RETINA AUSTRALIA RESEARCH GRANT (2020) - FINAL REPORT

The Australian Inherited Retinal Disease Registry & DNA Bank

Project: Provision of genetic research reports to Australian Inherited Retinal Disease Registry participants via their nominated ophthalmologist or clinical geneticist

The major aims of this project were to provide more than 200 genetic research reports to participants via their nominated clinicians to inform patient management, and to detail by publication the genetic spectrum of IRD in Australia.

Reports: During the grant period (2020), 261 genetic research reports were issued to nominated clinicians to assist with patient management, or to genetic counsellors for counselling/family planning purposes. Of those, 173 reports were issued on behalf of participants affected with an inherited retinal disease (IRD) (age range 5-92 years), and the remaining 88 reports were issued on behalf of family members (carriers and non-carriers of genetic mutations). These reports covered a diverse range of clinical diagnoses (Table 1) and causative genes (Table 2).

Table 1: Clinical diagnoses of the cohort.

Clinical diagnosis	**Cases**	**Clinical diagnosis**	**Cases**
achromatopsia	12	Goldmann-Favre disease	1
age-related macular degeneration	1	Leber congenital amaurosis	2
Best disease	3	macular dystrophy	6
bestrophinopathy	2	Multifocal pattern dystrophy simulating fundus flavimaculatus	1
blue cone monochromacy	1	pattern dystrophy	4
bradyopsia	2	pigmented paravenous chorioretinal atrophy	1
central areolar choroidal dystrophy	1	retinal dystrophy	2
choroideremia	3	retinitis pigmentosa	10
cone dystrophy	9	retinoschisis	1
cone-rod dystrophy	4	rod-cone dystrophy	58
congenital non-progressive cone-rod synaptic disorder	1	Stargardt disease	31
fleck retina	1	Usher syndrome (various types)	12
foveal hypoplasia	1	Vitelliform macular dystrophy	1
foveoschisis with perifoveal atrophy	1	vitreoretinochoroidopathy	1

Table 2: Diversity of causative genes in the cohort.

Causative genes
ABCA4, AHI1, ARHGEF18, BEST1, CABP4, CEP290, CEP78, CHM, CNGA3, CNGB3, CRB1, EYS, GUCA1A, GUCY2D, HK1, OPN1LW/MW, PCDH15, PDE6B, PRPF31, PRPH2, RGS9, RHO, RP9, RPE65, RPGR, RS1, SAG, SLC7A14, USH2A.

The 173 reports pertaining to participants with an IRD were sent to 31 different ophthalmologists/clinicians (164 reports) or genetic counsellors (9 reports). Of these, 9 were directly requested by participants, and 1 was requested for family planning purposes.

Of the 173 reports issued for individuals with an IRD, 120 were considered resolved/likely resolved, and 33 were unresolved. A further 20 cases are ongoing and have plausible candidate variants identified, subject to further testing of familial DNA samples and interpretation.

Publications: During the course of analysing, interpreting and reporting on these participants, the information provided contributed to numerous publications detailing part of the genetic spectrum of IRD in Australia, for the following genes; *ABCA4*[1-5], *CHM*[6], *CRB1*[7], *PRPF31*[8], *RPE65/BEST1*[9], *SAG*[10] *and USH2A*[11] (these publications are detailed in the references section below).

Additional outcomes:

This analysis revealed the syndromic nature of disease in one individual with an IRD, with hearing loss which was suspected to have occurred due to childhood meningitis. These results indicated the syndromic nature of disease (IRD plus hearing loss) due to mutations in the gene, *CEP78*.

The results of the analysis and reporting conducted throughout this project have identified a number of potential candidates for clinical trials, or therapies arising from these clinical trials;

Therapy[T] / Clinical Trial[CT]	**Relevant genetic information**	**Potential candidates**
Luxturna[T]	RPE65 gene therapy	1
ProQR QR-110[CT]	CEP290 c.2991+1655A>G therapy	1
Various at different stages of development[CT]	CHM gene therapy	3
Various at different stages of development[CT]	RPGR gene therapy	6
ProQR QR-421a[CT]	USH2A exon 13/62 skipping	1
Horama SA AAV2/5-hPDE6B[CT]	PDE6B gene therapy	3
Sanofi SAR439483[CT]	GUCY2D gene therapy	1

This study therefore provided genetic research reports that were used to assist with patient management, for genetic counselling, and family planning purposes, and the findings were used to inform scientific research into the genetic causes of IRDs in the Australian population. A number of potential candidates for clinical trials, or future therapies arising from these trials, were identified.

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ABCA4

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CHM

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CRB1

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PRPF31

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RPE65/BEST1

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SAG

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USH2A

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