Chapter 11

Sex-limitation and $G \times E$ Interaction

11.1 Introduction

As described in Chapter 8, the basic univariate ACE model allows us to estimate genetic and environmental components of phenotypic variance from like-sex MZ and DZ twin data. When data are available from both male and female twin pairs, an investigator may be interested in asking whether the variance profile of a trait is similar across the sexes or whether the magnitude of genetic and environmental influences are sex-dependent. To address this issue, the ACE model may be fitted independently to data from male and female twins, and the parameter estimates compared by inspection. This approach, however, has three severe limitations: (1) it does not test whether the heterogeneity observed across the sexes is significant; (2) it does not attempt to explain the sex differences by fitting a particular sex-limitation model; and (3) it discards potentially useful information by excluding dizygotic opposite-sex twin pairs from the analysis. In the first part of this chapter (section 11.2), we outline three models for exploring sex differences in genetic and environmental effects (i.e., models for sex-limitation) and provide an example of each by analyzing twin data on body mass index (BMI).

Just as the magnitude of genetic and environmental influences may differ according to sex, they also may vary under disparate environmental conditions. If differences in genetic variance across environmental exposure groups result in differential heritability estimates for these groups, a genotype $\times$ environment interaction is said to exist. Historically, genotype $\times$ environment ($G \times E$) interactions have been noted in plant and animal species (Mather and Jinks, 1982); however, there is increasing evidence that they play an important role in human variability as well (Heath and Martin, 1986; Heath et al., 1989b). A simple method for detecting
G × E interactions is to estimate components of phenotypic variance conditional on environmental exposure (Eaves, 1982). In the second part of this chapter (section 11.4), we illustrate how this method may be employed by suitably modifying models for sex-limitation. We then apply the models to depression scores of female twins and estimate components of variance conditional on a putative buffering environment, marital status.

11.2 Sex-limitation Models

11.2.1 General Model for Sex-limitation

Overview

The general sex-limitation model allows us to (1) estimate the magnitude of genetic and environmental effects on male and female phenotypes and (2) determine whether or not it is the same set of genes or shared environmental experiences that influence a trait in males and females. Although the first task may be achieved with data from like-sex twin pairs only, the second task requires that we have data from opposite-sex pairs (Eaves et al., 1978). Thus, the LISREL 7 script we describe will include model specifications for all 5 zygosity groups (MZ-male, MZ-female, DZ-male, DZ-female, DZ-opposite-sex).

To introduce the general sex-limitation model, we consider a path diagram for opposite-sex pairs, shown in Figure 11.1. Included among the ultimate variables in the diagram are female and male additive genetic (A_J and A_m), dominant genetic (D_J and D_m), and unique environmental (E_J and E_m) effects, which influence the latent phenotype of the female (P_J) or male (P_m) twin. The additive and dominant genetic effects are correlated within twin pairs (α = 0.50 for additive effects, and β = 0.25 for dominant effects) as they are for DZ like-sex pairs in the simple univariate ACE model. This correlational structure implies that the genetic effects represent common sets of genes which influence the trait in both males and females; however, since a_m and a_j or d_m and d_j are not constrained to be equal, the common effects need not have the same magnitude across the sexes.

Figure 11.1 also includes ultimate variables for the male member of the opposite-sex twin pair (A'_m and D'_m) which do not correlate with genetic effects on the female phenotype. For this reason, we refer to A'_m and D'_m as sex-specific variables. Significant estimates of their effects indicate that the set of genes which influences a trait in males is not identical to that which influences a trait in females. To determine the extent of male-female genetic similarity, one can calculate the male-female genetic correlation (r_g). As usual (see Chapter 2) the correlation is computed as the covariance of the two variables divided by the product of their respective standard deviations. Thus, for additive genetic effects we have

\[ r_g = \frac{a_m a_f}{\sqrt{a_f^2 (a_m^2 + a'_m^2)}} \]