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Inherited Macular Dystrophies and Differential Diagnostics

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Key Words: *inherited macular dystrophies; inheritance; clinical picture; diagnostics; differential diagnostics.*

Summary. *The inherited macular dystrophies are characterized by different grade central visual loss and different character macula atrophy, because of retinal pigment epithelium lesion. The cause of photoreceptors degeneration is still not known.*

In this article, we review subjective and objective ophthalmological examines essential to diagnosis and differential diagnosis of inherited autosomal dominant and autosomal recessive macular dystrophies.

It is known seven gene mutations (ABCA4, ELOVL4, PROML1, VMD2, Peripherin/RDS, TIMP3, XLRS), which may cause inherited macular dystrophies development. Inheritance type of inherited macular dystrophies, prevalence, beginning of disease, spread of the disease between female and male, clinic, electroretinography, electrooculography, differential diagnosis, genetic research and prognosis are also reviewed.

Introduction

The inherited macular dystrophies (MDs) comprise a heterogeneous group of diseases characterized by bilateral visual acuity loss and symmetrical different macular abnormalities. Most commonly, these diseases manifest at early age in the first 2 decades of life and progress to permanent visual acuity loss (1). The inherited MDs are classified into 3 large groups by a mode of inheritance: autosomal dominant inheritance, autosomal recessive inheritance, and X-linked inheritance. Currently, the following 7 genes associated with MDs have been identified: *ABCA4*, *ELOVL4*, *PROML1*, *VMD2*, *peripherin/RDS*, *TIMP3*, and *XLRS*. Further genetic studies are currently being carried out.

The inherited MDs differ by the manifestation of clinical forms, physiology, and histological abnormalities.

This article presents the clinic pictures of the most common inherited MD, their diagnostics, and the main aspects of differential diagnostics.

Diagnostics

Subjective and objective ophthalmological tests are used for the diagnosis of inherited MDs.

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I. Subjective Diagnostic Tests

1. *Color perception tests* are used to distinguish color from tone, intensity, and brightness. The following color perception tests are used: the Ishihara Color Test (for red-green color deficiencies), AO-HRR tables (for red-green and blue-yellow deficiencies), the Munsell Farnsworth 100 hue test (for red-green and blue-yellow deficiencies and tone), the Farnsworth D-15 test (for red-green and blue-yellow deficiencies), and the Nagel anomaloscope (for red-green deficiencies).

2. *Dark Adaptation.* Adaptation to dark occurs by 2 stages. The first stage is associated with an increase in light sensitivity of the eye linked to the cones, and the second is associated with the accommodation of rods. If the rod system does not function, the sensitivity of the eye to light remains unchanged. When the system of cones does not function, the eye accommodation starts after 10 minutes from light to dark (Table 1) (1).

3. *Visual Acuity Test.* The noncorrected and the best-corrected visual acuity (measured in decimals from 0.1 to 1.0) is evaluated using the Landolt's rings (C optotypes) by the Snellen test types at a 5-m distance from the chart.

4. *Visual Field Test.* The limits of visual field are measured by degrees and are determined by examining each eye by perimeter. The most precise evaluation of visual field is achieved using a computed perimeter. A device has different programs to test

Table 1. Functions of Retinal Rods and Cones

Functions of Rods	Functions of Cones
Distinction of movable objects	Distinction of unmovable objects
Dark vision (mesopic)	Daylight vision (photopic)
Vision of black and white colors	Color vision
Vision of large parts	Vision of small parts

different visual field disorders. The central visual field is examined with 30° and 40° (or 76 points) threshold program, and the peripheral visual field is examined with 30° and 60° (60 points) program of computed perimetry. The threshold of visual field in a healthy person with 5-mm white target testing by perimeter with an arch radius of 33 cm is as follows: outside, 90°; downwards, 60°–70°; inside, 60°; and upwards, 55°. The first symptom is an appearance of scotomas.

II. Objective Diagnostic Tests:

1. *Ophthalmoscopy*. A detailed examination of the retinal appearance starts with direct or indirect ophthalmoscopy through well-dilated pupils.

2. *Electroretinography*. During electroretinography (ERG), a total retinal response to light stimulus is recorded (2, 3). Typical ERG is comprised by a- and b-waves: a-wave is negative and generated by the outer segments of photoreceptors; b-wave, positive and is generated by Muller cells. B-wave reflects the processes occurring in the inner retinal layers. Various stimulation and registration techniques help record potentials of different retinal structures: early receptor potential, ERP; standard electroretinogram of full-field by ISCEV (International Society for Clinical Electrophysiology of Vision) (a- and b-waves, oscillatory potentials under photopic and scotopic conditions are evaluated); photopic negative response, PhNR; pattern (alternating contrast) ERG, pERG; multifocal ERG (mfERG).

3. *Electro-oculography*. Electro-oculography (EOG) represents the function of retinal pigment epithelium. During EOG, a difference in the potentials between the cornea and the posterior pole during dark adaptation and light adaptation is recorded; then, the ratio of the voltages (the Arden index) is assessed (3).

4. *Fluorescein Angiography (FFA)*. The fundus photographs are taken after the injection of sodium fluorescein, a water-soluble dye, into a vein of the elbow. The test allows evaluation of blood and fluid circulation in the choroid and retina, and gives additional information about the anatomical structures of the retina. The following stages of blood circulation are distinguished: choroidal, retinal, capillary transition, early venous, venous, and late venous.

5. *Genetic Testing*. The methods of genetics and molecular genetics are applied to identify specific genes that are associated with the development of MDs. Genome decoding is thought to explain the pathogenesis of diseases, furthermore, determination of abnormalities resulting in protein activity and protein interaction with different cell components will contribute to a more detailed analysis of pathogenesis strands (4).

Autosomal Recessive Inheritance

1. *Stargardt's Macular Dystrophy*

It is the most common inherited macular dystrophy. The estimated prevalence of this dystrophy is 1 in 8000 to 15 000 (5). The symptoms of Stargardt's macular dystrophy (STMD) may manifest in the first 2 decades of life and involve a gradual impairment of bilateral central visual loss (6). Visual acuity may range from 0.1 to 0.05 (7). Adults may also develop STMD; then the visual loss is mild (8). At the onset of disease, ophthalmoscopy does not show any macular abnormalities; however, a mild scattering of pigment and loss of macular reflex may be present (8). The further development of the disease is characterized by the presence of atypical fishtail-shaped flecks; later, a horizontal oval-shaped atrophy area of retinal pigment epithelium (RPE) (in size of 1.5–2 optic disc [OD]) similar to "beaten bronze" or "snail slime" is seen (Fig. 1). Sometimes, the lesion is surrounded by yellowish white spots (Fig. 2) (8). The image of "bull eye" may also be seen (Fig. 3), and due to RPE atrophy, the macular geographic atrophy may also develop around the normal RPE (6). Rarely cone or rode dystrophy may be present (6). In patients with STMD, the changes of visual field may be present or not; occasionally, central scotomas or a slight concentric constriction of visual field are seen (9). The further development of the disease is characterized by red-green color deficiencies (8).

A value of electrophysiological tests – electroretinography and electro-oculography – in the diagnosis of STMD is still being discussed. Most authors point out that ERG may show no abnormalities in the early stages of disease and may present with changes when the disease progresses (10). Based on the ERG findings, abnormalities in patients with STMD can be classified into the following 3 groups (11): group 1, severe pattern ERG abnormality with normal photopic and scotopic a- and b-waves during Ganzfeld ERG; group 2, additional loss of photopic a- and b-waves; and group 3, loss of photopic and scotopic a- and b-waves (11). Patients in the group 1 have better visual acuity, more restricted distribution of lesions, and smaller atrophy of the macula. The prognosis of visual function is bad in patients of group 3 (11). In all cases a loss of potentials of

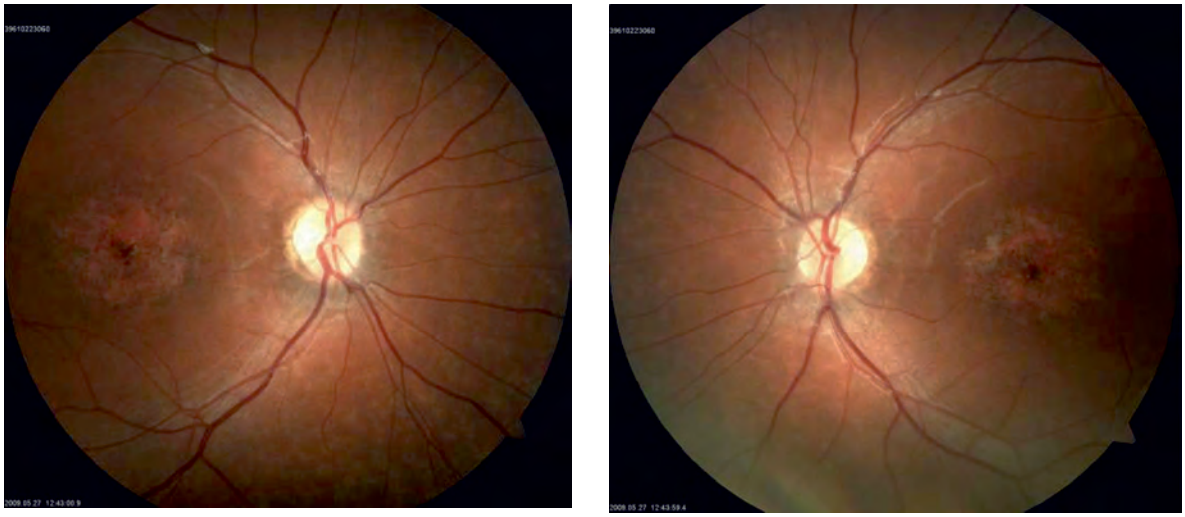

Fig. 1. Atypical flecks in the macula, absence of macular reflex, and horizontal oval-shaped area of atrophy of the retinal pigment epithelium (1.5 OND diameter in size)

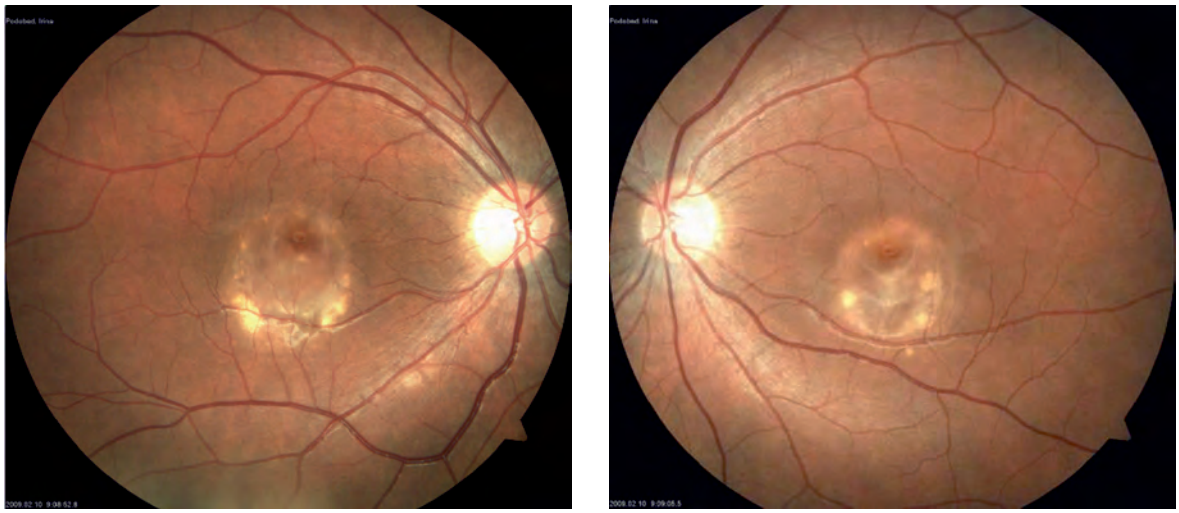

Fig. 2. Atypical flecks in the macula, absence of macular reflex, and horizontal oval-shaped area of atrophy of the retinal pigment epithelium (1.5 OND diameter in size)

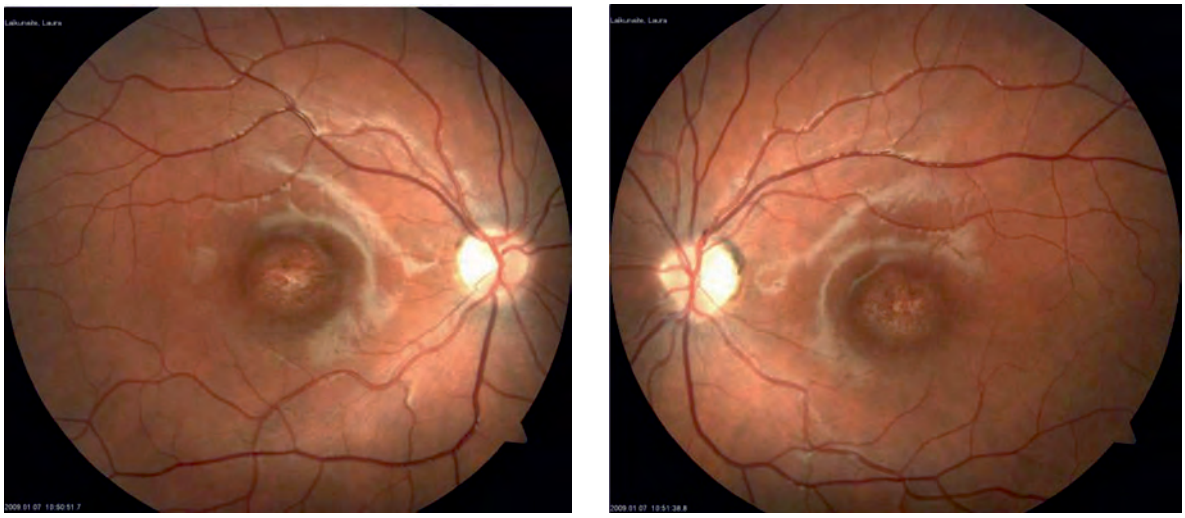

Fig. 3. "Bull eye" in the center of retina in SMD patients

central retina are recorded in multifocal ERG. Most commonly, no abnormalities are recorded on EOG; the changes may be present in more advanced stages (6). According to Fishman et al., in most cases, the EOG Arden index is changed; however, only when abnormalities of RPE are dramatic and seen on ophthalmoscopy and during fluorescein angiography test (12). Fluorescein angiography shows a silent choroid or a dark or masked choroid (11, 12). Commonly, marginal fluorescence due to the accumulation of lipofuscin pigments in the RPE is observed (11, 12). The retinal flecks appear to be hypofluorescent on FFA at the onset of their development, but at a later stage, they appear to be hyperfluorescent due to RPE atrophy (11, 12).

In autosomal recessive inherited STMD (MIM #248200), the locus of gene *ABCA4* has been identified on chromosome 1p (1p21–p13). Mutations in *ABCA4* implicated in STMD have variations from point mutations (the latter is most common) to elimination of several gene exons (gene is comprised from 50 exons) (13). To date, the known mutations of the *ABCA4* gene account for approximately 66%–80% of all identified mutations (14). The prognosis is bad; the disease usually progresses to permanent visual loss.

2. *Fundus Flavimaculatus*

It is a rare autosomal recessive inherited dystrophy of retinal pigment epithelium. Similar to autosomal recessive STMD, fundus flavimaculatus (FFM) is also caused by mutations in the same *ABCA4* gene (1p21–p13) (13). The estimated prevalence is 1 per 10 000 persons (15). Many researchers link this pathology to STMD due to the similar clinical appearance and fundus changes. The disease usually manifests in childhood between 8 and 14 years and is characterized by the appearance of yellow-white, small, not clearly circumscribed fundus flecks in the midperiphery, sometimes near the macula. Typically, both eyes are affected, and STMD may be present. FFA reveals point hyperfluorescent areas not fully corresponding to the yellowish lesions. Table 2 shows the stages of STMD and FFM and differences between them (16).

Autosomal Dominant Macular Dystrophies

1. *Autosomal Dominant Stargardt-Like Macular Dystrophy*

Autosomal dominant Stargardt-like macular dystrophy is a rare disease. Literature reports only sporadic cases of the disease (17). Typically, the disease manifests in adolescence. The deterioration of visual acuity is seen; fundus examination reveals RPE atrophy with or without subretinal flecks (Fig. 4).

The clinical picture is similar to the common autosomal recessive form of STGD; therefore, it is difficult to differentiate between them by single direct or indirect ophthalmoscopy (18). Rarely, a silent choroid seen on FFA is more characteristic of autosomal recessive STGD than dominant form of the disorder (19). Patients with STMD have good visual acuity; only slight color deficiencies are typical (19).

The abnormalities on ERG are described differently. Some researchers report reduced photopic, but normal scotopic b-waves; the others, reduced both photopic and scotopic b-waves (20, 21).

Currently, the role of 2 genes – *ELOVL4* (6q14) and *PROML1* (4p) – in the development of the disease is being investigated (17). The prognosis is satisfactory. The visual acuity may range from 1.0 to 0.01.

2. *Best's Vitelliform Dystrophy*

Best's vitelliform dystrophy (BVD) is a rare slowly progressing inherited MD. The prevalence is unknown. Typically, the disease manifests in childhood (between 3 and 15 years) and sometimes may

Table 2. Stages of Stargardt's Macular Dystrophy and Fundus Flavimaculatus

Stargardt's Macular Dystrophy	Fundus Flavimaculatus
Stage Ia	
Macular degeneration with or without perifoveal flecks is seen	Macular appearance normal or the presence of increased RPE pigmentation with parafoveal white flecks. Findings on EOG and ERG are normal
Stage Ia	
Macular degeneration and diffuse posterior pole perifoveal flecks	Diffuse posterior pole white flecks. Macular atrophy may be present or not. Findings on EOG and ERG are usually normal
Stage IIIa	
Central and peripheral retinal degeneration, changes of visual field, and normal diameter of retinal vessels.	Resorbing flecks and RPE atrophy with or without macular atrophy. Subnormal findings on ERG and EOG.
Stage Iva	
Centroperipheral RPE degeneration. Defects of peripheral visual field and "bone trabeculae" like retinal pigmentation, and attenuated retinal vessels.	Macular atrophic lesion present with generalized atrophic choriocapillaris; pigment clumping of PE and intraretinal pigment migration; attenuated retinal vessels and constricted peripheral fields; abnormal findings on EOG and ERG

RPE, retinal pigment epithelium; ERG, electroretinography; EOG, electro-oculography.

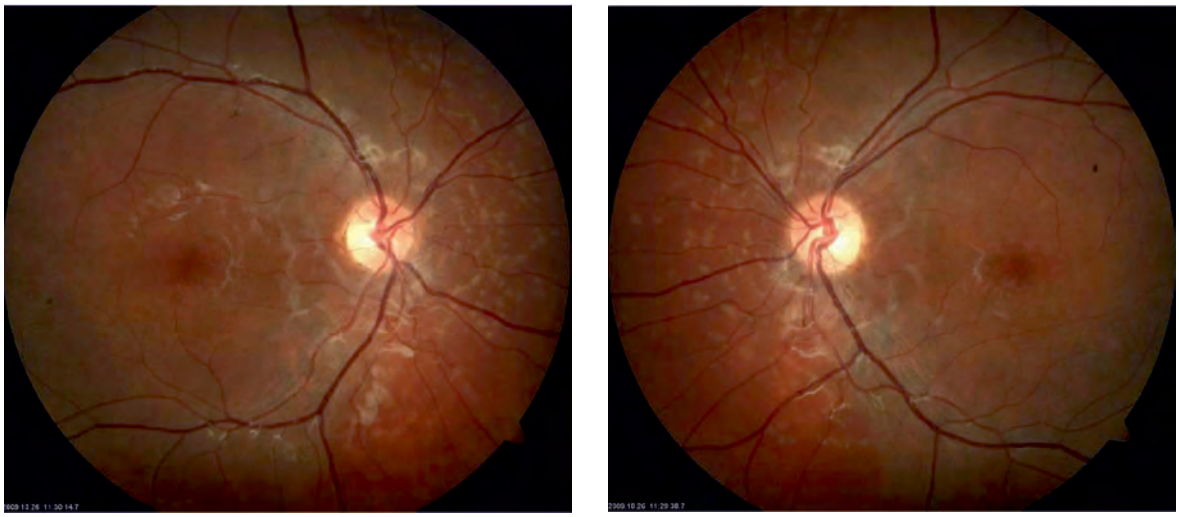

Fig. 4. Macular atrophy with atypical flecks; presence of small yellowish lesions and hyperpigmentation and absence of macular reflex bilaterally are observed

Yellowish flame-shaped hemorrhages/cotton wool exudates surrounding the optic disc and more localized nasal of the optic disk bilaterally.

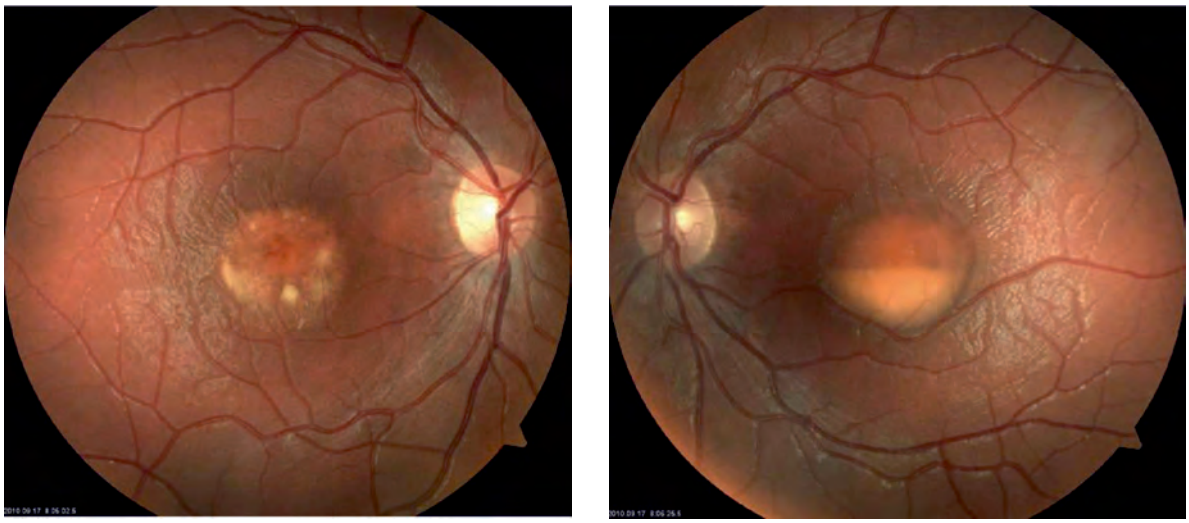

Fig. 5. Ophthalmoscopy findings

In the right eye, a big yellow macular lesion surrounded by a few smaller lesions with clear content and moderate retinal edema in the central part of the retina is seen (similar to BVD scrambled egg stage). In the left eye, a big round lesion with liquid line in the central part of the retina (similar to BVD pseudohypopion stage) is observed.

occur in adolescence. Patients have good visual acuity followed later by the constriction of visual field and the appearance of metamorphopsia. Dark adaptation and the peripheral visual field are normal. Since visual acuity remains normal for a long time and atrophy manifests only in the fifth decade of life, BVD is usually diagnosed late (8).

The development of BVD is characterized by 4 stages: 1, primary; 2, "egg yolk;" 3, "scrambled egg" (Fig. 5); and 4, final stage. The primary stage is described by the normal eye fundus; in the "scrambled egg" stage, a yellowish, round, elevated yolk-like lesion is seen in the center of the macula. The "scrambled egg" stage presents a scrambled egg-like lesion, which occurs after egg yolk "ruptures." The final stage is characterized by a hypertrophic scar, atrophic maculopathy, and fibrovascular scar associated with choroid neovascularization (8). Protanopia may be seen. The findings on standard ERG are normal; however, it shows a dramatically reduced or disappeared c-wave, which basically reflects the function of pigment epithelium (22). The essential test the EOG, which does not record photopic rise, and Arden index approximately remains as 1.0.

Most patients carrying a mutation in the *VMD2* gene (11p13) have abnormal findings on EOG, al-

though they do not present with clinical complaints, and the appearance of their macula may be normal (23). The visual prognosis is surprisingly good, with most patients aged 50 years retaining normal visual acuity. Sometimes, even during the first examination, the appearance of bilateral macular abnormalities phenotypically similar to other macular dystrophies, e.g., Stargardt or cone dystrophies, is documented. Differentiation should be based on the findings on FFA ("silent choroid" not typical in BVD) and EOG. Cone dystrophies are characterized by abnormalities on ERG and color deficiencies. EOG may also be helpful in distinguishing BVD from North Carolina macular dystrophy, which can be similar according to the clinical picture (24).

The prognosis is good; atrophic abnormalities develop after many years.

3. *Adult Vitelliform Dystrophy*

Adult vitelliform dystrophy involves some rare inherited MDs described by single researchers and includes the following diseases: specific foveamacular dystrophy, adult foveamacular vitelliform dystrophy, autosomal dominant macular dystrophy with a progressive history, and foveamacular pigment epithelium dystrophy manifesting at older age (24).

The disease is usually diagnosed in individuals aged more than 45 years.

The visual acuity is 0.2 or better. On ophthalmoscopy, round or oval, yellow, symmetrical, subretinal lesions are seen usually measuring one-third to half of the diameter of the optic disc (OND). The visual function typically remains good, and it is retained for a long time. Commonly abnormalities are seen in both eyes. The findings on ERG are normal; on EOG, normal or subnormal. EOG is performed to differentiate adult vitelliform macular degeneration from BVD.

A mutation in the *peripherin/RDS* gene (6p) has been identified in approximately 20% of patients with adult vitelliform dystrophy (25). The prognosis is good if complications, such as choroidal neovascularization, do not develop.

4. *Pattern Dystrophy*

Three types are distinguished: butterfly-like dystrophy, reticular dystrophy of the RPE (Sjögren disease), and macroreticular dystrophy. The term *pattern dystrophy* was proposed by Marmor and Byers in 1977 in order to group dystrophies of the RPE, which are characterized by a granular or reticular pattern of the RPE and has a benign clinical course (26). So far, literature presents a wide range of RPE dystrophies: reticular, butterfly-like, macroreticular, fundus pulverulentus, and other.

In some families, mutations in the *peripherin/RDS* gene (6p) have been identified (27), while in other families, mitochondrial DNA mutations were observed (28). However, in most families, no known gene mutations have been identified, and inheritance may be either autosomal dominant or autosomal recessive. Therefore, pattern dystrophy refers to a heterogeneous group of various genetic diseases that are responsible for the similar changes in the RPE (26). Since it is a rare disease, the prevalence is unknown.

The signs of the disease manifest in the middle age. Slight abnormalities of the visual function in one or both eyes are typical. The deterioration of visual acuity, color vision, contrast sensitivity is documented; the degree of these abnormalities depends on how severely the macula is affected. The visual field and dark adaptation for most patients remain normal, though sporadic cases with a decrease in the central visual field and subnormal dark adaptation are reported. Since patients do not present with dramatic abnormalities of visual function, pattern dystrophy is typically diagnosed as age-related macular degeneration. The disorder is characterized by bilateral, symmetrical, yellow-orange or gray lesions differently distributed in the macula. FFA is essential for diagnosis, since on ophthalmoscopy, only slight atypical abnormalities of pigmentation may be seen, and the presence of pigment deposits, redistribution, and scattering may be seen only during fluorescein angiography. In young and middle-aged patients, the findings on ERG are typically normal; on EOG, normal or subnormal with the Arden index ranging from approximately 1.5 to 1.8. Abnormalities are seen at older age; on ERG, a- and b-waves reach the lower normal limits or are slightly reduced, whereas the abnormalities on EOG almost do not change with age (29).

The prognosis is good.

5. *Autosomal Dominant Drusen and Macular Degeneration*

The term *dominant drusen* (DD) refers to a heterogenous group of autosomal dominant diseases. Penetrance is not always full, and regardless a genetic defect, the retina may remain normal. Therefore, the inheritance type is difficult to determine.

Drusen are fine extracellular deposits that accumulate on the Bruch's membrane beneath the retinal pigment epithelium. There are hard and soft drusen; the latter are linked to the local detachments of the RPE and are associated with degenerative changes. The mechanism of their development is still unknown (30). The visual acuity is 0.6–0.2; sometimes it decreases to 0.1. Color vision is normal.

Deposits appear at the posterior pole of the eye and may be distributed nasally and/or close to the optic disk. Inherited drusen form at earlier age as compared with age-related sporadic drusen, which do not present with any clinical symptoms over decades and are bilateral and symmetric in both eyes. Apart from these symptoms, there are no any other

signs between inherited and noninherited sporadic drusen (31). When a specific clinical form is determined, the following diseases are distinguished: Sorsby retinal dystrophy (some researchers describes this disease as distinct), Doyne honeycomb retinal dystrophy, Leventinese disease, and Hutchinson-Tay choroiditis. When a specific form is not determined, the pathology is described as dominant drusen.

Functional abnormalities, particularly at the onset of the disease, are typically minimal: impaired visual acuity, contrast sensitivity, and color vision dysfunction. The appearance of central scotoma and abnormalities of dark adaptation are typical when the disease progresses. Literature reports various psychophysiological and electrophysiological abnormalities. The findings on full-field ERG are typically normal or subnormal, and there are no any criteria to differentiate between inherited and noninherited drusen (32). The findings on EOG are also usually normal (33). A decrease of mfERG macular amplitude associated with macular dysfunction is recorded, and the abnormalities found are similar both in the presence of macular degeneration, and dominant drusen.

Mutations in 3 genes – *periferin/RDS*, *TIMP-3*, and *EFEMP1* – have been identified in the majority of cases with dominant drusen. The prognosis is good.

6. *Sorsby Fundus Dystrophy*

Sorsby fundus dystrophy is a rare, autosomal dominant macular dystrophy. Some researchers describe Sorsby fundus dystrophy as a distinct disease. The others associate the disease with dominantly inherited drusen. In 1949, Sorsby and co-authors described an autosomal dominant retinal dystrophy characterized by gradual visual acuity loss manifesting in the fifth to sixth decades of life (34). The onset of the disease is characterized by the appearance of night blindness; however, the findings on ERG are normal or subnormal. The abnormalities on EOG may vary from normal to moderately reduced. With visual acuity loss, a reduced or disappeared pERG is determined. It is thought that due to the thickened Bruch's membrane, the transport of vitamin A from the choriocapillaris to the photoreceptors is disturbed. It confirmed by the observation that treatment with high doses of vitamin A (50 000 IU per day) results in the restored parameters of psychophysical and electrophysiological functions (35).

On ophthalmoscopy, drusen are seen along the vessel arcades or nasally to the optic disk. FFA reveals delayed choriocapillary filling in the central part of the retina. Patients in their third to seventh decades of life develop central visual field loss due to dystrophy in the center of the retina or subretinal neovascular membrane. Large disciform scars are formed, which later become pigmented. In some families, tritanopia color vision deficiencies are described; however, in some patients, color vision may be normal.

Mutations in the gene *TIMP-3* (22q), namely Ser182Cys (30), Ser156Cys (31), and Tyr172Cys (36), resulting in RPE apoptosis have been identified (37). The prognosis is good. The median age when choroid neovascularization develops in one eye and both eyes is 48 and 50.3 years, respectively. The interval between the appearance of choroid neovascularization in one eye and another is 4.5 years. The median age when visual acuity reduces to 0.1 or less in one eye and both eyes is 48 and 54 years, respectively (38).

7. *RDS 172 Codon-Related Drusen*

A mutation in the RDS 172 codon, particularly an Arg172TRP mutation, has been implicated in the progressive inherited MD with autosomal dominant drusen. Although retinal abnormalities on ophthalmoscopy are already seen in adolescence, visual function loss develops only in the fifth decade of life. In the second decade of life, patients present with photophobia and disorders of dark adaptation. In the third decade of life, a slight deterioration of visual acuity is seen, abnormalities on pERG are recorded, and full-field ERG shows a reduction of the amplitude of cone a- and b-waves, whereas wave latency remains normal. The rod responses on ERG are normal until the sixth to seventh decades of life. The findings on EOG are normal. The appearance of absolute scotomas and increased areas of threshold sensitivity is seen; however, concentric constriction is absent (39).

The prognosis is satisfactory.

8. *EFEMP1-Related Drusen*

A mutation in the *EFEMP1* gene is implicated in the development of 3 disorders described as distinct nosological units: Doyne honeycomb retinal dystrophy, Leventinese dystrophy, and radial drusen maculopathy of Gass. The same mutation R345W in the *EFEMP1* gene on the short arm of chromosome 2p is identified in all these disorders (40).

The phenotype of Leventinese dystrophy is characterized by the development of early drusen distributed radically (radial distribution) at the macula and close to the optic disk. Typically drusen are also seen in the nasal part of the retina. A number of drusen increases when the disease progresses. FFA shows a radial distribution of the drusen at early and advanced stages of the disease. If the distribution of the drusen is not radial, and the drusen are larger and rougher, then the disease is described as Doyne honeycomb macular dystrophy. The radial distribution of the drusen is the only difference between Leventinese and Doyne honeycomb macular dystrophies (41). Radial drusen maculopathy is char-

acteristic of familial and between familial variability of phenotype. Some patients with this mutation present with only slight and nonprogressive clinical symptoms.

The symptoms do not manifest until patients are 40-years old. Later patients develop dark adaptation disorders, sometimes metamorphopsia of different degree, photophobia, and difficulties in reading due to paracentral scotomas. The visual acuity is retained to the fifth decade, but patients become blind by the seventh decade of life. Visual acuity loss typically occurs due to macular atrophy and less commonly due to the atrophy of the subretinal neovascular membrane.

Color blindness is typical. The abnormalities on ERG are recorded with age. Reduction of the amplitude of b-wave is more characteristic of age; the prolongation of wave latency is more expressed. Reduction in pERG is seen in almost all patients; some authors describe reduced oscillatory potentials of full-field ERG as well as delayed cone responses on ERG to a 30-Hz stimulus (42, 43).

The prognosis is satisfactory. The disease is progressive, although peripheral vision is retained.

9. *North Carolina Macular Dystrophy*

North Carolina macular dystrophy is an inherited macular dystrophy, which manifests in infancy, but rarely progresses (44).

In one-third of patients, the visual acuity ranges from 1.0 to 0.8 with the development of confluent drusen in the macula. Other third of patients present with confluent drusen and the mean visual acuity loss ranging from 1.0 to 0.5, and in the remaining patients, colobomatous or disciform abnormalities are seen, and the mean loss of visual acuity is 0.5–0.02. In the fundus, a few yellow drusen to larger confluent drusen and macular colobomatous-like lesions in the central part of the retina are observed. FFA shows the defects of the RPE and late staining of drusen; later, choriocapillary perfusion is disturbed. The cone photopic responses on ERG are normal or subnormal. The findings on EOG are normal or within the upper limits.

The gene associated with this dystrophy has not been identified. It is thought that the locus of disease-related gene is on chromosome 6 (6q16) (45). The prognosis is good.

10. *Progressive Bifocal Chorio-Retinal Atrophy*

In progressive bifocal chorio-retinal atrophy (PBCRA), abnormalities are seen at birth (46). The disease is characterized by myopia, congenital nystagmus, and progressive atrophic lesions of the central and nasal retina (47). The disease progresses slowly. The atrophic areas from the nasal area to the OND develop in the second decade of life and gradually increases.

Full-field ERG shows moderately reduced photopic and scotopic a- and b-waves, suggesting more quantitative rather than qualitative lesions of photoreceptors (47). A typical large circumscribed macular and choroidal atrophy with the accumulation of deposits in the retina is typical on FFA.

The gene associated with the disease has not been identified. It is though that the locus of disease-related gene is on chromosome 6 (6q14-q16.2) (48). The prognosis is satisfactory. The disease results in significant loss of visual acuity and legal blindness.

11. *Central Areolar Choroidal Dystrophy*

Central areolar choroidal dystrophy (CACD) is characterized by the lesions of layers of retinal pigment epithelium, photoreceptors, external nuclear and choriocapillaris (8). The symptoms of the disease manifest in the third decade of life (8).

In the onset of the disease, a subtle mottling of the RPE is observed, and with the progression of the disease, the atrophic area increases with no pigmentation and drusen (8).

The loss of visual function usually manifests in the fourth decade; the development of central scotomas leads to blindness at the age of 70 years (49).

Scotopic responses on full-field ERG are normal; photopic, normal or subnormal. mfERG shows the areas of impaired localized retinal function. The findings on EOG are normal or subnormal.

A mutation in the *peripherin/RDS* gene (Arg142Trp) and mutations on chromosome 17 (p13) have been investigated for a possible impact on the development of this disease (50, 51). The prognosis is bad.

12. *Dominantly Inherited Cystoid Macular Edema*

Dominantly inherited cystoid macular edema (DCMD) is a rare autosomal dominantly inherited macular dystrophy that manifests in the first to second decades with cystoid macular edema and gradual loss of visual acuity. Other signs include hyperopia of high degree, refractive error, and normal ERG (52). Altered red-green and blue-yellow color sensitivity is typical. FFA shows macular edema and perifoveal capillary leakage. The findings on ERG are normal; on EOG, normal or subnormal.

The gene responsible for this disease remains to be identified. It is thought that the locus of the gene is on chromosome 7p (7p15-p21) (53). The prognosis is bad. Visual acuity reduces from 0.1 to 0.01; a formation of central scotoma is seen.

X-Linked Inherited Macular Dystrophy

X-linked inherited macular dystrophy (XLRS) is X-linked juvenile foveal schisis also called congenital retinoschisis. This is a vitreoretinal degeneration commonly diagnosed in childhood. Male individuals are mostly affected. The disease manisfets in the first to second decades of life. If the disease is diagnosed at birth, it is called congenital retinoschisis;

if the symptoms appear later, it is called juvenile retinoschisis. The disease most commonly manifests at the age between 5 and 10 years. The penetrance of the defective *RS1* gene is typically full; however, gene expression is very variable. Therefore, the age at diagnosis presented in the literature varies from 3 months to 57 years (54).

The disease is characterized by reduced visual acuity. Typically, a moderate reduction of visual acuity approximately from 0.2 to 0.5 is observed.

Visual acuity comparing the eyes may considerably differ due to the complications of this disease. Visual acuity may deteriorate with age, and macular changes become more visible.

On ophthalmoscopy, macular changes of various degrees are found in almost all patients: from pigment redistribution of low degree to typical "a spoke-wheel" pattern, or clearly visible appearance of microcysts. Frequently, with age macular abnormalities change from a typical "a spoke-wheel" pattern to an atypical macular degeneration. Schisis of the peripheral retina is usually observed inferotemporally and is documented in approximately 40%–50% of cases (54).

The perimetry shows not significant constriction of visual field (55). Optic coherence tomography shows schisis extending through the inner nuclear layer. Fluorescein angiography demonstrates hyperfluorescence due to the window-type defects of the pigment epithelium, absence of typical cystoid macular edema (56). ERG shows a typical electronegative b-wave in the derivation of maximal response, and in the other derivations, a reduction or a disappearance of b-waves. The abnormalities on ERG are differentiated only in the presence of congenital night blindness; however, the determination of macular cystoid abnormalities and negative ERG leads to the diagnosis of XLRS (56).

A mutation in the *XLRS1* gene on X chromosome (p22.2) has been identified (57). Up to 2005, 127 *RS1* gene mutations were identified, 75 being point mutations (58). The prognosis is good.

Table 3 summarizes inherited macular dystrophies, their mutations, and findings of subjective and objective ophthalmological tests.

Summary

Inherited macular dystrophies are rare pathologies. Currently, 15 types of inherited dystrophies have been identified. Subjective and objective ophthalmological tests are used in the diagnosis of these diseases. However, regardless all these tests, a type

Table 3. Differential Diagnostics of Inherited Macular Dystrophies

Inherited Macular Dystrophies	OMIM Phenotype Number	Gene Mutation	ERG	EOG	DA
AR inheritance:					
Stargardt's macular dystrophy (STMD) (10, 11)	600110	*ABCA4* (1p2-p22)	N/S	N/S	N
Fundus flavimaculatus (FFM) (10)	248200	*ABCA4*, *ELOVL4*, *RDS* (*PRPH2*)	N	N	N
AD inheritance:					
Autosomal dominant Stargardt-like macular dystrophy (17)	600110	*ELOVL4* (6q14) and *PROML1* (4p)	N	N	N
Best vitelliform dystrophy (BVD) (22, 23)	153700	*VMD2* (11p13)	N	A	N
Adult vitelliform dystrophy (25)	608161	*Peripherin/RDS* (6p)	N	N	–
Pattern dystrophy (29)	169150	*Peripherin/RDS* (6p)			
1. Butterfly-like dystrophy			N	A	N
2. Reticular dystrophy RPE (AD/AR inheritance)			N	A	N/A
3. Macroreticular dystrophy			N	A	–
Autosomal dominant drusen and macular degeneration (DD) (32, 33)	–	(6q14)	N	N	N
Sorsby fundus dystrophy (34)	136900	*TIMP3* (22q)	N	N	N
RDS 172 codon-related drusen (38)	613105	Arg172TRP	A	N	A
EFEMP1-related drusen (41, 42)	126600	(2p16.1)	A	N	A
North Carolina macular dystrophy (44)	136550	(6q16)	N	N	–
Progressive bifocal chorio-retinal atrophy (PBCRA) (46)	600790	(6q14-q16.2)	A	A	–
Central areolar choroidal dystrophy (CACD) (49)	21550	Arg142Trp *Peripherin/RDS*	N	N	N
Dominantly inherited cystoid macular edema (DCMD) (51)	153880	(7p15-p21)	N	N/S	–
X-linked inherited MD					
X-linked inherited macular dystrophies (55)	304020	Xp11.4–21.1	A	N	N

MD, inherited macular dystrophies; OMIM, online Mendelian inheritance in man; ERG, electroretinography; EOG, electro-oculography; DA, dark adaptation; A, abnormal; N, normal; S, subnormal.

of inherited macular dystrophies commonly remains not complete clear. The prognosis of most inherited macular dystrophies is satisfactory, but there is no optimal treatment. Therefore, if inherited macular dystrophies are suspected, it is very important to perform all possible tests. Furthermore, genetic studies are very significant for diagnosis and differentiation of inherited macular dystrophies. It is thought that studies of genetic and molecular genetics will allow in the future to determine the mechanisms of pathogenesis responsible for the development and progression of inherited macular dystrophies, and will help seek treatment preventing from blindness.

Statement of Conflict of Interest

The authors state no conflict of interest.

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