Molecular genetics

Understanding colour vision

from J.D. Mollon

THOSE with deficient or anomalous colour vision live in different subjective worlds from the rest of us. Psychologists have been slow to take an interest in molecular genetics, but two recent papers by Jeremy Nathans and collaborators[1,2] allow us to trace one detailed mechanism by which specific variations in DNA lead to individual differences in perceptual ability and in subjective experience.

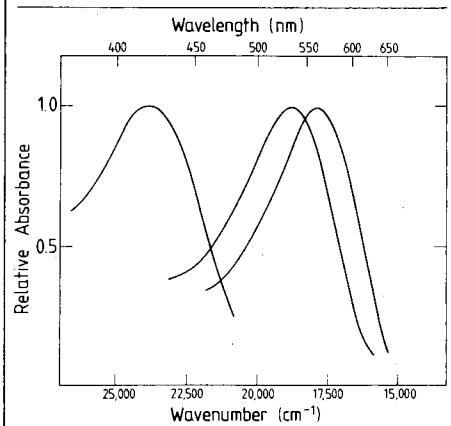
We already know that normal colour vision depends on the presence in the retina of three classes of cone cell, each containing a different photopigment[3] (see figure). A fourth pigment, contained in the rod cells, underlies our colourless vision at twilight. Each of these pigments consists of a protein molecule to which is bound a derivative of vitamin A_1, 11-*cis*-retinal. The 11-*cis*-retinal is common to all the pigments, but the pigment absorbs maximally at different wavelengths according to the protein component. We know in some detail how the photopigment, embedded in the infolded membranes of receptor cells, initiates electrical signals when light is absorbed. To work out the wavelengths falling on a local region of the retina, the nervous system must then find the ratio of the quantum catches in different classes of cone. We have a good idea of how this is done[4,5]. And we know something of how the local ratio is compared with those measured elsewhere in the visual field, so as to give us accurate colour perception despite changes in the spectral composition of the illumination[6].

A major addition to our knowledge is provided by the new reports of Nathans *et al.*, who isolated and sequenced the genes that specify the three proteins underlying normal vision[1] and show how the genes are altered in cases of colour deficiency[2]. Nathans *et al.* began with a radioactively labelled fragment of DNA derived from the gene that specifies the rod pigment of cattle. With this probe they were able to identify in human DNA not only the rather similar gene specifying the human rod pigment, but also — by manipulating the experimental temperature and thus the readiness of DNA to 'hybridize' with a partially mismatching probe — they were able to identify other, rather less similar, genes that were likely to be those that specify the cone pigments.

To localize genes on particular chromosomes, probes were prepared from each of the genes and were hybridized with DNA from a panel of mouse–human hybrid cells that retain various subsets of the human chromosomes. From the pattern of results, the gene for the rod pigment is localized on chromosome 3 and one of the putative cone genes is localized on chromosome 7; the latter gene was taken to be that for the short-wave pigment because disorders of this pigment are known not to be sex-linked. The other genes lie on the q-arm of the X-chromosome. To distinguish genes for the middle- and long-wave pigments, Nathans *et al.* examined 25 colour-deficient men, collating subjective measurements of colour vision with the pattern of hybridization to probes derived from the X-chromosome genes. One curious finding was that more than one middle-wave gene might be present on the X-chromosome of a colour-normal man. But there was never evidence for more than one long-wave gene.

Evolution of colour vision

Why are inherited anomalies of the short-wave cones very rare whereas anomalies of the middle- and long-wave receptors are so very common? Why are the absorbance curves of our photopigments (see figure) so unequally spaced in the spectrum? Why is our visual resolution in space and time so poor when it depends only on signals originating in the short-wave cones of the retina? These and other features of human vision can be explained by an evolutionary scheme that has recently been suggested by various lines of evidence and is now supported by the work of Nathans *et al.*



Absorbance spectra of the three cone pigments of human vision. These curves are plotted from Table 2 of ref. 3 and are based on microspectrophotometric measurements of cone cells from human retinas. Peak sensitivities lie in the violet (short-wave), green (middle-wave) and yellow–green (long-wave) regions of the spectrum.

Widespread among mammals is an ancient, dichromatic form of colour vision that depends on a comparison of the quantum catches in a short-wave class of cones with peak sensitivity near 430 nm; and in a second class of cones with peak sensitivity varying between species but usually in the range 510 to 570 nm (ref. 7). The short-wave cones are sparse[3,8,9] and are probably used only for colour vision, whereas all the other business of daytime vision (such as spatial discrimination and the detection of movement or flicker) depends on the second, more numerous, class of cones. The explicitly chromatic information — provided by the ratio of quantum catches in the two kinds of cone — is carried within the visual system by a sub-channel that seems to be electrophysiologically and morphologically distinct[10,11].

No doubt a trichromatic, or three-variable, system of colour vision has more than once appeared in the mammals. But our own form of trichromacy seems to be shared only with the Old World monkeys and the apes[12]. We, and these primate relatives, enjoy a second dimension of colour vision, provided by a comparison of the quantum catches of the 530- and 560-nm cones. This comparison allows us to make fine discriminations in the red–green part of the spectrum. A distinct retinal channel may not yet have evolved to handle this second type of chromatic information. It is carried by a class of retinal ganglion cells that also extract spatial contrast[4].

The very recent differentiation of the middle- and long-wave photopigments has probably been achieved by duplication of a single gene on the X chromosome. Nathans *et al.*[1,2] confirm that the genes for the middle- and long-wave pigments lie in the same region of the X chromosome and they show that 96 per cent of the inferred amino-acid sequence is identical for the two. By contrast, the short-wave pigment shows only a 43 per cent identity with the middle- and long-wave pigments. This is comparable with the degree of identity between the latter pigments and the human rod pigment.

Colour blindness

About 8 per cent of males in Caucasian populations inherit some form of colour deficiency or anomaly. About 2 per cent are dichromats, requiring only two primary wavelengths to match all colours. From reflection densitometry of the living fovea[12], and from microspectrophotometry of individual receptors[13], there is direct evidence that dichromats lack one of the three cone pigments. Six per cent of Caucasian males are anomalous trichromats, who, like normal observers, require three variables in a colour-matching experiment but who make matches that are different from the normal[14]. The most favoured explanation of anomalous trichromacy is that one of the three photopigments is shifted in its spectral position.

What are the genetic abnormalities that

underline dichromacy and anomalous trichromacy? Visual scientists have probably entertained rather simple notions of these disorders, assuming that local mutations of the gene lead to local substitutions in the sequence of amino acids. Nathans *et al.* show that such point mutations are unlikely to be a common source of colour deficiency. Rather, they suggest, the trouble lies in the juxtaposition and the similarity of the genes for the middle- and long-wave pigments. During the formation of ova and sperm cells, when crossing-over occurs between members of a pair of chromosomes, misalignments of the DNA may occur in the region that encodes the middle- and long-wave pigments. Because the sequences are so similar, the long-wave gene on one chromosome might get itself apposed to a middle-wave gene on the other chromosome. If now crossing-over occurs and if the breakpoint lies in the duplicated spacers between genes, then one chromosome might lose its middle-wave gene and the other chromosome end up with two. If, on the other hand, the breakpoint occurs within a gene, a hybrid gene might be formed that consists of part of the long-wave gene and part of the middle-wave gene.

A man who inherits an X chromosome that lacks the middle-wave gene will be a dichromat, but if the X chromosome carries a hybrid gene, then the outcome will depend on where the breakpoint occurred at the time of crossing-over. There is one sub-region of the gene that seems to determine the actual spectral sensitivity of the resulting photopigment. If this sub-region is drawn from the long-wave gene, then the hybrid gene may produce a photopigment very similar to the normal long-wave pigment; the owner of this chromosome will again be a dichromat. But there may be a whole range of possible breakpoints and some of these may produce hybrid genes that encode photopigments with spectral sensitivities intermediate between those of the normal long- and middle-wave pigments; a man who inherits such a hybrid gene will be an anomalous trichromat. □

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