Diploma Thesis

# A systematic review of retinitis pigmentosa and associated aspects of visual impairment


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## Statutory Declaration

I hereby declare that I have authored this diploma thesis fully on my own, that I have not used any other than the declared sources, and that I have explicitly marked all material which has been quoted either literally or by content from the used sources.

Graz, July 11th, 2016 Thomas Georgi eh.

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# Abstract

The World Health Organization estimates that 39 million patients are blind and 246 million have low vision. Due to this vast number of severely visual impaired patients the field of low vision rehabilitation has become an important discipline in ophthalmology. One of the leading causes for visual impairment and blindness in mid adulthood in the industrialized countries is retinitis pigmentosa (RP). It is a group of hereditary disorders leading to the degeneration of rod and cone photoreceptors. Currently, there is no curative therapy available to cease the degenerative process in RP and many patients remain in the state of severely impaired vision for a long period of time. For this reason, the disease has been subject to investigations dealing with innovative therapeutic approaches such as retinal prostheses. In this field of research, the accurate monitoring of visual improvement or deterioration plays an important role. The primary goal in low vision rehabilitation is the improvement of the quality of life (QOL). However, the simple measurement of visual functions represents only one aspect of the dysfunctions which contribute to a reduced QOL. Therefore, task performance tests have been developed to assess functional vision aspects in low vision patients.

The aim of this thesis was not only to provide a systematic review of RP, but also to draw the attention the functional aspects associated with severe visual impairment. For the comprehension of the rehabilitation processes in RP, the first part of this thesis examines the principles of the visual function, functional aspects in visual impairment and the development of task performance tests. The second part represents an analysis of the current expertise of RP from a clinical point of view.

For this thesis the existing literature including journal publications, books and accredited internet sources was analyzed. The PubMed database was searched for the terms ‘retinitis pigmentosa’, ‘low vision’, ‘visual function’, ‘functional vision’, ‘orientation’ and ‘mobility’, and also referred studies were screened for related information. From this broad variety of literature only relevant publications were used for the writing process.

# Zusammenfassung

Schätzungen der World Health Organization zufolge sind weltweit 39 Millionen Menschen erblindet und weitere 246 Millionen im Bereich der schweren Sehbehinderung einzustufen. Aufgrund dieser großen Anzahl von Patienten mit Seheinschränkungen gewann das Forschungsfeld der visuellen Rehabilitation innerhalb der Augenheilkunde zuletzt stark an Bedeutung. Eine der häufigsten Ursachen für schwere Seheinschränkungen und Blindheit in mittleren Erwachsenenalter ist in industrialisierten Ländern die Krankheit Retinitis Pigmentosa (RP). Es handelt sich hierbei um eine Gruppe von vererbten Störungen, die zu einer Degeneration der Stäbchen- und Zapfen-Photorezeptoren führen. Derzeit existiert kein kurativer Heilungsansatz um diesen degenerativen Prozess zu anzuhalten und viele RP Patienten verbleiben für lange Zeit schwer sehbehindert. Aus diesem Grund wurde RP ausführlich untersucht um innovative therapeutische Lösungsansätze wie den des künstlichen Sehens zu erforschen. Gerade in diesem Forschungsfeld spielt die Dokumentation von Seh-Verbesserungen oder -Verschlechterungen eine wichtige Rolle. Das primäre Ziel der visuellen Rehabilitation ist die Verbesserung der Lebensqualität. Allerdings stellt die Messung von visuellen Funktionen nur einen einzelnen Aspekt dar, der zur reduzierten Lebensqualität beiträgt. Aus diesem Grund wurden Funktionstests entwickelt, mit welchen verschiedenste Aspekte von funktionelle Sehfähigkeiten bei schwer seheingeschränkten Patienten ermittelt werden können.

Das Ziel dieser Diplomarbeit war nicht nur eine systematische Literaturrecherche, es sollten ebenfalls die funktionellen Aspekte, die mit schweren Sehbehinderungen einhergehen, hervorgehoben werden. Für das Verständnis der Rehabilitationsprozesse bei RP werden im ersten Teil dieser Arbeit die Prinzipien der visuellen Funktion, der funktionellen Aspekte von schweren Seheinschränkungen und die Entwicklung von Funktionstests behandelt. Der zweite Teil stellt eine ausführliche Literaturrecherche des derzeitigen Wissenstandes über RP aus klinischer Sicht dar.

Für diese Diplomarbeit wurde die vorhandene Literatur aus wissenschaftlichen Publikationen, Fachbüchern und legitimen Internetquellen analysiert. Die PubMed Datenbank wurde auf die Stichwörter „retinitis pigmentosa", "low vision", "visual function", "functional vision", "orientation" and "mobility" hin durchsucht.

Referenzierte Publikationen innerhalb dieser Quellen wurden ebenfalls begutachtet. Von dieser breiten Auswahl wurden nur relevante Publikationen für das Verfassen dieser Diplomarbeit verwendet.

# Table of contents

# Abbreviations

| Abbreviation | Full description |
|---|---|
| ADL | activities of daily living |
| BBS | Bardet-Biedl syndrome |
| BCVA | best corrected visual acuity |
| BKD | Bassen-Kornzweig disease |
| CF | counting fingers |
| CS | contrast sensitivity |
| DHA | Docosahexaenoic acid |
| ERG | electroretinogram |
| ETDRS | early treatment diabetic retinopathy study |
| FLA | fluorescein angiography |
| FrACT | Freiburg visual acuity test |
| GCL | ganglion cell layer |
| HM | hand movements |
| ICF | International classification of functioning |
| INL | inner nuclear layer |
| LCA | Leber congenital amaurosis |
| logMAR | logarithmic minimum angle of resolution |
| LP | light perception |
| MAR | minimum angle of resolution |
| NEI-VFQ | visual functioning questionnaire |
| NLP | no light perception |
| O&M | orientation and mobility |
| OCT | optic coherence tomography |
| ONL | outer nuclear layer |
| PPWS | percentage of preferred walking speed |
| QOL | quality of life |
| RP | Retinitis pigmentosa |
| RPE | retinal pigment epithelium |
| RPE65 | gene for encoding retinoid isomerohydrolase |
| SM | spatiotemporal scanning movements of the head |
| VA | visual acuity |
| $VA_{dec}$ | visual acuity in decimal numbers |
| $VA_{ft}$ | fraction visual acuity in feet |
| $VA_{m}$ | fraction visual acuity in meters |
| VF | visual field |
| WHO | World Health Organization |

# 1 Aspects of visual impairment

The measurements of visual acuity (VA) can be expressed in decimals ($VA_{dec}$), distance fractions in meters ($VA_m$) or feet ($VA_{ft}$), as well as in logarithmic minimum angle of resolution (logMAR). The definition of normal sight is 1.0, 6/6 m, 20/20 ft or 0.0 logMAR respectively. For low vision purposes logMAR seems to be the best notation due to the fact that the progression of the step sizes should be logarithmic and not linear, and fractions will result in high numbers.[1] See section *1.3.1 Visual acuity* for further explanations.

## 1.1 Blindness

According to the ICD-10 classification visual impairment is subcategorized by distance VA with blindness starting at 3/60 m ($VA_{dec}$: 0.05) or less at the better eye without compensable corrective errors (*Table 1*).[2]

| Category | Presenting distance visual acuity | |
|---|---|---|
| | **Worse than:** | **Equal to or better than:** |
| 0 Mild or no visual impairment | | 6/18<br>3/10 (0.3)<br>20/70 |
| 1 Moderate visual impairment | 6/18<br>3/10 (0.3)<br>20/70 | 6/60<br>1/10 (0.1)<br>20/200 |
| 2 Severe visual impairment | 6/60<br>1/10 (0.1)<br>20/200 | 3/60<br>1/20 (0.05)<br>20/400 |
| 3 Blindness | 3/60<br>1/20 (0.05)<br>20/400 | 1/60*<br>1/50 (0.02)<br>5/300 (20/1200) |
| 4 Blindness | 1/60*<br>1/50 (0.02)<br>5/300 (20/1200) | light perception |
| 5 Blindness | No light perception | |
| 9 | Undetermined or unspecified | |
| | * or counts fingers (CF) at 1 metre. | |

**Table 1:** ICD-10 Version 2010: H54 Visual impairment including blindness (binocular or monocular). The fractions in the first and second row disclose the $VA_m$, the third row discloses the $VA_{ft}$. Values in brackets disclose the $VA_{dec}$.

### 1.1.1 Legal Blindness

In Austria legal blindness is defined by two criteria: VA and visual field (VF).[3] Nursing allowance from the government can be claimed at the state of severe impaired vision or less; applicable at a $VA_m$ equal to 3/60 m ($VA_{dec}$: 0.05) or less, or a $VA_m$ of 6/6 m combined with a concentric VF constriction. Blindness is applicable at a $VA_m$ equal to 1/60 m or less, or a $VA_m$ of 6/60 m with a concentric

VF constriction. In the US legal blindness is accounted from a $VA_{dec} \leq 0.1$ or a residual VF of 20° or less.[4]

## 1.2 Low vision

Several diseases, such as RP, present a progressive decline of vision over years. Affected patients remain in an intermediate state between visual impairment and blindness for many years.[5–7] This state is often referred to as ‘low vision’, sometimes even ‘ultra low vision’. It is important to point out that the states of visual impairment and blindness must be considered as transient conditions at the basis of different underlying impairments. In RP these deteriorations of the visual function derive from deficits such as *"poor high contrast visual acuity", "poor low contrast visual acuity", "reduced peripheral visual field"* and *"reduced central visual field sensitivity"* [8], to mention just some of them. With regard to the impairment of the visual functions there is still a lack of clear definitions.[9] While earlier ICD classifications only distinguished between vision and blindness, later updates also include various grades of visual impairment (*Table 1: category 1,2*). These categories are mainly defined by the measurement of the VA, which is only one aspect of the visual function: *"the central resolution at high contrast"*.[10] Therefore, the International classification of Functioning (ICF) was developed to describe and measure health and disability based on international standards.[11,12] Regarding seeing functions (ICF number b210 - b229)[12], this classification also includes other qualities of the visual function next to the VA, such as VF, light sensitivity, color vision, CS, visual picture quality but also unspecified seeing functions.[10,13]

## 1.3 Visual function

The visual function, defined as *"how the eye functions"*[11], describes the synthesis of all aspects involved in the visual perception. The measurable loss of these specific functional capabilities is defined as ‘impairment’.[9] For clinical purposes of RP the VA, VF and CS are of special interest.

### 1.3.1 Visual acuity

Visual acuity is the ability to sense the form and contours of objects by discriminating two separate stimuli.[10,13,14] It can be understood as the central resolution of vision.[10] One of the first who described VA testing as a standardized

method was Hermann Snellen.[15] He used letters in which the thickness of the lines were exactly 1/5 of the height. Those letters were then presented to the patient in variable sizes. The thickness of the letter lines was measured in minutes of arc in relation to the distance of examination. The smaller the size of the arc, the better/higher is the VA, which is measured in 'minimum angle of resolution' (MAR). As a reference he used an angle of 5 arc minutes ($^1/_{12}$°) as the smallest distinguishable angle with normal sight.[15]

The idea of Snellen charts was adopted for clinical and research purposes. However, improvements were applied to eliminate inaccuracies.[16,17] Bailey & Lovie included a logarithmic progression of the angular sizes in 0.1 log-unit steps (logMAR).[1,18] It has been shown, that this mathematical progression is necessary in order to get accurate results over all degrees of visual impairment (especially for low vision).[1,19] Ferris et al. introduced a modified chart using only 5 letters per line of which three have to be identified correctly in order for the line to be correct.[20] Furthermore, they suggested the use of equally difficult letters of the Sloan series (C, D, H, K, N, O, R, S, V and Z).[21] The chart consists of a non-reflective white surface and is installed in a light box, producing high contrast letters with diffuse background illuminance of 80 to 320 cd/m².[18,20] Their chart design was investigated in a major project (early treatment diabetic retinopathy study) and since then is known as the ETDRS chart. Both the ETDRS chart and the Baily-Lovie chart are nowadays the most common approach for measuring and monitoring VA.

The best correct line represents the VA and the test should be conducted with the best corrected visual acuity (BCVA), starting with the right eye. When testing for VA, it is important that the patient is given enough time to adapt to the luminance of the test condition. This is especially important for RP patients, who have additional difficulties in light adaption.[22]

### 1.3.2 Visual field

The VF is defined as the entire region of space seen by the patient when fixating on a central target.[14] The physiological VF is only limited anatomically by the nose or orbita. In healthy individuals 60° nasal and upwards, 75° downwards and 100° temporal can be measured.[23] During the ophthalmological VF examination, also

called perimetry, these measurements can be achieved through either static or kinetic perimetry devices. The patient is asked to fixate the center of a half bowl while bright dots of varying size and luminosity are presented. The kinetic perimetry examination is mostly achieved with a Goldmann device, introduced in 1945.[24] The light source is connected to a mechanical pointer on a paper sheet, the gaze fixation to the center can be controlled by the operator through a duct. The light stimulus is moved systematically through the patient's VF on 24 meridians and positive or negative responses from the patient are noted manually by the operator. The area resulting from connecting the dots of visual thresholds is called isopter, and the size and luminosity of the light stimulus are described through the used light target, ranging from I1e (smallest/darkest) to V4e (biggest/brightest).[25] Resulting round circle isopters can then be declared in square cm, square degrees or square radians (steradians), the latter being the most precise as it corrects for distortion due to polar projection.[23,26] The static perimetry examination is achieved through electronic devices like the Octopus (Haag-Streit AG, Switzerland) or Humphrey Field Analyzer (Carl Zeiss Meditec AG, Germany), where the light stimuli are defined in location and luminosity according to the adjustable program.[27]

### 1.3.3 Contrast sensitivity

Contrast sensitivity (CS) is defined as the ability to distinguish an object from its background.[13] When the contrast decreases until the target cannot be identified reliably anymore, the contrast threshold is reached. The CS is the reciprocal of the threshold.[22,28] In the 1760s Pierre Bouguer was the first to measure a contrast threshold with a simple experiment with candles casting a shadow.[28,29] Further investigations by Masson and Young ultimately lead to the urge of a clinical CS test.[30] Although settings with several optotypes were introduced[31–34], the Pelli-Robson chart became widely accepted due to its similarity with the ETDRS charts and a good psychophysical setting.[35] The Pelli-Robson test consists of a chart with two groups of 3 letters in each line, the letters again following the Sloan series.[21] The letters in each group feature the same size and contrast, and in each successive group the CS is decreased by the factor of $1/\sqrt{2}$,[35] ranging from 0.05 to 2.30 log units. The examination distance is intended to be 3 m, however closer CS

can be measured for low vision purposes as well. Each group is judged positive when two or three letters are identified positively.

### 1.3.4 Visual function assessment in low vision

In the clinical setting the VA is one of the most used measurements to disclose visual performance, although it is not suitable to display all aspects of it.[36] Determining the VA threshold in low vision patients can be challenging in comparison to better sighted persons, as most measurement methods are designed for the better sighted. In regular VA measurements the test-retest reliability is given with a variance of less than 0.2 logMAR.[37–39] In low vision patients, especially in RP patients with deteriorated VFs, this variance shows to be greater and questions arise concerning the VA testing methods: can conventional VA tests be used for low vision patients and are the test results comparable with specially designed low vision tests?

Usually, when the largest optotype on the Baily-Lovie-chart cannot be recognized any more, clinicians use an ordinal scale of semiquantitative VA scores (counting fingers = CF; hand movements = HM; light perception = LP; and no light perception = NLP).[40,41] However, in the literature the size of these threshold steps is not clear.[42] Authors of studies investigating the VA in low vision patients came to the conclusion that semiquantitative VA scores vary strongly from one clinical site to another[40,42] and should be used with caution, since there is no standard way of performing these measurements.[41] New test methods have been developed to obtain more accurate VA results for low vision patients. Bach introduced a computer-based design (Freiburg visual acuity test, FrACT).[43] He used the optotypes of Landoldt-Cs in eight different directions and a psychometric test method called ‘best-PEST’, which is an efficient computer-based estimation of the best threshold for each next optotype presentation.[44] With this standardized method Schulze-Bonsel et al. discriminated the wide and undefined range of CF and HM in more detail. The Berkley rudimentary vision test, created by Bailey et al.[40], includes three tasks to extend the range of VA measurements for very low vision patients. This includes recognition of the orientation of a ‘tumbling E’, grating acuity and white field projection as well as black white discrimination. However, both tests were only partially evaluated with RP patients. Therefore, in previous studies with RP subjects a grating test (adapted to international

standards) was used [45–50] which has shown to distinguish visual acuities in the range of 1.6 logMAR and HM.[41] The test consists of a computer-generated circle with white and black gratings which can be de- or increased in logarithmic steps covering a range of 0.3 to 2.7 logMAR (see details in chapter *3.4 Visual acuity testing*) and the results have previously proven to be consistent with the results of ETDRS charts and FrACT.[41,50]

The accurate assessment of the VF and CS in visually impaired patients addresses similar problems as the VA testing. Conventional tests may not be operated adequately since many tasks are too demanding for low vision patients. A feasible alternative method has not been developed up to now.

## 1.4 Functional Vision

In contrast to the visual function (how the eye functions), the functional vision is described as *"how the person functions"*.[11,51] As Colenbrander states, it is important not to mix the denotation nor the assessment of these two areas.[11] Functional vision is influenced by a number of resources: sensory resources, such as vision and hearing; but also *"sensorimotor, cognitive, personality, and social resources".*[52] These abilities are required to accomplish vision-related everyday tasks, including *"reading, mobility, face recognition and activities of the daily living"*.[36] The loss of the capacity to perform certain tasks as a result of impairments is defined as ‘disability’.[9]

The measurement of vision-related abilities or disabilities is a complex undertaking, as it is difficult to determine the separate influencing resources. Vision, responsible for approximately 80% of the information perceived from the environment, remains to be the most important resource.[10] However, when the visual function declines, other senses gain more importance: auditory or tactile methods replace the visual input in order to access information from the environment (sensory substitution).[22] In order to assess disabilities during everyday life, questionnaires and task performance tests are used.

### 1.4.1 Questionnaires

Questionnaires are a widely used tool to assess health-related quality of life (QOL).[53] They reflect the patients’ subjective impression of their abilities to interact

with the environment. In ophthalmology numerous questionnaires have been developed, one of the most popular being the visual functioning questionnaire (NEI-VFQ).[53,54] It has been demonstrated that its results correlate with the clinical measures of VA, but not the VF.[55] Questions within the NEI-VFQ examine the ability to perform specific vision-related tasks as well as aspects of the QOL in general. However, the latter has a much wider context including bio-psycho-social aspects, which should be assessed separately.[36] In order to determine particular disabilities in tasks of everyday life, an enquiry about the activities of daily living (ADL) can be performed. This set of rudimentary tasks was created by Katz to measure disabilities in the population of the elderly.[56] Many of these activities are equally challenging for visually impaired persons and can therefore be used for a questionnaire assessment of functional vision. A representative set of tasks from the 'Bristol Activities of Daily Living Scale' is shown in *Table 2*.[57]

Besides the NEI-VFQ and the ADL, many other instruments have been developed to measure vision-related abilities during everyday life, such as the Activities of Daily Vision Scale[58], the Visual Functioning Index[59] or the Visual Status Inventory.[60] However, in most of them the mobility assessment is underrepresented. Turano et al. developed a questionnaire outlining 35 mobility situations and found the outcomes to correlate with parameters of the visual function.[61]

However, when assessing the functional vision with questionnaires the results are influenced subjectively and the assessment is *"an estimate of the patients' perceptions of their capabilities"*.[61] Especially amongst low vision patients, a great part of patients has difficulties to judge their abilities themselves, as they feel unsecure due to their handicap in the societal context. Furthermore, many questionnaires are specifically developed to evaluate the grade of disability associated with certain diseases, whereas other questionnaires seem to inquire too many aspects of the QOL. This could be a major disadvantage and may explain the variability of results in the literature.[62] Lastly, many questionnaires were developed with Likert-scores, whereas modern psychometric methods should rather be performed with Rasch analyses to allow interval-scaled latent ability traits and objective tests of validity and reliability of the estimated

measures.[63–65] Currently many questionnaires are being reviewed and adjusted to psychometric quality criteria.[64]

| | | |
|---|---|---|
| Preparing food | Bath/Shower | Telephone |
| Eating | Toilet/Commode | Housework/Gardening |
| Preparing drink | Transfers | Shopping |
| Drinking | Mobility | Finances |
| Dressing | Orientation – Time | Games/Hobbies |
| Hygiene | Orientation – Space | Transport |
| Dental care | Communication | |

**Table 2:** Bristol Activities of Daily Living Scale, 1996

### 1.4.2 Orientation & mobility tests

Mobility is defined as the ability to move safely from one position to another, whereas orientation is defined as the ability to determine one's position in the environment.[60,66] Since orientation and mobility (O&M) in familiar and unfamiliar environments is required for a multitude of ADL, it is a crucial component of the functional vision. Again, there are many factors which contribute to one's navigational ability, such as visual function, cognition, prior knowledge of vision, psychological factors and many more.[67,68] Many methods provided by certified O&M trainers can help maintaining independent O&M. These experts can point out techniques to cope with everyday situations and it can be assumed that O&M can be improved by such trainings and/or practical experience over many years.[69] Nevertheless, the navigating performance remains to be highly individual and some patients seem to profit from O&M training more than others.[70]

In order to determine the O&M performance, many research groups designed mobility test courses, in order to utilize task performance tests instead of questionnaires. Some of the courses took place in real world locations, such as streets, malls or university campuses.[66,71–73] Others were indoor courses with consistent test conditions, mostly conducted in corridors/hallways.[69,70,74–80] The latter have the advantage that many factors which influence the performance results are excluded. For instance, illumination and weather conditions can be distracting factors due to glaring symptoms which are typically seen in RP patients.[66] Also other disturbing influences, such as variably crowded places or noises from vehicles, are diminished in indoor tests. Therefore, it can be assumed that such tests depict one’s navigational ability accurately. Lastly, for ethical

reasons it is much safer for low vision subjects to walk in a controlled environment without external hazards such as cars. On the other hand, a disadvantage of laboratory courses is that the conditions might not represent everyday situations close enough to reality.[66]

In theory the test objectives of O&M courses differ from each other, but they can be distinguished by two aspects of navigation[81]: some courses were developed to observe attentional and obstacle detection competences[71], referred to as micro navigation. Other courses aim to investigate wayfinding and navigational aspects in the far space orientation, also called macro navigation. However, most existent mobility assessment tests analyze both qualities.

In literature the functional vision assessed with mobility test courses has proven to show correlations with parameters of the visual function.[22,82–85] In these studies a common performance parameter is the time taken to complete the mobility course. West et al. showed that even in easy courses the time is correlated to vision.[85] In some studies, subjects are asked to walk on a straight path with their normal walking speed before the actual mobility course. Instead of the time taken, the outcome measure was the percentage of preferred walking speed (PPWS).[71,75,76,78,86–88] The parameter of time or PPWS expresses the subjects' performance efficiency. A second common performance parameter is the number of contacts with obstacles or walls, also referred to as errors or mobility incidents. It often also includes bumps, stumbles or orientation loss.[89]

### 1.4.3 Head movements in locomotion

During locomotion spatiotemporal scanning movements of the head (SM) as well as eye movements are physiologically coordinated with the body movement.[90,91] As shown in literature, the sensory inputs are processed by the central nervous system in a feed-forward mode to regulate limb movements and adapt to obstacles on the path.[92] For that matter, also vestibular and proprioceptive sensory inputs have proven to be involved.[90,93] In a study with healthy volunteers, Grasso et al. showed that the SM pursue an anticipatory lead towards the future walking trajectory.[92] This anticipation allows the person to plan movements *"one step in advance in order to overcome the delays due to biomechanical inertia".*[92] Furthermore Grasso et al. found out that the SM also occur in blindfolded

locomotion and concludes that anticipation in head-eye coordination during locomotion is part of the *"behavioural repertoire of human navigation".*[92] In his study, an anticipatory lead of 1 s before a change in walking trajectory was found. Hicheur et al. also examined SM during locomotion in healthy volunteers.[80] Similar to the previous findings, in their study the anticipatory SM were influenced by the geometrical path as well as motor strategies to steer the whole body in the desired direction. On a curved walking path, they found an average anticipatory head deviation towards the future walking direction of approximately 30° to both sides. Patla et al. also conducted a study with healthy participants to investigate anticipatory gaze behavior.[77] He concluded that the *"gaze was fixated on the obstacle and in the 4 - 6 m range of the travel path"*.

The results of these studies provide important cues for the understanding of physiological SM during locomotion. However, it is not clear to which extent these behavioral SM patterns of healthy individuals can be transferred to people with severely impaired vision. To our knowledge, in low vision patients the role of SM during locomotion has not been investigated so far.

# 2 Retinal function outline

The visual process in the retina is based on an interaction of six main types of retinal neurons: photoreceptor cells, bipolar cells, horizontal cells, amacrine cells, interplexiform cells and ganglion cells.[94] At the very first step of the visual process incoming light is detected by photoreceptors, which are located in and next to the retinal pigment epithelium (RPE) in the outer segment of the eye (outer nuclear layer, ONL). Two types of photoreceptor cells can be distinguished, each type having a specific function in the visual process. Approximately 95 - 97% (60 million) of the photoreceptors are rod photoreceptors, which are disseminated on the whole retina especially aside the fovea centralis excluding fovea centralis per se.[94–96] They mediate the vision in dim light conditions and are responsible for night vision. The cone photoreceptors make up for only 3 - 5% (3 million) of all photoreceptors and are located in a very high density in the fovea centralis with an abrupt decrease of packing density towards the periphery.[94,95,97] Cones are responsible for high VA and color discrimination.[95,97] However, they require light intensities and therefore mediate vision in daylight.[94–96] Within the cone cells three

different types can be distinguished (trichromatic vision): L, M and S cones for red, green and blue colors respectively. S cones make up only 5% of all cone photoreceptors and are located also more peripheral than the rest of the cones.[95] L cones (65%) and M cones (30%) are more evenly distributed in the macular region. The visual pigment in the outer segment, needed for the functioning of photoreceptors, consists of intrinsic membrane proteins referred to as opsins and chromophores like retinol (vitamin A derivate).[95] Light stimuli trigger the activation and deactivation of the visual pigment through a series of protein changes and thus initiate the transformation from the photochemical reaction into the neuronal stimulus, called phototransduction.[94] Mutations which affect the rhodopsin (activated opsin) production have been proven to play a major role in many forms of night blindness and Retinitis Pigmentosa (RP). Therefore, these pathways have been extensively studied.[94–97]

After the phototransduction in the outer segment the neuronal stimulus is forwarded to bipolar cells, which interact with each other through synaptic connections and gap junctions of amacrine cells and horizontal cells (inner nuclear layer, INL). They act as modifiers of the stimulus and connectors of the rod and cone pathways. Finally, the signals of both pathways synapse to the ganglion cells (ganglion cell layer, GCL), whose axons carry the visual information into the brain, forming the optic tract.[94] Next to their function as neurons ganglion cells have also been proven to be photosensitive due to their function as regulator of the pupillary reflex and in the light dependent circadian rhythm.[98,99] The retina also contains glial tissue consisting mainly of Müller cells. They play an important role in the metabolism of neurotransmitters and the chromophore recycling.[95]

# 3 Retinitis pigmentosa

## 3.1 Definition

RP is a term for a heterogeneous group of disorders in the retina leading to retinal dysfunction caused by the degeneration of rods and cones.[22,100–103] It was first described over 150 years ago by Donders, a pathophysiologist who studied the anatomy of eyes.[104] He found changes in the RPE, such as white spots surrounded by dark pigments. In 1857 he was the first to mention the name ‘retinitis pigmentosa’ and soon a hereditary component was discovered by the

higher probability of affection in siblings.[104,105] Although the name suggests an inflammatory component, RP is a condition due to primary degeneration of the photoreceptors and the RPE.[27,103] There were several attempts to find other names, such as tapeto-retinal degeneration, rod-cone degeneration, primary pigmentary degeneration or dystrophia retinae pigmentosa.[27,96] Nowadays in the German-speaking region the name ‘retinopathia pigmentosa’ is commonly used. However, internationally ‘retinitis pigmentosa’ is still the preferred term.

RP has a great variability regarding the inheritance, clinical findings, symptoms and the manifestations like age at onset, severity and rate of progression, even within families.[95,106] However, in the majority of patients it leads to a final state of severe visual impairment resulting in a status defined as blindness by the WHO (see chapter *1.1 Blindness*). Before total blindness is reached, most patients remain in the state of low vision accounting for legal blindness in most patients.[107]

## 3.2 Epidemiology

RP is considered as an orphan disease.[108] In Europe this accounts for all diseases which concern not more than 5 in 10 000 patients seen by a general practitioner.[109] Still, RP is one of the leading causes for blindness and visual impairment in adulthood in industrialized countries.[94,110] According to the Pro Retina society there are currently about 3 million patients suffering from the disease all around the world, in Germany alone being 30 000 to 40 000 affected.[111] For Austria no demographic data are recorded yet, but similar numbers can be assumed. In epidemiologic studies around the world following figures are described: Bunker et al. found the prevalence of 1 in 4 756 in Maine[112], US; Bundey et al. found a prevalence of 1 in 4 869 in Birmingham, UK[113]; Haim et al. found a prevalence of 1 in 4 465 in Denmark[110]; and Amman et al. found a prevalence of 1 in 4 016 in Switzerland.[114] While these numbers do not differ a lot, Merin et al. found a prevalence of 1 in 2 000 in an Israel-based population[115] and also Haim et al. show higher prevalence frequencies of non-syndromic RP of 1 in 2 857 in males.[110] In literature most studies describe a prevalence of 1 in 5 000 to 1 in 2 000[5,95,101,102,110,116–118] whereas Haim et al. assumed that the prevalence is approximately equal in different parts of the world.[110] However, most calculation methods are not described in detail whereas Haim et al. published data from a RP

register including data from the time between 1850 and 1989 from eight ophthalmologic centers. Her calculations concur with the 'World Standardized Prevalence Rates' and are based on the assumption of a stable population.[110,119] Gender specific analysis revealed a higher occurrence of RP in males than in females with a ratio of about approximately 1.4, which is probably due to the x-linked inheritance of the disease.[110]

Still, the range of presented prevalence data is quite large. The differences could be explained by the usage of different diagnostic criteria, especially the inclusion or exclusion of syndromic RP, but also by the integrity of data and data verification. For example the prevalence often is based on assumptions such as that only one in ten RP patients will contact the study center.[120] Nevertheless, these figures give a crude overview over the occurrence of RP.

## 3.3 Etiology

Long before the time of genetic analyses the etiology of RP was known to be hereditary from observations. Several hypotheses like consanguinity of parentage or pigmentary changes in the retina as a part of syphilis were discussed, since the clinical findings can be similar.[5,121,122] In studies as early as 1909 the first systematic family histories for RP were assessed and showed evidence for autosomal-dominant (direct inheritance in an unbroken line), autosomal-recessive and x-linked (discontinuous line, but affected relatives) inheritance.[123] These findings were later approved in population-based studies and genetic analysis.[124–126] Although environmental factors could play a role in the development of RP, it is considered a hereditary disease.

In a publication from Berger et al. possible pathways are discussed: RP-causing genes have shown to affect functions of phototransduction, retinal metabolism, tissue development and maintenance, cellular structure and splicing.[94,95] Noteworthy pathomechanisms are gene mutations that encode the integral membrane protein rhodopsin. It is essential in the physiologic process of vision and numerous mutations have shown to result in the degenerative process of RP, although the linkage is not completely clear.[94]

As mentioned above the vitamin A derivate retinol is essential for photoreception and for the structural integrity of visual receptor cells (see chapter *2 Retinal*

*function outline*).[127] Campbell et al. found significantly lower amount of Vitamin A in blood examinations in 91% of all examined RP patients.[128] When absence of vitamin A is observed the visual threshold increases.[127,129] This can lead to symptoms like night blindness with varying degree of severity, which is presumably related to varying storage levels of the vitamin in the liver and RPE.[27] It is assumed that a shortage of vitamin A levels affects the rods more severely than cones, since cones can acquire vitamin A more efficiently.[127–129] The degree in which vitamin A levels affect the development and progression of RP is not fully understood, but its supplementation has shown to slow down the decline of ERG amplitudes typically seen in RP.[118,127]

### 3.3.1 Inheritance

Especially since the introduction of so-called next-generation-sequencing methods the tools for gene discovery have become faster, more powerful and cost-saving. Thus, the identification and mapping of genes and mutations responsible for RP progressed at a steady rate until now.[130] Daiger et al. reported that in 30 - 80% of all RP patients mutations can be found.[131] Databases like RetNet[132] or the Human Gene Mutation Database[133] have been established to collect phenotype-genotype information although many novel mutations are not listed in public databases.[131] Until 2006 roughly half of the causal genes were known.[102] In his review Daiger et al. assumes that the discovery of a great majority (95%) of all RP-causing genes and mutations will be accomplished until 2018,[131] although the remaining unidentified genes become rare and therefore more difficult to detect. It is expected that on the basis of genetical analysis the relationship of genotype and phenotype will be better understood, different forms of RP will be separated and individual progress will be predicted. Finally, specific intervention patterns could be established in the future.[95,131]

Still there is no clear assignation of genotype and clinical phenotype.[95,96,134,135] Daiger et al.[131] explain the variability of RP from a genetic point of view:

- genetic heterogeneity: one phenotype can be caused by different genes
- allelic heterogeneity: each gene can contain different disease-causing mutations
- phenotypic heterogeneity: different mutations in the same gene can cause different diseases
- clinical heterogeneity: the same mutations leads to different clinical findings (even in the same family)

So far 24 autosomal-dominant, 45 autosomal-recessive and 3 x-linked genes are known to cause RP only, 12 for Usher syndrome, 21 for Bardet-Biedl-Syndrome and 22 for Leber congenital amaurosis (autosomal-dominant and autosomal-recessive combined) (according to RetNet; accessed in August 2014)[132]. As far as the frequency of inheritance patterns is concerned Hartong et al. has shown in a review that responsible mutations are inherited autosomal-recessive in 50 - 60%, autosomal-dominant in 30 - 40%, and x-linked in 5 - 15% of all patients.[102] These numbers do not cover undefined inheritance patterns like isolated patients (simplex) with no family history[96] which are liable for about half of all RP patients[27,110,124,125,135] or multiplex (2 or more affected sibs).[6,94,100] As mentioned above (see section *3.2*), studies showed a slightly higher prevalence of RP in males than females, which may be accredited to the x-linked inheritance. There are also observations of non-mendelian inheritance patterns such as mitochondrial inheritance or digenic inheritance (determined by distinct genes), but only a small part of all patients belong to this group.[94,95,102]

A genetic examination can give advantages for appropriate counseling of the patient but also helps to identify homogeneous RP groups for further research.[27]

## 3.4 Forms

In the literature two main types of RP are defined in relation to their pathogenesis.[94,101] The more frequent rod-cone form primarily affects the rods localized mainly in the periphery and is referred to as typical RP.[101] It affects about 80 - 90% of all RP patients and shows the typical clinical picture of concentric VF loss as the disease progresses.[101] The cone-rod type is observed in 10 - 20% of

all patients only and primarily affects the cone photoreceptors localized in the macula. It results in different VF patterns with higher peripheral VF residuals.[101,102] However, in the end-stage both forms show similar aspects of visual impairment.[136]

Another way of categorizing RP is according to the genotypes. The method of biomolecular genotyping of relatively large study population (up to 140 patients) has made it possible to find associations of peculiar ERG amplitudes and single mutations.[118] Nonetheless, it has to be noted that these findings apply to a small percentage of RP patients only and exact predictions of the disease progression in general are still difficult to make.[27]

The phenomenon of pseudo RP describes non-hereditary diseases which may show the same clinical picture. They include inflammations and autoimmune diseases like lues, tuberculosis, borreliosis, toxoplasmosis or various intoxications.[111]

### 3.4.1 Syndromes

The following subsection gives an overview over the most common syndromic forms of RP. The clinical features of non-syndromic RP is described in the subsequent sections. Several syndromic forms of RP exist and according to literature they account for 10 - 30% of all patients with RP, most of them leading to a rod-cone dystrophy, as usually seen in RP.[101,102]

#### *3.4.1.1 Usher's syndrome*

One of the most prevalent syndromes is Usher's syndrome in which the majority of affected patients suffer from combined hearing impairment of the inner ear and RP. However, genetic analysis in several studies have also shown genotypes of Usher's syndromes occurring either without hearing loss or without RP[102,137]. Usher's syndrome accounts for 10 - 20% of all patients of RP and about half of all patients suffering from dual sensory loss.[5,101,102,138] The inheritance pattern is autosomal-recessive and related to mutations in 11 genes, as known so far.[5,102,131,138] Different mutations of these genes lead to the following sub-classification into three types.[5,102,137] Type I is characterized through congenital manifestation of profound hearing loss and vestibular ataxia; the onset of RP is approximately 21 years.[137] Also, talking will not develop adequately

unless the patient receives a cochlear implant very early. In type II the congenital hearing impairment is moderate in lower frequencies, but severe in higher frequencies and the vestibular system is not affected; and RP develops later in life (39 years). In the very rare type III the hearing impairment progresses over time and the vestibular reflex is variably impaired.

#### *3.4.1.2 Bardet-Biedl syndrome*

Bardet-Biedl syndrome (BBS) is a rare syndromic disorder characterized by pigmentary retinal dystrophy with associated clinical features which include renal dysplasia, polydactyly, obesity, hypogonadism and mental retardation.[102,131,136,139] Symptoms of renal dysfunction and retinal degeneration appear early. The average age of diagnosis of BBS is around 9 years.[136,140] However, such a profound disorder can be diagnosed earlier with ultrasound scans of the renal tract, and Tieder et al. suggest renal abnormalities to be accepted as a cardinal feature of BBS.[141] Typically, the retinal dystrophy presents itself as a rod-cone dystrophy with the first sign being night blindness.[140] Often the state of legal blindness is reached before the age of 20.[136] The inheritance is mendelian autosomal-recessive in most patients, although reports have shown BBS to be a more complex multifactorial disorder.[102,136,139] So far 17 BBS causing genes have been discovered.[131] The prevalence is ranging from 1 in 13 500 to 1 in 60 000 accounting for 5 - 6% of all RP patients.[102,136]

#### *3.4.1.3 Leber congenital amaurosis*

Leber congenital amaurosis (LCA) is the most severe form of inherited retinal blindness.[95,142] It is diagnosed by the clinical findings of RP present at birth or at least in the first year of life.[5,95,142,143] Other clinical features of the disease include a non-responsive ERG, sensory nystagm and amaurotic pupils.[5,96,136,142,144] In many reports other associated clinical features such as refractive errors (hyperopia and myopia), keratoconus, photoaversion, night blindness and the oculodigital sign are found.[142] Mental retardation has been discussed but is presently not proven to be associated with LCA[142], although several syndromes with overlapping clinical features of LCA exist. In the progression of the disease in 75% of the patients the visual function remains stable, a deterioration can be observed in 15% and improvements are seen in 10%.[142,144] In most patients the inheritance is

autosomal-recessive and has a rare prevalence of only 1 in 50 000.[95] However, 5% of all inherited retinopathies are caused by LCA and so far at least 7 causative genes which play a role in the pathological pathway of both RP and LCA have been identified.[95,142] It is worth mentioning that LCA acts as a model for the approach with gene therapy.[145–147]

#### *3.4.1.4 Bassen-Kornzweig disease*

Abetalipoproteinaemia, also referred to as Bassen-Kornzweig disease (BKD), is a very rare form of familiar hypobetalipoproteinaemia with a prevalence less than 1 in 1 000 000.[101,148] BKD was first described by Bassen and Kornzweig in 1950, who reported a patient with symptoms seen in Friedreich's ataxia, a neurological syndrome, but additionally found malformed erythrocytes as never described before.[149] In further reports the clinical picture of the disorder was completed: progressive ataxic neuropathy (Friedreich type ataxia), crenated acanthocytosis, malabsorption, steatorrhoea, fatloading of the small intestines and atypical RP[101,118,150,151]; in some patients the variation retinitis punctata albescens can be observed.[136] Usually, first symptoms of BKD are ataxia and poor development. The generalized muscle weakness can also lead to partial ptosis, unilateral exotropia and nystagm.[150] In the majority of patients blindness is reached by the age of 18. Although BKD is characterized by permanently low levels of apolipoprotein B and LDL cholesterol[148], Scott et al. showed in a review that serum betalipoprotein can also be normal.[151] BKD is caused by an alteration of the lipoprotein metabolism leading to a deficiency of fat-soluble vitamins in the plasma.[118] A possible pathomechanism is the malabsorbtion of Vitamin A, which is needed in the visual pigment for functioning of the photoreceptors. In that matter the role of Vitamin A plasma level was discussed in the pathogenesis of RP since a high dose treatment of Vitamin A showed to result in a normal ERG response within 24 hours.[127,128] Also, in more current literature BKD is one of three syndromic forms of RP considered to be treatable by high dose treatment of vitamin A, D, E and K if early begun.[5]

#### *3.4.1.5 Refsum disease*

Refsum disease, also named heredopathia atactica polyneuritiformis, is another inherited disorder characterized by following major clinical features: atypical RP,

peripheral neuropathy, cerebellar ataxia and elevated protein levels in the cerebrospinal fluid without an increased number of cells (albuminocytologic dissociation).[101,152,153] Further neurologic symptoms such as nerve deafness, anosmia, skeletal abnormalities, ichthyosis, cataracts and cardiac impairment may appear.[95] The disorder is caused by a metabolic defect leading to increased levels of phytanic acid, which interferes with vitamin A in the rhodopsin cycle.[27] Specific details such as onset of RP and progression patterns have not been investigated so far.

Other syndromic forms of RP, of which more than 30 are known[102], are not of particular clinical importance and therefore not worth mentioning here.

## 3.5 Symptoms

Visual impairment in RP patients is presented through separate clinical manifestations: deterioration of the VF with scotomas and worsening of the VA. A decrease in color vision (dyschromatopsia) is described as well.[5,137] The symptoms of typical RP can be subdivided into an early-stage, mid-stage and end-stage.[5,27]

### 3.5.1 Early-stage

In the early-stage the degeneration of peripheral located rod cells leads to a scotopic ERG, even before the appearance of clinical changes.[5] As the rods mediate vision in dim light, their degeneration results in the typical symptom of night blindness in the age of young adulthood.[5,27,96,102] The VA is usually not affected at this point and patients have no limitations during normal life since our night time environment often is electrically illuminated.[5] In this stage the loss of the cones is not present or at least not noticeable due to the fact that the VA is only affected after 90% of the cones are lost.[102]

### 3.5.2 Mid-stage

As the disease progresses the clinical picture of RP is complete in the mid-stage: total blindness is apparent during night or in environments with dimmed illumination. Patients also often suffer from difficulties with light and dark adaption.[22,27] Further degeneration and loss of rod photoreceptors result in constriction of the peripheral VF and lead to tunnel vision, a characteristic

symptom. Cone photoreceptors, responsible for detailed vision and color vision, are highly concentrated in the macula. They are also affected by the degeneration process, leading to a VF constriction advancing towards the center. Studies by Szlyk et al. and Virgili et al. demonstrated that task performance and reading abilities are affected when the VF decreases below 50° in diameter and the $VA_{dec}$ decreases below 0.5.[154,155] In the mid-stage also the cone sensitivity is reduced and VA decreases below mentioned threshold. 93% of all RP patients describe an uncomfortable glare during daylight and become photopic in diffuse light conditions like cloudy weather or snowy landscapes.[5,137,156] Yellow and blue hues often seem pale, which can also be observed in clinical color vision tests.[5,22,102] In about half of the patients a cataract is observed.

### 3.5.3 End-stage

In the end-stage proceeding dystrophic events minimize the VF to only a few remaining degrees in the center.[5] With this residual VF most patients cannot fixate and useful vision for tasks such as reading is not possible anymore.[5] Patients cannot move autonomously without mobility aids and the QOL decreases. In its natural course the disease progresses until light cannot be perceived anymore.

In the atypical form of RP the cones are the first photoreceptors being affected and hence the loss of VA and defective color vision are the first noticeable symptoms.[102] However, later symptoms also include night blindness and the loss of peripheral VFs.[117]

### 3.5.4 Age of onset

Usually, the age at onset of both RP form ranges from early childhood to adulthood.[5,95,102] In a study by Massof et al. the age at onset in typical RP was 28 ± 13.8 years.[6] Haim et al. also included atypical RP patients and found a mean age at onset of 6 - 18 years.[110] The age at onset varies highly since it depends on the report of the first symptom. However, patients are not equally aware of their visual impairment.[102] In patients with night blindness from infancy, this early symptom is likely to be ignored until severe VF constrictions appear.[102] In such cases a relatively rapid progression seems to occur later on. The impairment of vision progresses over a wide span of time and often more than 20 years pass by until total blindness is reached.[5] When measuring the progression of the VF loss,

the time to lose one half of the remaining VF is 8.4 ± 4.9 years.[6] In general, the state of legal blindness is reached by the age of 40 and loss of the remaining central vision is reached at the age of 60.[102,118] It must be noted that there is a great variability in the clinical picture and not all of described symptoms must develop for a diagnosis of RP.

## 3.6 Diagnosis

The diagnosis of RP can be rather difficult and a large proportion of patients are diagnosed not before the disease has progressed to the mid-stage, after many clinical features have developed.[131] Therefore, it is important to follow a basic diagnostic protocol which should include an ophthalmologic examination, VF testing, VA testing, an electroretinogram (ERG) and pedigree analysis.[101]
The diagnostic criteria for RP, resulting from those examinations were defined by the International Symposium of Ophthalmology in 1982[157,158]: bilateral involvement, concentric constriction of the VF, decreased or no response in the ERG and progressive loss of the photoreceptor function.

### 3.6.1 Fundus examination

The goal of fundus examination is to assess eye structures in detail. Allvar Gullstrand, a Swedish ophthalmologist and Nobel prize winner, invented the slit lamp in 1911 for the examination of anterior structures of the eye.[159] With this method a light source, almost parallel to the observation angle, is brought into the eye and structures can be magnified through the use of biomicroscopy. However, in order to examine the posterior pole of the eye, the refractive effect of the cornea needs to be abolished. In 1918 Koeppe was the first to examine the fundus with a slit lamp and a contact lens.[160,161] Further development lead to the use of concave lenses (Hruby) or convex lenses (El-Bayadi, Goldmann), the latter being better suited for assessment of the retina.[162] In modern slit lamp biomicroscopy the pupil is dilated to at least 5 mm and bi-convex non-contact lenses are held in front of the eye. A stereoscopic observation system also allows a three dimensional examination of retinal tissues. By asking the patient to look in different directions, the central and pericentral regions of the retina can be inspected.

The description of the morphological findings in RP again follows the classification into three stages (see section *3.5 Symptoms*).[27] However, it must be understood

that *"clinical features vary considerably with duration of disease"* and that this is a generalized overview with many dissimilarities being disregarded.[27]

In the first stage the retina seems normal. First diagnostic clues are the presence of cells in the vitreous during slit-lamp examination[27,94,102] and little pigment dots with depigmented surrounding areas.[5,27] These pigmentary deposits will form clumpings in the later course of the disease. The retinal vessels as well as the optic disc also appear normal.[5,27] In the mid-stage one of the most characteristic findings, the intraretinal pigmentation, is seen during the fundus examination.[5,94,101,102,117,118,163] These pigmentary changes result from the degenerative process of photoreceptors and the atrophy of the outer retina, described as a loss of the RPE. Simultaneously, the RPE migrates into the neural retina in response to photoreceptor cell-death.[5,102,163] The pigmentary deposits accumulate in clusters, so-called bone spicule shaped formations[5,94,101,102,117,163] which are generally seen in the mid-periphery along with the atrophic retina. The distribution of the intraretinal pigmentation can either appear in a concentric shape, but often only covers patchy areas of the retina as described as window-like holes.[27,101,117] Although pigmentary deposits are a key feature of RP, they are not found in some patients and therefore the term ‘retinitis pigmentosa sine pigmento’ arised.[27,123] These patients show the same symptoms and a clinically significant ERG, and suffer from atypical RP in most cases.[27,164] Another divergent finding, often described as ‘retinitis punctata albescens’, shows *"numerous white dots scattered across the retina rather than pigment deposits"*.[27,96] In the mid-stage the retinal arterioles typically are narrowed/attenuated.[5,27,102,117,118,134,165] A posterior central subcapsular cataract can be observed in 41% of all RP patients.[5,27,102,166] In the end-stage the pigment deposits expand further towards the center. The RPE loss often results in a lobule structure, building white and dark flecks, as also commonly seen in fundus flavimaculatus.[27] The macula appears normal in only 20 - 30%; other abnormal findings include a macular edema, surface wrinkling, bull’s eye, atrophic or cystic appearance.[102,103] An interesting finding is the para-arteriolar preservation of the RPE which means that the RPE adjacent to retinal arterioles stays intact.[167] The optic nerve head as well as the nerve fiber layer develop atrophic changes. The appearance of the optic disc is often described with the presentation of a waxy

pallor and a decreased cup-to-disc ratio.[5,27,94,102,163] Due to RPE loss the choroidal vessels become visible (translucent fundus).[27,117] However, also the choriocapillaris shows signs of atrophy, which is well demonstrated during fluorescein angiography.[27,168] Although clinical signs and symptoms arise in the mid-stage, it has been shown that significant loss of ganglion cells and the nerve fiber layer does not happen before the end-stage.[103] Histological postmortem studies by Humayun et al. and Santos et al. have found that the ONL was most affected by the degeneration and only up to 3% of cells were preserved.[169,170] The GCL was less affected with 20 - 30% being preserved. However, in the INL an average of 40% preservation was found in the macular region.

Several other retinal patterns attributed to RP with variable clinical findings have been observed, such as *"vitelliruptive macular dystrophy, butterfly-shaped pigment dystrophy, fenestrated sheen macular dystrophy, and reticular dystrophy"*, *"pigmented paravenous retinochoroidal atrophy, helicoid parapapillary chorioretinal degeneration, sector retinitis pigmentosa, retinitis punctata albescens, and retinitis pigmentosa sine pigmento"*.[167]

### 3.6.2 Electroretinogram

The ERG has become one of the diagnostic key tests for RP, after decreased and absent electrical responses were observed in RP patients in the 1950s.[5,27,102,117] During the ERG the electrical response of the retina to stimulating light flashes is measured with either a contact lens or an eyelid electrode.[27,95,102] In healthy individuals the response shows a negative peak (a-wave) and a subsequent positive peak (b-wave). The a-wave represents the repolarization of the photoreceptor cells, whereas the b-wave results from bipolar cells in the INL.[27,102,117] Depending on the light stimuli different retinal cells can be distinguished.[95] In a photopic ERG (with a well-lit background) the function of the cone system is measured, while rods are bleached out and therefore remain non-responsive.[27] On the contrary, the rod system can be measured in a scotopic test condition with dim blue light or white light flashes below the cone threshold after the patient is dark-adapted for at least 30 minutes.[27] A bright white flash in a dark adapted state measures the electric response of rod and cone cells combined. In RP patients the amplitudes of rod and cone cells are reduced and the waves are disrupted due to a delay in timing.[102,117,118,171] Normal cone

amplitudes are ≥ 50 µV, in RP they are often reduced to ≤ 10 µV.[102] Roughly, a cone response of less than 0.05 µV can be compared with legal blindness and the loss of useful VA.[22,118] In typical RP the rods are primarily affected and therefore the scotopic ERG is the first to reveal decreased amplitudes; for atypical RP vice versa results are observed.[5,171] In most cases of recessive or x-linked inheritance the ERG is non-recordable, but this may account for all end-stage RP forms.[27,102,117]

In general, the decline of the ERG amplitudes can be seen even before first clinical features or symptoms are observed.[5,118,171] It has the potential to distinguish typical and atypical RP, to determine severity and progression in repeated measurements and is used as a control for therapeutic approaches.[27,102] For the interpretation and comparison of ERG results usually an age-matched normative database is used.[171] During electrophysiological testing it is important to conduct all examinations according to a standardized test protocol, since wave forms vary highly from laboratory to laboratory.[27] In 2003 Brigell et al. published guidelines for the calibration and test procedures for many electrophysiological tests like the ERG and its use is recommended for both clinical and research purposes.[171,172]

### 3.6.3 Visual function assessment in RP

#### *3.6.3.1 Visual acuity*

Although the VA is preserved relatively long after the onset of first symptoms[22,27,107], its measurement is a primary diagnostic element in RP. It can be used to determine the current status, for monitoring disease progression and to define legal definitions of blindness. In order to find out the average VA of most RP patients Grover et al. examined 906 RP patients and found that 55% of all patients had a $VA_{dec}$ of 0.5 or better, and only 8% had a VA of CF or worse.[22,107] Most patients remain with a $VA_{dec}$ of 0.3 - 0.5 for a long period of time. However, Marmor et al. found out that once the $VA_{dec}$ is worse than 0.5 it will decrease below 0.1 within 6 years.[173] Variations in the inheritance of RP have shown to affect the disease progression: patients with autosomal dominant inheritance in general show better VA than those with x-linked inheritance.[107] In the majority of

RP patients both eyes are affected equally with a difference in VA of not more than two lines.[107]

Although patients are not always aware of it, refractive errors are often found in association with RP.[27,94,118,174] Their correction can lead to significant improvements of VA at least in particular stages and they can give hints about the inheritance: myopia of 2 or more diopters is often found in x-linked RP, whereas hyperopia is common in dominant inherited RP.[102]

#### *3.6.3.2 Visual field*

The VF testing of advanced RP patients often requires relatively big light stimuli which can be provided by a Goldmann V4e target. The VF examination often provides clarity about the symptomatic extent and therefore often correlates with the handicap during daily living. It can also be used to monitor disease progression, especially in the early- or mid-stage, when loss of the peripheral vision becomes evident.

In RP patients the VFs are mostly symmetrical.[27] In the early-stage the VF loss is reserved to peripheral scotomas which converge in later stages and build ring scotomas. Visual field examinations often reveal a distinction between the typical and the atypical form: while the VF constriction in the typical form are ring scotomas of 30 - 50° with a long preservation of the central VF, in the atypical form the ring scotomas are located at 5 - 30°.[27,101] Berson et al. reported that an average decline of 5° can be expected over a 3-year interval when tested with a V4e target on a Goldmann perimetry.[27] Other reports find a yearly VF loss of 4.6 - 13.5%.[22]

#### *3.6.3.3 Contrast sensitivity*

As described above, measurements of the VA are conducted in a high illumination and high contrast setting (*1.3.1 Visual acuity*). However, it has been observed that in RP patients the VA loss is disproportionately greater as the luminance is decreased to low-adapting conditions.[175] Even though functioning foveal cones are still able to transduce light stimuli, the light absorption in RP is not as effective as in normal cones.[176] This conforms to the finding of reduced amplitudes in ERG measurements of both rods and cones and the reported difficulties of RP patients in dimmed illumination environments. Therefore, the CS is reduced in comparison

to healthy individuals.[134,175] This explains cases with a poor subjective vision while the high contrast VA measurements show inexplicably good results.[102] Herse et al. suggest that logMAR charts for VA measurements in RP patients should be adapted to the individual preferred light level.[22]

#### *3.6.3.4 Other visual function tests*

In the so-called dark adaption test, the difficulty in adaption to dark environments in RP patients can be demonstrated. Patients fixate to a red dot in a dark room for a maximum time of 40 min. Subsequently a test spot which increases in light intensity is presented. As soon as the patient can perceive the light, the intensity threshold is noted.[27] Color vision tests like the Nagel anomaloscope or the Farnsworth-Munsell 100 Hue test are used to depict abnormal color perception.[177]

### 3.6.4 Further diagnostic tools

The optic coherence tomography (OCT) is a diagnostic method to display the retinal layers as a cross section. This can be useful to analyze the retinal thickness and the remaining photoreceptor cells or for the diagnosis of a macular edema.[5]

Fluorescein angiography (FLA) is a method to visualize the retinal and choroid vessels. Although it is not commonly used in the standard diagnostic protocol, it can give valuable information about the attenuation of vessels, especially in case of cystoid macular edema.[27] Furthermore, FLA is often used for research purposes and it has been observed that areas with the highest amounts of autofluorescence due to abnormal vasculature produce the lowest ERG amplitudes.[102] Repeated FLA measurements are a good way to depict disease progression.

Fundus photographs are typically not involved in RP diagnosis but they can be useful for documenting fundus examinations and quantify the deterioration of specific clinical appearances in comparison with baseline photographs.[27]

### 3.6.5 Pedigree analysis

Although the genetic aspects of RP encompass a great variety of disease patterns, each patient should be undertaken a detailed analysis of the family history in order to find clues about the inheritance pattern.[27] So far, research investigations of clinical findings and symptoms in genetically tested RP patients have found several peculiarities of certain genetic subtypes. This is relevant to

arrange further diagnosis, especially if non-ocular problems arise.[27] For instance, a hearing test should be scheduled when Usher syndrome is observed in family members. Furthermore, a pedigree analysis could be used for the prognosis or the establishment of treatment plans, since many treatments only show successful results in certain subtypes.[5,27] A common question of RP patients is the rate of transmission.[178] Although there is no clear answer, for some patients a careful estimation of the likelihood can be made, based on the fact that *"three-quarters of patients with RP are not at risk to have children with the disease but will either pass a normal gene or pass the gene in a carrier state mode"*.[27] Molecular diagnostics are not conducted regularly since these methods are still expensive. Furthermore, the therapeutic benefit from genetic diagnosis is poor and does not justify the effort in most cases.

### 3.6.6 Differential diagnosis

In the diagnosis of RP a few conditions showing similar clinical pictures have to be considered in order to distinguish RP and its syndromic forms from other diseases. Night blindness can be a consequence of panretinal photocoagulation therapy in proliferative diabetic retinopathy, due to zinc and vitamin A deficiency or choroideremia.[22] Furthermore, end-stage retinopathies from luetic chorioretinitis or congenital rubella can show similar fundus changes as seen in RP.[22,110] A blood test on FTA-ABS can be used to exclude a syphilis infection.[27] However, a full diagnostic examination is recommended in doubtful cases.

## 3.7 Therapy

In the treatment of RP two approaches can be distinguished. The causal therapy aims to preserve the remaining photoreceptors or at least to slow down the disease progress.[178] The second approach encompasses the rehabilitation for the patient including devices to support and facilitate daily living. In both approaches the biggest challenge is the broad variety of RP types and symptoms. Hence, the treatment has to be adapted on an individual base.[179]

Clinicians agree that an annual examination including funduscopy, VF and VA tests, refractive measures and intraocular pressure should be performed in any case.[27,180,181] ERG measurement should be conducted every 5 years.

### 3.7.1 Causal therapeutic approaches

In the past decade there have been several attempts to find causal treatment concepts, including approaches with vasodilating substances, biogenic stimulation through placentic tissue implantation, hyperbaric oxygenation, transcorneal electrostimulation or acupuncture.[5,111] However, none of them showed relevant effects when evidenced-based medicine criteria were applied. Currently there is no causal treatment available to cure RP.[178] More recent studies will be listed in the following.

#### *3.7.1.1 Nanometer-controlled filtering lenses*

It is known that the ultraviolet spectrum of light has the potential to cause damage to the retina through the release of radical oxygen.[178] A concern about reduced repair mechanisms in RP patients has been raised since observations showed more severe disease courses in patients working outside.[27] Although animal studies have shown a reduction in the rate of degeneration when kept in constant darkness[182], reports about the occlusion of one eye in humans showed no difference in the funduscopic appearance nor in the ERG.[102] Nonetheless, nanometer-controlled filtering lenses with orange, red or yellow filters are often used to reduce photopic symptoms.[5,22,178] They reduce potential toxic wavelengths in the blue and ultraviolet spectrum. The glasses should feature side shields, since patients report the most discomfort from oblique light. If a cataract extraction is intended, the implantation of violet or blue blocking lenses should be considered.

#### *3.7.1.2 Nutritional supplementation*

One of the most discussed topic is the nutritional intake of various antioxidant supplements like vitamin A, vitamin E or omega-3 fatty acids in order to slow down the disease process of RP.[102,118,128] The nutritional supplementation of antioxidants shows potential to slow down disease progression in RP.[102,118,128] The complementary intake of vitamin A palmitate is common in the US[183], mainly for the treatment of cancer but also for treating RP. Given the fact that vitamin A is essential in the retinal metabolism[129], a supplementation appears to be reasonable and doses above the daily biological need up to 25 000 IU have proven to have no toxic effect.[184] However, an annual control of liver enzymes and vitamin A levels are recommended.[102,181] The positive effect of vitamin A has been proven in

certain sub-groups of RP such as Refsum syndrome or BKD.[111] When it comes to the treatment of all forms of RP the proof of a positive effect is controversial. In a study with 601 RP patients who took 15 000 IU of vitamin A palmitate and 400 IU vitamin E over 4 - 6 years a slowed down decline of ERG amplitudes has been observed in comparison to the control group.[185] Vitamin E application showed a negative effect on ERG amplitudes. A subsequent analysis revealed also a slowed down VF loss during the supplementation of vitamin A.[102] In both studies the effect of a slowed down progression was significant, but modest. Therefore, a general recommendation of vitamin A supplementation is still questionable and possible hepatogene side effects should be kept in mind.[5,102,178] Another supplement which is under discussion for the treatment of RP is Docosahexaenoic acid (DHA). It is an omega-3 polyunsaturated fatty acid which is highly contained in photoreceptors. Therefore, a deficiency might play a role in the metabolic development of RP.[102] Patients with RP have lower DHA amounts in erythrocytes, but in a study by Hoffmann et al. with x linked RP patients the supplementary intake of 400 mg DHA per diem did not show significant improvements in comparison to placebos.[186] However, in another study where DHA was given combined with vitamin A, a slower decline of the VF sensitivity was observed.[187] Whether this effect can be attributed to vitamin A, DHA or the combination of those two supplements is still not clear and recommendations of DHA intake vary among clinicians.

#### *3.7.1.3 $Ca^{2+}$ channel blockers*

Further hypotheses about pharmaceuticals are still a topic of research. $Ca^{2+}$ channel blockers, as commonly used in coronary heart disease, might have a neuroprotective effect and could preserve the central VF in degenerative retinal diseases.[178,188] However, these hypotheses could not be confirmed yet in empirical studies.[5,189]

#### *3.7.1.4 Gene therapy*

During the last decade the therapeutic approach with gene therapy was intensively investigated with the model of LCA caused by a RPE65 mutation. In this disorder the activation of opsins in the visual cycle is affected and the initial process of light transduction is interrupted.[147,190] During the gene replacement therapy a normal

copy of the gene is injected subretinally and the local production of the missing protein is expected to lead to a correction of the biochemical abnormalities.[102,147] Animal studies in mice, canines and in dogs have demonstrated a significant rescue of photoreceptors.[5,102,147,190] Phase I human trials have shown the safety of this method. However, the resulting VA improvement is variable and photoreceptor cell death was still ongoing.[5,147,190] A similar method to the gene replacement therapy can be performed in autosomal dominant mutations: the mutant gene is removed by splicing and the residual normal genes are expected to express the functional proteins.[102] It must be kept in mind that both methods require residual photoreceptor cells in order to function and are not ready to be included as standard RP treatment.[191]

#### *3.7.1.5 Cell death prevention*

Further methods to prevent progressing cell death are under investigation, such as the gene transfer of antiapoptotic factors or the infection of cells which produce neuroprotective growth factors.[5] Although they have shown side effects in experimental studies, phase I clinical trials are ongoing.

#### *3.7.1.6 Treatment of comorbidities*

Last but not least, the treatment of comorbidities is an important part of the overall therapy of RP, since it can considerable improve the visual function in some patients. A posterior subcapsular cataract can be found in 41% of all RP patients.[27,178] Especially in typical RP the remaining central and paracentral vision can be blurred and therefore the role of lens opacities causing visual loss could be crucial for a longer preservation of the VA.[5,107] Furthermore, the cataract can aggravate photopic symptoms. A careful examination including BCVA with dilated and undilated pupils should be done in order to ensure visual improvement and avoid unnecessary cataract extractions, which could in turn aggravate an existing cystoid macular edema.[27,178] However, a macular edema is a typically seen complication observed in RP all patients.[5,102,178] It is induced by changes in vitreoretinal structures, tractional changes in the vitreoretinal limiting membrane or inflammatory processes.[178] The macular edema may be the cause of additional loss of VA and CS.[5,178] OCT measurements are used to determine the severity

and to decide whether or not to use carbonic anhydrase inhibitors (up to 500 mg daily) or corticosteroids for treatment.[5,102,181]

### 3.7.2 Rehabilitative management

The rehabilitative management aims to intervene at the stage of functional vision to relieve disabilities.[9] Modern treatment of visually handicapped patients should be multidisciplinary, which means not only supplying the best medical treatment, but also improving the visual function as best as possible, improving the everyday situation and helping to cope with the social and the psychological impact of blindness.[22,27,136]

#### *3.7.2.1 Psychological support*

The psychological coping with RP is the first step in the rehabilitation. Heckenlively describes two stressful periods for RP patients: at first, finding out about the disease and secondly, when the disease leads to disabilities in everyday life or the state of legal blindness.[27] Patients with visual disabilities can often be separated into two groups: those who accept their condition are likely to seek actively for further possibilities to improve their situation. Although having severe visual impairment they still show a good attitude towards coping with difficult or unfamiliar situations during daily life. On the contrary, those who fail to cope with their disease have poorer rehabilitation prospects and reports show that up to 25.7% of all RP patients develop a depression.[7,22,27,192] For clinicians it is important to diagnose a latent depression and provide professional psychological help for those in need. In any case, once the patient has accepted his condition, the rehabilitation is far more successful and patients become susceptible for further arrangements.[7,22]

#### *3.7.2.2 O&M Training*

An O&M training covers many important features in low vision rehabilitation. Patients learn strategies how to handle specific situations in public, on the street, in the workplace or at home. These strategies include how to navigate using their remaining vision, how to handle mobility aids, how to walk with a sighted guide or a guide dog, and how to use other senses in order to adjust to the environment (sensory substitution).[193,194] In addition, associations for the blind allow suffering

patients to gather experience from other persons concerned. Doctors and optometrists should not hesitate to refer patients to such organizations for rehabilitative treatment purposes.[22]

Typical RP patients have a restricted peripheral VF. Therefore, they often have difficulties in obstacle identification affecting O&M. Maintaining the ability to move to different places independently is an important societal demand for many ADL and can be improved with various techniques. The most widespread mobility aid is the long cane (or white cane).[22,195] It is a simple but reliable tool for the detection of obstacles from the waist below, surface textures, drop-offs or steps. In many countries streets are equipped with reliefs detectable for canes, leading the way to entrances of buildings, stops for public transportation or crosswalks. Additionally, disabled patients are easily recognizable in public and vehicle motorists can act with appropriate caution. Yet for many patients it is a psychological hurdle to take up a cane as they do not want to stand out from others in the public.

During the last decades many electronic mobility aids (or electronic travel aids) were developed to provide the visually impaired with environmental information through other sensory modalities (sound or vibration).[22] Such devices are based on ultrasound or laser sampling and can detect obstacles, help orientating or function as navigation systems.[70] Patients usually have to afford them on their own since health insurance does not cover their expenses in most countries. Furthermore, the use of mobility devices requires additional concentration for handling. For many patients this often does not stand in relation to their benefit.

#### *3.7.2.3 Low vision aids*

Although legally blind, many RP patients can use the remaining central VF for reading for a relatively long time. When CS and VA decrease, various near magnification devices are useful to preserve the reading ability: visolettes, bar magnifiers, hand magnifiers or so-called closed-circuit televisions (CCTV).[22,27] For distance magnification some patients may use hand-held telescopes with magnification of up to 3x.[22,27] A common problem of RP patients is the lack of peripheral object identification. Reversed telescopes can provide an extended VF, but with these tools objects are reduced in size and the use of telescopic aids may

restrict scanning movements of the eye. Therefore, these devices are often rejected by patients.[22]

For the operation of modern mobile smart phones with touch screens, many applications with gesture control and voice output are available so that blind patients can make phone calls, write short text messages or even search the internet.[196] While the capability of Braille reading is essential for many tasks such as office jobs, it can be expected that computer-directed activities with text-to-voice programs, virtual Braille technologies or audio books will gain importance in near future.[197,198]

#### *3.7.2.4 Retinal prostheses*

The development of artificial vision is a promising approach for the rehabilitative therapy of RP.[191,199,200] It is based on the principle to elicit visual perception by electrical stimulation of neurons[201,202], similar to the mechanism of cochlear implants. For vision restoration several approaches have been established: stimulation of the visual cortex, the optic nerve or the retina.[203–208] The latter requires preserved ganglion cells, an intact optic nerve and the preservation of successive neuron tracts for the signal transduction.[205] The pathologic findings of RP comply with these requirements and multiple research groups are now investigating the function of retinal implants in clinical trials.[116,202,209–215] During the past decade two strategies for triggering light flashes from the retina have been investigated in detail: the subretinal implant receives light with a microphotodiode array and transmits these stimuli electrically to the middle and inner retinal layers.[215] The second approach is the epiretinal placement of the electrodes which stimulate the neuroretinal network via the ganglion cells while the receiving computer chip is placed on the eye bulb.[201,202] A visual interface with a connected pocket processor serves as the recording and processing unit, forwarding the stimulation patterns via infrared or radiofrequency into the eye.[201] In both approaches there have been considerable developments during the last decade: products have been approved by the Food and Drug Administration and European Union (CE mark) and further phase III clinical trials are ongoing with refined technologies.[216]

The advantage of the electric retinal stimulation is that a defined point on the retina can be assigned to a localized visual sensation in the VF. However, it must be kept in mind that artificial vision only produces light flashes, which must be interpreted by the patient in order to use it for orientation. Hence, a rehabilitation process is necessary. Its goal is to give patients a rough impression of the environment and allow independent O&M.[74,191,205] This already has been proven in several studies.[215] Current resolutions reach from 7x7 to 38x40 pixels and it has been shown that this marginal information is enough for the orientation in unfamiliar areas, to identify objects, or even for reading large letters. After all, this novel kind of vision raises many further questions about the induction of appropriate visual stimuli, the long-term stimulation and the general use of artificial vision in daily life.

# 4 Conclusion

Based on the intensive research on therapeutic interventions at present, it has been proposed that new treatments will be able to help a subset of RP patients within the next 5 - 10 years.[102] Besides the therapeutical aims, it is an essential task to measure vision enhancement objectively in order to allocate money for health care for the visually impaired as well as the research in corresponding fields.[217,218] At present, legal blindness and the categorization of financial aids is defined by visual function criteria. However, in the field of low vision the measurement of visual functions (VA and VF) may not be appropriate to depict minor visual increments, since they only partially cover the aspects of visual disability.[36] An example is given by the measurement of VA: studies have found a variability of up to two lines in conventional VA tests.[39,219,220] In low vision patients the variability of these results is expected to be even higher.[41] Therefore, it can be assumed that the assessment of functional vision is the most suitable method to determine the degree of visual disability. Currently, the interdisciplinary network of researchers, clinicians, optometrists, low vision experts as well as politicians is in need of a method to measure functional vision accurately in low vision patients.[47] Once such a test is established, it can also be used to document vision improvement due therapeutical intervention such as retinal prostheses. There are manifold requirements for functional vision tests: On one hand such tests should examine the handicap in daily life. On the other hand, they should follow a standardized test method. Furthermore, a functional vision test should be designed to adequately challenge those persons within the range of visual impairment, which cannot be assessed by conventional ophthalmological methods. It has been shown that reading and mobility cause major problems for visually impaired individuals.[221,222] Special emphasis should be placed on the maintenance of navigational skills, since independent O&M is a major contributor to the functional vision.[74,222] Questionnaires can be used to document independent mobility[61], but may be biased by subjective influences. Therefore, it can be expected that task performance tests will play an important role for the monitoring of visual progress in the future.

# 5 References

## 5.1 List of literature


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## 5.2 List of tables