

ABOUT THE AUTHORS



ELISE HÉON, MD, FRCPC: Dr. Héon has been staff ophthalmologist at SickKids since 1996. Her career focusses on inherited eye disorders, now mostly on inherited retinal diseases. She directs the Ocular Genetics program providing comprehensive assessment, genetic testing and counseling of patients affected with inherited retinal disorders. She became Chief of Ophthalmology in 2003 when her laboratory was moved from the Toronto Western to SickKids Research Institute. She has trained numerous students of various academic levels from around the world. Dr. Héon's current research focusses on the genetic characterization of inherited retinal disorders when clinical genetic testing did not identify the disease-causing variant(s). Using Genome sequencing and sophisticated analytical protocol, her group has been successful in deciphering nearly 80% of cases. Dr. Héon has a specific interest in disease cause by genes affecting cilia, ciliopathy, namely Bardet Biedl syndrome. Using cells from patients and high throughput drug screening through the SPARC facility, her groups is trying to identify small molecules that may improve patient outcome. Lastly, Dr. Héon is exploring patient reported outcome measures (PROM) for IRD and especially in children, which would best represent the impact of the visual impairment on the patient daily living.



AJOY VINCENT MBBS, MS, FRCSC: Dr. Ajoy Vincent is trained in the field of Eye Genetics and Electrophysiology. He cares for patients with isolated and complex inherited retinal dystrophies (IRDs). He also serves as the Medical Director of Visual Electrophysiology Unit (VEU) at SickKids. He is actively involved in teaching Ophthalmology residents and fellows at SickKids. Dr. Vincent's research endeavors include discovering novel genes underlying inherited retinal dystrophies (IRDs), characterizing novel genotype-phenotype correlations in IRDs, uncovering disease pathways and mechanisms in IRDs, and conducting innovative pediatric clinical trials; all with the aim of improving patient outcomes.



ALAA TAYYIB, MD: Alaa Tayyib earned her Bachelor of Medicine and Surgery from King Abdulaziz University in Saudi Arabia, followed by her ophthalmology residency training at the Saudi Ophthalmology Residency Program. She is currently completing her clinical ocular genetics and inherited retinal diseases fellowship at the University of Toronto.

Genetics of retinal degeneration in 2023

Elise Héon¹ MD, FRCSC

Ajoy Vincent¹ MBBS, MS, FRCSC

Alaa Tayyib¹ MD

Affiliations:

1 SickKids Hospital, University of Toronto, Canada

Corresponding Author:

Dr. Elise Héon

Email: elise.heon@sickkids.ca

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Inherited retinal degenerations (IRDs) are of great interest with the development of novel therapies, thereby allowing this group of conditions to be “actionable” for the first time.

A molecular diagnosis can be obtained in nearly 70% of cases of IRD, with over 300 IRD-linked genes having been identified to date. Numerous animal models of different genetic subtypes of IRDs replicated the human phenotypes enough to develop and test novel therapies to improve outcomes for IRD patients.^{1,2} The first gene replacement therapy indicated for IRD, Luxturna (voretigene neparvovec-rzyl), was approved by Health Canada in October 2020 and is now available to patients with vision loss due to inherited retinal dystrophy caused by confirmed biallelic *RPE65* mutations. Clinicians from Ontario, Quebec and Alberta can now access this treatment through their province's public health plan.

This article aims to review some basic information and present new knowledge about IRDs to allow clinicians to better understand diagnosis and disease management

DIAGNOSIS

Inheritance

Autosomal recessive (AR) diseases usually affect only one generation unless there is consanguinity or the diseased-allele frequency in the population is unusually high. The latter is the case in Stargardt disease, which has an estimated incidence of 1 in 8,000–10,000 and a reported carrier frequency of 1 in 20.^{3,4,5} Parents who happen to both be carriers for a disease-causing gene variant have a 25% risk of having an affected child at each conception. The carriers of AR IRD usually do not manifest any signs or symptoms.

X-linked recessive diseases in principle affect men and are inherited through a female lineage. Occasionally, women can manifest signs and/or symptoms of the disease due to unfavourable inactivation of the X chromosome (lyonization). Examples of this include X-linked retinitis pigmentosa (RP), choroideremia, and X-linked ocular albinism.⁶ Most often, carriers of an X-linked retinoschisis variant do not show signs of the disease.

Autosomal dominant (AD) diseases affect both sexes, have variable expressivity and may show incomplete penetrance (skipped generation). AD is characterized by male-to-male transmission, when present. The risk of transmission of the genetic defect from an affected individual is 50% at each conception. Occasionally, an individual with an AR IRD can have an affected child if the other parent is a carrier of an AR variant in the same gene. This is referred to as pseudodominant inheritance and is seen more often in consanguineous populations.

It is necessary to assume a mode of inheritance to effectively interpret the results of genetic testing and to diagnose an IRD, whether you expect to find one or two variants. Specific mutations in approximately 10% of IRD-linked genes can be associated with AR or AD inheritance.

Mitochondrial diseases, which are mainly transmitted through the female to her offspring affect the retina in two distinct ways: retinal dystrophy and optic atrophy. The phenotypic manifestations of mitochondrial diseases are highly heterogenous and depend on the level of heteroplasmy (the amount of mutated mitochondrial DNA within the cell). This will not be reviewed further in this article.

Genotyping

Genetic testing aims to confirm a diagnosis and the inheritance pattern of a condition. It also guides in prognostication and determining eligibility for potential treatment or clinical trial enrolment. Patients with IRDs should be encouraged to seek genetic testing. Genetic testing requires a biological specimen (e.g. blood or saliva) and patient consent. The results must be interpreted in the context of the phenotype and when possible, with segregation analysis (testing of family members) to ensure only the affected individuals carry potential disease-causing variant(s). A diagnosis requires the integration of the phenotyping and genotyping information.

In Canada, genetic testing is supported by provincial health care, though there is an often-lengthy bureaucratic process to access it. Patients may choose to pay out-of-pocket or seek free genetic testing, however, in the case of free testing, data ownership resides with the testing company and genetic counselling is seldom offered by the companies. We recommend that all patients enter their genetic testing results in the National Fighting Blindness Canada patient registry (<https://www.fightingblindness.ca>), which allows patients to be contacted for the purpose of research or when new treatments become available.

Retinal Degeneration

IRDs are clinically and genetically heterogeneous conditions marked by progressive (though in some cases stationary) malfunction of retinal photoreceptors, retinal pigment epithelial cells, trans-synaptic signalling with bipolar cells, and/or the choriocapillaris complex. They usually present as bilateral and symmetrical. There are numerous classification systems for IRDs, with the most common based on the age of onset, the anatomical distribution of the disease, and/or the predominantly affected photoreceptor system (**Figure 1**). Detailed phenotyping is important, especially at the first visit, to guide the diagnosis and genetic testing. Documenting the natural history of change via yearly or bi-yearly follow-ups is also important to best understand the course of the condition. Based on the clinical understanding of the genotyping of IRDs, some conditions previously believed to be stationary, have shown progression when seen in follow up.

Phenotyping

Workup for a new IRD case often includes retinal electrophysiology tests, fundus imaging, fundus autofluorescence (FAF), optical coherence tomography (OCT), and some type of visual field test, depending on the condition. For a follow-up assessment of photoreceptor dysfunction, OCT and visual field tests are the most useful in determining progression. FAF is very useful for detecting progression of Stargardt disease and chorioretinal conditions, as the ring of autofluorescence often correlates to changes in the visual field and ellipsoid zone (EZ) line.⁷ The use of fundus photography should be limited on follow up visits as it is less informative as compared to other modalities. In addition, the use of intravenous fluorescein

angiogram (IVFA) testing is typically limited to vascular conditions.

The main elements to look for in phenotyping, are changes in a genotype-specific pattern, the type and cellular level of retinal degeneration, and complications (e.g. CME, macular hole, choroidal neovascular membrane, glaucoma, etc.).

Phenotyping tools

- a. **Visual acuity (VA):** Low-vision acuity charts may be used to quantify vision as much as possible. Near vision should also be assessed, as loss of eye accommodation typically presents early in the onset of IRDs.
- b. **Assessment of refractive errors:** Some phenotypes, such as congenital stationary night blindness (CSNB) and X-linked RP with myopia, are associated with specific refractive errors. Knowing the natural history of refractive errors in certain dystrophies can aid in management (e.g. using atropine eye drops to halt myopic progression).
- c. **Contrast sensitivity (CS):** CS is very useful in understanding subjective vision changes seen in early IRD.
- d. **Colour vision:** Colour vision assessments are useful in determining the degree of cone involvement.
- e. **Comprehensive eye exam:** Attention must be paid to the entire eye, as some retinal diseases may have anterior segment manifestations. Patients with some forms of Best disease are at risk of angle closure glaucoma. When posterior subcapsular cataracts are present, the field of vision must be taken into consideration.⁸ The diagnosis of glaucoma may be challenging in light of the pre-existing field changes but must be investigated.
- f. **Enhanced depth imaging optical coherence tomography (EDI-OCT):** the EDI-OCT is the most useful phenotyping tool as it can be used in the very young (4–5 years old) and the very visually impaired, even with nystagmus. In assessing the OCT for retinal degeneration, the key area of interest is the integrity of the outer retina, specifically the ellipsoid zone (the mitochondria-rich photoreceptor inner segments) and the outer nuclear layer (ONL) reflecting the photoreceptor nuclei. Central retinal thickness, maintenance or loss of lamination, and thickness of the inner retina and ganglion cells should also be assessed. EDI-OCT helps to evaluate the choriocapillaris and choroid-sclera junction, and hence it is used in disease grading. North Carolina macular dystrophy is a good example, where macular coloboma-like excavation (grade 3) presents with absent RPE and choriocapillaris and deep chorioretinal posterior bowing. EDI-OCT can also be used to

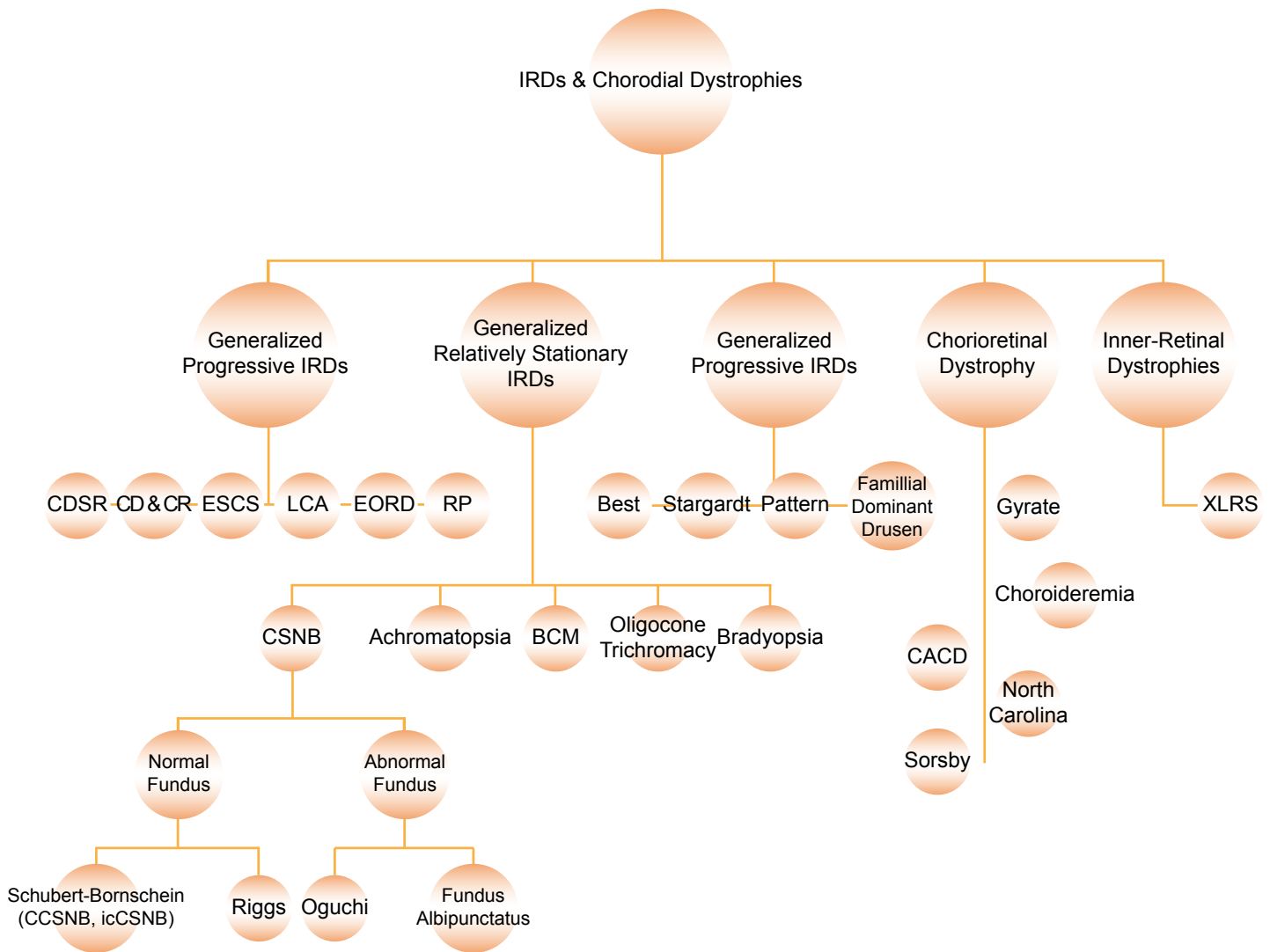


Figure 1: Classification of inherited retinal diseases and choroidal dystrophies.

RP: Retinitis pigmentosa **EORD:** Early-onset retinal dystrophy **LCA:** Leber congenital amaurosis
ESCS: Enhances S-cone syndrome **CD & CR:** Cone dystrophy & cone-rod dystrophy **CDSRR:** Cone dystrophy with supernormal rod response **CSNB:** Congenital stationary night blindness **cCSNB:** Complete form **icCSNB:** Incomplete form **BCM:** Blue cone monochromacy
CACD: Central areolar choroidal dystrophy **XLRS:** X-linked juvenile retinoschisis

document cystoid macular edema, schisis, macular hole, and depth of deposits. The presence or absence of ONL can be used to determine eligibility for gene replacement therapy, as it is indicative of the potential for outer segment revival.

- g. **FAF:** FAF is an indirect measure of retinal pigment epithelium (RPE) health and is useful in documenting the stage of disease. FAF can sometimes show early signs of RP (i.e. paramacular annular ring). In Stargardt disease, FAF will show a generalized increase in autofluorescence in the posterior pole with peripapillary sparing. Loss of fluorescence reflects RPE cell death, which is an important measure of disease progression.⁷
- h. **Fundus photography:** Fundus photography is most useful as a baseline, and wide-field fundus photography may be used to document a pattern. However, excessive light exposure can be toxic to the

retina,⁹ which is why fundus photography should be used sparingly and with purpose.

- i. **Intravenous fluorescein angiogram (IVFA):** IVFA is only indicated in familial exudative vitreoretinopathy (FEVR), Incontinentia Pigmenti, or on suspicion of a choroidal neovascular membrane as a complication to IRD. Although the “silent choroid” sign on IVFA was previously used as a diagnostic marker of Stargardt disease, FAF and OCT now provide better prognostic capability, and IVFA is not recommended. Excessive light exposure from IVFA can also be toxic to the macula.
- j. **Visual field tests:** For generalized retinal degeneration, our center prefers kinetic visual field tests using the I4e, III4e, or V4e stimuli. When the central field is under 20°, microperimetry may be useful as it also assesses the fixation stability.

k. **Electrophysiology:** A battery of electrophysiology tests may be performed to assist in diagnosis and prognosis and to inform disease progression.

1. Retinal function tests:

■ Generalized retinal function:

- Full-field electroretinogram (ffERG)
- Full-field stimulus testing (FST): measures sensitivity of the entire visual field successfully from a young age and beyond the sensitivity of ERG measurements

■ Macular function:

- Pattern ERG: informs retinal ganglion cell function
- Multifocal ERG: tests localised cone-driven retinal function.

2. RPE integrity test: The electrooculogram (EOG)

3. Optic nerve and visual pathway tests:

- Visual evoked potential (VEP): assesses the entire visual pathway up to the primary visual cortex.
 - Flash VEP: evaluates the integrity of the visual pathways.
 - Pattern reversal VEP: evaluates macular function, optic nerve function, and chiasmal and retro-chiasmal function.
 - Multi-channel pattern reversal VEP: evaluates intracranial misrouting in albinism, and post-chiasmal visual pathway function.

Phenotype Variability

Approximately 30% of IRD-related gene mutations are associated with more than one phenotype. For example, mutations in the genes *USH2A* (Usher syndrome type 2; RP and hearing loss) and *ABCA4* (Stargardt disease) are the most common causes of non-syndromic autosomal recessive retinitis pigmentosa (ARRP). Depending on the level of impairment of the *ABCA4* protein, mutations in *ABCA4* can lead to fundus flavimaculatus (no maculopathy), Stargardt disease, cone rod dystrophy, or RP (**Figure 2**).¹⁰ Stargardt disease may or may not have flecks but presents with increased autofluorescence.

Monoallelic mutations in *BEST1* can cause AD Best vitelliform macular dystrophy (BVMD), AD adult-onset vitelliform macular dystrophy, or more rarely AD vitreoretinopathopathy (ADVIRC) or MRCS (microcornea, rod-cone dystrophy, cataract, and posterior staphyloma).¹¹ Patients with *BEST1* mutations tend to have narrow anterior chambers and are at risk for closed-angle glaucoma. Biallelic mutations in *BEST1* cause the distinct AR bestrophinopathy (ARB) phenotype (**Figure 3**).¹²

Mutations in *RPE65* usually cause AR Leber congenital amaurosis (LCA) (early onset retinal degeneration) but may also cause ARRP, fundus albipunctatus, and AD RP. The latter group is ineligible for gene replacement therapy proposed for AR LCA, despite being caused by the same mutation. Patients with mutations in *RPE65* usually do not show any autofluorescence.

Retinitis pigmentosa (RP) may or may not show pigment, especially early in disease onset. Some cases, such as those associated with mutations of *RPE65*- and *GUCY2D*, show dissociation of structure-function, meaning the retina can look almost normal, but the function is severely reduced. These are optimal cases for gene replacement therapy. However, RP caused by other genetic variants, such as *TULP1*, *CRB1*, or *CEP290*, can show severe remodelling of the retina with loss of lamination.

DISEASE MANAGEMENT

Patients with visual impairment often benefit from a good refraction, a low vision assessment and should be referred to the Canadian National Institute for the Blind (CNIB). For young patients, the school should be informed of the disability. Patients in the workforce, have the right to be accommodated and may benefit from being connected to a social worker.

Annual or bi-annual follow-up appointments should be arranged to document the natural history of change and to monitor patients for cataracts and glaucoma. IRD patients tend to develop cataracts early, particularly posterior subcapsular cataracts (PSCs) and nuclear sclerotic cataracts. Cataract surgery may be indicated if glare is significant even though the cataract may not be classified as severe. Optimal outcomes of cataract surgery result when the ellipsoid zone is still present, the macula is not too thin (>200 µm), and central retinal function (HVF 10-2) can be documented.^{13,14} The better the vision pre-operatively, the greater the likelihood of having better vision post-operatively, as in advanced cases the central retina is prone to phototoxicity.¹³ The anterior segment should be examined carefully as some cases may have zonular instability.¹⁵ The vitreous of patients with RP is often cellular, though this is not a vitritis and should not be treated with steroids. That said, cells in the anterior chamber should be managed as per standard of care.

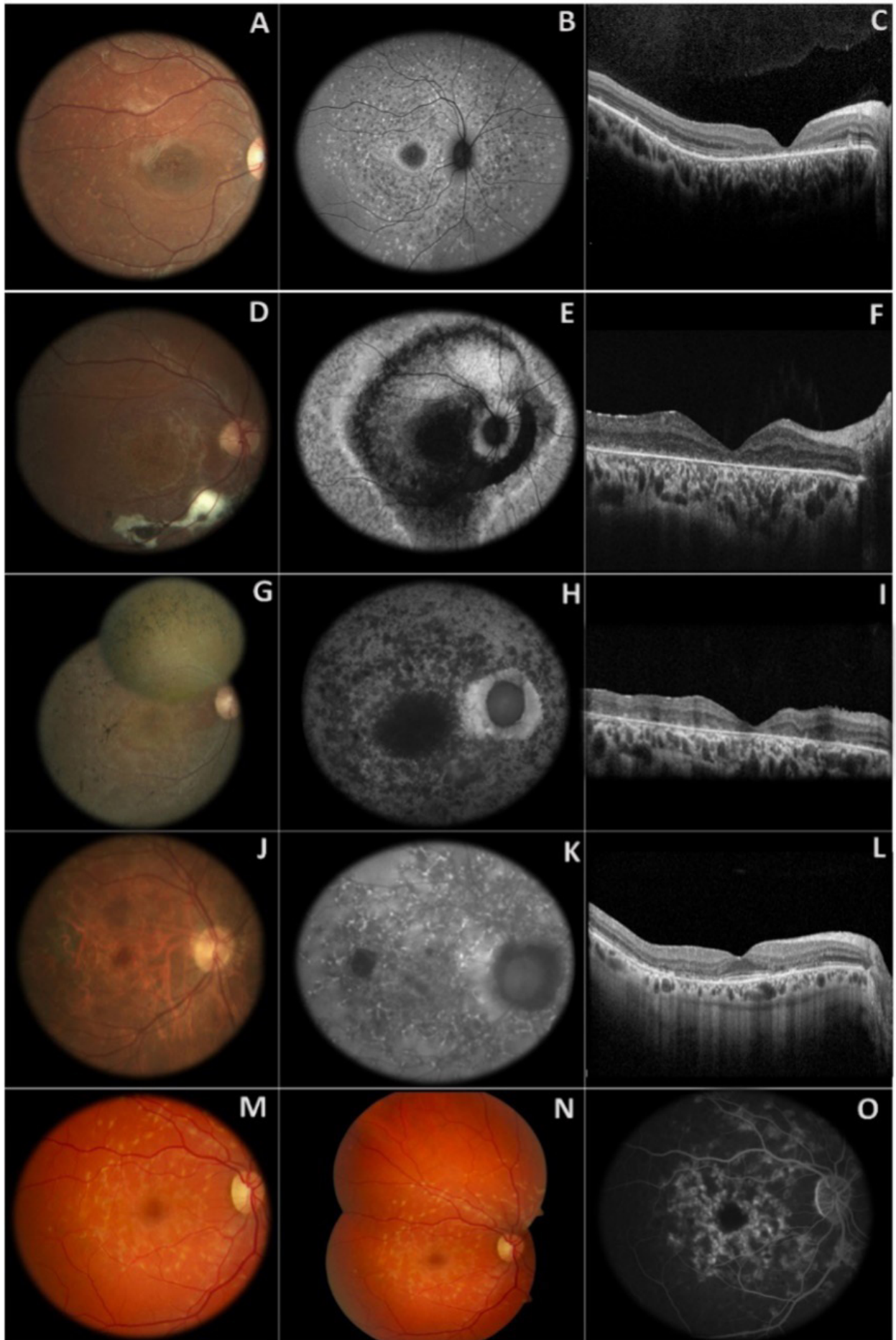


Figure 2. (A–C) The diagnostic triad of *ABCA4*-related retinal degeneration (maculopathy, retinal flecks, and peripapillary retina and RPE spared from degeneration) seen in the right eye of a 10-year-old male carrying compound heterozygous mutations in the *ABCA4* gene: c.3322C>T (p.Arg1108Cys) and c.4253+5G>A. (A) Fundus photo; (B) FAF showing a hyperautofluorescence background of the macula; (C) OCT. (D–F) Imaging findings in a 14-year-old female with cone-rod dystrophy due to homozygous mutation in the *ABCA4* gene: c.1357G>T (p.D453Y). (E) FAF imaging revealing more extensive abnormalities than funduscopy, with heterogeneous background autofluorescence and the central macula and crescent area nasal to disc showing definitely decreased autofluorescence, indicating a total loss of RPE in these areas. (F) OCT showing severe loss of ellipsoid zone and outer nuclear layer in the central foveal area. (G–I) Retinal imaging findings of *ABCA4*-associated AR retinitis pigmentosa, in a 20-year-old female carrying homozygous mutation in the *ABCA4* gene: c.885delC. (G) Fundus photo showing classic RP features (mid-peripheral bone spicules pigments migration and mottled RPE, and attenuated retinal vessels). (H) FAF showing mottled hypoautofluorescence extending from the mid-peripheral area to the central macula, with a spared peripapillary area. (I) OCT image of the foveal, parafoveal, and perifoveal areas showing disruption of the outer nuclear layer, external limiting membrane, and ellipsoid zone. (J–L) Retinal imaging revealing reticular pattern dystrophy in a 60-years-old female carrying two heterozygous mutations in the *ABCA4* gene: c.4139C>T (p.Pro1380Leu) and c.5603A>T (p.Asn1868Ile). (J) Fundus photograph showing multiple yellow deposits temporal to the macula and near the arcades, as well as macular pigmentary changes. (K) FAF showing scattered irregular linear areas of hyperautofluorescence with heterogeneous hypoautofluorescence in the posterior pole extending to arcades. (L) OCT of the central foveal area revealing a preserved island of outer retinal layers. (M–O) Fundus flavimaculatus, a milder form of Stargardt disease, in a 41-year-old female carrying heterozygous mutations in the *ABCA4* gene: c.5196+1137G>A - intron variant and (p.S445R). (M) Fundus photograph revealing diffuse flecks that are dispersed throughout the posterior pole and (N) extend to the mid-periphery. (O) Fundus fluorescein angiography confirming less involvement of the central macula, with a silent choroid and dispersed small areas of hyperfluorescence, indicating some RPE atrophy in the posterior pole.

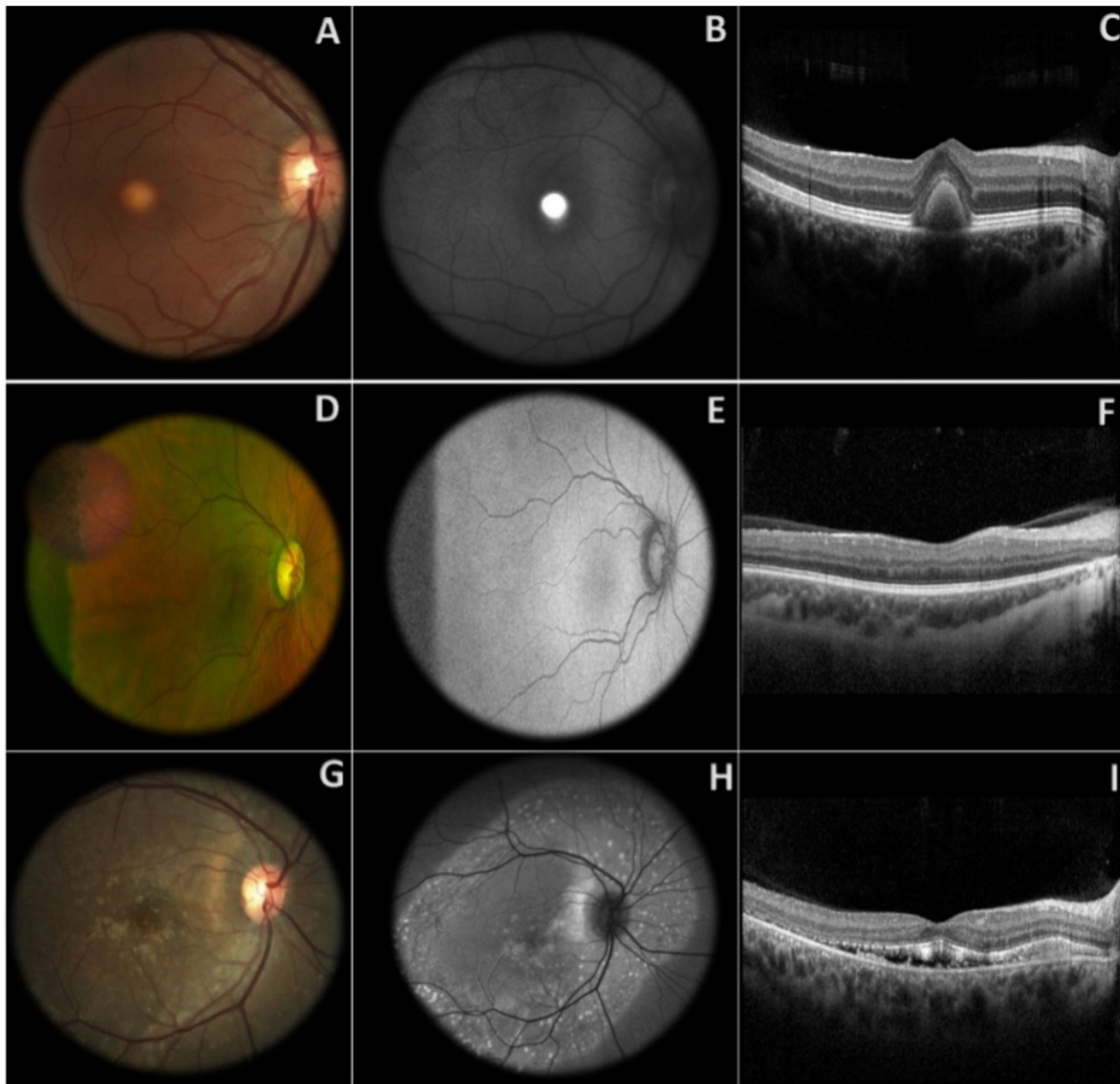


Figure 3. (A–C) Classic features of *BEST1*-associated autosomal dominant BVMD in a 26-year-old male carrying a heterozygous variant in *BEST1* gene: c.652C>T (p.Arg218Cys). (A) Coloured fundus photo showing “egg-yolk-like” vitelliform macular lesion; (B) FAF with hyperautofluorescence corresponding to lipofuscin-containing subretinal lesion; (C) OCT macular scan showing dome-shaped neurosensory retinal detachment. (D–F) Distinctive peripheral hyperpigmented band, a characteristic sign of ADVIRC, in a 23-year-old female carrying a heterozygous mutation in the *BEST1* gene: c.214T>A (p.Y72N). (F) OCT showing normal central foveal area. (G–I) Autosomal recessive bestrophinopathy (ARB) phenotype in a 45-year-old female carrying two mutations in the *BEST1* gene: c.341T>C (p.V114A) and c.400C>G (p.L134V). (G) A fundus photo showing scattered white-yellow retina lesions; (H) FAF showing presentation as hyperautofluorescence effect; (I) OCT showing neurosensory retinal detachment and irregularity of the ellipsoid zone.

Expert opinions vary with respect to nutritional supplementation, although most agree that antioxidant supplements (e.g., omega-3, lutein, zeaxanthin) can be beneficial for IRD patients.

Patients with Stargardt disease should avoid taking synthetic vitamin A supplements, although there are no side effects associated with vitamin A obtained through a normal diet. Although a 1993 study suggested that taking 15,000 IU/d of vitamin A could slow RP disease progression, this study was significantly flawed.¹⁶ We recommend vitamin A palmitate supplements only in RP cases caused by a rhodopsin mutation or for patients with a rare type of late-onset retinal degeneration due to a mutation in the *C1QTNF5* gene.

Regular exercise, stress management, sleep quality, avoiding smoking, and limiting direct eye exposure to UV rays in sunlight are also important cautionary factors in disease management.¹⁷ Many IRD patients struggle with depressive episodes due to the challenge of adapting to changes in vision, and should be encouraged to consult a psychologist. IRDs can be part of multi-systemic diseases, some as life-threatening as Batten disease,¹⁸ while others such as Refsum disease or abetalipoproteinemia may benefit from early management.^{19,20}

NOVEL TREATMENTS

There is no cure for IRDs. Some treatments are being developed for specific gene mutations (e.g., gene replacement therapy, gene editing, or pharmacotherapy.), while other treatments are gene-agnostic (e.g., cell transplants, stem cells, or optogenetics). Numerous clinical trials for IRD treatments are ongoing worldwide, including in Canada (clinicaltrials.gov).

The first-ever gene replacement therapy for AR early-onset retinal degeneration (LCA) caused by two mutations in the *RPE65* gene, Luxturna (voretigene neparvovec-rzyl), was approved by Health Canada in 2020. Reimbursement via provincial formularies is still evolving as the list price to treat both eyes exceeds \$1 million dollars. Once the therapy becomes accessible, patients with confirmed biallelic *RPE65* mutations will be able to be treated in Edmonton, Toronto, or Montreal. The results of the phase 3 trial showed improvement in retinal sensitivity (which translates to mobility at reduced light levels) and improved visual fields, but no improvement in visual acuity.²¹ For patients to be able to adapt to decreasing light levels is life changing. Minimum eligibility criteria for gene replacement therapy include ≥ 4 years of age and the presence of a viable retina (**Figure 4**).

Ongoing clinical trials include therapies for Stargardt disease, USH2A, XLR5, XLRP, achromatopsia, and choroideremia, among others. The future is very promising for IRD patients.

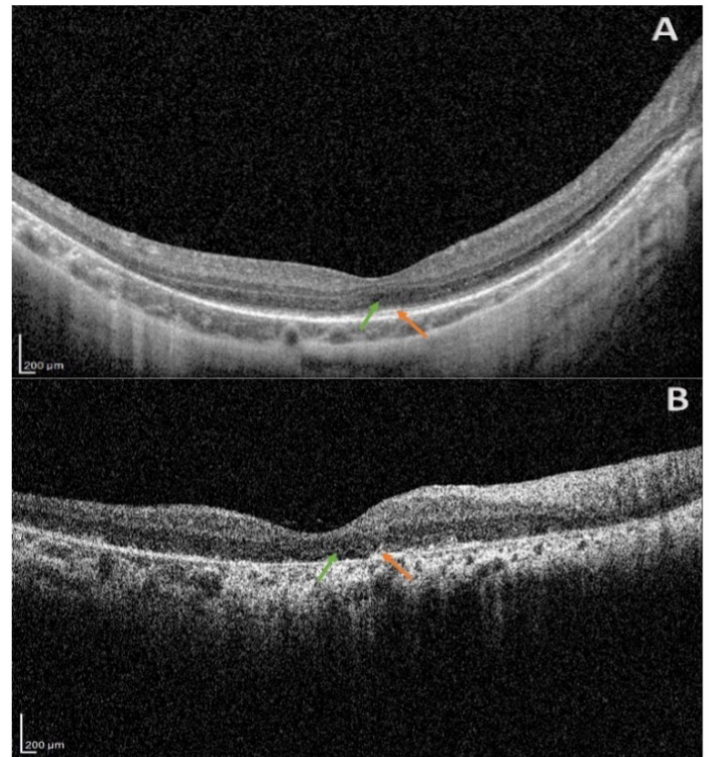


Figure 4: (A) An example of a patient eligible for gene therapy. OCT image of the right macula with the presence of ellipsoid zone (orange arrow) and the outer nuclear layer (green arrow) in the sub-foveal and parafoveal area. (B) An example of a poor candidate for gene therapy. OCT image of the right macula with diffuse loss of the ellipsoid zone except for a minimal remnant in the parafoveal area (orange arrow) and marked atrophy of the outer nuclear layer (green arrow).

COMPLEX RETINAL TRAITS:

Although diabetic retinopathy and age-related macular degeneration (AMD) have been linked to genetic predispositions, these are complex conditions with significant environmental influences and could not be included in this review. Genetic testing for these conditions is not routinely done but can be provided for patients with AMD.²²⁻²⁴

SUMMARY

Ocular genetics has become an important part of ophthalmology as conditions that were once considered untreatable are now becoming clinically actionable. As we learn more about IRDs, it is important to use our knowledge of inherited disease, retinal degeneration, genotyping, and phenotyping to aid in making accurate diagnoses. Clinicians will have novel therapeutic options available to treat IRDs which portends a new era for ophthalmologists and patients in terms of improved outcomes and quality of life.

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