FALCON: A prospective natural history study in patients with OPA1-autosomal dominant optic atrophy (ADOA)

STOKE THERAPEUTICS

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Disclosures

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ADOA is a severe, progressive optic neuropathy affecting 1 in 30,000 people globally[1,2]

Approximately 70% of ADOA cases are caused by *OPA1* variants[3] that lead to haploinsufficiency, mitochondrial dysfunction, retinal ganglion cell apoptosis, and progressive vision loss[4]

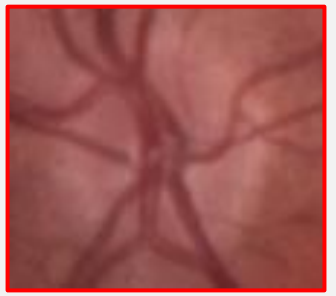
80% of patients are symptomatic by age 10[2]

Up to 46% of patients are legally blind[2]

Family with ADOA enrolled in the FALCON trial

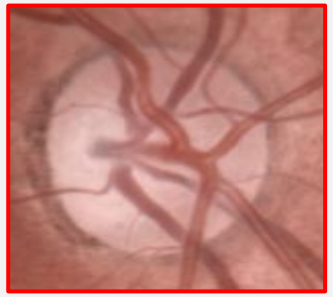
13-year-old with 20/50 vision OU

OD

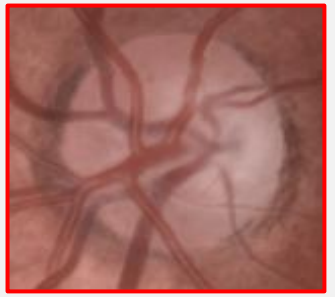


OS

Mother of three children with ADOA 20/150 vision OU



OD



OS

ADOA, autosomal dominant optic atrophy; OD, right eye; OPA1, optic atrophy gene; OS, left eye; OU, both eyes.

1. Lenaers G et al. Orphanet J Rare Dis 2012; 7: 46. 2. Yu-Wai-Man P et al. Ophthalmology 2010; 117 (8): 1538–1546. 3. Lenaers G et al. Prog Retin Eye Res 2021; 83: 100935. 4. Chun BY et al. Curr Opin Ophthalmol 2016; 27 (6): 475–480.

FALCON is a 24-month multicenter natural history study in patients with ADOA

FALCON aims to provide a better understanding of how multiple functional and anatomic parameters change over time to inform potential future interventional clinical trials

Eligibility criteria	✓ Clinical diagnosis of ADOA with confirmed heterozygous *OPA1* variant; ≥5 ETDRS letter score ✗ GOF variant; compound heterozygous or homozygous pathogenic/likely pathogenic variant; benign/likely benign variant (*OPA1* or other); phenotypic manifestation of syndromic ADOA
Study design	• 10 sites: 5 US, 2 Italy, 2 UK, 1 Denmark • 48 patients enrolled into three cohorts: 8–17 years, 18–40 years, and 41–60 years • Assessments at baseline, 6 months, 12 months, 18 months, 24 months
Primary endpoints	• Change from baseline to Month 24 in: BCVA (ETDRS), visual field sensitivity (Humphrey 10-2 automated perimetry), RNFL thickness (OCT), and macular GCL/IPL thickness (OCT)
Beacon sub-study	• *In vivo* imaging of retinal mitochondria using OcuMet Beacon™ (OcuSciences Inc.) • 16 patients have completed baseline Beacon evaluation

ADOA, autosomal dominant optic atrophy; BCVA, best corrected visual acuity; ETDRS, Early Treatment of Diabetic Retinopathy Study; GCL, ganglion cell layer; GOF, gain-of-function; IPL, inner plexiform layer; OCT, optical coherence tomography; OPA1, optic atrophy gene; RNFL, retinal nerve fiber layer; UK, United Kingdom; US, United States.

FALCON baseline demographics

Baseline demographics		8–17 years (n=15)	18–40 years (n=21)	41–60 years (n=11)	Total (N=47)
Age at screening (years)	mean (SD)	13.0 (2.9)	28.2 (6.2)	48.3 (6.0)	28.1 (14.1)
	median	14.0	29.0	48.0	27.0
	min–max	8–17	18–37	41–59	8–59
Sex (female)	n (%)	8 (53.3)	7 (33.3)	6 (54.5)	21 (44.7)
BCVA (Snellen equivalent)	mean	20/64	20/51	20/159	20/80*
	min–max	20/159–20/40	20/200–20/16	20/797–20/40	20/797–20/16
GCL/IPL global thickness	mean (SD)	15.8 (2.6)	15.3 (2.3)	14.4 (1.3)	15.2 (2.2)
RNFL global thickness	mean (SD)	70.6 (12.5)†	64.9 (13.5)	56.4 (9.2)	64.5 (13.1)‡

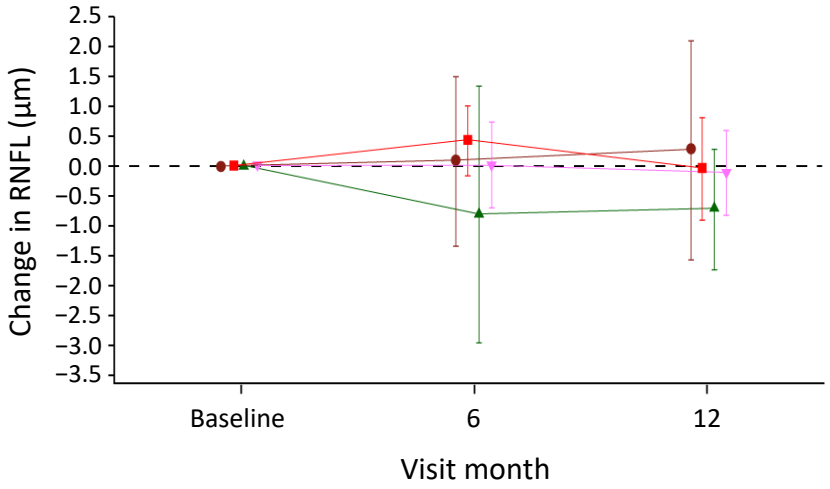
OPA1 genotype	n (%)
Nonsense	35 (74.5)
Missense	8 (17.0)
Splicing	2 (4.3)
Missing	2 (4.3)
TOTAL	**47 (100.0)§**

**Total BCVA is a rounded mean. †n=13. ‡n=45. §OPA1 genotype total only includes patients who completed at least one post-baseline visit.*
BCVA, best corrected visual acuity; GCL, ganglion cell layer; IPL, inner plexiform layer; max, maximum; min, minimum; OPA1, optic atrophy gene; RNFL, retinal nerve fiber layer; SD, standard deviation.

Minimal changes in RNFL thickness and VA are observed over 12 months in patients with ADOA

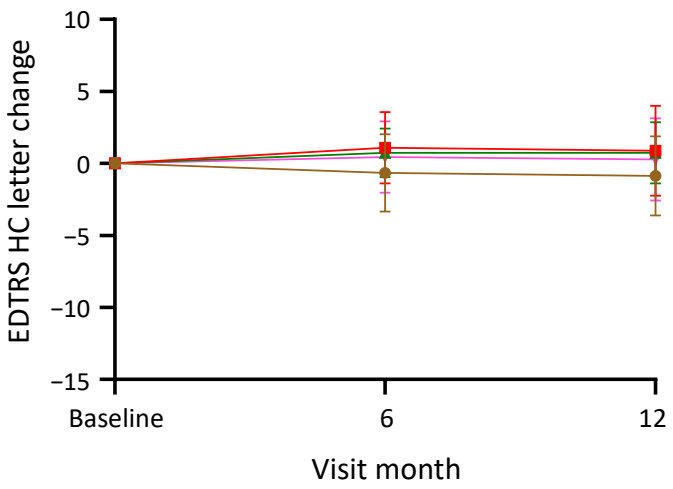
RNFL thickness

Change (±2 SE) in global thickness*

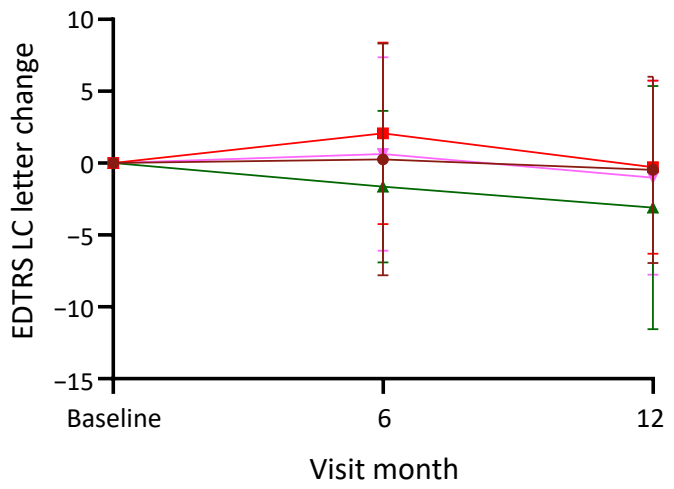


ETDRS VA

High contrast (100%)



Low contrast (2.5%)



Cohort 1: 8–17 years (n=13–15)† Cohort 2: 18–40 years (n=20–21)† Cohort 3: 41–60 years (n=11)† All cohorts (N=45–47)†

Data confirms that ADOA is a slowly progressing optic neuropathy with limited disease progression over 12 months

**Any data points that did not fall within ± 2 SE were excluded from the figure. †The number of patients vary depending on assessment and visit.*
ADOA, autosomal dominant optic atrophy; ETDRS, Early Treatment of Diabetic Retinopathy Study; HC, high contrast; LC, low contrast; RNFL, retinal nerve fiber layer; SE, standard error; VA, visual acuity.

Decline in low contrast VA is evident over 12 months when patients with ADOA are stratified based on baseline VA

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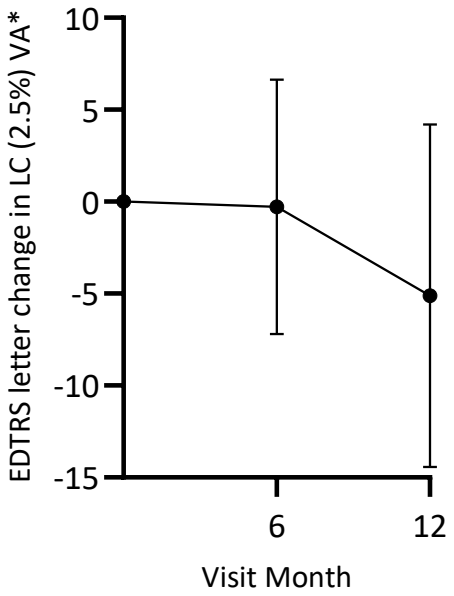
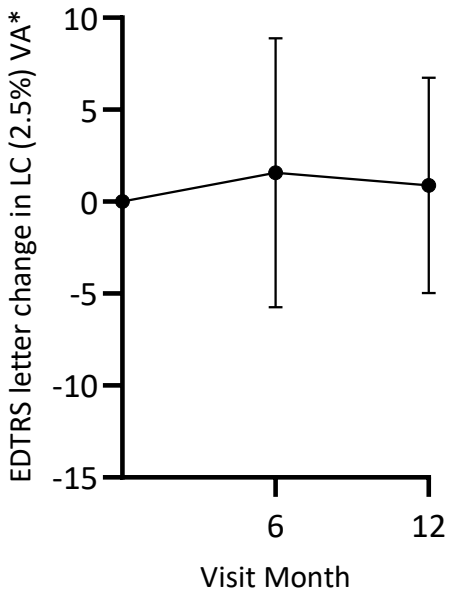
VA <0.3 logMAR



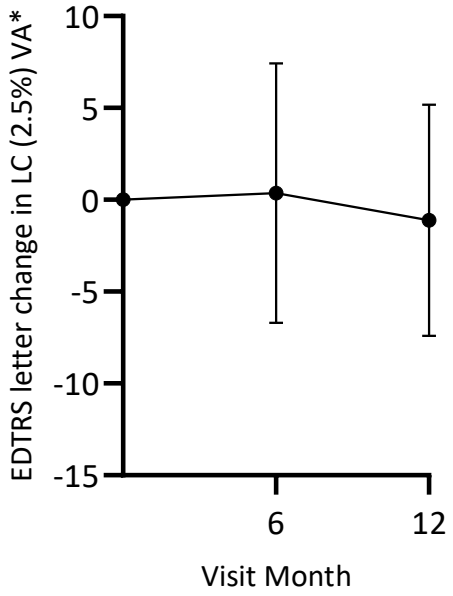
-5.1 letters; n=9

VA 0.3 to <0.6 logMAR



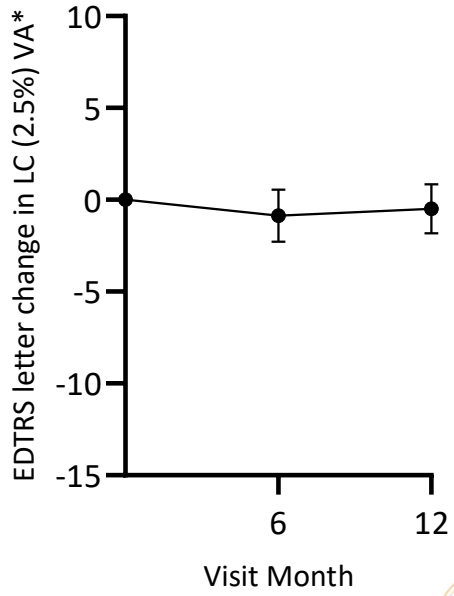
0.9 letters; n=19

VA 0.6 to <1.0 logMAR



-1.1 letters; n=15†

VA ≥ 1.0 logMAR



-0.5 letters; n=4

Patients with the highest baseline VA show the greatest decline (up to 5 letters) in low contrast VA over 12 months

**Mean EDTRS letter change in LC (2.5%) VA and standard deviations are plotted on the graphs. †n=15 and 14 at 6 months and 12 months, respectively.*
ADOA, autosomal dominant optic atrophy; ETDRS, Early Treatment of Diabetic Retinopathy Study; LC, low contrast; logMAR, log of the minimum angle of resolution; VA, visual acuity.

Patients with ADOA have particular difficulty with low contrast letters

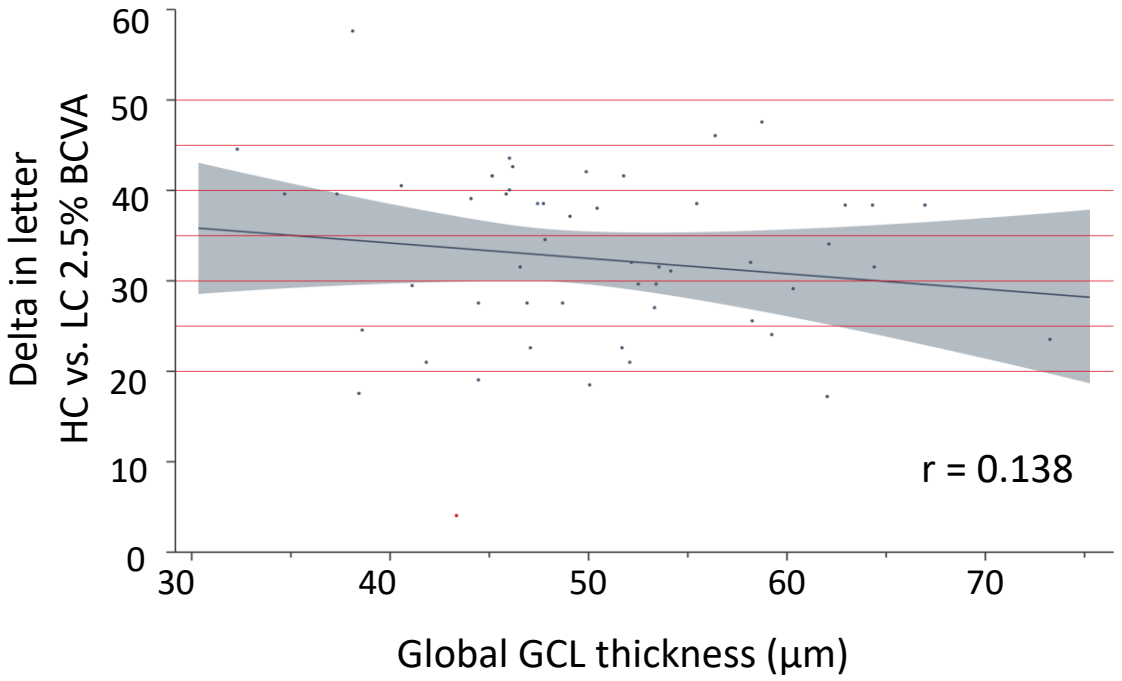
Assessment	Visual acuity	logMAR* mean			
	Control[1] (N=211)	VA <0.3 20/32 (n=9)	VA 0.3–0.6 20/50 (n=19)	VA >0.6–1.0 20/118 (n=15)	VA >1.0 20/283 (n=4)
HC BCVA	87	74	65	45	20
2.5% LC BCVA	67	41	30	13	1
Delta in letters†	**20**	**34**	**35**	**32**	**19**

The difference between high and low contrast VA in patients with ADOA is 13–15 letters greater than healthy patients

**logMAR values normalized to 100 letter scale. †Delta in letters is the difference in the number of letters read when viewed in HC vs LC.*
ADOA, autosomal dominant optic atrophy; BCVA, best corrected visual acuity; HC, high contrast; LC, low contrast; logMAR, log of the minimum angle of resolution; VA, visual acuity.
1. Little JA et al. Invest Ophthalmol Vis Sci 2013; 54 (1): 251–257.

The difference between high and low contrast VA in ADOA does not correlate with ganglion cell loss

- GCL/IPL and RNFL thickness are lower in patients with ADOA compared to healthy controls[1,2]
- These findings are consistent with ranges reported in other studies[1–4]
- The difference between high and low contrast VA are poorly correlated with GCL thickness
- Ganglion cell loss alone does not explain the difference between high and low contrast VA seen in patients with ADOA compared to controls



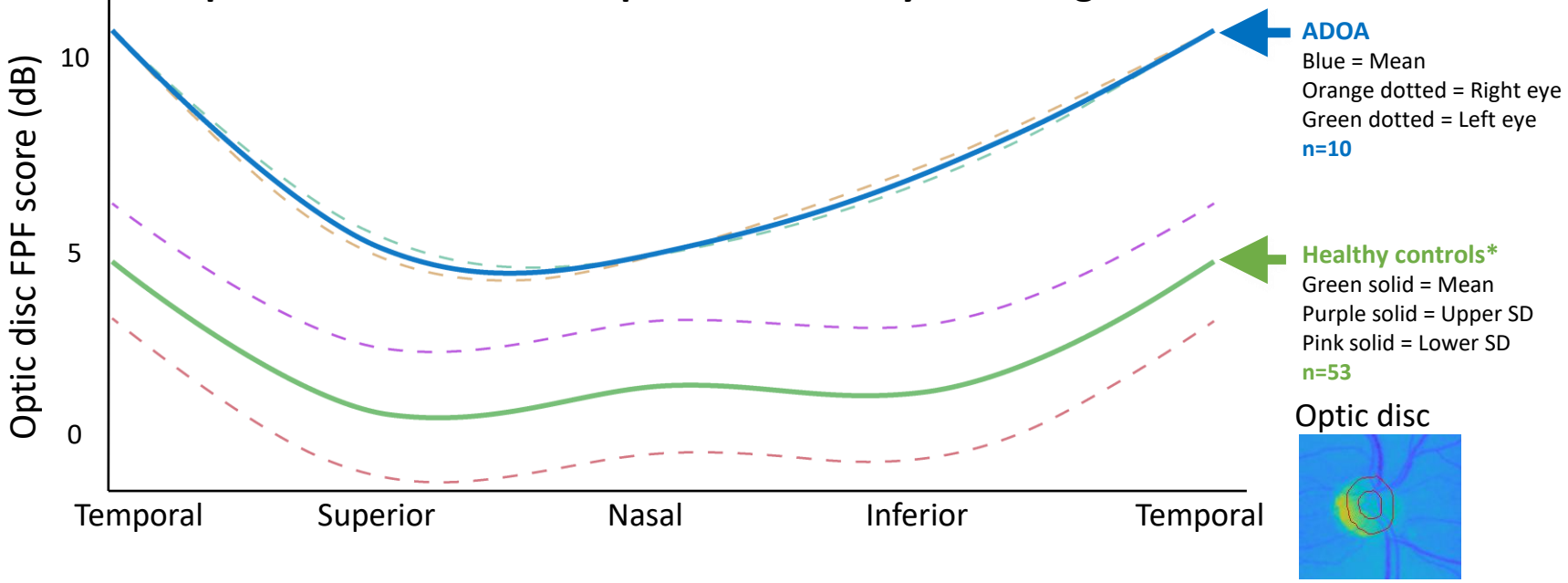
Data suggest factors other than ganglion cell loss contribute to the difference between high and low contrast VA in patients with ADOA

Each dot represents mean logMAR from both eyes.
ADOA, autosomal dominant optic atrophy; BCVA, best corrected visual acuity; GCL, ganglion cell layer; HC, high contrast; IPL, inner plexiform layer; LC, low contrast; logMAR, log of the minimum angle of resolution; RNFL, retinal nerve fiber layer; VA, visual acuity.

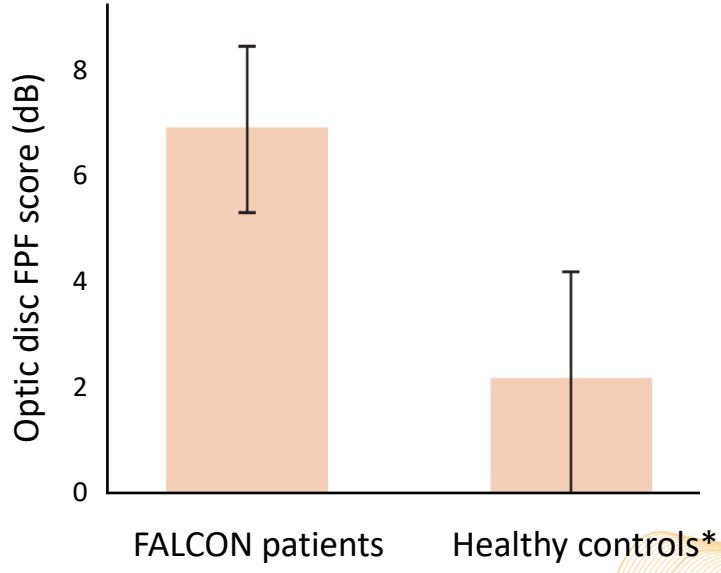
1. Corajevic N et al. Acta Ophthalmol 2018; 96 (3): 251–256. 2. Barboni P et al. Am J Ophthalmol 2014; 158 (3): 628–36.e3. 3. Barboni P et al. Ophthalmology 2011; 118 (10): 2076–2080. 4. Yu-Wai-Man P et al. Eye (Lond) 2011; 25 (5): 596–602.

Mitochondrial dysfunction as measured by FPF scores is higher in patients with ADOA

Optic disc FPF scores for patients 30–60 years of age



Optic disc FPF global scores



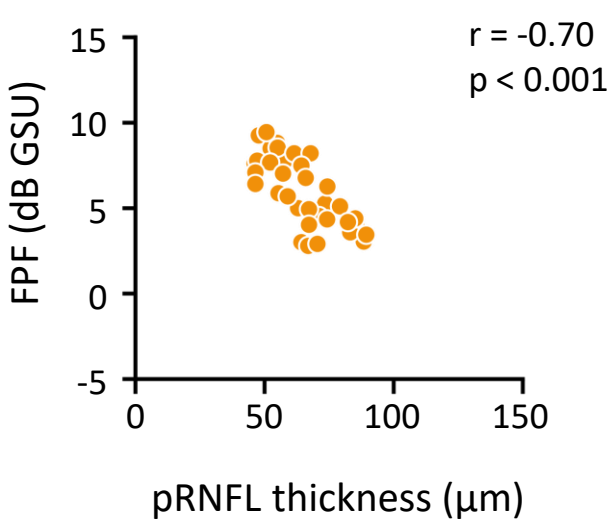
Optic disc FPF scores are higher across all sectors in patients with ADOA

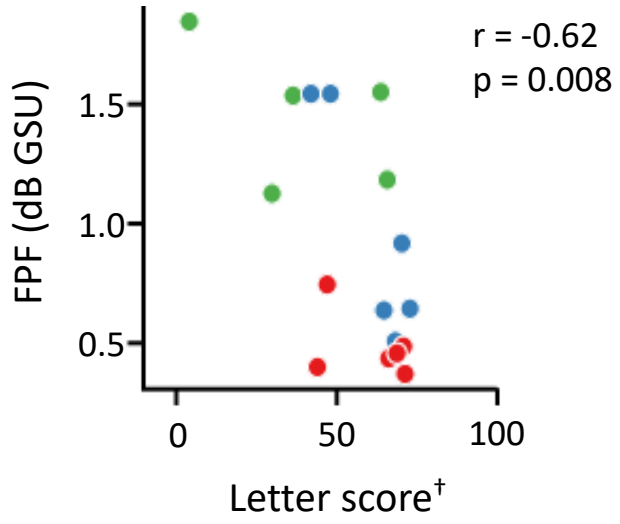
**Healthy control data supplied by OcuSciences™*
ADOA, autosomal dominant optic atrophy; dB, decibel; FPF, flavoprotein fluorescence; SD, standard deviation.

Mitochondrial dysfunction is correlated with decreased VA in patients with ADOA

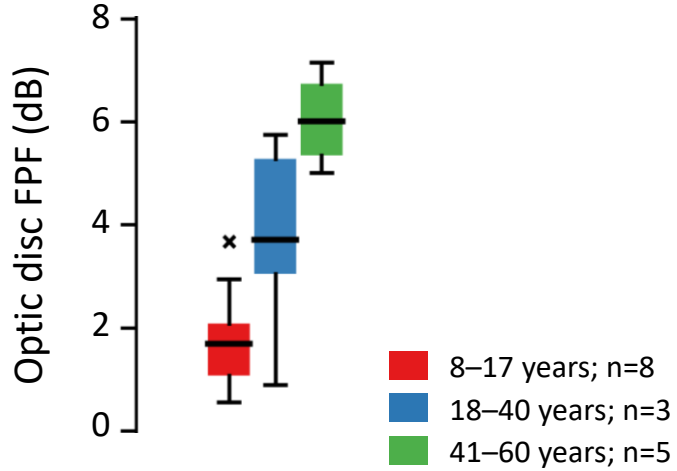
OcuMet Beacon (OcuSciences Inc) quantifies mitochondrial FPF to assess oxidative stress

Optic disc FPF negatively correlates with RNFL thickness and low contrast VA in patients with ADOA





Optic disc FPF is highest in older patients with ADOA*



Flavoprotein fluorescence is a potential biomarker for mitochondrial dysfunction in patients with ADOA

**Data points that fall below Q1−1.5×IQR or above Q3+1.5×IQR are considered outliers; FPF analyses conducted in Seaborn. †Scores were averaged across both eyes for 19 patients. Data were obtained under high-contrast (100%) and normalized to pRNFL thickness.*
ADOA, autosomal dominant optic atrophy; dB; decibel; FPF; flavoprotein fluorescence; GSU, grayscale units; IQR, interquartile range; pRNFL; peripapillary retinal nerve fiber layer; Q1, first quartile; Q3, third quartile; RNFL, retinal nerve fiber; VA, visual acuity.

Conclusions

1. FALCON data confirm that ADOA associated with *OPA1* variants is a slowly progressing disease that causes profound deficits in visual function and worsens with age
2. Low contrast VA is a potential valuable endpoint for demonstrating change in clinical trials for ADOA disease-modifying therapies
3. A lack of correlation between anatomy and difference between high and low contrast VA in ADOA suggests that visual impairment is driven in part by other factors
4. Mitochondrial dysfunction is detected in patients with ADOA and is correlated with decreased VA
5. Low contrast VA and FPF score provide measurable parameters in patients with ADOA for assessing potential efficacy of disease-modifying therapies over the course of one year

ADOA, autosomal dominant optic atrophy; FPF, flavoprotein fluorescence; OPA1, optic atrophy gene; VA, visual acuity.