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 2019

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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 2018 to June 2019.

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. Other funding sources include Telethon – Perth Children's Hospital, the Macular Disease Foundation of Australia and private donations.

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, especially Retina Australia, and directly involved with the IRD registry and DNA bank since July 2018 on a day to day basis are Dr Tina Lamey (Senior Research Scientist), Dr Jennifer Thompson (Graduate Research Scientist), and Ling Hoffmann (Research Assistant).

Early this year, Retina Australia (WA) awarded Tina the *Joy and Murray Witham Inherited Retinal Disease Fellowship,* in recognition of her outstanding contribution to our understanding of the genetics of inherited retinal disease in Australia. This award recognises the expertise and passion with which Tina has conducted this research for the past 18 years. Congratulations and well done Tina.

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

Significant and valued assistance is provided by the department's 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 30 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).

This project is carried out according to international standards with regard to its quality measures (ISO9001:2015). All relevant procedures, work instructions, records and standard forms and letters are kept in accordance with the ISO9001:2015 accredited quality documentation system. 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

Table 1 shows (a) the number of participants with information recorded in the registry, and (b) the number of participants with information recorded in the registry *and* with DNA stored in the DNA bank, from 2014 until now.

Table 1 Numbers of participants in the registry.

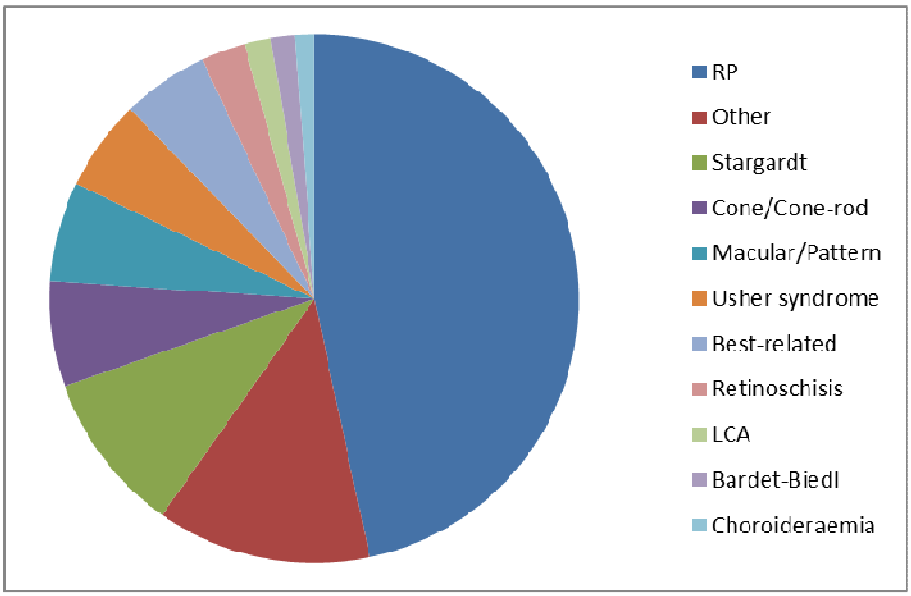
	Aug 2014	**Aug 2015**	**Aug 2016**	**Aug 2017**	**Jun 2018**	**Jun 2019**
Participants in registry	6152	6708	7376	7913	8414	8946
Participants with DNA stored	4658	5084	5543	6040	6454	6936

Table 1 shows that for the period June 2018 to June 2019 the number of subjects for whom information has been recorded in the registry has increased from 8414 to 8946, an increase of 532 subjects. The number of DNA samples stored has risen from 6454 to 6936, an increase of 482 samples. The rate of recruitment and DNA collection remains steady.

Of the 6936 DNA samples stored in the DNA bank, 2980 are sourced from affected participants, while the remainder are from unaffected family members or carriers. Assuming a prevalence of 1/2000 for IRD in Australia, we now have DNA stored for approximately 25% of all Australians affected with an IRD.

Figure 1 gives a breakdown of stored DNA by clinical diagnosis, for affected participants only.

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



Support of IRD-affected participants

We continue to provide an informed information resource to the many people affected with an inherited retinal disease and their family members. Some hours each week are spent in providing information to participants who are unable to obtain that information in other ways.

To date we have assigned a genetic diagnosis, based on genetic analysis of DNA followed by pathogenicity assessment, for more than 670 affected participants. Assessment of variant pathogenicity is interpreted in accordance with the joint guidelines of the American College of Medical Genetics & Genomics and the Association for Molecular Pathology.

Table 2 summarises family genetic diagnoses we have established for 673 AIRDR participants, as a result of genetic analysis followed by meticulous variant pathogenicity assessment.

These family genetic diagnoses represent families affected with autosomal dominant, autosomal recessive and x-linked disease. The variants involved are not shown. Many other potentially pathogenic variants have been found in the DNA of many other participants (see Table 3 further down), but these variants await formal pathogenicity assessment.

Table 2 Affected participants with a genetic diagnosis established, by gene.

Genetic Diagnosis	No.	Genetic Diagnosis	No.	Genetic Diagnosis	No.
ABCA4	191	*EYS*	5	*PRPF8*	1
ABCC6	2	*GPR98*	1	*RCBTB1*	2
AHI1	3	*GUCY2D*	14	*RDH12*	3
AIPL1	4	*GUCY2D; RP1*	4	*RDS/PRPH2*	19
BBS1	1	*IFT140*	1	*RHO*	15
BBS2	2	*IMPDH1*	4	*RP1*	27
BEST1	14	*IMPG2*	2	*RP1L1*	2
C21ORF2	1	*LCA5*	2	*RP2*	31
CACNA1F	3	*MT-ND1*	2	*RP9*	4
CDH23	3	*MT-ND4*	1	*RPE65*	2
CDHR1	1	*MT-TL1*	1	*RPGR*	18
CEP290	8	*MYO7A*	2	*RPGR_ORF15*	65
CEP78	1	*NMNAT1*	5	*RPGR_ORF15 + PRPF31*	2
CERKL	1	*NPHP1*	1	*RPGRIP1*	4
CHM	35	*NR2E3*	3	*RS1*	34
CLN3	4	*OPA1*	2	*SAG*	2
CNGA3	3	*OPA3*	1	*SNRNP200*	1
CNGB1	1	*OPN1LW*	2	*SPATA7*	2
CNGB3	1	*OTX2*	1	*TIMP3*	2
COL2A1	3	*PCDH15*	2	*TRPM1*	1
CRB1	19	*PDE6B*	1	*TULP1*	3
CRX	8	*PEX1*	1	*USH2A*	26
CRX; PITPNM3	1	*PROM1*	4		
CYP4V2	1	*PRPF3*	7		
EFEMP1	3	*PRPF31*	24	*TOTAL*	673

Since the last annual report (June 2018) we have provided 215 detailed research genetic analysis reports to participants' nominated genetic counselling services or ophthalmologists (with the participants' written consent). Not all of these reports provide a conclusive genetic diagnosis. This brings the total number of genetic research reports provided by this resource to 848.

This activity has proven to be extremely useful in informing patient management, especially in cases where we have identified syndromic disease, in preparation of patients for possible inclusion in gene-specific clinical trials or treatments, for informed genetic counselling and for the development of personalised therapies for some participants.

In the case of personalised therapy, stem cell lines have been established by Fred Chen's group at Lion's Eye Institute for AIRDR participants in whom we have established genetic diagnoses associated with the genes *RP1, USH2A, PRPF31, ABCA4, CRB1 and CLN3*.

Current research directions

Overview

The AIRDR has been collecting DNA from participants affected with an IRD and their family members Australia–wide since 2009. DNA has been collected in parallel from participants with the clinical diagnoses shown in Figure 1.

Since 2009, we have carried out more than 3800 genetic analyses of some form on the DNA of more than 2500 DNA samples in our care. These genetic analyses include next-generation sequencing (NGS) retinal dystrophy multi-gene panel analyses, whole-exome sequencing (WES), array CGH, qPCR, Asper micro-array analyses, bi-directional Sanger sequencing of specific genes, and targeted variant Sanger sequencing of family members where the familial mutation has been established.

One outcome of the above genetic analysis program is the establishment of many novel pathogenic variants in known genes. These novel variants are uploaded to the appropriate public scientific such as LOVD or ClinVar, as appropriate, for use by other researchers and clinicians.

Here we present a summary of the current state of analysis of some of the more advanced diagnostic cohorts.

Leber congenital amaurosis (LCA)

A study of this cohort is complete, resulting in two peer-reviewed publications.

An outcome of this study was the identification of a number of families that were suspected of having syndromic disease. These families are currently under further genetic and clinical investigation.

Choroideremia

We have published one peer-reviewed paper which described the genetic cause of choroideremia in 11 families. A further 14 choroideremia families have now had genetic confirmation of the disease, resulting in the identification of a cohort of 25 genetically confirmed families.

Retinoschisis

Participants of the AIRDR have been the subject of three peer-reviewed papers in the past. These papers have established the genetic cause of retinoschisis in 23 families. Since then, a further 17 families have been recruited to the AIRDR having a clinical diagnosis of retinoschisis. All genetic analysis and pathogenicity assessments have been completed for these families, resulting in the identification of a cohort of 40 genetically confirmed families.

X-linked retinitis pigmentosa (xlRP)

DNA from participants sourced from approximately 100 families affected with xlRP has been analysed, with the results forming the basis of several related projects.

In collaboration with Jon Ruddle and Dr Thomas Edwards (Royal Victorian Eye and Ear Hospital) genetic and phenotypic data are being collated for a large cohort of Australians affected with xlRP, in order to attract a gene-specific clinical trial to Australia.

Stargardt disease

A total of 540 participants diagnosed with Stargardt disease and their family members, sourced from 210 families, have had their DNA genetically analysed, in collaboration with John Chiang (Molecular Vision Laboratory, Oregon, USA). These genetic analysis results form the basis of several related projects, with Dr Fred Chen (Lions Eye Institute) being the principal clinician involved, as detailed in last year's report.

Isolates

A cohort of 84 families, for which there is one affected participant only (an isolate) and for which we have DNA from the affected person and both parents, is being genetically characterised via a collaboration with Professor Zi-Bing Jin (Professor of Ophthalmology, the Eye Hospital of Wenzhou Medical University, China) and John Chiang (Molecular Vision Laboratory, Oregon, USA).

We are continuing to collect phenotype information for the affected participants.

Usher syndrome

Genetic analysis has been performed on 218 affected, unaffected and carrier participants from 90 Usher-affected families. We aim to complete genetic analysis and pathogenicity assessment for all of our 160 Usher-affected families by late 2020.

Generation of induced pluripotent stem cells

A number of projects are underway involving the generation of pluripotent stem cells for participants harbouring inherited retinal disease caused by specific mutations we have established in specific genes. So far, this work has involved mutations in the genes *RP1, USH2A, PRPF31, ABCA4, CRB1 and CLN3*, as a first step in developing personalised therapies for the affected individuals. This work is a collaboration between ourselves, the Lions Eye Institute, the University of Western Australia and Royal Perth Hospital.

Recruitment of participants for research studies by other groups

We continue to aid in the recruitment of participants for research by other research groups and pharmaceutical companies. Under no circumstances do we release participant identification information to any of these groups or companies.

Clinical cases

A number of intractable clinical cases are currently the subject of extended studies with collaborating ophthalmologists and clinical geneticists. These studies are usually long-term studies involving serial clinical studies and extensive genetic analysis.

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Summary

Table 3 indicates the numbers of unique likely or confirmed pathogenic variants identified in our participants as a result of the above and other projects, as well as the spectrum of retinal dystrophy genes in which these variants have been found. We have established 1050 different confirmed or likely disease-causing variants in our participants. These variants are distributed across 209 different retinal dystrophy genes. (Table 3).

It is important to note that a number of these variants may be detected within a single individual. One or more of these will not necessarily be the primary cause for that individual's disease, but may affect the manifestation and progression of disease symptoms. The information in Table 3 represents a summary of the spectrum of IRD-associated genes in the Australian IRD population established by us to date.

Table 3 Confirmed or likely disease-causing variants across different retinal dystrophy genes in the AIRDR.

Gene	Different Mutations	Gene	Different Mutations	Gene	Different Mutations
ABCA4	156	*GNAT2*	2	*PROM1*	6
ABCC6	4	*GPR125*	4	*PRPF3*	2
ABCD1	1	*GPR179*	5	*PRPF31*	8
ABHD12	4	*GRK1*	2	*PRPF4*	2
ADGR1	1	*GRM6*	4	*PRPF6*	1
ADGRV1	19	*GRN*	3	*PRPF8*	1
AFT6	1	*GUCA1A*	2	*PRPH2*	17
AGK	1	*GUCY2D*	16	*PRPS1*	1
AHI1	2	*HGSNAT*	1	*RAX2*	1
AIPL1	6	*HK1*	2	*RBP3*	2
ALMS1	8	*HMCN1*	6	*RCBTB1*	2
AP5Z1	1	*IDH3B*	1	*RD3*	2
ARL13B	1	*IDUA*	1	*RDH12*	4
ARL6	1	*IFT140*	8	*RDH5*	1
B9D2	1	*IFT172*	5	*RGS9*	3
BBS1	2	*IMPDH1*	1	*RHO*	13
BBS10	3	*IMPG1*	4	*RIMS1*	1
BBS12	1	*IMPG2*	5	*RLBP1*	1
BBS2	5	*INPP5E*	1	*ROM1*	2
BBS5	1	*INVS*	1	*RP1*	13
BBS7	3	*IQCB1*	3	*RP1L1*	12
BEST1	19	*KCNV2*	3	*RP2*	11
C12orf65	1	*KIAA1549*	1	*RP9*	2
C1QTNF5	2	*KIF7*	2	*RPE65*	2
C21orf2	1	*LAMA1*	2	*RPGR*	34
CA4	1	*LCA5*	7	*RPGRIP1*	6
CABP4	3	*LRIT3*	1	*RPGRIP1L*	2
CACNA1F	6	*LRP5*	6	*RS1*	16
CACNA2D4	5	*MAK*	1	*SAG*	1
CC2D2A	2	*MERTK*	4	*SALL2*	1
CDH23	18	*MFRP*	1	*SAMD11*	1
CDH3	4	*MFSD8*	2	*SDCCAG8*	4
CDHR1	3	*MKKS*	1	*SEMA4A*	1
CEP164	2	*MKS1*	1	*SLC24A1*	3
CEP290	19	*MMACHC*	2	*SLC38A8*	1
CEP78	1	*MT-ND1*	2	*SLC4A7*	1

CERKL	3	*MT-ND4*	1	*SLC7A*	1
CFH	1	*MT-TL*	1	*SLC7A14*	9
CHM	25	*MYO7A*	20	*SNRNP200*	1
CKAP4	1	*NEK2*	1	*SPATA7*	4
CLN3	4	*NMNAT1*	4	*SPP2*	1
CLN5	3	*NPHP1*	4	*TCTN2*	1
CLN6	1	*NPHP4*	5	*TIMP3*	1
CLN8	1	*NR2E3*	7	*TMEM126A*	1
CLRN1	2	*NRL*	1	*TMEM185A*	1
CNGA3	13	*NYX*	1	*TMEM216*	1
CNGB1	7	*OCA2*	2	*TMEM231*	2
CNGB3	8	*OPA1*	6	*TOPORS*	2
CNNM4	1	*OPA3*	2	*TPP1*	1
COL2A1	1	*OPN1LW*	3	*TRIM32*	1
CPLANE1	2	*OR2W3*	1	*TRNT1*	2
CRB1	17	*OTX2*	2	*TRPM1*	8
CRX	4	*PCARE*	8	*TTC21B*	4
CSPP1	1	*PCDH15*	11	*TTC8*	1
CTSD	1	*PDE6A*	8	*TTLL5*	2
CTSF	1	*PDE6B*	16	*TUB*	2
CYP4V2	8	*PDE6C*	3	*TUBGCP6*	2
DFNB31	1	*PDZD7*	3	*TULP1*	5
DHCR7	1	*PEX1*	1	*TYR*	1
DHX38	4	*PEX12*	2	*USH1C*	4
DNAJC5	1	*PEX13*	1	*USH1G*	1
EFEMP1	1	*PEX2*	1	*USH2A*	89
EMC1	1	*PEX26*	1	*VCAN*	1
EYS	21	*PEX6*	1	*VPS13B*	10
FAM161A	3	*PEX7*	1	*WDPCP*	1
FSCN2	1	*PHYH*	4	*WDR19*	2
FZD4	1	*PITPNM3*	1	*WFS1*	6
GDF6	1	*PKM*	1	*ZNF423*	4
GJB2	5	*PNPLA6*	2		
GJB6	2	*PPT1*	1	**TOTAL**	**1050**

Recent publications co-authored by AIRDR researchers

- Zhang X, Moon S, Zhang D, Chen S, Lamey T, Thompson J, McLaren T, De Roach J, McLenachan S, Chen F. Generation of an induced pluripotent stem cell line from a patient with retinitis pigmentosa caused by *RP1* mutation. *Stem Cell Research* 37 (2019) 101452.
- McLenachan S, Wong E, Zhang X, Leith F, Moon S, Zhang D, Chen S, Thompson J, McLaren T, Lamey T, De Roach J, Atlas M, Dilley R, Chen F. Generation of two induced pluripotent stem cell lines from a patient with compound heterozygous mutations in the *USH2A* gene. *Stem Cell Research* 36 (2019) 101420.
- McLenachan S, Zhang D, Zhang X, Chen S, Lamey T, Thompson J, McLaren T, De Roach J, Fletcher S, Chen F. Generation of two induced pluripotent stem cell lines from a patient with dominant *PRPF31* mutation and a related non-penetrant carrier. *Stem Cell Research* https://doi.org/10.1016/j.scr.2018.11.018.
- Claassen J, Zhang D, Chen S, Moon S, Lamey T, Thompson J, McLaren T, De Roach J, McLenachan S, Chen F. Generation of the induced pluripotent stem cell line from a patient with autosomal recessive *ABCA4*-mediated Stargardt Macular Dystrophy. *Stem Cell Research* (in press).
- Chen F, Zhang X, Eintracht J, Zhang D, Arunachalam S, Thompson J, Chelva, E, Mallon D, Chen S, McLaren T, Lamey T, De Roach J, McLenachan S. Clinical and molecular characterisation of non-syndromic retinal dystrophy due to c.175G>A mutation in ceroid lipofuscinosis neuronal 3 (*CLN3*). *Documenta Ophthalmologica* 2019;138(1):55–70.
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Recent presentations co-authored by AIRDR researchers

- Moon S, Zhang X, Zhang D, Chen S, Mellough C, Thompson J, McLaren T, Lamey T, De Roach J, Chen F, McLenachan S. Modelling Of Retinitis Pigmentosa Caused By A Nonsense Mutation In The *RP1* Gene Using Induced Pluripotent Stem Cells. *ISSCR/KSSCR International Symposium 2019* Seoul, Korea.
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- Zhang X, Zhang D, Thompson J, McLaren T, Lamey T, De Roach J, Chen F, McLenachan S. Lysosomal accumulation in non-syndromic CLN3 retinal dystrophy using patient-derived induced pluripotent stem cell and retinal organoid models. *Science on the Swan 2019* Perth Australia.
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- Roshandel D, Charng J, Thompson J, McLenachan S, Zhang D, Lamey T, McLaren T, De Roach J, K Chen F (2019) Natural History of Autosomal Dominant Retinitis Pigmentosa Caused by a Novel Mutation in pre-mRNA Splicing Factor-31 (*PRPF31*) Gene in an Indigenous Australian Family. *Science on the Swan 2019* Perth Australia.
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- Zhang X, McLenachan S, Chen S, Zhang D, Arunachalam S, Thompson J, McLaren T, Lamey T, De Roach J, Chen F. Delayed retinal maturation and developmental gene expression profile in *CRB1* patient-derived retinal organoid. *Association for Research in Vision and Ophthalmology annual congress 2019* Vancouver, Canada.
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