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THE PARTIAL SEX-LINKAGE OF RECESSIVE SPASTIC PARAPLEGIA

BY J. B. S. HALDANE, F.R.S.

BELL (1939) has collected 273 pedigrees of Friedreich's ataxia, spastic ataxia, and spastic paraplegia in the literature, besides publishing forty-six new pedigrees from her own and Carmichael's observations. From the former group she generally excluded pedigrees including only one case of the disease.

She is inclined to regard Friedreich's ataxia and spastic ataxia as due to the same gene, or genes, perhaps influenced by modifiers. She is more doubtful in the case of spastic paraplegia. For a certain number of pedigrees exist in which some members would be classified as cases of Friedreich's ataxia, others of spastic ataxia. Spastic paraplegia seems to be more sharply defined.

Haldane (1936) reported the presence in man of a group of phenomena which are attributed to partial or incomplete sex-linkage. The genes responsible are thought to be carried in that part of the sex chromosomes which is homologous in the X and Y. Such genes may therefore cross over from one of these chromosomes to the other in a man. At first sight the pedigrees resemble those of autosomal genes. But they differ in the following ways. If a man receives a partially sex-linked gene from his father he hands it down, on an average, to a majority of his sons and a minority of his daughters. If he receives it from his mother he transmits it to a majority of his daughters and a minority of his sons. This can readily be detected in pedigrees of dominants. In the case of recessives it shows up in two ways. Where the parents are related we may assume that they derived the recessive gene from a common ancestor. If the father is related to the mother through his father we expect an excess of affected sons, if through his mother, an excess of affected daughters. If χ be the frequency of recombination between the gene and the differential segments of the sex chromosomes, and if ♂, ♀, ♂̄, ♀̄ represent normal and affected males and females, and a, c, b, d, their numbers, the expectations are:

	♂	♀	♂̄	♀̄
	a	c	b	d
Parents related through father's father	$1+\chi$	$2-\chi$	$1-\chi$	χ
Parents related through father's mother	$2-\chi$	$1+\chi$	χ	$1-\chi$

If the parents are unrelated, or their relationship unknown, Fisher (1936) showed that in a family containing s_1 and s_2 abnormals, the expected value of $u=(a-c-3b+3d)^2-(a+c+9b+9d)$ is $\frac{1}{9}(1-2\chi)^2k$, where $k=(s_1+9s_2)^2-(s_1+81s_2)$. And if $\chi=\frac{1}{2}$, the variance of u about its mean value of zero is $2k$. In a large group of families the sampling variance of the sum of the values of u is twice the sum of the values of k. This is true whatever the method of ascertainment, i.e. whether or not there is a bias in favour of families containing large numbers of abnormals.

Bell finds that a majority of the pedigrees of all three diseases are consistent with the condition being due to a recessive gene. Others show a probably dominant type of inheritance. A few show a sex-linked recessive type. In the pedigrees of spastic paraplegia she finds 55% affected in the sibships showing a dominant inheritance and (after suitable correction) 27·1% in those showing a recessive type. The age of onset is, with few exceptions, very close in members of the same sibship. For spastic paraplegia the correlation coefficient is 0·884. Thus we shall make few mistakes if we assume that the elder sibs of affected persons who had not developed the disease at the time of observation would not do so later. On this assumption we can draw up Tables 1 and 2. There is only one case in which the relationship of the parents is given, namely pedigree 562, given in my Fig. 1.

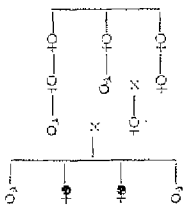

Fig. 1.

The affected daughters had developed symptoms at the ages of 3 and 4. The youngest son was aged 3, and therefore might have developed the disease later, though a clinician generally notes incipient disease before the age of onset. There were thus no cross-overs out of 3 or 4 sibs. The pedigree is consistent with partial sex-linkage, though of course it is of no great significance if taken alone. Table 1 is a summary of those sibships where all sibs except those dying in infancy are recorded. I have counted younger sibs as normal if they had passed the mean age of onset of their affected sibs. Where ages were not recorded I have assumed an interval of three years between sibs. Table 2 is a summary of those where

either the number, sex, or birth order of normal sibs was not recorded. Table 1 gives

$$S(u) = +1022, \quad S(k) = 23{,}570, \quad \sigma = 217{\cdot}1.$$

Table 1. *Sibships with complete information*

Pedigree	♂	♀	♂	♀	$u+$	$u-$	k
280	0	1	0	3	36	—	540
504	1	0	0	2	30	—	198
505	1	0	2	0	6	—	198
507	2	0	4	2	—	40	2648
508*	0	1	7+1?	0	420	—	3528
509	4	0	2	1	—	30	714
511	1	1	2	0	16	—	236
512	2	0	3	0	20	—	596
513	0	0	1	2	—	18	486
514	3	2	0	2	26	—	362
515	0	0	0	2	18	—	162
515	0	0	2	0	18	—	162
516	1	1	1	1	—	20	236
517	1	0	2	1	—	24	540
518	3	0	1	1	—	12	276
519	1	2	3	1	10	—	1194
520	3	0	1	2	6	—	654
521	0	3	0	4	42	—	1194
524	0	0	2	2	—	36	972
525	0	0	0	3	54	—	486
526	0	2	1	1	—	16	236
527	0	0	0	2	18	—	162
531	1	2	2	0	28	—	276
533	1	2	2	2	—	38	1194
534	0	1	3	0	72	—	540
535	0	0	1	1	—	18	162
536	0	4	3	0	138	—	714
537	3	0	2	0	—	12	276
538	1	0	0	2	30	—	198
556	1	0	3	0	36	—	540
557	1	1	0	2	16	—	236
559	3	0	0	3	114	—	654
563	0	1	4	1	54	—	1710
564	4	0	0	2	78	—	318
566	0	0	1	3	0	0	972
35	38	24	45	48	+1286	−264	23,570

* One pair of twins, possibly monozygotic.

Thus the sum of the values of u is 4·71 times its standard error on the base of sampling, and is undoubtedly significant. If family 508 is omitted, we have

$$S(u) = +602, \quad S(k) = 20{,}042, \quad \sigma = 200{\cdot}2.$$

Thus $S(u)$ is still over three times its standard error, and is, moreover, of the right sign, so that the probability of so large a deviation is 0·0013. In Table 2, u and k are calculated from the affected members only. Including it, we have

$$S(u) = 1130, \quad S(k) = 25{,}514, \quad \sigma = 225{\cdot}9.$$

Thus the sum exceeds zero by five times its standard deviation. There is no doubt at all that some anomaly is really present, and so far no hypothesis other than partial sex-linkage has been put forward which would explain it.

The last set of data give a recombination frequency χ of 18·43 % between the locus of the gene and the differential segments which carry the sex-linked genes. If the two twins in family 508 were dizygotic, we have

$$S(u)=1251, \quad S(k)=26{,}666, \quad \sigma=230{\cdot}9, \quad \chi=0{\cdot}1750.$$

If this family is omitted, we have

$$S(u)=710, \quad S(k)=21{,}986, \quad \chi=0{\cdot}2302.$$

However, there seems to be no good reason for omitting this family. It can hardly be explained by ordinary sex-linkage, for the mother had

Table 2. *Sibships with incomplete information*

Pedigree	♂	♀	⚷	⚲	$u+$	$u-$	k
499	—	—	0	3	54	—	486
506	—	—	1	1	—	18	162
510	1	1	2	0	18	—	162
522	0	1	0	2	18	—	162
523	4	1	2	0	18	—	162
529	—	—	0	2	18	—	162
530	5	1	2	1	—	18	486
532	—	—	2	0	18	—	162
8	—	—	9	9	144	36	1944

five normal brothers, and Bell states that "This family was very carefully investigated and the presence of the disease excluded in at least 70 members of the stock, in 5 generations; the parents were normal and not consanguineous". However, a standard error for χ can hardly be given in view of the uncertainty introduced by it and the fact that an autosomal recessive gene may be responsible for some cases. On the other hand, the sampling distribution of $S(u)$ is not seriously asymmetrical when we are dealing with forty-three families, as in this case, and the tests of significance are satisfactory.

We can now proceed to answer three questions. Is a partially sex-linked gene responsible for the dominant type of spastic paraplegia? This would be so if the dominant and recessive forms were allelomorphic, as seems to be the case with retinitis pigmentosa (Haldane, 1936). On examining the pedigrees showing undoubted dominance, in which a generation is never skipped, we find that the children of fathers who derived the disease from their fathers were

10 ♂, 8 ♀, 13 ⚷, 12 ⚲.

The children of fathers who derived it from their mothers were

$$7\,♂,\ 6\,♀,\ 6\,♂,\ 5\,♀.$$

Thus there were thirty-six affected out of sixty-seven (expected 33·5) and thirty-four cross-overs out of sixty-seven on the hypothesis of partial sex-linkage. There is thus not the faintest suggestion of this phenomenon, or of any other deviation from what is to be expected in the case of an autosomal dominant.

We can also settle the question, raised by Bell, as to whether the same main gene, perhaps modified by other genes or by environment, is responsible for the three diseases, Friedreich's ataxia, spastic ataxia, and spastic paraplegia.

There are six sibships derived from marriages of cousins whose relationship is known. These are summarized in Table 3. FA means that the families showed Friedreich's ataxia, SA denotes spastic ataxia, whilst FA + SA denotes families where both diseases occurred. Very possibly family 371 should be omitted, as the disease occurs in eight sibships in a large pedigree of related stocks. Though it is never transmitted from parent to offspring, we may be dealing with a very irregular dominant. The totals are compared with their expectations, where χ is the recombination frequency:

Obs.	8	2	12	3
Exp.	$\frac{10(2-\chi)}{3}$	$\frac{10(1+\chi)}{3}$	$15(1-\chi)$	15χ

Table 3. *Offspring of cousin marriages*

Pedigree	Type	♂	♀	♂	♀
	(*a*) Husband related through his father				
422 A	SA	0	0	2	1
463 A	SA	1	1	2	1
		1	1	4	2
	(*b*) Husband related through his mother				
267	FA	3	0	0	1
328	FA	2	0	0	3
371	FA + SA	2	1	1	2
372	FA + SA	0	0	0	2
		7	1	1	8

The probability of such large deviations from equality in the expected direction is, for the normals 7×2^{-7}, for the affected 9×2^{-9}. Thus the total probability is less than 0·003. This constitutes evidence in favour of partial sex-linkage. However, a search by the method of Tables 1 and 2 gave a negative result. 116 sibships of Friedreich's ataxia gave $S(u) = +48$, $s(k) = 56{,}728$, $\sigma = 336{\cdot}8$. Forty-eight sibships segregating for

spastic ataxia gave $S(u) = +162$, $S(k) = 10{\cdot}05$, $\sigma = 141{\cdot}8$. Or omitting pedigree 293, where there may be dominance, $S(u) = +170$, $S(k) = 7{\cdot}484$, $\sigma = 122{\cdot}35$, so that $S(u) = 1{\cdot}39\,\sigma$. The probability of so large a deviation in the positive direction, in the absence of linkage, is 0·08. Hence there is some reason to suspect the existence of linkage. However, it is very weak compared with that derived from the cousin marriages.

We can say with fair certainty that the gene which is responsible for a large fraction, at least, of the cases of recessive spastic paraplegia, is only responsible for a small fraction, at most, of the cases of Friedreich's ataxia and spastic ataxia. The indications of partial sex-linkage suggest that this gene is responsible for a few cases of these latter diseases, and that by chance two out of the six cases where the relationship of the parents is known were due to this gene. If only about one-quarter of all cases were due to it it would not be detected with certainty where the relationship of parents is unknown. Thus Bell is probably right in claiming some common genetic basis for spastic paraplegia and the other two diseases, but it is very unlikely that all three are due to the same gene. Even if we reject the hypothesis that the large positive value of $S(u)$ found for spastic paraplegia is due to partial sex-linkage, it is a fact which constitutes a difference between the genetics of this disease and those of the ataxias.

Table 4. *Ages of onset in spastic paraplegia*

Pedigree	u	Ages
508	420	1–2, ?, ?, ?, 1–2
521	42	11, 9, 8, 6
525	54	0–4, 0–4, 0–4
534	72	12, 12, 12
536	138	12, 14, 6
559	114	3, 3, 1
563	54	?, c. 37, c. 30, 29, ?
564	78	10, 16

The third question is whether we are dealing with a single partially sex-linked gene, or a series of allelomorphs. In an accompanying paper (Haldane, 1940) I have pointed out that the correlation between ages of onset in sibs is so high that it can only be explained by postulating different genes in different families. Modifiers could not account for it, as they would lead to a considerable variation in the age of onset within a sibship. Bell found the high correlation coefficient of 0·852 for recessive spastic paraplegia. It might be that the partially sex-linked gene gave a fairly uniform age of onset, the outlying cases being accounted for by one or more autosomal recessives. Table 4 shows that this is

not the case. The eight sibships are those with the largest values of u. Indeed, between them they furnish almost all the evidence for linkage. In the first family it is fairly clear that all the brothers developed symptoms in early childhood, though the age is only given in two cases. This table is intelligible if we are dealing with three allelomorphs, causing incidence round the ages of 2, 12, and 30 respectively. Between them they cover almost the whole range of ages of onset. Only five out of 132 cases developed the disease after the age of 40. It is most unlikely that we are dealing with several genes at different loci in the same section of a single chromosome. We are probably concerned with multiple allelomorphs at the same locus, such as certainly occur in the cases of colour-blindness and haemophilia, and possibly in that of retinitis pigmentosa. In accordance with Goldschmidt's theory, we may suppose that all are responsible for fundamentally the same process, but that its rate varies in different members of the series.

SUMMARY

1. Recessive spastic paraplegia is due to a partially sex-linked gene.

2. Dominant spastic paraplegia is due to an autosomal gene. Partially sex-linked recessives are probably responsible for a small fraction of all cases of Friedreich's ataxia and spastic ataxia.

3. There are probably three or more allelomorphs of the partially sex-linked gene, determining different ages of onset.

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