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Genetics

Molecular patterns of X chromosome-linked color vision genes among 134 men of European ancestry

(visual pigment genes/color vision defects)

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ABSTRACT **We used Southern blot hybridization to study X chromosome-linked color vision genes encoding the apoproteins of red and green visual pigments in 134 unselected Caucasian men. One hundred and thirteen individuals (84.3%) had a normal arrangement of their color vision pigment genes. All had one red pigment gene; the number of green pigment genes ranged from one to five with a mode of two. The frequency of molecular genotypes indicative of normal color vision (84.3%) was significantly lower than had been observed in previous studies of color vision phenotypes. Color vision defects can be due to deletions of red or green pigment genes or due to formation of hybrid genes comprising portions of both red and green pigment genes [Nathans, J., Piantanida, T. P., Eddy, R. L., Shows, T. B., Jr., & Hogness, D. S. (1986) *Science* 232, 203–210]. Characteristic anomalous patterns were seen in 15 (11.2%) individuals: 7 (5.2%) had patterns characteristic of deuteranomaly (mild defect in green color perception), 2 (1.5%) had patterns characteristic of deuteranopia (severe defect in green color perception), and 6 (4.5%) had protan patterns (the red perception defects protanomaly and protanopia cannot be differentiated by current molecular methods). Previously undescribed hybrid gene patterns consisting of both green and red pigment gene fragments in addition to normal red and green genes were observed in another 6 individuals (4.5%). Only 2 of these patterns were considered as deuteranomalous. Thus, DNA testing detected anomalous color vision pigment genes at a higher frequency than expected from phenotypic color vision tests. Some color vision gene arrays associated with hybrid genes are likely to mediate normal color vision.**

X chromosome-linked red–green color vision anomalies affect about 8% of Caucasian males. Among individuals with defective color vision, more than half have deuteranomaly (mild green color perception defect, G′), while the remainder comprise approximately equal proportions of those with deuteranopia (severe green color perception defect, G^-), protanopia (severe red color perception defect, R^-), and protanomaly (milder red color vision defects, R′) (Table 1).

Nathans *et al.* (9, 10) cloned the genes encoding the apoproteins of red and green visual pigments and showed that males with normal color vision have one red pigment gene and one or more green pigment genes. Vollrath *et al.* (11) showed these genes to be arranged in tandem with the red pigment gene 5′ to the green pigment gene(s). Red–green color vision anomalies resulted from homologous recombination or gene conversion between the red and green pigment genes leading to gene deletions or full-length hybrid genes consisting of portions of both red and green pigment genes (such as 5′-green–3′-red and 5′-red–3′-green). Close homology (98% sequence identity) between coding sequences and between introns (Fig. 1) was postulated to be the cause of relatively frequent crossovers between the red and green pigment genes leading to a great variety of visual pigment gene arrangements.

We have studied the nature and frequency of visual pigment gene arrangements in unselected Caucasian males. Anonymous DNA samples from 134 randomly chosen White men (whose color vision status was unknown) were analyzed by genomic Southern blot hybridization with probes that detect the 5′ end, middle, and 3′ end of the red and green pigment genes. The gene patterns were deduced from the relative hybridization signals of the green- and the red-specific fragments generated by various restriction enzymes. The previously described normal patterns of one red visual pigment gene with one, two, or three green visual pigment genes (9) were confirmed. In addition, we detected individuals who carried four or five green pigment genes. However, the frequency of individuals with a normal arrangement of color vision genes (84.3%) was lower than the >90% frequency of normal color vision expected for a male Caucasian population (Tables 1 and 2). In addition to patterns known to be associated with color vision anomalies (10, 17), we detected pigment gene patterns that were not described previously. We suggest that some of these patterns are associated with phenotypically normal color vision.

METHODS

Sample Population and Southern Blot Analysis. A population of unselected Caucasian men from the Seattle area, which included 46 medical students and 88 employees of a large industrial firm, was used for this study. The blood specimens had been obtained with permission for population studies on blood lipids and were used anonymously in this investigation. Phenotypic color vision status therefore was unknown and could not be tested. The probes for the color vision pigment gene were supplied by J. Nathans. DNA extraction, gel electrophoresis, Southern blotting, hybridization and washing of blots, autoradiography, and densitometry were described previously (17).

Interpretation of Southern Blot Patterns. A_g and A_r *Eco*RI fragments, detected with probe A, encompass the 5′ and middle portions of the green and the red pigment genes, respectively (Figs. 1 and 2). B_g, C_g, B_r, and C_r were subfragments of the A_g and A_r fragments generated by digesting genomic DNA with *Eco*RI and *Bam*HI and were detected with probe A (Figs. 1 and 2). The D_g and D_r *Rsa* I fragments were derived from the 3′ region of the green and red genes, respectively, and were detected on Southern blots with probe B (Figs. 1 and 2).

Nathans *et al.* (9) found that males with normal color vision had equivalent A_g/A_r, B_g/B_r, C_g/C_r, and D_g/D_r ratios. These ratios could be 1:1, 2:1, or 3:1 depending on the presence of

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Table 1. Color vision defects in male populations of European origin

Ref.	Country	No. studied	% of population (% of those with defects) Protanopia	Protanomaly	Deuteranopia	Deuteranomaly	Total
	Testing by color vision charts followed by anomaloscopy of color-defective subjects						
1	Norway	9,049	0.88 (11.0)	1.04 (13)	1.03 (12.8)	5.06 (63.2)	8.01
2	Switzerland	2,000	1.60 (20.1)	0.60 (7.5)	1.50 (18.9)	4.25 (53.5)	7.95
3	Germany	6,863	1.09 (14.1)	0.68 (8.8)	1.97 (25.4)	4.01 (51.7)	7.75
4	Belgium	1,243	0.97 (11.7)	1.05 (12.7)	1.37 (16.5)	4.91 (59.1)	8.30
5	Greece	21,231	1.00 (12.6)	1.20 (15.1)	1.14 (14.3)	4.61 (58.0)	7.95
6	Netherlands	1,586	1.00 (13.7)	1.40 (19.2)	0.9 (12.3)	4.00 (54.8)	7.30
	Testing by anomaloscopy of all individuals						
7	United Kingdom	1,338	1.27 (14.4)	1.27 (14.4)	1.20 (13.6)	5.08 (57.6)	8.82
8	United States	1,440	3.3 (33.7)		6.5 (66.3)		9.8

Values in parentheses refer to proportions of given color vision defect among all X-linked color vision defects in a population.

one or more green pigment genes with the single red gene (Fig. 3). Therefore, inequality in the green/red fragment ratios in any individual indicated the presence of abnormal gene arrays—i.e., complete gene deletion or hybrid genes comprising pieces of both red and green genes.

As DNA fragments of different sizes usually did not transfer and hybridize equally to give equivalent signals on autoradiography, means and standard deviations of the density ratios were calculated from males with normal color vision pigment gene arrays (Table 3). These values were used as standards for the determination of abnormal gene arrangements (see also legend to Table 3).

In one class of abnormal gene arrays, one or more of the green or red pigment gene fragments were completely missing. For example, individuals 1225 and 1526 (Fig. 4) who had all the red pigment gene fragments, but no detectable green fragments, were classified as deuteranopes (G^-). On the other hand, the first four individuals listed in Fig. 5 lacked the D_r fragment (3′ end of the red gene replaced by that of the green gene) and individual M640 lacked both the C_r and D_r fragments. These persons were classified as protans (R^- or R′), since protanopic (R^-) and protanomalous (R′) patterns are not distinguishable by current molecular methodology.

In another class of anomalous gene arrays, one or more 5′-green–3′-red fusion genes were found in addition to normal green and red genes. An example was the deuteranomalous (G′) individual 110 (Fig. 4). Each of his A_g/A_r, B_g/B_r, and C_g/C_r density ratios corresponded to a gene ratio of 2 and his D_g/D_r ratio was equivalent to 0.5. Thus, there were two copies of the B_g and C_g fragments compared with only one copy of the B_r and C_r fragments. The existence of only one copy of the D_g fragment as compared to two copies of the D_r fragment indicated the presence of a 5′ and middle green fragment fused to a 3′ red fragment. The density ratios of individual 336 (Fig. 6) for A_g/A_r, B_g/B_r, C_g/C_r, and D_g/D_r corresponded to gene ratios of 0.5, 2, 0.5, and 0.5, respectively. These ratios indicated the presence of one copy of the C_g and D_g fragments, two copies of the C_r and D_r fragments, two copies of the B_g fragment, and one copy of the B_r fragment, indicating the presence of a 5′ green fragment fused to a middle and 3′ fragment of the red gene (Fig. 6).

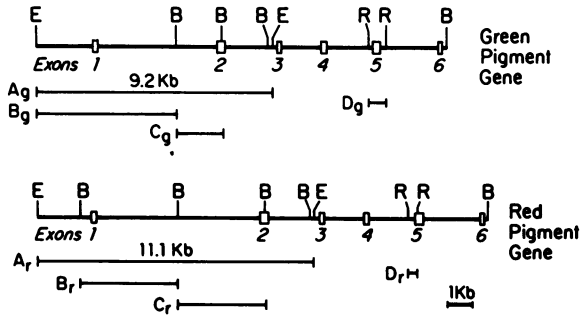


FIG. 1. X-linked color vision pigment genes. E, *Eco*RI cleavage site; *B*, *Bam*HI cleavage site; R, *Rsa* I cleavage site. A_g, B_g, C_g, and D_g are green pigment gene fragments; A_r, B_r, C_r, and D_r are red pigment gene fragments; A, B, and C fragments were detected by a 350-base-pair cDNA probe encompassing exon 1 and part of exon 2 of the red pigment gene (probe A). D fragments were detected by a 400-base-pair genomic DNA probe from the 3′ end of the fourth intron of the green pigment gene (probe B). kb, Kilobase.

A third class of anomalous gene arrangements, which most likely is the product of a double intragenic crossover event between a red and a green gene is illustrated by individual 1082 (Fig. 6). The A_g/A_r, B_g/B_r, C_g/C_r, and D_g/D_r density ratios corresponded to gene ratios of 1.5, 4, 1.5, and 4, respectively. This individual therefore had four copies of the B_g and D_g fragments, one copy of the B_r and D_r fragments, three copies of the C_g fragment, and two copies of the C_r fragment, indicating the presence of a fusion gene composed of the middle fragment of the red gene flanked by the 3′ and 5′ fragments of the green gene.

By relating the relative numbers of the 5′, middle, and 3′ fragments of the green and red pigment genes to the assumption that anomalous gene arrangements arose by homologous recombination, gene arrays can be inferred. More precise delineation of the fusion points in hybrid genes will have to await cloning and sequencing of these genes.

RESULTS

Of the 134 Caucasian men tested, 113 (84.3%) had green/red pigment gene ratios of 1:1 (n = 25), 2:1 (n = 58), 3:1 (n = 21), 4:1 (n = 6), or 5:1 (n = 3) based on their A_g/A_r and D_g/D_r ratios (Fig. 3, Table 3). These patterns were assumed to be normal color vision pigment gene arrays. Nathans *et al.* (9) had shown that males with normal color vision all had one red pigment gene in the presence of one, two, or three green pigment genes. We assumed normal color vision status for those with four or five green pigment genes. The other 21 patterns included 15 patterns that appeared to be similar to previously described gene rearrangements associated with color vision anomalies. These were divided into 9 deutan (G^- or G′; Fig. 4) and 6 protan (R^- or R′; Fig. 5) types. However, only the deutan types could be further classified into 2 deuteranopic (absence of green pigment gene, G^-) and 7 deuteranomalous (presence of green–red fusion gene, G′) individuals. The protan group included some gene patterns

Table 2. U.S. studies of color vision defects in White males (without subcategorization)

Ref.	Area	No. studied	% color-defective
12	Baltimore, MD	448	7.80
13	Stanford University, CA	1286	8.24
14	Denver, CO	795	8.40
15	Seattle, WA	4706	6.20

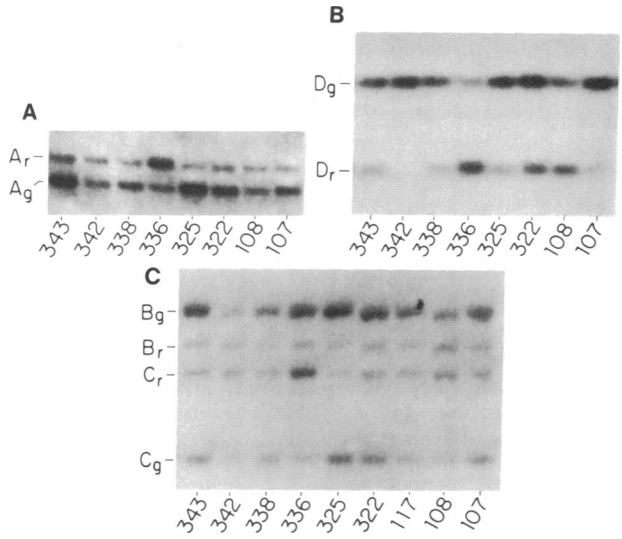


FIG. 2. Southern blots of X-linked color vision pigment genes. (*A*) *Eco*RI digest. A_r, 5′ fragment from red pigment gene; A_g, 5′ fragment from green pigment gene. (*B*) *Rsa* I digest. D_g, 3′ fragment from green pigment gene; D_r, 3′ fragment from red pigment gene. (*C*) *Bam*HI/*Eco*RI digest. B_g, 5′ fragment from A_g; B_r, 5′ fragment from A_r; C_r, 3′ fragment from A_r; C_g, 3′ fragment from A_g. Individuals 343, 338, 322, 108, and 107 have normal color vision pigment genes (see Fig. 3) with a green/red ratio of 3:1, 2:1, 3:1, 2:1, and 1:1, respectively; 342 has a protan (R^- or R′) pattern (see Fig. 5); 325 has a deuteranomalous (G′) pattern (see Fig. 4); and 336 has a "new" pattern (see Fig. 6).

that had been found previously (10, 17) in association with both protanopia (R^-) and protanomaly (R′). As we did not know the color vision status of individuals in our sample, we grouped all protan patterns (i.e., absence of an intact red pigment gene replaced by a red–green fusion gene) together. Individual 1238 was included in the protan group because Southern blot analyses showed that he did not have a complete red pigment gene: he had B_r and D_r bands but not a C_r band.

Six "new" pigment gene rearrangements (Fig. 6) were found. These rearrangements consisted of arrays with an intact red gene, intact green gene(s), and at least one previously undescribed hybrid gene. In four individuals (nos. 350, 352, 1082, and 1084) the C_g (middle) fragment of a green pigment gene had been replaced by the C_r fragment of a red pigment gene. The sequences derived from the red pigment gene could have included variable portions of this gene. Such segments might extend as far as the *Bam*HI site of intron 1 to include sequences up to and including exon 4 (Fig. 1). More

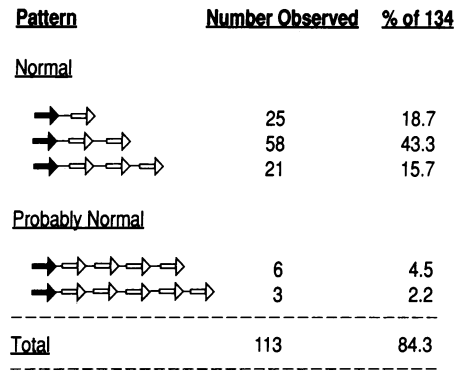


FIG. 3. Normal X-linked color vision pigment gene patterns. The solid and open arrows represent red and green pigment genes, respectively. All individuals have one red pigment gene and one or more green pigment genes.

than one intragenic crossover would have had to occur to produce these patterns. While these four arrays are most likely associated with normal color vision, a deuteranomalous (G′) phenotype cannot be ruled out. However, the relatively high frequency of these patterns make such an interpretation less likely.

In two individuals (nos. 336 and 986), hybrid genes had a small 5′ piece of a green pigment gene (B_g), while the rest of the gene was of red pigment origin. We suggest that these arrays are probably associated with deuteranomaly (G′), since the hybrid genes in these cases contain more DNA derived from the red pigment gene. The proportions found of deuteranopic (G^-) (11.8%), deuteranomalous (G′) (52.9%), and protan (R^- or R′) (35.3%) patterns among 17 arrays considered to be associated with abnormal color vision were similar to those expected from phenotypic testing (Table 1).

DISCUSSION

Nathans *et al.* (9, 10) elucidated the nature of normal and abnormal visual pigment gene arrangements. In an earlier report, we documented the molecular arrangements of a variety of X chromosome-linked color vision defects in a large kindred including women carriers (17), and one of us has discussed the implications of various molecular findings (16). The present investigation studied a larger, unselected population and detected a variety of different arrangements of visual pigment genes.

Three of these patterns—i.e., the presence of one, two, or three green pigment genes alongside one red pigment gene—were known to be associated with normal color vision (9). We

Table 3. Green/red pigment gene fragment ratios of males with normal pigment genes

Ratio of green genes to red genes	Fragment ratio, mean ± SD (*n* subjects)			
	A_g/A_r	B_g/B_r	C_g/C_r	D_g/D_r
	Standard procedure*			
1:1	1.05 ± 0.13 (23)	1.64 ± 0.81 (5)	0.63 ± 0.4 (5)	1.24 ± 0.34 (23)
2:1	2.02 ± 0.24 (48)	3.70 ± 1.02 (9)	1.2 ± 0.35 (9)	2.62 ± 0.64 (48)
3:1	3.04 ± 0.42 (19)	4.4 ± 1.65 (6)	2.09 ± 0.62 (6)	3.11 ± 0.89 (19)
4:1	4.01 ± 0.39 (5)	6.56 ± 1.88 (2)	3.13 ± 1.23 (2)	5.14 ± 1.06 (5)
≥5:1	5.45 (3)			6.50 (3)
	Modified procedure†			
2:1	1.96 ± 0.44 (10)	1.77 ± 0.61 (10)	1.57 ± 0.56 (10)	2.33 ± 0.53 (10)

Symbols A_g, A_r, etc. are explained in legend of Fig. 1.

*Ref. 17.

†Fifteen out of 113 individuals with normal patterns were studied with a modified procedure that included 15 min of acid (1 M HCl) treatment of the gels after electrophoresis and before denaturation. This alternative gave better transfer of DNA to nitrocellulose filters and resulted in B_g/B_r and C_g/C_r ratios that were closer to the expected ratios. This altered technique is therefore recommended. Ten out of the 15 normal individuals studied by the modified procedure had a 2:1 ratio.

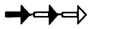
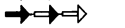
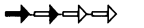
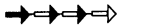
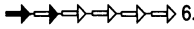
Subject	Gene Arrangement	Ag/Ar	Bg/Br	Cg/Cr	Dg/Dr
Deuteranopia (G⁻)					
1225		0	ND	ND	0
1526		0	0	0	0
Deuteranomalous* (G′)					
110		2.35	3.78	1.04	0.66
1226		2.10	3.36	1.15	0.55
M632		1.74	ND	ND	0.79
1216		2.87	6.77	1.56	1.38
117		2.88	4.07	1.11	0.63
990		2.75	ND	ND	0.59
325		6.20	ND	ND	2.29

FIG. 4. Deutan (G⁻ or G′) defects. See legend of Fig. 1 for explanation of A_g, B_g, C_g, D_g, A_r, B_r, C_r, and D_r; ND, not done. The solid and open arrows represent red and green pigment genes, respectively. Hybrid genes consist of both green and red pigment gene segments, as illustrated. For the deuteranomalous patterns (*) the position of the hybrid gene relative to the green pigment gene in each array cannot be determined with these methods. It is possible that one or several normal green genes are located 5′ to the hybrid gene.

also detected individuals with four or five green pigment genes who presumably also have normal color vision (Fig. 3). The distribution of the number of green pigment genes among the 113 individuals with normal gene arrangements was one, 22.1%; two, 51.3%; three, 18.6%; and four or more, 8.0%. These values approximated a normal distribution with a mode of two green pigment genes. This result corresponds to the findings of Nathans *et al.* (9), who found a distribution in 18 normal individuals of one, 16.7%; two, 61.1%; and three, 22.2%. If we assume that green/red pigment gene ratios from 1:1 to 5:1 are associated with normal color vision, the frequency of individuals with normal color pigment gene arrangements in our study (84.3%) was lower than that expected from the single study (8) of unrelated U.S. males that tested every subject with anomaloscopy (90.2%, $P < 0.05$; Table 1).† It is conceivable that the frequency of color vision anomalies in the sampled population was 15.7% (i.e., 100% − 84.3%), a value that is much higher than that observed in all phenotypic studies of populations of European origin and more than twice as high as the frequency of a previously studied Seattle population (15). It is more probable that four of the new patterns (individuals 350, 352, 1082, and 1084) found in this study (Fig. 6) are associated with normal color vision. With this interpretation the frequency of individuals postulated to have normal color vision (87.3%) resembled the anomaloscopic findings (90.2%, $P > 0.25$).

Among the various gene rearrangements associated with color vision anomalies (Figs. 4–6) deuteranopia (G⁻) can be qualitatively detected on Southern blots by the absence of one or more green pigment gene bands. Protanopia (R⁻) and protanomaly (R′) can also be readily detected by the absence of one or more of the red pigment gene bands. However, they cannot be differentiated from each other by the DNA techniques currently employed (10, 17). Detection of the most common defect, deuteranomaly (G′), requires densitometric quantitation of the red and green pigment gene bands.

At first glance, the finding of one red pigment gene and the presence of more than one green pigment gene in males with normal color vision seems to explain the higher frequency of

†It should be noted that the frequency of color vision defects was somewhat higher when anomaloscopy was done on all subjects (see Table 1). In most studies, color charts were initially utilized and anomaloscopy was done only on those found to be color-defective.

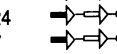
Subject	Gene Array	Ag/Ar	Bg/Br	Cg/Cr	Dg/Dr
Protanopia (R⁻) or Protanomaly (R′)					
342		1.02	2.22	0.97	∞
985		1.90	ND	ND	∞
1224		1.98	4.02	1.14	∞
347		2.72	3.37	1.18	∞
M640		∞	1.50	∞	∞
Possibly Protan (R⁻ or R′)					
1238		∞	5.38	∞	1.86

FIG. 5. Protan (R⁻ or R′) defects. See legend of Fig. 1 for explanation of A_g, B_g, C_g, D_g, A_r, B_r, C_r, and D_r; ND, not done. The solid and open arrows represent red and green pigment genes, respectively. Hybrid genes consist of both red and green pigment gene segments as illustrated.

deuteranomaly (G′), as one might then expect more green genes than red genes to participate in crossover events between red and green genes. However, modeling of recombination between pigment genes (Fig. 7) always yields equal frequencies of deuteranomaly (G′) and of protan (R⁻ or R′) defects. The presence of several green pigment genes as compared to only one red pigment gene therefore cannot account for the higher frequency of deuteranomalous patterns. However, all studies of populations of European origin (Table 1) showed deuteranomaly to be more frequent than protan color vision defects. This finding could be explained by nonreciprocal gene conversion or by selection for deuteranomaly or selection against other color vision defects.

It will be of interest to examine the color vision gene patterns of populations that have a lower incidence of color vision anomalies, such as the Japanese [5.05% (18)] and the American Blacks [3.9% (19)]. One might expect fewer color vision normal individuals with multiple green pigment genes in these populations as compared with Caucasian individuals, who often have two or more green pigment genes. With fewer green pigment genes the opportunities for nonhomologous crossover would be lessened, causing a lower frequency of deletions or fusion genes that are responsible for the various X-linked color vision defects.

This study extends data on the heterogeneity of genotypes for color vision among Caucasian males and establishes that some individuals may have as many as four or five green pigment genes. The lower-than-expected frequency of normal pigment gene patterns as well as the makeup of several hybrid gene patterns suggest that certain hybrid gene patterns may be associated with normal color vision. Further studies

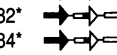
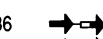
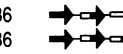
Subject	Gene Array	Ag/Ar	Bg/Br	Cg/Cr	Dg/Dr
Probably Normal					
352		0.93	7.06	0.86	2.89
350		0.30	5.54	0.17	5.45
1082*		2.02	3.47	1.17	3.59
1084*		1.87	2.41	1.46	4.02
Possibly Deuteranomalous					
336		0.42	3.97	0.39	0.58
986		1.49	9.97	0.80	0.84

FIG. 6. "New" pigment gene patterns. See legend of Fig. 1 for explanation of A_g, B_g, C_g, D_g, A_r, B_r, C_r, and D_r. The solid and open arrows represent red and green pigment genes, respectively. Hybrid genes consist of both green and red pigment gene segments, as illustrated. Subjects 1082 and 1084 (*) were studied by a modified Southern blotting method (see Table 3).

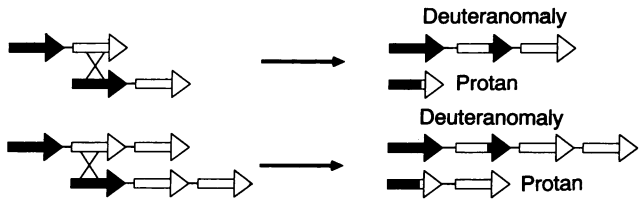


FIG. 7. Crossover products resulting from recombination between red and green pigment genes. The solid and open arrows represent red and green pigment genes, respectively. Hybrid genes consist of both red and green pigment genes, as illustrated. The expected ratio of deuteranomalous (G′) to protan (R′ and R^-) patterns is 1:1. However, all phenotypic color vision studies have shown an excess of deuteranomaly (G′).

with psychophysical methods for assessing color vision are needed.

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