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Stephen H. Tsang
Tarun Sharma *Editors*

Atlas of Inherited Retinal Diseases

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Atlas of Inherited Retinal Diseases

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To the memory of
James L. German, MD; Donald S. Coffey, PhD; and Victor A. McKusick, MD.

To all visually challenged brothers and sisters who have Inherited Retinal Dystrophy,
for inspiring us.

To George A. Cioffi, MD; Stanley Chang, MD; and Tongalp H. Tezel, MD,
for their motivating leadership.

To our teachers, Alan C. Bird, Lawrence A. Yannuzzi, and Anthony T. Moore,
for sharing their patients.

To our students, residents, and fellows,
for their stimulating questions.

To our family,
for their unconditional love.

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Stephen H. Tsang, MD, PhD, FARVO
(2018 ARVO Silver Fellow)
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Preface

This Atlas was conceived to fulfill the unmet needs of medical students, residents, fellows, PhD students, postdocs, and practicing retinal specialists who manage patients with inherited retinal diseases (IRD), whose aim is to keep pace with evolving genetic testing practice patterns, their influence on counseling, and emerging gene therapy trials.

The diagnosis of IRDs poses a great challenge to physicians because of their underlying genetic and phenotypic heterogeneity. As a group of genetic eye disorders, IRDs are a common cause of blindness in children and adults. They affect about 1 in 4000 people, nearly half of whom have no known family history of similar disorders.

Recent advances in molecular genetics have revealed that most IRDs have an underlying genetic basis. So far, over 250 different causative genes have been identified, and a causative mutation can be identified in up to 60–80% of patients with IRDs. In the future, physicians will need to understand not only the clinical or phenotypic characteristics of the patient's disease, but also their correlation with underlying genetic mutations (the genotype-phenotype correlation).

There has also been a surge in phase I and phase II gene therapy trials aimed at managing several of the IRDs, like X-linked retinitis pigmentosa (RP), choroideremia, retinoschisis, achromatopsia, Best disease, Stargardt disease, Usher syndrome, and *MERTK*-associated autosomal RP. In December 2017, the FDA approved for the first time the use of gene therapy to treat patients with Leber congenital amaurosis, caused by a mutation in the *RPE65* gene.

This Atlas is comprised of eight sections. The first section gives an overview of basic principles of various imaging modalities that are being used to manage patients with IRDs. The second, third, and fourth sections describe IRDs based on their inheritance pattern. The fifth section is dedicated to those IRDs that have associated systemic manifestations, including syndromic retinitis pigmentosa. The sixth section deals with phakomatoses with causative genetic bases. The seventh section illustrates various phenocopies of IRDs (particularly RP) that have no underlying genetic mutations. The last section provides a practical approach to IRDs and a basic understanding of genetic testing and its interpretation. This Atlas provides readers with images of various IRDs and concise text describing clinical features and associated genetic mutations.

The content of this Atlas will be readily understood by clinicians and students studying IRDs.

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We wish to acknowledge the support, hard work, and contribution of various team members, including photographers, technicians, residents, and fellows. Without their support and deep involvement, this Atlas could not have gone to print!

The authors would like to thank several of the eminent ophthalmologists for allowing staff at the Jonas Children's Vision Care to participate in the care of their patients: Irene H Maumenee, Philip Ferrone, Michael Nissen, Alan C. Bird, Richard F. Spaide, Philip Ferrone, Howard F. Fine, Daniel B. Roth, Golnaz Moazami, Anthony T. Moore, Bailey Freund, and Lawrence A. Yannuzzi. Authors thankfully acknowledge the partnership with Dr. Janet R. Sparrow in quantifying autofluorescence, and Drs. Rando L. Allikmets and Mahesh M. Mansukhani and their team for interpreting genetic testing.

We also would like to place on record our heartfelt thanks to the following team members and research faculties and research fellows: Gretchen Cuevas, Ruben Jauregui, Winston Lee, Nan-Kai Wang, Vivienne Greenstein, Sally Justus, Merry Ruan, Luz Amaro-Quireza, Yao (Iris) Li, Maarjaliis Paavo, Jesse Sengillo, Karen Sophia Park, Christine Xu, Thiago Cabral, Galaxy Cho, Jing Kong, Vítor Kazuo Lotto Takahashi, Júlia Takiuti, and Jane Heffner.

Last but not least, we wish to place on record our great appreciation and wholehearted thanks to Mr. Lee Klein, Senior Editor at Springer, and his dedicated team for their support and guidance at each and every step of the production of this Atlas and for maintaining their enthusiasm until the end.

The saying goes, "***As we share, so we grow***." We gratefully acknowledge the generosity of all those who support the educational endeavors of Harkness Institute.

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Section I
Basic Knowledge

CHAPTER 1

Retinal Histology and Anatomical Landmarks

Stephen H. Tsang and Tarun Sharma

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The wall of the eye consists of three layers: the sclera (the outermost layer), the choroid (the middle layer), and the retina (the innermost layer).

Retinal Layers

The retina can be divided histologically into 10 layers (Fig. 1.1). From the vitreous to the scleral side, these retinal layers are organized as follows:

1. **Internal Limiting Membrane (ILM)** is formed by the end feet of the Müller cells and astrocytes.
2. **Nerve Fiber Layer (NFL)** consists of the axons of ganglion cells, retinal vessels, and glial cells.
3. **Ganglion Cell Layer (GCL)** contains the nucleus of ganglion cells and glial cells.
4. **Inner Plexiform Layer (IPL)** has the synapses of bipolar, amacrine, and ganglion cells.
5. **Inner Nuclear Layer (INL)** comprises the nuclei from bipolar, horizontal, amacrine, and Müller cells.
6. **Outer Plexiform Layer (OPL)** has the synapses of photoreceptor cells, bipolar cells, and horizontal cells.
7. **Outer Nuclear Layer (ONL)** contains the nuclei of photoreceptor cells.
8. **Outer Limiting Membrane (OLM)** is formed by the junctional complexes between Müller cells, and between Müller and photoreceptor cells.
9. **Photoreceptor Layer (PL)** has tightly stacked rods and cones.
10. **Retinal Pigment Epithelium (RPE)** is a monolayer of RPE cells.

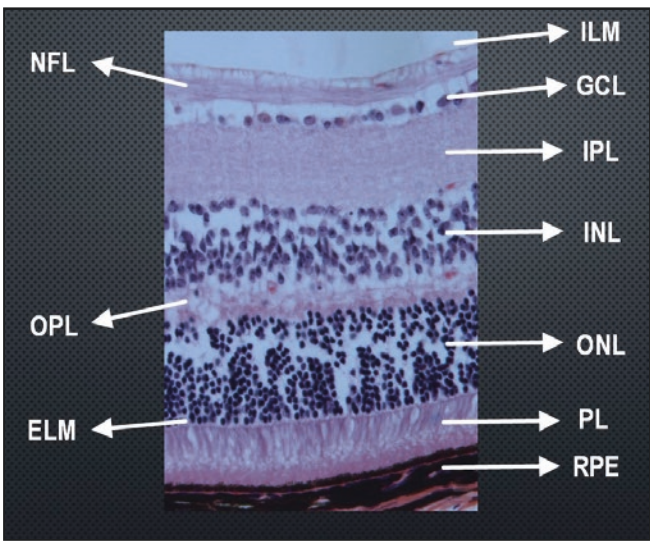

Fig. 1.1 Retinal histology

The retina otherwise is a structure of two lamina, an outer RPE and inner neural retina. The neural cells of the retina include photoreceptors (rods and cones), bipolar cells, interneurons (horizontal and amacrine cells), ganglion cells, and other structures like astroglia, oligodendroglia, Schwann cells, microglia, and vascular endothelium and pericytes.

Bruch's Membrane

The RPE is separated from the choroid (choriocapillaris) by the Bruch's membrane (BM). The BM is made up of five layers:

1. Basement membrane of the choriocapillaris
2. Outer collagenous layer
3. Central elastic layer
4. Inner collagenous layer
5. Basement membrane of the RPE

Choroid

The choroid is the middle layer of the eye wall. It consists of three layers of blood vessels:

1. **Choriocapillaris:** innermost
2. **Sattler layer:** middle and mid-caliber
3. **Haller layer:** outer and large-caliber

The choroid is about 0.2 mm thick at the macula and becomes progressively thinner anteriorly, to about 0.1 mm.

Anatomical Landmarks of The Macula

Figure 1.2 illustrates the anatomical landmarks of the macula:

- **Macula or central retina or posterior pole or macula lutea (from Latin, *macula* [spot] and *lutea* [yellow]):** The area between temporal arcades, about 5.5 mm in diameter from the temporal to optic disc; it has two or more layers of ganglion cells. The yellow color is due to lutein and zeaxanthin (xanthophyll carotenoids).
- **Fovea**: The central 1.5 mm (about 1 disc diameter or central 5°) of the macula is called the *fovea*. It has just cones, and no rods. The floor of the fovea is known as the *foveola* (about 0.35 mm, 350 μm); the central depression is called the *umbo* (about 0.15–0.20 mm, 150–200 μm). The foveal avascular

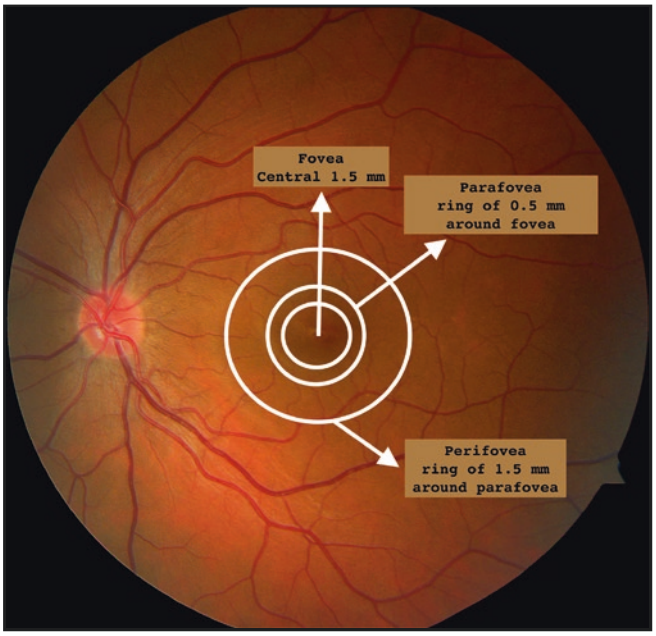

Fig. 1.2 Anatomical landmarks of the macula

zone (FAZ) is an area at the center of the macula (about 0.5–0.6 mm, 500–600 μm) that is devoid of any blood vessels.

- **Parafovea**: A ring surrounding the fovea, of 0.5 mm in width. The retina is thickest here; the OPL is called the *Henle layer*. The Henle layer is obliquely placed here, accounting for radial pattern of the macular star in hypertensive retinopathy. Beyond the macula, the OPL is perpendicular, not oblique.
- **Perifovea**: A ring surrounding the parafovea, 1.5 mm in width.

Did You Know?

- **Rods**: About 120 million, with the greatest density about 20° from fixation
- **Cones**: About six million, with 90% lying outside the fovea
- **RPE**: About four to six million cells
- **Photoreceptor:RPE ratio**: 45:1
- **Discs in the outer segment**: About 1000
- **Discs shed per day**: About 100
- **Discs ingested per day by each RPE cell:** About 4000

Suggested Reading

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CHAPTER 2

Fluorescein Angiography

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Principle and Technique

Fluorescein angiography (FA) is an imaging modality used to study the circulation of the retina and choroid. About 5 mL of 10% sterile aqueous solution of fluorescein dye (or 2–3 mL of a 25% solution) is injected in the antecubital vein. The fluorescein molecules excited by a blue light (465–490 nm) emit green-yellow light (520–530 nm) (Fig. 2.1). The reflected blue light and green-yellow light are passed through a barrier filter that allows only the green-yellow fluorescent light to pass through and blocks the blue reflected light.

Fluorescein injected through the peripheral vein reaches the eye via the ophthalmic artery in 10–12 s. There is a gradual filling up of retinal and choroidal circulation over a period of 20–25 s. The choroidal circulation fills about 1–2 s before the retinal circulation. It fills in a patchy manner; about 5 s later, it becomes intense and homogenous.

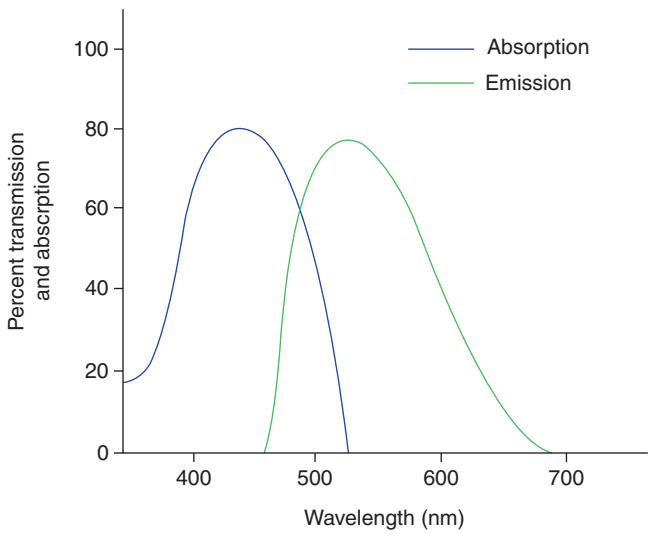

Fig. 2.1 Absorption and emission spectrum of sodium fluorescein dye

Dye-Transit Phases

The retinal circulation goes through various dye-transit phases:

1. **Arterial phase**, which follows the patchy choroidal phase (Fig. 2.2)
2. **Arteriovenous phase**, with complete filling of arteries and capillaries and laminar flow in the veins (Fig. 2.3); peak fluorescence is seen later in both artery and vein (Fig. 2.4)
3. **Recirculation phase**, when fluorescence gradually declines, about 30 s after injection (Fig. 2.5)

The direction of flow is from the artery to the vein: retinal artery, precapillary arterioles, capillaries, postcapillary venules, and finally the retinal veins. In the late phase (about 10 min after injection), most of the vessels are devoid of dye, but large choroidal vessels appear as a silhouette against the relatively brighter choroid and the stained sclera (Fig. 2.6).

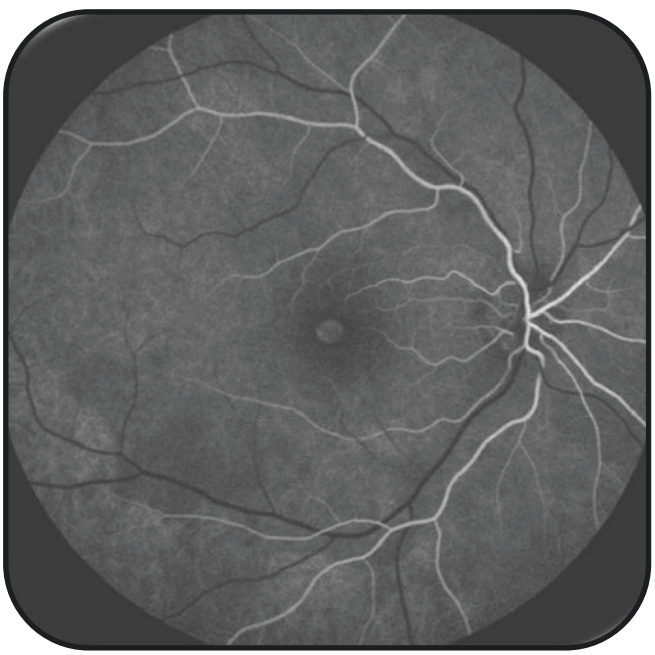

Fig. 2.2 Fluorescein angiogram, patchy choroidal and early arterial phase

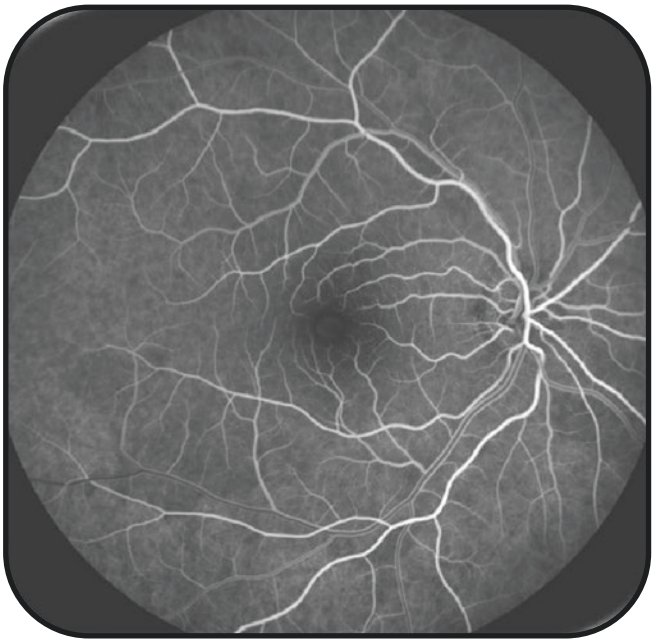

Fig. 2.3 Fluorescein angiogram, laminar flow in early venous phase

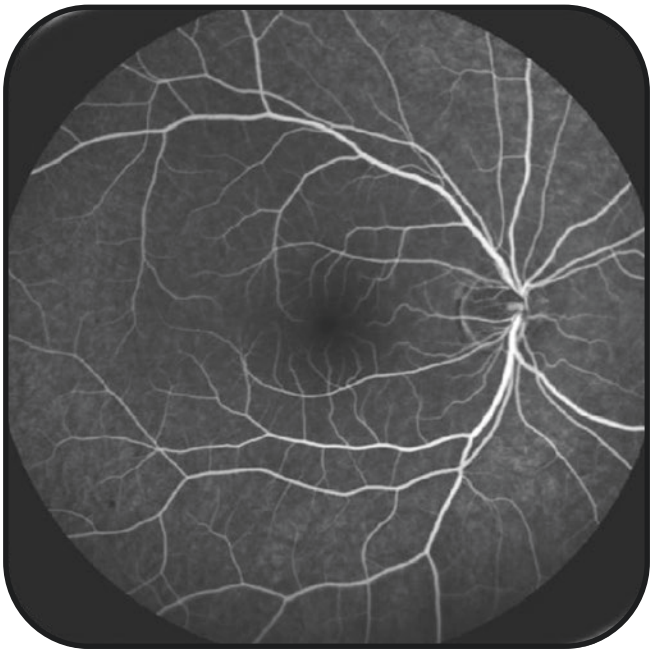

Fig. 2.5 Fluorescein angiogram, recirculation phase

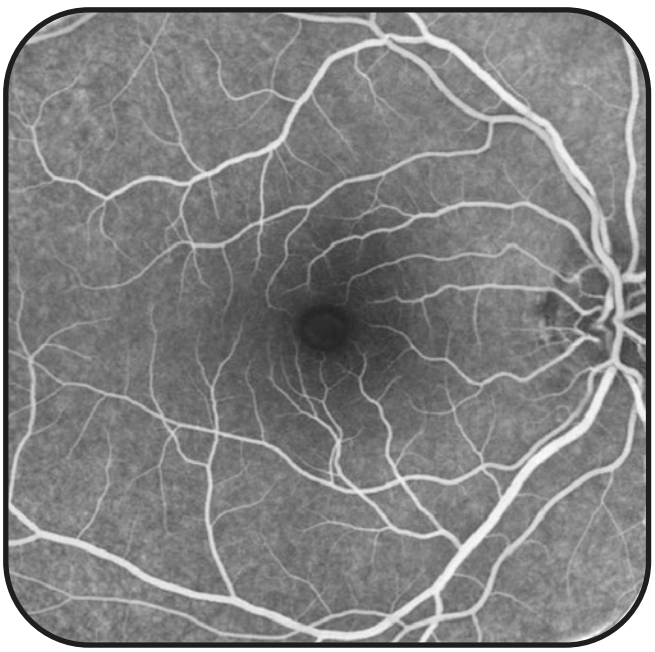

Fig. 2.4 Fluorescein angiogram, peak venous phase

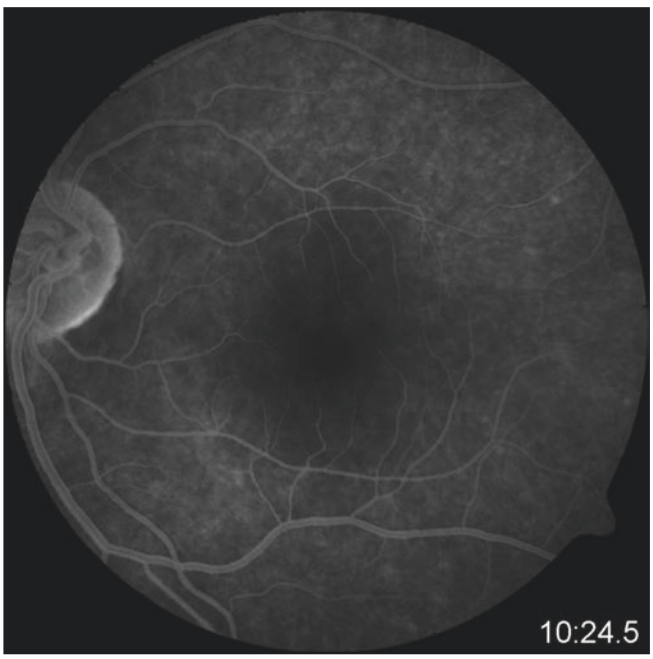

Fig. 2.6 Fluorescein angiogram, late phase

Blood-Retinal Barrier

The eye has two blood-retina barriers. One is formed by a tight junction of endothelial cells of retinal blood vessels, and the other, by the retinal pigment epithelial (RPE) cells. Both of these barriers prevent the fluorescein molecule from passing. The vessels of the choriocapillaris, however, have fenestrated walls and allow the dye to leak freely.

Suggested Reading

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CHAPTER 3

Optical Coherence Tomography

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Historical Perspective

Optical coherence tomography (OCT) has enhanced our understanding and management of retinal diseases, ever since the time-domain OCT was introduced in the early 2000s. The introduction of spectral-domain OCT in the mid-2000s and the later introduction of swept-source OCT provided faster scanning strategies and high-resolution images of the retina and choroid.

Principle

OCT uses the principle of low-coherence interferometry. A low-coherence light beam is directed onto the retina and choroid, and the back-reflected light is combined with a second or reference beam, which was split off from the original light beam. The interference patterns thus produced construct an axial A-scan, and multiple A-scans from adjacent points reconstruct a cross-sectional image of the target tissue, known as a B-scan.

Normal OCT Scans

Figure 3.1 shows the spectral-domain cross-sectional view (tomogram) of the retina and choroid, on a gray scale. Those tissues that are highly reflective (retinal pigment epithelium [RPE] or nerve fiber layer) appear brighter, and tissues with low reflectivity (vitreous or subretinal fluid) appear darker. Areas with intermediate reflectivity (retinal layers or edema) appear as shades of gray. The long wavelength of swept-source OCT (Fig. 3.2) allows a clear image of the deep ocular structures such as choroid.

In inherited retinal dystrophy, the ellipsoid zone (outer segment/inner segment junction) is an important landmark. If this zone is disrupted, discontinuous, or disorganized, it is an early indication of cell death. Progressive loss of photoreceptor cells is reflected by thinning of the outer segment, and later, of the outer nuclear layer.

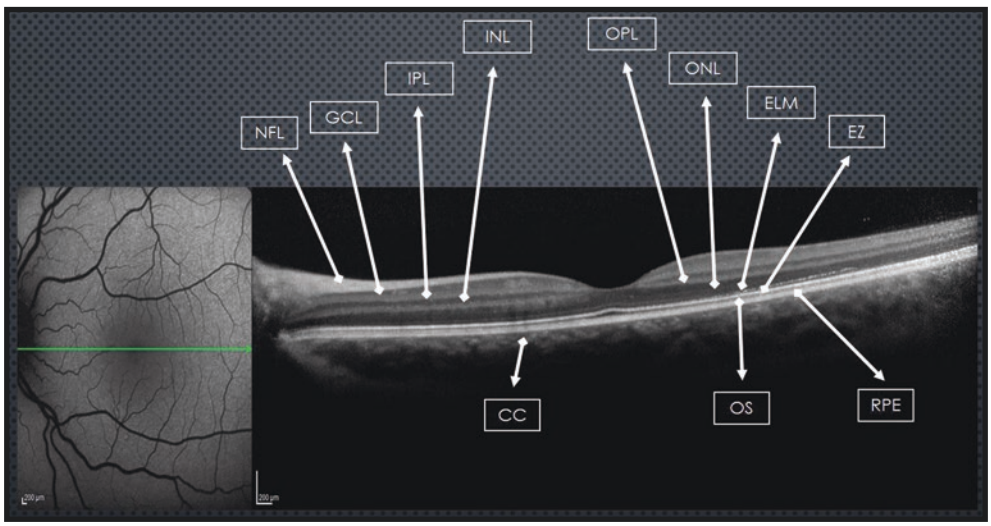

Fig. 3.1 Spectral-domain optical coherence tomography (SD-OCT) image of retinal layers. CC—choriocapillaris; EZ—ellipsoid zone; GCL—ganglion cell layer; INL—inner nuclear layer; IPL—inner plexiform layer; NFL—nerve fiber layer; OLM—outer limiting membrane; ONL—outer nuclear layer; OPL—outer plexiform layer; OS—outer segment; RPE—retinal pigment epithelium

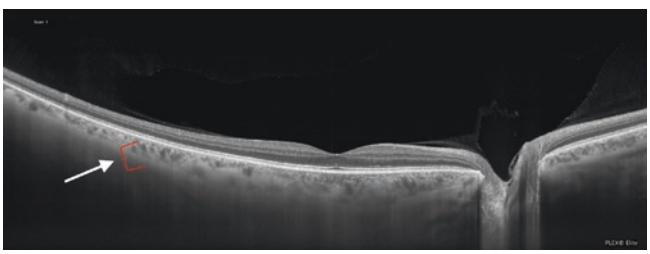

Fig. 3.2 Swept-source OCT showing enhanced visualization of choroidal blood vessels (*arrow*)

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CHAPTER 4

Fundus Autofluorescence

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Fundus autofluorescence (FAF) imaging is a rapid and noninvasive technique to evaluate retinal pigment epithelial (RPE) function. The predominant source of FAF in the macula is lipofuscin granules.

Typically, RPE cells ingest and digest photoreceptor outer segments and produce a by-product called lipofuscin; the pigment within lipofuscin that autofluoresces is A2E. The autofluorescence is the intrinsic fluorescence emitted by lipofuscin granules when stimulated by blue laser excitation energy (488 nm) with a barrier filter (500 nm), using a scanning laser ophthalmoscope.

A hallmark of aging is the gradual accumulation of lipofuscin granules in the RPE cells. Normal macula (Fig. 4.1) shows decreased AF at the center of the macula due to blockage by luteal pigments such as lutein and zeaxanthin. The rest of the macula shows a diffuse, homogenous signal; blood vessels and the optic disc appear black (no AF material).

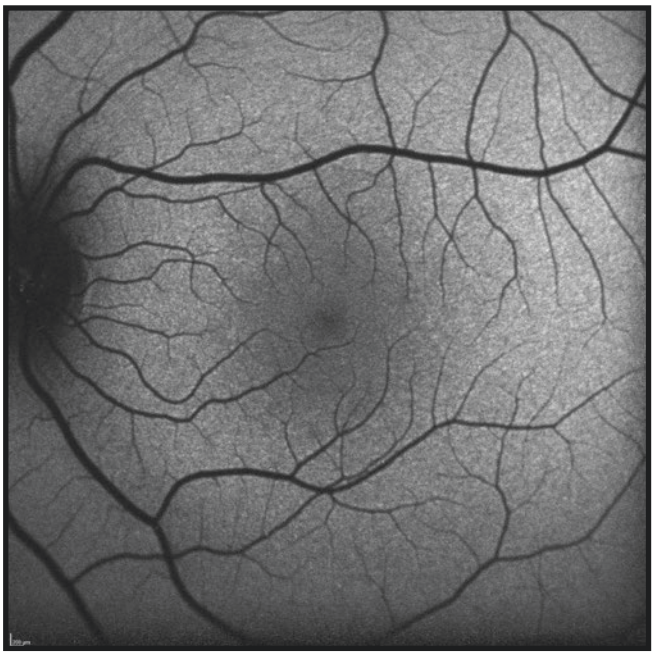

Fig. 4.1 Normal autofluorescence of the macula

FAF has become an important noninvasive tool in evaluating inherited retinal diseases, revealing the health of RPE cells both in diagnosis and in monitoring disease progression. In Best vitelliform dystrophy, the signal is increased owing to accumulation of lipofuscin, whereas in geographic atrophy, the signal is decreased owing to the loss of lipofuscin-containing RPE cells.

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Oishi M, Oishi A, Ogino K, Makiyama Y, Gotoh N, Kurimoto M, Yoshimura N. Wide-field fundus autofluorescence abnormalities and visual function in patients with cone and cone-rod dystrophies. Invest Ophthalmol Vis Sci. 2014;55:3572–7.

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CHAPTER 5

Electroretinography

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The electroretinogram (ERG) is a mass electrical response from the retina, evoked by a brief flash of light. ERG recording is done using an active electrode (a contact lens in contact with bulbar conjunctiva) and a reference electrode (at the outer canthus); the active electrode can also be a gold foil electrode or HK-loop electrode. There are three types of ERG: the full-field (Ganzfeld) ERG, the multifocal ERG, and the pattern ERG.

Full-Field ERG

A Ganzfeld bowl is used to illuminate the entire retina in a uniform fashion and the response from each eye is recorded (Fig. 5.1). The testing protocol, as suggested by the International Society for Clinical Electrophysiology of Vision (ISCEV), involves five different responses, with a suggested sixth to be recorded. The nomenclature is based on the adaptive state of the eye, light-adapted (LA) or dark-adapted (DA), and the flash strength in candela-seconds per meter squared ($cd.s.m^{-2}$).

1. **Dark-adapted 0.01 (rod-specific):** The response arises from ON-bipolar cells of the rod system (inner nuclear layer), so it has only a b-wave and no detectable a-wave.
2. **Dark-adapted 3.0 (mixed rod-cone):** Contains both a-waves and b-waves. The two a-wave peaks occur at about 15 and 21 ms. As only the first 8 ms represents photoreceptor hyperpolarization, ISCEV recommends an additional DA 10.0 testing.
3. **Dark-adapted 10.0:** This test helps to differentiate abnormality between photoreceptor and inner retina. If a wave is normal or near normal but the b-wave amplitude is lower (negative ERG), the dysfunction is at the inner retinal level.
4. **Oscillatory potentials (OPs):** The response arises from the amacrine cells. These OPs are reduced or absent in inner retinal ischemia and in subjects with congenital stationary night blindness.
5. **Light-adapted 3.0 single flash:** The a-wave originates from cone photoreceptor and OFF-bipolar cells; the b-wave originates from ON-bipolar and OFF-bipolar cells.
6. **Light-adapted 3.0 30-Hz flicker:** This is a more sensitive measure of cone function; both time and amplitude are important. A delayed time response suggests generalized cone dysfunction, whereas reduced amplitude with normal peak time is indicative of restricted cone dysfunction.

Pattern ERG

The central retinal function can also be assessed by the pattern ERG (PERG), elicited by using high-contrast checkerboard reversal (Fig. 5.2). There are two components, the positive P50 and the negative N95. The N95 component arises in the

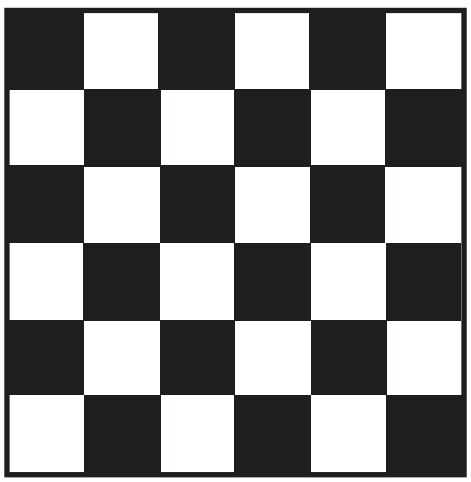

Fig. 5.2 Sample of an appropriate pattern ERG stimulus. Note the symmetry around the center, the sharp contrast between the squares, and the even luminance levels when averaged over any section of the pattern. In a reversal test, the pattern would reverse such that the top-left square would be white, and then reverse back to black; this would stimulate the retina at each reversal, or twice per cycle

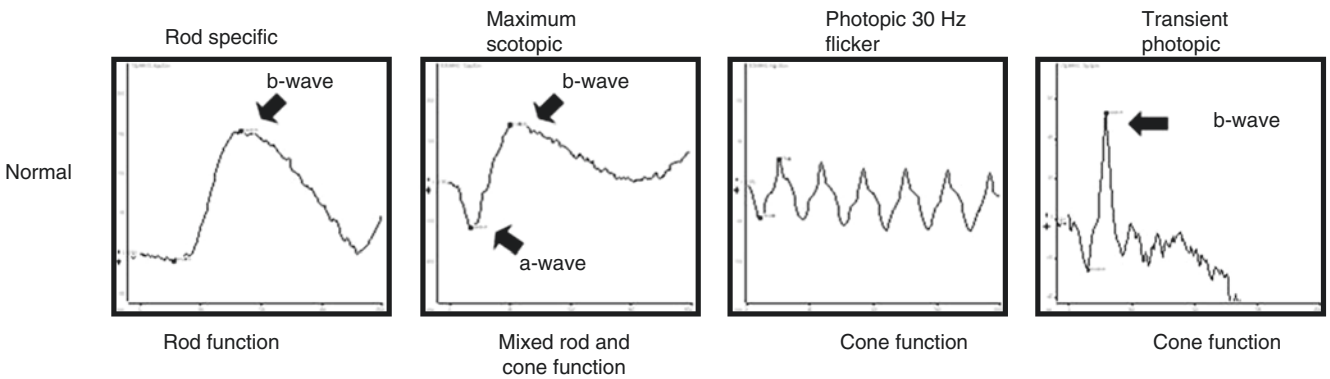

Fig. 5.1 Normal electroretinogram (ERG) tracings. The a-wave and b-wave are noted where applicable

ganglion cell layer, and the P50 component represents macular photoreceptors, even though a significant part arises in the retinal ganglion cells. Reduction of amplitude in the N95 component with preservation of the P50 component suggests dysfunction of retinal ganglion cells. This is a useful test in dominantly inherited optic atrophy or Leber hereditary optic neuropathy.

Multifocal ERG

The multifocal ERG (mfERG, Fig. 5.3) helps in evaluating macular function (cone system) and needs a stable fixation. The stimulus involves multiple hexagons (61 or 103), which are smaller in the center than in the periphery. The tested area is about

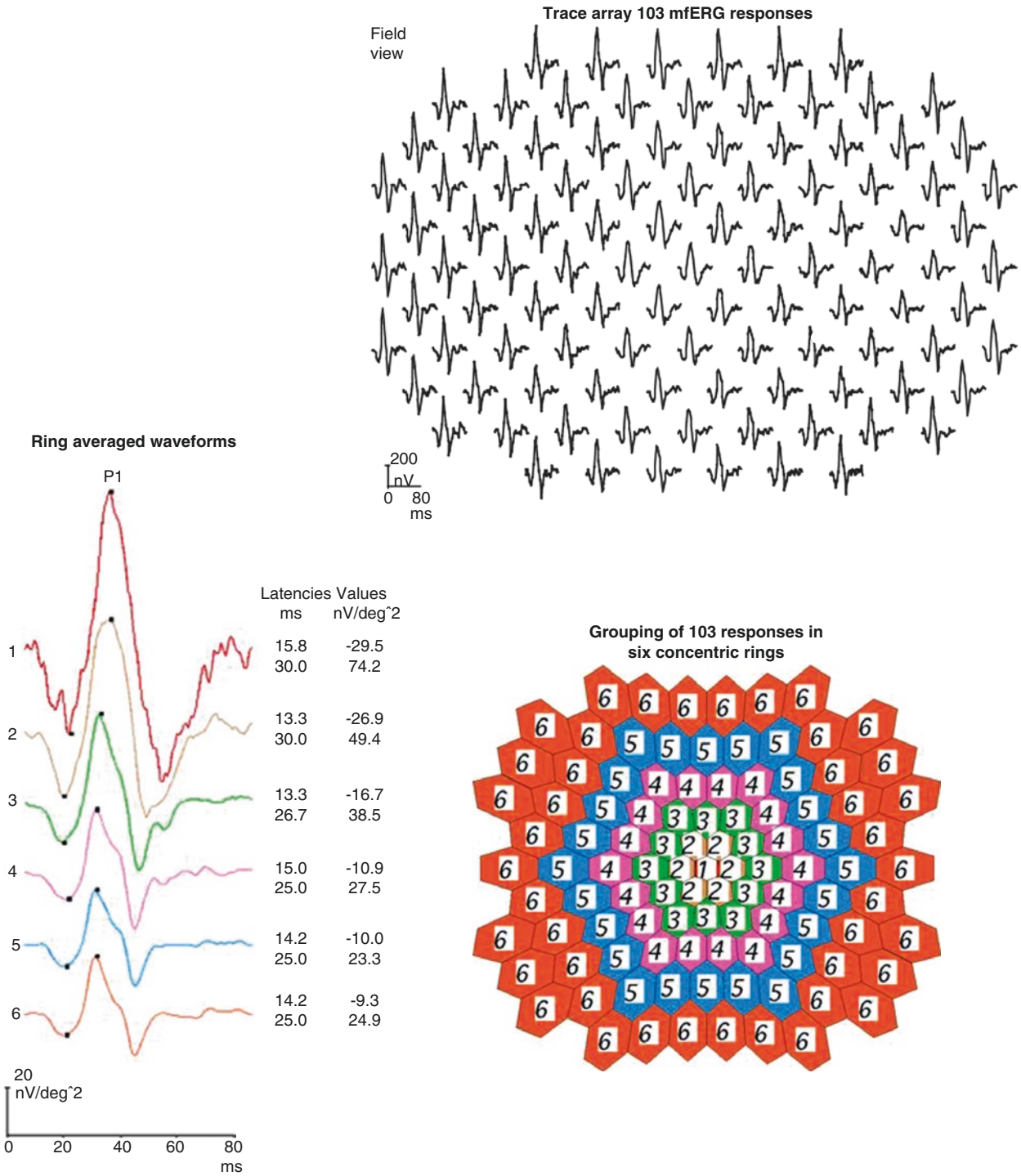

Fig. 5.3 Multifocal ERG tracing of a normal patient

20–30° on either side of the fovea. The hexagons are displayed on a television monitor, and each hexagon flashes on and off with a pseudorandom binary sequence (an M-sequence). Each response from the hexagon is calculated via a cross-correlation technique, generating multiple cone system ERG waveforms, thereby providing spatial information about the central cone system. The mfERG is useful in the early detection of hydroxychloroquine toxicity.

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CHAPTER 6

Electrooculography

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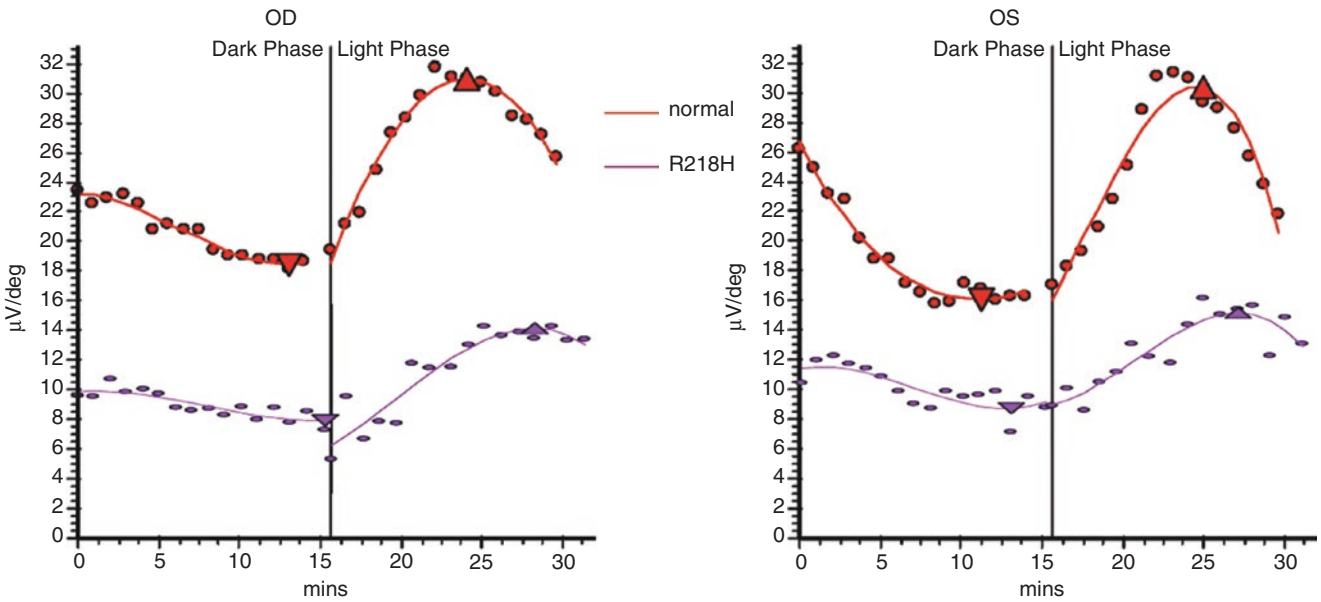

Fig. 6.1 Lack of EOG light rise is seen in a patient with R218H mutation (Best Disease)

The electrooculogram (EOG) assesses the function of the retinal pigment epithelium (RPE), and also the interaction between the RPE and photoreceptors. This is done by noting the changes in the corneoretinal standing potential (the difference between the retina and electropositive cornea) during the dark-adapted and light-adapted states.

During the test, the patient sits in a Ganzfeld bowl and makes fixed 30° lateral eye movements during a 15-min period of dark adaptation, followed by a 12-min period of light adaptation. The patient makes the eye movements for about 10 s each minute. Electrodes are placed at the medial and lateral canthi. The amplitude of the signal recorded between the electrodes reaches a minimum during dark adaptation (dark trough) and a maximum during light adaptation (light peak). The EOG is expressed as a percentage, the Arden index (or ratio), and is measured by calculating the size of the light peak in relation to the dark trough. The normal EOG light rise (Arden ratio) is greater than 170%.

In a normal individual, the development of the light peak requires normally functioning photoreceptors in contact with a normally functioning RPE and is due to progressive depolarization of the RPE basal membrane. The mechanism of this depolarization is rather poorly understood; it may be caused by a bestrophin protein for opening up of chloride channels.

In Best vitelliform macular dystrophy (Fig. 6.1), the Arden ratio is less than 170%, representing an absent light rise, but the full-field electroretinogram (ERG) is normal. In adult vitelliform macular dystrophy, the EOG is normal or mildly subnormal. In autosomal recessive bestrophinopathy (ARB), both the EOG and ERG are abnormal, but the carriers (unlike in Best) do not show EOG abnormality. The EOG is also abnormal in any condition that has widespread photoreceptor degeneration, such as retinitis pigmentosa.

Abnormal EOG – a marked reduction in light rise in the absence of a comparable degree of rod ERG abnormality - is also seen in subjects with acute zonal occult outer retinopathy (AZOOR), and this is helpful in distinguishing AZOOR from other causes of white dot syndrome.

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CHAPTER 7

Glossary of Relevant Genetic and Molecular/Cell Biology

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Genetics

Genes The basic physical and functional unit of heredity; made up of DNA, they act as instructions to make proteins. There are about 20,000–25,000 genes in humans, with size varying from a few hundred DNA bases to more than 2 million bases. Most genes are the same in all people; less than 1% differ. Each person has two copies of each gene, one inherited from each parent. Each chromosome contains many genes.

Chromosome Thread-like structures in the nucleus of each cell, in which the DNA molecules and a protein called *histone* are packaged. Each chromosome has a constriction point, the *centromere*, which divides the chromosome into a short arm ("p arm") and a long arm ("q arm").

In humans, each cell contains 23 pairs of chromosomes, for a total of 46. Twenty-two of these pairs, called *autosomes*, look the same in both males and females. In the 23rd pair, the sex chromosome, females have two copies of the X chromosome and males have one X and one Y chromosome. The chromosomes are numbered by size. The picture of the human chromosome lined up in pairs is called a *karyotype*.

Genetics The study of genes, genetic variation, and heredity in living organisms.

Genotype The genetic constitution of an individual.

Phenotype The set of observable or manifest characteristics of an individual due to an interaction of its genotype with the environment.

Genome The complete set of genes or genetic material in a cell.

Cell Basic building block of living organisms; the human body has trillions of cells. Cells contain genetic (hereditary) material and can make copies of themselves.

Cytoplasm A jelly-like fluid (cytosol) within each cell; it contains many organelles (organized or specialized structures, like endoplasmic reticulum, Golgi apparatus, or mitochondria).

Endoplasmic reticulum Organelle that transports molecules created by the cell to their destination either inside or outside the cell.

Golgi apparatus Organelle that packages molecules processed by the endoplasmic reticulum and transports them out of the cell.

Nucleus The command center of a cell, which contains DNA (nuclear DNA); it sends direction to the cell to grow, divide, mature, or die.

Mitochondria Organelle that produces energy through a process called oxidative phosphorylation, creating adenosine triphosphate (ATP) from oxygen and simple sugars. They have their own genetic material (mitochondrial DNA) that is separate from the DNA in the nucleus and make copies of themselves. Each cell contains hundreds to thousands of mitochondria.

Ribosomes Organelle in the cytoplasm that makes protein.

GDB Human Genome Database The official central repository for genomic mapping data resulting from the Human Genome Project.

DNA or deoxyribonucleic acid The hereditary material in humans and all other organisms. Nearly every cell has the same DNA, located in the nucleus or mitochondria. The information in the DNA is stored as a code made up of four chemical bases: adenine (A), guanine (G), cytosine (C), and thymine (T). These bases pair up with each other, A with T and C with G, to form units called *base pairs*.

Nucleotide Each base pair is attached to a sugar molecule and a phosphate molecule; together, a base, sugar, and phosphate are called a *nucleotide*. Nucleotides are the building block of DNA.

DNA structure Nucleotides are arranged in two long strands that form a spiral (double helix). The structure of the double helix is like a ladder, with the base pairs forming the ladder's rungs and the sugar and phosphate molecules forming the vertical sidepieces of the ladder.

Human genome Each cell contains approximately 3 billion base pairs, which reside in the 23 pairs of chromosome within the nucleus. Each chromosome contains hundreds to thousands of genes, which carry the instructions for making proteins. More than 99% of these bases are the same in all people.

DNA sequence The order or sequence of the bases determines the information available for building and maintaining an organism, similar to the way in which letters of the alphabet appear in a certain order to form words and sentences. An important property of DNA is that it can make copies of itself (replicate); this is critical when cells divide, because each new cell needs to have an exact copy of the DNA present in the old cell.

Mitochondrial DNA Besides producing energy, mitochondria also help in regulating apoptosis, the self-destruction of cells,

and they are essential to produce substances like cholesterol and heme (the component of hemoglobin that carries oxygen in the blood). Mitochondrial DNA has 37 genes: 13 provide instructions for making enzymes involved in oxidative phosphorylation, and the others provide instructions for making molecules called transfer RNAs (tRNAs) and ribosomal RNAs (rRNAs), both of which help assemble protein building blocks (amino acids) into functioning proteins.

Genetic Disorders

Aneuploidy A gain or loss of a chromosome from the normal 46 is called aneuploidy.

Trisomy Having three copies of a particular chromosome in cells instead of the normal two copies. People with Down syndrome typically have three copies of chromosome 21 in each cell, for a total of 47 chromosomes per cell.

Monosomy Having one copy of a particular chromosome in cells instead of the normal two copies. Women with Turner syndrome usually have one copy of the X chromosome in every cell, for a total of 45 chromosomes per cell.

Gene mutation A permanent change or alteration in the DNA sequence that makes up a gene. Mutations range in size from a single base pair to a large segment of chromosome that includes multiple genes.

Hereditary or germline mutations Mutations inherited from a parent (via egg or sperm cells, called *germ cells*) and present in virtually every cell in the body throughout a person's life.

Acquired or somatic mutation Mutation that occurs at some time during a person's life and is present only in certain cells, not in every cell. These changes can be caused by environmental factors such as ultraviolet radiation or may result from a mistake made as DNA copies itself during a cell division. These mutations cannot be passed to the next generation.

***De novo* (new) mutation** Mutation can be either germline or somatic. The germline mutation may occur in an egg, sperm cell, or fertilized egg; this may explain why a genetic disorder is present in a child, but the parents remain unaffected (no family history). Whereas the somatic mutation does not happen in egg or sperm cells or the fertilized egg but occurs a bit later in an embryo. All cells that arise from a cell with the mutated gene will have the mutation, but other cells will not; this situation is called *mosaicism*. Depending on the mutation and how many cells are affected, mosaicism may or may not cause health problems.

Genetic disorder A condition caused by mutations in one or more genes. Each cell depends on thousands of proteins doing their jobs in the right place at the right time, and gene mutations can prevent one or more of these proteins from working properly, causing it either to malfunction or to be missing. Not all mutations affect health and development. Some alter a gene's DNA sequence but do not change the function of the protein made by the gene.

DNA repair An important process by which the body protects itself from disease. As DNA can be damaged or mutated in many ways, each cell has a number of pathways/enzymes which recognize and repair mistakes in DNA.

Beneficial mutations A very small percentage of all mutations actually have a positive effect; a new version of proteins may help an individual to adapt better to changes in the environment.

Variants of unknown significance (VOUS or VUS) Because a person's genetic code can have a large number of mutations with no effect on health, diagnosing a genetic condition can be difficult. Sometimes, genes thought to be related to a particular genetic condition have mutations that are known as *variants of unknown significance* if it has not been determined whether the changes are involved in the development of the condition.

Missense mutation A change in one DNA base pair (point mutation, replacement of a single nucleotide) that results in the substitution of one amino acid for another in the protein made by a gene.

Nonsense mutation A change in one DNA base pair by which the altered DNA sequence prematurely signals the cell to stop building a protein. The result is a shortened protein that may not function properly.

Insertion The addition of one nucleotide, changing the amino acid sequence that follows; hence, the protein may not function properly.

Deletion Removal of one base pair or a few base pairs within a gene (small deletion) or removal of an entire gene or several neighboring genes (large deletion), altering the resulting protein.

Duplication Abnormal copying of a piece of DNA one or more times.

Frameshift mutation The addition or loss of DNA bases that changes a gene's reading frame (group of three bases that

code for one amino acid). Insertions, deletions, and duplications can all be frameshift mutations.

Repeat expansion Nucleotide repeats are short DNA sequences that are repeated a number of times in a row. A trinucleotide repeat is made up of sequences of three base pairs, and a tetranucleotide repeat is made up of sequences of four base pairs. The resultant protein is malfunctioning.

Complex of multifactorial disorders Common medical problems such as heart disease, diabetes, and obesity, which are associated with multiple gene defects as well as lifestyle and environmental factors, rather than having a single genetic cause.

Gene names The HUGO Gene Nomenclature Committee (HGNC) designates an official name and symbol (an abbreviation of the name) for each known human gene.

Molecular Biology

Proteins Large, complex molecules that do most of the work in cells and are needed for the structure, function, and regulation of the body's tissues and organs. Proteins are made up of hundreds or thousands of smaller units called *amino acids*, the building block of proteins, which are attached to each other in long chains. There are 20 different amino acids that can be combined to make a protein.

Gene expression The complex and tightly controlled journey from gene to protein within each cell; it involves two steps, transcription and translation.

Transcription The transfer of the information stored in a gene's DNA to another molecule (RNA) in the cell nucleus. This RNA carries the information or message from the DNA out of the nucleus into the cytoplasm, called messenger RNA (mRNA).

Translation In the cytoplasm, the mRNA interacts with a specialized complex, a ribosome, which reads the sequence of mRNA bases. Each sequence of three bases, called a codon, usually codes for one particular amino acid. A type of RNA called transfer RNA (tRNA) assembles the protein, one amino acid at a time; the protein assembly continues until the ribosome encounters a stop codon (a sequence of three bases that does not code for an amino acid).

Central Dogma Explanation of the flow of information from DNA to RNA to proteins; one of the fundamental principles of molecular biology.

Gene regulation Each cell expresses or turns ON only a fraction of genes; the rest are repressed or turned OFF. Gene regulation is an important part of normal development (for example, making a brain cell different from a muscle cell).

Transcription factor Protein activated by signals from the environment or from other cells. These proteins bind to regulatory regions of a gene and increase or decrease the level of transcription, thereby determining the amount of protein product that is made by a gene at any given time.

Epigenome A multitude of the chemical compounds that surround the genome; these are not part of DNA sequence, but are attached to DNA. These compounds can tell the genome what to do and can affect gene activity. Epigenetic changes can help determine whether genes are turned ON or OFF and can influence the production of proteins in certain cells. Some epigenetic changes can be passed on from generation to generation. Environmental factors such as diet and exposure to pollutants can also impact the epigenome.

Epigenomic modification or methylation When methyl groups are added to a particular gene, that gene is turned OFF or silenced, and no protein is produced from that gene. Conditions like cancers, metabolic disorders, and degenerative disorders have all been found to be related to epigenetic errors.

Human Epigenome Project A multinational project with the aim of identifying, cataloging, and interpreting genome-wide DNA methylation patterns of all human genes in all major tissues.

Cytogenetic location of a gene Describing the location of a particular gene on a chromosome. The cytogenetic location is based on a distinctive pattern of bands created when chromosomes are stained with certain chemicals. The combination of numbers and letters provide a gene's address on a chromosome. For example, in 15p12, the first number (15) describes the chromosome number. The next letter describes the arm of the chromosome, short (p) or long (q), and the next number describes the location on the p or q arm, designated by two digits, representing a region and a band. These are sometimes followed by a decimal point and one or two additional digits (representing sub-bands within a light or dark area). Therefore, 15p12 represents position 12 on the short arm of chromosome 15; 15p11 is closer to the centromere than 15p12.

Molecular location of a gene Molecular address that pinpoints the location of that gene in terms of base pairs, and also the size of the gene. The Human Genome Project determined the sequence of base pairs for each human chromosome. This sequence information allows the researcher to provide a more specific address than the cytogenetic location for many genes.

Inheritance

Hereditary disease Disease that results from a particular genetic composition and is passed from one generation to another.

Genetic disease Disease caused by a genetic defect, either acquired or inherited; not passed onto subsequent generations, and therefore, not hereditary.

Familial disease Disease that occurs in more than one member of a family. It may be hereditary, but not necessarily; it could be due, for example, to a common exposure to infectious agents, as in adenoviral conjunctivitis.

Mendelian disorder (single-gene disorder) A trait or medical disorder that follows patterns of inheritance suggesting that it is determined by a gene at a single locus (autosomal dominant, autosomal recessive, or X-linked recessive inheritance).

Autosomal dominant inheritance One mutated copy of the gene in each cell is sufficient for a person to be affected. The trait appears in multiple generations (vertical transmission).

Autosomal recessive inheritance Both copies of the gene in each cell must have mutations for the person to be affected. Typically, the trait appears only in the person's siblings, not the parents or offspring, and the trait is not seen in every generation of an affected family.

X-linked recessive inheritance Inheritance of traits caused by mutations in genes on the X chromosome. In males (who have only one X chromosome), one altered copy of the gene in each cell is sufficient to cause the condition. An affected father cannot pass X-linked traits to his sons (no male-to-male transmission), but all of his daughters are carriers.

Codominant inheritance Two different versions (alleles) of a gene are expressed at the same place on a chromosome, and each version makes a slightly different protein. Both alleles influence the genetic trait or determine the characteristics of the genetic disease.

Mitochondrial or maternal inheritance Because only egg cells contribute mitochondria to the developing embryo, only females can pass on mitochondrial mutations to their children. The trait can appear in every generation of a family and can affect both males and females.

Reduced or incomplete penetrance Only some people with a particular genetic change or mutation exhibit signs or symptoms of the genetic disorder.

Variable expressivity A range of signs or symptoms occurring in different people with the same genetic condition.

Clinical heterogeneity The production of different phenotypes by different mutations at the same locus (location of a gene on a chromosome); for example, mutation of peripherin/RDS can give rise to macular dystrophy or retinitis pigmentosa (same locus, different diseases).

Locus heterogeneity The production of a similar phenotype by mutations at different loci; for example, X-linked retinitis pigmentosa can result from *RP2* at Xp11 or *RP3* at Xp21 (different locus, same disease).

Allelic heterogeneity The production of the same phenotypic expression by different mutations within a single gene locus (same locus, same disease).

Anticipation The tendency for the signs and symptoms of some genetic conditions to become more severe and appear at an earlier age as the disorder is passed from one generation to the next.

Digenic inheritance Simultaneous inheritance of two nonallelic mutant genes; for example, retinitis pigmentosa caused by mutations of both the *ROM1* and peripherin/*RDS* genes.

Diagnosis and Treatment

Genetic testing A medical test that identifies changes in chromosomes, genes, or protein.

Molecular genetic test or gene tests Study of single genes or short lengths of DNA.

Chromosomal genetic tests Analysis of whole chromosomes or long lengths of DNA.

Biochemical genetic tests Study of the amount or activity level of proteins.

Positive genetic test Laboratory finding of a change in a particular gene, chromosome, or protein of interest. Depending on the purpose of the test, the result confirms a diagnosis, indicates that a person is a carrier of a particular genetic mutation, identifies an increased risk of developing a disease (*eg*, cancer) in the future, or suggests a need for further testing. A positive test may require similar genetic testing in the family, but it cannot predict the course or severity of a condition.

Negative genetic test Failure of the laboratory to find a change in the gene, chromosome, or protein under consideration. This result can indicate that a person is not affected by a particular disease, is not a carrier of a specific genetic mutation, or does not have an increased risk of developing a certain disease. It is possible, however, that the test missed a disease-causing genetic alteration, as many genetic tests cannot detect all genetic changes, so further testing may be required to confirm a negative result.

Uninformative or indeterminate test result Because everyone has common, natural variations in their DNA (polymorphisms) that do not affect health, a genetic test may find a change in DNA that has not been associated with a disorder in other people, and it can be difficult to tell whether the change is a natural polymorphism or a disease-causing mutation. This kind of uninformative test result cannot confirm or rule out a specific diagnosis.

Open reading frame (ORF) Any part of the genome that could be translated into a protein sequence due to an absence of stop codons (*e.g.*, exon).

Single nucleotide polymorphisms (SNPs) The most common type of genetic variation among people. Each SNP represents a difference in a single DNA building block, the nucleotide. SNPs occur normally throughout a person's DNA—on average, once in every 300 nucleotides, so there are roughly 10 million SNPs in the human genome. Most have no effect on health or development, but if SNPs occur within a gene or in a regulatory region near a gene, they may play a more direct role in disease by affecting the gene's function.

Genome-wide association study (GWAS) Method of searching the genome for small variations, SNPs; these changes occur more frequently in people with a particular disease than in people without the disease. Each study can look at thousands of SNPs at the same time.

Whole exome sequencing and whole genome sequencing Determining the order or sequence of DNA building blocks (nucleotides) in an individual is called *DNA sequencing*. Whole exome sequencing tests just the exons region (the exome), the protein-coding region of DNA that gives instructions to make proteins. (Exons are thought to make up just 1% of a person's genome.)

Whole genome sequencing tests both the exome and introns (non-coding region), as some DNA variations outside the exome can affect the gene activity and protein production and may lead to a genetic disorder.

Gene therapy The treatment or prevention of diseases by inserting a gene into a patient's cell instead of using drugs or surgery. This therapy can include replacing a mutated gene with a healthy copy of the gene, inactivating/knocking out a mutated gene, or introducing a new gene into the body to help fight a disease. Because a gene that is inserted directly into a cell usually does not function, a carrier called a *vector* is genetically engineered to deliver the gene; certain viruses are often used as vectors as they can deliver the new gene by infecting the cell. Retroviruses integrate their genetic material into a chromosome in the human cell; adenoviruses introduce their DNA into the nucleus of the cell, but the DNA is not integrated into a chromosome. The vector can be injected into the vitreous cavity or the subretinal space.

Genome surgery or gene editing allows to make specific changes to the DNA sequence; this is done by using CRISPR-Cas9 (Clustered Regularly Interspersed Short Palindromic Repeats-CRISPR associated protein 9) which acts as a molecular scissors and cuts at the specific DNA sequences. The cell's normal DNA repair mechanism then join the two cut ends of the DNA back together.

Precision medicine An emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person. This approach will allow more accurate prediction of which treatment and prevention strategies for a particular disease will work in the individual person.

Section II
X-linked Forms

CHAPTER 8

X-linked Retinitis Pigmentosa

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General Features

X-linked retinitis pigmentosa (XLRP) is considered to be one of the most severe forms of retinitis pigmentosa (RP). It accounts for about 6–20% of all RP cases, including about 10% in the United States and 25% in England.

It primarily affects males. Patients usually present with night blindness in the first decade of life, with reduction in the visual fields in the second decade, and severe visual loss (less than about 20/200) by the fourth decade.

Fundi show all the characteristic features of RP: bone spicule–like pigment deposit in the retina (Fig. 8.1), attenuation of retinal arterioles, waxy pallor of the optic disc, posterior subcapsular lens opacities, and grossly reduced or absent amplitude on electroretinogram (ERG).

Female Carriers

The female carrier shows only peripheral retinal pigment epithelium (RPE) changes, including pigmentary deposits (Fig. 8.2). ERG may show a reduced amplitude to white light or delayed cone-wave implicit times (Fig. 8.3). The carrier may also show a characteristic tapetal reflex, a golden, metallic luster in the perimacular area (Fig. 8.4). About 50% of female carriers may have these abnormalities: tapetal reflex, pigmentary alteration, ERG changes.

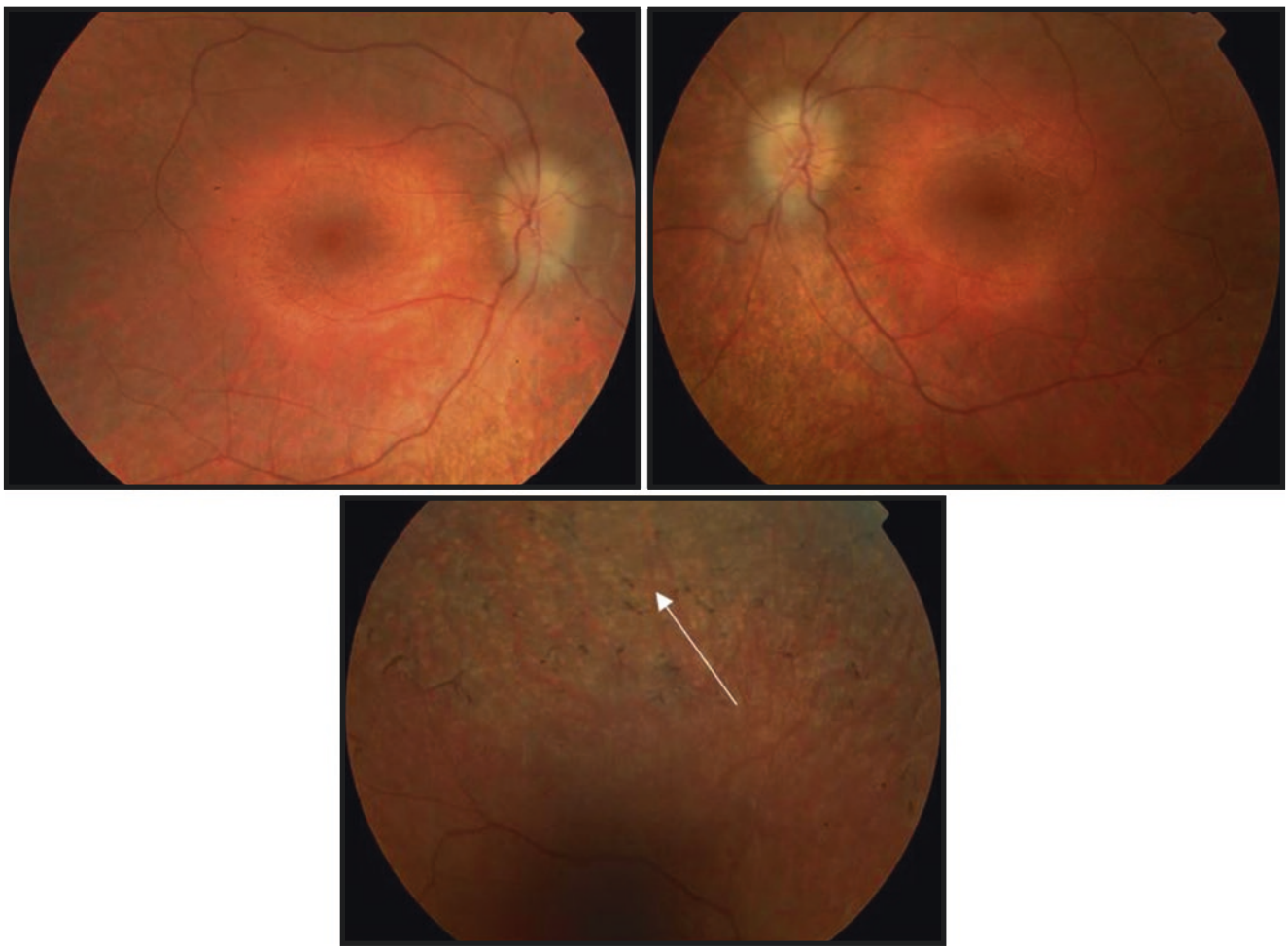

Fig. 8.1 X-linked retinitis pigmentosa. Color fundus photographs show pigmentary changes (*arrow*) in the periphery, with a relatively healthy macula, in a 10-year-old boy; note optic nerve drusen

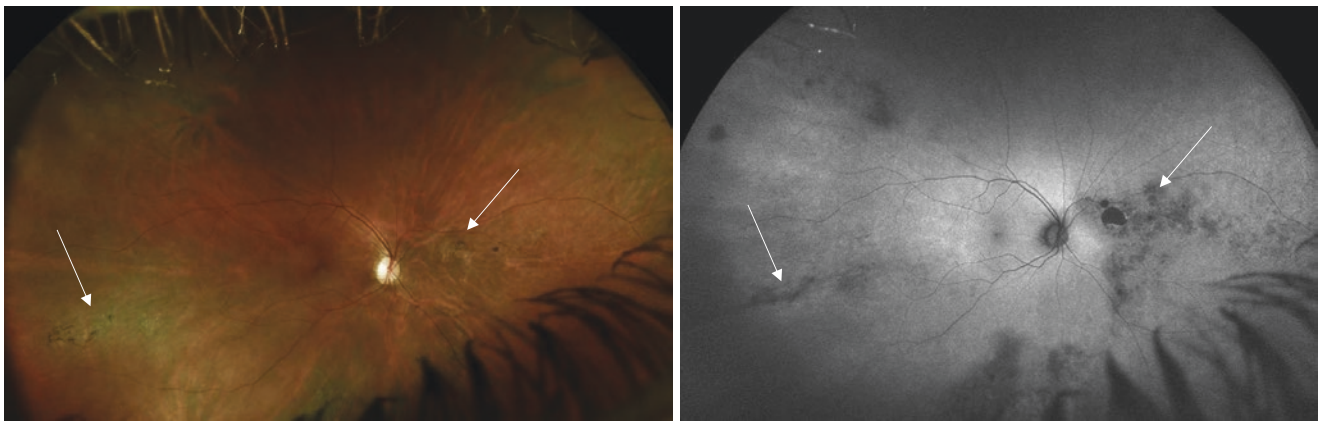

Fig. 8.2 Pigmentary deposits (arrow) in a female carrier of X-linked retinitis pigmentosa

Molecular Genetics

The most frequent single cause of X-linked RP is a mutation in the Retinitis Pigmentosa GTPase Regulator gene (*RPGR*), accounting for about 15–20% of cases in Caucasians. The other gene involved in the mutation is *RP2*. Of about 300 mutations in *RPGR* gene, nearly 95% are associated with XLRP. *RPGR* mutations affect about 15,000 people in the United States and tens of thousands more around the world. Of the reported *RPGR* mutations, 35–55% occur in a glutamic acid–rich domain within exon open reading frame 15 (*ORF15*).

RPGR Gene

RPGR gene produces different versions of RPGR protein, one of which contains an ORF15 exon. This is expressed predominantly in the photoreceptors and plays an important role by regulating the function of cilia. Mutation results in an abnormally short, malfunctioning protein.

The cytogenetic location of the gene is Xp11.4 (short arm of the X chromosome at position 11.4).

RP2 Gene

The RP2 protein may be involved in transporting proteins within photoreceptor cells. More than 70 mutations have been identified in subjects with XLRP; the mutations result in a short version of the RP2 protein. A few mutations change single building blocks (amino acids) in the RP2 protein. The cytogenetic location of the gene is Xp11.3 (short arm of the X chromosome at position 11.3).

Gene Therapy Trials

The *ClinicalTrials.gov* website lists three ongoing or planned trials of gene therapy for XLRP (as of January 2, 2018):

- A Clinical Trial of Retinal Gene Therapy for X-linked Retinitis Pigmentosa (Recruiting, ClinicalTrials.gov Identifier: NCT03116113)
- Gene Therapy for X-linked Retinitis Pigmentosa (XLRP) Retinitis Pigmentosa GTPase Regulator (RPGR) (Recruiting, ClinicalTrials.gov Identifier: NCT03252847)
- Safety and Efficacy of rAAV2tYF-GRK1-RPGR in Subjects With X-linked Retinitis Pigmentosa Caused by *RPGR-ORF15* Mutations (Not yet recruiting, ClinicalTrials.gov Identifier: NCT03316560)

Did You Know?

- Although the *RPGR* mutation causes XLRP most of the time, a few mutations in the *ORF15* exon result in cone-rod dystrophy, cone dystrophy, and atrophic macular degeneration.
- Some affected individuals with the *RPGR* mutation have chronic respiratory and sinus infections, recurrent otitis media, and hearing loss. These effects could be due to disruption of the function of cilia.

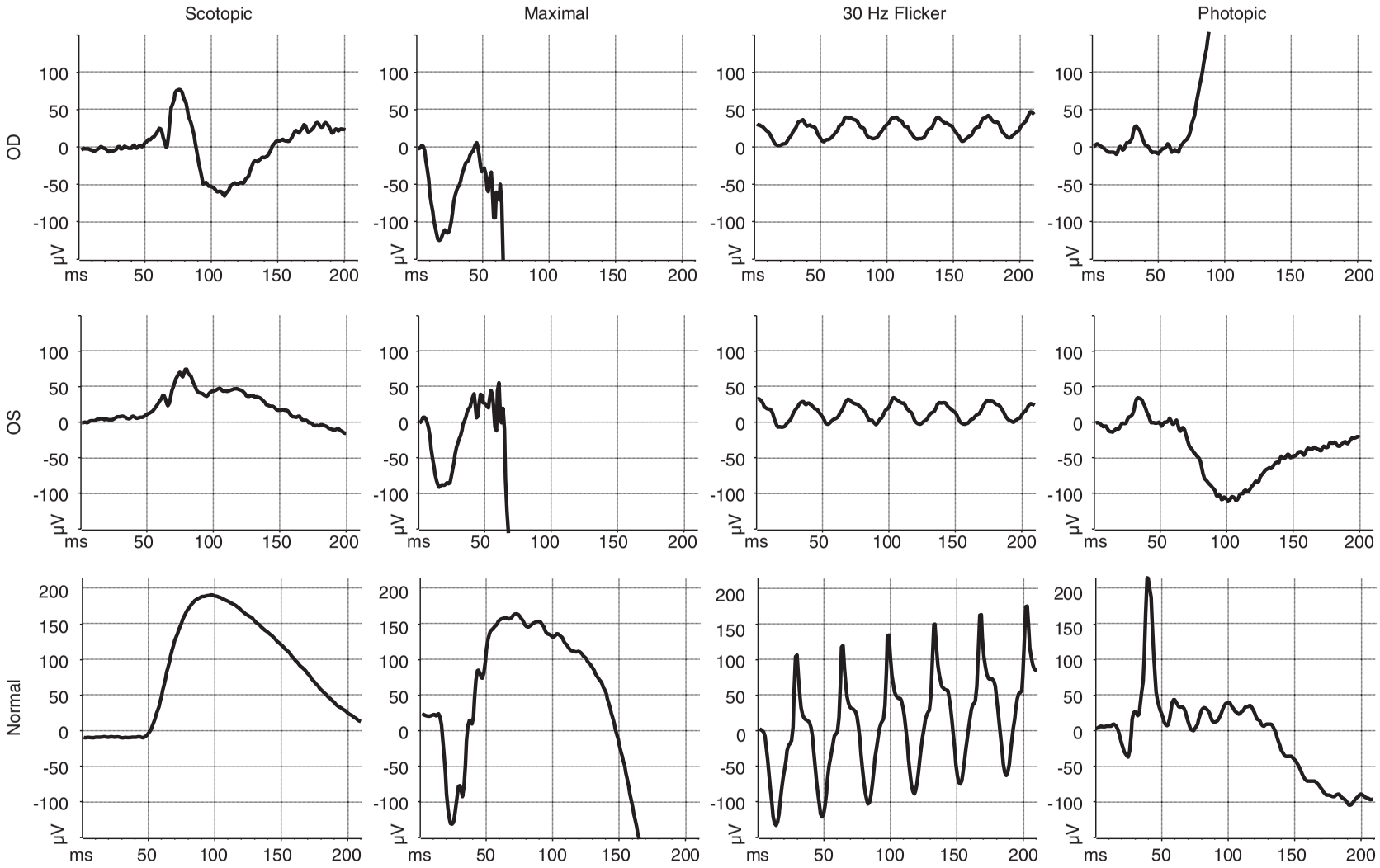

Fig. 8.3 Electroretinogram (ERG) in a female carrier of X-linked retinitis pigmentosa; note sub-normal response

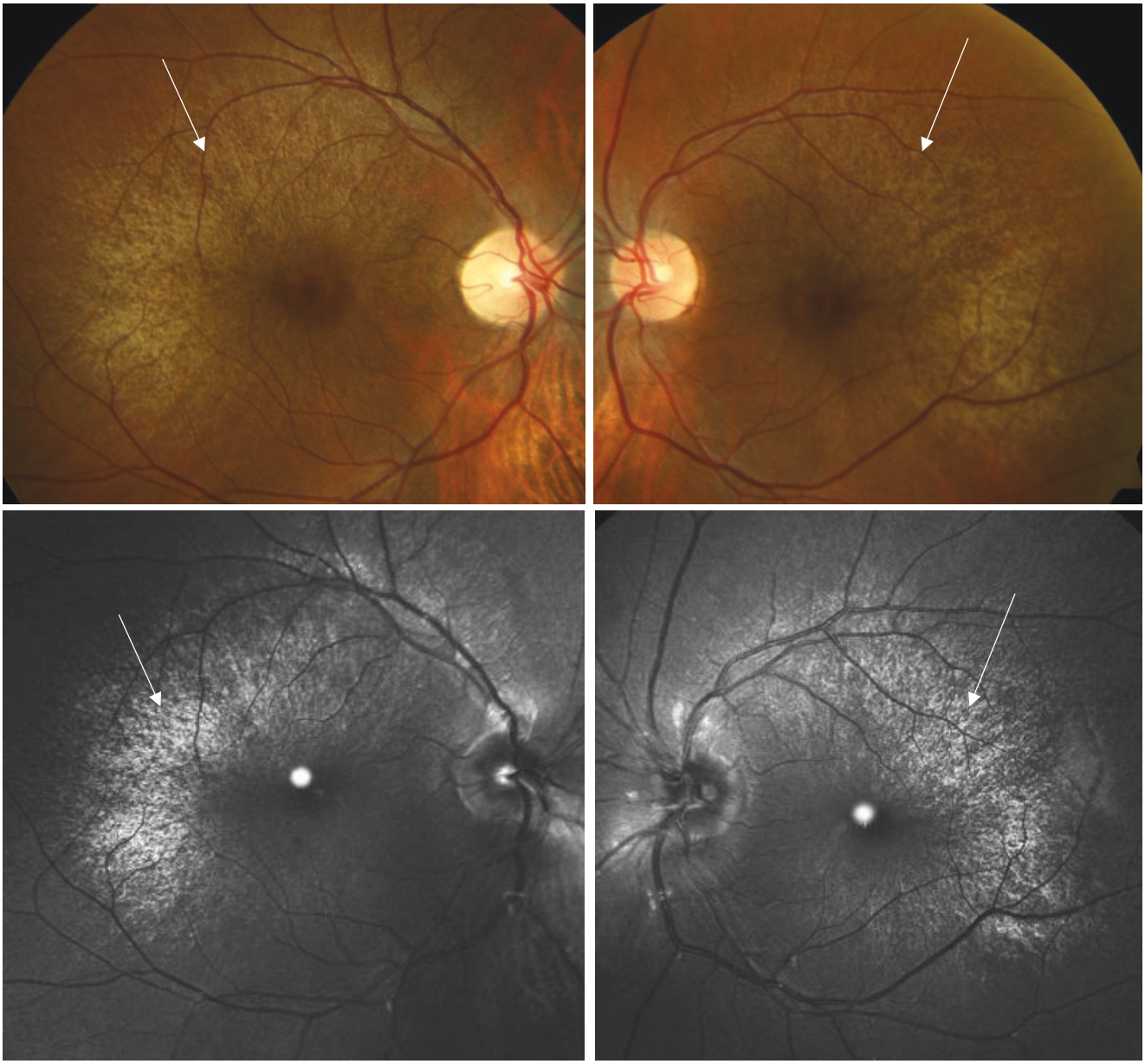

Fig. 8.4 Tapetal reflex in a female carrier of X-linked retinitis pigmentosa. The tapetal reflex can be appreciated in the perimacular region (upper temporal and temporal to fovea, *arrows*) as elongated lines formed by tiny, point-like reflexes

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CHAPTER 9

X-linked Choroideremia

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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_9

General Features

Choroideremia (CHM) is the most common X-linked hereditary choroidal dystrophy, characterized by progressive degeneration of the choriocapillaris, retinal pigment epithelium (RPE), and retina. Its prevalence is about 1 in 50,000–100,000 people.

Affected males present with impairment of night vision, usually in the first or second decade of life. Gradual peripheral field loss occurs over the next three to five decades. The disease starts with patchy areas of depigmentation ("salt and pepper" mottling) in the mid periphery; these spread centripetally. In the involved scalloped areas, there is diffuse atrophy of the choriocapillaris and RPE (Figs. 9.1 and 9.2). Underlying larger choroidal and overlying retinal blood vessels are preserved. Unlike in retinitis pigmentosa, patients with choroideremia do not show intraretinal pigmentation; the central visual acuity is preserved until the patient's 50s, and retinal blood vessels are not attenuated. The macular area remains intact until late in the disease course, with good visual acuity (Fig. 9.3). Responses on electro-

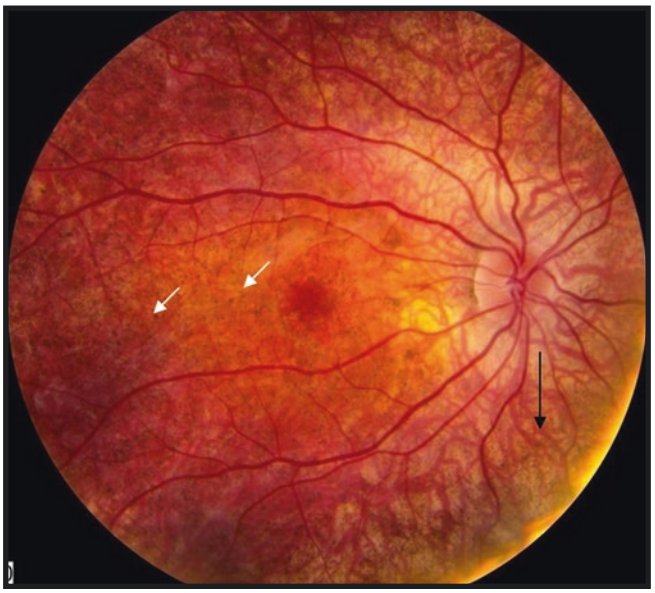

Fig. 9.1 Fundus of a 9-year-old choroideremia patient, showing "salt and pepper" appearance (*white arrows*) temporal to the macula. and visualization of large choroidal vessels below the disc (*black arrow*)

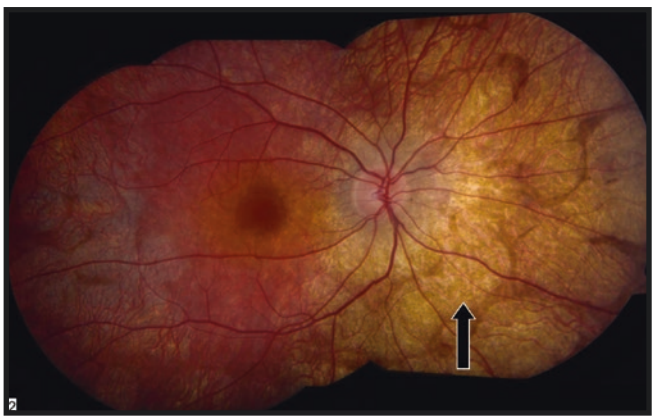

Fig. 9.2 Choroideremia. Right fundus showing patchy atrophy of the retinal pigment epithelium (RPE) (*arrow*)

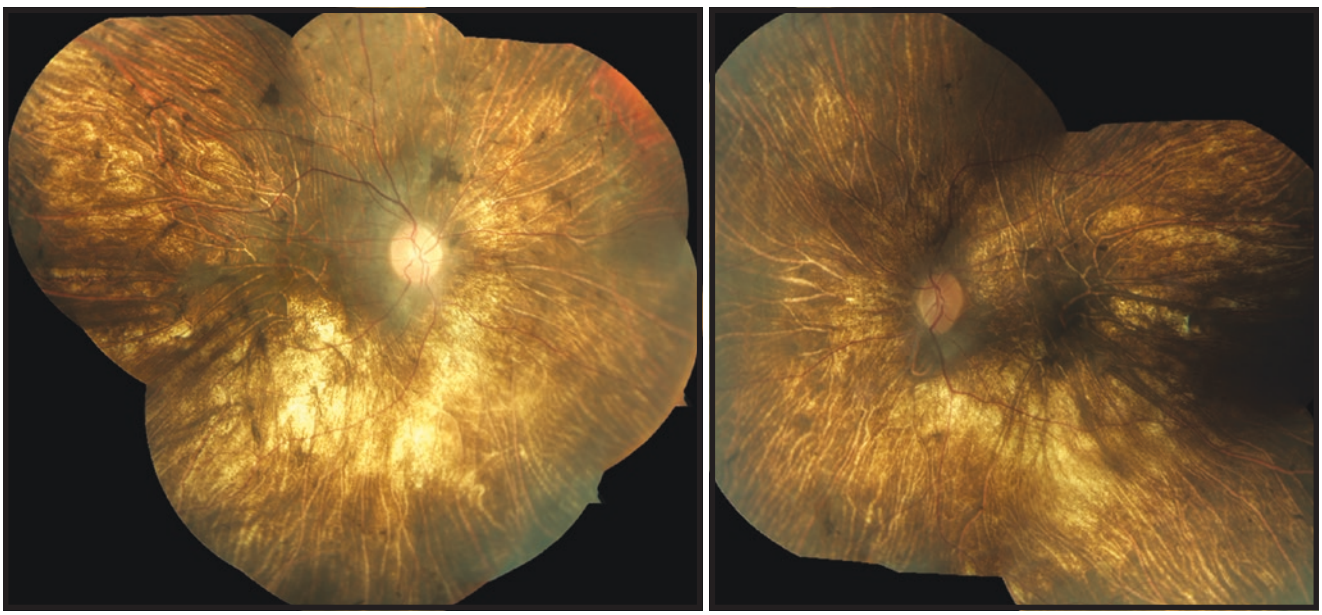

Fig. 9.3 An advanced case of choroideremia, abutting the fovea in the right eye and sparing it in the left eye

retinography (ERG) gradually become extinguished in the late stage. The end stage of choroideremia, however, resembles the end stage of RP.

In gyrate atrophy, the margin of the scalloped areas is well demarcated, with hyperpigmentation of the remaining RPE.

Imaging and Tests

- **Fluorescein angiogram** (Fig. 9.4) shows diffuse loss of choriocapillaris throughout, except for the macular area.
- **Visual field** (Fig. 9.5) reveals ring scotoma at the mid-periphery to start with; the scotomas later progress to complete loss of the peripheral field.
- **Fundus autofluorescence (FAF)** (Fig. 9.6) typically shows loss of fluorescence in areas of chorioretinal atrophy and an intact RPE/choriocapillaris patch in the macular area.
- **Optical coherence tomography (OCT)** (Fig. 9.7) images showing histopathological changes seen in choroideremia. The affected retina shows areas of RPE and choriocapillaris atrophy and corresponding thinning of outer retinal layers. In some cases, outer retinal tubulations occur, denoting end-stage photoreceptor degeneration.

Female Carriers

Heterozygous females may show RPE mottling in the mid-periphery ("moth-eaten" appearance) or radial bands that course from the equatorial retina toward periphery (Figs. 9.8 and 9.9), but their vision and ERG remain normal. Rarely, a

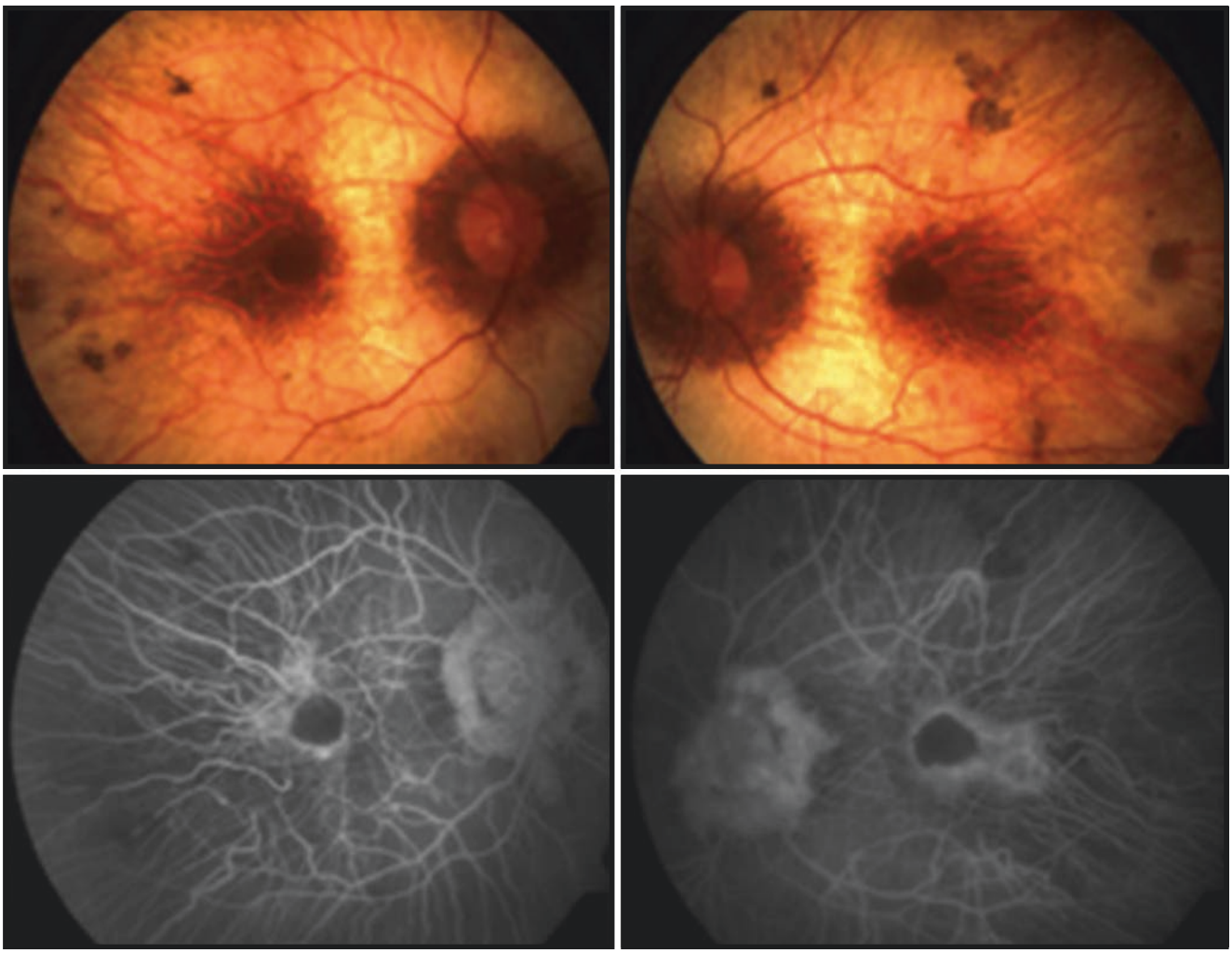

Fig. 9.4 Sparing of the macula in choroideremia; a fluorescein angiogram shows diffuse atrophy of the choriocapillaris throughout, except for the macula

female carrier might show changes like those of affected male patients, as a result of random inactivation of the wild type of X chromosome, known as *lyonization*.

Molecular Genetics

Choroideremia is caused by a mutation in the *CHM* gene, which encodes for a geranylgeranyl transferase Rab escort protein-1 (REP-1 protein). Rab proteins are involved in intracellular trafficking; as an escort protein, REP-1 attaches to Rab proteins in the cells and directs them to the membranes of various cell organelles. Mutations in the REP-1 protein affect intracellular trafficking, so the cells die prematurely.

More than 140 mutations in the *CHM* gene have been found to cause choroideremia. Most mutations result in protein truncation by replacement of an arginine residue with a stop codon. The cytogenetic location is Xq21.2, the long arm of the X chromosome at position 21.2.

Gene Therapy Trials

The *ClinicalTrials.gov* website lists three trials of gene therapy for XLRP that are currently recruiting (as of January 2, 2018):

- Natural History of the Progression of Choroideremia Study (NIGHT) (ClinicalTrials.gov Identifier: NCT03359551)
- "Natural History" Study of Choroideremia (ClinicalTrials.gov Identifier: NCT02994368)
- REP1 Gene Replacement Therapy for Choroideremia (REGENERATE) (ClinicalTrials.gov Identifier: NCT02407678)

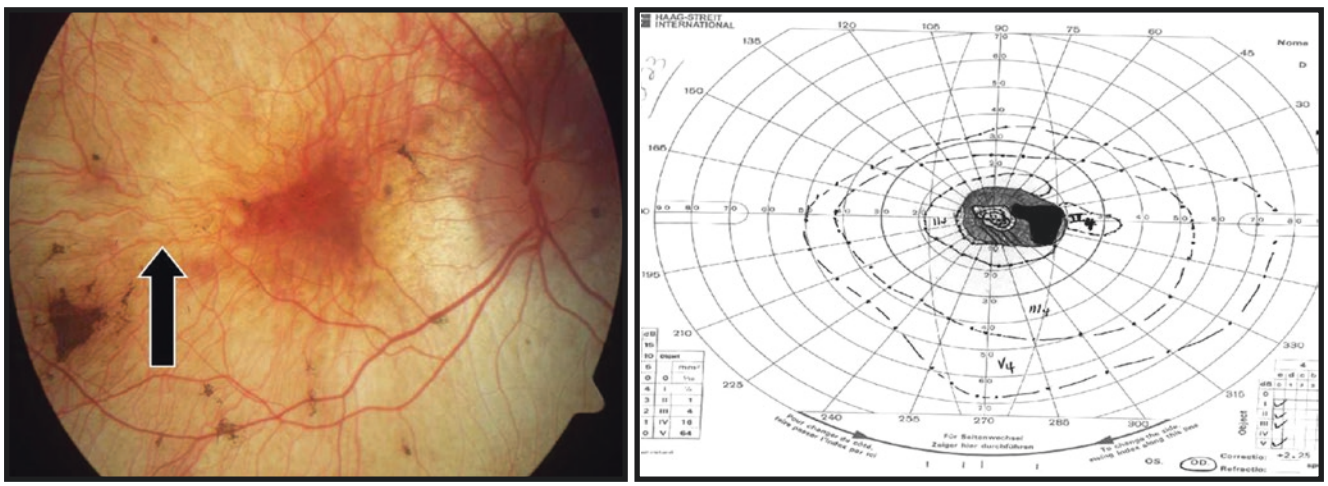

Fig. 9.5 Fundus showing severe atrophy of the RPE and choriocapillaris, allowing white sclera and choroidal blood vessels to be visible (*arrow*); the visual field shows scotomas (*shaded areas*)

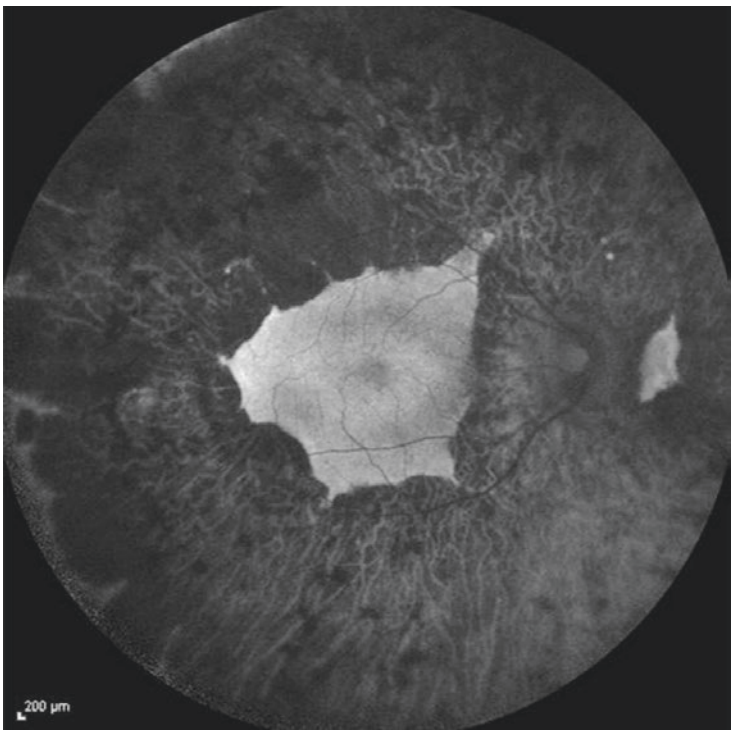

Fig. 9.6 Fundus autofluorescence shows an intact RPE patch at the macula

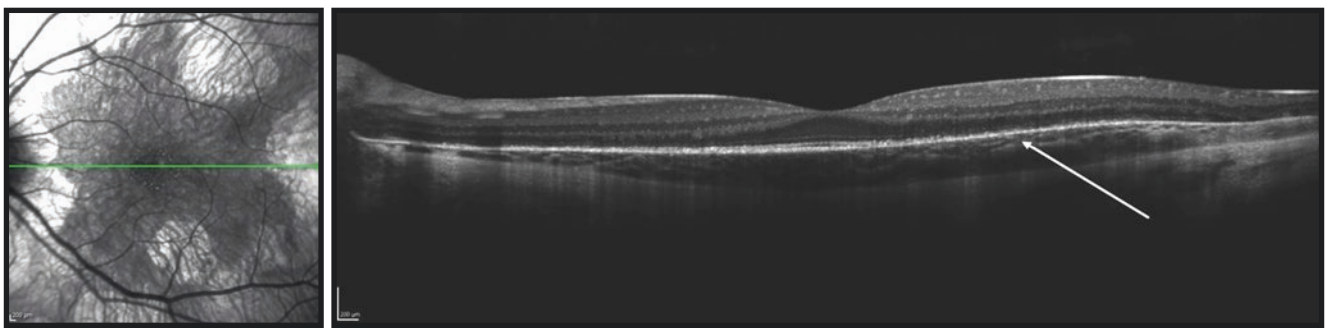

Fig. 9.7 Optical coherence tomogram (OCT) showing atrophy of the RPE and choriocapillaris (*arrow*)

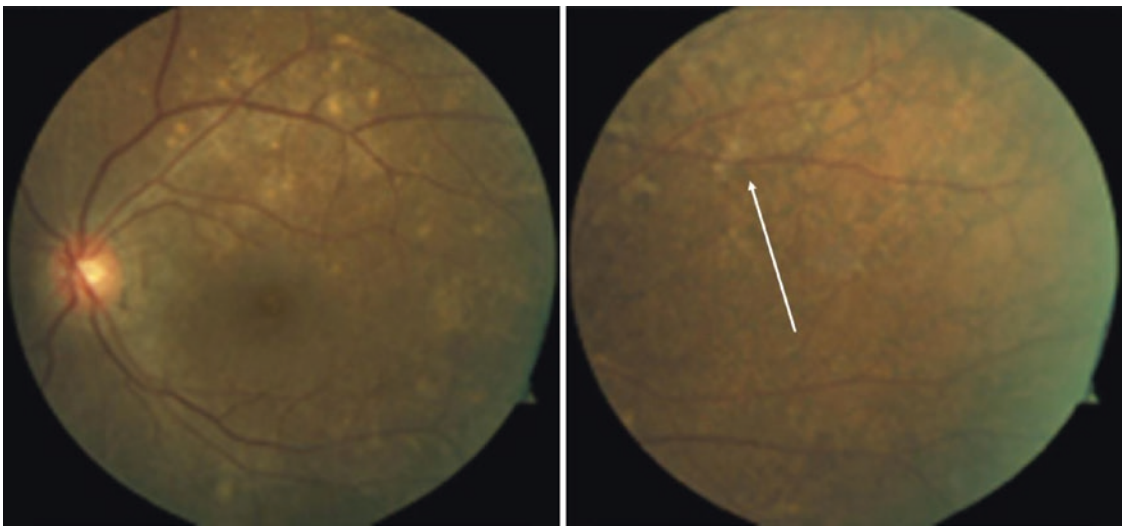

Fig. 9.8 In this female carrier of choroideremia, the fundus shows RPE mottling, predominantly in the periphery (*arrow*)

Fig. 9.9 In this female carrier of choroideremia, autofluorescence shows speckling of the RPE (*arrow*)

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CHAPTER 10

X-linked Juvenile Retinoschisis

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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_10

General Features

X-linked juvenile retinoschisis (XLRS) occurs exclusively in males and is characterized by visual loss that begins in early childhood; patients are usually school-age and are experiencing visual disturbances, especially in reading. The prevalence is estimated to be 1 in 5000–25,000 men, worldwide. XLRS has complete penetrance but variable expressivity. Carrier females generally remain asymptomatic.

The characteristic finding is foveal schisis: stellate or fine radial striae in a sort of spoke-like pattern (Fig. 10.1) due to small cystoid spaces. Unlike cystoid macular edema, these spaces do not leak on a fluorescein angiogram. The peripheral retina may show retinal pigment epithelial (RPE) alteration (Fig. 10.2). The splitting occurs predominantly within the inner retinal layers (neural retina) (Fig. 10.3). Visual acuity remains stable in most instances to 20/200.

Peripheral retinoschisis is present in about half of patients, and is visible as large holes, which may be so large as to extend from the arcade to the equator. In the inner retina, the retinal blood vessels are freely floating. Rarely, these vessels rupture and patients present with vitreous hemorrhage; retinal detachment occurs infrequently.

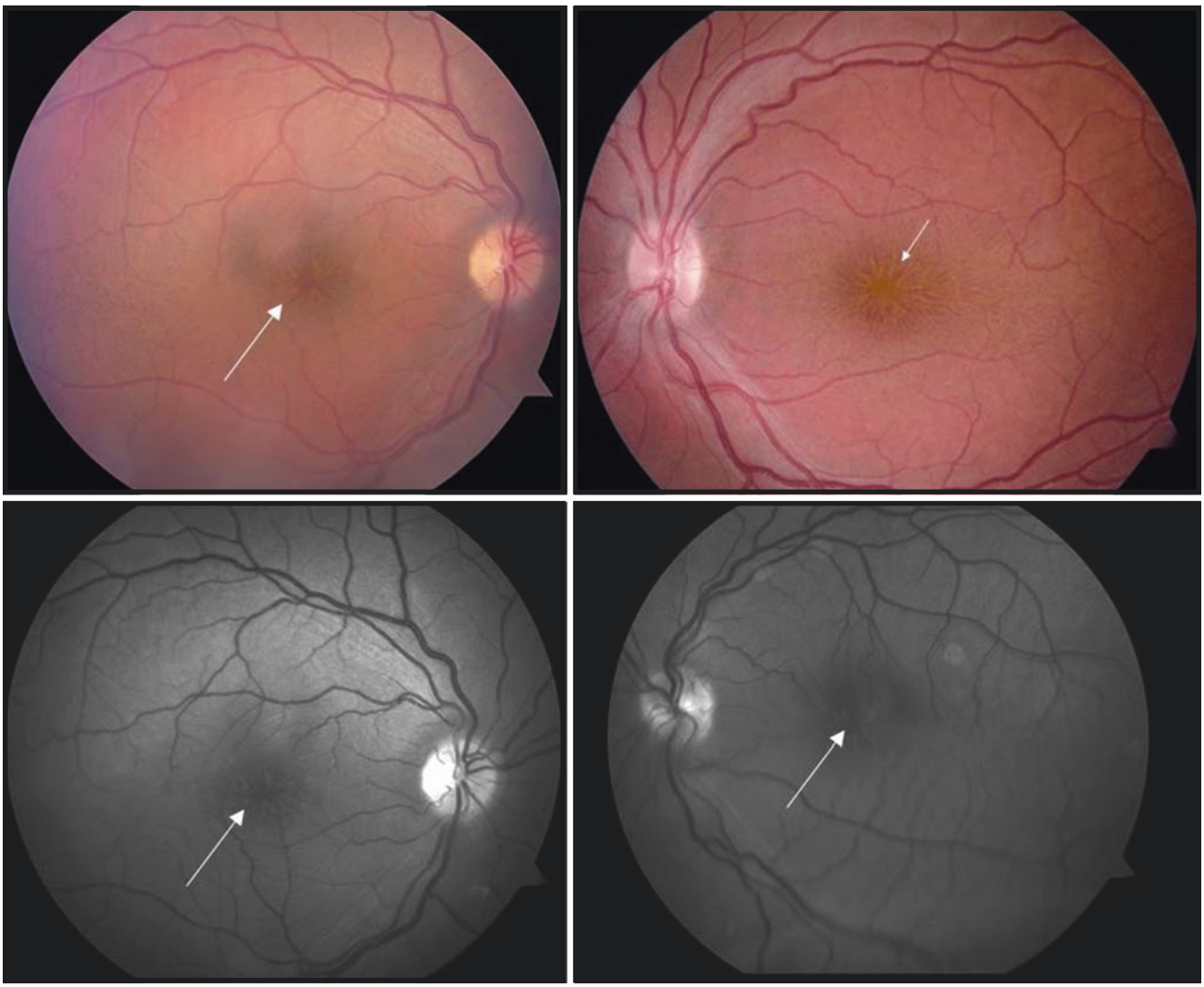

Fig. 10.1 X-linked juvenile retinoschisis. The central macula shows cystic changes around the fovea, in a spoke-like pattern (*arrows*)

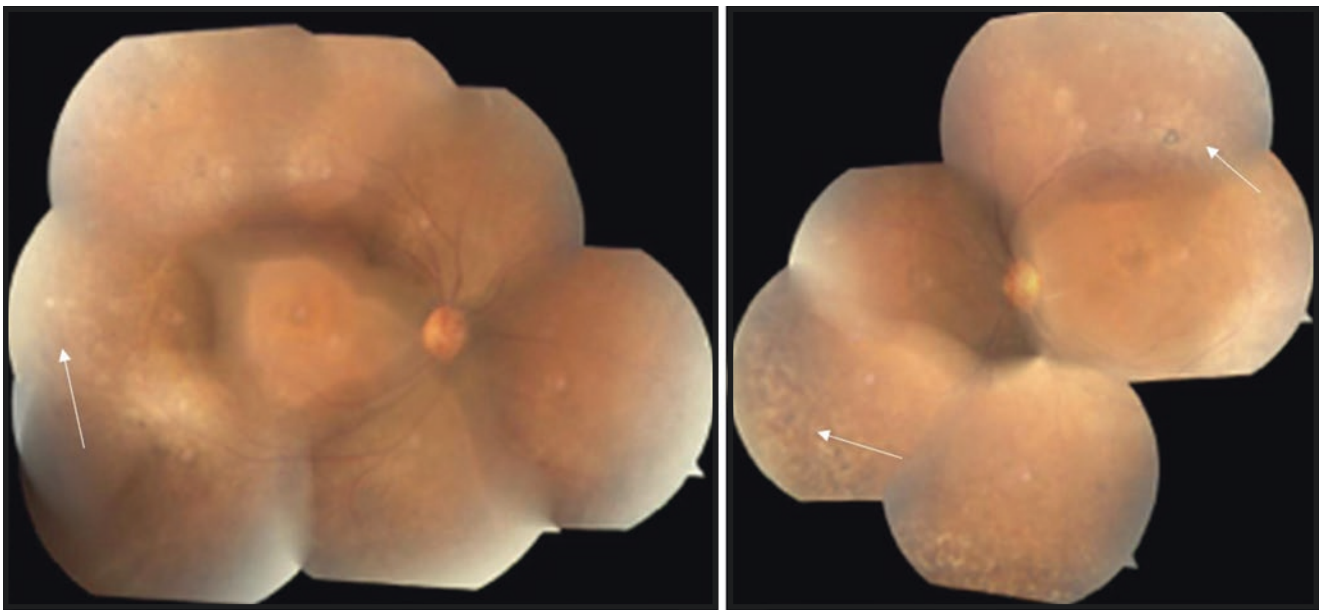

Fig. 10.2 X-linked juvenile retinoschisis. Besides cystic changes at the macula, the peripheral retina shows retinal pigment epithelial (RPE) alteration or mottling (*arrows*)

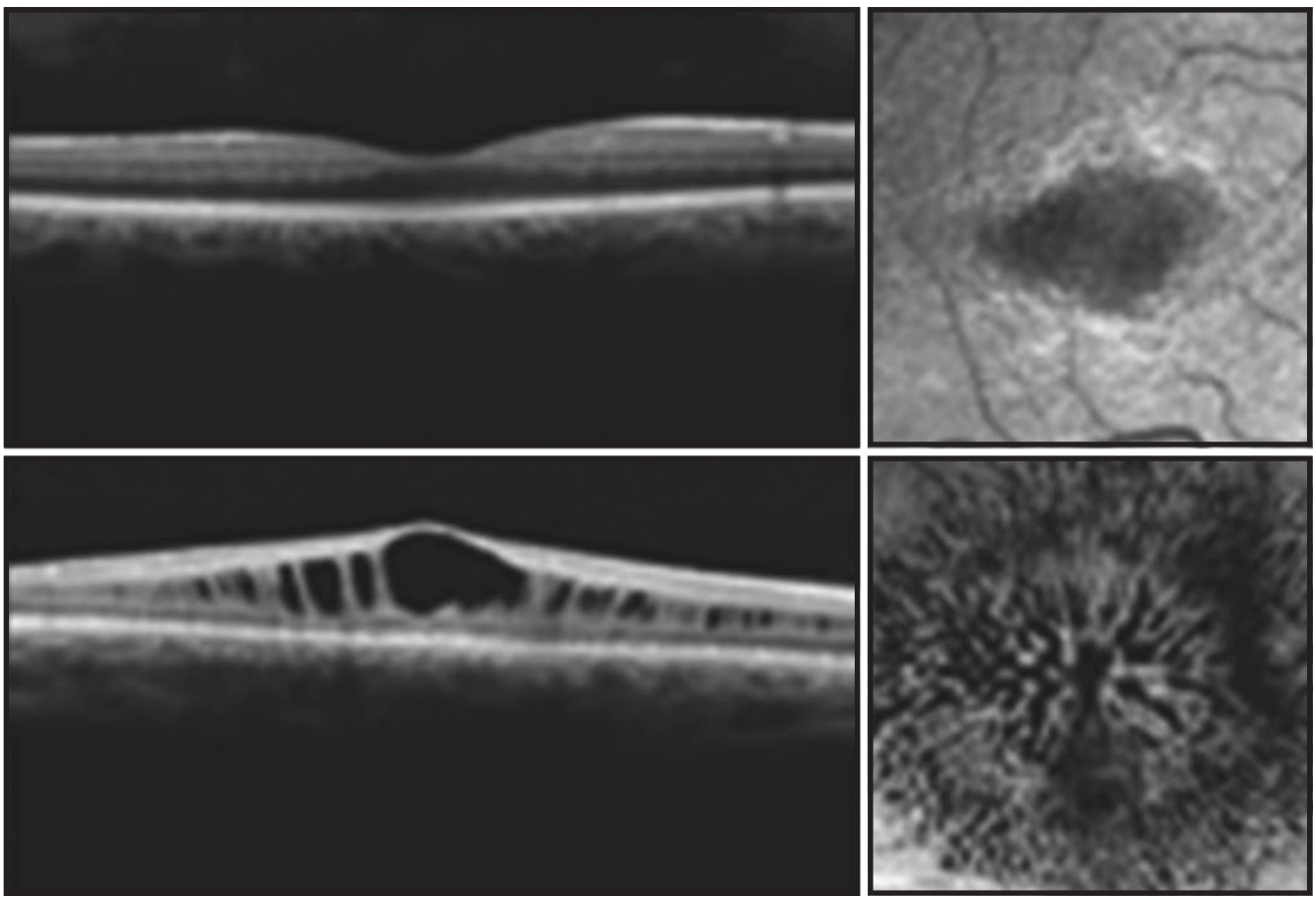

Fig. 10.3 Conventional and en-face optical coherence tomography (OCT) of a normal control (*upper row*) and a patient with (XLRS) (*lower row*). The conventional OCT (*lower left*) shows inner layer schisis, and en-face OCT (*lower right*) shows a cystic labyrinth

Imaging and Tests

- **Fundus autofluorescence (FAF)** shows modification of normal foveal autofluorescence with a radial pattern (Fig. 10.4). Over time, FAF can document progression in terms of RPE changes (Fig. 10.5).

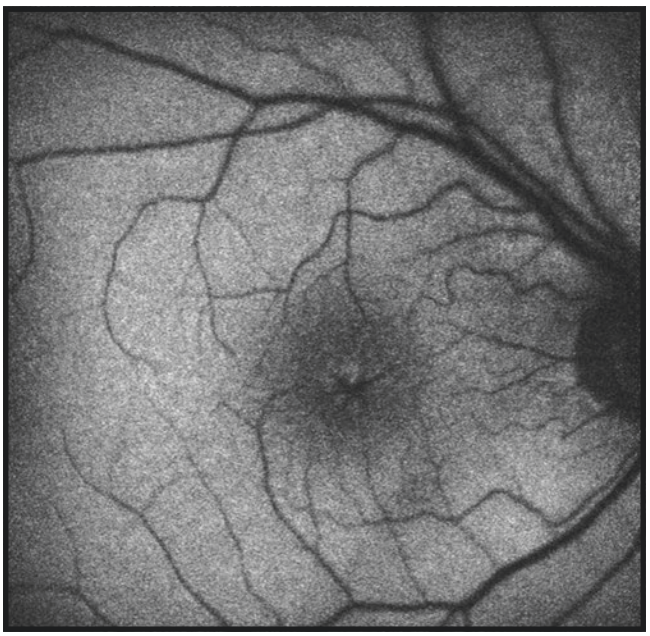

Fig. 10.4 Fundus autofluorescence (FAF) shows a radial pattern of hypofluorescence around the fovea in a patient with XLRS

- **Electroretinography (ERG)**: Negative waveform. The a-wave is preserved, but the amplitude of the b-wave is reduced; the alteration of the ratio of these waves (a-wave amplitude exceeding the b-wave amplitude) is an important diagnostic feature (Fig. 10.6). Multifocal ERG also demonstrates reduced amplitude, along with longer implicit time in the central macular area.

Molecular Genetics

The gene responsible for X-linked juvenile retinoschisis is *RS1*, which encodes a protein called retinoschisin; this protein is important for cell adhesion among all neuronal cells, including Müller cells. *RS1* gene mutations cause a complete loss of functional retinoschisin protein, so the maintenance and organization of cells in the retina is disrupted. As a result, the retina splits.

About 220 mutations of the *RS1* gene have been reported. Most mutations change one protein building block (amino acid) in the retinoschisin protein. The cytogenetic location is Xp22.13, the short arm of the X chromosome at position 22.13.

Treatments

Oral Acetazolamide

In selected patients, cystic spaces respond to oral acetazolamide and become less in size (Fig. 10.7).

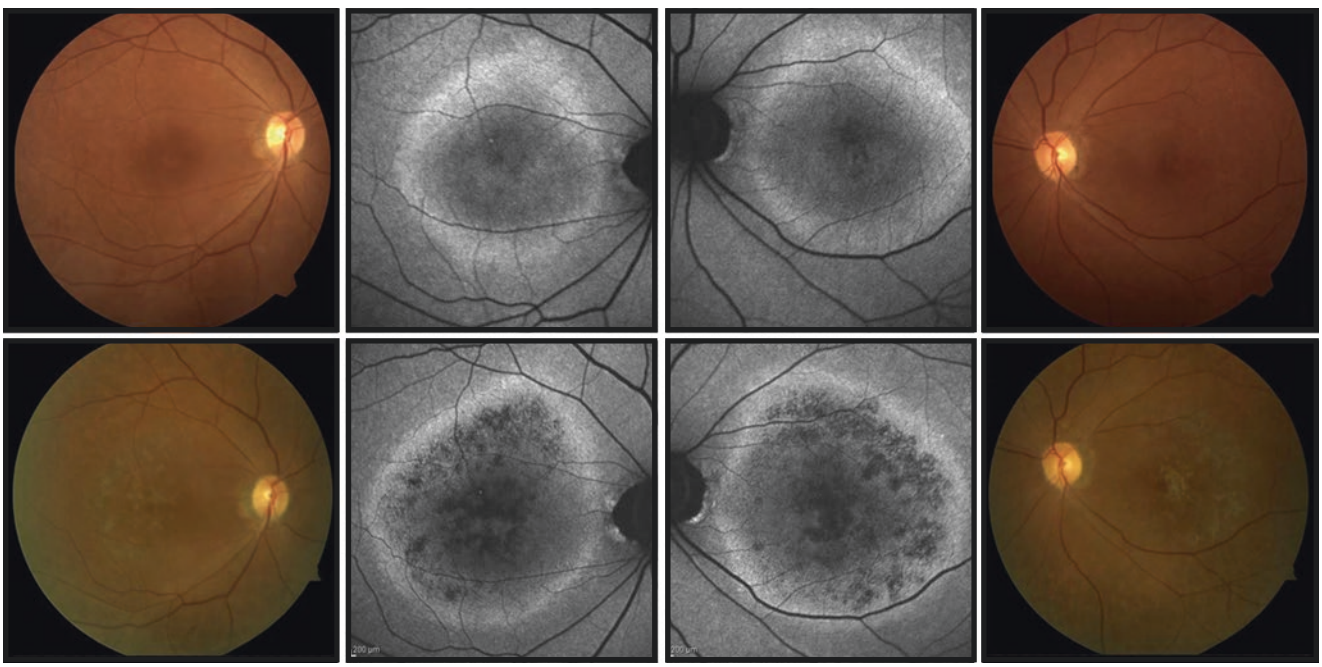

Fig. 10.5 Progression of XLRS as seen from an autofluorescence ring and RPE alteration

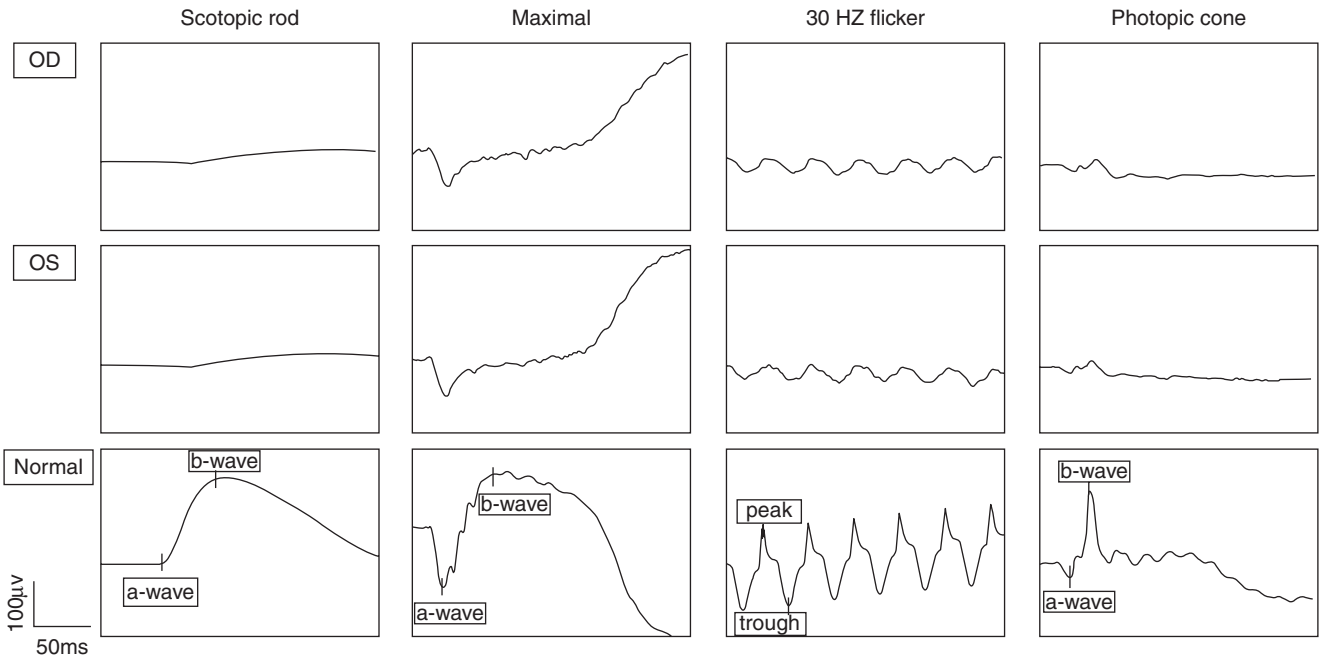

Fig. 10.6 Bilateral Electronegative waveforms in a patient with XLRS: b-waves amplitude are smaller than a-waves (marked reduction in "b" to "a" amplitude ratio); 30 Hz flicker ERG are delayed and of subnormal amplitude

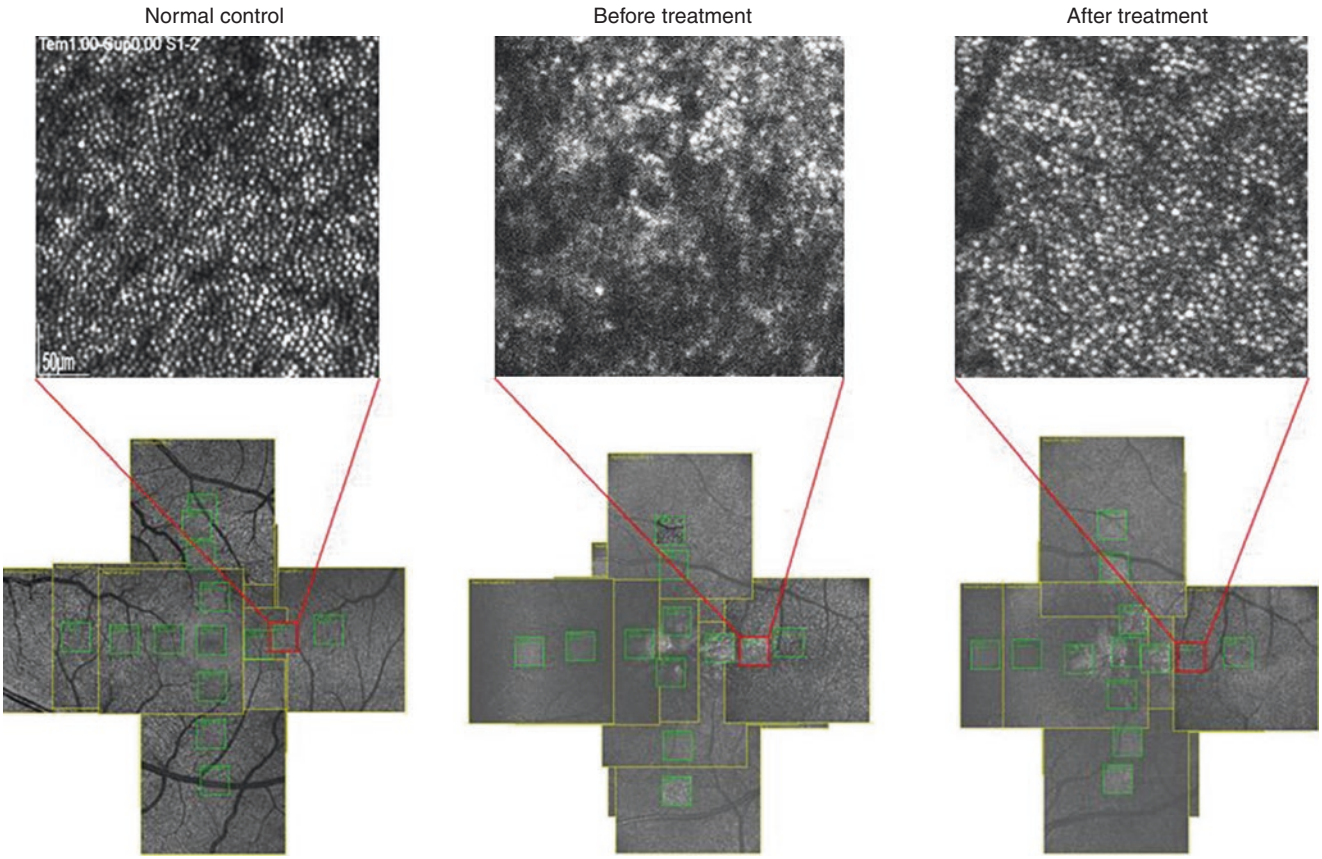

Fig. 10.7 Adaptive optics scanning laser ophthalmoscopy (SLO) showing imaging of a cone mosaic after treatment of XLRS with acetazolamide; the cone mosaic could not be imaged prior to treatment because of cystic cavities in the inner retina

Vitreoretinal Surgery

Patients who develop vitreous hemorrhage or rhegmatogenous retinal detachment may benefit from vitreoretinal surgery.

Gene Therapy

The *ClinicalTrials.gov* website lists three trials of gene therapy for XLRS that are currently recruiting (as of January 2, 2018):

- Safety and Efficacy of rAAV-hRS1 in Patients With X-linked Retinoschisis (XLRS) (ClinicalTrials.gov Identifier: NCT02416622)
- Clinical and Genetic Studies of X-Linked Juvenile Retinoschisis (ClinicalTrials.gov Identifier: NCT00055029)
- Study of RS1 Ocular Gene Transfer for X-linked Retinoschisis (ClinicalTrials.gov Identifier: NCT02317887)

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CHAPTER 11

X-linked Ocular Albinism

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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_11

General Features

The prevalence of X-linked ocular albinism (XLOA) is about 1 in 60,000 males. It affects only the eyes; the color of the skin and hairs are normal. Patients usually present with reduced vision, photophobia, nystagmus, and strabismus. Many patients have problem in perceiving depth (stereoscopic vision). The visual loss is permanent, but XLOA is a nonprogressive disorder and visual acuity remains stable throughout life.

Slit-lamp examination reveals a hypopigmented iris showing transillumination defect. The fundus shows hypopigmented fundus revealing underlying large choroidal blood vessels and foveal hypoplasia with no foveal reflex and no luteal pigment (Fig. 11.1). Flash and pattern visual evoked potential (VEP) shows an asymmetric occipital response, in view of the greater number of decussating fibers at the optic chiasma.

Female Carriers

A heterozygous female carrier of ocular albinism may show iris transillumination and a pattern of hypopigmentation and hyperpigmentation in the fundus, in a sort of mosaic pattern (Fig. 11.2).

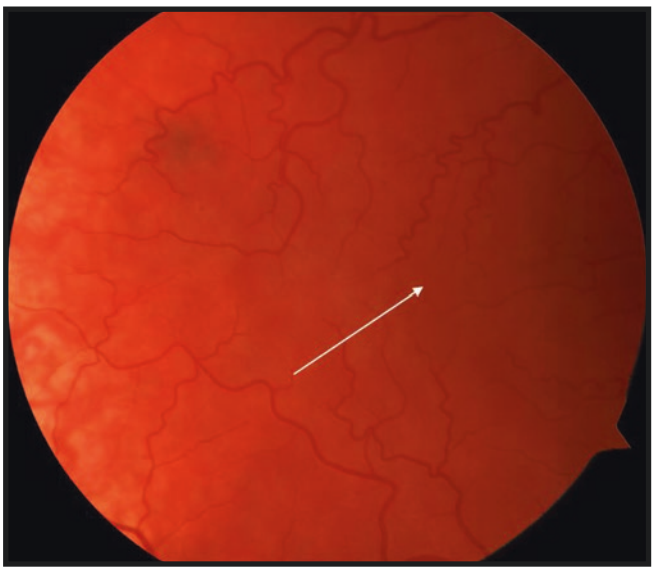

Fig. 11.1 A case of ocular albinism, with absent foveal reflex (*arrow*) and failure of retinal vasculature to wreathe the fovea

Oculocutaneous Albinism

Oculocutaneous albinism (OCA) is inherited in an autosomal recessive fashion; the estimated prevalence is about 1 in 20,000 people. In OCA, there is either a reduction or a complete absence of melanin pigment in the skin, hair, and eyes. Affected individuals have increased risk of skin damage (including skin melanoma) on long-term sun exposure.

Several types of OCA have been identified, depending on the gene and mutation involved (see below):

- Type 1: White hair, pale skin, and light-colored irises
- Type 2: Less severe than type 1; the skin is creamy white, and the hair is light yellow, blond, or light brown
- Type 3: Usually affects dark-skinned individuals and is also known as rufous oculocutaneous albinism; individuals have reddish-brown skin, red hair, and brown irises. Visual problems are milder than in other forms.
- Type 4: Features are similar to Type 2.

OCA is associated with two syndromes:

- **Hermansky-Pudlak syndrome** can feature easy bruising and severe bleeding due to a defect in platelet adhesion.
- **Chédiak–Higashi syndrome** can cause severe infection due to neutropenia or bleeding due to thrombocytopenia.

Molecular Genetics

Ocular Albinism

Ocular albinism is caused by mutations in the G protein-coupled receptor 143 (*GPR143*) gene, also known as *OA1*. Most of the mutations in the *GPR143* gene alter the size or shape of the GPR143 protein; this protein controls the growth of melanosomes, a cellular structure that produces and stores melanin pigment. Without functional GPR143 protein, melanosomes can grow abnormally large (macromelanosomes); how these large melanosomes are related to vision loss and other eye abnormalities is not yet known.

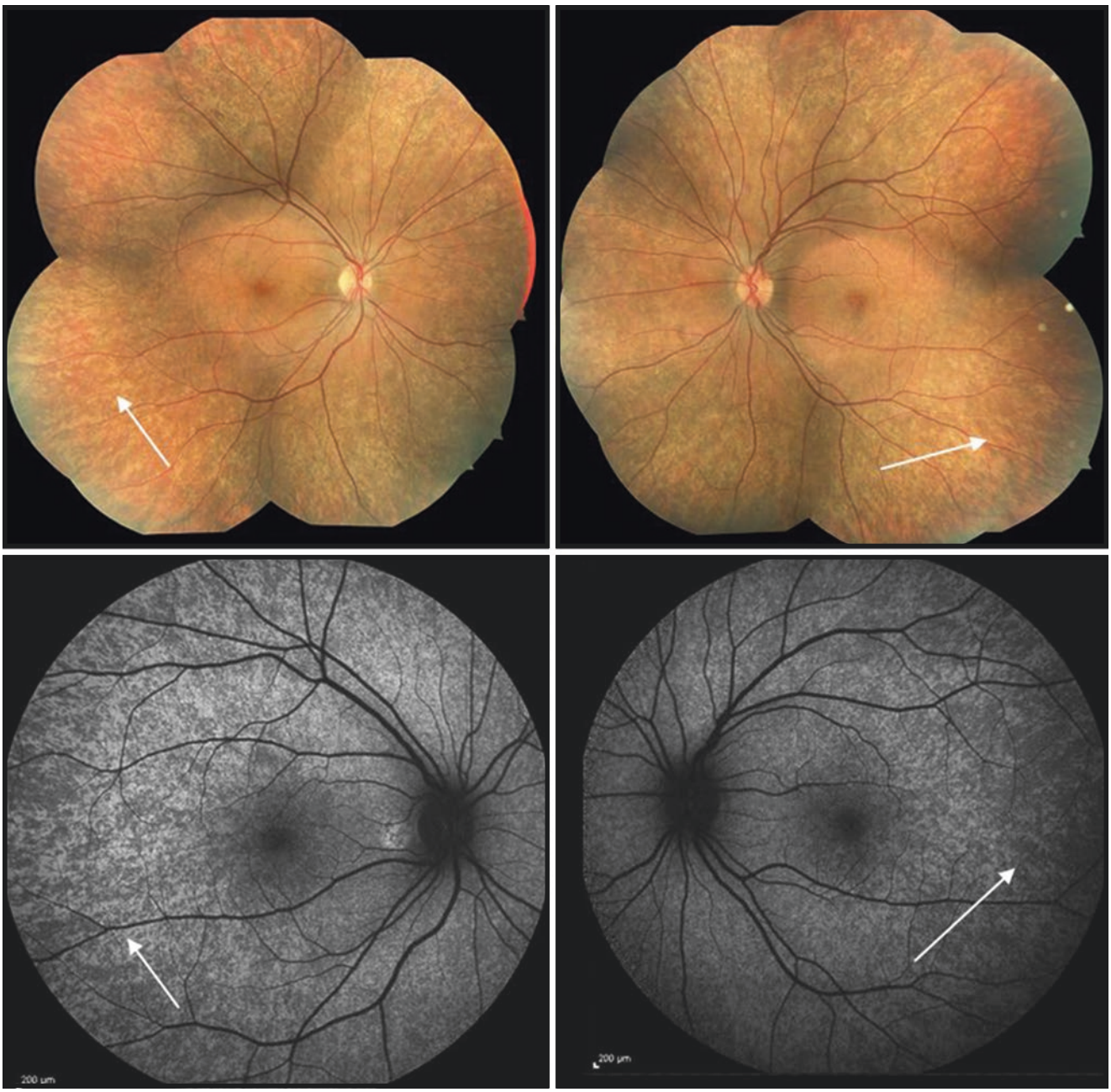

Fig. 11.2 Carrier of ocular albinism, showing areas of retinal pigment epithelial (RPE) mosaicism on color photographs (*arrows*). Autofluorescence shows radially distributed reflex as "mud-splatter" (*arrows*)

More than 60 *GPR143* mutations have been identified, resulting in the most common form of ocular albinism, called the Nettleship-Falls type or type 1. The cytogenetic location is Xp22.2, the short arm of the X chromosome at position 22.2.

Oculocutaneous Albinism

The enzyme tyrosinase is produced by the *TYR* gene, and this enzyme (located in the melanocytes) is needed for the synthesis of melanin. Tyrosinase converts a protein building block, the

amino acid tyrosine, to another compound called dopaquinone, and a series of other reactions converts dopaquinone to melanin. The cytogenetic location is 11q14.3, the long arm of chromosome 11 at position 14.3.

Various mutations in *TYR* are responsible for the types of OCA:

Type 1: *TYR* gene
Type 2: *OCA2* gene
Type 3: *TYRP1* gene
Type 4: *SLC45A2* gene

Suggested Reading

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CHAPTER 12

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

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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).

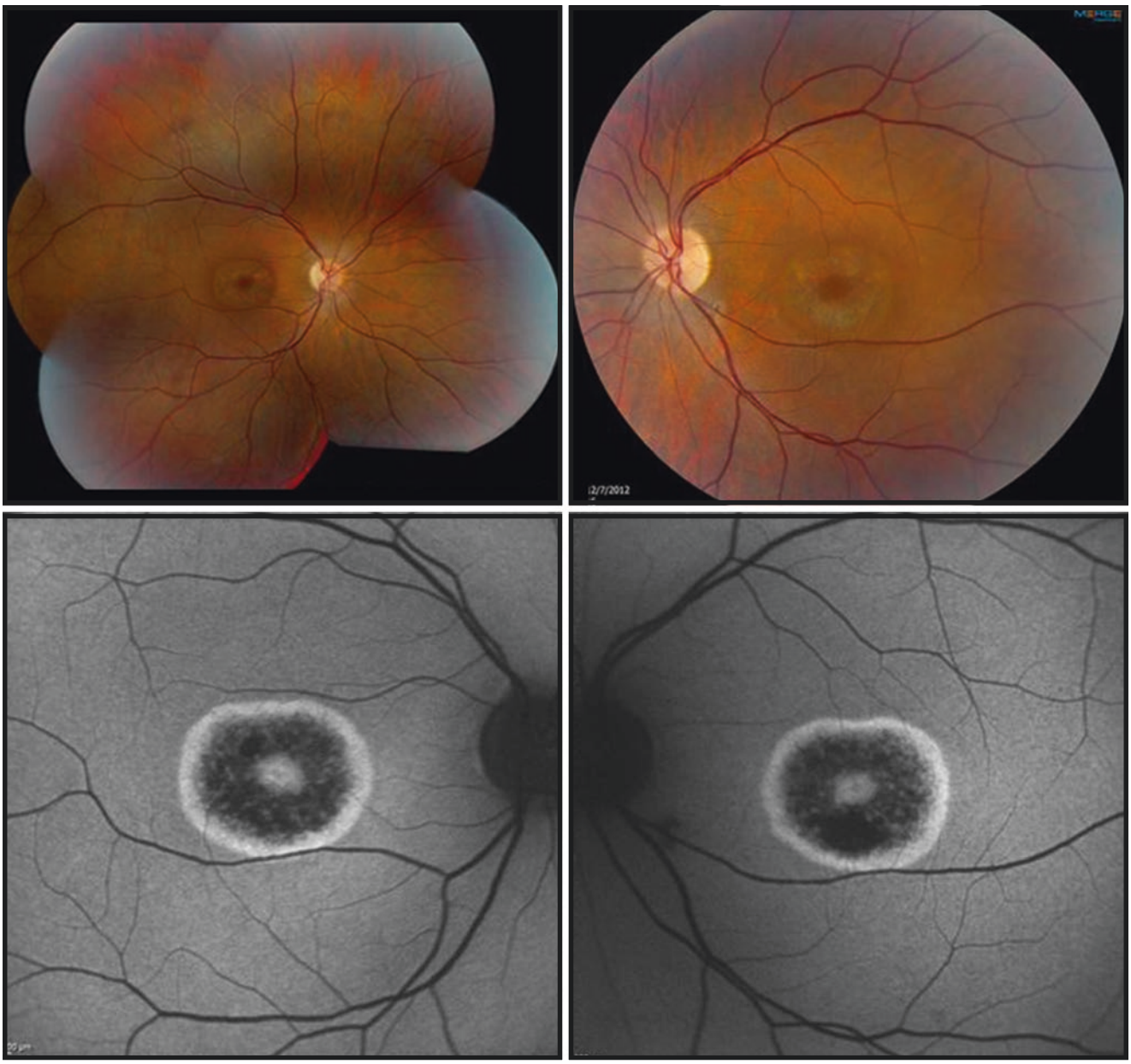

Fig. 12.1 A classic BEM in both eyes on color fundus photograph and corresponding FAF, areas of hypofluorescence surrounded by a ring of hyperfluorescence

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.

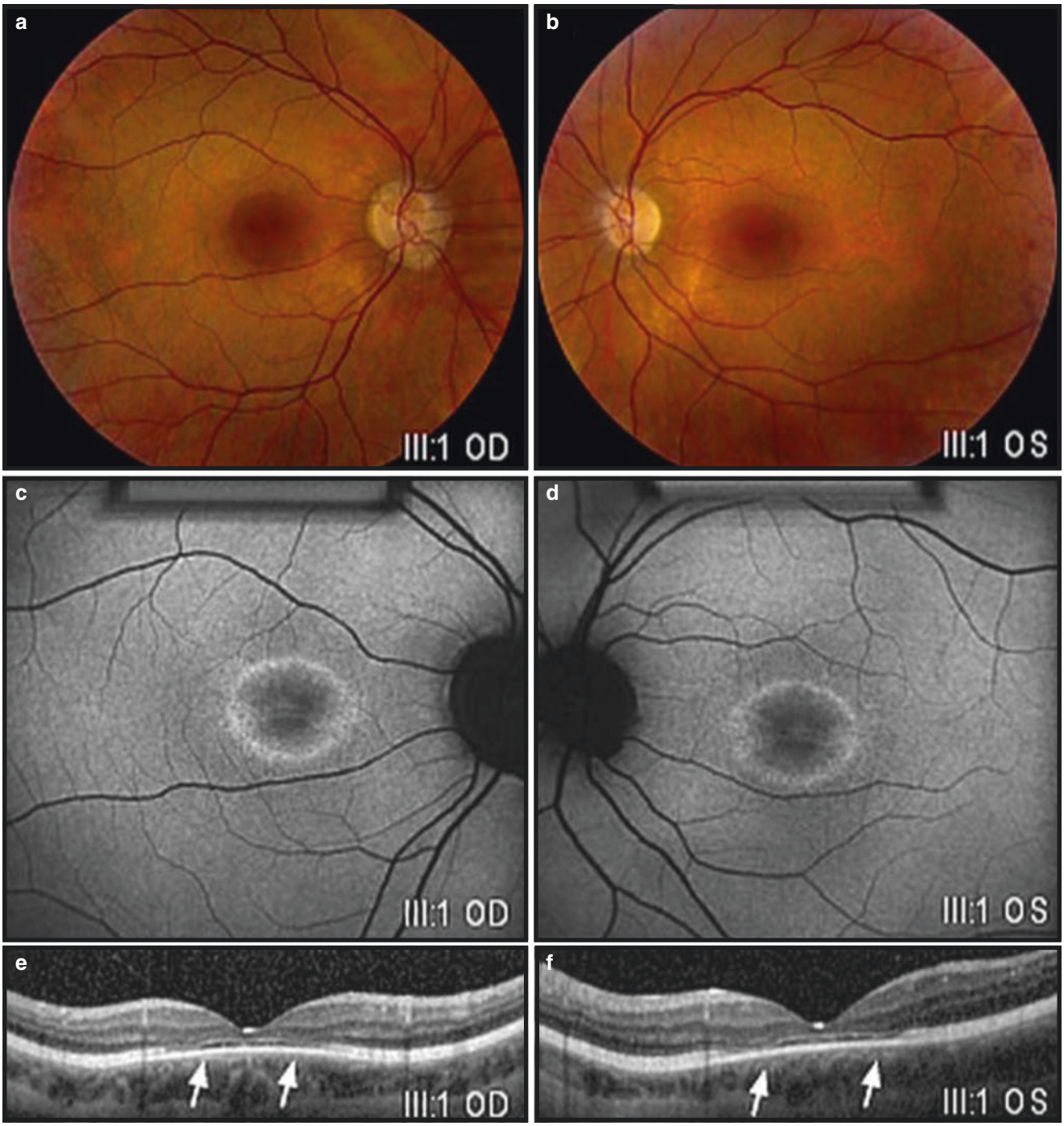

Fig. 12.2 A classic bull's eye maculopathy (BEM) on color fundus photograph (*upper row*). FAF (*middle row*) shows central hypofluorescence surrounded by a ring of hyperfluorescence. OCT (*lower row*) shows foveal thinning with loss of photoreceptors, loss of EZ line, loss of outer nuclear layer, and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

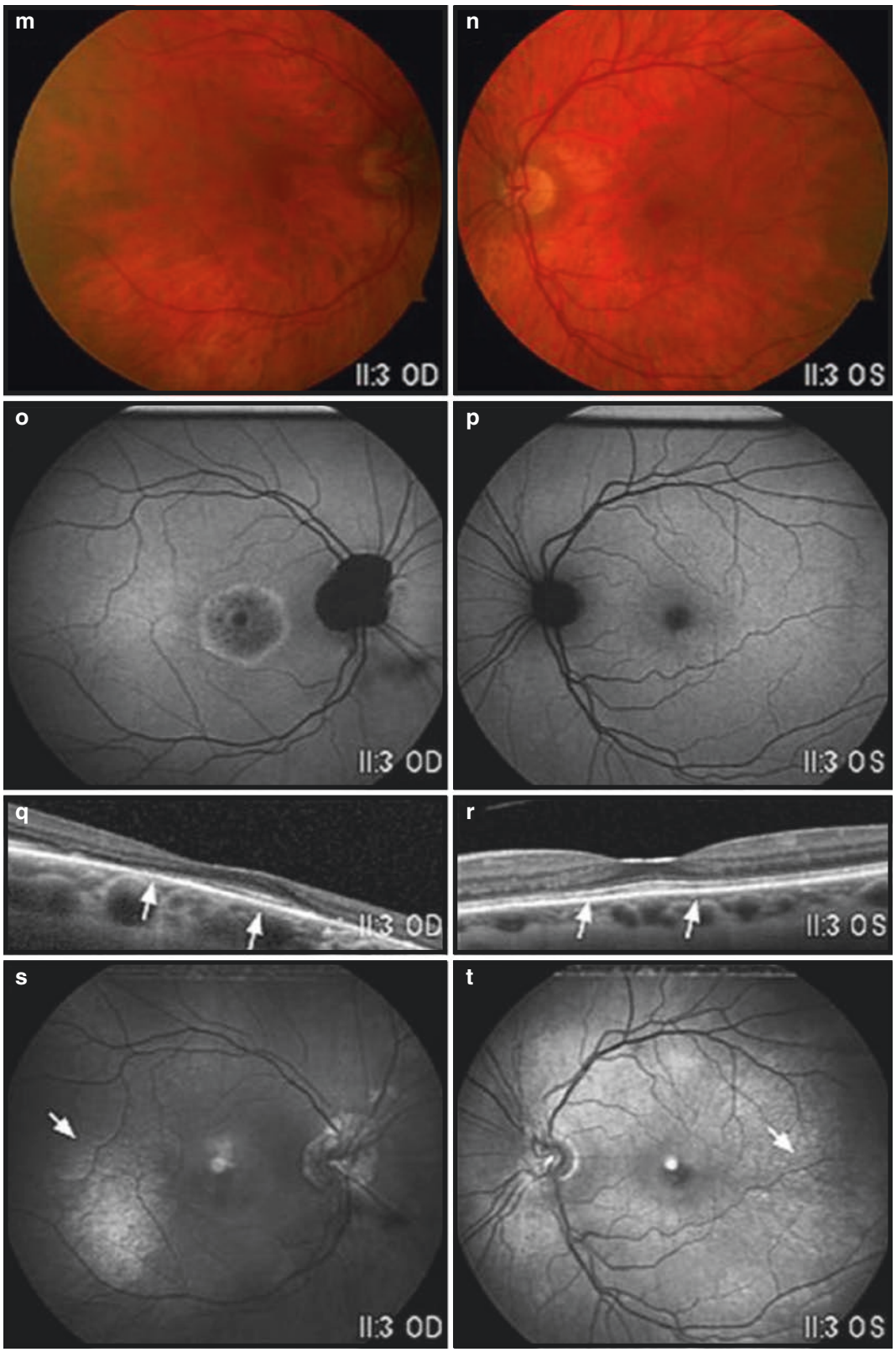

Fig. 12.3 Color photograph (*first row*) of a carrier, minimal RPE changes in the right macula, and the left looks normal. FAF (*second row*) shows bull's eye pattern with peripapillary atrophy in the right eye, and the left eye is normal. OCT (*third row*) shows disruption of EZ line in the perifoveal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

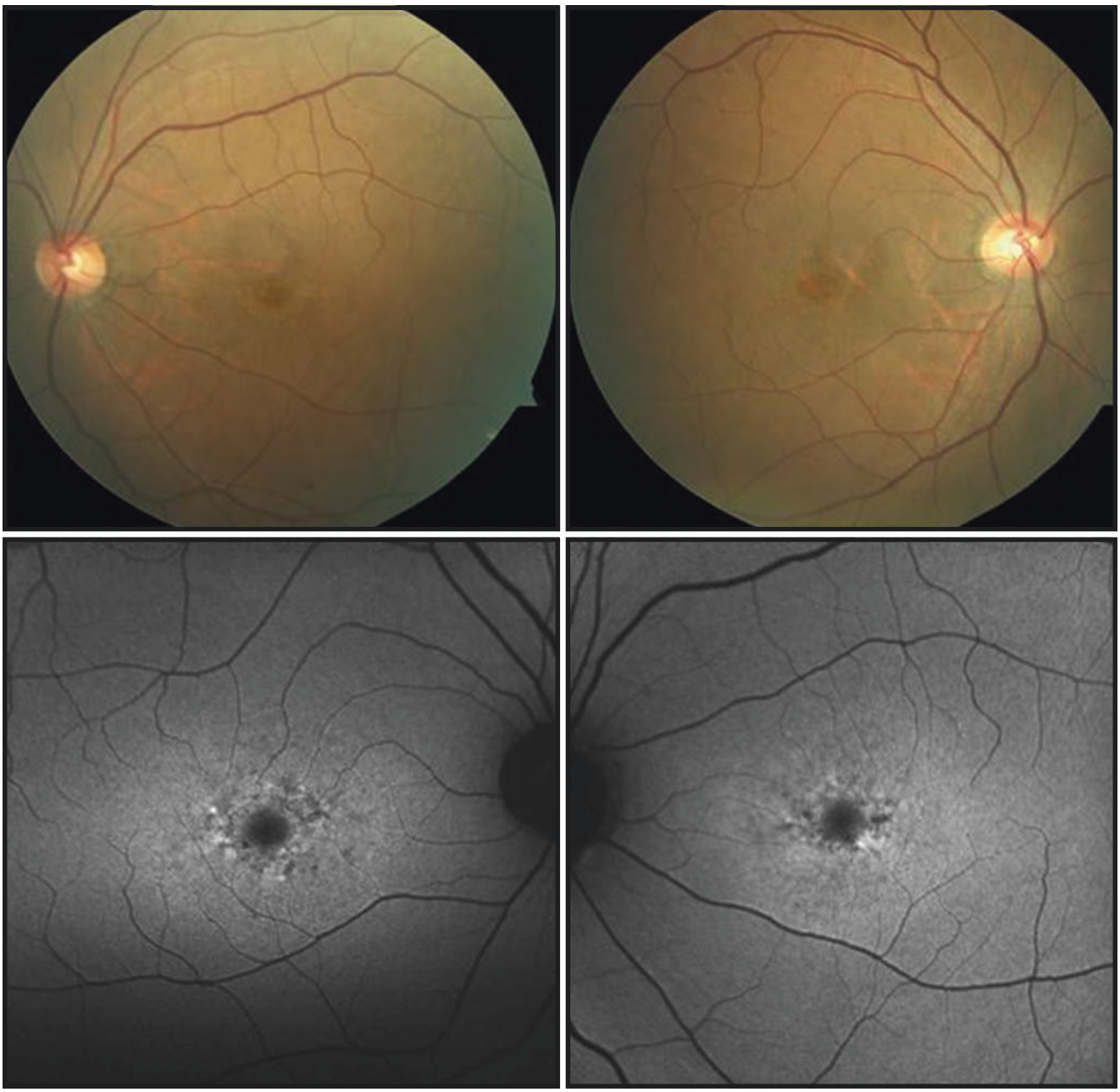

Fig. 12.4 Bull's eye maculopathy on color fundus photographs and corresponding RPE changes on FAF, a speckled appearance

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.

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CHAPTER 13

Congenital Stationary Night Blindness

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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_13

Congenital Stationary Night Blindness with Normal Fundi

In congenital stationary night blindness (CSNB), there is a defect in rod photoreceptor signal transmission. This disorder of night vision is non-progressive. The most common inheritance pattern is X-linked, though autosomal recessive and autosomal dominant patterns have been described (Fig. 13.1). There is genetic heterogeneity within these types.

Though these patients usually complain of defective night vision, the fundus is normal. Myopia is an associated common finding. Vision ranges from normal to about 20/200; patients with poor vision also have nystagmus, strabismus, or both.

Dark-adaptometry shows no rod adaptation.

Types

The electroretinogram (ERG) identifies two types of CSNB in these patients:

- **Riggs type**: Absence of a-wave in dark-adapted bright-flash ERG, suggesting a defect in the rod photoreceptor.
- **Schubert-Bornschein type**: Normal a-wave and a markedly decreased rod b-wave with an electronegative waveform under the same stimulus conditions, suggesting abnormal bipolar cell function (Fig. 13.2).

Two subtypes—complete and incomplete—have been described (Fig. 13.3):

– In the complete type, there is no detectable or recordable rod b-wave (dysfunction in ON-bipolar pathway), and there is a normal-amplitude wave on 30-Hz flicker ERG. Most patients with the complete form have night blindness and usually moderate to high myopia.
– In the incomplete type, there is some detectable rod b-wave (dysfunction in both ON and OFF pathways), and amplitude is markedly subnormal and delayed in the 30-Hz flicker ERG, with a distinctive peak suggestive of greater cone ERG abnormality than in the complete form. Night blindness is less constant in the incomplete form, and refractive error varies from myopia to hyperopia.

Molecular Genetics

- X-linked CSNB is associated with mutations in the *NYX* gene, causing the complete type of CSNB. The gene encodes nyctalopin protein, which plays an important role in the synaptic connection between photoreceptors and ON-bipolar cells. More than 50 mutations have been identified. The cytogenetic location is Xp11.4, the short arm of the X chromosome at position 11.4. The *NYX* mutation accounts for about 45% of cases of X-linked CSNB.
- Another mutation is in *CACNA1F*, causing the incomplete type of CSNB, in which patients have some detectable rod response on ERG. This gene encodes a transmembrane protein that functions as a retina-specific alpha-1 subunit of a

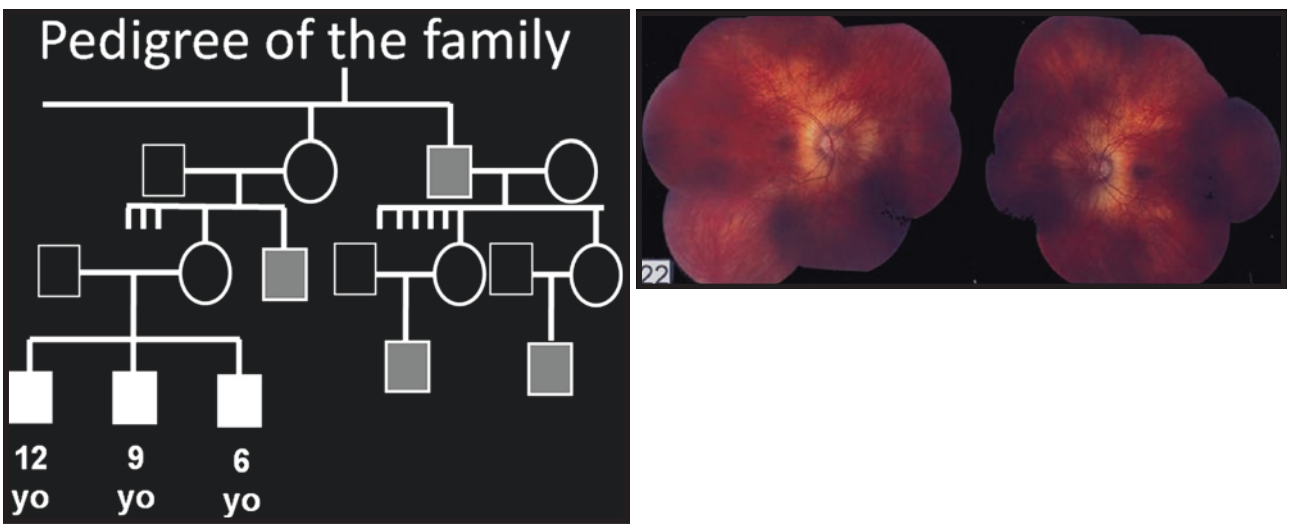

Fig. 13.1 A family with CSNB, only males are affected, and normal fundus

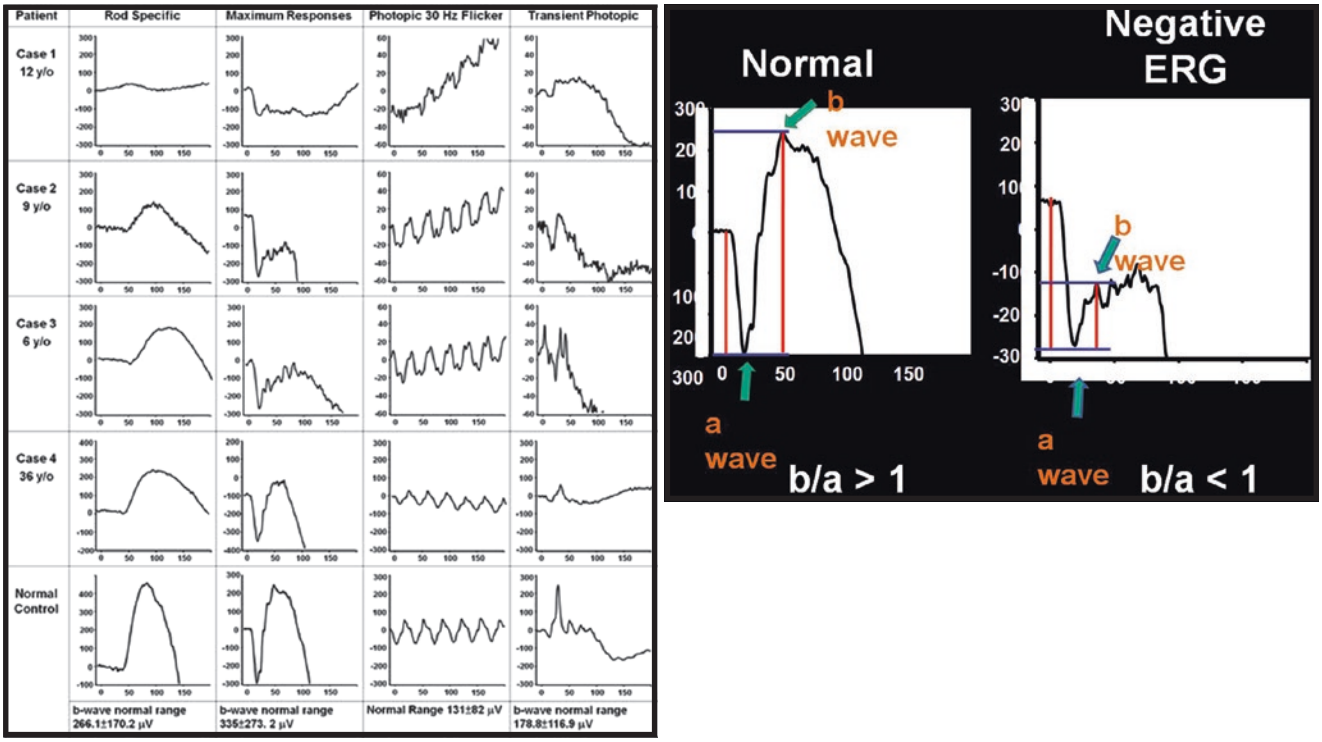

Fig. 13.2 ERG showing electronegative wave pattern

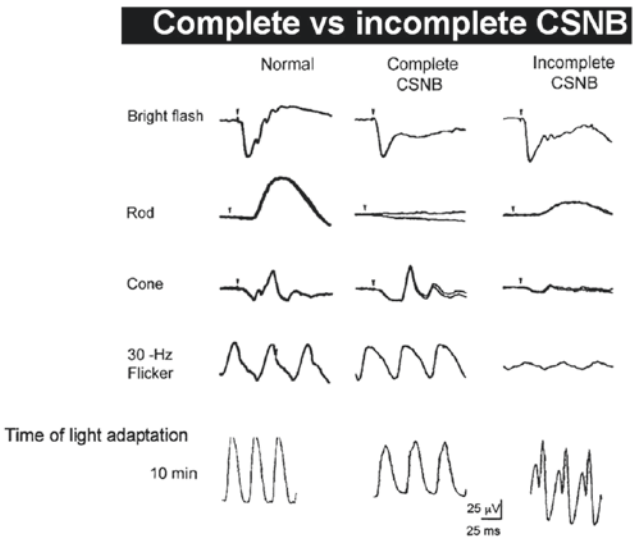

Fig. 13.3 Differentiating features between complete and incomplete CSNB

voltage-gated L-type calcium channel; it is responsible for regulation of glutamate release from photoreceptors to ON-bipolar and OFF-bipolar cells. The cytogenetic location is Xp11.23, the short arm of the X chromosome at position 11.23. The *CACNA1F* mutation accounts for about 55% of cases of X-linked CSNB.

Congenital Stationary Night Blindness with Abnormal Fundi

Fundus Albipunctatus

Patients with fundus albipunctatus have defective night vision from birth, with multiple white dots visible throughout the fundus, sparing the central fovea (Fig. 13.4). Visual acuity remains good. The inheritance pattern is autosomal recessive.

Imaging and Tests

- *Fundus autofluorescence (FAF)* is diffusely decreased because of less accumulation of lipofuscin pigment.
- *Optical coherence tomography (OCT)* shows hyperreflective lesions in the outer retina.
- *ERG* shows undetectable rod response but normal cone response. The ERG response may become normal after prolonged overnight dark adaptation, however.

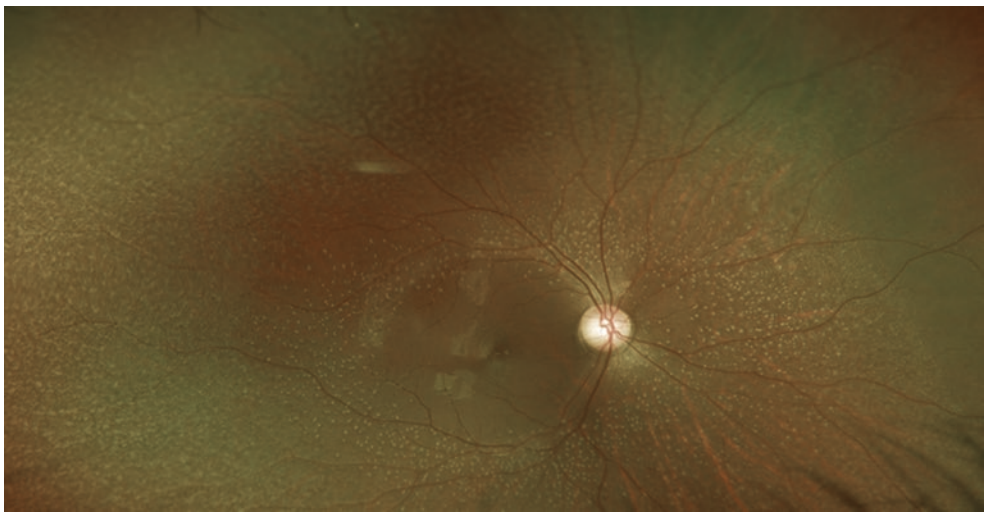

Fig. 13.4 Fundus Albipunctatus caused by RDH5 mutation. Note, innumerable 'white dots' throughout the fundus.

Molecular Genetics

There is a mutation in the *RDH5* gene (12q13–12q14). This gene encodes 11-cis-retinol dehydrogenase, which converts 11-cis-retinol into 11-cis-retinal, in the retinal pigment epithelium (RPE). Therefore, regeneration of visual pigment is delayed.

Oguchi Disease

Oguchi disease is most common in Japan. Its inheritance pattern is autosomal recessive. Patients have defective vision since birth.

Imaging and Tests

- *Fundus examination* shows a characteristic yellow tapetal sheen or reflex after a brief light exposure (described as the Mizuo-Nakamura phenomenon). The reflex disappears after 2–3 h of dark adaptation.
- If a *scotopic ERG* is performed after 20 min of dark adaptation, no rod a-wave is detected, but if it is performed after 1–2 h of dark adaptation, the first flash will produce an a-wave that is normal in both amplitude and implicit time. Response to the second flash will be reduced.

Molecular Genetics

Oguchi disease is due to mutation in the *SAG* (S-antigen visual arrestin) gene (2q37.1), which encodes for arrestin, or in the *GRK1* gene (13q34), encoding for rhodopsin kinase.

Suggested Reading

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CHAPTER 14

Blue Cone Monochromatism

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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_14

General Features

Unlike rod monochromatism, which is an autosomal recessive disease that affects all three types of cones, blue cone monochromatism (BCM) is an X-linked disease that affects only L-cones and M-cones. The rods and S-cones are normal. The estimated prevalence is 1 in 100,000 individuals.

Patients are usually myopes, with vision usually between 20/80 and 20/200. This vision is better than in patients with rod monochromatism, in whom hyperopia is more common.

Imaging and Tests

- **Fundus autofluorescence (FAF)** shows a fundus that is usually normal or may show subtle retinal pigment epithelial (RPE) changes.
- **Scotopic electroretinography (ERG)** is normal. An S-cone ERG (blue flashlight on yellow background) is preserved. The 30-Hz flicker ERG is undetectable, as the response is predominantly from L-cones and M-cones, but a low-amplitude single-flash photopic response may be present.
- **Optical coherence tomography (OCT)** may show foveal thinning and disruption of the photoreceptors or outer nuclear layer (Fig. 14.1).

Molecular Genetics

Mutation occur in the L-cone and M-cone opsin genes (*OPN1LW* and *OPN1MW*); the S-cone gene is located on chromosome 7.

Suggested Reading

Nathans J, Davenport CM, Maumenee IH, Lewis RA, Hejtmancik JF, Litt M, et al. Molecular genetics of human blue cone monochromacy. Science. 1989;245:831–8.

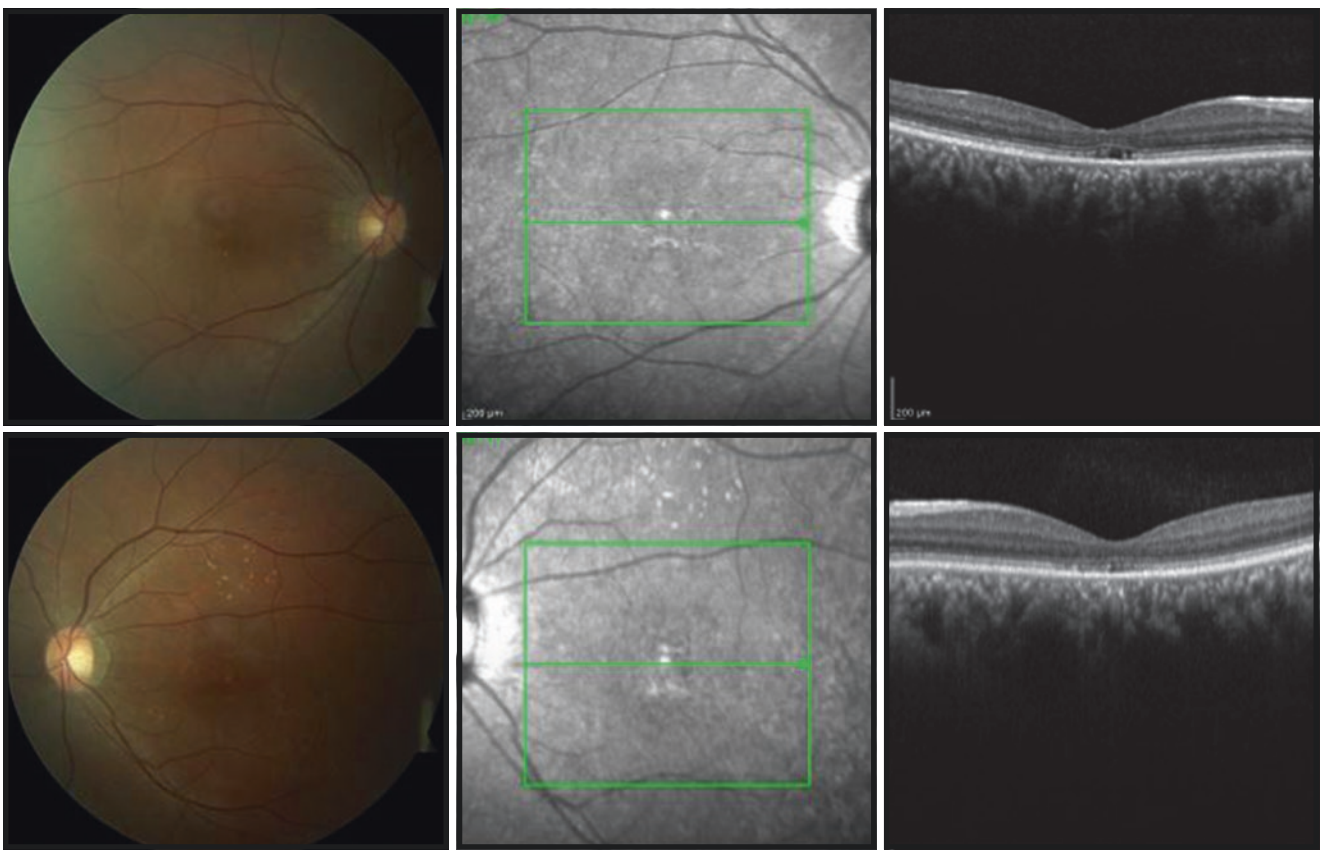

Fig. 14.1 Fundus nearly normal but for few yellowish dots in the left eye; OCT shows disruption of ellipsoid zone (EZ) line and optical empty cavities in the center

Section III

Autosomal Dominant Forms

CHAPTER 15

Autosomal Dominant Retinitis Pigmentosa

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General Features

More than 70 genes (over 3000 mutations) are known to cause non-syndromic retinitis pigmentosa (RP), including autosomal dominant (AD), autosomal recessive (AR), X-linked, and simplex forms (inheritance not known). The AD form accounts for approximately 15–25% of cases; AR, 5–20%; X-linked, 5–15%; and simplex, 40–50%.

About 26 gene mutations have been identified for the AD form, versus over 50 for the AR form. Patients with AD RP usually present late in life. The disease is less severe and it progresses slowly. The macula remains spared for a long period (Figs. 15.1 and 15.2).

Molecular Genetics

RHO Gene (RP4, Opsin-2)

- Mutations in the *RHO* gene (Fig. 15.3) are the most common cause of AD RP, accounting for 20–30% of all cases.
- This gene encodes for making rhodopsin protein, which is predominantly present in rods.
- Cytogenetic location: 3q22.1

PRPF3 Gene (RP 18, SNRNP90)

- Figure 15.4 presents an example of AD RP caused by this mutation.
- The removal of introns from nuclear pre-mRNAs occurs on spliceosomes, which are made up of four small nuclear ribonucleoproteins (snRNPs).
- Therefore, this gene participates in pre-mRNA slicing.
- Cytogenetic location: 1q21.2

RP1 Gene (ORP1)

- The *RP1* gene encodes a doublecortin domain, which binds microtubules and regulates microtubule polymerization.
- This microtubules-associated protein is needed for correct stacking of the outer segment disc (Figs. 15.5 and 15.6)
- Mutation in this gene also causes AR RP.
- Cytogenetic location: 8q11.23–q12.1.

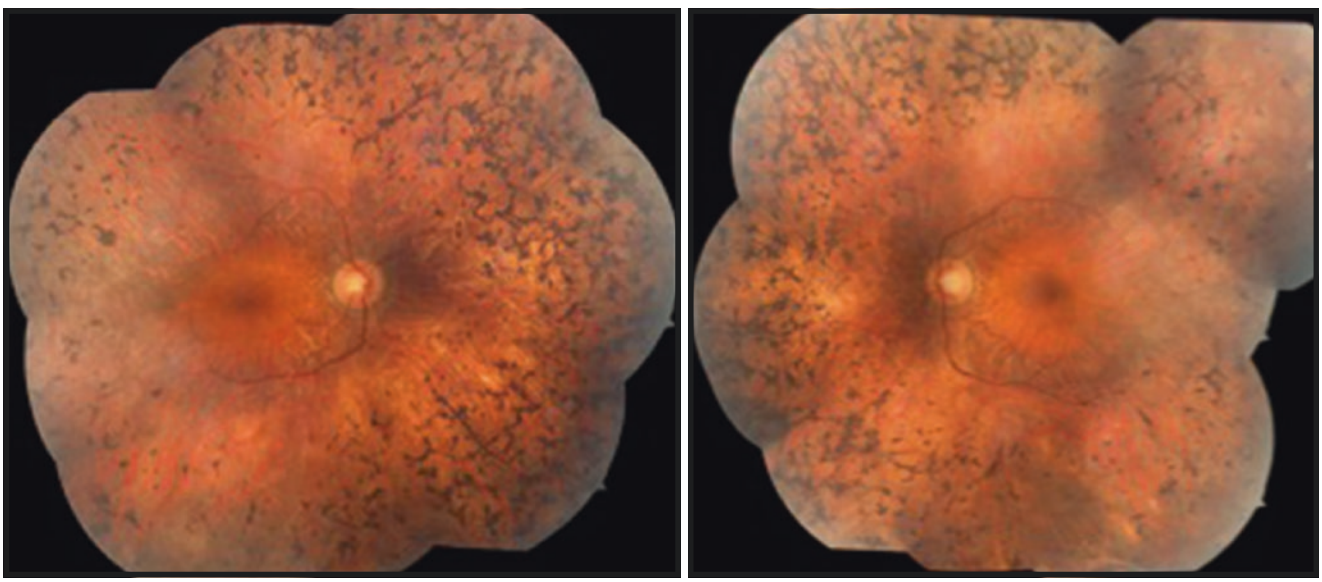

Fig. 15.1 A case of autosomal dominant (AD) retinitis pigmentosa (RP) showing all the classic features, but a healthy macula

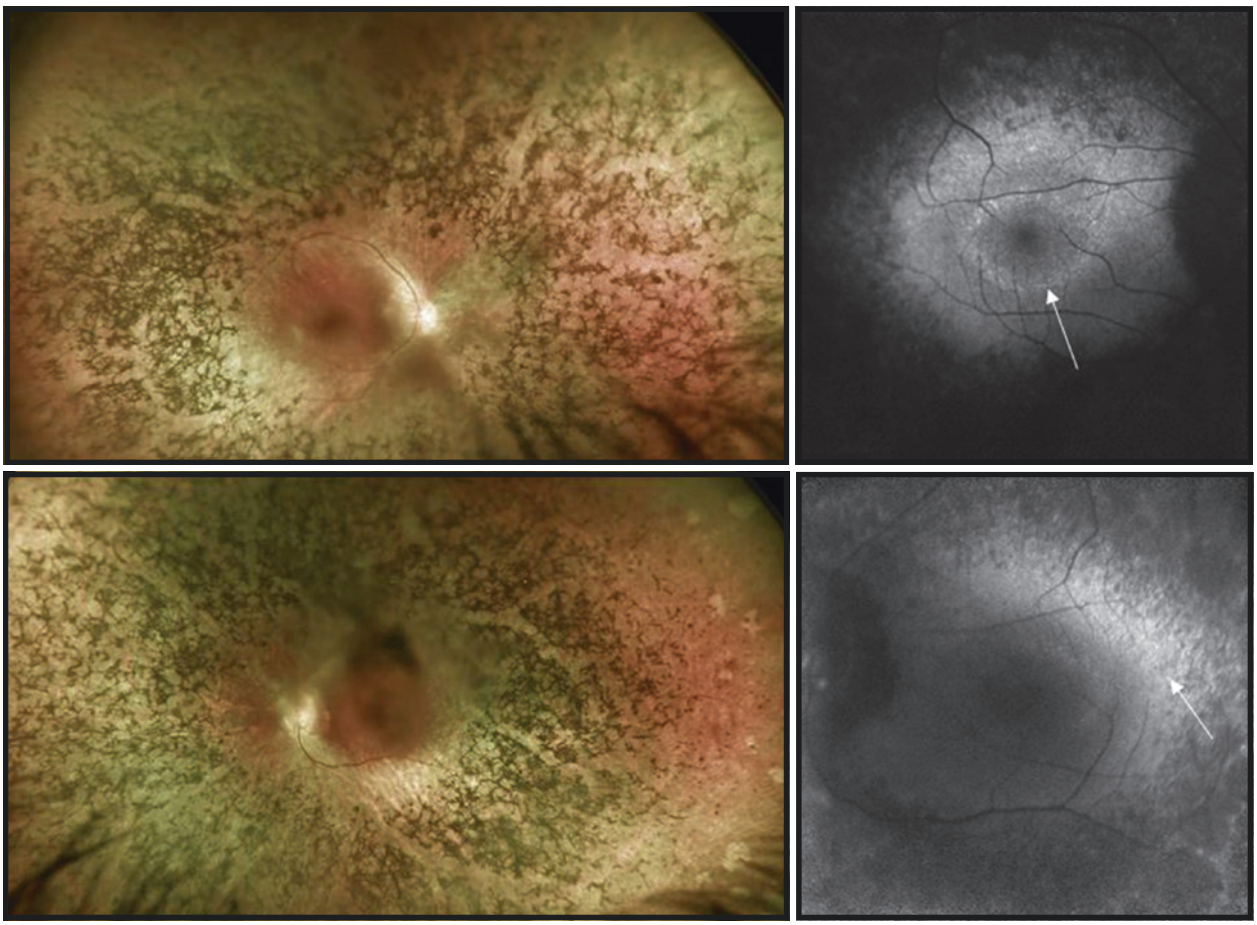

Fig. 15.2 AD RP sparing the macula. Fundus autofluorescence (FAF) shows a characteristic hyperfluorescent ring (*arrow*)

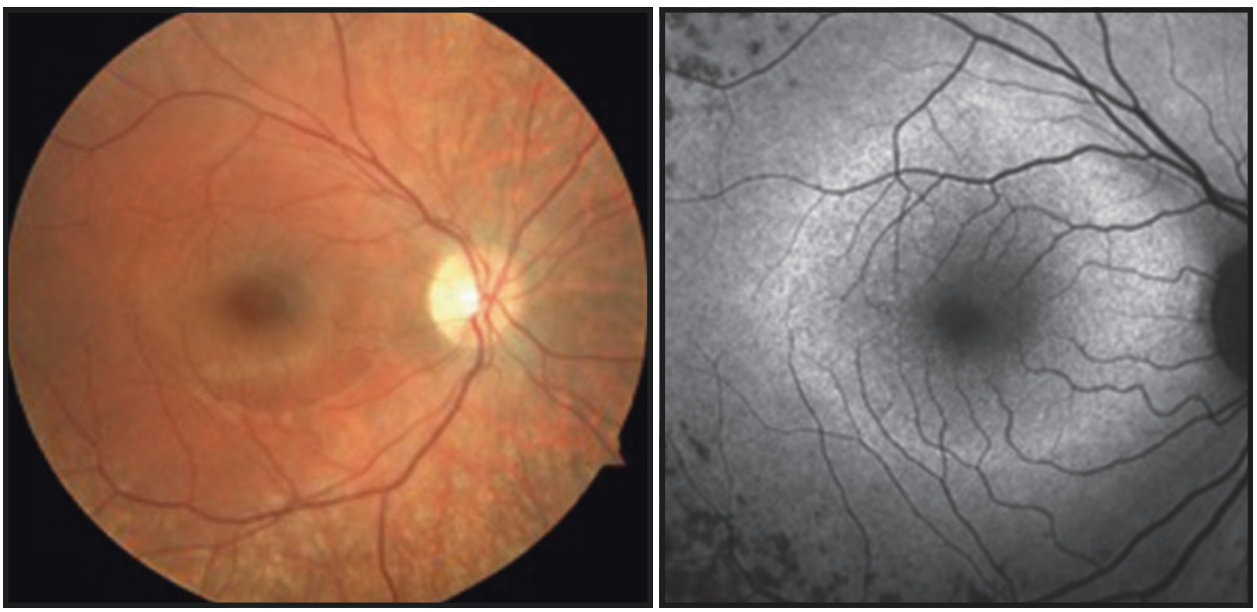

Fig. 15.3 A case of AD RP (*RHO* gene mutation), sparing the macula

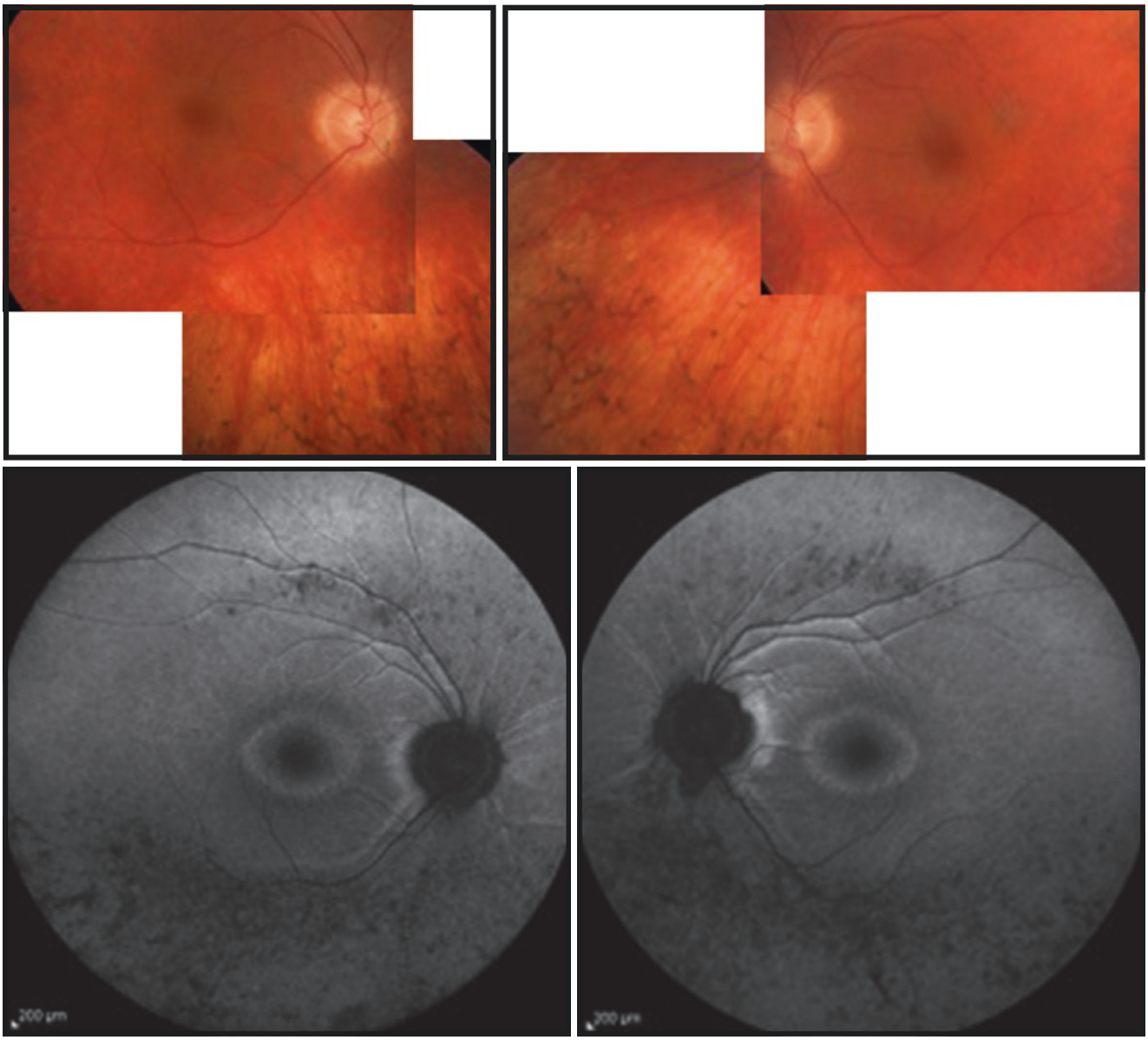

Fig. 15.4 AD RP caused by *PRPF* mutation, showing pigmentary changes in the lower periphery. FAF shows a ring of hyperfluorescence around the fovea

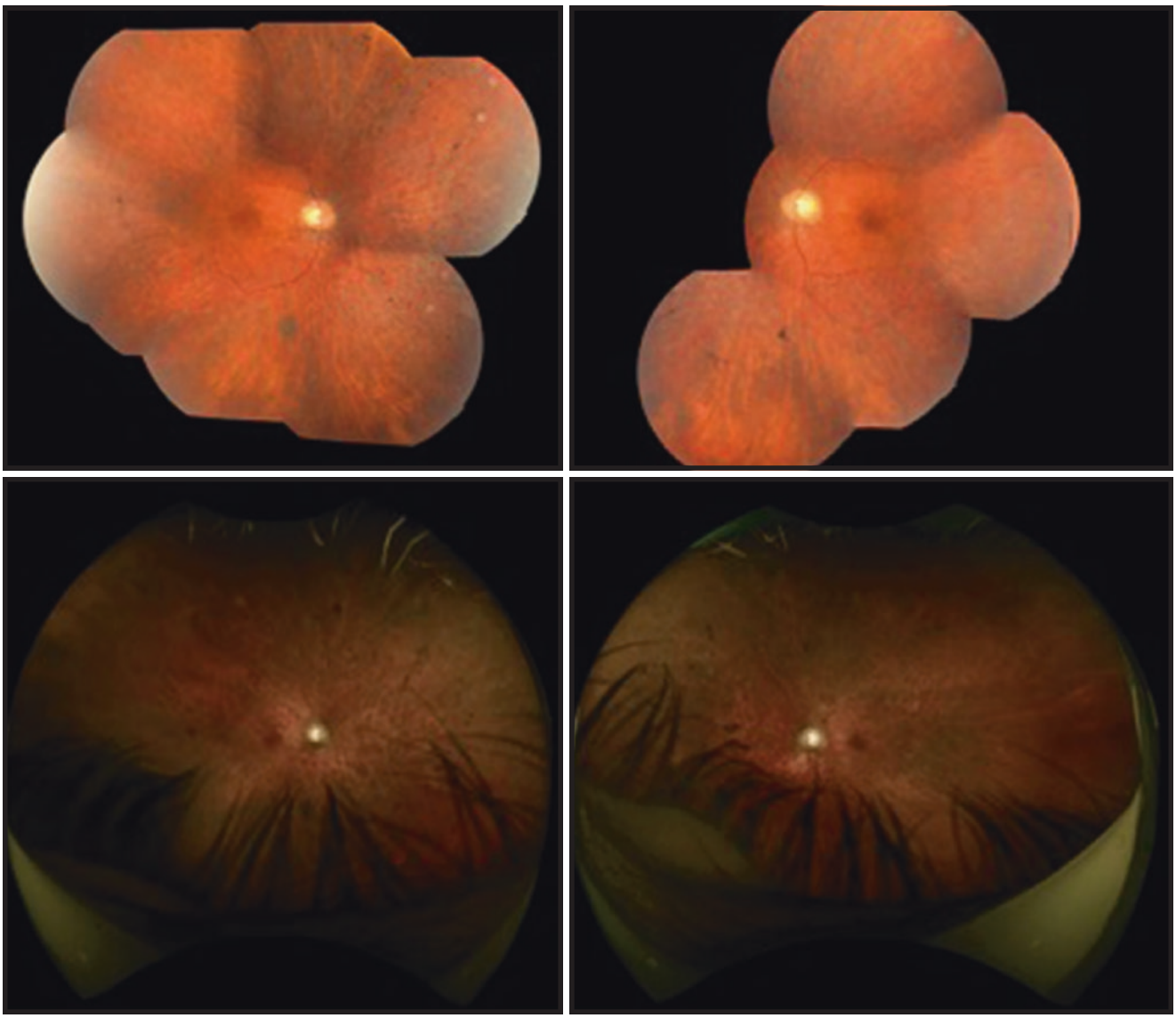

Fig. 15.5 A case of *RP1* mutation AD RP. The macula remains spared despite a 5-year follow-up

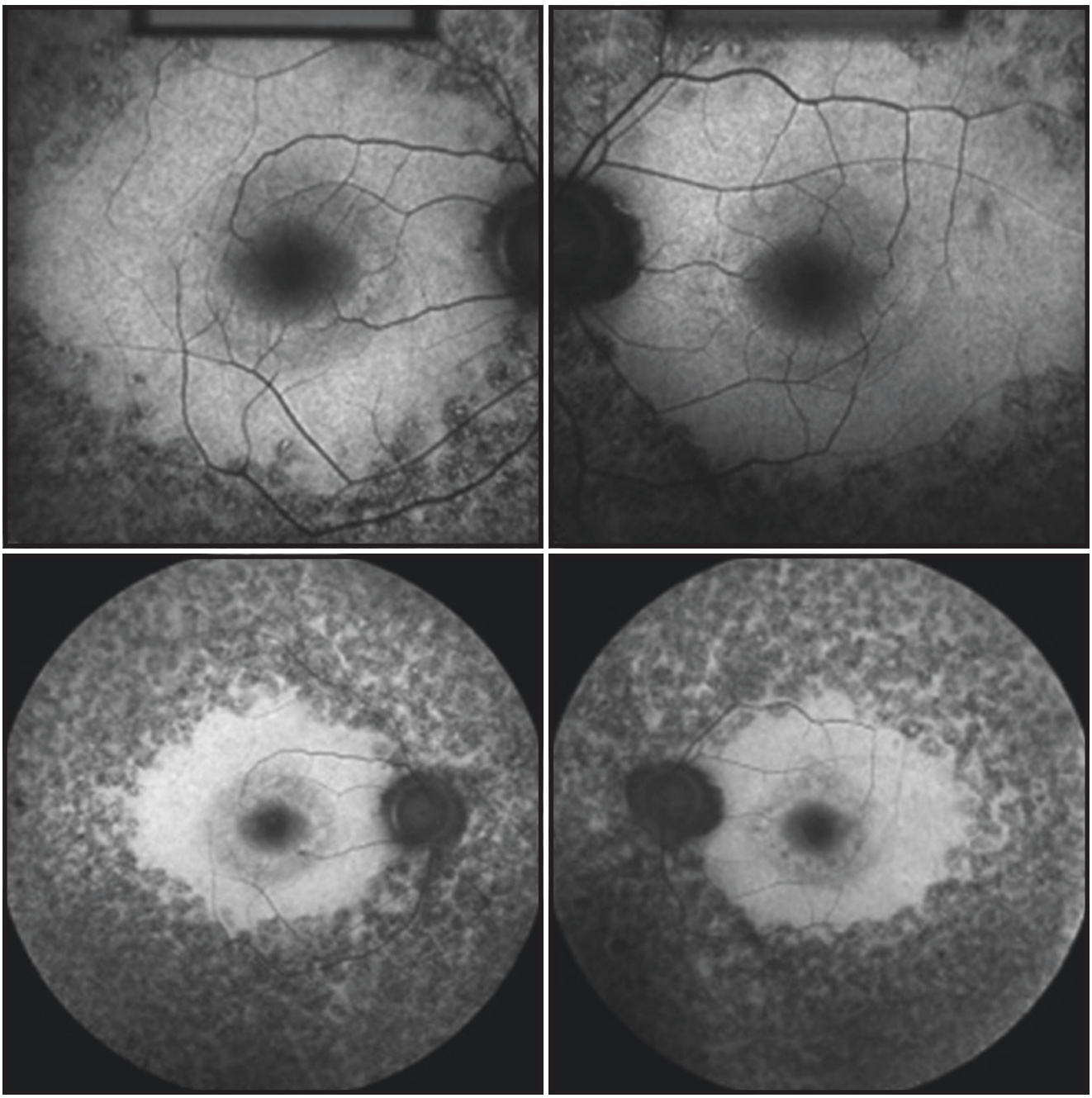

Fig. 15.5 (continued)

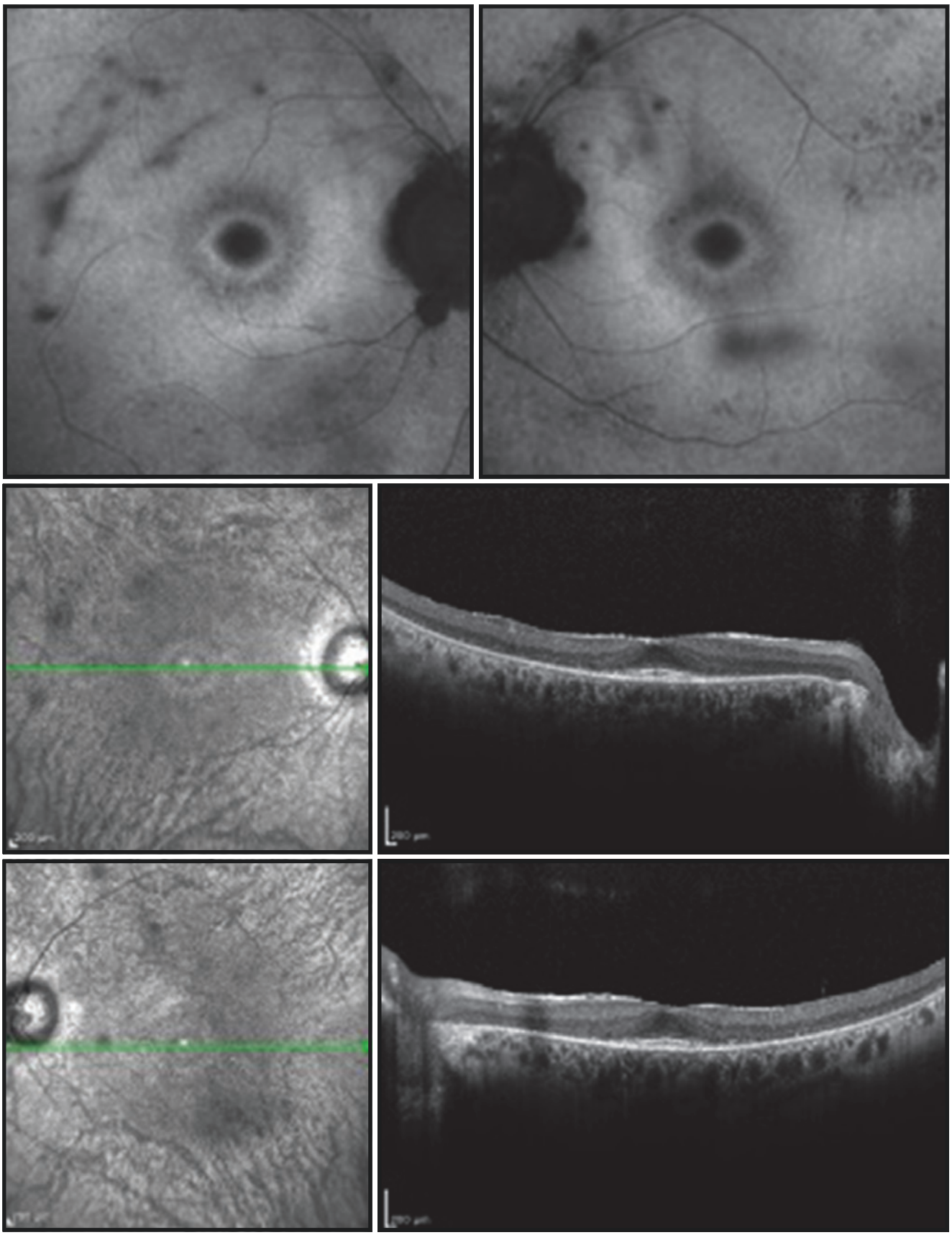

Fig. 15.6 AD RP caused by *RP1* mutation, showing a ring of hyperfluorescence on FAF and loss of the outer nuclear layer on optical coherence tomography (OCT). A 2-year follow-up showed no significant progression

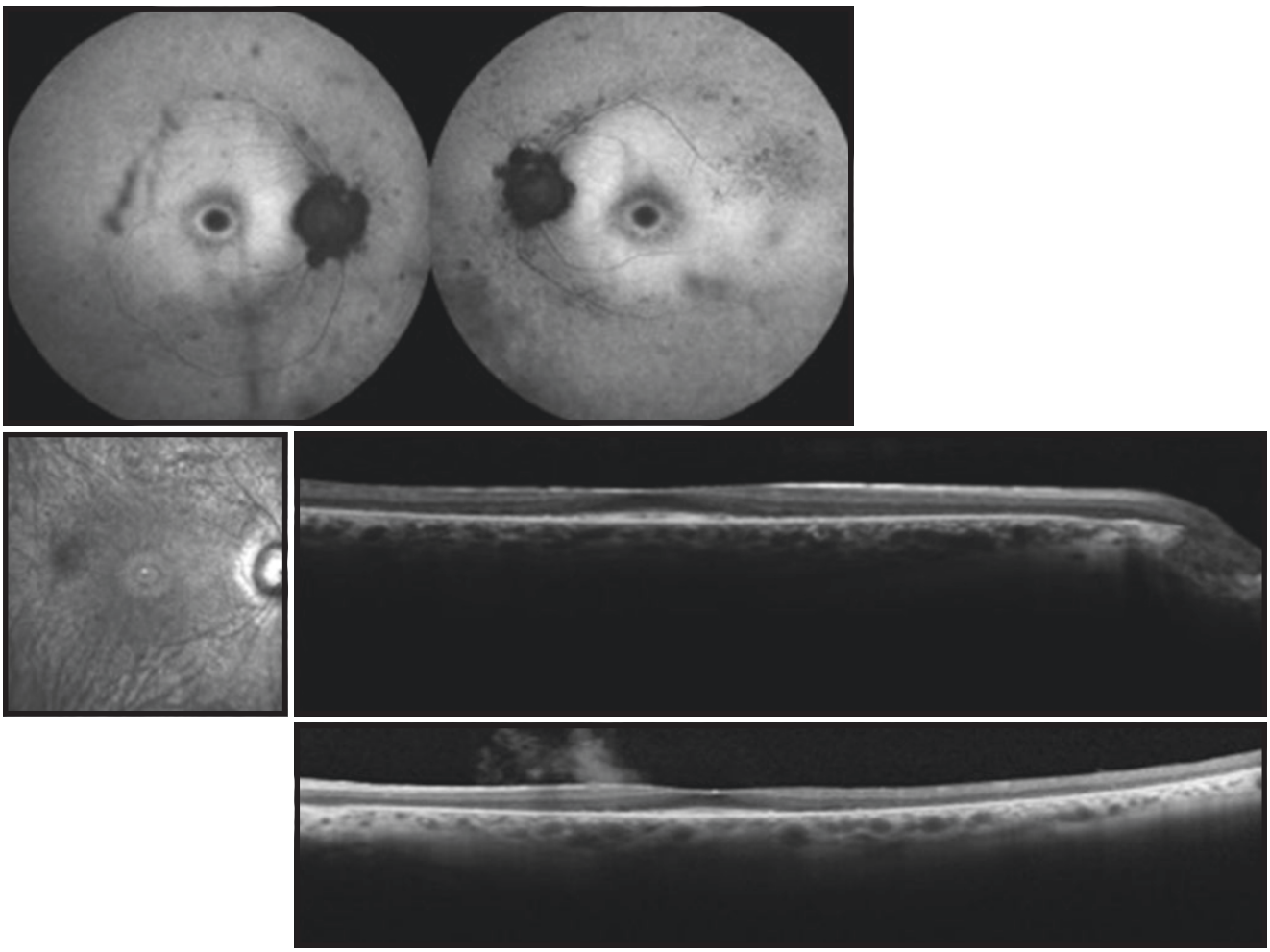

Fig. 15.6 (continued)

Suggested Reading

Borràs E, de Sousa Dias M, Hernan I, Pascual B, Mañé B, Gamundi MJ, et al. Detection of novel genetic variation in autosomal dominant retinitis pigmentosa. Clin Genet. 2013;84:441–52.

Daiger SP, Sullivan LS, Bowne SJ. Genes and mutations causing retinitis pigmentosa. Clin Genet. 2013;84:132–41.

CHAPTER 16

Best Vitelliform Macular Dystrophy

Stephen H. Tsang and Tarun Sharma

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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_16

General Features

Best vitelliform macular dystrophy (VMD or BVMD) is one of the most common macular dystrophies, affecting 1 in 10,000 individuals. The clinical presentation varies, depending on the stage of the disease at which the patient presents, usually one of these five stages:

- Previtelliform
- Vitelliform (Figs. 16.1, 16.2, 16.3 and 16.4)
- Pseudohypopyon
- Vitelliruptive (Fig. 16.5)
- Atrophic

The vitelliform stage is characterized by an egg yolk–like appearance in the central macula, due to deposition of yellowish material in the subretinal space. As the material breaks down, there is clear fluid in the upper part and yellowish material in the lower part, giving a picture of pseudohypopyon. As the condition progress, the yellow material breaks down and resembles a scrambled egg, and eventually appears as an atrophic scar. Surprisingly, vision remains good until the last stage of geographic atrophic appearance. The choroidal neovascular membrane develops in about 20% of cases and may account for decreased visual acuity.

Imaging and Tests

- **Fundus autofluorescence (FAF):** The yellowish material (photoreceptor outer segment and lipofuscin-like material) shows intense hyperfluorescence, but the pattern may change as the lesion passes through various stages.
- **Optical coherence tomography (OCT)** shows neurosensory detachment at the macula; rarely, choroidal neovascular membrane and scarring are also visible. The material involved is shed photoreceptor outer segments.
- **Electroretinography (ERG)** is normal, but **electrooculography (EOG)** is always abnormal, with an Arden ratio of about 1.0 or less than 1.5. This is an important marker in those with a normal fundus or poorly defined lesion.
- Some *BEST1* mutation carriers (previtelliform stage) do show an abnormal EOG; the fundus may be normal or just show some RPE alterations.

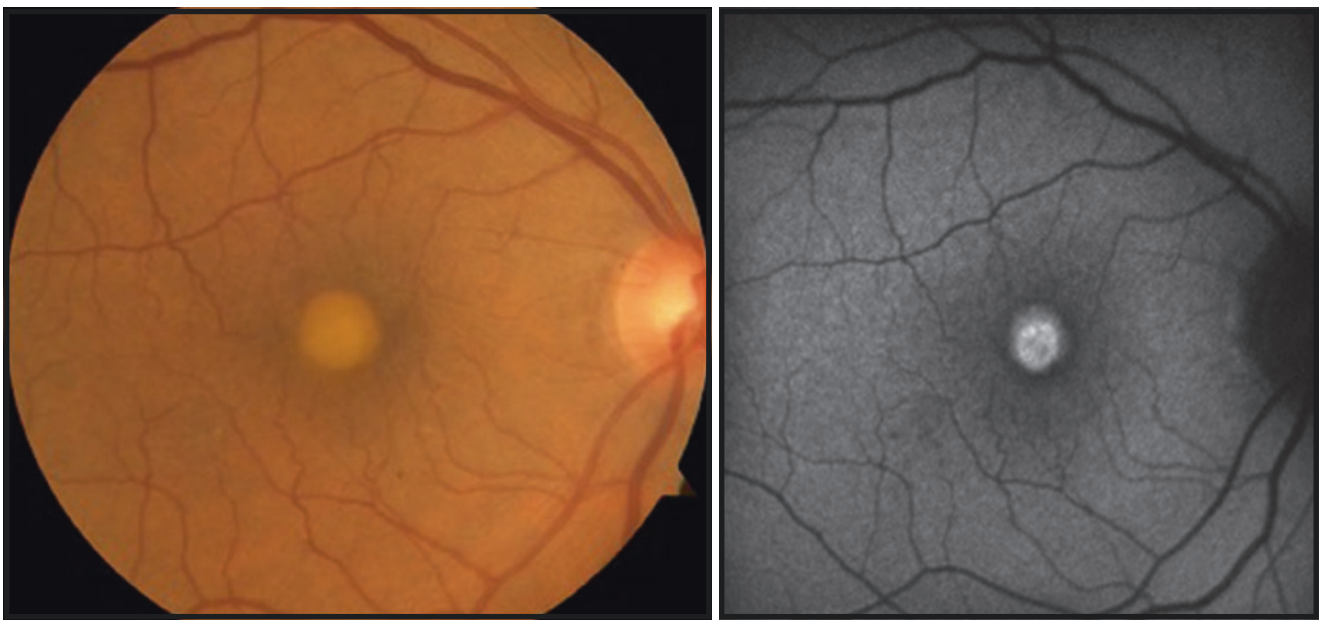

Fig. 16.1 Egg-yolk appearance on color fundus photograph, with corresponding intense hyperfluorescence on fundus autofluorescence (FAF)

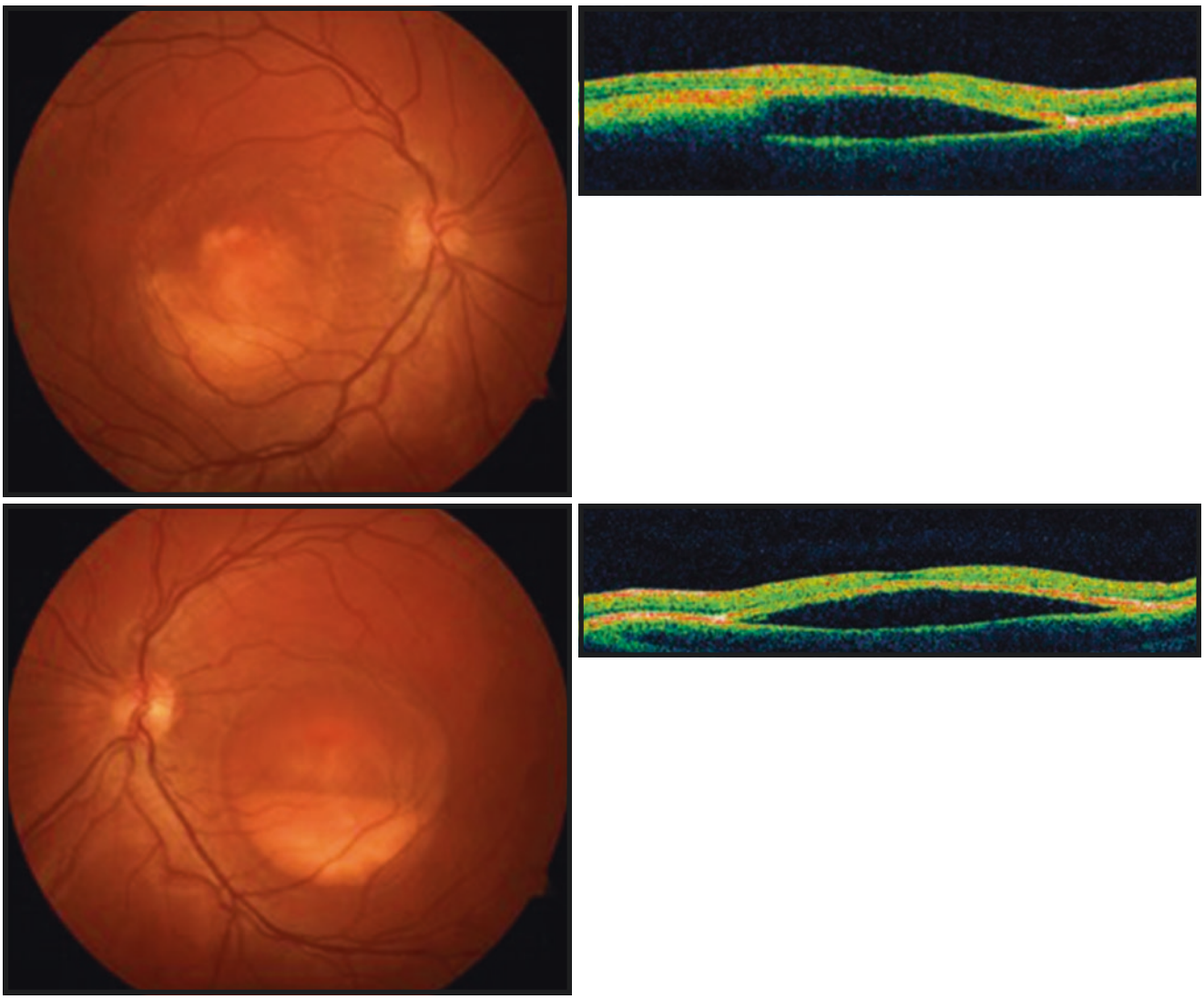

Fig. 16.2 Partially absorbed yolk on color fundus photograph, with neurosensory macular detachment

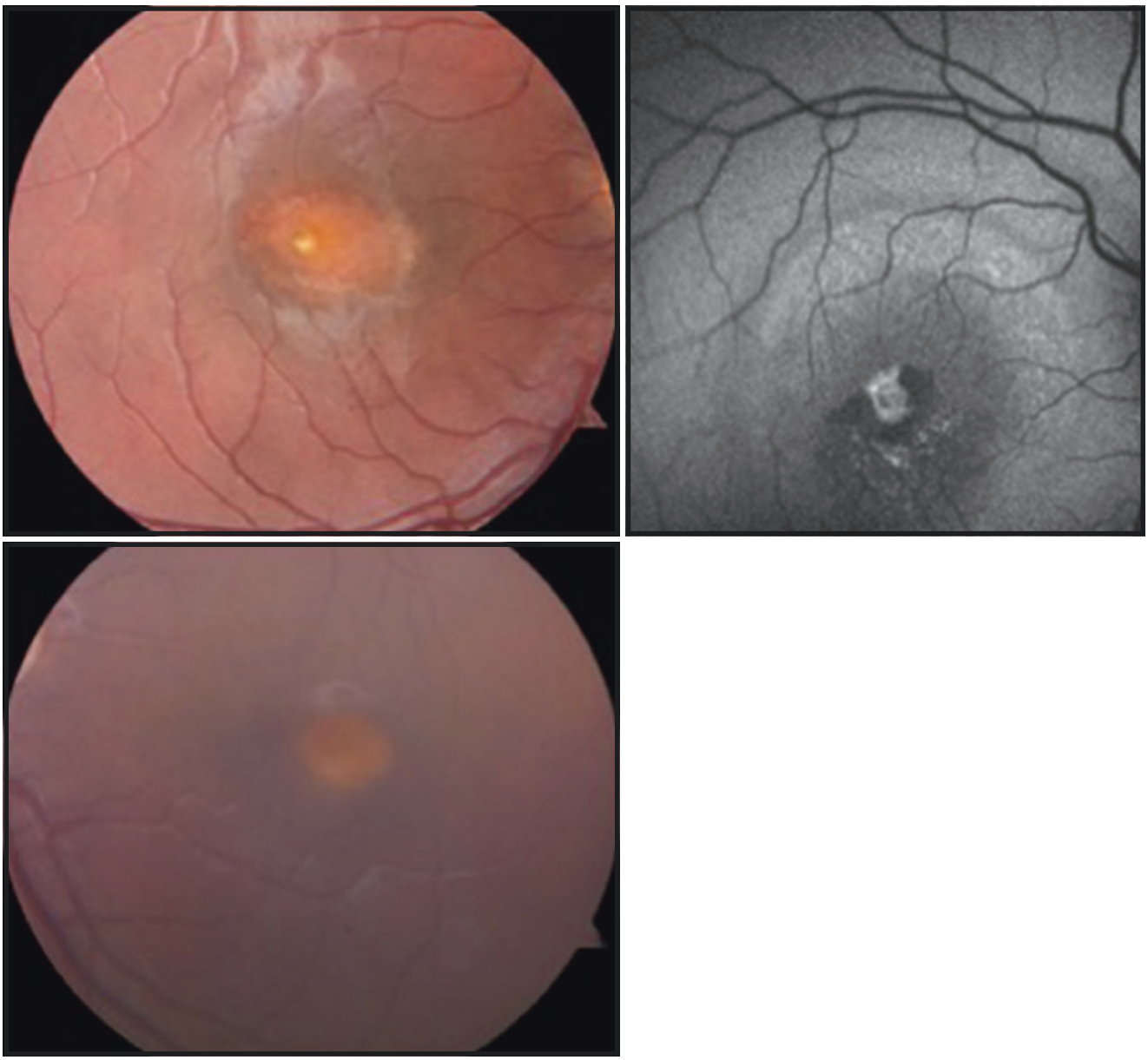

Fig. 16.3 Vitelliform lesion is getting absorbed. Autofluorescence shows retinal pigment epithelium (RPE) dysfunction in the right eye, and the left eye shows neurosensory detachment at the macula

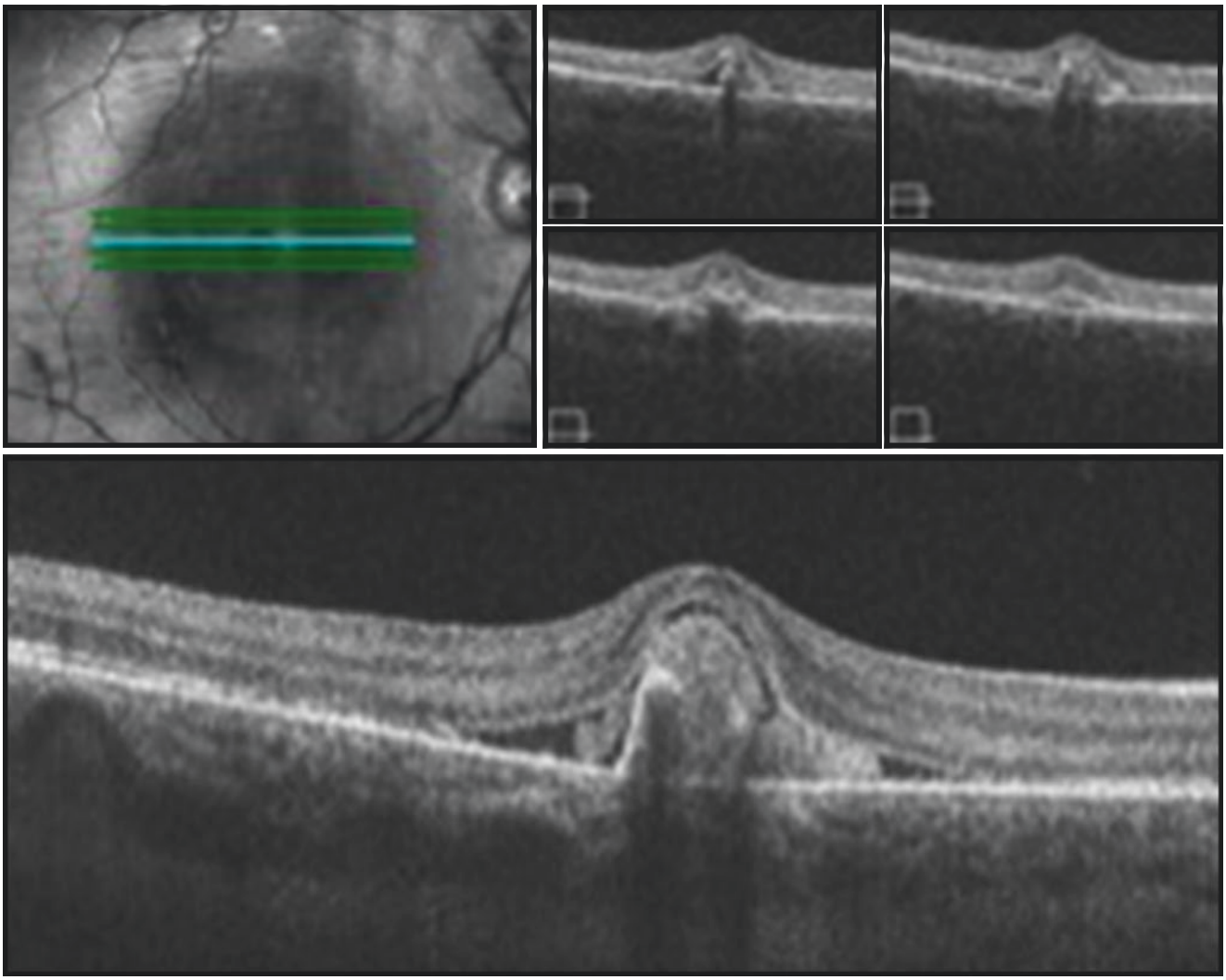

Fig. 3 (continued)

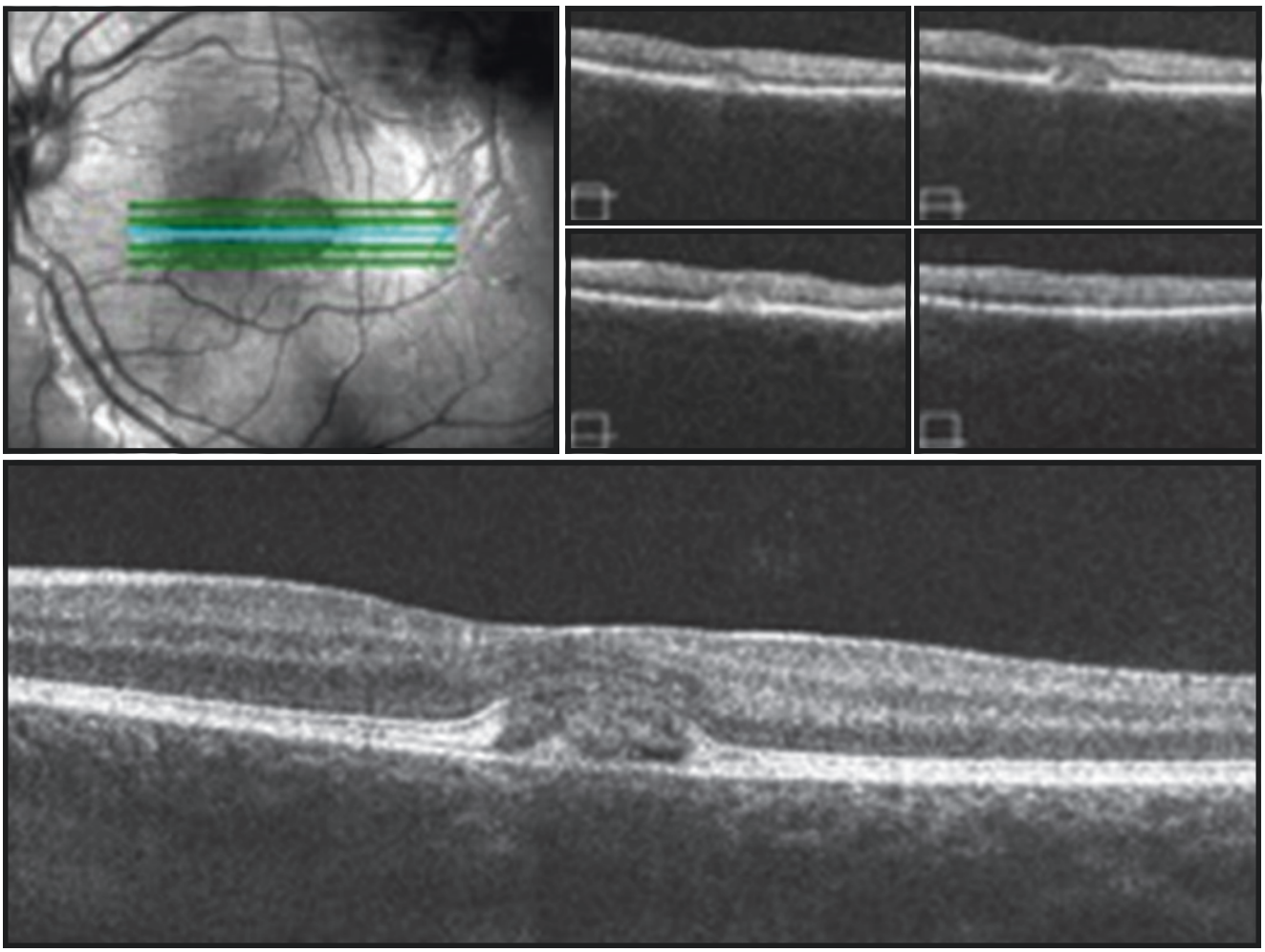

Fig. 3 (continued)

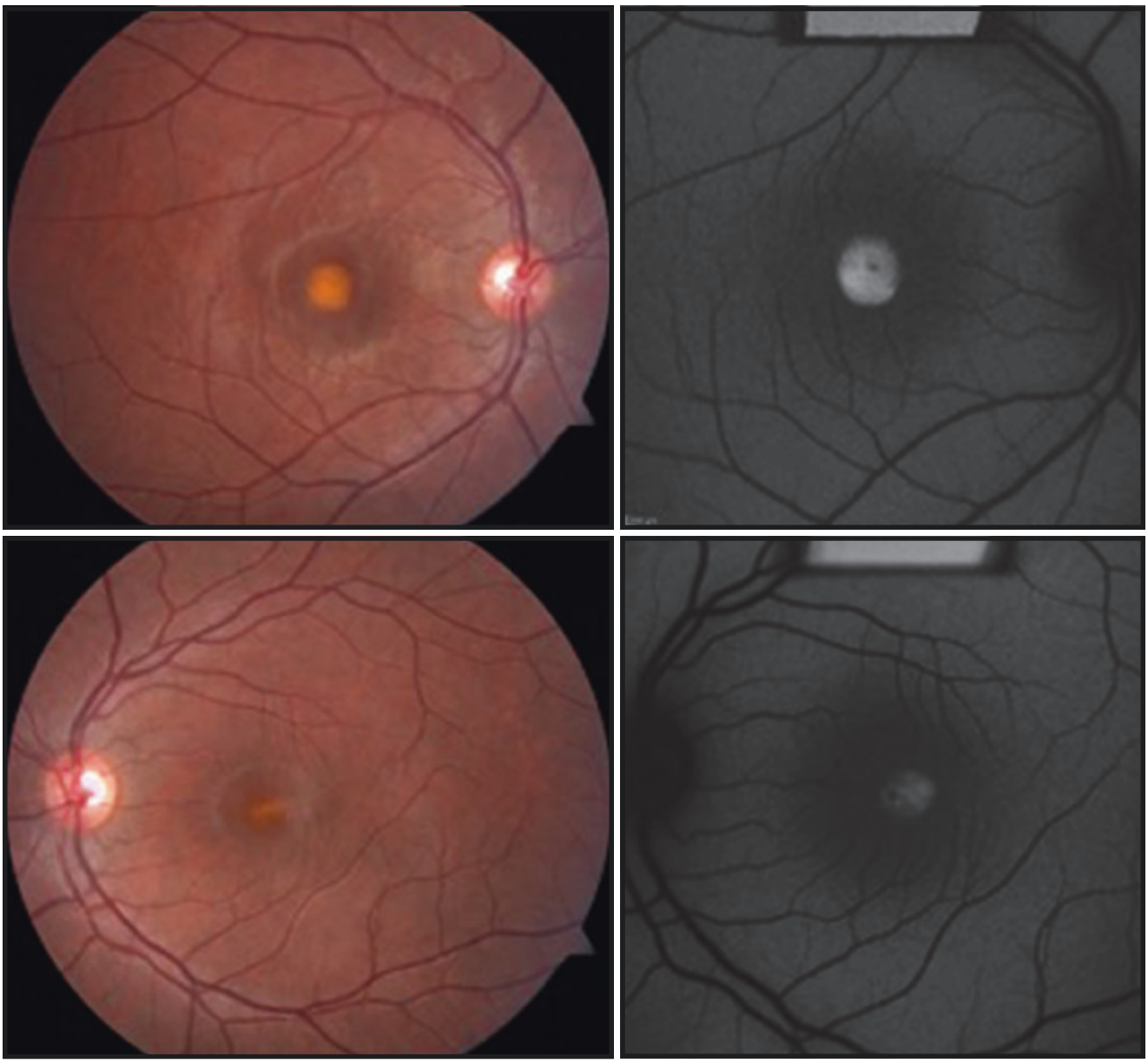

Fig. 16.4 In this asymmetrical picture, the yellowish yolk is less absorbed in the right eye than in the left one, with corresponding intense hyperfluorescence. Optical coherence tomography (OCT) shows hyperreflective material in the subretinal space

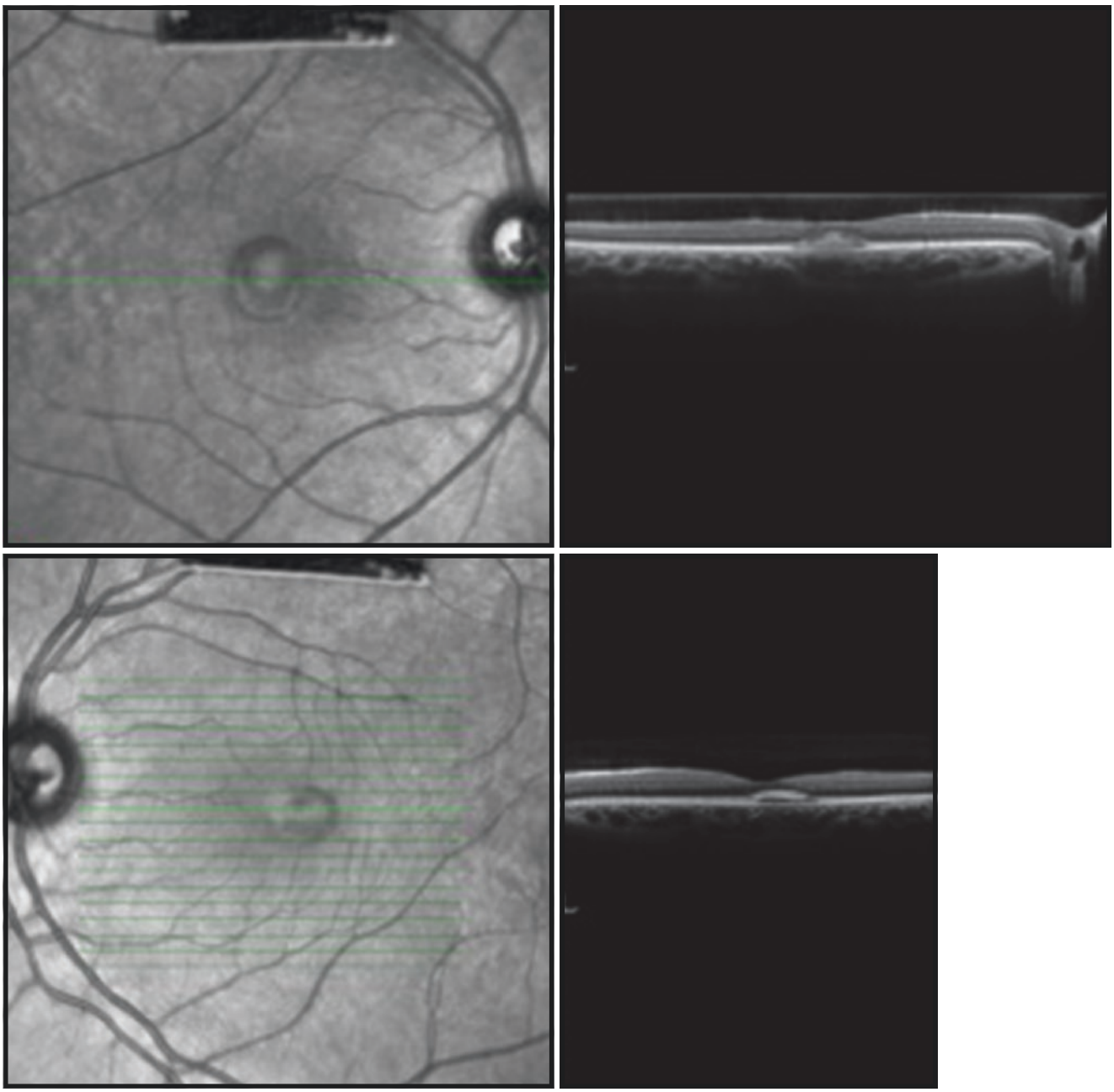

Fig. 4 (continued)

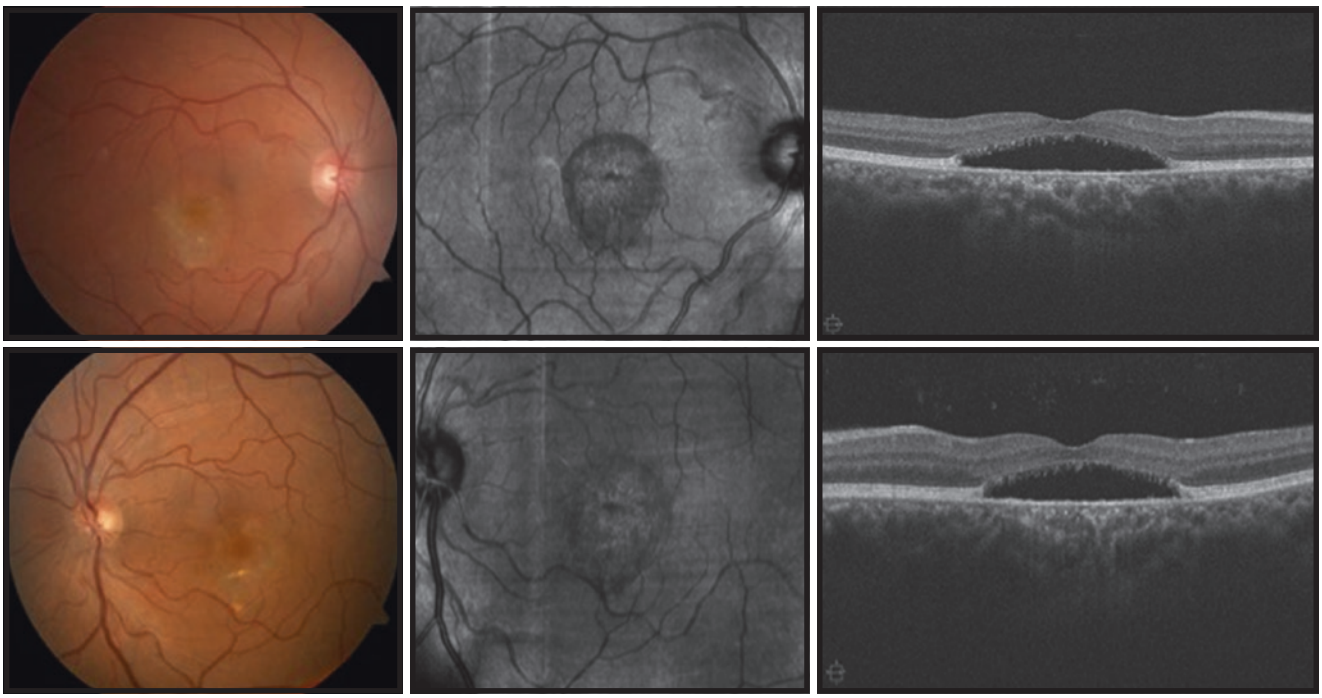

Fig. 16.5 Vitelliruptive stage; OCT shows persistence of neurosensory elevation

Subtypes

Adult-Onset Foveomacular Vitelliform Dystrophy (AFMD)

- This disorder resembles VMD, but its onset is at a higher age (30–60 years) and patients have normal EOG.
- The gene involved is *PRPH-2/RDS*.

Autosomal Recessive Bestrophinopathy (ARB)

- In this rare entity (Fig. 16.6), lesions are multifocal and may extend into the mid-periphery and be associated with flecks. ERG may show progressive photoreceptor damage affecting central vision.
- The macula may show cystoid intraretinal fluid.
- Hyperopia is common and patients do have abnormal EOG.
- Subretinal fibrosis is more common.

Autosomal Dominant Vitreoretinochoroidopathy (ADVIRC)

- These patients show a characteristic hyperpigmented band from equator to ora serrata (almost 360°), along with peri-papillary atrophy.
- Usually, patients are hyperopic.

Molecular Genetics

BEST1 Gene (*VMD2* Gene or *RP50* or *BMD*)

- Mutations in the *BEST1* gene causes Best VMD.
- The *BEST1* gene encodes for a multifunctional protein called bestrophin-1.
- Bestrophin-1, a chloride channel protein, is located on the basolateral membrane of the RPE; abnormal function results

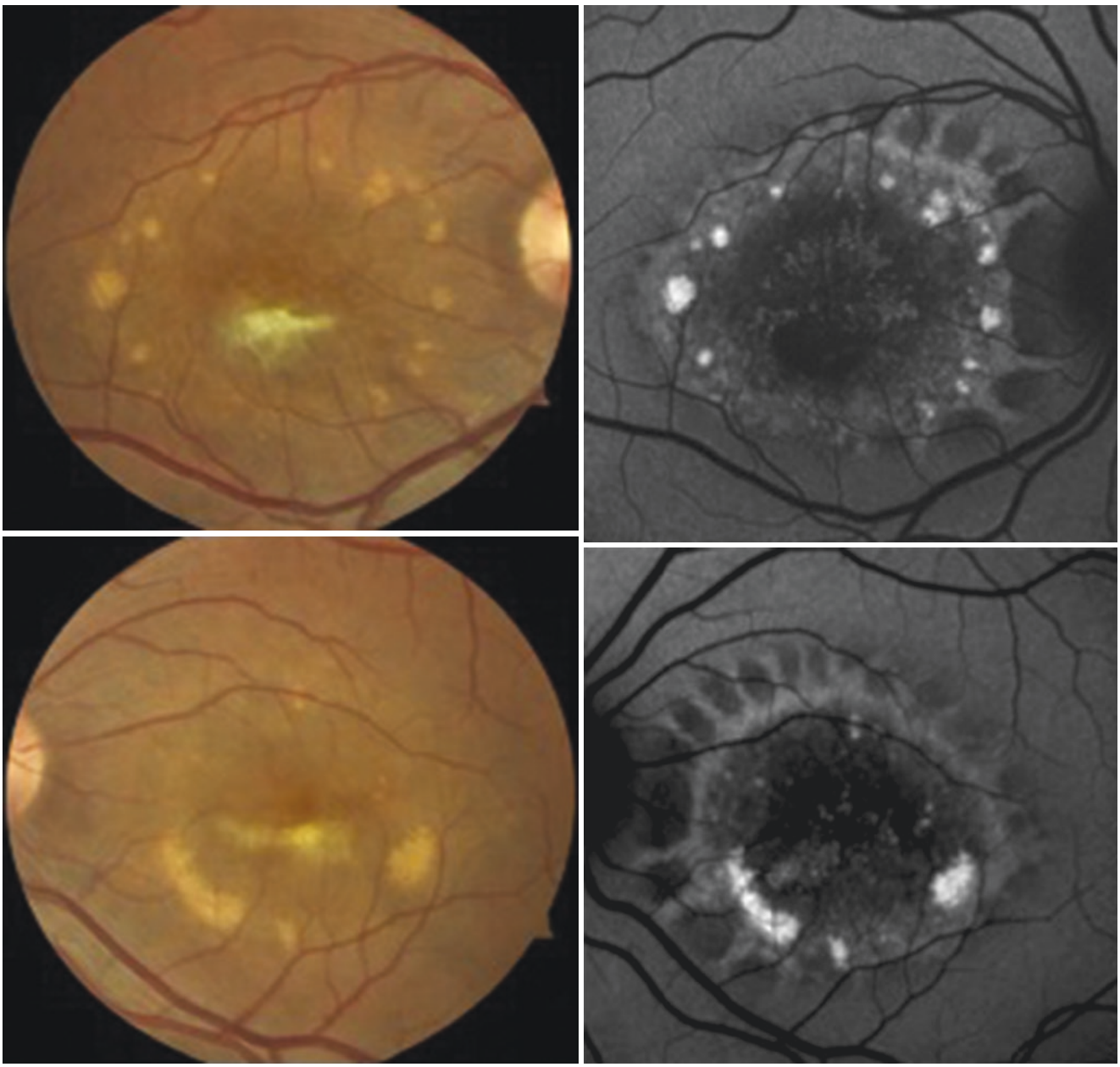

Fig. 16.6 Multifocal yellowish lesions surrounding the macula, with extensive RPE damage on FAF, suggestive of AR bestrophinopathy (ARB)

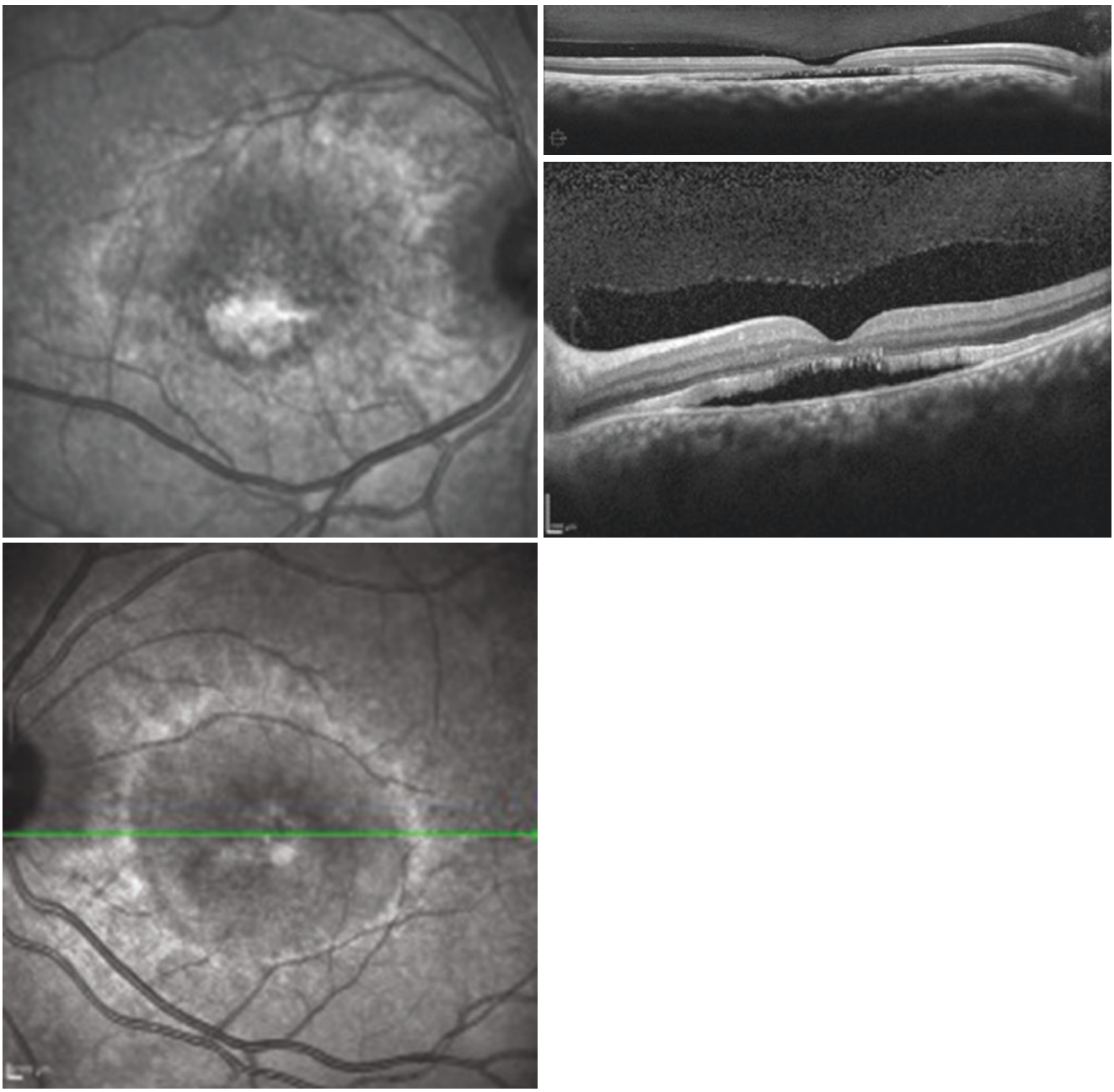

Fig. 6 (continued)

in accumulation of lipofuscin in the RPE and subretinal space. Prolonged neurosensory retinal detachment and overloading of the RPE with lipofuscin eventually result in photoreceptor and RPE dysfunction.

- About 150 mutations have been described in *BEST1*, with a broad range of phenotypes. The phenotypes most often associated with *BEST1* mutations are Best VMD and adult-onset foveomacular vitelliform dystrophy, confined to the macular area.
- On the other hand, autosomal recessive bestrophinopathy, autosomal dominant vitreoretinochoroidopathy (ADVIRC), and autosomal dominant MRCS (MRCS syndrome: microcornea, rod-cone dystrophy, cataract, and posterior staphyloma) have widespread ocular changes.
- Cytogenetic location: 11q12.3

PRPH2 Gene (Peripherin 2 or RDS or CACD2 or Tetraspanin-22)

- This gene makes a protein called peripherin 2, found in the photoreceptors.
- Mutation in *PRPH2* usually causes adult-onset foveomacular vitelliform dystrophy.
- Cytogenetic location: 6p21.1

Suggested Reading

Boon CJ, Klevering BJ, Leroy BP, Hoyng CB, Keunen JE, den Hollander AI. The spectrum of ocular phenotypes caused by mutations in the *BEST1* gene. Prog Retin Eye Res. 2009;28:187–205.

Guerriero S, Preising MN, Ciccolella N, Causio F, Lorenz B, Fischetto R. Autosomal recessive bestrophinopathy: new observations on the retinal phenotype – clinical and molecular report of an Italian family. Ophthalmologica. 2011;225:228–35.

CHAPTER 17

Pattern Dystrophy

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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_17

General Features

The pattern dystrophies of the retinal pigment epithelium (RPE) include a group of disorders:

- Butterfly-type pattern dystrophy (Figs. 17.1, 17.2, 17.3, 17.4 and 17.5)
- Adult-onset foveomacular vitelliform dystrophy
- Sjögren's reticular-type pattern dystrophy
- Fundus pulverulentus

Fundus details can vary considerably among affected family members or between the two eyes of an individual. Sometimes one pattern may evolve into another pattern over a period of time.

Visual loss is the result of either geographic atrophy or choroidal neovascular membrane. Another common complaint is delayed recovery from exposure to bright light.

Butterfly-Type Pattern Dystrophy

- The fundus shows a butterfly-shaped pigmentary lesion having three to five wings or arms, surrounded by an area of depigmentation.
- The lesion may begin as just pigmented dots or a faint, yellowish lesion that eventually evolves into a butterfly pattern over years.
- Some patients develop yellowish flecks in the macular region or beyond the arcades.
- Fundus autofluorescence (FAF) shows areas of hyperfluorescence or hypofluorescence corresponding to lipofuscin contents in the RPE.
- Most patients retain good vision for many years or decades, until the development of choroidal neovascularization or marked atrophy of the RPE.

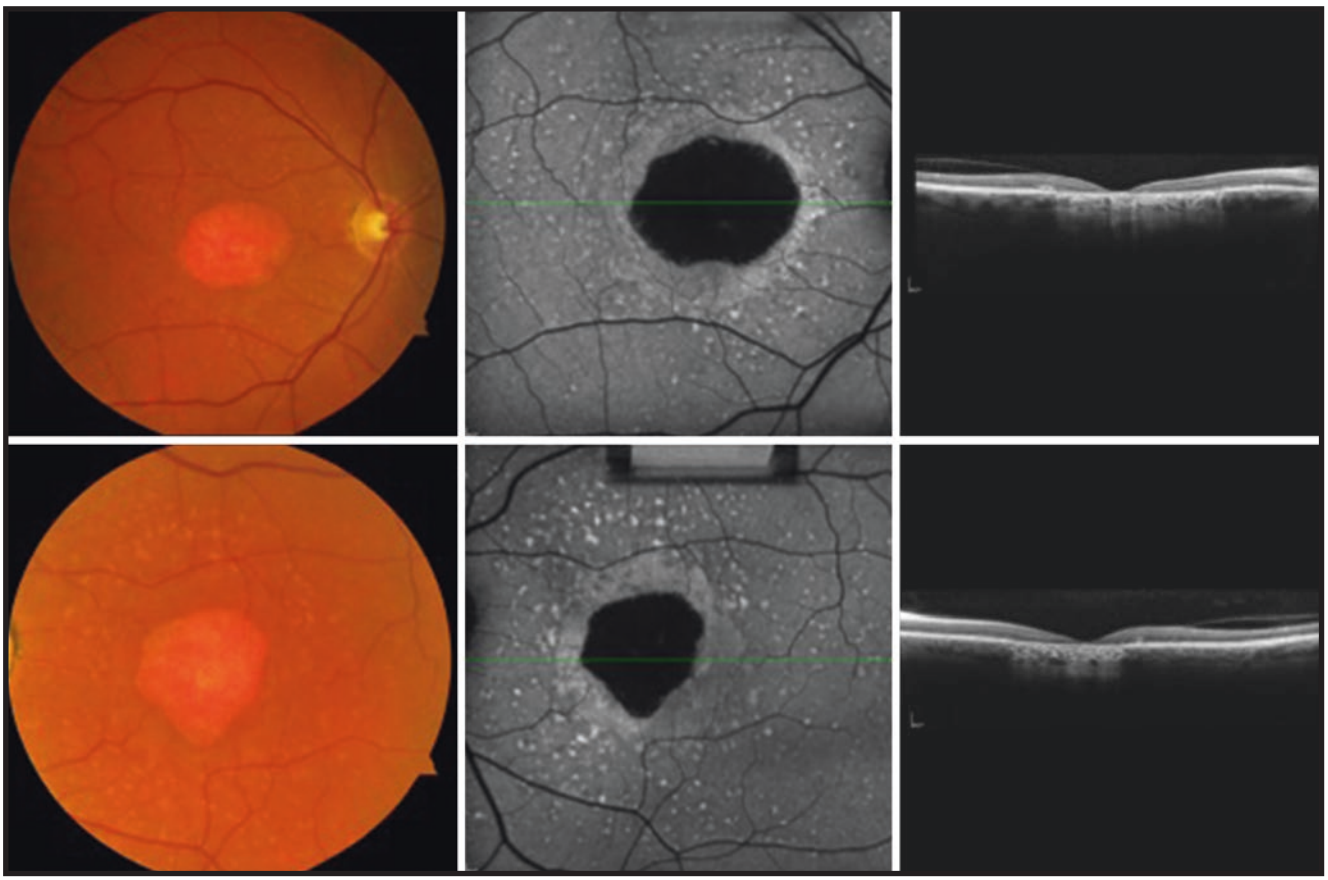

Fig. 17.1 In this patient with *PRPH2* mutation (late stage) an area of retinal pigment epithelial (RPE) atrophy is seen in the macular area, with multiple faint flecks. Fundus autofluorescence (FAF) shows a central area of RPE atrophy surrounded by hyperfluorescent dots. Optical coherence tomography (OCT) shows central RPE atrophy with increased transmission

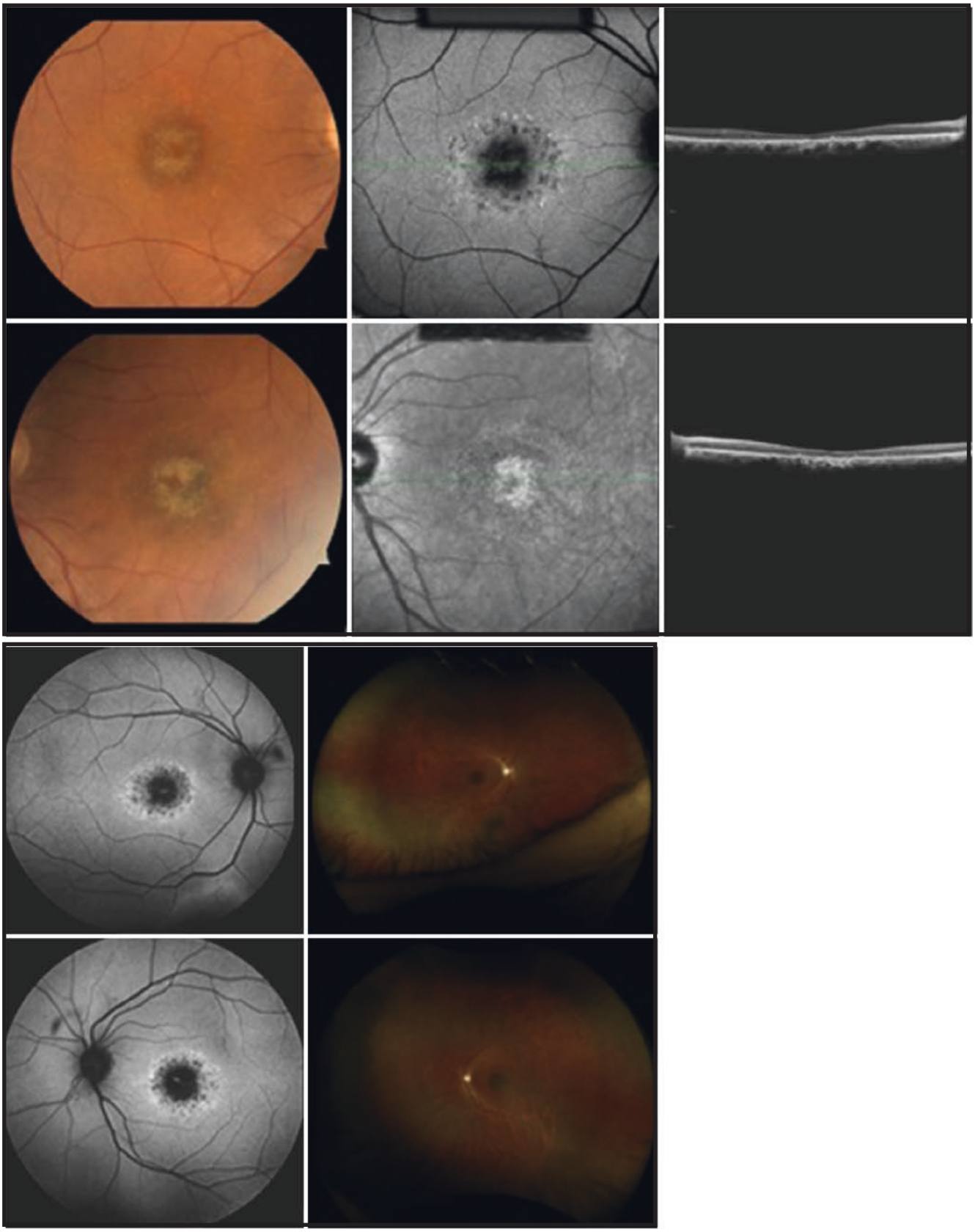

Fig. 17.2 A 5-year follow-up of a case of advanced-stage, pattern dystrophy. The right eye remains stable, but the left macula shows increasing RPE dysfunction

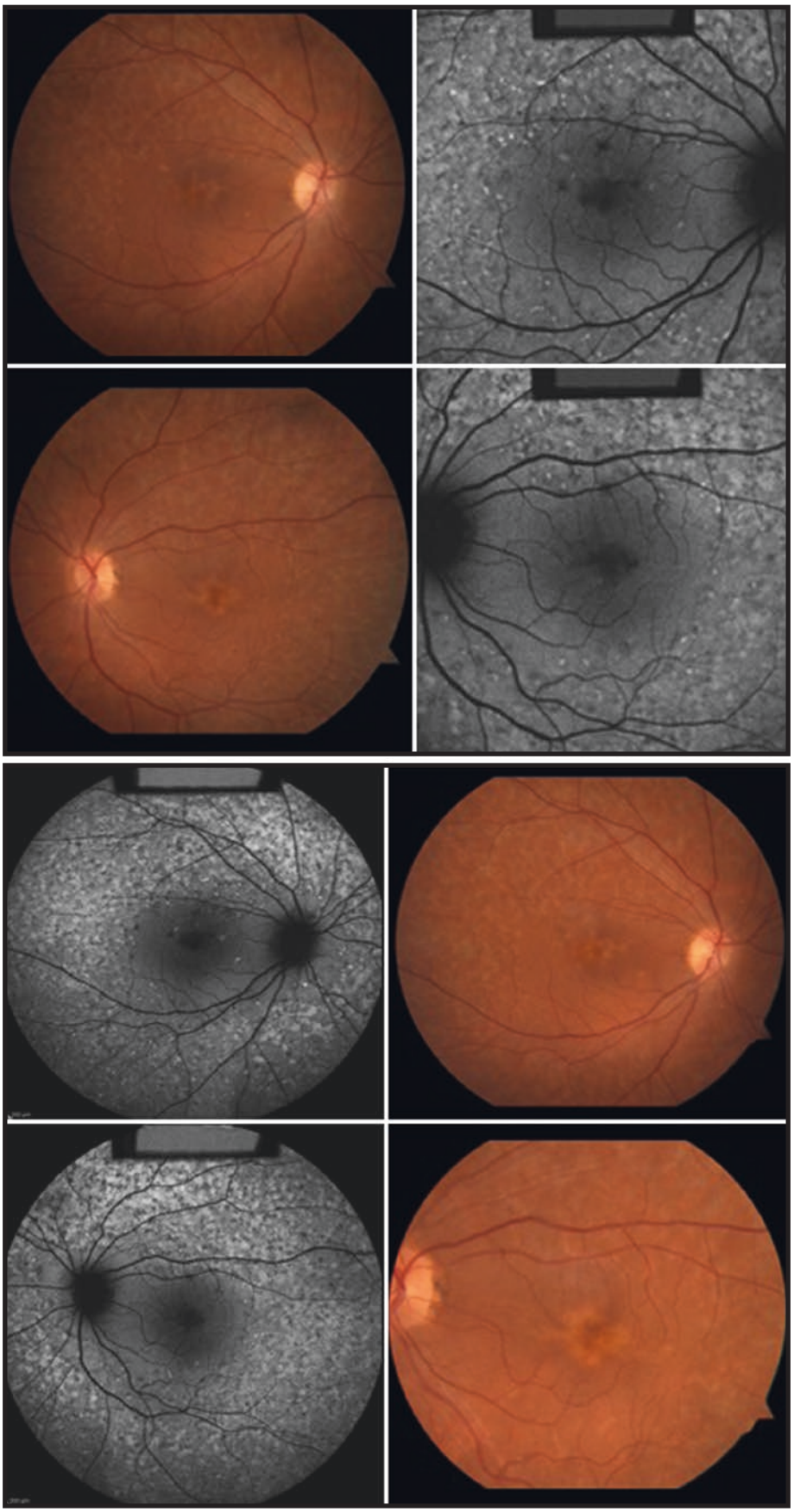

Fig. 17.3 A 2-year follow-up of a case of butterfly-type pattern dystrophy with *PRPH2* mutation. No change was observed in RPE dysfunction on FAF

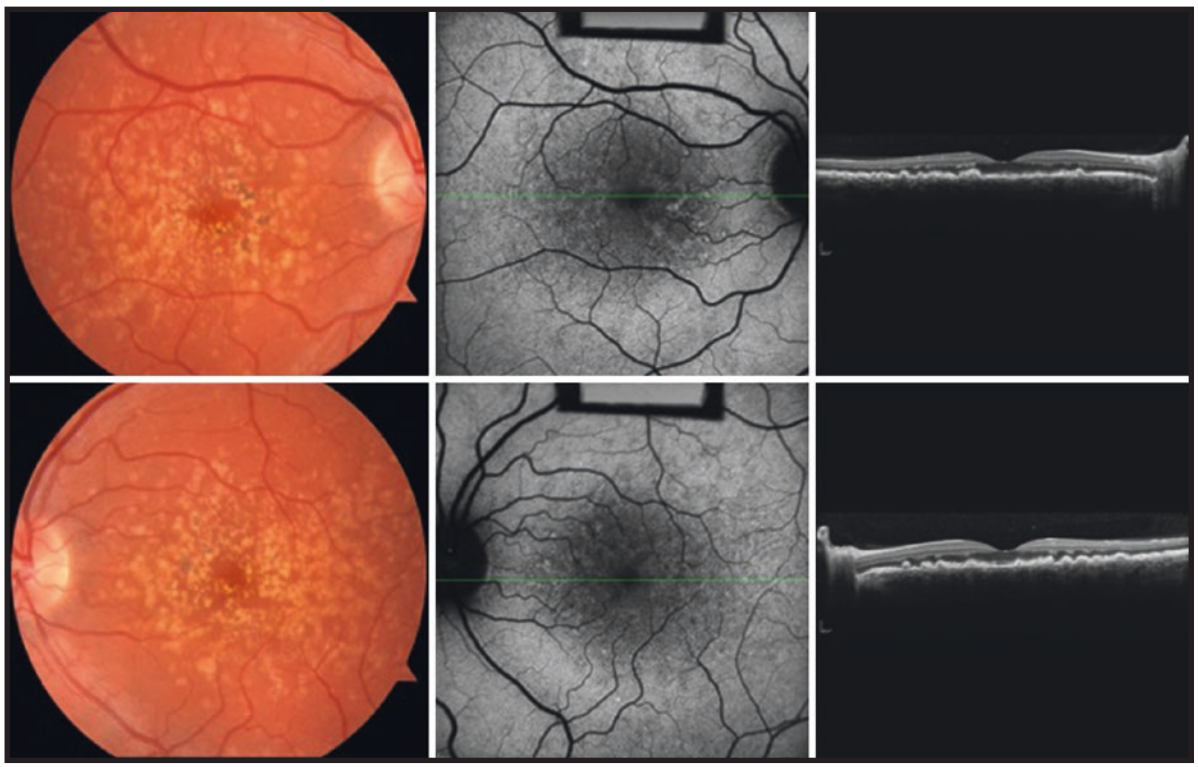

Fig. 17.4 A case of pattern dystrophy with drusen and *PRPH2* mutation. Color fundus shows pigmented dots surrounded by a halo and numerous drusen. FAF shows relatively good RPE function; OCT shows drusen excrescences

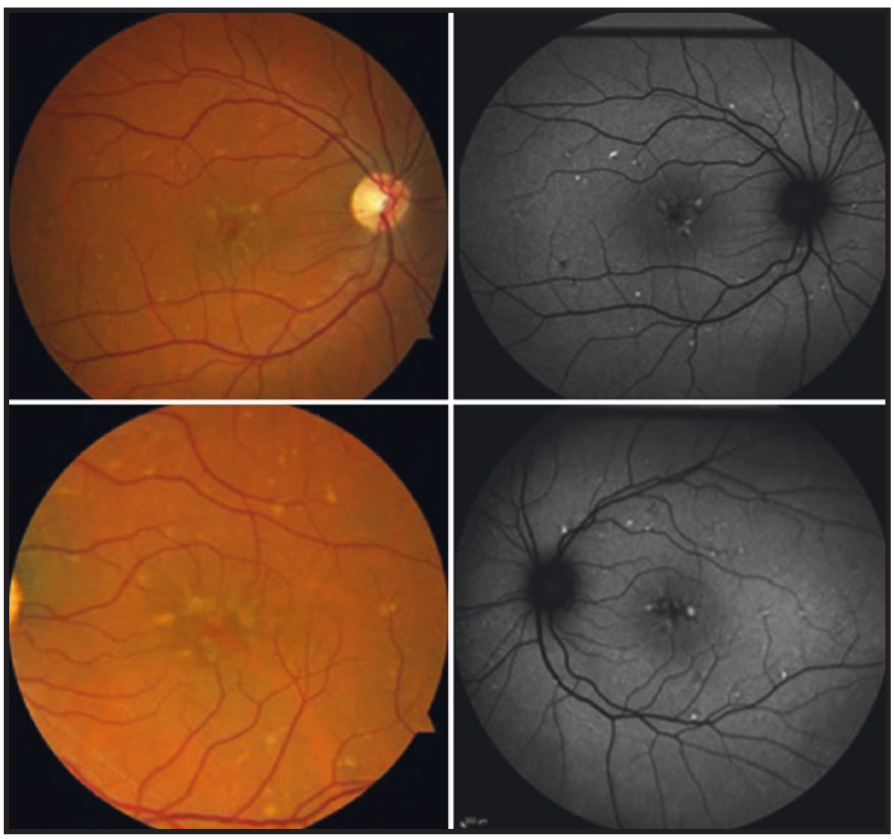

Fig. 17.5 A case of pattern dystrophy. A stellate pattern is more discernible on FAF

Adult-Onset Foveomacular Vitelliform Dystrophy

- The lesion mimics Best disease (see Chap. 16), but the yellow lesion is smaller and has an associated central pigment clump. Unlike Best disease, patients present late in life (fourth or fifth decade) with mild visual impairment, which progresses slowly. The Arden ratio is normal or slightly low. FAF shows hyperautofluorescence.
- With time, some lesions may evolve to butterfly-shaped pattern dystrophy or may develop flecks (as in Stargardt disease).

Sjogren's Reticular-Type Pattern Dystrophy

- As the name suggests, the lesion is a network of black-pigmented lines, crisscrossing like fishnet with knots, which may even extend to the periphery. The pattern is well delineated on fluorescein and FAF.

Fundus Pulverulentus

- In this rare entity, RPE stippling at the macula occurs with fine pigment clumping interspersed with areas of RPE depigmentation.

Molecular Genetics

PRPH2 Gene (*Peripherin/RDS* or *rd2* or *Peripherin-2* or *RDS*)

- Most of the pattern dystrophies are associated with mutations in *PRPH2*. Some cases of adult-onset vitelliform dystrophy may be associated with mutations in *BEST1* or *IMPG1* and *IMP*.
- The *PRPH2* gene is responsible for making a protein called peripherin 2.
- The peripherin 2 protein is located in the rim region of rods and cones' outer segment (OS) discs and lamellae; it plays a critical role in OS morphogenesis.
- *PRPH2* mutations result in an autosomal dominant phenotype in most situations, except for digenic retinitis pigmentosa (RP), which requires a mutation in the *ROM1* gene.
- *PRPH2* mutation results in vitelliform macular dystrophy, cone-rod dystrophy, RP, and butterfly-type pattern dystrophy. At least 100 mutations have been identified.
- Phenotypic variations are common even in the same family with identical *PRPH2* mutations, because of decreased penetrance and variable expression.
- Cytogenetic location: 6p21.1

Suggested Reading

Boon CJ, den Hollander AI, Hoyng CB, Cremers FP, Klevering BJ, Keunen JE. The spectrum of retinal dystrophies caused by mutations in the *peripherin/RDS* gene. Prog Retin Eye Res. 2008;27:213–35.

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CHAPTER 18

Doyne Honeycomb Retinal Dystrophy (Malattia Leventinese, Autosomal Dominant Drusen)

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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_18

General Features

In these conditions, drusen are present in childhood, but patients are asymptomatic, with good vision, until their 40s or 50s. Drusen are seen at the macula, around the edge of the optic nerve and/or nasal to the disc, in a radiating pattern (in particular, temporal to macula, as in Figs. 18.1, 18.2, 18.3, 18.4 and 18.5). The periphery is usually spared. Drusen increase in size and number with age. Peripapillary drusen are a characteristic finding. Visual loss later in life is due to pigment hyperplasia, geographic atrophy, and choroidal neovascular membrane (Figs. 18.6 and 18.7). Variability in the clinical picture is common within families.

Associated findings include hypertrophy of the retinal pigment epithelium (RPE) and irregular subretinal fibrosis. Drusen show areas of increased hyperautofluorescence, but reduced signal may be seen in areas of RPE atrophy. Optical coherence tomography (OCT) may show accumulation of the drusen material at the level of the RPE/choriocapillaris (CC) complex, under the RPE.

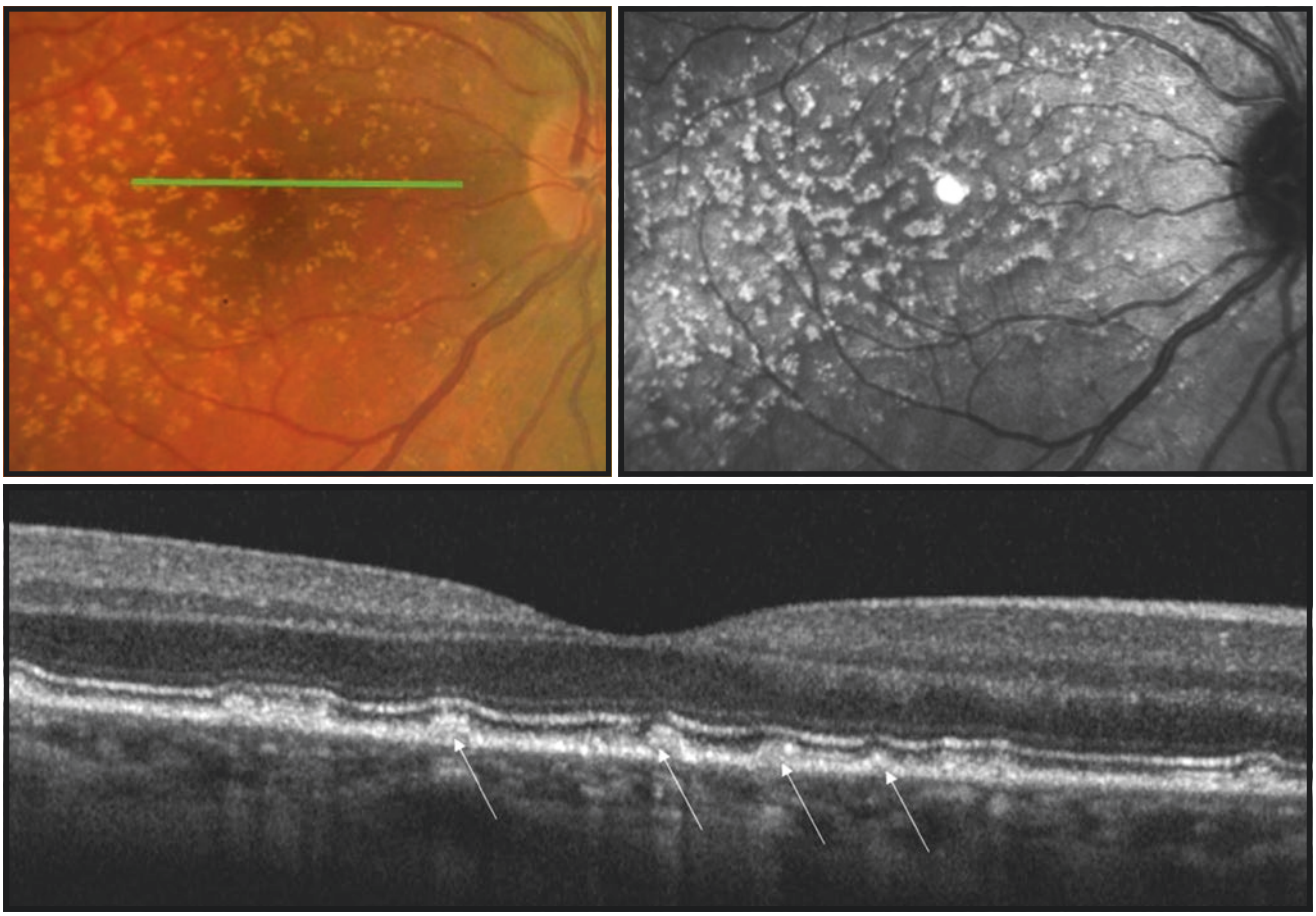

Fig. 18.1 Radial pattern of autosomal dominant drusen (upper row). Optical coherence tomography (OCT) shows drusen located under the retinal pigment epithelium (RPE) (lower row, *arrows*)

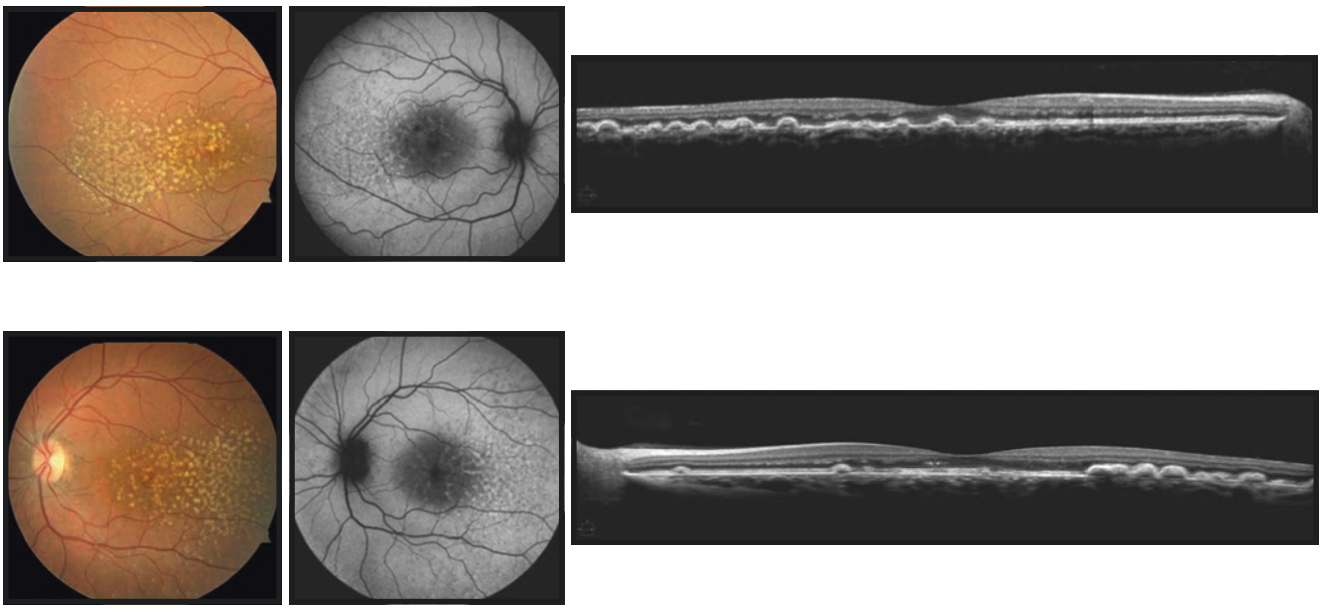

Fig. 18.2 Multiple drusen (Doyne-like or Pseudo-Doyne) along the horizontal raphe; fundus autofluorescence (FAF) shows good RPE function. OCT shows multiple bumps beneath the RPE

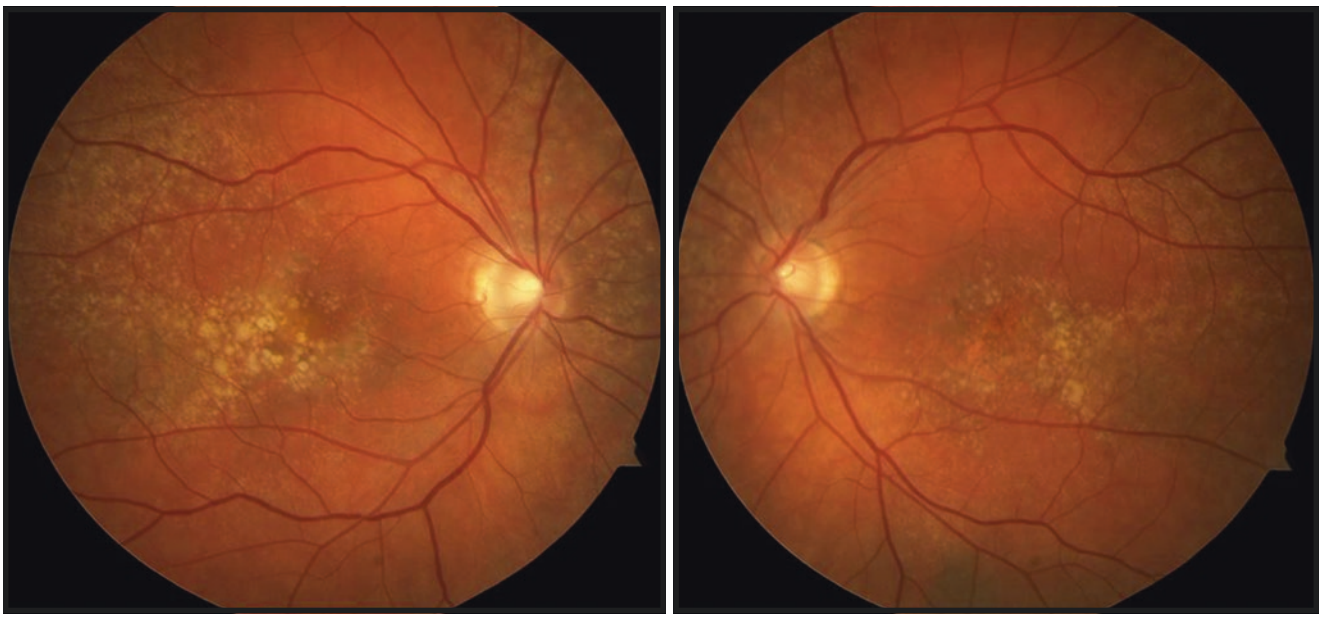

Fig. 18.3 Drusen at the macula and nasal to the optic disc; some of the drusen show pigmentation and some RPE shows atrophic changes

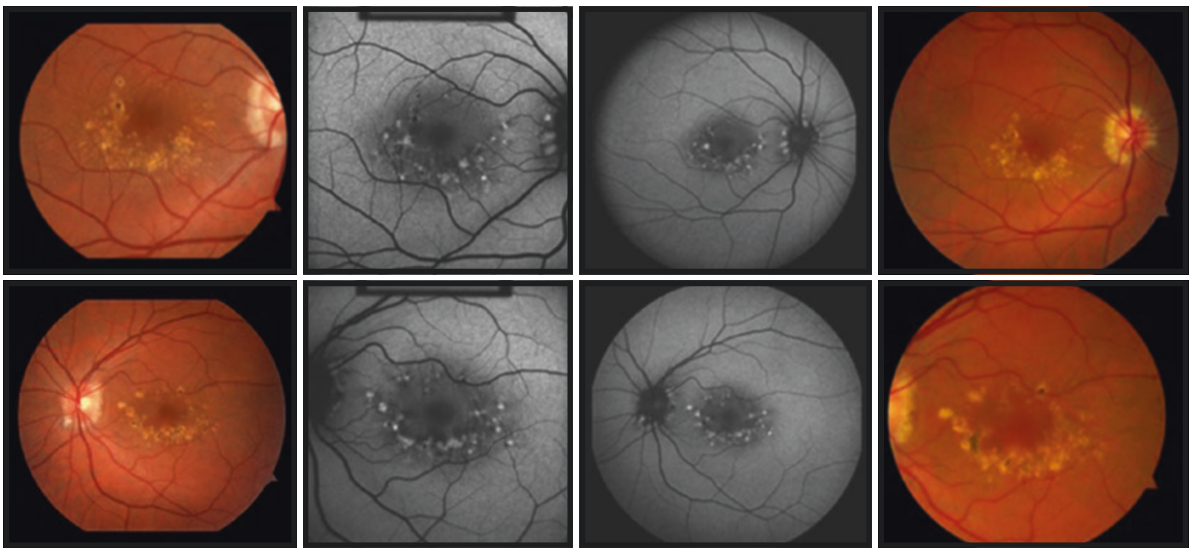

Fig. 18.4 Drusen at the macula and in the peripapillary area; FAF shows stable RPE function at a 2-year follow-up (p.Arg345Trp)

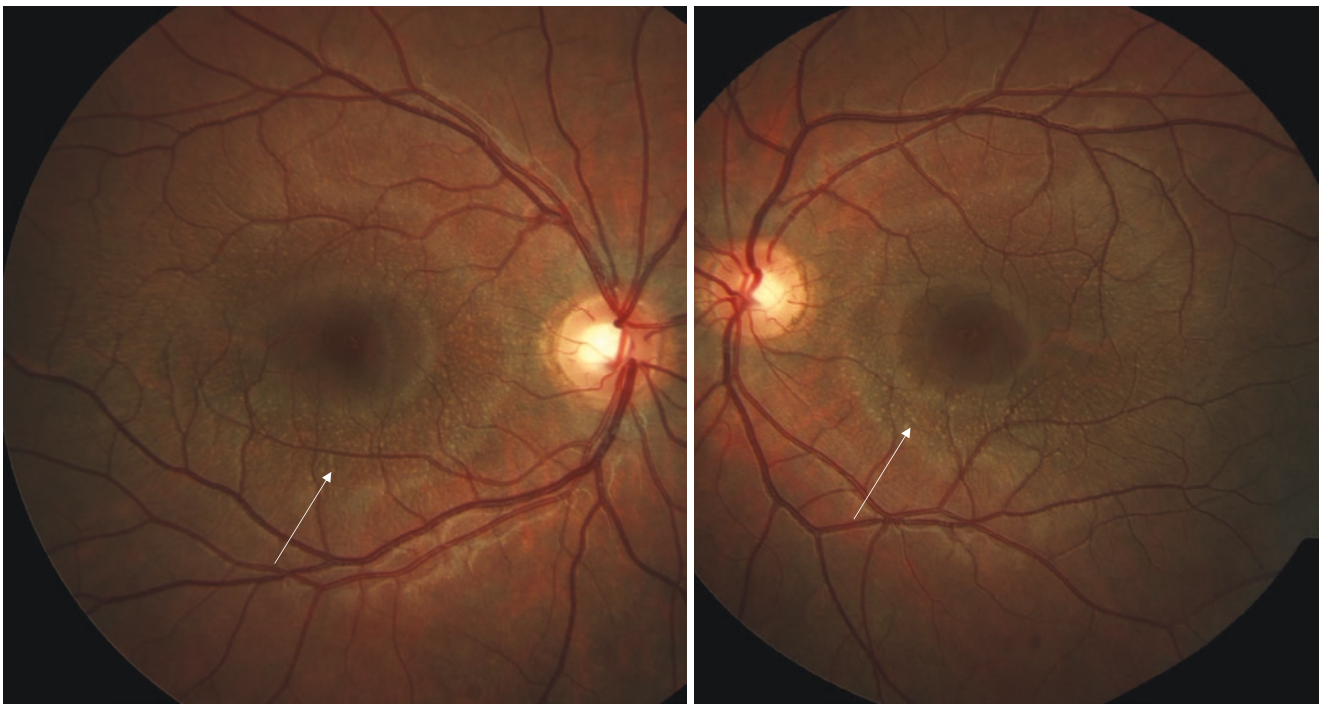

Fig. 18.5 Bilateral Doyne (*arrows*) almost encircling the fovea, in a young boy (p.Arg345Trp)

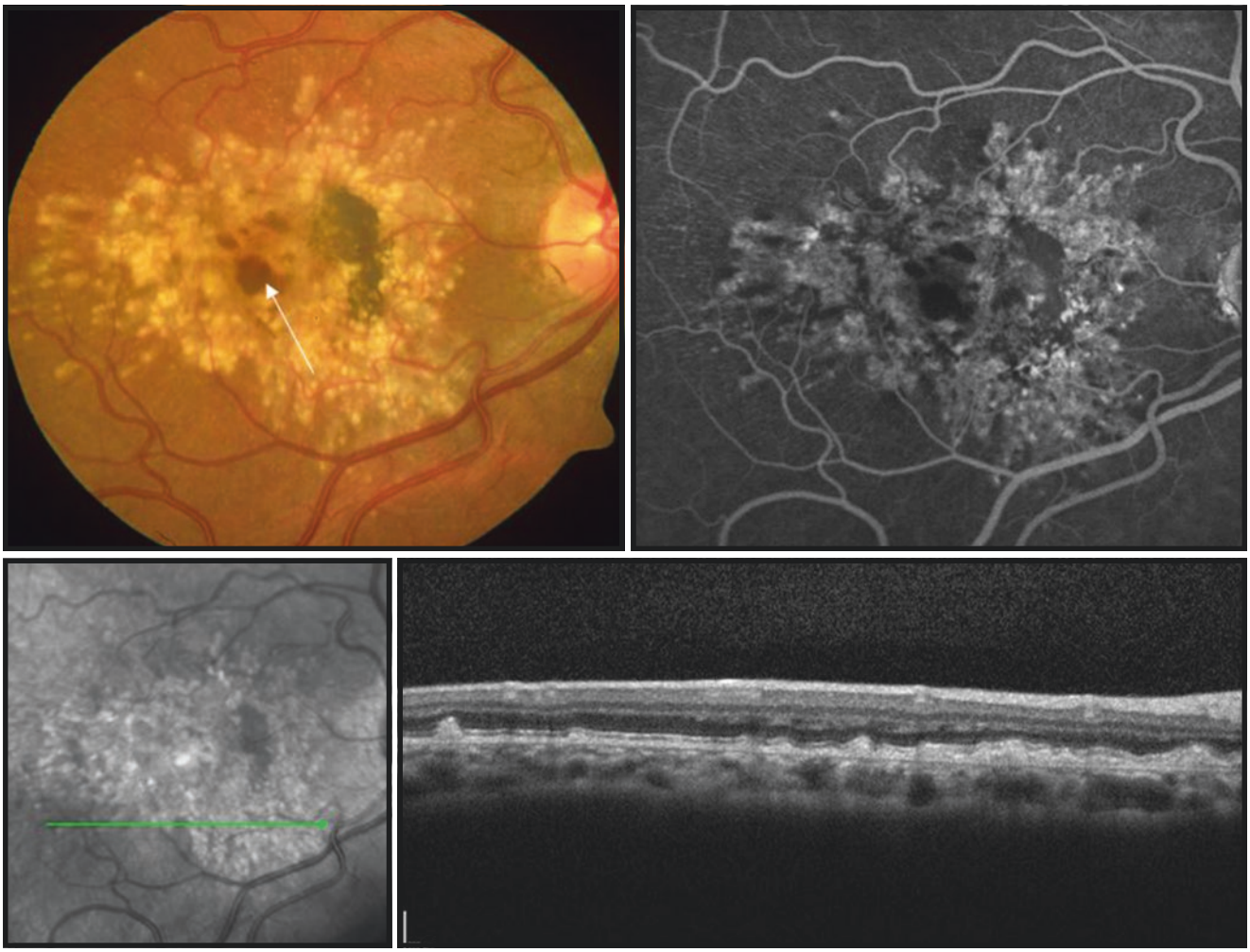

Fig. 18.6 Confluent drusen and radial pattern are discernible; the presence of hemorrhage (*arrow*) is suggestive of choroidal neovascular membrane (p.Arg345Trp)

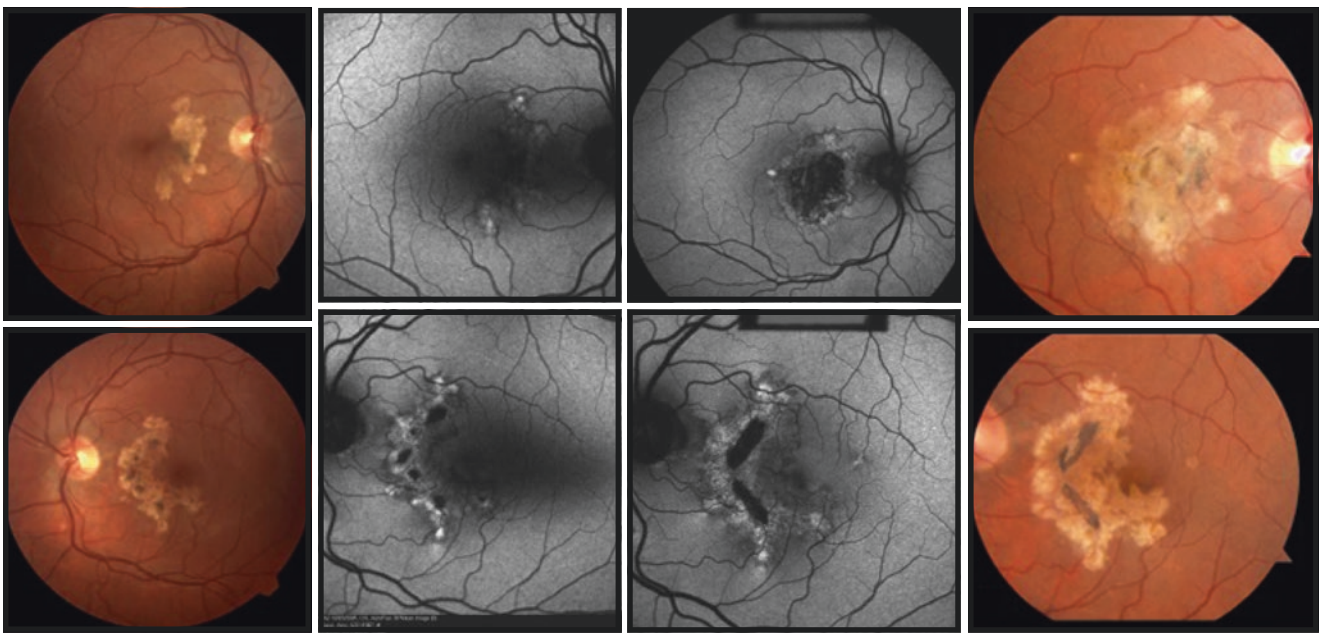

Fig. 18.7 Ten-year follow-up shows progression of drusen, which are becoming confluent, and FAF shows progressive RPE dysfunction (p.Arg345Trp)

Molecular Genetics

EFEMP1 Gene (*DHRD* or *DRAD* or *FBLN3* or *FIBL-3*)

- This gene is a member of the fibulin family of extracellular matrix glycoprotein.
- A single heterozygous missense mutation (p.Arg345Trp) in the *EFEMP1* (epidermal growth factor [EGF]–containing fibulin-like extracellular matrix protein 1) gene is responsible for this condition.
- Cytogenetic location: 2p16.1

Suggested Reading

Stone EM, Lotery AJ, Munier FL, Héon E, Piguet B, Guymer RH, et al. A single *EFEMP1* mutation associated with both Malattia Leventinese and Doyne honeycomb retinal dystrophy. Nat Genet. 1999;22:199–202.

Takeuchi T, Hayashi T, Bedell M, Zhang K, Yamada H, Tsuneoka H. A novel haplotype with the R345W mutation in the *EFEMP1* gene associated with autosomal dominant drusen in a Japanese family. Invest Ophthalmol Vis Sci. 2010;51:1643–50.

CHAPTER 19

Occult Macular Dystrophy

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General Features

Patients with occult macular dystrophy (OMD) are usually middle-aged and have progressive loss of central vision or notice central scotoma, but no significant abnormality is seen in the fundus or fluorescein angiography. Optical coherence tomography (OCT) shows loss of the ellipsoid band in the central area (Fig. 19.1). Full-field electroretinography (ERG) is normal or may show diminished cone response; multifocal ERG reveals diminished amplitude in the central retina.

Molecular Genetics

- The *RP1L1* (retinitis pigmentosa 1-like 1) mutation can result in varied patterns of retinal diseases, including autosomal dominant OMD and autosomal recessive retinitis pigmentosa.
- The gene (also known as *DCDC4B*, doublecortin domain-containing 4B) encodes a member of the doublecortin family and encodes a retina-specific protein. This protein and the RP1 protein have synergistic roles in outer segment morphogenesis.
- Cytogenetic location: 8p23.1

Suggested Reading

Ahn SJ, Cho SI, Ahn J, Park SS, Park KH, Woo SJ. Clinical and genetic characteristics of Korean occult macular dystrophy patients. Invest Ophthalmol Vis Sci. 2013;54:4856–63.

Hayashi T, Gekka T, Kozaki K, Ohkuma Y, Tanaka I, Yamada H, Tsuneoka H. Autosomal dominant occult macular dystrophy with an *RP1L1* mutation (R45W). Optom Vis Sci. 2012;89:684–91.

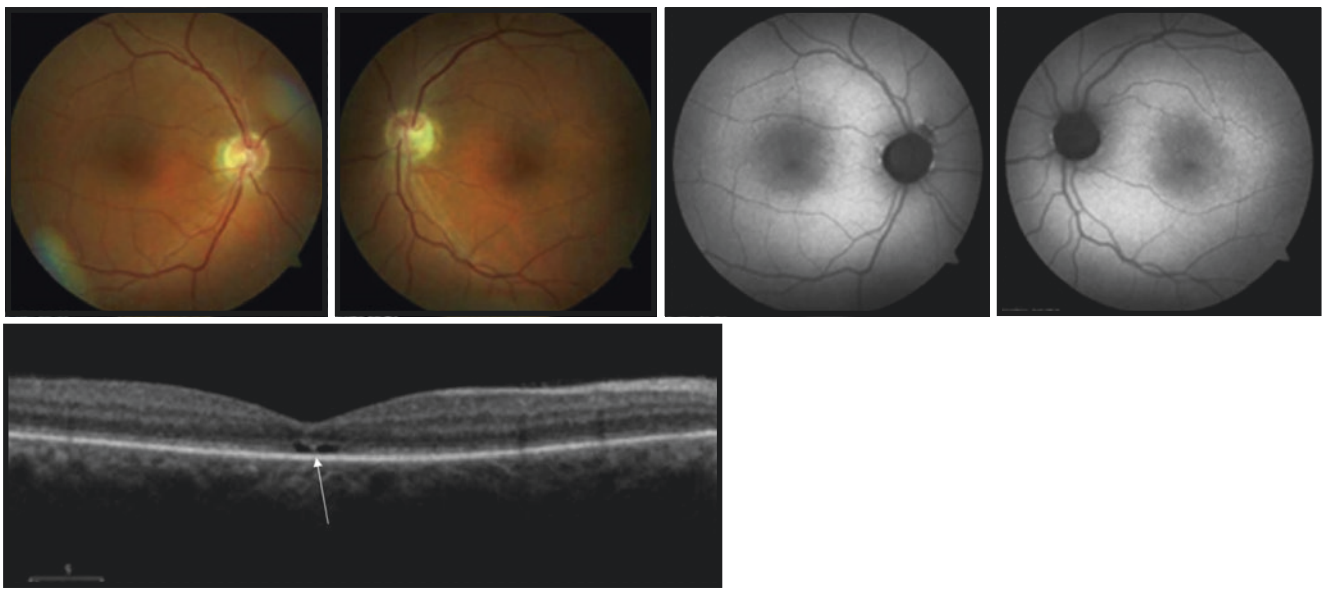

Fig. 19.1 Almost normal fundus and fundus autofluorescence (FAF) in a patient with occult macular dystrophy. Optical coherence tomography (OCT) shows an optical gap right at the center (*arrow*)

CHAPTER 20

Sorsby Pseudoinflammatory Fundus Dystrophy

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General Features

This dominantly inherited disease begins with fine, pale, drusen-like deposits or confluent faint yellow material or sheets beneath the retinal pigment epithelium (RPE), but it eventually progresses to either geographic atrophy with pigmentary clumps or scar due to choroidal neovascular membrane (at about 40 years of age) (Figs. 20.1, 20.2 and 20.3). The patient usually becomes symptomatic, with loss of central vision (about 20/200 or less), in the fourth to sixth decade of life. When neovascular membrane develops, it mimics age-related macular degeneration (AMD), but the age of onset is much earlier.

Initially, the fundus may be normal or may show fine, yellowish flecks or drusen. Fundus autofluorescence (FAF) does not show any hyperfluorescence in the early stage.

Molecular Genetics

TIMP3 Gene (K222 or SFD)

- The *TIMP3* gene encodes for a tissue inhibitor of metalloproteinase-3.
- Mutations reside in or affect exon 5 (C-terminal portion of the protein).
- Cytogenetic location: 22q12.3

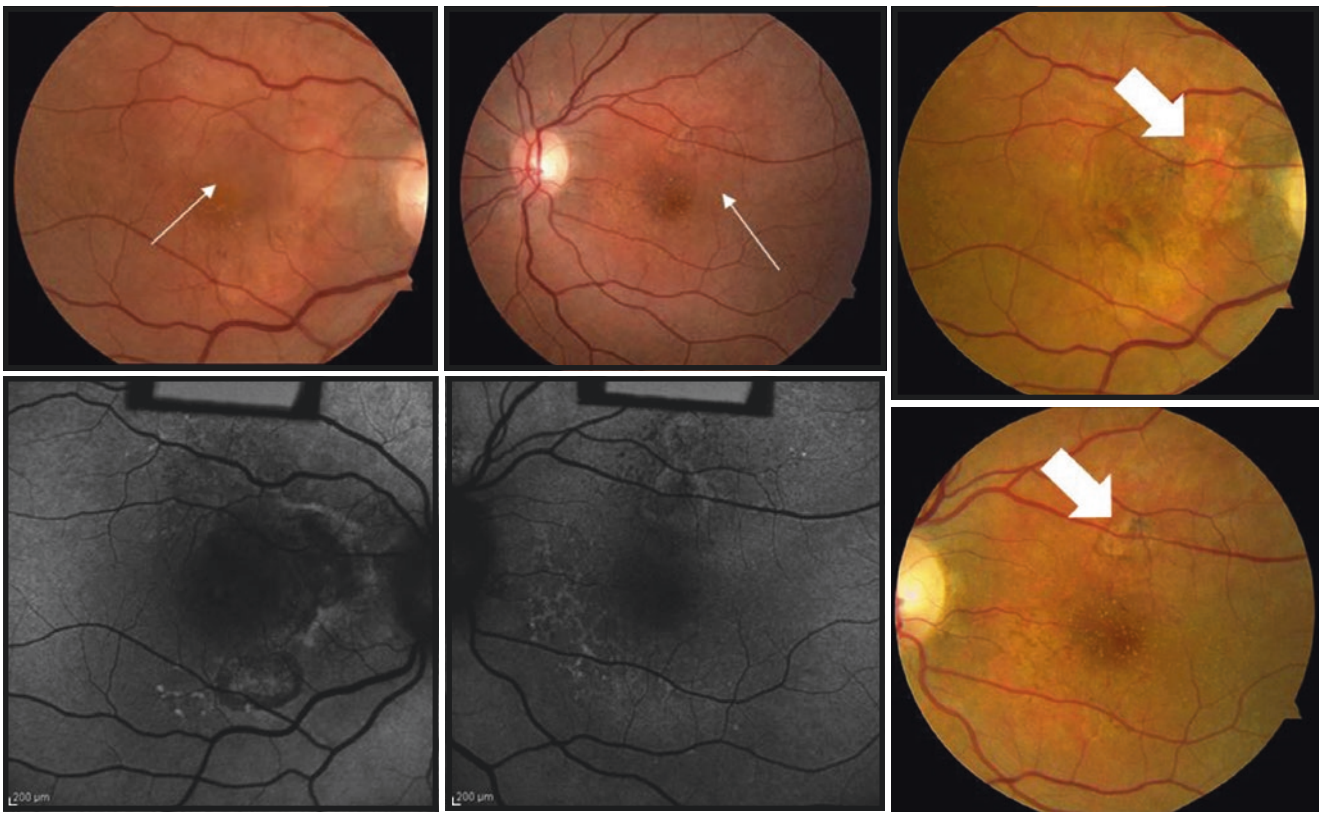

Fig. 20.1 At the initial visit (left), the fundus showed fine, yellowish flecks at the macula (*arrows*) and corresponding retinal pigment epithelial (RPE) dysfunction on fundus autofluorescence (FAF); 6 months later (right), it has progressed to RPE atrophy, more in the right eye than in the left (*thick arrows*)

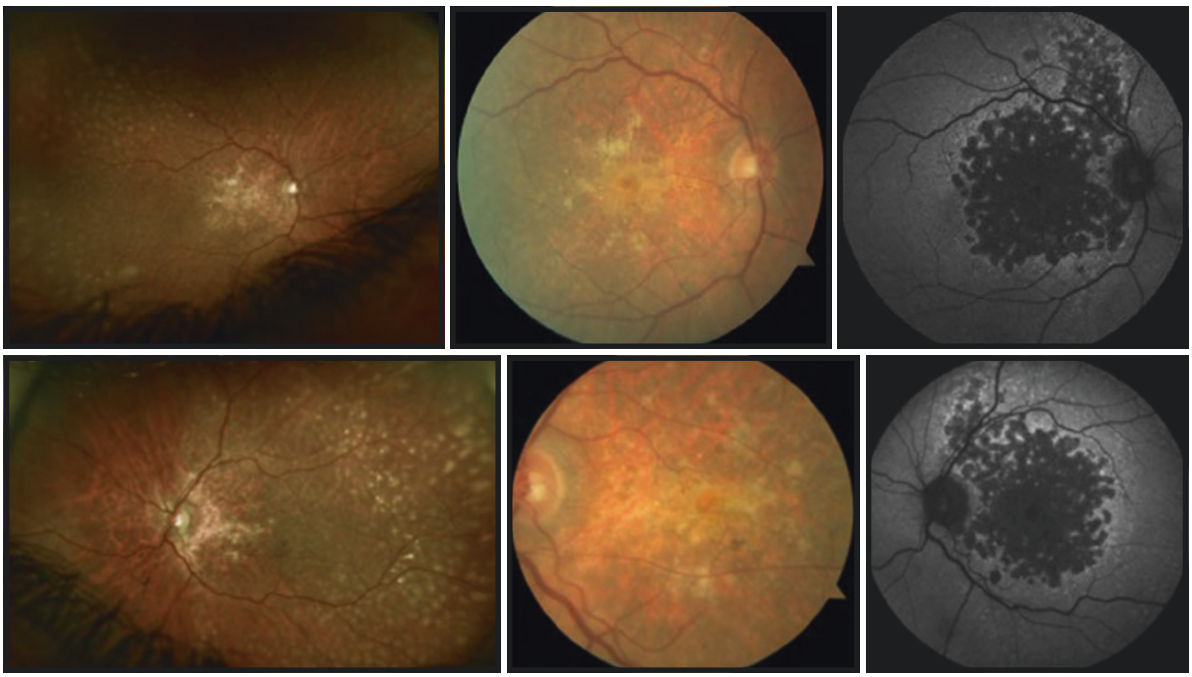

Fig. 20.2 Atrophic changes at the macula along with some peripheral yellowish deposit, and severe RPE dysfunction on FAF

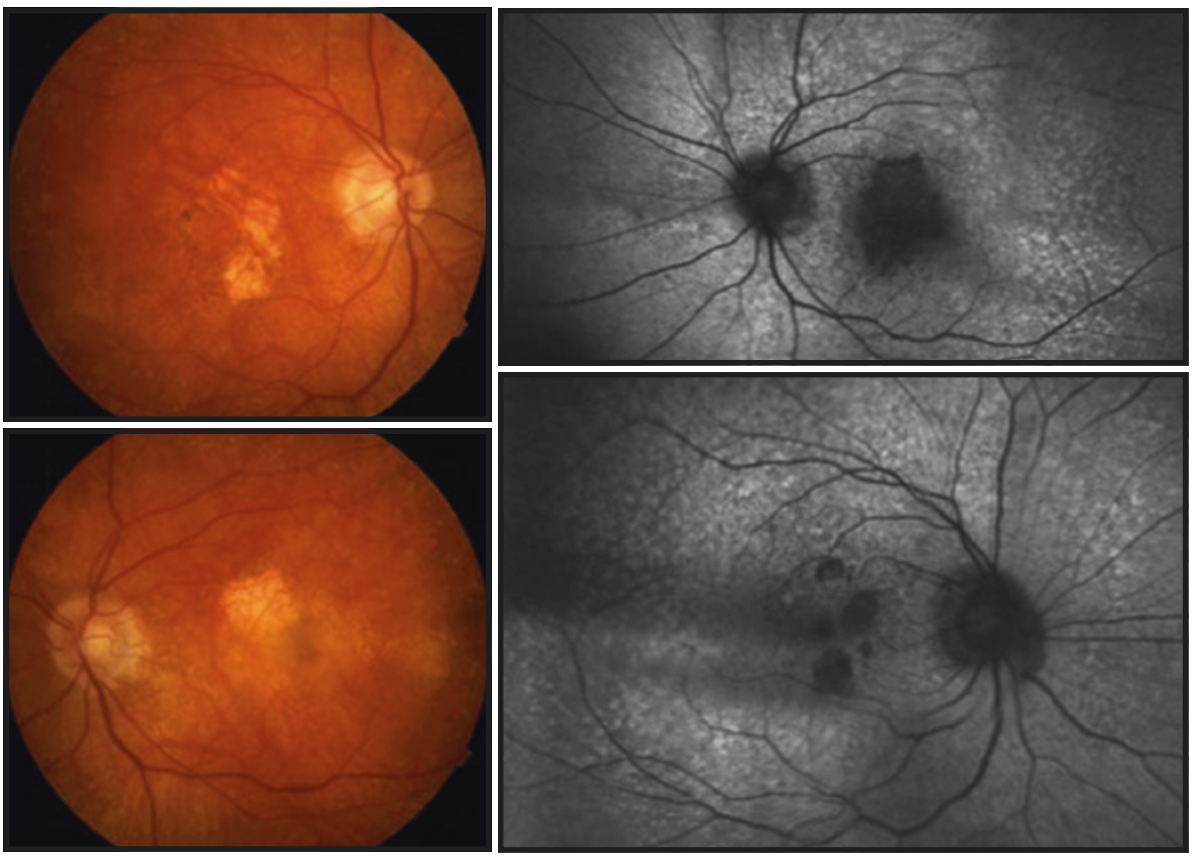

Fig. 20.3 *TIMP3* gene mutation causing Sorsby macular dystrophy with advanced RPE and choriocapillaris (CC) atrophy on color fundus and FAF (greater in the right eye)

Suggested Reading

Polkinghorne PJ, Capon MR, Berninger T, Lyness AL, Sehmi K, Bird AC. Sorsby's fundus dystrophy. A clinical study. Ophthalmology. 1989;96:1763–8.

Sorsby A, Mason ME. A fundus dystrophy with unusual features. Br J Ophthalmol. 1949;33:67–97.

CHAPTER 21

North Carolina Macular Dystrophy

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General Features

North Carolina macular dystrophy (NCMD) has a variable phenotype (Fig. 21.1). Patients are usually infants, in whom the fundus shows a cluster of yellowish-white lesions (like drusen) at the macula (grade 1); sometimes the lesions are confluent (grade 2). As the disease progresses, retinal pigment epithelial (RPE) atrophy sets in, and the lesion may appear excavated like a coloboma (grade 3) or a toxoplasmosis scar with a thick, white, fibrotic rim.)

Visual acuity is normal in grade 1 and grade 2, but there is central visual loss in grade 3. Most patients retain good vision despite advanced macular phenotype.

Molecular Genetics

The abnormal gene, *MCDR1*, is located on chromosome 6q. It causes abnormality in the regulation of the retinal transcription factor PRDM 13 (novel tandem duplication).

Suggested Reading

Reichel M, Kelseli R, Fan J, Gregory CY, Evans K, Moore AT, et al. Phenotype of a British North Carolina macular dystrophy family linked to chromosome 6q. Br J Ophthalmol. 1998;82:1162–8.

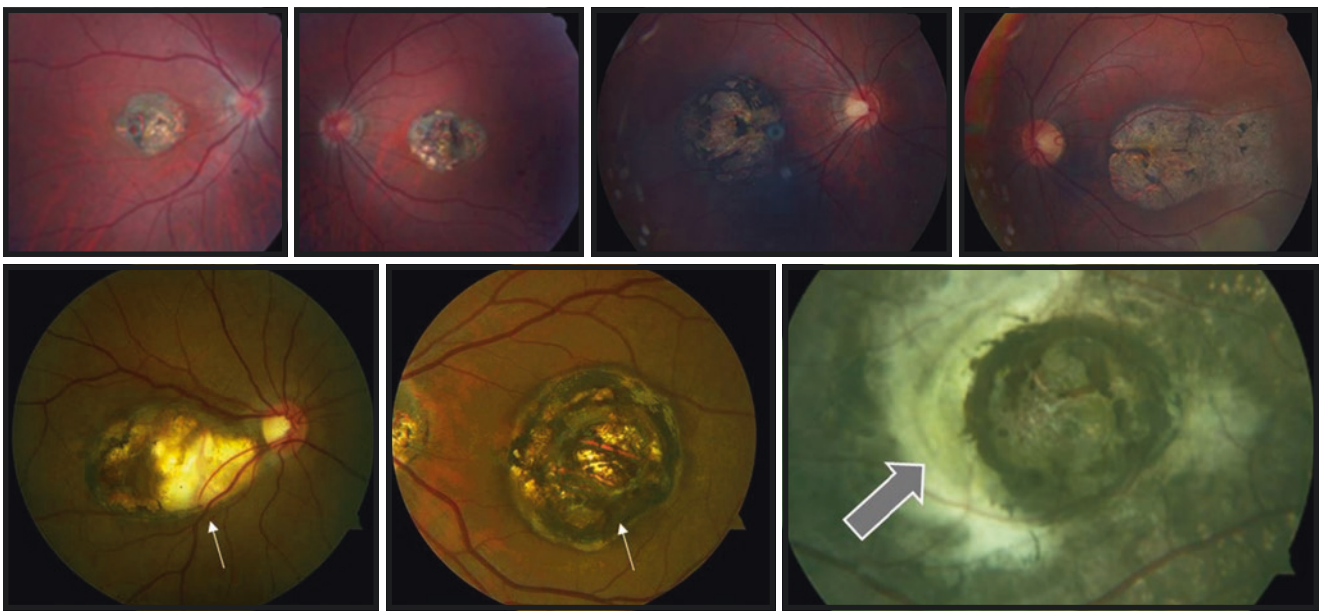

Fig. 21.1 Variable phenotype of North Carolina macular dystrophy: Upper row, macular scar; Bottom row, a bit of excavation (*thin arrows*) and thick, fibrotic rim (*thick arrow*)

CHAPTER 22

Pigmented Paravenous Chorioretinal Atrophy (PPCRA)

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General Features

As the name suggests, in pigmented paravenous chorioretinal atrophy (PPCRA), patches of chorioretinal atrophy and pigment clumping are distributed along the veins (Figs. 22.1 and 22.2). In most cases, the retinal vessels, macula, and optic discs are normal, and the disease is usually nonprogressive.

Molecular Genetics

The mutation is in the gene *CRB1*, located at 1q31.3.

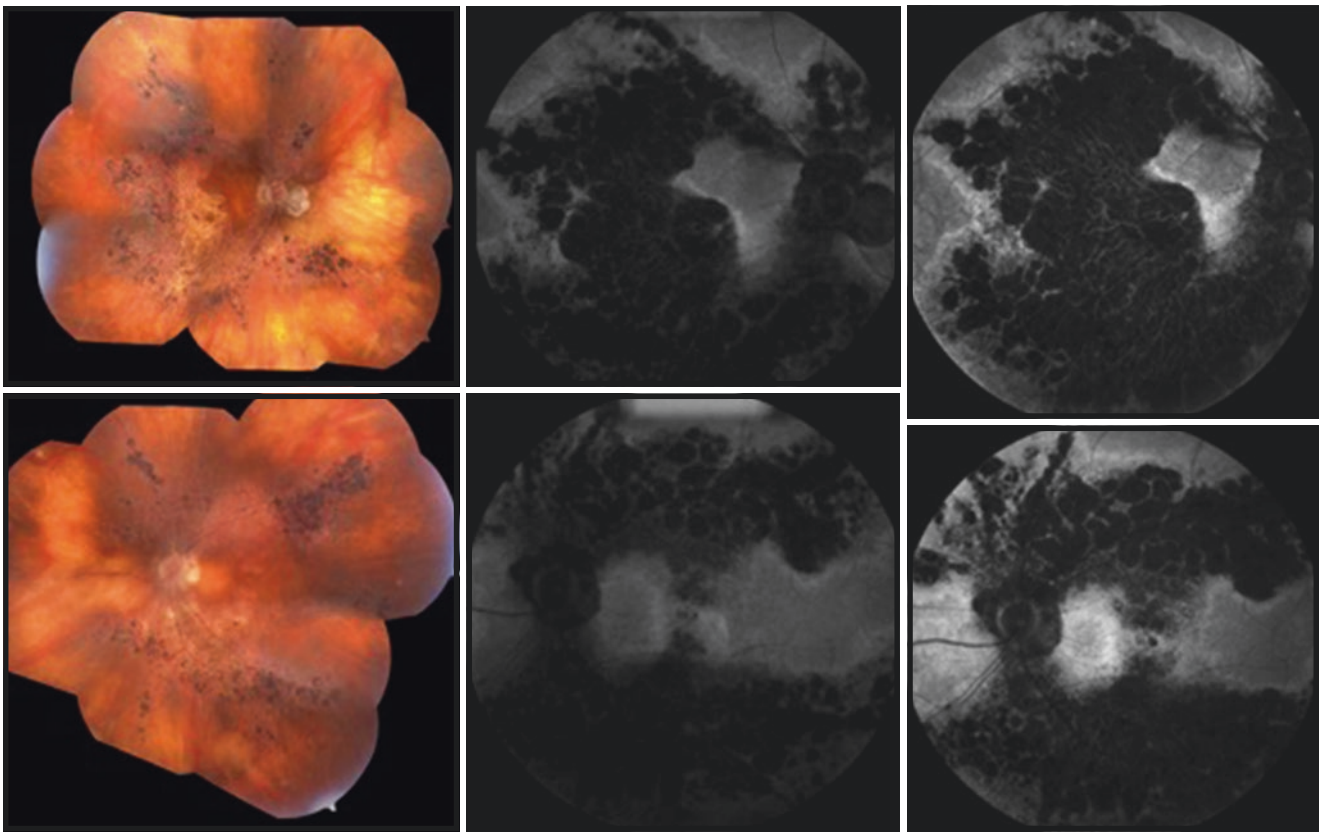

Fig. 22.1 Five-year follow-up of a case of pigmented paravenous chorioretinal atrophy (PPCRA), showing little progression

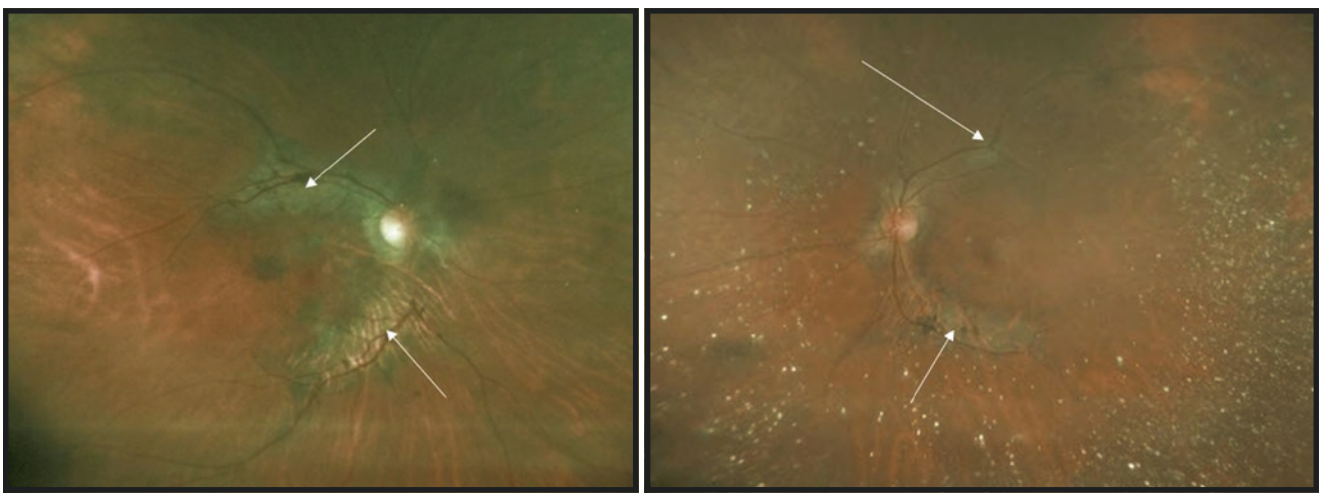

Fig. 22.2 Note the distribution of pigmentary changes along the veins (*arrows*)

Suggested Reading

Barteselli G. Fundus autofluorescence and optical coherence tomography findings in pigmented paravenous retinochoroidal atrophy. Can J Ophthalmol. 2014;49:144–6.

CHAPTER 23

Late-Onset Retinal Degeneration

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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_23

General Features

Patients with late-onset retinal degeneration (LORD) usually present with nyctalopia in the fifth or sixth decade of life. The fundus shows yellowish-white, punctate deposits, usually progressive and giving rise to scalloped areas of retinal pigment epithelium (RPE) atrophy in the mid-periphery and posterior pole (Fig. 23.1). The anterior segment shows elongated zonules with central lens insertion and transillumination defect in the iris, due to iris atrophy.

Molecular Genetics

C1QTNF5 Mutation (*CTRP5*)

- LORD is related to mutation in the *C1QTNF5* gene, which is expressed in the RPE, lens, and ciliary epithelium.
- The gene encodes a family of protein that functions as components of basement membranes and may play a role in cell adhesion.
- Cytogenetic location: 11q23.3

Suggested Reading

Cukras C, Flamendorf J, Wong WT, Ayyagari R, Cunningham D, Sieving PA. Longitudinal structural changes in late-onset retinal degeneration. Retina. 2016;36:2348–56.

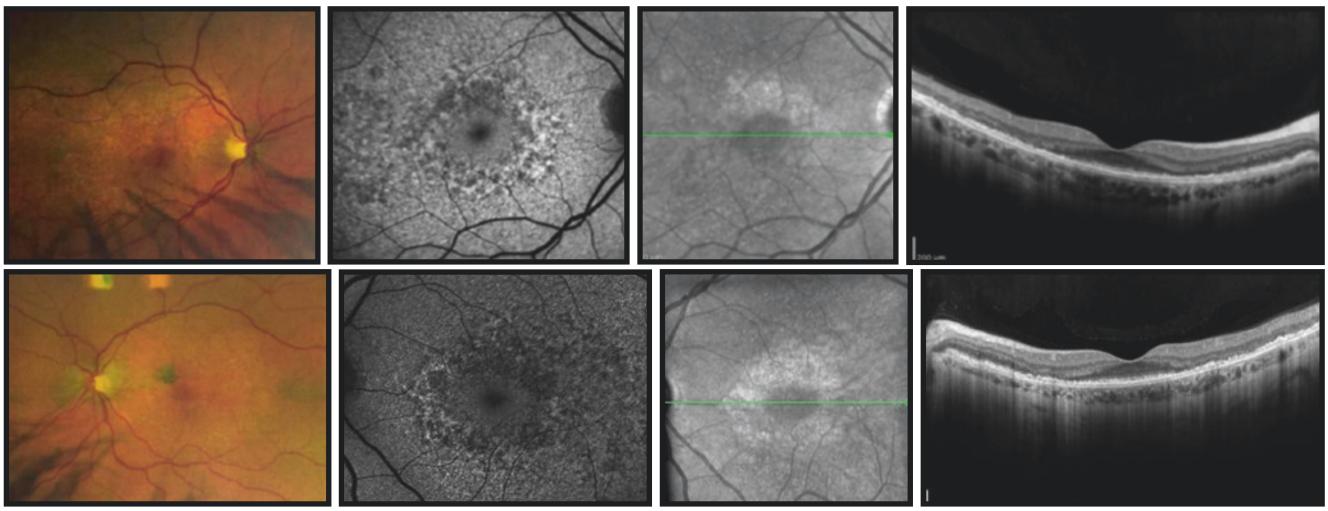

Fig. 23.1 Late-onset retinal degeneration (LORD) caused by *CTRP5* mutation. Fundus autofluorescence (FAF) shows a speckled pattern

Section IV

Autosomal Recessive Form

CHAPTER 24

Rod Monochromatism (Achromatopsia)

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General Features

- Rod monochromatism (achromatopsia) is a congenital cone photoreceptor disorder, which is rare, affecting about 1 in 30,000 individuals. These patients have normal rod function but no detectable cone function; therefore, everything they see is in shades of gray (total color blindness). Patients usually present in infancy with nystagmus and photophobia. Vision is usually about 20/200 or worse; patients have a hyperopic refractive error. Some patients show paradoxical pupillary response; that is, the pupils dilate in bright light. Fundus examination is normal, though pigmentary mottling and atrophic changes may be observed at the macula.
- *Incomplete achromatopsia*: Patients in this group have somewhat better visual acuity, about 20/80 to 20/120, with some residual functioning of cone photoreceptors. This milder form allows some color discrimination.
- Complete achromatopsia: It occurs in about 4–10% of Pingelapese islanders, who live on one of the Eastern Caroline Islands of Micronesia.

Stages

Figure 24.1 illustrates the stages of achromatopsia on the basis of spectral domain optical coherence tomography (SD-OCT):

- Stage 1: Intact outer retina
- Stage 2: Inner segment ellipsoid line disruption
- Stage 3: Presence of an optically empty space
- Stage 4: Optically empty space with partial retinal pigment epithelium (RPE) disruption
- Stage 5: Complete RPE disruption and/or loss of outer nuclear layer

On fundus autofluorescence (FAF) imaging, the presence of hypoautofluorescence is suggestive of progressive retinal degeneration (Fig. 24.2).

A full-field electroretinography (ERG) shows an affected cone response (Fig. 24.3), and a multifocal (mf) ERG shows an attenuated photopic response.

Molecular Genetics

- **CNGA3 (cyclic nucleotide gated channel alpha 3)**: responsible for about 20–30% of cases. It encodes for alpha subunit of cone cyclic guanosine monophosphate (cGMP)–gated cation channel. CNG channels remain open in darkness, allowing transport of positively charged atoms (cations). When light enters the eye, it triggers the closure of these channels, stopping the inward flow of cations. Cytogenetic location: 2q11.2
- **CNGB3**: accounts for 40–50% of cases and encodes for beta 3 subunit of the cGMP-gated cation channel. Cytogenetic location: 8q21.3
- **GNAT2 (G protein subunit alpha transducin 2)**: encodes for the alpha subunit of cone-related transducin. Cytogenetic location: 1p13.3
- **PDE6C (Phosphodiesterase 6C)**: encodes for cGMP-specific cone phosphodiesterase 6C alpha protein. Cytogenetic location: 10q23.33
- **PDE6H**: on chromosome 12, encodes for inhibitory Y subunit of the cone photoreceptor cGMP phosphodiesterase.

The latter three genes, GNAT2, PDE6C, and PDE6H, account for just 5% of all cases. Mutations in CNGA3 and PDE6H have been associated with incomplete achromatopsia.

All mutations except CNGA3 have been associated with progressive cone dystrophies, so achromatopsia may not always be a stationary disorder.

ATF6 (activating transcription factor 6) gene or ACHM7: may play a role in foveal development and cone function in the retina.

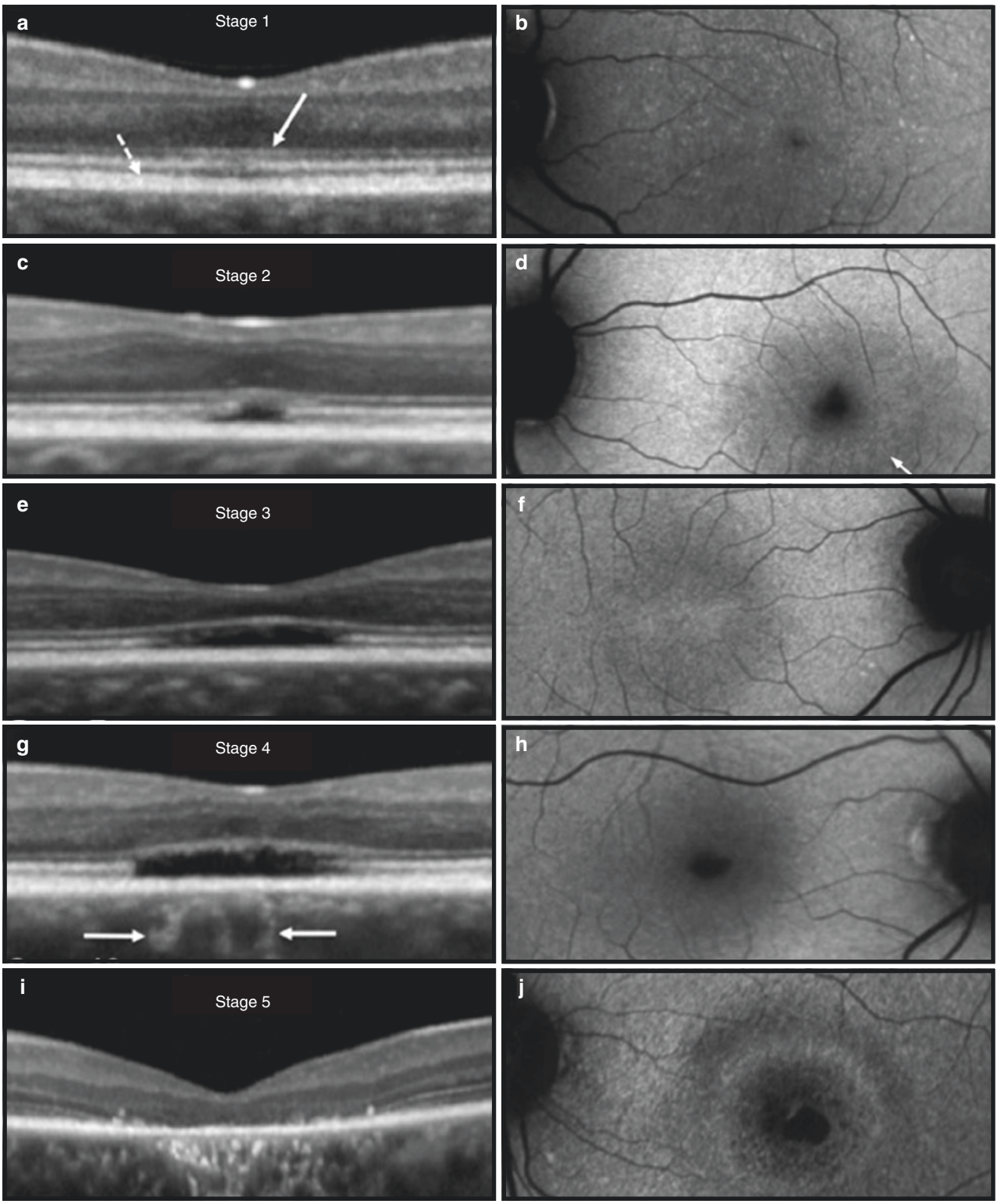

Fig. 24.1 (**a**) Spectral domain optical coherence tomography (SD-OCT) shows subtle discontinuity of the inner segment ellipsoid (ISe) line posterior to the foveola. The cone outer segment tip (COST) layer (*left arrow*) is thinned toward the foveal center, and the external limiting membrane (*right arrow*) is hyperreflective. (**b**) Fundus autofluorescence (FAF) imaging shows decreased macular pigment contrast and fine pigment hyperautofluorescent dots scattered across the macula. (**c**) SD-OCT shows disruption of the ISe line, interruption of the COST layer, and hyperreflectivity of photoreceptor inner segments. (**d)** FAF shows centrally reduced autofluorescence with subtle hyperautofluorescence around the inferotemporal fovea (*arrow*). (**e**) SD-OCT shows the classic optically empty space (OES), but the retinal pigment epithelium (RPE) is intact. (**f**) FAF shows hyperautofluorescence, with a stippled appearance. (**g**) SD-OCT shows an OES and partial RPE disruption (choroidal hyperreflectance, *arrows*). The roof of the OES shows reflective material, possibly from photoreceptor debris. (**h**) FAF shows a central area of reduced autofluorescence suggestive of some RPE dysfunction. (**i**) SD-OCT shows complete disruption of the RPE and loss of the outer nuclear layer. (**j**) FAF shows an area of hypofluorescence in the center (absent autofluorescence, due to RPE atrophy) with a surrounding hyperfluorescent ring

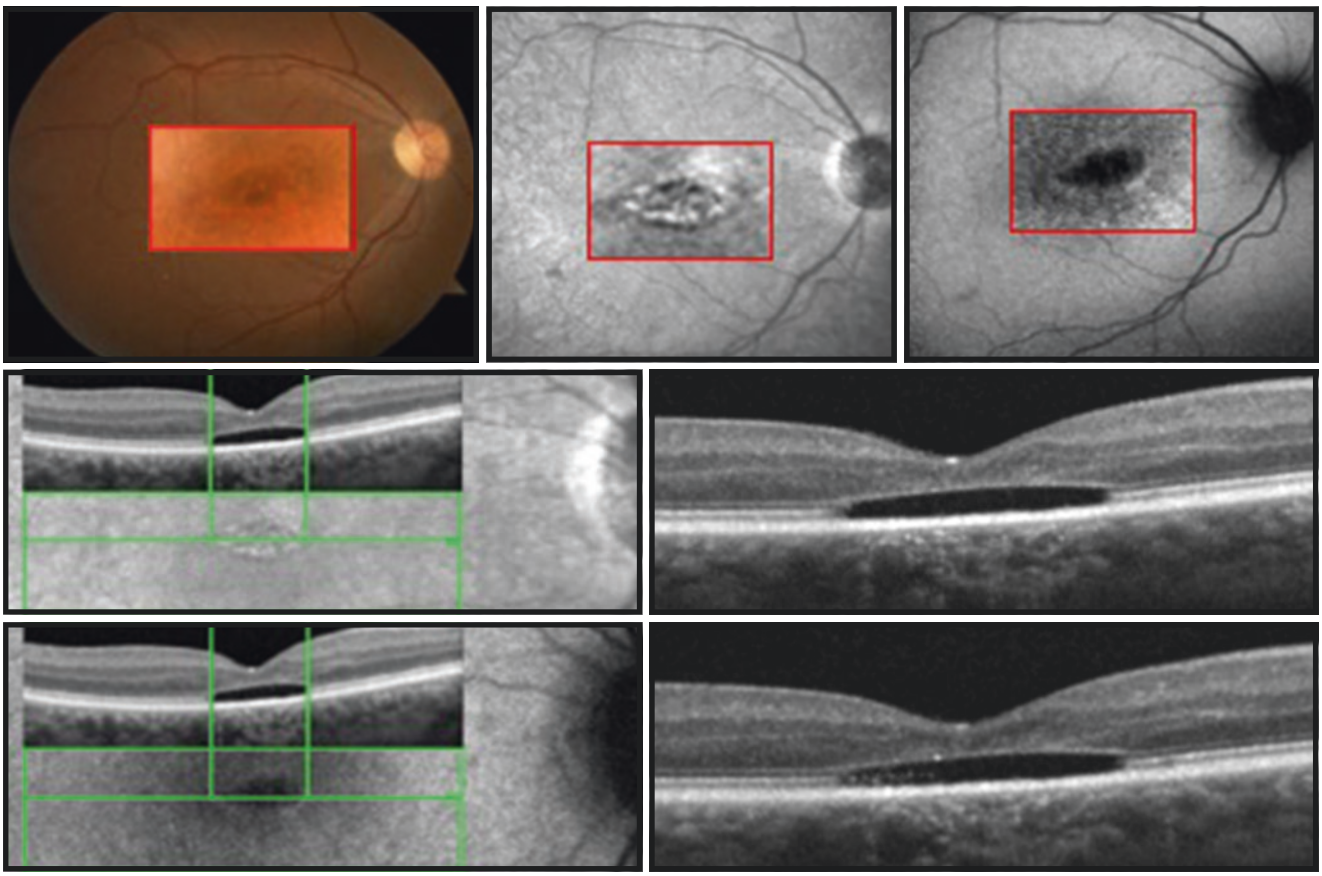

Fig. 24.2 Multimodal imaging of a case of achromatopsia, showing an optically empty space, discontinuation of ISe line and COST layer, partial disruption of RPE, and marked thinning of the outer nuclear layer on SD-OCT. FAF shows an area of absent autofluorescence in the central area

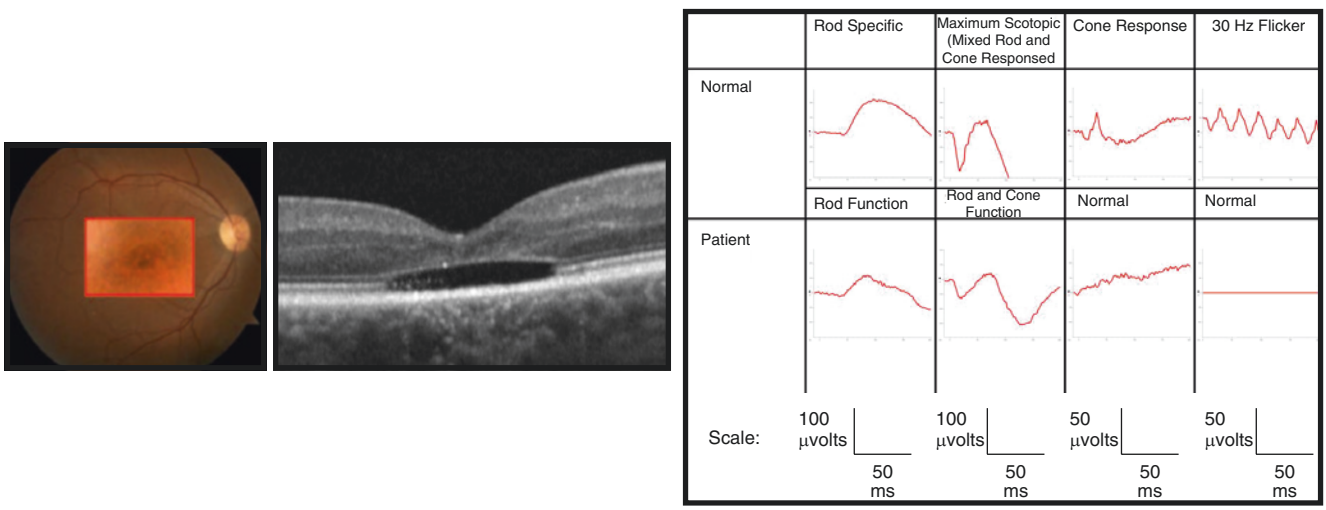

Fig. 24.3 Full-field electroretinography (ff-ERG) in achromatopsia, showing markedly affected cone response

Gene Therapy Trials

The *ClinicalTrials.gov* website lists four trials of gene therapy for achromatopsia that are currently recruiting (as of April 27, 2018):

Safety and Efficacy Trial of AAV Gene Therapy in Patients With CNGA3 Achromatopsia (AGTC) (ClinicalTrials.gov identifier: NCT02935517)

- Gene Therapy for Achromatopsia CNGB3 (MeiraGTx UK II Ltd)
- ClinicalTrials.gov Identifier: NCT03001310)
- Long-Term Follow-Up Gene Therapy Study for Achromatopsia CNGB3 (MeiraGTx UK II Ltd)
- ClinicalTrials.gov Identifier: NCT03278873)
- Safety and Efficacy Trial of AAV Gene Therapy in Patients With CNGB3 Achromatopsia (AGTC) (ClinicalTrials.gov identifier: NCT02599922)

Suggested Reading

Greenberg JP, Sherman J, Zweifel SA, Chen RW, Duncker T, Kohl S, et al. Spectral-domain optical coherence tomography staging and autofluorescence imaging in achromatopsia. JAMA Ophthalmol. 2014;132:437–45.

Khan NW, Wissinger B, Kohl S, Sieving PA. CNGB3 achromatopsia with progressive loss of residual cone function and impaired rod-mediated function. Invest Ophthalmol Vis Sci. 2007;48:3864–71.

Sundaram V, Wilde C, Aboshiha J, Cowing J, Han C, Langlo CS, et al. Retinal structure and function in achromatopsia: implications for gene therapy. Ophthalmology. 2014;121:234–45.

CHAPTER 25

Retinitis Pigmentosa (Non-syndromic)

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General Features

- Most of the genes causing autosomal recessive retinitis pigmentosa (AR-RP) are rare and cause 1% of all cases.
- Some of the genes, like *PDE6* (*PDE6A*, *PDE6B*, *PDE6G*), *RP25*, and *RPE65*, have higher prevalence, about 2–5% of all cases.
- Overall, autosomal recessive RP accounts for about 15–20% of all cases of RP.
- Clinically, it shows all the classic features of RP, such as attenuated retinal blood vessels, intraretinal pigmentation, waxy pallor of the optic disc, and hyperfluorescent rings on fundus autofluorescence (FAF) (Figs. 25.1, 25.2 and 25.3). The ring is suggestive of increased metabolic burden of the corresponding retinal pigment epithelium (RPE).

Genes and Mutations

PDE6 (Phosphodiesterase) (Fig. 25.4)

The PDE complex has one α, one β, and two γ subunits; the complex encodes a protein that play an important role in rod phototransduction and maintenance of the intracellular cGMP level. *PDE6G* might be associated with early-onset RP.

RP25 or *EYS* (Eyes Shut Homolog) (Fig. 25.5)

This gene accounts for 10–20% of AR-RP in Spanish populations. Cytogenetic location: 6q12.

TULP1 (Tubby-Like Protein 1) Gene or *RP14* or *TUBL1* or *LCA15* (Fig. 25.6)

The protein encoded by the *TULP1* gene is thought to play a role in the physiology of photoreceptors. Cytogenetic location: 6p21.31.

CERKL (Ceramide Kinase-Like) Gene or *RP26* (Fig. 25.7)

This gene encodes a protein with ceramide kinase-like domains; the protein may be a negative regulator of apoptosis in photoreceptor cells. Cytogenetic location: 2q31.3.

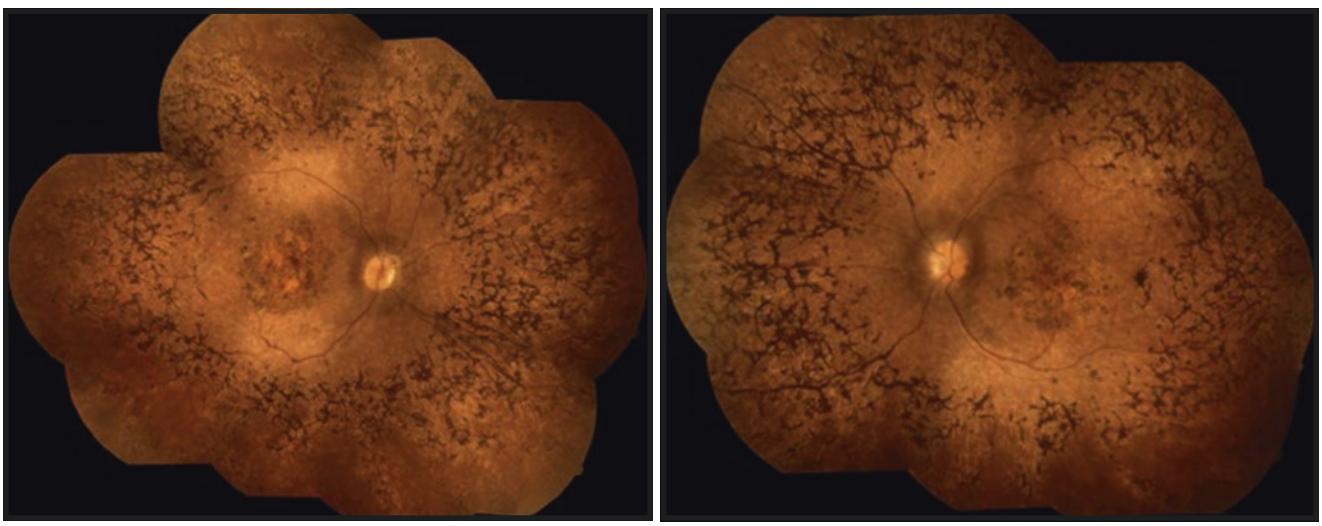

Fig. 25.1 Retinitis pigmentosa with attenuated vessels, intraretinal pigmentation, and macular involvement; mutation *RDH12*

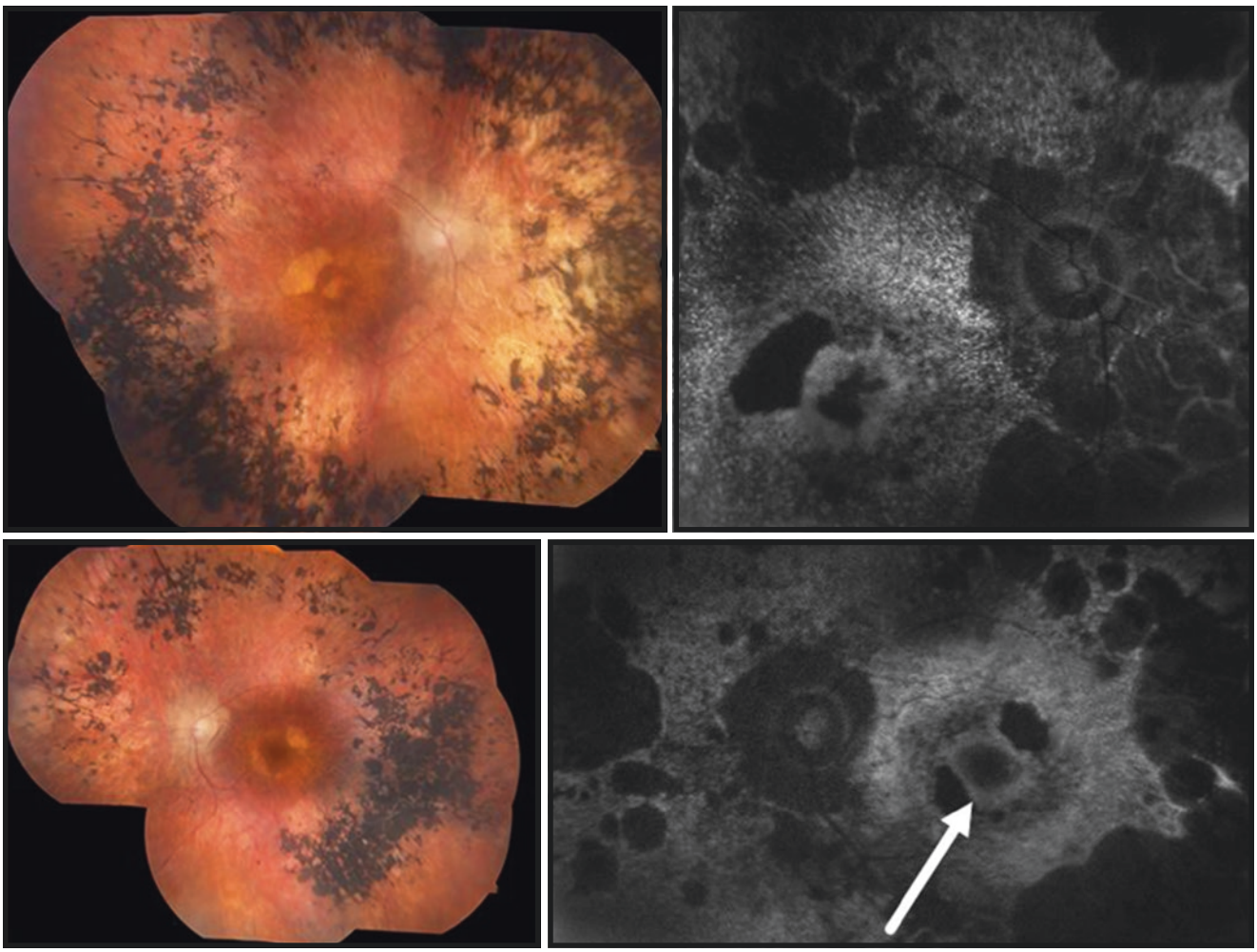

Fig. 25.2 Retinitis pigmentosa with attenuated vessels, intraretinal pigmentation, fundus autofluorescence (FAF) showing a hyperfluorescent ring around the fovea (*arrow*); mutation *PDE6B*

RPE65 Gene

This gene is expressed in the RPE and is vital for converting all-*trans*-retinyl esters into 11-*cis*-retinal, an important step in regeneration of visual pigment. The *RPE* gene (about 60 mutations) is responsible for around 2% of AR-RP and 16% of Leber congenital amaurosis. Cytogenetic location: 1p31.3.

Other Genes Associated with AR-RP

Among other genes are *ABCA4* (1p22.1, 680 mutations), *BEST1* (11q12.3, 232 mutations), *CRB1* (1q31.3, 183 mutations), *CRX* (19q13.32, 51 mutations), *MAK* (6p24.2, 9 mutations), and *MERTK* (2q13, 27 mutations).

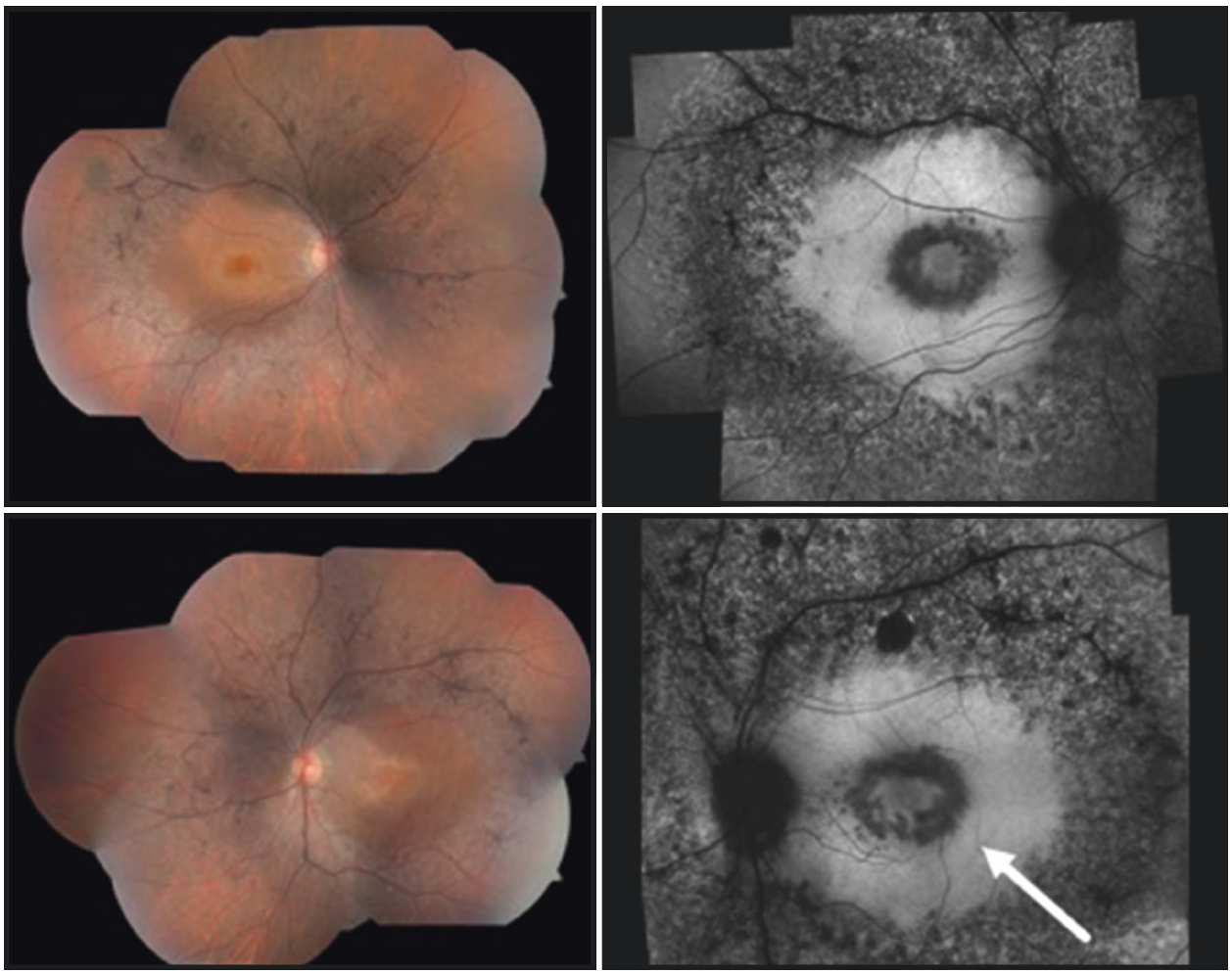

Fig. 25.3 Retinitis pigmentosa with attenuated vessels, intraretinal pigmentation, FAF showing a broad hyperfluorescent ring around the fovea (*arrow*); mutation *USH2A*

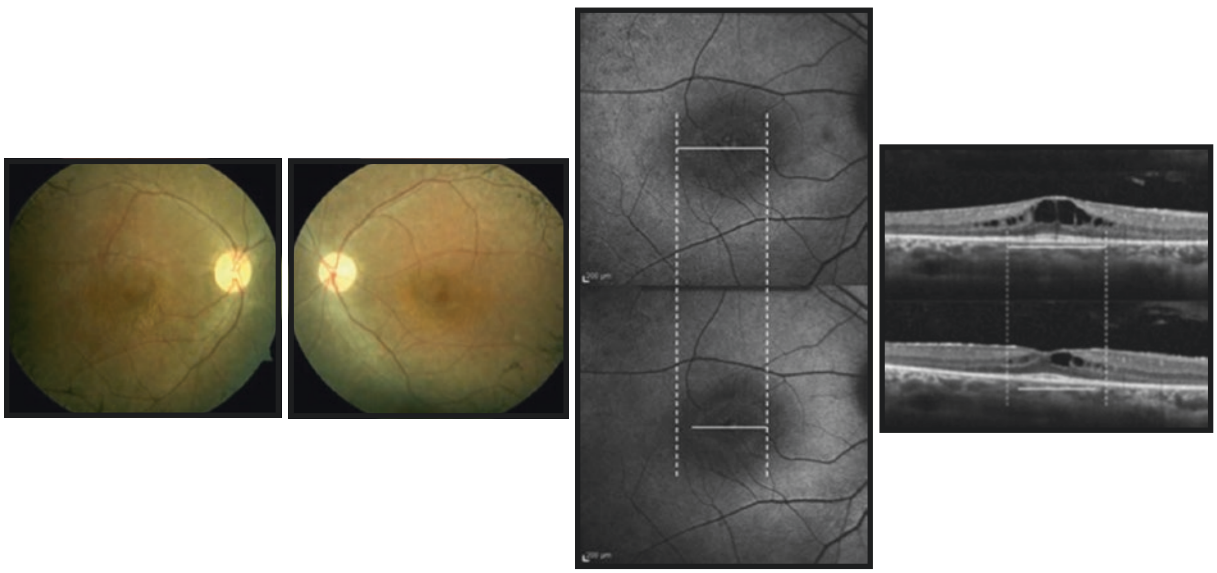

Fig. 25.4 Autosomal recessive retinitis pigmentosa (AR-RP). Rod-cone dystrophy secondary to PDE6B mutations. The size of the hyperfluorescent ring on AF and the length of the ellipsoid zone (EZ) decreased over a 2-year follow-up, suggestive of progressive rod photoreceptor damage

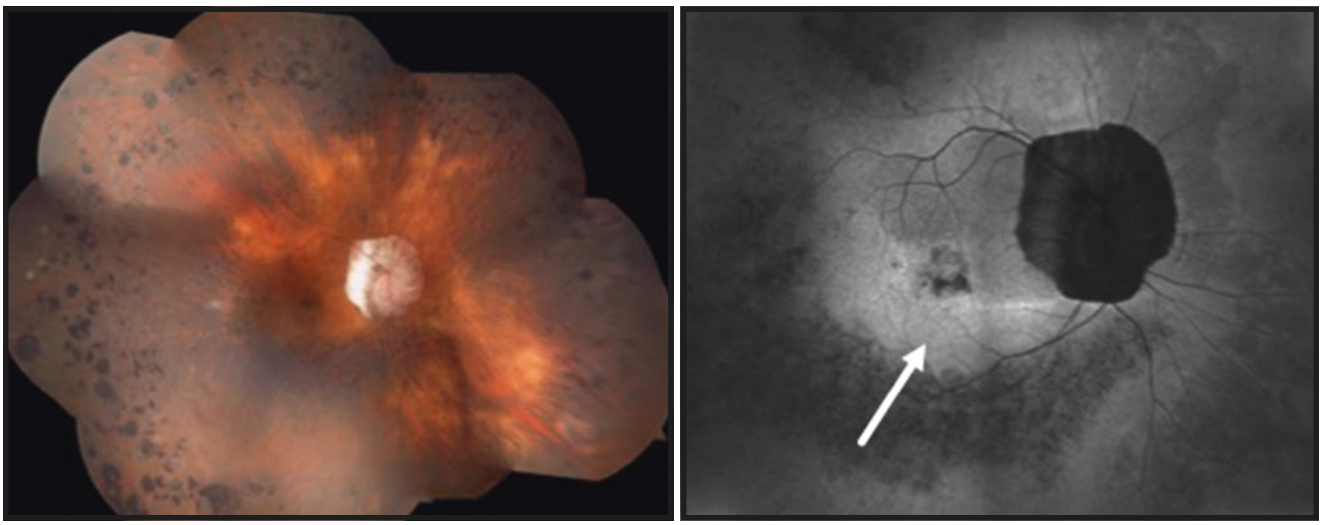

Fig. 25.5 AR-RP. Rod-cone dystrophy secondary to eyes shut homolog (*EYS*) mutations; FAF shows an atypical crescent-shaped hyperAF ring (*arrow*)

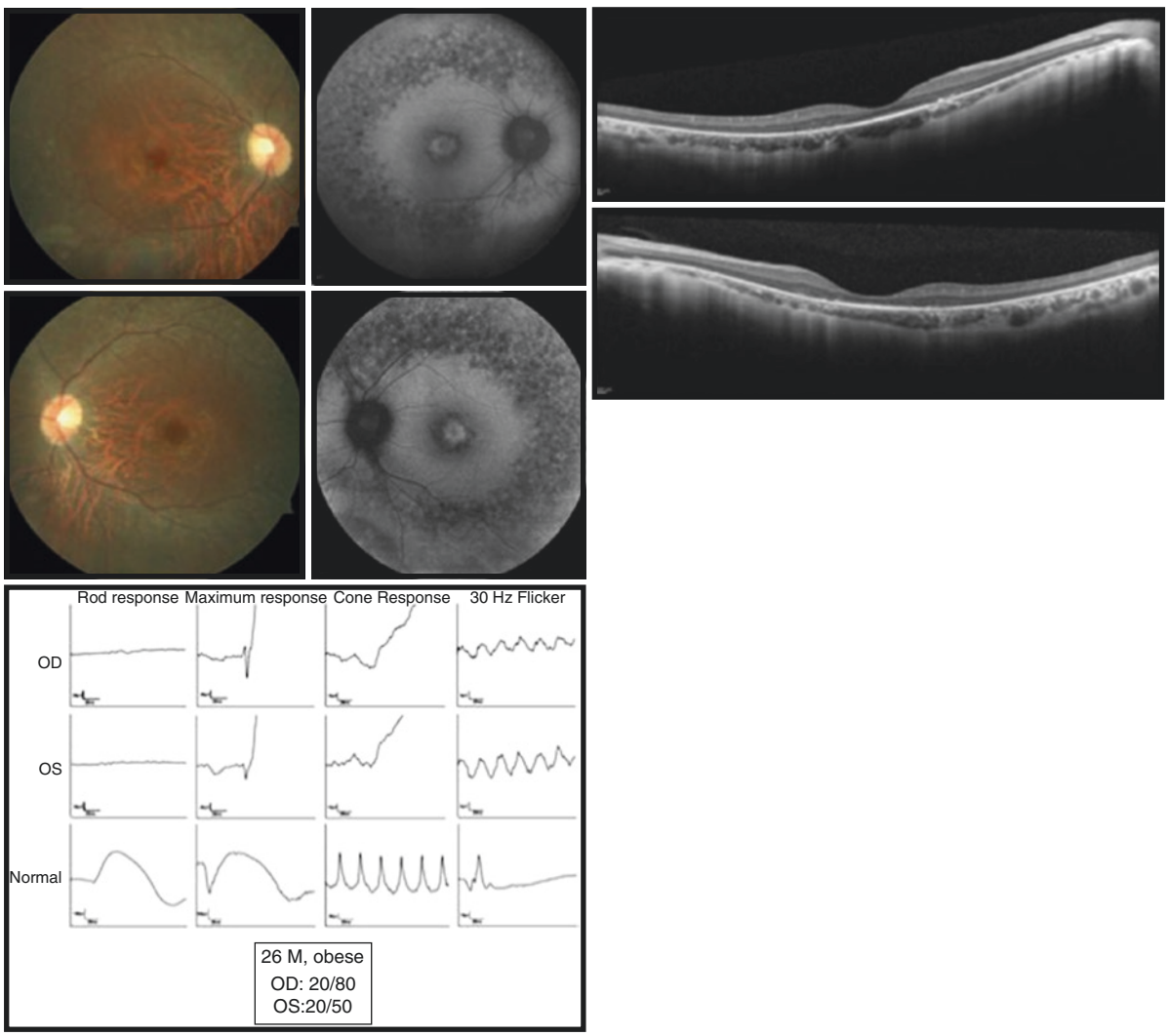

Fig. 25.6 AR-RP. Rod-cone dystrophy secondary to homozygous *TULP1* mutations and heterozygous *ABCA4* mutations; bulls-eye maculopathy (BEM) pattern along with peripheral involvement

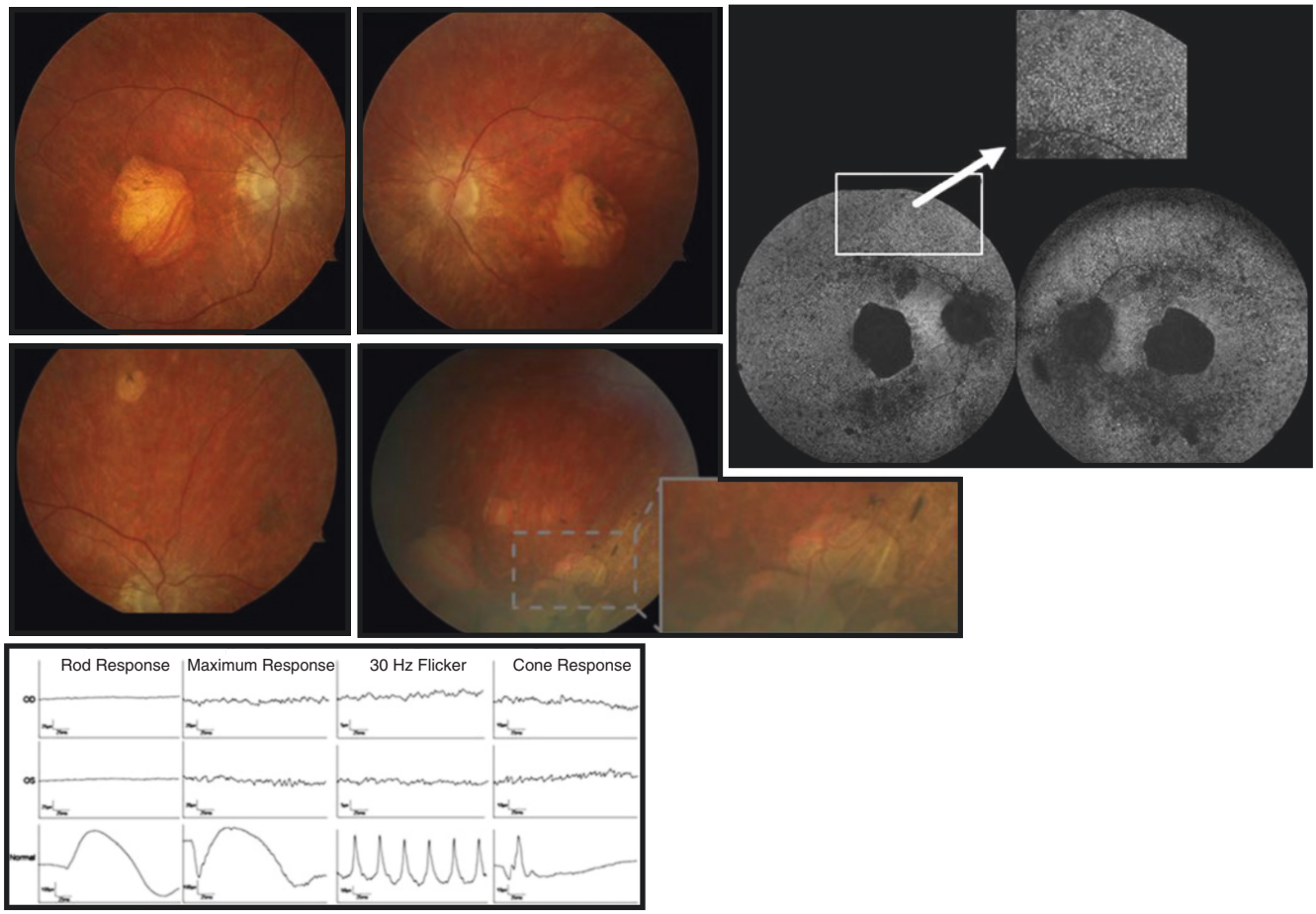

Fig. 25.7 AR-RP. Rod-cone dystrophy secondary to mutation in the ceramide kinase-like (*CERKL*) gene, with early-onset maculopathy, peripheral lacunae, intraretinal pigment migration, and white hyperAF dots on FAF (*arrow*)

Suggested Reading

Bravo-Gil N, González-Del Pozo M, Martín-Sánchez M, Méndez-Vidal C, Rodríguez-de la Rúa E, Borrego S, et al. Unravelling the genetic basis of simplex retinitis pigmentosa cases. Sci Rep. 2017;7:41937.

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Sharon D, Banin E. Nonsyndromic retinitis pigmentosa is highly prevalent in the Jerusalem region with a high frequency of founder mutations. Mol Vis. 2015;21:783–92.

CHAPTER 26

Leber Congenital Amaurosis

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General Features

- Leber congenital amaurosis (LCA) is a part of the spectrum of early-onset retinal dystrophy (EORD). It usually presents in the first few years of life, most often before the age of 1 year. The prevalence is about 1:80,000.
- Also known as congenital retinitis pigmentosa (RP), patients have wandering nystagmus, with reduced vision from birth. The fundus is almost normal to start with. Later, pigmentary disturbances develop.
- The best corrected visual acuity (BCVA) ranges from no light perception (in nearly one third of cases) to no better than 20/400, often with a hyperopic refraction (≥5.0D). Patients have absent pupillary reflex and some of them have keratoconus (*CRB1* and *AIPL1*).
- Oculodigital reflex (eye rubbing or poking) is a common association.
- Electroretinography (ERG) responses are almost undetectable.
- Patients may have normal intelligence, but some studies suggest that as many as 20% of children with LCA without associated anomalies develop intellectual disability.
- Patients with *GUCY2D* mutations have a stable clinical course; those with *RPE65* mutations show a period of limited improvement followed by progressive deterioration; and those with *AIPL1*, *CRB1*, *CEP290*, and *NMNAT1* mutations show gradual progression over several decades.

Molecular Genetics

Those with *CEP290* or *ICQB1* mutations should have a renal evaluation and neurological evaluation for Joubert syndrome or Senior Loken syndrome.

In December 2017, the U.S. Food and Drug Administration (FDA) approved a gene therapy, Luxturna (voretigene neparvovec-rzyl) for the treatment of patients with confirmed biallelic *RPE65* mutation–associated retinal dystrophy, which affects about 1000–2000 patients in the United States. Luxturna works by delivering a normal copy of the *RPE65* gene directly to retinal cells.

Specific Genotype and Phenotype Correlations

Most often LCA is inherited in an autosomal recessive manner. Rarely, it can be inherited in an autosomal dominant mode, particularly due to mutations in *IMPDH1*, *OTX2*, or *CRX* gene.

LCA1

- **Genotype**: *GUCY2D* gene located at 17p13.1, is expressed in photoreceptors and encodes for guanylate cyclase; needed to convert GTP into cGMP (recovery of photoreceptors after phototransduction). Accounts for 6–21% cases of LCA.
- **Phenotype**: Severe cone-rod dystrophy, poor stable vision, and no visual improvement.

LCA2 (Fig. 26.1)

- **Genotype**: *RPE65* located at 1p31, expressed in RPE and encodes for 65 KD protein; needed to convert all-*trans*-retinyl ester to 11-*cis*-retinol. Accounts for 3–16% cases of LCA.
- **Phenotype**: Rod-cone dystrophy. Early RPE mottling and small white intraretinal spots, with later intraretinal pigmentation. Some patients developed peculiar star-shaped maculopathy or have translucent RPE. Some have transient improvement in vision and eventual progressive visual loss.)

LCA3 (Fig. 26.2)

- **Genotype**: *SPATA7* located at 14q13.3, expressed in photoreceptors (IS) and testis; needed for spermatogenesis
- **Phenotype**: Rod-cone dystrophy, intraretinal pigmentation

LCA4

- **Genotype**: *AIPL1* located at 17p13.1, expressed in photoreceptors and pineal gland; needed for normal development of rods and cones. Accounts for 4–8% of cases of LCA.

- **Phenotype**: Cone-rod dystrophy; early macular involvement, progressive atrophic lesion with a well-defined margin, at times called a "macular coloboma." These patients have severe, marked pigmentary retinopathy, with maculopathy. A large subset have keratoconus and cataract.

LCA5

- **Genotype**: *LCA5* located at 6q14.1, expressed in photoreceptor cilia and microtubules; lebercilin, needed for various ciliary proteins. Accounts for 1–2% of cases of LCA.
- **Phenotype**: Rod-cone dystrophy

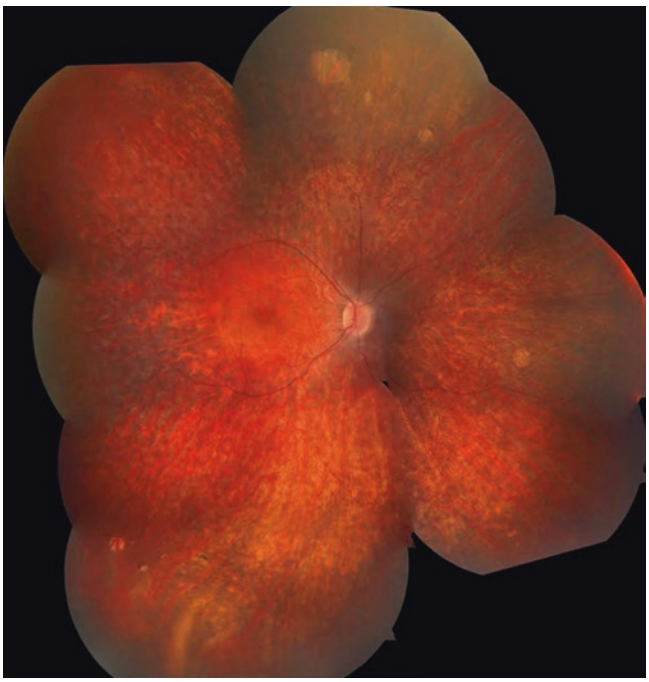

Fig. 26.1 Leber congenital amaurosis (LCA) caused by *RPE65* mutation; note extensive RPE mottling and pigmentary changes

LCA6

- **Genotype**: *RPGRIP1* located at 14q11, expressed in photoreceptors and other organs including heart, liver, spleen, kidney, testis, and brain; RP GTPase regulator protein. Accounts for 5% cases of LCA.
- **Phenotype**: Cone-rod dystrophy

LCA7 (Fig. 26.3)

- **Genotype**: *CRX* located at 19q13.33, expressed in photoreceptors, inner nuclear layer, and pineal gland; encodes cone-rod homeobox–containing transcription factor needed for photoreceptor development. Accounts for 3% of cases of LCA.
- **Phenotype**: Cone-rod dystrophy

LCA8 (Figs. 26.4 and 26.5)

- **Genotype**: *CRB1* located at 1q31.3, expressed in photoreceptors (IS) and other organs like testis and brain; encodes crumbs homolog 1 and is needed for outer limiting membrane (OLM) integrity and photoreceptor development.
- **Phenotype**: Rod-cone dystrophy, occasionally cone-rod dystrophy. Nummular intraretinal pigmentation and preservation of para-arteriolar RPE, pseudopapilledema, and prepapillary paravascular fibrosis. Coats-like vascular anomalies. Also progressive macular atrophic lesion and macular atrophic lesion with sharp border (like macular coloboma)

LCA9

- **Genotype**: *NMNAT1* located at 1p36.22, expressed ubiquitously; involved in retinal neuroprotection

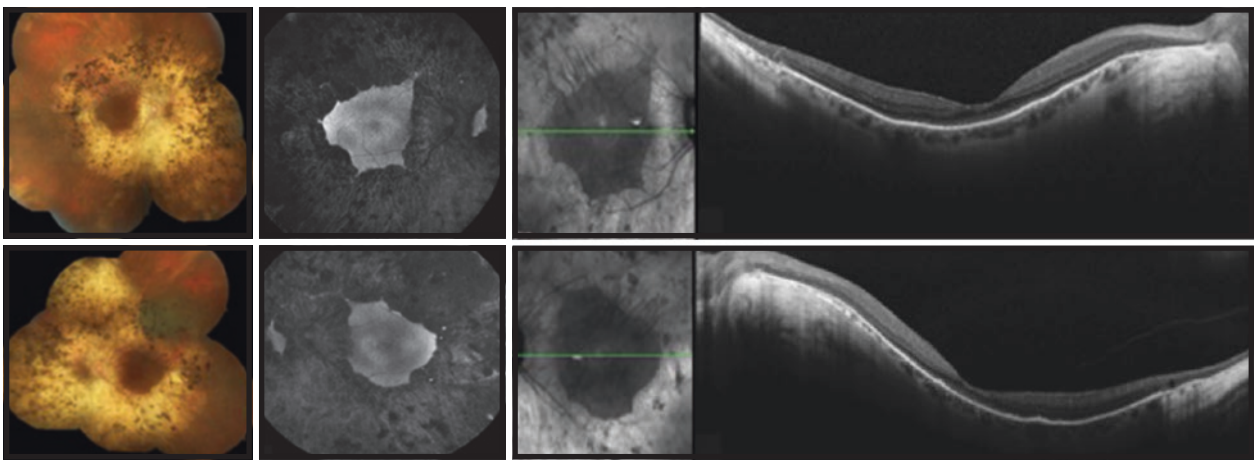

Fig. 26.2 LCA caused by *SPATA7* mutation. Note an unusual choroideremia-like phenotype in this 64-year-old man, with evidence of extensive RPE atrophy and choroidal sclerosis, extensive intraretinal pigment migration, and a centrally spared RPE island on fundus autofluorescence (FAF)

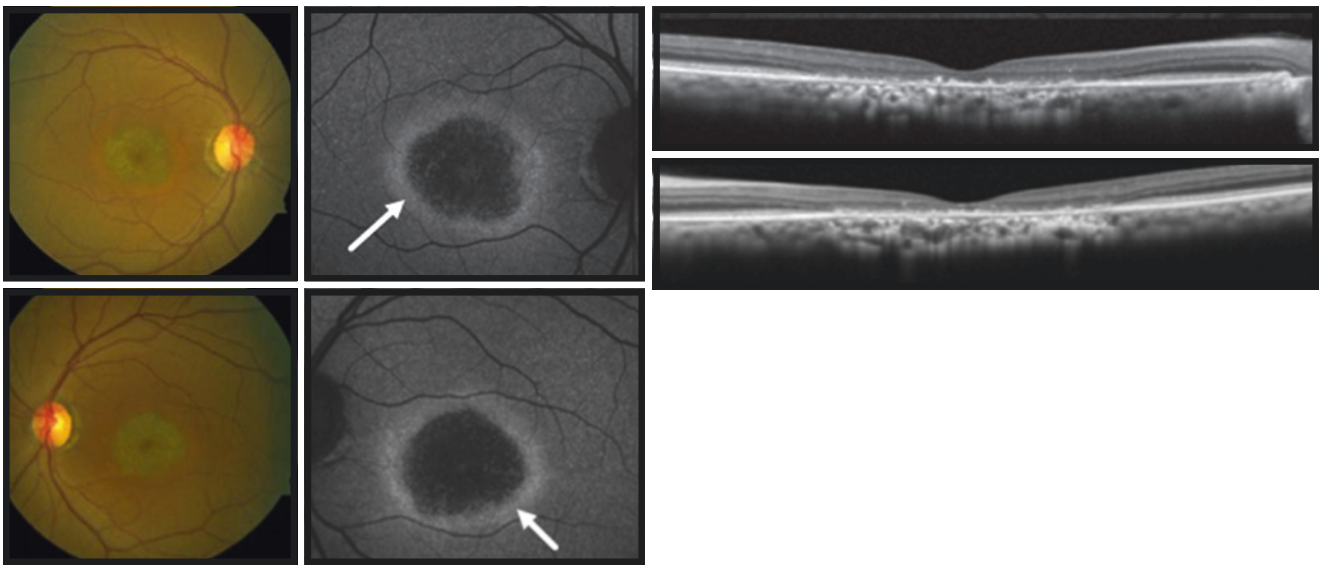

Fig. 26.3 LCA caused by *CRX* mutation; only macular involvement, with periphery spared. FAF shows annular hyperAF (*arrows*) surrounding the atrophic RPE

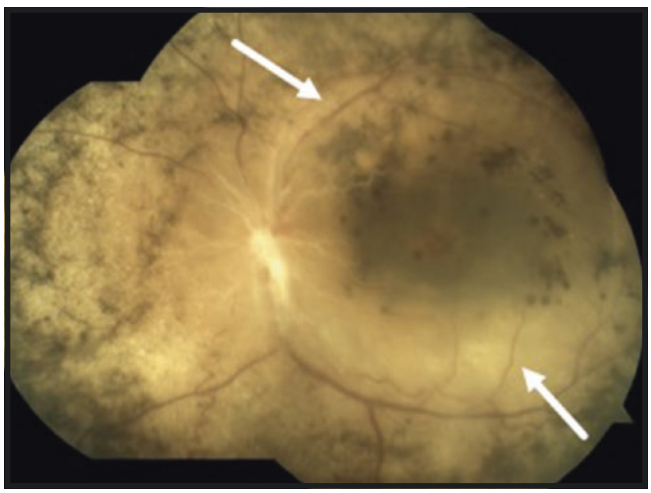

Fig. 26.4 LCA caused by *CRB1* mutation. Note the relative sparing of the para-arteriolar RPE (*arrows*)

- **Phenotype**: Cone-rod dystrophy, early optic atrophy, macular atrophic lesion with sharp border (like macular coloboma)

LCA10 (Fig. 26.6)

- **Genotype**: *CEP290* located at 12q21.32, expressed in photoreceptor cilium and also in ciliated and nonciliated cells of multiple organs, including the brain; encodes for centrosomal protein 290 KD. Accounts for ≤20% of cases of LCA.
- **Phenotype**: Cone-rod dystrophy. These patients may also have hypotonia, ataxia, or intellectual disability and autistic behavior.

LCA11

- **Genotype**: *IMPDH1* located at 7q31.1, expressed in photoreceptors (IS) and several other organs, ubiquitously; it catalyzes the rate-limiting step in de novo guanine synthesis.
- **Phenotype**: Rod-cone dystrophy

LCA12 (Figs. 26.7 and 26.8)

- **Genotype**: *RDH12* located at 14q24.1, expressed in photoreceptors (OS); involved in visual cycle with dual specificity for all-*trans*-retinols and all-*cis*-retinols. Accounts for 2.7% of cases of LCA.
- **Phenotype**: Rod-cone dystrophy, peripapillary sparing

LCA14

- **Genotype**: *LRAT* located at 4q32.1, expressed in RPE and involved in retinoid cycle.
- **Phenotype**: Rod-cone dystrophy

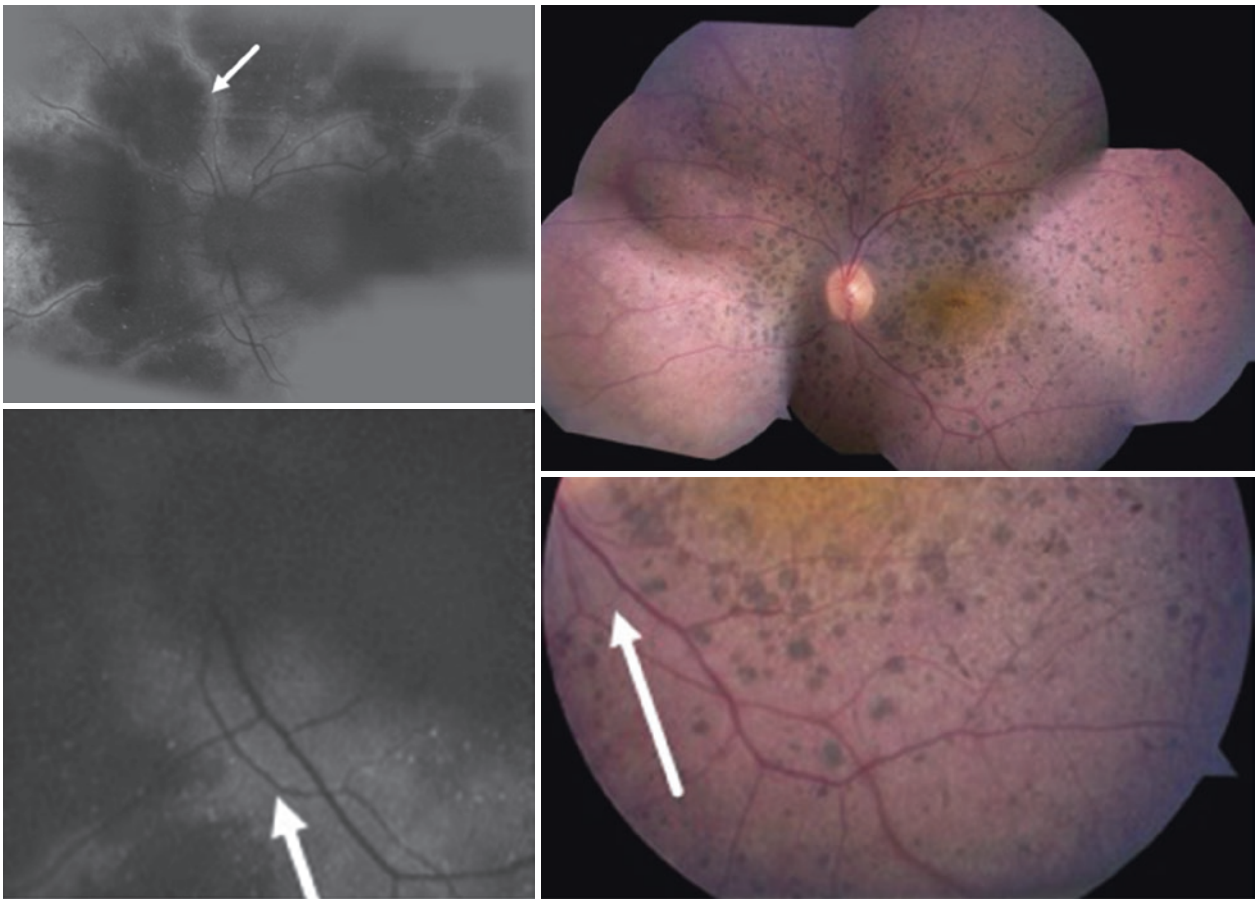

Fig. 26.5 LCA caused by *CRB1* mutation. Note the relative sparing of the para-arteriolar RPE (*arrows*)

LCA15

- **Genotype**: *TULP1* located at 6p21.31, expressed in photoreceptors and involved in tubby-like protein 1.
- **Phenotype**: Rod-cone dystrophy; pinpoint yellowish deposits at the macula, leading to atrophy and peripheral intraretinal pigmentation

LCA16

- **Genotype**: *KCNJ13* located at 2q37.1, expressed in RPE apical membrane and other ion-transporting epithelia of choroidal plexus, thyroid, prostate, kidney, and intestine; involved in potassium channel transport.
- **Phenotype**: Rod-cone dystrophy; extensive nummular intraretinal pigmentation

RP38

- **Genotype**: *MERTK* located at 2q14.1, expressed in RPE and sclera; needed for phagocytosis of outer segments by RPE.
- **Phenotype**: Rod-cone dystrophy; dot-like whitish deposits at macula, leading to atrophy and intraretinal pigmentation

LCA57

- **Genotype**: *PDE6G* located at 17q25.3, expressed in photoreceptors, in particular rod cGMP-specific phosphodiesterase 6.
- **Phenotype**: Rod-cone dystrophy, intraretinal pigmentation, and cystoid macular edema

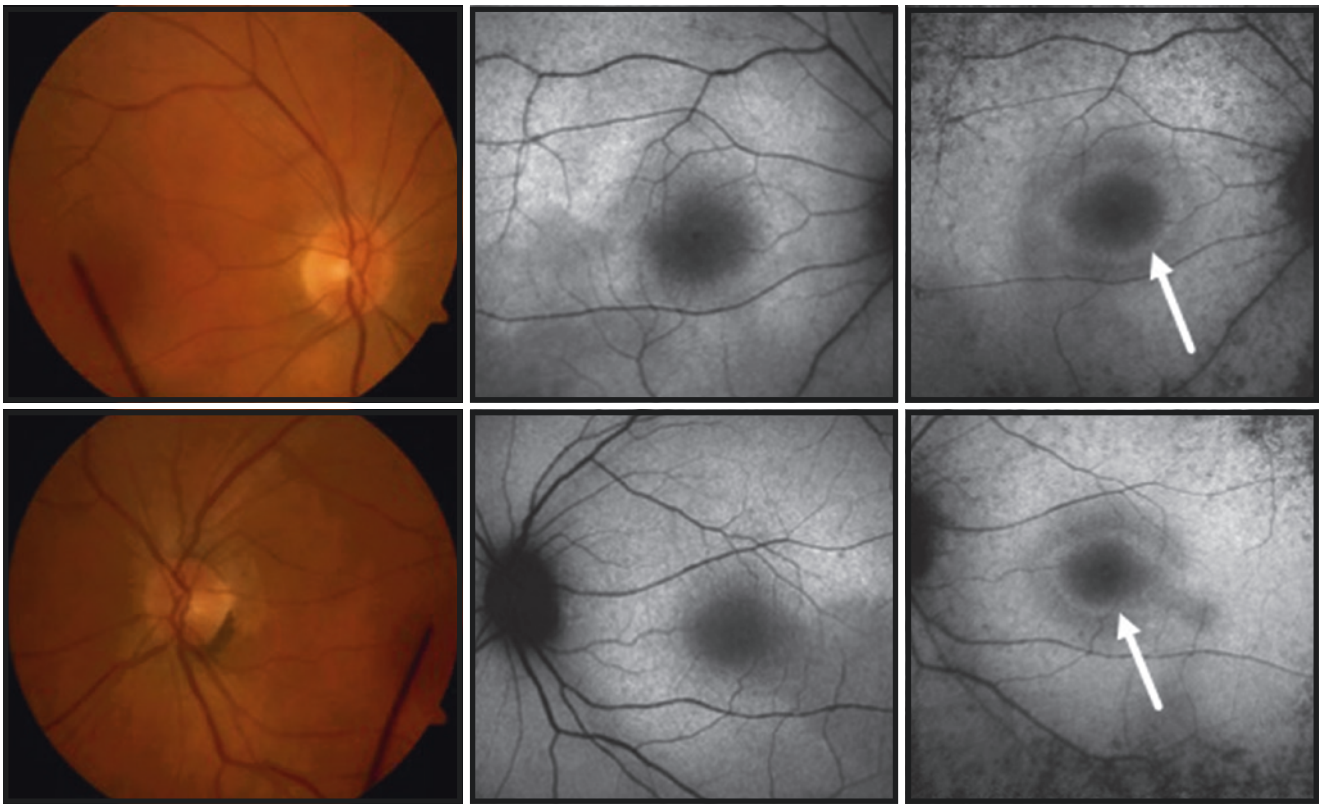

Fig. 26.6 LCA caused by *CEP290* mutation. Cone-rod dystrophy. Six-year follow-up progression of macular changes (hyperAF ring, *arrow*)

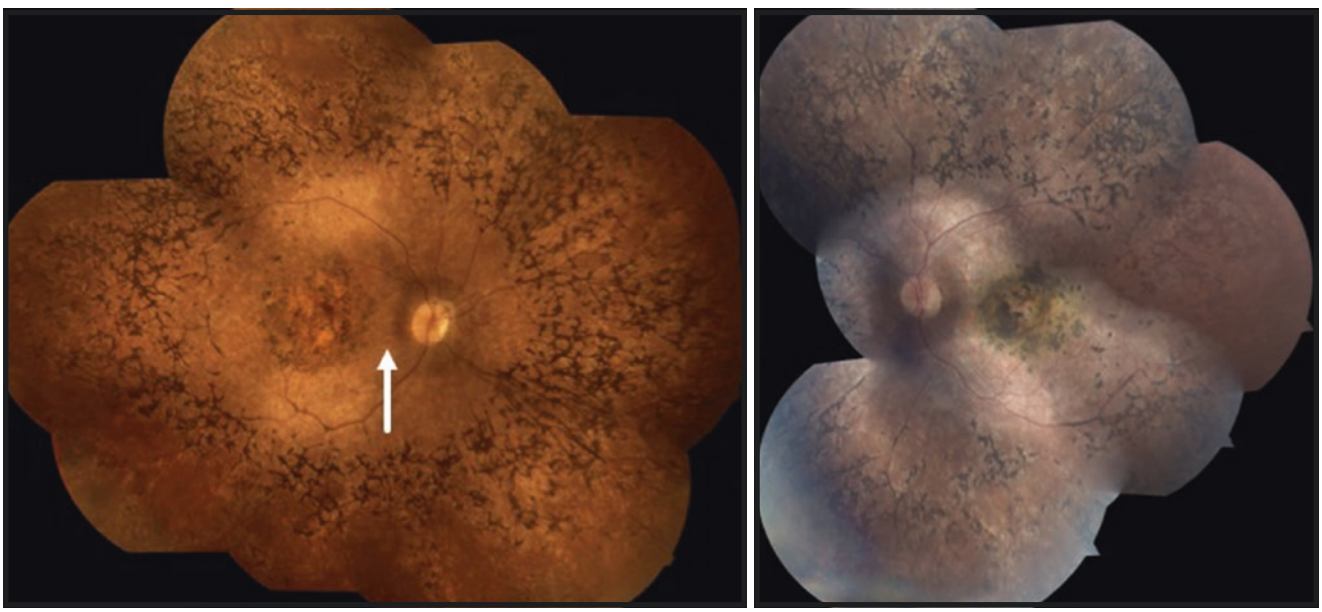

Fig. 26.7 LCA caused by *RDH12* mutation; note peripapillary sparing (*arrow*). Fundus shows involvement of both periphery and macula

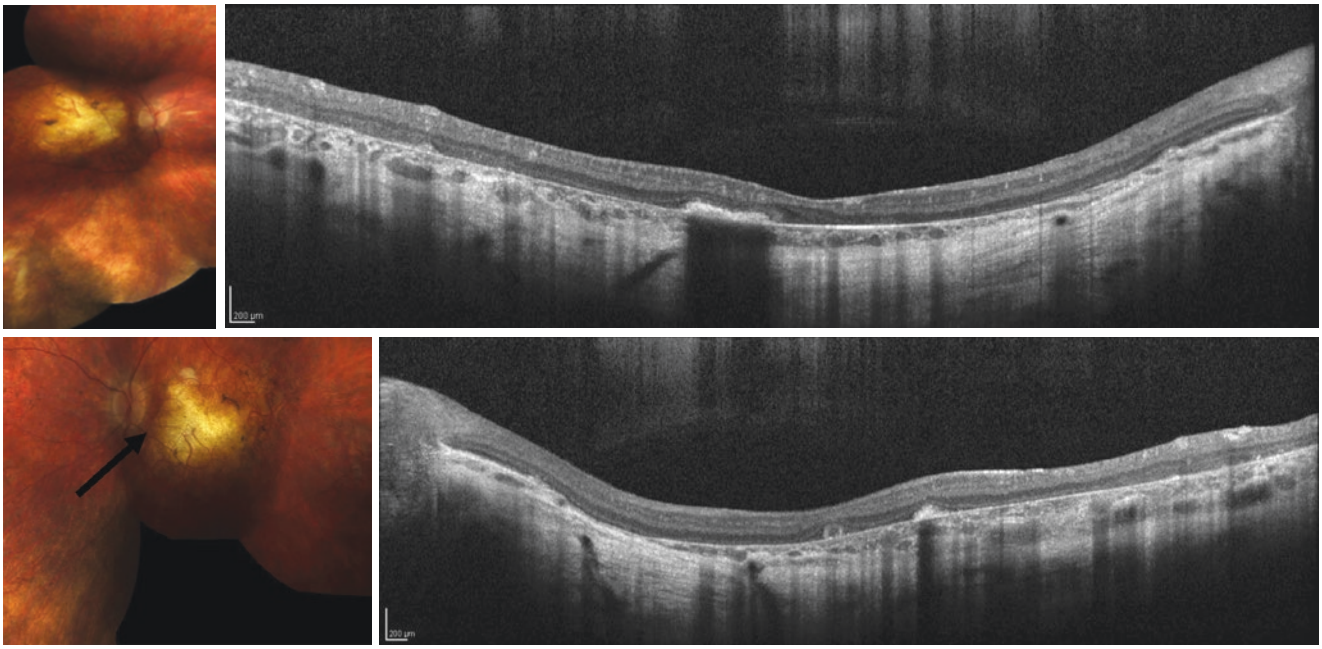

Fig. 26.8 LCA caused by *RDH12* mutation, note peripapillary sparing (*arrow*). There is a macular atrophy, no intraretinal pigment migration

SLSN5

- **Genotype**: *IQCB1* located at 3q21.1, expressed in photoreceptor cilium; needed for transport of cargo molecules photoreceptor outer segment.
- **Phenotype**: Rod-cone dystrophy

Suggested Reading

Kumaran N, Moore AT, Weleber RG, Michaelides M. Leber congenital amaurosis/early-onset severe retinal dystrophy: clinical features, molecular genetics and therapeutic interventions. Br J Ophthalmol. 2017;101:1147–54.

Sheck L, WIL D, Moradi P, Robson AG, Kumaran N, Liasis AC, et al. Leber congenital amaurosis associated with mutations in CEP290, clinical phenotype, and natural history in preparation for trials of novel therapies. Ophthalmology. 2018;125(6):894–903. https://doi.org/10.1016/j.ophtha.2017.12.013. [Epub ahead of print].

Takkar B, Bansal P, Venkatesh P. Leber's congenital amaurosis and gene therapy. Indian J Pediatr. 2018;85:237–42.

CHAPTER 27

Stargardt Disease

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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_27

General Features

- Stargardt disease (STGD) is one of the most common macular dystrophies in young adults. It progresses slowly. Its prevalence is about 1:8000–10,000.
- Age of onset is a surrogate marker: The earlier the onset, the more severe the disease course. Onset usually occurs in childhood or early adolescence, at about 10–15 years of age.
- Vision is between about 20/70 and 20/200.
- The fundus shows a bull's eye pattern or beaten-bronze appearance, with or without yellowish flecks (fundus flavimaculatus).
- Fluorescein angiography may show dark choroid in about 80% of cases.
- On fundus autofluorescence (FAF), newer flecks appear hyperautofluorescent (hyperAF); older ones become progressively more hypoAF with time. Some flecks are surrounded by a ring of decreased AF.
- Peripapillary sparing is one the characteristics of Stargardt disease, but this area can be involved in about 2–7% of cases. The reason for this sparing is unclear; this area may be more resilient to the deleterious effect of *ABCA4* gene mutation, and there might be a more favorable RPE photoreceptor ratio, resulting in less lipofuscin build-up, in the presence of a thicker overlying peripapillary retinal nerve fiber layer.
- Patients with Stargardt disease should avoid bright light and excessive vitamin A.

Clinical Stages and Groupings

Stages, Based on Fundus Appearance (Figs. 27.1, 27.2, 27.3, 27.4, 27.5 and 27.6)

STAGE I: Confined to macula, with beaten-metal appearance (discontinuous, as opposed to classic appearance); a discontinuous ring of flecks around fovea, about 1 disc diameter (DD). The electrooculogram (EOG) and electroretinogram (ERG) are normal.

STAGE II: Widespread flecks beyond temporal arcades and/or nasal to disc. Subnormal cone and rod response.

STAGE III: Re-absorption of flecks and widespread choriocapillaris (CC) atrophy. EOG shows subnormal ratio, and ERG shows cone/rod dysfunction.

STAGE IV: Further resorption of flecks, with extensive CC and RPE atrophy.

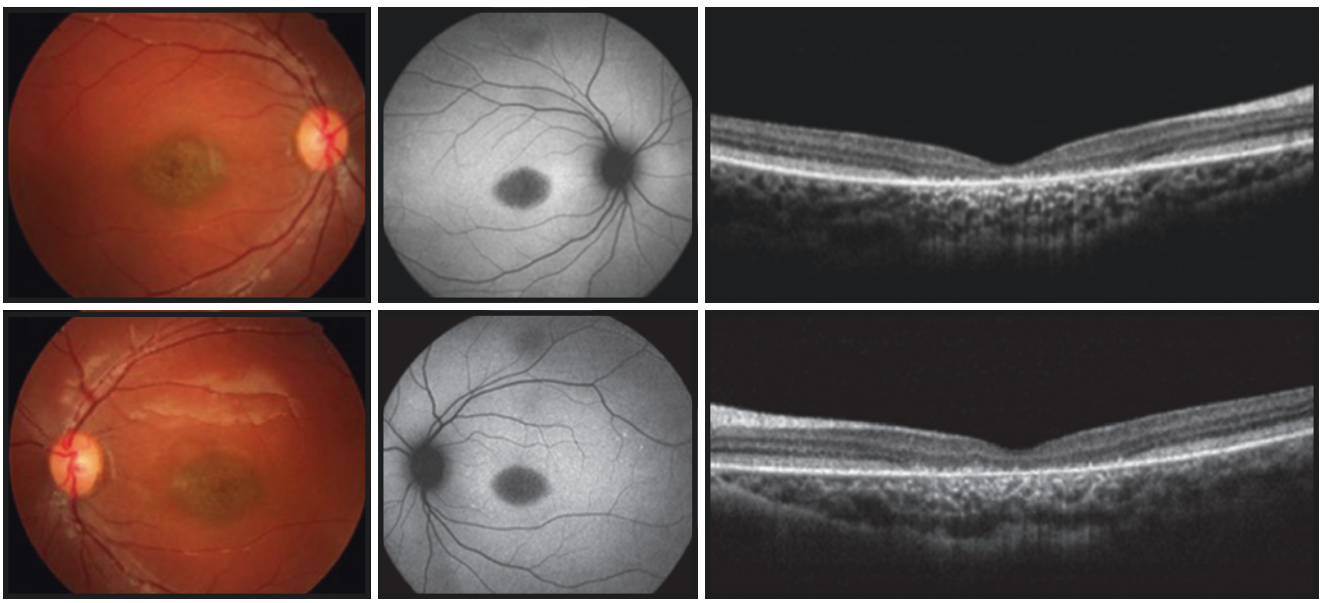

Fig. 27.1 Stargardt disease (STGD) presenting as bull's eye maculopathy (BEM), with no flecks. HypoAF on FAF. Optical coherence tomography (OCT) shows marked damage to photoreceptor layer and RPE (C4537delC; p.R107*)

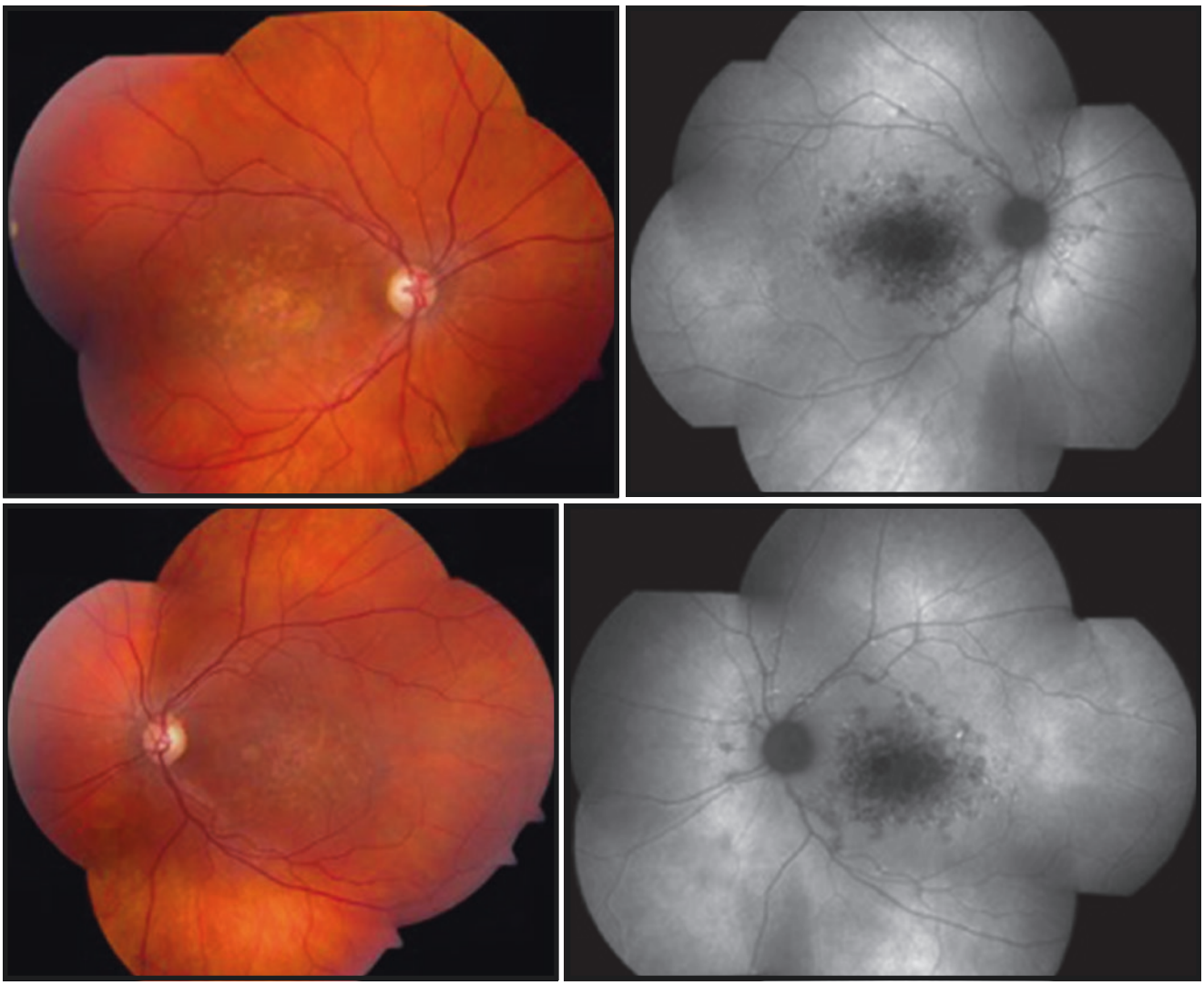

Fig. 27.2 STGD presenting as atrophic patch at the macula and flecks. Note sparing of the peripapillary area

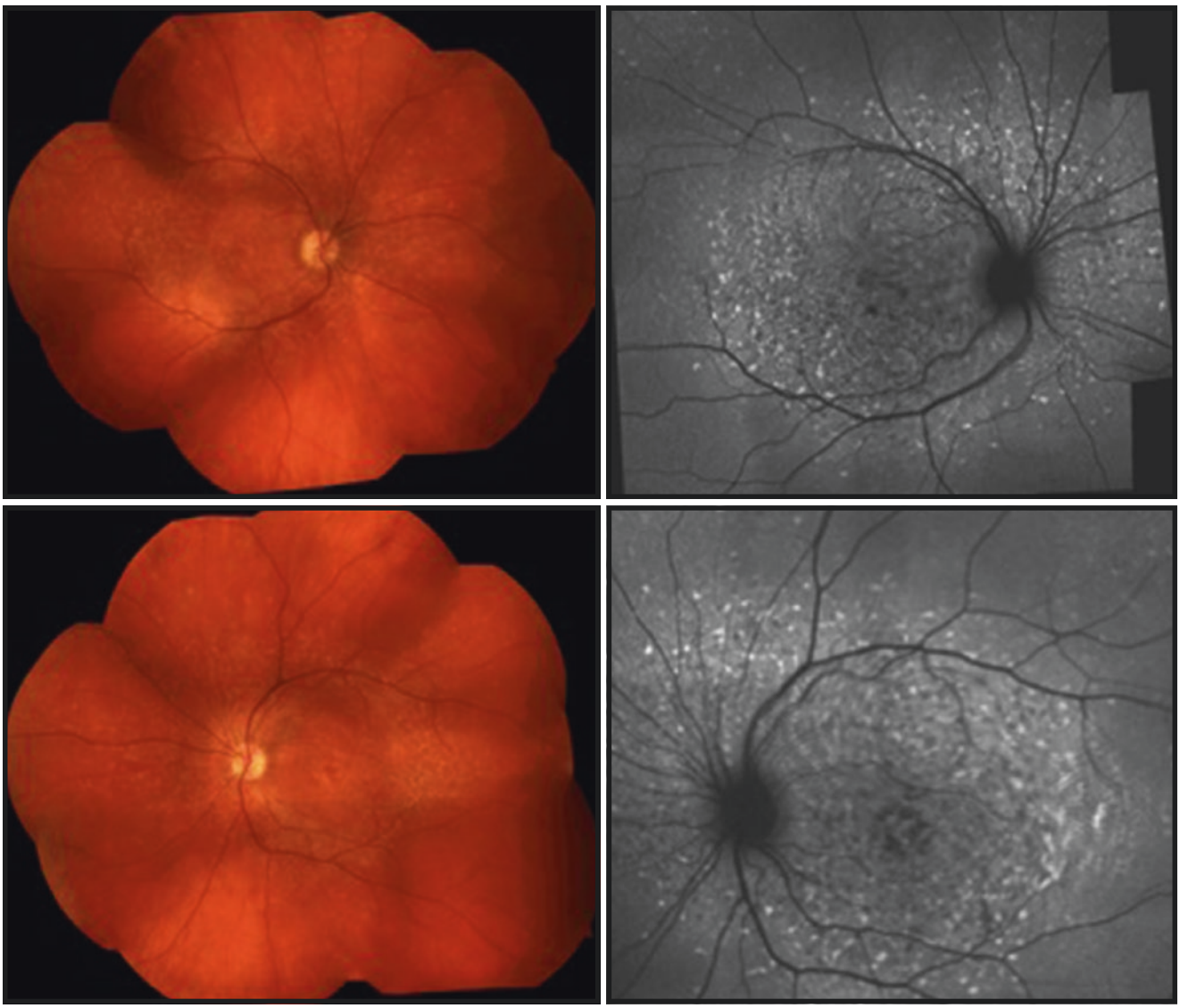

Fig. 27.3 STGD presenting as multiple flecks at the posterior pole, with a few atrophic patches at the macula

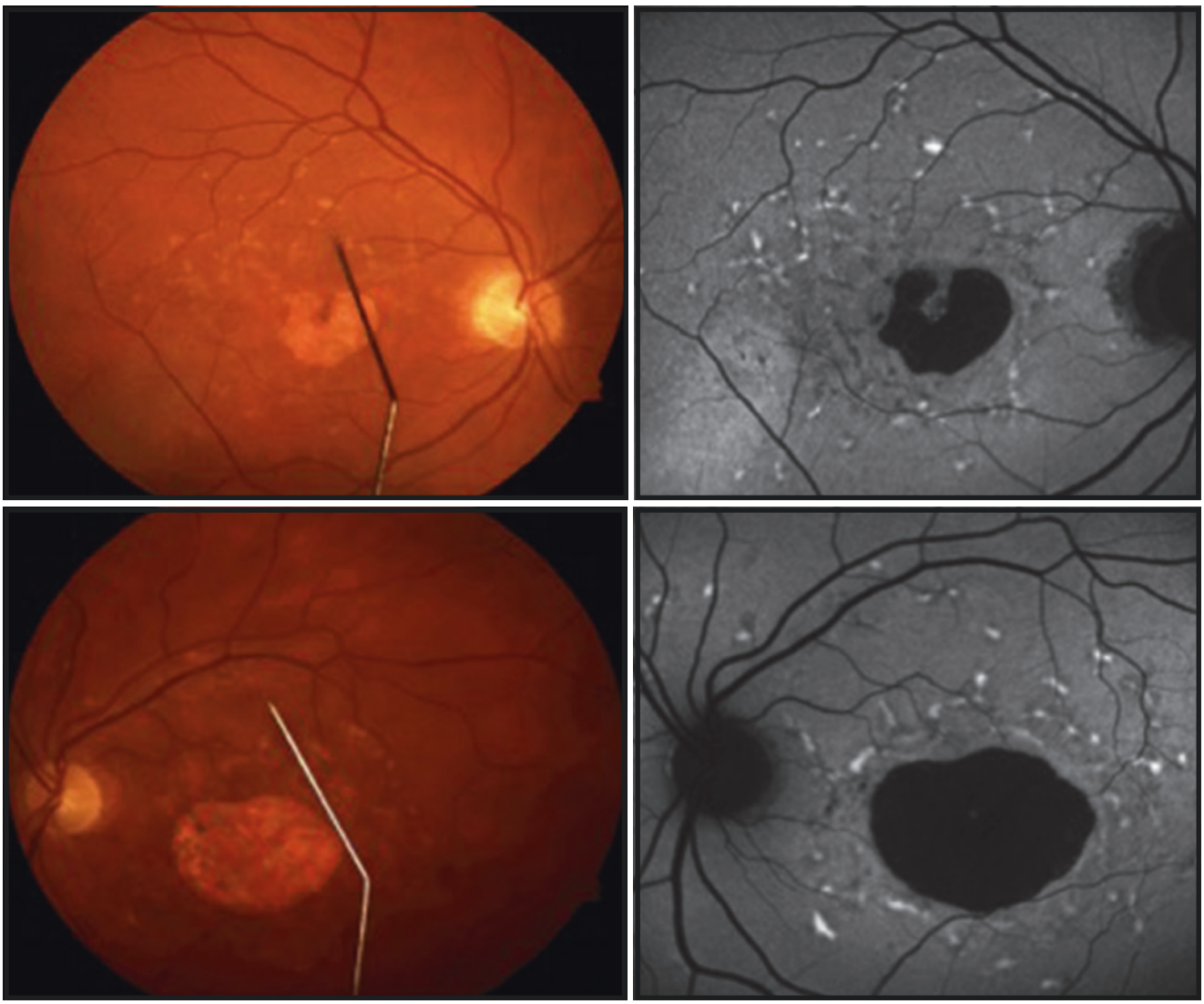

Fig. 27.4 STGD presenting as a large atrophic patch at the macula with a few flecks, some of them encroaching on the peripapillary area (28:p.P1380L, 36:p.S1696N)

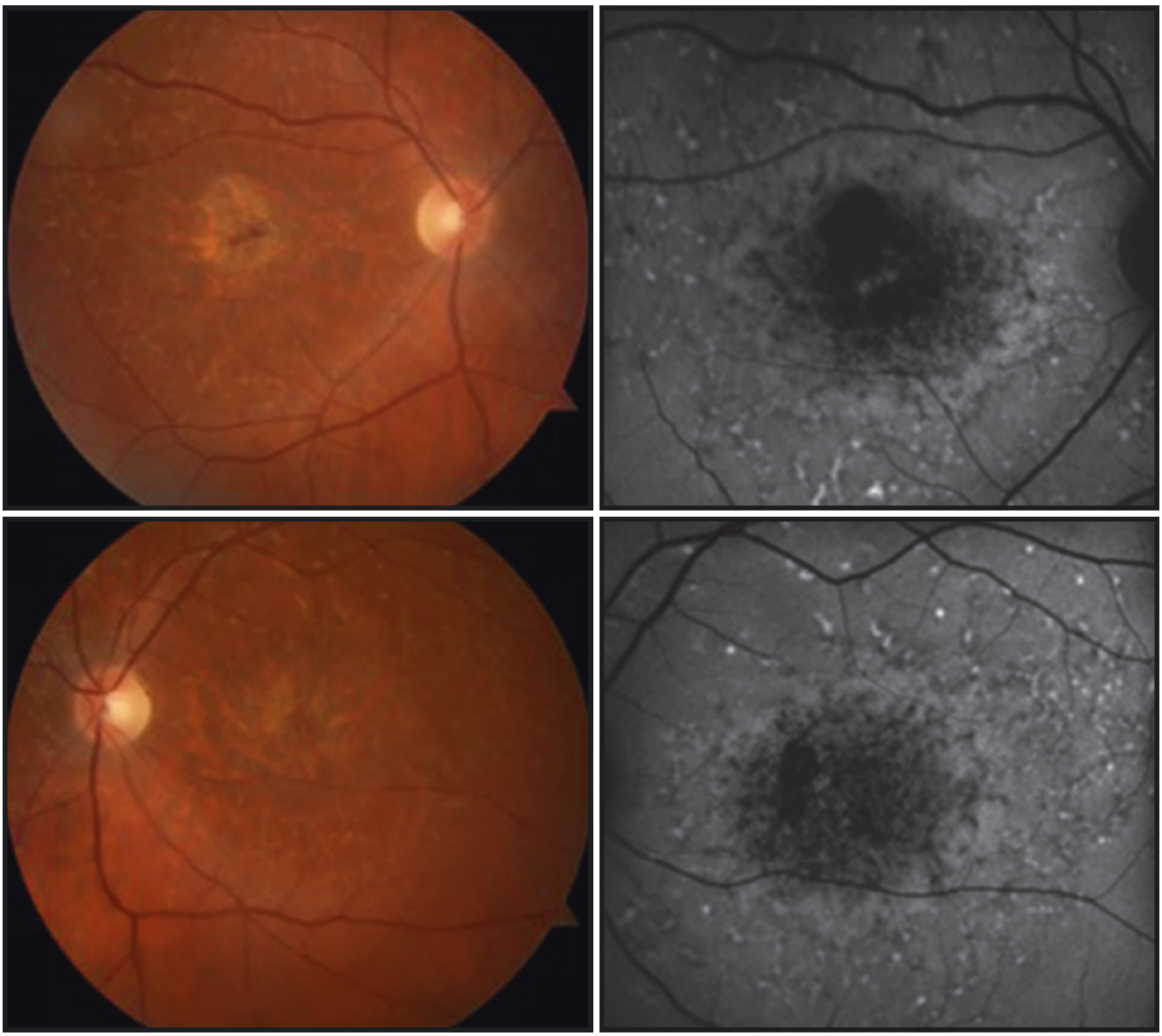

Fig. 27.5 STGD presenting as a large RPE atrophic area in the macula with sparse flecks, some of them showing RPE atrophy as well

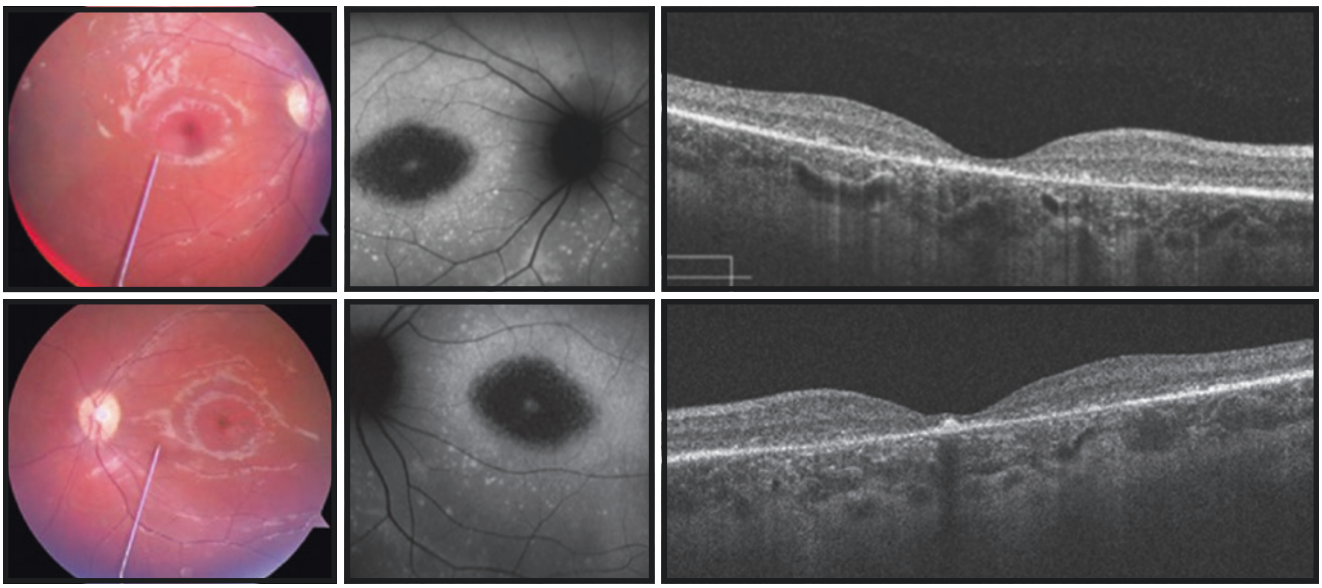

Fig. 27.6 STGD presenting as BEM with minimal flecks; OCT shows marked thinning of the central retina. Note peripapillary sparing

Groupings, Based on Electroretinography (ERG)

GROUP I: Isolated abnormalities in the flash ERG (FERG) and pattern ERG (PERG); normal photopic/scotopic full-field (FF) ERG.
GROUP II: Abnormal FERG, PERG, and photopic FF ERG; normal scotopic FF ERG.
GROUP III: Abnormal FERG, PERG, and photopic/scotopic FF ERG.

Types, Based on FAF (Figs. 27.7, 27.8, 27.9, 27.10 and 27.11)

TYPE A: Central hypofluorescence, surrounded by a hyperfluorescent ring.
TYPE B: Only central hypofluorescence without surrounding hyperfluorescence.
TYPE C: No central hypofluorescence; instead, a speckled pattern of alternating hypofluorescence and hyperfluorescence.

Classes, Based on Optical Coherence Tomography (OCT)

CLASS A: Flecks confined to outer segment (OS) layer
CLASS B: Flecks extend through junction of OS and inner segment (IS)
CLASS C: Protrude into outer nuclear layer (ONL)
CLASS D: Only in ONL
CLASS E: Drusen-like pigment epithelial detachment (PED). (Familial drusen shows echolucency in the center; flecks are echodense.)

Molecular Genetics

ABCA4 Gene (RIM Protein or ABCR)

Mutation in *ABCA4* gene, which encodes an ATP-binding cassette (ABC) transporter protein, expressed in the outer segment (OS) of rods. ABCA4 protein transports potentially toxic substances out of photoreceptor cells. These substances are formed after phototransduction. Buildup of the toxic substance—lipofuscin—in the photoreceptor cells and surrounding cells causes cell death. Cytogenetic location: 1p22.1.

The genetics is extremely heterogenous and may be responsible for wide variations in clinical presentations. Mild reduction in ABCA4 activity results in about 95% of cases of STGD; moderate loss of activity results in cone-rod dystrophy (about 30–50% of cases); and complete loss results in retinitis pigmentosa (RP) with complete loss of rod and cone function (about 8% of cases of autosomal recessive RP).

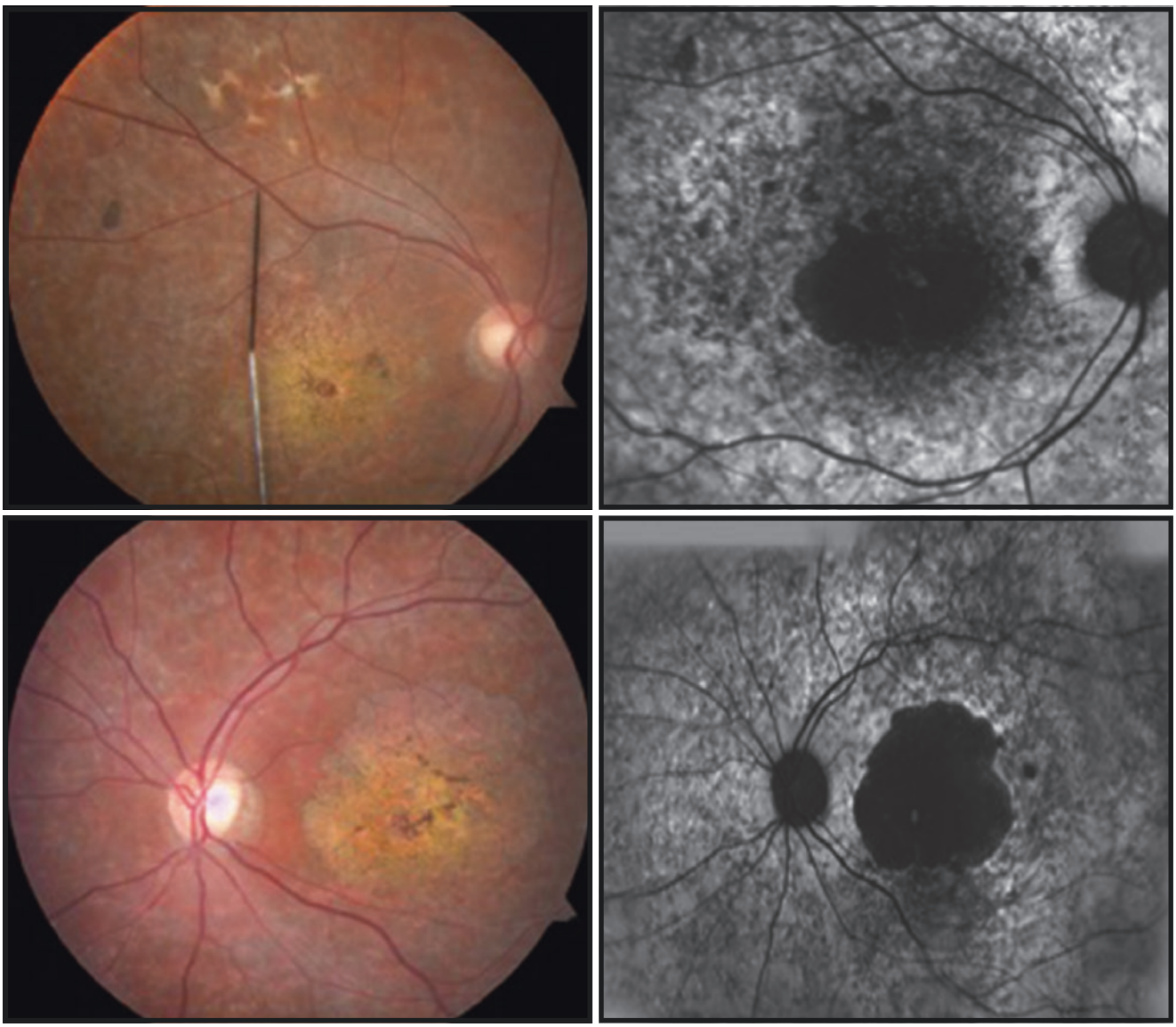

Fig. 27.7 An advanced case of STGD showing RPE atrophy over the macula and over all of the flecks as well. p.R18W and p.D2102E

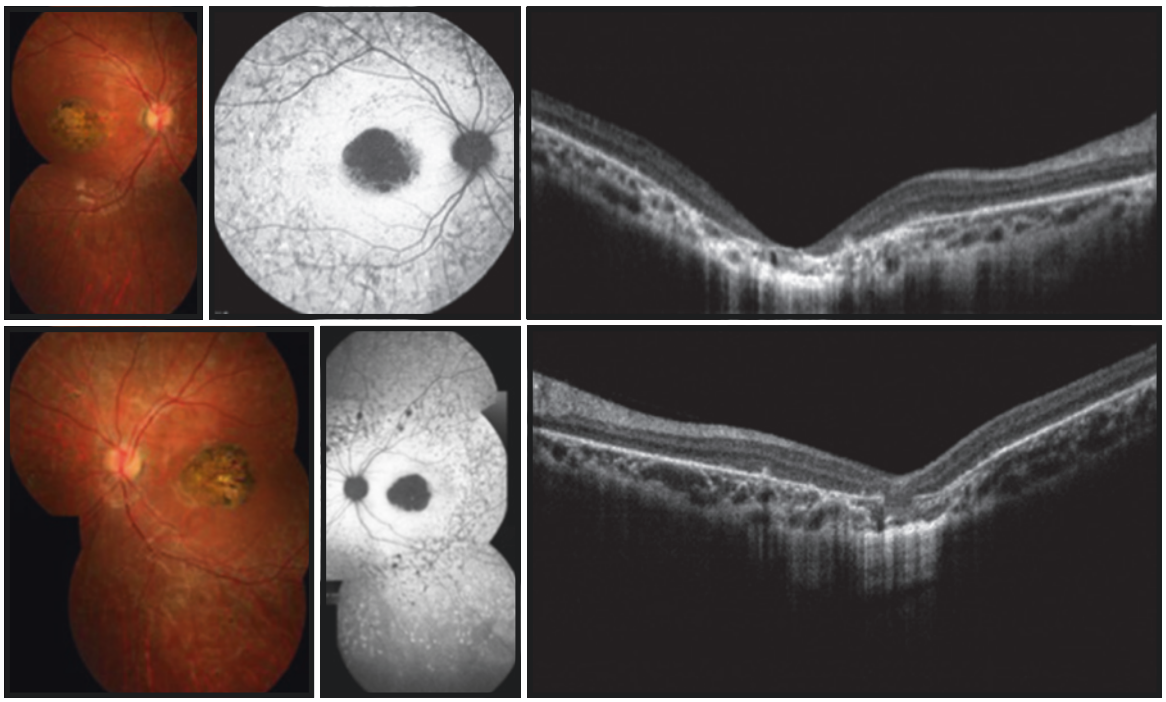

Fig. 27.8 STGD involving predominantly the macula, with sparse flecks in the periphery; OCT shows marked thinning of central retinal layers, including disruption of RPE layer (OS)

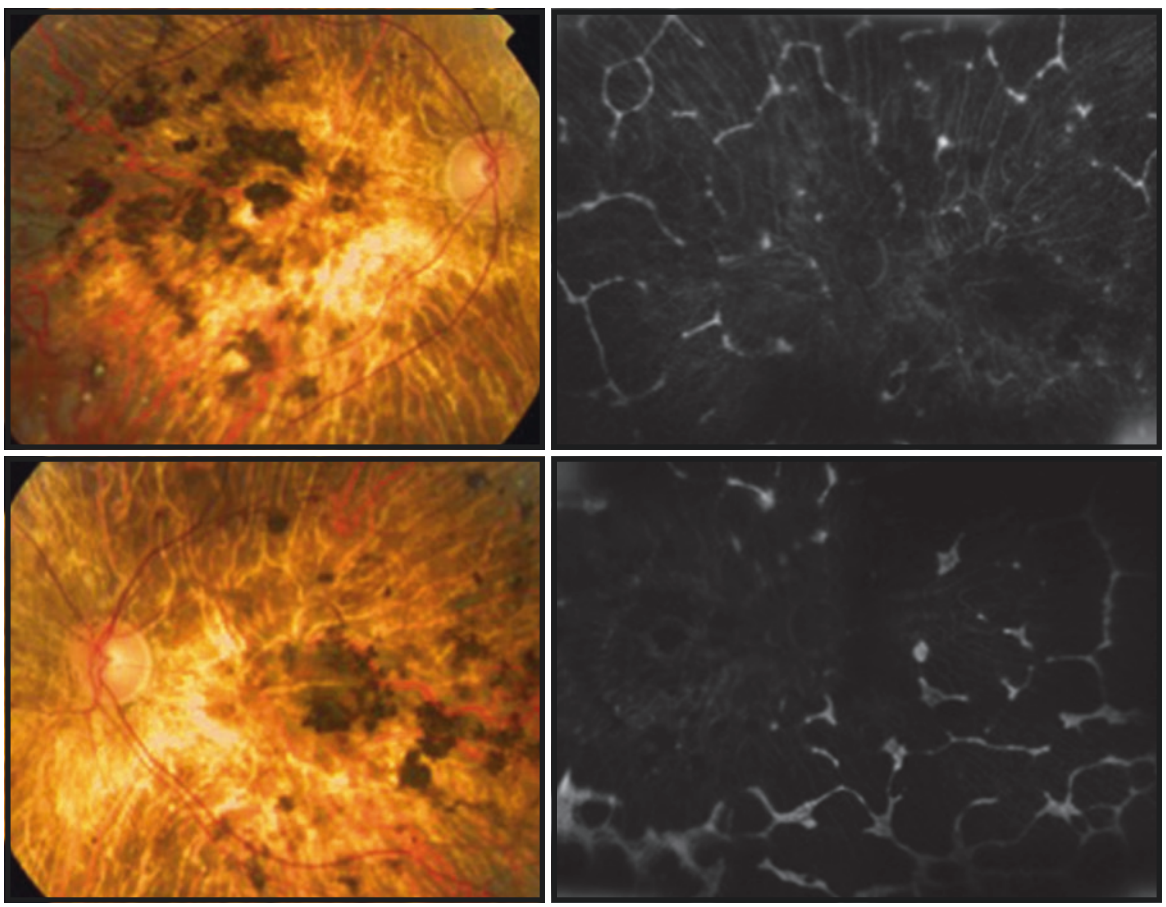

Fig. 27.9 An advanced stage of STGD, with marked RPE atrophy, confluent at the posterior pole (3:p.C54Y,IVS14:c.2160+1G>C) (Stargardt Group 3)

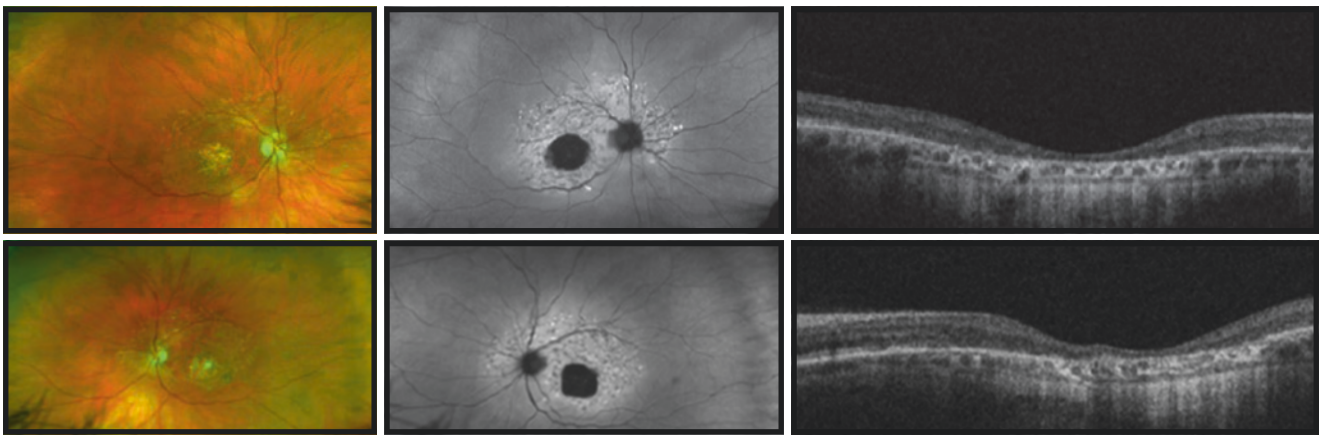

Fig. 27.10 STGD with just posterior involvement; the periphery is healthy. OCT shows marked thinning of the central retina. (Compare with Fig. 27.11, mother.) Two genetic variations: Cys54Tyr and Ala1038Val

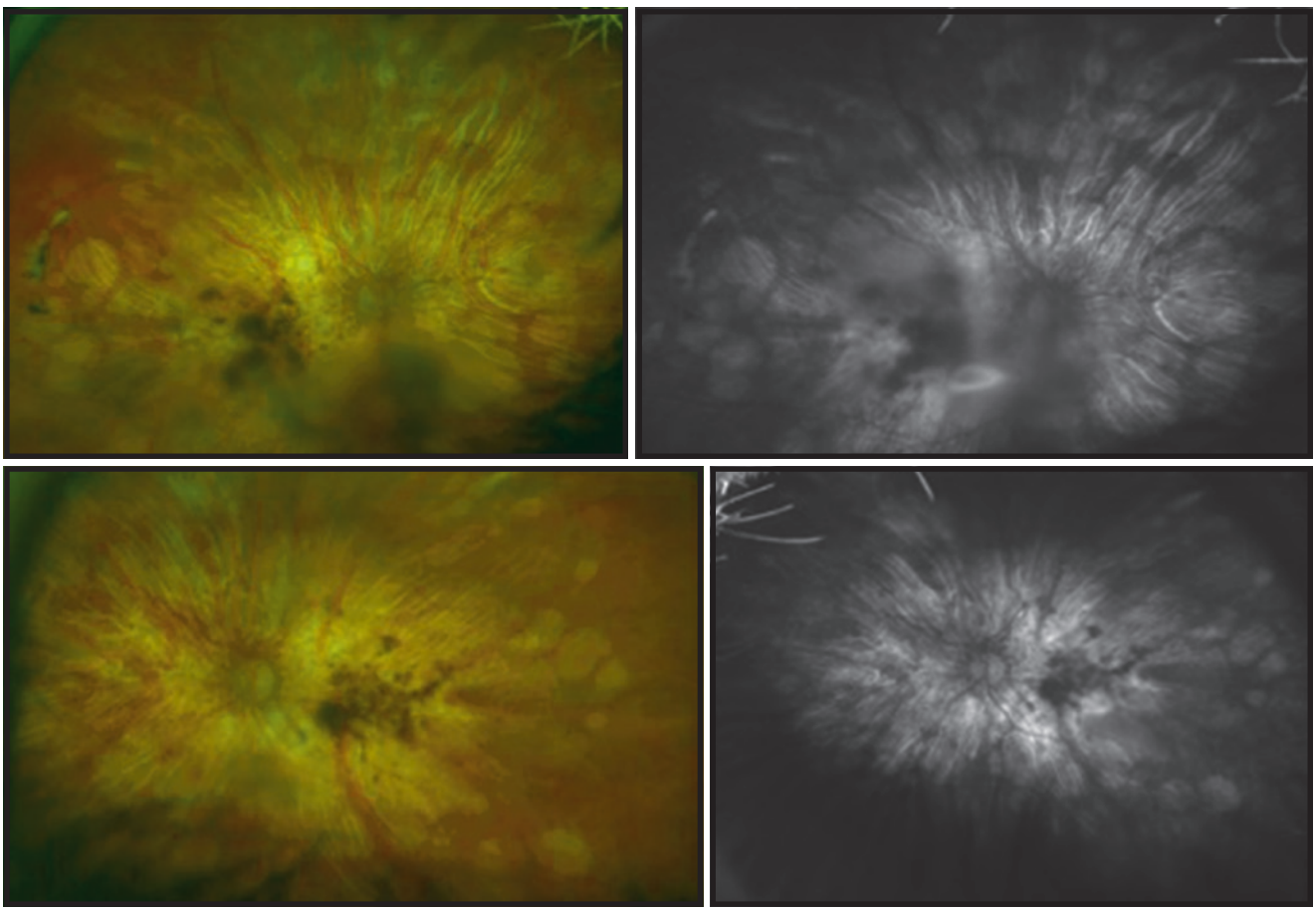

Fig. 27.11 STGD with involvement of the posterior pole and the periphery and marked atrophy of the RPE layer. (Compare with Fig. 27.10, son.) Two genetic variations: Cys54Tyr and Ala1038Val (Stargardt Group 3)

Other Mutations

Other mutations, accounting for the remaining 5% of STGD cases, are in the dominant genes *STGD4* and *ELOVL4* and *PRPH2*. The ELOVL4 protein plays a role in making a group of fats called very long-chain fatty acids. Mutations in the *ELOVL4* gene lead to the formation of ELOVL4 protein clumps in the cells, interfering with their activity and eventually leading to cell death. Cytogenetic location:6q14.1.

Genotype-Phenotype Correlation

c.5603A>T (p.Asn1868Ile) (Figs. 27.12, 27.13 and 27.14)

- This is a hypomorphic allele that is expressed only when in *trans* with a deleterious mutation.
- Phenotypes are late-onset (age about 36 years or later). About 85% of cases have foveal sparing and can masquerade as age-related macular degeneration (AMD).

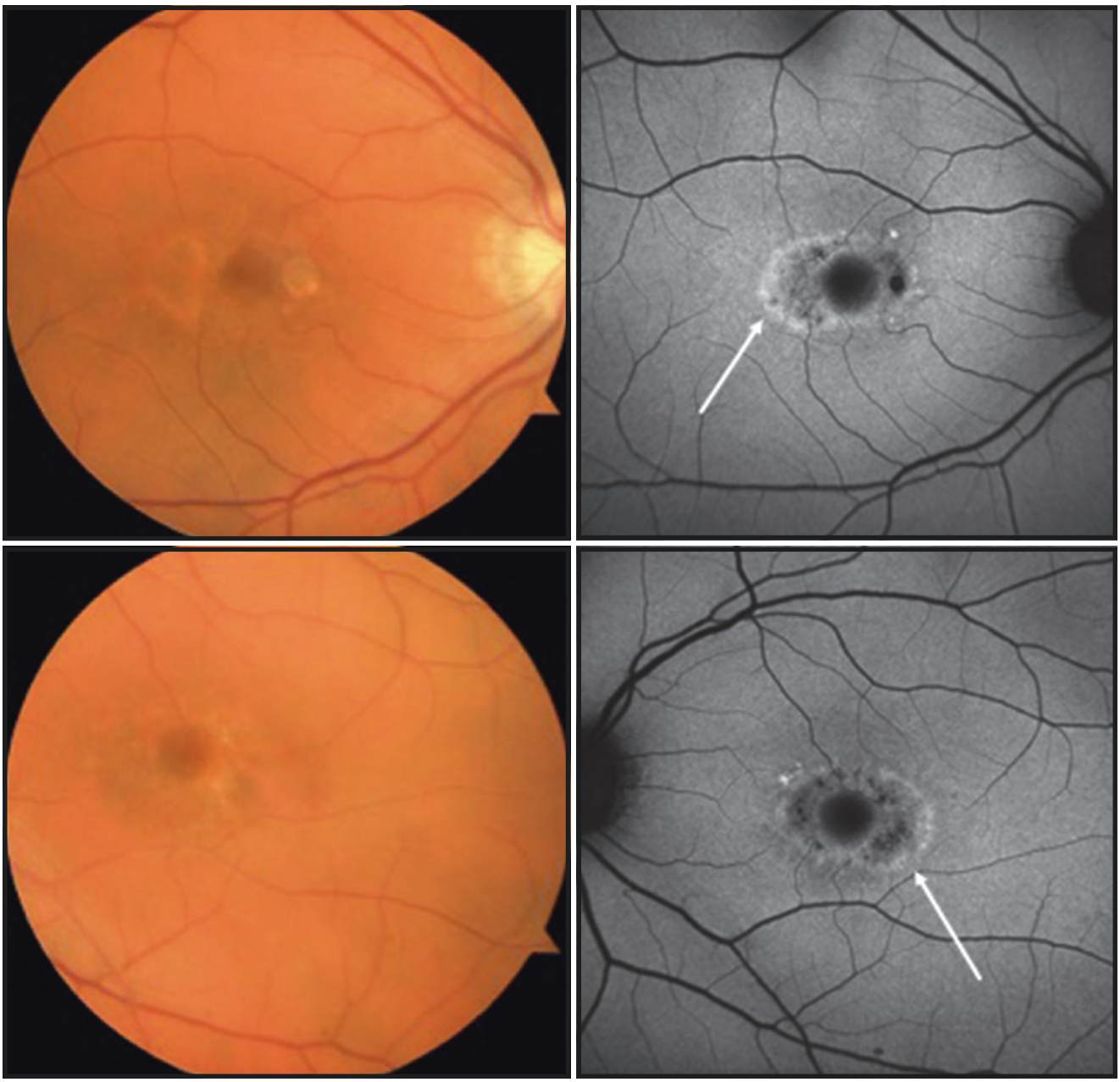

Fig. 27.12 STGD with predominant macular involvement; FAF shows central hypoAF surrounded by stippled AF ("pizza sign") (*arrows*)

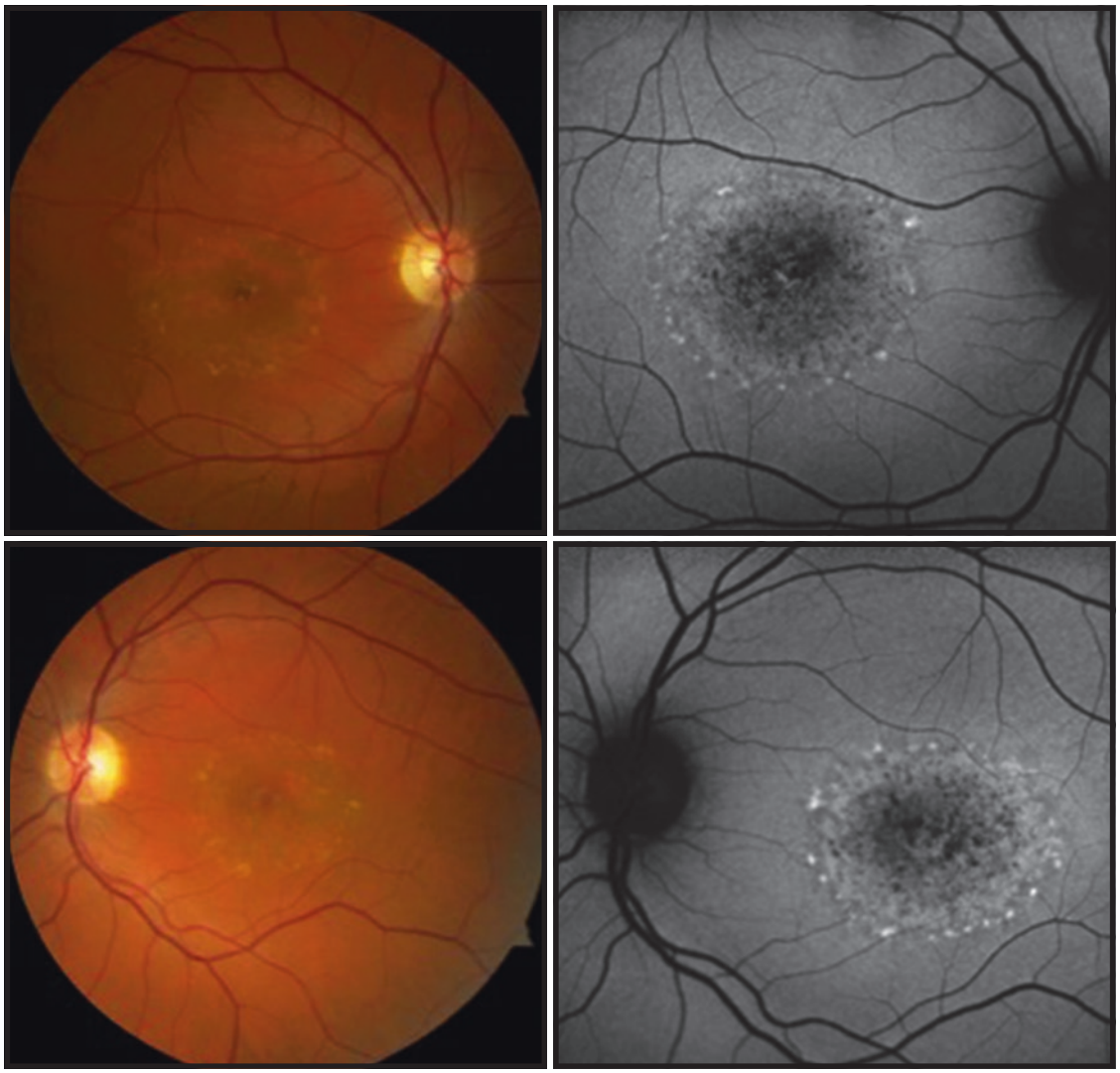

Fig. 27.13 STGD caused by c.5603A>T (p.N1868I). Note the characteristic "pizza sign"

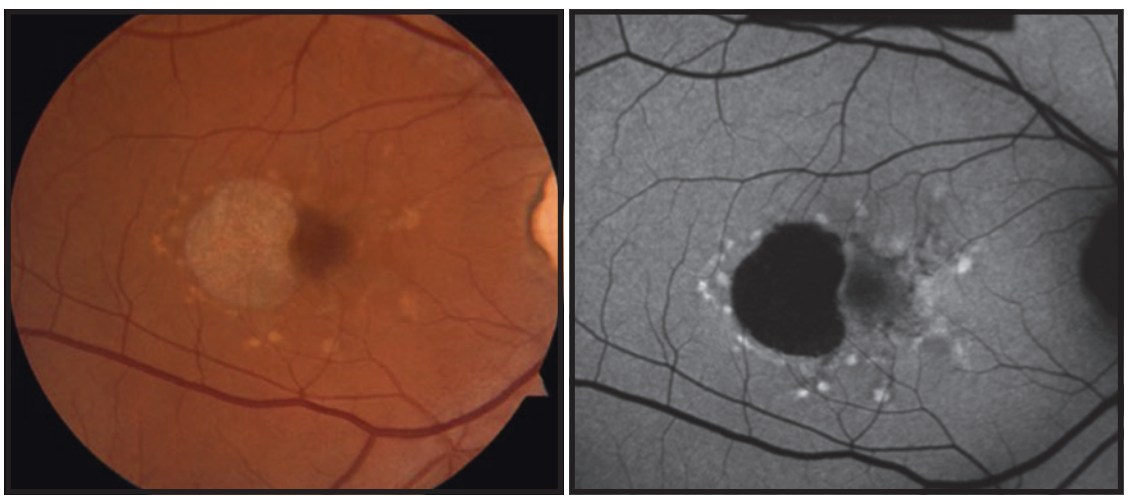

Fig. 27.14 STGD caused by c.5603A>T (p.N1868I). Note foveal sparing on AF. This mutation accounts for foveal sparing in about 80% of cases, along with late onset and mild progression

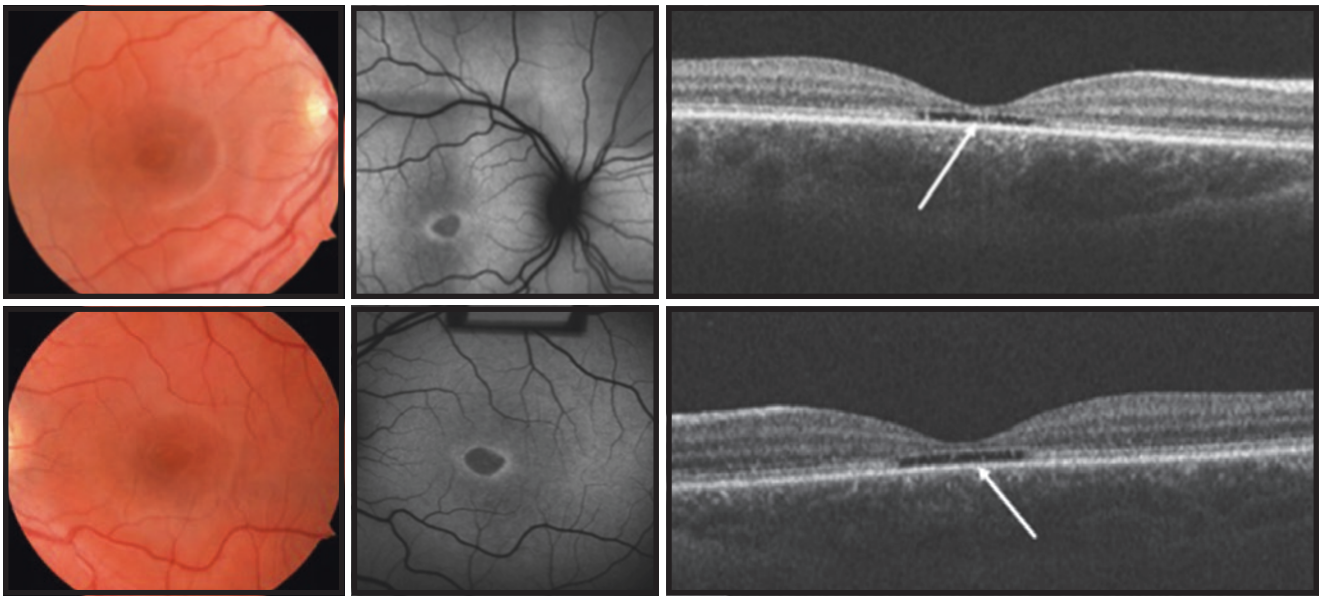

Fig. 27.15 STGD caused by c.5882G>A (p.G1961E) mutation. Note loss of foveal reflex, and central hypoAF surrounded by a hyperAF ring. OCT shows loss of the ellipsoid zone (EZ), causing an optical gap (*arrow*)

- Very few flecks are seen, which are somewhat larger, well-defined (a kind of "pizza sign"), and sparsely distributed.

c.5882G>A (p.Gly1961Glu) (Fig. 27.15)

- These patients exhibit mild disease expression, few specks, no confluence of flecks, and not much disease progression.
- Age of onset is about 23 years, with foveal sparing in about 40% of cases.
- Flecks are relatively large, well-defined, and sparsely distributed.
- On OCT, these patients show focal loss of the ellipsoid zone (EZ) (Stage I), an optical gap (Stage II), and eventual collapse of the optical gap.

Other *ABCA4* alleles

- These patients show innumerable flecks, which are confluent across the posterior pole and progressive; onset is about 18 years of age.
- Foveal sparing, about 30%

Biallelic Null *ABCA4*

- Age of onset about 10 years or earlier
- Confluent flecks appear early and progress more rapidly, leading to end-stage atrophy.

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Gelman R, Smith RT, Tsang SH. Diagnostic accuracy evaluation of visual acuity and fundus autofluorescence macular geographic atrophy area for the discrimination of Stargardt groups. Retina. 2016;36:159–601.

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CHAPTER 28

Enhanced S-Cone Syndrome (Goldmann-Favre Syndrome)

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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_28

General Features

- In enhanced S-cone syndrome (ESCS), rods and red and green cone receptors are degenerated, but S-cones are enhanced (increased in number).
- Patients have increased sensitivity to blue light, with night blindness from an early age (from birth) and impaired central vision.
- The fundus shows characteristic nummular pigmentary changes along the vascular arcades at the level of the retinal pigment epithelium (RPE). (In retinitis pigmentosa [RP], pigment is deposited within the retina.) Sometimes, there are white-yellow dots at the level of the RPE along the vascular arcades, along with focal hyperpigmentation within the arcades (Figs. 28.1 and 28.2).
- Patients may also have foveal schisis. (Goldmann-Favre syndrome consists of foveal schisis plus peripheral degeneration.)
- Fundus autofluorescence (FAF) shows a decrease or lack of AF outside the arcades, possibly due to loss of photoreceptors in this region; a ring of hyperautofluorescence (hyperAF) is seen in the transition zone between the region of absent AF beyond the arcade and the central zone of spoke-like, relatively increased AF, centered on the fovea; increased AF may be related to lipofuscin accumulation secondary to RPE-photoreceptor dysfunction in that area.
- Electroretinograms (ERGs) in ESCS are pathognomonic and show extinguished rod response and a similar wave form in both scotopic and photopic conditions.
  - The 30 Hz flicker responses are markedly delayed and are of lower amplitude. (Normally, flicker amplitude lies between that of the photopic a- and b-waves, but in ESCS, it is less than that of the photopic a-wave.)
  - With orange background (suppressing red and green cones), increased response to short wavelength (blue) is elicited, suggestive of functioning of S-cones. The multifocal ERG (mfERG) shows preservation of central responses, though somewhat delayed.
- ESCS is a slowly progressive disorder that often leads to severe visual loss in adults.

Molecular Genetics

- Mutation in *NR2E3* (located on chromosome 15q23); this gene encodes for photoreceptor nuclear transcription factor, which controls retinal progenitor cell fate.
- The *NR2E3* gene promotes differentiation and survival of rod photoreceptors by differentially regulating transcription of rod-specific and cone-specific genes.
- Mutation in *NR2E3* results in improper photoreceptor cell differentiation, possibly by encouraging S-cone pathway from rod photoreceptor pathway.

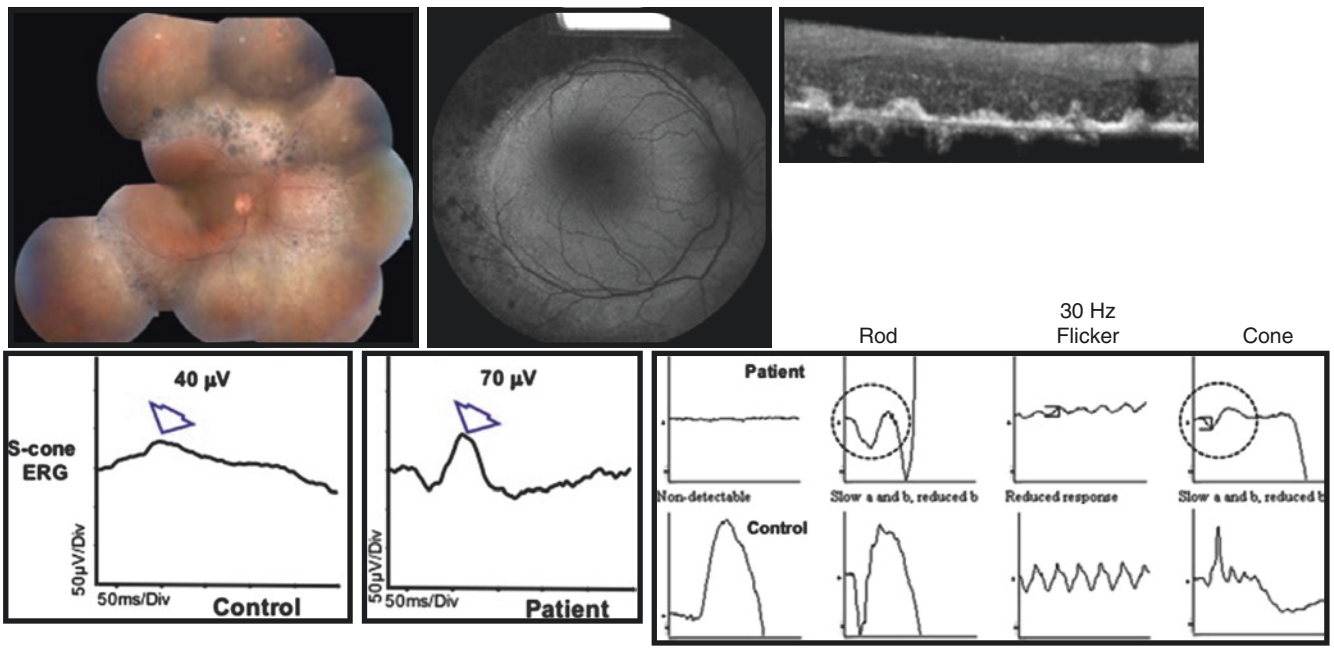

Fig. 28.1 A case of enhanced S-cone syndrome (ESCS) with *NR2E3* mutation. Note the nummular pigmentation pattern along the temporal arcades and nasal to the disc, as well as hyperAF in the involved area with hypoAF in the areas of pigmentation. Optical coherence tomography (OCT) shows pigmentation at the RPE level, and electroretinography (ERG) shows reduced response in both photopic and scotopic conditions, with decreased amplitude on 30 Hz flicker

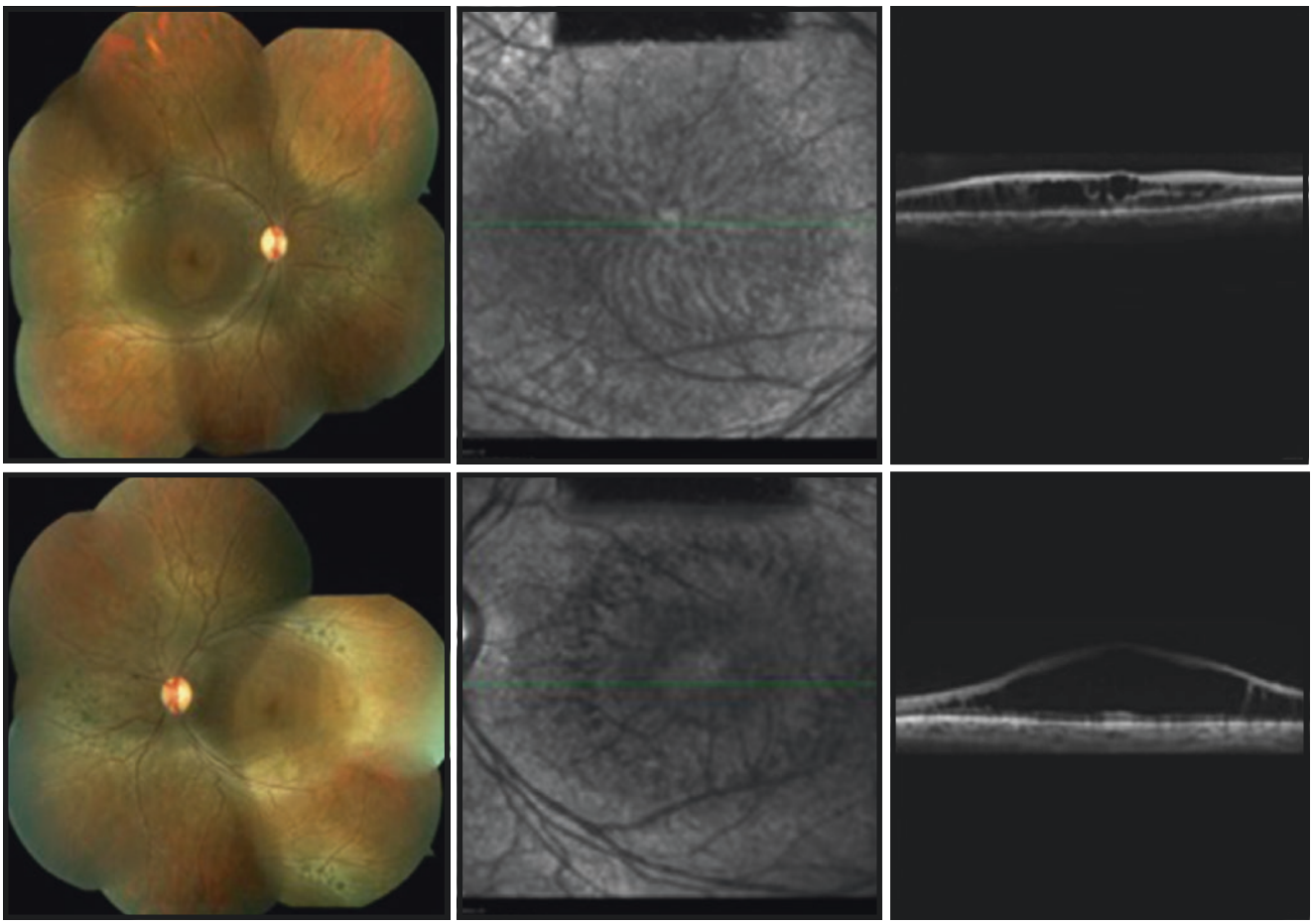

Fig. 28.2 *NR2E3* (homozygous R311Q) mutation, showing characteristic nummular pigmentation, macular schisis on OCT, and typical ERG findings (similar waveform in the maximum scotopic and photopic), with disproportionately reduced amplitude on 30 Hz flicker compared to single-flash cone amplitude

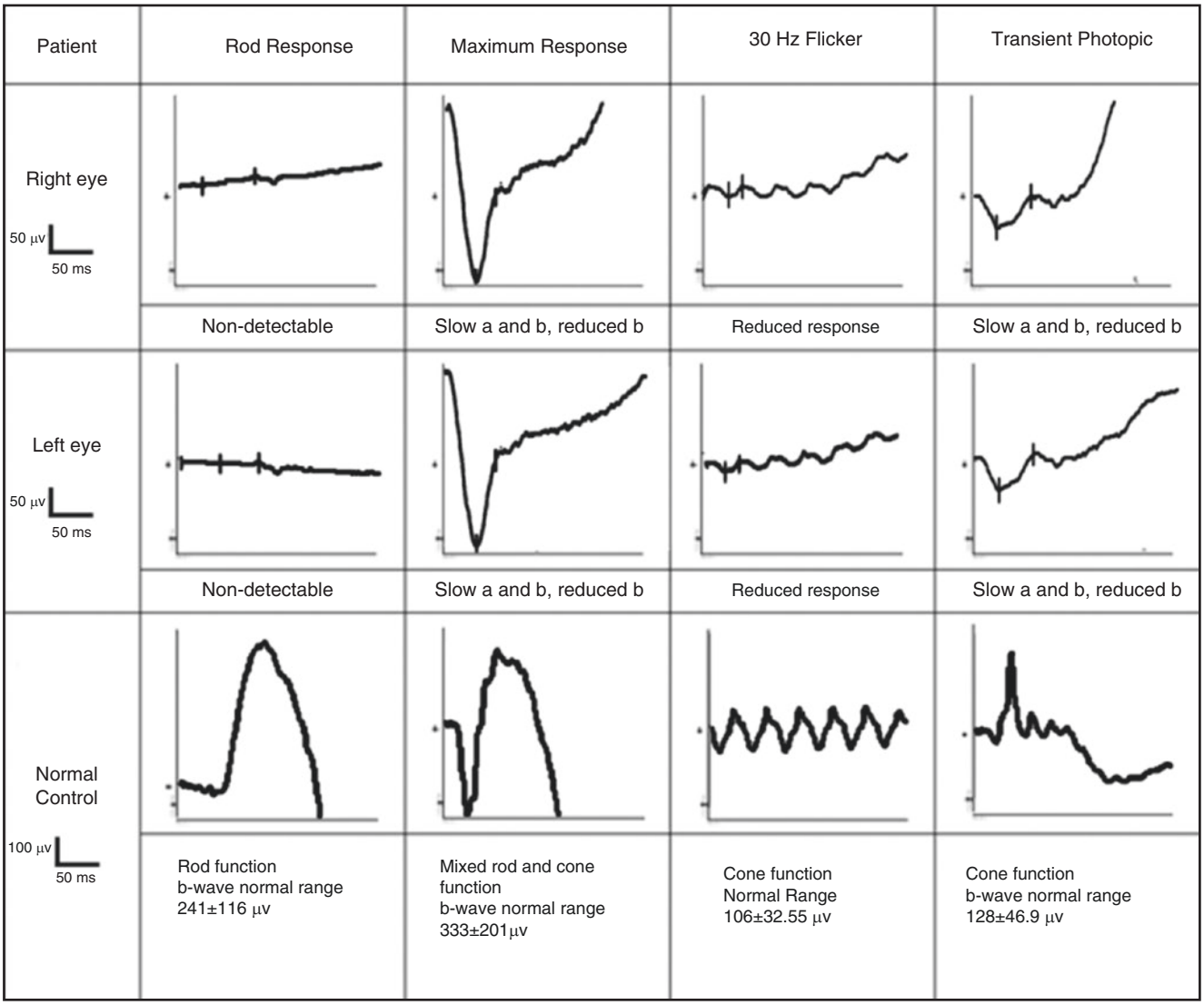

Fig. 28.2 (Continued)

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Gelman R, Greenberg JP, Duncker T, Nguyen HV, Yannuzzi LA, Tsang SH. Hyperautofluorescent macular ring in a series of patients with enhanced S-cone syndrome. Ophthalmic Surg Lasers Imaging Retina. 2014;45:592–5.

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CHAPTER 29

Best Vitelliform Macular Dystrophy

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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_29

General Features

- Autosomal recessive bestrophinopathy (ARB) results from a total absence of functional bestrophin-1 protein owing to two *BEST1* mutations, one on each of the chromosomes.
- If present at an early age, the presenting feature could be decreased vision due to amblyopia.
- Refractive error is hyperopia, predisposing these eyes for acute angle-closure glaucoma.
- The yellowish lesions are larger and more extensive—extending beyond the arcades—than in the typical autosomal dominant Best disease. Some of the eyes also show numerous yellowish subretinal dots. Lesions are multifocal (Fig. 29.1).
- Subretinal fibrosis in the macular area is a common feature.
- Optical coherence tomography (OCT) may show cystoid changes in the neurosensory retina.
- Fundus autofluorescence (FAF): Increased AF reflects lipofuscin accumulation in the RPE; decreased AF reflects RPE atrophy.
- Electroretinography (ERG): As panretinal photoreceptor dysfunction progresses with advancing age, full-field (FF) ERG shows delayed rod and cone responses.
- Electrooculography (EOG): Abnormal Arden ratio.

Suggested Reading

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Silva RA, Berrocal AM, Lam BL, Albini TA. Novel mutation in *BEST1* associated with retinoschisis. JAMA Ophthalmol. 2013;131:794–8.

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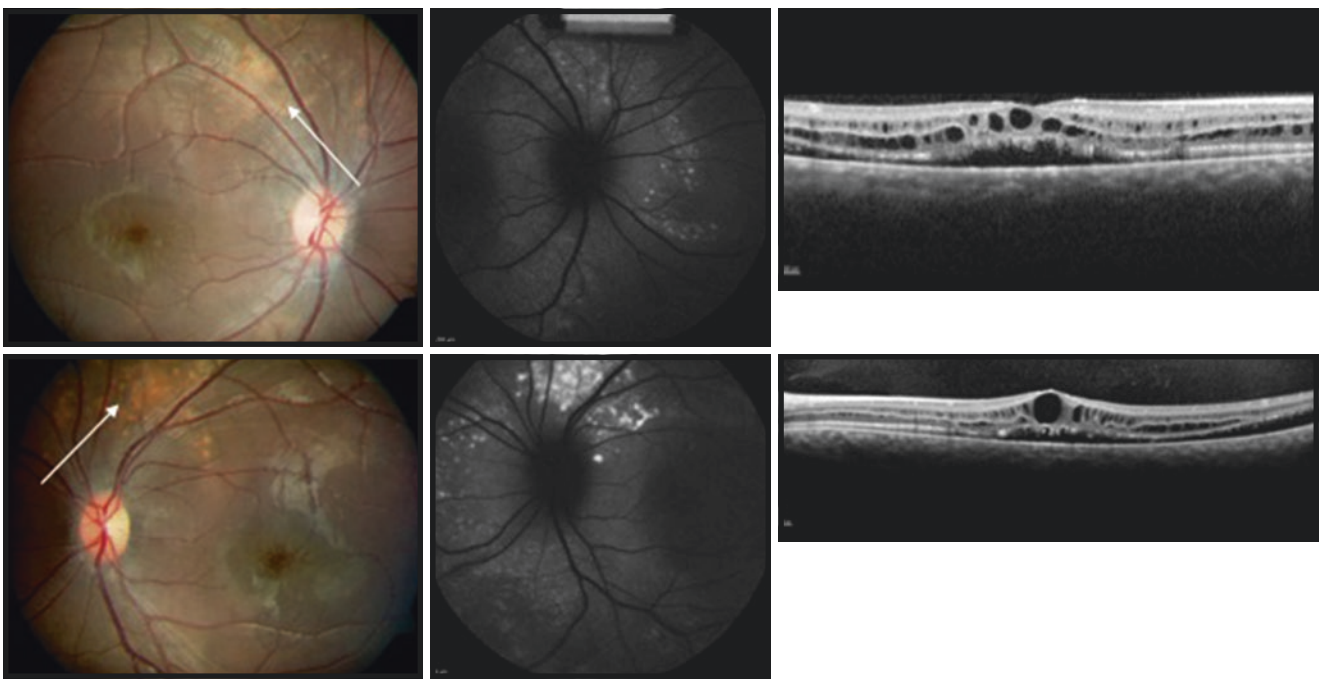

Fig. 29.1 Autosomal recessive Best macular dystrophy caused by mutation in the *BEST1* gene (homozygous truncation at F283 amino acid). Note the yellowish subretinal deposits (*arrows*), which show hyperautofluorescence. Optical coherence tomography (OCT) shows cystoid macular edema

Section V
Systemic Disorders

CHAPTER 30

Mitochondrial Disorder: Kearns-Sayre Syndrome

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General Features

- Mitochondrial diseases are multisystem disorders: anemia, myopathy, lactic acidosis, CNS abnormality, endocrine abnormalities, renal disease, sensorineural deafness, and retinal involvement. The clinical abnormalities are heterogeneous, and they usually begin in childhood. Premature death occurs because of cardiac conduction defects.
- The onset is usually before 20 years of age. The fundus shows pigmentary retinopathy, with a salt-and-pepper appearance (Fig. 30.1), but vision remains good in most patients.
- Systemic involvement includes chronic progressive external ophthalmoplegia (CPEO), with ptosis being the most common complaint, and cardiomyopathy.
- Other variable features are short stature; cerebellar symptoms; weakness of muscles of the face, pharynx, trunk, or extremities; and progressive hearing loss.
- Full-field ERG does show evidence of generalized retinal dysfunction, involving both rods and cones.
- Skeletal muscle biopsy shows ragged red fibers and abnormal mitochondria.

Molecular Genetics

Mitochondrial DNA (mtDNA) deletions can be identified, and rarely point mutation.

Suggested Reading

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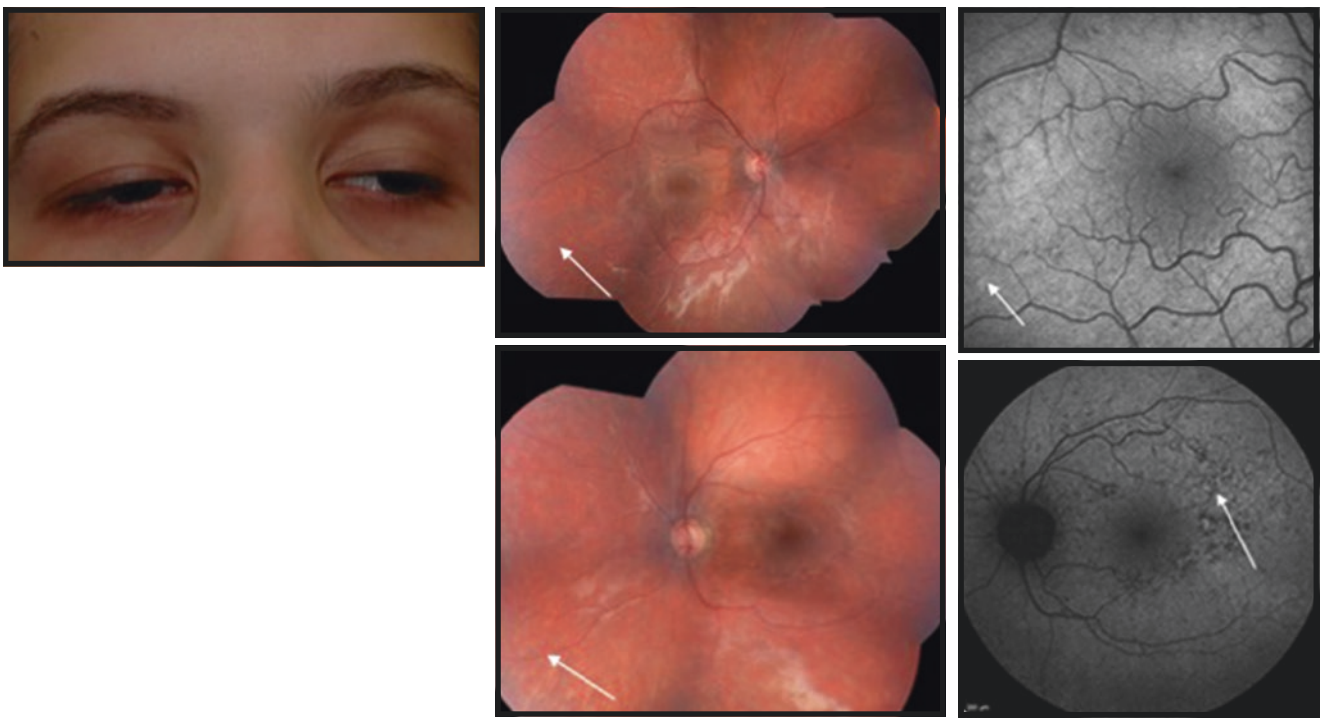

Fig. 30.1 Kearns-Sayre syndrome in this patient is evidenced by ptosis, more marked in the right eye; pigmentary retinopathy (*arrows*), and a stippled autofluorescence pattern (*arrows*)

CHAPTER 31

Mitochondrial Disorder: Maternally Inherited Diabetes and Deafness

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General Features

- Patients with maternally inherited diabetes and deafness (MIDD) have insulin-dependent diabetes with relatively low BMI; usually the onset of the diabetes is during the third or fourth decade of life and it is associated with progressive neurosensory deafness.
- The fundus shows circumferentially oriented but discontinuous patches of RPE and choriocapillaris (CC) atrophy around the macula, within the arcades (Fig. 31.1); mitochondrial A3243G mutation results in corneal endothelial polymegathism (Fig. 31.2).
- Vision is usually good, about 20/40 or better.
- Fundus autofluorescence (FAF) shows decreased AF in the areas of RPE atrophy, surrounded by a zone of speckled AF.
- No generalized retinal dysfunction is seen on full-field electroretinography (ERG), but pattern ERG or multifocal ERG shows abnormal function.

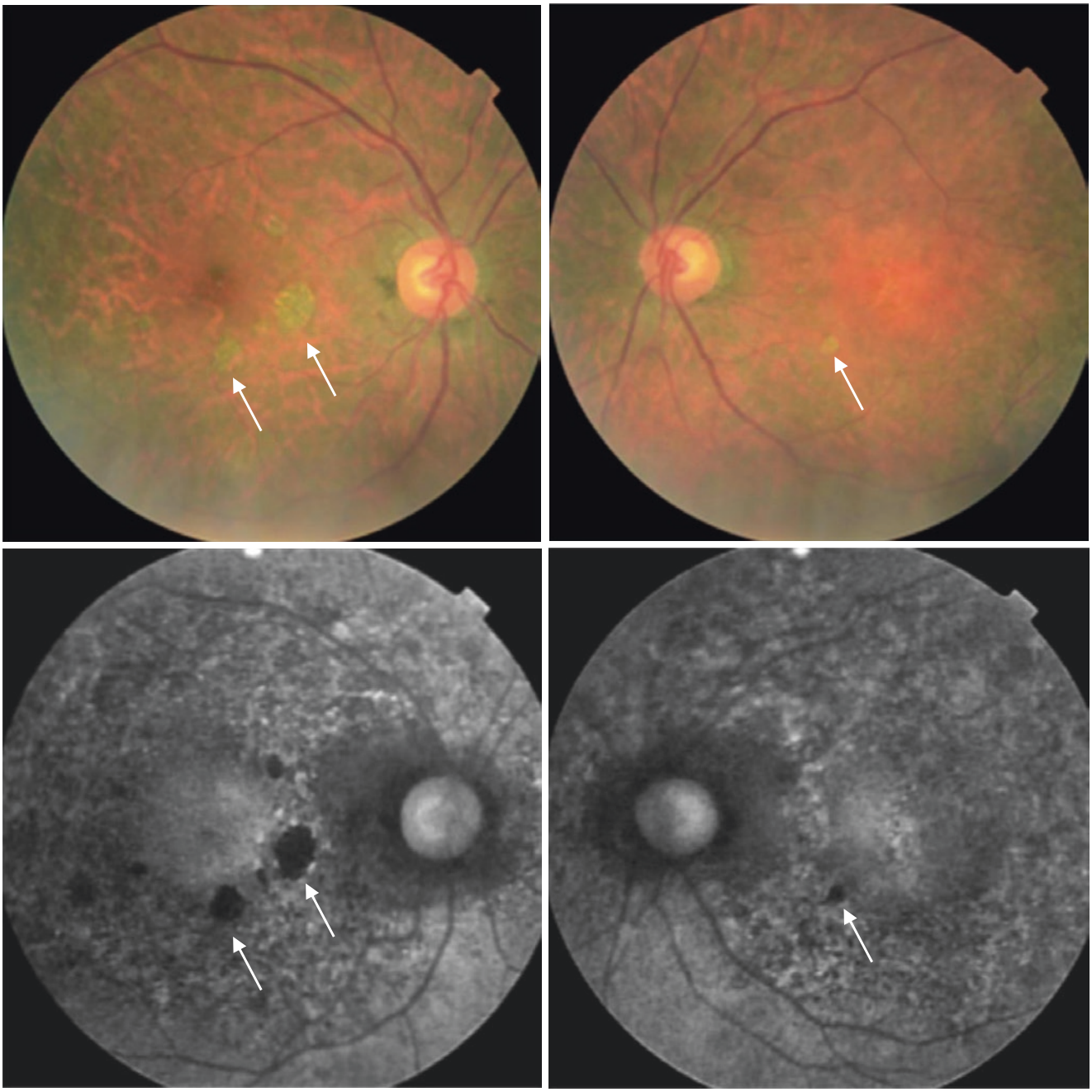

Fig. 31.1 The fundus of a patient with MIDD (A3243G mutation) shows circular area of RPE depigmentation *(arrows)* with corresponding hypoAF. (Reprinted by permission from Bakhoum et al., Springer Nature 2018)

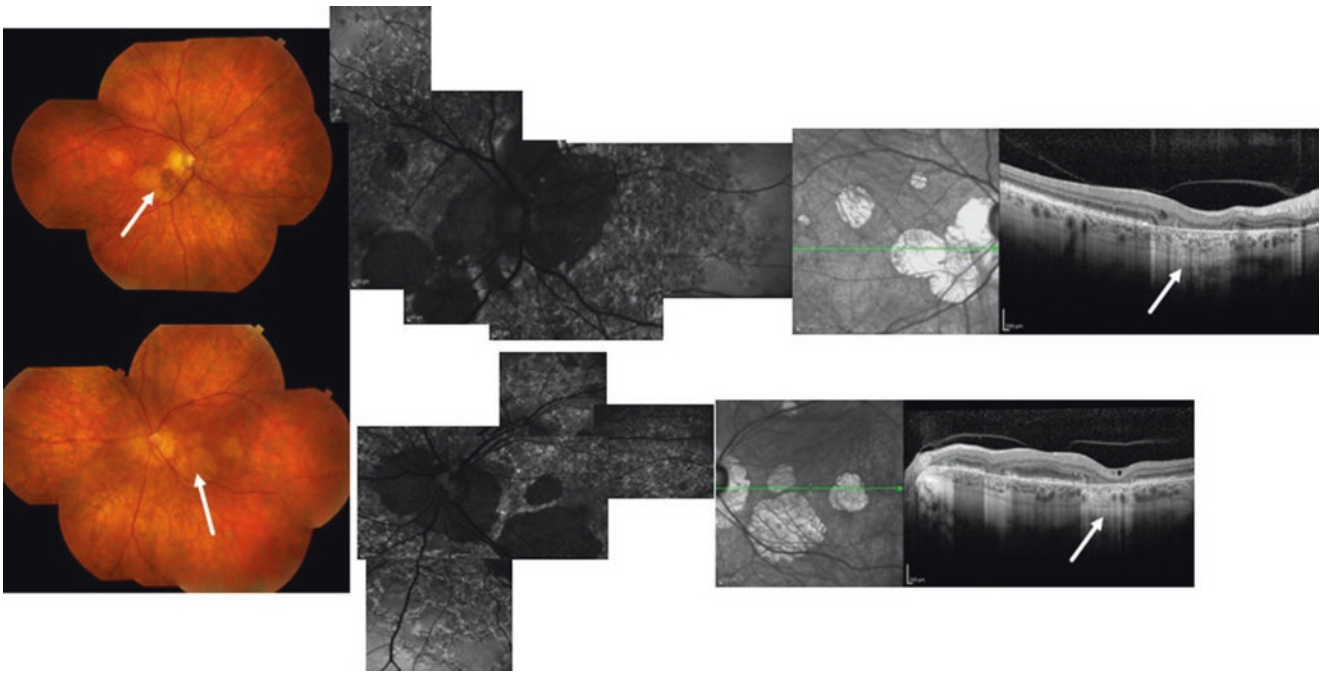

Fig. 31.2 MIDD. The fundus shows circular areas of RPE and choriocapillaris atrophy (*arrows*) at the posterior pole, with corresponding hypoAF and increased RPE transmission on optical coherence tomography (OCT). (Reprinted by permission from Mathieu et al. Mitochondrial A3243G mutation results in corneal endothelial polymegathism, DOI: 10.1007/s00417-018-3914-z, Springer Nature 2018.)

- Asymptomatic maternal relatives harboring the mutation may show pigmentary changes, hearing loss, and in some, diabetes.
- Another disorder associated with the same A3243G mitochondrial DNA (mtDNA) mutation as MIDD is Mitochondrial Encephalomyopathy with Lactic Acidosis and Stroke-like episodes (MELAS). The stroke-like episode (such as hemiplegia) occurs at about 5–15 years of age, and severe encephalopathy may cause death at a young age. Patients may also experience headache, vomiting, visual field defects, or cortical blindness.

Molecular Genetics

- The associated mutation is A3243G mtDNA point mutation (adenine-to-guanine transition at position 3243).
- The *MT-TL1*, *MT-TK*, and *MT-TE* genes provide instructions for making molecules called transfer RNAs; these tRNA molecules are present only in mitochondria and help to assemble proteins that are needed for producing energy for cells.
- In the pancreas, there are beta cells that play an important role in controlling the glucose level; mitochondria trigger the release of insulin in response to high glucose levels.

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CHAPTER 32

Ciliopathy: Usher Syndrome

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General Features

- Ciliopathies are a group of disorders caused by a defect in ciliogenesis, ciliary protein trafficking. Because nearly every cell in the body (including the photoreceptors) contains cilia, defects in ciliary proteins typically affect multiple organ systems.
- Usher syndrome is the most common syndromic cause of retinitis pigmentosa (RP) and accounts for 10–20% of cases of RP
- Inheritance is autosomal recessive, and the retinal dystrophy is usually rod-cone dystrophy (Figs. 32.1 and 32.2).
- These patients have RP with sensorineural hearing loss (partial or complete) since birth; some may have vestibular dysfunction.
- Most patients retain central vision of about 20/40 until about age 40.
- **Usher Syndrome 1 (USH1):** Profound congenital sensorineural hearing loss on audiometry, absent vestibular function, and typical RP (onset by 10 years of age); accounts for about 70% of all Usher cases. Patient may benefit from a cochlear implant. The retinitis pigmentosa occurs at an early age (childhood onset) and progress slowly.
- **Usher Syndrome 2 (USH2):** Moderate to severe congenital sensorineural hearing loss on audiometry (predominantly for higher frequencies), normal vestibular function, and typical RP (onset by 20 years of age); accounts for about 26% of all Usher cases.
- **Usher Syndrome 3 (USH3):** Progressive sensorineural hearing loss and typical RP (onset in second decade); accounts for about 4% of all Usher cases. Vestibular function is normal in about half of patients, but abnormal in the other half.

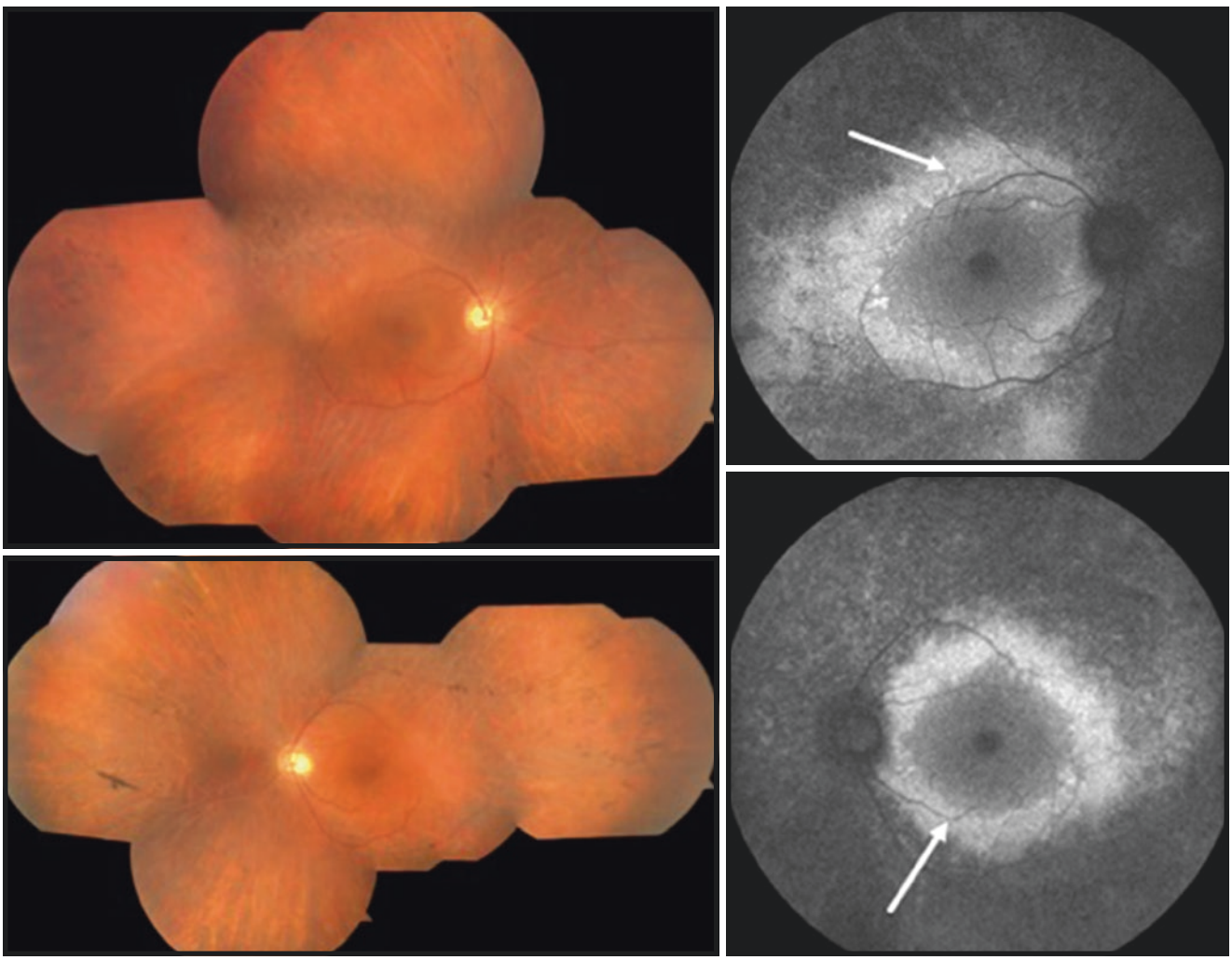

Fig. 32.1 A case of Usher showing a hyperautofluorescent ring around the fovea (*arrows*)

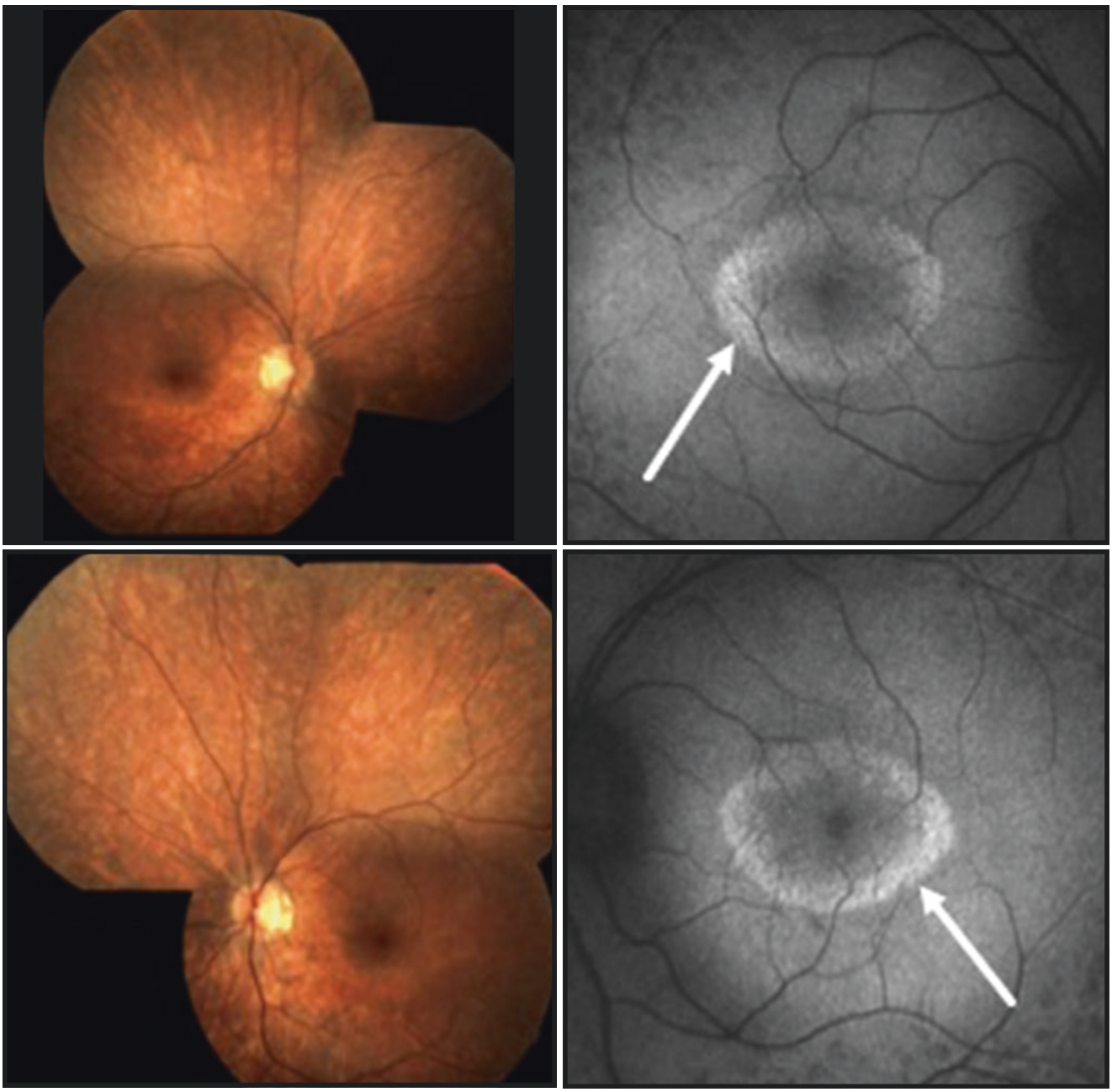

Fig. 32.2 A case of Usher showing a broad hyperautofluorescent ring along the arcades (*arrows*)

Molecular Genetics

USH1

There are nine known loci, USH1B to USH1K (no USH1A or USH1I).

- The most commonly mutated genes are *MYO7A* (USH1B, 53–63%), *CDH23* (USH1D, 7–20%, cadherin protein), *USH1C* (1–15%, harmonin protein), and *PCDH15* (USH1F, 7–12%, protocadherin 15).
- Almost all patients with *USH1C* mutations (specifically c.497-79_497-35 (VNTR exp) or p.V72=) have Acadian ancestry, whereas the p.R245X nonsense mutation in *PCDH15* is more common in Ashkenazi Jewish individuals.
- *MYO7A* produces unconventional myosin VIIa, a motor protein that is found in retinal pigment epithelium (RPE), photoreceptor cells, and cochlear and vestibular neuroepithelia.

USH2

There are three known genes associated with type II:

- *USH2A* (57–79%), Usherin protein, cytogenetic location 1q41
- *ADGRV1* (USH2C, 6.6–19%), G-protein coupled receptor 98, cytogenetic location 5q14.3
- *WHRN* (USH2D, 0–9.5%), Whirlin protein, cytogenetic location 9q32
- The hearing loss is non-progressive.

USH3

There are two known genes associated with this type:

- USH3A: Mutations in *CLRN1* (Clarin 1); cytogenetic location 3q25.1
- USH3B: Mutations in *HARS* (histidyl-tRNA synthetase); cytogenetic location 5q31.3

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CHAPTER 33

Ciliopathy: Bardet-Biedl Syndrome

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General Features

- Bardet-Biedl syndrome (BBS) is an autosomal recessive disease with a prevalence of about 1/125,000.
- The syndrome involves mixed rod-cone dystrophy (which becomes obvious by 6 years of age). About two thirds of patients have postaxial polydactyly, and sometimes syndactyly, brachydactyly, and/or clinodactyly may be present. Hypogonadism and renal involvement occur in about 40%, mental retardation in about 50%, and truncal obesity in about 70%; it is present early, along with insulin resistance, type 2 diabetes, dyslipidemia, and hypertension. Vision becomes markedly impaired by about age 30 years. The BBS is genetically heterogeneous entity with considerable phenotypic variability.
- Other associated problems include CNS-related ataxia, abnormal gait, and facial hypotonia, as well as anomalies such as high palate, hearing loss, and cardiac malformations. In males, there is oligospermia, leading to infertility.
- Around 50–80% of BBS patients have renal malformations (like cyst, agenesis or scarring) and renal dysfunction leading to end-stage renal disease.
- There are no pigmentary changes before the age of 1–2 years. Later, subtle pigmentary changes appear in the macula or peripapillary area. Several years later, pigments appear in the equatorial region, along with attenuation of retinal blood vessels and waxy pallor of the optic disc. Eventually, the macula may show atrophic changes (Figs. 33.1, 33.2 and 33.3).
- Electroretinography (ERG) shows involvement of rods and cones and is abnormal even before the fundus shows changes.
- A perimacular hyperfluorescent ring can be seen.

Molecular Genetics

- There are 19 known BBS-related genes (*BBS1–BBS19*) with critical roles in ciliary function. Their proteins are involved in lipid homeostasis, intraflagellar transport, establishing planar cell polarity, and regulation of intracellular trafficking and centrosomal functions. The most common variants are *BBS1* (23%) and *BBS10* (20%). In 25% of cases, the molecular cause is unknown.
- Seven BBS proteins (BBS1, BBS2, BBS4, BBS5, BBS7–9) form the BBSome, a protein complex required for ciliogenesis. The BBSome localizes to the nonmembranous centriolar satellites in the cytoplasm with PCM1, and to the ciliary membrane without PCM1. BBS1 promotes ciliary membrane growth by fusion of exocytic vesicles via RABIN8 and RAB8. The BBSome shares features of the canonical coat complexes (COPI, COPII, and clathrin AP1).
- BBS3 (ARL6) binds to the BBS protein complex; deletion of BBS3 blocks localization of the complex to cilia.
- *BBS1* variants often have less severe ophthalmologic involvement, whereas mutations in *BBS2*, *BBS3*, or *BBS4* typically cause early and severe ocular manifestations, with legal blindness by the second decade.

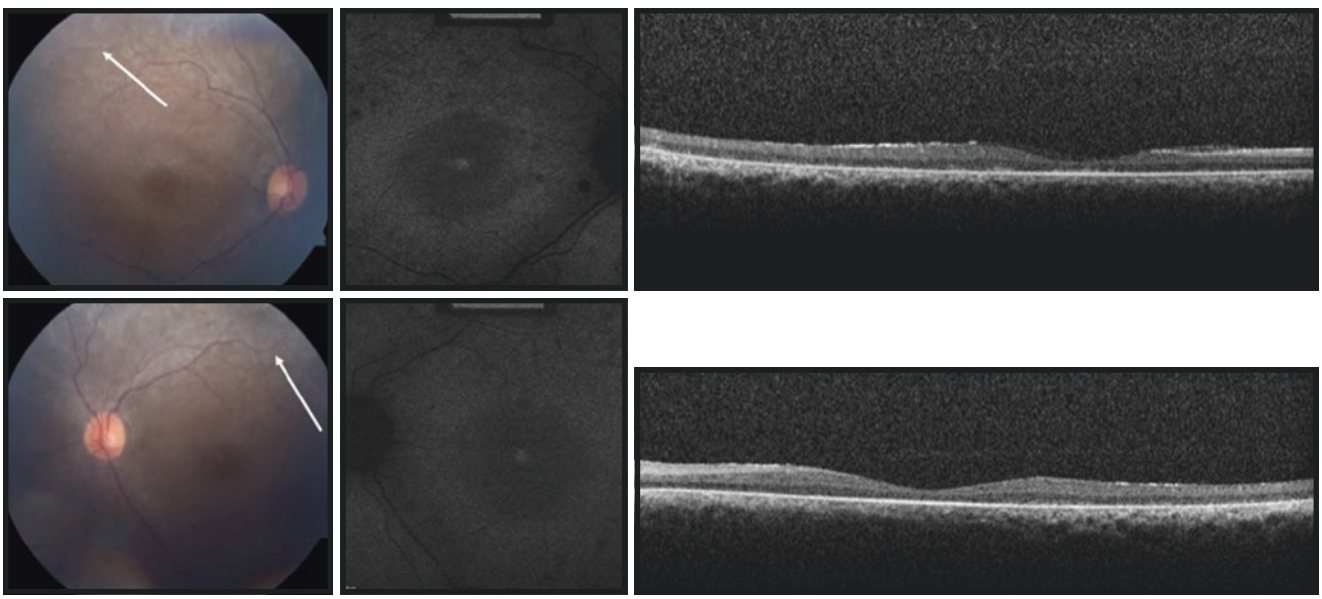

Fig. 33.1 Early in this case of Bardet-Biedl syndrome (BBS), subtle pigment mottling (*arrows*) is more prominently seen on fundus autofluorescence (FAF), with relative thinning of the fovea

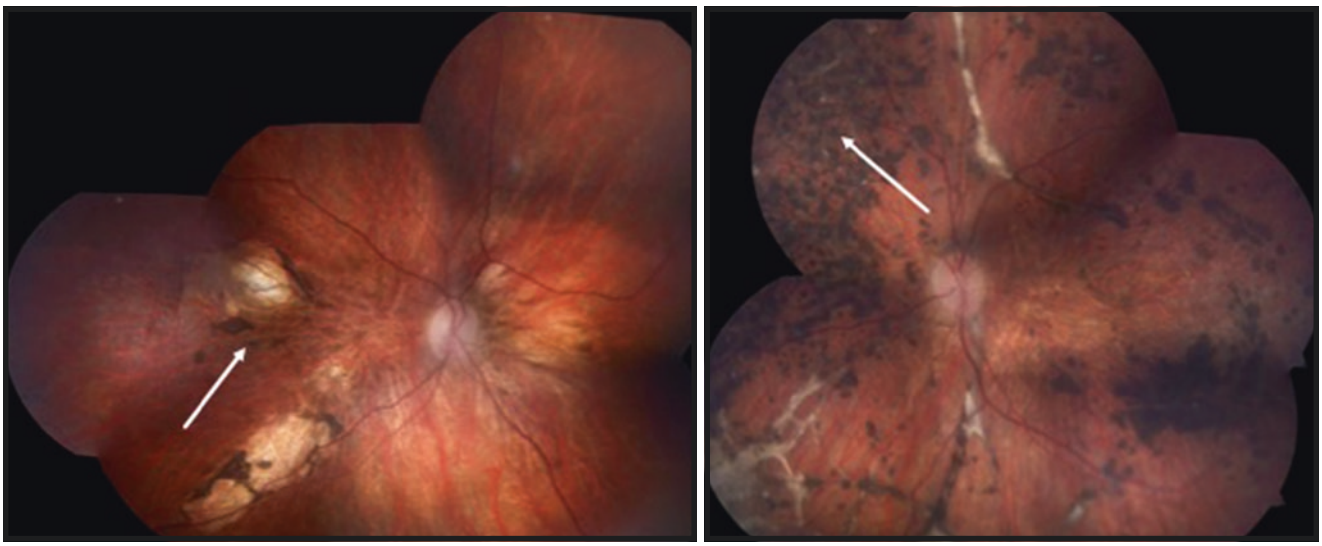

Fig. 33.2 An advanced case of BBS shows marked pigmentary changes, more In the OS>OD (*arrows*)

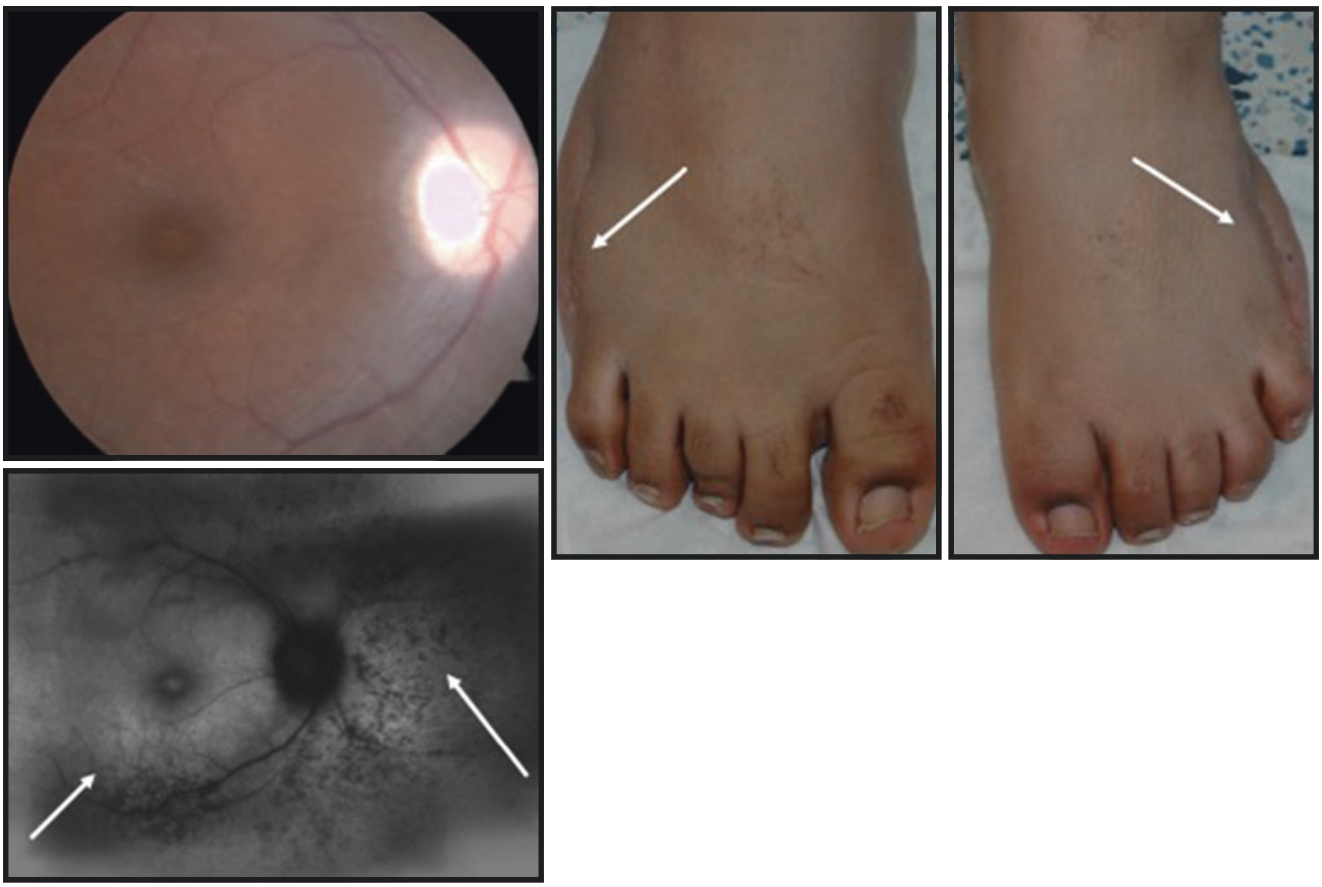

Fig. 33.3 An early case of BBS, with subtle pigment mottling (*arrows*). Scars on the feet (*arrows*) reflect that the patient had undergone surgery for polydactyly

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CHAPTER 34

Ciliopathy: Senior-Løken Syndrome

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General Features

- Senior-Løken syndrome is a rare autosomal recessive disease with a prevalence of 1:1,000,000.
- Retinopathy may progress as Leber congenital amaurosis (LCA), retinitis pigmentosa (RP), or sector RP (Figs. 34.1 and 34.2).
- Onset of photophobia, nystagmus, and hyperopia can occur in the first few years of life or later in childhood.
- Patients experience nephronophthisis, characterized by cystic kidney disease (medullary cystic kidney disease), reduced concentrating ability, and chronic tubulointerstitial nephritis, which progresses to end-stage renal disease.
- Hypertension is common.

Molecular Genetics

- Nine genes are known to cause Senior-Løken syndrome: *NPHP1*, *SLSN3*, *NPHP4*, *IQCB1/NPHP5*, *CEP290/NPHP6*, *SDCCAG8*, *WDR19/NPHP13*, *TRAF3IP1*, and *CEP164*. These genes encode for proteins that are likely to be involved in ciliogenesis and regulation of ciliary protein trafficking. They localize to cilia at the ciliary transition zone, inversin compartment, or subunits of the IFT complexes.
- *NPHP5/IQCB1* gene is located on chromosome 3q21.1 and encodes for nephrocystin-5 protein, which is expressed in the connecting cilia of photoreceptors and in primary cilia of renal epithelial cells. The nephrocystin-5 protein co-localized with RP GTPase regulator (RPGR), which is involved in X-linked RP and LCA.
- *NPHP1* and *NPHP4* regulate cell-cell junctions.
- *CEP164*, *SDCCAG8*, and *CEP290* are implicated in DNA damage response.
- *NPHP1* is allelic to LCA type X; *SDCCAG8* is allelic to Bardet-Biedl syndrome 16.
- *NPHP1* and *CEP290* cause tapeto-retinal degeneration. *NPHP1* produces flat ERG.
- With *SLSN3* mutations, patients have LCA, nystagmus, poor pupillary reflexes, and absent ERG.
- *NPHP4* causes RP with rotary nystagmus and diminished amplitude on ERG.
- *IQCB1* presents in infancy to early childhood with LCA; some do not manifest renal disease in the first decade.
- *TRAF3IP1* is associated with onset of RP in early childhood, as well as macular degeneration.

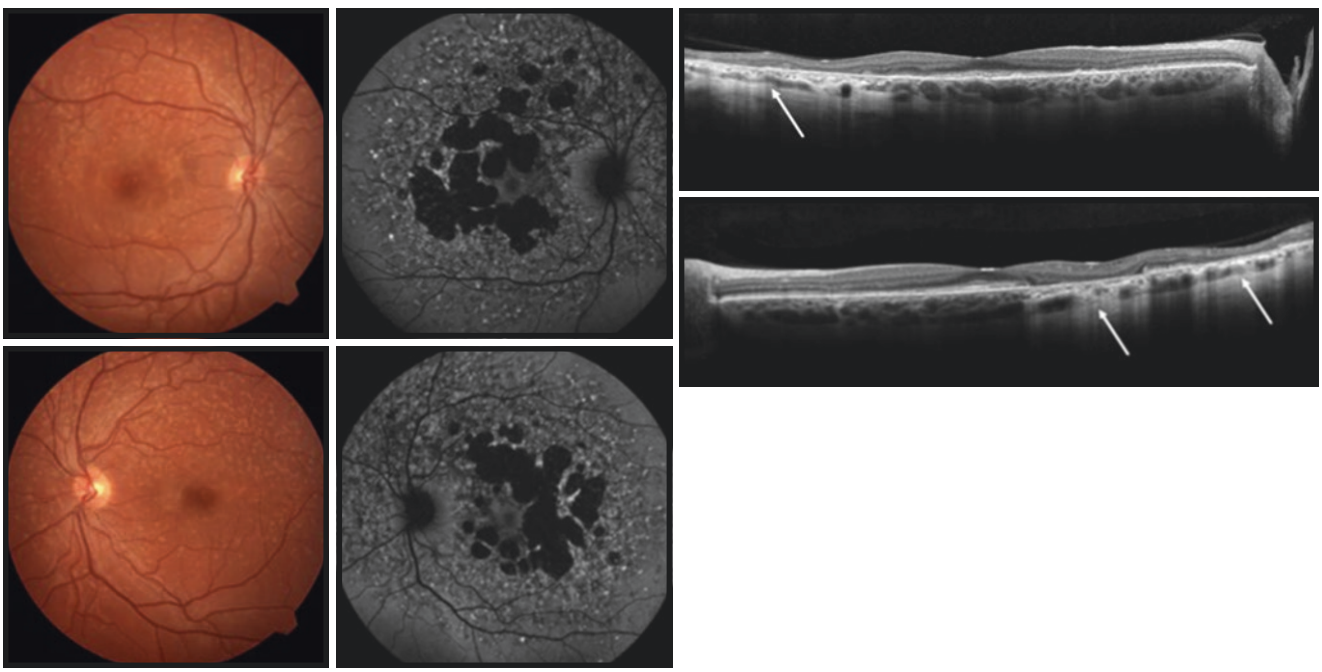

Fig. 34.1 This 37-year-old patient had a history of night blindness for the past 11 years and underwent renal transplantation about 10 years previously. Genetic testing showed a *WDR19*(*NPHP13*) mutation, characteristic of Senior-Løken syndrome. Areas of retinal pigment epithelium (RPE) changes are better seen on fundus autofluorescence (FAF), though color fundus images show a sort of flecked retina. Optical coherence tomography (OCT) shows disruption of the ellipsoid zone (EZ) line and RPE (*arrows*)

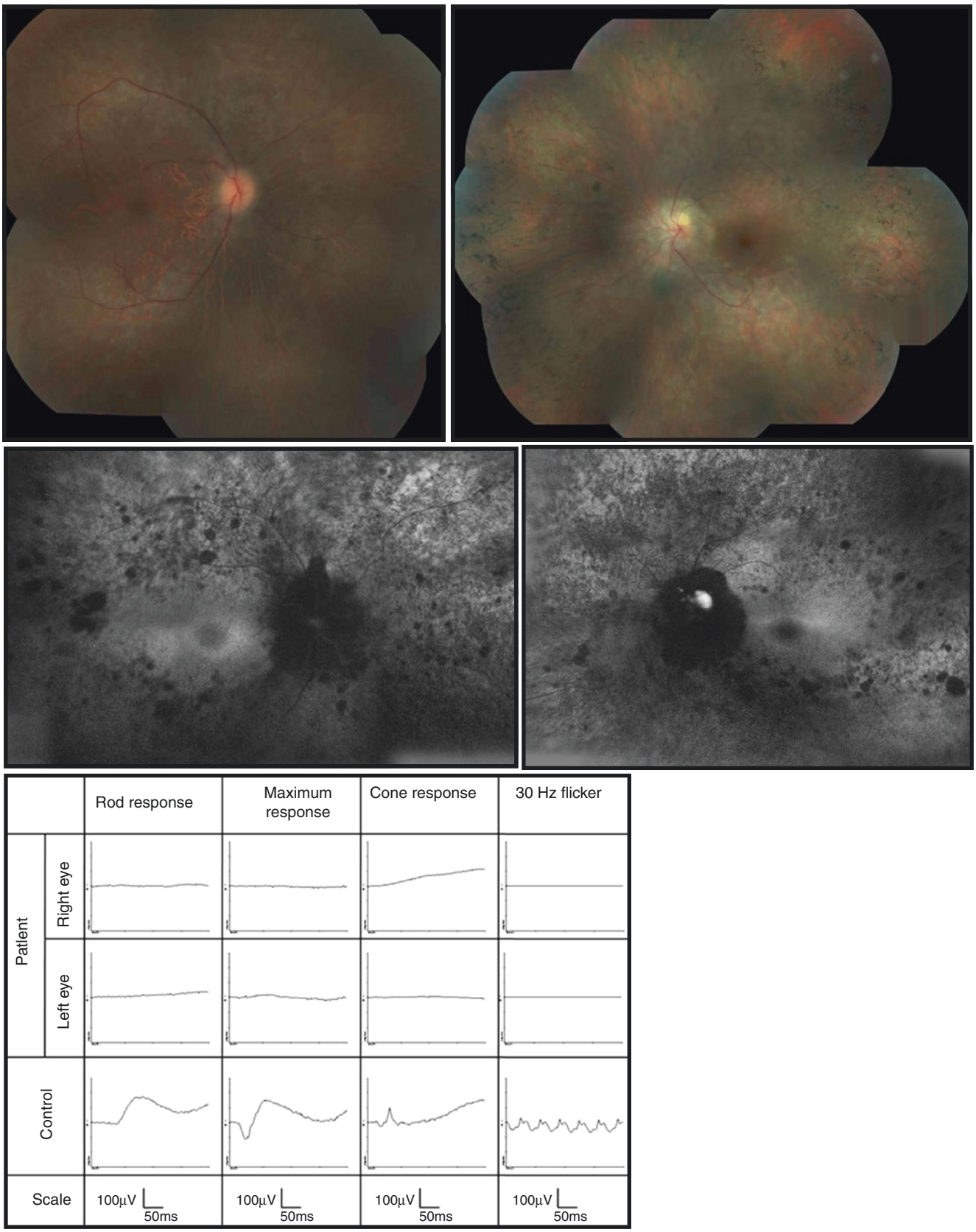

Fig. 34.2 A 20-year-old female with visual impairment (OD 20/200, OS 20/80) since childhood; she had history of renal transplant about 3-years ago. Genetic testing showed a ICQB1/NPHP5 mutation and clinical picture was suggestive of AR-RP

Suggested Reading

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CHAPTER 35

Ciliopathy: Alström Syndrome

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General Features

- Alström syndrome is an autosomal recessive disease with multisystem involvement, including cone-rod dystrophy, hearing loss, type 2 diabetes, insulin resistance with hyperinsulinemia, dilated cardiomyopathy, and progressive hepatic and renal failure.
- Patients present in childhood with photophobia and nystagmus, and mimic Leber congenital amaurosis (LCA). The fundus shows pigmentary retinopathy with peau d'orange appearance and some fine white dots like drusen around the macula; the disc is pale, with attenuated retinal vessels (Fig. 35.1).
- Patients have short stature; boys have hypogonadotropic hypogonadism and girls have polycystic ovary syndrome (PCOS).
- Obesity is always present, with markedly increased triglyceride and VLDL-C levels; arterial hypertension is diagnosed as early as 2 years of age. There is no polydactyly or syndactyly.
- About half have developmental delay, but intelligence is usually normal.

Molecular Genetics

- The only gene associated with Alström syndrome is *ALMS1*. Pathogenic variants are typically nonsense or frameshift, resulting in a truncated protein. The protein is ubiquitous, but its function is not known.
- The ALMS1 protein localizes to centrosomes and basal bodies of ciliated cells, which suggests a role in intracellular trafficking and ciliary function.
- The ALMS1 protein is involved in PCM1-dependent intracellular transport and is required for localization of NCAPD2 to the proximal ends of centrioles.
- The ALMS1 protein may be involved in endosome recycling through interaction with α-actinin and other components of that pathway.
- One study showed that pathogenic variants in exon 16 cause onset of retinal degeneration before 1 year of age.

Suggested Reading

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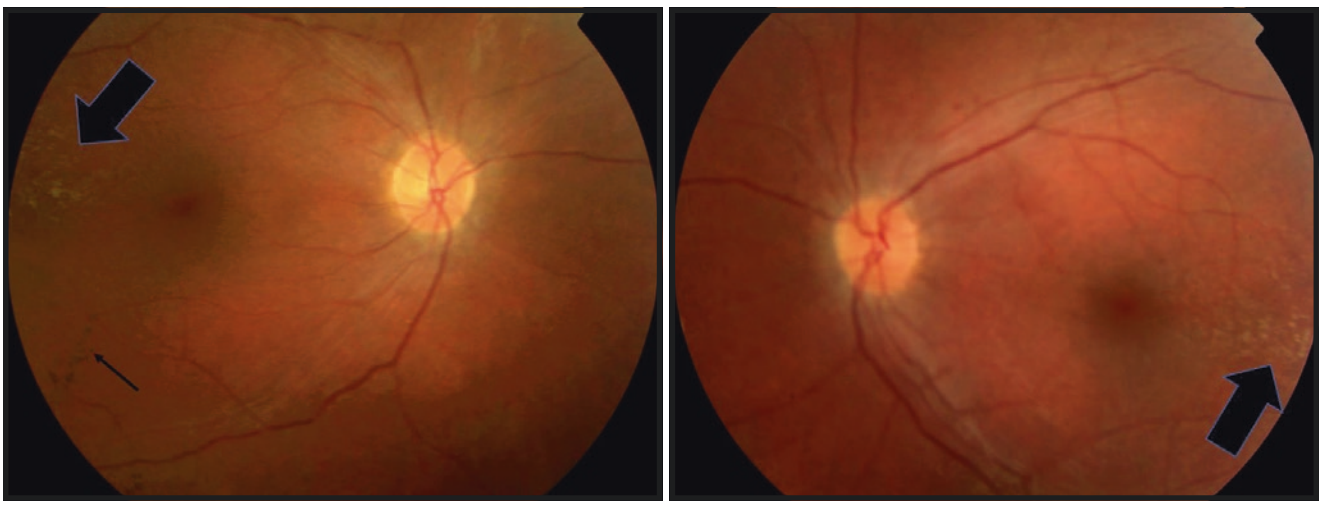

Fig. 35.1 A case of Alström syndrome showing pigmentary abnormality (*arrow*). Note fine dots like drusen located temporal to fovea (*thick arrow*), attenuated arterioles, and pale disc

CHAPTER 36

Ciliopathy: Sjögren-Larsson Syndrome

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General Features

- Glistening yellow-white crystalline inclusions in foveal and parafoveal areas are almost pathognomonic (Fig. 36.1). These inclusions are evident at 1–2 years old and increase with age.
- Patients may have corneal stromal opacities, punctate keratitis, myopia, and astigmatism.
- About 50% have pigmentary degeneration of the retina, with decreased visual acuity and marked photophobia.
- Patients have dry, scaly skin (ichthyosis). Affected infants tend to be born prematurely.
- They also have neurological problems due to leukoencephalopathy (affecting the white matter of the brain). Intellectual disability varies from mild to severe, along with dysarthria and delayed speech.

Molecular Genetics

- Sjögren-Larsson syndrome is caused by a mutation in the *ALDH3A2* gene, which produces fatty aldehyde dehydrogenase (FALDH). FALDH is a membrane-bound protein involved in fatty oxidation. Structural disturbance and poor metabolite clearance likely contribute to pathogenesis.
- When FALDH is deficient, excess lipids and aldehyde Schiff adducts accumulate within skin cells, disrupting formation of the plasma membrane, the protective barrier preventing water loss. Myelin formation in the brain is similarly affected.
- It is proposed that impaired degradation of leukotrienes (specifically LTB4) results in severe pruritus and retinal abnormalities.

Suggested Reading

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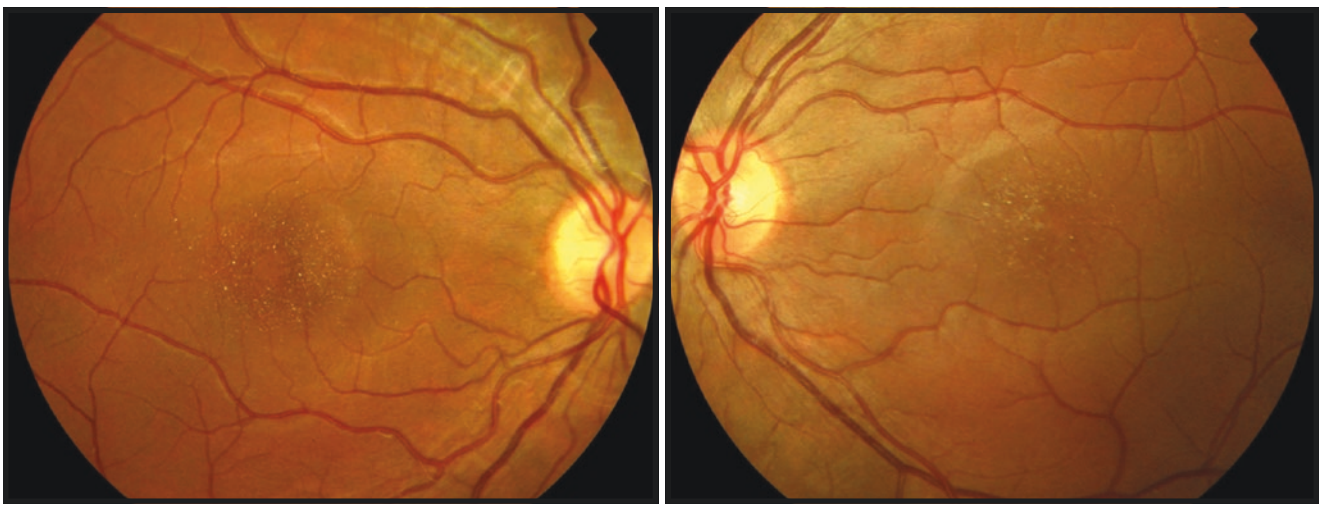

Fig. 36.1 Glistening, yellowish-white crystalline deposits in the central macular area, which are pathognomonic for Sjögren-Larsson syndrome

CHAPTER 37

Inborn Errors of Metabolism: Gyrate Atrophy

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General Features

- Gyrate atrophy is an autosomal recessive dystrophy in which night blindness starts early in the first decade of life.
- In the early stages, large areas of retinal pigment epithelium (RPE) and choriocapillaris (CC) atrophy in the far periphery (lobular shape, Fig. 37.1). (In choroideremia, atrophy appears in the mid periphery.) Later, these areas coalesce to form a characteristic scalloped border at the junction of healthy and diseased RPE.
- Myopia and subcapsular cataract are common by the end of second or third decade.
- Unlike in choroideremia (which is X-linked), patients with gyrate atrophy show areas of hyperpigmentation of the remaining RPE (Fig. 37.2). Patients with gyrate atrophy do not show the choroidal atrophy (as seen in choroideremia) until the late stages.
- Treatment includes a low-protein, arginine-restricted diet for all patients. In some cases, vitamin B6 (pyridoxine) may help in lowering plasma ornithine levels.

Molecular Genetics

- Mutation in the *OAT* (ornithine aminotransferase) gene, located on chromosome 10
- Deficiency of the enzyme ornithine delta-aminotransferase (OAT) results in a tenfold rise in plasma ornithine, which is toxic to RPE and choroid.

Suggested Reading

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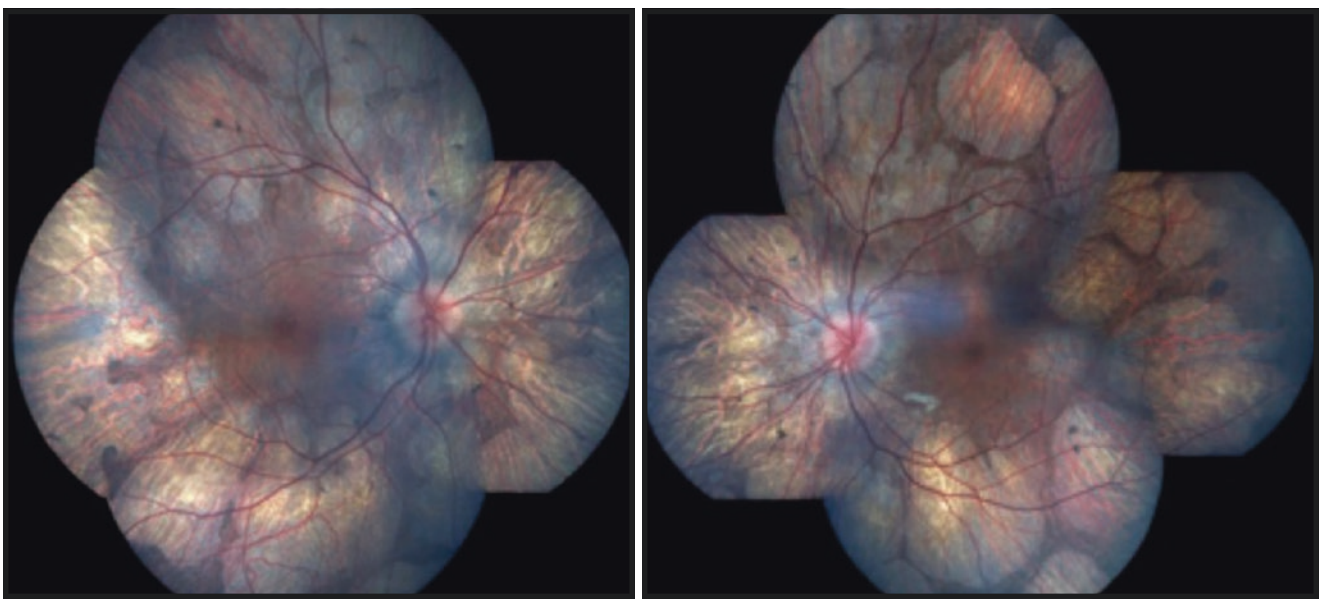

Fig. 37.1 Fundi showing characteristic lobular areas of chorioretinal atrophy with scalloped borders, sparing the macula, in the early stages of gyrate atrophy

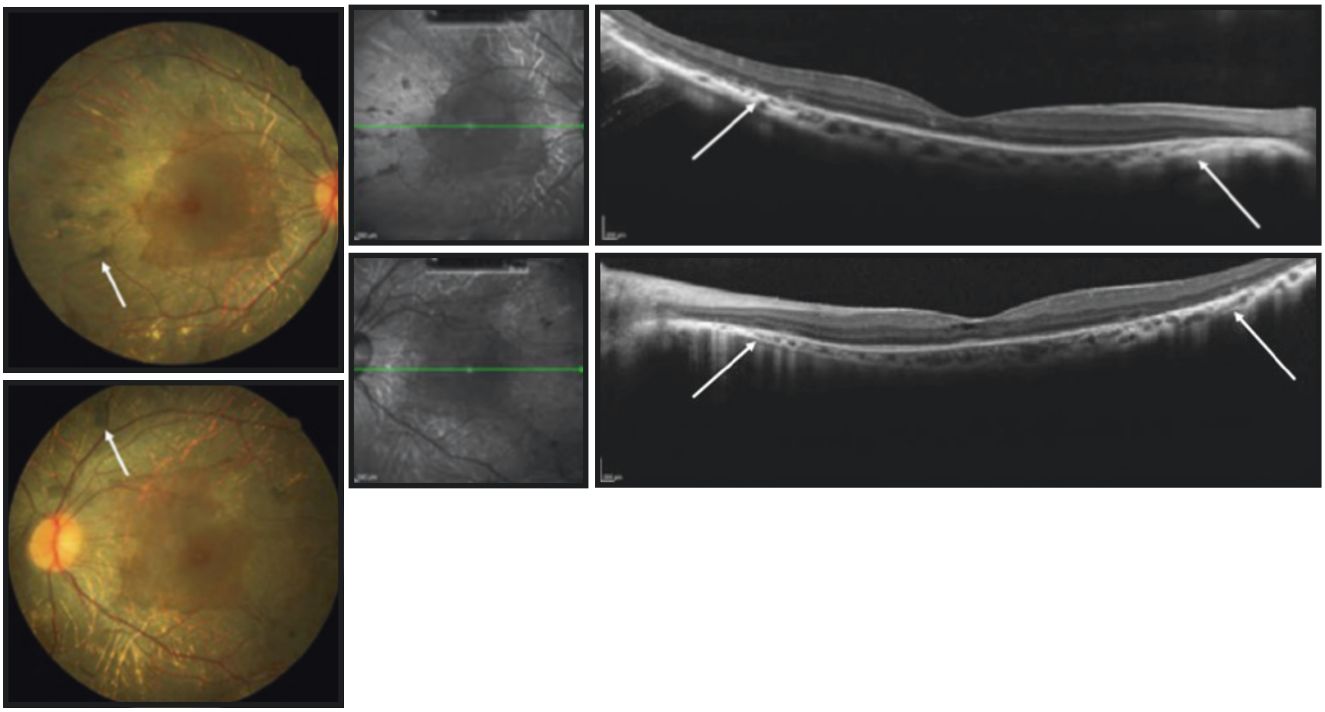

Fig. 37.2 Fundi showing confluent areas of chorioretinal atrophy, sparing a small island at the macula. Note areas of hyperpigmentation (*arrows*). Optical coherence tomography (OCT) shows thinning of the choriocapillaris (CC) and retinal pigment epithelium (RPE) (*arrows*)

CHAPTER 38

Inborn Errors of Metabolism: Pseudoxanthoma Elasticum

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General Features

- Pseudoxanthoma elasticum (PXE) is an autosomal recessive multisystem disorder that involves the skin, GI tract, and heart, as well as the eye.
- It affects approximately 1 in 50,000 people worldwide and is seen twice as frequently in females as in males.
- Fundus findings include angioid streaks (Fig. 38.1), reticular macular dystrophy, speckled appearance temporal to the macula (peau d'orange, like the dimpled texture of an orange peel), drusen of the optic nerve, and vitelliform-like deposits. Peau d'orange may precede the development of an angioid streak.
- "Comets," with or without a tail, are seen as solitary subretinal, nodular white bodies of retinal pigment epithelium (RPE) atrophy, usually present in the mid periphery (Fig. 38.2). The tail points toward the optic disc.
- Patients sometimes develop choroidal neovascular membrane.
- Skin changes (plucked chicken–like appearance) occur on the flexure areas, including the neck and axilla, as well as increased skin laxity with excessive skin folding.
- Cardiovascular changes include accelerated atherosclerosis with occlusive vascular disease leading to angina, hypertension, restrictive cardiomyopathy, mitral valve prolapse, and others.
- Progressive calcification and fragmentation of elastic fibers in the skin, eye, and cardiovascular system is the underlying pathophysiology.

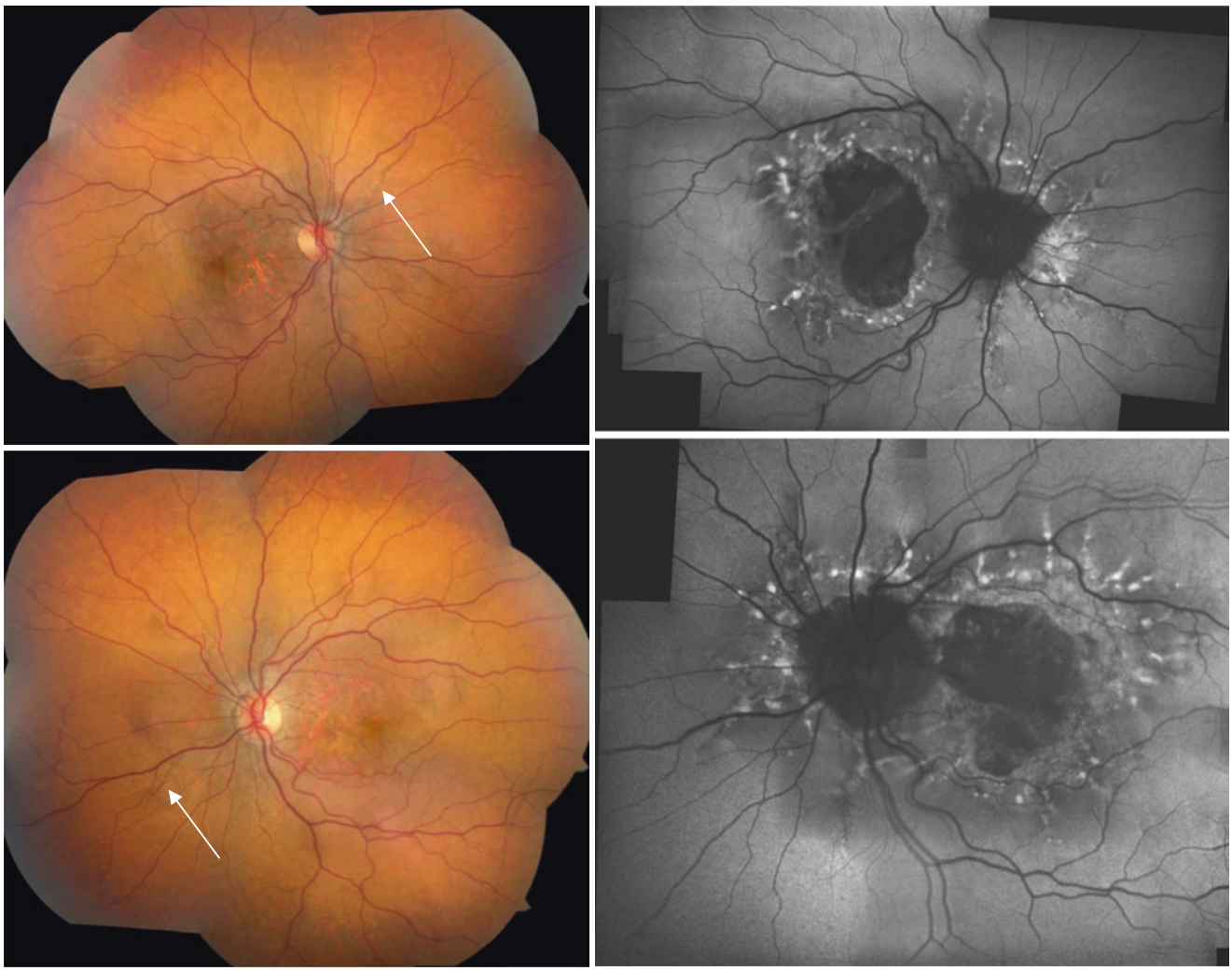

Fig. 38.1 A case of pseudoxanthoma elasticum (PXE) showing angioid streaks (*arrows*) and atrophic RPE changes at the macula, as evident on fundus autofluorescence (FAF)

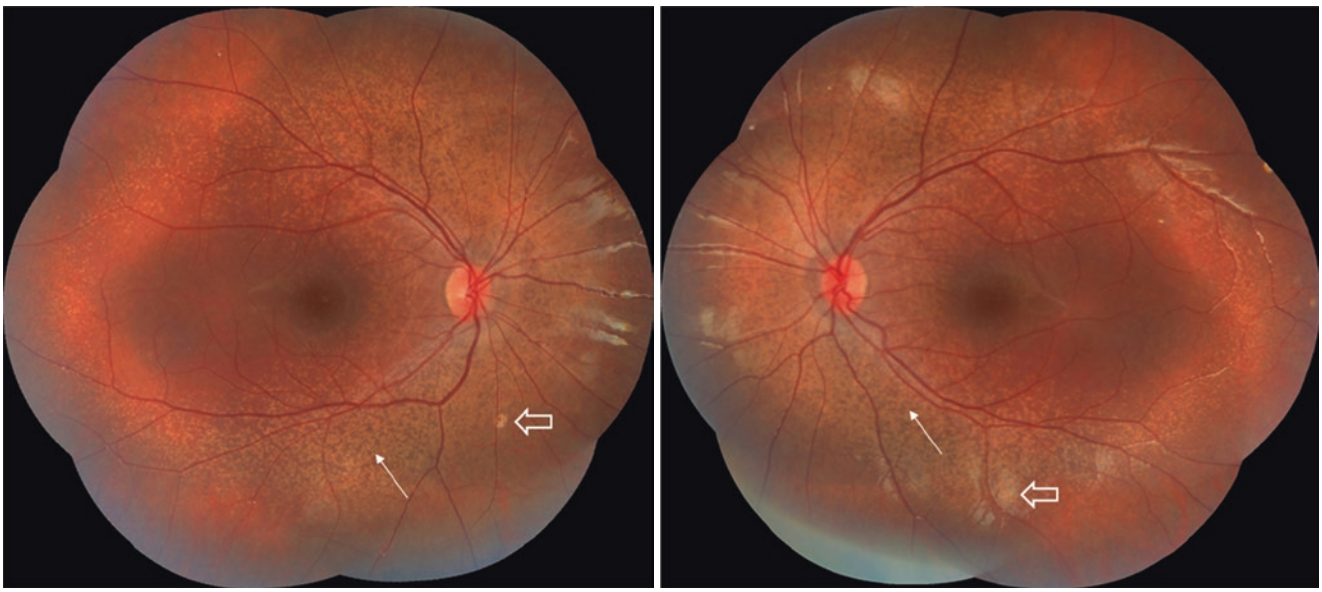

Fig. 38.2 A case of PXE showing peau d'orange (*white arrows*) and comets (*thick arrows*)

Molecular Genetics

- Biallelic mutations occur in the *ABCC6* gene, at chromosome 16.
- The gene provides instructions for making a protein called MRP6 (ABCC6 protein). This protein is found in the liver, kidney, skin, GI tract, blood vessels, and the eye. There is accumulation of deposits of calcium and other minerals in elastic fibers.
- Cytogenetic location: 16p13.11

Suggested Reading

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CHAPTER 39

Inborn Errors of Metabolism: Refsum Disease

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General Features

- Patient with Refsum disease present with nyctalopia, and the fundus shows progressive panretinal degeneration (Fig. 39.1). Vision gradually decreases, with progressive peripheral constriction. The pupil usually does not dilate well.
- Associated CNS symptoms include ataxia and weakness in the extremities, progressive peripheral neuropathy, and peripheral muscle wasting.
- Other features include sensorineural deafness and epiphyseal dysplasia (fourth toe riding on the dorsum of the foot and short, stubby thumbs, or asymmetrical length of toes and fingers).
- Other findings may include cardiac arrhythmia and anosmia.
- Owing to a deficiency of phytanic acid oxidation, phytanic acid levels are high in the blood (0.4–4.0 mg/L) and urine.
- An early diagnosis and treatment are aimed at reducing plasma phytanic acid levels that help to modify disease progression for retinopathy and peripheral neuropathy.

Molecular Genetics

- Mutation in the *PAHX* gene

Suggested Reading

Pakzad-Vaezi KL, Maberley DA. Infantile Refsum disease in a young adult: case presentation and brief review. Retin Cases Brief Rep. 2014;8:56–9.

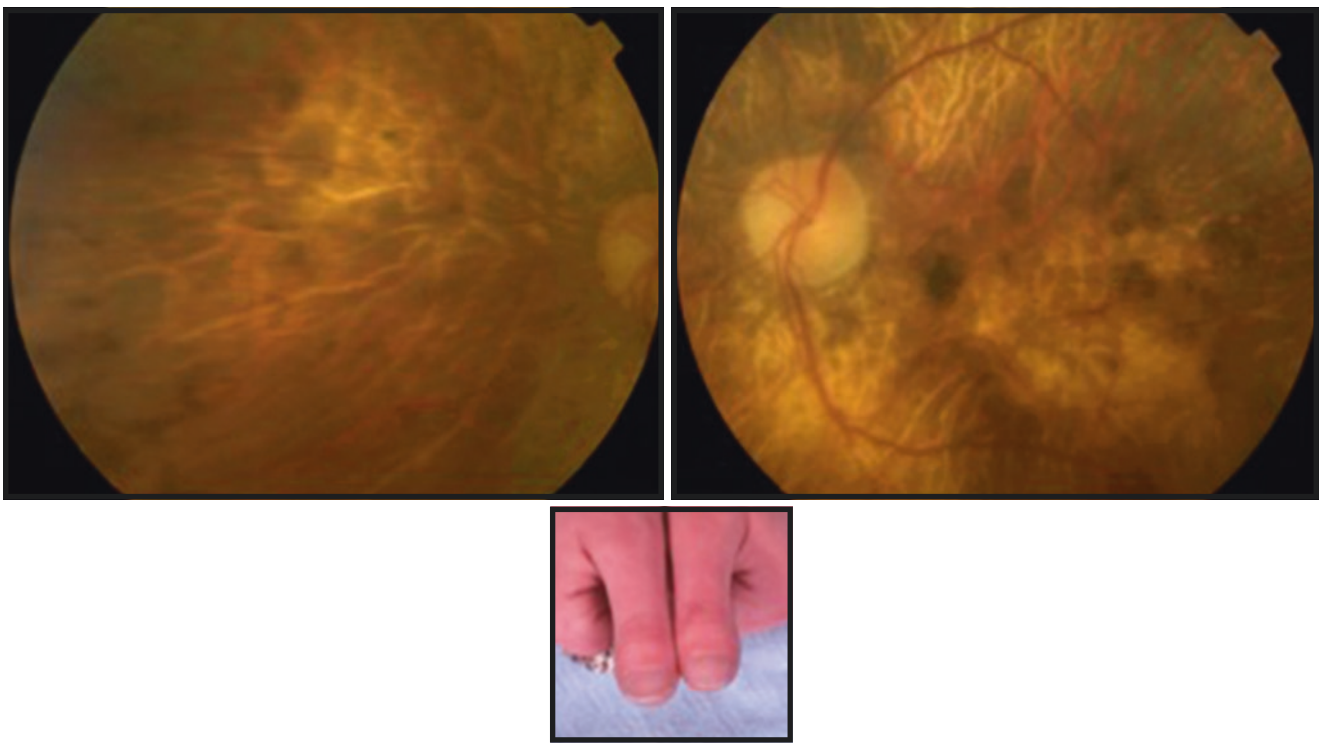

Fig. 39.1 Advanced panretinal degeneration and asymmetrical length of thumbs

CHAPTER 40

Inborn Errors of Metabolism: Bietti Crystalline Dystrophy

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General Features

- Bietti crystalline dystrophy (BCD) has been estimated to occur in 1 in 67,000 people; it is more common in people of East Asian descent.
- This autosomal recessive dystrophy presents with night blindness and paracentral scotomas around the third decade of life; some many have photophobia.
- BCD is characterized by multiple, small refractile crystalline deposits (fatty/lipid compounds) throughout the fundus, in both the outer and inner retina and choroid (Figs. 40.1 and 40.2). In some cases, these deposits are seen in the mid-stroma of the cornea and lens capsule.
- These crystalline deposits in the retina (some of which are located in front of the blood vessels) tend to disappear with time, leading to atrophic lesions.
- On fundus autofluorescence (FAF), crystals are not seen, but if there is atrophy, it appears as central hypoautofluorescence surrounded by a ring of hyperautofluorescence.
- Optical coherence tomography (OCT) shows hyperreflective dots in various layers of the retina and choroid.
- Over time, geographic areas of RPE and CC atrophy set in, predominantly at the posterior pole, and as atrophy sets in, crystals seem to disappear. In end-stage disease, the whole of the posterior pole shows areas of chorioretinal atrophy.
- Electroretinography (ERG) shows a pattern like cone-rod dystrophy, or sometimes a rod-cone dystrophy pattern.

Molecular Genetics

- Caused by mutation in the *CYP4V2* gene, located on chromosome 4, involved in lipid metabolism.
- This gene encodes for making a member of the cytochrome P450 family of enzymes. The CYP4V2 enzyme is involved in fatty acid oxidation, a multistep process in which lipids are broken down and converted into energy.
- Cytogenetic location: 4q35/1–4q35.2

STOP PRESS! On August 29, 2018, the US Food and Drug Administration (FDA) granted Orphan Drug Designation to AAV-based gene therapy product (AAV.CYP4V2) for treating BCD.

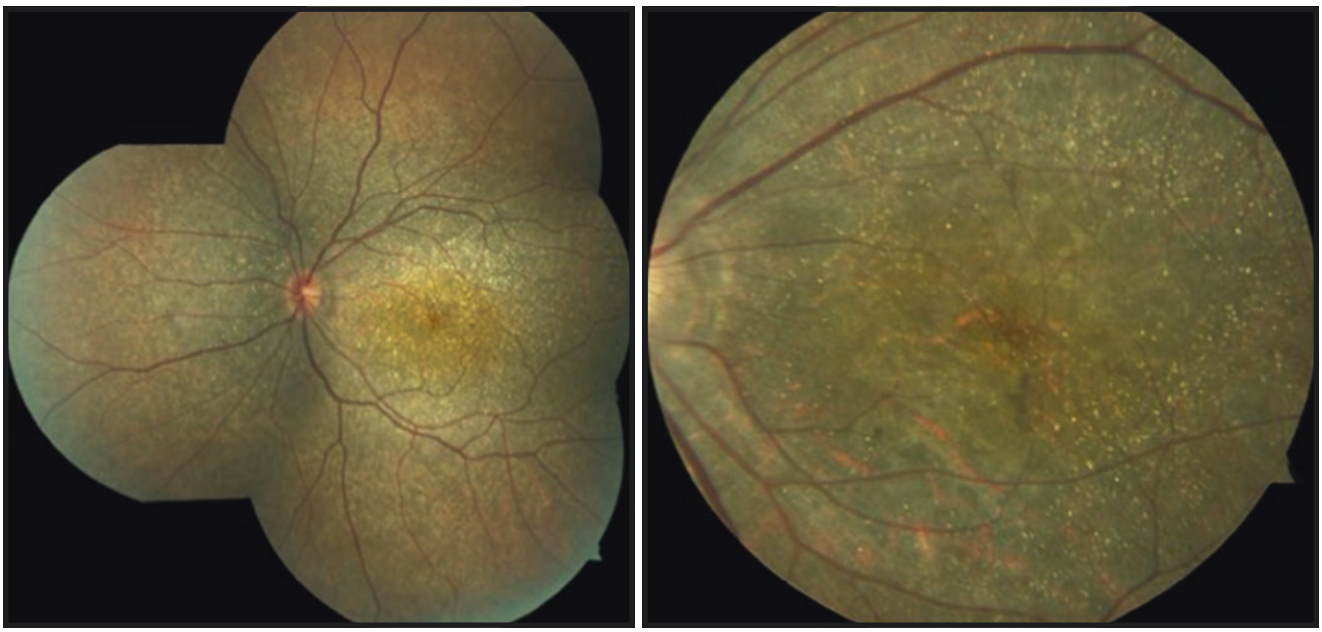

Fig. 40.1 Bietti crystalline dystrophy with mutation in CYP4V2 gene (c.802-8_810del17insGC & c.1062dupA). The whole of the posterior pole shows small, refractile crystalline deposits (*left fundus*). As these crystalline deposits fade, atrophic areas appear (*right fundus*).

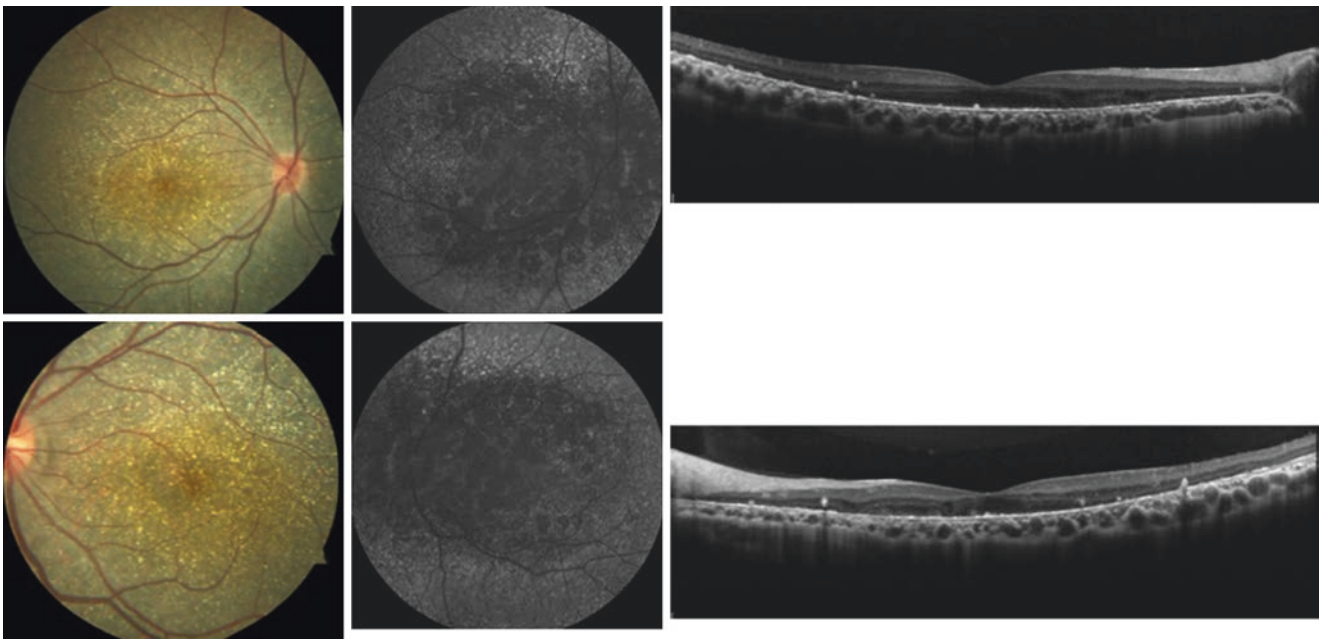

Fig. 40.2 Bietti crystalline dystrophy. Both fundi show crystalline deposits, with associated retinal pigment epithelium (RPE) atrophy on autofluorescence. Optical coherence tomography (OCT) shows the presence of these deposits at different levels of the neurosensory retina.

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CHAPTER 41

Extracellular Matrix: Alport Syndrome

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General Features

- Patients present with X-linked inheritance; Alport syndrome occurs in approximately 1 in 50,000 newborns.
- The systemic features include progressive interstitial nephritis, renal failure by the fifth decade, and neurosensory deafness.
- The ocular features include anterior lenticonus (about 25%, during the second or third decade), posterior polymorphous corneal dystrophy (about 3%), microspherophakia, and anterior/posterior subcapsular cataract. The fundus shows dot and fleck retinopathy, with multiple refractile/crystalline deposits in a ring configuration at the macula (about 85%). The retinopathy is usually diagnosed during an advanced stage of nephropathy (Fig. 41.1).

Molecular Genetics

- Mutation in the *COL4A3*, *COL4A4*, and *COL4A5* gene. In about 80% of cases, the disorder is X-linked, caused by mutation in *COL4A5*; in about 15%, it is autosomal recessive, due to mutations in *COL4A3* and *COL4A4*. In 5%, it could be autosomal dominant with mutation in *COL4A3* or *COL4A4*.
- These genes encode for making one component of a protein called type IV collagen. This protein plays an important role in glomeruli for removing water and waste products. Mutations impair this filtering; gradual scarring of the kidneys results in end-stage renal disease. The primary lesion is irregular thickening and progressive splitting of the basal membrane.
- Type IV collagen is also an important part of inner ear structures, especially the organ of Corti, which transforms sound waves into nerve impulses for the brain.
- In the eye, type IV collagen is important in maintaining the shape of the lens.

Suggested Reading

Savige J, Sheth S, Leys A, Nicholson A, Mack HG, Colville D. Ocular features in Alport syndrome: pathogenesis and clinical significance. Clin J Am Soc Nephrol. 2015;10:703–9.

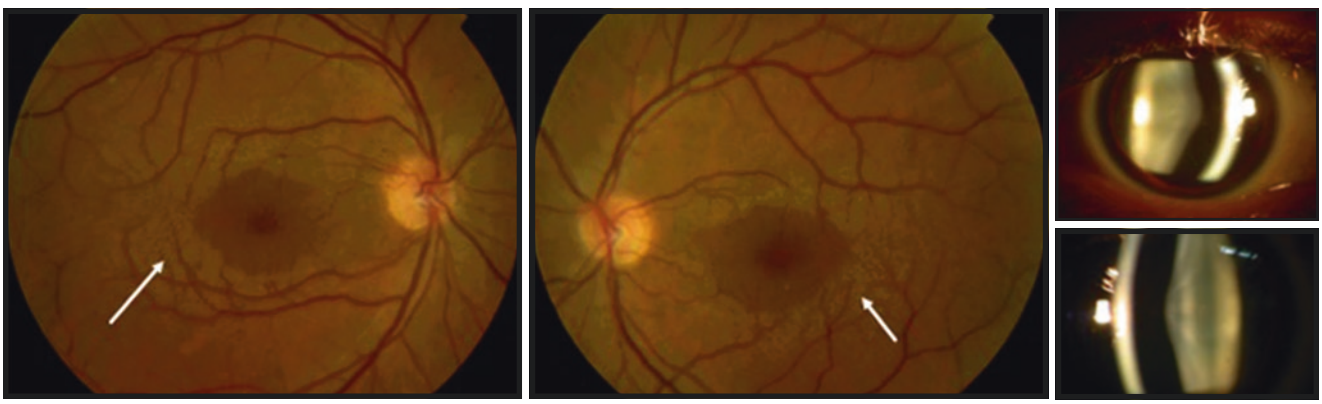

Fig. 41.1 Alport syndrome. Dot and fleck retinopathy (*arrows*) and anterior lenticonus. The patient, who also had renal problems and hearing loss, had a positive family history, with brothers affected

Section VI
Phakomatoses

CHAPTER 42

Von Hippel-Lindau Disease

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General Features of Phakomatoses

- Phakomatoses (*phakoma* = birthmark) are a group of diseases or syndromes that have hamartomas (tumorous malformations composed of tissues normally present at the location where they develop) of the skin, brain, and eye (oculoneurocutaneous syndromes)
- Phakomatoses include retinal and cerebellar hemangiomatosis (von Hippel-Lindau syndrome [VHL]), tuberous sclerosis (Bourneville syndrome, Chapter 43), neurofibromatosis (NF, von Recklinghausen syndrome, Chapter 44), encephalofacial hemangiomatosis (Sturge-Weber syndrome), and racemose angiomatosis (Wyburn-Mason syndrome).
- Most phakomatoses have an autosomal dominant (AD) inheritance with incomplete penetrance, except for Sturge-Weber and Wyburn-Mason.
- Most of the tumors that develop with phakomatoses are benign and are either stationary or slowly progressive. Occasionally, however, malignant or life-threatening tumors can develop, like cerebellar hemangioblastoma or renal cell carcinoma in VHL, or malignant schwannoma in NF.

General Features of Von Hippel-Lindau Disease

- The incidence of VHL is about 1 in 36,000 live births. Inheritance is AD, with a penetrance of over 90% by 65 years of age.
- These patients have a benign vascular neoplasm occurring either in the retina or optic disc, known as retinal hemangioblastoma (RH), retinal capillary hemangioma or hemangioblastoma, or retinal angioma.
- Systemic involvement includes hemangioblastoma of the brain (cerebellum) and spinal cord, renal cell carcinoma, pheochromocytoma, pancreatic neuroendocrine tumors, and renal or pancreatic cysts.
- Ocular involvement can be either unilateral (about 40%) or bilateral (about 60%). In about 85% of cases, the tumor involves the mid-peripheral location; about 8% are juxtapapillary, and about 7% affect both locations.
- The number of tumors varies. Usually multiple tumors occur; a new tumor may appear with the passage of time.
- Small tumors appear as a red dot, like a microaneurysm with no feeding vessels (sessile), but as the tumor grows, characteristic feeding and draining vessels appear, along with retinal edema, exudation, and traction (Fig. 42.1).

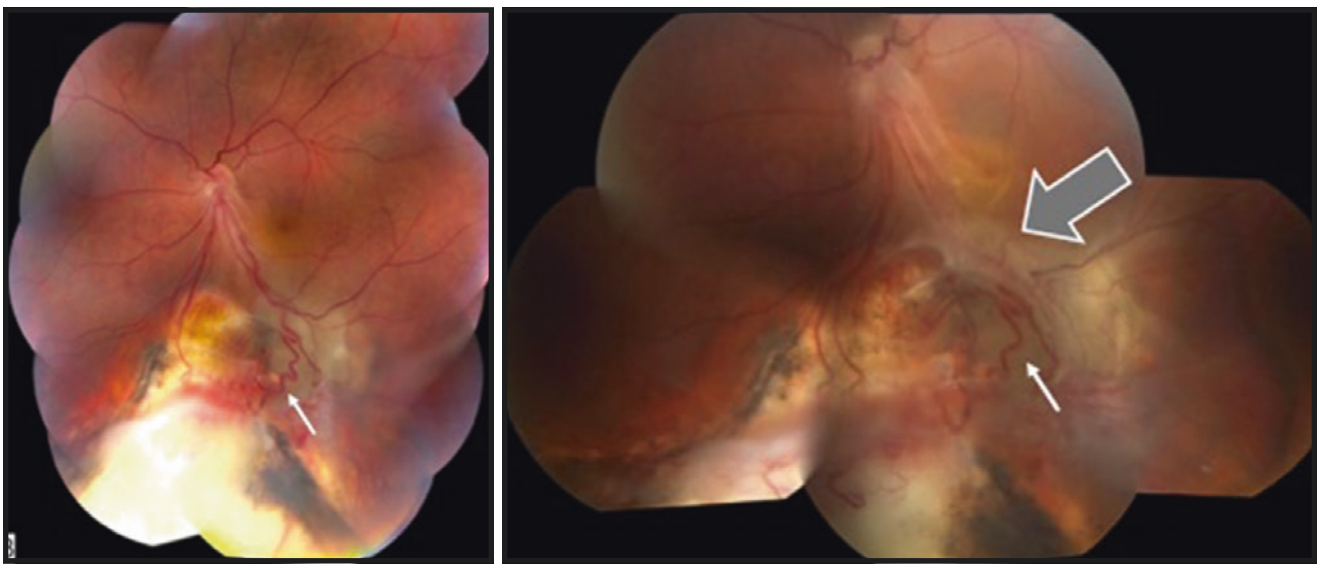

Fig. 42.1 (**Left**) Partially treated fundus in a case of von Hippel-Lindau disease; vessels are still dilated and tortuous (*small arrow*). (**Right**) Follow-up at 3 years shows a pigmented scar around a relatively flat angioma, with less tortuous vessels. Also note epiretinal membrane following treatment (*thick arrow*)

- Juxta-papillary tumors are usually sessile with some fine, lacy vascular pattern and fullness of the neural rim or disc margin in one localized sector.
- Fluorescein angiography helps to delineate all of the vascular tumors.
- Optical coherence tomography (OCT) is helpful for juxta-papillary tumors and to characterize macular edema or epiretinal membrane (ERM).
- Ultrasound B-scan shows a solid retinal mass with variable, moderate reflectivity and no orbital or choroidal shadowing.
- Vision loss is due to exudation involving the macula or traction/exudative retinal detachment. Vision can also be affected if there is an expanding cerebellar hemangioblastoma with intracranial hypertension and papilledema, or pheochromocytoma causing severe hypertension and hypertensive retinopathy.
- Besides an annual eye examination, these patients should be screened for systemic tumors. It is also necessary to rule out pheochromocytoma (with plasma or 24-hour urine catecholamines and metanephrines), renal cell carcinoma (ultrasound or CT scan of the abdomen), and CNS hemangioblastoma (MRI of the brain and spine).
- Treatment involves ablative therapy such as thermal laser photocoagulation, cryotherapy, radiation (brachytherapy, external beam), photodynamic therapy, and transpupillary thermotherapy.
- Vitreous surgery is needed for traction or rhegmatogenous retinal detachment, with guarded outcome.
- Photodynamic therapy is employed for juxta-papillary lesions.
- Anti–vascular endothelial growth factor (anti-VEGF) agents have been tried as an adjunct to other treatment modalities.

Molecular Genetics of Von Hippel-Lindau Disease

- VHL is caused by a mutation in the *VHL* tumor suppressor gene; the mutation varies, ranging from substitution of a base pair in a single codon to the complete deletion of the gene.
- Cytogenetic location of *VHL* gene: 3p25.3
- Most patients with VHL inherit a mutant copy of the *VHL* tumor suppressor gene from an affected parent, and a normal copy (wild-type) from the other parent. Neoplasia occurs from the somatic inactivation (second hit) of the normal allele in one or more cells of an individual with a germline mutation (first hit) in the other allele (Knudson's two-hit model).
- The *VHL* gene provides instructions for making a protein that is a part of the complex called VCB-CUL2 complex; this complex helps other proteins to be broken down when they are no longer needed.
- One of the targets of the VCB-CUL2 complex is a protein called hypoxia-inducible factor 2-alpha (HIF-2α), part of the HIF protein complex, which controls several genes involved in cell division, formation of new blood vessels, and production of red blood cells by the regulation of erythropoietin. HIF is particularly important when there is hypoxia. When adequate oxygen is available, the VCB-CUL2 complex prevents inappropriate buildup of HIF in cells.
- With *VHL* gene mutation, HIF builds up and upregulates several growth factors, including VEGF and platelet-derived growth factor (PDGF).

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CHAPTER 43

Tuberous Sclerosis

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General Features

- Tuberous sclerosis is characterized by a classic triad: seizures, mental retardation, and cutaneous angiofibromas; this triad occurs in about 30% of cases.
- **Major clinical diagnostic criteria:** Hypomelanotic macules (≥3 in number and at least 5 mm in diameter) or angiofibromas (≥3), ungual fibromas (≥2), shagreen patch, multiple retinal hamartomas, cortical dysplasias, subependymal nodules, subependymal giant cell astrocytoma, cardiac rhabdomyoma, lymphangioleiomyomatosis, angiomyolipomas (>2).
- **Minor clinical diagnostic criteria:** Confetti skin lesions, dental enamel pits (≥3), intraoral fibromas (≥2), retinal achromatic patch, multiple renal cysts, non-renal hamartomas.
- A **definite diagnosis** requires two major criteria or one major and two or more minor criteria, or the presence of *TSC1* or *TSC2* mutation (TSC, tuberous sclerosis complex).
- A **possible diagnosis** requires either one major or two or more minor criteria.
- Astrocytic hamartoma of the retina (Figs. 43.1 and 43.2) usually occurs in close proximity to the optic disc or at the disc; it presents as a large, whitish (calcified) nodular masses or mulberry-like, usually endophytic.
- In April 2018, the FDA approved everolimus (mTOR inhibitor) for the adjunctive treatment of Tuberous sclerosis complex-associated morbidity.

Molecular Genetics

- Mutation in *TSC1* or *TSC2* (tuberous sclerosis complex) is an independent diagnostic criterion. About 10–25% of tuberous sclerosis patients have no mutation, so a normal test does not rule out the clinical diagnosis.
- The mutation either prevents or inactivates the function of the TSC1 protein, hamartin, or the TSC2 protein, tuberin.
- Tuberous sclerosis has AD inheritance with incomplete penetrance and variable expressivity.
- The phenotype of *TSC1* mutation is mild; the *TSC2* gene accounts for approximately 90% of clinical cases.
- Cytogenetic location: *TSC1*, 9q34; *TSC2*, 16p13.3.

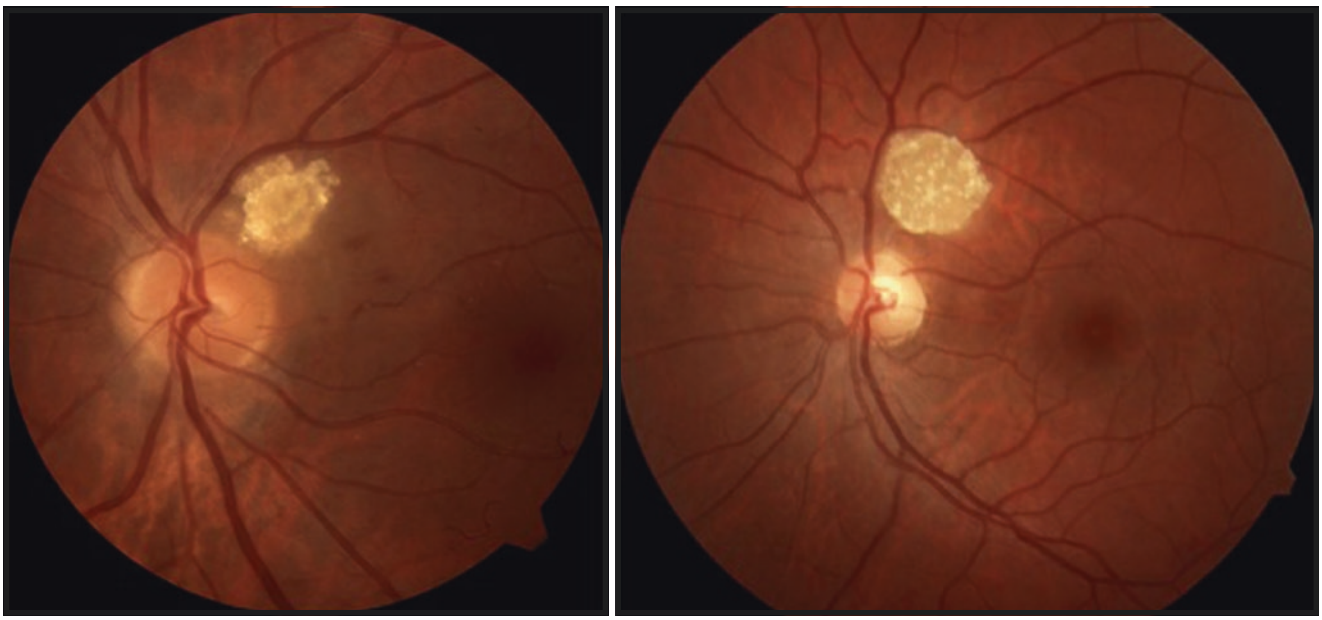

Fig. 43.1 Astrocytic hamartoma, seen as a whitish calcified lesion, mulberry-like, in close proximity to the optic disc

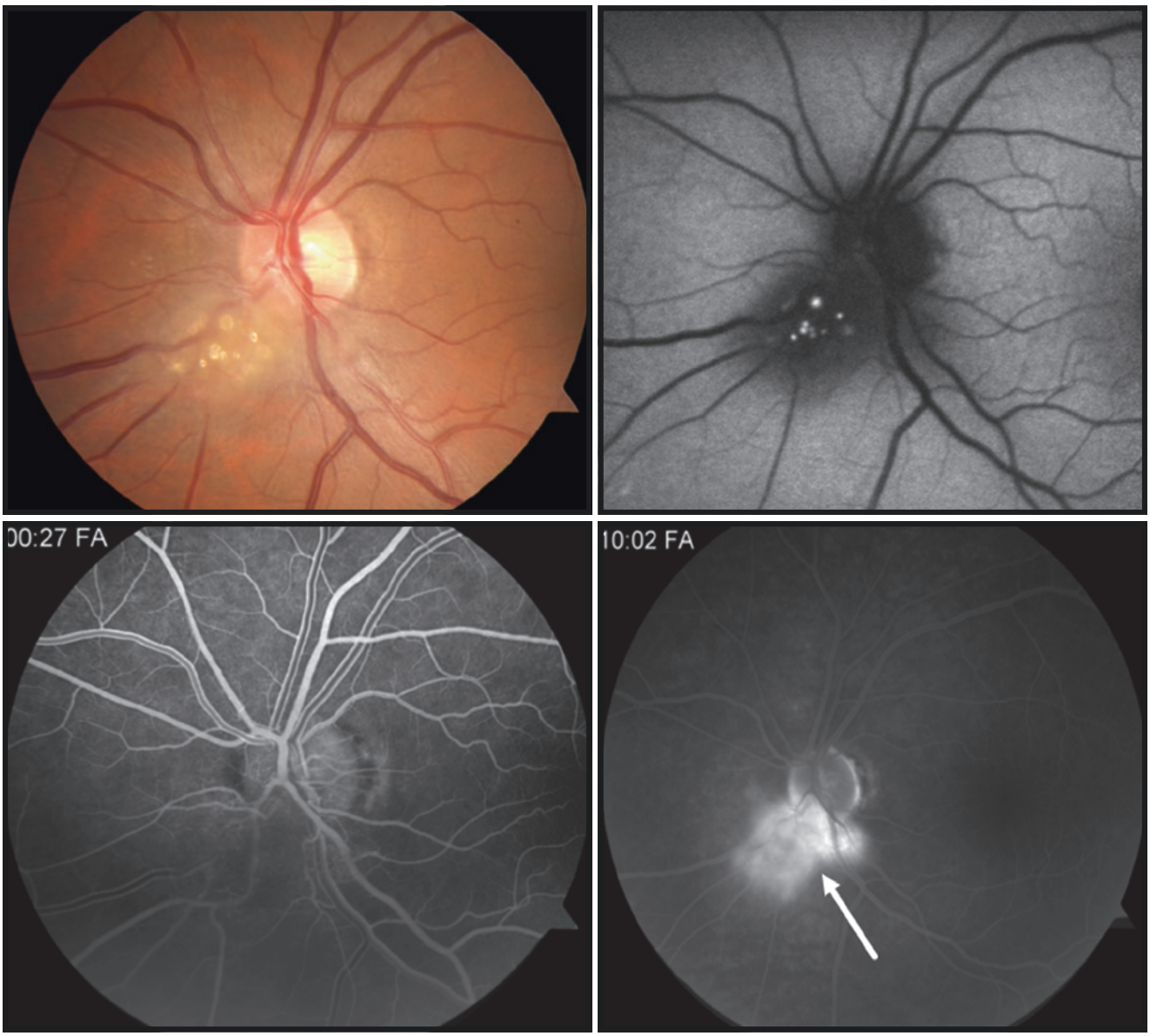

Fig. 43.2 Astrocytic hamartoma, seen as a whitish calcified lesion, located inferonasal to the optic disc. This lesion shows hyperautofluorescent dots, with staining on a fluorescein angiogram (*arrow*)

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CHAPTER 44

Neurofibromatosis

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General Features

- The mode of inheritance is autosomal dominant (AD), with about 80% penetrance, but about half of cases have spontaneous mutations with no family history.
- There are two types of neurofibromatosis (NF):
  - NF1 (type 1, peripheral NF, or von Recklinghausen syndrome)
  - NF2 (type 2, central or bilateral acoustic NF)

Neurofibromatosis Type 1

- NF1 occurs at a rate of 1 in 3000 individuals.
- Diagnosis requires at least two of the following criteria:
  - *Café-au-lait spots:* At least 6 spots larger than 5 mm in diameter if age is less than 10 years (prepubertal); or at least 15 mm in diameter if age is greater than 10 years (postpubertal).
  - *Freckles:* Axillary or inguinal
  - *Skin neurofibromas:* At least two typical neurofibromas or at least one plexiform neurofibroma
  - *Optic nerve glioma*
  - *Iris Lisch nodules:* At least two lesions
  - *Osseous lesion:* Sphenoid dysplasia
  - *Family history:* First-degree relatives (parent, sibling, or offspring) with above criteria.
- Ocular signs:
  - Eyelid involvement: diffuse thickening, typical S-shaped curvature
  - Multiple iris hamartomas, Lisch nodules
  - Congenital glaucoma
  - Optic nerve glioma
  - Multifocal choroidal freckling
  - Vasoproliferative tumor
  - Retinal astrocytic hamartoma

Neurofibromatosis Type 2

- NF2 occurs with a frequency of 1 in 33,000 people.
- Criteria for diagnosis:
  - Bilateral acoustic neuromas (vestibular schwannomas) *or*
  - Unilateral 8th cranial nerve tumor *plus* NF2 in a first-degree relative *or*
  - Two of the following:
    - Meningioma
    - Glioma
    - Schwannoma
    - Juvenile posterior subcapsular lens opacity plus NF2 in a first-degree relative
- Ocular signs:
  - Posterior subcapsular cataract in childhood
  - Combined hamartoma of the retina and retinal pigment epithelium (RPE) (Fig. 44.1)
  - Epiretinal membrane

Molecular Genetics

- **Neurofibromatosis Type 1:** The cause of NF1 is mutations in the *NF1* gene, which provides instructions for making a protein called *neurofibromin*. Neurofibromin acts as a tumor

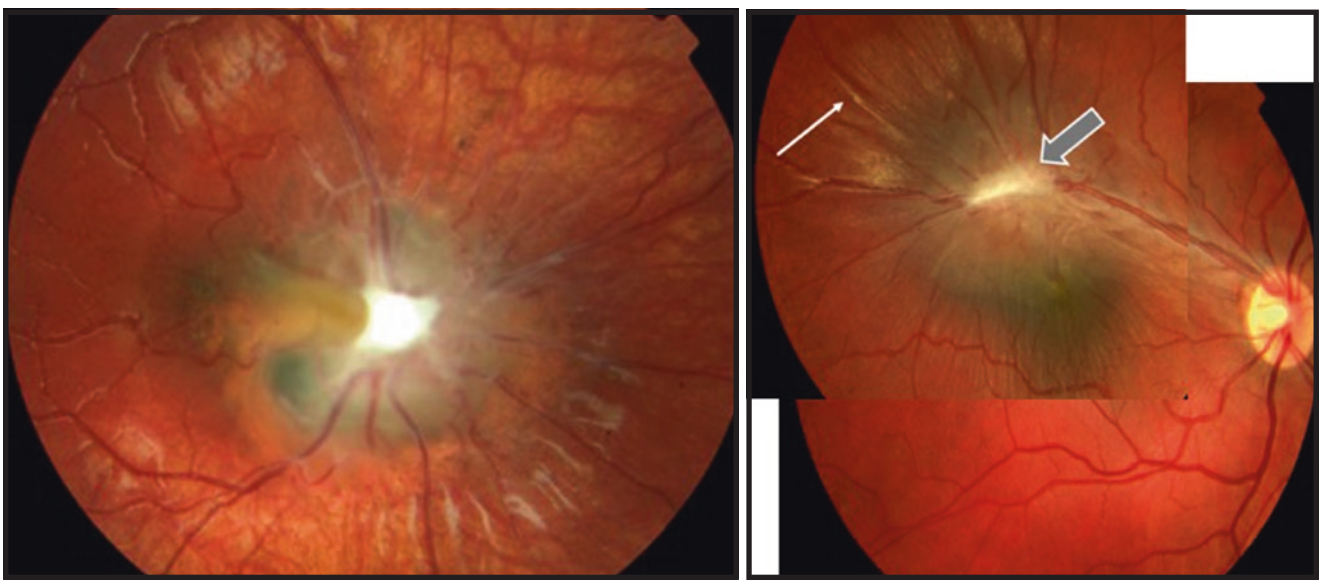

Fig. 44.1 Ocular manifestations of neurofibromatosis type 2, including combined hamartoma of inner retina and retinal pigment epithelium (RPE) and epiretinal membrane (*thick arrow*). Note the radial traction striae (*thin arrow*)

suppressor; it keeps cells from growing and dividing too rapidly or in an uncontrolled way. With a mutation in the *NF1* gene, nonfunctional neurofibromin cannot regulate cell growth and division.
  – Cytogenetic location: 17q11.2
- **Neurofibromatosis Type 2:** The cause of NF2 is mutations in the *NF2* gene, which gives instructions to make a protein called *merlin* (schwannomin). This protein is produced in the Schwann cells that surround and insulate neurons. Merlin also acts as a tumor suppressor, so loss of merlin allows Schwann cells to multiply rapidly and form the tumors.
  – Cytogenetic location: 22q12.2

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Section VII
Phenocopies

CHAPTER 45

Rubella Retinopathy

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General Features: Phenocopies

- **Definition:** A *phenocopy* is an individual showing features (phenotype) characteristic of a genotype but produced environmentally rather than genetically (not inherited); these features are not due to mutations, as the underlying DNA sequence of the phenocopy is not altered.
- Many acquired retinal diseases may be confused with retinitis pigmentosa (so-called *pseudoretinitis pigmentosa*); it is important to differentiate between these acquired diseases and RP, because the difference has a great bearing on the eventual prognosis and counseling offered to the family.

General Features: Rubella Retinopathy

- Rubella retinopathy is a part of congenital rubella syndrome and includes unilateral or bilateral pigmentary retinopathy, described as "salt-and-pepper" fundus ranging from finely stippled to gross pigmentary changes (25–50%), cataract (15%), and glaucoma (10%) (Figs. 45.1 and 45.2).
- Rubella retinopathy can be either stationary or progressive. Electroretinography (ERG) is not affected or is just mildly affected.
- Other associated features include cardiac malformations (patent ductus arteriosus, interventricular septal defects, and

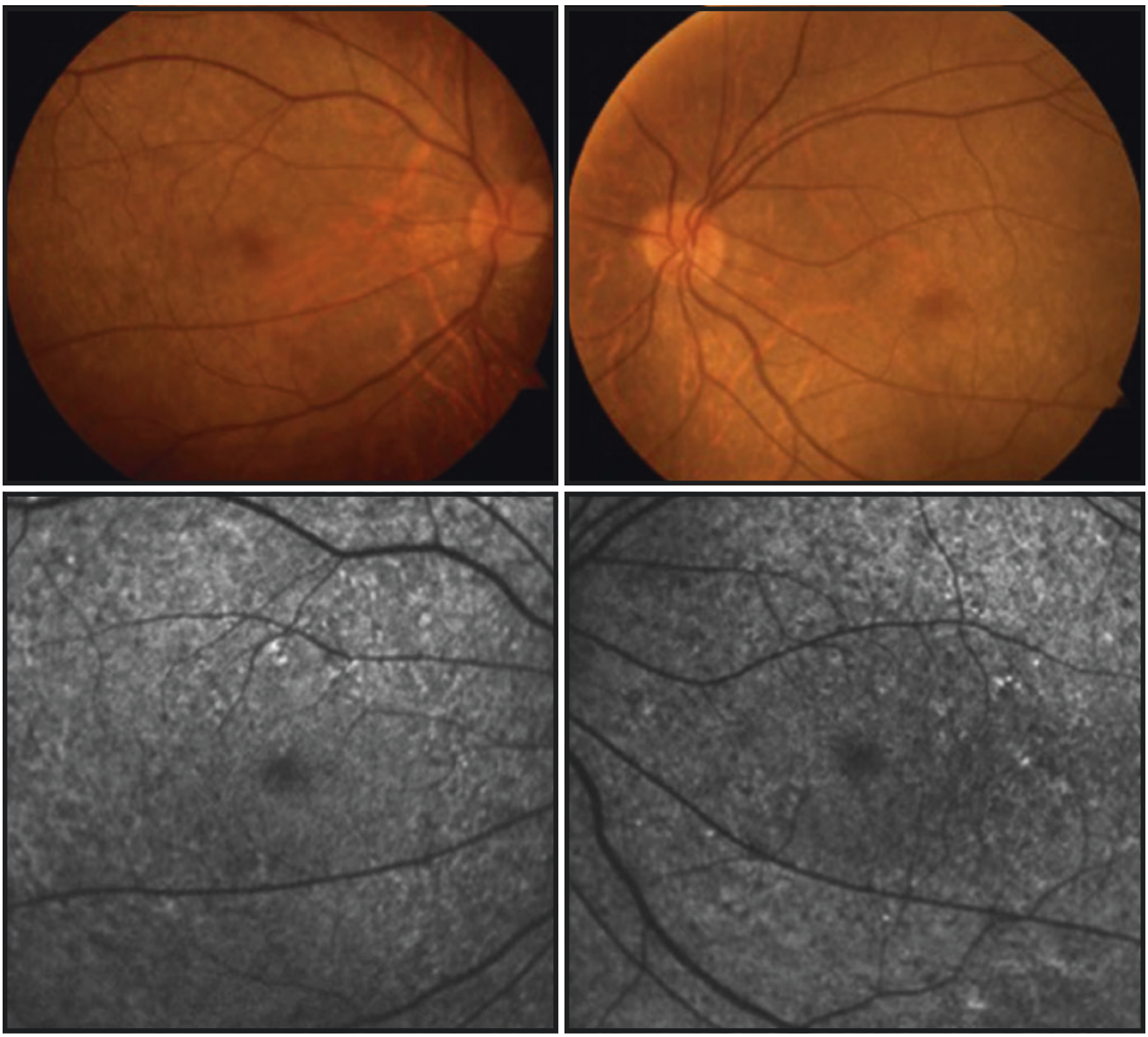

Fig. 45.1 Rubella retinopathy: Color photos show subtle pigmentary disturbances, but fundus autofluorescence (FAF) shows a stippled pattern

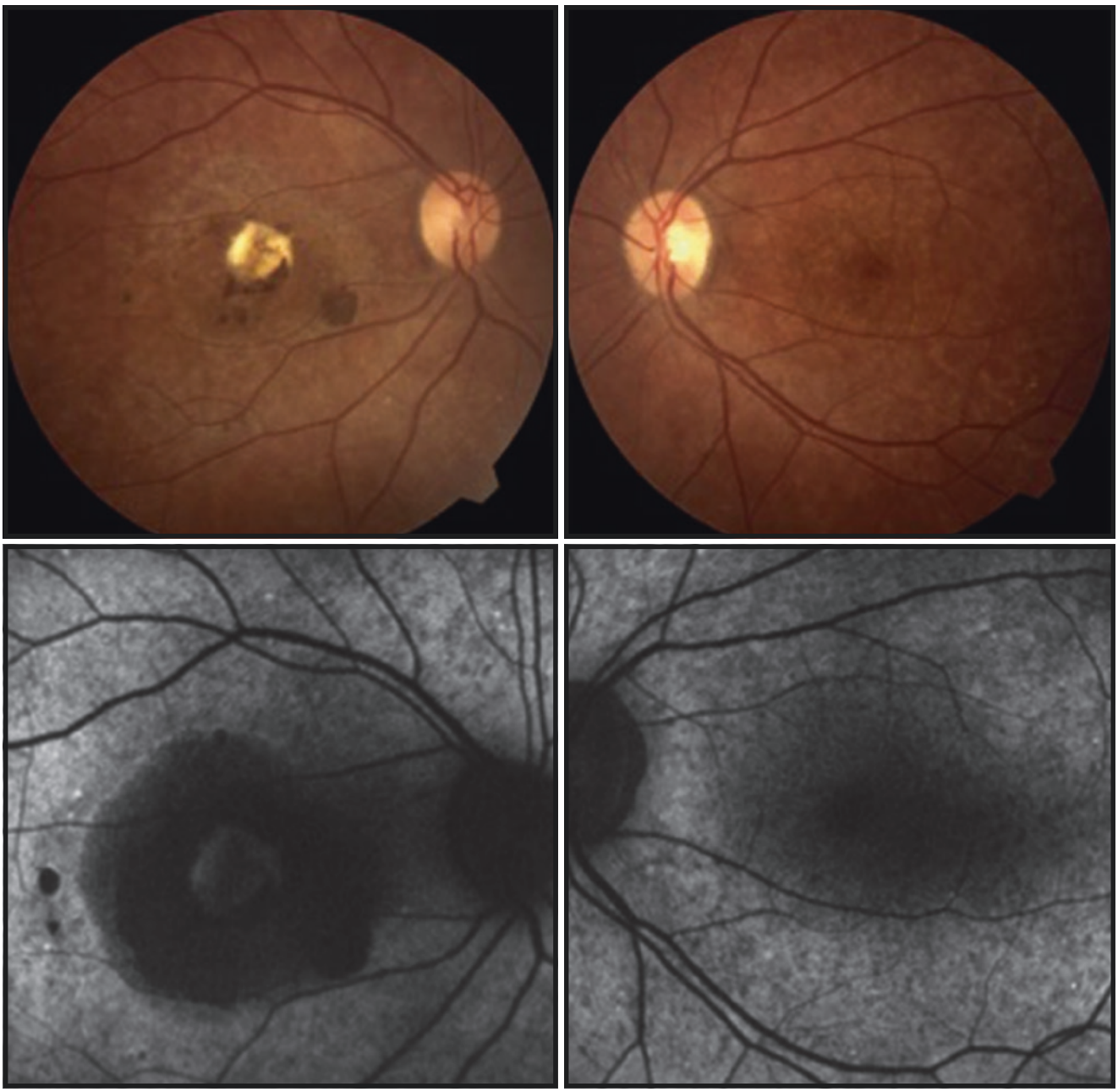

Fig. 45.2 Rubella retinopathy: The right fundus shows a central scar with pigment clumps around it and corresponding retinal pigment epithelium atrophy on FAF. The left fundus shows just subtle changes on the color photo, but a stippled pattern on FAF

pulmonary stenosis), and hearing loss (so the diagnosis may be confused with Usher syndrome).

- The fetus is infected by rubella virus during the first trimester, usually in the first 10 weeks. The persistence of viral replication after birth and resultant tissue damage is essential to congenital rubella syndrome and may explain late onset of hearing loss or ocular damage.
- Serology shows a fourfold increase in rubella-specific IgG (recent or past exposure) or IgM (new or current infection).

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CHAPTER 46

Syphilis

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General Features

- Syphilis is an infectious disease caused by a spirochete, *Treponema pallidum*; it is most commonly spread by sexual transmission.
- Syphilis is known as the "Great Imitator," as systemic manifestations are variable. It can involve any part of the eye, with syphilitic uveitis being the most common type.
- Congenital syphilis is characterized by Hutchinson's teeth, saddle nose deformity, deafness, and interstitial keratitis; pigmentary changes in the retina are varied and patchy.
- The manifestations of acquired syphilis change over time:
  - *Primary syphilis* (2–6 weeks after infection) has a painless chancre.
  - *Secondary syphilis* (4–10 weeks after infection) has fever/malaise and generalized rash involving the palms and soles.
  - *Tertiary syphilis* (months or years after the infection) has neurological and cardiovascular manifestations.
- *Ocular changes:* Syphilis can involve virtually any ocular structure, causing conjunctivitis, episcleritis, scleritis, interstitial keratitis, granulomatous uveitis, chorioretinitis, retinitis, vasculitis, or papillitis.
  - Acute syphilitic posterior placoid chorioretinopathy (ASPPC) (Fig. 46.1) is due to syphilitic infection of the retinal pigment epithelium (RPE) in the macular or peripapillary region. The lesions are large and placoid, and following resolution, the involved RPE shows a leopard-spot appearance on fluorescein angiography, with exudative retinal detachment.
  - Pigmentary retinopathy can occur in both congenital and acquired syphilis and may mimic advanced retinitis pigmentosa. Pigmentary changes are usually in clumps, along with chorioretinal scars; typical bony-spicule pigmentation is uncommon. Therefore, syphilis can masquerade retinitis pigmentosa (Pseudoretinitis pigmentosa).

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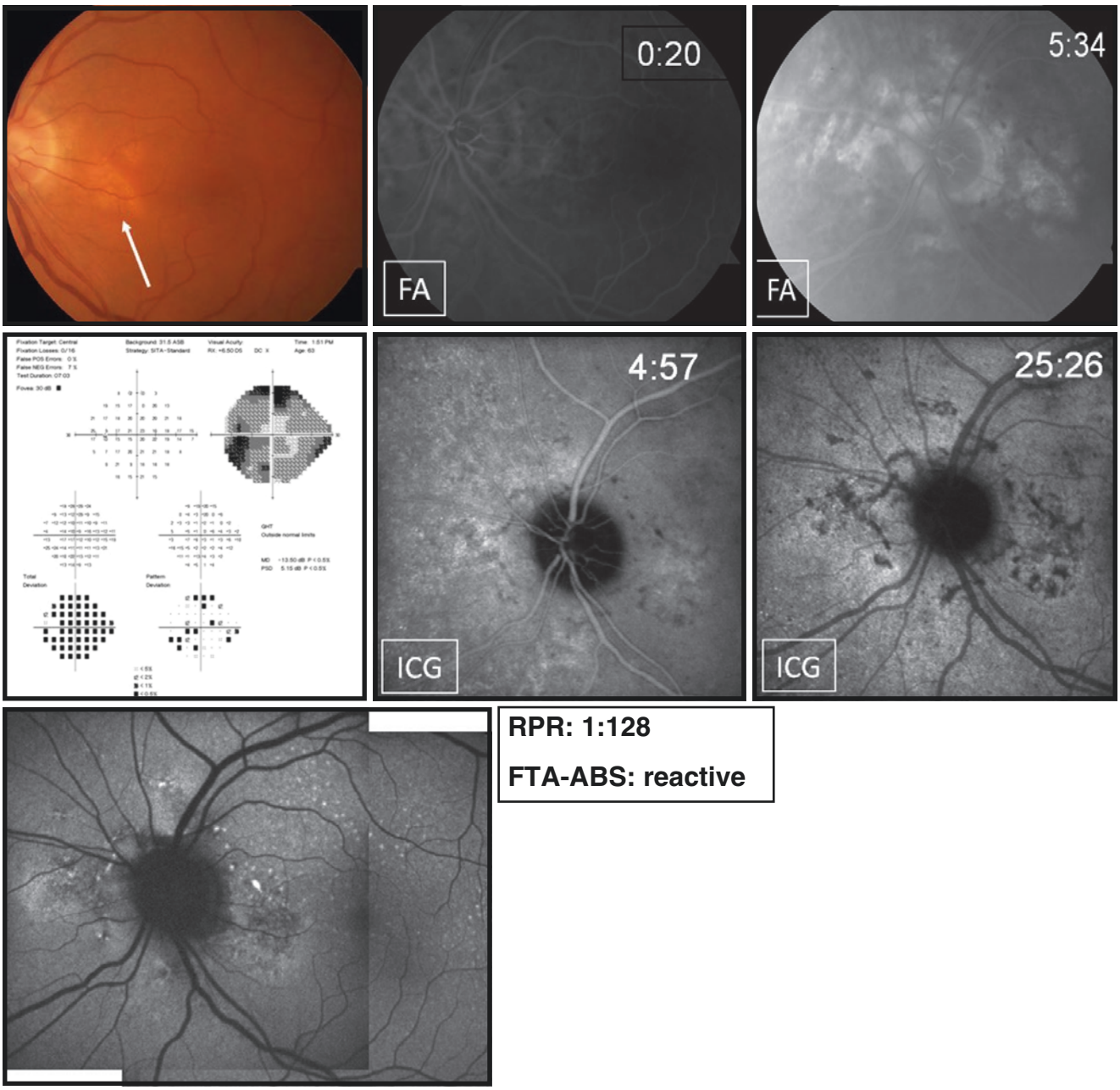

Fig. 46.1 Acute syphilitic posterior placoid chorioretinopathy. A 63-year-old patient presented with enlargement of the blind spot and decreased vision (20/160). Color fundus shows multiple grayish-white lesions at the deeper level (*arrow*) and corresponding scotoma. Fluorescein angiography (FA) shows early hypofluorescence and late staining. Indocyanine green angiography (ICG) shows hypofluorescence, and fundus autofluorescence (FAF) shows characteristic hyperautofluorescent dots in the peripapillary and macular area

CHAPTER 47

Autoimmune Retinopathy

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General Features: Autoimmune Retinopathies

- The autoimmune retinopathies (AIRs) are a group of inflammatory-mediated retinopathies that present with unexplained visual loss (both central and peripheral), visual field defects, usually a ring scotoma, photoreceptor dysfunction as evident on electroretinography (ERG), and circulating autoantibodies against retinal antigens. The fundus may be normal or may show vascular attenuation, retinal atrophy with or without pigmentary changes or waxy pallor of the optic disc, and no or minimal inflammatory cells.
- The AIRs can be categorized into two groups:
  - Paraneoplastic retinopathy or paraneoplastic autoimmune retinopathy, which includes cancer-associated retinopathy (CAR), melanoma-associated retinopathy (MAR), paraneoplastic vitelliform maculopathy (PVM), and bilateral diffuse uveal melanocytic proliferation (BDUMP)
  - Non-paraneoplastic autoimmune retinopathy

Paraneoplastic Retinopathy

- Paraneoplastic retinopathies can occur without systemic spread of the cancer tumor and may even precede a clinically evident tumor.
- **Cancer-associated retinopathy (CAR):** Patients typically experience rapidly progressive loss of central and peripheral vision, along with positive visual phenomena (photopsias or sparkles) and a ring scotoma, photosensitivity, impaired color vision, and night blindness. The fundus may show arterial narrowing with no pigment spiculation, though some pigment alteration can occur. ERG shows extinguished response or severely reduced a-waves and b-waves.
  - The most common malignancy associated with CAR is small cell carcinoma of the lung, but other malignancies that may be involved include those of the colon, uterus, cervix, breast, prostate/bladder, and systemic lymphoma.
  - In about 60% of patients with CAR, antibodies are produced against a 23-kDa calcium channel photoreceptor protein called *recoverin*.
  - Prednisone and immunomodulators have been used to stabilize visual function in some patients with CAR.
- **Cutaneous melanoma-associated retinopathy (MAR):** This is different from CAR in several ways: It is non-progressive, causes only central visual loss, and is associated with vitiligo (20%); ERG shows electronegative waveforms (selective reduction of b-wave); and MAR usually does not manifest before the clinical diagnosis of cutaneous malignant melanoma.
  - Antibodies against transducin, enolase, and aldolase A and C have been reported.
  - Photoreceptor functions are intact; the pathology lies in the bipolar cells.
- **Paraneoplastic vitelliform maculopathy (PVM):** Multiple oval, yellowish lesions are seen at the RPE levels along the arcades and surrounding the disc. Patients have mild visual loss (20/40–20/100) with mild night blindness and photopsias; fields are usually normal and ERG response is variable. An abnormal Arden ratio was noted in less than 50% of cases, suggesting relatively normal RPE function. The clinical picture is similar to acute exudative polymorphous vitelliform maculopathy (AEPVM).
  - PVM is associated with choroidal melanoma, lung carcinoma, and multiple myeloma.
  - Retinal autoantibodies have been noted against bipolar cells, enolase, rod outer segment proteins, and bestrophin.
- **Bilateral diffuse uveal melanocytic proliferation (BDUMP):** This is characterized by multiple, slightly elevated (about 2 mm), pigmented or nonpigmented uveal melanocytic tumors of the choroid, along with diffuse thickening of the uveal tract; multiple, round or oval, subtle red patches at the RPE level; rapidly progressive posterior subcapsular cataract; and exudative retinal detachment. Fluorescein angiography shows multiple areas of early hyperfluorescence.
  - Findings may precede the detection of systemic malignancies (*eg*, gastrointestinal, genitourinary, pulmonary, and non-Hodgkin lymphoma).
  - Plasmapheresis to remove the circulating ectopic peptides (presumed) has been used in some patients to stabilize the vision while treatment for the systemic malignancy is underway.

Non-paraneoplastic Autoimmune Retinopathy

- Non-paraneoplastic AIR is almost always bilateral, though asymmetric, with female preponderance (about 65%). The mean age of onset is between 51 and 56 years. These patients have no prior history of ocular symptoms, but start noticing photopsias, scotomas, acute or subacute visual loss,

photoaversion, color vision changes, and night blindness. The fundus is either normal-appearing or shows nonspecific retinal degeneration or RPE atrophy or mottling, attenuated blood vessels, and waxy pallor of the disc, with or without pigmentary changes. ERG shows abnormalities in photoreceptors and bipolar cells.

- Fluorescein angiography may show vascular leakage or staining and/or cystoid macular edema. Spectral domain OCT (SD-OCT) may show disruption of the ellipsoid zone, loss of photoreceptor layer, loss of external limiting membrane, and thinning of the outer nuclear layer (Figs. 47.1 and 47.2). On fundus autofluorescence (FAF), a hyperautofluorescent ring around the fovea is seen in some cases. There is absence of any overt intraocular inflammation.
  - There is a positive history of autoimmune disease in the patient or the patient's family.
  - These patients, like those with paraneoplastic retinopathy, demonstrate various antiretinal antibodies, including anti-recoverin or antibodies against inner plexiform layer or Müller cells (35 kDa).

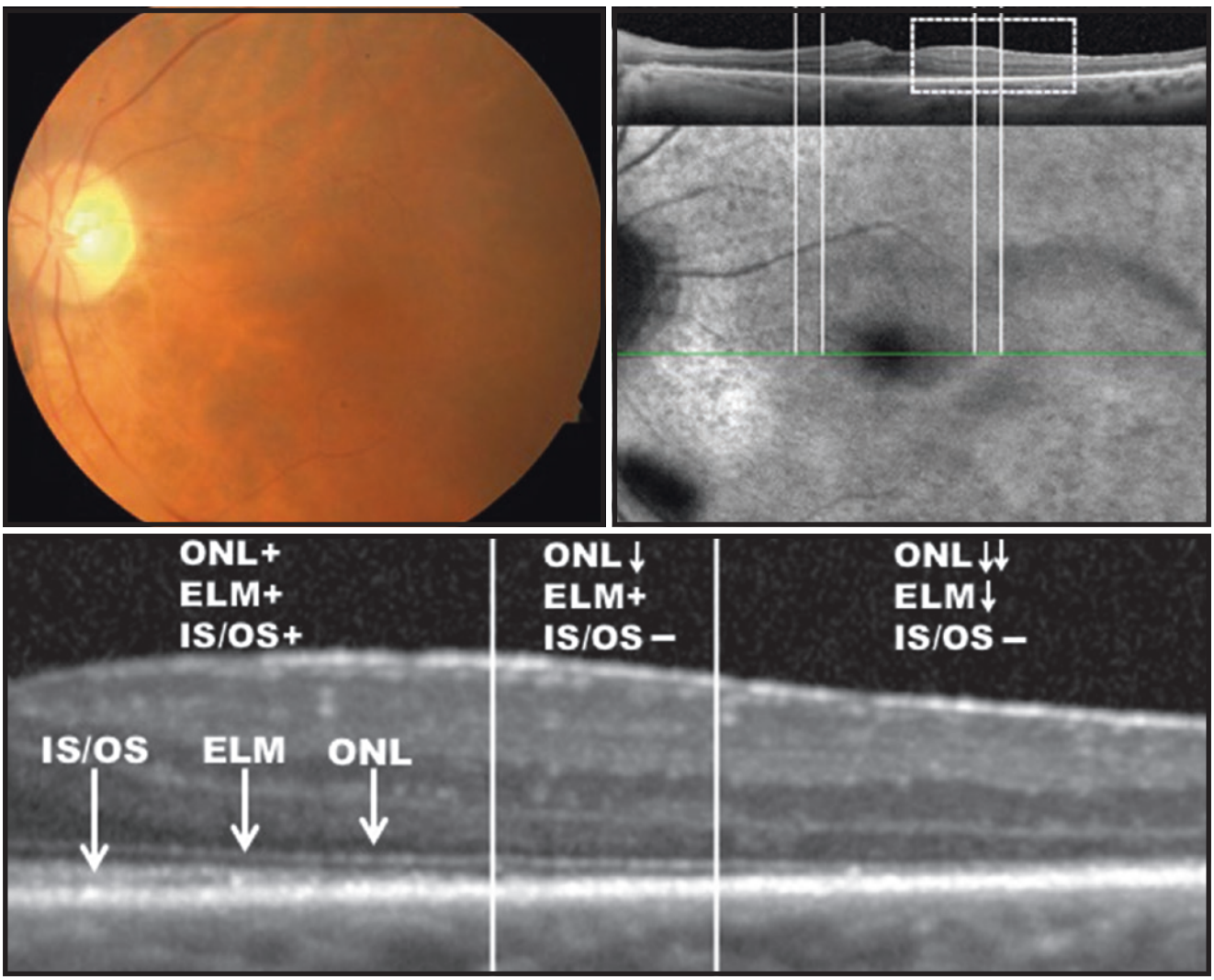

Fig. 47.1 Non-paraneoplastic autoimmune retinopathy. Note attenuation of vessels, thinning of the outer nuclear layer (ONL), disappearance of the external limiting membrane (ELM), and loss of the ellipsoid zone. IS/OS inner segment/outer segment junction

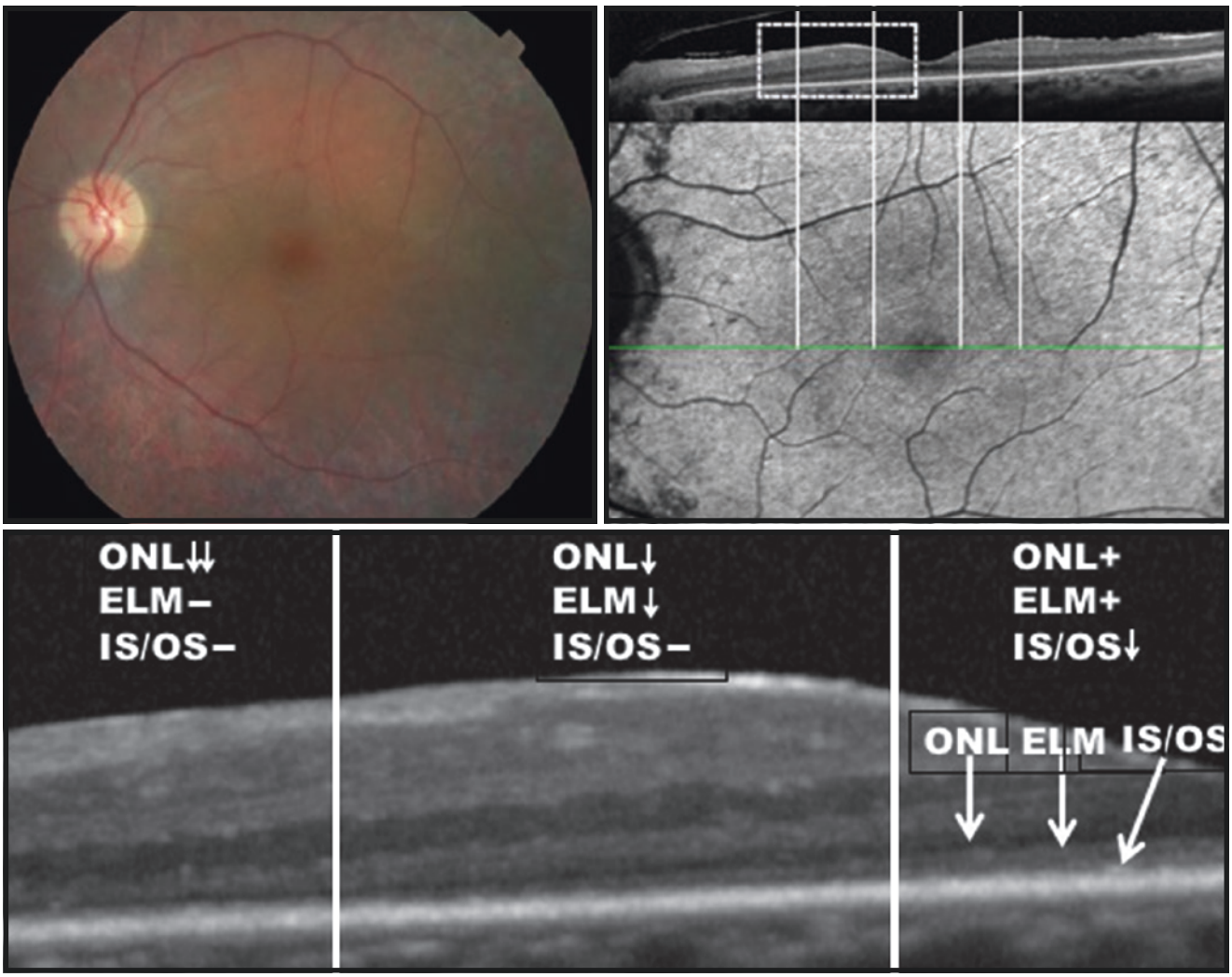

Fig. 47.2 Non-paraneoplastic autoimmune retinopathy. Note mild narrowing of the vessels, thinning of the ONL, disappearance of the ELM, and loss of the ellipsoid zone. IS/OS inner segment/outer segment junction

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CHAPTER 48

Drug-Induced Retinal Toxicity

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General Features

- Drug-induced retinal toxicity can occur from the use of systemic, intravitreal, or topical medications. Despite the presence of the blood-ocular barrier, the retina is vulnerable to toxic effects of systemic medications leading to dysfunction and retinal degeneration.
- These toxicities can be categorized as damage to the retinal pigment epithelium (RPE) and photoreceptor complex, vascular damage, ganglion cell or optic nerve damage, cystoid macular edema, crystalline retinopathy, uveitis, changes in color vision and electroretinography (ERG), and other miscellaneous effects.

Damage to RPE and Photoreceptor Complex

- **Chloroquine/hydroxychloroquine**
  - Used for malaria, amoebiasis, rheumatoid arthritis (RA), and systemic lupus erythematosus (SLE). Both medications bind to melanin in the RPE and uveal tissue, and interfere with metabolic function.
  - *Chloroquine:* The risk of toxicity is low with dosage 3 mg/kg per day, but the risk increases with a cumulative dose of 460 g.
  - *Hydroxychloroquine:* The risk of toxicity is low with dosage 5 mg/kg per day but increases with a cumulative dose of 1000 g. Other risk factors for toxicity are age > 60 years, obesity, short stature, age-related macular degeneration (AMD), kidney or liver disease, or concomitant use of tamoxifen.
  - The earliest manifestation of toxicity is bilateral paracentral scotoma or loss of ellipsoid zone (EZ) on SD-OCT (flying saucer sign). Later, subtle RPE stippling and loss of foveal reflex are seen, followed by classic bull's-eye maculopathy (Fig. 48.1). The end stage shows panretinal degeneration, like retinitis pigmentosa (RP).
  - Fluorescein angiography (FA): RPE window defects or pigmentary changes.
  - Fundus autofluorescence (FAF): perifoveal hypoautofluorescence with a border of hyperautofluorescent ring.
  - OCT: Atrophy of outer nuclear layer (ONL) and disruption of EZ. Also, perifoveal thinning of the inner plexiform layer (IPL) and ganglion cell layer (GCL) sometimes even precede photoreceptor damage.
  - Multifocal ERG (mfERG): reduced paracentral waveforms.
  - Baseline screening and follow-up include fundus examination/photo, SD-OCT, and automated threshold field testing (Humphrey, white or red object, 10–2 protocol); FAF and mfERG are also used for assessment. Annual screening (in particular after 5 years of use) should be done with Humphrey visual field 10–2 and SD-OCT.
  - Treatment should be stopped at the first sign of toxicity; otherwise toxic effects continue to progress despite discontinuation of the drug.
- **Phenothiazines**
  - Both chlorpromazine and thioridazine accumulate in the melanin of RPE and uveal tissue.
  - *Chlorpromazine* causes hyperpigmentation in the eyelid, conjunctiva, cornea, or anterior capsule of the lens; retinal toxicity is rare.
  - *Thioridazine:* Toxicity Is dependent on the daily dose rather than on the cumulative dose; it is rare at doses of 800 mg/day or lower.
  - Symptoms include blurred vision, color vision abnormality (reddish/brownish vision), and night blindness. In the early stage, there is a coarse RPE stippling in the posterior pole; at a later stage, nummular areas of RPE/choriocapillaris loss are seen from the posterior pole to mid-periphery. The late stage mimics choroideremia or Bietti crystalline dystrophy (BCD); vascular attenuation and optic atrophy are seen.
- **Clofazimine**
  - Used to treat dapsone-resistant leprosy and autoimmune disorders such as psoriasis and lupus
  - Toxicity: like bull's-eye maculopathy (BEM).
- **Deferoxamine**
  - Used to treat iron toxicity/overload, as an iron-chelating agent
  - Toxicity: Reticular or vitelliform form changes and/or macular edema due to RPE pump failure (Fig. 48.2).
- **Dideoxyinosine (DDI)**
  - Used to treat HIV/AIDS
  - *Toxicity:* Causes mitochondrial toxicity resulting in damage to the optic nerve and RPE; peripheral field loss occurs with concentric loss/mottling of RPE (areas of chorioretinal atrophy), beyond arcades to mid-periphery, bilaterally symmetrical.
- **MEK inhibitors**
  - Used to treat metastatic cancers
  - *Toxicity:* Multifocal serous retinal detachments (like central serous retinopathy [CSR])

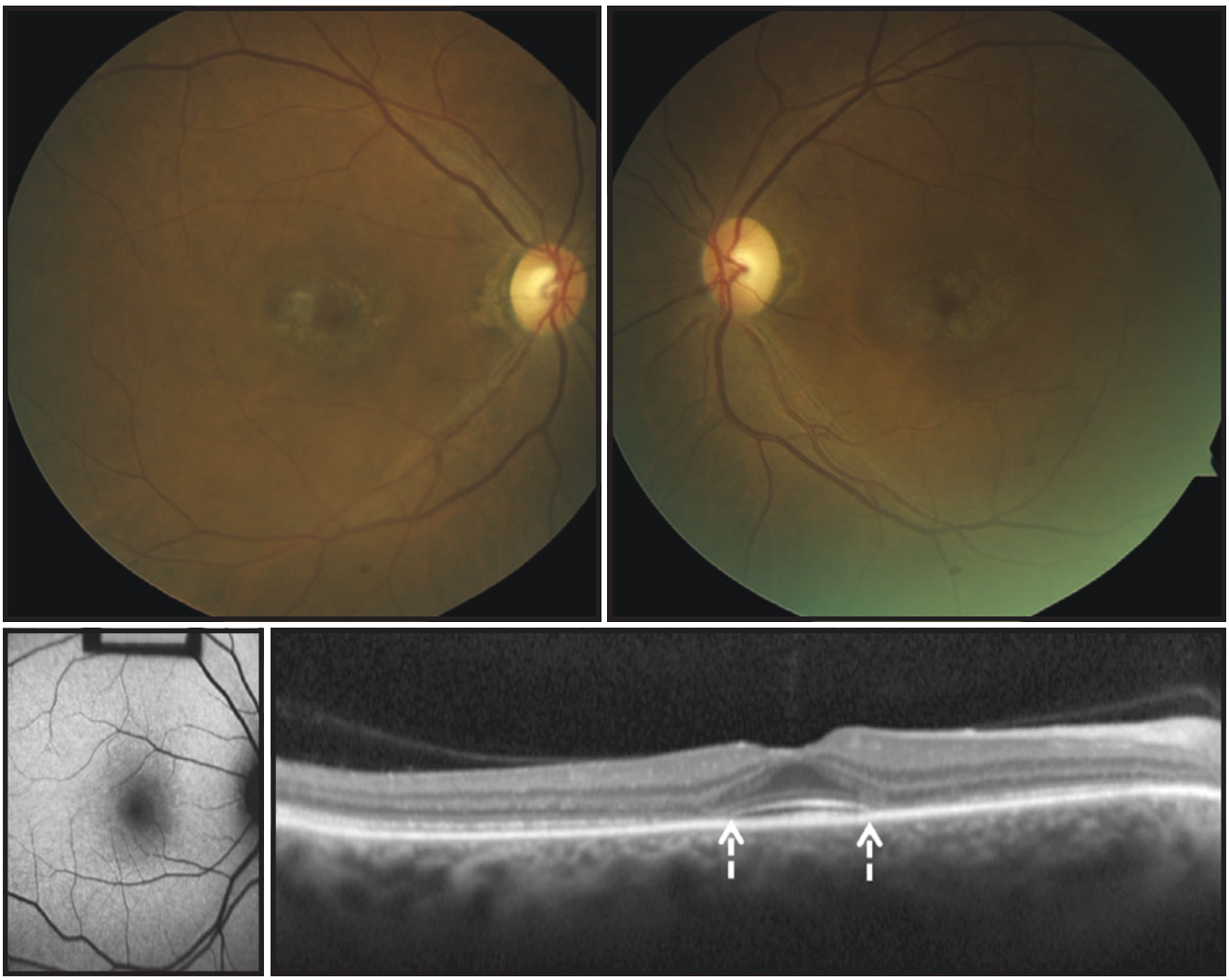

Fig. 48.1 Classic BEM; SD-OCT shows loss of inner segment ellipsoid band (flying saucer sign)

- **Sildenafil**
  - Used for erectile dysfunction
  - *Toxicity:* Serous macular detachment, possibly due to dilatation of choroidal vasculature. Transient blue tinting of the vision, and temporarily abnormal ERG, a delayed cone b-wave implicit time.
- **Corticosteroid**
  - *Toxicity:* Serous macular detachment
- **Poppers/Alkyl nitrates**
  - Used as recreational drugs for euphoric effect and enhanced sexual arousal
  - *Toxicity:* Disruption of EZ/foveal cones involvement; a yellow spot on fundus with central scotoma/photopsia
- **Cisplatin and carmustine**
  - Used for metastatic breast cancer and malignant gliomas
  - *Toxicity:* Pigmentary retinopathy at macula, or cotton-wool spots, hemorrhages, exudates, and disc swelling or arterial occlusion, vasculitis, and papillitis

Damage to the Vascular Bed or Microvasculopathy/ Occlusion

- **Interferon alfa-2a**
  - Used for viral hepatitis C
  - *Toxicity:* Multiple cotton-wool spots and hemorrhages
- **Ergot alkaloids**
  - Used for migraine
  - *Toxicity:* Retinal vasoconstriction
- **Gemcitabine**
  - Used for non-small-cell lung carcinoma or cancer of breast, ovary, or pancreas
  - *Toxicity:* Purtscher-like retinopathy with non-perfusion

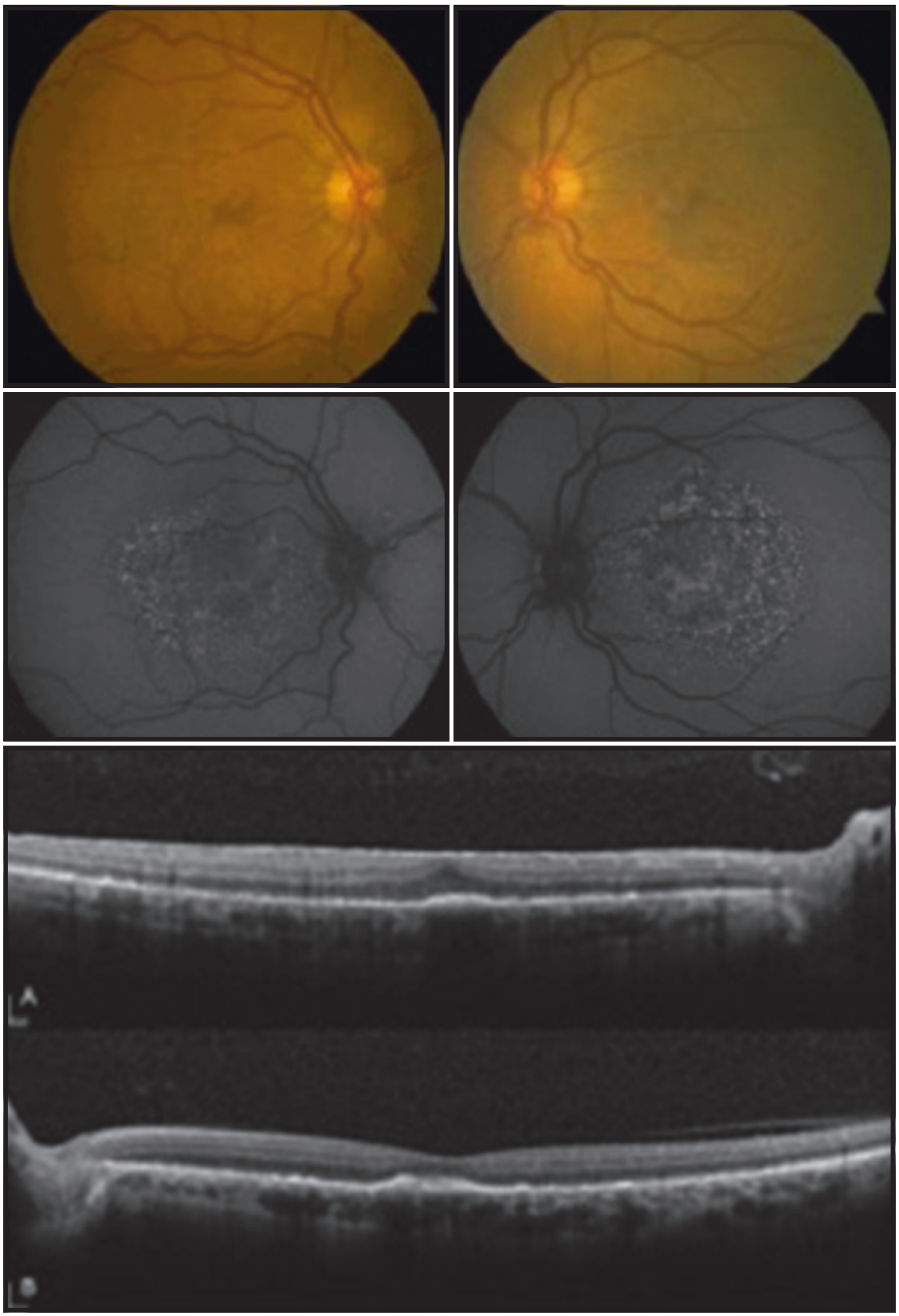

Fig. 48.2 Retinal toxicity due to deferoxamine. (**Left**) Color photos show pigmentary/RPE changes at the macula; FAF shows a stippled pattern of hypoautofluorescence and hyperautofluorescence; OCT shows hyperreflective material in the subretinal space with disruption of the ellipsoid zone. (**Below**) Five months after discontinuation of the deferoxamine, RPE alterations persist. Note some hyperreflective dots in the outer retina (nasal macula)

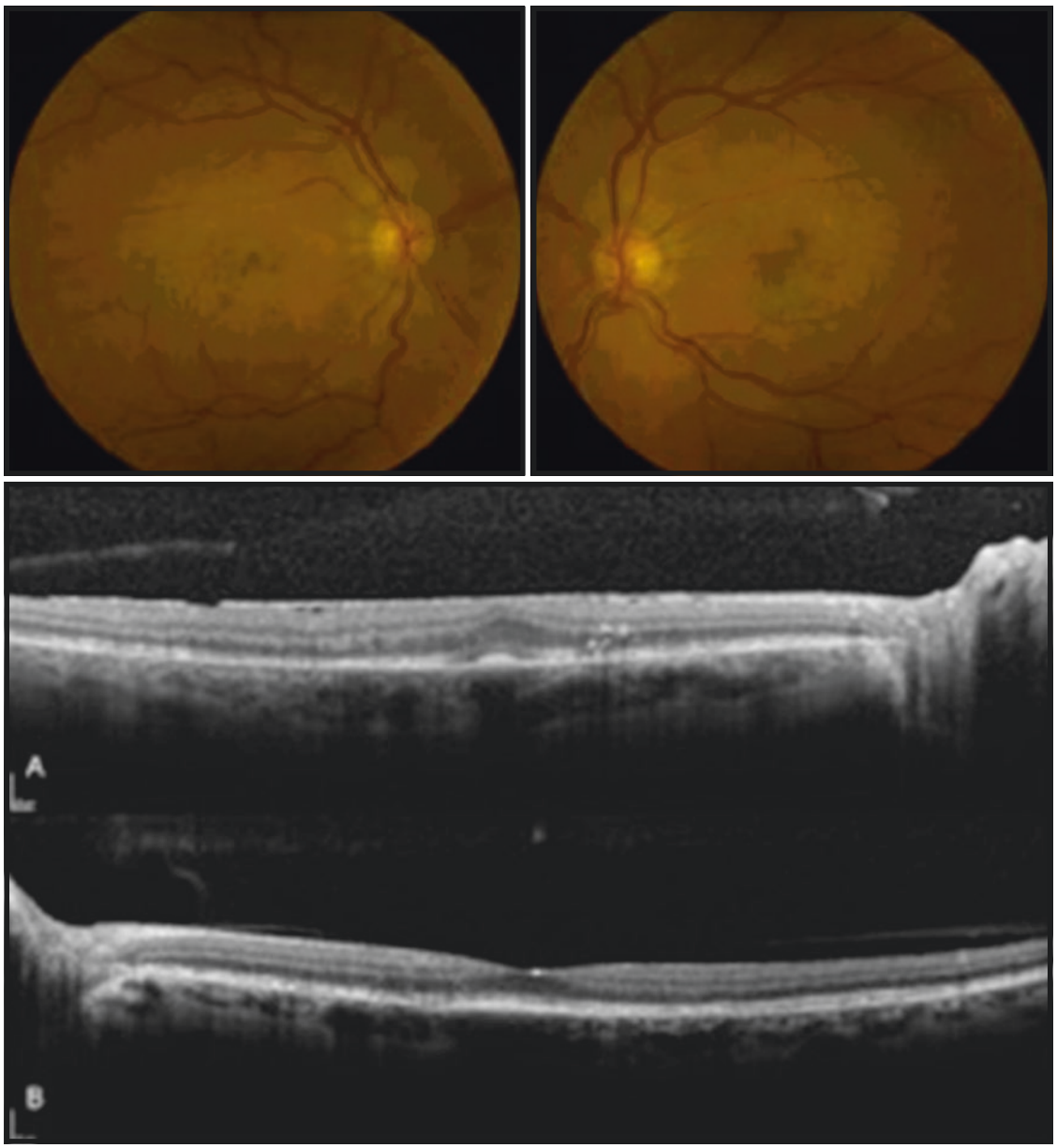

Fig. 48.2 (continued)

- **Oral contraceptives**
  - *Toxicity:* Vascular occlusions
- **Intraocular gentamicin/tobramycin/amikacin**
  - *Toxicity:* Macular ischemia, infarction
- **Intracameral vancomycin**
  - *Toxicity:* Hemorrhagic occlusive vasculitis, immune-mediated, especially when second eye is operated in close proximity
- **Talc**
  - Retinopathy common in intravenous drug users
  - *Toxicity:* Perifoveal yellow-white glistening crystals, later leading to ischemic retinopathy

Damage to Ganglion Cell Layer or Optic Nerve

- **Quinine sulfate**
  - Used for nocturnal muscle cramps or restless leg syndrome, or as an antimalarial
  - *Toxicity:* Safe if the dose is <2 g; toxic if the dose is >4 g; fatal if >8 g

  - Acute toxicity is like central retinal artery occlusion, cherry red spot, GCL thickening and hyperreflective on OCT, negative waveform on full-field ERG. Blindness is permanent.
- **Methanol**
  - *Toxicity:* Causes acute blindness, optic nerve head and macular edema; later, optic nerve atrophy due to diffuse loss of the GCL

Drugs Causing Cystoid Macular Edema

- Topical epinephrine
- High dose of nicotinic acid/niacin to treat dyslipidemia
- Paclitaxel/docetaxel to treat cancer of breast, lung or prostate
- Glitazones, rosiglitazone, and pioglitazone, as hypoglycemic agents
- Deferoxamine as iron-chelating agent
- Topical latanoprost

Drugs Causing Crystalline Retinopathy

- **Tamoxifen**
  - Used as an adjuvant therapy (as antiestrogen agent) in the treatment of estrogen-receptor–positive breast carcinoma
  - *Toxicity:* Rare if the daily dose is 20 mg/day; may occur with daily dose of 60–100 mg/day or cumulative dose >100 g. There are brilliant yellowish-white crystal deposits in the inner retina, around the fovea, and cystoid macular edema (CME) and loss of EZ on OCT.
- **Canthaxanthin**
  - Used as an oral tanning agent or for skin pigmentation in vitiligo
  - *Toxicity:* With cumulative dose >19 g over 2 years, causes glistening, ring-shaped yellowish-orange crystals in the inner retina, a doughnut pattern around the macula or in the juxtapapillary region. They do not cause visual loss and disappear after the treatment is discontinued.
- **Methoxyflurane**
  - Used as an inhalational anesthetic agent; no longer used in the United States
  - *Toxicity:* Numerous yellowish-white, punctate deposits in the macula and periarterially, deposited in both RPE and inner retina (more common in those with renal insufficiency)

Drugs Causing Uveitis

- Rifabutin: For the prevention and treatment of disseminated *Mycobacterium avium* complex (MAC)
- Cidofovir: for cytomegalovirus (CMV) infection
- Topical latanoprost

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CHAPTER 49

Acute Zonal Occult Outer Retinopathy (AZOOR) and Related Diseases

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General Features

- Acute zonal occult outer retinopathy (AZOOR) is a presumed inflammatory disorder with outer retinal dysfunction.
- Typically, the onset is acute and it is unilateral, with symptoms of photopsias and nasal field loss; scotoma is usually contiguous with the optic nerve. Later, the other eye is involved in nearly three fourths of patients. The central vision remains good in most cases.
- Patients are usually young women with myopia.
- *Fundus:* May be normal in the beginning, but may show a grayish-white line at the border of normal and involved retina, usually in peripapillary area. This line disappears within weeks and is replaced with an orange zone. With time, retinal vessels attenuate and a large zone of retinal pigment epithelium (RPE) depigmentation appears, sort of a sector retinitis pigmentosa (RP) or unilateral or asymmetric RP (Fig. 49.1).
- Rarely, mild vitritis may occur, and relative afferent pupillary defect (RAPD) is present in about 75% of cases.
- *Fluorescein angiography (FA):* In the acute stage, may show evidence of leakage/staining from retinal blood vessels and optic nerve; in the late stage, RPE window defects may be seen.
- *Field:* Areas of scotomas that enlarge with time
- *Indocyanine green angiography (ICG):* Area of late hypofluorescence
- *Optical coherence tomography (OCT):* Thinning or atrophy of the outer retina/outer nuclear layer (ONL), including disruption of the ellipsoid zone (EZ)
- *Fundus autofluorescence (FAF):* Shows characteristic trizonal pattern: hypoautofluorescence (hypoAF) in the involved area, speckled hyperAF at the border, and normal AF beyond the delineating line or border (Figs. 49.2 and 49.3).
- *Prognosis:* Usually stabilized in 6 months. Vision remains good in most cases.

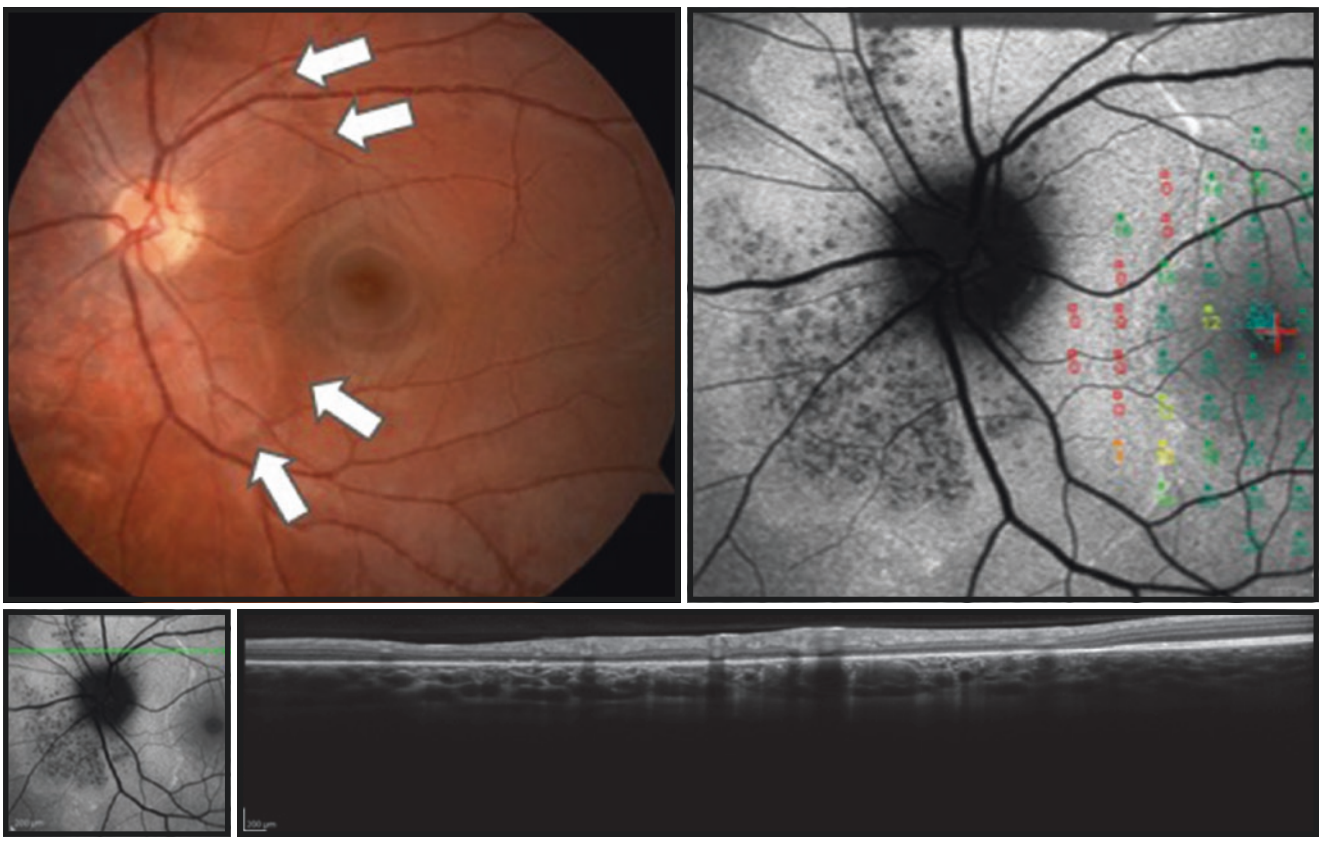

Fig. 49.1 A case of resolving acute zonal occult outer retinopathy (AZOOR). Note the wavy line (*arrows*) bordering the involved and healthy areas on fundus autofluorescence (FAF); superimposed microperimetry (MP) shows decreased sensitivity in the involved area. Optical coherence tomography (OCT) shows thinning of the retina

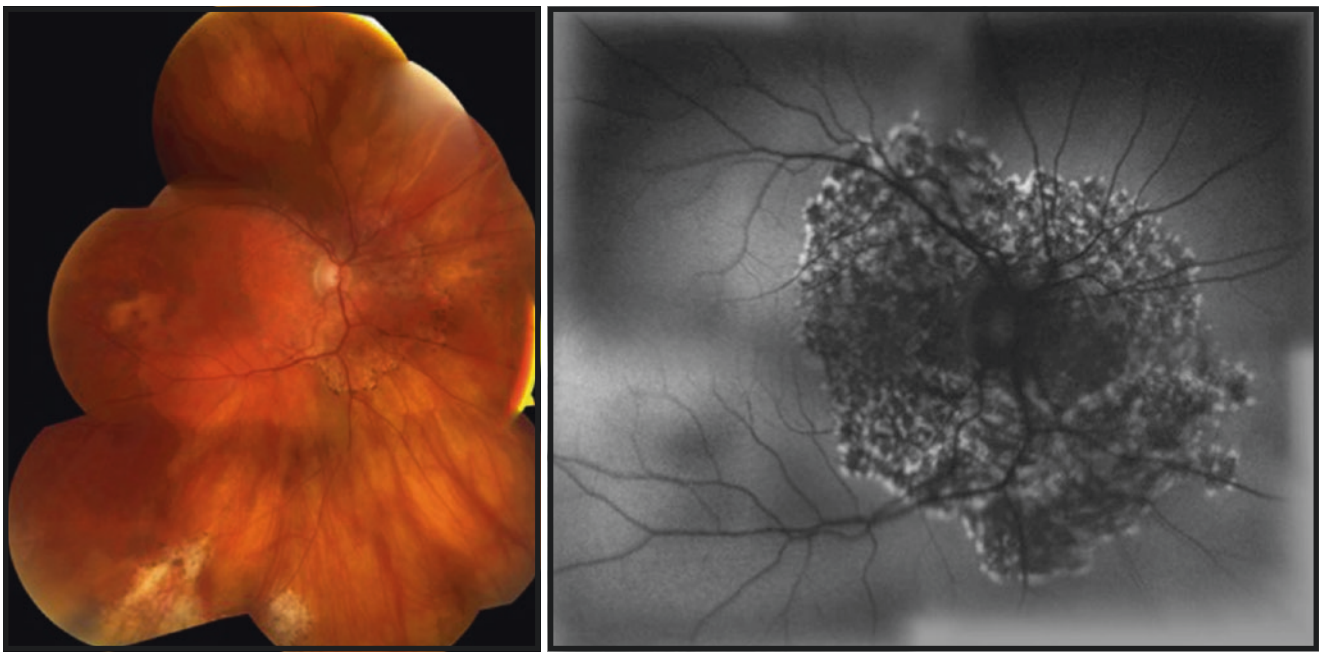

Fig. 49.2 A case of AZOOR around the peripapillary area. Note characteristic hyperAF dots In the peripheral zone of the involved area

AZOOR Complex

- Besides AZOOR, the complex includes MEWDS (multiple evanescent white dot syndrome), PIC (punctate inner choroidopathy), MFC (multifocal choroiditis), AMN (acute macular neuroretinopathy), and AIBSE (acute idiopathic blind spot enlargement).
- **MEWDS** (multiple evanescent white dot syndrome)
  - MEWDS has an acute onset with multiple small, grayish-white or yellowish-white dots at the RPE level at the posterior pole, along with blurred vision, temporal photopsias, and temporal scotoma (also enlarged blind spot) in one eye. The fovea shows an unusual granularity with tiny yellowish-orange flecks, and is characteristic of MEWDS.
  - Occurs commonly in young women (75%), with myopia.
  - Inflammatory signs in the anterior chamber or mild vitritis is present, along with an afferent pupillary defect. One third of patients have a flu-like prodrome.
  - *FA:* Punctate hyperfluorescent dots in a wreathlike pattern; disc may shows mild leakage/staining.
  - *ICG:* Hypofluorescent spots, which are greater in number than what is observed clinically or on FA.
  - *OCT:* There may be protrusion of hyperreflective material towards the ONL, disruption in the EZ band, and increased reflectivity in choroid in the acute phase.
  - *FAF:* HypoAF areas around the optic nerve (ON) and posterior pole (with some hyperAF dots). In the recovery phase, many hypoAF lesions fade, and hyperAF dots become smaller or are surrounded by a hypoAF ring.
  - *ERG:* Shows reduced a-wave amplitude (photopic) and/or delayed 30-Hz flicker response suggestive of photoreceptor involvement.
  - *Prognosis:* In most patients, symptoms improve without treatment in 2–6 weeks.
- **PIC/MFC** (punctate inner choroidopathy/multifocal choroiditis)
  - Patients are usually young women, who commonly present with decreased vision and scotomas.
  - In the acute phase, multiple yellowish, round/oval lesions are clustered at the macula and around the ON (Fig. 49.4), but they can extend up to mid-periphery or beyond and frequently are arranged in a linear configuration, called *Schlaegel lines*. Inflammatory cells are minimal in the anterior chamber or vitreous.
  - With time, these spots evolve into atrophic chorioretinal scars with pigmentation and subretinal fibrosis or napkin ring around the ON.
  - Choroidal neovascular membranes may develop in the macular area in one third of cases.
- **AMN** (acute macular neuroretinopathy)
  - AMN also occurs in young, healthy women, with acute paracentral scotomas, either unilateral or bilateral.
  - Fundus shows subtle findings: a triangular or wedge-shaped lesion around the fovea, with the tip pointing centrally.

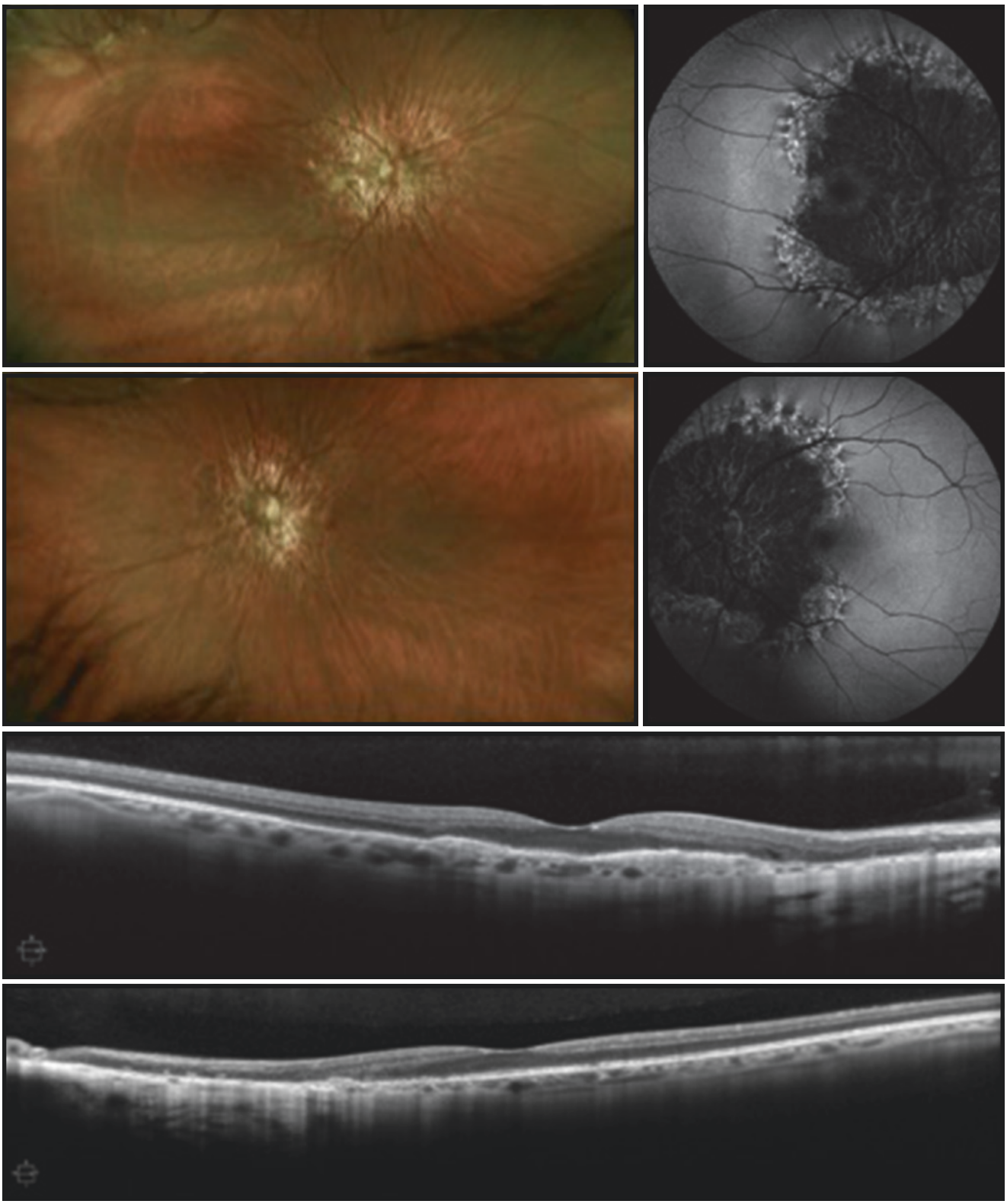

Fig. 49.3 AZOOR involving the circumpapillary area. HyperAF dots are seen at the margin of the involved area, and OCT shows thinning of the retinal pigment epithelium (RPE) and choriocapillaris (CC) layers

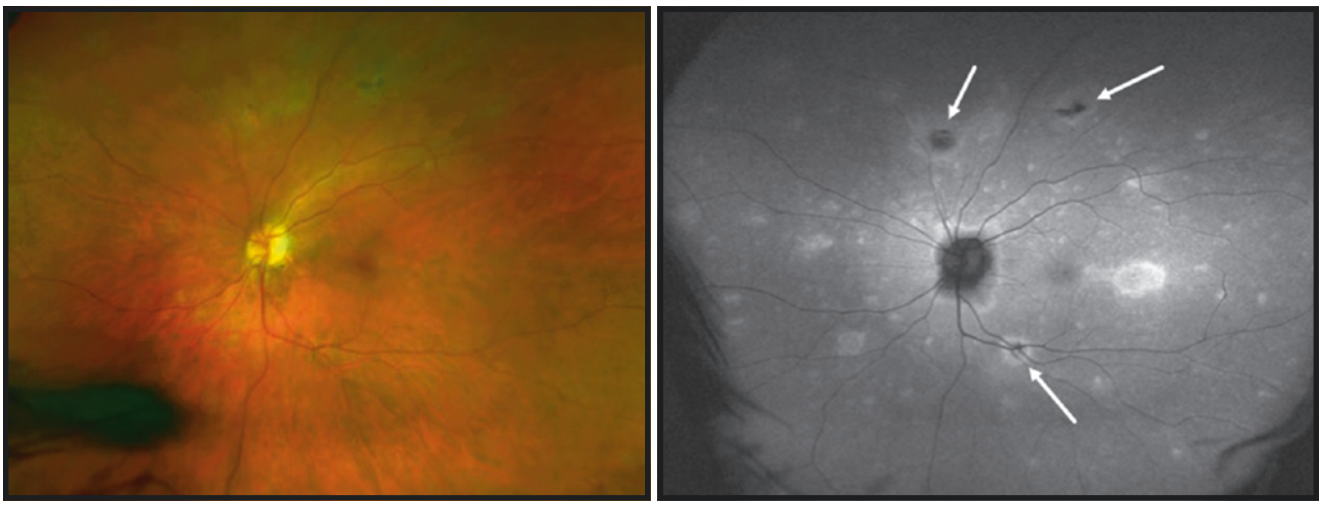

Fig. 49.4 A case of multifocal choroiditis (MFC) with punctate inner choroidopathy (PIC), showing multiple grayish, lightly pigmented lesions in the peripapillary region. They appear more widespread on FAF, with central hypoAF and a hyperAF border (*arrows*)

  - OCT shows either involvement of the inner nuclear layer (INL) (type 1) or ONL/hyperreflective band at the EZ level (type 2), probably due to ischemia of the deep capillary plexus.
  - The lesion resolves over a few weeks to months.
- **AIM** (acute idiopathic maculopathy)

  - AIM has no gender predilection. Patients are young and present with central or paracentral visual loss.
  - *Fundus:* Exudative/serous macular detachment, with mild disc swelling, hemorrhages, exudates/subretinal infiltrates, and vasculitis; mild or no inflammatory response
  - *FA:* Progressive, irregular hyperfluorescence at the RPE level, with late pooling
  - *ICG:* Early and persistent hypofluorescence
  - *Prognosis:* The lesion resolves and gives rise to a bull's-eye pattern.

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CHAPTER 50

Diffuse Unilateral Subacute Neuroretinitis (DUSN)

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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_50

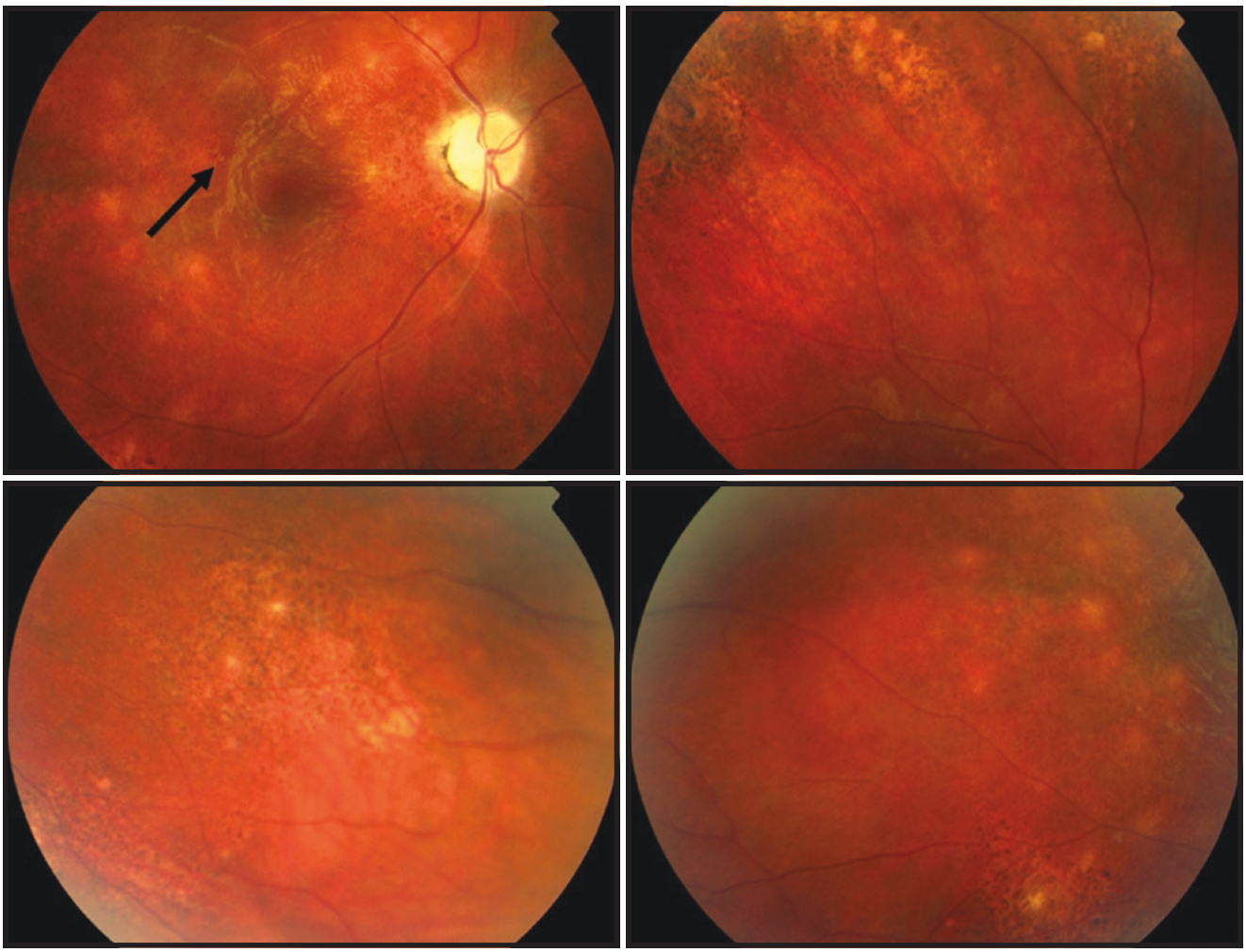

Fig. 50.1 Pigmentary Changes along with RPE atrophic patches, some are oval and some are linear, suggestive of movement tracks of live nematode

General Features

- Diffuse unilateral subacute neuroretinitis (DUSN) is caused by a subretinal live and mobile nematode.
- *Acute phase:* Patients usually present with severe pain, decreased vision, vitritis/papillitis, and tracks of grayish-white lesions—and a live nematode (Fig. 50.1).
- *Late phase:* Arterial narrowing, optic atrophy, diffuse disruption of the retinal pigment epithelium (RPE), with severe visual loss (Fig. 50.2)

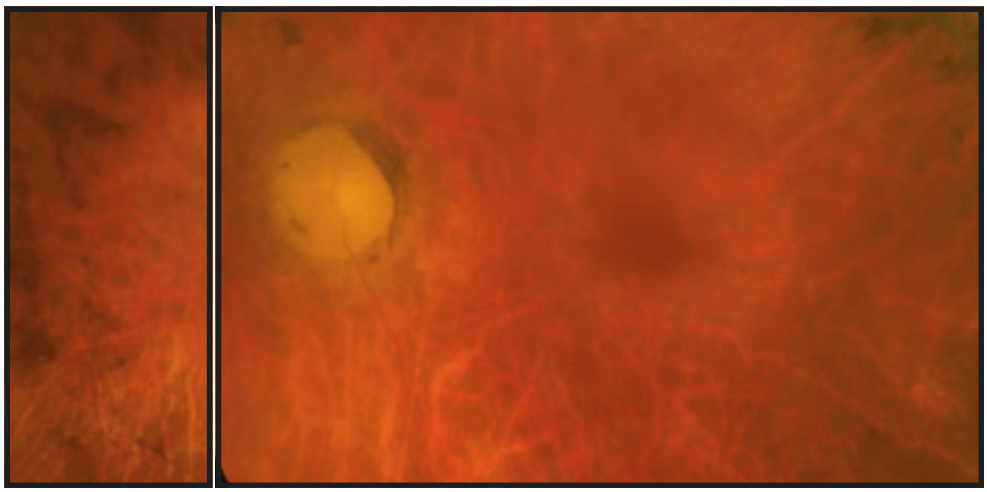

Fig. 50.2 DUSN. In the end stage, dense pigmentary changes are seen, with attenuation of vessels and optic atrophy

Suggested Reading

de Amorim Garcia Filho CA, Gomes AH, de A Garcia Soares AC, de Amorim Garcia CA. Clinical features of 121 patients with diffuse unilateral subacute neuroretinitis. Am J Ophthalmol. 2012;153:743–9.

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Section VIII
Managing IRDs in Clinics

CHAPTER 51

A Practical Approach to Retinal Dystrophies

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Genomic approaches to developing new diagnostic and therapeutic strategies in retinal dystrophies are among the most advanced applications of genetics (Tsang and Gouras 1996). The notion that "nothing can be done" for patients with retinal dystrophies is no longer true. Electrophysiological testing and autofluorescence imaging help to diagnose and predict the patient's course of disease. Better phenotyping can contribute to better-directed, cost-efficient genotyping. Combining fundoscopy, autofluorescent imaging, and electrophysiological testing is essential in approaching patients with retinal dystrophies. Emerging are new gene-based treatments for these devastating conditions.

Classification of retinal dystrophies can be confusing because they are both clinically and genetically heterogeneous (Bird 1995; Taylor and Hoyt 2005). There are several disease classification schemas; we present them as (1) stationary *versus* progressive and (2) central (macular) dystrophies *versus* generalized (Table 51.1). Important patient history includes specific symptoms such as central scotomas or night blindness, age of onset to determine severity of disease, and family history to establish the inheritance pattern. Examining other family members is often helpful. A complete past medical history and focused physical exam are important to relate systemic associations.

Examination and Testing

After a family history and clinical exam (Yannuzzi et al. 1995), the electroretinogram (ERG) is usually the first ancillary test for classifying retinal dystrophies (Berson et al. 1968). Full-field ERG is a noninvasive test of retinal function that measures mass response electrical activity after light stimulation and helps to exclude generalized retinal dysfunction. Full-field ERGs are performed on patients with dilated pupils using standards published by the International Society for Clinical Electrophysiology of Vision (ISCEV) (International Society for Clinical Electrophysiology of Vision. Standards, recommendations and guidelines 2007). The minimum protocol incorporates the rod-specific (Fig. 51.1, Column 1) and standard bright-flash ERGs (Fig. 51.1, Column 2), both recorded after a minimum of 20 min dark adaptation, and the photopic 30 Hz flicker (Fig. 51.1, Column 3) and transient photopic ERGs (Fig. 51.1, Column 4), both recorded after a standard period and intensity of light adaptation (Heckenlively and Arden 2006).

Though full-field ERG evaluates mass cone and rod system function, pattern ERG (checkerboard stimulus) is useful to distinguish decreased vision secondary to optic nerve disease *versus* macular disease (Holder 2001). An electrical response in a 30-Hz flicker ERG is an important prognostic tool because its presence confirms residual cone function (Berson 1993, 1974).

Scanning laser ophthalmoscopy (SLO) autofluorescence is a noninvasive imaging technique that detects the lipophilic cation N-retinyl-N-retinylidene ethanolamine (A2E) (a by-product of the visual cycle) in lipofuscin fluorophores, which accumulates in the retinal pigment epithelium (RPE) (Delori et al. 1995; Sparrow and Boulton 2005; von Ruckmann et al. 1995). Hypofluorescent or hyperfluorescent areas in SLO images are associated with abnormal accumulation or depletion of A2E fluorophore in RPE. Besides diagnosing malfunctioning RPE cells, using autofluorescence to follow patients with pathology can frequently predict their clinical course (Robson et al. 2004, 2003).

Stationary Retinal Dystrophies

It is important to distinguish stationary *versus* progressive disease because the patient's primary concern is whether sight will deteriorate. There are two common forms of stationary night blindness and several forms of stationary cone dysfunction syndrome.

Stationary Rod Dystrophies

Congenital stationary night blindness (CSNB), although most commonly inherited as an X-linked recessive (XLR) disorder, can also demonstrate autosomal dominant (AD) or autosomal recessive (AR) inheritance. All modes of inheritance result in normal-appearing fundi. The AR XLR forms of CSNB present in infancy with nystagmus, strabismus, and reduced vision. In contrast, the AD form of CSNB typically presents in teenage years with normal visual acuity and symptomatic night blindness (Salchow et al. 1999; Tsang et al. 1998, 2006a, b).

Because fundoscopy is normal in CSNB, ERG is important in making the diagnosis (Tsang et al. 2006b), as it detects severe dysfunction and an electronegative waveform (*see* Fig. 51.1 and Table 51.2). The defect in X-linked complete CSNB has been suggested to lie downstream from the photoreceptor neurons, possibly in the ON bipolar cells or their interconnections (Hood and Birch 1996). Visual acuity (VA) is diminished in X-linked CSNB patients because their ON bipolar cells fail to have proper interpretation of photoreceptor signal to noise.

Distinctive radial flecks in the retina characterize another form of night blindness, fundus albipunctatus, caused by delayed rhodopsin regeneration. Although usually stationary, there is a subtype of fundus albipunctatus associated with progressive cone dysfunction (Nakamura et al. 2000). Patients have discrete white flecks at the level of the RPE, most numerous in the midperiphery. Either patients present with night blindness, or the flecks are found on routine ophthalmoscopy. Fundus albipunctatus can be confused with retinitis punctata albescens, a form of

Table 51.1 Some genes implicated in inherited retinal degeneration

Stationary retinal dystrophies			***Central retinal dystrophies***		
Disease	**Gene**	**Protein**	**Disease**	**Gene**	**Protein**
Achromatopsia	*CNGA3*	Alpha subunit of cone cGMP-gated channel	Best disease	*VMD2*	Bestrophin
	CNGB3	Beta subunit of cone cGMP-gated channel	Doyne honeycomb retinal dystrophy	*EFEMP1*	EGF-containing fibrillin-like extracellular matrix protein 1
	GNAT2	Alpha subunit of cone transducin	North Carolina macular dystrophy	*MCDR1*	Unknown gene on chromosome 6
CSNB (dominant)	*GNAT1*	Alpha subunit of rod transducin	Sorsby fundus dystrophy	*TIMP3*	Tissue inhibitor of metalloproteinase-3
	PDE6B	Beta subunit of rod cGMP-PDE	Stargardt disease	*ABCA4*	ATP-binding cassette transporter
	RHO	Rhodopsin	Stargardt-like dominant macular dystrophy	*ELOVL4*	Elongation of very long chain fatty acid protein
CSNB (XL complete)	*NYX*	Nyctalopin	***Progressive generalized dystrophies (functional class)***		
CSNB (XL incomplete)	*CACNA1F*	Alpha1 subunit of Cav1.4 calcium channel	Juvenile retinoschisis	*XLRS1*	Retinoschisin
Fundus albipunctatus	*RDH5*	11-*cis* retinol dehydrogenase	Autosomal dominant RP	*RP1*	RP1
Oguchi disease	*GRK1*	G-protein coupled receptor kinase 1		*PRPF31, PRPF3, and PRPF8*	Pre-mRNA processing factor
	SAG	Arrestin		*RHO*	Rhodopsin
Early onset progressive retinal dystrophies			Autosomal recessive RP	*CNGA1*	Alpha subunit of rod cGMP-gated channel
Leber	*AIPL1*	Aryl hydrocarbon receptor interacting protein like-1		*CNGB1*	Beta subunit of rod cGMP-gated channel
	CRB1	Crumbs homolog 1		*PDE6A*	Alpha subunit of PDE
	CRX	Cone-rod homeobox		*PDE6B*	Beta subunit of PDE
	GUCY2D	Retinal guanylate cyclase		*RHO*	Rhodopsin
	RDH12	Retinal dehydrogenase 12		*SAG*	Arrestin
	RPE65	RPE-specific protein, 65 kD		*CNGA1*	Alpha subunit of rod cGMP-gated channel
	RPGRIP1	RP GTPase interacting protein 1		*CNGB1*	Beta subunit of rod cGMP-gated channel
	CEP290	Centrosomal protein		*USH2A*	Usherin

Mutations in structural proteins and transcription factors tend to cause dominant disease; abnormalities in metabolic enzymes tend to cause recessive diseases

retinitis pigmentosa (RP) with white spots on fundus exam. ERG recovers after prolonged dark adaptation in fundus albipunctatus because it allows the delayed rhodopsin regeneration to recover.

Stationary Cone Dysfunction Syndromes

There are three categories of individuals with congenital achromatopsia (Michaelides et al. 2004):

- Typical rod monochromats (complete achromats) lack all sensitivity mediated by cone pigments.
- Atypical rod monochromats (incomplete achromats) have some residual cone function and thus better VA and residual color vision.
- S-cone monochromats have rod and blue-cone function; these patients have better VA than either type of rod monochromat.

The two types of achromatopsia, complete and incomplete, are both autosomal recessive and have normal rod function.

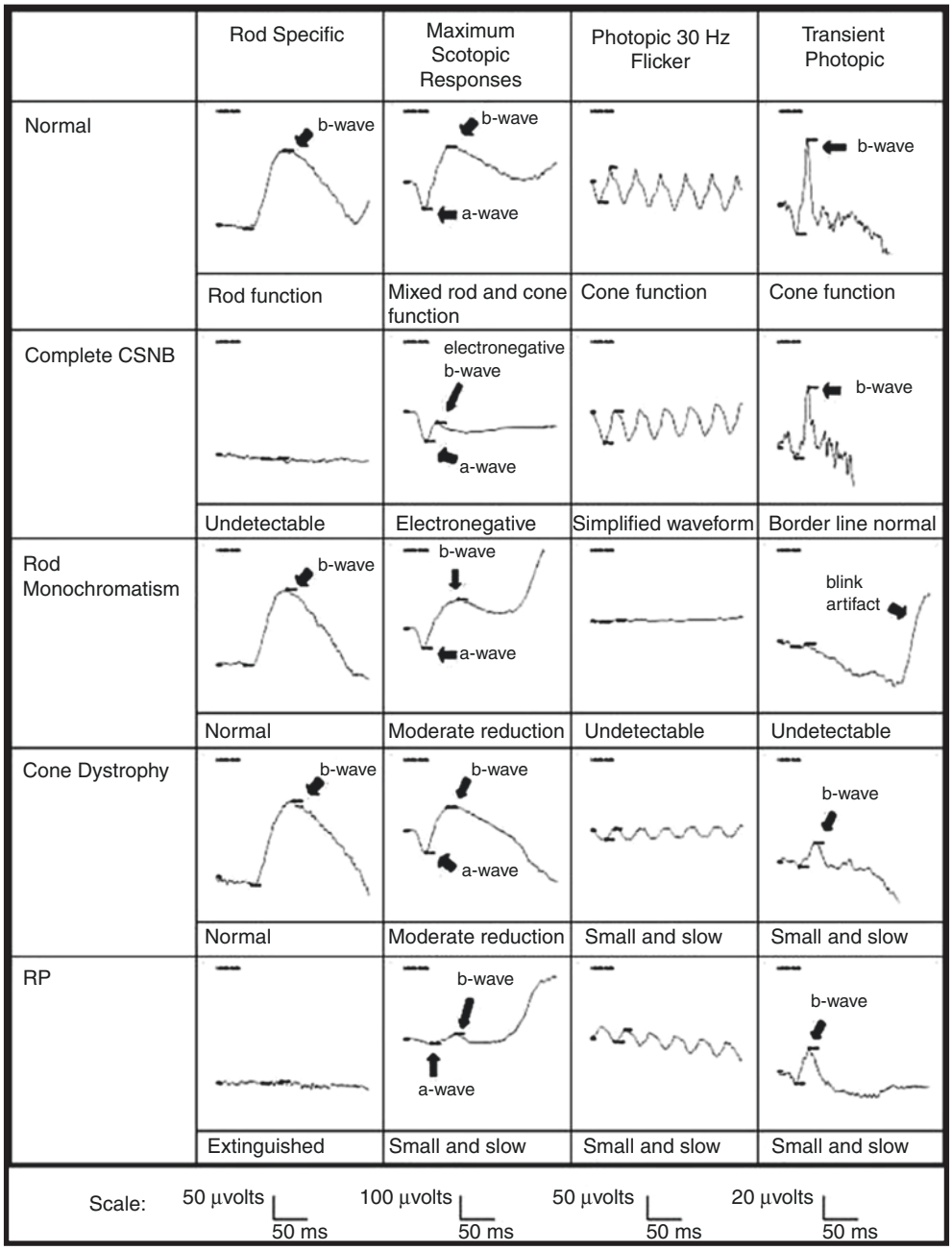

Fig. 51.1 Electroretinogram (ERG) testing. Full-field ERG measures mass response of the retina: photoreceptor (a-wave) and inner nuclear layers (b-wave). Full-field electroretinogram was performed using Dawson, Trick, and Litzkow recording electrodes and Ganzfeld stimulation according to International Society for Clinical Electrophysiology of Vision (ISCEV) standards. ERG tracings from a normal 40-year-old individual are shown in the top row. Typical tracings from different patients at 40–50 years of age are shown in other rows. RP retinitis pigmentosa

Table 51.2 Inherited causes of electronegative (b-wave negative) ERG

Congenital stationary night blindness
X-linked retinoschisis
Inner retinal dystrophy
Batten disease
Duchenne muscular dystrophy

Patients usually present in infancy with nystagmus, poor vision, and a preference for dim illumination. Because of the sensory nystagmus, CSNB, foveal hypoplasia, optic nerve hypoplasia, and cone dystrophy are in the differential. Extinguished-cone ERGs in achromatopsia help to establish this nonprogressive dystrophy.

Clinically, S-cone monochromatism presents like the other achromatopsias, with nystagmus and photophobia during infancy, but the disease is less severe. Family history can help distinguish this entity, because S-cone monochromatism is X-linked recessive, whereas the other achromatopsias are autosomal recessive. Special color testing or an ERG at a specified wavelength (440 nm) are useful diagnostic tools when interpreted in the correct clinical context (Michaelides et al. 2003, 2005).

Progressive Retinal Dysfunction

Retinitis pigmentosa (RP), also known as *rod-cone dystrophy*, has both genetic and allelic heterogeneity (Figs. 51.2 and 51.3) (Daiger et al. 2007). RP inheritance can be autosomal dominant, autosomal recessive, or X-linked recessive, and there is genetic heterogeneity even within each group. Retinal degeneration slow (RDS) protein and retinal-specific adenosine triphosphate (ATP)-binding cassette transporter (ABCA4) are examples of allelic heterogeneity in that they can cause macular dystrophy in some patients and cone-rod dystrophy in others.

Approximately 50% of patients have no family history of RP (termed *simplex RP*) or evidence of parental consanguinity; many of these cases are likely to be autosomal recessive, but some may be males who have X-linked disease from female carriers. Others may be new AD mutations or manifestations of AD disease with reduced penetrance. Accurate genetic counseling depends on identifying the causative mutation and mode of inheritance.

The age of onset of RP is variable, and patients do not always present with the classic triad of intraretinal pigment migration, optic nerve pallor, and attenuated vessels (Fig. 51.3). In general, patients who develop symptoms at younger ages have worse prognoses, and AD disease has a less severe natural history with later onset than XLR and AR variants. In RP, normal VA and smaller, higher-density autofluorescent rings correlate with worse pattern ERGs, representing a shrinking area of photoreceptor function as the disease progresses (Robson et al. 2004, 2003). In time, VA declines, visual fields coalesce to give the classic peripheral ring scotoma, and posterior subcapsular cataracts or cystoid macular edema (CME) may develop (Fig. 51.3).

Enhanced S-cone, also known as Goldmann-Favre syndrome, is a subtype of AR RP featuring larger photopic single-flash ERG a-wave than 30-Hz b-wave amplitudes. Patients also have supernormal S-cone function due to an increased number of S-cones, low numbers of L-cones and M-cones, and a lack of rods (Greenstein et al. 1996; Milam et al. 2002; Sharon et al. 2003). Goldmann-Favre is one of the most frequently described hereditary vitreoretinal disorders (Table 51.3). Although the fundus appearance is variable, patients may have deep, nummular-shaped RPE clumping in the mid-periphery, with central or peripheral retinoschisis.

Choroideremia is an XLR rod-cone dystrophy that has marked atrophy of the choroid and RPE but does not feature intraretinal pigment migration (MacDonald et al. 2004). It is important to distinguish carriers of this trait from carriers of

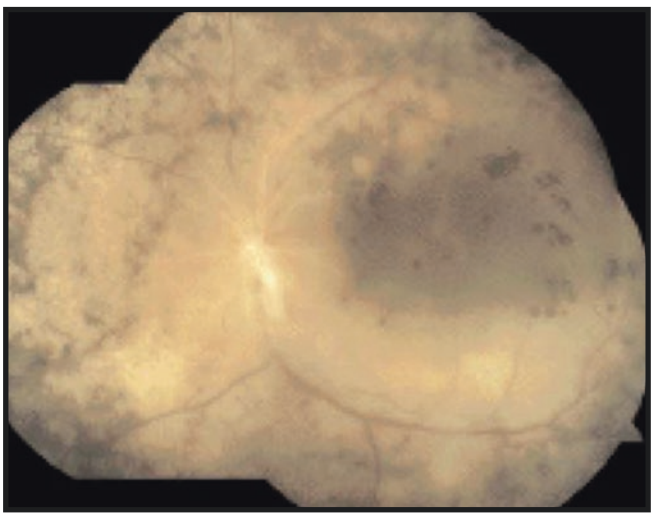

Fig. 51.2 Leber congenital amaurosis at its end stage in a 37-year-old woman with retinal pigment epithelium (RPE) migration, near-total loss of RPE cells, severe retinal atrophy, and peripapillary ghost vessels in her left eye. She retains light perception vision and has an extinguished full-field ERG response

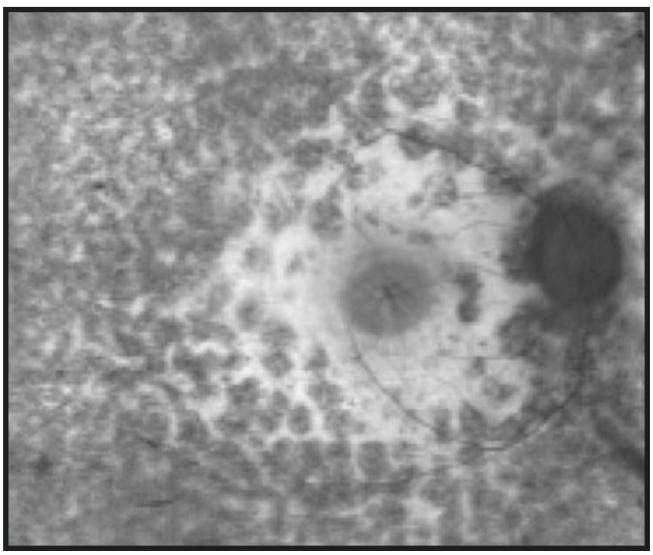

Fig. 51.3 Usher syndrome in a 34-year-old woman. Autofluorescence of the right eye shows RPE atrophy under degenerated rods. Note the cystoid macular edema, a common complication of rod-cone dystrophies

Table 51.3 Hereditary vitreoretinal disorders
X-linked juvenile retinoschisis
Goldmann-Favre syndrome
Wagner disease
Stickler syndrome
Familial exudative vitreoretinopathy
Autosomal dominant neovascular inflammatory vitreoretinopathy (large Iowan pedigree)
Autosomal dominant vitreoretinochoroidopathy

X-linked RP (XLRP) because they have similar fundi, but the prognosis for affected children is different (Fig. 51.4). Boys with XLRP are more severely impaired than those with choroideremia. The distinction can be made with ERG of their mothers at childbearing age: carriers of choroideremia are normal, whereas carriers of XLRP are often abnormal and sometimes asymmetrical (Berson et al. 1979).

Gyrate atrophy, an AR dystrophy, is part of the differential diagnosis of choroideremia. The characteristic fundus appearance of gyrate atrophy is hyperpigmented fundi with lobular loss of the RPE and choroid starting in the periphery. A defect in ornithine aminotransferase, which results in a tenfold increase in plasma ornithine, causes the disease. Although a diet restricted in arginine limits the disease (Kaiser-Kupfer et al. 2004), the diet is difficult to maintain and requires careful monitoring. Vitamin B6 lowers plasma ornithine levels in some patients.

Other well-known types of syndromic RP include Alström syndrome, Kearns-Sayre syndrome, Refsum syndrome, Werner syndrome, Cockayne syndrome, Flynn-Aird syndrome, Bardet-Biedl syndrome, Usher syndrome, Joubert syndrome, Batten disease, Zellweger syndrome, and spinocerebellar ataxia.

There are also progressive cone dystrophies, which, in contrast to the stationary cone dysfunction syndromes discussed above, usually present in older childhood or adulthood (Kurz-Levin et al. 2002). Patients' presenting symptoms are decreasing VA and color vision. In the late stages, fundus exam may show a typical bull's eye maculopathy, but subtle cases can be picked up earlier with ERG and occasionally autofluorescence imaging (Fig. 51.1) (Simunovic and Moore 1998).

Progressive cone-rod dystrophies (Simunovic and Moore 1998; Gouras et al. 1983) show the clinical features of cone dystrophy early on; eventually, rod involvement with associated night blindness becomes evident (Holopigian et al. 2004; Michaelides et al. 2006). There are reports of AD, AR, and XLR inheritance. The fundus exam progresses from macular atrophy in the early stages to peripheral retinal pigmentation, arteriolar attenuation, and optic nerve pallor in the later stages.

A number of acquired disorders with an abnormal ERG can phenocopy retinal dystrophies. These include cancer-associated retinopathy (CAR), melanoma-associated retinopathy, acute

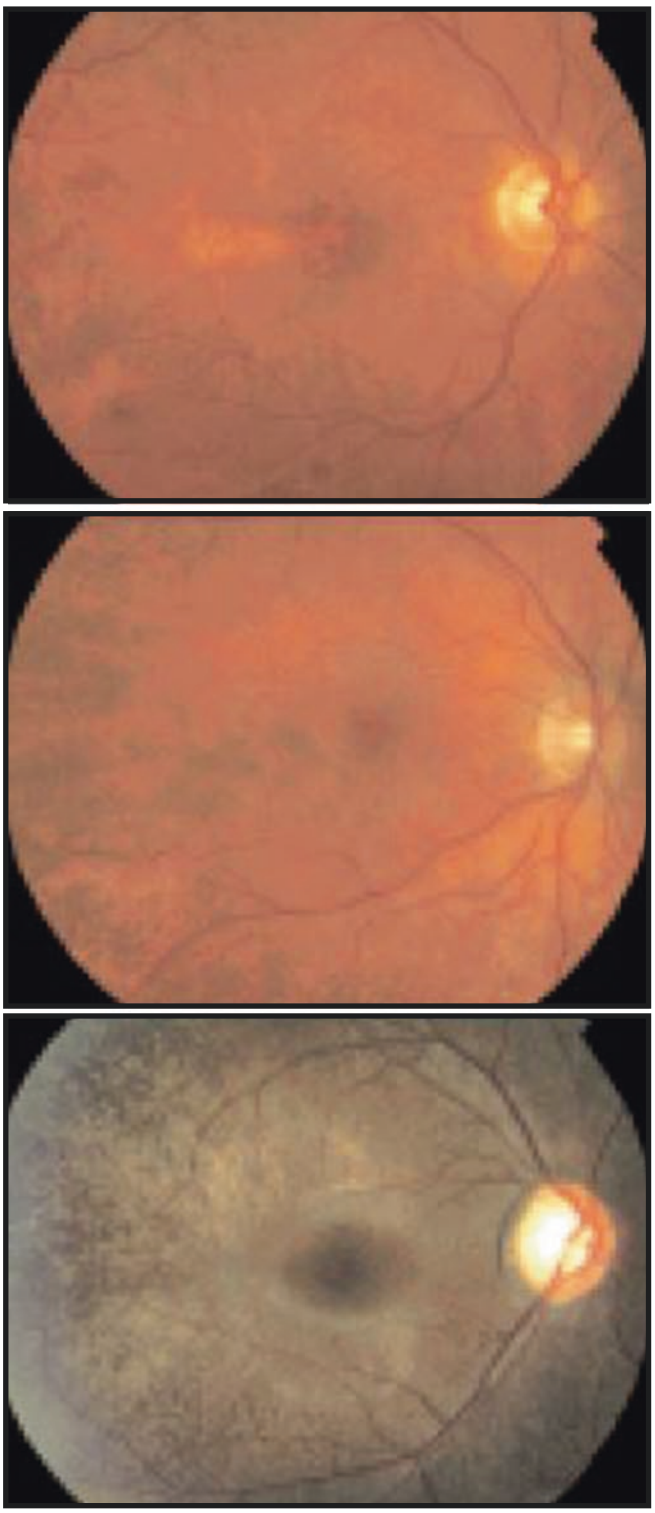

Fig. 51.4 Fundus photographs. (**Top**) Choroideremia carrier with RPE mottling. (**Middle**) Ocular albinism carrier with radially oriented mosaic RPE hypopigmentation. (**Bottom**) X-linked recessive RP carrier with a tapeto-like retinal sheen. Correct diagnosis in X-linked heterozygous carriers is important, but fundus distinctions may be subtle

zonal occult outer retinopathy, diffuse unilateral subacute neuroretinitis, syphilis, foreign body, drug toxicity, and trauma. Clinical history and/or unilateral presentation distinguish these entities from inherited retinal dystrophies.

Central Dystrophies

In general, only the ERG can establish the functional phenotype in patients with maculopathy. In contrast to global retinal diseases and cone-predominant degenerations, central or macular dystrophies have normal full-field ERG implicit time responses and normal peripheral visual fields. Macular dystrophies cause a reduction in central vision, but they usually progress slowly and patients retain some central vision. Thus, most individuals with central dystrophies can enjoy normal activities of daily living (unlike those with progressive, generalized, degenerative dystrophies).

A review of patients with bull's eye lesions showed normal full-field ERGs in most cases. Others showed cone dystrophy, cone-rod dystrophy, or rod-cone dystrophy, but the functional phenotype could not be established by fundus appearance (Kurz-Levin et al. 2002). Similarly, the functional phenotype in Stargardt disease could not be predicted from the fundus phenotype; only the ERG was concordant within affected families, and only the ERG gave prognostic information regarding retention of peripheral vision.

Central dystrophies appear in childhood or early adulthood. Discussed here are Stargardt disease, pattern dystrophy, Best disease, Sorsby pseudoinflammatory disease, and Doyne honeycomb retinal dystrophy.

Stargardt Disease

The most common form of inherited juvenile macular degeneration is Stargardt disease. Classically, Stargardt patients present in childhood with decreased central vision, foveal atrophy, and yellow pisciform flecks at the level of the RPE in the macula. Stargardt and fundus flavimaculatus are manifestations of the same genetic disorder, due to a recessive defect in the *ABCA4* gene (Allikmets et al. 1997). Stargardt patients should avoid a diet high in vitamin A, because the defective gene (*ABCA4*) encodes for a transmembrane transporter of A2E intermediates, a toxic by-product of vitamin A (Koenekoop 2003).

At least 80% of Stargardt patients have a "silent choroid," which is a dark choroid on fluorescein angiogram. A2E accumulation in the RPE causes this phenomenon (Bui et al. 2006). Stargardt patients' functional phenotypes may not be predictable from fundus exam, but ERG can help prognose peripheral vision of patients by dividing them into three groups:

- Type 1 patients (Figs. 51.5 and 51.6) have a normal full-field ERG.
- Type 2 patients have more loss of photopic function.
- Type 3 patients (Fig. 51.7) have both abnormal scotopic and photopic ERG, with a worse prognosis (Lois et al. 2001).

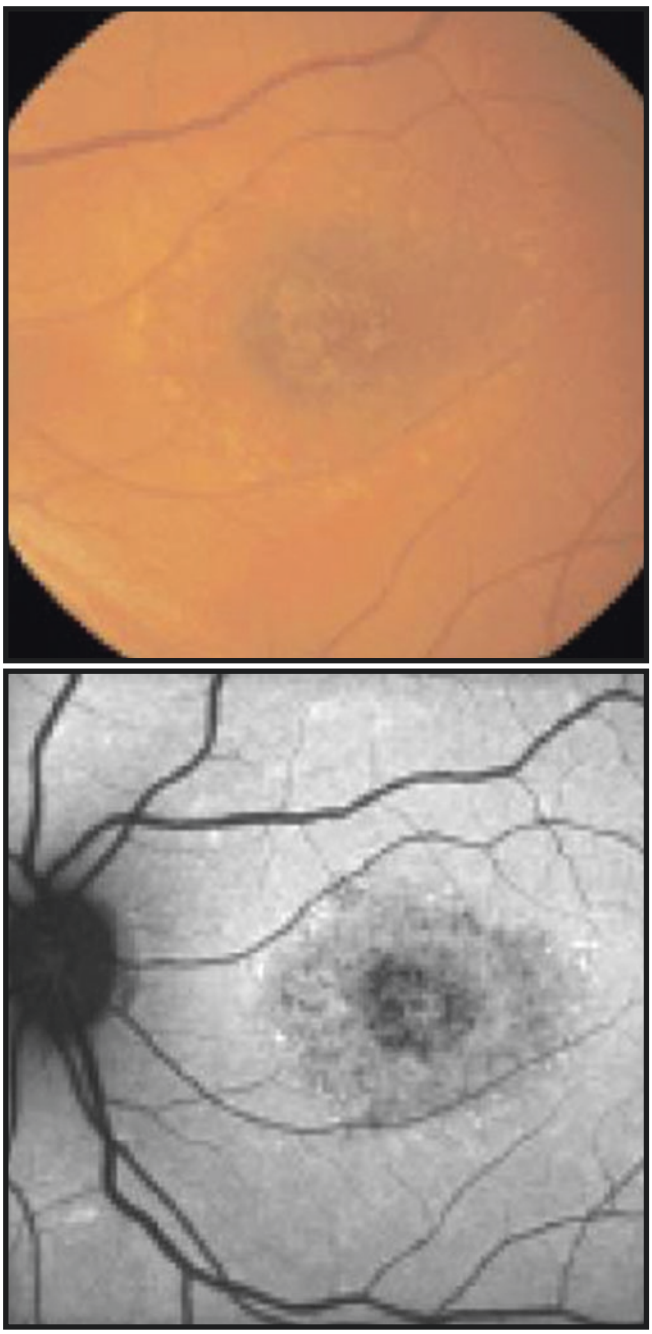

Fig. 51.5 Group 1 Stargardt disease in a 36-year-old woman. (**Top**) Color fundus photograph of the left eye shows macular flecks with a classic beaten bronze appearance. (**Bottom**) Autofluorescence of the same eye shows hyperfluorescent flecks and hypofluoresent, diseased RPE. This patient has extinguished P50 responses on pattern ERG and normal full-field ERG responses

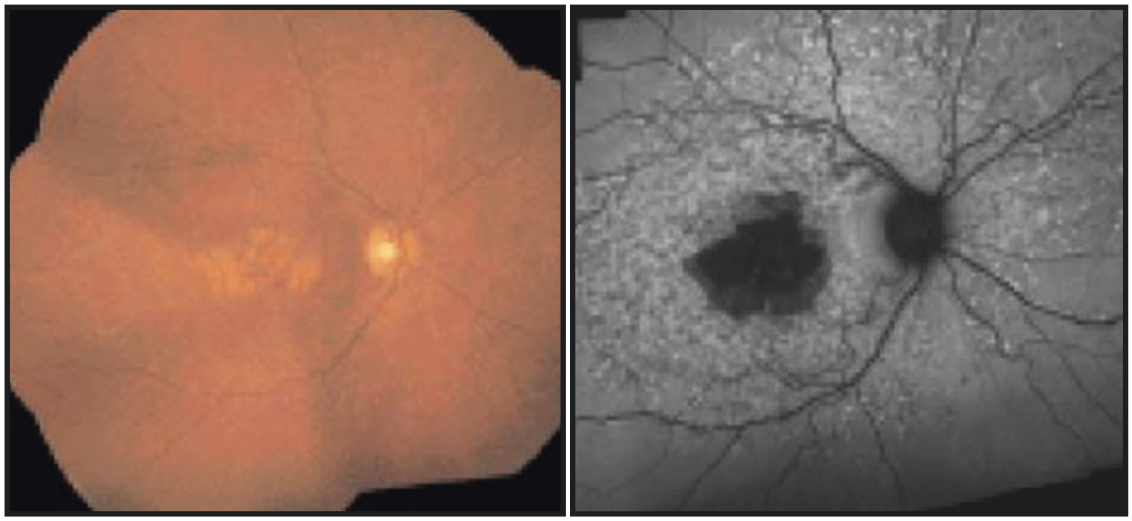

Fig. 51.6 Group 1 Stargardt disease in a 36-year-old man. Color fundus photograph of the right eye with macular atrophy and generalized flecks (*left*) and corresponding autofluorescent imaging (*right*) shows RPE atrophy (hypofluorescence) centrally and hyperfluorescent flecks. This patient has extinguished P50 responses and normal full-field ERG responses

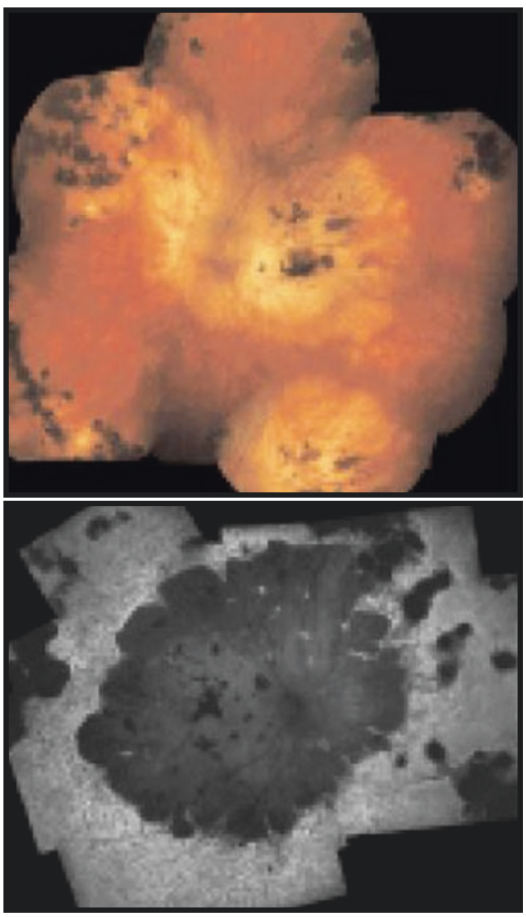

Fig. 51.7 Group 3 Stargardt disease in a 57-year-old woman with bilaterally symmetric disease. (**Top**) Color fundus photo of the left eye, with large areas of atrophic retina and pigment clumping. (**Bottom**) Autofluorescence of the right eye with a large area of missing RPE and generalized hyperfluorescent flecks peripherally. Both her scotopic and photopic ERG responses are diminished

It is important to subtype Stargardt patients for better counseling regarding their prognoses. Fundus flavimaculatus frequently manifests as type 1 Stargardt disease. Macular autofluorescence is usually abnormally high in Stargardt patients, but normal levels of lipofuscin could also indicate late disease in which the RPE cells have burnt out (Lois et al. 2004).

Other Central Dystrophies

Pattern dystrophies are a group of heterogeneous diseases that are caused by a defect in the *RDS* gene (Francis et al. 2005) and other genes. There are four recognized types, based on fundoscopic appearance: adult-onset vitelliform, butterfly, reticular, and fundus pulverulentus (Fig. 51.8). They present in adulthood with decreased vision and can be mistaken for age-related macular degeneration (AMD) (Daniele et al. 1996).

Best disease, or vitelliform dystrophy, is an AD maculopathy caused by a defect in the bestrophin gene. The yolk-like yellow lesion is autofluorescent and usually bilateral (Fig. 51.9). Vision is good during this initial stage but decreases during the scrambled-egg stage or secondary to geographic atrophy in the later stages. In addition, about 20% of patients develop a choroidal neovascular membrane, which, although self-limited, causes poorer vision. Electro-oculogram (EOG) shows a reduced light rise in Arden ratio in affected Best disease as well as AD vitreoretinochoroidopathy (ADVIRC). EOG is mildly subnormal or normal in adult vitelliform macular dystrophy. Best disease and ADVIRC (both caused by bestrophin gene defects) are examples of allelic heterogeneity, whereas Best disease and adult vitelliform macular dystrophy are examples of genetic heterogeneity.

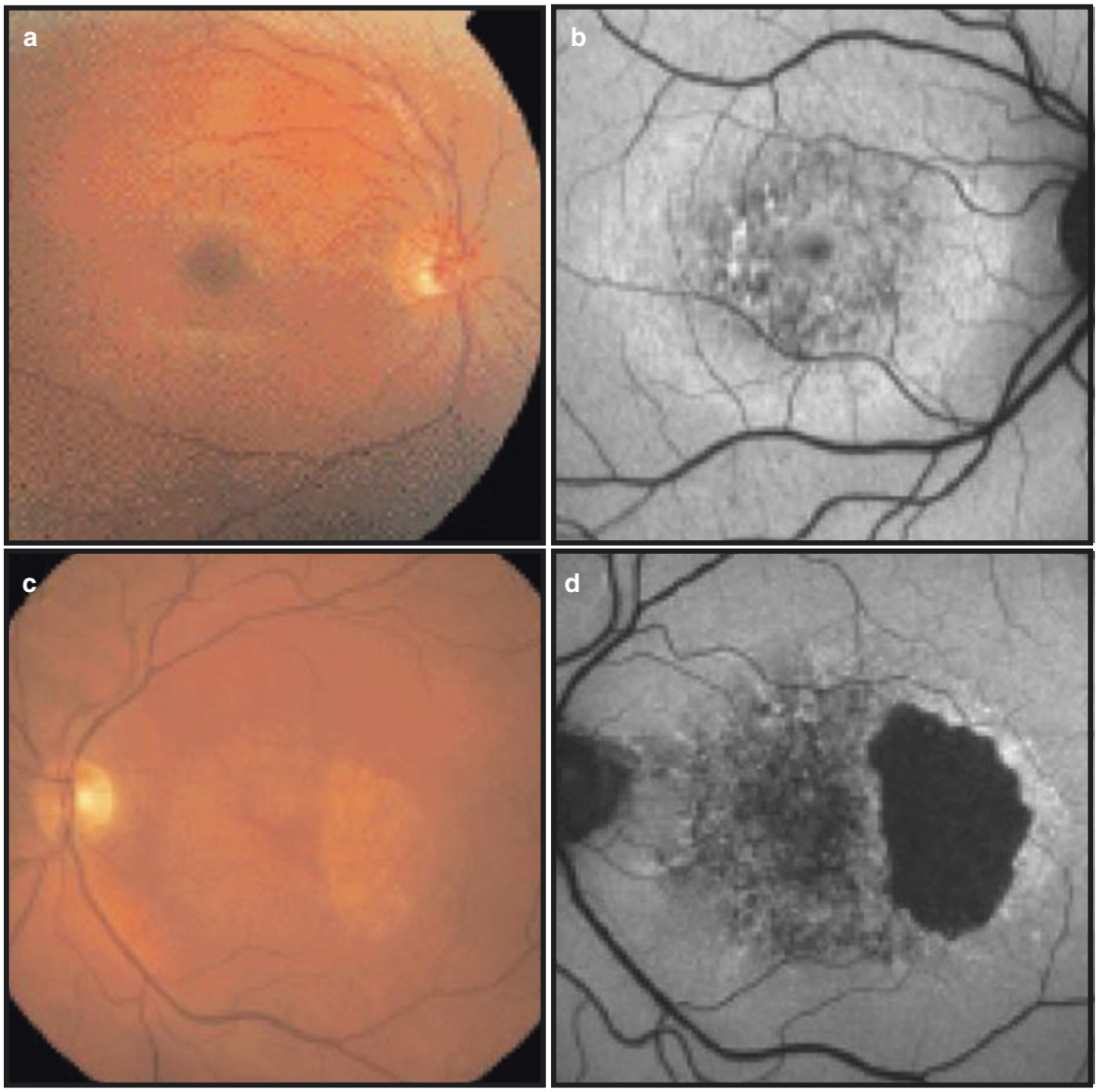

Fig. 51.8 Pattern dystrophy in a 26-year-old woman with 20/15 visual acuity in each eye. (**a**), Color fundus photograph of the right eye with subtle RPE irregularities in the macula. (**b**), Corresponding autofluorescence with speckled hyperfluorescence. (**c**, **d**) Her father had a larger area of RPE atrophy seen on a color fundus photograph of the left eye and corresponding autofluorescence. He had 20/40 vision in each eye

Sorsby macular dystrophy, a dominantly inherited disease with a defect in the tissue inhibitor of the metalloproteinase-3 gene, leads to eventual bilateral subfoveal choroidal neovascularization, although the disease may progress asymmetrically (Fig. 51.10). Beginning around the fifth decade of life, patients present with complaints of problems transitioning between light and dark, followed by central-vision abnormalities. Early on, fine drusen accumulate in the macula, and they later develop a pseudoinflammatory appearance, which may be misdiagnosed as punctate inner choroidopathy (Atan et al. 2004). Individuals with Sorsby have normal pattern ERGs until neovascularization develops.

Doyne honeycomb retinal dystrophy (malattia Leventinese) is a dominantly inherited dystrophy with drusen-like deposits in the macula and peripapillary retina. It can be mistaken for AMD

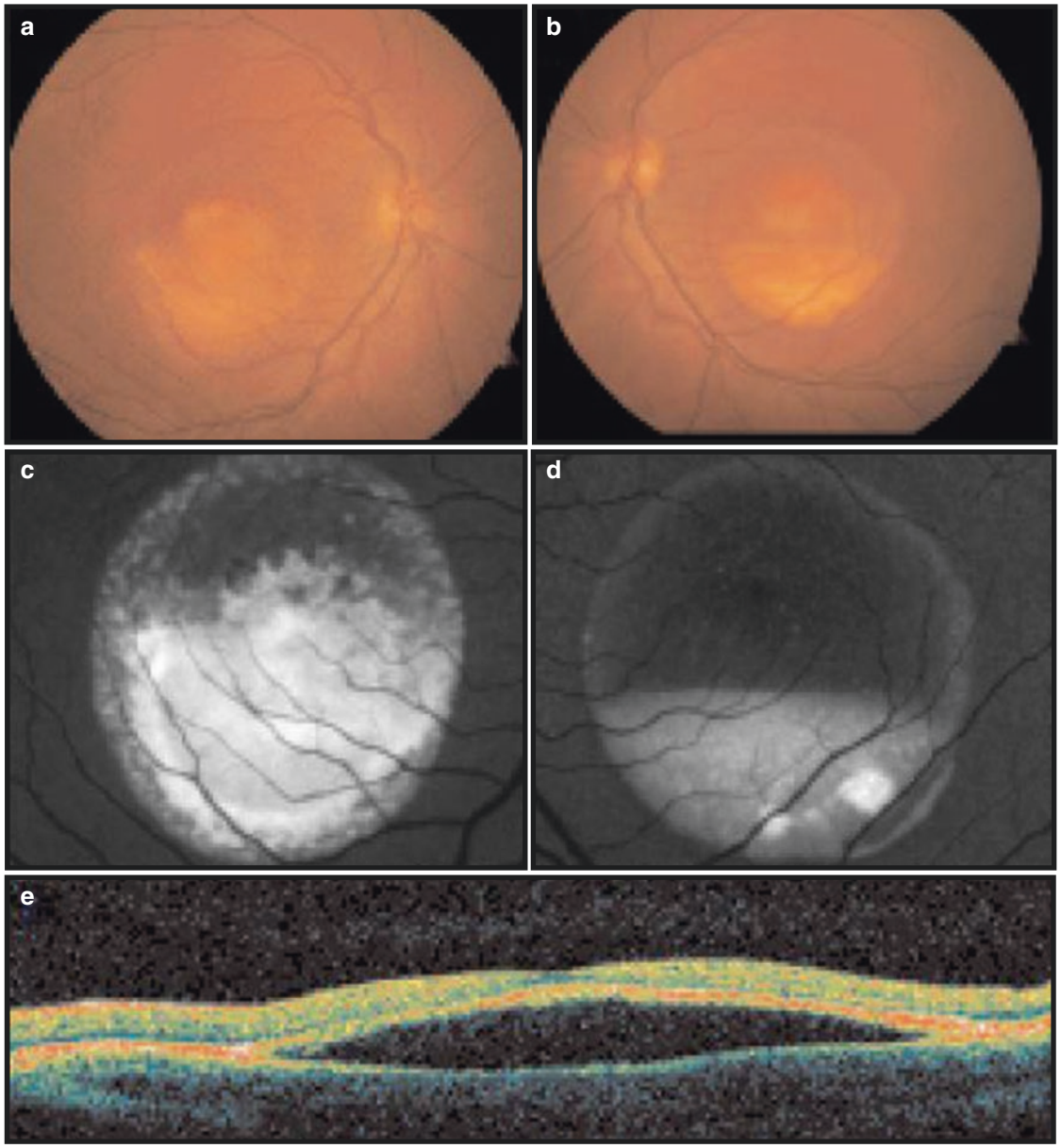

Fig. 51.9 Best vitelliform dystrophy in an 18-year-old man. Color fundus photo of the left eye (**a**) and right eye (**b**) with resolving egg-yolk lesion. Autofluorescence of the left eye (**c**) and right eye (**d**) with corresponding hyperfluorescence. Optical coherence tomography (**e**) shows splitting of the RPE layer with elevation. Visual acuity is 20/200 OD and 20/20 OS

but is distinguished by its characteristic finding of nasal drusenoid material and autofluorescence (Gregory et al. 1996). Individuals with Doyne honeycomb retinal dystrophy have normal full-field ERG responses.

North Carolina macular dystrophy is AD with complete penetrance. Initially, researchers hypothesized that the genetic defect originated from a single family, but the disease is actually present in many distinct genealogies. The clinical appearance is bilateral drusen and macular changes in a young child that may resemble a macular coloboma or staphyloma (Fig. 51.11) (Traboulsi 1998). Despite the severe-appearing fundus, the visual prognosis is good, and the disease is nonprogressive. Individuals with North Carolina macular dystrophy have normal full-field ERG recordings.

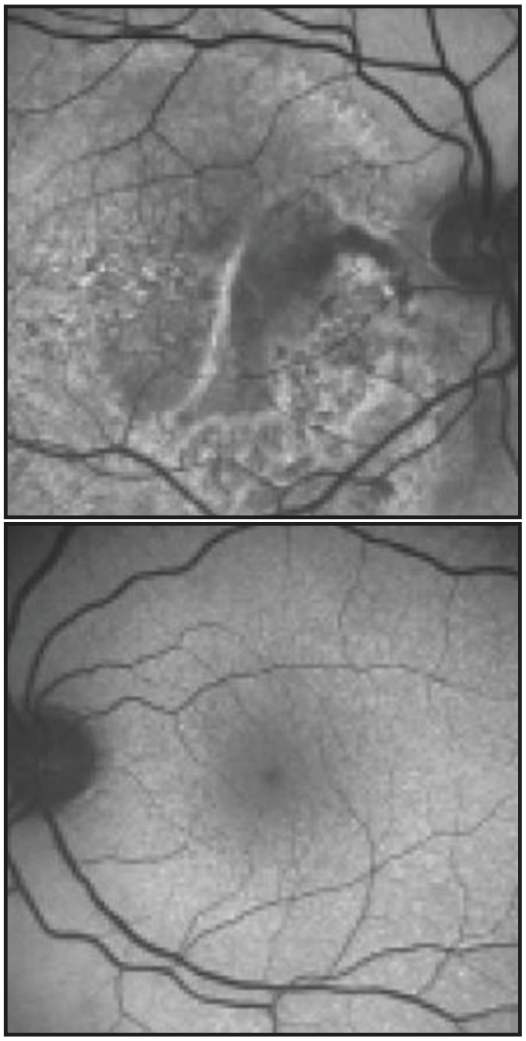

Fig. 51.10 Sorsby pseudoinflammatory dystrophy in a 53-year-old man with asymmetric disease who has an RPE tear in the right eye (count-finger vision) (**Top**) secondary to choroidal neovascularization (CNV), and fine drusen-like deposits in the left eye (20/20 visual acuity) on autofluorescence (**Bottom**)

Treatments

Dietary Treatment and Vitamins

It is important to recognize gyrate atrophy, Refsum syndrome, and abetalipoproteinemia because they are three types of retinal dystrophies that dietary treatment can help. The main clinical manifestations of Refsum syndrome are RP, cataracts, chronic polyneuropathy, cerebellar ataxia, and cardiac arrhythmias. Elevated serum phytanic acid levels are diagnostic. Avoiding foods high in phytanic acid (*eg*, fat and butter) and plasmapheresis help to improve all neurologic signs (Claridge et al. 1992; Leroy et al. 2003).

Bassen-Kornzweig syndrome (abetalipoproteinemia) is due to malabsorption of cholesterol, fats, and fat-soluble vitamins from the small intestine. Deficiencies of vitamin A and vitamin E cause failure to thrive, peripheral neuropathy with muscle weakness, spinocerebellar ataxia, and RP. Vitamin A (300 IU/kg/day) and vitamin E (100 IU/kg/day) restore function and slow the progression of retinal degeneration (Grant and Berson 2001).

There is also interest in whether vitamin A supplementation can help other forms of RP. A study in two mouse RP models with different alleles showed that vitamin A supplementation decreased the rate of photoreceptor degeneration caused by a class II rhodopsin mutation (*T17M*, defective in thermal stability/folding and cannot easily reconstitute with 11-cis-retinal), but it did not help the mice with a class I rhodopsin mutation (*P347S*, defective in outer-segment localization). It was hypothesized that vitamin A supplementation may work by stabilizing mutant opsins through increased availability of the chromophore (Li et al. 1998). Therefore, vitamin A may benefit a subset of patients with RP.

A randomized controlled study sponsored by the National Institutes of Health (NIH) looking at vitamin therapy for RP in adults showed that vitamin A (15,000 IU) delays the progression of cone ERG loss. The same study showed that vitamin E (400 IU) may have a deleterious effect on RP patients (Berson et al. 1993). These results have not been universally accepted in ophthalmic centers (Norton 1993). Subgroup analysis revealed that patients who started taking docosahexaenoic acid (1200 mg/day) at the same time as vitamin A may have a modest additional benefit of slowing RP (Berson et al. 2004). A safety study did not find substantial side effects of high-dose vitamin A therapy (Sibulesky et al. 1999). Currently, the NIH recommends that adult RP patients take a supplement of 15,000 IU of vitamin A daily under the supervision of an ophthalmologist and avoid use of high-dose vitamin E supplements (National Eye Institute. Information for doctors who follow patients with retinitis pigmentosa 2007).

Treatment of Complications

Physicians should follow RP patients at infrequent but regular intervals to detect treatable complications such as posterior subcapsular cataract, macular edema, and the rare autoimmune reaction. Cataract extraction can improve visual perception and brightness. CME can be treated with oral acetazolamide or topical carbonic anhydrase inhibitors (Fishman and Apushkin 2007). RP patients with a rapid progression of visual symptoms and ERG progression should have a Western blot analysis for anti-retinal antibody. If this serum test is positive, patients presumably have developed autoimmunoretinopathy or a CAR-like syndrome and should undergo evaluation for an occult malignancy (Heckenlively et al. 2000).

The Coats'-type variant of RP is thought to occur in as many as 3% of all RP patients. These fundi have typical bone spicules

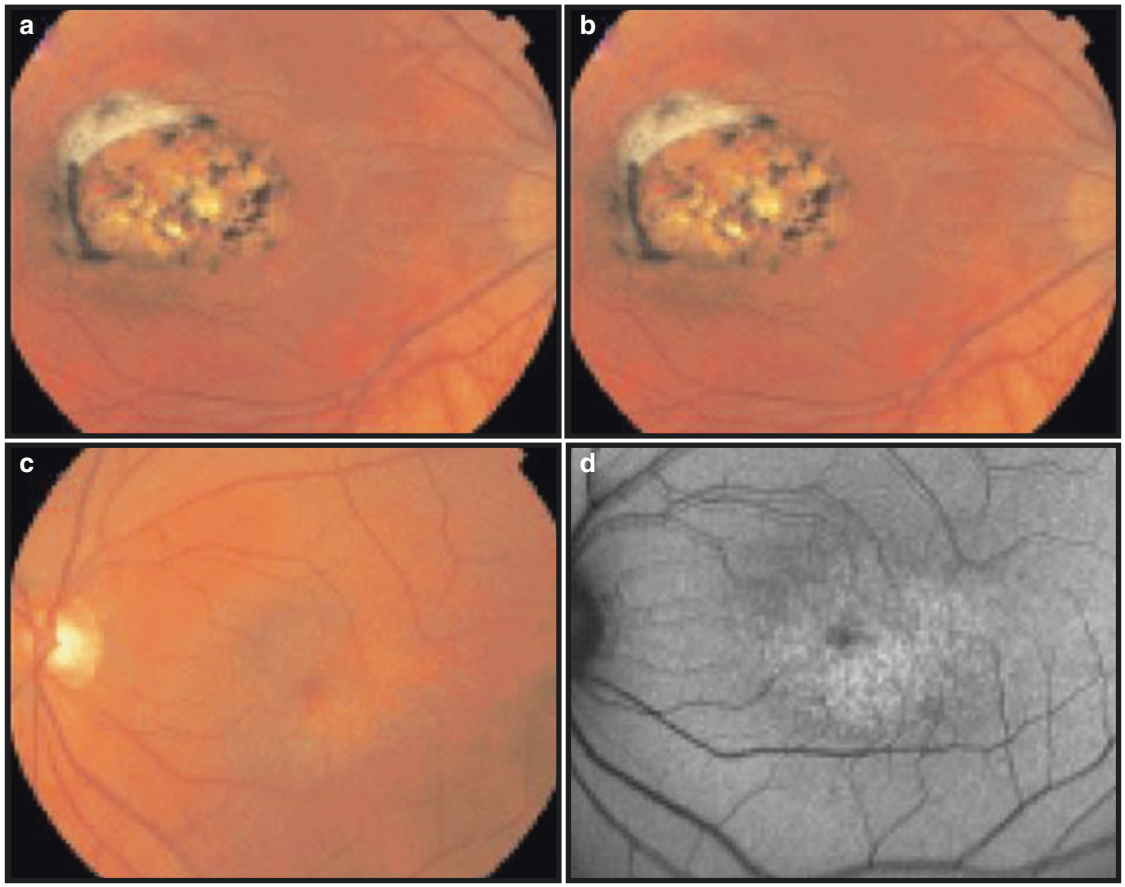

Fig. 51.11 North Carolina macular dystrophy in a 12-year-old girl. Color fundus photography shows coloboma-like defects with scalloped edges worse in her right eye (**a**) than her left eye (**b**). Her father (**c**) has a milder presentation (grade 1) of North Carolina macular dystrophy, with fine, drusen-like deposits that hyperfluorescence on autofluorescence (**d**)

of RP with Coats-type changes in the inferotemporal quadrants (Fig. 51.12). Retinal telangiectasia and exudative retinal detachments are treated with photocoagulation or cryosurgery as indicated (Khan et al. 1998).

Gene Therapy

Gene therapy is a promising future treatment for retinal degeneration (Bennett et al. 1996; Dunaief et al. 1995; Stone 2005). It is applicable when there is a loss of function due to genetic defect. The eye is an ideal organ for gene therapy because it is easily accessible, highly compartmentalized, and is an immune-privileged site. In 2001, vision was restored in *RPE65* deficient dogs, an animal model for one type of early-onset retinal dystrophy, known as Leber congenital amaurosis (LCA), by injecting subretinal adeno-associated virus (AAV) carrying *RPE65* (Acland et al. 2001; Bainbridge et al. 2006). Regain of function was demonstrated with ERG, pupillometry, and behavioral testing and was maintained for over 3 years (Acland et al. 2005).

This proof of principle demonstrating functional improvement following gene replacement of *RPE65* has led to clinical trials of recombinant AAV-mediated gene therapy for patients with LCA.

The key to gene-based treatments is efficient and accurate genotyping (Weleber 2005; Sieving and Collins 2007; Stone 2007). If genetic testing is not available on-site, blood can be

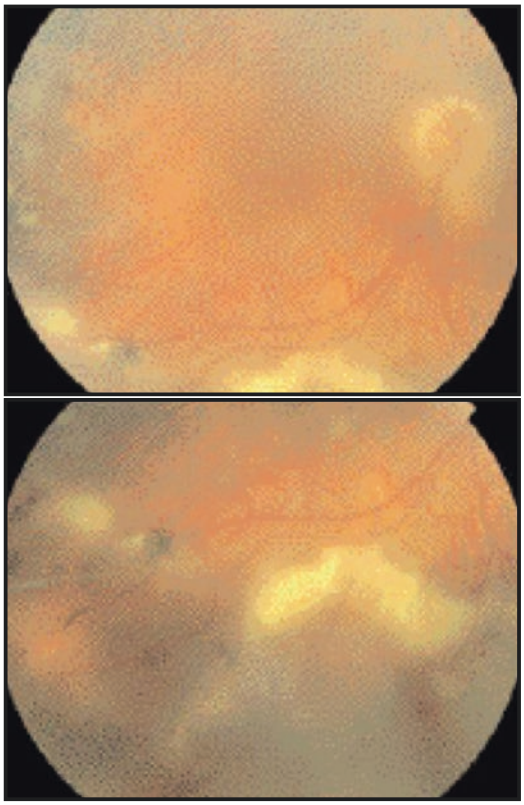

Fig. 51.12 Coats'-type, autosomal recessive RP in a 55-year-old man with vitreous haze centrally (**Top**) and subretinal exudates peripherally (**Bottom**) in his right eye

drawn in a tube with ethylenediaminetetraacetic acid (EDTA) and sent at room temperature to a Clinical Laboratory Improvement Amendment (CLIA)-certified laboratory for DNA testing (National Eye Institute. National Ophthalmic Disease Genotyping Network (eyeGENE) 2007; GeneTests Home Page 2007).

One commercially available method is a genotyping microarray (gene chip) for the *ABCA4* gene (Asper Ophthalmics 2007). Allelic heterogeneity in the *ABCA4* gene has been associated with five distinct phenotypes, including Stargardt disease/fundus flavimaculatus, cone-rod dystrophy, and AMD. This gene chip screens for more than 400 different *ABCA4* variants with >98% efficacy of finding them (Jaakson et al. 2003).

Other Emerging Therapies

Another promising idea in treating retinal degenerations has come from using ciliary neurotrophic factor (CNTF) to rescue photoreceptors. At least 13 animal models of RP show improvement with CNTF. Recently, a phase 1 trial evaluated surgically implanted capsules loaded with human RPE cells transfected with the CNTF gene. The treatment was well tolerated with minimal direct side effects, and the visual results were promising (Sieving et al. 2006).

Retinal-cell transplantation is another way to replace damaged photoreceptors, which has been worked on for many years (Gouras et al. 2002). Studies in mouse models (Tsang et al. 1996) show that timing of transplantation is crucial (MacLaren et al. 2006). There is a specific window period, coincident with the peak of rod genesis, during which the donor cells can be harvested that will enable the generation of new photoreceptors in diseased mice (MacLaren et al. 2006).

Clinical use of stem-cell transplantation is on the horizon (Columbia University Medical Center 2007).

Summary

Retinal dystrophies are a heterogeneous group of disorders whose classifications are evolving as retinal physicians better understand their phenotypes, genotypes, and pathophysiology. Genetic counseling is an important part of taking care of the patient. ERG continues to be the mainstay of diagnosis, and autofluorescence imaging has become essential for better phenotyping and following of disease progression. Electrophysiological studies are most helpful to phenotype different retinal conditions that ophthalmoscopy may show to be equivalent or similar.

Eyecare professionals have an active role in caring for patients with retinal dystrophies (Fishman et al. 2005; Sieving 2005) We manage complications that arise, such as cataracts, leaking vessels, and macular edema, and we also give genetic counseling and low-vision evaluations. Looking to the horizon, retinal physicians should help enroll patients in genetic registries so that they can contact patients when a specific genetic cure becomes available.

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CHAPTER 52

Genetic Testing for Inherited Retinal Dystrophy: Basic Understanding

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What Is Genetic Testing?

Genetic testing is a medical test that studies human DNA to discover genetic changes or mutations that could lead to genetic disease. Genetic testing is performed on samples of DNA that can be obtained from blood, hair, skin, saliva, amniotic fluid, or other tissues. The test results are then sent in writing to the doctor or the genetic counsellor for discussion with the patient and the family.

Which Retinal Diseases Would Benefit from Genetic Testing?

The American Academy of Ophthalmology Task Force on Genetic Testing recommends genetic testing on all patients with presumed or suspected inherited or Mendelian retinal diseases (monogenic diseases, which are due to a single defective gene or allele). Clinicians are currently advised to avoid routine genetic testing for genetically complex or multifactorial disorders such as age-related macular degeneration (AMD) or glaucoma. Routine genetic testing of complex diseases might become relevant in the future, if evidence shows that patients with specific genotypes benefit from a specific type of therapy or surveillance, but until then, routine testing is not warranted.

What Is the Role of the Ophthalmologist in Genetic Testing?

Whenever there is a suspected or presumed diagnosis of inherited retinal dystrophy (IRD), the role or potential value of genetic testing should be discussed with the patient and family. The ophthalmologist should be familiar with various types of IRDs and genetic testing, or the patient should be referred to another retinal specialist or a counselor who has expertise in the selection and interpretation of genetic tests.

Before testing, it is imperative that a patient and/or the family understand the testing procedure, the benefits and limitations of the test, and the possible consequences of the test results. Obtaining informed consent requires that the subject has enough information to make an educated decision about testing and signs a voluntary agreement to have the test done. In general, the informed consent should include the purpose of the test, description of the test, and the clinical diagnosis; what tissue sample will be obtained; the meaning of positive or negative test results; any physical or emotional risks; and use of results for research purposes.

The ophthalmologist should establish the clinical diagnosis on the basis of the ocular history, family history, use of any retinotoxic medications, clinical examination, evaluation of family members, and ancillary tests such as color fundus photos, fundus autofluorescence, spectral domain OCT, visual fields (including microperimetry, if available), electroretinography (full-field or multifocal ERG), and molecular genetic testing. A laboratory approved under the Clinical Laboratories Improvement Amendments (CLIA) should be able to estimate the pathogenicity of observed genetic variants, based on a review of the medical literature and databases of disease-causing and non–disease-causing variants.

The ophthalmologist should ensure that a written copy of the genetic test results is available to the patient and should be able to provide genetic counseling or to ensure that counseling is provided by a medical geneticist or genetic counselor.

What Are the Benefits of a Genetic Test?

A positive genetic test can improve the accuracy of diagnosis and prognosis and can help the physician to titrate treatment plans and to guide the family regarding specific inheritance risk. A causative mutation can be identified in up to 60–80% of patients with IRD. To date, about 260 different genes known to cause IRDs have been discovered, and more than 100 of these have been linked to retinitis pigmentosa (RP) and associated syndromes.

Genetic testing is being used to screen patients as possible subjects for clinical trials, and in December 2017, the FDA approved for the first time the use of gene therapy to treat patients with Leber congenital amaurosis (LCA), caused by mutation in the *RPE65* gene. The results of genetic testing can suggest other possible implications for treatment, such as these examples:

- Specific mutations may guide surveillance or systemic evaluation; for example, LCA with *CEP290* mutation would need evaluation of the CNS.

- Patients with mutation in *ABCA4* gene-related macular dystrophy should avoid supplementation of vitamin A.
- Patients with Usher syndrome may need a cochlear implant.
- Dietary modification can delay progression of the symptoms of Refsum disease.

Several phase I or phase II clinical trials are underway for IRDs, including choroideremia, achromatopsia, X-linked RP, Best disease, Stargardt disease, X-linked retinoschisis, Usher syndrome, and *MERTK*-associated autosomal recessive RP.

What Are the Risks of Genetic Testing?

Like any other intervention, genetic tests have certain inherent risks that may vary from patient to patient. The results can cause undue anxiety or guilt and can disturb the patient's relationship with other family members. The results can influence a patient's plan to have children. Therefore, the role of a skilled counselor is of great importance in clinical setting.

It is also important to know that although genetic testing is available, not all genetic mutations are identified. A false positive or false negative test result is possible, but the chances are very low, particularly in CLIA-certified laboratories.

Does Everyone with the Same Diagnosis Have the Same Genetic Mutation?

Not really, and this area makes the implications of genetic testing somewhat challenging. Three types of heterogeneity should be considered:

- *Genetic heterogeneity*: Mutations in different genes may cause the same disease.
- *Phenotypic heterogeneity*: Different mutations in the same gene may produce different diseases or phenotypes.
- *Clinical heterogeneity*: The same mutation in different individuals—even within the same family—may produce different clinical phenotypes.

What Information Is Given by Genetic Testing?

A genetic test may provide three different results:

- *Positive result*: The test found the mutation on a specific gene that is causing the disease.
- *Negative result*: The test could not identify a specific gene for the disease—but the test does not rule out the diagnosis of a retinal disease.
- *Inconclusive result*: The test may have looked at a gene panel that didn't affect that particular patient, or the mutant gene has not yet been identified. Additional testing might be required. This test does not mean that a person has no genetic mutations.

It is important for the patient and family to understand that the genetic test performed to identify IRD will not provide information about other diseases (such as cancer or diabetes) or their risk in the patient. Like all other personal health information, genetic test results are confidential; only the treating physician, the laboratory, and the subjects themselves know the result.

What Are the Types of Genetic Testing?

Several types of testing are available:

- *Single gene testing* is useful for the following diseases: X-linked retinoschisis (*RS1* gene), choroideremia (*CHM* gene), Stargardt disease (*ABCA4* gene), and vitelliform macular dystrophy (*PRPH2* or *BEST1* genes).
- *Multi-gene testing*, also called *panel testing*, is needed for a condition like RP (including syndromic types), in which 100 or more causative genes are known.
- *Whole exome sequencing* (WES) allows multiple strands of DNA to be sequenced simultaneously; the exome is the coding region of DNA. It makes up about 2% of an individual's entire genome and is thought to contain the majority of disease-causing mutations.
- *Whole genome sequencing* (WGS) studies or sequences the entire genome, and therefore reveals the impact of variation

within the exome/coding region and the non-coding region of the genome. WGS provides the option to "sequence once, study often." Currently, we analyze the area of the genome we understand, but if the whole genome has been captured, we can revisit other areas as we learn more without the need to obtain additional samples from the patient.

What Are the Structure and Function of the Genome?

Structure

A genome, in short, is the complete set of genetic information needed to build and maintain any type of organism; every organism has a genome. These "instructions for life" in a genome are encoded in DNA. The DNA is composed of four chemical letters in every organism, though the order (DNA sequence) of these letters varies, and these variations are the reason for differences between species or between individuals. We all have the same genetic architecture—the four chemical letters of DNA, adenine (A), guanine (G), cytosine (C), and thymine (T)—but the precise sequence of these letters makes each individual unique. The study of genomes is known as *genomics*.

The human genome has over three billion of the same four-chemical letters or bases of DNA. These bases are attached to a backbone made of sugar and phosphate (Nucleotide = base + sugar + phosphate). A DNA molecule has two paired strands twisted together like a spiral staircase, with bases forming pairs in the middle; A always pairs with T, and C with G.

The human genome has about 20,000 genes that provide the instructions for the thousands of proteins needed for our cells to carry out functions of our daily needs. A complete copy of the genome is available in almost every cell of our body. The genetic material of DNA is packaged into structures called chromosomes. Humans have 46 chromosomes (23 pairs, with one part of each pair inherited from each parent). Most of the DNA is held in the nucleus (nuclear DNA), but part is present in the mitochondria (mitochondrial DNA). If we took out the all the DNA from the nucleus, it would be 2 m long, but it is packaged concisely into the tightly coiled structures called chromosomes.

The levels of the human genome have been described as resembling the parts that make up a library: Letters…Words…Sentences…Chapters…Books…Reference library. DNA is composed of *letters* or bases (four chemical letters or bases), which forms *words* (codon, a group of three letters or bases), which in turn make *sentences* (genes), which are organized into *chapters* (chromosomes). In the *book*, genes provide the instructions for cells to form proteins from amino acids. There are 20 amino acids in humans, and the specific sequence of three letters (bases) that is unique to each amino acid is known as the "genetic code." So amino acids are the building blocks of life as they make proteins. Each cell is like a *reference library* that doesn't allow the genome (DNA sequence) to leave the nucleus. So, the cell makes a different molecule (messenger RNA) to carry the genetic information from the chromosome (within the nucleus) to the ribosomes (located in the cytoplasm), which make the protein.

Genes (the sentences) are stretches of DNA where a particular stretch of codon provides the instructions to make a protein. Of the whole genome, however, the protein-coding genes (coding region) comprise just a small fraction, 2% or less. The rest of the genome is non-coding DNA.

Within each chromosome, there are a number of genes, and the specific location of a gene on a chromosome is referred to as a locus (or loci). Variations of the genetic sequence (arrangement of chemical letters or bases) at these loci are called *alleles*.

Function

What is the function of a genome? To make proteins! Transcription is the first step of gene expression; here, the DNA sequence of a gene is transcribed (copied out) to make an RNA molecule, mRNA or messenger RNA (single-stranded; it has ribose sugar, and thymine/T is replaced with uracil/U).

Genes are composed of introns and exons. Exons are the coding sequence and contain the information to produce amino acids. Introns are the non-coding region, so they need to be removed via a process called splicing; then the final mRNA (mature RNA) has only exons. In the cytoplasm, mRNA goes to the ribosome (the factory to make proteins) to make chains of amino acids; every three bases on the mRNA codes for an amino acid, and this process of synthesis of protein from RNA is known as *translation*.

What Is Genomic or Genetic Variation?

As humans, we share almost 99.9% of our genetic information; the only variation is in the remaining 0.1%—though this contains millions of letters of DNA code. To study this *genomic variation* or *genetic variation* is the focus of genomics.

The introduction of variants into a DNA sequence can happen at two points. One is in the germ cells, the egg or sperm, during DNA replication, before meiosis. This is known as *germ cell variation* or *germline variation (mutation)*, and it will result in genetic variation in every cell of the body. The second variation occurs during mitosis, when one cell (somatic cells, other than

gametes, egg or sperm) is dividing to become two cells; this is known as *somatic variation*. Germline variation is passed on from parents to children, but somatic variations are not passed on.

Does Every Variation Result in a Disease?

No. We all have variations, and not all variations are bad. The relationship between genetic variation and disease is complex. Sometimes, a large variation is harmless, but sometimes, a single letter base change can have a devastating effect. It is the location of the change on the genome that dictates the consequences, and not the scale. Therefore, understanding the consequence of a particular genetic change or variant can be extremely complicated when we try to interpret the genetic results.

How Are Genomic Variants Classified in a Genetic Report?

The germline variants are classified into five categories, depending on the likelihood that they are disease-causing (pathogenic) variants:

- *Benign*: Clearly not pathogenic; these variants are not reported.
- *Likely benign*: Unlikely to be pathogenic; these variants are not reported.
- *Uncertain*: Variant of unknown significance (VUS); Evidence is insufficient to either support or reject pathogenicity. Additional data are needed to work out the effects of these variants.
- *Likely pathogenic*: Likely to be pathogenic; these variants are reported and confirm or at least are consistent with the diagnosis.
- *Pathogenic*: Clearly pathogenic; these variants are reported and confirm or at least are consistent with the disswwwagnosis.

Are Further Investigations Needed After the Genetic Testing?

In some cases, further investigations are necessary, especially if "pathogenic" or "likely pathogenic" variants are identified. One type of test uses immunohistochemistry to find out whether the expected protein is present. Another type, segregation studies, is used to find out if the variant has been passed down in the family, so family members are tested. This study also helps to determine if the variant has arisen *de novo*; that is, has developed for the first time in the individual under investigation.

Understanding the Genetic Testing Report

What Is a Genetic Code?

A genetic code is the set of rules used by living cells to map nucleotide triplets (trinucleotide sequences) in DNA or mRNA (called *codons*) to specific amino acids in the protein product. There are 64 codons in the genetic code to code for only 20 amino acids; so many amino acids can be coded for by more than one codon. That is the reason that some point mutations bear no effect on the amino acid coded for in the protein product.

Not all codons encode amino acids. Some act as a start codon (AUG for RNA or ATG for DNA, as in RNA, thymine is replaced by uracil), and the start codon always encodes for methionine. Some act as a stop codon (UAG or TAG, UAA or TAA, and UGA or TGA).

What Is Polymorphism?

Polymorphisms are normal variants that are not generally disease-causing. A significant number of the population (at least 1% or more) carry this variation.

What Is a Mutation?

A mutation is a disease-causing (pathogenic) change that is present in less than 1% of the population.

The term "sequence variant" can be used as an alternate term in place of *mutation* or *polymorphism*. Similarly, alternate terms can be used in place of *pathogenic* or *benign*: *affects function*, *probably affects function*, *unknown*, *probably does not affect function*, and *does not affect function*.

How Are Reference Sequence Variants Reported or Described?

The format is Reference:Description.

Example: NC_000011.9:g1234561 1G > A.

The reference file or reference sequence, before the colon, uses only public files from the National Center for Biotechnology Information (NCBI). The approved format is:

NC_#; NG_#; LRG_#; NM_#; NP_;# ENSG…; ENST… (for example, NC_000011.9). In this example, the *accession number* is 000011 and the *version number* is 9.

The description of the sequence appears after the colon. The reference sequences are reported at the DNA, RNA, or protein level, denoted by a prefix:

- For DNA
  - **g**, genomic reference sequence
  - **m**, mitochondrial reference
  - **c**, coding DNA reference sequence
  - **n**, non-coding DNA reference sequence
- For RNA
  - **r,** RNA reference sequence
- For protein
  - **p,** protein reference sequence

At the DNA level, the affected nucleotide is described in capital letters: **A** for adenine, **C** for cytosine, **G** for guanine, **T** for thymine.

At the RNA level, the affected nucleotide is described in lower-case letters, such as **a** for adenosine, **c** for cytidine, **g** for guanosine, **u** for uridine.

At the protein level, the affected nucleotide is described in "three-letter amino acid" code, such as **Ala** for alanine, **Cys** for cysteine, **Asp** for aspartic acid, **Met** for methionine, **Arg** for arginine.

Nucleotide Numbering

Nucleotide numbering is g.1, g.2, g.3, etc. from the first nucleotide to the last nucleotide of the reference sequence. Numbering starts at the start codon and ends at the stop codon, so numbering denotes the position of the affected nucleotide(s):

- Nucleotides upstream from the start codon are marked with a **"-** "(minus), and numbered as c.-1, c.-2, c-3, etc.
- Nucleotides downstream from the end codon are marked with an asterisk (*) and numbered as c.*1, c.*2, c*3, etc.
- An underscore (_) is used to denote range: g.1234_1267del
- Angled brackets—[and]— are used to denote alleles: g.[12345A > G]
- A semicolon (;) is used to separate variants and alleles; g.[12345A > G];[34567G > C]

Types of Variants

Substitution One letter of the nucleotide (DNA code) is replaced with another letter, as indicated by **">"**. For example, in "c.4375C > T" the nucleotide C is changed to T.

Deletion One or more letters of the DNA code are missing; indicated by "del". For example, in "c.4375_4379del" the nucleotides from position c.4375 to c.4379 are missing or deleted.

Duplication One or more letters of the DNA code are present twice; indicated by "dup". For example, in "c.4375_4379dup" the nucleotides from position c.4375 to c.4379 are present twice.

Insertion One or more letters are new (inserted) in the DNA code; indicated by "ins". For example, in "c.4375_4376insACCT" the new sequence, ACCT, was inserted between position c.4375 and c.4376.

Deletion/Insertion (Indel) One or more letters in the DNA code are missing (deleted) and replaced by the new sequence (inserted); indicated by "delins". For example, in "c.4375_4376delinsAGTT" or "c.4375_4376delCGinsAGTT" the nucleotides from position c.4375 to c.4376 (CG) are missing/deleted and replaced by a new sequence, AGTT.

Frame Shift (fs) The reading frame refers to the alignment, that is, to read three letters per codon. An open reading frame (ORF) is the part of a reading frame, a continuous stretch of codons that has both start and stop codons. A frameshift mutation is caused by indel of a number of nucleotides in a DNA sequence that is not divisible by three, such as "p.Arg456Glyfs*17".

How to Classify Variants

Table 52.1 lists the classifications of variants according to their evidence of pathogenicity and Table 52.2 outlines some rules for combining criteria to classify sequence variants.

Table 52.1 Classification of sequence variants by evidence of pathogenicity

Evidence of Pathogenicity	Category
Pathogenic very strong	**PVS1:** Null variant (causes *complete* lack of production of gene product or a product that does not function properly) in a gene where loss of function is a known mechanism of disease.
Pathogenic strong	**PS1:** Same amino acid change as a previously established pathogenic variant regardless of nucleotide change.
	PS2: De novo in a patient with the disease and no family history.
	PS3: Well-established in vitro or in vivo functional studies supportive of damaging effect on the gene or gene product.
	PS4: The prevalence of the variant in affected individuals is significantly increased compared with the prevalence in controls.
Pathogenic moderate	**PM1:** Located in a mutational hot spot and/or critical and well-established functional domain without benign variation
	PM2: Absent from controls in Exome Sequencing Project, 1000 Genomes Project, or Exome Aggregation Consortium.
	PM3: For recessive disorders, detected in *trans* with a pathogenic variant.
	PM4: Protein length changes as a result of in-frame deletions/insertions in nonrepeat region or stop-loss variants.
	PM5: Novel missense change at an amino acid residue where a different missense change determined to be pathogenic has been seen before.
	PM6: Assumed de novo, but without confirmation of paternity and maternity.
Pathogenic supporting	**PP1:** Co-segregation with disease in multiple affected family members in a gene definitively known to cause the disease.
	PP2: Missense variant in a gene that has a low rate of benign missense variation and in which missense variants are a common mechanism of disease.
	PP3: Multiple lines of computational evidence support a deleterious effect on the gene or gene product.
	PP4: Patient's phenotype or family history is highly specific for a disease with a single genetic etiology
	PP5: Reputable source recently reports variant as pathogenic, but the evidence is not available to the laboratory to perform an independent evaluation.
Benign stand-alone	**BA1:** Allele frequency is >5% in Exome Sequencing Project, 1000 Genome Project, or Exome Aggregation Consortium.
Benign strong	**BS1:** Allele frequency is greater than expected for disorder.
	BS2: Observed in a healthy adult individual for a recessive (homozygous), dominant (heterozygous), or X-linked (hemizygous) disorder, with penetrance expected at an early age.
	BS3: Well-established in vitro or in vivo functional studies show no damaging effect on protein or splicing
	BS4: Lack of segregation in affected members of a family.
Benign supporting	**BP1:** Missense variant in a gene for which primarily truncating variants are known to cause disease.
	BP2: Observed in *trans* with a pathogenic variant for a fully penetrant dominant gene/disorder, or observed in *cis* with a pathogenic variant in any inheritance pattern.
	BP3: In-frame deletions/insertions in a repetitive region without a known function.
	BP4: Multiple lines of computational evidence suggest no impact on gene or gene product.
	BP5: Variant found in a case with an alternate molecular basis for disease.
	BP6: Reputable source recently reports variant as benign, but the evidence is not available to the laboratory to perform an independent evaluation.
	BP7: A synonymous (silent) variant for which splicing prediction algorithms predict no impact to the splice consensus sequence nor the creation of a new splice site AND the nucleotide is not highly conserved.

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Table 52.2 Rules for combining criteria to classify variants

Pathogenic
1. 1 very strong (PVS1) *AND*
(a) ≥1 strong (PS1–4) *OR*
(b) ≥2 moderate (PM1–6) *OR*
(c) 1 moderate (PM1–6) and 1 supporting (PP1–5) *OR*
(d) ≥2 supporting (PP1–5) *OR*
2. ≥2 strong (PS1–4) *OR*
3. 1 strong (PS1–4) *AND*
(a) ≥3 moderate (PM1–6) *OR*
(b) 2 moderate (PM1–PM6) *AND* ≥ 2 supporting (PP1–5) *OR*
(c) 1 moderate (PM1–6) *AND* ≥ 4 supporting (PP1–5)
Likely pathogenic
1. 1 very strong (PVS1) *AND* 1 moderate (PM1–6) *OR*
2. 1 strong (PS1–4) *AND* 1–2 moderate (PM1–6) *OR*
3. 1 strong (PS1–4) *AND* ≥ 2 supporting (PP1–6) OR
4. ≥ 3 moderate (PM1–6) *AND* ≥ 2 supporting (PP1–5) *OR*
5. 2 moderate (PM1–6) *AND* ≥ 2 supporting (PP1–5) *OR*
6. 1 moderate (PM1–6) *AND* ≥ 4 supporting (PP1–5)
Benign
1. 1 stand-alone (BA1) *OR*
2. ≥2 strong (BS1–4)
Likely benign
1. 1 strong (BS1–4) *AND* 1 supporting (BS1–7) *OR*
2. ≥2 supporting (BP1–7)
Uncertain significance
1. Other criteria shown above are not met *OR*
2. The criteria for benign and pathogenic are contradictory

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