Retina Australia Research Grant 2021 – Final Report

Looking for disease causing mutations in families with dominant RP pedigrees

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Outline of Study:

Retinitis pigmentosa (RP) is a debilitating eye disease that affects I in 3,000 people in Australia. RPI I is a type of RP caused by mutations in the PRPF3/ gene and it is estimated to account for 250 cases in Australia. RPI I is dominantly inherited, meaning that only one copy of the gene with a mutation is required to cause disease. There is no treatment available to patients burdened with this condition. Our group, which combines the expertise of specialists in the fields of antisense oligonucleotides, ocular delivery technology, ocular tissue models and clinical trials, is currently developing a novel therapeutic to treat PRPF3 /-associated RP. In laboratory studies using engineered cells from patients, the molecule has rescued some of the functions missing in RP 11. The molecule has an excellent safety profile and it is on track to reach phase 1/2 clinical trials at the end of 2021.

The Australian Inherited Retinal Disease Registry and DNA Bank (AIRDR), and the Lions Eye Institute (LEI) are currently monitoring the disease progression rate in a cohort of 20 patients in Western Australia with disease-causing mutations in PRPF3 l. However, a larger pool of patients fulfilling the eligibility criteria is required for an Australia-wide phase 1/2 clinical trial. We will use specialized gene analysis techniques to rapidly identify PRPF3 I disease causing mutations in autosomal dominant RP families who have provided samples to the AIRDR and DNA bank, and select potential participants for future clinical studies. Analysis of these samples will also provide a genetic diagnosis to many of these families, presenting opportunities for them to make informed decisions regarding disease management and family planning.

Through this study, we will also gain greater understanding of the factors contributing to disease penetrance, age of onset and severity in RP 11 , through analysis of known modifying factors, such as the number of copies of a repeated sequence the 'MSRI' (upstream of PRPF3 I), and a 'Single Nucleotide Polymorphism' rs48067 I 8 in a modifier gene.

Both these elements are known to be predictors of RPI I disease severity, and it is important that we understand the interaction between with these modifiers, disease progression and response to treatment.

Results:

Retinitis pigmentosa (RP) can be inherited as an autosomal dominant trait in 20-25% of the families. One of the most common genetic causes of dominant RP is a mutation in the *PRPF31* gene. Given the recent development of gene-based therapy to treat *PRPF31* disease, we sought to find families with *PRPF31*-associated RP by performing a gene panel testing on 40 families presenting with a dominant pedigree.

Amongst the 684 patients presenting with an inherited retinal disease phenotype, we saw around 300 patients with typical RP. 42% are sporadic whilst 33% had a dominant pedigree.

A total of 40 dominant RP families were analysed and 23 (58%) returned a positive or likely positive result. These families had *RHO* (n=7), *RP1* (n=4), *PRPF31* (n=4), *HK1* (n=3), *PRPH2* (n=2), *SAG*, *RP9* and *SNRNP200*. Amongst the remaining 17 (42%) families with inconclusive results, further analysis was undertaken to resolve 9 of these families, identifying *PRPF31* (n=3), *PRPF6*, *SAG*, *RPE65*, *IMPG1*, *IMPDH1*, and *BEST1* as causative genes. This left 8 (20%) dominant RP pedigrees unresolved.

Additional analysis is now underway in these 8 unresolved families to find new mutations and new genes causing dominant RP.

In summary, we found *PRPF31* and *RHO* are the most common causes of dominant RP in Australia. *PRPF31* mutations can be missed without specific analysis for large deletions in the gene. In total, 13 different genetic diseases were found in 40 families with dominant RP. Many of these genes can manifest in other forms of inherited retinal disease aside from RP and may also have recessive inheritance.

In conclusion, success rate of gene panel testing can be improved from 58% to 80% with the independent variant curation, additional testing for large deletions and familial phase testing.