X Chromosome Mapping of Genes for Red-Green Colorblindness and Xg

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REPORTS OF an X-linked blood group antigen (Xg^a) by Mann *et al.* (1962) stimulated this study of linkage between the locus or loci for red-green colorblindness and the locus controlling this blood group. We believed that this information would extend the older work on the linkage relationships of red-green color blindness and other conditions and relate it to the more recent studies on the linkage relationships of *Xg*. Inspection of the pedigrees of colorblind individuals revealed that the loci were not closely linked (Jackson, Symon, and Mann, 1962), but estimation of the recombination fraction with the aid of a computer has suggested a loose linkage (Renwick and Schulze, 1964).

METHODS

A total of 544 individuals in 34 separate families were tested for Xg^a and for color vision. The colorblind probands had been detected in a population survey in our area and by surveys of several local schools. The pedigrees of the probands were explored as extensively as possible.

Color vision was tested with AO-HRR color plates. Selected families, in which both protan and deutan colorblindness were present, were retested using the anomaloscope and, in some instances, the Farnsworth-Munsell 100-Hue test, the Dvorine Color Test Plates, the Tokyo Medical College Plates, the Farnsworth Dichotomous test, and the Ishihara plates.

Immunohematologic testing was performed in duplicate. Blood was collected by venipuncture in ACD or Alsever's anticoagulant solution, except for a few children from whom only capillary blood could be obtained. Weak or uncertain reactions were repeated at least two additional times. The Xg^a antigen was detected by the indirect antiglobulin method. The ABO and Rh-Hr groups also were determined routinely, and MN group typing was performed in some cases.

RESULTS

Linkage data were obtained in 26 of the 34 families. The estimate of recombination derived from an analysis of these data on the IBM 7090 computer

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(Renwick and Schulze, 1964) was 0.42 (0.29 to ca. 0.5) for *Xg-deutan* data and 0.40 (0.24 to ca. 0.5) for the *Xg-protan* data. In only one of these families was an apparent exception found to the X-linked mode of inheritance of Xg^a proposed by Mann *et al.* (1962). In this instance, an Xg(a−) mother had one daughter who was Xg(a−) and one daughter who was Xg(a+). This is theoretically impossible under the proposed system of inheritance for full sisters, but we cannot preclude that they were actually maternal half sisters.

The results from doubly heterozygous female carriers are tabulated in Table 1. A complete tabulation of all other data of this study is available on request to the authors. Figure 1 shows pedigrees of some of the families studied.

DISCUSSION

These data together with those available in the literature allow construction of a provisional map of the human X chromosome (Fig. 2). The color vision (*CV*) locus or loci lie fairly close to the glucose-6-phosphate dehydrogenase (*G6PD*) locus according to Adam (1961) and Porter, Schulze, and McKusick (1962). Since *G6PD* is about 27 crossover units from the *Xg* locus according to data by Adam *et al.* (1962) and Adam and others (1963), we can place *G6PD* between *Xg* and *CV;* if *CV* were between *Xg* and *G6PD, CV* would be only about 22 units from *Xg* instead of 30-35 units or more as has been found in the present study. Our data corroborate those of Adam *et al.* (1963) in suggesting this probable order of these three genes on the X chromosome. They found seven probable recombinants and 13 nonrecombinants between *Xg* and deutan type of red-green colorblindness in five families. M. Siniscalco (personal communication) presented evidence of 26 probable recombinants and 61 nonrecombinants between the deutan type of red-green colorblindness and *Xg*. He stressed the fact that two-generation data can be misleading and that great care must be taken in assigning gene order on the basis of data presently available.

The *AHG* locus (classical hemophilia, hemophilia A, or antihemophilic globulin deficiency) is about 10-15 units from the color vision locus according to Whittaker, Copeland, and Graham (1962). Since *AHG* is a long distance from *Xg* according to data by O'Brien *et al.* (1962), this locus can be placed tentatively beyond *CV* on the side opposite to the *Xg* locus. Davies *et al.* (1963) also suggest this tentative map order.

The locus for the X-linked recessive form of childhood muscular dystrophy is a long distance from that for *Xg* according to Clark *et al.* (1962, 1963) and about 25 units from *CV* (Phillip and Walton, 1956), but more data are needed before this locus can be placed in a linkage map.

Hemophilia B (Christmas disease or PTC deficiency) is a long distance from the *Xg* locus according to Graham *et al.* (1962) and a long distance from *CV* according to Whittaker, Copeland, and Graham (1962). Therefore, this gene cannot be located relative to these marker genes.

The color vision loci are illustrated by two lines in Fig. 2 because of the

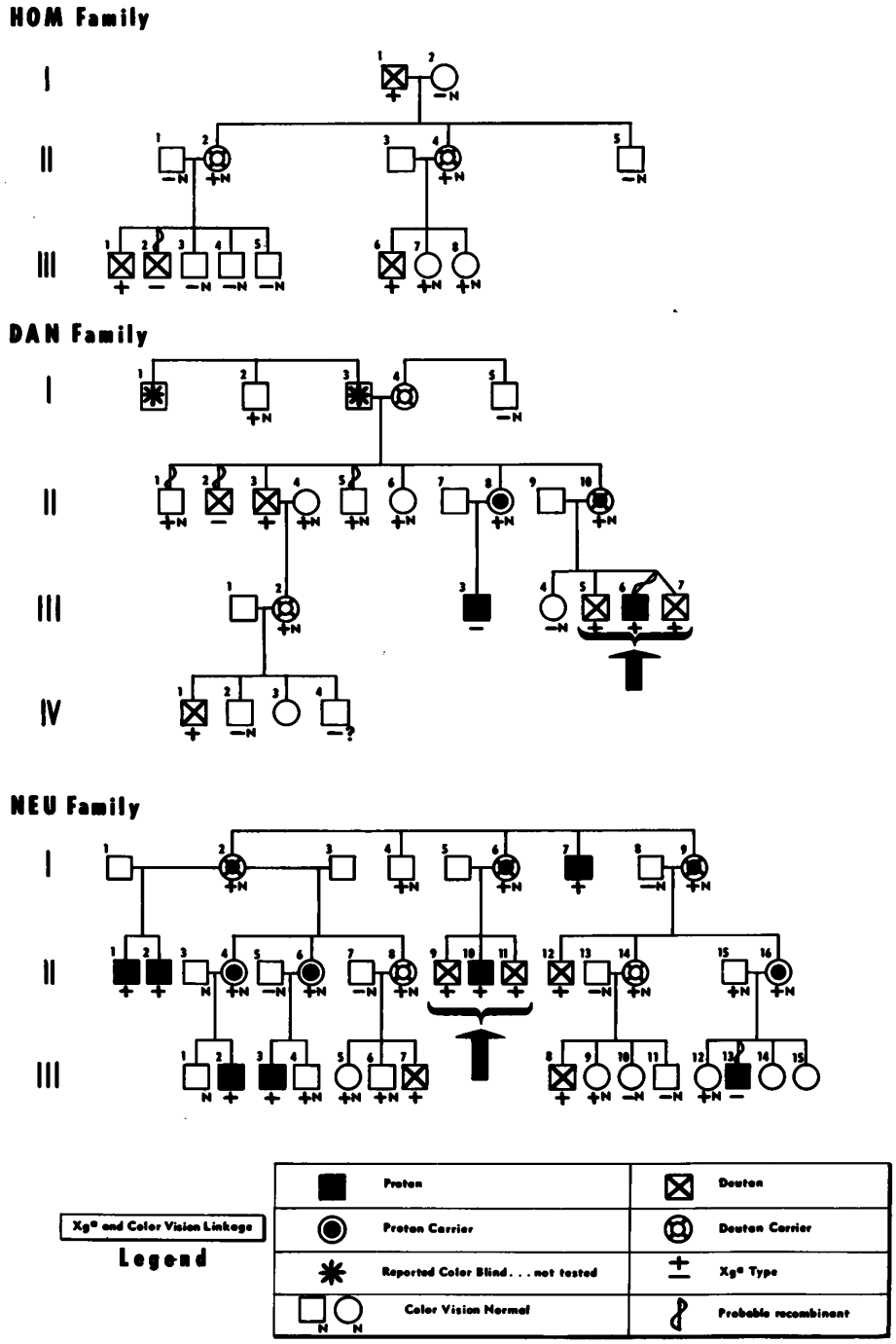

FIG. 1. Pedigrees of the *Hom, Dan,* and *Neu* families showing color vision and Xg^a results. Arrows indicate sibships in which both deutan and protan sons were observed.

TABLE 1. Xg^a AND COLOR VISION DATA FROM THE FAMILIES WITH DOUBLE HETEROZYGOTES

Individuals labeled M and F are the sons and daughters respectively of the parents listed in this particular family. Numbers in parentheses after an individual indicate the position of that individual in a previously listed family. For example, in family 4, the mother listed "(3-1)" is found in family 3 as the daughter listed "1. F." N represents normal color vision.

	Xg^a	Color vision
1. *Moc*		
Father	+	N
Mother	+	N
1. F	+	N
2. M	−	Deutan
3. M	−	N
2. *Dra*		
Father	+	N
Mother	+	N
1. M	−	Deutan
2. M	+	Deutan
3. M	−	Deutan
4. M	−	N
3. *Hom* (see Fig. 1)		
Father I-1	+	Deutan
Mother	−	N
1. F II-2	+	N
2. F II-4	+	N
3. M II-5	−	N
4. *Hom* (see Fig. 1)		
Father II-1	−	N
Mother II-2 (3-1)	+	N
1. M III-1	+	Deutan
2. M III-2	−	Deutan
3. M III-3	−	N
4. M III-4	−	N
5. M III-5	−	N
5. *Hom* (see Fig. 1)		
Mother II-4 (3-2)	+	N
1. F III-7	+	N
2. F III-8	+	N
3. M III-6	+	Deutan
6. *Hom*		
Father	+	N
Mother (maternal aunt of father 3)	+	N
1. F	+	N
2. M	+	Deutan
3. F	+	N
4. F	+	N
5. M	+	N
6. F	+	N
7. M	+	CB*
8. M	+	Deutan
7. *Hom*		
Father	−	N
Mother (6-4)	+	N
1. M	+	Deutan
2. M	+	Deutan
3. M	+	N
4. M	−	N
5. F	+	N
6. F	−	N
7. F	+	N
8. F	−	N
9. F	−	N
10. F	−	N
8. *Dec*		
Father	−	N
Mother	+	N
1. M	+	Deutan
2. M	−	Deutan
3. F	−	N
4. M	−	Deutan
9. *Scw*		
Father	−	N
Mother	+	N
1. M	+	N
2. M	+	Deutan
3. M	+	N
4. F	−	N
10. *Reb*		
Father	−	Protan
Mother	+	N
1. M	+	Deutan
2. M	+	Deutan
3. M	+	N
Mother's sister	−	N
11. *Lwa*		
1. M	−	N
2. M	+	N
3. M	−	Protan
4. M	−	N
5. M	+	Protan
6. M	+	N
7. F	−	N
8. M	+	N
9. M	−	Protan
12. *Bus*		
Father	−	N
Mother	+	N
1. F	−	N
2. M	−	Protan
3. M	+	N
13. *Kne*		
Mother	+ wk.	N
1. M	−	CB*
2. M	+	Protan
14. *Kyl*		
Mother	+	N
1. M	+	Protan
2. M	−	Protan
15. *Kyl*		
Mother (father was paternal uncle of mother 14)	+ wk.	N

*Colorblind type undetermined.

TABLE 1. *Continued*

	Xg[a]	Color vision
1. M	−	Protan
2. M	−	Protan
3. M	−	N
16. *Kyl*		
Father	Dead	
Mother (sister to mother 15)	+	N
1. F	+	N
2. M	−	Protan
3. M	+	N
4. M	−	Protan
5. M	+	N
17. *Kyl*		
Father	Dead	
Mother (maternal aunt was paternal grandmother to mother 14)	Dead	
1. M	+	N
2. M	+	Protan
3. M	+	N
4. M	+	Protan
5. M	+	N
6. M	−	Protan
18. *Orr*		
Father	Dead	
Mother	Dead	
1. M	+	CB*
2. M	−	Protan
19. *Dan* (see Fig. 1)		
1. M II-3	+	Deutan
2. M II-1	+	N
3. M II-2	−	Deutan
4. M II-5	+	N
5. F II-6	+	N
6. F II-8	+	N
7. F II-10	+	N
20. *Dan* (see Fig. 1)		
Mother III-2 (daughter of 19-1)	+	N
1. M IV-1	+	Deutan
2. M IV-2	−	N
3. M IV-4	−	N ?
21. *Dan* (see Fig. 1)		
Mother II-8 (19-6)	+	N
1. M III-3	−	Protan
22. *Dan* (see Fig. 1)		
Mother II-10 (19-7)	+	N
1. F III-4	−	N
2. M III-5	+	Deutan
3. M III-6 (fraternal twin to 4)	+	Protan
4. M III-7	+	Deutan
23. *Neu* (see Fig.1)		
Father 1-8	−	N
Mother 1-9	+	N
1. M II-12	+	Deutan
2. F II-14	+	N
3. F II-16	+ wk.	N
24. *Neu* (see Fig. 1)		
Father II-13	−	N
Mother II-14 (23-2)	+	N
1. M III-8	+	Deutan
2. F III-9	+	N
3. F III-10	−	N
4. M III-11	−	N
25 *Neu* (see Fig. 1)		
Father II-15	+	N
Mother II-16 (23-3)	+ wk.	N
1. F III-12	+	N
2. M III-13	−	Protan
26. *Dub*		
Mother	+	N
1. M	−	Deutan
2. M	+	N
27. *Dub*		
Father	+	N
Mother (sister to mother 26)	+	N
1. M	+	Deutan
2. M	−	Deutan
28. *Dub*		
Mother (sister to mother 26)	+	N
1. M	+	Deutan
2. F	+	N
3. F	+	N
4. F	−	N
5. F	+	N
29. *Dub*		
Father	−	N
Mother (28-2)	+	N
1. M	+	Protan
2. M	−	Protan
30. *Dub*		
Father	+	N
Mother (28-5)	+	N
1. M	−	Protan

possibility that the deutan and protan types of red-green colorblindness are nonallelic. The report of Vanderdonck and Verriest (1960) showing two crossovers in the offspring of a woman carrying both *deutan* and *protan* genes has strongly suggested that the two types lie at separate loci. Before Vanderdonck and Verriest's paper had appeared. Renwick (1961) had stated that in the families reported as having both deutan and protan sons, 21 sons were present with no sons with normal color vision. In the present study, two

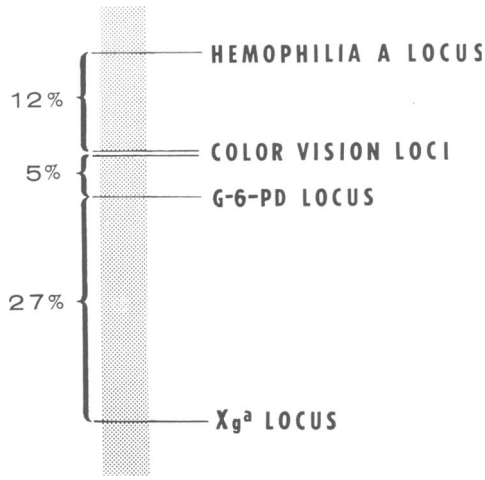

FIG. 2. Provisional map of the human X chromosome on the basis of recombination percentages. Our values of 40% and 42% for the recombination percentage between *color vision* and *Xg*^{a} are higher than the combined data shown on *color vision* and *G6PD* and *G6PD* and *Xg*^{a} but are compatible with this gene order.

additional families were found with both types of colorblindness and no normal sons (Fig. 1). The AO-HRR results for these six males were corroborated by Farnsworth-Munsell and anomaloscope studies, and both types of colorblindness were observed in other members of both families. Insufficient evidence concerning the linkage of the loci of these two types of colorblindness to other loci is available (Porter, Schulze, and McKusick, 1962, and Adam *et al.*, 1962) to determine their linkage relationship with each other.

SUMMARY

Studies of red-green colorblindness and the Xg^a blood group are reported for 544 individuals of 34 separate families. Linkage data were obtained in 26 of these families. Using these data and those in the literature, we suggest very tentatively that the relative order of genes on the X chromosome is probably *Xg – G6PD – CV – AHG*. Two families are reported in which both types of red-green colorblind sons are present (six sons) and no normal sons. Although no definite information is obtained from the present study for the one or two locus hypothesis of red-green colorblindness, the present evidence suggests that the postulated two loci for protan and deutan types of colorblindness are not widely separated.

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