CHAPTER 12

Progressive Cone Dystrophy and Cone-Rod Dystrophy (XL, AD, and AR)

Stephen H. Tsang and Tarun Sharma

S. H. Tsang
Jonas Children's Vision Care, Bernard & Shirlee Brown Glaucoma Laboratory, Columbia Stem Cell Initiative-Departments of Ophthalmology, Biomedical Engineering, Pathology & Cell Biology, Institute of Human Nutrition, Vagelos College of Physicians and Surgeons, Columbia University, New York, NY, USA

Department of Ophthalmology, Columbia University, Edward S. Harkness Eye Institute, NewYork-Presbyterian Hospital, New York, NY, USA
e-mail: sht2@cumc.columbia.edu

T. Sharma (✉)
Department of Ophthalmology, Columbia University, Edward S. Harkness Eye Institute, NewYork-Presbyterian Hospital, New York, NY, USA
e-mail: ts3118@cumc.columbia.edu

S. H. Tsang, T. Sharma (eds.), *Atlas of Inherited Retinal Diseases*, Advances in Experimental Medicine and Biology 1085, https://doi.org/10.1007/978-3-319-95046-4_12

General Features

A heterogenous group of diseases, progressive cone dystrophy usually begins in the mid-teenage years or later in life. The estimated prevalence is 1 in 30,000–40,000 individuals. Patients usually present with decreased central vision and a color vision deficit; the visual loss is progressive and often accompanied by day blindness (hemeralopia) and light intolerance (photophobia). Over time, affected individuals develop night blindness and loss of peripheral field. Visual acuity deteriorates to 20/200 or even counting fingers. There is some association between X-linked cone-rod dystrophy (CORD) and high myopia.

Fundi in the early stage may be normal, but later they may show a symmetric bull's-eye pattern (bull's-eye maculopathy, BEM) of macular dystrophy (Figs. 12.1, 12.2, 12.3, and 12.4). Fundus autofluorescence (FAF) shows alternating areas of hypoautofluorescence and hyperautofluorescence; as atrophy of the retinal pigment epithelium (RPE) sets in, more hypoautofluorescence is evident (Figs. 12.1, 12.2, and 12.3). Optical coherence tomography (OCT) shows foveal thinning and attenuation of the inner segment ellipsoid zone (Figs. 12.2 and 12.3).

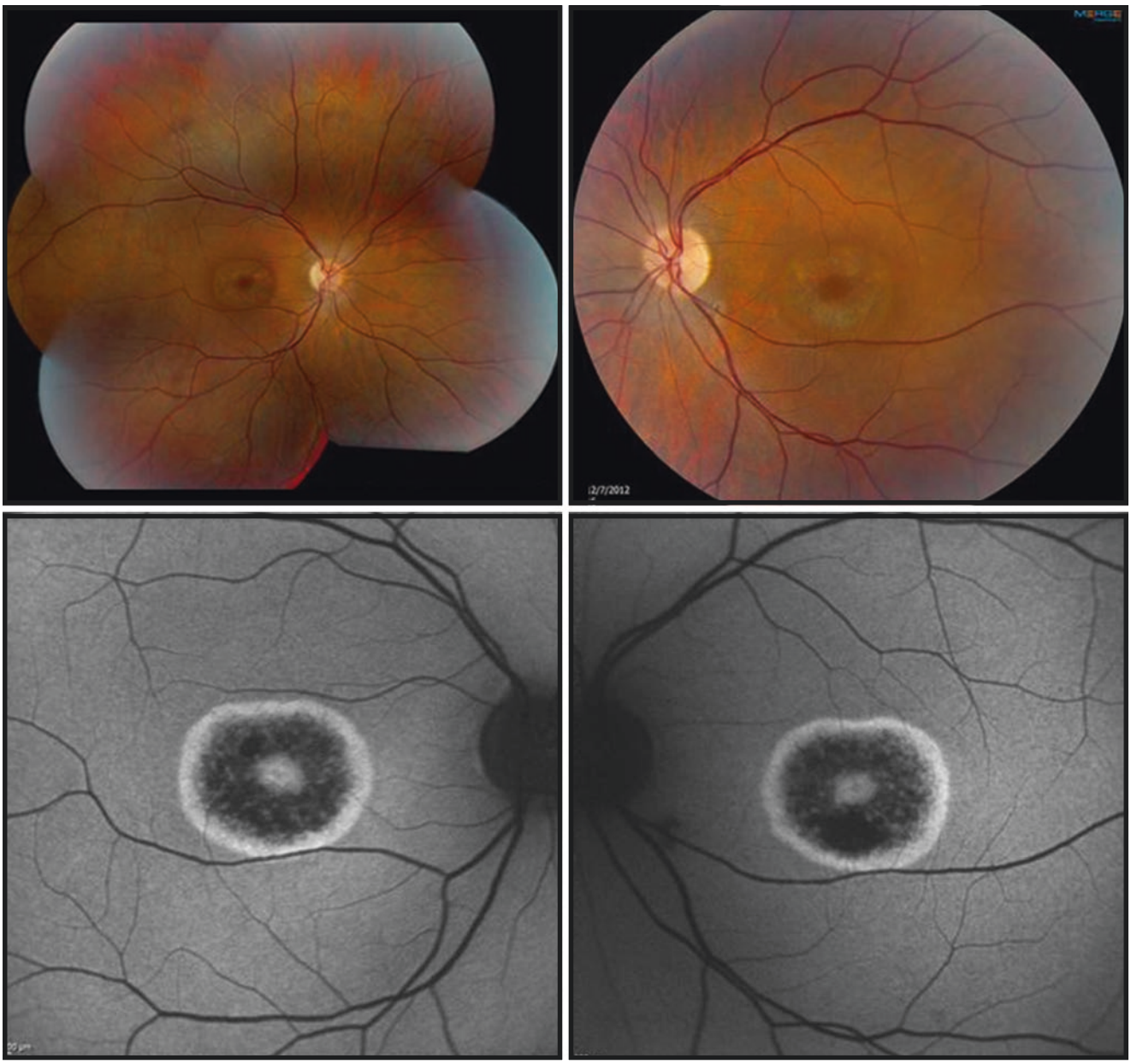

Fig. 12.1 A classic BEM in both eyes on color fundus photograph and corresponding FAF, areas of hypofluorescence surrounded by a ring of hyperfluorescence

The electroretinogram (ERG) shows undetectable photopic response and a normal or near-normal scotopic rod response; cone-flicker ERG response is almost invariably delayed.

Peripheral visual fields may remain normal, though central scotoma is present. In some patients, rod photoreceptors are also involved later in life, leading to cone-rod dystrophy (CORD). These patients may show bone spicule-like intraretinal pigmentation and notice defective night vision.

In adults with X-linked cone dystrophy, the fundus may show a tapetal-like reflex and Mizuo-Nakamura phenomenon.

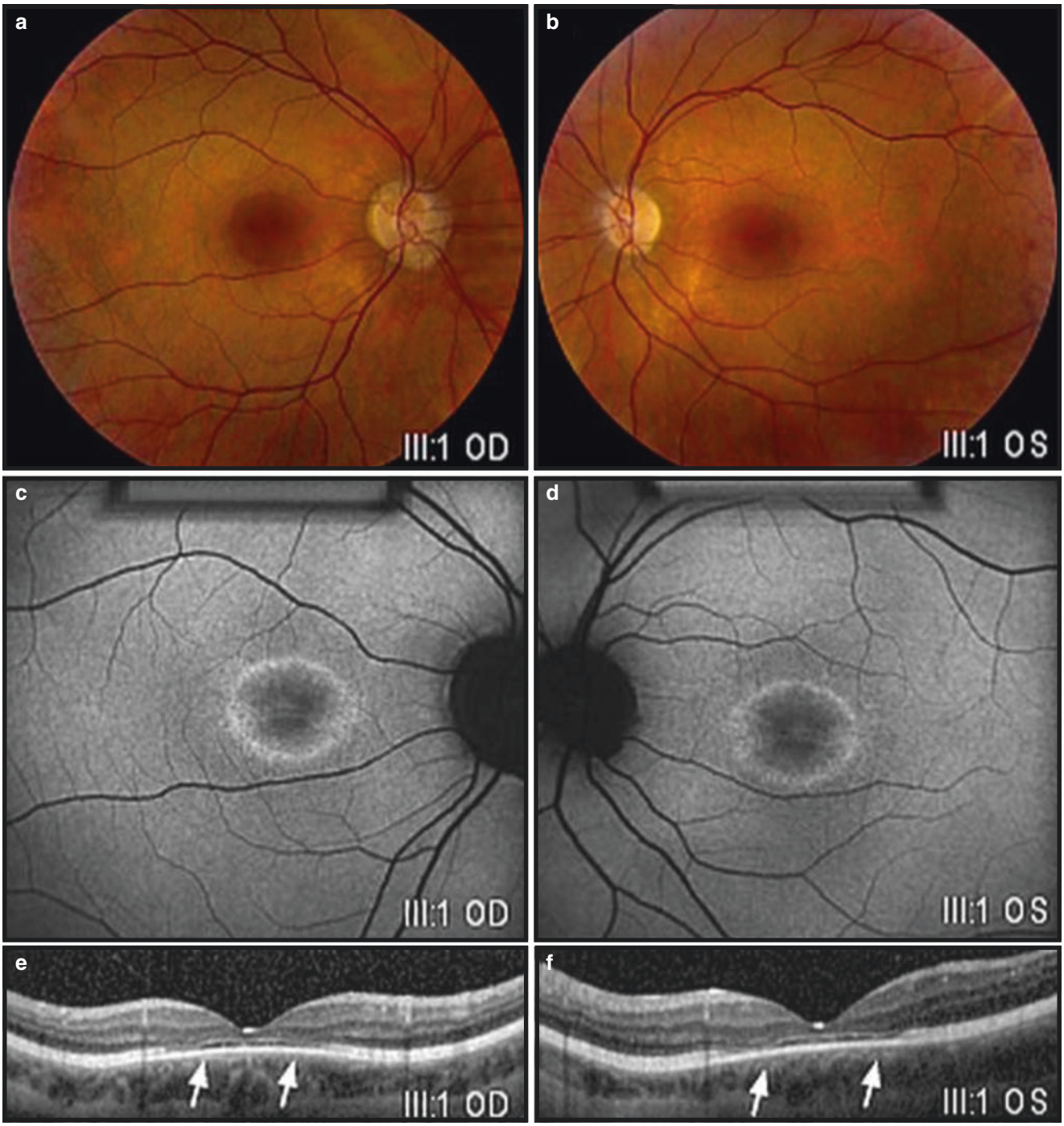

Fig. 12.2 A classic bull's eye maculopathy (BEM) on color fundus photograph (*upper row*). FAF (*middle row*) shows central hypofluorescence surrounded by a ring of hyperfluorescence. OCT (*lower row*) shows foveal thinning with loss of photoreceptors, loss of EZ line, loss of outer nuclear layer, and loss of RPE. A case of RPGR mutation

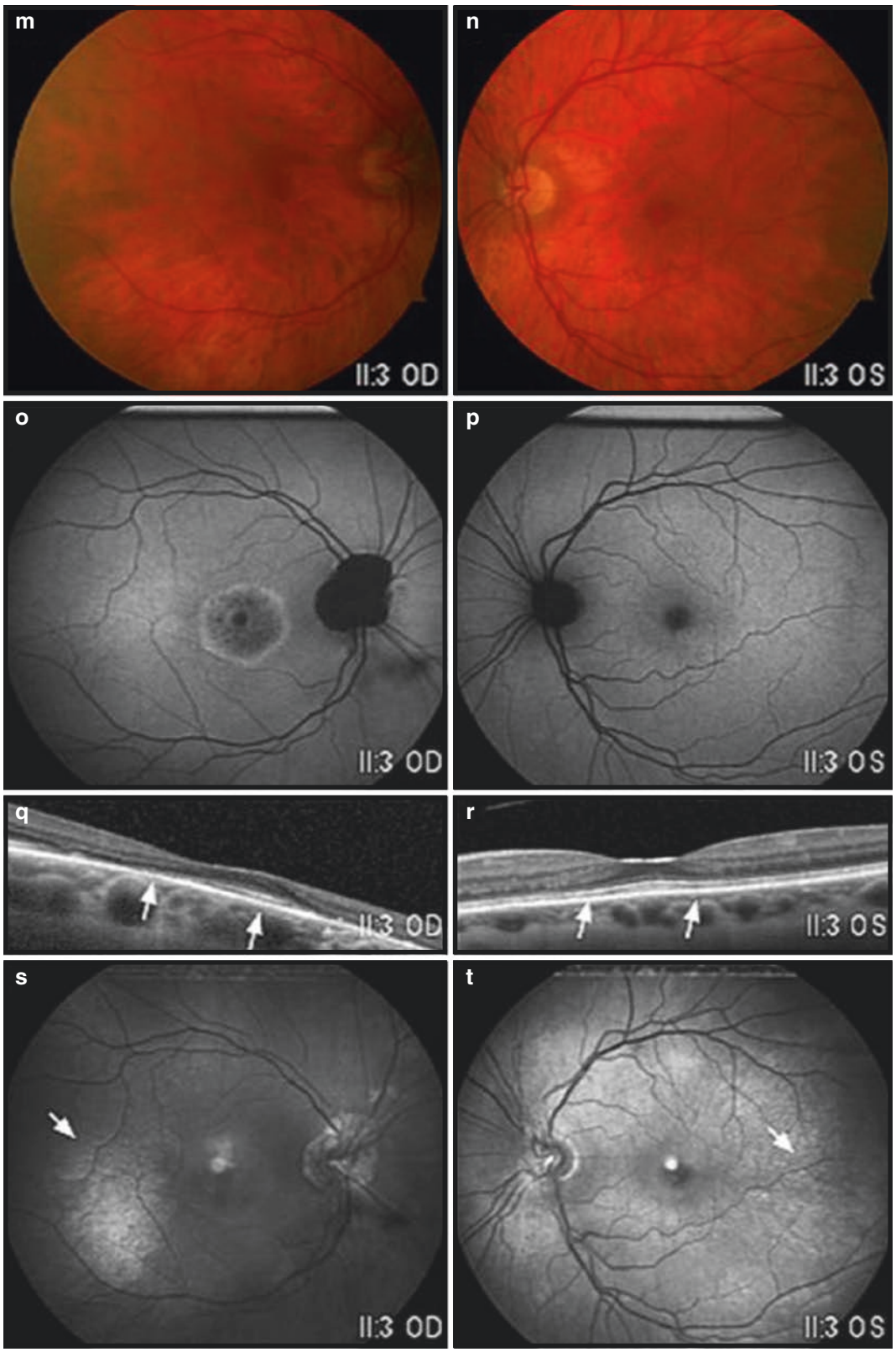

Fig. 12.3 Color photograph (*first row*) of a carrier, minimal RPE changes in the right macula, and the left looks normal. FAF (*second row*) shows bull's eye pattern with peripapillary atrophy in the right eye, and the left eye is normal. OCT (*third row*) shows disruption of EZ line in the perifoveal area in the right eye. The red-free image (*fourth row*) shows a tapetal reflex in an area temporal to macula (*arrow*)

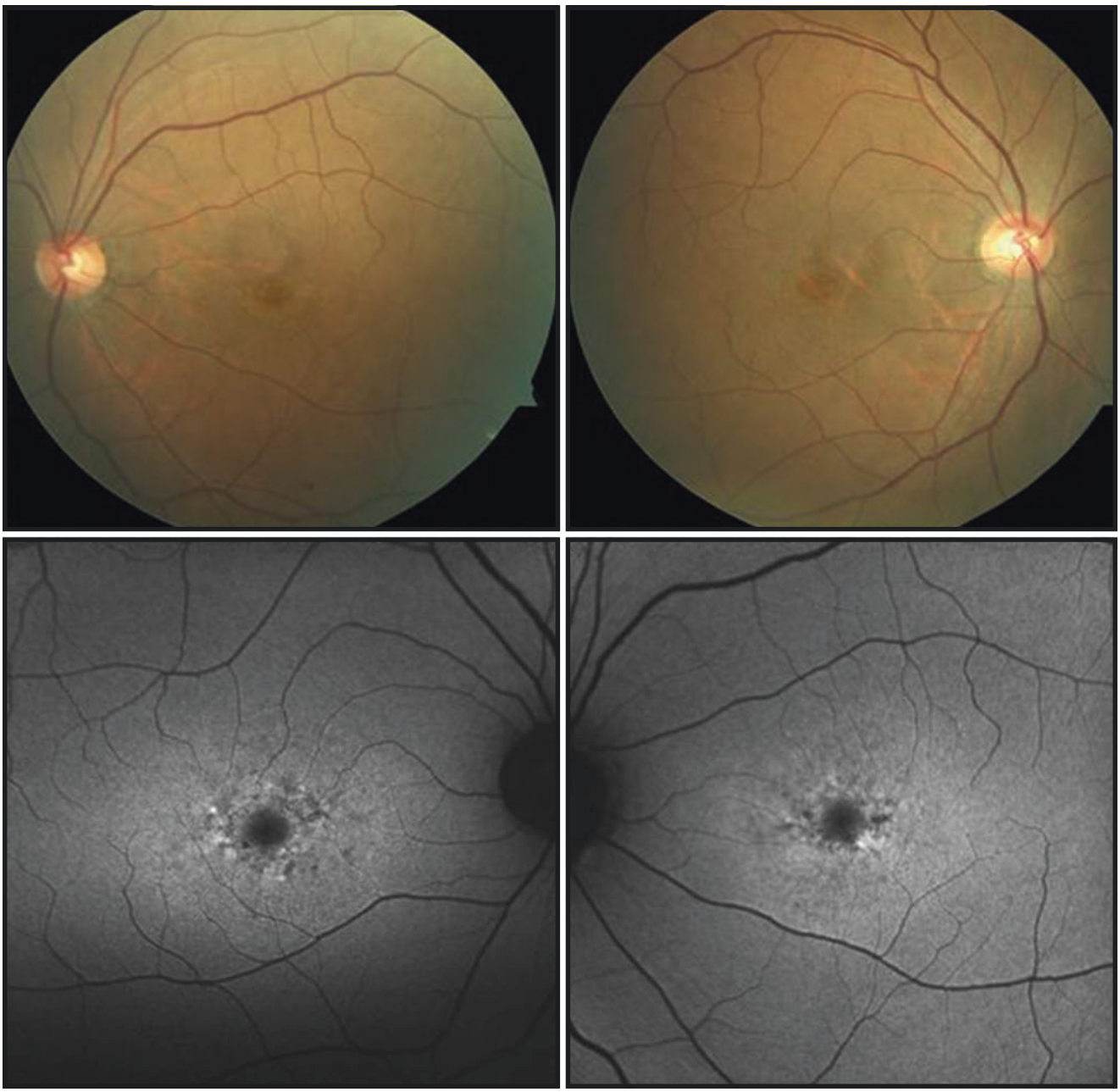

Fig. 12.4 Bull's eye maculopathy on color fundus photographs and corresponding RPE changes on FAF, a speckled appearance

Molecular Genetics

Mutations in about 30 genes are known to cause cone-rod dystrophy. Being genetically heterogenous, all three patterns of mendelian inheritance are seen: autosomal dominant, autosomal recessive, and X-linked recessive. Mutations in about 20 genes cause autosomal recessive cone-rod dystrophy, and about 10, an autosomal dominant pattern. The autosomal recessive pattern is the commonest (60–70%), followed by autosomal dominant (20–30%) and X-linked (5%). Cone-rod dystrophy has high genetic heterogeneity and also shows great variability in age of onset and associated systemic findings.

Autosomal dominant cone dystrophy is caused by mutations in the gene linked to 6p21.1; this gene encodes for granulate cyclase activator A (GUCA1A). Dominant cone-rod dystrophy is caused by a mutation in the *GUCY2D* gene and *CRX* genes.

For autosomal recessive cone dystrophy, the genes implicated are *ABCA4*, *CNGB3*, *KCNV2*, and *PDE6C*; *ABCA4* accounts for about 30–60% of cases.

For X-linked cases, the affected gene is *RPGR*.

Specific Genotype and Phenotype Correlation

ABCA4

Genotype Autosomal recessive

Phenotype This mutation causes both COD and CORD, with early onset (first to third decade) and BEM. FAF shows a ring of increased autofluorescence (AF) surrounding decreased macular AF and sparing of the peripapillary area.

Cytogenetic location 1p22.1

The mutation in the *ABCA4* gene accounts for 30–60% of cases of CORD. The ABCA4 protein removes from the photoreceptors one of the substances that is produced in phototransduction, called N-retinylidene-PE. With a mutation in *ABCA4*, the altered protein cannot remove the N-retinylidene-PE, and this substance then combines with another substance to produce N-retinylidene-N-retinylethanolamine (A2E). The A2E is toxic to photoreceptors, leading to CORD.

Tip CORD caused by *ABCA4* gene mutations tends to cause more severe visual loss than CORD caused by other genetic mutations.

ADAM9 (CORD9)

Genotype Autosomal recessive

Phenotype Usually CORD, with very early onset (first to second decade); the macula shows RPE atrophy to BEM.

Cytogenetic location 8p11.22

This gene encodes a member of the ADAM family (disintegrin and metalloprotease domain) and may mediate cell-cell or cell-matrix interactions and regulate the motility of cells via integrins.

RPGR1P1 (CORD13, Leber Congenital Amaurosis [LCA6])

Genotype Autosomal recessive

Phenotype Usually CORD, with very early onset (first to second decade); macula shows RPE granularity to atrophy.

Cytogenetic location 14q11.2

This gene encodes a photoreceptor protein, a scaffolding protein that is needed for normal location of RPGR at the cilium, and for normal disk morphogenesis and disk organization in the outer segment of photoreceptor cells.

KCNV2 (Potassium Voltage-Gated Channel Modifier Subfamily V Member 2)

Genotype Autosomal recessive

Phenotype Usually CORD, with very early onset (first to second decade); macula shows RPE alterations to atrophy. FAF shows reduced AF in areas of atrophy.

Cytogenetic location 9p24.2

This gene encodes a potassium channel subunit.

Tip ERG shows a supernormal rod response.

SEMA4A (Semaphoring 4A) (CORD10 or RP35)

Genotype Autosomal recessive

Phenotype Usually CORD, with very early onset (first to second decade); macula shows RPE granularity to atrophy.

Cytogenetic location 1q22.

GUCY2D (CORD6 or LCA1 or RCD2)

Genotype Autosomal dominant

Phenotype Usually CORD, with very early onset (first to second decade); macula shows RPE atrophy and peripheral changes. FAF shows increased foveal AF, and reduced AF in

areas of atrophy. ERG might show an electronegative response; usually reduced cone and rod responses.

Cytogenetic location 17p13.1.

The GUCY2D protein is involved in a reaction that helps return phototransduction to the dark state after light exposure.

GUCA1A (Guanylate Cyclase Activator 1A) (COD4 or CORD14)

Genotype Autosomal dominant

Phenotype Both COD and CORD, with late onset (third to fifth decade); macular RPE changes. FAF shows increased AF in the center of the macula, a perifoveal ring of increased AF, and reduced AF in areas of atrophy. ERG 30-Hz flicker may show normal implicit time.

Cytogenetic location 6p21.1

The gene encodes an enzyme that promotes the activity of retinal guanylyl cyclase-1 (GC1) at a low calcium concentration and inhibits GC1 at high calcium concentrations. This calcium-sensitive regulation of retinal guanylyl cyclase is an important event in recovery of the dark state of rod photoreceptors following light exposure.

PRPH2 (Peripherin 2 or RDS)

Genotype Autosomal dominant

Phenotype Usually CORD, with onset second to third decade; macula shows RPE mottling or atrophy. FAF shows speckled pattern, with areas of increased and decreased AF.

Cytogenetic location 6p21.1

This gene gives instruction to make peripherin 2 protein, which is involved in stability of the outer segment of photoreceptor cells.

CRX (CORD2 or LCA7 or CRD)

Genotype Autosomal dominant

Phenotype Usually CORD, with very early onset (within first decade); macula shows RPE atrophy. FAF shows reduced AF in areas of atrophy. Sometimes, electronegative ERG.

Cytogenetic location 19q13.33.

The gene provides instruction to make cone-rod homeobox protein, a transcription factor that is necessary for the normal development of photoreceptors.

RIMS1 (Regulating Synaptic Membrane Exocytosis 1, CORD7)

Genotype Autosomal dominant

Phenotype Usually CORD, with late onset (third to fifth decade); macula shows RPE mottling or atrophy or BEM, and later peripheral changes along with attenuation of blood vessels. FAF shows speckled pattern. FAF shows reduced AF in the center, surrounded by a ring of increased AF. ERG 30-Hz flicker may show normal implicit time.

Cytogenetic location 6q13.

The gene plays a role in the regulation of voltage-gated calcium channels during neurotransmission.

PITPNM3 (CORD5)

Genotype Autosomal dominant

Phenotype Usually COD, with early onset (first decade); macula shows RPE mottling or atrophy.

Cytogenetic location 17p13.2–p13.1.

The gene encodes a member of a family of membrane-associated phosphatidylinositol (PI) transfer domain–containing proteins and interacts with the protein tyrosine kinase PTK2B.

RPGR (COD1 or CORCX1 or RP3 or RP15 or XLRP3)

Genotype X-linked

Phenotype Both COD and CORD. For COD, late onset (fifth decade); for CORD, onset second to fourth decade. Macula shows RPE atrophy in COD, and peripheral involvement in CORD. FAF shows a perifoveal ring of increased AF.

Cytogenetic location Xp11.4.

The *RPGR* gene provides instruction for making protein that is essential for the function of a cilia. Several versions or isoforms of RPFG protein are produced; one of the versions is ORF15 exon, expressed predominantly in photoreceptors.

Suggested Reading

Michaelides M, Hardcastle AJ, Hunt DM, Moore AT. Progressive cone and cone-rod dystrophies: phenotypes and underlying molecular genetic basis. Surv Ophthalmol. 2006;51:232–58.

Rahner N, Nuernberg G, Finis D, Nuernberg P, Royer-Pokora B. A novel C8orf37 splice mutation and genotype-phenotype correlation for cone-rod dystrophy. Ophthalmic Genet. 2016;37:294–300.