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Morphological and functional aspects and quality of life in patients with achromatopsia

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Dedicated to the memory of my beloved grandmother, Rosemay

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1. Glossary

AAV - Adeno-associated virus

ACHM - Achromatopsia

ATF6 - Activating Transcription Factor 6

CNGA3 - Cyclic nucleotide-gated Channel Subunit Alpha 3 - Cyclic nucleotide-gated cation channel alpha-3 is a protein, that in humans is encoded by the CNGA3 gene. This gene encodes a member of the cyclic nucleotide-gated cation channel protein family, which is required for normal vision and olfactory signal transduction. CNGA3 is expressed in cone photoreceptors and is necessary for colour vision.

CNGB3 - Cyclic nucleotide-gated Channel Subunit Beta 3 - Cyclic nucleotide gated channel beta 3, also known as CNGB3, is a human gene encoding an ion channel protein.

CNTF - Ciliary neurotrophic factor

Dpt - Diopters

ER - Endoplasmic reticulum

ERG - Electroretinogram

GNAT2 - Guanine nucleotide-binding protein G subunit alpha transducin 2 - Guanine nucleotide-binding protein G(t) subunit alpha-2 is a protein that in humans is encoded by the GNAT2 gene. Transducin is a 3-subunit guanine nucleotide-binding protein which stimulates the coupling of rhodopsin and cGMP-phosphodiesterase during visual impulses.

SD-OCT - Spectral-domain optical coherence tomography

ISE - Inner segment ellipsoid

LogMAR - Logarithm of the minimum angle of resolution - A logMAR chart (Logarithm of the Minimum Angle of Resolution) is a chart consisting of rows of letters that is used by ophthalmologists, orthoptists, optometrists, and vision scientists to estimate visual acuity.

RPE - Retinal pigment epithelium

FAF - Fundus autofluorescence

FTRT - Foveal total retinal thickness

LVA - Low vision aids

ONL - Outer nuclear layer

PDE6C - Phosphodiesterase 6C - PDE6C (Phosphodiesterase 6C) is a protein-coding gene. Diseases associated with PDE6C include Cone Dystrophy 4 and Achromatopsia.

PDE6H - Phophodiesterase 6H - The *PDE6H* gene provides instructions for making one part (called the inhibitory gamma subunit) of an enzyme called cone-specific phosphodiesterase. This enzyme is found exclusively in light-detecting (photoreceptor) cells.

UKS - University Hospital of Saarland

UPR - Unfolded protein response

VA-CAL test – Visual acuity at different levels of contrast and ambient luminance test

2. Summary

2.1. Summary

Purpose: Achromatopsia is a very rare disease encompassing complete colour blindness, severe glare sensitivity and visual impairment. The natural course of the disease and impact on life are still not completely understood to this date. Here, we aimed to assess the morphological, functional characteristics, and quality of life in a large sample size of patients with achromatopsia.

Methods: A total of 94 people with achromatopsia were included in this retrospective cohort study. Sixty-four were patients of the Department of Ophthalmology, Saarland University Medical Centre in Homburg/Saar, Germany, between 2008 and 2021. Thirty further participants with achromatopsia from the German national support group (https://www.achromatopsie.de) were included using an online questionnaire. Statistical analysis was performed using SPSS Version 25.

Results: The 94 patients (37 males (39.4%) and 57 females (60.6%)) showed a mean age of 24.23 ± 18.53 years. Visual acuity was stable (1.0 logMAR ± 0.2) over a time of observation from 2008 to 2021. Refractive error was comparable to healthy subjects, with the mean spherical refraction being +1.83 diopters ± 3.76 and the mean astigmatic refraction being -1.86 diopters ± 0.88. However, it did not correlate with visual acuity. Pathological findings were seen in the anterior segments and the optic nerve head only in later adult years. The mean age of diagnosis established was 6.49 ± 1.50 years. The type of school visited (mainstream versus specialized low vision schooling) did not influence academic achievements. Edge filter glasses are the most used optical aids while reading glasses are the most used low vision aids. No genotype-phenotype correlation was found when both, functional and anatomical features were taken into account.

Conclusion: Our findings give a first insight into describing the natural development and the quality of life of achromatopsia. The results demonstrate that achromatopsia is a predominantly stationary disease with small morphological changes over time. Academic performance does not seem to be affected by achromatopsia. The individual prescription of edge filters and low-vision aids is essential following a personalised fitting.

2.2. Zusammenfassung

Ziel: Achromatopsie ist eine seltene Krankheit, deren natürlicher Verlauf und Auswirkungen auf das Leben bis zum heutigen Datum noch weitgehend unbekannt sind. Hier werden wir die morphologischen, funktionellen Merkmale und die Lebensqualität bei einer großen Stichprobe von Patienten mit Achromatopsie analysieren.

Methoden: In diese retrospektive Kohortenstudie wurden insgesamt 94 Personen mit Achromatopsie aufgenommen. 64 davon waren Patienten der Klinik für Augenheilkunde des Universitätsklinikums des Saarlandes in Homburg/Saar, Deutschland, zwischen 2008 und 2021. Weitere 30 Teilnehmer mit Achromatopsie aus der nationalen Selbsthilfegruppe wurden mithilfe eines Online-Fragebogens einbezogen. Die statistische Analyse wurde mit SPSS-Version 25 durchgeführt.

Ergebnisse: Die 94 Patienten (37 Männer (39,4%) und 57 Frauen (60,6%)) zeigten ein Durchschnittsalter von 24,23 ± 18,53 Jahren. Die Sehschärfe war über einen Beobachtungszeitraum von 2008 bis 2021 stabil (1,0 logMAR ± 0.2). Eine Refraktionsanomalie war häufig, korrelierte jedoch nicht mit der Sehschärfe. Pathologische Befunde wurden nur in fortgeschrittenem Alter in den vorderen Augenabschnitten und am Sehnervenkopf beobachtet. Das Durchschnittsalter bei der Diagnosestellung betrug 6,49 ± 1,50 Jahre. Die besuchte Schulart (Regelschule versus Schule mit Förderbedarf Sehen) beeinflusste nicht die schulischen Leistungen. Kantenfilterbrillen sind die am häufigsten verwendeten optischen Hilfsmittel, während Lesebrillen die am häufigsten verwendeten Sehhilfen sind. Es wurde keine Genotyp-Phänotyp-Korrelation, sowohl hinsichtlich funktionaler als auch anatomischer Merkmale, gefunden.

Diskussion: Unsere Ergebnisse geben erstmals Einblick in die Beschreibung des natürlichen Verlaufs und der Lebensqualität bei Achromatopsie. Die Ergebnisse zeigen, dass es sich bei Achromatopsie um eine überwiegend stationäre Erkrankung mit geringen morphologischen Veränderungen im Laufe der Zeit handelt. Die schulische Leistung scheint von Achromatopsie nicht beeinflusst zu werden. Die individuelle Verschreibung von Kantenfiltergläsern oder -kontaktlinsen und Refraktionskorrekturen, sowie Sehhilfenverordnungen ist nach einer personalisierten Anpassung unerlässlich.

3. Introduction

3.1. Background & Overview

Achromatopsia, known as colour blindness or rod monochromatism, is a seldom encountered hereditary condition that follows an autosomal recessive inheritance pattern. Its occurrence is estimated to be approximately 1 in 30,000 births globally [43].

To this date, researchers have linked 6 genes to achromatopsia, including the CNGA3 (OMIM #216900) [52], CNGB3 (OMIM #262300) [62], GNAT2 (OMIM #613856) [25], PDE6C (OMIM #613093) [13,23] and PDE6H (OMIM #610024) [33], which play a role in the phototransduction cascade [22]. These five genes play a role in encoding functional components of the phototransduction cascade. In addition to these five genes, ATF6 is also a gene implicated in ACHM, which manages the unfolded protein response (UPR) and maintains cellular endoplasmic reticulum (ER) homeostasis [38,39].

Achromatopsia is highly prevalent in the small coral island of Pingelap in the Western Pacific, belonging to the Federated States of Micronesia. Consanguinity is common, as 6-10% of Pingelapese islanders are affected, with 30% of inhabitants being carriers of the condition. This is because of the impact of Typhoon Lengkieki in around 1780, which devastated the island, leaving only 20 survivors, who had to go into complete geographical and cultural isolation [11,55].

It is typically characterized as a cone dysfunction syndrome [1]. Individuals with achromatopsia, often called achromats, encounter challenges in distinguishing colours along the three dimensions of colour vision, which correspond to the three types of cone cells: the protan or long-wavelength-sensitive cone dimension (associated with red), the deutan or middle-wavelength-sensitive cone dimension (associated with green), and the tritan or short-wavelength-sensitive cone dimension (associated with blue) [34].

Achromatopsia is categorized into two distinct types: Firstly, complete achromatopsia, characterized by the absence of any operational forms of the three cone types, resulting in total colour blindness. Secondly, partial achromatopsia or incomplete achromatopsia, which exhibits varying degrees of residual cone activity [47].

A special form of achromatopsia is acquired achromatopsia. It can be caused by a traumatic cerebral injury, a brain infection, ischaemia or encephalitis. This can lead to a small lesion in the ventral occipital cortex, which can cause a severe deficiency in colour vision. This condition

can be differentiated from complete achromatopsia, as it is typically associated with neurological signs [10].

3.2. Symptoms

The symptoms in achromatopsia are [9,16,34,48]:

- pendular nystagmus, typically with high frequency and very low amplitude
- severe photophobia (sometimes factual hemeralopia – day blindness)
- poor visual acuity (in complete ACHM less than 20/200; in incomplete ACHM between 20/80- 20/200)
- decreased / complete lack of colour perception (incomplete ACHM allows some degree of colour perception)
- eccentric fixation
- small central scotoma
- refractive error (with hypermetropic error being the most frequent)
- The Flynn phenomenon (a unique feature in ACHM, characterised by a paradoxical constriction of the pupils, 2-3 minutes after moving from brightness to darkness

Images 1 & 2: Normal (Trichromatic) vision & Monochromatic vision [42]

3.3. Diagnosis

The use of a series of various ophthalmological diagnostic techniques as well as molecular genetics analysis in the evaluation of ACHM patients proves highly beneficial to describe the condition and any related modifying factors [37].

Following tests are used to confirm the diagnosis of ACHM:

- Clinical and family history can help in determining the diagnosis by the mode of inheritance, with family trees being an important tool [46]
- Examination for nystagmus [50]
- Visual acuity testing [50]
- Colour vision testing [50] (can be unreliable since patients may distinguish colours based on variations in brightness / shades of grey or acquired knowledge of object-colour associations)

  - Rayleigh anomaloscope equation's red-green colour discrimination test is the most reliable colour vision test in ACHM. While a complete achromat can always match the spectral yellow primary to any spectral red and green primary mixture, a brightness match is only achievable with red primary-dominated mixtures [34].

  - Farnsworth Munsell 100 hue test, where no specific axis of colour confusion is found [34]

  - Panel D-15 test: The achromat axis, which arranges the constituent colour chips based on their rod-perceived brightness, is a unique feature of complete achromatopsia in both the saturated and desaturated forms [34]

When ACHM is suspected, additional testing can be performed:

- Funduscopic examination [50]

  - Four different phenotypes of fundus autofluorescence have been described [19]

  1) approximately normal appearance

  2) centrally increased signal

  3) central area with a decreased signal

4) central area with a decreased signal, surrounded by a ring of hyper-autofluorescence

- Spectral-domain OCT (SD-OCT):

  - Grading with five different morphological aspects of the fovea [54]:

  1) A continuous inner segment ellipsoid (ISE)

  2) A disrupted ISE

  3) Absence of ISE

  4) Presence of a hyporeflective zone

  5) Atrophy of outer retinal layers & RPE loss

- Visual field (can be challenging due to unstable fixation) [34]
- Electroretinogram (ERG)

  - Full-field ERG:

  In a full-field ERG, the limited number of photoreceptors in the fovea, compared to the entire retina, may obscure the detection of pathological changes in ACHM. Typically, photopic responses are significantly diminished, while scotopic responses remain relatively intact. In ACHM, a full-field ERG would reveal a lack of cone response due to the absence of functioning cones [34].

  - Mutifocal ERG:

  Multi-focal ERG eliminates the influence of the peripheral retina. Usually In ACHM, there is a reduced or no response from a 30 or 15-Hz stimulus in the fast cone pathway, evoked by intense light stimuli. However, with multi-focal ERG, it Is impossible to distinguish between complete and incomplete ACHM [7].

3.4. Management & Treatment

Although there is presently no established remedy, a number of methods can help relieve specific ACHM symptoms. One of the most challenging aspects of achromatopsia is photophobia, which requires a range of supportive measures to address effectively [2]. These can comprise of red-tinted contact lenses (so-called edge filters), sunglasses, wrap-around eyewear, as well as specialized filter glasses, all of which have demonstrated efficacy in alleviating light sensitivity and enhancing visual acuity [50].

Standardised tests, such as the visual acuity at different levels of contrast and ambient luminance (VA-CAL) test, show that using short-wavelength limit filter eyewear can improve the daily lives of individuals with achromatopsia by preventing the occurrence of pronounced visual disability when encountering differences in common objects and ambient lighting conditions [29]. Red-tinted edge filter contact lenses, in particular, have proven to be especially beneficial for individuals with achromatopsia due to their discreet nature when compared to darker, red-filtered eyewear. Assistive tools for individuals with reduced vision, like high-powered magnifiers and electronic devices, prove valuable for reading. To ensure children with ACHM fully utilize these tools (e.g., situated at the front of the classroom and shielded from disruptive glare or positioned away from windows), they should be granted priority seating in class [50,51].

Gene therapy has shown promise in treating hereditary diseases, including conditions like achromatopsia. In gene substitution therapy, a defective gene is replaced with a functional copy. These treatments are designed to slow the progression of the disease and, ideally, restore visual function. Gene therapy is typically delivered to the retinal cells through subretinal (SR) or intravitreal (IVT) injection methods [41,43,45]. Studies with several animal models, including dogs, mice, and sheep, have demonstrated the effectiveness of adeno-associated virus (AAV) based gene replacement to restore cone function in ACHM, with an improvement in visual acuity, colour discrimination and visually guided behaviour [4,8,14,17,18,26,35,44,61]. People afflicted with ACHM after gene therapy can discern a stimulus' colour attribute, albeit in a manner that varies significantly and is exceedingly limited compared to sighted individuals [40].

The Neuroprotective protein ciliary neurotrophic factor (CNTF) also demonstrated the ability to induce temporary restoration of cone function and visually directed behaviour in a CNGB3 dog model [36]. However, CNTF did not show a change or improvement in visual acuity, colour discrimination and no cone-driven photopic ERG responses were found [63].

Trials with the use of gene therapy in CNGA3-linked achromatopsia showed no significant safety concerns and correlated with an improvement in visual acuity [20,49] good lit choice. Thus, gene therapy shows a promising potential as a treatment for achromatopsia, offering a hopeful outlook for the future.

3.5. Contradictions & Gaps in literature

Researching ACHM poses significant challenges due to its rarity and the difficulty of obtaining a substantial sample size. This inherent complexity is amplified by an ongoing debate within the field regarding whether achromatopsia is a stationary or progressive condition. While some studies suggest that the disease stays stable, other studies imply that it may worsen over time, leading to contradictions in the literature. Some studies have found that visual acuity remains stable with age [5,25,54], while others have suggested that it deteriorates over time [12,56,59]. Similarly, some studies have reported stable SD-OCT changes [3,21,54], while others have found cone photoreceptor and outer retinal thickness loss over time [56,58,59]. Fundoscopy has also shown mixed results, with no fundus changes over time [54] or macular atrophy [32]. Furthermore, while some studies have reported no changes in FAF [3,30,60], others have suggested age dependent changes [19,27]. Here, of course, natural age-related changes have to be differentiated.

As human gene therapy trials advance rapidly, it becomes essential to clarify the natural course of achromatopsia and establish correlations between genotype and phenotype. This acquired knowledge will play a pivotal role in selecting suitable candidates and determining the most opportune timing for treatment.

Despite the significant impact that achromatopsia can have on an individual's ability to perform everyday tasks and engage in certain activities, there has been very little research conducted on this topic within the literature. While studies have largely focused on colour blindness [53], the further impacts of ACHM have been overlooked. Only one study to date has researched the impact of photoaversion in ACHM [2]. However, in order to identify effective interventions to improve the wellbeing of those affected by this condition, it is crucial to understand the important psychosocial aspects of achromatopsia. Thus, evaluating the quality of life of achromats is a critical step in gaining a comprehensive understanding of the effects of this condition on everyday life. By doing so, researchers and healthcare providers can develop targeted interventions that aim to improve the quality of life of those affected by ACHM.

3.6. Aims

The Department of Ophthalmology at the University of Saarland (UKS), known for its expertise in treating achromatopsia, attracts patients with this disease from all over Germany. The "Achromatopsie Selbsthilfegruppe" support group in Germany, led by Hans-Werner Merkelbach, comprises many individuals with achromatopsia. This inspired us to conduct a retrospective study with a significant sample size, including all of our achromatopsia patients who visited our clinic between 2008 and 2021, as well as voluntary participants from the support group.

The aims of this study were:

- To evaluate the morphological and functional features of ACHM during follow-up
- To assess the impact of the quality of life of achromats

4. Materials and Methods

4.1. Study design

Essential parts of this work have already been published [15]. This study is a retrospective cohort analysis of 94 patients who were diagnosed with achromatopsia, either clinically or molecularly. The cohort consisted of 64 patients who visited the Department of Ophthalmology, Saarland University Medical Center in Homburg/Saar, Germany between 2008 and 2021, and 30 participants from a German support group called "Achromatopsie Selbsthilfegruppe e.V" (www.achromatopsie.de). The exclusion criteria for participation were a lack of confirmation of achromatopsia diagnosis or the presence of other ocular diseases such as aniridia or blue cone monochromatism. The study was approved by the local ethics committee of Saarland (Ethikkommission bei der Ärztekammer des Saarlandes (Nr. 85-21) and adhered to the Declaration of Helsinki's principles.
Prof. Dr. Käsmann-Kellner primarily diagnosed and followed up with the patients in our department from 2008 to 2021, creating a list of all patients with achromatopsia. Before joining the self-help group, members needed to have a confirmed diagnosis of achromatopsia.

Target size
Due to the rarity of achromatopsia, studies with a large sample size are challenging to conduct, as noted in existing literature. This motivated us to undertake the present study, in which we aimed to include as many patients with confirmed achromatopsia cases as possible to improve our understanding of the population's characteristics.

Clinical diagnosis
A diagnosis of achromatopsia was clinically confirmed based on the presence of symptoms such as reduced visual acuity, colour vision impairment, photophobia, and nystagmus. It was confirmed by ERG.

Molecular diagnosis
The molecular diagnosis of achromatopsia was determined by identifying mutations in one of the six genes known to cause the condition: CNGA3, CNGB3, GNAT2, PDE6H, PDE6C, or ATF6.

4.2. Collection of data

Medical history

We collected essential medical data from our clinic's internal computer systems SAP and FIDUS, including medical letters from our clinic and other healthcare providers. Data from older patient visits were retrieved from SAP, while newer data was obtained from FIDUS. All patients with achromatopsia, regardless of their visit type (ambulatory or inpatient) or clinic source, had their files analysed. The data collected from the medical charts included various aspects such as age, gender, age at diagnosis, diagnosing physician, visual acuity of both eyes at first visit and currently, standardized colour tests, subjective colour perception, spherical and astigmatic refractive errors of both eyes, anterior segment findings, retinal arterial vessels, fundus periphery, macula, optic nerve head, presence of strabismus and nystagmus, low vision aids (LVA), LVA prescribed at our department, use of visual and electronic aids, and mutated gene.

4.3. Examination tests

4.3.1. Visual acuity

Visual acuity was assessed using a Landolt eye chart for each eye separately, and the mean of the right and left eye was calculated to determine the average visual acuity. In achromatopsia, it is well known that both eyes do not differ a lot in visual acuity.

4.3.2. Standardised colour tests and subjective perception of colours

To evaluate colour discrimination and subjective perception, the Ishihara colour test and the Farnsworth Panel D-15 test were conducted, in addition to a large area colour recognition test.

4.3.3. Refraction

Spherical and astigmatic refraction was determined using retinoscopy and autorefractometry.

4.3.4. Anterior segment findings

A slit-lamp was used to investigate the anterior segment findings.

4.3.5. Retinal arterial vessels, fundus periphery, macula, optic nerve head

The retinal arterial vessels, the fundus periphery, the macula and the optic nerve head were analysed with the help of a direct or indirect ophthalmoscope.

4.3.6. Strabismus

A prism cover test was used to detect a strabismus.

4.3.7. Nystagmus

A nystagmus was detected using Frenzel goggles (illuminated enlarging spectacles).

4.4. Survey

A questionnaire was created using SurveyMonkey (http://www.surveymonkey.com) and could be filled out on a voluntary basis between April 2021 until May 2021. It was sent by post to all of our patients with a confirmed diagnosis of achromatopsia as well as to all of the members of the self-help group (Achromatopsie Selbsthilfe e.V. Düsseldorf, Germany, www.achromatopsie.de, accessed on 20 March 2021). It could be answered by paper form and returned to our clinic's address or online, generated on the site surveymonkey.com.
It consisted of 39 questions, mostly based on psychosocial features such as education, treatment management, subjective impressions of living with achromatopsia. Included were demographic and non-demographic questions, with a free text-box after each answer for participants to add answers and to express themselves more clearly. The majority of non-demographic questions were multiple-choice with a few open-ended questions. The following data was collected: age, gender, age when diagnosis of achromatopsia was established, diagnosis of achromatopsia made by, actual visual acuity of right eye, actual visual acuity of left eye, school career, school qualification, further education/training, practiced occupation, degree of handicap, allowances for the blind, mutated gene, duration of the disability, visual aids (glasses without tint with diopter values for optical correction, contact lenses without tint with diopter values for optical correction, edge filter glasses without diopter correction, edge filter glasses with diopter correction, edge filter contact lenses without diopter correction, edge filter contact lenses with diopter correction, tinted glasses without edge filters (usually sunglasses), tinted overspecs, side protection, simple magnifying glass, monocular), electronic aids (electronic magnifying glass, screen reader, tablet, magnifying app, zoom-text, screen magnifier, smartphone, PC), colour system and primary concern. The following text is the original German version of the questionnaire.

Fragebogen zur Achromatopsie

Präambel:
Der Fragebogen zur Achromatopsie wurde erstellt von Caroline Chan, Doktorandin der Univ.-Augenklinik Homburg und Prof. Dr. Barbara Käsmann-Kellner, Sektionsleitung der Kinderophthalmologie und Low Vision. Wertvolle Hinweise und ergänzende Fragen hat Hans-Werner Merkelbach, Vorsitzender der Achromatopsie-Selbsthilfe, beigesteuert.

Bei der Achromatopsie handelt es sich, wie Sie wissen, um eine sehr seltene Erkrankung. Das Wissen darüber ist auch bei Ärzten und Therapeuten begrenzt.

Wir möchten im Rahmen der Doktorarbeit "Morphologische und funktionelle Aspekte der Achromatopsie" auch abseits der klinischen Parameter auf die individuelle Situation der Betroffenen näher eingehen und haben daher einen Fragebogen entwickelt, den wir Sie bitten, für sich oder Ihr Kind (falls mehrere betroffene Kinder, bitte mehrmals eintragen) auszufüllen. Wir haben uns bemüht, auch Kommentarfunktionen einzufügen, damit Sie ergänzende Angaben und Erfahrungen eintragen können.

In einem weiteren Zweig der Arbeit werden die klinischen Daten, die wir an der Univ.-Augenklinik Homburg bei Patienten erhoben haben, anonymisiert ausgewertet.

Wir erhoffen uns von dem zweigeteilten Zugang - individuelle Fragen und objektive klinische Befunde - ein größeres Wissen über die Achromatopsie und eventuell auch Ansatzpunkte, um die Betreuung von Achromaten zu verbessern. Die Ergebnisse werden wir Ihnen auf Ihren Wunsch nach der Auswertung zur Verfügung stellen.

Wir würden uns sehr freuen, wenn Sie an unserem Projekt für Achromatopsie teilnehmen würden!

Herzlichen Dank!

Dieser Fragebogen kann ebenfalls online ausgefüllt werden und steht unter dem folgenden Link zur Verfügung:

https://de.surveymonkey.com/r/ZTM57KY

Hinweise zum Ausfüllen des Fragebogens:

Die Antworten zu unserem Fragebogen werden grundsätzlich anonym behandelt und ausgewertet. Darum benötigen wir zunächst nur wenige Angaben zur Person der Achromatin, des Achromaten.

Je nach Alter der Achromatin, des Achromaten werden die Antworten zu den Fragen 6, 7 und 8 nur zum Teil beantwortet werden können. Wenn z.B. die Schulzeit noch nicht abgeschlossen ist, bleiben die Fragen zu Studium oder Beruf natürlich offen.

Falls der Fragebogen nicht von der Achromatin bzw. dem Achromaten selbst, sondern z.B. von einem Elternteil beantwortet wird, dann müssen die Fragen natürlich aus der Perspektive der Achromatin bzw. des Achromaten beantwortet werden.

❍ Ich bin selber von Achromatopsie betroffen

❍ Ich fülle den Fragebogen für mein/e Kind/er aus. Falls mehrere Kinder Achromatopsie haben, so füllen Sie bitte für jedes betroffene Kind einen Fragebogen aus.

1. Besteht eine Mitgliedschaft in einem Sehbehindertenverein?

❍ keins
❍ Achromatopsie Selbsthilfegruppe e.V.
❍ DBSV
❍ bebsk
❍ ProRetina
❍ andere _____

Bemerkungen/Ergänzungen

_____

2. Zur Person der Achromatin / des Achromaten

Alter _____ Geschlecht: _____

3. Augenärztliche Behandlung:

❍ Universitätsaugenklinik Homburg/Saar

❍ andere Universitätsklinik Ort: _____

❍ Augenarztpraxis

Bemerkungen/Ergänzungen

_____

4. Wurde die Achromatopsie durch einen Gentest nachgewiesen?

❍ JA ❍ NEIN

Falls JA, welches Gen ist betroffen? _____ _____

5. Wann wurde die Achromatopsie diagnostiziert?

In welchem Alter wurde die Achromatopsie festgestellt? _____

Wer hat die Diagnose gestellt? (Augenarzt, Augenklinik, Frühförderin - bitte ausführen)

_____

Bemerkungen/Ergänzungen

_____

6. Wie ist die Sehschärfe bzw. der Visus der Achromatin / des Achromaten?

Bitte geben Sie die Sehstärke entweder in Prozent (z.B. 10 % oder 5 %) oder als Visuswert (z.B. 0,1 oder 0,05) an:

Rechtes Auge: _____ linkes Auge _____

❍ leider nicht bekannt

7. Schulische Bildung der Achromatin / des Achromaten

Hier können mehrere zutreffende Betreuungsformen, Schulen usw. angekreuzt werden. Geben Sie auch an, ob es sich um eine Sonderform für Sehbehinderte handelt.

	Regelform	Speziell für Sehbehinderte	Mit Abschluss
Kindergarten	❍	❍	
Grundschule	❍	❍	
Hauptschule	❍	❍	❍
Realschule	❍	❍	❍
Gymnasium	❍	❍	❍
Fachschule	❍	❍	❍
Fachhochschule	❍		❍
Universität	❍		❍

8. Berufsausbildung der Achromatin / des Achromaten?

❍ keine abgeschlossene Berufsausbildung

❍ Berufsausbildung als

_____

❍ Studium – Fächer

_____

Bemerkungen/Ergänzungen

_____

9. Ausgeübte berufliche Tätigkeit der Achromatin / des Achromaten

❍ keine ❍ Arbeitsuchende

❍ in Ausbildung als

_____

❍ berufliche Tätigkeit

_____

❍ berentet

_____

Bemerkungen/Ergänzungen

_____

10. Behindertenausweis bzw. Grad der Behinderung?

❍ JA ❍ NEIN ❍ in Beantragung

Wenn JA: Grad der Behinderung:_____ %

Merkzeichen: ❍ H (hilflos) ❍ B (Begleitperson)
❍ G (gehbehindert) ❍ RF (Rundfunkbefreiung)
❍ aG (außergewöhnlich behindert)
❍ Bl (blind) ❍ Gl (schwerhörig/taub)
❍ sonstiges _____

Befristung: ❍ bis_____ ❍ unbefristet

Bemerkungen/Ergänzungen
_____

11. Sehbehinderten- oder Blindengeld?

❍ Sehbehindertengeld ❍ Blindengeld

Nach der Regelung welches Bundeslandes?
_____

Bemerkungen/Ergänzungen
_____

12. Welche optischen Korrekturen und Lichtschutz nutzen Sie / nutzt Ihr Kind im Alltag? (Mehrfachnennungen sind möglich)

❍ Brille ohne Tönung mit Dioptrienwerten zur optischen Korrektur (Sehschärfe)
❍ Kontaktlinsen ohne Tönung mit Dioptrienwerten zur optischen Korrektur (Sehschärfe)
❍ Kantenfilterbrille(n) ohne Dioptrien-Korrektur (z.B. F60, F90, 585)
Falls bekannt KF-Type(n): _____ _____ _____

❍ Kantenfilterbrille(n) mit Dioptrien-Korrektur (z.B. F60, F90, 585)
Falls bekannt KF-Type(n): _____ _____ _____

❍ Kantenfilterkontaktlinsen ohne Dioptrien-Korrektur
Falls bekannt KF-Type: _____

❍ Kantenfilterkontaktlinsen mit Dioptrien-Korrektur
Falls bekannt KF-Type: _____

❍ getönte Brille(n) ohne Kantenfilter, normalerweise Sonnenbrille(n)

❍ Überbrillen (über normalerweise getragene Brille)

❍ Seitenschutz

❍ andere _____

Bemerkungen/Ergänzungen – weitere Korrekturen?
_____

13. Welche vergrößernden Sehhilfen nutzen Sie / Ihr Kind?
(Mehrfachantworten möglich)

❍ einfache Lupe(n)

❍ Lupenbrille

❍ Monokular

❍ elektronische Lupe(n)

❍ Bildschirmlesegerät

❍ virtuelle Brille (z.B. orCAM)
Welche _____

Bemerkungen/Ergänzungen (bitte ggf. Sehhilfen ausführen)
_____

14. Welche weiteren Hilfsmittel nutzen Sie / Ihr Kind?
(Mehrfachantworten möglich)

❍ Langstock

❍ Farberkennungsgerät

❍ akustische Hilfen

Bemerkungen/Ergänzungen
_____

15. Unterstützung und Hilfe durch Computer und Programme/Apps (Mehrfachantworten möglich)

❍ Personal Computer PC

❍ mit Vergrößerungssoftware – welche? _____

❍ Smartphone ❍ Tablet

❍ Apps für Sehbehinderte

❍ Lupen-App ❍ App zur Farberkennung

❍ Vorlesefunktion ❍ Barcode-Erkennung

❍ Diktierfunktion ❍ verbale Befehle (z.B. Siri)

Bemerkungen/Ergänzungen

_____

16. Wird ein System zur Benennung von Farben genutzt?

❍ keins

❍ colorADD

❍ Mundhenk

❍ anderes _____

Bemerkungen/Ergänzungen

_____

17. Wenn Sie / Ihr Kind einen einzigen Wunsch bezüglich der Achromatopsie frei hätten, was würden Sie / Ihr Kind sich wünschen?

❍ intaktes Farbensehen?

❍ normale Sehschärfe?

❍ keine Blendungsempfindlichkeit mehr?

18. Was möchten Sie uns noch von Ihren persönlichen Erfahrungen Ihres Lebens mit Achromatopsie mitteilen? Wir würden uns über Ihre weiteren Kommentare, Ihre persönlichen Erfahrungen und Ihre Einschätzung, wie sehr Achromatopsie Ihr tägliches Leben beeinflusst, sehr freuen!

Schlussbemerkung:
In diesem Fragebogen haben Sie sehr persönliche Angaben gemacht. Diese werden, wie oben bereits zugesichert, anonym ausgewertet.

Falls Sie jedoch wünschen, dass wir mit Ihnen persönlich Kontakt aufnehmen, um Besonderheiten zu erfragen oder Erfahrungen mitzuteilen, so können Sie nachfolgend Ihre Kontaktdaten hinterlassen. Wir gewährleisten, dass diese unabhängig von der allgemeinen Auswertung aufbewahrt und behandelt werden.

Bitte geben Sie an, wozu wir Ihre persönlichen Daten nutzen dürfen:
(Mehrfachantworten möglich)

- ❍ Kontaktaufnahme bei Fragen oder Hinweisen
- ❍ Zusenden eines Ergänzungsfragebogens, falls dies im Rahmen der wissenschaftlichen Arbeit nötig erscheint
- ❍ Zusendung des Ergebnisses der Befragung

Name: _____ **Vorname:** _____

Adresse: _____

Telefon: _____ **Email:** _____

Wir bedanken uns ganz herzlich für Ihre Mithilfe bei unserem Achromatopsie-Projekt!!

4.5. Variables

The final variables collected from the medical history and the survey for the statistical evaluation were the following:

Age, gender, age when achromatopsia diagnosis was established, diagnosis of achromatopsia made by, visual acuity of right eye during first visit, visual acuity of left eye during first visit, average visual acuity of first visit, actual visual acuity of right eye, actual visual acuity of left eye, average actual visual acuity, standardised colour tests, subjective colour perception, spherical refraction right eye, spherical refraction left eye, average spherical refraction, astigmatic refraction right eye, astigmatic refraction left eye, average astigmatic refraction, anterior segment findings, retinal arterial vessels, fundus periphery, macula, optic nerve head, strabismus, nystagmus, present low vision aids, low vision aids prescribed at our department, school career, school qualification, further education/training, practiced occupation, degree of handicap, allowances for the blind, mutated gene, duration of the disability, visual aids (glasses without tint with diopter values for optical correction, contact lenses without tint with diopter values for optical correction, edge filter glasses without diopter correction, edge filter glasses with diopter correction, edge filter contact lenses without diopter correction, edge filter contact lenses with diopter correction, tinted glasses without edge filters (usually sunglasses), overspecs, side protection, simple magnifying glass, monocular), electronic aids (electronic magnifying glass, screen reader, tablet, magnifying app, zoom-text, screen magnifier, smartphone, PC), colour system and primary concern.

The average visual acuity during the first visit at the clinic was measured by taking the right and left visual acuity mean. The average visual acuity was measured by taking the right and left refraction mean during the last visit at the clinic. The average spherical refraction was calculated by taking the mean of the right and left spherical refraction. The average astigmatic refraction was calculated by taking the mean of the right and left astigmatic refraction.

For this study, we prepared the following research questions for statistical analysis:

1. Does the age of achromatopsia diagnosis correlate with the academic qualifications/achievements?
2. Do specialised schools (or a mix of specialised and mainstream) lead to better academic qualifications/achievements?
3. Does the degree of refraction influence visual acuity?
4. Does the degree of astigmatism influence visual acuity?
5. For achromats, does age influence visual acuity?
6. For achromats, do the eyes' morphology change with age:

i. Anterior segment findings
ii. Retinal arterial vessels
iii. Fundus periphery
iv. Macula
v. Optic nerve head
vi. Strabismus

7. Does the degree of handicap correlate with visual acuity and colour vision discrimination (to analyse if appropriate degree of handicap is given)?
8. Are optical aids used more than electronic aids?
9. What are the most used optical aids and electronic aids?
10. What is the primary concern of achromats?
11. Does the type of mutated gene influence visual acuity?
12. Does the type of mutated gene influence the degree of refraction?
13. Does the type of mutated gene influence the degree of astigmatism?
14. Does the type of mutated gene influence the retinal morphology of achromatopsia?
    i. Anterior segment findings
    ii. Retinal arterial vessels
    iii. Fundus periphery
    iv. Macula
    v. Papilla
    vi. Strabismus

15. Does the type of mutated gene correlate with the use of optical aids?
16. Does the type of mutated gene correlate with the use of electronic aids?
17. Does the age of when the diagnosis of achromatopsia was established correlate with the age of the patient?

4.6. Statistical Analysis

We conducted data analysis using SPSS Statistics software, Version 25 (IBM, Armonk, New York, USA). Continuous data were summarized using measures such as means, standard deviations, medians, minimums, and maximums. Categorical variables were represented as percentages and the Chi-Square test was used to compare them. For non-parametric variables, we applied the Wilcoxon test. The correlation between non-parametric variables was assessed using Spearman tests. Spearman's ρ (rho) represents a rank correlation coefficient suitable for analysing two ordinal variables or when one variable follows a continuous normal distribution, while the other is either categorical or non-normally distributed. This non-parametric test is ideal for variables with a non-normal distribution. We considered results statistically significant when P-values were less than 0.05.

5. Results

Parts of this work have already been published [15]. We used two different methods to gather data for this study: patient records obtained from our clinic's database and the questionnaire specifically developed for this research. While the clinical records were accessed to evaluate the morphological and functional findings, the questionnaire was used to evaluate the functional elements and the quality of life of individuals with achromatopsia. Among the 48 clinical assessments performed in domo, genetic analysis was not performed by three participants according to patient preference **(Table 1)**.

	Total number out of 94 achromats	Percentage number out of 94 achromats
Only clinical examinations performed in domo	48	51 %
Out of clinical examinations performed in domo; Molecular genetics confirmed	45	48 %
Clinical examinations performed in domo + answered questionnaire	16	17%
Only answered questionnaire	30	32 %

Table 1. Method for collecting data from the participant group

5.1. Demographics and genes of the population tested

The population of patients analysed in this study was based on a total of 94 patients, consisting of 37 males (39.4%) and 57 females (60.6%). The mean age of the population was 24.2 years old with a standard deviation of ±18.5 years.

At the genetic level, we collected the data of 94 patients, of which 12 (12.8%) patients exhibited the CNGA3 gene, 32 (34%) had the CNGB3 gene, 1 (1.1%) showed the PDE6C gene. For the remaining 49 patients (52,1%), no known achromatopsia-related genes were identified in

17 patients, while no genetic analysis was performed for 32 patients, despite being informed of the current clinical trials.

5.2. Present age and age of diagnosis of achromatopsia

For 67 responding patients, the mean age of when the diagnosis of achromatopsia was established was 6.4 years old (SD±12.2). The age of diagnosis in the eldest patient of 74 years old was at 71 years of age while the youngest patient of 8 years of age was diagnosed with achromatopsia shortly after birth. The majority of our patients were diagnosed at 3 years of age (26.9%) and had a mean age of 26 years at timepoint of study inclusion **(Figure 1)**.

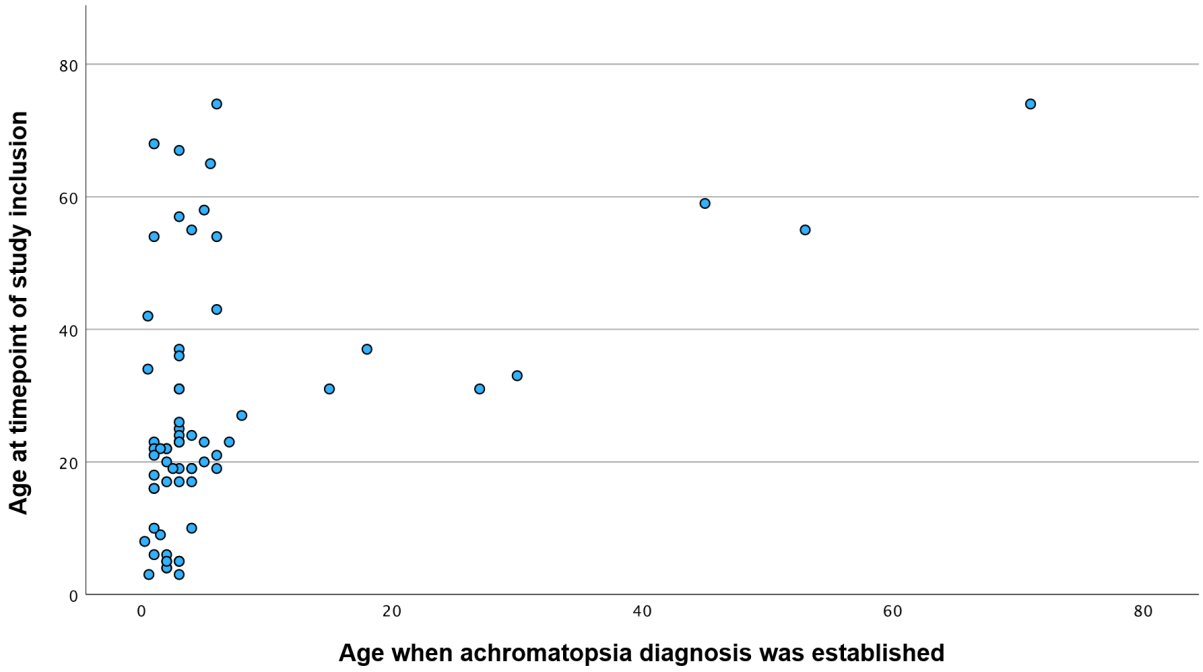

Figure 1: Age (in years) at timepoint of study inclusion and age when achromatopsia diagnosis was established.

5.3. Functional characteristics

To identify the natural process of achromatopsia (functional aspect), we examined visual acuity, along with the modifications in the refractive/orthoptic characteristics, as the age of individuals with achromatopsia advanced. Furthermore, we evaluated colour perception using colour-related tests.

5.3.1. Visual acuity

We conducted ophthalmological examinations on 62 patients and found that their average visual acuity was 1.0 logMAR (SD ± 0.22), with a range of 0.42 logMAR to 1.52 logMAR. Among 91 patients, which also comprised of those who responded to the survey, the mean visual acuity was measured as 1.0 logMAR (SD ± 0.23) as well, varying from 0.22 logMAR to 1.70 logMAR.

To assess the changes in visual acuity over time, we compared the first and final measurements taken during visits that occurred between 1 to 21 years apart. However, our analysis revealed no notable correlation between the two assessments (r=0.239, p=0.811). Additionally, we examined the correlation between visual acuity and age among the 91 patients and found no significant relationship (r=0.002 and p=0.985) as illustrated in Figure 2 **(Figure 2).**

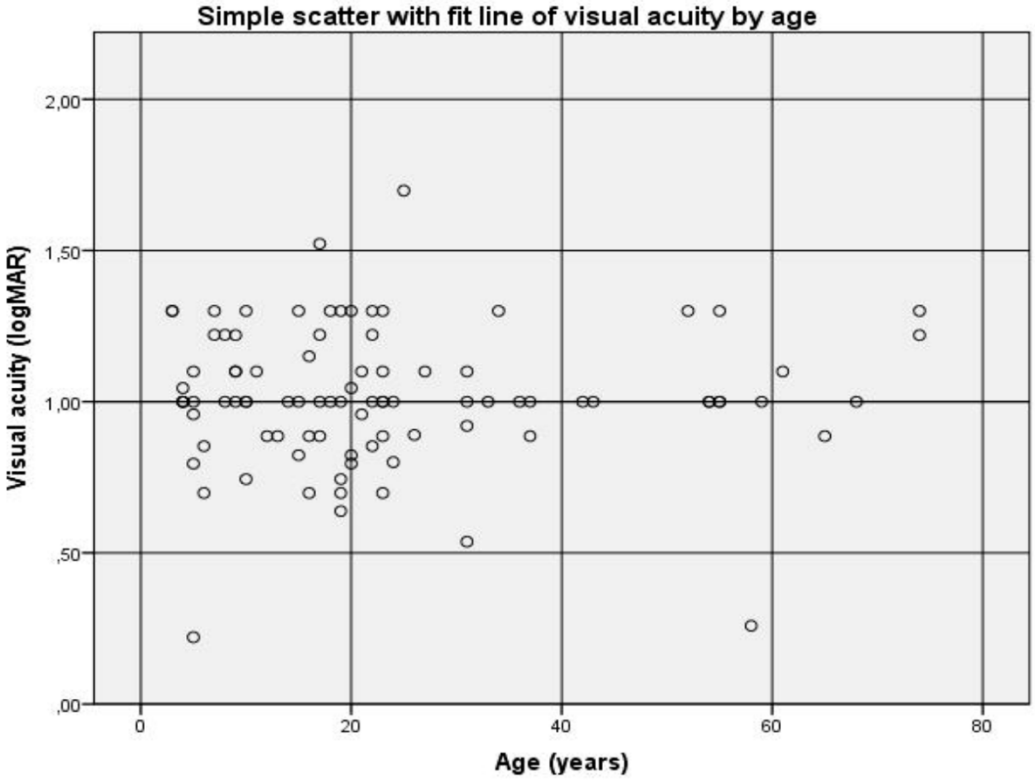

Figure 2: Relationship between age (in years) and visual acuity (in logarithm of the minimal angle of resolution = logMAR).

Among the 62 patients who underwent an ophthalmological evaluation, 12 patients presented with a mutation in the CNGB3 gene, 32 carried the CNGB2 gene mutation, 1 exhibited a mutation in the PDE6C gene, and genetic analysis was not performed for 17 individuals.
Among the 45 patients who underwent genetic testing, there was no discernible association between the gene type and visual acuity (r=-0.158, p=0.311).

5.3.2. Refractive and orthoptic findings (Refraction, Nystagmus, Strabismus)

The refractive and orthoptic findings of the study revealed that out of 62 patients, the mean spherical refraction was 1.83 diopters (SD ± 3.76, ranging from -4.38 to +8.5 dpt) and no relationship was discovered between the altered genes and the level of spherical refractive error (r=-0.075, p=0.669). The average astigmatism measurement was -1.86 diopters (SD ± 0.88, ranging from -3.0 to -0.5 dpt). Furthermore, no relationship was identified between visual acuity and spherical measurement (r=-0.111, p=0.393), visual acuity and astigmatic measurement (r=0.144, p=0.380) as well as mutated genes and astigmatic measurement (r=0.097, p=0.578).

Regarding nystagmus, 54 out of 61 (88.5%) patients had nystagmus, while 7 out of 61 (11.5%) did not present with nystagmus. We proceeded to assess our achromatic patients for strabismus. Out of 58 patients, 34 (58.6%) had no strabismus, 6 (10.3%) had a strabismus convergens, 17 (29.3%) presented a strabismus divergens, and 1 (1,7%) had both strabismus convergens and verticalis. The study did not find any relationship between age and strabismus (r=0.057, p=0.672), nor between the type of mutated gene and strabismus (r=-0.230, p=0.213).

5.3.3. Standardised colour tests

Out of 20 patients, 15 (75%) presented a negative Ishihara test, 1 (5%) presented a negative Panel saturated test and 4 (20%) had both tests negative and could not recognise colours of large areas.

5.3.4. Subjective colour perception

Out of 22 patients, 4 (18.2%) did not recognize any colours, 17 (77.3%) always recognised large areas of colours and 1 (4.5%) recognised colours by chance now and then.

5.4. Morphological findings

We examined the correlation between genotype and phenotype. Additionally, we also assessed the relationship between age and phenotype. The phenotype included modifications comprising the anterior segments, cataracts, retinal arterial vessels, the optic nerve, the retinal periphery, the periphery of the fundus as well as the macula.

5.4.1. Anterior segment findings / Cataracts

Among the 62 subjects, the majority, comprising 59 (95.2%) individuals, did not show any abnormality in anterior segment observations. Furthermore, 3 (4.8%) participants aged 50 years and older exhibited cataracts, which were attributed to age-related changes and were unrelated to achromatopsia. These three patients were not excluded from the patient cohort as they demonstrated no significant difference in visual acuity.

5.4.2. Retinal arterial vessels

Among the cohort of 60 patients, 32 individuals (53.3%) displayed regular retinal arterioles, 18 patients (30%) exhibited slightly restricted vessels, and 10 cases (16.7%) presented retinal arterial vessels with significant restriction. We could observe a slight association between age and retinal artery constriction (r=0.345, p=0.007). **(Figure 3)**

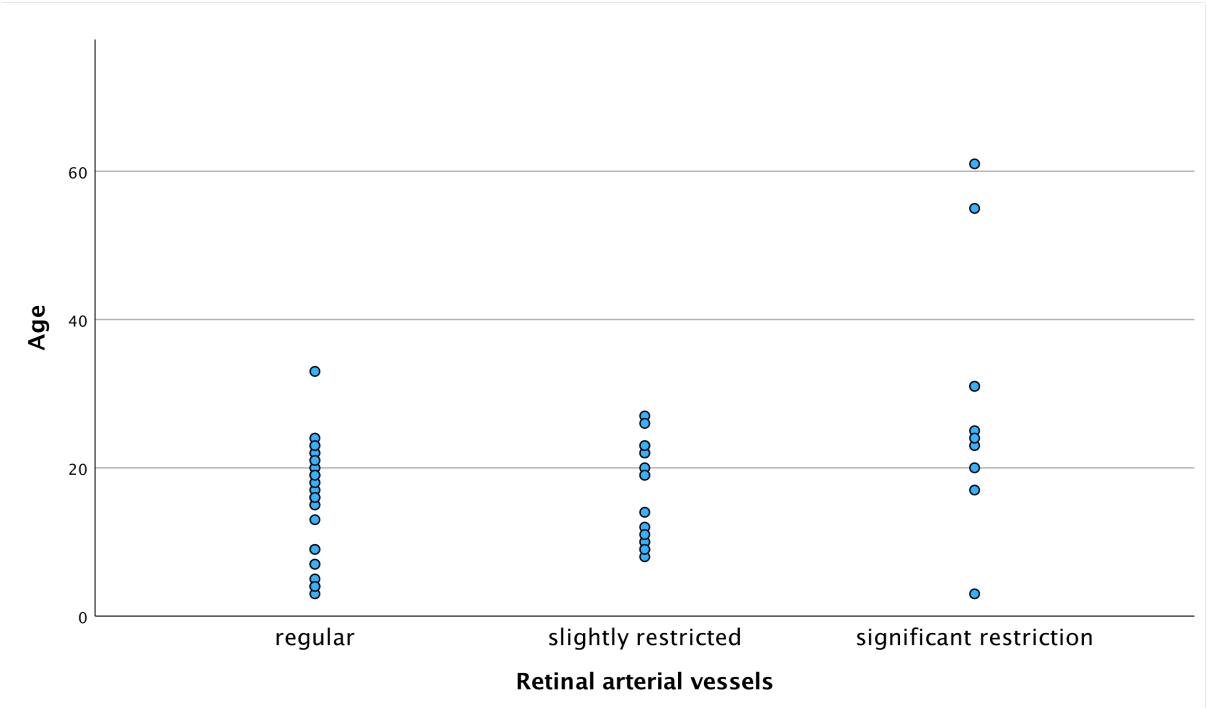

Figure 3: Progressive changes in the degree of restriction in the retinal arteries occurring with advancing age.

5.4.3. Optic nerve head

We observed a mild relationship between age and the morphology of the optic nerve head (r=0.280, p=0.027) **(Figure 4)**.

Among the 62 patients in our study, the majority (n=40, 64.5%) showed no abnormalities of the optic nerve head. However, 7 patients (11.3%) displayed a mildly pale optic nerve head, 3 (4.8%) presented a significantly pale optic nerve head, 7 (11.3%) exhibited a significant retinal optic atrophy, and 5 patients (8.1%) had optic disc drusen. No significant correlation was found between the type of mutated gene and optic nerve head changes (r=-0.249, p=0.148).

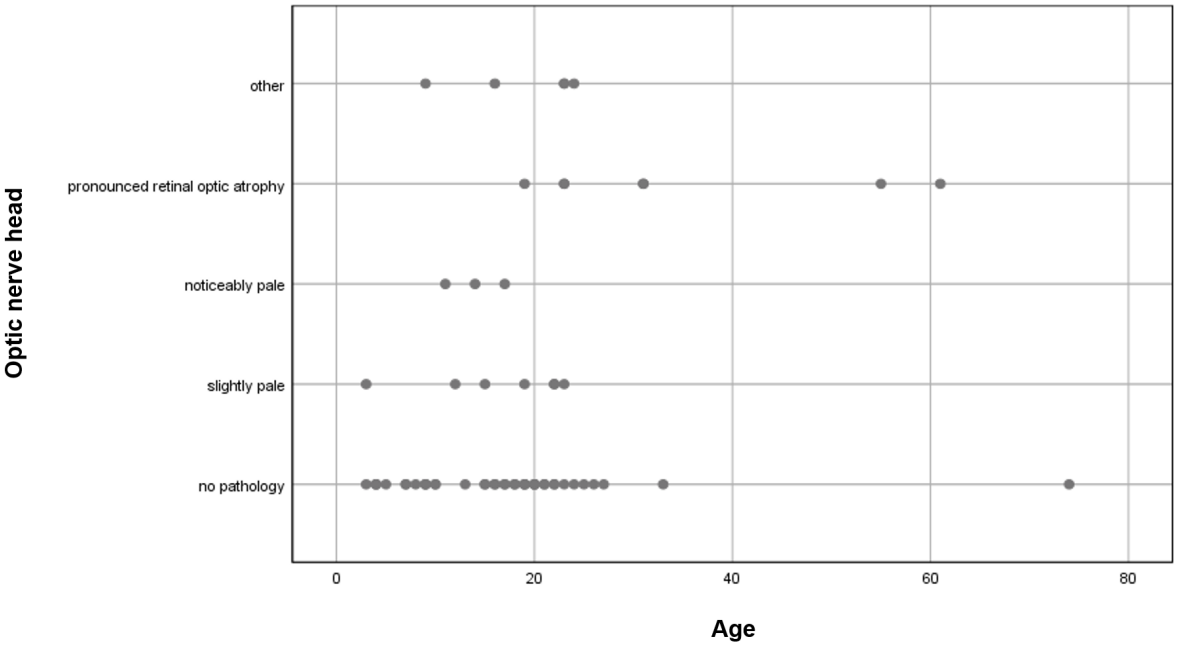

Figure 4: Relationship between optic nerve head morphology and age. A weak correlation between age and retinal optic atrophy was found (r=0.280; p=0.027).

5.4.4. Retinal periphery / Fundus periphery

Among the cohort of 61 patients, a predominant 52 (constituting 85.2%) exhibited normal peripheral retina findings, whereas 9 individuals (comprising 14.8%) manifested deposits adjacent to the pigment epithelium and additional alterations in the periphery of the fundus. Statistical analysis revealed no discernible association between age and fundus periphery abnormalities (r=0.057, p=0.660). Furthermore, no association was detected between the type of gene and abnormalities in the fundus periphery (r=-0.135, p=0.438).

5.4.5. Macula

In a group of 62 patients, we observed that 23 patients (37.1%) exhibited a morphologically unremarkable macula. Moreover, 20 patients (32.3%) displayed a clearly defined wall reflex without a clearly defined foveal reflex. In 16 cases (25.8%), the macular region lacked differentiation, while in the 3 other cases (4.8%), the macula showed undifferentiated features accompanied by changes in the retinal pigment epithelium **(Table 2)**. No statistically significant correlation between age and macular alterations was observed (r=0.121, p=0.348) and similarly, no statistically significant relationship was identified between the mutated gene and macular changes (r=-0.167, p=0.338).

	Number of patients (out of 62)	Percentage (%)
Morphologically unremarkable	23	37,1 %
Lack of foveal reflex	20	32,3 %
Lack of macular differentiation	16	25,8 %
Other changes	3	4,8 %

Table 2: Macular changes observed in patients with achromatopsia.

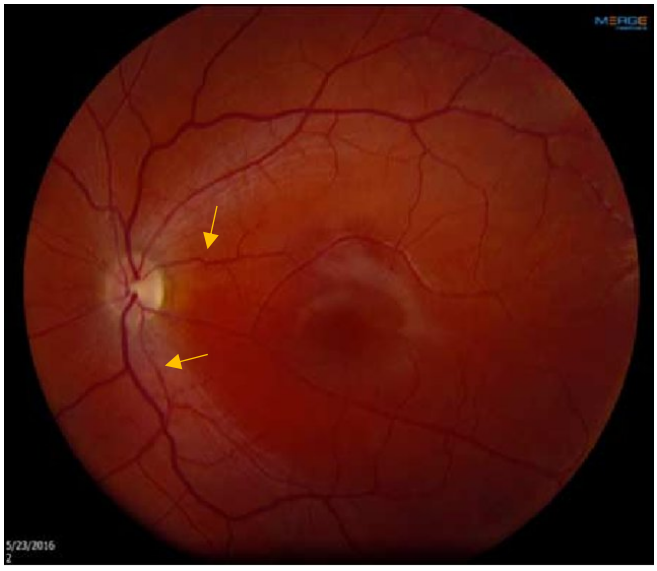

Image 1: Photo of the fundus of a 37-year-old patient with CNGB3-associated ACHM. Mild constriction of the arteries (yellow arrows), mild macula reflex, beginning of a retinal optic atrophy

5.5. Quality of life

5.5.1. School career

Among the 56 participants, most attended regular mainstream schools (n=40, 71.4%), while fewer attended specialized schools for individuals with visual impairments (n=9, 16.1%) or a combination of specialized and mainstream schools (n=7, 12.5%).

5.5.2. School qualification

We asked patients about their highest school qualification. Out of 28 respondents, one (3.6%) did not have a school qualification, one (3.6%) obtained a middle school diploma and 26 (92.9%) acquired a high school graduation.

5.5.3. Further education / training

We inquired our patients about their further education and trainings and noted that out of 26 respondents, one (3.8%) had an apprenticeship, one (3.8%) attended higher intermediate service and 24 (92.3%) attended university.

5.5.4. The impact of the age of diagnosis of achromatopsia on education

The relationship between the age of when achromatopsia was diagnosed with the different levels of education was determined by using a Spearman's correlation test. No correlation was found between the age of diagnosis with the school career (r=0.061, p=0.660), school qualification (r=0.273, p=0.168), nor further education/training (r=-0.335, p=0.102). No correlation was observed between the school type and the type of school qualification (r=-0.124, p=0.530), nor between the school type and further education (r=-0.206, p=0.313).

5.5.5. Professional career

The patients were engaged in various occupations, including teacher, consultant, IT, pastor, actor, educator, physiotherapeutic. Most of them worked in the social domain.

5.5.6. Degree of visual handicap

In alignment with the guidelines established by the German authorities for individuals with visual impairments, people with achromatopsia are assigned a visual impairment assessment that extends from 0% to 100%. Normally, the amount of allowance a person receives, depends on how severe the disability is. Among 61 respondents, 10 patients (16.4%) exhibited a visual disability level of 0% (Patients have not yet submitted an application to the state office), while 1 (1.6%) had a 50% degree of visual handicap. Furthermore, 9 respondents (14.8%) presented with a 70% degree of visual disability, 14 (23%) displayed an 80% degree of visual

handicap, 10 (16.4%) showed a 90% degree of visual handicap, and 17 (27.9%) were categorized with a full 100% degree of visual handicap.

5.5.7. The impact of handicap severity and gene mutation type

No significant correlation was found between the degree of handicap and type of gene mutation (r=-0.08; p=0,539). **(Figure 5)**

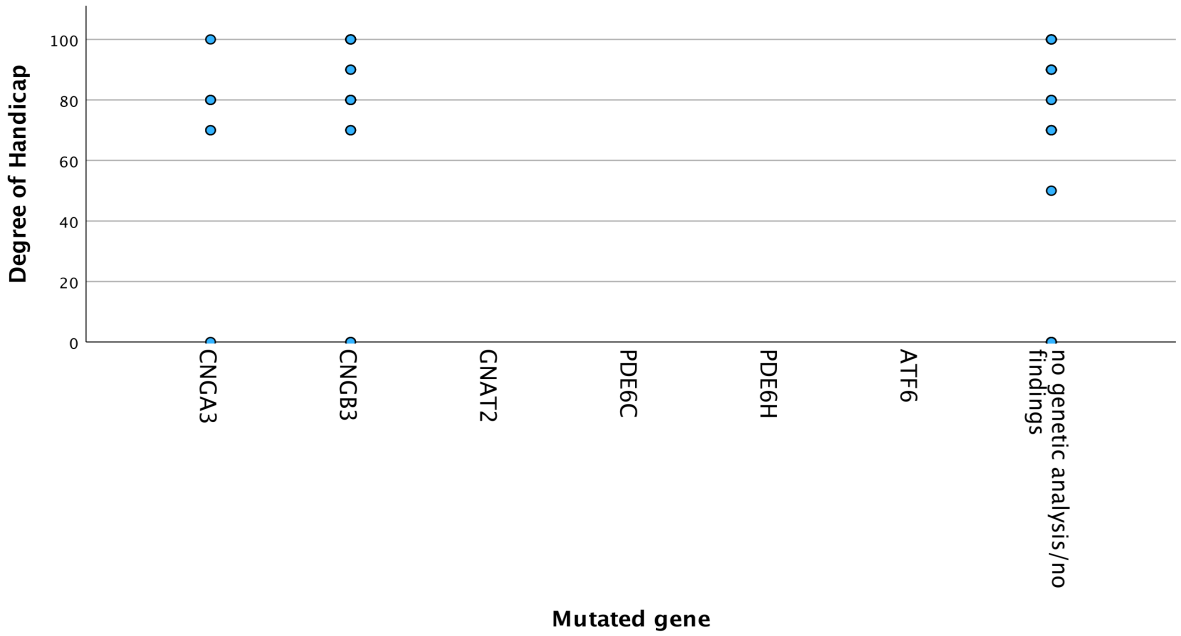

Figure 5: Relationship between the degree of handicap and the type of mutated gene. No significant correlation was found (r=0.08; p=0.539).

5.5.8. Allowances for the blind

Among a group of 67 patients, 10 individuals (14.9%) obtained allowances for blindness, while the remaining 57 (85.1%) did not get any allowances.

5.5.9. The effect of the severity of the degree of handicap and allowances for the blind with age

There was no significant relationship between the degree of disability and age (r=0.140; p=0.280), with the degree of disability remaining stable over the decades **(Figure 6)**.

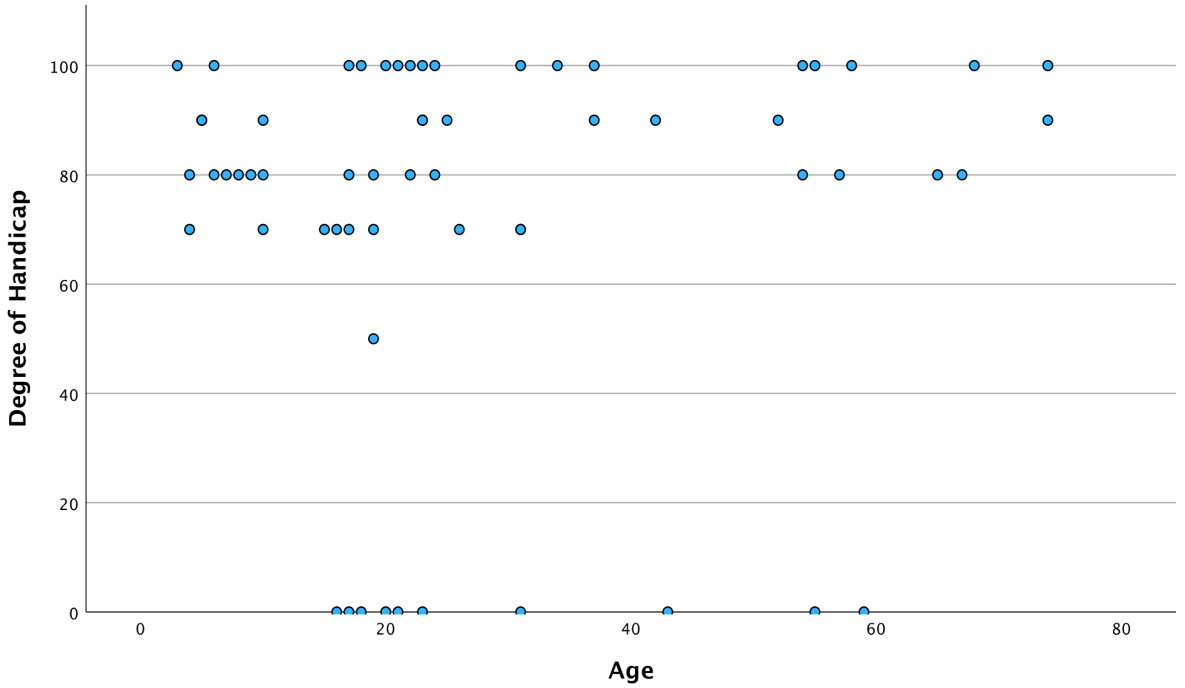

Figure 6: No correlation between the severity of the degree of handicap (in %) with age (in years).

5.5.10. Utilization of optical aids and assistive devices for low vision

Out of 87 subjects, 31% used optical aids, 63.2% used a combination of optical and low vision aids, while 5.7% did not use any aids.

Additionally, a significant number of individuals utilized multiple varieties of edge filter glasses with (43.7%) and without diopter (42.5%). The most used low vision aids were reading glasses (56.3%) and a simple magnifying glass (55.2%) **(Table 3 & 4)**.

	Number out of 87 patients	% out of 87 patients
Optical aids (for refractive error and glare sensitivity)		
Edge filter glasses with diopter correction	38	43.7 %
Edge filter glasses without diopter correction	37	42.5 %
Tinted glasses without edge filters, usually sunglasses	22	25.3 %
Edge filter contact lenses with diopter correction	13	14.9 %
Side Protection	10	11.5 %
Contact lenses with diopter values for optical correction	8	9.2 %
Edge filter contact lenses without diopter correction	8	9.2 %
Overspecs	2	2.3 %

Table 3: The distribution of use of optical aids among 87 patients.

	Number out of 87 patients	% out of 87 patients
Low vision aids		
Reading glasses	49	56.3 %
Simple magnifying glass	48	55.2 %
Smartphone	34	39.1 %
Tablet	33	37.9 %
Monocular	32	36.8 %
CCTV (close circuit TV)	27	31 %
PC	15	17.2 %

Magnifying app	13	14.9 %
Zoom-Text	13	14.9 %
Screen magnifier	12	13.8 %
Electronic magnifying glass	10	11.5 %

Table 4: The distribution of use of low vision aids among 87 patients.

5.5.11. Primary concerns

As a primary concern, out of 43 respondents, the majority of 26 (60.5%) patients wished for normal visual acuity, while 15 (34.9%) wanted to eliminate photophobia and 2 patients (4.7%) solely wished for retaining intact colour vision **(Figure 3)**.

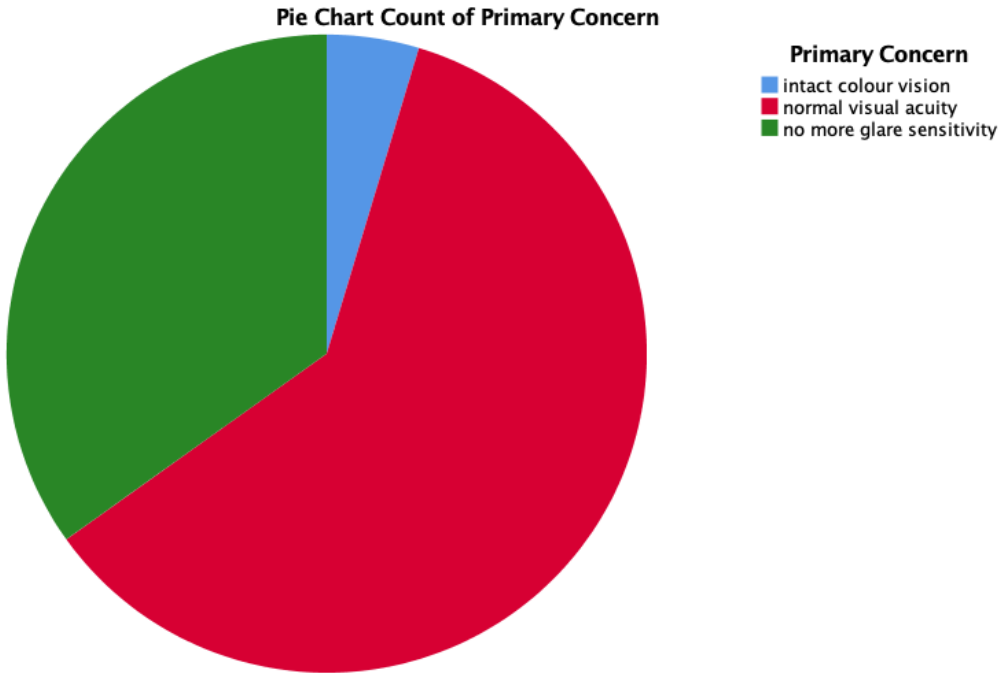

Figure 7: A pie chart demonstrating the percentage of primary wishes of patients with achromatopsia.

5.5.12. Colour detection system

Among 44 survey participants, the majority (30 individuals, constituting 68.2%) reported not using any particular colour detection system, while 7 respondents (15.9%) utilised the colorADD system, and 7 other individuals (15.9%) opted for an alternative colour system, which was not further specified.

5.5.13. Subjective impressions - Further comments from people living with achromatopsia

As mentioned above, for people living with achromatopsia, seeing colours is not their biggest concern as one might think, but rather visual acuity, followed by glare sensitivity. Many explain that not being able to see colour does not affect them as much as they have seen the world in different shades of grey and don't know it differently. They also state that colour aid systems do not work, are unprecise and even when using a colour detection system, they do not recognise the right colour. Most respondents have stated that they ask their surroundings to identify colours.

A lot of respondents have stated that they were relieved when the diagnosis of achromatopsia was found, especially because it is predominantly stationary and a none degenerative disease with stability of the symptoms. Many have stated that more eye doctors and opticians should be aware about achromatopsia and be able to diagnose it early and give the appropriate treatments.

While some struggle to live daily with achromatopsia, others can live easily with this condition with the right aids although they need more time to complete tasks than other people. They don't feel as though achromatopsia is a handicap. A big task is to recognise people, some even recognise their surroundings only through their voice. Sometimes the surroundings forget that they have achromatopsia, as it cannot physically be seen. They especially experience discrimination within society and institutions. Often, they are mocked by strangers for wearing unusual tinted sunglasses or sunglasses when there is no sun and some even experience bullying in school. It is particularly difficult for achromats, as there is no clear classification concerning the degree of handicap. As a result, many have reported difficulties with health insurance when trying to obtain aids. In individual cases, participants even had a bad conscience about using a guide dog, because although they fulfil the criteria for low vision and blindness as defined by law, their visual acuity is still better in contrast to people who are completely blind.

Support and inclusion in society is the most important factor for them, this helps them gain motivation and lead a more 'normal' life. Many got help from their surroundings which made their life easier, while others indicated that they often felt lonely as they felt excluded and the family didn't understand them, that they give a lot to reach the same level as others who don't

present a handicap and sometimes can't do things others can do. The period during the coronavirus pandemic was especially tough as they rely on people but had to go everywhere on their own and keeping a distance was difficult as they have bad visual acuity. Many stated that one should not generalise achromatopsia and that achromats should be able to go to regular school if they desired. Interestingly, one was able to compare a regular school with a visually impaired school and that the ones going to regular school were more independent than the ones going to a visually impaired school.
It can be difficult for parents, especially with small children, who do not voice out how they feel.
Not having a driver's license is a big problem for many. Children can't join ball sports in school. Many depend on their smartphone for orientation but are independent in usual places. Most avoid new situations and places, as this stresses them out.

5.5.14. A few other comments from people living with ACHM

„Kämpfen lohnt sich. Allerdings müssten viel mehr die Augenärzte auch auf diese seltene Erkrankung hingewiesen werden."
"Fighting is worth it. However, the ophthalmologists should also be made aware of this rare disease."

„Beim Schwerbehindertenausweis wird weder der Nystagmus, noch der fehlende Farbsinn, die Blendempfindlichkeit berücksichtigt. Zusätzlich sollte man intensiver die Photophobie behandeln bzw. generell eine Behandlung von Achromatopsie stärker vorantreiben."
"With the severely handicapped ID, neither the nystagmus nor the lack of colour sense or the glare sensitivity are taken into account. In addition, photophobia should be treated more intensively or achromatopsia treatment in general should be promoted."

„In meinem täglichen Leben beeinträchtigt mich die Achromatopsie eigentlich kaum. Ich bin sehr selbstständig und brauche nur wenige Hilfsmittel. Meiner Meinung nach verdanke ich dies wohl zum größten Teil der Erziehung meiner Mutter. Sie hat von Beginn an dafür gesorgt, dass ich möglichst alles mache, was andere Kinder auch tun."
"In my daily life, achromatopsia hardly affects me. I am very independent and only need a few resources. I think I owe this to my mother's upbringing for the most part. Right from the start she made sure that I do everything that other children do as well."

„Bekannte Wege und Orte sind meist in Ordnung zu meistern. Alltäglich schränkt die Achromatopsie vor allem bei unbekannten Szenarien stark ein. Sucht man im Supermarkt ein unbekanntes Produkt oder trifft sich mit jemandem an einem unbekannten Ort, sorgt die Achromatopsie bei mir oft zu Verunsicherung und leichter Aufregung.“
“Familiar paths and places are usually easy to master. Every day, achromatopsia severely restricts, especially in unknown scenarios. If you are looking for an unfamiliar product in the supermarket or if you meet someone in an unfamiliar place, achromatopsia often causes me to feel insecure and slightly agitated.”

„Ich hatte immer das Gefühl, sobald ich meine Brille aufziehe, sehe ich weniger gut aus. Und ich muss zugeben, auch heute fällt es mir noch nicht super leicht, sie immer zu akzeptieren. Da spielen natürlich auch andere Personen mit rein, die einem beispielsweise sagen "ohne Brille siehst du viel besser aus" oder die Personen, die einen auf der Straße anstarren oder gar ein Kommentar hinterherwerfen. Einmal saß ich in der Bahn und hörte zwei junge Frauen lautstark sagen "Ja, ist denn schon Fasching?", nachdem die beiden mich absolut auffällig anstarrten. So Momente machen einen sehr wütend, zumindest mich.”
“I've always had the feeling that as soon as I put my glasses on, I look less good. And I have to admit, even today it is still not super easy for me to always accept them. Of course, other people also play a role in this; for example, they tell you “You look much better without glasses" or the people who stare at you in the street or even throw comments after you. Once I was sitting on the train and heard two young women loudly say "Yes, is it already Mardi Gras?” After they both stared at me in an absolutely noticeable way. Moments like that make you very angry, at least me.”

„Die Farbenblindheit ist für mich eher ein Funfact oder Small talk Thema als dass sie meinen Alltag behindert. Dies tun eher die Lichtempfindlichkeit und der Visus - beides ähnlich stark.“
“For me, colour blindness is more of a fun fact or small talk topic than it hinders my everyday life. This is more likely to be done by the light sensitivity and the visual acuity - both of which are similarly strong.”

„Die Achromatopsie hat mein gesamtes Leben sehr stark geprägt. Schule: Kinder können sehr grausam sein. "Sag mir die Farbe oder ich verprügele dich". In der 2ten Klasse habe ich dann einen der entsprechenden Jungen aus der 4ten Klasse wie eine Katze angesprungen, hab mich an ihm festgekrallt und gekratzt und gebissen, ihn ziemlich zugerichtet. Das gab Ärger.”
“Achromatopsia has had a very strong impact on my entire life. School: Children can be very cruel. "Tell me the colour or I'll beat you up". In the 2nd grade I jumped at one of the boys from

the 4th grade like a cat, clawed at him and scratched and bitten him, pretty much messed him up. That caused trouble."

6. Discussion

6.1. Discussion

Our findings contribute to the growing body of literature on the demographic and genetic characteristics of individuals with achromatopsia.
The gender distribution in our study had a higher proportion of female participants (60.6%). Our study included participants across a wide age spectrum, with a mean age of 24.23 years (SD ±18.53 years). This diverse age range provides valuable insights into the manifestation and progression of achromatopsia across various life stages. The fact that a predominant portion of participants did not undergo genetic analysis could be because there may not be a cure or specific treatment available for ACHM and this information would not help for the management of their quality of life. Gene therapy exists for two genetic types, namely CNGA3 and CNGB3, which, however, have not resulted in significant life-relevant changes in adult subjects. It may be different for children, as the first treatment trials with children are now starting at the University of Tübingen [20,43,49]. Most patients with accessible genetic information displayed mutations in either the CNGA3 or CNGB3 gene. This corresponds with a previous study of achromatopsia, where these genes constituted over 70% of reported cases [43].
No correlation between phenotype and genotype was found in the present study, suggesting that the clinical manifestations associated with genetic mutations in CNGA3 and CNGB3 were comparable, consistent with prior research [3,12,21,30,56,57].

The mean age at diagnosis, which stands at 6.49 years in the present study, implies that even though symptoms of achromatopsia are present at birth or in early infancy, the condition tends to be identified too late in childhood. Many patients in the study received their diagnosis through specialized eye clinics. Interestingly, two patients managed to self-diagnose through online research and later had achromatopsia confirmed by an eye doctor, who at first did not recognize the condition. This emphasizes the relative unfamiliarity of achromatopsia among non-specialized ophthalmologists. Nevertheless, it’s worth noting that older patients tended to receive their diagnosis at a more advanced age. This suggests that achromatopsia awareness has grown in recent times, leading to earlier diagnoses compared to the past. These results show a broad range of ages of diagnosis, with a concentration in early childhood, highlighting the importance of an early diagnosis and intervention for achromats.

Our study indicates that age has no evident impact on visual acuity, and, typically, visual acuity remains stable with age (mean=1.0; logMAR ± 0,2). These findings correlate with previous research, which has similarly concluded to an absence of significant changes in visual acuity

associated with age [25,30,54,56,58,59]. Our results demonstrate relatively consistent average visual acuity levels across the different ages of the patients. However, results from other studies, which analysed achromatopsia-associated deteriorations, showed a decrease in visual acuity [12,57]. The lack of significant relationships between alterations in visual acuity over time and between visual acuity and age within the studied group suggests that no additional factors significantly influence visual acuity outcomes in individuals with ACHM. Furthermore, the absence of a correlation between the type of mutated gene and visual acuity implies that these genetic variations may not directly predict visual acuity outcomes.

Refractive anomalies, nystagmus and strabismus were prevalent characteristics observed in our participant group, with hyperopia emerging as the predominant refractive anomaly. No discernible correlation was found between the extent of spherical refraction, astigmatism, strabismus with visual acuity, nor with the type of mutated gene. In Anderson's study [6], the frequency of refractive errors was also widely spread. Astigmatism was also prevalent but did not increase with the patients' age, as observed in our study too.

The fact that some patients had negative results on both tests implies the challenges they may face in everyday situations involving colour recognition. These colour tests highlight the variability in colour perception abilities among the patients of our cohort, emphasizing the complex nature of colour vision in the context of ACHM. The different shades of grey (luminance levels) most likely help the patients in identifying the colours. Achromats often use different tones of grey and variations in brightness to help identify and differentiate objects.

In terms of morphological findings, the lack of anterior segment abnormalities indicates that this feature is not commonly related to achromatopsia. This observation supports the notion that retinal dystrophies, including ACHM, primarily affect the neurosensory retina while sparing the anterior segment in most cases. We also observed a subtle narrowing of the retinal arterial vessels with advancing age, a feature that may also be seen in achromatopsia [34]. Nevertheless, such narrowing in the quality of the retinal vasculature could equally be attributed to the normal aging process. While vascular constrictions are common in retinal dystrophy, they can also occur as a natural consequence of aging in individuals with healthy eyes. Additionally, structural changes in the optic nerve head became more apparent with increasing age, indicating a potential progression toward retinal atrophy. These findings highlight the higher prevalence of optic nerve abnormalities in patients with retinal dystrophies. The observed optic atrophy may be linked to altered retinal metabolism and degenerative processes inherent to these conditions, potentially contributing to a higher incidence of optic atrophy compared to populations without retinal dystrophies. A notable proportion of patients

had optic disc drusen, a condition frequently linked to inherited retinal dystrophies, including ACHM. This prevalence is significantly higher compared to the general population, where optic disc drusen occur in approximately 0.3% to 2% of individuals [28]. However, we detected no discernible relationship between changes in the fundus periphery and age, nor between alterations in the macula and age. Changes in the fundus periphery typically increase with age in visually healthy individuals. A normal macula is unusual in such a severe cone dysfunction syndrome. These results suggest that while progressive retinal changes may occur, they are likely to evolve gradually. This aligns with previous research, which showed minimal macular changes with time and illustrates the predominantly stationary nature of achromatopsia [3,21,30,54]. The challenge in differentiating between age-related changes and those associated with ACHM remains evident.

Most of the participants attended regular schools, earned high school diplomas, and pursued higher education, demonstrating that individuals with ACHM do not face academic limitations and appear to be more independent in a regular school setting. Achromatopsia is associated with increased early childhood plasticity, which enables individuals to compensate for sensory deficits. It is therefore presumed that these individuals may have above-average intelligence. This correlates with the high number of university degrees obtained by participants compared to other visually healthy individuals and those with visual impairments from other causes. Moreover, we observed no significant correlation between attending schools for the visually impaired and academic performance within this patient group. Furthermore, an earlier age of diagnosis had no impact on education, confirming that achromats do not experience academic disadvantages. Nevertheless, it would be inaccurate to imply that achromatopsia poses no societal challenges. It is important to acknowledge a potential limitation in our study, as individuals with higher academic performance may have a greater tendency to respond to the questionnaire.

The variability in the level of disability among our patients, despite their consistently uniform visual acuity, highlights the frequent inappropriateness of the current degree of handicap classification. It is important that the legal categorization of disabilities aims to assess and categorize patients solely through standardized assessments and impartial examinations of their abilities. Several participants have expressed difficulties in obtaining support or benefits for the visually impaired, primarily because institutions assess the degree of handicap in achromats solely based on visual acuity, neglecting the significant impact of colour vision impairments and severe light sensitivity. We suspect that a small portion of patients with ACHM who do not have a disability ID may not have applied for one yet, and therefore reported a degree of handicap of 0%. Furthermore, the severity of the handicap is not influenced by or

related to the type of gene mutation. This indicates that the impact of gene mutations on handicap severity may not vary significantly based on the specific type of mutation.

Based on our findings, it becomes evident that a majority of achromatopsia patients require optical aids to reduce their symptoms. This underlines the significance of early and accurate diagnosis in order to effectively address these symptoms with tailored visual aids. These aids must be customized to address the unique symptoms of each individual. Among the available options, edge filter glasses emerge as the most commonly utilized, while contact lenses are less frequently chosen by our patients. This may be attributed to the reluctance of many survey participants to use edge filter glasses outdoors, possibly to avoid potential social discrimination. This observation reflects the adaptive nature of achromatopsia individuals as they seek to integrate into society. Consequently, contact lenses present a viable but comparatively expensive option. Unfortunately, in the German insurance system edge filter contact lenses are not covered. When it comes to low-vision aids, reading glasses and simple magnifying glasses are the most frequently employed due to their ease of use in contrast to electronic devices. Nevertheless, it is noteworthy that many patients are also embracing modern technologies such as smartphones and tablets as practical low-vision aids.

Typically, the primary desire for the majority of patients is to attain regular visual acuity. Following this, they often seek relief from heightened sensitivity to glare and improvements in colour perception. These observations align with the research of Aboshiha et al. [2], who similarly noted that excellent visual acuity ranked as the foremost aspiration among achromats. Subsequently, they expressed a strong concern about alleviating glare sensitivity and enhancing colour vision. In the consultation, patients primarily complain about glare sensitivity, less about reduced vision. It is surprising to note that the desire for intact colour vision is so low. Glare sensitivity seems to be much more disturbing than visual impairment, and it remains unclear why this was answered differently in the questionnaire. Moreover, it was observed that the majority of participants did not rely on a colour recognition system. These results suggest that in cases of complete colour blindness, colour recognition is not the most prevalent challenge. Surprisingly, the primary concerns are often related to visual acuity and sensitivity to glare, which contrasts with common expectations.

6.2. Limitations of the study

Our study is limited by its retrospective nature, which led to incomplete data on the morphological and functional characteristics of patients who visited our clinic between 2008 and 2021, with varying lengths of follow-up. The most significant weakness lies in the heterogeneous and inconsistent data set, which was collected by different physicians or ophthalmologists without a shared standard. This issue is particularly evident in the subjective classification criteria, such as the distinction between “vital” and “pale” for the optic nerve or “slightly restricted” or “significantly restricted” for the retinal arterial vessels, which is highly subjective. Drawing significant correlations from such data may therefore be overly ambitious.

Additionally, less than 50% of the achromatopsia patients included in the study were confirmed through molecular genetic testing. This testing is crucial for providing definitive confirmation of the diagnosis by identifying specific genetic mutations responsible for the disease. Without this confirmation, diagnoses may rely solely on clinical observations, which can be less accurate and more prone to misclassification.

There were also instances of missing data, as not all individuals with achromatopsia participated in the questionnaire, and some did not respond to all questions. Furthermore, our study predominantly included younger participants with a follow-up duration of 13 years. We also acknowledge the possibility of subjective bias in the clinical assessments and questionnaire responses.

To address these limitations, future prospective studies with a longer follow-up period and the inclusion of older participants should be conducted. This approach would enable a more precise examination of the relationships between morphological and functional aspects in individuals with achromatopsia and facilitate the development of more effective interventions to improve their quality of life.

6.3. Conclusions

To conclude, the following points summarize the key aspects of achromatopsia and its impact on affected individuals:

Visual acuity stability:

- Despite aging, visual acuity in ACHM remains remarkably stable. This suggests that while the condition is lifelong and persistent, it does not necessarily deteriorate with age, providing a degree of predictability for managing the condition over time.

Slow morphological changes:

- The retinal changes associated with ACHM occur at a slow pace. This slow progression indicates that while the condition is stable, it does not lead to rapid deterioration of the retinal structures.

Optic nerve atrophy:

- Advances in age are associated with increasing retinal optic atrophy. This progression, though gradual, reflects a slow but ongoing impact on the optic nerve head, underscoring the chronic nature of the condition.

Stable condition:

- ACHM remains predominantly stable throughout an individual's life. Modern deterioration methods have significantly improved, allowing for earlier diagnosis and potentially better management strategies.

Academic achievement:

- Most individuals with ACHM are able to successfully complete their education, attending regular schools, high school, and to a surprisingly high percentage university. This demonstrated that despite their condition, they can achieve academically with only slight impairments.

Visual handicap variation:

- There is a notable variation in the degree of visual handicap among individuals with similar visual acuity levels. This discrepancy highlights that standard assessments may not fully capture the functional challenges faced by individuals, suggesting the need for more personalized evaluation and support.

Need for optical aids:

- The use of optical aids is essential for managing visual impairments in ACHM. Edge filters, reading glasses, and magnifying glasses are the most commonly used aids. These tools, especially simpler ones like magnifying glasses, are preferred over electronic devices due to ease of use.

Primary concern:

- While many might assume that the primary concern for those with ACHM is the lack of colour vision or high light sensitivity, the most significant challenge reported by individuals is their low visual acuity. This highlights the profound impact that reduced visual acuity has on their daily lives. However, during consultations, most patients indicate that glare sensitivity is more troublesome than visual acuity.

In summary, ACHM is a stable condition with slow progression, where individuals generally maintain a stable visual acuity and can achieve significant educational milestones. Despite advances in early detection and the availability of optical aids, the low visual acuity remains the most challenging aspect for those affected.

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8. List of Publications / Citations

1. Chan C, Seitz B, Käsmann-Kellner B (2021) Morphologische und funktionelle Aspekte und Lebensqualität bei Patienten mit Achromatopsie. Wissenschaftliche Sitzung, 94. Versammlung des Vereins Rhein-Mainischer Augenärzte e.V., Koblenz, 30.10.2021

2. Chan C, Seitz B, Käsmann-Kellner B (2023) Morphological and Functional Aspects and Quality of Life in Patients with Achromatopsia. J Pers Med 13(7):1106

3. Chan C, Seitz B, Käsmann-Kellner B (2024) Kantenfiltertest bringt Licht ins Dunkel. Z prakt Augenheilkd 45:19-23

4. Käsmann-Kellner B, Hoffmann MB (2023) Achromatopsia-Clinic, diagnostics, genes, brain and quality of life. Ophthalmologie 120(9):975-986

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10. Curriculum vitae

The curriculum vitae was removed from the electronic version of the doctoral thesis for reasons of data protection.