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ARTICLE

A Practical Approach to Retinal Dystrophies

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A Practical Approach to Retinal Dystrophies

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Genomic approaches to developing new diagnostic and therapeutic strategies in retinal dystrophies are among the most advanced applications of genetics.¹ The notion that “nothing can be done” for patients with retinal dystrophies is no longer true.

Electrophysiological testing and autofluorescence imaging help to diagnose and predict the patient’s course of disease. Better phenotyping can contribute to better-directed, cost-efficient genotyping. Combining fundoscopy, autofluorescent imaging, and electrophysiological testing is essential in approaching patients with retinal dystrophies. Emerging are new gene-based treatments for these devastating conditions.

Classification of retinal dystrophies can be confusing because they are both clinically and genetically heterogeneous.^{2,3} There are several disease classification schemas and we present them as (1) progressive vs stationary, and (2) central (macular) dystrophies vs generalized (see **Table 1**).

Important patient history includes specific symptoms such as central scotomas or night blindness, age of onset to determine severity of disease, and family history to establish the inheritance pattern. Examining other family members is often helpful. A complete past medical history and focused physical exam are important to relate systemic associations.

After a family history and clinical exam,⁴ the electroretinogram (ERG) is usually the first ancillary test for classifying retinal dystrophies.⁵ Full-field ERG is a noninvasive test of retinal function that measures mass response electrical activity after light stimulation and helps to exclude generalized retinal dysfunction. Full-field ERGs are performed on patients with dilated pupils using published International Society for Clinical Electrophysiology of Vision (ISCEV) standards.⁶ The minimum protocol incorporates the rod-specific (**Figure 1, Column 1**) and standard bright-flash ERGs (**Figure 1, Column 2**), both recorded after a minimum of 20 minutes dark adaptation, and the photopic 30 Hz flicker (**Figure 1, Column 3**) and transient photopic ERGs (**Figure 1, Column 4**), both recorded after a standard period and intensity of light adaptation.⁷

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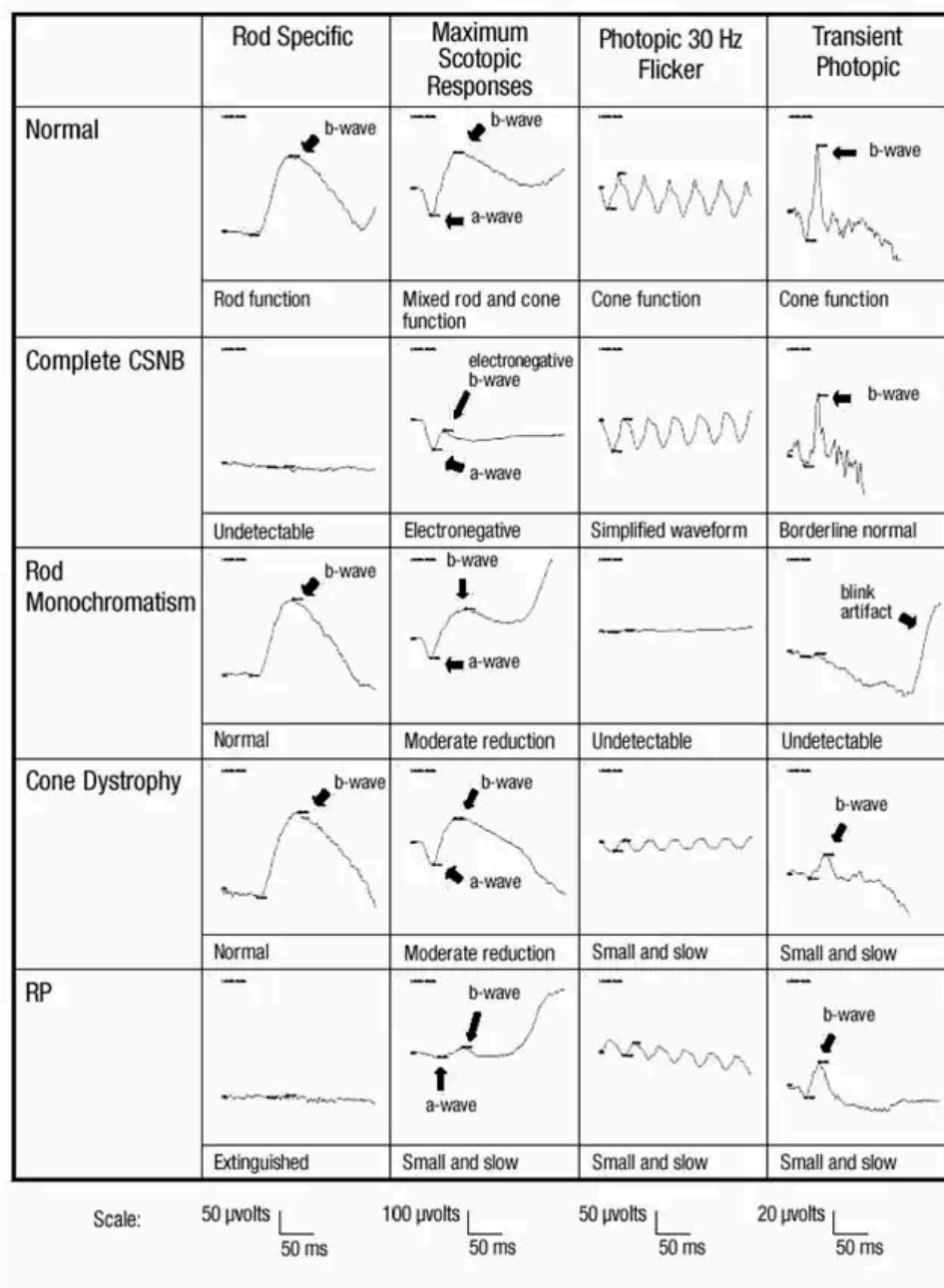
Figure 1: Summary of classic electrophysiological findings in retinal dystrophies.

Figure 1. Electroretinogram (ERG) testing. Full-field ERG measures mass response of the retina: photoreceptor (a-wave) and inner nuclear layers (b-wave). Full-field electroretinogram was performed using Dawson, Trick, and Litzkow recording electrodes and Ganzfeld stimulation according to ISCEV standards. ERG tracings from a normal 40-year-old individual are shown in the upper panel. Typical tracings from different patients at 40 to 50 years of age are shown in other panels.

While full-field ERG evaluates mass cone and rod system function, pattern ERG (checkerboard stimulus) is useful to distinguish decreased vision secondary to optic nerve vs macular disease.⁸ An electrical response in a 30-Hz flicker ERG is an important prognostic tool because its presence confirms residual cone function.^{9,10}

Scanning laser ophthalmoscopy (SLO) autofluorescence is a noninvasive imaging technique that detects the lipophilic cation N-retinyl-N-retinylidene ethanolamine (A2E) (a by-product of the visual cycle) in lipofuscin fluorophores, which accumulates in the retinal pigment epithelium (RPE).^{11,12,13} Hypofluorescent or hyperfluorescent areas in SLO images are associated with abnormal accumulation or depletion of A2E fluorophore in RPE. Besides diagnosing malfunctioning RPE cells, using autofluorescence to follow patients with pathology can frequently predict their clinical course^{14,15}

Table 1. Some Genes Implicated In Inherited Retinal Degenerations

* Mutations in structural proteins and transcription factors tend to cause dominant disease, while abnormalities in metabolic enzymes tend to cause recessive diseases.

Stationary Retinal Dystrophies			Central Retinal Dystrophies		
Disease	Gene	Protein	Disease	Gene	Protein
Achromatopsia	CNGA3	Alpha subunit of cone cGMP-gated channel	Best Disease	VMD2	Bestrophin
	CNGB3	Beta subunit of cone cGMP-gated channel	Doyne Honeycomb Retinal Dystrophy	EFEMP1	EGF-containing fibrillin-like extracellular matrix protein 1
	GNAT2	Alpha subunit of cone transducin	North Carolina Macular Dystrophy	MCDR1	Unknown gene on Chromosome 6
CSNB (Dominant)	GNAT1	Alpha subunit of rod transducin	Sorsby Fundus Dystrophy	TIMP3	Tissue inhibitor of metalloproteinases e-3
	PDE6B	Beta subunit of rod cGMP-PDE	Stargardt Disease	ABCA4	ATP-binding cassette transporter
	RHO	Rhodopsin	Stargardt-like Dominant Macular Dystrophy	ELOVL4	Elongation of very long chain fatty acid protein
CSNB (XL Complete)	NYX	Nyctalopin	Progressive Generalized Dystrophies (Functional Class)		
CSNB (XL Incomplete)	CACNA1F	Alpha1 subunit of Ca _v 1.4 calcium channel	Juvenile Retinoschisis	XLRS1	Retinoschisin
Fundus Albipunctatus	RDH5	11- <i>cis</i> retinol dehydrogenase	Autosomal Dominant RP	RP1	RP1
Oguchi Disease	GRK1	G-protein coupled receptor kinase 1		PRPF31, PRPF3, and PRPF8	Pre-mRNA processing factor
	SAG	Arrestin		RHO	Rhodopsin
Early Onset Progressive Retinal Dystrophies			Autosomal Recessive RP	CNGA1	Alpha subunit of rod cGMP-gated channel
Leber	AIP1	Aryl hydrocarbon receptor interacting protein like-1		CNGB1	Beta subunit of rod cGMP-gated channel
	CRB1	Crumbs homolog 1		PDE6A	Alpha subunit of PDE
	CRX	Cone-rod homeobox		PDE6B	Beta subunit of PDE
	GUICY2D	Retinal guanylate cyclase		RHO	Rhodopsin
	RDH12	Retinal dehydrogenase 12		SAG	Arrestin
	RPE65	RPE-specific protein, 65 kD		CNGA1	Alpha subunit of rod cGMP-gated channel
	RPGRIP1	RP GTPase interacting protein 1		CNGB1	Beta subunit of rod cGMP-gated channel
	CEP290	Centrosomal Protein		USH2A	Usherlin

STATIONARY ROD DYSTROPHIES

It is important to distinguish stationary vs progressive disease because the patient's primary concern is whether sight will deteriorate. There are 2 common forms of stationary night

blindness and several forms of stationary cone dysfunction syndrome.

Congenital stationary night blindness (CSNB), although most commonly inherited as an X-linked recessive (XLR) disorder, can also demonstrate autosomal dominant (AD) or autosomal recessive (AR) inheritance. All modes of inheritance result in normal-appearing fundi. The AR and XLR forms of CSNB present in infancy with nystagmus, strabismus, and reduced vision. In contrast, the AD form of CSNB typically presents with normal visual acuity in teenage years with symptomatic night blindness.^{16,17,18,19}

Because fundoscopy is normal in CSNB, ERG is important in making the diagnosis,¹⁹ as it detects severe dysfunction and an electronegative waveform (see **Figure 1** and **Table 1**). The defect in X-linked complete CSNB has been suggested to lie downstream from the photoreceptor neurons, possibly in the ON bipolar cells or their interconnections.²⁰ Visual acuity (VA) is diminished in X-linked CSNB patients because their ON bipolars fail to have proper interpretation of photoreceptor signal to noise.



Figure 2. Leber congenital amaurosis at its end stage in a woman 37 years of age with RPE migration, near total loss of retinal pigment epithelium cells, severe retinal atrophy, and peripapillary ghost vessels in her left eye. She retains light-perception vision and has an extinguished full-field ERG response.

Distinctive radial flecks in the retina characterize another form of night blindness, fundus albinipunctatus, caused by delayed rhodopsin regeneration. Although usually stationary, there is a subtype of

fundus albipunctatus associated with progressive cone dysfunction.²¹ Patients have discrete white flecks at the level of the RPE, most numerous in the mid-periphery. Either patients present with night blindness or the flecks are found on routine ophthalmoscopy. Fundus albipunctatus can be confused with retinitis punctata albescens, a form of retinitis pigmentosa (RP) with white spots on fundus exam. ERG recovers after prolonged dark adaptation in fundus albipunctatus because it allows the delayed rhodopsin regeneration to recover.

STATIONARY CONE DYSFUNCTION SYNDROMES

There are 3 categories of congenital achromatopsia:²² (1) Typical rod monochromats (complete achromats) lack all sensitivity mediated by cone pigments; (2) Atypical rod monochromats (incomplete achromats) have some residual cone function and thus better VA and residual color vision; and (3) S-cone monochromats have rod and blue-cone function. These last patients have better VA than either type of rod monochromat.

The 2 types of achromatopsia, complete and incomplete, are both autosomal recessive and have normal rod function. Patients usually present in infancy with nystagmus, poor vision, and a preference for dim illumination. Because of the sensory nystagmus, CSNB, foveal hypoplasia, optic nerve hypoplasia, and cone dystrophy are in the differential. Extinguished-cone ERGs in achromatopsia help to establish this nonprogressive dystrophy (Figure 1).

Table 2. Inherited Causes of Electronegative (b-wave negative) ERG

- Congenital stationary night blindness
- X-linked retinoschisis
- Inner retinal dystrophy
- Batten disease
- Duchenne muscular dystrophy

Clinically, S-cone monochromatism presents like the other achromatopsias, with nystagmus and photophobia during infancy, but the disease is less severe. Family history can help distinguish this entity because S-cone monochromatism is X-linked recessive,

whereas the other achromatopsias are autosomal recessive. Special color testing or an ERG at a specified wavelength (440 nm) are useful diagnostic tools when interpreted in the correct clinical context.^{23,24}

PROGRESSIVE RETINAL DYSFUNCTION

Retinitis pigmentosa, also known as rod-cone dystrophy, has both genetic and allelic heterogeneity (**Figures 2 and 3**).²⁵ RP inheritance can be autosomal dominant, autosomal recessive, or X-linked recessive, and there is genetic heterogeneity even within each group. Retinal degeneration slow (RDS) protein and retinal-specific adenosine triphosphate (ATP)-binding cassette transporter (ABCA4) are examples of allelic heterogeneity in that they can cause macular dystrophy in some patients and cone-rod dystrophy in others.

Approximately 50% of patients have no family history of RP (termed simplex RP) or evidence of parental consanguinity, and likely, many of such cases are autosomal recessive. However, some may be males who have X-linked disease from female carriers, and other cases may be new autosomal-dominant mutations or manifestations of autosomal-dominant disease with reduced penetrance. Accurate genetic counseling depends on identifying the causative mutation and mode of inheritance.

The age of onset of RP is variable and patients do not always present with the classic triad of intraretinal pigment migration, optic nerve pallor, and attenuated vessels (**Figure 3**). In general, patients who develop symptoms at younger ages have worse prognoses, and dominant disease has a less severe natural history with later onset when compared to X-linked and recessive variants. In RP, patients with normal VA and smaller, higher-density autofluorescent rings correlate with worse-pattern ERGs. This represents a shrinking area of photoreceptor function as disease progresses.^{14,15} In time, VA declines, visual fields coalesce to give the classical peripheral ring scotoma, and posterior subcapsular cataracts or cystoid macular edema (CME) may develop (**Figure 3**).

Enhanced S-cone, also known as Goldmann-Favre syndrome, is a subtype of autosomal-recessive RP featuring larger photopic single-flash ERG a-wave than 30-Hz b-wave amplitudes. Patients also have

supernormal S-cone function, which is due to an increased number of S-cones, low numbers of L- and M-cones, and a lack of rods.^{26,27,28} Goldmann-Favre is one of the most frequently described hereditary vitreoretinal disorders (**Table 3**). Although the fundus appearance is variable, patients may have deep, nummular-shaped RPE clumping in the mid-periphery with central or peripheral retinoschisis.

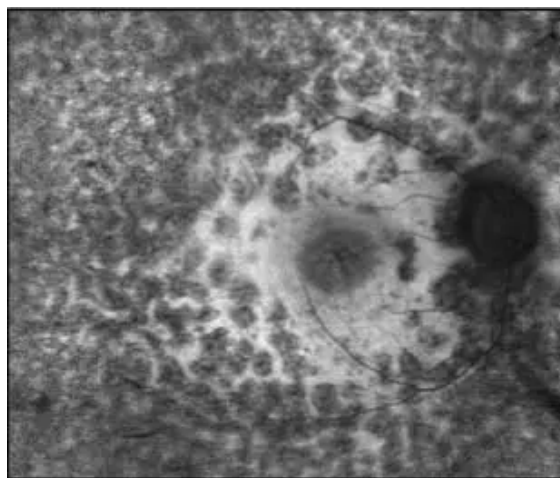


Figure 3. Usher syndrome in a woman 34 years of age. Autofluorescence of the right eye shows RPE atrophy underneath degenerated rods. Note the cystoid macular edema, a common complication of rod-cone dystrophies.

Choroideremia is an X-linked recessive rod-cone dystrophy that has marked atrophy of the choroid and RPE but does not feature intraretinal pigment migration.²⁹ It is important to distinguish carriers of this trait from carriers of X-linked RP (XLRP) because they have similar fundi, but the prognosis for affected children is different (**Figure 4**). Boys with XLRP are more severely impaired than those with choroideremia. The distinction can be made with ERG of their mothers at child-bearing age: carriers of choroideremia are normal, while carriers of XLRP are often abnormal and sometimes asymmetrical.³⁰



Figure 4. Choroideremia carrier with RPE mottling (top), ocular albinism carrier with radially oriented mosaic RPE hypopigmentation (middle), X-linked recessive RP carrier with a tapeto-like retinal sheen (bottom). X-linked heterozygous carriers are important to diagnose correctly, but fundus distinctions may be subtle.

Gyrate atrophy, an autosomal-recessive dystrophy, is part of the differential diagnosis of choroideremia. The characteristic fundus appearance of gyrate atrophy is hyperpigmented fundi with lobular loss of the RPE and choroid starting in the periphery. A defect in ornithine aminotransferase, which results in a tenfold increase in plasma ornithine, causes the disease. Although a diet restricted in arginine limits the disease,³¹ it is difficult to maintain and requires careful monitoring. Vitamin B₆ lowers plasma ornithine levels in some patients.



Other well known types of syndromic RP include Alström syndrome, Kearns-Sayre syndrome, Refsum syndrome, Werner syndrome, Cockayne syndrome, Flynn-Aird syndrome, Bardet-Biedl syndrome, Usher syndrome, Joubert syndrome, Batten disease, Zellweger syndrome, and spinocerebellar ataxia.

There are also progressive cone dystrophies, which, in contrast to the stationary cone dysfunction syndromes discussed above, usually present in older childhood or adulthood.³² Patients' presenting symptoms are decreasing VA and color vision. In the late stages, fundus exam may show a typical bull's eye maculopathy, but subtle cases can be picked up earlier with ERG and occasionally autofluorescence imaging (**Figure 1**).³³

Progressive cone-rod dystrophies^{33,34} show the clinical features of cone dystrophy early on and, eventually, rod involvement with associated night blindness becomes evident.^{35,36} There are reports of autosomal-dominant, autosomal-recessive, and X-linked-recessive inheritance. Fundus exam progresses from macular atrophy in the early stages to peripheral retinal pigmentation, arteriolar attenuation, and optic nerve pallor in the later stages.



Figure 5. Group 1 Stargardt disease in a woman 36 years of age. Color fundus photograph of the left eye (top) shows macular flecks with a classic beaten bronze appearance. Autofluorescence of the same eye (bottom) shows hyperfluorescent flecks and hypofluorescent, diseased RPE. This patient has extinguished P50 responses on PERG and normal full-field ERG responses.

There are a number of acquired disorders with an abnormal ERG that phenocopy retinal dystrophies, such as cancer-associated retinopathy (CAR), melanoma-associated retinopathy, acute zonal occult outer retinopathy, diffuse unilateral subacute neuroretinitis, syphilis, foreign body, drug toxicity, and trauma. Clinical history and/or unilateral presentation distinguish these entities from inherited retinal dystrophies.

CENTRAL DYSTROPHIES

In general, only the ERG can establish the functional phenotype in patients with maculopathy. In contrast to global retinal diseases

and cone-predominant degenerations, central or macular dystrophies have normal full-field ERG implicit time responses and normal peripheral visual fields. Macular dystrophies cause a reduction in central vision, but they usually progress slowly and patients retain some central vision. Thus, most individuals with central dystrophies can enjoy normal activities of daily living (unlike those with progressive, generalized, degenerative dystrophies).

A review of patients with bull's eye lesions showed normal full-field ERGs in most cases. Others showed cone dystrophy, cone-rod dystrophy, or rod-cone dystrophy, but the functional phenotype could not be established by fundus appearance.³² Similarly, the functional phenotype in Stargardt disease could not be predicted from the fundus phenotype; only the ERG was concordant within affected families and only the ERG gave prognostic information regarding retention of peripheral vision.

Central dystrophies appear in childhood or early adulthood. We will discuss Stargardt disease, pattern dystrophy, Best disease, Sorsby pseudoinflammatory disease, and Doyne honeycomb retinal dystrophy.

The most common form of inherited juvenile macular degeneration is Stargardt disease. Classically, Stargardt patients present in childhood with decreased central vision, foveal atrophy, and yellow pisciform flecks at the level of the RPE in the macula. Stargardt and fundus flavimaculatus are manifestations of the same genetic disorder due to a recessive defect in the *ABCA4* gene.³⁷ Stargardt patients should avoid a diet high in vitamin A because the defective gene (*ABCA4*) encodes for a transmembrane transporter of A2E intermediates, a toxic by-product of vitamin A.³⁸

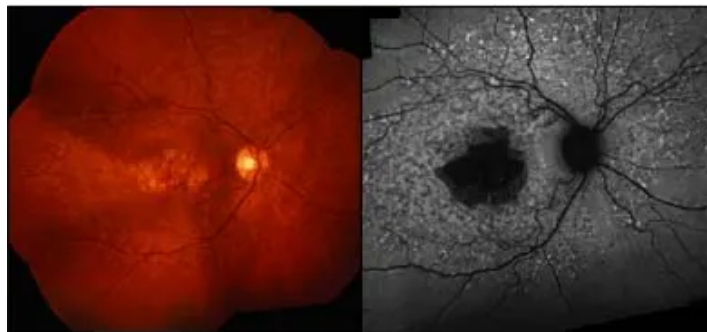


Figure 6. Group 1 Stargardt disease in a man 36 years of age: Color fundus

photograph right eye with macular atrophy and generalized flecks (left) and corresponding autofluorescent imaging (right) shows RPE atrophy (hypofluorescent) centrally and flecks (hyperfluorescent). This patient has extinguished P50 responses and normal full field ERG responses.

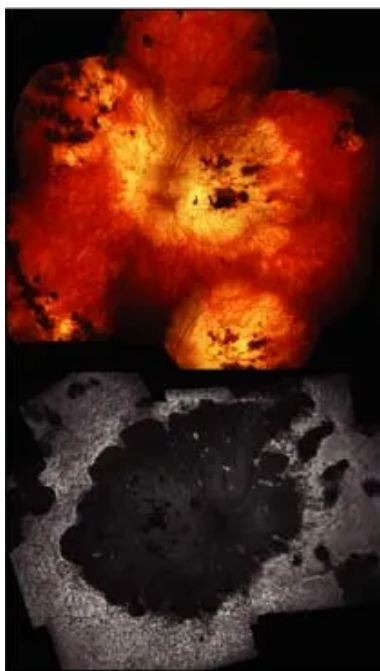


Figure 7. Group 3 Stargardt disease in a woman 57 years of age with bilaterally symmetric disease: Color fundus photo left eye with large areas of atrophic retina and pigment clumping (top), and autofluorescence right eye with large are of missing RPE and generalized hyperfluorescent flecks peripherally (bottom). Both her scotopic and photopic ERG responses are diminished.

At least 80% of Stargardt patients have a “silent choroid,” which is a dark choroid on fluorescein angiogram. A2E accumulation in the RPE causes this phenomenon.³⁹ Stargardt patients’ functional phenotypes may not be predictable from fundus exam, but ERG can help prognose peripheral vision of patients by dividing them into 3 groups. Type 1 patients (**Figures 5 and 6**) have a normal full-field ERG; type 2 patients have more loss of photopic function; type 3 patients (**Figure 7**) have both abnormal scotopic and photopic ERG with the worse prognosis.⁴⁰ It is important to subtype Stargardt patients for better counseling regarding their prognoses. Fundus flavimaculatus frequently manifests as type 1 Stargardt disease. Macular autofluorescence is usually abnormally high in Stargardt

patients, but normal levels of lipofuscin could also indicate late disease where the RPE cells have burnt out.⁴¹

Pattern dystrophies are a group of heterogeneous diseases that are caused by a defect in the RDS⁴² and other genes. There are 4 recognized types, based on fundoscopic appearance: adult onset vitelliform, butterfly, reticular, and fundus pulverulentus (**Figure 8**). They present in adulthood with decreased vision and can be mistaken for age-related macular degeneration (AMD).⁴³

Best disease, or vitelliform dystrophy, is an autosomal-dominant maculopathy caused by a defect in the bestrophin gene. The yolk-like yellow lesion is autofluorescent and usually bilateral (**Figure 9**). Vision is good during this initial stage but decreases during the scrambled-egg stage or secondary to geographic atrophy in the later stages. In addition, about 20% of patients develop a choroidal neovascular membrane, which although self-limited, causes poorer vision. Electro-oculogram (EOG) shows a reduced light rise in Arden ratio in affected Best disease as well as autosomal-dominant vitreoretinchoroidopathy (ADVIRC). EOG is mildly subnormal or normal in adult vitelliform macular dystrophy. Best disease and ADVIRC (both caused by bestrophin gene defects) are examples of allelic heterogeneity, whereas Best disease and adult vitelliform macular dystrophy are examples of genetic heterogeneity.

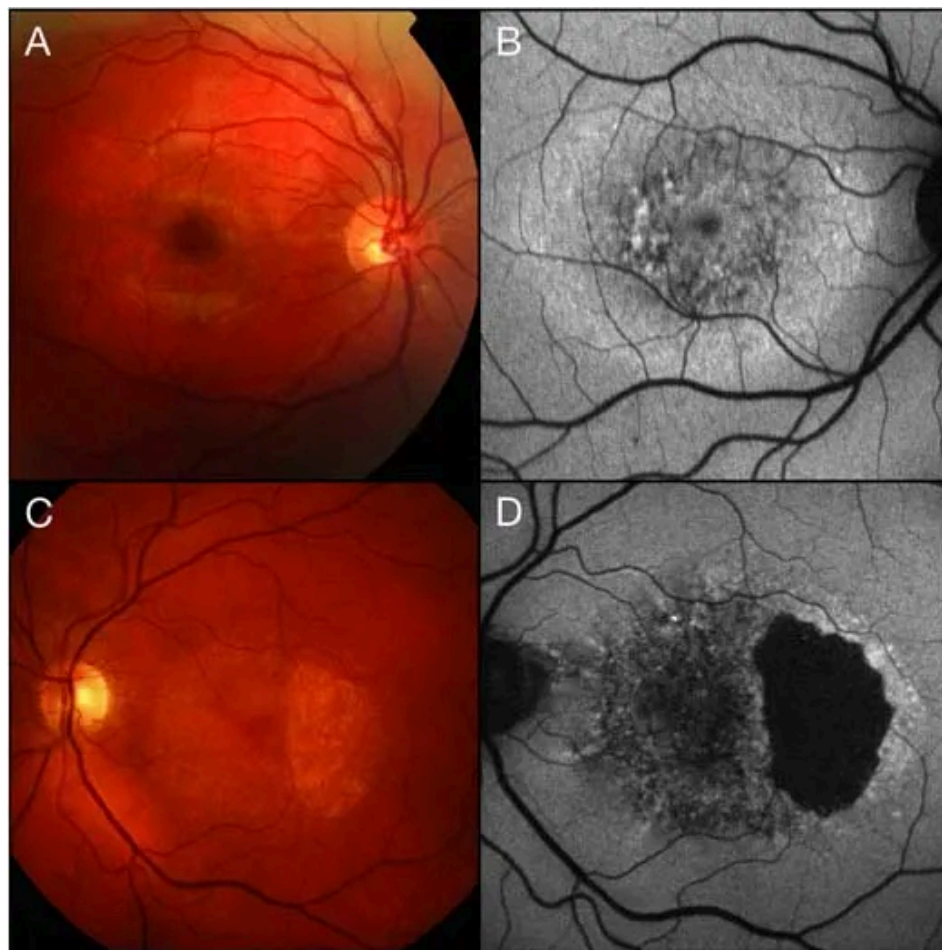


Figure 8. Pattern dystrophy in a woman 26 years of age with 20/15 visual acuity in each eye. (A) Color fundus photograph right eye with subtle RPE irregularities in the macula. (B) Corresponding autofluorescence with speckled hyperfluorescence. Her father had a larger area of RPE atrophy seen on (C) color fundus photograph left eye and (D) corresponding autofluorescence. He had 20/40 vision in each eye.

Sorsby macular dystrophy, a dominantly inherited disease with a defect in the tissue inhibitor of the metalloproteinases-3 gene, leads to eventual bilateral subfoveal choroidal neovascularization, although the disease may progress asymmetrically (**Figure 10**). Beginning around the fifth decade of life, patients present with complaints of problems transitioning between light and dark, followed by central-vision abnormalities. Early on, fine drusen accumulate in the macula, and they later develop a pseudoinflammatory appearance, which may be misdiagnosed as punctate inner choroidopathy.⁴⁴ Individuals with Sorsby have normal pattern ERGs until neovascularization develops.

Doyne honeycomb retinal dystrophy (malattia leventinese) is a dominantly inherited dystrophy with drusen-like deposits in the macula and peripapillary retina. It can be mistaken for AMD but is distinguished by its characteristic finding of nasal drusenoid material and autofluorescence.⁴⁵ Individuals with Doyne honeycomb retinal dystrophy have normal full-field ERG responses.

North Carolina macular dystrophy is autosomal dominant with complete penetrance. Initially, researchers hypothesized that the genetic defect originated from a single family, but the disease is actually present in many distinct genealogies. The clinical appearance is bilateral drusen and macular changes in a young child that may resemble a macular coloboma or staphyloma (**Figure 11**).⁴⁶ Despite the severe appearing fundus, visual prognosis is good and the disease is nonprogressive. Individuals with North Carolina macular dystrophy have normal full-field ERG recordings.

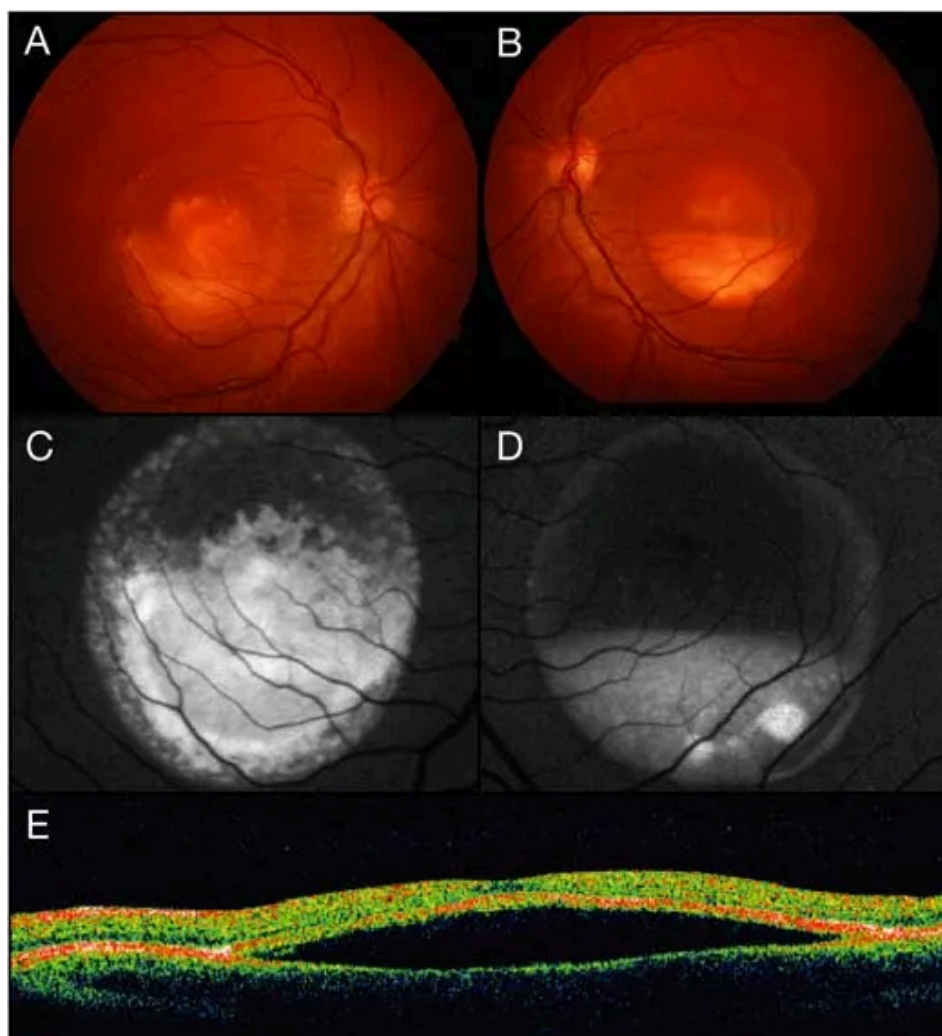


Figure 9. Best vitelliform dystrophy in a man 18 years of age. Color fundus photo (A) left eye and (B) right eye with resolving egg-yolk lesion. Autofluorescence (C) left eye and (D) right eye with corresponding hyperfluorescence. (E) Optical coherence tomography shows splitting of the RPE layer with elevation. Visual acuity is 20/200 OD and 20/20 OS.

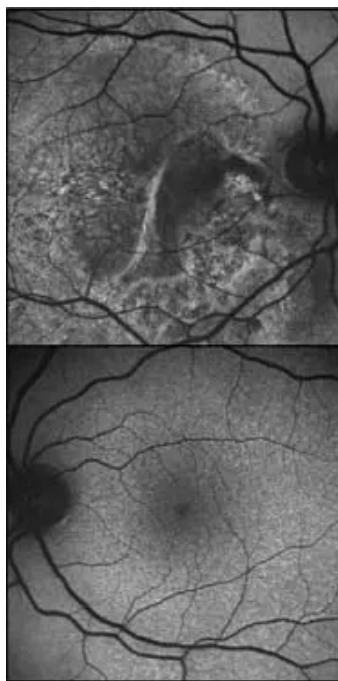


Figure 10. Sorsby pseudoinflammatory dystrophy in a man 53 years of age with asymmetric disease who has (top) an RPE tear in the OD (count finger vision) secondary to CNV and (bottom) fine drusen-like deposits in the left eye (20/20 visual acuity) on autofluorescence.

TREATMENTS

It is important to recognize gyrate atrophy, Refsum syndrome, and abetalipoproteinemia because they are 3 types of retinal dystrophies that dietary treatment can help. The main clinical manifestations of Refsum syndrome are RP, cataracts, chronic polyneuropathy, cerebellar ataxia, and cardiac arrhythmias. Elevated serum phytanic acid levels are diagnostic. Avoiding foods high in phytanic acid (eg, fat and butter) and plasmaphoresis help to improve all neurologic signs.^{47,48}

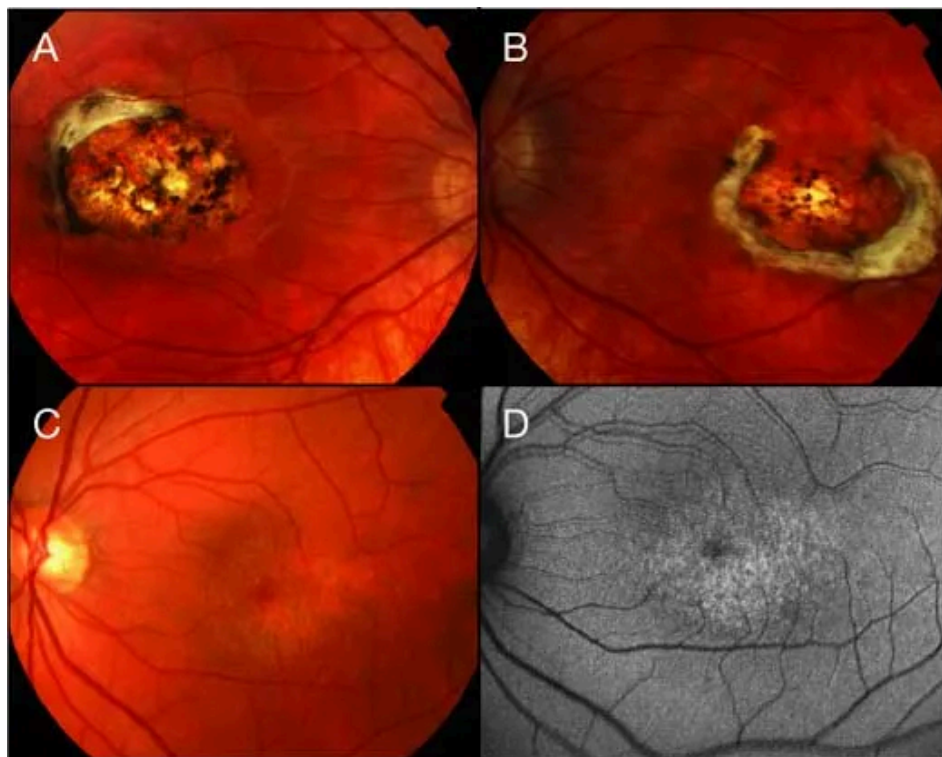


Figure 11. North Carolina macular dystrophy in a girl 12 years of age. Color fundus photography shows coloboma-like defects with scalloped edges worse in her right eye (A) than her left eye (B). Her father (C) has a milder presentation (grade 1) of North Carolina macular dystrophy with fine drusen-like deposits that (D) hyperfluorescence on autofluorescence.

Bassen-Kornzweig syndrome (abetalipoproteinemia) is due to malabsorption of cholesterol, fats, and fat-soluble vitamins from the small intestine. Deficiencies of vitamin A and vitamin E cause failure to thrive, peripheral neuropathy with muscle weakness, spinocerebellar ataxia, and RP. Vitamin A (300 IU/kg/day) and vitamin E (100 IU/kg/day) restore function and slow the progression of retinal degeneration.⁴⁹

There is also interest in whether vitamin A supplementation can help other forms of RP. A study in 2 mouse RP models with different alleles showed that vitamin A supplementation decreased the rate of photoreceptor degeneration caused by a class II rhodopsin mutation (*T17M*, defective in thermal stability/folding and cannot easily reconstitute with 11-cis-retinal), but it did not help the mice with a class I rhodopsin mutation (*P347S*, defective in outer-segment localization). It was hypothesized that vitamin A

supplementation may work by stabilizing mutant opsins through increased availability of the chromophore.⁵⁰ Therefore, vitamin A may benefit a subset of patients with RP.

A randomized controlled study sponsored by the National Institutes of Health (NIH) looking at vitamin therapy for RP in adults showed that vitamin A (15 000 IU) delays the progression of cone ERG loss. The same study showed that vitamin E (400 IU) may have a deleterious effect on RP patients.⁵¹ These results have not been universally accepted in ophthalmic centers.⁵² Subgroup analysis revealed that patients who started taking docosahexaenoic acid (1200 mg/day) at the same time as vitamin A may have a modest additional benefit of slowing RP.⁵³ A safety study did not find substantial side effects of high-dose vitamin A therapy.⁵⁴ Currently, the NIH recommends that adult RP patients take a supplement of 15 000 IU of vitamin A daily under the supervision of an ophthalmologist and avoid use of high-dose vitamin E supplements.⁵⁵

Physicians should follow RP patients at infrequent but regular intervals to detect treatable complications such as posterior subcapsular cataract, macular edema, and the rare autoimmune reaction. Cataract extraction can improve visual perception and brightness. CME can be treated with oral acetazolamide or topical carbonic anhydrase inhibitors.⁵⁶ RP patients with a rapid progression of visual symptoms and ERG progression should have a Western blot analysis for antiretinal antibody. If this serum test is positive, patients presumably have developed autoimmunoretinopathy or a CAR-like syndrome and should undergo evaluation for an occult malignancy.⁵⁷

There is a Coats'-type variant of RP thought to occur in as many as 3% of all RP patients. These fundi have typical bone spicules of RP with Coats'-type changes in the inferotemporal quadrants (**Figure 12**). Retinal telangiectasia and exudative retinal detachments are treated with photocoagulation or cryosurgery as indicated.⁵⁸

Gene therapy is a promising future treatment for retinal degeneration.^{59,60,61} It is applicable when there is a loss of function due to genetic defect. The eye is an ideal organ for gene therapy because it is easily accessible, highly compartmentalized, and it is an immune-privileged site. In 2001, vision was restored in RPE65 deficient dogs, an animal model for one type of early-onset retinal

dystrophy, known as Leber congenital amaurosis (LCA), by injecting subretinal adeno-associated virus (AAV) carrying RPE65.^{62,63} Regain of function was demonstrated with ERG, pupillometry, and behavioral testing and was maintained for over 3 years.⁶⁴

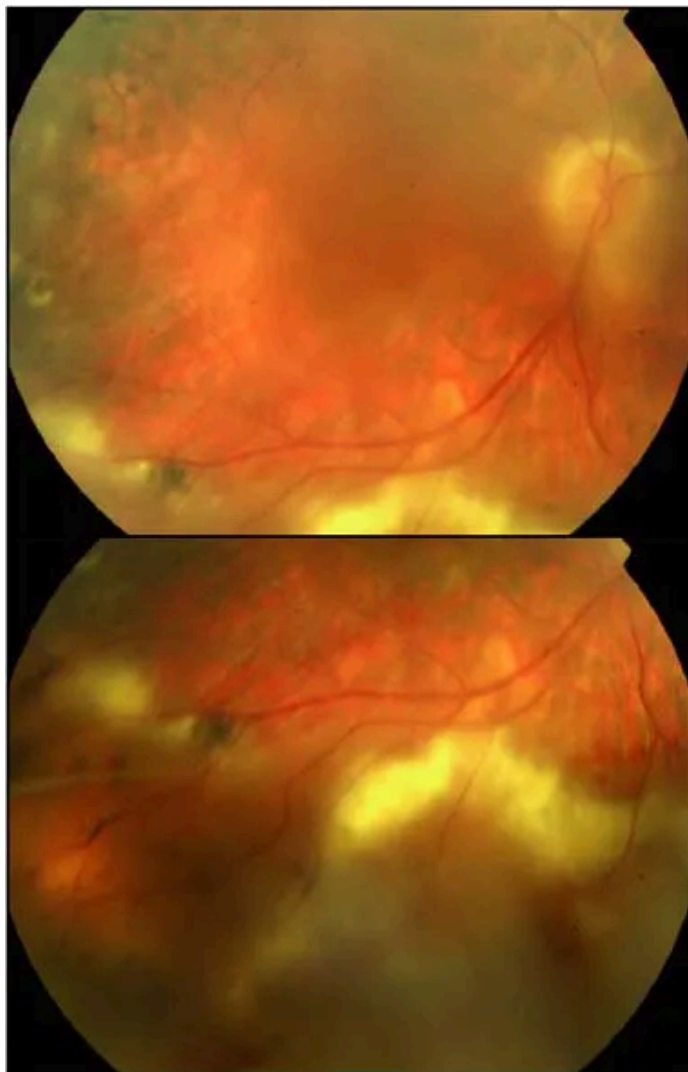


Figure 12. Coats type, autosomal recessive retinitis pigmentosa in a man 55 years of age with (A) vitreous haze centrally and (B) subretinal exudates peripherally in his right eye.

This proof of principle demonstrating functional improvement following gene replacement of RPE65 has led to clinical trials of recombinant AAV-mediated gene therapy for patients with LCA. The NIH Recombinant DNA Advisory Committee has granted ethical approval for 3 proposed trials in the United States and the Gene

Therapy Advisory Committee has approved a trial in the United Kingdom to begin this year.

The key to gene-based treatments is efficient and accurate genotyping.^{65,66,67} If genetic testing is not available on-site, blood can be drawn in a tube with ethylenediaminetetra-acetic acid and sent at room temperature to a Clinical Laboratory Improvement Amendment (CLIA)-certified laboratory for DNA testing.^{68,69}

One commercially available method is a genotyping microarray (gene chip) for the ABCA4 gene.⁷⁰ Allelic heterogeneity in the ABCA4 gene has been associated with 5 distinct phenotypes, including Stargardt disease/fundus flavimaculatus, cone-rod dystrophy, and AMD. This gene chip screens for more than 400 different ABCA4 variants with >98% efficacy of finding them.⁷¹

Another promising idea in treating retinal degenerations has come from using ciliary neurotrophic factor (CNTF) to rescue photoreceptors. At least 13 animal models of RP show improvement with CNTF. Recently, a phase 1 trial evaluated surgically implanted capsules loaded with human RPE cells transfected with the CNTF gene. The treatment was well tolerated with minimal direct side effects, and the visual results were promising.⁷²

Retinal-cell transplantation is another way to replace damaged photoreceptors that has been worked on for many years.⁷³ Studies in mouse models⁷⁴ show that timing of transplantation is crucial.⁷⁵ There is a specific window period, coincident with the peak of rod genesis, during which the donor cells can be harvested that will enable the generation of new photoreceptors in diseased mice.⁷⁵ Clinical use of stem-cell transplantation is on the horizon.⁷⁶

SUMMARY

In summary, retinal dystrophies are a heterogeneous group of disorders whose classifications are evolving as retinal physicians better understand their phenotypes, genotypes, and pathophysiology. Genetic counseling is an important part of taking care of the patient. ERG continues to be the mainstay of diagnosis, and autofluorescence imaging has become essential for better phenotyping and following of disease progression. Electrophysiological studies are most helpful to phenotype different

retinal conditions that ophthalmoscopically may show to be equivocal or similar.

Eyecare professionals have an active role in caring for patients with retinal dystrophies.^{77,78} We manage complications that arise such as cataracts, leaking vessels, and macular edema, and we also give genetic counseling and low vision evaluations. Looking to the horizon, retinal physicians should help enroll patients in genetic registries so that they can contact patients when a specific genetic cure becomes available. **RP**

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