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Molecular genetics of colour vision deficiencies

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Common variation in colour vision exists among both colour normal and colour deficient subjects. Differences at a few amino acid positions that influence the spectra of the L and M cone pigments account for most of this variation. The genes encoding the L and M photopigments are arranged in head-to-tail arrays on the X-chromosome, beginning with the L and followed by one or more M pigment genes. The L and M pigment genes are highly homologous, which predisposed them to unequal crossing over (recombination) resulting in gene deletions and in formation of L/M hybrid genes that encode a variety of pigments with either L-like or M-like spectra that account for the majority of colour vision defects. Only the first two pigment genes of the L/M array are expressed in the retina and, therefore, need to be considered in predicting colour vision. A common single amino acid polymorphism (serine or alanine) at position 180 of the L-pigment plays an important role both in variation in normal colour vision and in the severity of colour vision defects. Blue cone monochromacy is a rare form of colour vision deficiency that results from mutations that abolish function of both the L and M pigment genes. All the above defects are inherited as X-linked recessive traits. Tritanopia is also a rare autosomal dominant colour vision defect caused by mutations in the S pigment gene located on chromosome 7. Total colour blindness (achromatopsia or rod monochromacy) is a rare autosomal recessive trait caused by mutations in genes encoding the proteins of the photoreceptor cation channel or cone transducin that are essential for function of all classes of cone.

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Humans normally have trichromatic colour vision and possess three distinct classes of retinal cone photoreceptors. These cones contain either short-wave sensitive (S), middle-wave sensitive (M) or long-wave-sensitive (L) photopigments. Colour perception results from comparison of the outputs of all three classes of cone. The L, M and S photopigments have overlapping spectra with peaks of maximal absorption (λ_{max}) at 560, 530 and 420 nm, respectively. The 30 nm difference between the L and M pigments is accounted for by differences in amino acids at three positions: Ala 180 Ser (~4 nm), Phe 277 Tyr (~10 nm) and Ala 285 Thr (~16 nm), with the amino to the left of the number being in the M pigment and that to the right being in the L pigment. Trichromatic colour perception relies on comparison between outputs from these three cone photoreceptor classes. Therefore, the correct overlap between the spectra of cones is critical for colour discrimination.

All Old World primates and some New World primates have trichromatic colour vision. In the New World primates, trichromacy is limited to a subset of females because of polymorphisms in the single X-chromosome linked pigment gene. Due to X-chromosome inactivation, females who are heterozygous for a polymorphism that influences pigment

spectral tuning would have three classes of cone in their retinae and trichromatic colour vision. The majority of the other mammals have dichromatic colour vision.[1] The introduction of trichromacy into the Old World lineage occurred about 40 million years ago as a result of duplication of the ancestral middle-long photopigment gene on the x-chromosome, followed by their divergence into the L and M pigment genes. There is evidence to suggest that the evolution and maintenance of trichromatic colour vision among primates is associated with the advantage of being more efficient than dichromats in detecting particular ripe fruits against a background of leaves in dappled light.[2-5] Soon after cloning of the cone photopigment genes and deduction of the sequence of the encoded pigments,[6-7] the molecular basis of red-green and blue colour vision defects was elucidated[8-9] and genotype-to-colour vision phenotype emerged.[10-13]

The L and M photopigments exist in several forms that are generated by formation of L/M hybrid genes and by a common polymorphism at position 180 of the L pigment.[14] There is the group of pigments that is L-like and another that is M-like, however, each cone photoreceptor contains one of these pigments. Individuals who have different combinations of these pigments largely explain variation in normal and defective colour vision in the population.

The red-green colour vision deficiencies, which are inherited as X-chromosome recessive traits, are by far the most common, reaching an incidence as high as eight per cent among males of northern European extraction and, for unknown reasons, are lower (ranges between one and five per cent) among other ethnic groups.[15] The other forms are rare. This review focuses on describing recent advances in our understanding of the molecular mechanisms underlying the inherited colour vision deficiencies. For further detailed information the reader is referred to recent reviews on this topic.[15-18]

CLASSES OF RED-GREEN COLOUR VISION DEFECTS

Red-green colour vision defects are a group of abnormalities that can be divided into four subclasses based on severity and on the type of cone photoreceptor pigment that is missing or is anomalous (Table 1). When either the L or M photoreceptor is completely absent, colour vision is dichromatic rather than trichromatic. Dichromatic colour vision is dependent on the S and either L or M cones. Dichromats have severely deficient colour vision in that they perceive the visible spectrum as lacking red, orange, green, blue and cyan.[15] Those who lack the L-sensitive cones are referred to as protanopes and those who lack the M-sensitive cones are called deuteranopes. The frequency of each of these traits in the Caucasian population is approximately one per cent. The other two classes of red-green colour vision defects are due to the presence of either an anomalous L (L′) or anomalous M (M′) pigments. These defects are milder than dichromatic defects and individuals who have them are referred to as anomalous trichromats. Green and red colours are not absent from the spectrum but appear weakened in intensity. Deuteranomaly is considered to be the mildest anomaly. Anomalous trichromats who possess normal M- and L′-sensitive cones (in addition to normal S) are referred to as protanomalous trichromats, and those who possess normal L- and M′-sensitive cones are referred to as deuteranomalous trichromats (Table 1). The frequency of deuteranomaly in Europeans ranges between four and five per cent, while the frequency of protanomaly is about one per cent.

In protanomals, the λ_{max} of the L′ pigments is very close to that of the normal M (difference of two to seven nanometres instead of the 28 nm difference between M and L). Similarly, the λ_{max} of the M′ pigments is very close to that of the normal L. The significant reduction in the overlap between the L and M spectra is the basis for loss of colour discrimination capacity in anomalous trichromats. Considerable variation in the severity of the trichromatic abnormalities (protanomaly and deuteranomaly) has been observed. The severity of deuteranomaly is roughly correlated with the spectral separation between the normal and anomalous pigments expressed in the retina. As would be expected, the greater the separation, the milder is the defect.[11,13,19]

INHERITANCE OF RED-GREEN COLOUR VISION DEFECTS

Red-green colour vision defects are inherited as X-chromosome linked recessive traits. This pattern of inheritance is illustrated in Figure 1. The general pattern observed is that of a colour-defective male transmitting the defect through his carrier daughter (normal colour vision) to half of his grandsons. Because of the high frequency of X-linked colour vision defects among males, it is estimated that about 16 per cent of women are carriers of red-green colour vision defects (most of whom have normal colour vision) and if they marry a colour defective male, they may produce colour-defective female offspring (Figure 1).

MOLECULAR GENETICS OF RED-GREEN COLOUR VISION DEFECTS

Nathans, Thomas and Hogness[6] determined the sequence of the genes that encode the three cone photopigments. The L and M pigment genes constitute an array of one L and one or more M pigment genes arranged head-to-tail.[20] They and other groups established that the majority of males with red-green colour vision defects have arrays that suffered either deletion of the M pigment gene or contained full-length hybrid genes consisting of portions of both L and M pigment gene segments that result from unequal (illegitimate) recombination between the highly homologous L and M pigment genes (98 per cent identity in DNA sequence of exons, introns and intergenic regions).

With few exceptions, the deletion of L pigment genes was associated with deuteranopia (Figure 2A), 5' M-L hybrid genes with either deuteranomaly or deuteranopia and 5' L-M hybrids with either protanopia or protanomaly[8,10,11] (Figure 2B). Hybrid

Class	Frequency	Retinal cones	Inheritance
Normal		(S) (M) (L)	
Protanopia (severe)	1%	(S) (M) —	X-linked recessive
Protanomaly (mild	1%	(S) (M) (L′)	X-linked recessive
Deuteranopia (severe)	1%	(S) (L) —	X-linked recessive
Deuteranomaly (mild)	5%	(S) (L) (M′)	X-linked recessive
Tritanopia (mild-severe)	1/1000	— (M) (L)	Autosomal dominant
Blue cone monochromacy (very severe)	<1/100,000	(S) — —	X-linked recessive
Achromatopsia (very severe)	1/30,000	— — —	Autosomal recessive

Table 1. Classes of colour vision defects. L′ cones (circles) contain anomalous L pigments that have absorption maxima close to that of normal M and are encoded by L-M pigment gene hybrids. M′ cones contain anomalous M pigments that resemble normal L and are encoded by M-L pigment gene hybrids. (-)$_{7}$ absence of cone class.

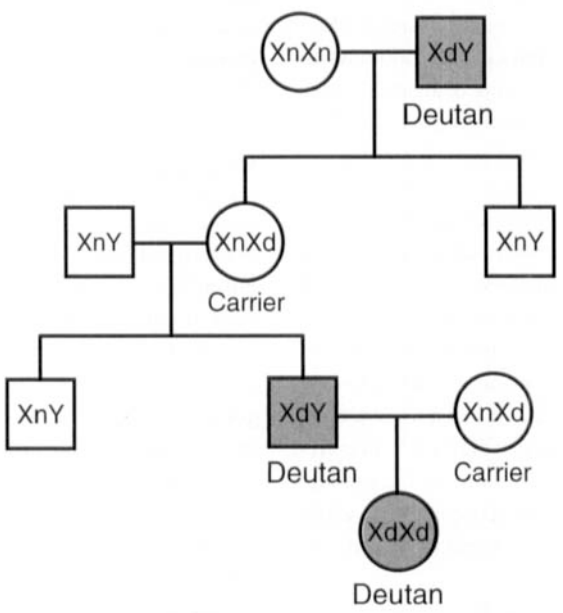


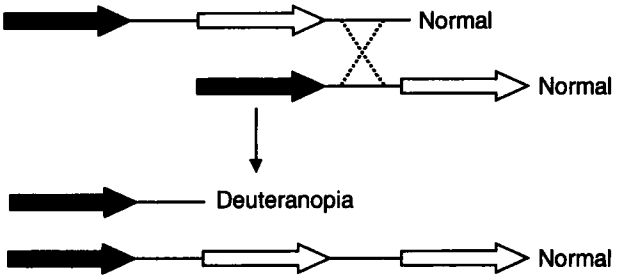
Figure 1. A typical pattern of inheritance of a red-green colour vision defect. Xn and Xd denote X-chromosomes with normal and colour-defective (deutan) colour vision genes, respectively. Y denotes the Y-chromosome. Circles and squares represent females and males, respectively. Shaded circles and squares indicate colour defective (deutan) colour vision. All other individuals, including carrier females, have normal colour vision.

genes are associated with dichromatic colour vision, when the pigment they encode is identical or near identical in spectrum to the normal pigment. For example, in a male with deutan colour vision deficiency, if his L and M′ pigments have absorption maxima (λ_{max}) that are separated by three to seven nanometres, he would have deuteranomalous colour vision. On the other hand if the two pigments have absorption maxima that are identical or differ by one nanometre, deuteranopic colour vision would be predicted (Figure 3).

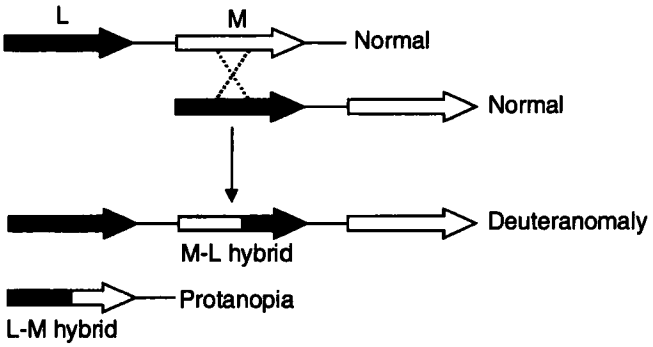
The order of the L and M pigment genes in the array influences their expression in the retina and their contribution to colour vision. The idea that not all the genes of the X-linked array are expressed in the retina and contribute to colour vision stemmed from the observation that males, whose arrays comprise one L, one M-L hybrid and one or more M pigment genes, may have either normal or deuteranomalous colour vision. Studies of gene expression in the retina and of correlation between gene order and the colour vision phenotype established that only the first two genes of the array (L and the adjacent gene) are expressed in the retina sufficiently to influence colour vision.[21-23] Therefore, the pigments encoded by only the first two genes of the array need to be considered in predicting the colour vision phenotype. Deutan colour vision results if the M-L hybrid gene occupies the second position of the array, and normal colour vision results if the hybrid occupies the third or more distal positions (Figure 4). So far, the technology for determining gene order is applicable only to arrays containing two or three genes. Therefore, if an M-L hybrid gene exists together with more than one normal M pigment genes (more than a total of three genes in the array), presently, it is not possible to determine if the hybrid gene occupies the second position in the array to predict the colour vision phenotype.

The genetics of colour vision in females and the potential for tetrachromacy

Female heterozygotes for the X-linked colour vision defects are common among



2a. Shown are gene arrays in a female with the L pigment gene (filled arrows) followed by an M pigment gene (open arrows). Pairing between the two X-chromosomes during gamete formation is sometimes out of register, allowing crossing over to occur within the intergenic regions (thin lines) of the L and M pigment genes. This results in deletion of the M pigment genes from one chromosome and an increase in the number of M genes in the other. This explains the observed polymorphism in the number of M-pigment genes in the array.



2b. Unequal crossing over within the L and M pigment genes results in the formation of L-M and M-L hybrid genes that encode a variety of anomalous pigments, depending on where along the genes the cross-over occurred. Filled and open segments of the arrows represent L and M pigment gene segments, respectively.

Figure 2. Deletions and hybrid gene formation resulting from unequal crossing between the L and M pigment genes

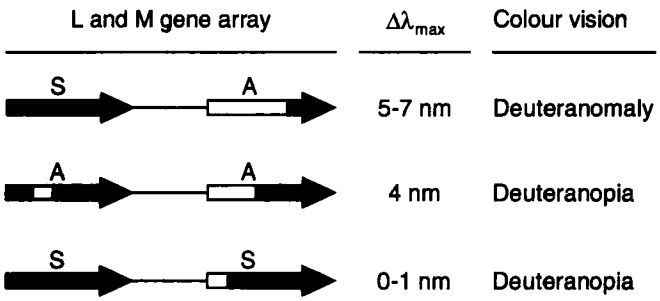


Figure 3. Spectral separation between pigments encoded by the first two genes of the array is correlated with severity of colour vision defect. S and A represent the amino acids serine and alanine at position 180 of the L pigment gene. The L pigment gene is highly polymorphic at this site (60 per cent S and 40 per cent A). Alanine is the amino acid most often found in the M pigment gene. This polymorphism contributes to spectral tuning of the pigment. The λ_{max} of the pigment with S is about four nanometres longer than that with A. Shown are the differences ($\Delta\lambda_{max}$) between the pigments encoded by the first two genes of each array in a male.

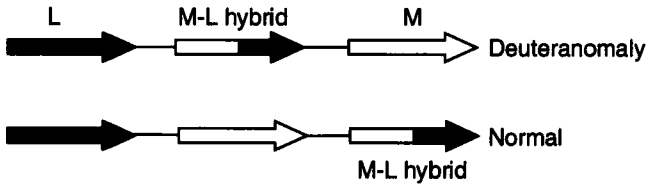


Figure 4. The role of gene order in red-green colour vision. Shown are two X-chromosome arrays, each comprising L, M and M-L hybrid genes. As only the first two genes of the array are expressed in the retina, a male with the top array is colour vision deficient since he cannot express the normal M. A male with the bottom array expresses both normal M and L pigment genes but not the hybrid.

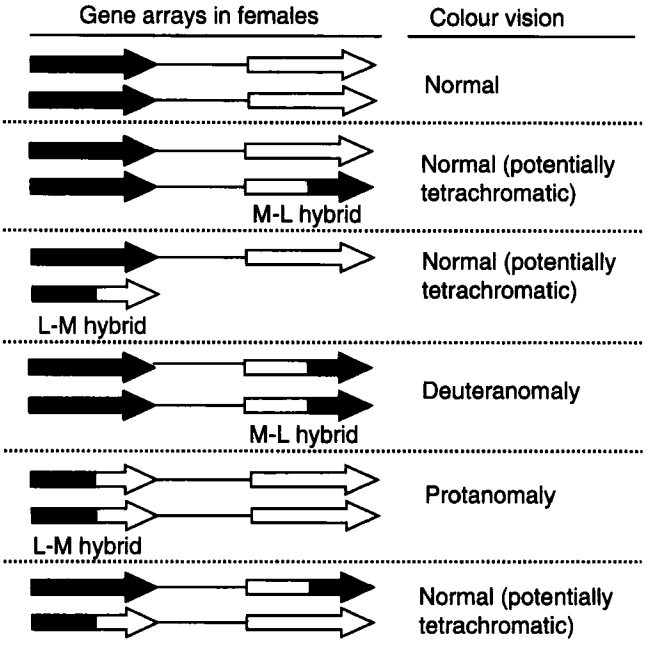


Figure 5. The genetics of red-green colour vision defects in females. Shown are diagrams of X-chromosome pairs of L and M gene arrays carried by females. Heterozygote carriers of M-L (deutan) and L-M (protan) arrays usually have normal and potentially tetrachromatic colour vision. Homozygotes for these hybrid genes have colour vision deficiency. Double heterozygotes for protan and deutan arrays (bottom pair) have normal and potentially tetrachromatic colour vision.

Caucasians and usually do not manifest colour vision defects. Due to X-chromosome inactivation during early development, heterozygotes are mosaics for two populations of cones, one expressing visual pigment genes encoded by an X-chromosome that would cause colour vision defects in males, and the other expressing genes that would confer normal colour vision on a male. In support of this, patches of defective colour perception were detected by shining a very narrow beam of red or green light into the retinas of female heterozygotes for X-linked colour vision defects.[24] The majority of heterozygote women (carriers of colour vision defects) have normal colour vision (Figure 5). However, some heterozygotes may have colour vision defects 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.[25]

Interestingly, some of the female heterozygotes may have four instead of three classes of cone photoreceptors (for example, L, M, M´ and S) in their retinae that may allow some to have tetrachromatic colour vision.[26] Females who are homozygous for genes associated with protan or deutan colour vision would exhibit the respective colour vision defects. However, females who carry one array associated with protan and another array associated with deutan colour vision would have normal colour vision, as their retinae would contain normal L and M cone photoreceptors.

Blue cone monochromacy (BCM), also known as X-chromosome linked incomplete achromatopsia is a rare X-linked ocular disorder, characterised by severely reduced colour discrimination capacity, poor visual acuity, infantile nystagmus and photophobia. Sometimes, it is associated with progressive macular atrophy. Subjects with BCM have no functional L and M cones but preserve S cone and rod function. Under photopic conditions, BCM individuals experience total colour blindness, while at intermediate light levels, interactions between rod and blue cone signals allows for crude hue discrimination.

The causes of BCM are mutations in the L and M pigment genes or in a region located near the L pigment gene that acts as a major regulatory region (called the locus control region, LCR) for expression of both the L and M pigment genes.[9,27] Deletions encompassing the LCR are a common cause of BCM.

Tritan or blue-yellow colour vision defects

Tritan colour vision deficiency is due to defective S cones and is characterised by blue-yellow colour confusion. It is a rare (less than 1/1000) autosomal dominant trait with severe (tritanopia) and mild (tritanomaly) forms. Mutations in the S pigment gene, located on chromosome 7, have been implicated in causing tritanopia.[28,29] The diagnosis of tritan defects is not simple. The most frequently used test is based on the Moreland equation, in which an observer is asked to match a mixture of lights at 436 nm (indigo) and 490 nm (green) to a cyan standard (fixed ratio of 480 and 580 nm) light.

Achromatopsia

Achromatopsia, also referred to as total colourblindness or rod monochromacy is a rare (prevalence of 1 in 30,000) autosomal recessive trait characterised by loss of function of all cone classes, severe photophobia under daylight conditions and nystagmus. Visual acuity is strongly reduced to less than 0.2 and colour discrimination is impossible. This trait is caused by mutations in *CNGA3* and *CNGB3* genes that encode the channel-forming α- and β-subunits of the heterotetrameric cone photoreceptor cGMP-gated (CNG) channel, respectively,[30-32] (see review by Deeb and Kohl[17]).

Mutations in the *GNAT2* gene on chromosome 1p13 have been shown to account for a small percentage (approximately two per cent) of this rare disorder.[33] *GNAT2* encodes the cone-specific α-subunit of transducin, a protein that couples to the cone visual pigments and is essential for transducing the signal resulting from activation of the cone pigments by light.

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REFERENCES

1. Jacobs GH. The distribution and nature of colour vision among the mammals. *Biol Rev Camb Philos Soc* 1993; 68: 413-471.
2. Regan BC, Julliot C, Simmen B, Vienot F, Charles-Dominique P, Mollon JP. Frugivory and colour vision in Alouatta seniculus, a trichromatic platyrrhine monkey. *Vision Res* 1998; 38: 3321-3327.
3. Regan BC, Julliot C, Simmen B, Vienot F, Charles-Dominique P, Mollon JP. Fruits, foliage and the evolution of primate colour vision. *Philos Trans R Soc Lond B Biol Sci* 2001; 356 (1407): 229-283.
4. Smith AC, Buchanan-Smith HM, Surridge AK, Osorio D, Mundy NL. The effect of colour vision status on the detection and selection of fruits by tamarins (Saguinus spp.). *J Exp Biol* 2003; 206 (Pt 18): 3159-3165.
5. Dominy NJ, Svenning JC, Li WH. Historical contingency in the evolution of primate color vision. *J Hum Evol* 2003; 44: 25-45.
6. Nathans J, Thomas D, Hogness DS. Molecular genetics of human color vision: the genes encoding blue, green, and red pigments. *Science* 1986; 232 (4747): 193-202.
7. Nathans J. The genes for color vision. *Sci Am* 1989; 260: 42-49.
8. Nathans J, Piantanida TP, Eddy RL, Shows TB, Hogness DS. Molecular genetics of inherited variation in human color vision. *Science* 1986; 232 (4747): 203-210.
9. Nathans J, Davenport CM, Maumenee IH, Leris RA, Hejtmancik JF, Litt M, Lovrien V, Weleber R, Bachynski B, Zwas F et al. Molecular genetics of human blue cone monochromacy. *Science* 1989; 245 (4920): 831-838.
10. Deeb SS, Lindsey DT, Hibiya Y, Sanocki E, Winderickx J, Teller DV, Motulsky AG. Genotype-phenotype relationships in human red/green color-vision defects: molecular and psychophysical studies. *Am J Hum Genet* 1992; 51: 687-700.
11. Neitz J, Neitz M, Kainz PM. Visual pigment gene structure and the severity of color vision defects. *Science* 1996; 274 (5288): 801-804.
12. Neitz M, Neitz J. Molecular genetics of color vision and color vision defects. *Arch Ophthalmol* 2000; 118: 691-700.
13. Jagla WM, Jagle H, Hayashi T, Sharpe LT, Deeb SS. The molecular basis of dichromatic color vision in males with multiple red and green visual pigment genes. *Hum Mol Genet* 2002; 11: 23-32.
14. Winderickx J, Lindsey DT, Sanocki E, Teller DV, Motulsky AG, Deeb SS. Polymorphism in red photopigment underlies variation in colour matching. *Nature* 1992; 356 (6368): 431-413.
15. Sharpe LT, Stockma A, Jagle H, Nathans J. Opsin genes, cone photopigments, color vision and color blindness. In: Gegenfurtener KR, Sharpe LT, eds. Color Vision: From Genes to Perception. Cambridge, UK: Cambridge University Press; 1999.
16. Motulsky AG, Deeb SS. Color vision and its genetic defects. In: Scriver CR, Baudet AL, Sly WS, Valle D, eds. The Metabolic and Molecular Bases of Inherited Disease. Eighth ed. Vol IV. New York: McGraw-Hill, 2001: p 5955-5976.
17. Deeb SS, Kohl S. Genetics of color vision deficiencies. *Dev Ophthalmol* 2003; 37: 170-187.
18. Neitz M, Neitz, J. Molecular genetics of human color vision and color vision defects. In: Chalupa LM, Werner J, eds. The Vision Neurosciences. Vol 2. Cambridge, MA: MIT Press; 2004; p 974-988.
19. Crognale MA, Teller DY, Motulsky AG, Deeb SS. Severity of color vision defects: electroretinographic (ERG), molecular and behavioral studies. *Vision Res* 1998; 38: 3377-3385.
20. Feil R, Aubourg P, Heilig R, Mandel JL. A 195-kb cosmid walk encompassing the human Xq28 color vision pigment genes. *Genomics* 1990; 6: 367-373.
21. Winderickx J, Battisti L, Motulsky AG, Deeb SS. Selective expression of human X chromosome-linked green opsin genes. *Proc Natl Acad Sci U S A* 1992; 89: 9710-9714.
22. Yamaguchi T, Motulsky AG, Deeb SS. Visual pigment gene structure and expression in human retinae. *Hum Mol Genet* 1997; 6: 981-990.
23. Hayashi T, Motulsky AG, Deeb SS. Position of a 'green-red' hybrid gene in the visual pigment array determines colour-vision phenotype. *Nat Genet* 1999; 22: 90-93.
24. Grutzner P, Born G, Hemminger HJ. Coloured stimuli within the central visual field of carriers of dichtomatism. *Mod Probl Ophthalmol* 1976; 17: 147-150.
25. Jorgensen AL, Philip J, Raskind WH, Matsushita M, Christensen B, Dreyer V, Motulsky AG. Different patterns of X inactivation in MZ twins discordant for red-green color-vision deficiency. *Am J Hum Genet* 1992; 51: 291-298.
26. Jordan G, Mollon JD. A study of women heterozygous for colour deficiencies. *Vision Res* 1993; 33: 1495-1508.
27. Nathans J, Maumenee IH, Zrenner E, Sadowski B, Sharpe LT, Lewis RA, Hansen E, Rosenberg T, Schwartz M, Heckenlively JR et al. Genetic heterogeneity among blue-cone monochromats. *Am J Hum Genet* 1993; 53: 987-1000.
28. Weitz CJ, Miyake Y, Shinzato K, Montag E, Zrenner E, Went LN, Nathans J. Human tritanopia associated with two amino acid substitutions in the blue-sensitive opsin. *Am J Hum Genet* 1992; 53: 498-507.
29. Weitz CJ, Went LN, Nathans J. Human tritanopia associated with a third amino acid substitution in the blue-sensitive visual pigment [letter]. *Am J Hum Genet* 1992; 51: 444-446.
30. Sundin OH, Yang JM, Li Y, Zhu D, Hurd JN, Mitchell TN, Silva ED, Maunenee IH. Genetic basis of total colour blindness among the Pingelapese islanders. *Nat Genet* 2000; 25: 289-293.
31. Kohl S, Marx T, Giddings I, Jagle H, Jacobson SG, Apfelstedt-Sylla E, Zrenner E, Sharpe LT, Wissinger B. Total colour blindness is caused by mutations in the gene encoding the alpha-subunit of the cone photoreceptor cGMP-gated cation channel. *Nat Genet* 1998; 19: 257-259.
32. Kohl S, Baumann B, Broghammer M, Jagle H, Sieving P, Kellner U, Spegal R, Anastasi M, Zrenner E, Sharpe LT, Wissinger B. Mutations in the CNGB3 gene encoding the beta-subunit of the cone photoreceptor cGMP-gated channel are responsible for achromatopsia (ACHM3) linked to chromosome 8q21. *Hum Mol Genet* 2000; 9: 2107-2116.
33. Kohl S, Baumann B, Rosenberg T, Kellner U, Lorenz B, Vadala M, Jacobson SG, Wissinger B. Mutations in the cone photoreceptor G-protein alpha-subunit gene GNAT2 in patients with achromatopsia. *Am J Hum Genet* 2002; 71: 422-425

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