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Cross-sectional Phenotypical Differentiation of Major Blinding Eye Diseases in Europe: Inherited Retinal Dystrophies in Focus

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I would like to dedicate this Doctoral dissertation to my grandmother, Dr. Ida Balyasnikova, whose enthusiasm led me into the world of science.

Contents

Abbreviations list

ARMD.....age-related macular degeneration

BBD.....Bardet-Biedl syndrome

BCVA ..... best corrected visual acuity

CACD .....central areolar choroidal dystrophy

CI..... confidence interval

CD ..... cone dystrophy

CHRD.....choroideremia

CHR2 ..... channelrodopsin

CRD .....cone-rod dystrophy

CSNB .....congenital stationary night blindness

ERG .....elecroretinogramm

ICD ..... International classification of diseases

logMAR ..... log minimal angle of resolution

IOP .....intra ocular pressure

IRD .....inherited retinal dystrophies

LCA ..... Leber Congenital Amaurosis

MD..... macular dystrophy

mfERG .....multifocal electroretinogram

NEI-VFQ-25.....the National Eye Institute Visual Function Questionnaire

NIDDM ..... non-insulin-dependent diabetes mellitus

Pub-Med..... Medline database

QALY..... quality adjusted life years

RP .....retinitis pigmentosa

RP-SIM..... RP-simplex

RP-NSIH.....RP non-specified inheritance

STD ..... Stargardt disease

USH I..... Usher syndrome type I

USH II..... Usher syndrome type II

VA ..... visual acuity

VF.....visual field

VRQL ..... visual-related quality of life

I Introduction:

We all like to maintain good visual function as we get older. At some point in time almost everybody visits an ophthalmologist, but it is often too late for prevention and sometimes even for treatment.

I.1 Epidemiology of major eye diseases leading to blindness in Europe: How much do we know?

Currently it is estimated that 45 million people worldwide are blind, with an increase of 1-2 million each year [1]. In addition, 135 million people worldwide have low vision, defined as a visual acuity of lower than 6/18 and equal to or better than 3/60 in the better eye with best correction [1]. Age-related macular degeneration (ARMD) (26%), glaucoma (20.5%), cataract (11.2%), and diabetic retinopathy (8.9%) are the most frequent causes of blindness in Europe [2].

ARMD is the most common cause of severe vision loss worldwide and is characterized by the loss of central vision. Blindness due to ARMD occurs in advanced age; over 80% of those affected become blind after 70 years of age [3]. The overall prevalence of ARMD in Europe ranged between 9% and 25% [4] . It is higher in women (1.03% [95% CI, 0.11-1.96]) than in men (0.90% [95% CI, 0-2.08]) at 65-69 years of age [5]. The prevalence of ARMD has been found to vary between 40% in France [6], 39% in Germany [7], 36.3% in the Netherlands [8], 16.30% in the European North of Russia [9], and 14% in Bulgaria [2]. The incidence rate of ARMD increased with age from 0 [95% CI, 0-1.0] for the age group 55-64, 0.75 [95% CI, 0.15-2.2] for the age group 65-74 and 3.07 [95% CI, 1.1-6.7] for the population between 74 and 84 years of age [10].

Diabetic retinopathy is one of the most sight-threatening complications of diabetes mellitus and one of the most important emerging causes of blindness. It accounts for about 2.4 million cases of blindness globally [11]. 4.8% of the global population have diabetic retinopathy [12], while 3% [12] to 4.1% [13] of Europeans are affected. A prospective multinational WHO cohort study showed

that the incidence of any diabetic retinopathy in patients with diabetes type II was the highest in the UK (43.3%), followed by Switzerland (42.3%), Poland (31.8%), and Germany (29.9%) [14]. A population-based survey performed in Germany showed that men 60 to 74 years old had a higher incidence of diabetic retinopathy (29%) than women in the same age range (16.51%) [15].

67 million persons globally, of whom 25 million live in Europe, are affected by glaucoma [16]. It has been estimated that 12.3% of the worldwide population and 21.8% of European adults (including 18% of those over 50 years of age) have been diagnosed with glaucoma [12, 17, 18]. Overall, glaucoma is responsible for 5.2 million cases of blindness (15% of the world's blindness) [19]. According to recent epidemiological studies, Germany (14%) [7] has the highest prevalence of glaucoma in Europe followed by the European North of Russia (11.9%) [9]. The lowest prevalence of any type of glaucoma was in France (3.4%) [20] and the United Kingdom (3.3%) [21]. A Spanish epidemiological study showed that primary open-angle glaucoma (2.1% (99% CI, 1.9-2.3)) was greater in men (2.4%) than in women (1.7%) [22]. A cross-sectional study performed in the UK every year from 2000 to 2003 estimated that open-angle glaucoma and ocular hypertension were increasing both in men (from 3.41% to 3.6%) and in women (from 2.96% to 3.12%), but always with a higher prevalence in men than in women [23]. Open-angle glaucoma accounts for 56.5% of all cases of glaucoma in Russia [17]. On average, this type of glaucoma accounts for 80% of all glaucoma cases and becomes more common with increasing age [19].

Cataract is a leading cause of visual impairment worldwide [24]. Despite the fact that 90% of cataracts in the world are reported in developing countries, its social, physical and economical impact is still substantial in the developed world [12, 24]. Cataract surgery still remains as a major health care cost factor in Europe as in many Western countries. Global prevalence of cataract in adults over 50 years old was estimated at 47.8% [12]. Crude prevalence of cataract in European adults in year 2007 was 19.3% [13]. The prevalence of cataract in

Europe increased with age from 5% for the 52-62 age group [25], 30% for 60-69 years of age, and 64% for the population over 70 years old [26]. Cataracts causing a reduction of visual acuity under 0.7 in the worst eye were found in 4% of subjects 40-49 years old, 8.7% of subjects 50-59, 21.5% of subjects 60-69, and in 54.4% of subjects 70 years old or over [27]. The highest overall cataract prevalence for adults was seen in Bulgaria (51%) [2], followed by Germany (25.20%) [28], Italy (21%) [2], Orlean, France (13.3%) [6], the European North of Russia (12.20%) [9], and the Netherlands (6%) [2]. Sex specific cataract prevalence in a Spanish study was higher in men over 64 years of age (69.50%) than in women (65.50%) at the same age ($p>0.05$) [29].

The eye diseases discussed above are the most common causes of visual impairment in the elderly, whereas inherited retinal dystrophies (IRD) remain one of the main causes of low vision and blindness at younger ages [30]. IRD are rare diseases with prevalence of 1:1490 in Europe [31]. Patients with IRD are more likely to be registered as blind at a much younger age, and have a longer duration of blindness and visual impairment, which significantly decreases their quality of life [32]. Despite that fact, there is a very limited number of studies on the epidemiology of IRD in Europe. The data on such rare conditions as IRD is difficult to collect on the population level; therefore very few population-based studies had been conducted.

Retinitis pigmentosa (RP) is the name commonly given to a group of hereditary eye diseases characterized by progressive visual field loss, night blindness and abnormal or non- recordable electroretinogram (ERG). This broad definition includes a large amount of primary (ocular only) and secondary (other organs or systems involved) diseases [33]. It is an inherited retinal dystrophy caused by the loss of photoreceptors and characterized by retinal visual deposits visible on fundus examination [34].

The most common form of IRD is a rod-cone dystrophy, which affects approximately 1 in 3000-4500 persons of the general population [35]. The most

common first symptom of RP is night blindness followed by visual field constriction that eventfully leads to blindness after several decades. Some cases may have very fast progression over two decades or mild progression that never leads to blindness [36]. Night vision impairment, peripheral vision loss, and light sensitivity generally begin between the second and fifth decades of life. Visual acuity and macular function are usually relatively spared until late in the disease [37]. Visual field changes are characterized by patchy losses in peripheral vision evolving to ring shape scotoma, and eventually to tunnel vision [38].

Cone-rod dystrophies (CRD) are characterized by the predominant involvement of cones, or sometimes combined cone and rod involvement, and the opposite sequence of events in comparison to RP. It is characterized by the decrease of visual acuity, color vision defects, decreased sensitivity in the central visual field, and later followed by progressive loss in peripheral visual field and night blindness [39]. It is known that the typical course of CRD is usually more severe and rapid than IRD; however these two types of IRD become similar as they progress and can be difficult to differentiate [34].

Cone dystrophies (CD) are characterized by unimpaired rods. The main clinical signs of this disease are loss of visual acuity, photophobia, dyschromatopsia, and exclusive cone involvement in ERG. In the later stages of CD, rods can become involved in the pathologic process, which makes a differential diagnosis difficult [34]. In contrast to CRD, rode responses are still recordable in the late stages of CD and macular lesion is absent for many years, despite of visual acuity decrease [40].

Leber Congenital Amaurosis (LCA) is autosomal recessive retinal dystrophy characterized by a high degree of visual impairment (VA lower than 1/20), which is already present at birth, and appears as either a cone- or rod-predominant disease. At the time of diagnosis in infancy, the retinal appearance may be normal or demonstrate macular dysplasia or coloboma. Other associated

features of LCA include hyperopia, keratoconus, cataract, mental retardation, cystic renal disease, skeletal disorders, and hydrocephalus [41]. Differential diagnosis with early onset CRD can be quite difficult, because they share similar clinical findings. The presence of a lapse time of several years before dramatic worsening of visual disability helps to classify a visual disorder as CRD [34].

Bardet-Biedl (BBD) is an autosomal recessive disease with prevalence from 1/13500 to 1/60000 and is characterized by obesity, mild mental retardation, severe progressive pigmentary retinopathy, polydactyly, and hypogonaism [34, 42]. Visual impairment in BBD is usually apparent in the first two decades of life and blindness is often reached at the age of 20. Ocular findings include optic nerve atrophy and progressive pigmentary retinal degeneration [34, 35].

Usher syndrome (USH) is a pigmetary degeneration associated with sensori-neural hearing loss. Patients with type I Usher syndrome have severe congenital deafness and vestibular dysfunction, whereas patient with USH II have less profound congenital hearing loss and normal vestibular function. Ocular findings and degree of visual impairment can be variable even between similar genotypes. Visual signs and symptoms of Usher syndrome are similar to severe early onset RP and are represented by night vision impairment, peripheral vision loss, and light sensitivity, which generally begin by the second decade of life [43]. At any given age visual acuity, visual field, and ERG responses tend to be more impaired in USH I than in USH II, however these forms frequently considerably overlap. mfERG can be a key for correct diagnosis [35]. Seeliger et al. showed similar first order kernel mfERG reduction in RP and USH I, whereas USH II patients had only slightly prolonged implicit time in comparison with RP and USH I [44].

Several types of retinal disorders predominantly involve macular. Macular dystrophy is characterized by the worsening of visual acuity with age, although the progression is quite slow, only 20% of Best disease patients have a visual

acuity of 20/40 in at least one eye at the age of 40 [45]. The other form of macular disorders is Stargardt Disease (STD). It affects about 1 in 10000 people [35]. Visual acuity is variable, but is around 20/200 in 90% of STD patients [46].

Central areolar choroidal dystrophy (CACD) is an autosomal dominant or autosomal recessive disease and characterized by progressive loss of central vision, which is associated with the development of macular and choroidal dystrophy. It is characterized by color vision impairment and visual acuity decrease predominantly in the central field, which corresponds to the area of fundus dystrophy [35].

Choroideremia is an X-linked recessive dystrophy characterized by the progressive early-onset atrophy of the choroid and retina. Males affected with choroideremia usually have severe night vision disturbances and peripheral visual acuity decrease during the first two decades of life. Visual acuity tends to remain good until the seventh decade of life. Choroideremia female carriers are usually asymptomatic, but have typical fundus changes [35, 47].

This overview of different IRD types showed that clinical, symptomatic and electrophysiological signs can frequently overlap and make differential diagnosis in a variety of IRD difficult. One of the main problems in distinguishing the various types of RP on clinical examination is that there is a commonality to the fundus findings. Electrophysiological findings can also be similar in the later stages of IRD. Therefore more sophisticated approaches are needed in order to improve the efficacy of early differential diagnostic process. Further studies in this direction will help to formulate a combined algorithm for early IRD differential diagnosis and are of high importance of the formulation of clinical trial inclusion criteria, as well as for the creation of software to help in the diagnostic process.

The lack of European epidemiological data has greatly hampered detailed planning, monitoring, evaluation, and implementation of new innovative

treatments strategies for IRD patients in Europe. The absence of comprehensive epidemiological data on IRD in the European population limits further analysis of visual impairment trends and the timely development of appropriate and effective treatment strategies. Availability of reliable epidemiological data and cost-effective interventions for the control of eye diseases has demonstrated the importance of strengthening national initiatives for the preservation of eye health.

Only few literature reviews on the epidemiology of IRD have been published in Europe. As a result, European health services and research policies still lack the myriad benefits of such collated information. Moreover, existing studies focus for the most part only on the epidemiology of blindness and the most frequent forms of IRD such as retinitis pigmentosa [15, 30]. Despite the high value of data from these studies, there is still a pressing need for a complete picture of the epidemiological status of IRD in Europe. Therefore the first aim of this dissertation is to describe the present status of epidemiological research with respect to the prevalence and incidence of IRD in Europe through a systematic literature review.

I.2 The pressing need for the estimation of age of disease onset in monogenic retinal dystrophies with predominantly central and peripheral involvement.

Low vision and blindness are important public health problems worldwide and in Germany. According to the German Federation of Blind and Visually Impaired People, the number of blind people in Germany is about 145,000 and the number of partially sighted people is approximately 500,000 [48, 49].

Inherited retinal dystrophies (IRD) are heterogeneous disorders characterized by progressive loss of visual acuity (VA) and visual field (VF). IRD are in many instances monogenic disorders [50]. They can manifest in every age of life, but mostly affect young people and lead to blindness when the patient is in his or her most productive age, reducing their ability to work and maintain an

independent lifestyle [32]. To date, therapeutic possibilities for IRD are limited. Nevertheless, there are a few treatment approaches that have been shown to be successful in vitro models, such as: gene replacement therapy for treating retinitis pigmentosa (RP) [51-53], genetic targeting of bipolar and/or ganglion cells with engineered photo-gates [54-56]–or light-sensitive proteins such as channelrhodopsin-2 (ChR2) [57-61], and using a protective effect of the neurotrophic factor [62].

However, current gene therapies have some limitations, since they are specific to a single gene mutation and necessarily require the maintenance of photoreceptors [52]. ChR2 activation requires light stimulation levels that are 5 orders of magnitude greater than the threshold of cone photoreceptors [63], and has a substantially limited dynamic range (2 log units) [64]. An ideal therapy would be able to treat blindness independent of genetic mutation, in the absence of photoreceptors, and with reasonable response sensitivity. Several independent research groups have recently developed microelectronic retinal prostheses with the ultimate goal of restoring vision in blind subjects by stimulating the remaining retinal cells [65-68].

These recent advances in the treatment strategies of IRD suggest that a deeper understanding of the onset of IRD will aid in the timely application of future therapeutic strategies. Comprehensive epidemiological data on IRD in Europe is limited to blindness and the most common types of retinitis pigmentosa [69-76].

A retrospective longitudinal study of inherited retinal dystrophies (IRD), performed in Northern France showed the importance of such studies for the establishment of IRD prevalence as well as the age of its diagnosis in the population [31]. Earlier epidemiological studies were based on information received from social services and were focused on the estimation of the onset of blindness, but not of the disease itself [49]. Only a few studies report on the epidemiological status of IRD in Europe, including age of disease onset

estimation and geographic distribution [32, 77, 78], therefore much more detailed knowledge is required. Consequently, the second aim of this dissertation is to apply an epidemiological approach for the estimation of age of disease onset in central (Stargardt disease, central areolar choroidal dystrophy (CACD), Best's disease, pseudovitelliform macular dystrophy, pattern macular dystrophy, and progressive macular dystrophy) and peripheral IRD (Bardet-Biedl, Usher Syndrome and Usher II, choroideremia).

I.3 Main visual symptoms onset and special clinical signs of the electrophysiology of the visual system in a variety of IRD.

A comparison of the pattern of visual symptoms onset in different types of IRD is extremely important for the calculation of their manifestation risk, early diagnosis, differential diagnosis, consultation of patients, prognosis, and the application of future treatment strategies. Deeper understanding of the pattern of disease onset and its differences in various forms of IRD will make it possible to identify IRD patients who can be selected for clinical trials and benefit from new treatment strategies during early stages of the disease.

Disease history such as typical age of visual symptoms onset and clinical signs is certainly important for the early differential diagnosis of IRD and can guide clinicians through the diagnostic process. Nevertheless, these parameters alone are not sufficient for a final differential diagnosis.

Electrophysiological examination of the visual system has a significant effect on the diagnosis and management of a patient's treatment [79]. Full-field electroretinograms (ERGs) provide a basis for establishing the diagnosis of widespread forms of retinitis pigmentosa in early life, even at a time when fundus abnormalities visible with an ophthalmoscope are minimal or absent [80]. ERG amplitudes are objective measures of retinal function and are useful for accurate diagnosis of the disease, assessment of disease severity [81], follow-up of the course of disease [82], prognosis for visual function [83], and for measurement of responses to treatment, especially when running clinical trials

[83]. The multifocal ERG simultaneously records ERG signals from multiple retinal areas, and is a valuable tool for the assessment of topographical photopic retinal function [35]. It is also useful for the explanation of the range of responses obtained from full-field ERG [84].

Previous studies of full-field and mfERG focused on the estimation of the normal values and age-related changes [85], as well as on the study of specific changes that are typical for more widespread IRD types [44, 86, 87], or long-term follow-up studies of ERG changes in patients with retinitis pigmentosa [88]. Systematic comparison of full-field and mfERGs in patients with a variety of IRD subgroups (USH I, USH II, STD, RP, MD, CD, CRD, CHRD, CACD, BBD), as well as with normal ERG values, is important for differential diagnosis at early diseases stages, as well as for patient counseling, prognosis, and disease progression and treatment outcomes assessment. Despite its high importance, to the best of our knowledge there are no studies that comprehensively compare full-field and mfERG in such a wide variety of IRD. Thus, the third aim of this dissertation is to apply a differential approach in order to compare the typical pattern of visual symptoms onset and to analyze and compare special clinical signs in the electrophysiology of the visual system in a wide variety of IRD types.

I.4 Visual-Related Quality of Life Assessment in IRD patients.

Despite the high importance of estimation of age of the most important visual symptoms/disease onset in IRD, as well as definition of the special clinical signs in the electrophysiology of the visual system in inherited retinal dystrophies, a comprehensive characterization of these diseases would not be complete without a quality of life assessment. Visual impairment has a substantial impact on quality of life. The importance of evaluating vision-related quality of life is now recognized as a standard patient reported outcome value and widely used in the assessment of the effectiveness of different therapeutic strategies [89]. There is high interest in the evaluation of disease-related subjective

impairments in visually impaired patients, specifically due to the intensive development of new treatment strategies for a variety of eye diseases. Patients with IRD suffer considerably from the impacts of diminished visual, physical, functional, mental, and social aspects of their quality of life. Currently little is known about vision-related quality of life (VRQL) in patients with different forms of IRD. Only few studies related to VRQL in IRD patients have been published. Previous studies were devoted mostly to questions of VRQL association with visual acuity, visual field and electroretinogram, age [90-92], and the relationship between perceived and actual performance in tests of visual function [93, 94]. To our knowledge, no comparison of VRQL has been made between patients with different types of IRD. For that reason, the fourth aim of this dissertation is to characterize the VRQL of patients with different forms of IRD using the NEI-VRQ-25 questionnaire, which is considered as a standardized approach for the assessment of VRQL in a variety chronic eye diseases. The questionnaire is divided into several domains, covering different aspects of patient quality of life. It measures the influence of visual disability and health domains on the generic health domains such as emotional well-being and social functioning, in addition to task oriented domains related to daily visual functioning. It is also widely applied as a patients reported outcome and therefore was considered as an appropriate tool for this study.

The following main aims of the dissertation were defined:

1. To describe the present status of epidemiological research with respect to the prevalence and incidence of inherited retinal dystrophies in Europe through a systematic literature review.

2. To propose and apply an epidemiological approach for the estimation of disease onset in central and peripheral monogenic retinal disorders.

3. To apply a differential approach in order to compare the typical pattern of visual symptoms onset and to analyze and compare special clinical signs

in the electrophysiology of the visual system in a wide variety of IRD types.

4. To characterize the visual-related quality of life (VRQL) of patients with different forms of IRD.

II Materials and Methods:

The dissertation consists of four studies, therefore the materials and methods chapter is subdivided into four sections, which consequently correspond to the aims of the dissertation, as well as to sections in the results chapter.

II.1 Search strategies for the systematic literature review on the epidemiology of inherited retinal dystrophies in Europe.

The first aim of the dissertation is to analyze the present status of epidemiological research with respect to the prevalence and incidence of inherited retinal dystrophies in Europe through a systematic literature review.

A literature search was performed in the Medline database (Pub-MED), using the controlled vocabulary (MeSH) search terms: “Retinitis Pigmentosa” [Mesh] AND “Epidemiology” [Mesh]; “Retinitis pigmentosa” [Mesh] AND “statistics and numerical data” [Subheading]; and “Retinitis Pigmentosa” [Mesh] AND “statistics and numerical data” [Subheading]. The free text search terms were used to find articles that are not yet indexed and included: “inherited retinal dystrophies”, “retinitis pigmentosa”, "prevalence", "incidence", "population-based", "cross-sectional", "longitudinal cohort studies", "epidemiology", and "statistical data".

Only those studies were included which: a) were carried out in a European population of Caucasian origin with no age limitation, b) were based on diagnoses made by ophthalmological examination in accordance with ICD-10 (International Classification of Diseases); c) included a detailed description of sampling and diagnostic procedures as well as data resources; d) involved a sample size >300, and e) were published between January 1990 and December 2008.

Articles written in English, Spanish, German, Russian, and French were assessed. Only studies using standardized procedures for disease diagnosis were included.

We also included studies that used self-reported data and certificates of low vision from social services. The abstracts of the articles identified were reviewed and copies of those considered of high and medium relevance were obtained.

Special attention was given to studies focusing on prevalence and incidence by age and gender. Prevalence quantifies the proportion of individuals in a population who have a disease at a specific instant. In contrast to prevalence, incidence quantifies the number of new events or cases of the disease that develop in a population of individuals at risk during specific time interval. Additionally, attention was also given to articles referenced in the selected articles.

The data on prevalence will be reported here in percent, with 95% or 99% confidence intervals (CI); incidence will be presented in percent or in the number of cases per population size or person-years.

II. 2 Retrospective, cross-sectional study on the estimation of disease onset in monogenic retinal dystrophies.

The second aim of the dissertation is to use an epidemiological approach for the estimation of disease onset in central and peripheral monogenic retinal dystrophies.

II.2.1 Data collection

Data from 3,787 patients with monogenic retinal degenerations seen at the University Eye Hospital, Tuebingen from 1994 to 1999 were stored in an RP-clinical access-based database. The time frame for this study was chosen as during this period all clinical data was collected in a highly standardized manner, using an electronic database system. Records of 259 patients with hereditary retinal dystrophies were selected for the study from this database according to the inclusion criteria (diagnosis).

II.2.2 Inclusion and exclusion criteria

Two groups of hereditary retinal dystrophies were selected for our study: the first group with central visual field involvement included Stargardt (n=89) and central areolar choroidal dystrophy (CACD) (n=20), Best's disease (n=12), pseudovitelliform macular dystrophy (n=2), pattern macular dystrophy (n=8) and progressive macular dystrophy (n=3); the second group with predominantly peripheral visual field involvement included Bardet-Biedl (n=13), Usher I (n= 19) and Usher II (n=58) Syndromes, choroideremia (n=35). Patients with uncertain diagnosis and those who did not have a complete disease history collected in a standardized manner were excluded from the study.

II.2.3 Data management

The first visit data were retrospectively analyzed, including general information, disease history, data about color discrimination defects, and best-corrected VA.

General information contained the main demographic characteristics of the study population: age, sex, and nationality. Age of the patient was estimated as

the age when she/he had their first visit to the special clinic for inherited retinal degenerations in Tuebingen. Disease history included information about disease onset and evolution of clinical appearance of the disease over time, such as the age of first diagnosis, age of visual acuity decrease, night blindness, photophobia onset, and types of VF defects and age of patient at its onset, which were reported by the patient. Age at onset of symptoms was defined as the age at which these symptoms were either first reported by the patient and/or diagnosed by the ophthalmologist. Age at first diagnosis was defined as the age at which the first correct diagnosis was made, as indicated by the patient. Final diagnosis was recorded as a diagnosis that was established during the last visit of the patient within the defined study period.

Types of VF defects, color discrimination defects, and best-corrected VA were obtained from the results of clinical examination. For the purpose of analysis, patients were divided into two homogenous groups according to predominant type of visual field defect: group 1 (with predominantly central involvement, including Stargardt disease, macular dystrophy, and CACD), and group 2 (predominantly peripheral involvement, including Bardet-Biedl syndrome, Usher Syndrome I and II, and choroideremia). For further analysis, data was extracted from a MS Access 2000-based RP-clinical database using Structured Query Language (SQL) selection, and transferred to an Excel spreadsheet that was used for data management.

Statistical analysis was performed in SPSS 18.00 for Windows. Descriptive statistics, including mean and standard deviation and frequency calculation, were used for data analysis in the study on estimation of age at disease onset. Data concerning age distribution, age at first diagnosis, age at night blindness, photophobia and VA decrease onset, and age at emergence of VF defects were further stratified by diagnosis, which made it possible to see the contribution of each diagnosis in each age group. VA distribution data was stratified by age. Frequency of diagnosis and blindness was defined as the number of patients with this condition divided by the study population.

II.3 Comparison of the pattern of the visual symptoms onset in a variety of IRD.

The third aim of the dissertation is to use a differential approach to compare the pattern of visual symptoms onset of IRD and to analyze the special signs in electrophysiological examination of the visual system in a wide variety of IRD.

II.3.1 Inclusion criteria and exclusion criteria

Records of 544 patients with IRD seen at the University Eye Hospital in Tuebingen, Germany from 2005 to 2008 were selected for this study. This period was chosen for the study, since in 2005 new clinical database system was introduced in the University Eye Hospital, therefore reliable information collected by senior ophthalmologists in highly standardized was available for larger number of patients. Patients with the following diagnoses were included for both parts of the study: patients with predominantly central visual field involvement - Stargardt disease (STD) (n=69), central areolar choroidal dystrophy (CACD) (n=7), cone dystrophies (CD) (n=37), cone-rod dystrophies (CRD) (n=13), macular dystrophy (MD) (n=17), and patients with predominantly peripheral visual field involvement: retinitis pigmentosa (RP) (n=276), Bardet-Biedl syndrome (BBD) (n=13), Usher syndrome I (USH I) (n=5) and II (USH II) (n=18), choroideremia (CHRD) (n=21), and Leber congenital amaurosis (LCA) (n=15). Records of patients that did not have a final diagnosis and a full history of the disease collected using a standardized approach were excluded from the study. Age limitation was applied for the patients with LCA: only those patients older than 7 years of age were included in the study.

II.3.2 Data collection using Ophthabase

Patient records were obtained using standardized forms by a team of senior resident ophthalmologists specialized in hereditary retinal disorders, and have been transferred to an electronic database for data management and statistical evaluation. Ophthabase is a generic patient registry that was designed at the Institute for Ophthalmic Research, University of Tuebingen, and was used for

the collection, storage and management of patient data [95, 96]. IRD specific data included disease history: age at which first typical visual symptoms commenced (i.e. noticeable loss of visual acuity, night vision disturbances, glare sensitivity, or signs of restricted visual field), and age at first clinical diagnosis. Genetic testing was performed in some patients and it was possible to verify the type of inheritance in a fraction of them. Patients were diagnosed with retinitis pigmentosa of non-specified inheritance if genetic testing was not done and pedigree data was unavailable or did not provide enough data to detect the inheritance pattern. Simplex retinitis pigmentosa was diagnosed in patients if all other inheritance modes were excluded as a result of genetic tests.

II.3.3 Data management

This study focused on the analysis of best corrected visual acuity (BCVA) and visual field, since these parameters have been reported to be strongly correlated with a patient's perceived difficulty in the performance of daily activities [90]. Static and kinetic perimetry with an Octopus 101 (Haag-Streit, Switzerland) and a Goldmann perimeter were used for visual field examination. VF data were graded by ophthalmologists using a common clinical approach. BCVA was calculated in logMAR and was stratified into categories by severity of visual impairment according to the International Statistical Classification of Diseases by the World Health Organization [97].

Descriptive statistics such as frequency calculations were employed as cross-sectional quantitative data. Non-normally distributed data, such as age of onset of major visual symptoms and age at disease diagnosis were represented by median, 25th and 75th quantiles, while approximately normally distributed data were represented by their mean and standard deviation. Age at first diagnosis and first subjective visual symptoms were stratified by main ophthalmic diagnosis.

II.4 Study on special signs in the electrophysiology of IRD.

II.4.1 The flow of the study

The retrospective cross-sectional study on special signs in the electrophysiology of the visual system in a wide variety of IRD was broken into two stages: 1) random subsamples of patients with IRD and subjects with normal ophthalmological findings were selected to evaluate the distribution of full-field and mfERG values in normal subjects, in the IRD population overall, and in each of the IRD subgroups (USH I, USH II, STD, RP, MD, CD, CRD, CHRD, CACD, BBD), and to compare them, 2) a qualitative evaluation was performed on a much larger sample of patients.

The first stage of the study was aimed at the estimation of typical values for the amplitudes and implicit times in normal subjects in the IRD population as a whole, and in each of the disease groups. Normal subjects had no medical history of eye disease, and did not show any pathological signs in best corrected visual acuity, Goldmann or semiautomatic kinetic perimetry, color testing (Panel D15 test), examination of the anterior segment, funduscopy, Ganzfeld ERG and mfERG according to current ISCEV protocols.

The disease duration at first visit was calculated for each of the IRD types and represented the difference between the age at which patient first visited the eye hospital and the age when a patient first experienced the symptoms of the disease. The median amplitudes and implicit times for a and b-waves with 25th and 75th and 5th and 95th quantiles was calculated for full-field ERG, as well as for mfERG. The comparison of the parameters' medians between different IRD types was performed using box-plots [98] and a Kruskal-Wallis test [99]. For this purpose 21 patients were randomly selected from the population, including the whole IRD study population from the study of the visual symptoms pattern in a variety of IRD (n=544) (this was done for estimation of the median of IRD population as a whole and definition of the criteria for the qualitative data assessment in the second part of the study), as well as from subsets including

each above mentioned IRD (for calculation of the median values for each IRD and for the median comparison). 21 patients with normal ophthalmological findings were selected as a reference group. The sample size of 21 patients/controls for the random selection was chosen based on the fact that a sample size equal to 21 patients/controls enables us to estimate the median with a very low variance, whereas increasing the sample size over 21 will not substantially influence the variance of the estimate [100]. Random selection allowed us to ascertain that both patients with predominantly peripheral and predominantly central visual field involvement have an equal chance to be selected, which justifies the choice of having one reference group with normal subjects for comparison in this study.

Response parameters of the first order kernel of the mfERG were analysed by grouping the responses into five concentric rings and averaging them. The median, 5th, and 95th quantiles of the amplitudes and implicit times in Ring 1 (RI), Ring 2 (RII), Ring 3 (RIII), Ring 4 (RIV), and Ring 5 (RV) were calculated for the reference group and a random sample from the IRD study population. mfERG parameters were compared between the different types of IRD and normal subjects. Implicit times were also averaged for each of the concentric rings and further compared between different IRD types and subjects with normal ophthalmological findings. Criteria for the qualitative evaluation of mfERGs in IRD patients were defined.

The second stage of the study was aimed at a qualitative assessment of a larger sample (n=355) of full-field and mfERGs. Patients with IRDs who underwent a full-field and mfERG were selected at this stage of the study from an Eye Hospital Information System. The data were qualitatively assessed by using the criteria formulated in the first part of the study. All values that were above the 95^{th} or below the 5^{th} quantile of the normal values estimated by us were considered abnormal. Amplitudes ranging from the maximum of IRD population values to the 25^{th} quantile of the IRD population were considered moderately reduced. The amplitudes lower than the 25^{th} quantile for the IRD

population were considered to be severely reduced. Implicit times that were higher than the maximal normal value and lower than the 75th quantile of IRD population values were characterized as moderately prolonged. Implicit times exceeded the 75th quantile and were equal to or exceeded the maximum implicit time values of the IRD population median were characterized as severely prolonged.

II.4.2 Data collection

Electrophysiological examination included full-field electroretinography and multifocal electroretinography (mfERG). Full-field electroretinograms were recorded according to ISCEV standard [101] with an espion E^2 system and ColorDome Ganzfeld stimulator (Diagnosys UK Ltd, Cambridge, UK) using DTL electrodes. A stimulus of 0.007 cds/m^2 was used for recording dark adopted rod b-wave. White flashes at a standard flash intensity of 2.25 cds/m^2 were used for maximum a and b-waves as well as for the oscillatory potentials recordings. L-cone single red flashes (650 nm) at a flash intensity of 2.25 cds/m^2 in a light adapted state (34 cd/m^2) were used for photopic cone signals recording. mfERG was performed according to the method described by Sutter and Tran [102] using the VERIS system with luminance of the screen elements 100 cd/m^2 in the lighted background.

II.4.3 Data management

Patient data was obtained by senior ophthalmologists specialized in IRD and stored electronically in a generic patient registry (Ophthabase). The structure and technical details of Ophthabase design were described by us earlier [96, 103]. Electronically stored data was entirely pseudonymized. Access to the patients' data was limited to researchers taking part in the study. Collected data included general information such as age, sex, postal code, history of the disease (age of the typical symptoms onset and age at first diagnosis), and clinical data (best corrected visual acuity and perimetry data), as well as technical data (full-field and mfERG).

II.5 Visual-Related Quality of life assessment in a variety of IRD.

The fourth aim of the dissertation is to evaluate visual-related quality of life in patients with IRD, as a baseline for clinical trials effectiveness assessment.

II.5.1 Data collection

The German validated version of the National Eye Institute Visual Function Questionnaire (NEI-VFQ-25) [104, 105] was chosen for VRQL evaluation in different types of IRD. The questionnaire was administered to all patients with MD, RP, STD, USH I and II types, CACD, CD, CRD, CHRD, LCA and congenital stationary night blindness (CSNB).

The patients were enrolled during the 4-month period starting in July 2009. Visual field (VF) data and BCVA in logMAR were obtained. The aim and content of the study was explained to the patients/or their legal guardians by the examining ophthalmologist. Oral informed consent was received from all patients who agreed to participate in the study. Patients were informed about the possibility of withdrawal from the study at any stage. Substantial time was given to the patients to consider participation in this study. The NEI-VFQ-25 takes on average 10 minutes to be administered. Patients were given as much time as required to fill out the form. The questionnaires were completed by the patients themselves while they were waiting for their eye examination, unless their sight was too poor to complete the form without assistance. Patients were asked to bring a filled in questionnaire to their ophthalmologic examination. Questionnaires were pseudonymized by the examining ophthalmologist using the patients' ID numbers from the electronic patient file system. The patients' ID numbers enabled us to separate the information about patients' identities from relevant clinical data such as final diagnosis. All questionnaires were accompanied by a letter for the patient, which briefly described the aim of the study and instructions for filling it in. A general information form was attached to all questionnaires and contained questions about sex, family status, living situation, completed education, and profession. The general information form

also included questions about the use of vision assistive devices, such as glasses and contact lenses, and the patients' views on their effectiveness. Patients were also asked whether or not they have any other eye disorders, and if so to name them. The 25-item NEI-VFQ-25 in the German version consists of 12 subscales: general health, general vision, near vision, distance vision, driving, peripheral vision, color vision, ocular pain, and vision-specific questions such as role limitations, dependency, social functioning, and mental health. Each question is assigned a 5- or 6-scale rating, which is subsequently transformed to a 0-100 scale, where 100 means no difficulty, 75 - little difficulty, 50 – moderate difficulty, 25-extrime difficulty, and 0 – unable to perform a task because of eyesight.

II.5.2 Data management

Descriptive statistics were used to characterize the demographic, socio-economic and clinical characteristics of the study population as a whole. Patients were divided into groups according to their clinical diagnosis. The overall composite NEI-VFQ-25 score, represented by an unweighted average of the responses to all 12 subscale items, was calculated as an arithmetic mean for each patient. The overall score for each of the items was stratified by age, sex, clinical diagnosis, education level and best corrected visual acuity. A Kruskal-Wallis test was use to identify statistically significant differences between groups.

Final diagnosis in all of the above described studies was established by a team of four senior resident ophthalmologists at the University Eye Hospital, Tuebingen, and was based on a comprehensive analysis of medical history, clinical investigation including best corrected visual acuity, Goldmann or semiautomatic kinetic perimetery, color testing (Panel D15 test), examination of anterior segment and funduscopy, Ganzfeld ERG (in every patient), and mfERG (in selected patients) according to current ISCEV protocols [101, 106].

Informed consent was obtained from all persons involved in the studies or from their legal guardians in accordance with the tenets of the 1964 Declaration of Helsinki. All information was handled with a special guarantee of confidentiality in order to avoid unwanted back-tracing of participants. Access to research databases (RP-access database, Ophthabase) and to the patients' data was restricted to researchers directly involved in these studies. Electronically stored data was entirely pseudonymized. The study protocols for all above presented studies were reviewed and approved by the Ethics Commission of the Medical Faculty, Eberhard-Karls University, Tuebingen, Germany.

III Results:

III.1 Epidemiology of inherited retinal dystrophies in Europe.

RP is a term commonly given to a group of inherited and progressive retinal disorders that affect the photoreceptors of the retina. The prevalence of non syndromic RP is approximately 1/4000 [107]. At the same time the epidemiological status of retinitis pigmentosa varies between different countries. RP causes 7% of blindness in Ireland and 8.1% in Baden, Germany [108, 109]. A prospective study in Puerto Rico estimated the prevalence of RP at 44/10000 (0.44%), 34.1% of all patients had RP as a part of Bardet-Biedl syndrome [76]. Results of another Spanish study of RP indicated that Usher syndrome type I and Usher syndrom type II were the most frequent varients of syndromic RP [77]. A Valencian Community study in Spain determined the autosomal recessive type of RP (31.8%) to be the most frequent, and the X-lined type the most rare (1.5%). The autosomal dominant type was responsible for 14.4% of cases, and simplex cases constituted half of the total prevalence of RP registered in the region [110]. A similar trend was detected in a retrospective study in Amsterdam, the Netherlands: simplex cases (37.1%), autosomal recessive (30.1%), autosomal dominant (22.4%), and X-linked (10.4%) [78]. A prevalence study in Slovenia showed that the prevalence of RP was 1/6023. The highest prevalence of RP in the Slovene population was found in the age group over 65 years (1/1902). The autosomal dominant RP type (27%) was the most prevalent in Slovenia, followed by autosomal recessive (21%) and X-linked (1.5), 47.5% of cases were determined to be the result of isolated causes. Usher syndrome was present in 12% of all RP cases, and Bardet-Biedl in 5% [70]. A retrospective study performed at the University Eye Clinic Tübingen, Germany detected the same trend: Usher syndrome types I and II (34%) were the most prevalent types of RP, while Bardet-Biedl syndrome was detected in 5% of all patients [32]. 37% of patients in the 21-40 age group and 36% in the 41-60 age group were registered as legally blind, indicating a strong impact of monogenic retinal degenerations on the incidence of blindness in

highly productive age groups. Despite this fact, it was observed that a relatively high number of patients with monogenic retinal dystrophies retained quite good visual acuity, which shows that early and properly planned rehabilitation strategies could increase quality of life for these patients [32].

Overall, the present literature review showed that the epidemiological data is lacking for inherited retinal dystrophies. Very few studies on the epidemiology of RP are nation-wide and population-based; this is mostly due to the fact that these diseases are very rare. Most of these studies address only the most frequent forms of IRD, and are often based on data derived from certificates of legal blindness, which do not provide information on the burden of IRD itself. Very few studies deal with disease onset and progression of IRD. We were unable to find any studies that compare clinical electrophysiological data between different IRD types. Such studies would be especially useful for the identification of patients who may benefit from new treatments. We address this shortcoming in the next chapter of the dissertation by performing a study on age of disease onset estimation in central and peripheral IRD using an epidemiological approach.

III.2 An epidemiological approach for the estimation of disease onset in Central Europe in central and peripheral monogenic retinal dystrophies.

Estimation of disease onset in central and peripheral IRD using an epidemiological approach is extremely important for differentiation between these two groups of IRD during the early stages of the diagnostic process, as well as for the estimation of the optimal age for therapeutic intervention and rehabilitation.

Records of 259 patients were studied. In total, group 1 (predominantly central involvement) included 134 patients and group 2 (predominantly peripheral involvement) 125 patients. Sex distribution: sex distribution analysis revealed that in both groups men predominated in comparison with women. The same trend was revealed when stratifying the data according to diagnosis in both groups (Figures 1, 2a). Group 1 included 87 male and 47 female patients; group 2 included 72 male and 53 female patients. In the subgroup of patients with choroideremia, men predominate, as the disease is inherited via an X-linked recessive mechanism. At the same time, our data contained women who were mostly obligatory carriers of the disease with or without symptoms, and one case was diagnosed with choroideremia. The distribution of women in the Choroideremia subgroup is shown in Figure 2b.

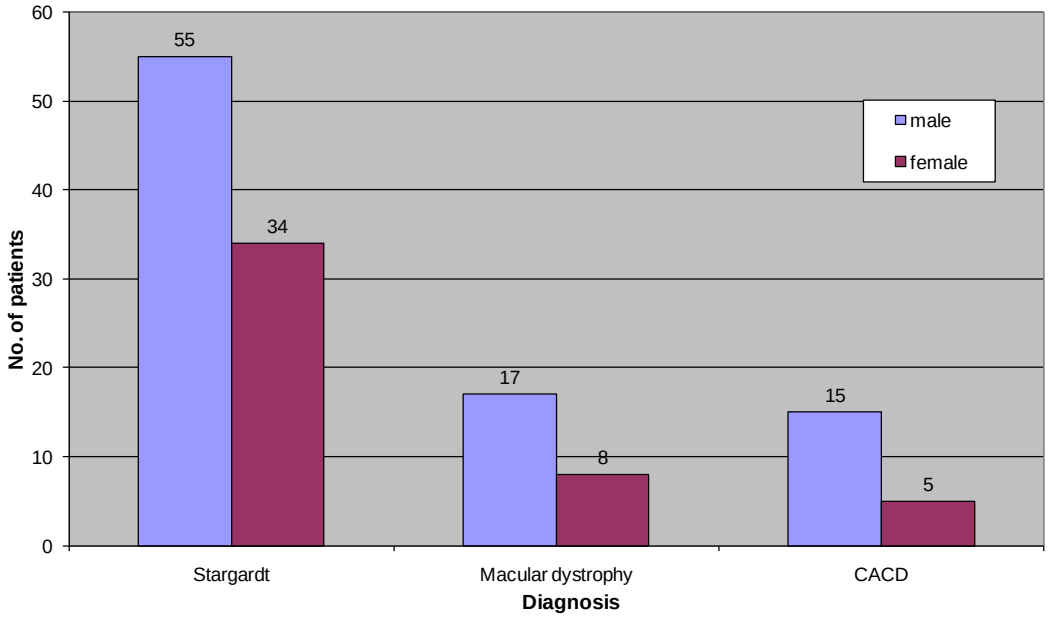
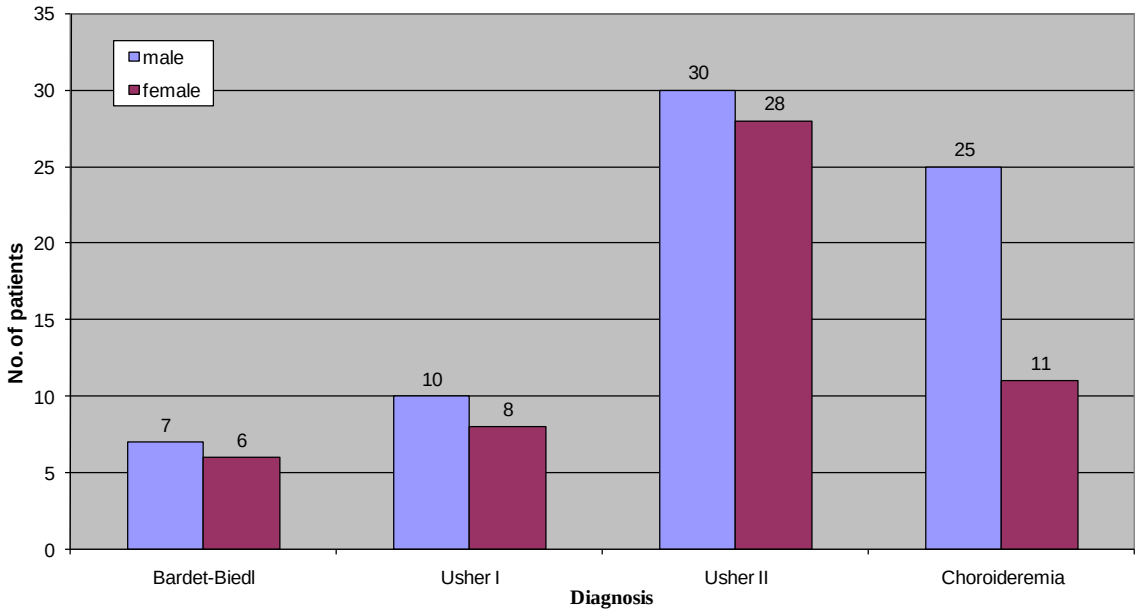


Figure 1. Sex distribution in group 1 (predominantly central retina involvement), stratified by diagnosis

a



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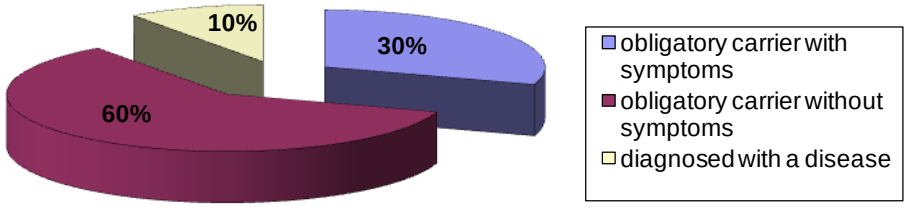


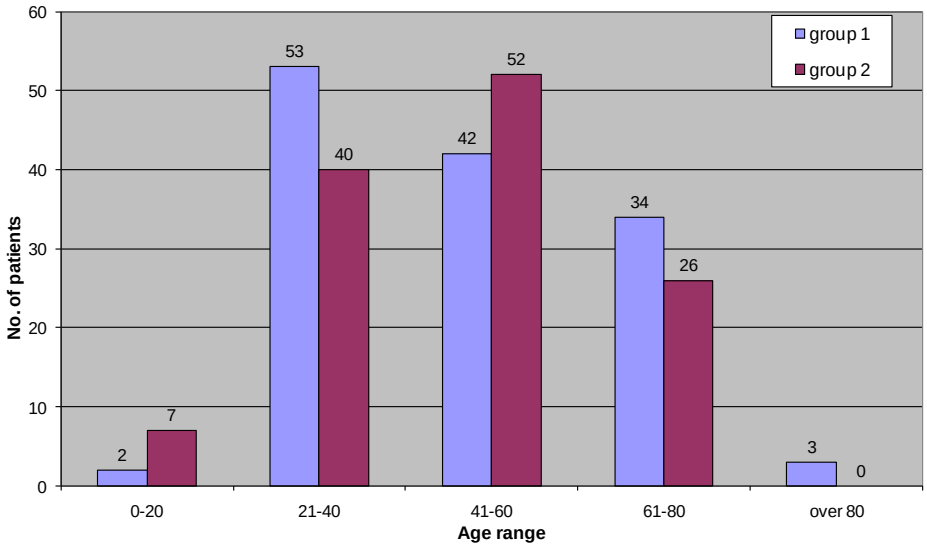
Figure 2 a. Sex distribution of patients in group 2 (predominantly peripheral involvement), stratified by diagnosis. b. Distribution of women in the Choroideremia subgroup

Age distribution

Age distribution analysis showed that patients between 21 and 40 years old (n=53) represented the majority in group 1. The age group 41–60 years old included 42 patients in group 1; age groups 0–20, 61–80, and over 80 were presented by two, 34 and three patients respectively (Figure 3a). Fifty-two patients in group 2 were between 41 and 60 years old, 40 between 21 and 40 years old; 26 patients were aged between 61 and 80 years old, and there were no patients older than 80 (Figure 3a). The mean age for the entire study population was 47.2 years old (SD=15.6). A stratification of subgroups with specific diseases according to contribution of certain age groups of the patients is shown in Figure 3b. Nationality distribution of the patients: German patients were predominant in both groups; in group 1 Germans represented 87 patients,

and in group 2, 76 patients. 47 and 49 patients, respectively, originated from other central European countries.

a



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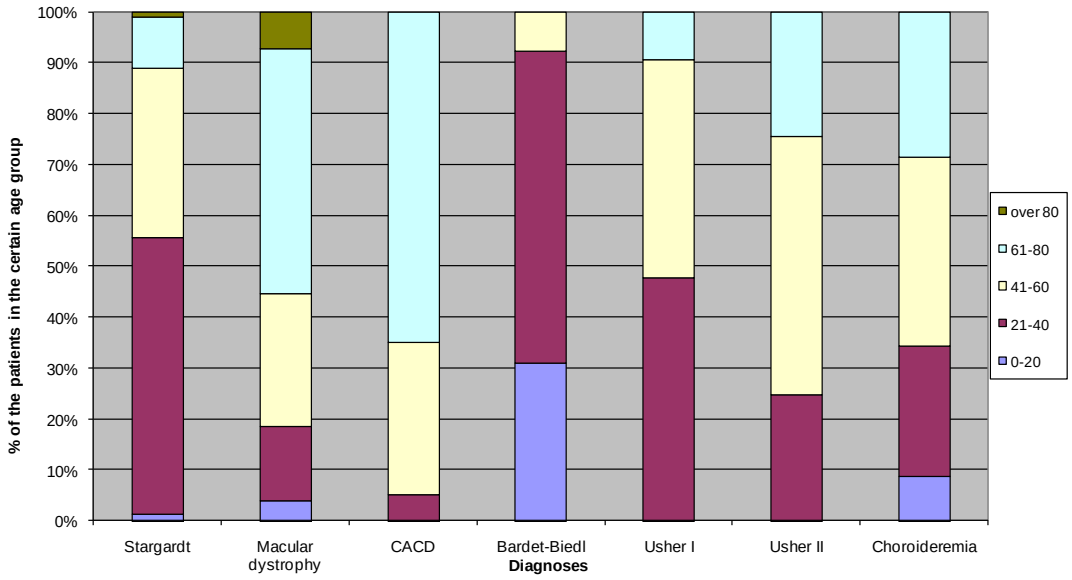


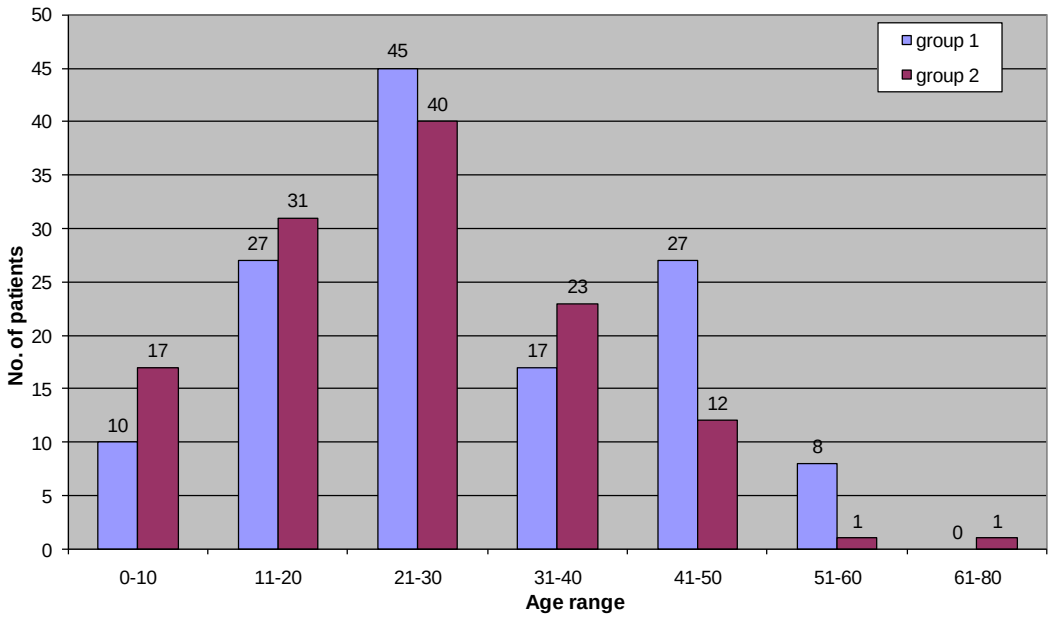
Figure 3 a. Age distribution of the patients in groups 1 and 2. b. A stratification of subgroups with specific diseases according to the age of the patients at first visit in the special clinic on inherited retinal degenerations in Tuebingen.

History of the disease data

History of the disease data incorporated age at first diagnosis, age at visual acuity decrease, age at night blindness onset, photophobia onset and age at visual field defects emergence.

Age at first diagnosis showed the same trend for groups 1 and 2. In group 1 we observed that ten patients were diagnosed for the first time before 10 years of age, 27 between 11 and 20 years, 45 between 21 and 30, 17 between 31 and 40, 27 between 41 and 50, and eight patients between 51 and 60 years of age (Figure 4a). In group 2, 17 patients were first diagnosed before age 10, 31 between 11 and 20 years old, 40 between 21 and 30, 23 between 31 and 40, 12 between 41 and 50, and two were first diagnosed after 51 years of age (Figure 4a). Age at first diagnosis stratified by diagnosis is shown in Figure 4b.

a



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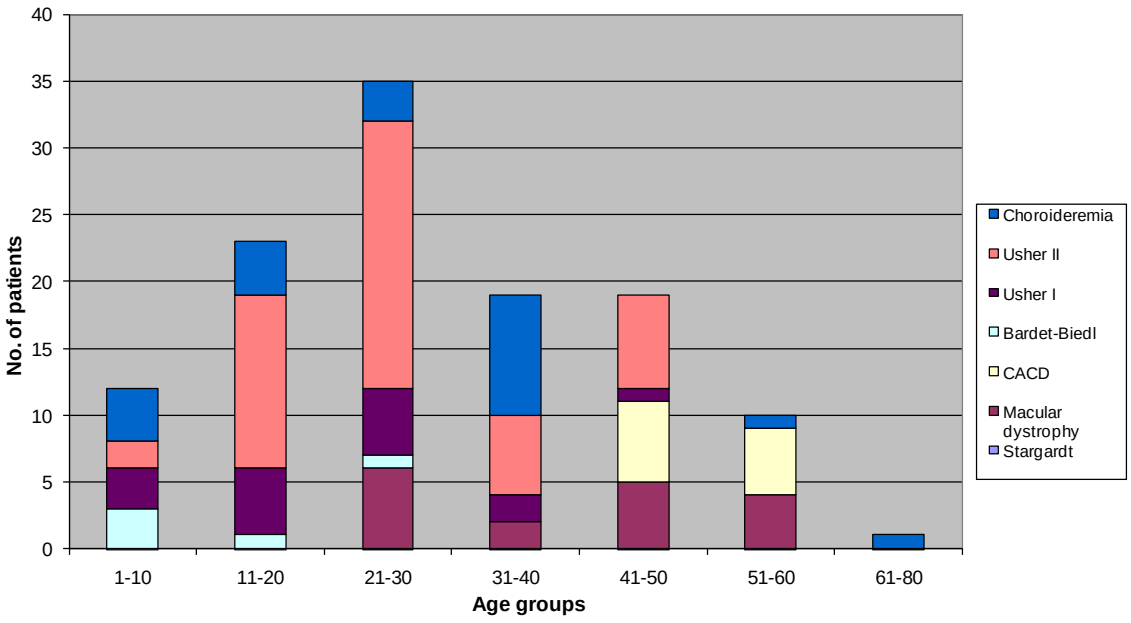
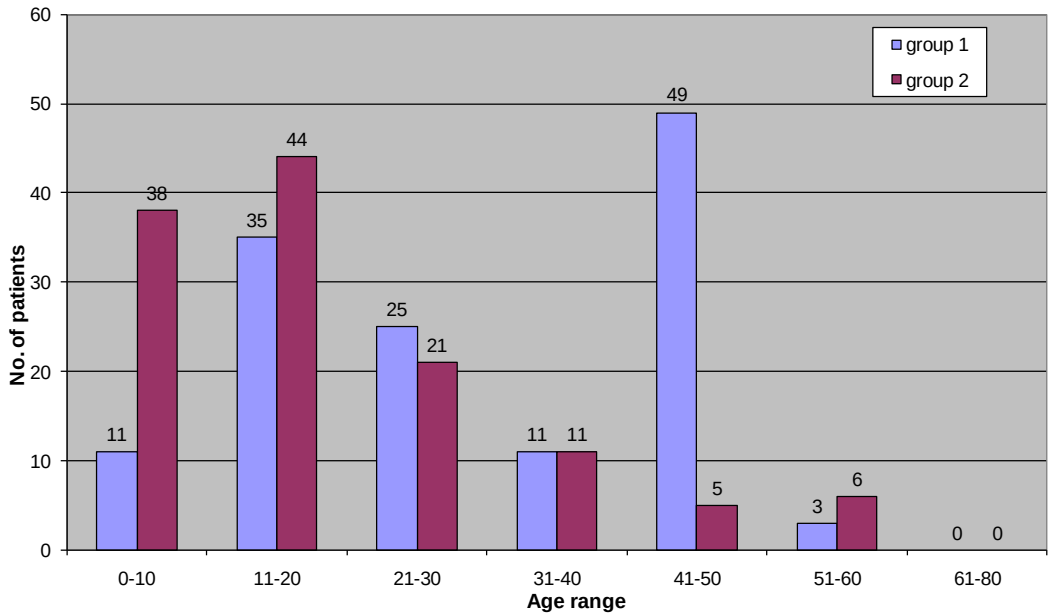


Figure 4 a. Age at first diagnosis in groups 1 and 2. b. The age when the first correct diagnosis was made, as indicated by patient, stratified by diagnosis.

Night blindness onset is one of the most important signals for detecting the onset of monogenic retinal degenerations with rod system involvement. Information about night blindness onset was separately analyzed for groups 1 and 2. Forty-nine patients in group 1 first noticed night blindness when they were between 41 and 50 years old, 35 patients in this group noticed the presence of night blindness between 11 and 20 years of age, and 11 patients each between 1 and 10, and between 31 and 40 years of age; the remaining three patients first experienced night blindness between 51 and 60 years of age. A different trend was observed in group 2: 38 patients in this group first noticed the presence of night blindness before 10 years of age, 44 between 11 and 20, 21 between 21 and 30 years of age, 11 between 31 and 40 years of age, five patients each between 41 and 50, and three between 51 and 60 years old (Figure 5a). A stratification of age of night blindness onset according to the disease is shown in Figure 5b.

a



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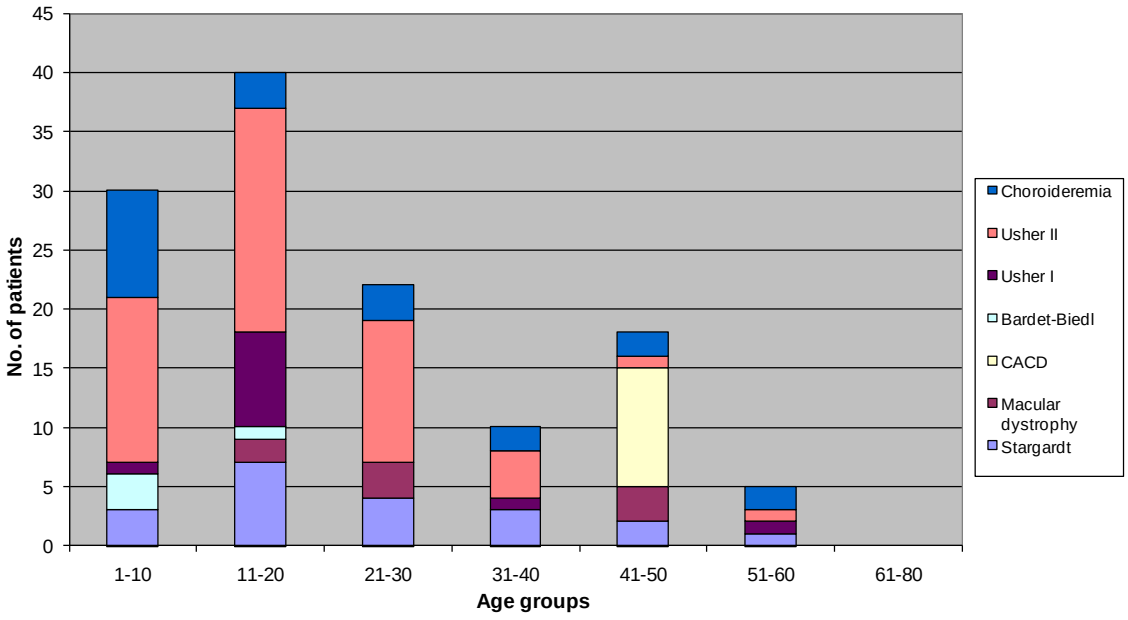
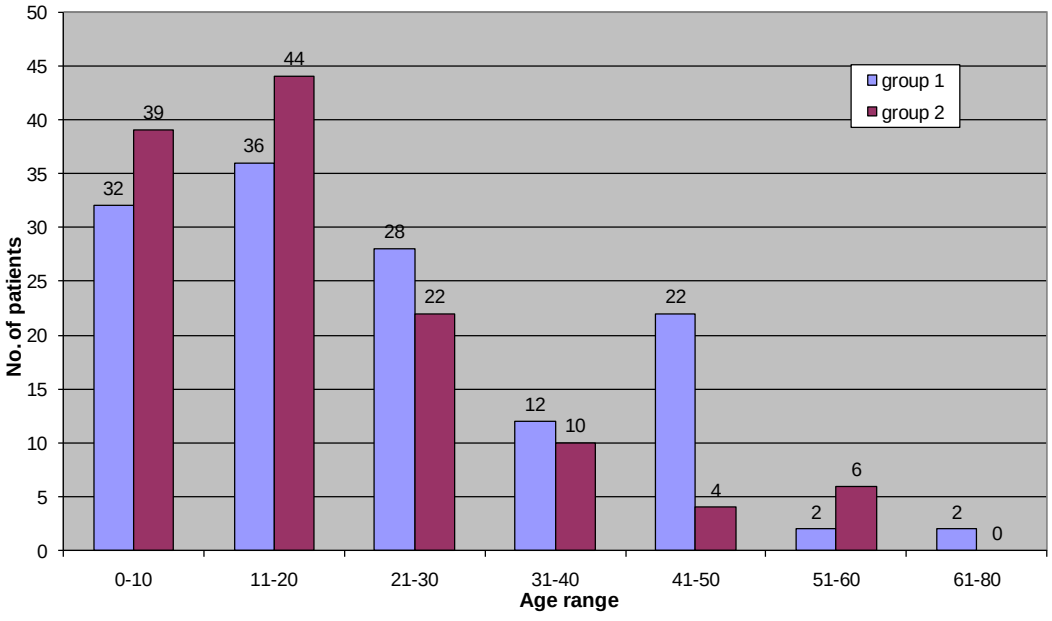


Figure 5 a. Age of night blindness onset in group 1 and group 2. b. The age of night blindness, stratified by diagnosis

Photophobia is one of the middle-stage symptoms of monogenic retinal degeneration. A similar tendency was observed in patients of both groups; the majority in both groups first noticed photophobia when they were younger than 30 years old. In group 1, ten patients first reported photophobia before the age of 10, 27 between 11 and 20 years old and 45 between 21 and 30 years old; of the remaining 52 patients, 17 patients first recognized photophobia between 31 and 40 years old, 27 between 41–50, and eight after the age of 51 years (Figure 6a). In group 2, 17 patients first reported photophobia before the age of 10, 31 between 11 and 20 years old and 40 between 21 and 30 years old. 23 patients reported photophobia between 31 and 40 years of age, 12 between 41 and 50 years old, and two patients after 50 years old (Figure 6a). Both groups were quite similar with respect to photophobia onset, and the mean age of onset for both groups was 26 years old (SD=15). A stratification of age of photophobia onset in accordance to diagnosis is shown in Figure 6b.

a



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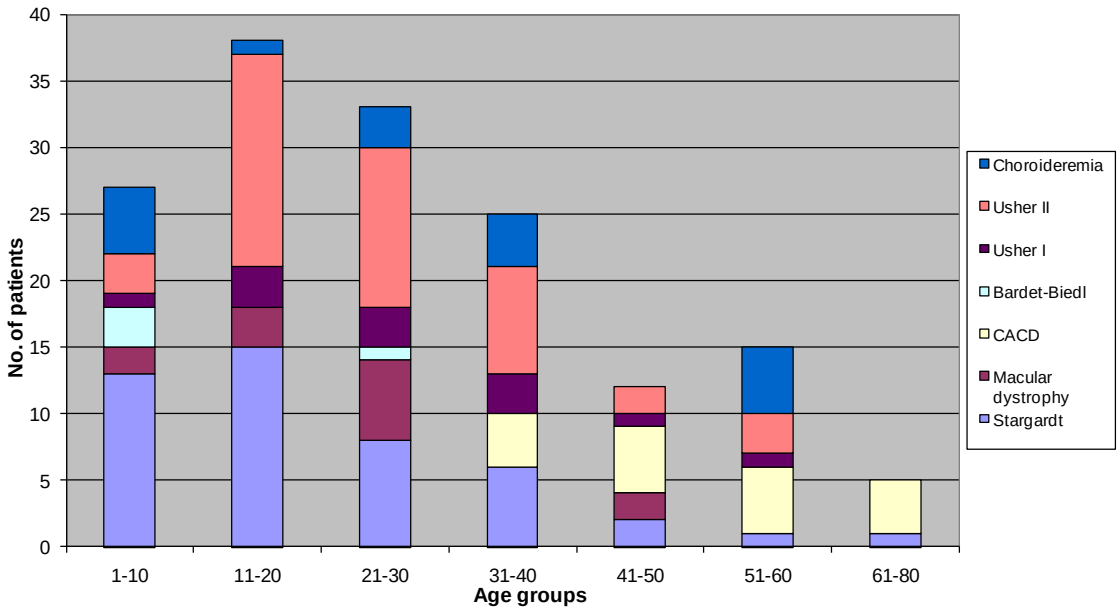
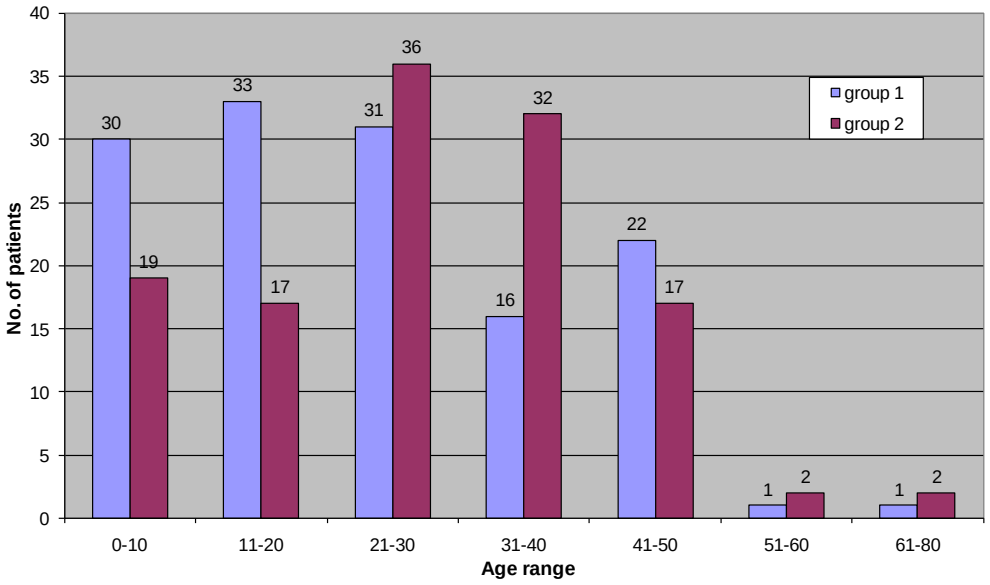


Figure 6 a. Age of photophobia onset in group 1 and 2. b. Stratification of photophobia onset according to diagnosis

The age of onset of visual acuity decrease had different trends in the two groups. The data were collected for right and left eyes; results showed that there was no difference found in onset of visual acuity decrease between right and left eyes. In group 1, the majority of patients (n=94) noticed a decrease in visual acuity before 30 years old: 30 patients before 10, 33 between 11 and 20 years of age, and 31 between 21 and 30 years old. The remaining 40 patients first noticed or were diagnosed with decreased visual acuity after 31 years of age: 16 patients between 31 and 40 years old, 22 between 41 and 50, and two patients after 51 years of age (Figure 7a). In group 2, 36 patients had visual acuity decrease between 21 and 30 years old, and 32 between 31 and 40 years old. 36 patients noticed visual acuity decrease before 20 years old: 19 of them before 10, and 17 patients between 11 and 20 years old. A relatively high number of patients (n=17) recorded visual acuity decrease between 41 and 50

years of age and four patients after 51 years of age (Figure 7a). Age of onset of visual acuity decrease stratified by diagnosis is shown in Figure 7b.

a



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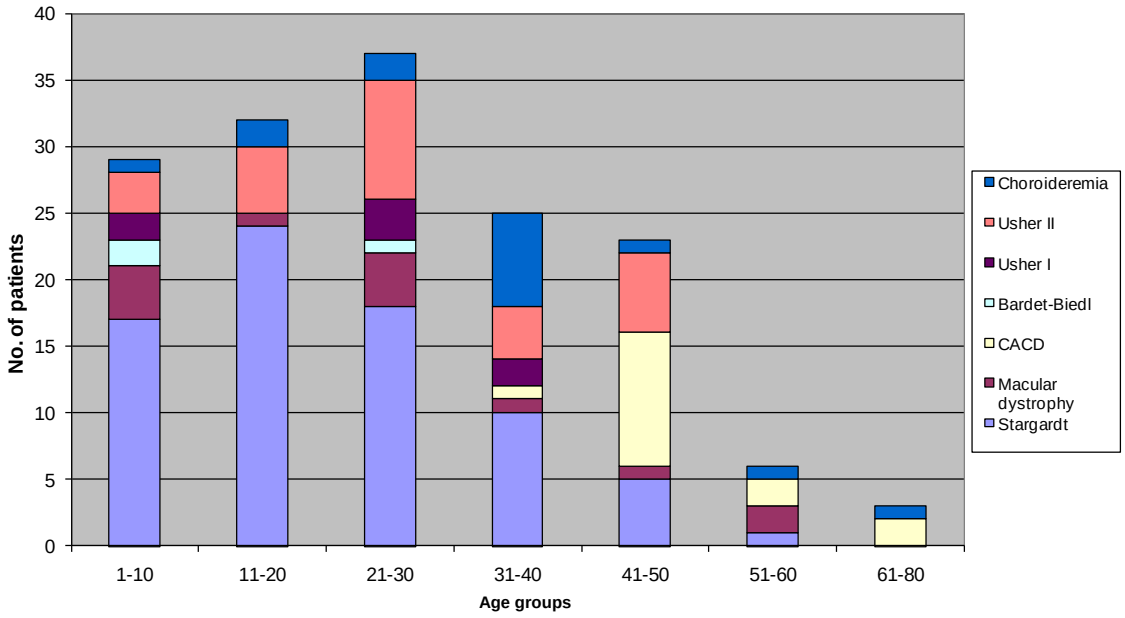
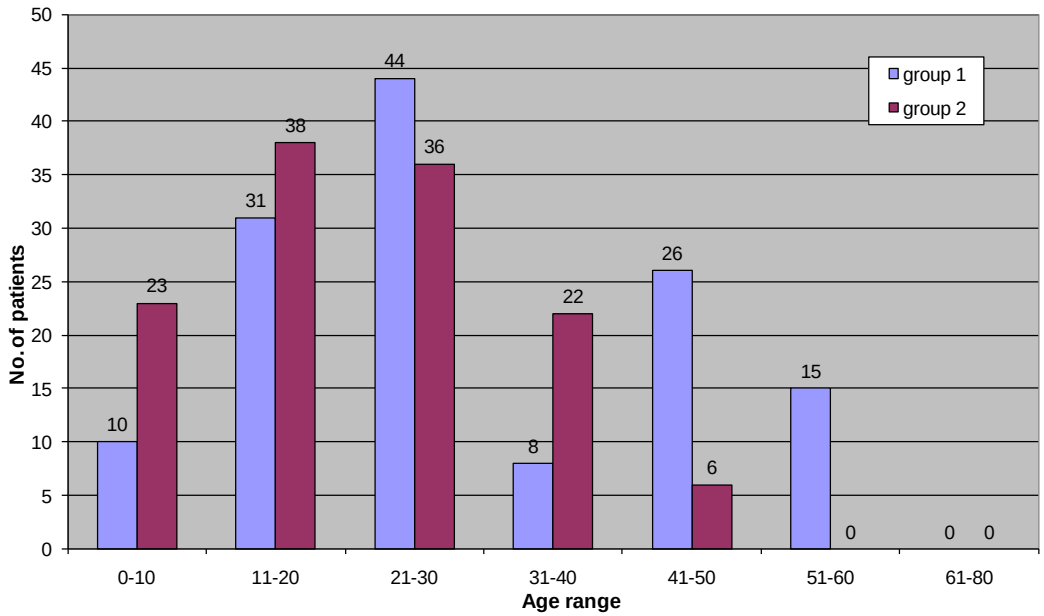


Figure 7 a. Age of visual acuity decrease onset in groups 1 and 2. b. Age of visual acuity decrease stratified by diagnosis.

It was observed that in both groups visual field defects emergence was reported by a majority of patients before the age of 30 years. In the first group, 44 patients reported emergence of visual field defects at an age between 21 and 30 years old, 31 between 11 and 20 years old, and 26 between 41 and 50 years old. The remaining patients reported early visual defects appearance: ten below 10 years of age, eight between 31 and 40 years old, and 15 between 51 and 60 years old (Figure 8a). In group 2, 38 and 36 patients presented visual field defects at age periods 11–20 and 21–30 years old, respectively; 23 patients in this group first observed visual field defects at an age before 10 years old, 22 at an age between 31 and 40, and six in the 41–50 age range. No patients in group 2 reported first onset of visual field defects beyond the age of 50 years (Figure 8a). Visual defects appearance trends were quite similar between the groups, and mean age onset for both groups was 26 years old (SD=14.5). A stratification of emergence of visual defects according to diagnosis is shown in Figure 8b.

a



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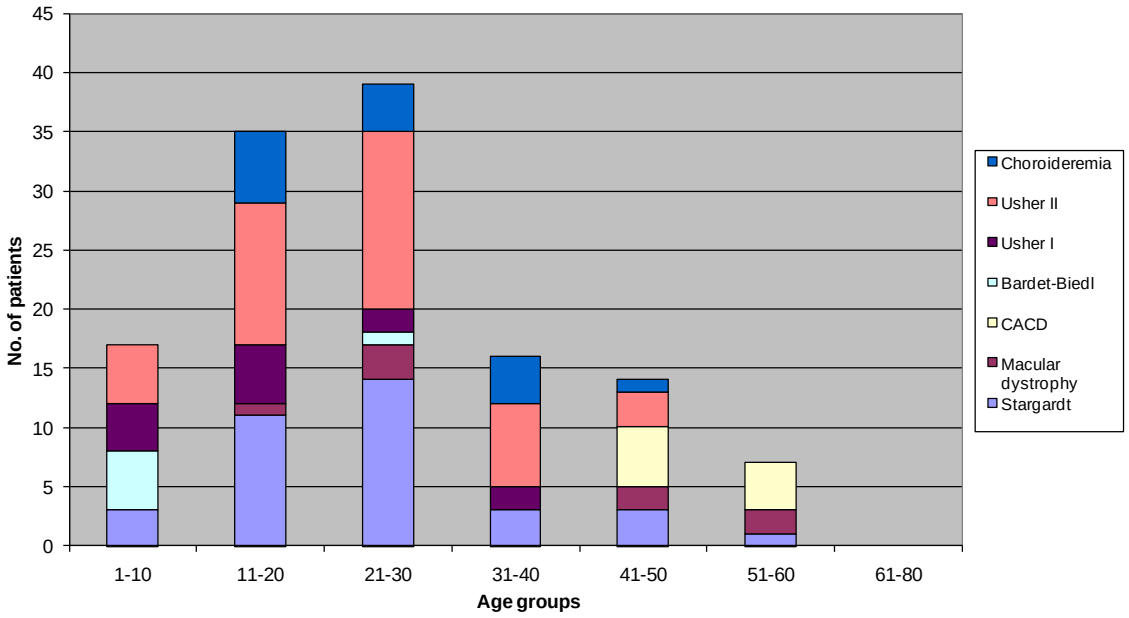
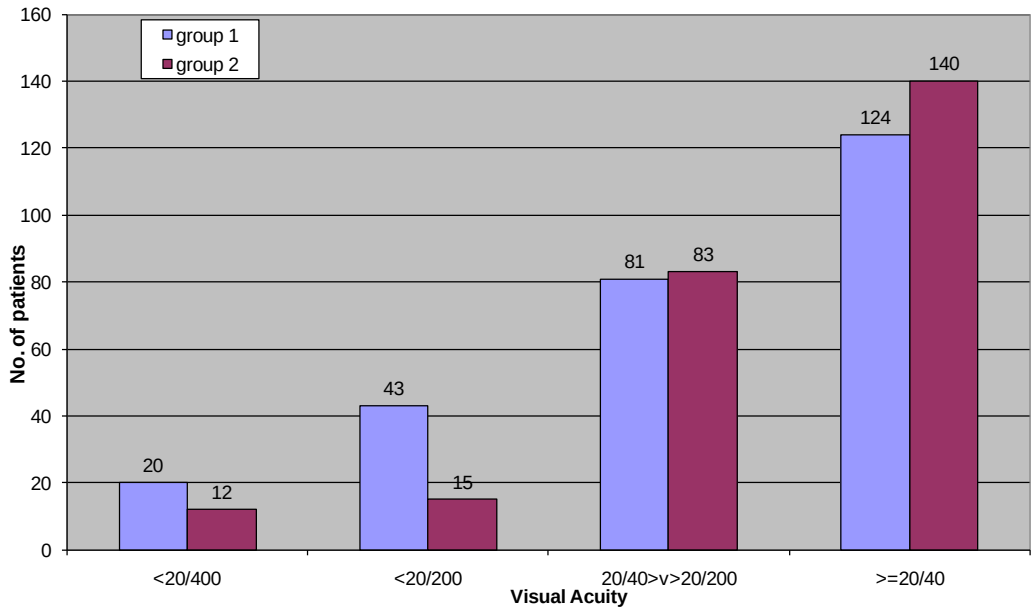


Figure 8 a. Age at visual field defects appearance. b .Emergence of visual field defects appearance stratified by diagnosis

The clinical data analyzed included best-corrected VA (BCVA), types of visual field defects and color perception problem diagnoses. BCVA was measured for both eyes of the patients. Visual acuity better than or equal to 20/40 was detected in 124 eyes in group 1 and 140 eyes in group 2; best-corrected visual acuity lower than 20/40 and higher than 20/200 was observed in 81 eyes in group 1 and 83 in group 2; lower than 20/200 was determined in 43 eyes from group 1 and 15 from the second group (Fig. 9a). We defined legally blind patients as having visual acuity lower than 20/400 or visual field less than 5° in the better eye, according to the WHO definition [97]. Twenty eyes in group 1 and 12 eyes in group 2 had a visual acuity that corresponded to the criteria for legal blindness (Figure 9a). Overall, 7% of patients in group 1 and 6% in the second group were registered as legally blind. Best-corrected visual acuity stratified by age is shown in Figure 9b.

A stratification of BCVA by age showed an interesting pattern: BCVA higher or equal to 20/40 was observed in 35% of patients 41–60 years of age. Half of the patients with BCVA less than 20/40 but higher than 20/200 were in the 21–40 age range, while the other half was in the 61–80 age range. Forty percent of patients in the age group 41–60 and 39% in 21–40 had visual acuity less than 20/200. Thirty-seven percent of patients in the 21-40 age group and 36% in the 41-60 age group were registered as legally blind (Figure 9b).

a



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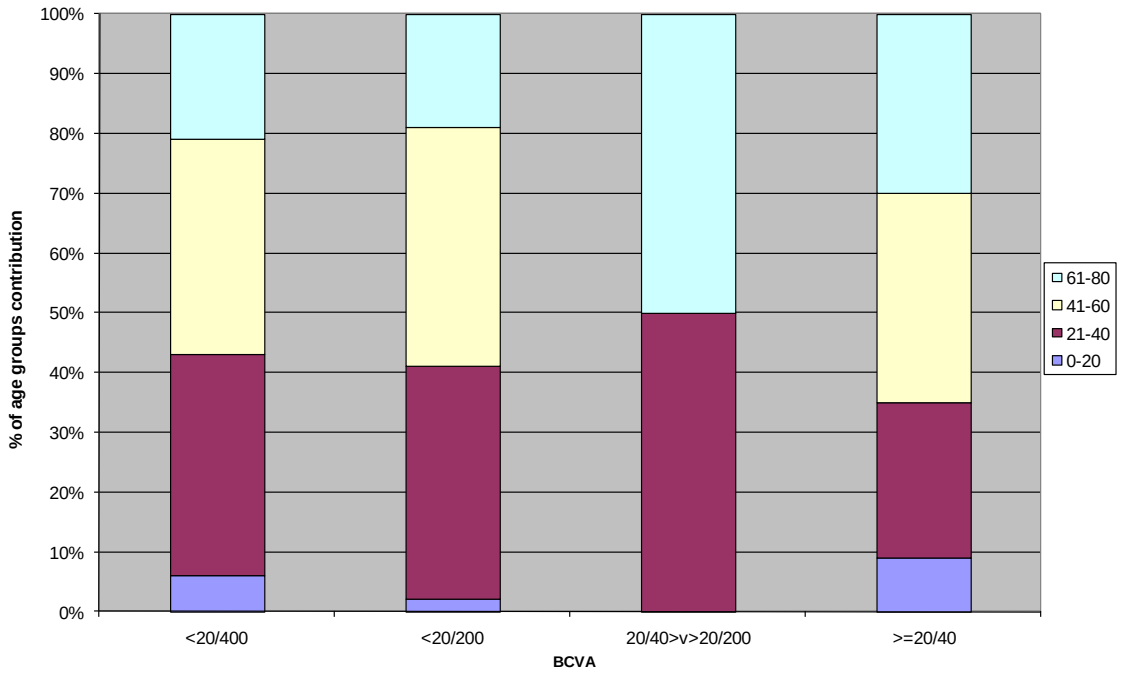

Figure 9a. BCVA in group 1 and group 2. b. BCVA stratified by age for both groups.

The types of visual field defects are as important as the age of their onset, since they define the level of decrease of the patient's quality of life and the effectiveness of further rehabilitation. Patients from group 1 had a higher frequency of central scotoma (n=115), whereas concentric constriction (n=13) and ring scotoma (n=6) were detected less frequently. By contrast, in group 2 concentric constrictions were observed in 81 patients, central scotoma in 34, and ring scotoma in ten patients.

Both groups showed a quite similar tendency concerning the presence of color perception problems. In group 1, color perception problems were present in 68 patients and absent in 68, while in group 2 color perception defects were detected in 60 and were absent in 54.

The frequencies of main diagnoses in the study population were analyzed for both groups together. Diagnosis frequency was Usher I and II 34%, Stargardt disease 31%, macular dystrophy 10%, CACD 8%, and Bardet-Biedl syndrome 5%.

Eighty-two patients (out of a total of 134) in group 1 and 89 patients (out of a total of 125) in group 2 were genetically tested in the Genetics Department of the University Eye Hospital Tuebingen. In the first group, 51 patients were genetically verified to have Stargardt disease; ten macular dystrophy, including six patients with Best's disease; and 21 central choroidal dystrophy (CACD). In the second group, six patients were genetically verified to have Bardet-Biedl syndrome; 18 Usher syndrome I; 51 Usher syndroms II, and 14 patients had choroideremia.

Overall, the results of our study showed that these monogenic retinal dystrophies are more frequent among men than among women. We also found that relatively high numbers of patients in both groups retained quite good visual acuity, which shows that early and properly planned rehabilitation strategies could be beneficial in order to increase quality of life for these patients. Moreover, for both groups an age for optimal therapeutic intervention was

defined. It is recommended that this should be taken into account while screening for patients to take part in clinical trials for testing new treatment strategies. It was also shown in the study that color perception problems didn't appear to be a very specific symptom in both groups; this may be a consequence of the "bystander effect."

III.3 Pattern of Visual Symptoms Onset in Inherited Retinal Dystrophies.

The application of an epidemiological approach for the age of disease onset estimation in IRD with predominantly central and peripheral involvement is essential for the early differential diagnosis between two groups of IRD, as well as for the definition of the optimal age for treatment. Nevertheless, an even more differential approach is required in order to obtain a deeper understanding of the pattern of disease onset and its differences in various forms of IRD. Therefore, the aim of our study is to compare the pattern of the typical visual symptoms onset in different types of IRD.

III.3.1 General information about the study population.

Sex distribution analysis showed that men (n=302) were more prevalent than women (n=242) in the study population. The same trend was observed when stratifying the data by diagnosis. Choroideremia patients were represented in the vast majority by men; nevertheless 4 female obligatory carriers with symptoms were identified and included in the study population. Sex distribution of the study population, stratified by diagnosis, is shown in Figure 10a.

Age distribution was based on the age of the patients at first visit to the hospital and was analyzed for each disease separately, which enabled a comparison of age groups within individual diseases as well as between different diseases. The age of the patients at the first visit in the hospital was approximately normally distributed: the mean age of patients was 43.46 (SD=18.34) years old. 208 patients were between 21-40 years of age, 152 between 41-60 years of age and 142 were 0-20. 41 patients were 60-80 years of age, and one patient was over 80 years of age. Patients younger than 20 years of age were diagnosed with RP (n=55), CRD (n=26), CD (n=16), STD (n=17), BBD (n=7), LCA (n=6), USH II (n=5), and USH I (n=4). The vast majority of patients with RP (n=106), STD (n=41), CRD (n=26), CD (n=9), LCA (n=8), or MD (n=7) were in the age group between 21-40 years old. The age group between 41 and 60 years of age was mostly represented by patients with RP (n=91), CRD (n=14),

CHRD (n=10), CD (n=9), and STD (n=8). The majority of patients in the age group between 61 and 80 years of age had diagnosis of RP (n=24), CRD (n=5) and MD (n=4). The age distribution of patients with IRD is shown in Figure 10b.

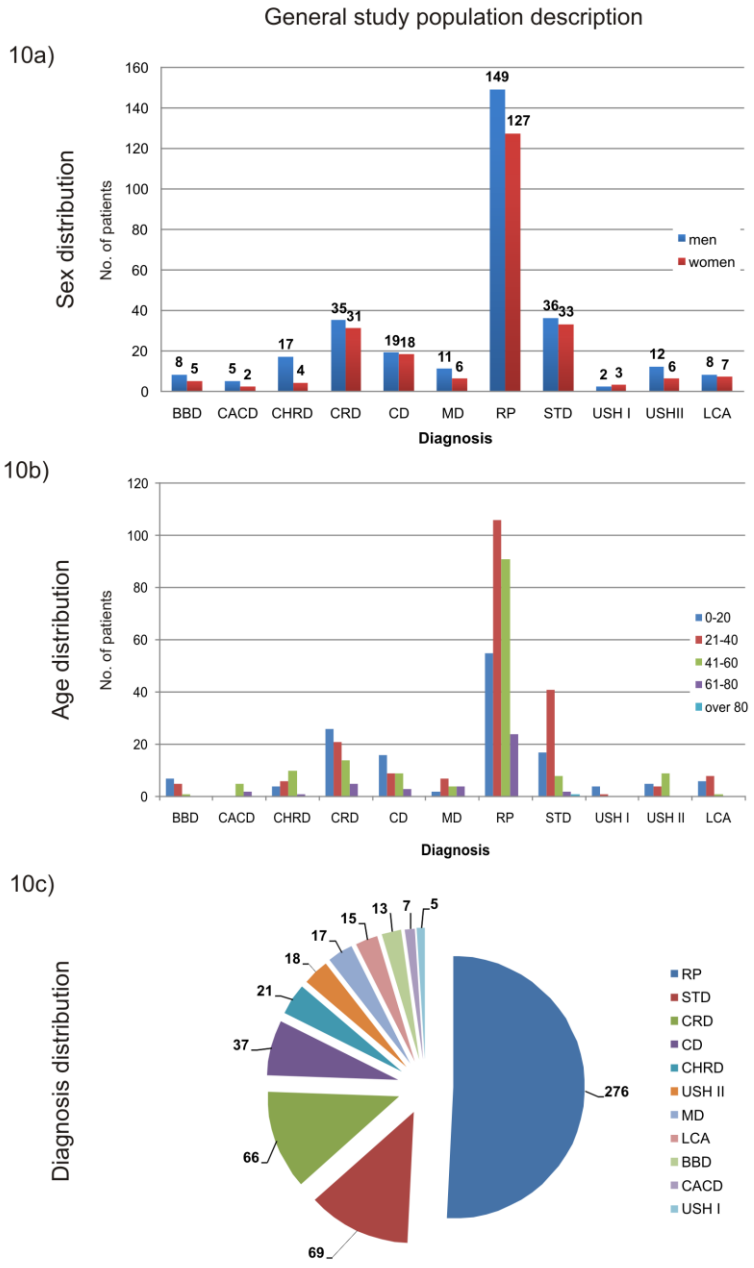

Figure 10 General study population description: 1a) sex distribution of the study population, stratified by diagnosis 1b) the age distribution of patients with IRD 1c) the distribution of final diagnoses.

Diagnosis distribution: Analysis revealed that RP, Stargardt disease, CRD, and CD were the most wide spread diagnoses among patients in the study population, whereas CHRD and MD were less frequent. The distribution of final diagnoses is shown in Figure 10c.

The geographic distribution of patients in the study population was analyzed by accounting for the first number in the postal code, which divides Germany into ten regions. The geographic distribution of the patients in absolute numbers is shown in Figure 11. As indicated in the figure majority of the patients were from the South-West, where Eye University Hospital is located. Nevertheless, patients with IRD were forwarded to the Hospital from all over Germany.

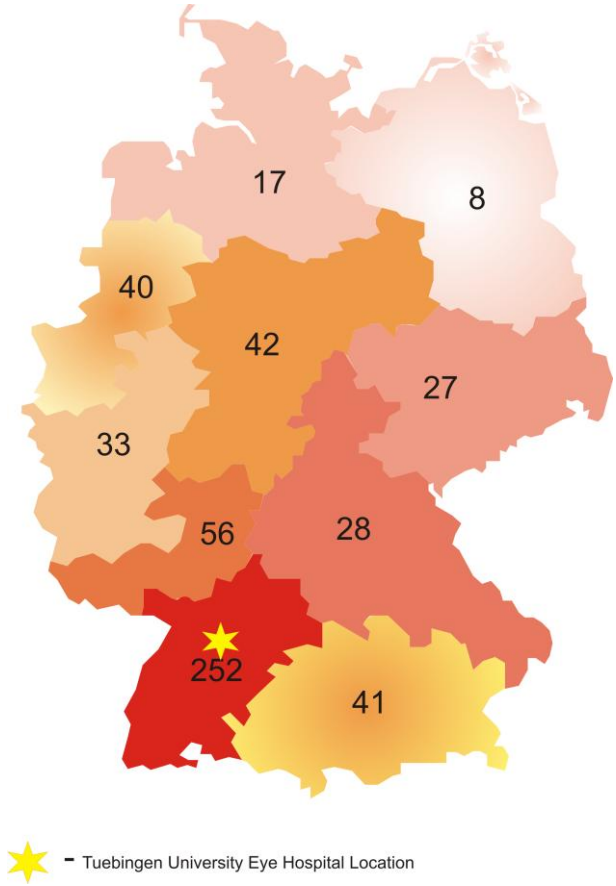

Figure 11 Geographic distribution of the study population across Germany.

III.3.2 Comparison of the pattern of the main visual symptoms onset in a variety of IRD.

Night blindness appearance is one of the earliest symptoms indicating the involvement of rods. Age at night blindness onset was compared between different IRD. LCA and BBD had the earliest median onset of night blindness followed by Stargardt disease, X-linked RP, USH II, ADRP, RP of non-specified inheritance (RP-NSI) and CHRD. Comparatively late median onset of night blindness was experienced by patients with CRD, CD, ARRP, and USH I syndrome. Median onset of night blindness later than 25 years of age was found in MD, SIM-RP, and CACD. A high variation of age at night blindness onset from birth to maximum 69 years of age was noted in patients with autosomal dominant RP. This can be explained by a general high variation of the disease onset, which can be at almost any age. A comparison of the age of night blindness onset is shown in box-plots [98] in Figure 12a.

Photophobia is one of the most important early symptoms for dystrophies with a predominantly cone involvement or mixed cone-rod dystrophies. Patients with BBD and LCA had an onset of photophobia early in their lives. CD had a relatively early median onset of photophobia, where as patients with CRD had a later median onset. Late photophobia onset was also detected in patients with ADRP, USH II type, SIM-RP, and CACD. A comparison of age at photophobia onset is presented in Figure 12b.

Visual acuity decrease is typically the earliest symptom of cone and cone-rod dystrophies as well as one of the symptoms that has the greatest impact on the patients' quality of life. Median visual acuity decrease was quite early in LCA and BBD as well as in CRD and CD patients. Patients with X-RP and RP- NSI had an earlier median onset of visual acuity decrease in comparison with other RP types. Later median onset of visual acuity decrease was noticed in STD, ARRP, ADRP, USH I type, MD and SIM-RP. Visual acuity decreased after 30

years of age in patients with USH II type, CHRD, and CACD. A comparison of age at first reported visual acuity decrease is shown in Figure 12c.

Visual field defects are highly anti-correlated with performance of daily activities by the patient [90]. Visual field defects were reported very early in patients with LCA and BBD. USH I, X-RP were characterized by early median appearance of visual field defects. RP-NSI, CD and CRD had a later median onset of visual field defects. Patients with USH II, STD, and ARRP had a median onset of visual field defects in their twentieth year. CHRD, ADRP, SIM-RP, MD and CACD were characterized by late (after 30 years old) median visual field defects onset. Comparison of age at visual field defects onset is shown in Figure 12d. The median age of onset for typical symptoms of IRS is shown in Table 7.

Table 7. The median age of onset for typical symptoms of IRD.

IRD types	Median age at night blindness onset (25;75 quantiles)	Median age at visual acuity decrease (25;75 quantiles)	Median age at photophobia onset (25;75 quantiles)	Median age at visual field defects appearance (25;75 quantiles)	Median age at 1st diagnosis (25;75 quantiles)
ADRP	17 (0;35.5)	25 (8.8;49.8)	34 (27.5; 44.5)	33 (21.5; 43.5)	27 (15.5; 57)
ARRP	20 (9;30)	21 (13.5; 46.5)	25.5 (9.3; 33)	25 (13; 37)	16.5 (14.25; 22)
SIM-RP	30.5 (15; 46)	28.5 (16; 44)	38 (25.3; 9.8)	34 (21; 47)	31 (16.25; 70.3)
X-RP	16 (7; 25)	16 (6; 28)	19 (16; 32.3)	17 (7; 30.3)	20 (20; 79.5)
NSPI-RP	18 (10; 40)	15 (6; 41.5)	25 (14.8; 40.3)	20 (10;37)	24.5 (24.5; 55)
BBD	7 (3; 8.75)	5 (2.5; 12)	3 (1; 15.5)	6.5 (3.3; 18)	5.6 (3.5; 7)
CACD	47 (46.5; 58)	44 (32; 49)	45 (35; 50)	52 (39; 56)	55.5 (43.25; 9.75)
CHRD	18 (10; 23)	36.5 (11.5; 42.8)	24 (15.8; 40)	30 (15; 41)	16.5 (10; 43)
CD	20 (10; 40)	12.5 (5.75; 38.3)	12 (5; 31)	30 (25; 40)	19 (10; 45.3)
CRD	18 (7; 32)	10 (6.5; 34)	20 (8;4 0.5)	22 (9; 37.3)	12 (6; 26.5)
MD	27 (19.25; 36)	27 (7.5; 39.75)	19.5 (7.5; 27.8)	40´(30; 51)	33.5 (27.25; 51.75)
STD	14 (12; 28)	17.5 (10; 28)	18 (10; 31)	24.50 (15.8;34.3)	23 (15; 32.5)
USH I	23 (7; 36.5)	25 (8.5; 37)	27.17 (16; 32)	11.5 (6.25; 17.8)	14 (7; 15)
USH II	16 (6; 24.5)	30 (16.3; 36.3)	35 (19.3; 42.8)	24 (17;31. 5)	23.50 (19; 34)
LCA	3 (2; 6)	3 (2; 6)	11.5 (4; 15.3)	3 (3; 6)	3 (3; 6)

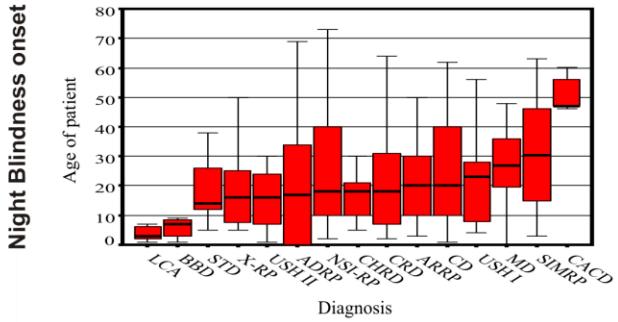

Figure 12a. Box-plots of age of night blindness onset in IRD.

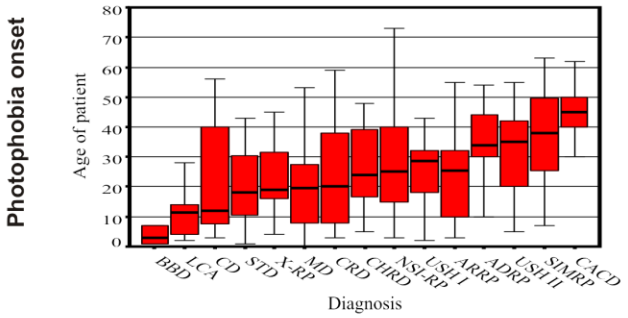

Figure 12b. Box-plots of photophobia onset in IRD.

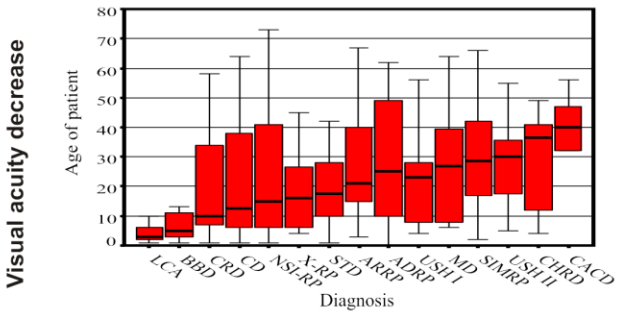

Figure 12c. Box-plots of visual acuity decrease onset in IRD.

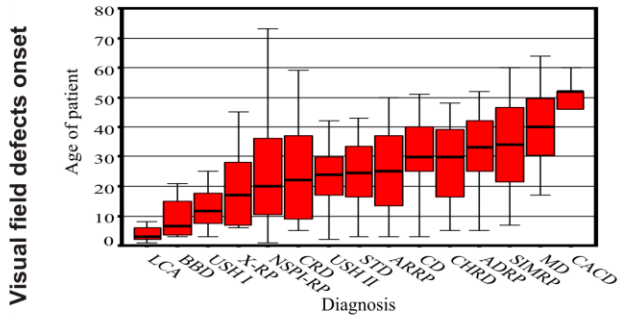

Figure 12d. Box-plots of age of visual field defects onset in IRD.

Figure 12 Comparison of age at visual symptoms onset in IRD.

BCVA was analyzed for the patient's first visit and was calculated in logMAR. No significant difference was found between the two eyes; therefore results are reported here in number of patients. 117 patients had BCVA≤0.3, 151 patients had 0.3<BCVA≤0.5; 182 patients had 0.5<BCVA≤1.0, 57 patients had 1<BCVA≤1.3, and 31 patients had 1.3<BCVA≤1.8. Only six patients were legally blind according to the WHO definition of blindness and had BCVA higher than 1.8. Patients with RP (n=84), STD (n=19), CRD (n=15), and CD (n=14) fell into the category 0.3<BCVA≤0.5, which corresponds to the first category of visual impairment defined by the World Health Organization [97]. A large amount of patients with RP (n=20), CD (n=102) and STD (n=23) had 0.5<BCVA≤1.0, which corresponds to the second category of visual impairment. The third stage of visual impairment, 1<BCVA≤1.3, was represented by patients with RP (n=25), STD (n=13), and CRD (n=10). 17 patients with RP, 5 patients with CRD, 4 patients with BBD and 3 patients with STD had 1.3<BCVA≤1.8. 117 patients had a BCVA <0.3 and 6 patients were legally blind with BCVA>1.8. BCVA of the study population is shown in Figure 13a.

Visual field defect appearance can significantly reduce the quality of patients' lives. Some difference in isolated peripheral constriction was detected in patients with USH I (n=4). Most of the patients in the study population had a combination of central and peripheral defects. A combination of peripheral (n_1) and central (n_2) visual field involvement was observed in eyes of patients with RP (n_1=152 and n_2=45) and in eyes of the patients with CRD (n_1=23 and n_2=31). Patients with such IRD as LCA (n_1=9), USH II (n_1=15), CHRD (n_1=11) and BBD (n_1=8) had predominantly peripheral constriction. Central scotoma was a more typical visual field defect in patients with Stargardt disease (n_2=48), MD (n_2=7), and CD (n_2=23). CACD was characterized by a mixture of peripheral (n_2=2) and central defects (n_1=3). A detailed distribution of visual defects stratified by diagnosis is shown in Figure 13b.

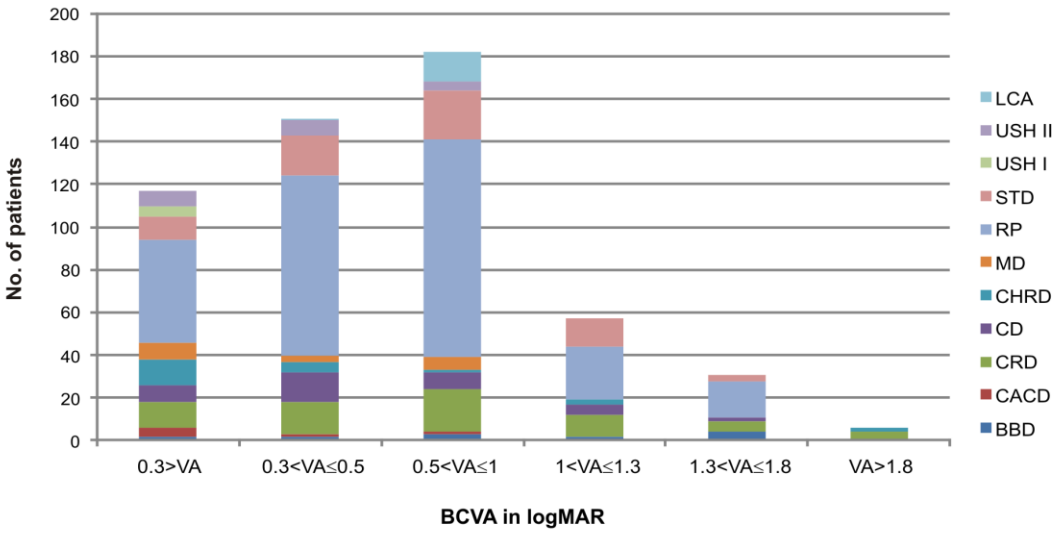

Figure 13a. BCVA at first visit according to the International classification of visual impairment, stratified by diagnosis.

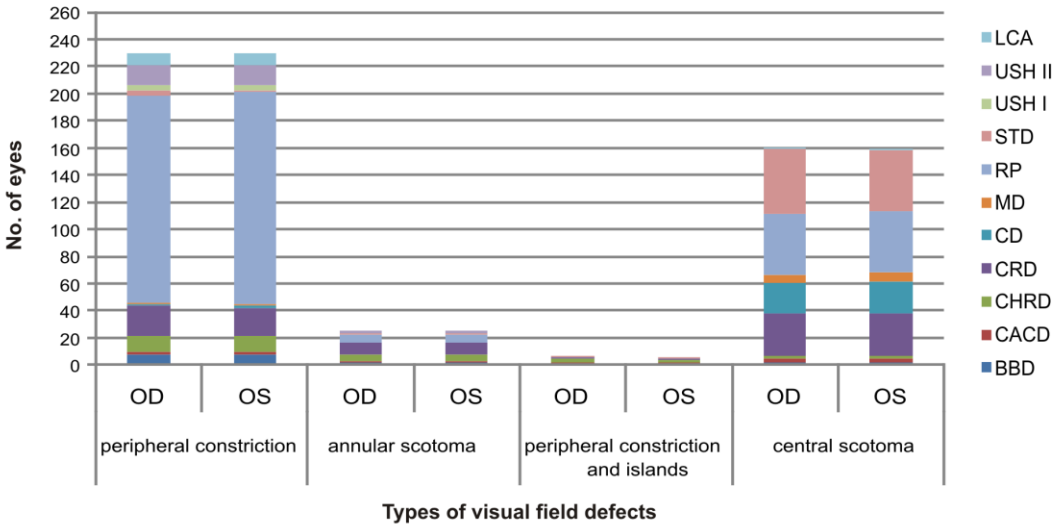

Figure 13b.Visual field defects stratified by diagnosis.

Figure 13 Clinical characteristics of the study population.

In order to better understand the differences in the pattern of disease onset in RP and CRD, the relationship between the BCVA and the period of time between the time point when the patient first experienced a decrease in visual acuity and the time when he/she underwent the first ophthalmological examination was studied. All CRD patients (n=66) and a fraction of RP patients (n=48), including ADRP (n=6), ARRP (n=5), early onset RP (n=18), SIMRR (n=9), and X-RP (n=4), responded to the questions concerning their age at first experienced VA decrease. The age at which they first were examined by the ophthalmologist and BCVA at first visit to ophthalmologist were obtained from their patient records. RP patients who were unable to specify when they first experienced the first VA decrease were compared to those who were able to reply. The group of non-respondents was not different by age, sex distribution or reason for visit to the ophthalmologist from those who replied to the questions. BCVA measured at first ophthalmological examination was plotted versus the difference between the age at which the patient first visited the ophthalmologist and the age at which he/she experienced the first VA decrease. The scatter plot of BCVA plotted versus age in patients with RP is shown in Figure 14a. The scatter plot of BCVA versus age in patients with CRD is shown in Figure 14b.

It is noted that early onset RP patients as well as patients with simplex RP had more stable BCVA than other RP types. Although we were unable to define the exact change of BCVA in other types of RP when stratified by diagnosis, due to a low sample size in the groups, it was found that most of the patients with RP who had a relatively good visual acuity delayed their visit to the ophthalmologist for many years. It was also observed that some patients who had on average better BCVA visited the ophthalmologist in the early disease stages. We therefore speculate that it could be due to some other major eye symptoms onset, for example due to the onset of a combination of central and peripheral VF defects typical of the RP population in our study. Interestingly, when studying the BCVA as a function of time in CRD patients, we observed that the

trend of BCVA change was similar to VF area change described in a two-stage hypothesis for the natural course of retinitis pigmentosa [111].

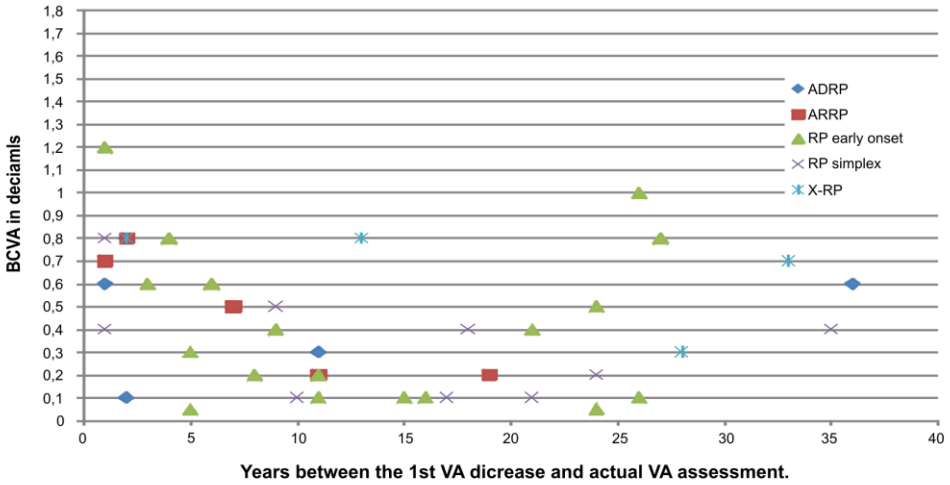

Figure 14a. Scatter plot of BCVA versus the period betweent the first VA decrease and actual VA assessment in different forms of RP.

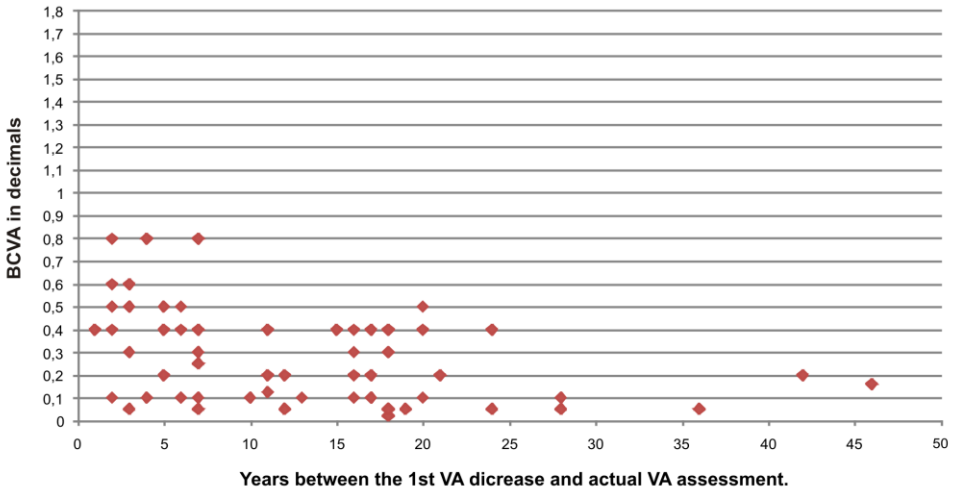

Figure 14b. Scatter plot of BCVA versus the period betweent the first VA decrease and actual VA assessment in patients with CRD.

Figure 14 The relationship between BCVA versus the period between the first VA decrease and actual VA assessment in RP and CRD.

Overall, the results of this study show that the age at onset can provide an extra clue for early differential diagnosis of patients with IRD. It can guide the clinician through further diagnostic processes, although the final diagnosis requires a more complex approach. Furthermore, knowledge of the age of the typical visual symptoms onset in different types of IRD is extremely important for the assessment of manifestation risk, patient counselling, and prognosis. Additionally, it will play an important role in the early identification and selection of patients that can benefit from new treatments. The study also showed that severe loss of visual acuity in patients with CRD occurs earlier than in RP, which in combination with mixed visual field defects can lead to early disability and requires special attention that should be taken into account when treating these patients.

III.4 Special Signs in the Electrophysiology of the Visual System in Inherited Retinal Dystrophies.

III.4.1 Quantitative assessment of the full-field and mfERG parameters and their comparison between a variety of IRD and normal values.

The study had a retrospective cross-sectional study design. Records of 544 patients with IRD seen at the University Eye Hospital in Tuebingen, Germany from 2005 to 2008 were selected for this study. 21 patients were randomly selected from the population, including the whole IRD study population (n=544) (this was done for estimation of the median of IRD population as a whole and definition of the criteria for the qualitative data assessment in the second part of the study), as well as from subsets including each IRD type (USH I, USH II, STD, RP, MD, CD, CRD, CHRD, CACD, BBD) (for calculation of the median values for each IRD and for the median comparison). 21 patients with normal ophthalmological findings were selected as a reference group. The sample size of 21 patients/controls for the random selection was chosen based on the fact that a sample size of 21 patients/controls enables us to estimate the median with a very low variance, whereas increasing the sample size over 21 will not substantially influence the variance of the median estimate.

Disease duration at first visit was considered as one of the confounders that can potentially influence the comparison of full-field and mfERG parameters in a variety of IRD. Therefore, the data on disease duration was analyzed for each IRD and compared using a Kruskal-Wallis test. Medians and 25^{th} and 75^{th} quartiles of disease duration for each IRD type are shown in Table 8. The disease duration was not significantly different between the IRD types ($p=0.23$) (Figure 15), which justifies the comparison of full-field and mfERG parameters between the selected IRD patients.

Median values for full-field and mfERG parameters in normal subjects and randomly selected IRD patients were calculated and used for the definition of the assessment criteria for evaluation of the full-field and mfERG parameters in

the second (qualitative) part of the study are shown in Table 9. Median, minimal, and maximum values, 5th, 25th, 75th, 95th quantiles of full-field ERG for normal subjects and a random selection of IRD patients were calculated and are shown in Table 9. mfERG is shown in Table 10.

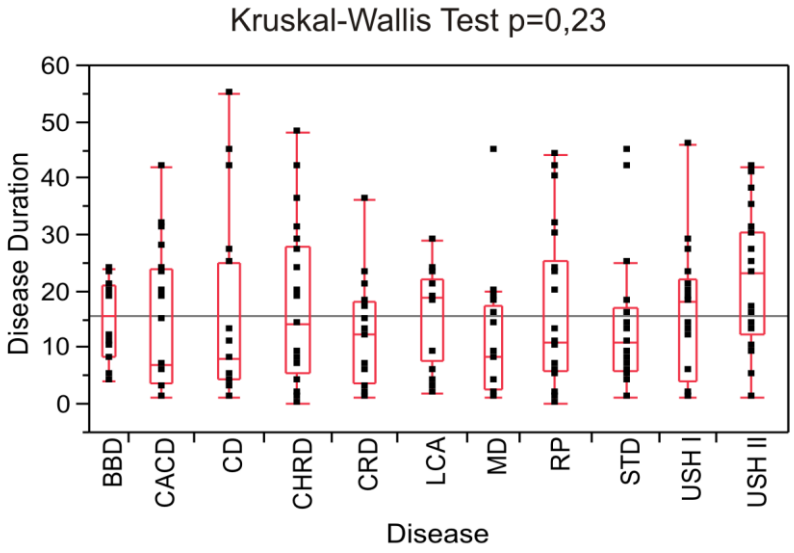

Figure 15 Box-plots of the disease duration at first visit to the eye hospital.

Table 8. Disease duration at first visit the University Eye Hospital, Tuebingen.

Disease	Median	25th Quantile	75th Quantile
USH I	18	4	22
USH II	23	12.25	30.25
STD	11	6	17
RP	11	5.75	25.5
MD	8.5	2.5	17.5
CRD	12.5	3.75	18
CD	8	4.5	25
CHRD	14	5.5	28
CACD	7	3.75	23.75
BBD	15.5	8.5	21
LCA	19	7.5	22

Table 9. Full-field ERG for normal subjects and a random selection of IRD patients.

Type of wave	Median	Min.	5th Quantile	25th Quantile	75th Quantile	95th Quantile	Max.
Reference group							
rod b-wave amp, mV	292.9	157.9	163.7	236.3	374.8	435.6	437.7
rod b-wave imp.time, ms	84	53	58.1	77.5	89	97.1	98
max ERG a-wave amp., mV	227.1	99.6	106.7	184.2	275.9	322.2	326.3
max ERG a-wave imp.time, ms	15.5	14	14.3	15	16.8	25.5	26
max ERG b-wave amp., mV	415.2	275.6	277.2	330.5	490.9	640.1	663.2
max ERG b-wave imp.time, ms	46	42	42.3	45	51.5	55.8	56
OP amp, mV	78.8	63.1	65.6	76.3	80.8	95.1	95.5
OP imp. time, ms	21.6	21	21	21.4	22.1	22.6	22.6
photopic a-wave amp., mV	39.2	15.8	18.3	33.3	45.2	61.5	61.7
photopic a-wave imp.time, ms	14	12	12.3	14	15	16	16
photopic b-wave amp., mV	171.1	76.3	79.4	121.8	205.6	271.4	283.9
photopic b-wave imp.time, ms	30	28	28	29	31	32.7	33
30 HZ amp.,mV	101.4	57.9	59.7	78.8	117.2	136.9	138.1
30 Hz imp. Time, ms	59	45	48.3	57.5	60.3	61.9	62
Random selection of IRD patients							
rod b- wave amplitude, mV	79.1	60.3	60.3	72.8	111.5	192.7	192.7
rod b-wave imp.time, ms	100.5	66.5	66.5	90	120.5	131.5	131.5
max ERG a-wave amp., mV	138.7	21.1	22.4	67.1	195.1	261.2	262.5
max ERG a-wave imp.time, ms	18.3	16	16	16.5	22.5	24	24
max ERG b-wave amp., mV	273.6	15.4	17.6	149.2	389.5	535.2	535.9
max ERG b-wave imp.time, ms	52	38.4	38.5	44.9	59	81.05	82
OP amp, mV	27.6	10.9	10.9	19.9	43.8	59.7	59.7
OP imp. Time. ms	24.8	10.8	10.8	23.5	25.4	33	33
photopic a-wave amp., mV	21.9	6.8	6.8	11.96	28.1	49.1	49.1
photopic a-wave imp.time, ms	16.5	15	15	15.1	17.8	21.5	21.5
photopic b-wave amp., mV	77.5	8.8	9.2	45.2	151.5	183.1	183.2
photopic b-wave imp.time, ms	32	29	29	30.2	35.1	40.5	40.5
30 HZ amp., mV	44.8	19.7	19.8	31.6	96.1	138.9	140.04
30 Hz imp. Time, ms	62.4	58.8	58.8	60.3	69	73.9	74

Table 10. The quantitative characteristics of mfERG parmeters in the reference group and IRD.

mfERG Parameter	Median	Min.	5th Quantile	25th Quantile	75th Quantile	95th Quantile	Max.
Reference Group							
RIAmplitude, mV	61.3	23.7	25.2	43.7	79.1	84.8	85.6
RII Amplitude, mV	34.5	14.2	14.7	24.6	43.95	53.3	55.4
RIII Amplitude, mV	20.2	9.6	9.9	16.5	26.3	29.5	29.8
RIV Amplitude, mV	14	7.4	7.5	10.3	19	27.1	28.8
RV Amplitude, mV	13.3	5.4	5.9	8.2	16.4	21.5	21.9
RI Implicit time, ms	29.2	7.9	13.8	29.1	30	30.8	30.8
RII Implicit time, ms	29.2	26.6	26.6	28.3	30	30	30
RIII Implicit time, ms	28.3	25.8	26.04	27.9	29.2	29.8	30
RIV Implicit time, ms	29.2	25.7	25.97	28.2	29.2	31.99	32.5
RV Implicit time, ms	29.2	26.6	26.6	28.3	30	35.5	37.5
Random selection of IRD patients							
mfERG Parameter	**Median**	**Min.**	**5th Quantile**	**25th Quantile**	**75th Quantile**	**95th Quantile**	**Max.**
RIAmplitude, mV	12.9	5.4	5.4	9.9	22.7	34	34
RII Amplitude, mV	8.9	2.1	2.1	5.1	12.2	15.3	15.3
RIII Amplitude, mV	7.4	1.5	1.5	2.8	11.05	18.9	18.9
RIV Amplitudel, mV	6.3	1.4	1.4	2.2	10.3	18.5	18.5
RV Amplitude, mV	6.6	1.4	1.4	2.5	9.95	15.3	15.3
RI Implicit time, ms	30	25.7	25.7	29.2	32.9	38.3	38.3
RII Implicit time, ms	31.2	27.4	27.4	28.95	34.6	44.1	44.1
RIII Implicit time ,ms	31.3	27.4	27.4	29.1	35.8	42.5	42.5
RIV Implicit time, ms	33.8	27.4	27.4	29.8	36.2	45	45
RV Implicit time, ms	33.8	28.2	28.2	30.6	36.9	45	45

III.4.1.1 Comparison of median values of full-field ERG amplitudes in a variety of IRD types.

Kruskal-Wallis test (Chi^2-test for more than 2 groups) was used for the comparison of full-field and mfERG amplitudes and implicit times of IRD subgroups and with subjects with normal ophthalmological finding. Photopic a-wave was non-detectable in USH I and USH II, and BBD patients and was the most reduced in patients with CRD, CACD, CHRD (p=0.0001) (Figure 16a). Interestingly, the photopic a-wave was almost equally reduced in patients with RP and CD, whereas patients with STD and MD had amplitude close to the normal range. BBD, CHRD, CRD and RP patients had the most reduced amplitudes of the maximum b-wave (p=0.0001) (Figure 16b). A similar trend was observed when analyzing the amplitude of the maximum a-wave. It was found to be most reduced in patients with BBD, CHRD, CRD, RP, and CACD in comparison with CD, STD and MD, in which amplitudes were closer to normal values (p=0.0001) (Figure 16c). Oscillatory potentials were non-detectable in BBD, and USH I and II patients. Patients with CHRD, RP, CRD, and CACD had on average lower median oscillatory potentials amplitude than those with MD, CD, and STD, which were again closer to the normal values (p=0.0001) (Figure 16d). Rod b wave amplitude was non-detectable in BBD, or USH I and II types. It was significantly reduced in patients with CHRD, CRD, CACD, RP and STD, whereas patients with MD and CD had amplitudes close to normal (p=0.0039) (Figure 16e). 30 Hz flicker were significantly more reduced in patients with USH I, RP, BBD, CHRD, CRD, and CD, whereas patients with USH II, and CACD had a slightly less reduced amplitude, and amplitudes of those with STD and MD were close to normative values (p=0,0001) (Figure 16f). USH I and CHRD had the most reduced photopic b-wave amplitude, with low variance, whereas patients with RP, CRD and CD had slightly less reduced amplitudes with higher variance (p=0,0001). Patients with CACD, STD, and MD had amplitude close to normative values (Figure 16g). A detailed comparison of the amplitudes in a variety of IRD is shown using box-plots in Figure 16. The comparison of

amplitudes between different IRDs types and with normal parameters using a Kruskal-Wallis test is shown in Appendix 1.

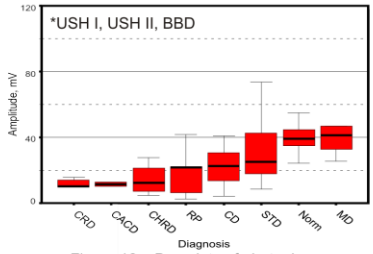

Figure 16a. Box-plots of photopic a-wave amplitude in different IRD types.

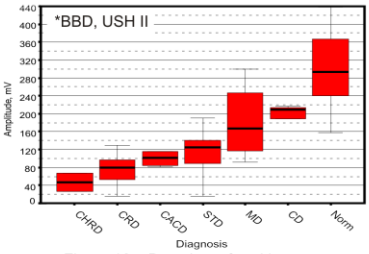

Figure 16e. Box-plots of rod b-wave amplitude in different types of IRD.

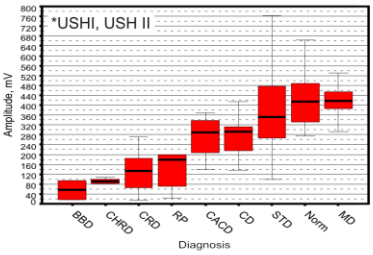

Figure 16b. Box-plots of maximum b-wave amplitude in different IRD types.

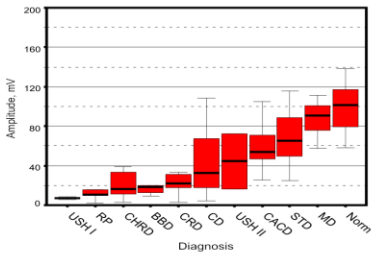

Figure 16f. Box-plots of 30 Hz flicker amplitude in different types of IRD.

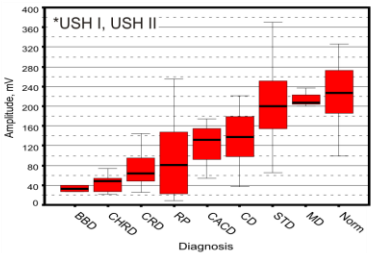

Figure 16c. Box plots of maximum a-wave amplitude in different types of IRD.

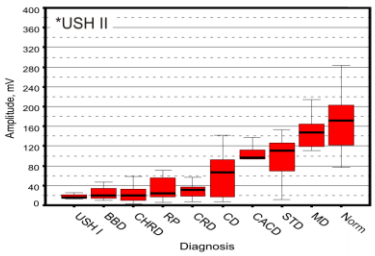

Figure 16g. Box-plots of photopic b-wave amplitude in different IRD types.

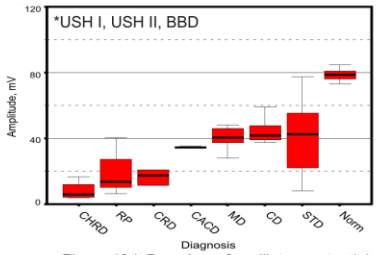

Figure 16d. Box-plots of oscillatory potential amplitude in different IRD types.

*- patients with non-detectable full-field ERG

Figure 16 Box-plots of full-field ERG amplitudes in normal subjects and a variety of IRD

III.4.1.2 Comparison of the median values of full-field ERG implicit time in a variety of IRD types.

Implicit times were observed to be less variable in comparison with amplitude. The implicit time of photopic a-wave was significantly more prolonged in patients with RP, CRD, and CHRD (p=0.0001) (Figure 17a), whereas photopic b-wave implicit time was observed to be in a normal range in patients with MD and was significantly more prolonged in patients with BBD, RP, CRD, CHRD, and USH I than those with CACD, STD, and CD (p=0.0001) (Figure 17g). The difference between the implicit times of the maximum b-waves was not significant (p=0.221). Nevertheless, it was observed that implicit times of maximum b-wave were slightly more variable in CRD patients (Figure 17b). Maximum a-wave implicit time was close to normal in all the observed IRD types. Slight prolongation was noted in CRD, STD, CD, RP, and CHRD, but no statistical significant difference was found (p=0.4392) (Figure 17c). Oscillatory potentials implicit times differ just slightly between different IRD types and were not recordable in BBD, USHI, USHII patients. The implicit times values were close to normal ones and vary slightly more in patients with CD, CRD, and RP (p=0.0001) (Figure 17d). The implicit time of the rod b-wave was within the normal range in patients in CD and CHRD, and slightly prolonged in CACD, STD, RP, MD, and CRD (p=0.0097) (Figure 17e). 30 Hz flicker implicit time was significantly more prolonged in patients with BBD, CHRD, CRD, RP, and CD than in those with CACD, USH I, STD, and MD (p=0.0001) (Figure 17f). The median of the USH II patients was significantly lower than the median of the normal group, although the variance of the implicit time parameter was very high due to fewer USH II patients having a recordable 30 Hz flicker wave. The comparison of implicit times between different IRD types and with normal parameters, using a Kruskal-Wallis test is shown in Appendix 1.

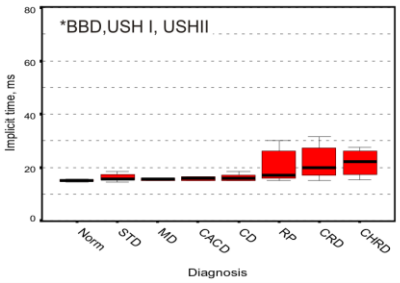

Figure 17a. Box-plots of photopic a-wave implicit time in different IRD types.

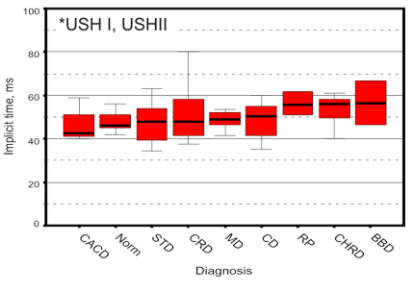

Figure 17b. Box-plots of maximum b-wave implicit time in different IRD types.

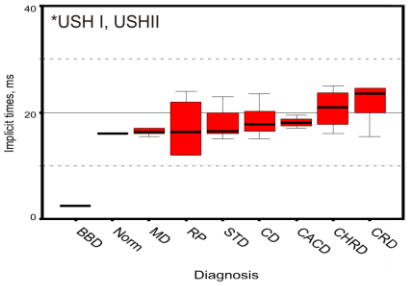

Figure 17c. Box-plots of maximum a-wave implicit time in different IRD types.

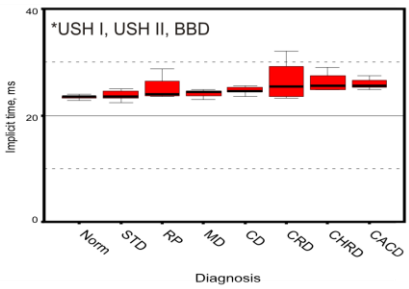

Figure 17d. Box-plots of oscillatory potentials implicit time in different IRD types.

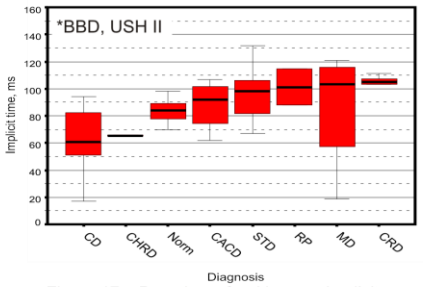

Figure 17e. Box-plots of rod b-wave implicit time in different IRD types.

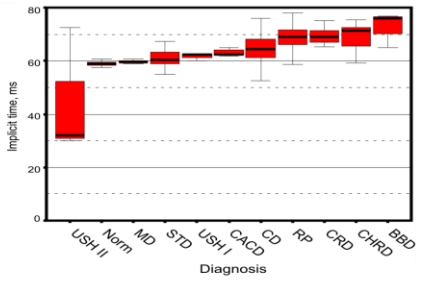

Figure 17f. Box-plots of 30 Hz flicker implicit time in different IRD types.

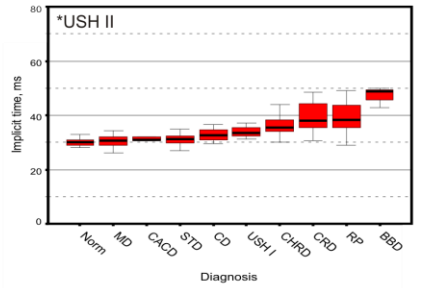

Figure 17g. Box-plots of photopic b-wave implicit time in different types of IRD.

*- patients with non-detectable full-field ERG

Figure 17 Box-plots of full-field ERG implicit time in a variety of IRD.

III.4.1.3 Comparison of median mfERG amplitudes in a variety of IRD.

The amplitude in the first ring (RI) of the mfERG was significantly more reduced in patients with USH I, STD, USH II, CACD, CD, and CHRD than in those with CRD, RP, and MD (p=0.0001). which were closer to the lower limit of the normal values (Figure 18a). The amplitude of the second ring (RII) was in the normal range in patients with RP, and significantly reduced in CD, CHRD, CRD, and USH II. RP RII amplitude was quite variable and the maximum of RII amplitude in RP reached the minimum normal value. A similar trend was observed in CD and CRD patients. These differences were statistically significant (p=0.0001) (Figure 18b). The third ring (RIII) amplitude was significantly more reduced in CRD, RP, CHRD, and USH I in comparison with CD, USH II, CACD, STD, and MD (p=0.0001) (Figure 18c). The amplitude of RIII in MD was detected to be in the normal range. The high variation in STD and CD resulted in their maximum values being in the normal range. The amplitude of the fourth ring (RIV) was significantly more reduced in USH I, USH II, RP, CRD, CHRD, and CACD (p=0.0001) (Figure 18d). Patients with CD, and STD had high variation in their amplitude values and therefore the values of these patients were on average closer to normal and had a more moderate reduction in comparison with other IRD types. The amplitude of the fifth ring was characterized by a significant amplitude reduction in USH II, CHRD, CRD, RP, and CD. CACD patients had a mild RV amplitude reduction, whereas STD and MD had RV amplitudes within a normal range (p=0.0001) (Figure 18e). The comparison of mfERG amplitudes between different types of IRD and with normal values is shown in Appendix 2.

III.4.1.4 Comparison of mfERG implicit time in a variety of IRD types.

mfERG implicit times were characterized by less variability than mfERG amplitudes (Figure 18 f-j). Implicit time of the first ring (RI) was in the range of normal values in USH I and USH II. Patients with CHRD and CACD had more prolonged implicit times in RI in comparison with other patients who were diagnosed with CRD, MD, RP, CD and STD (p=0.0032) (Figure 18f). Implicit

amplitude of the second mfERG ring was close to normal in USH II and USH I patients. It was observed that CACD had significantly more prolonged implicit times than other IRD types (p=0.0382) (Figure 18g). Implicit times of the third and the fourth rings showed a similar trend when comparing between different IRD types: USH I implicit times were significantly less prolonged than those in USH II in both RIII (p=0.0001) (Figure 18h) and in RIV (p=0.0001) (Figure 18i). Overall, ring 3 was characterized by significantly more prolonged implicit times in patients with USH II, CRD, CACD, CHRD and CD (p=0.0001) in comparison with other IRD types (Figure 18h). Ring 4 implicit times were significantly more prolonged in USH II, CRD, CACD, and CHRD (p=0.0001) (Figure 18i). Implicit times in ring 5 were significantly more prolonged in USH II, CRD, and CHRD in comparison with other IRD types (p=0.0001). USH I had no signal detectable in ring 5 (Figure 18j). The comparison of mfERG implicit times between different types of IRD and with normal values is shown in Appendix 2.

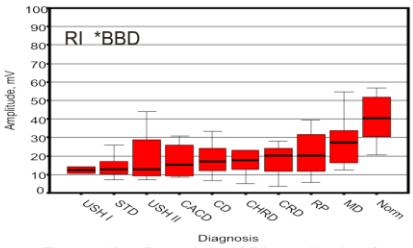

Figure 18a. Box-plots of RI amplitude of mfERG in different IRD types.

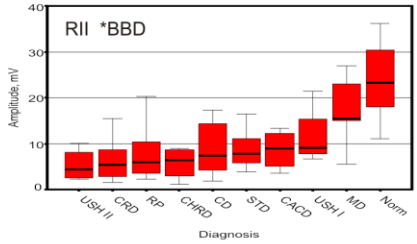

Figure 18b. Box-plots of RII amplitude of mfERG in different IRD types.

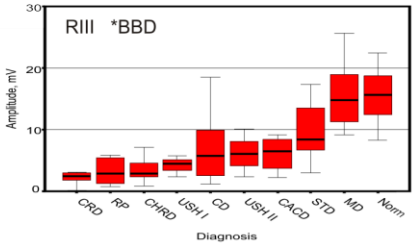

Figure 18c. Box-plots of RIII amplitude of mfERG in different IRD types.

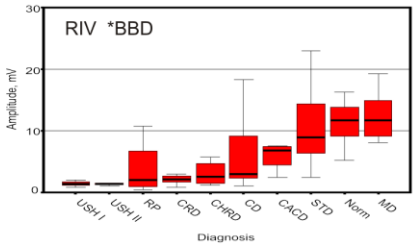

Figure 18d. Box-plots of RIV amplitude of mfERG in different IRD types.

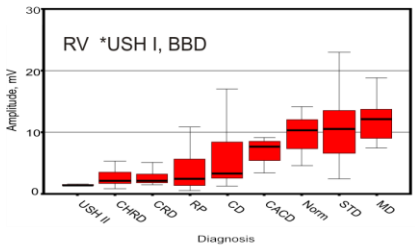

Figure 18e. Box-plots of RV amplitude of mfERG in different IRD types.

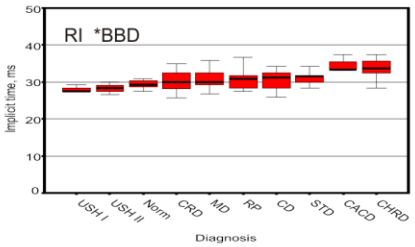

Figure 18f. Box-plots of RI implicit time of mfERG in different IRD types.

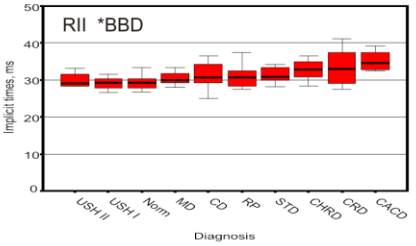

Figure 18g. Box-plots of RII implicit time of mfERG in different IRD types.

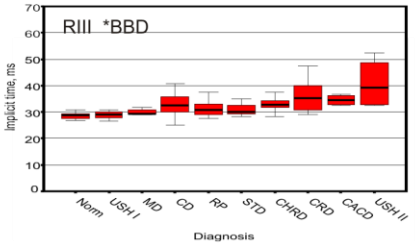

Figure 18h. Box-plots of RIII implicit time of mfERG in different IRD types.

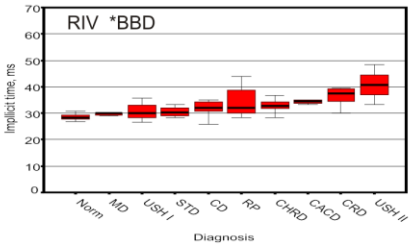

Figure 18i. Box-plots of RIV implicit time of mfERG in different IRD types.

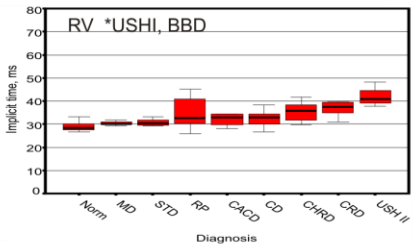

Figure 18j. Box-plots of RV implicit time of mfERG in different IRD types.

*-patients with non-recordable mfERG

Figure 18 Box-plots of mfERG amplitudes and implicit times in a variety of IRD.

III.4.2 Qualitative assessment of the full-field and mfERG parameters and their comparison between the variety of IRD types.

Full-field ERGs of 355 IRD patients with RP (132), STD (43), CRD (62), CD (32), CHRD (19), MD (14), USH I (4), USH II (15), LCA (15), BBD (13), CACD (7) and mfERGs of 316 patients with IRD: RP (151), STD (41), CRD (39), CD (28), CHRD(14), MD (15), USH I (3), USH II (10), LCA (5), BBD (4), CACD (6) were analyzed. mfERG was not recorded in all patients from the study population due to difficulties resulting from nystagmus or other concentration problems.

Analysis of full-field ERGs was directed to the comparison of changes in amplitude and implicit times of a and b-waves under different conditions in a variety of IRD, whereas analysis of mfERG aimed at the identification of the spatial characteristics of changes identified in full-field ERG. Patients included in this study were recruited from a larger study population that comprised 544 patients with IRD. The detailed characteristics of the study population, including age, sex distribution, geographic distribution, genetic testing data, comparison of age of typical visual symptoms onset, and analysis of major clinical parameters (best corrected visual acuity and perimeter results) were discussed by us in a previous chapter. The results were calculated in absolute numbers of patients, as well as in percentages of patients within a given IRD subgroup. The number of patients with a-wave changes is denoted n_1, and n_2 denotes the number with b-wave changes. Similar findings were revealed in the left and right eyes of the patients, therefore when reporting the results we refer to a number of patients (and not a number of eyes). The number of patients with a-wave change will be denoted by n_1, and the number with b-wave change n_2. If the number represents patients that are similar in both cases we use the notation $n_{1,2}$ and in case of oscillatory potentials and 30-Hz flicker the number of patients with changes will be reported as n. In all cases the numbers will be shown in absolute values as well as in percentage of patients within that group.

III.4.2.1 Rod system ERG

Scotopic amplitudes: It is known that scotopic a-wave is related to the kinetics of phototransduction [112], and the positive b-wave is generated post-receptorally [113]. Normal a and b amplitudes were observed in all patients with macular dystrophy ($n_{1,2}$=14/100%). A majority of patients with STD (n_1=28/65%, n_2=33/77%), CD (n_1=22/69%, n_2=23/72%), and CACD (n_1=4/67%, n_2=4/67%) also had normal a and b-amplitudes. A smaller proportion of patients with cone-rod dystrophy (n_1=14/22%, n_2=15/24%) had normal scotopic a and b- waves amplitudes.

Moderately reduced a and b-waves were detected in patients with cone-rod dystrophy (n_1=24/39%, n_2=31/50%). A smaller proportion of patients with STD (n_1=15/35%, n_2=10/23%), CD (n_1=10/31%, n_2=9/28%) and CACD (n_1=2/33%, n_2=2/33%) had moderately reduced amplitudes. Moderately reduced a and b-amplitudes were also observed in four patients with CHRD (21%). Patients with retinitis pigmentosa had moderately reduced a and b-waves (n_1=5/4% and n_2=41/31%).

Severely reduced amplitudes were detected in a large proportion of RP patients (n_1= 45/34%, n_2= 43/33%) waves. Patients with other diseases were represented in significantly smaller proportions: USH II (n_1=5/33%, n_2=11/73%), CRD (n_1=8/13%, n_2=7/11%), CHRD (n_1=5/26%, n_2=4/21%), and BBD (n_1=3/23%, n_2=3/23%).

A vast majority of patients with RP had non-detectable a (n_1=82/62%) and b-amplitudes (n_2=48/36%). Patients diagnosed with USH II (n_1=10/67%, n_2 =4/27%) and I types (n_1=4/100%, n_2=3/75%), CRD (n_1=16/26%, n_2=9/15%), CHRD (n_1=10/53%, n_2=10/53%) and BBD (n_1=10/77%, n_2=9/69%) also had non-detectable scotopic a and b-waves. Scotopic amplitudes are illustrated in Figures 19a and 19c.

Scotopic implicit times: Scotopic implicit times also showed symmetric changes for left and right eyes. All patients with macular dystrophy had normal scotopic implicit times for both a and b-waves. A majority of patients diagnosed with STD (n_1=28/65%, n_2=33/77%), CD (n_1=26/81%, n_2=27/84%), CRD (n_1=16/26%, n_2=26/42%), and CACD (n_1=4/67%, n_2=4/67%) also had normal scotopic implicit times for a and b-waves. CHRD was represented by only one patient in the category of normal standard flash b-wave.

Moderately prolonged scotopic implicit time was noted both in CRD (n_1=18/29%, n_2=28/45%) and RP (n_1=8/6%, n_2=16/12%). These patients represented a majority of the study population with moderately prolonged a and b-waves. Patients with STD (n_1=15/35%, n_2=10/23%), CD (n_1=4/13%, n_2=5/16%), and CACD (n_1=2/33%, n_2=2/33%) also had moderately prolonged scotopic implicit times.

Severely prolonged scotopic a and b-wave implicit times were observed in a relatively large number of patients with RP (n_1=42/32%, n_2=68/51%). In the category of severely prolonged scotopic b-wave USH II (n_2=9/60%), CRD (n_2=8/13%) and CHRD (n_2=9/47%) were almost equally represented. BBD accounted for six patients in this category. The patients with severely reduced scotopic a-wave were represented by patients with CRD (n_1=16/26%), BBD (n_1=10/77%), USH II (n_1=10/67%), and CHRD (n_1=9/53%).

Non-detectable scotopic a and b-wave implicit times were noted in all patients with LCA, and a majority of patients with RP had non-detectable a (n_1=82/62%) and b (n_2= 48/36%) wave implicit times. The remaining study population with non-detectable a and b-wave implicit times were represented by patients with CHRD (n_1=10/53%, n_2=10/53%), and USH I (n_1=4/100%, n_2=3/75%) and II types (n_1=10/67%, n_2=4/27%). Assessment of scotopic implicit times is shown in Figures 19b and 19d.

Maximum ERG a and b-wave amplitude: The response to the 1.5-3.0 cd.s.m^{-2} flash under scotopic conditions, with fully dilated pupil, is called standard, mixed

or maximum. This response is often regarded as the “typical” ERG. Although there is a cone contribution to it, the maximum response is dominated by rod driven activity.

Normal a and b-wave amplitudes were detected in a small number of patients with RP (n_1=17/13%, n_2=19/14%), in all patients with MD ($n_{1,2}$=14/100%), and in patients with USH II ($n_{1,2}$=7/47%), and CHRD (n_2=2/11%). Moderately reduced a and b-wave amplitudes were observed in patients with RP (n_1=17/13%, n_2=19/14%), CRD (n_1=26/41%, n_2=7/11%), CD (n_1=5/16%, n_2=4/12,5%), and in a few STD patients (n_1=4/9%, n_2=2/5%). Severely reduced a and b-wave amplitudes were detected in CRD (n_1=20/32%, n_2=6/10%), CD (n_1=20/63%, n_2=6/19%), RP (n_1=16/12%, n_2=16/12%), and STD (n_1=16/37%, n_2=10/23%). Non-detectable maximum ERG a- and b-wave amplitudes were detected in a majority of patients with RP (n_1=81/61%, n_2=78/59%), STD (n_1=20/47%, n_2=26/60%), CRD (n_1=16/26%, n_2=41/66%), CD (n_1=5/16%, n_2=19/59%), and LCA (n_1=10/67%, n_2=10/67%). Maximum ERG a- and b-wave amplitudes in a variety of IRD are shown in Figures 19e and 19g.

Maximum ERG a and b-wave implicit times were classified as normal in a minority of RP patients (n_1=25/19%, n_2=26/20%), in some patients with CRD (n_1=10/16%, n_2=4/7%), in all patients with MD ($n_{1,2}$=14/100%), in STD (n_1=9/20%, n_2=4/9%), and in USH II patients (n_1=8/53%, n_2=6/40%). Moderately prolonged maximum ERG a and b-wave implicit times were detected in RP patients (n_1=8/6%, n_2=14/11%), CRD patients (n_1=11/18%, n_2=4/7%), and in CD patients (n_1=7/22%, n_2=2/6%). Severely prolonged maximum ERG a and b-wave implicit times were observed in patients with RP (n_1=18/14%, n_2=14/10%), CRD (n_1=25/40%, n_2=13/21%), and STD (n_1=7/16%, n_2=9/21%). Not recordable a and b-wave implicit times were noted in patients with RP (n_1=81/61%, n_2=78/59%), CRD (n_1=16/25%, n_2=41/66%), LCA (n_1=10/66%, $n_{,2}$=10/66%), BBD (n_1=10/77%, n_2=9/69%), and CHRD (n_1=10/53%, n_2=8/42%). Maximum ERG a- and b-wave implicit times in a variety of IRD are shown in Figures 19f and 19h.

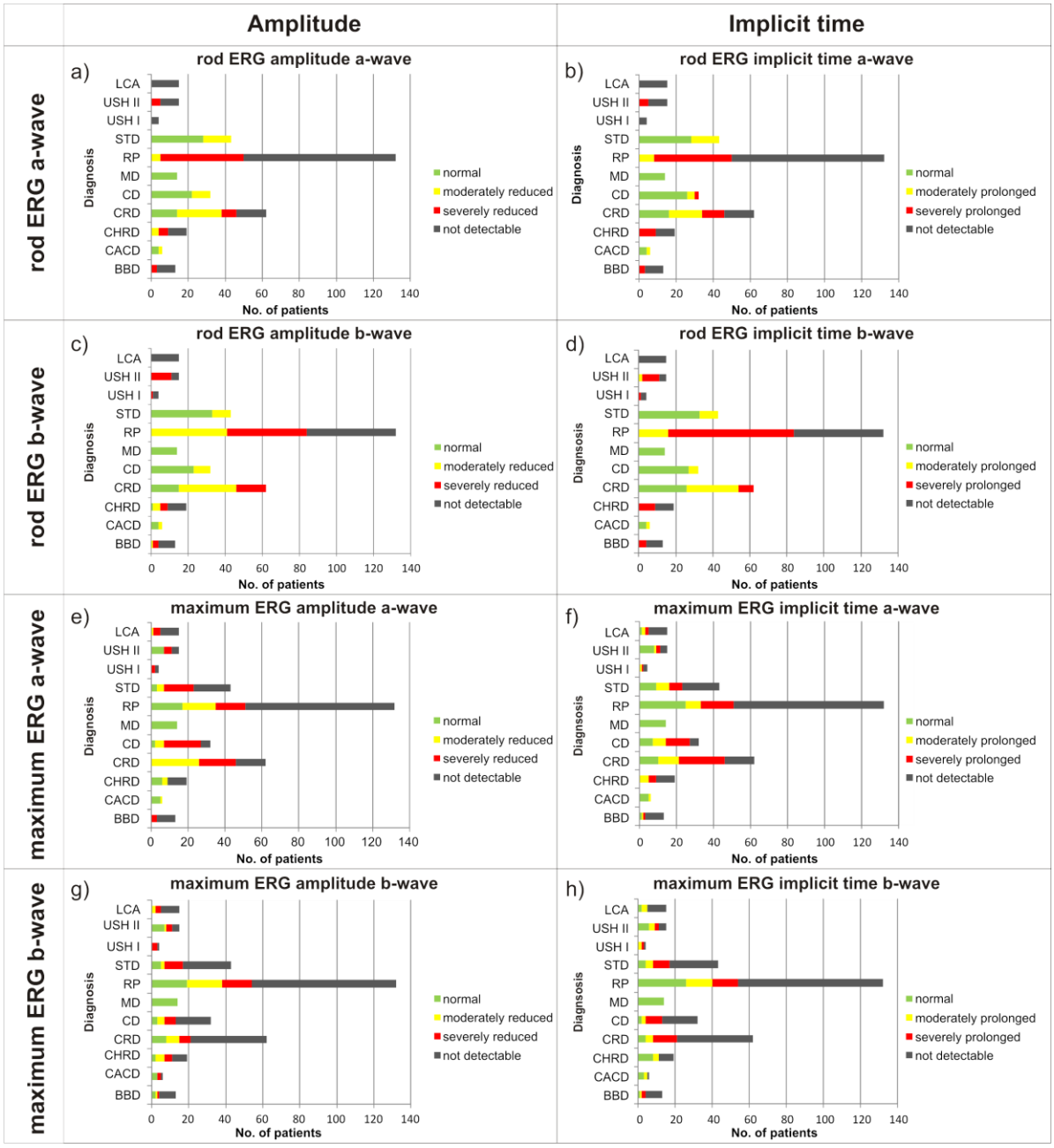

Figure 19 Scotopic full-field ERG in a variety of IRD: a) rod ERG amplitude a-wave b) rod ERG implicit time a-wave c) rod ERG amplitude b-wave d) rod ERG implicit time b-wave e) maximum ERG amplitude a-wave, f) maximum implicit time a-wave g) maximum ERG amplitude b-wave h) maximum ERG implicit time b-wave

III.4.2.2 Cone system ERG

Patients with STD (n1=22/51%, n2=31/72%), RP (n1=80/61%, n2=84/64%), and all patients with MD (n1=14/100%, n2=14/100%) had normal photopic a and b-wave amplitudes. All patients with CACD (n1=6/100%) had normal photopic a-wave amplitudes.

Patients with moderately reduced amplitudes of photopic a and b-waves were mostly diagnosed with RP (n_1=52/39%, n_2=48/36%), and STD (n_1=21/48%, n_2= 12/28%). However, patients with predominantly cone involved dystrophies also appeared in this group: CRD (n_1=16/26%, n_2=17/27%), CD (n_1=2/6%), and CHRD (n_1=2/11%, n_2=5/26%).

Severely reduced photopic a and b amplitudes were mostly detected in patients with CRD (n_1=20/32%, n_2=26/41%), USH II (n_1=13/87%), CD (n_1=4/12.5%, n_2=7/22%), CHRD (n_1=7/37%, n_2=4/21%), BBD (n_1=4/31%, n_2=4/31%), and USH I (n_1=2/50%, n_2=2/50%).

Non-detectable photopic a and b amplitudes were observed in all patients with LCA (n_1=15/100%, n_2=15/100%) and a vast majority of patients with CD (n_1=26/81%, n_2=25/78%), CRD (n_1=26/42%, n_2=19/31%), CHRD (n_1=9/47%, n_2=8/42%), and BBD (n_1=9/69%, n_2=9/69%). Photopic amplitudes of a and b-waves stratified by diagnosis are demonstrated in Figures 20a and 20c.

All patients with macular dystrophy (n_1=14/100%, n_2=14/100%), a large proportion of patients with RP (n_1=104/79%, n_2=96/73%) and STD (n_1=23/54%, n_2=33/77%), as well as patients with USH II (n_1=6/40%, n_2=5/33%) had normal photopic implicit times for a and b-waves.

Almost equal numbers of patients with RP (n_1=28/21%, n_2=36/27%), STD (n_1=20/47, n_2=10/23%), CRD (n_1=0, n_2=23/37%), and CD patients (n_1=6/14, n_2=9/22%) had moderately prolonged implicit times of photopic a and b-waves. The rest of patients in this group were represented with CACD (n_1=4/67%, n_2=5/83), USH I (n_1=3/75%, n_2=4/100%) and USH II (n_1=9/60%, n_2=5/33%).

Severely prolonged photopic a and b-wave implicit times were detected in BBD (n_1=4/31%, n_2=4/31%), and in some of patients with CD (n_1=10/24%, n_2=0), CRD (n_1=36/58%, n_2=20/32%), and CHRD (n_1=0, n_2=5/26%). 10 patients (67%) with USH II had a severely prolonged photopic b-wave implicit time. Implicit times of photopic a and b-waves in a variety of IRD are presented in Figures 20b and 20d.

30 Hz-flicker full-field ERG: Normal 30 Hz flicker amplitudes were detected in patients with RP (n=95/72%), STD (n=30/70%), and MD (n=14/100%). Patients with CRD (n=11/18%) were also represented in this group, as well as patients with CACD (n=4/67%) and CHRD (n=1/5%). Moderately reduced 30 Hz flicker amplitudes were observed in patients with RP (n=37/28%), USH I (n=13/87%), STD (n=12/28%), CRD (n=20/32%), CD (n=6/19%), and CACD (n=2/33%) patients. 30-Hz flicker amplitudes are shown in Figure 20e. CRD (n=15/24%), CD (n=13/41%), CHRD (n=5/26%), and BBD (n=4/31%) had severely reduced 30 Hz flicker amplitudes. A majority of patients with non-detectable 30 Hz amplitudes had CRD (n=16/26%), CD (n=13/41), and CHRD (13/68%). All patients with LCA and nine patients with BBD (69%) had non-detectable amplitudes.

A relatively large number of patients with RP (n=79/60%) had normal implicit times, as well as all patients with MD (n=14/100%) and a vast majority of STD (n=40/93%). 43 RP patients (33%) had moderately prolonged implicit time, as well as 11 patients (18%) with CRD, and 14 patients (93%) with USH II. The group with severely prolonged 30 Hz flicker implicit times was represented by patients with CD (n=21/59%), CRD (n=41/66%), and CHRD (n=6/32%). All patients with LCA (n=15/100%), and some with CHRD (n=13/68%), CD (n=13/41%), CRD (n=10/16%), and BBD (n=9/69%) had non-recordable 30 Hz implicit time. 30Hz implicit time stratified by diagnosis is shown in Figure 20f.

Oscillatory potentials: The oscillatory potentials, small wavelets on the ascending limb of the b-wave, are probably generated in relationship to

amacrine cell activity. Normal oscillatory potentials wave amplitudes in our study were typical for patients with RP (n=48/36%) and macular dystrophy diseases group such as MD (n=14/100%) and STD (n=30/67%). Moderately reduced oscillatory potential amplitudes were observed in a majority of patients with RP (n=84/64%). Patients diagnosed with CRD (n=11/18%), USH II (n=10/67%), STD (n=9/21%), CACD (n=3/50%), and CHRD (n=2/11%) also had moderately reduced oscillatory potential amplitudes. Severely reduced amplitudes of oscillatory potentials were mostly noted in patients with predominantly cone dystrophies: CD (n=10/31%), CRD (n=10/16%) and CHRD (n=5/26%). The remaining patients with severely reduced oscillatory potentials were patients with USH II (n=5/33%), USH I (n=3/75%), and BBD (n=2/15%). Non-detectable oscillatory potential amplitudes were noted in all patients with LCA, as well as in a majority of patients with cone dystrophies pathology such as: CD (n=22/69%), CRD (n=34/55%), and CHRD (n=12/63%), as well as in BBD patients (n=9/69%), and a small group of STD patients (n=4/9%). Amplitudes of oscillatory potentials are shown in Figure 20g.

Some patients with predominantly rod or macular involvement such as RP (n=64/49%), STD (n=27/63%), and MD (n=14/100%) had normal implicit time of oscillatory potentials, as well as nine patients with USH II and two patients with CACD. The same trend was observed in the category of moderately prolonged implicit time: 68 patients with RP (51%), and 12 with STD (28%). Patients with CRD (n=17/27%) also appeared in this category, despite the expectation that they would be more severely affected. The rest of this group is represented by patients with USH I (n=1/25%) and II (n=6/40%), and CACD patients (n=3/50%). Severely prolonged implicit times were detected in patients with CRD (n=11/18%), CD (n=7/22%), CHRD (n=7/37%), BBD (n=4/31%), and USH I (n=3/75%). Non-detectable implicit times were observed in all patients with LCA and a majority of BBD patients (n=9/69%). Patients with dystrophies with predominantly cone involvement represented a majority in this group: CD

(n=25/78%), CRD (n=34/55%) and CHRD (n=12/63%). Implicit times of the oscillatory potentials are shown in Figure 20h.

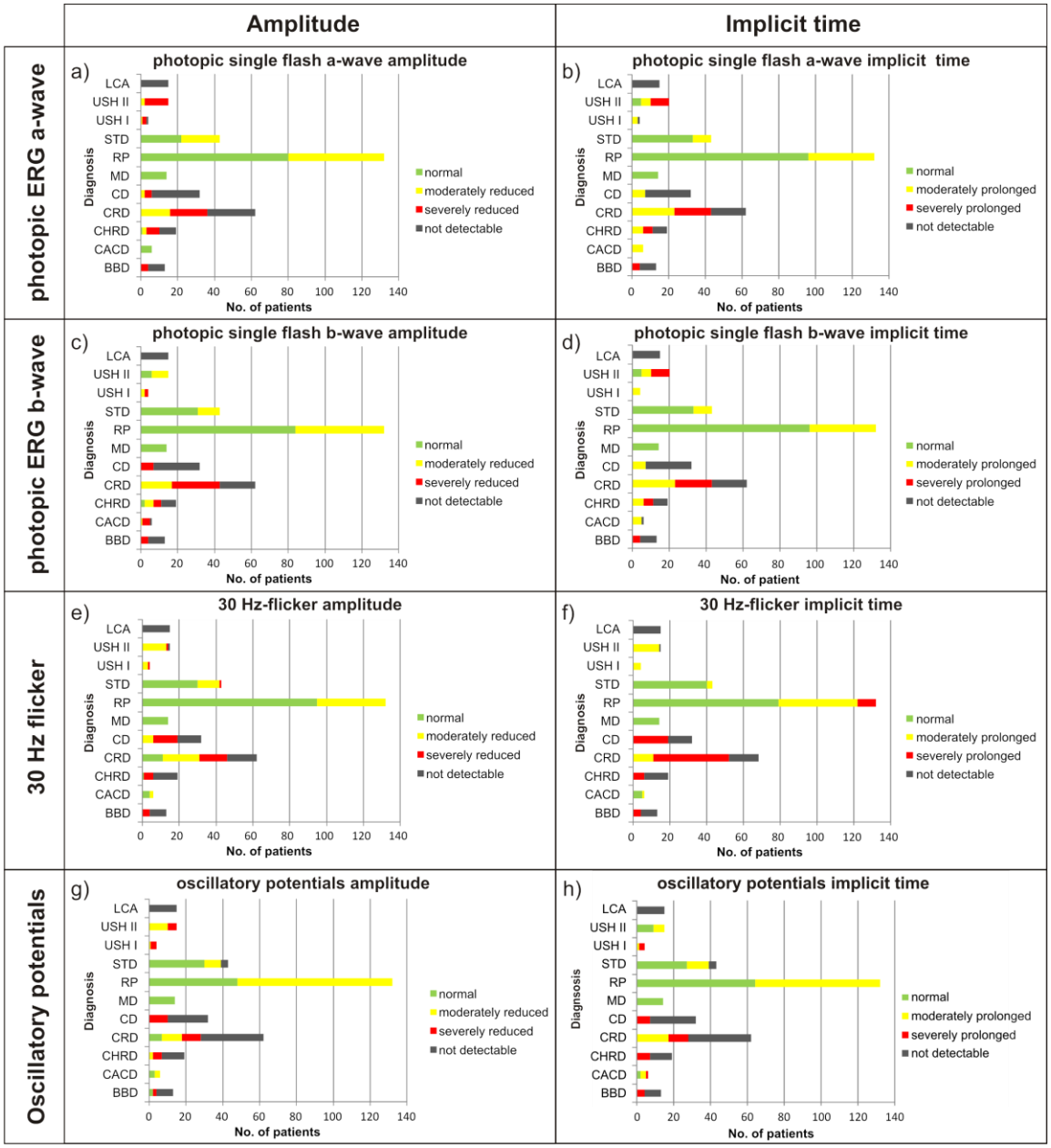

Figure 20 Photopic full-field ERG in a variety of IRD: a) photopic single flash a-wave amplitude; b) photopic single flash a-wave implicit time; c) photopic single flash b-wave amplitude; d) photopic single flash b-wave implicit time e) 30 Hz-flicker amplitude; f) 30 Hz-flicker implicit time, g) oscillatory potentials amplitude h) oscillatory potentials implicit time

III.4.3 mfERG in a variety of inherited retinal dystrophies.

The local effect of IRD can be studied using mfERG. mfERG is an important tool for the assessment of cone function and for studying outer retinal disorders, it also provides spatial information, which is not available in full-field ERG, as well as the possibility for better follow-up on the pathologic process and differential diagnosis. The results were calculated in absolute numbers of patients, as well as in percentage of patients within a given IRD subgroup. The number of patients with changes in the first ring (RI), in the second ring (RII), in the third ring (RIII), in the fourth ring (RIV), and in the fifth ring (RV) were denoted nI, nII, nIII, nIV, and nV, respectively.

Patients with MD had a predominantly central decrease of mfERG amplitude with slightly more normal values on the periphery (nI=4/12.5%, nII=5/16%, nIII=7/22%, nIV=8/25%; nV=8/25%). Moderately reduced amplitudes were detected in I (n=3/12%), II (n=6/23%), III (n=5/19%), IV (n=6/23%), and V (n=6/23%), with a slight predominance in the periphery. Central (I-III) rings were characterized by fewer patients with normal recordings (nI=4/12.5%, nII=5/16%) or moderately reduced amplitudes (nI=3/12%), in comparison with severely reduced amplitudes (nI=6/55%, nII=2/18%). In contrast, the peripheral rings had a higher frequency of normal (nIII=7/22%, nIV=8/25%, nV=8/25%) and moderately reduced amplitudes (nII=6/23%, nIII=5/19%, nIV=6/23%, nV=6/23%). At the same time, only few patients with MD had an abnormal implicit time. A relatively large number of MD patients had a normal implicit time in all rings (nI=11/21%, nII=10/19%, nIII=11/21%, nIV=11/21%, nV=10/19%). Few patients had moderately (nI=2/18%, nII=3/27%, nIII=1/9%, n=2/18%, n=3/27%) or severely prolonged implicit time (nIII=1/20%, nIV=2/40%, nV=2/40%). 2 patients had a non-detectable implicit time in the central (I-III) rings. mfERG amplitudes and implicit times in patients with MD are shown in Figures 21a and 21b, respectively.

A higher frequency of normal mfERG amplitudes in RP patients was observed in the central mfERG rings (nI=15/35%, nII=14/33%) in comparison with the periphery (nIII=5/12%, IV=5/12%, nV=4/9%) for both eyes. RP patients had an approximately equal representation of severely reduced amplitudes in central (nI=44/20%, nII=43/20%) and peripheral rings (nIII=50/23%, nIV=41 /19%, nV=38/18%), whereas non-detectable amplitudes were more predominant in the periphery (nIII=81/20%, nIV=92/23%, nV=96/24%) in comparison with central rings (nI=66/16%, nII=67/17%). In contrast with amplitudes, implicit times were classified as normal in a significant proportion of RP patients. Some RP patients had normal implicit times in the central rings (nI=50/31%, nII=44/27%, nIII=27/17%), and non-detectable mfERGs were observed on the periphery (nIII=81/20%, nIV=92/23%, nV=96/24%), which supports the predominantly peripheral location of the pathological photoreceptors. A smaller group of patients was observed with moderately prolonged implicit times (nI=13/17%, nII=18/23%, nIII=20/26%, nIV=13/17%, n=14/18%). The high frequency of severe prolongation (nI=22/20%, nII=22/20%, nIII=23/20%, nIV=24/20%, nV=24/20%) in a relatively large number of RP patients indicates an unfavorable prognosis for future visual function. mfERG amplitudes are shown in Figure 21c, and implicit times in Figure 21d.

STD mfERG amplitudes were moderately (nI=6/17%, nII=5/14%, nIII=7/19%, nIV=10/28%, nV=8/22%) to severely reduced (nI=23/30%, nII=24/31%, nIII=21/27%, nIV=4/5%, nV=6/8%) or non-detectable (nI=7/37%, nII=6/32%, nIII=5/26%, nIV=1/5%, nV=0), with a predominance of changes in the center (I-III rings) in comparison with the periphery (IV-V). Although a relatively large number of STD patients had normal implicit times (nI=14/15%, nII=13/14%, nIII=16/17%, nIV=27/28%, nV=26/27%), severe (nI=13/24%, nII=16/30%, nIII=13/24%, nIV=5/9%, nV=7/13%) and moderate reductions (nI=7/38%, nII=6/33%, nIII=7/28%, nIV=9/24%, nV=8/22%) were the second and the third most frequent categories of implicit time change. It was observed that severe mfERG prolongation in STD patients was more predominant in the central

mfERG rings (I-III) in comparison with the periphery. mfERG amplitudes and implicit times are shown in Figures 21e and 21f, respectively.

USH II was revealed to have more severe changes in mfERG than USH I, although the small number of patients with USH I syndrome should be considered when taking this difference into account. Patients with USH II type syndrome were revealed to have non-detectable amplitudes in the central rings (I-III) (nI=9/33%, nII=9/33%, nIII=9/33%) and moderately (nIV=1/20%, nV=4/80%) or severely prolonged implicit times (nIV=9/50%, nV=6/33%) predominantly on the periphery (IV-V). USH I had more mild changes in mfERG implicit time, represented by a lower number of patients who had severely prolonged implicit (nIV=9/50%, nV=6/33%) in comparison with USH II patients, a majority of whom had moderately prolonged implicit times in the peripheral rings (nIV=2/29%, nV=2/29%). mfERG amplitudes in patients with USH I and USH II syndrome are shown in Figures 21g and 21i, and mfERG implicit times in Figures 21h and 21j, respectively.

BBD and LCA are autosomal recessive diseases with early onset of retinal dystrophies. LCA can usually be diagnosed within several months after birth, and BBD is apparent in the first two decades of life. mfERGs of LCA patients demonstrated symmetric changes in both eyes. Non-detectable mfERG signals were observed in all patients in the outer II-V rings (n=5/100%), central mfERG rings I-II were characterized by predominantly non-detectable signals in 4 patients/80%, and 1 patient/20% had a severely reduced signal in the central rings and non-detectable signal on the periphery. Severely reduced implicit time was observed in center rings I-II, whereas no signal was detectable on the periphery. Amplitudes and implicit times of mfERG in LCA are shown in Figures 21k and 21l.

BBD mfERGs had slightly milder changes: amplitudes and implicit times were also mostly non-recordable: 3 patients were observed having non-detectable mfERG in each of the mfERG rings. One patient (nI-V=1/20%) had moderately

reduced amplitudes in the central rings (I-II) and peripheral rings (III-V). Implicit times were observed to be detectable in one BBD patient and were graded as severely prolonged in the central rings (I-III) to moderately prolonged on the periphery (IV-V rings). mfERG amplitudes and implicit times in patients with BBD are shown in Figures 22a and 22b, respectively.

mfERG in CACD patients was characterized by predominantly severe central reduction of the amplitude in I-III rings (nI=3/21%, nII=4/29%, nIII=3/21%) and normal in the periphery (nIV=2/33%, nV=2/33%). Moderately reduced amplitude was observed in 2 patients and was equally represented in central and peripheral rings. Implicit time was equally severely reduced in the central and peripheral rings (nI=4/19%, nII=5/24%, nIII=5/24%, nIV=4/19%, nV=3/14%). Few eyes with CACD had normal recordings (nI=2/25%, nII=1/13%, nIII=5/24%, nIV=4/19%, nV=3/14%). Interestingly, the change in implicit time was characterized by milder changes in rings I, IV, and V, and slightly more severe changes in rings II and III, which was symmetric in both eyes. mfERG amplitudes and implicit times in CACD patients are shown in Figures 22c and 22d.

Patients with CHRD had on average severely reduced (nI=6/19%, nII=6/19%, nIII=6/19%, nIV=7/22%, nV=22%) and/or non-detectable amplitudes (nI=6/20%, nII=6/20%, nIII=6/20%, nIV=6/20%, nV=6/20%), and severely prolonged (nI=3/20%, nII=3/20%, nIII=3/20%, nIV=3/20%, nV=3/20%) or non-detectable implicit times (nI=6/20%, nII=6/20%, nIII=6/20%, nIV=6/20%, nV=6/20%), whereas only a small proportion of recordings had normal (nI=1/20%, nII=1/20%, nIII=1/20%, nIV=1/20%, nIII=1/20%) or moderately reduced amplitudes (nI=1/33%, nII=1/33%, nIII=1/33%). In contrast, a significant proportion of CHRD patients had normal amplitudes (nI=4/22%, nII=4/22%, nIII=4/22%, nIV=3/17%, nV=3/17%). Amplitude change was more predominant in comparison with implicit time changes. mfERG amplitudes and implicit times in CHRD patients are presented in Figures 22e and 22f.

CRD patients' mfERGs were characterized by overall amplitude reduction and severe implicit time prolongation in all rings. A majority of CRD patients had moderately (nI=5/13%, nII=6/16%, nIII=9/24%, nIV=9/24%, nV=9/24%), severely reduced (nI=19/21%, nII=19/21%, nIII=16/18%, nIV=18/20%, nV=18/20%), or non-detectable (nI=11/21%, nII=11/21%, nIII=12/23%, nIV=9/17%, nV=9/17%) amplitudes, with fewer patients having normal mfERG amplitudes (nI=4/27%, nII=3/20%, nIII=2/13%, nIV=3/20%, nV=3/20%). The majority of CRD patients had severely prolonged implicit times that were present more often on the periphery (nIII=15/19%, nIV=18/23%, nV=18/23%) in comparison with central rings (nI=14/18%, nII=14/18%). Many CRD patients had non-detectable implicit times (nI=11/21%, nII=11/21%, nIII=12/23%, nIV=9/17%, nV=9/17%), whereas normal (nI=11/27.5%, nII=9/22.5%, nIII=8/20%, nIV=6/15%, nV=6/15%) and moderately prolonged implicit times (nI=3/12,5%, nII=5/21%, nIII=4/17%, nIV=6/25%, nV=6/25%) were recorded in a small proportion of patients. mfERG amplitudes and implicit times in patients with cone-rod dystrophies are shown in Figures 22g and 22h, respectively.

The majority of patients with CD had severely (nI=15/21%, nII=18/25%, nIII=15/21%, nIV=12/17%, nV=12/17%) or moderately (nI=5/16%, nII=4/13%, nIII=7/22%, nIV=8/25%, nV=8/25%) reduced amplitudes. A smaller number of CD patients had normal (nI=3/13%, nII=3/13%, nIII=4/17%, nIV=7/29%, nV=7/29%) and non-detectable amplitudes (nI=5/42%, nII=3/25%, nIII=2/17%, nIV=1/8%, nV=1/8%). mfERGs in patients with CD were characterized by predominantly severe or moderate reduction of amplitudes, which was more notable on the periphery for moderate reduction. Severe amplitude reduction was more typical in the center (I-III rings). A relatively large number of eyes with a cone dystrophy had normal implicit times (nI=8/21%, nII=8/21%, nIII=7/18%, nIV=8/21%, nV=7/18) in mfERG. Nevertheless, severely (nI=9/17%; nII=10/19%, nIII=13/24%, nIV=11/20%, nV=11/20%) and moderately prolonged (nI=6/17%, nII=7/19%, nIII=6/17%, nIV=8/22%, nV=9/25%) waves were also present in all mfERG rings. Few patients had a non-recordable implicit time

(nI=5/42%, nII=3/25%, nIII=2/17%, nIV=1/8%, nV=1/8%). mfERG amplitudes and implicit times in patients with cone dystrophies are demonstrated in Figures 22i and 22j, respectively.

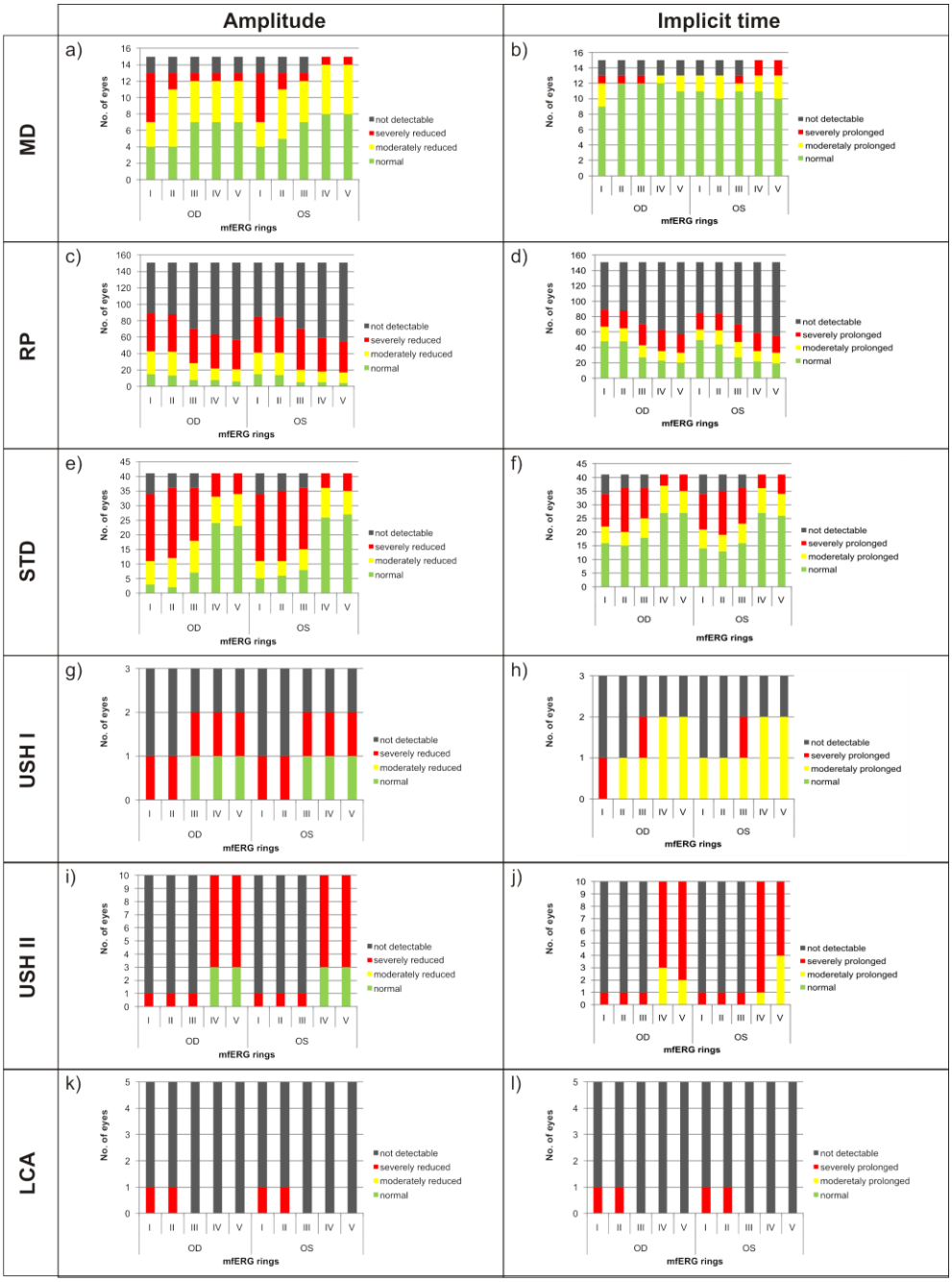

Figure 21 Changes of mfERG in a variety of rare IRD: a) mfERG amplitude in MD b) mfERG implicit time in MD c) mfERG amplitude in RP d) mfERG implicit time in RP e) mfERG amplitude in STD f) mfERG implicit time in STD g) mfERG amplitude in USH I h) mfERG implicit time in USH I i) mfERG amplitude in USH II j) mfERG implicit time in USH II k) mfERG amplitude in LCA l) mfERG implicit time in LCA.

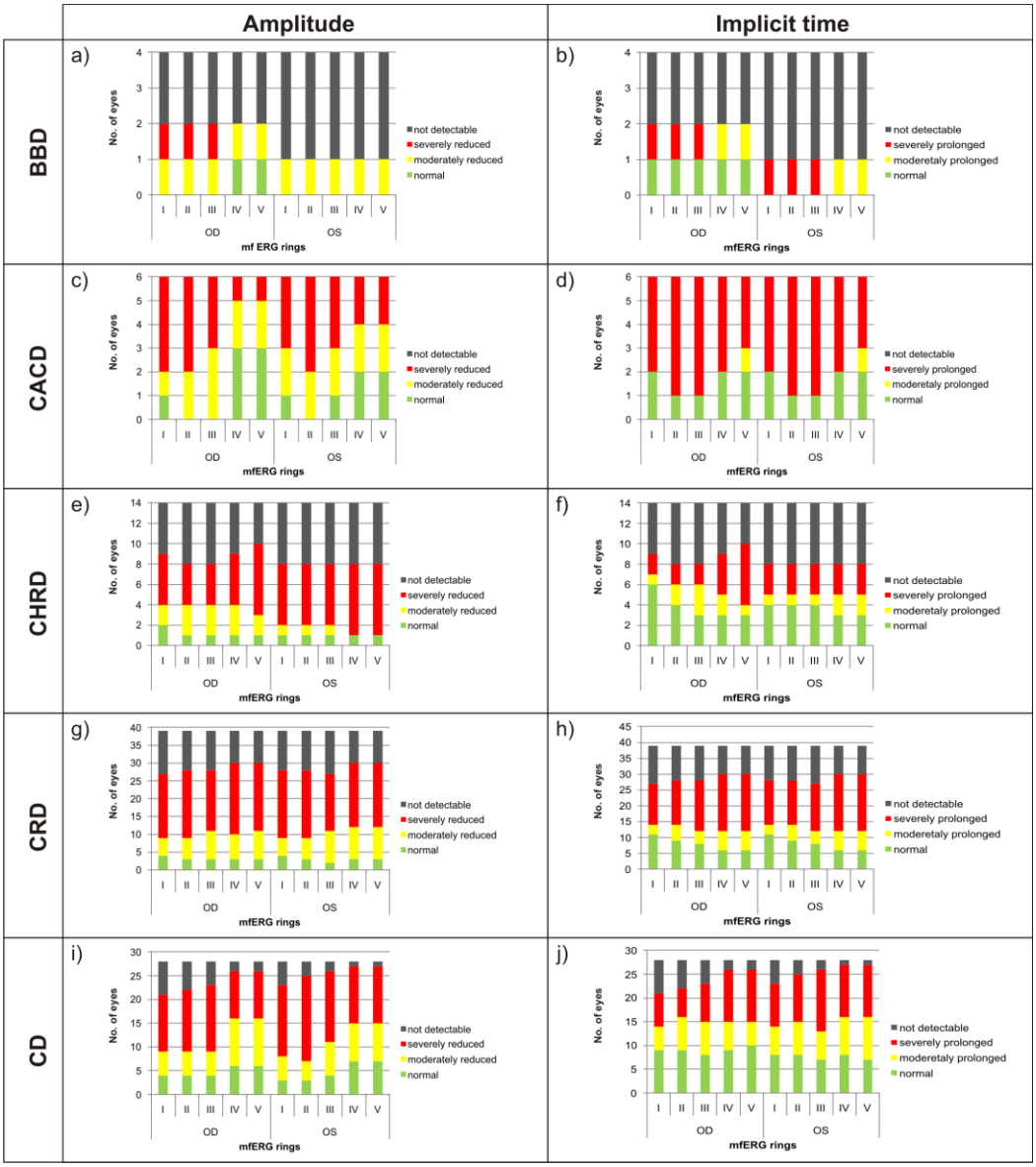

Figure 22 Changes of mfERG in a variety of rare IRD (cont.): a) mfERG amplitude in BBD b) mfERG implicit time in BBD c) mfERG amplitude in CACD d) mfERG implicit time in CACD e) mfERG amplitude in CHRD f) mfERG implicit time in CHRD g) mfERG amplitude in CRD h) mfERG implicit time in CRD i) mfERG amplitude in CD j) mfERG implicit time in CD.

III.5 Visual-related quality of life in patients with inherited retinal dystrophies - a baseline for assessing clinical trial efficacy

Differential diagnostic approaches including epidemiological approaches for differentiation between predominantly central and peripheral IRD, as well as analysis of pattern of disease onset, and a comparison of clinical signs in the electrophysiology of the visual system in eleven rare IRD, helps to identify and select IRD patients who can benefit from new treatment strategies in very early stages of the disease that can prevent decrease of visual function and disability. Active and successful development of new treatment strategies for IRD requires their effectiveness assessment. Vision-related quality of life is now recognized as a standard patient reported outcome value and is widely used in the assessment of the effectiveness of different therapeutic strategies. Because the existing literature is limited in its cover of this topic, the third aim of the dissertation was is to characterize the visual-related quality of life (VRQL) of patients with different forms of IRD and to estimate a baseline for assessing efficacy of clinical trials in IRD patients.

The National Eye Institute Visual Function Questionnaire (NEI-VFQ-25), using a German validated version, was administered to patients with macular dystrophy (8), retinitis pigmentosa (34), Stargardt disease (31), Usher I and II types (10), central areolar choroidal dystrophy (3), cone (4) and cone-rod dystrophies (13), choroideremia (2), Leber congenital amaurosis (1) and CSNB (2). Visual field (VF) data and BCVA in logMAR were obtained. The mean and standard deviations were calculated.

108 patients (62 men/46 women) were studied. The mean age was 39.5 (SD=1.5). Equal numbers of patients in the study population were married or single, and a minority was divorced. The majority of them lived with their family and graduated from secondary school or university, and were studying or employed half to full-time. 78% used corrective glasses or contact lenses. 84% of the study population considered themselves near-sighted and 75% described

their visual field as constricted. Table 11 shows a general description of the study population: sex, family status, living situation, education, working situation. Table 12 demonstrates the results of the patients' subjective perception of their vision abilities (including subjective perception of their visual field and visual acuity), use of glasses and contact lenses.

Table 11. Socio-demographic description of the study population.

Sex	**N**	**%**
men	62	58 %
women	46	42%
Family situation		
married	47	43 %
single	44	40 %
divorced	18	17%
Living Situation		
in family	91	84%
alone	17	16%
Education		
Grammar/secondary/commercial school	43	40%
University	27	25%
Elementary School	21	19%
Gymnasium	17	16%
Work		
full-time employed	51	47%
pupil	18	16%
half-time employed	13	12%
pensioner	9	8%
unemployed	6	6%
housewife	5	5%
not able to work	3	3%
student	3	3%

Table 12. Ophthalmological characteristics of the patients

Use of glasses/contact lenses	**N**	**% from total**
yes	79	73%
no	27	25%
no data	2	2%
Subjective perception of the visual acuity changes		
near-sighted	52	48%
far-sighted	10	9%
could not define	46	43%
Subjective perception of the visual field changes		
constricted	82	76%
normal	17	16%
could not define	9	8%

III.5.1 Visual-Related Quality of life in the IRD patient population

The mean NEI-VFQ composite score was 59 (SD=13.7). The most reduced subscales were role limitations (35.9; SD=18.8), mental health (30.3; SD=15.6), and dependence on others (26.12; SD=20.7). Social functioning (69.2; SD=22.6), ocular pain (79.3; SD=19.96), and color vision (82.5; SD=26.2) were least reduced. The mean and SD of NEI-VRQL questionnaire subscales are shown in table 13.

Table 13. NEI-Visual-Related Quality of life in population with IRD.

Subscales	Mean	SD
Dependence on others	26.1	20.7
Mental health	30.3	15.6
Role limitations	35.9	18.8
General vision	43.1	18.6
Peripheral vision	56.3	29.2
Near vision	56.8	26.9
General health	59.9	22.5
Driving	62.4	26.7
Distance vision	62.5	22.1
Social functioning	69.2	22.6
Ocular pain	79.3	19.9
Color vision	82.5	26.2

III.5.2 Visual-Related Quality of life in a variety of rare IRD.

The general health subscale was the most reduced in patients with USH II, CACD, and RP (range 37.5-57.5). Whereas patients with CRD, STD, MD, CD, CHRD, USH I, and congenital stationary night blindness (CSNB) (range 65-77.5) had the same level of general health and were characterized only by a very moderate reduction.

The second subscale, which characterizes general vision, was the most reduced in CHRD, CACD, CRD, and CD (20-35). Moderate reduction of this

subscale was observed in RP, STD, USH II, MD, and CSNB (range 40-50). The smallest reduction was observed in patients with USH I (70).

The ocular pain subscale was shown to be the least reduced in the overall VRQL analysis, as well as when stratified by disease. The score varied from 75 in RP, USH II, and MD, to 81.25-87.5 in CRD, CD, CSNB, and USH I, and was normal (100) in CHRD, CACD, and STD.

The near vision subscale was the most reduced in CRD, MD, and CHRD (range 37.5-45.8). Moderate reduction of this subscale was observed in CACD, STD, and RP (range 50-56.25). The lowest reduction was observed in patients with USH II, CD, CSNB, and USH II (range 79.2-85.4).

The distance vision subscale was most reduced in patients with CRD, CACD, and CHRD (range 37.5-47.9). Moderate reduction of this subscale was observed in patients with MD, RP, USH II, and STD (range 54.2-68.8). The least reduced distance vision subscale was observed in CD, CSNB, and USH II (range 75-85.4).

The social functioning subscale was found to be the most reduced in patients with CSNB, CACD, MD, and USH I (range 17.5-25). Patients with USH II, RP, and STD had a similar level of social functioning and were characterized by a moderate reduction in this subscale. Patients with CRD and CHRD had the least reduced social function in comparison with other IRD (range 42.5-55).

The mental health subscale was most reduced in CACD, USH I, and STD (range 31.25-34.4). Moderately reduced mental health subscale was observed in MD, USH II, RP, CD, and CRD patients (range 37.5-43.7), whereas the least reduced mental health subscale in comparison with other IRD was observed in CHRD (range 46.8-50).

Dependence on others was observed to be one of the most reduced subscales for the entire IRD study population, as well as when stratified by diagnosis. The most reduced scores were observed in USH I, STD, USH II, and RP (range 3.1-

21.9). Moderate reduction of this subscale was observed in MD, CACD, CD, CRD, and CSNB (31.2-37.5). This subscale was the least reduced in patients with CHRD in comparison with other IRD patients.

Only 24 patients from the study population were still driving: RP (n=8), STD (n=5), CRD (n=5), MD (n=5), USH II (n=2), CD (n=1), CACD (n=1). The greatest difficulty in driving was experienced by patients with CACD and USH II (range 8.3-17.7). Moderate reduction of this subscale was noted in patients with CRD, RP, STD, and MD (range 58.3-66.7). No reduction of this subscale was observed in CD patients.

The color vision subscale was the one of the least reduced subscales for the IRD study population, as well as for all IRD when stratified by diagnosis. A slight reduction of this scale was observed in patients with CACD, USH II, CRD, RP, and CHRD. No reduction was observed in STD, MD, CD, USH I, and CSNB patients.

The peripheral vision subscale was most reduced in USH II, CRD, CHRD, and RP patients (range 25-37.5). Moderate reduction of this subscale was observed in patients with CACD, MD, CD, USH I, and CSNB (range 50-75). No reduction was observed in STD patients. A graphic representation of the VRQL in a variety of rare IRD is shown in Figure 23.

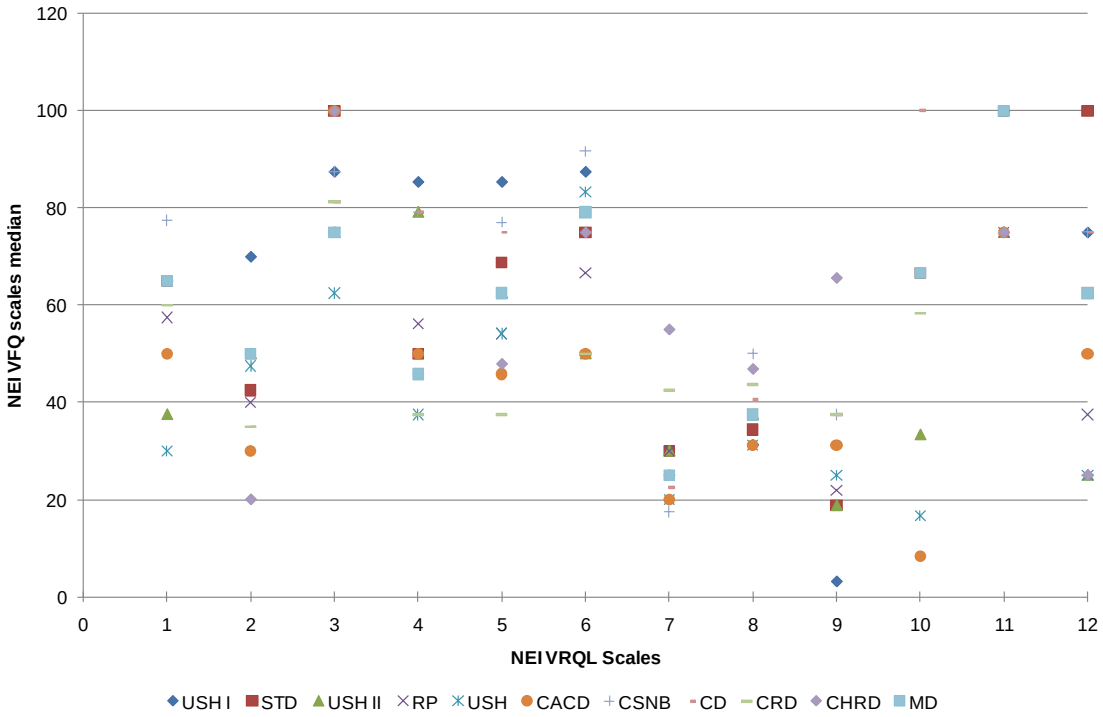

Figure 23 Vision- Related Quality of life in a variety of rare IRD. VRQL subscales: 1. General Health, 2. General Vision, 3. Ocular Pain, 4. Near Vision, 5. Distance Vision, 6. Social Functioning, 7. Mental Health, 8. Role Limitations, 9. Dependency, 10. Driving, 11. Color Vision, 12. Peripheral Vision

III.5.3 The relation of the VRQL and clinical data.

The next step of the study was aimed at detection of the factors/clinical parameters that are highly correlated with certain subscales of the NEI VFQ-25 in patients with IRD. It was found that sex had a significant influence on the changes observed in general health, general vision and ocular pain scores. Women reported lower scores in general health and ocular pain in comparison with men, whereas men had more reduced general vision scores. It was also observed that those with lower BCVA had decreased general ($p<0.0251$), near ($p<0.003$), distance vision ($p<0.03$), and social functioning ($p<0.0069$) scores

(Table 14). The peripheral vision score was significantly lower in patients with concentric VF constriction ($p<0.0076$) (Figure 30).

Overall, we showed that the composite score, role limitations, mental health, and dependence on others were the most reduced subscales in the overall IRD study population, as well as when stratifying by diagnosis. We also compared all subscales between a variety of rare IRD. The near and distance vision subscales were the most reduced in CRD, whereas the peripheral vision scale was most reduced in CRD, CHRD, USH II, and RP. The role limitation score was the most reduced in CACD, USH I, and STD; mental health was most impaired in CSNB, CACD, CD, and USH I; dependence on others in USH I, STD, USH II, and RP. The lowest composite scores were noted in USH II and CACD. A lower peripheral vision score was associated with concentric VF constriction. Lower general, near, distance vision, and social functioning scores were linked to BCVA decrease. The results of this study can be used as a baseline for the assessment of clinical trials efficacy.

Table 14. VRQL-scores changes in relation to different factors.

NEI-VFQ-25 Subscales	General patient data and clinical parameters			
	Sex	Age	BCVA	Peripheral vision
General Health	**0.0285***	0.262	0.7571	0.2729
General Vision	**0.0234***	0.134	**0.0251***	0.2337
Ocular Pain	**0.0423***	0.468	0.6330	0.4167
Near Vision	0.8932	0.184	0.003*	0.4189
Distance vision	0.5344	0.388	**0.00325***	0.6026
Social functioning	0.8703	0.545	**0.0069***	0.5406
Mental Health	0.1204	0.441	0.1729	0.5501
Role limitations	0.7378	0.461	0.2210	0.5584
Dependence on others	0.5840	0.363	0.1697	0.2135
Driving	0.2995	0.305	0.4920	0.4739
Color vision	0.2747	0.617	0.1541	0.4068
Peripheral vision	0.5544	0.257	0.2482	**0.0385***
Composite score	0.3285	0.403	0.6998	0.4784

*-indicates statistical significance; Kruskal-Wallis test (Chi^2-test for more than 2 groups) was used for the association assessment.

IV Discussion

In order to understand the current epidemiological status of eye diseases leading to blindness in Europe the most recent literature on age-related macular dystrophy, diabetic retinopathy, intraocular hypertension, glaucoma, and inherited retinal dystrophies, was reviewed. This review showed that there are fewer epidemiological data in Europe on retinitis pigmentosa in comparison with other eye disease (ARMD, diabetic retinopathy, glaucoma, and cataract) that lead to blindness.

The above mentioned diseases lead to blindness and visual impairment in older ages, whereas IRD cause blindness in young people decreasing their ability to work and maintain an independent lifestyle, decreasing their quality of life [94].

IRD is one of the most frequent causes of blindness in younger Europeans. The level of blindness in Europe due to IRD varied from 7 to 8%. The study from Spain showed that Usher I and II syndromes were the most widespread form of syndromic IRD in this population. Studies performed in Valencia, Spain and Slovenia reported autosomal dominant RP to be the most common form of non-syndromic IRD, whereas X-linked RP was the most rare one. Simplex RP appeared to be the most common form in a study from the Netherlands. Only few studies report on the epidemiological status of IRD in Europe, including age of disease onset estimation and geographic distribution [32, 77, 78].

Previous literature reviews related to the epidemiology of eye diseases leading to blindness in Europe have focused mostly either on the incidence of blindness and its causes [109] or on a specific disease within a specific country or geographic region, e.g. age-related macular degeneration [12-14], diabetic retinopathy [15-17], glaucoma [19, 36], or cataract [110]. Studies on RP were mostly based on blindness data obtained from social services. One of the most comprehensive and recent literature reviews was conducted in 2002 within the WHO Programme for the Prevention of Blindness and Deafness and contained data on the prevalence of blindness and low vision in WHO regions as well as

on the percentage of total blindness for each cause [109]. Data was significantly lacking for Europe in comparison with other WHO regions, and a comparison of different countries was not included. The study included results from twenty five European population-based studies published between 1982 and 2000.

Kocur and Resnikoff reviewed five European studies on major eye diseases published from 1970 to 1998 [2]. While they summarized the impact of these diseases on visual impairment within each country, they failed to make a comparison of epidemiological data among the studies. This review did not include data on IRD.

The present review compared data from (to the best of the authors' knowledge) all most recent studies on IRD. Overall, the present review showed that, despite the large number of epidemiological studies of eye diseases leading to blindness performed worldwide, accurate data are still largely lacking for Europe. This review highlighted the importance of undertaking multi-centre, population-based studies of eye diseases leading to blindness in Europe. It also showed that the amount of epidemiological data on IRD is considerably lacking in comparison with the diseases leading to blindness older ages. In the light of active and successful development of new treatments for IRD, a deeper knowledge of the disease is required for selection of the patients for clinical trials and further treatment.

Estimation of age of disease onset, as well as an optimal age for therapeutic intervention is important for an early differential diagnosis and selection of patients for clinical trial participation. Therefore, an epidemiological approach was applied in order to estimate the age of onset in central and peripheral monogenic retinal degeneration. The results of this study suggested that monogenic retinal degenerations are more frequent among men than among women. This may be due to X-recessive inheritance mechanism of some of the diseases, such as macular dystrophy and choroideremia. The majority of

patients in the study population were first diagnosed by an ophthalmologist at an age between 11 and 30 years old, which is in line with the results obtained by Tsujikawa et al. in the study of age at onset curves of retinitis pigmentosa [114].

A large number of patients in both groups retain good visual acuity equal or better to 20/40, with 124 eyes in group 1 (predominantly central involvement) and 140 eyes in the second group (predominantly peripheral involvement). This result is in line with other studies conducted earlier [69, 115]. BCVA for both groups by age showed that 37% of patients in age group 21–40 and 36% in age group 41–60 were registered as legally blind, indicating a strong impact of monogenic retinal degenerations on incidence of blindness principally in a productive age group.

Color perception problems didn't appear to be a very specific symptom in either group, since an equal number of patients in both groups indicated the presence or absence of color vision problems. This is surprising, since color vision discrimination problems should be more common primarily in diseases affecting the central retina than in diseases affecting the periphery. This may be a consequence of the "bystander effect", when cones are effected secondarily because of rod degeneration and production of rod-derived cone viability factor (RdCVF) [116].

Usher syndrome I and II, Stargardt disease, and choroideremia were the most frequent diagnoses in this study. This corresponds to the results of other studies, where Usher syndrome types I and II were found to be the most frequent types of monogenic retinal dystrophies in Germany and in Spain [49, 77].

Overall, the results of our study showed that these monogenic retinal dystrophies are more frequent among men than among women. It was also found that relatively high numbers of patients in both groups retained quite good visual acuity, which shows that early and properly planned rehabilitation

strategies and/or timely application of new treatment strategies could be beneficial in order to increase quality of life for these patients. Moreover, for both groups an age for optimal therapeutic intervention was defined. It is recommended that this should be taken into account while screening for patients to take part in clinical trials for testing new treatment strategies.

Furthermore, this study showed that the age at disease onset can be estimated on the basis of an epidemiological approach, which is based on an epidemiological analysis of age at main symptoms onset, derived from the history of the disease, and main clinical parameters. An epidemiological approach to the estimation of the disease onset could be used by clinicians for detecting the duration of the disease and its prognosis, planning rehabilitation measures, and for researching future possibilities for treatment. Further long-term, follow-up studies of clinical parameters are needed for the establishment of a decision-making algorithm for the estimation of disease prognosis and rehabilitation.

Differentiation of IRD into two groups with predominantly central or predominantly peripheral involvement is essential in early diagnostic stages, and even more precise differentiation is needed for the final diagnosis. Furthermore, an even more granular approach is necessary to obtain an understanding of the pattern of the disease onset in a variety of rare IRD. Therefore, the pattern of major visual symptoms onset was studied in eleven rare IRD. The results of this study suggested that patients with USH II were 3 times more frequent than USH I patients, which is also supported by earlier results [72]. SIM-RP was the most frequent mode of inheritance followed by X-RP, ADRP, and ARRP. Previous studies of the frequency of RP inheritance mechanisms in different populations detected a simplex “sporadic” inheritance as most frequent [117]. The X-linked inheritance mechanism was more frequent in our study population compared with other studies [118, 119], although similar findings were observed in a nation-wide study in Denmark [120]. This result can

be explained by the higher frequency of mutation identification when testing X-chromosomes.

Onset of the most typical IRD visual symptoms was analyzed in eleven rare IRD. Early night blindness was detected in patients with rare forms of IRD such as LCA and BBD, as well as in STD and in IRD with predominantly rod involvement, such as X-RP, USH I syndrome, ADRP and RP-NSI. In contrast CHRD, CRD, and CD had a later onset of night blindness. Early night blindness onset was mostly typical for the IRD with predominantly peripheral visual field involvement such as LCA, BBD, X-RP, USH II, ADRP, as well as for STD patients (predominantly central visual field involvement). A high variation of the age at night blindness onset was noted in patients with ADRP. CD and CRD (predominantly central visual field involvement group) had an earlier onset of photophobia and decrease in visual acuity than is normally observed in these diseases, due to predominantly cone involvement in the pathological process [34]. Early onset of photophobia was also observed in BBD, LCA, and X-RP (predominantly peripheral visual field involvement group). Patients with X-RP and RP-NSI (predominantly peripheral visual field involvement) reported visual acuity decrease and visual field defects onset earlier than other types of RP, excluding LCA and BBD. CRD and CD (predominantly central visual field involvement) also noted visual acuity decrease early in life. Interestingly, patients with predominantly peripheral visual field involvement (LCA, BBD, USH I, X-RP, NSPI-RP) reported earlier visual field defects onset in comparison with those, who had a predominantly central visual field involvement.

During the analysis of the dependence of BCVA measured at first visit to the ophthalmologist versus the period between the age first experienced VA decrease and the first ophthalmological examination, it was noted that early onset RP and RP simplex had a more stable BCVA in comparison with other RP types. CRD patients had a shorter period between first VA decrease appearance and first visit to an ophthalmologist, and had on average worse BCVA at a first visit than RP. This indicates that RP patients have a more stable

BCVA through the disease and tend to visit an ophthalmologist later, whereas those RP patients who had an ophthalmological examination early in the disease history usually had some other symptom than VA decrease. Patients with CRD had a decrease of BCVA early in the disease and most of them tended to visit an ophthalmologist early in the disease. Our findings are in line with the observation that patients with CRD normally have a severe loss of visual acuity earlier than those with RP [34]. Previous studies of the visual acuity in RP patients showed that visual acuity can remain normal even in individuals in advanced disease stages, with only a small island of remaining visual field [121]. Furthermore, patients with RP are known to suffer irreversible and progressive loss of visual field as they age. Simple logistic regression showed that decrease in the visual field depended strongly on age [122]. Therefore, we speculate that the report of early decrease of visual acuity by some of RP patients, as well as the shorter period between the first experienced VA decrease and the first visit to an ophthalmologist in some RP patients can be explained by combined central and peripheral visual field defects that can potentially lead to the subjective perception of lowered visual acuity. The trend observed by us when plotting BCVA versus the period between first experienced VA decrease and the first visit to ophthalmologist in CRD was very similar to the trend of visual field area plotted against the period between the first VF defects experience and time of the ophthalmological examination, as measured by Massof et al., when studying a two-stage hypothesis for the natural course of retinitis pigmentosa [111].

A significant number of patients had BCVA within a normal range and only 6 patients were registered as legally blind according to the WHO definition. Previous findings indicate that it is rare for such patients to lose all vision in both eyes, and more than half of them retain good BCVA at a level less than 0.3 [32, 37]. Visual field defects were found to be often of a mixed nature. A combination of central scotoma and peripheral constriction was observed in patients with RP and CRD, while peripheral constriction with annular scotoma was observed in

CHRD patients. Follow-up studies of RP showed that the smallest amount of change occurred for visual acuity and the greatest amount of change occurred for visual field area [82]. Visual field defects in this disease tend to progress from mid-peripheral visual field loss to the loss of far peripheral vision, and then to the development of tunnel vision [121]. A combination of central and peripheral visual field defects can be explained by the advance of the disease. Although, RP is characterized by peripheral visual field loss, whereas CRD typically have central scotoma, both of these diseases in later stages are characterized by a combination of central and peripheral visual field loss, which explains our findings [34, 121].

Disease history such as typical age at onset of visual symptoms and clinical signs is important for the early identification and differential diagnosis of IRD and can guide clinicians through the diagnostic process. Nevertheless, these parameters alone are not sufficient for a final differential diagnosis. Evaluation of full-field and mfERGs is essential for the establishment of the final diagnosis of IRD.

Previous publications focused on the detection of normative values for full-field ERG parameters as well as values for single IRD types such as CD, CRD, and STD [123], the estimation of normal values for mfERG [124], or on the differential diagnosis of the subtypes of frequent IRD types such as differentiation between Usher syndrome subtypes [44]. Despite the very high value of this research, the comparison of the electrophysiological data between normal subjects and different IRD types as well as between IRD types is still largely lacking. Furthermore, there are no generally accepted qualitative and quantitative criteria for the reduction in electrophysiological parameters, which are necessary for the assessment of disease severity and are required to better communicate test results to patients.

Van Lith established that qualitative descriptions or labels of ERG wave-forms are less desirable to use in clinical practice than quantitative determinations

[125]. He proposed to determine the lower limit by obtaining a standard deviation value of 2 in reference to the mode, and then the reduction of amplitude was expressed in the percentage of the mode and the lower limit. Nevertheless, one could argue that the standard deviation would not be most optimal to use in order to characterize non-normally distributed ERG data. Therefore in this study non-parametric statistics (median and quantiles) were used to describe the ERG data. In addition, Fishman and coauthors noted that describing an ERG result as solely “subnormal” is inexact and in need of quantitative documentation [126]. Despite this fact, such qualitative descriptions are still quite often used to describe ERG data along with quantitative data. Therefore in this study we formulated the approach of using both quantitative and qualitative characteristics for full-field and mfERG data. Indeed, the interrelated use of qualitative and quantitative measures will assist in the comparison of electrophysiological data between disease groups and will increase the efficacy of communication of information to the patient. Moreover, quantitative and qualitative characteristics of ERG values can be further applied to the creation of software that will allow the automatic classification of the recording into a specific disease and degree of severity.

As a result of this study we were able to estimate the normal parameters of full-field and mfERG, which were used as a reference for the current study and could be potentially helpful in future studies. We also calculated the median and 25-75 and 5-95 quantiles for the random sample of IRD population that enabled us to define the criteria for qualitative assessment of full-field and mfERGs. Importantly, as a result of this study we calculated the median and 5-95 quantiles of each full-field ERG and mfERG parameter for each IRD type. Furthermore, medians of the identical parameters of full-field and mfERGs were compared between IRD types using a Kruskal-Wallis test. Observed differences can be used as a guideline for differential diagnosis of IRD. The qualitative characteristics of full-field and mfERG amplitudes were considered as moderately reduced if the amplitudes ranged from the maximum of IRD

population values to the 25th quantile of the IRD population median, and severely reduced if amplitudes were lower than the 25th quantile and higher than the minimum amplitude of the IRD population. Implicit times that were higher than maximal normal values and lower than the 75th quantile of IRD population values were characterized as moderately prolonged. Implicit times exceeding the 75th quantile and equal or exceeding the maximal implicit time values of IRD population median were categorized as severely prolonged.

We observed that patients with RP, despite their predominant affection of the rod system, also often had substantially decreased amplitudes and prolonged implicit times in photopic ERG. On the other hand CRD, besides the decrease of photopic amplitudes, were characterized by decreased scotopic amplitudes as well as prolonged implicit times. Similar findings were described by Fishman et al. [127] and can be interpreted in CRD as a sign of the beginning of cone involvement in the first stage and rod involvement in the second stage. Furthermore, our study also showed that USH I has significantly less prolonged mfERG implicit times than USH II, which corresponds to previous findings [44]. Interestingly, the described differences were mostly observed in peripheral mfERG rings, whereas in central rings these differences were not as obvious.

Full-field ERG has been shown to be a very useful tool for the early diagnosis of IRD when symptoms are not yet noticed by patients [128, 129]. The qualitative part of our study was performed on relatively large sample of patients, and was aimed at revealing specific qualitative differences that will allow further specification of typical electrophysiological signs and symptoms of rare IRDs. The qualitative study showed that scotopic amplitudes and implicit times were severely reduced and non-detectable in a majority of patients with retinitis pigmentosa, which indicates the presence of diffuse retinopathy [127]. Photopic ERG was characterized by more moderate changes in comparison with scotopic. Patients with RP frequently had moderately reduced implicit times in photopic ERG, which suggests that they were more likely to have a better prognosis [86]. Patients with CD and CRD had both reduced and prolonged

scotopic and photopic ERG with a predominance of scotopic changes, which is a sign of the beginning of a mixed cone-rod dystrophies processes, and can lead to difficulties in the differential diagnosis between cone-rod [130] and cone dystrophy patients [35]. MD was represented by a normal full-field ERG, which differentiates it from other IRD and conforms to the results of other studies [35]. The majority of patients with STD had scotopic and photopic full-field ERG within a normal range with moderately reduced amplitudes and moderately prolonged implicit times, which corresponds to previous findings [131]. A vast majority of patients with LCA and BBD had non-detectable or severely impaired full-field ERG [132-137], which suggests severe retinal dystrophies and unfavorable prognosis for the visual function of these patients. USH I had slightly more decreased amplitudes and more prolonged implicit times in comparison with USH II, which corresponds to the fact that USH I usually has earlier onset and progresses faster in comparison with USH II syndrome [43]. CACD was characterized by normal or moderately reduced amplitudes and normal or moderately prolonged implicit time in both scotopic and photopic conditions, which corresponds to previous findings [138, 139]. Photopic b-wave amplitude was severely reduced, which indicated continued disease progression [140].

With the progression of dystrophies, full-field ERG often becomes non-detectable and therefore has only a limited diagnostic utility. In such cases mfERG response can still be obtained. mfERG gives information about cone system dysfunction and is a very valuable tool for following up on disease progression and detecting spatial retinal changes. If recordable, mfERG implicit times were moderately and severely prolonged in USH I patients and non-detectable and severely reduced in USH II patients. Patients with MD had a predominantly central decrease of mfERG amplitude with slightly more normal values on the periphery and normal implicit time, which is in concordance with previous studies [141]. STD mfERG amplitudes were either moderately to severely reduced or non-detectable, and implicit times were moderately or

severely prolonged, with more severe changes in the center [142]. That RP patients had severely prolonged implicit time, as reported in previous studies, indicates cone system damage [143]. Implicit times in mfERG of patients with USH I showed a significantly milder change than in USH II patients, especially in the peripheral rings, which corresponds to findings in previous studies [44]. In our study mfERG was shown to be more sensitive in the evaluation of such disease as macular dystrophy, Stargardt disease, retinitis pigmentosa, Usher I, and Usher II syndromes.

This study is, to the best of our knowledge, the only study with evaluation of both full-field and mfERG in such a wide variety of IRD. Overall, these studies show that knowledge of the pattern of the onset of the key diagnostic symptoms provides an extra clue for clinicians and can guide them through the further diagnostic process. Specific electrophysiological signs of the vision system in a variety of IRD, along with knowledge of the pattern of the disease onset will be very helpful for the selection of patients for ongoing clinical trials.

The active development and testing of new treatment strategies for IRD requires efficient methods for testing their efficacy. It was shown that, although certain ERG amplitude measures did show positive correlations with some self-reported activities, overall, the ERG amplitude measures showed the least relationship with patients' self-reported data [90]. Thus, ERG alone cannot be used as a reliable test of the efficacy of clinical trials. Questionnaires for visual-related quality of life assessment were shown to be more sensitive than clinical parameters [105], therefore they should be used in parallel with the evaluation of visual function.

Visual-related quality of life (VRQL) is widely recognized as a patient related outcome and is used in clinical trials in the pharmaceutical industry [144, 145], and in assessment of the efficacy of rehabilitation measures [146]. Ongoing clinical trials for testing IRD treatments require a baseline for clinical trial efficacy assessment. Previous studies report on VRQL in different patients

populations such as patients with age-related macular degeneration [147, 148], refractive error [149], blepharospasm [150], cataract, and glaucoma [151]. Only few studies are devoted to the evaluation of the VRQL in patients with RP [90, 91, 93, 94]. These studies are mostly focused on the correlation between the results of the self-reported VRQL and BCVA/visual field or the efficacy of rehabilitation measures. The only up-to-date study related to the psychological well-being of patients taking part in a clinical trial for testing subretinal implants was done in the Tuebingen University Eye Hospital by Peters et al. [152]. The Brief Symptom Inventory that was used in the study allowed the evaluation of the emotional state of the patient, but did not give any idea on VRQL changes before and after implantation. Consequently, there is a high need for the assessment of VRQL in RP patients, which can be later used as background for clinical trials efficacy evaluation.

In our study we included patients with eleven rare inherited retinal degenerations. We were able to define VRQL changes in the overall IRD population, as well as for each IRD type and to reveal the differences between eleven rare IRD types. The results of the study showed that the composite score, role limitations, mental health, and dependence on others subscales were the most reduced in the IRD study population, as well as when stratifying by diagnosis. As a result, it is recommended to especially focus on the changes in the mentioned above subscales when following-up with patients with RP in any clinical trial.

As different IRD types are quite heterogeneous in their pathogenesis, main symptoms, and trends of progression, it is especially important to define differences in VRQL change. To the best of our knowledge, there are no previous studies that cover this question. Therefore, all subscales of NEI-VFQ-25 were compared across eleven rare IRD. The near and distance vision subscales were the most reduced in CRD, whereas the peripheral vision subscale was the most reduced in CRD, CHRD, USH II and RP. Role limitation was the most reduced in CACD, USH I and STD; mental health was the most

impaired in CSNB, CACD, CD, USH I; dependence on others in USH I, STD, USH II, and RP. The lowest composite score was noted in USH II and CACD. Revealed differences are very helpful for assessing the efficacy of clinical trials, and are of very high value for the planning of rehabilitation, dependent on diagnosis and the patient's individual needs.

Burstedt et al. found a strong relationship between objective tests of visual function and patient perceived VRQL as assessed by a questionnaire. Visual acuity was the strongest predictor of the variability of the composite score [91]. Nevertheless, previous studies did not identify which subscales of NEI-VFQ-25 were correlated with BCVA changes. In the current study it was found that lower general, near, distance vision, and social functioning scores were linked to BCVA decrease. We also found that a lower peripheral vision score was associated with concentric VF constriction. This finding is supported by the conclusion of Szlyk et al., who showed that a perceived difficulty in performing common tasks was most strongly related to level visual fields in patients with RP [90]. The results of this study provide insight into the VRQL changes both in overall IRD population as well as in eleven rare IRD types. These data will be used as a baseline for the assessment of clinical trials efficacy. Furthermore, the study of VRQL in the IRD population showed that women with IRD often had more reduced general health and ocular pain scores, whereas men reported lower general vision scores. Results obtained in the study will help to develop an individual approach to the assessment of clinical trials efficacy.

The studies that are part of the current dissertation have some limitations. The literature review that was performed to make an update on the epidemiology of ÍRD in Europe included all relevant papers without restriction to any specific ethnicity. Available publications did not adequately report on the epidemiology of these diseases in non-Caucasian populations. Therefore, the scope of the literature review was limited in order to perform a comprehensive analysis of data available on people of Caucasian origin. The issue of ethnic differences is quite complicated, and, unfortunately, rarely described in the literature.

Furthermore, most of the studies reported were based on the data from social sources and represented blindness data, rather than data on prevalence and incidence of IRD itself. Moreover, some caution is also advisable in a comparison of different epidemiological studies, especially from different European countries, since such studies often use different age group definitions and diagnostic methods.

We attempted to minimize this limitation by using very specific and strict inclusion criteria. The reported studies used similar diagnostic procedures and approaches. Where differences remained, we have clarified this to ensure the reliability of conclusions derived from this systematic literature review.

Further clinical studies had a retrospective cross-sectional design, and the data was obtained from a clinical database or patients' paper files, which were not initially designed for research purposes. This limited us to the analysis of data that were available. Furthermore, the age of symptoms onset estimation was based on the patients' perceptions, and therefore is subjective. The analysis was limited to information obtained during the patients' first visit to the eye hospital. The relatively small sample size of RP patients who were able to define their age at first VA decrease did not allow us to see a trend of VA change for all types of RP in the study of the pattern of the visual symptoms onset in IRD. It was also not always possible to record both full-field and mfERG in all patients due to difficulties resulting from nystagmus or other concentration problems.

The literature review study data represents the most recent and complete overview of (to the best of the authors' knowledge) all recent European studies on the epidemiology of IRD. A summary and comparison of overall and specific prevalence and incidence estimates of major eye diseases in Europe is presented, and the natural progression, economic impact, and methods of treatment were discussed.

The study on the use of epidemiological approach for the estimation of the disease onset in IRD was based on clinical data obtained from a database, and included all patients with a diagnosis of interest, whereas earlier studies performed by Krumpatszky derived data from social services and focused only on those patients that were already registered as blind. Furthermore, the study included a high percentage of patients originating from other countries, which will make it possible to more effectively compare to other non-German studies performed in the future.

The data for the study of the pattern of the visual symptoms onset was collected over a four-year period, which enabled us to obtain a relatively large sample size of patients with a wide variety of rare IRD. Patients with more prevalent and rare types of IRD were represented in the study population. Patients from all over Germany were represented in the study population, which allows us to conclude that the study population is representative of the whole IRD population in Germany and that the results of the study can be generalized. Moreover, we were able to see the main trend of VA change in RP and to compare it with VA change in CRD. We also were able to define the trend of visual acuity change for a few RP types. Further study of BCVA change in different types of RP requires a larger sample size for each of the observed types of RP inheritance. This is the first study in which a combined analysis of disease history and clinical data was done in such a wide variety of rare IRD types. The results of this study will give the reader a deeper understanding of IRD, and revealed the differences between its types.

The study on the typical clinical signs of the electrophysiology of the visual system in IRD was done on a sufficiently large sample size of a wide variety of rare IRD. In this study it was also possible to ascertain that patients with different IRD types were not different in respect to the disease duration, which removes selection bias and justifies the comparison between patients in this sample. The study led to the estimation of quantitative mf and full-field ERG criteria for normal subjects and a variety of IRD, which had not been done

before, and enables differentiation between different IRD types. Furthermore, it resulted in the formulation of qualitative criteria that will help to estimate the severity of IRD and to enhance doctor-patient communication. These criteria will be of high value for the estimation of prognosis as well as for planning rehabilitation and/or treatment measures.

The study on VRQL in the IRD population had a prospective cross-sectional design. All patients therefore were observed at one point in time and the information of the disease onset was not always available from all patients that took part in the study. Consequently, it was not possible to make sure that all patients were at the same disease stage, which can potentially lead to selection bias. Nevertheless, the prospective design of the study allowed us to collect all the information of interest. Furthermore, in comparison with previous studies we focused on the specification of the decrease in certain subscales and its correlation with visual function. We also were able to describe the differences between VRQL changes in eleven rare IRD. These results provide useful background for the assessment of new treatments. As the diseases we are studying are rare, it took a considerable amount of time in order to reach the achieved sample size. Nevertheless, some of the disease groups still had a relatively small sample size. Therefore further study is needed.

This dissertation gives the most recent and complete systematic literature meta-analysis on epidemiology of IRD, which will help researchers and patient organizations to better understand this question. It is the author's hope that these results will also lead to the establishment of a common set of preventative measures based on solid epidemiological data and will make it possible to monitor the effects of such prevention and intervention. Furthermore, this dissertation included the first study that showed that the age of disease onset in central and peripheral monogenic retinal dystrophies can be estimated on the basis of an epidemiological approach. The results are based on analysis of age at main symptoms onset, derived from the history of the disease and main clinical parameters, which can be used by clinicians to detect the duration of the

disease and its prognosis, to plan rehabilitation measures, and to research future possibilities for treatment.

This dissertation also covered the question of the pattern of the major visual symptoms onset. A comparison of such a wide variety of rare IRD has not been performed previously. It was shown that the pattern of major visual symptoms onset can provide an extra clue for early differential diagnosis of IRD, and can guide the clinician through the subsequent diagnostic process, although the final diagnosis requires a more refined approach. Additionally, it will play an important role in the early identification of patients that can benefit from new treatments in early disease stages. The study also showed that severe loss of visual acuity in patients with CRD occurs earlier than in RP, which in combination with mixed visual field defects can lead to early disability and requires special attention.

Moreover, this dissertation also includes a study of the special clinical signs of the visual system in IRD. This study was the first that led to the estimation of quantitative mf and full-field ERG criteria for normal subjects and a variety of IRD. We additionally derived qualitative criteria, which will help to estimate the severity IRD. It is often very difficult to differentiate between various types of IRD, especially in later stages of the disease. Furthermore, ophthalmologists specialized in such a wide range of IRD do not exist. The simultaneous application of quantitative and qualitative criteria in software for full-field and mfERG assessment is essential and will lead to a significant improvement in the efficacy and the precision of differential diagnosis, as well as the communication of results to the patient.

It is well known that clinical criteria are not sufficient for the assessment of treatment/rehabilitation efficacy in patients with visual impairment. In light of the successful development of treatment strategies for IRD, the estimation of a baseline for the effectiveness estimation is essential. There were no existing studies that provided this data. Our study on VRQL in patients with RP included

the assessment of VRQL change in the IRD population as a whole, as well as in eleven rare IRD types, which has not been done previously by other researchers. It was also possible to reveal differences between the VRQL changes in different types of IRD that should be considered when testing new treatments. Furthermore, the subscales that were correlated with BCVA and visual field changes were identified.

Overall, the results of the studies included in this dissertation will help to update researchers, politicians, and decision makers on the current state of epidemiology of eye diseases leading to blindness in Europe with special focus on IRD, and we hope they will stimulate further multi-centre, population based studies and will be provide a background for the increased funding of these studies. An epidemiological approach can be applied in clinical practice for differential diagnosis between central and peripheral IRD, as well as for prognosis estimation and finding possibilities for further treatment. Patterns of visual symptoms onset, together with quantitative and qualitative criteria for full-field and mfERG assessment, will be used for the creation of software for differential diagnosis and prognosis estimation, and are of very high importance for the selection of the patients for the clinical trials participation. The results of the VRQL study of patients with IRD will be essential background for the evaluation of new treatment strategies for IRD.

Abstract

This dissertation includes the most recent systematic literature meta-analysis on the epidemiology of inherited retinal degenerations (IRD) in Europe. Very few studies on the epidemiology of retinitis pigmentosa (RP) are nation-wide and population-based. Existing studies address only the most frequent forms of inherited retinal dystrophies (IRD) and do not provide data on prevalence and incidence of individual eye diseases. Only few studies deal with the onset and progression of IRD and none compares clinical electrophysiological data of different IRD types.

This shortcoming is addressed in a chapter that describes an epidemiological approach for estimating age of disease onset in central and peripheral IRD. Interestingly a relatively high number of patients in both groups retained quite good visual acuity. An age for optimal therapeutic intervention was defined.

Moreover the pattern of the onset of major visual symptoms in a variety of IRD was investigated, providing for the first time such a comprehensive analysis. It was shown that the pattern of major visual symptoms onset can provide an extra cue for early differential diagnosis of IRD. Moreover severe loss of visual acuity in patients with cone-rod dystrophies (CRD) in combination with mixed visual field defects can lead to early disability and requires special attention. This dissertation also includes a study of particular clinical signs of the visual system in IRD. Multifocal (mf) and full-field electroretinogram (ERG) of normal subjects is compared with those obtained in IRD.

A further chapter on visual-related quality of life (VRQL) in patients with RP includes the assessment of VRQL change in the IRD population as a whole, as well as in eleven rare IRD types, which has not been performed previously by others. It was also possible to reveal differences between the VRQL changes in different types of IRD, which should be considered when testing new treatments. This epidemiological approach can be applied in clinical practice for

differential diagnosis between central and peripheral IRD, as well as for prognosis estimation and selection of treatment strategies.

The results described here will help to properly inform researchers, politicians, and decision makers about the current state of the epidemiology of IRD in Europe and to stimulate further multi-centre population-based studies.

Zusammenfassung

In der vorliegenden Promotionsarbeit wird eine systematische Meta-Analyse der aktuellen Literatur zu erblichen Netzhautdystrophien (inherited retinal dystrophies, IRD) vorgestellt. Es gibt nur wenige Untersuchungen zur die Epidemiologie der Retinitis Pigmentosa, weder länderübergreifend noch auf der Grundlage von bestimmten Populationen. Vorhandene Studien beziehen sich nur auf die häufigsten Formen der angeborenen Netzhautdegenerationen und sagen nichts aus über die Ausbreitung und die Häufigkeit von einzelnen Augenerkrankungen. Nur wenige Studien widmen sich dem Auftreten und der Ausbreitung von IRD. Um diese Lücke zu füllen, beschreibt diese Promotionsarbeit eine epidemiologische Untersuchung des Anfangsalters der Patienten bei erstmaligem Auftreten von zentraler und peripherer IRD. Interessanterweise behielten Patienten in beiden Gruppen eine recht gute Sehschärfte. Das für eine Therapie am besten geeignete Alter wurde ermittelt. In einem weiteren Kapitel wurde das Muster der wichtigsten Symptome bei Netzhautdegenerationen erstmals untersucht. Das jeweilige, für eine Erkrankung typische Muster erstmals auftretender Symptome kann demnach als zusätzlicher Hinweis für eine frühzeitige Differentialdiagnose dienen. Der Verlust an Sehschärfe, kombiniert mit unterschiedlichen Gesichtsfeldstörungen führt zu einer frühen Behinderung und erfordert besondere Aufmerksamkeit.

Die Promotionsarbeit widmet sich auch den besonderen klinischen Zeichen im visuellen System bei IRD. Es wurden in dieser Studie erstmals quantitative Kriterien aufgestellt, um multifokale und Ganzfeld-Elektroretinogramme bei normalsichtigen und bei fehlsichtigen Probanden miteinander zu vergleichen. Es wurden qualitative Kriterien abgeleitet, die es ermöglichen, die Schwere der individuellen Erkrankung abzuschätzen.

Die vorliegende Studie über Sehvermögen-bezogene Lebensqualität (VRQL) in RP-Patienten beinhaltet erstmals eine Bewertung von VRQL-Veränderungen in der gesamten IRD-Population, wie auch in elf seltenen Formen von IRD. Es konnten unterschiedliche VRQL-Veränderungen bei unterschiedlichen Formen

von IRD aufgezeigt werden; bei der Evaluierung neuartiger Therapien sollten die Ergebnisse der VRQL-Studie berücksichtigt werden.

Dieser epidemiologische Ansatz dient in der klinischen Praxis der Differentialdiagnose zwischen zentraler und peripherer IRD, sowohl im Hinblick auf die Verlaufsprognose als auch auf die Wahl der therapeutischen Strategie.

Die hier vorgelegten Ergebnisse sollen auch dazu beitragen, Forschern, Politikern und Entscheidungsträgern den gegenwärtigen Stand der IRD-Epidemiologie in Europa zu vermitteln sowie weitere multizentrische, auf Populationen basierte Studien anzuregen.

Appendix 1. Comparison of full-field ERG values between different types of IRD and with normal values

Parameter/ IRD type	USH II	USH I	STD	RP	MD	CD	CRD	CHRD	CACD	BBD	Normal controls	Kruskal-Wallis-Test (Chi^2 test)
Rod b-wave amplitude, mV	nd	nd	124.67 (15.88; 189.9)	109.37 (19.24; 199.5)	166.295 (92.8; 300)	208.41 (128.8; 273.2)	79.92 (15.88; 130.2)	46.155 (25.95; 66.36)	100.67 (81.22; 115.7)	nd	292.93 (163.667; 435.602)	p=0.0001*
Rod b-wave implicit time, ms	nd	nd	98 (67.2; 131.5)	101.25 (88; 114.5)	103.5 (19; 121)	60.8 (17; 94)	104.75 (76;111)	65.5 (65;66)	91.9 (62; 106.5)	nd	84 (58.1; 97.1)	p=0.0097*
Maximum a-wave amplitude, mV	nd	nd	200.445 (64.82; 370.7)	81.155 (8.469; 254.8)	206.9 (199.95; 236.8)	137.75 (38.529; 220. 729)	63.44 (25.33; 193.5)	47.61 (21.84; 73.51)	132.15 (53.34; 174.68)	33.14 (27.22; 39.06)	227.07 (106.6; 322.2)	p=0.0001*
Maximum a-wave implicit time, ms	nd	nd	16.5 (15; 23)	16.3 (12; 24)	16.3 (15.5; 17)	17. 75 (15; 23.5)	23.5 (15.5; 24.5)	21 (16; 25)	18 (17;19.5)	2.4 (2.4;2.6)	16 (15.5;17)	p=0.004*
Maximum b-wave amplitude, mV	nd	nd	352.05 (97.9; 763.3)	177.42 (21.78; 467.6)	416.5 (292; 531.71)	292.4 (35.915; 412.361)	131.96 (14.32; 271.678)	90.08 (27.58; 108.9)	288.575 (140.3; 369)	55.32 (16.4;94.2)	415.185 (277;15; 640.05)	p=0.0001*

Maximum b-wave implicit time, ms	nd	nd	48 (34.4;63)	55.5 (51;84)	49 (41.6;53.5)	50.5 (35.32; 59.95)	48 (37.6; 78.5)	56 (40; 61)	42.7 (40; 59)	56.5 (46.4;66.6)	46 (42.25;55.75)	p=0.2221
OP amplitude, mV	nd	nd	42.53 (7.99; 109)	13.64 (6.48; 40.62)	40.6 (28.03; 80)	41.6 (37.6; 59)	17.315 (11.43; 40.13)	6 (3.716; 16.52)	34.54 (33.95; 35.41)	nd	78.83 (65.59; 95.06)	p=0.0001*
OP implicit time, ms	nd	nd	23.6 (22.4; 29.2)	24 (23.5; 28.8)	24.4 (23;24.8)	24.5 (23.6; 25.5)	25.4 (23.2; 32)	25.5 (24.8;29)	25.6 (24.8; 27.5)	nd	23.6 (22.5;24.7)	p=0.0012*
Photopic a-wave amplitude, mV	nd	nd	25.27 (8.623; 79.37)	21.53 (2.618; 41.56)	41.24 (25.53; 104.8)	22.455 (4.058; 63.68)	10.355 (0.4; 21.35)	12.442 (4.771; 27.49)	11.35 (10.06; 12.64)	nd	39.18 (15.81; 61.45)	p=0.0001*
Photopic a-wave implicit time, ms	nd	nd	15.5 (15;18.5)	17 (15.5;30)	15.5 (15; 19.6)	16 (15;17.125)	19.75 (16.75; 27.38)	22.16 (16.38; 26.8)	15.75 (15;16.5)	nd	14 (12.25; 16)	p=0.0001*
Photopic b-wave amplitude, mV	nd	16.09 (13.23; 26.16)	110.645 (12.829; 225.8605)	24.39 (6.1; 172.7)	147.36 (110.4; 214.55)	66.435 (6.43; 141.4)	30.59 (7.587; 68.97)	19.82 (2.771; 58.12)	97.1 (45.14; 137.89)	19.74 (10; 46.94)	171.13 (79.41; 271.38)	p=0.0001*
Photopic b-wave implicit time, ms	nd	33.6 (31.2; 37.2)	31.2 (27.1; 41.33)	38.4 (29;59)	30.5 (26.2; 59.4)	32.75 (29.4; 42.58)	38 (17.85; 74.4)	35.4 (30; 43.9)	31 (30.6; 34.2)	48.8 (42.8; 49.8)	30(28;33)	p=0.0001*

30 Hz flicker wave amplitude, mV	44.47 (16.64; 72.3)	6.93 (5.47; 8.45)	65.515 (24.88; 179.456)	10.82 (2.22; 103)	90.81 (57.48; 111.6)	32.83 (4.54; 108.51)	22.19 (2.812; 67.5)	16.64 (3.12; 39.17)	54.09 (25.45; 104.62)	18.185 (9.12;20)	101.41 (59.676;136.958)	p=0.0001*
30 Hz flicker implicit time, ms	32 (30; 72.6)	62.4 (60; 62.4)	60.5 (47.4;73.2)	68.9 (45; 78)	59.5 (58.2; 61)	64.5 (52.6; 75.9)	69 (60; 75)	71.4 (30.5; 75.5)	62.4 (61.8; 65)	75.9 (65;76.8)	59 (48.3; 61.85)	p=0.0001*

nd- not detectable; *-indicates that the difference was found to be statistically significant; 5^{th} and 95^{th} quantiles are indicated in brackets; Kruskal-Wallis test (Chi^2-test for more than 2 groups) was used for the comparison of IRD subgroups and with subjects with normal ophthalmological finding.

Appendix 2. Comparison of mfERG values between different types of IRD and with normal values

Parameters/IRD types	USH II	USH I	STD	RP	MD	CD	CRD	CHRD	CACD	BBD	Normal controls	Kruskal-Wallis-Test (Chi^2 test)
RI Amplitude, mV	12.9 (7; 43.9)	12.55 (10.8; 14.3)	12.65 (7.2; 38.1)	20.3 (5.5; 39.5)	27.4 (12.5; 63)	16.9 (6.9; 33.5)	20.2 (3.7;28.1)	17.7 (4.8; 45.8)	15.4 (8.6; 30.9)	nd	61.3 (25.17; 84. 82)	p=0.0001*
RII Amplitude, mV	4.4 (2.3;10.1)	9.1 (6.6; 21.4)	7.8 (3.9; 25.5)	6 (2.3; 21.6)	15.4 (5.5; 39.4)	7.4 (1.9; 17.3)	5.35 (1.6;15.4)	6.4 (1.1; 21.6)	9.1 (6.6; 39.4)	nd	23.25 (11.2; 36.07)	p=0.0001*
RIII Amplitude, mV	6.1 (2.3;10.1)	4.5 (2.3;5.7)	8.4 (3.1; 23.7)	2.85 (0.7; 15.4)	14.8 (9.1; 25.6)	5.7 (1.2; 18.5)	2.4 (0.1; 12.8)	2.9 (0.8; 10.6)	6.45 (2.2; 9.2)	nd	15.65 (8.3; 22.4)	p=0.0001*
RIV Amplitude, mV	1.4 (1.1;1.5)	1.4 (0.9; 2)	8.95 (2.6; 22.8)	2.1 (0.4; 10.7)	11.7 (8.1;19.3)	2.95 (1.1; 18.3)	2.15 (0.9;11.8)	2.6 (1.2; 5.7)	6.85 (2.5;7.6)	nd	11.65 (5.3;16.3)	p=0.0001*
RV Amplitude, mV	1.4 (1.3;1.6)	nd	10.5 (4.7; 14.03)	2.4 (0.5;10.8)	12.1 (7.4;18.8)	3.3 (1.3; 9.2)	2.1 (1.5;11.4)	2.1 (0.9; 10.15)	7.65 (3.4; 9.2)	nd	10.35 (4.7; 14.03)	p=0.0001*
RI Implicit time, ms	28.3 (26.6; 29.9)	27.5 (27.4; 29.2)	31.5 (24.9; 40)	30.8 (20.8; 36.7)	30 (26.7; 35.8)	31.25 (25.8; 40)	30 (25.7; 35)	33.75 (28.3; 42.3)	33.3 (33.2; 37.5)	nd	29.2 (25.8; 34.16)	p=0.0032*
RII Implicit time, ms	29.1 (28.3; 33.2)	29.2 (26.6; 31.6)	30.8 (28.2; 44.1)	30.7 (19.2; 37.5)	30 (15.4; 33.3)	30.7 (25.44.1)	32.9 (27.4. 41.1)	32.85 (24.2; 44)	34.55 (32.4; 39.1)	nd	29.2 (26.7; 39.2)	p=0.0382*
RIII Implicit time, ms	39.1 (32.5; 52.5)	29.1 (26.6; 30.8)	29.95 (28.2; 47.08)	30.8 (27.5; 41.5)	29.2 (11.4; 31.7)	32.4 (25; 40.8)	35.3 (0.8; 63.2)	32.85 (28.3; 37.4)	34.55 (32.4; 36.7)	nd	28.75 (26.7; 32.41)	p=0.0001*
RIV Implicit time, ms	40.8 (33.3; 48.3)	30 (26.6; 35.8)	30.4 (28.2; 46.72)	32.1 (28.3; 44)	30 (9.1; 31.7)	32.1 (28.3; 44)	37.45 (30; 60.7)	32.85 (28.3; 36.7)	34.55 (33.2; 35)	nd	28.3 (25.8; 32.4)	p=0.0001*
RV Implicit time, ms	40.8 (37.7; 48.3)	nd	30.35 (29.1; 43.85)	32.9 (26.7; 46.6)	30 (8.5;33.2)	32.9 (26.7; 46.6)	37.45 (30.8; 69.1)	35.8 (29.9; 41.6)	32.9 (28.2; 34.2)	nd	28.3 (26.7; 33;2)	p=0.0001*

nd- not detectable; *-indicates that the difference was found to be statistically significant; 5^{th} and 95^{th} quantiles are indicated in brackets; Kruskal-Wallis test (Chi^2-test for more than 2 groups) was used for the comparison of IRD subgroups and with subjects with normal ophthalmological finding.

Bibliography

1. West, S. and A. Sommer, Prevention of blindness and priorities for the future. Bull World Health Organ, 2001. **79**(3): p. 244-8.

2. Kocur, I. and S. Resnikoff, Visual impairment and blindness in Europe and their prevention. Br J Ophthalmol, 2002. **86**(7): p. 716-22.

3. Gohdes, D.M., A. Balamurugan, B.A. Larsen, and C. Maylahn, Age-related eye diseases: an emerging challenge for public health professionals. Prev Chronic Dis, 2005. **2**(3): p. A17.

4. van Leeuwen, R., C.C. Klaver, J.R. Vingerling, A. Hofman, and P.T. de Jong, The risk and natural course of age-related maculopathy: follow-up at 6 1/2 years in the Rotterdam study. Arch Ophthalmol, 2003. **121**(4): p. 519-26.

5. Augood, C.A., J.R. Vingerling, P.T. de Jong, U. Chakravarthy, J. Seland, G. Soubrane, L. Tomazzoli, F. Topouzis, G. Bentham, M. Rahu, J. Vioque, I.S. Young, and A.E. Fletcher, Prevalence of age-related maculopathy in older Europeans: the European Eye Study (EUREYE). Arch Ophthalmol, 2006. **124**(4): p. 529-35.

6. Cohen, D., M. Sartral, P. Nounou, M. Hamar, M.E. Drouard, A. El Alamy, and K. Bendeddouche, [Evaluation of moderate and severe visual impairments in patients attending an ophthalmology clinic. A prospective study of 1,172 patients]. J Fr Ophtalmol, 2000. **23**(5): p. 437-43.

7. Gruener, F., Pravalenz, Inzidenz und Ursache von Blindheit und wesentlicher Sehbehinderung in Hessen, Marburg. 2001, Philipps-Universitat: Marburg.

8. Despriet, D.D., C.C. Klaver, J.C. Witteman, A.A. Bergen, I. Kardys, M.P. de Maat, S.S. Boekhoorn, J.R. Vingerling, A. Hofman, B.A. Oostra, A.G. Uitterlinden, T. Stijnen, C.M. van Duijn, and P.T. de Jong, Complement factor H polymorphism, complement activators, and risk of age-related macular degeneration. JAMA, 2006. **296**(3): p. 301-9.

9. Bannikova, R.V., A.L. Sannikov, and A.V. Konovalov, [Characteristics of ophthalmic pathology under the conditions of the European North of Russia]. Probl Sotsialnoi Gig Zdravookhranenniiai Istor Med, 2002(3): p. 35-6.

10. Klaver, C.C., J.J. Assink, R. van Leeuwen, R.C. Wolfs, J.R. Vingerling, T. Stijnen, A. Hofman, and P.T. de Jong, Incidence and progression rates of age-related maculopathy: the Rotterdam Study. Invest Ophthalmol Vis Sci, 2001. **42**(10): p. 2237-41.

11. Kristinsson, J.K., Diabetic retinopathy. Screening and prevention of blindness. A doctoral thesis. Acta Ophthalmol Scand Suppl, 1997(223): p. 1-76.

12. Resnikoff, S., D. Pascolini, D. Etya'ale, I. Kocur, R. Pararajasegaram, G.P. Pokharel, and S.P. Mariotti, Global data on visual impairment in the year 2002. Bull World Health Organ, 2004. **82**(11): p. 844-51.

13. Simmons, D., G. Clover, and C. Hope, Ethnic differences in diabetic retinopathy. Diabet Med, 2007. **24**(10): p. 1093-8.

14. Keen, H., E.T. Lee, D. Russell, E. Miki, P.H. Bennett, and M. Lu, The appearance of retinopathy and progression to proliferative retinopathy: the WHO Multinational Study of Vascular Disease in Diabetes. Diabetologia, 2001. **44 Suppl 2**: p. S22-30.

15. Krumpaszky, H.G., R. Ludtke, A. Mickler, V. Klauss, and H.K. Selbmann, Blindness incidence in Germany. A population-based study from Wurttemberg-Hohenzollern. Ophthalmologica, 1999. **213**(3): p. 176-82.

16. Michelson, G. and M.J. Groh, Screening models for glaucoma. Curr Opin Ophthalmol, 2001. **12**(2): p. 105-11.

17. Shurshukov, Y.Y., I.M. Konovalov, E.S. Savelieva, and A.V. Konovalova, Investigation of distribution of eye diseases and supplementary apparatus basing on the monitoring data. Zdravoochrananie Rossiiskoi Federatii, 2007(4): p. 53-54.

18. Bourne, R.R., Worldwide glaucoma through the looking glass. Br J Ophthalmol, 2006. **90**(3): p. 253-4.

19. Thylefors, B. and A.D. Negrel, The global impact of glaucoma. Bull World Health Organ, 1994. **72**(3): p. 323-6.

20. Weinreb, R.N. and P.T. Khaw, Primary open-angle glaucoma. Lancet, 2004. **363**(9422): p. 1711-20.

21. Gray, S.F., P.G. Spry, S.T. Brookes, T.J. Peters, I.C. Spencer, I.A. Baker, J.M. Sparrow, and D.L. Easty, The Bristol shared care glaucoma study: outcome at follow up at 2 years. Br J Ophthalmol, 2000. **84**(5): p. 456-63.

22. Anton, A., M.T. Andrada, V. Mujica, M.A. Calle, J. Portela, and A. Mayo, Prevalence of primary open-angle glaucoma in a Spanish population: the Segovia study. J Glaucoma, 2004. **13**(5): p. 371-6.

23. Owen, C.G., I.M. Carey, S. De Wilde, P.H. Whincup, R. Wormald, and D.G. Cook, The epidemiology of medical treatment for glaucoma and ocular hypertension in the United Kingdom: 1994 to 2003. Br J Ophthalmol, 2006. **90**(7): p. 861-8.

24. Abraham, A.G., N.G. Condon, and E. West Gower, The new epidemiology of cataract. Ophthalmol Clin North Am, 2006. **19**(4): p. 415-25.

25. Мошетова, Л.К., А.П. Нестеров, and Е.А. Егоров, Катаракта, in Офтальмология. Клинические рекомендации., Л.К. Мошетова, А.П. Нестеров, and Е.А. Егоров, Editors. 2008, ГЭОТАР-Медиа: Москва. p. 72-83.

26. Das, B.N., J.R. Thompson, R. Patel, and A.R. Rosenthal, The prevalence of eye disease in Leicester: a comparison of adults of Asian and European descent. J R Soc Med, 1994. **87**(4): p. 219-22.

27. Giuffre, G., R. Giammanco, F. Di Pace, and F. Ponte, Casteldaccia eye study: prevalence of cataract in the adult and elderly population of a Mediterranean town. Int Ophthalmol, 1994. **18**(6): p. 363-71.

28. Blum, M., C. Kloos, N. Muller, A. Mandecka, R. Berner, B. Bertram, and U.A. Muller, [Prevalence of diabetic retinopathy. Check-up program of a public health insurance company in Germany 2002-2004]. Ophthalmologe, 2007. **104**(6): p. 499-500, 502-4.

29. Navarro Esteban, J.J., J.A. Gutierrez Leiva, N. Valero Caracena, J. Buendia Bermejo, M.E. Calle Puron, and V.J. Martinez Vizcaino, Prevalence and risk factors of lens opacities in the elderly in Cuenca, Spain. Eur J Ophthalmol, 2007. **17**(1): p. 29-37.

30. Krumpaszky, H.G. and V. Klauss, Epidemiology of blindness and eye disease. Ophthalmologica, 1996. **210**(1): p. 1-84.

31. Puech, B., B. Kostrubiec, J.C. Hache, and P. Francois, [Epidemiology and prevalence of hereditary retinal dystrophies in the Northern France]. J Fr Ophtalmol, 1991. **14**(3): p. 153-64.

32. Prokofyeva, E., R. Wilke, G. Lotz, E. Troeger, T. Strasser, and E. Zrenner, An epidemiological approach for the estimation of disease onset in Central Europe in central and peripheral monogenic retinal dystrophies. Graefes Arch Clin Exp Ophthalmol, 2009. **247**(7): p. 885-94.

33. Heckenlively, J.R., S.L. Yoser, L.H. Friedman, and J.J. Oversier, Clinical findings and common symptoms in retinitis pigmentosa. Am J Ophthalmol, 1988. **105**(5): p. 504-11.

34. Hamel, C.P., Cone rod dystrophies. Orphanet J Rare Dis, 2007. **2**: p. 7.

35. Lam, B., Electrophysiology of vision. Clinical testing and applications. Vol. 33487-2742. 2005, Boca Raton, FL: Taylor and Francis Group. 507.

36. Berson, E.L., B. Rosner, C. Weigel-DiFranco, T.P. Dryja, and M.A. Sandberg, Disease progression in patients with dominant retinitis pigmentosa and rhodopsin mutations. Invest Ophthalmol Vis Sci, 2002. **43**(9): p. 3027-36.

37. Grover, S., G.A. Fishman, R.J. Anderson, M.S. Tozatti, J.R. Heckenlively, R.G. Weleber, A.O. Edwards, and J. Brown, Jr., Visual acuity

impairment in patients with retinitis pigmentosa at age 45 years or older. Ophthalmology, 1999. **106**(9): p. 1780-5.

38. Grover, S., G.A. Fishman, and J. Brown, Jr., Patterns of visual field progression in patients with retinitis pigmentosa. Ophthalmology, 1998. **105**(6): p. 1069-75.

39. Thiadens, A.A. and C.C. Klaver, Genetic testing and clinical characterization of patients with cone-rod dystrophy. Invest Ophthalmol Vis Sci, 2010. **51**(12): p. 6904-5.

40. Simunovic, M.P. and A.T. Moore, The cone dystrophies. Eye (Lond), 1998. **12 (Pt 3b)**: p. 553-65.

41. Traboulsi, E.I., The Marshall M. Parks memorial lecture: making sense of early-onset childhood retinal dystrophies--the clinical phenotype of Leber congenital amaurosis. Br J Ophthalmol, 2010. **94**(10): p. 1281-7.

42. Abu Safieh, L., M.A. Aldahmesh, H. Shamseldin, M. Hashem, R. Shaheen, H. Alkuraya, S.A. Al Hazzaa, A. Al-Rajhi, and F.S. Alkuraya, Clinical and molecular characterisation of Bardet-Biedl syndrome in consanguineous populations: the power of homozygosity mapping. J Med Genet, 2010. **47**(4): p. 236-41.

43. Tsilou, E.T., B.I. Rubin, R.C. Caruso, G.F. Reed, A. Pikus, J.F. Hejtmancik, F. Iwata, J.B. Redman, and M.I. Kaiser-Kupfer, Usher syndrome clinical types I and II: could ocular symptoms and signs differentiate between the two types? Acta Ophthalmol Scand, 2002. **80**(2): p. 196-201.

44. Seeliger, M.W., E. Zrenner, E. Apfelstedt-Sylla, and G.B. Jaissle, Identification of Usher syndrome subtypes by ERG implicit time. Invest Ophthalmol Vis Sci, 2001. **42**(12): p. 3066-71.

45. Renner, A.B., H. Tillack, H. Kraus, S. Kohl, B. Wissinger, N. Mohr, B.H. Weber, U. Kellner, and M.H. Foerster, Morphology and functional

characteristics in adult vitelliform macular dystrophy. Retina, 2004. **24**(6): p. 929-39.

46. Walia, S. and G.A. Fishman, Natural history of phenotypic changes in Stargardt macular dystrophy. Ophthalmic Genet, 2009. **30**(2): p. 63-8.

47. Ohba, N. and Y. Isashiki, Clinical and genetic features of choroideremia. Jpn J Ophthalmol, 2000. **44**(3): p. 317.

48. Knauer, C. and N. Pfeiffer, [Blindness in Germany--today and in 2030]. Ophthalmologe, 2006. **103**(9): p. 735-41.

49. Krumpatszky, H.G., Epidemiology of blindness and eye disease. Ophthalmologica 1996. **210**: p. 1–84

50. Bok, D., Contributions of genetics to our understanding of inhereted monogenic retinal diseases and age-related macular degeneration. Arch Ophthalmol, 2007. **125**: p. 160-164.

51. Jacobson, S.G., T.S. Aleman, A.V. Cideciyan, A. Sumaroka, S.B. Schwartz, E.A. Windsor, E.I. Traboulsi, E. Heon, S.J. Pittler, A.H. Milam, A.M. Maguire, K. Palczewski, E.M. Stone, and J. Bennett, Identifying photoreceptors in blind eyes caused by RPE65 mutations: Prerequisite for human gene therapy success. Proc Natl Acad Sci U S A, 2005. **102**(17): p. 6177-82.

52. Tan, M.H., A.J. Smith, B. Pawlyk, X. Xu, X. Liu, J.B. Bainbridge, M. Basche, J. McIntosh, H.V. Tran, A. Nathwani, T. Li, and R.R. Ali, Gene therapy for retinitis pigmentosa and Leber congenital amaurosis caused by defects in AIPL1: effective rescue of mouse models of partial and complete Aipl1 deficiency using AAV2/2 and AAV2/8 vectors. Hum Mol Genet, 2009. **18**(12): p. 2099-114.

53. Tam, L.C., A.S. Kiang, A. Kennan, P.F. Kenna, N. Chadderton, M. Ader, A. Palfi, A. Aherne, C. Ayuso, M. Campbell, A. Reynolds, A. McKee, M.M. Humphries, G.J. Farrar, and P. Humphries, Therapeutic benefit derived from RNAi-mediated ablation of IMPDH1 transcripts in a murine model of autosomal

dominant retinitis pigmentosa (RP10). Hum Mol Genet, 2008. **17**(14): p. 2084-100.

54. Chambers, J.J., M.R. Banghart, D. Trauner, and R.H. Kramer, Light-induced depolarization of neurons using a modified Shaker K(+) channel and a molecular photoswitch. J Neurophysiol, 2006. **96**(5): p. 2792-6.

55. Banghart, M., K. Borges, E. Isacoff, D. Trauner, and R.H. Kramer, Light-activated ion channels for remote control of neuronal firing. Nat Neurosci, 2004. **7**(12): p. 1381-6.

56. Szobota, S., P. Gorostiza, F. Del Bene, C. Wyart, D.L. Fortin, K.D. Kolstad, O. Tulyathan, M. Volgraf, R. Numano, H.L. Aaron, E.K. Scott, R.H. Kramer, J. Flannery, H. Baier, D. Trauner, and E.Y. Isacoff, Remote control of neuronal activity with a light-gated glutamate receptor. Neuron, 2007. **54**(4): p. 535-45.

57. Lagali, P.S., D. Balya, G.B. Awatramani, T.A. Munch, D.S. Kim, V. Busskamp, C.L. Cepko, and B. Roska, Light-activated channels targeted to ON bipolar cells restore visual function in retinal degeneration. Nat Neurosci, 2008. **11**(6): p. 667-75.

58. Nagel, G., T. Szellas, W. Huhn, S. Kateriya, N. Adeishvili, P. Berthold, D. Ollig, P. Hegemann, and E. Bamberg, Channelrhodopsin-2, a directly light-gated cation-selective membrane channel. Proc Natl Acad Sci U S A, 2003. **100**(24): p. 13940-5.

59. Boyden, E.S., F. Zhang, E. Bamberg, G. Nagel, and K. Deisseroth, Millisecond-timescale, genetically targeted optical control of neural activity. Nat Neurosci, 2005. **8**(9): p. 1263-8.

60. Bi, A., J. Cui, Y.P. Ma, E. Olshevskaya, M. Pu, A.M. Dizhoor, and Z.H. Pan, Ectopic expression of a microbial-type rhodopsin restores visual responses in mice with photoreceptor degeneration. Neuron, 2006. **50**(1): p. 23-33.

61. Lin, B., A. Koizumi, N. Tanaka, S. Panda, and R.H. Masland, Restoration of visual function in retinal degeneration mice by ectopic expression of melanopsin. Proc Natl Acad Sci U S A, 2008. **105**(41): p. 16009-14.

62. Dong, A., J. Shen, M. Krause, S.F. Hackett, and P.A. Campochiaro, Increased expression of glial cell line-derived neurotrophic factor protects against oxidative damage-induced retinal degeneration. J Neurochem, 2007. **103**(3): p. 1041-52.

63. Schnapf, J.L., T.W. Kraft, and D.A. Baylor, Spectral sensitivity of human cone photoreceptors. Nature, 1987. **325**(6103): p. 439-41.

64. Wang, H., J. Peca, M. Matsuzaki, K. Matsuzaki, J. Noguchi, L. Qiu, D. Wang, F. Zhang, E. Boyden, K. Deisseroth, H. Kasai, W.C. Hall, G. Feng, and G.J. Augustine, High-speed mapping of synaptic connectivity using photostimulation in Channelrhodopsin-2 transgenic mice. Proc Natl Acad Sci U S A, 2007. **104**(19): p. 8143-8.

65. Gerding, H., [Development of a minimally invasive retinal implant system]. Ophthalmologe, 2008. **105**(5): p. 463-73.

66. Stieglitz, T., Development of a micromachined epiretinal vision prosthesis. J Neural Eng, 2009. **6**(6): p. 065005.

67. Zrenner, E., Will retinal implants restore vision? Science, 2002. **295**(5557): p. 1022-5.

68. Zrenner, E., The subretinal implant: can microphotodiode arrays replace degenerated retinal photoreceptors to restore vision? Ophthalmologica, 2002. **216 Suppl 1**: p. 8-20; discussion 52-3.

69. Grondahl, J., Estimation of prognosis and prevalence of retinitis pigmentosa and Usher syndrome in Norway. Clin Genet, 1987. **31**(4): p. 255-64.

70. Peterlin, B., N. Canki-Klain, V. Morela, B. Stirn, S. Rainer, and V. Cerar, Prevalence of retinitis pigmentosa in Slovenia. Clin Genet, 1992. **42**(3): p. 122-3.

71. Rosenberg, T., M. Haim, A.M. Hauch, and A. Parving, The prevalence of Usher syndrome and other retinal dystrophy-hearing impairment associations. Clin Genet, 1997. **51**(5): p. 314-21.

72. Spandau, U.H. and K. Rohrschneider, Prevalence and geographical distribution of Usher syndrome in Germany. Graefes Arch Clin Exp Ophthalmol, 2002. **240**(6): p. 495-8.

73. Michaelides, M., D.M. Hunt, and A.T. Moore, The genetics of inherited macular dystrophies. J Med Genet, 2003. **40**(9): p. 641-50.

74. Kellner, U., H. Tillack, and A.B. Renner, [Hereditary retinochoroidal dystrophies. Part 1: Pathogenesis, diagnosis, therapy and patient counselling]. Ophthalmologe, 2004. **101**(3): p. 307-19; quiz 320.

75. Rozet, J.M., S. Gerber, D. Ducroq, C. Hamel, J.L. Dufier, and J. Kaplan, [Hereditary macular dystrophies]. J Fr Ophtalmol, 2005. **28**(1): p. 113-24.

76. Tous, H.M. and N.J. Izquierdo, Retinitis pigmentosa in Puerto Rico. P R Health Sci J, 2006. **25**(4): p. 315-8.

77. Ayuso, C., B. Garcia-Sandoval, C. Najera, D. Valverde, M. Carballo, and G. Antinolo, Retinitis pigmentosa in Spain. The Spanish Multicentric and Multidisciplinary Group for Research into Retinitis Pigmentosa. Clin Genet, 1995. **48**(3): p. 120-2.

78. van den Born, L.I., A.A. Bergen, and E.M. Bleeker-Wagemakers, A retrospective study of registered retinitis pigmentosa patients in The Netherlands. Ophthalmic Paediatr Genet, 1992. **13**(4): p. 227-36.

79. Corbett, M.C., J.S. Shilling, and G.E. Holder, The assessment of clinical investigations: the Greenwich Grading System and its application to

electrodiagnostic testing in ophthalmology. Eye (Lond), 1995. **9 (Pt 6 Su)**: p. 59-64.

80. Berson, E.L., Electroretinographic findings in retinitis pigmentosa. Jpn J Ophthalmol, 1987. **31**(3): p. 327-48.

81. Iannaccone, A., E. Rispoli, E.M. Vingolo, P. Onori, K. Steindl, D. Rispoli, and M.R. Pannarale, Correlation between Goldmann perimetry and maximal electroretinogram response in retinitis pigmentosa. Doc Ophthalmol, 1995. **90**(2): p. 129-42.

82. Holopigian, K., V. Greenstein, W. Seiple, and R.E. Carr, Rates of change differ among measures of visual function in patients with retinitis pigmentosa. Ophthalmology, 1996. **103**(3): p. 398-405.

83. Berson, E.L., B. Rosner, M.A. Sandberg, K.C. Hayes, B.W. Nicholson, C. Weigel-DiFranco, and W. Willett, A randomized trial of vitamin A and vitamin E supplementation for retinitis pigmentosa. Arch Ophthalmol, 1993. **111**(6): p. 761-72.

84. Hood, D.C., Assessing retinal function with the multifocal technique. Prog Retin Eye Res, 2000. **19**(5): p. 607-46.

85. Langrova, H., E. Zrenner, A. Kurtenbach, and M.W. Seeliger, Age-Related Changes in Retinal Functional Topography. Invest. Ophthalmol. Vis. Sci., 2008. **49**(11): p. 5024-5032.

86. Iijima, H., S. Yamaguchi, and O. Hosaka, Photopic electroretinogram implicit time in retinitis pigmentosa. Jpn J Ophthalmol, 1993. **37**(2): p. 130-5.

87. Scholl, H.P., H. Langrova, C.M. Pusch, B. Wissinger, E. Zrenner, and E. Apfelstedt-Sylla, Slow and fast rod ERG pathways in patients with X-linked complete stationary night blindness carrying mutations in the NYX gene. Invest Ophthalmol Vis Sci, 2001. **42**(11): p. 2728-36.

88. Nagy, D., B. Schonfisch, E. Zrenner, and H. Jagle, Long-term follow-up of retinitis pigmentosa patients with multifocal electroretinography. Invest Ophthalmol Vis Sci, 2008. **49**(10): p. 4664-71.

89. Finger, R.P., H.P. Scholl, and F.G. Holz, [Patient reported outcomes. Relevance and application in ophthalmology]. Ophthalmologe, 2008. **105**(8): p. 722-6.

90. Szlyk, J.P., G.A. Fishman, K.R. Alexander, B.I. Revelins, D.J. Derlacki, and R.J. Anderson, Relationship between difficulty in performing daily activities and clinical measures of visual function in patients with retinitis pigmentosa. Arch Ophthalmol, 1997. **115**(1): p. 53-9.

91. Burstedt, M.S., E. Monestam, and O. Sandgren, Associations between specific measures of vision and vision-related quality of life in patients with bothnia dystrophy, a defined type of retinitis pigmentosa. Retina, 2005. **25**(3): p. 317-23.

92. Fanke GH, E.J., The psychological impact of visual impairment in patients of different age, in Special Needs of Blind and Low vision, S.H.-E. Wahl H-W, Editor. 2001, IOS Press.

93. Turano, K.A., D.R. Geruschat, J.W. Stahl, and R.W. Massof, Perceived visual ability for independent mobility in persons with retinitis pigmentosa. Invest Ophthalmol Vis Sci, 1999. **40**(5): p. 865-77.

94. Szlyk, J.P., W. Seiple, G.A. Fishman, K.R. Alexander, S. Grover, and C.L. Mahler, Perceived and actual performance of daily tasks: relationship to visual function tests in individuals with retinitis pigmentosa. Ophthalmology, 2001. **108**(1): p. 65-75.

95. Tröger, E., E. Prokofyeva, R. Wilke, and E. Zrenner, Reusability in patient registries-Implamention of genericextensible web-based Patient registry system, in Second International Conference on Health Informatics, HEALTHINF 2009, L.A. Azevedo L, Editor. 2009, INSTICC Press: Porto, Portugal. p. 438-441.

96. Tröger, E., R. Wilke, E. Prokofyeva, and E. Zrenner, Ophthabase: a generic extensible patient registry system. Acta Ophthalmologica, 2008. **86**(s243): p. 0-0.

97. International Statistical Classification of Diseases and Related Health Problems 10th revision Current version Version for 2003 Chapter VII H54 Blindness and low vision. 2003 05.04.2006 [cited 2009 15.09.2009]; Available from: http://www.who.int/classifications/icd/en/

98. McGill, R., J.W. Tukey, and W.A. Larse, Variations of Boxplots. The American Statistician, 1978. **32**: p. 12-16.

99. Kruskal, W.H. and W.A. Wallis, Use of ranks in one-criterion variance analysis. Journal of the American Statistical Association, 1952. **47**(260): p. 583–621.

100. Maritz, J.S., Jarrett, R.G., A Note on Estimating the Varience of the Sample Median. Journal of American Statistical Association, 1978. **73**(361): p. 194 -196.

101. Marmor, M.F., A.B. Fulton, G.E. Holder, Y. Miyake, M. Brigell, and M. Bach, ISCEV Standard for full-field clinical electroretinography (2008 update). Doc Ophthalmol, 2009. **118**(1): p. 69-77.

102. Sutter, E.E. and D. Tran, The field topography of ERG components in man--I. The photopic luminance response. Vision Res, 1992. **32**(3): p. 433-46.

103. E Tröger, E.P., R Wilke, E Zrenner Reusability in patient registries-Implamention of genericextensible web-based Patient registry system, in Second International Conference on Health Informatics, HEALTHINF 2009, L.A. Azevedo L, Editor. 2009, INSTICC Press: Porto, Portugal. p. 438-441.

104. Mangione, C.M., P.P. Lee, J. Pitts, P. Gutierrez, S. Berry, and R.D. Hays, Psychometric properties of the National Eye Institute Visual Function Questionnaire (NEI-VFQ). NEI-VFQ Field Test Investigators. Arch Ophthalmol, 1998. **116**(11): p. 1496-504.

105. Mangione, C.M., P.P. Lee, P.R. Gutierrez, K. Spritzer, S. Berry, and R.D. Hays, Development of the 25-item National Eye Institute Visual Function Questionnaire. Arch Ophthalmol, 2001. **119**(7): p. 1050-8.

106. Hood, D.C., M. Bach, M. Brigell, D. Keating, M. Kondo, J.S. Lyons, and A.M. Palmowski-Wolfe, ISCEV guidelines for clinical multifocal electroretinography (2007 edition). Doc Ophthalmol, 2008. **116**(1): p. 1-11.

107. Hamel, C., Retinitis pigmentosa. Orphanet J Rare Dis, 2006. **1**: p. 40.

108. Kelliher, C., D. Kenny, and C. O'Brien, Trends in blind registration in the adult population of the Republic of Ireland 1996-2003. Br J Ophthalmol, 2006. **90**(3): p. 367-71.

109. Rohrschneider, K. and S. Greim, [Epidemiology of blindness in Baden, Germany]. Klin Monbl Augenheilkd, 2004. **221**(2): p. 116-21.

110. Najera, C., J.M. Millan, M. Beneyto, and F. Prieto, Epidemiology of retinitis pigmentosa in the Valencian community (Spain). Genet Epidemiol, 1995. **12**(1): p. 37-46.

111. Zrenner, E., Krastel, H., Goebel, H-H., ed. Research in Retinitis Pigmentosa. Advances in the bioscience, ed. J. Price, Colborne, A.J. Vol. 62. 1987, Pergamon Press: Oxford. 465.

112. Hood, D.C. and D.G. Birch, Rod phototransduction in retinitis pigmentosa: estimation and interpretation of parameters derived from the rod a-wave. Invest Ophthalmol Vis Sci, 1994. **35**(7): p. 2948-61.

113. Shiells, R.A. and G. Falk, Contribution of rod, on-bipolar, and horizontal cell light responses to the ERG of dogfish retina. Vis Neurosci, 1999. **16**(3): p. 503-11.

114. Tsujikawa, M., Y. Wada, M. Sukegawa, M. Sawa, F. Gomi, K. Nishida, and Y. Tano, Age at onset curves of retinitis pigmentosa. Arch Ophthalmol, 2008. **126**(3): p. 337-40.

115. Marmor, M.F., Visual loss in retinitis pigmentosa. Am J Ophthalmol, 1980. **89**(5): p. 692-8.

116. Lorentz, O., J. Sahel, S. Mohand-Said, and T. Leveillard, Cone survival: identification of RdCVF. Adv Exp Med Biol, 2006. **572**: p. 315-9.

117. Haim, M., Prevalence of retinitis pigmentosa and allied disorders in Denmark. III. Hereditary pattern. Acta Ophthalmol (Copenh), 1992. **70**(5): p. 615-24.

118. Hayakawa, M., M. Matsumura, N. Ohba, M. Matsui, K. Fujiki, A. Kanai, M. Tamai, T. Shiono, T. Tokoro, Y. Akazawa, and et al., A multicenter study of typical retinitis pigmentosa in Japan. Jpn J Ophthalmol, 1993. **37**(2): p. 156-64.

119. Dickinson P, M.L., A survey of hereditary aspects of pigmentary retinal dystrophies. Aust N Z J Ophthalmol, 1989. **17**(3): p. 247-256.

120. Haim, M., Epidemiology of retinitis pigmentosa in Denmark. Acta Ophthalmol Scand Suppl, 2002(233): p. 1-34.

121. Hartong, D.T., E.L. Berson, and T.P. Dryja, Retinitis pigmentosa. Lancet, 2006. **368**(9549): p. 1795-809.

122. Kiyoshi A, M.S., Yoshiki H, Yoshihisa O, Shigekuni O, Progression of visual field loss in patients with retinitis pigmentosa of sporadic and autosomal recessive types. Ophthalmic Res, 1998(30): p. 11-22.

123. Scholl, H.P.N., Photoreceptor type-specific electroretinorgapy in inherited retinal disorders. 2004, Norderstedt: Books on Demand GmbH. 150.

124. Langrova, H., E. Zrenner, A. Kurtenbach, and M.W. Seeliger, Age-related changes in retinal functional topography. Invest Ophthalmol Vis Sci, 2008. **49**(11): p. 5024-32.

125. van Lith, G., Subnormal and absent ERGs: what do we mean with this terms? Doc Ophthalmol Proc Ser, 1982. **31**: p. 13-17.

126. Fishman, G.A., Birch D.G., Holder G.E., Brigel M.G., Electrophisiology testing in disorders of Retina, Optic Nerve, and Visual Pathways. Ophthalmology Monographs. 2001, Singapore: The Foundation of the American Avademy of Ophthalmology. 308.

127. Fishman, G.A., K.R. Alexander, and R.J. Anderson, Autosomal dominant retinitis pigmentosa. A method of classification. Arch Ophthalmol, 1985. **103**(3): p. 366-74.

128. Berson, E.L., Retinitis pigmentosa and allied diseases: applications of electroretinographic testing. Int Ophthalmol, 1981. **4**(1-2): p. 7-22.

129. Gouras, P. and R.E. Carr, Electrophysiological Studies in Early Retinitis Pigmentosa. Arch Ophthalmol, 1964. **72**: p. 104-10.

130. Birch, D.G. and G.E. Fish, Rod ERGs in retinitis pigmentosa and cone-rod degeneration. Invest Ophthalmol Vis Sci, 1987. **28**(1): p. 140-50.

131. Lois, N., G.E. Holder, C. Bunce, F.W. Fitzke, and A.C. Bird, Phenotypic subtypes of Stargardt macular dystrophy-fundus flavimaculatus. Arch Ophthalmol, 2001. **119**(3): p. 359-69.

132. Schroeder, R., M.B. Mets, and I.H. Maumenee, Leber's congenital amaurosis. Retrospective review of 43 cases and a new fundus finding in two cases. Arch Ophthalmol, 1987. **105**(3): p. 356-9.

133. Lambert, S.R., A. Kriss, D. Taylor, R. Coffey, and M. Pembrey, Follow-up and diagnostic reappraisal of 75 patients with Leber's congenital amaurosis. Am J Ophthalmol, 1989. **107**(6): p. 624-31.

134. Lorenz, B., P. Gyurus, M. Preising, D. Bremser, S. Gu, M. Andrassi, C. Gerth, and A. Gal, Early-onset severe rod-cone dystrophy in young children with RPE65 mutations. Invest Ophthalmol Vis Sci, 2000. **41**(9): p. 2735-42.

135. Weiss, A.H. and W.R. Biersdorf, Visual sensory disorders in congenital nystagmus. Ophthalmology, 1989. **96**(4): p. 517-23.

136. Fulton, A.B., R.M. Hansen, and R.J. Glynn, Natural course of visual functions in the Bardet-Biedl syndrome. Arch Ophthalmol, 1993. **111**(11): p. 1500-6.

137. Jacobson, S.G., F.X. Borruat, and P.P. Apathy, Patterns of rod and cone dysfunction in Bardet-Biedl syndrome. Am J Ophthalmol, 1990. **109**(6): p. 676-88.

138. Yanagihashi, S., M. Nakazawa, J. Kurotaki, M. Sato, Y. Miyagawa, and H. Ohguro, Autosomal dominant central areolar choroidal dystrophy and a novel Arg195Leu mutation in the peripherin/RDS gene. Arch Ophthalmol, 2003. **121**(10): p. 1458-61.

139. Carr, R.E., Central Areolar Choroidal Dystrophy. Arch Ophthalmol, 1965. **73**: p. 32-5.

140. Ponjavic, V., S. Andreasson, and B. Ehinger, Full-field electroretinograms in patients with central areolar choroidal dystrophy. Acta Ophthalmol (Copenh), 1994. **72**(5): p. 537-44.

141. Gerber, D.M. and G. Niemeyer, [Ganzfeld and multifocal electroretinography in Malattia Leventinese and Zermatt Macular Dystrophy]. Klin Monbl Augenheilkd, 2002. **219**(4): p. 206-10.

142. Kretschmann, U., M.W. Seeliger, K. Ruether, T. Usui, E. Apfelstedt-Sylla, and E. Zrenner, Multifocal electroretinography in patients with Stargardt's macular dystrophy. Br J Ophthalmol, 1998. **82**(3): p. 267-75.

143. Hood, D.C., E.J. Wladis, S. Shady, K. Holopigian, J. Li, and W. Seiple, Multifocal rod electroretinograms. Invest Ophthalmol Vis Sci, 1998. **39**(7): p. 1152-62.

144. Brody, B.L., A.C. Roch-Levecq, A.C. Gamst, K. Maclean, R.M. Kaplan, and S.I. Brown, Self-management of age-related macular degeneration and quality of life: a randomized controlled trial. Arch Ophthalmol, 2002. **120**(11): p. 1477-83.

145. Brody, B.L., A.C. Roch-Levecq, R.G. Thomas, R.M. Kaplan, and S.I. Brown, Self-management of age-related macular degeneration at the 6-month follow-up: a randomized controlled trial. Arch Ophthalmol, 2005. **123**(1): p. 46-53.

146. Stelmack, J.A., T.R. Stelmack, and R.W. Massof, Measuring low-vision rehabilitation outcomes with the NEI VFQ-25. Invest Ophthalmol Vis Sci, 2002. **43**(9): p. 2859-68.

147. Wahl, H.W., V. Heyl, and N. Langer, [Quality of life by limited vision in old age: the example of age-related macula degeneration]. Ophthalmologe, 2008. **105**(8): p. 735-43.

148. Finger, R.P., M. Fleckenstein, F.G. Holz, and H.P. Scholl, Quality of life in age-related macular degeneration: a review of available vision-specific psychometric tools. Qual Life Res, 2008. **17**(4): p. 559-74.

149. Vitale, S., O.D. Schein, C.L. Meinert, and E.P. Steinberg, The refractive status and vision profile: a questionnaire to measure vision-related quality of life in persons with refractive error. Ophthalmology, 2000. **107**(8): p. 1529-39.

150. Reimer, J., K. Gilg, A. Karow, J. Esser, and G.H. Franke, Health-related quality of life in blepharospasm or hemifacial spasm. Acta Neurol Scand, 2005. **111**(1): p. 64-70.

151. Lee, B.L. and M.R. Wilson, Health-related quality of life in patients with cataract and glaucoma. J Glaucoma, 2000. **9**(1): p. 87-94.

152. Peters, T., S. Klingberg, H. Oelman, C. Kuttenkeuler, R. Wilke, T. Zabel, E. Zrenner, and B. Wilhelm, Changes of Emotional State of Blind Patients in a Pilot Trial With a Subretinal Implant. Invest. Ophthalmol. Vis. Sci., 2007. **48**(5): p. 671-.

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Prokofyeva E, Wilke R, Lotz G, Troeger E, Strasser T, Zrenner E. An epidemiological approach for the estimation of disease onset in Central Europe in central and peripheral monogenic retinal dystrophies. Graefes Arch Clin Exp Ophthalmol. 2009 Jul;247(7):885-94.

Work in Progress:

Prokofyeva E, Troeger Eric, Wilke R, Zrenner E, „Longituinal study of visual acuity changes in cone and cone-rod dystrophies“ under submission

Prokofyeva E, Troeger Eric, Wilke R, Zrenner E, “Early Visual Symptoms Patterns in Inherited Retinal Dystrophies”, under submission

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Prokofyeva E, Zrenner E, “Epidemiology of Major Eye Diseases Leading to Blindness in Europe: A Literature Review”, under submission.

Books:

Balyasnikova I., Prokofyeva E. Children and Vision. Arkhangelsk, Russia: Pravda Severa; 2007

Balyasnikova I., Prokofyeva E. Methodological Recommendations for shortsighted patients. Arkhangelsk, Russia: Pravda Severa; 2010

Reviews:

Prokofyeva E, Wilke R, Zrenner E. Diabetic Retinopathy in Europe: Meta-Analysis Based on a Systematic Literature Review. European Journal of Epidemiology, 24(1).

Prokofyeva E, Wilke R, Zrenner E. Epidemiology of cataract in Europe. Pharmacoepidemiology and drug safety 2009; 18: S229S230. Published online in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/pds.1806

Prokofyeva E, Wilke R, Zrenner E. Prevalence and Incidence of Age-Related Macular Degeneration in Europe: Meta-Analysis Based on a Systematic Literature Review. Invest Ophthalmol Vis Sci. 2009 April 11, 2009;50(5):267-.

Prokofyeva E, Wilke R, Zrenner E. Cataract is a frequent adverse effect of widely used drugs. pharmacoepidemiology and drug safety; 19: S1–S347 Published online in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/pds.19-S1

Abstracts:

Prokofyeva E, Bernd, A, Wilke R, Zrenner E. Visual-related quality of life in patients with inherited retinal dystrophies - a baseline for assessing clinical trial efficacy. EVER 2010, Creta, Greece

Prokofyeva E,Wilke R, Troeger E, Zrenner E. Longitudinal study of visual acuity changes in cone and cone-rod dystrophies. World Congress of Ophthalmology 2010, Berlin, Germany

Prokofyeva E, Troeger E, Wilke R, Zrenner E. Age of Visual Symptoms Onset In Different Types of Inherited Retinal Degenerations. Invest. Ophthalmol. Vis. Sci. 2010 51: E-abstract 3548.

Troeger E, Prokofyeva E., Wilke R., Zrenner E. (2009) Reusability in patient registries-Implementation of a generic extensible web-based Patient registry system. International conference on Health Informatics, Porto, Portugal.

Troeger E, Wilke R, Prokofyeva E, Zrenner E. Ophthabase: a generic extensible patient registry system. Acta Ophthalmologica. 2008;86(s243):0-.

Prokofyeva E., Wilke R. , Lotz G., Tröger E., Strasser T., Zrenner E (2008) Distribution and clinical peculiarities of monogenic retinal dystrophies at the Center for Ophthalmology, University of Tübingen. EVER congress, Slovenia, Portoroz.

Prokofyeva E., Wilke R. , Lotz G., Tröger E., Strasser T., Zrenner E.(2008) An epidemiological approach for the estimation of disease onset in inherited retinal dystrophies. 106 DOG (German Ophthalmologic Society Congress), Berlin, Germany.

Prokofyeva E., Wilke R., Lotz G., Tröger E., Strasser T, Zrenner E. (2008) Epidemiological study of inherited retinal degenerations in T¨ubingen University Eye Clinic. 4th Pro- retina Research-Colloquium, Potsdam, Germany.

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Elena Prokofyeva, Michelle McIntosh, Richard G Boulton, Daphne L McCulloch (2008) Stroboscopic and square wave flicker for visual pathway assessment. BriSCEV, Cardiff, UK.

Michelle McIntosh, Elena Prokofyeva, Richard G Boulton, Daphne L McCulloch (2008) Steady state pattern VEPs: onset-offset checks are more effective than pattern reversal for frequency domain detection. BriSCEV, Cardiff, UK.

Prokofyeva E, Balyasnikova I, Soloviev. (2007) Differential diagnosis of visual system disorders in alcohol intoxications: Methodological recommendations, editor: Professor Sidorov P. Archangelsk, Northern scientific center, North-west department of Russian academy of medical sciences

Patents:

Sidorov P, Soloviev A, Balyasnikova I, Prokofyeva Patents E, inventors; A method for detecting the severity of alcohol-induced optic nerve disorders. Patent for invention 2370203, registered 20.10.2009 (Russia)

Sidorov P, Soloviev A, Balyasnikova I, Prokofyeva E, inventors; A method for measuring the visual field. Patent for invention 2304917, registered 30.12.2005 (Russia)

Balyasnikova I, Sidorov P, Soloviev A, Prokofyeva E, inventors; A method for differential diagnosis of optical nerve and retina disorders in acute methanol poisonings and severe ethanol intoxication. Patent for invention 2262299, registered, 20.10.2005 (Russia)

Balyasnikova I, Sidorov P, Soloviev A, Prokofyeva E, inventors; A method for differential diagnosis of optical nerve toxic lesions in patients with alcohol dependence in methanol and ethanol poisonings. Certificate for rationalization proposal 15/03, 17.06.2003 (Russia)