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Detecting Sex-Associated Variation With the Families of MZ and DZ Twins

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Abstract. Phenotypic variation in human population may contain contributions from a number of different sex-associated genetic influences. These influences include maternal effects, the effects of sex-linked loci, and the effects of sex-limited autosomally linked loci. The families produced by MZ and DZ twins provide statistics which permit the detection and estimation of these effects. In particular, they provide statistics derived from various types of age-matched half-sibs and cousins in addition to those derived from the more usually studied full-sib or parent-offspring relationships. Specific models for genetic maternal effects, sex-linkage and sex-limitation are used to explore the use of extended twin design for the detection of and the discrimination between various sex-associated effects. The sample sizes required to detect maternal effects and sex-linkage were considered for some simple cases and it is concluded that comparison derived from the progeny of twins will often provide better tests for these effects than those derived from parent-offspring comparison.

Key words: Extended twin design, Twin families, Maternal effects, Sex-linkage, Sex-limitation

INTRODUCTION

This paper is concerned with the influences of various sex-associated effects on human phenotypic variation and how these influences may permit the detection of the effects. The effects under consideration are:

1) Maternal effects: these occur when the mother makes a contribution to the phenotype of her progeny over and above that due to her direct genetic contribution to the nucleus of the zygote.

2) Sex-linked genetic variation: where at least some of the variation in a trait is due

to loci carried on a sex-chromosome. We will only consider linkage to the X chromosome, as this occurs much more frequently than Y linkage.

3) Sex-limited genetic variation: this is trait variation due to autosomally linked loci which are sex-limited in their expression, ie, genes may have different degrees of expression in the two sexes or the same trait may be influenced by different sets of genes in the two sexes.

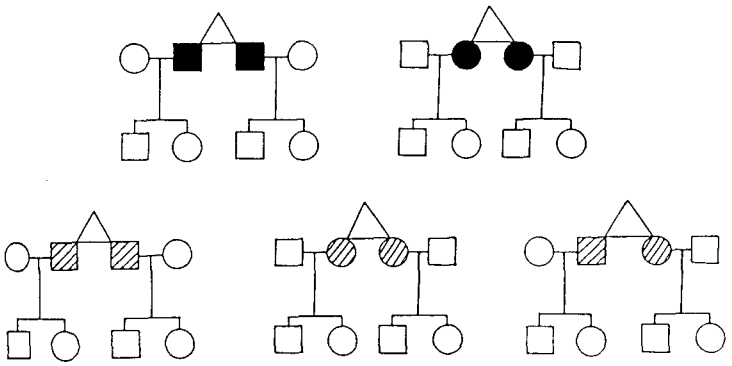
THE DATA

The statistics considered here for the detection of sex-associated effects are those derived from monozygotic (MZ) and dizygotic (DZ) twins and their families, ie, male and female MZ twins and their spouses and offspring, and male, female and opposite-sexed DZ twins and their spouses and offspring. The idealized family structure of such data is shown in the Figure. Data derived from these families provides all the statistics usually utilised for the detection of maternal effects, sex-linkage and sex-limitation, plus some others. An important feature of such a research design is that it provides families of maternally or paternally related, age matched half-siblings (derived from the MZ families) and cousins (derived from the DZ families).

The simplest method of data analysis is to use simple comparisons of statistics to detect individual sources of variation. This method may more readily detect some individual sources of variation than some more versatile methods of analysis, but is too wasteful of information and unwieldy to be generally satisfactory. The simple comparisons used may be of different correlations between relatives, and correlations between relatives can also be used as a basis of a more general model-fitting approach. Alternatively, Nance and Corey [16] have shown how data from the progeny of twins may be subjected to a hierarchical analysis of variance yielding three mean squares from each type of twin family:

MS_W : between progeny within full-sib families;
MS_B : between the two families or full-sibs produced by pairs of twins;
MS_A : among the pedigrees.

Comparison of the mean squares from analyses of families produced by different types of twins once again provide tests for individual sources of variation. These mean squares can also be used as a basis for model fitting via a weighted least squares method. However, the analyses of variance become difficult to apply when the family structures are unbalanced and the problem is exacerbated when the presence of sex-linked or sex-limited effects make it necessary to keep the progeny sexes separate during analysis. With the increasing complexity of the data analysed and the models which are required to explain the data, it becomes increasingly desirable to analyse the data via some form of pedigree analysis, such as that based upon maximum likelihood methods developed by Lange et al [10]. Note that sex-linked or sex-limited genetic variation can cause the total variances of males and females to differ; these differences may contribute to the detection of the effects and must not be obscured by the analytical techniques utilised.



THE MODELS

In order to understand the influences of maternal effects, sex-linkage and sex-limitation on the statistics derived from twin families, and how the statistics may be utilised to detect these effect, it is necessary to build plausible causative model for these effects. To do this, the well tried and experimentally tested methods of biometrical genetics [13, 14] have been utilised [7,8].

MATERNAL EFFECTS

There are a number of different factors which can lead to maternal effects, for example, cytoplasmic effects or the effects of the mother's genotype or phenotype on the development of the offspring. The illustrative model developed is based upon the effects of the maternal genotype on the offspring. This model is applicable when the maternal genotype contributes to the maternal effect but is also likely to remove much of the variance attributable to other types of maternal effect.

We can consider two basic forms of this model. In the one-character model, the loci producing the maternal effect due to the parent are also those producing the direct effect in the progeny. Thus, a mother not only contributes genes for a particular trait to the zygote, but also her own genotype for that trait has an effect on the phenotypic development of her progeny. In the two-character model, different sets of loci produce the maternal effect and the direct effect in the progeny. Thus, a mother contributes genes for a trait to the zygote, but it is her genotype for a second trait which influences the phenotypic development of the first trait in her progeny.

Assuming Hardy-Weinberg equilibrium, the one-character model for a single locus with two alleles, A and a with frequencies u and v, can be written as follows:

Genotype	AA	Aa	aa
Frequency	u^2	2uv	v^2
Direct effect of genotype on progeny	d	h	-d
Effect of mother of that genotype on progeny	md	mh	-md

Summing over a number of such loci, independent in inheritance and action, the genetic contribution to second-degree statistics derived from human populations can be cast in

TABLE 1 - The Genetic Expectations of Relationship from MZ and DZ Twin Families

	D_R	H_R	Maternal effects				Sex-linkage				Sex-limitation					
			MD_R	MH_R	DMD_R	HMH_R	D_S	D_U	D_B	H_X	D_{Rf}	H_{Rf}	D_{Rmf}	H_{Rmf}	D_{Rm}	H_{Rm}
Total variance (female)	1/2	1/4	1/2	1/4	1/2	.	1/2	.	.	1/4	1/2	1/4	.	.	.	.
Total variance (male)	1/2	1/4	1/2	1/4	1/2	.	.	.	1	.	.	.	.	.	1/2	1/4
Sister-sister cov.	1/4	1/16	1/2	1/4	1/2	.	3/8	.	.	1/8	1/4	1/16	.	.	.	.
Sister-brother cov.	1/4	1/16	1/2	1/4	1/2	.	.	1/4	.	.	.	.	1/4	1/16	.	.
Brother-brother cov.	1/4	1/16	1/2	1/4	1/2	.	.	.	1/2	.	.	.	.	.	1/4	1/16
Mother-daughter cov.	1/4	.	1/4	.	5/8	1/4	1/4	.	.	.	1/4	.	.	.	.	.
Mother-son cov.	1/4	.	1/4	.	5/8	1/4	.	1/2	.	.	.	.	1/4	.	.	.
Father-daughter cov.	1/4	.	.	.	1/8	.	.	1/2	.	.	.	.	1/4	.	.	.
Father-son cov.	1/4	.	.	.	1/8	.	.	.	.	.	.	.	.	.	1/4	.
Female MZ twin families																
Female half-sib cov.	1/8	.	1/2	1/4	1/2	.	1/8	.	.	.	1/8	.	.	.	.	.
Female-male half-sib cov.	1/8	.	1/2	1/4	1/2	.	.	1/4	.	.	.	.	1/8	.	.	.
Male half-sib cov.	1/8	.	1/2	1/4	1/2	.	.	.	1/2	.	.	.	.	.	1/8	.
Twin aunt-niece cov.	1/4	.	1/4	.	5/8	1/4	1/4	.	.	.	1/4	.	.	.	.	.
Twin aunt-nephew cov.	1/4	.	1/4	.	5/8	1/4	.	1/2	.	.	.	.	1/4	.	.	.
Male MZ twin families																
Female half-sib cov.	1/8	.	.	.	.	.	1/4	.	.	.	1/8	.	.	.	.	.
Female-male half-sib cov.	1/8	.	.	.	.	.	.	.	.	.	.	.	1/8	.	.	.
Male half-sib cov.	1/8	.	.	.	.	.	.	.	.	.	.	.	.	.	1/8	.
Twin uncle-niece cov.	1/4	.	.	.	1/8	.	.	1/2	.	.	.	.	1/4	.	.	.
Twin uncle-nephew cov.	1/4	.	.	.	1/8	.	.	.	.	.	.	.	.	.	1/4	.
Female DZ twin families																
Female cousin cov.	1/16	.	1/4	1/16	1/4	.	3/32	.	.	.	1/16	.	.	.	.	.
Female-male cousin cov.	1/16	.	1/4	1/16	1/4	.	.	3/16	.	.	.	.	1/16	.	.	.
Male cousin cov.	1/16	.	1/4	1/16	1/4	.	.	.	3/8	.	.	.	.	.	1/16	.
Twin aunt-niece cov.	1/8	.	1/4	.	3/8	1/16	3/16	.	.	.	1/8	.	.	.	.	.
Twin aunt-nephew cov.	1/8	.	1/4	.	3/8	1/16	.	3/8	.	.	.	.	1/8	.	.	.
Male DZ twin families																
Female cousin cov.	1/16	.	.	.	.	.	1/8	.	.	.	1/16	.	.	.	.	.
Female-male cousin cov.	1/16	.	.	.	.	.	.	.	.	.	.	.	1/16	.	.	.
Male cousin cov.	1/16	.	.	.	.	.	.	.	.	.	.	.	.	.	1/16	.
Twin uncle-niece cov.	1/8	.	.	.	1/8	.	.	1/4	.	.	.	.	1/8	.	.	.
Twin uncle-nephew cov.	1/8	.	.	.	1/8	.	.	.	.	.	.	.	.	.	1/8	.
Female-male DZ twin families																
Female cousin cov.	1/16	.	.	.	1/8	.	1/16	.	.	.	1/16	.	.	.	.	.
Daughter of female twin-son of male twin cov.	1/16	.	.	.	1/8	.	.	.	.	.	.	.	1/16	.	.	.
Daughter of male twin-son of female twin cov.	1/16	.	.	.	1/8	.	.	1/8	.	.	.	.	1/16	.	.	.
Male cousin cov.	1/16	.	.	.	1/8	.	.	.	.	.	.	.	.	.	1/16	.
Twin aunt-niece cov.	1/8	.	.	.	1/8	.	1/8	.	.	.	1/8	.	.	.	.	.
Twin aunt-nephew cov.	1/8	.	.	.	1/8	.	.	.	.	.	.	.	1/8	.	.	.
Twin uncle-niece cov.	1/8	.	1/4	.	3/8	1/16	.	1/8	.	.	.	.	1/8	.	.	.
Twin uncle-nephew cov.	1/8	.	1/4	.	3/8	1/16	.	.	1/4	.	.	.	.	.	1/8	.

terms of six parameters:

$$D_R = \sum_i 4u_i v_i \, (d_i + (v_i - u_i) \, h_i)^2$$

$$H_R = \sum_i 16 u_i^2 v_i^2 \, h_i^2$$

which are the additive and dominance components of variance, respectively, due to the direct effects of the loci ($1/2D_R = V_A$ and $1/4H_R = V_D$);

$$MD_R = \sum_i 4u_i v_i \, (md_i + (v_i - u_i) \, mh_i)^2$$

$$MH_R = \sum_i 16 u_i^2 v_i^2 \, mh_i^2$$

which are the additive and dominance components of variance, respectively, due to the maternal effects of the loci;

$$DMD_R = \sum_i 4u_i v_i \, (d_i + (v_i - u_i) \, h_i) \, (md_i + (v_i - u_i) \, mh_i)$$

$$HMH_R = \sum_i 16 u_i^2 v_i^2 \, h_i \, mh_i$$

which represent the covariance between the direct and maternal effects for the additive and dominance effects, respectively. The latter two components are covariances and may be negative. The contribution of these parameters to the statistics derived from MZ and DZ twin families is shown in Table 1. The two-character model of genetic maternal effects requires only four parameters: D_R, H_R, MD_R, and MH_R; the omission of DMD_R and HMH_R from the expectations given in Table 1 gives the genetic expectations of the two-character model.

We should note that maternal effects will only contribute towards intergenerational statistics if the character studied is the same in both generations. This may not be the case, for example, if the character is age-limited in its expression in some way; the same measured trait in parents and offspring may be subject to different environmental and genetic control in the two generations. In the presence of age limitation, the contribution of direct genetic effects and maternal genetic effects to the covariances between generations will be reduced and may even be zero; nevertheless, the expectations of the statistics derived from the progeny remain unchanged.

The families of twins provide several comparisons which may be diagnostic for the presence of maternal effects. The two most useful comparisons are those between the maternal and the paternal parent-offspring covariance, and between the half-sib covariance in the families of female MZ twins and that in the families of male MZ twins. The expected contributions of direct genetic and maternal effects to these statistics are.

Parent-offspring covariances

Maternal	$1/4D_R + 1/4MD_R + 5/8DMD_R + 1/4HMH_R$
Paternal	$1/4D_R + 1/8DMD_R$

Half-sib covariances

Maternal	$1/8D_R + 1/2MD_R + 1/4MH_R + 1/2DMD_R$
Paternal	$1/8D_R$

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A test for maternal effects can thus be produced from a comparison of the maternal and paternal correlations derived from these covariances. Alternatively, a test can be derived from the mean squares from the hierarchical analyses of variance of the progeny of the twins as long as the distribution of family sizes is similar in the maternal and paternal families. The most powerful direct comparison of mean squares is derived from MZ families and is that between MS_{Bm} and MS_{Bp} (the mean squares between the two families of full-sibs produced by MZ female twins and MZ male twins, respectively). The expectations of these mean squares depend upon the number of offspring per family, with two offspring in every family, and the only environmental variation being that between individuals within families, the expectations are:

$$MS_{Bm} = E_W + 1/2D_R + 5/16H_R$$

$$MS_{Bp} = E_W + 1/2D_R + 5/16H_R + MD_R + 1/2MH_R + DMD_R$$

where E_W is the within-family environmental variance. Thus, with this model, the F ratio $(MS_{Bp})/(MS_{Bm})$ provides a test for maternal effects. A final method for detecting maternal effects is to utilise model-fitting procedures to fit models which omit maternal effects to the complete data set, or a subset of it, and to determine whether the models are adequate.

In order to assess the relatives merits of the methods for detecting maternal effects, a variety of different models were investigated with a view to discovering the sample sizes required for each method to reject the null hypothesis of no maternal effects. The models chosen for study only included variation due to the within-family environment, to additive genetic direct effects, and to additive genetic maternal effects. In different models, the proportional contribution of genetic effects, both direct and maternal, to the total variation was set at 0.2 or 0.5 or 0.8, and the proportion of this due to maternal effects was set at 0.2 or 0.5 or 0.8. Thus, the proportion of the variation due to maternal effects varies between 0.04 and 0.64. Two models for maternal effects were studied, the one-character model and the two-character model. In the one-character model, the variation was divided between MD_R and DMD_R assuming a correlation of one between the direct and maternal effects of a locus. In the two-character model, the variation is solely due to MD_R.

The power of three tests to detect maternal effect was considered. These tests were the comparison of maternal and paternal parent-offspring correlations, the comparison of maternal and paternal half-sib correlations, and the F ratio test $(MS_{Bp})/(MS_{Bm})$. All of these were considered as single-tailed tests. The approximate sample sizes required to reject the null hypothesis at the 5% level of significance in 95% of cases, were derived for the correlations by finding the sample size such that the difference between the z-transformed correlations produced a t value of 3.2896 [18], and by the methodology described by Kearsey [9] for F ratios. Also considered were the sample sizes required to reject models which excluded maternal effects, fitted by the method of weighted least squares, to the mean squares derived from an analysis of MZ twin progeny. The sample sizes required for the chi-square testing the model which only included E_W and D_R to be significant at the 5% level in 95% of cases, were derived using the method of Martin et al [11]. To simplify the analyses, equal numbers of maternal and paternal statistics were used, and for the F ratio test and the model fitting all families had two offspring

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TABLE 2 - Sample Sizes Required to Detect Maternal Effects at the 5% Significance Level on 95% of Occasions

Model			One-character model Test				Two-character model
E_W	$1/2\ D_R$	$1/2(MD_R+DMD_R)$	1*	2*	3+	4+	Test 1*
0.8	0.16	0.04	15835	13425	6755	7030	53235
0.8	0.1	0.1	3230	2140	1075	1170	8560
0.8	0.04	0.16	1720	830	415	475	3555
0.5	0.4	0.1	2235	2065	1075	1340	7800
0.5	0.25	0.25	455	320	165	225	1290
0.5	0.1	0.4	250	120	60	90	515
0.2	0.64	0.16	675	750	415	575	2560
0.2	0.4	0.4	135	110	60	96	445
0.2	0.16	0.64	80	35	20	40	185

Tests:

1) Comparison of parent-offspring correlations.
2) Comparison of half-sib correlations.
3) F ratio $(MS_{Bp})/(MS_{Bm})$ from analysis of variance of progeny of MZ twins.
4) Least squares model fitting to progeny of MZ twins.

* Number of independent pairs of observations required.

+ Number of MZ twin pedigrees of each type (male or female) each with two offspring per family.

per family. The required sample sizes are given in Table 2. These sample sizes represent the number of independent pairs of observations for the comparisons of correlations and the number of families of each type (male or female MZ) for the F ratio test and the model fitting. For all tests, except the comparison of parent-offspring correlations, the one- and two-character models give the same results, thus the results for the two-character model are only given for this latter test.

Inspection of Table 2 reveals that, over the range of models investigated, the half-sib correlations provide a more powerful test for maternal effects than do the parent-offspring correlations; this is particularly the case with the two-character model of maternal effects. Comparison of the results for the F ratio test and the model-fitting reveal that the F ratio is slightly more powerful. The test involving correlations are not directly comparable with the F ratio test or the model fitting. Although each MZ family would contribute four pairs of observations to each correlation (if each twin has two offspring), as individuals are contributing to more than one pair each and individuals within families are correlated, the effective degrees of freedom contributed by each family are less than four [6,17]. Thus, there may not be a great deal to choose between a comparison of half-sib correlations and the F ratio test for the detection of maternal effects.

We can use the expectations given in Table 1 to develop a test which examines the nature of maternal effects for characters which are not age-limited. The genetic contributions to the avuncular covariances from DZ twin families are:

Aunt-Niece/Nephew Covariance $1/8D_R + 1/4MD_R + 3/8DMD_R + 1/16HMH_R$

Uncle-Niece/Nephew Covariance $1/8D_R + 1/8DMD_R$

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If the two-character model of maternal effects is applicable (ie, $DMD_R = HMH_R = 0$), the difference between these covariances should be $1/4\ MD_R$, which is the same as the difference between the parental covariances. Thus, a comparison of the difference between the parent-offspring covariances and the DZ twin avuncular covariances provides information on the precise nature of any maternal effects. In a similar manner, the genetic contributions to the MZ twin avuncular covariances are the same as to the parent-offspring covariances (ie, MZ aunt-niece/nephew covariance = mother-offspring covariance and MZ uncle-niece/nephew covariance = father-offspring covariance). The parent-offspring covariances may in practice be greater than the avuncular covariances due to an environmental covariance between members of the same family. However, the maternal effect as detected by a comparison of the parent-offspring covariances will only be greater than that detected by a comparison of the MZ twin avuncular covariances if there is an environmental contribution to the maternal effect. Thus, a comparison of the difference between the parent-offspring and MZ twin avuncular covariances may reveal if the genetic maternal effects model is adequate.

In practice, the detection of maternal effects is further complicated as families will be variable in size and, as shown later, sex-linkage may simulate maternal effects. These problems will tend to favour the use of model-fitting techniques for the analysis as indeed does the requirement for parameter estimation. We have shown that model-fitting techniques may be only slightly less powerful than individual tests for the detection of maternal effects. Their power may be increased if it is possible to fit the same model to both parents and offspring. Preliminary investigations indicate that the inclusion of data from MZ twins, their progeny and the covariances between them can provide a test for maternal effects which is very economical in terms of the numbers of families required.

SEX-LINKAGE

To build a model for sex-linked effects we follow the example of Mather and Jinks [12, 13] and allow for the sex-linked effects to be sex-limited and for the existence of dominance of sex-linked effects in the female. So, for a single locus with two alleles in Hardy-Weinberg equilibrium we can write:

	Females			Males	
Genotype	AA	Aa	aa	A	a
Frequency	u^2	$2uv$	v^2	u	v
Effect	dx	hx	-dx	dx'	-dx'

Summing over all such loci, the contribution of sex-linked genetic variation to second degree statistics derived from human populations can be written in terms of four parameters:

$$D_S = \sum_i 4u_i v_i\ (dx_i + (v_i - u_i)\ hx_i)^2$$

$$H_X = \sum_i 16u_i^2 v_i^2\ hx_i^2$$

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which represent the additive and dominance components of variance, respectively, due to sex-linked variation in females;

$$D_B = \sum_i 4u_i v_i \, dx_i'^2$$

which represents the additive component of variance due to sex-linked variation in males;

$$D_U = \sum_i 4u_i v_i \, dx_i' \, (dx_i + (v_i - u_i) \, hx_i)$$

which represents the covariance between males and female of the additive effects of sex-linked loci. The contributions of these four parameters to the relationships derivable from MZ and DZ twins and their families are shown in Table 1.

The relative magnitudes of D_S, D_B and D_U will depend upon the exact form of the sex-linked effects. In the simplest and most usually considered case, when there is no sex-limitation of the effects and no dominance in females, $D_S = D_B = D_U$ and $H_X = 0$ thus D_S, D_B and D_U can be replaced in the expectations by a single parameter D_X. In more complex situations, when there is sex-limitation of the sex-linked effects or dominance in the females, D_S, D_B and D_U may take virtually any values relative to one another subject to the limitations that D_S and D_B must be positive and the absolute value of the correlation between additive effects in males and females (ie, $(D_U)/\sqrt{[(D_S)(D_B)]}$) cannot be greater than one. Thus D_U may be zero or even negative whilst at the same time D_S and D_B take appreciable values. The range of possible values of D_S, D_B and D_U must be borne in mind when considering the use of population derived data for the detection of sex-linked effects.

The presence of sex-linked effects may result in a difference between the means of males and females. This in itself is not a particularly useful diagnostic as a mean difference could result from a number of causes some of which do not have consequences for the covariances between relatives. However, if a mean difference between sexes exists it should be removed prior to the use of analysis of variance techniques.

Sex-linkage produces a complex pattern of covariances between relatives and may result in a difference between the variances within males and females. The contributions of sex-linked variation to the most useful statistics for developing tests to detect sex-linkage are:

		Female	Male	
	Total variance	$1/2\ D_S + 1/4\ H_X$	D_B	
	Mother-Daughter	Mother-Son	Father-Daughter	Father-Son
Parent-offspring covariances	$1/4\ D_S$	$1/2\ D_U$	$1/2\ D_U$	0
	Sister-Sister	Sister-Brother	Brother-Brother	
Full-sib covariances	$3/8\ D_S + 1/8\ H_X$	$1/4\ D_U$	$1/2\ D_B$	

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Half-sib covariances	Female-Female	Female-Male	Male-Male
Female MZ progeny	$1/8\ D_S$	$1/4\ D_U$	$1/2\ D_B$
Male MZ progeny	$1/4\ D_S$	0	0

One important point arises from a consideration of the parent-offspring and half-sib covariances. That is, that most patterns of sex-linked inheritance will result in the average covariance between mothers and their offspring being greater than that between fathers and their offspring, and the average covariance between maternally related half-sibs being greater than that between paternally related half-sibs. These relationships are those expected in the presence of maternal effects and may occur even when sex-linkage does not produce differences between the means or total variances of the sexes. There will, however, be differences between the covariances dependent upon the progeny sex, and thus it is essential to ensure that covariances are homogeneous over progeny sexes before proceeding with individual tests for maternal effects.

In situations in which the pattern of covariances between relatives is suggestive of sex-linkage, the relationships shown above can be utilised to build tests for sex-linkage. The use of analysis of variance techniques to analyse the progeny of MZ or DZ twins is complicated by the presence of offspring of both sexes within families. Thus, we shall only consider individual tests which utilise the correlations derived from the covariances between relatives. Of the intergenerational statistics, a comparison of the father-daughter and father-son correlations provides a test for sex-linkage which is free from maternal effects. However, D_U may be near zero or even possibly negative, although this latter alternative is unlikely, and in these cases the mother-daughter correlation will be greater than the mother-son correlation. A comparison of the male half-sib correlation from female MZ families with that from male MZ families also provides a test for sex-linkage as in its presence the former will always be greater than, or equal to, the latter. This test is however confounded with maternal effects and so may only be performed if the female half-sib correlation from female MZ families is not greater than that from male MZ families.

In order to obtain an idea of the sample sizes required to detect sex-linkage using the tests discussed above, a number of different sex-linkage models were examined. In all the models there was no sex-limitation or dominance of the sex-linked effects, thus $D_S = D_B = D_U = D_X$. In different models the proportion of variation in females which was genetic in origin was set to 0.2 or 0.5 or 0.8, and the proportion of this due to maternal effects was set at 0.2 or 0.5 or 0.8. The approximate sample size required to reject the null hypothesis of no sex-linkage at the 5% level in 95% of cases was calculated as previously for the comparison of father-daughter and father-son correlations and the comparison of maternal and paternal male half-sib correlations. The required sample sizes are shown in Table3. All tests were performed as single tailed tests.

Inspection of Table 3 reveals that, over the range of models examined, a comparison of father-offspring correlations provides a more powerful test, in terms of the number of

TABLE 3 - Sample Sizes Required to Detect Sex-Linked Effects at the 5% Significance Level on 95% of Occasions

Model			Test	
E_W	$1/2\ D_R$	$1/2\ D_X$ +	1*	2*
0.8	0.16	0.04	12755	14531
0.8	0.1	0.1	2230	2600
0.8	0.04	0.16	945	1120
0.5	0.4	0.1	1780	2520
0.5	0.25	0.25	355	515
0.5	0.1	0.4	165	250
0.2	0.64	0.16	565	1040
0.2	0.4	0.4	130	240
0.2	0.16	0.64	65	125

Tests:
1) Comparison of father-daughter and father-son correlations.
2) Comparison of maternal and paternal male half-sib correlations.

* Number of independent pairs of observations required.

\+ $D_X = D_S = D_U = D_B$

independent pairs of observations required for sex-linkage, than does the comparison of male half-sib correlations. Furthermore, father-offspring pairs are obtainable in larger numbers than are pairs of male half-sibs, even from studies including only MZ twins and their families. However, if the sex-linked loci are age-limited (the sets of loci influencing the trait in parents and offspring being not 100% concordant) or sex-limited (particularly if the correlation between their effects in males and females is not unity) then a comparison of father-offspring correlations may be less powerful than a comparison of male half-sib correlations.

Sex-linked inheritance leads to particular patterns of relationships within families which will vary dependent upon the precise model. As has been already noted, neither of the tests considered above can be used to detect sex-linkage in all situations. Thus, we might suspect that model-fitting approaches are a more useful general method for the detection of sex-linkage as in its presence diagnostic information is found in many of the relationships from MZ and DZ families. However, as is shown below, sex-limited autosomal genetic variation may mimic sex-linkage in parent-offspring and full-sib statistics and so model-fitting approaches will often have difficulty in distinguishing between these two effects. Thus, simple comparisons of half-sib correlations will often be the best way of separating sex-linked and sex-limited autosomal effects.

SEX-LIMITED GENETIC VARIATION

Following the example of Eaves [3], we can write a model for sex-limited genetic variation which is autosomally linked. Thus, we can replace the two paramters D_R and H_R of the non-sex-linked model with D_{Rf} and H_{Rf} in the variance and covariances of females, with D_{Rm} and H_{Rm} in the variance and covariances of males and with D_{Rmf} and H_{Rmf} in the covariances between opposite-sexed relatives. The contributions of these six parameters to the relationships derivable for MZ and DZ twins and their families are

shown in Table 1. It should be noted that in order to develop a fully sex-limited model it is possible to write the environmental contributions to the variances and covariances within sexes and the covariances between sexes separately.

As was the case with sex-linked effects, the range of possible values of the additive components D_{Rf}, D_{Rm} and D_{Rmf} are limited only by the constraints that the components of variance D_{Rf} and D_{Rm} must not be negative and that the absolute value of $(D_{Rmf})/\sqrt{[(D_{Rf})(D_{Rm})]}$ must not be greater than one. The effects of sex-limited autosomal genetic effects mimic sex-linked effects in that they may produce differences in the means of the sexes which should be removed prior to analysis of variance. Looking at the contribution of additive sex-limited effects to the statistics considered in the case of sex-linkage, we find:

	Female	Male
Total variance	$1/2\ D_{Rf}$	$1/2\ D_{Rm}$

	Mother-Daughter	Mother-Son	Father-Daughter	Father-Son
Parent-offspring covariances	$1/4\ D_{Rf}$	$1/4\ D_{Rmf}$	$1/4\ D_{Rmf}$	$1/4\ D_{Rm}$

	Sister-Sister	Sister-Brother	Brother-Brother
Full-sib covariances	$1/4\ D_{Rf}$	$1/4\ D_{Rmf}$	$1/4\ D_{Rm}$

Half-sib covariances	Female-Female	Female-Male	Male-Male
Female Mz progeny	$1/8\ D_{Rf}$	$1/8\ D_{Rmf}$	$1/8\ D_{Rm}$
Male MZ progeny	$1/8\ D_{Rf}$	$1/8\ D_{Rmf}$	$1/8\ D_{Rm}$

These relationships demonstrate that sex-limited variation may result in differences beween the variances of the two sexes and a pattern of full-sib covariances which could be mistaken for sex-linkage (when $D_{Rf} > D_{Rmf} < D_{Rm}$). A comparison of parent-offspring covariances could also be mistaken for some models of sex-linkage in which D_U is small or negative. However, if the three possible half-sib covariances (between females, between males and between opposite-sexed individuals) are the same in both male and female MZ families but different from one another, this is good evidence for sex-limited autosomal genetic effects.

DISCUSSION

We have considered how our models of maternal effects, sex-linkage and sex-limited autosomal effects contribute to statistics which can be utilised for their detection. It has been suggested that in some cases model-fitting approaches may provide an economical method for the detection of certain effects. This is because these methods may incorporate data from data from several diagnostic relationships and are thus effectively joint tests. Model-fitting approaches also permit simultaneous estimation of a number of parameters. If model fitting approaches are to be used, it is instructive to see how far the components of our genetic models may be separated by different data structures.

The progeny of MZ twins are sufficient, on their own, to avoid any confusion between maternal effects, sex-linked effects and sex-limited autosomal effects. However, with these data, it is not possible to separate the direct and covariance components of maternal effects and thus to distinguish between the one-and two-character models of maternal effects. It is possible to discriminate between the one- and two-character models if the trait under study is not age-limited, because it is then possible to include data on the MZ twin parents and their relationship with their progeny. Alternatively, if data from the progeny of both MZ and DZ twins are analysed, it is not necessary to incorporate parental data in order to distinguish the two maternal effects models, as long as data from the progeny of DZ opposite-sexed twins is included in the analysis.

With sufficient data, the effects due to the models we have examined are not likely to be confused with one another, but it is instructive to examine briefly the problems that might have been caused by the adoption of other plausible models. Of the models we have explored, that for maternal effects is least likely to be universally applicable, for some traits models other than a purely genotypic model may be more realistic. Thus, we might develop phenotypic equilibrium models, such as that for a single character system developed by Falconer [5], or models of vertical cultural transmission with asymmetry between the effects of parents [eg, 1]. If these models contained a genetic contribution, their effects would still be detected as maternal effects by the tests we have described, and would be unlikely to cause the failure of models which assumed only genetic maternal effects. We have described one test for the presence of an environmental contribution to maternal effects, but in most cases fostered individuals would be necessary for the discrimination between genotypic and phenotypic maternal effects. Maternal effects may also be cytoplasmic in origin as mothers provide the majority of their offsprings' cytoplasm. In this case the maternal effects will still contribute to the maternal half-sib covariance and in some cases to the mother-offspring covariance. Corey et al [2] have shown how the grandchildren of MZ twins may be used to distinguish cytoplasmic effects from other types of maternal effect. In general, practically any type of maternal effect will contribute to the similarity of maternally related half-sibs. Fewer types of maternal effects contribute towards the similarity of mothers and their offspring, as in most cases this is only possible when there is some overlap in the characters measured in parents and offspring (ie, the trait expression is not completely age dependent).

Two effects we have not as yet examined may mirror maternal effects. Firstly, assortative mating of an asymmetric type, as investigated by Eaves and Heath [4], could cause an increased half-sib correlation in maternally related families [15,4] and thus be naively detected as maternal effects (it could equally cause an increased half-sib correlation in paternally related families). This form of asymmetry should result in

patterns of correlations between twins and their spouses which differ between male and female pairs of twins and are thus detectable in principle. Secondly, if some of the legal fathers are not the genetic fathers of the progeny, then, as the fathers are on average less closely related to their progeny than the mothers, this could produce a pattern of statistics resembling that due to maternal effects. This would include the father-offspring correlation being less than the mother-offspring correlation and the paternal half-sib correlation being less than the maternal half-sib correlation. This problem can only be reduced by screening the families under study to exclude as many cases of non-paternity as possible. Nevertheless, in the absence of screening, the problem is probably not a serious one. For example, with a narrow heritability of 0.8 and a frequency of random non-paternity as high as 10%, the mother-offspring correlation would be 0.4 and the father-offspring correlation would be 0.36 and the maternal half-sib correlation would be 0.2 whereas the paternal half-sib correlation would be 0.162. That only these small differences occur even when the heritability and the frequency of undetected non-paternity are high suggests that apparent large maternal effects are unlikely to be due to undetected non-paternity.

In conclusion, although it will always be the case that any set of data is amenable to more than a single explanation, data from MZ and DZ twins and their spouses and offspring provide a useful method for detecting and estimating variation due to maternal effects, sex-linked loci and sex-limited autosomal loci. Where model-fitting approaches to data analysis are utilised, data from DZ twins and their spouses and offspring, in addition to that from MZ twin families, is invaluable, allowing the formulation of more complex models of environmental and genetic causation than are possible with MZ twin families alone. Where, as is the case here, sex-associated traits are under investigation, the data from DZ opposite-sexed twins and their spouses and offspring is particularly useful and should not be neglected. The illustrative models we have explored here may well be applicable in a wide range of circumstances, but, as with any models, any deficiencies they have may only become fully apparent when they are applied to real data. Thus, the immediate need is for the collection of sufficient data from MZ and DZ twins and their families and offspring to allow these models to be tested in practice.

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