

Received: 29 November 2020

Revised: 7 April 2021

Accepted: 10 April 2021

DOI: 10.1111/cge.13967

ORIGINAL ARTICLE

Molecular genetics of inherited retinal degenerations in Icelandic patients

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Icelandic Student Innovation Fund: 206542 - 0091; The Icelandic Association of the Visually Impaired; The Richard P. Theodore and Dora Sigurjonsdottir Fund for improving scientific knowledge on blindness

Abstract

The study objective was to delineate the genetics of inherited retinal degenerations (IRDs) in Iceland, a small nation of 364,000 and a genetic isolate. Benefits include delineating novel pathogenic genetic variants and defining genetically homogenous patients as potential investigative molecular therapy candidates. The study sample comprised patients with IRD in Iceland ascertained through national centralized genetic and ophthalmological services at Landspítali, a national social support institute, and the Icelandic patient association. Information on patients' disease, syndrome, and genetic testing was collected in a clinical registry. Variants were reevaluated according to ACMG/AMP guidelines. Overall, 140 IRD patients were identified (point prevalence of 1/2,600), of which 70 patients had a genetic evaluation where two-thirds had an identified genetic cause. Thirteen disease genes were found in patients with retinitis pigmentosa, with the *RLBP1* gene most common ($n = 4$). The c.1073 + 5G > A variant in the *PRPF31* gene was homozygous in two RP patients. All tested patients with X-linked retinoschisis (XLRs) had the same possibly unique *RS1* pathogenic variant, c.441G > A (p.Trp147X). Pathologic variants and genes for IRDs in Iceland did not resemble those described in ancestral North-Western European nations. Four variants were reclassified as likely pathogenic. One novel pathogenic variant defined a genetically homogenous XLRs patient group.

KEYWORDS

eye diseases, genetics, hereditary, human genetics, Iceland, population, retinitis pigmentosa

1 | INTRODUCTION

Inherited retinal degenerations (IRDs) are a large group of diseases, which are both clinically and genetically heterogeneous.^{1,2} IRD affects the retina, a specialized, light-sensitive nervous tissue, and the innermost layer of the eye.³ The photoreceptors are most commonly

affected.¹ Collectively, these diseases are among the leading causes for blindness worldwide,^{4,5} with an estimated prevalence of about 1/2,000–1/3,000.⁶

A total of 271 genes are known to cause IRDs.⁷ Their protein products function in various biological pathways, such as eye development, the retinal cells' structure, phototransduction, regeneration of

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the retinoid substance, retinal enzymatic function, and photoreceptor survival.² Despite the number of known disease genes, the genetic causality can only be identified in about two-thirds of IRD patients.^{1,2,8} IRDs are almost always inherited by monogenic inheritance, where the disease gene comes from either parent or both, and by mitochondrial inheritance, from mother to child.⁴ IRDs can also rarely be inherited by digenic inheritance.⁹ IRD can affect the whole retina or a specific portion of it, for example, the macula. Either rods or cones, or both, can be affected, and the visual effect can be either night blindness and loss of visual field, loss of color sensation and central vision, or both. IRD can be restricted to the retina, or it can be part of a more extensive syndrome.⁴ The most common IRDs are retinitis pigmentosa (RP), non-syndromic and syndromic, Stargardt disease, X-linked retinoschisis (XLRs), achromatopsia, choroideremia, and Leber congenital amaurosis.¹⁰

The genetics of IRDs as a group has not been described before in Iceland, a nation of approximately 364,000,¹¹ and descendants of Nordic and Gaelic populations.¹² As the genetics of IRDs is gradually being elicited, it is important to report the genetics of IRDs in small nations, especially genetic isolates like Iceland. In small populations, it can sometimes be easier to evaluate pathogenic variants. In a small nation a group of patients can be defined with the same pathogenic variant, which would be optimal for future molecular therapies. In Iceland, the genetics of IRDs is limited to a study on the genetics of Sveinsson's chorioretinal atrophy (SCRA), also referred to as helicoid peripapillary chorioretinal degeneration or atrophia areata. SCRA is substantially common in the Icelandic population, with about 116 patients diagnosed.¹³ Interestingly, every reported patient with SCRA in other countries has an Icelandic ancestry.¹³ Thus, this study did not include that disease.

Knowing the genetic causes for IRDs improves understanding of prognosis for individual patients and facilitates the identification of relatives at risk. A genetic diagnosis also allows reproductive choices with either a preimplantation or prenatal genetic diagnosis. Knowledge of the genetic causes of IRDs is also necessary for Icelandic IRD patients to participate in clinical trials in genetic and molecular therapies and to benefit from them as they become available. Our study aimed to delineate the genetic causes of IRDs in Icelandic patients by summarizing the results of genetic evaluations.

2 | MATERIALS AND METHODS

2.1 | Patient inclusion criteria

This study used the Retinal Information Network (RetNet)⁷ information bank about the genetics of IRDs. All patients were diagnosed by an ophthalmologist. Diagnosis methods generally included fundoscopic examination, slit lamp (biomicroscope) examination, visual field testing, ERG testing, and recently optical coherence tomography. Patients were included if their phenotype matched an IRD and if they had previously undergone a genetic evaluation by a medical geneticist for disease genes registered at RetNet. Patients were excluded if the reason for a genetic evaluation was a differential

diagnosis and their phenotype did not match IRD. SCRA patients were excluded from the study, both in the description of genetic findings and prevalence calculations. Both patients and their family members, that underwent a genetic evaluation for risk assessment and segregation analyses, were registered in the study's data registry.

2.2 | Patient ascertainment

The study's sample comprised all patients with IRD that had undergone a genetic evaluation at the Department of Genetics and Molecular Medicine (GMM) at Landspítali- National University Hospital. A systematic search was performed at the GMM, dating back to the year when the department was established in 2002.

A registry of visual electrophysiological recordings performed on patients at the Department of Ophthalmology at Landspítali was accessed, which included electroretinograms (ERG) and electrooculograms (EOG). That electrophysiology registry consisted of every ERG and EOG recording since the first test was performed in Iceland in 1991. These recordings were obtained in compliance with the International Society for Clinical Electrophysiology of Vision (ISCEV) standards for these procedures in force at each given time.

An ICD10 code search was also performed, using H35.5 (Hereditary Retinal Dystrophy) and Z82.1 (Family History of Blindness and Visual Loss). The ICD10 search was performed at Landspítali, Akureyri Hospital, and the Icelandic National Institute for the Blind, Visually Impaired, and Deafblind, also referred to as the Center. A registry of members with RP at Blindrafelagid, the Icelandic Association of Visually Impaired (BIAVI), was also obtained.

2.3 | Data registry

A data registry was assembled for this study, comprising patients' medical information. Data collected were ophthalmic medical records, especially diagnosis, other medical issues, genetic evaluation results, and patient's family history. The data registry was sorted by disease diagnosis with 18 different variables assigned to each patient. These variables were patient's name, social security number, gender, diagnosis, year of diagnosis by a genetic evaluation, age of diagnosis by a genetic evaluation, disease gene, inheritance, NCBI reference code, genetic variant, biochemical consequences, genotype, pathogenic classification, type of genetic test, phenotype, ERG results, parental testing, and family history.

In this study, patients were classified as to whether they had (1) a known genetic cause, (2) an unclear result, or (3) no identified genetic cause. A genetic cause was defined if a patient had two pathogenic/ likely pathogenic (P/LP) variants in trans, causing autosomal recessive (AR) disease, one P/LP pathogenic variant that causes autosomal dominant (AD) disease, a P/LP variant in an X-linked disease among males, and a P/LP variant in mitochondrial inheritance. An unclear result was defined if only one heterozygous P/LP

TABLE 1 Overview of RP patients

Patient	Phenotype	ERG	Gene	Inh	Genotype	Genetic Variant	Protein/ RNA splicing	Class	ClinVar ^{§§}	gnomAD ^{¶¶}
RP1	RP. Symptoms 20 y	Consistent with RP ^{..} , atypical RP ^{..}	<i>EYS</i>	AR	Ht	c.2620C>T	p.Gln874 [*]	P [~]	Yes	4e-5
RP2	RP. Symptoms 20 y	Consistent with RP	<i>EYS</i>	AR	Ht	c.6725+1G>C	Interferes with splicing	LP	No	N/A
			<i>EYS</i>	AR	Ht	c.7228+1G>A	Interferes with splicing	P	Yes	3.48e-5
RP3	Cone-rod dystrophy, late-onset, symptoms about 60 y	Consistent with CAR or MAR	<i>HGSNAT</i>	AR	Ho	c.1843G>A	p.Ala615Thr	LP	Yes	3.82e-3
RP4	Early-onset RP, about 8 y	Consistent with RP	<i>HK1</i>	AD	Ht	c.626A>G	p.Asp209Gly	LP	No	N/A
RP5	Late-onset RP, symptoms about 30 y, slowly progressing	Consistent with RP	<i>OTX2</i>	AD	Ht	c.106G>C	p.Ala36Pro	VUS	No	N/A
			<i>IFT172</i>	AR	Ht	c.4907_4908del	p.His1636Argfs*5	P [~]	No	N/A
RP6	Early-onset RP, diagnosed 22 y	N/A	<i>PDE6A</i>	AR	Ht	c.2053G>A	p.Val685Met	LP	Yes	3e-5
			<i>PDE6A</i>	AR	Ht	c.1621-6T>G	Could affect splicing	LP	No	N/A
RP7	Early-onset RP, diagnosed about 20 y	N/A	<i>PDE6A</i>	AR	Ht	c.2053G>A	p.Val685Met	LP	Yes	3e-5
			<i>PDE6A</i>	AR	Ht	c.1621-6T>G	Could affect splicing	LP	No	N/A
RP8	Early-onset RP, diagnosed 12 y	N/A	<i>PDE6B</i>	AR	Ho	c.1685G>A	p.Gly562Asp	LP	Yes	3e-5
RP9	Late-onset RP, diagnosed 41 y	Consistent with RP	<i>PRPF31</i>	AD	Ho	c.1073+5G>A	Could affect splicing	LP	Yes	1.1e-4
RP10	Late-onset RP, diagnosed about 30 y	Consistent with RP	<i>PRPF31</i>	AD	Ho	c.1073+5G>A	Could affect splicing	LP	Yes	1.1e-4
RP11	Early-onset RP	Consistent with RP	<i>RHO</i>	AD	Ht	c.1040C>T	p.Pro347Leu	P	Yes	3e-5
RP12	Early-onset RP, symptoms about 20 y	Consistent with RP	<i>RLBP1</i>	AR	Ht	c.677T>A	p.Met226Lys	P	Yes	3e-5
			<i>RLBP1</i>	AR	Ht	c.832C>T	p.Gln278 [*]	P	No	N/A
RP13	Early-onset RP, symptoms about 20 y	Consistent with RP	<i>RLBP1</i>	AR	Ht	c.677T>A	p.Met226Lys	P	Yes	3e-5
			<i>RLBP1</i>	AR	Ht	c.832C>T	p.Gln278 [*]	P	No	N/A
RP14	RP, onset of symptoms at 20-30 y	N/A	<i>RLBP1</i>	AR	Ht	c.677T>A	p.Met226Lys	P	Yes	3e-5
			<i>RLBP1</i>	AR	Ht	c.832C>T	p.Gln278 [*]	P	No	N/A
RP15	Early-onset RP, diagnosed 24 y	Consistent with RP	<i>RLBP1</i>	AR	Ho	c.832C>T	p.Gln278 [*]	P	No	N/A
RP16	RP, diagnosed 27 y	N/A	<i>RP1</i>	AR	Ho	c.491C>G	p.Pro164Arg	VUS	Yes	N/A
RP17	RP, diagnosed 20 y	N/A	<i>RPE65</i>	AR	Ht	c.1409C>G	p.Pro470Arg	LP [~]	No	N/A
			<i>PRPF8</i>	AD	Ht	c.37C>G	p.Pro13Ala	VUS	Yes	N/A

Note: The additional sign “~” indicates that the association of the genetic variant with patient's disease is unclear. ^{§§} Variant reported in ClinVar, ^{¶¶} Allele frequency reported in gnomAD.

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; CAR, cancer-associated retinopathy; ERG, electroretinogram; *EYS*, NM_001292009.1; Hemiz, hemizygous; Heteropl, heteroplasmic; *HGSNAT*, NM_152419.2; *HK1*, NM_000188.2; Ho, homozygous; Homopl, homoplasmic; Ht, heterozygous; *IFT172*, NM_015662.2; Inh, inheritance; LP, likely pathogenic; MAR, melanoma-associated retinopathy; Mito-inh, mitochondrial inheritance; N/A, not available; *OTX2*, NM_001270525.1; P, pathogenic; *PDE6A*, NM_000440.2; *PDE6B*, NM_000283.3; *PRPF31*, NM_015629.3; *PRPF8*, NM_006445.3; RF, risk factor; *RHO*, NM_000539.3; *RLBP1*, NM_000326.4; RP, retinitis pigmentosa; *RP1*, NM_006269.1; *RPE65*, NM_000329.2; VUS, variant of unknown significance; XL-D, X-linked dominant; XL-R, X-linked recessive.

variant was identified that causes AR disease, a variant of unknown significance (VUS) was identified that causes AD disease, a VUS was identified that causes X-linked disease among males, and a VUS identified in mitochondrial DNA. No identified genetic cause was defined if there were no identified VUS or P/LP variants, if only a single heterozygous VUS was identified in AR disease, and if

there were VUS identified in a disease gene that did not match the patient's phenotype.

Variants excluded from the tables were single heterozygous VUS for AR diseases unless another P/LP variant, or VUS was identified also in the same gene. Variants with a higher allele frequency than 1% were not reported in the tables except in case of a well-known risk factor.

TABLE 2 Overview of variants in the *ABCA4*^A gene in patients with Stargardt disease

Patient	Phenotype	ERG	Exon/ Intron	Genotype	Genetic Variant	Protein/ RNA splicing	Class	ClinVar ^{§§}	gnomAD ^{¶¶}
SD1	SD, diagnosed 6 y	N/A	5	Ht	c.634C>T	p.Arg212Cys	P	Yes	6e-5
			16	Ht	c.2537A>T	p.Asp846Val	LP	Yes	N/A
SD2	SD, diagnosed 70 y	Consistent with SD	6	Ht	c.768G>T	p.Val256Val	P	Yes	9e-5
			13	Ht	c.1964T>G	p.Phe655Cys	P	Yes	N/A
SD3	SD, congenital visual impairment, diagnosed 6 y	N/A	6	Ht	c.768G>T	p.Val256Val	P	Yes	9e-5
			16	Ht	c.2537A>T	p.Asp846Val	LP	Yes	N/A
SD4	SD, symptoms 35 y, also hearing impairment	Delayed signal conduction in the optic nerve or radiation	6	Ht	c.768G>T	p.Val256Val	P	Yes	9e-5
			40	Ht	c.5693G>A	p.Arg1898His	VUS	Yes	1.56e-3
SD5	SD, symptoms 46 y	Non-typical SD, mild functional changes in macula	6	Ht	c.768G>T	p.Val256Val	P	Yes	9e-5
			43	Ht	c.6089G>A	p.Arg2030Gln	P	Yes	3.5e-4
SD6	SD, symptoms about 50 y	Consistent with SD, flat pattern ERG	6	Ht	c.768G>T	p.Val256Val	P [†]	Yes	9e-5
SD7	SD, diagnosed 49 y	Consistent with SD, flat pattern ERG	6	Ht	c.768G>T	p.Val256Val	P [†]	Yes	9e-5
SD8	SD, diagnosed 13 y	N/A	11	Ho	c.1622T>C	p.Leu541Pro	p	Yes	1.5e-4
			20	Ho	c.3113C>T	p.Ala1038Val	P	Yes	2.36e-3
SD9	SD, symptoms 40 y, slowly progressing	Consistent with SD	27	Ht	c.4179del	p.Ile1394Serfs*10	LP	No	N/A
			39	Ht	c.5603A>T	p.Asn1868Ile	RF	Yes	0.04255
SD10	SD, diagnosed 47 y	Consistent with SD	36	Ht	c.5196 +1137G>A	Affects introns, enhances splice site	P	Yes	9.56e-5
			38	Ht	c.5461-10T>C	Affects introns	P		2.20e-4

Note: ^AInheritance pattern is autosomal recessive.

Abbreviations: *ABCA4*, NM_000350.2; AD, autosomal dominant; AR, autosomal recessive; CAR, cancer-associated retinopathy; ERG, electroretinogram; *EYS*, NM_001292009.1; Hemiz, hemizygous; Heteropl, heteroplasmic; *HGSNAT*, NM_152419.2; *HK1*, NM_000188.2; Ho, homozygous; Homopl, homoplasmic; Ht, heterozygous; *IFT172*, NM_015662.2; Inh, inheritance; LP, likely pathogenic; MAR, melanoma-associated retinopathy; Mito-inh, mitochondrial inheritance; N/A, not available; *OTX2*, NM_001270525.1; P, pathogenic; *PDE6A*, NM_000440.2; *PDE6B*, NM_000283.3; *PRPF31*, NM_015629.3; *PRPF8*, NM_006445.3; RF, risk factor; *RHO*, NM_000539.3; *RLBP1*, NM_000326.4; RP, retinitis pigmentosa; *RP1*, NM_006269.1; *RPE65*, NM_000329.2; SD, Stargardt disease; VUS, variant of unknown significance; XL-D, X-linked dominant; XL-R, X-linked recessive.

2.4 | Informatics and analysis

The standard protocol at the GMM for genetic testing for IRD patients is comprehensive retinal dystrophy panel sequencing in a leading clinical laboratory with an increasing number of genes tested over time. Lately, testing has been based on in silico extraction from whole-exome sequencing data and dup/del evaluation using data from next-generation sequencing. Specific testing for structural variants was not done. Co-segregation analysis and de novo testing were recommended and done on accessible relatives.

To determine the significance of genetic variants, we used the Alamut Visual v.2.14 software (<https://www.interactive-biosoftware.com/alamut-visual/>), VarSome,¹⁴ Human Genome Mutation Database (HGMD) Professional 2020.1,¹⁵ Genome Aggregation Database (gnomAD),¹⁶ and ClinVar.¹⁷ The Online Mendelian Inheritance in Man (OMIM)¹⁸ database was used to obtain information about disease genes and their associated phenotypes. The American College of Medical Genetics and Genomics (ACMG) and The Association for Molecular Pathology (AMP) guidelines¹⁹ were used to classify genetic variants. Information about the most recent population count on January 1, 2020, was obtained from the Institution of Statistics

in Iceland.¹¹ A confidence level of 95% was used to estimate confidence intervals (CI) for prevalence calculations. The Icelandic Genealogical Database²⁰ was used to determine if patients were related.

2.5 | Permission

This study was granted permission by the National Bioethics Committee in Iceland (NBC). Reference number 20-012-V1. Patients' personal information was treated in concordance with the regulation from the Data Protection Authority in Iceland.

3 | RESULTS

Overall, 140 IRD patients were identified, of which 1 was deceased, yielding a point prevalence in Iceland of 1/2.600 (CI: 1/3.100–1/2.250). Of those 70 patients, in 58 families, had undergone a genetic evaluation. No additional patients with a genetic evaluation were ascertained when the ICD10 lists and the list from the BIAVI were reviewed. These additional searches were done to confirm that

TABLE 3 Overview of LHON patients

Patient	Phenotype	ERG	Gene	Inh	Genotype	Genetic Variant	Protein/ RNA splicing	Class	ClinVar ^{§§}	gnomAD ^{¶¶}
LHON1	LHON, onset of vision loss 18 y, completely blind 19 y	Consistent with LHON	<i>MT-ND1</i>	Mito-inh	Homopl	m.3460G>A	p.Ala52Thr	P	Yes	1.77e-5
LHON2	LHON, symptoms 23 y	N/A	<i>MT-ND1</i>	Mito-inh	Homopl	m.3460G>A	p.Ala52Thr	P	Yes	1.77e-5
LHON3	LHON, symptoms 46 y	Signals from macula to visual cortex impaired	<i>MT-ND1</i>	Mito-inh	Homopl	m.3460G>A	p.Ala52Thr	P	Yes	1.77e-5
LHON4	LHON, legally blind, still has scotopic vision	N/A	<i>MT-ND1</i>	Mito-inh	Homopl	m.3460G>A	p.Ala52Thr	P	Yes	1.77e-5
LHON5	Progressively worsening vision in left eye, optic neuritis	N/A	<i>MT-CYB</i>	Mito-inh	Homopl	m.15446C>T	p.Leu234Phe	VUS	Yes	1.77e-5

Note: ^{§§} Variant reported in ClinVar, ^{¶¶} Allele frequency reported in gnomAD.

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; CAR, cancer-associated retinopathy; ERG, electroretinogram; EYS, NM_001292009.1; Hemiz, hemizygous; Heteropl, heteroplasmic; HGSNAT, NM_152419.2; HK1, NM_000188.2; Ho, homozygous; Homopl, homoplasmic; Ht, heterozygous; IFT172, NM_015662.2; Inh, inheritance; LP, likely pathogenic; MAR, melanoma-associated retinopathy; Mito-inh, mitochondrial inheritance; N/A, not available; OTX2, NM_001270525.1; LHON, Leber hereditary optic neuropathy; *MT-CYB*, YP_003024038.1; *MT-ND1*, YP_003024026; P, pathogenic; *PDE6A*, NM_000440.2; *PDE6B*, NM_000283.3; *PRPF31*, NM_015629.3; *PRPF8*, NM_006445.3; RF, risk factor; *RHO*, NM_000539.3; *RLBP1*, NM_000326.4; RP, retinitis pigmentosa; *RP1*, NM_006269.1; *RPE65*, NM_000329.2; VUS, variant of unknown significance; XL-D, X-linked dominant; XL-R, X-linked recessive.

TABLE 4 Overview of patients with Usher syndrome

Patient	Phenotype	ERG	Gene	Inh	Genotype	Genetic Variant	Protein/ RNA splicing	Class	ClinVar ^{§§}	gnomAD ^{¶¶}
US1	USH2C, congenital hearing impairment vision loss 12 y	N/A	ADGRV1	AR	Ho	c.9140T>G	p.Leu3047 [*]	P	No	N/A
US2	USH2A, hearing impairment 3-4 y, RP about 25 y	Consistent with RP	USH2A	AR	Ht	c.5907C>G	p.Tyr1969 [*]	P	No	N/A
			USH2A	AR	Ht	c.11867C>G	p.Ser3956 [*]	P	Yes	N/A
US3	USH2A, congenital hearing impairment RP diagnosis about 40 y	Consistent with RP	USH2A	AR	Ht	c.13316C>T	p.Thr4439Ile	P	Yes	2e-5
			USH2A	AR	Ht	c.10601A>G	p.Tyr3534Cys	LP	No	N/A
			USH2A	AR	Ht	c.10564A>G	p.Arg3522Gly	VUS	Yes	2.5e-4
US4	USH2A, hearing impairment at adolescence, RP symptoms about 20 y	Consistent with RP	USH2A	AR	Ht	c.13316C>T	p.Thr4439Ile	P	Yes	2e-5
			USH2A	AR	Ht	c.10601A>G	p.Tyr3534Cys	LP	No	N/A
			USH2A	AR	Ht	c.10564A>G	p.Arg3522Gly	VUS	Yes	2.5e-4

Note: ^{§§} Variant reported in ClinVar, ^{¶¶} Allele frequency reported in gnomAD.

Abbreviations: ABCA4, NM_000350.2; AD, autosomal dominant; AR, autosomal recessive; CAR, cancer-associated retinopathy; ERG, electroretinogram; EYS, NM_001292009.1; Hemiz, hemizygous; Heteropl, heteroplasmic; HGSNAT, NM_152419.2; HK1, NM_000188.2; Ho, homozygous; Homopl, homoplasmic; Ht, heterozygous; IFT172, NM_015662.2; Inh, inheritance; LP, likely pathogenic; MAR, melanoma-associated retinopathy; Mito-inh, mitochondrial inheritance; N/A, not available; OTX2, NM_001270525.1; P, pathogenic; PDE6A, NM_000440.2; PDE6B, NM_000283.3; PRPF31, NM_015629.3; PRPF8, NM_006445.3; RF, risk factor; RHO, NM_000539.3; RLBP1, NM_000326.4; RP, retinitis pigmentosa; RP1, NM_006269.1; RPE65, NM_000329.2; SD, Stargardt disease; USH2A, Usher Syndrome Type 2A; USH2C, Usher Syndrome Type 2C; ADGRV1: NM_032119.3; USH2A: NM_206933.2; VUS, variant of unknown significance; XL-D, X-linked dominant; XL-R, X-linked recessive.

no IRD patient had been missed after the search at the GMM and after reviewing the Electrophysiology registry. GMM, Electrophysiology at the Department of Ophthalmology, the Center, and BIAVI are the only institutions in Iceland that provide these types of services, thus suggesting a very high ascertainment. The number of family members tested at the GMM was 45, and the number of patients at the GMM that have not yet undergone a genetic evaluation was 5.

The genetic tests were done from 2004 to October 2020. Most patients were tested between 2015 and 2020. The number of different IRD diseases registered at the GMM was 20. Non-syndromic RP was the most common diagnosis, followed by Stargardt disease, Leber hereditary optic neuropathy (LHON), X-linked retinoschisis, and Usher syndrome.

3.1 | Non-syndromic RP

Sixty-three alive patients had RP, yielding a point prevalence of 1/5.800 (CI: 1/7.700–1/4.650). Nineteen had undergone a genetic evaluation, of which 13 had a genetic cause for their disease

(Table 1), five had an unclear result, and one had no identified genetic cause. The number of disease genes found in patients with RP was 13. Variants in the *RLBP1* gene was most common ($n = 4$). The most common variant in the *RLBP1* gene was c.832C > T, found once in a homozygous state and three times in a heterozygous state. The second most common variant in the *RLBP1* gene was c.677 T > A, found three times in a heterozygous state with the c.832C > T variant. Patients RP9 and RP10 had the same genetic variant in a homozygous state, NM_015629.3(*PRPF31*):c.1073 + 5G > A. According to ACMG/AMP guidelines, this variant was reclassified by the GMM as likely pathogenic (ACMG/AMP score: PS4, PM2, PP1, PP3). Patients RP9 and RP10 were not related. Patient RP3 had the genetic variant NM_152419.2 (*HGSNAT*): c.1843G > A:(p.Ala615Thr) in a homozygous state and patient RP17 had the genetic variant NM_000329.2 (*RPE65*):c.1409C > G:(p.Pro470Arg) in a heterozygous state. These genetic variants were reclassified as likely pathogenic (ACMG/AMP score for (*HGSNAT*): c.1843G > A: PS4, PP2, PP3) (ACMG/AMP score for (*RPE65*): c.1409C > G: PM1, PM2, PM5, PP2, PP3). Patients with an unclear result in Table 1 were RP1, RP5, RP16, and RP17.

TABLE 5 Overview of patients with other IRD

Patient ^a	Phenotype	ERG	Gene	Inh	Genotype	Genetic Variant	Protein/ RNA splicing	Class	ClinVar ^b	gnomAD
A1	Tunnel vision on left eye, progressively worsening vision at 22 y	Degeneration of photoreceptors in left eye. Right eye normal	CNGB3	AR	Ht	c.1148del	p.Thr383Ilefs*13	P ⁻	Yes	1.99e-3
AgS1	Increased pressure on optic nerve	N/A	JAG1	AD	Ht	del20p12.1-p12.2	-	P	No	N/A
AS1	Visual impairment, nystagmus, and cone-rod dystrophy	Consistent with Alström sx.	ALMS1	AR	Ho	c.7542G>A	p.Trp2514 [*]	P	No	N/A
AS2	Visual impairment, nystagmus, and cone-rod dystrophy	Consistent with Alström sx.	ALMS1	AR	Ho	c.7548G>A	p.Trp2516 [*]	LP	No	N/A
BBS1	RP, mental deficiency, and obesity	N/A	BBS1	AR	Ht	c.1169T>G	p.Met390Arg	P ⁻	Yes	2.05e-3
BD1	Visual impairment 5 y, diagnosed with retinal degeneration 8 y	ERG flat except during 30 Hz flicker	CLN3	AR	Ht	1.02-kb del	-	P	No	N/A
CHM1	Early-onset RP, diagnosed 8 y	Consistent with RP	CLN3	AR	Ht	c.944_945dupA	p.Hys315Glnfs*381	P	No	N/A
CHM2	Early-onset RP, visual impairment 8 y, whole fundus pigmented	Consistent with RP	CHM	XL-D	Hemiz	c.476delC	p.Pro159Glnfs*9	LP	No	N/A
CMT1	CMT with optic nerve changes	Normal ERG but flat flash VEP	MFN2	AD	Ht	c.310C>T	p.Arg104Trp	P	Yes	N/A
CRD1	Photophobia about 20 y then progressively worsening of vision	Maculopathy, conduction in optic nerves impaired	TTL5	AR	Ht	c.94T>A	p.Trp32Arg	VUS ⁻	No	N/A
CSNB	Nystagmus, visual impairment, and hyperopia	Flat ERG	TTL5	AR	Ht	c.143C>A	p.Ala48Asp	VUS ⁻	No	N/A
XLCSNB1	Congenital nystagmus, visual impairment, and myopia	Consistent with „incomplete type“ of XLCSNB	TTL5	AR	Ht	c.625C>T	p.Arg209Cys	VUS ⁻	No	N/A
XLCSNB2	Reduced visual acuity	Consistent with „incomplete type“ of XLCSNB	CABP4	AR	Ho	c.366+1G>T	Affects splicing	LP	No	1.31e-5
XLCSNB3	Nystagmus in childhood. Color blind, retinal degeneration	N/A	CACNA1F	XL-R	Hemiz	c.1685-1G>C	Disrupts acceptor splice site	LP	No	N/A
LCA1	Congenital blindness. Senior-Loken sx	N/A	CACNA1F	XL-R	Hemiz	c.1685-1G>C	Disrupts acceptor splice site	LP	No	N/A
LCA2	Congenital nystagmus, fundus changes detected about 1 y	Consistent with RP and related diseases	CEP290	AR	Ht	c.774insT	p.Asn250fs	P ⁻	No	N/A
OA1	Atrophy of the optic nerve. Reduced visual acuity from 24 y	Normal ERG	TULP1	AR	Ho	c.1560C>A	p.Tyr520 [*]	P	No	6.57e-6
			OPA1	AD	Ht	c.2334G>A	p.Trp778 [*]	P	Yes	N/A

TABLE 5 (Continued)

Patient ^a	Phenotype	ERG	Gene	Inh	Genotype	Genetic Variant	Protein/ RNA splicing	Class	ClinVar ^{b,c}	gnomAD ^d
PE1	Skin rash and fundus changes	N/A	ABCC6	AR	Ho	c.3419G>A	p.Arg1138Gln	P	Yes	8e-5
S1	Visual impairment 23 y due to retina detachment. Myopia. Hypermobility in joints.	N/A	COL11A1	AD	Ht	c.5274G>A	p.Ala1758Ala	VUS	No	N/A

Note: ^a A: Achromatopsia, AgS: Alagille Syndrome, AS: Alström Syndrome, BSS: Bardet-Biedl Syndrome, BD: Batten Disease, CHM: Choroideremia, CMT: Charcot-Marie-Tooth disease, CRD1: Cone-Rod Dystrophy, CSNB: Congenital Stationary Night Blindness, XLCSNB: X-linked Congenital Stationary Night Blindness, LCA: Leber Congenital Amaurosis, OA: Optic Atrophy, PE: Pseudoxanthoma Elasticum, S: Stickler syndrome, ^{b,c}Variant reported in ClinVar, ^dAllele frequency reported in gnomAD. Abbreviations: ABCC6, NM_001171.5; AD, autosomal dominant; ALMS1, NM_015120.4; AR, autosomal recessive; BBS1, NM_024649.5; CACNA1F, NM_005183.2; CABP4, NM_145200.3; CAR, cancer-associated retinopathy; CEP290, NM_025114.4; CHM, NM_000390.3; CLN3, NM_001042432.1; CNGB3, NM_019098.4; COL11A1, NM_001854.3; ERG, electroretinogram; EYS, NM_001292009.1; Hemiz, hemizygous; Heteropl, heteroplasmic; HGSNAT, NM_152419.2; HK1, NM_000188.2; Ho, homozygous; Homopl, homoplasmic; Ht, heterozygous; IFT172, NM_015662.2; Inh, inheritance; JAG1, NM_000214.2; LP, likely pathogenic; MAR, melanoma-associated retinopathy; MFN2, NM_014874.3; Mito-inh, mitochondrial inheritance; N/A, not available; OPA1, NM_015560.2; OTX2, NM_001270525.1; P, pathogenic; PDE6A, NM_000440.2; PDE6B, NM_000283.3; PRPF31, NM_015629.3; PRPF8, NM_006445.3; RF, risk factor; RHO, NM_000539.3; RLBP1, NM_000326.4; RP, retinitis pigmentosa; RPI, NM_006269.1; RPE65, NM_000329.2; TLL5, NM_015072.5; TULP1, NM_003322.6; VUS, variant of unknown significance; XL-D, X-linked dominant; XL-R, X-linked recessive.

3.2 | Stargardt disease

Twenty-one alive patients had Stargardt disease, yielding a point prevalence of 1/17.000 (CI: 1/30.000–1/12.000). Eleven had undergone a genetic evaluation, of which seven had a genetic cause, but four had an unclear result. Three had only one genetic variant, patients SD6 and SD7 in Table 2. The third patient had a VUS. The most common variants in the *ABCA4* gene were missense variants ($n = 9$, pathogenic $n = 7$), variants that affect splicing ($n = 3$), which were both pathogenic, and a deletion ($n = 1$), which was pathogenic. The most common variant was c.768G > T. That variant was found six times, every time in a heterozygous state, four times with another variant, and two times where it was the only variant that was found (Table 2).

3.3 | Leber hereditary optic neuropathy

Six alive patients had LHON disease, yielding a point prevalence of 1/60.000 (CI: 1/304.000–1/34.000). Four patients had a genetic cause (Table 3). All had the same pathogenic variant, m.3460G > A: (p.Ala52Thr) in the *MT-ND1* gene, which is one of three most common genetic variants in LHON worldwide.²¹ The patients with this pathogenic variant were all related. One patient, LHON5 (Table 3), had a variant of unknown significance in the *MT-CYB* gene. One patient had a clinical diagnosis of the disease but no identified genetic cause.

3.4 | X-linked retinoschisis

Thirteen alive patients had XLRS, yielding a point prevalence of 1/28.000 (CI: 1/61.000–1/18.000). Of those 13 patients, five had undergone a genetic evaluation. These patients belonged to three families, where two families had a common ancestor in the 19th century. The patient that belonged to the third family was not related to the other two families. Every patient that underwent a genetic evaluation had the same genetic variant on the X chromosome, c.441G > A: (p.Trp147X) in the *RS1* gene.

3.5 | Usher syndrome

Nine alive patients had Usher syndrome, yielding a point prevalence of 1/40.000 (CI: 1/117.000–1/24.00). Of those nine patients, four had undergone a genetic evaluation. Three patients had the USH2A phenotype and variants in the *USH2A* gene (Table 4). Of those three, two patients, US3 and US4, had a variant of unknown significance, the variant NM_206933.2(*USH2A*):c.10601A > G:(p.Tyr3534Cys). The variant was reclassified as a likely pathogenic variant according to ACMG/AMP guidelines (ACMG/AMP score: PM1, PM2, PM3, PP2, PP3). One patient had the USH2C phenotype and variants in the *ADGRV1* gene (Table 4).

3.6 | Other IRDs

Twenty-four patients had 15 other IRDs diseases and a genetic evaluation. Of those 24 patients, 14 had a genetic cause, five had an unclear result, and five had no identified cause (Table 5). Two patients had choroideremia but had been previously diagnosed with RP. Three patients had X-linked congenital stationary night blindness (XLCSNB) and had the same hemizygous variant, NM_005183.2 (*CACNA1F*): c.1685-1G > C. These patients with XLCSNB were all related.

4 | DISCUSSION

In this study, we delineated the genetic causes of IRDs in Icelandic patients by summarizing their genetic evaluation results. Our results showed that out of 70 patients that had undergone a genetic evaluation, about two-thirds had an identified genetic cause, similar to the proportion reported worldwide.^{1,2,8} The prevalence of IRDs in Iceland is about 1/2,600, also similar to the reported world prevalence.⁶

The prevalence of RP is estimated to be about 1/5,800 in Iceland, which is similar to reported world prevalence, 1/4,000.^{22,23} However, previous studies have reported that the average prevalence in American and European populations is 1/5,260.²⁴ In contrast, prevalence has been reported as high as 1/2,000 in Västernorrland county in Northern Sweden.²⁵ A total of 13 disease genes were found in Icelandic patients, and the most common disease gene was *RLBP1* ($n = 4$). A Norwegian study reported a total of 23 different disease genes in 468 RP patients, and among them was the *RLBP1* gene ($n = 2$). The variant c.677 T > A in the *RLBP1* gene was also reported in Norwegian patients, both in a heterozygous and homozygous form.²⁶ The c.832C > T variant has been reported exclusively in the European population.²⁷ The variant c.677 T > A has also exclusively been reported in the European population with allele frequency even higher than the c.832C > T variant.²⁷ A Danish study reported a total of 32 disease genes in 294 RP patients, among them was the *RLBP1* gene ($n = 2$). However, the most common gene in Danish patients was *USH2A* ($n = 41$),²⁸ the most common disease gene in AR RP worldwide.²³ An Irish study reported that the most common disease gene in Irish patients with RP was *RHO*,²⁹ which is also the most common in AD RP worldwide.²³ A Japanese study reported that the most common disease gene in Japanese patients with RP is *EYS*,³⁰ which is also common in Chinese and Spanish patients.³¹

Patients RP9 and RP10 were homozygous for the same genetic variant NM_015629.3 (*PRPF31*): c.1073 + 5G > A. This variant has been reported in Danish patients with RP, in a heterozygous state with a different VUS.²⁸ Alamut Visual v.2.14 predicts that this variant affects splicing of the mRNA transcript. The allele frequency of this variant worldwide is low, about 0.011%, according to gnomAD. Interestingly, the allele frequency of this variant in the Icelandic population is substantially higher, about 0.24% (Patrick Sulem, personal communication). The estimated number of heterozygotes in Iceland for this variant is about 1,750. However, pathogenic variants in the *PRPF31*

gene cause AD RP (OMIM: 606419). A co-segregation analysis had been performed on patient's RP10 unaffected siblings, a total of six. Five were heterozygous for the variant, and one was not a carrier, consistent with an AR inheritance pattern. We assume that this variant causes AR RP because of a hypomorphic allele effect and was accounted for in the ACMG/AMP classification. However, this is a hypothesis not corroborated by experimental data. Blueprint Genetics has previously reported finding three patients with RP and homozygous for the c. 1073 + 5G > A. Another splicing variant c.855 + 3G > C is also assumed to cause AR RP.³²

Patient RP17 had a heterozygous VUS in the *PRPF8* gene, which causes AD RP (OMIM: 607300), and a newly reclassified LP c.1409C > G variant in the *RPE65* gene, which causes AR RP (OMIM: 180069). The variant in the *PRPF8* gene was the most rational choice for a possible genetic cause. However, there have been reports of a genetic variant in the *RPE65* gene causing AD RP, the variant c.1430G > A (p. Asp477Gly).³³⁻³⁵ In 2005, Takahashi et al. showed that if the glutamic acid positioned at 469 in RPE65 protein was substituted with alanine or glutamine, then the enzymatic activity was reduced.³⁶ However, the patient's RP17 family history and disease pattern do not support a dominant disease. Yet, there have been reports that dominant variant expressions in the *RPE65* gene can vary between individuals, from non-penetrance to severe, resembling choroideremia.³⁷

Patient RP3 was homozygous for the variant c.1843G > A (p. Ala615Thr) in the *HGSNAT* gene, which was reclassified as likely pathogenic by us. This variant has been described by Schiff et al. in a homozygous state in patients with late-onset RP, but with incomplete penetrance.³⁸ Presumably, unidentified factors affect penetrance for the disease in these patients.

Patient RP1 was heterozygous for a pathogenic variant in the *EYS* gene and three different variants of unknown significance in the *PROM1*, *ABCA4*, and *PDE6B* genes (not in Table 1), all known to cause recessive RP (OMIM: 604365; 601691; 180072). However, digenic inheritance in the *EYS* gene and *CDH23* gene has been reported in a patient with RP and a mild hearing impairment.²⁸ Since digenic inheritance has been described,⁹ one or more VUSs in patient RP1 could possibly augment the pathogenic effect of the variant in *EYS*, resulting in RP phenotype.

The most common genetic variants in the *ABCA4* gene in Stargardt disease were missense variants, about 70% (54% if only pathogenic and likely pathogenic variants were considered). This proportion, 70%, is similar to what has been reported worldwide.³⁹ The most common variant was c.768G > T, a variant also common in Danish, Dutch, Norwegian, and Swedish patients.^{26,28,40,41}

Three patients had only one identified variant in the *ABCA4* gene, which is similar to the proportion found worldwide.³⁹ Patients SD6 and SD7 were both heterozygous for the c.768G > T variant. They had in common that their symptoms started at about 50 years of age and their pattern ERG was flat. Multiple studies have suggested an association between being heterozygous for only one variant in the *ABCA4* gene and developing age-related macular degeneration.⁴²⁻⁴⁴ In 2015, Kjellström reported that individuals who were heterozygous for

the c.768G > T variant had signs of degeneration in the macula.⁴¹ However, in our study, one individual was heterozygous for the c.768G > T variant, but did not have any ocular-related medical problems that could be discerned from his medical records. That individual underwent a genetic evaluation to determine the significance of genetic variants found in his family member. Also, patient SD2 was heterozygous for the c.768G > T variant and the pathogenic missense variant c.1964 T > G, and his symptoms were late-onset, at 70 years of age. Thus, there is probably an unidentified variant in patients SD6 and SD7.

Patient SD9 was heterozygous for a pathogenic variant and the c.5603A > T variant, which is considered a risk factor if it is in *trans* with a pathogenic variant in *ABCA4* gene.⁴⁵ However, it has been reported that penetrance of Stargardt disease is low in patients carrying this variant in *trans*.⁴⁶

Every patient with XLRS, which underwent a genetic evaluation, had the same variant, NM_000330.3 (*RS1*): c.441G > A: (p.Trp147*), also known as p.W147X. This alteration leads presumably to nonsense-mediated mRNA decay. This variant was not in HGMD, ClinVar, nor gnomAD databases. We assume this variant to be a unique Icelandic variant. This is an example of the benefits of studying the genetics of IRDs in a small population and a genetic isolate. These patients could be potential candidates for future variant-specific molecular therapy trials for XLRS, eliminating possible variability due to genetic causation.

The most common disease genes in patients with Usher syndrome was *USH2A* ($n = 3$). A Danish study reported that *USH2A* is also the most common disease gene in Danish patients with Usher syndrome ($n = 2$).²⁸ However, variants found in the Icelandic patients were not found in Danish patients²⁸ nor in Norwegian patients.²⁶ The variant c.13316C > T in the *USH2A* gene has been described exclusively in the European population.²⁷ The *USH2A* gene is also the most common disease gene in Irish patients with Usher syndrome.²⁹

4.1 | Limitations

World prevalence of Stargardt disease, Leber hereditary optic neuropathy, X-linked retinoschisis, and Usher syndrome is 1/8,000–1/10,000,⁴⁷ 1/27,000–1/45,000,²¹ 1/5,000–1/20,000,^{48,49} and 1/6,000,⁵⁰ respectively. The study's calculated prevalence of these diseases was lower. Four reasons could explain that. First, the ascertainment was incomplete. However, the list of patients in the various registries combined should closely reflect the number of patients in Iceland. Second, these diseases could in reality be rarer in Iceland because of a founder effect or a genetic drift enhanced by the small population size and genetic isolation. Third, a misdiagnosis is possible, but not likely, since the healthcare services, clinical workup, and supervision of these patients are considered to be among the best in the world.⁵¹ Fourth, the study's calculated prevalence could be a statistical coincidence, considering Iceland's small population compared to other studies reporting prevalence in larger populations.

The clinical parameters of the study sample do not suggest that there was significant bias in what proportion of IRD patients have undergone a genetic evaluation. About half of patients in every disease category of IRDs have undergone a genetic evaluation. However, an ascertainment bias is possible regarding the age of patients having had a genetic evaluation. New patients, including children, have in recent years been referred for a genetic evaluation by an ophthalmologist. Middle-aged patients often undergo a genetic evaluation because of concern for their children's risk. Other groups, that is, stable young adults and the elderly, are probably somewhat underrepresented in the genetic evaluation group.

A major limitation of the study is that the genetic evaluations were performed over a long period, about 16 years. Over the period of the genetic evaluation in the study, the number of genes tested were increased, and dup/del testing was introduced. Methods, technology, and the knowledge needed to accurately diagnose these patients have become progressively advanced. The major limitations of genetic tests today are that they do not diagnose variants in regulatory regions, deep intron sequence, and structural variants. When genetic tests for these variants become clinically available, it might be possible to delineate the genetics of patients with unclear results or no identified genetic cause.

5 | CONCLUSIONS

IRDs in Iceland are a complex group of diseases with a heterogeneous and unique genetic pattern, which could be explained by a founder effect and a genetic drift. This contribution from a small genetically isolated nation improves the world's knowledge of the molecular genetics of IRDs. Because of our small population size, we could reclassify two variants as likely pathogenic and therefore provide a genetic cause for four patients. Our findings suggest that the variant c.1073 + 5G > A in the *PRPF31* gene possibly causes AR RP, and the allele frequency is substantially higher in the Icelandic population compared to the world. The variant c.441G > A in XLRS patients is likely a unique Icelandic variant and was found in every genetically tested XLRS patient. The potential benefit of defining a patient population with the same pathogenic variant is that they could become candidates for future molecular therapy trials.

ACKNOWLEDGEMENTS

Blindrafelagid, the Icelandic Association of the Visually Impaired, for encouraging and funding this project. The Icelandic National Institute for the Blind, Visually Impaired, and Deafblind for information on the number of IRD patients. The staff in the Department of Genetics and Molecular Medicine, for aiding in data collection and the use of the Icelandic Genealogical Database. Dr. Patrick Sulem at deCode Genetics, for providing information on allele frequencies.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHORS' CONTRIBUTIONS

Planning: Daniel A. Thorsteinsson, Jon J. Jonsson. Collection of data: Daniel A. Thorsteinsson. Result interpretation: Daniel A. Thorsteinsson, Thor Eysteinnsson, Jon J. Jonsson. Writing the manuscript: Daniel A. Thorsteinsson, Jon J. Jonsson. Critical revision of the manuscript: All authors.

DATA AVAILABILITY STATEMENT

Results of Alamut v.2.14 and Varsome analyses and ACMG/AMP classification are available upon request.

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How to cite this article: Thorsteinsson DA, Stefansdottir V, Eysteinnsson T, Thorisdottir S, Jonsson JJ. Molecular genetics of inherited retinal degenerations in Icelandic patients. *Clinical Genetics.* 2021;100:156-167. <https://doi.org/10.1111/cge.13967>