AUSTRALIAN INHERITED RETINAL DISEASE REGISTRY & DNA BANK

DEPARTMENT OF MEDICAL TECHNOLOGY & PHYSICS
Sir Charles Gairdner Hospital

ANNUAL REPORT

The Australian Inherited Retinal Disease Registry and DNA Bank

Status Report

as at June 2022

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Introduction

This is the annual status report for the resource *The Australian Inherited Retinal Disease (IRD) Registry and DNA Bank* for the period July 2021 to June 2022.

The custodian for this resource is the Department of Medical Technology and Physics, Sir Charles Gairdner Hospital, Western Australia.

The creation and development of this resource has been made possible by the generous funding from Retina Australia (WA) (since 1984), Retina Australia and its state branches (since 2009), and by the continued support of Sir Charles Gairdner Hospital.

The purpose of this project is to establish and maintain a public and enduring Australian resource for use by approved scientists and clinicians embarking on inherited retinal disease research, including those undertaking clinical trials and offering therapies. The resource consists of (1) a registry of consenting Australians affected with an IRD and their family members, and (2) a DNA bank containing DNA from consenting individuals.

Information within the registry includes results of electrophysiology tests, psychophysical measurements and ophthalmic examinations; demographic information; family and clinical data; and details of genetic analyses completed, including the defect causing the disease within each family where this has been established.

Information and DNA held within this resource may be made available to approved scientists and clinicians upon request. Information that may identify an individual will not be released without prior negotiation with the individual, and only if he or she chooses to become involved.

Project Staff

Staff funded by research funding and directly involved with the IRD registry and DNA bank on a day to day basis are Dr Jennifer Thompson (Graduate Research Scientist) and Ling Hoffmann (Research Assistant).

Departmental staff directly involved with the project include Dr John De Roach (Principal Medical Physicist), Terri McLaren (Medical Scientist-in-Charge), Dr Tina Lamey (Senior Research Scientist) and Isabella Urwin (Quality Manager).

Significant and valued assistance is provided by the department's visual electrophysiology, reception, secretarial, purchasing, information technology and other staff.

We work closely with a number of clinicians. Of particular note are Dr Fred Chen and Dr David Mackey of the Lions Eye Institute, and Dr Jon Ruddle of the Royal Children's Hospital, Melbourne.

We also collaborate with clinicians and researchers from more than 45 national and international institutions, for the purposes of conducting research, writing research papers or applying for project funding.

Ethics and Quality Assurance

Approval for this project was granted by the SCGH Human Research Ethics Committee on 25th May 2001 (approval number 2001-053).

As this Ethics approval is now more than 20 years old, we are currently embarking on a program of significantly bringing our Ethics documentation up to date. This process is expected to be completed by the end of 2022. Investigators on the updated approval are Dr John De Roach, Dr Tina Lamey, Terri McLaren, Dr Jennifer Thompson, Ling Hoffmann, Isabella Urwin, A/Prof. Fred Chen, Prof. David Mackey, Prof. Alex Hewitt and Dr. Jon Ruddle.

This project is carried out according to international standards with regard to its quality measures (ISO9001:2015). All associated processes are subject to both internal and external audit every 12 months.

Website

Our public website can be found at:

http://www.scgh.health.wa.gov.au/Research/InheritedRetinal.html

This website contains information about the registry and DNA bank, as well as contact details and links that allow downloading of a brochure (including an expression of interest), ordering of printed brochures, making a donation, making a bequest or downloading a copy of our most recent annual report.

Participant Recruitment

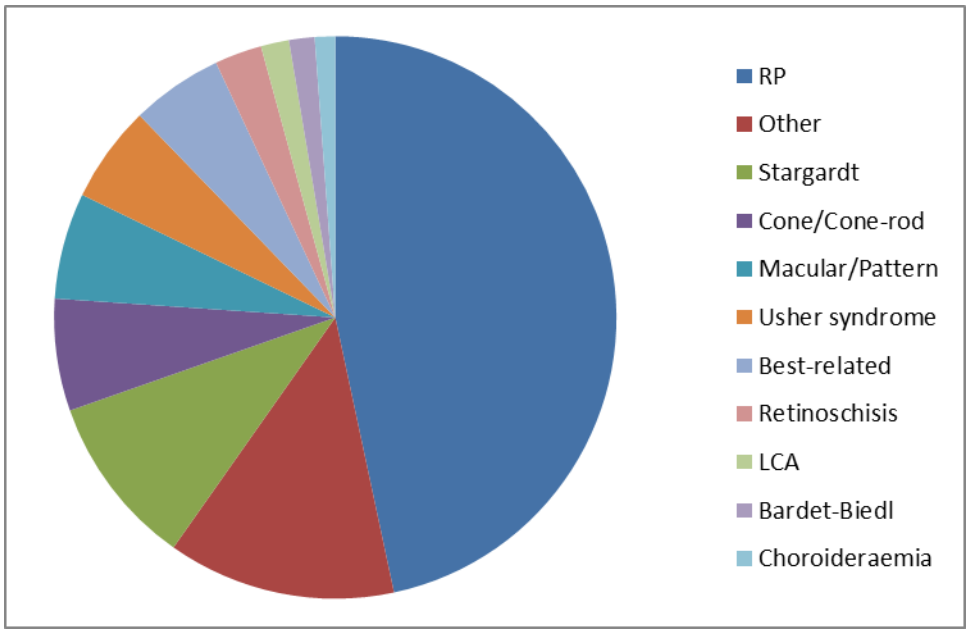
During 2021/2022, approximately 700 participants were removed from the registry. These participants had been carried over from a database that was established prior to when our Ethics approval was obtained, the participants had not provided DNA, and in updating our Ethics approval it was deemed appropriate to remove their details from the registry.

Demographic details of 9350 participants are recorded in the registry, 3894 (42%) of whom are classified as affected and 1691 (18%) as carriers.

DNA has been obtained from 7910 (85%) participants, 3429 (43%) of whom are classified as affected and 1531 (20%) as carriers.

The categorisation of DNA samples from affected participants by clinical diagnosis is shown in Figure 1.

Figure 1 DNA samples collected from 3429 affected participants, stratified by clinical diagnosis.



Genetic analysis

Based on genetic analysis of DNA followed by subsequent inspection of bioinformatics data and possibly full pathogenicity assessment, a research genetic diagnosis was assigned for 1091 affected participants from 734 families (Table 1).

Many other candidate pathogenic variants have been established for other participants, but these await assessment.

Table 1: Number of affected participants and families with a causative gene established.

Causative gene	No. parts.	No. fams.	Causative gene	No. parts.	No. fams.	Causative gene	No. parts.	No. fams.
ABCA4	277	212	*EFEMP1*	3	3	*PDE6B*	11	7
ABCC6	2	2	*EYS*	13	12	*PDE6C*	1	1
ADGRV1	2	1	*GPR98*	1	1	*PEX1*	1	1
AHI1	2	1	*GUCA1A*	2	1	*PITPNM3*	1	1
AIPL1	4	2	*GUCY2D*	17	9	*PROM1*	4	4
ALMS1	1	1	*GUCY2D; RP1*	4	1	*PRPF3*	7	2
AP5Z1	1	1	*HGSNAT*	4	3	*PRPF31*	38	15
ARHGEF18	1	1	*HK1*	4	3	*PRPF6*	2	2
BBS1	8	7	*IFT140*	2	2	*PRPF8*	1	1
BBS2	2	2	*IMPDH1*	4	2	*PRPH2*	40	23
BEST1	24	13	*IMPG1*	1	1	*PRPS1*	1	1
C1QTNF5	3	2	*IMPG2*	2	2	*RCBTB1*	2	1
C21ORF2	1	1	*INPP5E*	1	1	*RDH12*	3	2
CABP4	1	1	*IQCB1*	1	1	*RGS9*	1	1
CACNA1F	3	2	*LCA5*	2	1	*RHO*	35	17
CDH23	4	3	*MERTK*	3	3	*RP1*	39	15
CDHR1	3	3	*MFRP*	1	1	*RP1L1*	4	4
CEP290	11	9	*MT-ND1*	2	1	*RP2*	31	11
CEP78	1	1	*MT-ND4*	1	1	*RP9*	4	1
CERKL	2	2	*MT-TL1*	1	1	*RPE65*	4	4
CHM	42	30	*MYO7A*	5	5	*RPE65; BEST1*	3	1
CLN1	1	1	*MYO7A; RP1*	1	1	*RPGR*	21	13
CLN3	7	6	*NMNAT1*	6	6	*RPGR_ORF15*	78	36
CNGA1	1	1	*NPHP1*	1	1	*RPGRIP1*	5	3
CNGA3	9	7	*NR2E3*	4	4	*RS1*	38	21
CNGA3; CNGB3	2	1	*NYX*	2	2	*SAG*	3	1
CNGB1	1	1	*OPA1*	5	4	*SNRNP200*	2	2
CNGB3	32	26	*OPA3*	1	1	*SPATA7*	2	1
COL2A1	3	1	*OPN1LW/MW*	10	7	*TIMP3*	2	1
CRB1	24	15	*OTX2*	1	1	*TRPM1*	2	2
CRX	9	4	*PCARE*	1	1	*TULP1*	4	3
CRX; PITPNM3	1	1	*PCDH15*	4	4	*USH2A*	104	86
CYP4V2	1	1	*PDE6A*	1	1	**TOTAL**	**1091**	**734**

AIRDR Outcomes

Research results established by the AIRDR in the past 12 months facilitated the further development of national and international IRD research and improved patient management.

Significant outcomes from this resource include:

1. *Establishing the genetic spectrum of IRD in Australia:* Based on an IRD prevalence of 1/2000, we estimate that the registry contains DNA for approximately 27% of IRD-affected Australians (3429/12500). Genetic analysis of this cohort is establishing a published representation of the genetic spectrum of IRD in Australia. This research, which has identified many novel pathogenic variants, facilitates a greater understanding of the genetic aetiology of IRD in Australia, thereby directing research into areas likely to have the greatest impact. Since 2009, we have carried out more than 5600 genetic analyses on more than 3800 DNA samples in our care. To date, over 3700 different IRD-associated variants have been identified across 400 retinal dystrophy genes. Details are available in our peer-reviewed publications (see publications section for examples).

2. *Provision of research diagnostic genetic reports:* In the past 12 months, 324 research diagnostic genetic reports were provided to participants' nominated ophthalmologists or genetic counsellors free of charge, totalling 1677 reports to date. Of these 1677 reports, 1133 (67%) reports were provided for affected participants, 890 (78%) of which indicated the likely causative variant(s) in the affected participants' IRD.

   Reports were also provided to 383 carrier participants, 32 participants who were classified as non-penetrant, and 129 other family members, some of whom may have previously been suspected of being a carrier or pre-symptomatic. Reports were provided to 103 different ophthalmologists or genetics counsellors, for interpretation in the clinical context. The receiving ophthalmologists and genetics counsellors were advised to confirm our research findings in a NATA accredited laboratory.

   The 1752 participants for whom we have DNA but remain unreported either have not had genetic analysis performed, have had some form of genetic analysis performed that was not instructive, or are awaiting pathogenicity assessment or report creation. The intention is to establish the causative gene for all affected participants and to report that research finding to participants' nominated ophthalmologist or clinical genetics service. This is currently the case for 48% of affected participants who have provided DNA.

   These reports significantly improved patient management for many participants. Genetic counselling was provided for family-planning purposes, in some cases facilitating preimplantation genetic diagnosis. AIRDR genetic findings have also alerted clinicians to more sinister syndromic disease that required further clinical evaluation.

Informed patient management enabled more reliable prognoses and unravelled competing differential diagnoses, thereby saving expense, inconvenience, time and possible inappropriate treatment of patients. Many reports were issued that revealed mutations in genes that were relevant to current clinical trials, alerting participants via their ophthalmologists to the need for routine clinical monitoring of the natural history of disease. This enhanced participants' opportunities to participate in emerging gene-based clinical trials or to benefit from outcomes of these trials.

3. *Identification of potential candidates for gene-specific and other clinical trials*. We have identified mutations in many genes that are currently the target of international trials or treatments, including those for the genes *RPGR* (X-linked retinitis pigmentosa), *CHM* (choroideremia), *RS1* (retinoschisis), *PRPF31* (dominant retinitis pigmentosa), *CNGB3* and *CNGA3* (achromatopsia) and *USH2A* (Usher syndrome). Participants with pathogenic variants in these genes are alerted to have the progress of their disease monitored annually by a retinal specialist to enhance their prospects of inclusion in a future trial as a result of having a genetic diagnosis and a documented disease history.

4. *Development of personalised therapies*: Appropriate participants in whom we established the genetic cause of disease were referred to the Ocular Tissue Engineering Laboratory at the Lions Eye Institute. Here, fibroblasts were reprogrammed into pluripotent stem cells and subsequently differentiated into retinal tissues carrying the same mutations that exist in the participant. Experiments were then carried out to assess or correct the mutation *in vitro*, with subsequent analysis confirming that the established mutation was disease-causing, enabling investigation into correcting the mutation *in vitro* as the basis for future retinal therapies. Pluripotent stem cell lines have been established by the Lions Eye Institute for AIRDR participants associated with the genes *RP1, USH2A, PRPF31, ABCA4, CRB1, RCBTB, SNRNP200, RP1 and CLN3*, leading to the publication of 16 papers in the past three years. These patient-derived stem cell lines are currently being used in projects aimed at validating variant pathogenicity, elucidating molecular pathogenesis and screening potential treatments, such as gene-replacement therapies and splice-modifying antisense oligonucleotides.

5. *Recruitment of participants and provision of genetic and clinical information for external research projects.* During the past 12 months we have contacted more than 1200 of our participants, inviting them to participate in the research of external research groups, including the Centre for Eye Research Australia, the University of Melbourne, Queensland Eye Institute, a survey headed by Heather Mack and Australian and American therapeutics companies. Genes being researched by these groups include *USH1C, CDHR1, CEP290, CNGA3, CNGB3, GUCY2D, PITPNM3, RP2, RPGR, CHM, USH2A, MYO7A, PRPF31* and *PCDH15*. Diseases involved include Usher syndrome, retinitis pigmentosa, Leber congenital amaurosis, achromatopsia and choroideremia. We provide genetic and other information to the Victorian Natural History Study of Inherited Retinal Diseases and the Bionic Eye Project.

6. *Establishment of specific cohorts for therapy development:* In addition to identifying potential trial candidates through provision of genetic research reports, we also actively engaged with companies researching topically relevant therapies. Collaborations with gene biotechnology companies were formed to establish cohorts for *RPE65* gene therapy, novel drug delivery systems and antioxidant therapies.

7. *Elucidation of the genetic cause of disease compared with clinical presentation in complex or unusual cases*, particularly syndromes that ultimately affect multiple systems in the body, but for which retinal symptoms are the first identified, alerting clinicians to the potential for systemic disease.

8. *Collaboration with Radboud University Medical Centre, The Netherlands:* Approaching 1000 DNA samples from participants affected with Stargardt disease, autosomal recessive RP and autosomal dominant RP have been sent to Frans Cremers' laboratory in Radboud University Medical Centre in The Netherlands for advanced genetic analysis.

   This collaboration has so far resulted in genetically solving previously unsolved AIRDR cases with Stargardt disease and allied maculopathies using single molecule Molecular Inversion Probe (smMIP) technology, culminating in 2020 in the '*ABCA4*-Stargardt disease' genomic and transcriptomic landscape paper in Genetics in Medicine.

   The collaboration is currently genetically analysing 600 to 700 DNA samples from AIRDR probands affected with autosomal recessive retinitis pigmentosa using advanced analysis methods, seeking to establish the genetic cause of disease in these participants. Principally, disease-causing *RPE65* variants are being sought to identify potential candidates for Luxturna gene-replacement therapy targeting *RPE65*-mediated disease.

   This collaboration is also analysing 200 AIRDR DNA samples from probands affected with autosomal dominant retinitis pigmentosa, seeking to establish the genetic cause of disease in these participants and to perform genetic characterisation of RP17-associated variants.

9. *Reporting of novel pathogenic variants* established by us to public scientific databases.

10. *Development of genetic analysis tools and methods:* The AIRDR has developed or has assisted in the validation of various genetic analysis tools and methods. These include the first clinically validated, high-throughput clinical testing method for X-linked RP for the difficult-to-sequence ORF15 region of the *RPGR* gene, in collaboration with Dr John Chiang (Molecular Vision Laboratory, Oregon, USA) and Dr Jon Ruddle (Royal Victorian Eye and Ear Hospital/Clinical Genetics Unit, University of Melbourne). Through validation against a cohort of previously Sanger-sequenced samples, we have created the first clinically validated NGS-based method for ORF15 screening. This high-throughput diagnostic method has since been used in commercial diagnostic screening for >13000 individuals worldwide.

The AIRDR has also been instrumental in other new developments, such as smMIP analysis in patients with Stargardt disease in whom only one *ABCA4* mutation is known, a suite of programs to semi-automate pathogenicity assessment and patient reporting, and a custom SNP genotyping panel for genetic analysis of autosomal recessive RP cases.

11. *An information resource:* We provided an information resource to many people throughout Australia affected with an IRD and their family members. Some hours each week were spent providing information to participants who were otherwise unable to obtain that information.

Publications co-authored by AIRDR researchers

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