

**HEREDITARY RETINAL DYSTROPHIES:  
CURRENT SCIENTIFIC KNOWLEDGE**

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*Mini Review*

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**Abstract**

Hereditary retinal dystrophies are a heterogeneous group of inherited diseases characterized by involvement of different layers of the retina, most often the complex retinal pigment epithelium (RPE) – photoreceptors and cause severe visual impairment – loss of night vision, visual field, colour vision and visual acuity in the initial stages and lead to progressive and severe loss of visual function by altering the anatomy and function of the retina.

The development of medical science and technology has led to the introduction of new, increasingly sophisticated methods for early diagnosis of these diseases – the electrophysiological studies have become more complex and informative. Together with computer automated perimetry, optical coherence tomography (OCT), angio-OCT, fluorescein angiography (FA), fundus autofluorescence (FAF) and adaptive optics, they allow very accurate topographical localization of the defect. And along with the advances in genetics, optogenetics, molecular biology, retinal biochemistry and regenerative medicine, they provide a better understanding of the mechanism of these diseases and increase the therapeutic opportunities.

The treatment of many of these diseases is still problematic, but because most of them are severely disabling the individual, the scientists' efforts are focused on finding an appropriate therapy. For many of these diseases, there are clinical trials worldwide, the results of some of them are quite encouraging, and many effective therapies for these currently incurable diseases are expected to be introduced in the near future.

The purpose of this study is to analyze the scientific knowledge, as well as the therapeutic opportunities that are being experimented to date.

**Key words:** hereditary retinal dystrophies, electrophysiology, gene therapy, rare eye disease

**Introduction.** Hereditary retinal dystrophies are a heterogeneous group of inherited diseases characterized by involvement of different layers of the retina, most often the complex retinal pigment epithelium (RPE) – photoreceptors and cause severe visual impairment – loss of night vision, visual field, colour vision and visual acuity in the initial stages and lead to progressive and severe loss of visual function by altering the anatomy and function of the retina.

These are diseases with a relatively low frequency in the human population. This is the reason why they are included in the group of “rare eye diseases”. According to different sources, about 750 are the retinal, choroidal, or both dystrophies with a specific gene defect identified in about 270 of them [1].

**Modern diagnostic methods.** The development of medical science and technology has led to the introduction of new, increasingly sophisticated methods for early diagnosis of these diseases – the electrophysiological (EF) studies have become more complex and informative. Together with computer automated perimetry, optical coherence tomography (OCT), angio-OCT, fluorescein angiography (FA) fundus autofluorescence (FAF) and adaptive optics, they allow very accurate topographical localization of the defect. And along with the advances in genetics, optogenetics, molecular biology, retinal biochemistry, and regenerative medicine, they provide a better understanding of the mechanism of these diseases and increase the therapeutic opportunities.

The wide availability of modern diagnostic methods enables improved assessment of the retinal structure and function.

**Electrophysiological (EF) methods** are the most important in the diagnosis of hereditary retinal dystrophies. They are the “golden standard”, especially valuable in the initial stages or in asymptomatic forms, when the subjective symptoms are absent and in many cases with normal fundus. They are especially important for monitoring the changes in dynamics, which is of particular importance for the prognosis of disability [18]. After the family history and clinical examination, ERG is the next test to differentiate the retinal dystrophies.

EF methods are objective methods for studying the visual analyzer function. These include electroretinography (ERG), electrooculography (EOG) and visual evoked potentials (VEPs) [2].

**Fullfield ERG (ffERG)** is an EF method for objective measurement of total retinal function, isolated total cone function, and isolated total rod function. It is especially informative in generalized retinal dystrophies as retinitis pigmentosa (RP) and other rod-cone dystrophies as Leber congenital amaurosis, cone-rod- or cone dystrophies [3].

**Multifocal ERG (mfERG)** was introduced by SUTTER and TRAN in 1992 [4]. This is a relatively new technique that allows local ERG responses to be recorded simultaneously from many regions of the retina. The responses in mfERG are thought to originate from the cones, as it has been proved to have a close relationship in the generation and the signal shape of mfERG, on the one hand, and the fERG-cone response, on the other. MfERG is very useful in macular dystrophies as Stargardt disease or Best disease, as well as for detection of localized abnormalities in the retina [4,5].

**Electrooculography (EOG)** has been popularized in clinical practice by ARDEN [18]. Unlike ERG, EOG is not a stimulated response, it records the constant potential that exists in the eyeball. The potentials recorded during the EOG are used to calculate the Arden ratio. It is obtained by dividing the peak amplitude (A) under photopic conditions to the maximum decrease in A during dark adaptation. The EOG mainly reflects the function of RPE, but depends on the integrity of RPE, photoreceptors and interphotoreceptor matrix. For this reason, EOG is pathological in photoreceptor diseases, and other generalized diseases of the external retina and RPE such as Best disease. FfERG is in many cases normal in the early stages of this disease, that is why EOG test is very important for the diagnosis because it demonstrates characteristic abnormal waveform at each stage of the disease as the Arden coefficient is usually less than 1.5, most often between 1.0 and 1.3 [6].

**Fluorescein angiography (FA)** is used to visualize the blood circulation in the retinal and choroidal vessels. As we know, the pathological symptoms that can be observed in this type of examination are: hypo-, hyper- and autofluorescence.

**Fundus autofluorescence (FAF)** is used to assess the RPE function. After irradiation with excitable light, some ocular structures have the ability to fluoresce. Such structures are the pigments in RPE cells, druses, lipofuscin in Best disease [1]. Lipofuscin, which is produced by the destruction of the outer segments discs of the photoreceptors, is stored in RPE. When stimulated with light of appropriate wavelength, it serves as a marker for the activity of the photoreceptor-RPE complex. Hyperautofluorescence suggests increased activity that may reflect photoreceptor cell stress, while hypoautofluorescence is a sign of cell death. Stargardt disease has a characteristic autofluorescence pattern [7].

The study of contrast sensitivity, adaptation, colour vision and visual field are also very important in the diagnosis of these diseases, but they are well-known, time-tested studies.

**Optical coherence tomography (OCT)** provides noninvasive, objective assessment of the different retinal layers. It allows to perform optical cross sections of the retina with high resolution. In hereditary retinal diseases, which are a very heterogeneous group, atrophy of the affected layers of the retina is most often observed – a decrease in the thickness of neurosensory retina, the layer of photoreceptors or RPE.

Recently, the latest **angio-OCT** devices, which in some way combine the information obtained by OCT and FA studies, are being increasingly used. Its advantage is that a three-dimensional image of the retinal and choriocapillary vessels is obtained in different depths with a tendency to develop technologies that allow visualization of the choroid vessels, which will enrich the scientific knowledge of how the different retinal dystrophies change the retinal and choroid vasculature. A significant disadvantage of the currently available equipment is the lack of information about the retinal periphery, very important in some of the retinal dystrophies and especially significant in patients with RP.

However, the equipment we currently have does not have the necessary resolution to visualize the individual photoreceptors on a cellular level.

**Adaptive optics** is a new strategy in which the individual photoreceptor cells are visualized by measuring the aberration of light exiting the eye through complex systems. Some devices visualize only the photoreceptors with preserved outer and inner segments, others – only the cones with preserved inner segments, and others visualize RPE cells [1].

Adaptive optical systems are not yet widely available, but they are valuable research tools that help to study on a cellular level the mechanism of photoreceptor damage in different stages of retinal dystrophies and have a potential as a new sensitive, objective method for detecting the pathomorphological mechanisms and to ensure the safety and efficacy of clinical trials of different new therapies in patients with these diseases [1].

**Genetic tests.** The genetics of retinal dystrophies are complex: the same disease can be caused by a defect in several genes. In some cases the same gene can be linked to different diseases. To date, more than 270 genes associated with retinal degeneration have been described, but many more are thought to be identified [7].

Recently, much effort has been focused on the search of genetic defects and the pathophysiological mechanisms of retinal dystrophies. It is very important to establish the exact location of the mutation, as it is known that depending on this, the gene may have different expression or even different phenotypes. This phenomenon has been observed in a number of autosomal dominant genes. For example, mutations in PRPH2 gene can cause cone-rod dystrophy or RP, mutations in RHO gene can cause stationary night blindness (CSNB) or RP and mutations in CRX gene can lead to Leber congenital amaurosis or cone-rod dystrophy [8].

Autosomal recessive genes also exhibit different phenotypes depending on the location and type of mutation within the gene. For example, mutations in ABCA4 gene cause Stargardt disease, juvenile macular dystrophy, RP, or cone-rod dystrophy [9,10].

**Classification.** Different classifications are available, but the most commonly used is the anatomical one, which is based on the primary affected layer – retina, macula, RPE, choroid, vitreous/retina. But this approach is not always

the right one, because in some dystrophies several layers or areas are affected at the same time.

Another type of classification is based on heredity. Many genealogies have been studied, which clarifies the ways of inheritance passing to generations [11].

There is a third type of classification, which is based on the phenotypic assessment performed after clinical examination, electrophysiological and psychophysical studies. Careful analysis of all these studies results makes it possible to assign them to a particular nosological group clinically, and later to be confirmed by molecular genetics [11].

For clinical identification purposes, dystrophies with primary diffuse photoreceptor involvement are classified separately from those with predominant central (macular) involvement, as they differ significantly by symptoms and prognosis.

Diffuse photoreceptor dystrophy is divided according to the primary affected type of photoreceptors into cone-rod and rod-cone dystrophies.

There are also groups with primary choroidal involvement, as well as vitreoretinal dystrophies.

Depending on the course of the disease, they are divided into stationary and progressive.

Some of the dystrophies appear in early childhood, while others have a later onset and a better prognosis. The family history is extremely important because most of them have a pronounced heredity.

Sometimes the patient may have a “de novo” mutation, which can be inherited in the next generations, or in some family members the disease may be relatively asymptomatic. For this reason, it is always important to examine the clinically healthy family members.

Hereditary eye diseases have bilateral symmetrical involvement and if the process is unilateral, other causes should be sought – intrauterine infections, trauma or inflammatory diseases.

There are isolated forms with ocular involvement only, as well as syndromic dystrophies, which are part of a systemic disease involving other tissues and organs [11].

***Diffuse photoreceptor dystrophy.*** A group that includes many inherited retinal diseases in which both types of photoreceptor cells are affected, but not in the same degrees. We distinguish between rod-cone dystrophies with predominant involvement of rods, and cone-rod dystrophies with predominant involvement of cones [2]. This group includes the different forms of RP in which the scotopic response in ERG is affected first. On computer perimetry, a concentrically narrowed visual field is observed, as the scotomas begin in the middle periphery and, as the process progresses, extend more peripherally, with a narrow centrally preserved visual field until the secondary involvement of the macula. In patients with cone-rod dystrophy, concentric paracentral scotomas are initially observed, which progress later peripherally and centrally. Central scotomas are the most common in cone dystrophies [11].

**Rod-cone dystrophies. Retinitis pigmentosa** (RP) was first described in 1853 by van Trigt, and the term was first used by Donders in 1857 [2]. It combines a group of genetic diseases that are characterized by recognizable phenotypic retinal changes. This is a clinically and genetically diverse group of inherited diffuse degenerative diseases of the retina, initially affecting the rods and later the cones. That is why it is considered a rod-cone dystrophy. This is the most common hereditary retinal dystrophy, with a prevalence of approximately 1:3500 population; there are about 2.5 million patients with RP worldwide. The onset of the disease, the degree of progression, the possible loss of vision and the associated ocular involvement depend on the mode of inheritance. Currently, more than 100 different genetic types of RP (or similar degenerations) have been described, and all inheritance patterns have been observed. To date, more than 60 different chromosomal loci have been identified, with defective genes and specific mutations identified in 50 of them [2,12]. Many cases are due to a mutation in the rhodopsin synthesis gene. The mutations found are very diverse, which determines the severity of the disease. For example, stationary night blindness is due to a mutation in codon 90, while severe forms are associated with mutations that interfere with the binding of vitamin A to the rhodopsin protein. Mutations in PRPH2 gene have a very wide clinical manifestation, ranging from typical RP to late-onset vitelliform dystrophy, but it is the most common cause of hereditary autosomal dominant maculopathy. Their distinction is made by functional studies [13-17].

Forms with autosomal dominant (AD), autosomal recessive (AR) and X-recessive (XR) inheritance occur. XR form is the rarest (5-15%), but is the most severe and usually leads to complete blindness until the third or fourth decade. To date, mutations have been identified at 6 loci on X chromosome. AR diseases (50-60% of all cases) can also be severely disabling. AD diseases usually have the best prognosis, they are about 20-30% of all cases of RP. According to other sources, 50% of cases are sporadic, which means that this is the most common form of RP. Rare cases of mitochondrial and X-linked dominant inheritance have been reported in patients with RP [13].

The typical fundus finding in patients with RP includes arterioles narrowing, pale optic nerve disc and varying amounts of pigment cells peripherally and around the vessels most commonly. The peripheral retina and RPE appear atrophic, even if pigment cells are absent (RP sine pigmento), cystoid macular edema or epiretinal membrane is usually observed in the macula in advanced stages. Posterior subcapsular cataract may also occur [11,18].

The most informative study of the disease is ffERG, which demonstrates a reduced scotopic response in the early stages and a non-registering wave in the more advanced stages. Depending on the degree of cones involvement, the photopic response is affected to varying degrees. MfERG is less informative, but faster than ffERG. OCT gives information about the condition of the macula [2].

Patients develop progressive photoreceptor degeneration, and subsequently the visual acuity is affected. It begins with manifestations of impaired night vision, affected peripheral vision, and later the central vision is decreased [19,20]. Changes in ERG may precede the characteristic retinal pigment changes in all genetic variants (retinitis pigmentosa sine pigmento). In most cases, in patients with AR or XR inheritance, an unregistered ERG or ERG with very low A is found in the initial stage of the disease. In the recessive type of inheritance, different variants of ERG can be observed [21].

AD forms are the mildest in which the symptoms are minimally expressed by the age of 50.

Some of the XR gene carriers have the characteristic pigmentary changes focally in the retina, but in almost all of them an amplitude reduction in ERG is found [22].

The unilateral RP is considered to be a pigment degeneration with low amplitude or unregistered ERG, if the fellow eye has normal morphology and EF studies results. Many authors consider that this is a secondary manifestation of traumatic, vascular or inflammatory damage and not an unilateral manifestation of RP, especially in absence of ERG changes in the fellow eye and a family history [23].

Sometimes sectorial RP is observed. It occurs symmetrically in both eyes with the characteristic pigment and vascular manifestations in only one quadrant (most often inferior or nasal). ERG in most cases is subnormal, similar to the initial stages of AD forms of RP. The inheritance is AD with a slow progression. Some authors believe that this is RP with asymmetric involvement of the different quadrants, as they found functional changes in the visibly unaffected areas of the retina [2]. These forms have a better prognosis.

**Leber congenital amaurosis** is an inherited disease that includes several rod-cone retinal dystrophies with an early onset, often with low vision and nystagmus presented at birth. Its frequency is 1:33 000 population. Until now three AD and eighteen AR mutations have been identified. The mutation in RPE65 gene, which encodes the enzyme isomerohydrolase required for the production of 11-cis retinal needed for rhodopsin synthesis, is best studied [13].

The visual acuity can range from 0.1 to lack of light perception. The fundus may appear normal at first, but in the advanced stages there is a picture of retinitis pigmentosa with optic disc atrophy. Most children have normal intelligence, but there are also systemic associations, including mental retardation, deafness, epilepsy, renal abnormalities, skeletal malformations and endocrine dysfunction. Cataract and keratoconus may occur in older children. Both the scotopic and photopic responses are affected in fERG, but there is some residual cones activity [13,16].

In many children, lack of ERG activity is registered at birth. This distinguishes the disease from the other generalized retinal dystrophies, in which

electrophysiological activity decreases slowly and gradually with age such as RP, albinism and others.

For one of the Leber amaurosis forms with mutation in the two alleles of RPE65 gene, since 2018 gene therapy (Voretigene neparvovec) has been approved for use, after successful clinical trials.

In many syndromes similar changes in ERG occur – from slightly reduced A to unregistered ERG. Such are the syndromes of Usher, Laurence–Moon–Bardet–Biedl, Alstrom, Bassen–Kornzweig, Joubert, Senior–Loken, Cohen, and others. In some of mucopolysaccharidosis, the same characteristic changes in ERG also occur.

EF studies in retinitis punctata albescens are similar to those in RP, depending on the severity, first the scotopic and later the photopic response are affected with a decrease amplitude and prolonged latency.

Similar whitish flakes in the fundus as in *retinitis punctata albescens* are found in fundus albipunctatus. Some researchers, based on genetic evidence, suggest that they are variations of the same disease with a more benign course in fundus albipunctatus. In support of this is the mutation in RLBP1 gene, which can cause both diseases. Unlike retinitis punctata albescens, fundus albipunctatus has no narrowed blood vessels, no narrowed peripheral visual fields, and has a normal optic nerve disc. The visual acuity remains normal [24,25]. According to other authors, it is an independent disease with AR inheritance, nyctalopia is observed [26]. It is characterized by prolonged adaptation of both rods and cones. The recovery of ERG and EOG responses is severely delayed, which corresponds to the time required for regeneration of visual pigments. The disease is thought to be due to a defect in the cycle of this regeneration, as a result of which it is prolonged. A mutation has been identified in the gene responsible for the synthesis of the enzyme 11-cis retinol dehydrogenase, which is found in RPE and serves as a catalyst for the conversion of 11-cis retinol to 11-cis retinal. The reduced amount of this enzyme is the reason for the delayed regeneration of visual pigments in both types of photoreceptors. Fundus albipunctatus is classified in the group of congenital stationary night blindness because it does not progress [24].

**Congenital stationary night blindness (CSNB).** Unlike RP, which is characterized by progressive night blindness and progressive photoreceptor damage, CSNB is a group of congenital inherited retinal diseases with non-progressive night blindness and no structural photoreceptor damage. The patient may not even notice that he has night blindness if the symptoms are mild. Schubert–Bornschein type CSNB is the most common and is characterized by negative fERG wave (when b-wave A is lower than the a-wave A in the combined response. The peak of b-wave is below the isoelectric line and the amplitude ratio b/a is under 1).

The CSNB with a normal fundus has AD, AR or XR type of inheritance and mutations have been observed in 17 different genes. It is characterized by reduced



rods function and preserved cones function in fERG. Later the photopic function is also affected. Usually in AD inheritance the visual acuity is normal, but in AR and XR forms the vision is reduced, nystagmus and high-grade myopia are common [2].

CSNB is one of the diseases that are included in the term “stationary night blindness”. The group includes also Oguchi disease, the Kandori retina and congenital monochromatism (achromatopsia). But in CSNB only the fundus is normal [2].

**Cone-rod dystrophies.** The distinction between cone-rod dystrophy and cone-dystrophy is very difficult, it is based on electroretinographic findings and is not accepted by all authors, as in most cases in the final stages there is always an impact on the rods function. The distinction is made taking into account the ERG result in the initial stages, in which in some of the diseases there is a big dissociation between the very impaired function of the cones and the very preserved function of the rods. These diseases are distinguished by some researchers in a separate group of cone-dystrophies. The group of cone-rod dystrophies includes those diseases in which the function of the rods is affected relatively early, even slightly [27].

Molecular genetics helps to distinguish the specific causes of the different diseases. According to recent studies, mutations that cause a phenotype of pronounced Leber congenital amaurosis can also cause cone-rod dystrophy, depending on whether there are two different mutations in the same gene or the mutation is in the same allele. A mutation in GUCY2D gene can cause dominant cone-rod dystrophy, while a recessive mutation can lead to Leber amaurosis. Various mutations in CRX gene can cause cone-rod dystrophy, Leber amaurosis, or RP. To date, more than 25 gene mutations are known to cause progressive cone- and cone-rod dystrophies [11].

Cone-rod dystrophy is a heterogeneous group of inherited diseases with AD, AR or XR inheritance, in which the cones are affected earlier and more severely. In the advanced stages, the rods are also affected. In the early stages, the fundus in many cases looks almost normal, in the more advanced stages only, we can find changes in the macula. It occurs with a visual acuity decrease, affected colour vision, central and paracentral perimetric scotomas and decreased A in photopic and scotopic ERG. Some patients may also have nystagmus and photophobia. In fERG, the cone response is almost unregistered. The scotopic ERG in the initial stages may be preserved, but later it is also changed, although significantly more preserved than the photopic one. In some patients, characteristic vascular and pigmentary changes may occur in some areas of the fundus, more commonly in the macula, as well as a manifestation of night blindness. In these cases, it is difficult to decide whether it is cone-rod or rod-cone dystrophy. Leading are the primary symptoms at the beginning of the disease, as well as which ERG response is more preserved [28].

**Cone dysfunction.** It describes hereditary diseases that can be inherited by all genetic patterns. As a rule, they are more often progressive, but can also be stationary. A distinction must be made between them and the colour vision disorders, which are also hereditary but are associated with a defect in only one of the cones functions; they do not progress, do not lead to reduced visual acuity and central perimeter defects. Diseases with cone dysfunction should also be distinguished from hereditary maculopathies, in which the cones in the centre of the macula are primarily affected [29].

The onset of the progressive forms is usually in puberty or later. Nystagmus, photophobia, hemeralopia, decreased visual acuity, impaired colour vision may be observed. They usually have a normal fundus, but atrophy of RPE in the macula can be seen, visualized as discrete “window effect” to the typical “bull’s eye” pattern of general RPE atrophy in the macula [27].

On fERG the photopic activity is usually unrecorded, while the scotopic activity is normal or slightly subnormal. They are much less common than combined retinal dystrophies, which affect both types of photoreceptor cells. In the advanced stages, the function of the rods is almost always slightly affected, which is the reason why some authors think that they are also cone-rod dystrophies with much more severe and earlier cones involvement [29].

**Hereditary macular dystrophies.** They are characterized by an irreversible gradual decrease in central vision, significant decrease in the visual acuity at a relatively young age. Sometimes the differential diagnosis is not easy and the therapy is currently problematic [11,18].

**Stargardt disease/fundus flavimaculatus.** It is considered to be a variant of the same disease. This is the most common juvenile macular dystrophy and a common cause of loss of central vision before the age of 50, with the first manifestations occurring at different times, even in members of the same family. Visual acuity usually remains within a few tenths, central perimetric defects can be observed. The disease is slowly progressive, its frequency is 1:8000 population. Inheritance is most often AR and is due to mutations in ABCA4 gene, which encodes the synthesis of a transport protein expressed in the outer segment of the rods. The role of this protein is to help transport vitamin A (needed to form photosensitive pigments in rods and cones) from photoreceptors back to RPE cells, where vitamin A molecules are recycled for reuse. In Stargardt disease, this protein is either absent or has a significantly reduced function, causing vitamin A dimers to accumulate in PPE cells as well as in photoreceptor cells and damage them [30].

The gene is very large (50 exons) and is characterized by pronounced polymorphism, so far more than 900 variants of mutations have been identified. Other mutations that cause the same phenotype are STGD4 and ELOVL4, as well as mutations in PRPH2 and PROM1 genes [10].

The classic phenotype of Stargardt disease is characterized by atrophy of the fovea, surrounded by discrete, yellowish, round spots at the level of RPE, beginning in adolescence. If the spots are scattered all over the fundus, the condition is called fundus flavimaculatus [31].

Characteristic changes were observed in FAF: peripapillary atrophy of RPE, hypoautofluorescence of the fovea, and alternating radial streaks of hyper- and hypo-autofluorescence in a peripheral direction. The clinical diagnosis of Stargardt disease can be confirmed by the presence of the so-called “choroidal silence” in FA, due to the masking of the underlying choroidal fluorescence from the vast area of abnormal RPE. Areas of hypo- and hyperfluorescence are observed in the macula. As the disease progresses, lipofuscin-like material accumulates in the RPE. Vitamin A should be avoided in patients with Stargardt disease, as it increases the accumulation of lipofuscin [32].

On ERG the photopic response is normal or subnormal, the scotopic response is usually normal. EOG is usually subnormal. The differential diagnosis includes all conditions that lead to the picture of “bull’s eye” – the various cone- and cone-rod dystrophies [33].

**Best viteliform dystrophy.** It is named after the ophthalmologist who first described it in 1905. It is the second most common hereditary maculopathy after Stargardt disease. It covers several congenital diseases with different transmission mechanisms. The typical Best disease is an AD disease, with variable expression and penetrance. It usually manifests in the first decade of life, affects both eyes, but asymmetrically and develops very slowly. It is due to a defect in BEST1 (VMD2) gene, located in the long arm of chromosome 11 and responsible for the synthesis of a protein bestrofin, which regulates the transport of fluids and ions through the membranes of RPE cells and alters the junction between RPE and photoreceptors, which leads to the accumulation of lipofuscin in the macular area. A mutation in the same gene can also cause RP. Best disease has five stages: During the first phase, no changes in the macula are observed. The second, viteliform stage is defined by a characteristic yellowish deposit with sharp borders in the macula with an appearance of egg yolk. In the third, pseudohypopyon stage, the lipofuscin slowly begins to disperse, making the macula look like the so-called “scrambled eggs” – at this stage the visual acuity starts to decrease slightly. The last stage is atrophic with atrophy of RPE. These phases are very clearly differentiated by FA. Hyperautofluorescence of deposited lipofuscin is detected on FAF. OCT demonstrates the accumulation of lipofuscin in RPE as a hyperreflective area [2,34].

This disease is characterized by a big dissociation between severely altered fundus and the preserved visual function. ERG is usually normal. Pathognomonic is EOG, which is used as a marker to diagnose Best disease. The EOG response is always abnormal, the light peak is greatly reduced or absent, which leads to a decrease in Arden coefficient, even in a normal fundus. Therefore, EOG is also

used to find the gene carrier among the parents in an established disease in the child. It can also be used to diagnose atypical undifferentiated macular lesions; if the EOG is altered, it is most likely Best disease [35].

The group of macular dystrophies includes several other diseases – AR bestrofinopathy, AD vitreoretinoblastopathy, the vitelliform retinal lesions with late onset, the so-called “pattern dystrophies”, “North Carolina” macular dystrophy and the familial druses with early onset.

**Choroidal dystrophies.** Conditions in which the primary involvement of the retina or RPE causes choriocapillary atrophy. Their name comes from the past because of the clinically visible involvement of the choroid, but it does not reflect the current molecular knowledge. They are characterized by nyctalopia, peripherally narrowed visual fields and reduced visual acuity. In fERG is found decreased scotopic amplitude, the photopic response is less affected. The distinguishing feature of this disease, in contrast to RP, is that here the implicit time remains unchanged, in contrast to RP, where it is strongly prolonged, along with the reduced amplitude [11, 18].

**Diffuse degeneration. Chorioideremia.** A rare inherited disease (1:50 000 population cases in Europe), many of which are concentrated in northern Finland. The name comes from ancient Greek and means “zone without choroid”. Nowadays we know that the choroid atrophy is a late stage of the disease and does not reflect its etiology, which is important in the development of therapeutic strategies [36].

This is an X-linked chorioretinal dystrophy, characterized by diffuse, progressive degeneration of RPE and choriocapillaris. It is due to mutations in CHM gene, which is located in Xq21.2 and encodes the synthesis of geranylgeranyl-transferase transport protein. Histological examination proved that the defect is in RPE and not in the choroid. In the affected men, the degeneration initially manifests as pigmented spots in the area of the equator and the macula, which gradually become confluent and lead to atrophy of RPE and choriocapillaris in these areas. The fovea remains intact for a very long time [36].

Patients complain of nyctalopia and slow, progressive peripheral loss of visual field. Visual acuity remains relatively good for a long time. Hypofluorescent atrophic areas are found in FA and FAF, and the large choroidal and retinal vessels remain intact. Usually the scotopic ERG is abnormal in the initial stages and as the process progresses it becomes unregistered, the photopic ERG is also affected. In advanced stages, optic atrophy may also be observed. Carriers of the gene mutation are usually asymptomatic, but very often isolated small atrophic areas can be seen in the fundus, which, however, do not affect the ERG signal [37].

**Gyrate atrophy** is an AR dystrophy caused by mutations in the gene responsible for the synthesis of ornithine aminotransferase (OAT), an enzyme which is a major factor in the degradation of ornithine. The gene is located on chromosome 10. As a result of the mutation, plasma levels of ornithine are greatly elevated and it is toxic to RPE and the choroid. In the early stages in the fundus

there are characteristic equatorial areolar areas with atrophy of RPE and choriocapillaris, which later merge and form a generalized peripheral atrophy with a characteristic appearance – with a pronounced demarcation line between the peripheral atrophic and the normal central area. This atrophy progresses over time peripherally and centrally, but the fovea is spared for a very long time [11,38].

Nyctalopia usually develops in the first decade, as well as concentric narrowing of the visual field and later reduced visual acuity. It is often combined with myopia. Diagnosis is easy with elevated serum levels of ornithine. Molecular confirmation is performed by proving the mutation. Hypofluorescent atrophic fields are visualized on FA. The scotopic ERG early become unregistered, the photopic one is also changed [11,38].

The treatment includes pyridoxine (vitamin B6), which can normalize ornithine levels in plasma and urine. Clinically, there are two types of patients – the first group does not respond to this therapy, while the second group responds well to this treatment. That is why their disease is not so severely manifested and progresses more slowly. An arginine-poor diet is also considered.

**Hereditary vitreoretinal dystrophies** is a heterogeneous group of hereditary dystrophies with degenerative changes in the vitreous and retina.

**Juvenile X-linked retinoschisis** is an XR inherited disease, with a defect in RS1 gene localized in Xp22.2, which is characterized by bilateral maculopathy and peripheral retinoschisis in 50% of cases, as well as degenerative changes in the vitreous; it is optically empty or with fibrillar destruction from childhood. The defective gene has been found to be responsible for the synthesis of an adhesive protein called retinoschisin, which is found in all retinal neurons but is also involved in Mueller cells, which carry out the integrity between the retinal cells. The defect in Mueller cells results in splitting of the RNFL from the rest of the sensory retina, in contrast to acquired retinoschisis, in which the splitting occurs in the outer plexiform layer. The incidence of this disease is 1:5000–1:25 000 population. Boys are affected, usually the disease is asymptomatic in the mothers-carriers. The prognosis depends on the severity of maculopathy, which often leads to a significant reduction in the visual acuity at a young age. Foveal schisis with cystoid changes is often found, there is no foveolar reflex. These changes are well visualized in OCT – cystic spaces are visible in the outer plexiform layer. In FA and FAF, central hypofluorescence is found in the macula, surrounded by a hyperfluorescent zone. The peripheral schisis is most common in the lower temporal quadrant. It usually does not progress, but hemorrhages within the schisis or vitreous, development of neovascularization and rarely rhegmatogenous or tractional retinal detachment and traumatic rupture of the foveal schisis may occur. ERG in severe peripheral retinoschisis is characterized by a negative b-wave in fERG. The treatment is symptomatic depending on the complications. Gene therapy is currently being developed as the only effective way to correct the protein defect [18].

**Stickler syndrome.** It is also called hereditary arthro-ophthalmopathy. This is a genetically heterogeneous group with a defect in collagen connective tissue (mutation in COL2A1 and COL11A1 genes). The inheritance is AD or AR with full penetrance and variable expression. A mutation was found in the 12th chromosome. This is the most common cause of retinal detachment in children. Ocular manifestations are observed in type STL1 and STL2. The triad symptoms are myopia, cataract, and vitreoretinal degenerations with fibrillar vitreous destruction and radial lattice-like degenerations with PPE hyperplasia and peripheral sclerosed vessels. Retinal detachment often occurs. Sometimes it is combined with glaucoma. Systemic manifestations include musculoskeletal malformations, changes in the oral cavity, often deafness [18,39].

The treatment is prophylactic laser therapy or 360 ° cryotherapy and in case of complications – vitrectomy, which, however, is not very successful. Cataract surgery is often required.

**Wagner syndrome** is an AD inherited disease with a mutation in VCAN gene. It is extremely rare, similar to Stickler syndrome, but without systemic manifestations. Severe fibrillar vitreous destruction and formation of traction membranes is observed, chorioretinal atrophy with sclerosed vessels occurs in the periphery of the retina, which leads to peripheral narrowing of the visual field and nyctalopia. Retinal detachment often occurs. Cataract and myopia are observed, possibly glaucoma [18,39].

In the initial stages, ERG is normal or slightly altered, the scotopic ERG becomes abnormal with the development of extensive peripheral atrophic areas, and the photopic ERG with changes in the macula [44].

The treatment is symptomatic.

**Familial exudative vitreoretinopathy.** Most often AD (chromosome 11q13-q23), but also AR or XR inherited disease, with high penetrance and variable expression. It is characterized by slow progression due to improper vascularization of the temporal retinal periphery, similar to that observed in retinopathy of prematurity. It manifests in early childhood and has several stages: peripheral temporal avascularity with a sharp demarcation line between the vascular and avascular retina, peripheral retinal degeneration “white without pressure”, vitreoretinal adhesions, vitreous destruction. In the second stage, the formation of preretinal fibrovascular proliferations begins, which at a later stage leads to traction on the macula and detachment of the retina, hemophthalmos. It is possible to have high-grade myopia [18,39]. The treatment is prophylactic laser therapy of the altered temporal retina, intravitreal anti-VEGF therapy, vitrectomy. The prognosis is not good.

**Goldmann–Favre syndrome** (S-cones hyperfunction). Inherited AR disease with variable expression, the defective gene is NR2E3. A very rare condition in which there is severe impairment of the function of the rods and two types of cones (M- and L-cones), while the third type of cones (S-cones) are in hyperfunc-

tion. It is characterized by nyctalopia in childhood and sometimes hemeralopia, increased sensitivity to blue light, pigmentation along the vascular arcades and middle periphery, where peripheral schisis can be seen. Vitreous destruction is observed, and cystoid maculopathy or schisis in the macula [18,39]. The prognosis is bad.

**Treatment, perspectives, social aspects.** All described hereditary retinal dystrophies belong to the so-called “rare eye diseases” – about 900 in number and like the other rare diseases (about 7000, 70% of them are caused by genetic factors) are a challenge for treatment for each national health system [40].

Special attention should be paid to the diagnosed patients, especially when discussing the likelihood of blindness. It is necessary to explain accurately and in detail that these are chronic, slowly progressing diseases that lead to severe impairment of the visual function. For this reason, patients should be trained to use their residual vision.

It is obligatory to perform genealogical and medico-genetic analyses in order to establish the damage and to trace the spread of the disease within the genealogy. Family planning and the possibilities for using prenatal diagnostics are also essential for these patients.

When patients are sufficiently informed, they can also make better decisions about the organization of their home environment, career opportunities, visual rehabilitation and the ability of movement. Today there are many additional tools for the inclusion of these people in the society – specialized computer systems, special telescopic devices.

At this stage, it is difficult to talk about an actual treatment of many of them, although in recent years high expectations have been placed on modern experimental treatments with subretinal embryonic stem cells transplantation, implantation of special chips in the retina connected to external devices for stimulation of the rest of the functioning retina to obtain some useful vision. Although such devices are already available, hard work is still being done to improve them. Many hopes are placed on gene therapy, which in most diseases is still in an experimental stage (with one exception) and has one significant disadvantage – the very high cost, unaffordable for the patient and for most health systems.

The discovery of mutated genes allows for the development of gene therapy in these otherwise incurable diseases. Recently, a new class of pharmaceutical products called biopharmaceuticals has been introduced. They are products derived from recombinant organisms and represent an active gene or protein that can correct the gene mutation by modifying the genetic composition of human cells with the introduction of a new DNA code. The modern concept of gene therapy includes the delivery of genes from recombinant viruses, the delivery of non-viral genes and modifying gene technologies such as RNA technology [41].

Gene therapy aims to replace the mutated gene with a healthy copy, to inactivate the action of the mutated gene, or to introduce a new gene into the body to help it cope with the disease [41].

One of the biggest barriers to the efficacy of gene therapy is the cell membrane. Therefore, the property of viruses to pass through it and deliver their own genes to the cell is used, thus forcing it to start producing a certain product. With the development of the recombinant technologies, the viral genome can now be manipulated by removing the part that causes disease and replication, but preserving the genes useful for its role as a vector (gene transporter). The free region in the virus genome, obtained at the site of the removed genes, is then used to insert the therapeutic gene. In this way, recombinant viruses become carriers of a portion of human DNA that encodes the therapeutic gene. The technology for the production of recombinant viruses has now been mastered and can effectively perform both functions – to penetrate the cell through the cell membrane and deliver the therapeutic gene to the DNA of the human cell, and after a short delay it begins to produce therapeutic protein. Thus its normal function is restored. It is important to note that none of the recombinant viruses used as vectors can reproduce. Different types of viruses can be used as gene therapy vectors, and in terms of ophthalmic applications, adeno-associated viruses have been shown to be most appropriate [41].

Another modern approach to the treatment of hereditary disease is implanting stem cells, the so-called regenerative medicine. The term “stem cell” is currently used to describe a wide range of different progenitor cell types, denoted by different terms, including “embryonic”, “adult”, “pluripotent” and “multipotent”, as well as tissue-specific such as nerve or hematopoietic stem cells. The use of fat stem cells is not currently recommended [7,42]. Each of these stem cells has a unique ability to differentiate in a specific direction, which makes it possible to replace a defective cell type [10,41].

Recent studies in animal models show that transplantation also transfers cytoplasmic material from the donor cell to the recipient photoreceptors [43–45]. It is also possible to transfer material between cells for therapeutic purposes, e.g. stimulation of host Mueller cells to their differentiation into photoreceptors [44]. Experimental studies are also performed in this direction.

Another promising approach is the use of “in vitro” derived retinal organelles, resulting from the cultivation of autologous pluripotent stem cells which is used for therapeutic purposes, the so-called 3D printed models of retinal tissues [36,46]. LAVIK et al. [46] won the 2017 award of the American National Eye Institute, offering a method for obtaining 3D printed models of retinal tissues. In laboratory conditions they created layers of different types of neurons in the retina, and the method allows the cells to be properly oriented to mimic the structure of the human retina.



As already mentioned, for one of the forms with mutation in the two alleles of RPE65 gene, phenotypically expressed as Leber congenital amaurosis, the first gene therapy of hereditary retinal dystrophy (Voretigene neparvovec) has been approved for use since 2018, after successful clinical trials. It uses adeno-associated viruses as vectors to replace the defective gene. The results show a lasting improvement in visual acuity to distinguishing objects, improved perimeter results, improved mobility, the appearance of a pronounced pupillary reaction, without significant side effects [8].

Several clinical trials are currently underway for the treatment of XR RP, which results in severe photoreceptor damage in early childhood. Adenoviral vectors (AAV8) were used to replace the mutation in the defective RPGR gene, which was inserted subretinally. The studies are not yet complete, but the first results have already been published and show an improvement in perimetric results, as well as an improvement in the visual acuity, which sounds encouraging. There are no serious side effects, the only disadvantage is the very high cost [15].

There is another clinical study using an oral substance codenamed QLT091001 (Zuretinol acetate) to treat Leber amaurosis or RP caused by AR-transmitted mutations RPE65 or LRAT [12,13,16].

Another clinical study examines the efficacy of a substance codenamed QR-421a, which is an intravitreal RNA oligonucleotide administered once in patients with RP and Usher syndrome with a mutation in exon 13 of USH2A gene. The results are expected after about 2 years [8,17,47].

Another clinical study currently underway is for a treatment of Stargardt disease, in which a subretinal adenoviral vector SAR422459 is injected to replace the defective gene. The results are encouraging [9].

Another oral drug codenamed ALK-001 for a treatment of Stargardt disease, which aims to prevent the formation of toxic vitamin A dimers in the retina, is also being tested.

Another clinical study investigated a new oral drug for a treatment of Stargardt disease called Emixustat, which was developed to slow the accumulation of toxic waste products thought to be responsible for the loss of visual function in this disease [10].

Another randomized, controlled clinical trial evaluating the safety and efficacy of Zimura (avacincaptad pegol) for intravitreal administration targeting the “complement system”, which is thought to activate and cause retinal cell damage following the accumulation of toxic vitamin A waste products in Stargardt disease has been carried out [10].

Another clinical study tested N-acetylcysteine (NAC) and N-acetylcysteine amide (NACA), derivatives of N-acetylcysteine, which is an antioxidant designed to slow vision loss by protecting retinal cells from oxidative stress. The oxidative stress is known to be a process that accelerates and exacerbates degeneration in many inherited retinal conditions. The study was performed in patients at an early stage of RP [48,49].

Another drug, known as LBS-008, is being tested. It is designed to prevent the accumulation of toxic waste products in the eye (lipofuscin and lipofuscin-related material), which causes retinal damage in Stargardt disease [8].

Another drug that is being studied for a treatment of Stargardt disease is Remofuscin, whose action is also to prevent the accumulation of waste products in Stargardt disease [9].

Various protein kinase inhibitors have also been studied, which in a range of animal models have shown a delay of the retinal degeneration, but the trials are still on animals [9].

A study on gene therapy in patients with achromatopsia with a defect in CNGA3 and CNGB3 genes is currently underway in the UK [1,50].

In patients with Congenital stationary night blindness, a small study with oral administration of 9-cis Beta-carotene was performed, which showed efficacy in improving the visual field and ERG amplitudes in patients with RDH5 mutation [1].

Tests of the protective effect of a ciliary neurotrophic factor (CNTF) and the so-called Rod Derived Cone Viability Factor (RdCVF) have also been performed on animal models [1].

Optogenetics is a modern strategy that provides an opportunity to transmit new photosensitive features to the neurons from the inner layers of the retina, such as bipolar and ganglion cells, which we know do not have such. In this experimental treatment, a gene encoding a photosensitive protein called channelrhodopsin-2 or halorhodopsin is transferred to the internal neurons of the retina. It can be sensitive to all rays of the visible spectrum of light, or by genetic modification to filter its sensitivity to rays of a certain wavelength for photoprotection. This combination of gene therapy and electronics allows the stimulation of a large number of neurons by using viral vectors through intravitreal application [1,51,52]. A clinical trial is currently underway using a single dose of intravitreally administered drug GS030-DP (recombinant adeno-associated viral vector), followed by repeated light stimulation in patients with advanced RP using an experimental device (stimulating glasses). The ability of object recognition and independent mobility are assessed [37].

Another modern challenge is the use of robotics in ophthalmic surgery – robotic systems are being developed through which the subretinal application of both stem cells and various biopharmaceutical agents in gene therapy is performed [1].

In 2013, the use of an epiretinal-implanted retinal stimulator (visual prosthesis) in patients with very advanced RP to improve their visual acuity was approved in the United States. The requirement for its use is the presence of functioning ganglion cells and a healthy optic nerve disc, as well as the patient to have previous visual experience (not to have been born blind). The stimulator together with an antenna is sutured to the sclera, and the electrode is placed epiretinally

after vitrectomy. The electrodes are connected to a screen or special glasses. The purpose of the device is to assist in image acquisition and to ensure independent mobility of patients with very low vision. A total of about 200 patients worldwide currently use this device with satisfactory effect [53–57].

About 31 clinical trials of various treatments for hereditary retinal dystrophies are currently being conducted worldwide.

The study of the human genome and the discoveries about the capabilities of stem cells provides new perspectives for reprogramming many of the inherited diseases and expanding the range of tools for influencing these diseases.

The conclusion we can draw is that the pharmaceutical companies show great interest in scientific advances in gene therapy and new, effective drugs for the treatment of these debilitating diseases should be expected soon.

There is still a long and difficult way to go, we are currently looking for the chemical formulas, specifying dosages, looking for the most effective and harmless way of application, because as it turns out, at present most therapies that are being tested are for intravitreal application, which is technically more difficult to implement and not the safest option.

Another difficulty in conducting clinical trials in these diseases is the early age of those affected, which is an obstacle to performing this type of activity. Most studies include adult individuals whose functional retinal capacity, however, is very small, the impairments are already very advanced, and hence the chances of recovery are lower.

In order to pool together the expertise and knowledge scattered throughout its territory, the European Commission set up in 2017 24 European Reference Networks for 'rare diseases', including the European Reference Network for "rare eye diseases" (ERN-EYE). It brings together in a working network specialized expert centres for cross-border knowledge sharing and patient counseling within a virtual clinic. This creates access to expert care for patients from disadvantaged geographical regions. The purpose of the virtual clinic is the information about the patients to travel, not the patients themselves [40].

**Conclusion.** Hereditary retinal dystrophies are "rare eye diseases", but due to the severe disability they lead to, they are very relevant at the moment and in the very near future many promising new therapies are expected to appear to improve the good medical care for these patients and to make these diseases treatable.

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