Genetic Heterogeneity Between the Three Components of the Autism Spectrum: A Twin Study

ANGELICA RONALD, PH.D., FRANCESCA HAPPÉ, PH.D., PATRICK BOLTON, F.R.C.PSYCH., LEE M. BUTCHER, M.SC., THOMAS S. PRICE, PH.D., SALLY WHEELWRIGHT, M.A., SIMON BARON-COHEN, PH.D., AND ROBERT PLOMIN, PH.D.

ABSTRACT

Objective: This study investigated the etiology of autistic-like traits in the general population and the etiological overlap between the three aspects of the triad of impairments (social impairments, communication impairments, restricted repetitive behaviors and interests) that together define autism spectrum disorders. **Method:** Parents of 3,400 8-year-old twin pairs from the Twins Early Development Study completed the Childhood Asperger Syndrome Test, a screening instrument for autism spectrum symptoms in mainstream samples. Genetic model-fitting of categorical and continuous data is reported. **Results:** High heritability was found for extreme autistic-like traits (0.64–0.92 for various cutoffs) and autistic-like traits as measured on a continuum (0.78–0.81), with no significant shared environmental influences. All three subscales were highly heritable but showed low covariation. In the genetic modeling, distinct genetic influences were identified for the three components. **Conclusions:** These results suggest the triad of impairments that define autism spectrum disorders is heterogeneous genetically. Molecular genetic research examining the three components separately may identify different causal pathways for the three components. The analyses give no indication that different genetic processes affect extreme autistic impairments and autistic impairments as measured on a continuum, but this can only be directly tested once genes are identified. *J. Am. Acad. Child Adolesc. Psychiatry,* 2006;45(6):691–699. **Key Words:** twins, genetics, autism spectrum disorders.

Within the clinical field, the existence of a spectrum of autistic impairments is widely accepted (Wing, 1981). Autism spectrum disorders (ASDs) is used here to refer to autistic disorder, Asperger's disorder, and pervasive developmental disorder not otherwise specified, all of which fall under the *DSM-IV* category of pervasive developmental disorders (American Psychiatric Association, 1994). All ASDs represent variations in manifestation of the triad of social impairments (SIs), communication impairments (CIs), and restricted, repetitive behaviors and interests (RRBIs). Twin studies (see Plomin et al., 2001) show that diagnosed autism is highly heritable, with monozygotic (MZ) twins showing 60% to 90% concordance and dizygotic (DZ) twins showing <5% concordance (Bailey et al., 1995; Folstein and Rutter, 1977; Steffenburg et al., 1989).

The first aim of our study was to investigate the extent of genetic and environmental influences on autistic-like traits. Conceptualizing impairments characteristic of ASDs as dimensions rather than categories has been proposed by several research groups (e.g., Baron-Cohen et al., 2001; Constantino et al., 2000). Twin studies have begun to investigate autistic behaviors as quantitative dimensions: In a community sample of 7- to 15-year-olds, autistic behaviors were found to be highly heritable using the Social Responsiveness Scale (Constantino et al., 2000, 2003). An

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All of the authors are with the SGDP Centre, Institute of Psychiatry, King's College London, except Dr. Price, who is affiliated with the Institute for Translational Medicine and Therapeutics, University of Pennsylvania School of Medicine, and Ms. Wheelwright and Dr. Baron-Cohen, who are affiliated with the Autism Research Centre, Cambridge University, United Kingdom.

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Reprint requests to Angelica Ronald, Social Genetic and Developmental Psychiatry Centre, Institute of Psychiatry, De Crespigny Park, London SE5 8AF, UK; e-mail: a.ronald@iop.kcl.ac.uk.

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earlier report from the same study including 232 twin pairs found high heritability (76%), no shared environment, and moderate nonshared environment (24%; Constantino and Todd, 2000). However, a later report with a larger sample (N = 788 pairs) found evidence for moderate to strong genetic influences (48%), significant shared environment (32%) as well as nonshared environment (20%; Constantino and Todd, 2003). An independent study of social cognitive skills in 5-to 17-year-olds (N = 656 pairs) also reported substantial heritability, but shared environment was negligible (Scourfield et al., 1999). It was also found that SIs and RRBIs are both highly heritable and show no shared environmental influence in univariate models, in a study of more than 3,000 twin pairs from the same sample as used in the present study assessed on an ad hoc measure at an earlier age (Ronald et al., 2005). The aim of the present study was to clarify the rudimentary issue of the extent to which genes and environment influence individual differences in autistic-like traits in a large community sample of 8-year-olds using a recently published measure designed for community samples, the Childhood Asperger Syndrome Test (CAST; Scott et al., 2002).

The second question this study addresses is whether autistic-like traits are etiologically heterogeneous. SIs and RRBIs were shown to be highly heritable but largely genetically independent in the only previous twin study to investigate this issue (Ronald et al., 2005). This finding suggests that most of the genes influencing SIs and RRBIs are likely to be nonoverlapping. A recent family study of quantitative traits related to autism has also examined this issue using multivariate polygenic models and a sample of 201 nuclear families ascertained through the existence of at least two children affected with ASDs (Sung et al., 2005). This study found low or nonsignificant familiality (0.08–0.19) for five autism-related traits and "genetic" correlations between the traits were mainly not statistically significant, suggesting genetic heterogeneity. However, unlike the twin study findings, one high genetic correlation of 0.92 was found between social motivation and range of interest/flexibility. It is important to note these two studies have very different samples: multiplex families with affected children (average IQ of 80) versus twins in the general population. Other family studies have found that relatives of individuals with ASDs sometimes show only one of the three components, that is, some relatives have SIs, some have RRBIs, some have CIs, and some have a combination (e.g., Bolton et al., 1994). Splintering of the autism phenotype among family members who share proportions of the proband's genetic makeup suggests that different causative factors influence the three components, but little empirical evidence exists to support this supposition.

METHOD

Participants

Participants were a subsample of the Twins Early Development Study (TEDS), a United Kingdom–based study of twins contacted from birth records (Trouton et al., 2002). In 75% of cases, zygosity was diagnosed using DNA; for others, a parent-rated instrument was used (Price et al., 2000).

For this study, questionnaires were sent to 7,687 families when the twins were age 8 (mean = 8.09, SD = 0.48). A total of 3,807 families (49.5%) returned completed questionnaires. Specific exclusion criteria are described elsewhere (Ronald et al., 2005). The final sample with data after exclusions was 3,419 pairs: 573 male MZ (MZM), 571 male DZ (DZM), 648 female MZ (MZF), 558 female DZ (DZF), and 1,069 opposite-sex DZ pairs (DZOS).

Comparing participating families and families invited to participate but who did not send data back: 93.9% versus 89.8% were white, 14.8% versus 10.6% of mothers had A levels as their highest educational qualification (equivalent of college entrance exams), and 45.1% versus 38.0% of mothers were working.

Measure

The CAST (Scott et al., 2002; Williams et al., 2005) is a 31-item screening instrument for ASDs, for parents to complete in nonclinical settings. Items are scored additively and a score of ≥15 (i.e., answering yes on ≥15 items) is the cutoff for identifying children at risk of ASDs. No changes were made from the published instrument. The CAST total showed good internal consistency in the TEDS data (α = .73). We divided the items into three subscales, based on *DSM-IV* criteria (American Psychiatric Association, 1994), which had modest α values of 0.56 (SIs), 0.64 (CIs), and 0.48 (RRBIs).

Children With ASDs

At age 7, 90 TEDS children (89% male) were known to have ASDs according to parental reports that were confirmed with scores above the recommended cutoff of 15 on the Social and Communication Questionnaire (SCQ; Rutter et al., 2003), which out of the total sample who provided first contact details (13,429 families) suggests a prevalence rate of 34/10,000. This is likely to be an underestimation because of sample attrition and unconfirmed diagnoses.

The CAST includes a section on ASD diagnoses. Excluding missing responses, approximate rates for autism of 69/10,000, and Asperger's syndrome of 27/10,000 were found at age 8. This information from parents is being followed up. After exclusions, 147 children scored above the CAST cutoff (≥15), equivalent to scoring in the highest 2.1% of the distribution. Of cases so far identified by parents as having an ASD and followed up with the

SCQ, 82% (with data) scored above cutoff on the CAST; 38 of 51 (75%) children said to have autism at age 8 scored above cutoff, and 11 of the 20 children (55%) said to have Asperger's syndrome at age 8 scored above the cutoff.

Analyses

All scales were created by summing items and converting to proportions of the total possible score given the number of items completed (which had to be more than half). If there were data for less than half the items, then the total score was coded as missing (N = 9–34 individuals for all scales).

Heritability refers to the proportion of variation of a trait in a population explained by genetic influences: narrow heritability refers to only additive genetic effects; broad heritability includes additive and nonadditive genetic effects. Under an additive model, genetic effects on the phenotype add up within and across loci. When MZ twins are more than twice as similar than DZ twins, this suggests nonadditive genetic influences such as dominance (interaction of two alleles at the same loci) and epistasis (interaction of alleles at different loci), or possible contrast effects, which are described later (Saudino et al., 2000). Hence, causative influences are divided into additive genetic (A), shared environment (experiences that make children growing up in the same family similar [C]), and nonshared environment (environmental influences that contribute to differences between family members [E]; Plomin et al., 2001). Nonadditive genetic influences (D) replace C in ADE models.

Model fitting was carried out using raw data and the Mx program to provide parameter estimates and confidence intervals (Neale et al., 2003). Qualitative sex differences, which refer to the extent that genes and shared environment overlap between males and females, and quantitative sex differences, which refer to differing magnitudes of genetic or environmental influences for males and females, were both tested for. The likelihood ratio $\Delta\chi^2$ test (LRT) was used to compare nested models and the Akaike information criterion was used to compare unnested models. The LRT uses the log likelihood statistic -2LL with associated p values and is used to select the model with the best fit given the number of degrees of freedom (df).

Analyses of Extremes

Causes of extreme autistic-like traits were assessed using probandwise concordances, liability threshold (LT) modeling, and DeFries-Fulker (DF) extremes analysis. All analyses were repeated using four cutoffs (98%, 95%, 90%, 85%), to observe the extent to which extreme autistic-like traits show different etiologies at varying cutoffs. For probandwise concordances and LT modeling, quantitative data were converted into categorical data: affected probands labeled 1, unaffected individuals labeled 0. Probandwise concordances, the ratio of the number of probands in concordant pairs to the total number of probands, were calculated for MZ, same-sex DZ (DZSS), and DZOS pairs.

LT Modeling. LT modeling is often used with categorical data to estimate genetic and environmental parameters. LT models assume that many factors (genetic and environmental) together contribute to an underlying liability for a disorder. ADE, ACE, and AE models were employed. In each model, qualitative and quantitative sex differences were tested for, with and without different thresholds across sex.

DF Extremes Analysis. DF extremes analysis is a means-based regression analysis of twin data in which a cotwin's quantitative score is predicted by a proband score and the twin pair's coefficient of genetic relatedness (DeFries and Fulker, 1988). Critically, by comparing the regression to the population mean for MZ and DZ cotwins of the probands, it is possible to infer the degree of genetic influence on extreme scores. The extent to which genetic factors account for the mean difference between probands and the population is called group heritability. Transformed cotwin means, which can be interpreted as twin group correlations comparable to traditional twin correlations, are calculated by dividing the quantitative trait scores of the cotwins by the proband mean, specific to each sex and zygosity group. A recent model-fitting extension of DF analysis was used that allows inclusion of DZOS pairs and tests for etiological sex differences (Purcell and Sham, 2003). Both LT and DF extremes model fitting were used because both provide estimates of genetic and environmental influences on extreme traits, but they have different assumptions and advantages.

Univariate Analyses of Total Sample

In accordance with standard quantitative genetics procedure, scores were corrected for age and sex. Twin similarity coefficients (intraclass correlations) were used to compare twin similarity (Shrout and Fleiss, 1979). A univariate sex-limitation model was employed, which apportions the phenotypic variance into genetic and environmental influences and tests for etiological sex differences (for a full description of this model, see Ronald et al., 2005). The following models were tested in univariate analyses: ADEs, ADE, AEs, AE, ACE; the s refers to another parameter that can be added to the univariate model, representing a form of phenotypic interaction between twins (Neale et al., 2003). When modeling parent report data, a negative phenotypic interaction may occur because it exists in the children's behavior toward each other or because there is a contrast effect in the parental ratings of their behavior.

Multivariate Analyses

Multivariate genetic analysis decomposes the variance within variables and the covariance between variables into genetic and environmental components. We present the results in the form of an independent pathway model (Neale et al., 2003). Two other models were also tested: the Cholesky decomposition model, and the common pathways model. Independent pathway models have the advantage of not asserting causal priority of one variable over the other, unlike Cholesky decomposition models (Loehlin, 1996). The independent pathway model includes etiological influences shared between the variables as well as etiological influences specific to each phenotype. It is useful to convert the Cholesky model into a correlated factors model, from which additive genetic, nonadditive genetic, shared and nonshared environmental correlations (r_g, r_d, r_c, and r_s, respectively) can be obtained. In this context, these correlations vary between 0 and 1, indicating extent of overlap in causal influences between traits. DZOS were excluded from these analyses.

RESULTS

The CAST distribution was positively skewed (1.66), with scores varying from 0 to 30 (high score = impairment), mean = 5.23, SD = 3.57. Analyses of variance (ANOVAs) showed males scored significantly higher on the total CAST ($F_{1,3,417} = 146.14$, $p < .001$, $d = 0.41$),

TABLE 1
Descriptive Statistics

Group	Raw Score Cutoff	*Z* Score Cutoff	No. of Probands	% Male	CAST Mean (SD)	SIs Mean (SD)	CIs Mean (SD)	RRBIs Mean (SD)
100%	—	—	6,838 individuals	49	5.23 (3.57)	.14 (.13)	.17 (.16)	.22 (.18)
>85%	≥8.27	0.82	996	66	11.71 (3.53)	.30 (.18)	.42 (.17)	.43 (.21)
>90%	≥10.0	1.31	690	68	12.93 (3.62)	.34 (.18)	.46 (.17)	.47 (.21)
>95%	≥12.0	1.86	371	73	15.09 (3.76)	.41 (.19)	.54 (.17)	.52 (.22)
>98%	≥15.0	2.69	147	77	18.66 (3.68)	.53 (.20)	.64 (.17)	.65 (.21)

Note: Subscales scored between 0 and 1. CAST = Childhood Asperger Syndrome Test; SIs = social impairments; CIs = communication impairments; RRBIs = restricted repetitive behaviors and interests.

SIs ($F_{1,3,417} = 213.26$, $p < .001$, $d = 0.53$), CIs ($F_{1,3,417} = 33.23$, $p < .001$, $d = 0.19$), and RRBIs ($F_{1,3,406} = 50.39$, $p < .001$, $d = 0.27$). For zygosity, small but significant differences were found, with MZs tending to score lower than DZs for total CAST and SIs and RRBIs. ANOVAs showed that sex-by-zygosity interaction was also significant for total CAST and SIs and RRBIs. Sex and zygosity together accounted for 5% of the variance for total CAST and for 7%, 1%, and 2% of the variance for SIs, CIs, and RRBIs, respectively. Table 1 presents descriptive statistics for the whole sample (100%) and >85%, >90%, >95%, and >98% extreme groups (based on the total CAST score). With increasingly extreme cutoffs, the proportion of males increased.

For the 42 ASD children with data, their average CAST score was 18.96, 3.84 SDs above the sample mean. Their mean scores on SIs, CIs, and RRBIs (scored out of 1) were 0.59, 0.61, and 0.66, respectively, and 3.46, 2.75, and 2.44 SDs from the mean, respectively.

Table 2 presents extreme group results for the total CAST. MZ similarity was consistently higher than DZ similarity, suggesting significant genetic influence on extreme autistic-like traits. MZ probandwise concordances, tetrachoric correlations, and group correlations were high for the four extreme groups, with the highest values for MZ tetrachoric correlations (0.82–0.93). DZ probandwise concordances, tetrachoric correlations, and group correlations tended to be half or less than half of the MZ values, suggesting additive and possibly nonadditive genetic effects. DZ similarity tended to be lower for more extreme groups, for example, the DZM tetrachoric correlation was 0.42 for the >85% group and 0.29 for the >98% group, hinting that more nonadditive genetic influences may affect the most extreme groups (although confidence intervals overlapped). However, DZF tetrachoric correlations were erratic, with values of 0.63 and −0.63 for the >95% and >98% groups, respectively, which may be the result of the small sample of females in these extreme groups (numbers shown in Table 2). MZ values less than unity suggested moderate nonshared environment. Comparing group correlations and tetrachoric correlations across sex, males consistently had equivalent or higher correlations than females in all extreme groups for MZ pairs and similarly for DZ pairs in the >85% and >90% groups, although differences in correlations between genders were modest (0.00–0.07). In the >95% and >98% groups, DZF for the most part had higher correlations than DZM, suggesting lower heritability for females, although twin model fitting is required to test the significance of this trend. DZOS twin correlations were never lower than the average of DZM and DZF correlations, suggesting no qualitative sex differences.

Probandwise concordances for children diagnosed with ASDs, including both children with and without CAST data, were 20/25 (80.0%) for MZs and 14/65 (21.5%) for DZs, which are similar to those shown in Table 2 for the extreme groups.

As presented in Table 2, the LT and DF extremes model fitting confirmed that extreme autistic-like traits show high heritability, no shared environment, and modest nonshared environment. Higher heritability was reported in LT modeling ($h^2 = 0.86–0.92$) than from DF extremes analysis ($h^2_g = 0.64–0.73$). No striking differences were found in the etiology of the cutoffs. For all of the cutoffs, thresholds were equated across twins and across zygosity groups, but they had to be modeled separately by sex, with males showing a higher threshold.

TABLE 2
Results of Extremes Analyses for CAST Total

	>85%	>90%	>95%	>98%
Probandwise concordances				
MZ	0.68	0.61	0.58	0.62
DZSS/DZOS	0.36/0.37	0.32/0.27	0.20/0.17	0.07/0.08
Extreme group correlations (no. of probands)				
MZM	0.80 (195)	0.78 (134)	0.78 (71)	0.79 (34)
MZF	0.75 (121)	0.71 (78)	0.77 (33)	0.75 (8)
DZM	0.32 (236)	0.30 (165)	0.23 (94)	0.10 (38)
DZF	0.32 (112)	0.28 (69)	0.29 (34)	0.21 (16)
DZOS	0.37 (332)	0.31 (244)	0.23 (139)	0.15 (51)
Tetrachoric correlations (95% CIs)				
MZM	0.90 (0.84–0.94)	0.88 (0.80–0.93)	0.88 (0.78–0.94)	0.93 (0.81–0.98)
MZF	0.85 (0.76–0.91)	0.82 (0.70–0.91)	0.88 (0.73–0.96)	0.93 (0.63–0.99)
DZM	0.42 (0.27–0.55)	0.45 (0.29–0.60)	0.25 (0.01–0.47)	0.29 (−0.10–0.60)
DZF	0.40 (0.20–0.57)	0.44 (0.20–0.65)	0.63 (0.35–0.82)	−0.63 (−1.00–0.56)
DZOS	0.57 (0.46–0.66)	0.46 (0.33–0.58)	0.41 (0.22–0.58)	0.36 (−0.01–0.65)
DeFries-Fulker group estimates (95% confidence intervals)				
h^2_g	0.73 (0.65–0.81)	0.70 (0.61–0.79)	0.66 (0.54–0.77)	0.66 (0.53–0.80)[a] 0.64 (0.39–0.88)[b]
Residual	0.27 (0.19–0.35)	0.30 (0.21–0.39)	0.34 (0.23–0.46)	0.34 (0.20–0.47)[a] 0.36 (0.12–0.61)[bc]
Liability threshold parameter estimates (95% CIs)				
h^2	0.89 (0.84–0.92)	0.86 (0.80–0.91)	0.88 (0.80–0.93)	0.92 (0.81–0.97)
e^2	0.11 (0.08–0.16)	0.14 (0.09–0.20)	0.12 (0.07–0.20)	0.08 (0.03–0.19)

Note: CAST = Childhood Asperger Syndrome Test; MZM = monozygotic males; DZM = dizygotic males; DZSS = DZ same-sex twin pairs; MZF = MZ females; DZF = DZ females; DZOS = DZ opposite-sex twin pairs; CIs = confidence intervals; h^2_g = group heritability; h^2 = heritability of liability; e^2 = nonshared environment estimate.

[a] Male estimates.

[b] Female estimates.

[c] Genetic coefficient of relationship between DZOS twins = 0.23 (0.04–0.43).

No significant etiological sex differences were found from extremes model fitting, except for the >98% group, in which the DF extremes model allowing quantitative and qualitative sex differences fit the data best (indicated in Table 2 by different estimates for males and females and a genetic coefficient of relatedness between DZOS of <0.5), but this was not replicated in LT modeling.

Figure 1 shows twin correlations for the total CAST and the three subscales, indicating they are highly heritable: MZ correlations were substantially higher than DZ correlations. Twin correlations also suggested no significant shared environment because MZ correlations were more than twice the DZ correlations. Nonshared environment was indicated by MZ correlations being less than unity. In addition, DZ correlations being less than half the MZ correlations suggested evidence for either nonadditive genetic influences, or sibling contrast effects, for the total CAST and SIs and RRBIs. Effect sizes of sex differences in the twin correlations, calculated using Fisher z transformation of r (Cohen, 1988), were small (q = 0.03–0.29). The only significant differences ($p < .01$) were the higher female than male MZ twin correlations for RRBIs and the higher male than female MZ twin correlations for total CAST and SIs.

Univariate model-fitting confirmed these suggestions gleaned from twin correlations. The best-fitting model for total CAST estimated broad heritability of 0.86 for males: 0.78 (0.58–0.82) from additive genetic influences, 0.08 (0.03–0.27) from nonadditive genetic influences, and a narrow heritability of 0.81 (0.78–0.84) for females. There was no significant shared environment, and nonshared environment was modest: 0.14 (0.12–0.16) for males and 0.19 (0.16–0.22) for females. A small negative sibling interaction parameter was included in the best-fitting model (s = −0.04), which could be equated across sex. Repeated analyses excluding children with ASDs, and also with a transformed scale, also found high heritability (75%–83%), no shared environment, small nonshared environment (17%–25%), small quantitative

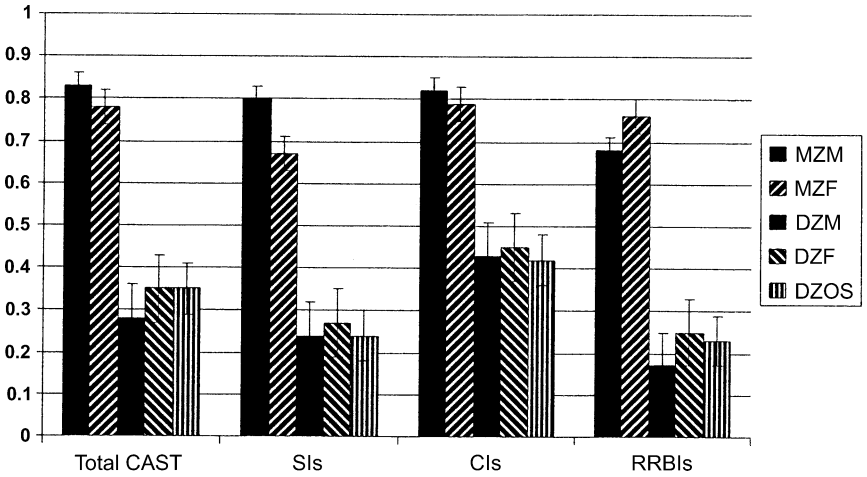

Fig. 1 Twin correlations with 95% confidence intervals for total CAST and subscales. MZM = monozygotic males; MZF = monozygotic females; DZM = dizygotic males; DZF = dizygotic females; DZOS = DZ opposite-sex twin pairs; CAST = Childhood Asperger Syndrome Test; SIs = social impairments; CIs = communication impairments; RRBIs = restricted repetitive behaviors and interests.

sex differences, but no nonadditive genetic influences, and the sibling interaction parameters differed in magnitude for males and females. The results for the three subscales are described next in relationship to the multivariate analysis.

The three autistic-like trait components were only moderately correlated: 0.34 between SIs and CIs, 0.23 between SIs and RRBIs, and 0.38 between CIs and RRBIs. Males showed higher correlations between subscales, and using Fisher *z* transformation, small effect sizes between genders were found for SIs-CIs and SIs-RRBIs correlations (q = 0.11 and 0.15, respectively, $p < .01$) and for CIs-RRBIs (q = 0.09, not significant).

Table 3 presents the multivariate model fitting; the results of the best-fitting independent pathway model are depicted as a path diagram in Figure 2. The fit of the second best-fitting model, the Cholesky decomposition model, was similar: LRT = 132.25 (73 *df*), Akaike information criterion = −13.75. The independent pathway model is preferred to the Cholesky because it does not assert causal priority for one variable over another. The common factor model yielded similar results, but the fit was worse.

Estimates are presented separately for males and females because it was not possible to equate them without a significant worsening of fit. Paths could be dropped for specific nonadditive genetic influences for all three variables, specific additive genetic influences for CIs and RRBIs, and the common nonadditive genetic path for CIs, because they were estimated at zero or their confidence intervals overlapped with zero. The best-fitting model included a contrast effect (omitted from Fig. 2) for SIs that was moderate and negative (−0.09) and equal across sex. Most important, in the Cholesky model, r_g between SIs and RRBIs could be dropped because it was not significantly different from zero. However, r_g was modest between SIs and CIs (0.42 for males, 0.30 for females) and high between CIs and RRBIs (0.91 for males, 0.90 for females). Because the nonadditive genetic parameter was dropped for CIs, there is no r_d between SIs and CIs or between RRBIs and CIs. Although r_d was estimated at 1.00 between SIs and RRBIs, there was so little nonadditive genetic variance for SIs that this estimate is not reliable.

In Figure 2, all of the variance components that a variable loads on add up to the total phenotypic variance for that variable; therefore, relative contributions of each path are calculated by dividing the variance component for a particular path by the sum of all of the variance components that the variable loads on. These results indicate that genetic variance, both additive (A) and nonadditive (D), is largely unique for SIs, CIs, and RRBIs. For SIs, specific additive genetic influences are seen simply as residual genetic variance that accounts for 70.5% of the variance for males and 70.2% of the variance for females. Although CIs dominate the common additive genetic latent variable (explaining 82.5% of the variance for males, 79.0% for females), this is actually a factor that is largely specific to

TABLE 3
Multivariate Model-Fitting Results of CAST Subscales for Total Sample

Fit Statistics	−2LL	*df*	Parameters	LRT (*df*)	AIC
Saturated model	34,318.69	13,985	108		
Best-fitting model (Fig. 2)	34,458.77	14,062	31	140.08 (77)	−13.92
Parameter estimates and 95% confidence intervals	A_{Spe}	E_{Spe}	A_{Com}	D_{Com}	E_{Com}
Males					
SIs	0.91 (0.83–0.99)	0.16 (0.13–0.19)	0.17 (0.13–0.22)	0.02 (0.01–0.05)	0.03 (0.01–0.05)
CIs	—	0.17 (0.13–0.20)	0.94 (0.86–1.02)	—	0.03 (0.01–0.07)
RRBIs	—	0.27 (0.18–0.32)	0.20 (0.15–0.25)	0.57 (0.51–0.64)	0.07 (0.03–0.16)
Females					
SIs	0.55 (0.49–0.60)	0.12 (0.05–0.15)	0.05 (0.03–0.07)	0.004 (0.0002–0.01)	0.06 (0.03–0.13)
CIs	—	0.15 (0.12–0.17)	0.64 (0.58–0.69)	—	0.02 (0.01–0.04)
RRBIs	—	0.18 (0.15–0.21)	0.12 (0.09–0.16)	0.53 (0.48–0.58)	0.03 (0.01–0.05)

Note: −2LL = log likelihood fit statistic; *df* = degrees of freedom; LRT(*df*) = likelihood ratio χ^2 test with Δdf comparing model to the saturated model; AIC = Akaike information criterion; A_{Spe}/E_{Spe} = subscale-specific additive genetic/nonshared environment estimates; $A_{Com}/D_{Com}/E_{Com}$ = additive genetic/nonadditive genetic/nonshared environment effects in common across subscales; SIs = social impairments; CIs = communication impairments; RRBIs = restricted repetitive behaviors and interests. Model included contrast effect for SIs (-0.09) equal across males and females.

CIs because SIs and RRBIs load only modestly on this factor. Similarly, RRBIs dominate the common nonadditive genetic latent variable with no appreciable loading from SIs or CIs.

DISCUSSION

High heritability, no shared environment, and modest nonshared environmental effects were found for autistic-like traits both at the extreme and as measured on a continuum in the population. Extreme autistic-like traits showed an etiology similar to that of both autism and to autistic-like traits in the whole sample; there was no obvious indication that there were different causative processes at the extreme. The pattern of tetrachoric correlations and group correlations suggested more nonadditive genetic influences in the most extreme groups than in the less extreme groups and the general population, but this was not borne out in the model fitting. The substantial group heritability estimate from the DF analysis suggested strong genetic links between the extremes of probands and quantitative trait scores of their cotwins. A limitation of extremes analyses is that the number of probands in each zygosity group was smaller in the most extreme groups, providing less power to estimate parameters.

The main multivariate finding was genetic heterogeneity among the three ASD components. Genetic variance for each of the CAST subscales was largely specific. SIs showed this most clearly because nearly all of the genetic variance was specific, but both CIs and RRBIs had genetic influences that were for the most part not shared with the other variables. No common or specific shared environment was found, but there were modest common and specific nonshared environmental influences.

Our finding of no shared environment differs from one previous study that found moderate shared environment (Constantino and Todd, 2003), a difference that could be caused by the measures (CAST versus Social Responsiveness Scale) or age of samples (age 8 versus ages 7–15). The majority of Social Responsiveness Scale items refer to SIs, giving it a higher internal consistency than the CAST (0.97 versus 0.73). It is possible that these measures are not robust to the error inherent in measuring diverse autistic-like behaviors. One explanation for the MZ correlations for total CAST and SIs being significantly higher for males than females is that autistic-like traits may be affected by X-linked loci because this pattern of twin correlations falls in line with the hypothesis that nonidentical X chromosome expression may cause MZ females to correlate less strongly than MZ males on complex behavioral traits (Loat et al., 2004).

Because estimates of nonadditive genetic effects should be viewed with caution in light of power considerations, we also investigated an AE multivariate model that ignored nonadditive genetic effects. In sum, a similar

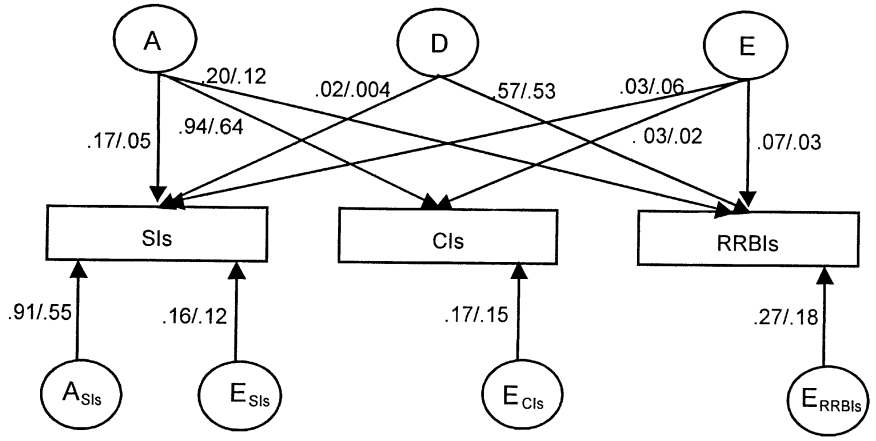

Fig. 2 Best-fitting independent pathway model with variance components presented for males and females, respectively. Within-variable sibling interaction path for social impairments not shown in figure. A = Additive genetic effects; D = nonadditive genetic effects; E = nonshared environment; SIs = social impairments; CIs = communication impairments; RRBIs = restricted repetitive behaviors and interests.

picture emerged: heterogeneity indicated by modest genetic overlap between subscales (r_g = 0.18–0.50), suggesting that one half to two thirds of the genes influencing the triad of impairments are specific to each component. This result is similar to that in an earlier study, which also reported low genetic correlations between SIs and RRBIs (r_g = 0.40 for males, 0.25 for females; Ronald et al., 2005).

The finding of low phenotypic correlations between the three subscales is consistent with the finding from family studies that have reported that the autism phenotype "splinters out" among relatives. One hypothesis is that at the genetic level, SIs and RRBIs are largely distinct but that CIs show greater genetic overlap. Thus, molecular genetic analyses using traditional diagnoses of ASDs may be mixing genetically heterogeneous aspects of ASDs, making it more difficult to identify genes. Indeed, several linkage findings have increased in strength in analyses limited to subsamples with particular autistic characteristics (e.g., Buxbaum et al., 2001).

Limitations

A major limitation of our study is reliance on parent report; future studies will obtain data from multiple raters. Our study is subject to the usual limitations of the twin method, and it is optimal to triangulate on these issues with family and adoption designs (Plomin et al., 2001). The developmental status of this sample is important: It is possible that a different genetic architecture exists in earlier childhood. The low internal consistency of the CAST subscales encourages caution in interpretation because it could reflect several different underlying constructs, the small number of items in each subscale, or measurement error. The sample's attrition bias and small amount of missing data are also factors that could contribute to the results. Finally, it is still feasible from these data that homogeneity exists across symptoms within ASDs, whereas genetic heterogeneity explains autistic-like traits.

The ultimate test linking the continuum and the extreme will come when genes associated with ASDs are identified. Although our sample includes children with ASDs, even the >98% group are overall less extreme than clinical ASD samples, and because of unconfirmed diagnoses still being followed up in the sample, the sensitivity of the measure is not likely to be accurately reflected here. We predict that genes associated with ASD extremes or ASD clinical diagnoses will also be associated with normal variation in these behaviors for the whole population, known as the quantitative trait locus model (Plomin et al., 1994). Molecular genetic studies are required to test this hypothesis definitively.

Implications

The evidence of genetic heterogeneity leads us to predict that through molecular genetic research, different genes will be found to be associated with SIs, CIs, and RRBIs. Autism and autistic-like traits appear to lie on a continuum of impairment, with the male-to-female ratio increasing toward the impaired extreme. Our analyses give no indication that different etiological processes affect the continuum versus extreme, but this can only be

tested directly once genes are identified. The model-fitting analyses found little evidence of involvement of sex-specific genes, although the patterns of twin correlations for total CAST and SIs matched those predicted by the X-inactivation hypothesis, suggesting possible involvement of X-linked genes.

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Why Do Women Stop Breastfeeding? Findings From the Pregnancy Risk Assessment and Monitoring System
Indu B. Ahluwalia, MPH, PhD, Brian Morrow, MA, Jason Hsia, PhD

Objective: We examined breastfeeding behaviors, periods of vulnerability for breastfeeding cessation, reasons for breastfeeding cessation, and the association between predelivery intentions and breastfeeding behaviors. *Study Design:* Using 2 years (2000 and 2001) of data from the Pregnancy Risk Assessment and Monitoring System we assessed the percentage of women who began breastfeeding, continued for <1 week, continued for 1 to 4 weeks, and continued for >4 weeks and their reasons for not initiating or stopping. Predelivery breastfeeding intentions of women and their relationship with subsequent breastfeeding behaviors were examined also. *Results:* We found that 32% of women did not initiate breastfeeding, 4% started but stopped within the first week, 13% stopped within the first month, and 51 % continued for >4 weeks. Younger women and those with limited socioeconomic resources were more likely to stop breastfeeding within the first month. Reasons for cessation included sore nipples, inadequate milk supply, infant having difficulties, and the perception that the infant was not satiated. Women who intended to breastfeed, thought they might breastfeed, or had ambivalent feelings about breastfeeding were more likely to initiate breastfeeding and to continue through the vulnerable periods of early infancy than were those who did not plan to breastfeed. *Conclusions:* Our findings indicate a need to provide extensive breastfeeding support after delivery, particularly to women who may experience difficulties in breastfeeding. **Pediatrics** 2005;116:1408–1412.