

Masqueraders of Age-related Macular Degeneration

A number of inherited retinal diseases phenocopy AMD.

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Age-related macular degeneration (AMD) is a leading cause of central visual loss among the elderly population in the developed world. The non-neovascular form is characterized by macular drusen and other abnormalities of the retinal pigment epithelium (RPE) such as geographic atrophy (GA) and hyperpigmented areas in the macula. The neovascular form is heralded by choroidal neovascularization (CNV), with subsequent development of disciform scarring.

This article reviews the pathologic and diagnostic characteristics of inherited diseases that may masquerade as AMD. The review is organized by the following patterns of inheritance: autosomal recessive (Stargardt disease and cone dystrophy); autosomal dominant (cone dystrophy, adult vitelliform dystrophy, pattern dystrophy, North Carolina macular dystrophy, Doyme honeycomb dystrophy, and Sorsby macular dystrophy); X-linked (X-linked retinoschisis); and mitochondrial (maternally inherited diabetes and deafness).

AUTOSOMAL RECESSIVE

Autosomal recessive (AR) Stargardt disease (STGD), also known as fundus flavimaculatus, is caused by a mutation in the ABCA4 gene.¹ STGD is an important consideration in the differential diagnosis of AMD because its pigmentary changes and RPE atrophy may be confused with features of AMD.

ABCA4 retinopathy may present with a wide spectrum of phenotypic variability, from AMD² in heterozygous carriers to bull's-eye maculopathy,^{3,4} AR-cone-rod dystrophy, and AR retinitis pigmentosa.⁵⁻⁹ STGD has an estimated prevalence of 1 in 8,000 to 10,000.¹⁰ The true prevalence may be higher because the frequency for an

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ABCA4 defect heterozygote carrier may be as high as one in 20.^{11,12} An estimated 600 disease-causing mutations in the ABCA4 gene exist, of which the three most common mutations account for less than 10% of the disease phenotypes.¹³

The underlying pathology of disease in STGD involves accumulation of lipofuscin in the RPE through a process of disc shedding and phagocytosis.^{14,15} Lipofuscin is toxic to the RPE; furthermore, A2E, a component of lipofuscin, causes inhibition of 11-cis retinal regeneration¹⁶ and complement activation.

STGD typically has an onset at 10 to 20 years of age, and its earliest symptoms are consistent with slowly progressive central vision loss.¹⁷ Later ages of onset have been associated with a more favorable visual prognosis.^{18,19} Cases of asymptomatic patients may be diagnosed before the onset of symptoms by the diagnosis of a symptomatic sibling.²⁰

STGD has been described as proceeding through four stages.²¹ Stage I is confined to the fovea or parafoveal macula, with pigmentary changes and atrophy of the RPE in this region. A discontinuous ring of flecks approximately one disc diameter in size often encircles the fovea. The electro-oculogram (EOG) and dark adaptation as measured with electroretinogram (ERG) are nor-

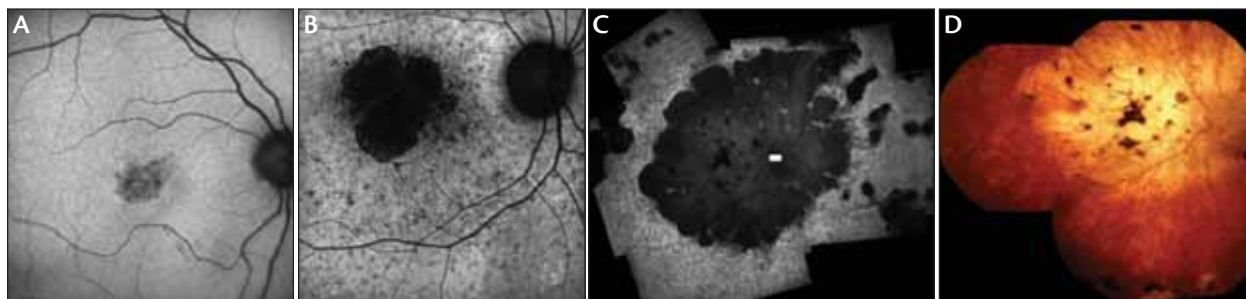


Figure 1. Autofluorescence (AF) imaging of a 61-year old Stargardt group 1 woman with a homozygous G1961E mutation showing atrophy (hypofluorescence) centrally and A2E related flecks (hyperfluorescence) in the outer edge of her fovea (A); a 20-year old woman with Stargardt group 2 (B); a 56-year old woman with Stargardt group 3. Areas of RPE atrophy appear black, retina appears gray, and areas of increased AF appear to be a lighter gray or white. A well-defined area with patchy decreased AF may represent an area where there is still some viable RPE (C). Corresponding color fundus photograph of the patient in C (D).

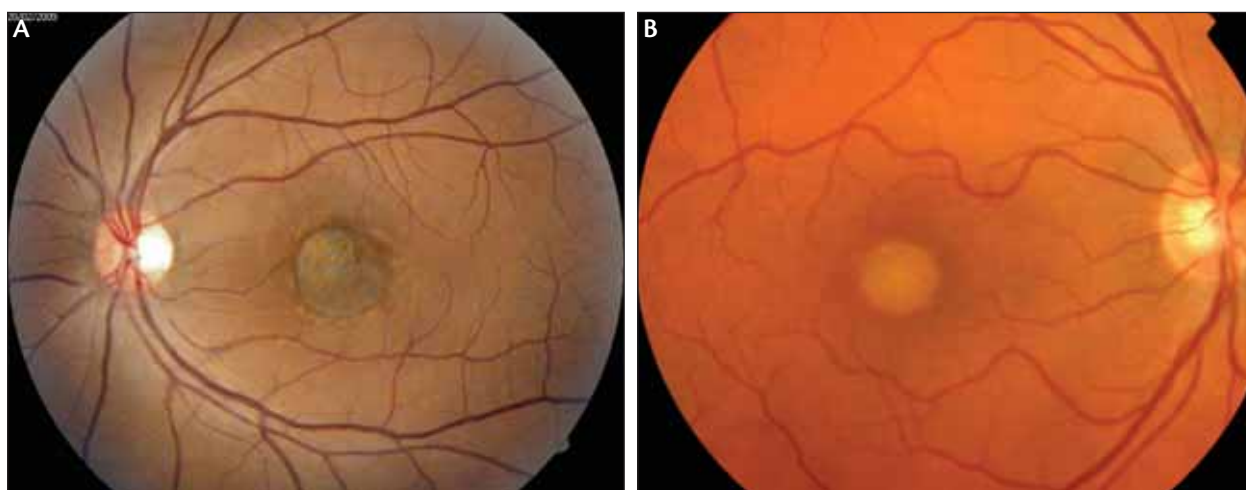


Figure 2. Examples of a cone dystrophy (A) and an adult vitelliform dystrophy (B).

mal. In stage II disease the flecks become more widespread, extending anterior to the vascular arcades and/or nasal to the optic disc. Subnormal cone and rod response may be observed in this group with delayed dark adaptation. Resorption of the flecks is seen in stage III, with widespread atrophy of the choriocapillaris. In stage IV disease there is further resorption of flecks with extensive atrophy of choriocapillaris and RPE. Progression of visual field changes can be expected, and marked abnormality of both cone and rod systems is detected with ERG.

Currently, there are no published guidelines to prognosticate STGD macular degeneration. Stratification into groups 1, 2 and 3 (Figure 1)¹⁸ and counseling on prognosis of STGD patients has been challenging based on funduscopic examination, but our preliminary data suggest that autofluorescence (AF) imaging, optical coherence tomography (OCT), and functional testing are of value in classification and in the prediction of patients' future

visual function. Patients may be divided into three categories according to the full-field ERG:¹⁸ Group 1 patients have normal rod- and cone-mediated ERGs; group 2 patients have relative loss of generalized cone function; group 3 patients have abnormal rod and cone ERGs and also have the worst prognosis for retention of peripheral vision. It is important to subtype STGD patients in order to better counsel them and to plan interventional trials. Macular autofluorescence is usually abnormally high in STGD patients. Observation of loss of function alleles (null or frame-shift) of ABCA4 and/or abnormal cone-rod physiology (group 3)¹⁸ at the initial visit is likely to be a reliable predictor of disease severity.

The presence of a "dark" or "silent" choroid on fluorescein angiography (FA) has assisted in making the clinical diagnosis of STGD, with a commonly quoted frequency for this sign being 85.9%.²² Importantly, its absence does not rule out a diagnosis of ABCA4 disease. The masking of background choroidal fluorescence occurs due to a

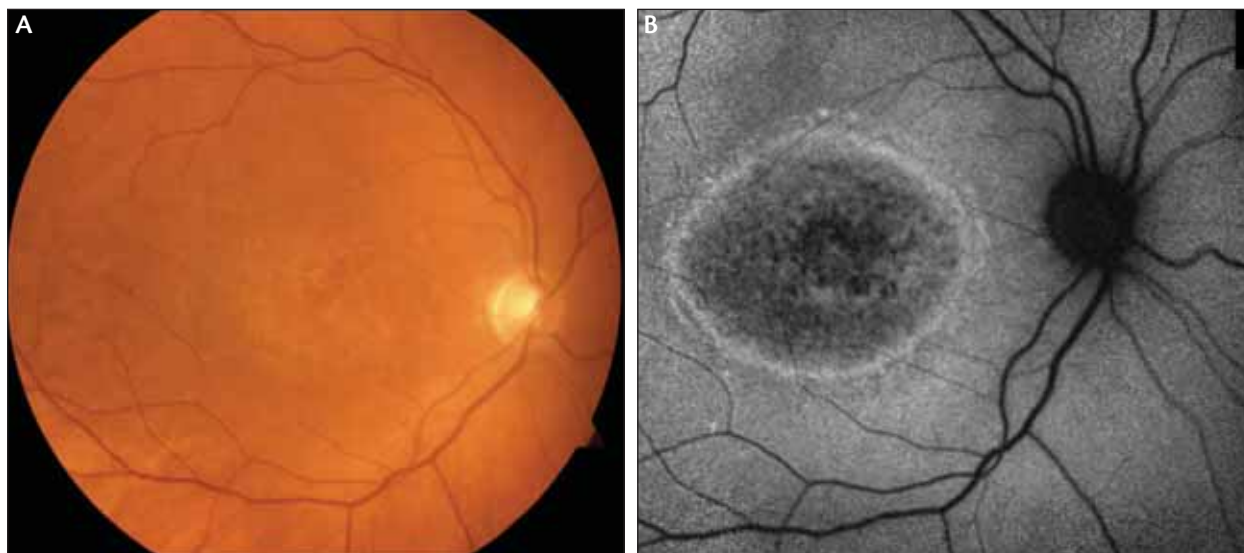


Figure 3. An example of a pattern dystrophy (A) and the corresponding fundus autofluorescence (FAF[B]). On FAF, punctate regions of discrete hyperfluorescence can be seen in the central macula.

buildup of lipofuscin in the RPE causing absorption of short-wavelength light.

Fundus autofluorescence (FAF) allows qualitative assessment of the buildup and distribution of lipofuscin in ABCA4 disease and also allows detection of changes in the function of the RPE before these can be appreciated on fundus biomicroscopy.^{23,24} Flecks in STGD are commonly seen as regions of focal hyperfluorescence, while atrophy of the RPE gives hypofluorescence due to the absence of fluorophores in this region (Figure 1). Loss of the inner segment-outer segment (IS-OS) junction seen with OCT has been correlated with atrophy as seen on FA and FAF.²⁵ With more widespread retinal disease, total loss of the IS-OS junction is seen in the macula, and this is associated with widespread thinning of the inner and outer retina and the RPE.

AUTOSOMAL DOMINANT

Autosomal dominant retinal dystrophies that may masquerade as AMD include cone dystrophy, adult vitelliform dystrophy, pattern dystrophy, North Carolina macular dystrophy, Doyme honeycomb dystrophy and Sorsby macular dystrophy.

Autosomal dominant cone dystrophy typically demonstrates bull's-eye maculopathy, while other cases may show varying degrees of macular atrophy similar to AMD (Figure 2); the peripheral retina is invariably normal in a cone dystrophy without rod involvement.²⁶ Age of onset is usually in the teens or early adulthood. Photophobia is a common symptom, and affected patients have varying degrees of color vision loss. The temporal portion of the optic nerve may have pallor. ERG findings are consistent

with cone involvement, specifically a reduced 30-Hz flicker amplitude and increased implicit time with normal rod responses. AF is useful to define the regions of macular atrophy.

Adult vitelliform dystrophy usually develops in the fourth to sixth decades of life.²⁷ Its associated yellow, yolk-like macular deposits may be confused with Best vitelliform dystrophy (Figure 2); however, the younger age of onset and characteristically abnormal EOG help differentiate Best vitelliform dystrophy from the adult form. The macular lesions may eventually resolve, leaving areas of RPE atrophy that may be mistaken for AMD later in life.

Pattern dystrophy inherited in an autosomal dominant form has been linked to RDS/peripherin gene mutations.²⁸ Pattern dystrophy can present with various forms of RPE pigment deposits in the macula (Figure 3). Among the patterns is the butterfly type, which shows a characteristic yellow pigment pattern in the macula. Affected individuals present in midlife and may be asymptomatic. Some patients may eventually develop areas of macular GA, and a small subset may develop CNV, thus mimicking AMD.

North Carolina macular dystrophy typically has its onset in infancy, with stabilization of the dystrophy by the teenage years.²⁹ It is mapped to the MCDR1 gene on chromosome 6. Although first described in families living in the mountains of North Carolina, this dystrophy has been found in unrelated families in other parts of the world. The clinical appearance of affected patients may share features of AMD, varying from drusen-like deposits in the macula to areas of severe atrophy that appear staphylomatous or colobomatous (Figure 4).



Figure 4. Examples of North Carolina (A), Doyme honeycomb (B), and Sorsby (C) macular dystrophies.



Figure 5. An example of X-linked retinoschisis (A) and the corresponding FAF (B).

Doyme honeycomb dystrophy, also known as malattia leventinese, is caused by mutations in the EFEMP1 gene on chromosome 2.³⁰ Affected individuals typically develop drusen in the macula and on the nasal side of the optic disc in their third decade of life (Figure 4). Drusen deposits may fade in older patients, and the development of peripapillary and/or macular atrophy and CNV may simulate AMD. ERG and EOG are typically normal; AF may help to highlight the abnormal deposits.

Sorsby macular dystrophy has its onset at about 40 years of age, with the presenting symptom being difficulty transitioning between light and dark environments.³¹ Central vision abnormalities ensue, followed by late loss of peripheral vision. The underlying cause of the disease is a mutation in the tissue inhibitor of metalloproteinases-3 (TIMP3) gene. Drusen-like deposits may form early in the disease with areas of GA (Figure 4). Later in the course of the disease, bilateral CNV invariably develops, with subsequent disciform scars. These features share similarities with AMD, and therefore Sorsby macular dystrophy may be mistaken for AMD.

Accurate diagnosis of [macular degeneration] may be difficult based on fundus appearance alone, especially if the patient presents later in life.

X-LINKED

X-linked retinoschisis (XLRS) is caused by a defect in the XLR1 gene, which encodes retinoschisin, a protein thought to be involved in cell adhesion.³² XLRS has an estimated prevalence of 1 in 5,000 to 25,000. More than 100 distinct gene mutations exist, causing similar phenotypes. XLRS often presents with early vision loss in affected males. XLRS carrier females typically do not exhibit the clinical or ERG findings of affected males.

Clinical findings include a radial pattern of folds emanating from the fovea, which contains schisis cavities. Peripheral schisis, typically in the nerve fiber layer, may

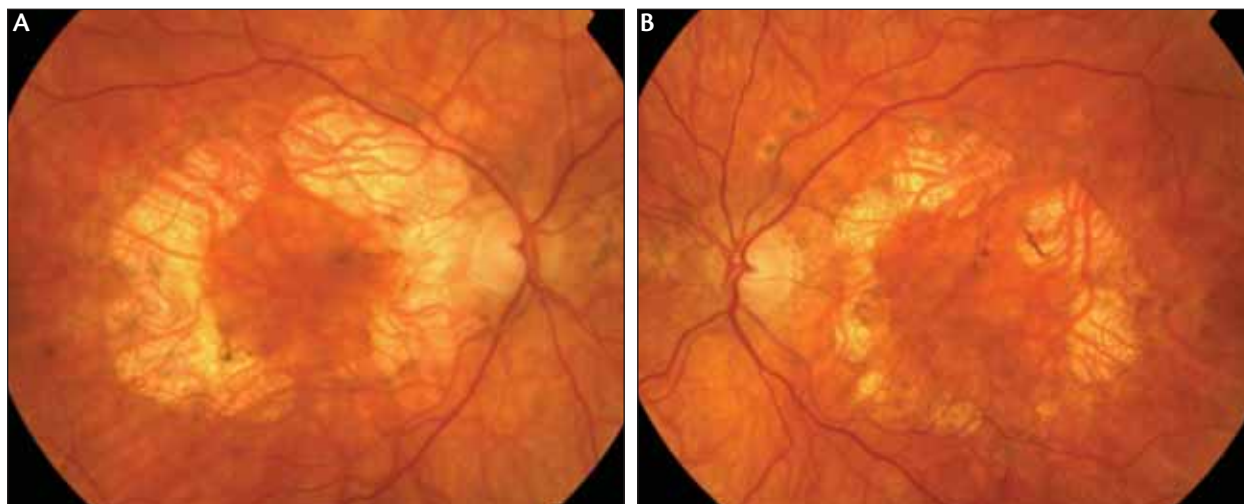


Figure 6. Foveal sparing in the right (A) and left fundi (B) in a patient with maternally inherited diabetes and deafness.

develop in 50% of cases. In older patients, these areas of schisis may resolve, and the development of pigmentary changes and RPE atrophy may mimic AMD (Figure 5).

The FA typically does not show leakage of fluorescein in XLR5. OCT may provide detailed, histopathologic-quality images of the schisis cavities. An electro-negative ERG is typical, where the a-wave is normal with a reduced b-wave, indicating sparing of the photoreceptors and involvement of the inner retina in XLR5. Diagnosis can be confirmed with testing of the XLR51 gene.

MITOCHONDRIAL

Maternally inherited diabetes and deafness (MIDD) is caused by mitochondrial gene defects involved in the oxidative production of energy.³³ This entity is characterized by an insulin secretion defect leading to diabetes, hearing loss, and a macular pattern dystrophy. Patients with macular findings are typically in their fifth decade of life and may present with a spectrum ranging from small pigmented lesions in the macula to large areas of macular atrophy (Figure 6). The macular findings may suggest AMD, but the history of maternally inherited diabetes, sensorineural hearing loss, and kidney failure related to mitochondrial renal disease suggests a diagnosis of MIDD. Genetic testing to identify the 3243 mitochondrial DNA mutation can confirm the diagnosis.

CONCLUSION

A number of inherited retinal diseases phenocopy AMD. Accurate diagnosis may be difficult based on fundus appearance alone, especially if the patient presents later in life. However, by careful review of the patient's family history, as well as the judicious use of diagnostic studies such as ERG and FAF in conjunction with genetic

testing, the real identities of these AMD masqueraders can be revealed.

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