DEPARTMENT OF MEDICAL TECHNOLOGY & PHYSICS
Sir Charles Gairdner Hospital

INTERNAL REPORT

The Australian Inherited Retinal Disease Register and DNA Bank

Status Report

as at August 2016

Report prepared by

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Introduction

This is a status report for the resource *The Australian Inherited Retinal Disease (IRD) Register and DNA Bank* as at August 2016.

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 register of consenting Australians affected with an IRD and their family members, and (2) a DNA bank containing DNA from consenting individuals.

Information within the register 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 Retina Australia and directly involved with the IRD register and DNA bank since August 2015 on a day to day basis are Dr Tina Lamey (Senior Research Scientist), Ling Hoffmann (Research Assistant), Hannah Montgomery (Graduate Research Scientist), Caitlyn Kap (Research Assistant) and Dr Jennifer Thompson (Graduate Research Scientist).

Tina Lamey was awarded a Doctor of Philosophy in genetics in November 2015. Congratulations, Tina.

Hannah Montgomery is currently undertaking an (unpaid) 18 month research project on the genetic causes of Usher syndrome in Australia, as part of her medical degree at the University of Western Australia.

Caitlyn Kap resigned as a Research Assistant in November 2015. Caitlyn made very significant contributions to this project over a period of 5 years, and she will be greatly missed.

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

Other departmental staff noted as co-investigators on the project's SCGH Human Research Ethics Committee application are Enid Chelva (Clinical Physicist Manager), Sarina Laurin (Senior Medical Scientist) and Monika Dolliver (Senior Medical Scientist).

Professor David Mackey, Dr Alex Hewitt, Professor Ian Constable and A/Professor Piroska Rakoczy of the Lion's Eye Institute also have involvement with this project, and are noted as co-investigators, as is Professor Roger Price, Head of the Department of Medical Technology and Physics, Sir Charles Gairdner Hospital.

A/Professor Robyn Jamieson (Children's Hospital at Westmead and the Children's Medical Research Institute, NSW) and A/Professor John Grigg (Sydney Eye Hospital and the Save Sight Institute, NSW) are also co-investigators for this project.

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

Ethics and Quality Assurance

Approval for this project was granted by the SCGH Human Research Ethics Committee on 25th May 2001.

This project is carried out according to international standards with regard to its quality measures (ISO9001:2008). All relevant procedures, work instructions, records and standard forms and letters are kept in accordance with the ISO9001:2008 accredited quality documentation system. All associated processes are subject to both internal and external audit every 12 months.

Websites

The website:

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

invites interested scientists and clinicians to apply to make use of this resource. This website includes a link to a document which lists all genes in which we have established pathogenic variants in our population. No subject identification information is available on this website.

A more user-friendly, but less detailed, website is also available, for use by ophthalmologists, researchers, participants and interested persons. This website may be found at http://www.IRDregister.org.au

DNA Collection

Table 1 shows (a) the number of participants with information recorded in the register, and (b) the number of participants with information recorded in the register *and* with DNA stored in the DNA bank, from 2011 until now.

Table 1 Statistics relating to the numbers of individuals currently held in the database.

	Aug 2011	**Aug 2012**	**Aug 2013**	**Aug 2014**	**Aug 2015**	**Aug 2016**
Participants in register	3671	5129	5611	6152	6708	7376
Participants with DNA stored	2461	3754	4210	4658	5084	5543

Table 1 shows that for the one year period August 2015 to August 2016 the number of subjects for whom information has been recorded in the register has increased from 6708 to 7376, an increase of 668 subjects. The number of DNA samples stored has risen from 5084 to 5543, an increase of 459 samples. The rate of recruitment and DNA collection remains steady.

Included in the figures in Table 1 are DNA samples stored for 95 non-related individuals with no known family history of retinal disease, and deemed normal following ophthalmic and electrophysiology testing. This DNA is used as control DNA.

Table 2 shows the distribution of DNA collection by place of origin. The 'Unassigned Mackey' DNA originates mainly from Tasmania and Victoria, but the details are yet to be documented.

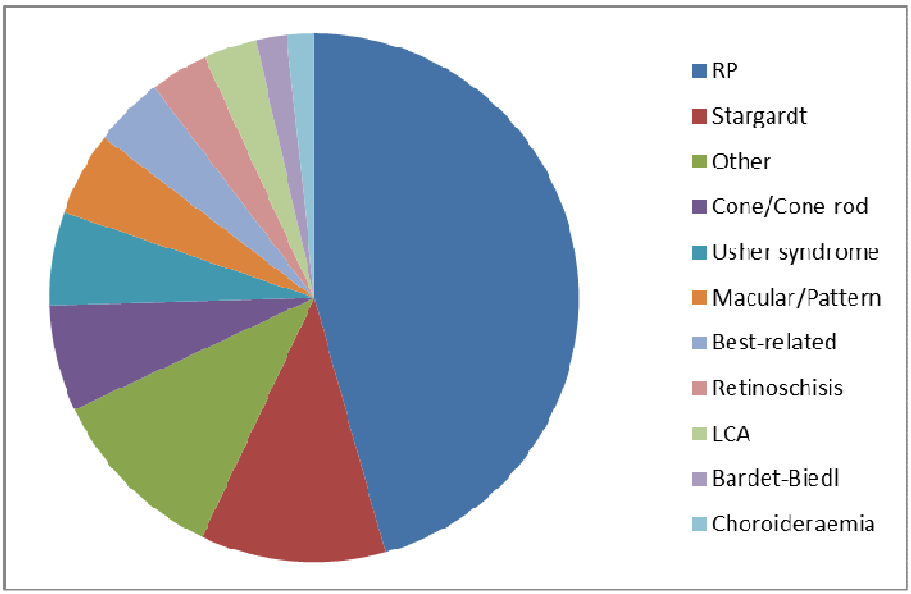
Table 2 Number of individuals on the register and number of DNA samples in the DNA bank by place of origin.

Origin	**No. DNA samples**
ACT	75
NSW	930
NT	13
QLD	605
SA	300
TAS	115
VIC	1106
WA	1739
Unassigned Mackey DNA	429
International/Unassigned	231
TOTAL	5543

Table 2 shows that 31% of all DNA has been collected from Western Australians. DNA has been being collected from Western Australians since 2001, and the DNA bank became a national resource in 2009. A long-term goal of this project is to have each of the states and territories represented on a population basis to at least the level at which Western Australia is currently represented.

Figure 1 gives a breakdown of stored DNA by clinical diagnosis, for affected and carrier subjects only. Genetic analysis projects are underway for diagnostic cohorts representing more than 90% of all DNA stored.

Figure 1 DNA samples collected from affected or carrier subjects, by diagnosis.



Genetic Analysis

Samples sent

Since the last annual report, 486 DNA samples have been sent to external providers for genetic analysis. Of these, 441 were sent to Casey Eye Institute, Oregon, USA (CEI) and 38 to the Australian Genome Research Facility (AGRF).

The samples sent to CEI included 111 samples for Next Generation Sequencing panel analysis. As many as 280 IRD genes are analysed on these panels.

DNA samples sent in the past 12 months include those from participants diagnosed with Stargardt disease (189 samples), xlRP (74), Leber congenital amaurosis (45), and retinoschisis (20). The remaining samples included are for other research cohorts or for participants requiring feedback for significant patient management reasons.

Awaiting results

In total, we are currently awaiting results for 471 DNA samples sent, including 252 samples sent early last year to a collaborator Professor Zi-Bing Jin (Professor of Ophthalmology, the Eye Hospital of Wenzhou Medical University, China). These 252 samples represent all families in which there is only one affected person noted and for which we have DNA for the affected person and both parents. These will be mainly but not exclusively arRP affected families.

Other outstanding samples for which we are waiting analysis include those for Leber congenital amaurosis (7) and Stargardt disease (165).

Samples to be sent

We are in the process of dispatching a further 190 DNA samples for genetic analysis, including for Usher syndrome (22), choroideremia (5), retinoschisis (21), xlRP (9) and Leber congenital amaurosis (6).

Results received

Of all the DNA samples dispatched for analysis in the past 12 months, we have received results for 290 of them. Once genetic analysis results are received, assessments have to be made with respect to the variants identified by the genetic analysis laboratory in order to determine which of them are likely to be disease-causing for each individual. This is an extremely labour intensive process and is primarily where most of our focus has been this year.

As a result of all of the above work, we are coming to the completion of our analyses of participants diagnosed with Leber congenital amaurosis, retinoschisis, xlRP, arRP and a second cohort of choroideremia participants. We expect to submit papers to the peer reviewed literature on these results in the near future.

In addition to this, genetic analysis and pathogenicity assessment is well advanced for Usher syndrome and Stargardt disease, and these will be the next cohorts to be published.

An outcome of this genetic analysis program is the establishment of many novel pathogenic variants in known genes. These novel variants are uploaded to the appropriate public scientific websites for use by other researchers and clinicians.

Table 3 indicates the numbers of likely or confirmed pathogenic variants identified in our participants as well as the spectrum of retinal dystrophy genes in which these variants have been found. We have established 749 confirmed or likely disease-causing variants across 154 different retinal dystrophy genes (Table 3). It is important to note that a number of such variants are often detected within a single individual. One or more of these will not necessarily be the primary cause for that individual's disease, but may in some way affect the manifestation and progression of disease symptoms and therefore also clinical treatment windows. 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 Occurrences of confirmed or likely disease-causing variants across different retinal dystrophy genes in the Australian IRD population.

Gene	Mutations	Gene	Mutations	Gene	Mutations
ABCA4	478	GJB6	2	PITPNM3	1
ABCC6	3	GNAT2	1	PNPLA6	1
ABCD1	1	GPR125	4	PROM1	15
ABHD12	4	GPR179	6	PRPF3	8
AFT6	2	GPR98	21	PRPF31	11
AHI1	5	GRK1	2	PRPF4	1
AIPL1	12	GRM6	3	PRPF6	2
ALMS1	7	GRN	3	PRPF8	1
ARL13B	1	GUCA1A	2	PRPH2	24
ARL6	1	GUCY2D	27	RAX2	1
BBS1	2	IDH3B	7	RBP3	2
BBS10	2	IFT140	8	RD3	3
BBS12	3	IFT172	4	RDH12	9
BBS2	7	IMPDH1	2	RGS9	7
BBS5	1	IMPG1	2	RHO	17
BBS7	4	IMPG2	4	RIMS1	1
BEST1	23	IQCB1	5	RLBP1	1
C1QTNF5	1	KCNV2	4	ROM1	2
C21orf2	2	KIAA1549	2	RP1	32
C2ORF71	4	KIF7	5	RP1L1	9
C5ORF42	1	LCA5	12	RP2	36
CA4	1	LRIT3	1	RP9	2
CACNA1F	11	LRP5	5	RPE65	6
CACNA2D4	5	MAK	1	RPGR	115
CC2D2A	1	MFRP	1	RPGRIP1	20
CDH23	14	MFSD8	1	RPGRIP1L	1
CDH3	2	MKKS	1	RS1	48
CDHR1	2	MTND1	1	SDCCAG8	2
CEP164	2	MTND4	2	SEMA4A	1
CEP290	32	MYO7A	22	SLC24A1	3
CHM	39	NMNAT1	13	SLC7A14	6
CKAP4	3	NPHP1	1	SNRNP200	1
CLN3	22	NPHP4	3	SPATA7	10
CLN5	5	NR2E3	14	TIMP3	2
CLN8	1	NRL	1	TMEM126A	1
CNGA3	5	OPA1	3	TMEM216	2
CNGB1	9	OPA3	1	TMEM231	1
COL2A1	1	OTX2	4	TOPORS	3
CRB1	50	PCDH15	3	TRIM32	1
CRX	2	PDE6A	11	TRPM1	3
CYP4V2	13	PDE6B	18	TTC21B	8
DFNB31	1	PDE6C	1	TTC8	1
DHX38	5	PDZD7	1	TULP1	10
DNAJC5	1	PEX1	1	USH1C	7
EFEMP1	3	PEX12	4	USH1G	1
EMC1	1	PEX13	1	USH2A	136
EYS	14	PEX2	2	VPS13B	10
FAM161A	3	PEX26	1	WDPCP	1
FSCN2	1	PEX6	1	WDR19	2
FZD4	2	PEX7	2	WFS1	6
GDF6	1	PHYH	2	ZNF423	2
GJB2	3				

Results Reporting

Since the last annual report (August 2015) we have provided 128 detailed genetic analysis reports to participants' nominated genetic counselling services or ophthalmologists (with the participants' written consent). This brings the total number of genetic research reports provided by this resource to 407. This activity is not part of our research remit, is labour intensive and is currently unfunded. We continue to strive to seek establishment funding for this activity in order to significantly increase the number of formal genetics reports we can issue each year.

A project was completed during the year *Translation of genetic analysis research results into clinical practice*. This project was funded by a Western Australian State Health Research Advisory Council research grant. The project demonstrated that patient management would be significantly improved and that the Health Department would reduce its costs if a Research Scientist were employed to collate our research results into a form suitable for provision to ophthalmologists and clinical genetics services. This outcome will be reported at the 5th NHMRC Symposium on Research Translation in Melbourne in November.

Clinical Trials

We have identified confirmed or likely pathogenic variants in individuals in the following genes, which are currently the subject of international human clinical trials: ABCA4 (478 variants), CHM (39), MYO7A (22), PDE6A (11), RPE65 (6), RPGR (115) and RS1 (48). (Note that the numbers in brackets refer to the number of such variants established, not the number of participants in whom they were found.)

An international pharmaceutical company is currently seeking de-identified genetic and clinical information from us, in collaboration with Lions Eye Institute, in order to assess the feasibility of conducting a gene-specific clinical trial in Australia.

Collaborations

A number of important collaborations have continued in the past 12 months. These include:

- Close collaboration with the Lions Eye Institute, including valuable ophthalmological input from Professor David Mackey and Associate Professor Fred Chen.
- Collaborations with John Chiang (formerly Casey Eye Institute, now Molecular Vision Laboratory Oregon, USA) in Stargardt disease, x-linked retinitis pigmentosa and the application of NGS sequencing panels to the genetic analysis of inherited retinal disease.
- A collaboration with Professor Zi-Bing Jin (Professor of Ophthalmology, the Eye Hospital of Wenzhou Medical University, China) in analysis of isolate inherited retinal disease participants.
- Investigation of genetic causes of various cone and cone-rod disease phenotypes with Professor David Hunt's team at the University of Western Australia.

- Investigation of genetic causes of various macular IRDs with Dr Jane Khan, Sir Charles Gairdner Hospital.
- Investigation of genetic causes of x-linked retinitis pigmentosa with Professor Alison Hardcastle of the Institute of Ophthalmology, University College London and Regional Genetics Laboratories, Manchester, UK, and with Dr Jon Ruddle of the Royal Victorian Eye and Ear Hospital.
- Continued close collaborations with the Centre for Eye Research Australia (Dr Alex Hewitt, Sandra Staffieri, Lisa Kearns and Dr Lauren Ayton).
- Membership of the Translation of Genetic Eye Research (ToGER) Centre of Excellence.
- Various collaborations with Sydney Children's Hospital Network and Sydney Eye Hospital (Associate Professors Robyn Jamieson and John Grigg) and many ophthalmologists, clinical geneticists and other specialists, for the investigation of specific clinical cases.

Recent peer-reviewed publications

- Huynh E, De Roach J, McLaren T, Montgomery H, Kap C, Hoffmann L, Lamey T. (2016) A method for automation of variant pathogenicity assessment from the literature followed by automated production of patient molecular genetics reports. *Australasian Physical and Engineering Sciences in Medicine*. March 2016;39(1):239-245.
- Chiang J, Lamey T, McLaren T, Thompson J, Montgomery H, De Roach J. (2015) Progress and prospects of NGS testing for retinal dystrophy. *Expert Review of Molecular Diagnostics* 2015;15(10):1269-75.
- McLaren T, De Roach J, Montgomery H, Hoffmann L, Kap C, Lamey T. (2015) Genetic analysis of choroideremia families in the Australian population. *Clinical and Experimental Ophthalmology* 2015;43(8):727-34.
- Rose L, Staffieri S, De Roach J, McLaren T, Mackey D, Hewitt A, Lamey T. (2015) Molecular and clinical characterisation of females affected by X-linked retinoschisis *Clinical and Experimental Ophthalmology* 2015;43(7):643-7.
- Crowley C, Paterson R, Lamey T, McLaren T, De Roach J, Chelva E, Khan J. Autosomal recessive bestrophinopathy associated with angle-closure glaucoma *Documenta Ophthalmolica*. 2014;129(1):57–63.

Recent presentations

- De Roach J, McLaren T, Lamey T (2016) Translation of genetic analysis research results into clinical practice. *2016 NHMRC Symposium on Research Translation*, Melbourne, Australia. (upcoming).
- De Roach J, McLaren T, Montgomery H, Thompson J, Hoffmann L, Campbell I, Lamey T (2016) Current status of research into the genetic causes of Usher syndrome at the Australian Inherited Retinal Disease Register and DNA Bank *10th National Deafblind conference 2016* Fremantle, Western Australia. (upcoming).

- McLaren T, De Roach J, Montgomery H, Thompson J, Hoffmann L, Campbell I, Lamey T (2016) Current national and international research into diagnosis and treatment of inherited vision loss associated with deafblindness *10th National Deafblind conference 2016* Fremantle, Western Australia. (upcoming).
- Chen Y, Chew A, Bukowska D, McLaren T, Lamey T, De Roach J, Mackey D, Chen F (2016) Is inherited retinal disease truly symmetrical: a case-control study using spectral domain optical coherence tomography? *Royal Australian and New Zealand College of Ophthalmologists annual congress 2016* Melbourne, Australia. (upcoming).
- Thompson J, De Roach J, McLaren T, Hoffmann L, Campbell I, Lamey T (2016) The Genetic Profile of Leber Congenital Amaurosis in the Australian Population. *27th International Symposium on Retinal Degeneration*, Kyoto, Japan. (upcoming).
- De Roach J, McLaren T, Montgomery H, Thompson J, Kap C, Hoffmann L, Lamey T (2015) Evaluation of the utility of using Next Generation Sequencing panels in genetic diagnosis of inherited retinal disease. *Royal Australian and New Zealand College of Ophthalmologists annual congress 2015* Wellington, New Zealand.
- McLaren T, De Roach J, Chen F, Ruddle J, Montgomery H, Thompson J, Kap C, Hoffmann L, Lamey T (2015) Establishment of compound heterozygous *CLN3* mutations in two unrelated patients not presenting with neurodegenerative disease. *Royal Australian and New Zealand College of Ophthalmologists annual congress 2015* Wellington, New Zealand.
- Lamey T, McLaren T, De Roach J (2015) Genetic spectrum of inherited retinal diseases in Australia. *Retina Australia National Congress* 2015, Melbourne, Australia (invited talk).
- De Roach J, McLaren T, Lamey T (2015) Current status and outcomes of the Australian Inherited Retinal Disease Register and DNA Bank. *Retina Australia National Congress* 2015 Melbourne, Australia (invited talk).

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Translation of Genetic Eye Research (ToGER) Centre of Excellence colleagues
The Western Australian DNA Bank (NHMRC Enabling Facility)