ARTICLE

Characteristics and Concordance of Autism Spectrum Disorders Among 277 Twin Pairs

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Objectives: To examine patterns of autism spectrum disorder (ASD) inheritance and other features in twin pairs by zygosity, sex, and specific ASD diagnosis.

Design: Cross-sectional study.

Setting: Internet-based autism registry for US residents.

Participants: Survey results from 277 twin pairs (210 dizygotic [DZ] and 67 monozygotic [MZ]) aged 18 years or younger with at least 1 affected twin.

Main Exposures: Zygosity and sex.

Outcome Measures: Concordance within twin pairs of diagnosis, natural history, and results from standardized autism screening.

Results: Pairwise ASD concordance was 31% for DZ and 88% for MZ twins. Female and male MZ twins were 100% and 86% concordant, respectively, and DZ twin pairs with at least 1 female were less likely to be concordant (20%) than were male-male DZ twin pairs (40%). The hazard ratio for ASD diagnosis of the second twin after a first-twin diagnosis was 7.48 for MZ vs DZ twins (95% confidence interval, 3.8-14.7). Affected DZ individual twins had an earlier age at first parental concern and more frequent diagnoses of intellectual disability than did MZ twins; MZ twins had a higher prevalence of bipolar disorder and Asperger syndrome and higher concordance of the latter. Results of autism screening correlated with parent-reported ASD status in more than 90% of cases.

Conclusions: Our data support greater ASD concordance in MZ vs DZ twins. Overall higher functioning, psychiatric comorbidity, and Asperger syndrome concordance among affected MZ vs DZ twins may also suggest differential heritability for different ASDs. For families in which one MZ twin is diagnosed with ASD, the second twin is unlikely to receive an ASD diagnosis after 12 months. In addition, Internet parent report of ASD status is valid.

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ALTHOUGH DIAGNOSES OF autism spectrum disorders (ASDs) are increasing in the United States, the genetic and environmental bases of these heritable[1] (>85%) yet heterogeneous neuropsychiatric disorders still are not well understood.[2-7] In this article, ASD refers to a subset of the pervasive developmental disorders described in the *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition, Text Revision) (*DSM-IV-TR*).[8]

Only 10% of ASD cases can be directly attributed to an underlying medical condition, such as fragile X syndrome,[9] and idiopathic autism is likely caused by a combination of genetic and environmental factors.[9-12] Although molecular genetic research has made some advances among ASD multiplex families in elucidating specific genetic linkages,[6] there have been few ASD twin studies.[9-11,13] To our knowledge, only 5 epidemiologically based, distinct twin samples with at least 1 autistic proband have been described since 1977, and all described fewer than 50 twin pairs[14-19]; pairwise monozygotic (MZ) concordance for ASD ranges from 36% to 95% and dizygotic concordance (DZ) from 0% to 23%.

Recently, the Interactive Autism Network (IAN) was developed as an online community within a research framework, in part to reduce the challenges of recruiting participants with autism. The IAN may now represent the largest research cohort of twins with at least 1 proband with ASD (N=277). In this study of data from the IAN, we test 4 hypotheses. First, although this is not an epidemiologic sample, we expect that the rates of concordance among MZ and DZ twin pairs will be consistent with past population-based studies. In comparing MZ and DZ concordant pairs, we anticipate there will be significantly more homogeneity in the presentation, natural history, and medical history among MZ pairs, including age

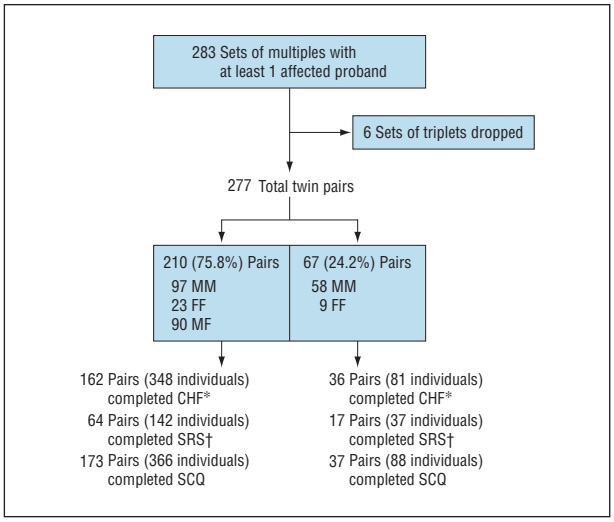

Figure 1. Participant inclusion and comparison of form completion by twin type. CHF indicates child history form; FF, female-female; MF, male-female; MM, male-male; SCQ, Social Communication Questionnaire; and SRS, Social Responsiveness Scale. *χ^2 $P<.05$ for dizygotic (DZ) and monozygotic (MZ) twin pairs and individual form completion. †Completion among eligible (age ≥4 years) participants only. A total of 190 MZ and 57 DZ twin pairs had access to the SRS.

at diagnosis and Social Communication Questionnaire (SCQ)[20] and Social Responsiveness Scale (SRS)[21] scores. Second, we hypothesize that, given the heterogeneous causes of ASD and the complex interplay between genetics and the environment, affected DZ and MZ twins may have different disease characteristics and natural histories.[22-24] Third, considering that genetic contributions to specific components of the 3 ASDs appear to differ,[25,26] we anticipate that ASD diagnostic concordance will also differ by sex.[19,23,27] Fourth, we will demonstrate the utility of the IAN as a new twin registry for autism, which can provide unique knowledge because of its large sample size. By using data from parent-completed questionnaires, including SCQ and SRS scores, we will demonstrate that parent-reported ASD data are a reasonable proxy for determining ASD status.[22,27-29]

METHODS

PARTICIPANTS

The IAN is an online, US-based research database begun in April 2, 2007, with more than 25 000 individuals enrolled, including 9000 children with an ASD and their immediate family members. The database is continually updated, recruitment is ongoing, and all data are voluntarily submitted by families. A pilot phase of data collection began on September 11, 2006, and the current analysis was conducted with data received as of 12:34 PM on July 15, 2008. The IAN is an open resource, with deidentified data made available to other research groups.

Of registered respondents with ASD, all self-identified twins were selected. Multiple births beyond twins were excluded. The IAN includes family members without ASD, and any twin pairs in which neither twin is identified as having an ASD were eliminated (**Figure 1**). Twins with diagnoses of autistic disorder (AD), pervasive developmental disorder, not otherwise specified (PDD-NOS), and Asperger syndrome (AS) were included; respondents choosing a diagnosis of ASD or PDD were included in the category "other ASDs." Rett syndrome is an exclusion criterion for registering with IAN, and respondents with childhood disintegrative disorder were excluded from this analysis. Data from twins who met inclusion criteria were then linked to data from their co-twins, both affected and unaffected. Families with at least 1 affected twin received an e-mail message in May 2008 asking them to complete any unfinished IAN questionnaires, particularly the child profile form.

Demographic and other general characteristics of the study sample are provided in **Table 1**. Options for race/ethnicity were provided by the registry; parents could decline to answer or could report 1 or more races.

QUESTIONNAIRES AND SCREENING

The IAN Project data collection consists of multiple topic-specific questionnaires, authored by the IAN research team in collaboration with other researchers, and 2 standardized instruments (SCQ and SRS) commonly used in ASD research.

IAN Questionnaires

All families complete the initial registration forms and are then invited to complete several other questionnaires, including a profile for each affected child and his/her siblings; once registered, families receive reminders every 2 weeks to complete outstanding questionnaires. These questionnaires were developed by IAN staff in collaboration with members of the IAN Science Advisory Committee and were tested during pilot studies and revised as needed. All participants completed a second-generation version of the questionnaire (Figure 1).

Participants were categorized as having an intellectual disability (ID) if they reported either a diagnosis of mental retardation or an IQ score of less than 70.

Social Responsiveness Scale

The SRS (Western Psychological Services, Los Angeles, California) is a validated, 65-item, parent/teacher-completed, norm-referenced screening tool designed to differentiate between individuals with ASD and those without ASD and/or with other psychiatric conditions, primarily by examining social deficits, in particular, social reciprocity.[21,30] Clinical *t* score screening categories of less than 55, 55 to 59, 60 to 75, and more than 75 suggest likely unaffected status and borderline, mild to moderate, or severe autistic features, respectively. The SRS parent form was included for all IAN participants aged 4 to 18 years as of February 26, 2008.

Social Communication Questionnaire

The SCQ,[20] originally called the Autism Screening Questionnaire, is a widely used, dichotomous autism screening tool consisting of 40 items based on *DSM-IV-TR* criteria for ASDs and the Autism Diagnostic Interview–Revised (Western Psychological Services). A *t* score of 15 or more is suggestive of ASDs. For clinical use, the SCQ cutoff score for marked verbal impairment for siblings of affected children is 12 or higher to adjust for the increased probability that they have ASD. The SCQ, lifetime version, was made available to all IAN participants aged 2 to 18 years as of April 2, 2007.

DATA COLLECTION

Electronic consent was elicited from participating families under the auspices of The Johns Hopkins Medicine Institutional Re-

Table 1. Demographic and Natural History Characteristics of 554 Individual Twins and 277 Twin Pairs[a]

	DZ Twins	MZ Twins	All Twin Pairs
No. of twin pairs	210	67	277
Mean (SD) age, y	7.6 (3.5)	7.8 (3.6)	7.7 (3.5)
Race[b]			
White	194 (92.4)	64 (95.5)	258 (93.1)
Black/African American	9 (4.3)	1 (1.5)	10 (3.6)
Native Hawaiian/Pacific Islander	1 (0.5)	0	1 (0.4)
Asian	6 (2.9)	2 (3.0)	8 (2.9)
American Indian/Alaskan Native	1 (0.5)	0	1 (0.4)
Other	6 (2.9)	2 (3.0)	8 (2.9)
Unknown	0	0	0
Ethnicity			
Hispanic (207 DZ and 67 MZ pairs)	8 (3.9)	7 (10.5)	15 (5.4)
Total individual twins	420	134	554
Male sex	284 (67.6)	116 (86.6)	400 (72.2)
Individuals with ASDs[b]	274 (65.2)	126 (94.0)	400 (72.2)
Autism	155 (56.6)	68 (54.0)	223 (55.8)
PDD-NOS	61 (22.3)	29 (23.0)	46 (22.5)
Asperger syndrome	26 (9.5)	20 (15.9)	90 (11.5)
Other	32 (11.7)	9 (7.1)	41 (10.3)
Natural/medical history, No. of co-twins with ASD	274	126	400
Male sex	220 (80.3)	108 (85.7)	329 (82.3)
With completed forms	203 (74.1)	73 (58.0)	276 (69.0)
Severe prematurity, <34-wk gestational age (n=265)	39/196 (19.9)	18/69 (26.1)	57 (21.5)
Mean (SD) age at diagnosis, mo (n=274)	37.8 (21.3)	38.1 (17.6)	37.9 (20.4)
Age at which parents were first concerned (n=273),[b] mo	202	72	274
0-17	113 (55.9)	29 (40.3)	149 (51.8)
≥18	89 (44.1)	43 (59.7)	139 (48.2)
Any skills lost	74 (36.5)	25 (34.3)	99 (35.9)
Loss of social or communication skills at age <3 y[c]	60 (29.6)	20 (27.4)	80 (29.1)
Educational level			
Any special education (n=248)	150/183 (82.0)	48/65 (73.9)	198 (79.8)
Has aide (n=270)	104 (52.5)	32 (44.4)	136 (50.4)
Comorbidities per parent report			
"Mental retardation"/intellectual disability (n=274)[d]	51/201 (25.4)	12/73 (16.4)	64 (23.0)
Attention-deficit/hyperactivity disorder	40 (19.7)	15 (20.6)	55 (19.9)
Bipolar disorder[d]	3 (1.5)	4 (5.5)	7 (3.5)
Anxiety disorder	26 (12.3)	9 (12.3)	36 (13.0)
Seizures/epilepsy	13 (6.4)	4 (5.5)	17 (6.2)
SCQ, Affected twins			
Completed SCQ	223/274 (81.4)	81/126 (64.3)	304/400 (76.0)
Positive results			
Cutoff score >15 for all	202 (90.6)	72 (89.0)	274 (90.1)
Cutoff score >15; <13 if sibling	212 (95.1)	77 (95.1)	289 (95.1)
SRS, Affected twins			
Completed SRS/No. eligible (% completing SRS)[e]	81/250 (32.4)	32/107 (29.9)	113/357 (31.7)
Mean (SD) *t* score	86.0 (16.2)	81.6 (13.9)	84.8 (15.6)
Category			
Severe	59 (72.8)	20 (62.5)	79 (69.9)
Mild to moderate	18 (22.2)	11 (34.4)	29 (25.7)
Borderline	3 (3.7)	0	3 (2.7)
Likely unaffected	1 (1.2)	1 (3.3)	2 (1.8)

Abbreviations: ASD, autism spectrum disorder; DZ, dizygotic; MZ, monozygotic; PPD-NOS, pervasive developmental disorder, not otherwise specified; SCQ, Social Communication Questionnaire; SRS, Social Responsiveness Scale.

[a] Data are given as number (percentage) of participants unless otherwise indicated. For "Race/Ethnicity," parents could report 1 or more races.

[b] $P \leq .05$.

[c] A total of 24 children were younger than 3 years when data were collected and thus were still at risk for loss of skills.

[d] $P \leq .10$.

[e] For the SRS, participants are eligible if aged 4 years or older; SRS was made available to Interactive Autism Network families in February 2008. Categories based on *t* score were defined as: likely unaffected, <55; borderline, 55-59; mild to moderate, 60-75; severe, >75.

view Boards. All survey data were entered by parents and maintained in the Internet-Mediated Research System (Medical Decision Logic, Inc, Baltimore, Maryland). If families skipped a question based on an answer to the previous question, answered "don't know," or declined to answer a question, data were recorded as missing. All analyses are based on nonmissing data.

STATISTICAL ANALYSIS

For descriptive analysis, comparison between MZ and DZ twin pairs was performed at both the pair and individual levels based on available data using the paired *t* test and χ^2 proportion test. To compare twin-type distribution with population averages,

Table 2. ASD Concordance Among All Twin Pairs by Twin Type[a]

	DZ Twins	MZ Twins
No. of pairs	210	67
Pairwise concordance[b]	64 (30.5)	59 (88.1)
Probandwise concordance,[b] %	46.7	93.7
Total No. of concordant pairs[c,d]	52	51
Diagnosis		
Autism/PDD-NOS for both twins	40 (76.9)	42 (82.4)
Asperger syndrome for both twins	2 (3.9)	7 (13.7)
Autism/PDD-NOS and Asperger syndrome	10 (19.2)	2 (3.9)

Abbreviations: ASD, autism spectrum disorder; DZ, dizygotic; MZ, monozygotic; PPD-NOS, pervasive developmental disorder, not otherwise specified.

[a] Data are given as number (percentage) of participants unless otherwise indicated.

[b] $P<.001$.

[c] $P<.02$.

[d] Excludes pairs with more than 1 member with "other ASD."

the 2-sample test of proportions was used. To assess the validity of parent-reported ASD among children enrolled in IAN, available SRS and SCQ scores for all affected and nonaffected twins were analyzed using published cutoff points for binary designation of ASD status and compared using κ interrater agreement.

Pairwise and probandwise[31] concordance was calculated using unweighted and weighted χ^2 analysis, respectively, assuming an ascertainment ratio of 1.0. For exact diagnosis concordance, we considered collapsing the "other ASD" category with PDD-NOS. However, there were significant differences in the proportion of positive SCQ screening results and mean age at diagnosis between these groups, suggesting real differences; therefore, we were unable to combine them (data not shown).

A nonparametric Kaplan-Meier procedure was used to estimate the diagnosis-free time for twin B, using the lag time between diagnosis of twin A and twin B (twin A was defined as the first diagnosed twin; if both twins were diagnosed simultaneously, twin A status was assigned to the first twin registered in the IAN). In addition, the association between the risk of diagnosis in twin B and type of twin (MZ or DZ) was assessed using a semiparametric Cox proportional hazards model.

Data from twin pairs with completed forms were compared using χ^2 analysis and Fisher exact 1- and 2-tailed tests (categorical variables) or a *t* test weighted for unequal variance (continuous variables). Analyses were completed using STATA statistical software, version 9.2 (STATACorp, College Station, Texas) on the live database.

RESULTS

Racial/ethnic, age, and sex distributions were similar for DZ and MZ twin pairs, although whites are overrepresented in the entire sample. Overall, MZ pairs constituted 25% of the total twin sample (Table 1). Significantly fewer child profiles were completed for MZ than for DZ twins; logistic regression suggested that presence of concordance was the determining factor for incomplete child profile forms (data not shown). Among affected individual twins, significantly more DZ participants reported a diagnosis of "other ASD," and more MZ participants reported having AS (Table 1). Parents of affected DZ individuals were significantly more likely (44.1%) to first become concerned before the child reached age 18 months, compared with those with MZ twins (59.7%; $P=.02$). In addition, DZ twins were more likely to report diagnoses of ID (by parent report or IQ score) ($P=.12$) and less likely to report having bipolar disorder ($P=.06$). Among affected twins, there was no difference in SRS or SCQ score distribution or screening results between twin types.

Table 2 shows that concordance was significantly higher among MZ twins than DZ twins. Given the assumption that PDD-NOS is a milder form of AD, but markedly different from AS, we labeled twin pairs as severity concordant if both twins had AD and/or PDD-NOS or if both twins had AS; otherwise, twins were considered discordant (103 pairs). Among ASD-concordant pairs with a *DSM-IV-TR* diagnosis, significantly more MZ pairs than DZ pairs (96.1% vs 80.8%) were severity concordant ($P=.02$). This difference was mainly because of the higher prevalence and concordance of AS among MZ twins.

Table 3 demonstrates that there were no female-female MZ twins diagnosed as having AS. Among male-male twin pairs, 58 (14%) MZ and 97 (2%) DZ pairs were AS concordant, although there was no significant difference in the proportion of AS diagnoses in twin A (6/31 vs 8/43; $P=.93$). Further analysis of differences by zygosity found that, among DZ pairs, having at least 1 female conferred a significantly decreased risk ($P<.01$) of concordance (relative risk, 0.55; 95% confidence interval [CI], 0.36-0.84). The adjusted relative risk ratio (0.70) for concordance by twin type (DZ:MZ) was significantly different for pairs with at least 1 female member compared with male-male twins ($P<.001$; 95% CI, 0.36-0.84).

Figure 2 shows that, among concordant twins with a known age at diagnosis, MZ co-twins had a significantly higher risk than DZ cotwins (hazard ratio, 7.5; 95% CI, 3.8-14.7; $P<.001$). By approximately 3 months after the twin A diagnosis, the proportion of autism diagnoses for twin B was 51% for MZ twins and 94% for DZ twins. Mean time between diagnosis of twin A and twin B among concordant pairs was 5.0 months (95% CI, 1.5-8.5) and 1.8 months (95% CI, 0.6-3.0) for DZ and MZ pairs, respectively ($P=.08$; 95% CI, 0.41-6.91) (Figure 2).

Table 4 demonstrates that, among concordant pairs who completed child profile forms (59 pairs), DZ twins were significantly more discordant for lost skills. In addition, a trend was seen for DZ twins being more discordant for ID, timing of developmental milestones, and specific early skill loss.

There was no significant difference in SRS or SCQ scores between DZ vs MZ twins (**Table 5**). For SRS and SCQ (cutoff score, ≥15) screening tests, percentage agreement with reported ASD status was 92.1% ($\kappa=0.8$); for the SCQ with the adjusted cutoff point (see the "Social Communication Questionnaire" subsection in the "Methods" section), agreement and κ were even higher (94% and 0.88, respectively). Among reportedly unaffected twins, 9 of 150 (6.0%) and 9 of 66 (13.6%) had positive results on the SCQ and SRS, respectively; of reportedly affected twins, 14 (5%) and 5 (4.4%) had negative results from SCQ and SRS, respectively.

Table 3. ASD Concordance by Twin Type and Sex

	No. of Twin Pairs	Overall ASD Concordance	Neither Twin Had Undefined ASD, No. of Twin Pairs	Diagnoses, % of Twin Pairs				*P* Value (Fisher Exact Test)	
				AS for Both	AD/PDD-NOS for Both	AD/PDD-NOS and AS	Affected and Unaffected	MM vs FX	MM MZ vs MM DZ
MZ									
MM	58	86.2	50	14.0	70.0	2.0	14.0		
FF	9	100	8	0.0	87.5	12.5	0.0	.30	<.01
Total	67	88.1	58	. . .	. . .	. . .	. . .		
DZ									
MM	97	40.2	82	2.2	26.8	8.5	62.5		
FF and FM	113	22.1	103	0.0	17.5	2.9	79.6		
FF	23	26.1	21	0.0	19.1	4.8	76.2	.03	. . .
FM	90	21.1	82	0.0	17.1	2.4	80.5		
Total	210	30.5	185	. . .	. . .	. . .	. . .		

Abbreviations: AD, classic autism or autistic disorder; AS, Asperger syndrome; ASD, autism spectrum disorder; DZ, dizygotic; ellipses, not applicable; FF, female-female; FM, female-male; FX, pairs with at least 1 female member; MM, male-male; MZ, monozygotic; PPD-NOS, pervasive developmental disorder, not otherwise specified.

COMMENT

This study is the largest to date of proband-ascertained twin pairs with at least 1 autistic proband (N=277); our findings confirm the importance of genetic and nongenetic factors in contributing to ASDs and the validity of a new Internet-based autism registry.[15-19,32,33] Our data also suggest that zygosity and sex may contribute to ASD heritability.

CONCORDANCE IN DZ VS MZ TWINS

Concordance rates among DZ twins are consistent with other studies, including the largest and most recent twin study in Japan, which also reported an overall DZ concordance rate of approximately 30%.[15,19] Other studies have reported concordance rates among DZ twins as low as 0%, although the largest sample size was fewer than 60 pairs.[16-18] This moderately high concordance among DZ twins, especially male-male pairs, also contrasts with previously reported rates of nontwin sibling occurrence of ASD between 3% and 14%, and at least 20% if including the broad autism phenotype.[4,12,15,19,27-29,34-38] This discrepancy may be owing to selection bias for multiplex families, which is inherent in voluntary registries such as IAN, or for families with higher socioeconomic status[33,38]; lack of stoppage rules for twins; or secular changes in diagnostic trends.[18,24,28] However, in our study, MZ concordance for ASDs is consistent with earlier literature, which reported rates of 80% to 100%, suggesting that our data are reliable.[15-19]

As expected, concordance of developmental milestones and other natural history features, including ID, within DZ twin pairs was lower than within MZ twin pairs. In addition, DZ twins had significantly more discordance for overall skill loss, and somewhat more for early social skills loss, which is an intriguing finding because autistic regression has emerged as a controversial topic in clinical practice and research.[39]

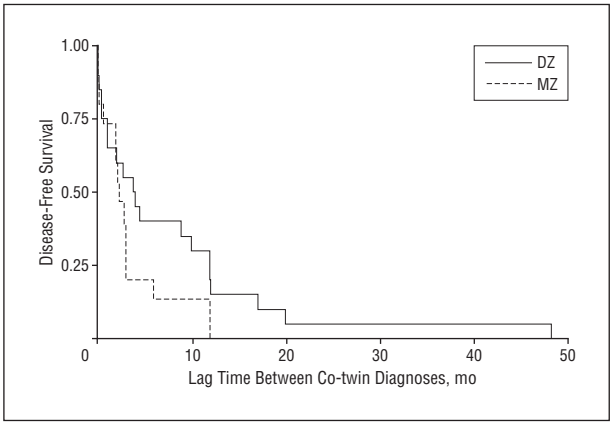

Figure 2. Lag in autism spectrum disorder diagnosis among concordant twin pairs, dizygotic (DZ) (n=32) vs monozygotic (MZ) (n=29).

ROLE OF ZYGOSITY IN ASD PHENOTYPE

Apart from overall concordance, we found several unexpected patterns relating ASD type with zygosity. Overall, affected DZ individuals had higher proportions of ID and AD and significantly earlier age at onset than their MZ counterparts (Table 1). The latter may be partly owing to a rater contrast effect or because DZ individuals with ASDs display a different, more severe subtype of ASD with obvious developmental delays, necessitating earlier medical attention.[40] However, the proportion of DZ individuals with AS is lower than the 10% to 15% estimates for AS within ASDs. We did not control for age in this population, but there was no significant difference in mean age between twin types.

In addition, among concordant male-male twin pairs, DZ twins were significantly less likely to be concordant for AS than for AD or PDD-NOS and significantly more likely to show severity discordance (Table 3). Our data also support the theory that AS is inherited differently than AD and PDD-NOS because concordant MZ twin pairs are much less likely to have 1 twin with AS and 1 with AD or PDD-NOS (Table 3). In addition, the high AS-AS

Table 4. Intrapair Discordance of Features Among 59 Concordant Twin Pairs

	No. (%) Discordant/ Total No. of Pairs			*P* Value (Fisher Exact Test)	
	DZ Twins	MZ Twins	χ^2 DZ vs MZ	1-Tailed	2-Tailed
Total No. of pairs	31	28			
Age at first concern, before or after 18 mo	7 (23)/31	4 (14)/28	0.67	.32	.51
Development					
Any lost skills[a]	9 (33)/27	2 (8)/25	5.00	.03	.04
Specific lost skills[a]	7 (26)/27	2 (8)/25	2.92	.09	.14
Approximate age at walking	11 (36)/31	5 (18)/28	2.31	.11	.15
Approximate age at talking	20 (65)/31	11 (39)/28	3.76	.05	.07
Approximate age at toilet training	15 (48)/31	9 (32)/28	1.61	.16	.29
Education					
Has aide	11 (37)/30	7 (26)/27	0.76	.28	.38
Any special education	6 (19)/31	3 (11)/28	0.85	.29	.48
Comorbidities					
Attention-deficit/hyperactivity disorder	6 (19)/31	2 (7)/28	1.87	.16	.26
Bipolar disorder	2 (7)/31	2 (7)/28	0.01	.65	1.0
Anxiety disorder	6 (19)/31	3 (11)/28	0.85	.29	.48
Seizure disorder	4 (13)/31	2 (7)/28	0.53	.39	.67
Intellectual disability	6 (19)/31	1 (4)/28	3.51	.07	.11

Abbreviations: DZ, dizygotic; MZ, monozygotic.
[a] Refers to moderate to severe loss of social and/or communication skills before age 3 years.

Table 5. Autism Screening Discordance by Twin Type Among Concordant Pairs

	Social Responsiveness Scale				Social Communication Questionnaire		
Twin Type	No. Completed/ Total Eligible[a]	Mean *t* Score Difference (95% Confidence Interval)	*P* Value (*t* Test)	No. (%) of Screenings Discordant, by Severity Category[b]	No. Completed/ Total Eligible[a]	No. (%) of Pairs Discordant	*P* Value (χ^2)
DZ	9/60	2.22 (−17.9 to 22.3)	.81	3/9 (33.3)	36/64	9/36 (25.0)	.88
MZ	13/50	4.34 (−3.8 to 12.6)	.27	5/13 (38.5)	30/59	5/30 (16.7)	
DZ:MZ	. . .	2.16 (−19.9 to 15.6)	.80	. . .	. . .	. . .	. . .

Abbreviations: DZ, dizygotic; MZ, monozygotic.
[a] Completed for both twins; twins were eligible if both were concordant and met age criteria (see the "Social Responsiveness Scale" subsection in the "Methods" section).
[b] Categories based on *t* score: likely unaffected, <55; borderline, 55-59; mild to moderate, 60-75; severe, >75.

concordance, along with higher proportions of normal IQ and affective disorder among MZ vs DZ male-male twins, suggests that AS phenotype is strongly influenced by genes involved in selective aspects of social interaction.[7,41] This is a particularly interesting finding given speculation that environmental factors play a larger role in the heritability of AS by affecting discrete social and communication traits unlinked to functional ability[42]; our data, with low discordance among MZ twins, suggest that AS may be transmitted along different pathways than AD and PDD-NOS. These puzzling data warrant further examination.

In AD, which disproportionately affects males by about 4.3:1 (and perhaps twice as much in AS), the role of sex is complex and important.[4,43] Because no consistent variation on the X chromosome has been found, there may exist different propensities or even modalities for expression of ASDs in females vs males.[11,44] The 100% concordance among female-female MZ twins compared with 86% concordance among male-male MZ twins, although not statistically significant, and the lack of AS among female-female MZ twins suggest that some other factor may protect against full expression of the ASD phenotype in one member of male-male MZ twin pairs. However, our small sample size prohibits us from making a more definite conclusion.[19,33] This sex variation also is evident in DZ concordance data, with significantly increased risk of concordance among male-male DZ pairs compared with female-female and female-male DZ pairs, which perhaps suggests increased susceptibility for an ASD diagnosis among males.

At the clinical level, several issues emerged from this study. Of particular relevance to families and health care providers, the longitudinal pattern seen in the Kaplan-Meier survival curve of lag time in age at ASD diagnosis among concordant twins (Figure 2) suggests that the early months after a proband diagnosis are most important for risk of co-twin ASD diagnosis. Also, a diagnosis of PDD (not PDD-NOS) or ASD did not represent misdiagnosed PDD-NOS and instead suggests that current *DSM-IV-TR* criteria conflict with regional and evaluator variation.

Last, the rate of parent-reported ID (<20%) among our entire ASD twin population is much lower than in other literature. This finding may reflect the true rate of

ID diagnosis in the community and/or selection bias for incomplete participation by families with 2 affected twins with ID. Similar to our data on psychiatric comorbidites, mental retardation or ID status is most appropriately viewed as a comparison of status within a sibship rather than as an absolute measure of those disorders in the ASD population.

STUDY LIMITATIONS

The parent-reported, Web-based voluntary registry has potential reliability limits. However, current research supports Web-based surveys on medical information as a reliable means of data collection.[45] This is also the experience of one of us (W.E.K.) with InterRett, the Rett syndrome database based predominantly on parent-reported data, which has led to several critical publications on this related neurodevelopmental disorder.[46] First, in the design of the IAN Project, consenting families complete detailed demographic information and are only permitted one registration per household; the process involves several steps, including confirmation of e-mail address as well as informed consent to participate in IAN Project research. Furthermore, the risk of fabricated diagnosis or self-diagnosis of ASDs is reduced via multiple detailed questions about ASD diagnosis.

Parent-reported data may also suffer from decreased validity. For example, we cannot be certain that data about zygosity are accurate; considering that parents err by misclassifying DZ twins as MZ twins,[47] the lower-than-expected percentage of MZ twins in this study does not support that bias.[45] For overall ASD status, most affected individuals had positive results on the SCQ (>95%) and SRS (>97%) (Table 1); we realize that the SCQ is neither 100% sensitive nor specific. The IAN is currently analyzing data as part of a validity study, which will help to allay these concerns.

Other threats to validity are secular trends in diagnosis, including trends over time and by location. In particular, although there is some concern that AS is not consistently diagnosed at the community level (and is, anecdotally, overdiagnosed), we believe that because of diagnostic comparisons within twin pairs, the high rates of positive SCQ results among all affected individuals, and the distinct diagnostic differences between AS and the other ASDs in terms of level of functioning, our findings warrant further investigation.

Finally, although there are demographic and selection biases within the IAN population (eg, higher parental education level and lower minority enrollment), our conclusions focus on intrapair variation and not comparisons with the general US or ASD populations, and we assume that such biases are evenly distributed throughout the IAN registry. Also, the IAN does not specifically target families of twins nor is it geographically limited, making these data less prone to these types of ascertainment bias, although multiplex families may be more likely to engage in IAN research.[33] Overall, these data have the advantage of reflecting actual practice patterns rather than the more strictly defined but less generalizable environment of clinical research laboratories.

CONCLUSIONS

This cross-sectional study includes the largest sample of twins with at least 1 ASD-affected sibling, culled from a US online autism registry. Further investigation of phenotypes, ASD in multiplex families, and more sophisticated genetic modeling, especially focusing on sex as a risk factor, would help in revealing potential nongenetic influences on concordance among different types of twins. Because the genetic basis of this highly heritable[1] yet heterogeneous neuropsychiatric disorder is still not well understood, further family and twin studies, including IAN data on multiplex families, could help elucidate inheritance patterns, phenotypes,[22-24] and, ultimately, genetic targets for identification and treatment.[10,11,38]

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I'm bored with that line. I never use it anymore. My new line is, "In 15 minutes, everybody will be famous."
—Andy Warhol