The genetics of inherited macular dystrophies

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The inherited macular dystrophies comprise a heterogeneous group of disorders characterised by central visual loss and atrophy of the macula and underlying retinal pigment epithelium (RPE). The different forms of macular degeneration encompass a wide range of clinical, psychophysical and histological findings. The complexity of the molecular basis of monogenic macular disease is now beginning to be elucidated with the identification of many of the disease-causing genes. Age related macular degeneration (ARMD), the leading cause of blind registration in the developed world, may also have a significant genetic component to its aetiology. Genes implicated in monogenic macular dystrophies are good candidate susceptibility genes for ARMD, although to date, with the possible exception of ABCA4, none of these genes have been shown to confer increased risk of ARMD.

The aim of this paper is to review current knowledge relating to the monogenic macular dystrophies, with discussion of currently mapped genes, chromosomal loci and genotype-phenotype relationships. Inherited systemic disorders with a macular dystrophy component will not be discussed. A classification based upon molecular pathology would be more satisfactory but research into the molecular genetic basis of this group of disorders is still at an early stage. Seven disease-causing genes have been identified to date (table 1) and their identification has provided new insights into the pathogenesis of macular degeneration. Age related macular degeneration (ARMD) also has a genetic contribution to its aetiology. Approximately 20% of patients have a positive family history and twin studies support a strong genetic component. Genes implicated in monogenic macular dystrophies are potential candidates for genes conferring risk for ARMD.

**AUTOSOMAL RECESSIVE INHERITANCE**

**Stargardt disease and fundus flavimaculatus**

Stargardt macular dystrophy (STGD) is the most common inherited macular dystrophy with a prevalence of 1 in 10,000 and an autosomal recessive mode of inheritance. It shows a very variable phenotype with a variable age of onset and severity. Most cases present with central visual loss in early teens and there is typically macular atrophy with white flecks at the level of the RPE at the posterior pole on ophtalmoscopy (fig 1). Fluorescein angiography classically reveals a dark or masked choroid. The reduced visualisation of the choroidal circulation in the early phase of fundus fluorescein angiography (FFA) is believed to be secondary to excess lipofuscin accumulation in the RPE, thereby obscuring fluorescence emanating from choroidal capillaries. The retinal flecks appear hypofluorescent on FFA early in their evolution but at a later stage they appear hyperfluorescent due to RPE atrophy. Recently a new method has been developed to visualise the RPE, autofluorescence imaging, which takes advantage of its intrinsic fluorescence derived from lipofuscin. Autofluorescence imaging with a confocal scanning laser ophthalmoscope can provide useful information about the distribution of lipofuscin in the RPE, and give indirect information on the level of metabolic activity of the RPE which is largely determined by the rate of turnover of photoreceptor outer segments. There is evidence of continuous degradation of autofluorescent material in the RPE. Progressive loss of lipofuscin occurs when there is reduced metabolic demand due to photoreceptor cell loss, which appear as areas of decreased autofluorescence (AF). Areas of increased AF correspond to a group of RPE cells containing higher quantities of lipofuscin than their neighbours and may represent areas at high risk for photoreceptor cell death.

**Abbreviations:** adMD, autosomal dominant atrophic macular degeneration; AF, autofluorescence; ARMD, age related macular degeneration; AVMD, adult vitelliform macular dystrophy; CACD, central areolar choroidal dystrophy; CORD, cone-rod dystrophy; EOOG, electro-oculography; ERG, electroretinography; FFA, fundus fluorescein angiography; PBCRA, progressive bilateral choroidal atrophy; RP, retinitis pigmentosa; RPE, retinal pigment epithelium; SFD, Sorsby fundus dystrophy; SRNVM, subretinal neovascular membrane; VEGF, vascular endothelial growth factor.
loss. It has been demonstrated histologically that the number of photoreceptor cells is reduced in the presence of increased quantities of lipofuscin in the RPE, leading to the proposal that autofluorescent material may accumulate prior to cell death. The abnormal accumulation of lipofuscin, the presence of active and resorbed flecks, and RPE atrophy all contribute to a characteristic appearance on fundus auto-fluorescence imaging in STGD.

Histopathology of donated eyes has revealed that changes in the RPE begin near the equatorial peripheral retina and include increasingly excessive lipofuscin content and cell loss towards the macula. The changes in the retina parallel those in the RPE, including accumulation of lipofuscin in photoreceptor inner segments, loss of photoreceptors, and reactive Muller cell hypertrophy. Scanning electron microscopy shows a progressively marked heterogeneity in the size of RPE cells.

Stargardt disease may also present in adult life when the visual loss may be milder. When the retinal flecks are seen without atrophy the term fundus flavimaculatus (FFM) is often used to describe the phenotype but it appears that Stargardt disease and FFM are caused by mutations in the same gene and both patterns may be seen within the same family. In a recent detailed phenotypic study, based on electroretinography (ERG) findings, patients with STGD/FFM could be classified into 3 groups. In group 1, there was severe pattern ERG abnormality with normal scotopic and full-field ERGs. In group 2, there was additional loss of photopic function, and in group 3, there was loss of both photopic and scotopic function. Differences among groups were not explained on the basis of differences in age of onset or duration of disease, suggesting that these electrophysiological groups may represent different phenotypic subtypes, and thereby be useful in helping to provide an accurate prognosis. Patients in group 1 generally had better visual...

Table 1 Chromosomal loci and causative genes in inherited macular dystrophies

<table>
<thead>
<tr>
<th>Macular dystrophy</th>
<th>OMIM number</th>
<th>Mode of inheritance</th>
<th>Chromosome locus</th>
<th>Mutated gene</th>
<th>References</th>
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<tr>
<td>Stargardt disease/fundus flavimaculatus, 248200</td>
<td>Autosomal recessive</td>
<td>1p21-p22 (STGD1)</td>
<td>ABCA4</td>
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<td>PROM1*</td>
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<td>4p (MCDR2)</td>
<td>PROM1*</td>
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<td>Peripherin/RDS</td>
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<td>TIMP3</td>
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*Unpublished data, see text.
acuity, more restricted distribution of flecks and macular atrophy, whereas those in group 3 had the worst visual acuity, more widespread flecks and macular atrophy was universal.\textsuperscript{19} The locus for STGD/FFM was mapped to chromosome 1p using homozygosity mapping in inbred families,\textsuperscript{15} and the causative gene characterised, \textit{ABCA4} (previously denoted \textit{ABCR}).\textsuperscript{14} Subsequently mutations in \textit{ABCA4} have been implicated in other disorders, including retinitis pigmentosa (RP),\textsuperscript{16} and cone-rod dystrophy (CORD).\textsuperscript{17} \textit{ABCA4} encodes a transmembrane rim protein located in the discs of rod and foveal cone outer segments, that is involved in ATP dependent transport of retinoids from photoreceptor to RPE.\textsuperscript{18} Failure of this transport results in deposition of a major lipofuscin fluorophore, A2E (N-retinylidene-N-retinal-lethanolamine), in the RPE.\textsuperscript{19} It is proposed that this accumulation may be deleterious to the RPE, with consequent secondary photoreceptor degeneration.

Mutation screening of patients with STGD/FFM has been performed by several groups in recent years.\textsuperscript{20–23} The high allelic heterogeneity of \textit{ABCA4} is clearly demonstrated by the fact that approximately 400 sequence variations in this gene have been reported. This highlights the potential difficulties in confidently assigning disease-causing status to sequence variants detected when screening such a large (50 exons) and polymorphic gene. Nonsense mutations that can be predicted to have a major effect on the encoded protein can be confidently predicted to be disease-causing. However a major problem occurs with missense mutations since sequence variants are common in controls and therefore establishing pathogenicity may be problematic. Hence large studies assessing whether particular sequence variants are statistically more frequently seen in STGD patients than controls are likely to be helpful.\textsuperscript{24} Direct evidence of pathogenicity can be established by functional analysis of the encoded mutant protein,\textsuperscript{25} although such studies are very time consuming and labour intensive. The availability of multiple independent families with the same mutation may also provide evidence in support of disease causation. It is currently believed that: (1) homozygous null mutations cause the most severe phenotype of autosomal recessive RP, (2) combinations of a null mutation with a moderate missense mutation result in autosomal recessive CORD, and (3) combinations of null/mild missense or two moderate missense mutations cause STGD/FFM.\textsuperscript{26}

Assessment of functional activity of mutant \textit{ABCA4} transporter has been performed by Sun et al.\textsuperscript{27} For example the missense mutations, L541P and G1961E, are associated with severely reduced but not abolished ATPase activity, whereas nonsense mutations would be predicted to have a more severe effect on protein function. Such predictions and functional assay results\textsuperscript{27} have been used to establish whether genotype-phenotype correlations can be reliably made. Gerth \textit{et al.}\textsuperscript{27} have recently reported a detailed assessment of the phenotype of sixteen patients with STGD/FFM with known \textit{ABCA4} mutations. Correlation between the type and combination of \textit{ABCA4} mutations with the severity of the phenotype in terms of age of onset and level of photoreceptor dysfunction was possible in many cases. However in some siblings there were unexplained differences in phenotype. It has been proposed that in these instances other genes may have a modifying effect or environmental factors may have a role to play.\textsuperscript{28} This is a recurring theme in the inherited macular dystrophies, in that the underlying “genetic context” within which mutations associated with disease are expressed can influence the eventual phenotype observed. In addition, variable retinal phenotype within families may be explained by different combinations of \textit{ABCA4} mutations segregating within a single family.\textsuperscript{29}

The ocular phenotype in \textit{ABCA4} knockout mice has been determined. Knockout mice (\textit{abca4}) show delayed dark adaptation, increased all-trans-retinaldehyde (all-trans-RAL) following light exposure, and striking deposition of the major lipofuscin fluorophore, A2E, in the RPE. Delayed dark adaptation is likely to be due to the accumulation in outer segment discs of the non-covalent complex between opsin and all-trans-RAL.\textsuperscript{30} Delayed recovery of rod sensitivity after light exposure is also a clinical feature of human subjects with both STGD and ARM.\textsuperscript{30} Heterozygous loss of the \textit{ABCA4} protein has also been shown to be sufficient to cause a phenotype in mice similar to STGD and ARM in humans.\textsuperscript{31} These data are consistent with the suggestion that the STGD carrier-state may predispose to the development of ARM.

Light-exposed A2E-laden RPE exhibits a propensity for apoptosis especially with light in the blue part of the spectrum.\textsuperscript{32} During RPE irradiation (430 nm), \textit{ABCA4} self-generates singlet oxygen with the latter in turn reacting with A2E to generate epoxides.\textsuperscript{33} It has been recently demonstrated that these A2E epoxides exhibit damaging reactivity towards DNA.\textsuperscript{34} Moreover, mass spectrometry revealed that the antioxidants vitamins E and C reduce A2E epoxidation, with a corresponding reduction in the incidence of DNA damage and cell death. Vitamin E produced a more pronounced decrease in A2E epoxidation than vitamin C. Studies in which singlet oxygen was generated by endoperoxide in the presence of A2E, revealed that vitamin E reduced A2E epoxidation by quenching singlet oxygen.\textsuperscript{35} This study raises the exciting possibility of a simple therapy. The potential for pharmacological manipulation of \textit{ABCA4} activity has also been demonstrated by in vitro studies.\textsuperscript{36} For example, amiodarone has been found to enhance ATPase activity in vitro.\textsuperscript{37} Therefore such compounds which act to augment \textit{ABCA4}-related retinoid transport may prove to be beneficial in vivo in patients with STGD or in a subset of individuals at risk for ARM.

A different strategy of reducing A2E related toxicity, by inhibiting the formation of such lipofuscin pigments has also been reported.\textsuperscript{38} It has been shown that A2E synthesis can be virtually blocked by raising \textit{abca4} RNA in mice, in total darkness.\textsuperscript{39} Recently it has been demonstrated in the \textit{abca4} knockout mouse model that isoretinoin blocked the formation of A2E and the accumulation of lipofuscin pigments in the RPE.\textsuperscript{40} Isoretinoin (13-cis-retinoic acid) is known to slow the synthesis of 11-cis-retinaldehyde and regeneration of rhodopsin by inhibiting 11-cis-retinol dehydrogenase in the visual cycle. Light activation of rhodopsin results in the release of all-trans-RAL, which constitutes the first reactant in A2E biosynthesis. Treatment with isoretinoin, an established treatment for acne, may inhibit lipofuscin accumulation and thus delay the onset of visual loss in STGD.\textsuperscript{41} It remains to be assessed whether isoretinoin is a potential treatment for other forms of macular degeneration associated with lipofuscin accumulation.

## Autosomal Dominant Inheritance

### Autosomal dominant Stargardt-like macular dystrophy

The clinical appearance of autosomal dominant (AD) Stargardt-like macular dystrophy is so similar to the common autosomal recessive form of the disorder that it is difficult to differentiate between them by fundus examination alone.\textsuperscript{42} However individuals with features of AD STGD-like dystrophy have a milder phenotype with relatively good functional vision, minimal colour vision defects and no significant electro-oculography (EOG) or ERG abnormalities.\textsuperscript{43} The “dark choroid” sign on fluorescein angiography which is typical in the recessive form, but not diagnostic, is uncommon in the dominant form of the disorder.
Two chromosomal loci have been identified, 6q14 (STGD3) and 4p (STGD4). Two mutations, a 5-bp deletion and two 1-bp deletions separated by four nucleotides, in the gene ELOVL4 have been associated with STGD3 and other macular dystrophy phenotypes including pattern dystrophy.\textsuperscript{46} ELOVL4 is expressed in the rod and cone photoreceptor inner segments. The protein product is believed to be involved in retinal fatty acid metabolism since it has significant homology to a family of proteins involved in fatty acid elongation. A missense mutation in PROML1 has recently been found to co-segregate with disease in the STGD4 pedigree (personal communication, K Zhang). The gene PROML1 encodes human prominin (mouse)-like 1, which belongs to the prominin family of five-transmembrane domain proteins. PROML1 is expressed in retinoblastoma cell lines and adult retina, and the product of the mouse orthologue (prom) is concentrated in membrane evaginations at the base of the outer segments of rod photoreceptors.\textsuperscript{46} A homozygous mutation in PROML1 has been identified in an Indian pedigree with an autosomal recessive retinal dystrophy. The mutation results in the production of a truncated protein and functional studies in transfected CHO cells has demonstrated that the truncated prominin protein fails to reach the cell surface, indicating that the loss of prominin may lead to retinal degeneration via the impaired generation of evaginations or conversion to outer segment disks.\textsuperscript{46}

We have recently reported a British family with an autosomal dominant “Bull’s-Eye” macular dystrophy (MCDR2) also mapping to chromosome 4p,\textsuperscript{47} and overlapping the STGD4 disease interval reported by Kniazeva \textit{et al.} The MCDR2 phenotype that we have described is clinically distinct from that of STGD4 in that retinal flecks are absent and there is also no evidence of a dark choroid on fluorescein angiography, both of which are prominent features of the STGD4 family. We have however identified the same missense mutation in PROML1 as has been found in the STGD4 pedigree (unpublished data). This therefore represents another example where the eventual macular dystrophy phenotype observed would appear to be dependent on the genetic context/background within which a mutation in a particular gene is expressed.

\textbf{Best disease (vitelliform macular dystrophy)}

Best disease is a dominantly inherited macular dystrophy which is characterised clinically by the classical feature of a round or oval yellow subretinal macular deposit. The yellow material is gradually resorbed over time, leaving an area of RPE atrophy and often subretinal fibrosis (fig 2). The flash ERG is normal but the EOG shows a very reduced or absent light rise indicating that there is widespread dysfunction of the RPE.\textsuperscript{48} In common with STGD, histopathology of donated eyes from patients with Best disease has shown accumulation of lipofuscin throughout the RPE.\textsuperscript{49} Although the ophthalmoscopic abnormality is usually confined to the macular region, this evidence of more widespread retinal involvement is in common with the majority of inherited macular dystrophies described to date. The disease shows very variable expressivity. Most individuals carrying mutations in the VMD2 gene on chromosome 11q13\textsuperscript{50}–\textsuperscript{53} have an abnormal EOG, but the macular appearance may be normal in some.\textsuperscript{50} There is only one individual reported with evidence of non-penetrance, in that he is a mutant VMD2 gene carrier with a normal fundus examination and normal EOG.\textsuperscript{55} The visual prognosis in Best disease is surprisingly good, with most patients retaining reading vision into the fifth decade of life or beyond. Family members who carry a mutation in the VMD2 gene and who have minimal macular abnormality or a normal fundus appearance (but abnormal EOG) in early adult life, usually retain near normal visual acuity long term.

The protein product of VMD2, bestrophin, has been localised to the basolateral plasma membrane of the RPE where it forms a component of a chloride channel responsible for maintaining chloride conductance across the basolateral membrane of the RPE.\textsuperscript{56} This chloride current regulates fluid transport across the RPE, and it has been suggested following optical coherence tomography of patients with Best’s, that impaired fluid transport in the RPE secondary to abnormal chloride conductance may lead to accumulation of fluid and/or debris between RPE and photoreceptors and between RPE and Bruch’s membrane, leading to detachment and secondary photoreceptor degeneration.\textsuperscript{57,58}

The variable expression of Best disease remains unexplained, and here once again, other genes in addition to VMD2, and/or environmental influences may play a role in the wide range of clinical expression seen.

\textbf{Adult vitelliform macular dystrophy}

Adult vitelliform macular dystrophy (AVMD) is often confused with Best disease, although as the name suggests it has a later onset, lacks the typical course through different stages of macular disease seen in classical Best’s, and the electro-oculogram (EOG) is usually normal.\textsuperscript{59} The typical clinical appearance is of bilateral, round or oval, yellow, symmetrical, sub-retinal lesions, typically one third to one half optic disc diameter in size.

Mutations in the \textit{peripherin/RDS} gene on chromosome 6p have been identified in AVMD.\textsuperscript{60,61} It has been proposed that mutations in \textit{peripherin/RDS} are present in approximately 20% of patients with AVMD,\textsuperscript{62} which implies further genetic heterogeneity.

\textbf{Pattern dystrophy}

The pattern dystrophies are a group of inherited disorders of the RPE which are characterised by bilateral symmetrical yellow-orange deposits at the macula in various distributions, including butterfly or reticular-like patterns. These dystrophies are often associated with a relatively good visual prognosis, although in some cases a slowly progressive loss of central vision can occur. There is usually psychophysical or electrophysiological evidence of widespread photoreceptor dysfunction.\textsuperscript{63} Electrophysiological findings usually reveal abnormal pattern ERG, normal flash ERG, but abnormal EOG.

Mutations in the \textit{peripherin/RDS} gene on chromosome 6p have been identified in patients with pattern dystrophies,\textsuperscript{64} and have also been implicated in autosomal dominant RP.\textsuperscript{65,66} The RDS gene was originally identified in a strain of mice.
with a photoreceptor degeneration known as “retinal degeneration, slow” (rdS). Subsequently, the orthologous human peripherin/RDS gene was shown to cause autosomal dominant RP.9 10 Mutation in codon 172 of peripherin/RDS has also been implicated in autosomal dominant macular dystrophy.11 The peripherin/RDS protein is a membrane associated glycoprotein restricted to photoreceptor outer segment discs in a complex with ROM1. It may function as an adhesion molecule involved in the stabilisation and maintenance of a compact arrangement of outer segment discs.12 Peripherin has also been shown to interact with the GARP domain (glutamic acid- and proline-rich region) of the beta-subunit of rod cGMP-gated channels, in a complex including the Na/Ca-K exchanger.13 This interaction may have a role in anchoring the channel-exchanger complex in the rod outer segment plasma membrane. Weleber et al described a single family in which a 3-bp deletion in peripherin/RDS resulted in retinitis pigmentosa, pattern dystrophy and FFM in different individuals.14 This represents a further example of the likely modifying effects of genetic background or environment.

The rdS mouse, which is homozygous for a null mutation in peripherin/RDS, is characterised by a complete failure to develop photoreceptor discs and outer segments, down-regulation of rod opsin expression, and apoptotic loss of photoreceptor cells. Ali et al15 have demonstrated that subretinal injection in these mice of recombinant adenovirus encoding a peripherin/RDS transgene, resulted in the generation of outer segment structures and formation of new stacks of discs containing both peripherin/RDS and rhodopsin. Moreover, electrophysiological function was also preserved. This study demonstrates in an animal model the efficacy of in vivo gene transfer to restore structure and more importantly function.16 Further assessment of this model has shown that the potential for ultrastructural improvement is dependent upon the age at treatment, but the effect of a single injection on photoreceptor ultrastructure may be long lasting.17 These findings suggest that successful gene therapy in patients with photoreceptor defects may ultimately depend upon intervention in early stages of disease and upon accurate control of transgene expression.

Doyne honeycomb retinal dystrophy (malattia leventinese; autosomal dominant drusen)

In this disorder small round yellow-white deposits under the RPE are characteristically distributed at the macula and around the optic disc, and begin to appear in early adult life (fig 3). Visual acuity is maintained through the fifth decade, but patients usually become legally blind by the seventh decade. Visual loss is usually due to macular atrophy, but less commonly may follow subretinal neovascular membrane (SRNVM). The presence of drusen-like deposits makes this dystrophy potentially very relevant to ARMD.

A single mutation, Arg-345-to-Trp (R345W) in the gene EFEMP1 on chromosome 2p has been identified in the majority of patients with dominant drusen.18 EFEMP1 is a widely expressed gene of unknown function. Based on its sequence homology to the fibulino and fibrillin gene families, EFEMP1 is predicted to be an extracellular matrix glycoprotein, but otherwise is uncharacterised. However, it has been recently proposed that misfolding and aberrant accumulation of EFEMP1 within RPE cells and between the RPE and Bruch’s membrane may underlie drusen formation in Doyne Honeycomb retinal dystrophy and ARMD. EFEMP1 itself does not appear to be a major component of the drusen.19

Genetic heterogeneity in autosomal dominant drusen has been suggested by Tarttelin et al20, since they found that only seven of the 10 families (70%) and one of the 17 sporadic patients (6%) investigated had the R345W mutation. No other EFEMP1 mutation was detected in these patients. Other families showing linkage to chromosome 2p16 raise the possibility of an upstream EFEMP1 promoter mutation or a second dominant drusen gene at this locus.

Autosomal dominant drusen and macular degeneration (DD)

Stefko et al21 have described a highly variable clinical phenotype in a North American family with an autosomal dominant drusen disorder with macular degeneration (DD). Most young adults had fine macular drusen and good vision. Affected infants and children may have congenital atrophic maculopathy and drusen. There was also evidence of progression in late adulthood with moderate visual loss.

The gene for the disease has been mapped to chromosome 6q14 and appears to be adjacent to but distinct from the locus for North Carolina macular dystrophy (MCDR1).22 The disease interval overlaps with that of STGD3 and an autosomal dominant atrophic macular degeneration (adMD),23 raising the possibility that they may be allelic disorders. However the phenotype of DD differs from that of STGD3 and adMD. Macular drusen are a hallmark of DD, whilst RPE atrophy and subretinal flecks are prominent features of STGD3 and adMD. The true situation will only be resolved by the identification of the underlying genetic mutations.

North Carolina macular dystrophy

North Carolina macular dystrophy (MCDR1) is an autosomal dominant disorder which is characterised by a variable macular phenotype and a non-progressive natural history. Bilaterally symmetrical fundus appearances in MCDR1 range from a few small (less than 50 μm) yellow drusen-like lesions in the central macula (grade 1) to larger confluent lesions (grade 2) and macular colobomatous lesions (grade 3) (fig 4).24 Occasionally MCDR1 is complicated by SRNVM formation at the macula. EOG and ERG are normal indicating that there is no generalised retinal dysfunction.

Linkage studies have mapped MCDR1 to a locus on chromosome 6q16. To date, MCDR1 has been described in various countries and no evidence of genetic heterogeneity has been reported.25 The identification of the gene

Figure 3 Doyne honeycomb retinal dystrophy. Fundus photograph of a right eye showing multiple drusen-like deposits at the macula and around the optic disc. Small drusen-like deposits can also be seen to radiate from the periphery of the main drusen mass. The established complication of subretinal neovascular membrane (SRNVM) is present centrally.

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known mutations in TIMP3 mediated extracellular matrix turnover leading to the abnormal tertiary protein structure. This may alter TIMP3 resulting in inappropriate disulfide bond formation and an abnormality of the C-terminus of the protein, thereby introducing potentially unpaired cysteine residues in the C-terminus of the protein, thereby resulting in inappropriate disulfide bond formation and an abnormal tertiary protein structure. This may alter TIMP3 mediated extracellular matrix turnover leading to the thickening of Bruch’s membrane and the widespread accumulation of abnormal material beneath the RPE that is seen histologically.

The finding that treatment with high doses of oral vitamin A reverses night blindness in this disorder suggests that retinal dysfunction may be due to a reduction in the permeability of Bruch’s membrane, resulting in the hindrance of transport of vitamin A from the choriocapillaris to the photoreceptors by accumulated extracellular debris beneath the RPE. In addition, Majid et al. have demonstrated that mutant TIMP3 can induce apoptosis of RPE cells suggesting that apoptosis may be the final pathway for cell death in this disorder. Furthermore, TIMP3 has been recently shown to be a potent inhibitor of angiogenesis, which may account for the recognised complication of choroidal neovascularisation seen in SFD.

TIMP3 inhibits vascular endothelial growth factor (VEGF)-mediated angiogenesis, most probably by blockade of VEGF-2 receptors.

Further insights into the pathophysiology of SFD may follow the development of a knock-in mouse carrying a disease-related Ser156Cys mutation in the orthologous murine TIMP3 gene. Immunolabelling studies and biochemical data from these mice suggested that site-specific excess rather than absence or deficiency of functional TIMP3 may be the primary consequence of the known TIMP3 mutations.

Central areolar choroidal dystrophy (CACD)

CACD is characterised by bilateral, symmetrical, subtle mottling of the RPE at the macula in the early stages. The mottling then progresses to atrophy of the RPE and choriocapillaris.

An Arg142Trp mutation in peripherin/RDS has been implicated as one cause of this rare autosomal dominant macular dystrophy. Sporadic cases of CACD have also been described but no mutations were found in peripherin/RDS. A second locus at chromosome 17p13 has also been identified by a genome wide linkage search in a large Northern Irish family.

Dominant cystoid macular dystrophy (dominant cystoid macular oedema)

This rare autosomal dominantly inherited macular dystrophy was first described by Deutman et al. Cystoid macular oedema with leaking perifoveal capillaries on fluorescein angiography is seen in all affected patients. Other features include onset usually in the fourth decade, typically a...
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moderate to high hypermetropic refractive error, and a normal ERG. Genetic linkage has been established to 7p15-p21. The causative gene remains to be identified.

In addition to those described above there are several other autosomal dominant macular dystrophies whose phenotypes are not well described.

X LINKED INHERITANCE

X linked juvenile retinoschisis (XLRS)

XLRS is a vitreoretinal degeneration which presents either in an infant with nystagmus, or more commonly in childhood with mild loss of central vision. The characteristic fundus abnormality is a cystic spokewheel-like maculopathy (foveal schisis) in virtually all affected males (fig 6). Peripheral retinal abnormalities including bilateral schisis cavities, vascular closure, inner retinal sheen, and pigmented retinopathy are seen in approximately 50% of cases. Flash ERG typically reveals a negative waveform, in that the a-wave is larger in amplitude than the b-wave. Prognosis is good in most affected males as long as retinal detachment or vitreous haemorrhage does not occur. The histopathological findings in XLRS include splitting within the superficial layers of the retina, degeneration of photoreceptors, thinning of the ganglion cell layer, and a focally absent or proliferative RPE.

XLRS has been linked to Xp22.2 and mutations in the gene XLRS1 (also recently referred to as RS1) have been identified. Juvenile retinoschisis shows a wide variability in the phenotype between, as well as within, families with different genotypes. XLRS1 encodes a 224 amino acid protein, retinoschisin (RS1), which contains a highly conserved discoidin domain implicated in cell–cell adhesion and cell–matrix interactions, functions which correlate well with the observed splitting of the retina in XLRS.

Many missense and protein truncating mutations of XLRS1 have now been identified and are thought to be inactivating. It has been demonstrated that although XLRS1 is expressed predominantly in photoreceptors, it is also expressed in bipolar cells. RS1 is assembled in photoreceptors of the outer retina and bipolar cells of the inner retina as a disulphide-linked oligomeric protein complex. The secreted complex associates with the surface of these cells, where it may function as a cell adhesion protein to maintain the integrity of the central and peripheral retina. To gain further insight into the function of the retinoschisin protein, knockout mice have been generated, deficient in Rs1h, the murine orthologue of the human XLRS1 gene. The hemizygous Rs1h-/- male mouse was shown to share several diagnostic features with human XLRS, including the typical “negative ERG” response and the development of cystic structures within the inner retina, followed by a dramatic loss of photoreceptor cells. Whilst the major pathology in the retina of the retinoschisin deficient mouse seemed to be a generalised disruption of cell layer architecture, atypical ribbon synapse formation at the photoreceptor terminals was also noted. This suggests a direct or indirect role of RS1 in the assembly and stabilisation of this synaptic region of the cell. Failure to establish or maintain these synaptic connections could lead to subsequent photoreceptor cell death.

MITOCHONDRIAL INHERITANCE

Maternally inherited diabetes and deafness (MIDD)

MIDD is a recently described subtype of diabetes mellitus that co-segregates with an adenine-to-guanine transition at position 3243 of mitochondrial DNA (A3243G), in a transfer RNA leucine (tRNALeu (UUR)) encoding region. This mitochondrial DNA mutation can also be associated with a severe encephalopathy with death at a young age (MELAS: mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes).

Macular pattern dystrophy (MPD) has been found in association with MIDD. In a multicentre study, 86% of MIDD patients were found to have bilateral MPD, characterised by RPE hyperpigmentation that can surround the macula or be more extensive and also encompass the optic disc. In advanced cases areas of RPE atrophy encircling the macula can be seen, which may coalesce and involve the fovea at a late stage (fig 7). However prognosis is generally good, with 80% of patients in the multicentre study having visual acuity of 6/7.5 or better in both eyes. As the prevalence of MPD in MIDD is high, the association of a MPD with diabetes should raise the possibility of screening for a mutation of mitochondrial DNA.

AGE RELATED MACULAR DEGENERATION

ARMD is by far the most common form of macular degeneration. ARMD is the leading cause of blindness in patients over the age of 65 years in the western world. Despite its prevalence, its aetiology and pathogenesis are still poorly understood, and, currently, effective treatment options are limited for the majority of patients.
ARMD has a genetic contribution to its aetiology. Putative susceptibility loci have been identified on chromosomes 1q25-31, chromosome 17q21-25 and on chromosomes 5, 9, and 10, whereas it has been suggested that the 6q4 allele of the apolipoprotein E gene and an Alu polymorphism in the angiotensin-converting enzyme gene may have a protective effect on ARMD risk.

Inherited monogenic macular dystrophies share many important features with ARMD and have the advantage that they are more readily studied. One of the major difficulties in studies of ARMD is its late onset. Parents of affected individuals are often deceased and their children have yet to manifest the disease. In contrast, there are several forms of macular dystrophy, such as STGD/FFM, Best disease and MCDR1, which manifest signs and symptoms at an early age. These dystrophies and others have been characterised in large numbers of family members, spanning several generations, thereby making them far more amenable to genetic analysis. Furthermore, several of these macular dystrophies share many important clinical and histopathological similarities with ARMD, including an abnormal accumulation of lipofuscin in the RPE and a concomitant loss of function of photoreceptors and central vision.

However to date, with the possible exception of ABCA4, none of these genes have been shown to confer increased risk of ARMD. However, all new macular dystrophy genes represent good candidates for ARMD.

CONCLUSIONS

Although in some inherited macular dystrophies, the disease is confined to the macular region, in other disorders, perhaps the majority, there is electrophysiological, psychophysical, or histological evidence of widespread retinal dysfunction. This may partly account for the fact that to date, genes implicated in monogenic macular dystrophies have not been found yet to have a significant role in the genetic predisposition to ARMD.

Another possible reason for the lack of significant ARMD association with variation in the monogenic macular dystrophy genes so far identified is the hypothesis that the co-occurrence of subclinical mutations in a number of genes involved in the formation and function of the macula could be responsible in a polygenic fashion for cases of ARMD. However, it also remains a possibility that the susceptibility genes are neither specifically retinal nor macular.

Improved knowledge of the mechanisms of inherited macular dystrophy and the underlying molecular genetics, has not only raised the potential for future development of rational therapeutic regimens, but has helped to refine diagnosis, disease classification and prognosis, and improved genetic counselling.

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REFERENCES


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areolar choroidal dystrophy to chromosome 17p.


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