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Sir,

Angioid streaks with severe macular dysfunction and generalised retinal involvement due to a homozygous duplication in the *ABCC6* gene

Pseudoxanthoma elasticum (PXE, OMIM no. 264800) is a recessive disorder characterised by dystrophic calcification of elastic fibers in connective tissues with primary involvement of the skin. Mutations in the *ABCC6* gene on chromosome 16p13.1, encoding an ATP-binding cassette transmembrane transporter protein, are associated with PXE.[1] Ocular manifestations ranging from angioid streaks, disc drusen, peau d'orange and focal chorioretinal comettial lesions are seen, although these do not appear to affect visual function. Visual loss can occur secondary complications such as choroidal neovascularization from angioid streaks or choroidal rupture from minor ocular trauma. Approximately 10–15% of patients develop various forms of pattern macular dystrophy.[2] Retinal function was thought to be unaffected in PXE;[3] until recently, a small number of electrophysiological studies demonstrated generalised retinal dysfunction associated with PXE on electroretinogram (ERG).[4,5] We report the unusual ophthalmological presentation of a patient with a novel *ABCC6* mutation.

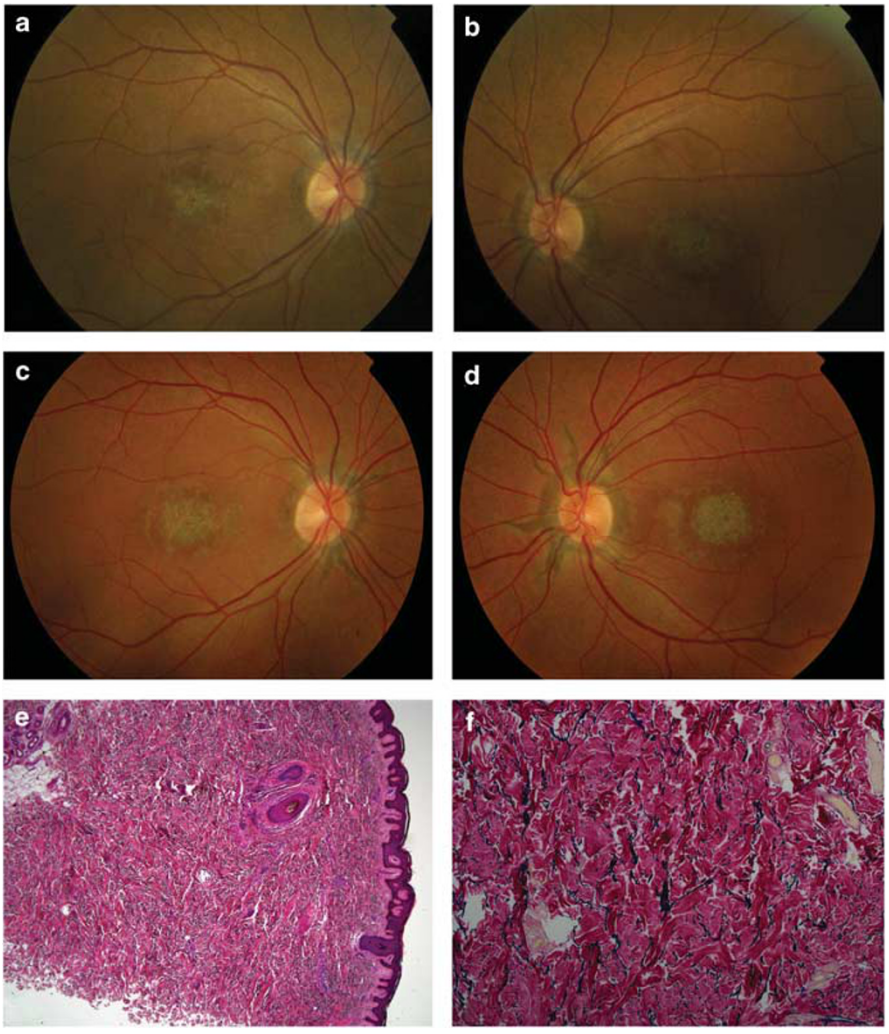

Figure 1 (a, b) Fundus photographs of the right (a) and left (b) eyes, showing early macular abnormalities with RPE mottling. The optic disc and peripheral retina were unremarkable. (c, d) Fundus photographs of the right (c) and left (d) eyes taken 5 years later, showing visible angioid streaks originating from the optic discs. The macular abnormalities have progressed with marked RPE atrophy. (e, f) Histological analysis of the skin biopsy showed fragmentation of basophilic elasin fibres and confirmed the diagnosis of PXE.

Case report

A 24-year-old man of Somalian extraction from a consanguineous marriage was initially referred 7 years ago for reduced vision. There was no relevant family history. His best-corrected visual acuity at presentation was 0.9 and 1.0 LogMAR in the right and left eye, respectively. Fundus examination showed bilateral early macular abnormalities (Figures 1a and b). Over the next several years, the macular changes progressed to macular atrophy. Scotopic and photopic full-field ERG performed later showed generalised rod and cone system dysfunction (Figure 2), and undetectable pattern ERG P50 component consistent with severe macular dysfunction. Fundus autofluorescence showed an area of reduced signal at the fovea, surrounded by a ring of increased autofluorescence (Figure 3). After 5 years, mild peripapillary streaks were seen (Figures 1c and d) and some cutaneous laxity around the neck and flexures was noted. A skin biopsy showed basophilia and fragmentation of elastic fibers in the reticular dermis, confirming a mild form of PXE (Figures 1e and f).

Sequencing of the *ABCC6* gene in our patient revealed a novel homozygous duplication of two base pairs in exon 7, p.Trp237fsX21 (c.708_709dupCT), that localises to the third transmembrane domain of the *ABCC6* protein. The mutation causes a frameshift with premature termination codon, producing a truncated protein that is likely to succumb to nonsense-mediated decay.

Comment

Duplications are extremely rare in the *ABCC6* gene; until now, only one such mutation (c.3544_3544dupC; p.L1182PfsX96) has been described in heterozygous state in an Italian patient with classic PXE symptoms.[6] Interestingly, the vision in this patient was unaffected. Genotype–phenotype correlations in PXE have generally been difficult to establish because of clinical variability.[7] This is highlighted in our patient's case, where visual loss associated with atypical macular lesions and ERG abnormalities were the only early signs of PXE, with other well-known manifestations of PXE appearing many years later. Characteristic skin changes may be subtle and the systemic diagnosis not apparent when visual symptoms first develop.

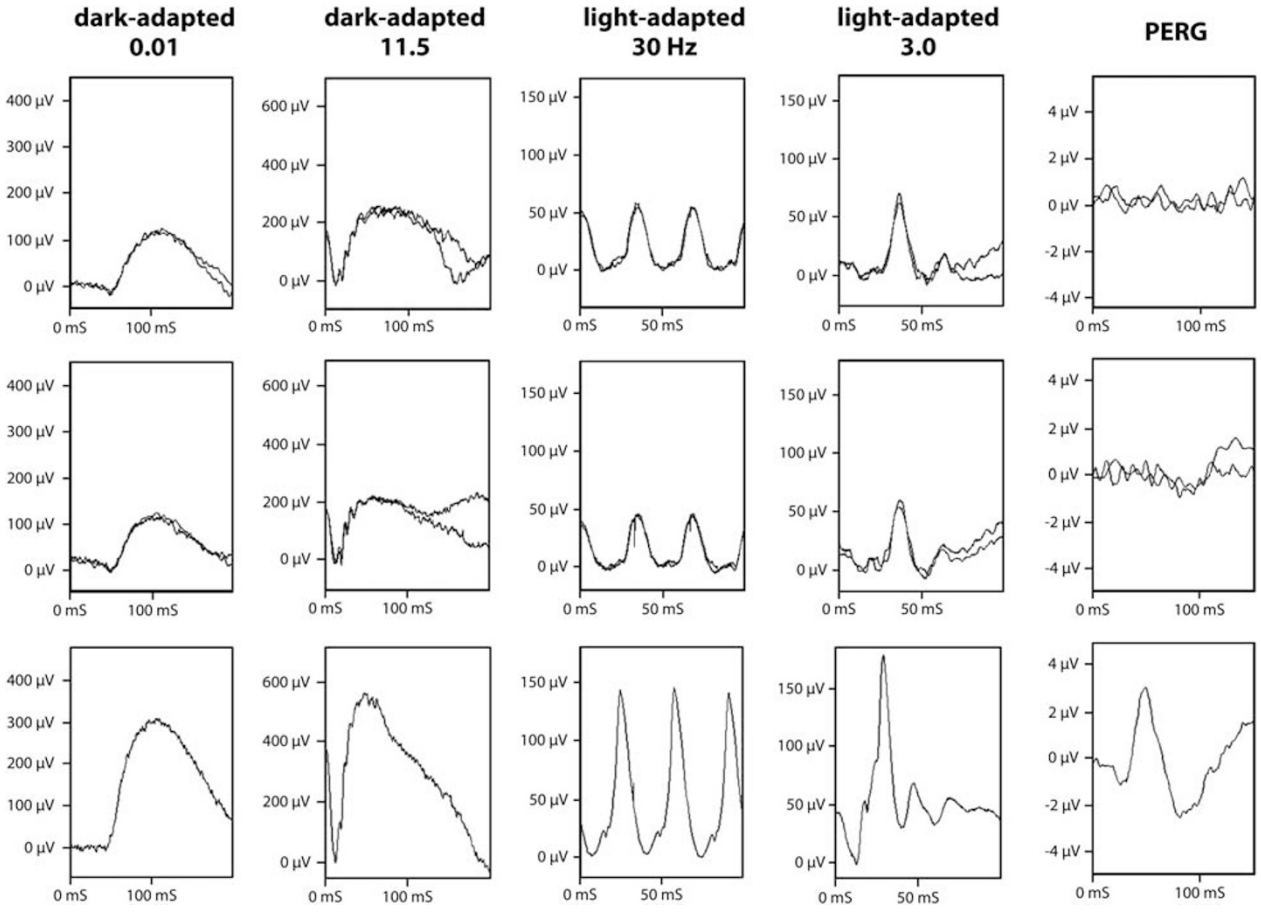

Figure 2 International-standard full-field and pattern ERGs from the right and left eyes of the patient (top and middle rows), and normal examples for comparison (bottom row). Dark-adapted responses are shown for flash strengths of 0.01 and 11.5 cd.s/m^2; light-adapted ERGs are shown for flash strength 3.0 cd.s/m^2 (30 and 2 Hz). Pattern ERGs were recorded to an alternating checkerboard ($12^\circ \times 15^\circ$; check size 0.75°; 2 Hz).

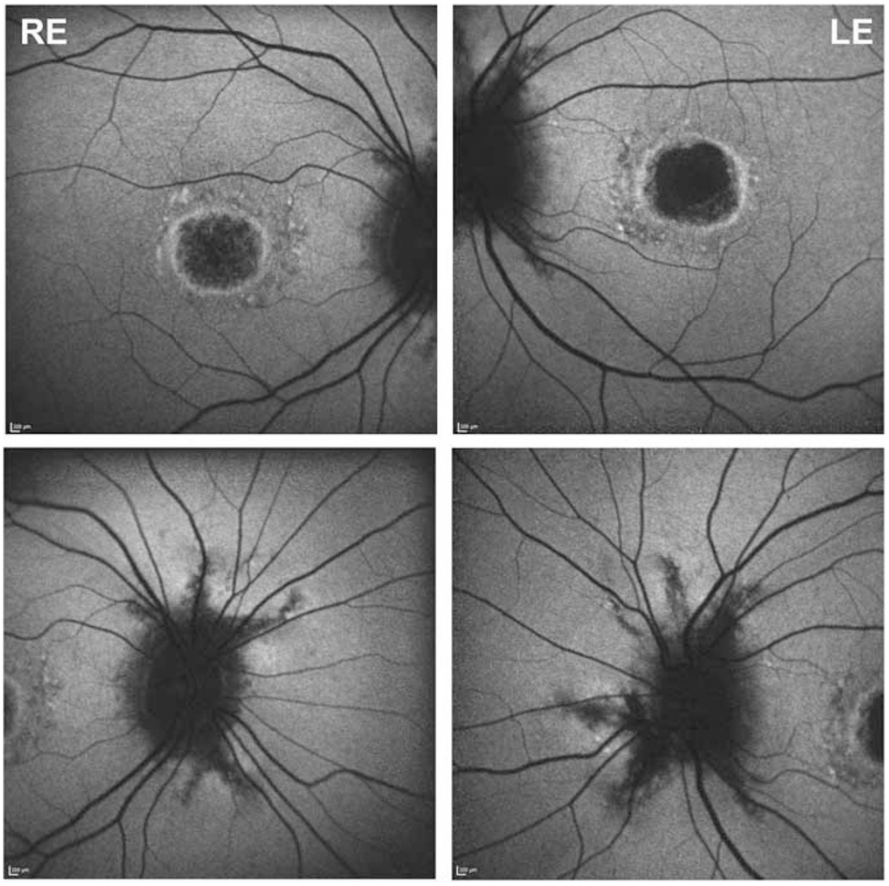

Figure 3 Autofluorescence imaging showed central area of reduced autofluorescence at the fovea, surrounded by a ring of increased signal (top figures). Angioid streaks were visible as irregular lines of reduced autofluorescence running outwards from the optic discs.

Conflict of interest

The authors declare no conflict of interest.

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