#3157

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

Andrea L Vincent, [1, 2] Alix Coysh ,[1] Katherine van Bysterveldt,[1] Verity F Oliver,[1] Graeme C Black. [3, 4]

1.Ophthalmology,New Zealand National Eye Centre, University of Auckland, 2.Eye Department, Greenlane Clinical Centre, Auckland District Health Board, Auckland, New Zealand. 3. Manchester Centre for Genomic Medicine, Institute for Human Development, University of Manchesster..4. Central Manchester University Hospitals NHS Foundation Trust, Manchester Academic Health Sciences Centre (MAHSC), St Mary's Hospital, Manchester, United Kingdom.

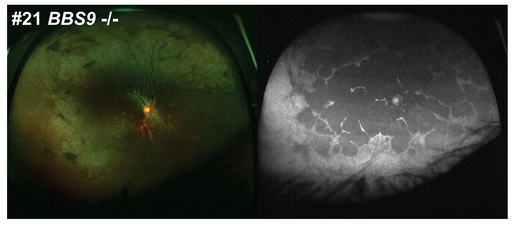
CR : ALV none, AC none, KvB none, VFO none, GCB none

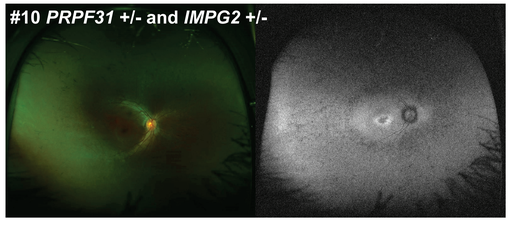
Purpose: Small ethnically diverse populations represent a diagnostic challenge for genetic characterisation of inherited retinal disease (IRD), because of the presence of rare founder mutations, and an under-representation in databases of human variation. We aim to elucidate the genetic cause in Māori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

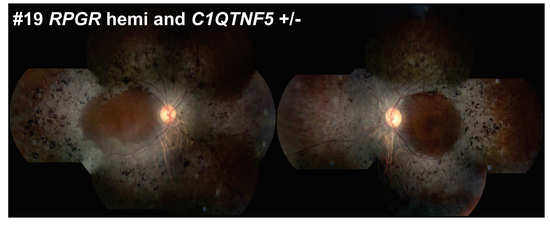
Methods: Patients of Māori and Polynesian ancestry, genetically uncharacterised with microarrays (Asper), were identified from the NZ IRD Database. Clinical history, examination, imaging (OCT, fundal photography, fundus autofluorescence), and electrophysiology were obtained for each patient. DNA underwent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

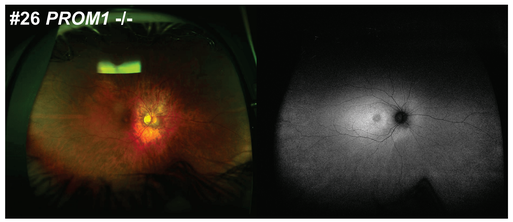
ID	Ethnicity	Clinical diagnosis	Result Gene	Variant	Protein	Zygosity	Novel	Allele Frequency Ethnic match	Allele Frequency EVS/Exac
Presumed AR RC dystrophy (ARRP) n=15									
1	Maori	ARRP	PDE6B	c.2197G>C	p.(Ala733Pro)	Hom	Novel	1/132	0
2	Maori	ARRP	PDE6B	c.2197G>C	p.(Ala733Pro)	Hom	Novel	1/132	0
3	Maori	ARRP	PDE6B	c.2197G>C	p.(Ala733Pro)	Hom	Novel	1/132	0
			PDE6B	c.2197G>C	p.(Ala733Pro)	Hom	Novel	1/132	0
4	Maori	ARRP	BEST1	c.624G>A	p.(Gln208Gln)	Het	equivocal		<0.0001
			USH2A	c.15427C>T	p.(Arg5143Cys)	Het	Novel		<0.0001
7	Samoan	ARRP	TOPORS	c.2484_2486delTTC	p.(Ser830del)	Het	prev reported		<0.0001
10	Samoan	ARRP	PRPF31	c.682G>C	p.(Ala228Pro)	Het	Novel		0
			IMPG2	c.331C>T	p.(arg111Ter)	Het	Novel		<0.0001
14	Samoan	ARRP	ABCA4	c.667A>C	p.(Lys223Gln)	Het	prev reported		<0.0001
Presumed AR LCA n=3									
15	Maori	LCA	LCA5	c.194delC		Het	prev reported		0
			LCA5	c.103C>T	p.(Arg35Ter)	Het	Novel		0
16	Tongan	LCA	RD3	c.127C>T	p.(Gln43Ter)	Hom	Novel		0
17	Samoan	LCA	SPATA7	c.738_739dupAA		Hom	Novel	0/132	0
AD or XL RC dystrophy n=2									
18	Maori	ADRP	IMPDH1	c.968A>G	p.(Lys323Arg)	Het	prev reported		0
			C1QTNF5	c.583dupG		Het	Novel		0
19	Samoan	ADRP/ XLRP?	RPGR	c.283G>A	p.(Gly95Arg)	Hemi	Novel		0
AR Macular/Cone/Dystrophy n=8									
20	Maori	Occult	RP1L1	c.133C>T.	p.(Arg45Trp)	Het	prev reported		<0.0001
21	Maori	Maculopathy AR	BBS9	c.205C>A	p.(Leu69Ile)	Het	Novel		0
			BBS9	c.1014_1015delinsTT)	p.(Leu338_His339delinsPheTyr)	Het	Novel		0
22	Samoan	Maculopathy AR	ABCA4	c.1804C>C	p.(Arg602Trp)	Het	prev reported		0
			FSCN2	c.72delG		Het	equivocal	0/132	0.003
26	Maori	Cone rod AR	PROM1	c.1354dupT		Hom	prev reported	0/132	0.002
27	Maori	Cone rod dystrophy	CRX	c.774T>G	p.(Tyr258Ter)	Het	Novel		0

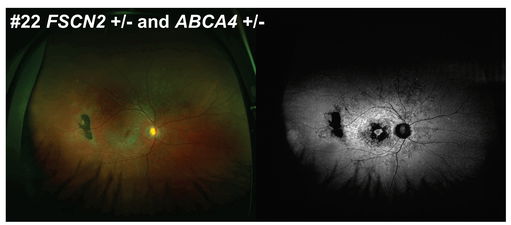
Table1: Individual's phenotype, and genetic variants identified on NGS panel, with allele frequencies, both within an ethnically matched cohort, and from publically available databases of human variation (ExAC, EVS and 1000Genome)











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

#21 Onset age 30, cone-rod dystrophy, VA CF OU age 43, No syndromic features

#26 Onset age 3, cone-rod dystrophy, VA 6/15, 6/24 age 7, No syndromic features

#10 Onset age 11, rod-cone dystrophy, VA 6/7.5 OU age 19, cystic maculopathy

#22 Onset age 55, Maculopathy, VA 6/9 OU age 59, ffERG normal, pERG abnormal

#19. Onset nyctalopia age 23, Rod-cone dystrophy, VA 6/9 OU age 46, 20 degree VF

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.

Acknowledgements: This work was supported by funding from :Save Sight Society of New Zealand,(AV), Retina NZ (AV,) Ombler Charitable Trust (AV, AC), Fight for Sight UK, (AV, GB)