THE GENETIC EXTENT OF THE INSERTION INVOLVED IN THE FLECKED TRANSLOCATION IN THE MOUSE[1,2]

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Received August 22, 1966

THE flecked translocation, *T(X;I)Ct*, in the mouse was first described by CATTANACH (1961). He showed that the translocation involves an exchange between the X chromosome and chromosome I and that the wild-type alleles of *c* and *p* are translocated to the X chromosome. The flecked (*fd*) translocation is regarded as a 3-break nonreciprocal translocation in which a piece from the central region of chromosome I is inserted into the middle of the X chromosome (X^{fd}). This conclusion is based on cytological evidence presented by OHNO and CATTANACH (1962). The present paper is intended to support this conclusion by genetic evidence.

In the case of the *fd* translocation, the usual translocation mapping methods cannot be employed. Even though cytological evidence for chiasmata between the X^{fd} chromosome and an autosome I has been obtained at diakinesis and metaphase I of *fd* male mice (EICHER 1965), recombinational offspring have never been recovered (CATTANACH 1961; EICHER, unpublished data). It was therefore decided to test for the extent of the insertion by the use of a method employing the phenotypic expression of marker genes from autosome I in diploid and trisomic condition. The marker genes chosen (Figure 1) are the most extreme ones on the map of autosome I, frizzy (*fr*) and pudgy (*pu*), in order to confirm that the translocation is an insertion involving two breaks in autosome I. Furthermore, shaker-1 (*sh-1*) was used in order to determine more closely the position of one of the breakage points on chromosome I.

MATERIALS AND METHODS

Animals carrying *fd* can exist in two forms, Type I and Type II (Figure 2) (CATTANACH 1961). Type I animals have one undeleted autosome I, the other one carrying the deletion (I^{Df}); Type II mice carry two normal autosomes in addition to X^{fd}, and are therefore trisomic for the translocated piece of chromosome I. Type I mice when crossed to normal mice produce Type I, Type II, and normal offspring, while crosses of Type II animals to normals produce only Type II and normal progeny. Type II males are usually runts, but are fertile, while Type I males are normal in appearance but are usually sterile.

Type I and Type II females can be distinguished by their mosaic color patterns. Since the translocated piece contains the wild-type alleles at the *c* and *p* loci, females heterozygous for *fd* and carrying the recessive alleles *p* and/or c^{ch} on autosome(s) I are mosaic for *p* and/or c^{ch} and the wild phenotype, as expected under the Lyon hypothesis (LYON 1962, 1963) and the

[1] Submitted in partial fulfillment of requirements for the degree Doctor of Philosophy.

[2] This research was supported in part by a Public Health Service Training Grant, 5 T1 GM 658.

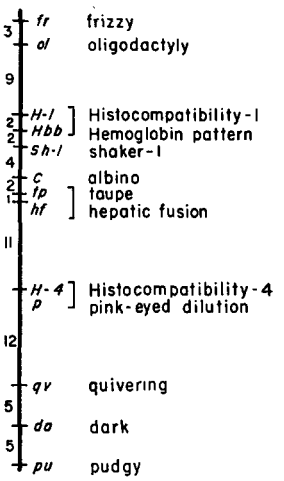

FIGURE 1.—Linkage map of chromosome I, after SIDMAN, GREEN, and APPEL (1966). The brackets indicate uncertainty as to actual gene order. The numbers are cM units.

single active X-chromosome hypothesis of L. B. RUSSELL, based on the observation of a possible directional inactivation (RUSSELL 1963, 1964). The heterozygous c^{ch}/c condition is phenotypically intermediate between c^{ch}/c^{ch} and c/c. The deletion in autosome I^{Df}, hereafter designated as Df when used in conjunction with known genes on chromosome I, has in combination with

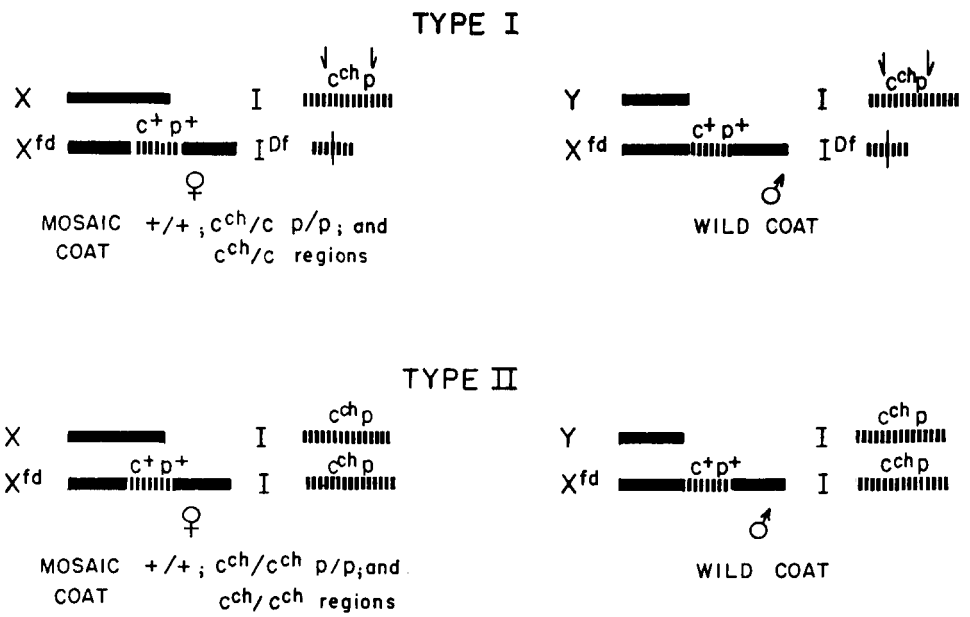

FIGURE 2.—Diagram of chromosomes X, Y and I in Type I and Type II animals. A solid line represents the X and Y chromosomes. A broken line represents chromosome I. The symbol I^{Df} is used to designate the autosome I deficient for the region translocated to the X-chromosome. The symbol X^{fd} represents the X chromosome which includes the piece from autosome I. The line through chromosome I^{Df} designates where the deletion occurred.

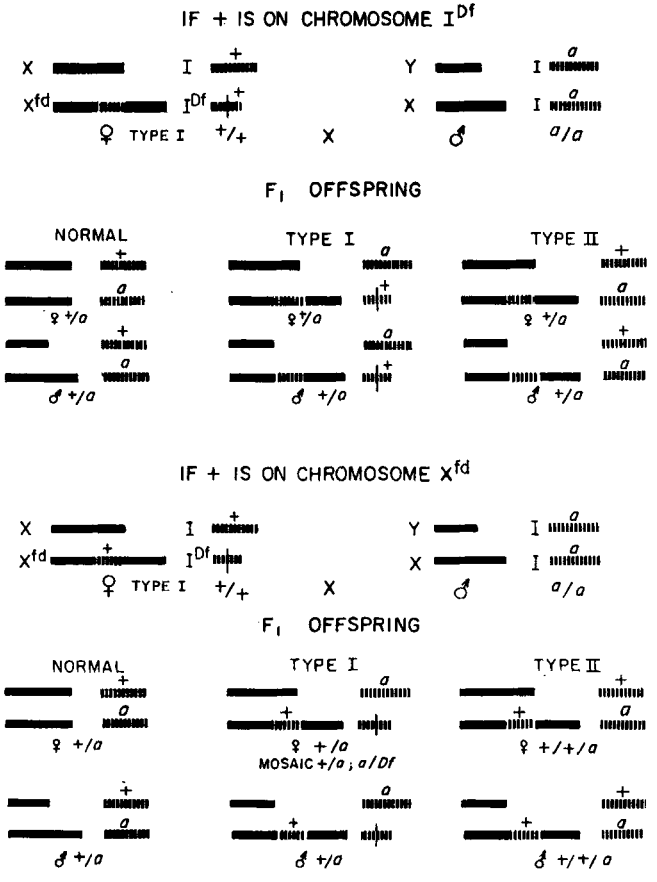

FIGURE 3.—Expected results of an outcross of a wild Type I female to a homozygous recessive male. Both the possibilities of the placement of + in chromosome I^{Df} or X^{fd} are considered. The solid line represents chromosomes X and Y. The broken line represents chromosome I.

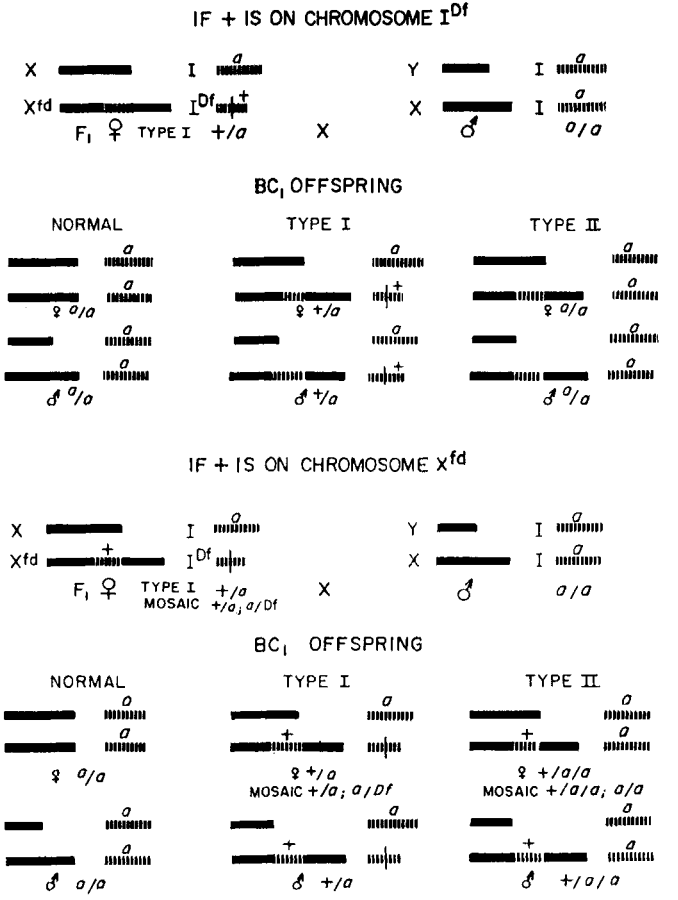

FIGURE 4.—Expected results of the BC_1 generation considering the possibility of the placement of + on chromosome I^{Df} or X^{fd} (crossovers are not considered). The solid line represents chromosomes X and Y. The broken line represents chromosome I.

c^{ch} the same phenotypic effect as *c*. The mutant spots of Type I (*fd*/+; c^{ch}/Df) females appear phenotypically like c^{ch}/c while in Type II (*fd*/+; c^{ch}/c^{ch}) females the mosaic spots appear c^{ch}/c^{ch}. All Type I and Type II males are wild type.

The argument used to decide whether a particular locus is included in the *fd* translocation is presented in Figures 3 and 4 using a hypothetical gene pair + and *a*. The original translocation appeared in the wild-type strain CBA, which contains the + alleles of all known loci in autosome I. The crosses in Figures 3 and 4 are designed to decide whether this + allele is located on the X^{fd} chromosome or on chromosome I^{Df}.

As seen in Figures 3 and 4, if the + allele is present on chromosome I^{Df}, simple autosomal behavior will be obtained, all F_1 animals being heterozygous for the locus. If the + allele is located on X^{fd}, its expression may be altered by its location on an X chromosome in females, as predicted by the Lyon hypothesis (LYON 1962) and the single active X-chromosome hypothesis (RUSSELL 1963), and by its trisomic condition in Type II males. More specifically, in the F_1 and BC_1 Type I female offspring a mosaic phenotype will be expected for any character if the expression of gene activity is sufficiently localized, while otherwise the character may show intermediate expression. If Type I females carrying + on the X^{fd} chromosome and its mutant allele on autosome I are crossed to homozygous mutant males, the Type II female offspring would also be expected to show mosaicism or intermediate expression as explained for the Type I females, while the Type II males would be trisomics. These Type II males should express the + character, at least to some degree, since no cases are known in which the phenotype of a triploid or trisomic containing one dominant allele equals that of the homozygous recessive. Complete loss of the locus tested which may be imagined to have occurred close to the site of the breaks, would result in recessive Type I offspring.

The proof for the location of + on chromosome I^{Df} rather than on the X^{fd} chromosome would be further strengthened if any BC_1 non-*fd* or BC_1 Type II animals were obtained which were wild type for *a* and BC_1 Type I animals which were *a*/*a*. These phenotypes could only occur by the exchange of + and *a* between chromosomes I^{Df} and I, respectively.

All three markers used (*fr*, *sh-1*, and *pu*) are easily recognizable: pudgy can be identified at birth by an extreme shortening of the tail and of the hindquarters; frizzy can be distinguished on the second day after birth by short, curly whiskers and later by the rough appearance of the coat; shaker-1 is recognizable at about 14 days of age by definite abnormal head movements, the development of a waltzing gait before weaning which is extreme when the animal is handled, and deafness which can be demonstrated by 6 weeks (at sexual maturity).

Only coat color was used to distinguish *fd* from non-*fd* mice in crosses with the c^{ch} gene. In crosses with the *p* allele, the separation of *fd* from non-*fd* mice could be accomplished at birth by the fact that all *fd* mice have wild-type eye color and all non-*fd* mice (*p*/*p*) have pink eyes. All loci investigated were used in combination with c^{ch} *p* or c^{ch} so that the above methods of distinguishing Type I, Type II and non-*fd* mice from each other could be employed. All Type I and Type II males were wild type regardless of the condition of the *c* or *p* genes.

In general, Type I and Type II females were mated to males of the stocks carrying the mutant genes in question. The F_1 Type I females and F_1 Type II males and females were backcrossed to mutant stock animals and their offspring analyzed for the expression of the mutants under investigation. The crosses involving the Type II females would add information as to the phenotype of Type II males with various genotypes which otherwise might be difficult to obtain using crosses involving Type I females. Since *pu* was considered in crosses separate from *sh-1* and *fr* and was kept in a heterozygous condition within the mutant stock, the specific methods for the mutants are given with the results.

The Type I *fd* stock was obtained through the courtesy of DR. MARY F. LYON, Harwell, England, and the Type II *fd* stock was kindly supplied by DR. MARGARET C. GREEN, The Jackson Laboratory. Both stocks carried c^{ch} on autosomes I. A strain homozygous for *fr sh-1* c^{ch} *p* was obtained from MRS. ELIZABETH WOODWORTH, The Jackson Laboratory. The *pu* stock, obtained from DR. MARGARET C. GREEN, was homozygous for c^{ch} and *p*, but *pu* was kept in heterozygous condition because of the low viability and fertility of *pu*/*pu* animals. I wish to

thank each of these workers for supplying the stocks of mice which have made this research possible.

A stock homozygous for c^{ch} and *p* was developed from a BC_1 male ((J/129 × BALB/Ci) × BALB/Ci) supplied by DR. PETER HULL which had been mated to a BALB/Ci female. The offspring from this cross were mated to each other to recover homozygous animals for c^{ch} and *p*. Many of the Type I and Type II stock animals had been mated to this homozygous c^{ch} *p* stock before the mapping experiment was initiated.

EXPERIMENTAL RESULTS

The analysis of frizzy and shaker-1: Two female Type II mice (c^{ch} *p*/c^{ch} *p* and c^{ch}/c^{ch}) were outcrossed to homozygous mutant males *fr sh-1* c^{ch} *p*. All F_1 females and some of the F_1 *fd* males were backcrossed to the homozygous mutant strain. The offspring from these crosses are recorded in Tables 1 and 2. The data show that the fr^+ allele has not been translocated to the X^{fd} chromosome: there was no phenotypic difference in the expression of the frizzy condition in the *fd* and non-*fd* mice. In Table 1, the segregation of *fr* in *fd* animals (females) was approximately normal, 16 out of 41 animals, as against 20 out of 47 in the non-*fd* controls (males) ($\chi^2 = 0.112$, 1 df. $p>0.7$).

The results for shaker-1, as represented in Table 1, also appear normal; but there is actually a difference between the non-*fd* males and *fd* females with respect to this character. All 20 *sh-1* males showed complete expression of the character at 3 to 4 weeks. The 12 *fd* females classified as *sh-1* expressed in reality an intermediate phenotype showing some slight head movements weaker than those of known shaker-1 animals. Most of these "intermediate" *fd* females became deaf after their shaker-1 non-*fd* sibs had developed deafness (in some cases up to 4 weeks later). The lack of the fully expressed shaker-1 condition in *fd*

TABLE 1

Backcross 1 segregation data for* fd *and autosomes I genes* fr, sh-1 *and* p

Cross: ♀ *fr sh-1* c^{ch} *p*/*fr sh-1* c^{ch} *p* × †♂ *fd*/Y;*fr sh-1* c^{ch} *p*/+ + c^{ch} +

	Males (all non *fd*)	Females (all *fd*)	Total
+ + +	16	14	30
fr sh-1 p	15	7‡	22
+ + *p*	7	9	16
fr sh-1 +	1	3‡	4
fr + +	4	1	5
+ *sh-1 p*	4	1‡	5
+ *sh-1* +	0	1‡	1
fr + *p*	0	5	5
Total	47	41	88

* Only animals which survived long enough to classify for the shaker-1 phenotype are included.

† Some males were carrying *c* instead of c^{ch} on the non-*fr* chromosome. Only recombination between *fr*, *sh-1* and *p* are considered.

‡ These females did *not* display the shaker-1 phenotype but they did display some abnormal head movements and/or become deaf. They are referred to as "intermediate."

TABLE 2

Backcross 1 segregation data for* fd *and autosome I genes* fr *and* sh-1

Cross: ♀ *fd/+; fr sh-1 c^{ch} p/+ + c^{ch} p* × ♂ *fr sh-1 ch^{ch} p/fr sh-1 c^{ch} p*

	Males		Females		
	X^{fd}	X	X^{fd}	X	Total
+ +	1†	4	6	4	15
fr sh-1	0	6	2‡	0	8
fr +	0	0	0	3	3
+ *sh-1*	0	2	0	1	3
Total	1	12	8	8	29

* Only animals which survived long enough to classify for the shaker-1 phenotype are included.
† Male was *fd fr*+ but the condition of *sh-1* is unknown.
‡ These females did *not* display the shaker-1 phenotype but they did display some abnormal head movements. They are referred to as "intermediate."

females cannot be the result of selective mortality of *fd/+; sh-1/sh-1* animals, since this would result in a disturbed sex ratio in the cross which is not the case. It must therefore be concluded that the wild-type allele for *sh-1* is included in the translocation, and that trisomic females (*+/sh-1/sh-1*) show an intermediate phenotype. Only one *fd* male (Type II) questionable as to shaker-1 lived to maturity (Table 2); he showed no abnormal head movements.

The original Type II *fd* stock was segregating for Snell's waltzer (*sv*) in linkage group II. Therefore, in no case in the crosses just described were any F_2 crosses made as *sv*, in homozygous condition, might have been accidentally classified as shaker-1, or might have masked the shaker-1 phenotype. None of the 39 F_1 animals showed any abnormal head movements or became deaf. GRÜNEBERG (1956) reported that when the gene waltzer (*v*), linkage group X, was present in heterozygous condition with a heterozygous condition for shaker-1 (*+/v; +/sh-1*), the animals became deaf after several months. Since deafness and abnormal behavior characteristic of shaker-1 animals were encountered only in the BC_1 and BC_2 generations and approximately 50% of the non-*fd* animals were distinctly shaker-1 in phenotype by 3 to 4 weeks, either heterozygous *sv* and *sh-1* do not interact during the time the animals were studied, or the *sv* allele was not present in the two females which were used to produce the F_1 generation.

It is also clear that the frequency of recombination between *sh-1* and *p* and between *fr* and *sh-1* is not in agreement with the linkage map (Figure 1) if the *fd* offspring (Table 1) are considered. The published distances between *sh-1* and *p* and between *fr* and *sh-1* are 18 and 16 map units respectively (SIDMAN, GREEN and APPEL 1966). The *fd* females show a recombination frequency of 43.9% between *sh-1* and *p* and 18.18% between *fr* and *sh-1*. The male offspring (all non-*fd*) show a recombination between *sh-1* and *p* of 17.02% and for *fr* and *sh-1* as 17.02%. Thus, if only the non-*fd* offspring (males) are considered, the frequency of recombination between the genes on autosomes I is in good agree-

ment with the published frequency of recombination. This discrepancy for the *fd* mice (females) is obviously due to misclassification of the shaker-1 condition in shaker-1 *fd* females. If the recombinational frequency for *fr* and *p* is considered, the males give a value of 34.04% and the females a value of 34.14%.

Unfortunately, imperforate vagina among *fd* females, which was also noted by CATTANACH and ISAACSON (1965) upon inbreeding Type II *fd* animals, and low viability after birth of Type II males was encountered in the BC_1 generation. This inhibited the study of the shaker-1 condition in Type II males (Table 2) and prevented the backcross of many intermediate Type II females to known shaker-1 males to test for homozygosity at the *sh*-1 locus on autosomes I. Thirteen intermediate BC_1 Type II females which were backcrossed to shaker-1 stock males produced 44 offspring. Of these 44 offspring, 37 were non-*fd* and all of these were shaker-1. This does not prove that *all* the Type II females classified as "intermediate" were actually *+/sh-1/sh-1* but it does prove that not all of them could have been *+/+/sh-1*. One Type II female which displayed deafness and abnormal head movements produced a number of non-*fd* offspring sufficient to permit independent analysis for the shaker-1 condition on autosomes I. In total, ten non-*fd* mice were born (6 males and 4 females) which survived for determination of the shaker-1 phenotype. All were shaker-1. The decrease in ratio of *fd* to non-*fd* animals in crosses involving inbreeding was also noted by CATTANACH and ISAACSON (1965).

Type I females (c^{ch}/Df) were outcrossed to male BALB/Ci (*b/b*; *c/c*) and the *fd* females born which showed albino patches of coat color (Type I) were crossed to homozygous *fr sh-1* c^{ch} *p* males. Those *fd* female offspring of this cross (designated as F_1) which expressed the pink-eye dilution gene in mosaic patches were known Type I females. After 17 weeks, two of the ten Type I F_1 females carrying *sh-1* on autosome I had become deaf. The original Type I stock used was not segregating for *sv*. Thus, a haploid condition of shaker-1 produced in some cells by the inactivation of the wild-type allele in the X^{fd} chromosome seems, in time, to also permit deafness to ensue. No abnormal head movements have ever been observed in either the preceding 10 F_1 Type I females or in a total of 15 F_1 *fd* male sibs which were not runts (most likely Type I). After several months, none of these 15 F_1 *fd* males have become deaf.

The abnormal behavior of BC_1 Type II *fd/+*; *sh-1/sh-1* females may be due to functional trisomy in some cells and disomy in others (Table 1). The two cell populations, organ of Corti and saccular macula, which are affected by the shaker-1 allele (DEOL 1956) seem to be differentially affected by dosage and/or by X-chromosome inactivation. This would account for some Type II females (*+/sh-1/sh-1*) being deaf and showing weak abnormal head movements, some Type I females (*+/sh-1*/Df) developing deafness without adnormal head behavior, and Type I males (*+/sh-1*/Df) appearing completely normal. The situation with Type II males cannot be determined at this time. Because the genetic background was not identical for Type I and Type II animals; its influence is unknown at the present time.

The results with frizzy and shaker-1 show that the breakage point is between

sh-1 and *fr* (Figure 1). This allows an extension of the known amount of autosome I material transferred to the X chromosome from 14 map units (distance from *c* to *p*) to 18 map units (distance from *sh-1* to *p*).

The work of WOLFE (1967) has confirmed that frizzy is outside the translocated region by showing that the *Hbb* locus is also outside this region. In combination, the data show that the breakage point is located between *Hbb* and *sh-1* which are 2 map units apart on the linkage map.

Preliminary evidence for crossing over between fr^+ in chromosome I^{Df} and *fr* in chromosome I was noted in crosses of Type I *fd*/+; *fr sh-1* c^{ch} *p*/Df females mated to homozygous *fr sh-1* c^{ch} *p* males. Non-*fd* offspring which are fr^+ have been recovered. Counts of bone marrow cells showed 40 chromosomes present. Thus, the use of the gene frizzy allows for the phenotypic distinction between males carrying the translocation in the Type I and Type II condition. Type I females carrying *fr* on autosome I and fr^+ on autosome I^{Df} mated to *fr*/*fr* males, barring any crossing over between chromosomes I^{Df} and I, would produce all Type I males which appear non-frizzy and all Type II males which appear frizzy. No other phenotypic difference other than possibly body size, which is not always reliable, or testis size, has previously permitted the separation of Type I and Type II males.

Analysis of pudgy: The analysis of pudgy differs from that used for shaker-1 and frizzy because of the early death of many *pu*/*pu* animals. Type I and Type II females, c^{ch} *p* pu^+ for autosome(s) I, were outcrossed to males c^{ch} *p pu*/c^{ch} *p* + of the mutant stock. The F_1 Type I and Type II females were then backcrossed to c^{ch} *p pu*/c^{ch} *p* + males of the same mutant stock. All BC_1 Type II females known to be *p*/*p* and BC_1 Type I females known to be *p*/Df were backcrossed to the pudgy stock to produce the segregation data for pudgy and *fd* (BC_2 generation). In some cases Type II females of the BC_2 generation were again backcrossed to the pudgy stock. Only females which proved to carry *pu* on autosome I, i.e., which produced at least one *pu*/*pu* offspring, were considered.

The results of the BC_2 and BC_3 generations involving the Type II crosses and BC_1 and BC_2 generations involving the Type I crosses are given in Tables 3 and 4. The data clearly show that the pu^+ allele is located on autosome I^{Df} since typical pudgy Type II males and females were observed which would not be expected if pu^+ were located in the X^{fd} chromosome.

TABLE 3

Backcross 2 and 3 segregation data for fd *and* pu

Cross: ♀ *fd*/+; c^{ch} *p pu*/c^{ch} *p* + × ♂ c^{ch} *p pu*/c^{ch} *p* +

	X^{fd} pu^+	X^{fd} *pu*	X pu^+	X *pu*	Total
Males	14	4	24	10	52
Females	28	5	24	7	64
Total	42	9	48	17	116

Expected pudgy: 25.0%.
Observed pudgy: 22.5%.

TABLE 4

Backcross 1 and 2 segregation data for fd *and* pu

Cross: ♀ *fd*/+; c^{ch} *p pu*/Df × ♂ c^{ch} *p pu*/c^{ch} *p* +

	X^{fd} *pu*+	X^{fd} *pu*	X *pu*+	X *pu*	Total
Males	24	6	9	7	46
Females	27 {8=I* 1=II*	9 {1=I* 2=II*	13	8	57
Total	51	15	22	15	103

Expected pudgy: 33.33%.
Observed pudgy: 29.12%.
* Only 12 females lived long enough to be classified as to Type I versus Type II by the color of the mosaic patches on their coats. These 12 females are further subdivided as to Type I versus Type II.

A single Type I pudgy female was produced (her mosaic coat color showing c^{ch} *p*/*c p* regions) (Table 4) which would not be expected since the *pu*+ allele is carried by chromosome I^{Df}. No offspring were obtained from this female. This Type I pudgy female, therefore, is assumed to be the result of crossing over between the *pu*+ allele on autosome I^{Df} and the breakage point on autosome I. Of the nine *fd* females produced (Table 4) which did not display the pudgy phenotype, eight were Type I females. This is evidence that *pu*+ was not deleted from autosome I^{Df}. Further evidence has been obtained as to the position of *pu*+ in crosses of females Type I *fd*/+; c^{ch} *p*+ *pu*/Df to males which were homozygous c^{ch} *p pu*. To date, several non-*fd pu*+ offspring have been recovered. Although chromosome counts have not been made, it is assumed that these mice are the result of crossing over between *pu*+ on chromosome I^{Df} and *pu* on chromosome I.

The lower proportion of expected to actually recovered pudgy mice in crosses of Type I and Type II females to heterozygous pudgy males is in agreement with the reduced frequency of pudgy mice obtained by GRÜNEBERG (1961).

It must be concluded from the above data that one of the two breaks in autosome I must lie between *p* and *pu* (Figure 1).

Deepest appreciation is expressed to PROFESSOR ERNST W. CASPARI for providing many valuable suggestions concerning the writing of this manuscript. I am indebted to DR. MARGARET C. GREEN for her criticism of the techniques used in this paper and the suggestion of testing the questionable shaker-1 *fd* mice for deafness. Criticism and help in the preparation of the manuscript was also kindly provided by DR. ALLEN B. GRIFFEN. Appreciation is expressed to MISS SUE BETLEM for technical assistance.

SUMMARY

By the expression of various recessive alleles located in autosome I in relation to Type I and Type II animals, the *fd* translocation in the house mouse has been shown to involve an insertion from the middle region of chromosome I into the X chromosome. The genes *fr* and *pu* have been mapped outside the region of insertion whereas *sh-1* is located inside this region.—Type I males carrying *sh-1*+ in the X^{fd} chromosome and *sh-1* in autosome I do not show any effect of shaker-1,

while some of the Type I females become deaf. Type II females carrying *sh-1*$^+$ on the X^{1d} chromosome and *sh-1* on both of their autosomes I, show a low intensity of shaking behavior and most of them become deaf. The condition with Type II males is unknown because of their low viability in the backcross generations.

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