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# Color matches of patients with retinitis pigmentosa

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*The color matches of 46 retinitis pigmentosa (RP) patients were found to differ significantly from those of 55 unaffected observers. The color matches of group I (trichromatic) RP observers were more protanomalous (i.e., required a greater red/green mixture ratio) than those of unaffected observers. The matches of group II (dichromatic) RP observers were more protanopic (i.e., required less yellow to match the red primary) than those of the group II unaffected observers. In view of current evidence, this difference can be attributed to reductions in the pigment optical density of cone photoreceptors in eyes of RP patients.*

**Key words:** color matches, optical density, cone, retinitis pigmentosa

**H**istologic and densitometric evidence suggests that the effective optical density of retinitis pigmentosa (RP) photoreceptors is reduced. (The term *optical density* will be used here to refer to the light-absorbing ability of individual photoreceptors. The greater the optical density, the greater the ability of a receptor to absorb photons).

In retinal areas with advanced disease, few photoreceptors remain<sup>1-2</sup>; hence there is a dramatic loss of ability to absorb and transduce light into visual signals. In better preserved areas of the retina, usually the fovea, the morphologic alterations are relatively less marked. Among other findings, the outer segments of remaining photoreceptors are shortened and tilted; their discs often are disoriented.<sup>3-5</sup>

Few studies, however, have actually measured the effective optical density of photoreceptors in the living RP eye. The principal technique for such studies is retinal densitometry. Thus far, results have demonstrated in several patients that rod pigment (rhodopsin) density is reduced.<sup>6-7</sup> Rod density is lowest in the retinal areas where rod vision is severely impaired. In one patient, measurement of foveal cone pigments had also been made<sup>7</sup>; however, no abnormal changes were found.

The present study explores the use of color matches as an *in vivo* index of cone optical density reduction in RP patients. The rationale is as follows. Changes in the normal optical density of cone photoreceptors necessarily result in changes in the observer's color matches.<sup>8</sup> Thus it should be possible to monitor the alterations in cone optical density by following the changes in the patient's performance on a colorimeter such as the Nagel anomaloscope. In practice, however, such a technique has not been tried before in the study of RP. Therefore the aims of the present investigation are (1) to determine whether or not the color matches of RP patients differ from those of the normal, (2) to assess how large the difference is, and (3) to exam-

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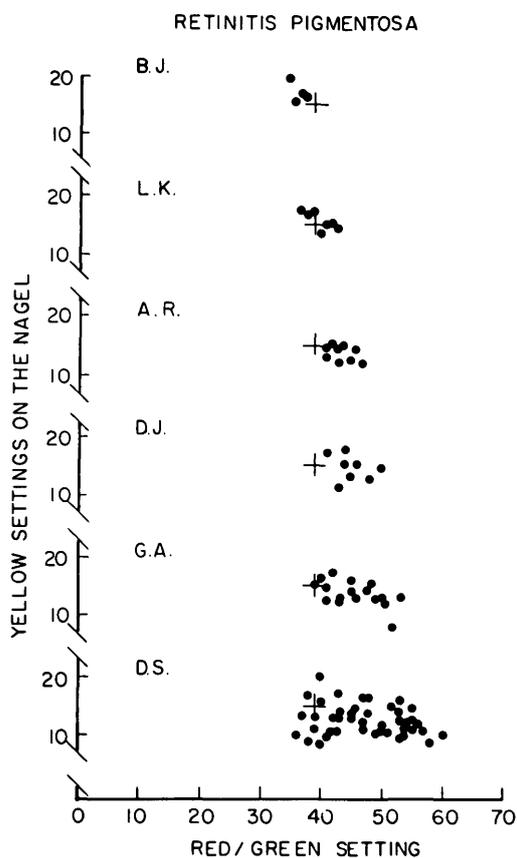


Fig. 1. Color matches of representative group I RP patients. Each data point represents the patient's setting of the yellow primary to match different mixtures of the red and green primaries.

ine whether the difference is consistent with the reduction of cone pigment density.

### Methods

**Retinitis pigmentosa patients.** Forty-six patients from an estimated total of 350 RP patients in our files composed the RP group. For 40, there was no *a priori* basis for selection. They had come to the clinic between 1977 and 1978 for periodic examination, and at that time color matches were tested on them. The remaining six, however, were patients who were requested to return for color vision examination. These six were selected and included in this study because, from prior examination, they were suspected of having a congenital color vision trait in addition to the RP disease. The age of the 46 patients ranged from 13 to 65 with a median age of 29 and a mean of 33. Fifteen were known to have an autosomal dominant form of the

disease, 10 had autosomal recessive disease, 5 had Usher's syndrome, 5 had the X-linked recessive form, and the remaining 11 were isolated cases.

The criteria for their diagnosis included fundus examination, visual testing, and family history. In the fundus examination, the presence of bone spicule pigmentation in the midperiphery, a waxy-appearing optic disc, and attenuated blood vessels were carefully noted; fundus photographs were also obtained for documentation. Night blindness was verified by either electroretinography or dark adaptometry. Examination of other family members, when possible, was also made to confirm the diagnosis.

**Unaffected observers.** Fifty-five observers composed the unaffected group. An unaffected observer was defined as one who did not have a retinal/choroidal eye disease. The 55 unaffected observers were separated into two subgroups: (1) those who were color-normal and (2) those who had a congenital color vision deficiency.

The majority of the color-normal observers were staff members of the Illinois Eye and Ear Infirmary. Others, however, included unaffected relatives of patients or unaffected individuals who were seen for routine examination. The observers with congenital color vision deficiency were recruited either from those who responded to newspaper advertisements or from those who were diagnosed as color-deficient at the eye clinic.

**Color matching procedures.** Color matches were made on a model I Nagel anomaloscope that projected a 2.5 deg bipartite field onto the observer's retina. The intensity of the yellow field had a scale range of 0 to 87; the red/green mixture field had a scale range of 0 to 73. At maximum setting, the yellow field emitted  $5.38E + 8$  quanta/sec/sq deg ( $3.06E + 02$  trolands); the red field,  $1.16E + 09$  quanta/sec/sq deg ( $2.46E + 01$  trolands); and the green field,  $8.45E + 07$  quanta/sec/sq deg ( $6.70E + 01$  trolands). The dominant wavelengths of the primaries were about 545, 589, and 670 nm. To determine a color match, the experimenter set the red/green mixture (in a nonsystematic order) and the observer was instructed to fixate the center of the field and adjust the intensity of the yellow field for a match (when a match was possible).

In accordance with previous studies of individual differences among unaffected observers,<sup>9</sup> two subgroups of observers are distinguished. Group I (composing the majority) are observers who accept color matches only over a limited range of red/green mixtures. Group II (compos-

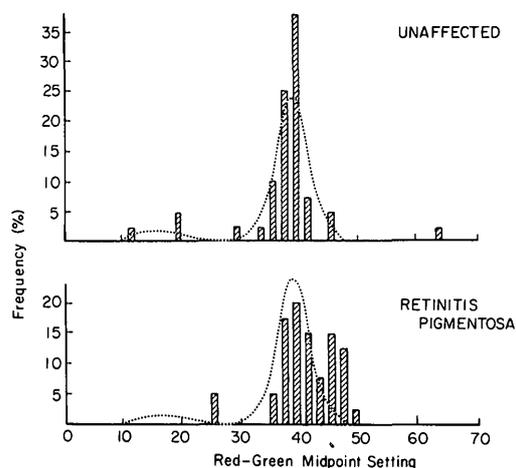


Fig. 2. Frequency distributions of the red/green midpoint settings. The frequency was based on a grouping interval comparable to a 0.05 log anomalous quotient step. The dotted curves illustrate the expected distribution of unaffected observers based on the data of previous investigators.<sup>11-12</sup>

ing the minority) includes observers who accept matches over the entire range of red/green mixtures. Those belonging to group I are trichromats, whereas those belonging to group II are usually dichromats. An exception to the latter generalization cited in Alpern and Wake.<sup>10</sup>

To compare the color matches among group I observers, the midpoint red/green match setting was computed for each observer. To compare the color matches among group II observers, the log sensitivity ratio at the red and green primary wavelengths was computed in accordance with the method of Alpern and Wake.<sup>10</sup>

### Results

**Group I observers: RP vs unaffected.** Fig. 1 shows the color matches of representative RP observers. This figure illustrates the kind of variability found for different patients.

Fig. 2 shows the frequency (percent observers) distribution of the red/green midpoint settings for both unaffected and RP group I observers. The unaffected sample was composed of 39 observers (23 men and 16 women); the RP sample was composed of 43 (23 men and 20 women).

The dotted curves illustrate the expected frequency distribution for unaffected observers, based on the data of Nelson<sup>11</sup> (his

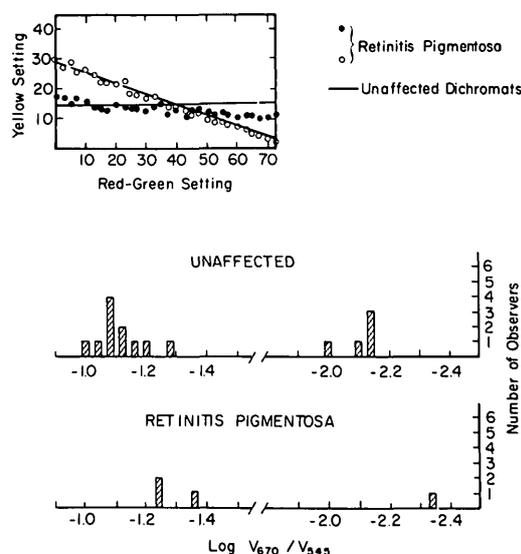


Fig. 3. Below, Frequency distribution of the log sensitivity ratios for deuteranopes (left) and protanopes (right). The upper distribution illustrates the unaffected, and the lower distribution, the RP data. Inset, Representative dichromatic color matches. The open symbols represent the data of a protanopic RP and the closed symbols represent those of a deuteranopic RP patient.

Fig. 2) and Schmidt<sup>12</sup> (his Fig. 3). (To compare Nelson's or Schmidt's data with those made on a Nagel anomaloscope, their data, expressed in log anomalous quotient, had to be scaled so that the central tendency would peak at the Nagel red/green setting of about 40, i.e., at the theoretical match setting for a trichromat as predicted from the color matches of our 11 deuteranopes and five protanopes.<sup>10</sup>) The results of the group I observers are shown to concur reasonably well with the expectation for unaffected observers. The color matches of most observers fell within 1.5 to 1/1.5 of the central tendency. These observers are called "color normal" or "typical trichromats." In addition, a few observers had matches that required less than the normal red/green mixture ratio; these observers are called "deuteranomalous trichromats." One observer was found to match with a greater than normal red/green ratio; he is referred to as a "protanomalous trichromat."

If RP has no effect on the optical density of

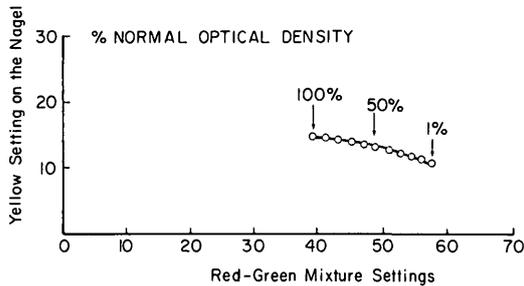


Fig. 4. Color matching settings predicted for decreasing cone optical density. Each point represents a decrement of 10% except the last point which is labeled 1%. The prediction assumes that both the red and green cone optical density are reduced simultaneously by the disease process. However, if one or the other cones are reduced at a faster rate, the new prediction is qualitatively similar to that illustrated by this figure.

cones, then the color matches of RP patients should be distributed along a frequency curve identical to that for the unaffected observers. To test this null hypothesis quantitatively, the mean of the unaffected color matches (excluding that of the protanomalous observer, since there was no protanomalous observer with RP) was compared to the mean of the color match settings of the RP sample. The difference between the means was found to be highly significant;  $p = 0.00044$  (one tail) for  $t = 3.456$  with 79 deg of freedom. The mean setting of the RP was to the right of that of the unaffected observers. When the deuteranomalous trichromats were excluded, the difference between the means was again highly significant ( $p = 0.000054$  for  $t = 4.0956$  with 73 degrees of freedom). Hence we reject the null hypothesis.

**Group II observers: RP vs. unaffected.** Sixteen (11 deuteranopes and five protanopes) unaffected and four RP (three deuteranopes and one protanope) observers composed group II. All were men. Representative color matches are illustrated in Fig. 3, inset. The yellow field settings for protanopes decreased with higher red/green ratios. The yellow settings for deuteranopes on the other hand remained fairly constant.

Fig. 3 (lower half) plots the log sensitivity

ratio for the red and green primaries. The difference between the means of the 16 unaffected and four RP dichromatic observers was found to be highly significant;  $p = 0.0017$  (one tail) for  $t = 3.633$  with 18 degrees of freedom. The log sensitivity ratios for the group II RP observers were shifted toward the right of that for the unaffected observers. Thus again we found a difference between the color matches of the RP and unaffected observers.

### Discussion

The dichotomy between groups I and II observers is expected on the basis of the frequency of X-linked recessive color vision traits in the human population. Most observers (unaffected or RP) were typical trichromats; they were both men and women. The remaining observers were anomalous trichromats or dichromats, and they were all men.

The main finding of this study is that the color matches of unaffected and RP observers differ in a specific way. The color matches of group I RP observers, on the average, were more protanomalous (i.e., required a greater than normal red/green mixture ratio) than the group I unaffected observers. The color matches of the group II RP observers, on the average, were more protanopic (i.e., required less yellow to match the red) than the group II unaffected observers. Similar changes in the color matches of some RP patients have been reported by previous investigators.<sup>13</sup>

Although our understanding of the effects of RP is incomplete, both the histology of donor eyes<sup>1-5</sup> and in vivo densitometry measurements<sup>6, 7</sup> suggest that the quantum-catching ability of certain photoreceptors in RP eyes is reduced. In particular, the densitometry measurements have shown reduced amounts of rhodopsin in affected retinas. This loss may reflect a shortening of the rod outer segments,<sup>7</sup> disorientation of their directionally sensitive discs, or reduction in visual pigment concentration.

The difference in the RP color matches re-

ported in this paper can be interpreted as evidence that the effective optical density of RP cone photoreceptors is also reduced. In accordance with the Beers-Lambert law, reduction in optical density alters the relative absorption spectrum of the photoreceptors.<sup>14</sup> The relative absorption spectrum becomes more narrow as the optical density is reduced, until the limiting case is reached in which the spectrum approaches the shape of the visual pigment extinction spectrum. This change in the cone absorption spectrum would necessarily alter an observer's color matches.<sup>15</sup> At low optical density, the color matches of trichromatic observers are expected to shift toward the protanomalous side of the normal Rayleigh equation.<sup>8</sup> For dichromatic observers, the expectation is a protanopic-like shift (i.e., a decrease in the log  $V_r/V_g$  ratio).<sup>16</sup> The results of the present study show just this sort of change in both groups of RP observers.

If the above interpretation is correct, estimates of the RP pigment density reduction can be calculated.<sup>15</sup> For typical group I observers, the relationship between cone pigment density and color matching settings on our Nagel anomaloscope is as shown in Fig. 4. From this curve, one can estimate that the optical density of the group I RP observers, on the average, is about 75% of normal. From similar calculations, the optical density of the deuteranopes with RP is estimated to be about 25% of normal. The reason for the greater reduction in the cone optical density of deuteranopes is not clear. It may perhaps be related to the extent of their disease progression. The mean age of the group I RP patients was about 32 vs. about 45 years for the deuteranopes. In addition, the youngest RP deuteranope had the more severe (X-linked) form of the disease. Alternatively, one could speculate that the red cones were affected to a greater extent than the green cones. In this case, our estimate of the optical density of group I RP observers will be less.

There are, however, other hypotheses which can explain the difference in the RP color matches. First, the difference in the

color matches may stem from a shift in the patients' fixation from the fovea to some eccentric retinal area. Others<sup>17</sup> have shown that color matches are shifted toward the protanomalous side of the normal Rayleigh equation when the stimulus field encompasses more and more eccentric retinal area. Presumably, this shift results from the greater input of extrafoveal cones that have an appreciably lower optical density than that of foveolar cones. In our ongoing investigation of deuteranopes with RP, we have found (using the fixation pointer in a Zeiss fundus camera) that one of three patients fixated eccentrically. The other two were found to fixate consistently within the fovea. We are uncertain as to the number of trichromatic RP observers who fixate eccentrically.

Second, the difference in the RP color matches may reflect a short-wavelength shift in the cone pigment extinction spectrum. Third, the difference may reflect the presence of a shearing force at the photoreceptor layer, so that the cones are no longer pointing towards the pupil center.

Finally, one can hypothesize that the difference in the RP color matches is attributable to a change in the transmissivity of their ocular media, although this appears to be the least likely explanation. If ocular transmissivity were the sole factor altering the color matches of RP observers, one would expect that the midpoint, match settings, and the matching range should not be correlated, since no correlation is normally found among unaffected observers.<sup>18</sup> In evaluating our raw data, however, we observe that the midpoint and matching values appear correlated. In general, the matching range is greater among individuals whose midpoint settings are greater (see Fig. 1). The correlation coefficient was found to be 0.48, which is significantly different from zero (at  $p < 0.01$  level).

In summary, our results provide evidence that the color matches of RP and unaffected observers differ. In the light of available known histological and densitometric alterations, the difference in the RP color matches

can best be attributed to a reduction of the cone optical density. Alternative hypotheses could also account for the present results.

**Note:** In the revision of the manuscript for publication, appendices describing quantitative procedures involved in our color matching procedures and limitations inherent in them were omitted for the sake of brevity.

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