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Mini Review

The molecular basis of variation in human color vision

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Common variation in red-green color vision exists among both normal and color-deficient subjects. Differences at amino acids involved in tuning the spectra of the red and green cone pigments account for the majority of this variation. One source of variation is the very common Ser180Ala polymorphism that accounts for two spectrally different red pigments and that plays an important role in variation in normal color vision as well as in determining the severity of defective color vision. This polymorphism most likely resulted from gene conversion by the green-pigment gene. Another common source of variation is the existence of several types of red/green pigment chimeras with different spectral properties. The red and green-pigment genes are arranged in a head-to-tail tandem array on the X-chromosome with one red-pigment gene followed by one or more green-pigment genes. The high homology between these genes has predisposed the locus to relatively common unequal recombination events that give rise to red/green hybrid genes and to deletion of the green-pigment genes. Such events constitute the most common cause of red-green color vision defects. Only the first two pigment genes of the red/green array are expressed in the retina and therefore contribute to the color vision phenotype. The severity of red-green color vision defects is inversely proportional to the difference between the wavelengths of maximal absorption of the photopigments encoded by the first two genes of the array. Women who are heterozygous for red and green pigment genes that encode three spectrally distinct photopigments have the potential for enhanced color vision.

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The human retina contains two types of photoreceptors, rods that are used for vision in dim light and cones that are used for vision in daylight and for color vision. Normal color vision in humans is trichromatic, being based on three classes of cone that are maximally sensitive to light at approximately 420 nm (blue cones), 530 nm (green cones), and 560 nm (red cones) (Fig. 1). Comparison by neural circuits of light absorption by the three classes of cone photoreceptors allows perception of red, yellow, green, and blue colors individually or in various combinations (Fig. 1).

The synthesis of a single class of visual photopigment with a distinct absorption spectrum in each cone photoreceptor cell is fundamental to color discrimination. Photopigments are G-protein coupled receptors composed of a protein moiety (opsin) that forms a transmembrane heptahelical bundle within which the chromophore 11-*cis* retinal is embedded (Fig. 2). The absorption of a single photon of light causes isomerization of the chromophore from the 11-*cis* to the all-*trans* configuration and the formation of an activated photopigment. This triggers the signal amplification cascade that culminates in closure of cGMP-gated membrane cation channels and hyperpolarization of the photoreceptor cell. Differences in spectral characteristics of the photopigments are dictated by the interaction of amino acid side chains at key positions in the opsin with the chromophore. For example, amino acids at positions 180, 277, and 285 are positioned to interact with and tune the spectrum of the chromo-

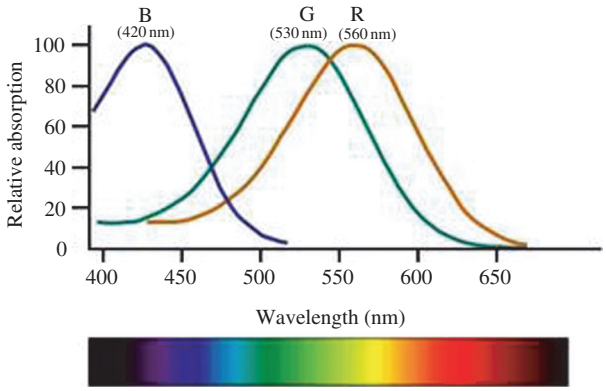

Fig. 1. The light absorption spectra of the three classes of cone photopigments of humans with normal trichromatic color vision. Relative absorption is plotted against wavelength in nanometers (nm), the wavelength of maximal absorption of the blue (B), green (G) and red (R) pigments are indicated above the curves. These three classes of cone are also found in Old World monkeys, some New World monkeys, and in apes, with small variation in absorption between species. Bottom panel: the visible spectrum as it appears to observers with normal color vision.

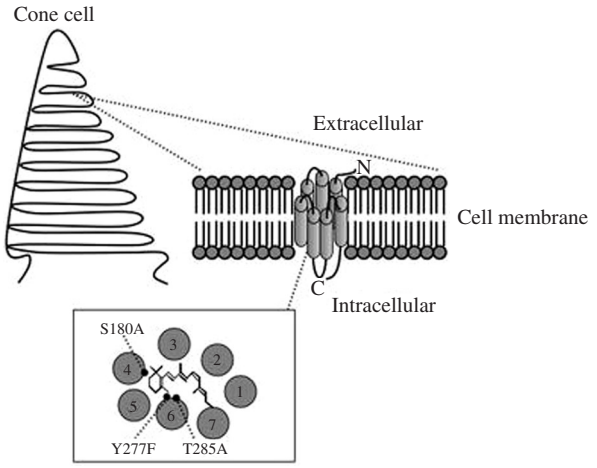

Fig. 2. Diagram of the enfolded membrane discs of the outer segment of a cone photoreceptor cell (upper left), the embedded photopigment molecules and the amino acids that interact with the chromophore to tune the spectrum. The outer segment of a cone is composed of about 1500 enfolded membrane discs that contain about 10 billion photopigment molecules. The protein (opsin) folds into a characteristic topographical model of a 7 α-helical transmembrane bundle within which the covalently linked chromophore 11-*cis* retinal is embedded. The α-helices are linked by loops that project into the extracellular and intracellular surfaces of the discs (modeled after the crystal structure of rhodopsin (43). Although the opsins have the same chromophore, the differences in their absorption curves are due to interaction of amino acid side chains with the chromophore. The majority of the difference in spectra between the red and green pigments is contributed by amino acids at positions 180, 277, and 285 (bottom panel, amino acids to the left of the residue numbers are found in the red and those to the right are found in the green pigments). However, in the red pigment, Ala or Ser can exist at position 180.

phore to generate either a red or a green pigment (Fig. 2) which differ in the wavelength of maximal absorption (λ_{max}) by approximately 30 nm (1–7). Differences at positions 277 and 285 (encoded by exon 5) contribute the majority of the difference in λ_{max} between the red and green pigments. In addition, differences at positions 116, 230, 233, and 309 play minor roles (6). The red and green opsins show 96% amino acid sequence identity but only 46% identity with the blue opsin (8).

The genes encoding the red (*OPN1LW*) and green (*OPNL1MW*) photopigments are arranged in a head-to-tail tandem array on the X-chromosome (Xq28) (8). The array is composed of a single red-pigment gene followed by one or more green-pigment genes (Fig. 3). Approximately 25% of male Caucasians have a single green-pigment gene, 50% have two while the rest have three or more green-pigment genes. However, it was shown that having more than one green pigment gene has no effect on either the relative ratio of red to green cones in the retina (9) or the color vision phenotype because only the first two genes (red and proximal green) are expressed in the retina. The blue-pigment gene (OPN1SW) is located on chromosome 7 (8).

A master switch for the genes of this locus, called the locus control region (LCR), located between 3.1 and 3.7 kb 5′ of the gene array was shown to be essential for expression of both the red and green-pigment genes. Individuals with deletions of the LCR have no functional red and green cones (blue cone monochromats) and are unable to see colors during daylight (10), however, they may have residual dichromatic

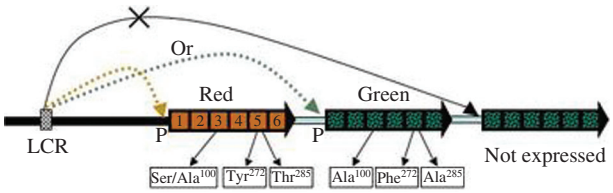

Fig. 3. Structure of the human X-chromosome-linked red/green gene array and model of mutually exclusive expression of the genes in retinal cones. The array consists of one red pigment gene followed by one or more green pigment genes. Squares represent the six exons of the red and green pigment genes, and lines represent intergenic and 5′ regions. The red and green pigment genes are approximately 15 and 13 kb, respectively, and the intergenic region is approximately 25 kb in length. The locus control region (LCR) is necessary for expression of genes in the array. Mutually exclusive expression of the two pigment genes in individual cone cells is fundamental to color vision. A model by which this is accomplishes involves permanent coupling (mediated by DNA binding proteins) of the LCR either to the red gene promoter (P) to form red cones, or to the promoter of the proximal green gene to form green cones. The LCR has a very low probability to couple to the distal green promoters. Exons that encode the three amino acids at positions 180, 277 and 285 that contribute the majority of the spectral difference between the red and green pigments are indicated. In addition, amino acids encoded by exon 2 (116) and by exon 4 (230 and 233) contribute minor differences.

color vision at twilight based on interaction between blue cones and rods (11). Subsequently, it was demonstrated in transgenic mice that the LCR plays an important role in cone-specific expression of the genes (12) and in their segregated expression in separate cones (13). Our group and that of Jeremy Nathans proposed a mechanism by which the LCR ensures segregated expression of the red and green pigments into their respective cone photoreceptors (9, 12–16). In this model, the LCR stably couples either to the red gene promoter to express the red pigment and form red cones or to the green gene promoter to form green cones (Fig. 3). The relative frequency of LCR coupling to the two promoters may contribute to the red-to-green cone ratio in the human retina, which ranges from 1:1 to 9:1 as measured electrophysiologically (17, 18) and by analysis of retinal mRNA (9, 17).

Molecular analysis of the gene arrays in normal and color vision defective subjects and of mRNA in male postmortem retinae revealed that only the red and the adjacent green genes of the array are expressed in the retina and determine the color vision (9, 15, 19). It is hypothesized that the third and more distal green pigment genes are too distant from the LCR to be activated.

Recently, it has become evident that common spectral variants of both the red and green (but not the blue) photopigments exist in the general population and impact the color vision phenotype. Therefore, this review will focus on the molecular basis of common variation in red-green color vision. The reader is referred to comprehensive reviews on various aspects of the genetics of variation in normal and defective color vision (20–22).

The molecular basis of variation in normal color vision

Subtle variation in color perception in the red-green region of the spectrum has been observed among females and males considered to have normal color vision, as determined by color matching tests (23–25). Male subjects were distributed into two groups with respect to the fraction of red in a mixture of red and green lights that matched a standard yellow light, proposed to be due to the presence of two spectral variants of the red pigment. Females showed a third group with intermediate matches, suggesting X-linked inheritance of two alleles of the red pigment gene (25).

Subsequently, studies by our group revealed the presence of a common polymorphism at amino acid residue 180 of the red pigment. In the Caucasian population, 62% of males have Ser and 38% have Ala at that position (2). Previous studies had indicated a role for position 180 in spectral tuning of the red and green pigments (1, 26). We hypothesized that the Ser180Ala polymorphism in the red pigment may account for the observed variation in normal color vision. To test this hypothesis, we investigated the association between the Ser180Ala polymorphism and color matching in 50 Caucasian males with normal color vision. In a color-matching test (anomaloscope), the observer is asked to match a standard yellow (590 nm) light with a mixture of red (644 nm) and green (541 nm) lights. The subjects fell into two overlapping groups with respect to the fraction of red in the mixture of red and green needed to match the yellow light. Higher sensitivity to red light (less red light required for matching) was strongly correlated with the presence of Ser at position 180 (2) (Fig. 4). Further evidence for this genotype-to-phenotype correlation was obtained on nine males who have a single red-pigment gene and no green-pigment gene (27). Two additional, but much less frequent, polymorphisms at positions 230 and 233 of the red pigment were also observed. Amino acids at these two positions are known to contribute (approximately 3–4 nm) to spectral tuning of the pigments, as determined by *in vitro* expression (5, 6), thus generating two additional spectral forms

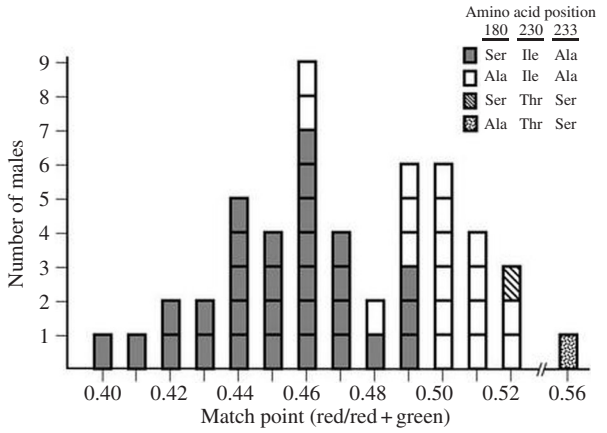

Fig. 4. Frequency distribution of the color matching points and the polymorphic amino acids of the red pigment. The color match point was determined by asking each of the 50 males with normal color vision to match a standard yellow light with a mixture of red and green lights. Each rectangle represents a male subject. Those who were more sensitive to red light used less of it in the mixture with green to match the yellow. The Ser180Ala polymorphism was significantly correlated with sensitivity to red. Those with Ser are more sensitive to red and perceive a deeper red in a natural scene than those with Ala. Two additional, but much less frequent, polymorphisms at positions 230 and 233 of the red pigment were also observed. Individuals who carried these variants were among the least sensitive to red light (2).

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The λ_{max} of a red pigment with Ser at position 180 was subsequently shown to be approximately 4–7 nm longer than that with Ala when expressed *in vitro* (4, 6) (Fig. 8). As will be discussed below, the Ser180Ala polymorphism also plays an important role in determining the severity of red-green color vision defects.

The Ser180Ala polymorphism was found in a number of ethnic groups. The frequency of the Ala allele among African Americans is 20% and among Japanese is 16% (20). This Ser180Ala polymorphism was also observed in the green pigment, but at a much lower frequency (96% Ala and 4% Ser). This polymorphism may have been generated by gene conversion from the green pigment gene that encodes Ala.

The molecular basis of variation in defective color vision

Phenotypic variation

In addition to variation within the normal range of red-green color vision, there is a wide range of variation in defective color vision, with severity ranging from very mild to very severe. A variety of tests are used to detect color vision defects. The spectral anomaloscope is the standard reference test for diagnosing red-green color vision defects. The instrument provides color matching of a standard yellow light with a mixture of red and green lights. Printed pseudoisochromatic plates (Ishihara, for example) are most widely used in the clinic (see reference (28) for detailed methods of diagnosis of color vision defects). Males who either have no functional red cones (protanopes, approximately 1% of males) (Fig. 5a) or no functional green cones (deuteranopes, approximately 1% of males) (Fig. 5b) have severe color vision defects. They are referred to as having dichromatic color vision that is based on blue plus either green or red cone classes). Males with milder color vision defects have, in addition to blue cones, either normal green plus anomalous green-like cones (protanomalous, approximately 1%) (Fig. 5c), or normal red plus anomalous red-like cones (deuteranomalous, approximately 5%) (Fig. 5d). These individuals have anomalous trichromatic color vision. The anomalous pigments are red/green chimeras encoded by hybrid genes.

The frequency of red-green color vision defects among populations of Northern European origin is around 8% of males and 0.5% of females, as determined by anomaloscopy in many studies; reviewed in (20, 21). The frequency of protanopia, protanomaly, and deuteranopia all range around 1%. Interestingly, deuteranomaly ranges between 4 and 5% of the male population. The frequency of color vision defects was found to be lower in practically all other populations as compared with Europeans. Among Chinese and Japanese, the frequency of red-green color vision defects is around 5%. Lower frequencies (4% or less) have been found among populations of African origin. The lower frequency among non-

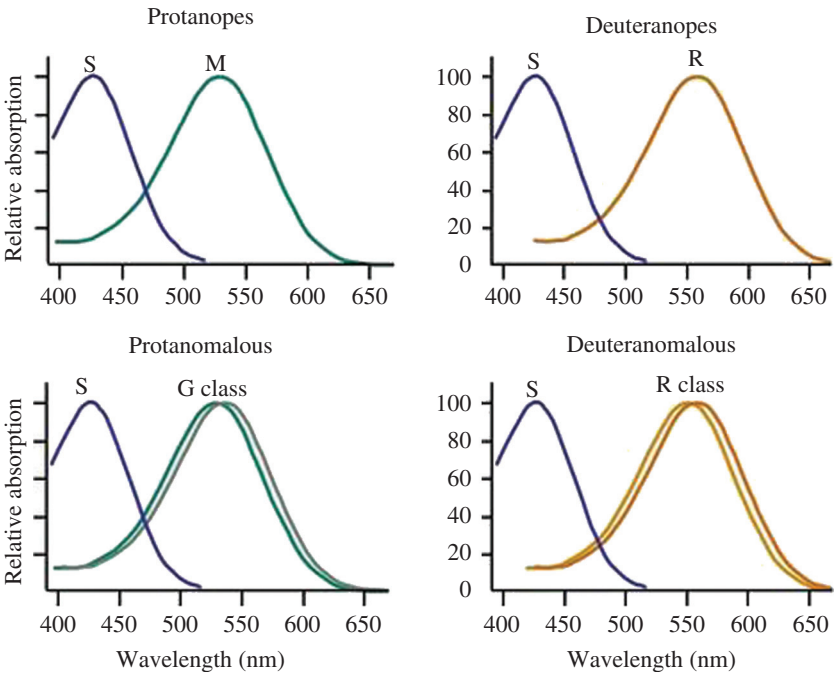

Fig. 5. Absorption spectra of retinal cones of males with defective color vision. The retina of a protanope has only blue and green cones, that of a deuteranope has blue and red cones and both have severe color vision defects. Protanomalous males have blue, green and green-like cones (G class); deuteranomalous males have blue, red and red-like cones (R class) and both have milder color vision defects.

Europeans is largely due to fewer deuteranomalous males. Deuteranopia is seen at frequencies of 1–2% in practically all populations, while protanopia occurs somewhat less frequently (0.2–1.2%). The reported frequencies of color vision defects vary with the method of testing. The frequency is slightly higher when initially detected by anomaloscopy than that determined using psudoisochromatic plate tests.

The normal red and green pigment spectra overlap significantly but are well separated (by λ_{max} approximately 30 nm). The ratio of light absorbed by the red and green cones at various wavelengths is the basis for color perception. Different colors (wavelengths of light) give different ratios of absorption. Protanomalous subjects have a normal green plus a green-like pigment with spectra that differ in λ_{max} by only approximately 2–6 nm, and deuteranomalous subjects have a normal red plus a red-like pigment that differ in λ_{max} by only approximately 2–9 nm. Therefore, these anomalous trichromats have diminished color discrimination capacity due to reduced ratios of light absorption from the red and green cones at various wavelengths.

There are rare cases of individuals who have no functional blue cones (tritanopes, <1:10,000) due to mutations in the blue-pigment gene on chromosome 7 (21). How males with normal, protanopic, deuteranopic, or tritanopic color vision perceive a natural scene is shown in Fig. 6.

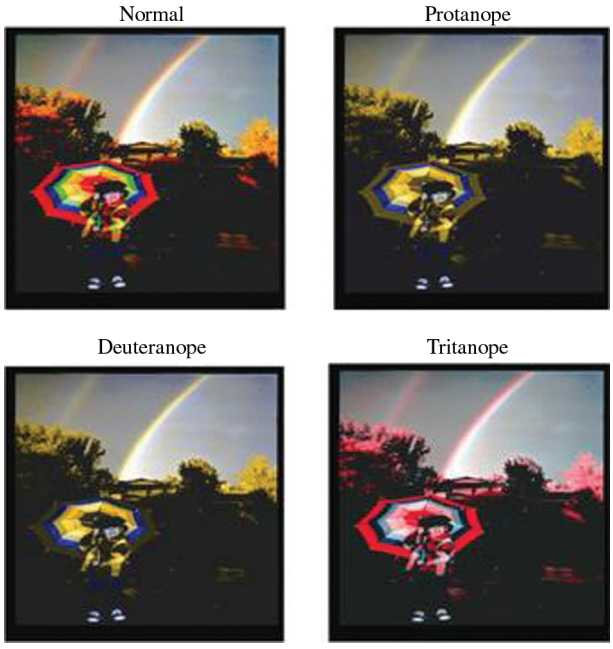

Fig. 6. Appearance of a natural seen to individuals with normal color vision and simulated images perceived by various types of color vision defective individuals. Simulation of images seen by protanopes, deuteranopes and tritanopes was performed by software from VisCheck (freely available at http://www.vischeck.com/).

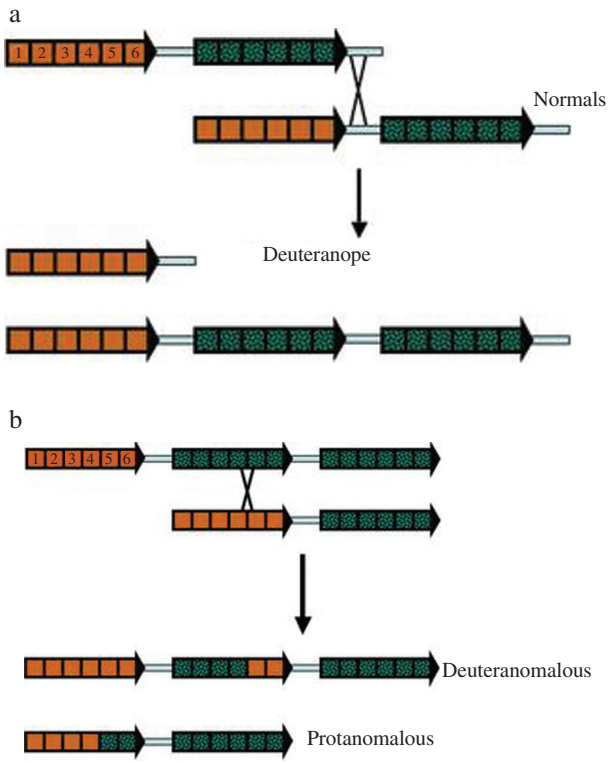

Fig. 7. Generation of deletions and of red/green hybrid genes that encode chimerical photopigments. (a) Homologous but unequal recombination in the intergenic region results in changes in the number of green pigment genes, including their deletion, as observed in deuteranopes. Squares represent the six exons of the red- and green-pigment genes. (b) Intragenic recombination leads to the formation of 5′-green-red 3′hybrid genes generally observed in males with deuteranomalous color vision defects, and of the reciprocal 5′ red-green 3′hybrid genes generally observed in males with protanomalous color vision defects. The normal green-pigment gene that occupies the third position of the array is not expressed in the retina and does not influence color vision (9, 44) (see Fig. 3).

Molecular basis

Cloning of the genes that encode the blue, red, and green photoreceptor pigments by Nathans and colleagues (8) paved the way to discovery of the molecular basis of the common red-green color vision deficiencies. The proximity and high sequence homology between the red- and green-pigment genes have predisposed this locus to frequent unequal or illegitimate crossing-over events between the two X-chromosomes during gamete formation in females. These illegitimate recombination events result either in changes in the number of green-pigment genes (including their deletion) (Fig. 7a) or in the formation of 5′ red-green 3′ and the reciprocal 5′-green-red 3′ hybrid genes (Fig. 7b) that encode chimerical opsins. Such

events have been shown to cause the majority of cases of red-green color vision defects (3, 29–33). A rare cause of such defects is a point mutation (C203R) that changes a highly conserved amino acid residue (33, 34). This mutation is known to inactivate the encoded photopigment and most likely result in loss of the photoreceptor cells in which it is expressed. Direct evidence that loss of functional cones in the retina could result from the expression of mutant pigments has recently been obtained by adaptive optics retinal imaging (35, 36). A recent study of 247 Japanese males with deutan (deuteranopic and deuteranomalous) color vision indicated an association of the defect with an A to C substitution at position −71 of the promoter of the M-pigment gene (37). Interestingly, in all deutans these A-7T substitutions were in the gene that occupies the second position of the array, while in subjects with normal color vision, the substitutions were in more distant positions. This is consistent with the previous observation that only the first two genes of the array contribute to the color vision phenotype. However, it is unlikely that the −71 substitution is the causative substitution because it can only reduce pigment gene expression and not result in the expression of an anomalous pigment. It is possible that this substitution is in linkage disequilibrium with the causative mutation.

Changes in gene number result from unequal recombination in the intergenic region whereas hybrid genes are generated by intragenic recombination. A variety of hybrid genes result from unequal recombination in different introns and encode chimerical pigments with different λ_{max} (Figs. 8a, b). Note that exon 5 encodes the two amino acids at positions 277 and 285 that account for the majority of the spectral difference between the red and green pigments. Therefore, the exchange of exon 5 converts a red pigment to a green-like pigment and *vise versa*. These chimerical pigments have significantly expanded the repertoire of spectrally distinct red-like and green-like pigments and have substantially widened variation of the color vision phenotype.

Whereas dichromats have severe color vision defects, anomalous trichromats vary in the degree of loss of color discrimination capacity. The severity of color vision defects among anomalous trichromats is strongly correlated with the difference in λ_{max} between the red and red-like pigments of deutans, and the green and green-like pigments of protans. The smaller the λ_{max} separation, the more severe is the defect (3, 31–33, 38) (Fig. 9). Because only the first two genes of the array are expressed in the retina, severity of anomalous trichromacy is determined by difference in $\Delta\lambda_{max}$ between the two pigments encoded by these two genes. Note that the Ser180Ala polymorphism plays an important role in the spectral separation between the red-green hybrid and normal pigments and therefore in the severity of both protan and deutan color vision defects.

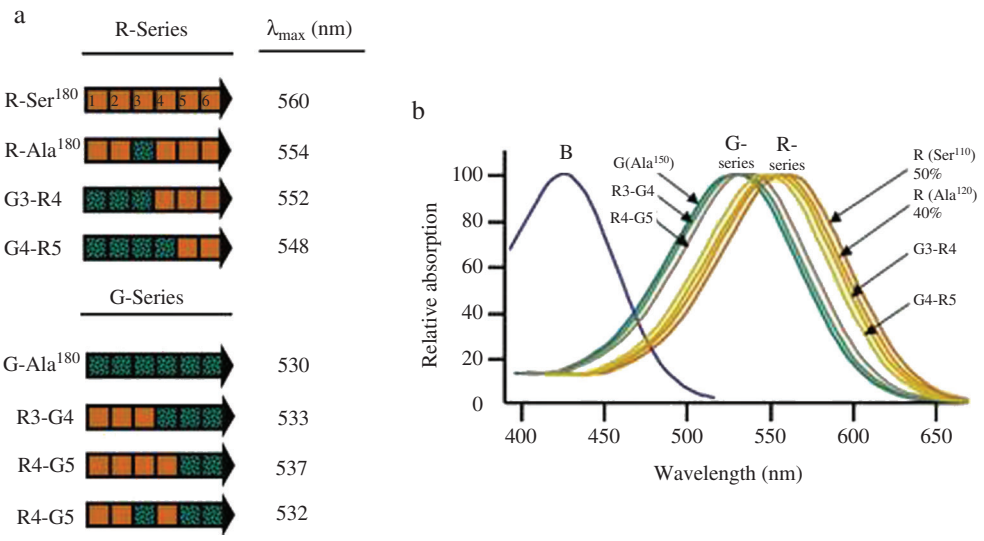

Fig. 8. Hybrid genes and the absorption spectra of the encoded chimerical pigments. (a) Shown are a variety of hybrids of the red and green pigment genes and the λ_{max} values of the encoded pigments. R2-G3, R3-G4, and R4-G5 represent hybrid genes formed as a result of recombination in introns 2, 3, and 4, respectively. The same applies for the G-R series of hybrids. R-series of genes encode red or red-like pigments and G-series encode green or green-like pigments. (b) The absorption spectra of normal and of some green-like (G-series) and red-like (red-series) chimerical photopigments that exist in the general population. A male expresses a combination of no more than two of such pigments. Note the role of the Ser180Ala of the red pigment in generating additional variants. The λ_{max} values are those of *in vitro* expressed and reconstituted photopigments (5, 6).

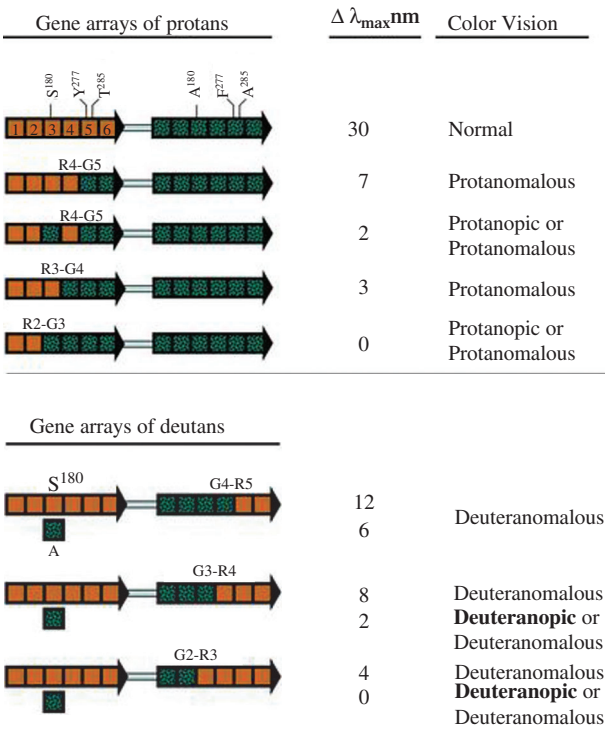

Fig. 9. The molecular basis of severity of the color vision defect. Shown are the genotype-color vision phenotype correspondence for protans and deutans. The severity of the color vision defect is strongly associated with the difference between the wavelengths of maximal absorption ($\Delta\lambda_{max}$) of the pigments encoded by the first two genes of the array. In general, the greater the difference, the milder is the color vision defect. When the $\Delta\lambda_{max}$ values are <2 nanometers (nm), the color vision defects are usually severe but classification into dichromacy or anomalous trichromacy is variable because of small contributions of cone optical density differences in a single retina. See Fig. 8 for designation of hybrid genes. The $\Delta\lambda_{max}$ values are derived from *in vitro* expressed and reconstituted photopigments (5, 6).

The correlation between severity of color vision defects and the inferred $\Delta\lambda_{max}$ values appears to be strong when the $\Delta\lambda_{max}$ values are 3 nm and above, with larger values being associated with milder defects. However, this correlation seems to become weak among males with $\Delta\lambda_{max}$ values of 0–2 who may have severe anomalous trichromacy or the more severe dichromacy. Even some of those who have a single red-pigment gene have tested as severe anomalous trichromats. One explanation for the lack of genotype-phenotype correlation at low $\Delta\lambda_{max}$ values is variation in optical density of cones that express pigments with identical or almost identical λ_{max} values. If the concentration of pigment is lower in enough cones that express the same pigment, then such cones will have a flatter absorption curve than other cones in the retina, providing a basis for extracting some chromatic discrimination by comparison of the two spectra. Such small effects of cone optical density differences are significant only when $\Delta\lambda_{max}$ values are small (38–40).

Color vision of females

Because the frequency of the Ser180Ala polymorphism in the red-pigment gene is 62 and 38%, respectively, based on Hardy–Weinberg statistics about 47% of Caucasian females are expected to be heterozygotes. Due to X-chromosome inactivation, about half of the red cones in heterozygous females will have Ala and the other half Ser at position 180. Therefore, such women would have four types of cone: blue, green, and two spectrally different red cones and have the potential for enhanced color vision capacity or full tetrachromatic vision. In support of this hypothesis, there is evidence that female heterozygotes for Ser/Ala have increased color discrimination capacity than homozygote females (41). However, full tetrachromacy has not been demonstrated.

Because the total frequency of color vision defects among Caucasian males is 8%, about 16% of females are expected to be heterozygote carriers of either protan or deutan gene arrays. The majority of women who carry gene arrays associated with color vision defects have normal color vision. However, some heterozygotes may be color vision defective due to an extremely skewed X-inactivation that by chance has inactivated most of their normal X chromosome and thus express the mutant X chromosome (14).

Female heterozygote carriers of anomalous trichromacy (approximately 6%) may have four instead of three classes of cone photoreceptors (for example, red, green, green-like, and blue) in their retinae that again may allow some to have enhanced color vision or full tetrachromatic color vision. In a study of such female carriers of anomalous trichromacy, Jordan and Mollon (42) provided evidence that some may have superior color discrimination capacity but not full tetrachromacy. Perhaps the human visual system is not plastic enough to accommodate full tetrachromatic color vision.

Females who are homozygous for genes associated with protan or deutan color vision would exhibit the respective color vision defects (frequency of approximately 0.5%). However, females who are compound heterozygotes for protan and deutan arrays would have normal color vision because their retinae would contain both normal red and green cone photoreceptors. Compound *trans*-heterozygotes for protanomaly and protanopia or deuteranomaly and deuteranopia exhibit the milder form (anomalous trichromacy) of color vision deficiency.

In conclusion, a large number of common variants of the red and green cone pigments have been generated by either gene conversion (as is proposed for the Ser180Ala polymorphism) or unequal recombination (as in the pigment chimeras) underlie the common variation in normal and defective color vision, respectively. The juxtaposition and high degree of sequence homology between the red and green pigment genes explain the relatively frequent occurrence of these genotypic and phenotypic variants.

Acknowledgement

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Glossary

Color vision phenotypes

Trichromatic color vision
Normal human color vision is trichromatic and is based on the three types of retinal cone photoreceptors that are sensitive in the blue, green, and red regions of the spectrum. Each photoreceptor cell contains a single type of photopigment that is composed of a protein moiety (opsin) to which the chromophore 11-*cis* retinal is covalently bound.

Dichromatic color vision
Severely defective color vision based on the use of only two types of photoreceptors, blue plus green (protanopia) or blue plus red (deuteranopia).

Anomalous trichromacy
Trichromatic color vision based on a blue, green, and an anomalous green-like photoreceptor (protanomaly), or a blue, red, and an anomalous red-like photoreceptor (deuteranomaly). The color vision defect is generally mild but may in certain cases be severe.

Protan
Protanopia and protanomaly.

Deutan
Deuteranopia and deuteranomaly.

Blue cone monochromacy
Severely defective color vision based on only blue cones during daylight. Such individuals may have residual dichromatic color vision based on rods and blue cones during twilight.

Hybrid genes

R3-G4 hybrid
5′Red-Green3′ hybrid gene in which exons 1–3 are derived from the red-pigment gene and exons 4–6 are derived from the green-pigment gene. This type of hybrid is associated with protan color vision defects.

R4-G5 hybrid
5′Red-Green3′ hybrid gene in which exons 1–4 are derived from the red-pigment gene and exons 5–6 are derived from the green-pigment gene. This type of hybrid is associated with protan color vision defects.

G3-R4 hybrid
5′Green-Red′ hybrid gene in which exons 1–3 are derived from the green-pigment gene and exons 4–6 are derived from the red-pigment gene. This type of hybrid is associated with deutan color vision defects.

G4-R5 hybrid
5′Green-Red′ hybrid gene in which exons 1–4 are derived from the green-pigment gene and exons 5–6 are derived from the red-pigment gene. This type of hybrid is associated with deutan color vision defects.

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