Characterising X-linked Inherited Retinal Disease in New Zealand identifies unique population demographics and genotypes.

Andrea L Vincent 1,2 Eileen Song1 Shilpa Kuruvilla 1,2 Naz Raoof 1,2 Katherine van Bysterveldt 1 Verity F Oliver1
1 Ophthalmology New Zealand National Eye Centre University of Auckland, 2 Eye Department, Greenlane Clinical Centre, Auckland District Health Board, Auckland, New Zealand,

Purpose: To characterize the spectrum of X-linked inherited retinal dystrophy (XL-IRD), and to establish a genotype-phenotype correlation within the New Zealand population.

Methods: Proband with XL-IRD (rod-cone dystrophy RP, choroideremia CHM, congenital stationary night blindness CSNB, retinoschisis RS, blue cone monochromatism BCM, and ocular albinism OA) were identified through family history and positive gene testing, from the 652 patients recruited in the IRD Database. Familial segregation and clinical data for affected male and obligate carrier females was undertaken. Bioinformatics of novel variants included pathogenicity prediction and frequency in population databases. Reported mutations were identified in LOVD.

Table 1: XLRP Pathogenic Variants identified in RPGR and RP2

Table 2: Pathogenic variants identified in Choroideraemia, XL Congenital Stationary Night Blindness, and XL Retinoschisis

Results
X-Linked inherited retinal disease was molecularly proven in 42 probands. (XLRP n=19, CHM n=7, CSNB n=5, XLRS n=7, BCM n=2, XLOA n=2), and segregation confirmed in family members where available.

XLRP: 17 unique pathogenic variants were present, of which 10 (58.8%) were not previously described. Mutations in exon ORF15 of RPGR accounted for only 31% (6/19) of XLRP. One novel ORF15 change in a NZ Māori family, segregated with disease in 16 family members Figure 1.2. Keratoconus also was observed co-segregating with the variant. Two reportedly unrelated Caucasian families had the same novel mutation (RPGR, c.248-10A>G). One novel RP2 mutation was identified. Novel variants were present in all Polynesian/NZ Māori families (n=4). Five families showed significant manifestations in female carriers, (Figure 1.2,3) and 2/5 were initially diagnosed with dominant disease.

CHM: 57% of variants were novel, and 57% were indels.

Conclusion
A knowledge of regional IRD genotypes and disease manifestation facilitates diagnosis for patients, in addition to using a targeted strategy for gene identification. In an era where clinical trials for some XL-IRD are already underway, a timely diagnosis is necessary.

The spectrum of genotypes in an XL-IRD New Zealand population differs significantly that reported in other populations. The majority of variants identified were unique, with 58.8% of XLRP changes not previously reported. The frequency of ORF15 variants in XLRP was only 33%, suggesting screening RPGR prior to ORF15 is a more cost effective strategy in our population. Significant disease manifestation in female carriers was observed, consistent with the observation that XLRP may mimic autosomal dominant inheritance.

This study highlights the importance of local knowledge in retinal diseases, to optimize diagnosis, management, and ultimately treatment.