The Journal of Heredity 72:107–112. 1981.

Inheritance of alternative states of the fused gene in mice

ABSTRACT: The genetics of the fused (Fu) *gene in the house mouse,* Mus musculus, *was studied by use of the closely linked recessive marker, tufted* (tf). *Evidence was obtained indicating that* Fu *passes from a phenotypically active state to inactive:* Fu ⇄ [Fu]. *These alternative states may be genetically transmitted. It is suggested that the activation of a "dormant"* Fu *gene may underlie this passage.*

D. K. Belyaev

A. O. Ruvinsky

P. M. Borodin

EVIDENCE has accumulated during the last decades permitting us to consider ontogeny as a process resulting in the differential activity of various genes during individual development. The alternating gene states are stably inherited by successive cell generations. It cannot be excluded that essentially similar processes may also occur during sexual reproduction.

We have shown that this is plausible, in principle, with respect to the star (*S*) gene in silver-black foxes[3]. The *S* gene determines a specific piebald pattern on the head and body. The experimental data on the behavior of this gene was explained by its capacity to pass from an active state to an inactive one and vice versa with a high frequency. Intense artificial selection was presumed to be the main factor promoting the emergence of this capacity at the locus in question[1].

A similar phenomenon has been observed at the fused locus in the house mouse. The fused (*Fu*) gene is located in the precentromeric region of chromosome 17 (linkage group IX). The tail is shorter than normal and is fused in *Fu*/ + mice (Figure 1A). Extreme degrees of tail abnormalities are observed in *Fu*/*Fu* homozygotes, which also show decreased viability[6,13]. The tufted (*tf*) gene, which determines specific baldness in mice, is at a distance of 1 map unit from the *Fu* gene[8]. This makes it an advantageous marker of any homologue of chromosome 17. Being 100 percent penetrant, it does not express itself in a heterozygous condition.

This paper presents the results of genetic analysis of the inheritance features of the *Fu* gene in the house mouse.

Materials and Methods

Fu and *tf* diheterozygous mice were obtained from *Fu*/+ (129/Rr Dg × C3H/He)F_1 × *tf*/*tf* (C57BL/6) crosses; individuals of both sexes with fused, non-tufted phenotype and, hence, with the *Fu*+/+*tf* genotype were chosen from the F_1. These individuals were further involved in three types of crosses:

1. ♀♀ *Fu*+/+*tf* × ♂♂ +*tf*/+*tf*
2. ♀♀ +*tf*/+*tf* × ♂♂ *Fu*+/+*tf*
3. ♀♀ *Fu*+/+*tf* × ♂♂ *Fu*+/+*tf*

It was expected that crosses 1 and 2 would yield progenies with either fused, non-tufted (*Fu*+/+*tf*) or non-fused, tufted (+*tf*/+*tf*) phenotype. According to expectations, there would be only 1 percent recombination with either *Fu*, *tf* (*Fu tf*/+*tf*) or non-*Fu*, non-*tf* (++/+*tf*) phenotypes. Because of the slightly reduced penetrance of the *Fu* gene[13], there would be an additional number of phenotypically normal animals. From cross 3, besides these classes, *Fu*+/*Fu*+ individuals segregated and classes of recombinants, phenotypically indistinguishable from noncrossovers, would appear. The arisal frequency of these recombinants would not exceed 1 percent.

Results

The results of ♀♀ *Fu*+/+*tf* × ♂♂ +*tf*/+*tf*

Dr. Belyaev is director, and Drs. Ruvinsky and Borodin are scientific workers, Institute of Cytology and Genetics of the Siberian Department of the Academy of Sciences U.S.S.R., Novosibirsk-90, U.S.S.R.

crosses are presented in Table I, where the proportion of phenotypes observed is given in the line "Phenotypic identification." It is of interest that there was an unexpectedly large number of mice with normal phenotype. Each phenotypically normal mouse was crossed to a *+tf/+tf* tester. When testcrossed, 22 of 30 mice with normal phenotype produced progenies among which some were phenotypically fused. Based on the testcross data on the remaining eight mice, it was concluded that the *Fu* gene is not phenotypically manifest in this or in subsequent generations (Figure 1*B*). Judging by the crossover frequency between *Fu* and *tf*, it appeared very unlikely that eight mice would bear ++ crossover chromosomes. This suggested that the *Fu* gene may be in a blocked, functionally inactive state in some of these mice.

We earlier assigned the symbol [*S*] to the blocked state of the star gene in silver-black foxes[2]; analogously, we propose the symbol [*Fu*] to denote the functionally inactive state of the *Fu* gene in the house mouse.

The results of the cross ♀♀ *+tf/+tf* × ♂♂ *Fu+/+tf* are summarized in Table II. The F_1 segregation pattern from this cross was the same as that from cross 1, but the number of individuals with normal phenotype was smaller. Of these, only male no. 3 did not produce phenotypically fused young.

As shown in Table III, ♀♀ *Fu+/+tf* × ♂♂ *Fu+/+tf* crosses also yielded a large number of individuals with normal phenotype; of the 24 testcrossed mice, 6 did not produce phenotypically fused progenies.

As already indicated, phenotypically normal individuals might have arisen in the crosses either as a result of recombination of nonmanifestation of the *Fu* gene.

Of the total number of mice born, merely 0.5 percent phenotypically normal young could be due to a recombination event. These normal individuals, certainly, did not produce any fused progenies.

If the *Fu* gene failed to manifest itself during individual development, the frequency of phenotypically normal mice would be much higher in the segregated progeny, being related to the penetrance of *Fu*. Accordingly, testcrosses would give some mice with the fused phenotype. In fact, such animals—normal in phenotype—were obtained in all three crosses (Tables I, II, and III). However, there were 15 mice with normal phenotype that did not produce fused progenies. One cannot explain their appearance by recombination inasmuch as their frequencies were significantly higher than expected, nor by reduced penetrance since *Fu* was not manifest in the progenies from the testcrosses.

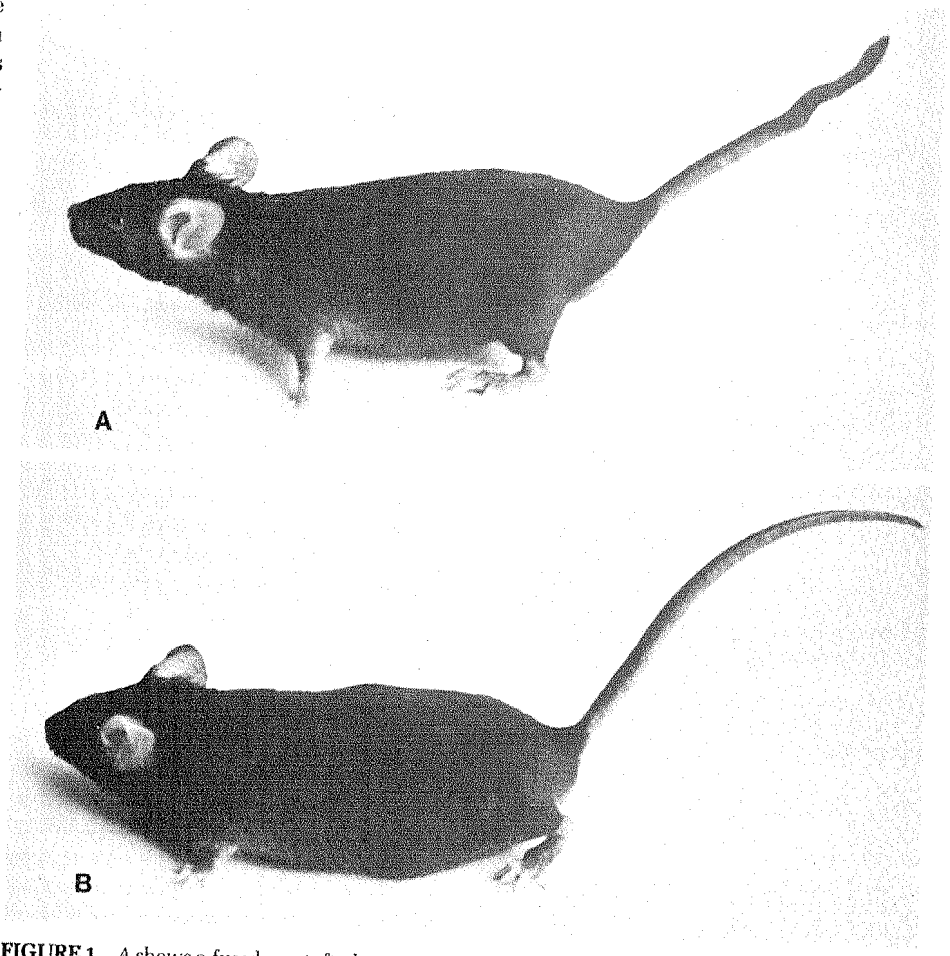


FIGURE 1 *A* shows a fused, nontufted mouse with genotype *Fu+/+tf*. *B* — a non-fused, non-tufted phenotype, with [*Fu*]*+/+tf* genotype.

The data on testcrosses involving phenotypically normal males and those involving phenotypically normal females are shown in Tables IV and V, respectively. Six males were testcrossed to *+tf/+tf* females, their F_2 progenies were composed of 211 non-fused and 3 fused individuals (Table IV). Of these phenotypically fused mice, one female was testcrossed. Her progeny consisted of 20 non-fused and 2 fused young.

Table I. Results of ♀♀ *Fu+/+tf* × ♂♂ *+tf/+tf* crosses in mice

	No. crosses	No. progenies	Phenotypes of progeny: *Fu*, non-*tf*	non-*Fu*, *tf*	*Fu*, *tf*	non-*Fu*, non-*tf*	*Fu* nonmanifestation %
Phenotypic identification (observed progeny phenotypes)	29	216	85	99	2	30	26
Genotypic identification (based on testcross data)			Genotypes of progeny: *Fu+/+tf*	*+tf/+tf*	*Fu tf/+tf*	*++/+tf* and(or) [*Fu*]*+/+tf*	*Fu* inactivation %
	29	216	85 + 22*	99	2	8†	7–0.5

* 22 non-*Fu*, non-*tf* mice were identified as *Fu+/+tf* on the basis of testcross data
† ♂ 16, ♂ 17, ♀ 11, ♀ 16, ♀ 28, ♀ 33, ♀ 36, ♀ 44

FIGURE 2 A mouse obtained from the cross ♀♀ [Fu]+/+*tf* × ♂♂ Fu *tf*/+*tf*, with the presumptive genotype, Fu *tf*/Fu+.

The ratio of phenotypically normal to tufted in 1½–2-month-old F_2 mice was 50 non-tufted:50 tufted. This excluded differential viability of gametes, zygotes, embryos, and newborns as possible causes of the absence of fused animals in F_2 (Table IV). The F_3 obtained from F_2 × +*tf*/+*tf* crosses was composed of 201 non-fused mice and 1 fused mouse; when testcrossed, this fused mouse gave birth to three normal young. F_2 × F_2 crosses were expected to yield not only heterozygotes, but also homozygotes; contrary to expectations, 170 normal mice were obtained from these crosses. Thus, among a total of 675 F_2, F_3, and F_4 mice, only 4, i.e., less than 1 percent, were phenotypically fused.

The testcross data on non-fused females are presented in Table V. These data agree with those obtained for non-fused males. There were only 4 fused mice among 607 F_2, F_3, and F_4 animals. The almost complete depletion of fused individuals in this case, again could not be attributed to differential viability, because the segregation ratio was 38 non-tufted:49 tufted, insignificantly deviating from the 1:1 expected. Of four mice exhibiting the fused character, two were testcrossed; one was a fused male (*Fu*+/+*tf*) that produced 1 fused and 17 normal young; and one was a fused female *Fu*+/+*tf* that gave birth to 1 fused and 10 normal mice.

In all, there were 15 straight-tailed (normal) mice. They made up 6 percent of the total number of non-fused mice, which do not as a rule produce fused animals. The occurrence frequency of such mice significantly exceeded (F_φ = 25.1, $P > 0.99$) that of recombinants. Theoretically, the number of +*tf*/++ recombinants among non-fused, non-tufted mice should not surpass 2–3 and the rest should have the *Fu*+/+*tf* genotype. However, the *Fu* gene was not manifest in these mice and their progenies, except 1 percent of the total number of mice. The question may be raised whether the non-manifestation of the *Fu* gene in 15 pedigree groups of mice is possibly due to the effect of a set of modifier genes suppressing the manifestation of *Fu*. The results obtained provide a negative answer.

In Table VI are shown the data pertaining to crosses between [Fu]+/+*tf* and mice of strains SWR, CBA, C3H, and A. All 239 young from these crosses were straight-tailed. The data show that the *Fu* gene is stably suppressed in mice with four very different genetic backgrounds. This strongly suggests that the gene *Fu* has become heritably blocked in these animals. The passage from active to inactive state will be designated as *Fu* → [*Fu*].

It is noteworthy that a parent carrying an inactivated [*Fu*] gene produces phenotypically fused young with a frequency of 1 percent (Tables IV and V). This demonstrates that the reverse [*Fu*] → *Fu* is a real event.

An experimental situation increasing the frequency of the [*Fu*] → *Fu* transition was produced. Among offspring from ♀♀ [Fu]+/+*tf* × ♂♂ *Fu tf*/+*tf* crosses (Table VII) there were three mice phenotypically similar to homozygotes for fused and non-tufted (Figure 3). The genotype of these mice was, quite probably, *Fu tf*/*Fu*+. When crossed to ♂ +*tf*/+*tf* one of these three mice gave birth to 5 litters; of 19 young born, 13 had the fused phenotype and 6 were normal.

In progenies from crosses between mice carrying an active *Fu* and an inactive [*Fu*], [*Fu*] → *Fu* transition frequency seems to be increased. This transition may be dependent on the genotype, judging by the fact that homozygotes appeared in the two pedigree groups derived from male no. 16 and female no. 37.

Table VIII convincingly shows that the *Fu* alleles, one active and one inactive, are compatible within the same genome. In fact, offspring from *Fu tf*/[*Fu*]+ × +*tf*/+*tf* crosses have either fused, tufted or non-fused, non-tufted phenotypes. This is another case where an inactivated gene state is inherited as a discrete Mendelian unit.

In Reed's experiments[13], all the F_1 hybrids from crosses between *Fu*/*Fu* mice and *Mus bactrianus* were normal. F_1 backcrosses to a *Mus musculus* laboratory

Table II. Results of ♀♀ +*tf*/+*tf* × ♂♂ *Fu tf*/+*tf* crosses in mice

	No. crosses	No. progenies	Phenotypes of progeny				Fu nonmanifestation %
			Fu, non-*tf*	non-*Fu*, *tf*	*Fu*, *tf*	non-*Fu*, non-*tf*	
Phenotypic identification	11	50	23	24	—	3	11
			Genotypes of progeny				
Genotypic identification			*Fu*+/+*tf*	+*tf*/+*tf*	*Fu tf*/+*tf*	++/+*tf* and(or) [Fu]+/+*tf*	Fu inactivation %
	11	50	23 + 2*	24	—	1†	4–0.5

* 2 non *Fu*, non *tf* mice were identified as Fu+/+*tf* on the basis of testcross data
† ♂ 3

Table III. Results of ♀♀ *Fu*+/+*tf* × ♂♂ *Fu*+/+*tf* crosses in mice

	No. crosses	No. progenies	Phenotypes of progeny				Fu nonmanifestation %
			Fu, non-*tf*	non-*Fu*,*tf*	*Fu*,*tf*	non-*Fu*, non-*tf*	
Phenotypic identification	25	155	79	52	—	24	23
			Genotypes of progeny				
Genotypic identification			Fu+/+*tf*; Fu+/Fu+	+*tf*/+*tf*	*Fu tf*/+*tf*	++/+*tf* and(or) [Fu]+/+*tf*	Fu inactivation %
	25	155	79 + 18*	52	—	6†	10–1

* 18 non-*Fu*, non-*tf* mice were identified as Fu+/+tf on the basis of testcross data
† ♂ 19, ♂ 22, ♂ 23, ♀ 29, ♀ 30, ♀ 37

stock also produced exclusively straight-tailed young. In silver-black foxes, the *S* gene behaves similarly, its penetrance being significantly higher in domesticated foxes than in wild ones[3]. In this vein are the results of crosses between homozygotes for the *Fu* gene and normal individuals; in the upper line of Table IX are listed the breeding data on C3H mice. Having been subjected to selection for hundreds of generations, this laboratory stock is tame. The *Fu* allele does not express itself in only 9 percent of heterozygous offspring in hybrid mice, but in the lower line of this table are listed the breeding data on crosses between *Fu* homozygotes and wild-caught mice in the environs of Novosibirsk, and here *Fu* is not manifest in 63 percent of wild F_1 heterozygotes. The young from crosses between phenotypically normal mice, which were proven heterozygotes (*Fu*/+), segregated in a ratio of 8 *Fu*: 16 normal, instead of the 18 *Fu*: 6 normal expected. It may be inferred that the nonmanifestation frequency of the *Fu* allele rises from 9 to 63 percent and, possibly, also its inactivation frequency in F_1 hybrids between wild mice and *Fu*/*Fu* homozygotes.

Discussion

The fused (*Fu*) appears to pass spontaneously from an active to an inactive state and revert toward the initial one. The frequency of the *Fu* → [*Fu*] transition is about 6 percent. It may vary depending on the direction of the cross. The reverse [*Fu*] → *Fu* occurs with a frequency of about 1 percent. Having entered one of the alternative states, the *Fu* gene is heritably transmitted to genotypically different progenies in this state, indicating that this state behaves as a distinct entity.

This transition and some of its parameters are schematically represented in Figure 3. In surveying this scheme, the question is raised as to what mechanisms underlie transition. The extremely frequent transition of the *Fu* gene from one state to another makes it difficult to explain in terms of the classical mutation theory. It is also difficult to attribute this manifestation-nonmanifestation of the *Fu* gene to the influence of a set of modifier genes. The whole body of evidence obtained refutes this possibility. The results of genetic analysis of animals having the *Fu* gene, active or inactive, in homologous chromosomes indicate that either state is independently inherited (Table VIII). The reasonable inference is that the state of the *Fu* gene is related to intrinsic properties of the chromosome bearing it, but not to the genotypic environment, although this does not rule out the effect of the latter on its transition probability from one state to another. There are even grounds for assuming that the inactivation frequency of the *Fu* gene is higher in wild mice (Table IX). However, judging by our data, the active-inactive state of the *Fu* gene is almost consistently heritable although conclusions as to the mechanisms of this alternating transition are premature.

Loci showing high frequencies of mutation-like events have been described in the literature[11]. Mechanisms of rather diverse kinds have been invoked when dealing with abnormal behavior of loci. These include insertions, transposons, and migrating genetic segments capable of modifying the

Table IV. Genetic analysis of non-fused, non-tufted males, obtained from *Fu*+/+*tf* × +*tf*/+*tf* and *Fu*+/+*tf* × *Fu*+/+*tf* crosses

NN	F_1 × + *tf*/+*tf** Normal: *Fu*	Normal: *tf*	F_2 × +*tf*/+*tf** Normal: *Fu*	$F_2 \times F_2$* Normal: *Fu*	F_3 × +*tf*/+*tf** Normal: *Fu*	$F_3 \times F_3$* Normal: *Fu*	Total Normal: *Fu*
♂ 3	39:1	9:13	29:0	17:0	—	32:0	117:1
♂ 16	39:1	7: 8	25:0	56:0	—	—	120:1
♂ 17	47:1	6: 7	37:0	29:0	—	3:0	116:1
♂ 19	49:0	11:11	43:0	38:0	—	7:0	137:0
♂ 22	36:0	7: 8	30:1	23:0	7:0	—	96:1
♂ 23	41:0	7: 3	37:0	7:0	—	—	85:0
Total	251:3	50:50	201:1	170:0	7:0	42:0	671:4

* Mice from F_1 F_2, F_3 had [*Fu*]+/+*tf* and/or ++/+*tf* genotypes

Table V. Genetic analysis of non-fused, non-tufted females, obtained from *Fu*+/+*tf* × +*tf*/+*tf* and *Fu*+/+*tf* × *Fu*+/+*tf* crosses

NN	F_1 × +*tf*/+*tf** Normal: *Fu*	Normal: *tf*	F_2 × +*tf*/+*tf** Normal: *Fu*	$F_2 \times F_2$* Normal: *Fu*	F_3 × +*tf*/+*tf** Normal: *Fu*	$F_3 \times F_3$* Normal: *Fu*	Total Normal: *Fu*
♀ 11	23:0	4:10	20:0	20:0	—	—	63:0
♀ 16	22:0	7: 9	54:0	26:0	—	—	102:0
♀ 28	32:0	1: 5	—	—	—	—	32:0
♀ 29	13:0	5: 3	17:0	35:1	7:0	21:0	93:1
♀ 30	23:0	4: 1	9:2	20:0	—	20:0	72:2
♀ 33	15:0	2: 4	13:0	38:0	—	—	66:0
♀ 36	21:1	5: 3	35:0	9:0	—	—	65:1
♀ 37	15:0	5:10	26:0	—	—	4:0	45:0
♀ 44	28:0	5: 0	14:0	23:0	—	—	65:0
Total	192:1	38:49	188:2	171:1	7:0	45:0	603:4

* Mice from F_1, F_2, F_3 had [*Fu*]+/+*tf* and/or ++/+*tf* genotypes

Table VI. Testcrosses of mice with [*Fu*]+/+ *tf* genotype to mice of varions strains

Genotypes ♂♂/Strains	Strain/genotypes ♀♀	Phenotypes of progeny straight-tailed	fused
[*Fu*]+/+*tf**	SWR	88	0
[*Fu*]+/+*tf*	CBA	64	0
[*Fu*]+/+*tf*	C3H	73	0
SWR	[*Fu*]+/+*tf*	7	0
A	[*Fu*]+/+*tf*	7	0
Total		239	0

* [*Fu*]+/+*tf* mice used in this table were chosen on basis of results of genetic analysis; see Table IV and V (♀ 29, ♀ 30, ♀ 36, ♂ 3, ♂ 16, ♂ 17, ♂ 22)

properties of loci into which they are incorporated. Although not ruling out the possibility that such mechanisms might be involved in the case of the *Fu* gene, a more likely explanation is as follows.

Upon close examination of the *Fu* locus, one sees that it is peculiarly located in the genome—in linkage group IX (chromosome 17)—in the vicinity of the *T*-locus, at which, so far, 7 dominant and more than 100 recessive alleles have been located. These alleles exhibit many unusual properties such as marked segregation distortion, high transition frequency from one allelic state to another, and crossing over suppression[4]. The kinky gene, which is thought to be allelic to the *Fu* gene[6], has been located in the same region as *Fu*. A consequential circumstance is that this region is near the centromere containing a large heterochromatin block.

It should be noted that in ♀♀ [Fu]+/+*tf* × ♂♂ *Fu tf*/+*tf* crosses, the [Fu] gene was activated in the zygote, presumably under the effect of its active partner. In this respect, the genetics of the *Fu* locus in mice is similar to the behavior of the *R* alleles in maize[5].

We also traced a parallel between behavior at the *Fu* locus and that at the earlier described star (*S*) locus. Similar to the *S* gene, *Fu* behaves differently in the genotypes of wild and domestic animals (Table IX). It will be recalled that wild and laboratory strains of rodents strongly differ in physiological traits. Their defense response to man is very different, and so are the

Table VII. Results of *Fu tf*/+*tf* × [*Fu*]+/+*tf* crosses in mice

Genotypes ♂♂	Genotypes ♀♀	No. crosses	No. progenies	Segregation in progeny		
				Fu tf/Fu+	*Fu tf*/+*tf*; *Fu tf*/[Fu]+	[Fu]+/+*tf*; +*tf*/+*tf*
Fu tf/+*tf*	[Fu]+/+*tf**	15	89	3	34	52
[Fu]+/+*tf*	*Fu tf*/+*tf*	6	44	—	19	25

* [Fu]+/+*tf* mice used in this table were chosen on basis of results of genetic analysis; see Table IV and V (♀ 29, ♀ 30, ♀ 36, ♂ 3, ♂ 16, ♂ 17, ♂ 22)

Table VIII. Results of *Fu tf*/[*Fu*]+ × +*tf*/+*tf* crosses

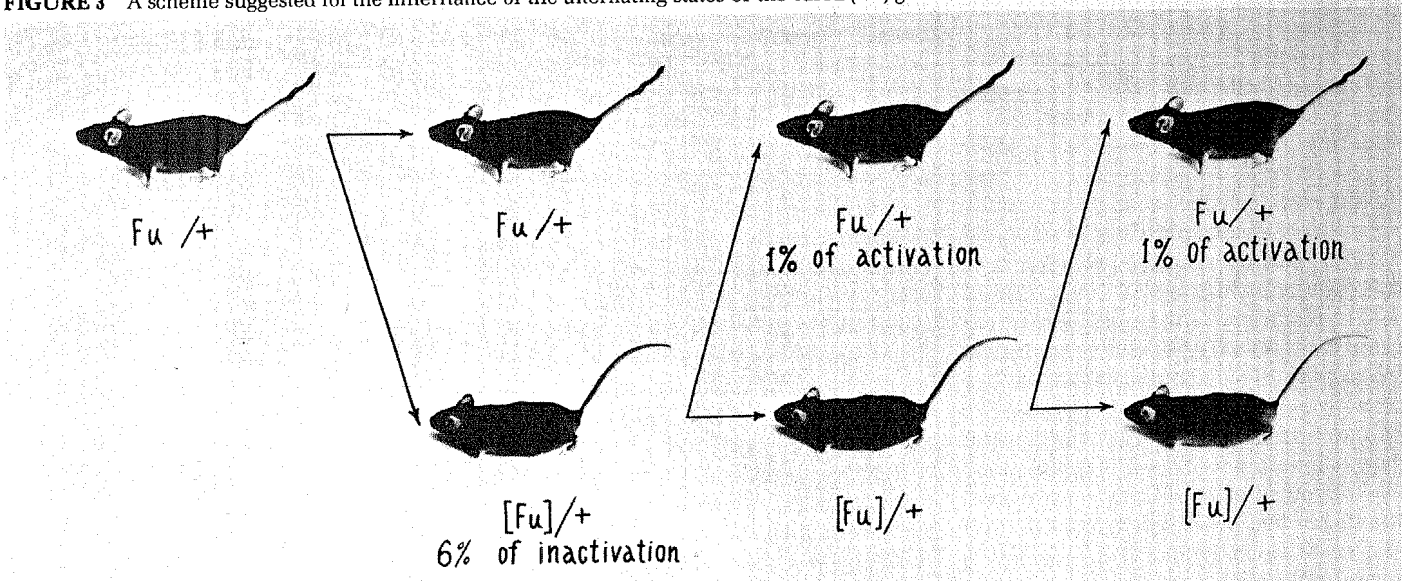
NN	Genotypes ♂♂	Genotypes ♀♀	No. progenies	Segregation ratio	
				Fu,tf (*Fu tf*/+*tf*)	non-*Fu*, non-*tf* ([Fu]+/+*tf*)
1.	*Fu tf*/[Fu]+*	+*tf*/+*tf*	4	—	4
2.	*Fu tf*/[Fu]+*	+*tf*/+*tf*	20	9	11
3.	+*tf*/+*tf*	*Fu tf*/[Fu]+	12	7	5
4.	+*tf*/+*tf*	*Fu tf*/[Fu]+	33	13	20
5.	+*tf*/+*tf*	*Fu tf*/[Fu]+	11	5	6
6.	+*tf*/+*tf*	*Fu tf*/[Fu]+	11	2	9
7.	+*tf*/+*tf*	*Fu tf*/[Fu]+	6	3	3
8.	+*tf*/+*tf*	*Fu tf*/[Fu]+	18	12	6
Total			115	51	64

* *Fu tf*/[Fu]+ mice were obtained in ♀♀ [Fu]+/+*tf* × ♂♂ *Fu tf*/+*tf* crosses

Table IX. Results of crosses *Fu*/*Fu* homozygotes with C3H and wild mice

Cross types	No. progenies	Fused	Straight-tailed	*Fu* nonmanifestation %
Fu/*Fu* × C3H	25	23	2	9
Fu/*Fu* × wild	27	10	17	63

FIGURE 3 A scheme suggested for the inheritance of the alternating states of the fused (*Fu*) gene in the house mouse.



levels of hormones[9]. Quite plausibly, both transitions $Fu \rightleftarrows [Fu]$ and $S \rightleftarrows [S]$ are dependent on alterations in the hormonal status. Hormones are well known regulators of gene activity and affect chromatin packing[14].

The alternating states of the *Fu* gene may be related to hereditary changes in the precentromeric heterochromatin of chromosome 17. That the heterochromatized state of a chromosome persists during cell division is a well known fact. Furthermore, homologous chromosomes polymorphic for C-heterochromatin and identical with respect to G-banding patterns have been identified. Such chromosomes also have been detected in related species having a common ancestor[12]. This suggests gametic transmissibility of the hetero- or euchromatized condition of some chromosomal loci.

The explanation offered relies on the supposition that inactive ("dormant") genes may be activated and reverted toward an inactive state. A similar reliance on gene activation-inactivation has been implied by many investigators, including Muller[10]. Since then, Zuckerkandl and Pauling[15] formulated it in their "dormant gene" hypothesis, and Belyaev[2] extended it to the process of domestication.

It is worth emphasizing that "dormant" genes are activated by evolutionary stimuli eventually resulting in profound metabolic changes in the cell. With regard to mice, a strong stimulus has been selection in the course of domestication.

References

1. BELYAEV, D. K. The genetic aspects of animal domestication. *In* The Problems of Animal and Plant Domestication. Nauka. Moskow (in Russian). p. 39–45. 1972.
2. ———. Destabilizing selection as a factor in domestication. *J. Hered.* 70: 301–308. 1979.
3. ———, A. O. RUVINSKY, and L. N. TRUT. Inherited activation-inactivation of the star gene in foxes: its bearing on the problem of domestication. *J. Hered.* 72: in press. 1981.
4. BENNETT, D. The *T*-locus of the mouse. *Cell* 6:441–454. 1975.
5. BRINK R. A. Paramutation. *Annu. Rev. Genet.* 7:129–152. 1973.
6. DUNN L. C. and E. CASPARI. A case of neighboring loci with similar effects. *Genetics* 30: 543–568. 1945.
7. ——— and S. GLUECKSON-WAELSCH. A genetic study of the mutation "Fused" in the house mouse, with evidence concerning its allelism with a similar mutation, "Kink." *J. Genet.* 52: 383–391. 1954.
8. LYON, M. F. Hereditary hair loss in the tufted mutant of the house mouse. *J. Hered.* 47:101–103. 1956.
9. MARKEL A. L., P. M. BORODIN, A. V. OSATCHIK, P. A. HUSAINOV, and V. V. PLOTNIKOV. Genotypical differences in hypertensive response to emotional stress. *Trans. Suberian Branch of USSR Acad. Sci.* No. 5, p. 117–121. 1976.
10. MULLER, H. J. Further studies on the nature and cause of gene mutations. *Proc. Int. Congr. Genet. 6th.* 1:213–255. 1932.
11. OHNO S. Evolution by Gene Duplication. Springer-Verlag, N.Y. 1970.
12. RADJABLI, S. I. C-heterochromatin in evolution of mammalion karyotype. *Proc. Acad. Sci. USSR* (in Russian). 234:935–936. 1977.
13. REED, S. C. The inheritance and expression of fused, a new mutation in the house mouse. *Genetics* 22:1–13. 1937.
14. TOMKINS, G. and D. MARTIN. Hormones and gene expression. *Annu. Rev. Genet.* 4:91–106. 1970.
15. ZUCKERKANDL, E. and L. PAULING. Molecular disease evolution and genetic heterogenity. *In* Horizons in Biochemistry. Academic Press, N.Y. p. 148–173. 1962.