

Independent Effects of APOE ε4 and Amyloid-β on Inner Retinal Thickness Revealed by Retinal Imaging in Older Adults

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APOE4 and amyloid-β status independently drive inner retinal thinning in cognitively healthy older adults - both must be accounted for to unlock OCT's potential as a non-invasive, preclinical Alzheimer's biomarker.

INTRODUCTION

Older adults carrying the apolipoprotein E ε4 (APOE4) allele — the strongest genetic risk factor for Alzheimer's disease (AD) — show altered retinal and choroidal thickness, suggesting genetic risk may influence ocular structure. However, findings across studies have been inconsistent.

Cerebral amyloid-β (Aβ) accumulates decades before clinical AD and may leave a parallel signature in the retina.

We hypothesised that accounting for cerebral Aβ burden alongside APOE4 status would clarify APOE4-related retinal and choroidal changes, and improve the utility of retinal imaging as a non-invasive biomarker of preclinical AD.

METHODS

Baseline optical coherence tomography (OCT) imaging of the retina and choroid was obtained from both eyes of 106 predominantly cognitively preserved older adults enrolled in the Deep and Frequent Phenotyping study¹, with known APOE4 and Aβ status.

After excluding scans with poor image quality and/or confounding retinal pathology, eyes were stratified into a control group (APOE4-/Aβ-; 12 eyes) and three risk groups: APOE4+/Aβ- (32 eyes), APOE4-/Aβ+ (14 eyes) and APOE4+/Aβ+ (146 eyes).

Multivariable linear regression using generalised estimating equations (GEE) assessed associations between group status and OCT-derived measures, with APOE4-/Aβ- as reference.

Models were adjusted for age, sex, vascular risk factors (VRF), smoking status and family history of dementia (FHD). Significance was determined following false discovery rate (FDR) correction.

RESULTS

Mean age was 71.3±5.7 years (60–84); 45.8% were female; mean MMSE was 29.0 (24–30). FHD (45.3%), VRF (44.3%) and smoking (36.7%) did not differ significantly between groups.

Risk group	Inner retina	Total retina	pRNFL
APOE4+/Aβ-	-11.86 (-20.56, -3.17)**	-12.00 (-20.61, -3.40)**	-16.59 (-26.97, -6.22)**
APOE4-/Aβ+	-16.91 (-28.80, -5.02)**	-17.36 (-29.02, -5.71)**	-20.15 (-39.45, -0.84)*
APOE4+/Aβ+	-8.39 (-15.53, -1.25)**	-9.12 (-16.23, -2.01)**	-8.88 (-16.42, -1.35)*

Table 1. Association between Alzheimer's disease risk group and retinal thickness. Values represent the mean difference in thickness (μm) with 95% confidence intervals for inner retina, total retina, and peripapillary retinal nerve fibre layer (pRNFL), comparing each APOE4/Aβ risk group to the reference group (APOE4-/Aβ-). Negative values indicate thinner retina relative to the reference group.
* p<0.05 vs. reference ** q<0.05 (FDR-corrected)

Only pRNFL thinning in the APOE4+/Aβ- group survived FDR correction; macular total and inner retinal thinning were significant across all three risk groups.

No significant associations were found for outer retinal thickness, choroidal thickness, or choroidal vascularity index.

CONCLUSIONS

APOE4 and Aβ status are independently associated with inner retinal thinning in predominantly cognitively preserved older adults.

Future studies of APOE4-related retinal changes should account for amyloid status to better characterise genetic risk and improve the utility of OCT as a non-invasive, preclinical AD biomarker.

REFERENCE:
Koychev, et al. Deep and Frequent Phenotyping study protocol: an observational study in prodromal Alzheimer's disease. BMJ Open. 2019;9(3):e024498. PMID: 30904851.

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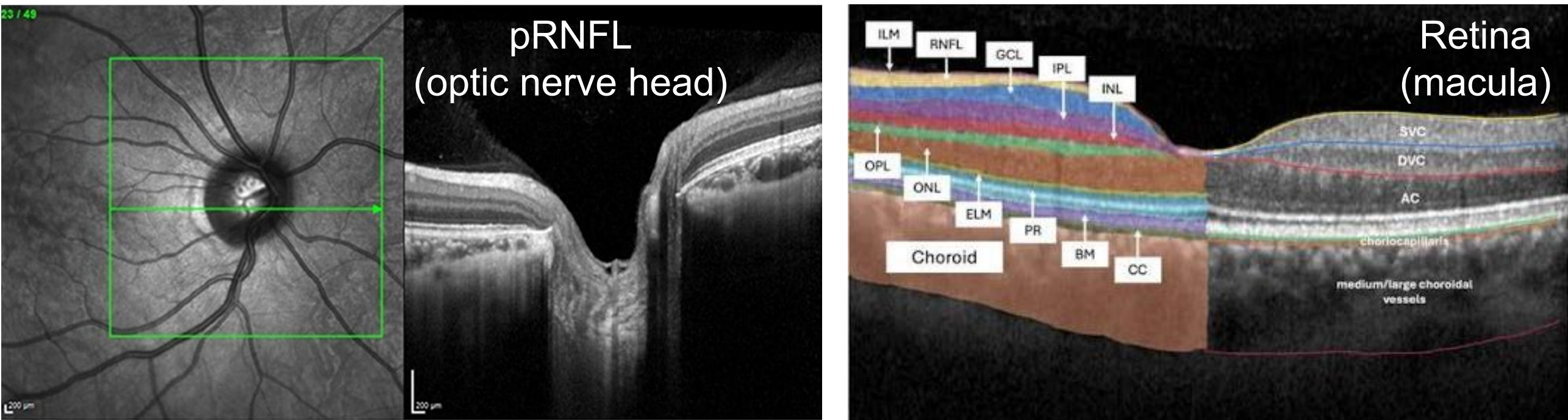


Figure 1. Representative optical coherence tomography (OCT) scans of the peripapillary retinal nerve fiber layer (pRNFL) and macular retina. Left: infrared fundus image centered on the optic nerve head and corresponding OCT B-scan used to quantify pRNFL thickness. Right: OCT B-scan of the macula with automated segmentation of individual retinal layers, from the inner retina to the choroid.

Abbreviations: OCT, optical coherence tomography; pRNFL, peripapillary retinal nerve fiber layer; ILM, inner limiting membrane; RNFL, retinal nerve fiber layer; GCL, ganglion cell layer; IPL, inner plexiform layer; INL, inner nuclear layer; OPL, outer plexiform layer; ONL, outer nuclear layer; ELM, external limiting membrane; PR, photoreceptor layer; BM, Bruch's membrane; CC, choriocapillaris.