#2899

Novel Genotype-Phenotype correlations in a Māori and Polynesian Population with Autosomal Recessive Inherited Retinal Disease, using a Next Generation Targeted Retinal Panel.

Andrea L Vincent [1, 2] Nandoun Abeysekera[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 Manchester,4. Central Manchester University Hospitals NHS Foundation Trust, Manchester Academic Health Sciences Centre(MAHSC), St Mary's Hospital, Manchester, United Kingdom.

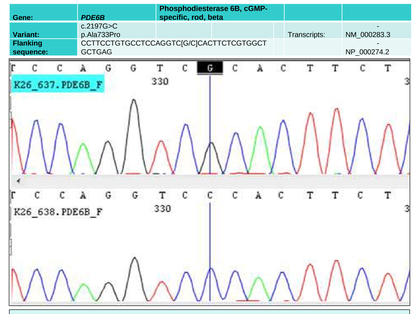
CR : ALV none, NA none, KvB none, VFO none, GCB none

Purpose: To phenotypically characterize presumed autosomal recessive rod-cone retinal dystrophies (ARRP) in Māori and Polynesian patients with no previous identified gene mutation; to elucidate the gene mutations which are associated with retinal dystrophies in this population using a Next Generation sequencing targeted Retinal disease panel, , and to establish phenotype-genotype correlations.

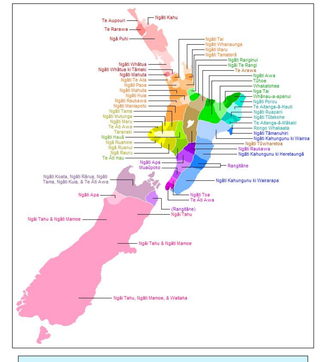
Methods: Thirty-six patients of Māori and Polynesian ancestry with no causative mutation detected on disease microarrays (Asper, Estonia), were identified from the Inherited Retinal and Optic Nerve Disorders Database. Clinical history and examination, pedigrees, OCT, fundal photography, fundus autofluorescence, and electrophysiology were obtained and reviewed for each patient. DNA of 15 of these patients with presumed ARRP underwent NGS of a targeted retinal disease gene panel(105 genes) (NGS-TRDGP). An ethnically matched control population was screened for identified changes. Subsequent patients seen with a similar phenotype were tested for the novel change.

ID	Sex	Phenotype	Symptoms Age at diagnosis	Age at Exam	RVA	LVA	Family Hx	Consanguinity	Mutation *PDE6B*	Other mutation	Other	Iwi Mother	Iwi Father	Smoker
8	F	AR RCD	40's	54	6/12	6/15	Y	N	p.A733P hom	nil	T2DM	Ngā Puhi	Ngā Puhi	NK
10	F	AR RCD	mid teens	22	6/15	6/12	B	N	p.A733P hom	nil	Rheumatic heart disease	Ngā Puhi	Ngāti Maniapoto	N
11	M	AR RCD	nyctalopia as child 36	55	HM	PL	Y	N	p.A733P hom	nil	Ca Prostate	Ngāti Porou	Ngāti Porou	ex 2 yrs
20	M	AR RCD Cystic Maculopathy	Truck driver til late 40's 55	66	6/120	6/9	N	Maybe	p.A733P hom	BEST1 p.Q208Q splice site	T2DM	Ngā Puhi	Ngā Puhi	ex 8 yrs
21	F	AR RCD	nyctalopia all life 40	41	6/6	6/7.5	N	Y	p.A733P hom	ND		Ngāti Pahauwera	Ngāti Kahungunu	N
22	F	AR RCD	late 20's	55	6/7.5	HM	Y	N	p.A733P hom	ND	T2DM	Ngā Puhi	Ngā Puhi	Y
23	F	AR RCD	20's	36	6/7.5	6/7.5	N	Y	p.A733P hom	ND		Ngāti Porou	Ngāti Porou	ex
24	F	AR RCD	20's	52	6/60	CF	N	N	p.A733P hom	ND		Ngā Puhi	Tongan	Y

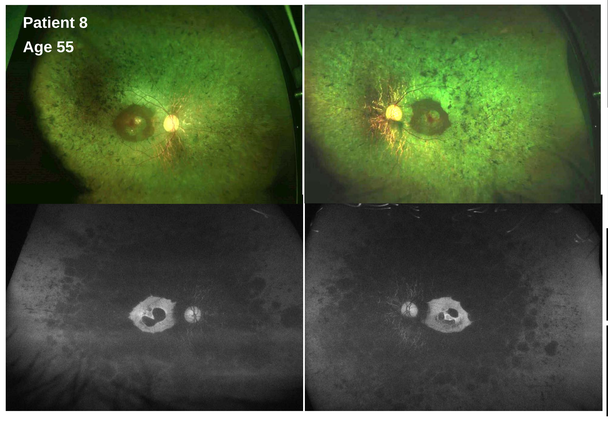
Table 1.Demographics and clinical features of patients with the homozygous *PDE6B* mutation.
Legend.F = female, M = male, AR RCD = Autosomal recessive rod cone dystrophy, Y = yes, N = no, ND = not done, NK = not known, hom = homozygous, T2DM = Type 2 Diabetes Mellitus. Māori Iwi (Tribes) as reported by patients.

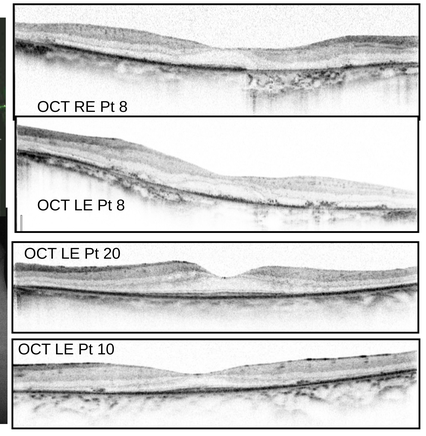


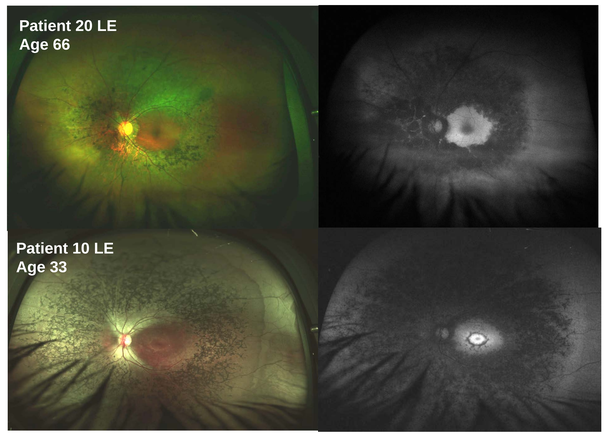
Electropherogram of *PDE6B* sequencing.
Above: wild type, below: homozygous affected.



Map of New Zealand showing the Māori Iwi (Tribe) locations.
The Iwi of our affected individuals originate from the middle and top of the North Island, and East Cape regions







Results

Of the Māori and Polynesian patients studied, probable disease-causing mutations were detected in 40% using NGS-TRDGP: A novel homozygous *PDE6B* mutation c.2197C>G, p.Ala733Pro, was present in 4 NZ Māori. This change is not present in databases of human variation, and is predicted to be pathogenic by PolyPhen2, SIFT and Mutation Taster. Segregation was confirmed in 2 families. The homozygous mutation was found in 4/5 other Māori with a strikingly similar phenotype. This phenotype is consistent with previously described *PDE6B* - associated disease. This change was present in 1/124 ethnically matched alleles.

Conclusions

NGS is a superior technique to other commercially available techniques for causative gene mutations in ARRP. The majority of Māori and Polynesian patients tested have no disease causing pathogenic variant(s) detected, which is strongly supportive of novel genetic mechanisms causative of disease in this population. The novel *PDE6B* mutation, p.Ala733Pro, is not in high frequency in a Māori control population, and is predicted to be deleterious. The phenotype-genotype correlation allows identification of the likely causative gene, resulting in targeted and cost effective gene screening. Within the Māori and Polynesian population there are still unknown genetic mechanisms accounting for the majority of disease.

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