Photoreceptors, color vision [ENCYCLOPEDIA OF COLOR SCIENCE AND TECHNOLOGY]

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Synonyms

cone pigments, visual pigments, opsin genes, photoreceptor cells

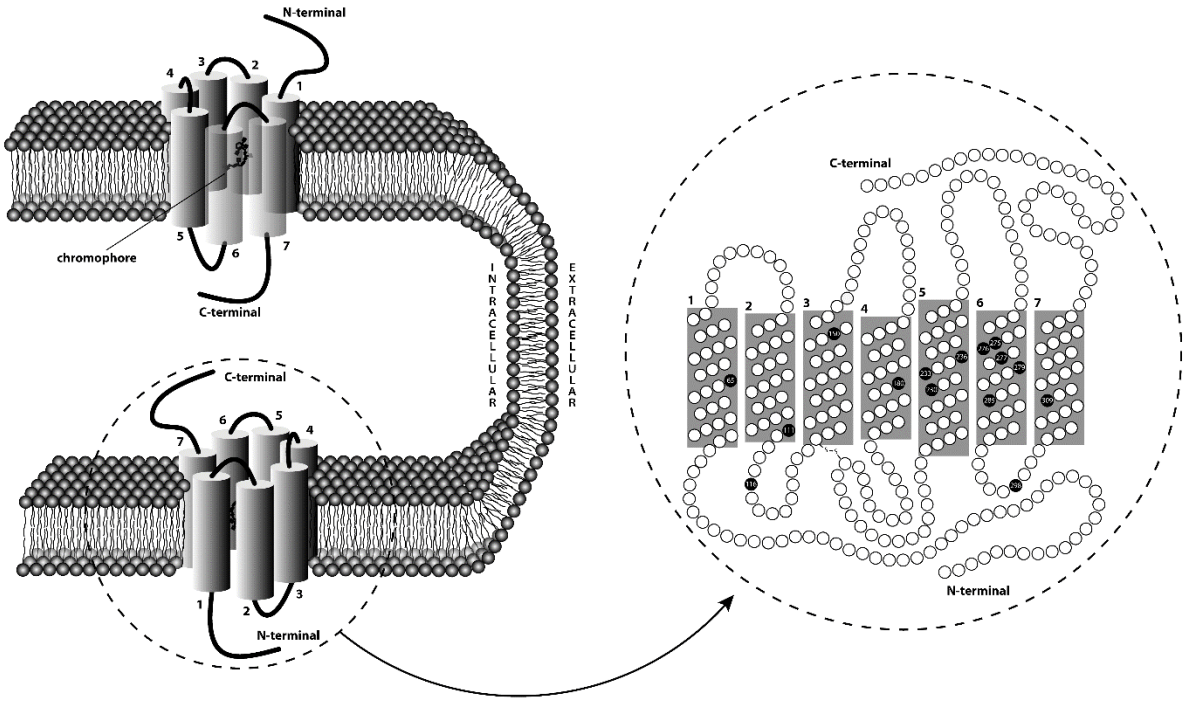
Definition

The expression and molecular structure of the genes encoding the human cone photopigments is the first step in determining our color vision. Alterations in these genes have consequences for the spectral sensitivity of the cone photoreceptors, which in turn affect how color-normal and color-deficient individuals see the world.

Overview

Normal trichromats can match any given color by combining three suitably chosen primaries (such as red, green and blue) in appropriate proportions. Color-deficient individuals differ from normal trichromats with respect to the proportions of the primaries required for a match: they may use the three primaries in unusual quantities or they may only use two primaries. The first type of variation is known as anomalous trichromacy, which is assumed to arise when three classes of cones are present, one of which contains a photopigment with an anomalous absorption spectrum. The second type of variation is known as dichromacy, which occurs if only two of the three classes of cones are present. Any of the three classes of cone – short (S), middle (M), or long (L) wavelength-sensitive – may be affected, manifesting in different color vision phenotypes. The different phenotypes are associated with predictable patterns of color-matching behaviour, which can be identified easily using psychophysical tests of color vision. The presence and sequence of the genes encoding the photopigment genes ultimately determines the individual's genotype and can be identified by examining their deoxyribonucleic acid (DNA). Research into the empirical relation between underlying genotype and expressed phenotype has led to improved understanding of the physiological mechanisms responsible for variations in human color vision.

Nathans and colleagues [1] were the first to utilize advances in molecular genetics to study human photopigment genes, using a technique that involves in vitro construction of DNA molecules to produce recombinant DNA. Photopigments are the light-absorbing molecules that mediate vision, with absorption maxima (λmax) at approximately 420 nm (S-cone), 530 nm (M-cone), and 560 nm (L-cone). Structurally, they consist of opsin – transmembrane heptahelical proteins of a single polypeptide chain, composed of either 364 (*OPN1LW* and *OPN1MW* for the L- and M-cones respectively) or 348 (*OPN1SW* for the S-cone) amino acids – bound to a chromophore: 11-*cis* retinal. Photon absorption by the pigment molecules causes isomerization of the chromophore from "11-*cis*" to "all-trans" form, which initiates a signal cascade, known as phototransduction. The binding socket site of the chromophore in both the cone and rod opsins is located in helix 7 (Figure 1).

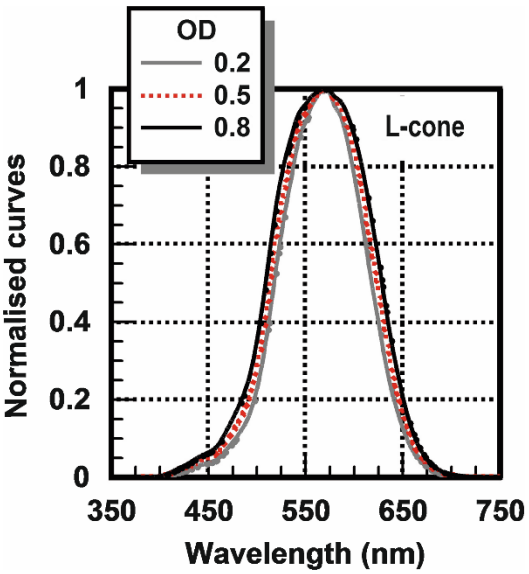


Photoreceptors, color vision, Fig 1 Arrangement of visual pigments in a cone photoreceptor. The infolding membrane of the cone outer segment is packed with photopigment molecules. The molecule consists of seven α-helices which span the membrane of the cell surrounding the chromophore: 11-*cis* retinal. The NH2 (N) terminus is extracellular, whereas the COOH (C) terminus is intracellular. Shown in the bottom right is the sequence of amino acids that make up this heptahelical molecule. White circles represent amino acids that are identical across the L- and M-cone pigments and black circles represent amino acids that are different. The substitutions at positions 180, 277 and 285 are believed to contribute most of the spectral difference between the M- and L-cone pigments. Adapted from Sharpe [2] and Nathans [1].

The precise λmax of a given pigment will be determined by the amino acid sequence of the opsin and the interaction of specific amino acids with retinal [3]. Whereas the λmax of 11-*cis* retinal is 375 nm [4, 5]], the exact amino acid sequence of opsin "spectrally tunes" the pigment to a specific wavelength [6, 7] by shifting it towards the "red" end of the spectrum. Research with retinal organoids suggests that the fate of a given cone cell is determined by thyroid hormone

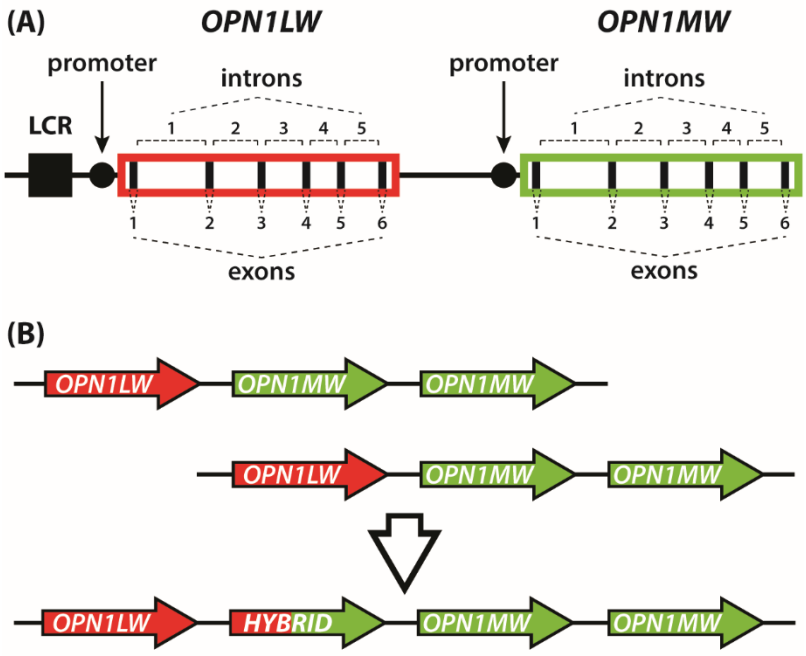
signalling, with specification of S-cones occurring early in development and the remaining cones being specified as L vs M later [8]. The number and distribution of the three cone classes is not equal, either between individuals or across a given retina. In the normal eye, S-cones comprise approximately 7-10% of the total cone population and are even sparser at the fovea [9, 10] which may account for some of the variation in chromatic sensitivity observed across the retina [11]. The remaining cones are specified as L or M; the proportion of which, unlike S-cones, is highly variable and has been shown to range from around 50-95% L-cones [12].

The genes encoding the S-cone pigments reside alone as a single copy on the q-arm (long arm) of chromosome 7 [13]. The genes encoding the L- and M-cone pigments reside on the q-arm of the X-chromosome, organized in a tandem array [1] of up to six exons (coding regions of DNA) separated by relatively long introns (non-coding regions of DNA) (Fig. 3). The S-cone pigment shows only 43 ± 1% analogy in the amino acid sequence when compared to either the M- or L-cone photopigments. In contrast, the M- and L-cone pigment genes are 96% homologous, differing only in 15 amino acids [2]. The approximate 30 nm spectral difference between these two visual pigments is attributable to substitutions at these particular amino acid positions confined to exons 2-5. The largest shifts in λmax are produced by substitutions at two key sites within exon 5: amino acid positions 277 (~7 nm) and 285 (~14 nm) (Fig. 1). These result in spectral shifts of 15-25 nm; the exact value depends on sequences in exons 2-4. Substitutions within exons 2-4 produce much smaller shifts of less than ~4 nm, and may be responsible for the subtle individual differences in color vision among normal and anomalous trichromats. Both in vitro methods to investigate protein sequence variation [1, 6] and in vivo methods to probe spectral sensitivity [14] have shown that amino acid substitutions in exon 2 contribute very little to spectral tuning (0.0-0.7 nm) [6, 14]. More recently, it has been speculated that the amino acid differences in exon 2 are involved in controlling the optical density of the L- and M-cone photopigments [15]. The optical density depends on the concentration of the photopigment in the cone outer segment, the length of the cone outer segment and also the extinction coefficient, which describes the probability of a photon being absorbed [16]. An increase in effective optical density of cones causes a broadening of the spectral sensitivity curve (Figure 2), such that if two genes that differ only in their exon 2 sequences are expressed, the resulting differences in the optical density of the photopigments may account for some residual color discrimination [15].



Photoreceptors, color vision, Fig 2 Theoretical spectral sensitivity curves for the L-cone sensitive pigment. Changes in the optical density of the cone pigment may occur from amino acid substitutions in exon 2, altering the stability of the molecule or the efficiency with which it absorbs light. For wavelengths near the peak, the optical density qualitatively mimics the difference that would be produced by a spectral shift.

The high homology of the L- and M-cone pigment genes suggests evolution from a single gene. Comparison of amino acid sequences indicates that S-cones and rod receptors arose first from a common ancestral receptor. From comparisons with contemporary New World monkeys, which have only two cone photopigments, it is thought that a long wavelength gene duplicated and diverged to originate the red and green photopigments, at the time when Old World monkeys (trichromatic) separated from New World monkeys [1, 17]. The location of the *OPN1LW* and *OPN1MW* genes on the X-chromosome can account for the larger number of (red/green) color-deficient men compared to women, as men have only one X-chromosome. The head to tail arrangement of the *OPN1LW/OPN1MW* genes makes them susceptible to mispairing during meiosis, leading to unequal crossing over between gene arrays. If the crossover occurs between genes, this will result in the deletion of a gene from one chromosome and its addition to the other, whereas a crossover within a gene will lead to the production of a hybrid gene that combines regions of the L and M genes into a single gene. Such hybrid genes are thought to be the genetic basis responsible for the majority of color vision defects [1].



Photoreceptors, color vision, Fig. 3 Schematic of the tandem array of L- and M-cones on the q-arm of the X chromosome. (A) The LCR (Locus Control Region) can activate only one of the promoter regions just upstream of a gene. The promoters are regulatory units upstream (or to the left) of the transcription site and regulate the rate of DNA transcription into RNA and hence the amount of opsin gene expression. The opsin-coding sequences are divided into exons (black bars). The intron sequences (gaps) are silent or non-coding and have no apparent function. (B) Schematic of unequal intragenic crossover that would produce hybrid genes. Adapted from Neitz and Neitz [18].

Figure 3 shows an example of how the formation of hybrid genes produces pigments with abnormal spectral sensitivity. The spectral sensitivity of the photopigment will depend on which of the *OPN1LW/OPN1MW* genes the crossover originated from [19]. Visual pigment gene

arrays for people with normal color vision have an *OPN1LW* gene in the most upstream (or leftmost) position, with one or more *OPN1MW* genes downstream (or to the right) of the *OPN1LW* gene. Normal trichromats usually have only one copy of *OPN1LW*, multiple copies of *OPN1MW* and possibly a number of hybrids [2]. There is good evidence from studies of gene expression in the retina and from studies involving genotype-phenotype relationships [20] that only the first two genes are expressed and play a significant role in color vision. Whereas normal trichromats have *OPN1LW* and *OPN1MW* occupying the two most proximal positions of the array from the Locus Control Region (LCR), anomalous trichromats instead have a hybrid gene positioned in either the first or second position. Deutan deficiencies arise when there is no M-sensitive photopigment, whereas protan deficiencies arise from a lack of L-sensitive photopigment. If there is only one opsin gene, or two with identical spectral sensitivity, the resulting phenotype will be dichromacy (deuteranopia or protanopia). If, however, the first two genes in the array encode opsins with different spectral sensitivity, as can be introduced by a hybrid, the result will be anomalous trichromacy (deuteranomaly or protanomaly) [7]. The propensity for the *OPN1LW* and *OPN1MW* genes to cross over creates the opportunity for multiple combinations, producing numerous polymorphisms and hybrid variants, which are thought to underlie the high variability in red/green color vision observed even within the normal population [18].

In addition to the creation of hybrid genes, mutations within the *OPN1LW/OPN1MW* array can produce cones that are non-functional and even degenerative, depending on the amount of correctly spliced precursor messenger ribonucleic acid (RNA) [21]. High resolution retinal imaging has shown that those with genes encoding functional (even if altered) opsin in one or both proximal positions of the array present with a contiguous mosaic of cone photoreceptors [22]. As such, other non-chromatic aspects of visual function in single or multi-gene dichromats are usually unaffected [23]. In contrast, retinal imaging in those with genes encoding non-functional opsin reveals variable disruption of the cone mosaic [24], which may be associated with other visual deficits, such as myopia [25].

The *OPN1SW* opsin gene sequence is nearly invariant in the human population; however further genotype-phenotype studies are yet to be performed to prove this. Intragenic crossover – the mechanism that permits the frequent manifestation of anomaly in protan and deutan defects – has no analogy in tritan defects. Six mutations have been established causing amino acid substitutions that perturb the structure or stability of the S-cone photopigment [13, 26], therefore strongly affecting the performance of the S-cone photoreceptors. On the other hand, no polymorphisms causing shifts in λmax have been reported so far and only one substitution was found in the coding sequences and exon-intron junctions, which has no impact on its spectral characteristics [27]. However, abnormalities as a result of genetic variation in *OPN1SW* may have less likelihood of being detected, as any small variations in λmax would be difficult to dissociate from individual variations in macular pigment and lens density measured psychophysically or in vivo. Testing patients with blue-cone monochromacy, for whom cone function is isolated to the S-cones [28], may enable detection of individual differences in S-cone spectral sensitivity, although its low prevalence (~1/100,000) limits the opportunities for such research studies.

Future directions

An important consideration in the study of human color vision is how spectral differences between photopigments translate to performance on color-related tasks. There are numerous retinal and cortical factors that influence chromatic discrimination; it is therefore insufficient to simply compare differences in λmax. For example, there have been shown to be large differences in L:M cone ratio [12] even among family members with the same genotype [25]; how such differences could interact with hybrid genes and mutations to affect color vision is not well understood. When color vision depends on subtle differences between L- and M-cone pigments, as in anomalous trichromacy, polymorphisms that might affect optical density as well as those that shift λmax must be accounted for. It has been suggested that a L/M separation greater than ~20 nm would be sufficient to account for normal color vision, implying that normal trichromats can, in principle, have visual pigments encoded by hybrid genes, providing that the λmax values of the two hybrids remains greater than 20 nm apart.

Changes in λmax, photoreceptor optical densities and/or post-receptoral amplification of cone signals appear to be the most important parameters that affect our red-green chromatic sensitivity. In addition to cone photoreceptors, rods and melanopsin also form part of the process [29], particularly under certain low lighting conditions [30] or in color deficiency or cone dysfunction [31, 32]. Establishing the relative importance of each of these parameters in determining an individual's color discrimination performance therefore remains a difficult task. A marriage of information derived from genetic analysis of pigment genes, in vitro and in vivo characterization of cone cells, psychophysical data on chromatic sensitivity, and theoretical modelling is therefore needed in order to produce a comprehensive description of mechanisms that underlie human color vision in all its complexity.

Cross-References

Chromophore

Macular pigment and lens density

Trichromacy

Dichromacy

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