Chapter 6:

Inherited Ocular Disease in the New Zealand Māori; Novel genetic mechanisms and founder effects

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Abstract

New Zealand is a small island nation at the bottom of the South Pacific, with a population of 4.7 million, and the largest Polynesian population in the world. 15% identify as Māori, and 7% as Pacific Peoples, and the spectrum of inherited eye disease encountered in this population varies from that seen in those identifying as NZ European. Keratoconus is more common, while primary open angle glaucoma is rare. A number of founder pathogenic variants have been elucidated in autosomal recessive ectopia lentis, and a common *PDE6B* variant causing up to 16% of autosomal recessive inherited retinal disease in the Māori population. Although many of those with inherited retinal disease remain genetically uncharacterised, research to date shows a range of novel variants in a many genes, Understanding the population-specific genetic disease spectrum, clinical phenotypes, and a knowledge of regional ancestry and iwi (tribe), aids in simplifying the diagnostic process.

Keywords

Māori, Pacific peoples, genetic testing, inherited retinal disease, *PDE6B, ADAMTSL4*

Introduction

New Zealand is a small island nation situated at the bottom of the South Pacific, with an estimated population of 4,793,700 (2017, Stats NZ, www.stats.govt.nz). With migration, New Zealand has an increasingly ethnically diverse population, with 15% identifying as Māori, and also the largest concentration of Pacific peoples, recorded as 260,000 (7%) in the 2013 census (Stats NZ). The Māori people of New Zealand were the first inhabitants, with their arrival from Eastern Polynesia (Cook Islands, Tahiti, Hawai'i) estimated to occur around the year 1280. [1] Based on genetic investigation, it is believed the Eastern Polynesians are descended from Taiwan Aborigines, with subsequent mixing with Melanesians and European ethnic groups.[2, 3] Of Polynesians, the Māori represent a relatively new population genetically (about 35 generations), and have the smallest signal of external relationship, consistent with extensive genetic drift.[2] It has been hypothesised that in the migration through the Pacific, the sea-faring ancestors would likely have been subject to multiple founder effects, and consistent with this, small numbers of haplotypes and reduced genetic diversity have been demonstrated.[4]

This chapter will provide an overview of the spectrum of Inherited eye diseases observed in the New Zealand population, specifically discussing the findings and genetic associations seen in the New Zealand Māori and Pacific Peoples, based on study data, publications, and observations.

Identification of unique genetic variants in this specific population adds a further layer of complexity in determination of pathogenicity. This population is underrepresented in databases of human variation; therefore, the frequency of any allele of interest needs to be determined in an ethnically matched control population.

Investigation of genetic variants in these populations requires an understanding of, and sensitivity to, cultural beliefs and customs. Our studies have all been undertaken with institutional ethical approval, including review by the Auckland District Health Board Māori Research Review committee. Our research follows the principles of the Treaty of Waitangi, and follows the tenets of the Declaration of Helsinki. All participants have provided informed consent.

Cornea.

Keratoconus.

Keratoconus is a progressive corneal dystrophy leading to a characteristic pattern of thinning and bulging of the cornea (ectasia), with induced irregular astigmatism. Onset is usually in the teens, and the incidence within the general population is estimated at 1 in 2000.[5] In NZ, keratoconus is disproportionately the major indication for corneal transplantation, accounting for 41% of keratoplasties over a 10 year period, and 67% of all paediatric surgeries.[6] This compares with rates of 11.4 – 28.8% in the USA and France.[7-9] The incidence is thought to be higher in the Māori and Pacific populations; based on corneal topographic values, suspected keratoconus in Māori/Pacific students was 26.9% compared with 12.9% in NZ European (p=0.0014),[10] and 31%

of affected Māori/Pacific peoples reporting a positive family history of keratoconus.[11] Keratoconus is a complex disorder with putative genetic and environmental contributions.[12] The visual system homeobox gene 1 (*VSX1*) is one gene implicated in this disease, but in our study, no pathogenic variants were detected in 26 Polynesian probands.[13] Another gene, *ZNF469*, is associated with the autosomal recessive disorder Brittle cornea syndrome, and in genome wide association studies (GWAS) common variants in this gene play a role in determination of central corneal thickness, and keratoconus.[14] In a NZ population, of which 49% were Polynesian, a large number of heterozygous variants in *ZNF429* were detected, including in 12 of the 21 Polynesian probands.[15] 2 of the variants (p.(R2129K), p.(G3415V)) were absent or very rare in databases of human variation, and predicted to be harmful, but were present in a higher frequency in the control Polynesian population. 5 probands carried 2 *ZNF469* variants, including 3 Polynesian families, but segregation was not complete in all families. In other populations, variants in this gene have not been shown to be of significance to disease pathogenesis. A larger study is required to determine if variants in this gene may explain, in part, the higher prevalence of keratoconus in this population.

Corneal Dystrophies.

Many of the corneal dystrophies have been genetically characterised,[16] with a consensus classification established, and updated, by The International Committee for Classification of Corneal Disease (IC3D).[17]

In our studies probing the genetics of corneal dystrophies, the prevalence of disease is not clearly different from the general population, however our numbers are small. In individuals of Polynesian ethnicity, probing the *TGFB1, VSX1* and *ZEB1* genes, we have not identified the genetic cause for disease (stromal fleck n=1, posterior polymorphous dystrophy n=3).[13, 18-21]

Anterior segment dysgenesis.

A NZ Māori woman had an historical diagnosis of aniridia, and congenital glaucoma, but on presentation had an enucleated right eye, and extensive surgeries to the remaining eye, making clear phenotyping difficult, however we excluded a PAX6 mutation. She subsequently gave birth to a son, affected with posterior embryotoxon and iris hypoplasia. A novel *PITX2* missense variant, c.344G>A; p.(Arg115His) at a highly conserved residue in the homeobox domain, was identified, which segregated with disease in the family.[22] It was predicted to be pathogenic, and not present in 100 ethnically matched alleles. This pathogenic variant segregated with disease in the family.

Autosomal Recessive Ectopia Lentis.

Isolated, non-syndromic ectopia lentis attributable to mutations in the *ADAMTSL4* gene (AREL), has been observed in multiple populations, with a common 20 base pair deletion described in the European population, with evidence for a founder mutation over 4000 years ago.[23] In a cohort of 11 AREL patients, we identified a recurrent

population specific variant, c.2237G>A, p.(Arg746His).[24] This variant was present in 81% (9/11), of probands with an early onset (under the age of 5 years) of AREL. (Figure 1) 77.8% (7/9) of these probands were Polynesian (Cook Island Māori n=5, NZ Māori n=2), and the remainder were NZ European. All individuals with this variant, regardless of ethnicity, shared a common haplotype, suggestive of a founder effect. This pathogenic variant had previously been reported once, in Turkey,[25] and we hypothesised that it is possible this variant travelled from the Northern hemisphere, and was introduced into a small community by European sailors in the early 1800s.

Glaucoma

Primary open angle glaucoma is not common in the NZ Māori population. In an assessment of the demographics of Glaucoma in 567 individuals in NZ, Māori and Pacific peoples were underrepresented for all types of glaucoma except primary angle closure.[26] In our series of 115 POAG patients in which we screened known glaucoma genes (*MYOC*, *CYP1B1 OPTN* and *WDR36*), none were from these ethnic groups.[27] A recent case report describes the first recorded observation of pseudoexfoliation syndrome (PXF) and glaucoma in a Māori male.[28] A previous study in Rarotonga, Cook Islands, observed PXF in 3 of 1000 subjects examined.[29] *LOXL1* variants were not studied in any of these reports.

Retinoblastoma

In a retrospective audit of Retinoblastoma genetics seen through the Auckland Hospital Ophthalmology service, for a 5 year period from 2003-2008, we identified 20 patients, including one family, with a 100% mutation detection rate.[30] Four individuals were Māori (20%), and germline mutations accounted for 75% of their disease, and a further 3 patients were Pacific peoples (15%). Disease in 2 Māori patients and one Cook Island Māori patient was attributed to a *de novo* germline mutation. Although the numbers are small, and therefore not statistically significant, this higher percentage of this disease in these ethnic groups may indicate a predisposition to *de novo* mutations or heritable disease, as has been shown with US Latino patients with retinoblastoma, compared to non-Latinos.[31]

Inherited retinal dystrophies (IRD)

In 2009, the New Zealand Registry of Inherited Retinal and Optic Nerve disease was established, with all participating patients recruited from the Ocular Genetic Clinic, at the Eye Department, Greenlane Clinical Centre, Auckland District Health Board. This is a tertiary referral clinic, with patients from all over NZ referred for assessment. All individuals in this public hospital clinic are extensively phenotyped; history, pedigree, visual acuity, dilated slit lamp and fundal examination, OCT, fundus photography and fundus autofluorescence, and if possible, electrophysiology. Genetic testing is initiated at the end of the consultation if appropriate, and only at this time is the invitation to participate in the IRD database given, and informed consent obtained to enrol. Participation means that if no genetic diagnosis is made at commercially available testing facilities, the option to explore the underlying genetic cause for disease on a

research basis is permitted. To date there are over 700 probands, and family members. This is a valuable tool to determine the incidence, nature and spectrum of different IRD phenotypes and genotypes in New Zealand.

Commercially available testing has evolved over the years, however the cost of testing is the main determinant in a publically funded eye clinic. Asper Ophthalmics in Estonia, offers a microarray platform, which using an APEX based methodology, tested for known mutations in known genes on a "disease" microarray – e.g. autosomal recessive retinitis pigmentosa (ARRP), or autosomal dominant RP (ADRP). These traditionally have had a low yield in our population. More recently their technology has been updated to incorporate a next generation sequencing (NGS) strategy around the regions of known mutations, but still does not sequence the gene(s) in its entirety. Specific genes have been genotyped over the years at a variety of institutions including the Carver Lab, Iowa, and the Molecular Vision Laboratory (MVL, formerly Casey Eye Institute), Portland, Oregon, as well as the Genomic Diagnostics Laboratory, Manchester Centre for Genomic Medicine, Manchester, UK, for X-linked RP genes. Newer technologies such as NGS targeted disease panels are available, with reducing prices, allowing more targeted and comprehensive screening of candidate genes, e.g. the Macular panel at MVL costs $500USD and fully sequences 13 genes, including *ABCA4*, and includes the intronic regions. Retinal disease panels incorporating hundreds of genes are available – but at the time of writing are still cost-prohibitive for our public health system.

The yield for a positive genetic diagnosis is low in the Māori and Pacific peoples cohort using the microarray panels, (discussed under individual diseases below). Using a NGS targeted retinal disease panel (105 genes, Manchester Centre for Genomic Medicine) we undertook analysis in a cohort of 28 Māori and Pacific peoples with IRD. (Vincent et al, IOVS 2016:57;12 ARVO e-abstract 3157). The diagnosis in these patients was autosomal 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 4 (*PDE6B, RD3, SPATA7, PROM1*). All LCA and ADRP cases were solved. Two ARRP cases had mutations in ADRP genes. 60% of ARRP cases remain unsolved.[32]

Leber Congenital Amaurosis/ Early onset severe retinal dystrophy (LCA/EOSRD)

Childhood blindness due to IRD carries a significant social and economic burden, and is estimated to affect 3-4 children in 10,000. LCA and EOSRD are at the severe end of this spectrum of disease, with children presenting at birth, or in the first few years of life with poor vision, roving eye movements and non-recordable retinal electrical responses.

Of the estimated 56-140 children affected with LCA / EOSRD in NZ, we have identified 41 children from the database, for which 25 have no genetic diagnosis. The genetic cause for disease is identified in 16 individuals from 14 families, with mutations in

CRB1 (n=5 probands*), RPE65* (n=2), and singletons for *GUCY2D, CRX, LCA5, SPATA7, TULP1, PROM1* and *RD3.* 4 of these probands are NZ Māori/Pacific peoples, with pathogenic variants observed in *LCA5, RD3, RPE65* and *SPATA7*, of which novel changes were identified in 75% using a NGS targeted panel (105 retinal genes) in 2013. (Vincent AL *et al*, IOVS 2016.57:12 ARVO E-Abstract 3157) (Table 1, Figure 2)

Rod cone dystrophies.

Autosomal Dominant Rod cone dystrophy (ADRP)

The NZ IRD database includes 48 families with presumed ADRP, including 4 Māori, 1 Tongan, 1 Niuean, and 1 Samoan. A genetic diagnosis has been made in 26 (54%) of the entire ADRP cohort. IN the Māori/Pacific peoples cohort, the genetic cause has been identified in 3 families, in *IMPDH1, PRPF31,* and *GUCA1A*. (Table 1)

Patient #5, a 32 y.o. Māori male, had an onset of his symptoms at primary school, and by age 27 had 6/60 vision OU (Figure 3 a,b). His father was affected, and a previously reported pathogenic variant in *GUCA1A* c.149C>T, p.Pro50Leu[33] was identified that segregated with disease in the family.

A 19 year old Samoan female **(Patient #6),** described an onset of symptoms, particularly nyctalopia, from the age of 8 years. Reportedly her brother, mother, and maternal grandmother also had similar symptoms, in particular night vision difficulties. On examination her BCVA was 6/7.5 OU, with a relatively featureless fundi with peripheral atrophy, significant vessel attenuation, sparse pigment and optic disc pallor, and bilateral cystic maculopathy (Figure 3 c-f). The presumed diagnosis was autosomal dominant (AD) rod cone retinal dystrophy. NGS identified a rare novel missense mutation in *PRPF31*, c.682G>C,p.(Ala228Pro), and predicted to be pathogenic. A second pathogenic variation in *IMPG2* (c.331C>T, p.(Arg111*) previously undescribed, was also present. *IMPG2* is associated with both recessive and dominant Vitelliform Macular Dystrophy(VMD).[34]

Patient #7, a 28 year old Maori male, had nyctalopia for all of his life, with subsequent restriction of visual fields and gradual deterioration of central vision in his early 20's. His mother (Ngati Putenga Hauraki), was also affected, On examination, BCVA was NPL OD from trauma, 6/21 OS, with a diagnosis of presumed AD rod cone dystrophy (Figure 3 g,h). The NGS panel identified an previously identified *IMPDH1* disease causing variant c.968A>G, p.(Lys323Arg).

Autosomal Recessive Rod cone dystrophy (ARRP)

There are 117 probands with presumed ARRP in the NZ IRD database, which includes those with sporadic disease, and no other affected family members, and no known consanguinity. The X-linked RP genes have been excluded in many of the affected sporadic males. Thirty-one of the probands (26%) are of Māori or Pacific peoples

ethnicity (Māori n-17, Samoan n=9, Cook Island Māori n=3, Niuean n=1, Tongan n=1). The diagnostic yield in this cohort using the Asper ARRP microarray was zero, and a causative genetic diagnosis has only been possible using the NGS targeted disease panel as described in our recent publication.[32]

A novel homozygous *PDE6B* variant, c.2197G > C; p.(Ala733Pro) was initially identified in 4 probands (#8) on the NGS panel, and subsequently in a further 6 probands, based on similarity of the retinal phenotype, and their iwi (tribe). Nearly all probands came from the Northern region of the North Island (Iwi Ngā Puhi) or the Gisborne, East Cape region (Iwi Ngāti Porou). Nearly 200,000 (30%) of NZ Māori identify with these two iwi. Based on our observed minor allele frequency of 0.0076, and assuming Hardy Weinberg equilibrium, we would only expect 11 affected individuals, and we have already identified 10. However, the carrier frequency is likely higher within certain iwi, and this *PDE6B* variant may account for 16% of recessive IRD in Māori.

The phenotype across all affected individuals, was fairly consistent, with onset usually described around the age of 20 with nyctalopia, and the fundus appearance showing a fairly lacy pattern of mid-peripheral bone spicule pigmentation, and often a bullseye maculopathy. (Figure 4)

A careful history, pedigree ascertainment, and knowledge of familial iwi in a NZ Māori patient presenting with a rod-cone retinal dystrophy, and familiarity with the retinal appearance of the PDE6B variant, should always be considered, and potentially simplifies the diagnostic process – i.e. genetic testing for the single *PDE6B* variant can be initiated instead of a more expensive, multigene NGS panel or array.

PDE is a protein that has a high concentration in the peripheral membrane of retinal photoreceptors, and integral to the phototransduction cycle. It consists of two catalytic subunits, PDE6A and PDE6B, and two gamma inhibitory subunits. This protein reduces the level of cyclic guanine monophosphate (cGMP) by hydrolyzation thereby resulting in channel closure in response to light.[35, 36] Mutations of the *PDE6B* gene results in accumulation of cGMP due to a dysfunctional PDE protein, leading to photoreceptor cell death.[37, 38] Although autosomal recessive rod cone dystrophy is the most common phenotype described in association with mutations in this gene, a CSNB (Congenital stationary night blindness) phenotype is also described. The majority of pathogenic variants occur within the C terminal catalytic terminal domain, including p.Ala733Pro, and lead to complete loss of enzymatic activity and subsequent accumulation of cGMP. The intracellular build-up of cGMP is known to cause photoreceptor toxicity.

By understanding the pathophysiology, it is feasible to target an aberrant process created by the pathogenic variants in the *PDE6B* gene. Using animal models, *rd1* and r*d10* mice, treated with PARP inhibitors, and cGMP analogues, Sahaboglu *et al* demonstrated a reduction in cGMP accumulation, and increased photoreceptor survival, confirming *in vivo* neuroprotection.[39]

We are currently creating a zebrafish model of disease, with morpholino and CRISPR/Cas9 gene editing techniques, specific to the *pde6b* p.(Ala733Pro), to utilize as a resource for high throughput drug screening.

X-Linked disease

Choroideraemia

Of the 7 probands with a clinical diagnosis of choroideraemia and a positive genetic test of the *CHM1* gene, none are Māori or Pacific peoples

X-Linked Retinoschisis

Of 7 probands with X-Linked Retinoschisis and mutation positive *RS1* genetic analysis, all are of NZ European ethnicity. (Vincent AL *et al*, IOVS 2017.58:8 ARVO E-Abstract 2770)

X-Linked Congenital Stationary Night blindness

The clinical features of a large pedigree of Māori ethnicity with incomplete CSNB have been described by Hope *et al* [40], and attributable to the previously undescribed *CACNA1F* c.2267T>C, p.Ile756Thr (also known as p.Ile745Thr) allele. All affected males demonstrated severe non-progressive visual impairment, with congenital nystagmus, altered colour vision, hyperopia and normal fundi. Some of these males were also intellectually disabled. In this family, the obligate carrier females all showed a moderate to severe ocular phenotype, with decreased vision, congenital nystagmus, and were often highly myopic. In both male and females, the ERG showed a characteristic negative wave form with reduction of both rod and cone responses.

Further individuals from the extended family have subsequently been identified, and genotype confirmed, although did not always directly know of the familial association. A careful history, knowledge of the phenotype, and identification of iwi, usually will help target the genetic testing strategy and diagnostic algorithm.

X-Linked Rod Cone retinal dystrophy (XLRP)

We have characterised 19 families with XLRP, attributable to mutations in the *RP2* gene (n=1) and *RPGR*, including ORF15(n=18) (Vincent AL *et al*, IOVS 2017.58:8 ARVO E-Abstract 2770) Of these families, 3 were NZ Māori, and 1 Samoan, and the disease causing variants observed in this ethnic group were not previously reported, and segregated with disease in the family. In *RP2*, the variant c.945_946insT is predicted to cause a premature termination of the protein p.(Asn316*).

The other three variants were in *RPGR*; c.283G>A, p.(Gly95Arg), a missense variant, in exon 10, c.1236_1239delAAGA also resulting in premature termination p.(Glu414GlyfsTer10), and an ORF15 deletion c.2630delA, which segregated with disease in 18 members of the family(#12). A number of obligate carrier females showed significant disease manifestation. In this family keratoconus also segregated with disease, however the high incidence of keratoconus in this population has previously been discussed. (Vincent AL *et al*, IOVS 2017.58:8 ARVO E-Abstract 2770)

In a further male proband (#11), with 3 affected daughters, two variants were detected. A heterozygous variant in *C1QTNF5*, c.583dupG, p.(Ala195Glyfs*8) is rare, and predicted to be damaging, and he was also hemizygous for *RPGR* c.283G>A

p.(Gly95Arg). We were however unable to confirm segregation, the phenotype was not typical for Late onset retinal dystrophy (LORD) described with *C1QTNF5*, and as his sister's son was also reportedly affected, the *RPGR* variant was thought to be the causative allele.

Maculopathies and Cone/Cone Rod Dystrophies

ABCA4-associated disease

In the NZ IRD database, 81 probands have at least one pathogenic variant or VUS in ABCA4, and a clinical picture consistent with disease. Six of these probands identify as Māori, including two sib pairs.

A novel homozygous variant c.5584G>T, p.(Gly1862Cys) observed in one proband (#13) with a maculopathy occurs in the last nucleotide of exon 39, and is predicted to be probably damaging by PolyPhen-2 with the maximum score of 1.000. This variant does not occur in databases of human variation, and was also homozygous in his affected sibling. Both siblings had a similar manifestation of disease.

This variant was not detected initially using the *ABCA4* Asper microarray in 2010, but only subsequently in 2015 with testing on the MVL NGS macular panel, which sequences *ABCA4* in its entirety, including probing for deep intronic variants.

Non-ABCA4 maculopathies

At the end of 2016, we identified patients with maculopathies or Cone-rod dystrophies (CORD), in which *ABCA4* had been excluded as the cause of disease, or a pathogenic variant(s) identified in a gene consistent with the phenotype. 80 patients were diagnosed with a maculopathy and 22 with a CORD. Vitelliform macular dystrophies (VMD) were the most common maculopathy (25.0%) of which 50.0% were *BEST1* positive. Interestingly none of the individuals with VMD were Māori or Pacific people. The CORDs showed a higher proportions of males (68.2%), Māori (27.3%), and Polynesian (9.1%) patients than the maculopathies. A high proportion of Māori and Polynesian patients also lacked genetic characterization. 11 patients were identified with *RDS/PRPH2* mutations and exhibited wide phenotypic variability, yet once again none of these individuals were Māori or Pacific peoples, adding further weight to a different genetic spectrum of disease in these ethnic groups.

CRX CORD

Patient #14 had a novel heterozygous nonsense variant, c.774T p.(Tyr258ter), in the *CRX* gene when analysed by the Manchester NGS retinal panel . This change was not present in databases of human variation. This patient had simplex inheritance with a late onset (age 50) severe cone – rod dystrophy, with vision 6/60 OU at age 55 years. Fundal photography showed paramacular greying and atrophy of retinal pigment epithelium with a bulls eye pattern, and a central area of loss of photoreceptors on OCT, and a central dark area with a hyperfluorescent ring on FAF(Figure 5a).

Electrophysiology was performed to ISCEV standards. Rod mediated function was identified with reduced photoreceptor A wave amplitude, but relatively normal B wave. Cone mediated function was identified but significantly reduced in amplitude to about 50% normal and increase in latency for both photopic, flash and for flicker at 30 Hz. The pattern ERG was poorly defined.
Mutations in the *CRX* gene have been shown to be associated with autosomal dominant LCA type III and as well as AD cone rod dystrophy and maculopathy.[41]

Occult macular dystrophy
A 48 year old NZ Māori male (**Patient#15**), noticed an onset of deterioration in his vision in his late teens, and was troubled by glare. His vision measured 6/60 OD, and 6/48 OS, with a localised area of photoreceptor abnormality subfoveally (Figure 5b). Full field ERG was unremarkable, and a pattern ERG showed a reduced p50 wave, consistent with a localised macular abnormality. He was heterozygous for the most commonly reported pathogenic variant in *RP1L1*, c.133C>T. p.(Arg45Trp), as was his affected sister (Figure 5b). Occult macular dystrophy has been reported predominantly in the Japanese population.[42]

***BBS9* CORD**
A 43 year old NZ Māori male (**Patient#16**) became aware of shadows in his vision in this early 30s, with vision measuring 6/9 at the time, but deteriorating to 6/60 2 years later, and to 1/60 age 43. Electrophysiology initially showed marked attenuation of cone function, and mildly affected rod photoreceptor function. When repeated age 43, rod function was now barely recordable. The fundus appearance showed widespread sharply demarcated areas of atrophy, and small islands of residual retina. The retinal arterioles are mildly attenuated and both maculae have sub-retinal fibrosis (Figure 5c). The patient had no other systemic features, but described multiple relatives on both sides of the family with polydactyly. Testing with the Manchester NGS retinal panel identified compound heterozygosity for two novel variants in *BBS9*; c.205C>A; p.(Leu69Ile), and c.1014_1015delinsTT p.(Leu338_His339delinsPheTyr), both of which are rare and predicted to be pathogenic. His parents were heterozygotes for a single change each, but other family members were not available for clinical nor genetic characterisation.

***PROM1* CORD.**
At the age of 3 years, a NZ Māori male was noted to have poor vision and was very light sensitive. Initially a myopic correction was prescribed. When seen at age 7 years, his visual acuity was 6/18 OD, 6/21 OS, with fine granularity noted at each fovea (Figure 5d). Electrophysiology showed reduced rod-mediated amplitudes, and non-recordable cone function and pattern ERG. On the NGS panel, a homozygous *PROM1* pathogenic variant c.1354_1355insT, p.(Y452Lfs*13) was present, and confirmed heterozygously in his non-consanguineous parents.

Conclusions

Local knowledge and characterisation of disease prevalence and genetic variation within the New Zealand Māori and Pacific peoples has identified ethnic-specific variation in the spectrum of inherited eye disease compared to the NZ European population. Keratoconus is more frequent, but glaucoma less common. Several founder mutations are identified in *ADAMTSL4* associated with autosomal recessive ectopia lentis, and *PDE6B* in ARRP. Knowledge of these changes, the presenting phenotype, and the regional origin and iwi of the patient can simplify the diagnostic algorithm, to inform targeted genetic testing. As this population is not well represented in databases of human variation, segregation and *in silico* analysis is paramount to determining pathogenicity of any variant detected.

Although many of our probands have not undergone state-of-the-art NGS gene panel investigation, the unique and novel variants identified to date provide a strong argument to justify further investigation within the NZ Māori and Pacific peoples, and a high likelihood of identification of further novel genetic variation as the cause for their eye disease.

Compliance with Ethical Requirements

Author ALV has no conflicts of interest to declare.

Informed Consent

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from all patients for being included in the study.

Additional informed consent was obtained from all patients for which identifying information is included in this article.

No animal studies were carried out by the authors for this article

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Figure Legends.

Figure 1. Autosomal recessive Ectopia Lentis. Slit lamp photo demonstrating lens subluxation in autosomal recessive ectopia lentis in a patient homozygous for *ADAMTSL4* c.2237G>A, p.(Arg746His).

Figure 2. Retinal images of an 18 year old female with Leber Congenital Amaurosis (Patient #4) homozygous for *RPE65* IVS1+5 G>A. a. Optos widefield fundus photo showing mottling of the retina with mild vessel attenuation, but no pigment, and b. Fundus autofluorescence showing a paramacular ring of hyperautofluoresence.

Figure 3. Clinical features of Autosomal Dominant Rod cone dystrophies. *GUCA1A* c.149C>T, p.Pro50Leu (Patient #5) Optos widefield photo OD (a) and fundus autofluorescence OD (b). *PRPF31*, c.682G>C,p.(Ala228Pro), (Patient #6) - Optos widefield photo OD (c) and fundus autofluorescence OD (d), and OCT images of coexisting cystic maculopathy (e) OD and (f) OS, with loss of photoreceptors outside the subfoveal region. *IMPDH1* c.968A>G, p.(Lys323Arg).(Patient #7) Optos widefield photo OS (g), and fundus autofluorescence OS (h).

Figure 4. Clinical imaging of the founder *PDE6B* c.2197G > C; p.(Ala733Pro) variant associated with autosomal recessive rod cone dystrophy. Optos widefield photos (OD(a) and OS (b) demonstrating the characteristic mid peripheral dense bone spicule pigmentation, and retinal atrophy, vessel attenuation, and sparing of the macula in a 45 year old. Fundus autofluorescence with the Optos OD (c), OS (d), and Spectralis OD (e), OS(f), with a perimacular hyper fluorescent ring and bullseye appearance.

Figure 5 Clinical images of 4 patients with Maculopathies/ Cone rod dystrophies.
a. ***CRX*** Patient #14 with a heterozygous *CRX* variant , c.774T p.(Tyr258*): macula photo (i), fundus autofluorescence (ii) and OCT (iii).
b*.* Occult macular dystrophy Optos photo (i) OD in patient #15 with *RP1L1* c.133C>T. p.(Arg45Trp), and fundus autofluorescence (ii) and OCT (iii) in his affected sister (all OD).

c. *BBS9*. Patient #16, a compound heterozygote for two novel *BBS9* variants**,** c.205C>A; p.(Leu69Ile), and c.1014_1015delinsTT p.(Leu338_His339delinsPheTyr) demonstrating sparse pigment clumping and sharply demarcated areas of retinal atrophy (i), corresponding to areas of hypoautofluoresence (ii), and marked thinning of the outer retina and loss of photoreceptor architecture (iii).
d. *PROM1* Retinal phenotype of autosomal recessive *PROM1* CORD c.1354_1355insT, p.(Y452Lfs*13) disease (Patient #17), with foveal granularity and peripapillary atrophy (i), reduced macular autofluorescence(ii), and disturbance of the photoreceptor outer segments in the foveal and perifoveal regions (iii).

Table 1. Genetic Variants identified in Inherited Retinal Dystrophies in the NZ Māori and Pacific Peoples.
Hom=homozygous, het = heterozygous, hemi = hemizygous, EVS = Exome variant Server, EXAC = Exome aggregation consortium,