UWA Research Publication

De Roach, JN, McLaren, TL, Paterson, RL, O'Brien, EC, Hoffman, L, Mackey, D.A., Hewitt, A. & Lamey, IM (2012). Establishment and evolution of the Australian Inherited Retinal Disease Register and DNA Bank. CLINICAL AND EXPERIMENTAL OPHTHALMOLOGY, 41(5), 476-483.

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Category: Original Article – Clinical Science

Establishment and evolution of the Australian Inherited Retinal Disease Register
and DNA Bank

John N. De Roach PhD¹, Terri L. McLaren BSc¹, Rachel L. Paterson BSc(Hons)¹,
Emily C. O'Brien BSc(Hons)¹, Ling Hoffmann¹, David A. Mackey FRANZCO²,
Alex W. Hewitt PhD^{2,3}, Tina M. Lamey BSc(Hons)¹

1. Australian Inherited Retinal Disease Register and DNA Bank, Department of
Medical Technology and Physics, Sir Charles Gairdner Hospital, Perth, Western
Australia.

2. Lions Eye Institute, Centre for Ophthalmology and Visual Science, University of
Western Australia, Australia.

3. Centre for Eye Research Australia, University of Melbourne, Royal Victorian
Eye and Ear Hospital, Melbourne, Australia.

ADDRESS FOR CORRESPONDENCE:

Dr John De Roach
Principal Medical Physicist
Sir Charles Gairdner Hospital
Hospital Avenue
Nedlands, WA, 6009 Australia
Ph: +61 8 9346 2327
Fax: +61 8 9346 3466
email: john.deroach@health.wa.gov.au

RUNNING TITLE: Australian IRD Register.

FINANCIAL DISCLOSURE STATEMENT: The authors have nothing to disclose.

CONFLICT OF INTEREST STATEMENT: No authors of this paper have any competing interests related to this research.

FUNDING SOURCES: Retina Australia, Retina Australia (WA) and Retina Australia (SA) funded the development of the Australian Inherited Retinal Disease Register and DNA Bank. The authors gratefully acknowledge the assistance of the Western Australian DNA Bank which was supported by a National Health and Medical Research Council (NHMRC) Enabling Facility grant. AWH is supported by a NHMRC Early Career Fellowship. Ongoing support is also provided by the Centre for Research Excellence grant for Translation of Genetic Eye Research, from the NHMRC.

ABSTRACT

BACKGROUND: Inherited retinal disease represents a significant cause of blindness and visual morbidity worldwide. With the development of emerging molecular technologies, accessible and well-governed repositories of data characterising patients with uncommon disease is becoming increasingly important. This manuscript introduces such a repository - the Australian IRD Register and DNA Bank.

METHODS: Demographic, clinical and family information was collected from affected participants and family members. Information stored in the register for each participant included demographic details, clinical indicators, and family history. A diagnosis, clinical status and likely mode of inheritance were assigned. When available, clinical data were also stored. In 2001, we began collecting DNA from Western Australian participants. In 2009 this activity was extended Australia-wide (www.IRDregister.org.au). Genetic analysis results were stored in the register as they were obtained.

RESULTS: Demographic details of 4193 participants are currently recorded in the database, and DNA has been obtained from 2873 participants. 61.0% of affected participants have a diagnosis of retinitis pigmentosa, whilst Stargardt disease and Usher syndrome participants comprise 9.9% and 6.4% of the register, respectively. For the retinitis pigmentosa participants in whom the inheritance mode has been determined, the majority of participants (53.2%) have an autosomal dominant inheritance mode.

CONCLUSION: This national resource is a valuable tool for investigating the aetiology and genotype-phenotype relationships of inherited retinal diseases. As new molecular technologies are translated into clinical applications, this well-governed repository of clinical and genetic information will become increasingly important for tasks such as identifying candidates for gene-specific clinical trials.

KEY WORDS:

Retinitis pigmentosa; Stargardt disease; retinoschisis; choroideraemia; Usher syndrome; Leber congenital amaurosis; Best disease; macular degeneration.

INTRODUCTION

Retinal disease represents a significant cause of blindness and visual morbidity worldwide. Given the typical young age of onset, the individual and socioeconomic impacts of inherited retinal disease (IRD) are profound.¹ However, the heterogeneous clinical and genetic nature of IRD poses a major barrier to research.² Nonetheless, advances in our understanding of the pathogenic mechanisms of IRD have led to dramatic improvements in both blindness prevention and treatment.

Major developments in gene-specific vision-restoring therapy have been made in recent years. Human trials for *RPE65*-associated Leber congenital amaurosis (LCA) are now well underway, following successful restoration of vision using replication-deficient adeno-associated viral vectors in a naturally occurring canine model.³⁻⁵ Similarly, recombinant viral treatment was successful in treating an animal model of *RPGR ORF15*-associated X-linked retinitis pigmentosa (RP).⁶ This is a rapidly evolving field and recombinant viral therapy is being developed for a number of retinal diseases including Stargardt disease, choroideraemia and retinoschisis. It is clear that many other genetically tailored therapies will be developed in the near future, rapidly increasing the need for the existence of organised and extensive repositories of phenotypic and genetic information of participants affected with these diseases.

Herein, we describe the establishment and evolution of the Australian Inherited Retinal Disease Register and DNA Bank. This resource represents a solid foundation for a comprehensive Australian repository for (a) phenotypic information obtained from participants affected with an IRD, (b) relationships within families containing IRD-affected members, (c) DNA obtained from both affected and unaffected members of those pedigrees, and (d) genetic analysis results obtained from archived DNA. The extent and richness of this information will continue to grow as the resource continues to mature.

METHODS

Establishment of the Australian IRD Register:

The Department of Medical Technology and Physics (DMTP) at the Sir Charles Gairdner Hospital (SCGH), Western Australia, provides a state-wide service for

visual electrophysiological testing. Generally, at least one member from an IRD pedigree in Western Australia would be referred and clinically screened by this Department.¹² The DMTP was therefore an effective funnel for such patients and was seen as an appropriate starting point for a local IRD register. Consequently, in 1984 pertinent clinical details of RP patients and their relatives were compiled centrally.¹² The scope of the register was subsequently broadened to include families with members affected with any form of IRD. In 2001 we began collecting DNA samples from Western Australian participants, and since April 2009 we have collected DNA and clinical and family information from participants Australia-wide.

Ethical and quality assurance:

Approval for this project was granted by the Sir Charles Gairdner Hospital (SCGH) Human Research Ethics Committee on the 25th May 2001 (HREC number 2001-053). All related activities were conducted in accordance to international standards with regard to its quality measures. All relevant procedural protocols, work instructions, participant or family records and referral forms, as well as correspondence, were stored in compliance with DMTP's ISO9001:2008 accredited quality documentation system. All associated processes were subject annually to both internal and external audit.

Participant Selection and Referral:

Participants were referred and recruited into this register via several means. As noted earlier, the DMTP is the Western Australian state referral centre for visual electrophysiology testing. The provisional diagnosis coded on the Patient Management System (PMS) for each patient was actively reviewed, and potential candidates were invited to participate in the IRD register. This was the most significant source of participants until April 2009.

To be included in this register participants were required to have a provisional or confirmed diagnosis of an inherited retinal disease. The most common diseases included retinitis pigmentosa, Stargardt disease, Leber congenital amaurosis, Usher syndrome, retinoschisis, Bardet-Biedl syndrome and other inherited rod, cone or macular disorders. Diagnoses were assigned a confidence level, depending on the

perceived level of reliability of the diagnosis. Exclusion criteria included a diagnosis of age-related macular degeneration.

With the expansion of this resource into a national register and DNA bank in April 2009, circulation of the Retina Australia membership list was the prime (but not exclusive) means of recruitment in the first instance. Using this strategy, during the following three years the number of DNA samples stored reached 3000. External ophthalmologists and eye care providers also directly identified participants during this period, and an additional significant source of participant recruitment was the recruitment of relatives of probands.

Greater emphasis on the inclusion of ophthalmologists in the recruitment of participants was initiated in April 2012. Using a mailing list provided by RANZCO for this purpose, recruitment kits were sent to more than 800 ophthalmologists practising in Australia. These kits contained a letter outlining the resource, 20 brochures for handing to possible participants, and a means of ordering additional brochures. Ophthalmologists were also made aware of the contact details for the Australian IRD Register and DNA Bank at www.IRDregister.org.au.

Structure of the Register Data:

Demographic details, clinical indicators and family history for each participant were stored in the register. A diagnosis was assigned for each participant, according to standard clinical definitions. Clinical status was assigned as being either: affected, unaffected, carrier, obligate carrier, family member or unknown.

A three-tiered confidence level was assigned to the diagnosis and clinical status, in order to identify less reliable information for future scrutiny and investigation. In the case of participants who were recruited as a result of their referral to the DMTP, detailed results of an array of psychophysical and visual electrophysiological tests were electronically captured and included in the register.

Where the IRD assigned to a family did not strongly indicate the inheritance mode, such as in the case of RP, an inheritance mode was assigned to a family either from the ophthalmologist's medical records or, if this was unavailable, as follows:

- 1) **Autosomal dominant** was assigned to a family if it exhibited direct vertical transmission in three successive generations, and where the family did not exhibit consanguinity.
- 2) **Autosomal recessive** was assigned to a family if there were multiple affected siblings and unaffected parents or parental consanguinity.
- 3) **X-linked recessive** was assigned to a family if there were multiple affected males and/or affected male(s) and female carrier(s) as ascertained by fundoscopic examination and ERG testing.
- 4) **Isolate** was assigned to a family if the proband was the only documented affected member.
- 5) **Unclassified** was assigned to a family if the family history was unknown, or if there were multiple affected members but none of the inheritance modes above applied.

Inheritance modes were further qualified as definite, probable or possible, based on the amount and clarity of available information for the application of the above classification scheme.

If genetic analysis of a participant's or a family's DNA subsequently clarified the inheritance mode of a disease within a family, then that inheritance mode was the one recorded for that participant or family.

The Australian IRD Register and DNA Bank consists of separate but inter-related data entities.

Hardcopy records:

An individual folder for each participant recruited into the register was constructed and stored securely at the SCGH. Files included completed consent forms, clinical request forms, results of electrophysiological tests, and other written, graphical or pictorial information or correspondence relevant to each participant. These files represent the gold standard of data storage for each registrant.

There was no attempt to consistently gather clinical data stored in the files of ophthalmologists for each participant, such as fundus photographs, autofluorescence,

OCT, or electrophysiology tracings. Family history and best known diagnosis (with an assigned confidence level) were included as the minimum data set with respect to clinical information. When a participant gave informed consent, that consent included consent for the investigators to seek relevant medical records from eye care providers. When a cohort was being considered for genetic analysis, additional clinical information was sought from its custodians at that time if it was deemed necessary. This proved to be the most efficient use of resources.

Electronic records and register database:

A secure Microsoft Access (Microsoft, Redmond, USA) database contains demographic, clinical, visual electrophysiological and psychophysical data, as well as information relating to the collection and analysis of biological samples.

Upon enrolment, each participant was assigned a unique identification code, and demographic data, such as gender, date of birth and contact details, were collected. Contact details for the participant's ophthalmologist or referring clinician were also recorded.

In the special case of participants recruited from DMTP patients, clinical data were automatically transferred from the SCGH PMS and clinic-based personal computers, which controlled all visual electrophysiology/psychophysical testing from the vision clinical laboratories. The DMTP routinely undertakes electroretinography, pattern electroretinography, multifocal electroretinography (since 2006) and electrooculography testing. All of these tests are conducted according to ISCEV standards, and all have extensive clinic-specific normal ranges. Psychophysical data include: best-corrected visual acuity, colour vision results, and contrast sensitivity results.

When provided, all available clinical data were entered for participants referred to the register from outside the DMTP.

A standalone database was used for documenting all pedigree information. Available family medical history was ascertained from each participant and data stored and displayed using Cyrillic v2.02 (Cyrillic Software, Oxfordshire, United Kingdom).

This database contains a representation of the family structure for every pedigree in the IRD register, and displays graphically the relationships between all affected and unaffected members of each family. Family information recorded included family relationships (including any occurrences of known consanguinity), family number, family name, and the IRD occurring within the family, as well as its presumed inheritance mode. All participants who were recorded in the IRD register appear once in the family tree information in the Cyrillic database, although not every person entered into the Cyrillic database is represented in the IRD register.

Biological specimens:

Once informed written consent was obtained to collect and store DNA, three 10 ml vials of blood (EDTA) were collected. Two vials were transferred to the Western Australian DNA Bank (WADB), where genomic DNA was extracted from blood leukocytes using standard procedures. 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. All samples were identified by a unique code. The DNA remains the property of and under the control of the investigators of this project. The services of the WADB are used for DNA extraction according to best practice and as a secure repository for the DNA, until such time as it is requested by the investigators for genetic analysis.

Extracted DNA was stored in two different locations at -40°C. The buffy coat was extracted from the third vial, and stored at -80°C. Saliva was an alternative source of DNA. Saliva samples were collected using the Oragene Saliva Kit (2ml; Oragene™ DNA Self collection kit OG-500; DNA Genotek Inc., Canada) and DNA was extracted according to the manufacturer's instructions.

For all collected specimens, data regarding availability of DNA, collection date, the source of the DNA (blood or saliva), storage format and location were entered into the electronic IRD database.

All data obtained by DNA genetic analysis were stored in the secure IRD database. A mutation-ID table lists all genetic variants identified in this DNA databank. Genomic nomenclature was standardised using the Mutalyzer resource.¹³ Information recorded

includes: a unique mutation identification number, the gene and a brief description of the likely functional significance of the variant. Details relating to each genetic analysis conducted for a participant were electronically documented. All identified variants were coded, along with the method of analysis (microarray, sequencing, etc), analysis batch number, date, specific array name (and version if appropriate), primer identification, as well as hyperlinks to the laboratory report and summary of the results.

Additionally, the database contains a data table recording information regarding all DNA PCR primers used, including genomic location targeted, primer sequence and supporting literature.

Access to the Register and DNA Bank:

All information was entered into the register and all DNA was deposited into the DNA bank by the custodians of the register and DNA bank.

A complete list of (de-identified) DNA samples stored, together with associated diagnoses and disease-causing mutations, where known, is available from the website <http://www.scgh.health.wa.gov.au/Research/InheritedRetinal.html>. This website is updated every six months.

Researchers wishing to have access to further information or to DNA samples for genetic analysis may do this by contacting the first author of this paper, or by using the contact information at www.IRDRegister.com.au. Researchers are required to show evidence of approval of their project by a recognised human research ethics committee before information or DNA can be released. Information identifying a participant will only be released after further written consent has been obtained by a participant for the specific required purpose.

This resource has been used to recruit participants for several studies being carried out by other groups by this means. Not all of these studies are associated with the genetics of retinal disease. For example, subjects have been recruited from this resource for possible participation in a bionic eye project.

It is anticipated that participants suitable for gene-specific clinical trials will be identified via this resource. We are currently genetically analysing the DNA obtained from participants affected with choroideraemia, sourced from eight families, and we continue to genetically analyse DNA obtained from participants affected with Leber congenital amaurosis.

Genetic analysis results obtained for a participant were reported to a participant when they were available, via the participant's designated ophthalmologist or genetics counselling service. This was done at the request of the participant, the request of an ophthalmologist, or at the instigation of the investigators. An additional level of informed written consent was obtained from the participant before this occurred. Note that results were established in a research context, and further confirmation of the indicated cause of disease may have been required using a NATA accredited laboratory if the result was to be used in a clinical setting. However, confirmation of an anticipated mutation is much quicker and cheaper than initial identification of the suspected mutation. Work is underway to consolidate this clinical service that has arisen from this research study. Ongoing funding and confirmation of disease-causing mutations by a NATA accredited laboratory are two important issues that need to be addressed.

RESULTS

Demographic details of 4193 participants are currently recorded in the database, and DNA has been obtained from 2873 (68.5%) participants (Table 1). Approximately 80% of all DNA collected was obtained from peripheral blood samples. Additionally, DNA collected from 95 unrelated individuals with no known family history of retinal disease, and who have been found to have no ocular disease after comprehensive clinical and electrophysiology examination, has also been stored. These additional samples were used as non-retinal disease control participants to help determine the allele frequency of novel, potentially pathogenic variants in our population.

A total of 2195 (52.3%) participants currently reside in Western Australia; however, under half (42.0%) of all DNA samples stored are from people living in Western Australia (Table 2). The rate of DNA collection increased dramatically during 2009,

when we commenced specimen collection from participants throughout Australia (Figure 1).

DNA was collected from 34 participants resident outside Australia (Table 2). These participants were blood relatives of probands of Australian families. For these international participants, DNA was collected as saliva using saliva kits and transported to the DNA bank.

Over half (61.0%) of the affected and obligate carrier participants with DNA stored have a clinical diagnosis of RP or are related to a proband with a clinical diagnosis of RP, whilst Stargardt disease and Usher syndrome participants comprise approximately 9.9% and 6.4% of the register, respectively (Figure 2). When the inheritance pattern in participants with RP can be determined (41.2%), the majority of participants (53.2%) have been found to have an autosomal dominant mode of inheritance (Figure 2).

During the period April 2009 until March 2012 we collected and genetically analysed DNA from Western Australian participants, and collected but did not analyse DNA from other Australian participants. Genetic analysis was carried out using custom microarray analysis (Asper Ophthalmics, Estonia) or bi-directional Sanger sequencing. To date, some form of genetic analysis has been conducted on 19.2% of all DNA samples stored, and the probable disease-causing variant has been identified in 53.0% of these samples. Detailed genetic analysis methods and results using DNA from this resource are the subject of additional papers in preparation. However, a summary of disease-causing mutations identified to date is presented in Table 3.

Since April 2012 the rate of genetic analysis has significantly accelerated, as DNA obtained from participants from throughout Australia has been analysed since then. DNA analysis is actively being performed on DNA from participants having diagnoses which include adRP, arRP, xLRP, RP (inheritance mode unknown), choroideraemia, Stargardt disease, retinoschisis, Usher syndrome, Leber congenital amaurosis and macular/pattern disorders. Analysis methods include Sanger sequencing, microarray analysis, whole exome sequencing, SNP chip analysis and whole exome microarray analysis, as appropriate.

DISCUSSION

It is anticipated that within the next decade the genetic aetiology for the vast majority of Mendelian diseases will be known.¹⁴ Rapid technological advances have dramatically reduced genotyping costs.^{15,16} Clearly, ongoing research into understanding the pathogenic cellular mechanisms and methods by which to circumvent or overcome them will be required. Knowledge of the disease-specific mutation spectrum in a population is a fundamental facet of predictive risk profiling and allows targeted investigation of therapeutic screening.¹⁷ To date, Australian researchers have made an important contribution to the understanding of IRD. For example, the mutation spectrums for X-linked retinoschisis,^{18,19} Best disease,²⁰ and *ORF*-associated X-linked RP²¹ have been reported. A national repository, such as the Australian IRD Register and DNA Bank, allows for coordinated investigation and clinical translation of such research findings.

Translating research findings into clinical applications is an ongoing focus for the IRD Register. We have recently developed a clinical service arm, and have begun reporting genetic analysis results to participants when potentially clinically relevant results are available. Results are reported via a participant's nominated ophthalmologist or professional genetic counselling service. Prior to the release of results, each participant is contacted for specific informed written consent, allowing us to provide their results to their nominated clinician.

The IRD Register and DNA Bank did not become a national resource until 2009. Prior to 2009, more than 80% of all DNA stored was collected from Western Australian participants. DNA is now being collected relatively uniformly throughout Australia each year. At present, 42.1% of all DNA originates from Western Australia (Table 1), representing a fraction per head of population of four to five times that of the remainder of Australia. This imbalance is steadily being redressed, and a long-term aim of this project is to have each of the Australian states and territories represented on a population basis to a level comparable to that which Western Australia is currently represented.

It is noteworthy that currently over half of participants diagnosed with RP in the Australian IRD Register and DNA Bank have not been assigned an inheritance mode for their disease. For the majority of cases this is because they are the only known affected member of their family. Given the long duration of follow-up for many participants and their families over successive generations, spontaneous de novo mutations are unlikely to account for a major proportion of these isolated cases. It is more probable that the majority of RP participants with an unassigned inheritance mode will eventually be found to harbour mutations that cause disease via autosomal recessive mechanisms. Determining the genetic classification of these participants into dominant, recessive or X-linked disease inheritance is a current focus of this IRD research.

The Australian Inherited Retinal Disease Register and DNA Bank is now a well established resource. It is envisaged that it will continue to be actively utilised both by clinicians and researchers to facilitate ongoing improvements in clinical care. This clinical and molecular repository will enable future study of IRD pathogenesis and treatment. Following specific ethical approval, research-related requests for access to information and DNA contained in this resource are welcomed.

ACKNOWLEDGEMENTS

This resource could not have been created without the assistance and support of many ophthalmologists and eye care providers throughout Australia. Retina Australia, Retina Australia (WA) and Retina Australia (SA) funded the development of the Australian Inherited Retinal Disease Register and DNA Bank. The authors gratefully acknowledge the assistance of the Western Australian DNA Bank (National Health and Medical Research Council (NHMRC) Enabling Facility), the electrophysiology staff and reporting ophthalmologists, Jane Khan and Steve Colley, of the Visual Electrophysiology Clinic in the DMTP, SCGH. The continued support of the Head of Department of DMTP, Roger Price, is gratefully acknowledged. Significant contributions were made by staff of the SCGH Eye Clinic and the Lions Eye Institute. AWH is supported by a NHMRC Early Career Fellowship. Ongoing support is also provided by the Centre for Research Excellence grant for Translation of Genetic Eye Research, from the NHMRC.

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FIGURE LEGENDS

Figure 1.

Number of people included on the Australian IRD Register and DNA Bank over time. The solid line represents all participants, whilst the dashed line displays the number of DNA samples which have been collected and stored.

Figure 2.

Disease composition of stored DNA samples from affected or obligate carriers. The right panel displays the breakdown of patients with retinitis pigmentosa by mode of inheritance. Abbreviations: XLRS, X-linked retinoschisis; BBS, Bardet-Biedl syndrome; LCA, Leber congenital amaurosis; AD, autosomal-dominant; XL, X-linked; AR, autosomal-recessive.

Table 1.

Demographic details of individuals currently participating in the Australian IRD Register.

	Number	(%)
Participants in Australian IRD Register	4193	
Female	2339	(55.8% of participants)
Mean age years +/- 1 SD	48.0	+/- 20.3
Families in register	1637	
Genetic Testing		
DNA samples stored	2873	(68.5% of participants)
DNA samples screened	553	(19.2% of all DNA)
No. participants with mutation identified	293	(53.0% of screened)
No. families with mutation identified	117	(7.1 % of all families)

Abbreviation: IRD, inherited retinal disease; SD, standard deviation.

Table 2.

Number of participants on the Australian IRD Register and number of DNA samples in the DNA bank by place of origin.

Origin	Number of participants in register	Number of DNA samples	No. DNA samples per million population
Western Australia	2195	1209	576
New South Wales	766	661	96
Victoria	452	380	73
Queensland	350	296	70
South Australia	271	217	136
Australian Capital Territory	55	44	129
Tasmania	26	23	46
Northern Territory	10	9	41
International	68	34	-
TOTAL	4193	2873	136

Table 3

Disease-causing mutations identified by diagnosis.

Clinical Diagnosis	Disease-causing gene	Number of occurrences
adRP	<i>RHO</i>	6
	<i>PRPH2</i>	5
	<i>RP1</i>	4
	<i>PRPF3</i>	2
	<i>RP9</i>	1
arRP	<i>USH2A</i>	9
	<i>CRB1</i>	5
	<i>PDE6B</i>	4
	<i>NR2E3</i>	2
xLRP	<i>RPGR</i>	1
RP (unknown inheritance)	<i>USH2A</i>	19
	<i>PROM1</i>	5
	<i>ABCA4</i>	3
	<i>PDE6B</i>	3
	<i>RP1</i>	2
	<i>PDE6A</i>	1
	<i>NR2E3</i>	1
Stargardt disease	<i>ABCA4</i>	51
Cone-rod dystrophy	<i>ABCA4</i>	13
	<i>PRPH2</i>	1
Usher syndrome	<i>USH2A</i>	23
	<i>MYO7A</i>	5
X-Linked Retinoschisis	<i>RS1</i>	10
Leber congenital amaurosis	<i>CEP290</i>	3
	<i>CRB1</i>	2
	<i>GUY2CD</i>	1
Best disease	<i>BEST1</i>	5

Abbreviations: ad, autosomal-dominant; xl, X-linked; ar, autosomal-recessive; RP, Retinitis Pigmentosa.

Figure 1.

Figure 2.