Suggested Reference


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Diagnostic Utility of a Next Generation Sequencing Retinal Panel in a Māori and Polynesian Population with Inherited Retinal Disease

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Purpose: Small ethnically diverse populations represent a diagnostic challenge for genetic characterisation of inherited retinal disease (IRD), because of the presence of rare founder mutations, and an under-representation in databases of human variation. We aim to elucidate the genetic cause in Māori and Polynesian patients with IRD, using a next generation sequencing (NGS) targeted retinal disease gene panel, and to establish phenotype-genotype correlations.

Methods: Patients of Māori and Polynesian ancestry, genetically uncharacterised with microarrays (Asper), were identified from the NZ IRD Database. Clinical history, examination, imaging (OCT, fundal photography, fundus autofluorescence), and electrophysiology were obtained for each patient. DNA underwent NGS with a targeted retinal disease gene panel (Manchester, UK). An ethnically-matched control population was screened for identified changes.

Results: In the cohort of 28 patients (recessive rod-cone dystrophy (ARRP n=15), dominant RP (ADRP n=2), Leber congenital amaurosis (LCA n=3), Maculopathy (n=4) or Cone/Cone-rod dystrophy (CORD n=4)), 21 unique, pathogenic variants (12 novel) were observed, allowing a definitive genetic diagnosis in 16/28 (57%) cases. Homozygosity was seen for 3 (PDE6B, RD3, SPATA7).

All LCA and ADRP cases were solved. Two ARRP cases had mutations in ADRP genes. 60% of ARRP cases remain unsolved. Phenotype-genotype correlation included a late onset, isolated, non-syndromic maculopathy associated with recessive BBS9 mutations, and coexistence of RPGR and C1QTNF5 mutations in ADRP.

Conclusions: This study highlights the cost effectiveness of the NGS platform to determine genetic diagnosis in this Māori and Polynesian IRD cohort. A definitive molecular diagnosis was possible in 57%, consistent with many populations recently described. The most prevalent mutation was in PDE6B, homozygously, suggesting a founder effect, and phenotype correlation now allows targeted and cost effective gene screening. A large number of novel changes were present. Recessive disease, particularly ARRP, still remains most elusive with nearly two thirds genetically undiagnosed, suggesting further novel molecular mechanisms are responsible for disease in this population. Knowledge of allele frequency in ethnic populations not represented in databases of human variation remains one of the most significant challenges when considering pathogenicity of observed variants.

#21 BBS9 +/– #25 PROM1 +/– #22 FSCN2 +/– and ABCA4 +/– #10 PRPF31 +/– and IMPG2 +/– #19 RPGR hemi and C1QTNF5 +/–

Table 1: Individual’s phenotype, and genetic variants identified on NGS panel, with allele frequencies, both within an ethnically matched cohort, and from publically available databases of human variation (ExAC, EVS and 1000Genomes).

Figures: Fundus images (Optos ultra-widefield, or Topcon mosaic), and Fundus Autofluorescence (Optos) when available, of patients in cohort

CR: ALV none, AC none, KvB none, VFO none, GCB none

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