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Maternal genotype effects can alias case genotype effects in case–control studies

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With the increasing popularity of case–control association studies in human genetics, it is worth recalling that other genetic mechanisms may masquerade as case genotype effects. In particular, in a case–control study, any maternal genotype effects are aliased with case genotype effects. The maternal genotype partially determines the uterine environment, leading to the possibility of detrimental effects in the developing fetus. Such maternal genotype effects have been implicated in developmental disorders, such as spina bifida and autism.[1–4] Maternal–fetal interactions are a separate phenomenon not discussed here.[5]

When an allele contributes to susceptibility only in the mother, the offspring will be enriched for that allele simply by Mendelian inheritance. At a locus with two alleles A and a, with frequencies p and $q=1-p$, respectively, let r_1^m be the relative risk of disease given a single copy of A in the mother and r_2^m the relative risk of disease given two copies of A in the mother. Writing D_c for 'disorder present in the child,' M for the number of copies of the A allele in the mother, and C for the number of copies of the A allele in the child, we have

$$\begin{aligned} P(D_c|C=j) &= \sum_i P(D_c|M=i,C=j)P(M=i|C=j) \\ &= \sum_i P(D_c|M=i)P(M=i|C=j) \\ &= b\sum_i r_i^m P(M=i|C=j) \end{aligned}$$

where b is the prevalence of the disorder among offspring with mothers with genotype aa and $r_0^m=1$. The conditional frequencies, under Hardy–Weinberg equilibrium, of the mothers' genotypes can be easily calculated[6] but are given in Table 1 for easy reference.

By way of example, suppose $p=0.1$, $r_2^m=2$, and $r_1^m=1.5$. For an aa child, by Table 1, the probability of an Aa mother

Table 1 Conditional probability of mother's genotype given child's genotype

	Probability that mother has genotype		
	AA	*Aa*	*Aa*
Given: child AA	*p*	*q*	0
Given: child Aa	*p*/2	1/2	*q*/2
Given: child aa	0	*p*	*q*

Table 2 Apparent relative risks

	Maternal effect	
Parameter	Analysis of cases versus controls	Analysis of mothers of cases versus mothers of controls
Apparent relative risk of Aa	$\frac{1+r_1^m+p(r_2^m-1)}{2+2p(r_1^m-1)}$	r_1^m
Apparent relative risk of AA	$\frac{r_1^m+p(r_2^m-r_1^m)}{1+p(r_1^m-1)}$	r_2^m
	Case effect	
Parameter	Analysis of cases versus controls	Analysis of mothers of cases versus mothers of controls
Apparent relative risk of Aa	r_1^c	$\frac{1+r_1^c+p(r_2^c-1)}{2+2p(r_1^c-1)}$
Apparent relative risk of AA	r_2^c	$\frac{r_1^c+p(r_2^c-r_1^c)}{1+p(r_1^c-1)}$
	Maternal imprinting effect	
Parameter	Analysis of cases versus controls	Analysis of mothers of cases versus mothers of controls
Apparent relative risk of Aa	$(r^j+1)/2$	$(r^j+1)/2$
Apparent relative risk of AA	r^j	r^j

is $p=0.1$ and the probability of an aa mother is $q=0.9$. The Aa mother gives an elevated risk of 1.5 times baseline to her child, whereas the aa mother gives the baseline risk to her child. Thus an aa child has $0.1\times1.5+0.9\times1=1.05$ times the baseline risk. Similarly, an AA child has an AA mother with probability 0.1 and an Aa mother with probability 0.9, so that child's risk is $0.1\times2+0.9\times1.5=1.55$ times the baseline risk. Thus, the apparent relative risk of an AA child relative to an aa child is $1.55/1.05=1.48$. For an Aa child, the probability of an AA mother is 0.05, that of an Aa mother 0.5, and that of an aa mother is 0.45, so an Aa child's risk is $0.05\times2+0.5\times1.5+0.45\times1=1.3$ times baseline, with apparent relative risk (relative to an aa child) equal to $1.3/1.05=1.24$. As this example illustrates, the apparent risk for the case's genotype will be attenuated from the actual risk for the mother's genotype. General expressions for relative risks based on the formula above and Table 1 are given in the upper panel of Table 2.

Even the mode of inheritance can be masked: a recessive model in mothers (so that $r_1^m=1$) will appear to be additive in the cases, with the apparent relative risk of AA equal to $1+p(r_2^m-1)$ and the apparent relative risk of Aa equal to $1+p(r_2^m-1)/2$. Similarly, a multiplicative model in mothers, with $r_2^m=(r_1^m)^2$, will generate an apparently additive model in cases with the apparent case relative risk of AA equal to $1+(r_1^m-1)$ and of Aa equal to $1+(r_1^m-1)/2$.

It is important to note that these apparent relative risks will reappear in a replication study; they are a function of the underlying biology and the study design, not an artifact of chance. Unlike the effects of population stratification on the results of a case–control design, the aliasing of maternal and case-genetic effects cannot be resolved by more refined statistical techniques. The use of family designs, however, can allow maternal and case effects to be distinguished.[7–9] The log-linear test,[7] in particular, can be used with a case–parents design to estimate maternal effects independently of case effects, as well as allowing a test of parental imprinting.

A 'mothers of cases' and controls study also cannot distinguish between maternal effects and case effects. Table 2 shows the apparent relative risks for mothers when there is a case genotype effect based on similar calculations as above. For completeness, the table also shows the apparent relative risks for mothers when there is a maternal imprinting effect on cases.

Although family-based designs offer excellent robustness to population stratification, they cost more per case than case–control designs and involve more difficult ascertainment. For example, among the six studies in the Genetic Association Information Network,[10] one is a family-based design. Thus just one of these high-profile genome-wide association studies can distinguish the effects on cases due to the maternal genotype, by the uterine environment, from the direct effects of genotype on the cases. The vast preponderance of genes can be expected to act directly in subjects. However, until the biological mechanism of a suspected causal variant is determined, given only case–control association studies, we must recall that a statistical association is only an association. In addition to confounders, such as population stratification, there is the question of whether the statistical association of a disorder is really with one's genotype or with one's mother's

genotype. A family-based association study can give a direct answer.

Competing interests

The author declares no competing financial interests.

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