Genetic Linkage Studies in a Negro Kindred with Norrie's Disease

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Norrie's disease is a rare type of hereditary blindness that is transmitted as a sex-linked recessive trait. Although the eyes of affected individuals may be normal at birth, bilateral retinal vascular proliferation typically occurs in the first few weeks of life, leading to the formation of pseudoglioma and subsequently to cataracts, corneal clouding, and phthisis bulbi. Associated findings that have been reported in some cases include hearing loss (Warburg 1963), mental retardation (Warburg 1966), and hypogonadism (Hara et al. 1969). Genetic linkage data have been reported previously by Warburg et al. (1965), who found no suggestion of measurable linkage between the Norrie's disease and *Xg* blood group loci. The present report describes an American Negro kindred in which genes for Norrie's disease, red-green colorblindness, glucose-6-phosphate dehydrogenase deficiency, and the Xg^a blood group factor were segregating. The data are consistent with loose linkage between the Norrie's disease locus and glucose-6-phosphate dehydrogenase locus.

MATERIALS AND METHODS

The proband, a male Negro infant, was first noted to have developed cataracts and corneal clouding at six weeks of age. At that time, the family history revealed a total of eight similarly affected males in three generations of the kindred, in a pattern consistent with X-linked recessive inheritance. Two years later, an affected male sibling of the proband was born. The pedigree is shown in figure 1; the clinical findings in the seven living affected family members have been described elsewhere (Hansen 1968; Hara and Hansen 1968; Hara et al. 1969). Blood was obtained for Xg^a and glucose-6-phosphate dehydrogenase typing from 46 family members, and color vision was tested whenever possible with the use of Ishihara charts. Glucose-6-phosphate dehydrogenase typing was performed by starch-gel electrophoresis, as described previously (Nance 1968).

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RESULTS

The typing results are shown in Appendix A. In addition to the Norrie's disease locus (*Nd*), genetic variants at the red-green colorblindness (*Cb*), glucose-6-phosphate dehydrogenase (*Gd*), and the *Xg* blood group loci were segregating in the kindred in a manner that provided information about the frequency of recombination between *Nd* and *Gd* (θ_1), *Nd* and *Xg* (θ_2), and *Gd* and *Xg* (θ_3). *Lod* scores were calculated for each of the three linkages separately, according to the method of Morton (1955).

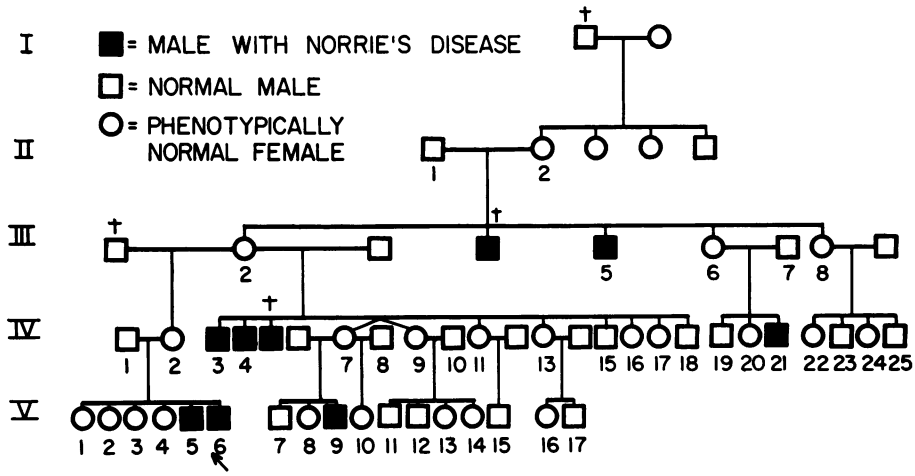

FIG. 1.—Pedigree of family with Norrie's disease. Pedigree numbers identify individuals from whom blood samples were obtained (see Appendix A).

Nd *versus* Gd (θ_1)

In four females who were heterozygous carriers of both the gene for Norrie's disease (*nd*) and the Gd^{A-} allele, the linkage phase could be determined from the pedigree data. In a fifth female, II-2, the linkage phase was indeterminate. Three other females, III-8, IV-11, and IV-13, with four normal sons were possible carriers of *nd*. All "certain" carriers of *nd* were proven by progeny test except IV-9, who was a twin of a known carrier. The twins had always been assumed to be identical by the parents, their appearance was very similar, and identity was further supported by blood-typing results which showed no differences in any of the blood-group factors for which the twins were tested. The probability of dizygosity, estimated from the typing results, was less than .02 (Appendix B). The *lod* scores for θ_1 are summarized in table 1. Very close linkage is unlikely, but the data are compatible with loose linkage with a maximum z score of 0.33657 at $\theta_1 = 0.3101$. The odds favoring linkage at this value of θ_1 are only 2.2:1, however, so that little confidence can be placed in the estimate.

Nd *versus* Xg (θ_2)

Four doubly heterozygous females were of known linkage phase; three additional females, III-8, IV-11, and IV-13, who were heterozygous for Xg^a, were possible

carriers of *nd*. The *lod* scores (table 2) provide no evidence of measurable linkage between the *Xg* and *Nd* loci. When pooled with the data of Warburg et al. (1965), the results suggest that even a recombination fraction of 0.20 is quite unlikely.

Gd *versus* Xg (θ_3)

All six doubly heterozygous females were of known linkage phase; the *lod* scores (table 3) provided no suggestion of measurable linkage, a result that agrees with

TABLE 1

NORRIE'S DISEASE AND *Gd*: *Lod* SCORES FOR VALUES OF θ_1

PEDIGREE NO.	ASSUMED VALUE OF THE RECOMBINATION FRACTION (θ_1)								
	.05	.10	.15	.20	.25	.30	.35	.40	.45
II-2	−0.7212	−0.4437	−0.2924	−0.1938	−0.1249	−0.0757	−0.0410	−0.0177	−0.0044
III-6	−0.7212	−0.4437	−0.2924	−0.1938	−0.1249	−0.0757	−0.0410	−0.0177	−0.0044
III-8	−0.0768	−0.0595	−0.0448	−0.0325	−0.0223	−0.0141	−0.0079	−0.0035	−0.0009
IV-2	−0.7212	−0.4437	−0.2924	−0.1938	−0.1249	−0.0757	−0.0410	−0.0177	−0.0044
IV-7	0.5575	0.5105	0.4609	0.4082	0.3522	0.2923	0.2279	0.1584	0.0828
IV-9	0.5575	0.5105	0.4609	0.4082	0.3522	0.2923	0.2279	0.1584	0.0828
IV-11	−0.1549	−0.1327	−0.1154	−0.0969	−0.0792	−0.0621	−0.0458	−0.0300	−0.0147
IV-13	0.1139	0.1027	0.0911	0.0792	0.0669	0.0544	0.0414	0.0280	0.0142
Total	−1.1664	−0.4015	−0.0246	0.1848	0.2950	0.3354	0.3206	0.2581	0.1511
Relative probability	.0681	.3967	.9344	1.5304	1.9724	2.1650	2.0906	1.8120	1.4162

TABLE 2

NORRIE'S DISEASE AND *Xg*: *Lod* SCORES FOR VALUES OF θ_2

PEDIGREE NO.	ASSUMED VALUE OF THE RECOMBINATION FRACTION (θ_2)								
	.05	.10	.15	.20	.25	.30	.35	.40	.45
III-2	−1.1637	−0.6321	−0.3544	−0.1835	−0.0738	−0.0053	0.0320	0.0437	0.0327
III-6	−0.7212	−0.4437	−0.2924	−0.1938	−0.1249	−0.0757	−0.0410	−0.0177	−0.0044
III-8	0.1824	0.1608	0.1392	0.1179	0.0969	0.0763	0.0561	0.0366	0.0179
IV-7	−2.0000	−1.3979	−1.0458	−0.7959	−0.6021	−0.4437	−0.3098	−0.1938	−0.0915
IV-9	−0.7212	−0.4437	−0.2924	−0.1938	−0.1249	−0.0757	−0.0410	−0.0177	−0.0044
IV-11	0.1139	0.1027	0.0911	0.0792	0.0699	0.0544	0.0414	0.0280	0.0142
IV-13	−0.1549	−0.1347	−0.1154	−0.0969	−0.0792	−0.0621	−0.0458	−0.0300	−0.0147
Total	−4.4648	−2.7887	−1.8701	−1.2668	−0.8411	−0.5320	−0.3079	−0.1509	−0.0502
Warburg et al. (1965)	−3.6912	−2.3242	−1.5570	−1.0689	−0.7218	−0.4667	−0.2805	−0.1463	−0.0558
Grand total	−8.5160	−5.1129	−3.4271	−2.3357	−1.5629	−0.9987	−0.5884	−0.2972	−0.1060
Relative probability	< .0001	< .0001	.0004	.0046	.0274	.1003	.2580	.5015	.7835

recent evidence that the two loci are not measurably linked in a Jewish population (Adam et al. 1967) or in a Sardinian population (Siniscalco et al. 1966).

Three females were heterozygous at all three loci and could in theory provide information about double crossovers. Three additional females, III-8, IV-11, and IV-13, were possible triple heterozygotes. The combined z score for all three linkages, wherein

TABLE 3

Gd AND *Xg*: *Lod* SCORES FOR VALUES OF θ_3

PEDIGREE NO.	ASSUMED VALUE OF THE RECOMBINATION FRACTION (θ_3)								
	.05	.10	.15	.20	.25	.30	.35	.40	.45
III-6	−1.7212	−1.1427	−0.8153	−0.5918	−0.4260	−0.2976	−0.1959	−0.1146	−0.0501
III-8	−0.7212	−0.4437	−0.2924	−0.1938	−0.1249	−0.0757	−0.0410	−0.0171	−0.0044
IV-7	−2.0000	−1.3979	−1.0458	−0.7959	−0.6021	−0.4437	−0.3098	−0.1938	−0.0915
IV-9	−0.7212	−0.4437	−0.2924	−0.1938	−0.1249	−0.0757	−0.0410	−0.0177	−0.0044
IV-11	−1.0000	−0.6990	−0.5229	−0.3979	−0.3010	−0.2218	−0.1549	−0.0969	−0.0458
IV-13	−2.0000	−1.3979	−1.0458	−0.7959	−0.6021	−0.4437	−0.3098	−0.1938	−0.0915
Total	−8.1637	−5.5249	−4.0146	−2.9691	−2.1810	−1.5583	−1.0523	−0.6347	−0.2876
Relative probability	< .0001	< .0001	< .0001	.0011	.0066	.0276	.0887	.2319	.5157

the three possible gene sequences *Gd-Nd-Xg*, *Nd-Xg-Gd*, and *Xg-Gd-Nd* are assumed to be equally likely, is given by

$$z = \log \frac{524288}{45}\theta_1(1-\theta_1)[\theta_1^2(1-\theta_1)+\theta_1(1-\theta_1)^2]\theta_2^2(1-\theta_2)^3\theta_3^3$$
$$\times [\theta_1\theta_2^4(1-\theta_1)^5(1-\theta_2)^2+\theta_2^4\theta_3^5(1-\theta_2)^2(1-\theta_3)+\theta_1\theta_3^5(1-\theta_1)^5(1-\theta_3)]$$
$$\times [\theta_3(1-\theta_3)+\tfrac{1}{3}\{\theta_1\theta_2(1-\theta_1)(1-\theta_2)+\theta_2\theta_3^2(1-\theta_2)+\theta_1\theta_3^2(1-\theta_1)\}]$$
$$\times [\theta_3+\tfrac{1}{3}\{\theta_2(1-\theta_1)+\theta_2\theta_3+\theta_3(1-\theta_1)\}]$$
$$\times [\theta_3+\tfrac{1}{3}\{\theta_1(1-\theta_2)+\theta_3(1-\theta_2)+\theta_1\theta_3\}] .$$

A "peak" in the probability hypersurface was found at $\theta_1 = .31$, $\theta_2 = .50$, $\theta_3 = .50$, by iteration, with a program written for a SIGMA-7 computer. The maximum z score was only −1.9979, however, corresponding to the low probability that the three loci are mutually mappable.

SUMMARY

A linkage analysis has been performed on typing results from 46 members of a Negro kindred in which a gene for Norrie's disease and genetic variants at three other sex-linked loci, *Cb*, *Xg*, and *Gd*, were segregating. The data provide no evidence for measurable linkage between the *Nd* and *Xg* loci or between the *Xg* and *Gd* loci, but are compatible with loose linkage between the *Nd* and *Gd* loci. The odds favoring linkage are very low, however, and further observations will be required before any conclusion can be reached.

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APPENDIX A

Xg^a, GLUCOSE-6-PHOSPHATE DEHYDROGENASE (GD), AND COLOR VISION TYPING RESULTS

Pedigree No.	Sex	Xg^a	Gd	Cb	Norrie phenotype
II-1	♂	+	A−	+	+
II-2	♀	−	A−/B	+	(+/*n*)
III-2	♀	(+/−)	(*A*−/*A*−)	+	(+/*n*)
III-5	♂	−	A−	*	n
III-6	♀	(+/−)	A−/B	+	(+/*n*)
III-7	♂	−	B	+	+
III-8	♀	(+/−)	A−/B	+	+
IV-1	♂	−	B	cb	+
IV-2	♀	−	A−/B	+	(+/*n*)
IV-3	♂	−	A−	*	n
IV-4	♂	−	A−	*	n
IV-7	♀	(+/−)	A−/B	+	(+/*n*)
IV-8	♂	+	B	+	+
IV-9	♀	(+/−)	A−/B	+	(+/*n*)
IV-10	♂	+	A+	+	+
IV-11	♀	(+/−)	A−/B	+	+
IV-13	♀	(+/−)	A−/B	+	+
IV-15	♂	−	A−	+	+
IV-16	♀	(+/−)	A−/B	+	+
IV-17	♀	−	A−/B	+	+
IV-18	♂	+	A−	+	+
IV-19	♂	−	A−	+	+
IV-20	♀	−	(*B*/*B*)	+	+
IV-21	♂	−	A−	*	n
IV-22	♀	*	B	+	+
IV-23	♂	+	A−	+	+
IV-24	♀	+	B	+	+
IV-25	♂	+	B	+	+
V-1	♀	−	B	(*cb*/+)	+
V-2	♀	−	B	(*cb*/+)	+
V-3	♀	−	B	(*cb*/+)	+
V-4	♀	−	B	(*cb*/+)	+
V-5	♂	−	B	*	n
V-6	♂	−	A−	*	n
V-7	♂	+	B	*	+
V-8	♀	+	B	*	+
V-9	♂	−	A−	*	n
V-10	♀	+	B	+	+
V-11	♂	+	B	+	+
V-12	♂	−	B	+	+
V-13	♀	+	(*A*−/*A*+)	+	+
V-14	♀	+	(*A*−/*A*+)	+	+
V-15	♂	−	A−	*	+
V-16	♀	−	A−	*	+
V-17	♂	+	B	*	+

NOTE—Under Xg^a, + indicates presence of Xg^a antigen. Elsewhere in the table, + indicates presence of normal allele. Where the genotype of females can be inferred from the pedigree data, it is given in parentheses.

* Indicates typing not performed.

APPENDIX B

PROBABILITY THAT TWINS IV-7 AND IV-9 ARE DIZYGOTIC (CALCULATED FROM GENE FREQUENCIES IN NEGRO POPULATIONS)*

System	Phenotype	Relative Chance of Dizygosity	Gene Frequencies and Typing of Relatives	Reference
ABO	O	0.7242	$O=.70$	Moore (1955)
MNSs	MNSs	0.4377	$NS=.07$, $Ns=.45$, $MS=.07$, $Ms=.41$	Pollitzer (1956)
Rh	R^0R^2	0.4649	$R^o=.43$, $R^2=.12$	Wiener (1954)
P	+	0.9609	$P=.75$	Pollitzer (1958)
Kell	K−	0.9801	$k^b=.98$	Mourant (1954)
Lutheran	a−b+	0.9604	$Lu^b=.96$	Mourant (1954)
Duffy	a−b−	0.8326	$Fy=.82$	Race and Sanger (1958)
Xg	a+	0.5000	Mother Xg^a/Xg, father Xg	
Haptoglobin	2FS–2FS	0.7030	$Hp^{2FS}=.41$, Mother Hp 2FS–2FS	Nance (1968)
Transferrin	C	0.9595	$Tf^C=.92$, mother $Tf\ C$	Nance (unpublished observation)
Gc	1–1	0.9460	$Gc^2=.89$, mother Gc 1–1	Bearn et al. (1964)
Ceruloplasmin	B	0.9720	$Cp^B=.94$, mother $Cp\ B$	Shreffler et al. (1967)
Hemoglobin	A	0.5000	Mother Hb A, sibling Hb AS	
G6PD	A−/B	1.0000	Mother Gd^{A-}/Gd^{A-}	
6PGD	A	0.9820	$Pd^A=.96$, mother Pd A	Davidson (1967)
Catalase	A	0.9970	$Ct^A=.994$, mother Ct A	Nance (unpublished observation)
LDH A&B	Normal	0.9985	Normal=.997, mother normal	Vesell (1965)
Initial probability	.....	2.4592	.....	Guttmacher (1953)
Likeness in sex	.....	0.5000	.....	

Combined relative probability, $P(D) = .0207$

Probability of dizygosity, $P'(D) = \frac{P(D)}{1 + P(D)} = .0202$

* For description of methods, see Stern (1960).

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