

Analysis of the visual system in Friedreich ataxia

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Abstract To use optical coherence tomography (OCT) and contrast letter acuity to characterize vision loss in Friedreich ataxia (FRDA). High- and low-contrast letter acuity and neurological measures were assessed in 507 patients with FRDA. In addition, OCT was performed on 63 FRDA patients to evaluate retinal nerve fiber layer (RNFL) and macular thickness. Both OCT and acuity measures were analyzed in relation to genetic severity, neurologic function, and other disease features. High- and low-contrast letter acuity was significantly predicted by age and GAA repeat length, and highly correlated with neurological outcomes. When tested by OCT, 52.7 % of eyes ($n = 110$) had RNFL thickness values below the fifth

percentile for age-matched controls. RNFL thickness was significantly lowest for those with worse scores on the Friedreich ataxia rating scale (FARS), worse performance measure composite Z_2 scores, and lower scores for high- and low-contrast acuity. In linear regression analysis, GAA repeat length and age independently predicted RNFL thickness. In a subcohort of participants, 21 % of eyes from adult subjects ($n = 29$ eyes) had macular thickness values below the first percentile for age-matched controls, suggesting that macular abnormalities can also be present in FRDA. Low-contrast acuity and RNFL thickness capture visual and neurologic function in FRDA, and reflect genetic severity and disease progression independently.

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This suggests that such measures are useful markers of neurologic progression in FRDA.

Keywords Friedreich ataxia · Optical coherence tomography · Neurology

Introduction

Friedreich ataxia (FRDA) is an autosomal recessive neurological disorder resulting from mutations of the *FXN* (frataxin) gene [1]. With a prevalence of 1 in 50,000 in European populations [1], it is the most common inherited ataxia. Of patients with FRDA, 97 % have an expanded GAA triplet repeat in the first intron of both alleles, while the remaining 3 % carry an expanded GAA repeat on one allele and a point mutation on the other [2–5]. This leads to decreased mRNA transcription and a deficiency of the protein frataxin. Frataxin deficiency ultimately leads to the features of FRDA, including ataxia, areflexia, loss of sensation and proprioception, and dysarthria [1, 6–9]. Individuals with FRDA can also develop cardiomyopathy, scoliosis, diabetes mellitus, hypacusis, and urinary dysfunction [1, 8, 9].

Though visual symptoms are not always recognized in FRDA, both afferent and efferent visual abnormalities may be found. Oculomotor findings associated with Friedreich ataxia include square wave jerks and difficulty with fixation [10]. Clinical or subclinical optic neuropathy is found in approximately two-thirds of people with FRDA, although severe visual loss is uncommon [11]. Visual field defects range from severe visual field impairment to isolated regions of reduced sensitivity [11]. Still, a few individuals have rapid visual loss, similar to that observed in Leber's hereditary optic neuropathy [12, 13].

As in other optic neuropathies, anatomic features of the retina can be evaluated with optical coherence tomography (OCT), a non-invasive, high resolution technique that uses near infrared light to quantify the thickness of the retinal nerve fiber layer (RNFL, the ganglion cell axons comprising the optic nerves, chiasm, and tracts) [14–17]. OCT can also image the ganglion cell and photoreceptor layers in the macular area, fovea, and optic disc, and has been used to examine various diseases of the retina and optic nerve, including optic neuritis, glaucoma, and multiple sclerosis [16, 18–21]. In multiple sclerosis, OCT reveals a decrease in RNFL thickness even in individuals who did not experience episodes of acute optic neuritis, suggesting that this technique can be useful in detecting anatomic abnormalities associated with subclinical visual loss, as is frequently found in FRDA [16].

Because of the highly quantifiable nature of visual function using measures such as low-contrast letter acuity (LCLA) and the highly reproducible results obtained

through OCT in other conditions, such measures of visual function are attractive outcome measures for intervention studies in FRDA for detection of subclinical and clinically significant changes. The current study examined a large cohort of individuals with Friedreich ataxia using LCLA and a subcohort with OCT, and assessed the relation of these measures to visual and neurologic abilities in FRDA.

Methods

Friedreich ataxia clinical outcome measure study cohort

Five hundred and seven subjects participating in the Friedreich Ataxia—Clinical Outcome Measures Study (FA-COMS) were evaluated at 1 of 12 sites. Data collected as part of this study included medical history and several quantitative measures: (1) visual function testing using high- and low-contrast vision charts, (2) timed 25-foot walk (T25FW), (3) timed 9-hole peg test (9HPT), and (4) the Friedreich ataxia rating scale (FARS), a quantified neurological exam used in the evaluation of FRDA. The T25FW, 9HPT, and FARS were performed according to protocols described previously [22–24]. Genetic confirmation was obtained via commercial or research testing. De-identified data were extracted from the most recent evaluation. In a subset of patients, frataxin protein levels in buccal cells and whole blood were available, as well as homeostatic model assessment–insulin resistance (HOMA-IR) values from fasting insulin and glucose levels [25, 26].

Contrast letter acuity testing was performed using retro-illuminated vision charts. High-contrast acuity was tested both monocularly and binocularly. Binocular low-contrast letter acuity testing was performed using the 2.5 and 1.25 % Low-Contrast Sloan Letter Charts (LCSLC) at a distance of 2 m (Precision Vision, LaSalle, IL, USA), based on a protocol used to measure visual dysfunction in MS and FRDA [15, 27]. A total binocular visual acuity score was computed using the single high-contrast chart and the 2.5 and 1.25 % LCSLC (score out of a total of 210 letters). Subjects used their standard refractive correction for distance. Visual function testing was performed by trained technicians.

Optical coherence tomography

OCT was performed on both eyes of FRDA patients to evaluate RNFL and macular thickness. Medical history was reviewed before testing, and none of the subjects who underwent OCT testing had underlying ophthalmological disease present, such as cataract and optic neuropathy, according to their most recent clinical evaluations. For each eye, the OCT protocol adopted was the fast RNFL thickness scan, performed using the *STRATUS* OCT 3 with OCT 4.0

software (Carl Zeiss Meditec, Inc., Dublin, CA, USA). This protocol was used for all RNFL imaging, and was performed by trained technicians. Quadrant thickness for each eye was also measured using the Fast RNFL Thickness Scan as described previously [28]. Average RNFL thickness was compared to a control population consisting of individuals evaluated at the University of Pennsylvania and other sites ($n = 533$). To evaluate macular thickness, macular cube 200×200 scans were also performed on a subset of the population using *CIRRUS* OCT (Carl Zeiss Meditec, Inc., Dublin, CA, USA), which uses spectral domain rather than time domain technology to produce higher resolution images at a higher speed than *STRATUS* OCT.

Statistics

Summary statistics, correlations and linear regressions were calculated using STATA 12.0 (Stata; StataCorp LP, College Station, TX, USA). Visual acuity and OCT were separately compared with measures of visual and neurological function in FRDA as well as age and GAA repeat lengths. All calculations use the length of the shorter GAA repeat. In addition, monocular and binocular visual acuity scores were compared across the cohort to assess for binocular summation.

Results

FA-COMS Cohort

The FA-COMS cohort ($n = 507$) was 49 % female with mean age of 28.1 years (range 7–78). Mean length of the

shorter GAA allele was 608 repeats, with 16 people carrying point mutations in conjunction with a single expanded allele. Mean age of onset was 13.8 years. The average FARS neurological exam score was 68.2, which typically corresponds to an individual ambulating with substantial difficulty. Levels of frataxin protein in buccal cells in this cohort had an average of 22.8 % of average frataxin levels in controls ($n = 188$) (Table 1).

Upon assessment with high-contrast vision charts, subjects read an average of 53.6 out of 70 letters with the right eye, 53.0 out of 70 letters with the left eye, and 58.1 out of 70 letters with both eyes (a Snellen visual acuity equivalent of 20/20) (Table 1). Thus, FRDA patients had minimal loss of central acuity, even though binocular visual acuity was slightly worse than in control subjects tested similarly and in an analogous cohort of subjects with multiple sclerosis [16, 27]. Additionally, 2 % of individuals ($n = 10$) had better monocular vision than binocular vision, which was not significantly predicted by age ($p = 0.77$) or by GAA repeat length ($p = 0.76$) accounting for sex. In addition, 29.2 % of individuals in this cohort had inter-eye differences in visual acuity of at least one acuity equivalent on a high-contrast vision chart (one line = five letters), while only 8.3 % had inter-eye differences of at least two acuity equivalents.

In general, letter acuity results reflected disease severity as assessed by genetic, temporal, neurological and biochemical measures. Scores from the binocular high- and low-contrast charts inversely correlated with GAA repeat length and length of disease duration. These scores and the total binocular score also were predicted independently by GAA repeat length and age in linear regression models

Table 1 Demographics

	FA-COMS Cohort ($n = 507$)	OCT Cohort ($n = 63$)
Age (years)	28.1 ± 15.2 (7–78)	28.2 ± 15.9 (8–67)
GAA repeat length	608 ± 246	588 ± 218
Subjects with point mutations	16	3
Age of onset (years)	13.8 ± 9.6	15.0 ± 10.6
Disease duration (years)	14.4 ± 10.5	13.3 ± 10.0
Sex (% female)	49	55
FARS score	68.2 ± 21.4	64.8 ± 20.3
High contrast visual acuity	58.1/70 ± 10.9	61.4/70 ± 10.7
Overall Snellen Score	20/20	20/20
Avg. 2.5 % LCSLC	29.4/70 ± 15.6	32.6/70 ± 14.0
Avg 1.25 % LCSLC	20.5/70 ± 13.9	24.0/70 ± 13.5
Hypertrophic cardiomyopathy (%)	54.0	38.8
Scoliosis (%)	78.7	89.8
Diabetes (%)	6.0	4.1
Hearing Loss (%)	15.7	4.1
Frataxin level, buccal cell (% control)	22.8 ± 19.4	26.8 ± 20.5
HOMA value (nL value <2.0)	4.0 ($n = 32$)	3.5 ($n = 21$)

Demographics from the Friedreich Ataxia—Clinical Outcomes Measures (FA-COMS) study ($n = 507$) and from the subcohort evaluated using optical coherence tomography (OCT) ($n = 63$)

Table 2 Correlations of letter acuity and OCT scores with disease features

	Binocular high contrast	2.5 % LCSLC	1.25 % LCSLC	Total low contrast	Total bin. acuity	RNFL thickness
GAA repeat length	-0.25*	-0.23*	-0.22*	-0.23*	-0.25*	-0.39**
Disease duration	-0.28*	-0.38*	-0.37*	-0.39*	-0.38*	-0.52*
FARS score	-0.50*	-0.64*	-0.65*	-0.66*	-0.66*	-0.72*
Z ₂ score	-0.45*	-0.62*	-0.63*	-0.64*	-0.63*	-0.62*
Age of onset	0.17*	0.18*	0.18*	0.18*	0.19*	0.39***
RNFL thickness	0.52*	0.55*	0.51*	0.54*	0.57*	

Data presented as the correlation coefficient with significance value designated. In the cross-sectional FA-COMS population, letter acuity results reflected disease severity as assessed by multiple measures. All visual acuity scores correlated with GAA repeat length and length of disease duration. Visual acuity scores more strongly correlated with the FARS exam and Z₂ composite score including timed 9HPT and T25FW. Similarly, RNFL thickness correlated with GAA repeat length and disease duration, with the strongest correlations with the FARS exam and Z₂ score. All visual acuity scores correlated strongly with RNFL thickness

* $p < 0.001$, ** $p = 0.004$, *** $p = 0.003$

Table 3 Linear regression analysis of visual function and RNFL thickness

	Binocular high con.	2.5 % LCSLC	1.25 % LCSLC	Total bin. acuity	RNFL thickness
GAA repeat length	-0.02 ± 0.002*	-0.03 ± 0.003*	-0.02 ± 0.003*	-0.07 ± 0.01*	-0.04 ± 0.01*
Age	-0.23 ± 0.03*	-0.40 ± 0.05*	-0.33 ± 0.05*	-0.96 ± 0.12*	-0.37 ± 0.14**
Sex	0.73 ± 0.91	0.67 ± 1.33	0.02 ± 1.20	1.43 ± 3.12	1.08 ± 3.30
Overall model	*	*	*	*	***
R ²	0.14	0.16	0.14	0.18	0.26

Visual acuity scores and RNFL thickness were all significantly and independently predicted by GAA repeat length and age in linear regression models accounting for sex. This suggests that visual acuity and RNFL thickness reflect both temporal disease progression and genetic severity. Data are presented as a regression coefficient and standard deviation, with statistical significance indicated

* $p < 0.001$, ** $p = 0.013$, *** $p = 0.002$

accounting for sex (Tables 2, 3). Visual acuity scores also reflected neurological function. Performance on the binocular high- and low-contrast charts, and the total binocular score, inversely correlated with the FARS exam score and the Z₂ score summary measure of 9HPT and the T25FW (Table 2).

Visual acuity testing also reflected biochemical data in linear regression models. Scores on the binocular high- and low-contrast charts were significantly predicted by frataxin protein levels obtained from buccal cells ($p = 0.007$, $p = 0.005$, and $p = 0.001$, respectively) accounting for age and sex (Table 4).

Finally, visual dysfunction as assessed by total binocular acuity score was associated with specific related clinical phenomena. The presence of diabetes ($p < 0.001$), hearing loss ($p < 0.001$), and hypertrophic cardiomyopathy ($p < 0.001$) predicted total binocular acuity and LCSLC performance after accounting for GAA repeat length, age, and sex (Table 4). In contrast, the presence of scoliosis did not significantly predict any visual measure (data not shown). Additionally, the presence of a point mutation ($n = 16$) did not significantly predict visual acuity in linear regression models accounting for disease duration and sex (Table 5).

As an alternative method of evaluation, we explored the effect of distinct variables on the likelihood of having abnormal visual acuity, defined by a binocular visual acuity of worse than 20/32. In this population, 10.1 % of the cohort ($n = 51$) had a Snellen acuity score of <20/32. Increasing age ($p < 0.001$) and GAA repeat length ($p < 0.001$) independently predicted reduced visual acuity beyond 20/32 accounting for sex. This was also significantly predicted by the presence of hearing loss ($p < 0.001$) accounting for age, GAA repeat length, and sex. Presence of diabetes predicted reduced visual acuity; however, this did not reach significance ($p = 0.019$). Scoliosis and hypertrophic cardiomyopathy did not significantly predict visual acuity below 20/32 in models accounting for age, GAA repeat length, and sex. Similarly, frataxin protein levels did not predict reduced visual acuity in models accounting for age and sex. The presence of a point mutation also did not significantly predict acuity below 20/32 when accounting for length of disease duration and sex.

OCT cohort

A subgroup of patients with FRDA from the primary site were evaluated with OCT ($n = 63$). All except three were

Table 4 Effect of frataxin level, presence of diabetes, hearing loss, or cardiomyopathy on visual acuity

	Regression coefficients of total binocular acuity score			
Frataxin (BC)	0.47 ± 0.14*			
Diabetes	−24.68 ± 7.06*			
Hearing Loss	−25.28 ± 4.53**			
HCM	−10.59 ± 3.66***			
GAA Repeat	−0.07 ± 0.01**	−0.06 ± 0.01**	−0.07 ± 0.01**	−0.07 ± 0.01**
Age	−0.75 ± 0.17**	−0.97 ± 0.12**	−0.85 ± 0.12**	−1.13 ± 0.13**
Sex	1.18 ± 5.16	2.71 ± 3.17	−0.27 ± 3.14	1.10 ± 3.25
Overall Model	<0.001	<0.001	<0.001	<0.001
R ²	0.11	0.22	0.25	0.21

Linear regression models were constructed to evaluate the ability of frataxin level, presence of diabetes, hearing loss, or cardiomyopathy to predict visual function scores, accounting for age, sex, and (except for frataxin level) GAA repeat length. Binocular acuity score was significantly predicted by frataxin protein level in a model accounting for age and sex and was also significantly and independently predicted by the presence of diabetes, hypertrophic cardiomyopathy (HCM), and hearing loss in models also accounting for GAA repeat length, age, and sex. Data are presented as the regression coefficient and standard deviation, with statistical significance indicated

* $p = 0.001$, ** $p < 0.001$, *** $p = 0.004$

Table 5 Effect of point mutations on visual function

	Binocular High Con.	2.5 % LCSLC	1.25 % LCSLC	Total bin. acuity
Presence of point mutation	−4.45 ± 2.63	−0.49 ± 3.74	−1.78 ± 3.37	−6.72 ± 8.85
Disease duration	−0.33 ± 0.04*	−0.60 ± 0.06*	−0.51 ± 0.06*	−1.44 ± 0.15*
Sex	1.06 ± 0.93	0.88 ± 1.33	0.16 ± 1.20	2.10 ± 3.14
Overall model	*	*	*	*
R ²	0.12	0.17	0.15	0.17

Linear regression models were constructed to assess the effect of point mutations on visual loss, accounting for sex and disease duration. The presence of a point mutation ($n = 16$ out of 507) did not significantly predict visual acuity on high or low contrast vision charts. Data are presented as a regression coefficient and standard deviation, with statistical significance indicated

* $p < 0.001$

homozygous for GAA expansions in the *FXN* gene; the remaining three subjects, from separate kindreds, were compound heterozygotes with one GAA repeat expansion and a point mutation on the other allele. Two of these individuals had a point mutation presumed to affect RNA splicing (165 + 5 G > C) [29]. The third carried the missense mutation G130 V (Table 1) [3]. In six of the 63 individuals evaluated, OCT could not be performed because of severe visual loss, fixation instability, or ptosis. Thus, all calculations involving the OCT cohort were performed using data from the 57 evaluable subjects. Of these, we obtained usable data for a total of 110 eyes due to eye movements or ptosis in a few individuals.

The average RNFL thickness in this cohort was $85.3 \pm 13.9 \mu\text{m}$, below the fifth percentile for age-matched controls ($104.0 \pm 11.5 \mu\text{m}$). Considered separately, 52.7 % of eyes ($n = 110$) had RNFL thickness below the fifth percentile for age-matched controls. When the quadrants of each eye were assessed separately, the mean inferior, nasal, and temporal quadrant average thickness values were normal, above the fifth percentile for age-matched controls;

however, 32 % of eyes were below the fifth percentile in the inferior quadrant, and 25 % of eyes were below the fifth percentile in each the nasal and temporal quadrants. The mean superior quadrant thickness in this cohort was abnormally thin, with RNFL values at the fifth percentile when compared with age-matched controls, and 51 % of individual eyes below the fifth percentile.

We then determined the disease-related factors associated with OCT values. When comparing RNFL thickness with measures of visual acuity, all vision scores correlated with RNFL thickness (Table 2). In linear regression analysis, all acuity scores also predicted RNFL thickness in models accounting for sex and GAA repeat length (Table 6). RNFL thickness correlated with GAA repeat length, FARS exam score, disease duration, Z_2 score, and age of onset (Table 2). In linear regression analysis, GAA repeat length and age both predicted RNFL thickness in models accounting for sex (Table 3), showing that RNFL thickness reflects both temporal disease progression and genetic severity. Z_2 score ($p < 0.001$) also significantly predicted average RNFL thickness accounting for age, sex,

Table 6 Relation of RNFL to visual function, GAA repeat length, and sex of subjects with FRDA

	Regression coefficients of RNFL thickness		
Binocular high-contrast acuity	0.56 ± 0.12*		
Total binocular acuity	0.18 ± 0.05*		
Total low-contrast acuity	0.22 ± 0.07*		
GAA repeat length	-0.02 ± 0.01	-0.02 ± 0.01	-0.02 ± 0.01
Sex	-2.22 ± 3.29	-0.02 ± 3.1	0.99 ± 3.20
Overall model	**	**	**
R ²	0.32	0.34	0.31

In linear regression analysis, visual acuity scores predicted RNFL thickness in models accounting for sex and GAA repeat length. Data are presented as regression coefficient ± standard deviation, with statistical significance indicated

* $p = 0.001$, ** $p < 0.001$

Table 7 Relation of RNFL to neurologic function

	Regression coefficients of RNFL thickness
Z ₂ Score	-5.35 ± 1.3 ($p < 0.001$)
GAA repeat length	-0.02 ± 0.01 (0.082)
Age	-0.01 ± 0.15 (0.96)
Sex	1.42 ± 2.97 (0.63)
Overall model	<0.001
R ²	0.46

Z₂ score, the summary measure including the timed 9-hole peg test (9HPT) and 25-foot walk (T25FW), significantly predicted average RNFL thickness in a linear regression model accounting for age, sex, and GAA repeat length. Data are presented as a regression coefficient and standard deviation, followed by significance in *parentheses*

Table 8 Correlations of macular thickness values with RNFL thickness and neurological function

	Cube volume	Cube average thickness
Disease duration	-0.34 (0.31)	-0.33 (0.32)
FARS score	-0.15 (0.66)	-0.16 (0.65)
RNFL thickness	0.04 (0.91)	0.04 (0.92)

Measures of macular thickness correlated with disease duration; however, these data did not reach significance. Macular thickness did not strongly correlate with the FARS neurological exam. Measured in ten individuals, the correlations between macular thickness and RNFL thickness were low and also did not reach significance. Data are presented as the r value followed by significance in *parentheses*

and GAA repeat length (Table 7). This suggests that RNFL thickness reflects neurologic abilities even beyond GAA repeat length. In contrast, average RNFL thickness was not

predicted by insulin resistance in linear regressions accounting for age, sex, and GAA repeat length, or by frataxin protein levels accounting for age and sex. In addition, the presence of scoliosis, hearing loss, diabetes, and hypertrophic cardiomyopathy do not show significant relationships with average RNFL thickness (data not shown).

Additionally, we performed parallel OCT with the *CIRRUS* protocol to evaluate macular anatomy more precisely. RNFL thickness measured by *STRATUS* OCT and *CIRRUS* OCT correlated well ($r = 0.92$; $p = 0.003$). In subjects evaluated for macular thickness using the *CIRRUS* OCT ($n = 23$), the average central subfield thickness was 249 μm, average cube volume was 10.0 mm³, and cube average thickness in this cohort was 277.4 μm in the evaluable subjects ($n = 16$). A total of 20.7 % of eyes from adult subjects ($n = 29$ eyes) had cube volume and average thickness below the first percentile. Measures of macular thickness correlated with disease duration; however, these data did not reach significance (Table 8). When macular thickness was compared to RNFL thickness as measured by *STRATUS* OCT 3 ($n = 10$ individuals), the correlations between average cube volume and average cube average thickness and RNFL thickness were low and did not reach significance (Table 8).

Discussion

The present study demonstrates that visual measures predict neurologic function in Friedreich ataxia, allowing the use of such measures for long-term assessment of disease progression. Visual function, particularly low-contrast vision, reflected neurologic function, a finding which matches those in smaller studies [27]. Similarly, RNFL thickness correlated highly with visual and neurological function. Genetic severity and age, both representative of disease severity, also independently predicted OCT and low-contrast acuity. Interestingly, correlations of OCT were even slightly higher with neurologic function than with visual function, showing that OCT may ultimately be useful as a level four anatomic biomarker of structural neuronal loss in FRDA in clinical drug trials designed to test efficacy. Alternatively, the correlations between RNFL thickness and visual acuity may be lowered by floor and ceiling effects of acuity testing. Still, low-contrast acuity and OCT can serve as functional and anatomic measures of neurologic progression in FRDA in intervention studies.

The data from this cohort, consistent with previous studies, show that visual loss in FRDA follows a specific pattern. Low-contrast acuity was better associated with neurologic severity, age and genetic severity than high-contrast acuity, suggesting loss of peripheral fields more

than central fields. Similarly, only a minority of patients had central acuities in the abnormal range, predicted by older age and longer GAA repeat length. Thus central vision is spared early in the disease but eventually can be lost in a small subset of the FRDA population. These possible differences between central and peripheral acuity suggest that visual field testing might specifically be useful in Friedreich ataxia, as has been performed in previous studies; however, such testing is substantially confounded because FRDA causes impairment of the hand movements needed to effectively participate in automated visual field testing. This limits the utility of visual field testing as a vision specific measure in FRDA. High-contrast scores were almost always better binocularly than with either eye alone, reflecting binocular summation. Thus, efferent dysfunction, which should affect binocular vision but not monocular vision, is not a major cause of functional vision loss in FRDA.

Furthermore, the pattern of RNFL loss in FRDA is distinctive. While the RNFL for all quadrants were affected in FRDA, the superior quadrant was somewhat more affected. In other mitochondrial diseases, the temporal quadrant seems to be affected by disease processes to a larger extent than other quadrants. The optic neuropathy in FRDA is likely to involve different disease mechanisms, leading to slightly different areas of selective vulnerability.

The relative symmetry between eyes shows the bilateral nature of dysfunction in FRDA. Perhaps in conjunction with the occipital lobe abnormalities that can occur in FRDA, the dominant cause of visual dysfunction in FRDA is a symmetric optic neuropathy affecting peripheral more than central visual fields. However, this presumptive peripheral optic neuropathy is not reflected in a corresponding loss of visual acuity. If the underlying RNFL thinning present in FRDA spares central vision, this may explain the average visual acuity of 20/20 across this cohort.

While correlations between scores on visual tests and neurologic and genetic severity were high, they did not approach unity, suggesting that other factors affect visual loss in FRDA. Although increased GAA repeat length predicts increasing visual loss, the presence of hearing loss also predicted visual function independent of genetic severity or age. This is most likely explained by the presence of modifying factors exacerbating the triad of optic neuropathy, hearing loss and diabetes, matching associations from studies performed before genetic testing was available. The presence of scoliosis did not predict acuity, suggesting independent factors altering their course in FRDA. Reduced visual function in FRDA has also been associated with the presence of point mutations. We could not confirm this connection; however, this may be attributed to the small number of individuals in this cohort with point mutations (3 %). It is possible that point mutations are associated with more severe vision loss, especially for

individuals with more severe mutations such as those with exon deletions or disruption of frataxin function, such as 493 C > T (R165C) or 165 + 5 G > C, a mutation which is predicted to disrupt normal gene splicing [4].

A surprising aspect of the present work is the amount of functional and anatomic loss across this broad cohort in a disorder that is not typically associated with dominant visual symptomatology. Visual acuity is abnormal compared to control subjects tested similarly, and are roughly the same as the low-contrast acuity observed in individuals with MS tested by an identical protocol [16, 27]. In multiple sclerosis, OCT has identified decreased RNFL thickness even in individuals who did not experience episodes of acute optic neuritis; this correlates with visual acuity scores [16]. In contrast, in the present FRDA cohort, RNFL thinning did not correspond to a proportionate loss of visual acuity. This suggests that the slow loss of retinal axons in FRDA could be mitigated by compensatory central or peripheral mechanisms.

Several individuals in this FRDA cohort showed abnormal macular anatomy, suggesting that FRDA may affect macular cells as well as ganglion cell axons in selected subjects. Macular changes could reflect the presence of retinal neuropathy as well as axonopathy in FRDA. Alternatively, macular loss could result from a primary dying back from injured axons with eventual loss of cell bodies. Interestingly, previous research using electroretinography has not detected substantial retinal abnormalities in FRDA, and the loss of low-contrast and peripheral visual field with preservation of high-contrast vision is not suggestive of a primary macular disease [30]. The present data suggest that macular features may be a component of the most advanced FRDA visual loss, and could clinically affect vision only in the most severely affected patients. Still, identification of macular abnormalities is crucial for understanding the limitations of regenerative capacities in FRDA.

Future studies focusing on more clearly defining the extent of macular loss and its clinical implications will be important in this field. In addition, a large longitudinal study of RNFL thickness will be helpful to determine the rate of change in this population as compared to normal controls. The high correlation between RNFL measurements obtained with *STRATUS* OCT and *CIRRUS* OCT suggests that the more advanced instrument, *CIRRUS* OCT, can be solely and reliably utilized in future studies as a level four outcome measure.

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Ethical standard All protocols were approved by the Institutional Review Board at the Children's Hospital of Philadelphia and other sites. Informed consent was obtained before participation.

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