Genetica **89**: 297–305, 1993.

Behavioral phenodeviance: a Lerneresque conjecture

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Received 11 May 1993 Accepted 17 May 1993

Abstract

Developmental instability, detectable in morphological and meristic characters, is typically associated with reduced fitness. The actual mechanism by which fitness is reduced in these cases is difficult to identify. We propose that developmental instability also manifests itself at the behavioral level and that when this occurs, behavioral phenodeviance is the result. According to this model, abnormal or phenodeviant behavior compromises fitness. Examples are provided from *Drosophila* and man.

Introduction

Understanding the mechanisms which maintain genetic variation in natural populations is a major goal of evolutionary biology. While mutational and recombinational events generate the original sources of all heritable variation, other evolutionary forces such as drift or directional selection act to reduce genetic variation. Balancing or stabilizing selection, on the other hand, is attributed with being a major variation-maintaining process. While examples of balancing selection are more easily defined for single rather than multiple locus systems, the mechanism of the disadvantage to homozygotes is not usually well understood. Below, we propose a model in which a major phenomenon underlying balancing selection is the 'behavioral phenodeviance' of phenotypically extreme individuals and of homozygotes in general.

In order to develop this concept, we will first review I. Michael Lerner's original concept of morphological phenodeviance and its genetic and developmental basis as presently understood. We will then define the term 'behavioral phenodeviant', going on to exemplify the concept by drawing upon observations in *Drosophila* and man.

Phenodeviants: genetics and developmental homeostasis

Lerner (1954) coined the term 'phenodeviant' to designate the sporadic occurrence of abnormal morphological deviants caused by multigenic Mendelian inheritance in which chance segregation produces a small number of individuals who are homozygous at a certain threshold level of trait-relevant loci. Lerner observed an increase in these morphological abnormalities, such as crooked toes in chickens, as a consequence of processes which increase population homozygosity, i.e. artificial selection and inbreeding.

Lerner linked the appearance of morphological phenodeviants to the reduced ability of homozygotes to display developmental homeostasis or ontogenetic self-regulation. The opposite is true of heterozygotes, whose enhanced ability to self-regulate following developmental disturbances results in a more canalized, evolutionarily pre-programmed phenotype. Homozygosity thus can be seen as eroding the buffering capability of the epigenetic landscape conceptualized by Waddington (1957), leading to a less canalized phenotype. Figure 1 has been adapted from Lerner to illustrate this concept for continuously distributed traits having a polygenic basis. The predicted relationship be-

tween the increased number of homozygous loci and reduced developmental homeostasis is clearly seen. The way in which inbreeding, which increases homozygosity, might result in the production of phenodeviants follows from the figure. In addition, by examining this relationship in the broader context of the Gaussian distribution of phenotypes for a quantitative trait, the link between individual developmental homeostasis and populational or genetic homeostasis becomes clear as well: extreme phenotypes found in the tails of the distribution tend to be more homozygous and thus should be less developmentally stable.

An increase in homozygosity, brought about either by inbreeding or by artificial directional selection, is known to reduce fitness. A certain level of homozygosity automatically will be generated by segregation, but is further increased by inbreeding or by artificial directional selection. In natural populations the reduced fitness of homozygous

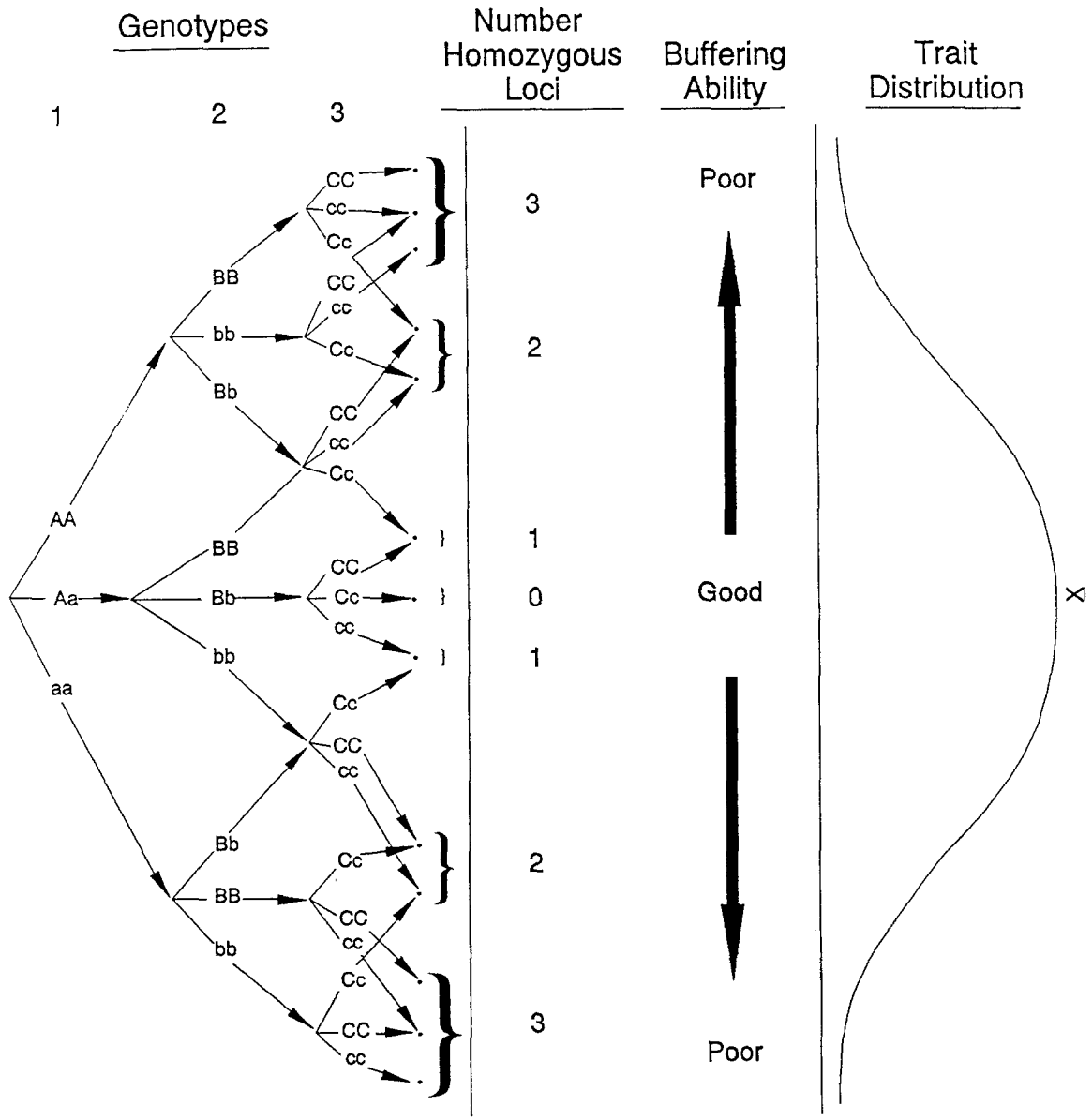

Fig. 1. Hypothetical relationship between three locus genotypes underlying a quantitative trait, phenotype distribution, and buffering ability. Although no dominance or recessiveness exists, upper and lower case letters are used for simplicity. Elements of this figure are based upon Lerner (1954).

phenotypic extremes should result in balancing selection, and thus in the maintenance of heterozygosity and phenotypes which cluster near the population mean.

Several relationships remain unclear in this proposed scenario. One is exactly how, at the physiological level, heterozygosity results in increased developmental stability or buffering. While there is evidence in the literature to support a link between heterozygosity and developmental stability in some systems (Leary, Allendorf & Knudsen, 1984), a number of studies have failed to find this relationship (Patterson & Patton, 1990; Hartl *et al.*, 1991; Zink, Smith & Patton, 1985; Zakharov, 1987), leading Zakharov (1992) to suggest that certain loci, such as those affecting growth rate, are more important than others in their influence on developmental homeostasis. Clarke (this volume) credits reduced coadaptation, rather than homozygosity *per se*, with being the cause of developmental instability in the majority of cases in which there is a genetic component. The issue of mechanisms needs to be addressed empirically across a broad range of taxa.

Another related issue is how impaired developmental stability actually reduces reproductive fitness. The nature of those phenotypic elements underlying reduced fitness are addressed in the model proposed below. A typical effect of inbreeding and artificial selection is the loss of reproductive capacity. However, inspection of the non-reproductive individuals frequently fails to reveal any consistent phenotypic explanation, i.e. reproductive systems are intact and functional, and no gross physical abnormalities are apparent which appear capable of impeding successful reproduction.

It is in these cases that we propose the importance of aberrations in the behavioral phenotype, which usually go undetected because they are rarely the subject of investigation. 'Behavioral phenodeviants' may be defined as sporadically occurring, behaviorally abnormal phenotypes whose inheritance modes are difficult to identity. As with morphological phenodeviants, their incidence may be increased with inbreeding or selection. While their structural and neurophysiological bases may be less developmentally severe, enabling them to reach adulthood, the delicate nature of the relationship between species-appropriate (canalized) behavior and survival and reproduction may make such individuals more vulnerable to exclusion from the pool of eligible mating partners during the mature stages in their lives. While a number of non-genetic stressors (e.g. teratogens such as alcohol or cocaine) may also alter the behavioral phenotype, we confine our discussion to those phenotypes generated by the same genetic mechanisms as the morphological phenodeviants described by Lerner (1954) and discussed by Zakharov (1992), whether these are associated with single or multilocus homozygosity or with loss of coadaptation leading to interlocus interactions such as epistasis.

Mechanisms of behavioral phenodeviance

The most broadly employed measure of morphological developmental instability is fluctuating asymmetry (FA). Simply described, FA is the difference between the right and left sides for paired bilateral traits. Because the deviations from symmetry in FA are random with respect to side, they will be distributed about a mean of zero. The larger the unsigned difference between sides, the greater the developmental instability (but see Palmer, Strobeck & Chippindale, this volume).

What are the potential mechanisms by which developmental instability could reduce fitness? One possibility is that asymmetries measured in bilateral structures examined are the actual cause. We agree with Clarke and McKenzie (1992) that this is unlikely. It is difficult to envision, for example in *Drosophila*, why different numbers of sternopleural bristles on the right and left sides should cause reduced mating success. A similar argument exists for the dermatoglyphic asymmetries in schizophrenic subjects. It is unlikely that finger ridge asymmetry causes reduced fitness. We propose instead, that in these cases, the organ system controlling behavior, the central nervous system, exhibits developmental instability which then goes on to impair the normal behavioral repertoire expected for the species. Thus the FA revealed in ridge counts is simply the echo of endophenotypic CNS developmental instability. This model is schematically presented in Figure 2. The bilateral CNS illustrated is a simplified representation of the hemispheric organization found in man and other vertebrates. However, it can easily be extended to invertebrates, especially those with a segmental somatic

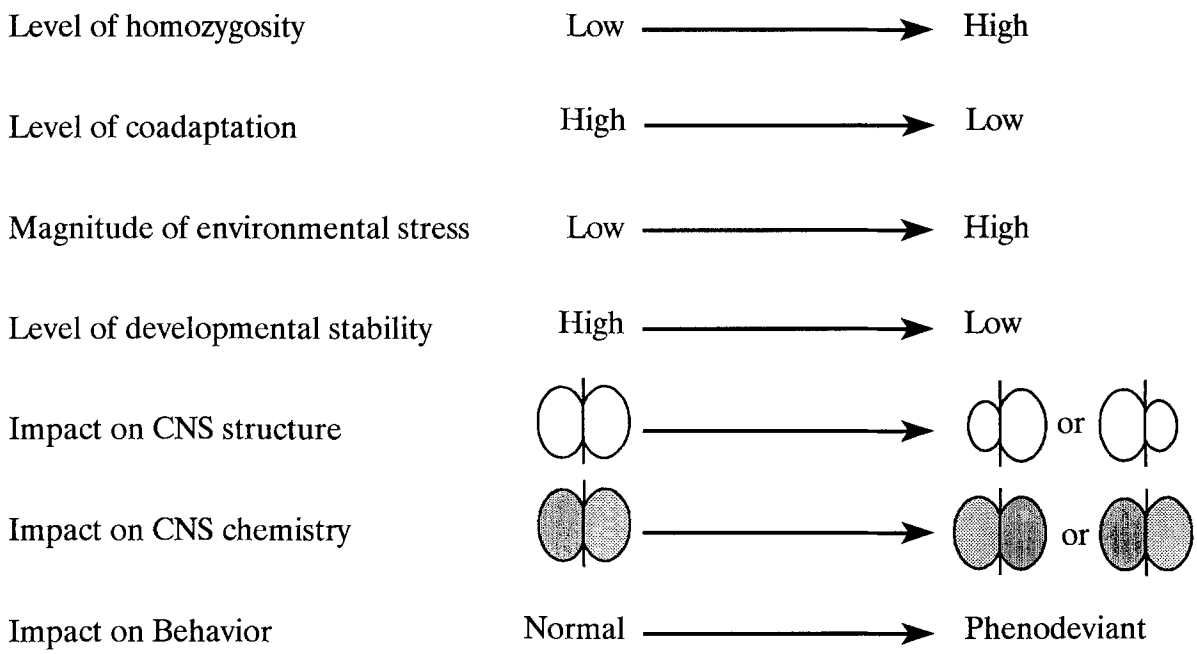

Fig. 2. Hypothetical relationship between genotypic and environmental factors and the neurobiological underpinnings of behavioral phenodeviance.

plan: developmental instability could alter the symmetry of neuronal numbers, chemistry, or connections and thus modify behavior. The quality and quantity of the behavioral abnormalities will depend upon the region and extent of CNS perturbation which in turn will depend upon the genotypic vulnerability, as well as the nature, extent, and timing of environmental results.

Developmental instability and behavioral phenodeviance: predictions

If the existence of behavioral phenodeviants is real and if they actually provide a mechanism of natural or sexual selection, several predictions follow which should be easily testable.

1) Behavioral phenodeviants should be associated with inbreeding in naturally outbreeding populations, and with phenotypic extremes for continuous traits.
2) Behaviorally phenodeviant traits will be heritable but their modes of inheritance will be complex and elusive. In other words, genetic studies will reveal similar patterns as reported for morphological phenodeviants such as crooked toes in chickens (Lerner, 1954), extra crossveins in *Drosophila* (Dubinin, 1948 as discussed in Lerner 1954, 1958), and cleft lip in man (Woolf & Gianas, 1976).
3) Behavioral phenodeviants should have reduced reproductive success compared to other phenotypes in the same natural population.
4) Behavioral phenodeviants as a group should show increased developmental instability in other traits, including the nervous system.

Recognizing the behavioral phenodeviant: testing the predictions

A critical first step in testing these predictions is the identification and measurement of the behavioral phenodeviant. For morphological phenodeviants, a variety of measures are employed for assessment. Some phenodeviant characters, such as crooked toes in chickens, are obvious. Less profound deviation may be quantified along the lines of fluctuating asymmetry (FA; see above) or scales for minor physical anomalies (MPAs; Waldrop & Halvorson, 1971). Behavioral phenodeviance as a new concept, however, has not yet enjoyed the attention neces-

sary for development of standardized measures. In whatever way they come to be measured, behavioral aberrations will be most obvious in our own species and in species whose normal behavior has been exhaustively or at least intensively studied, such as *Drosophila melanogaster*. As the model and its predictions are new, there have been no *a priori* tests as yet. However, we have been able to pull together a range of *a posteriori* observations which address the predictions.

The first prediction deals with the association between individuals with extreme phenotypes for continuous traits with a multifactorial-polygenic basis and their relative homozygosity. From Figure 1, it is clear that for continuous traits, individuals whose phenotypes lie within the central portion of the distribution should be more heterozygous at the responsible loci, while homozygosity increases in extreme phenotypes. This very basic assumption has yet to be widely tested, but conflicting observations (Leary, Allendorf & Knudsen, 1984; Livshits & Smouse, this volume) underscore the need for critical experiments. In addition, this proposed relationship predicts that individuals in the tail ends of distributions for continuous traits should also exhibit an increase in behavioral phenodeviance. A corollary of this prediction is that behavioral phenodeviance should increase with inbreeding.

Evidence exists in the *Drosophila* literature to support the first prediction. Body size in *Drosophila*, as in other organisms, is a continuous trait with a polygenic basis (Falconer, 1989). In many organisms, large male size is typically associated with increased courtship success, and this tendency is present for *Drosophila* males of a variety of species as well (Markow, 1985, 1987a, 1988; Partridge, Hoffman & Jones, 1987; Partridge, Ewing & Chandler, 1987). However, when male courtship success is tabulated as a function of male size distribution in a population, it is clear that not only the very smallest, but also the very largest males are less successful in stimulating females to mate with them (Markow, 1987a; Markow & Sawka, 1992; Markow & Ricker, 1992). The same is true of inbred strains of *Drosophila melanogaster*. Whether inbreeding is accomplished by sib-mating or by making entire chromosomes isogenic, experiments using both *D. melanogaster* and *D. pseudoobscura* show significant reductions in male courtship success as homozygosity increases (Brittnacher, 1981; Partridge, MacKay & Aitken, 1985; Sharp, 1984; Miller, Glasner & Hedrick, 1992).

Multivariate analysis of courtship behavior reveals striking differences among wild-type *D. melanogaster* males (Markow, 1987b). Unsuccessful phenodeviant males show aberrations in courtship component sequences, levels of performance of various elements within the sequence, and appropriateness of courtship delivery. These aberrations may be thought of as analogous to morphological abnormalities regarded as phenodeviant by Lerner. Furthermore, while we can detect them with sensitive measures, surely these behavioral aberrations must be even more obvious and pronounced to conspecifics.

Planned experiments in humans are not feasible or ethical for the purpose of evaluating our predictions, so we must make do with 'naturalistic observations' that bear on the answers. Both incestuous and consanguineous matings lead to tests for the effects of inbreeding on behavioral phenodeviance (prediction number one). The picture will be confounded by the fact that abnormal personalities will almost always be involved in incestuous matings while consanguineous marriages are often the rule in some populations. It will also be difficult to disentangle the appearance of Mendelizing recessive abnormalities from the simulations of Mendelism (Edwards, 1960) and from the effects predicted by Lerner for polygenic traits under inbreeding. The absence of metabolic diseases in the offspring produced by matings of interest here strengthen the inference that effects are attributable to excessive homozygosity for polygenic traits.

In the largest series of offspring from incestuous matings (Seemanova, 1971), 138 of 161 children born (1933 to 1970) to 141 mothers in Czechoslovakia lived long enough to be evaluated. The incestuous dyads arose from 88 father-daughter, 72 brother-sister, and 1 mother-son unions. A control group was formed from the 95 children born to 46 of the same mothers but with unrelated fathers, that is they are half-sibs with matches for mothering and associated psychosocial variables. Twenty mothers and eight fathers were known to be mentally retarded in the incest group, three mothers were diagnosed as schizophrenics, and 13 fathers as chronic alcoholics (four fathers comitted suicide after the discovery of incest). Only offspring intelligence was evaluated in the behavioral domain: 40 (29%)

of the children of the incestuous matings were severely retarded and 28 (70%) of these children had neither parent retarded, thereby implicating excessive homozygosity as an explanation. No half-sibs were noted to be retarded. Such a sample needs to be examined for a broader range of psychopathology or behavioral phenodeviance.

In a more recent series of incest offspring (from 20 brothers and nine fathers) from British Columbia (Baird & McGillivray, 1982), eight of 21 children were retarded or had conspicuous developmental delays; three of the eight may have had retarded parents.

Costeff *et al.* (1977) examined the families of 904 mentally retarded patients in Israel without significant metabolic disorders. The very high frequencies of first-cousin marriages among Israeli ethnic populations (e.g., 21% Iraqi, 24% Irani, 15% Tunisian) and valid assessment of IQ provided strong evidence for autosomal recessive genes causing severe retardation for only 3.2% of the families. Although not discussed by the investigators, their finding of 19.6% of first cousin marriages among the normal parents of 276 severe 'idiopathic' retardates and of 18.8% first cousin marriages among the normal parents of 165 mild 'idiopathic' retardates is compatible with polygenic homozygosity causing this form of behavioral phenodeviance.

A long-standing tradition of cousin marriages may have the paradoxical effect of reducing the number of abnormalities associated with homozygosity for behavioral deviance if the society uses information about behavior to screen out some potential cousin matings (Saugstad & Odegaard, 1987).

The second prediction of our model is that behaviorally phenodeviant traits will be heritable but the genetic mechanisms will be difficult to identify. Attempts at genetic analysis of behavioral phenodeviants are common in the human genetics literature due to the clinical and social problems presented by affected individuals. For example, schizophrenia has an incidence of about 1% in the general population. Vulnerability to this disorder has a genetic basis which, as yet, is undefined. Gottesman and Shields (1967), in proposing a model for the inheritance of schizophrenia, suggested similarities in occurrence of this disorder and the morphological phenodeviants discussed by Lerner (1954). Genetic epidemiological studies are most consistent with a multifactorial threshold model in which a certain number of genetic factors is required to cross the threshold necessary for the phenotype to be expressed. The threshold may be moved in different directions by either predisposing (stressful) or protective (favorable) environments. All studies to date in which single molecular genetic markers have been sought have been unsuccessful (reviewed by McGuffin, Owen & Gill, 1992), which is exactly what is expected if schizophrenia, like other phenodeviants, is generated by segregation at a number of trait-relevant loci. There is a large and growing body of evidence to show that other major and some of the less severe mental disorders are under an appreciable degree of genetic influence, usually polygenic (McGuffin & Murray, 1991; Gottesman, 1991; Katz & McGuffin, 1993; McGue & Gottesman, 1989). Thus affectation status and severity both imply greater homozygosity at the relevant susceptibility-conferring loci.

Our third prediction deals with the reduced fitness of behavioral phenodeviants. In the *D. melanogaster* examples discussed previously, male behavioral phenodeviants were initially identified because they were at a disadvantage in mating, even though they were phenotypically normal in other respects (Markow, 1987a,b; Markow & Sawka, 1992). In these cases, reduced fitness was due to either lack of male mating or reduced fertility in males who did mate.

The marital status and the fertility of psychiatric patients becomes of interest for the evidence it provides about human behavioral phenodeviance in an evolutionary context. More than a dozen studies of the marital status and reproductive rates of persons suffering from schizophrenia have been conducted since 1935, some better than others in regard to diagnostic validity and control groups (Haverkamp, Propping & Hilger, 1982). The studies are in agreement that the marriage rate of schizophrenics as a whole is greatly reduced compared to the general population, ranging from 30% to 40% for males and 50% to 60% for females. Marital fertility *per se* is not reduced in some studies and is somewhat reduced to 70-80% of expected in others. The net effect on fertility of schizophrenics is marked. In the most recent study, using Research Diagnostic Criteria on charts and conducted during the era of effective pharmacological interventions, only 42%

of males and 84% of females with a diagnosis of schizophrenia had any offspring (Hilger, Propping & Haverkamp, 1983). For a much larger sample admitted to the Bethlem/Maudsley Hospitals (Slater, Hare & Price, 1971) in London 1952-1966, only 39% (of 1,086) female schizophrenics and 22% (of 1,003) male schizophrenics had any children. An estimate of the relative 'fitness' of those females with schizophrenia who reach age 35, taking into account probability of marriage, age at marriage, and the census data for English women, yields a value of 43%.

Many fewer studies have been conducted on other mental disorders. Research available on the affective disorders usually does not break down the data into bipolar/unipolar/'other' or into psychotic vs. non-psychotic levels of severity; there are many reasons to believe that bipolar disorders can be largely accounted for by a single major locus model and thus are not relevant to the context of phenodeviance. The category of manic-depressive disorder/disease contains a mixture of recurrent severe affective disorders. Manic-depressives' fitness was studied in Norway (Odegaard, 1960) with values of 77% for males and 75% for females (as contrasted with values for schizophrenics in the same period of 36% and 48%, respectively by sex); marriage rates for the group as a whole were close to the non-psychiatric population. Slater, Hare and Price (1971) also computed important data on their large sample of manic-depressives: 79% of males and females were ever married, 58% of males and 61% of females had children, and the relative fitness of females with manic-depression reaching the age of 35 was 73%.

Obsessive-compulsive personality disorder is quite an interesting condition to explore in the context of homozygosity and balancing selective forces. The pervasive pattern of perfectionism, inflexibility, and friendship-avoidance might be expected to lead to lowered fitness; an optimal amount of traits on the same dimensions, however, might actually be adaptive. Slater, Hare and Price (1971) selected obsessional neuroses out of the broader group of 'neuroses' to examine their fertility (229 males and 235 females admitted as inpatients and therefore markedly ill). Only 74% of females and 47% of males were ever married, 52% of females and 34% of males had children, and the estimate of relative fitness of obsessive-compulsive females reaching the age of 35 was 46%, putting them in the same class as schizophrenics who had much more obvious pathology. Both sexes of obsessives had the lowest marital fertility of any groups studied.

If behavioral phenodeviance is actually associated with decreased developmental stability, evidence of developmental instability should be detectable in other characters as well. Waldrop and Halvorson (1971) report an increase in minor physical anomalies in children exhibiting a range of behavioral abnormalities (see also Yeo & Gangestead, this volume). Fluctuating asymmetry or the occurrence of random right-left differences in paired bilateral structures is another, easily quantified measure of developmental instability which has been shown in several studies to be associated with behavioral phenodeviance. This association was first measured by Markow (1987a) for male *Drosophila melanogaster* who were unsuccessful in courting females. Such males were found to exhibit increased sternopleural bristle asymmetry compared to successfully mating males, providing the initial evidence that sexual selection may be mediated by developmental stability. Subsequent studies on other insects (Thornhill, 1992) and a vertebrate (Moller, 1992) have supported this relationship, although Markow and Ricker (1992) report conditions under which the relationship between FA and sexual selection does not exist.

In man, several studies have measured fluctuating dermatoglyphic asymmetry in patients with schizophrenia (Markow & Wandler, 1986; Markow & Gottesman, 1989; Mellor, 1992). In each case, the prediction was supported in that schizophrenic subjects as a group showed significantly greater FA than control subjects. Similarly, Malina and Buschang (1984), upon measuring FA for morphometric traits in mentally retarded males of complex etiology, found significantly greater developmental instability compared to controls. Finally, Durfee (1974) reported that a sample of boys with minimal brain dysfunction (now termed attention deficit disorder/hyperactivity disorder or AD/HD) also showed significantly higher asymmetry than boys without this history.

Our last prediction, that behavioral phenodeviants should show elevated instability in anatomical features, is intimately related to what may actually underlie or exacerbate some abnormal behaviors as

discussed earlier and presented in Figure 2. Behavior is rooted in the nervous system. The degree to which the nervous system can tolerate structural or physiological variability has not yet been fully explored, although a number of clinically defined behavioral phenotypes clearly have abnormal neurological correlates. No studies have been reported yet to look *a priori* for developmental instability in the nervous system of any organism. However, a large body of literature exists (reviewed by Markow, 1992) which is consistent with the existence of developmental instability in the CNS of subjects with schizophrenia, including structural, neurochemical, and functional departures from normal symmetry/asymmetry patterns.

The concept of behavioral phenodeviance as a manifestation of developmental instability has the capacity to explain many things. Behavioral phenodeviance may be an important phenotypic link between either balancing selection and the maintenance of genetic variability or selection and the evolution of coadapted gene complexes. The predictions provided here should be subjected to *a priori* testing across a range of taxa and traits. Furthermore, behavioral traits should be included among the metric characters examined by investigators seeking to define the relationship between genotypic and environmental factors and developmental stability.

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