Is Idiopathic Convulsive Disorder Partially Sex-linked?

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FOLLOWING the description by Haldane of partially sex-linked traits in man, Snyder and Palmer published an account of a neurological syndrome which they designated as "idiopathic convulsive disorder." They tentatively localized the gene as being on the homologous segments of the sex chromosomes. The disorder appeared in three sibships descended from two brothers six generations removed. In the sibship which contained three normal males and four affected females the father was related to the mother of the affected children by way of his mother, the ideal situation in which a partially sex-linked gene could descend to four daughters and to none of the sons. There was at least one crossover in the kindred, since a son and daughter were affected in one sibship. Snyder and Palmer state "It thus becomes impossible to make any estimate of the crossover frequency in this pedigree, and, indeed it cannot be insisted that the gene is located on the homologous portions of the sex chromosomes at all." Nevertheless, in his latest text on Principles of Heredity Snyder still places the gene for this disorder on the homologous segment of the sex chromosome, although not specifying its exact location.

It is the purpose of the following note to point out that the crossover frequency can be readily determined from the pedigree, and that the frequency is such as to make it advisable to reconsider locating this gene on the sex chromosomes. Since it is only in the transferral of such a gene by the male parent that the effect of crossing over is noticeable, the number of such crossovers can be directly estimated from Snyder and Palmer's data. Figure 1 is an adaptation of their pedigree, omitting all irrelevant persons, and indicating the sites at which crossing over or non-crossing over must occur if the gene in question is to be transferred from father to child in order to reappear in the 7th generation.

Analysis of the pedigree. Examination of the pedigree shows that there are two brothers in the first generation whose descendants are the affected children in the seventh generation. In VII-4, 6, 7, and 9, the genes are obviously brought down from I-1 through the father and the mother. In VII-1 and 2, they are transmitted from I-1 on the maternal side, and possibly also from the paternal side, since VI-2 bears the same surname as the males in generations III and IV. The manner of relationship, if any, of VI-2 to VI-1 is unknown, hence the

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number of possible crossovers which have occurred to make him a heterozygote cannot be estimated. Finally, VII-12 may have the gene of I-1 duplicated in her, or she may have the genes from I-1 and I-2 present, since her father is descended on his mother's side from I-2 and on his father's side from I-1.

A complete pedigree such as this enables one to estimate the upper and lower limits of the crossover value necessary to produce such a group of affected offspring. First it may be assumed that all the affected children in the seventh generation received their genes from I-1 and that it is purely coincidental that VI-7 was also descended from I-2. This is designated as Pathway I. The gene must have been located on either the X or the Y chromosome in I-1. Table 1-A shows the total number of crossovers and non-crossovers necessary to bring the mutant gene from the X chromosome of I-1 to the seven affected children in the seventh generation. Thus, in order that VII-1 may carry the

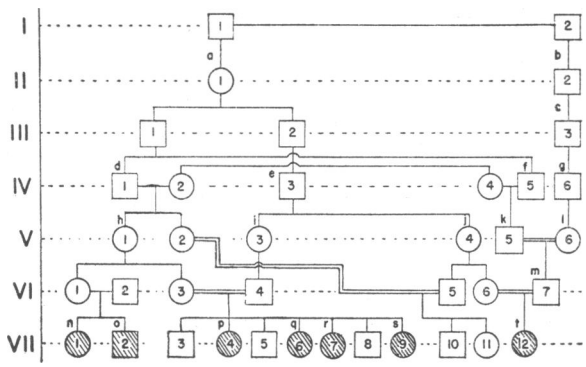

FIG. 1

gene derived from I-1, two crossovers and one non-crossover are essential if we assume the X chromosome of I-1 carried the gene. It takes three crossovers if the gene is on the Y chromosome of I-1. This is based on the assumption that the gene in VI-2 is located on the X chromosome. If it is on the Y chromosome in VI-2 the daughter represents a crossover, the son a non-crossover. Similarly, if the crossovers essential to the production of VII-1 have occurred, it requires two more crossovers and four non-crossovers to produce VII-4, 6, 7 and 9. An additional three crossovers and two non-crossovers give the affected child VII-12. A minimum of eight crossovers and eight non-crossovers is necessary to explain the pedigree, giving a C.O.V. (crossover value) of 50%. Viewing the matings in a similar manner, but assuming that the mutant gene was located on the Y chromosome of I-1 (Table 1-B) one finds that a minimum of nine crossovers and seven non-crossovers must occur in order to produce the affected offspring, a C.O.V. of 56.3%.

Pathway II is the one followed if the assumption is made that the male VI-7 derived his mutant gene from his mother descended from I-2, rather

TABLE 1. ESTIMATION OF CROSSOVER FREQUENCY

Pathway I. Duplication in 7th generation of genes from I-1

A. GENE LOCATED ON X CHROMOSOME OF I-1

Sibship	Path of gene from male parent to offspring	No. crossovers	No. non-cross-overs	Individuals affected
1	I-1 to II-1 through a		1	
	III-1 to IV-1 through d	1		
	IV-1 to V-1 through h	1		
	VI-2 to VII-1* through n		1	VII-1
	VI-2 to VII-2* through o	1		VII-2
2	III-2 to IV-3 through e	1		
	IV-3 to V-3 through i	1		
	VI-4 to VII-4, 6, 7, 9 through p, q, r, s		4	VII-4, 6, 7, 9
3	IV-3 to V-4 through j	1		
	III-1 to IV-5 through f	1		
	IV-5 to V-5 through k		1	
	V-5 to VI-7 through m		1	
	VI-7 to VII-12 through t	1		VII-12
Total.....		8	8	
C.O.V.....		50%		

B. GENE LOCATED ON Y CHROMOSOME OF I-1

Sibship	Path of gene from male parent to offspring	No. crossovers	No. non-cross overs	Individuals affected
1	I-1 to II-1 through a	1		
	III-1 to IV-1 through d	1		
	IV-1 to V-1 through h	1		
	VI-2 to VII-1* through n		1	VII-1
	VI-2 to VII-2* through o	1		VII-2
2	III-2 to IV-3 through e	1		
	IV-3 to V-3 through i	1		
	VI-4 to VII-4, 6, 7, 9 through p, q, r, s		4	VII-4, 6, 7, 9
3	IV-3 to V-4 through j	1		
	III-1 to IV-5 through f	1		
	IV-5 to V-5 through k		1	
	V-5 to VI-7 through m		1	
	VI-7 to VII-12 through t	1		VII-12
Total.....		9	7	
C.O.V.....		56.3%		

* The gene has been assumed to be on the X chromosome of VI-2 in this arrangement. If it were on the Y chromosome of VI-2, there would be a crossover necessary to produce VII-1 and no crossover to produce VII-2. This note applies also to Table 2.

TABLE 2. ESTIMATION OF CROSSOVER FREQUENCY

Pathway II. Duplication in 7th generation of genes from I-1 and I-2

A. GENE LOCATED ON X CHROMOSOMES OF I-1 AND I-2

Sibship	Path of gene from male parent to offspring	No. crossovers	No. non-cross-overs	Individuals affected
1	Same as for Table 1 Part A	2	2	VII-1
		1		VII-2
2	Same as for Table 1 Part A	2	4	VII-4, 6, 7, 9
3	I-2 to II-2 through b	1		
	II-2 to III-3 through c		1	
	III-3 to IV-6 through g		1	
	IV-6 to V-6 through l	1		
	VI-7 to VII-12 through t		1	
	IV-3 to V-4 through j	1		
	III-1 to IV-5 through f*		1	VII-12
Total		8	10	
C.O.V.		44.4%		

B. GENE LOCATED ON THE Y CHROMOSOME OF I-1 AND I-2

Sibship	Path of gene from male parent to offspring	No. crossovers	No. non-cross-overs	Individuals affected
1	Same as for Table 1 Part B	3	1	VII-1
		1		VII-2
2	Same as for Table 1 Part B	2	4	VII-4, 6, 7, 9
3	I-2 to II-2 through b		1	
	II-2 to III-3 through c		1	
	III-3 to IV-6 through g		1	
	IV-6 to V-6 through l	1		
	VI-7 to VII-12 through t		1	
	IV-3 to V-4 through j	1		
	III-1 to IV-5 through f*		1	VII-12
Total		8	10	
C.O.V.		44.4%		

* Only one possibility at point f is given, it being the minimal number of crossovers or non-crossovers essential to the blocking of the gene from passing through the paternal line of VI-7 to VI-7 himself. Two other possibilities exist.

than from his father V-5. Had the father also carried it, a crossover would have to occur at that point in order to prevent VI-7 from being affected. Table 2-A shows that at least eight crossovers and ten non-crossovers are needed to produce the affected children with the genes being carried on the X chromo-

somes of I-1 and I-2. Eight crossovers and ten non-crossovers are also demanded in order that the requirements be fulfilled when the genes are on the Y chromosomes of the two brothers in the first generation (Table 2-B). Of course, crossovers may occur when the female is transmitting the gene, but the probability of passing the gene on is always ½.

The crossover values, therefore, range from a minimum of 44.4 per cent to a maximum of 56.3 per cent. Although Fisher has presented evidence of the possibility of a crossover value of more than 50 per cent, it would seem unwise to assume this value of 56.3 per cent as valid for this gene on the basis of one isolated pedigree. If all four possibilities are assumed to be equally probable in this kindred, namely that transmission was from I-1 only with the gene located: (1) on the X chromosome; (2) on the Y chromosome; that transmission was through both brothers with the genes: (3) on the X chromosome in both; (4) on the Y chromosome in both, then the sum of all the crossovers is 33 and of the non-crossovers is 35, with the average C.O.V. of 48.5%. With a gene located at this distance from the differential segment, it is impossible to distinguish between partial sex linkage and autosomal inheritance without an extremely large sample. It would seem unwise to invoke partial sex linkage as an explanation merely because one small segment of a pedigree suggests it, when the analysis of the entire pedigree places the site of the gene at a point indistinguishable in this sample from that of autosomal inheritance.

As Table 1 shows, the whole group of affected children are as readily interpreted as having received their duplicate genes from I-1 as from I-1 and I-2. There would still have been a sibship of three unaffected sons and four affected daughters, suggesting partial sex linkage. Combining the values in Parts A and B of Table 1, there are 17 crossovers and 15 non-crossovers essential for the production of this pedigree, giving a C.O.V. of 53.1%. This is quite different from the C.O.V. of 0 that the isolated sibship alone suggests. Snyder and Palmer state that "The peculiar sex distribution of the trait in the family of the propositus, however, coupled with the fact that the parents are related in precisely the manner that would be necessary to produce this particular sex distribution of an incompletely sex-linked gene, make it a reasonable inference that the gene is located on the homologous portions of the X and Y chromosomes". It must be pointed out that although finding all daughters affected and all sons normal in a family of four daughters and three sons is unusual, it could be expected to occur once in every 35 families of three boys and four girls, even were the gene on an autosome.

The next point is that with the large probability that these affected children all derived their mutant gene from I-1, the inference that it is sex linked is not as reasonable as that it is autosomal. With a C.O.V. of 53.1% and given a family of three boys and four girls, one would have expected this peculiar

distribution of the defect *less often* were the gene partially sex linked than if it were on an autosome.

Up to this point, I have dealt with the pedigree in its entirety, since if the gene is partially sex linked in one sibship it must of necessity be similarly linked in all parts. In sibship 1, however, we do not know how many crossovers, if any, were essential to have the gene present in VI-2, because we cannot be sure that VI-2 derived his gene from this line. We can only calculate the number of crossovers necessary to have the gene descend from I-1 to VI-1 assuming that the gene did so descend with no mutation between I-1 and VI-1 to account for the defect in VII-1 and 2. Similarly, in sibship 3, we cannot say whether VI-7 derived his mutant gene from his father or his mother, and so cannot calculate *exactly* the number of crossovers necessary to produce VII-12; we can only estimate two values equally probable. With respect to sibship 2, however, the only reasonable probability is that both the parents who are related, derived their mutant gene from I-1. For this sibship, therefore, which is the one which suggested partial sex-linkage, the crossover value can be directly calculated. Since sibships 1 and 3 are to be omitted from the discussion for reasons above stated, the number of crossovers necessary to produce sibship 2 must begin with I-1, the common ancestor of the two heterozygous parents VI-3 and VI-4. If the gene is on the X chromosome of I-1, there must be crossovers at d, h, e and i, and no crossovers at a, p, q, r, s, or four crossovers and five non-crossovers. If the gene is on the Y chromosome of I-1, there must be crossovers at a, d, h, e, i, and none at p, q, r, s; or a total of five crossovers and four non-crossovers. The average value for crossovers for the only sibship in which the minimal number essential can be calculated, is, therefore, 50 per cent, indistinguishable from random assortment of the genes determining the trait and sex.

Two more possibilities exist, although they are less probable than those already mentioned. It may be that the parents of I-1 and I-2 were related, and that each was a heterozygote, so that I-1 may have had the mutant gene on his X, and I-2 on his Y chromosome, or vice versa. If the first of these possibilities is correct, (and of courth Pathway II must be involved in such a situation), the total number of crossovers would be seven, and of non-crossovers eleven; with a C.O.V. of 38.8%. If the second possibility were true, there would be nine crossovers and an equal number of non-crossovers, making a C.O.V. of 50%. The average C.O.V. for both these possibilities would be 44.4%. These two possibilities were included merely to make the analysis of the four possible sites of the genes on the chromosomes complete, XX, YY, XY and YX. There is no need to invoke the latter two possibilities, since they go beyond the range of the pedigree; the other possibilities tabulated keep strictly within known limits.

SUMMARY

The pedigree of idiopathic convulsive disorder reported by Snyder and Palmer for which partial sex-linkage was suggested as the mode of inheritance is reviewed. It is possible to determine the minimal crossover percentages necessary to produce such a pedigree if partial sex-linkage is involved. The average C.O.V. is shown to be 48.5, with a minimum of 44.4 and a maximum of 56.3 per cent. One method of interpretation of the pedigree, namely, that all the affected derived their mutant gene from one man, which is equally as probable as the alternative interpretation that two brothers were involved, gives a C.O.V. of 53.1 per cent. The one sibship which suggested partial sex-linkage shows, on closer inspection, that the average minimal number of crossovers necessary to produce these affected children is equal to the average minimal number of non-crossovers necessary. It is suggested, therefore, until more evidence is forthcoming to substantiate the localization of this gene on the homologous segments of the sex chromosome, that it be considered as exhibiting autosomal recessive inheritance.

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