DOMINANCE IN THRESHOLD CHARACTERS. A COMPARISON OF TWO TABBY ALLELES IN THE MOUSE

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TWO alleles of the sex-linked gene tabby, Ta and Ta^c , reduce the number of secondary facial vibrissae in the mouse. Dominance on the phenotypic level in this system is considerably affected by background modification, so that estimates of dominance based directly on observations are difficult to interpret. The present analysis was based on a model which allowed transformation of the discontinuous observations to a postulated continuous scale of amount of gene product. With this accomplished, the dominance relationships of the alleles were investigated at a more fundamental level, relatively independent of genetic background.

MATERIALS AND METHODS

The original tabby allele (Ta), here called Ta^f , arose in a strain selected for large size on a low plane of nutrition (FALCONER 1953). Ta^c arose in a line selected for body weight (Mouse News Letter 1966), and resembles another tabby allele of independent origin, Ta^j (Mouse News Letter 1963). The effect of Ta^f and Ta^c on vibrissa number was examined for each allele on its original stock background, and on the backgrounds produced after a number of crosses to the inbred strains, JU/Fa and A/Fa. These strains differed in their ability to favor mutant expression (SOFAER 1969).

For each allele, the material collected was composed of five groups of animals according to background genotype: the stock background; the background after one cross to JU ($\frac{1}{2}$ JU), and after two crosses to JU ($\frac{3}{4}$ JU), and the background after one cross to A ($\frac{1}{2}$ A), and after two crosses to A ($\frac{3}{4}$ A). The Ta^f ($\frac{3}{4}$ JU) group could not be completed because of poor fertility and was therefore not examined. All animals were the progeny of heterozygous mothers and tabby fathers, and all four genotypes of offspring were scored ($Ta+$ and $TaTa$ ♀♀, and $+$ and Ta ♂♂). The number of individuals of each genotype in each background varied between 21 and 26.

FRASER, NAY and KINDRED (1959) showed that there was no significant difference between tabby homozygotes and tabby hemizygotes with respect to vibrissa number. These two genotypes were therefore pooled so that in each background group for each allele there were three major-genotype classes of animals: $+$, $Ta+$, and $TaTa$ plus Ta . Only the mean vibrissa scores of each of these genotypic classes were available for the analysis.

The secondary facial vibrissae are divided into four groups. On each side of the face there are 1 or 2 supraorbital, 0 or 1 postorbital, and 0, 1, or 2 postoral vibrissae; and beneath the chin there is a single group of 1, 2, or 3 interramal vibrissae. Animals with scores outside these ranges are rare, and none occurred in the present study. These four groups appear to be under nearly independent genetic control (FRASER, NAY and KINDRED 1959; FRASER and KINDRED 1962; SOFAER 1969). Any analysis of vibrissa number is then best carried out for each group separately.

THE MODEL

The model on which the analysis was based assumed a continuous scale of gene

product expressed on the phenotypic level in discrete categories (each phenotypic category being a particular number of vibrissae in a given vibrissa group). The values on the gene product scale corresponding to the different phenotypic categories were taken to be separated by constant thresholds. Within each background, each major-genotype class of animals was assumed to be normally distributed on the gene-product scale and, since animals of the same class were always to some extent inbred, the bulk of the variance within each class was considered to be environmental rather than genetic. As only mean vibrissa scores were available, the variance within all classes was of necessity assumed to be the same.

For the three bilateral vibrissa groups, the scores on the two sides of one individual, say L_i and R_i , can be regarded as two independent realizations of the same vibrissa-producing potential. Thus for these groups, the number of phenotypic categories was taken as the number of possible phenotypes on a single side (1 or 2 vibrissae at the supraorbital site, 0 or 1 at the postorbital site, and 0, 1 or 2 at the postoral site). The mean score of a class of N animals was then $[\Sigma(L_i + R_i)]/2N$. For the interrampal group there were three possible phenotypes at this single site (1, 2 or 3 vibrissae), and the mean of a class of N animals was simply taken as $(\Sigma X_i)/N$, where X_i was an individual's interrampal score. Thus a two-phenotype category or one-threshold model was used for the supraorbital and postorbital groups, and a three-phenotype category or two-threshold model was used for the postoral and interrampal groups.

The mean phenotype of a class of animals clearly depends on how the distribution of the class on the gene product scale is partitioned by the thresholds. Figure 1 illustrates the two-threshold situation. The one-threshold situation can be re-

FIGURE 1.—The relationship between gene product and phenotypic scales. The two thresholds, separated by t standard deviations, divide the distribution of a class of individuals on the gene-product scale into those with minimum, intermediate, and maximum vibrissa scores, in the proportions p , q , and r , respectively. When $t = 0$, then $q = 0$, and the distribution is divided by a single threshold in the proportions p and r . For the purposes of illustration, the supraorbital (SO:rb), postorbital (PO:rb), postoral (PO), and interrampal (IR) phenotypic scales have been superimposed. This is not meant to imply that they are equivalent.

garded as a special case with the threshold interval, t , being equal to zero. If the scores given to each phenotypic category when there are two thresholds are n , $n+1$, $n+2$, and if p , q , and r are the proportions of a distribution that fall, respectively, below both thresholds, between the two thresholds, and above both thresholds, then the mean phenotypic score produced by that distribution is: $np + (n+1)q + (n+2)r$. If when $t = 0$ the scores given to each phenotypic category are n and $n+1$, and if p and r are the proportions of the distribution that then fall, below and above, respectively, the single threshold, then the mean phenotypic score is: $np + (n+1)r$.

Consider a series of distributions of given variance spread out along the gene-product scale. The means of these distributions plotted against their corresponding mean phenotypes produce a sigmoid curve. The shape of this curve depends on the relationship between the common standard deviation of the distributions (σ) and the threshold interval (t). Different values of t in relation to σ produce different curves. When $t = 0$, and there is only one threshold, the resulting curve is simply that of the cumulative normal distribution. As t increases, a central plateau in the curve appears. The size of this plateau is an indication of the range in which changes on the gene-product scale have little effect on moving the mean phenotype away from the intermediate value. It is therefore an expression of canalization at this level. Curves for $t = 0$, σ , 2σ and 3σ are illustrated in Figure 2.

These curves, used inversely, represent possible transformations of the data

FIGURE 2.—The relationship between gene product and phenotypic means produced by a series of normal distributions of given variance spread out along the gene-product scale across two thresholds separated by t standard deviations. All curves have been adjusted to the same range. SOrb, POrb, PO and IR refer to supraorbital, postorbital, postoral and interramal vibrissa number.

from the observed mean vibrissa scores to their corresponding class-distribution means on the gene-product scale. The choice of an appropriate transformation allows dominance to be investigated at this more fundamental level.

The appropriate transformation for the one-threshold situation is clearly represented by the curve of $t = 0$. The choice of transformation for the two-threshold situation is based on the postulate that differences between means of different classes on the gene-product scale are due not only to allele substitution at the tabby locus but also to differences in genetic background, and that a given background change moves all class means on the gene-product scale by the same amount in the same direction. Thus, over a number of backgrounds, the variances due to background change at each of the three major-genotype levels are assumed to be equal on the gene-product scale. The transformation which minimizes the differences between these three background variances is therefore considered the most appropriate. For practical purposes, this is represented by the curve which produces, in the transformed data, a ratio between a combined background variance for its extremes (mutant and wild-type homozygote and hemizygote levels), say V_x , and a background variance for its middle (heterozygote level), say V_m , which is closest to unity.

RESULT AND DISCUSSION

The observed mean vibrissa scores for each major-genotype class in each background are shown in Table 1.

In the supraorbital and postorbital groups there were no animals with less than the maximum number of vibrissae in all the wild-type classes. The positions of the distribution means of these classes on the gene-product scale could, therefore, not be estimated. Dominance calculations for these two groups were consequently restricted to untransformed data.

TABLE 1

Mean vibrissa scores for the three major-genotype classes (+, Ta+, TaTa and Ta) in different genetic backgrounds at the supraorbital (SOrb), postorbital (POrb), postoral (PO), and interramal (IR) sites

Allele and background	SOrb			POrb			PO			IR		
	+	Ta+	TaTa plus Ta	+	Ta+	TaTa plus Ta	+	Ta+	TaTa plus Ta	+	Ta+	TaTa plus Ta
<i>Ta^f</i> stock	4.00	3.86	2.12	2.00	1.68	0.00	3.59	2.00	1.82	2.86	2.05	1.21
<i>Ta^f</i> $\frac{1}{2}$ <i>JU</i>	4.00	3.68	2.00	2.00	1.82	0.00	3.59	1.95	0.91	2.95	2.41	1.28
<i>Ta^f</i> $\frac{1}{2}$ <i>A</i>	4.00	3.50	2.24	2.00	1.55	0.00	3.95	2.00	1.45	2.86	1.55	1.05
<i>Ta^f</i> $\frac{3}{4}$ <i>A</i>	4.00	3.45	2.03	2.00	1.27	0.00	3.86	2.00	0.98	2.50	1.14	1.05
<i>Ta^c</i> stock	4.00	3.81	2.10	2.00	2.00	0.05	3.95	2.67	1.65	2.41	2.33	1.26
<i>Ta^c</i> $\frac{1}{2}$ <i>JU</i>	4.00	4.00	2.04	2.00	1.96	0.00	3.32	2.00	0.52	2.91	2.74	1.37
<i>Ta^c</i> $\frac{3}{4}$ <i>JU</i>	4.00	3.77	2.03	2.00	1.36	0.00	2.86	1.86	0.14	2.68	2.27	1.03
<i>Ta^c</i> $\frac{1}{2}$ <i>A</i>	4.00	3.95	2.34	2.00	1.77	0.00	3.91	2.18	1.45	2.77	1.77	1.03
<i>Ta^c</i> $\frac{3}{4}$ <i>A</i>	4.00	3.59	2.27	2.00	1.73	0.03	3.95	2.09	1.41	2.55	1.64	1.03

Each row contains data collected for either *Ta^f* or *Ta^c* in one background group. Each figure represents the mean score at one site in one class of animals. Figures in the bilateral groups are the means of individuals, not sides.

The postoral and interramal observations were transformed for several different values of t , and estimates of V_x and V_m were made on each transformed scale. The two background variances were estimated by first calculating the squared deviations of the mean vibrissa scores of each genotypic class for each allele, from its own within-genotype within-allele mean. The deviations of the wild-type and tabby homozygote or tabby hemizygote classes were then averaged to arrive at an estimate of V_x , and the deviations of the heterozygote classes were averaged to arrive at an estimate of V_m .

In the postoral group, the two variances were equal with a t value between 2σ and 3σ . The value of $t = 2.5\sigma$, with $V_x/V_m = 0.94$, was taken to be representative of this. At $t = 2\sigma$, $V_x/V_m = 2.06$; and at $t = 3\sigma$, $V_x/V_m = 0.49$. The transformations included in this range are enclosed in the area between the $t = 2\sigma$ and $t = 3\sigma$ curves in Figure 2.

In the interramal group, the two variances were most nearly equal when $t = 0$, with $V_x/V_m = 0.53$. This clearly could not have been the true value of t as some mice did have 2 interramal vibrissae. However, transformation is rather insensitive to changes in t in the range $t = 0$ to $t = \sigma$. This is illustrated in Figure 2 by the similarity of the $t = 0$ and $t = \sigma$ curves. A small threshold interval would therefore be just as compatible with this result as none at all. At $t = \sigma$, V_x/V_m was only reduced to 0.34.

The degree of dominance is defined as d/a where $2a$ is the difference between wild-type and mutant homozygote (or hemizygote) values, and where d is the amount by which the heterozygote exceeds $\bar{H}$, the mid-homozygote point. Thus if $d = 0$, then $d/a = 0$, and there is no dominance; if $d = +a$, then $d/a = +1$, and the wild-type allele is completely dominant over the mutant allele; and if $d = -a$, then $d/a = -1$, and the mutant allele is completely dominant over the wild-type allele.

The degree of dominance on the gene-product scale was calculated for each allele in each genetic background following transformation with $t = 2\sigma$, 2.5σ , and 3σ , for the postoral group; and transformation with $t = 0$ and $t = \sigma$ for the interramal group. The results, together with those of similar calculations in the untransformed data of all four groups, are illustrated in Figure 3. Each point in Figure 3 represents the degree of dominance calculated from the means of the three major-genotype classes for one allele in one background group.

The tendency at the phenotypic level was for a greater degree of dominance over wild-type to be associated with Ta^f than with Ta^c , but there was considerable overlap between the alleles in all vibrissa groups. Transformation of the postoral and interramal data had a marked effect on this overlap. All transformations in the ranges $t = 2\sigma$ to $t = 3\sigma$ for the postoral group, and $t = 0$ to $t = \sigma$ for the interramal group, reduced overlap. The transformations estimated to be the most appropriate on the basis of equality of background variance ($t = 2.5\sigma$ for the postoral group, and $t = 0$ for the interramal group) produced complete and maximal separation between alleles, and resulted in minimal variance of degree of dominance within alleles. The clarity of these results suggests that the assumptions involved in the model were not unreasonable.

FIGURE 3.—The degree of dominance on the phenotypic scale (P) for the supraorbital (SOrb), postorbital (POrb), postoral (PO), and interrimal (IR) vibrissa groups; and the degree of dominance on transformed scales for different values of t in the postoral and interrimal groups. Each point represents the degree of dominance associated with one allele in one background genotype group. Closed circle = Ta' ; open circle = Ta^c .

The nature of the dominance calculation is such that inequality of background variance at the three major-genotype levels imposes an association between d/a and the general level of expression in any one background, which can be represented by $\bar{H}$, the mid-homozygote point. If the extreme genotypes vary more than the heterozygote, d/a will be negatively correlated with $\bar{H}$. This was the case with the postoral vibrissa scores, where the correlation between d/a and $\bar{H}$ was $r = -.80$. Conversely, if the extreme genotypes vary less than the heterozygote, d/a will be positively correlated with $\bar{H}$. This was the case with the interrimal scores, where the correlation of d/a with $\bar{H}$ was $r = +.42$. An indication of the efficiency of the most appropriate transformations is that, in the transformed data, the correlation of d/a with $\bar{H}$ demonstrated no significant association between dominance and general level of expression ($r = -.14$ and $r = +.15$ in the postoral and interrimal groups, respectively).

These transformations increased the correlation between degree of dominance in the postoral and interrimal groups from $r = .59$ (untransformed) to $r = .73$ (transformed). This increase with transformation is good evidence for a real dominance association between these two groups. The correlation between degree of dominance in the untransformed supraorbital and postorbital data was also $r = .59$, but, as no transformation could be made, it is possible that $r = .59$ represents an association between the general levels of expression in the two groups. However, as evidence that it represents a dominance association, at least

TABLE 2

Values of d/a on transformed scales for Ta^f and Ta^c , and D , the absolute value of the difference between them in different backgrounds, for the postoral (PO) and interramal (IR) vibrissa groups

		$\frac{3}{4}$ JU	$\frac{1}{2}$ JU	Stock	$\frac{1}{2}$ A	$\frac{3}{4}$ A
PO ($t = 2.5\sigma$)	Ta^f	..	-.29	-.48	-.40	-.22
	Ta^c	-.06	+.04	+.20	.00	-.15
	D	..	0.33	0.68	0.40	0.07
IR ($t = 0$)	Ta^f	..	+.06	-.03	-.20	-.62
	Ta^c	+.60	+.56	+.87	+.12	+.18
	D	..	0.50	0.90	0.32	0.80

to some extent, the correlations of d/a values of each of these two groups with d/a on the transformed scale of the postoral and interramal groups (shown above to be independent of general level of expression) were all around $r = .50$. Thus, common fluctuations in the degree of dominance, for whatever reason, appear to be expressed in all four vibrissa groups.

Finally, it should be mentioned that this demonstration of a dominance difference does not necessarily imply an intrinsic difference between the alleles. There is evidence that gene activity on the X chromosome is controlled from an "inactivation center," and that different X chromosomes may have different inactivation properties (RUSSELL 1964; CATTANACH and ISAACSON 1967). Moreover, the inactivation center appears to be in the neighborhood of the tabby locus (RUSSELL and MONTGOMERY 1965). Thus, an apparent difference between alleles could be accounted for by a difference between closely linked controlling factors derived from the two mutant stocks. Evidence for the existence of controlling factors is provided by the fact that the difference between the alleles appeared to be reduced by crossing. Table 2 shows d/a values for Ta^f and Ta^c , and the absolute value of the difference between them (D), for the different levels of inbred backgrounds on the best transformed scales of the postoral and interramal vibrissa groups. The tendency was for D to decrease as the background was made more common to both alleles.

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SUMMARY

In all the secondary facial groups of vibrissae there was a suggestion of a difference in dominance between Ta^f and Ta^c on a number of genetic backgrounds at the phenotypic level. Common fluctuations in dominance appeared to be reflected

in all vibrissa groups. Observed postoral and interramal vibrissa scores were each transformed to a postulated continuous scale of amount of gene product, and in each case the transformation judged to be the most appropriate on the basis of other criteria resulted in complete separation of the alleles with respect to degree of dominance, minimal variance of degree of dominance within alleles, and a high positive correlation between degrees of dominance in these two vibrissa groups. There is therefore little doubt that there was a real dominance difference associated with the alleles at a fundamental level. However, at least some of this difference appeared to be attributable to a difference between controlling factors derived from the two original mutant stocks.

LITERATURE CITED

- CATTANACH, B. M. and J. H. ISAACSON, 1967 Controlling elements in the mouse X chromosome. *Genetics* **57**: 331-346.
- FALCONER, D. S., 1953 Total sex-linkage in the house mouse. *Z. Vererbbl.* **85**: 210-219.
- FRASER, A. S. and B. M. KINDRED, 1962 Selection for an invariant character, vibrissa number, in the house mouse. III. Correlated responses. *Australian J. Biol. Sci.* **15**: 188-206.
- FRASER, A. S., T. NAY and B. M. KINDRED, 1959 Variation of vibrissa number in the house mouse. *Australian J. Biol. Sci.* **12**: 331-339.
- Mouse News Letter, 1963. **29**: 40.
- Mouse News Letter, 1966. **35**: 24.
- RUSSELL, L. B., 1964 Another look at the single-active X hypothesis. *Trans. N.Y. Acad. Sci.* **26**: 726-736.
- RUSSELL, L. B. and C. S. MONTGOMERY, 1965 The use of X-autosome translocations in locating the X chromosome inactivation center. *Genetics* **52**: 470-471.
- SOFAER, J. A., 1969 Aspects of the tabby-crinkled-downless syndrome. II. Observations on the reaction to changes of genetic background. *J. Embryol. Exptl. Morphol.* **22**: 207-227.