An Analysis of Some Data on the Linkage Between Xg and Colorblindness in Man

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INTRODUCTION

JACKSON, SYMON AND MANN (1964) in the preceding paper have presented extensive pedigree data bearing on the linkage between the *Xg* blood group locus and the *deutan* and *protan* sites on the X chromosome. The lod scores (log odds) are here calculated from 26 pedigrees in that study. A further eight small pedigrees were totally uninformative. An IBM 7090 computer was used (Renwick and Schulze, 1961), the program treating each pedigree as a single unit and considering all possible genotypes for persons of uncertain or unknown genotype. In these calculations, the usual frequencies for Americans of European origin were used for the Xg^a, *deutan*, and *protan* alleles (0.64, 0.06, 0.02), although it appears possible, from evidence in the pedigrees themselves, that the frequency of protan defects in this inbred group might be somewhat higher than such figures would predict. For example, there are two men with a protan defect and one with a deutan defect among 36 unrelated husbands tested for color vision and lacking tested grandsons via daughters. (Any such grandson might, by being colorblind, have caused the pedigree to be selected for study. Hence the maternal grandfather in these pedigrees is rather more likely to be colorblind than the average man in the same community and has been excluded from the count.)

RECOMBINATION FRACTION BETWEEN *Xg* AND THE *DEUTAN-PROTAN* REGION OF THE X

Table 1 gives the lod scores (Morton, 1955; Smith, 1959) for various values of the recombination fraction, θ, between *Xg* and the *deutan-protan* region (on the approximation that the *deutan* and *protan* sites are sufficiently close together that they have very similar true recombination fractions, θ, with *Xg*). In this analysis, no allowance has been made for possible misclassification of phenotype or for any undetected illegitimacies. There was no selection at all at one locus (the *Xg* locus), and therefore no ascertainment correction is needed (Morton, 1955). Figure 1 (antilods plotted against θ) shows the relative likelihood of obtaining these families for various values of θ, the peak being at $\theta = 0.42$ (0.42, 0.40 for *Xg* : *deutan* and *Xg* : *protan* separately).

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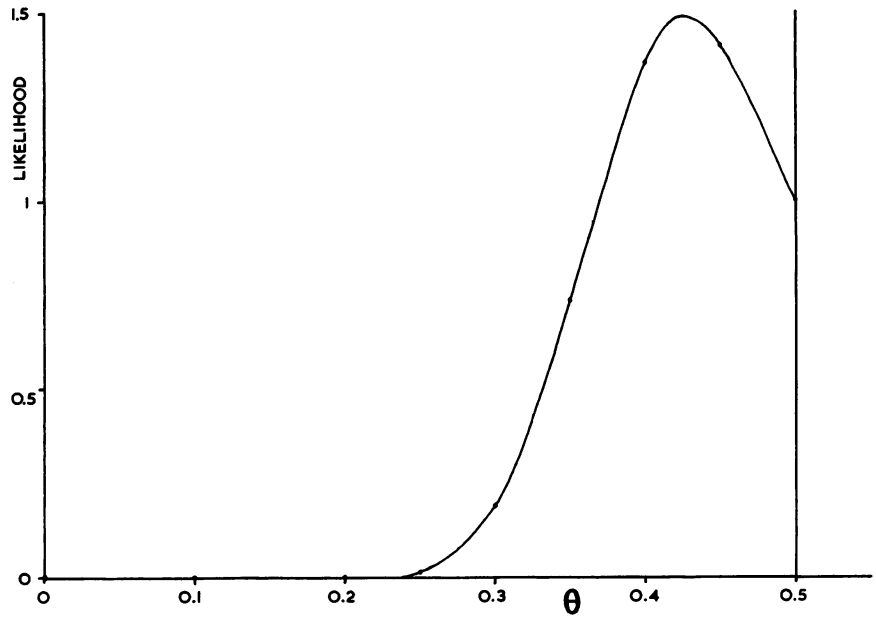

FIG. 1. Relative likelihoods (antilods) plotted against the recombination fraction, θ, between *Xg* and the *deutan-protan* region. Prior probabilities are not included here.

PROCEDURE FOR ESTIMATING LIMITS

To obtain an estimate and limits of the map interval, after incorporating prior probabilities, a graphical method has been used (see Fig. 2), in which the final relative probabilities are plotted against the map interval, w (as suggested for a slightly different method by Dr. J. H. Edwards, personal communication) using a suitable transformation for θ to w. The formula, $4w = \tanh^{-1} 2\theta + \tan^{-1} 2\theta$, is the best of the simpler transformations so far available for mouse data (Carter and Falconer, 1951) and has been used here. The usual formula, $2w = \tanh^{-1} 2\theta$, of Kosambi (1944) was found by Carter (1954) to give a rather poor fit, i.e. mouse map intervals are not closely additive if the Kosambi formula is used. Table VIIi of Fisher and Yates (1963), $z = \frac{1}{2}\tanh^{-1} r$, is invaluable for both transformation procedures. See Bailey (1961) for an excellent review of mapping transformations.

The prior probabilities of map intervals are assumed to be proportional to $L - w$ (Morton, 1955), where L is the genetical (map) length of the chromosome. Our estimate of L for the human X chromosome is two morgans. (One morgan, M, = 100 centimorgans, cM, or 100 map units. The map interval, in morgans, if small, is equal to the recombination fraction expressed as a decimal.)

This estimate is based on approximately 30 M for the total autosomal map length in males, as deduced from chiasma counts (Ford and Hamerton, 1956). In mammals (and in other orders), recombination fractions and, therefore, total genetical lengths in the XX sex are generally greater than in the opposite sex (Haldane, 1922). Human linkage data show that man is probably no

TABLE 1. LOD SCORES BEARING ON THE LINKAGE RELATIONSHIP BETWEEN THE *Xg* LOCUS AND THE *deutan-protan* REGION

			Map interval, w (in morgans), by Carter and Falconer's formula										
			0	.10	.20	.26	.31	.37	.44	.55	.69	.95	2.0
			Recombination fraction, θ										
Loci	Pedigree name	Sibship	0	.10	.20	.25	.30	.35	.40	.45	.482	.4975	.5
Xg : *deutan*	Reb	10	−∞	−1.151	−.597	−.429	−.300	−.197	−.115	−.050			0
	Ove	133-134	+.062	+.050	+.038	+.032	+.026	+.019	+.013	+.007			0
	Lud	135-136	+.034	+.028	+.021	+.018	+.014	+.011	+.007	+.004			0
	Joh	122-124	+.200	+.139	+.087	+.065	+.046	+.030	+.017	+.007			0
	Tho	129-130	−.057	−.036	−.022	−.016	−.011	−.008	−.004	−.002			0
	Rom	119	−.023	−.010	−.003	−.002	−.001	≅0	≅0	≅0			0
	Sla	128	+.086	+.057	+.033	+.023	+.015	+.008	+.004	+.001			0
	Scw	9	−2.500	−.444	−.194	−.125	−.076	−.041	−.018	−.004			0
	Hai	144-148	+.063	+.041	+.024	+.017	+.011	+.006	+.003	+.001			0
	Dra	2	−∞	−.887	−.388	−.250	−.151	−.082	−.035	−.009			0
	Moc	1	−∞	−.891	−.418	−.288	−.193	−.122	−.068	−.028			0
	Dec	8	−∞	−.855	−.364	−.223	−.124	−.057	−.016	+.003			0
	°Hom	3-7	−∞	−1.919	−.622	−.308	−.109	+.008	+.059	+.055			0
	Kyl	63	−.107	−.066	−.036	−.024	−.015	−.009	−.004	−.001			0
Xg : *protan*	Har	132	−.107	−.066	−.036	−.024	−.015	−.009	−.004	−.001			0
	Bus	12	+.455	+.321	+.185	+.121	+.065	+.021	−.006	−.014			0
	Nib	137-140	−.121	−.080	−.049	−.036	−.025	−.016	−.009	−.004			0
	Swa	11	−∞	−1.536	−.648	−.405	−.235	−.119	−.045	−.007			0
	Ton	149-152	−.005	−.001	+.002	+.003	+.004	+.004	+.003	+.002			0
	Kyl	14-17	−∞	−.468	+.309	+.417	+.424	+.358	+.242	+.106			0
	Hau	141-143	+.021	+.002	−.008	−.010	−.011	−.010	−.008	−.004			0
	Reb	50-52	+.336	+.251	+.169	+.130	+.095	+.063	+.037	+.015			0
	Kne	13	−.931	−.363	−.167	−.109	−.066	−.036	−.016	−.004			0
	Orr	18	−.819	−.342	−.159	−.104	−.064	−.035	−.015	−.004			0

Xg : deut-prot	Neu	23-25	$-\infty$	−.024	+.207	+.223	+.204	+.163	+.110	+.054		0
	Dan	19-22	$-\infty$	−.971	−.262	−.092	+.007	+.053	+.059	+.037		0
	Ste	120-121	−.062	−.027	−.010	−.006	−.003	−.001	−.001	≅0		0
	Orr	64	−.057	−.036	−.020	−.014	−.009	−.005	−.002	−.001		0
	Dub	27-30	$-\infty$	−1.629	−.674	−.422	−.250	−.129	−.052	−.011		0
	Lods (*Xg : deut-prot*)		$-\infty$	−10.913	−3.602	−1.838	−.747	−.132	+.136	+.148	+.060†	+.007†	0
a	Antilods (Fig. 1)		0	≅0	.0002	.014	.179	.738	1.368	1.406	1.148	1.016	1
b	Relative prior probability ($L - w$)		2.00	1.90	1.80	1.74	1.69	1.63	1.56	1.45	1.31	1.05	0
$a \times b$	Final relative probability (*Xg : deut-prot*) if $L = 2M$ (Fig. 2)		0	≅0	.0004	.024	.302	1.203	2.134	2.039	1.504	1.067	0
	Lods (*Xg : deutan*)‡		$-\infty$	−6.531	−2.284	−1.230	−.556	−.150	+.053	+.096	+.042†	+.005†	0
c	Antilods		0	≅0	.005	.059	.278	.708	1.130	1.247	1.102	1.012	1
$c \times b$	Final relative probability (*Xg : deutan*) if $L = 2M$		0	≅0	.009	.103	.470	1.154	1.763	1.808	1.444	1.063	0
	Lods (*Xg : protan*)‡		$-\infty$	−4.381	−1.318	−.608	−.190	+.018	+.082	+.053	+.019†	+.002†	0
d	Antilods		0	≅0	.048	.247	.646	1.042	1.208	1.130	1.044	1.005	1
$d \times b$	Final relative probability (*Xg : protan*) if $L = 2M$		0	≅0	.086	.430	1.092	1.698	1.884	1.638	1.368	1.055	0

*Includes unpublished additional sibships.

†By graphical interpolation on lod/θ curve.

‡Including the relevant contribution from the deutan-protan families.

Additions have been made since the analysis of these data by Davies *et al.* (1963).

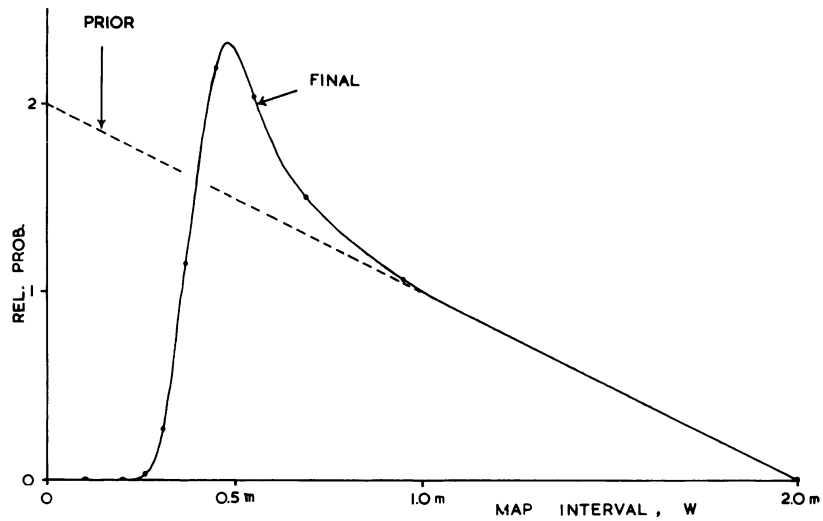

FIG. 2. Relative probability densities plotted against the map interval, w, between *Xg* and the *deutan-protan* region using Carter and Falconer's transformation of θ to w. The prior distribution of w (dotted line) is assumed proportional to $L - w$ where L, the genetical length of the X, is estimated as 2.0 morgans. The final distribution (continuous line) incorporates this prior distribution.

exception (Renwick, 1963; Cook, 1965; Renwick and Schulze, 1965) but more extensive data are available in the mouse, where the ratio is about 1.25:1 (Green *et al.*, 1962; Carter, 1954). The cytological data of Slizynski (1960) suggest 1.15:1. The ratio 1.25:1 would imply a human female autosome map of 37.5 M. An estimate of about 2 M is then obtained for the X by assuming that physical lengths in mitotic metaphase are roughly proportional to genetical lengths, provided that the chromosomes appear to be equally densely coiled in mitosis. This condition is met reasonably well in male somatic cells, and in such cells the Ferguson-Smiths, Ellis, and Dickson (1962) find the X to be equal to 5.43% of the total length of the autosomal haploid set. The above condition is probably also met in the female for the autosomes and for the one X which is not late-replicating.

For the four *Drosophila melanogaster* chromosomes, the correlation coefficient is 0.97 between the ***actual*** genetical lengths, i.e. 0.66, 1.08, 1.06, 0.03 M (Warren and Novitski, 1962), and the genetical lengths which would be ***expected***, 0.52, 1.05, 1.23, 0.03 M—if the same total genetical length were distributed among the chromosomes proportionally to their physical lengths measured from the (presumed interphase) salivary gland chromosomes (Bridges, 1942). The data of Elliott (1953) on two flowering plant species show correlations of more than 0.98 between the mitotic metaphase lengths of individual chromosomes and their deduced genetical lengths estimated from chiasma counts. For maize, the correlation between genetical lengths (Rhoades, 1962) and cytological lengths is only 0.8, whether the expectations are based on the mitotic diagrams of McClintock (1929) or on the meiotic prophase measurements of Longley (1939).

ESTIMATES OF MAP INTERVALS AND OF THEIR LIMITS

Estimates of map interval, derived with the aid of the Carter-Falconer transformation of θ to w, are given in Table 2a (see also Fig. 2) and those

derived with the aid of the Kosambi transformation in Table 2b. In both tables, the modal (maximum probability) and median estimates obtained graphically are accompanied by the appropriate 95% probability limits and by the corresponding θ values (recombination fractions). Values are given for the pooled *Xg* : *deutan* – *protan* data and for the *Xg* : *deutan* and *Xg* : *protan* intervals separately. The modal estimates of the three map intervals correspond to θ values of 0.42, 0.42, 0.40 on the Carter-Falconer scale, values which are almost identical to those given by the Kosambi scale or to the direct maximum likelihood estimates of θ from the raw lod scores (Table 1, Fig. 1). The prior assumptions have had a negligible effect on these estimates but they have allowed limits of the map intervals to be found. The data (on the Carter-Falconer scale) give a modal estimate of $w = 0.48$ morgans for the *Xg* : *deutan* - *protan* interval and the *narrowest limits* which encompass 95% of the probability (i.e. 95% of the area under the graph shown in Fig. 2) are 0.31 M and 1.64 M ($\theta = 0.30$ and approximately 0.5).

The graphical determination of such limits is facilitated by the fact that these are also the limits which have the same relative probabilities (same ordinates) as each other and which together exclude 5% of the area under the curve, $y = f(w)$. That this is so, even for an asymmetrical distribution (provided that it is unimodal and has no truncation or other discontinuity at either of the narrowest limits) can be shown by considering any two w values, w_1 and $w_1 + D$, which have an area, A (95% of total area under curve), between them. These are then the narrowest limits when w_1 is such that D is a minimum.

Suppose the lower limit is moved by δw and the upper limit is moved in the same direction by $\delta w + \delta D$, without change in the area, A, between the new limits. Then the changes in area at the two limits must be equal. Thus

$$\delta w \cdot f(w_1) = (\delta w + \delta D) \cdot f(w_1 + D) \quad \text{approximately.}$$

Hence
$$\delta D/\delta w = \frac{f(w_1) - f(w_1 + D)}{f(w_1 + D)}$$

At the limit, as $\delta D/\delta w$ tends to zero,

$$f(w_1) = f(w_1 + D)$$

i.e. the ordinates are equal. This is the condition for a minimal D and not for a maximal D, as is shown by the fact that d^2D/dw^2 is necessarily positive for the unimodal types of distribution specified above:

$$d^2D/dw^2 = \frac{f(w_1 + D)t_1 - f(w_1)t_2}{[f(w_1 + D)]^2}$$

where t_1 and t_2 are the tangents to the curve at $w = w_1$ and $w = w_1 + D$ respectively. t_2 is negative and the other items are positive, hence d^2D/dw^2 is positive. (A closely related result is given by Neyman and Pearson, 1936.)

The narrowest limits are thus readily found by trial and error, using a planimeter, and have the reassuring property that the maximum probability value necessarily lies between them if the curve is unimodal. Similar non-central limits for a parameter with a skewed distribution are more usually obtained, e.g. Morton (1956), by a symmetrizing transformation (with subsequent retranslation of the limits into original units) or by the ratio method of Haldane and Smith (1947), but the first is not possible here and the second

TABLE 2A. MAXIMUM PROBABILITY ESTIMATES AND MEDIAN ESTIMATES (IN MORGANS) OF MAP INTERVAL, w, BETWEEN *Xg* AND THE *deutan-protan* REGION, ON THE ASSUMPTION THAT THE X CHROMOSOME IS TWO MORGANS LONG

Corresponding values of the recombination fractions, θ, are also given. Carter and Falconer's transformation, $4w = \tanh^{-1}2\theta + \tan^{-1}2\theta$, has been used.

Type of estimate	Locus	From *Xg*		Narrowest (asymmetrical) limits accounting for 95% of the probability	
		w	θ	w	θ
Maximum probability estimates	*deutan-protan*	0.48	0.42	0.31 & 1.64	0.30 & ≅0.5
	deutan	0.49	0.42	0.30 & 1.65	0.29 & ≅0.5
	protan	0.44	0.40	0.25 & 1.64	0.24 & ≅0.5
				Conventional (symmetrical) limits accounting for 95% of the probability	
				w	θ
Median estimates	*deutan-protan*	0.77	0.49	0.36 & 1.73	0.34 & ≅0.5
	deutan	0.79	0.49	0.34 & 1.74	0.33 & ≅0.5
	protan	0.76	0.49	0.29 & 1.73	0.28 & ≅0.5

TABLE 2B. ON THE SCALE OF THE KOSAMBI TRANSFORMATION, $2w = \text{TANH}^{-1}2\theta$

Type of estimate	Locus	From *Xg*		Narrowest (asymmetrical) limits accounting for 95% of the probability	
		w	θ	w	θ
Maximum probability estimates	*deutan-protan*	0.60	0.42	0.37 & 1.65	0.31 & ≅0.5
	deutan	0.62	0.42	0.33 & 1.66	0.29 & ≅0.5
	protan	0.53	0.39	0.26 & 1.65	0.24 & ≅0.5
				Conventional (symmetrical) limits accounting for 95% of the probability	
				w	θ
Median estimates	*deutan-protan*	0.81	0.46	0.43 & 1.74	0.35 & ≅0.5
	deutan	0.83	0.47	0.39 & 1.75	0.33 & ≅0.5
	protan	0.79	0.46	0.32 & 1.74	0.28 & ≅0.5

suffers, when applied to limited data, from an uneconomical safety factor. Central (i.e. conventional) 95% limits are also given in Table 2 together with the median estimate, the estimate to which they are clearly more appropriate.

TEST FOR ADDITIVITY OF MAP INTERVALS

The section of chromosome between *Xg* and *deutan* is spanned also by the two intervals *Xg* : *G6PD* (0.26 morgans by the above method) Adam *et al.*, 1963; Fraser *et al.*, 1964), and *G6PD* : *deutan*, 0.05 morgans (Porter, Schulze, and McKusick, 1962), *G6PD* being the symbol for the glucose 6-phosphate dehydrogenase locus. The combined length, 0.32 morgans, falls far short of the present estimate, 0.48 morgans, for the *Xg* : *deutan* interval but

the discrepancy is not surprising in view of the wide limits of all the estimates. *Xg* : *G6PD* has narrowest 95% limits of 0.13 M and 0.52 M, corresponding to $\theta = 0.13$ and 0.43. If the Kosambi formula is used throughout, the discrepancy from additivity is much larger, the estimate of the combined lengths remaining at 0.32 morgans and the *Xg* : *deutan* interval rising to 0.62 morgans.

When the publication of X-linkage data being collected by other workers is complete, it should be possible to construct a consistent map of the X chromosome and to discriminate further between the suitabilities of various mapping transformations for man.

SUMMARY

From the data of Jackson, Symon, and Mann (1964), linkage between the *Xg* blood group locus and the *deutan-protan* region of the X chromosome has been estimated via scores calculated by an IBM 7090 computer. The maximum probability estimate of the map interval is 0.48 morgans (48 map units) and corresponds to a recombination fraction, θ, of 0.42. The narrowest 95% limits of this estimate are wide and, on the basis of the mapping formula of Carter and Falconer (1951), may be estimated as 0.31 morgans and 1.64 morgans, if available knowledge of the probable genetical length of the X chromosome is used. A length of two morgans for the X chromosome has been chosen here, on the basis of indirect evidence. The data, although allowing estimates to be made of the map distance of *Xg* from the *deutan* and *protan* sites separately (0.49 M and 0.44 M) are inadequate to determine the ordering of *deutan* and *protan* with respect to *Xg*.

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