Am. J. Hum. Genet. 71:941–946, 2002

On the Twin Risk in Autism

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Autism is considered by many to be the most strongly genetically influenced multifactorial childhood psychiatric disorder. In the absence of any known gene or genes, the main support for this is derived from family and twin studies. Two recent studies (Greenberg et al. 2001; Betancur et al. 2002) suggested that the twinning process itself is an important risk factor in the development of autism. If true, this would have major consequences for the interpretation of twin studies. Both studies compared the number of affected twin pairs among affected sib pairs to expected values in two separate samples of multiplex families and reported a substantial and significant excess of twin pairs. Using data from our epidemiological study in Western Australia, we investigated the possibility of an increased rate of autism in twins. All children born between 1980 and 1995 with autism, Asperger syndrome, or pervasive developmental disorder not otherwise specified (PDD-NOS) were ascertained. Of the 465 children with a diagnosis, 14 were twin births (rate 30.0/1,000) compared to 9,640 children of multiple births out of a total of 386,637 births in Western Australia between 1980 and 1995 (twin rate weighted to number of children with autism or PDD per year 26.3/1,000). These data clearly do not support twinning as a substantial risk factor in the etiology of autism. We demonstrate that the high proportion of twins found in affected-sib-pair studies can be adequately explained by the high ratio of concordance rates in monozygotic (MZ) twins versus siblings and the distribution of family size in the population studied. Our results are in agreement with those of two similar studies by Croen et al. (2002) in California and Hultman et al. (2002) in Sweden.

Introduction

Autism (MIM 209850) is a neurodevelopmental disorder characterized by impairment of social interactions, abnormal language, and a lack of imaginative play, in combination with restricted interests and repetitive behaviors. Although individual case reports of autistic-like disorders had been previously described (see, e.g., reviews by Carrey 1995; Ssucharewa and Wolff 1996), the disorder did not find wide recognition until the influential article by Kanner in 1943. The etiology of the disorder has been debated since. Theories ranged from purely psychological and sociological to biological. During the past 3 decades, the notion that genetic factors strongly influence autism has gained more and more influence, and today autism is considered by many to be among the most heritable psychiatric disorders.

In the absence of any known gene or genes conferring a higher risk of developing autism (Hallmayer et al. 1996; IMGSAC 1998, 2001; Barrett et al. 1999; Auranen et al. 2000; Buxbaum et al. 2001; Liu et al. 2001; Phillipe et al. 1999; Risch et al. 1999; Shao et al. 2002), the main support for autism being genetic is derived from family and twin studies. Estimates of the prevalence of autism in the siblings of probands with autism in studies utilizing direct assessment have been 1%–6% (August et al. 1981; Tsai et al. 1981; Baird and August 1985; Ritvo et al. 1989; Gillberg et al. 1992; Szatmari et al. 1993; Bolton et al. 1994). Szatmari et al. (1998) calculated the combined sibling risk of the family studies published so far to be 2.2%. Even though this recurrence rate in siblings is modest, it is considerably above the general population prevalence of 11–25/10,000 children (Chakrabarti and Fombonne 2001). There are three general population-based twin studies of autism, all of which show a much higher MZ than DZ concordance. A study carried out in Scandinavia (Steffenburg et al. 1989) is the only one with nearly complete ascertainment of twins. The authors reported concordance rates of 90% in MZ twins and of 0% in DZ twins. The most recent study (Bailey et al. 1995) is an extension of an earlier study by Folstein and Rutter (1977), in which concordance rates were 73% in MZ

Received June 13, 2002; accepted for publication July 17, 2002; electronically published September 12, 2002.

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0002-9297/2002/7104-0021$15.00

twins, compared with 0% in DZ twins. Taken together, these studies argue for a substantial MZ-to-DZ concordance ratio. Besides these population-based studies, a study by Ritvo et al. (1985) found a 95% MZ concordance and 24% DZ concordance; this study was based on a sample drawn from an advertisement, which may have led to inflated concordance rates. On the basis of family and twin studies, the heritability has been estimated to be >90% (Bailey et al. 1996). The large difference in concordance rate between MZ and DZ twins has been interpreted as an indication of oligogenic or polygenic inheritance.

Greenberg et al. (2001), however, challenged this conclusion on the basis of their analysis of families with more than one family member affected with autism recruited into the Autism Genetic Resource Exchange (Geschwind et al. 2001). They restricted their analyses to families in which two siblings were affected. Comparing the number of twins among the sib pairs to expected values, they reported a substantial and significant excess of twin pairs ($P < 10^{-6}$). They further claim to have demonstrated "that to ascribe the excess of twins with autism solely to ascertainment bias would require very large ascertainment factors" and estimated that affected twin pairs need to be, on average, ~10 times more likely to be recruited into the study. A recent letter by Betancur et al. (2002) supports the findings by Greenberg et al. (2001). They found a similar increase in the rate of twins among affected sibling pairs with autism in a sample recruited by the Paris Autism Research International Sibpair (PARIS) study. In contrast to the original study by Greenberg et al. (2001), the deviation from population rates was significant only for MZ twins (14-fold increase).

These results have been interpreted to suggest that the twinning process itself is an important risk factor in the development of autism, with major consequences for our interpretation of twin studies (Greenberg et al. 2001). One possible explanation may be that the genetic factors are related to genes in the parents rather than to genes in the offspring (Greenberg et al. 2001). The results have also been taken as evidence of influences of maternal effects that occur in the antenatal or early postnatal periods of life (Korvatska et al. 2002). In addition, among affected sib pairs, Greenberg et al. (2001) found a remarkably higher proportion of MZ twin pairs (more than 10-fold above expected values), compared to the proportion observed in DZ twin pairs (4- to 5-fold above expected values). In the data set by Betancur et al. (2002), only the rate of MZ twin pairs was significantly increased (14-fold). These results strongly suggest estimates of heritability based on concordance for autism in MZ pairs versus DZ pairs to be overestimates.

The studies by Greenberg et al. (2001) and Betancur et al. (2002), because they derive from studies focused on multiplex affected sibships, do not allow for quantifying the increased risk of autism in twins. Such an estimate can only be derived from systematic population-based samples, collected according to epidemiologic principles. In this article, we will discuss twin rates among individuals diagnosed with autism from epidemiological studies carried out in Western Australia, California, and Sweden. These studies do not support the idea that being a twin represents a strong risk factor for autism. We will also demonstrate how the previous finding of a higher rate of autism among twins can be entirely explained by restricting the recruitment to affected sib pairs.

Subjects and Methods

Western Australia has a centralized diagnostic and service delivery system for people with autism. Nearly all diagnoses of autism are made at one of five centers. To develop a retrospective register, diagnostic reports from all persons diagnosed with autism or having autistic features were examined, and a comprehensive listing of all the people diagnosed in Western Australia between 1986 and 1999 was created. All known individuals diagnosed with an autism spectrum disorder born between 1980 and 1995 in Western Australia were linked to the Maternal and Child Health Research Database (MCHRDB) (Stanley et al. 1994). The MCHRDB contains information on every birth in Western Australia since 1980. The Midwives Form, a statutory form completed on all births, forms the basis of the MCHRDB. It contains information on parental demographics and maternal obstetric history; data on pregnancy, delivery, and the neonate; and links to siblings. Information on zygosity of twin births was not known from the birth records.

The total number of linked subjects was 465 (314 with autism, 67 with Asperger syndrome, and 84 with pervasive developmental disorder–not otherwise specified [PDD-NOS]). Two control groups were selected: The first control group was the unaffected, non-cotwin siblings of the cases born after 1980; the second group was the total number of births in Western Australia 1980–1995 ($n = 386{,}637$).

Results

Among the cases (see table 1) there were 14 twins (rate 30/1,000), including both twins from the sole concordant pair (one autism diagnosis, one PDD-NOS diagnosis). Among the 12 discordant pairs, the index case was diagnosed with autism in 10 instances and with PDD-NOS in 2 instances. When the phenotype is restricted to autism, the rate of twins among individuals diagnosed with autism was calculated to be 35/1,000.

Table 1

Number of Individual Twins (and Higher-Order Multiples) among Individuals Diagnosed with Autism in Western Australia, among Their Unaffected Nontwin Siblings and among All Births in Western Australia, 1980–1995

	No. of Individual Twins/ Multiples with		No. of Unaffected Non-Cotwin Siblings	Total No. of Births, 1980–1995
	Autism and PDD	Autism Only		
Individuals from a multiple birth	14	11	16	9,640[a]
Singletons	451	303	453	376,997
Twin rate (per 1,000)	30	35	34	26[b]

[a] Including 339 triplets, 12 quadruplets, and 5 quintuplets.
[b] Twin rate weighted to number of children born per year with autism, Asperger disorder, or PDD.

For autism, Asperger disorder, and PDD-NOS combined, the rate of twins was 30/1,000. There were 16 unaffected twin siblings (eight pairs of twins) among the unaffected, non-cotwin siblings of cases (rate 34/1,000). The rate of multiples in the total Western Australia population was 24.93/1,000 births. Comparisons between case and control individuals were nonsignificant, irrespective of which control group was used (Pearson's $\chi^2 P > .25$). Both the number of twins born and the number of children diagnosed with autism, Asperger disorder, or PDD-NOS increased during the sampling period. The twin rate weighted to number of children with autism, Asperger disorder, or PDD-NOS born per year was calculated to be 26/1,000. Thus, the rate ratio for multiple births comparing autism to total births is 1.35; when PDD-NOS, Asperger disorder, and autism are combined, the ratio is 1.15.

Discussion

The results from our study in Western Australia clearly do not support the excess of autism among twins reported by Greenberg et al. (2001) and Betancur et al. (2002). All children known to diagnostic centers and service providers who were born in the state of Western Australia between 1980 and 1995 and who had received a diagnosis of autism, Asperger disorder, or PDD-NOS were recruited into the study regardless of whether they had an affected sibling. Twin status was obtained by electronic linkage to the MCHRDB. (Data from birth registrations, death registrations, and other sources are linked to the Midwives data to form the database.) Twin rates in this population-based sample of autism spectrum disorders were very similar to—and not statistically significantly different from—those in control individuals. Extending the case definition to include other autism spectrum disorders, such as PDD-NOS or Asperger disorder, did not change the results.

Our results are in good agreement with two recently published population-based studies (Croen et al. 2002; Hultman et al. 2002). Croen et al. (2002) investigated children born in California between 1989 and 1994. Children with autism were ascertained from the California Department of Developmental Services, a statewide agency responsible for coordinating diagnostic and remedial services for individuals with developmental disabilities. They estimated that children enrolled in the regional center system represent ~75%–80% of the total population of California's children with autistic disorder. They electronically linked identifying information, including names, on children. In this study, Asperger disorder, childhood disintegrative disorder, Rett disorder, and PDD-NOS were not included. They compared the linked data set ($n = 4,356$) to the total population of California live births ($n = 3,497,870$). In the autism group, 170 individuals were from multiple births, corresponding to a multiple birth rate of 39/1,000. The calculated rate of 22 multiple births/1,000 (77,880 multiple births out of a total of 3,497,870) in the denominator population group was modestly, but significantly, lower (22/1,000). The estimated adjusted rate ratio for multiple births compared to singletons was 1.7 (95% CI 1.4–2.0), considerably less than postulated by Greenberg at al. (2001) or Betancur et al. (2002).

Hultman et al. (2002) conducted a case-control study comparing 408 children discharged with a main diagnosis of autism from any hospital in Sweden from 1987 to 1994 to control children individually matched by sex, year of birth, and hospital of birth (five children per case, $n = 2,040$). Among the 408 children diagnosed with autism were 11 twin individuals. The number of twin individuals in the control group was 46. Differences between groups were not significant and the odds ratio for twins compared to singletons was calculated to be 1.2 (95% CI 0.6–2.4).

The combined sample size of 195 children from multiple births in these three population-based studies of autism (or autism spectrum disorder) is certainly sufficient to detect an increase in the risk of the magnitude reported by Greenberg et al. (2001) or Betancur et al. (2002) from affected sib-pair samples. In the three studies, the increase in risk for twins to be diagnosed with

Table 2

Proportion of Twin Pairs with Both Twins Affected among Affected Sib Pairs

Percentage of Families with Two Pregnancies Resulting in a Birth	Results for Model 1			Results for Model 2		
	No. of Affected Sib Pairs	Percentage of Affected Twin Pairs per Affected Sib Pairs	Percentage of MZ Twin Pairs per Affected Sib Pairs	No. of Affected Sib Pairs	Percentage of Affected Twin Pairs per Affected Sib Pairs	Percentage of MZ Twin Pairs per Affected Sib Pairs
0	44	100.0	87.2	131	100.0	63.7
10	99	44.1	38.4	599	21.8	13.9
20	152	28.7	25.0	1,048	12.5	7.9
30	197	22.2	19.3	1,428	9.1	5.8
40	235	18.6	16.2	1,753	7.4	4.7
50	268	16.2	14.2	2,036	6.4	4.1
60	297	14.7	12.8	2,283	5.7	3.6
70	323	13.5	11.8	2,500	5.2	3.3
80	346	12.6	11.0	2,694	4.8	3.1
90	366	11.9	10.4	2,867	4.6	2.9
100	385	11.3	9.9	3,023	4.3	2.7

NOTE.—In model 1, the parameters are: disorder with a disease frequency of 0.0012, a sibling recurrence risk of 0.03, and a 70% concordance rate for MZ twins. In model 2, the parameters are: disease frequency of 0.004, sibling recurrence risk of 0.08, and a 37% concordance rate for MZ twins. The same values for twin birth rates were assumed as used by Greenberg et al. (2002): 1/62.5 for DZ twins and 1/130 for MZ twins.

autism, in comparison to singletons, is modest at best and cannot explain the difference in concordance rates between MZ and DZ twins described in previous studies (Folstein and Rutter 1977; Steffenburg et al. 1989; Bailey et al. 1995). The genetic inference derived from these twin studies remains valid.

The question arises how these seemingly contradictory results can be explained. The studies by Greenberg et al. (2001) and Betancur et al. (2002) compared the number of affected sib pairs to the "expected" number of twin pairs with both twins affected. The "expected" twinning rate per sib pair was calculated as double the published twinning rate per birth for European populations. The calculations did not take into account either the high ratio of concordance between MZ and DZ twins in autism or the distribution of the number of siblings in the population.

In the case of autism, the average MZ concordance has been estimated to be 70%, compared with a DZ rate of 0% (Folstein and Rosen-Sheidley 2001). The observed rate of 0% results from the small number of DZ pairs studied, and the true rate is probably closer to the sibling recurrence risk of 3%. It is obvious when recruiting sib pairs that the majority of MZ twins will be concordant (i.e., both twins will be affected); however, in the case of siblings and DZ twin pairs, over 95% will be singleton, and in only a small proportion of families will both sibs be affected. The proportion of MZ twins is therefore substantially increased when ascertainment is restricted to families with two affected siblings.

Equally important is the distribution of the number of children per family. Twin pairs and sib pairs are confined to families with more than one child. In 2000 in the United States, the proportion of families with one child was 41% of all families with children. Another 38% of families have two children, and only 21% of families have three or more. This leads to a higher proportion of twins among families with two or more children. To demonstrate the potential influence, we calculated the proportion of twin pairs with both twins affected among affected sib pairs for a hypothetical birth cohort of 10,000,000 individuals (table 2). For simplicity, we assumed only two types of families. The first type has exactly one pregnancy resulting in one or more live births. The second type has two pregnancies. We varied the percentage of families with two pregnancies versus one, as shown in table 2. The parameters underlying model 1 are based on epidemiological studies of autism (Folstein and Rosen-Sheidley 2001). Model 2 corresponds to Insulin-Dependent Diabetes Mellitus (IDDM) (Rich 1990).

In the extreme case that families have only one pregnancy, all affected sib pairs are twins. For example, a side effect of the one-child policy adopted in China is a very high proportion of affected twins in sib pair studies. But even at higher proportions of families with two pregnancies, the percentage of affected twin pairs among affected sib pairs is substantially higher in comparison to the 2.4% "expected" by Greenberg et al. (2001). In the Greenberg et al. (2001) study, this proportion is 18% for the total sample and 23% for the narrow diagnostic grouping.

Greenberg et al. (2001) carried out a comparable

analysis in a sib-pair sample of IDDM, which was reported to be ascertained in a similar way as the autism sample. The ratio between the concordance rate of MZ twins and the sibling recurrence risk ratio is substantially lower in this disorder (~2–5). No increase in the rate of all twins compared to expectations was found. The parameters for model 2 are based on studies of IDDM (Rich 1990). The proportion of affected twin pairs among sib pairs is substantially lower. For IDDM, Greenberg et al. (2001) reported 15 twin pairs out of a total of 649 affected sib pairs (2.3%), which is within the range of our calculations.

Our calculations suggest that the proportion of affected twin pairs among affected sib pairs is dependent on a number of population-based parameters, including twinning rate, family size, sibling recurrence risk, and concordance rates. Twinning rates and family size vary considerably, both geographically and in time. A realistic estimate of the expected number of affected twins can only be achieved through systematic ascertainment based on an epidemiological framework.

Population-based studies in California (Croen et al. 2002), Sweden (Hultman et al. 2002), and Western Australia, as reported here, found only a slight-to-moderate increase in the risk for multiples, compared to singletons, to be diagnosed with autism. Even for this relatively small increase, one should not ignore the potential of ascertainment bias. Twin pairs concordant for the disorder have a higher chance to be referred to diagnostic and treatment centers. There may also be an increased probability of diagnosing autism in the cotwin of an individual already diagnosed with autism. The high proportion of twins found in affected sib pair studies is most likely explained by the high ratio of concordance rates in MZ twins versus siblings and the distribution of family size in the population studied.

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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