Achromatopsia: On the Doorstep of a Possible Therapy

Ditta Zobor^a Gergely Zobor^a Susanne Kohl^b

^aInstitute for Ophthalmic Research, and ^bMolecular Genetics Laboratory, Institute for Ophthalmic Research, University of Tübingen, Tübingen, Germany

Key Words

Achromatopsia · Genetic background · Clinical manifestation · Treatment · Gene replacement therapy

Abstract

Achromatopsia (ACHM) is a rare autosomal recessive inherited retinal disorder with an incidence of approximately 1 in 30,000. It presents at birth or early infancy and is typically characterized by reduced visual acuity, nystagmus, photophobia, and very poor or absent color vision. The symptoms arise from isolated cone dysfunction, which can be caused by mutations in the crucial components of the cone phototransduction cascade. Although ACHM is considered a functionally nonprogressive disease affecting only the cone system, recent studies have described progressive age-dependent changes in retinal architecture. Currently, no specific therapy is available for ACHM; however, gene replacement therapy performed on animal models for three ACHM genes has shown promising results. Accurate genetic and clinical diagnosis of patients may therefore enhance and enable therapeutic intervention in the near future. This short review summarizes the genetic background, pathophysiology, clinical findings, diagnostics, and therapeutic perspectives in ACHM.

© 2015 S. Karger AG, Basel

Introduction

Achromatopsia (ACHM, synonym: rod monochromatism) is a rare autosomal recessive inherited retinal disorder with an incidence of approximately 1 in 30,000 [1, 2]. The disease presents at birth or early infancy with nystagmus and photophobia, and further ophthalmological examinations typically reveal reduced visual acuity and very poor or absent color vision. The clinical diagnosis of ACHM is based on symptoms supported by morphological and functional – especially electrophysiological – findings [1, 2]. They arise from dysfunction of all three types of cones (S, M, and L), and are caused by mutations in the *CNGA3*, *CNGB3*, *GNAT2*, *PDE6C*, and *PDE6H* genes, all of which encode crucial components of the cone phototransduction cascade [1–11]. Most recently, mutations in the activating transcription factor 6 (ATF6), a key regulator of the unfolded protein response (UPR), have also been associated with ACHM [28]. Although ACHM is considered a functionally stationary disease affecting only the cone system, recent studies have described age-dependent progressive changes in retinal architecture, including photoreceptor cell loss as well as macular changes [12–14].

Currently, no specific therapy is available for ACHM. Dark or special filter glasses or red-tinted contact lenses

can be helpful in reducing photophobia and potentially improving visual acuity. Further, low-vision aids, such as high-powered magnifying glasses, can be useful for patients [1, 2]. Most recently, gene replacement therapy performed on animal models for three ACHM genes (*CNGA3*, *CNGB3*, and *GNAT2*) have shown promising results [15–19]. Accurate genetic and clinical diagnosis of patients will therefore enhance and enable therapeutic intervention in the near future [1, 3, 4, 12, 13].

This short review summarizes the genetic background, pathophysiology, clinical findings, diagnostics, and therapeutic perspectives in ACHM.

Genetic Background and Pathophysiology

The human retina has approximately 6 million cone photoreceptors and 120 million rod photoreceptors. Cones are primarily responsible for central, fine-resolution, and color vision under photopic conditions (i.e. photopic vision). They are primarily concentrated in the central macula, comprising nearly 100% of the photoreceptors residing in the fovea, the region responsible for the highest resolution and maximal visual acuity. In contrast, rods are responsible for peripheral, low-light, and night vision (i.e. scotopic vision) and are primarily found in the peripheral retina and perimacular region.

Six genes have been implicated, accounting for ~75–80% of cases of ACHM so far. *CNGA3* and *CNGB3* encode the channel-forming α - and the modulatory β -subunits of the cyclic nucleotide-gated (CNG) cation channel of the cone photoreceptor [5, 6, 20], *GNAT2* encode the catalytic α -subunit of the G-protein transducin [11, 21], and *PDE6C* and *PDE6H* encode the catalytic α - and the inhibitory γ -subunits, respectively, of the cone photoreceptor-specific phosphodiesterase [10, 11, 22]. These polypeptides are fundamental components of the cone phototransduction cascade (opsin-transducin-phosphodiesterase-CNG channel) in the outer segment of the cone photoreceptor.

CNGA3 and *CNGB3* are the most important ACHM genes in patients of Northern European descent, as they account for 40–50 and 25% of cases, respectively [7, 23]. Of all mutations, a 1-bp deletion, i.e. c.1148delC, in *CNGB3* is by far the most frequent, accounting for ~75% of all *CNGB3*-mutant alleles. It is most likely due to a founder effect [24]. Mutations in *GNAT2* and *PDE6C* are rare (~1–2%), and a single homozygous nonsense mutation is to date the only genetic defect observed in *PDE6H* [11]. Very recently, *ATF6* was identified as a new ACHM

gene, suggesting a crucial and unexpected role of *ATF6A* in human foveal development and cone function. This was surprising as *ATF6* encodes the ubiquitously expressed ATF6, a key regulator of the UPR, and cellular endoplasmic reticulum (ER) homeostasis. This adds to the list of genes that, despite a ubiquitous expression, when mutated can result in an isolated retinal photoreceptor phenotype [28].

Most mutations in the ACHM genes result in complete function loss of the respective polypeptide. In few cases, a partial function loss has been reported, resulting in milder forms like incomplete ACHM, oligocone trichromacy, and cone dystrophy [25–27].

Clinical Manifestation and Diagnostics

The clinical diagnosis of ACHM is based on the medical history and psychophysical (visual acuity, visual field, and color vision), electrophysiological, and morphological examinations. Since these individuals see the world only with their rods, the clinical findings arise consequentially from missing cone and intact rod functions [1, 2, 25].

Congenital ACHM is usually recognized at birth or in the first months due to striking pendular nystagmus and an increased sensitivity to light (photophobia). On functional examinations, reduced visual acuity, a small central scotoma, eccentric fixation, and reduced or complete loss of color discrimination can be detected. Most individuals have complete ACHM with a total lack of cone function. Rarely, individuals have incomplete ACHM in which one or more cone types may be partially functioning [1, 2, 25]. The clinical findings in incomplete ACHM are similar to those in the complete form, but milder. Hyperopia is common, but not obligatory. The best visual acuity varies with the severity of the disease; it is 20/200 or less in complete ACHM and may be as high as 20/80 in incomplete cases. Visual acuity is usually stable over time; both nystagmus and photophobia may improve slightly. Electroretinographic examinations typically show absent or markedly reduced cone responses, while rod responses are reported to remain normal or nearly normal [1, 2, 25]. However, deficits in rod and rod-mediated function have also been demonstrated by Moskowitz et al. [26].

Although the fundus is usually normal, macular changes and vessel narrowing may be present. Several clinical studies in recent years have investigated outer retinal architecture and foveal morphology in detail using high-resolution optical coherence tomography (OCT) and adaptive optics [12–14, 27, 29–34]. The macular ap-

pearance in OCT can show either normal lamination or variable degrees of disruption of the photoreceptor layers and loss of retinal pigment epithelium. Sundaram et al. [12] categorized ACHM patients into the following five groups based on outer retinal OCT findings: (1) continuous inner segment ellipsoid (Ise), (2) Ise disruption, (3) absent Ise, (4) foveal hyporeflective zone, and (5) outer retinal atrophy.

Some Inconsistencies regarding the Progressive Nature of Morphological Changes

Thiadens et al. [14] concluded that ACHM is not a stationary disease but is rather a disorder that shows a progressive loss of cone photoreceptors. Thomas et al. [13] also showed progressive longitudinal changes in retinal morphology in children and described an interesting OCT sign, i.e. a hyperreflective zone which appears to be the precursor of the hyporeflective zone seen in later ages. On the contrary, Genead et al. [29] provided evidence that cone loss is not age dependent. To draw valid conclusions about the continuous presence of cones in ACHM, further studies with a substantial number of patients from different age groups, but with a homogenetic background, are needed. Typical findings of retinal morphology are shown in figure 1.

The technology of adaptive optics enables direct visualization of rod and cone photoreceptors in the human retina in vivo. In recent years, several studies have investigated photoreceptor morphology in ACHM [29–34]. Carroll et al. [32] observed a severely disrupted cone mosaic in the fovea and parafoveal area of a single patient with mutations in *CNGB3*. Genead et al. [29] reported residual cone structures in all 9 patients carrying mutations in either *CNGA3* or *CNGB3*, though the majority of cones had a reduced reflectance. While methods for quantifying cones are well established, further tools and studies including larger patient groups are still needed in order to assess residual photoreceptor integrity.

The newly introduced *ATF6*-related ACHM phenotype was found to show severe foveal hypoplasia with a poorly formed or absent foveal pit. This may be a hallmark of the *ATF6*-related disease which distinguishes it from other forms of ACHM, where the pathogenesis relates to abnormalities of the cone phototransduction pathway [28].

Although the retinal structure seems to show great variability and a slow progressive cone loss has been suggested [12–14, 33, 35–39], no clear association between

Fig. 1. Characteristic findings on funduscopy (a), fundus autofluorescence (b), and OCT (c) imaging of an ACHM patient.

retinal structure and function could be described [12]. Therefore, ACHM can be best described as a functionally stationary disorder with slow degeneration of cone photoreceptors.

The clinical diagnosis is easily determined based on characteristic features and typical functional and morphological findings; however, some retinopathies may be confused with ACHM. These differential diagnoses include blue-cone monochromatism, *KCNV2* retinopathy, oligocone trichromacy, hereditary green-red color vision defects, and cone dystrophies [2, 35, 36].

In order to make an early and confident diagnosis, knowledge of detailed genotype-phenotype correlations is crucial. This information may become important when identifying suitable candidates and the optimal timing for therapy and when assessing the effect of intervention in the future.

Therapeutic Perspectives

To date, no established therapy is available; therefore, social and professional consequences are essential tasks to deal with. The current standard of care consists of managing symptoms by limiting retinal light exposure

with tinted contact lenses and/or very darkly tinted sunglasses. Tinted contact lenses and cutoff filters typically transmit light at wavelengths between 400 and 480 nm, thereby reducing photophobia. Furthermore, magnifying aids and contact lenses with magnification are recommended to improve visual acuity. However, even with the best external aid techniques in place, daily tasks such as driving and going to school present significant obstacles [1, 2].

Enormous efforts have been made in research in recent years to develop a possible cure for ACHM, and the new gene replacement therapeutic approaches are promising. ACHM has long been considered an ideal target for gene therapy based on the observation that – in contrast to other progressive retinal dystrophies – functioning photoreceptors are expected to be largely preserved [27–34]. A further advantage is that small- (mouse) and large- (dog and sheep) animal models exist for all three major genetic forms (*CNGA3*, *CNGB3*, and *GNAT2*) of the disease in which this hypothesis could be tested [15–19]. In recent years, multiple successful applications of gene replacement therapy using adeno-associated viral vectors in these animal models have been published [15–19]. These preclinical studies showed that such a therapy could restore cone-specific visual processing in the central nervous system even if cone photoreceptors had been nonfunctional from birth. Treated *Cnga3*^{−/−} mice were able to generate cone photoreceptor responses and transfer these signals to bipolar cells [16]. Furthermore, ganglion cells from treated, but not from untreated, *Cnga3*^{−/−} mice displayed cone-driven, light-evoked, spiking activity, indicating that signals generated in the outer retina are transmitted to the brain. This newly acquired sensory information was translated into cone-mediated, vision-guided behavior. The therapeutic effect was stable for at least 8 months after the treatment [16]. Another study in a naturally occurring mouse model of ACHM with a *CNGA3* mutation, i.e. the *cpfl5* mouse, confirmed these results, showing restored cone-mediated function and arrested cone degeneration; the observed therapeutic effect lasted for at least 5 months after the injection [19].

AAV-mediated gene replacement has also been employed in animal models of *CNGB3*-related ACHM. Carvalho et al. [18] successfully tested the efficacy of gene therapy in *Cngb3*^{−/−} mice using an AAV8 vector containing a human cone arrestin promoter driving the expression of human *CNGB3*. The therapy resulted in long-term improvement of retinal function in *Cngb3*^{−/−} mice, which was shown by restoration of cone electroretinographic

amplitudes of up to 90% of the wild-type level and a significant improvement in visual acuity. Although successful restoration of cone function was also observed when the treatment was initiated at 6 months of age, restoration of normal visual acuity was only possible in 2- to 4-week-old animals [18].

Komaromy et al. [15] showed restoration of cone function and day vision in two canine models of *CNGB3*-related ACHM. However, an age-dependent reduction in the cone therapy success rate was also observed. In a subsequent study, combination of the gene therapeutic approach with administration of ciliary neurotrophic factor (CNTF) could solve this problem and led to a successful gene therapy in all dogs aged 14–42 months [39]. This success initiated a human study including five *CNGB3* achromats, where intraocular microcapsules releasing CNTF were implanted into 1 eye in each of the participants. After 1 year of follow-up, CNTF did not measurably enhance cone function, which reveals a species difference between human and canine *CNGB3*-ACHM-mutant cones in response to CNTF [40].

In conclusion, the positive effects observed in preclinical studies on animal models of ACHM hold promise for future therapeutic approaches in human patients. Gene replacement trials for both *CNGA3* and *CNGB3* are in preparation. The observations of the human phenotype showing only a very slow progression in cone degeneration and no specific correlation between functional and morphological findings suggest a wider therapeutic window than presumed earlier. However, there is still a need to elucidate the relationship between cone structure and function, and to study the ability of the visual system to respond to the novel input in order to establish the most appropriate protocols to identify suitable patients and follow the therapeutic effect.

Acknowledgement

This work was supported by the Tistou and Charlotte Kerstan Foundation (RD-CURE Project).

Disclosure Statement

The authors have no commercial interests related to the subject of this paper or the entities discussed in this paper.

References

- Kohl S, Hamel C: Clinical utility gene card for: achromatopsia – update 2013. *Eur J Hum Genet* 2013, DOI: 10.1038/ejhg.2013.44.
- Kohl S, Jägle H, Wissinger B: Achromatopsia; in Pagon RA, Adam MP, Ardinger HH, Bird TD, Dolan CR, Fong CT, Smith RJH, Stephens K (eds): *GeneReviews*[®]. <http://www.ncbi.nlm.nih.gov/books/NBK1418/>. Seattle, University of Washington, 1993–2014.
- Thiadens AA, Slingerland NW, Roosing S, van Schooneveld MJ, van Lith-Verhoeven JJ, van Moll-Ramirez N, van den Born LI, Hoyng CB, Cremers FP, Klaver CC: Genetic etiology and clinical consequences of complete and incomplete achromatopsia. *Ophthalmology* 2009;116:1984–1989.e1.
- Thiadens AA, Roosing S, Collin RW, van Moll-Ramirez N, van Lith-Verhoeven JJ, van Schooneveld MJ, den Hollander AI, van den Born LI, Hoyng CB, Cremers FP, Klaver CC: Comprehensive analysis of the achromatopsia genes CNGA3 and CNGB3 in progressive cone dystrophy. *Ophthalmology* 2010;117:825–830.e1.
- Kohl S, Marx T, Giddings I, Jagle H, Jacobson SG, Apfelstedt-Sylla E, Zrenner E, Sharpe LT, Wissinger B: Total colour-blindness is caused by mutations in the gene encoding the alpha-subunit of the cone photoreceptor cGMP-gated cation channel. *Nat Genet* 1998;19:257–259.
- Kohl S, Baumann B, Broghammer M, Jagle H, Sieving P, Kellner U, Spiegel R, Anastasi M, Zrenner E, Sharpe LT, Wissinger B: 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;9:2107–2116.
- Kohl S, Varsanyi B, Antunes GA, Baumann B, Hoyng CB, Jagle H, Rosenberg T, Kellner U, Lorenz B, Salati R, Jurkles B, Farkas A, Andreasson S, Weleber RG, Jacobson SG, Rudolph G, Castellan C, Dollfus H, Legius E, Anastasi M, Bitoun P, Lev D, Sieving PA, Munier FL, Zrenner E, Sharpe LT, Cremers FP, Wissinger B: CNGB3 mutations account for 50% of all cases with autosomal recessive achromatopsia. *Eur J Hum Genet* 2005;13:302–308.
- Kohl S, Baumann B, Rosenberg T, Kellner U, Lorenz B, Vadalà M, Jacobson SG, Wissinger B: Mutations in the cone photoreceptor G-protein alpha-subunit gene GNAT2 in patients with achromatopsia. *Am J Hum Genet* 2002;71:422–425.
- Grau T, Artemyev NO, Rosenberg T, Dollfus H, Haugen OH, Cumhur Sener E, Jurkles B, Andreasson S, Kernstock C, Larsen M, Zrenner E, Wissinger B, Kohl S: Decreased catalytic activity and altered activation properties of PDE6C mutants associated with autosomal recessive achromatopsia. *Hum Mol Genet* 2011;20:719–730.
- Thiadens AA, den Hollander AI, Roosing S, Nabuurs SB, Zekveld-Vroon RC, Collin RW, De Baere E, Koenekoop RK, van Schooneveld MJ, Strom TM, van Lith-Verhoeven JJ, Lotery AJ, van Moll-Ramirez N, Leroy BP, van den Born LI, Hoyng CB, Cremers FP, Klaver CC: Homozygosity mapping reveals PDE6C mutations in patients with early-onset cone photoreceptor disorders. *Am J Hum Genet* 2009;85:240–247.
- Kohl S, Coppieters F, Meire F, Schaich S, Roosing S, Brennenstuhl C, Bolz S, van Genderen MM, Riemsdijk FC, European Retinal Disease Consortium, Lukowski R, den Hollander AI, Cremers FP, De Baere E, Hoyng CB, Wissinger B: A nonsense mutation in PDE6H causes autosomal-recessive incomplete achromatopsia. *Am J Hum Genet* 2012;91:527–532.
- Sundaram V, Wilde C, Aboshiha J, Cowing J, Han C, Langlo CS, Chana R, Davidson AE, Sergouniotis PI, Bainbridge JW, Ali RR, Dubra A, Rubin G, Webster AR, Moore AT, Nardini M, Carroll J, Michaelides M: Retinal structure and function in achromatopsia: implications for gene therapy. *Ophthalmology* 2014;121:234–245.
- Thomas MG, McLean RJ, Kohl S, Sheth V, Gottlob I: Early signs of longitudinal progressive cone photoreceptor degeneration in achromatopsia. *Br J Ophthalmol* 2012;96:1232–1236.
- Thiadens AA, Somervuo V, van den Born LI, Roosing S, van Schooneveld MJ, Kuijpers RW, van Moll-Ramirez N, Cremers FP, Hoyng CB, Klaver CC: Progressive loss of cones in achromatopsia: an imaging study using spectral-domain optical coherence tomography. *Invest Ophthalmol Vis Sci* 2010;51:5952–5957.
- Komaromy AM, Alexander JJ, Rowlan JS, Garcia MM, Chiodo VA, Kaya A, Tanaka JC, Acland GM, Hauswirth WW, Aguirre GD: Gene therapy rescues cone function in congenital achromatopsia. *Hum Mol Genet* 2010;19:2581–2593.
- Michalakakis S, Muhlfriedel R, Tanimoto N, Krishnamoorthy V, Koch S, Fischer MD, Becirovic E, Bai L, Huber G, Beck SC, Fahl E, Buning H, Paquet-Durand F, Zong X, Gollisch T, Biel M, Seeliger MW: Restoration of cone vision in the CNGA3^{-/-} mouse model of congenital complete lack of cone photoreceptor function. *Mol Ther* 2010;18:2057–2063.
- Pang JJ, Alexander J, Lei B, Deng W, Zhang K, Li Q, Chang B, Hauswirth WW: Achromatopsia as a potential candidate for gene therapy. *Adv Exp Med Biol* 2010;664:639–646.
- Carvalho LS, Xu J, Pearson RA, Smith AJ, Bainbridge JW, Morris LM, Fliesler SJ, Ding XQ, Ali RR: Long-term and age-dependent restoration of visual function in a mouse model of CNGB3-associated achromatopsia following gene therapy. *Hum Mol Genet* 2011;20:3161–3175.
- Pang JJ, Deng WT, Dai X, Lei B, Everhart D, Umino Y, Li J, Zhang K, Mao S, Boye SL, Liu L, Chiodo VA, Liu X, Shi W, Tao Y, Chang B, Hauswirth WW: AAV-mediated cone rescue in a naturally occurring mouse model of CNGA3-achromatopsia. *PLoS One* 2012;7:e35250.
- Sundin OH1, Yang JM, Li Y, Zhu D, Hurd JN, Mitchell TN, Silva ED, Maumenee IH: Genetic basis of total colour blindness among the Pingelapese islanders. *Nat Genet* 2000;25:289–293.
- Aligianis IA, Forsheve T, Johnson S, Michaelides M, Johnson CA, Trembath RC, Hunt DM, Moore AT, Maher ER: Mapping of a novel locus for achromatopsia (ACHM4) to 1p and identification of a germline mutation in the alpha subunit of cone transducin (GNAT2). *J Med Genet* 2002;39:656–660.
- Chang B, Grau T, Dangel S, Hurd R, Jurkles B, Sener EC, Andreasson S, Dollfus H, Baumann B, Bolz S, Artemyev N, Kohl S, Heckelively J, Wissinger B: A homologous genetic basis of the murine cpfl1 mutant and human achromatopsia linked to mutations in the PDE6C gene. *Proc Natl Acad Sci USA* 2009;106:19581–19586.
- Wissinger B, Gamer D, Jagle H, Giorda R, Marx T, Mayer S, Tippmann S, Broghammer M, Jurkles B, Rosenberg T, Jacobson SG, Sener EC, Tatlipinar S, Hoyng CB, Castellan C, Bitoun P, Andreasson S, Rudolph G, Kellner U, Lorenz B, Wolff G, Verellen-Dumoulin C, Schwartz M, Cremers FP, Apfelstedt-Sylla E, Zrenner E, Salati R, Sharpe LT, Kohl S: CNGA3 mutations in hereditary cone photoreceptor disorders. *Am J Hum Genet* 2001;69:722–737.
- Wisniewski W, Lewis RA, Lupski JR: Achromatopsia: the CNGB3 p.T383fsX mutation results from a founder effect and is responsible for the visual phenotype in the original report of uniparental disomy 14. *Hum Genet* 2007;121:433–439.
- Pokorny J, Smith VC, Pinckers AJ, Cozijnsen M: Classification of complete and incomplete autosomal recessive achromatopsia. *Graefes Arch Clin Exp Ophthalmol* 1982;219:121–130.
- 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;50:950–958.
- Thomas MG, Kumar A, Kohl S, Proudlock FA, Gottlob I: High-resolution in vivo imaging in achromatopsia. *Ophthalmology* 2011;118:882–887.

- 28 Kohl S, Zobor D, Chiang WC, Weisschuh N, Staller J, Gonzalez-Menendez I, Chang S, Beck SC, Garrido MG, Sothilingam V, Seeliger MW, Stanzial F, Benediceni F, Inzana F, Héon E, Vincent V, Beis J, Strom TS, Rudolph G, Roosing S, den Hollander AI, Cremers FPM, Lopez I, Ren H, Moore AT, Webster A, Michaelides M, Koenekoop RK, Zrenner E, Kaufman RJ, Tsang SH, Wissinger B, Lin J: Mutations in the unfolded protein response regulator *ATF6* cause the cone dysfunction disorder achromatopsia. *Nat Genet* 2015, DOI: 10.1038/ng.3319.
- 29 Genead MA, Fishman GA, Rha J, Dubis AM, Bonci DM, Dubra A, Stone EM, Neitz M, Carroll J: Photoreceptor structure and function in patients with congenital achromatopsia. *Invest Ophthalmol Vis Sci* 2011;52:7298–7308.
- 30 Greenberg JP, Sherman J, Zweifel SA, Chen RW, Duncker T, Kohl S, Baumann B, Wissinger B, Yannuzzi LA, Tsang SH: Spectral-domain optical coherence tomography staging and autofluorescence imaging in achromatopsia. *JAMA Ophthalmol* 2014;132:437–445.
- 31 Scoles D, Sulai YN, Langlo CS, Fishman GA, Curcio CA, Carroll J, Dubra A: In vivo imaging of human cone photoreceptor inner segments. *Invest Ophthalmol Vis Sci* 2014;55:4244–4251.
- 32 Carroll J, Choi SS, Williams DR: In vivo imaging of the photoreceptor mosaic of a rod monochromat. *Vision Res* 2008;48:2564–2568.
- 33 Aboshiha J, Dubis AM, Cowing J, Fahy RT, Sundaram V, Bainbridge JW, Ali RR, Dubra A, Nardini M, Webster AR, Moore AT, Rubin G, Carroll J, Michaelides M: A prospective longitudinal study of retinal structure and function in achromatopsia. *Invest Ophthalmol Vis Sci* 2014;55:5733–5743.
- 34 Dubis AM, Cooper RF, Aboshiha J, Langlo C, Sundaram V, Liu B, Collison F, Fishman GA, Moore AT, Webster AR, Dubra A, Carroll J, Michaelides M: Genotype-dependent variability in residual cone structure in achromatopsia: towards developing metrics for assessing cone health. *Invest Ophthalmol Vis Sci* 2014;55:7303–7311.
- 35 Wissinger B, Schaich S, Baumann B, Bonin M, Jägle H, Friedburg C, Varsányi B, Hoyng CB, Dollfus H, Heckenlively JR, Rosenberg T, Rudolph G, Kellner U, Salati R, Plomp A, De Baere E, Andrassi-Darida M, Sauer A, Wolf C, Zobor D, Bernd A, Leroy BP, Enyedi P, Cremers FP, Lorenz B, Zrenner E, Kohl S: Large deletions of the *KCNV2* gene are common in patients with cone dystrophy with supernormal rod response. *Hum Mutat* 2011;32:1398–1406.
- 36 Zobor D, Kohl S, Wissinger B, Zrenner E, Jägle H: Rod and cone function in patients with *KCNV2* retinopathy. *PLoS One* 2012;7:e46762.
- 37 Reicher S, Seroussi E, Gootwine E: A mutation in gene *CNGA3* is associated with day blindness in sheep. *Genomics* 2010;95:101–104.
- 38 Sidjanin DJ, Lowe JK, McElwee JL, Milne BS, Phippen TM, Sargan DR, Aguirre GD, Acland GM, Ostrander EA: Canine *CNGB3* mutations establish cone degeneration as orthologous to the human achromatopsia locus *ACHM3*. *Hum Mol Genet* 2002;11:1823–1833.
- 39 Komaromy AM, Rowlan JS, Corr AT, Reinstein SL, Boye SL, Cooper AE, Gonzalez A, Levy B, Wen R, Hauswirth WW, Beltran WA, Aguirre GD: Transient photoreceptor deconstruction by CNTF enhances rAAV-mediated cone functional rescue in late stage *CNGB3*-achromatopsia. *Mol Ther* 2013;21:1131–1141.
- 40 Zein WM, Jeffrey BG, Wiley HE, Turriff AE, Tumminia SJ, Tao W, Bush RA, Marangoni D, Wen R, Wei LL, Sieving PA: *CNGB3*-achromatopsia clinical trial With CNTF: Diminished rod pathway responses with no evidence of improvement in cone function. *Invest Ophthalmol Vis Sci* 2014;55:6301–6308.