Phenotype and genotype of 15 Saudi patients with achromatopsia: A case series

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Abstract:

PURPOSE: Achromatopsia is a rare stationary retinal disorder that primarily affects the cone photoreceptors. Individuals with achromatopsia present with photophobia, nystagmus, reduced visual acuity (VA), and color blindness. Multiple genes responsible for achromatopsia have been identified (e.g. cyclic nucleotide-gated channel subunit alpha 3 [*CNGA3*] and activating transcription factor 6). Studies have assessed the role of gene therapy in achromatopsia. Therefore, for treatment and prevention, the identification of phenotypes and genotypes is crucial. Here, we described the clinical manifestations and genetic mutations associated with achromatopsia in patients from Saudi Arabia.

METHODS: This case series study included 15 patients with clinical presentations, suggestive of achromatopsia, who underwent ophthalmological and systemic evaluations. Patients with typical achromatopsia phenotype underwent genetic evaluation using whole-exome testing.

RESULTS: All patients had nystagmus (n = 15) and 93.3% had photophobia (n = 14). In addition, all patients (n = 15) had poor VA. Hyperopia with astigmatism was observed in 93.3% (n = 14) and complete color blindness in 93.3% of the patients (n = 14). In the context of family history, both parents of all patients (n = 15) were genetic carriers, with a high consanguinity rate (82%, n = 9 families). Electroretinography showed cone dysfunction with normal rods in 66.7% (n = 10) and both cone–rod dysfunction in 33.3% (n = 5) patients. Regarding the genotypic features, 93% of patients had variants in *CNGA3* (n = 14) categorized as pathogenic Class 1 (86.7%, n = 13). Further, 66.7% (n = 10) of patients also harbored the c.661C>T DNA variant. Further, the patients were homozygous for these mutations. Three other variants were also identified: c.1768G>A (13.3%, n = 2), c.830G>A (6.6%, n = 1), and c. 822G >T (6.6%, n = 1).

CONCLUSION: Consanguinity and belonging to the same tribe are major risk factors for disease inheritance. The most common genotype was *CNGA3* with the c.661C>T DNA variant. We recommend raising awareness among families and providing genetic counseling for this highly debilitating disease.

Keywords:

Achromatopsia, activating transcription factor 6, color blindness, cyclic nucleotide-gated channel subunit alpha 3, electroretinography, genetic screening

Introduction

Retinal dystrophies are degenerative diseases of the retina with underlying genetic mutations. They have many presentations, depending on which part of the retina is affected, leading to partial or complete blindness. Some are relatively stationary rather than progressive. Retinal dystrophies present as isolated retinal diseases or as a part of a systemic condition.[1,2] One such isolated dystrophy that is relatively stationary is achromatopsia.[3,4]

Achromatopsia is an autosomal recessive genetic disease of cones, also known as rod monochromacy, affecting approximately 1:30,000 births.[5] Individuals with achromatopsia present with an increased sensitivity to light (photophobia), nystagmus, visual acuity (VA) of <20/200, and variant color blindness depending on the amount of residual cone function.[5] It is categorized as complete and incomplete,

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with the former being the more severe form.[5-10] Multiple genes that are important in the phototransduction cascade of photoreceptors are associated with achromatopsia, including cyclic nucleotide-gated channel subunit alpha 3 (*CNGA3*), cyclic nucleotide-gated channel subunit beta 3, G protein subunit alpha transducin 2, *PED6C*, *PED6H*, and activating transcription factor 6 (*ATF6*).[5,11-16] The diagnosis of such cases is mainly based on high clinical suspicion, particularly when a physician encounters a patient with signs, symptoms, family history, examination, and ancillary testing that suggest achromatopsia; once suspected, the molecular diagnosis can be confirmed with genetic testing.[5,7,11] The current management methods are mainly dependent on symptom management and not on the underlying process of the disease itself. Being a disorder caused by genetic mutations, genetic counseling is the main consideration in the management plan.[5] Numerous studies have investigated methods of gene therapy in retinal dystrophies, gene delivery, replacement, sequencing, and editing.[17,18] Animal studies have assessed the role of gene therapy for achromatopsia, and some have suggested that cone function can be restored at many levels of intervention. The response to treatment is governed by the age at intervention and the amount of damage to the retina and photoreceptors.[5,11,19,20] A nonrandomized controlled trial assessed the safety and visual outcomes in nine patients with *CNGA3*-related achromatopia, and this showed the activation of cone photoreceptors in adult patients, along with a safe profile for subretinal injections of the adeno-associated virus encoding the gene.[21] The outcomes of gene therapy in animals and humans differed ranging from no significant improvement to promising changes.[22-24] A study assessed visual cortex changes after gene therapy using functional magnetic resonance imaging and size algorithms of population-receptive fields and found evidence for cortical changes, described as a decrease in the receptive field size in treated eyes, suggesting that the cortex is able to perceive and encode new input.[22]

In this case series, we aimed to describe the ophthalmic manifestations and pathogenic variants associated with achromatopsia in 15 Saudi patients and identify phenotypic and genotypic correlations for future treatment and prevention.

Methods

This was a consecutive case series study involving 15 Saudi patients conducted from August 2021 to February 2023 at King Fahad Armed Forces Hospital of Jeddah and Riyadh in Saudi Arabia. Patients with clinical presentations suggestive of achromatopsia were recruited for this study. A full ophthalmological examination was done, including VA, intraocular pressure, extraocular motility, pupil examination, orthoptic evaluation, refraction, anterior segment examination, and dilated fundus examination. A full systemic assessment was made by a pediatrician, including cardiac, respiratory, gastrointestinal, musculoskeletal, central nervous system, and hearing assessment. Ophthalmic investigations included optical coherence tomography (OCT) of the macula and optic disc, fundus autofluorescence (FAF), fundus photography, and full-field electroretinography (ERG). Patients with the typical phenotype of achromatopsia underwent genetic evaluation using whole-exome sequencing. Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 27 (IBM, Armonk, NY, USA). We used descriptive analysis, Chi-squared test, and 95% confidence intervals. $P < 0.05$ was considered statistically significant. Our study followed the ethical standards and was approved by the Unit of Biomedical Ethics of King Fahad Armed Forces Hospital, Jeddah, Saudi Arabia (IRB number: REC 566). Consent was obtained from all participants and from their guardians if the participants' age was <18 years.

Results

We identified 15 patients (11 families) from two centers in Saudi Arabia. The 15 participants had an average age of 12.20 ± 10.0 years and belonged to 11 different families (six tribes). The majority were originally from the south of Saudi Arabia but lived in the Western region (73.3%, $n = 11$) and belonged to one tribe (66.7%, $n = 10$). The sociodemographic characteristics of the participants are shown in Table 1.

Table 2 shows the ocular manifestations in the patient cohort. All patients had nystagmus ($n = 15$), and most had photophobia (93.3%, $n = 14$). In terms of VA, all patients ($n = 15$) had poor vision, defined as VA <20/80. Most of the participants had either hyperopia (33.3%, $n = 5$) or hyperopia with astigmatism (33.3%, $n = 5$). Most patients (93.3%, $n = 14$) also had total color blindness as tested using Ishihara plates. Most of the patients did not have strabismus (93.3%, $n = 14$). Anterior (100.0%, $n = 15$) and posterior segment examinations (86.7%, $n = 13$) were within normal limits. Systemic manifestations (73.3%, $n = 11$) and autofluorescence (66.7%, $n = 10$) were mostly normal. OCT of the macula was normal in 26.6% ($n = 4$) of cases; abnormal OCT findings were as follows: shallow foveal pit in 20.0% ($n = 3$), shallow foveal pit with inner segments/outer segments (IS/OS) zone disruption in 20.0% ($n = 3$), foveal thinning in 13.3% ($n = 2$), and shallow foveal pit with empty space in 6.66% ($n = 1$).

The mean age of onset was 1.44 ± 2.1 years (min = 0.08, max = 6.00, $n = 13$), mean age of diagnosis was

Table 1: Sociodemographic characteristics of the studied patients ($n = 15$)

Variables	*n*	Minimum	Maximum	Mean±SD
Family	11	1	11	6±7.0
Age (years)	15	2	35	12.20±10.0
			Count, *n* (%)	
Total			15 (100.0)	
Region				
Central of Saudi Arabia			4 (26.7)	
Western of Saudi Arabia			11 (73.3)	

SD: Standard deviation

Table 2: Ocular manifestations of achromatopsia (presented by the studied patients (*n*=15)

Ocular symptoms	Count, *n* (%)
Total	15 (100.0)
Nystagmus	
None	0
Yes	15 (100.0)
Photophobia	
None	1 (6.7)
Yes	14 (93.3)
Poor vision	
None	0
Yes	15 (100.0)
Strabismus	
None	14 (93.3)
Yes (esotropia)	1 (6.7)
Nyctalopia	
None	14 (93.3)
Yes	1 (6.7)
VA	
20/150 both eyes	3 (20.0)
20/200 both eyes	6 (40.0)
20/400 both eyes	1 (6.7)
20/80 both eyes	1 (6.7)
Counting finger both eyes	2 (13.3)
Not following or fixing both eyes	1 (6.7)
20/100 both eyes	1 (6.7)
Refractive errors	
Hyperopia with astigmatism	5 (33.3)
Hyperopia	5 (33.3)
Myopia	2 (13.3)
Myopia with astigmatism	1 (6.7)
Astigmatism	2
Color vision	
Cannot be assessed (preverbal patient)	1 (6.7)
Total color blindness	14 (93.3)
Anterior segment examination	
Normal	15 (100.0)
Posterior segment examination	
Normal	13 (86.7)
Bulls eye maculopathy	1 (6.7)
Optic nerve pallor	1 (6.7)
General/systemic examination	
Normal	13 (86.7)
Hearing defect	1 (6.7)
Eczema	1 (6.7)
Dysmorphic features	
None	15 (100.0)
Systemic associations	
Normal	11 (73.3)
With systematic manifestation	4 (26.7)
Autofluorescence	
Normal	10 (66.7)
Bull's eye maculopathy	3 (20.0)
OCT macula	
Not done	2 (13.3)
Normal	4 (26.6)
Foveal thinning	2 (13.3)
Shallow foveal pit	3 (20.0)
Shallow foveal pit with empty space	1 (6.66)
Shallow foveal pit, IS/OS zone disruption	3 (20.0)
Full-field ERG	
Cone dysfunction with normal rods function	10 (66.7)
Cone–rod dysfunction	5 (33.3)

ERG: Electroretinography, OCT: Optical coherence tomography, OS: Outer segment, IS: Inner segments, VA: Visual acuity

5.96 ± 8.6 years (min = 0.17, max = 35.00, *n* = 15), mean duration of symptoms of 20.00 ± 21.2 years (min = 5.00, max = 35.00, *n* = 2), and the mean number of siblings (excluding the patient) was 4 (min = 1, max = 7, *n* = 15). Regarding family history, all patients (*n* = 15) were confirmed to have both parents as carriers of the disorder. The consanguinity rate was high (81.8%, *n* = 9). As detected by ERG, most patients had cone dysfunction with normal rods (66.7%, *n* = 10), whereas 33.3% (*n* = 5) showed cone–rod dysfunction. Examples of the patients' clinical presentations and investigations are shown in Figures 1-3.

Table 3 summarizes the genotypic features of the patients. The results showed that, of the 15 patients, 93.3% (*n* = 14) harbored a homozygous variant of the *CNGA3* with a pathogenic Class 1 (86.7%, *n* = 13) mutation. Further, 66.7% (*n* = 10) of these patients harbored the c.661C>T DNA variant, corresponding to the p.(Arg221*) in the protein. One patient (6.7%, *n* = 1) had *ATF6* gene mutation. All mutations were homozygous. The actual genotypic features of each patient, such as gene, variant (DNA), protein, zygosity, pathogenicity, and PMID (PubMed IDentifier), are shown in Table 3.

The association between ERG findings and DNA variants was evaluated. The statistical correlation between ERG findings and the type of DNA variant was limited because the majority of the samples had the c.661C>T variant. The results revealed no significant association between the cone dysfunction and cone–rod dysfunction with reference to the ERG findings ($P > 0.05$) when compared to the different variants (DNA). This suggests that DNA variants are not significant risk factors when interpreting ERG findings.

Discussion

In terms of clinical presentation, individuals with achromatopsia have high variability in the severity of their symptoms; however, generally, the affected patients present with a significant decrease in VA, photophobia, and nystagmus starting from birth, associated with color vision impairment or complete color blindness.[5,7,9] Based on the severity of cone photoreceptor dysfunction and clinical symptoms, achromatopsia can be classified into complete and incomplete forms.[25-28] Our patients had severe cone dysfunction with a VA of 20/200 or less and a total absence of color vision, which met the definition of complete achromatopsia. Most of our patients had hyperopia with astigmatism, which is

Table 3: Patient's genotype details (*n*=15)

Patient	Mother carrier status	Father carrier status	Consanguinity	Gene	Variant (DNA)	Protein	PMID	Zygocity (homo, hetero)	Pathogenicity	Reference sequence number
1	Carrier	Carrier	Positive	*CNGA3*	c.101+1G>AP c.661C>T	p.(Arg221*)	23105016_30289319	Compound heterozygous	Pathogenic class 1	NM_001298.3
2	Carrier	Carrier	Positive	*CNGA3*	C.661C>T;	p.(Arg221*)	23105016	Homozygous	Pathogenic class 1	NM_001298.3
3	Carrier	Carrier	Positive	*GNCA3*	c.661C>T	p.(Arg221*)	23105016	Homozygous	Pathogenic class 1	NM_001298.3
4	Carrier	Carrier	Negative	*CNGA3*	C.661C>T;	p.(Arg221*)	23105016	Homozygous	Pathogenic class 1	NM_001298.3
5	Carrier	Carrier	Negative	*CNGA3*	C.661C>T;	p.(Arg221*)	23105016	Homozygous	Pathogenic class 1	NM_001298.3
6	Carrier	Carrier	Negative	*CNGA3*	C.661C>T;	p.(Arg221*)	23105016	Homozygous	Pathogenic class 1	NM_001298.3
7	Carrier	Carrier	Negative	*CNGA3*	C.661C>T;	p.(Arg221*)	23105016	Homozygous	Pathogenic class 1	NM_001298.3
8	Carrier	Carrier	Negative	*CNGA3*	C.661C>T;	p.(Arg221*)	23105016	Homozygous	Pathogenic class 1	NM_001298.3
9	Carrier	Carrier	Positive	*CNGA3*	C.661C>T;	p.(Arg221*)	23105016	Homozygous	Pathogenic class 1	NM_001298.3
10	Carrier	Carrier	Positive	*CNGA3*	c.101+1G>AP c.661C>T	p.(Arg221*)	23105016_30289319	Compound heterozygous	Pathogenic class 1	NM_001298.3
11	Carrier	Carrier	Negative	*ATF6*	c.511del	p.(Ile171Phefs*3)		Homozygous	Likely pathogenic class 2	NM_007348.3
12	Carrier	Carrier	Positive	*CNGA3*	c.830G>A.	p.(Arg277His)	11536077	Homozygous	Pathogenic class 1	NM_001298.3
13	Carrier	Carrier	Positive	*CNGA3*	c.1768G>A	p.(Glu590Lys)	9662398	Homozygous	Pathogenic class 1	NM_001298.3
14	Carrier	Carrier	Positive	*CNGA3*	c.822G>T	p.(Arg274Ser)	9662398	Homozygous	VUS class 3	NM_001298.3
15	Carrier	Carrier	Positive	*CNGA3*	c.1768G>A	p.(Glu590Lys)	9662398	Homozygous	Pathogenic class 1	NM_001298.3

Y: Year, M: Month, D: Days, *CNGA3*: Cyclic nucleotide-gated channel subunit alpha 3, *ATF6*: Activating transcription factor 6, PMID: PubMed IDentifier, VUS: Variant of undetermined significant

Figure 1: Optical coherence tomography macula showing shallow foveal pit with empty space, fundus autofluorescence showing subtle foveal changes, fundus photograph showing normal retina, electroretinography showing cone dysfunction

Figure 2: Optical coherence tomography macula showing shallow foveal pit with empty space, fundus autofluorescence showing early bull's eye maculopathy, fundus photograph showing normal retina, electroretinography showing sever cone dysfunction

Figure 3: Optical coherence tomography macula showing shallow foveal pit with inner segments/outer segments zone disruption, fundus autofluorescence showing subtle foveal changes, fundus photograph showing normal retina, electroretinography showing sever cone dysfunction

the most common type of refractive error reported in the literature.[7,29] The anterior segment examination of the eye is almost always unremarkable in patients with achromatopsia. In addition, the fundus examination is usually normal; however, sometimes, it may show macular changes such as bull's eye maculopathy, vessel narrowing, and attenuations, especially in older individuals with achromatopsia. Anterior segment and fundus examinations were both unremarkable in our patients.[7]

Most had no systemic associations, consistent with previous reviews.[5,7] The age of onset for achromatopsia can be as early as the 1st year of life or as late as the sixth decade.[5] Our patients had a mean age of onset of 1–2 years. OCT of the macula was normal in few patients, whereas others showed changes such as a shallow foveal pit, optically empty space, IS/OS zone disruption, and retinal thinning which are described in the literature as common findings in achromatopsia patients.[30] FAF patterns correlated with the OCT findings. FAF imaging reflects the distribution of lipofuscin in the retina and is an important sign of photoreceptor integrity. FAF in patients with achromatopsia can be normal, hyperautofluorescent, or hypoautofluorescent, depending on the extent of photoreceptor damage.[31-33] In our study, it was normal in almost all patients.

The ERG is an important diagnostic tool for achromatopia. Cone-mediated responses are markedly affected by normal or partial effects of rod photoreceptors. Although it is mainly a cone photoreceptor disease, dysfunction in rod photoreceptors has also been reported, which can be explained by decreased rod number, shorter rod OS, and changes in rod circuitry.[13,34-37] In our patients, we found that most had cone dysfunction with normal rods, whereas a minority showed cone–rod dysfunction.

In this study, we describe a novel variant of *ATF6* c. 511del (p. lle171Phefs*3). This 1 bp deletion creates a frameshift mutation and is listed in ClinVar as likely pathogenic. We also found the homozygous nonsense variant c.661C>T (p. Arg221*) in exon 7 of the *CNGA3* gene in five unrelated families, but in the same tribe, which echoes the study conducted by Abdelkader *et al*. at King Khaled Eye Specialist Hospital.[12] This can be explained by a founder effect in Saudi Arabia. Another reported pathogenic *CNGA3* variant, c.1768G>A, was found in two unrelated patients from the same tribe. The other variants are listed. We did not find a phenotype–genotype correlation between the gene and variants.

Achromatopsia is an autosomal recessive disease, and this mode of inheritance is related to the presence of carrier parents; therefore, consanguinity is a major risk factor for the disease.[38,39] All our patients were from consanguineous marriages. Finally, consanguinity is considered a major risk factor for the development of achromatopsia in our population. Screening for any systemic manifestations of syndromic retinal dystrophies in the presence of any suspicious physical findings and counseling regarding future pregnancies and other family members' marriages are advised.[1,5,7,40]

Conclusion

Our assessment revealed that among the patients, the most common gene associated with achromatopsia was found to be the *CNGA*3 gene with the c.661C>T DNA variant. Consanguinity is a major risk factor for this disease. Therefore, as a preventive approach, we highly recommend raising awareness among families and providing genetic counseling for this highly disabling disease. With a streamlined process, it is strongly advised to conduct genetic testing before marriage, especially in patients who intend to be involved in the same tribe marriages with consanguinity and a strong family history. Through our research, we found that genetic services and counseling in Saudi Arabia are limited. Hence, additional institutions and centers offering these facilities are required. We believe that the precision of our findings will improve with sufficient collection of research data from patients in the future. Our research observed a trending demand for support for all aspects of this disease, including social, educational, psychological, and low-vision aid services. We strongly encourage health institutions to provide aid services to enhance patients' quality of life.

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Conflicts of interest

There are no conflicts of interest.

References

1. Werdich XQ, Place EM, Pierce EA. Systemic diseases associated with retinal dystrophies. Semin Ophthalmol 2014;29:319-28.
2. Patel N, Aldahmesh MA, Alkuraya H, Anazi S, Alsharif H, Khan AO, *et al.* Expanding the clinical, allelic, and locus heterogeneity of retinal dystrophies. Genet Med 2016;18:554-62.
3. Nentwich MM, Rudolph G. Hereditary retinal eye diseases in childhood and youth affecting the central retina. Oman J Ophthalmol 2013;6:S18-25.
4. Hohman TC. Hereditary retinal dystrophy. Handb Exp Pharmacol 2017;242:337-67.
5. Remmer MH, Rastogi N, Ranka MP, Ceisler EJ. Achromatopsia: A review. Curr Opin Ophthalmol 2015;26:333-40.
6. Johnson S, Michaelides M, Aligianis IA, Ainsworth JR, Mollon JD, Maher ER, *et al.* Achromatopsia caused by novel mutations in both *CNGA3* and CNGB3. J Med Genet 2004;41:e20.
7. Kohl S, Jägle H, Wissinger B, Zobor D. Achromatopsia. In: Adam MP, Everman DB, Mirzaa GM, Pagon RA, Wallace SE, Bean LJ, *et al.*, editors. GeneReviews. Seattle (WA): University of Washington, Seattle; 2004.
8. Poloschek CM, Kohl S. Achromatopsia. Ophthalmologe 2010;107:571-80.
9. Tsang SH, Sharma T. Rod monochromatism (achromatopsia). Adv Exp Med Biol 2018;1085:119-23.
10. Rüther K, Sharpe LT, Zrenner E. Dual rod pathways in complete achromatopsia. Ger J Ophthalmol 1994;3:433-9.
11. Hirji N, Aboshiha J, Georgiou M, Bainbridge J, Michaelides M. Achromatopsia: Clinical features, molecular genetics, animal models and therapeutic options. Ophthalmic Genet 2018;39:149-57.
12. Abdelkader E, Brandau O, Bergmann C, AlSalamah N, Nowilaty S, Schatz P. Novel causative variants in patients with achromatopsia. Ophthalmic Genet 2018;39:678-83.
13. Zelinger L, Cideciyan AV, Kohl S, Schwartz SB, Rosenmann A, Eli D, *et al.* Genetics and disease expression in the *CNGA3* form of achromatopsia: Steps on the path to gene therapy. Ophthalmology 2015;122:997-1007.
14. Ansar M, Santos-Cortez RL, Saqib MA, Zulfiqar F, Lee K, Ashraf NM, *et al.* Mutation of ATF6 causes autosomal recessive achromatopsia. Hum Genet 2015;134:941-50.
15. Kohl S, Baumann B, Broghammer M, Jägle H, Sieving P, Kellner U, *et al.* Mutations in the CNGB3 gene encoding the beta-subunit of the cone photoreceptor cGMP-gated channel are responsible for achromatopsia (ACHM3) linked to chromosome 8q21. Hum Mol Genet 2000;9:2107-16.
16. Kohl S, Zobor D, Chiang WC, Weisschuh N, Staller J, Gonzalez Menendez I, *et al.* Mutations in the unfolded protein response

regulator ATF6 cause the cone dysfunction disorder achromatopsia. Nat Genet 2015;47:757-65.
17. Ziccardi L, Cordeddu V, Gaddini L, Matteucci A, Parravano M, Malchiodi-Albedi F, *et al*. Gene therapy in retinal dystrophies. Int J Mol Sci 2019;20:5722.
18. Broadgate S, Yu J, Downes SM, Halford S. Unravelling the genetics of inherited retinal dystrophies: Past, present and future. Prog Retin Eye Res 2017;59:53-96.
19. Michalakis S, Gerhardt M, Rudolph G, Priglinger S, Priglinger C. Achromatopsia: Genetics and gene therapy. Mol Diagn Ther 2022;26:51-9.
20. Pang JJ, Alexander J, Lei B, Deng W, Zhang K, Li Q, *et al.* Achromatopsia as a potential candidate for gene therapy. Adv Exp Med Biol 2010;664:639-46.
21. Fischer MD, Michalakis S, Wilhelm B, Zobor D, Muehlfriedel R, Kohl S, *et al.* Safety and vision outcomes of subretinal gene therapy targeting cone photoreceptors in achromatopsia: A nonrandomized controlled trial. JAMA Ophthalmol 2020;138:643-51.
22. McKyton A, Averbukh E, Marks Ohana D, Levin N, Banin E. Cortical visual mapping following ocular gene augmentation therapy for achromatopsia. J Neurosci 2021;41:7363-71.
23. Banin E, Gootwine E, Obolensky A, Ezra-Elia R, Ejzenberg A, Zelinger L, *et al.* Gene augmentation therapy restores retinal function and visual behavior in a sheep model of *CNGA3* achromatopsia. Mol Ther 2015;23:1423-33.
24. Dai X, He Y, Zhang H, Zhang Y, Liu Y, Wang M, *et al*. Long-term retinal cone rescue using a capsid mutant AAV8 vector in a mouse model of *CNGA3*-achromatopsia. PLoS One 2017;12:e0188032.
25. Sundaram V, Wilde C, Aboshiha J, Cowing J, Han C, Langlo CS, *et al.* Retinal structure and function in achromatopsia: Implications for gene therapy. Ophthalmology 2014;121:234-45.
26. Aboshiha J, Dubis AM, Carroll J, Hardcastle AJ, Michaelides M. The cone dysfunction syndromes. Br J Ophthalmol 2016;100:115-21.
27. Brunetti-Pierri R, Karali M, Melillo P, Di Iorio V, De Benedictis A, Iaccarino G, *et al*. Clinical and molecular characterization of achromatopsia patients: A longitudinal study. Int J Mol Sci 2021;22:1681.
28. Pokorny J, Smith VC, Pinckers AJ, Cozijnsen M. Classification of complete and incomplete autosomal recessive achromatopsia. Graefes Arch Clin Exp Ophthalmol 1982;219:121-30.
29. Andersen MK, Kessel L. Ametropia and emmetropization in CNGB3 achromatopsia. Invest Ophthalmol Vis Sci 2021;62:10.
30. Thiadens AA, Slingerland NW, Roosing S, van Schooneveld MJ, van Lith-Verhoeven JJ, van Moll-Ramirez N, *et al.* Genetic etiology and clinical consequences of complete and incomplete achromatopsia. Ophthalmology 2009;116:1984-9.e1.
31. Fahim AT, Khan NW, Zahid S, Schachar IH, Branham K, Kohl S, *et al.* Diagnostic fundus autofluorescence patterns in achromatopsia. Am J Ophthalmol 2013;156:1211-9.e2.
32. Greenberg JP, Sherman J, Zweifel SA, Chen RW, Duncker T, Kohl S, *et al.* Spectral-domain optical coherence tomography staging and autofluorescence imaging in achromatopsia. JAMA Ophthalmol 2014;132:437-45.
33. Schmitz-Valckenberg S, Holz FG, Bird AC, Spaide RF. Fundus autofluorescence imaging: Review and perspectives. Retina 2008;28:385-409.
34. Aboshiha J, Luong V, Cowing J, Dubis AM, Bainbridge JW, Ali RR, *et al.* Dark-adaptation functions in molecularly confirmed achromatopsia and the implications for assessment in retinal therapy trials. Invest Ophthalmol Vis Sci 2014;55:6340-9.
35. Khan NW, Wissinger B, Kohl S, Sieving PA. CNGB3 achromatopsia with progressive loss of residual cone function and impaired rod-mediated function. Invest Ophthalmol Vis Sci 2007;48:3864-71.
36. Moskowitz A, Hansen RM, Akula JD, Eklund SE, Fulton AB. Rod and rod-driven function in achromatopsia and blue cone monochromatism. Invest Ophthalmol Vis Sci 2009;50:950-8.
37. Schallhorn CS, Granet DB, Ferreyra HA. Electronegative electroretinogram in achromatopsia. Retin Cases Brief Rep 2018;12:143-8.
38. Pedurupillay CR, Landsend EC, Vigeland MD, Ansar M, Frengen E, Misceo D, *et al.* Segregation of incomplete achromatopsia and alopecia due to PDE6H and LPAR6 variants in a consanguineous family from Pakistan. Genes (Basel) 2016;7:41.
39. Rojas CV, María LS, Santos JL, Cortés F, Alliende MA. A frameshift insertion in the cone cyclic nucleotide gated cation channel causes complete achromatopsia in a consanguineous family from a rural isolate. Eur J Hum Genet 2002;10:638-42.
40. Alkuraya FS. Saudi genetic ophthalmology research: The local and global impact. Saudi J Ophthalmol 2010;24:109-10.