

Fluctuating asymmetry in the *Mus musculus* hybrid zone: a heterotic effect in disrupted co-adapted genomes

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SUMMARY

Developmental stability reflects the organism's ability to buffer minor developmental accidents and is often estimated by measuring the fluctuating asymmetry. Either implicitly or explicitly, numerous authors have assumed that developmental stability is correlated with overall fitness. If this is the case, changes in morphological asymmetry across a hybrid zone could be used as a measure of the selection on hybrid genomes. Developmental stability in hybrid populations is theoretically related to the genetic distance between hybridizing taxa, and results from a balance between the stabilizing effect due to increased heterozygosity and the disruptive effect caused by breakdown of genomic co-adaptation. Here we have compared the amount of fluctuating asymmetry across a transect of the hybrid zone between the two European subspecies of the house mouse (*Mus musculus domesticus* and *M. m. musculus*) in Denmark. For the first time in any natural hybrid zone we found an increased developmental stability in the populations with mixed genomes. Moreover, the apparently beneficial effect of hybridization on the developmental stability of the hybrid mice contrasts with the results of both genetic and parasitological studies which show that hybrid dysgenesis occurs in this zone. Our results suggest that the barrier to gene flow in the *Mus musculus* hybrid zone may result from the disruption of relatively few gene systems. They also lead us to reassess the relation between developmental stability expressed as fluctuating asymmetry, co-adaptation and overall fitness.

1. INTRODUCTION

Hybrid zones occur when two genetically distinct populations meet, mate and produce offspring of mixed ancestry (Barton & Hewitt 1989; Harrison 1990). The dynamics and the evolutionary fate of a hybrid zone will depend on the selective forces acting on it. Several models propose that hybrid zones are transient phenomena and that hybridization will lead either to speciation or to fusion of hybridizing taxa (Endler 1977). Other models consider hybrid zones as stable barriers maintained either as the result of a balance between gene flow and selection (Barton 1979; Barton & Hewitt 1985) or a balance of selection in favour of hybrids in an ecotone (Moore 1977).

The house mouse, *Mus musculus*, which underwent a recent radiation followed by range expansion (Boursot *et al.* 1993; Sage *et al.* 1993) provides a good model for investigating the relative importance of independent genetic divergence and selection after secondary contact in the process of speciation. Two subspecies are present in Europe: *Mus musculus domesticus*, which occurs in western and southern Europe, and *M. m. musculus*, which is found in eastern and northern

Europe. A narrow hybrid zone resulting from secondary contact between the two subspecies crosses Europe from Denmark to Bulgaria (see Boursot *et al.* 1993; Sage *et al.* 1993 for review). The initial contact probably occurred 6000 years ago in south-east Europe when *M. m. domesticus* moved up from the Mediterranean basin and *M. m. musculus* moved in from continental Europe (Auffray *et al.* 1990, 1992). In northern Europe they are not thought to have met before 2400 years ago. Autosomal, mitochondrial and sex chromosome markers have been analysed across several transects of the 1200 mile zone, and they show similar introgression patterns whether in Denmark (Hunt & Selander 1973; Vanlerberghe *et al.* 1986; Vanlerberghe *et al.* 1988a), Germany (Sage *et al.* 1986; Tucker *et al.* 1992; Prager *et al.* 1993) or Bulgaria (Vanlerberghe *et al.* 1986, 1988b). Within a transect, the centres of the various clines are all coincident in location, although those of the sex chromosomes are much steeper than those for the other markers. The similarity between the patterns of introgression across the geographically different transects suggests that this contact zone is a tension zone (Sage *et al.* 1986; Vanlerberghe *et al.* 1988a) maintained by two opposing

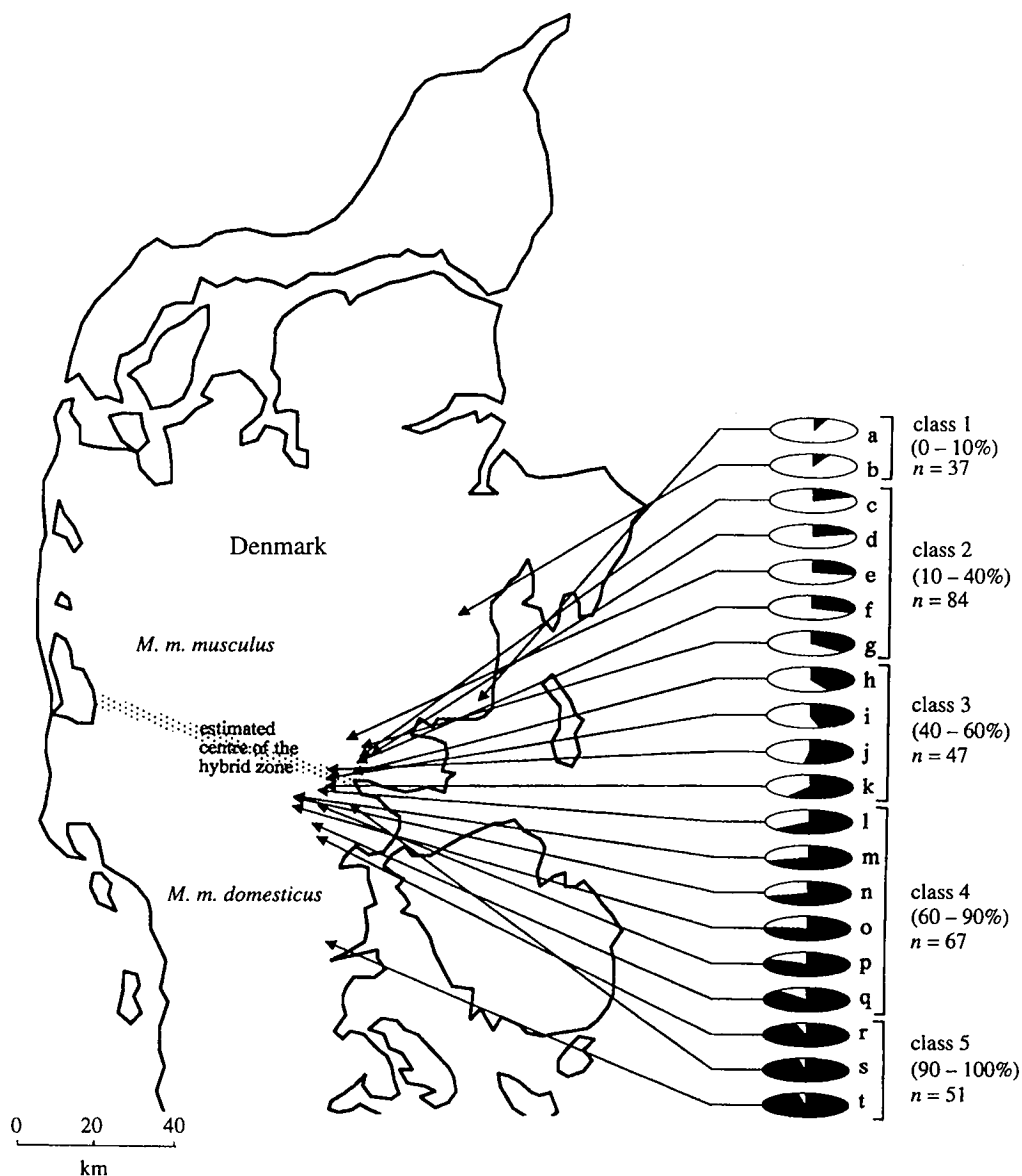


Figure 1. Location of sample sites across the Danish hybrid zone. Samples were grouped in five classes according to their introgression index (n = sample size). Black and white portions correspond to the percentage of *Mus musculus* alleles and *M. m. domesticus* alleles, respectively. Localities (values in parentheses represent the introgression index): a, Gosmer (5%); b, Klank (6%); c, Kollerup (19%); d, Baastrup (21%); e, Givskud (28%); f, Hörup (31%); g, Vindelev (37%); h, Rugballe (43%); i, Balle (46%); j, Södover (52%); k, Raving (59%); l, Store-Lihme (64%); m, Plougslund 1 (70%); n, Plougslund 2 (70%); o, Tröllund (76%); p, Ödsted (82%); q, Törskind (88%); r, Egtved (96%); s, Jerlev (97%); t, Simmersted (97%).

forces: the rate of dispersal of the individuals across the zone, and the selection against hybrids due to the disruption of differentiated gene systems in the mixed genomes (Barton 1979; Barton & Hewitt 1985). The steep clines for the sex chromosomes suggest that selection on sex chromosomes is stronger than on the other loci studied (Vanlerberghe *et al.* 1986, 1988*b*; Tucker *et al.* 1992; Dod *et al.* 1993).

However, there is little direct evidence of hybrid unfitness in the contact zone, and the only known phenotypic trait that suggests selection against hybrids is the greater susceptibility of the hybrid populations to intestinal worms (Sage *et al.* 1986; Moullia *et al.* 1991). This differential susceptibility to infestation is genetically determined (Moullia *et al.* 1993) and is thought to be due to a disruption of the co-adapted gene systems involved in the immune response to these parasites in

mice with hybrid genomes. Before an overall picture of the selective forces acting on this zone can be obtained, other estimations of selection need to be made.

It is difficult to estimate fitness in natural populations directly, so several studies have proposed that the degree of developmental stability can be used in its place (Tebb & Thoday 1954; Soulé 1982; Leary *et al.* 1984; Jones 1987). Developmental stability is generally defined as the ability of organisms to correct perturbations occurring during development. Given that the two sides of a bilaterally symmetrical character of an organism are produced by the same genome, any random deviation from symmetry is considered to reflect a reduction in developmental stability. These small random differences are commonly defined as fluctuating asymmetry (FA) (Van Valen 1962). Increased FA is known to occur under both genomic and

environmental stresses, and therefore has often been associated with reduced fitness of individuals and a lack of adaptation of a population as a whole (Tebb & Thoday 1954; Soulé 1982; Leary *et al.* 1984; Jones 1987).

Although the genetic basis of developmental stability is still under discussion (Clarke 1993), two major genomic factors are commonly invoked: heterozygosity, and genomic co-adaptation. Numerous reports have focused on the relation between heterozygosity and developmental stability. Even if some authors have pointed out that such a relation is less clearly established in homoiotherms than in poikilotherms (Handford 1980; Wooten & Smith 1986), a significant positive correlation between heterozygosity and stability of development has been reported in many studies. Homozygous individuals exhibit higher levels of FA, and thus are considered to be less developmentally stable than heterozygous ones (Vrijenhoek & Lerman 1982; Leary *et al.* 1984; Mitton & Grant 1984). The biological explanation is still unknown, but heterotic mechanisms of dominance, over-dominance or fortuitous combination of particular genes are generally invoked (Vrijenhoek & Lerman 1982; Leary *et al.* 1984; Mitton & Grant 1984). The relation between developmental stability and genomic co-adaptation is even more speculative (for review see Graham (1992)), but the best evidence comes from several studies reporting higher FA levels in hybrid populations between species (Graham 1992; Clarke 1993). Mixing two distinct genomes which have evolved independently is thought to reduce the efficiency of the developmental processes by disruption of the coordination between genes (Soulé 1967).

Developmental stability in hybrid populations should result from a balance between the stabilizing effect due to increased heterozygosity and the disruptive effect caused by breakdown of genomic co-adaptation. In theory, the relative importance of the opposing effects depends on the genetic distance between the hybridizing taxa (Graham 1992).

The aim of our study was to determine to what extent *M. m. domesticus* and *M. m. musculus* have diverged in terms of gene systems coordinating development, and hence, by using a highly multigenic character, to estimate the degree of selection which occurs in this hybrid zone.

2. MATERIALS AND METHODS

FA was measured in several populations of house mice collected from 1985 to 1992 along a transect of the hybrid zone in Denmark. As hybrid zones are composed of subpopulations which may have different developmental stabilities that are related to their introgression levels (Graham 1992; Palmer & Strobeck 1992), hybrids were not treated as a single group. Grouped in this way, the combination of subpopulations may have leptokurtic distribution (i.e. with long tails and high mean), and some FA indices could be sensitive to non-normality (Palmer & Strobeck 1986). It is also possible that a single hybrid population which contains a majority of slightly introgressed individuals would mask the effect of hybridization of the more introgressed individuals. Because, in our study, the

populations from several localities did not exhibit sample size high enough to be treated individually, we grouped them into five classes (figure 1) on the basis of their allozymic introgression index.

This index corresponds to the percentage of *M. m. domesticus* alleles averaged over 7–10 diagnostic loci (Vanlerberghe *et al.* 1986; B. Dod & A. Orth, unpublished results). Class 1 and 5, although very slightly introgressed, can be considered genetically as potential parental populations.

Asymmetry was estimated on the width (WM) and length (LM) of the three lower molars (M_1 , M_2 and M_3) using a 'Nikon measuroscope' measuring to 0.001 mm accuracy. All measurements were made by S.R. As recommended by Palmer & Strobeck (1986), the choice of the FA index requires preliminary data treatments to detect factors liable to affect its discriminatory ability. We first did a two-way mixed-model ANOVA (side (right or left): fixed, introgression class: random) adapted from Palmer & Strobeck (1986) on the raw measurement dataset. This analysis showed that, for the six characters, mean squares were not significant for side factor, showing that neither side was consistently larger than the other and, thus, excluding the occurrence of directional asymmetry (LM_1 , $F_{[1,566]} = 0.046$, n.s.; LM_2 , $F_{[1,566]} = 3.015$, n.s.; LM_3 , $F_{[1,566]} = 0.000$, n.s.; WM_1 , $F_{[1,566]} = 0.323$, n.s.; WM_2 , $F_{[1,566]} = 1.995$, n.s.; WM_3 , $F_{[1,566]} = 0.000$, n.s.). Normality tests were done on the distribution of the right minus left values (R–L) to test the presence of systematic non-directional deviation from bilateral symmetry (i.e. antisymmetry). Fisher's method for combining independent tests (Manly 1985) applied for each character did not reveal any antisymmetry (LM_1 , $\chi^2_{[10]} = 12.71$, n.s.; LM_2 , $\chi^2_{[10]} = 16.07$, n.s.; LM_3 , $\chi^2_{[10]} = 16.43$, n.s.; WM_1 , $\chi^2_{[10]} = 13.06$, n.s.; WM_2 , $\chi^2_{[10]} = 14.22$, n.s.; WM_3 , $\chi^2_{[10]} = 15.127$, n.s.). Normality of these distributions also suggests an apparent homogeneity between developmental stabilities of the constituting populations of the introgression classes. Size scaling appeared unnecessary as no correlations were found between the magnitude of FA (R–L) and character size (R+L) (LM_1 , $r = -0.013$; LM_2 , $r = -0.181$; LM_3 , $r = -0.101$; WM_1 , $r = -0.134$; WM_2 , $r = -0.018$; WM_3 , $r = -0.030$; none of the p values obtained by the sequential Bonferroni technique (Rice 1989) were significant). Finally, no effect of sex was detected (LM_1 , $F_{[1,280]} = 3.57$, n.s.; LM_2 , $F_{[1,280]} = 0.80$, n.s.; LM_3 , $F_{[1,280]} = 0.68$, n.s.; WM_1 , $F_{[1,280]} = 1.75$, n.s.; WM_2 , $F_{[1,280]} = 0.18$, n.s.; WM_3 , $F_{[1,280]} = 0.08$, n.s.).

In the light of these preliminary treatments, the FA levels within the five introgression classes were assessed, for the six characters, by the variances of the distribution of the individual R–L values (Palmer & Strobeck 1986). In this manner, each introgression class was characterized by six FA indices. Comparisons between introgression classes were assessed by two tailed F -tests with the correction of the sequential Bonferroni technique on the p values. In addition, Kendall's coefficient of concordance (W) was used to test the independence of the ranking order, obtained on the basis of the FA levels for each character, between the introgression groups (Siegel & Castellan 1980).

3. RESULTS

For all the characters except LM_3 , the FA levels clearly decreased towards the centre of the hybrid zone (figure 2a). When equivalent introgression classes are considered, i.e. *M. m. musculus* or *M. m. domesticus* classes having the same proportion of foreign diagnostic alleles, there are no differences between levels of FA for all characters. This was tested by the variance ratio

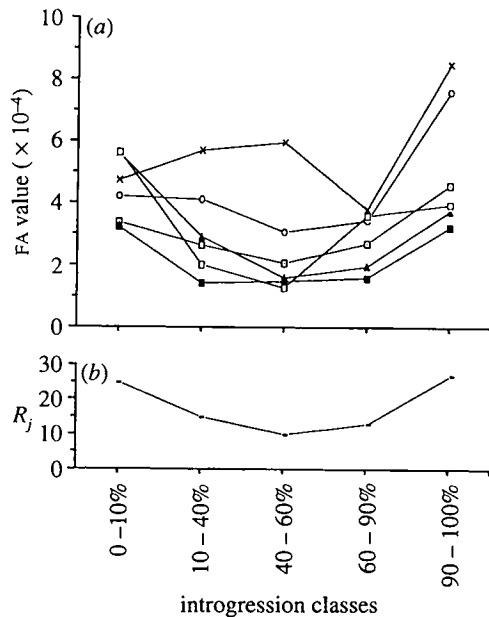


Figure 2. Fluctuating asymmetry (FA) levels across the hybrid zone. (a) FA levels in the five introgression classes for the six characters (LM, lower molar lengths, WM, lower molar widths): LM₁ (dotted open squares), LM₂ (open circles), LM₃ (crosses), WM₁ (filled triangles), WM₂ (filled squares), WM₃ (open squares). (b) Graphic representation of the sum of the ranks (R_j) of the FA levels for each character across the five introgression classes. Note that an estimation of the overall rank of the introgression classes is obtained by ordering the R_j .

between classes 1 and 5 and between classes 2 and 4 (table 1).

This allows us to conclude that in equivalent introgression classes the FA values are the same in the two parental backgrounds. However, between the parental genotypes (classes 1 and 5) and the ones found in the centre of the hybrid zone (class 3), the FA levels are statistically different for all molar widths and for LM₁ and LM₂ between classes 3 and 5.

We found no significant correlation between the

bilateral differences of the six characters (class 1, $-0.252 < r < 0.413$; class 2, $-0.156 < r < 0.251$; class 3, $-0.136 < r < 0.308$; class 4, $-0.091 < r < 0.291$; class 5, $-0.358 < r < 0.318$; no significant p values by the sequential Bonferroni technique per class), which excludes an 'organism-wide' or 'dentition-wide' effect on the degree of FA and suggests that within individuals the R-L values are independent. Despite the peculiar pattern of FA exhibited by LM₃, Kendall's coefficient of concordance shows that the ranking order of introgression groups obtained on the basis of the FA levels for each character are not independent ($w = 0.633$; $p < 0.01$). In other words, these results imply a significant association of FA levels at a population level but not at an individual level. Moreover, the overall rankings of these groups (R_j values) confirms that there is a global and symmetrical decrease of FA towards the centre of the hybrid zone (figure 2b), suggesting that hybridization plays a significant role on the developmental stability of the dental characters considered.

4. DISCUSSION

If FA does in fact reflect general developmental stability (Van Valen 1962; Soulé 1967; Soulé & Cuzin-Roudy 1982; Leary *et al.* 1984; Leary & Allendorf 1989), our results on molars suggest that, in the *M. musculus* hybrid zone, mice with mixed genomes are developmentally fitter. This contrasts with the decrease in reproductive fitness in hybrids that is suggested by the reduced sex chromosome introgression across the zone (Vanlerbergh *et al.* 1986, 1988b; Tucker *et al.* 1992; Dod *et al.* 1993). The higher parasite loads of hybrids also suggests that disruption of some other co-adapted gene system occurs. Our results therefore suggest that, even at the level of divergence that exists between *M. m. domesticus* and *M. m. musculus*, the increase in heterozygosity, at the loci involved in such a polygenic character as tooth morphology, have a greater effect on developmental stability than the

Table 1. F values (variances ratios of R-L distributions) obtained to compare FA levels between introgression classes for the six characters considered

(Probabilities calculated by the sequential Bonferroni technique per line.)

| Introgression classes compared | LM ₁ | LM ₂ | LM ₃ | WM ₁ | WM ₂ | WM ₃ |
|--------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| 1-2 | 1.291 | 1.036 | 1.203 | 1.910 | 2.246* | 2.806*** |
| 1-3 | 1.671 | 1.393 | 1.256 | 3.556*** | 2.224* | 4.412*** |
| 1-4 | 1.267 | 1.242 | 1.251 | 2.841** | 2.068 | 1.588 |
| 1-5 | 1.355 | 1.798 | 1.791 | 1.483 | 1.010 | 1.432 |
| 2-3 | 1.294 | 1.345 | 1.044 | 1.862 | 1.010 | 1.572 |
| 2-4 | 1.019 | 1.199 | 1.505 | 1.487 | 1.086 | 1.767 |
| 2-5 | 1.717 | 1.863* | 1.489 | 1.288 | 2.223** | 1.959* |
| 3-4 | 1.319 | 1.121 | 1.571 | 1.252 | 1.076 | 2.779** |
| 3-5 | 2.263* | 2.505** | 1.426 | 2.398* | 2.202* | 3.080** |
| 4-5 | 1.717 | 2.234* | 2.241* | 1.915* | 2.047* | 1.108 |

* $p < 0.05$.

** $p < 0.01$.

*** $p < 0.001$.

disruption of intraspecific genomic combinations. These results for hybrid mice with highly recombined genomes are similar to heterosis reported for F₁ crosses between isogenic strains of laboratory mice whose genomes have a much lower degree of differentiation. Bader (1965), using lower molar width measurements, concluded that, for all three teeth, inbred strains of mice had a lower developmental stability than the hybrids obtained when they were crossed. Similarly, Leamy (1984, 1992), studying ten pairs of osteometric traits, found that the inbred strains of mice showed significantly more FA than the hybrids.

Until now, however, it has been argued that, at the level of genetic divergence found in natural interspecific or intersubspecific hybridization, the effect due to the disruption of differentiated co-adapted gene systems should be greater than that due to heterosis (Graham & Felley 1985; Zakharov 1989; Graham 1992; Clarke 1993). This was supported by the fact that there have been no earlier reports of heterosis in hybrids (for review see Graham (1992)). A decrease in developmental stability, expressed either as an increase in FA or as an increased frequency of developmental abnormality, was found in 8 of the 15 studies cited in this review and occur in a variety of organisms including birds (unpublished results cited in Graham (1992)), fish (Graham & Felley 1985; Leary *et al.* 1985; Zakharov 1989), frogs (Watson 1972; Szymura & Barton 1986), insects (Ross & Robertson 1990) and plants (Manley & Ledig 1979). To explain why nearly half of the studies showed no differences in FA between parental and hybrid populations (Jackson 1973; Felley 1980; Vrijenhoek & Lerman 1982; Lamb *et al.* 1990; Freeman *et al.* 1991), Graham & Felley (1985) suggested that, when the zone is old enough, selection of newly co-adapted gene systems may appear and maintain the stability of development in hybrid genomes. Nevertheless, on the basis of the available data it is difficult to assess the correlations between the age of a hybrid zone, the degree of differentiation of the parental populations and developmental stability. However, it is possible that, in some of these cases, differences in developmental stability may have been masked because the hybrids were not grouped according to their degree of introgression (see Methods).

Because of the large number of gene systems that are presumably involved in development, its stability has been considered to reflect the co-adaptation of the entire genome (Zakharov 1989; Graham 1992). Our results, however, suggest that, although tooth ontogeny appears to profit from heterosis, other gene systems, such as those involved in the immune response to parasites and sex chromosome functions, appear to be more sensitive to disruption in recombined genomes. The apparently opposite effect that hybridization has on these different functions is in some ways similar to the somatic vigour exhibited by many sterile hybrids. In spite of their sterility, they are often more viable or show a faster rate of growth than either parental species (see, for example, Dobzhansky 1937). Hybridization has also been shown to affect reproduction but not developmental stability in inter-genera hybrids between bison (*Bison bonasis*) and domestic cattle (*Bos*

taurus) (unpublished results cited in Graham (1992)). In the *Mus musculus* hybrid zone, the contrasting results provided by the different approaches imply that the effects of hybridization differ with the system investigated. This could be related to the particular type function. For instance, one might expect a co-adapted gene system that depends on a limited number of strongly interactive genes to be more sensitive to breakdown than a highly multigenic character with a phenotype that results from the addition of many genes that are only weakly interactive or to a large extent independent. In addition, the greater disruption of gene systems involving the sex chromosomes may also reflect a faster rate of evolution compared with the autosomes that results from the lack of recombination between the hemizygous sex chromosomes in males (Coyne 1992).

Our results show, therefore, that there is not necessarily a direct correlation between developmental stability as measured by FA and overall hybrid fitness in natural hybrid zones as heterotic effects are not necessarily negligible. Graham (1992) has pointed out that, in hybrids, the relation between developmental stability and reproductive fitness is complex, and that these two parameters may be out of phase. This is because the development and survival of parents are pre-meiotic components of reproductive success, whereas viability of gametes and survival of offspring are post-meiotic. At present, the strength of the barrier to gene flow between the two *Mus musculus* populations is difficult to estimate, and it is not known to what extent the increased parasite load in the hybrid mice affects their survival. Our results, therefore, support the possibility that there is a correlation between a decrease in FA and an overall increase in viability. If this is the case then the genomic disruption in this hybrid zone must be limited to relatively few systems. Linkage disequilibrium, due to the clustering of alleles derived from the same parental populations that results from balance between dispersion and selection against hybrids (Barton & Gale 1993), is predicted to be maintained in a hybrid zone. The fact that it has not been detected for the autosomal protein markers studied so far (Hunt & Selander 1973; B. Dod, unpublished data) also suggests that the number of loci that come under selection may not be very large.

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