Retinal findings in a patient with mutations in *ABCC6* and *ABCA4*

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The authors declare they have no conflict of interest.

Funding Support:

NIHR Biomedical Research Centre at Moorfields Eye Hospital and the UCL Institute of Ophthalmology; Wellcome Trust (206619/Z/17/Z).

Running Title: Retinopathy in *ABCC6* and *ABCA4*

Word count: 498 words

Sir,

In 2012, a case was reported in this journal, from our service,[1] of a 24 year-old male of Somali ancestry (from consanguineous parents), referred initially due to reduced central vision. Fundus autofluorescence (FAF) showed angioid streaks but also a reduced signal in the central macula indicative of retinal pigment epithelium atrophy (Figure 1). Severe macular dysfunction and generalised retinal involvement were shown on electrophysiological testing. Skin biopsy was consistent with a mild form of pseudoxanthoma elasticum (PXE) and a homozygous mutation in exon 7 of the *ABCC6* gene (c.708_709dupCT, p.(Trp237fsX21)) was subsequently found. The severity, early onset and distribution of maculopathy were atypical for PXE and considered worthy of report. The purpose of the present correspondence is to provide an update to the case's interpretation.

Given the appearance of the maculopathy, the possibility of additional ABCA4-retinopathy was considered, particularly homozygosity for c.5882G>A (p.G1961E),[2-5] a common allele in the Somali population.[5] Subsequently, PCR-amplification and Sanger sequencing of Exon 42 of *ABCA4* confirmed homozygosity for this allele . Later, DNA was tested for mutations in a number of genes implicated in macular dystrophies (Stargardt/Macular dystrophy SmartPanel v5; Molecular Vision Laboratory, Hillsboro, Oregon), and the findings were confirmed, with no additional pathogenic mutations identified. Thus, this patient has bi-allelic variants in both *ABCC6* and *ABCA4*, and the phenotype includes features of both, with the maculopathy more likely to be *ABCA4*-related. Figure 1 depicts FAF imaging when the patient was 31 years old, and also ultra-widefield FAF imaging 9 years later. There has been mild enlargement of the areas of hypo-autofluorescence (both in the central macula and the peripapillary angioid streaks), although the peripheral retina appears unaffected.

Patients homozygous for this *ABCA4* mutation have been reported previously to have limited retinal disease with no peripheral involvement.[2-4] Our patient's ultra-widefield imaging appears to fit with this phenotype, although electrophysiological testing did show evidence of generalised retinal

dysfunction as detailed in the first report,[1] and the PXE might be contributory. Generalised retinal dysfunction in PXE has been previously reported.[6]

It is tempting to speculate that the two distinct molecular pathologies might interact. The c.5882G>A (p.G1961E) ABCA4 allele is too prevalent in the general population (http://gnomad.broadinstitute.org/variant/1-94473807-C-T) to be a fully penetrant allele and so other modifying factors are likely to be acting. It is possible that many from Somalia with this *ABCA4* genotype remain normally sighted, but that, in this case, the additional compromise of RPE and/or photoreceptor function due to mineralisation of Bruch's from PXE, might contribute to early visual dysfunction.

The case is of particular interest: i) it reminds clinicians of the possible co-occurrence of two unlinked recessive disorders in consanguineous families; ii) It demonstrates that in some cases, a person's ethnic background can efficiently direct molecular testing (in this case a specific DNA base substitution in a single gene was suggested and confirmed using a single-amplimer PCR reaction in the laboratory); iii) there remains no evidence that PXE can produce a maculopathy that resembles that seen in Stargardt disease.

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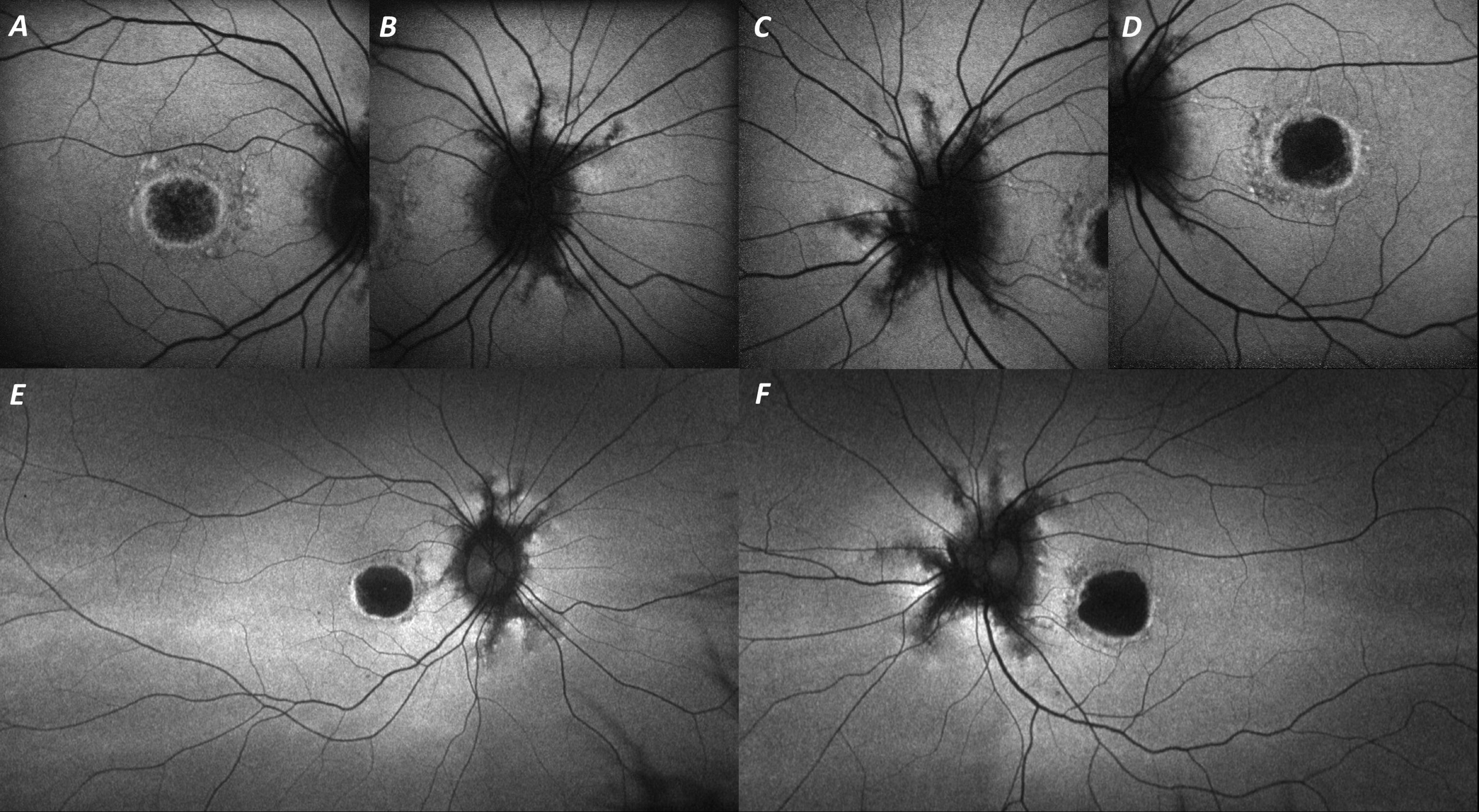
Figure Legends.

Figure 1. Fundus autofluorescence findings nine years apart. *A*-*D*, short wavelength (488 nm) autofluorescence imaging (Spectralis, Heidelberg, Germany) obtained age 31. Angioid streaks are visible as well as central macular hypo-autofluorescence (with a surrounding hyperautofluorescent ring and some discrete hyperautofluorescent lesions in close proximity to the ring). *E, F*, ultra-widefield autofluorescence (532 nm) imaging (Optos plc, Dunfermline, UK) acquired 9 years later.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