CHAPTER 12

Hereditary Retinal and Choroidal Disease

Highlights

- Congenital color vision defects are stationary and usually affect both eyes equally. When hereditary, they are most frequently X-linked recessive red-green abnormalities.
- Patients with retinal dystrophies should be monitored regularly for treatable causes of vision loss associated with their condition: cataract, macular edema, glaucoma, and retinal exudation.
- Drusen are not only seen in older-adult eyes; macular dystrophies affecting young adults typically include drusenlike deposits and may lead to choroidal neovascularization.
- Patients with minimal signs of ocular pathology who present with unexplained vision loss or are suspected of malingering may in fact have early stages of retinal dystrophy.
- Genetic screening can assist in confirming a diagnosis of retinal degeneration, establishing the inheritance pattern, informing at-risk relatives, and identifying candidates for gene therapies.

Color Vision Abnormalities

Defects in color vision, termed *dyschromatopsias,* are caused by abnormalities of the cone system. Dyschromatopsia can be either static (stationary) or progressive. Stable dyschromatopsia is usually, although not always, congenital. Congenital color vision defects are stationary and usually affect both eyes equally, whereas acquired color vision defects may be progressive and/or uniocular. This chapter describes the nonprogressive forms of color vision loss. For further discussion of optic neuropathies that may lead to acquired vision loss, refer to BCSC Section 5, *Neuro-Ophthalmology.*

Congenital Color Deficiency

Congenital color vision defects are traditionally classified by an individual's performance on color-matching tests. A person with normal color vision (*trichromatism,* or *trichromacy*) can match any colored light by varying a mixture of the 3 primary colors (eg, a long-wavelength red, middle-wavelength green, and short-wavelength blue light).

Individuals with anomalous trichromatism, who make up the largest group of color-deficient persons, can also use 3 primary colors to match a given color. However, because

1 of their cone photopigments has an abnormal absorption spectrum, they use different proportions of colors than those used by persons with normal color vision. Some individuals have only a mild abnormality. Others have poor color discrimination and may appear to have dichromatism on some of the color vision tests.

Hereditary congenital color vision defects are most frequently X-linked recessive red-green abnormalities; they affect 5%–8% of males and 0.5% of females. Acquired defects are more frequently of the blue-yellow, or *tritan,* variety and affect males and females equally. Table 12-1 shows the traditional classification of color vision deficits based on color-matching test results.

Individuals who need only 2 primary colors to make a color match have *dichromatism* (also called *dichromacy*). It is assumed that such individuals lack 1 of the cone photopigments. Approximately 2% of males have dichromatism.

An absence of color discrimination, or *achromatopsia,* means that any spectral color can be matched with any other solely by intensity adjustments. The congenital achromatopsias are disorders of photoreceptor function. Essentially, there are 2 forms of achromatopsia: rod monochromatism and blue-cone (S-cone) monochromatism. Both disorders typically present with infantile nystagmus syndrome (congenital nystagmus), poor vision, and photophobia. Electroretinography (ERG) testing helps differentiate achromatopsia from infantile nystagmus syndrome or ocular albinism, both of which are associated with normal cone ERGs (see Chapter 3, Fig 3-2).

Rod monochromatism (complete achromatopsia) is the most severe form; affected individuals have normal rod function but no detectable cone function and thus see the world in shades of gray. Patients may have partial to full expression of the disorder, with visual acuity

Table 12-1 Classification and Male-Population Incidence of Color Vision Defects

Color Vision	Inheritance	Incidence in Male Population, %
Hereditary		
Trichromatism		
Normal	–	92.0
Deuteranomalous[a]	XR	5.0
Protanomalous[b]	XR	1.0
Tritanomalous[c]	AD	0.0001
Dichromatism		
Deuteranomalous	XR	1.0
Protanomalous	XR	1.0
Tritanomalous	AD	0.001
Achromatopsia (monochromatism)		
Typical (rod monochromatism)	AR	0.0001
Atypical (blue-cone monochromatism)	XR	Unknown
Acquired		
Protanomalous-deuteranomalous (red-green)	Unknown	Unknown
Tritanomalous (blue-yellow)	Unknown	Unknown

AD = autosomal dominant; AR = autosomal recessive; XR = X-linked recessive.
[a] Deuteranomalous means reduced sensitivity to green light.
[b] Protanomalous means reduced sensitivity to red light.
[c] Tritanomalous means reduced sensitivity to blue light.

ranging from 20/80 to 20/200. Nystagmus is usually present in childhood and may improve with age. Characteristically, the ERG pattern in patients with rod monochromatism shows an absence of cone-derived responses and normal rod responses. Dark adaptometry shows no cone plateau and no cone–rod break. The disorder has autosomal recessive inheritance.

In *blue-cone (S-cone) monochromatism,* the function of rods and S cones is normal, but L- and M-cone function is absent. ("S" refers to short wavelength.) The condition is usually X-linked and can be difficult to distinguish clinically from rod monochromatism in the absence of a family history or results from specialized color or ERG testing. Individuals with blue-cone monochromatism exhibit preserved S-cone ERG responses, severely reduced light-adapted (LA) 3.0 30-Hz responses**,** and normal rod ERGs. These individuals typically have a visual acuity of approximately 20/80, which is better than the visual acuity of individuals with typical rod monochromatism.

Night Vision Abnormalities

Deficiencies in night vision, termed *nyctalopia,* are caused by abnormalities of the rod system. These are typically static (stationary) and associated with normal visual acuity.

Congenital Night-Blinding Disorders With Normal Fundi

Congenital stationary night blindness (CSNB) is a nonprogressive disorder of night vision. CSNB has 3 genetic subtypes:

- X-linked (most common)
- autosomal recessive
- autosomal dominant (rare)

Snellen visual acuities of patients with CSNB range from normal to occasionally as poor as 20/200, but most cases of decreased vision are associated with significant myopia. The appearance of the fundus is usually normal, except for myopic changes in some cases. Patients commonly present with difficulty with night vision, nystagmus, and reduced visual acuity. Some patients may have a paradoxical pupillary response, in which the pupil initially constricts when the ambient light dims. Dark-adaptometry curves reveal markedly reduced responses.

Electroretinography is important in the diagnosis of CSNB. The most common ERG pattern seen in patients with CSNB is the *negative* ERG (the Schubert-Bornschein form of CSNB), in which the 10.0/30.0 response has a normal (or near-normal) a-wave but a markedly reduced b-wave. The normal a-wave excludes significant rod photoreceptor dysfunction, and this result helps to differentiate CSNB from the potentially blinding disorder retinitis pigmentosa (see Chapter 3 for discussion of electrophysiologic testing). The differential diagnosis of CSNB includes other conditions with a negative ERG, such as X-linked juvenile retinoschisis, central retinal artery occlusion, birdshot chorioretinopathy, and melanoma-associated retinopathy; the latter demonstrates an ERG pattern identical to that of CSNB but usually presents with acquired nyctalopia (night blindness) and shimmering photopsias.

X-linked CSNB has been categorized into 2 types: complete and incomplete. Patients with *complete CSNB* have an undetectable dark-adapted (DA) 0.01 (rod-specific) ERG response and psychophysical thresholds that are mediated by cones (see Chapter 3, Fig 3-2B). Patients with *incomplete CSNB* have some detectable rod function on ERG and an elevated dark-adaptation final threshold (Fig 12-1). Mutations in the *NYX* and *CACNA1F* genes, which encode proteins involved in the transmission of signals between photoreceptors and bipolar cells, are responsible for complete and incomplete CSNB, respectively.

Congenital Night-Blinding Disorders With Fundus Abnormality

Fundus albipunctatus results from a mutation in *RDH5* (12q13–q14). *RDH5* encodes 11-*cis*-retinol dehydrogenase, a microsomal enzyme in the retinal pigment epithelium (RPE) that is involved in the regeneration of rhodopsin. Patients with fundus albipunctatus have very delayed rhodopsin regeneration; and although levels eventually normalize, the process may require many hours in the dark. Affected individuals have night blindness from birth and usually exhibit yellow-white dots in the posterior pole that extend into the midperiphery but spare the fovea (Fig 12-2). ERG responses commonly show a cone-isolated retina pattern, with undetectable DA 0.01 ERG response, and a severely reduced

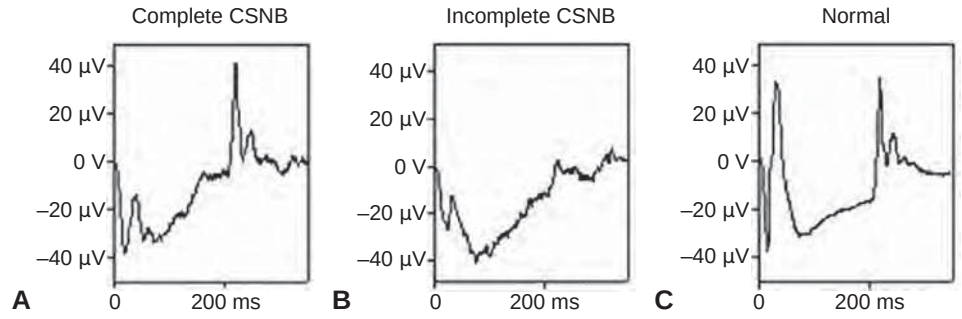

Figure 12-1 Electroretinography (ERG) patterns of on- and off-responses in congenital stationary night blindness (CSNB). The stimulus has a 200-millisecond (ms) duration to enable independent recording of the ERG responses to onset and offset. **A,** The pattern of a patient with complete CSNB shows a negative-waveform on-response but a normal off-response. **B,** The pattern of a patient with incomplete CSNB shows both on- and off-response abnormalities. **C,** Pattern of a subject with normal responses. *(Courtesy of Graham E. Holder, PhD.)*

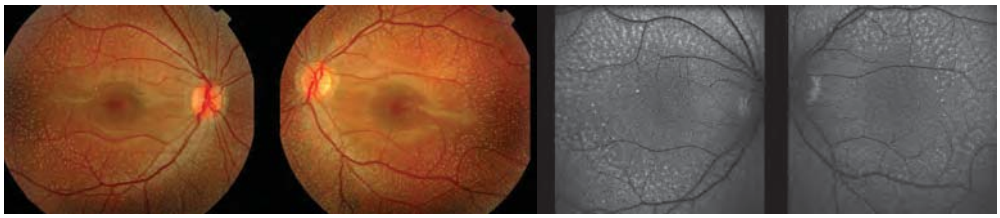

Figure 12-2 Fundus photographs and fundus autofluorescence (FAF) images from a patient with fundus albipunctatus, showing multiple spots of unknown material scattered primarily throughout the deep retina. *(Reproduced from Sergouniotis PI, Sohn EH, Li Z, et al. Phenotypic variability in RDH5 retinopathy (fundus albipunctatus).* Ophthalmology. *2011;118(8):1661–1670, with permission from Elsevier.)*

DA 10.0/30.0 response (arising in dark-adapted cones) that normalizes with sufficiently extended dark adaptation (Fig 12-3).

The differential diagnosis of fundus albipunctatus includes *retinitis punctata albescens,* a disorder related to mutation in *RLBP1,* which encodes cellular retinaldehyde-binding protein. In this condition, which is a progressive rod–cone dystrophy, the white dots may be finer than those of fundus albipunctatus, and the retinal vessels may be attenuated (Fig 12-4). ERG responses are usually very subnormal: although they show some recovery with extended dark adaptation, they do not normalize.

Patients with *Oguchi disease* also are night blind from birth. This condition is due to a mutation either in *SAG* (2q37), which encodes arrestin, or in *GRK1* (13q34), which encodes rhodopsin kinase. This very rare disorder is most common in Japanese patients. The fundus in eyes with Oguchi disease is normal after dark adaptation but shows a peculiar yellow iridescent sheen after even brief exposure to light (the *Mizuo-Nakamura phenomenon*; Fig 12-5).

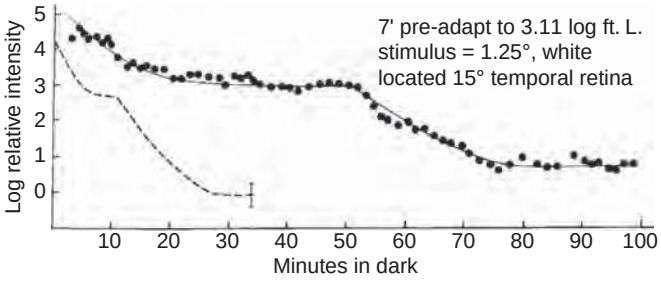

Figure 12-3 Dark-adaptometry curve in stationary night blindness. The dark-adaptometry curve of this patient *(dotted curve)* with good vision and nyctalopia and clinical findings of fundus albipunctatus shows no rod adaptation. *Dashed curve* indicates normal response. *(Reproduced from Margolis S, Siegel IM, Ripps H. Variable expressivity in fundus albipunctatus.* Ophthalmology. *1987;94(11):1416–1422. Copyright 1987, with permission from Elsevier.)*

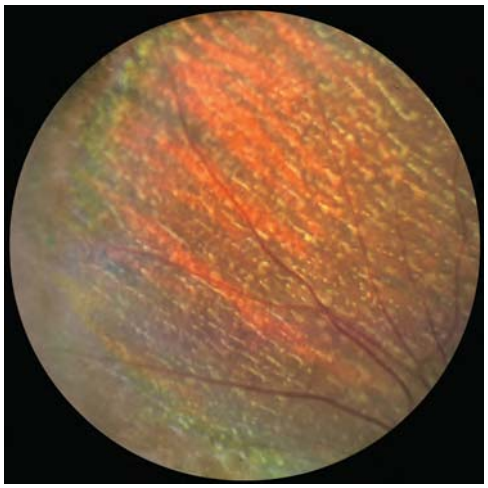

Figure 12-4 Fundus photograph of a patient with retinitis punctata albescens shows numerous deep retinal white dots. *(Courtesy of John R. Heckenlively, MD.)*

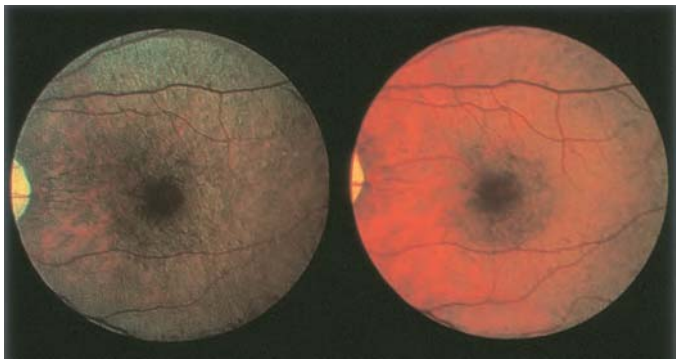

Figure 12-5 Fundus photographs showing the Mizuo-Nakamura phenomenon. The fundus of this patient with X-linked cone dystrophy is unremarkable in a dark-adapted state *(right)* but has a yellow iridescent sheen after exposure to light *(left)*.

De Silva SR, Arno G, Robson AG, et al. The X-linked retinopathies: physiological insights, pathogenic mechanisms, phenotypic features and novel therapies. *Prog Retin Eye Res*. 2021;82:100898.

Zeitz C, Robson AG, Audo I. Congenital stationary night blindness: an analysis and update of genotype-phenotype correlations and pathogenic mechanisms. *Prog Retin Eye Res*. 2015;45:58–110.

Retinal and Choroidal Dystrophies

Classification and Terminology

Most retinal and choroidal dystrophies were originally named and described purely on the basis of ophthalmoscopic appearance and clinical course, many years before the discovery of DNA. Over time, identification of additional affected patients and families, coupled with advances in gene mapping and molecular biology, has led to a compendium of specific gene defects associated with previously known phenotypes.

The Online Mendelian Inheritance in Man website (www.omim.org) lists nearly 1000 genetic disorders with significant involvement of the retina, choroid, or both. The Retinal Information Network, RetNet (https://sph.uth.edu/retnet/), lists more than 300 different retinal degenerations for which the gene locus and often the specific gene defect have been identified. These websites are regularly updated with the most current information regarding genetic aspects of retinal and choroidal disorders.

Growing knowledge of the genetic basis for these diseases further demonstrates the complexity of the association of genotype and phenotype. For example, in families in which a single mutation has been identified, the onset, severity, and course of disease can vary widely among family members (termed *variable expressivity*). Some diseases and syndromes display distinctive clinical features and are associated with only 1 gene. However, most conditions are associated with multiple genes that give rise to a similar clinical picture (termed *genetic heterogeneity*).

Historically, retinal and choroidal dystrophies have been classified in various ways, each with its logic and limitations:

- On the basis of which retinal layer is involved, such as retina, RPE, choroid, and vitreoretinal interface. These distinctions are helpful clinically but do not always correspond to the site(s) of expression of the causative gene.
- On the basis of inheritance pattern of the disease (eg, autosomal dominant, X-linked recessive, etc). However, due to genetic heterogeneity, the same phenotype may be caused in some cases by a gene on an autosomal chromosome and in other cases by a gene on the X chromosome, and each may be transmitted in either a dominant or recessive pattern.
- On the basis of disease phenotype through clinical examination and electrophysiological and psychophysical testing. However, different genes can give rise to similar phenotypes.

For convenience, this chapter organizes the retinal and choroidal dystrophies on the basis of clinical phenotypes and anatomical involvement rather than on molecular genetics. Thus, the reader will note that some genes are causative across multiple phenotypes (genetic heterogeneity), and only in rare instances is a specific phenotype defined by a unique causative gene. In this schema, disorders that typically affect the photoreceptors of the entire retina are classified separately from those that typically affect the macula predominantly, as the symptoms and prognoses of these disorders often differ. The category of disorders that affect photoreceptors diffusely or "retina-wide" is further subdivided into diseases that affect predominantly rods *(rod–cone dystrophies),* diseases that affect predominantly cones *(cone–rod dystrophies),* and diseases that affect predominantly the choroid.

Daiger SP, Sullivan LS, Bowne SJ. Genetic mechanisms of retinal disease. In: Schachat AP, Wilkinson CP, Hinton DR, Sadda SR, Wiedemann P, eds. *Ryan's Retina*. Vol 2. 6th ed. Elsevier/Saunders; 2018:711–721.

General Diagnostic Considerations

With rare exceptions, hereditary diseases of the eye have bilateral, symmetric involvement. If ocular involvement is unilateral, other causes—such as birth defects, intrauterine or antenatal infections, inflammatory diseases, or trauma—should be considered. Because retinal degenerations can also occur as part of a systemic disorder, obtaining a thorough medical history is crucial, as is ruling out any reversible or treatable cause of retinal dysfunction, such as vitamin A deficiency, autoimmune disorders, and paraneoplastic or infectious retinopathy.

Clinical diagnostic evaluation, assessment of disease severity, and monitoring of progression of chorioretinal dystrophies usually involve some combination of fundus autofluorescence (FAF), optical coherence tomography (OCT), perimetric testing, ERG, and genetic testing. Several photoreceptor dystrophies have typical phenotypes, such as the deep retinal white dots or flecks in retinitis punctata albescens (see Fig 12-4), choriocapillaris atrophy in choroideremia *(CHM),* or the crystalline deposits associated with Bietti crystalline dystrophy *(CYP4V2).* Distinctive phenotypes are the exception, however.

Generally, panretinal dystrophies or degenerations of the RPE and retina are divided into 2 groups: nonsyndromic retinopathies and syndromic retinopathies. The term *nonsyndromic*

panretinal dystrophies refers to hereditary disorders that diffusely involve photoreceptor and pigment epithelial function; these conditions are characterized by progressive visual field loss, central vision loss, and subnormal ERG responses. The disease process is confined to the eyes and is not associated with systemic manifestations. In *syndromic (secondary) panretinal dystrophies,* the retinal degeneration is associated with 1 or more organ systems, such as hearing loss (in Usher syndrome) or neurodegeneration and nephronophthisis (in Joubert syndrome; for discussion of retinal degenerations associated with systemic disease, see Chapter 13). Occasionally, when the etiology is unknown and no associated disease is present, the term *pigmentary retinopathy* is used to describe the disorder. The focus of this chapter is on the nonsyndromic retinopathies.

General Genetic Considerations

All inheritance patterns are represented among the currently known inherited retinal dystrophies. Thus, obtaining an accurate and complete family history is essential in determining the dystrophy's inheritance pattern (ie, autosomal dominant, autosomal recessive, X-linked recessive, X-linked dominant, or mitochondrial). However, patients with retinal dystrophies may have a negative family history for a variety of reasons, including lack of information, variable expressivity or incomplete penetrance within the family, or de novo mutations. It is helpful to examine relatives for any signs of asymptomatic retinal degeneration.

Molecular genetic testing helps to confirm a suspected diagnosis of retinal degeneration, to identify the causative gene(s) of a generalized phenotype, to uncover a de novo mutation, and to identify asymptomatic relatives and carriers. This type of testing is also useful for identifying syndromic versus nonsyndromic causes of retinal dystrophies, but it does not predict the penetrance, expressivity, or rate of progression of these conditions. Testing asymptomatic individuals to determine a potential future risk of vision loss is generally not warranted (unless a treatment is available), given the wide variability of expressivity.

Stone EM, Aldave AJ, Drack AV, et al. Recommendations of the American Academy of Ophthalmology Task Force on Genetic Testing. February 2014. Accessed January 5, 2022. https://www.aao.org/education/clinical-statement/recommendations-genetic-testing-of-inherited-eye-d

General Management Considerations

Management of patients with retinal degeneration should include ophthalmic evaluations every 1–2 years. Follow-up visits are appropriate to address refractive management and to monitor for the development of treatable ocular conditions: cystoid macular edema (CME), cataract, glaucoma, and retinal exudation. CME develops in 10%–20% of patients with retinal degenerations.

Patients with retinal dystrophies may understandably fear that they will become blind in the near future. The clinician should help these patients understand that total blindness is an infrequent endpoint but that the disease's impact on visual function (eg, reduced visual acuity, reduced visual field) may affect their activities and quality of life. Patients and their family members may benefit from psychological and genetic counseling. Patients with subnormal visual acuity may benefit from low vision aids, while those with advanced disease may need vocational rehabilitation and mobility training. The American Academy

of Ophthalmology's Initiative in Vision Rehabilitation, available on the ONE Network, provides information and a variety of resources, including a patient handout (www.aao.org/education/low-vision-and-vision-rehab).

Diffuse Dystrophies: Photoreceptor Dystrophies

Rod–cone dystrophies

Patients with rod–cone dystrophies, usually referred to as *retinitis pigmentosa (RP),* often present with history of nyctalopia and peripheral visual field loss. These findings correlate with the location and primary function of rod photoreceptors. The history may not be clear; patients may assume that their visual function is normal, because it is "normal" for them not to be able to see in the dark. Validated methods and instruments (such as dark-adapted ERG and visual field testing or low-luminance questionnaires) are also available for quantification of visual dysfunction.

Typical fundus findings in rod–cone dystrophy include arteriolar narrowing, with or without optic nerve head pallor, and variable amounts of bone spicule–like pigmentary changes (Fig 12-6). These pigmentary changes result from intraretinal pigment deposition by macrophages that migrate into the retina to process degenerating retinal cells. This form of pigment deposition within the retina occurs in regions of outer retinal atrophy (eg, following retinal detachment or inflammatory retinopathies) and is not specific to hereditary retinopathies. The peripheral retina and RPE may be atrophic even if intraretinal pigment is absent *(RP sine pigmento),* and the macula typically shows a loss of the foveal reflex and irregularity of the vitreoretinal interface. Autofluorescence imaging can often identify additional areas of retinal involvement that are not evident on clinical examination.

Vitreous cells, CME, epiretinal membranes, optic disc drusen, and posterior subcapsular cataracts are commonly observed in eyes with panretinal dystrophies. CME, which is detected by OCT in about one-quarter of cases, may be treatable with oral carbonic anhydrase inhibitors (Fig 12-7). In approximately 2%–5% of patients with panretinal dystrophies, areas of vascular hyperpermeability and areas of exudative retinopathy (the so-called *Coats reaction;* Fig 12-8) will develop. Eyes with rod–cone degenerations typically develop partial- to full-ring scotomata in midequatorial regions; these often expand into the periphery, leaving only a small central island of visual field (Fig 12-9). The coexistence of cataract, vitreous cells, and macular edema can sometimes lead to the mistaken diagnosis of uveitis.

The ERG response in eyes with rod–cone dystrophies typically shows a marked reduction in rod-derived responses, more than in cone-derived responses. Both a- and b-waves are reduced because the photoreceptors are primarily involved. The b-waves are characteristically prolonged in duration and diminished in amplitude. Individuals with the carrier state of X-linked recessive RP often show a mild reduction or delay in b-wave responses. Eyes with postinflammatory retinopathies (eg, retinopathies resulting from rubella) often have better preservation of the ERG than eyes with similar-appearing pigmentary changes from a hereditary retinopathy. Although the rod and cone amplitudes are reduced in postinflammatory retinopathies, the implicit times are usually within normal ranges because the remaining photoreceptors are essentially normal. In contrast, in patients with a hereditary retinopathy, the remaining photoreceptors are impaired by the

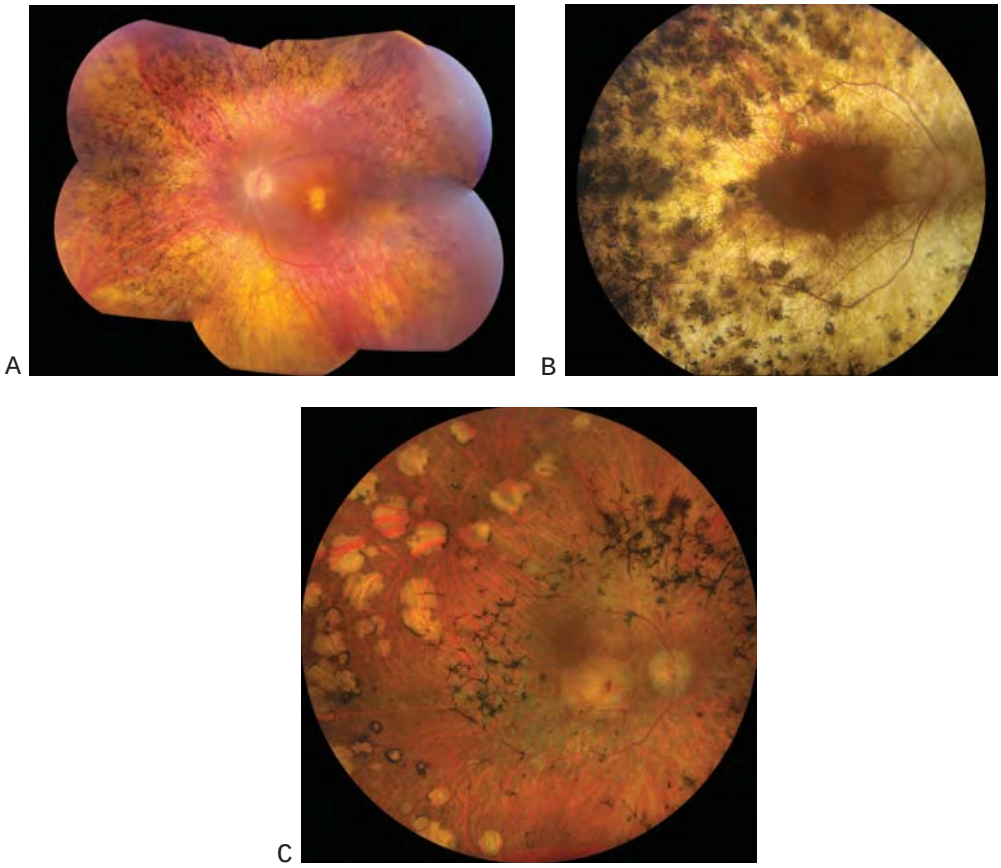

Figure 12-6 Examples of fundus findings characteristic of rod–cone dystrophy. **A,** Fundus of a 54-year-old woman with *USH2A* mutation shows optic nerve head pallor, arteriolar attenuation, macular atrophy, and widespread peripheral pigmentary alteration. Corrected distance visual acuity (CDVA) was hand motions. **B,** Fundus of a 66-year-old man with *USH2A* mutation shows extensive peripheral retinal pigment epithelium (RPE) atrophy but relative preservation of the optic nerve, macula, and arterioles. CDVA was 20/30. Note the wide differences in phenotypes between panels A and B, despite involvement of the same gene. **C,** Fundus of a 45-year-old woman with mutations in the *PCARE* and *CRB1* genes shows arteriolar attenuation, prominent RPE hyperplasia (so-called *bone spicules*) posterior to the equator, and lacunar RPE atrophy in the periphery. A tiny island of healthy retina remains in the fovea. CDVA was 20/100. *(Courtesy of Franco M. Recchia, MD.)*

genetic condition, and the ERG response shows prolonged implicit times. In conventional testing of many rod–cone dystrophies, the ERG responses may initially present as undetectable or become undetectable over time. Unless the patient has a treatable condition, such as vitamin A deficiency or an autoimmune retinopathy, repetitive ERG testing has minimal benefit for monitoring disease progression.

Sector RP refers to disease that involves only 1 or 2 sectors of the fundus (Fig 12-10). This condition is generally symmetric between eyes, which helps rule out acquired damage (eg, from trauma, vascular insult, or inflammation). Unilateral RP is extremely rare. Typical causes of unexplained unilateral pigmentary retinopathy are infection (rubella,

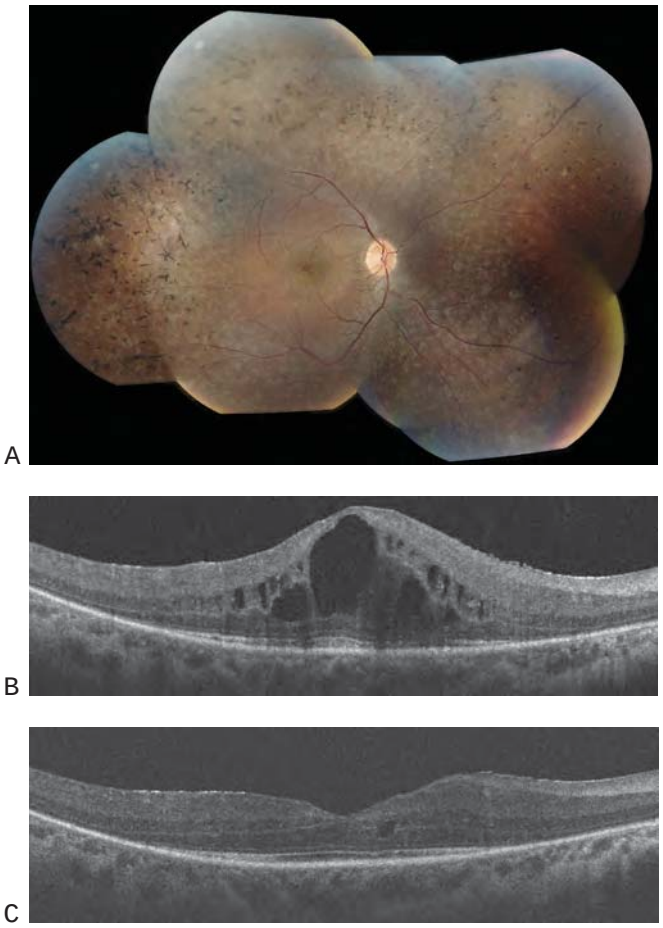

Figure 12-7 Rod–cone dystrophy (associated with a pathogenic *RDH12* variant) complicated by cystoid macular edema (CME). Montage fundus photograph **(A)** and spectral-domain optical coherence tomography (SD-OCT) **(B)** at presentation show cysts in the foveal area. CDVA was 20/50. **C,** SD-OCT 3 months after treatment was initiated with oral acetazolamide, 500 mg daily, shows a substantial reduction in macular edema. CDVA was 20/40. *(Courtesy of Franco M. Recchia, MD.)*

syphilis), inflammation, remote trauma, and retained intraocular metallic foreign body. Most cases of pigmented paravenous retinopathy are postinflammatory, have interocular asymmetry, and are usually nonprogressive.

When a suspected panretinal dystrophy is being evaluated in a patient with a negative family history *(sporadic retinal dystrophy),* it is important to consider acquired causes of retinal degeneration that can mimic hereditary conditions, including previous bilateral ophthalmic artery occlusions, diffuse uveitis, infections (eg, syphilis), paraneoplastic syndromes, and retinal drug toxicity. Syndromic forms of pigmentary retinopathy associated with metabolic or other organ system disease must also be considered (see Chapter 13).

Gregory-Evans K, Pennesi ME, Weleber RG. Retinitis pigmentosa and allied disorders. In: Schachat AP, Wilkinson CP, Hinton DR, Sadda SR, Wiedemann P, eds. *Ryan's Retina*. Vol 2. 6th ed. Elsevier/Saunders; 2018:861–935.

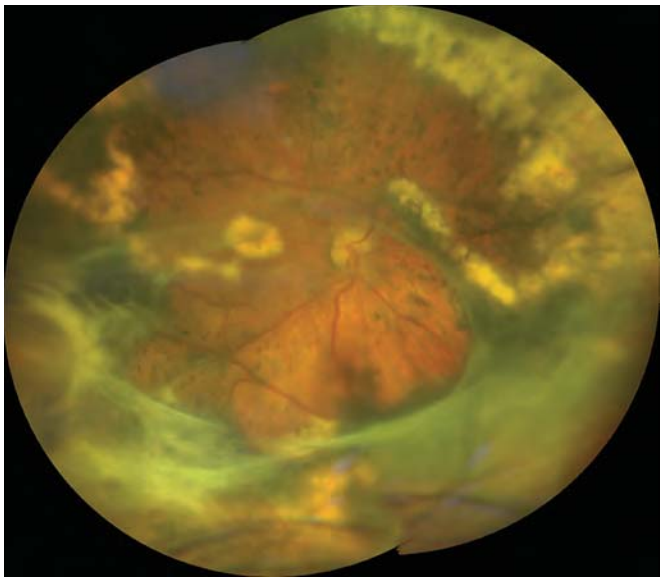

Figure 12-8 Exudative retinopathy and subsequent traction-exudative retinal detachment complicating a case of *USH2A*-associated rod–cone dystrophy. Background arteriolar attenuation and peripheral pigmentary changes are also present. *(Courtesy of Franco M. Recchia, MD.)*

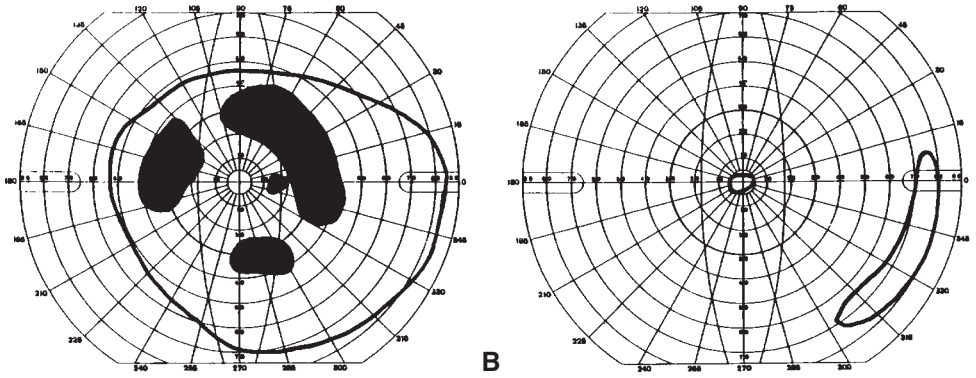

Figure 12-9 Examples of visual fields in retinitis pigmentosa (RP), which were obtained with a Goldmann III-4 test object. **A,** Early disease: midperipheral scotomata. **B,** Late disease: severe loss, sparing only a central tunnel and a far-peripheral island, which may eventually disappear. *(Courtesy of Michael F. Marmor, MD.)*

Management One large study reported that 15,000 IU/day of vitamin A palmitate slowed the decline of ERG response in eyes with RP. This generalized neuroprotective effect was not replicated in a more recent reanalysis of the original data, and avoiding vitamin E supplementation >30 IU/day is still advised. A slight benefit from supplementation with omega-3 fatty acids has been reported.

Excessive light exposure may play a role in retinal degenerations caused by rhodopsin mutations and/or genes that contribute to lipofuscin accumulation, such as *ABCA4*. Recommendations for patients to wear UV-absorbing sunglasses and brimmed hats for

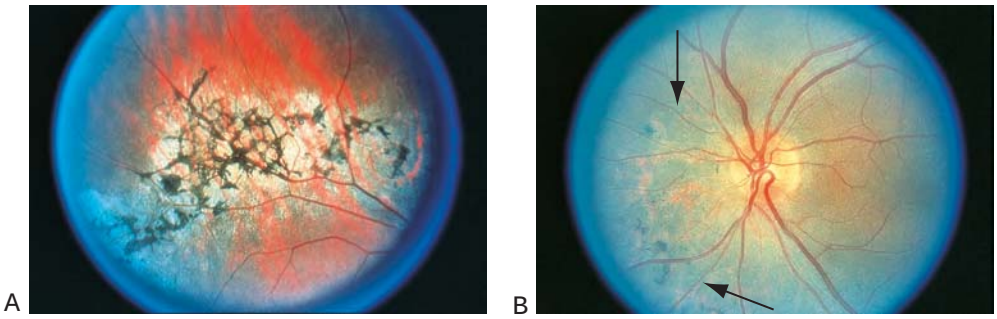

Figure 12-10 Fundus photographs of delimited forms of inherited retinal dystrophies. Note the sharp demarcation between the areas of degeneration and other regions of the fundus that appear healthy. It is important to assess interocular symmetry and the pattern of cell damage to consider acquired forms of retinopathy (such as pigmented paravenous retinopathy). **A,** Fundus with degenerative changes near the arcades. **B,** Fundus with sector RP *(between arrows),* showing vascular narrowing and spicules only in the inferonasal quadrant. *(Courtesy of Michael F. Marmor, MD.)*

protection from high levels of light exposure seem prudent, despite the absence of direct evidence of benefit.

Efforts to restore at least some vision in patients rendered completely blind from RP have included the use of electronic chips that interface with the remaining retinal tissue or directly with the visual cortex. At least 5 variations of a "retinal prosthesis" have been, or continue to be, investigated. Other therapeutic investigative efforts involve gene therapy and stem cell transplantation.

Comander J, Weigel DiFranco C, Sanderson K, et al. Natural history of retinitis pigmentosa based on genotype, vitamin A/E supplementation, and an electroretinogram biomarker. *JCI Insight*. 2023;8(15):e167546. doi:10.1172/jci.insight.167546

Salvatore S, Fishman GA, Genead MA. Treatment of cystic macular lesions in hereditary retinal dystrophies. *Surv Ophthalmol.* 2013;58(6):560–584.

Cone and cone–rod dystrophies

The cone dystrophies comprise a heterogeneous group of hereditary diseases with more than 25 identified causative genes. Patients with *cone dystrophy* typically present with progressive loss of central vision and color discrimination (reflecting the primary location and function of cone photoreceptors). They may also experience hemeralopia (day blindness) and photophobia (discomfort and/or pain in the presence of normal levels of light). Onset of symptoms typically occurs in the teenage years or later adulthood. Ophthalmoscopy may be normal early in the course of the disease. In other patients, ophthalmoscopy may reveal the typical symmetric bull's-eye pattern of macular atrophy (Fig 12-11) or more severe atrophy, such as demarcated circular macular lesions. Mild to severe temporal optic atrophy and tapetal retinal reflexes (with a glistening greenish or golden sheen) may also be present. Unlike macular dystrophies, the cone dystrophies are more associated with color discrimination symptoms and photophobia; and as such, they must be differentiated from color vision defects.

Cone dystrophies are diagnosed when ERG results indicate a subnormal or undetectable photopic ERG response and a normal or near-normal rod-isolated ERG response. When present, the LA 3.0 30-Hz ERG response is almost invariably delayed, in keeping with generalized

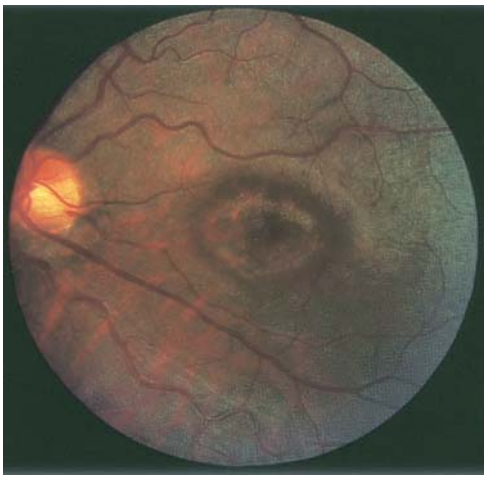

Figure 12-11 Fundus photograph of cone dystrophy shows the bull's-eye pattern of central atrophy.

cone system dysfunction. Peripheral visual fields may remain normal. The cone dystrophies are progressive. In some patients, secondary rod photoreceptor involvement develops in later life, suggesting overlap between progressive cone dystrophies and cone–rod dystrophies.

Similar to patients with cone dystrophies, patients with *cone–rod dystrophies* typically present with reduced central vision and symptoms of dyschromatopsia and photophobia. On visual field testing, some patients show a tight ring or central scotoma within the central 20° or 30° of the visual field. Ophthalmoscopy may initially be normal; later, it may demonstrate intraretinal pigment in areas of retinal atrophy in the fundus periphery, and patients may report progressive nyctalopia. The diagnostic ERG hallmark of a cone–rod dystrophy is that the cone-derived full-field ERG responses are more subnormal than the rod ERG responses (see Chapter 3, Fig 3-2).

Leber congenital amaurosis

The dystrophies that are typified by early onset and rapid progression of severe bilateral vision loss are collectively termed *Leber congenital amaurosis* (*LCA;* see also BCSC Section 6, *Pediatric Ophthalmology and Strabismus,* Chapter 24). LCA is characterized by severely reduced vision from birth, usually associated with wandering nystagmus. Infants exhibit limited to no visual response, and visual acuities tend to range between 20/200 and no light perception. Some infants with LCA rub or poke their eyes (the *oculodigital reflex*) in order to create visual stimulation, as do other infants with poor vision.

In the early stages, obvious fundus changes are rare, and molecular genetic testing offers the best method of distinguishing stationary and progressive hereditary retinopathies. In addition, because there are both syndromic and nonsyndromic forms of LCA, a molecular genetic diagnosis can help identify potential systemic features that warrant medical management. Some forms of LCA involve developmental defects, while others appear to represent degenerations of normally formed retina. Postinfectious etiologies should be considered based on history and clinical findings. Central macular atrophic lesions (sometimes incorrectly referred to as *macular colobomas*) are often seen in eyes with LCA, in addition to early-onset cataracts and keratoconus in older children. Most children

with nonsyndromic LCA have normal intelligence, and some of the observed psychomotor impairment may be secondary to sensory deprivation.

The ERG response is typically minimal or undetectable, but ERG testing cannot differentiate stationary (CSNB or achromatopsia) from progressive (rod–cone dystrophy or cone–rod dystrophy) conditions. LCA typically progresses the most rapidly of these conditions.

Autosomal dominant and autosomal recessive inheritance of LCA have been linked to at least 3 genes and 23 genes, respectively. There is some overlap in the genes responsible for LCA and those that cause later-onset retinal dystrophies (both rod–cone and cone–rod). In 2017, the US Food and Drug Administration issued the first approval for a gene therapy, voretigene neparvovec-rzyl (Luxturna, Spark Therapeutics), for *RPE65*-linked LCA in individuals aged 1 year or older. See Chapter 20 for further discussion of gene therapy.

Russell S, Bennett J, Wellman JA, et al. Efficacy and safety of voretigene neparvovec (AAV2-hRPE65v2) in patients with RPE65-mediated inherited retinal dystrophy: a randomised, controlled, open-label, phase 3 trial. *Lancet*. 2017;390(10097):849–860. Published correction appears in *Lancet*. 2017;390(10097):848.

Enhanced S-cone syndrome

The most prominent features of the severe form of enhanced S-cone syndrome (ESCS), also known as *Goldmann-Favre syndrome,* include nyctalopia, increased sensitivity to blue light, pigmentary retinal degeneration, an optically empty vitreous, hyperopia, pathognomonic ERG abnormalities, and varying degrees of peripheral to midperipheral visual field loss (Fig 12-12). The posterior pole may show round, yellow, sheenlike lesions along the arcades, accompanied by areas of diffuse degeneration. Deep nummular pigmentary deposition is usually observed at the level of the RPE around the vascular arcades. Macular (and sometimes peripheral) schisis may be present, overlapping the phenotype of X-linked retinoschisis. The ERG response includes no detectable DA 0.01 signal; delayed and simplified responses to a brighter flash that have the same waveform under both DA and LA conditions; and a LA 3.0 30-Hz response of lower amplitude than that of the LA 3.0 (photopic single-flash) a-wave.

Eyes with ESCS have an overabundance of blue cones, a reduced number of red and green cones, and few, if any, functional rods. This condition is unique in that it is both a developmental and degenerative photoreceptor retinopathy. ESCS is autosomal recessive and results from homozygous or compound heterozygous mutations in *NR2E3*. The visual prognosis is highly variable.

Diffuse Dystrophies: Choroidal Dystrophies

Widespread primary retinal or RPE disease that causes advanced atrophy of the choriocapillaris occurs in choroideremia, gyrate atrophy, Bietti crystalline dystrophy, and phenothiazine-related retinal toxicity (see also Chapter 14). In FAF imaging, hypoautofluorescence in the areas of atrophy is typically observed in all of these conditions and is therefore helpful for monitoring the disease progression.

Choroideremia

Patients with choroideremia have nyctalopia and show progressive peripheral visual field loss over 3–5 decades. Most patients maintain good visual acuity until a central island of

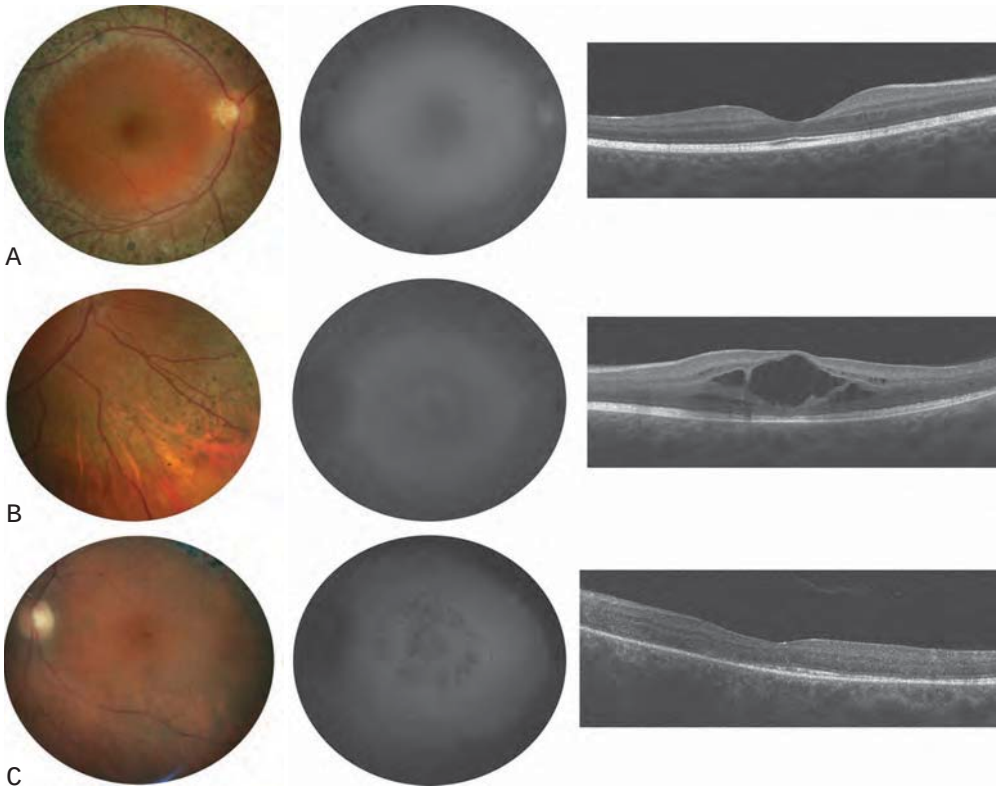

Figure 12-12 Clinical characteristics of enhanced S-cone syndrome. In the early stages, the fundus may be normal. In older subjects, the fundus usually shows 360° nummular pigmentary changes outside the vascular arcades at the level of the RPE **(A–C).** The macula may show changes resulting from schisis or nonspecific pigment epithelial changes **(C).** The autofluorescence is variable **(D–F).** There may be hyperautofluorescence within the arcades that either spares or involves the foveal region. SD-OCT imaging of the macula may be normal **(G)** or show schitic and/or cystoid changes **(H)** or outer retinal abnormalities **(I).** *(Reproduced with permission from Vincent A, Robson AG, Holder GE. Pathognomonic (diagnostic) ERGs. A review and update.* Retina. *2013;33(1):5–12. doi:10.1097/IAE.0b013e31827e2306)*

foveal vision is lost. The degeneration initially manifests as mottled areas of pigmentation in the anterior equatorial region and macula. The anterior areas gradually degenerate toward the posterior pole to form confluent scalloped areas of RPE and choriocapillaris loss; larger choroidal vessels are preserved (Fig 12-13). The retinal vessels appear normal, and there is no optic atrophy.

On fluorescein angiography, the changes are pronounced: the scalloped areas of missing choriocapillaris appear hypofluorescent next to brightly hyperfluorescent areas of perfused choriocapillaris with intact overlying RPE. FAF imaging shows a characteristic speckled pattern of autofluorescence in the nonatrophic areas. The ERG response is subnormal early in the course of the disease and is generally extinguished by midlife. Because phenotypes can overlap with other conditions, especially other choroidal dystrophies, the clinical and imaging features should not be considered pathognomonic.

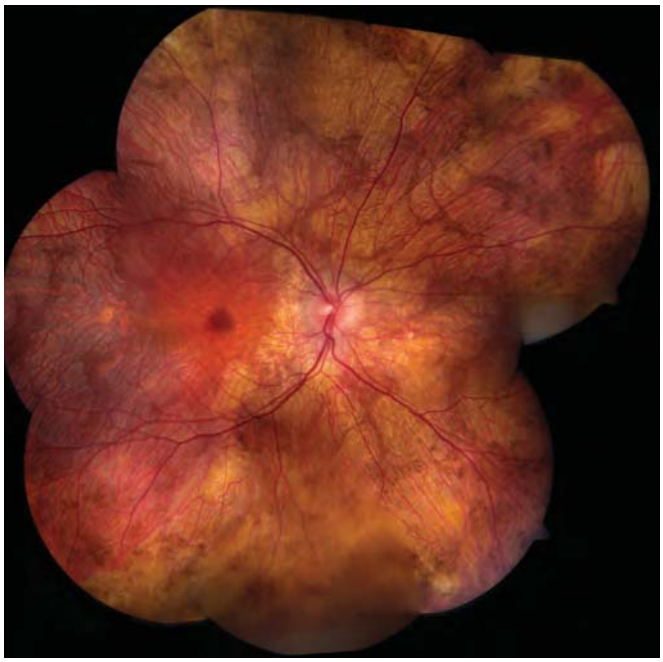

Figure 12-13 Montage fundus photograph of a 22-year-old patient with choroideremia. *(Courtesy of Cagri G. Besirli, MD.)*

Choroideremia is X-linked and caused by mutations in *CHM,* which is constitutively expressed and encodes geranylgeranyl transferase Rab escort protein (REP1). REP1 plays an essential role in the intracellular trafficking of proteins, substrates, and organelles by mediating proper lipid modification (prenylation) of specific G proteins called *Rab proteins.* Carriers of choroideremia are usually asymptomatic and have normal ERGs. However, they often show patches of subretinal black mottled pigment, and occasionally, older female carriers show a lobular pattern of choriocapillaris and RPE loss. Gene therapy trials for choroideremia are ongoing.

Edwards TL, Jolly JK, Groppe M, et al. Visual acuity after retinal gene therapy for choroideremia. *N Engl J Med.* 2016;374(20):1996–1998.

Gyrate atrophy

Patients affected by gyrate atrophy usually develop nyctalopia during the first decade of life and experience progressive loss of visual field and visual acuity later in the course of the disease. Macular edema is commonly present. In the early stages of the disease, patients have large, geographic, peripheral paving-stone–like areas of atrophy of the RPE and choriocapillaris, which gradually coalesce to form a characteristic scalloped border at the junction of normal and abnormal RPE (Fig 12-14). Gyrate atrophy is an autosomal recessive dystrophy caused by mutations in *OAT,* the gene for ornithine aminotransferase. The diagnosis is supported by elevated plasma levels of ornithine, as well as by genetic testing for mutations of *OAT*. If started at a young age, aggressive dietary restriction of

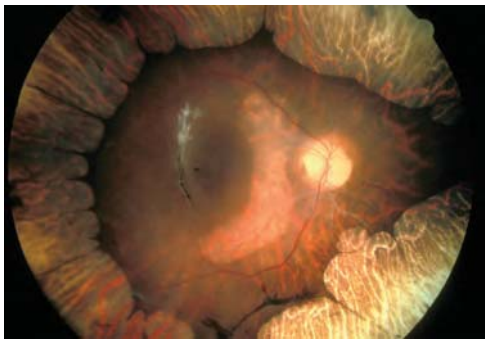

Figure 12-14 Gyrate atrophy. Wide-angle fundus photograph shows scalloped edges of the remaining posterior retina, as is typically seen in gyrate atrophy. A crescent of nasal macular atrophy is also present. *(Courtesy of Colin A. McCannel, MD.)*

arginine intake and, in some cases, vitamin B_6 supplementation can slow or halt progression of the retinal degeneration.

Bietti crystalline dystrophy

Individuals with Bietti crystalline dystrophy develop symptoms of nyctalopia, decreased vision, and paracentral scotomata in the second to fourth decades of life. On examination, intraretinal yellow-white crystals are visible in the posterior retina and in the peripheral cornea near the limbus. As the disease progresses, widespread retinochoroidal atrophy develops and peripheral vision worsens. The condition is a very rare autosomal recessive disorder caused by mutations in the gene *CYP4V2*. There is no known treatment.

Macular Dystrophies

Stargardt disease

With an incidence of roughly 1 in 10,000, Stargardt disease is the most common juvenile macular dystrophy and a common cause of central vision loss in adults younger than 50 years. The visual acuity in Stargardt disease typically ranges from 20/50 to 20/200.

The classic Stargardt phenotype is characterized by a juvenile-onset foveal atrophy surrounded by discrete, yellowish, round or pisciform (fish-shaped) flecks at the level of the RPE (Fig 12-15). These flecks represent excessive accumulation of lipofuscin, a waste product of RPE metabolism, within the RPE cells. On fluorescein angiography, 80% or more of patients with Stargardt disease have a "dark choroid," in which blocking of choroidal fluorescence by swollen, lipofuscin-laden RPE cells accentuates the retinal circulation (see Fig 12-15B). FAF imaging is a more reliable means of demonstrating elevated background autofluorescence and characteristic findings, including peripapillary sparing of RPE changes, central macular hypoautofluorescence, and over time, an outward expanding pattern of hyperautofluorescent flecks that leave hypoautofluorescent areas in their wake. Full-field ERGs are not diagnostic for this condition.

The age at onset and presentation of the clinical features in Stargardt disease vary, sometimes even among individuals in the same family. The condition is usually slowly progressive with the accumulation of lipofuscin in the RPE (Fig 12-16). In later stages, atrophic maculopathy, with or without lipofuscin flecks and panretinal degeneration, can be observed.

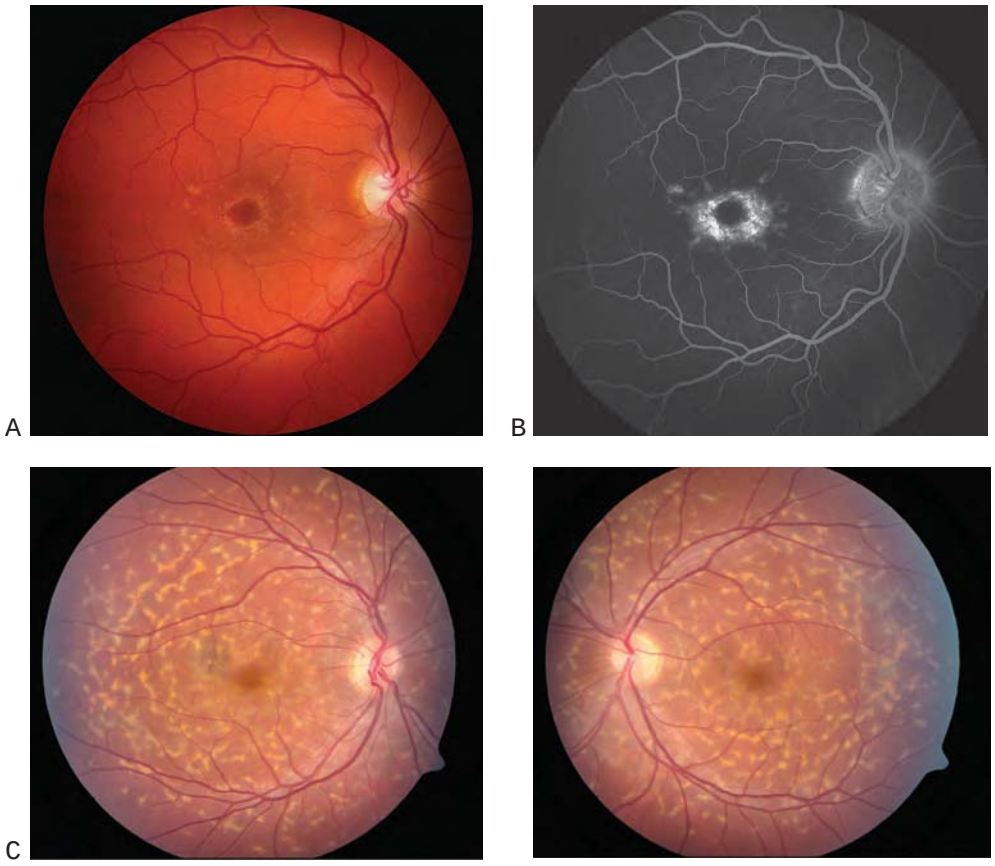

Figure 12-15 Examples of Stargardt disease. **A,** Fundus photograph shows paramacular yellowish flecks and "beaten-bronze" central macular atrophy. **B,** Fluorescein angiography image of the same eye shows a dark choroid, hyperfluorescence associated with the flecks, and bull's-eye pattern of macular transmission defect. **C, D,** Fundus photographs of the right and left eye, respectively, show classic multiple, discrete, yellowish, pisciform (fish-shaped) flecks scattered throughout the posterior pole. *(Parts A and B courtesy of Mark W. Johnson, MD; parts C and D courtesy of Paul Sternberg Jr, MD.)*

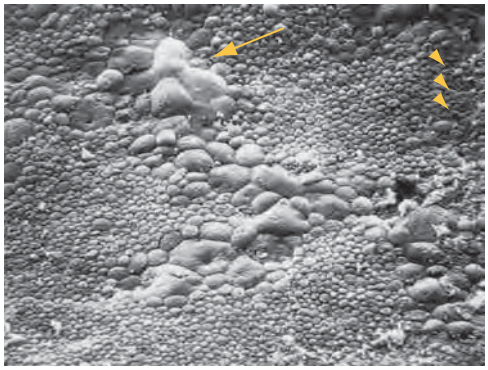

Figure 12-16 Scanning electron micrograph of the RPE in Stargardt disease. The regions of RPE cells engorged with abnormal lipofuscin-like material *(arrow)* are seen clinically as yellowish flecks. Note that the cells comprising the normal RPE monolayer are substantially smaller *(arrowheads)*. *(Reproduced from Eagle RC Jr, Lucier AC, Bernardino VB Jr, Yanoff M. Retinal pigment epithelial abnormalities in fundus flavimaculatus: a light and electron microscopic study.* Ophthalmology. *1980;87(12):1189–1200. Copyright 1980, modified with permission from Elsevier.)*

Most cases of Stargardt disease are autosomal recessive and are caused by mutations in *ABCA4*. However, autosomal dominant transmission patterns can result from mutations in other genes, most notably *ELOVL4, PROM1,* and *PRPH2 (RDS/peripherin)*. The *ABCA4* gene encodes an adenosine triphosphate (ATP)-binding cassette transporter protein expressed by rod outer segments and RPE. Dysfunction of this transporter protein impairs the proper disposal of lipofuscin, which is toxic to RPE cells. In animal models of *ABCA4*-related disease, vitamin A supplementation accelerates the accumulation of lipofuscin pigments in the RPE and, in conjunction with blue light, also accelerates retinal cell death. Drug therapies to reduce lipofuscin accumulation, gene therapies, and stem cell treatments are currently undergoing clinical trials.

A clinical variant termed *fundus flavimaculatus* results from mutations in the same genes that cause Stargardt disease and can be present in families with the classic Stargardt phenotype. In patients with the variant, the flecks are widely scattered throughout the fundus but spare the macula.

Best disease, or Best vitelliform dystrophy

Individuals affected by Best disease frequently develop a yellow, egg yolk–like *(vitelliform)* macular lesion in childhood. The solid-appearing vitelliform lesion eventually breaks down, leaving a mottled geographic atrophy appearance (Fig 12-17). The breakdown of the solid lesion can proceed over years or even decades. Late in the course of the disease, the geographic atrophy may be difficult to distinguish from other types of macular degeneration or dystrophy. Some patients (up to 30% in some series) have extrafoveal vitelliform lesions in the fundus. The macular appearance in all stages is deceptive, as most patients maintain relatively good visual acuity throughout the course of the disease. Even patients with "scrambled-egg" macular lesions typically have visual acuities from 20/30 to 20/60. In approximately 20% of patients, a choroidal neovascular membrane develops in at least 1 eye.

The ERG response is characteristically normal, but the electro-oculogram (EOG) result is almost always abnormal, even in apparently unaffected, asymptomatic individuals who have the causative genetic variant but have normal-appearing fundi (ie, carriers). The light peak to dark trough ratio (Arden ratio) of the EOG (see Chapter 3) is typically 1.5 or less. Before ordering an EOG to rule out Best disease, the clinician should ensure that the full-field ERG is normal.

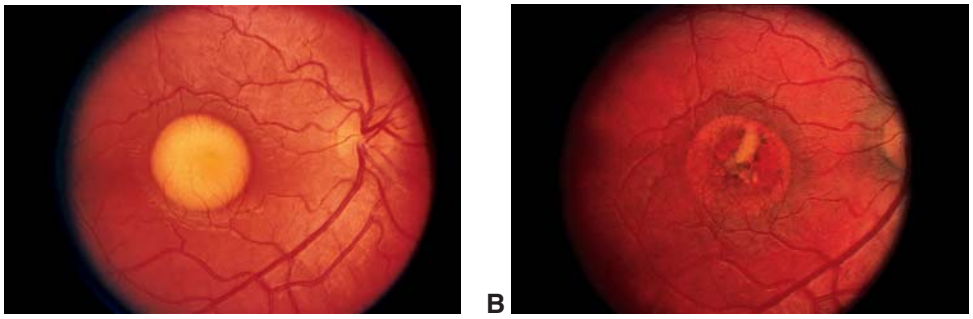

Figure 12-17 Fundus photographs of Best vitelliform dystrophy. **A,** Characteristic "yolk" stage, during which visual acuity is typically good. **B,** Atrophy and scarring after the yolk breaks down. *(Courtesy of Mark W. Johnson, MD.)*

Best disease is an autosomal dominant maculopathy caused by mutations in the *BEST1* gene (also known as *VMD2*). The encoded protein bestrophin localizes to the basolateral plasma membrane of the RPE and functions as a transmembrane ion channel. Although some *BEST1* variants cause autosomal dominant disease, other mutations, when present as homozygous or compound heterozygous variants, can give rise to *autosomal recessive bestrophinopathy (ARB).* Unlike Best disease, ARB is associated with progressive retinal dysfunction on the full-field ERG, loss of visual acuity, diffuse irregularity of the RPE, and dispersed punctate flecks that are distinct from extramacular vitelliform lesions.

Agarwal A. *Gass' Atlas of Macular Diseases*. 5th ed. Saunders; 2011:278–280.
Boon CJ, Klevering BJ, Leroy BP, Hoyng CB, Keunen JE, den Hollander AI. The spectrum of ocular phenotypes caused by mutations in the *BEST1* gene. *Prog Retin Eye Res.* 2009; 28(3):187–205.

Conditions and disorders with adult-onset vitelliform lesions

Several conditions and disorders feature adult-onset macular vitelliform lesions. The most common of these disorders, *adult-onset foveomacular vitelliform dystrophy,* is one of the pattern dystrophies (discussed later in this chapter). It is characterized by yellow subfoveal lesions that are bilateral, round or oval, and typically one-third disc diameter in size; they often contain a central pigmented spot (Fig 12-18). Occasionally, when the lesions are larger, the patient may be misdiagnosed as having Best disease or even age-related macular degeneration. This dystrophy generally appears in the fourth to sixth decades of life in patients who either are visually asymptomatic or have mild blurring and metamorphopsia. Eventually, the lesions may fade, leaving an area of RPE atrophy, but most patients retain reading vision in at least 1 eye throughout their lives. Autosomal dominant inheritance has been recognized in some affected families. The most common causative gene is *PRPH2,* and there is evidence of genetic heterogeneity for this phenotype.

Patients with numerous basal laminar (cuticular) drusen may develop an unusual *vitelliform exudative macular detachment* (Fig 12-19), which can be mistaken for choroidal neovascularization (CNV) because of the subretinal hyporeflectivity on OCT. The diagnosis of CNV can be confirmed by the presence of leakage (enlarging and increasing hyperfluorescence over time) on fluorescein angiography or OCT angiography. In the absence of CNV, the angiographic findings are early blockage by the subretinal material and late staining without lesion enlargement.

Some patients with large soft drusen have a large, central coalescence of drusen, or *drusenoid RPE detachment,* which may occasionally mimic a macular vitelliform lesion (Fig 12-20). Such lesions often have pigment mottling on their surface and are surrounded by numerous other individual or confluent soft drusen. They may remain stable (and allow good vision) for many years, but eventually they tend to flatten and evolve into geographic atrophy.

Early-onset "drusenoid" macular dystrophies

Drusen are commonly seen in the aging fundus but are also a component of age-related macular degeneration (AMD), which is exceedingly rare before the age of 50. The term *early-onset drusen,* therefore, refers to the spectrum of deep and subretinal yellow-white lesions that occur in younger patients. Macular dystrophies associated with early-onset drusen are entities that are typically distinct from AMD in their presentation and clinical course. However,

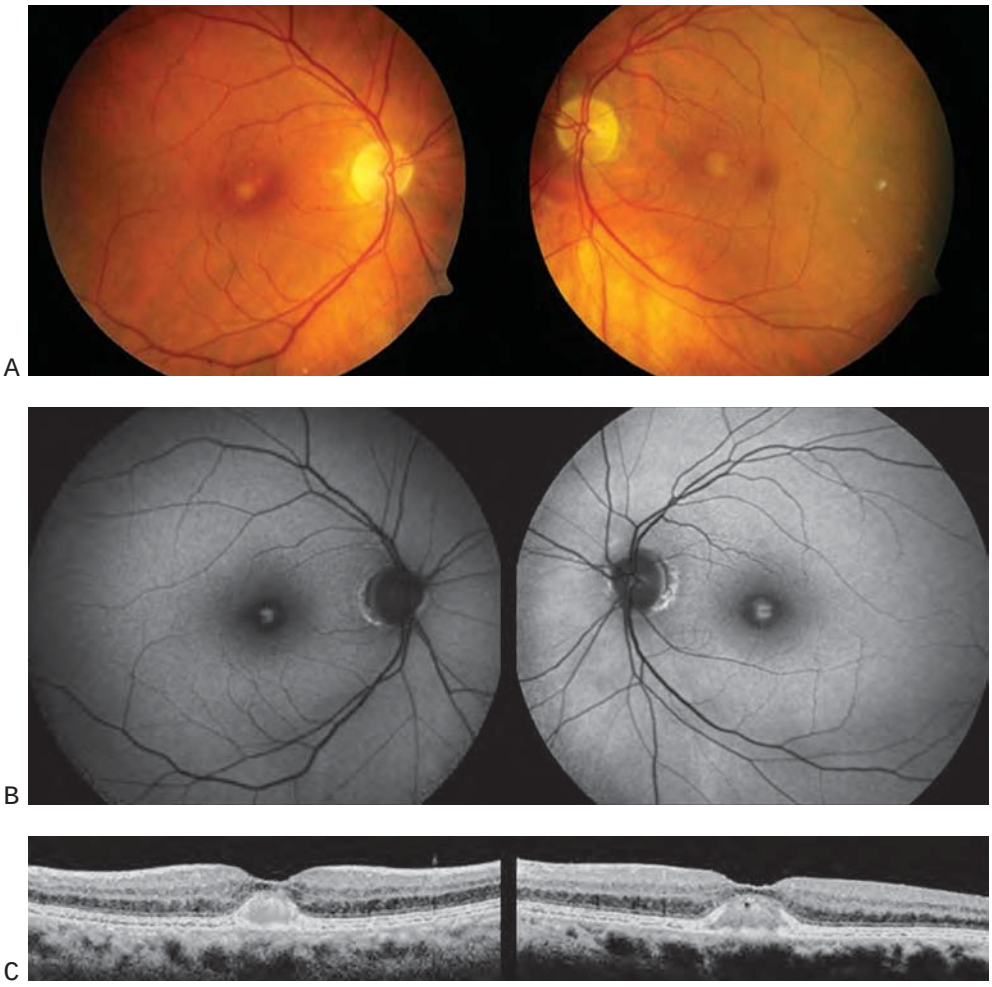

Figure 12-18 Adult-onset foveomacular vitelliform dystrophy. (*Left panels* in each part show the right eye, and *right panels* show the left eye of the same patient.) **A,** Fundus photographs demonstrate small, round, yellow subfoveal lesions. **B,** The lesions are hyperautofluorescent on autofluorescence imaging. **C,** SD-OCT images show the reflective, dome-shaped subfoveal material elevating the overlying neurosensory retina. *(Courtesy of Stephen J. Kim, MD.)*

the causative genes in several juvenile and early-onset macular dystrophies are the same as the genes that have been implicated in the complex genetic disorder of AMD. Although they are frequently referred to as *familial* or *autosomal dominant drusen,* the clinician needs to establish whether other family members are affected before assuming an inheritance pattern.

Drusen are numerous and of various sizes, typically extending beyond the vascular arcades and nasal to the optic nerve head (Fig 12-21). Early-onset drusen have been classified into 3 entities: large colloid drusen, Malattia Leventinese drusen, and cuticular drusen (Fig 12-22). On fundus examination, large colloid drusen appear as bilateral large, yellowish lesions located in the macula and/or the periphery of the retina. The vitelliform lesions are hyperautofluorescent on FAF and are thought to be made up of lipofuscin, while the associated

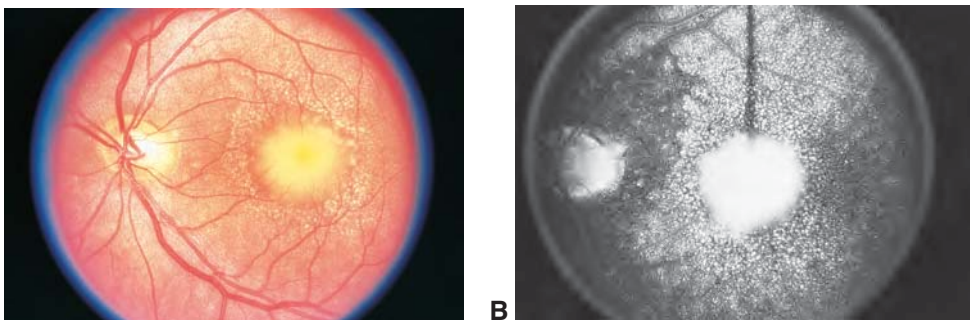

Figure 12-19 Vitelliform exudative macular detachment. **A,** Fundus photograph of a vitelliform lesion associated with numerous cuticular (basal laminar) drusen. **B,** Corresponding late-phase fluorescein angiography image shows staining of the drusen and vitelliform lesion. *(Courtesy of Michael F. Marmor, MD.)*

Figure 12-20 Fundus photograph shows central coalescence of large drusen simulating a macular vitelliform lesion. *(Courtesy of Mark W. Johnson, MD.)*

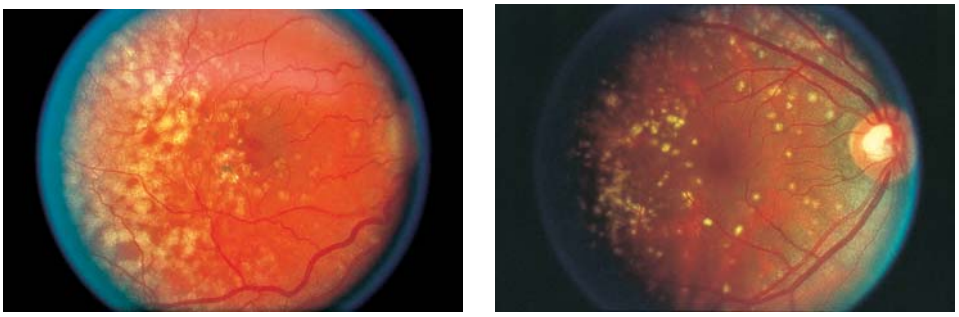

Figure 12-21 Fundus photographs of different manifestations of early-onset drusen. Variable size and distribution of the drusen are evident. *(Courtesy of Michael F. Marmor, MD.)*

surrounding cuticular drusen and/or subretinal drusenoid deposits are generally not autofluorescent. The drusen of *Malattia Leventinese* (also called *Doyne honeycomb dystrophy*) often show a distinctive pattern of radial extensions of small and intermediate-sized deposits emanating from the fovea. The condition is caused by a shared single autosomal dominant mutation in the gene *EFEMP1*, which to date has not been associated with AMD risk. Patients generally retain good central visual acuity through their sixth decade, after which visual acuity generally deteriorates to 20/200 or worse because of progressive RPE atrophy.

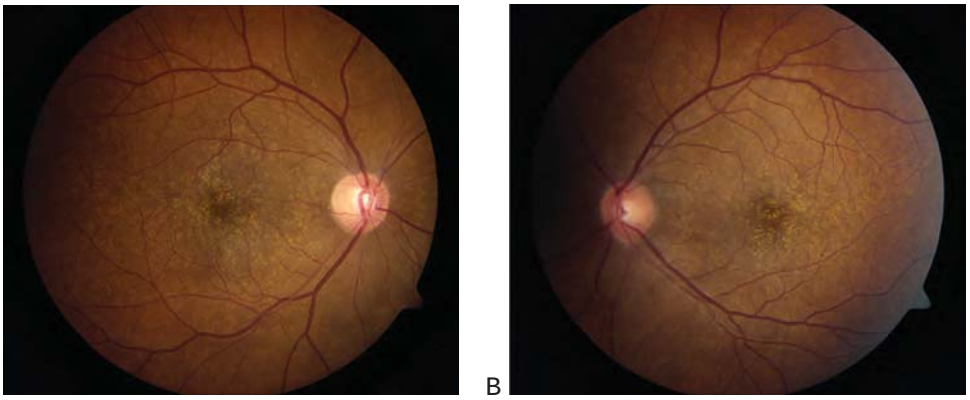

Figure 12-22 Basal laminar (cuticular) drusen. Fundus photographs of the right **(A)** and left **(B)** eyes of a 38-year-old man with numerous round, yellow drusen scattered in the macula. Basal laminar (cuticular) drusen are present between the plasma membrane of the RPE and its basement membrane and are more easily seen on angiography and in young patients with brunette fundi. *(Courtesy of Stephen J. Kim, MD.)*

Sorsby macular dystrophy (SMD) is a rare cause of bilateral central vision loss by the fifth decade of life. Early signs of SMD are yellowish-gray drusenlike deposits or a confluent plaque of yellow material at the level of Bruch membrane within the macula and along the temporal arcades. The deposits progress over time to include the central macula and take on the appearance of geographic atrophy, with pronounced clumps of black pigmentation around the central ischemic and atrophic zone (a pseudoinflammatory appearance). Vision loss results from expansion of macular atrophy or from development of subfoveal CNV (Fig 12-23). SMD is inherited in an autosomal dominant pattern and results from mutations in *TIMP3,* which plays an important role in the regulation of extracellular matrix turnover. Both common and rare variants of *TIMP3* have been implicated in the pathogenesis of AMD.

Other drusenlike deposits that manifest before 50 years of age include those associated with several hereditary basement membrane abnormalities that lead to significant renal disease. They include Alport syndrome, membranoproliferative glomerulonephritis type II, and atypical hemolytic uremia syndromes.

Pattern dystrophies

The pattern dystrophies are a group of disorders characterized by the development, typically in midlife, of various patterns of yellow, orange, or gray pigment deposition at the level of the RPE within the macula. These dystrophies have been divided into 5 major subtypes according to the distribution of pigment deposits:

- adult-onset foveomacular vitelliform dystrophy (discussed earlier in this chapter)
- butterfly-type pattern dystrophy (Fig 12-24)
- reticular-type pattern dystrophy (Fig 12-25)
- multifocal pattern dystrophy simulating fundus flavimaculatus (Fig 12-26A)
- fundus pulverulentus ("dustlike," coarse pigment mottling (Fig 12-26B)

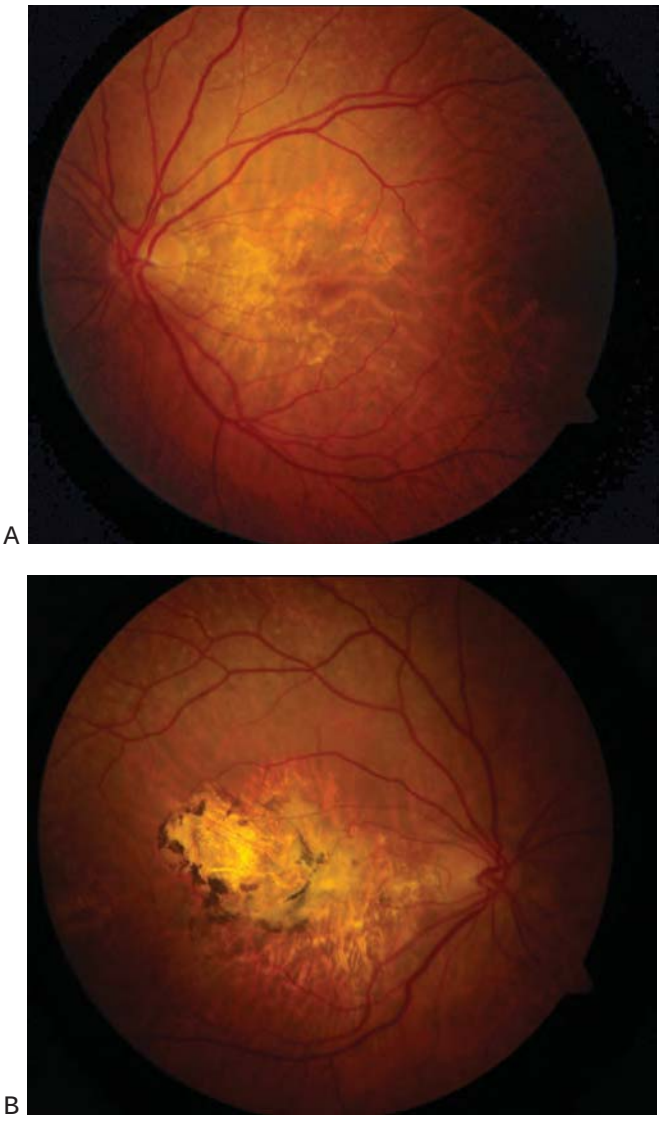

Figure 12-23 Fundus photographs from a 54-year-old woman with Sorsby macular dystrophy. Characteristic pale drusen are seen just outside the macula in both eyes. **A,** There is fovea-sparing geographic atrophy in the left eye. **B,** The more severely affected right eye has subretinal fibrosis as well as geographic atrophy. *(Courtesy of Cagri G. Besirli, MD.)*

Pattern dystrophy may best be considered as a single disease with variable expressivity. Different patterns are known to occur in members of the same family carrying an identical mutation. Furthermore, one pattern can evolve into another within a single patient.

Patients are often asymptomatic and diagnosed incidentally. The most common presenting symptom is diminished visual acuity or mild metamorphopsia. Overall, the visual prognosis is good, as the risk of developing CNV is low. Geographic macular atrophy may eventually develop in some cases.

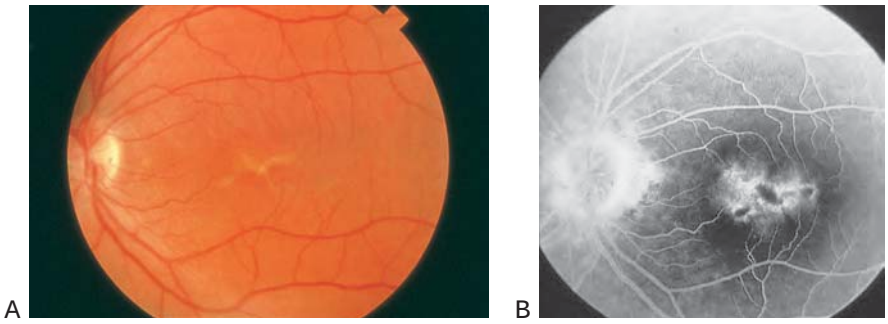

Figure 12-24 Butterfly-type pattern dystrophy. **A,** Color fundus photograph from a 56-year-old woman shows a typical yellow macular pigment pattern. **B,** Fluorescein angiography image shows blocked fluorescence of the pigment lesion itself and a rim of hyperfluorescence from surrounding RPE atrophy. *(Reproduced from Song M-K, Small KW. Macular dystrophies. In: Regillo CD, Brown GC, Flynn HW Jr, eds.* Vitreoretinal Disease: The Essentials. *Thieme; 1999:297. With permission from Thieme. www.thieme.com)*

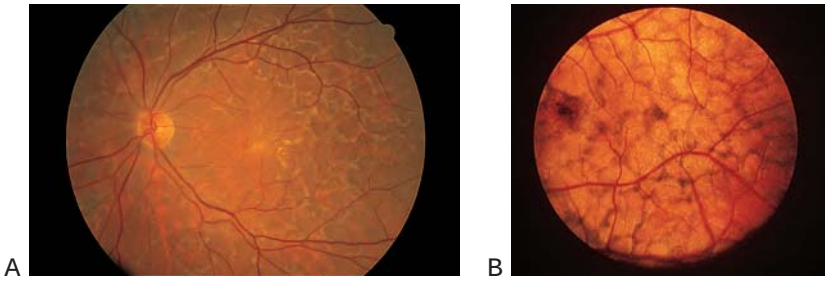

Figure 12-25 Fundus photographs show 2 examples of reticular-type pattern dystrophy, characterized by a "fishnet" pattern of yellowish-orange **(A)** or brown **(B)** pigment deposition in the posterior fundus. *(Courtesy of Mark W. Johnson, MD.)*

The pattern of inheritance is often autosomal dominant, but other modes of inheritance have been observed, including autosomal recessive and mitochondrial. Most cases of autosomal dominant pattern dystrophy have been associated with mutations in *PRPH2*. Mutations in *BEST1* and *CTNNA1* have also been identified. Associations of pattern dystrophy with pseudoxanthoma elasticum and various forms of muscular dystrophy have been reported.

Atypical and occult macular dystrophies

Several atypical macular dystrophies have been described. Among them are central areolar choroidal dystrophy, North Carolina macular dystrophy, and occult macular dystrophy.

Central areolar choroidal dystrophy is a hereditary (usually autosomal dominant) retinal disorder typically resulting in a well-defined area of atrophy of the RPE and choriocapillaris in the center of the macula (Fig 12-27). Dysfunction of macular photoreceptors usually leads to a decrease in visual acuity by the age of 30–60 years. The genes *PRPH2, GUCY2D,* and *GUCA1A* have been identified as causative.

North Carolina macular dystrophy is an autosomal dominant, completely penetrant, congenital, and stationary maldevelopment of the macula. There is substantial phenotypic

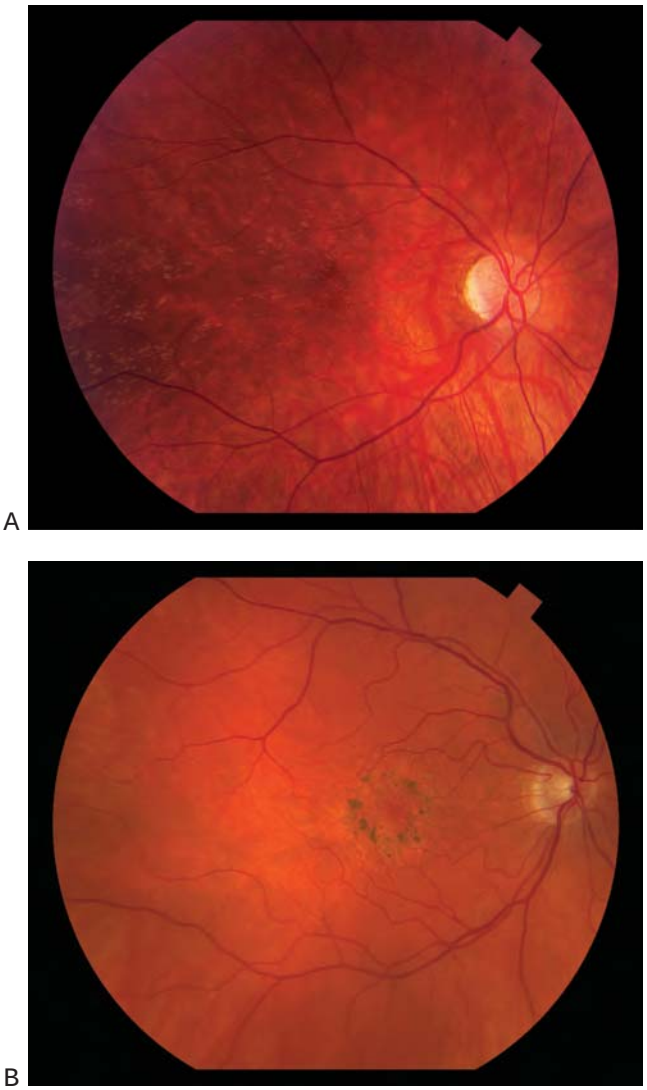

Figure 12-26 Two additional patterns of early-onset macular dystrophy. **A,** Multifocal pattern dystrophy simulating fundus flavimaculatus. **B,** Fundus pulverulentus. *(Courtesy of Franco M. Recchia, MD.)*

variability, with 3 grades of severity: grade 1, drusen; grade 2, confluent drusen; and grade 3, coloboma-like excavated defects in the macula that sometimes resemble the lesions of toxoplasmosis (Fig 12-28). The visual acuity in eyes with North Carolina macular dystrophy can be surprisingly good, given the appearance of the macula. However, CNV and fibrosis can develop and lead to deterioration in visual acuity. Three chromosomal loci, from which 1 gene *(PROM1)* has been identified, have been implicated.

Occult macular dystrophy was first described by Miyake as a hereditary (autosomal dominant) macular dystrophy without visible fundus abnormalities. In all patients, the

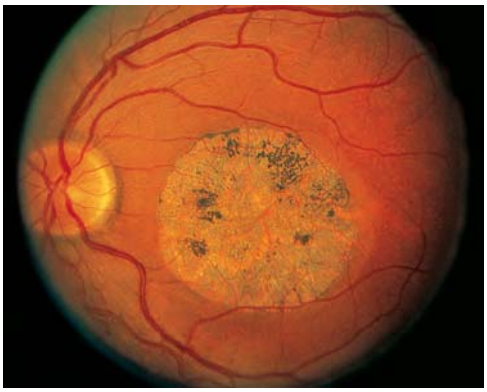

Figure 12-27 Fundus photograph of central areolar choroidal dystrophy in a patient with an autosomal dominant inheritance pattern. *(Courtesy of Mark W. Johnson, MD.)*

results of focal macular ERG were significantly subnormal, making this test the gold standard for diagnosis. Several years later, after patients with similar findings were described in other parts of the world, the condition was named occult macular dystrophy, and mutations in *RP1L1* and *MFSD8* have been reported to give rise to this phenotype. The most striking clinical finding is disruption (either focal or diffuse) of the central ellipsoid layer on OCT.

Rahman N, Georgiou M, Khan KN, Michaelides M. Macular dystrophies: clinical and imaging features, molecular genetics and therapeutic options. *Br J Ophthalmol*. 2020; 104(4):451–460.

Inner Retinal Dystrophies

X-linked retinoschisis

X-linked retinoschisis (XLRS) is the most common form of juvenile-onset retinal degeneration in male adolescents. Female carriers are almost always unaffected. XLRS typically presents in the first to second decade of life in a variety of ways, depending on the severity of disease (Fig 12-29). The most severe cases are diagnosed in infants presenting with nystagmus, strabismus, or decreased visual behavior and found to have dense vitreous hemorrhage or bullous retinal detachment (see Fig 12-29F, G). Less severe cases are usually diagnosed in later childhood by routine vision screening or as a result of decreased central vision.

Retinoschisis refers to a splitting of the neurosensory retina. These hallmark splits are typically seen in the macula and appear ophthalmoscopically as spokelike folds or fine striae radiating from the fovea (see Fig 12-29A, B). Approximately 50% of affected male adolescents also have peripheral schisis, involving the outer plexiform and nerve fiber layers (see Fig 12-29D). Extensive elevation of the peripheral inner retinal layers may be virtually indistinguishable from retinal detachment. Other clinical findings include a metallic sheen of the fundus, pigmentary changes, white spiculations, "vitreous veils" of condensed posterior vitreous or inner retinal tissue, and vitreous hemorrhage arising from shearing of retinal vessels traversing the schisis cavity (see Fig 12-29C, D). Pigmentary deposits may develop in peripheral areas destroyed by the disease process such that advanced cases of XLRS may be mistaken for RP (see Fig 12-29E).

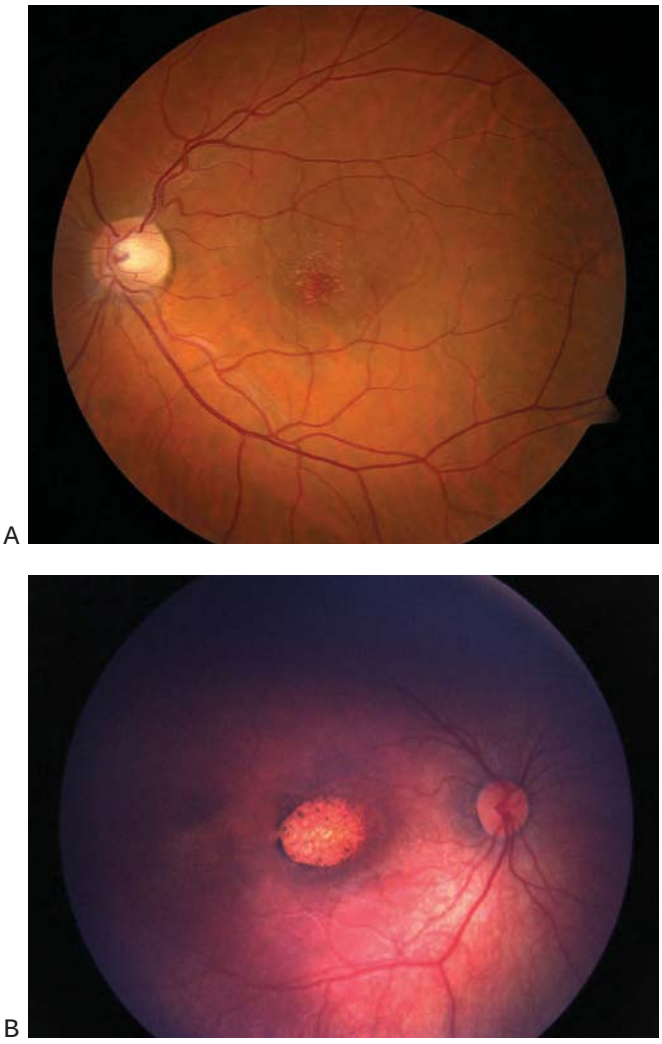

Figure 12-28 Fundus photographs showing clinical variations of North Carolina macular dystrophy in 2 members of the same family. **A,** The father has nonconfluent drusen typical of grade 1 of the disease. **B,** His 1-year-old son has an atrophic, coloboma-like defect characteristic of grade 3. *(Courtesy of Cagri G. Besirli, MD.)*

CLINICAL PEARL

X-linked retinoschisis is high in the differential diagnosis of vitreous hemorrhage in a boy, along with trauma and pars planitis.

OCT can readily show splitting of the retinal layers (see Fig 12-29B). Angiography reveals a petaloid pattern of hyperfluorescence without leakage. The panretinal involvement and inner retinal location of the disease are reflected in the ERG response, which

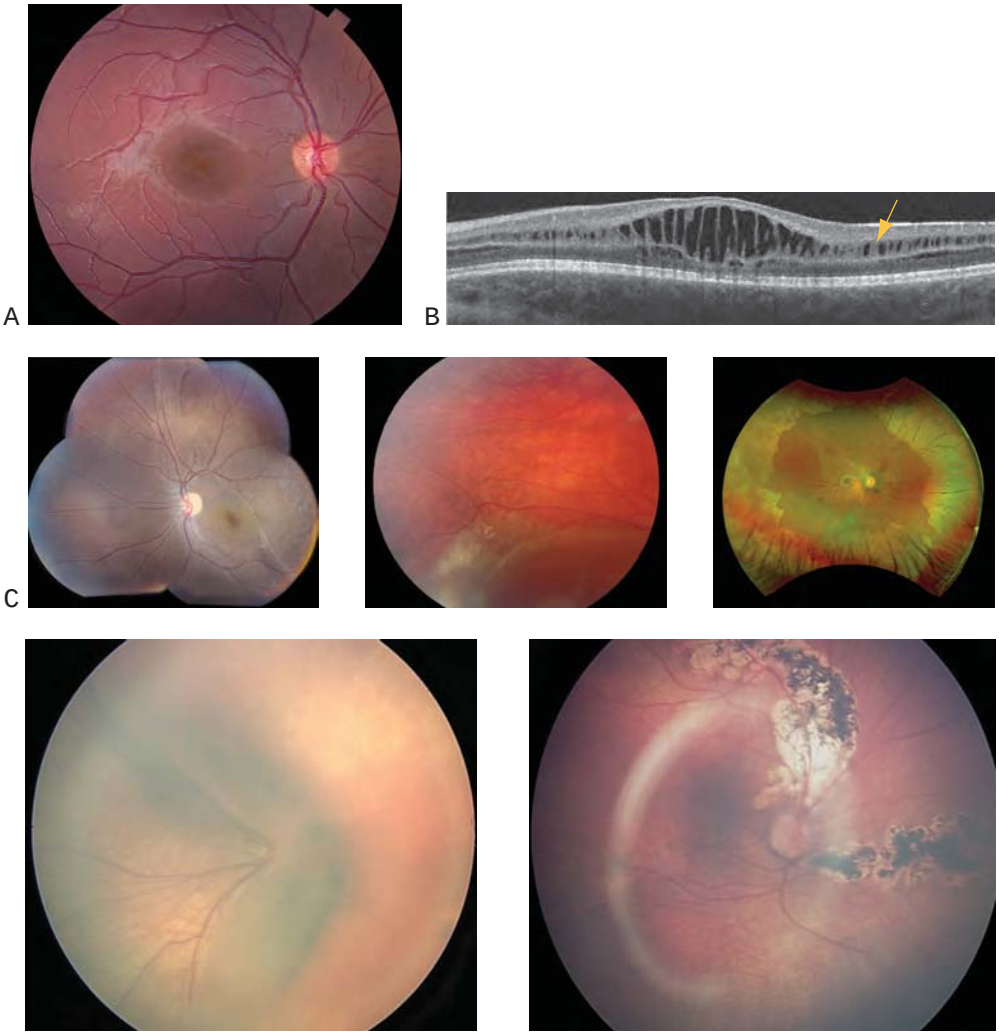

Figure 12-29 Spectrum of clinical findings in congenital retinoschisis. All examples are from boys with mutations in the *RS1* gene. **A,** Fundus photograph shows the central radial yellow spokes consistent with foveal schisis. (The whitish patches in the outer macula represent light reflex from healthy internal limiting membrane and is a typical, normal finding in children.) **B,** Corresponding SD-OCT shows macular schisis. Compared with OCT findings in CME, those in macular schisis include more pronounced elongation of the inner retinal cavitations centrally and involvement beyond the parafoveal region *(arrow).* **C,** Montage photograph shows radial striae in the macula, "vitreous veils" traversing obliquely, and whitish spiculations in the superior and temporal periphery. **D,** Inferior periphery of the right eye shows a smooth, domed, convex elevation consistent with peripheral retinoschisis. **E,** Ultra-wide-field fundus photograph shows extensive central and peripheral RPE atrophy consistent with advanced X-linked retinoschisis that is easily confused with rod–cone dystrophy. **F,** This 7-month-old boy, referred for nystagmus and strabismus, was found to have bilateral bullous schisis involving the superior macula (right eye is shown). **G,** Postoperative fundus photograph 2 months after vitrectomy, inner wall retinectomy, endolaser photocoagulation, and placement of silicone oil. *(Courtesy of Franco M. Recchia, MD.)*

has a negative waveform in which the a-wave is normal or near normal, but the b-wave is reduced (see Chapter 3, Fig 3-2).

The vast majority of cases of XLRS are caused by variants in the *RS1* gene. *RS1* encodes an adhesion protein called *retinoschisin,* which is crucial for the structural integrity of the retina provided by the Müller cells; it also acts in neurosynaptic transmission.