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# Inherited activation-inactivation of the star gene in foxes

## Its bearing on the problem of domestication

*ABSTRACT*: A frequency of more than $10^{-2}$ of the de novo arisal of piebald spotting (star) was established in silver-black foxes selected for domestic behavior. The star phenotype is determined by the autosomal semidominant gene *S*. Ten genealogical groups of foxes, in which star arose independently, were analyzed. Of these, the star character is determined by *S* alleles in at least seven groups. The *S* gene is located in a linkage group other than the earlier described *W* (Georgian white) locus. The star gene is incompletely penetrant, but its penetrance is significantly higher in offspring from tame mothers than from aggressive ones, or when *S* is received from a heterozygous vixen (*Ss*). There was a notable shortage of homozygous (*SS*) offspring from *Ss* × *Ss* crosses, which cannot be adequately explained by selective embryonic mortality, differential zygotic and gametic death, or transgression of homozygous and heterozygous phenotypes. Some foxes, proven carriers of a homozygous (*SS*) genotype, showed the phenotype and mode of inheritance characteristic of heterozygotes (*Ss*). Presumably, the mechanism responsible for these observations is a heritable functional activation-inactivation of the star gene. Some implications of this concept in terms of destabilizing selection are discussed.

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DURING the last 20 years, we have expended much effort to select foxes resembling the domestic dog in behavior characteristics. In this work, we have proceeded from the concept that the hereditary reorganization of behavior is one of the key mechanisms of the domestication of animals[3].

During these years, such selection of foxes has, indeed, profoundly modified their behavior and culminated in the production of dog-like individuals. Behavioral changes in fox groups that were most domesticated were associated with a series of morphological variations (piebald or white spotting, modified ear and tail carriage) and physiological shifts (extraseasonal rhythms of reproduction and molt)[4]. Taken together, these changes were homologous, in Vavilov's sense of the term, to those that had occurred in the domestic dog.

One such change is the variation of piebald spotting, a morphological trait with a specific mode of inheritance, designated as the star character. This spotting frequently arose in the experimental population of foxes that had been selected for tame behavior.

This paper presents the results of genetic analysis that was undertaken to gain better insight into the mechanisms of domestication.

## Results

### *A phenotypic characterization of the piebald pattern*

In 1969, a peculiar piebald spotting was first observed in a male fox (no. 1001). This animal was from an experimental population of farm-bred foxes subjected to selection for domestic behavior. His head was spotted, which was unusual for foxes, as was the lower jaws, paws, breast, and belly (Figure 1*A*). Phenotypically similar foxes were subsequently identified in other groups of foxes unrelated to male no. 1001. Foxes with a similar discrete star between the ears also appeared in the control population at the "Cherepanovo" and "Lesnoy"

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fur farms. It seems probable that white spotting variations on the head have not arisen earlier in any other fox populations and have not been described in the literature.

The phenotypic expression (expressivity) of this spotting varies largely from one group to another, but also within the same litter (Figure 2). This variation ranges from 3–5 entirely unpigmented hairs gathered in a cluster to a spot (2–3 $cm^2$) and sometimes significantly more. Foxes with well defined stars consistently show spottings of the lower jaw, breast, and belly.

### *Frequency of the star phenotype*

Pups from parents with standard phenotypes were regularly observed for recording the de novo occurrence of the star phenotype. These observations were carried out from 1971–1979 at the "Cherepanovo" and "Lesnoy" fur farms and at the Experimental Farm of the Institute of Cytology and Genetics. The pertinent data are summarized in Table I. The frequency of the star character was much higher in the group of domestic foxes than in foxes at "Cherepanovo" and "Lesnoy". The expressivity of this character was very low: at "Cherepanovo" it was weakly expressed in 38 foxes and was well defined in 8; at "Lesnoy", it was weakly expressed in 42 and well defined in 2. This is in contrast to the Experimental Farm, where 25 percent of the foxes had a pronounced star. As a rule, when the star arose, it affected one pup per litter. At the Experimental Farm, pups with stars appeared in 48 litters; of these, 11 litters had 2 to 3 such pups.

### *Pedigree data*

From a survey of the genealogy of star-marked foxes, it is immediately apparent that five families gave rise to the majority of such foxes at the Experimental Farm. In this respect, female no. 300 is outstanding, as 20 cases of star are traced back to this female and her offspring (sons and daughters); female no. 326 ranks next (17 cases), followed by males no. 293, 8016, and 501 (7 cases each). What is noteworthy is that the star appeared in those groups that were most domesticated, with extraseasonal sexual activation and conformational changes.

Pedigree data indicate that the minority of families produced the majority of descendants with the star, whereas the majority rarely, if ever, produced star-marked descendants. In all, the star arose de novo in 48 families at the Experimental Farm. The ancestors of these probands did not have the star. It should be reemphasized that 35 of these families were remarkable in their high degree of tameness.

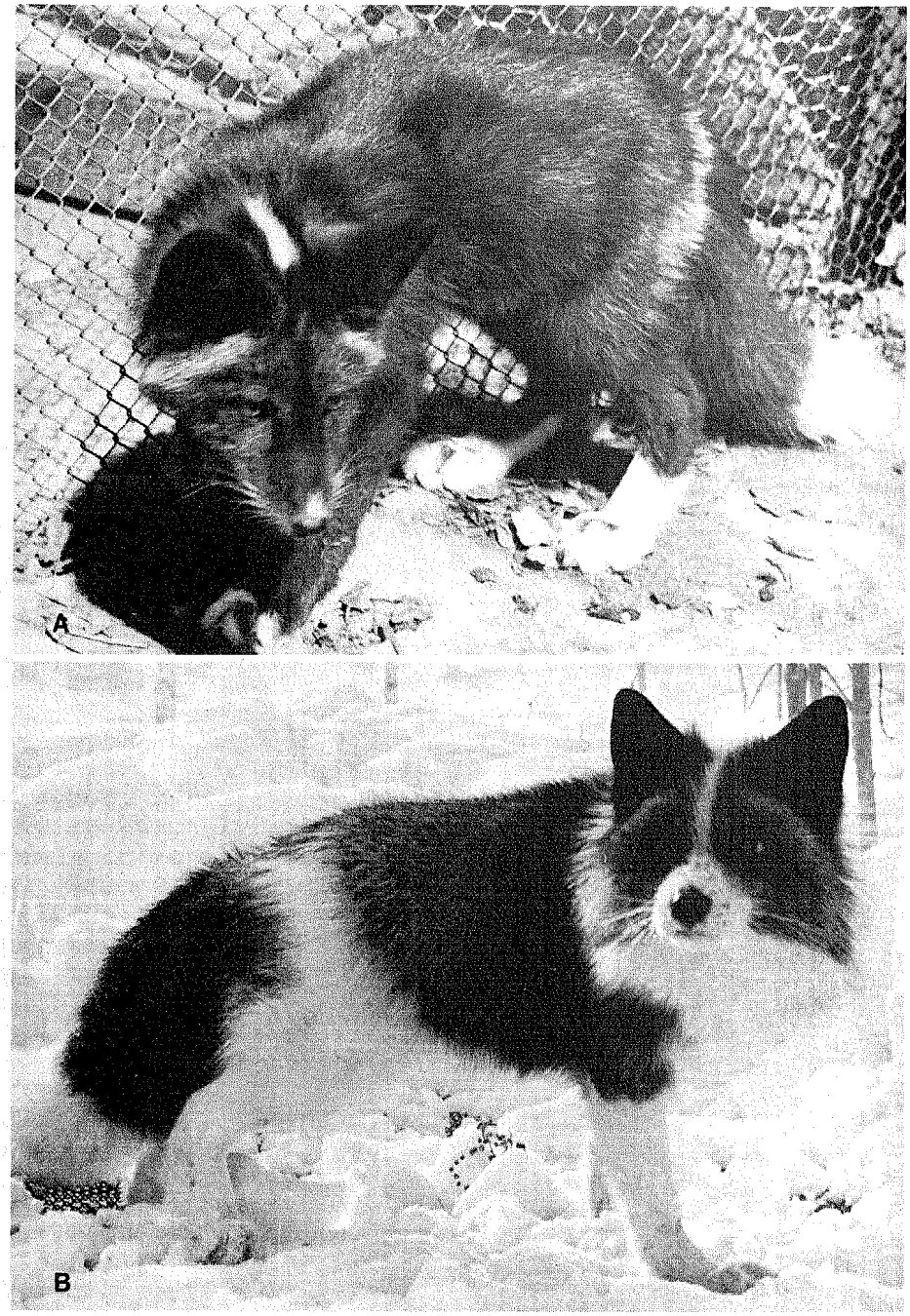


**FIGURE 1** *A* shows fox heterozygous for the star gene (*Ss*). *B*—a fox homozygous for the star gene (*SS*).

### *Inheritance of the star character*

Genetic data indicate that star is an autosomal monogenic semidominant. Figure 4 shows a part of the pedigree of a group of foxes derived from male no. 1001. This group was most thoroughly studied. Individuals marked with the star are heterozygotes. Henceforth, they will be designated as *Ss*. Homozygotes, *SS*, differ sharply from heterozygotes in phenotype; the blaze between the ears spreads along the nose, sometimes producing white-faced individuals; confluent spots may form a collar

**FIGURE 2** Variability in the expression of the star character in heterozygous *Ss* foxes in a litter.

(collared pied) or belt (belted pied); variations in these homozygotes include dorsal white with spotting extending over to the chest, belly, navel, hind feet and tail (Figure 1*B*). In all *SS* foxes, heterochromia of the iridis is observed. When homozygous, the *S* gene affects hearing, sometimes producing complete deafness. It is also characteristic of these homozygotes to periodically twist their necks backwards, which is symptomatic of a pathological condition of the vestibular apparatus (Figure 3). Cryptorchism is also frequently observed in *SS* males; when bilateral, this developmental abnormality confers sterility.

Despite their phenotypic variability, *SS* individuals are always different from *Ss* ones. There was no disagreement over this point. One also can distinguish, with certainty, *SS* homozygotes from the earlier described platinum and white-faced foxes that are heterozygous[5].

This analysis also includes nine other genealogical groups independently appearing from their respective star-marked probands. The proband and his (or her) descendants were crossed either to standard silver-black foxes (*ss*) or to descendants (*Ss*) of male no. 1001. This male and his descendants were used as testers for allelism. The results are shown in Table II. In seven genealogical groups examined, the gene determining the star phenotype was found to be allelic to the gene of male no. 1001. Data on the remaining three groups were not available. Thus, all 10 genealogical groups exemplify the situation where a character is a Mendelian semidominant; allelism was proven for seven of the genes studied.

The genealogical group of male no. 1001 deserves some consideration. Table III presents evidence for a maternal effect of the *S* gene. In the case of paternal derivation of *S*, there is a statistically significant ($P > 0.95$) shortage of star-marked foxes. Conversely, in the case of maternal derivation, the segregation pattern of *S* does not deviate from the one theoretically expected. The two crosses definitely differ in the penetrance of the gene in question. Surprisingly, ♀♀ *ss* × ♂♂ *Ss*, involving individuals of the genealogical group of male no. 1001, yielded two segregation patterns, the difference between which was related to maternal behavior (Table IV). The number of star-marked offspring was significantly lower ($P > 0.99$) than expected in crosses in which vixen, unselected for tameness (relatively wild), were mated to males with the star. In contrast, the offspring from all crosses of vixen, selected for tame behavior, to males with the star did not show any significant departures from the theoretically expected segregation ratios. This is clearly shown in Table IV.

The offspring from crosses between heterozygotes segregated in a remarkable way (Table V). Immediately apparent is the significant shortage of *SS* homozygotes. It was thought that, perhaps, homozygotes had died during embryonic development. This possibility was closer examined in quantitative studies of corpora lutea and placenta in 12 *Ss* vixen mated to *Ss* males. Among 72 pups born to these females, 43 were heterozygous, 29 were standard, and none was homozygous. These studies were done 2–2.5 months after parturition, when conditions allow precise estimates of the number of corpora lutea and placenta. Total embryonic mortality for these females was 14.7 percent, which did not exceed that established for silver foxes[5,9]. Nor did their actual fertility (number of pups born) differ from mean values. Preimplantation embryonic mortality was low, about 4 percent. These do not indicate that selective mortality during embryonic development caused a shortage of homozygotes. This excluded the effect of this factor from further analysis.

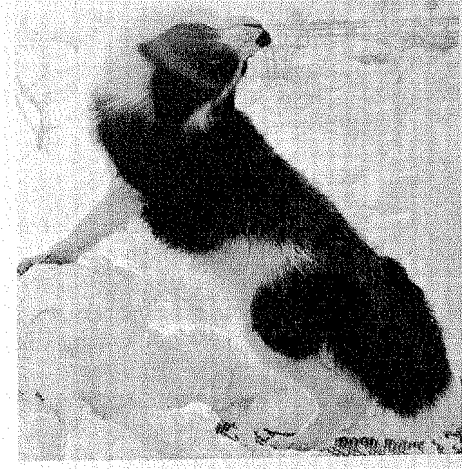

**FIGURE 3** Abnormal behavior often observed in homozygous star (*SS*) foxes.

**Table I. Frequency of de novo appearance of the star character in fox populations**

| Populations | Experimental Farm | | Fur farm | |
|---|---|---|---|---|
| | selected | unselected | "Cherepanovo" | "Lesnoy" |
| Total no. pups | 1050 | 2360 | 3900 | 6000 |
| No. pups with star from normal parents | 39 | 26 | 46 | 44 |
| Star frequency | $3.7 \times 10^{-2}$ | $1.1 \times 10^{-2}$ | $1.1 \times 10^{-2}$ | $7 \times 10^{-3}$ |

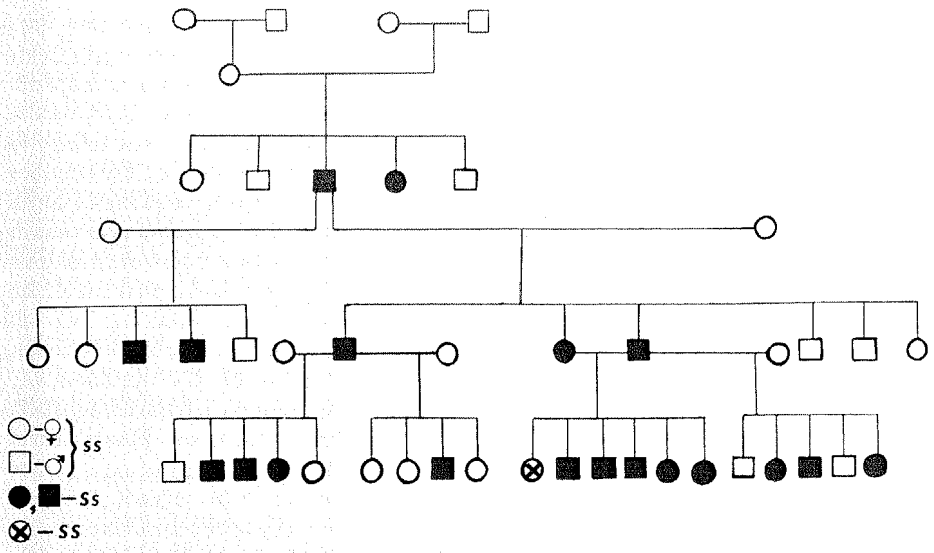


**FIGURE 4** A part of the pedigree of male no. 1001 (Ss).

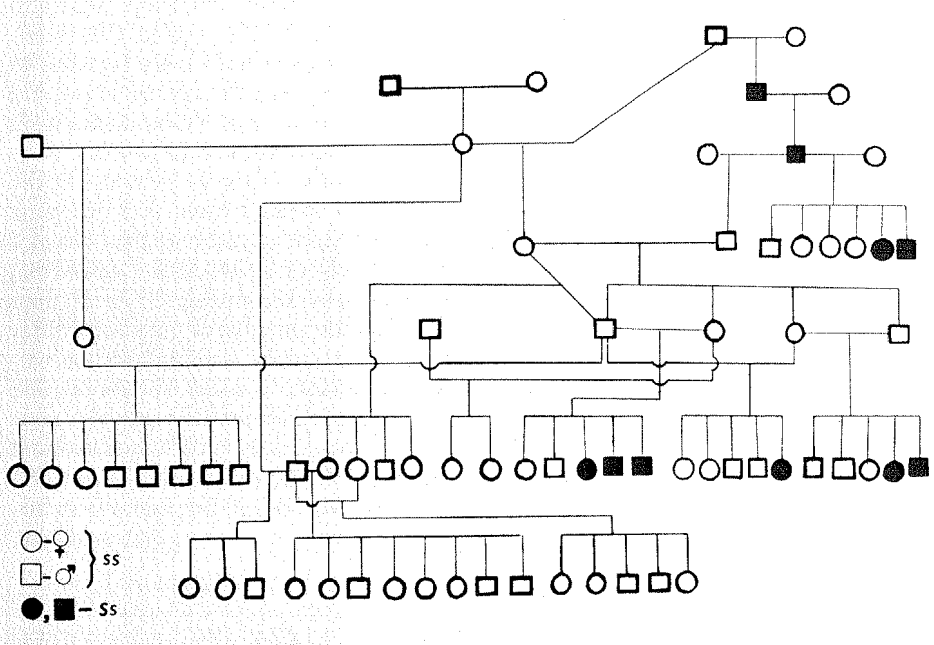


**FIGURE 5** A part of the pedigree of male no. 4935 (Ss).

Could the differential death of gametes of a particular sort be implicated? From Table V it is evident that the ratio of the grand total of homozygotes plus heterozygotes to the number of phenotypically normal foxes conforms to 3:1, the one expected from the classical monohybrid cross. The differential death of gametes was thereby also excluded as a factor responsible for lack of homozygotes. The alternative possibility then envisaged was that perhaps some homozygotes for the S gene were phenotypically indistinguishable from individuals carrying it in a heterozygous condition. The whole set of data leads to the inevitable conclusion that the entrance of two homologous chromosomes bearing the *S* gene into the zygote does not provide the phenotype specific to *SS* homozygotes. While homozygotes and heterozygotes for the *S* gene differ sharply (see Figures 1 and 2), nevertheless, in some cases it was impossible to determine with certainty the genotypes of phenotypically heterozygous individuals.

This raised the question as to whether homozygosity of such phenotypically heterozygous foxes is detectable by means of genetic analysis. To answer this question, testcrosses were carried out involving phenotypically heterozygous foxes that were born to heterozygous parents in litters having no homozygotes. In these litters, total offspring numbered 46 heterozygotes to 16 standard, i.e., segregation conformed to 3:1. The actual fertility of these females was normal (6.3). There was not a single homozygote among the foxes tested, as shown in Table VI, yet the probability that all those tested were true heterozygotes was only 0.0003. The data in this table indicate that all the foxes tested produced offspring with segregation ratios that should be expected in heterozygotes. As already mentioned, the shortage of homozygotes cannot be ascribed to selective embryonic mortality. We are thus faced with a situation in which individuals definitely homozygous by their genetic constitution show a phenotype and mode of inheritance that is, beyond any doubt, heterozygous. This is hard to reconcile within the framework of the concept of incomplete gene penetrance. As an alternative explanation, the inherited functional blockage of one of the alleles shall now be considered.

The analysis of breeding data on homozygotes for the *S* gene disclosed novel aspects of this phenomenon. Tables VII and VIII show that the probability transmission of *S* is almost 100 percent, although standard foxes, with definitely heterozygous constitutions, rarely appeared in some crosses. When tested, three of these females, with the genetic constitution of heterozygotes but normal phenotypes, gave birth to 19 pups all of which were standard. This further supports the presumed hereditary inactivation of the star gene.

The inheritance pattern of the star gene in the genealogical group derived from male no. 4935 is also suggestive of a functional activation-inactivation of this gene (Figure 5).

As seen in Table VIII, direct and reciprocal crosses yielded the same proportions of phenotypes in the offspring. Unexpected was the very high proportion of homozygotes in *SS* × *Ss* crosses. It should be reemphasized here that the percentage of segregated homozygotes in the *Ss* × *Ss* crosses was only 58 percent of the theoretically predicted number, i.e., significantly less than 100 percent, $P > 0.95$ (Table V).

These data are additional evidence against selective embryonic mortality of homozygotes.

Hence, the phenotype characteristic of homozygotes always develops when at least one of the alleles from either homozygous parent enters into the zygote.

### *Genetic relationships at the* W *and* S *loci*

The *W* locus in silver-black foxes has been studied in some detail[5,10]. The three alleles established at this locus are *W*, white-face; $W^p$, platinum; and $W^g$, Georgian-white. These genes are semidominant; when homozygous, they exert a lethal effect. The white-face and platinum mutations produce specific spottings, somewhat similar to those caused by the star gene. This posed the question of relationships at these two loci. Crosses between white-face (*Ww*) and star-marked (*Ss*) foxes gave rise to individuals of four phenotypic classes: white-face, star, silver-black, and to a class with a hitherto undescribed phenotype. As demonstrated by the results of the testcrosses, the latter class is composed of diheterozygotes (*Ww Ss*), and, hence, the genes *W* and *S* are located in different linkage groups (Table IX). Depigmentation in individuals with *wwSs*, *wwSS*, and *WwSS* constitution is not random; it is restricted to particular regions of the body much like spotting patterns in mice[18]. It is noteworthy that the spotted areas increase and color is diluted over the whole body as a result of the interaction of dominant alleles at the *W* and *S* loci (Figure 6).

**Table III. Results of testcrosses of star-marked foxes derived from male no. 1001**

| Cross | Segregation ratio *Ss* | Segregation ratio *ss* | $\chi^2$ | Penetrance of heterozygotes % |
|---|---|---|---|---|
| ♀♀ *ss* × ♂♂ *Ss* | 305 | 429 | 10.4 ($P > 0.99$) | 83 |
| ♀♀ *Ss* × ♂♂ *ss* | 85 | 95 | 0.55 | 94 |

The differences between direct and reciprocal crosses are statistically significant, $F = 9.07$ ($P > 0.99$)

**Table IV. Effect of maternal defensive behavior on segregation ratio in ♀♀ *ss* × ♂♂ *Ss* crosses**

| Maternal behavior | Segregation ratio *Ss* | Segregation ratio *ss* | $\chi^2$ | Penetrance of heterozygotes % |
|---|---|---|---|---|
| Wild | 179 | 287 | 25.03 ($P > 0.99$) | 77 |
| Tame | 126 | 142 | 0.95 | 94 |

The difference between wild and tame mothers are statistically significant, $F = 25.65$ ($P > 0.99$)

**Table V. Segregation ratio in offspring from *Ss* × *Ss* crosses**

| | Segregation ratio *SS* | *Ss* | *ss* | $\chi^2$ | Penetrance of homozygotes (*SS*) |
|---|---|---|---|---|---|
| Observed | 65 | 261 | 120 | 26.5* | 58% |
| Expected at 1:2:1 ratio | 111.5 | 223 | 111.5 | — | — |
| Observed | 326 | | 120 | 0.42† | — |
| Expected at 3:1 ratio | 334.5 | | 111.5 | — | — |

*The deviation from the expected segregation ratio is significant ($P > 0.999$)
†The deviation is insignificant

**Table II. Genetic analysis of 10 independently arisen genealogical groups of foxes with star**

| No. of proband (*Ss*) | Cross: Proband × *ss* observed *Ss* | observed *ss* | expected *Ss* | expected *ss* | $\chi^2$ | Proband × *Ss* observed *SS* | observed *Ss* | observed *ss* | expected *SS* | expected *Ss* | expected *ss* | $\chi^2$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ♂ 1001 | 390 | 524 | 457 | 457 | 19.6* | 36 | 139 | 63 | 59.5 | 119 | 59.5 | 12.6* |
| ♂ 4935 | 21 | 24 | 22.5 | 22.5 | 0.2 | 10 | 15 | 6 | 7.75 | 15.5 | 7.75 | 1.0 |
| ♂ 227 | 9 | 13 | 11 | 11 | 0.7 | 1 | 14 | 10 | 6.25 | 12.5 | 6.25 | 30.0* |
| ♂ 2309 | 10 | 14 | 12 | 12 | 0.6 | 3 | 14 | 11 | 7 | 14 | 7 | 4.5 |
| ♂ 1127 | 16 | 32 | 24 | 24 | 5.3* | 5 | 16 | 11 | 8 | 16 | 8 | 2.2 |
| ♂ 95 | 5 | 16 | 10.5 | 10.5 | 5.8 | 6 | 13 | 4 | 5.75 | 11.5 | 5.75 | 0.7 |
| ♂ 4035 | 26 | 78 | 52 | 52 | 26.0* | 4 | 50 | 15 | 17.25 | 34.5 | 17.25 | 17.4* |
| ♂ 73 | 5 | 13 | 9 | 9 | 3.5 | — | 9 | 4 | 3.25 | 6.5 | 3.25 | 5.3 |
| ♀ 512 | 0 | 5 | 2.5 | 2.5 | 8.7* | — | 11 | 4 | 3.75 | 7.5 | 3.75 | 4.9 |
| ♀ 396 | 6 | 5 | 5.5 | 5.5 | 0.0 | — | 6 | 3 | 2.25 | 4.5 | 2.25 | 2.8 |
| Total | 488 | 724 | 606 | 606 | 45.9* | 65 | 287 | 131 | 120.75 | 241.5 | 120.75 | 35.2* |

*Observed segregation ratio differed significantly from one expected ($P > 0.95$)
**Foxes of the genealogical group of male no. 1001 served as testers (*Ss*) for allelism

## Discussion

The dominantly inherited star gene arises with a frequency exceeding, by far, that established for gene mutations. In a fox population, selected for domestic behavior, the arisal frequency of the star character is especially high. A maternal effect was disclosed in this genetic analysis. The highest probability transmission of the *S* gene (significant enhancement of the *S* penetrance) was observed in offspring from tame mothers. These observations and the appearance of morphological and physiological aberrations suggest causal relationships between behavior, the associated hormonal level, and the process that gives rise to new forms of animals. The spontaneous emergence of the star gene in commercial fur farms supports these relationships in view of the fact that animals with higher fertility have been unconsciously selected for because of the positive correlation between fertility and defense behavior. The high arisal frequency and abnormal mode of inheritance of the star gene are, indeed, difficult to explain in terms of the classical mutation theory; this warrants search for other genetic mechanisms. The genetic analysis of the star gene also disclosed a puzzling segregation distortion of a seemingly simple inheritance pattern. When crossed between themselves, heterozygotes produced offspring with a disproportionately low number of homozygotes and a perfect 3 aberrant to 1 normal ratio. That this disproportionality is not ascribable to selective embryonic, zygotic and gametic mortality was demonstrated by special analysis of experimental data. The segregation pattern in offspring from matings of (SS) homozygotes to (Ss) heterozygotes also permitted us to exclude these factors, because of the good agreement of the number of homozygous pups with the expected values (Table VIII).

Could, then, the observed phenomena possibly be the result of some recombinational event? It will be recalled that in mice the large set of *t*-alleles had all arisen by crossing over[7]. Also of relevance is that it was thought at one time or another that recombinational mechanisms might give rise to new proteins in the $\beta$-system of blood groups in cattle[19], changes at the LDH *B*-locus in the brook trout[24], new allotypes of tissue incompatibility[2], and unusual electrophoretic fractions of 6-phosphogluconate dehydrogenase in quail[15]. In all of these cases, the alleles have arisen de novo with a frequency of $10^{-2} - 10^{-3}$ and behaved like mutants.

Many instances are known where increases in inherited variability rate have been explained by mechanisms such as the incorporation of episome-like elements[13], insertions[12], or position effect[20].

Recognizing these mechanisms, we cannot apply them to the case of the star gene, particularly to the elucidation of the hereditary functional blockage of genes and the inactivation of one of the alleles (its phenotypic manifestation) in indubitable homozygotes.

The arisal frequency and inheritance pattern of the star gene become compre-

**Table VI. Results of (*S*– × *ss*) testcross foxes with heterozygous phenotype, derived from parents (*Ss* × *Ss*) that had no phenotypically homozygous offspring**

| No | S-foxes tested | Segregation ratio | |
|---|---|---|---|
| | | Ss | ss |
| 1 | ♂ 7299 | — | 4 |
| 2 | ♂ 1099 | 7 | 17 |
| 3 | ♂ 1903 | 1 | 4 |
| 4 | ♂ 7325 | 5 | 14 |
| 5 | ♂ 2319 | 5 | 17 |
| 6 | ♂ 1191 | 12 | 11 |
| 7 | ♂ 2731 | 4 | 15 |
| 8 | ♂ 2509 | 1 | 3 |
| 9 | ♂ 1307 | 8 | 5 |
| 10 | ♂ 4623 | 16 | 15 |
| 11 | ♂ 1135 | 6 | 12 |
| 12 | ♂ 1181 | 8 | 22 |
| 13 | ♂ 1183 | 6 | 7 |
| 14 | ♀ 6838 | — | 7 |
| 15 | ♀ 400 | 7 | 9 |
| 16 | ♀ 1030 | 5 | 5 |
| 17 | ♀ 452 | 4 | 4 |
| 18 | ♀ 1102 | 4 | 2 |
| 19 | ♀ 1736 | 4 | 2 |
| 20 | ♀ 6600 | — | 5 |
| 21 | ♀ 1080 | 4 | 7 |
| 22 | ♀ 1074 | 4 | 8 |
| 23 | ♀ 1150 | 6 | 5 |
| 24 | ♀ 1176 | — | 5 |
| 25 | ♀ 1116 | 1 | 4 |
| 26 | ♀ 2066 | 1 | 4 |
| 27 | ♀ 1146 | 4 | 1 |
| 28 | ♀ 1176 | — | 5 |
| 28 | ♀ 132 | 1 | 2 |

**Table VII. Results of genetic analysis of *SS* foxes**

| Crosses | Segregation ratio | | | Penetrance % |
|---|---|---|---|---|
| | SS | Ss | ss | |
| ♂♂ SS × ♀♀ ss | — | 40 | 3 | 93 |
| ♂♂ ss × ♀♀ SS | — | 12 | 1 | 93 |
| Total | — | 52 | 4 | 93 |
| SS × SS | 21 | — | — | 100 |

**Table VIII. Results of *SS* × *Ss* crosses**

| Crosses | Segregation ratio | | | Penetrance of homozygotes (SS) % |
|---|---|---|---|---|
| | SS | Ss | ss | |
| ♀♀ Ss × ♂♂ SS | 72 | 71 | 8 | 97 |
| ♀♀ SS × ♂♂ Ss | 35 | 31 | 2 | 100 |
| Total | 107 | 102 | 10 | 98 |

**Table IX. Results of *WwSs* × *wwss* crosses**

| | Segregation ratio | | | |
|---|---|---|---|---|
| | WwSs | Wwss | wwSs | wwss |
| Observed | 8 | 8 | 17 | 13 |
| Expected | 11.5 | 11.5 | 11.5 | 11.5 |

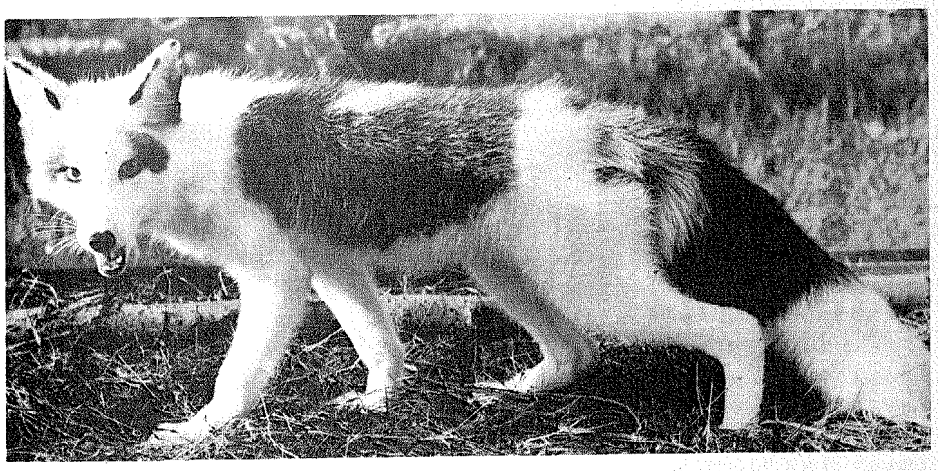

**FIGURE 6** A fox with the *Ww SS* genotype.

hensible under the assumption that they are the result of the functional activation of a gene that has been hitherto opaque (dormant). As seems probable, gene activation was provided by selection for domestic behavior, i.e., by novel genotypic conditions set up by selection. However, once entered into an active state, the gene subsequently behaves like a discrete Mendelian unit. The idea of functional activation-inactivation of genes has permeated through the literature. It has been shared by Müller[14] and explicitly stated as the dormant gene hypothesis by Zuckerkandl and Pouling[25]. There was no experimental substantiation of this idea.

As suggested by the star studies, once brought out of dormancy, a gene would become functionally active and relatively stably inherited in the new state; sometimes it would become inactive, thereby distorting classical segregation patterns. The phenomenon of gene activation-inactivation cannot be explained only by the influence of the genotypic environment for the reason that within the same genotypic environment (the same organism) one of the homologous genes can be active and the other inactive.

The data obtained permit judgement as to what degree the newly arisen functional activity of a gene is stable. To begin with, the de novo arisen activated state of a gene is functionally unstable. This seems likely because, in some of the indubitable homozygotes, only one *S* allele was manifest, the other, being inherited in a functionally blocked state, was phenotypically opaque; clearly, these individuals behaved like heterozygotes in the testcrosses (Table VI).

Of importance is the fact that some indubitable heterozygotes (*Ss*) from *SS* × *ss* crosses behave as homozygotes for the normal allele in the testcrosses. The tendency for the functional blockage to be stable from one generation to another does not seem to be absolute. The blockage may be transient, in which case the dormant gene becomes active and is manifested in the offspring (see Figure 5). This is suggestive of a functional gene blockage being a discrete event essentially different from the known versatile manifestations (penetrance) of a gene under the effects of environmental and genotypic conditions[21].

Thus, the *S* gene determines the development of spotting in foxes and behaves, in terms of star arisal frequency and inheritance pattern, otherwise than usual mutations. There is a parallel between our observations and the paramutation phenomenon described by Brink[6]. His point was that the capacity for paramutation heritably altering the functional state of a locus is dependent on factors residing within the chromosome: "Paramutability is an intrinsic property of the $R^r$ allele."

In the case considered, functional gene activation is related to a particular direction of selection that modifies behavior and hormonal parameters[4]. Inasmuch as this directional selection produces a series of morphological and physiological variations, it may arouse many dormant genes. Zuckerkandle and Pouling have suggested that such activation occurs under the effect of fluctuations in the internal milieu[25]. Such shifts in the hormonal balance in foxes selected for tame behavior have been demonstrated[23]. The role of hormones as metabolic regulators of gene functional activity is now unquestionable[22].

Acceptance of the concept of hereditary gene activation-inactivation, i.e., dormant genes, calls for additional genetic symbols. It is suggested that [ ] should be used to denote hereditary functional blockage of a gene. We believe this is a justified specification because a gene in an activated state is, in principle, different from a recessive gene. Thus, *S* and [*S*] will refer to the active and blocked state of the gene considered, respectively. However, the symbol [ ] is applicable only when one is sure that a gene is functionally blocked; if that is not the case, convential genetic symbols should be used.

Based on the data obtained, it is possible to evaluate the frequency of the functional activation-inactivation of the *S* gene. As shown in Table I, $[S] \rightarrow S$ is an event occurring with a frequency of not less than 1 percent, a value increasing with continuous selection for tame behavior. The frequency of the reverse $S \rightarrow [S]$ event considerably surpasses the activation frequency. The shortage of homozygotes for the *S* gene in the genealogical group of male no. 1001 is 38 percent, as can be calculated (Table II). Genetical analysis indicated that [*S*] *S* individuals behave as though they are heterozygotes in the testcrosses. The nonmanifestation of the *S* gene in the genealogical group of male no. 1001 is the sum of the percentage for the nonmanifestation of the paternally derived *S* in ♂♂ *Ss* × ♀♀ *ss* crosses (33 percent, Table IV) and that for the one maternally derived in ♂♂ *ss* × ♀♀ *Ss* crosses (6 percent, Table III). In other words, the grand total is 33 percent plus 6 percent to 39 percent, which is close to the percentage (38 percent) of the nonmanifestation of the *S* gene in homozygotes. Therefore, approximate estimates of the inactivation frequency of a gene can be based on the percentage of its nonmanifestation in homozygotes. These estimates range from 6 to 33 percent.

From comparisons of Table V and VIII, it is evident that *Ss* × *Ss* differ markedly from *SS* × *Ss* crosses in the proportion of homozygotes yielded. In *Ss* × *Ss* crosses, there is a great shortage of homozygotes, but not in *SS* × *Ss* crosses. An unambiguous interpretation of this difference is hardly possible. The explanations envisaged are as follows: 1) perhaps the phenotype of a homozygous individual has, in some unknown way, a stabilizing influence on the functional state of the *S* gene and on its manifestation in subsequent generations; 2) the phenotypic characteristic of a homozygote may be the result of a random gene combination that confers high penetrance; and, 3) the emerging stability may be the consequence of the direct cooperation of the two activated *S* alleles.

An inevitable question might now be asked. What mechanisms underlie the heritably transmitted activation-inactivation of a gene? Our data do not provide a direct answer. A putative mechanism may be the hereditary state of variable degrees of heterochromatization of certain chromosome regions that either block or enhance their transcriptional activities. It has been well established that chromosomes can be in a stable state of heterochromatization during the cell cycle[16]. Homologous chromosomes polymorphic for C-heterochromatin, but with identical G-banding patterns, have been identified by means of differential staining techniques. Similar observations have been made on closely related species having a common ancestor[17]. These data seem to indicate that the euchromatized and heterochromatized state of some certain chromosome regions may be heritably transmitted.

As to foxes, the number of cell clones with additional heterochromatic microchromosomes has considerably increased as the result of selection for domestic behavior[6]. This may be taken to mean that domestication has somehow affected the pre-existing heterochromatized elements or the mechanisms determining the quantity of supernumerary chromosomes.

A basic point must now be stated before going on with further discussion. The unusually high arisal frequency of the character controlled by the *S* gene and its peculiar mode of inheritance are related to the specific direction of selection acting on the fox population under consideration. Selection for behavior elicits a spectrum of changes in morphological characters and functions ensured by stabilizing selection. The term destabilizing has been proposed to refer to this kind of selection[3,4]. Acting through systems of hormonal regulation, destabilizing selection leads to a drastic increase in variability and acceleration of the process that gives rise to new forms.

From the data obtained, it is reasonable to assume that one of the mechanisms through which destabilizing selection operates is the heritable functional activation of dormant genes. The contribution of these genes to the total reservoir of hereditary variability may be large and of evolutionary consequence. In stressful situations such as domestication, this reservoir is released.

Clearly, under the pressure of destabilizing selection, the same mechanisms of developmental control are unidirectionally modified; this produces novel states of regulatory systems (predominantly hormonal) that are, in their essence, similar in different species. This may be the possible source of homologous series in variation in distant taxonomic groups, in Vavilov's sense, a phenomenon reflected in the domestication process.

The literature abounds in descriptions of variable phenotypic manifestations of mutational changes and their unusual inheritance. In 1929, Astaurov[1] concluded from his studies on the homoetic mutation tetraptera in *Drosophila melanogaster* that the phenotypic manifestation-nonmanifestation of a character, even within an organism, is irreducible to external fluctuations, nor to those of the genotypic environment; it is rather due to the randomness of the developmental process resulting from local (within an organism) fluctuations of developmental microconditions.

If, indeed, microconditions in a cell (or organism) interfere with development so as to render a character alternatingly variable, this would mean that the function of a gene (or its product) is highly sensitive to the slightest alterations of these conditions, i.e., the gene itself is functionally unstable. This is quite conceivable with reference to just-activated genes.

Tetraptera seems to be a good example of the long evolutionary persistence of a dormant gene somehow awakened in laboratory conditions, but not yet stabilized by selection and so unstable in phenotypic expression. Thus, possibly, may be regarded the arisal of an array of genes in laboratory conditions and their peculiar inheritance[11].

The cornerstones of the theory of evolution, variability, and selection, are traditionally separate entities. Modern concepts of the genetic basis of evolution continue treating mutation and selection as independent events. In this work, we conceptually linked together selection and variability in a concrete evolutionary setting, in which selection gains access to influential regulators of ontogeny, thereby functionally activating dormant genes that give rise to homologous variation. Does this reflect a more general situation? Such information would promote understanding of some evolutionary processes.

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