Thieme

Diagnosis of Inherited Retinal Diseases

Diagnose erblicher Netzhauterkrankungen

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ABSTRACT

Inherited retinal diseases are a frequent cause of severe visual impairment or blindness in children and adults of working age. Across this group of diseases, there is great variability in the degree of visual impairment, the impact on everyday life, disease progression, and the suitability to therapeutic intervention. Therefore, an early and precise diagnosis is crucial for patients and their families. Characterizing inherited retinal diseases involves a detailed medical history, clinical examination with testing of visual function, multimodal retinal imaging as well as molecular genetic testing. This may facilitate a distinction between different inherited retinal diseases, as well as a differentiation from monogenic systemic diseases with retinal involvement, and from mimicking diseases.

ZUSAMMENFASSUNG

Erbliche Netzhauterkrankungen sind eine häufige Ursache für eine schwere Sehbehinderung oder Erblindung bei Kindern und Erwachsenen im erwerbsfähigen Alter. Aufgrund einer großen Heterogenität besteht eine hohe Variabilität hinsichtlich Einschränkungen der Sehfunktion, Auswirkungen auf das alltägliche Leben, auf die Lebensplanung sowie hinsichtlich neuer Therapieverfahren. Insofern ist eine frühzeitige und präzise Diagnose für Patienten und ihre Familien von Bedeutung. Die Charakterisierung einer erblichen Netzhauterkrankung umfasst eine detaillierte Anamnese, eine umfassende klinische Untersuchung mit Testung der Sehfunktion, eine multimodale retinale Bildgebung als auch eine molekulargenetische Diagnostik. Neben der Unterscheidung verschiedener erblicher Netzhauterkrankungen ist eine Abgrenzung zu monogenen Systemerkrankungen mit einer Netzhautbeteiligung, sowie eine Abgrenzung zu Erkrankungen, die eine Netzhautdystrophie imitieren, wichtig.

Inherited retinal diseases are among the most frequent causes of severe visual impairment and blindness in children and adults of working age. They result from mutations in genes that, in the most part, play an essential role in the structure, function or metabolism of the outer retinal layers. An early, accurate diagnosis not only facilitates therapeutic measures and the provision of visual support, but also enables social and psychological support to be sought at an early stage and may guide life planning (i. e. help to minimize the effects of the disease on education and professional choices).

The diagnosis of an inherited retinal disease is often complex due to pronounced heterogeneity [1–6]. While it is relatively straightforward to determine the extent of symptoms and visual function, accurate identification of the underlying disease cause often depends on various investigations including molecular genetic testing, and on the experience of the clinician.

Many patients with inherited retinal diseases experience a diagnostic odyssey before receiving an accurate diagnosis and comprehensive disease counseling. To prevent this, it is essential to suspect or recognize an inherited retinal disease at an early stage and to initiate further investigations in a specialized center. This may require the expertise of a multidisciplinary team (i. e. including geneticists and genetic counsellors). Even comprehensively characterized patients sometimes seek advice from several centers as they feel they are missing therapeutic opportunities. Therefore, it is essential not only to examine patients, but also to provide comprehensive patient counseling, follow-up examinations, and to connect them to patient advocacy groups.

Core elements of the characterization of inherited retinal diseases, which may serve as a cornerstone for thorough patient and family counseling, include:

- Detailed ocular history
- Comprehensive general medical history to reveal comorbidities and/or systemic disorders
- Comprehensive family history
- Clinical examinations
- Determination of visual function (including electrophysiology, if indicated)
- Multimodal retinal imaging
- Molecular genetic testing

For patients and their families, the following may be of particular importance:

- Classification of visual function (whether the individual satisfies the legal visual criteria for driving, workplace design), advice regarding current limitations, and some indication of the likelihood, and rate, of future visual loss
- Information on (novel) therapeutic approaches and clinical studies
- Differentiation from non-genetic diseases
- Investigation of suspected syndromal or systemic manifestations
- Information regarding likelihood of heritability
- Information regarding patient organizations and disease-specific patient groups
- Information regarding patient registers, for example the patient register of PRO RETINA in Germany (www.pro-retina.de/patientenregister), MyEyeSite in the UK (https://myeyesite.health) or My Retina Tracker Registry by the Foundation Fighting Blindness in the USA (www.myretinatracker.org)

Medical History

In a routine clinical setting, a variety of symptoms may signify an inherited retinal disease, particularly when symptoms cannot be explained by other diseases or anomalies. Examples include difficulties seeing in the dark, visual field restriction or delayed adaptation to a change between different light environments. Although the development of symptoms in the first 2–3 decades of life and progressive visual difficulties are characteristic of most inherited retinal diseases, neither advanced age nor stationary findings can exclude a diagnosis. A detailed medical history can substantiate an initial suspicion of inherited retinal disease and may guide further examinations. The age of onset and nature of the initial symptoms can also guide disease classification, especially when advanced degenerative changes do not allow a morphology-based classification.

Patients with inherited retinal diseases often are accustomed to (some of) the symptoms and develop specific coping strategies. Accordingly, detailed questioning may be required to obtain relevant information, which is particularly the case in patients with functional limitations since birth or early childhood. Specific questions, when phrased in different ways, often succeed in revealing such changes in visual function. It may, for instance, be the case that scotopic vision is compromised if the patient feels uncomfortable in unfamiliar surroundings but is quite comfortable in familiar surroundings. Glare may be a problem if the patient prefers being indoors, and/or wears sunglasses or tinted glasses more frequently than others. However, such glasses are also worn by some patients to improve contrast in their vision.

The general medical history is also important. Retinal changes may be associated with systemic syndromes (e.g. Usher or Bardet-Biedl syndrome) or may be a manifestation of a systemic disease which involves various organ systems. Examples of such systemic diseases include pseudoxanthoma elasticum (PXE) with an increased cardiovascular risk, primary hyperoxaluria type 1 with renal dysfunction, and mitochondrial diseases such as Kearns-Sayre syndrome, or McArdle disease with muscle problems [7–11]. A precise medication history is also essential, so that, for instance, retinopathy due to hydroxychloroquine or pentosan polysulfate can be differentiated [12–18]. Immunomodulatory therapies, whether for tumour therapy (melanoma, basal cell carcinoma), rheumatological conditions or ophthalmic diseases, may not only have ocular side-effects, but may also point to systemic conditions associated with vision problems (e. g. vitamin A deficiency associated with ulcerative colitis). Dietary and lifestyle factors should also be considered: For example, there are indications of possible negative effects on the disease course when patients with variants in the *ABCA4* gene take high-dose vitamin A, or when patients with retinitis pigmentosa smoke [19, 20].

A family history of (eye) diseases can also suggest the underlying disease. Inherited retinal diseases can be passed on to descendants via autosomal-dominant, autosomal-recessive, X-chromosomal or mitochondrial inheritance. Whenever possible, documentation of a pedigree should encompass at least 3 generations and 2nd-degree relatives, which may reveal X-chromosomal inheritance patterns or dominant inherited diseases with reduced penetrance (i. e. that not every carrier develops the disease). Even if no other family members are affected, a pedigree should be recorded. It may, for instance, document consanguinuity, which is often associated with autosomal-recessive disorders, and may identify other family members in whom examination may be contributory. Furthermore, detailed enquiries of medical history is worthwhile: If the parents are not known to be related, this does not exclude consanguinuity, e. g. if they are from the same village or neighbouring villages, or met at a family celebration. Furthermore, it is important to document the age at death of deceased family members: For example, if one parent died at an age at which the disease may not yet have been symptomatic, this person cannot be considered healthy with certainty (especially in

case of late-onset symptoms/disease). Comprehensive documentation of other systemic diseases of family members may also be important. For instance, diabetes mellitus in the mother and hearing impairment in her sister may point to a mitochondrial disease, even if each affected person develops different organ manifestations. Furthermore, apparently separate eye diseases may sometimes point to the genetic cause: Family members with a mutation in the *KIF11* gene, for example, may manifest different retinal changes (familial exudative vitreoretinopathy, cone-rod dystrophy or congenital chorioretinal atrophies) [21, 22]. Documentation of ethnicity may help in interpreting differences in regional incidence of genetic variants and disease.

Examination of Visual Function

Refraction and best corrected visual acuity are important parameters that may provide useful information for differential diagnosis. Visual acuity testing and refraction is usually reliable in adults, but it can take several visits to obtain accurate visual acuity and refraction in children under the age of 2. Under this age, refraction should be determined in cycloplegia. The established method for determination of near vision is to measure line vision, e.g. with LEA symbols or Landolt rings. Another important aspect is to differentiate/exclude amblyopia. Besides visual acuity, symptoms such as nystagmus may indirectly allow conclusions regarding visual function. Reduced visual acuity in children is, however, not restricted to the spectrum of inherited retinal diseases. Differential diagnosis may, for instance, include delayed visual maturation, central visual disorders or optic nerve hypoplasia [23, 24]. In young patients with mild visual impairment and subtle changes on retinal imaging, colour vision examination can also be helpful, for instance in differentiating inherited retinal diseases from optic neuritis.

The refraction may also be considered in the differential diagnostic workup. For example, patients with mutations in the bestrophin gene are often hyperopic, whereas patients with retinitis pigmentosa or congenital stationary night blindness are often myopic.

Visual field examinations provide information regarding peripheral and central visual field defects and may support the diagnosis as well as classification of inherited retinal diseases. Particularly in advanced disease stages, Goldmann perimetry often provides more information than static computer perimetry as it better depicts residual visual field "islands" [25]. In addition to its value in diagnosis and follow-up examinations, Goldmann perimetry may provide valuable information regarding insurance, liability and social security assessments such as reduced earning capacity, ability to operate vehicles, workplace risks or disability allowances for the blind and visually handicapped [25, 26].

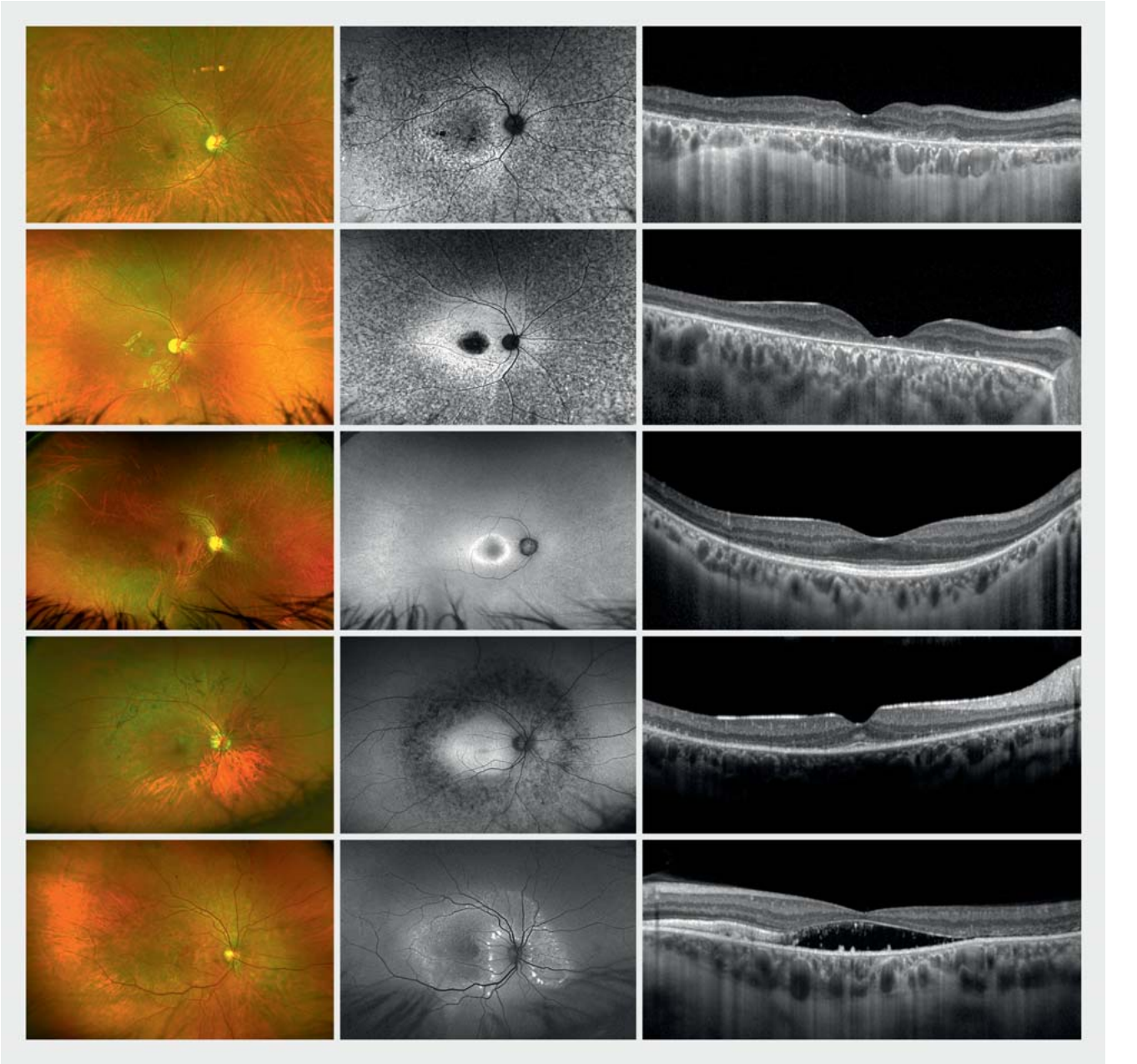
Historically, electrophysiology was often critical in diagnosing retinal diseases, but recent developments in retinal imaging and molecular genetic testing have reduced its importance. Electroretinography (ERG), however, is still useful in the differentiation of panretinal from macular dystrophies, for diagnosing generalized retinal dysfunction such as CSNB or achromatopsia, and to identify characteristic gene-specific patterns, for example in patients with variants in the *KCNV2* or *NR2E3* gene. Electrophysiological examination can also be useful when interpreting genetic variants of undetermined significance, or in differentiating mimicking diseases (see below). The importance of electrooculography (EOG) has also decreased due to developments in imaging and molecular genetics, and even in Best disease EOG readings are not necessarily abnormal [27]. Furthermore, there is no benefit in performing an EOG if ERG responses are severely reduced or absent.

Retinal Imaging

Retinal imaging facilitates the detection of retinal pathologies including changes that are barely visible or cannot be detected on fundus examination alone. In addition to conventional colour fundus photography, used to document funduscopic findings, established technologies include high-resolution optical coherence tomography (OCT) and fundus autofluorescence (AF) (▶ **Fig. 1**) [3 – 6]. Changes over the course of a disease can often be precisely tracked and measured using AF and OCT imaging. This is particularly important for clinical studies, since visual acuity often does not change significantly within the timeframe of a study, whereas disease progression may be traceable in the images.

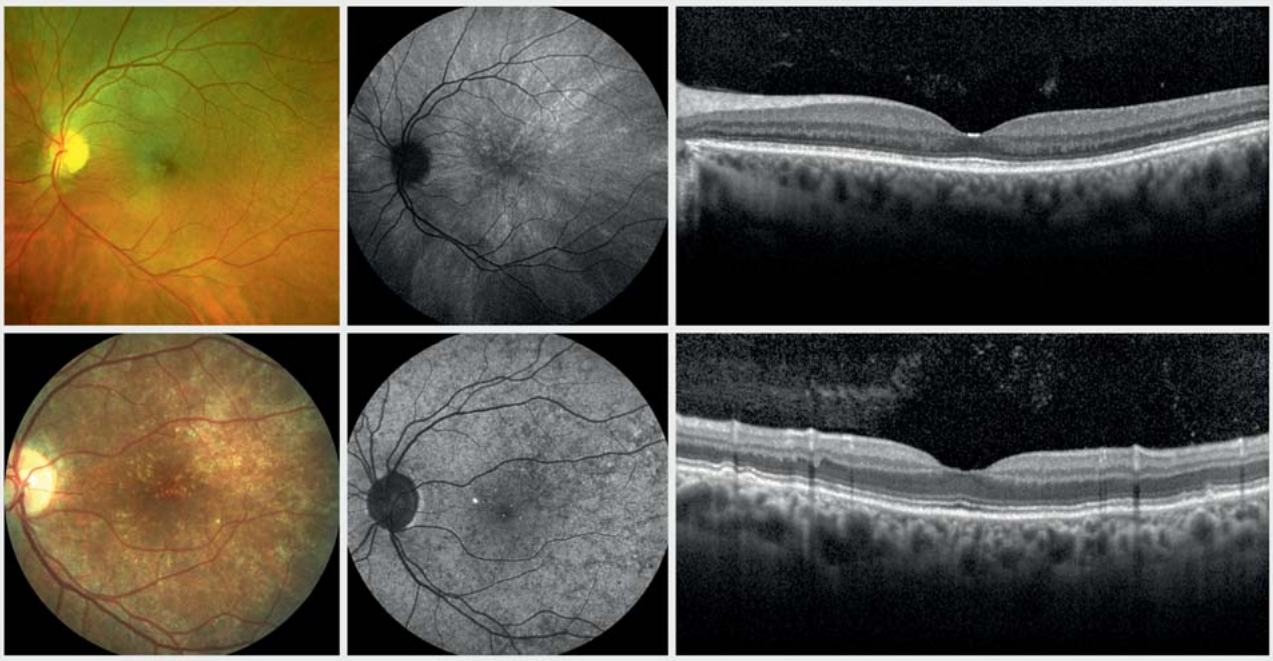
OCT generates "quasi histological" cross-sectional images of the retina with rapid image acquisition. In retinal dystrophies, important aspects include assessment of the integrity of the retinal pigment epithelium (RPE) and the photoreceptor layers (e.g. ellipsoid zone, outer nuclear layer). Most patients with retinitis pigmentosa (RP) initially show peripheral thinning and atrophy of the outer retina due to a primary or predominant rod degeneration [28, 29]. By contrast, patients with cone-rod dystrophies (CRD) with primary macular degeneration show mainly central atrophic changes in the outer retina (▶ **Fig. 1**). Furthermore, using OCT examinations, these two disease entities can be differentiated from stationary diseases that typically show little or no changes on OCT imaging such as congenital stationary night blindness or achromatopsia [30 – 32]. OCT can also detect macular oedema that occurs frequently in RP patients, which is hardly noticeable on fluorescein angiography. The strength of OCT imaging lies in the documentation of detailed follow-up examinations, and OCT imaging is particularly useful when it is combined with additional imaging modalities, such as blue or near-infrared AF.

AF visualizes the distribution of ocular fundus fluorophores, commonly using short-wavelength excitation light in the blue or green spectrum. This can reveal valuable diagnostic information regarding the topographic distribution and extent of retinal disease, and may often allow conclusions regarding retinal function [33 – 36]. RP provides a good example: At the transition between mainly intact central retina and degenerated peripheral retina a concentric ring of increased autofluorescence with no visible funduscopic correlate is typically found [37 – 39]. Even if the exact origin of this phenomenon is not completely understood, OCT examinations have demonstrated that the ring corresponds to loss of the ellipsoid band and pronounced thinning or even loss of the photoreceptor layer. In keeping with this interpretation, a correlation was also found between the diameter of the ring and the size of the remaining visual field [40]. Thus a ring of increased autofluorescence is not only diagnostically valuable, it also pro-



▶ **Fig. 1** Representative inherited retinal diseases using widefield color imaging, fundus autofluorescence (AF) and optical coherence tomography (OCT) (from left to right). Rows 1 and 2: *ABCA4*-associated retinopathy (Stargardt disease) with spots of increased and reduced autofluorescence as well as a central chorioretinal atrophy. Row 3: Retinitis pigmentosa (RP) sine pigmento with characteristic RP findings on AF (ring of increased autofluorescence) as well as on OCT (central photoreceptor band retained with adjacent thinning and atrophy of outer retina). Row 4: "Classic" retinitis pigmentosa. Row 5: Autosomal-recessive bestrophinopathy with spots of increased AF as well as serous subretinal fluid in OCT imaging.

vides information on the extent of retinal dysfunction [38,41]. Rings of increased autofluorescence can also be found at the edges of degenerative retina in other diseases, confirming the necessity of detailed disease characterization (see section on mimicking retinal diseases). Further characteristic findings include spots of increased autofluorescence, e.g. in patients with *ABCA4*-associated retinopathy, or a vitelliform lesion with increased autofluorescence in patients with autosomal-dominant Best disease or in cases with *IMPG2* mutations [42]. AF is also valuable in the early stages of retinal dystrophies. AF-alterations may be apparent even though funduscopy does not detect obvious abnormalities and patients have no, minimal or non-specific symptoms. Furthermore, in carriers of X-linked diseases (e.g. *RPGR*-associated RP or choroideremia), characteristic changes may appear in AF imaging (▶ **Fig. 2**) that may facilitate a reliable diagnosis even before genetic testing is performed [43–47].



▶ **Fig. 2** Fundus color image (left), fundus autofluorescence (middle) and optical coherence tomography (right) of female carriers of X-linked retinal dystrophies. The upper row shows a carrier for *RPGR*-associated retinitis pigmentosa and the lower row for choroideremia.

Near-infrared fundus autofluorescence (NIR-AF) is an alternative imaging modality to conventional AF using longer wavelength excitation light (787 nm) [48]. Even though the NIR-AF signal is less intense and this imaging modality is used less frequently, it has numerous advantages over conventional AF: The image acquisition process is more comfortable for patients due to reduced glare, cataract has less impact on the images, and interpretation of the central retina is not compromised by macular pigment, allowing even minor changes to be analyzed. Due to the lower energy, there is also less concern of retinal light toxicity. Assuming good image quality, similar changes may be observed in patients with inherited retinal diseases in these two imaging modalities, although precise analysis can certainly detect qualitative differences (▶ **Fig. 3**) [36, 49 – 52]. A further benefit of NIR-AF may lie in the differential diagnosis of non-inherited retinal changes [26, 53, 54].

Along with these established retinal imaging modalities, new developments include quantitative autofluorescence [55, 56], which provides an indirect measure of RPE lipofuscin content, adaptive optics, allowing visualization of the retina at a cellular level [57, 58] and OCT angiography enabling non-invasive visualization of vessels of the ocular fundus [59 – 61]. However, the value and feasibility of these modalities have yet to be established. The relevance of angiography in inherited retinal diseases is practically nil, with applications still useful in special cases only, such as suspected choroidal neovascularization or retinal vascular changes with exudation.

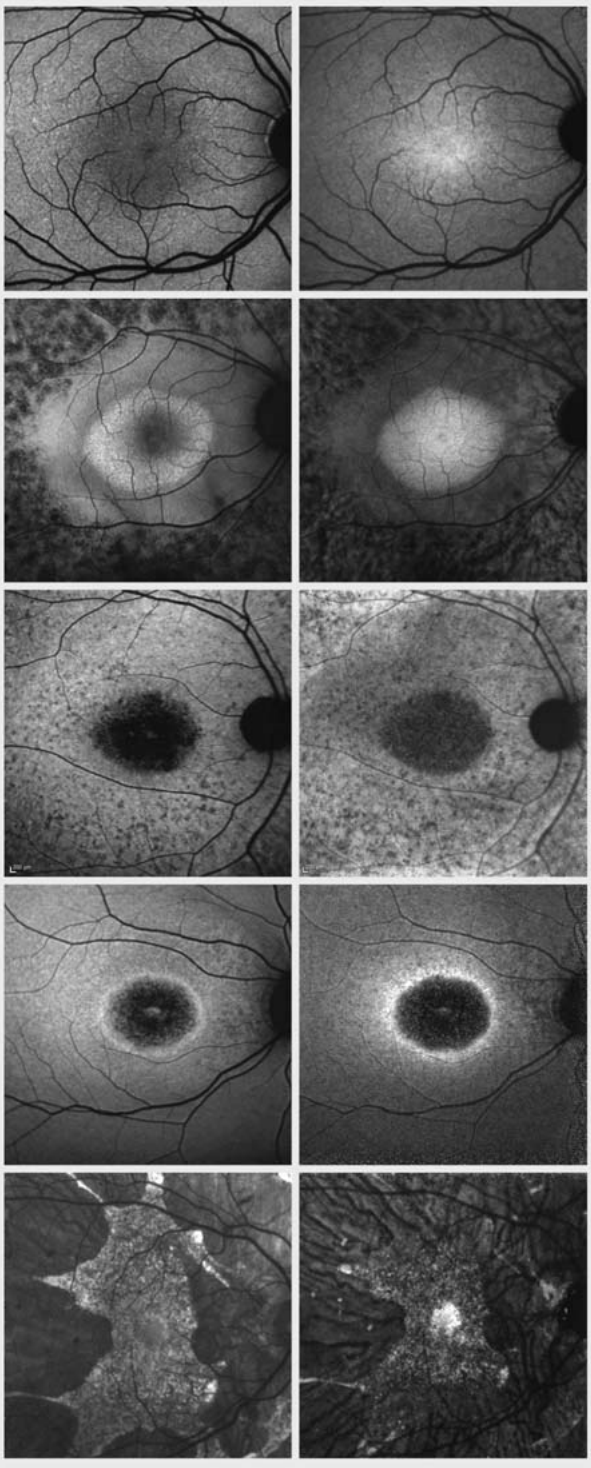
Classification and Terminology of Inherited Retinal Diseases

The terminology used in the description of inherited retinal diseases is inconsistent. This may result in a patient receiving apparently different diagnoses from different ophthalmologists, and communicating the reason for apparent inconsistencies to patients may be appropriate to ensure trust.

An initial clinical classification is often based on the medical history and disease course. Inherited retinal diseases are predominantly progressive, as seen in cone-rod dystrophies and retinitis pigmentosa, although stationary findings are also possible as in congenital stationary night blindness or achromatopsia.

Subsequently, a classification can be established based on the retinal cell types primarily involved. Historically, this was based mainly on the results of full-field ERG testing: A macular dystrophy is characterized by normal photopic and scotopic responses with a reduced-pattern ERG and cone dystrophy by reduced photopic responses. In cone-rod dystrophies, the photopic readings are more affected than the scotopic readings, which is the opposite in rod-cone dystrophies (retinitis pigmentosa). In routine clinical practice, this terminology is also used frequently even if the required ERG testing has not been performed. However, the approach of using electrophysiological terminology to describe structural observations may be incorrect or occasionally inadequate.

Proper names have been established for numerous inherited retinal diseases, where first describers summarized observations



▶ **Fig. 3** Exemplary images using blue-light fundus autofluorescence (left) and near-infrared fundus autofluorescence (right). Good image quality often reveals similar changes with these imaging modalities, although precise analysis does detect qualitative differences. From top to bottom a healthy control and patients with retinitis pigmentosa, *ABCA4*-associated retinopathy, macular dystrophy as well as choroideremia are shown, respectively.

or a constellation of symptoms into one disease. Although this may be appropriate in diseases with distinct phenotype-genotype correlations, such as Best disease, choroideremia or Bietti's crystalline dystrophy, it is often inaccurate for diseases with a broad genetic and/or phenotypic heterogeneity.

The use of proper names can result in morphological-functional as well as molecular inaccuracies. For example, "Stargardt disease" is also called – occasionally depending on the presentation – Stargardt disease type 1 (STGD1), fundus flavimaculatus, macular dystrophy, cone-rod dystrophy, cone dystrophy or *ABCA4*-associated retinal dystrophy. Despite this Babylonian confusion, whereby different terms evoke different associations, "Stargardt disease" usually refers to the autosomal-recessive disease due to mutations in the *ABCA4* gene (STGD1). Historically, however, three additional conditions with a similar retinal phenotype were designated as Stargardt disease (STGD2–4). It turned out that both STGD2 and STGD3 are caused by mutations of the *ELOVL4* gene ("STGD2" is no longer in use), and that STGD4 is caused by mutations of the *PROM1* gene. The consecutive numeration of Stargardt disease was no longer used to describe patients with similar retinal features. This would, for example, also include patients with particular mutations in the *PRPH2* gene. Autosomal-dominant mutations in *ELOVL4, PROM1* and *PRPH2* result in a retinal phenotype that may be similar to "true" Stargardt's disease patients, but these conditions are clinically, genetically and pathophysiologically different [62]. In addition, autosomal-recessive mutations in *ELOVL4* and *PROM1* also cause other conditions: *ELOVL4* mutations may also lead to spinocerebellar ataxia as well as to ichthyosis, spastic quadriplegia, and learning difficulties [63, 64]; autosomal-recessive *PROM1* mutations may cause an RP phenotype [65 – 69]. Some variants in the *PRPH2* gene may also lead to central areolar choroidal dystrophy (CACD) or retinitis pigmentosa [70 – 72].

Thus, the nosology of inherited retinal diseases is complicated since mutations in the same gene may cause multiple retinal diseases (phenotypic heterogeneity) [73]. Furthermore, mutations in different genes may cause a similar phenotype (genotypic heterogeneity), and there may be other (as yet largely unknown) genetic and/or environmental factors that may have an influence on the disease manifestation [19, 74 – 77].

The use of proper names may also confound the distinction between syndromal and non-syndromal conditions. For instance, variants in *USH2A* are typically associated with Usher syndrome, in which patients exhibit RP in addition to mild to severe hearing loss [78]. With increased frequency of molecular genetic testing, however, it became evident that many RP patients with *USH2A* mutations do not exhibit hearing impairment and that these patients do not show a syndromic disease [2, 79, 80]. If these patients are described as patients with Usher syndrome, this may imply hearing impairment, which, however, is not present. Likewise, mutations in Bardet-Biedl syndrome-associated genes may also be present in patients with non-syndromic RP [81, 82] or mutations in *CEP290*, classically associated with Senior-Løken, Joubert or Meckel-Gruber syndrome, may also be identified in non-syndromic Leber's congenital amaurosis (LCA) or RP [2, 83 – 86]. Monogenic systemic diseases with retinal involvement should also be considered in the differential diagnosis. The transition from

"classic" retinal dystrophies to systemic diseases with a retinal phenotype may be indistinct, as it is the case in PXE, some ciliopathies, or mitochondrial diseases [10, 87 – 92].

Until a generally accepted, consensus-based terminology is established, the following pragmatic principle can be applied: be as precise as possible and as vague as necessary. With increasing diagnostic certainty, this can be modified: For example, a "retinal dystrophy" can be diagnosed at first non-specifically, followed by more precise specification once the results of electrophysiological and molecular genetic testing are known (e.g. "*ABCA4* associated macular dystrophy"). If a stationary (e.g. CSNB) or mimicking disease cannot be excluded, this should be mentioned early in the differential diagnostics process. In order to not unsettle the patient, it is often worth providing a brief explanation of uncertainties in the diagnostic workflow. The diagnostic efficiency also depends on the experience and expertise of the clinician: a reliable diagnosis can often be established at the first consultation when characteristic disease features are present. However, a previously made diagnosis should always be reassessed and confirmed or rejected in the context of additional information or current findings/disease progression.

It may also be helpful to use terminology that links retinal alterations with monogenic systemic diseases. Examples include "PXE-associated retinopathy" or "mitochondrial retinopathy". It may also be reasonable to indicate the affected gene or subtype of a disease, especially if (gene-)specific therapies are in development or available.

Differentiation from Mimicking Retinal Diseases

There are many diseases that can mimic an inherited retinal disease (mimicking diseases). This includes post-inflammatory retinal conditions (e.g. rubella retinopathy or post-uveitic conditions), adverse drug effects (e.g. of hydroxychloroquine, deferoxamine or pentosan retinopathy) and the spectrum of autoimmune retinopathies. Vitelliform macular lesions may also be observed occasionally associated with age-dependent macular degeneration, chronic vitreomacular traction or central serious chorioretinopathy (to name only a few) (▶ **Fig. 4**). The diagnosis of a mimicking disease is of great relevance. For example, rubella retinopathy does not show significant progression, and in cases of adverse drug effects the causative therapeutic should be discontinued. In autoimmune processes, tumor screening may be indicated or, if necessary, immunosuppression may be considered.

This may also be relevant for family counselling, since the risk for family members is often less direct. Diagnosing a mimicking disease requires a detailed medical history and recognition of characteristic morphological features. Post-inflammation and autoimmune retinopathies in particular present with less symmetry compared to inherited diseases, although asymmetry may also be observed in retinal dystrophies, particularly in the early stages. Negative molecular testing may support but not confirm the diagnosis of a mimicking disease, as the causative mutation(s) are also not always identified in monogenic diseases [1, 2, 93 – 97].

Genetic Testing

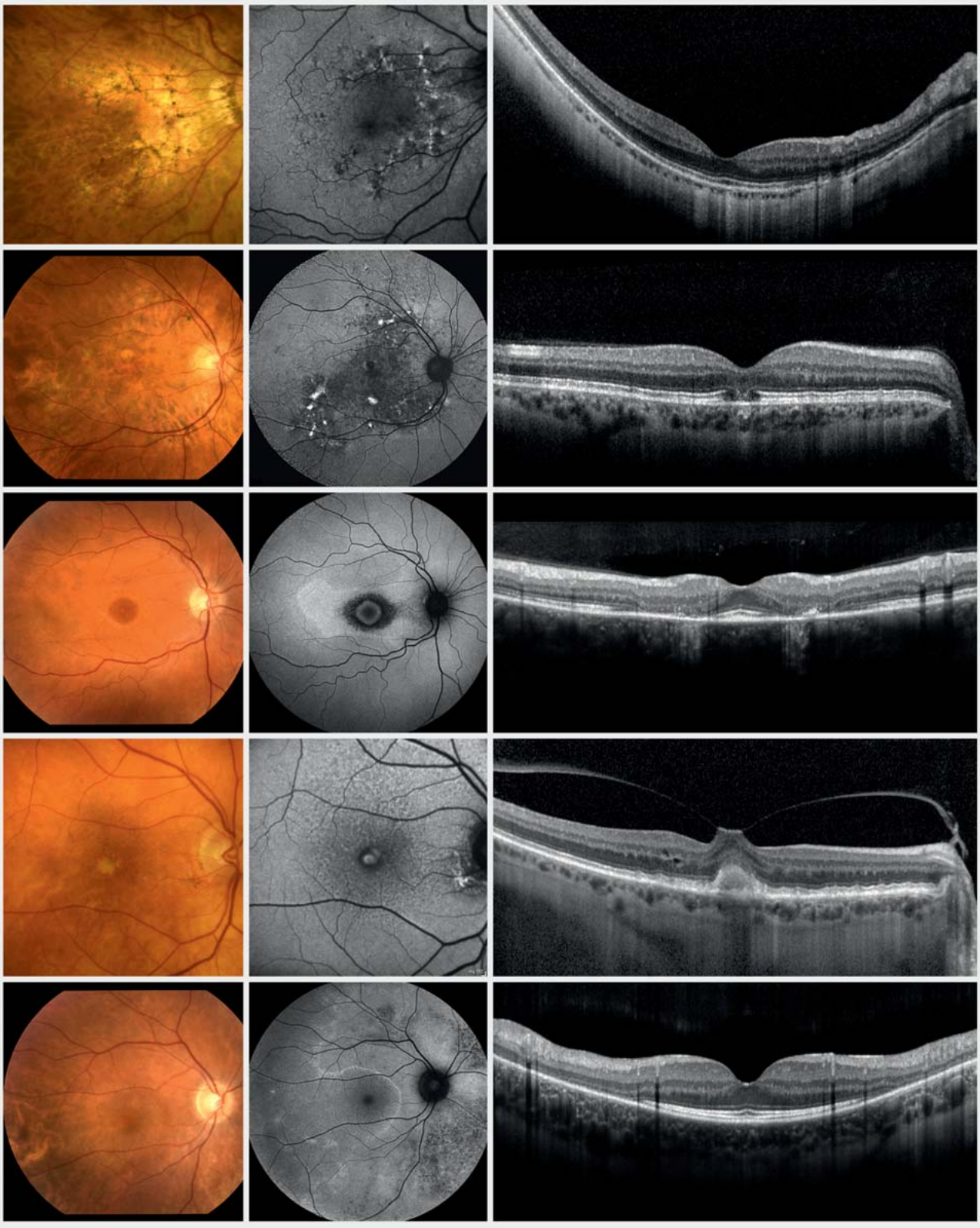
A cornerstone in the diagnosis of inherited retinal dystrophies is molecular genetic testing [1, 2, 96 – 105]. Identification of the molecular cause can not only provide information regarding the potential disease course or inheritance, but is also essential in light of (potential) disease-specific therapeutic options, including gene therapy, dietetic measures (e.g. a diet low in phytanic acid in Refsum disease) and pharmacotherapies (e.g. deuterated vitamin A [106] or visual cycle inhibitors in *ABCA4*-associated retinopathy/Stargardt disease). The approval of the first gene therapy (voretigene neparvovec) for patients with Leber's congenital amaurosis, due to mutations in the *RPE65* gene, is likely just the beginning as it is expected that further novel therapies will become available [107]. For instance, gene therapies for choroideremia and X-linked RP (*RPGR* mutations) are currently in the late stages of clinical development [108 – 111]. In advanced cases of inherited retinal diseases, where the exact phenotype cannot be determined due to widespread retinal degeneration, molecular testing may still enable a specific diagnosis.

Molecular testing can also result in the correction of an initial clinical diagnosis, may uncover an unexpected diagnosis, and may guide further investigations (e. g. hearing impairment, renal dysfunction, dyslipidemia, cardiomyopathy, diabetes) if the retinal disease suggests a syndromal condition [21]. Overall, a multidisciplinary approach involving geneticists, ophthalmologists, and potentially additional disciplines is essential in the interpretation of clinical ophthalmologic and molecular results. This sometimes includes a phenotypic re-evaluation following identification of a (potentially) causative molecular variant. After an interdisciplinary interpretation of the molecular results, comprehensive genetic counseling should be offered to patients and their families. If family members without disease signs or symptoms consider predictive genetic testing, counseling by a clinical geneticists or specialists qualified for this purpose is required beforehand.

Although detection of the molecular disease cause has become more accessible, the clinical diagnosis cannot be supported by genetic testing in all patients. However, a "negative" molecular result (no variant explaining the clinical findings detected) does not exclude the diagnosis of an inherited retinal disease – the clinical diagnosis remains in these cases. Furthermore, the detection of variant(s) in genes associated with retinal diseases does not exclude the possibility that mutations in other gene(s) are responsible for the phenotype.

Summary

Inherited retinal diseases may cause severe challenges in everyday life, physically as well as emotionally. For patients and their families, an accurate and comprehensive diagnosis is critical to prepare for the lifelong interpersonal, social and occupational impact of the diagnosis as well as for the potential loss of vision. A multidisciplinary approach is often essential, involving ophthalmologists, geneticists and other medical specialists.



▶ **Fig. 4** Exemplary retinal diseases that may mimic inherited retinal diseases. From top to bottom, patients with deferoxamine, rubella and hydroxychloroquine retinopathies, as well as a vitelliform macular lesion and autoimmune retinopathy. Fundus photography (left), blue-light fundus autofluorescence (middle) and optical coherence tomography (right).

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Conflict of Interest

The authors declare that they have no conflict of interest.

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