DEPARTMENT OF MEDICAL TECHNOLOGY & PHYSICS
Sir Charles Gairdner Hospital

INTERNAL REPORT

The Australian Inherited Retinal Disease Register and DNA Bank

Status Report

as at September 2012

Report prepared by

Ms Tina Lamey tina.lamey@health.wa.gov.au

Ms Terri McLaren terri.mclaren@health.wa.gov.au

Dr John De Roach john.deroach@health.wa.gov.au

Introduction

This is a status report for the resource "The Australian Inherited Retinal Disease (IRD) Register and DNA Bank" as at September 2012. 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 Retina Australia (South Australia), 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 (best known diagnosis being a crucial item), and details of genetic analyses undertaken and genetic information gathered, including the defect causing the disease within each family where this has been established.

This group has undertaken to meet the following outcomes on behalf of Retina Australia by March 2013:

1. The collection, processing, and storage of DNA samples and related clinical and family history information, such that at least 3370 DNA samples from affected subjects or their family members are stored.

2. Analysis of the DNA from at least 274 affected families.

Publication of the results of DNA collection and analysis on the website:

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

3. Facilitation of genetic counselling for participants, with particular emphasis on subjects who may be appropriate for gene-specific clinical trials or therapies.

In addition, we have undertaken to meet the following outcomes on behalf of Retina Australia (South Australia) in the 12 month period ending in March 2013:

1. The collection, processing, and storage of at least 40 DNA samples and related clinical and family history information from South Australian or Northern Territory families.

2. Analysis of the DNA from at least 36 South Australian or Northern Territory families.

3. Publication of the results of DNA collection and analysis on the website noted above.

4. Facilitation of genetic counselling for South Australian and Northern Territory participants, with particular emphasis on subjects who may be appropriate for gene-specific clinical trials or therapies.

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 on a day to day basis are Tina Lamey (Senior Research Scientist), Ling Hoffmann (Research Assistant), Hannah Montgomery (Research Assistant), Emily O'Brien (Research Assistant, resigned February 2012) and Rachel Paterson (Research Assistant, resigned August 2012).

Departmental staff directly involved with the project include Dr John De Roach (Principal Medical Physicist) and Terri McLaren (Senior Medical Scientist).

Other departmental staff noted as co-investigators on the project's S.C.G.H. 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 A/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) have also recently been included as co-investigators for this project.

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

As previously reported, Rachel Paterson completed her BSc(Hons) honours project in this department using the IRD DNA bank, under the supervision of Tina Lamey. Rachel was awarded first class honours for this project, and has subsequently been awarded a Rhodes scholarship.

Ethics and Quality Assurance

Approval for this project was granted by the S.C.G.H. Human Research Ethics Committee on 25th May 2001.

This project is carried out according to international standards with regard to its quality measures (ISO9001:2000). 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 six months.

DNA Collection

Table 1 shows (a) the number of participants and families with information recorded in the register, and (b) the number of participants and families with information recorded in the register *and* DNA stored in the DNA bank, from 2005 until now.

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

	Aug 2005	**Aug 2006**	**Aug 2008**	**Aug 2010**	**Aug 2011**	**Aug 2012**
Participants in register	1209	1285	1680	2854	3671	5129
Families in register	715	735	882	1230	1484	1926
Participants per family	1.69	1.75	1.90	2.32	2.47	2.67
Participants with DNA stored	405	444	724	1728	2461	3754
Families with DNA stored	204	214	323	631	846	1195

Table 1 shows that for the one year period August 2011 to August 2012 the number of subjects for whom information has been recorded in the register has increased from 3671 to 5129, an increase of 1458 subjects. The number of DNA samples stored has risen from 2461 to 3754, an increase of 1293 samples.

Note that the average number of participants in each family has steadily risen from 1.69 in 2005 to 2.67 in 2012. This is probably attributable in part to an increasing emphasis on gathering information from an entire family, rather than from individual participants, as this project has matured.

During 2012, 720 DNA samples were added to the DNA bank as a result of the consolidation of this DNA bank with the (mainly) Tasmanian and Victorian IRD DNA bank under the custodianship of Professor David Mackey. As a result of this consolidation, DNA from 660 participants previously not recorded in this resource have been added. In addition, another 60 samples have been added from participants for whom we already had DNA samples. Some work is still required to complete the documentation of these 720 recently added DNA samples, including the recording of the state of origin of each sample.

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 from mainly Tasmania and Victoria, but the details are yet to be documented.

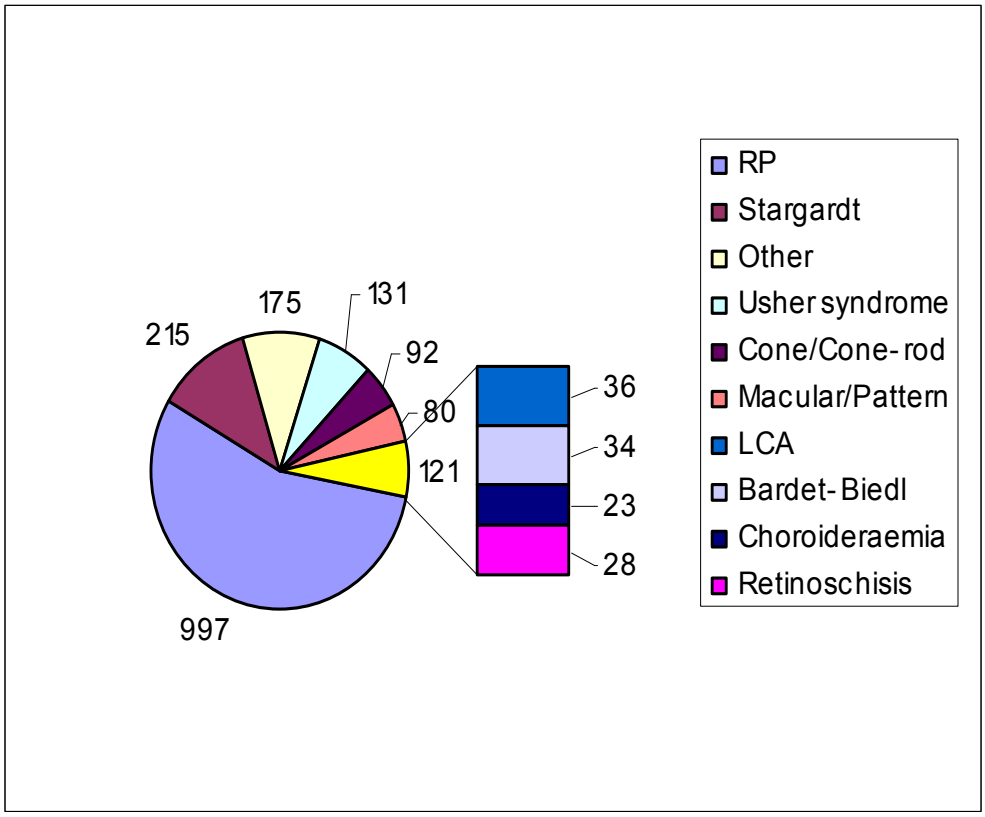
Table 2 Number of individuals on the register and number of DNA samples in the DNA bank by place of origin.

Origin	No. DNA samples
ACT	52
NSW	713
NT	9
QLD	322
SA	228
TAS	30
VIC	444
WA	1259
Unassigned Mackey DNA	656
International/Unassigned	41
TOTAL	3754

Table 2 shows that 34% of all DNA has been collected from Western Australians (compared with 45% in 2011 and 100% in 2002). 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 (for affected and carrier subjects only). Genetic analysis projects are underway for diagnostic cohorts representing more than 90% of all DNA stored (i.e. all shown except 'other').

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



Genetic Analysis

Genetic analysis performed to date has been carried out using genotyping microarray analysis (Asper Ophthalmics) or bi-directional Sanger sequencing. So far, some form of genetic analysis has been conducted on 20% of all DNA samples stored, and the probable disease-causing variant has been identified in 53% of these samples.

Table 3 indicates the occurrences of genes in the Australian population identified so far which contain a disease-causing mutation, broken down by diagnosis and affected gene.

Table 3 Occurrences of genes in which disease-causing mutations have been identified, by diagnosis.

Clinical Diagnosis	Gene	Occurrences
RP (unclassified)	*USH2A*	18
	RP1	1
	ABCA4	3
	CRB1	7
	NR2E3	1
	PDE6A	1
	PDE6B	4
	PROM1	5
adRP	*RHO*	6
	RDS	2
	RP1	4
	RP9	1
	PRPF3	7
arRP	*CRB1*	3
	USH2A	10
	NR2E3	2
	PDE6B	4
	RP1	1
Stargardt	*ABCA4*	51
Cone-rod	*ABCA4*	14
	RDS	1
LCA	*CEP290*	3
	CRB1	2
	GUCY2D	1
Usher	*USH2A*	23
	MY07A	5
Retinoschisis	*RS1*	10
Best	*BEST1*	5

Prior to April 2012, we were funded to carry out genetic analysis on Western Australian participants only, but to collect DNA Australia-wide. Since April 2012 we have been funded to analyse DNA from participants irrespective of their residency, as detailed in the introduction. As a result, we currently have a number of major genetic analysis programs underway, which will ensure we exceed the agreed targets for this funding period.

In addition to the results presented above, the following DNA has been accessed from the DNA bank and is currently undergoing analysis:

- 150 samples, mainly RP (especially isolate RP) are undergoing analysis using whole exome microarray analysis.

- 50 xlRP DNA samples were recently analysed at the Regional Genetics Laboratories Service in Manchester, UK, seeking mutations in a hot spot in the gene *RPGR* (open reading frame 15). This analysis has so far identified disease-causing mutations in 17 participants, but analysis is incomplete and these results are not reported above.

- 12 RP DNA samples are undergoing whole exome analysis via a collaboration with Robyn Jamieson. It is anticipated that future genetic analyses will increasingly use this analysis method.

- 70 Stargardt and cone-rod DNA samples are being sent for microarray analysis.

- Analysis of 12 choroideraemia samples is almost complete.

- Genetic analysis by sequencing of 7 retinoschisis DNA samples is underway.

- Genetic analysis by microarray or sequencing is underway for various other diagnoses, including many Usher DNA samples.

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 (1) all DNA samples collected, (2) the best diagnosis relating to the subject from whom each DNA sample was obtained, (3) the probable causal mutation where identified and (4) the place of origin of the DNA. No subject identification information is available on this website. This website is updated every six months.

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

Results Reporting

Since the last annual report (August 2011) we have provided 62 detailed genetic analysis reports to participants' ophthalmologists (with the participants' written consent) for Australian participants.

Acknowledgments

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

Retina Australia
Retina Australia (WA)
Retina Australia (SA)
Drs Steve Colley and Jane Khan
Staff of the Department of Medical Technology & Physics, S.C.G.H.
Staff of the Lion's Eye Institute
Staff of the S.C.G.H. Eye Clinic

APPENDIX: STRUCTURE OF THE AUSTRALIAN INHERITED RETINAL DISEASE REGISTER AND DNA BANK

The Australian IRD Register and DNA Bank consists of four entities:

Hard copy records
These files include consent forms, consultant's request forms, results of electrophysiological tests, and other written, graphical or pictorial information relevant to a subject's condition. There are approximately 3600 files in the register.

Access Database
A Microsoft ACCESS database, containing demographic, clinical, visual electrophysiological and psychophysical data, and fields to indicate whether or not DNA is available for a subject, when it was collected, in what form, and where it is stored. This database also records any genetic information established for each subject, and details of specific genetic analyses undertaken for each individual or family.

Cyrillic Database
Family tree and related family information is stored and displayed using the Cyrillic software package. The main unit of information in this database is the family, rather than the individual. The Cyrillic database contains a representation of the family tree for each family showing the relationships between all affected and unaffected members of the family, as best as can be ascertained. Family information recorded includes family relationships (including any occurrences of consanguinity), family number, family name, and the IRD occurring within the family. Some redundancy exists in this representation with respect to the Access database, such as each individual's unique identification number, name and date of birth.

DNA Bank
All DNA is stored in the Western Australian DNA Bank (WADB). The WADB is a state service that specialises in the storage of DNA, plasma and human tissue for research purposes in accordance with best practice principles. Note that the DNA remains the property of and under the total control of the DNA custodian (the authors of this document). Physical DNA samples are identified by the custodians using a coded number.

This department operates the state visual electrophysiology service, and Western Australian residents are referred to this clinic for diagnostic testing. Patients suspected of having an IRD usually undergo all or most of electroretinography, pattern and multifocal electroretinography and electrooculography testing. Since 2001 detailed results from all electrophysiological and psychophysical tests carried out in this department on IRD patients have been automatically electronically captured and transferred to the IRD ACCESS database. As a result of a typical patient visit, values for more than 110 different parameters are electronically captured and automatically transferred to the IRD database.