variability in visual acuity is seen, with a slow decline to 20/200 or less in most patients in the fourth and fifth decade. After the age of 60, many DCMD patients are legally blind. Choroidal neovascularization does not occur, but on rare occasions, peripheral vascular dilations with leakage of exudates may develop. The CFCs may decrease in response to topical or oral treatment with carbonic anhydrase inhibitors.[4]

10.3.4 Differential Diagnosis

DCMD should be differentiated from X-linked juvenile retinoschisis (XLRS). Apart from the different mode of inheritance, the "cystoid" schisis cavities in XLRS are often more confluent, with eventually only small strands of tissue bordering these spaces. On fluorescein angiography, no leakage is seen into the schisis spaces in XLRS. Fundus autofluorescence and red-free photography show a typical radial pattern of abnormalities in the fovea in XLRS, in contrast to DCMD. Other differential diagnostic entities include retinitis pigmentosa with cystoid macular edema and other conditions that can be associated with cystoid macular edema, such as uveitis, idiopathic parafoveal telangiectasia, and diabetic retinopathy.

10.3.5 Conclusion

DCMD is an autosomal-dominantly inherited dystrophy characterized by bilateral early-onset CFCs in the macula, which distinguishes this disorder from other retinal dystrophies. With time, progressive chorioretinal atrophy and pigmentary changes develop in the posterior pole.

10.4 Juvenile Macular Dystrophy and Hypotrichosis

10.4.1 Background

Juvenile macular dystrophy and hypotrichosis is caused by autosomal recessive mutations in *CDH3* on chromosome 16q22 and was first described by Wagner in 1935 [11]. *CDH3* encodes for P-cadherin, a protein linked to hair and retinal development [12]. As visual deficits are suspected to arise already in early childhood, some authors suggested "hypotrichosis with cone-rod dystrophy" to be a more fitting name [13].

10.4.2 Clinical Findings

Alopecia develops shortly after birth with partial and short regrowth of hair during puberty (Fig. 10.3a). Visual function is reduced from childhood onwards with progressive degeneration extending beyond the macular region. ERG testing shows progressive cone and rod system dysfunction.

The macula typically appears with nummular patterns of atrophic and hyperpigmented patches (Fig. 10.3b). Demarcation lines clearly divide affected and intact retina but sometimes can be obscured by diffuse pigmentary changes and white-yellowish flecks.

10.4.3 Disease Course

Visual function is affected already in school age with visual acuity ranging from 20/32 to 20/200. Fundoscopy reveals first signs of a macular dystrophy, and ERG responses indicate both rod and cone system dysfunction. Fundoscopic changes and functional deficits are slowly progressive but are not known to develop into complete blindness.

10.4.4 Differential Diagnosis

Ectodermal dysplasia, ectrodactyly, and macular dystrophy syndrome can also result from *CDH3* mutations and features hypotrichosis with concomitant macula dystrophy. However, it also includes digital abnormalities, sparse and short eyebrows and eyelashes, and partial anodontia [14].

10.4.5 Conclusion

Juvenile macular dystrophy and hypotrichosis is caused by autosomal recessive mutations in the *CDH3* gene and should be called "hypotrichosis with cone-rod dystrophy."

10.5 Late-Onset Retinal Degeneration (L-ORD)

10.5.1 Background

Late-onset retinal degeneration (L-ORD) was first described as a disease entity by Kuntz et al. in 1996, with histopathologic evidence of a retina-wide layer of extracellular material of 20–40 μm thickness between the RPE and Bruch's membrane [15]. An autosomal-dominant founder mutation (p.Ser163Arg) in the complement 1q tumor necrosis factor 5 gene (*C1QTNF5*) was identified as causative, which can be traced back to a single ancestor from southeast Scotland. *C1QTNF5* is co-expressed in the RPE with the membrane frizzled-related protein MFRP, which is mutated in autosomal recessive nanophthalmos. L-ORD has been termed differently across the literature with autosomal-dominant hemorrhagic macular dystrophy, late-onset macular degeneration, and late-onset retinal macular degeneration all pointing towards the clinically significant involvement of the macula.

10.5.2 Clinical Findings

The most consistent finding associated with L-ORD is a thick layer of extracellular sub-RPE deposit evident on spectral-domain optical coherence tomography (SD-OCT) imaging. This layer is often thicker in the macula but extends to the extreme retinal periphery. Other clinical findings depend on the stage of the disease and can include anomalies in the anterior segment, such as long anteriorly inserted zonules (which may complicate capsulorhexis cataract surgery), iris atrophy, and trabecular pigment deposition (Fig. 10.4) [16, 17]. The posterior segment can demonstrate signs of retinal atrophy such as midperipheral bone spicules with well-demarcated lines between viable and atrophic areas of retina. Hallmark features of the macula are perimacular yellow dots and choroidal neovascularization.

10.5.3 Disease Course

As the name suggests, patients rarely become symptomatic before age of 40 in this progressive disorder (Table 10.3). The only finding in this asymptomatic first stage may be long anteriorly inserted lens zonules, iris atrophy, and trabecular pigment deposition, which in some cases may evolve into secondary glaucoma.

Stage 2 is characterized by the first primary symptoms such as difficulties with dark adapta-

Fig. 10.2 Clinical classification of dominant cystoid macular dystrophy (*DCMD*) into three stages: (**a**–**d**) stage 1 DCMD, (**e**–**h**) stage 2 DCMD, and (**i**–**k**) stage 3 DCMD. (**a**) Color fundus photograph of a 15-year-old patient with stage 1 DCMD showing wrinkling of the inner limiting membrane, cystoid fluid collections (*CFCs*) and fine pigment changes in the macula. (**b**) Fluorescein angiogram (late phase) showing hyperfluorescent CFCs in the fovea and more diffuse hyperfluorescent intraretinal edema in the posterior pole. (**c**) Fundus autofluorescence image showing areas of punctiform mildly increased autofluorescence and mild diffuse hyperautofluorescence in the macula. (**d**) Optical coherence tomography (*OCT*) scan through the fovea showing CFCs in the inner and outer nuclear layer. (**e**) Color fundus photograph of a patient with stage 2 DCMD showing atrophic pigment changes in the macula. (**f**) Fluorescein angiogram showing central hyperfluorescence caused by the atrophic retinal pigment epithelium (*RPE*) window defect and residual hyperfluorescent cystoid edema, surrounded by mild, indistinct hyperfluorescence. (**g**) Fundus autofluorescence image showing moderately decreased autofluorescence in the central macula. (**h**) OCT scan showing mild diffuse retinal edema and some small residual CFCs, irregularity of the outer photoreceptor structures, but an RPE layer that seemed largely intact. (**i**) Color fundus photograph of stage 3 DCMD, displaying profound chorioretinal atrophy in the macula with attenuated arterioles and coarse hyperpigmentations. (**j**) Fundus autofluorescence image showing a large area of markedly decreased autofluorescence due to RPE atrophy. (**k**) OCT scan showing chorioretinal atrophy and a mild epiretinal membrane

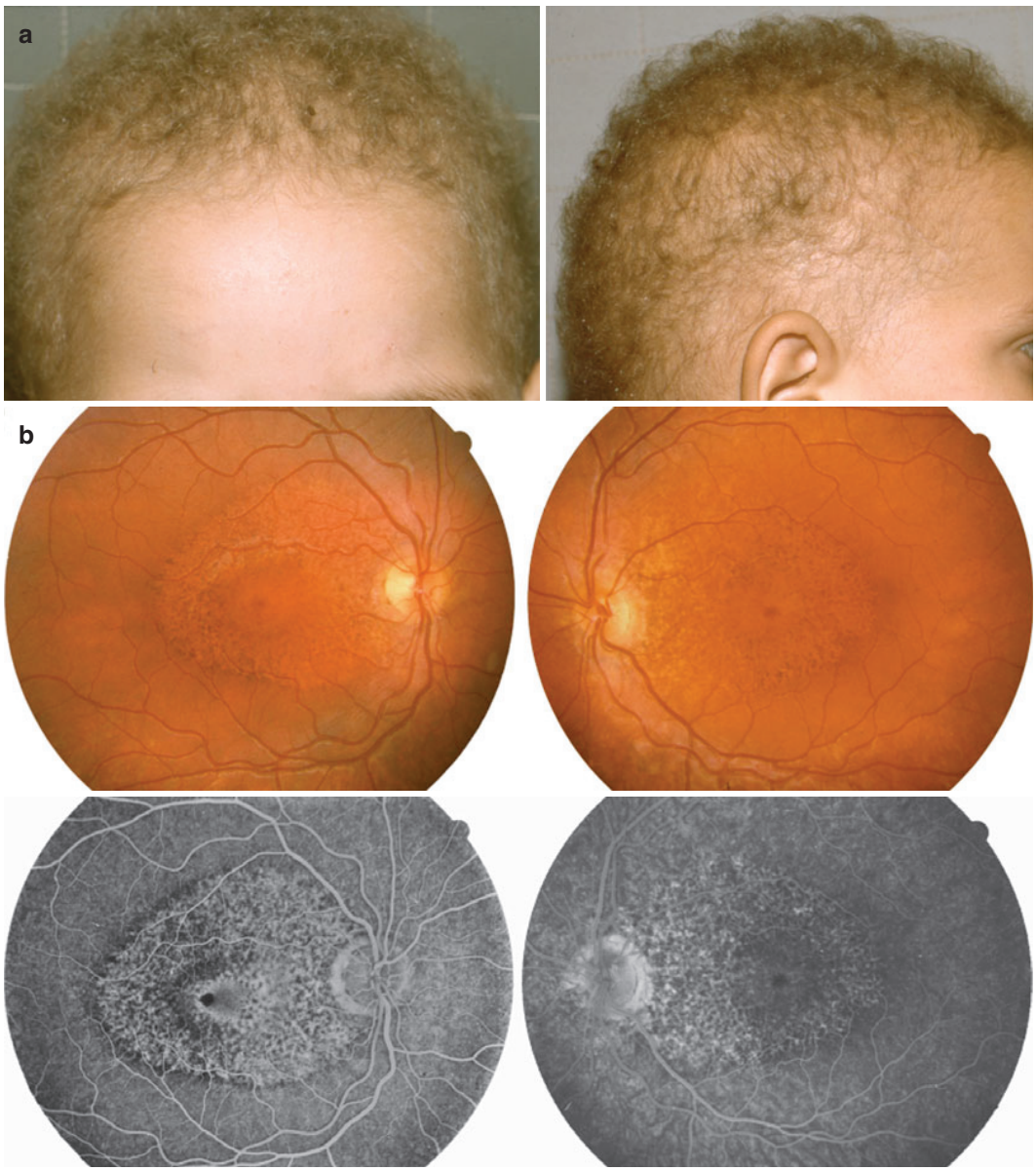

Fig. 10.3 (**a**) Hypotrichosis due to *CDH3* mutations. (**b**) Macular dystrophy due to *CDH3* mutations