Flavoprotein fluorescence in the 24-month FALCON natural history study of autosomal dominant optic atrophy: A potential biomarker for mitochondrial dysfunction

ARVO 2025 Annual Meeting

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ADOA is an inherited, progressive optic neuropathy primarily caused by mutations in the *OPA1* gene

1 in **35,000** people are affected globally[1]*

>400 different *OPA1* gene mutations have been reported in patients with ADOA[2]

46% of patients are registered as legally blind[1]

80% of patients are symptomatic by age 10[1]

65–90%
of cases are caused by mutations in *OPA1* gene[3]

→

50%
OPA1 protein expression and disease manifestation

ADOA NATURAL HISTORY STUDY

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

- **OPA1 protein** is essential for proper mitochondrial function
- Mitochondrial stress can be measured in patients with ADOA and is believed to correlate with disease progression
- FALCON aims to provide a better understanding of how ADOA disease parameters change over time to inform potential future interventional clinical trials

**Incidence in Denmark estimated to be closer to 1 in 10,000 due to founder effect. †FALCON study design – 10 sites: 5 USA, 2 Italy, 2 UK, 1 Denmark. Assessments taken at baseline, 6-, 12-, 18-, 24-month visits. Last patient visit scheduled for July 2025.*
ADOA, autosomal dominant optic atrophy; OPA1, OPA1 mitochondrial dynamin like GTPase.

1. Yu-Wai-Man P *et al. Ophthalmology* 2010; 117 (8): 1538–1546. 2. Le Roux B et al. *Orphanet J Rare Dis* 2019; 14 (1): 214. 3. Chun BY *et al. Curr Opin Ophthalmol* 2016; 27 (6): 475–480.

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)
logMAR	mean	0.53	0.45	0.85	0.57
	min–max	0.3–0.9	-0.1–1.0	0.3–1.6	-0.1–1.6
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)†

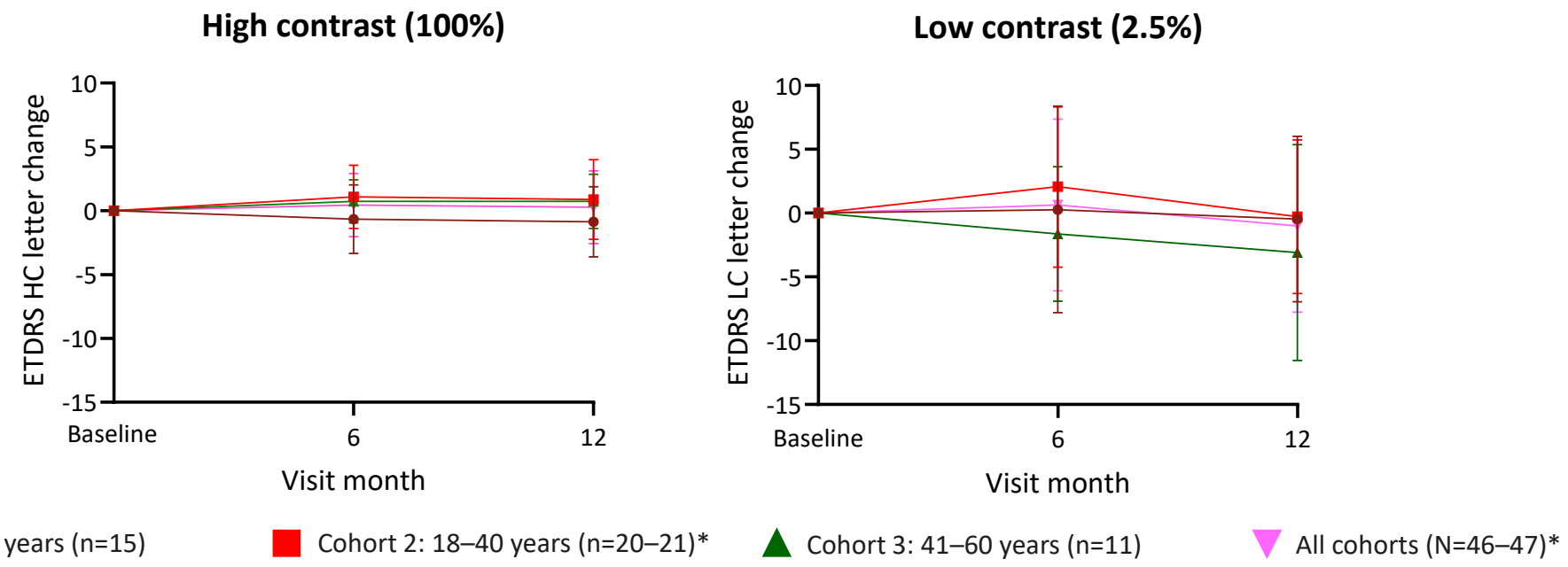
OPA1 genotype	n (%)
Nonsense	36 (74.5)
Missense	9 (17.0)
Splicing	2 (4.3)
TOTAL	**47 (100.0)‡**

*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; OPA1, OPA1 mitochondrial dynamin like GTPase; RNFL, retinal nerve fiber layer; SD, standard deviation.

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

ETDRS VA



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

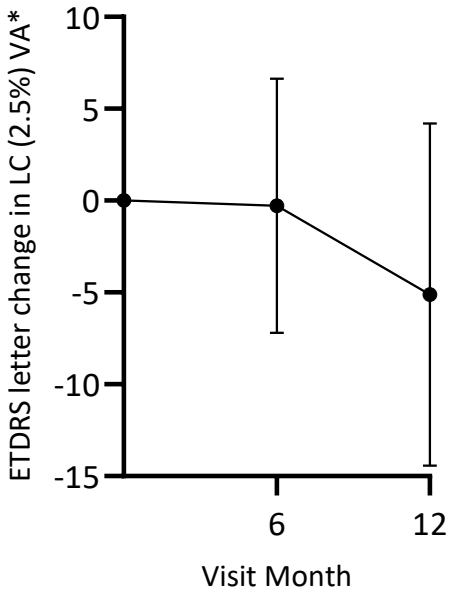
Month 12 data cut: July 31, 2024.

**n=21 and 20 and 6 months and 12 months, respectively for cohort 2.*

ADOA, autosomal dominant optic atrophy; ETDRS, Early Treatment Diabetic Retinopathy Study; HC, high contrast; LC, low contrast; VA, visual acuity.

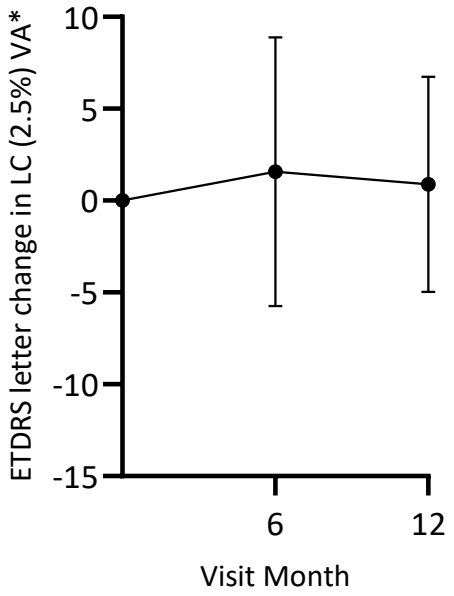
Decline in LCVA (2.5%) is detected over 12 months in patients with ADOA with good baseline VA

VA <0.3 logMAR



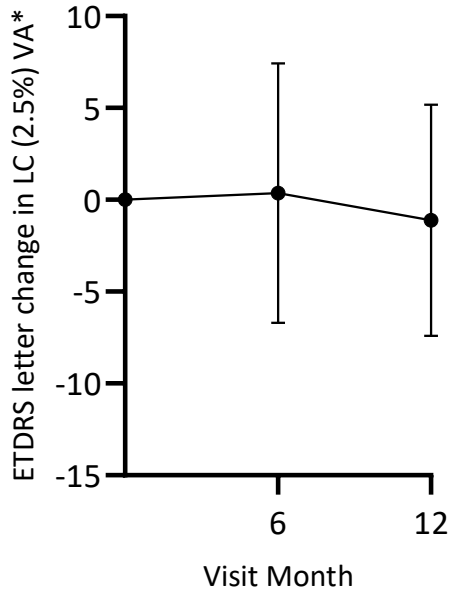
−5.1 letters; n=9

VA 0.3 to <0.6 logMAR



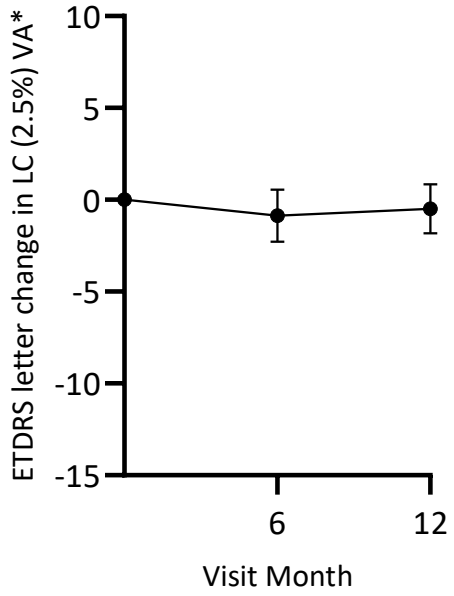
0.9 letters; n=19

VA 0.6 to <1.0 logMAR



−1.1 letters; n=15†

VA ≥1.0 logMAR



−0.5 letters; n=4

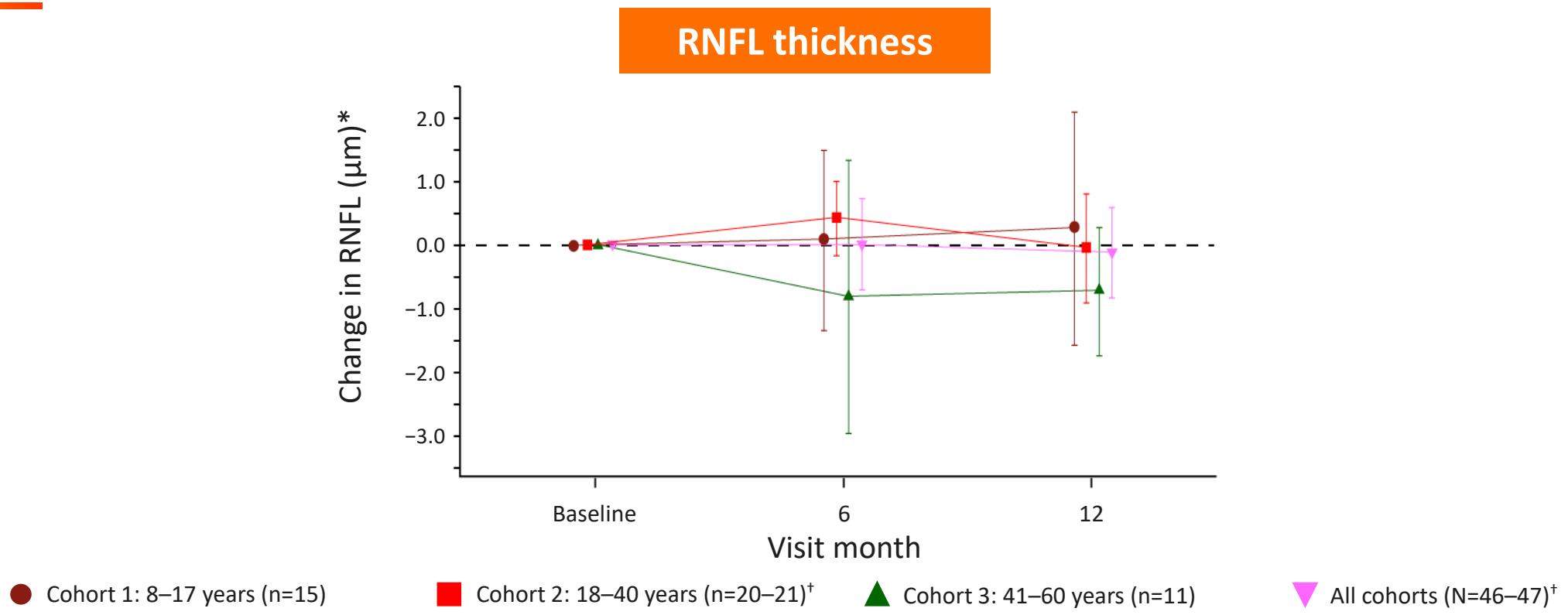
Patients with the highest baseline VA experience the greatest decline (up to 5 letters) in LCVA over 12 months

Month 12 data cut: July 31, 2024.

**Mean ETDRS 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 Diabetic Retinopathy Study; LC, low contrast; LCVA, low-contrast visual acuity; logMAR, log of the minimum angle of resolution; VA, visual acuity.

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



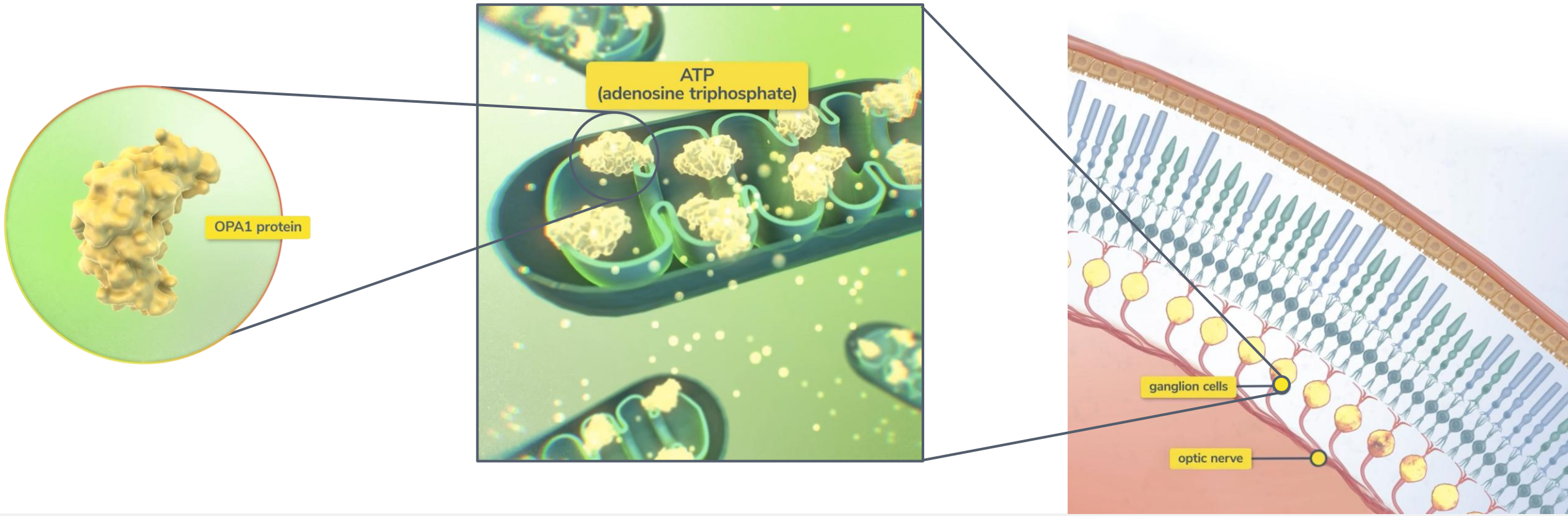
Given the minimal change in RNFL thickness in patients with ADOA, factors other than retinal ganglion cell loss are likely responsible for the decline in LCVA

Month 12 data cut : July 31, 2024.

**Error bars represent 95% confidence intervals. †*n=21 and 20 and 6 months and 12 months, respectively for cohort 2.*

ADOA, autosomal dominant optic atrophy; LCVA, low-contrast visual acuity; RNFL, retinal nerve fiber layer; SE, standard error.

Retinal ganglion cells rely heavily on mitochondrial function to meet the high metabolic demands required for visual signaling

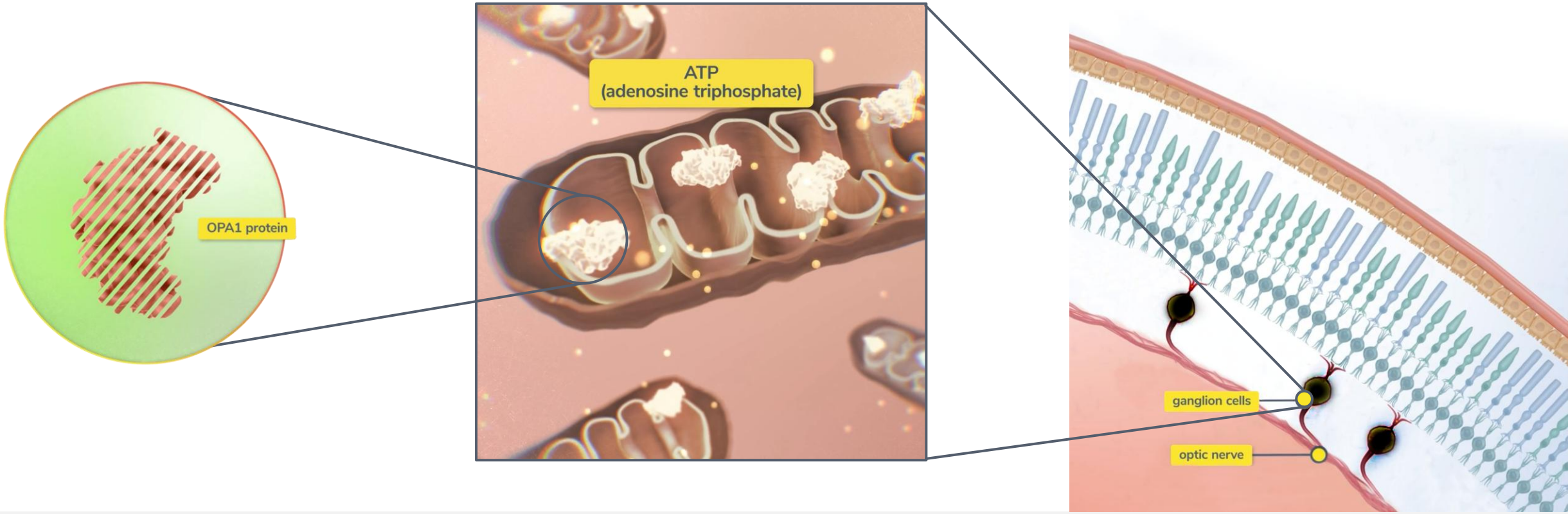


OPA1 protein in ganglion cell mitochondria is critical for normal mitochondrial function, efficient ATP energy production, and cellular health

ATP, adenosine triphosphate; OPA1, OPA1 mitochondrial dynamin like GTPase.

Ng WSV *et al*. *Ther Adv Rare Dis* 2021; 2: 26330040211029037.

In ADOA, OPA1 protein deficiency leads to mitochondrial stress, ganglion cell dysfunction, and impaired vision



Loss of OPA1 disrupts mitochondrial dynamics, reduces energy production, and increases susceptibility to ganglion cell death

ADOA, autosomal dominant optic atrophy; ATP, adenosine triphosphate; OPA1, OPA1 mitochondrial dynamin like GTPase.

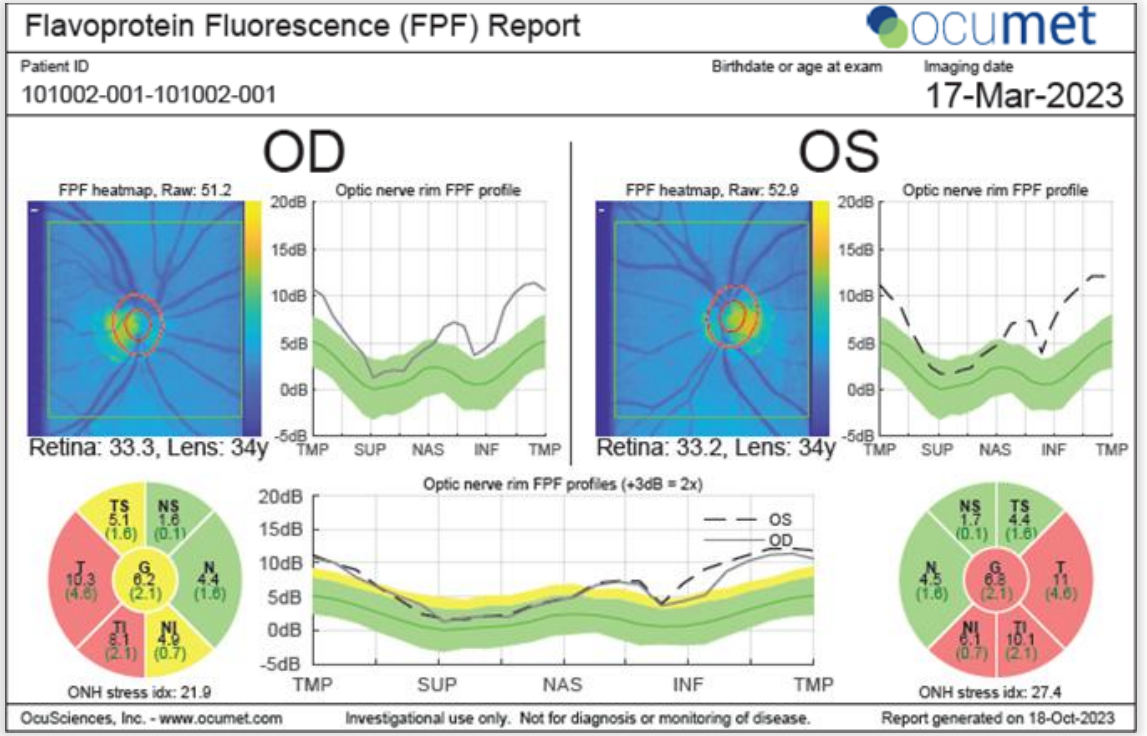
Ng WSV *et al*. *Ther Adv Rare Dis* 2021; 2: 26330040211029037.

Flavoprotein fluorescence: A promising biomarker for mitochondrial stress in patients with ADOA

OcuMet Beacon quantifies mitochondrial flavoprotein fluorescence, a well-studied precursor of retinal cell death[1]

- OcuMet Beacon is a non-invasive assessment to detect retinal metabolic function in a patient's eye
- Under oxidative stress, mitochondrial flavoproteins emit increased fluorescence when stimulated with blue light
- OcuMet Beacon quantifies this fluorescence to generate a retinal FPF score
- FPF functions as a promising biomarker for mitochondrial stress *in vivo*

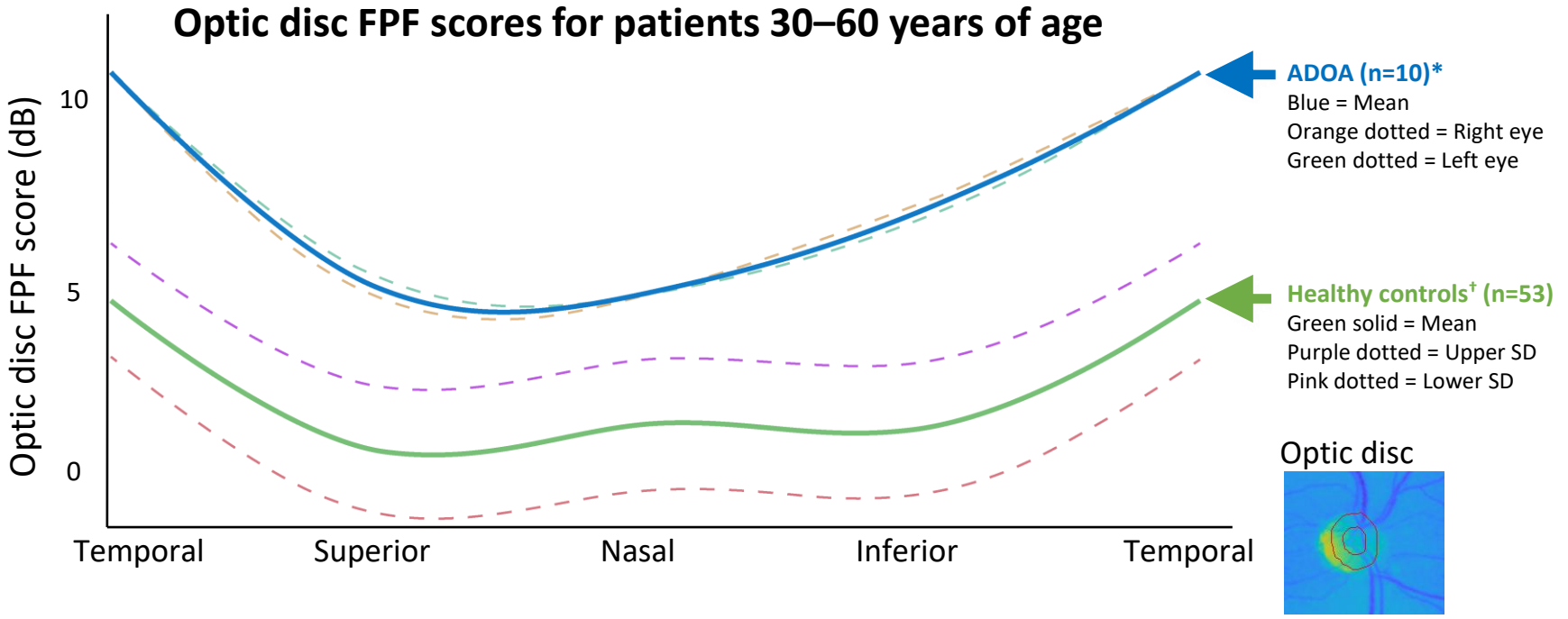
Representative OcuMet Beacon FPF report

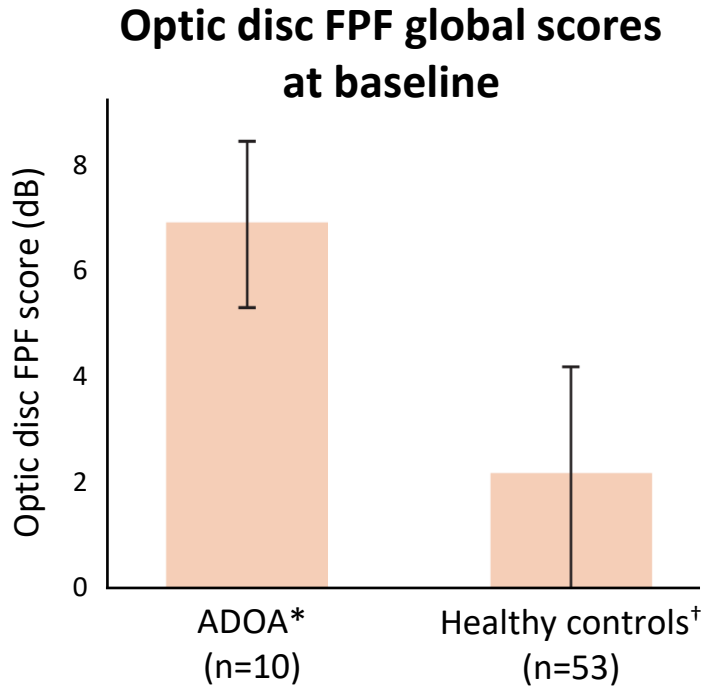


ADOA, autosomal dominant optic atrophy; dB, decibel; FPF, flavoprotein fluorescence; G, global; INF, inferior; N, nasal; NAS, nasal; NI, nasoinferior; NS, nasosuperior; OD, right eye; ONH, optic nerve head; OS, left eye; SUP, superior; T, temporal; TI, tempoinferior; TMP, temporal; TS, temposuperior; y, year.

1. Chen A et al. Eye 2021; 35 (1): 74–92.

Mitochondrial stress as measured by FPF score is higher in patients with ADOA

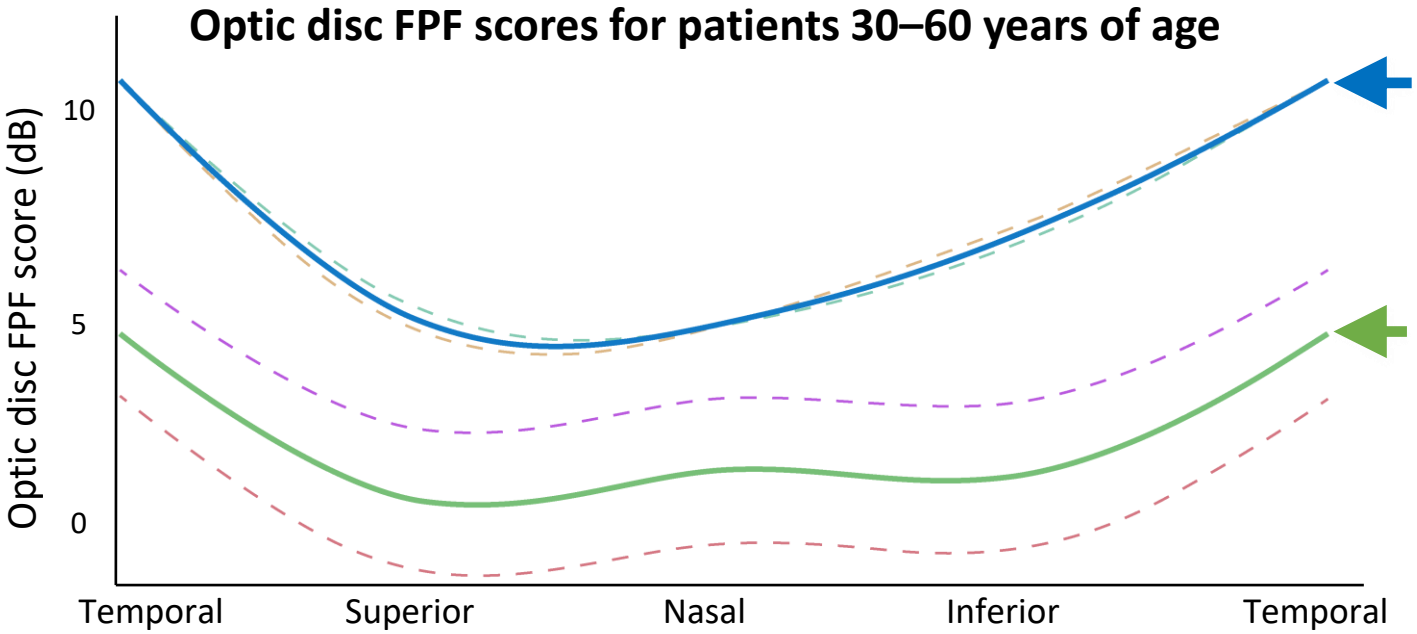


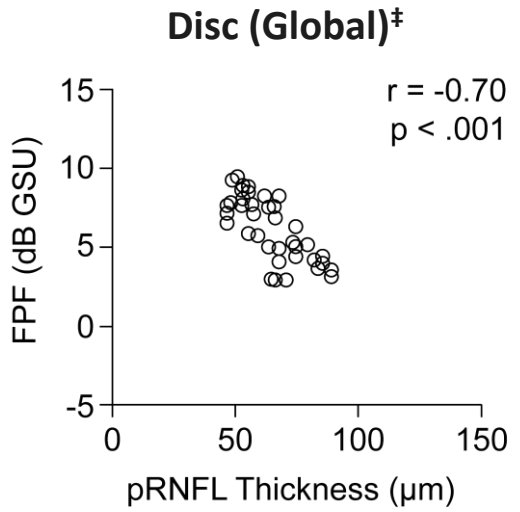


FPF scores are higher across all sectors in patients with ADOA compared to healthy controls

**ADOA data obtained from patients enrolled in the FALCON study. †Healthy control data supplied by OcuSciences.*
ADOA, autosomal dominant optic atrophy; dB, decibel; FPF, flavoprotein fluorescence; SD, standard deviation.

FPF scores are higher in advanced ADOA despite reduced pRNFL thickness

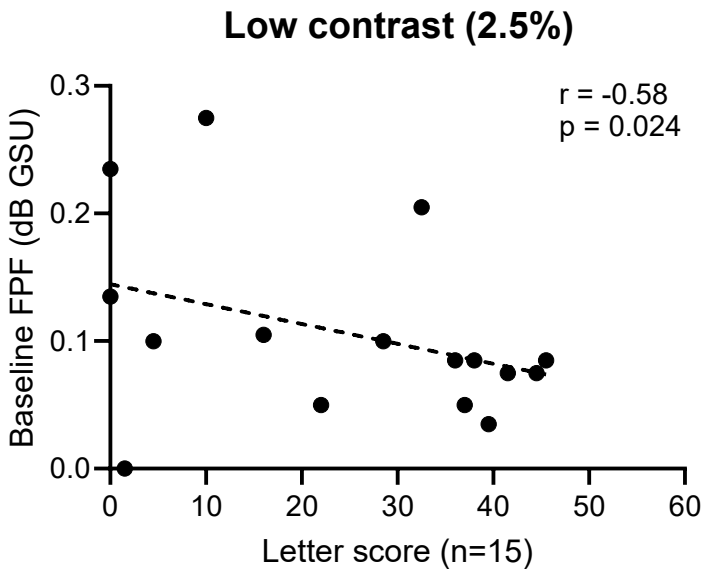


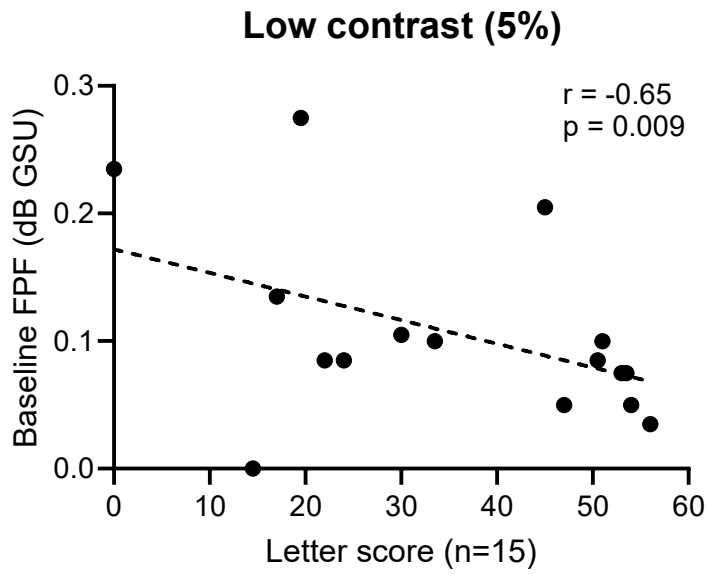


FPF scores are higher across all sectors in patients with ADOA compared to healthy controls

**ADOA data obtained from patients enrolled in the FALCON study. †Healthy control data supplied by OcuSciences. ‡n=38 eyes (19 patients with ADOA). Baseline optic FPF values are presented for patients with ADOA.*
ADOA, autosomal dominant optic atrophy; dB, decibel; FPF, flavoprotein fluorescence; GSU, grayscale units; pRNFL, peripheral retinal nerve fiber layer; SD, standard deviation.

High FPF scores are correlated with lower VA at baseline and Month 12 in FALCON patients





Month 12 data show a similar trend

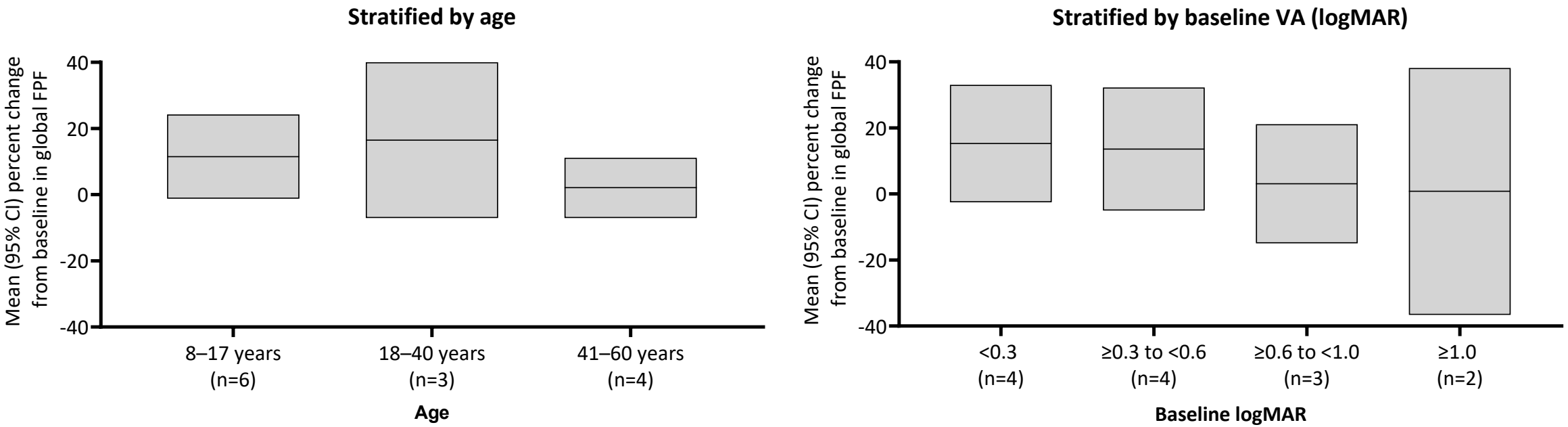
High FPF scores suggest greater mitochondrial stress in patients with ADOA who have reduced VA

Month 12 data cut: July 31, 2024. Data were normalized to pRNFL thickness.

ADOA, autosomal dominant optic atrophy; dB, decibel; FPF, flavoprotein fluorescence; GSU, grayscale units; pRNFL, peripapillary retinal nerve fiber layer; VA, visual acuity.

Patients aged 18–40 years and those with the highest baseline VA show the greatest increase in FPF scores over 12 months

Percent change in normalized FPF score at Month 12



Data suggest that patients with ADOA with the highest VA show the largest increase in mitochondrial stress over 12 months

Month 12 data cut: July 31, 2024. Baseline is defined as the value obtained from the baseline visit assessment. Normalized values are created by dividing the OcuMet Beacon value with corresponding RNFL.
ADOA, autosomal dominant optic atrophy; CI, confidence interval; FPF, flavoprotein fluorescence; logMAR, log of the minimum angle of resolution; RNFL, retinal nerve fiber layer; VA, visual acuity.

Conclusions

Patients with ADOA with high baseline VA experienced a 5.1 letter loss in LCVA over 12 months

LCVA decline occurred independently of RNFL changes, suggesting other factors may be responsible for short term changes in VA

Mitochondrial stress, as measured by FPF score, is elevated in patients with ADOA

FPF is a promising novel biomarker for mitochondrial stress, and offers a measurable outcome to evaluate the efficacy of future treatments targeting retinal mitochondrial dysfunctions

Restoring mitochondrial function by increasing OPA1 protein has the potential to slow or even halt ADOA disease progression

ADOA, autosomal dominant optic atrophy; FPF, flavoprotein fluorescence; LCVA, low-contrast visual acuity; OPA1, OPA1 mitochondrial dynamin like GTPase; RNFL, retinal nerve fiber layer; VA, visual acuity

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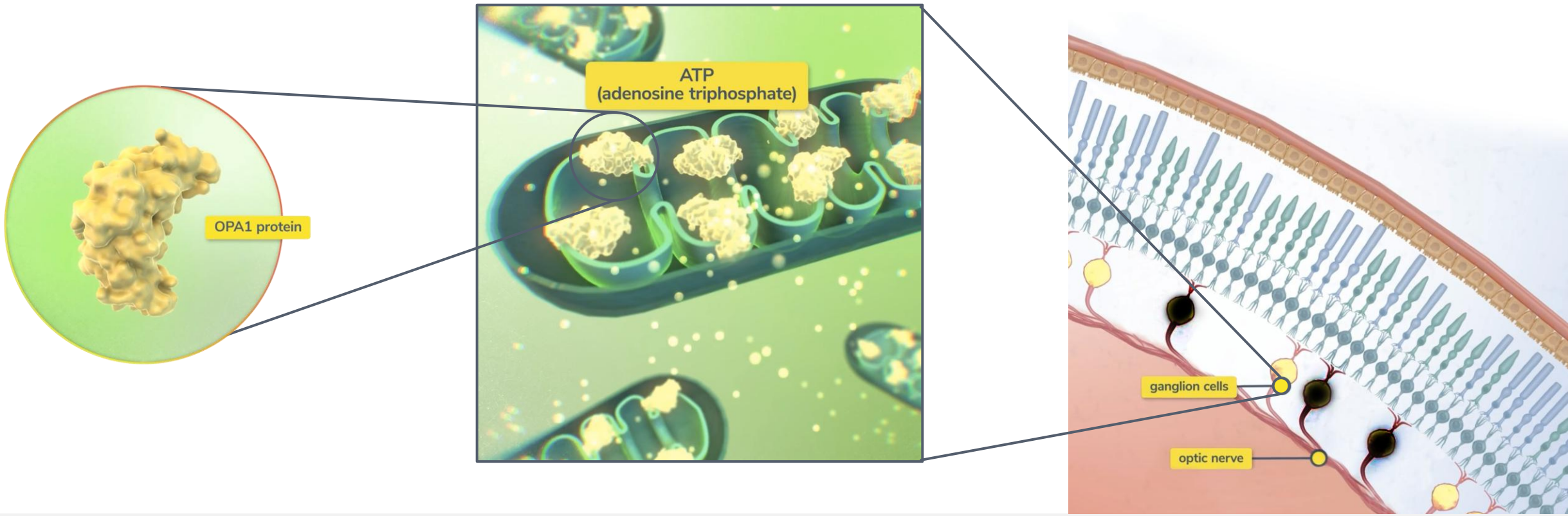
Restoring OPA1 protein levels may offer a promising strategy to improve patient outcomes in ADOA



Increasing OPA1 protein has the potential to slow or prevent mitochondrial stress and ganglion cell degeneration, thereby halting vision loss

ADOA, autosomal dominant optic atrophy; OPA1, OPA1 mitochondrial dynamin like GTPase.

Ng WSV *et al*. *Ther Adv Rare Dis* 2021; 2: 26330040211029037.