Analysis of ABCA4 genotypes in patients with the Arg2107His variant prevalent in those of African ancestry

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Purpose

- *ABCA4* is the gene most frequently associated with inherited retinal disease.
- Whilst many variants prevalent in Europeans have been characterised, less is known about other variants, particularly in non-European ancestries.
- The *ABCA4* p.Arg2107His missense variant is present in around 1 in 50 genomes of individuals of African ancestry.[1,2]
- We explored ABCA4 genotypes in patients diagnosed with ABCA4-retinopathy in association with this variant.

Methods

- Patients (from two UK centres) diagnosed with ABCA4-retinopathy who carried this variant on at least one allele were included.
- Genotypes were analysed to investigate whether any patients were homozygous for this variant and also to explore the severity grading of the other *ABCA4* allele in patients who were apparently compound heterozygotes.
- Demographic and clinical data were also noted.

Results

Demographics at first visit

- The search identified 42 patients (21 females), none of whom were homozygous for this variant.
- Of 34 patients, for whom self-reported ethnicity data were available, 25 (74%) were Black.
- Looking at previously published classifications,[3] we found severity grades for the second *ABCA4* variant in 29 of our cases. Of these:
  - 17 (59%) were "severe"
  - 5 (17%) were "moderate"
  - 5 (17%) were "mild/moderate"
  - Only 2 (7%) were "mild".
- Mean (SD) age at first visit was 42.9 (17.8) years; mean (SD) visual acuities were 0.56 (0.44) and 0.56 (0.39) for right and left eyes respectively.
- Full-field ERG data were available in 34 patients: of these, 28 (82%) showed either normal ERGs or mild/borderline retinal dysfunction.

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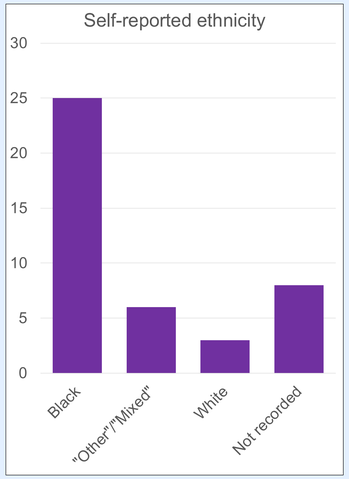

Figure 1 (left). Self-reported ethnicity.

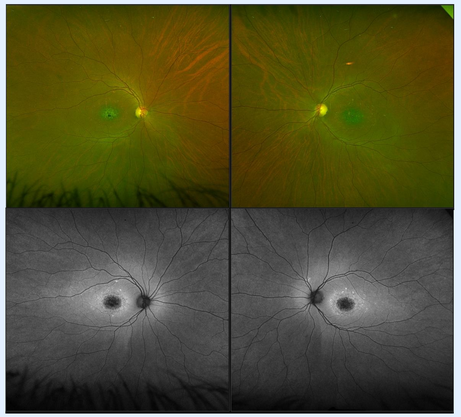

Figure 2 (left). Retinal imaging from a 55 year old female.

Upper panels, ultra-widefield pseudo-colour imaging (Optos plc).
Lower panels, ultra-widefield green auto-fluorescence imaging. Many patients showed peripheral retinal preservation.

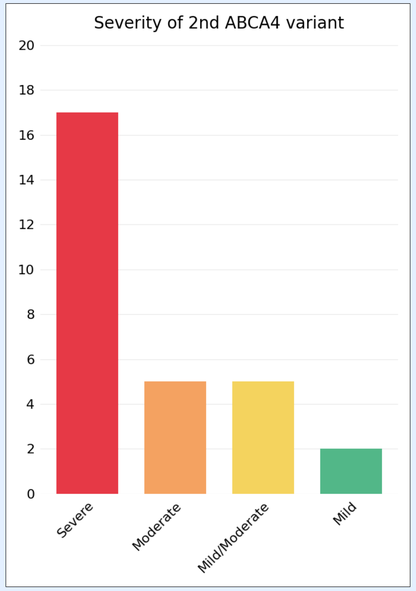

Figure 3 (above). Severity of 2nd *ABCA4* variant.

The majority of second variants were reported as "moderate" or "severe".

Discussion

- No patients in the cohort were homozygous for this variant. This, together with the presence of 17 homozygous individuals in the genome aggregation database (gnomAD v4), supports the notion that homozygosity for this change may not lead to manifest disease.
- The majority of second variants in these patients were moderate or severe (only 2 cases had second variants graded as "mild"). This would be consistent with the need for this variant to be in trans with a more severe variant for disease to occur. Finally, disease associated with this variant appears relatively mild compared to *ABCA4*-retinopathy in general.
- These findings can inform prognostic discussions with patients and also the design of future therapeutic trials.

References:

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