Longitudinal flavoprotein fluorescence (FPF) in the optic nerve as a biomarker of oxidative stress in a nonhuman primate model of autosomal dominant optic atrophy (ADOA)

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***Abstract*:**

Purpose: To explore longitudinal trajectories of global optic nerve head (ONH) FPF in *OPA1* A8S heterozygous (*OPA1* Het) rhesus macaques. Methods: The Beacon imaging device (OcuMet Beacon®, OcuSciences Inc.) was used to image 32 *OPA1* Het and 54 *OPA1* WT macaques. At repeated visits, FPF was measured in the ONH, alongside electrophysiology (pattern ERG, PERG) and peripapillary retinal nerve fiber layer thickness (RNFLT) by optical coherence tomography (OCT). Results: ONH FPF/RNFLT increased from approximately 7 years in *OPA1* Het, diverging from *OPA1* WT; by approximately 14 years the separation was clear and it widened at older ages (Fig. 1A). At ≤7 years the ratio was similar (WT 0.068 ± 0.016 dB/µm; HET 0.071 ± 0.017 dB/µm), whereas it was higher in *OPA1* Hets thereafter (>7-≤14 years: WT 0.067 ± 0.014 vs HET 0.084 ± 0.023 dB/µm; >14 years: WT 0.074 ± 0.022 vs HET 0.096 ± 0.026 dB/µm; Fig. 1B). In *OPA1* Hets, global ONH FPF increased with thinner RNFL (R = −0.29, *P* = 0.0255) and with higher IOP (R = 0.41, *P* = 0.0038), with no association with PERG P50-N95 at 48 min (R = −0.03, *P* = 0.9157); likely due to the smaller sample size (Fig. 1C-E). Conclusions: ONH FPF worsens with age in *OPA1* mutant NHPs, which supports the use of FPF (and the ONH FPF/RNFLT ratio) as sensitive longitudinal endpoints for evaluating progression and therapeutic interventions.

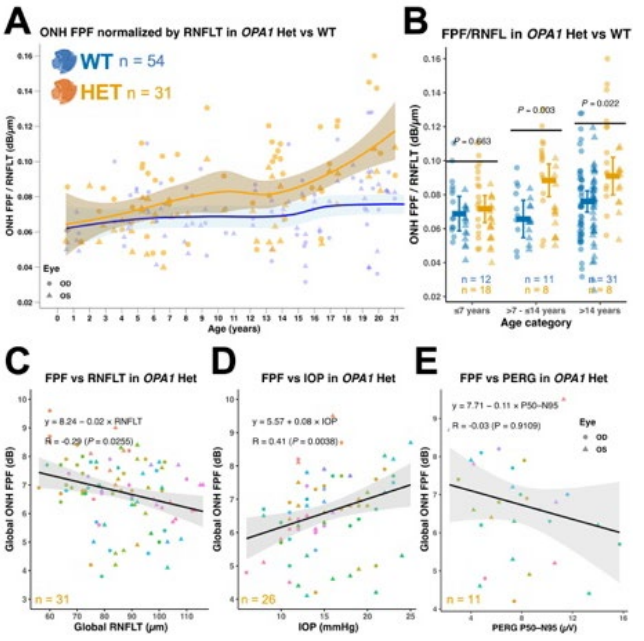

Figure 1. Global optic nerve head (ONH) flavoprotein fluorescence (FPF) in *OPA1* heterozygotes diverges from WT at 7 years and correlates inversely with retinal nerve fiber layer thickness (RNFLT) and positively with intraocular pressure (IOP). A, Global ONH FPF normalized by RNFLT across ages; LOESS mean ± CI. B, FPF/RNFLT ratio summarized by age categories; mean ± SD. C-E, Associations in *OPA1* heterozygotes: C, global ONH FPF vs global RNFLT (R = −0.29, *P* = 0.0255); D, global ONH FPF vs IOP (R = 0.41, *P* = 0.0038); E, global ONH FPF vs pattern ERG P50-N95 amplitude at 48 minutes (R = −0.03, *P* = 0.9109). C-E, each color denotes an individual animal.

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