

HUMAN LINKAGE STUDIES

H. Warner Kloefer
Dakota Wesleyan University

There are twenty-four pairs of chromosomes in each cell of every person, and these chromosomes carry all the hereditary factors which are passed from parents to children. When factors for two or more different traits are carried on the same pair of chromosomes, the traits are said to be linked. Information concerning linkage relationships, makes possible the mapping of the chromosomes to show locations of the hereditary factors. Although much is known about the chromosomal location of hereditary factors in many common plants and animals, only within recent years has progress been made toward the mapping of human chromosomes.

The primary interest in testing for linkage relations in man is to find genes for two or more traits that are located on the same pair of chromosomes. However, negative results also have value because they indicate that the genes involved are on separate pairs of chromosomes. A survey of the literature as recently as 1941 shows that 10 linkage studies have been carried out involving variations in blood groups, blood types, taste deficiency to phenyl-thio-carbamide, taste deficiency to mercapto-benzo-selenazol, eye color, hair color, mid-digital hair, and sex.

The first human linkage investigation was made by Snyder¹ involving eye color and the blood groups. Bernstein² showed by the use of his y-score that the blood groups and blood types were inherited independently. Hogben³ used a refinement of Bernstein's method and

¹Snyder, L. H., 1926 Studies in human inheritance—The linkage relations of the blood groups. *Zeitschrift für Immunitätsforschung und experimentelle Therapie* 49: 464-480.

²Bernstein, Felix, 1930 Zur Grundlegung der Chromosomentheorie der Vererbung beim Menschen mit besonderer Berücksichtigung der Blutgruppen. *Zeitschrift für induktive Abstammungs- und Vererbungslehre* 57: 113-138.

³Hogben, Lancelot, and Pollack, Ray, 1935 A contribution to the relation of the gene loci involved in the iso-agglutinin reaction, taste blindness, Friedreich's ataxia and major brachydactyly of man. *Journal of Genetics* 31: 353-361.

found no evidence for linkage between blood groups and taste deficiency to phenyl-thio-carbamide hereafter referred to as P.T.C.

The first evidence for autosomal linkage in man was suggested by Penrose⁴ between factors for blood groups and hair color. He used the 2 x 2 Table method. His data included only 50 sib-pairs. Penrose found no evidence for linkage between eye color and the blood groups, or eye color and hair color. Zieve, Wiener, and Fries⁵ using the Q-statistics by Wiener⁶ found no evidence of linkage between the blood groups, blood types, eye color, taste deficiency to P.T.C., and sex. Finney⁷ used the same data of Zieve, Wiener, and Fries with a refinement of Fisher's u-score, but found no evidence of linkage between these common traits. Snyder⁸ using the 2 x 2 Table method found no evidence for linkage involving the blood groups, blood types, taste deficiency to P.T.C., and sex. Burks⁹ used data involving 14 to 70 sib-pairs in a study of taste deficiency to P.T.C., mid-digital hair, blood groups, hair color, and sex. She used the 2 x 2 Table method and the phi-statistic of Penrose¹⁰. Snyder, Baxter, and Knisely¹¹

⁴Penrose, L. S., 1935. The detection of autosomal linkage in data which consists of pairs of brothers and sisters of unspecified parentage. *Annals of Eugenics* 6: 133-138.

⁵Zieve, I., Wiener, A. S., Fries, J. H., 1936. On the linkage relations of the genes for allergic disease and the genes determining the blood groups, MN types and eye colour in man. *Annals of Eugenics* 7: 163-178.

⁶Wiener, A. S., 1932. Method of measuring linkage in human genetics; with special reference to the blood groups. *Genetics* 17: 335-350.

⁷Finney, D. J., 1939. An apparent linkage of the ABO blood groups with allergic disease. *Seventh International Congress of Genetics*.

⁸Snyder, L. H., 1941. Studies in human inheritance XX—Four sets of alleles tested for incomplete sex linkage. *Journal of Heredity* 32: 402-403.

⁹Burks, Barbara S., and Helen Wyandt, 1941. Oval blood cells in human subjects tested for linkage with taste for P.T.C., mid-digital hair, hair color, A-B agglutinogens, and sex. *Genetics* 26: 223-233.

¹⁰Penrose, L. S., 1938. Genetic linkage in human graded character. *Annals of Eugenics* 8: 233-238.

¹¹Snyder, L. H., Baxter, R. C., and Knisely, A. W., 1941. Studies in human inheritance XIX—The linkage relations of the blood groups, the blood types, and taste deficiency to P.T.C. *Journal of Heredity* 32: 22-25.

found no evidence of linkage between factors for taste deficiency to mercapto-benzo-selenazol hereafter referred to as M.B.S., the blood groups, blood types, and sex. They used the 2 x 2 Table method on data from 118 to 227 sib-pairs. Boyd and Boyd¹² in the largest body of data published to that time studied blood groups, blood types, mid-digital hair, taste deficiency to P.T.C., hair color, and eye color. He used the phi-statistic in his comparisons involving an average of 500 sib-pairs.

An analysis of these previous studies shows that 24 linkage comparisons have been made, although 28 are possible using the traits mentioned. Six different statistical methods have been used but only the methods of Penrose have been used in more than one study. Of these 24 linkage comparisons cited, 9 have been used in linkage studies only once, and the greatest number involved in any one study was 15.

The purpose of this paper is to report the results obtained by two modifications of Penrose's phi-statistic in a study of all 28 possible linkage comparisons involving the 8 traits cited in the literature. There were approximately 900 sib-pairs included in each of these 28 comparisons.

It is beyond the scope of this paper to explain in detail the refinements in the application of the phi-statistic which appears for the first time in this study. Penrose's original phi-statistic called for adjusting differences of one trait with respect to the differences in another trait before performing the calculations. Penrose (personal communication) suggested that this adjustment could best be computed by subtracting the correlation squared from phi. In the study of Kloepfer¹³ the calculations for this procedure are explained in detail and it is called the phi-r² statistic. Penrose¹⁴ also recommended a procedure for normal-

¹²Boyd and Boyd, 1941. Data for testing for linkage on 500 pairs of sibs. *Annals of Eugenics* 2: 1-9.

¹³Kloepfer, H. Warner, 1942. An Investigation of 171 possible linkage relationships in man. Doctorial Dissertation, Ohio State University.

¹⁴Penrose, L. S., 1942. On the assignment of precise normal scale values to frequency distributions. *Bulletin of the Canadian Psychological Association* 2: 1-2.

izing frequency distributions. He suggested (personal communication previously mentioned) the desirability of normalizing the frequency distribution before applying the ϕ - r^2 statistic. Detailed procedures for carrying out both of these refinements are given by Kloefer and the procedure has been called the ϕ -statistic.

Discussion

The results of the present study are summarized in Table 1. A t -value of 2 or larger for either the ϕ - r^2 or ϕ -statistics would be expected to occur upon the basis of chance less than once in 20 samples, and is taken statistically to mean significance. A t -value of 3 or more (which means a ϕ - r^2 or ϕ -statistic value of 3 or more times its standard error) would be expected to occur upon the basis of chance less than once in 100 times, indicating high significance in statistical terminology. The 119 t -value obtained in connection with the two taste compounds is therefore highly significant and suggests the possibility of linkage. There was a significant association between these two traits within the individuals, but the effects of this association are supposed to be cancelled out in the statistical formula for the test.

The t -values enclosed in parenthesis indicate wrong direction for linkage. In the rc table set up in computing ϕ - r^2 and ϕ -statistics, only the numbers in the upper left and lower right cells tend to be higher in the presence of linkage. Larger numbers in the upper right and lower left cells will contribute to a high t -value, but such values even if significant would not indicate linkage. In the absence of linkage, t -values of a large number of linkage comparisons would be expected to fall on a normal bell shaped curve whose median is zero.

In contrasting the results of the two statistics used, it will be noted that there is almost complete agreement with no discrepancy greater than .8. In some cases the ϕ - r^2 value is higher and in some cases the ϕ value is higher. The ϕ -statistic should be preferable to both ϕ - r^2 and Penrose's original ϕ -statistic.

It will be noted that sex has been treated in this study as a trait. According to Koller and Darlington¹⁵ chiasmata occur between homologous portions of the X and Y chromosomes in mammals. Consequently in the event that genes for a certain variation are located on this portion of the X and Y chromosomes, their behavior with respect to sex would be similar to the behavior between two pairs of autosomal genes on the same pair of chromosomes.

According to the literature, comparisons for linkage between taste deficiency to M.B.S. and mid-digital hair; taste deficiency to M.B.S. and hair color; taste deficiency to M.B.S. and eye color; and taste deficiency to M.B.S. and taste deficiency to P.T.C. have never been made before.

The results in this study are in complete agreement with those cited in the literature with the exception of the comparison between the blood groups and hair color by Penrose. No evidence for linkage was found between these traits in this study, nor was such evidence found by Burks or Boyd and Boyd. Since Penrose's data involved only 50 sib-pairs, his conclusions undoubtedly were premature.

Summary and Conclusions

Using two refinements of Penrose's ϕ -statistic evidence was found that genes responsible for variation in blood groups, blood types, hair color, eye color, taste deficiency to P.T.C., taste deficiency to M.B.S., and mid-digital hair are located on separate pairs of chromosomes with the exception of the two taste compounds. Evidence for linkage was found between taste deficiency to P.T.C. and taste deficiency to M.B.S. There was no evidence in this study that any of the genes involved are located on the homologous sections of the sex chromosomes.

¹⁵Koller, P. C., and Darlington, C. D., 1934 The genetical and mechanical properties of the sex chromosomes. I. *Rattus norvegicus*. *Journal of Genetics* 29: 159-173.

TABLE 1

t-values from the results of comparisons for linkage by use of the phi-r (upper number) and phi (lower number) statistics

	Blood Groups	Blood Types	P.T.C.	M.B.S.	Eye Color	Hair Color	Mid-digital Hair
Sex	(.05) .06	.50 .63	(1.6)) .8)	(.3) (.3)	.63 .07	.59 .77	.56 .42
Mid-digital Hair	.03 (.05)	1.80 1.59	(1.0) (1.1)	(1.0) (1.6)	(.3) .22	.0 (.3)	
Hair Color	.24 (.35)	(.3) (.2)	.48 .79	.76 .65	(1.6) (1.4)		
Eye Color	.18 (.26)	(1.3) (1.7)	(1.3) (1.4)	(1.3) (1.4)			
M.B.S.	.14 .18	(.9) (.7)	11.5* 11.9*				
P.T.C.	.94 .59	(.5) (1.0)					
Blood Types	1.87 1.56						

Note:

*—indicates highly significant.
()—in wrong direction for linkage.