A CONTRIBUTION TO THE RELATION OF THE GENE LOCI INVOLVED IN THE ISOAGGLUTININ REACTION, TASTE BLINDNESS, FRIEDREICH'S ATAXIA AND MAJOR BRACHYDACTYLY OF MAN.

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I. Introduction.

It has been shown by Bernstein (1931), Wiener (1932) and one of the writers that it is possible to test for linkage between two genes located on human chromosomes provided that the gene frequency of one of them is of the same order of magnitude as that of its allelomorph. There is, therefore, now substantial basis for the hope that it will be possible to map human chromosomes for genes affecting morbid conditions. Of the two loci which fulfil the necessary condition stated above, **A–R–B**, which determines the isoagglutinin or common blood-group reaction, and **T–t**, which determines ability to taste phenyl-thio-urea and allied compounds, have been firmly established through the work of Bernstein (1930), Snyder (1932) and many other investigators. The requisite data for linkage analysis on these lines must necessarily accumulate gradually, and positive conclusions are most likely to emerge from the pooled results of numerous enquiries. The present communication is intended as a contribution to such a common fund of information. It is based on the application of tests for taste blindness and the blood groups A and B to sibs and parents of fraternities containing individuals affected with (*a*) Friedreich's ataxia, (*b*) brachydactyly.

II. Friedreich's ataxia.

Friedreich's ataxia begins as a rule in childhood or about the age of puberty. It affects both sexes equally, and tends to affect several members of a family. The onset is usually insidious, and the progress slow. It commences usually in the legs and the earliest symptom is clumsy and unsteady walking. There is incoordination of a jerky, unsteady kind affecting first the lower extremities. The gait is irregular and swaying. This incoordination extends later to the trunk and arms. In many cases there are tremors and irregular movements of the head, and lateral nystagmus is usually present as an early sign, but this is not

invariably so. Speech is altered in more advanced stages. It becomes slurred, slow or explosive, and often there is a definite hesitation in speaking. These changes are due to ataxia of the muscles of speech. Reflexes are usually lost early, and the extensor response is nearly always present. Sensation is usually normal, but in the late stages there may be slight changes. There is no pain. Deformities of the feet are present in nearly all cases of some duration. There may be pes cavus in some early cases, and this is seen in late cases in association with hammer toes and a hyperextension of the big toe. Curvature of the spine—scoliosis or kyphosis—is often present. The cranial nerves are usually unaffected, and the pupil is usually normal. There is usually no weakness of the muscles until the later stages, but finally this becomes extreme. The disease is slowly progressive, and walking becomes increasingly difficult and finally impossible. Later the patients are completely bedridden, but may live many years subsequently. It is thought to be due to a degeneration of the posterior and lateral columns of the cord[1].

(*a*) *Age of onset.*

With reference to the age of onset Table I summarises the cases examined. The youngest subject in whom the onset of the disease was

TABLE I.

Onset of Friedreich's ataxia.

	Age in years					
	5–7	8–10	11–13	14–16	17–19	20–22
Males	3	3	2	4	5	0
Females	6	4	0	4	3	0
Total	9	7	2	8	8	0

already manifest was 4 years. The oldest age at which onset of the disease occurred in all the families was 18. The distribution of age of onset is apparently bimodal. The smaller number of cases round about the age of puberty is, however, in agreement with the general trend of vital statistics. Since one family contained four affected individuals who first

[1] The following is a list of the hospitals from which cases were taken and the physicians in charge: Great Ormond Street, Dr B. Schlesinger; National Hospital, Queen's Square, Dr Collier, Dr Hinds-Howell, Dr Critchley, Dr Walshe, Dr Kinnier-Wilson, Dr Holmes; London Hospital, Dr Miller; West-end Hospital for Nervous Diseases, Dr Worster-Drought, Dr Macnamara; Cardiff Royal Infirmary, Prof. A. M. Kennedy, Dr A. Howell; North Middlesex County Hospital, Upper Edmonton, Dr Bruce-Young, Dr Galloway; Guy's Hospital, Dr Symonds; Hospital for Epilepsy and Paralysis, Dr Feiling, Dr Wyllie; Westminster Hospital, Dr H. Carlill; Leicester Infirmary, Dr Tanner; Bristol Royal Infirmary, Dr Charles; Manchester Royal Infirmary, Dr Core.

showed signs of onset at 7, 10, 14, 17 years respectively, the apparent bimodality of the distribution provides no reason to suppose that there are two different clinical or genetic types involved.

(*b*) *Consanguinity.*

Of the twenty-two families examined, the parents of two were first cousins, and of one other family the parents were second cousins. In the three fraternities with consanguineous parentage there were in all three affected individuals; the age of onset in one case being 6 years, in both the other two 11 years.

(*c*) *Familial incidence.*

Further evidence for the view that Friedreich's ataxia is determined by a single recessive gene substitution, whose manifestation is not affected

TABLE II.

Friedreich's ataxia.

	Partial fraternities 10 and over				Partial fraternities 18 and over			
S	n_s	Observed	Expected	Variance	n_s	Observed	Expected	Variance
1	2	2	2·000	0·000	3	3	3·000	0·000
2	4	4	4·571	0·490	1	1	1·143	0·122
3	4	5	5·189	1·052	2	3	2·595	0·526
4	3	3	4·388	1·260	2	2	2·926	0·840
5	1	2	1·639	0·592	2	6	3·278	1·184
6	3	7	5·484	2·328	3	5	5·484	2·328
7	1	1	2·020	0·970	1	2	2·020	0·970
8	3	9	6·668	1·172	—	—	—	—
9	1	1	2·433	1·380	—	—	—	—
10	0	0	—	—	—	—	—	—
Total	22	34	34·392	9·244	14	22	20·446	5·970

by the differences of environment ordinarily operative within a family group, is provided by the following table of familial incidence. Since some fraternities included members who had either died before the mean age of onset or had not yet reached it, the data are summarised under two headings:

(*a*) Partial fraternities of 10 years or over.
(*b*) Partial fraternities of 18 years or over.

The expected incidence calculated by the method given by one of the writers (Hogben, 1932) is (*a*) $34{\cdot}4 \pm 3{\cdot}1$ as compared with an observed number 34, and (*b*) $20{\cdot}4 \pm 2{\cdot}4$ as compared with an observed number 22.

TABLE III.

Friedreich's ataxia and the blood groups.

		Offspring			
(I) Matings A × O	*S*	A (or B)	O*f*	A*f* (or B*f*)	O
I	6	2	—	1	3
II	2	1	1	—	—
IV	5	2	—	1	2
V	6	2	—	1	3
XII	1	—	—	1	—
XIV	6	2	4	—	—
XV	2	—	1	—	1
XVI	11	4	—	1	6
XIX	5	2	1	—	2
XX	5	3	1	—	1
XXI	3	1	1	1	—
XXII	7	2	1	—	4
(II) Matings A × A					
XI	2	1	—	1	—
XVII	6	5	—	1	—
(III) Matings AB × O					
III	2	1 (B)	—	1 (A*f*)	—
(IV) Matings O × O					
VI	4	—	1	—	3
VII	4	—	1	—	3
VIII	2	—	1	—	1
IX	7	—	2	—	5
X	9	—	4	—	5
XIII	1	—	1	—	—
XVIII	8	—	1	—	7

TABLE IV.

Matings **AaFf × aaFf.**

Family	Mating	*S*	$\mu\nu$ observed	$\mu\nu$ calculated	Variance	$\mu\nu$ calculated* by Haldane's formula
I	A × O	6	8	7·510	3·758	7·540
II	,,	2	0	0·381	0·236	0·333
III	AB × O	2	1	0·500	0·250	0·250
IV	A × O	5	6	5·003	2·547	5·032
V	,,	6	8	7·510	3·758	7·540
XIV	,,	6	0	7·510	3·758	7·492
XV	,,	2	1	0·381	0·236	0·333
XVI	,,	11	28	27·503	13·719	27·509
XIX	,,	5	6	5·003	2·547	5·032
XX	,,	5	4	5·003	2·547	5·032
XXI	,,	3	2	1·436	0·810	1·429
XXII	,,	7	12	10·511	5·228	10·535
		Totals	76	78·251	39·394	78·057

* The extreme right-hand column is calculated by a more rigorous method due to Haldane. Comparison between the totals in columns V and VII shows that the difference between the expected values calculated by the two formulae is very small.

(*d*) *Blood group distribution.*

In Table III the blood group distribution is represented by the usual signs. The Roman numerals indicate the classified number of the fraternity. The letter *f* signifies individuals with the disease.

In Table IV, for families which contain the requisite information the expected values are calculated by the product method (*vide* Hogben, 1934) on the assumption that segregation is independent (*i.e.* that $c=\frac{1}{2}$).

TABLE V.

Friedreich's ataxia and taste blindness.

No. of family	*S*	T	N*f*	T*f*	N
(*a*) Matings N × N					
III	2	0	1	0	1
IV	5	0	1	0	4
XII	1	0	1	0	0
XIII	1	0	1	0	0
XX	5	0	1	0	4
XXII	7	0	1	0	6
(*b*) Matings T × T					
VI	4	3	0	1	0
XIX	5	4	0	1	0
(*c*) Matings N × T					
I	6	3	1	0	2
II	2	1	1	0	0
V	6	2	2	0	2
VII	4	2	0	1	1
VIII	2	0	1	0	1
IX	7	2	1	1	3
X	9	1	1	3	4
XI	2	0	1	0	1
XIV	6	1	3	1	1
XV	2	0	0	1	1
XVI	11	7	1	0	3
XVII	6	2	0	1	3
XVIII	8	6	0	2	0
XXI	3	0	2	0	1

The observed value of the product is 76. The expected is $78{\cdot}3 \pm \sqrt{39{\cdot}4}$ or $78{\cdot}3 \pm 6{\cdot}3$. Thus the difference (2·3) while deviating in the direction of linkage, is less than a half the standard error (6·3)[1]. In other words, there is no reason to suppose that the gene f (Friedreich's ataxia) is in the same chromosome as the **A–B–R** locus.

(*e*) *Taste blindness reaction.*

The distribution of taste blindness with reference to phenyl-thio-urea among families with sibs suffering from Friedreich's ataxia are summarised below in Table V. In this table Tasters are denoted by T and

[1] Excluding eleven normal individuals under 10 years of age, the observed product would be 51, and the calculated value $53{\cdot}6 \pm 5{\cdot}2$.

Non-tasters by N. The calculated product values are based on the assumption that $c=\frac{1}{2}$, *i.e.* that there is no appreciable linkage.

The relevant matings for linkage analysis are summarised in Table VI. In this the expected product is $92{\cdot}0 \pm \sqrt{46{\cdot}27}$ or $92{\cdot}0 \pm 6{\cdot}8$. The difference (2·3) between the observed (90) and expected values, while deviating in the direction of linkage, is less than half its standard deviation. So it is evident that there is not high linkage between **f** and **t**.

TABLE VI.

Matings **Tt Ff × tt Ff.**

Family	S	μ	ν	$\mu\nu$ observed	$\mu\nu$ calculated	Variance
I	6	4	2	8	7·510	3·758
II	2	2	0	0	0·381	0·236
V	6	4	2	8	7·510	3·758
VII	4	2	2	4	2·981	1·576
VIII	2	1	1	1	0·381	0·236
IX	7	3	4	12	10·511	5·228
X	9	2	7	14	18·007	8·958
XI	2	1	1	1	0·381	0·236
XIV	6	4	2	8	7·510	3·758
XV	2	0	2	0	0·381	0·236
XVI	11	8	3	24	27·503	13·719
XVII	6	2	4	8	7·510	3·758
XXI	3	2	1	2	1·436	0·810
			Totals	90	92·002	46·267

III. Brachydactyly.

Through the kindness of Prof. Ruggles Gates we were able to get directly into touch with a physician who was acquainted with the family investigated by Drinkwater in North Wales. At the time of Drinkwater's enquiry, as reported in this *Journal*, forty-nine brachydactyls could be traced over six generations. Our enquiries have brought the present number up to sixty-three brachydactylous offspring of unions between a brachydactylous and normal parent. The total offspring of these unions was 124. So the expectation is $62 \pm 5{\cdot}4$. Of these sixty-three individuals thirty were tested for blood grouping and taste reaction together with thirty-eight of their normal relatives. In only five families of the pedigree did we succeed in testing both parents and some of their offspring of brachydactylous unions. One of these families would not submit to the taste blindness test.

The results of these tests are summarised in Tables VII and VIII, the first of which gives the blood group distribution. In these tables Br signifies a brachydactyl and br a normal person. The only[1] family

[1] It has been pointed out by Haldane that the homozygous condition of an individual belonging to group B is very rare. A family such as III is thus presumably relevant. In this case the linkage value can be assessed by a special method (Haldane).

which yields clear cut information about linkage is II (x). The two classes are

(a) (A B br, A Br, B br, O Br) $=0$.
(b) {A B Br (0), A br (1), B Br (1), O br (3)} $=5$.

Clearly it would be useless to draw any conclusions from this isolated case.

The tests carried out on five families for taste blindness yielded the information summarised in Table VIII. Two families (V) and (VI) bear

TABLE VII.

*Relation between Brachydactyly—***A–R–B**.

Index No.	Parents	Known S	Offspring							
			A Br	A br	B Br	B br	O Br	O br	AB Br	AB br
I (x)	B Br × B br	2	—	—	1	1	—	—	—	—
II (x)	B Br × A br	5	—	1	1	—	—	3	—	—
III (x)	B Br × O br	2	—	—	1	1	—	—	—	—
V (x)	O Br × A br	2	—	2	—	—	—	—	—	—
VI (x)	A Br × A br	4	3	1	—	—	—	—	—	—

TABLE VIII.

Relation between **T–t** *and brachydactyly.*

Index No.	Parents	S	Offspring			
			Br–**T**	Br–t	br–**T**	br–t
I (x)	Br–t × br–t	2	—	1	—	1
II (x)	Br–t × br–**T**	5	—	1	3	1
V (x)	Br–**T** × br–t	2	—	—	1	1
VI (x)	Br–**T** × br–t	4	1	2	—	1

on the linkage relations of (Br) and **t**. In one there was one cross-over and one non-cross-over. In the other of four offspring the ratio of cross-overs to non-cross-overs was also 1:1.

IV. INTERNAL CONSISTENCY OF THE DATA.

No data collected in this investigation reveal any departure from the results of previous enquiries in so far as they bear on issue of matings between parents classified by their blood groups alone or by their reaction to phenyl-thio-urea. All data bearing on taste blindness may be summarised thus:

	No. of families	T	N
T × T	2	9	0
N × T	17	42	43
N × N	7	0	23
Totals	26	51	66

All data bearing on blood group distribution may be summarised thus:

	No. of families	O	A	B	AB
O × O	7	35	0	0	0
O × A	13	32	29	0	0
A × A	3	0	12	0	0
O × B	1	0	0	2	0
B × B	1	0	0	2	0
O × AB	1	0	1	1	0
B × A	1	3	1	1	0
Totals	27	70	43	6	0

Five families yielded information with respect to linkage between **T–t** and **A–B–R**. These are summarised in Table IX which gives the expected product when $c=\frac{1}{2}$. One other family Z_1 examined by Dr I. Zieve has been included. Of forty families tested for **A–B–R** and **T–t** only six provided relevant information. The expected value of the product

TABLE IX.

Taste blindness and blood groups.

Family	*S*	AT	ON	OT	AN	$\mu\nu$ observed	$\mu\nu$ calculated	Variance
(*a*) Class (i): AT × ON								
I	6	1	1	2	2	8	7·498	3·763
II	2	2	1	0	0	0	0·444	0·247
XV	2	0	1	1	0	1	0·444	0·247
XVI	11	3	2	4	2	30	27·500	13·750
XXI	3	0	1	0	2	2	1·469	0·780
(*b*) Class (ii): OT × AT or AN × AT								
Z 1	3	0	1	1	1	2	1·436	0·810
					Totals	43	38·791	19·597

(38·8) differs from the observed (43) by 4·2 which barely exceeds the standard error (4·4), the deviation being in the opposite direction to linkage. It is clear that there is not high linkage between **A–B–R** and **T–t**, though five families are not sufficient to justify the conclusion that they segregate independently.

V. Conclusions.

The following conclusions may now be stated:

(1) Friedreich's ataxia is determined by a single recessive gene substitution (**f**).

(2) The locus **F–f** is not strongly linked to **T–t** (phenyl-thio-urea taste blindness) or **A–B–R** (isoagglutinin reaction). As far as the present evidence permits any inference it appears to segregate independently.

(3) The locus **Br–br** (brachydactyly) is not strongly linked to **T–t**, neither is **A–B–R**. The data are insufficient to justify the statement that **A–B–R** or **Br-br** segregates independently with respect to **T–t**.

(4) The yield of relevant information obtained in linkage studies confined to a few genes is very small. In consequence the method of routine testing of hospital patients with a battery of tests would seem to be the most efficient way of advancing the mapping of human chromosomes.

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