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 2021

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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 2020 to June 2021.

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 (in the future) 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 detailed results of electrophysiology tests, psychophysical measurements and ophthalmic examinations, demographic information, family and clinical data, and details of genetic analyses undertaken and genetic information gathered, 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 since July 20209 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 (Research Assistant).

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 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 2021.

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.

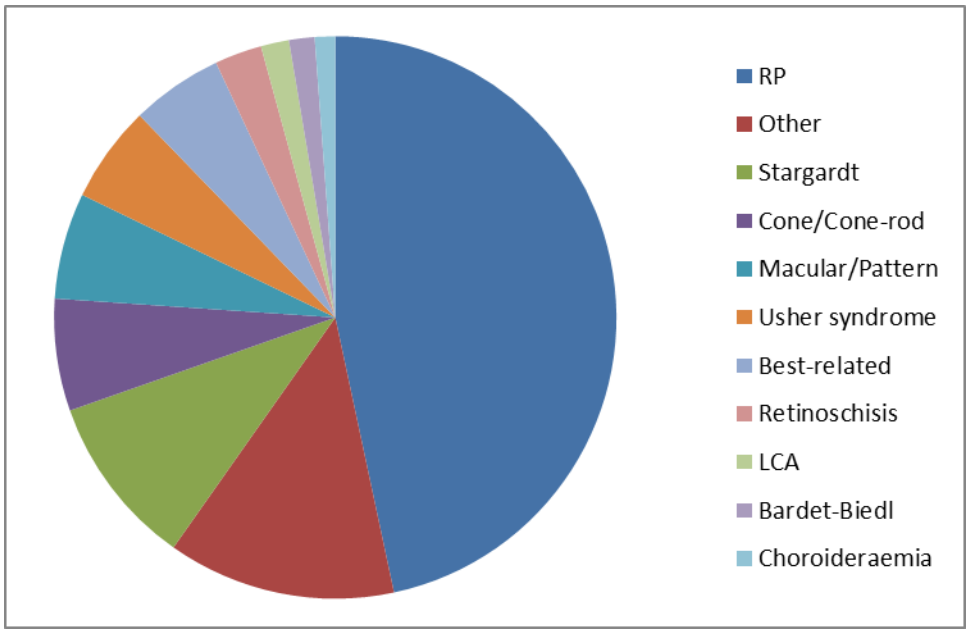
DNA Collection

Demographic details of 9650 participants are recorded in the registry, 4219 (44%) of whom are classified as affected and 1590 (16%) as carriers.

DNA has been obtained from 7566 (78%) participants, 3206 (42%) of whom are classified as affected and 1433 (19%) as carriers.

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

Figure 1 DNA samples collected from 3206 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 1015 affected participants from 669 families (Table 1).

Each of these cases represents a family affected with Mendelian or mitochondrial disease. 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	269	203	EFEMP1	3	3	PDE6B	9	6
ABCC6	2	2	EYS	9	8	PDE6C	1	1
ADGRV1	2	1	GPR98	1	1	PEX1	1	1
AHI1	3	2	GUCA1A	2	1	PITPNM3	1	1
AIPL1	4	2	GUCY2D	17	10	PROM1	4	4
AP5Z1	1	1	GUCY2D; RP1	4	1	PRPF3	7	2
ARHGEF18	1	1	HGSNAT	4	3	PRPF31	34	14
ARL13B	1	1	HK1	2	1	PRPF6	1	1
BBS1	6	5	IFT140	2	2	PRPF8	1	1
BBS2	2	2	IMPDH1	7	3	PRPH2	37	20
BEST1	22	12	IMPG1	1	1	RCBTB1	2	1
C1QTNF5	1	1	IMPG2	2	2	RDH12	3	2
C21ORF2	1	1	INPP5E	1	1	RGS9	1	1
CABP4	1	1	IQCB1	1	1	RHO	35	17
CACNA1F	3	2	LCA5	2	1	RP1	35	14
CDH23	3	2	MERTK	1	1	RP1L1	3	3
CDHR1	1	1	MT-ND1	2	1	RP2	31	11
CEP290	9	7	MT-ND4	1	1	RP9	4	1
CEP78	1	1	MT-TL1	1	1	RPE65	4	4
CERKL	2	2	MYO7A	5	5	RPE65; BEST1	3	1
CHM	38	26	MYO7A; RP1	1	1	RPGR	20	12
CLN1	1	1	NMNAT1	6	6	RPGR_ORF15	76	36
CLN3	7	6	NPHP1	1	1	RPGRIP1	5	3
CNGA3	9	7	NR2E3	3	3	RS1	38	21
CNGA3; CNGB3	2	1	NYX	1	1	SAG	3	1
CNGB1	1	1	OPA1	4	4	SNRNP200	3	2
CNGB3	27	21	OPA3	1	1	SPATA7	2	1
COL2A1	3	1	OPN1LW	2	1	TIMP3	2	1
CRB1	23	15	OPN1LW/MW	5	4	TRPM1	1	1
CRX	8	3	OPN1MW	1	1	TULP1	3	2
CRX; PITPNM3	1	1	OTX2	1	1	USH2A	91	73
CYP4V2	1	1	PCDH15	4	4	**TOTAL**	**1015**	**669**

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. This was achieved as a result of:

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.

Provision of research diagnostic genetic reports: In the past 12 months, 331 research diagnostic genetic reports were provided to participants' nominated ophthalmologists or genetic counsellors, totalling 1415 reports to date. Of these 1415 reports, 946 (67%) reports were provided for affected participants, 715 (76%) of which indicated the likely causative variant(s) in the affected participants' IRD.

Reports were also provided to 321 carrier participants, 26 participants who were classified as non-penetrant, and 122 other family members, some of whom may have previously been suspected of being a carrier or pre-symptomatic.

Reports were provided to 87 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 2260 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 30% of affected participants who have provided DNA.

Table 2 shows the number of reports issued to participants, indicating the causative gene where known, by participant status.

Table 2 Number of reports provided for all participants, stratified by causative gene and clinical status

Causative gene	All	Affected	Carrier	Non penetrant	Other	Causative gene	All	Affected	Carrier	Non penetrant	Other
Not established	**304**	231	27	1	45	MYO7A;RP1	**1**	1			0
ABCA4	**383**	214	145	12	12	NMNAT1	**6**	4	2		0
ABCC6	**2**	2			0	NPHP1	**2**	2			0
AHI1	**6**	4	2		0	NR2E3	**2**	1	1		0
AIPL1	**3**	2	1		0	OPA1	**2**	2			0
ARHGEF18	**4**	2	1		1	OPN1LW/MW	**7**	5	2		0
ARL13B	**1**	1			0	OPN1MW	**1**	1			0
BBS1	**7**	4	3		0	OTX2	**6**	1			5
BBS2	**1**	1			0	PCDH15	**4**	2	2		0
BEST1	**29**	21	4	1	3	PDE6B	**7**	6	1		0
C1QTNF5	**1**	1			0	PITPNM3	**1**	1			0
CABP4	**2**	2			0	PRPF3	**1**	1			0
CDH23	**6**	4	2		0	PRPF31	**58**	37		5	16
CEP290	**13**	7	6		0	PRPF6	**1**	1			0
CEP78	**4**	3	1		0	RCBTB1	**2**	2			0
CHM	**54**	31	18		5	RDH12	**5**	2	3		0
CLN3	**6**	3	3		0	RDS/PRPH2	**45**	32	2	2	9
CNGA3	**9**	6	2		1	RGS9	**4**	2	2		0
CNGA3+CNGB3	**1**	1			0	RHO	**25**	20		1	4
CNGB3	**20**	15	5		0	RP1	**17**	14			3
COL2A1	**4**	3			1	RP1L1	**3**	3			0
CRB1	**40**	24	15		1	RP2	**15**	12	3		0
CRX	**1**	1			0	RP9	**9**	5		1	3
CYP4V2	**3**	1	2		0	RPE65	**5**	4	1		0
EFEMP1	**4**	4			0	RPE65; BEST1	**5**	4		1	0
EYS	**18**	10	7		1	RPGR	**4**	4			0
GPR98	**1**	1			0	RPGR_ORF15	**54**	42	11		1
GUCA1A	**4**	3			1	RPGRIP1	**10**	8	2		0
GUCY2D	**15**	12	3		0	RS1	**18**	14	1		3
GUCY2D; RP1	**4**	4			0	SAG	**5**	3		1	1
HGSNAT	**6**	6			0	SLC24A1	**2**		2		0
HK1	**4**	3			1	SNRNP200	**2**	1			1
IFT140	**4**	4			0	SPATA7	**1**	1			0
IMPDH1	**5**	5			0	TIMP3	**2**	1			1
IMPG2	**3**	2	1		0	TULP1	**11**	7	3		1
INPP5E	**1**	1			0	USH2A	**94**	58	33	1	2
IQCB1	**1**	1			0						
MT-ND4	**1**	1			0						
MYO7A	**3**	1	2		0	**TOTAL**	**1415**	**946**	**321**	**26**	**122**

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.

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 anti-oxidant therapies.

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 26% of IRD-affected Australians (3206/12500). 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.

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, single molecule Molecular Inversion Probe (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.

Collaboration with Radboud University Medical Centre, The Netherlands: Approaching 1000 DNA samples from participants affected with Stargardt disease, autosomal recessive RP, autosomal dominant RP and macular dystrophies have been or are being 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 cases with Stargardt disease and allied maculopathies using smMIPs technology, culminating in 2020 in the '*ABCA4*-Stargardt disease' genomic and transcriptomic 'landscape' paper in Genetics in Medicine.

Identification of cohorts not related to genetic findings: The AIRDR also contacted appropriate participants required by other researchers for non-genetic research related to visual impairment, including studies regarding lifestyle, attitudes or knowledge of support services for visually compromised people, and also for a survey on patients' knowledge and expectations regarding future gene therapy trials for inherited retinal dystrophy.

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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Acknowledgments

The project investigators wish to sincerely thank the following for their invaluable contributions towards this project:

All AIRDR participants
Retina Australia and its state branches
Our private donors

Drs Steve Colley and Jane Khan
Staff of the Department of Medical Technology & Physics, SCGH
Dr Fred Chen and Professor David Mackey (Lions Eye Institute)
The Lions Eye Institute DNA Bank
Other staff of the Lions Eye Institute
Genetics Services of Western Australia
Too many other Australian ophthalmologists and clinical genetics services to note separately (but thank you)