During the relatively early stages of degeneration, porcine tissues also demonstrate early aberrant neuritic sprouting in the glycinergic and GABAergic amacrine cell populations (Fig. 9c, d), identical to that observed in rodent models [24] and human RP [26, 74]. Some of the more dramatic retinal remodeling revisions are held at bay so long as cone photoreceptors appear to be present. By the time cone photoreceptors are decreasing in number, Müller cell hypertrophy begins and forms the Müller cell seal, walling off the neural retina from the remnant RPE and choroid (Fig. 10b). During the later stages, when the cone photoreceptors have gone, the retina begins more dramatic revisions, including the formation of microneuromas and neuronal translocation through the axis of the retina (Fig. 11), duplicating findings observed in human (Fig. 7) [26, 74].

The obvious question is whether other retinal degenerative diseases also show retinal remodeling, even though the principal mechanisms of retinal degeneration are different. Does retinal remodeling happen in age-related macular degeneration (AMD) for instance? Could retinal remodeling also exist in glaucoma, even though the retina is not deafferented in a top-down fashion?

The documentation on negative plasticity or aberrant remodeling in other retinal degenerative diseases is sparse, though some labs have demonstrated bipolar cell sprouting and synaptic abnormalities in human AMD [23] and in potential animal models of AMD [13]. Additional preliminary work in our lab revealed that remodeling events in both glycinergic and GABAergic amacrine cells in human geographic atrophy (GA), as shown in Fig. 12a, b, also reveal the earliest histologically observable signs of retinal remodeling. YGE > rgb imaging (Fig. 12a) also shows aberrant sprouting in both the glycine signals as well as in GABA signals (inset). TQE > rgb signals show some early indications of Müller cell variation in metabolism (inset), but no evidence at this time point of gross morphological alterations or responses in Müller cell populations.

These cells are tertiary network cells in the retina, representing critical interneurons with a complex network topology [92] that is fundamental to visual processing. Alterations of connectivities in these populations

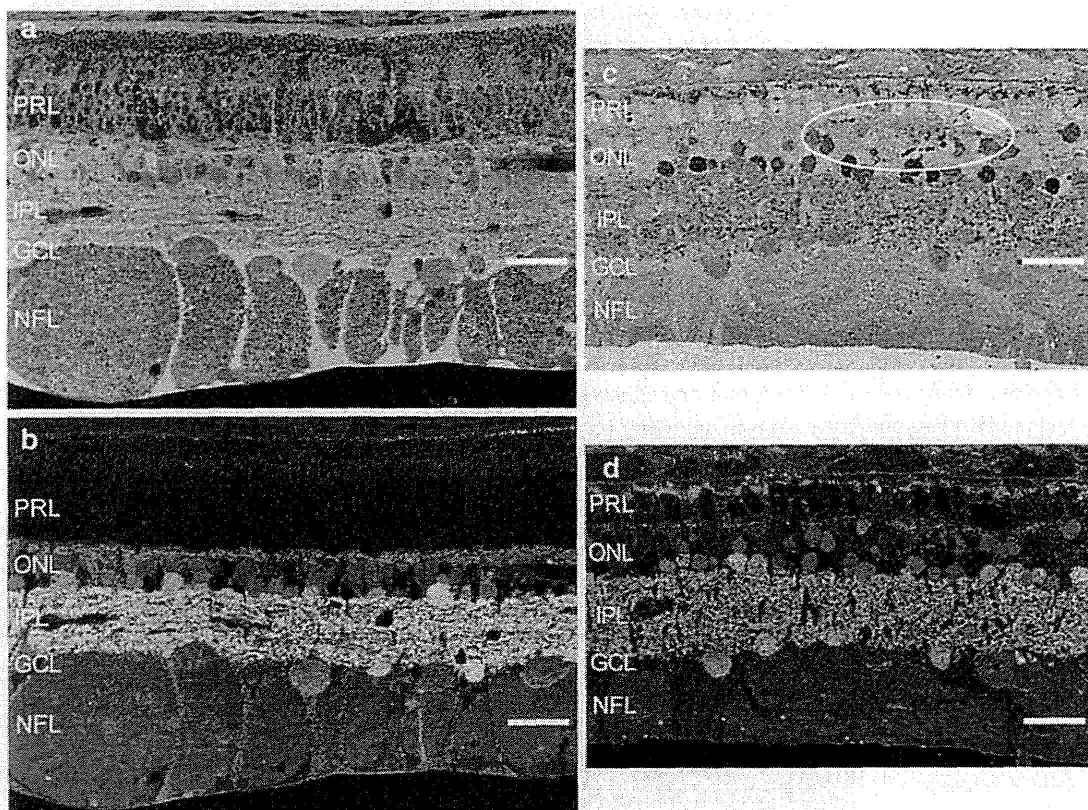


Fig. 9 Early-stage porcine P23H model of retinal degeneration. **a** Taurine, glutamine, glycine::r, g, b showing reduced photoreceptor outer segment length and early stages of Müller cell stress and alteration of molecular signatures (*green/yellow*). **b** GABA, glycine, glutamate::r, g, b of the same region showing normal-appearing OPL, IPL, and neuronal signatures. **c** Glycine immunohistochemistry demonstrating early retinal remodeling/sprouting in the glycinergic amacrine cell populations. **d** GABA, glycine, glutamate::r, g, b mapping shows dramatically truncated photoreceptor outer and inner photoreceptor segments with the glycine signal shown in **c** in the *green* channel, demonstrating remodeling events. *Scale bar* 30 μm

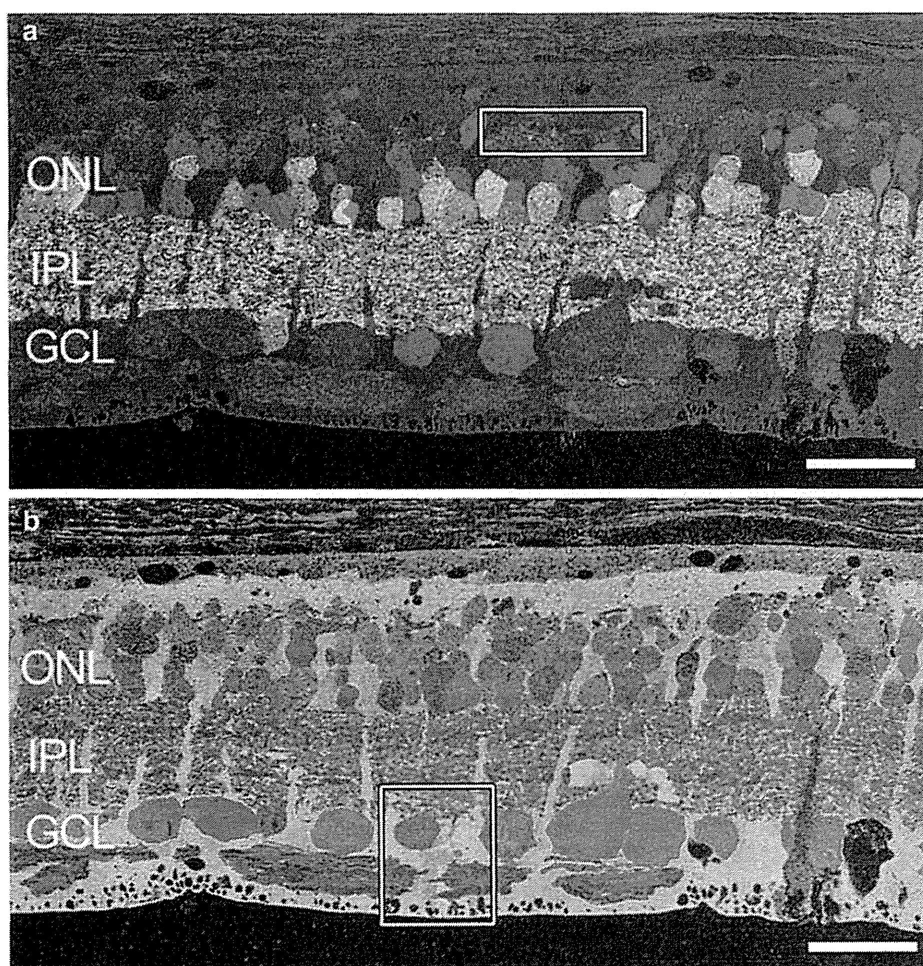


Fig. 10 **a** GABA, glycine, glutamate::r, g, b mapping of a 746-day-old GHL rabbit, showing a glial column with migration of amacrine and bipolar cells into the ganglion cell layer. Microneuroma (*rectangle*) has also formed distal to the heavily depleted inner nuclear layer. **b** Taurine, glutamine, glycine::r, g, b mapping of the same P347L rabbit tissue, revealing normal and abnormal Müller cells (*box*) in the mid-stage degenerate retina. *Scale bar* 30 μm

presumably dramatically disrupt visual processing, even in the presence of surviving afferent photoreceptors.

Retinal negative plasticity in glaucoma is also sparsely represented in the literature, though with a notable exception. Nico Cuenca demonstrated remodeling events in ON rod bipolar cells and horizontal cells in a model of glaucoma [93]. Work in our lab in collaboration with Monica Vetter and Alejandra Bosco demonstrated dramatic remodeling events of GABAergic amacrine cell processes in the DBA/2J mouse model of glaucoma (Fig. 13). Additional work with different disease models is beginning to show evidence for retinal remodeling in a number of animal models not traditionally associated with retinal disease, including spinocerebellar ataxia [94].

Mechanisms

Many mechanisms may be responsible for the various observed pathologies identified in retinal remodeling, including alterations in glutamate channel expression, changes in integrin expression/signaling, and other disparate molecular pathways that ultimately result in retinal circuit reprogramming and restructuring or topological revision of the surviving retina. In this review, we present three potential mechanisms that may be responsible for some of the sequelae identified in retinal remodeling: retinal cell reprogramming mediated by alterations in GluR expression, topological restructuring mediated by integrin expression or alterations in integrin expression, and neuritic sprouting found in remodeling retina mediated by retinoic acid receptors (RARs).

Retinal cell reprogramming (alterations in iGluR expression)

Retinal degenerative diseases result in functional reprogramming of the retina in at least three distinct ways. (1) Defined bipolar cell pathways of mGluR6- and iGluR-mediated ON and OFF responses may become corrupted. (2) Alternatively, in the absence of externally mediated drive, intrinsic drive from specific cell populations in the

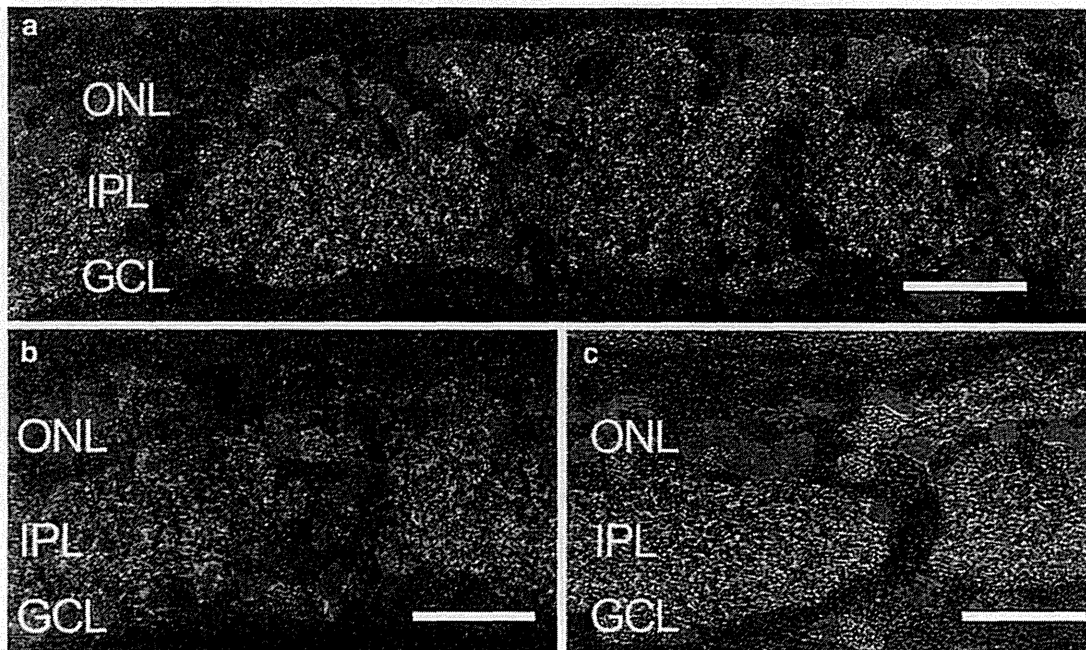


Fig. 11 a GABA, glycine, glutamate::r, g, b mapping of a 900-day-old RCS rat retina. This image shows three columns of neuronal translocation from ONL to GCL in which bipolar and amacrine cells are migrating through the retinal axis. **b** GABA, glycine, glutamate::r, g, b mapping of a 630-day-old rd1 mouse, demonstrating a column of neurons bridging the depleted inner nuclear layer with bidirectionally migrating amacrine and bipolar cells. **c** GABA, glycine, glutamate::r, g, b mapping of a 746-day-old GHL mouse, showing a glial column with migration of amacrine and bipolar cells into the ganglion cell layer. A microneuroma has also formed distal to the heavily depleted inner nuclear layer. *Scale bar* 60 μm

retina occurs, resulting in self signaling. (3) Cone-sparing forms of retinal degeneration alter iGluR expression, thus functionally changing phenotypic response profiles [26].

Retinal bipolar cell reprogramming is a universal feature in retinal degenerative diseases in humans, rodents, and rabbits [26, 74]. In retinal degenerative diseases and animal models of the same diseases that ablate both rods and cones, all evidence indicates that bipolar cell dendrites are lost [20–22], as are any responses mediated by glutamate [75]. Additionally, experiments with AGB (Fig. 8) demonstrate an absence of a cation current in these tissues [26], implying that the mGluR6-mediated signal transduction is defective through potential alteration or elimination of the receptors, or due to alterations in mGluR6 trafficking to other regions of the neuron [20–22].

Most notably, the presence of cones partially rescues the overall retinal structure, and the remaining bipolar cells underneath the surviving cones alter their response profiles so that the ratios of OFF cone to ON cone and ON rod bipolar cells shift from roughly 40:30:30 to ~80:15:05 [26, 74]. Normally, in primates, rodents, and rabbit, ON and OFF cone bipolar cells and rod bipolar cells each comprise about 33 % of all bipolar cells.

Unmasking of autoexcitatory retinal signaling also occurs in retinas bereft of photoreceptor input [26], perhaps through variations in intrinsic calcium levels that result in alterations of amacrine cell potentials [95]. These variations in responsivity or excitation may be due to oscillating inhibitory feedback from remaining glycinergic or GABAergic inputs. An alternative mechanism could arise from an existing excitatory cell type in the retina that is spontaneously active and has extensive input to both ON and OFF pathways. The dopaminergic amacrine cell has considerable input into AII amacrine cell pathways [96, 97], demonstrates spontaneous spike activity in the absence of synaptic input [98], and exhibits glutamatergic signatures. Additionally, dopaminergic amacrine cells are strongly activated by release from inhibition, and perhaps function by increasing tonic excitatory drive via synaptic glutamate release [99].

Light-induced retinal degeneration (LIRD) represents an effective tool for coherent photoreceptor loss that results in retinal remodeling and reprogramming [13]. Though the overall anatomy of the neural retina, and especially the inner nuclear layer, inner plexiform layer, and ganglion cell layer seem normal early in LIRD, key synaptic markers in the inner retina demonstrate rapid inner retina responses to photoreceptor stress that lead to fundamental reprogramming of neuronal responses and may represent an attempt to prevent excitotoxic damage and/or cell death.

In LIRD, GluR2 subunits of AMPA receptors predominantly associated with inner retinal processing display

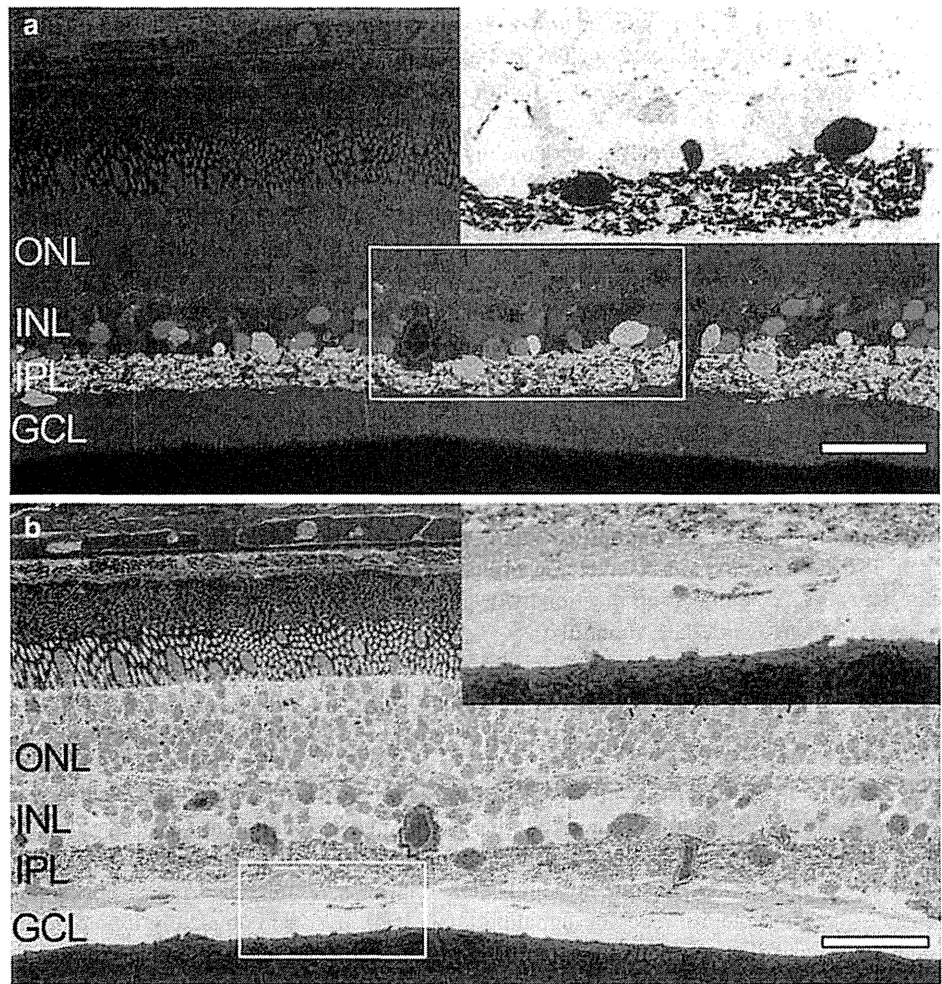


Fig. 12 **a** GABA, glycine, glutamate::r, g, b mapping in human geographic atrophy/AMD tissue demonstrates processes arising from both glycinergic and GABAergic amacrine cells (GABAergic processes extending into the outer plexiform layer in *inset*). These processes are the beginnings of microneuroma formation. **b** Taurine, glutamine, glutamate::r, g, b mapping demonstrates alterations in Müller cell signatures, notably an increase in the amount of taurine in subsets of Müller cells indicative of Müller cell stress (*inset*). *Scale bar* 90 μm

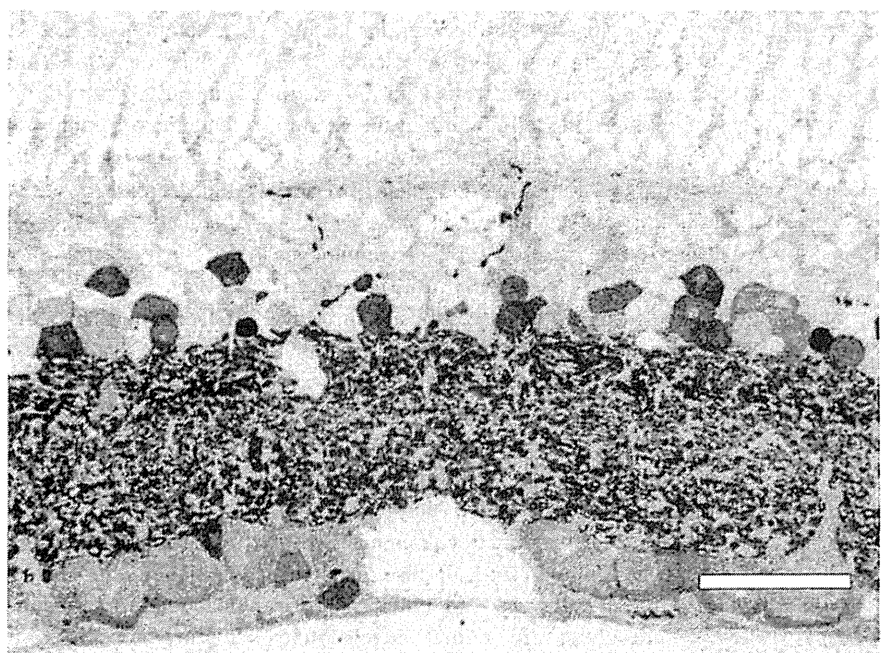


Fig. 13 Retina from a 23-month-old male DBA/2J mouse labeled for GABA, demonstrating aberrant GABAergic amacrine cell remodeling with new neurites projecting upwards into the outer plexiform layer. *Scale bar* 30 μm

rapid and significant alterations in protein levels and may reflect the same pathways used in CNS for neuroprotection [100]. Examination of GluR expression in LIRD demonstrates alterations in GluR expression over 60 days post light damage. Specifically, low-conductance AMPA receptor GluR2 subunits increase by 65 % (measured by protein level), high-conductance KA receptor GluR5 subunits decrease by 50 %, while AMPA receptor GluR1 subunits show no significant change in expression (Lin et al., submitted). A 65 % increase in GluR2 subunit availability is sufficient to stochastically add one subunit to every AMPA receptor that does not already express one, potentially performing three protective actions: (1) decreasing the Ca^{2+} permeability of the entire channel unitary conductance by 10×, (2) decreasing the conductance of the entire channel by over 50 %, and (3) preventing GluR1 phosphorylation-dependent increases in channel conductance. Combined, these effects potentially play a powerful role in neuroprotection by decreasing Ca^{2+} loads in neurons (Lin et al., submitted).

Topological restructuring via alterations in integrin expression

Other potential mechanisms involved in the observed topological restructuring of degenerate retina lie in alterations of integrin-mediated signaling. It is thought that virtually all adult tissue remodeling and cell migration involves integrin–integrin receptor signaling [101, 102]. It could be argued that the activation or reconfiguration of integrins might change cell–cell recognition or contact programming without substantial alterations in gene expression. If this is the case, clinical interventions that are designed to modulate integrin arginyl-glycyl-aspartic acid (RGD) motif binding in the remnant retina may work to modify or attenuate retinal remodeling without the need to resort to gene therapies. These studies in vivo are complicated by the slow progression in many models of retinal degeneration, particularly those that mimic human retinal degenerative diseases more precisely in their inhomogeneity or patchy degeneration. One possibility is to perform the modeling of integrin-mediated alterations in in vitro systems, but substantial evidence is present to suggest that cell–cell adhesion mechanisms are very different in in vitro systems as opposed to in vivo systems [103].

Evidence from Usher syndrome studies reveals links between the Usher protein complex and cadherins/catenins in junction-associated complexes which may play substantial roles in specific static or developmental cell polarity and tissue organization [104]. It also begs the question of whether these pathways and other integrin-mediated pathways are altered in retinal degenerative diseases.

Neuritic sprouting mediated by retinoic acid receptors (RARs)

Other pathways, including retinoic acid (RA) mediated signaling pathways, are likely involved in retinal remodeling in the adult retina. RA-mediated signaling is activated in the LIRD model, where coherent photoreceptor loss and early dendritic remodeling occur. Additionally, exogenous application of RA leads to robust neuritic growth in primary cultured rod bipolar cells [105]. We believe that RA signaling displays large alterations early in retinal degeneration, suggesting that RA signaling pathways may be responsible for survival-related neuritogenesis and subsequent plasticity. Deficiencies in RA signaling may contribute to neurite degeneration, and retinoic acid (RA) and RA/retinoid receptor (RAR/RXR)-dependent pathways in retina incur the activation of neuritogenesis, resulting in the formation and elaboration of complex circuits and structures comprising all of the remaining retinal neuronal classes.

We demonstrated that RAR/RXR signaling is a mechanism driving pathological neuritogenesis. Even more compellingly, RAR/RXR antagonists appear to attenuate neuritogenesis from BC populations, while CaMKII inhibitors block neuritogenesis [105–107]. RAR/RXR signaling in phase 3 remodeling appears to induce anomalous neuronal sprouting and outgrowth, forming fascicles and microneuromas. This sometimes leads to retinas becoming so completely topologically restructured that the tissue no longer resembles retina. The model is that loss of photoreceptors eliminates retinoid buffering capacity (opsins) and increases retinoid precursor availability, leading to the generation of RA. RAR/RXR transcription subsequently induces sprouting and neuritogenesis. This occurs simultaneously with the loss of photoreceptors, which reduces glutamate-mediated neurotransmission and, by extension, decreases Ca^{2+}-mediated signaling. βCaMKII then detects the decrease in Ca^{2+} flux and contributes to RAR/RXR-mediated neuritogenesis through RXR binding.

Circuit outcomes of retinal remodeling

By hybridizing light microscopy with TEM analysis, phenotypic identity can be established for neurons, glia, and processes in ultrastructural datasets (Fig. 14) [24, 108], and circuitry can be defined for those phenotyped neurons [92, 109]. Analysis of over 30 animal models of RP and human RP samples indicates that, as remodeling progresses, the retinal circuitry substrate is altered. Beginning with bipolar cell dendritic truncation and polyaxonal growth early in the disease process [26] through to amacrine and ganglion cell neuritogenesis [24], evolving into anomalous fascicles and

Fig. 14 GABA, taurine, glutamate::r, g, b overlay on a TEM image of a peptidergic GABAergic amacrine cell (*asterisk*) adjacent to a forming microneuroma in the RCS rat retina. Overlay CMP/TEM imaging enables connectomics and pathoconnectomics projects that elucidate precise, ultrastructural reconstruction of neuronal circuitry. *Scale bar* 6 μm

microneuromas, the retina is restructuring its connectivities. Whether or not those connectivities are proper or improper is currently unknown and will only be answered through complete connectomic approaches [92, 109]. This is work that is underway in the P347L rabbit [110], the RCS rat [111], and the light-induced retinal degeneration mouse model [26], and it is so far demonstrating that these novel structures are not synaptically silent. Microneuromas exhibit numerous synaptic structures from both ribbon and conventional synapses, but it is still too early to judge their viability as functional or nonfunctional visual circuits.

Implications for retinal vision rescue

Retinal remodeling as a phenomenon introduces substantial barriers to any therapy designed to recover vision loss. Interventions in the remaining populations of neurons are complicated by the loss of BCs during the remodeling process [26]. More importantly, as discussed above, the initial response of the neural retina likely induces a substantial change to the retinal circuitry prior to cell loss, with initial alterations in BC connectivities and programming eliminating targets for photoreceptor progenitor cell or fetal retina transplants.

Retinas are reactive when deafferented and demonstrate enhanced remodeling in response to direct intervention. Retinal transplants, for example, remodel more aggressively than the host degenerate retina [112]. Prevention of neurite/dendritic loss appears to be critical to holding off phase 3 remodeling events, yet that loss appears to be one of the earliest indicators of neural disease in retina [20], cortex [113], and midbrain [114], with dendrites appearing to be far more sensitive to pathophysiological alterations than axons. Early changes include the aforementioned mislocalization of mGluR6 receptors [20–22], followed by bipolar cell regression and loss of iGluR expression in the dendrites, which effectively reprograms the physiologic response profiles of these bipolar cells and—one would presume—all subsequent downstream elements. Bipolar cells do not recover iGluR expression and thus the ability to signal through iGluR-mediated circuitry [26], making them poor targets for intervention strategies. Once downstream circuit revision occurs, there is persistent loss of iGluR expression in other cell populations as well [26], which leads to irrevocable alterations of the topology and circuitry of the retina [7–9, 11–13, 24, 26, 79].

Failing the prevention of dendritic loss of bipolar cells, secondary targets might prove successful by preventing horizontal, amacrine, and ganglion cells from sprouting aberrantly. A number of approaches aimed at reducing aberrant neuronal sprouting have been attempted, including electrical stimulation, which appears to enhance sprouting (data not published), tetrodotoxin (TTX) exposure in post-traumatic epilepsy models [115], and manipulation of integrins and retinoid X receptors [105], as discussed above. These approaches appear promising, as the loss of photoreceptors removes retinoid binding pools, thus increasing the availability of retinoid precursors. RA becomes available [106, 116], which subsequently triggers neuritogenesis through RAR/RXR transcriptional activity [117]. Simultaneously, photoreceptor loss reduces neural Ca^{2+} influx, activating the βCaMKII and driving neuritogenesis [107, 118]. This opens the door to therapeutic interventions that are designed to antagonize CaMKII, among other therapies.

Another approach we are working on in collaboration with Wolfgang Baehr is an early intervention with AAV-rRho-shRNA vectors to suppress rod opsin synthesis while patients still have photoreceptors, in order to arrest or delay photoreceptor cell death and prolong vision preservation by

decreasing the continued retinal stress and bystander killing effects of dying rods on cones. If one were to presume that rod opsin mediated toxicity, either via misfolding or mistrafficked opsins, is responsible for rod photoreceptor stress and subsequent cell death, it might be appropriate to reduce total overall rod opsin expression levels. The fundamental idea is to prolong rod photoreceptor life and limit the bystander killing effect on cone photoreceptors. This strategy has shown promise in GCAP1-Y99C transgenic mice, delaying vision loss through the expression of a GCAP1 shRNA by recombinant scAAV2/8 [119].

Other molecular changes occur in degenerate retina, and there is no evidence to suggest that retinal remodeling has an end point or arrest point [7, 24, 26]. More needs to be done in these areas, and possibly also in controlling or manipulating integrin-mediated contact on cell surfaces, which brings up the possibility of other forms of reprogramming in neural systems that have been deafferented. Other molecular changes are unquestionably occurring in the degenerate retina, and substantial evidence indicates that remodeling does not have an arrest point [7, 24, 26]. Fundamentally, these approaches are designed to slow the progression of retinal degeneration and not to recover vision that has already been lost.

A number of approaches are proposed that are designed to recover lost vision, but these approaches all have the same number of problems. The fundamental problem in rescuing vision is to define windows of opportunity or when to intervene. Current therapeutic interventions are designed for those patients that have already lost some, if not all, of their vision. These patients often present at a late stage with advanced retinal degeneration (Fig. 4), and are likely to exhibit early profound alterations to the retinal circuitry that corrupt any surrogate inputs. Any visual prosthetic design will depend upon the stage of retinal degeneration of the patient. Specifically, intervening in a highly remodeled retina to recover vision will represent an entirely different set of bioengineering or bionic engineering hurdles than intervening in a retina that has most or all of its circuitry still intact. It might be supposed that unless one actually knows what the fundamental circuitry is in the normal retina, one cannot predict what the output of the neural retina will be. Additionally, early evidence indicates that synaptic contacts in the remodeling retina are inappropriate, with some models [26] predicting that circuits may generate oscillatory ringing, which is incompatible with normal visual processing. Therefore, predicting what the ganglion cell output of the retina will be is difficult at best.

Other approaches, including stem cell transplants or embryonic sheet transplants, will have to overcome a number of issues, such as (and not limited to) improper wiring, cell fusion, and the rather scary possibility of transplant "rescues" being co-opted into Frankenstein-like assemblies of defective or nonfunctional cell populations by resident neurons and glia. A number of reports of transplanted stem cells that co-opt the phenotypes of host cells are documented as instances of cell fusion [120]. In addition to the documented circuit revision that occurs in retinal remodeling, there is a question of patterning, as remodeling retinas likely have altered spacing and visual functions that are related to alterations in cell–cell spacing. Cell populations that are introduced into an existing retina, albeit remodeled, do not have a history of normal developmental structuring such as that which occurs during retinal maturation, and no proposed research has ever discussed re-patterning the retina to recapitulate spacing rules. So, if introduced cell populations are to be successful, properly phenotyping transplanted cells [121] becomes a critical task in order to track identity and any positional issues that might impact visual field processing, though most efforts to date document a rejection of transplant cells [122] or a loss of the transplant cells' own mature phenotypes at various time points post-transplantation.

Fundamentally, most bionic or biological transplant/implant approaches presume or are engineered on the belief that the underlying neural retina is normal. The degenerate retina, on the other hand, is not normal, and most of its cell types show abnormality. The basic assumptions of transplant technologies (intactness, receptivity, and capacity of the host neural retina to carry the signals offered by the implant/transplant) are false.

However, we believe that there is a way forward using approaches pioneered in the optogenetics community, utilizing existing, remnant cell populations with intervention prior to large-scale restructuring of the retina. These genetic, therapeutic approaches using AAV-mediated channelrhodopsins/halorhodopsin vectors that target appropriate classes of retinal neurons could conceivably happen as a relatively late intervention when patients have lost functional photoreceptors [123–125]. This approach has been used before in ON bipolar cells in mouse to deliver channelrhodopsin2 [125]. The key here will be to target the right classes of neurons, as photoreceptor loss in RP effectively deafferents approximately 20 different ganglion cell pathways [10, 126]. Targeting broad ganglion cell classes with channelrhodopsins [127] is tricky, as separate ganglion cell outflow channels will then be generating the same signals to the cortex and other regions simultaneously. This is likely to set up errors in higher visual signal processing, so the decision about which specific retinal cell classes to target will be critical.

Human tissues

Tissue from patients with advanced RP and early GA/AMD were obtained from the Lion's Eye Bank donor pool at the

University of Utah within 3 h of death. The Lion's Eye Bank donor procurement and distribution complies with the Declaration of Helsinki. All data were de-identified in accordance with the HIPAA Privacy Rule.

Acknowledgments We would like to thank Carl B. Watt for his work in electron microscopy, imaging, and manuscript review. William Drew Ferrell was invaluable in data preparation and in reviewing the manuscript. Kevin Rapp assisted with confocal microscopy, which resulted in figure construction. Maggie Shaw and Jia-Hui Yang assisted with data acquisition, tissue preparation, immunocytochemistry, and ultramicrotomy. James R. Anderson assisted in ultrastructural data assembly. Monica Vetter and Alejandra Bosco helped provide the DBA/2J mouse tissues, provided guidance, and helped to review the manuscript. Support: NIH EY015128 (RM), NIH EY02576 (RM), EYO14800 Vision Core, an unrestricted grant from Research to Prevent Blindness to the Moran Eye Center; Edward N. and Della L. Thome Memorial Foundation grant for Age-Related Macular Degeneration Research (BWJ), a Research to Prevent Blindness Career Development Award (BWJ), Moran Eye Center Tiger Team Translational Medicine Award (BWJ), Sciences Research Grant H16-sensory-001 from the Ministry of Health, Labor and Welfare, Japan (MK).

References

1. Aleman TS, Cideciyan AV, Sumaroka A, Schwartz SB, Roman AJ, Windsor EAM, et al. Inner retinal abnormalities in X-linked retinitis pigmentosa with RPGR mutations. Invest Ophthalmol Vis Sci. 2007;48:4759–65.
2. Cuenca N, Pinilla I, Sauvé Y, Lu B, Wang S, Lund RD. Regressive and reactive changes in the connectivity patterns of rod and cone pathways of P23H transgenic rat retina. Neuroscience. 2004;127:301–17.
3. Cuenca N, Pinilla I, Sauvé Y, Lund RD. Early changes in synaptic connectivity following progressive photoreceptor degeneration in RCS rats. Eur J Neurosci. 2005;22:1057–72.
4. de Raad S, Szczesny PJ, Munz K, Remé CE. Light damage in the rat retina: glial fibrillary acidic protein accumulates in Müller cells in correlation with photoreceptor damage. Ophthalmic Res. 1996;28:99–107.
5. Fariss RN, Li ZY, Milam AH. Abnormalities in rod photoreceptors, amacrine cells, and horizontal cells in human retinas with retinitis pigmentosa. Am J Ophthalmol. 2000;129:215–23.
6. Fletcher EL, Kalloniatis M. Neurochemical architecture of the normal and degenerating rat retina. J Comp Neurol. 1996;376:343–60.
7. Jones BW, Marc RE. Retinal remodeling during retinal degeneration. Exp Eye Res. 2005;81:123–37.
8. Jones BW, Marc RE, Watt CB, Vaughan DK, Organisciak DT. Neural plasticity revealed by light-induced photoreceptor lesions. Adv Exp Med Biol. 2006;572:405–10.
9. Jones BW, Watt CB, Marc RE. Retinal remodelling. Clin Exp Optom. 2005;88:282–91.
10. Marc RE, Jones BW. Molecular phenotyping of retinal ganglion cells. J Neurosci. 2002;22:413–27.
11. Marc RE, Jones BW. Retinal remodeling in inherited photoreceptor degenerations. Mol Neurobiol. 2003;28:139–47.
12. Marc RE, Jones BW, Watt CB, Strettoi E. Neural remodeling in retinal degeneration. Prog Retin Eye Res. 2003;22:607–55.
13. Marc RE, Jones BW, Vazquez-Chona F, Vaughan DK, Organisciak DT. Extreme retinal remodeling triggered by light damage: implications for age related macular degeneration. Mol Vis. 2008;14:782–805.
14. Kolb H, Gouras P. Electron microscopic observations of human retinitis pigmentosa, dominantly inherited. Invest Ophthalmol. 1974;13:487–98.
15. Li ZY, Kljavin IJ, Milam AH. Rod photoreceptor neurite sprouting in retinitis pigmentosa. J Neurosci. 1995;15:5429–38.
16. Machida S, Kondo M, Jamison JA, Khan NW, Kononen LT, Sugawara T, et al. P23H rhodopsin transgenic rat: correlation of retinal function with histopathology. Invest Ophthalmol Vis Sci. 2000;41:3200–9.
17. Pu M, Xu L, Zhang H. Visual response properties of retinal ganglion cells in the Royal College of Surgeons dystrophic rat. Invest Ophthalmol Vis Sci. 2006;47:3579–85.
18. Specht D, Tom Dieck S, Ammermüller J, Regus-Leidig H, Gundelfinger ED, Brandstätter JH. Structural and functional remodeling in the retina of a mouse with a photoreceptor synaptopathy: plasticity in the rod and degeneration in the cone system. Eur J Neurosci. 2007;26:2506–15.
19. Stasheff SF. Emergence of sustained spontaneous hyperactivity and temporary preservation of OFF responses in ganglion cells of the retinal degeneration (rd1) mouse. J Neurophysiol. 2008;99:1408–21.
20. Strettoi E, Pignatelli V. Modifications of retinal neurons in a mouse model of retinitis pigmentosa. Proc Natl Acad Sci USA. 2000;97:11020–5.
21. Strettoi E, Pignatelli V, Rossi C, Porciatti V, Falsini B. Remodeling of second-order neurons in the retina of rd/rd mutant mice. Vision Res. 2003;43:867–77.
22. Strettoi E, Porciatti V, Falsini B, Pignatelli V, Rossi C. Morphological and functional abnormalities in the inner retina of the rd/rd mouse. J Neurosci. 2002;22:5492–504.
23. Sullivan RK, Woldemussie E, Pow DV. Dendritic and synaptic plasticity of neurons in the human age-related macular degeneration retina. Invest Ophthalmol Vis Sci. 2007;48:2782–9.
24. Jones BW, Watt CB, Frederick JM, Baehr W, Chen CK, Levine EM, et al. Retinal remodeling triggered by photoreceptor degenerations. J Comp Neurol. 2003;464:1–16.
25. Sullivan R, Penfold P, Pow DV. Neuronal migration and glial remodeling in degenerating retinas of aged rats and in nonneovascular AMD. Invest Ophthalmol Vis Sci. 2003;44:856–65.
26. Marc RE, Jones BW, Anderson JR, Kinard K, Marshak DW, Wilson JH, et al. Neural reprogramming in retinal degeneration. Invest Ophthalmol Vis Sci. 2007;48:3364–71.
27. Baehr W, Frederick JM. Naturally occurring animal models with outer retina phenotypes. Vision Res. 2009;49:2636–52.
28. Chang CJ, Lai WW, Edward DP, Tso MOM. Apoptotic photoreceptor cell death after traumatic retinal detachment in humans. Arch Ophthalmol. 1995;113:880–6.
29. Frederick JM, Krasnoperova NV, Hoffmann K, Church-Kopish J, Rüther K, Howes K, et al. Mutant rhodopsin transgene expression on a null background. Invest Ophthalmol Vis Sci. 2001;42:826–33.
30. Humphries MM, Rancourt D, Farrar GJ, Kenna P, Hazel M, Bush RA, et al. Retinopathy induced in mice by targeted disruption of the rhodopsin gene. Nat Genet. 1997;15:216–9.
31. Aguirre GD, Baldwin V, Pearce-Kelling S, Narfström K, Ray K, Acland GM. Congenital stationary night blindness in the dog: common mutation in the RPE65 gene indicates founder effect. Mol Vis. 1998;4:23.
32. Gu SM, Thompson DA, Srikumari CR, Lorenz B, Finckh U, Nicoletti A, et al. Mutations in RPE65 cause autosomal recessive childhood-onset severe retinal dystrophy. Nat Genet. 1997;17:194–7.
33. Morimura H, Fishman GA, Grover SA, Fulton AB, Berson EL, Dryja TP. Mutations in the RPE65 gene in patients with

autosomal recessive retinitis pigmentosa or Leber congenital amaurosis. Proc Natl Acad Sci USA. 1998;95:3088–93.
34. Allikmets R, Singh N, Sun H, Shroyer NF, Hutchinson A, Chidambaram A, et al. A photoreceptor cell-specific ATP-binding transporter gene (ABCR) is mutated in recessive Stargardt macular dystrophy. Nat Genet. 1997;15:236–46.
35. Allikmets R. Simple and complex ABCR: genetic predisposition to retinal disease. Am J Hum Genet. 2000;67:793–9.
36. Allikmets R, Shroyer NF, Singh N, Seddon JM, Lewis RA, Bernstein PS, et al. Mutation of the Stargardt disease gene (ABCR) in age-related macular degeneration. Science. 1997;277:1805–7.
37. Cremers FP, van de Pol DJ, van Driel M, den Hollander AI, van Haren FJ, Knoers NV, et al. Autosomal recessive retinitis pigmentosa and cone-rod dystrophy caused by splice site mutations in the Stargardt's disease gene ABCR. Hum Mol Genet. 1998;7:355–62.
38. Molday LL, Rabin AR, Molday RS. ABCR expression in foveal cone photoreceptors and its role in Stargardt macular dystrophy. Nat Genet. 2000;25:257–8.
39. D'Cruz PM, Yasumura D, Weir J, Matthes MT, Abderrahim H, LaVail MM, et al. Mutation of the receptor tyrosine kinase gene Mertk in the retinal dystrophic RCS rat. Hum Mol Genet. 2000;9:645–51.
40. Duncan JL, Yang H, Vollrath D, Yasumura D, Matthes MT, Trautmann N, et al. Inherited retinal dystrophy in Mer knockout mice. Adv Exp Med Biol. 2003;533:165–72.
41. Li JB, Gerdes JM, Haycraft CJ, Fan Y, Teslovich TM, May-Simera H, et al. Comparative genomics identifies a flagellar and basal body proteome that includes the BBS5 human disease gene. Cell. 2004;117:541–52.
42. Yen HJ, Tayeh MK, Mullins RF, Stone EM, Sheffield VC, Slusarski DC. Bardet-Biedl syndrome genes are important in retrograde intracellular trafficking and Kupffer's vesicle cilia function. Hum Mol Genet. 2006;15:667–77.
43. Dryja TP, Berson EL, Rao VR, Oprian DD. Heterozygous missense mutation in the rhodopsin gene as a cause of congenital stationary night blindness. Nat Genet. 1993;4:280–3.
44. Zeitz C, Gross AK, Leifert D, Kloeckener-Gruissem B, McAlear SD, Lemke J, et al. Identification and functional characterization of a novel rhodopsin mutation associated with autosomal dominant CSNB. Invest Ophthalmol Vis Sci. 2008;49:4105–14.
45. Sommer ME, Farrens DL. Arrestin can act as a regulator of rhodopsin photochemistry. Vision Res. 2006;46:4532–46.
46. Sommer ME, Smith WC, Farrens DL. Dynamics of arrestin-rhodopsin interactions: acidic phospholipids enable binding of arrestin to purified rhodopsin in detergent. J Biol Chem. 2006;281:9407–17.
47. Huang SH, Pittler SJ, Huang X, Oliveira L, Berson EL, Dryja TP. Autosomal recessive retinitis pigmentosa caused by mutations in the alpha subunit of rod cGMP phosphodiesterase. Nat Genet. 1995;11:468–71.
48. McLaughlin ME, Ehrhart TL, Berson EL, Dryja TP. Mutation spectrum of the gene encoding the beta subunit of rod phosphodiesterase among patients with autosomal recessive retinitis pigmentosa. Proc Natl Acad Sci USA. 1995;92:3249–53.
49. McLaughlin ME, Sandberg MA, Berson EL, Dryja TP. Recessive mutations in the gene encoding the beta-subunit of rod phosphodiesterase in patients with retinitis pigmentosa. Nat Genet. 1993;4:130–4.
50. Clarke G, Goldberg AF, Vidgen D, Collins L, Ploder L, Schwarz L, et al. Rom-1 is required for rod photoreceptor viability and the regulation of disk morphogenesis. Nat Genet. 2000;25:67–73.
51. Dryja TP, McGee TL, Berson EL, Fishman GA, Sandberg MA, Alexander KR, et al. Night blindness and abnormal cone electroretinogram ON responses in patients with mutations in the GRM6 gene encoding mGluR6. Proc Natl Acad Sci USA. 2005;102:4884–9.
52. Zeitz C, van Genderen M, Neidhardt J, Luhmann UF, Hoeben F, Forster U, et al. Mutations in GRM6 cause autosomal recessive congenital stationary night blindness with a distinctive scotopic 15-Hz flicker electroretinogram. Invest Ophthalmol Vis Sci. 2005;46:4328–35.
53. Vasireddy V, Uchida Y, Salem N Jr, Kim SY, Mandal MNA, Reddy GB, et al. Loss of functional ELOVL4 depletes very long-chain fatty acids (≥C28) and the unique ω-*O*-acylceramides in skin leading to neonatal death. Hum Mol Genet. 2007;16:471–82.
54. Zhang K, Kniazeva M, Han M, Li W, Yu Z, Yang Z, et al. A 5-bp deletion in ELOVL4 is associated with two related forms of autosomal dominant macular dystrophy. Nat Genet. 2001;27:89–93.
55. Chen CK, Burns ME, He W, Wensel TG, Baylor DA, Simon MI. Slowed recovery of rod photoresponse in mice lacking the GTPase accelerating protein RGS9-1. Nature. 2000;403:557–60.
56. Hu G, Wensel TG. R9AP, a membrane anchor for the photoreceptor GTPase accelerating protein, RGS9-1. Proc Natl Acad Sci USA. 2002;99:9755–60.
57. Hu G, Zhang Z, Wensel TG. Activation of RGS9-1GTPase acceleration by its membrane anchor, R9AP. J Biol Chem. 2003;278:14550–4.
58. Wensel TG. Signal transducing membrane complexes of photoreceptor outer segments. Vision Res. 2008;48:2052–61.
59. Boon CJF, Klevering BJ, Hoyng CB, Zonneveld-Vrieling MN, Nabuurs SB, Blokland E, et al. Basal laminar drusen caused by compound heterozygous variants in the CFH gene. Am J Hum Genet. 2008;82:516–23.
60. Cameron DJ, Yang Z, Gibbs D, Chen H, Kaminoh Y, Jorgensen A, et al. HTRA1 variant confers similar risks to geographic atrophy and neovascular age-related macular degeneration. Cell Cycle. 2007;6:1122–5.
61. Chen H, Yang Z, Gibbs D, Yang X, Hau V, Zhao P, et al. Association of HTRA1 polymorphism and bilaterality in advanced age-related macular degeneration. Vision Res. 2008;48:690–4.
62. Dewan A, Liu M, Hartman S, Zhang SS, Liu DT, Zhao C, et al. HTRA1 promoter polymorphism in wet age-related macular degeneration. Science. 2006;314:989–92.
63. Edwards AO, Ritter R III, Abel KJ, Manning A, Panhuysen C, Farrer LA. Complement factor H polymorphism and age-related macular degeneration. Science. 2005;308:421–4.
64. Gold B, Merriam JE, Zernant J, Hancox LS, Taiber AJ, Gehrs K, et al. Variation in factor B (BF) and complement component 2 (C2) genes is associated with age-related macular degeneration. Nat Genet. 2006;38:458–62.
65. Hageman GS, Anderson DH, Johnson LV, Hancox LS, Taiber AJ, Hardisty LI, et al. A common haplotype in the complement regulatory gene factor H (HF1/CFH) predisposes individuals to age-related macular degeneration. Proc Natl Acad Sci USA. 2005;102:7227–32.
66. Jakobsdottir J, Conley YP, Weeks DE, Mah TS, Ferrell RE, Gorin MB. Susceptibility genes for age-related maculopathy on chromosome 10q26. Am J Hum Genet. 2005;77:389–407.
67. Kaplan J, Gerber S, Larget-Piet D, Rozet JM, Dollfus H, Dufier JL, et al. A gene for Stargardt's disease (fundus flavimaculatus) maps to the short arm of chromosome 1. Nat Genet. 1993;5:308–11.
68. Maller JB, Fagerness JA, Reynolds RC, Neale BM, Daly MJ, Seddon JM. Variation in complement factor 3 is associated with risk of age-related macular degeneration. Nat Genet. 2007;39:1200–1.

69. Stone EM, Braun TA, Russell SR, Kuehn MH, Lotery AJ, Moore PA, et al. Missense variations in the fibulin 5 gene and age-related macular degeneration. N Engl J Med. 2004;351:346–53.
70. Yates JRW, Sepp T, Matharu BK, Khan JC, Thurlby DA, Shahid H, et al. Complement C3 variant and the risk of age-related macular degeneration. N Engl J Med. 2007;357:553–61.
71. Phipps JA, Yee P, Fletcher EL, Vingrys AJ. Rod photoreceptor dysfunction in diabetes: activation, deactivation, and dark adaptation. Invest Ophthalmol Vis Sci. 2006;47:3187–94.
72. Choi SS, Zawadzki RJ, Lim MC, Brandt JD, Keltner JL, Doble N, et al. Evidence of outer retinal changes in glaucoma patients as revealed by ultrahigh-resolution in vivo retinal imaging. Br J Ophthalmol. 2011;95:131–41.
73. Milam AH, Li ZY, Fariss RN. Histopathology of the human retina in retinitis pigmentosa. Prog Retin Eye Res. 1998;17: 175–205.
74. Jones BW, Kondo M, Terasaki H, Watt CB, Rapp K, Anderson J, et al. Retinal remodeling in the Tg p347l rabbit, a large-eye model of retinal degeneration. J Comp Neurol. 2011;519: 2713–33.
75. Varela C, Igartua I, De la Rosa EJ, De la Villa P. Functional modifications in rod bipolar cells in a mouse model of retinitis pigmentosa. Vision Res. 2003;43:879–85.
76. Chua J, Fletcher EL, Kalloniatis M. Functional remodeling of glutamate receptors by inner retinal neurons occurs from an early stage of retinal degeneration. J Comp Neurol. 2009;514: 473–91.
77. Peng YW, Hao Y, Petters RM, Wong F. Ectopic synaptogenesis in the mammalian retina caused by rod photoreceptor-specific mutations. Nat Neurosci. 2000;3:1121–7.
78. Park SJ, Kim IB, Choi KR, Moon JI, Oh SJ, Chung JW, et al. Reorganization of horizontal cell processes in the developing FVB/N mouse retina. Cell Tissue Res. 2001;306:341–6.
79. Marc RE, Jones BW, Watt CB. Retinal remodeling: circuitry revisions triggered by photoreceptor degeneration. In: Pinaud R, Tremere L, De Weerd P, editors. Plasticity in the visual system: from genes to circuits. New York: Springer; 2006. p. 33–54.
80. Li ZY, Possin DE, Milam AH. Histopathology of bone spicule pigmentation in retinitis pigmentosa. Ophthalmology. 1995;102: 805–16.
81. Spraul CW, Lang GE, Grossniklaus HE, Lang GK. Histologic and morphometric analysis of the choroid, Bruch's membrane, and retinal pigment epithelium in postmortem eyes with age-related macular degeneration and histologic examination of surgically excised choroidal neovascular membranes. Surv Ophthalmol. 1999;44(Suppl 1):S10–32.
82. Carter-Dawson LD, LaVail MM, Sidman RL. Differential effect of the rd mutation on rods and cones in the mouse retina. Invest Ophthalmol Vis Sci. 1978;17:489–98.
83. Margolis DJ, Detwiler PB. Cellular origin of spontaneous ganglion cell spike activity in animal models of retinitis pigmentosa. J Ophthalmol. 2011. doi:10.1155/2011/507037.
84. Sekirnjak C, Hulse C, Jepson LH, Hottowy P, Sher A, Dabrowski W, et al. Loss of responses to visual but not electrical stimulation in ganglion cells of rats with severe photoreceptor degeneration. J Neurophysiol. 2009;102:3260–9.
85. Lewis GP, Linberg KA, Fisher SK. Neurite outgrowth from bipolar and horizontal cells after experimental retinal detachment. Invest Ophthalmol Vis Sci. 1998;39:424–34.
86. Linberg KA, Lewis GP, Matsumoto B, Fisher SK. Immunocytochemical evidence that rod-connected horizontal cell axon terminals remodel in response to experimental retinal detachment in the cat. Mol Vis. 2006;12:1674–86.
87. Wong RO, Herrmann K, Shatz CJ. Remodeling of retinal ganglion cell dendrites in the absence of action potential activity. J Neurobiol. 1991;22:685–97.
88. Beltran WA, Hammond P, Acland GM, Aguirre GD. A frameshift mutation in RPGR exon ORF15 causes photoreceptor degeneration and inner retina remodeling in a model of X-linked retinitis pigmentosa. Invest Ophthalmol Vis Sci. 2006;47:1669–81.
89. Ray A, Sun GJ, Chan L, Grzywacz NM, Weiland J, Lee EJ. Morphological alterations in retinal neurons in the S334ter-line3 transgenic rat. Cell Tissue Res. 2010;339:481–91.
90. Iandiev I, Uckermann O, Pannicke T, Wurm A, Tenckhoff S, Pietsch UC, et al. Glial cell reactivity in a porcine model of retinal detachment. Invest Ophthalmol Vis Sci. 2006;47: 2161–71.
91. Ross JW, Fernandez de Castro JP, Zhao J, Samuel M, Walters E, Rios C, et al. Generation of an inbred miniature pig model of retinitis pigmentosa. Invest Ophthalmol Vis Sci. 2012;53:501–7.
92. Anderson JR, Bones JW, Watt CB, Shaw MV, Yang JH, Demill D, et al. Exploring the retinal connectome. Mol Vis. 2011;17: 355–79.
93. Cuenca N, Pinilla I, Fernández-Sánchez L, Salinas-Navarro M, Alarcón-Martínez L, Avilés-Trigueros M, et al. Changes in the inner and outer retinal layers after acute increase of the intraocular pressure in adult albino Swiss mice. Exp Eye Res. 2010;91:273–85.
94. Yefimova MG, Messaddeq N, Karam A, Jacquard C, Weber C, Jonet L, et al. Polyglutamine toxicity induces rod photoreceptor division, morphological transformation or death in spinocerebellar ataxia 7 mouse retina. Neurobiol Dis. 2010;40:311–24.
95. Firth SI, Feller MB. Dissociated GABAergic retinal interneurons exhibit spontaneous increases in intracellular calcium. Vis Neurosci. 2006;23:807–14.
96. Voigt T, Wassle H. Dopaminergic innervation of A II amacrine cells in mammalian retina. J Neurosci. 1987;7:4115–28.
97. Kolb H, Cuenca N, Dekorver L. Postembedding immunocytochemistry for GABA and glycine reveals the synaptic relationships of the dopaminergic amacrine cell of the cat retina. J Comp Neurol. 1991;310:267–84.
98. Feigenspan A, Gustincich S, Bean BP, Raviola E. Spontaneous activity of solitary dopaminergic cells of the retina. J Neurosci. 1998;18:6776–89.
99. Jones BW, Marc RE, Watt CB. Dopaminergic amacrine and interplexiform cells exhibit glutamatergic signatures. Invest Ophthalmol Vis Sci. 2004;45:E (abstract 5435).
100. VanLeeuwen JE, Petzinger GM, Walsh JP, Akopian GK, Vuckovic M, Jakowec MW. Altered AMPA receptor expression with treadmill exercise in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-lesioned mouse model of basal ganglia injury. J Neurosci Res. 2010;88:650–68.
101. Kim M, Carman CV, Springer TA. Bidirectional transmembrane signaling by cytoplasmic domain separation in integrins. Science. 2003;301:1720–5.
102. Shimaoka M, Takagi J, Springer TA. Conformational regulation of integrin structure and function. Annu Rev Biophys Biomol Struct. 2002;31:485–516.
103. Cukierman E, Pankov R, Stevens DR, Yamada KM. Taking cell-matrix adhesions to the third dimension. Science. 2001;294: 1708–12.
104. Kremer H, van Wijk E, Märker T, Wolfrum U, Roepman R. Usher syndrome: molecular links of pathogenesis, proteins and pathways. Hum Mol Genet. 2006;15(Spec No 2):R262–70.
105. Lin Y, Jones BW, Liu A, Tucker JF, Rapp K, Luo L, et al. Retinoid receptors trigger neuritogenesis in retinal degenerations. FASEB J. 2011;36:81–92.
106. Lin Y, Jones BW, Rapp K, Shaw MV, Yang J-H, Watt CB, et al. Roles of retinoic acid signaling in neuritogenesis during light-induced retinal degeneration. ARVO Meeting Abstracts. 2010;51: 5592.

107. Lin Y, Jones BW, Rapp K, Shaw MV, Yang J-H, Watt CB, et al. CaMKII signaling is contributive to neuritogenesis in light-induced retinal degeneration. ARVO Meeting Abstracts. 2011;52: 1846.
108. Marc RE, Liu W. Fundamental GABAergic amacrine cell circuitries in the retina: nested feedback, concatenated inhibition, and axosomatic synapses. J Comp Neurol. 2000;425:560–82.
109. Anderson JR, Jones BW, Yang J-H, Shaw MV, Watt CB, Koshevoy P, et al. A computational framework for ultrastructural mapping of neural circuitry. PLoS Biol. 2009;7:e1000074.
110. Kondo M, Sakai T, Komeima K, Kurimoto Y, Ueno S, Nishizawa Y, et al. Generation of a transgenic rabbit model of retinal degeneration. Invest Ophthalmol Vis Sci. 2009;50: 1371–7.
111. Gal A, Li Y, Thompson DA, Weir J, Orth U, Jacobson SG, et al. Mutations in MERTK, the human orthologue of the RCS rat retinal dystrophy gene, cause retinitis pigmentosa. Nat Genet. 2000;26:270–1.
112. Seiler MJ, Aramant RB, Thomas BB, Peng Q, Sadda SR, Keirstead HS. Visual restoration and transplant connectivity in degenerate rats implanted with retinal progenitor sheets. Eur J Neurosci. 2010;31:508–20.
113. Baloyannis SJ. Dendritic pathology in Alzheimer's disease. J Neurol Sci. 2009;283:153–7.
114. Bywood PT, Johnson SM. Dendrite loss is a characteristic early indicator of toxin-induced neurodegeneration in rat midbrain slices. Exp Neurol. 2000;161:306–16.
115. Prince DA, Parada I, Scalise K, Graber K, Shen F. Epilepsy following cortical injury: cellular and molecular mechanisms as targets for potential prophylaxis. Epilepsia. 2009;50(Suppl 2): 30–40.
116. Duncan T, Wiggert B, Whittaker N, Darrow R, Organisciak DT. Effect of visible light on normal and p23h-3 transgenic rat retinas: characterization of a novel retinoic acid derivative present in the p23h-3 retina. Photochem Photobiol. 2006;82:741–5.
117. Clagett-Dame M, McNeill E, Muley P. Role of all-trans retinoic acid in neurite outgrowth and axonal elongation. J Neurobiol. 2006;66:739–56.
118. Thiagarajan TC, Piedras-Renteria ES, Tsien RW. Alpha and beta CAMKII: inverse regulation by neuronal activity and opposing effects on synaptic strength. Neuron. 2002;36:1103–14.
119. Jiang L, Boye SL, Dizhoor A, Hauswirth WW, Baehr W. Knock-down of GCAP1 by RNA interference delays photoreceptor degeneration in GCAP1-Y99C transgenic mice. Invest Ophthalmol Vis Sci. 2011;51:4488.
120. Terada N, Hamazaki T, Oka M, Hoki M, Mastalerz DM, Nakano Y, et al. Bone marrow cells adopt the phenotype of other cells by spontaneous cell fusion. Nature. 2002;416:542–5.
121. Canola K, Angénieux B, Tekaya M, Quiambao A, Naash MI, Munier FL, et al. Retinal stem cells transplanted into models of late stages of retinitis pigmentosa preferentially adopt a glial or a retinal ganglion cell fate. Invest Ophthalmol Vis Sci. 2007;48: 446–54.
122. Bull ND, Limb GA, Martin KR. Human Muller stem cell (MIO-M1) transplantation in a rat model of glaucoma: survival, differentiation, and integration. Invest Ophthalmol Vis Sci. 2008;49: 3449–56.
123. Busskamp V, Duebel J, Balya D, Fradot M, Viney TJ, Siegert S, et al. Genetic reactivation of cone photoreceptors restores visual responses in retinitis pigmentosa. Science. 2010;329:413–7.
124. Lagali P, Balya D, Awatramani GB, Münch TA, Kim DS, Busskamp V, et al. Light-activated channels targeted to ON bipolar cells restore visual function in retinal degeneration. Nat Neurosci. 2008;11:667–75.
125. Doroudchi MM, Greenberg KP, Liu J, Silka KA, Boyden ES, Lockridge JA, et al. Virally delivered channelrhodopsin-2 safely and effectively restores visual function in multiple mouse models of blindness. Mol Ther. 2011;19:1220–9.
126. Marc R. Injury and repair: retinal remodeling. In: Dana R, editor. Encyclopedia of the eye. Amsterdam: Elsevier; 2009.
127. Ivanova E, Pan Z-H. Evaluation of the adeno-associated virus mediated long-term expression of channelrhodopsin-2 in the mouse retina. Mol Vis. 2009;15:1680–9.

Doc Ophthalmol (2012) 125:75–80
DOI 10.1007/s10633-012-9329-y

CLINICAL CASE REPORT

A case of bilateral, acquired, and acute dysfunction of short-wavelength-sensitive cone systems

Kazuki Kuniyoshi · Hiroyuki Sakuramoto · Akira Nakao · Sonoko Takada · Yoshikazu Shimomura

Received: 8 April 2012 / Accepted: 23 April 2012 / Published online: 20 May 2012
© Springer-Verlag 2012

Abstract To report a case of bilateral, acquired, and acute dysfunction of short-wavelength-sensitive (SWS) cone systems. The case was a healthy 39-year-old man. He noticed sudden onset of bilateral abnormal color vision. Ophthalmic examinations revealed normal fundi in both eyes. Farnsworth panel D-15 test and Farnsworth–Munsell 100-hue test showed tritanopia. White-on-white static perimetry showed no abnormality; however, blue-on-yellow static perimetry detected remarkably reduced sensitivity at the lower visual field in both eyes. ISCEV-standard full-field electroretinograms (ERGs) were normal; however, blue-on-yellow ERGs showed reduced amplitude of b-wave that was derived from SWS cone systems in both eyes. He was observed for 1 year, and no improvement in color vision was found during the observation. This is a unique case which showed bilateral, acquired, and acute dysfunction of SWS cone systems. The cause of the acquired tritanopia remains to be known.

Keywords Acquired tritanopia · Color blindness · Electroretinogram · Short-wavelength-sensitive cone · Blue-on-yellow perimetry

K. Kuniyoshi (✉) · H. Sakuramoto · A. Nakao · S. Takada · Y. Shimomura
Department of Ophthalmology, Kinki University Faculty of Medicine, 377-2 Ohno-Higashi, Osaka-Sayama, Osaka 589-8511, Japan
e-mail: kazuki@med.kindai.ac.jp

Introduction

Acquired tritanopia is shown in various retinal diseases and optic nerve diseases [1], or after exposure to toxic chemicals [2].

In this paper, authors report a case with bilateral, acquired, and acute dysfunction of short-wavelength-sensitive (SWS) cone systems which had no history of general or ophthalmic diseases.

Case

The case was a healthy 39-year-old man. He had no past history of general disease or medication. He was working as an office worker. He noticed abnormal color vision in both eyes when he woke up on the morning of June 2, 2009. He complained that yellow color looked whitish, human skin of Asian looked vivid pink, and it was difficult to distinguish between blue and green. He had not been exposed to strong light nor chemical materials such as organic solvents that were reported as cause of acquired color discrimination impairment. He did not take much alcoholic drinks before the symptoms, nor tobacco, except several electronic cigarettes. He visited a nearby clinic and was referred to us for further examinations.

At the first visit to our clinic, the corrected visual acuity was (1.2) in both eyes with normal intraocular pressure. Ophthalmic examinations revealed that the anterior segments, optic media, and fundi were

unremarkable in both eyes (Fig. 1). Fluorescein fundus angiography, indocyanine-green fundus angiography, and optical coherence tomography were performed, and they were also unremarkable (Figs. 2, 3). Farnsworth panel D-15 test and Farnsworth–Munsell 100-hue test showed tritanopia in both eyes (Fig. 4). Goldmann kinetic perimetry and white-on-white static perimetry showed no abnormality in either

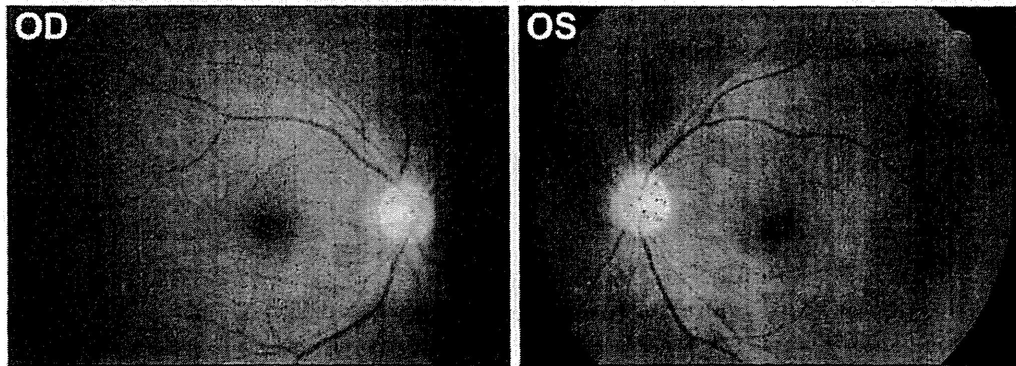


Fig. 1 Fundus photographs. No abnormality was found in both eyes

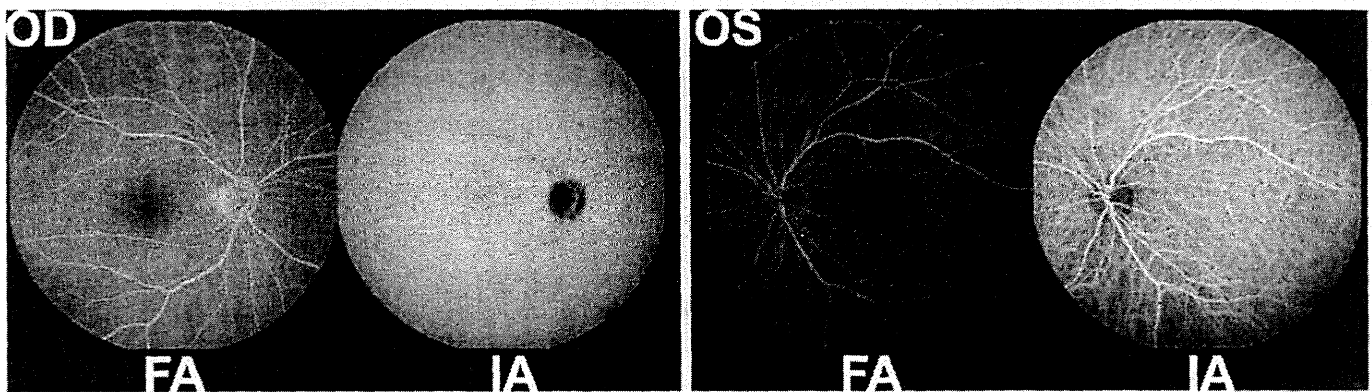


Fig. 2 Results of fluorescein and indocyanine-green fundus angiograms (FA and IA). FA and IA were performed simultaneously using HRA™2 (Heidelberg Engineering, Heidelberg, Germany)

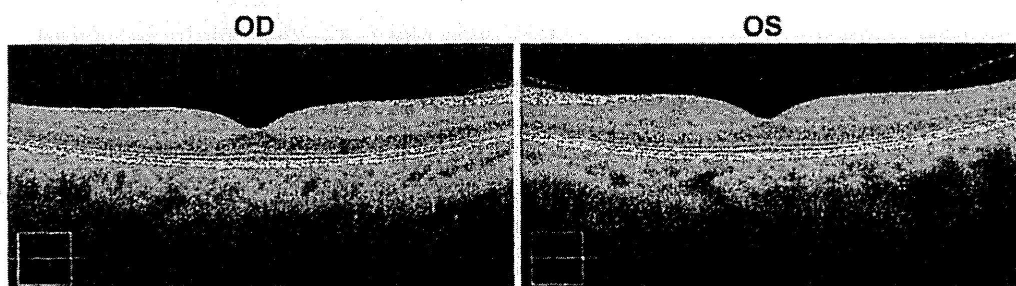


Fig. 3 Results of optical coherence tomography (OCT). Horizontal section of macular area was shown. Retinal structure was normal including photoreceptor layer, middle layer, and nerve fiber layer. OCT was performed using Cirrus™ HD spectral-domain optical coherence tomography (Cirrus™ HD-OCT; Carl Zeiss Meditec, Dublin, CA)

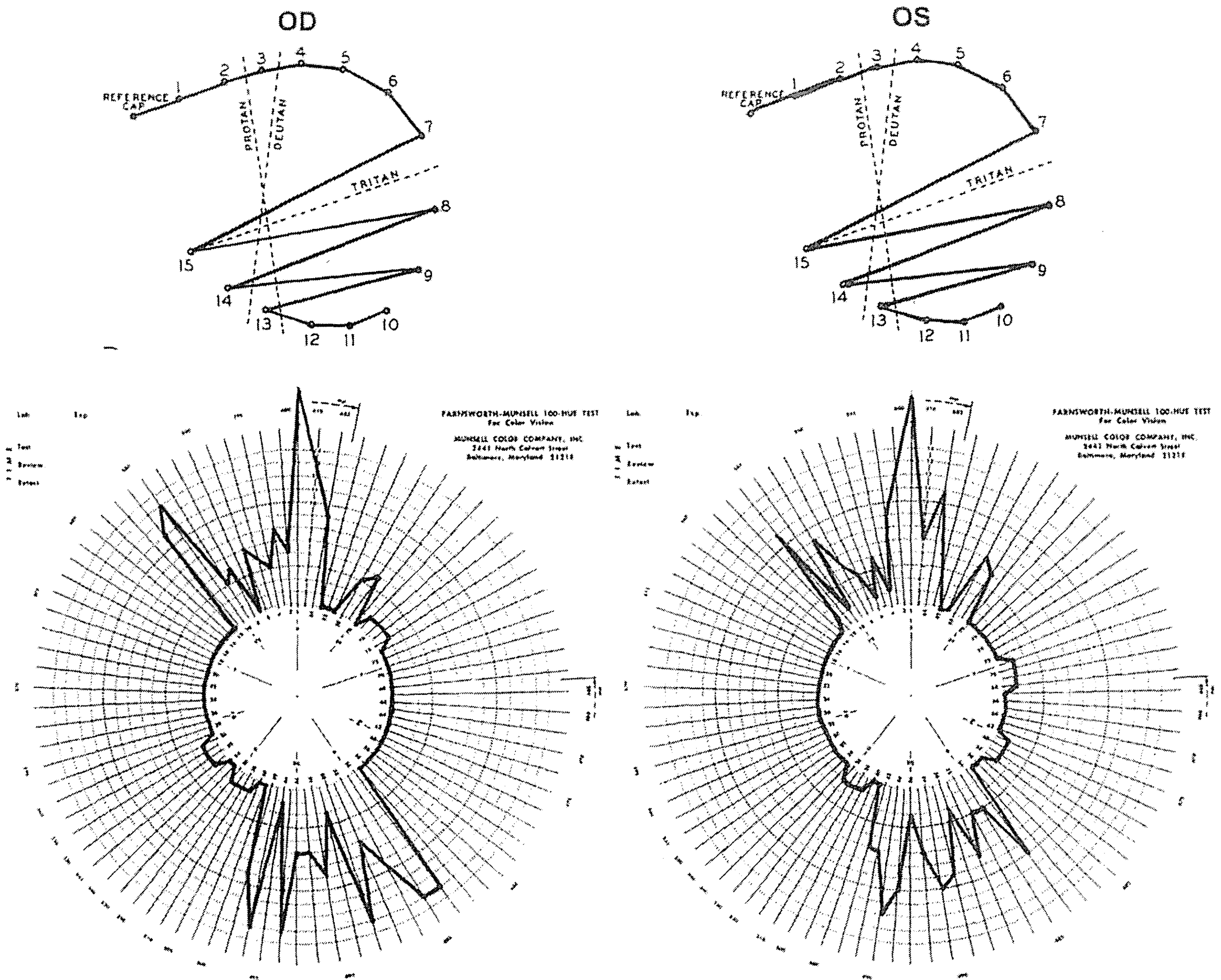


Fig. 4 Results of Farnsworth panel D-15 test (*upper row*) and Farnsworth–Munsell 100-hue test (*lower row*). Tritanopia is suggested clearly in both eyes

eye; however, blue-on-yellow static perimetry detected remarkably reduced sensitivity at the lower visual field in both eyes (Fig. 5).

ISCEV-standard full-field electroretinograms (ERGs) [3] were normal (Fig. 6); however, blue-on-yellow ERGs [4] showed attenuated b-wave that was derived from SWS cone systems in both eyes (Fig. 7).

Optic nerve and central nervous system were investigated using magnetic resonance imaging and recording of visual evoked potentials, and they were unremarkable.

The patient quitted smoking the electronic cigarette after the symptom, and he was observed for 1 year. However, his condition was stationary with no improvement or worsening of color vision, visual acuity, and fundus appearance.

Discussion

The SWS cone system is vulnerable in retinal diseases compared to middle- and long-wavelength-sensitive (MWS and LWS) cone systems [5–8].

The results of color vision test indicated distinct tritanopia (Fig. 4). And the reduction in SWS-cone ERG (Fig. 7) indicated that the tritanopia was caused

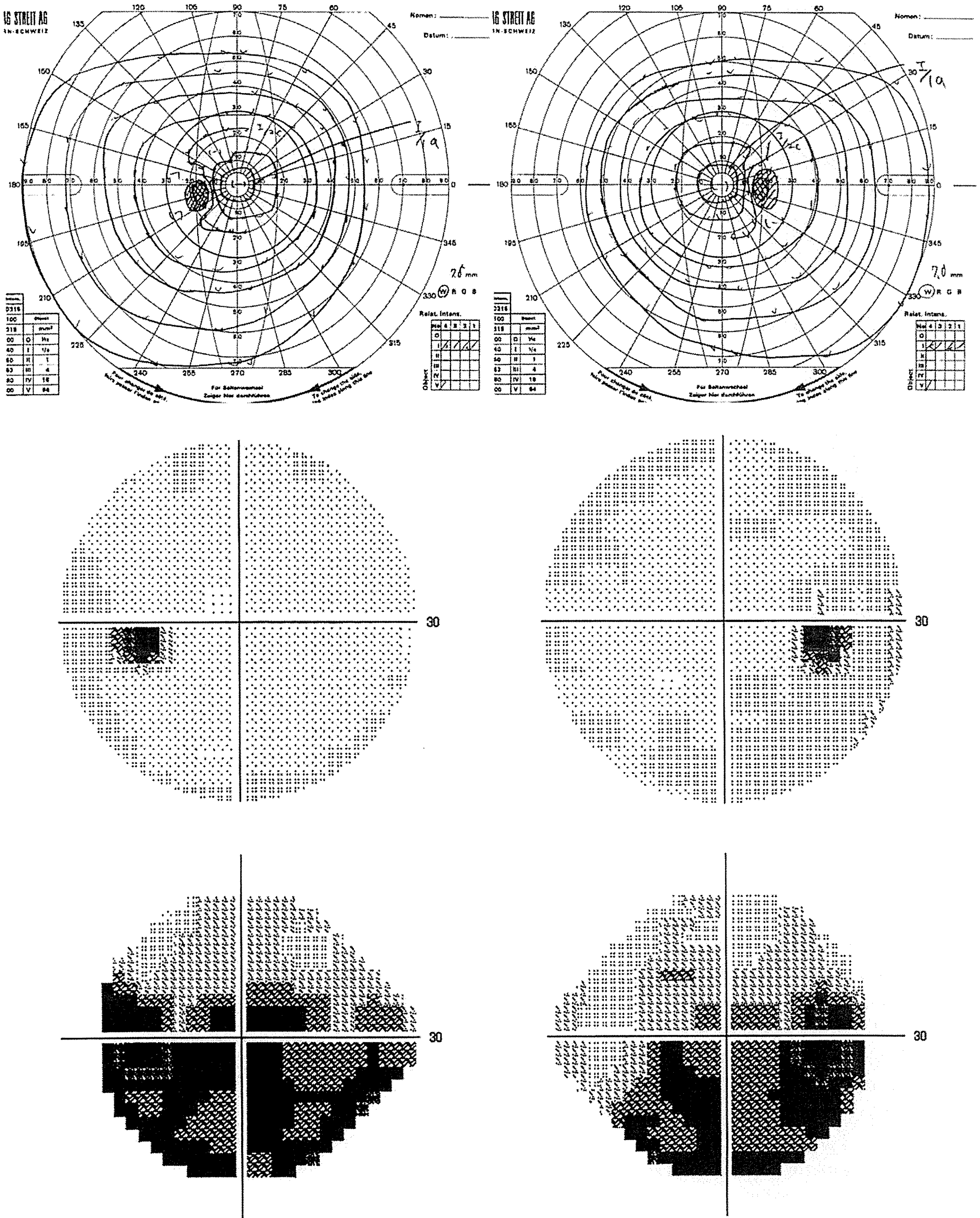


Fig. 5 Results of Goldmann kinetic perimetry (GP *upper row*), Humphrey white-on-white static perimetry (W/W *middle row*), and Humphrey blue-on-yellow static perimetry (B/Y *lower row*). No visual field defects were detected except in blue-on-yellow static perimetry

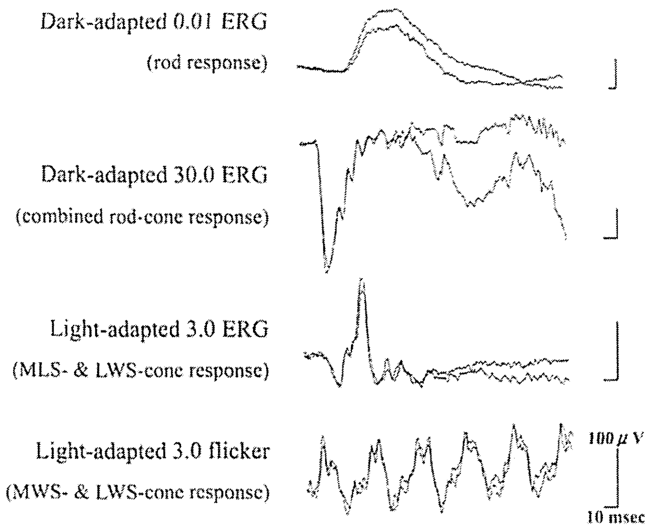


Fig. 6 ISCEV-standard ERGs [3]. Responses from both eyes were superimposed. Photopic and flicker ERG that were derived from middle- and long-wavelength-sensitive (MWS and LWS) cone systems showed normal responses

by dysfunction of SWS cone systems in the retina, in spite of the fact that the fundus appearance was normal. LWS and MWS cone systems seemed to be healthy in this case, because Farnsworth–Munsell 100-hue test showed very few errors in red-green color vision, and full-field photopic and flicker ERG that were derived from MWS and LWS cone systems showed normal responses (Figs. 4, 6). These facts suggest a selective functional disturbance of SWS cone systems in this case.

The patient reported that he had used electronic cigarettes several days before the symptom. Although World Health Organization (WHO) has denied safety of the electronic cigarette [9], relationship between the electronic cigarette and the SWS cone dysfunction was not clear in this case, because authors did not examine the electronic cigarettes he took.

To our knowledge, acquired tritanopia and acute tritanopia due to SWS cone system dysfunction with no ophthalmic diseases have never been reported except by Okuno et al. [10]. They reported a case of sudden-onset tritanopia with no ophthalmic nor general disease. The color vision abnormality in the Okuno's case [10] was unilateral, which is different from our case.

Bilateral and acute dysfunction of SWS cone systems in the case presented here is quite unique. Authors were not able to find any causes of this dysfunction during the 1-year follow-up.

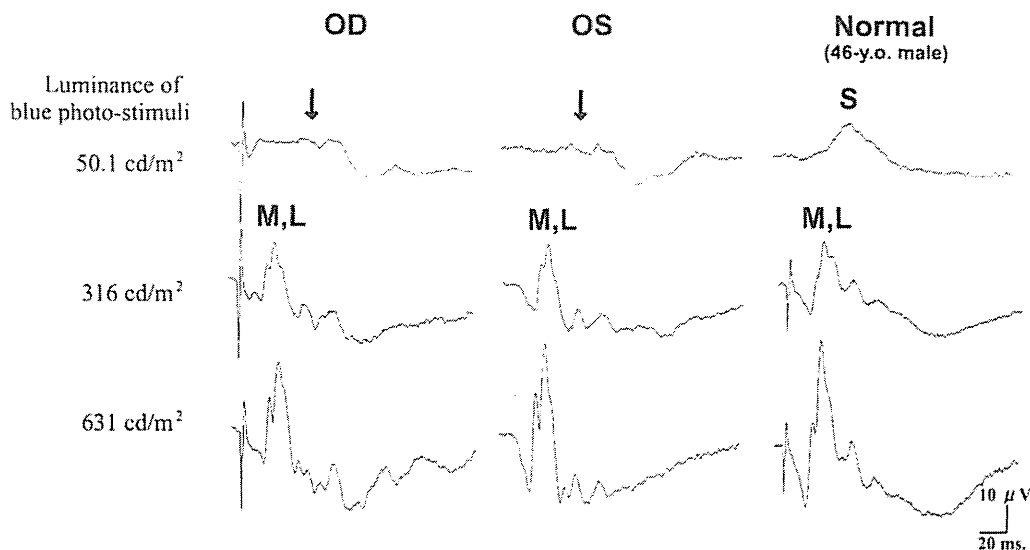
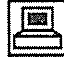


Fig. 7 Blue-on-yellow ERGs [4]. The case showed severely attenuated b-wave (*arrows*) that was derived from short-wavelength-sensitive cones in a normal subject (S), whereas b-waves from middle- and long-wavelength-sensitive cones (M, L) were normal in both eyes. Luminance of the yellow background was 640 cd/m^2, and duration of the blue photo-stimuli was 2 ms

Conflict of interest The authors declared that there is no conflict of interest.

References

1. Krill AE, Fishman GA (1971) Acquired color vision defects. Trans Am Acd Ophthalmol Otolaryn 75:1095–1111
2. Iregren A, Andersson M, Nylén P (2002) Color vision and occupational chemical exposures: I. An overview of tests and effects. Neurotoxicology 23:719–733
3. Marmor MF, Fulton AB, Holder GE, Miyake Y, Brigell M, Bach M (2009) ISECV standard for full-field clinical electroretinography (2008 update). Doc Ophthalmol 118:69–77
4. Kuniyoshi K, Uno N, Irifune M, Shimomura Y (2003) Electroretinography of short-wavelength-sensitive cones with a LED built-in electrode and its normal values. Doc Ophthalmol 106:311–318
5. Greenstein VC, Hood DC, Ritch R, Steinberger D, Carr RE (1989) S (blue) cone pathway vulnerability in retinitis pigmentosa, diabetes and glaucoma. Invest Ophthalmol Vis Sci 30:1732–1737
6. Nork TM, Millecchia LL, Strickland BD, Linberg JV, Chao G (1995) Selective loss of blue cones and rods in human retinal detachment. Arch Ophthalmol 113:1066–1073
7. Yamamoto S, Takeuchi S, Kamiyama M (1998) The short wavelength-sensitive cone electroretinogram in diabetes: relationship to systemic factors. Doc Ophthalmol 94:193–200
8. Yamamoto S, Hayashi M, Takeuchi M (1999) S-cone electroretinogram to Ganzfeld stimuli in patients with retinitis pigmentosa. Doc Ophthalmol 99:183–189
9. World Health Organization Media centre (2008) Marketers of electronic cigarettes should halt unproved therapy claims. http://www.who.int/mediacentre/news/releases/2008/pr34/en/. Accessed 1 April 2012
10. Okuno T, Minami M, Oku H, Sugasawa J, Ikeda T (2010) A case of unilateral impairment of short-wavelength-sensitive cone with sudden onset. J Jpn Ophthalmol Soc 114:527–533

Novel Mutations in Enhanced S-cone Syndrome 

Dear Editor:

Enhanced S-cone syndrome (ESCS) is a rare and unique retinal dystrophy with a pattern of autosomal-recessive inheritance.[1-3] Patients with ESCS show night blindness and high sensitivity to short-wavelength light, because of the 2-fold increased number of short-wavelength-sensitive cones (S cones) with absence of rods in the retina. Since the first discovery of mutations in the *NR2E3* gene on chromosome 15q23 in patients with ESCS,[4] >40 mutations have been reported as causes of ESCS and allied diseases (Fig 1, available online at http://aaojournal.org).

In this letter, we report novel mutations in the *NR2E3* gene that were discovered in 2 cases with ESCS.

Cases are 2 Japanese patients who were reported previously.[3] Case 1 was a 31-year-old man whose parents were consanguineous. His vision was 0.7 in the right eye and 0.3 in the left eye. Funduscopy revealed retinal degeneration surrounding the vascular arcade with cystic changes in both maculae (Fig 2, available online at http://aaojournal.org). Perimetry showed ring-shaped scotoma and electrophysiology showed unique responses corresponding to ESCS (Figs 3–6, available online at http://aaojournal.org). During 23-year clinical follow-up, clumped pigmentation has appeared in the retinal degeneration and the cystic changes in the foveal region have become ambiguous (Fig 2). His latest vision was 0.5 in the right eye and 0.3 in the left eye at age 53.

Genetic analysis revealed a novel nucleotide substitution (c.151G>A) in exon 2 homozygously, resulting in a novel missense mutation (a glycine-to-arginine substitution) at amino acid position 51 (p.G51R; Fig 7; available online at http://aaojournal.org).

Case 2 was a 78-year-old woman.[3] Funduscopy showed diffuse mild retinal degeneration with no pigmentation in both eyes (Fig 8, available online at http://aaojournal.org). Optical coherence tomography showed a subtle foveal schisis in the left eye, although the structure of the retina including the outer nuclear layer in the macular area was relatively well maintained (Fig 8). After cataract surgery, her vision improved to 0.3 in the right eye and 0.2 in the left.

Genetic analysis revealed compound heterozygous mutations of c.142C>T (exon 2) and c.311G>A (exon 3), resulting in an arginine-to-cysteine substitution at amino acid position 48 (p.R48C) and an arginine-to-glutamine substitution at amino acid position 104 (p.R104Q; Fig 7).

A daughter of case 2 who was asymptomatic and had normal fundus appearance showed only the p.R48C mutation heterozygously, that indicated she was an unaffected carrier relative (Fig 7).

NR2E3 protein, a photoreceptor-specific orphan nuclear receptor, plays an important role in the development and differentiation of rods and all cone classes. NR2E3 has 2 functionally important domains, namely, the DNA-binding domain (DBD) and the ligand-binding domain (Fig 1). Mutations within these domains result in serious dysfunction of NR2E3 protein leading to abnormal process of development and differentiation of multipotent progenitor cells to rods and cones.

Genetic analysis revealed a homozygous mutation (p.G51R) in case 1 and compound heterozygous mutations of (p.R48C) and (p.R104Q) in case 2. Among these mutations, (p.G51R) and (p.R48C) are novel as causative mutations of ESCS.

The mutation (p.G51R) found in case 1 resides in the first zinc finger of the DBD, and the compound heterozygous mutations (p.R48C and p.R104Q), which were found in case 2 reside in the first and second zinc fingers of the DBD. Because the zinc fingers are necessary for maintenance the structure of NR2E3 protein, these mutations in the zinc fingers of NR2E3 result in phenotypes as ESCS (Fig 1).

Clinically, case 1 with a homozygous missense mutation (p.G51R) showed typical features as ESCS, whereas case 2 with compound heterozygous mutations (p.R48C and p.R104Q) showed mild retinal degeneration and has kept some level of vision and construction of the macula despite advanced age. In the past, the mutation (p.R104Q) has never been reported except in 1 case, which demonstrated the normal structure and function of the macula with recordable rod electrophysiology.[5] These facts indicate the mutation (p.R104Q) may be correlated with the relatively mild clinical findings as ESCS.

We identified 2 novel missense mutations (p.G51R and p.R48C) as causes of ESCS. To our knowledge, the finding of case 1 is the longest-observed clinical case ever reported, and case 2 is the oldest case among all the patients with ESCS so far reported.

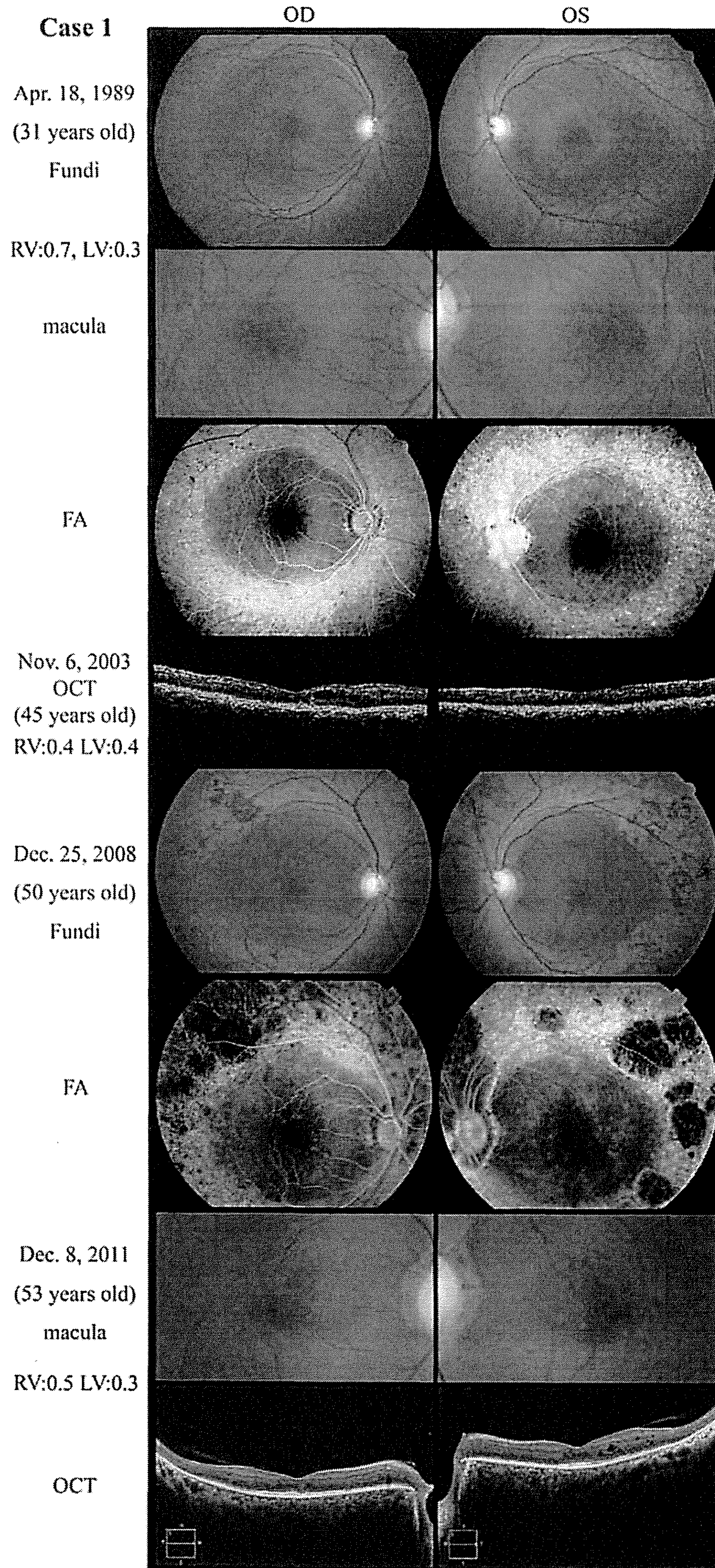
Kazuki Kuniyoshi, MD,[1] Takaaki Hayashi, MD,[2] Hiroyuki Sakuramoto, MD,[1] Akira Nakao, MD,[1]
Takashi Sato, MD,[1] Tomohiro Utsumi,[2] Hiroshi Tsuneoka, MD,[2] Yoshikazu Shimomura, MD[1]
[1]Department of Ophthalmology, Kinki University, Faculty of Medicine, Osaka, Japan; [2]Department of Ophthalmology, The Jikei University School of Medicine, Tokyo, Japan

References

1. Marmor MF, Jacobson SG, Foerster MH, et al. Diagnostic clinical findings of a new syndrome with night blindness, maculopathy, and enhanced S cone sensitivity. Am J Ophthalmol 1990;110:124–34.
2. Jacobson SG, Marmor MF, Kemp CM, Knighton RW. SWS (blue) cone hypersensitivity in a newly identified retinal degeneration. Invest Ophthalmol Vis Sci 1990;31:827–38.
3. Sato T, Kuniyoshi K, Nakao A, et al. Long-term observation of two cases of enhanced S-cone syndrome. J Jpn Ophthalmol Soc 2009;113:980–90.
4. Haider NB, Jacobson SG, Cideciyan AV, et al. Mutation of a nuclear receptor gene, *NR2E3*, causes enhanced S cone syndrome, a disorder of retinal cell fate. Nat Genet 2000;24:127–31.
5. Hayashi T, Gekka T, Goto-Omoto S, et al. Novel *NR2E3* mutations (R104Q, R334G) associated with a mild form of enhanced S-cone syndrome demonstrate compound heterozygosity. Ophthalmology 2005;112:2115–22.

Financial Support: This study was supported by grants from the Ministry of Health, Labour and Welfare of Japan and the Vehicle Racing Commemorative Foundation.

Figure 1. NR2E3 protein structure and mutations in cases presented in this letter and reported in past papers. Bold characters with no marks indicate mutations reported as a cause of enhanced S-cone syndrome (ESCS). Red characters and arrow indicate homozygous missense mutation discovered in Case 1 (p.G51R). Blue characters and arrows indicate compound heterozygous missense mutations discovered in case 2 (p.R48C and p.R104Q). p.G51R and p.R48C are novel mutations as causes of ESCS. adRP = autosomal-dominant retinitis pigmentosa; arRP = autosomal-recessive retinitis pigmentosa; CPRD = clumped pigmentary retinal degeneration; DBD = DNA-binding domain; del = deletion mutation; fs = frame shift of amino acids; LBD = ligand-binding domain.


Case 1
OD
OS
Apr. 18, 1989
(31 years old)
Fundi
RV:0.7, LV:0.3
macula
FA
Nov. 6, 2003
OCT
(45 years old)
RV:0.4 LV:0.4
Dec. 25, 2008
(50 years old)
Fundi
FA
Dec. 8, 2011
(53 years old)
macula
RV:0.5 LV:0.3
OCT