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Genetic phenotypic characteristics and inheritance patterns of patients with achromatopsia at a large academic institution and a review of the literature and gene therapies

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Purpose: Achromatopsia (ACHM) is a cone dysfunction syndrome associated with low color vision, photophobia, and congenital nystagmus. Pathogenic variants in the *CNGA3* and *CNGB3* genes are the most common causes of ACHM. Identifying the underlying genetic etiology in patients with clinical findings of ACHM is critical to establishing the diagnosis and selecting targets for gene therapies. This study utilizes the inherited retinal disease (IRD) database at the University of Minnesota (UMN) to understand clinical features of achromatopsia, potential diagnostic methods, and genetic variability at one large academic institution.

Methods: This retrospective cohort study examined patients with a genetically confirmed diagnosis of ACHM evaluated at the UMN/M Health IRD clinic between May 2015 and August 2022. Data were collected through UMN's electronic health record system and included information on demographics, history of ocular illness, visual acuity, and diagnostic exam results, such as electroretinogram, fundus autofluorescence, and optical coherence tomography (OCT) imaging. Genetic testing was performed using next-generation sequencing panels of varying sizes, and variants were interpreted according to American College of Medical Genetics guidelines.

Results: A total of 21 patients with a genetically confirmed ACHM were included in the study. Most patients were female (67%) and white (76%). The cohort included one pair of twin siblings and one group of three siblings. The median age of genetic testing conducted was 12 years (interquartile range, 12-20 years). One-third of patients had nyctalopia. All patients experienced difficulties with color vision, 20 of 21 (95.2%) had photosensitivity, and 18 of 21 patients reported congenital nystagmus. Diagnostic imaging showed most patients with a normal scotopic response and absent photopic response on electroretinogram, macular hyperfluorescence on fundus autofluorescence, and normal optical coherence tomography imaging.

Conclusion: This study contributes to an understanding of the phenotypes and distribution of genetic variants associated with achromatopsia at a single academic institution in the state of Minnesota, particularly those involving the *CNGA3* and *CNGB3* genes. Future research could explore the prevalence of these variants in larger cohorts to enhance clinical management and treatment strategies for patients with achromatopsia.

Achromatopsia (ACHM) is an inherited retinal disease (IRD) associated with reduced visual acuity from birth, low color discrimination, photophobia, pendular nystagmus, and a small central scotoma on visual field testing [1]. ACHM is the most common cone dysfunction syndrome, with a prevalence of 1/30,000; its pathophysiology involves defects to the cone photoreceptors, which process daylight and color vision [2,3]. In comparison to color blindness, which entails the loss of only spectral vision, ACHM impacts short, medium, and long cone photoreceptors, leading to complete reliance on rod function, also known as monochromatic vision [4]. Presentation often begins at birth with low visual acuity, congenital nystagmus, and a paradoxical pupil, or constriction of the pupil in the dark as opposed to the light, as some of the first findings [5]. On examination and imaging, ACHM presents with normal fundus, normal scotopic response with no photopic response, fundus autofluorescence (FAF), and optical coherence tomography (OCT) ranging from normal to hyper- or hypofluorescence and foveal atrophy, respectively [1,6].

Complete ACHM is inherited in an autosomal recessive pattern. Causative genes include cyclic nucleotide gated channel subunit alpha 3 (*CNGA3*, Gene ID: 1261), cyclic nucleotide gated channel subunit beta 3 (*CNGB3*, Gene ID: 54714), G protein subunit alpha transducin 2 (*GNAT2,* Gene ID: 2780), phosphodiesterase 6C (*PDE6C*, Gene ID: 5146), phosphodiesterase 6H (*PDE6H*, Gene ID: 5149), and activating transcription factor 6 (*ATF6*, Gene ID: 22926) [7]. Except for *ATF6*, all genes are involved in the cone photoreceptor signal transduction pathway. *CNGA3* and *CNGB3* encode the alpha and beta subunits for the cone cyclic nucleotide-gated (CNG) channel [8,9]. *GNAT2* encodes the alpha

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subunit of the cone photoreceptor transducin [10]. *PDE6C* and *PDE6H* are subunits of the phosphodiesterase (PDE) protein [11,12]. CNG channels are located in the cellular membrane of the outer photoreceptor membrane. In dark conditions, guanylate cyclase converts guanosine triphosphate to cyclic guanosine monophosphate (cGMP), a ligand for CNG channels. High levels of cGMP allow Na^+ and Ca^{2+} to enter the cell and keep it in a depolarized state. Glutamate is released to downstream second-order neurons such as bipolar and horizontal cells. When light enters the eye, individual photons bind with opsins on the cell membrane, causing a change in conformation. Opsin activation releases the G-protein transducin, which activates the PDE to mediate cGMP hydrolysis. Lower levels of cGMP cause the CNG channels to close, and the photoreceptor cell is hyperpolarized, leading to a signal being sent to the brain [7,13]. The absence or dysfunction of the genes encoding this process leads to dysfunction of the photoreceptor pathway. *ATF6* is a protein involved in the unfolded cellular response, managing enzymes involved in protein folding in the endoplasmic reticulum (ER) [14]. This mechanism is present within many different cell types. It is thought that endoplasmic reticulum stress and damage during retinal development could lead to ACHM in patients with pathogenic variants in this gene, although the exact mechanism is still unclear. The prevalence of causative gene variants varies by population. *CNGA3* and *CNGB3* variants make up 90% of gene variants found in patients with ACHM, *PDE6H* and *PDE6C* make up <5%, *GNAT2* represents <3%, and *AFT6* variants are found in <2% of the population [7].

Electrophysiological and imaging methods for ACHM include full-field and multifocal electroretinogram (ERG), fundus photos, OCT, and FAF. Electrical activity can provide information on the functionality of different parts of the retina. On ERG, patients with ACHM are typically found to have absent or markedly reduced cone response with normal response of rods [15]. FAF uses the fluorescent properties of lipofuscin present within the lysosomal breakdown of photoreceptor segments to produce a photo of the retinal pigment epithelium (RPE). Retinal pathologies often cause RPE dysfunction and accumulation of lipofuscin in response, leading to abnormalities seen on FAF [16]. For patients with ACHM, FAF typically shows macular hyperfluorescence or an oval-shaped area of hypofluorescence at the fovea with a surrounding ring of hyperfluorescence [17,18]. OCT is used as a method to look at high-quality retinal images. In particular, the ellipsoid zone (EZ), the hyperreflective OCT band in the junction of the outer and inner photoreceptor, is a marker of photoreceptor health and mitochondrial function [19]. Findings on OCT range from normal to foveal atrophy and an absent or disrupted EZ band [18,20]. As ACHM is a cone dysfunction disorder, EZ band disruption begins centrally and extends outwardly in contrast to rod conditions, such as retinitis pigmentosa, which is characterized by peripheral loss of the EZ band [21].

New gene therapies are continuing to be developed to treat ACHM. One example is the utilization of viral vectors such as adeno-associated virus; a transgene, along with a cone-specific promoter, is injected in the subretinal space [22]. With the functional gene, cones can restore photoreceptor function. As the potential for gene therapies increases, it is critical to understand the genetic variety seen within populations, common methods of diagnosis, and phenotypic variability to allow for safer and more targeted treatments. This study utilizes the IRD database at the University of Minnesota (UMN) to understand clinical features of ACHM, potential diagnostic methods, and genetic variability in Minnesotan patients.

METHODS

In this retrospective cohort study, patients with clinical features and confirmed genetic diagnoses of ACHM evaluated at the UMN/M Health IRD Clinic between May 1, 2015, and August 5, 2022, were included. Data were collected using UMN's electronic health care record system, EPIC. REDCap, an online software to securely collect and manage data, was used to create a database of patients with IRD. This review was performed in accordance with the Health Insurance Portability and Accountability Act of 1996 and the Declaration of Helsinki. The institutional review board at UMN approved the study protocol. Written informed consent was obtained from all patients whose images were included.

Patients with a clinical diagnosis of ACHM, cone dystrophy, or other variations and confirmed genetic diagnosis of ACHM were included in the study. ACHM was considered genetically confirmed if patients had pathogenic/likely pathogenic variants of *CNGA3*, *CNGB3*, *GNAT2*, *PDE6C*, *PDE6H*, or *ATF6*. Patients without confirmatory genetic testing were excluded. A data collection form was created to record demographic information, history of ocular illness, and diagnostic examination results for each patient based on chart review. Data that could not be directly found through chart review were labeled as "unknown" and denominators reflect only cases with data present. Demographic questions consisted of age, sex, and self-identified race. History of illness included age of onset, visual acuity for both eyes, presence of visual field loss, and symptoms including photosensitivity, nyctalopia, and color vision loss. Visual acuity was stratified into Snellen scores of above 20/40, between 20/40 and 20/80, and below 20/80. Visual field loss was assessed using Goldmann

field testing. Color vision was assessed by Ishihara color plates. Diagnostic electrophysiological and imaging studies included ERG, FAF, and OCT, all available in the IRD clinic. ERG testing was used to assess the degree of cone versus rod photoreceptor responsiveness. LKC (LKC Technologies, Gaithersburg, MD) and Diagnosys (Diagnosys LLC, Lowell, MA) were the two types of ERG used in the clinic. Tested values included dark-adapted response, light-adapted flicker, and light-adapted single-flash response. Each ERG device had its own range of reference values to assess a reduced or absent response. FAF allowed for analysis of macular or peripheral ring hyper- or hypoautofluorescence, assessing retinal damage. FAF was conducted using Optos ultrawide field imaging, which provides a 200-degree view of the retina. Spectralis OCT imaging was also used for both FAF and measurement of EZ band loss and retinal atrophy. Loss of EZ banding was manually measured using the embedded measurement tool. EZ band loss was considered a sign of structural retinal damage.

Genetic testing was offered to all patients during the IRD evaluation. Family members of patients were also invited to complete genetic counseling and testing at the clinic. Genomic data were analyzed by a variety of methods ranging from single-gene targeted testing to panels of over 260 genes reported to cause isolated or syndromic retinal disease, including cone-rod dystrophy or retinitis pigmentosa. For patients with known familial variants, single-gene testing was conducted. Testing was performed via next-generation sequencing. Genetic testing laboratories used included Invitae Laboratory (San Francisco, CA) and the University of Minnesota Molecular Diagnostic Laboratory (Minneapolis, MN). Outcomes of genetic testing included pathogenic or likely pathogenic (P/LP) variants for genes known to cause the phenotype, P/LP variants for genes associated with phenotypes not present in the patient, variants of uncertain significance (VUS), or no variants. Variants were interpreted by the respective laboratories according to the American College of Medical Genetics guidelines. Results were reviewed with a genetic counselor and ophthalmologist. Autosomal recessive pattern of inheritance, as expected for patients with ACHM, was confirmed by the presence of P/LP variants in two copies of the gene.

RESULTS

Demographics: A total of 21 patients diagnosed with ACHM were included in the study. Most (14/21) patients were female, and 16 of 21 were white. Seven of 17 patients had a family history of retinal disease. The cohort included one pair of twin siblings and one group of three siblings. Median age of genetic testing conducted was 12 years (interquartile range, 12-20 years).

Table 1. Distribution of achromatopsia patient demographics and symptoms.

Demographics	Number and proportion of patients, N (%)
Sex	
Female	7 (33.3)
Male	14 (66.7)
Race	
White	16 (76.2)
Asian	3 (14.3)
Unknown	2 (9.52)
Age of Genetic Testing	
0 – 9 years	10 (47.6)
10 −19 years	5 (23.8)
20 – 40 years	5 (23.8)
Above 40 years	1 (4.76)
Symptoms	
Nyctalopia	5 (33.3)
Photosensitivity	20 (95.2)
Color vision loss	21 (100)
Visual field loss	11 (52.4)
Congenital nystagmus	18 (85.7)
Paradoxical pupil	9 (42.9)

Symptoms: Twelve of 21 patients received a clinical diagnosis of ACHM at birth, 5 of 21 before 1 year of age and 4 of 21 before age 10 years. All patients had binocular disease. Five of 15 experienced nyctalopia. All patients had difficulties with color vision, and 20 of 21 experienced photosensitivity. Eleven of 21 patients had evidence of visual field loss. Eighteen of 21 patients reported congenital nystagmus. Nine of 21 patients displayed paradoxical pupil findings (Table 1)

Visual acuity: Eighteen of 21 patients had worse than 20/80 vision in the right eye, and 19 of 21 patients had worse than 20/80 vision in the left eye. The remaining patients had worse than 20/40 vision and greater than 20/80 vision.

Electroretinogram: ERG was available for 13 patients. Most ERG results showed normal or reduced scotopic response and no or reduced photopic response (Figure 1).

Fundus autofluorescence: FAF was available for 10 patients. Five demonstrated macular hyperfluorescence, 2 showed macular hypofluorescence, and three FAFs were normal. No peripheral fluorescence changes were noted.

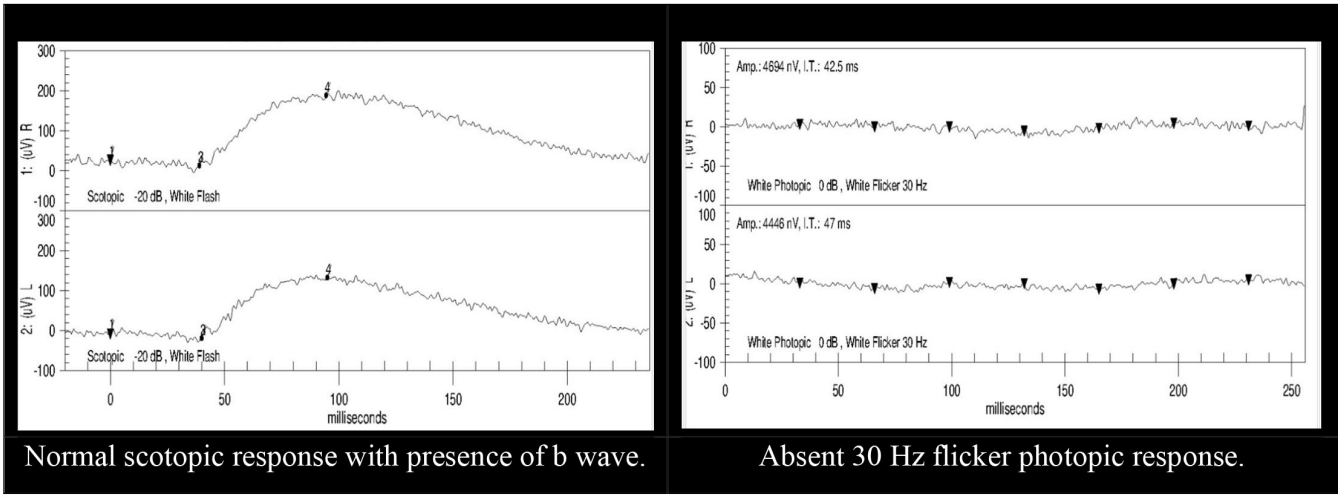

Figure 1. Normal scotopic response and absent photopic response on electroretinogram seen in the patient cohort. (Upper is OD; lower is OS.)

OCT imaging/EZ band loss: OCT imaging was available for 11 patients. Two patients demonstrated central foveal EZ band loss. Median EZ band disruption was 1874 (interquartile range, 1805-1968). The remaining seven patients showed no loss of EZ banding (Figure 2).

Genetic distribution: Sixteen patients had variants in *CNGB3* identified, and five had variants in *CNGA3* identified. Ten patients had homozygous P/LP variants identified, and 11 had compound heterozygous variants. All patients in our cohort with *CNGA3*-related ACHM were compound heterozygous for two different variants. One set of three siblings was compound heterozygous for an intronic variant (c.395+1G>A) and a missense variant (c.605T>C p.Leu202Pro). The remaining two patients were compound heterozygous for two different missense variants (c.800G>A p.Gly267Asp; c.1328A>G p.Tyr443Cys and c.1641C>A p.Phe547Leu; c.1981C>T p.Arg661Cys; Appendix 1). Two of these variants, c.1328A>G p.Tyr443Cys and c.395+1G>A, were reported to be novel by the reporting laboratory. All patients in our cohort with *CNGB3*-related ACHM had homozygous or compound heterozygous nonsense variants identified. Ten of the 16 patients were homozygous for the common frameshift c.1148del p.Thr383Ilefs *13 variant, 5 of 16 were compound heterozygous for the c.1148del p.Thr383Ilefs *13 variant and a different *CNGB3* pathogenic variant (c.886_896delinsT p.Thr296 TyrfsX9; c.819_826delC AGACTCC p. Arg274ValfsX 13; c.1006G>Tp. Glu336X), and the final patient was compound heterozygous for two different *CNGB3* variants (c.819_826del p.Arg274Valfs X13 and c.886_896deli nsT p.Thr296 TyrfsX9). Fifteen patients had genetic testing completed using the UMN Molecular Diagnostic Laboratory, and six had testing via the Invitae Laboratory. Two of these patients underwent single-gene testing for a familial variant (Appendix 1).

DISCUSSION

The UMN IRD database included 21 patients with clinically and genetically confirmed achromatopsia. We identified 16 patients with *CNGB3*-related achromatopsia and 5 with *CNGA3*-related achromatopsia. The cohort included two sets of siblings—one comprised of three individuals (Appendix 1, patients 370-372) and the other with two (Appendix 1, patients 380 and 381). Each group of siblings demonstrated the same variants as their family members. Most of the patients in our database self-identified as white. Previous studies of northern European populations, including one in the Netherlands and one in Hungary, noted a high prevalence of *CNGB3* and *CNGA3* variants, without a significant phenotypic difference [23,24]. Our cohort's genetic distribution aligns with the expected genetic spectrum associated with these conditions. All patients in our cohort with *CNGA3* dysfunction showed missense variants, one of which was a novel variant, p.Tyr443Cys, similar to trends seen in the literature, indicating little tolerance for substitutions in the functionality of this receptor [9,25,26]. Three related patients displayed a novel splice site variant, c.395+1G>A, in a highly conserved donor splice site consequence sequence. A previous study has noted the importance of splice site variants in the

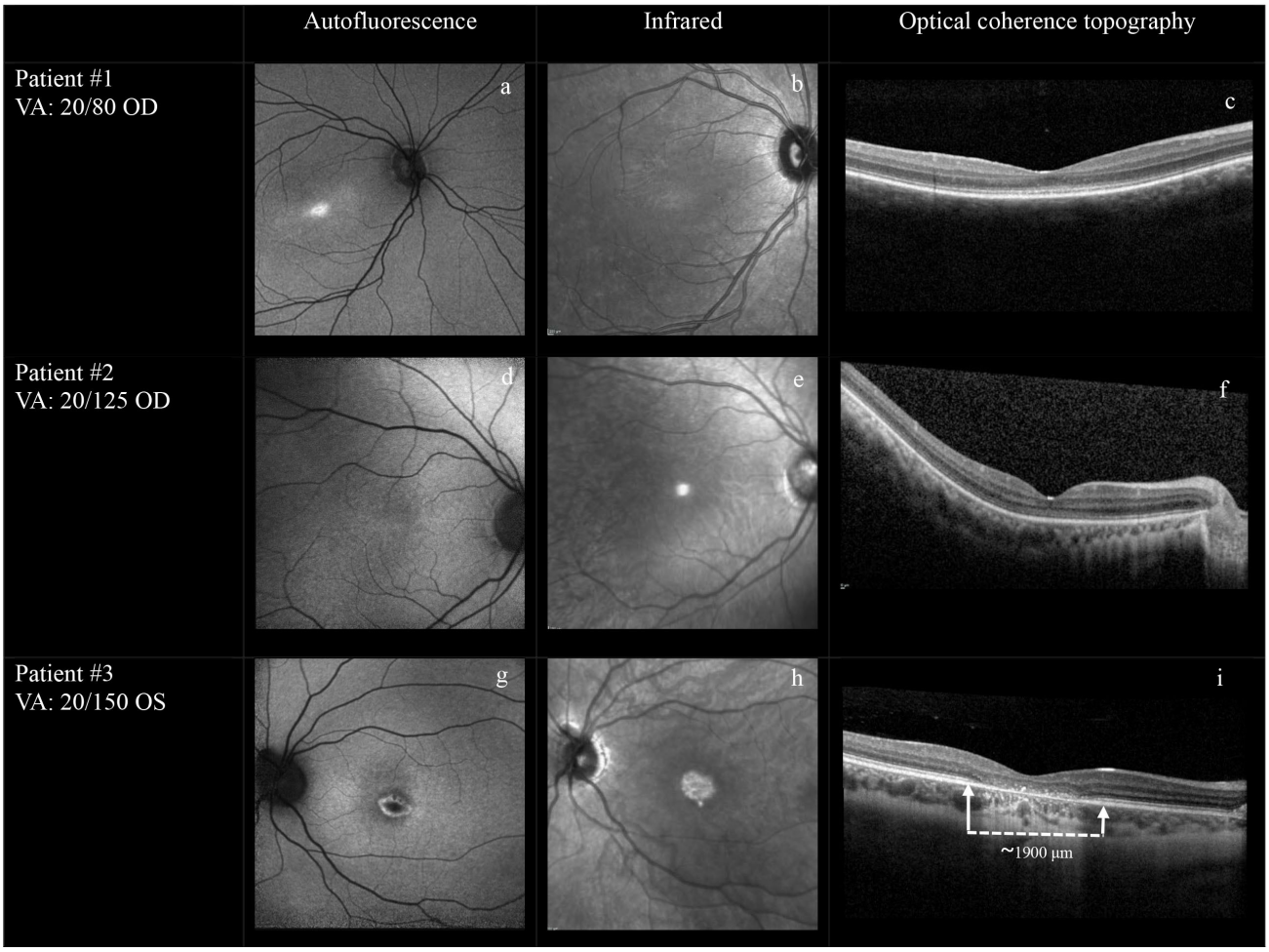

Figure 2. Examples of multimodality images in three patients with achromatopsia. Patient 1 demonstrates central hyperautofluorescence of the fovea. **A**: Infrared (IR) shows a normal reflectivity pattern. **B**: OCT shows stippling of the ellipsoid zone. **C**: No outer segment loss or other abnormalities appear in the retinal layers. Patient 2 demonstrates a normal autofluorescence pattern. **D**: IR shows central foveal hyper-reflectance. **E**: OCT shows stippling of the ellipsoid zone. F: No outer segment loss or other abnormalities appear in the retinal layers. Patient 3 shows central foveal hypoautofluorescence with a hyperautofluorescent halo. **G**: IR shows hyper-reflectance at the fovea lesion. **H**: OCT demonstrates foveal outer retina atrophy with secondary choroidal hyperreflectivity. **I**: Retinal layers outside the fovea are well preserved.

pathogenesis of *CNGA3* and reported variants c.395+1G>T and c.395+9C>T, which were found to cause splice defects [27]. Splice defects can lead to frameshift variants, insertions, and deletions that may cause dysfunction in the final transcript of the gene. The likely pathogenicity of both novel variants warrants further investigation to confirm their role in achromatopsia and as a potential target for gene therapies. Another patient was found to have a *CNGA3* variant currently classified as a VUS, c.1981C>T p.Arg661Cys. Given the clinical phenotype of ACHM and finding an additional pathogenic *CNGA3* variant in this patient, these results were interpreted as diagnostic. In the *CNGB3* gene, frameshift variants were found in all patients. In particular, the c.1148del (p.Thr383Ilefs*13) transcript is considered the most recurrent pathogenic variant noted in patients with autosomal recessive ACHM, with studies showing the prevalence of this variant in around 66% of patients with *CNGB3* [28,29]. There were 15/16 patients in our cohort who demonstrated this variant, again highlighting its significance as a key target for gene therapies.

Presenting symptoms in our patient cohort included congenital nystagmus, diminished color vision, photosensitivity, low visual acuity, and paradoxical pupil. The lack of photopic response with an intact scotopic response on ERG was also a significant prompt for initiation of genetic testing. Most patients with available data displayed macular

hyperfluorescence on FAF, suggesting increased levels of RPE lipofuscin due to RPE dysfunction. Previous studies have noted the finding of macular hyperfluorescence as a sign of early ACHM [18]. Notably, patients in our cohort with hypofluorescence on FAF also had a ring of hyperfluorescence surrounding it. One study further describes this as a "punched-out lesion" or an area of hypofluorescence surrounded by an area of hyperfluorescence that may be a signature finding of ACHM, specifically associated with increased age of the patient [17]. Additionally, the presence of predominantly macular changes versus peripheral changes typically seen on FAF for patients with retinitis pigmentosa is also notable as a unique feature [21]. The presence of hyper- or hypofluorescence did not appear to be correlated with vision.

OCT findings ranged from normal to foveal atrophy and EZ band disturbance. Most our cohort displayed a normal appearance of OCT imaging, without EZ band disruption. One patient with *CNGA3*-related ACHM and one patient with *CNGB3*-related ACHM had evidence of EZ band disruption. The patient with *CNGA3*-related ACHM had a P missense variant and a VUS (Appendix 1, patient 373). The patient with *CNGB3*-related ACHM had a frameshift variant and a splice donor site variant and was the oldest member of the cohort (Appendix 1, patient 375). Both patients were the only members of the cohort to show hypofluorescence on FAF. In the literature, EZ band disruption in ACHM has not shown clear associations with either age or genomic markers [30]. In comparison, patients with retinitis pigmentosa, for example, typically have initial peripheral loss of EZ banding with progressive loss until complete blindness. More severe forms of the disease are noted with X-linked retinitis pigmentosa [21]. Further research with a larger cohort would be helpful in solidifying relationships between genotypes and phenotypes in relation to imaging findings for patients with ACHM. Notably, the high proportion of patients with normal OCT findings and no photopic function suggests that foveal structure is largely maintained even after functional loss. As such, patients with ACHM may have a larger therapeutic window to receive gene therapies. However, close monitoring of patients is necessary as foveal atrophy and EZ band disruption, when it does begin, can be fatal for vision.

Initial gene therapy testing has been conducted in mouse, canines, and sheep models [31-33]. The presence of light-adapted ERG response after therapies is considered restorative. Thus far, it was noted that mice treated at older ages have a poor response to treatment [31]. Prompt genetic testing when there is clinical suspicion of ACHM can aid in early diagnosis and potentially increase a patient's opportunities for gene therapies. Current registered clinical trials for ACHM have focused on *CNGB3* and *CNGA3*-related ACHM due to their relatively higher prevalence in the population (Table 2). Replacements of *CNGB3* and *CNGA3* genes are delivered using an adeno-associated virus capsid through a subretinal injection [7,22]. As of June 2025, there are three active ACHM gene therapy clinical trials. Genetic sequencing can expand prior understanding of ACHM distribution and assist in the selection of genetic marker targets for clinical trials.

There are a few limitations to this study. This was a retrospective study with a small sample size and lack of available diagnostic and ocular history data for each patient. Due to the low incidence of ACHM, it was difficult to identify many patients from a single institution. Additionally, all family members of patients diagnosed with an IRD at the clinic are invited to undergo genetic counseling and testing. However, many family members do not choose to undergo genetic testing, likely due to the cost and the lack of

Table 2. Summary of achromatopsia gene therapy clinical trials.

NCT Registration #	Phase	Gene	Vector	Sponsor	Status	Route	Year of Last Update
2935517	Phase I/II	CNGA3	rAAV2tYF-PR1.7-hCNGA3	Beacon Therapeutics	Active, not recruiting	Sub-retinal	2022
2599922	Phase I/II	CNGB3	rAAV2tYF-PR1.7-hCNGB3	Beacon Therapeutics	Active, not recruiting	Sub-retinal	2022
3758404	Phase I/II	CNGA3	AAV2/8-hG1.7p.coCNGA3	MeiraGTx UK II Ltd	Completed	Sub-retinal	2022
3001310	Phase I/II	CNGB3	AAV2/8-hCARp.hCNGB3	MeiraGTx UK II Ltd	Completed	Sub-retinal	2023
2610582	Phase I/II	CNGA3	rAAV.hCNGA3	STZ eyetrial	Active, not recruiting	Sub-retinal	2024

additional clinical utility, which limits our available information regarding familial structure. These limitations should be considered when interpreting the results of this study.

Conclusion: Genetic testing is a key diagnostic tool in patients who present with clinical signs of ACHM as it may predict the clinical course of the disease and identify therapeutic targets. This study contributes to the growing body of knowledge regarding the genetic variants in ACHM, particularly those involving the *CNGA3* and *CNGB3* genes. Our findings expand the known variant spectrum of these genes, with the identification of novel variants such as p.Tyr443Cys and c.395+1G>A, which may offer new insights into the pathophysiology of achromatopsia. Future research should focus on larger cohort studies, which will be crucial for establishing genotype-phenotype correlations that may inform clinical management and treatment strategies for patients. The continued advancement of genetic testing technologies holds promise for improving early diagnosis, patient care, and potential therapeutic interventions for individuals with IRDs.

APPENDIX 1. SUPPLEMENTAL TABLE.

To access the data, click or select the words "Appendix 1."

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