Cardiac and Neurological Characterization of Friedreich's Ataxia

An Exploratory Analysis of a Hispanic Cohort

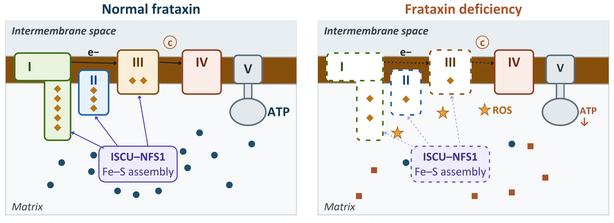
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Introduction

Friedreich ataxia (FRDA) is a rare autosomal recessive neurodegenerative disorder. GAA repeat expansions in intron 1 of *FXN* reduce frataxin[1] and impair iron–sulfur (Fe–S) cluster biogenesis in mitochondria[2] (Fig. 1). Cardiac complications largely determine survival[3], and neurological and cardiac involvement have been studied together[4]. How these domains and circulating biomarkers relate remains poorly characterized in Hispanic populations.

Figure 1 · Mitochondrial basis



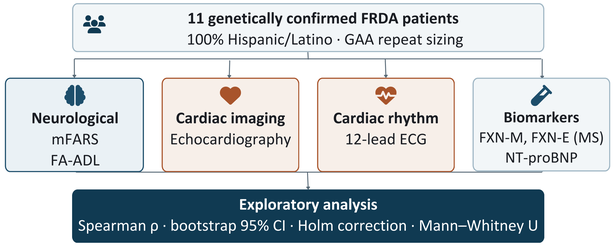
Frataxin supplies iron to the ISCU–NFS1 machinery, which builds Fe–S clusters for complexes I–III; complex IV and ATP synthase (V) carry none. With frataxin deficiency, cluster loading and electron transfer fall and unused iron accumulates[2]; electron leak may raise ROS.

OBJECTIVES

1. Describe neurological severity (mFARS, FA-ADL) and cardiac phenotype (echo, ECG).
2. Relate frataxin isoforms (FXN-M, FXN-E) to genotype, neurological and cardiac data.
3. Explore whether age at symptom onset relates to left ventricular (LV) mass.

Methods

Figure 2 · Study design

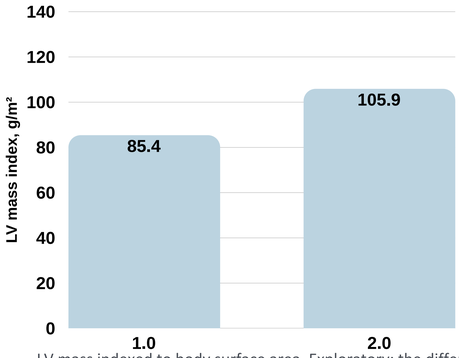


Results

Table 1 · Cohort characteristics, n = 11, median (IQR).

Variable	Median (IQR)	Variable	Median (IQR)
Age, years	**24.0 (21.5–33.5)**	FXN-M, ng/mL	**4.30 (2.42–4.91)**
Age at symptom onset, years	**13.0 (11.5–15.5)**	FXN-E, ng/mL	**3.59 (1.45–5.58)**
Disease duration, years	**14.0 (10.5–18.0)**	LVEF, %	**57 (53–60)**
GAA, shorter allele	**956 (811.5–1011)**	LV mass, g	**171 (132.5–185.5)**
GAA, longer allele	**1022 (903–1160.5)**	LV mass index, g/m²	**88.3 (85.2–105.9)**
mFARS total	**59.0 (52.3–65.5)**	IRT, ms	**100 (100–120)**
FA-ADL total	**17.5 (15.0–21.3)**	NT-proBNP, pg/mL	**53.4 (none > 125)**

Figure 3 · LV mass index by age at symptom onset



+24%

Median LV mass index, later vs earlier onset (105.9 vs 85.4 g/m²; Mann–Whitney p = 0.042). Absolute: 199 vs 140 g.

Onset age ↔ LV mass index
ρ = +0.61, p = 0.045

LV mass indexed to body surface area. Exploratory: the difference weakens after adjusting for age (p = 0.09), does not survive multiple-testing correction, and sex-specific thresholds could not be applied.

Figure 2 · Spearman correlations with bootstrap 95% CI

Association	Spearman ρ	ρ [95% CI]	p
FXN-M with			
mFARS lower-limb subscore		**−0.78** [−0.93, −0.33]	**0.005***
Isovolumetric relaxation time		**−0.66** [−0.95, +0.06]	0.029
Total mFARS		**−0.58** [−0.92, +0.03]	0.060
FXN-E with			
mFARS lower-limb subscore		**−0.81** [−0.96, −0.38]	**0.002***
Isovolumetric relaxation time		**−0.60** [−0.97, +0.08]	0.052
Total mFARS		**−0.61** [−0.97, +0.10]	0.047
Other associations			
Shorter GAA ↔ total mFARS		**+0.81** [+0.36, +0.98]	**0.003***
Lower-limb mFARS ↔ IRT		**+0.74** [+0.24, +0.98]	0.009
Onset age ↔ LV mass index		**+0.61** [−0.08, +0.99]	0.045

n = 11; 10,000 bootstrap resamples. * Survives Holm correction across 12 planned tests. Intervals are wide, so associations without * are exploratory.

Discussion

Frataxin measured by mass spectrometry tracked both genotype and lower-limb involvement: both isoforms fell with longer GAA repeats and worse lower-limb scores, the only frataxin associations that survived multiple-testing correction. With 11 patients, however, frataxin and GAA length could not be separated, so larger cohorts are needed to test whether frataxin adds information beyond repeat length. Lower frataxin and worse lower-limb function were also associated with longer isovolumetric relaxation time while LVEF and NT-proBNP remained largely normal, an exploratory signal that impaired ventricular relaxation may accompany neurological involvement at a subclinical cardiac stage. Finally, later onset was associated with a greater LV mass index (105.9 vs 85.4 g/m²), opposite to reports linking longer repeats and earlier onset to more severe cardiac disease[3,6]; age at assessment and the small sample may explain this unexpected direction.

CONCLUSION

In this Hispanic FRDA cohort, frataxin isoforms measured by mass spectrometry tracked GAA length and lower-limb impairment, and lower frataxin was linked to slower ventricular relaxation while systolic function was preserved. Frataxin isoforms merit evaluation as genotype-linked markers of neurological and early cardiac involvement in larger, prospective Latin American cohorts.

Limitations, References and Complementary Material