RECOMBINATION VALUE BETWEEN PROTAN-TYPE AND DEUTAN-TYPE COLOR-BLINDNESS LOCI¹⁾

KATUMI TANAKA

Department of Human Genetics,
Tokyo Medical and Dental University, Tokyo

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Among the several hypotheses proposed for the genetics of the red-green color-blindness, the two-locus hypothesis is widely accepted on the ground that (1) the frequency of color-blind females is smaller than the figure expected from the frequency of all protan- and deutan-type color-blinds among males, (2) women having two abnormal genes, one of the deutan series and the other of the protan series, usually have normal color vision, and (3) a sibship reported by Vanderdonck and Verriest (1960) in which segregation has occurred into 1 protan, 2 deutan and 2 normal brothers — this sibship is regarded by many authors as affording a decisive evidence of the recombination between the deutan and protan-type loci.

If this two-locus hypothesis is valid, the recombination value between the loci could be estimated. The color-blindness genes as well as the Xg blood type gene are important markers on the X-chromosome. Most of the previous linkage studies involving color-blindness genes were carried out without discriminating the protan- and deutan-type anomalies. If these loci are very closely linked, such discrimination might not be necessary for practical purpose. If, on the other hand, the recombination value between them is large enough, linkage tests should be made separately.

The linkage value may be estimated by two different means. First, data of recombinations between a marker gene and the gene for each type of color-blindness would fit for the purpose. Such study has been made by using the Xg blood-type gene and the glucose-6-phosphate dehydrogenase (G6PD) deficiency gene as markers. Adams et al. (1963) found no significant deviation from 0.5 for the recombination value between the locus for the Xg and that for color-blindness. On the other hand, Porter et al. (1962) estimated the recombination value between the locus for G6PD deficiency and that for deutan-type anomaly as 5 %, and that for G6PD deficiency

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and that for protan-type anomaly as 0 %, based on data of 6 families and 2 families respectively. The basic data of this study, however, seem to be too meager to enable one to estimate the exact distance between these color-blindness loci.

Second, the recombination value between the loci may be estimated directly without intermediation of any other marker gene. Renwick (1961) believes a very close linkage of the two loci, since normal sib nor any sib with both protan- and deutan-type anomalies were found among the 21 males from well-documented sibships, each of which contained at least two different-type color-blind male members. According to him, it is unlikely (at the 5 % significance level) that the recombination value between these two loci is greater than 12 %. However, as pointed out below, the two-boy families used by him (Jaeger 1951; Waaler 1927; etc.) are unsuitable for his purpose. This makes his estimate rather uncertain. In the following, a more elaborate method for the estimation will be presented.

EPISTASIS IN THE MANIFESTATION OF COLOR-BLINDNESS TRAIT

Provided that the two types of color-blindness are governed by mutant genes located on different loci, an important problem would present itself concerning the phenotype of the man who has the both genes.

There seems to be the following five possibilities: He may be

- (1) normal (Pickford 1950),
- (2) totally color-blind (Kuhn 1942),
- (3) color-blind with compound anomaly of protan and deutan series (Walls and Mathews 1952),
- (4) color-blind of the deutan type (Vogt et al. 1922; Ichikawa et al. 1963), or
- (5) color-blind of the protan type (Nemoto et al. 1961).

The possibilities (1) and (2) may be left out of regard, since they have never been supported by any other author. The most serious difficulty in hypothesis (3) is, as pointed out by Stern (1958), that only very few cases of such double type anomalies have been reported, while their occurrence should be much commoner (i. e. 1.5 % among the Caucasian and 0.7 % among the Japanese color-blind males). Stern (1958) claims that this discrepancy is a strong evidence for the single locus hypothesis. However, Vanderdonck and Verriest's pedigree seems to stand firmly for the two-locus hypothesis. Moreover, there are some evidences indicating that a man having the abnormal genes on both loci may show either protan- or deutan-type anomaly. Vogt and Klainguti (1922) report on a family consisting of a deuteranopic father, a normal mother, and a protanopic daughter. A similar family discovered in Hokkaido by Ichikawa et al. (1963) includes a deuteranopic father, a normal mother and a

Fig. 1. Pedigrees of color-blindness suggesting epistasis and explanation given by original authors.

protanomalous daughter. A plausible explanation of these pedigrees is that (1) the mothers were heterozygous for an abnormal gene of the protan series, (2) the fathers were doubly hemizygous for the abnormal genes of both series, but expressed the deutan-type anomaly only. Thus, in these families the deutan-type gene seems to be epistatic in manifestation over the protan-type gene.

On the other hand, Nemoto and Murao (1961) report on a family found in Nagasaki which includes a normal father, a deuteranopic mother, a deuteranopic son and two protanomalous sons. The authors' explanation is that the mother was probably homozygous for the deuteranopic gene and heterozygous for the protanomalous gene, the protanomalous sons were doubly hemizygous for both anomalous genes, and, accordingly, the protan-type gene might be epistatic over the deutan-type gene. However, there may be another possibility that the mother was doubly heterozygous for both anomalous genes and manifested the deuteranopic anomaly only.

These cases seem to provide evidence for the phenomenon of epistatic relation in the manifestation of color-blindness genes, though it remains to be clarified whether the double hemizygote always manifests the deutan-type anomaly or it manifests the protan-type anomaly in some instance.

ESTIMATION OF THE RECOMBINATION VALUE

If it is accepted that one type of color vision anomaly is epistatic over the other in manifestation, recombination value between the loci for the two color vision anomalies may be estimated by modifying Smith's method for linkage test (1959) based upon Bayes' theorem.

Let $\text{Prob}(F_i | \theta)$ denote the chance of getting Family F_i when the recombination value is known to be θ , and $\text{Prob}(S | \theta)$ the chance of the observed sample S which contains $F_1, F_2, \dots, F_n$ families.

We can write

$$\text{Prob } (S \mid \theta) = \text{Prob } (F_1 \mid \theta) \cdot \text{Prob } (F_2 \mid \theta) \cdots \cdots \text{Prob } (F_h \mid \theta).$$

Let

$$\lambda(\theta) = \text{Prob } (S \mid \theta) = \text{Prob } (F_1 \mid \theta) \cdot \text{Prob } (F_2 \mid \theta) \cdots \cdots \text{Prob } (F_h \mid \theta) \cdots \cdots (1)$$

Since the genes for the red-green color-blindness are known to be located on the X-chromosome, their linkage is beyond question. But, the recombination value at which $\lambda(\theta)$ distribution has a peak is to be found.

For the purposes of practical computation, it is much more convenient to work with the logarithm of the value than the value itself. Thus, let

$$\log \lambda(\theta) = z_1(\theta) + z_2(\theta) + \cdots \cdots + z_h(\theta) = Z(\theta)$$

where $z_i(\theta)$ denotes

$$\log \text{Prob } (F_i \mid \theta).$$

Scores $z(\theta)$ are calculated as follows.

In the subsequent discussion, minor variations in each color-blindness series, such as protanomaly, extreme protanomaly, protanopy, etc., are not distinguished.

Let P be the abnormal gene of the protan series,

P^+ the normal gene of this series,

D the abnormal gene of the deutan series,

D^+ the normal gene of this series, and

θ recombination value between these loci.

It is assumed first a man who is doubly hemizygous for P and D , manifests the deutan type anomaly. If a woman is doubly heterozygous for both loci in the phase of coupling, $P^+ \cdot D^+ / P \cdot D$, her sons will be segregated into

Genotype	$P \cdot D^+$	$P^+ \cdot D$	$P \cdot D$	$P^+ \cdot D^+$
Ratio	$\frac{\theta}{2}$	$\frac{\theta}{2}$	$\frac{1-\theta}{2}$	$\frac{1-\theta}{2}$
Phenotype	Protan	Deutan		Normal
Ratio	$\frac{\theta}{2}$	$\frac{1}{2}$		$\frac{1-\theta}{2}$

If she is doubly heterozygous in the phase of repulsion, $P^+ \cdot D / P \cdot D^+$, her sons would be

Genotype	$P \cdot D^+$	$P^+ \cdot D$	$P \cdot D$	$P^+ \cdot D^+$
Ratio	$\frac{1-\theta}{2}$	$\frac{1-\theta}{2}$	$\frac{\theta}{2}$	$\frac{\theta}{2}$
Phenotype	Protan	Deutan		Normal
Ratio	$\frac{1-\theta}{2}$	$\frac{1}{2}$		$\frac{\theta}{2}$

Obviously, the genotype of the father is not concerned with the estimation; therefore, sons of a mother, but of different fathers can be used for the purpose.

If the probability of getting protan-type, deutan-type and normal sons are p , d , and n , respectively ($p + d + n = 1$), the distribution of families having s sons may be expressed by expansion of $(p + d + n)^s$. Of these terms, those containing both p and d correspond to families usable for the linkage study.

For the detection of a doubly heterozygous mother, the sibship should contain at least one deutan type son and one protan type son. If she has two sons only, no information for recombination value could be obtained. Families suitable for the present study should have

- (1) a normal mother,
- (2) three boys or more examined, of whom
- (3) at least one shows the protan-type anomaly and another the deutan-type anomaly.

For example, probabilities of usable three-son families are expected to be

3 p^2d for families containing 2 protan and 1 deutan type sons (F_{PPD} family),

3 pd^2 for families containing 1 protan and 2 deutan type sons (F_{PDD} family),

6 pdn for families containing 1 protan, 1 deutan and 1 normal sons (F_{PDN} family).

By putting the segregation ratios listed above into 3 p^2d , 3 pd^2 and 6 pdn , probabilities of getting families of each type for various recombination values can be calculated (Table 1).

Table 1. Probability that different types of 3 boy family usable for linkage study occur

Type of family			Phase of mother		Sum	Proportion expected in a random sample
Protan	Deutan	Normal	$P^+ \cdot D^+ / P \cdot D$	$P^+ \cdot D / P \cdot D^+$		
2	1	0	$3 \left(\frac{\theta}{2} \right)^2 \left(\frac{1}{2} \right)$	$3 \left(\frac{1-\theta}{2} \right)^2 \left(\frac{1}{2} \right)$	$\frac{3(1-2\theta+2\theta^2)}{8}$	$\frac{1-2\theta+2\theta^2}{2(1+\theta-\theta^2)}$
1	2	0	$3 \left(\frac{\theta}{2} \right) \left(\frac{1}{2} \right)^2$	$3 \left(\frac{1-\theta}{2} \right) \left(\frac{1}{2} \right)^2$	$\frac{3}{8}$	$\frac{1}{2(1+\theta-\theta^2)}$
1	1	1	$6 \left(\frac{1-\theta}{2} \right) \left(\frac{1}{2} \right) \left(\frac{\theta}{2} \right)$	$6 \left(\frac{1-\theta}{2} \right) \left(\frac{1}{2} \right) \left(\frac{\theta}{2} \right)$	$\frac{12\theta(1-\theta)}{8}$	$\frac{2\theta(1-\theta)}{1+\theta-\theta^2}$
Total					$\frac{6(1+\theta-\theta^2)}{8}$	1

If the sample is chosen at random and equal incidence of coupling and repulsion phases in the population is assumed, the proportion of the three types of families in the sample would be

$(1 - 2\theta + 2\theta^2) / 2(1 + \theta - \theta^2)$ for F_{PPD} families,

$1/2(1 + \theta - \theta^2)$ for F_{PDD} families, and

$2\theta(1 - \theta) / (1 + \theta - \theta^2)$ for F_{PDN} families, respectively.

Thus, for example z score for a F_{PPD} family is, if $\theta = 0.1$, given by

$$z(0.1) = \log \left\{ \frac{1 - 2(0.1) + 2(0.1)^2}{2\{1 + 0.1 - (0.1)^2\}} \right\}$$

Similar calculations were made for various family sizes and recombination fractions, the value thus obtained being listed in Table 2.

Table 2. Scores $z(\theta)$ for 3-5 boy families

Type of family			θ						
P	D	N	0.05	0.10	0.15	0.20	0.30	0.40	0.50
2	1	0	— .3645	— .4247	— .4810	— .5330	— .6204	— .6785	— .6990
1	2	0	— .3212	— .3385	— .3531	— .3655	— .3838	— .3944	— .3979
1	1	1	—1.0424	— .7821	— .6456	— .5593	— .4595	— .4122	— .3979
3	1	0	— .6448	— .7430	— .8393	— .9333	—1.1094	—1.2466	—1.3010
2	2	0	— .4453	— .5165	— .5917	— .6407	— .7381	— .8016	— .8239
1	3	0	— .5781	— .6064	— .6299	— .6493	— .6778	— .6937	— .6990
2	1	1	—1.4243	—1.1750	—1.0473	— .9681	— .8783	— .8364	— .8239
1	1	2							
1	2	1	—1.1232	— .8740	— .7463	— .6671	— .5772	— .5354	— .5229
4	1	0	— .9126	—1.0429	—1.1713	—1.2992	—1.5522	—1.7750	—1.8751
3	2	0	— .5892	— .6956	— .7978	— .8962	—1.0778	—1.2177	—1.2730
2	3	0	— .5658	— .6451	— .7163	— .7797	— .8826	— .9489	— .9720
1	4	0	— .8235	— .8600	— .8894	— .9132	— .9470	— .9659	— .9720
3	1	1	—1.5881	—1.3898	—1.3097	—1.2745	—1.2593	—1.2676	—1.2730
1	1	3							
2	2	1	—1.3687	—1.1276	—1.0058	— .9310	— .8467	— .8076	— .7959
1	2	2							
1	3	1	—1.2437	—1.0026	— .8808	— .8060	— .7217	— .6826	— .6709
2	1	2	—2.3909	—1.8723	—1.5992	—1.4258	—1.2234	—1.1263	—1.0969

By summing up $z(\theta)$ scores for all families the total score $Z(\theta)$ is obtained. A peak of $\lambda(\theta)$ [= antilog $Z(\theta)$] distribution would give an estimate of recombination fraction, if it is assumable that the θ distribution is approximately uniform on the linkage map.

NUMERICAL EXAMPLE

Five suitable pedigrees have been found in the literature (Göthlin 1924; Brunner 1930; Kondo 1941 Family I and II; Ichikawa et al. 1963). In addition, Vanderdonck and Verriest's pedigree (1960) may be used if the protanomalous mother is regarded as a double heterozygote for color-blindness genes of the two series.

Computations of $z(\theta)$ scores of these 6 families for various recombination values and the total score $Z(\theta)$ are presented in Table 3. Under assumption that the deutan type is pistatic over the protan type in manifestation the distribution of $\lambda(\theta)$ has its

Fig. 2. Pedigrees used for estimation of recombination value.

peak near 0.05. A more elaborate calculation reveals that the peak is located at about 0.06.

If the protan type is assumed to be epistatic over the deutan type, $z(\theta)$ scores could be obtained by exchanging p and d in the foregoing calculations; i.e., $z(\theta)$ scores for, say, F_{PPD} under one assumption is given by scores for E_{PDD} under the other assumption. In the second assumption, the peak of $\lambda(\theta)$ distribution should be found at about 0.15.

Obviously, the available data are too meager to yield an exact recombination

Table 3. Total z score for linkage test of color-blindness

1) Assuming that the deutan type gene is epistatic over the protan type gene.

	P	D	N	0.05	0.10	0.15	0.20	0.30	0.40	0.50
Kondo, I	3	1	0	— .6448	— .7430	— .8393	— .9333	— 1.1094	— 1.2466	— 1.3010
Kondo, II	2	1	0	— .3645	— .4247	— .4810	— .5330	— .6204	— .6785	— .6990
Ichikawa	2	2	0	— .4453	— .5165	— .5917	— .6407	— .7381	— .8016	— .8239
Göthlin	2	2	0	— .4453	— .5165	— .5917	— .6407	— .7381	— .8016	— .8239
Brunner	1	2	0	— .3212	— .3385	— .3531	— .3655	— .3838	— .3944	— .3979
Vanderdonck et al.	1	2	2	— 1.3687	— 1.1276	— 1.0058	— .9310	— .8467	— .8076	— .7959
Total score $Z(\theta)$				— 3.5898	— 3.6668	— 3.8626	— 4.0442	— 4.4365	— 4.7303	— 4.8416
$\lambda(\theta) = \text{antilog } Z(\theta) \times 10^5$				25.716	21.538	13.722	9.032	3.660	1.861	1.440
$\lambda(\theta)/\lambda(0.5)$				17.86	14.96	9.53	6.27	2.54	1.29	1

2) Assuming that the protan type gene is epistatic over the deutan type gene.

	0.05	0.10	0.15	0.20	0.30	0.40	0.50
Kondo, I	-.5781	-.6064	-.6299	-.6493	-.6778	-.6937	-.6990
Kondo, II	-.3212	-.3385	-.3531	-.3655	-.3838	-.3944	-.3979
Ichikawa	-.4453	-.5165	-.5917	-.6407	-.7381	-.8016	-.8239
Göthlin	-.4453	-.5165	-.5917	-.6407	-.7381	-.8016	-.8239
Brunner	-.3645	-.4247	-.4810	-.5330	-.6204	-.6785	-.6990
Vanderdonck et al.	-2.3909	-1.8723	-1.5992	-1.4258	-1.2234	-1.1263	-1.0969
Total score $Z(\theta)$	-4.5453	-4.2749	-4.2466	-4.2550	-4.3816	-4.4961	-4.5406
$\lambda(\theta) = \text{antilog } Z(\theta) \times 10^5$	2.849	5.310	5.668	5.559	4.153	3.191	2.880
$\lambda(\theta)/\lambda(0.5)$	0.99	1.84	1.97	1.93	1.44	1.11	1

Fig. 3. Distribution of relative probability [shown by $\lambda(\theta)/\lambda(0.5)$] for the recombination value, assuming the deutan type gene is epistatic over the protan type gene.

value. Thorough informations of families suitable for such linkage studies are to be looked for. The sample must be selected randomly, since if families suggesting crossing-over are chosen with preference, recombination value may be estimated as higher than the real value. It is also hoped that more data concerning the epistasis relationship between the two color-blindness types genes will be obtained.

SUMMARY

Evidences indicate that a man, doubly hemizygous for the abnormal genes of both series of color-blindness, manifests anomaly either of the protan- or the deutan-type. A method for estimating recombination value between the loci for the two

color-blindness genes has been devised by modifying Smith's method for linkage test based upon Bayes' theorem, and $z(\theta)$ scores for various values of family size and recombination fraction are presented.

Families usable for such study should have (1) a phenotypically normal mother, (2) three or more boys examined for color vision of whom (3) at least one shows the protan-type anomaly and another the deutan-type anomaly.

Calculation based on 6 suitable pedigrees has yielded that the recombination value, at which the probability obtaining such a sample is highest, is about 0.06 under the assumption that the deutan type anomaly is epistatic over the protan type anomaly and about 0.15 if it is assumed that the protan type is epistatic over the deutan type.

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