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On the Autistic Spectrum Disorder concordance rates of twins and non-twin siblings

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ABSTRACT

Using the Interactive Autism Network Research Database, the Autistic Spectrum Disorder concordance rates for twins and non-twin siblings were calculated. For males, females and both genders together, the concordance rate for dizygotic twins is approximately twice that of non-twin siblings. We also determined that the concordance rate for non-twin siblings decreases as the interval between pregnancies increases. Our results appear to indicate that the uterine environment may contribute to autism concordance rates.

Introduction

In studies of Autistic Spectrum Disorder (ASD) it is reasonable to assume, on the basis of genetics, that if the first born child in a family is autistic the probability that the second child is also autistic should be the same for fraternal twins as for non-twin siblings. In this paper we present our calculations of the Autistic Spectrum Disorder (ASD) concordance rates for twins and non-twin siblings. Data used in the preparation of this article were obtained from the Interactive Autism Network (IAN) Research Database at the Kennedy Krieger Institute and Johns Hopkins Medicine-Baltimore, sponsored by the Autism Speaks Foundation, version dated August 16, 2010. For up-to-date information see www.ianproject.org. After outlining our methodology, the results are set forth with accompanying explanations. Following that section, we discuss interpretations arising from our analyses and results.

Methodology

For clarity, we begin by setting down the mathematical formulations of several different definitions of concordance rates. Consider the following example for the concordance rate of non-twin male siblings: Suppose that N sets of parents each have a first-born son; then if 1% of these are affected by ASD the number of ASD children is $n(x_1) = 0.01N$ where x denotes ASD and the subscript refers to the birth order within a family. The number of unaffected males is $n(o_1) = 0.99N$ where o denotes children without ASD, and the subscript again refers to birth order within a family. Assuming the same 1% ASD rate for the second-born males of the same parents, there are $n(x_2) = 0.01N$ and $n(o_2) = 0.99N$ among the N second-born males. Here the concordance rate S_A is defined by counting the number of x_1x_2 pairs, that is the number of pairs of siblings both of whom are affected by ASD, and dividing this by the total number of sibling pairs which includes an x_1. Thus:

$$S_A = \frac{n(x_1x_2)}{n(x_1x_2) + n(x_1o_2)} \tag{1}$$

where $n(x_1x_2)$ is the number of x_1x_2 pairs and $n(x_1o_2)$ is the number of pairs where the first born child has ASD, x_1, and the second born child does not have ASD, o_2.

Consider next the concordance rate of any one of the gender combinations (MM, FF, MF and FM) for a set of twins. The calculation here is different since in counting the pairs of twins it is not possible to distinguish between x_1 and x_2, nor between o_1 and o_2. A concordance rate in this case can be defined as:

$$S' = \frac{n(x_1x_2)}{n(x_1x_2) + n(x_1o_2) + n(o_1x_2)} = \frac{n(x_1x_2)}{n(x_1x_2) + 2n(x_1o_2)} \tag{2}$$

where x_1 and x_2 are indistinguishable, and o_1 and o_2 are indistinguishable.

For non-twin siblings, if:

$$n(x_1o_2) = n(o_1x_2), \text{it follows that} \tag{3a}$$

$$S_A = \frac{2S'}{S' + 1} \tag{3b}$$

Note that for twins the equality expressed in (3a) always holds. However, in the IAN data base for non-twin siblings (3a) does not hold. We find that $n(x_1o_2) > n(o_1x_2)$ for all gender combinations.

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Table 1
Concordance rates S_A and S_B for non-twin siblings and S_B for fraternal twins and identical twins.

	All gender	Males only	Females only
Non-twin siblings			
$n(x_1x_2)$	208	127	17
$n(x_1o_2)$	1487	608	132
$n(o_1x_2)$	1034	394	98
$S_A = n(x_1x_2)/[n(x_1x_2) + n(x_1o_2)]$	(12.3 ± 0.8)%	(17.3 ± 1.4)%	(11.4 ± 2.7)%
$S_B = n(x_1x_2)/\{n(x_1x_2) + 0.5[n(x_1o_2) + n(o_1x_2)]\}$	(14.2 ± 0.9)%	(20.2 ± 1.6)%	(12.9 ± 3.0)%
Fraternal twins (DZ)			
$n(xx)$	32	19	3
$n(xo) + n(ox)$	166	66	21
S_B	(27.8 ± 4.2)%	(36.5 ± 6.5)%	(22.2 ± 11.4)%
Identical twins (MZ)			
$n(xx)$		27	4
$n(xo) + n(ox)$		9	2
S_B		(85.7 ± 6.7)%	(80.0 ± 18.1)%

Possible reasons for that will be touched on in the Discussion section below. We now introduce the following definition of S_B [which reduces to S_A when (3a) holds, i.e., when $n(x_1o_2) = n(o_1x_2)$].

$$S_B = \frac{n(x_1x_2)}{n(x_1x_2) + \frac{1}{2}[n(x_1o_2) + n(o_1x_2)]} \tag{4}$$

Note that when $n(x_1o_2) > n(o_1x_2)$ the concordance rate $S_B > S_A$.

The S and S′ definitions given here carry various designations in the literature. For example, Rosenberg et al. [1], following the usage discussed in McGue [2], use the term "pairwise concordance" for our S′, and "probandwise concordance" for our S_B; since their report concerns only twins the difference between S_A and S_B does not arise.

From the IAN data, we arrived at the pair numbers we used for our analyses as follows: In counting the sibling pairs of x_1x_2, x_1o_2, and o_1x_2, families were determined by the father–mother ID given in the IAN data base. For non-twin siblings only those children whose family birth orders are one or two are included in our count. At least one child, x_1 or x_2, in each family is affected by ASD. We exclude from our count IAN families which included birth order coding problems (i.e., two children coded with the same birth order number). For non-twin sibling counts multiple births were excluded. For gender specific counts we include only those families where the first two children are of the same gender. For twin counts birth order within the family was not used as a selection criterion.

Results

Table 1 presents the concordance rates S_A and S_B, which we have calculated from the IAN data base for non-twin siblings and fraternal (dizygotic or DZ) twins for both genders together, for males only, and for females only, and for identical (monozygotic or MZ) twins for males and for females. The standard deviations in Table 1 were calculated using (Favro [3])

$$\sigma = \frac{1}{N+2}\left[\left(\frac{N-2n}{N}\right)^2 + \frac{(N+1-n)(n+1)}{N+3}\right]^{1/2} \tag{5}$$

where $n = n(xx)$ and $N = n(xx) + n(xo)$ for S_A and $N = n(xx) + \frac{1}{2}[n(xo) + n(xo)]$ for S_B.

From genetic considerations alone one would not expect any difference in the concordance rates between non-twin siblings and DZ twins. A striking feature of these results is that there appears to be a substantial difference, approximately 2:1, in the ratios of DZ twin concordance rates to non-twin concordance rates in each of the three categories. For all gender and male results the DZ/Sib concordance ratios, not only S_A but also S_B, are clearly outside of the standard deviation range.

We also calculated the ASD concordance rate using the first and second born children in a family as a function of the age difference (defined as the difference in the birth years) between the two siblings. The weighted linear least squares fit to the data gives

$$S_A(\text{all gender}) = [(16.3 \pm 1.9) - (1.5 \pm 0.6)x]\% \tag{6}$$

where x is the sibling age difference in years (Fig. 1). For males the weighted linear least squares fit to the data gives

$$S_A(\text{male}) = [(20.1 \pm 3.8) - (0.9 \pm 1.4)x]\% \tag{7}$$

If the all gender non-twin concordance rate is extrapolated back to zero age difference, ~16%, it is distinctly different from the all gender DZ twin rate of ~28% (Table 1). In addition, the concordance rate for non-twin siblings decreases as the interval between pregnancies increases. These results suggest that non-genetic factors, environmental or perhaps epigenetic, in the uterus, impinge upon the concordance rates. Cheslack-Postava et al. [4] show that there is also an increased odds of a second child having autism (with the first child not having autism) for closely spaced pregnancies.

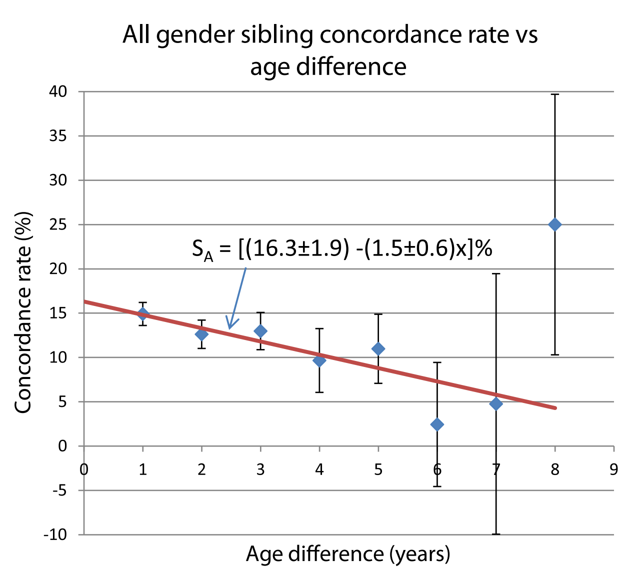

Fig. 1. The all gender ASD concordance rate $\{S_A = n(x_1x_2)/[n(x_1x_2)+n(x_1o_2)]\}$ using the first and second born children in a family as a function of the age difference between the siblings.

Table 2
A comparison of the twin concordance rates calculated in this article, labeled BSH, and those taken from Rosenberg et al. [1] labeled RLY.

	All gender		Males only		Females only	
	BSH	RLY	BSH	RLY	BSH	RLY
DZ twins						
$n(xx)$	32	64	19	39	3	6
$n(xo)+n(ox)$	166	146	66	58	21	17
S_B	(27.8 ± 4.2)%	46.7%	(36.5 ± 6.5)%	57.4%	(22.2 ± 11.4)%	41.3%
MZ twins						
$n(xx)$			27	50	4	9
$n(xo)+n(ox)$			9	8	2	0
S_B			(85.7 ± 6.7)%	92.6%	(80.0 ± 18.1)%	100%

Discussion

The hypothesis set forth in the article by Bohm and Stewart [5] proposes the existence of a uterine environmental effect on MZ twin concordance rates. It differs from the effect we see in the present data in that it deals with a difference in concordance rates between MZ-monchorionic (MZ/MC) and the MZ-dichorionic (MZ/DC) cases, whereas the present data shows a concordance rate difference between fraternal twins (DZ) and non-twin siblings. But it is reasonable to suggest that an MC/DC environmental effect may well be related to the DZ/Sib effect for which evidence has been presented here; neither phenomenon appears to follow simple genetic rules.

The differences in concordance rates between DZ twins and non-twin siblings shown here suggest the possibility of uterine environmental effects for simultaneous birth siblings as compared to time separated sequential siblings. In addition, our results suggest that a short interpregnancy interval increases the incidence of autism among siblings, again indicating that the uterine environment may play a role in contributing to autism concordance rates.

The largest and most recent study on twin concordance rates that we are aware of is Rosenberg et al. [1]. Like the present paper, the data on which their detailed analysis is based also comes from the IAN data base. Where we have comparable results, these are shown in Table 2. The numbers and percentages shown in Table 2 in the columns labeled BSH are from this article and those in the columns labeled RLY (Rosenberg et al. [1]) are calculated from their Tables 2 and 3. Both studies yield an approximate 2:1 ratio between MZ and DZ concordance rates.

The concordance rates listed in Table 1 for non-twin siblings are generally higher than those found in the literature for both all gender and single gender samples (Bailey et al. [6], Newschaffer et al. [7], Smalley et al. [8]). The concordance rates for twins listed in Table 2 (both this article and Rosenberg et al. [1]) are also generally higher than the rates previously reported (Newschaffer et al. [7], Smalley et al. [8], Taniai et al. [9]). Those previous studies were conducted using relatively small sample sizes that may have underestimated concordance rates. The IAN database allowed us to perform statistical analyses on a much larger sample of families with at least one ASD-affected sibling.

It should be noted that Zhao et al. [10] present a calculation to correct their data for an "ascertainment bias." This is an effort to correct their input data (by 14%) for under participation in their database by families with fewer autistic siblings (males). Our S_A and S_B equations represent a less sophisticated effort to recognize that families in which the first child is not affected by ASD but the second is may be less likely to be included in the voluntary IAN data base than families in which the first child is affected by ASD. The S_A values correct the S_B values for such an effect.

Another effort to adjust our input data for possible underrepresentation of DZ and sibling pairs with only one ASD child rather than two ASD children, is to introduce the Zhao et al. [10] 1.14 multiplier to the *xo* count found in Table 1. For male non-simultaneous siblings this lowers the S_A from (17.3 ± 1.4)% to (15.5 ± 1.3)%, and the male DZ rate from (36.5 ± 6.5)% to (33.6 ± 6.2)%. Thus, the DZ concordance rate remains twofold greater than that of non-twin siblings after including the multiplier.

Conclusions

This paper presents analyses of statistical evidence that appears to indicate that the uterine environment may contribute to the autism concordance rates of siblings, both twin and non-twin. It also shows a decreasing concordance rate with increasing age difference between siblings.

Conflicts of intersest

There are no conflicts of interest.

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