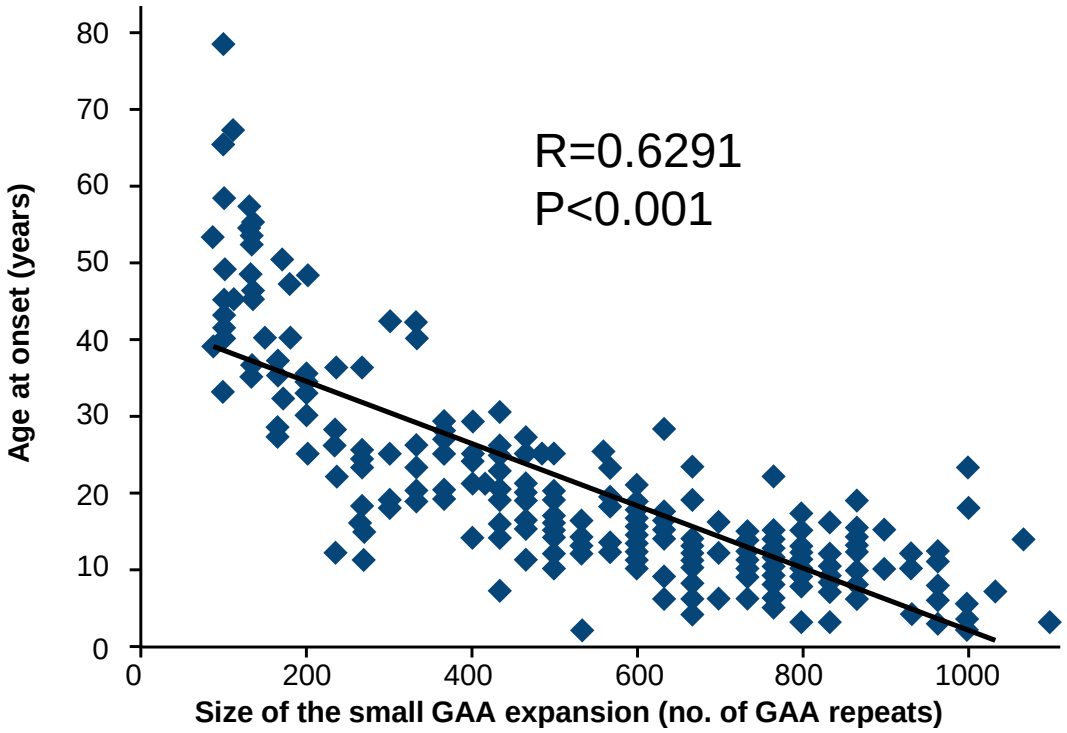
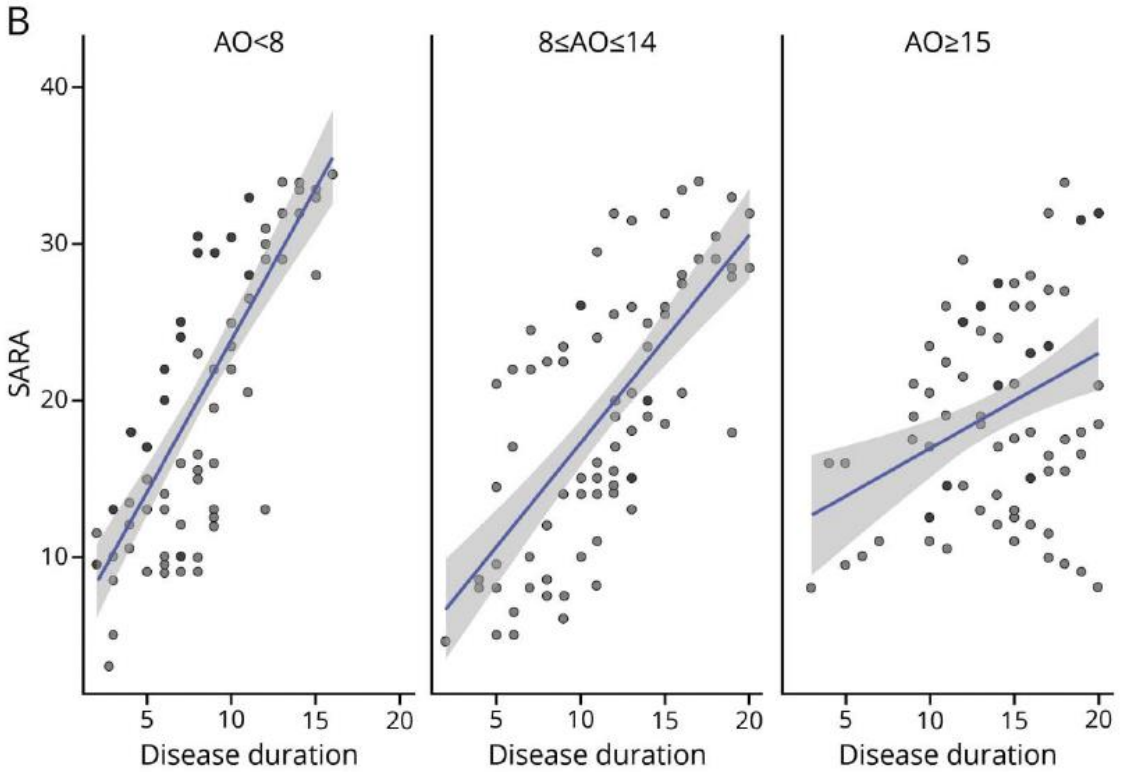
GAA repeat size, Age of Onset, Speed of progression

Longer GAA1 repeats, as determined by the small of the 2 gene expansion sizes, drives earlier age of onset[1-5]



Earlier onset is associated with faster progression[6-8]



GAA1: the shorter GAA repeat; AO, age of onset; EFACTS, European Friedreich's Ataxia Consortium for Translational Studies; FA, Friedreich ataxia; FA-COMS; Friedreich Ataxia Clinical Outcome Measures Study; GAA, guanine-adenine-adenine; R, correlation coefficient.
Figures adapted from Lecocq C, et al. 2016. and from Pandolfo 2020.

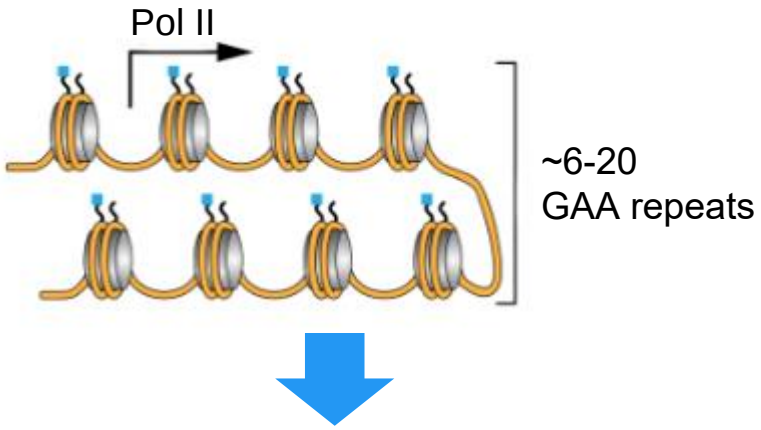
1. Dürr A, et al. N Engl J Med 1996; 335:1169. 2. Montermini L, et al. Ann Neurol 1997; 41:675.. 3. Lecocq C, et al. Mov Disord. 2016;31(1):62–69. 4. Filla A, et al., Am J Hum Genet. 1996 Sep;59(3):554-60. 5. Pandolfo M. Neurol Genet. 2020; 6(3): e415. 6. Rummey C, et al. Neurology 2022; 99:e1499. 7. Rummey C, et al., Neurology. 2022 Oct 3;99(14):e1499-e1510. 8. Pandolfo M. Neurol Genet. 2020; 6(3): e415.

GAA repeats result in reduced expression of FXN gene[1]

1

Healthy individuals

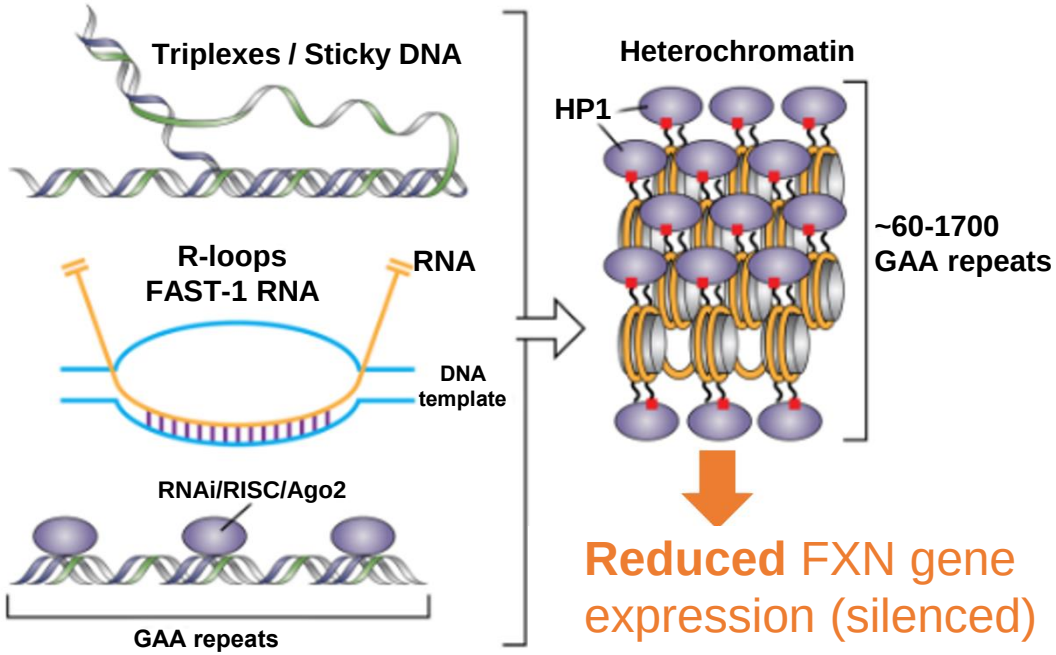
"Open" chromatin configuration to allow access for FXN gene transcription



Normal FXN gene expression

Individuals with FA

Increased GAA repeats create a **condensed chromatin structure** and renders the FXN gene inaccessible for transcription



Reduced FXN gene expression (silenced)

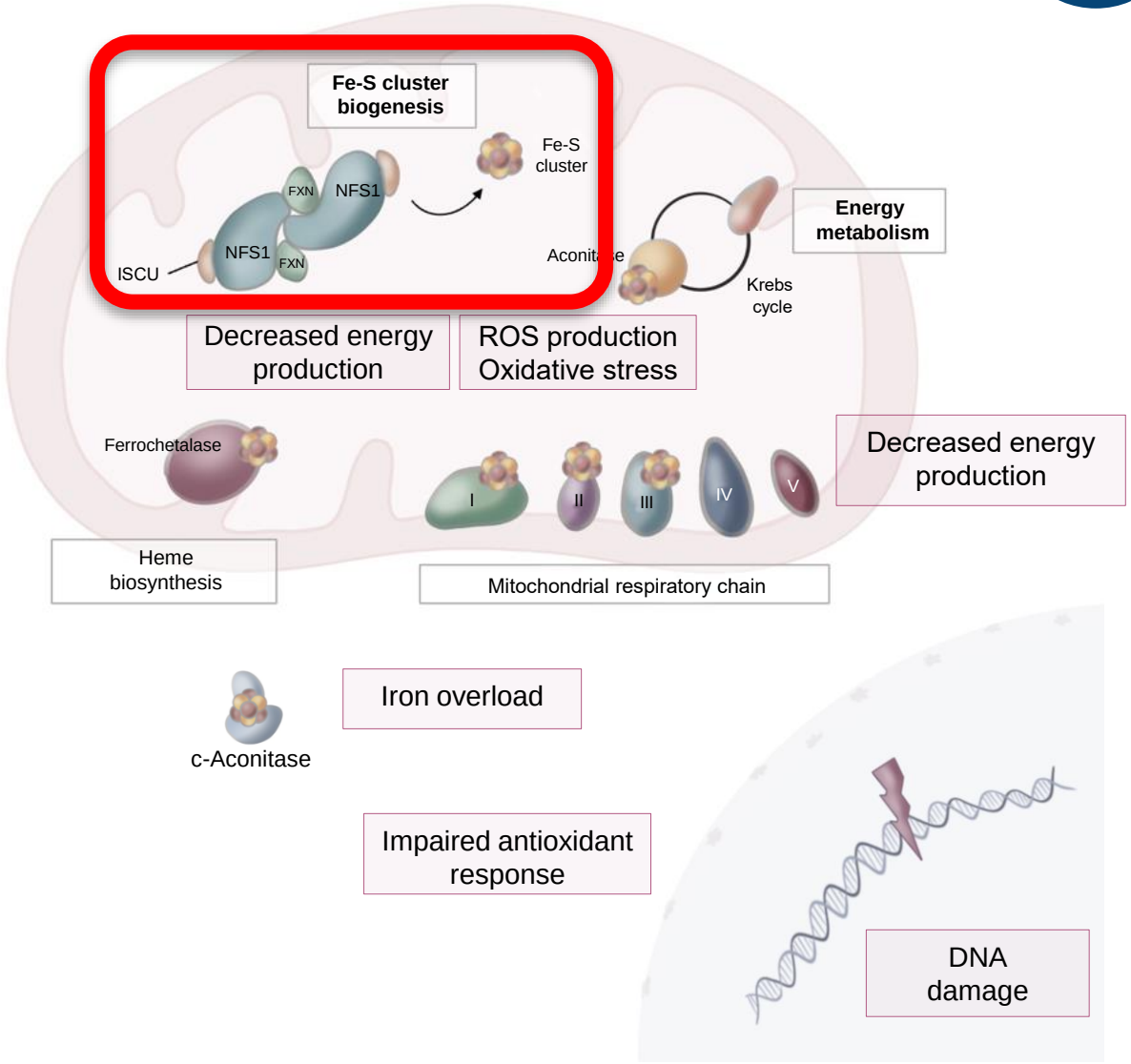
Ago2, Argonaut 2; FAST-1; DNA, Deoxyribonucleic acid; FXN antisense transcript 1; FXN, frataxin; GAA, guanine-adenine-adenine; Pol II, polymerase II; RNA, ribonucleic acid

1. Gottesfeld JM. Neurotherapeutics. 2019 Oct;16(4):1032-1049.

Frataxin deficiency impacts on Fe-S cluster biogenesis, energy production, and oxidative stress[1]

1

- Frataxin is a highly conserved protein with ubiquitous expression, localized in mitochondria, and plays a critical role in activating iron-sulfur (Fe-S) cluster biogenesis.[2]
- **Frataxin deficiency:**[3-7]
  - **Reduced production of Fe-S proteins**
  - **Decreased energy production**
  - **Iron overload**
  - **Reactive oxygen species production**
  - **DNA damage**
  - **Impaired antioxidant response**



DNA, deoxyribonucleic acid; FA, Friedreich ataxia; Fe-S, iron-sulfur; ROS, reactive oxygen species;

1. Babcock M et al Science 1997; 276:1209-1212. 2. Rötig A et al. Trends Mol Med. 2002; 8(5): 221-4; 3. Pastore A, Puccio H. J Neurochem. 2013; 126 Suppl 1: 43-52; 4. Lill R, Freibert SA. Annu Rev Biochem. 2020; 89: 471-499; 5. Das D et al. J Biol Chem. 2019; 294(23): 9276-9284; 6. Willis JH et al. Mol Genet Metab. 2008; 94(4): 491-497; 7. Pandolfo M, Pastore A. J Neurol. 2009; 256 Suppl 1: 9-17.

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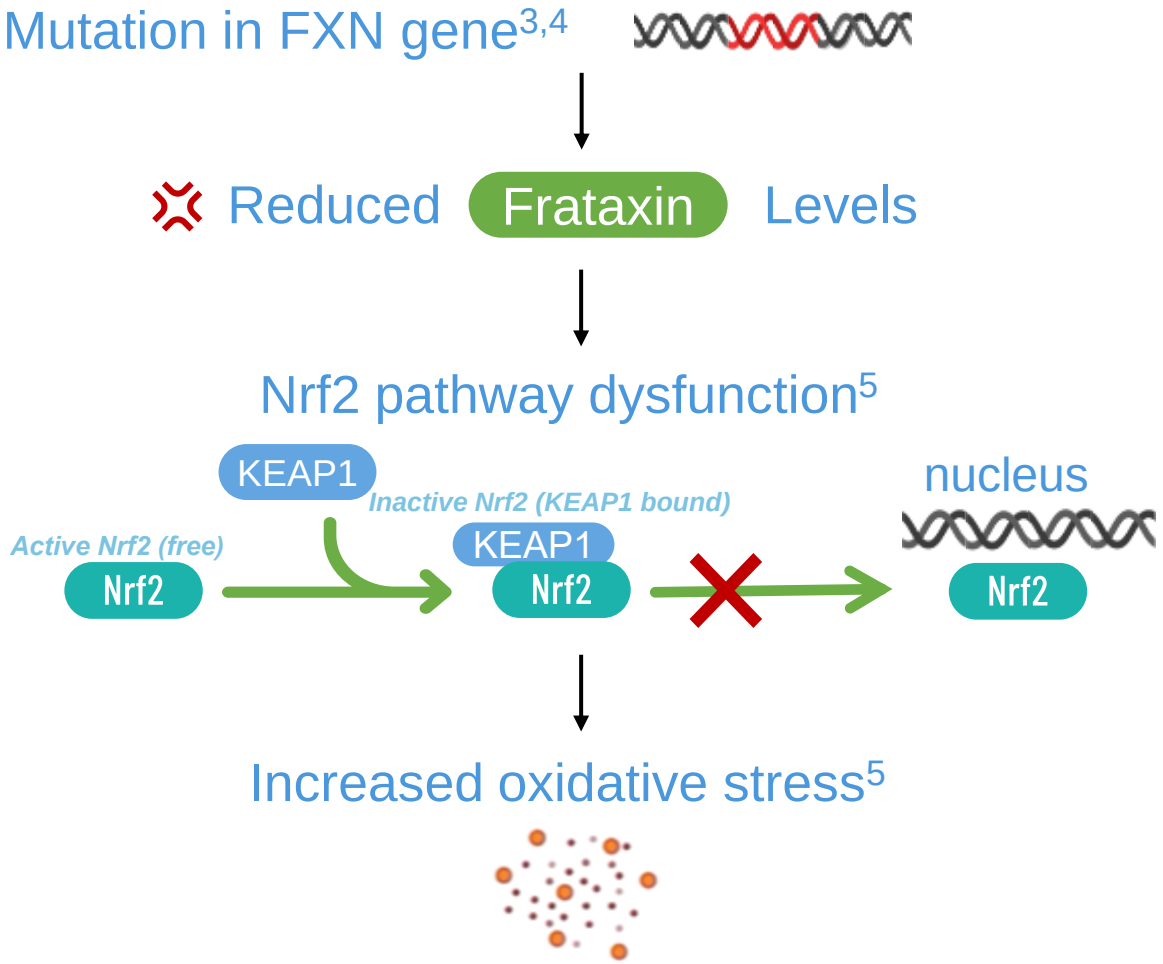
Reduced frataxin protein expression also leads to Nrf2 pathway dysfunction, further enhancing oxidative stress and reduced ATP production[1,2]



ATP, Adenosine triphosphate; FXN, frataxin; KEAP1/Keap1, Kelch-like ECH-associated protein 1; NRF2/Nrf2, nuclear factor erythroid 2–related factor 2

1. Paupe V et al. PLoS One 2009; 4(1): e4253; 2. Seminotti B et al. Front Cell Neurosci 2021; 15: 785057.3. National Institute of Neurological Disorders and Stroke. National Institutes of Health. Friedreich ataxia. 2023. Accessed August 1, 2023. https://www.ninds.nih.gov/friedreich-ataxia-fact-sheet. 4. Fogel BL, et al. Lancet Neurol. 2007;6(3):245-257. 5. Lynch DR, et al. Ann Neurol. 2021;89(2):212-225.

FA neuropathology leads to multiple associated neurological symptoms

1

Hypoplasia and loss of large dorsal root ganglia neurons, degeneration of posterior column and spinocerebellar tracts

AFFERENT ATAXIA

Degeneration of dentate nucleus of cerebellum

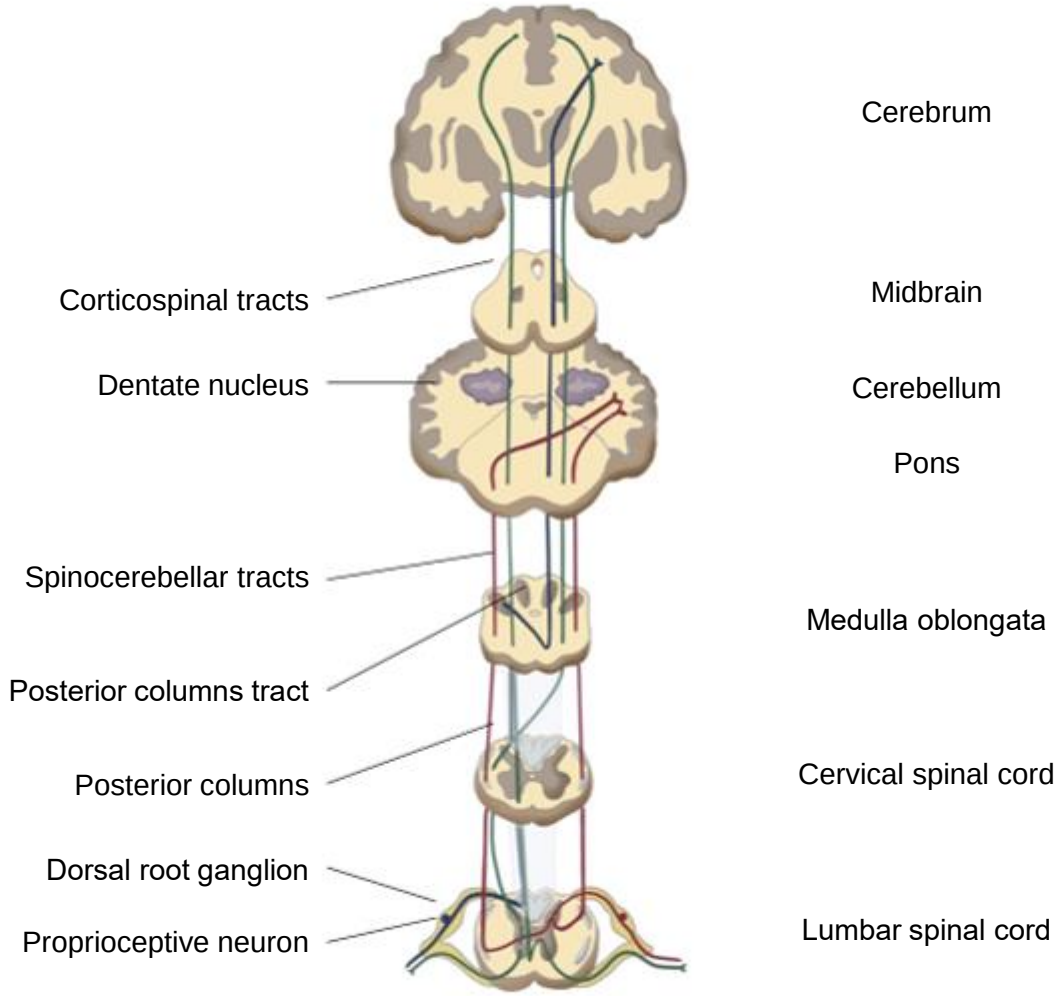
CEREBELLAR ATAXIA, CCAS

Degeneration of pyramidal tracts

WEAKNESS, SPASTICITY

Degeneration of auditory and visual pathways

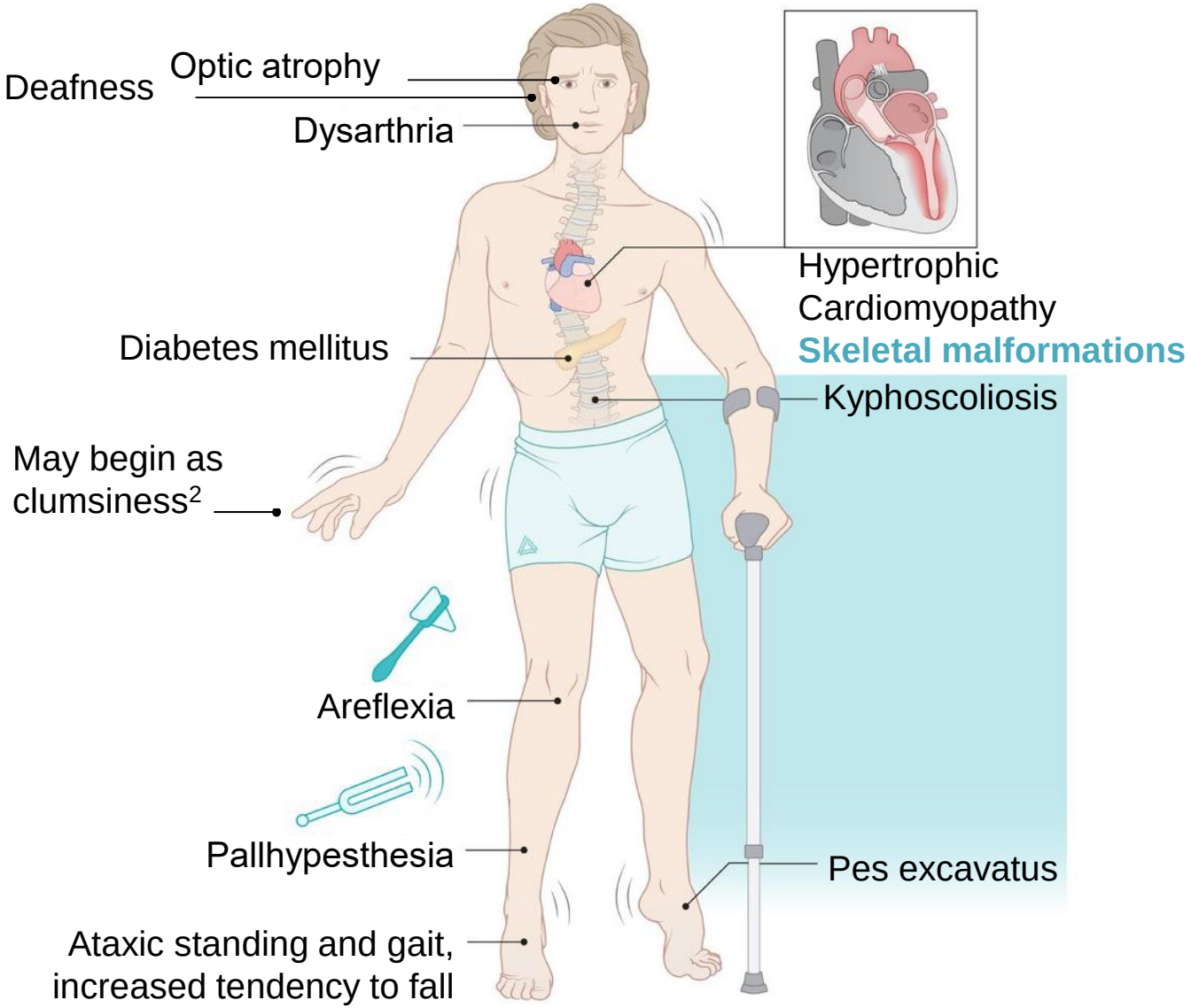
HEARING IMPAIRMENT, VISUAL LOSS



2 Foundations in Management

FXN dysfunctions leads to a range of clinical manifestations[1]

1



Life expectancy and death

- Mean age at death of people with FA is 36.5 (range: 12–87) years[2]
- The primary cause of death is cardiac dysfunction:[2]
  - Congestive heart failure
  - Arrhythmia

FA Foundations

FA, Friedreich ataxia.; FXN, frataxin

1. Gottesfeld JM. Neurotherapeutics. 2019 Oct;16(4):1032-1049. 2. Cook A and Giunti P. Br Med Bull. 2017;124(1):19–30.

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FA symptomatic management requires holistic, monitoring and multidisciplinary pharmacological therapies

2

Holistic care

Monitoring

Specialist medical

Neurological Symptoms

- Gabapentin or Pregabalin
- Baclofen or Tizanidine
- Clonazepam

Musculoskeletal Symptoms

- Nonsteroidal anti-inflammatory drugs (NSAIDs)
- Bisphosphonates (e.g., Alendronate)

Cardiomyopathy

- Beta-blockers (e.g., Metoprolol)
- Angiotensin-converting enzyme (ACE) inhibitors (e.g., Enalapril)
- Diuretics (e.g., Furosemide)

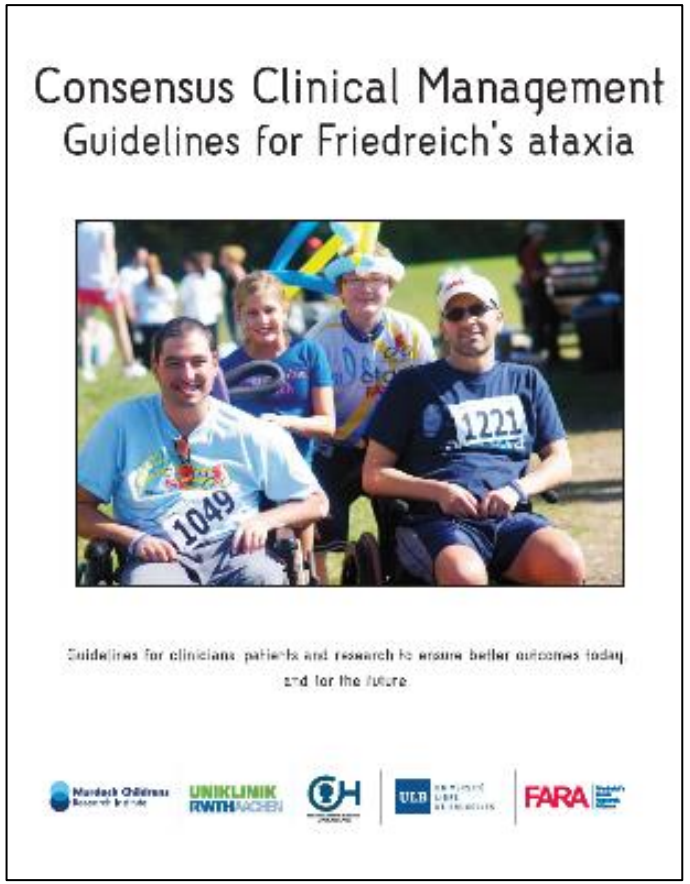
Other Therapies

FA, Friedreich ataxia;

1. Cook A and Giunti P. Br Med Bull. 2017;124(1):19–30; 2. de Silva RN, et al. Pract Neurol. 2019;19(3):196–207; 3. Ataxia UK. Management of the ataxias towards best clinical practice. Third edition. 2016. Available at: www.ataxia.org.uk/wp-content/uploads/2021/05/Ataxia-UK-Medical-Guidelines.-Final-Third-Edition-updated-helpline-number.pdf (Accessed: November 2024); 4. ERN-RND. Consensus Clinical Management Guidelines for Friedreich's ataxia. Available at: www.ern-rnd.eu/wp-content/uploads/2019/10/ERN-RND-Affirmed-FA-Guidelines_Final.pdf (Accessed: November 2024); 5. Lynch DR, et al. J Multidiscip Healthc. 2021;14:1645–1658.

International guidelines to standardize FA care

2



Clinical management guidelines for Friedreich ataxia: best practice in rare diseases

Louise A Corben [1,2,3,✉], Veronica Collins [1], Sarah Milne [1,2,4,5], Jennifer Farmer [6], Ann Musheno [6], David Lynch [7], Sub Subramony [8], Massimo Pandolfo [9], Jörg B Schulz [10,11], Kim Lin [12], Martin B Delatycki [1,2,13]; the Clinical Management Guidelines Writing Group

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PMCID: PMC9652828 PMID: 36371255

Clinical Management Guidelines for Friedreich Ataxia (FRDA):

FA, Friedreich ataxia.

1. ERN-RND. Consensus Clinical Management Guidelines for Friedreich's ataxia. Available at: www.ern-rnd.eu/wp-content/uploads/2019/10/ERN-RND-Affirmed-FA-Guidelines_Final.pdf (Accessed: November 2024); 2. Corben L, et al. Orphanet J Rare Dis. 2022;17:415.

mFARS: Clinically validated set of neurological assessments that measures FA progression[1,2]

2

Total scores for mFARS range from 0–93 points, with higher scores correlating with poorer neurological function[1-3]

Bulbar
5 points

Upper limb
36 points

Lower limb
16 points

Upright stability/gait functions
36 points

Total score of

93

mFARS composite scores in patients generally show an average annual increase of approximately 2 points.[2]

FA, Friedreich ataxia; mFARS, modified Friedreich's Ataxia Rating Scale.

1. Tai G, et al. Mov Disord Clin Pract. 2021;8(5):688–693; 2. Patel M, et al. Ann Clin Transl Neurol. 2016;3(9):684–694; 3. Rummey C, et al. Neurol Genet. 2019;5(6):371. 4. Saute JA, et al. Cerebellum. 2012;11(2):488–504.

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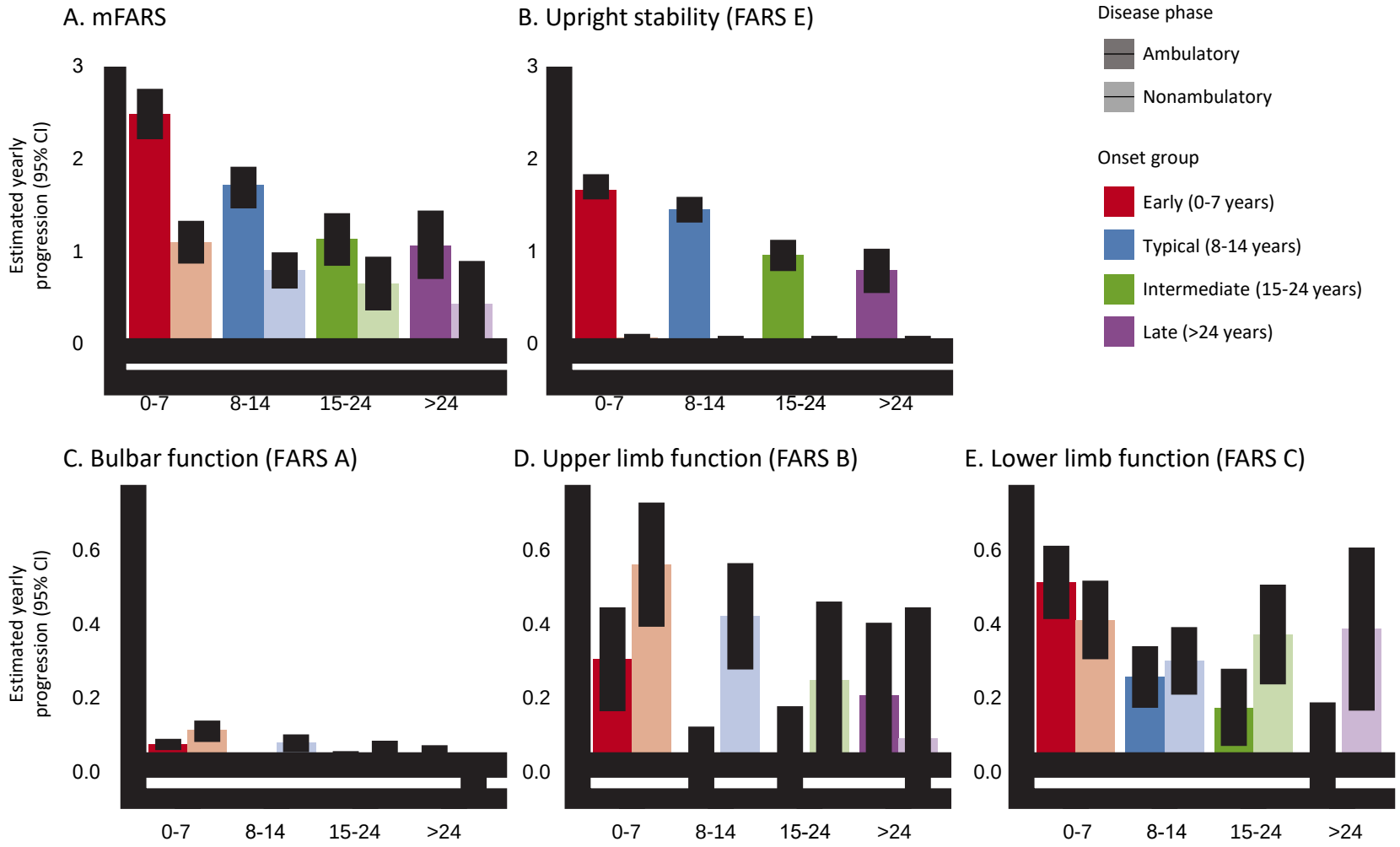
mFARS effectively captures the variable progression of FA

2



Upright stability is a robust marker in ambulatory individuals

Loss of upright stability

FA, Friedreich ataxia; mFARS, modified Friedreich Ataxia Rating Scale

Rummey C, et al., Neurology. 2022 Oct 3;99(14):e1499-e1510

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What do the changes in mFARS scores mean clinically?

mFARS component	Representative assessment	Examples of 1-point worsening	Clinical impact
 **Upper limb coordination**	**Finger taps (15 times)**	**Score 1** misses 1–3 taps ↓ **Score 2** misses 4–9 taps	**Deterioration may mean loss of ability to type**
 **Upright stability**	**Gait**	**Score 1** mild ataxia; no support needed for safety ↓ **Score 2** definite ataxia; intermittent support needed for safety	**Impaired ambulation; increased risk of fall**
 **Lower limb coordination**	**Heel to shin taps (8 times)**	**Score 2** misses shin 3–5 times ↓ **Score 3** misses shin > 5 times	**Increasing spasticity; weakness with impaired ambulation**
 **Bulbar function**	**Spontaneous speech (repeat specific sentences)**	**Score 1** most words understandable ↓ **Score 2** most words not understandable	**Impaired ability to communicate**

mFARS, modified Friedreich Ataxia Rating Scale.

Friedreich Ataxia Research Alliance. Friedreich Ataxia Rating Scale (FARS) and Modified Friedreich Ataxia Rating Scale. March 2023. Available at: https://www.curefa.org/pdf/Instructions-for-administering-the-mFARS.pdf (Accessed: June 2024).

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SARA: assessment scale quantifying eight items that reflect neurological manifestation of cerebellar ataxia[1–3]

2

Total scores for SARA range from 0–40 points, with higher scores correlating with poorer neurological function[3,4]

Disease progression, as measured by SARA, worsens by 0.82 points per year in the overall FA population
Higher in patients who were ambulatory (1.2 points) than non-ambulatory (0.50)[5]

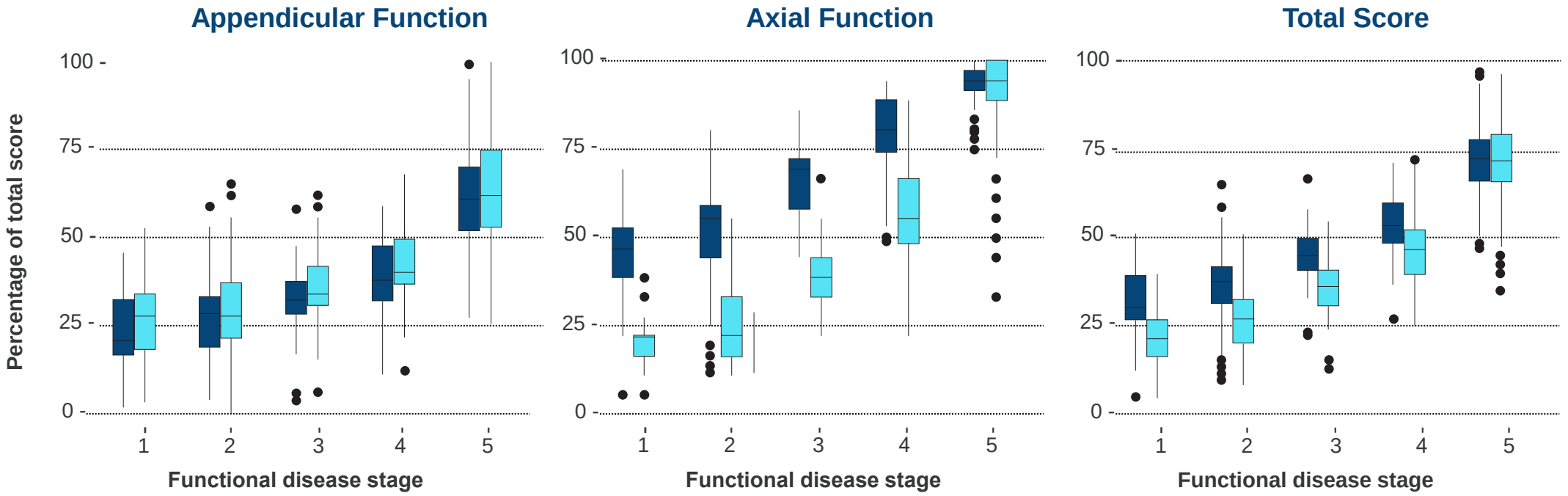
SARA, Scale for the Assessment and Rating of Ataxia.

1. Weyer A, et al. Mov Disord. 2007;22(11):1633–1637; 2. Schmitz-Hübsch T, et al. Neurology. 2006;66(11):1717–1720; 3. Physiopedia. Scale for the Assessment and Rating of Ataxia (SARA). Available at: https://www.physio-pedia.com/Scale_for_the_Assessment_and_Rating_of_Ataxia_(SARA) (Accessed: June 2024). 4. Schmitz-Hubsch et.al Neurology. 2006 5. Porcu L, et al. Ann Clin Transl Neurol. 2023 Nov;10(11):2000-2012.

mFARS and SARA show unified decline across disease stages

2

Appendicular, axial and total scores percentage by functional disease stage



mFARS assessment is more sensitive to disease progression at early stage

mFARS, modified Friedreich Ataxia Rating Scale; SARA, Scale for the Assessment and Rating of Ataxia.

Rummey C, et al. Ann Clin Transl Neurol. 2022;9(12):2041–2046.

With respect to mFARS:

a) I used it but only for research

b) I use it clinically

c) Do not use it but would like training on it

d) Do not use it

mFARS, modified Friedreich Ataxia rating scale; SARA, Scale for the Assessment and Rating of Ataxia.

With respect to SARA:

a) I used it but only for research

b) I use it clinically

c) Do not use it but would like training on it

d) Do not use it

 mFARS, modified Friedreich Ataxia rating scale; SARA, Scale for the Assessment and Rating of Ataxia.

2

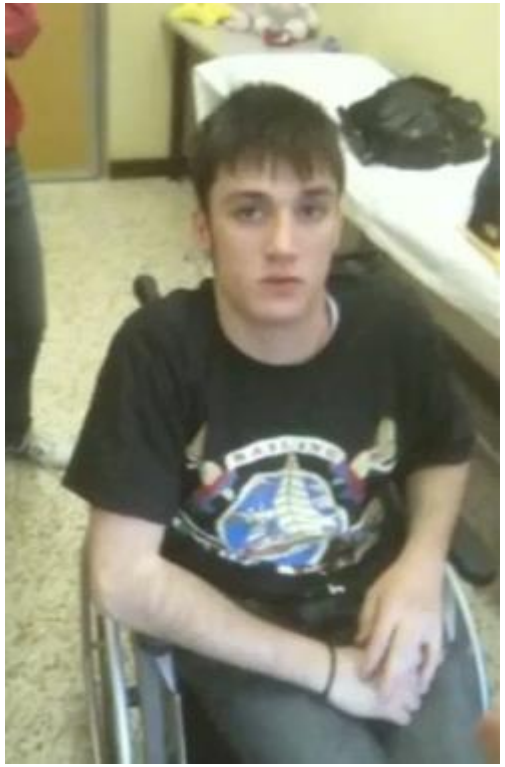
How do you manage these patients?

What care plan would you devise for this patient?

2

Patient with early-onset FA

Age	22
Social history	Attends vocational school; mother is the main caregiver
Medical history	Pre-diabetic Hypertrophic changes in the heart with normal LVEF Scoliosis present before FA diagnosis, Foot deformity (pes cavus)
Symptoms at presentation	Onset at age 10; Ataxia and dysarthria
Referral	General neurology



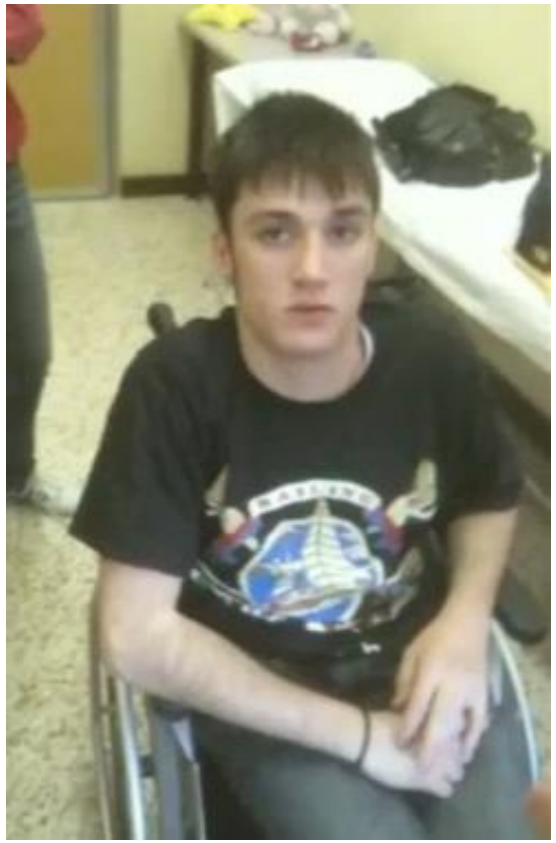
Goals of therapy

Treatment plan

What care plan would you devise for this patient?

2

Patient with early-onset FA



Goals of therapy

- Preserve functional independence
- Safeguard communication abilities
- Support mental health
- Address cardiac health
- Manage diabetes
- Correct skeletal abnormalities

Treatment plan

1. **Rehabilitation**: Engage in physiotherapy and occupational therapy to maintain mobility (transfers) and functional independence for upper limb function.
2. **Speech and auditory support**, if necessary.
3. **Vision support**: Utilize material adapted for those with low vision.
4. **Manage fatigue, pain, incontinence:** Offer appropriate non-pharmacologic and pharmacologic treatment.
5. **Psychological care**: Address mental health needs.
6. **Cardiac management**: Treat heart failure and arrhythmias and implement measures to prevent cardioembolic stroke.
7. **Diabetes care**: Utilize oral antidiabetic medications and insulin to manage blood sugar levels.
8. **Surgical intervention**: Perform spine surgery as required to correct kyphoscoliosis.

What care plan would you devise for this patient?

2

Patient with late-onset FA

Age	72
Social history	Retired; lives with a partner who is supportive
Medical history	Mild gait/balance issues Dysarthria, instability of fixation, mild upper limb ataxia Mild hypertrophic changes in heart (no heart failure) No scoliosis, no foot deformity Preserved gait; using walker for safety
Symptoms at presentation	Onset at age 55; Ataxia
Referral	General neurology

Goals of therapy

Treatment plan

FA Foundations

MP

What care plan would you devise for this patient?

2

Patient with late-onset FA

Goals of therapy

- Preserve functional independence
- Safeguard communication abilities
- Support mental health

Treatment plan

1. **Rehabilitation**: Engage in physiotherapy and occupational therapy to maintain ability to walk and functional independence for ADLs.
2. **Speech and auditory support**: Incorporate speech therapy and provide hearing aids, if necessary.
3. **Manage fatigue, pain, incontinence:** Offer appropriate non-pharmacologic and pharmacologic treatment.
4. **Psychological care**: Offer psychological support to address mental health needs.

ADL, activities of daily living; FA, Friedrich ataxia

Discussion and Questions about Management

3

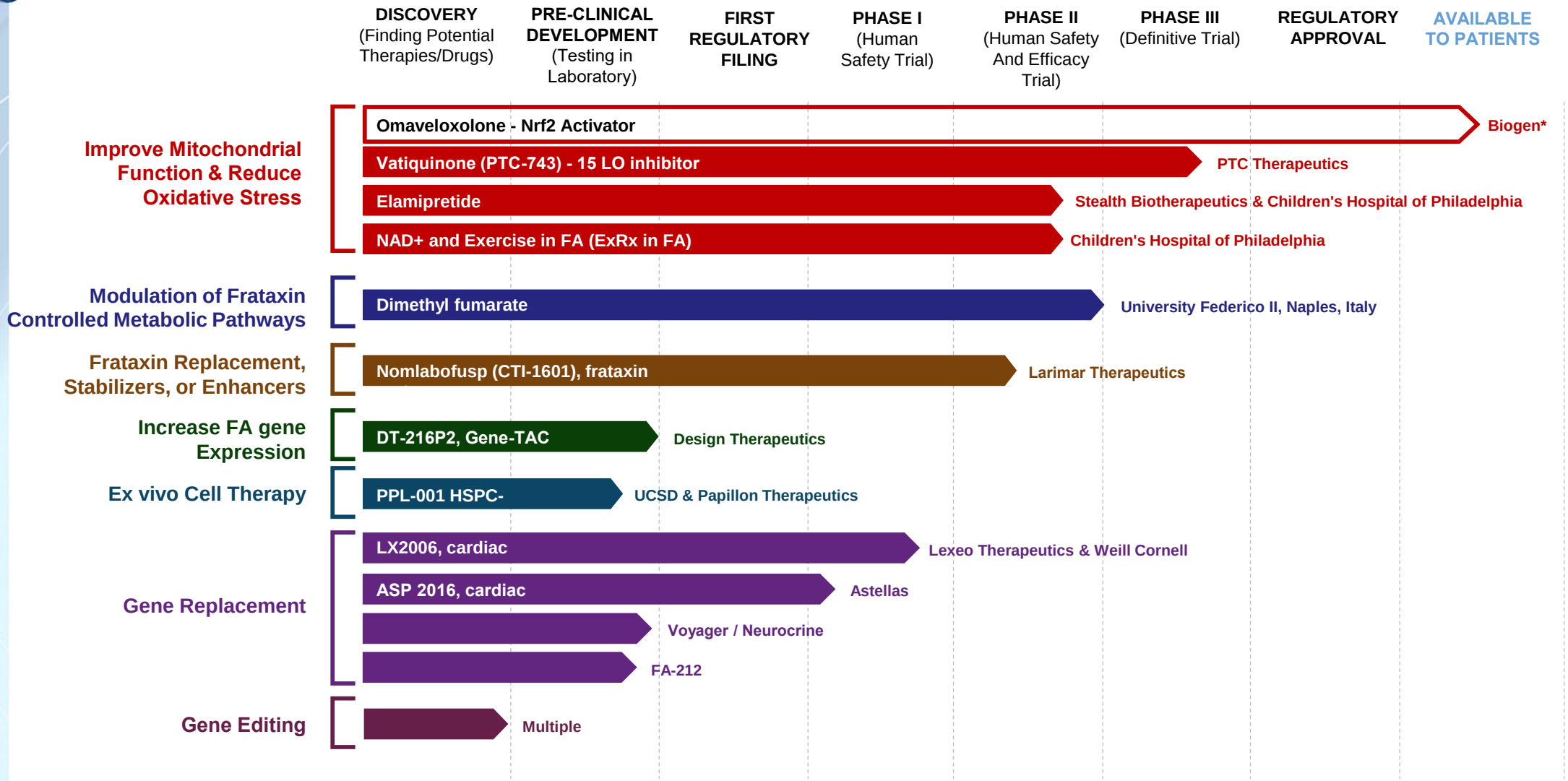
Frontiers in Therapies

3

Omaveloxolone is the only approved therapy for FA in Canada

FA, Friedreich ataxia
https://www.ninds.nih.gov/health-information/disorders/friedreich-ataxia#:~:text=Treating%20Friedreich%20ataxia,currently%20no%20cure%20for%20FA.

Therapeutic pipeline for FA



FA, Friedrich ataxia; NAD+, Nicotinamide adenine dinucleotide

*Omaveloxolone is available to patients in USA. Omaveloxolone is an investigational agent that has not been approved for use by Health Canada.

2025 Friedreich's Ataxia Research Alliance. Updated Feb 2025: https://www.curefa.org/drug-development/

Omaveloxolone MOA Overview

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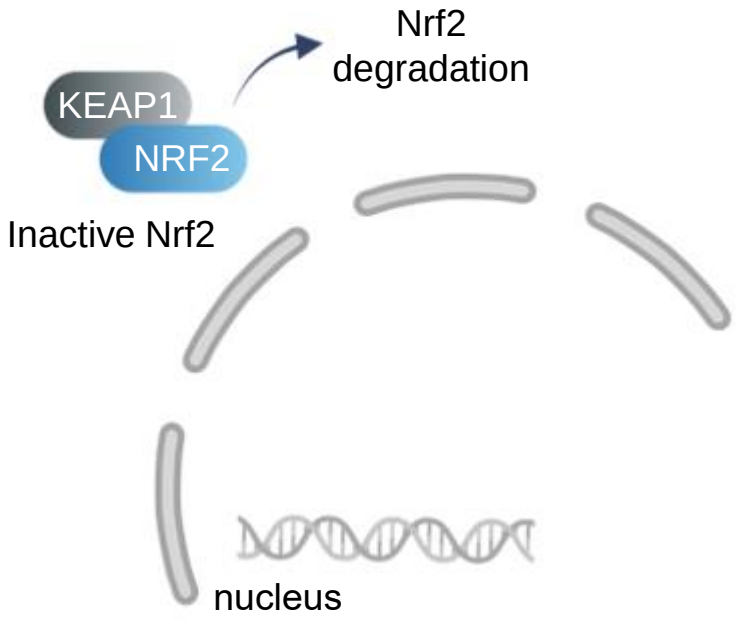
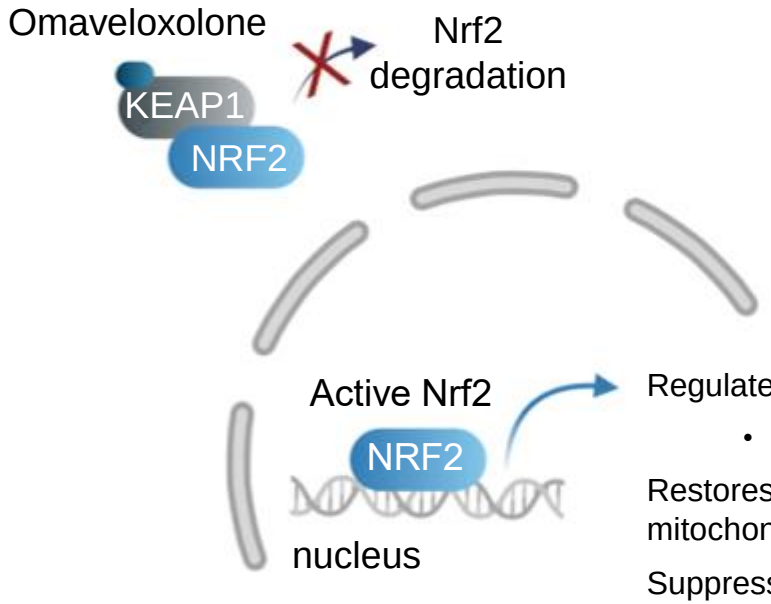
Nrf2 is a transcription factor that regulates the expression of genes involved in mitochondrial metabolism, redox balance, and inflammation as a part of the Keap1-Nrf2 system.[1-3]



Available preclinical data support the rationale that Nrf2 activation by omaveloxolone can improve mitochondrial dysfunction, oxidative stress, and inflammation in Friedreich's Ataxia.[4-6]



Regulates antioxidant gene expression

- NQ01, HMOX1, GCLM

Restores redox balance & improves mitochondrial function

Suppresses NF-KB & inflammation

The precise mechanism by which omaveloxolone exerts its therapeutic effect in patients with Friedreich ataxia is unknown.

GCLM, glutamate–cysteine ligase, modifier subunit; HMOX1, heme oxygenase 1; KEAP1/Keap1, Kelch-like ECH-associated protein 1; MoA, mechanism of action; NF-κB, nuclear factor kappa-B; NRF2/Nrf2, nuclear factor erythroid 2–related factor 2; Nqo1, NAD(P)H dehydrogenase, quinone 1

1. Holmström KM, et al. Curr Opin Toxicol 2016;1:80–91; **2.** Kobayashi M, et al., Adv Enzyme Regul 2006;46:113–40; **3.** Kobayashi EH, et al. Nat Commun 2016;7:11624; **4.** Cuadrado A, et al., Nat Rev Drug Discov. 2019;18(4):295-317. **5.** Probst BL, et al. PLoS One 2015;10(4):e0122942; **6.** Abeti R, et al. Front Cell Neurosci 2018;12:188.

Omaveloxolone: MOXIe Trial Study Design

3

Study Design

Description: An international, multicenter, registered, double-blinded interventional study evaluating the safety and efficacy of omaveloxolone150 mg daily in patients with Friedreich's Ataxia

Randomization (n=103): 1:1, omaveloxolone 150 mg orally or placebo once daily x 48 weeks; all randomized population (ARP)*

Primary Endpoint: Change from baseline in mFARS at week 48; full analysis set (FAS) per study protocol (n=82) of patients without pes cavus

Key Inclusion and Exclusion Criteria

Inclusion criteria

- 16-40 years of age
- Baseline mFARS: 20-80 points
- Able to complete maximal exercise testing
- Left ventricular ejection fraction of at least 40%
- With or without severe pes cavus
- Ambulatory and non-ambulatory†

Exclusion criteria

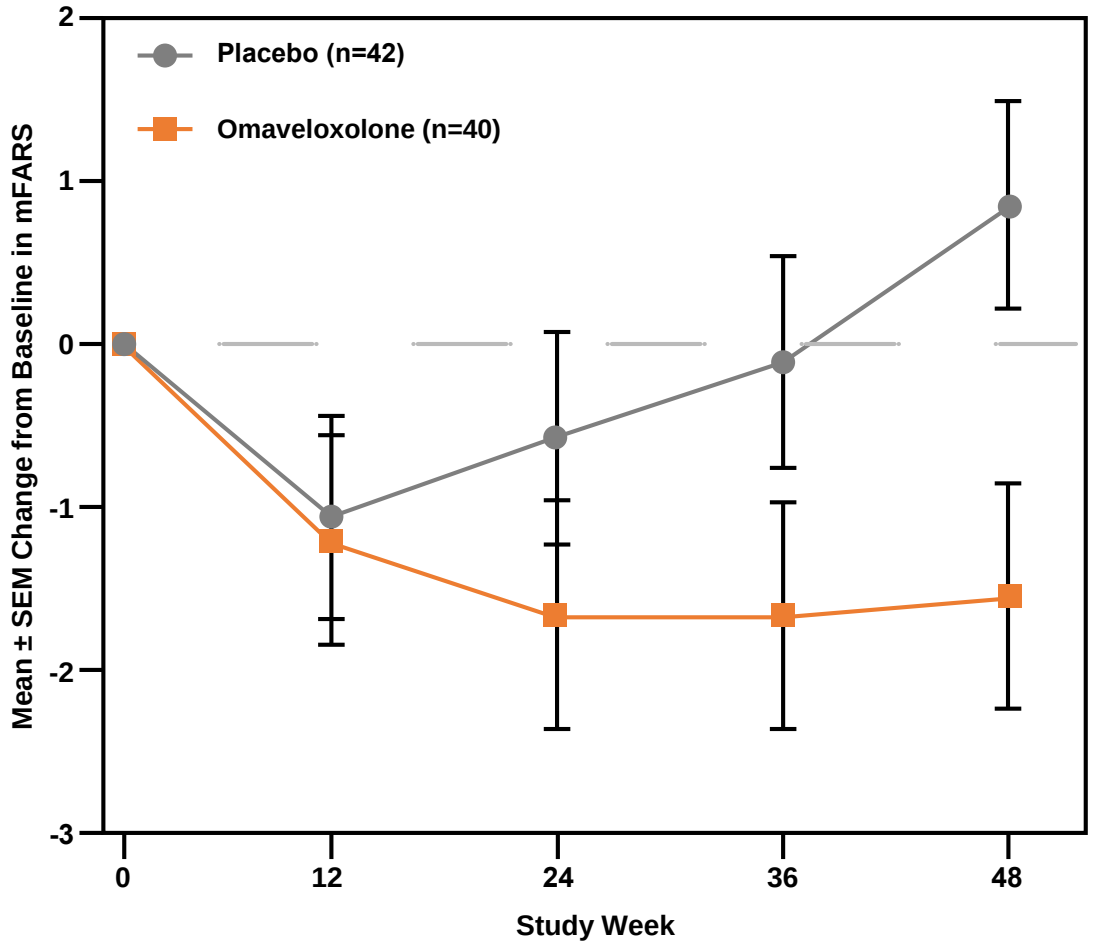
- Uncontrolled diabetes
- Clinically significant cardiac disease
- Active infections

mFARS, modified Friedreich Ataxia Rating Scale

Full Analysis Set per study protocol (n=82); mixed models repeated measured (MMRM) analysis used. No patients with severe pes cavus. 1. Lynch DR, et al. Ann Neurol. 2021;89(2):212-225. 2. SKYCLARYS Prescribing Information. Cambridge, MA: Reata Pharmaceuticals, Inc; 2024.

Omaveloxolone: Demonstrated a statistically significant 2.4-point improvement in mFARS score at week 48 in the MOXIe Trial

3



mFARS, modified Friedreich Ataxia Rating Scale

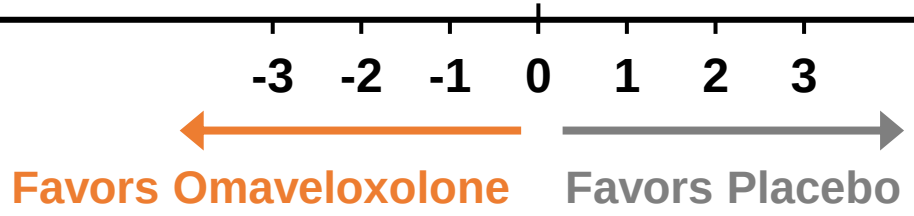
Full Analysis Set per study protocol (n=82); mixed models repeated measured (MMRM) analysis used. No patients with severe pes cavus. 1. Lynch DR, et al. Ann Neurol. 2021;89(2):212-225. 2. SKYCLARYS Prescribing Information. Cambridge, MA: Reata Pharmaceuticals, Inc; 2024.

Omaveloxolone: mFARS treatment difference at week 48 in MOXIe Part 2 Full Analysis Set

3

Secondary Endpoints

	Number of Patients Contributing Data		Week 48 mFARS Treatment Difference (95% CI)	p-value
	Omav	Placebo		
Upper Limb Coordination	40	42	**-1.29** (-2.51, -0.06)	0.0397
Upright Stability	40	42	**-0.72** (-1.67, 0.23)	0.1385
Lower Limb Coordination	40	42	**-0.21** (-1.17, 0.76)	0.6701
Bulbar Function	40	42	**-0.17** (-0.37, 0.04)	0.1112



CI, Confidence Interval; FAS, Full Analysis Set; mFARS, modified Friedreich's Ataxia Rating Scale
Study 408-C-1402, Part 2 corrected case data, Table 14.2.11-cc

MOXIe Extension: Delayed-start analysis indicated a persistent clinical benefit of early treatment with omaveloxolone

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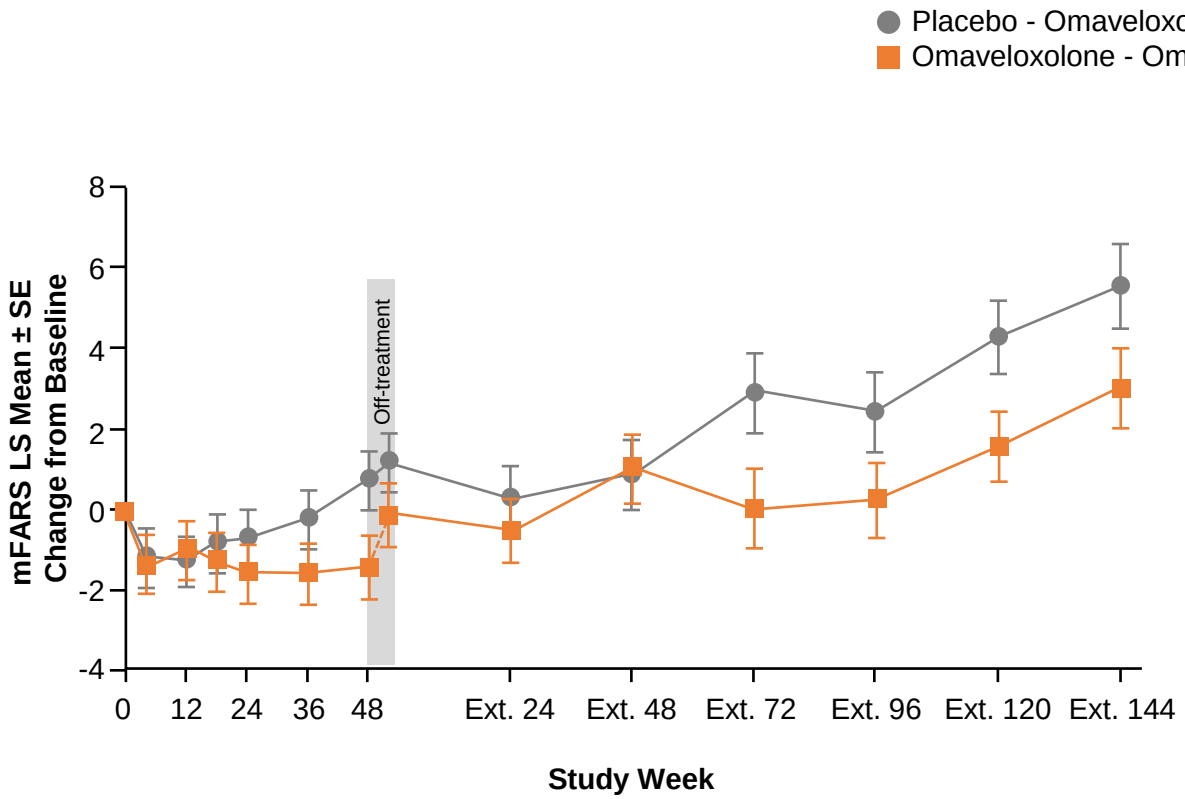
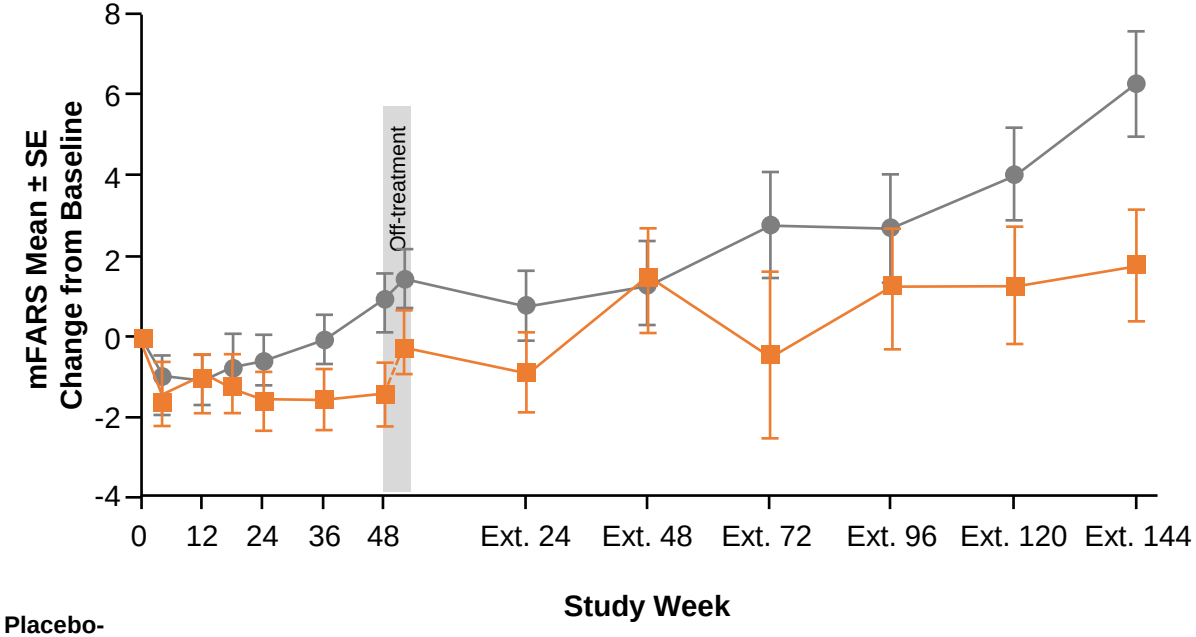




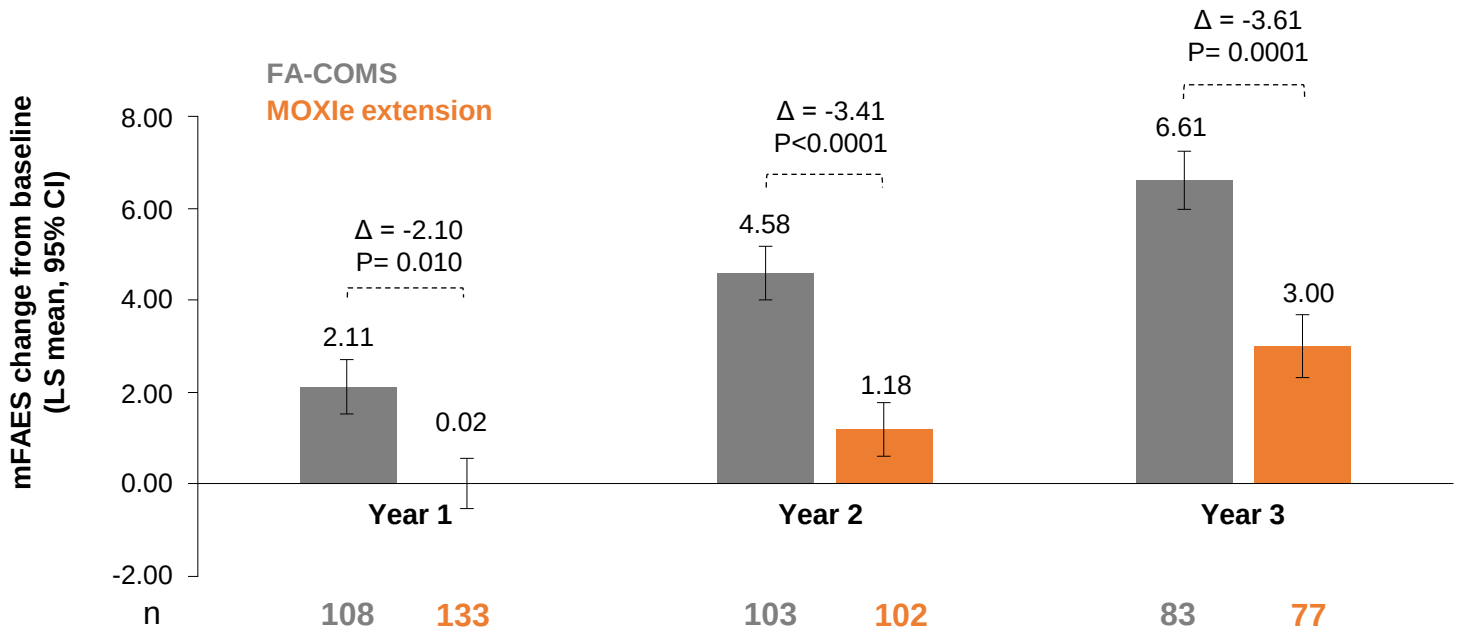
Placebo-Omav (n)	42	42	41	41	41	27	22	14	15	24	15
Omav-Omav (n)	40	40	36	35	34	28	20	17	22	27	17

Data presented from full-analysis set.
LS, least squares; mFARS, modified Friedreich Ataxia Rating Scale; omav, omaveloxolone; OLE, open-label extension; SE, standard error.
Lynch DR, et al. Mov Disord. 2023;38(2):313–320.

Omaveloxolone: Provided a persistent benefit over time

Open-Label MOXIe Extension and FA-COMS: Propensity-matched analysis[1]

Mean change in mFARS from baseline over time



55%

slowing of disease progression compared to natural history controls

Over the 3-year period, omaveloxolone provided a clinically meaningful slowing of FA disease progression compared with untreated, propensity-matched natural history controls (FA-COMS)

. *Logistic regression was used to determine propensity-matched scores, with prognostic factors selected as covariates. Some prognostic factors were not available in both studies.
FA, Friedreich ataxia; FA-COMS, Friedreich Ataxia Clinical Outcome Measures; mFARS, modified Friedreich Ataxia Rating Scale.

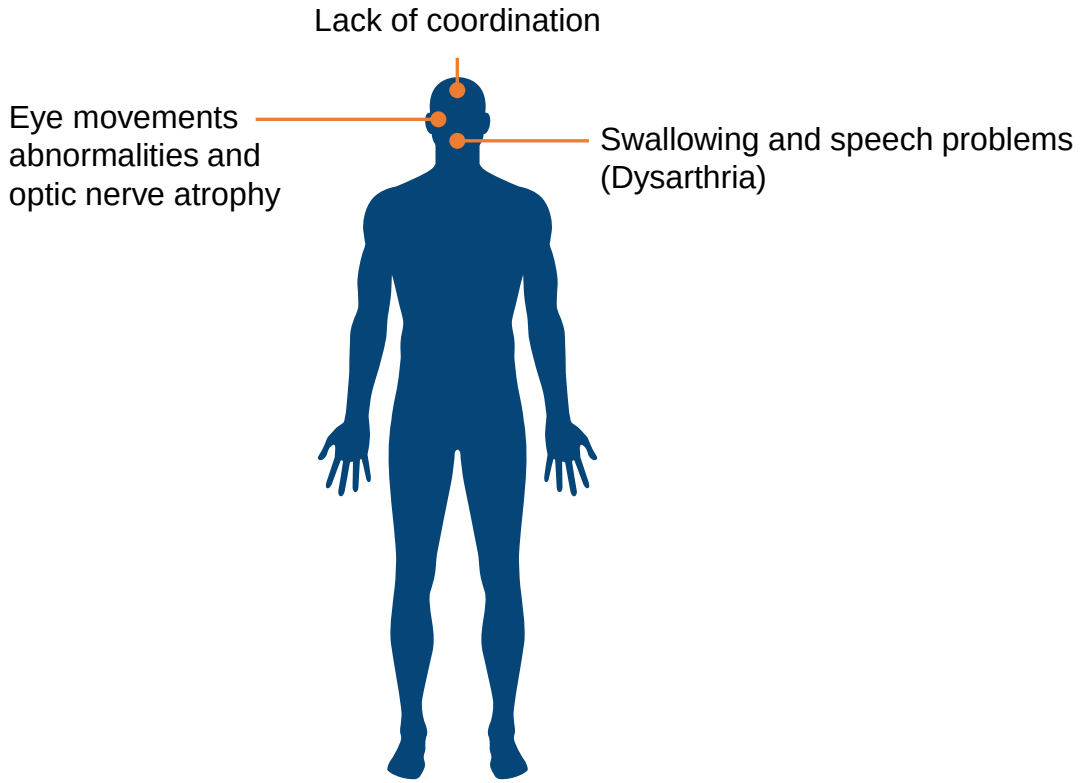
1. Lynch DR, et al. Ann Clin Transl Neurol. 2024;11(1):4–16; 2. ClinicalTrials.gov (NCT03090789). Available at: https://classic.clinicaltrials.gov/ct2/show/NCT03090789 (Accessed: June 2024).

Vatiquinone

3

- Inhibits 15-lipoxygenase (15-LO) and improves mitochondrial function
- Suppresses RSL3 and BSO/Fe(III)C induces cell death
- Synthetic vitamin E analogue

Vatiquinone aims to improve:



BSO, Buthionine sulfoximine; RSL3, RAS-selective lethal 3
Kayser EB, et al. Res Sq [Preprint]. 2024 Jun 3:rs.3.rs-4202689.
Tiberi J, et al., Biomedicines. 2023;11(5):1293.

MOVE-FA: a global registration-directed trial of vatiquinone in pediatric and young adult patients with FA

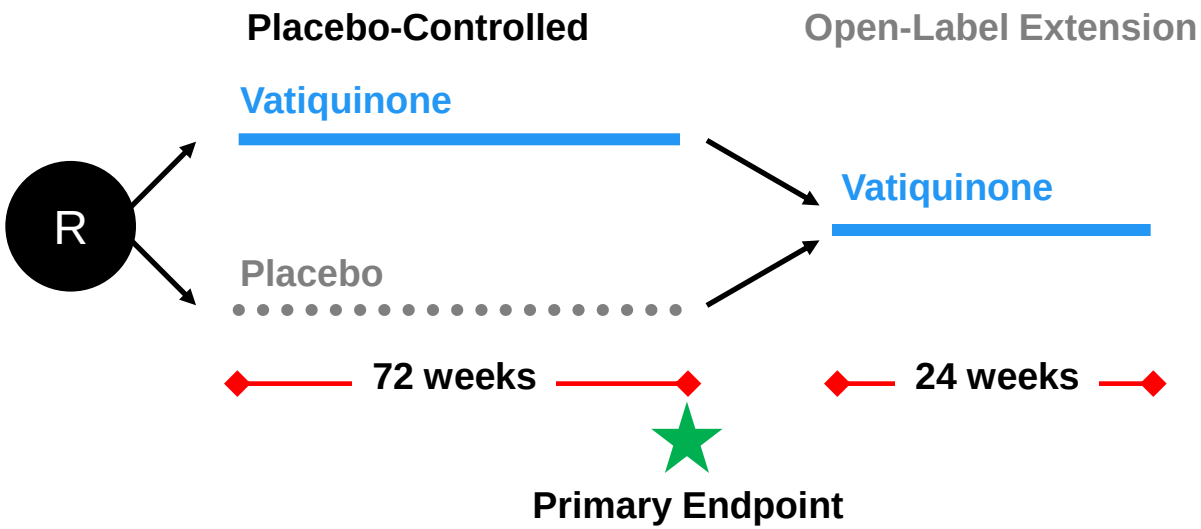
3

Primary Analysis Population:
Ambulatory FA subjects
7-21 years old

Overall Enrolled Population:
Ambulatory FA subjects
≥ 7 years old

Primary Endpoint
Change from baseline in mFARS at 72 wks

Other Key Endpoints
Change from baseline at 72 wks:
FARS- ADL
1 Minute Walk Test
Upright Stability Subscale
Modified Fatigue Impact Scale



Participating Countries

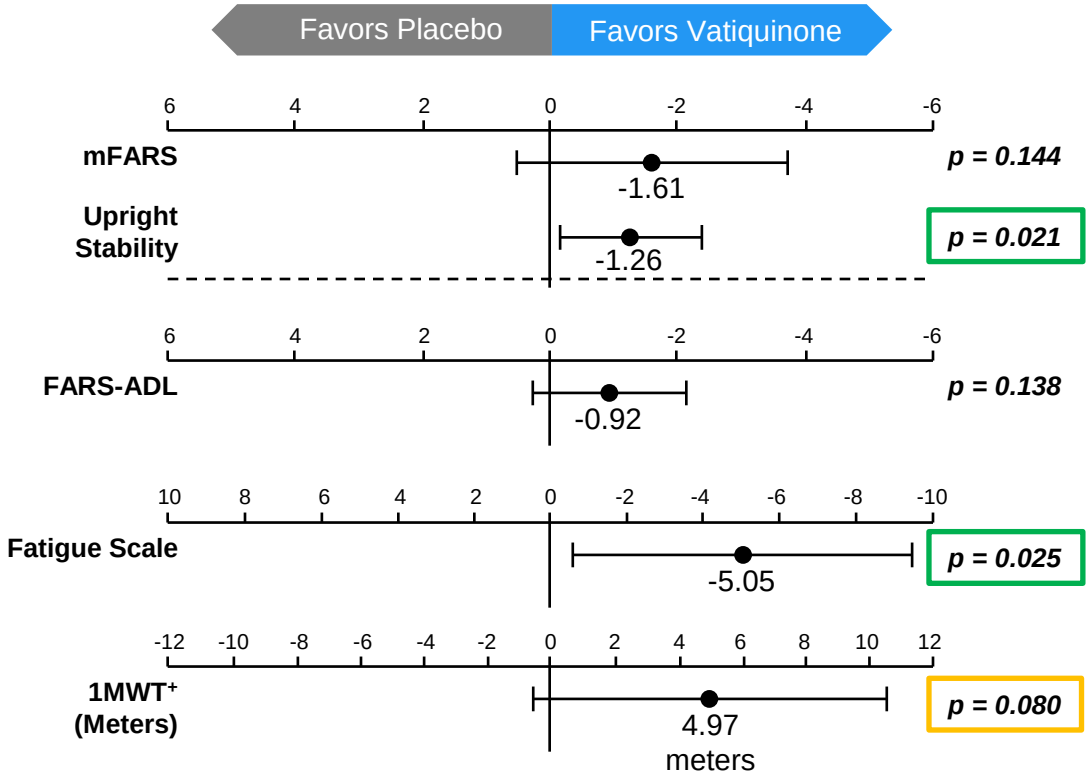
Australia, Brazil, Canada, France, Germany, Italy, Spain, New Zealand, USA

ADL, activities of daily living; FA, Friedreich ataxia; FARS, Friedreich Ataxia Rating Scale
The MOVE-FA study

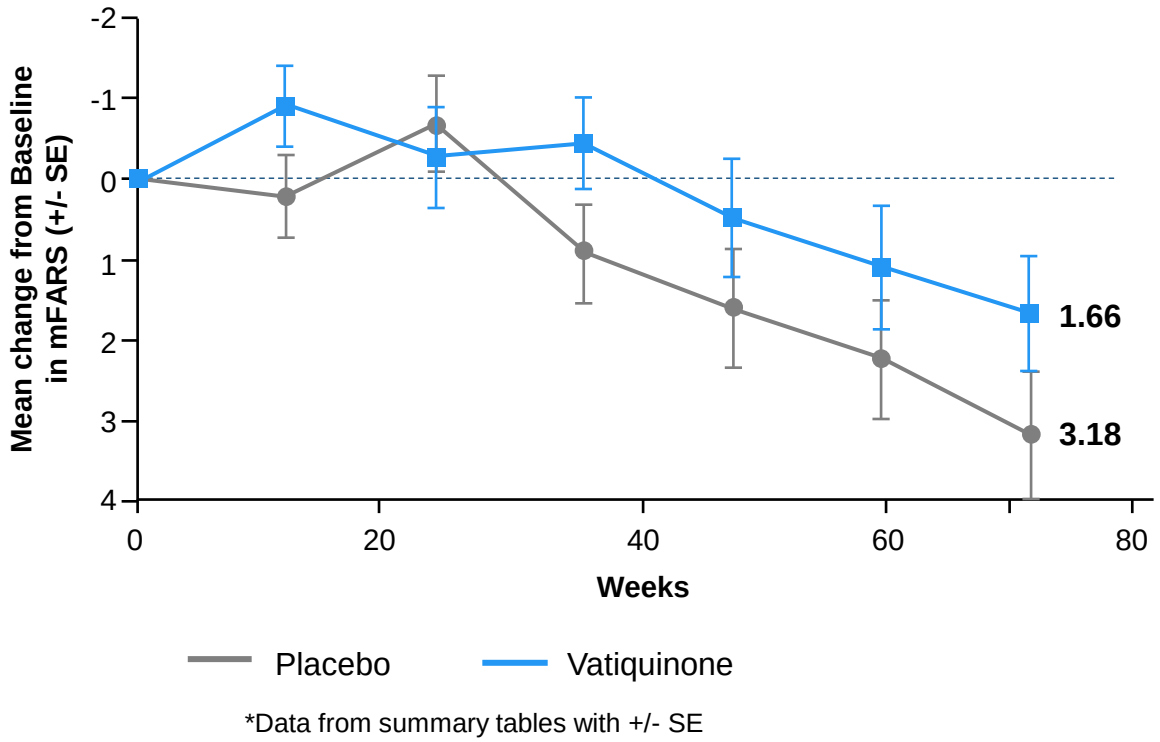
Vatiquinone: Demonstrated improvement over placebo in across primary, secondary and exploratory endpoints

3

Primary Analysis (mITT) population (LS Mean with 95% CI)



Primary Analysis population (mITT)



*Data from summary tables with +/- SE

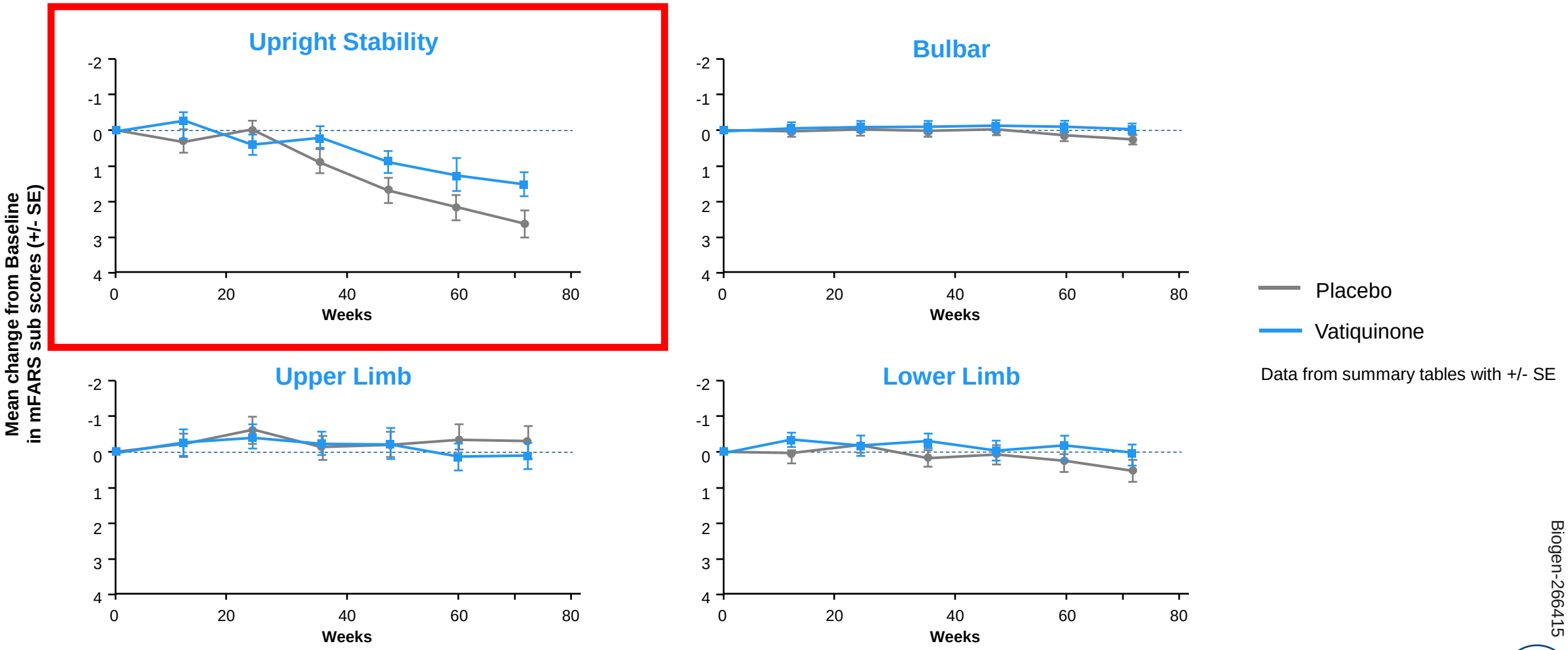
ADL, activities of daily living; FA, Friedreich ataxia; mFARS, modified Friedreich Ataxia Rating Scale; mITT, modified intent-to-treat; SE, standard error;
The MOVE-FA study

Vatiquinone: Improves subscale/FARS E for upright stability

3

Safety Data

Primary Analysis Population (mITT)

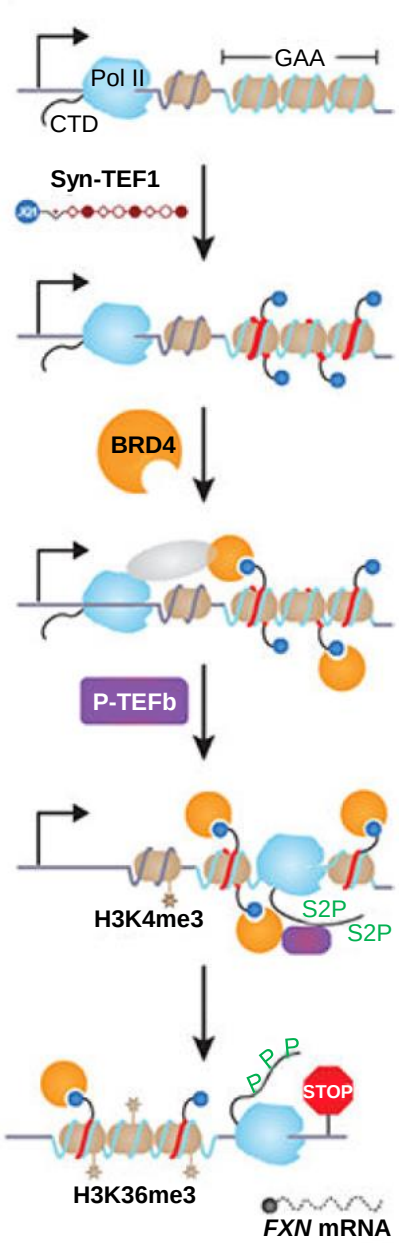


mFARS, modified Friedreich Ataxia Rating Scale; mITT, modified intent-to-treat; SE, standard error
The MOVE-FA study

Epigenetic therapy: Synthetic transcription elongation factors (Syn-TEFs) selectively activate FXN expression and have potential as therapeutic agents in treatment of FA

3

- Proof-of-principle in cell models and in GAA expansion carrying mice.
- Two phase 1 human trials
- Before moving to the clinic:
  - Specificity for the mutated FXN gene
  - Biodistribution, PK
  - Toxicity
- Ongoing trial with synthetic transcription elongation factors



FXN, frataxin; GAA, guanine-adenine-adenine; PK, pharmacokinetics

Erwin GS, et al., Science. 2017 Dec 22;358(6370):1617-1622. Erratum in: Science. 2023 Apr 7;380(6640):eadi0634.

Genetic therapy: Gene replacement and editing strategies target FXN deficiency with potential as therapeutic agents in FA

3

- Proof-of-principle in cell models (gene editing) and in cardiac + CNS conditional KO mice (gene replacement therapy).
- Before moving to the clinic:
  - Biodistribution/delivery
  - Control of transgene expression (enough not too much)
  - Off target effects (gene editing)
  - Immune response

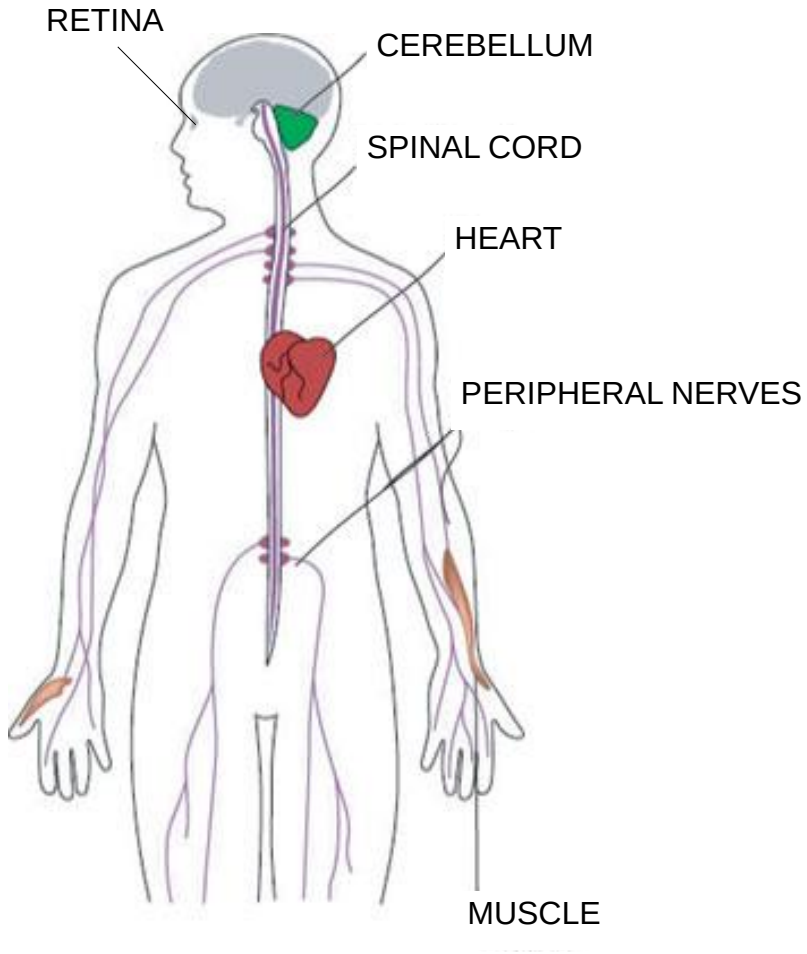
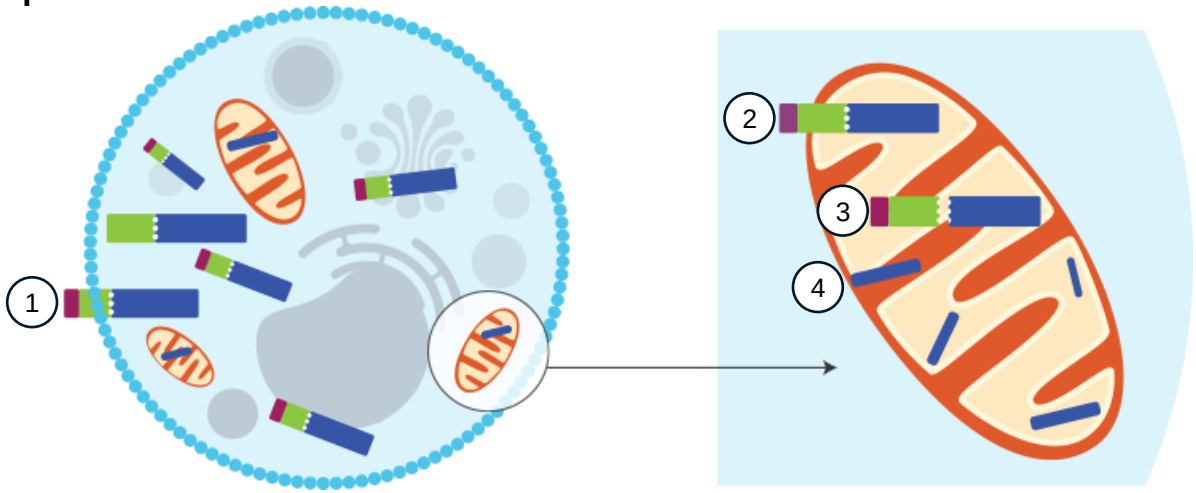


IMAGE: MODIFIED FROM MUSCULAR DYSTROPHY ASSOCIATION

FA, Friedreich ataxia; FXN, frataxin; CNS, central nervous system; KO, knock out
Wang JH, et al., Signal Transduct Target Ther. 2024 Apr 3;9(1):78.

Tat-Frataxin (nomlabofusp) - Larimar

- Nomlabofusp is a recombinant fusion protein manufactured as a cell penetrating peptide bound to frataxin, which allows it to cross cell membranes, carrying frataxin through the mitochondrial membrane and restoring energy production.



- Phase 1 and 2 trials in adults confirmed Nomlabofusp safety and ability to penetrate mitochondria in skin and buccal cells. A Phase 2 adolescent study is ongoing. Phase 3 is planned to start mid-2025.

Adapted from the Larimar web site: https://larimartx.com/our-science/scientific-approach/

Summary

FA is a multisystem progressive recessive disease due to intronic GAA repeat expansions in the FXN gene

Multisystem impacts require a multidisciplinary approach and standardized tools like mFARS and SARA for assessment and monitoring

Unified efforts in natural history studies and guidelines aim to improve and standardize diagnosis and care

Omaveloxolone and vatiquinone show promise in improving motor functions

Gene, epigenetic, and frataxin replacement therapies hold potential to target the root cause of FA

FA, Friedreich ataxia; FXN, frataxin; GAA, guanine-adenine-adenine; mFARS, modified Friedreich's Ataxia Rating Scale.

1. de Silva RN, et al. Pract Neurol. 2019;19(3):196–207; 2. Naidu SD and Dinkova-Kostova AT. Trends Pharmacol Sci. 2023;44(6):394–395; 3. Lynch DR, et al. Mov Disord. 2023;38(2):313–320; 4. Lynch DR, et al. Ann Clin Transl Neurol. 2024;11(1):4–16;

Q&A

Feel free to ask any questions by raising your hand.

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