Gene–Environment Interactions

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INTRODUCTION

Most genetic-epidemiological approaches used in the study of the aetiology of individual differences in psychiatric disease in humans assume that the effects of genes and environment are additive. That is, it is assumed that the effect of an environmental risk factor does not depend on the genotype of the individual, or, stated differently, that the expression of the genotype does not depend on the subject’s environment. Kendler and Eaves (1986) discuss several models for the joint effects of genes and environment on the liability to psychiatric illness that extend this simple additive approach. In addition to the additive effects of genes and environment, they consider models for the genetic control of sensitivity to the environment (gene–environment interaction) and models for the genetic control of exposure to the environment (gene–environment correlation). We begin this chapter by briefly introducing the ideas of Kendler and Eaves, and by considering the predictions for risk of illness in relatives when for both probands and relatives their environmental exposure can be assessed. Next, we focus in more detail on genotype × environment (G × E) interaction, and present some designs, using twin data, to assess its significance. We illustrate these models with published data on depression, disinhibition and alcohol use in Australian and Dutch twins.

Kendler and Eaves (1986; see also Eaves, 1982 and Eaves, 1984) describe three basic models that represent how genes and environment may jointly influence the liability to psychiatric disorder. Liability to psychiatric disorder is considered a quantitative dimension that is unobserved, or latent, and that underlies the probability of becoming affected. Individuals with a high liability have a high probability of illness, while individuals who score low on the liability scale have a low probability. Many traits that vary in a discontinuous manner, but do not show a pattern of simple Mendelian inheritance, may have an underlying continuous liability scale with a threshold that imposes a discontinuity (e.g. affected or unaffected for the disorder) on the visible expression. The variation in liability may be caused by both genetic and environmental influences (Falconer, 1989).

Kendler and Eaves (1986) propose three models that explain variation in liability:

1. Genes and environment contribute additively to liability of a disorder.
2. Genes and environment interact; this interaction model can be thought of as genes controlling sensitivity to the environment, or as the environment controlling gene expression.
3. Genes and environment are correlated; genes alter the exposure to relevant environmental risk factors.

These explanations for the variation in disease liability are not mutually exclusive; part of the variance may be explained by the additive actions of genes and environment and another part by their interaction. The properties of such complex models are a mixture of the characteristics of the three basic models, and we limit ourselves to the presentation of these basic models. In discussing some of the predictions based on these models, it is assumed that the environment can be dichotomized into ‘protective’ or ‘predisposing’, and that environmental risk can be assessed in the proband (the index case or patient from whom other family members are identified) and in his or her relatives.

In the additive model (model 1), an individual’s liability to disorder is the sum of the contributions of genes and environment. Under this model, the effect of a given environment is the same, regardless of genotype. The risk to relatives to become affected is highest when an affected proband is or was exposed to a protective environment. The risk of developing the disorder is always higher in monozygotic co-twins of probands (who share all their genetic material with the proband) than in their siblings or other first-degree relatives (who share, on average, 50% of their genetic material with the proband).

When there is G × E interaction (model 2), genes determine the degree to which a subject is sensitive to the environment. Individuals with a ‘sensitive’ genotype have the greatest increase in scores on the liability scale in the predisposing environment and the largest decrease in the protective environment. In individuals with an ‘insensitive’ genotype, their scores on the liability scale do not change, or change to a lesser extent, as a function of their environment. The risk to relatives to become affected is highest when an affected proband is or was exposed to a protective environment. The risk to relatives is lowest when both proband and relative have been exposed to a predisposing environment and risk is higher in monozygotic co-twins than in siblings only when both proband and relative have been exposed to the same kind of environment. If, for example, the proband is exposed to a protective environment and the relative to a predisposing environment, then the risk to siblings may be higher than in monozygotic co-twins.

Genetic control to environmental exposure (model 3) implies that the heritability of illness can be explained (entirely or to a certain extent) by an indirect path of genetic influence on the probability of exposure to a predisposing environment. If the heritability of the disorder is explained entirely by this mechanism, then the liability of disease does not depend on genotype once environmental exposure is taken into account. If this mechanism operates, then it will be very difficult to distinguish it from a pure genetic model (Eaves et al., 1977).
A CLOSER LOOK AT GENOTYPE × ENVIRONMENT INTERACTION

The models outlined by Kendler and Eaves (1986) offer a first conceptualization of the joint effects of genotype and environment on psychiatric disease liability or on a (quantitative) psychiatric phenotype. We now take a closer look at \( G \times E \) interaction. As stated above, \( G \times E \) interaction can be thought of as the effect of an environmental risk factor depending on the genotype of the individual, or as the expression of the genotype depending on the subject’s environment. Measures of either the subject’s genotype or of a relevant aspect of their environment are therefore required to assess the significance of \( G \times E \) interaction (Martin et al., 1987). With respect to measures of the genotype that are possibly relevant to the development of psychiatric disease, no strong empirical findings have yet emerged that unambiguously identify susceptibility loci for psychiatric disorder. This is not for lack of trying. Polymorphisms in large numbers of candidate genes have been tested in genetic association studies. These include polymorphisms in pathways of neurotransmitters, such as serotonin, dopamine, noradrenaline and \( \gamma \)-aminobutyric acid (GABA). Not all variants that have been tested, however, have yet been shown to be functional at the transcription or enzyme activity level (Stoltenberg and Burmeister, 2000). Terwilliger and Weiss (1998) present an overview of the results obtained in association studies of candidate genes and psychiatric disorder published in American Journal of Medical Genetics (Neuropsychiatric Genetics) and Psychiatric Genetics in 1997. The distribution of the 261 reported significance levels is almost uniform between 0 and 1, which leads Terwilliger and Weiss to conclude: ‘even the significant results may not be real, as there are just as many P values that are too large as those that are too significant.’ The published P values are consistent with the absence of gene effects in all published analyses. It may be that for some candidate genes that have been studied, the relevant variants have not yet been investigated. For example, for both the serotonin transporter gene (SERT) and the dopamine transporter gene (DAT), it has recently been reported that they contain many more variants than the simple repeat polymorphisms that, until now, were used in genetic association studies (Nakamura et al., 2000; Miller et al., 2001). Another possibility to explain the absence of any strong findings of risk genotypes for psychiatric disorder is population stratification. If in case–control studies investigating candidate genes the effect of stratification is in the opposite direction to the stratification, this will lead to false negative results (Cardon, personal communication). Alternative approaches to model the effects of candidate genes that test the association of particular alleles and disorders both between and within families (Fulker et al., 1999) overcome the problem of stratification but do not tell us whether the same or different genes are expressed in the different groups. To address this issue, data from twins discordant for environmental exposure or longitudinal data from twins (or other genetically related subjects), are required. If in a longitudinal design the same subjects can be measured under different environmental conditions, then the extent to which the same genes are expressed in different environments can be assessed. Falconer (1989) (see also Lynch and Walsh, 1998) proposed that the same character measured on the same subjects in two different environments can be treated as two different traits. \( G \times E \) interaction can then be detected in a bivariate genetic analysis from the genetic correlation between the two traits. If the genetic correlation is high, then trait values in different environments are very nearly determined by the same set of genes. If the genetic correlation is low, then the trait is influenced by different sets of genes in different environments, and this provides evidence for \( G \times E \) interaction. A genetic correlation across environments of unity need not imply the absence of \( G \times E \) interaction, because, as was discussed above, this still leaves open the possibility that the relative importance of genetic factors in explaining individual differences is a function of environmental exposure.

Not all traits can be studied in a longitudinal design. Lynch and Walsh (1998) distinguish between ’labile’ and ’nonlabile’ traits. Labile traits are those for which phenotypic expression can adjust within individuals, through physiological and/or behavioural means, to changes in the environment, e.g. behavioural traits in the presence of competitors or mates, blood pressure or cortisol in response to stress (Boomsma et al., 1998), and behavioural and emotional problems during development (Van der Valk et al., 2001). Nonlabile traits become fixed during some sensitive period of development (e.g. height, age at first major depression) and thus cannot be studied in a longitudinal design that requires the same subjects to participate under different environmental conditions. Both labile and nonlabile traits can show \( G \times E \) interaction, but whereas for a labile trait the entire reaction norm can be determined at the individual level by measuring the same individual in a number of environments, for nonlabile traits, different individuals need to be studied in different environments. A particularly informative design for nonlabile traits is one that includes twin pairs who are concordant and discordant for a certain environmental exposure. The extent to which the resemblance (expressed as a correlation between trait values of twin 1 and twin 2) in discordant twin pairs gives an estimate of the extent to which the genetic correlation differs from unity. In the next section, we present a brief introduction to the estimation of genetic and environmental parameters (e.g. heritabilities and correlations) and to formal testing of \( G \times E \) interaction.
STATISTICAL APPROACH

In analysing G × E interaction, we will use structural equation modelling (SEM) or genetic covariance structure modelling (GCSM) to obtain estimates of parameters and to carry out hypothesis testing. These techniques provide a general and flexible framework for the analysis of data gathered in genetically informative samples. In applying GCSM, genetic and environmental effects are modelled as the contribution of latent (unmeasured) variables to the phenotypic individual differences, or to a liability dimension, which itself is also unobserved (e.g. Martin and Eaves, 1977; Neale and Cardon, 1992). The latent genetic and environmental factors represent the effects of many unidentified influences. In the case of a genetic factor, these effects are due to a possibly large, but unknown, number of genes (polygenes). The latent environmental factors can be distinguished into environmental influences common to family members and environmental influences specific to an individual. The contributions of the latent variables are estimated as regression coefficients in the linear regression of the observed phenotype on the latent variables. Given an appropriate design providing sufficient information to identify these coefficients, actual estimates may be obtained using a number of well-known computer programs, such as LISREL (Joreskog and Sorbom, 1995), or Mx (Neale, 1997).

Identification of genetic models, especially the identification of the effect of shared family environment versus shared genes, can be achieved by several designs, such as adoption or twin designs. We focus on the classical twin design (Martin et al., 1997), which includes monozygotic (MZ) and dizygotic (DZ) twins. MZ twins are genetically identical, while DZ twins (and siblings) share on average 50% of their segregating genes. If MZ twins resemble each other more than DZ twins do, then this is evidence for the importance of genetic influences on the trait under consideration. One advantage of structural equation modelling is that this approach is easily generalized to multivariate and longitudinal data. Twin data are used to decompose the variance for a single trait into a genetic and a non-genetic part. Likewise, bi- and multivariate twin data can be used to decompose the covariance between traits, or between repeated measures of the same trait, into a part due to correlated genetic influences and a part due to correlated environmental influences (Martin and Eaves, 1977; Boomsma and Molenar, 1986). The flexibility of GCSM is also evident in the relative ease with which measured genotypic (e.g. DNA marker data) or environmental information can be incorporated into the analysis.

In both univariate and multivariate genetic analysis, the identification of genetic and environmental parameters depends on a multigroup analysis in which data from MZ and DZ twins are analysed simultaneously. For a univariate phenotype, the phenotype (P) can be expressed as a function of an individual’s genotype (G), the environment common to family members (C), and the environment unique to the individual (E):

\[ P_i = gG_i + cC_i + eE_i \]

where \( i = 1, \ldots, N \) individuals.

The coefficients \( g, c \) and \( e \) are population parameters that represent the strength of the relation between the measured phenotype and the latent (unmeasured) factors G, C and E. The latent genetic and common environmental factors are correlated in family members. In MZ twins, the genetic factors are correlated 1, and in DZ twins the correlation is 0.5. The common environmental factors are correlated 1 in both MZ and DZ twins, unless the twins are of opposite sex. For DZ opposite-sex (DOS) twins, the correlation of their common environmental factors may be less than 1 if the family environment exerts a different influence on boys and girls. Likewise, the correlation between genetic factors may be less than 0.5 in DOS twins if different genes are expressed in males and females.

Assuming that all latent variables have been standardized to have unit variance, and that the latent factors are uncorrelated (no gene–environment correlation), then the variance of \( P \) may be written as:

\[ V(P) = g^2 + c^2 + e^2 \]

where \( V(P) \) is the variance of the phenotype, and \( g^2, c^2 \) and \( e^2 \) represent the genetic, common environmental and unique environmental variances. The standardized genetic variance (i.e. \( g^2 \) divided by the phenotypic variance \( V(P) \)) is called the heritability of the phenotype, often symbolized by \( h^2 \).

The parameters \( g, c \) and \( e \) may be estimated by maximum likelihood, implemented in, for example, LISREL or Mx. Their significance can be assessed by likelihood ratio tests. For example, the goodness of fit of a model that constrains the genetic variance to be zero can be compared with a model in which the genetic variance is estimated freely. The difference in goodness-of-fit parameters then provides a test of significance for the genetic effect. In multigroup designs with, for example, MZ and DZ twins who were assessed in a protective or a predisposing environment, equality of parameter estimates across exposure groups can also be assessed by likelihood ratio tests (Neale and Cardon, 1992).

Estimates of the genetic correlation between two traits (or between values of the same trait assessed twice in the same twins under different environmental conditions) can be obtained from the bivariate generalization of this model. The correlation (\( r_g \)) between two phenotypes P1 and P2 is given by:

\[ r_g = h_1 h_2 c_{g12} + c_{11} c_{22} + e_{11} e_{22} \]

where \( r_g, r_c \), and \( r_e \) are the correlations between genetic, common and unique environmental factors that influence phenotype 1 and phenotype 2 (or the same trait measured in environment 1 and environment 2). These correlations are weighted by the square roots of the standardized heritabilities for trait 1 and 2 (\( h_1 \) and \( h_2 \), respectively) and the square roots of the standardized environmentalities (Plomin et al., 2001). The significance of these correlations may also be tested by likelihood ratio tests, comparing the likelihood of a more restricted model (e.g. \( r_g = 0 \)) with the likelihood of a less restricted model (in which \( r_g \) is estimated).

EMPIRICAL EXAMPLES

Information on personality, anxiety and depression, alcohol initiation and several aspects of religion was collected by mailed survey in 1974 Dutch families consisting of adolescent and young adult twins and their parents (Boomsma et al., 1999; Koopmans et al., 1999). These data were used to explore the influence of religion on personality traits and alcohol initiation. First, the influence of different aspects of religion on average scores for personality characteristics, such as neuroticism, extraversion and sensation seeking, and for depression and anxiety was investigated. Several traits were associated significantly with religion. The association between religion and personality was found to be especially strong for the disinhibition scale of the sensation seeking questionnaire (Zuckerman, 1971; Feij et al., 1997). Therefore, this scale was selected to look at the genetic architecture of disinhibition in male and female twins with and without a religious upbringing. The familial resemblance for different aspects of religion — upbringing, religious affiliation and active participation — was large, and genetic factors did not contribute to this familial resemblance.

We tested whether in addition to an effect on means, there was any evidence for an interaction between genotype and environment (G × E) on disinhibition scores. When there is no interaction, the influence of genetic and environmental factors should not differ
between twins with and without a religious upbringing. If genetic effects are modified by religious upbringing (differ significantly between the religious and non-religious groups), then this constitutes evidence for G × E interaction. In these analyses, religious upbringing is thus considered to be the shared environment, and disinhibition and alcohol use are the phenotype. Table XIII.1 presents the correlations between twins for disinhibition and for alcohol use conditional on religious upbringing. Both for disinhibition and alcohol use, the MZ and DZ correlations do not differ, or differ very little, from each other in twin pairs from a religious background. In contrast, in the twin pairs who were brought up in a non-religious environment, MZ correlations are larger than DZ correlations, though more so for disinhibition than for alcohol use. Table XIII.2 gives the estimates for heritability and the amounts of variance explained by common environmental factors shared by family members and by unique (or idiosyncratic) environmental factors (Boomsma et al., 1999; Koopmans et al., 1999). In males, the difference in heritabilities between religious and non-religious groups is significant for both variables. In females, the differences between religious and non-religious groups are in the same direction as for males, but they are not statistically significant. In subjects with a religious upbringing, the influence of their genotype on disinhibition and alcohol use is much lower than in subjects from a non-religious background. Indeed, in religious males, the point estimates for heritability are zero. These findings suggest that in subjects raised in a religious home environment, the expression of genetic factors is restricted. The influence of genetic factors is larger in adolescents and young adults who have been brought up without religion.

Further examples suggest that the environmental dichotomy of married/partnered versus having no life partner is a powerful modifying factor on expression of genetic variation for a number of traits in females, including alcohol consumption (Heath et al., 1989) and depression (Heath et al., 1998), although since being married successfully is itself under partial genetic control (Jockin et al., 1996), these may not be straightforward cases of G × E interaction. Our first example did not include any twin pairs who were discordant for religious upbringing (all pairs grew up in the same family), but the study on alcohol consumption in adult Australian twins includes a group of older females discordant for marital status. In comparison to the concordant groups, MZ female twins who are discordant for being married resemble each other less. The correlation for alcohol use in discordant DZ twins is near zero, but a similar low correlation was observed in concordant unmarried DZ females. Due to the small number of pairs in some of the groups, a statistically based discrimination between different models of G × E interaction was not possible, but all analyses pointed to the conclusion that the importance of genetic factors is larger in older, unmarried respondents. The estimate for the genetic correlation between alcohol consumption in the married and in the unmarried state was 0.59, indicating that different genes may be expressed under these two conditions.

**POWER**

The number of twin pairs needed to detect a statistically significant difference in heritabilities between two groups may be quite large. The number depends on the size of the heritabilities in the two groups, on the significance level, and on the power chosen by the researcher. We investigated through simulation (e.g. Neale and Cardon, 1992) the sample sizes required to detect G × E interaction in the classical MZ/DZ twin design. Some results are presented in Table XIII.3. The standardized heritability of the trait was always 60% in one of the exposure groups, and was smaller in the second group (between 0% and 40%). In the second group, there could be an additional contribution of common environment, accounting for 20–60% of the variance. The left-hand part of Table XIII.3 gives the results for the situation in which there is always contribution of common environment to trait variance (in this case, the MZ correlations in both exposure groups are always 0.6, and only the DZ correlations differ, e.g. when \( h^2 = r^2 = 0.3 \), the DZ correlation is 0.45). The right-hand part of Table XIII.3 gives the required sample sizes when heritabilities differ between groups, but when there is no contribution of common environment. In this case, both MZ and DZ correlations differ from those in the group where \( h^2 = 0.6 \). The columns labelled N1 give the required number of twin pairs for a design in which the sample consists of equal numbers of MZ and DZ pairs, and the columns labelled N2 for a design in which the sample consists of 40% MZ and 60% DZ pairs, for power equal to 50, 80 or 90%. The test of significant differences in genetic architecture

### Table XIII.1 Twin correlations for disinhibition and alcohol use as a function of religious upbringing in adolescent and young adult Dutch twins

<table>
<thead>
<tr>
<th></th>
<th>Disinhibition</th>
<th>Alcohol use</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MZM</td>
<td>DZM</td>
</tr>
<tr>
<td>Religious</td>
<td>0.62</td>
<td>0.62</td>
</tr>
<tr>
<td>Non-religious</td>
<td>0.62</td>
<td>0.35</td>
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</tbody>
</table>

### Table XIII.2 Percentage of variance in disinhibition and alcohol use explained by genetic factors (G), common environment (C) and unique environment (E) for males (M) and females (F) as a function of religious upbringing. Parameter estimates with 95% confidence intervals in parentheses

<table>
<thead>
<tr>
<th></th>
<th>Disinhibition</th>
<th>Alcohol use</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>G</td>
<td>C</td>
</tr>
<tr>
<td>F, religious</td>
<td>37 (22–55)</td>
<td>25 (9–37)</td>
</tr>
<tr>
<td>F, non-religious</td>
<td>61 (7–67)</td>
<td>0 (0–48)</td>
</tr>
<tr>
<td>M, Religious</td>
<td>0 (0–22)</td>
<td>62 (43–69)</td>
</tr>
<tr>
<td>M, Non-religious</td>
<td>49 (14–69)</td>
<td>11 (0–40)</td>
</tr>
</tbody>
</table>
between groups had three degrees of freedom (df), allowing for differences in the contributions of genetic, common and unique environmental factors, although it could be argued that a 2 df test is more appropriate (which would require smaller sample sizes), because the type of $G \times E$ interaction of interest does not include a difference between groups in the contribution of unique environmental factors.

Table XIII.3 shows that for a power of 80% and for relatively small differences in heritabilities between groups (0.3 or smaller), large samples are needed, especially if there is also a contribution of common environment to familial resemblance. When this is the case, a design with 40% MZ pairs and 60% DZ pairs has more power than a design with equal numbers of MZ and DZ pairs (e.g. when for the second group $h^2 = c^2 = 0.3$, a study with an equal number of MZ and DZ pairs requires 2507 pairs, i.e. more than 5000 individuals, whereas an N2 design requires 2087 pairs).

Fewer twin pairs are needed to detect a significant difference in heritabilities between exposure groups, when genes are the only source of familial resemblance and there is no contribution of common environment. In this case, as shown in the right-hand part of Table XIII.3, a design with an equal distribution of MZ and DZ twins has the highest power.

### LEVEL GENES AND VARIABILITY GENES

It is possible that there are genes that have no effect on the mean expression level of a trait but, depending on environmental circumstances, have a greater or lesser variance of expression. It is not difficult to think of molecular mechanisms, e.g. promoters of different binding efficiency, to explain the existence of such variability genes. MZ twins offer a unique opportunity to test for the presence of such genes if a measured genotype is available. Most readers will be familiar with the ABO and Rh blood groups, which are polymorphisms in proteins of the red blood cells determined by genes on chromosomes 9 and 1, respectively. The MN blood group is another such polymorphism in a cell-surface protein, which is coded for by a gene on chromosome 4. Magnus et al. (1981) showed that the intrapair variance for cholesterol in MZ pairs who were blood group M— (i.e. blood group N) was significantly greater than in MZ pairs who were M+ (i.e. blood groups M and MN); this was replicated by Martin et al. (1983). From this observation, Berg et al. (1989) introduced the idea of ‘variability genes’ as opposed to ‘level genes’. Level genes affect the mean expression of a trait, or prevalence in the case of a disease, and are the usual target of association studies. Variability genes do not need to influence trait levels, but they determine the influence of the environment on intra-individual variability. Thus, Birley et al. (1997) were able to predict from these results that blood group N subjects would have a greater drop in serum cholesterol levels in response to a low-fat diet than MN heterozygotes, and indeed this was observed. Potentially, variability genes can be even more important than level genes. An allele that increases environmental variance by 50% (the approximate effect size of the N allele on cholesterol variability) will increase the proportion of cases above the second standard deviation by more than two-fold, and those above the third standard deviation by more than five-fold. Unfortunately, however, the power of the variance ratio test to detect heterogeneity of varianses is not large (Martin, 2000).

If the genes that contribute to sensitivity to the environment are correlated (distribution or action) with genes affecting the mean expression of a trait, then MZ twins offer an opportunity to detect $G \times E$, without the requirement that they are genotyped (Jinks and Fulker, 1970; Eaves et al., 1977). The difference in trait values between MZ twins is an estimate of the environmental effect, whereas the sum of MZ twins’ scores is a function of their (shared) genetic deviation and their family environmental deviation. Assuming that there is some genetic contribution to the trait — as evidenced by a greater MZ than DZ correlation — any relationship between the absolute trait differences of MZ pairs and their corresponding sums is evidence of $G \times E$ interaction. Jinks and Fulker (1970) suggested that as a preliminary step to any biometrical genetic analysis of twin data, one should therefore regress the MZ absolute pair differences on their pair sums to check for $G \times E$ interaction. In practice, this form of $G \times E$ is often predictable as a function of the non-normality of the scale distribution and can be removed by an appropriate transformation of the scale of measurement. Thus, positive skewness (tail to the right) produces positive correlations between MZ differences and sums, and negative skewness produces a negative correlation. The often observed ‘basement–ceiling’ effect in psychometric scales, where there is good discrimination of differences in the middle of the range but a bunching at the low and high extremities, produces an inverse U-shaped quadratic relationship of means and intrapair differences.

### DISCUSSION

‘No aspect of human behavior genetics has caused more confusion and generated more obscurantism than the analysis and interpretation of the various types of non-additivity and non-independence of gene and environmental action and interaction . . .’ (Eaves et al., 1977). This statement is as true today as when it was written. Often, the term ‘$G \times E$ interaction’ is used simply to denote that both
genes and environment are important. A better term to describe this situation is 'genotype–environment coaction' (Martin, 2000). We should reserve the term 'G × E interaction' for its statistical sense of different genotypes responding differently to the same environment, or, viewed from the other end, some genotypes being more sensitive to changes in the environment than others (different reaction ranges). From the extensive literature on crops and domesticated animals, the overwhelming message regarding G × E interaction is that it is extremely common (Lynch and Walsh, 1998), although it may explain only a relatively small proportion of the total trait variance. There are, however, still few data on its significance in natural populations. In a review of gene-mapping strategies, Tanksley (1993) discusses some of the first empirical results for Environment by quantitative trait loci (QTL; genes that influence quantitative traits) interactions in plants. QTLs affecting quantitative traits in maize and tomato in one environment (e.g. the USA) are often active in other environments (e.g. the Middle East) as well. QTLs showing the largest effects in one environment seemed more likely to also be detected in other environments, suggesting little interaction by QTL interaction. QTLs with minor effects seemed more likely to show interactions with the environment. If similar results would apply to QTLs influencing personality traits and psychiatric disorders in humans, then this might conceivably explain the sometimes inconsistent results observed in candidate gene studies, in which genes of minor effect are tested. Examples of candidate genes that fail to show consistent replication across different populations include the dopamine receptor DRD4 (Plomin and Caspi, 1998), the serotonin transporter promoter region (Ebstein et al., 2000), and the NODCH4 gene in schizophrenia (McGinnis et al., 2001; Sklar et al., 2001). These are all examples of QTLs that, when found to be associated significantly with personality or psychiatric disorder, explain only a small proportion of the variance and can be considered minor QTLs.

We have shown how the analysis of G × E interaction can be conducted in the classical MZ/DZ twin design, using measures of environmental exposure or direct measures of the genotype. If measures of either environment or genotype are not available, i.e. in the majority of the quantitative genetic studies of metric human phenotypes, then the detection of G × E interaction is more difficult. One test for G × E interaction is the test suggested by Jinks and Fulker (1970) discussed above, involving examination of the association between the means and differences of MZ twin pairs. Another approach to test for genotype–environment interaction when measures of the environment or the genotype are not available is based on the analysis of the higher-order moments of genetic and environmental factor scores. Molenaar and Boomsma (1987) and Molenaar et al. (1990, 1999) have shown that the effects of certain types of interaction cannot be detected at the level of second-order moments (i.e. variances and covariances), but that they do lead to specific values of the third- and fourth-order moments (i.e. skewness and kurtosis) of genetic and environmental factor scores. These methods do not require measurements of the environment or the genotype, but require multiple indicators of the phenotype for the calculation of factor scores (Boomsma et al., 1990) and the estimation of the higher-order moments of these factor scores. This approach to the detection of interaction factors hinges on the estimation of fourth-order moments. Unfortunately, the sampling variability of these estimates is very high, therefore large samples of phenotypic values are needed in order to secure the reliability of the detection tests. In simulation studies (where it is certain that the generated phenotypic values constitute a homogeneous sample), it was found that estimates of fourth-order moments depend strongly on the extreme phenotypic values in a sample, and that removal of these extreme observations (which are often interpreted as outliers in empirical studies) could lead to severe bias.

When G × E is present, but not modelled explicitly (e.g. because no measures of environmental exposure or genetic sensitivity are available), the interaction terms will be confounded with other terms in the model. For example, an interaction of genotype with unique environmental factors will be confounded with the unique environmental influences and cannot be separated from it in an analysis of second-degree statistics (Eaves et al., 1977). Likewise, an interaction between genes and common environmental factors will be confounded with genetic effects. This might explain why it is so rare to observe a main effect of common environment shared by family members on psychiatric disorders (or many other traits). If the effects of parental rearing style and the shared family environment depend on the genetic constitution of an individual, then these will show up in most analyses as pure genetic effects.

The phenomenon of G × E interaction was introduced in this chapter in a statistical manner. Kendler (1998) outlines some of the biological phenomena underlying gene structure and function that may explain genetic sensitivity to the environment. Genes have dual functions: their template function guarantees reliable replication, and their transcriptional function regulates gene expression in the cell. Although almost all cells of the body contain all genes, in any given cell only a small proportion of genes is expressed. The expression of genetic information takes place when RNA is synthesized from DNA. RNA specifies the synthesis of polypeptides, which form proteins. The manufacture of specific proteins by a subset of genes in any given cell is thus highly regulated, and this regulation of gene expression is responsive to environmental factors. Learning, social interaction, stress and hormones (Strachan and Read, 1999) can alter the binding of transcriptional regulators to enhancer elements of genes, which, together with the promoter, usually lie upstream of a gene's coding region. After transcriptional regulators have bound to the promoter region, RNA synthesis is initiated. As demonstrated by studies of learning in simple animals, environmental triggers and experience can produce sustained changes in neural connections by altering gene expression. Certain environments may produce alterations in gene expression that produce structural changes in the brain, which may underlie psychiatric disorder. It remains an intriguing question as to what causes some individuals to experience more of such environmental triggers than others. As already pointed out by Kendler and Eaves (1986), exposure to certain environments may itself be under genetic control.

In conclusion, one might observe that G × E interaction has been the topic of much loose speculation over the years, with extravagant claims made for its potential importance, and precious few well-documented examples, at least in the human domain. Those presented above are some of the few we know of. One of the most exciting prospects now that we have the human genome sequence, and are on the brink of identifying QTLs for many complex traits, is that we shall at last be able to see just how widespread and important a phenomenon it really is.

REFERENCES


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