Macular Dystrophies

Clinical Findings and Genetic Aspects

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Core Messages

- A clinical diagnosis in juvenile macular dystrophies is essential for genetic counselling as well as for direct molecular genetic investigations
- Stargardt disease, Best vitelliform macular dystrophy and X-linked juvenile retinoschisis are the most prevalent macular dystrophies in Western Europe
- Stargardt disease contributes to a spectrum that includes other retinal dystrophies associated with *ABCA4* gene mutations, such as autosomal recessive forms of cone-rod dystrophy and retinitis pigmentosa
- Cataract, retinal detachment and especially choroidal neovascularization are associated with some of these macular dystrophies. Since these complications may be amenable to treatment, regular follow-up of patients with macular dystrophies is important
- Pattern dystrophies may be associated with systemic abnormalities, including pseudoxanthoma elasticum and myotonic dystrophy
- Many of these so-called macular dystrophies also display abnormalities of the peripheral retina as demonstrated by ophthalmoscopy and electrophysiology

3.1 Introduction

A variety of dystrophies, principally located at the macula, can be distinguished according to fundus appearance, inheritance pattern and, in some cases, molecular genetic analysis. Although these disorders are all characterized by loss of central vision and atrophic changes in the macula and underlying retinal pigment epithelium (RPE), they are highly heterogeneous as to the clinical findings and the underlying genetic cause. The macular dystrophies are a significant cause of blindness, especially in the young. Nevertheless, surprisingly few data are available as to the exact prevalence of these disorders. For Stargardt disease and X-linked juvenile retinoschisis – with Best vitelliform macular dystrophy among the most common macular dystrophies – a prevalence of respectively 1:10,000 and 1:5,000 to 1:25,000 has been reported. Despite the term "macular dystrophies", which suggests localized pathology, many of these disorders are at a molecular level panretinal disorders, in which the macular region shows greater susceptibility to the degeneration.

The past few decades have witnessed impressive advances in molecular genetics. Also in the field of inherited macular dystrophies many genes and loci have been implicated. Only a few macular dystrophies disorders turn out to be genotypically ho-

mogeneous. More often, these disorders display a considerable genetic heterogeneity, which means that mutations in different genes result in clinically similar phenotypes.

The advent of molecular genetics in modern medicine has made it possible to analyse a disease from the "inside out". The identification of the underlying genetic defect in macular dystrophies is only the first step in understanding the fundamental causes of the disease. Hopefully, our increasing knowledge of the pathophysiologic mechanisms will enable the development of future treatment regimes.

Current classifications are still based on clinical observations, in selected cases supplemented with the underlying genetic defect. A correct clinical diagnosis remains of the utmost importance, not only to facilitate or even enable analysis of the underlying genetic abnormality, but also to provide the patient with the most accurate prognosis.

In this chapter we address the various clinical findings in the most common monogenic macular dystrophies. When possible, the underlying genetic defect and pathophysiological mechanisms will be discussed. Although age-related macular degeneration could be considered a macular dystrophy, in view of the genetic associations, this disorder will be discussed separately.

3.2 Macular Dystrophies

3.2.1 Stargardt Disease

3.2.1.1 Clinical Findings

Autosomal recessive Stargardt disease (STGD1) is arguably the most common hereditary macular dystrophy. Most patients with STGD1 experience bilateral loss of visual acuity in childhood or early adulthood. In a large study of 150 unrelated and genetically proven STGD1 patients, the mean age of onset was 15.2 years [42]. However, the age at which STGD1 patients develop visual loss may range from 4 to 65 years. Most patients experience a decrease in visual acuity to 0.05–0.1.

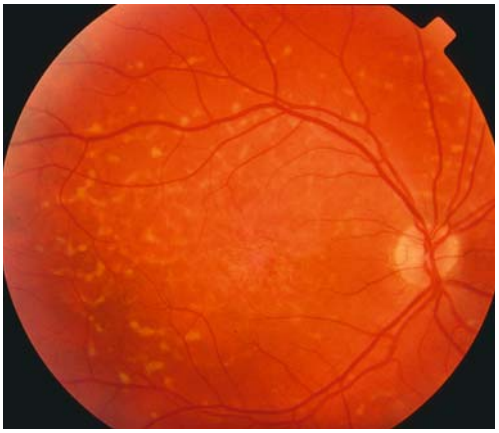

Fig. 3.1. Stargardt disease with pisciform yellow flecks and macular atrophy

Typically, pisciform yellow flecks can be observed in the posterior pole at the level of the RPE. These flecks are variable in size, shape and distribution and may extend as far as the equator (Fig. 3.1). As the disease spreads centrifugally new flecks may appear while older flecks resorb, during which time their colour changes from yellow to grey. Histological studies have shown that these flecks represent aggregates of swollen RPE cells engorged to 10 times their normal size with lipofuscin. Occasionally, the clinical findings in STGD1 may be minimal or atypical. The yellow flecks may be absent, especially in young children, or may be quite small in size and number. Some individuals demonstrate minimal fundus abnormalities with a heavily pigmented RPE that is easy to overlook ('vermillion fundus') [23]. With progression of the disease, atrophy of the RPE in

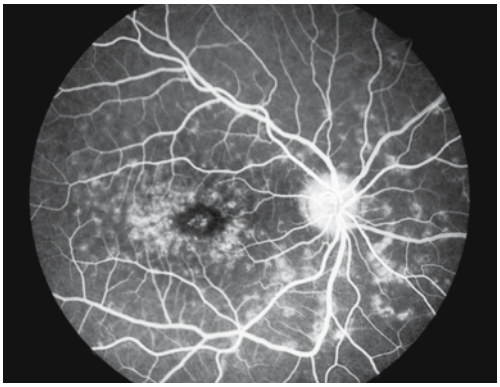

Fig. 3.2. Obscuration of the normal choroidal background in Stargardt disease, in combination with typical hyperfluorescent spots

the central macula may result in geographical atrophy, a beaten bronze appearance of the macula or a bull's eye pattern. In addition, progression of the STGD1 phenotype to a more widespread retinal disorder resembling cone-rod dystrophy is not uncommon.

In 1962 Franceschetti described the fundus flavimaculatus (FFM) phenotype characterized by a somewhat later age of onset and similar yellow flecks although greater in number and extending to the peripheral retina. In view of the similarities, both in fundus abnormalities as well as the underlying genetic cause, FFM and STGD1 are now considered to be variants of the same disorder.

Obstruction of the normal choroidal background fluorescence (a dark or silent choroid) is considered an important feature of STGD1 and is estimated to be present in 50–85 % of patients (Fig. 3.2). Increased levels of lipofuscin in the RPE are thought to absorb the blue excitatory light and cause this characteristic finding.

There is a marked variation in the reports on the electrophysiological abnormalities in STGD1. The multifocal electroretinogram (ERG) and pattern ERG are both used to assess functional abnormalities at the macula and are abnormal in almost all STGD1 patients. STGD1 patients may also demonstrate abnormalities on the standard ERG, more often in the cone than in the rod driven pathway. Abnormalities in the electro-oculogram (EOG), although variable, may also be found. Full-field electrodiagnostic abnormalities are clearly an indication of more extensive photoreceptor dysfunction, but no consistent relation between these findings and the presence and distribution of the fundus abnormalities has been demonstrated. However, it has been shown that it is unlikely that patients with normal scotopic and photopic ERGs in the early stage will demonstrate an abnormal ERG on follow-up [44].

3.2.1.2 Genetic Aspects and Pathophysiology

Autosomal recessive (ar) STGD1 is considered a monogenic disorder and is caused by mutations in the photoreceptor-specific ATP-binding cassette transporter (*ABCA4*) gene at 1p22.1 [2]. In contrast, a limited number of patients with autosomal dominant Stargardt-like macular dystrophy have been described, which have been linked to ELOVL4 at chromosome 6q14 (STGD3) and PROML1 at chromosome 4p (STGD4).

Besides STGD1, mutations in the *ABCA4* gene are involved in approximately 65 % of ar cone-rod dystrophy cases and 5–10 % of ar retinitis pigmentosa cases.

The *ABCA4* gene encodes the ABCR protein, which is located at the rim of the membrane discs in the photoreceptor outer segments. In rods, ABCR acts as a transmembrane transporter of all-*trans*-retinal, as *N*-retinylidene-phosphatidylethanolamine, from the interior of the disc membrane to the cytoplasm. All-*trans*-retinal can then enter the visual pigment cycle to be reisomerized to the 11-*cis*-retinal

chromophore. However, the functional impairment of ABCR in STGD1 patients will lead to build up of all-*trans*-retinal in the photoreceptor outer segment and subsequent accumulation of its degradation product (A2-E) in the cells of the RPE. A2-E is a major component of lipofuscin and toxic to the RPE cells; eventually, the build-up of A2-E will result in degeneration of the overlying photoreceptors.

These improved insights in the underlying mechanisms of STGD1 and other *ABCA4*-associated retinal disease will hopefully lead to the development of rational therapeutic options. Recently, an attempt was made to prevent the build-up of all-*trans*-retinal with isotretinoin in an animal model of this disorder. It was shown that this drug not only suppressed formation of A2-E in *Abca4* knockout mice but also reduced A2-E accumulation in wild-type mice by ~40 %. Furthermore, in view of the pathophysiology of Stargardt and other *ABCA4*-associated disease, patients with these retinal disorders should avoid excessive light exposure for two reasons. First, light induces the formation of all-*trans*-retinal from 11-*cis*-retinal [47]. Second, there is increasing evidence that photooxidative damage contributes to the development of *ABCA4*-associated retinal dystrophies. On theoretical grounds the supplementation of vitamin A (all-*trans*-retinol) and beta-carotene should be discouraged in these patients, since these substances act as precursors of 11-*cis*-retinal.

Summary for the Clinician

- **Autosomal recessive Stargardt disease is one of the commonest macular dystrophies and is characterized by a decrease in visual acuity to 0.050–0.1, pisciform yellow flecks in the posterior pole, some form of macular atrophy and blocking of the choroidal background fluorescence on the fluorescein angiogram**
- **On theoretical grounds, patients with Stargardt disease should be advised to avoid vitamin A supplements and avoid overexposure to sunlight**

3.2.2 X-Linked Juvenile Retinoschisis

3.2.2.1 Clinical Findings

X-linked (juvenile) retinoschisis (XLRS) is a relatively common cause of macular dystrophy in males. XLRS displays almost full penetrance but the expression is variable. While some individuals experience severe visual loss, other members of same family, carrying the same genetic defect, demonstrate only mild symptoms. Female carriers show no clinically detectable retinal abnormalities.

Most patients experience a moderately severe decrease in visual acuity between the ages of 5 and 10 years. In the majority of XLRS patients the visual acuity is better than 0.2. The typical picture is that of a spoke wheel maculopathy, which may be easily overlooked and is best seen with red-free light (Fig. 3.3). This characteristic finding is formed by small folds in the internal limiting membrane that radiate outward from a foveal retinoschisis. In older patients the fine cystic changes disappear and the macula may become atrophic in a non-specific way. In about 50 % of patients peripheral retinoschisis may be observed, usually in the inferotemporal quadrants. The most common complications are retinal detachment (5–22 %) and vitreous haemorrhage (4–40 %). Hyperopia is strongly associated with XLRS, although cases of emmetropia and even myopia have also been reported. Other features of XLRS in-

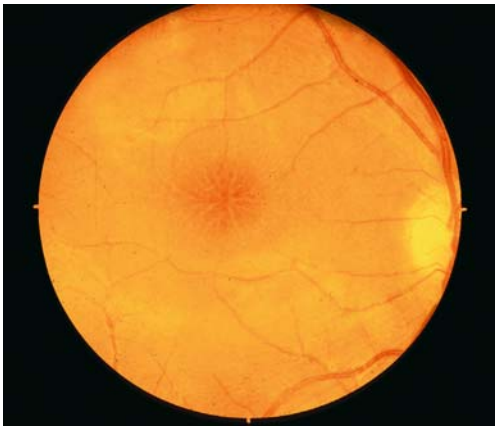

Fig. 3.3. X-linked juvenile retinoschisis

clude macular ectopia, optic nerve abnormalities (atrophy, pseudopapilloedema and dragging of the optic disc) and yellowish flecks in the posterior pole. Cataract is associated with this disorder and may be present at an early age. Since this is a treatable cause of visual loss it is advisable to examine patients with XLRS every few years [72].

XLRS patients demonstrate a so-called negative ERG that is characterized by a reduced b-wave amplitude in combination with relative preservation of the a-wave amplitude. The normal b/a ratio of the light adapted ERG is greater than 1.4. In XLRS the b/a ratio is almost always smaller than 1.0 [71].

Histopathologically, there is a splitting of the inner retina, primarily within the nerve fibre layer, although schisis may extend in some cases to outer retinal layers. Optical coherence tomography of the macula in an early case of XLRS revealed a wide hyporeflective space that split the neurosensory retina with a large intraretinal cyst located at the fovea [56].

3.2.2.2 Genetic Aspects and Pathophysiology

The gene involved in XLRS has been located on Xp22.2 [63]. This RS1 (XLRS1) gene encodes retinoschisin, a protein that is expressed and assembled in photoreceptors and bipolar cells. It functions as a cell adhesion protein to maintain the cellular organization and synaptic structure of the retina [53].

A few cases of autosomal dominant and recessive forms of familial retinoschisis have been reported.

Summary for the Clinician

- **Characteristic findings in X-linked juvenile retinoschisis include a spoke wheel maculopathy and a 'negative' ERG**
- **This disorder may be complicated by vitreous haemorrhage, retinal detachment and juvenile cataract**
- **Mutations in the RS1 gene are the cause of this relatively common retinal dystrophy**

3.2.3 Best Vitelliform Macular Dystrophy

3.2.3.1 Clinical Findings

The expression of vitelliform macular dystrophy or Best disease is highly variable and may range from isolated EOG abnormalities to loss of central vision due to central RPE atrophy and/or choroidal neovascularization. Vitelliform macular dystrophy has been divided into five stages (Figs. 3.4–3.7) [8]. Stage 1 (pre-vitelliform stage) is a carrier status with no abnormalities besides an abnormal EOG. Stage 2 (vitelliform stage) is characterized by the subretinal deposition of yellow material in

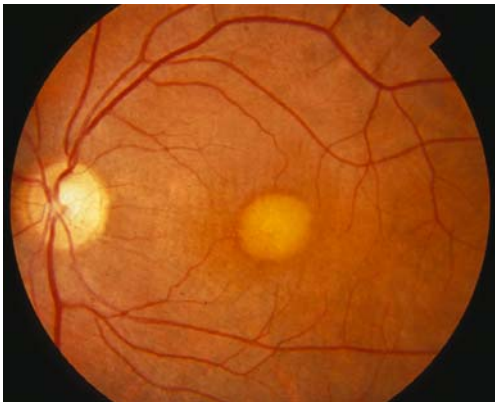

Fig. 3.4. Best disease; vitelliform stage

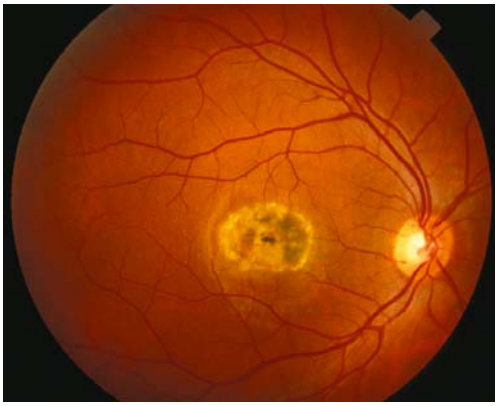

Fig. 3.7. Best disease; atrophic stage

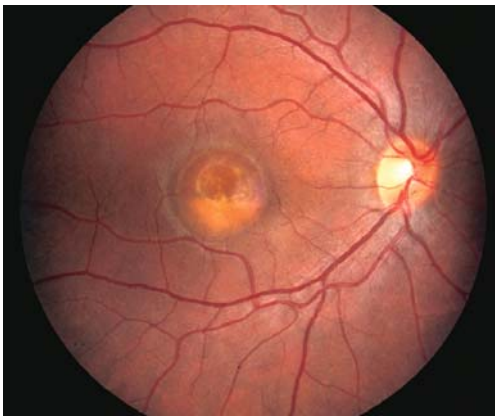

Fig. 3.5. Best disease; pseudohypoyon stage

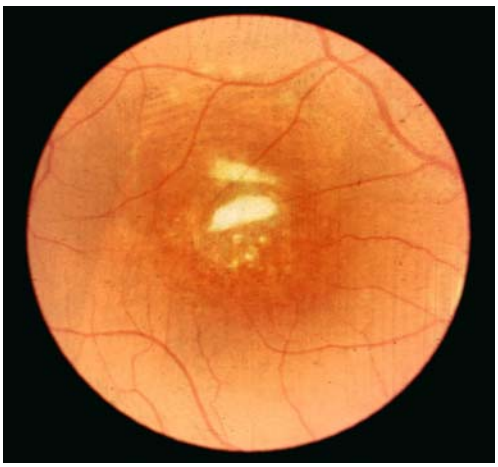

Fig. 3.6. Best disease; vitelliruptive stage

the macula during infancy or early childhood. The typical lesion resembles an egg yolk and may be 0.5–5 mm in diameter. Occasionally, the vitelliform lesion may present unilaterally; it may also occur outside the macular area and/or may be multiple. On the fluorescein angiogram the vitelliform lesion corresponds with an area of blocked choroidal fluorescence. In stage 3 (pseudohypopyon stage) the yellow material has broken through the RPE and gravitates inferiorly in the subretinal space. This typically occurs by the time the patient reaches puberty. The visual acuity in stages 2 and 3 is often surprisingly well preserved. In stage 4 (vitelliruptive stage) the vitelliform lesion begins to break up and resembles a scrambled egg. The visual acuity is usually decreased in this stage, often to a level of 0.2–0.6. Stage 5 (atrophic stage) follows the resorption of the yellow material and is characterized by an oval area of RPE atrophy often accompanied by plaques of white subretinal fibrotic tissue. Choroidal neovascularization may complicate this stage. There is a severe visual impairment of 0.1 or less.

The ERG is typically normal during all stages of vitelliform macular dystrophy. The EOG is abnormal, also in carriers, indicative of a widespread dysfunction of the

RPE [13]. Overall, the visual prognosis is good, most patients retaining reading status with at least one eye [23].

Histopathologic examination reveals that the RPE throughout the fundus has accumulated excessive amounts of lipofuscin. A heterogeneous material has also accumulated between Bruch's membrane and the pigment epithelium in the fovea; it appears to be derived from degenerating pigment epithelial cells and contains few intact lipofuscin granules. Photoreceptor loss occurs above these subfoveal areas of accumulation [22, 55, 70, 78].

3.2.3.2 Genetic Aspects and Pathophysiology

Although highly variable in expression, vitelliform macular dystrophy is considered fully penetrant because virtually all individuals carrying the genetic defect display EOG abnormalities. This autosomal dominant disorder is caused by mutations in *VMD2*, which is located on chromosome 11q13 and encodes the bestrophin protein [58]. Approximately 50 disease-associated mutations in the *VMD2* gene have been identified [70]. Bestrophin has been localized to the basolateral plasma membrane of RPE cells and is important in the formation of oligomeric chloride channels [46, 70]. Abnormalities in chloride conductance might create an imbalance in intracellular or intravesicular pH and disturb the fluid transport across the RPE. This could result in accumulation of debris between RPE and photoreceptors and between RPE and Bruch's membrane [59, 70].

Summary for the Clinician

- **Best vitelliform macular dystrophy is a relative common macular dystrophy that may be divided into five stages:**
  1. **An abnormal EOG without fundus abnormalities (carrier status)**
  2. **Vitelliform stage**
  3. **Pseudohypopyon stage**
  4. **Vitelliruptive stage**
  5. **Atrophic stage**
- **A disturbed EOG is a typical finding, especially when found in combination with a normal ERG.**
- **Best disease is caused by mutations in the VMD2 gene**

3.2.4 Progressive Cone Dystrophy

3.2.4.1 Clinical Findings

Retinal disorders with impaired cone functions may be stationary or progressive. The latter should be distinguished from the cone dysfunction syndromes that are stationary and include conditions such as achromatopsia, oligocone trichomacy, cone monochromatism and blue cone monochromatism. Progressive cone dystrophy (PCD) should actually be considered a group of disorders and this is also reflected in the large number of genes and loci that have been linked to this condition (Table 3.1). Although cone photoreceptor death in PCDs is not limited to the macula, it will be discussed in this section in view of the prominent macular pathology in these patients.

PCDs usually present in adolescence or early adult life. Predominant symptoms are progressive loss of visual acuity, pronounced photophobia and day blindness. In addition, nystagmus is a common finding in these patients. In contrast with most other macular disorders, colour vision abnormalities are present early in the course of the disease. Usually, all three classes of photoreceptors are affected, thereby producing colour vision defects along all three colour axes [27]. These symptoms often

Table 3.1. Summary of identified genes and loci in macular dystrophies. *MIM,* Mendelian inheritance of man; *PCD,* progressive cone dystrophy; *AD,* autosomal dominant; *AR,* autosomal recessive

Retinal dystrophy	MIM number	Mode of inheritance	Disease genes	Mapped loci
Adult-onset vitelliform dystrophy	608161	AD	*Peripherin/RDS* [20] *VMD2* [64]	
Autosomal dominant cystoid macular oedema	153880	AD		7p15.3 [40]
Benign concentric annular macular dystrophy	153870	AD	*VMD2* [1]	6p12.3-q16 [43]
North Carolina macular dystrophy	136550	AD		6q14-q16.2 [66]
Best vitelliform macular dystrophy	153700	AD	*VMD2* [58]	
Central areolar choroidal atrophy	215500	AD	*Peripherin/RDS* [31]	17p13 [45]
Doyne honeycomb retinal dystrophy/Malattia Leventinese	126600	AD	*EFEMP1* [68]	6q14 [38]
Juvenile retinoschisis	312700	X-linked	*XLRS1* [63]	
Pattern dystrophy	169150	AD	*Peripherin/RDS* [54]	5q21.2-q33.2 [12]
Progressive bifocal chorioretinal atrophy	600790	AD		6q14-q16.2 [35]
The progressive cone dystrophies				
– COD1	304020	X-linked	*RPGR* [79]	
– COD2	303800	X-linked		Xq27 [6]
– COD3	602093	AD	*GUCA1A* [57]	
– An unclassified PCD	–	AR	*CNGB3* [49]	
– RCD1	180020	AD		6q25-q26
– RCD2	601251	AD		17p12-p13 [5]
Sorsby fundus dystrophy	136900	AD	*TIMP3* [77]	
Stargardt retinal dystrophy (STGD1)	248200	AR	*ABCA4* [2]	
Stargardt-like macular dystrophy (STGD3)	600110	AD	*ELOVL4* [81]	
Stargardt-like macular dystrophy (STGD4)	603786	AD	*PROML1* [50]	

precede the fundus abnormalities, which include a bull's eye maculopathy or, less frequently, granular pigment alterations in the posterior pole (Fig. 3.8). Rarely, a central atrophy of RPE may be found. The optic disc may show a variable degree of temporal pallor. Visual field testing generally reveals central scotomas, sometimes with relative central sparing; the peripheral visual field remains unaffected. The ERG shows loss of the cone-mediated responses with normal rod-mediated responses [41].

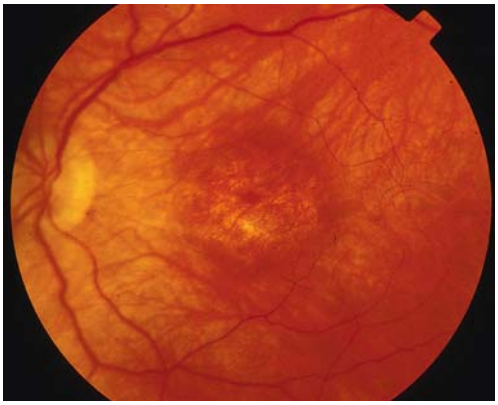

Fig. 3.8. Cone dystrophy

A substantial number of patients that are initially diagnosed with PCD will eventually progress to a cone-rod dystrophy, with night blindness and abnormalities in the rod mediated ERG recordings.

3.2.4.2 Genetic Aspects

The clinical heterogeneity of PCD is matched by the genetic heterogeneity. All three classic modes of Mendelian inheritance, autosomal recessive, autosomal dominant and X-linked recessive, have been described. Many cases of PCD are sporadic but in patients with a family history autosomal dominant inheritance is most common. In addition to a number of loci, three genes have been identified in PCD (Table 3.1). COD1 is X-linked and has been associated with mutations in the *RPGR* gene [79]. Mutations in this gene have also been associated with retinitis pigmentosa. In the case of COD3 (an autosomal dominant PCD) mutations have been identified in the *GUCA1A* gene [57]. This gene encodes the GCAP1 protein, which is present in cones and rods, and is thought to have an important regulatory function in the phototransduction cascade. Finally, an autosomal recessive form of PCD has been associated with mutations in the *CNGB3* gene [49]. This gene encodes a cone-specific β-subunit of the cGMP-gated cation channel protein. Mutations in this gene are commonly found in achromatopsia, a stationary cone dysfunction syndrome.

Summary for the Clinician

- **The group of progressive cone dystrophies is characterized by an early loss of visual acuity and colour vision in combination with pronounced photophobia**
- **The photopic (cone) ERG is disturbed, but the scotopic (rod) ERG is typically normal**
- **Progression to cone-rod dystrophy is not uncommon in the course of the disease**

3.2.5 Adult-Onset Vitelliform Macular Dystrophy

3.2.5.1 Clinical Findings

Patients with adult-onset vitelliform macular dystrophy (AVMD) usually present with mild loss of visual acuity or metamorphopsia in the 4th to 5th decade of life. AVMD is characterized by the bilateral symmetric appearance of a round or oval shaped yellowish foveal lesion (Fig. 3.9). The lesions vary in size, but are mostly between one-third and one-half optic disc diameter in size. These yellow deposits often develop a central grey spot of pigment. Small, extrafoveal yellow flecks may also be observed in these patients. Fluorescein angiography typically reveals a ring of hyperfluorescence surrounding a hypofluorescent area that corresponds with the foveal lesion. In most patients the EOG is normal [9, 24].

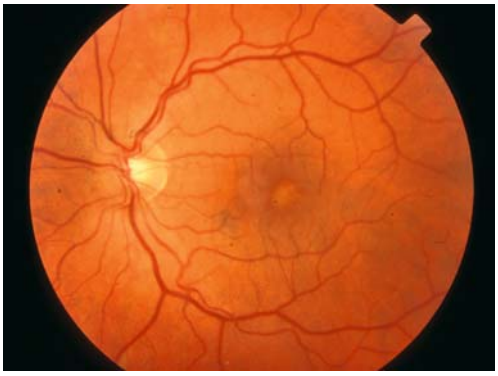

Fig. 3.9. Adult-onset vitelliform macular dystrophy

Occasionally, larger yellow deposits in AVMD may be confused with the vitelliform stage of Best disease. AVMD may be differentiated from this disorder by the later age of onset, the smaller sized lesions that lack the progression through different stages and the EOG, which is normal in most cases.

3.2.5.2 Genetic Aspects

Families with AVMD may display an autosomal dominant pattern of inheritance [9]. There is genetic heterogeneity since both the *VMD2* gene and the *peripherin/RDS* gene have been implicated in this disease [20, 64]. It has been suggested that sequence variations in the *peripherin/RDS* gene account for approximately 20 % of the AVMD cases [20]. Nevertheless, in many patients with AVMD the underlying genetic cause is unknown.

Summary for the Clinician

- **Adult-onset vitelliform macular dystrophy is a pattern dystrophy characterized by the presence of one or more yellow lesions in both eyes**
- **In contrast with Best disease the EOG is normal in most patients**

3.2.6 Autosomal Dominant Cystoid Macular Edema

3.2.6.1 Clinical Features

Autosomal dominant cystoid macular edema (CYMD) has so far been described only in a large Dutch family and a small Greek family [15, 21]. CYMD is characterized by an early onset cystoid macular edema that eventually results in atrophy of the macular region (Fig. 3.10). Visual acuity ranges from 1.0 in early stage to HM as the disease progresses. In the later stages, peripheral hyperpigmentations and attenuated arterioles may be observed. In most cases there is a moderate to high axial hypermetropic refractive error. The EOG is abnormal early in the course of the disease; the photopic and scotopic ERG may become affected in the later stages.

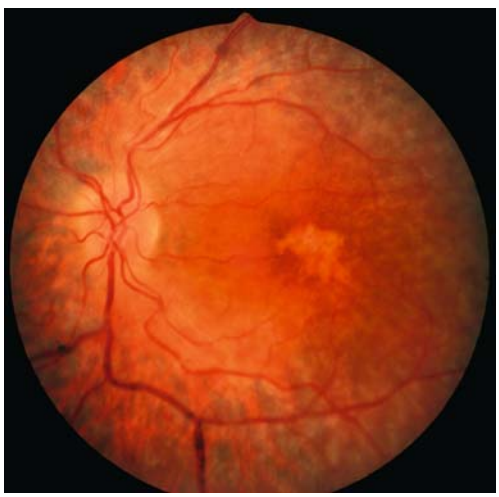

Fig. 3.10. Autosomal dominant cystoid macular edema

3.2.6.2 Genetic Aspects

The gene defect underlying autosomal dominant CYMD maps to chromosome 7p15.3 [40]. The causative gene has not yet been identified.

Summary for the Clinician

- **Autosomal dominant cystoid macular edema is a very rare disorder**
- **Besides macular edema, typical findings include early EOG abnormalities and axial hypermetropia**

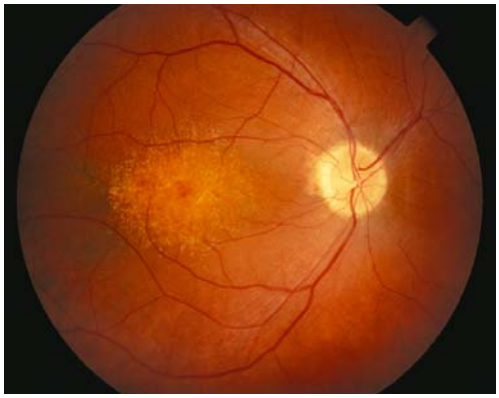

Fig. 3.11. Benign concentric annular macular dystrophy

3.2.7 Benign Concentric Annular Macular Dystrophy (Bull's Eye Macular Dystrophy)

3.2.7.1 Clinical Findings

Patients with benign concentric annular macular dystrophy (BCAMD), which is considered synonymous with bull's eye macular dystrophy by some authors, initially display a ringlike depigmentation around the fovea, resembling a bull's eye (Fig. 3.11). This occurs at the age of 30 years and is generally not associated with significant loss of visual acuity. In this rare disorder there is no history of (hydroxy)chloroquine medication and it lacks the typical findings associated with cone dystrophy, such as photophobia [14]. In the 4th to 5th decades the macular dystrophy may evolve to a more widespread retinal disorder. This puts the term 'benign' somewhat in perspective, especially since the visual acuity may also begin to deteriorate. In this stage patients with BCAMD complain of night blindness; the visual acuity ranges from 0.3 to 1.0. Ophthalmoscopy may reveal bone spicule-like pigmentations in the midperiphery [75]. Electroretinographic testing reveals increasing photoreceptor dysfunction with a slight predominance of rod dysfunction. The EOG is subnormal often early in the course of the disease and becomes progressively disturbed. Colour vision tests may reveal an acquired blue-yellow defect with pseudoprotanomaly. Histological studies have not been performed, but the well-preserved visual acuity over a long period of disease suggests primary involvement of the RPE or rod photoreceptors.

Another autosomal dominant macular dystrophy (MCDR2) that features a bull's eye lesion in the macula has been recently described in a British family [51]. The clinical findings in this family resemble the abnormalities in BCAMD, although the bull's eye seems to appear at an earlier age.

3.2.7.2 Genetic Aspects

BCAMD is an autosomal dominant disorder. In a single patient with bull's eye maculopathy, Allikmets and co-workers identified a *VMD2* mutation [1]. In addition, the gene defect in a Dutch family with this disorder has been mapped to chromosome

6p12.3-q16 [43]. In the MCDR2 family mutations were found in the *PROML1* gene [50, 51].

Summary for the Clinician

- **Benign concentric annular macular dystrophy is a not very well-defined macular disorder characterized by macular depigmentation in a bull's eye pattern around the age of 30**
- **Visual loss and or (mid)peripheral retinal abnormalities may occur later in life**
- **The relation with other types of bull's eye macular dystrophy has not yet been resolved**

3.2.8 Central Areolar Choroidal Dystrophy

3.2.8.1 Clinical Findings

Central areolar choroidal dystrophy (CACD) is a rare dystrophy of the posterior pole. The end stage of this disorder bears a resemblance to the geographic atrophy that is seen in age-related macular degeneration. The initial symptom is a decrease in visual acuity, which typically manifests in early adulthood. During the course of CACD, the visual acuity steadily declines, often to counting fingers when patients reach their 6th decade. The earliest ophthalmoscopically observable abnormalities are small areas of RPE atrophy in the para-foveal region. These early changes are more obvious on the fluorescein angiogram as small hyperfluorescent window defects. Over time, the RPE lesions gradually merge until a well demarcated area of geographic atrophy has developed in the posterior pole (Fig. 3.12). Small drusen may be seen at the border of this lesion. In most cases the EOG and ERG recordings are normal. However, in the final stage of CACD the photopic ERG may become subnormal. Colour vision tests may initially demonstrate a blue-yellow defect that turns into a red-green defect when atrophy of the central cone photoreceptors occurs [30].

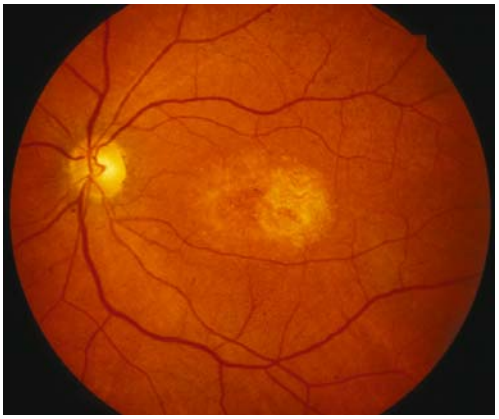

Fig. 3.12. Central areolar choroidal dystrophy

3.2.8.2 Genetic Aspects and Pathophysiology

CACD is inherited in an autosomal dominant fashion; however, rare cases of autosomal recessive inheritance have been reported. In several Dutch families, CACD was linked to an Arg142Trp mutation in the *Peripherin/RDS* gene [31]. This gene encodes the peripherin/RDS or peripherin-2 protein that occurs in the rim and incisures of the membrane discs in the rod and cone photoreceptor outer segments. There it forms a heterotetrameric complex with another structural protein: rod outer segment protein 1 (ROM-1). These integral membrane proteins play a crucial role in outer segment morphogenesis [74]. In addition, the peripherin/RDS-ROM1 is shown to interact with the β-subunit of rod cGMP-gated channels. These interactions may contribute to the connections between the disc

and plasma membrane that are important in the formation and stabilization of the rod outer segment structure [61].

The structural importance of peripherin/RDS is highlighted by the variety of autosomal dominant retinal dystrophies that are associated with mutations in the *peripherin/RDS* gene. These include retinitis pigmentosa, retinitis punctata albescens, unspecified macular dystrophies besides CACD, pattern dystrophy and adult-onset vitelliform dystrophy, as well as digenic retinitis pigmentosa (in combination with null mutations in ROM-1) [34, 39].

An additional CACD locus at 17p13 has been reported in a Northern Irish family [45].

Summary for the Clinician

- **Central areolar choroidal dystrophy is characterized by a progressive geographic atrophy in the posterior pole**
- **Early abnormalities are small, parafoveal areas of RPE atrophy that are best appreciated on the fluorescein angiogram**
- **Over the years, visual acuity gradually declines, often to counting fingers by the 6th decade**
- **This autosomal recessive disorder has been linked to mutations in the peripherin/RDS gene**

3.2.9 Autosomal Dominant Drusen (Malattia Leventinese; Doyne Honeycomb Retinal Dystrophy)

3.2.9.1 Clinical Findings

Several dominantly inherited macular diseases with early onset drusen as the prominent feature have been described [60]. It is as yet unclear whether the dominant drusen phenotype represents one or a number of distinct disorders. However, two major phenotypes of dominant drusen, Malattia Leventinese and Doyne honeycomb dystrophy, have been linked to a single mutation in the same gene [68].

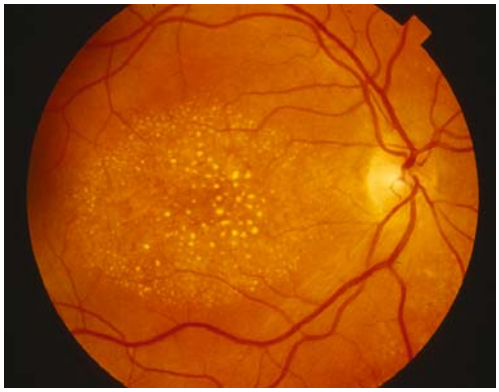

Fig. 3.13. Autosomal dominant drusen

In these disorders drusen deposits at the macula and around the optic nerve head occur in early adult life (Fig. 3.13). In addition to central drusen, the Malattia Leventinese phenotype also displays small, hard drusen that radiate into the peripheral retina (radial drusen). Over time, progression to form a mosaic pattern, termed 'honeycomb' by Doyne, may occur. Generally, patients with dominant drusen retain excellent visual acuity through the 5th decade, but subsequent visual loss and metamorphopsia render these patients legally blind by the age of 70 years. Loss of vision is often related to atrophy of the macular area. Less commonly, visual acuity is lost due to the formation of subretinal choroidal neovascular membranes.

Fluorescein angiography reveals hyperfluorescent or hypofluorescent drusen. ERG tracings and dark adaptation tests remain normal, except in very severe cases. EOG testing is initially normal, but may become subnormal depending on the degree of peripheral retinal involvement.

3.2.9.2 Genetic Aspects

The majority of familiar cases of dominant drusen have been associated with a single mutation (Arg345Trp or R345W) in the EFEMP1 gene [epithelial growth factor (EGF)-containing fibulin-like extracellular matrix protein] at 2p16 [48, 68, 73].

The protein encoded by the *EFEMP1* gene was identified as a strong binding protein for TIMP-3, which is associated with Sorsby fundus dystrophy (SFD). Possibly, complexes containing abnormal TIMP-3 and EFEMP1 may provide a barrier to the trafficking of molecules across Bruch's membrane. This may lead to the accumulation of other molecules and finally the formation of the sub-RPE deposits observed in SFD and dominant drusen [36].

In a few other dominant drusen families that show linkage to 2p16, no mutations were found in the *EFEMP1* gene, suggesting a mutation in the *EFEMP1* promoter sequence or a second dominant drusen gene at this locus [73]. Strikingly, the phenotypes in this study that did not have an EFEMP1 mutation displayed soft macular drusen but none seemed to exhibit juxtapapillary or hard radial drusen. Additional proof of genetic heterogeneity was found in one dominant drusen family, where the underlying genetic defect was mapped to 6q14 [38]. Finally, in three other families with a phenotype characterized by dominant drusen at an early age with subsequent progression to central geographic atrophy resembling CACD, a single mutation in the *peripherin/RDS* gene was identified [37].

Summary for the Clinician

- **Malattia leventinese and Doyne dominant drusen both display drusen deposits in early adult life**
- **The drusen are located at the macula and around the optic disc**
- **The visual acuity may remain undisturbed until the 5th decade**
- **Both types are inherited in an autosomal dominant fashion and have been linked to the EFEMP1 gene**

3.2.10 The Pattern Dystrophies

3.2.10.1 Clinical Findings

A number of autosomal dominant dystrophies that primarily affect the macular RPE are collectively known as pattern dystrophies. Overall, the visual prognosis is good in patients with these disorders. A mild disturbance of central vision and metamorphopsia usually occurs around midlife. The macular lesions are typically bilateral and symmetrical. They consist of accumulated yellowish or pigmented material at the level of the RPE. The shape of the macular lesions is variable and includes butterfly patterns as well as knotted fishnet patterns that extend into the periphery (Fig. 3.14). Gass discerned five different groups: (1) adult-onset vitelliform macular dystrophy (AVMD); this disorder is discussed separately; (2) butterfly-shaped macular dystrophy; (3) reticular dystrophy; (4) multifocal pattern dystrophy resembling Stargardt disease; and (5) fundus pulverulentus [16, 17, 23, 32]. With regard to the different groups it is important to note that the fundus abnormalities of the individual patient may not fall precisely into one group. A marked variability in the expression of these patterns exists. This variation has been described within families as well as in individual patients [25]. Some patients may progress from one pattern to another over a period of years and a few patients even display different patterns in each eye [23, 28].

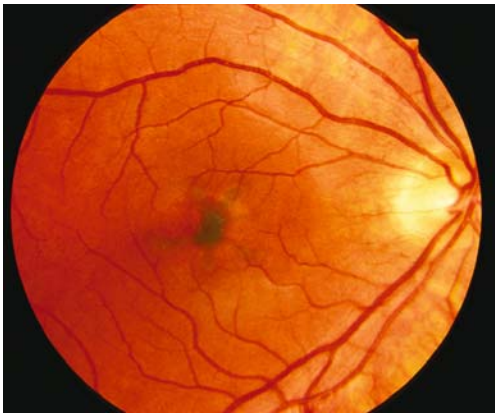

Fig. 3.14. Pattern dystrophy; butterfly-shaped lesion

Occasionally, these disorders are complicated by choroidal neovascularization. On the fluorescein angiogram these patterns are clearly outlined by the choroidal fluorescence. The EOG is subnormal. The pattern ERG is abnormal but the full-field ERG is undisturbed. Colour vision is generally not affected.

Pattern dystrophy can be associated with systemic abnormalities. It may be seen in 10–20 % of the pseudoxanthoma elasticum patients and is frequently seen in myotonic dystrophy (Curschmann-Steinert) [4]. Histopathologic examination in these patients reveals an area of total loss of the RPE and overlying photoreceptor cell layer, in combination with an intact choriocapillaris and lipofuscin-containing cells in the subretinal space. The intact RPE cells are greatly distended by lipofuscin [80].

3.2.10.2 Genetic Aspects

The pattern dystrophies are inherited in an autosomal dominant fashion. So far, pattern dystrophy has only been associated with mutations in the *peripherin/RDS* gene on 6p [54]. As stated earlier (CACD section), this gene encodes an integral membrane protein that plays an important role in morphogenesis and the maintenance of the disc structure of the photoreceptor outer segments. Mutations in this gene have also been associated with a number of other distinct retinal dystrophies [39]. Genetic heterogeneity in pattern dystrophy was demonstrated when a family with butterfly-shaped macular dystrophy showed linkage with 5q21.2-q33.2 and not with the *peripherin/RDS* gene [12].

Summary for the Clinician

- **The group of pattern dystrophies comprises a number of autosomal dominant macular dystrophies with bilateral and symmetrical lesions at the level of the RPE**
- **The most common types include adult-onset vitelliform macular dystrophy and butterfly-shaped macular dystrophy**
- **Pattern dystrophies may be complicated by choroidal neovascularization**

3.2.11 Progressive Bifocal Chorioretinal Atrophy

3.2.11.1 Clinical Findings

Progressive bifocal chorioretinal atrophy is a slowly progressive dystrophy characterized by reduced visual acuity (counting fingers – 0.3), nystagmus, myopia and large atrophic macular and nasal retinal atrophic lesions. Large macular lesions are evident a few weeks after birth and are accompanied by white deposits nasal to the optic disc as well as in the peripheral retina. Gradually, the macular lesion enlarges and the nasal lesions coalesce into a confluent white lesion of chorioretinal atrophy. Finally, both lesions will expand towards the op-

tic disc. Fluorescein angiography reveals an absence of choroidal perfusion in the atrophic macular and nasal lesions as well as staining of peripheral deposits, suggestive of chorioretinal abnormalities. The ERG shows diminished photopic and scotopic responses. The EOG is also abnormal. The electrophysiological findings suggest a diffuse dysfunction of RPE and neuroretina in PBCRA [18, 26].

3.2.11.2 Genetic Aspects

The gene underlying PBCRA has not been identified, but maps to chromosome 6q16-q16.2 [35]. This region overlaps with the locus for North Carolina macular dystrophy (MCDR1). Since there are important phenotypic differences, such as the slow progression and disturbed colour vision and electrophysiology in PBCRA, these disorders may be caused by mutations in two different adjacent genes. Alternatively, if these disorders are associated with the same gene, it is likely different mutations are involved in their aetiology.

Summary for the Clinician

- **Progressive bifocal chorioretinal atrophy is a rare disorder with large areas of geographic atrophy of the posterior pole and nasal retina**
- **Both the ERG and EOG are abnormal**

3.2.12 Sorsby Fundus Dystrophy

3.2.12.1 Clinical Findings

This dystrophy is characterized by night blindness during the 3rd decade and a subacute loss of visual acuity due to choroidal neovascularization, generally in the 4th or 5th decade. Subretinal haemorrhage and disciform scar formation may follow the neovascularization. Later in life, progressive atrophy of the peripheral choroid and RPE occurs and leads to loss of ambulatory vision [29]. Early findings in Sorsby fundus dystrophy (SFD) patients are drusen deposits at the level of Bruch's membrane and a deposit of faintly yellow subretinal material throughout the fundus (Fig. 3.15). This yellow material becomes less apparent with age.

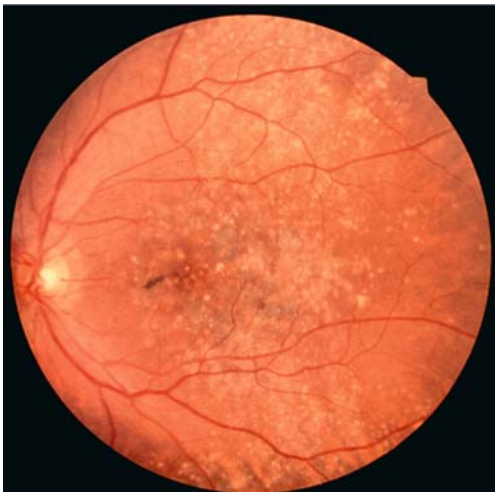

Fig. 3.15. Sorsby fundus dystrophy

Fluorescein angiography shows a delay in choroidal perfusion and mottling of the RPE. The ERG and EOG are initially normal, but become abnormal in advanced stages, when sizable parts of the retina are involved [11]. Dark adaptation tests reveal a delayed or absent cone-rod break [67]. It has been suggested that a blue-yellow colour defect is an early finding in SFD [7].

Histopathology shows an abnormal accumulation of lipid-containing material in the inner portion of Bruch's membrane [10]. It has also been theorized that this subretinal deposit could act as a barrier to diffusion of nutrients to the photoreceptors. To test the hypothesis that the entry of

sufficient vitamin A into the photoreceptors was disturbed, Jacobson and co-workers administered high dose vitamin A in SFD patients. In patients in the early stages of SFD this treatment was able to reverse night blindness [33].

Recently, it was demonstrated in a single case that oral or sub-Tenon steroids might be beneficial in the management of choroidal neovascularization in this disorder [3].

3.2.12.2 Genetic Aspects and Pathophysiology

SFD is inherited in an autosomal dominant fashion and has been associated with mutations in the *TIMP3* gene on 22q [77]. *TIMP3* encodes a tissue inhibitor of metalloproteinase (TIMP), which is involved in extracellular matrix remodelling. In SFD, the disturbed balance between the dysfunctional TIMP3 protein and its metalloproteinase may lead to thickening of Bruch's membrane and the widespread deposit of material that is observed histologically [19]. Furthermore, TIMP3 has been shown to act as a potent angiogenesis inhibitor, probably by blockade of vascular endothelial growth factor (VEGF)-2 receptors, and this may account for the choroidal neovascularization in SFD [62]. A knock-in mouse that carries the disease-related Ser156Cys mutation in the orthologous murine *Timp3* gene has been generated. This knock-in mouse displays the early features of age-related changes in Bruch's membrane and the RPE that may represent the primary clinical manifestations of SFD [76].

Summary for the Clinician

- **Patients with Sorsby fundus dystrophy typically develop night blindness in their 3rd decade and loss of vision due to choroidal neovascularization in the 4th or 5th decade**
- **Fundus abnormalities include drusen and the presence of a faint yellow subretinal material throughout the fundus**
- **Mutations in the TIMP3 gene are the cause of this autosomal dominant macular dystrophy**

3.2.13 North Carolina Macular Dystrophy

North Carolina macular dystrophy (MCDR1) is a rare dystrophy with complete penetration and variable expressivity. The age of onset is very variable and fundus changes have been described in a 3-year-old child. In general this macular dystrophy tends to show little or no progression. The fundus abnormalities are bilateral and symmetric and might differ considerably even between patients within one family. Three grades of severity may be discerned in MCDR1, each type affecting approximately one-third of the affected individuals.

Grade 1 involves yellow drusen-like lesions in the central retina; visual acuity is typically normal in these patients (0.8–1.0). In grade 2 confluent drusen are observed with a moderate impairment of vision (0.5–1.0) (Fig. 3.16). Grade 3 MCDR1

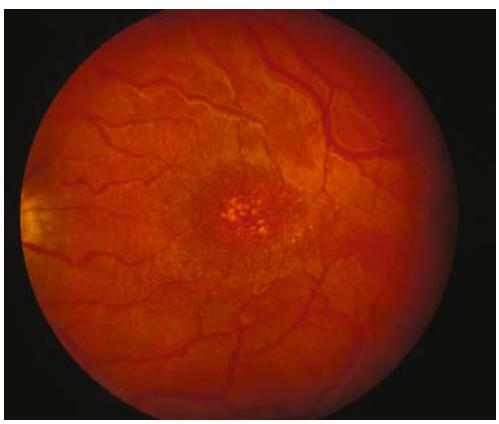

Fig. 3.16. North Carolina macular dystrophy, grade 2

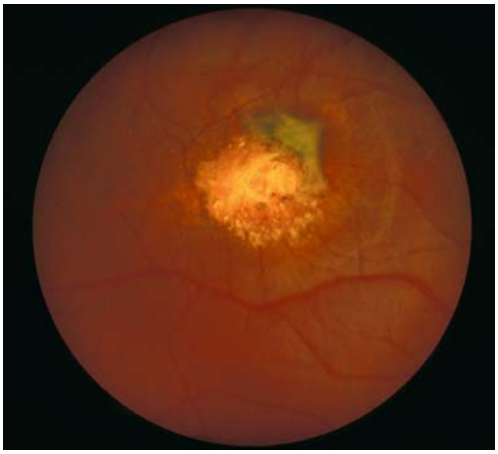

Fig. 3.17. North Carolina macular dystrophy, grade 3

(Fig. 3.17) shows colobomatous or disciform-appearing lesions in the macula with a moderate to severe loss of visual acuity [65].

3.2.13.1 Genetic Aspects

MCRD1 has been described in different countries and in various ethnic groups. The gene for this autosomal dominant disorder has been linked to 6q14-q16.2. The gene itself has not yet been identified [66].

Another macular dystrophy that shares characteristics with the MCDR1 phenotype has recently been linked to chromosome 5p (MCDR3 at 5p13.1-p15.33) [52].

Summary for the Clinician

- **The findings in North Carolina macular dystrophy are highly variable and range from drusen-like deposits to colobomatous lesions in the macula**
- **There is little or no progression**

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