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POLYMORPHISM IN NORMAL HUMAN COLOR VISION AND ITS MECHANISM

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Abstract—Earlier we reported that Rayleigh matches made by males with normal color vision fall into distinct groups, and proposed that this behavior reflects an X-chromosome linked polymorphism in the spectral positioning of cone pigments (Neitz & Jacobs, 1986). In the present experiments two different color matches were obtained from each of 60 color normal males. Comparisons of the data from these two matches allowed variations in color matching that are produced by individual differences in the spectral positioning of middle and long wavelength cone pigments to be distinguished from color vision variations caused by other factors. Considered together with findings from molecular biology and spectral measurements of individual cone pigments, these results suggest that among color normal humans: (1) there are discrete variations in both middle and long wavelength cone pigments, and (2) most individuals have more than three different cone pigment types.

Photopigments Genetics Polymorphism Cones Color matching X-chromosome

INTRODUCTION

Over the years a substantial effort has been invested in specification of the cone fundamentals. It has been usual in such studies to assume that all individuals with normal color vision share an identical complement of cone pigments. Recently, however, the conventional view that all color normals have the same cone pigments has been challenged by new evidence, indicating the existence of significant individual variation in human cone pigment spectra (reviewed in Neitz, 1986).

In an effort to better understand the nature of these photopigment variations we previously obtained Rayleigh matches from a large group of color normal observers (Neitz & Jacobs, 1986). Under stimulus conditions designed to favor the detection of variations in the spectral positions of middle and long wavelength cone pigments, the Rayleigh matches of color normal males fell into discrete groups and the distribution of Rayleigh matches made by females differed significantly from those made by males. These findings led us to suggest that discrete variation in Rayleigh matching comes about because of an X-chromosome linked polymorphism in the spectral placement of the cone pigments.

In the experiments reported here we sought to reinforce and extend our previous findings by obtaining color matches from 60 additional color normal males. Each subject completed two matches. The first match employed stimulus lights that were identical to those used in the original experiment (Neitz & Jacobs, 1986); the second match employed a red primary light of considerably shorter wavelength. Taken together, the results obtained from these two different matches make it possible to distinguish variations that are produced by individual differences in the spectral positions of the middle and long wavelength cone pigments from other factors that may influence the Rayleigh match.

METHODS

Subjects

Observers were male undergraduate students enrolled in Introductory Psychology at the University of California, Santa Barbara.

Apparatus

A three channel Maxwellian-view optical system was used. A schematic drawing of the optical system appears in Fig. 1. The three beams were drawn from the same source, a 12 V, 100 W tungsten halogen lamp, which was under-run at 11.10 V from a stabilized power supply. High-speed electromagnetic shutters

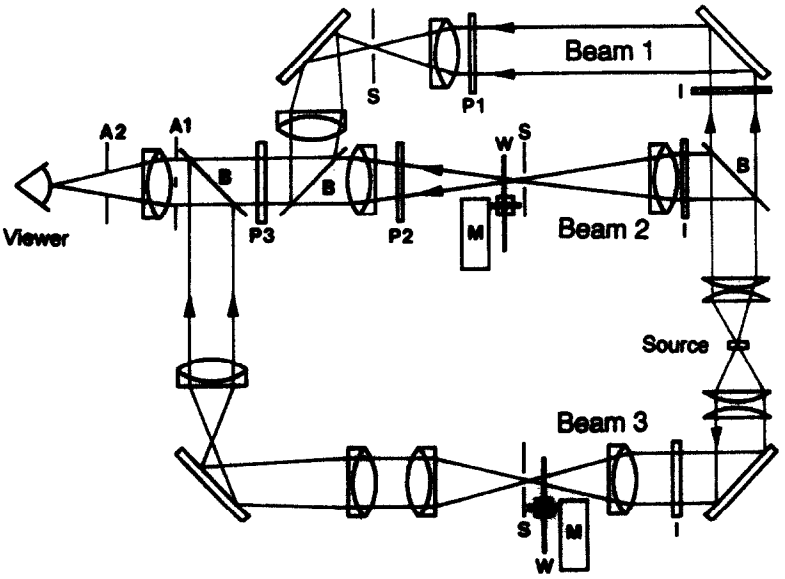

Fig. 1. Schematic diagram of the three-beam Maxwellian view optical system. I, interference filter; W, circular neutral density wedge filter; M, stepper motor; S, shutter; B, beam splitter; P1, P2 and P3, polarizing filters; A1, A2, apertures.

(Unibiltz, Vincent Associates) located in each of the beams were used to control the presentation of the stimuli. The lights were rendered monochromatic by interference filters (Optical Thin Films, 10 nm bandpass) placed in collimated portions of the beams. The green primary light, the red primary light, and the comparison light were derived from beams 1, 2 and 3 respectively. Neutral linear polarizers (Rolyn), labeled P1 and P2 in Fig. 1, were positioned in collimated sections of beam 1 and beam 2 such that the two beams were plane polarized orthogonal to one another. Beam 1 and beam 2 were combined by a beam splitter (a 1 mm thick piece of untreated plate glass) to provide the mixture light in the match. A third polarizer (P3) was positioned beyond the beam splitter that combined these two beams. This polarizer was mounted in a high resolution 360° polar rotator that had a bidirectional readout accuracy = ± 3.0 min arc. Rotation of the plane of polarization of this polarizer allowed the relative proportion of the red and green primaries to be precisely varied while keeping the luminance of the mixture of the two approximately constant. The intensity of the comparison light could be varied by means of a circular, nickel-alloy-coated neutral density wedge filter (Kodak) that was mounted directly on the shaft of a stepping motor. This third beam was combined with the other two by a second beam splitter (1 mm plate glass). The beams were brought into Maxwellian view by a final lens (focal length = 120 mm). Apertures placed in the beams (near the shutters) at optical conjugates of the focal point of the final lens produced a final image size of 0.7 mm. Care was taken to accurately superimpose optical axes and the images from the three beams. The small size of the final image helped to insure that none of the light from the optical system was obstructed by the pupil when the subject was in Maxwellian view. An annular stop (A1) placed immediately behind the final lens produced a stimulus field with an inner diameter of 3° and an outer diameter of 11°. Subjects held their right eye in Maxwellian view with the aid of a chin rest mounted on an X–Y–Z positioner. An aperture (A2) was placed approximately halfway between the final lens and the subjects eye. The subject was able to keep his eye aligned in Maxwellian view by positioning his head so that the stimulus field was exactly centered in this aperture.

Procedure

Unlike conventional color matching, where mixture and comparison lights are viewed simultaneously as two halves of a small spot in the center of the visual field, in this experiment the mixture and comparison lights were temporally alternated. The following stimulus sequence (adapted from Nagy, 1980) was repeated continuously throughout the test session: the comparison light appeared for 0.5 sec followed by 0.1 sec with no stimulus, then the mixture light appeared for 1.9 sec followed by 0.1 sec of no

stimulus. The test and comparison lights were of different durations to make them easily identifiable by the subject. The mixture and comparison lights each produced a retinal illuminance of about 1000 photopic trolands. The experiments were conducted in a lighted room.

The subjects were naive and trained as follows. First, with the aid of a series of diagrams, subjects were trained to position their eye so as to obtain Maxwellian view. They were told to position their head so that the annular test field was centered in the aperture placed between their eye and the final lens and instructed to make judgments about the appearance of the lights only when the test field was exactly centered and when the center of the annulus was fixated. The observers were told that one of the lights they were viewing was a mixture of red and green and that changes in the relative proportion of the mixture components would change the color of the light. They were familiarized with the appearance of the lights by first showing them a mixture that appeared green and then progressively changing the mixture proportion until the field appeared quite reddish. The mixture was next set to a red/green ratio that the observer found difficult to distinguish from the comparison light. The red/green ratio was adjusted slightly away from the match point in each direction and the subject was told how the mixture light had been changed. This procedure was repeated with a series of red/green ratios that fell around the match point until the subject became familiar with the change in relative appearance of the lights as the mixture was changed and was able to discriminate small changes in the mixture.

Once the observer was trained, color matches were obtained using a procedure modified from that of Linksz (1964). In this procedure the experimenter controlled the proportion of red to green light in the mixture and the subject controlled the intensity of the comparison light. A series of red/green settings centered around the estimated match location were presented. Once the subject adjusted the intensity of the comparison to satisfaction he was asked to make one of three choices for each red/green setting: the mixture was indistinguishable from the comparison light, the mixture appeared as if too much green had been added, or too much red had been added in comparison to the mixture. Each mixture setting was presented at least four times and their ordering was randomized. At each setting the subject was allowed to view as many presentations of the mixture and comparison lights as he wished before making a response. This allowed the subject to adjust his head position to insure that his eye was precisely positioned in Maxwellian view before making a judgment.

The subjects responses were recorded after each trial. The settings judged "redder" and "greener" on all trials defined the limits of the matching range. Each subject completed two different matches. In the first match the wavelengths of the primaries were 546 nm and 690 nm and the comparison light was 600 nm. The second match used the same green primary (546 nm), but the red primary was much shorter (600 nm) and the comparison light was slightly shorter (580 nm).

Controls

To preclude any possibility of experimenter bias, a procedure was instituted that kept the experimenter from knowing the relative red/green ratios of individual subjects during the experiment. This was accomplished by keeping the experimenter blind to the absolute position of the analyzer in the polar rotator. The polar rotator (P3) consisted of a rotating stage mounted in a support housing that was in turn mounted to the optical table. The rotating stage had a central aperture in which the polarizer was mounted. A stage-mounted circular dial that was concentric with the polarizer provided position read out. The numbers and markings on the read-out dial were completely covered with a movable ring that was marked off in the same way as the dial it covered. Before each subject was run, an assistant removed the ring, set the stage mounted dial to a randomly selected position, and then replaced the ring (hiding the true polarizer setting from the experimenter) so that the polarizer position as indicated by the covering ring read zero degrees. During the test session the experimenter read the polarizer settings from the ring. The true position of the polarizer was decoded after the test session by adding the randomly-selected, blind dial setting to the dial readings made from the covering ring during the experiment.

To determine the test/retest reliability of the measurements a randomly selected subset of subjects were retested approximately 5 months after their first test. In addition to the control against experimenter bias described above, the subjects first test results were not known to the

experimenter at the time of the retest. Subjects who participated in the retest were also tested using mixture and comparison lights of equal duration (1.9 sec). For this experiment a cueing tone accompanied the presentation of the comparison light.

Calibration

Energy measurements were made with a silicon diode photodetector (model PIN 10 DL, United Detector Technology). The detector was calibrated from 400 to 900 nm at the United Detector Technology Metrology laboratory using reference standards traceable in accuracy to the National Bureau of Standards.

RESULTS

Color matches: 690 nm primary

Seventy-one subjects were recruited for these experiments. An attempt was made to obtain matches from all the subjects. The data for 60 subjects (mean age = 19.2 yr, SD = 1.1 yr) are reported here. Results from individual subjects were excluded for any of three reasons:

(1) Three color defectives were excluded. These individuals made errors on the AO HRR pseudoisochromatic plates that indicated red–green color vision defects. They also made matches that fell far outside the distribution of matches for the rest of the subjects.
(2) Data from 6 individuals who were not Caucasians were excluded. Variations in spectral sensitivity are associated with variations in ocular pigmentation of different races (Wyszecki & Stiles, 1967). These variations will translate into variations in color matching. To minimize this source of variability, the subjects whose data were included in the final sample were all Caucasians.
(3) Data were excluded from subjects who failed to complete both matches. Two individuals fell into this category.

The color matches previously obtained from 100 males and 100 females (Neitz & Jacobs, 1986) are summarized in Fig. 2. The frequency histogram of match midpoints for the 60 subjects of the present experiment obtained with the same test lights are shown in Fig. 3. As for the males of Fig. 2, the majority of subjects fell into one of two discrete groups (B, C). The matching locations of these two groups and the relative frequencies of subjects falling into each group

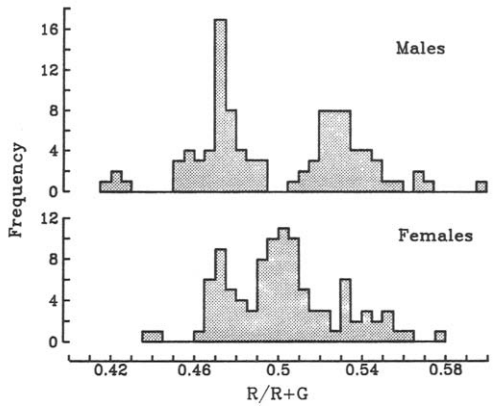

Fig. 2. Distribution of Rayleigh match midpoints for individuals with normal color vision. The R and G values used to compute $R/R+G$ are the energies of the primary lights (546 and 690 nm) multiplied by constants so that the average match midpoint is equal to 0.50. A given $R/R+G$ value (X) from the abscissa can be converted to the actual ratio of the energy of the red primary to the energy of the green primary (R/G) using the formula: $R/G = [X/(1-X)] \times 179.33$. The wavelength of the comparison light was 600 nm. Distribution of match midpoints obtained for 100 males (top) and the distribution of match midpoints obtained for 100 females (bottom) (replotted from Neitz & Jacobs, 1986).

are nearly identical to those found in the original study (compare Figs 2 and 3). Previously a few individuals were found who made matches that fall outside of the two large groups and a similar pattern is seen in the present experiment. The facts that the individuals who make matches that fall to the left of the two large groups tend to cluster together, and that the difference between the outliers and the nearest large group is similar in magnitude to the separation between the two large groups suggests that the outliers belong in groups of their own (identified as A and D).

Color discrimination was uniformly good under the conditions used in this experiment, i.e.

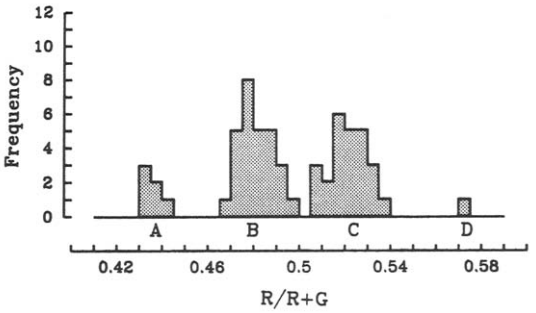

Fig. 3. Distribution of Rayleigh match midpoints for 60 color normal males. The primaries were 546 nm and 690 nm and the comparison light was 600 nm. The scale of $R/R+G$ values is the same as that in Fig. 2.

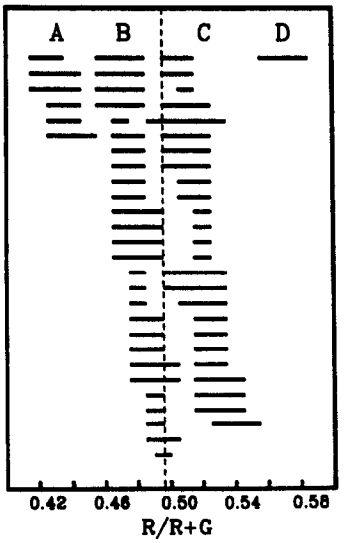

Fig. 4. Matching ranges obtained from the subjects of Fig. 3. Each horizontal bar represents the range of red/green mixtures an individual subject could not reliably distinguish from the comparison light. At each setting over this range the subject reported that the mixture matched the comparison light on at least one trial, or the subjects responses were mixed on different trials, i.e. on some trials he reported the mixture to have too high a proportion of the red primary light relative to the comparison light and on other trials to much of the green primary. The endpoints of each bar extend halfway between the most extreme red/green setting that the subject could not reliably distinguish from the comparison light and the adjacent setting in which the subject reported "too red" (left endpoint) or "too green" (right endpoint) on all trials. Subjects were tested at $R/R+G$ intervals in steps of approximately 0.01. Within each group the matching ranges are arranged in order of decreasing proportion of red primary required in the match. The dashed vertical line illustrates that the majority of matching ranges from individuals of group B do not overlap with the matching ranges of any of the individuals in group C. The scaling of the abscissa is the same as that used in Fig. 3.

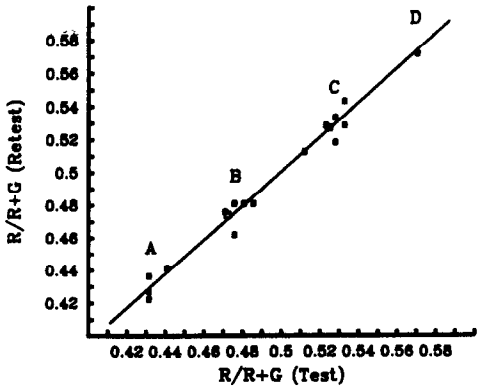

Fig. 5. Comparison of test and retest Rayleigh matches. Each data point represents the match obtained for an individual in a first test vs the match obtained approximately 5 months later in a second test under the same conditions. The regression line best fitting these data is also shown. $R/R+G$ scales are the same as Fig. 3.

the range of red/green ratios over which observers found the mixture difficult to reliably distinguish from the comparison light was usually small. The matching ranges for the subjects of Fig. 3 are shown in Fig. 4. Although differences in the color matches made by subjects in different groups are small, in general the matching ranges for individuals falling into the different groups do not overlap.

In absolute terms the separation between the different groups is quite small. The mean red/green ratios for groups B and C, for example, are different by slightly less than 0.1 log unit. The precision of measurement must, therefore, be very high if these small differences are to be considered as meaningful. A subset of the subjects whose data are shown in Figs 3 and 4 were retested approximately 5 months later. The subjects chosen for the retest were randomly selected, although an effort was made to include individuals from all four groups. The test/retest results are shown in Fig. 5. The individual matches are highly reliable (test/retest, $r = 0.99$; average deviation $= 0.0066\ R/R+G$). Note that all of the individuals that were retested fell into the same groups on test and retest.

In the experiments just described, the alternating fields were presented for different durations. Jordan and Mollon (1988) have suggested that such as asymmetry might allow post-receptoral differences between subjects to influence their matches. To evaluate this possibility, the subjects who participated in the retest were also testing using mixture and comparison lights of equal duration (1.9 sec). The results for the two procedures are compared in Fig. 6. It can be seen that changing the relative duration of the lights has no systematic effect on the distribution of matches.

Chorio-retinal degenerative changes are common in individuals with severe myopia (Giovannini & Colombati, 1980). Individuals with such conditions have been shown to require slightly more red light in the Rayleigh match than normal observers (Pokorny, Smith, Verriest & Pinckers, 1979). Figure 7 shows the results of Fig. 3 when all non-emmetropic observers are excluded. This does not preferentially exclude subjects from any one group. The relative frequencies of individuals falling into the different groups in Fig. 7 are similar to those obtained for the entire sample (Fig. 3). However, as expected, the elimination of non-emmetropic observers

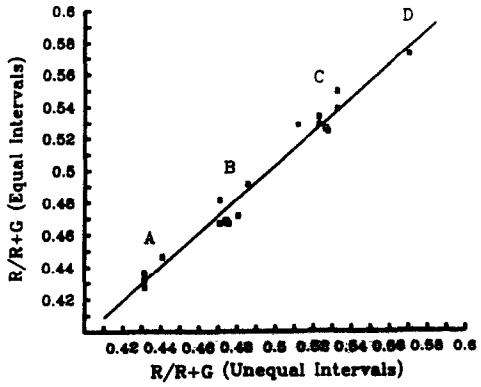

Fig. 6. Comparison of Rayleigh matches obtained under two different conditions. Each data point represents the match obtained for an individual when the mixture and comparison lights were of different durations (1.9 sec and 0.5 sec respectively) vs the match obtained when the mixture and comparison lights were of equal duration (1.9 sec). The regression line that best fits the relationship between these two matches is also illustrated. The scaling of the $R/R+G$ values is the same as that used in Fig. 3.

tends to preferentially exclude observers who require slightly more of the red primary in each group.

Color matches: 600 nm primary

Several factors may influence the Rayleigh match: the density of the preretinal filters, signals from short wavelength cones and rods, the spectral positions of the middle and long wavelength photopigments, and photopigment optical density. The experiments described above employed an unusually long wavelength red primary (690 nm). This primary was chosen to maximize any color matching differences that come about because of small shifts in the spectral position of the middle and long wavelength cone pigments, i.e. a shift in the spectral position of the middle or long wavelength pigment has a much larger effect on sensitivity at 690 nm than on sensitivity to wavelengths closer to the spectral peaks of the photopigments. The subjects of Fig. 3 were tested in a second match which employed the same green primary (546 nm) but with a shorter wavelength red primary (600 nm) and comparison (580 nm) light. If the different groups in Fig. 3 arise from variations in the spectral positions of middle or long wavelength cones, the differences between groups should be substantially smaller for this second match.

The distribution of match midpoints for the second match is shown in Fig. 8. Note that the range of variation is considerably smaller for the second match and that the discrete groups collapse into a single distribution. The implication from this result is that the different groups arise from variations in the spectral positioning of their cone pigments.

Results from the two different matches can be compared to the individual predictions for each of the factors that might explain the difference in color matching between groups in Fig. 3. For instance, the lens and macular pigments absorb most strongly in the short wavelengths and changing the density of either of these will affect the sensitivity to 546 nm light (the primary

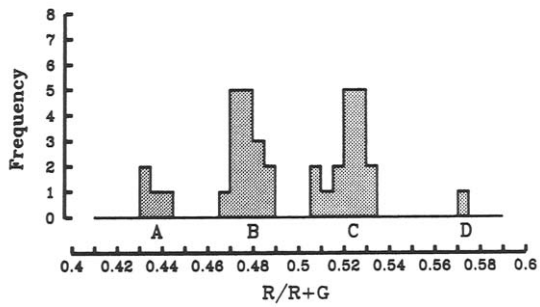

Fig. 7. Distribution of Rayleigh match midpoints from the emmetropic observers of Fig. 3.

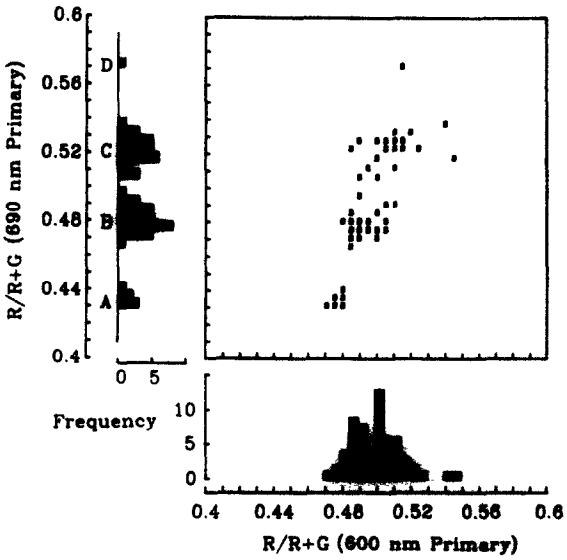

Fig. 8. Comparison of match midpoints for two different Rayleigh matches. Each data point represents the match of a 580 nm comparison light to a mixture of 546 nm and 600 nm primary lights (match no. 2 for an individual vs his match of a 546 nm and 690 nm mixture to a 600 nm comparison light (match no. 1). The frequency histogram for match no. 1 (Fig. 3) is reproduced along the ordinate and a frequency histogram for match no. 2 is shown along the abscissa. The $R/R+G$ scaling for match no. 1 is the same as the previous figures. The $R/R+G$ values for match no. 2 were adjusted so that the mean match value equals 0.50. A given $R/R+G$ value (X) from the abscissa can be converted to the actual red/green irradiance ratio (R/G) from match no. 2 using the formula: $R/G = [X/(1-X)] \times 1.883$.

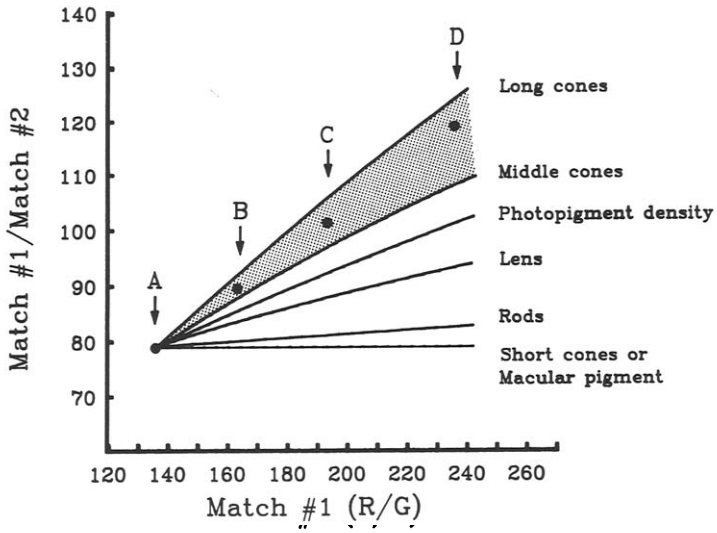

Fig. 9. Comparison of the average matches from groups A, B, C and D (Fig. 3) with the matches predicted under the assumption that the differences between groups are produced by variations in: photopigment optical density, lens density, macular pigment density, contributions from short wavelength cones, rod intrusion, the spectral positions of middle and long wavelength cones. The filled circles show the average match no. 1 to match no. 2 ratio vs the match no. 1 average for each of the four groups. The curves represent the predictions for changes in each of the factors that could account for the differences in color matching between groups (see text). The photopigment density curve assumes the same density change for both the middle and long pigments. The shaded area indicates where data points are predicted to fall if the variation between groups is produced by individual differences in the spectral placement of the X-chromosome linked cone pigments. The values used for match no. 1 and match no. 2 are the uncorrected ratios of the primaries in energy units.

common in both matches) much more than it will affect the sensitivity to either the 600 nm or the 690 nm light. The same holds for changes in the relative contributions of rods and short wavelength cones to the match. If, thus, two individuals make different matches when tested using the mixture with the 690 nm primary (Fig. 3), and the disparity in the matches is produced by differences in preretinal absorption or by differential contributions of rods or short wavelength cones, then the two individuals will make similarly different matches when tested in the second match with the 600 nm primary. It follows that the match no. 1 to match no. 2 ratio will be similar for the two individuals.

The opposite is true for shifting the spectral position of the middle or long wavelength cone pigments, i.e. a small spectral shift in one of these photopigments will produce a very small change in sensitivity to the red primary (600 nm) used in match no. 2 compared to the change in sensitivity to the red primary (690 nm) of match no. 1. The ratio of match no. 1 to match no. 2 will thus be greatly different for individuals who have different middle or long cone pigments.

The curves of Fig. 9 show the predicted ratios of match no. 1 to match no. 2 as a function of match no. 1. These were derived for changes in each of the factors that could account for differences in color matching between groups as follows. Starting with group A (Fig. 3), the average quantal red/green ratios for the two different matches were corrected for preretinal absorption (Wyszecki & Stiles, 1967) and the two best fitting spectral sensitivity functions that correspond to putative middle and long wavelength cone mechanisms were determined by solving simultaneously the color matching equations and polynomial expressions for pigment absorption curves. In this calculation a photopigment optical density of 0.25 was assumed, and contributions from rods and short wavelength cones were taken to be negligable. Starting from the values that account for the mean group A data, each of seven factors that might account for the differences between groups in Fig. 3 were varied independently; the predicted changes in red/green ratios for the two different matches were calculated for changes in each factor.

In general, those factors that absorb much more strongly at 546 nm than at longer wavelengths (preretinal filters that vary across individuals in their density, and rods and short wavelength cones that might vary in their contribution to the Rayleigh match) produce curves

in Fig. 9 with shallow slopes. Shifts in the spectral position of the cone pigments have their greatest effect at wavelengths where the two matches are the most different and produce curves with much steeper slopes. Changing the photopigment optical density alters the width of the photopigment absorption curves and produces a curve with an intermediate slope. The predicted curves incorporate the following assumptions:

(1) The predicted results in Fig. 9 for varying rod contributions use the rod sensitivity values from Wyszecki and Stiles (1967) under the assumption that any rod contribution is independent of the middle and long cones. The alternative assumptions, that the rods contribute in an additive combination with one or the other of the cone pigments or that they add equally to both cone pigments, also yield predictions that deviate substantially from the experimental results.
(2) The spectral sensitivity function obtained from short wavelength cones in macaque monkeys (Baylor, Nunn & Schnapf, 1987) was used to derive the curve showing the predicted results of varying the contribution of short wavelength cones. The short wavelength cone sensitivity at 690 nm was extrapolated from the slope of the measured values for the extreme long wavelengths. Human short wavelength cones may have a different peak from macaque monkeys (humans: Dartnall, Bowmaker & Mollon, 1983; macaque monkeys: Baylor et al., 1987; Mansfield, Lavine, Lipetz, Collins, Raymond & MacNichol, 1980), but since the match wavelengths are on the extreme long wavelength side of the short wavelength pigment curve where the falloff is linear, a small discrepancy in the peak would have no effect on the predicted curve shown in Fig. 9.
(3) The predictions for changes in macular pigment and lens density were calculated from the absorption curves for those pigments (Wyszecki & Stiles, 1967).
(4) The predictions for shifting the spectral position of the middle and long wavelength cone mechanisms in Fig. 9 depend on the assumed shapes of their spectral sensitivity curves. We used a polynomial expression for the absorption curve of chicken iodopsin (Dawis, 1981) to obtain sensitivity values at 546, 580 and 600 nm. For these wavelengths the chicken iodopsin curve is identical in shape to the human long wavelength fundamental derived by Smith and Pokorny (1975), is in agreement with the Estevez (1979) fundamental, and with the spectral sensitivity functions measured electrophysiologically from individual long wavelength cones in monkeys (Baylor et al., 1987) and humans (Schnapf, Kraft & Baylor, 1987). To obtain sensitivity curves for the middle and long wavelength cone mechanisms, the iodopsin curve was translated on a log wave number axis. Plotted in this way primate cones assume a common shape (Baylor et al., 1987). The relative sensitivity values at 690 nm were determined using the extreme long wavelength slopes of the spectral sensitivity functions for human middle and long wavelength cones (Schnapf et al., 1987).

The predictions of Fig. 9 depend primarily on the shapes of the curves for each factor and very little on the assumptions used to initially fit the group A data. Thus, the values of the factors used to initially fit the group A data can be varied over a wide range without affecting the curves given in Fig. 9.

The solid symbols in Fig. 9 show the average ratio of match no. 1 to match no. 2 for each of the four groups. These values increase steeply for the groups that require increasing proportions of red primary in match no. 1 as is predicted for variations in the spectral position of middle and long wavelength cones. It is clear from Fig. 9 that individual variations in lens or macular pigment density, varying contributions of short wavelength cones or rods, photopigment optical density, or any combination of these does not account for the difference in color matching between any of the four groups.

DISCUSSION

Earlier we reported a discrete X-linked polymorphism in color matching among color normal observers (Neitz & Jacobs, 1986). The replication of this experiment (Fig. 3) yielded a nearly identical distribution of color matches for color normal males. In both experiments the data from the two large groups of males were tested for bimodality (Giacomelli, Wiener, Kruskal, Pomeranz & Loud, 1971). In each case the test yielded a probability of less than 1% that the samples could have been drawn from a unimodal distribution.

How can these results be explained? The explanations that the distributions reflect some bias on the part of the subjects or the experimenters can be rejected. The experimenters were blind to the location of the match being made by the subjects, and thus the possibility that experimenter bias could influence the data can be eliminated. The different groups cannot have been produced by some subject bias for several reasons: (1) the distribution of matches made by males is significantly different from the distribution of matches made by females (Fig. 2) and that difference is the one predicted for X-chromosome linked inheritance, (2) in general, the matching ranges from individuals in different groups do not overlap indicating that they are truly making different pigment matches, and (3) the distribution of male matches depends on the wavelength of the red primary; any subject bias would be expected to independent of the wavelength of the red primary.

The matches obtained in these experiments are highly reliable over long periods of time. In addition to the reliability data on naive subjects (Fig. 5), a few subjects were tested repeatedly over a period of 3 years (some have been tested dozens of times) and their match reliability is similar to that shown in Fig. 5. The conclusion drawn from these experiments is that there is a discrete variation in color vision among color normals; this variation comes about because of a polymorphism in some stationary feature of the visual system that is sex linked.

A priori it seems unlikely that the different groups could be produced by variations in lens or macular pigment density because these filters have little differential absorption for the wavelengths used in these matches (Wyszecki & Stiles, 1967); this would be especially true in such a homogeneous sample of young subjects. The possibility that the polymorphism of color matching comes about because of variable contributions from rods or short wavelength cones also seems unlikely because rods are almost completely saturated at the light levels employed in these experiments (Aguilar & Stiles, 1954) and for the wavelengths employed the sensitivity of the short wavelength cones is down more than 2 log units from its peak. Furthermore, none of these features of the visual system would be expected to be distributed differently among males than among females.

Earlier we examined the possibility that the different groups result from differences in photopigment optical density by testing subjects from each of the two large groups following a full bleach (Neitz & Jacobs, 1986). Although the matches changed following the bleach, as expected, they did not become more similar as would happen if the different groups arise from differences in photopigment optical density.

In the present experiments we were able to test whether the different groups come about as the result of these various factors in yet another way, through an examination of results from two different matches. It can be seen (Fig. 9) that none of the factors mentioned above (lens pigment, macular pigment, short wavelength cones, rods, photopigment density) can individually, or in any combination, account for the differences in color matching between groups. Figure 9 does show that the differences in color matching between groups are those expected if the polymorphism comes about because of variations in the spectral position of the middle and long wavelength cone mechanisms. The conclusion is that there are discrete variations in the spectral positions of the X-linked cone mechanisms.

Which cone mechanism varies?

Which cone mechanism varies: is it only the middle wavelength cone mechanism, only the long wavelength cone mechanism, or do both vary? In the previous analysis (Neitz & Jacobs, 1986) we focused our attention on the two large groups (B and C). A calculation based on the average red/green ratios and the average intensities of the comparison light for these two groups led us to suggest that these two large groups had different long wavelength cone mechanisms that are peak separated by about 2.7 nm. Because the majority of subjects fell into one of two groups, it was assumed in the previous analysis that only one of the cone mechanisms varied among color normals. This assumption now seems incorrect. From the results of the present experiments it has become clear that the other two (less frequent) groups (A and D) come about because the individuals falling into those groups have different photopigment complements that subjects in either group B or C. In Fig. 9, if only the long wavelength cone mechanism varied across all four groups, the mean match data points should lie along the line marked "long cones"; if only the middle wavelength cone mechanism varied the data points should lie along the line marked "middle cones". The average data points for groups B, C and D lie in between the two lines, suggesting that both pigments must

vary in spectral position to account for the full range of variation of color matching among color normal males. Given that both cone mechanisms vary, there are two possibilities. (1) Between any two adjacent groups only one cone mechanism varies, but between more distantly spaced groups both middle and long wavelength cone mechanisms differ. For example, all males in group B might have a shorter middle wavelength cone mechanism than individuals in group A, but the difference between groups B and C might be only in the long wavelength mechanism. If so, groups A and C would differ in both middle and long wavelength cone mechanisms. (2) A second possibility is that there is more than one kind of individual in each group. A feature of the matches made using the 690 nm light is that the predicted changes in red/green ratio are similar no matter whether the middle or the long wavelength mechanism is shifted. For example, the difference in red/green ratio between group B and group C in Fig. 3 can be accounted for by a shift in the long wavelength mechanism of slightly less than 3 nm, but the same change in red/green ratio could be produced by a shift in the middle wavelength mechanism of approximately the same amount. It is easy to imagine that several combinations of different cone mechanisms could make up a single group. For instance, if a first pair of cone mechanisms predict a match like that of group C in Fig. 3, shifting the long wavelength mechanism of this pair 3 nm toward the long wavelengths produces a second combination of cone mechanisms that predict a match like that of group B. Shifting the middle wavelength mechanism of this second combination 3 nm toward the short wavelengths, to produce a third combination of cone mechanisms, brings the match back into group C. The first and third combinations have different middle and long wavelength cone mechanisms, yet they predict similar matches that fall into the same group.

From the data it is not clear which of these two possibilities is the correct one. What does seem clear is that among individuals with normal color vision the discrete variations in color matching are produced by discrete variations in the spectral positions of both the middle and long wavelength cone mechanisms. The variant cone mechanisms are separated by approximately 3 nm.

Previous studies suggesting discrete variation

Although the color vision polymorphism described here is not evident in many earlier experiments where Rayleigh matches have been obtained from large numbers of individuals, there have been other studies that provide evidence for discrete variation in X-chromosome linked cone pigments. The results from these experiments are summarized in Table 1. Taken as a group, the results from the psychophysical studies that report discrete variation yield a consistent picture; (1) the (two) studies that looked for evidence for sex linkage found it: (2) the number of different groups of males was always two, or two main groups were found along with two much smaller groups; (3) the separation between groups is that predicted by

Table 1. Studies that provide evidence for discrete variation in the spectral positioning of the X-chromosome linked photopigments among color normal humans

Psychophysics	Number of groups of males	Evidence for sex linkage	Predicted separation between cone mechanisms
Stiles and Birch (1959) (re-analyzed by Neitz & Jacobs, 1989)	2 large 2 small	—	2.6 nm
Waaler (1973)	2	yes	—
Eisner and Macleod (1981)	2*	—	2.7 nm
Neitz and Jacobs (1986)	2 large 2 small	yes	2.7 nm
Elsner and Burns (1988)	2	—	—
Neitz and Jacobs (present study)	2 large 2 small	—	*ca* 3 nm

MSP	Number of photopigment types	Evidence for sex linkage	Separation between cone types
Dartnall, Bowmaker and Mollon (1983)	2 M types and 2L types	—	*ca* 6 nm

*Includes both males and females.

variant cone mechanisms separated by slightly less than 3 nm.

The MSP results summarized in Table 1 stand as an exception to the other data in that the variant types of middle and long pigments are suggested to be peak separated by at least twice the distance between cone mechanisms predicted from psychophysical experiments. If the subgroups suggested by MSP are real, then, in order to resolve the discrepancy between MSP and psychophysical results, at least some color normal males must have both middle wavelength cone types or both long wavelength cone types suggested by the MSP experiments. For example, if some individual males have both long wavelength cone types in approximately equal numbers, while others have only one of the long wavelength cone types, the spectrum of the summative combination of two long wavelength pigment types separated by 6 nm is one individual compared to the spectrum of only one of the long wavelength pigment types in another individual would yield a difference similar to that observed between adjacent groups in color matching. In recognition of the possibility that in psychophysical experiments one may sometimes be measuring the combination of relatively closely spaced photopigment types rather than individual cone pigment spectra, in this discussion the term "cone mechanism" has been used when inferences are drawn from psychophysical data while the term cone pigment has been reserved for cases where it is reasonably certain that single cone pigment type is being measured. The issue of what actual cone pigment types are involved in normal color vision is discussed below.

The photopigment basis of color vision polymorphism

Examination of rod photopigment spectra in a wide range of teleost fishes led Dartnall and Lythgoe (1965) to suggest that photopigments are not distributed continuously throughout the spectrum; rather, absorption peaks occur at regularly spaced spectral locations. The interval between successive spectral location has a mean value of about 6 nm. A more recent survey of cone pigment spectra in a variety of mammals leads to a similar conclusion (Jacobs & Neitz, 1985). It appears from these data that the spectral positioning of photopigments is constrained, limiting the available photopigment absorption maxima to well defined locations separated by 6 nm intervals. Since the human color matching data (above) indicates a separation between cone mechanisms of about 3 nm, there is a clear discrepancy between the prediction of 6 nm spacing from individual pigment measurements and the psychophysical results. This section suggests a resolution.

The color matches of normal males fall into four equally spaced groups. Thus, what is required is a mechanism that will produce a series of incrementally spaced color vision phenotypes, where both middle and long pigments vary, but no two individual pigments differ by less than about 6 nm. Under these constraints, the simplest model requires four different X-chromosome linked cone pigment types among individuals with normal color vision: two different middle wavelength pigments peak separated by approximately 6 nm, and two different long wavelength pigments also peak separated by approximately 6 nm. We assume that the occurrence of the combination of a pair of pigments separated by 6 nm cannot be discriminated in color matching experiments from a single pigment 3 nm shifted from either pigment in the pair occurring singly. The two middle wavelength pigment types are refered to as M and M + 6 respectively to indicate that they are peak separated by approximately 6 nm; the two long wavelength pigment types are L and L + 6. Assuming that an individual male with normal color vision may have either one of middle wavelength pigments alone (M or M + 6) or a nearly equal contribution from both of them (M and M + 6), and either one of the long wavelength pigments alone (L or L + 6) or a nearly equal contribution from both of them (L and L + 6), then, any individual male might have one of three different middle wavelength pigment combinations and any one of three different long wavelength pigment combinations. This allows the possibility of nine different cone pigment complements among color normal males. As pointed out earlier, because small shifts in either middle or long wavelength cone mechanisms lead to similar changes in color matches, not all different conbinations are expected to lead to discriminable differences in color matching. For example, an individual with only the longest long wavelength pigment (L + 6) and the shortest middle wavelength pigment (M) would be expected to make a similar match to an individual with only the shortest long wavelength pigment (L) and the longest middle wavelength pigment (M + 6). The nine possible different combinations would, thus, be

DIFFERENCE PREDICTED FROM COLOR MATCHING			MIDDLE WAVELENGTH MECHANISM	LONG WAVELENGTH MECHANISM
	GROUP I	1.	M+6	L+6
3 nm				
	GROUP II	2.	M+6 and M	L+6
		3.	M+6	L+6 and L
3 nm				
	GROUP III	4.	M+6 and M	L+6 and L
		5.	M+6	L
		6.	M	L+6
3 nm				
	GROUP IV	7.	M+6 and M	L
		8.	M	L+6 and L
3 nm				
	GROUP V	9.	M	L

Fig. 10. The nine possible photopigment combinations among individuals with normal color vision based on the assumption of two different middle wavelength pigment types peak separated by 6 nm, (M and M + 6) and two different long wavelength pigment types peak separated by 6 nm, (L and L + 6). Photopigment combinations predicted to yield similar color matches are enclosed in brackets (labeled groups I–V). The difference in color matching between groups is that predicted by a shift in either the middle or long wavelength cone mechanism of approximately 3 nm; this is indicated in the first column.

expected to produce only five distinguishable groups of color matches. These are illustrated in Fig. 10. There is no reason to assume that all the nine possible different combination are equally frequent or, in fact, that all combinations occur.

Undoubtedly the most controversial aspect of the model outlined above is that it requires at least some individual males to have not the classically accepted three different cone pigment types (short, middle and long), but instead to have four or even five different pigment types (short, two different middle wavelength pigment types, and two different long wavelength pigment types). However, the idea that some males have more than three different cone pigments is consistent with recent findings from molecular biology. Molecular genetic experiments reveal that the majority of color normal males have more than two photopigment genes on the X-chromosome (Nathans, Thomas & Hogness, 1986b). These cone pigment genes appear to be arranged in a head-to-tail array. This arrangement, together with the fact that the genes are located near the end of the long arm of the X-chromosome, is believed to promote frequent homologous recombination events (Nathans, Piantanida, Eddy, Shows & Hogness, 1986a; Nathans et al., 1986b; Vollrath, Nathans & Davis, 1988). Assuming that all pigment genes are expressed, then in order to have only two different X-linked cone pigments in individuals that have three X-linked cone pigment genes, two of the genes must encode identical cone pigments. An example is illustrated in Fig. 11. An individual X-chromosome (X-chromosome 1) might be arranged with one long (labeled L)

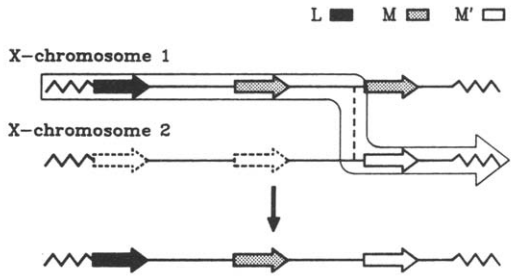

Fig. 11. Proposed recombination event that produces an X-chromosome with genes encoding three different types of photopigments. Each arrow represents a single photopigment gene. Lines between arrows represent homologous intergenic sequences. Regions of two different X-chromosomes are illustrated. X-Chromosome 1 has one long wavelength pigment gene (L) and two middle wavelength pigment genes that encode the same photopigment (M). X-Chromosome 2 has a gene that encodes a different middle wavelength pigment (M'). The dashed line between chromosomes represents one possible recombination event in which one product (shown at the bottom of the figure) receives a long wavelength pigment gene and two different middle wavelength photopigment genes (M and M').

and two identical middle wavelength cone pigment genes (each labeled M). Given that there are genetic variations in the middle wavelength cone pigments, other individual X-chromosomes must carry genes that code for a different middle wavelength cone type. Such a chromosome is illustrated by the arrangement labeled "X-chromosome 2" in Fig. 11 and a gene encoding a different middle wavelength cone type is labeled M′. To keep this illustration more general, we leave open the number and identity of the other photopigment genes on this chromosome, but to hold to the requirement that individuals have no more than two different pigment types encoded on the X-chromosome, all copies of middle wavelength genes on this chromosome must encode identical (M′) photopigments and any copies of long wavelength pigment genes must encode identical photopigments. It is possible to imagine a population with X-chromosomes that adhere to these rules. However, given the high homology between X-linked photopigment genes and intervening gene sequences, recombination events between chromosomes like those illustrated in Fig. 11 are expected to occur with high frequency (Nathans et al., 1986a, b; Vollrath et al., 1988). One possible crossover is illustrated. The result of such crossovers are X-chromosomes with genes that encode more than two different middle wavelength pigment types.

Our model assumes that all the pigment genes on the X-chromosome are usually expressed. Obviously, at least two of the genes in the array are expressed in color normals. The additional genes in the array that occur in most males are proposed to arise from unequal homologous cross overs (Nathans et al., 1986b). Genes that are duplicated in this way will be complete, i.e. any *cis*-acting regulatory elements that are responsible for the expression of the gene will also be duplicated intact. Since the duplicated genes have the same regulatory elements as the originals, it seems reasonable to expect that all the genes in the array will be expressed.

The essential features of the proposed model are: (1) There are four different X-linked pigments among color normal humans, two different middle wavelength pigments and two different long wavelength pigments, and (2) color normal individuals inherit these photopigment types in combinations that give rise to discrete variations in color matching where the separation between adjacent groups is smaller than would be obtained for the same photopigment polymorphism if each individual had only one of the middle wavelength pigment types and only one of the long wavelength pigment types. The pigment combinations shown in Fig. 10 illustrate one way in which different combinations could occur to give rise to the groups observed in psychophysical experiments. The actual relationship between photopigment complement and color vision phenotype could be even more complicated than this suggests, and the next step, understanding the relationship between the X-linked genes and the photopigment complements they produce, is surely more complicated. For example, some individual males with four X-linked photopigment genes might have a single long wavelength pigment gene and three middle wavelength pigment genes, say, two that code for the M + 6 photopigment and one that codes for the M pigment. Predicting the color match that this individual would make depends on how the number of gene copies translates into the amount of photopigment produced. If two M + 6 genes and one M gene results in twice as many photoreceptors expressing M + 6 as expressing M then the match made by such an individual would be similar to (but slightly shifted from) a male that had the same long wavelength pigment type and only M + 6 pigment genes. The occurrence of such individuals may contribute to the variation within color matching groups.

Nathans and colleagues have assigned identities to the genes found in color normal subjects (Nathans et al., 1986a, b). In their scheme all the normal males have a single long wavelength pigment gene; individuals with more than two X-linked pigments genes are proposed to have multiple middle wavelength pigment genes. In Fig. 10 some males are allowed to have multiple long wavelength pigments and this may seem to conflict with the Nathans et al. results. However, one might question the reliability of their identification scheme on two grounds. (1) The identification of whether a gene encodes a middle wavelength pigment or a long wavelength pigment is based on the examination of Southern blot data from dichromats. Although four different restriction fragments were visualized from each X-chromosome linked photopigment gene, deuteranopes differed consistantly from protanopes only in the presence of a single gene fragment: all the deuteranopes tested had fragment "D_r" but lacked "D_g" while 5 of the 6 protanopes had "D_g" but lacked "D_r". The restriction site polymorphism that gives rise to

"D_g" vs "D_r" requires only a single nucleotide substitution (Nathans et al., 1986b). Given that photopigments are encoded by approximately 1000 nucleotides it seems unlikely that the difference between a middle wavelength pigment gene and a long wavelength pigment gene could always be determined from knowing the identity of a single nucleotide. (2) Using their identification scheme Nathans et al. (1986a) find deuteranomalous individuals to have both normal middle and normal long wavelength pigment genes in addition to "hybrid" pigment genes. They propose that deuteranomaly arises from the expression of both a normal middle wavelength pigment and anomalous pigment in the same cones. The problem is that this proposed arrangement predicts much less extreme matches than those actually obtained from deuteranomalous subjects. If one examines the matches predicted by a normal long wavelength pigment and the combination of a normal middle wavelength pigment plus an anomalous pigment, as a function of the peak wavelength of the anomalous pigment, one finds the greatest deviations from the normal match for theoretical anomalous pigments with peaks about halfway between the two normal pigments. As the anomalous pigment is shifted in either direction from this intermediate position, the predicted match midpoints approach the normal match. There is no position of the anomalous pigment that predicts a match that is extreme as the matches obtained from deuteranomalous subjects. One possible resolution is that in deuteranomalous subjects the scheme proposed by Nathans et al. (1986a, b) incorrectly identifies genes that actually encode longer wavelength pigments as normal middle wavelength pigment genes. If so, some genes in normals may also have been incorrectly identified using their scheme.

Even if males have no more than one long wavelength pigment gene is does not conflict with the basic features of the model. Figure 10 could be easily modified to reflect the restriction that males have no more than one long wavelength pigment gene by removing all combinations with two long wavelength photopigments. Limiting the number of different possible photopigment combinations in this way does not alter the number of predicted phenotypically distinguishable groups.

It is noteworthy that the proposed 6 nm separation between middle and long wavelength photopigment subtypes among color normal humans is very close to the magnitude of the separation that has been proposed to exist between X-chromosome linked photopigments in human anomalous trichromats (Pokorny, Smith & Katz, 1973; Nagy, Purl & Houston, 1985). It is possible that four different X-chromosome linked pigments drawn in various numbers and combinations by different individuals may account not only for variations in color matching among normal humans, but also that anomalous trichromacy may result from drawing only the closely spaced combinations of these same pigments.

Photopigment polymorphism vs variation

Earlier observations that cone pigments appear to vary in spectral sensitivity left open questions about the nature of the variation and its cause. One possibility has been that photopigments are inherently variable and that for any nominal photopigment "type" there exists a range of possible spectral positions that are continuously distributed around a mean λ_{max} value (Alpern, 1987; Webster & MacLeod, 1988). Spectral sensitivities determined by recording photocurrents from single outer segments from macaque monkeys (Baylor et al., 1987) have received a great deal of attention with regard to this possibility. In macaque monkeys, for each cone type, λ_{max} values showed a standard deviation of less than 1.5 nm. Baylor (1987) suggests that this residual variation probably represents experimental error and that "individual cones of a given type normally contain pigments with very similar or identical spectral properties". We had previously arrived at the same conclusion for cones in ground squirrels (Jacobs, Neitz & Crognale, 1985). The distribution of λ_{max} values for the predominant cone type in ground squirrels measured using the electroretinogram had a standard deviation of 1.07 nm. In these experiments (unlike measurements of individual cones) it is possible to obtain an independent measure of experimental error by measuring the spectrum from same animal repeatedly. Repeated measurements of the spectral peak of cones in an individual ground squirrel showed a standard deviation of 0.93 nm, very close to that measured across animals, indicating a high probability that the small variation in these measurements is principally due to experimental error. Individual cone pigment types in a number of other mammals measured with this same ERG procedure (Jacobs and Neitz, 1985; 1987) show similarly

small standard deviations. If we assume that the experimental error in those measurements is similar to that measured for the ground squirrel then the variability in measurement within a photopigment type is also mostly or completely attributable to experimental error.

In contrast to the idea that all photopigment types are continuously variable, systematic variations in photopigment type do occur in some species. These photopigment polymorphisms have a number of characteristic features: (1) The variant photopigments occur as distinct types. (2) The different photopigment types are separated in peak by discrete steps that are approximate multiples of 6 nm. (3) The different photopigment variants are limited to a small number. (4) Variations in photopigment complements are inherited as X-chromosome linked traits. These features appear to be present in the cases of photopigment polymorphisms so far identified among non-human primates. These include, squirrel monkeys (Jacobs & Neitz, 1987a), cebus monkeys and titi monkeys (Jacobs & Neitz, 1987b), tamarins (Jacobs, Neitz & Crognale, 1987), and marmosets (Travis, Bowmaker & Mollon, 1988). It is argued here that these same features can be attributed to the color vision polymorphism found among color normal humans.

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