Mitochondrial Dysfunction in Autosomal Dominant Optic Atrophy (ADOA) Assessed in FALCON, A Non-interventional, Natural History Study

#5268

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Disclosures: *Stoke Therapeutic clinical investigators; [6]Stoke Therapeutic employees

FALCON

INTRODUCTION

- ADOA is the most common inherited neuro-ophthalmic disorder. Patients typically present in the 1st decade of life and >1/2 of all patients are registered legally blind by the 5th decade.
- Most cases are caused by a heterozygous nuclear gene *OPA1* mutation, often leading to OPA1 protein haploinsufficiency. This is associated with impaired mitochondrial function in retinal ganglion cells leading to apoptosis causing progressive and irreversible vision loss.
- In presence of retinal oxidative stress, mitochondrial-flavoproteins, when stimulated by blue light, display increased fluorescence measured as green light. OcuMet Beacon™ (OcuSciences Inc., Ann Arbor, MI) leverages this by quantitating this light emission, generating a retinal flavoprotein fluorescence (FPF) score. FPF functions as a mitochondrial dysfunction biomarker *in vivo.*
- We present the initial baseline FALCON data from a patient subset who were imaged with the Beacon.

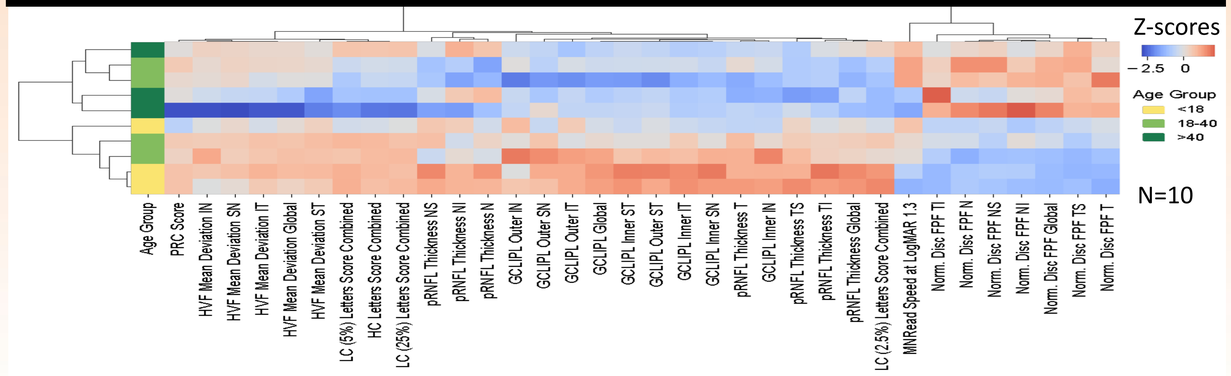
STUDY DESIGN

- 7 sites: 5 US, 2 UK
- 19 patients in 3 age cohorts (8-17, 18-40, 41-60y) were imaged with the Beacon
- All data points are averages for both patients' eyes
- **Scan QR code for more information**

DEMOGRAPHICS

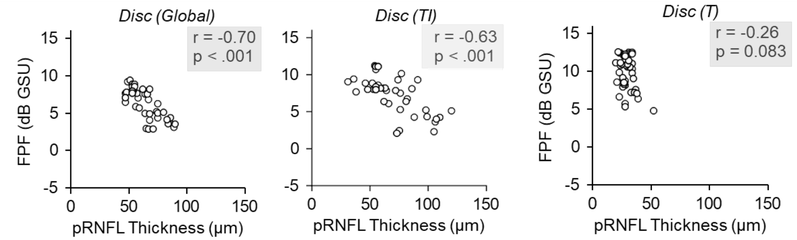
Demographics	8 - 17y	18 - 40y	41 - 60y
N	8	6	5
Median age (Min, Max)	12.5 (8.0,15.0)	33.5 (27.0,40.0)	48.0 (41.0,59.0)
Mean age (SD)	11.9 (3.23)	33.5 (4.23)	49.2 (6.46)
Female (%)	5 (62.5)	3 (50.0)	4 (80.0)
White (%)	8 (100.0)	6 (100.0)	5 (100.0)

FPF HIERARCHICAL CLUSTERING



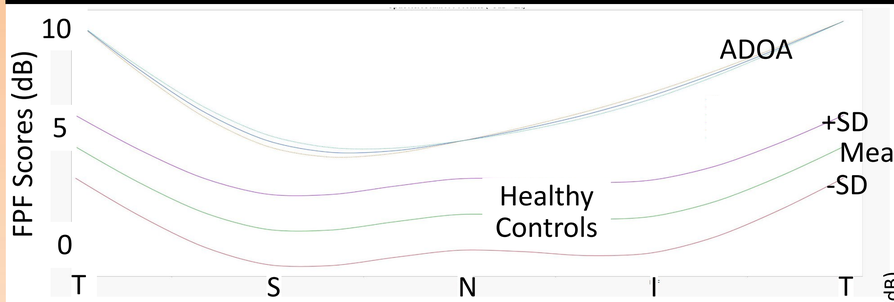
Patients >40y have worst only patients completing visual functions, thinner than average OCT, and higher FPF. Patients <18y have better visual function, thicker OCT, and lower FPF. Each row indicates a single patient. N=10/19, all assessments included.

DISC FPF and pRNFL

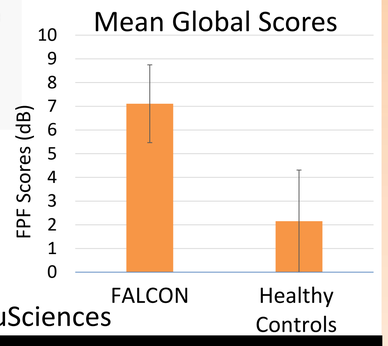


- Significant negative correlations across all sectors except for temporal
- pRNFL thickness in temporal region was thinner vs other sectors

OPTIC NERVE FPF SCORES

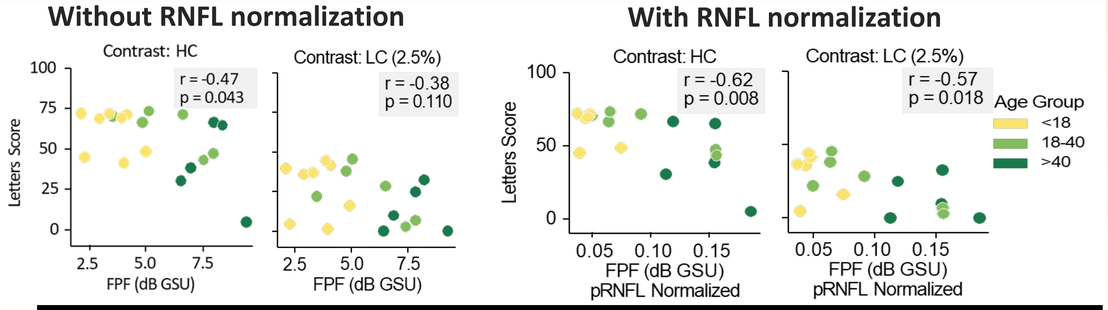


Healthy Controls SD range=1.45-1.68



- Beacon scores for patients 30-60y
- Healthy control data provided by OcuSciences

HC AND LC LETTER SCORE



CONCLUSIONS

- Disc FPF is a highly valuable novel biomarker for mitochondrial stress in ADOA
  - It worsens with age and significantly correlates with visual function and pRNFL
- Mitochondrial dysfunction as measured by FPF appears to correlate with visual acuity in ADOA; may be a useful biomarker to assess mechanism-based treatment interventions

ACKNOWLEDGEMENTS

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Abbreviations: BCVA, best corrected visual acuity; ETDRS, visual acuity chart; GCL, ganglion cell layer; IPL, inner plexiform layer; MNREAD, visual acuity chart; OCT, optical coherence tomography; pRNFL, peripapillary retinal nerve fiber layer; HVF, Humphrey Visual Function; LC, low contrast; HC; high contrast; IN, inferior nasal; SN, superior nasal; TI, inferior temporal; ST, superior temporal.

FALCON: A Prospective Natural History Study of Patients with Autosomal Dominant Optic Atrophy (ADOA): Determining Mitochondrial Dysfunction

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FALCON

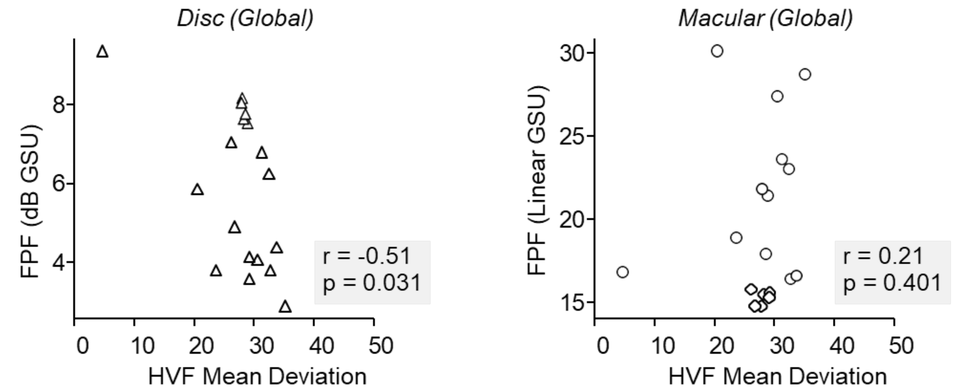
BACKGROUND

- The goal of a natural history study is to better understand disease progression as well as to potentially identify the best biomarkers for monitoring treatment effects, particularly to distinguish the effects of aging from those of disease in visual functions and structures
- FALCON aims to identify variables that significantly change with disease progression but minimally change with normal aging
- Limitations: lack of a control group and longitudinal data
- Strategies to mitigate limitations:
  - Use published normative data for healthy subjects to estimate age effects on variables of interest
  - Employ statistical methods that can estimate and remove age effects from ADOA group, assuming that the age effect is linear and similar in both populations
  - Use publications of known validated biomarkers that change minimally with age
  - Use machine learning algorithms to analyze the data and identify potential biomarkers that fulfill criteria. This can include feature selection techniques that can handle the confounding effects of age

STUDY DESIGN

- **Duration:** 24 months; assessments at baseline, 6, 12, 18, and 24 months
- **Primary endpoints:** Change from baseline to 24 months in visual acuity chart (ETDRS) best corrected visual acuity (BCVA), Humphrey Visual Field, retinal nerve fiber layer (RNFL), optical coherence tomography (OCT), macular ganglion cell layer/inner plexiform layer (GCL/IPL) thickness
- **Exploratory endpoints:** Retinal mitochondrial dysfunction were imaged with the Beacon
- **Key inclusion criteria:** ADOA clinical diagnosis with confirmed heterozygous *OPA1* variant, ≥5 ETDRS
- **Key exclusion criteria:** Gain-of-function or compound heterozygous *OPA1* variants, extraocular phenotypic manifestations of (syndromic) ADOA (ADOA-plus)

HUMPHREY 10-2 VISUAL FIELD MD



- FPF as a function of Humphrey 10-2 Visual Field (HVF) threshold test mean deviation (MD)
  - Left scatter-plot shows relationship between HVF MD and global disc FPF
    - Correlation coefficient r = -0.51 and p = .031 suggests a moderate negative correlation
  - Right scatter-plot shows HVF MD as a function of macular FPF
    - No significant correlation

RESULTS

BCVA LogMAR and Visual Acuity Letter Scores

		8 - 17y		18 - 40y		41 - 60y	
		OD	OS	OD	OS	OD	OS
BCVA LogMAR	**Median (min, max)**	0.38 (.24,1.1)	0.32 (.22,.80)	0.30 (.24,.82)	0.40 (.26,.90)	0.92 (.38,1.6)	0.98 (.40,1.6)
	Mean (SD)	0.54 (.31)	0.46 (.24)	0.45 (.28)	0.50 (.25)	0.87 (.51)	0.92 (.52)
Visual Acuity Letter Scores	**Median (min, max)**	66.00 (32,73)	69.00 (45,74)	70.00 (44,73)	65.00 (40,72)	39.00 (4.0,66)	36.00 (4.0,65)
	Mean (SD)	58.25 (16)	62.00 (12)	62.33 (14)	60.00 (13)	41.40 (25)	38.80 (26)