Clinical and biochemical footprints of inherited metabolic disorders. VII. Ocular phenotypes

Garanto, A.; Ferreira, C.R.; Boon, C.J.F.; Karnebeek, C.D.M. van; Blau, N.

Molecular Genetics and Metabolism 135 (2022) 311–319

Contents lists available at ScienceDirect

Molecular Genetics and Metabolism

journal homepage: www.elsevier.com/locate/ymgme

Review article

Clinical and biochemical footprints of inherited metabolic disorders. VII. Ocular phenotypes

Alejandro Garanto [a,b,*], Carlos R. Ferreira [c], Camiel J.F. Boon [d], Clara D.M. van Karnebeek [a,e], Nenad Blau [f]

[a] Department of Pediatrics, Amalia Children's Hospital Radboud Center for Mitochondrial and Metabolic Diseases, Radboud Institute for Molecular Life Sciences, Radboud University Medical Center, Nijmegen, the Netherlands
[b] Department of Human Genetics, Radboud Institute for Molecular Life Sciences, Radboud University Medical Center, Nijmegen, the Netherlands
[c] National Human Genome Research Institute, National Institutes of Health, Bethesda, MD, USA
[d] Department of Ophthalmology, Leiden University Medical Center, Leiden, The Netherlands and Amsterdam University Medical Centers, Academic Medical Center, Department of Ophthalmology, University of Amsterdam, Amsterdam, the Netherlands
[e] Departments of Pediatrics and Human Genetics, Emma Children's Hospital, Amsterdam Reproduction and Development, Amsterdam University Medical Centers, Amsterdam, the Netherlands
[f] Division of Metabolism, University Children's Hospital, Zürich, Switzerland

ARTICLE INFO

Article history:
Received 31 October 2021
Received in revised form 19 January 2022
Accepted 11 February 2022
Available online 15 February 2022

Keywords:
Eye
Inborn errors of metabolism
Ocular phenotypes
Inherited metabolic disorders
Ophthalmologic
Retina
Optic atrophy
IEMbase

ABSTRACT

Ocular manifestations are observed in approximately one third of all inherited metabolic disorders (IMDs). Although ocular involvement is not life-threatening, it can result in severe vision loss, thereby leading to an additional burden for the patient. Retinal degeneration with or without optic atrophy is the most frequent phenotype, followed by oculomotor problems, involvement of the cornea and lens, and refractive errors. These phenotypes can provide valuable clues that contribute to its diagnosis. In this issue we found 577 relevant IMDs leading to ophthalmologic manifestations. This article is the seventh of a series attempting to create and maintain a comprehensive list of clinical and metabolic differential diagnoses according to system involvement.

Contents

1. Introduction . . . 312
2. The eye . . . 312
3. Signs and symptoms . . . 312
   3.1. Extraocular structures: Eyelids . . . 312
   3.2. Anterior segment: cornea, iris, pupil and lens . . . 313
   3.3. Posterior segment: Retina and optic nerve . . . 313
      3.3.1. The retina . . . 313
      3.3.2. The optic nerve . . . 314
   3.4. Oculomotor and refractive errors . . . 315
4. Differential diagnosis . . . 315
   4.1. Biochemical diagnosis and red flags . . . 315
5. Prognosis and treatment . . . 316
6. Conclusion . . . 317

* Corresponding author at: Departments of Pediatrics and Human Genetics, Radboud University Medical Center, 6525 GA Nijmegen, the Netherlands.
E-mail addresses: alex.garanto@radboudumc.nl (A. Garanto), carlos.ferreira@nih.gov (C.R. Ferreira), camiel.boon@amsterdamumc.nl (C.J.F. Boon), c.d.vankarnebeek@amsterdamumc.nl (C.D.M. van Karnebeek), nenad.blau@kispi.uzh.ch (N. Blau).

https://doi.org/10.1016/j.ymgme.2022.02.002

Acknowledgements . . . 317
Appendix A. Supplementary data . . . 317
References . . . 317

1. Introduction

With this series of articles, we provide a comprehensive list of inherited metabolic disorders (IMDs) associated with specific organ involvement. The previous six issues are associated with movement disorders [1], metabolic liver disorders [2], psychiatric presentations [3], cardiovascular diseases [4], cerebral palsy [5] and skin manifestations [6]. This article is the seventh in this series and focuses on ocular phenotypes.

The list follows the classification in the knowledgebase of IMDs (IEMbase) [7], the proposed nosology of IMDs [8] and the international classification of IMDs (ICIMD) [9]. Data source is the IEMbase (http://www.iembase.org).

2. The eye

The eye is the window to the world around us. Vision enables us to be able to read, distinguish products at the supermarket, or recognize faces or emotions. Several studies have shown that about one third of IMD cohorts had ophthalmological abnormalities [10,11], resulting in partial or even total vision loss. These manifestations vary extremely and can be congenital or "acquired", appearing as the first symptom of an IMD or in the advanced/late stages of disease [12]. Some IMDs even present with an isolated ocular phenotype, i.e., without developing clinically significant manifestations in other organs. Thus, detailed clinical evaluation and targeted diagnostics are crucial to identify the metabolic disease, its prognosis and possible treatment.

The eye is located in the orbit and surrounded by the extraocular muscles that control the movement of the eye itself as well as the eyelids. The anatomy of the eye is well-defined and contains distinguishable structures (Fig. 1). The anterior segment is the part of the eye with the cornea on the most external side. The cornea is a transparent avascular tissue that provides the strongest focusing power, and at the same time plays a role in protecting the inner eye from the external environment [13]. The crystalline lens additionally contributes to the focusing power of the eye. The iris controls the amount of light entering the eye [14]. Behind the lens, we find the vitreous chamber filled with a clear and acellular gel called the vitreous humor. The overall function of this compartment is to maintain the spherical shape of the eye. In addition, it allows the light to pass without refraction and suspends the lens, therefore playing an indirect role in focusing the light on the retina, which is located in the posterior part of the eye. The retina is a complex and specialized multilayered neuronal tissue that consists of many subtypes of cells. In brief, the photosensitive cells (photoreceptors) capture the light and transform it into chemical and electrical signals that travel through the other layers of the retina until reaching the ganglion cells. Once there, those signals travel to the brain through the optic nerve, which is formed by the axons of the ganglion cells. Finally, the brain processes these signals and generates an image [15]. The pigmented cell layer called the retinal pigment epithelium (RPE) protects the photosensitive cells from overexposure to light as well as detoxifies and recycles certain proteins or compounds derived from the visual cycle and photoreceptor function [15]. These cells together with the retinal vascular endothelium form the blood-retinal barrier. All these different structures may be affected in IMDs.

Of all the IMDs with ocular phenotypes tabulated in the IEMbase ($n = 577$, Supplemental Table 1), approximately 30% show involvement of the frontal part of the eye (cornea and lens) and around 50% of the neuroretina, with or without optic nerve involvement. Oculomotor manifestations appear in about 200 IMDs (~40%). The major IMDs associated with eye abnormalities are those related to lipid, carbohydrate, protein and metal metabolism. In addition, all enzymes involved in the visual cycle lead to isolated retinal abnormalities when mutated, despite the discrepancies between databases regarding their inclusion as IMDs. Overall, these ocular defects have symmetrical bilateral involvement [16,17]. Below we discuss some of the ocular phenotypes for a few IMDs.

3. Signs and symptoms

3.1. Extraocular structures: Eyelids

Manifestations in the anterior part of the eye are frequently visible and detectable by external examination of the eye and the ocular adnexa. **Ptosis** is the dropping of the eyelid. This can be caused by either damage of the nerves or the extraocular muscles. This sign is a common feature and despite being often overlooked it can lead to the identification of a severe disorder when observed during childhood [18]. This common feature is observed at all ages and can be unilateral or bilateral. Congenital ptosis of eyelid has been associated with neuromuscular and

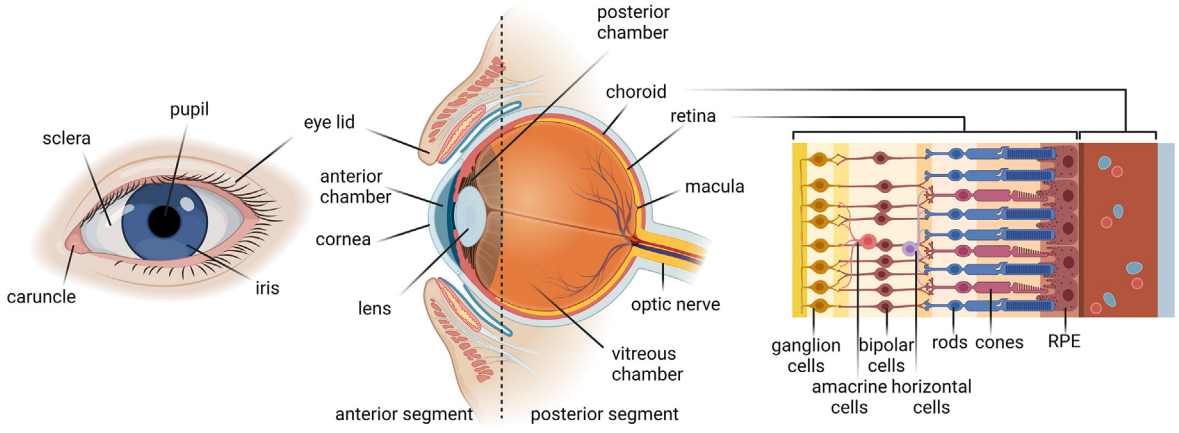

Fig. 1. Schematic representation of the anatomy of the eye and the retina. Created with BioRender.com.

mitochondrial diseases [19]. In addition, ptosis has a higher prevalence in infantile cases of Pompe disease (a glycogen storage disease caused by pathogenic variants in *GAA*), in which bilateral involvement has been observed in almost all cases as reported previously [20].

3.2. Anterior segment: cornea, iris, pupil and lens

Anterior segment manifestations can be readily detected on cursory eye examination using a slit lamp microscope. Frequently, the ophthalmic phenotypes are associated with opacity or clouding of the cornea or lens.

IMDs often present **corneal opacities** or clouding. In this condition, the cornea loses its transparency and may even develop a cloudy/whitish appearance with advance disease. As a result, they can cause irritation, blurry vision, photophobia (sensitivity to light) or vision loss.

Gaucher disease is caused by biallelic pathogenic variants in *GBA1*, in which all parts of the eye can be affected, but the white corneal opacities are most frequently reported, probably due to the accumulation of deposits of glucocerebroside [21]. Corneal opacities are also common to other lysosomal storage diseases. In fact, this distinctive trait is a key player in early detection and diagnosis of X-linked Fabry disease (*GLA*), since >70% of patients present with this symptom (cornea verticilata) [22]. Amongst the majority of the mucopolysaccharidoses (MPS), congenital yellowish-grey color deposits of glycosaminoglycans progressively accumulate in all the layers of the cornea thereby leading to loss of visual acuity. This feature is often reported in type I, IV and VI MPS, but rarely in type II, and also not detected in type III MPS [23]. The accumulation of lipids causing corneal clouding is also found in patients with mucolipidoses [24]. In Wilson disease, a defect in copper metabolism, a ring consisting of copper deposits can be observed in the Descemet's membrane and eventually encircling the cornea of both eyes in 65–95% of patients [25]. This manifestation is known as **Kayser-Fleischer rings**. A second ophthalmic sign caused by the deposition of copper in the anterior capsule of the lens, called sunflower cataract, is observed in this disease. However, it is postulated that this manifestation is not a pathognomonic sign of the disease [26]. Cystine crystals in the periphery of the cornea appear as of 16 month and extend with the disease progression in all forms of cystinosis [27–29].

Coloboma constitutes a tissue defect of the eye, that may affect the iris, retina, choroid and/or optic disc. This condition occurs during eye development and can affect one or both eyes, but not necessarily affecting the same region. A coloboma of the iris is the most common type and mildest form of coloboma in IMDs. However, severe colobomas can also be present and they virtually affect all ocular structures causing severe visual dysfunction. Coloboma is frequently observed in patients suffering from congenital disorders of glycosylation (CDG), such as SRD5A3-CDG [30,31]. This phenotype has also been reported in uncontrolled maternal phenylketonuria and sporadic patients with other CDGs such as ALG2-CDG, ALG3-CDG and PIGL-CDG (CHIME syndrome) [32,33,24].

The iris is also affected by several IMDs. For instance, in albinism the iris is nearly translucent due to lack of pigmentation. This iris transillumination, however, is not exclusive to albinism, and is associated with other non-metabolic diseases. Albinism is caused by mutations in 15 genes and besides the iris transillumination, patients also present refractive errors like myopia, nystagmus and strabismus (see section 3.3), photophobia (sensitivity to light) and poor vision amongst other symptoms [34]. **Aniridia** is a congenital condition in which the iris is not present. This phenotype has been reported in a large consanguineous Italian family suffering from hyperprolinemia type I [35]. This study was published in 1976 and the gene associated with aniridia (*PAX6*) was identified by positional cloning in 1991. Therefore, it is plausible that eventually pathogenic variants in *PAX6* were segregating within the family, explaining this isolated case of a metabolic disease in combination with aniridia.

A diminished **pupillary reflex** can be observed in several IMD. In a normal situation, the pupil contracts in the presence of bright light to regulate the amount of light entering the eye, and the opposite occurs in dim light conditions. This process is regulated by a small group of photosensitive retinal ganglion cells and examples are described in section 3.3.

Cataract is an opacification of the crystalline lens, leading to decreased vision. Although they are commonly associated with ageing in the general population, in IMDs they may already present congenitally, neonatally or at different ages in life as a consequence of the biochemical defect.

Several IMDs manifest congenital cataract in the majority of patients: peroxisomal biogenesis disorders [36] and Lowe syndrome [37]. These can be initial signs that can contribute to the identification of the IMD. Galactosemia is an inherited recessive disease affecting galactose metabolism. In classical galactosemia, a significant percentage of patients develop bilateral cataracts in the newborn period. The cause of opacities in the lens is the accumulation of galactitol [38]. The type of cataract may be indicative of the underlaying IMD: e.g. galactosemia patients typically show an 'oil droplet' aspect of the cataract in the nucleus of the lens [39]. This is one of the few symptoms that can be reversed upon dietary galactose restriction if initiated early [40]. The number of IMDs including cataract development in infancy and later stages increases compared to the congenital and neonatal stages. Nevertheless, for some IMDs this manifestation can differentially help to identify the metabolic cause. Some examples are sialidosis, alpha-mannosidosis, mevalonic aciduria, Wilson disease (see above) or cerebrotendinous xanthomatosis (CTX). CTX is a rare disease affecting the breakdown of cholesterol. Patients suffering from CTX present early-onset cataract and chronic diarrhea. Remarkably, the ocular symptoms may precede other neurological and systemic manifestations [41].

Dislocation of the lens, also called *ectopia lentis,* is another possible manifestation in IMDs. Classical homocystinuria is an inherited autosomal recessive disease caused by pathogenic variants in the *CBS* gene. Lens dislocation is noticed in 35% of patients at 5 years of age. This number dramatically increases to 90% at the age of 25 years [42]. In another study, it was reported that 86% of patients were found to have *ectopia lentis* [43]. Thus, classical homocystinuria should be included in the differential diagnosis of lens dislocation [44,45]. Due to weakness of the lens zonules, the lens of homocystinuria patients is typically subluxated inferiorly, in contrast to patients with Marfan syndrome, in which the lens is subluxated superiorly [46]. Similarly, lens dislocation is observed during the first year of life in sulfite oxidase deficiency and molybdenum cofactor-deficient patients [47]. Other IMDs can, in a very small percentage of patients, show lens dislocation. For example, ~5% of a cohort of 58 patients with aminoacidopathies developed this condition [11].

In some cases, these features may not be obvious during a general inspection due to the discrete involvement. Therefore, more specialized examinations may be required to rule out or identify mild corneal opacities, cataract or other anterior segment anomalies.

3.3. Posterior segment: Retina and optic nerve

Involvement of the posterior eye relies more on the symptomatology described by the patient (e.g., night blindness, tunnel vision, etc.) and in-depth ophthalmic evaluation by examining the fundus of the eye.

3.3.1. The retina

Retinal degeneration, especially retinal dystrophy due to monogenic inherited disorders, is often characterized by early-onset photoreceptor cell death leading to progressive loss of vision. There are multiple subtypes of retinal dystrophy and they are classified based on the first involved cell type in the pathology, the progression, or the genetic cause. For instance, retinitis pigmentosa (RP) is one of the most

common retinal degeneration associated with IMDs. RP consists of the degeneration of rods, followed by the death of cones. This leads to night blindness, and progressive loss of peripheral vision (also called tunnel vision) that can ultimately result in total blindness. At the ophthalmologic level, RP is characterized by abnormal dark pigment in the fundus, decreased electrical activity of the photoreceptors (as measured by electroretinography), progressive reduction in the peripheral visual field, and eventually central vision loss in advanced disease. However, other subtypes of retinal degenerations can also be observed in IMDs: The retina is a highly metabolically active tissue; thus, defects in energy metabolism can have a dramatically detrimental effect. Isolated retinal diseases are often caused by pathogenic variants in genes that affect exclusively the function of the retina. For example, IMDs with isolated ocular manifestations can be caused by deficiency of the enzymes involved in vitamin A metabolism, and therefore the visual cycle (i.e., *RPE65, LRAT, RDH12,* etc.). Pathogenic variants in these genes lead to Leber congenital amaurosis (LCA), a congenital and severe form of retinal disease. Another example of IMD with a predominant eye phenotype is ornithine aminotransferase (OAT) deficiency, which affects the retina and secondarily the choroid in the form of **gyrate atrophy**. This condition leads to progressive night blindness and peripheral vision loss from the first decade of life onwards. Central vision and macular structure are usually preserved up to the fifth decade of life, after which the macula can also become affected with consequent severe vision loss [48,49]. Although the pathophysiology of the gyrate atrophy is not yet well understood, several hypotheses have been postulated: direct toxic effect due to ornithine accumulation or one of its metabolites; impairment of creatine biosynthesis due to high levels of ornithine; or reduction of proline levels [50]. Regardless of the mechanism, treatment with creatine supplementation did not halt progression of the disease [51]. Dietary treatment, however, has been shown to slow down disease progression to varying degrees, but is not preventative [49]. Remarkably, in hyperornithinemia-hyperammonemia-homocitrullinuria (HHH) syndrome, also characterized by high ornithine levels, no retinal phenotype has been reported. Conversely, similar fundus characteristics in the presence of normal ornithine levels are associated with iminoglycinuria. Iminoglycinuria is an autosomal recessive metabolic disease caused by pathogenic variants in either *SLC36A2, SLC6A20* or *SLC6A19,* which affects the renal reabsorption of glycine, proline and hydroxyproline. It is a condition observed in newborns whose clinical features can subside after about 6 months [52]. It is usually a benign disorder, though in some cases it can lead to gyrate atrophy [53,54].

In syndromic diseases, the eye can also be affected if the enzyme conducts a crucial function in the retina. As highlighted before, RP is often the most commonly observed retinal degeneration in many, but not all multisystemic IMDs. This is for example the case of several CDG. Furthermore, it is known that photoreceptors require lipids to form their outer segment discs, in which the visual phototransduction is initiated and the basis of vision lies [46]. Ten percent of these discs are recycled every day; therefore, it is expected that disruption of lipid metabolism would have a big impact on the retina. In fact, complex lipid disorders like Sjögren-Larsson syndrome (SLS) show skin, brain, and eye involvement. SLS patients present abnormal macular morphology and pigmentation with early onset. Intraretinal crystals detected as hyperreflective dots are visible in the retinal nerve fiber layer, inner plexiform layer and outer plexiform layer of both eyes [55]. With the progression of the disease, the central part of the retina is damaged, leading to RPE atrophy followed in some cases by neovascularization [55]. Pathogenic variants in the very long-chain fatty acid elongase 4 (*ELOVL4*) have been associated with retinal phenotypes. Other hypothesized sphingolipid-related genes have been associated with RP. This is the case of *CERKL*. Initially, it was believed that CERKL was a ceramide kinase [56] and it was shown that its downregulation affected the levels of several sphingolipid species in the mouse retina [57]. More recently, it has been shown that the CERKL protein regulates mitochondrial function [58].

Cherry-red spot is a fundoscopic finding consisting of a small red circular shape in the macula that can be a key finding when diagnosing an IMD. This aspect is the result of a retinal edema caused by a central retinal artery occlusion or traumatic retinal ischemia. A cherry-red spot appearance is common in Tay-Sachs disease, acid sphingomyelinase deficiency, Sandhoff disease or galactosialidoses, and can be occasionally observed in other sphingolipidoses/lipid storage diseases such as Gaucher, Farber or Krabbe diseases [24,17,12,59]. In the latter case, retinal degeneration and optic atrophy are observed and can lead to blindness in the late stages of the disease [60], although optic nerve enlargement from globoid cell accumulation can also be seen.

Another group of IMDs which often presents with retinal degeneration is neuronal ceroid lipofuscinosis. For instance, patients suffering of CLN3 disease develop early ocular symptoms that range from loss of visual acuity, color vision or peripheral vision that can be accompanied by nyctalopia, nystagmus and photophobia. With progression of the disease, the eyes remain normal except for the retina and optic nerve which degenerate [61]. Another subtype of neuronal ceroid lipofuscinosis, CLN7 caused by pathogenic variants in *MFSD8*, is also characterized by progressive loss of vision due to retinal changes described as “salt and pepper” appearance. However, the first symptoms in those patients are generalized seizures (around 5 years of age) and within 2–3 years (around age 8) visual impairment is observed [62]. Furthermore, in the case of *MFSD8*-associated retinal phenotypes, the severity of the variant determines the degree of involvement ranging from isolated degeneration of the macula to a syndromic neurological disease [63,64].

Other diseases in which the retina is affected are errors in mitochondrial energy metabolism (e.g. Kearns-Sayre syndrome), copper metabolism or cobalamin C deficiency, or some CDG, as well as albinism.

3.3.2. The optic nerve

Optic atrophy is a manifestation of the degeneration of the optic nerve caused by multiple factors. It can result from damage of the optic nerve either at the retinal ganglion cells, whose axons form the optic nerve, or in the path to the brain. Other factors that can lead to optic atrophy are glaucoma, physical pressure on the optic nerve or congenital malformation of the optic nerve. Often, this degeneration leads to irreversible vision loss. Glaucoma is one of the most common causes of optic atrophy due to abnormally high pressure in the eye. Aicardi-Goutières syndrome is caused by pathogenic variants in the genes involved in nucleic acid metabolism (*SAMHD1, TREX1, RNASEH2A, RNASEH2B* and *RNASEH2C*) and can present with congenital glaucoma as part of the disease manifestations [65]. Similarly, defects in the *PEX* genes leading to peroxisome biogenesis disorders in the Zellweger syndrome spectrum, are known to affect nearly every organ, and in the eye, almost all parts can become involved. Patients suffering from these diseases might present multiple ocular manifestations such as corneal clouding, cataracts, glaucoma, retinal abnormalities and optic atrophy [66].

Besides glaucoma, optic atrophy can also occur when the optic nerve has not been developed properly due to an inflammatory process. Several IMDs present optic atrophy, especially those resulting from defects in energy metabolism [67]. For instance, Leber hereditary optic neuropathy is the most common mitochondrial genetic disease and patients present severe loss of optic nerve fibers [68]. Similarly, defects in mitochondrial fusion genes, such as *OPA1* and *OPA3*, cause autosomal dominant optic atrophy 1 (OPA1) and autosomal dominant optic atrophy and cataract (ADOAC) or autosomal recessive Costeff syndrome, respectively. In ADOAC, cataract can also be recognized in the first decade [69] and the molecular mechanism is believed to be a dominant-negative effect. In Costeff syndrome, in contrast, the mechanism appears to be haploinsufficiency [67].

Another optic nerve-related symptom is a slow or absent pupillary reaction. A diminished **pupillary reflex** can indicate a retinal

abnormality and can be seen in nicotinamide mononucleotide adenylyltransferase 1 deficiency caused by pathogenic variants in *NMNAT1*, or lecithin retinol acyltransferase deficiency from variants in *LRAT*. In contrast, in other diseases with optic nerve involvement such as Leber hereditary optic neuropathy (LHON) or mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS), the pupillary light reflexes are to some extent preserved [70].

Optic atrophies can also be found in mitochondrial energy metabolism defect such as Leigh syndrome, in leukodystrophies, Menkes disease, or Friedreich ataxia amongst others.

3.4. Oculomotor and refractive errors

Oculomotor or eye movement manifestations are often reported as neurological symptoms in IMDs [71]. Oculomotor errors are often caused by neuronal defects, but can also occur due to abnormalities of the external ocular muscles. Refractive errors are caused by light rays entering the eye but not focused on the retina, leading to blurred vision. **Myopia** is a common refractive error caused by the curvature of the cornea. Interestingly, almost all homocystinuria patients suffer from myopia [72] and this trait is also prevalent in ornithine aminotransferase deficiency patients [73]. This trait is also associated with albinism patients, as previously described. High myopia is associated with severe degenerative abnormalities of the posterior part of the eye, such as macular degeneration, retinal detachment, and even a severe circumscribed outpouching of the wall of the globe called staphyloma [74].

Strabismus is the occasional or constant misalignment of the eyes when looking at an object. It can be caused by muscle imbalance but also refractive errors. In IMDs, strabismus and nystagmus are often present simultaneously. **Nystagmus** is the involuntary movement of the eye that has a peripheral (retina, optic nerve, and vestibular system) or central origin (central visual pathways, cortex, cerebellum and midbrain). This condition can present in different ways depending on the disease. For example, in Sandhoff disease, nystagmus can be accompanied with impaired horizontal and vertical saccades [75]. In contrast, a broad range of oculomotor manifestations, including nystagmus, strabismus and **fixation** problems, can be observed in several CDG [31]. In some cohorts of patients suffering from urea cycle disorders, nystagmus or strabismus have been observed in up to 33% of the cases [11]. Morquio syndrome (MPS IVA) children can present nystagmus and it has been suggested that these patients are slower in detecting visual targets and showed problems maintaining fixation [76,77]. **Progressive ophthalmoplegia** is another condition in which eye movements are impaired. It can have multiple origins, usually with a neurological or muscular cause. It has been reported in patients suffering from PMM2-CDG [31], several mitochondrial disorders such as Kearns-Sayre syndrome [78], and Leigh syndrome [79] and lysosomal disorders like Gaucher disease or Niemann-Pick disease type C [80]. Comprehensive tables of nystagmus and other eye movement conditions in IMDs have been reported elsewhere [71,19].

4. Differential diagnosis

Ophthalmic examinations are often non-invasive and can provide essential functional and structural information about the eye. Initial standard ocular examination starts with the assessment of visual acuity and pupillary reflex, followed by an ophthalmoscopic examination. This technique allows the examination of the anterior segment (cornea, iris, lens) as well as the posterior part back of the eye including the retina and the optic disc. Another non-invasive structural test is optical coherence tomography (OCT), which allows to cross-sectionally evaluate the retina. With this technology, high resolution images are obtained to assess the retina and its layers at micrometer resolution. The functional evaluations consist of color vision and visual field testing as well as electroretinography (or in short ERG). The visual field test determines the area that the eye can see when focusing on a central point to identify blind spots. ERG is a diagnostic test that is able to record the electrical activity of the retina upon a light stimulation. By measuring these currents, it is possible to elucidate the type of cells that are affected (e.g., preferentially rod and/or cone photoreceptors), and provide diagnostic clues. The intraocular pressure can be measured using tonometers and it is an important aspect in the evaluation of glaucoma. Finally, fluorescein angiography is an invasive technique in which the administration of a specific dye allows the examination of the blood flow in the retina and can be combined with structural ophthalmoscopic examinations and fundus imaging. Overall, all these measurements can contribute to the differential diagnosis of retinal diseases.

However, the ocular manifestations in IMDs are extremely variable. While in many cases the ocular phenotype is an early or late manifestation of a multi-organ metabolic disease, in several IMDs only an isolated eye phenotype is observed. It has been postulated that the differences in the diseases severity might be associated to the heterogeneity of the gene expression and residual protein/enzyme activity [81]. The age at onset of the ocular manifestations is also variable, but many ocular complications already manifest in the first two decades, and sometimes even after birth. The cause of these ocular complications can directly be linked to the lack of a function of an enzyme, toxic effects triggered by abnormal metabolic products or accumulation of normal metabolites in the same pathway [12]. Thus, the presence of other non-related eye phenotypes affecting the skin, hearing, etc., might contribute to the diagnosis of the different syndromes. Of note, the co-existence of neurological and ocular symptoms is common to a large proportion of IMDs, making the differential diagnosis challenging [17]. Still, ocular findings not only can be extremely useful to raise the suspicion and the establishment of an early diagnosis of IMDs in some cases, but also to add clues that can help to better delineate the disease and its progression.

Some ocular abnormalities are so rare and exclusive for certain IMDs that they can strongly point to the exact diagnosis. For instance, reduced or absent tear production (alacrima) is a rare symptom that can be associated with very few IMDs, therefore facilitating the diagnosis of these rare diseases (e.g., claudin 10 deficiency, glycolate oxidase I deficiency, PIGQ-CDG, GMPPA-CDG and N-glycanase 1 deficiency).

An extremely unusual poking and rubbing of the eye, also known as Franceschetti's oculo-digital sign, in babies or children might highly suggest a severe early-onset retinal dystrophy called LCA. This condition causes early-onset blindness due to pathogenic variants in the genes involved in the vitamin A/visual cycle pathway, and it is often accompanied by nystagmus.

4.1. Biochemical diagnosis and red flags

An inherited metabolic disease should always be suspected when ocular features remain unexplained, once more common etiologies such as infections, ageing and focal eye lesions have been ruled out. Red flags suggesting that an ocular phenotype might be caused by an IMD include: 1) early age at onset (the earlier the onset, the more likely a metabolic etiology); 2) associated neurologic or extra-neurologic signs and symptoms; 3) dysmorphic features and/or coarsening of features; 4) progressive neurodegeneration (+/− triggered by catabolic stress); 5) consanguinity; 6) family history of similar disorder; 6) behavioral and/or psychiatric diseases; 7) paroxysmal episodic events; and 8) other sensory disorders. A list of laboratory investigations to aid in the diagnosis of the various listed IMDs is summarized in Table 1. For more details see Supplemental Table 1. When aforementioned clinical findings are present, a referral to a metabolic diseases specialist should be considered. The metabolic physician can initiate appropriate workup by ordering some of the tests mentioned in Table 1, depending on the specific combination of signs and symptoms. A referral to an ophthalmologist is often warranted for an extensive ophthalmological screening. Conversely, the ophthalmologist might raise suspicion of an IMD and refer to the metabolic physician for further evaluation. Regardless,

Table 1
Biochemical investigations in metabolic diseases affecting eye.

Basic tests	Profiles	Special tests
Blood count	Amino acids (P,U)	Iron (S)
ASAT/ALAT (P)	Organic acids (U)	Transferrin (S)
CK (P)	Acylcarnitines (DBS, P)	Ferritin (S)
ALP (P)	Sialotransferins (S)	Zinc (S, U)
LDH (P)	Sterols (P)	Manganese (B)
CRP (P)	Bile acids (U)	Lysosomal Enzymes (S)
Lactate (P)	Oligosaccharides (U)	Vitamins (S)
Glucose (P)	Mucopolysaccharides (U)	Flavins (B)
Ammonia (B)	VLCFA (P)	SAM & SAH (P)
Copper (S,U)	Lipid panel (S)	Coagulation factors
Ceruloplasmin (S)	Biogenic amines (CSF)	Immunoglobulins
Cholesterol (P)	Pterins (CSF)	Interferon signature (PBMC)
Triglycerides (P)	Guanidino compounds (U,P,CSF)	
	Polyols (P,U)	

careful examination of all eye structures is required, and the diagnostic approach, as with all IMDs, should prioritize treatable disorders [82].

We categorized the signs and symptoms of metabolic disease presenting with ophthalmologic features as: 'Oculomotor involvement', 'Retinal involvement', 'Lens involvement', 'Optic nerve involvement', 'Corneal involvement', 'Refractive errors' and 'Other' (Supplemental Table 2).

Oculomotor involvement, retinal involvement, optic nerve involvement and lens involvement are the most common ocular abnormalities reported in 227/577 (~39%), 157/577 (~27%), 141/577 (~24%), 117/577 (~20%) of IMDs with ophthalmologic involvement, respectively, followed by corneal involvement in 52/577 (~9%), and refractive errors in 32/577 (~6%) (Fig. 2). Of the signs and symptom in the group 'Other', most frequently reported amongst all disorders are 'Diminished visual activity (~80%), 'Glaucoma' (~37%), 'Vision loss' (~33%), 'Total blindness' (~29%), 'Microphthalmia' (~22%), 'Coloboma' (~13%), 'Ocular albinism' (~11%) and 'Photophobia' (~10%) (Supplemental Table 1). Some of them are, however, specific for particular disorder groups, e.g., 'Glaucoma' in disorders of nucleotide and nucleic acid metabolism and disorders of peroxisomal biogenesis, or 'Ocular albinism' in disorders of lysosome-related organelle biogenesis.

It is often challenging, however, to identify an IMD based on an early ocular phenotype. First, one third of all IMDs can present some type of ocular manifestation. Furthermore, clinical ophthalmologic symptoms often overlap between different diseases. The overall picture becomes more complicated if we consider that several IMDs present exclusively with ocular defects, but at the same time, deficiencies in the same pathway can result in different outcomes. In that sense, genetic analysis to pinpoint a specific genetic defect is a very powerful tool to help in solving the puzzle [83]. Furthermore, identifying the genetic cause of the disease can also contribute to determining a possible therapeutic intervention [84]. Early management of ocular symptoms can improve the quality of life of these patients. For instance, pathogenic variants in *ELOVL4* can result in a dominant form of Stargardt Disease 3 (STGD3) with only retinal involvement; pathogenic variants in the same gene can lead to pseudo-Sjögren-Larsson syndrome or spinocerebellar ataxia type 34 [85]. This is also the case of the *OPA3*-associated diseases described previously. Other examples in which genetics plays a crucial role to understand the outcome and progression of possible multisystemic IMD include lysosomal storage diseases. For instance, pathogenic variants in *HGSNAT* and *MFSD8* have been classified as severe or mild [86,87]. Severe variants in these genes lead to MPS 3C (Sanfilippo syndrome type C) or CLN7, respectively; mild variants, on the other hand, cause isolated retinitis pigmentosa (RP) or macular degeneration, respectively. Thus, establishing proper genotype-phenotype correlations is crucial for some IMDs.

Isolated ocular manifestations are usually present as RP or LCA, and they are caused by pathogenic variants in the IMD-related genes *IMPDH1, NMNAT1, IDH3A, IDH3B, SLC7A14* or *LRAT* [88–93]. Interestingly, variants in the IMD-associated mitochondrial genes *MT-TH* and *MT-TS2* have been associated with both RP and hearing loss, as is the case for variants in *ARSG* [94–96]. Furthermore, the optic nerve can be involved in conditions caused by variants in genes associated with metabolic pathways such as *RTN4IP1, TMEM126A* (both leading to optic atrophy) and *OAT* (causing gyrate atrophy) [97–99]. Variants in the glutamate metabotropic receptor 6 (*GRM6*) are responsible for congenital stationary blindness [100]. Except for *IMPDH1* (autosomal dominant inheritance) and mitochondrial genes, all other causal variants for metabolic conditions with isolated ocular phenotypes are inherited in an autosomal recessive manner.

In conclusion, a low threshold for ophthalmological evaluation is necessary for all IMDs, as phenotypes have yet to be fully delineated, and repeated exams are often required to screen for disease progression, especially since IMDs can have unpredictable courses [17].

5. Prognosis and treatment

Depending on the part of the eye affected, the symptoms and possible treatments will differ. While some forms of involvement in the

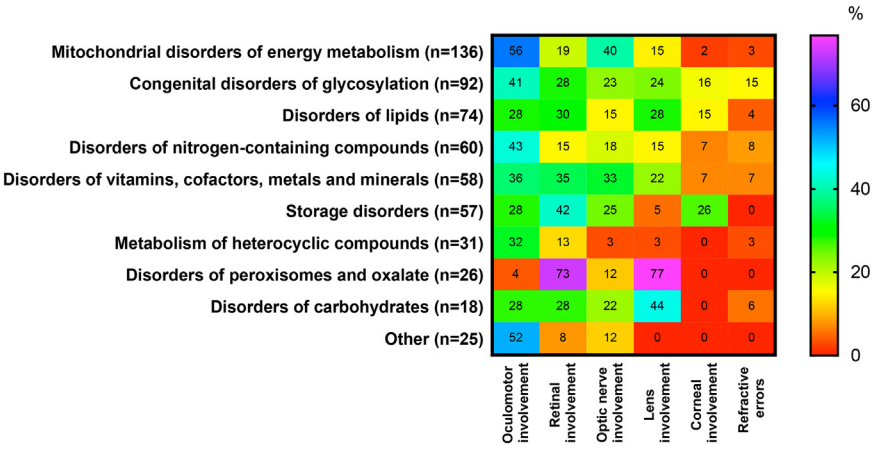

Fig. 2. Occurrence (%) of symptoms associated with disorders presenting with ocular phenotype in 10 categories of IMDs. The percentages for eye involvement were calculated using as the denominator the total number of IMDs in each category presenting with any with ocular phenotype. Heat scale ranges from red (0%) for diseases with no particular symptoms reported to violet (100%) for diseases with particular symptoms occurring with highly frequency within the disorders group. For definition of 10 categories of disorders affecting eye see Supplemental Table 1. For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.

frontal part of the eye such as corneal opacity or cataracts can be corrected by surgery (e.g., corneal transplants), in contrast the majority of the defects in the neuroretina are not treatable yet. However, the eruption of genetic and molecular therapies for the eye has shown that progression of photoreceptor degeneration can be halted or slowed down, significantly improving the life of the patient [101]. In fact, the first FDA-approved gene therapy was marketed for an autosomal recessive form of retinal degeneration caused by variants in *RPE65*, which is involved in the metabolism of the vitamin A [102]. Furthermore, a customized RNA-based molecule (antisense oligonucleotide) for a patient suffering CLN7 caused by a splicing variant in *MFSD8* was delivered to the brain to ameliorate the seizures [103]. Unfortunately, this child already lost her vision before the initiation of treatment; still the delivery of these molecules to the eye has been shown to be safe and well tolerated [104]. Currently, many other genetic therapies are being investigated at preclinical and clinical levels. However, these potential treatments are often variant- or gene-specific and aim to treat disease with only retinal manifestations. Unfortunately, for most of IMDs the ocular phenotypes are often secondary and eclipsed by life-threatening manifestations in other organs which require urgent intervention if possible.

Supplemental Table 1 includes information on primary treatment options for the mentioned IMDs, i.e., treatment that addresses at least one aspect of the pathophysiology of the disease, when available. Strategies vary from vitamin/cofactor/amino acid supplements, dietary restriction (e.g., protein, fat), chelation therapy, pharmacologic treatment, and organ transplants. Often these interventions are disease modifying only. With the advent of stem cell transplantation and genetic therapies, the future looks brighter as a cure is in sight. Early diagnosis is essential, as this optimizes the window of opportunity; newborn screening has proven an excellent tool for prevention altogether, but not all IMD are covered due to the limited amount unique and stable biomarkers.

6. Conclusion

In this seventh issue we provided a comprehensive summary of ophthalmologic features associated with IMDs. The full list can be accessed for free at http://www.iembase.org/gamuts (last accessed 31-10-2021) and will be curated and updated on regular basis.

Acknowledgements

The authors would like to thank Prof. Dr. Saskia Wortmann for her input. This work was supported, in part, by the Intramural Research Program of the National Human Genome Research Institute.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ymgme.2022.02.002.

References

[1] C.R. Ferreira, G.F. Hoffmann, N. Blau, Clinical and biochemical footprints of inherited metabolic diseasesI. Movement disorders, Mol. Genet. Metabolism 127 (1) (2019) 28–30, https://doi.org/10.1016/j.ymgme.2019.03.007.
[2] C.R. Ferreira, D. Cassiman, N. Blau, Clinical and biochemical footprints of inherited metabolic diseases. II. Metabolic liver diseases, Molecular Genetics and Metabolism 127 (2) (2019) 117–121, https://doi.org/10.1016/j.ymgme.2019.04.002.
[3] G.A. Horvath, R.M. Stowe, C.R. Ferreira, N. Blau, Clinical and biochemical footprints of inherited metabolic diseasesIII. Psychiatric presentations, Molecular Genetics and Metabolism 130 (1) (2020) 1–6, https://doi.org/10.1016/j.ymgme.2020.02.007.
[4] C.R. Ferreira, N. Blau, Clinical and biochemical footprints of inherited metabolic diseasesIV. Metabolic cardiovascular disease, Molecular Genetics and Metabolism 132 (2) (2021) 112–118, https://doi.org/10.1016/j.ymgme.2020.12.290.
[5] G.A. Horvath, N. Blau, C.R. Ferreira, Clinical and biochemical footprints of inherited metabolic disease. V. Cerebral palsy phenotypes, Molecular Genetics and Metabolism, 2021, https://doi.org/10.1016/j.ymgme.2021.03.008.
[6] C.R. Ferreira, D. Cassiman, N. Blau, Clinical and biochemical footprints of inherited metabolic diseases. VI. Metabolic dermatoses, Molecular Genetics and Metabolism (2021) https://doi.org/10.1016/j.ymgme.2021.07.005.
[7] J.J.Y. Lee, W.W. Wasserman, G.F. Hoffmann, C.D.M. van Karnebeek, N. Blau, Knowledge base and mini-expert platform for the diagnosis of inborn errors of metabolism, Genetics in Medicine 20 (1) (2018) 151–158, https://doi.org/10.1038/gim.2017.108.
[8] C.R. Ferreira, C.D.M. van Karnebeek, J. Vockley, N. Blau, A proposed nosology of inborn errors of metabolism, Genetics in Medicine 21 (1) (2019) 102–106, https://doi.org/10.1038/s41436-018-0022-8.
[9] C.R. Ferreira, S. Rahman, M. Keller, J. Zschocke, ICIMD Advisory Group, An international classification of inherited metabolic disorders (ICIMD), Journal of Inherited Metabolic Disease 44 (1) (2021) 164–177, https://doi.org/10.1002/jimd.12348.
[10] D.P. Tsagaraki, A.E. Evangeliou, M. Tsilimbaris, M.G. Spilioti, E.P. Mihailidou, C. Lionis, I. Pallikaris, The significance of opthalmologic evaluation in the early diagnosis of inborn errors of metabolism: the cretan experience, BMC Ophthalmol. 2 (2002) 2, https://doi.org/10.1186/1471-2415-2-2.
[11] N. Jafari, K. Golnik, M. Shahriari, P. Karimzadeh, S. Jabbehdari, Ophthalmologic findings in patients with neuro-metabolic disorders, J. Ophthalmic Vis. Res. 13 (1) (2018) 34–38, https://doi.org/10.4103/jovr.jovr_242_16.
[12] B.T. Poll-The, Maillette de Buy, C.J. Wenniger-Prick, The eye in metabolic diseases: clues to diagnosis, European Journal of Paediatric Neurology 15 (3) (2011) 197–204, https://doi.org/10.1016/j.ejpn.2011.03.005.
[13] M.S. Sridhar, Anatomy of cornea and ocular surface, Indian J. Ophthalmol. 66 (2) (2018) 190–194, https://doi.org/10.4103/ijo.IJO_646_17.
[14] D.W. DelMonte, T. Kim, Anatomy and physiology of the cornea, J Cataract Refract Surg 37 (3) (2011) 588–598, https://doi.org/10.1016/j.jcrs.2010.12.037.
[15] H. Kolb, How the retina works, Am. Sci. 91 (1) (2003) 28–35 citeulike-article-id:1560678.
[16] M. Rajappa, A. Goyal, J. Kaur, Inherited metabolic disorders involving the eye: a clinico-biochemical perspective, Eye 24 (4) (2010) 507–518, https://doi.org/10.1038/eye.2009.229.
[17] B.T. Poll-The, Maillette de Buy, L.J. Wenniger-Prick, P.G. Barth, M. Duran, The eye as a window to inborn errors of metabolism, J. Inherit. Metab. Dis. 26 (2–3) (2003) 229–244, https://doi.org/10.1023/a:1024493318913.
[18] P. Pavone, S.Y. Cho, A.D. Pratico, R. Falsaperla, M. Ruggieri, D.K. Jin, Ptosis in childhood: a clinical sign of several disorders: case series reports and literature review, Medicine (Baltimore) 97 (36) (2018), e12124. https://doi.org/10.1097/MD.0000000000012124.
[19] J.E. Davison, Eye involvement in inherited metabolic disorders, Ther Adv Ophthalmol 12 (2020) https://doi.org/10.1177/2515841420979109 2515841420979109.
[20] S. Ravaglia, P. Bini, K.S. Garaghani, C. Danesino, Ptosis in pompe disease: common genetic background in infantile and adult series, J. Neuroophthalmol. 30 (4) (2010) 389–390, https://doi.org/10.1097/WNO.0b013e3181f9a923.
[21] A. Eghbali, S. Hassan, G. Seehra, E. FitzGibbon, E. Sidransky, Ophthalmological findings in gaucher disease, Mol. Genet. Metab. 127 (1) (2019) 23–27, https://doi.org/10.1016/j.ymgme.2019.02.002.
[22] A. Sodi, A.S. Ioannidis, A. Mehta, C. Davey, M. Beck, S. Pitz, Ocular manifestations of Fabry's disease: data from the fabry outcome survey, Br. J. Ophthalmol. 91 (2) (2007) 210–214, https://doi.org/10.1136/bjo.2006.100602.
[23] A. Del Longo, E. Piozzi, F. Schweizer, Ocular features in mucopolysaccharidosis: diagnosis and treatment, Ital. J. Pediatr. 44 (Suppl 2) (2018) 125, https://doi.org/10.1186/s13052-018-0559-9.
[24] A. Michalski, J.V. Leonard, D.S. Taylor, The eye and inherited metabolic disease: a review, J. R. Soc. Med. 81 (5) (1988) 286–290, https://doi.org/10.1177/014107688808100517.
[25] D.S. Amalnath, D.K. Subrahmanyam, Ocular signs in Wilson disease, Ann. Indian Acad. Neurol. 15 (3) (2012) 200–201, https://doi.org/10.4103/0972-2327.99716.
[26] E. Langwinska-Wosko, T. Litwin, K. Dziezyc, A. Czlonkowska, The sunflower cataract in Wilson's disease: pathognomonic sign or rare finding? Acta Neurol. Belg. 116 (3) (2016) 325–328, https://doi.org/10.1007/s13760-015-0566-1.
[27] W.A. Gahl, E.M. Kuehl, F. Iwata, A. Lindblad, M.I. Kaiser-Kupfer, Corneal crystals in nephropathic cystinosis: natural history and treatment with cysteamine eyedrops, Mol. Genet. Metab. 71 (1–2) (2000) 100–120, https://doi.org/10.1006/mgme.2000.3062.
[28] S.J. Folz, J.D. Trobe, The peroxisome and the eye, Surv. Ophthalmol. 35 (5) (1991) 353–368, https://doi.org/10.1016/0039-6257(91)90185-i.
[29] E. Tsilou, M. Zhou, W. Gahl, P.C. Sieving, C.C. Chan, Ophthalmic manifestations and histopathology of infantile nephropathic cystinosis: report of a case and review of the literature, Surv. Ophthalmol. 52 (1) (2007) 97–105, https://doi.org/10.1016/j.survophthal.2006.10.006.
[30] J. Jaeken, D.J. Lefeber, G. Matthijs, SRD5A3 defective congenital disorder of glycosylation: clinical utility gene card, EuropeanJournal ofHuman Genetics : EJHG 28 (9) (2020) 1297–1300, https://doi.org/10.1038/s41431-020-0647-3.
[31] E. Morava, H.N. Wosik, J. Sykut-Cegielska, M. Adamowicz, M. Guillard, R.A. Wevers, D.J. Lefeber, J.R. Cruysberg, Ophthalmological abnormalities in children with congenital disorders of glycosylation type I, Br. J. Ophthalmol. 93 (3) (2009) 350–354, https://doi.org/10.1136/bjo.2008.145359.
[32] C.R. Ferreira, R. Altassan, D. Marques-Da-Silva, R. Francisco, J. Jaeken, E. Morava, Recognizable phenotypes in CDG, J. Inherit. Metab. Dis. 41 (3) (2018) 541–553, https://doi.org/10.1007/s10545-018-0156-5.
[33] C.R. Ferreira, D. Cassiman, N. Blau, Congenital disorders of N-linked glycosylation and multiple pathway overview, in: C.R. Ferreira, D. Cassiman, N. Blau (Eds.), GeneReviews((R)), 1993 , Seattle (WA).

[34] M. Martinez-Garcia, L. Montoliu, Albinism in Europe, J. Dermatol. 40 (5) (2013) 319–324, https://doi.org/10.1111/1346-8138.12170.
[35] G. Fusco, S. Carlomagno, A. Romano, E. Rinaldi, G. Cedrola, L. Cianciaruso, A. Curto, S. Rosolia, G. Auricchio, Type I hyperprolinemia in a family suffering from aniridia and severe dystrophia of ocular tissues, International Journal of Ophthalmology 173 (1) (1976) 1–10, https://doi.org/10.1159/000307812.
[36] S.J. Bell, N. Oluonye, P. Harding, M. Moosajee, Congenital cataract: a guide to genetic and clinical management, Therapeutic Advances in Rare Disease 1 (2020) https://doi.org/10.1177/2633004020938061 2633004020938061.
[37] M. Loi, Lowe syndrome, Orphanet journal of rare diseases 1 (2006) 16, https://doi.org/10.1186/1750-1172-1-16.
[38] L. Welling, L.E. Bernstein, G.T. Berry, A.B. Burlina, F. Eyskens, M. Gautschi, S. Grunewald, C.S. Gubbels, I. Knerr, P. Labrune, J.H. van der Lee, A. MacDonald, E. Murphy, P.A. Portnoi, K. Ounap, N.L. Potter, M.E. Rubio-Gozalbo, J.B. Spencer, I. Timmers, E.P. Treacy, S.C. Van Calcar, S.E. Waisbren, A.M. Bosch, N. Galactosemia, International clinical guideline for the management of classical galactosemia: diagnosis, treatment, and follow-up, J. Inherit. Metab. Dis. 40 (2) (2017) 171–176, https://doi.org/10.1007/s10545-016-9990-5.
[39] A. Medsinge, K.K. Nischal, Pediatric cataract: challenges and future directions, Clin. Ophthalmol. 9 (2015) 77–90, https://doi.org/10.2147/OPTH.S59009.
[40] D. Stambolian, Galactose and cataract, Surv. Ophthalmol. 32 (5) (1988) 333–349, https://doi.org/10.1016/0039-6257(88)90095-1.
[41] J.R. Cruysberg, Cerebrotendinous xanthomatosis: juvenile cataract and chronic diarrhea before the onset of neurologic disease, Arch. Neurol. 59 (12) (2002) 1975, https://doi.org/10.1001/archneur.59.12.1975-a.
[42] S.H. Mudd, F. Skovby, H.L. Levy, K.D. Pettigrew, B. Wilcken, R.E. Pyeritz, G. Andria, G.H. Boers, I.L. Bromberg, R. Cerone, et al., The natural history of homocystinuria due to cystathionine beta-synthase deficiency, Am. J. Hum. Genet. 37 (1) (1985) 1–31.
[43] F. Skovby, M. Gaustadnes, S.H. Mudd, A revisit to the natural history of homocystinuria due to cystathionine beta-synthase deficiency, Mol. Genet. Metab. 99 (1) (2010) 1–3, https://doi.org/10.1016/j.ymgme.2009.09.009.
[44] P.I. Gus, K.C. Donis, D. Marinho, T.F. Martins, C.F.M. de Souza, R.B. Carloto, G. Leivas, I.V.D. Schwartz, Ocular manifestations in classic homocystinuria, Ophthalmic Genet. 42 (1) (2021) 71–74, https://doi.org/10.1080/13816810.2020.1821384.
[45] J.R. Cruysberg, G.H. Boers, J.M. Trijbels, A.F. Deutman, Delay in diagnosis of homocystinuria: retrospective study of consecutive patients, BMJ 313 (7064) (1996) 1037–1040, https://doi.org/10.1136/bmj.313.7064.1037.
[46] G.H. Boers, T.W. Polder, J.R. Cruysberg, H.C. Schoonderwaldt, J.J. Peetoom, T.W. Van Ruyven, A.G. Smals, P.W. Kloppenborg, Homocystinuria versus Marfan's syndrome: the therapeutic relevance of the differential diagnosis, Neth. J. Med. 27 (6) (1984) 206–212.
[47] H. Claerhout, P. Witters, L. Regal, K. Jansen, M.R. Van Hoestenberghe, J. Breckpot, P. Vermeersch, Isolated sulfite oxidase deficiency, J. Inherit. Metab. Dis. 41 (1) (2018) 101–108, https://doi.org/10.1007/s10545-017-0089-4.
[48] K.K. Takki, R.C. Milton, The natural history of gyrate atrophy of the choroid and retina, Ophthalmology 88 (4) (1981) 292–301, https://doi.org/10.1016/s0161-6420(81)35031-3.
[49] B.M. Balfoort, M.J.N. Buijs, A. Ten Asbroek, A.A.B. Bergen, C.J.F. Boon, E.A. Ferreira, R.H. Houtkooper, M. Wagenmakers, R.J.A. Wanders, H.R. Waterham, C. Timmer, C.D. van Karnebeek, M.M. Brands, A review of treatment modalities in gyrate atrophy of the choroid and retina (GACR), Mol. Genet. Metab. (2021) https://doi.org/10.1016/j.ymgme.2021.07.010.
[50] A. Ganesh, F. Al-Murshedi, S. Al-Zuhaibi, K. Al-Thihli, Ocular Manifestations of Inborn Errors of Metabolism, in: A.V. Levin, R.W. Enzenauer (Eds.), The Eye in Pediatric Systemic Disease, Springer International Publishing, Cham 2017, pp. 359–460, https://doi.org/10.1007/978-3-319-18389-3_13.
[51] I. Sipila, J. Rapola, O. Simell, A. Vannas, Supplementary creatine as a treatment for gyrate atrophy of the choroid and retina, New Engl J Med 304 (15) (1981) 867–870, https://doi.org/10.1056/Nejm198104093041503.
[52] S. Bröer, Iminoglycinuria, in: F. Lang (Ed.), Encyclopedia of Molecular Mechanisms of Disease, Springer, Berlin Heidelberg, Berlin, Heidelberg 2009, pp. 1033–1034, https://doi.org/10.1007/978-3-540-29676-8_934.
[53] S. Hayasaka, K. Mizuno, K. Yabata, T. Saito, K. Tada, Atypical gyrate atrophy of the choroid and retina associated with iminoglycinuria, Arch. Ophthalmol. 100 (3) (1982) 423–425, https://doi.org/10.1001/archopht.1982.01030030425007.
[54] T. Saito, S. Hayasaka, K. Yabata, K. Omura, K. Mizuno, K. Tada, Atypical gyrate atrophy of the choroid and retina and iminoglycinuria, Tohoku J. Exp. Med. 135 (3) (1981) 331–332, https://doi.org/10.1620/tjem.135.331.
[55] P. Staps, J.R.M. Cruysberg, N. Roeleveld, M. Willemsen, T. Theelen, Retinal morphology in sjogren-larsson syndrome on OCT: from metabolic crystalline maculopathy to early-onset macular degeneration, Ophthalmol Retina 3 (6) (2019) 500–509, https://doi.org/10.1016/j.oret.2019.01.023.
[56] M. Tuson, G. Marfany, R. Gonzalez-Duarte, Mutation of CERKL, a novel human ceramide kinase gene, causes autosomal recessive retinitis pigmentosa (RP26), Am. J. Hum. Genet. 74 (1) (2004) 128–138, https://doi.org/10.1086/381055.
[57] A. Garanto, N.A. Mandal, M. Egido-Gabas, G. Marfany, G. Fabrias, R.E. Anderson, J. Casas, R. Gonzalez-Duarte, Specific sphingolipid content decrease in Cerkl knockdown mouse retinas, Exp. Eye Res. 110 (2013) 96–106, https://doi.org/10.1016/j.exer.2013.03.003.
[58] C.R. Ferreira, D. Cassiman, N. Blau, CERKL, a retinal dystrophy gene, regulates mitochondrial function and dynamics in the mammalian retina, Neurobiology of disease 156 (2021) 105405, https://doi.org/10.1016/j.nbd.2021.105405.
[59] M.M. McGovern, M.P. Wasserstein, A. Aron, R.J. Desnick, E.H. Schuchman, S.E. Brodie, Ocular manifestations of niemann-pick disease type B, Ophthalmology 111 (7) (2004) 1424–1427, https://doi.org/10.1016/j.ophtha.2003.10.034.
[60] H. Chen, A.Y. Chan, D.U. Stone, N.A. Mandal, Beyond the cherry-red spot: ocular manifestations of sphingolipid-mediated neurodegenerative and inflammatory disorders, Surv. Ophthalmol. 59 (1) (2014) 64–76, https://doi.org/10.1016/j.survophthal.2013.02.005.
[61] M.M. Ouseph, M.E. Kleinman, Q.J. Wang, Vision loss in juvenile neuronal ceroid lipofuscinosis (CLN3 disease), Ann. N. Y. Acad. Sci. 1371 (1) (2016) 55–67, https://doi.org/10.1111/nyas.12990.
[62] H. Mandel, K.C. Katsanelson, M. Khayat, I. Chervinsky, E. Vladovski, T.C. Iancu, M. Indelman, Y. Horovitz, E. Sprecher, S.A. Shalev, R. Spiegel, Clinico-pathological manifestations of variant late infantile neuronal ceroid lipofuscinosis (vLINCL) caused by a novel mutation in MFSD8 gene, European Journal of Medical Genetics 57 (11–12) (2014) 607–612, https://doi.org/10.1016/j.ejmg.2014.09.004.
[63] C.R. Ferreira, D. Cassiman, N. Blau, C.R. Ferreira, D. Cassiman, N. Blau, C.R. Ferreira, D. Cassiman, N. Blau, Specific alleles of CLN7/MFSD8, a protein that localizes to photoreceptor synaptic terminals, cause a spectrum of nonsyndromic retinal dystrophy, Investigative Ophthalmology & Visual Science 58 (7) (2017) 2906–2914, https://doi.org/10.1167/iovs.16-20608.
[64] S. Roosing, L.I. van den Born, R. Sangermano, S. Banfi, R.K. Koenekoop, M.N. Zonneveld-Vrieling, C.C.W. Klaver, J.J.C. van Lith-Verhoeven, F.P.M. Cremers, A.I. den Hollander, C.B. Hoyng, Mutations in MFSD8, encoding a lysosomal membrane protein, are associated with nonsyndromic autosomal recessive macular dystrophy, Ophthalmology 122 (1) (2015) 170–179, https://doi.org/10.1016/j.ophtha.2014.07.040.
[65] V.K. Gowda, H. Vegda, S.K. Shivappa, N. Benakappa, Aicardi-goutieres syndrome presenting with congenital glaucoma, Indian J. Pediatr. 87 (8) (2020) 652, https://doi.org/10.1007/s12098-020-03196-0.
[66] S.J. Steinberg, G. Dodt, G.V. Raymond, N.E. Braverman, A.B. Moser, H.W. Moser, Peroxisome biogenesis disorders, Biochim. Biophys. Acta 1763 (12) (2006) 1733–1748, https://doi.org/10.1016/j.bbamcr.2006.09.010.
[67] M. Huizing, B.P. Brooks, Y. Anikster, Optic atrophies in metabolic disorders, Mol. Genet. Metab. 86 (1–2) (2005) 51–60, https://doi.org/10.1016/j.ymgme.2005.07.034.
[68] P.F. Chinnery, M.A. Johnson, T.M. Wardell, R. Singh-Kler, C. Hayes, D.T. Brown, R.W. Taylor, L.A. Bindoff, D.M. Turnbull, The epidemiology of pathogenic mitochondrial DNA mutations, Ann. Neurol. 48 (2) (2000) 188–193, https://doi.org/10.1002/1531-8249(200008)48:2<188::AID-ANA8>3.0.CO;2-P.
[69] C. Verny, P. Amati-Bonneau, F. Dubas, Y. Malthiery, P. Reynier, D. Bonneau, An OPA3 gene mutation is responsible for the disease associating optic atrophy and cataract with extrapyramidal signs, Rev. Neurol. 161 (4) (2005) 451–454, https://doi.org/10.1016/s0035-3787(05)85075-1.
[70] J.A. Fraser, V. Biousse, N.J. Newman, The neuro-ophthalmology of mitochondrial disease, Surv. Ophthalmol. 55 (4) (2010) 299–334, https://doi.org/10.1016/j.survophthal.2009.10.002.
[71] L.H. Koens, M.A.J. Tijssen, F. Lange, B.H.R. Wolffenbuttel, A. Rufa, D.S. Zee, T.J. de Koning, Eye movement disorders and neurological symptoms in late-onset inborn errors of metabolism, Movement Disorders 33 (12) (2018) 1844–1856, https://doi.org/10.1002/mds.27484.
[72] R.H. Taylor, J. Burke, M. O'Keefe, B. Beighi, E. Naughton, Ophthalmic abnormalities in homocystinuria: the value of screening, Eye 12 (Pt 3a) (1998) 427–430, https://doi.org/10.1038/eye.1998.100.
[73] M. Michaelides, G.E. Holder, A.T. Moore, Chapter 44 - Inherited retinal disorders, in: C.S. Hoyt, D. Taylor (Eds.), Pediatric Ophthalmology and Strabismus (Fourth Edition), W.B. Saunders, London 2013, pp. 449–473.e442, https://doi.org/10.1016/B978-0-7020-4691-9.00044-3.
[74] K. Ohno-Matsui, Pathologic Myopia, Asia Pac. J. Ophthalmol. (Phila) 5 (6) (2016) 415–423, https://doi.org/10.1097/APO.0000000000000230.
[75] C.R. Ferreira, D. Cassiman, N. Blau, Homozygous p.R284* mutation in HEXB gene causing Sandhoff disease with nystagmus, Eur. J. Paediatr. Neurology 18 (3) (2014) 399–403, https://doi.org/10.1016/j.ejpn.2014.02.002.
[76] B. Kasmann-Kellner, J. Weindler, B. Pfau, K.W. Ruprecht, Ocular changes in mucopolysaccharidosis IV a (Morquio a syndrome) and long-term results of perforating keratoplasty, Int. J. Ophthalmology 213 (3) (1999) 200–205, https://doi.org/10.1159/000027420.
[77] C. Romani, Cognitive impairments in inherited metabolic diseases: promises and challenges, Cogn. Neuropsychol. 35 (3–4) (2018) 113–119, https://doi.org/10.1080/02643294.2017.1417249.
[78] A. Barrientos, J. Casademont, J.M. Grau, F. Cardellach, J. Montoya, X. Estivill, A. Urbano-Marquez, V. Nunes, Progressive external ophthalmoplegia and the kearns-Sayre syndrome: a clinical and molecular study of 6 cases, Med. Clin. (Barc.) 105 (5) (1995) 180–184.
[79] V. Laugel, V. This-Bernd, V. Cormier-Daire, C. Speeg-Schatz, A. de Saint-Martin, M. Fischbach, Early-onset ophthalmoplegia in Leigh-like syndrome due to NDUFV1 mutations, Pediatr. Neurol. 36 (1) (2007) 54–57, https://doi.org/10.1016/j.pediatrneurol.2006.08.007.
[80] D.G. Cogan, F.C. Chu, D. Reingold, J. Barranger, Ocular motor signs in some metabolic diseases, Arch. Ophthalmol. 99 (10) (1981) 1802–1808, https://doi.org/10.1001/archopht.1981.03930020676010.
[81] F. Iwata, M.I. Kaiser-Kupfer, Ocular manifestations of metabolic disorders, Curr. Opin. Ophthalmol. 5 (6) (1994) 79–83, https://doi.org/10.1097/00055735-199412000-00013.
[82] E.M.M. Hoytema van Konijnenburg, S.B. Wortmann, M.J. Koelewijn, L.A. Tseng, R. Houben, S. Stöckler-Ipsiroglu, C.R. Ferreira, C.D.M. van Karnebeek, Treatable inherited metabolic disorders causing intellectual disability: 2021 review and digital app, Orphanet J. Rare Dis. 16 (1) (2021) 170, https://doi.org/10.1186/s13023-021-01727-2.

[83] N. Dragojlovic, A.M. Elliott, S. Adam, C. van Karnebeek, A. Lehman, J.C. Mwenifumbo, T.N. Nelson, C. du Souich, J.M. Friedman, L.D. Lynd, The cost and diagnostic yield of exome sequencing for children with suspected genetic disorders: a benchmarking study, Genet. Medicine 20 (9) (2018) 1013–1021, https://doi.org/10.1038/gim.2017.226.

[84] J.J. Shen, S.B. Wortmann, L. de Boer, L.A.J. Kluijtmans, M. Huigen, J. Koch, S. Ross, C.D. Collins, R. van der Lee, C.D.M. van Karnebeek, M.R. Hegde, The role of clinical response to treatment in determining pathogenicity of genomic variants, Genet. Medicine 23 (3) (2021) 581–585, https://doi.org/10.1038/s41436-020-00996-9.

[85] C.R. Ferreira, D. Cassiman, N. Blau, Agbaga MP, Stiles M.A. <collab>Agbaga MP</collab>, The Elovl4 spinocerebellar Ataxia-34 mutation 736T>G (p.W246G) impairs retinal function in the absence of photoreceptor degeneration, Mol. Neurobiol. 57 (11) (2020) 4735–4753, https://doi.org/10.1007/s12035-020-02052-8.

[86] L. Haer-Wigman, H. Newman, R. Leibu, N.M. Bax, H.N. Baris, L. Rizel, E. Banin, A. Massarweh, S. Roosing, D.J. Lefeber, M.N. Zonneveld-Vrieling, O. Isakov, N. Shomron, D. Sharon, A.I. Den Hollander, C.B. Hoyng, F.P. Cremers, T. Ben-Yosef, Non-syndromic retinitis pigmentosa due to mutations in the mucopolysaccharidosis type IIIC gene, heparan-alpha-glucosaminide N-acetyltransferase (HGSNAT), Hum. Mol. Genet. 24 (13) (2015) 3742–3751, https://doi.org/10.1093/hmg/ddv118.

[87] S. Roosing, L.I. van den Born, R. Sangermano, S. Banfi, R.K. Koenekoop, M.N. Zonneveld-Vrieling, C.C. Klaver, J.J. van Lith-Verhoeven, F.P. Cremers, A.I. den Hollander, C.B. Hoyng, Mutations in MFSD8, encoding a lysosomal membrane protein, are associated with nonsyndromic autosomal recessive macular dystrophy, Ophthalmology 122 (1) (2015) 170–179, https://doi.org/10.1016/j.ophtha.2014.07.040.

[88] S.J. Bowne, L.S. Sullivan, S.H. Blanton, C.L. Cepko, S. Blackshaw, D.G. Birch, D. Hughbanks-Wheaton, J.R. Heckenlively, S.P. Daiger, Mutations in the inosine monophosphate dehydrogenase 1 gene (IMPDH1) cause the RP10 form of autosomal dominant retinitis pigmentosa, Hum. Mol. Genet. 11 (5) (2002) 559–568, https://doi.org/10.1093/hmg/11.5.559.

[89] P.W. Chiang, J. Wang, Y. Chen, Q. Fu, J. Zhong, Y. Chen, X. Yi, R. Wu, H. Gan, Y. Shi, Y. Chen, C. Barnett, D. Wheaton, M. Day, J. Sutherland, E. Heon, R.G. Weleber, L.A. Gabriel, P. Cong, K. Chuang, S. Ye, J.M. Sallum, M. Qi, Exome sequencing identifies NMNAT1 mutations as a cause of leber congenital amaurosis, Nat. Genet. 44 (9) (2012) 972–974, https://doi.org/10.1038/ng.2370.

[90] L.H.M. Pierrache, A. Kimchi, R. Ratnapriya, L. Roberts, G.D.N. Astuti, A. Obolensky, A. Beryozkin, M.J.H. Tjon-Fo-Sang, J. Schuil, C.C.W. Klaver, E. Bongers, L. Haer-Wigman, N. Schalij, M.H. Breuning, G.M. Fischer, E. Banin, R.S. Ramesar, A. Swaroop, L.I. van den Born, D. Sharon, F.P.M. Cremers, Whole-exome sequencing identifies biallelic IDH3A variants as a cause of retinitis pigmentosa accompanied by pseudocoloboma, Ophthalmology 124 (7) (2017) 992–1003, https://doi.org/10.1016/j.ophtha.2017.03.010.

[91] D.T. Hartong, M. Dange, T.L. McGee, E.L. Berson, T.P. Dryja, R.F. Colman, Insights from retinitis pigmentosa into the roles of isocitrate dehydrogenases in the Krebs cycle, Nat. Genet. 40 (10) (2008) 1230–1234, https://doi.org/10.1038/ng.223.

[92] M. Sugahara, M. Oishi, A. Oishi, K. Ogino, S. Morooka, N. Gotoh, I. Kang, N. Yoshimura, Screening for SLC7A14 gene mutations in patients with autosomal recessive or sporadic retinitis pigmentosa, Ophthalmic Genet. 38 (1) (2017) 70–73, https://doi.org/10.3109/13816810.2015.1136336.

[93] A. Dev Borman, L.A. Ocaka, D.S. Mackay, C. Ripamonti, R.H. Henderson, P. Moradi, G. Hall, G.C. Black, A.G. Robson, G.E. Holder, A.R. Webster, F. Fitzke, A. Stockman, A.T. Moore, Early onset retinal dystrophy due to mutations in LRAT: molecular analysis and detailed phenotypic study, Invest. Ophthalmol. Vis. Sci. 53 (7) (2012) 3927–3938, https://doi.org/10.1167/iovs.12-9548.

[94] M. Crimi, S. Galbiati, M.P. Perini, A. Bordoni, G. Malferrari, M. Sciacco, I. Biunno, S. Strazzer, M. Moggio, N. Bresolin, G.P. Comi, A mitochondrial tRNA(His) gene mutation causing pigmentary retinopathy and neurosensorial deafness, Neurology 60 (7) (2003) 1200–1203, https://doi.org/10.1212/01.wnl.0000055865.30580.39.

[95] F.C. Mansergh, S. Millington-Ward, A. Kennan, A.S. Kiang, M. Humphries, G.J. Farrar, P. Humphries, P.F. Kenna, Retinitis pigmentosa and progressive sensorineural hearing loss caused by a C12258A mutation in the mitochondrial MTTS2 gene, Am. J. Hum. Genet. 64 (4) (1999) 971–985, https://doi.org/10.1086/302344.

[96] S. Khateb, B. Kowalewski, N. Bedoni, M. Damme, N. Pollack, A. Saada, A. Obolensky, T. Ben-Yosef, M. Gross, T. Dierks, E. Banin, C. Rivolta, D. Sharon, A homozygous founder missense variant in arylsulfatase G abolishes its enzymatic activity causing atypical usher syndrome in humans, Genet. Medicine 20 (9) (2018) 1004–1012, https://doi.org/10.1038/gim.2017.227.

[97] C. Angebault, P.O. Guichet, Y. Talmat-Amar, M. Charif, S. Gerber, L. Fares-Taie, N. Gueguen, F. Halloy, D. Moore, P. Amati-Bonneau, G. Manes, M. Hebrard, B. Bocquet, M. Quiles, C. Piro-Megy, M. Teigell, C. Delettre, M. Rossel, I. Meunier, M. Preising, B. Lorenz, V. Carelli, P.F. Chinnery, P. Yu-Wai-Man, J. Kaplan, A. Roubertie, A. Barakat, D. Bonneau, P. Reynier, J.M. Rozet, P. Bomont, C.P. Hamel, G. Lenaers, Recessive mutations in RTN4IP1 cause isolated and syndromic optic neuropathies, Am. J. Hum. Genet. 97 (5) (2015) 754–760, https://doi.org/10.1016/j.ajhg.2015.09.012.

[98] S. Hanein, I. Perrault, O. Roche, S. Gerber, N. Khadom, M. Rio, N. Boddaert, M. Jean-Pierre, N. Brahimi, V. Serre, D. Chretien, N. Delphin, L. Fares-Taie, S. Lachheb, A. Rotig, F. Meire, A. Munnich, J.L. Dufier, J. Kaplan, J.M. Rozet, TMEM126A, encoding a mitochondrial protein, is mutated in autosomal-recessive nonsyndromic optic atrophy, Am. J. Hum. Genet. 84 (4) (2009) 493–498, https://doi.org/10.1016/j.ajhg.2009.03.003.

[99] J.K. Park, B.J. Herron, J.J. O'Donnell, V.E. Shih, V. Ramesh, Three novel mutations of the ornithine aminotransferase (OAT) gene in gyrate atrophy, Genomics 14 (2) (1992) 553–554, https://doi.org/10.1016/s0888-7543(05)80271-x.

[100] C. Zeitz, M. van Genderen, J. Neidhardt, U.F. Luhmann, F. Hoeben, U. Forster, K. Wycisk, G. Matyas, C.B. Hoyng, F. Riemslag, F. Meire, F.P. Cremers, W. Berger, Mutations in GRM6 cause autosomal recessive congenital stationary night blindness with a distinctive scotopic 15-hz flicker electroretinogram, Invest. Ophthalmol. Vis. Sci. 46 (11) (2005) 4328–4335, https://doi.org/10.1167/iovs.05-0526.

[101] I. Vazquez-Dominguez, A. Garanto, R.W.J. Collin, Molecular therapies for inherited retinal diseases-current standingOpportunities and Challenges, Genes (Basel) 10 (9) (2019) https://doi.org/10.3390/genes10090654.

[102] J.J. Darrow, Luxturna: FDA documents reveal the value of a costly gene therapy, Drug Discov. Today 24 (4) (2019) 949–954, https://doi.org/10.1016/j.drudis.2019.01.019.

[103] J. Kim, C. Hu, C. Moufawad El Achkar, L.E. Black, J. Douville, A. Larson, M.K. Pendergast, S.F. Goldkind, E.A. Lee, A. Kuniholm, A. Soucy, J. Vaze, N.R. Belur, K. Fredriksen, I. Stojkovska, A. Tsytsykova, M. Armant, R.L. DiDonato, J. Choi, L. Cornelissen, L.M. Pereira, E.F. Augustine, C.A. Genetti, K. Dies, B. Barton, L. Williams, B.D. Goodlett, B.L. Riley, A. Pasternak, E.R. Berry, K.A. Pflock, S. Chu, C. Reed, K. Tyndall, P.B. Agrawal, A.H. Beggs, P.E. Grant, D.K. Urion, R.O. Snyder, S.E. Waisbren, A. Poduri, P.J. Park, A. Patterson, A. Biffi, J.R. Mazzulli, O. Bodamer, C.B. Berde, T.W. Yu, Patient-customized oligonucleotide therapy for a rare genetic disease, N. Engl. J. Med. 381 (17) (2019) 1644–1652, https://doi.org/10.1056/NEJMoa1813279.

[104] A.V. Cideciyan, S.G. Jacobson, A.V. Drack, A.C. Ho, J. Charng, A.V. Garafalo, A.J. Roman, A. Sumaroka, I.C. Han, M.D. Hochstedler, W.L. Pfeifer, E.H. Sohn, M. Taiel, M.R. Schwartz, P. Biasutto, W. Wit, M.E. Cheetham, P. Adamson, D.M. Rodman, G. Platenburg, M.D. Tome, I. Balikova, F. Nerinckx, J. Zaeytijd, C. Van Cauwenbergh, B.P. Leroy, S.R. Russell, Effect of an intravitreal antisense oligonucleotide on vision in leber congenital amaurosis due to a photoreceptor cilium defect, Nat. Med. 25 (2) (2019) 225–228, https://doi.org/10.1038/s41591-018-0295-0.