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Increased Rate of Twins among Affected Sib Pairs

To the Editor:

Recently, Greenberg et al. (2001) and Betancur et al. (2002) reported an excess of twin pairs among affected sib pairs with autism (MIM 209850). Greenberg et al. (2001) reported an excess of both MZ and DZ pairs, whereas Betancur et al. (2002) found an excess of MZ pairs only. Both studies tested the rates of twin pairs among a sample of affected sib pairs against the population rates. The hypothesis put forward was that being a twin is in itself a risk factor for autism. The purpose of this letter is to show that an excess of twin pairs among affected siblings—in particular, an excess of MZ pairs—is what would be expected if genetic factors are implicated in the etiology of a disorder and does not in itself suggest that being a twin confers a risk. Hence, the reported results could be a logical consequence of the affected sibling ascertainment scheme.

The proportion of twin pairs among a random sample of affected siblings from the population depends on the population incidence of twinning and on the concordance rate for the disorder. Let p be the incidence of the disorder in the population; f_{MZ} and f_{DZ} the population rates of MZ twins and DZ twins, respectively; and r_S, r_{DZ}, and r_{MZ} be the (casewise) concordance rates (i.e., the probability that one sibling is affected, given that the other sibling is affected) for nontwin siblings, DZ, and MZ twins, respectively. For each of the three kinds of sib pairs, the probability of 0, 1, and 2 affected individuals is, for $r = r_S$, r_{DZ}, r_{MZ},

$$P(0 \text{ affected}) = (1-p) - p(1-r)$$
$$P(1 \text{ affected}) = 2p(1-r)$$
$$P(2 \text{ affected}) = rp \ .$$

It follows that the proportion of MZ pairs among all pairs of affecteds is

$$f^*_{MZ} = \frac{f_{MZ} r_{MZ}}{f_{MZ} r_{MZ} + f_{DZ} r_{DZ} + (1 - f_{DZ} - f_{MZ}) r_S} \ .$$

Note that this proportion is independent of the population incidence. For small DZ and MZ population rates, $f^*_{MZ} \approx f_{MZ} r_{MZ} / r_S$; that is, we would expect an increase in the rate of MZ twins that is proportional to the increase in the concordance rate relative to nontwin siblings. From epidemiological studies, the estimates for the concordance rates for autism in MZ pairs, DZ pairs, and nontwin siblings are approximately 0.4–0.7, 0.0–0.03, and 0.03, respectively (see Lauritsen and Ewald [2001] and Folstein and Rosen-Sheidley [2001] for reviews), consistent with a very high heritability on a liability scale and the existence of nonadditive genetic variation for liability (see, e.g., Smith 1970). These estimates suggest that the proportion of MZ twin pairs in a random sample of affected sib pairs is approximately 13–23 times larger than the population MZ twinning rate. The observed increases in the MZ rate in the Greenberg et al. (2001) and Betancur et al. (2002) reports are 13 and 16, respectively; they are in accordance with the published concordance rates.

Greenberg et al. (2001) also report a significant increase (a nearly fivefold increase) in the proportion of DZ twins among the affected sib pairs. Estimates of DZ concordance rates have been similar to or lower than the rates among nontwin siblings but have been based on small numbers of observations (Folstein and Rosen-Sheidley 2001; Lauritsen and Ewald 2001). An increase in the rate of DZ twins relative to nontwin siblings could be due to common environmental factors or due to the "stoppage" phenomenon, in which parents with one affected child choose not to have more children. Lastly, Greenberg et al. (2001) compare their observed increased rates of autism in affected twin pairs with the rates for insulin-dependent diabetes mellitus (IDDM). They found a deficit of DZ twin pairs but an excess of MZ twin pairs. These results are also consistent with the genetic epidemiology of IDDM, with reported concordance rates of 0.06, 0.11, and 0.30–0.50 for nontwin siblings, DZ twins, and MZ twins, respectively (see, e.g., Kyvik et al. 1995; Field 2002).

In this letter, I have suggested another explanation for the observed excess of twin pairs among affected sibling pairs; that it is simply the effect of ascertaining pairs of affected siblings. Is multiple birth an important risk factor for autism? The data presented by Greenberg et al. and Betancur et al. do not allow the testing of this hypothesis. A population-based study, in which the incidence of autism among MZ twins, DZ twins, and nontwin siblings is estimated should clarify this important issue.

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Electronic-Database Information

Accession numbers and URLs for data presented herein are as follows:

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim/ (for autism [MIM 209850])

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Response to Visscher

To the Editor:

We must admit that Dr. Visscher (2002 [in this issue]) is quite correct and that in our two reports of twins in autism (Greenberg et al. 2001; Betancur et al. 2002) we overlooked the elementary application of Bayes's rule in this situation, namely: If MZ twin pairs are more likely to be concordant than nontwin pairs, then sampling concordant pairs will produce an excess of MZ twin pairs relative to nontwin pairs. This excess says nothing about the relative strengths of genetic or nongenetic effects in autism, contrary to what we concluded in our papers.

However, the points made by Dr. Visscher explain only part of our observations, and they also highlight the sensitivity of the conclusions to the accuracy of the population data. Because twin concordance rates vary from study to study, the issue of increased autism risk to twins is not yet settled. In particular, interpreting the findings from the DZ twins remains problematic.

We begin with some calculation issues. First, Visscher's formulas contain an error, although the error does not affect his conclusions and may even strengthen them. The probability of both members of a sib pair being affected, his $P(2 \text{ affected})$, does not equal rp, as he states. (We use his notation of r for the "pairwise concordance rate," but note that p should represent disease population prevalence, not incidence.) Rather, $P(2 \text{ affected})$ is given by Kp, where K is the "recurrence risk" for that particular kind of sib pair (James 1971; Risch 1990).

To see why, let us use π_i for Visscher's $P(i \text{ affected})$—that is, the probability that a sib pair has i affected sibs. The standard definition (also used by Visscher) says that the pairwise concordance rate r gives the probability that both sibs are affected, given that *at least one* is affected—that is, $r \equiv \pi_2/(\pi_2 + \pi_1)$. In contrast, the recurrence risk K is defined as the recurrence risk to the sib of an affected individual—that is, $P(\text{sib \#2 is affected} \mid \text{sib \#1 is affected})$, which can be written as $\pi_2/P(\text{random individual is affected}) = \pi_2/p$. Since $K = \pi_2/p$,

$$\pi_2 = P(2 \text{ sibs affected}) = Kp \; . \qquad (1)$$