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Genotypic-Phenotypic analysis of ABCA4 mutation heterozygotes and possible modifying effects of second mutations in a North American population

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Purpose:
ABCA4 is amongst the most commonly implicated genes in retinal dystrophy and is associated with a broad array of recessively inherited phenotypes. High carrier rates of ABCA4 mutation in the general population and the broad range of allelic heterozygosity at this locus have raised interest in ABCA4 mutation heterozygosity and its role in the phenotype of retinal disease, given that some ABCA4 heterozygotes, who carry only a single mutation in ABCA4, are known to manifest clinical disease. In this study we aim to characterize genotypic-phenotypic correlation in ABCA4 heterozygotes, identify novel ABCA4 mutations and the influence of additional gene mutations at other loci.

Methods:
Records at a single, large vitreo-retinal practice were queried for patients who had undergone targeted genetic panel sequencing for retinal disease, and records were selected for patients who had tested positive for a single mutation in ABCA4. Sequence variants were queried against public databases including LOVD, gnomAD, EVS and ClinVar. In silico analysis of identified variants was conducted using predictive tools including Polyphen-2, SIFT and Mutation Taster.

Results:
128 patient charts who had undergone genetic panel testing were identified. Of 37 patients with ABCA4 mutations, 8 patients (21.6%) with a single heterozygous mutation in ABCA4 were selected for inclusion in the study. We detected three novel ABCA4 mutations (GRCh37 hg19 1.p22.1(94542998_94544254)x1, c.6482T>C, p.Phe2161Ser and c.2779C>T, p.Pro927Ser) and we describe two previously reported but phenotypically uncharacterized ABCA4 mutations (c.3194G>A, p.Gly1065Asp and c.6286G>A, p.Glu2096Lys). In addition, gene mutations were identified in PRPH2, IFT140, MAK, TTC8, IMPG2, PITPNM3, TRPM1, ADAMTS18 and P3H2, which may exert a gene modifying or an additive effect upon the phenotype, in conjunction with ABCA4.

Conclusions:
Genetic panel testing is effective in identifying heterozygous mutations in ABCA4. Large deletions, deep intronic variants, additional gene mutations, and environmental factors may play a role in the phenotype of affected patients.