RETINA AUSTRALIA RESEARCH GRANT (2021) - FINAL REPORT

The Australian Inherited Retinal Disease Registry & DNA Bank

Project: Provision of genetic research reports to research participants via their nominated ophthalmologists or clinical geneticists

The major aims of this project were to provide more than 200 genetic research reports to participants via their nominated ophthalmologists or clinical geneticists, and to enhance the knowledge of the genetic spectrum of inherited retinal disease (IRD) in Australia via publications.

Reports:
Throughout the period of the grant (2021), 363 genetic research reports related to 323 participants were provided to nominated clinicians and genetic counsellors to assist with patient management, and to facilitate genetic counselling and family planning.

This cohort included 185 IRD-affected participants, 6 asymptomatic individuals with familial mutations, and 132 unaffected family members (carriers and non-carriers of familial mutations).

These reports detailed the likely genetic cause of disease in participants with a diverse range of clinical diagnoses (Table 1), caused by pathogenic DNA changes in 37 different genes (Table 2), and were issued on behalf of AIRDR participants to 29 different ophthalmologists throughout Australia.

Table 1: Diverse clinical diagnoses of the cohort.

Clinical diagnosis	**Cases**	**Clinical diagnosis**	**Cases**
achromatopsia	11	late-onset retinal degeneration	1
vitreoretinochoroidopathy	2	Leber congenital amaurosis	18
bestrophinopathy	1	macular dystrophy	20
Bardet-Biedl syndrome	1	pattern dystrophy	1
blue cone monochromacy	3	pattern dystrophy of the retinal pigment epithelium	1
choroideremia	5	pericentral retinal degeneration	2
Cohen syndrome	1	retinal dystrophy	5
cone dystrophy	10	retinitis pigmentosa	42
cone-rod dystrophy	24	retinoschisis	2
congenital stationary night blindness	3	rod-cone dystrophy	82
familial exudative vitreoretinopathy	1	Stargardt disease	60
fleck retina	3	syndromic retinal dystrophy	1
Goldmann-Favre disease	1	Usher syndrome (various types)	20
hereditary optic neuropathy	2		

Table 2: Genes associated with the diverse clinical diagnoses of the cohort.

Causative genes
ABCA4, AIPL1, AP5Z1, BBS1, BEST1, C1QTNF5, CEP290, CHM, CLN3, CNGB3, CRB1, EYS, GUCY2D, HGSNAT, HK1, IFT140, IQCB1, MFRP, NMNAT1, NR2E3, NYX, OPN1LW, OPN1MW, PDE6A, PDE6B, PRPF3, PRPF31, PRPH2, RHO, RP1, RP1L1, RPE65, RPGR, RPGRIP1, RS1, TULP1 and USH2A.

Of the 185 participants affected with an IRD, 133 participants had the likely cause of disease reported, and 52 participants were unresolved. Of the 52 unresolved participants, 10 are possibly resolved and awaiting further familial analysis to resolve these cases.

Publications:

The genetic results identified in these reports have contributed to various publications enhancing knowledge of the genetic spectrum of IRDs in the Australian population, including the following genes: *ABCA4*[1-5], *PRPF31*[6-7] and *PRPH2*[8].

Additional outcomes:

The results of the analysis and reporting undertaken for this project have contributed to the identification of potential candidates for clinical trials or future therapies arising from these trials (subject to specific exclusion/inclusion criteria imposed in the trials/treatments).

Clinical Trial	Relevant genetic information	Potential candidates
Various trials	*ABCA4* drug/dietary therapies	39
Various trials	*CEP290* c.2991+1655A>G therapy	1
Various trials	*CHM* gene/dietary/drug therapies	2
Various trials	*CLN3* gene/drug therapies	1
Various trials	*CNGB3* gene/implant therapies	5
NCT03920007; SAR439483	*GUCY2D* gene therapy	3
NCT05203939; OCU400	*NR2E3* drug therapy	1
NCT04611503; rAAV.hPDE6A	*PDE6A* gene therapy	1
NCT03328130; AASV2/5- hPDE6B	*PDE6B* gene therapy	4
NCT05203939; OCU400	*RHO* drug therapy	4
NCT03999021; N-Acetylcysteine	*RP1* drug therapy	7
Various trials	*RPE65* gene/drug therapies	1
Various trials	*RPGR* gene/drug therapies	3
Various trials	*RS1* gene therapies	1
Various ProQR QR-421a trials	*USH2A* gene therapy	7

One participant was re-evaluated for syndromic IRD (for IRD + other clinical symptoms).

The provision of the genetic research reports undertaken in this project have contributed to patient management, including for genetic counselling (6 participants) and family planning (4 participants) purposes. These findings further informed scientific research into the genetic spectrum of IRD in Australia, facilitated investigation into personalised medicine therapies, and identified potential candidates for clinical trials or future therapies arising from these trials.

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