

UPDATE ON THE GENETICS OF MACULAR DYSTROPHIES

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Learning Objectives

After completion of this article, the reader will be able to 1) describe the mode of inheritance of various macular dystrophies, 2) list the known genetic defect or chromosomal localization of mutations for each, and 3) discuss genetic associations between distinct phenotypic entities.

Although it was once argued that hereditary macular dystrophies represent a single dystrophic process,¹ it has become clear through advances in molecular genetics that this is not the case. Each year brings exponentially more knowledge of the various defects leading to macular disease. They are catalogued and updated regularly by the Laboratory for the Molecular Diagnosis of Inherited Eye Diseases at <http://www.sph.uth.tmc.edu/RetNet/>. Beginning with North Carolina macular dystrophy, the first to have its disease-causing gene mapped on the human genome, the list has progressed to include Stargardt disease, Best macular dystrophy, X-linked retinoschisis, and several pattern dystrophies. Studies leading to the identification of mutations allow an understanding of the pathophysiology from the gene forward and eventually a mechanism for treatment.

Most present classifications of retinal dystrophies

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are based on phenotype, the characterization of which includes features such as age at onset, mode of inheritance, number, location, size, and shape of lesions. Splitting rather than lumping of phenotypes often occurred when only a few affected individuals were studied at a time. An extreme example of inappropriate splitting is North Carolina macular dystrophy, which at one time had six different names for the same disease in a single family.² Although it is well known that a single disease can manifest in a variety of ways, the tendency, erroneously in the authors' opinion, has been toward separation and splitting these phenotypes even when a wide variability is observed within a single family. With such revelations as Doyme dystrophy and Malattia leventinese having the same mutation³ as a result of a common founder, the possibility of lumping disorders through genetic analysis seems more appropriate. Autosomal dominant macular dystrophy phenotypes as diverse as dominant Stargardt disease, pattern dystrophy, and atrophic macular degeneration were subsequently shown to be caused by ELOVL4 mutations.⁴ Molecular genetic data are showing just how broad the phenotype of a disease can be and generally support lumping rather than splitting.

Stargardt Disease

Stargardt disease is the most prevalent inherited macular dystrophy accounting for roughly 7% of all types.⁵ It is usually inherited as an autosomal recessive disorder but autosomal dominant inheritance has been rarely described.⁶ It is typically characterized by juvenile-onset macular dystrophy, alterations of the peripheral retina, and subretinal deposition of lipofuscin-like material. When the flecks show an adult onset and do not primarily involve the posterior pole, the term fundus flavimaculatus is traditionally used.

Initially, genetic linkage analysis of eight Stargardt

families assigned the disease locus to chromosome 1p13–21.⁵ Subsequent analysis by the same French research group found that fundus flavimaculatus was also linked to the same locus. They concluded that despite differences in age at onset, clinical course, and severity, these two dystrophies are allelic disorders (i.e., same gene with different mutations).⁷ This was subsequently shown to be the case. This provides another example in which lumping was correct.

Within the Stargardt region, 1p13–21, a gene encoding an ATP-binding cassette transporter (ABCR or ABCA4) was found.⁸ This protein is one member of the ABC transporter superfamily of proteins involved in the energy-dependent transport of substrates across membranes. ABCA4 is expressed primarily in rod photoreceptor disks⁹ but has also been more recently localized in cone outer segments.¹⁰ It is thought to flip *N*-retinylidene-phosphatidylethanolamine from the luminal to the cytosolic face of the photoreceptor disks.¹¹ Mutational analysis of ABCA4 in Stargardt disease and fundus flavimaculatus families has identified a total of 109 mutations in the ABCA4 gene.¹² In one study of 150 families, 10 families showed 2 mutations on a single chromosome, thus resulting in several complex alleles. Truncating and missense mutations in the amino terminal portion of the gene were associated with early-onset disease.¹³ Another study of 55 patients found that severe mutations were associated with Stargardt disease, whereas milder alterations were associated with late-onset fundus flavimaculatus with maculopathy.¹⁴ Current detection rate of mutations in patients with Stargardt disease is approximately only 50%. Because ABCA4 gene mutations seem to impair the processing of vitamin A, it has been suggested that vitamin A supplements may actually exacerbate Stargardt disease. Therefore, such vitamin supplements are not recommended.

Studies of the lipofuscin that accumulates in the retinal pigment epithelium (RPE) show that a major autofluorescent and toxic component is A2E (a bis-retinoid pyridinium salt *N*-retinylidene-*N*-retinylethanolamine).¹⁵ Accumulation of this toxic product within the RPE leads to RPE then photoreceptor degeneration and vision loss. Patients with Stargardt disease and mice lacking ABCA4 (*abcr* $-/-$) accumulate A2E at a much higher rate, and when the knockout mice were raised in total darkness, they do not form this fluorophore.¹⁶ Because formation of this component is light-dependent and there are at least three precursors to this product, treatment of Stargardt and other diseases associated with lipofuscin accumulation may include limitation of light exposure or target the precursors for intervention. This has already been shown as a viable method in mice. Isotretinoin

(Accutane), which blocks the first reaction in A2E biosynthesis, inhibited the accumulation of A2E in *abcr* $-/-$ mice and also slowed the age-dependent accumulation of lipofuscin in wild-type mice.¹⁷

Recent observations in a consanguineous pedigree found homozygotes for a null splice mutation to manifest autosomal recessive retinitis pigmentosa (RP19), whereas compound heterozygotes with one null allele and a presumed hypomorphic allele manifest an unusual cone-rod dystrophy, similar to Stargardt disease but with severely reduced electroretinographic responses and no pigmentary changes.¹⁸ In another pedigree in which the proband has Stargardt disease, the proband's paternal grandmother shared the same mutant allele (P1380L) and manifested exudative age-related macular degeneration (ARMD).¹⁹ A third pedigree in which identical ABCA4 complex alleles (W1408R, R1640W) are associated with more than one retinal disease phenotype was reported by Shroyer et al²⁰ of a Stargardt proband whose mother and maternal uncle had retinitis pigmentosa.

To date, ABCA4 mutations have been described in five disease phenotypes: retinitis pigmentosa, cone-rod dystrophy, Stargardt disease, fundus flavimaculatus, and ARMD. Of note, cosegregation analysis of 22 families manifesting Stargardt disease and ARMD found that the ARMD-affected patients were more likely to be carriers of pathogenic Stargardt alleles than predicted by chance alone.²¹ Most of those alleles resulted in abnormal protein expression, ATP binding, or ATPase activity. Another comprehensive mutation analysis of a German population with Stargardt disease, ARMD, and controls found no difference in frequency of the probable disease chromosomes in the latter two groups.²² They concluded that the study might be large enough to rule out a major contribution of mutant ABCA4 alleles in predisposition to ARMD but that it may not have been powerful enough to allow more modest effects to be discerned. A similar study performed on patients recruited from the United States and Canada also found no difference in frequency of ABCA4 disease-causing alleles between the ARMD and control population.²³ An international consortium tried to clarify the role of Stargardt disease alleles in ARMD by screening for two common ABCA4 variants in more than 1,200 patients with ARMD and a similar number of controls. They confirmed a significant increased frequency of both mutations in the ARMD group, suggesting a causative role.²⁴

In contrast to autosomal recessive Stargardt disease, which seems to map to the ABCA4 locus, autosomal dominant Stargardt disease has been mapped to chromosome 4p (STGD4)²⁵ and 6q (STGD3).²⁶ The

Table 1. Macular Dystrophies: Inheritance Pattern, Known Chromosomal Loci, and Gene Defect

Dystrophy	Inheritance	Chromosome Location	Gene	Mutation Type
Stargardt disease	AR	1p13-21	ABCR or ABCA4 (ATP-binding cassette transporter in rod and cone outer segments, flips N-retinylidene-phosphatidylethanolamine from the luminal to the cytosolic face of the photoreceptor discs)	Truncation, missense
Stargardt disease	AD	4p (STGD4)	—	—
Stargardt disease	AD	6q14 (STGD3)	ELOVL4 (photoreceptor-specific membrane-bound protein for elongation of very long chain fatty acids)	Truncation
Progressive cone dystrophy	AD	17p12-13 (CORD5=CORD6)	GUCY2D (RetGC-1, a retina-specific guanylate cyclase)	Missense
Rod monochromatism	AR	2q11 (ACHM3)	CNGA3 (α -subunit of cone cGMP-gated cation channel)	Missense
Rod monochromatism	AR	8q21	CNGB3 (β -subunit of cone cGMP-gated cation channel)	Missense, truncation, deletion, splice site alteration
Rod monochromatism	AR	1p13	GNAT2 (α -transducin, a G-protein that couples cone pigments to cGMP-phosphodiesterase for phototransduction)	Frameshift
Blue cone monochromatism	X-linked	X	Red and green opsin gene cluster	Transcriptional control element deletion, loss of function from homologous recombination and (various) point mutations of resultant single gene, exon deletion
Progressive cone-rod dystrophy	AD	19q13.32 (CORD2)	CRX (cone-rod homeobox gene)	Frameshift, missense
Progressive cone-rod dystrophy	AD	17p13.1 (LCA4=Leber's congenital amaurosis)	AIPL1 (aryl-hydrocarbon interacting protein-like 1, protein may be involved in nuclear transport or chaperone activity and localizes to rods only, from inner segments through outer plexiform layer)	Deletion
Progressive cone-rod dystrophy	AD	17q (CORD4)	—	—
Progressive cone-rod dystrophy	AD	17q11.2	UNC119 (photoreceptor synaptic protein)	Missense
Progressive cone-rod dystrophy	AD	6q (CORD7)	RIMS1 (regulating synaptic membrane exocytosis 1) RIM family of proteins that likely function as protein scaffolds to help regulate synaptic vesicle exocytosis	Deletion
Progressive cone-rod dystrophy	AD	6q25-26	RCD1 (dominant retinal cone dystrophy 1)	Deletion
Progressive cone-rod dystrophy	AD	6p	Peripherin/RDS (cone and rod outer segment glycoprotein in disk membranes for structural integrity)	Missense
Progressive cone-rod dystrophy	AD	6p21.1 (COD3)	GUCA1A (guanylate cyclase activating protein 1A)	Missense
Progressive cone-rod dystrophy	AR	1q12-24 (CORD8)	—	—

(Table continues)

Table 1. *Continued*

Dystrophy	Inheritance	Chromosome Location	Gene	Mutation Type
Progressive cone-rod dystrophy	AR	8p11 (CORD9)	—	—
Progressive cone-rod dystrophy	AR	1p22.1 (CORD3)	ABCR or ABCA4 (ATP-binding cassette transporter in rod and cone outer segments)	Splice site mutations
Progressive cone-rod dystrophy	AR	12q13.2 (fundus albipunctatus)	RDH5 (11-cis retinol dehydrogenase 5, an RPE microsomal enzyme involved in converting 11-cis retinol to 11-cis retinal)	Null (extremely delayed rod and cone resensitization)
Progressive cone-rod dystrophy	X-linked	Xp11.4-21.1 (COD1)	RPGR (GTPase regulator) same chromosome as X-linked retinoschisis	Nonsense
Progressive cone-rod dystrophy	X-linked	Xq27 (COD2)	—	—
Progressive cone-rod dystrophy	Mitochondrial	—	—	—
Doyle dystrophy and Malattia leventinese	AD	2p16	EFEMP1 (EGF-containing fibrillin-like extracellular matrix protein 1)	Missense, promoter mutation
Dominant drusen with macular degeneration	AD	1q25-31	—	—
Dominant drusen with macular degeneration	AD	6q14 (STGD3)	ELOVL4 (photoreceptor-specific membrane-bound protein for elongation of very long chain fatty acids)	5-bp deletion
Dominant drusen with macular degeneration	AD	6q14 (overlaps MCDR1)	—	—
Dominant drusen with macular degeneration	AD	6p	Peripherin/RDS (cone and rod outer segment glycoprotein in disc membranes for structural integrity)	Missense
Best disease	AD	11q12.3 (VMD2)	Bestrophin (chloride channel)	Missense
Adult vitelliform dystrophy	AD	6p	Peripherin/RDS (cone and rod outer segment glycoprotein in disk membranes for structural integrity)	Null, point mutations
Butterfly pattern dystrophy	AD	6p	Peripherin/RDS (cone and rod outer segment glycoprotein in disc membranes for structural integrity)	Deletion, missense, nonsense mutations
Butterfly pattern dystrophy	AD	6q14 (STGD3)	ELOVL4 (photoreceptor-specific membrane-bound protein for elongation of very long chain fatty acids)	Truncation
Sorsby macular dystrophy	AD	22q12.3	TIMP-3 (tissue inhibitor of metalloproteinases)	Missense
X-linked retinoschisis	X-linked recessive	Xp22.2	XLRS1 (cell-cell interaction protein)	Missense, nonsense, frameshift, splice site mutations
Dominant cystoid macular dystrophy	AD	7p21-15 (CYMD)	—	—
North Carolina macular dystrophy	AD	6q (MCDR1)	—	—
Atrophia areata	AD	11p15	—	—
Central areolar choroidal dystrophy	AD	6p	Peripherin/RDS (cone and rod outer segment glycoprotein in disk membranes for structural integrity)	Missense
Central areolar choroidal dystrophy	AD	17p13	—	—

AR, autosomal recessive; AD, autosomal dominant; RPE, retinal pigment epithelium.

Table 2. Phenotypic Characteristics of Macular Dystrophies⁸³

Macular Dystrophy	Age at Onset	ERG and EOG	Ophthalmoscopic Features	Fluorescein Angiography
Stargardt disease	Juvenile onset, usually 6–20 years of age	Photopic and scotopic ERG, normal to slightly longer implicit times and normal amplitudes. If chronic with pigmentation in periphery, can have decreased amplitudes; EOG, subnormal	Initial, no distinctive features; early, loss of foveal reflex, RPE level gray-yellow perifoveal flecks; late, horizontal oval of RPE atrophy with surrounding broad ring of flecks that can extend to mid periphery	Initial, central hyperfluorescent RPE defect surrounded by faint oval of hyperfluorescent flecks +/-dark choroid; early, blotchy hyperfluorescence with blocking by flecks; late, central choroidal atrophy
Cone dystrophy	Congenital or childhood to adulthood	Single-flash photopic ERG, very low to unrecordable; photopic flicker, minimal response or absent; scotopic ERG, normal if early, subnormal if advanced; EOG, normal if early, subnormal if advanced	Initial, no distinctive features; late, (4 types): bull's eye, sharply defined atrophic RPE surrounding darker area; pigment stippling, diffuse round pigment clumps in posterior pole, possibly with bone spicules in midperiphery; discrete RPE atrophy; Stargardt-like	Initial, central hyperfluorescent RPE defect; bull's eye, oval hyperfluorescence surrounding nonfluorescent center; pigment stippling, diffuse hyperfluorescence of posterior pole; choroidal atrophy, loss of choroidal fluorescence; Stargardt-like blotchy hyperfluorescence with blocking by flecks

ERG, electroretinogram; EOG, electrooculogram; RPE, retinal pigment epithelium.

STGD3 locus at 6q14 is of particular interest because it encodes a photoreceptor-specific membrane-bound protein responsible for elongation of very long chain fatty acids (ELOVL4).²⁷ Two different types of mutations (a 5–base pair deletion and two 1–base pair deletions 4 nucleotides apart) result in truncation of the ELOVL4 protein, implying that disruption of fatty acid synthesis can result in macular disease.⁴ The truncated protein has been associated with three diseases: autosomal dominant macular dystrophy, autosomal dominant Stargardt disease, and pattern dystrophy once again showing that lumping phenotypes is more accurate.⁴ None of these ELOVL4-mediated autosomal dominant macular dystrophy phenotypes shows blocking of the choroidal fluorescence on fluorescein angiography. Autosomal dominant Stargardt disease, though sharing many clinical similarities to autosomal recessive Stargardt disease, may not have excessive lipofuscin deposition as a pathogenic mechanism.

Previously, the autosomal dominant STGD2 locus²⁸ had been linked to chromosome 13q. However, extensive genealogy studies by Donoso et al²⁹ showed that members of the STGD2 (chromosome 13) family clearly descended from the same ancestors of the STGD3 (chromosome 6q) family and all had the same mutation in ELOVL4 (chromosome 6q). Closer examination of the STGD2 testing results showed a surprisingly high number of recombinant individuals, including double recombinants within 10 centimorgans, raising the possibility of a type I statistical error.³⁰ As

a result, the STGD2 locus has been withdrawn from the human genome map.

Cone Dystrophy and Cone-Rod Dystrophy

Cone dystrophies and cone-rod dystrophies (CORDs) have historically been grouped together. This is incorrect by phenotype and genotype data. Patients with cone dystrophy have photophobia, progressive macular pigmentation or atrophy, and decreased cone electroretinographic responses with relative preservation of rod function as evidenced by the electroretinogram, normal peripheral vision, and absence of nyctalopia. True CORDs, however, are similar to retinitis pigmentosa but has earlier or more severe involvement of the macula and cones. Patients with CORDs usually develop loss of peripheral visual field and nyctalopia, but only after central loss of macular function. There are autosomal dominant, autosomal recessive, X-linked, mitochondrial, and sporadic modes of inheritance. The onset of cone dystrophy can be congenital or progressive with presentation during childhood, early adulthood, or even later. Within a single family, the severity and rate of progression can vary greatly. However, all show cone dysfunction on electroretinography; cone responses are reduced or absent with relative sparing or only late involvement of rods. Most have reduced visual acuity, abnormal color vision, and photophobia.

Subtypes of the congenital or stationary cone dystrophies inherited in an autosomal recessive fashion

have several associated genes identified: CNGA3 on 2q11 (ACHM2 locus), which encodes the α -subunit of the cGMP-gated channel in cone photoreceptors;³¹ CNGB3 on 8q21 (ACHM3 locus) which encodes the β -subunit of the cone photoreceptor cGMP-gated cation channel;³² GNAT2 on 1p13 (ACHM4 locus) which encodes for α -transducin, the G-protein that couples cone pigments to cGMP-phosphodiesterase for phototransduction.³³ X-linked blue cone monochromatism is differentiated by normal S-cone photoreceptors in addition to intact rods. This disorder results from various genetic defects of the red and green photopigment gene cluster on chromosome X.^{34–36}

Cone dystrophy, when severe, is characterized by central atrophy, photophobia, and depressed cone electroretinographic responses with preservation of rod function. CORDs classically have additional clinical features of visual field defects and peripheral fundus atrophy or pigmentation in the late stages with nyctalopia. Autosomal dominant cone dystrophy has unfortunately been designated as CORD5. CORD5 is actually a fairly pure cone dystrophy in all respects. Additionally, CORD5 and CORD6 have been found to share the same mutations in GUCY2D³⁷ on chromosome 17p and are the same disease, once again reinforcing the principle of lumping. Mutations at the other end of GUCY2D cause autosomal recessive Leber congenital amaurosis.³⁸

Most CORDs are considered a severe variation of retinitis pigmentosa with early and severe involvement of the cones. The most straightforward classification of cone dystrophies and CORDs is by mode of inheritance. Within the autosomal dominant pattern, at least seven genes have been identified as disease-causing (<http://www.sph.uth.tmc.edu/RetNet/>). Defects have been mapped to chromosome 19q (CRX, cone-rod homeobox gene),³⁹ 17p (AIPL1, aryl-hydrocarbon interacting proteinlike 1),⁴⁰ CORD5/GUCY2D encodes RetGC-1, a retina-specific guanylate cyclase⁴¹, 17q (CORD4⁴² and UNC119, photoreceptor synaptic protein⁴³), 6q (CORD7⁴⁴ and RCD1⁴⁵) and 6p (peripherin/RDS⁴⁶ and GUCA1A, guanylate cyclase activating protein 1A).⁴⁷ Two loci for autosomal recessive CORD have been identified (CORD8⁴⁸ and CORD9⁴⁹). Two genes have been found: ABCA4 on chromosome 1p22.1⁵⁰ (the Stargardt gene) and RDH5, or 11-*cis* retinal dehydrogenase 5, on chromosome 12q13.2 (RetNet).

In pedigrees with X-linked inheritance, one locus has been mapped and cloned (Xp11.4/COD1 encodes RPGR, a GTPase regulator)⁵¹ and another identified (Xq27/COD2).⁵² It is noteworthy that COD1 is actually a variation of X-linked retinitis pigmentosa. Again, had the phenotypes been lumped, the COD1

mutations would have been found sooner. Blue cone monochromatism and X-linked progressive cone dystrophy seem to have some overlap in that most blue cone families have stationary disease but some pedigrees show a slow progression to fundus changes and reduction of scotopic ERG responses.^{34,53} Another form of inheritance was documented recently as mitochondrial from mother to son.⁵⁴

Dominant Drusen

Dojne⁵⁵ was the first to describe inheritance of posterior pole drusen a century ago in a British family, known as Dojne hereditary retinal dystrophy. Vogt⁵⁶ later reported autosomal dominant inheritance of a similar disorder in a Swiss family, referred to as Malattia leventinese, named after the Swiss valley where the family resided. Both diseases are characterized by subretinal deposits in the central and peripheral retina and macular degeneration with increasing age. Despite perceived clinical differences, the two disorders are currently recognized as being identical at the genetic level because both have been mapped to the same region on chromosome 2p and the same mutation has been characterized (of EFEMP1, EGF-containing fibrillin-like extracellular matrix protein 1).³ This supports the system of lumping rather than splitting.

Other forms of dominantly inherited drusen with macular degeneration have been described in some individuals of families mapping to chromosome 1q25–q31,⁵⁷ 6q14 (ELOVL4),⁵⁸ 6p (peripherin/RDS),⁵⁹ and 6q14 (overlapping MCDR1 and phenotypically identical to North Carolina macular dystrophy).⁶⁰ Indeed, this new dominant drusen locus is nothing more than mischaracterization of North Carolina macular dystrophy and was reported by the same group that mismapped STGD2. It is noteworthy that the Arg142Trp mutation of peripherin/RDS was noted to occur in all individuals of three families with autosomal dominant central areolar choroidal dystrophy and drusen but that individuals without the mutation did not manifest drusen.

Best Disease or Vitelliform Dystrophy

Best disease, also known as vitelliform macular dystrophy type 2, usually presents with bilateral lesions, although unilateral and multifocal presentations have been described. The lesions can vary from a small, round, yellowish dot at the foveola to an atrophic chorioretinal scar resembling toxoplasmosis retinochoroiditis, depending on the stage of disease. This autosomal dominant form of macular dystrophy is the first one to have its cause identified as a molecular

defect in the RPE. The gene for Best disease has been mapped to chromosome 11q12.3 (VMD2) and identified as bestrophin, a chloride channel.⁶¹ Fifteen different missense mutations aggregating in four regions of the bestrophin protein result in a significant amino acid change. The homozygous patient in a Swedish family shows no clinical difference from heterozygous individuals, so the mutations likely result in a dominant negative effect.⁶²

Atypical vitelliform macular dystrophy (VMD1) no longer exists because of more informative gene mapping techniques and the realization that the initial phenotype was mischaracterized.⁶³

Atypical presentations of Best disease still exist. One intriguing report by Seddon et al⁶⁴ of VMD2 mutations in patients with macular lesions characteristic of adult-onset foveomacular pigment epithelial dystrophy and age-related macular degeneration reinforces the observation that different mutations of one gene can result in multiple phenotypes.

Adult-Onset Foveomacular Pigment Epithelial Dystrophy

There is extensive variation in the vitelliform lesions of this autosomal dominantly inherited pattern dystrophy. Thus far, six mutations of peripherin/RDS, including two presumed null allele mutations, have been reported. In a study of 28 patients with adult vitelliform dystrophy, 18% were found to carry various point mutations in peripherin/RDS, suggesting that the variable phenotypes are caused in part by genetic heterogeneity.⁶⁵ One of the point mutations (S212T) illustrates how a change in a single amino acid can result in different clinical phenotypes. A change from serine to threonine resulted in adult vitelliform dystrophy, while a change from serine to glycine (S212G) cosegregates with autosomal dominant retinitis pigmentosa. The null alleles in this study were found to result in multifocal vitelliform lesions, whereas previous studies had found null alleles of peripherin/RDS in retinitis punctata albescens, autosomal dominant fundus flavimaculatus, butterfly pattern dystrophy, and simplex retinitis pigmentosa.⁵⁸

Pattern Dystrophy

The lesions in this dystrophy may form several patterns, one of which is bilateral, butterfly-shaped pigmentations at the level of the RPE. This butterfly pattern dystrophy has a slowly progressive course, with most patients retaining relatively normal visual acuity for life. The mode of inheritance may be autosomal dominant because father-to-son transmission has been documented.⁶⁶ Several deletion, missense,

and nonsense mutations in the peripherin/RDS gene have been associated with this dystrophy.^{67,68} Recently, the first clinicopathologic correlation of butterfly pattern dystrophy caused by a defined mutation (a cysteine-to-tyrosine switch at codon 213) in the peripherin/RDS gene was published.⁶⁹ It is noteworthy that the adjacent codon 214, which also codes for cysteine, has been localized as a disease-causing site also. The Cys214Ser mutation has been reported in a family with autosomal dominant retinitis pigmentosa.⁷⁰ It is unclear why these adjacent mutations produce distinct clinical entities, although it is well known that peripherin/RDS mutations can cause numerous distinct phenotypes. Mutations in ELOVL4 in some individuals also manifest clinically as pattern dystrophy.⁴

Sorsby Macular Dystrophy

This extremely rare autosomal dominantly inherited disorder has many variations within a single family. In a study of a seven-generation pedigree and literature review, Hamilton et al⁷¹ distinguished three presentations. In the first and most common, white to yellow fundus spots, which are not drusen, accompany a disciform macular degeneration. In the second, the fundus spots are absent. In the third, the yellow deposits are associated with atrophic macular degeneration. Atrophy of the retina, RPE, and choroid then slowly progresses toward the periphery. Patients lose central vision between the second and fourth decades of life. Although variations in this dystrophy may be examples of genetic heterogeneity, Sorsby fundus dystrophy is a distinct clinical disorder. Patients have been found to have several mutations of TIMP-3, a tissue inhibitor of metalloproteinases, located on chromosome 22q12.3.⁷² All the mutations seem to affect the C-terminus of the mature TIMP3 protein, causing an amino acid change to cysteine. This suggests a critical role for the additional C-terminal free thiol group in the pathogenesis of Sorsby macular dystrophy.⁷³ In addition to the inhibition of metalloproteinases of the extracellular matrix, TIMP-3 has recently been shown to have another role in the process of vascular endothelial growth factor-mediated angiogenesis. Qi et al⁷⁴ have discovered that TIMP-3 binds directly to vascular endothelial growth factor receptor-2 (KDR) in a manner independent of its metalloproteinase inhibitory activity. Because of the complex pathway leading to neovascularization, it is not surprising to find that the disease-associated protein has multiple functions within the signaling cascade.

X-Linked Juvenile Retinoschisis

Foveal retinoschisis is the characteristic lesion, and it seems to be present at birth. True retinoschisis of the retinal periphery, usually in the lower temporal quadrant, may not be present, and true retinal detachment is rare. The pattern of inheritance is clearly X-linked recessive for most patients. Autosomal recessive inheritance may be another possibility because three affected daughters of healthy parents in a nonconsanguineous marriage have been reported. The retinoschisis gene has been localized to Xp22.2, and several mutations have been identified.⁷⁵ Expression analysis predicts a protein (XLRS1, retinoschisin) containing a highly conserved motif, called a discoidin domain, implicated in cell–cell interaction. Retinoschisin is secreted from photoreceptors and bipolar cells and seems to form an oligomeric complex that may be disulphide-bonded. Mutation of this protein can thus result in defective cell adhesion processes during retinal development. Attempts at clarification of this protein using a murine model support this hypothesis. Knockout mice for Rs1 hours, the murine equivalent of XLRS1 protein, showed generalized disruption of cell layer architecture, particularly of the outer plexiform and inner nuclear layers, with loss of cone photoreceptors more than rods.⁷⁶ Besides serving a structural function, Rs1 hours may have a role in the formation and stabilization of synapses. Weber et al⁷⁵ proposed that failure to establish or maintain the proper synaptic connections could lead to subsequent photoreceptor cell death. Parallel studies in human cell lines indicate that most mutant proteins are not secreted, which may explain why disease severity is not mutation-specific.⁷⁷

Dominant Cystoid Macular Dystrophy

This extremely rare autosomal dominant disease affects primarily the Müller cells of the inner nuclear layer of the retina. Early onset of cystoid macular edema resulting in macular atrophy and occasional pericentral pigment deposits characterizes this disease. On fluorescein angiography, leakage from perimacular capillaries or even from those throughout the posterior pole is seen. The defect has been mapped to chromosome 7p21–15 (CYMD).⁷⁸

North Carolina Macular Dystrophy

This congenital or infantile-onset macular dystrophy is inherited in an autosomal dominant fashion. The macular appearance can vary from a few drusen-like deposits to large disciform colobomatous lesions, all within the same family. The lesions do not seem to

be progressive and move from one grade to the next, indicating the defect may be in a macular development gene. First reported in a family from North Carolina, this dystrophy has subsequently been described in pedigrees from Germany, England, France, Italy, and Belize. Affected individuals are from diverse ethnic backgrounds: white, black, and Mayan Indian. Linkage analysis and mapping have localized the gene to a 700-kilobase pair region on chromosome 6q now known as MCDR1 (MC, macular; D, dystrophy; R, retinal; 1, first macular dystrophy mapped).⁷⁹ Haplotype analysis indicates independent origins of the mutation worldwide. Clinicopathologic correlation showed focal absence of photoreceptor cells and the RPE with attenuated Bruch's membrane and choriocapillaris atrophy.⁸⁰

Atrophia Areata

This rare autosomal dominant disease has been reported only in families from Iceland. Bilateral symmetric ring-shaped extensions of marked choroidal atrophy radiate from the optic disk. The atrophy begins in childhood and is slowly progressive with visual acuity depending on the amount of macular atrophy. Often, high myopic astigmatism exists. The funduscopic appearance is characteristic, especially in advanced cases, with two or more rings that do not follow the major retinal vessels. Mapping has localized the disease-causing gene to chromosome 11p15.⁸¹

Central Areolar Choroidal Dystrophy

Central areolar choroidal dystrophy is a macular dystrophy characterized by subtle, mottled depigmentation of the posterior pole in the early stages. In time, this geographic depigmentation gradually enlarges until an oval or round area of atrophy of RPE and choriocapillaris is formed. Typically, no flecks or drusen are observed in this type of chorioretinal dystrophy. The Arg142Trp mutation in the peripherin/RDS gene has been implicated as a cause of some autosomal dominant central areolar choroidal dystrophy. Sporadic cases have also been described but could not be attributed to mutations in the peripherin/RDS gene.⁸² Finally, a type of autosomal dominant central areolar choroidal dystrophy described in a Northern Irish family has been linked to chromosome 17p13.⁸³

Conclusions

As genetic studies progress, unification of separate clinical disorders by underlying molecular defect be-

comes possible. The findings of Doyne dystrophy and Malattia leventinese sharing the same EFEMP-1 mutation, then of autosomal recessive Stargardt disease and retinitis pigmentosa of ABCA4, and of autosomal dominant Stargardt disease and butterfly pattern dystrophy of ELOVL4 show the phenotypic variability of a single defect. Other disorders, such as cone dystrophies and CORDs show the growing complexity of causative mutations. In the end, a classification system of macular dystrophies by mutation may not be possible because of the inherent complexity of the eye; however, the knowledge gained through these studies may allow molecular diagnosis before vision loss, with the ultimate goal of preventing blindness. Not only will patients with the hereditary macular dystrophies benefit, but so will patients with ARMD, a disease with similar clinical and histopathologic characteristics and affecting far more of the world's population.

Key words: genetics, macular, dystrophy, inherited, cone, visual impairment, electrophysiology

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