ORIGINAL ARTICLE

Evidence That Autistic Traits Show the Same Etiology in the General Population and at the Quantitative Extremes (5%, 2.5%, and 1%)

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Context: Genetic factors play an important role in the etiology of both autism spectrum disorders and autistic traits. However, little is known about the etiologic consistency of autistic traits across levels of severity.

Objective: To compare the etiology of typical variation in autistic traits with extreme scoring groups (including top 1%) that mimicked the prevalence of diagnosed autism spectrum disorders in the largest twin study of autistic traits to date.

Design: Twin study using phenotypic analysis and genetic model-fitting in the total sample and extreme scoring groups (top 5%, 2.5%, and 1%).

Setting: A nationally representative twin sample from the general population of England.

Participants: The families of 5968 pairs aged 12 years old in the Twins' Early Development Study.

Main Outcome Measure: Autistic traits as assessed by the Childhood Autism Spectrum Test.

Results: Moderate to high heritability was found for autistic traits in the general population (53% for females and 72% for males). High heritability was found in extreme-scoring groups. There were no differences in heritability among extreme groups or between the extreme groups and the general population. A continuous liability shift toward autistic trait affectedness was seen in the cotwins of individuals scoring in the top 1%, suggesting shared etiology between extreme scores and normal variation.

Conclusion: This evidence of similar etiology across normal variation and the extremes has implications for molecular genetic models of autism spectrum disorders and for conceptualizing autism spectrum disorders as the quantitative extreme of a neurodevelopmental continuum.

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Autism spectrum disorders (ASDs) are a set of phenotypically heterogeneous neurodevelopmental syndromes of primarily genetic etiology. Monozygotic (MZ) twins display from 60% to 90% concordance for ASD; the concordance in dizygotic (DZ) twins has been estimated from 0% to 30%.[1-7] This evidence suggests that ASD are one of the most highly heritable behavioral disorders.

Modest to high heritability has been reported for autistic traits assessed quantitatively in the general population,[8-13] although assessments have varied in their estimates of genetic and environmental contributions.[14-21] Reported values of heritability vary from 36%[18] to 87%.[12,18]

One hypothesis regarding the causes of ASD or extreme autistic traits is that the same variants that influence risk for extreme behavioral profiles also influence mild or subthreshold autism-like behavior.[16,22,23] Under this hypothesis, it is predicted that the etiologic structure of extreme autistic traits would be consistent across the range of impairment.[24] Furthermore, if extreme traits are genetically linked to subthreshold variation, one would expect to see a shift toward affectedness in the continuous trait distribution of family members of extreme-scoring individuals, a shift that is dependent upon the family members' coefficient of genetic relatedness.[25,26] In other words, extreme scores should not only predispose family members to equally severe levels of impairment but also predict an increased liability toward mild or moderate autism-like behavior.[17,26-29]

The etiology of extreme autistic traits (eg, >95th percentile) was examined in the present sample when the cohort was 8 years old.[23] Those findings suggested that extreme autistic traits appeared to show similar etiology as diagnosed ASD. That study, however, was not large enough to

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examine an extreme group (top 1%) that shows a prevalence and average symptom burden similar to those of individuals with an ASD. In the present study, we use a sample that is 75% larger (n=11 936) in order to examine—to our knowledge, for the first time—the etiologic consistency of autistic traits from the general population across a clinically comparable threshold.

To test whether the etiology of extreme autistic traits was consistent across the range of impairment, heritability estimates were reported for the full sample and for individuals scoring in the top 5% (n=615), 2.5% (n=342), or 1% (n=120) of the general population. Leveraging the size and clinical comparability of the top 1% group, this study also presents the first direct examination of whether a quantitative shift in sibling liability to less extreme impairment is associated with extremely severe affectation in a representative twin sample, a phenomenon that would be indicative of etiologic overlap between very extreme scores and regular variation in autism-like behavior.

METHODS

SAMPLE

Participants were recruited from the Twins' Early Development Study (TEDS),[30] which is a cohort of twins in England born between 1994 and 1996. The original registry was established through birth records; zygosity of the twins was confirmed in more than 75% of cases on the basis of DNA markers. The remaining zygosity assessments were conducted using a validated scale.[31] The TEDS was approved by the King's College London Ethics Committee, and all parents completed informed consent.

At age 12, the Childhood Autism Spectrum Test (CAST)[32] was completed and returned by the parents of 11 970 eligible children. This represents 60.6% of the original TEDS sample who actively participate in the TEDS. The response among individuals with scores above the 95th percentile on the CAST at age 8 was approximately 10% lower (54.8%). Twin pairs were ineligible if 1 or more of the twins had a noted non-ASD syndromic condition (eg, Down syndrome or chromosomal abnormalities) or had substantial pregnancy or perinatal complications, or if zygosity was unclear. Twin pairs were included if their parent completed at least half of the CAST items (≥15) for both twins (5968 pairs). The scores of those missing less than half of the items (1142 individuals) were adjusted such that their final value reflected the proportion of questions answered. Compared with participants included in the analysis, the eligible TEDS participants without valid CAST data were more likely to be pairs, containing male twins (51.4% vs 47.6%; $\chi^2=7.9$; $P=.01$) and to have lower socioeconomic status ($t_{11\,028}=19.5$; $P<.001$), assessed using a combined measure including family income, maternal education, and maternal occupation. There was no difference between responders and nonresponders with regard to race or ethnicity (93.5% vs 93.0% white; $\chi^2=0.6$; $P=.44$).

The final sample included 1936 male MZ twins (MZM, 16.2%), 2316 female MZ twins (MZF, 19.4%), 1862 male DZ twins (DZM, 15.6%), 2042 female DZ twins (DZF, 17.1%), and 3780 opposite-sex DZ twins (DZOS, 31.7%). In total, the 11 936 twins (5968 pairs) were 47.7% male and 93.6% white. Nearly half (42.2%) of their mothers worked, and 32.4% had completed at least 1 A-level (school examinations taken at age 18). This sample is comparable with the England population as a whole. Using results from the General Household Survey (Office for National Statistics, 2005), 92% of the population is white, 50% of children are male, and 32% of mothers have completed 1 or more A-levels.

MEASURE

The CAST is a 30-item, dichotomous (yes or no) response scale. Items address all 3 core domains of symptoms that currently characterize ASDs in *DSM-IV-TR* (social impairments, communication impairments, and restrictive and repetitive behaviors and interests).[33] The CAST is designed for parents to complete. As a screening tool for ASD, with a designated cut point of 15, the CAST has been shown, in a sample of children clinically assessed using the Autism Diagnostic Interview–Revised and Autism Diagnostic Observation Schedule, to have a sensitivity of 100%, a specificity of 97%, and a positive predictive value of 50%.[34] In the TEDS sample, the CAST displayed adequate overall internal consistency (Kuder-Richardson 20=0.74) and strong within-individual correlations across a 4-year period from ages 8 to 12 ($r=0.64$).[35] The parents of 80 children with a suspected ASD diagnosis based on the Development and Well-Being Assessment telephone parent interview[36] completed the CAST when their child was aged 12, including both twins in a pair. As reported previously,[37] a rate of likely ASD cases in the sample has been estimated at 1.10%, which is comparable with the rate of 1.16% reported for all ASDs in an England epidemiological study.[38] The suspected ASD group had a mean (SD) score of 18.26 (4.99), between the 98th and 99th percentile of the population distribution. Those within the 99th percentile of the general population accordingly had parent-reported traits equal to or greater than the number endorsed for children meeting Development and Well-Being Assessment criteria for an ASD diagnosis. As such, the top 5%, 2.5%, and 1% extreme-scoring groups ranged from subthreshold to suspected diagnostic group–level severity.

CONTINUOUS SHIFT IN LIABILITY ACROSS THE TRAIT DISTRIBUTION

The continuous liability shift analysis was designed to investigate the relationship between very extreme scores (≥99%) in one twin (proband) and autistic traits in their sibling (co-twin). The effects of the sex of both twins and the age of the twin pair were regressed out of the raw data before analysis. Across the sample, 1 twin from each pair was selected at random to be the proband (twin 1). Probands were placed into 3 groups: (1) those scoring below the 99th percentile, (2) DZ probands scoring at or above the 99th percentile, and (3) MZ probands scoring at or above the 99th percentile. Mann-Whitney tests were used to examine the difference in average co-twin trait scores between each of the groups; *P* values were corrected for multiple comparisons (3 comparisons).[39]

The empirical distributions of the 3 groups were plotted as kernel density estimates (smoothed histograms) to examine the nature of the co-twin shift in liability to autistic traits. There are conditions under which an increase in the co-twin mean (given extreme scores in probands) may not indicate an etiologic relationship between the extremes and normal variation. For example, an increase in co-twin liability only to extreme scores may appear in the form of a bimodality in the co-twin distribution: co-twins are either affected at the severity of the proband or quantitatively unaffected by the risk. This would result in an increase in co-twin mean scores but reflect distinct etiologies between extreme and normal range traits. A continuous shift in liability, however, in which co-twins of extreme-scoring probands are at increased risk for higher scores across the range of impairment, would suggest an etiologic relationship between the extreme scores of the proband and normal variation in their siblings. A model

that considers only the average scores of co-twins, like DeFries-Fulker (DF) extremes models, cannot distinguish between these potential sources of mean change. The plot of the co-twin distributions in the **Figure**, however, is designed to consider whether these data indicate a true continuous shift in liability across the range of scores. A greater continuous shift in MZ than in DZ twins would suggest a genetic relationship between very extreme scores and variation in co-twins.

CATEGORICAL SHIFT IN LIABILITY TO LESSER EXTREME SCORES

Etiologic overlap between different levels of affectation can also be investigated using a categorical approach. Reich et al[26] demonstrated that etiologic independence between severe (narrow) and milder (broad) forms of a disorder is demonstrated through the absence of an association between the narrow form in probands and the broad form in their family members. In the case of a quantitative trait distribution, narrow and broad forms correspond to varying levels of affectation (eg, the narrow, most severe form is indicated by scores at or above the 99th percentile; the broad, milder form is indicated by scores at or above the 95th and 90th percentiles). In the context of twin analyses, the null hypothesis of no etiologic relationship between the narrow and broad forms can be tested by estimating tetrachoric correlations between the narrow form (1 = present and 0 = absent) in probands (twin 1) and broad form (1 = present and 0 = absent) in their cotwins (twin 2).[27,28] As described in the "Continuous Shift in Liability Across the Trait Distribution" subsection, 1 twin from each pair is selected at random to act as the proband. Correlations between narrow and broad forms that are significantly different from zero suggest shared familial etiology between severe (≥99%) and subthreshold impairment.[26] Given varying coefficients of genetic relationship, correlations for MZ and DZ twins are estimated separately. We assumed no qualitative sex effects and included DZOS twins. Monozygotic cross-twin, cross-level correlations greater than DZ cross-twin, cross-level correlations suggest shared genetic influence between the narrow and broad forms. Narrow form was defined as scores at or above the 99th percentile. Two broad forms were considered: at or above the 95th and 90th percentiles.

THE TWIN DESIGN AND ESTIMATES OF HERITABILITY

Twin analyses are designed to partition the variation of quantitative traits into genetic and environmental components. This is accomplished through comparison of MZ and DZ twin similarity. Monozygotic twins share more than 99% of their DNA code; DZ twins share on average half. Heritability is suggested when MZ twins display greater similarity than DZ twins on a measured trait.

The fraction of influence attributable to genetic factors includes additive (A) and nonadditive (D) genetic effects. Additive genetic effects are independent genetic influences. Nonadditive genetic effects are characterized by interactions either within (dominance) or between (epistasis) relevant loci. Environmental influence is divided into that which is shared (C) and that which is nonshared (E) (unique to the individual). Shared environmental effects refer to environmental influences that make children growing up in the same family similar; nonshared environmental effects refer to environmental influences that make children growing up in the same family different, and include measurement error in their estimation. Total phenotypic variance is calculated by summing the specific variance attributable to A, D, C, and E.[40]

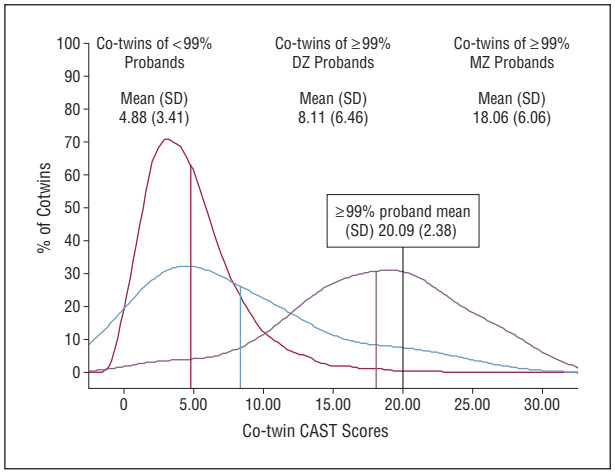

Figure. Shift in co-twin trait distribution associated with proband scores at or above the 99th percentile. Note: One twin from each pair was selected at random to act as the proband. CAST indicates Childhood Autism Spectrum Test; curves denote kernel density estimates (smoothed histograms). Red, all cotwins of probands with scores below the 99th percentile. Blue, dizygotic (DZ) co-twins of probands with scores at or above the 99th percentile. Purple, monozygotic (MZ) co-twins of probands with scores at or above the 99th percentile. Colored lines indicate mean values for each group; all mean differences were significant (purple > blue > red, $P < .001$ for all comparisons; see text for analytic details regarding comparison of means).

FULL-SAMPLE ANALYSES

Twin Correlations

Twin correlations were estimated for each sex and zygosity group. Twin data suggest shared environmental effects when DZ twin correlations are more than half the MZ twin correlations. They suggest nonadditive genetic effects when DZ correlations are less than half those of the MZ twins. Nonadditive and shared environmental effects cannot be tested for simultaneously using a twin-only design. Accordingly, ACE and ADE models were run separately to investigate both possibilities.

Twin Model-Fitting

Univariate ACE, ADE, CE, AE, and E structural equation models were used to estimate the relative contribution of genetic and environmental influences on variation in autistic traits. The CAST scores were log-transformed before model-fitting to correct for skewness. Both qualitative and quantitative sex effects were examined. Quantitative sex effects indicate variation in the *magnitude* of genetic or environmental effects between males and females. Qualitative sex effects indicate that *different* genetic or environmental effects may be influencing males and females. Nested models were compared using the log-likelihood criterion; nonnested models were compared using the Akaike Information Criterion. The most parsimonious model achieved without a significant reduction in fit was considered the best match to the data. Mean effects of sex and age were controlled for in all analyses.

Analyses of the Extremes

The sample (n = 11 936) was large enough to examine heritability in 3 very high-scoring groups: the top 5%, 2.5%, and 1%. For each of the high-scoring categories, probandwise concordances, extreme group correlations, and tetrachoric correlations were estimated to examine autistic trait heritability at the extremes of the general population. For each measure, genetic

Table 1. Descriptive Statistics

Variable	Raw Score Cutoff	*z* Score Cutoff	No. of Individuals	% Male	CAST Score, Mean (SD)
Analysis group, %					
100	. . .	. . .	11 936	47.65	4.96 (3.54)
≥95	12.00	1.99	615	66.67	15.03 (3.25)
≥97.5	14.00	2.55	342	69.30	17.07 (3.07)
≥99	18.00	3.68	120	74.17	20.47 (2.64)
ASD	. . .	. . .	80	78.75	18.26 (4.99)
Zygosity group					
MZM	. . .	. . .	1936	. . .	5.25 (3.78)
MZF	. . .	. . .	2316	. . .	4.27 (3.16)
DZM	. . .	. . .	1862	. . .	5.39 (3.74)
DZF	. . .	. . .	2042	. . .	4.55 (3.18)
DZOS	. . .	. . .	3780	. . .	5.25 (3.65)

Abbreviations: ASD, autism spectrum disorder; CAST, Childhood Autism Spectrum Test; DZF, dizygotic female twins; DZM, dizygotic male twins; DZOS, opposite-sex dizygotic twins; MZF, monozygotic female twins; MZM, monozygotic male twins.

influences were implicated when MZ twins displayed more similarity than DZ twins.

Estimates of the Heritability of Extreme Scores

The heritability of extreme scores was investigated using 2 methods. The first, DF extremes analysis, investigates the role of genes and environment in the difference between the mean scores of extreme groups and the population as a whole.[41] In doing so, one uses the quantitative data available. The second method, using liability threshold models, investigates the fraction of variation in categorical status (eg, high scoring or not) attributable to genetic and environmental factors.[42,43] The liability threshold and DF analysis sets were designed to determine whether the heritability of extreme scores is consistent across varying levels of severity (≥95%, ≥97.5%, and ≥99%), using both categorical and continuous outcome definitions. Heritability, or familiality, that differs substantially between varying levels of severity suggests differences in etiology between the more severe and less severe forms of a phenotype. For example, differences in familial liability toward low IQ have been noted on the basis of the level of intellectual disability in probands: the family members of individuals with mild intellectual disability are at increased risk for low IQ themselves, the family members of individuals with severe intellectual disability are not.[44] In the context of twin analyses, such a pattern would be reflected in a reduction of heritability in the most extreme scoring groups and would indicate that severe impairment and mild impairment arise from distinct etiologic processes. In contrast, consistent heritability would support a singular distribution of liability across the range of extreme scores, as would be expected when etiologies are shared across levels of impairment.[24]

Sex effects were not examined in any of the DF or liability threshold models as a result of the very limited number of female probands in the group above the 99th percentile (n=21). This afforded consistency in analytic technique across the high scoring categories. Because sex effects were not estimated, DZOS twins were excluded from these analyses.

DF Extremes Analyses

A model-based extension of classic DF regression analysis was used to estimate the etiology of quantitatively defined extreme scores in the general population, estimating group heritability, shared environmental effects, and unique environmental effects.[41,45] Because DF models use a continuous outcome, the heritability estimates derived from these models can be compared with those obtained in the full sample analyses. An etiologic continuum across the range of scores would be evidenced by similar heritability between the full sample and DF models. Age and sex were regressed out of raw scores; the residuals were then transformed before analysis. Transformed scores were calculated by dividing co-twin scores by the proband mean for each zygosity group. DeFries-Fulker estimates of heritability, and the associated confidence intervals, were constrained to the MZ transformed co-twin mean,[34] the empirically derived upper limit of twin similarity.

Liability Threshold Models

Liability threshold models were used to estimate the etiology of categorically defined extreme scores.[43] Liability threshold models assume that a bivariate normal liability distribution underlies risk for the categorical phenotype. The ACE, ADE, CE, AE, and E structural equation models were examined.

RESULTS

DESCRIPTIVES

The sample overall mean (range) was 4.96 (0.00-28.80) (skewness, 1.56). Because the CAST response options were dichotomous (0 or 1), this corresponds to an average of slightly less than 5 endorsed autistic traits per child. Males scored 1.16 points higher on average than females, and MZ twins scored 0.34 points lower on average than DZ twins. There was no birth order effect on the mean (no difference in CAST scores between first- and second-born twins; $P=.78$). Sex and zygosity together explained 3% of total variation in parent-rated autistic traits. Mean CAST scores for each sex and zygosity group are presented in **Table 1**.

CONTINUOUS SHIFT IN LIABILITY ACROSS THE TRAIT DISTRIBUTION

The Figure presents the distribution of co-twin CAST values, where cotwins are grouped by extreme scoring status and zygosity of the proband. Both MZ (n=22; mean,

Table 2. Cross-twin Cross-Affectation-Level Correlations[a]

Variable	Tetrachoric Correlation (95% CI)		
	≥99% T2	≥95% T2	≥90% T2
MZ twins			
≥99% T1 (n=22)	0.89 (0.81-0.98)	0.86 (0.78-0.95)	NE
≥95% T1 (n=86)	0.79 (0.68-0.90)	0.89 (0.84-0.93)	0.85 (0.80-0.90)
≥90% T1 (n=225)	0.63 (0.49-0.77)	0.76 (0.70-0.83)	0.84 (0.80-0.88)
DZ twins			
≥99% T1 (n=36)	0.51 (0.31-0.71)	0.37 (0.20-0.54)	0.31 (0.16-0.46)
≥95% T1 (n=230)	0.25 (0.07-0.43)	0.36 (0.26-0.46)	0.36 (0.28-0.44)
≥90% T1 (n=568)	0.18 (0.02-0.34)	0.32 (0.24-0.41)	0.37 (0.30-0.43)

Abbreviations: DZ, dizygotic; MZ, monozygotic; NE, not estimated; T1, twin 1; T2, twin 2.
[a] One tetrachoric correlation could not be estimated because only 1 T2 scored below the 90th percentile (high scores too strongly associated; odds ratio, 179.84).

18.06) and DZ (n=36; mean,8.11) co-twins of scorers at or above the 99th percentile displayed significantly greater autistic trait scores (corrected $P<.005$ for both comparisons) than the cotwins of probands below the 99th percentile (n=5910; mean,4.88), suggesting an etiologic relationship between extreme scores and co-twin autistic trait variation. The shift in liability was continuous—cotwins of affected probands had higher scores across the distribution—indicating a relationship between extreme scores and co-twin variation in the normal range. The MZ increase in co-twin mean was significantly greater than the DZ increase (corrected $P<.001$), suggesting a genetic relationship between autistic trait scores across the distribution.

CATEGORICAL SHIFT IN LIABILITY TO LESSER EXTREME SCORES

Table 2 presents the results from the cross-twin, cross-affectation-level correlations. All MZ (r=0.63-0.89) and DZ (r=0.18-0.51) correlations were significantly different from zero, within and across the 3 extreme-scoring categories. Because the cross-level correlations (eg, ≥99% twin 1 and ≥90% twin 2) were nonzero, we reject the null hypothesis of no shared etiology between top 10%, 5%, and 1% affectation.[26] Because MZ correlations were, on average, twice or more than twice the DZ correlations, these data are consistent with shared genetic influence on autistic traits above and below the top 1% threshold, a level consistent with ASD prevalence and severity.

ESTIMATING THE GENETIC AND ENVIRONMENTAL INFLUENCE ACROSS THE BEHAVIORAL RANGE

Twin Correlations for Full Sample

Monozygotic twins displayed significantly greater similarity than DZ twins, suggesting that autistic traits were heritable in the general population at age 12. The MZ correlations were more than twice the same-sex DZ correlation for males (MZ, r=0.78; 95% CI, 0.75-0.80; DZ, r=0.26; 95% CI, 0.20-0.32) but less than twice the same-sex DZ correlation for females (MZ, r=0.75; 95% CI, 0.73-0.78; DZ, r=0.42; 95% CI, 0.37-0.47). This suggests additive and possibly nonadditive genetic effects in males, additive genetic and shared environmental effects in females, and quantitative sex effects in the general population. For both sexes, MZ correlations less than unity indicated unique environmental effects. The opposite-sex DZ correlation (raw, r=0.27; 95% CI, 0.23-0.31) was not lower than the geometric mean of the same-sex DZ correlations when sex effects on the means were accounted for (adjusted, r=0.34; 95% CI, 0.30-0.38), suggesting no influence of qualitative sex effects.

Twin Similarity in Extreme Groups

Table 3 presents the analyses of heritability at the extremes of the general population. The probandwise concordances, extreme group correlations, and tetrachoric correlations were strong for MZ twins across the extreme-scoring categories. The MZ concordances (0.55-0.65) were more than twice the DZ concordances (0.12-0.17), suggesting additive and possibly nonadditive genetic influences on extreme autistic traits. The small negative values seen in some of the DZ extreme-group correlations arise from the ceiling effect imposed by group definition in the probands: when group definition becomes more restrictive, the range of possible proband CAST scores is limited. Because the negative correlations are not significantly different from zero, they can be interpreted as null. Overall, the relationship between twins did not systematically increase or decrease across cutoff levels (top 5%, 2.5%, and 1%) in any of the comparisons.

Extreme Group Heritabilities

The lower section of Table 3 presents the DF estimates of group heritability. The DF analyses displayed high group heritability (0.68-0.70), no shared environmental effects, and modest unique environmental effects. Heritability estimates were stable with changes to the cutoff criterion, suggesting similar quantitative etiologic patterns across affectation levels. The liability threshold models also indicated consistent and high heritability: estimated additive heritability ranged from 0.88 to 0.90. The liability threshold models suggested neither dominance nor shared environmental effects. Unique environmen-

Table 3. Extremes Analyses-CAST at Age 12[a]

Variable	Cutoff Level ≥95%	≥97.5%	≥99%
Probandwise concordances			
MZ	0.65	0.63	0.55
DZSS/DZOS	0.17/0.17	0.13/0.13	0.12/0.16
Extreme group correlations (No. of probands)			
MZM[b]	0.51 (125)	0.47 (76)	0.60 (32)
MZ[b]	0.81 (62)	0.84 (40)	0.87 (13)
DZM	0.08 (121)	−0.01 (71)	−0.34 (24)
DZF	−0.12 (75)	−0.12 (34)	−0.22 (8)
DZOS	0.06 (232)	0.00 (121)	−0.11 (43)
Tetrachoric correlations			
MZM	0.91 (0.86 to 0.96)	0.92 (0.86 to 0.98)	0.86 (0.74 to 0.99)
MZF	0.82 (0.71 to 0.93)	0.86 (0.75 to 0.97)	0.94 (0.82 to 1.00)
DZM	0.26 (0.05 to 0.46)	0.41 (0.18 to 0.64)	0.36 (−0.08 to 0.80)
DZF	0.50 (0.30 to 0.71)	0.46 (0.12 to 0.80)	0.80 (0.45 to 1.00)
DZOS	0.35 (0.21 to 0.48)	0.36 (0.17 to 0.55)	0.51 (0.24 to 0.78)
DF estimates			
H_g^2	0.70 (0.64 to 0.75)	0.69 (0.61 to 0.75)	0.68 (0.52 to 0.74)
Residual	0.30 (0.25 to 0.36)	0.31 (0.25 to 0.39)	0.32 (0.23 to 0.44)
LT estimates			
H^2	0.88 (0.83 to 0.92)	0.90 (0.84 to 0.94)	0.89 (0.78 to 0.95)
E^2	0.12 (0.08 to 0.17)	0.10 (0.06 to 0.16)	0.11 (0.05 to 0.22)

Abbreviations: CAST, Childhood Autism Spectrum Test; DF, DeFries-Fulker; DZF, dizygotic female twins; DZM, dizygotic male twins; DZOS, dizygotic opposite-sex twins; DZSS, dizygotic same-sex twins; E^2, nonshared environment estimate; H^2, heritability estimate; H_g^2, group heritability; LT, liability threshold; MZ, monozygotic; MZF, monozygotic female twins; MZM, monozygotic male twins.

[a] Data are given as mean (95% CI) unless otherwise indicated.

[b] Significant at $P < .05$.

tal effects were estimated to influence from 10% to 12% of categorical variation.

Full-Sample Heritability

Table 4 presents the full-sample heritability models. The best-fitting model suggests that, at age 12, autistic traits were moderately to highly heritable, and a small portion of their variability was attributable to shared environmental effects. Unique environmental effects explained approximately 23% of phenotypic variation. The best-fitting model indicated quantitative sex differences in the etiology of general population autistic traits. Males displayed significantly greater additive heritability (0.72; 95% CI, 0.68-0.76) than females (0.53; 0.44-0.62). Females displayed significantly greater shared environmental effects (0.25, 0.17-0.33) than males (0.04, 0.02-0.08). There was no evidence of qualitative sex effects.

The best-fitting variance components model did not fit as well as the saturated (likelihood ratio test = 26.32; $df = 15$, $P = .03$). This occurs frequently in studies with very large sample sizes because minimal variance differences between groups can be highly statistically significant. In this case, there was a small but significant sex effect on variance ($P = .003$) that the saturated model accounts for but that the variance components model assumes is equal.

The heritabilities predicted by the best-fitting, full-sample model were similar to those derived for the extreme groups. The 95% CI of the male full-sample heritability estimate (0.68-0.76) overlapped with the group heritability estimates of each DF model; the female full-sample heritability estimate overlapped with the group heritability estimates of the 97.5% and 99% DF models. Although not a statistical assessment of equivalency, this suggests consistent etiologic structure between the general population and the extremes when using the same (continuous) outcome definition.[24] One would anticipate lesser agreement between the female-specific full-sample values and overall estimates at the extremes because most high scorers were male and a sex difference in heritability was noted in the general population. To test whether this was the source of the modest deviation between females in the general population and at the extremes, we estimated an additional DF model at the 95% level in which male and female values were estimated separately. As expected, female heritability values at the extremes (estimated group heritability, 0.67; 95% CI, 0.62-0.67) were less deviant from those in the general population when specified independently, and the CIs overlapped.

COMMENT

We compared the etiology of typical variation in autistic traits with extreme scoring groups (including 1%) that mimicked the prevalence of diagnosed ASDs in the largest twin study of autistic traits to date. Although individuals in the most extreme group (top 1%) had parent-rated CAST scores as high as those with Development and Well-Being Assessment interview–identified ASD, the estimated heritability of autistic traits did not differ among the extreme groups (top 1%, 2.5%, and 5%). Using a continuous outcome definition, the heritability estimates at the extremes were highly similar to those derived from

Table 4. Full Sample Univariate Models[a]

Model	–2LL	*df*	Par	LRT (*df*)	ΔAIC	A (95% CI)	C/D (95% CI)	E (95% CI)
Saturated	18 776.51	11 910	26	. . .	18 828.51	. . .	. . .	. . .
ACE fix DZOS covariance								
Male estimates	18 802.83	11 925	11	26.32 (15)	–3.68	0.72 (0.68-0.76)	0.04 (0.02-0.08)	0.24 (0.22-0.26)
Female estimates						0.53 (0.44-0.62)	0.25 (0.17-0.33)	0.22 (0.20-0.24)
P value				.03				
ADE models								
Sex-limited ADE								
Male estimates	18 831.62	11 875	13	. . .	+29.11	0.73 (0.64-0.79)	0.04 (0.00-0.13)	0.23 (0.21-0.26)
Female estimates						0.79 (0.76-0.80)	0.00 (0.00-0.04)	0.21 (0.20-0.23)
ADE Fix DZOS covariance								
Male estimates	18 331.62	11 925	11	0.00 (1)	+25.11	0.73 (0.64-0.79)	0.04 (0.00-0.13)	0.23 (0.21-0.26)
Female estimates						0.79 (0.76-0.80)	0.00 (0.00-0.02)	0.23 (0.21-0.23)
P value				>.99				
AE								
Male estimates	18 832.37	11 927	9	0.75 (4)	+21.86	0.77 (0.74-0.79)	. . .	0.23 (0.21-0.26)
Female estimates						0.79 (0.77-0.80)	. . .	0.21 (0.20-0.25)
P value				.95				
ACE models								
Sex-limited ACE								
Male estimates	18 802.83	11 924	12	. . .	–1.68	0.72 (0.68-0.76)	0.04 (0.02-0.08)	0.24 (0.22-0.26)
Female estimates						0.53 (0.44-0.62)	0.25 (0.17- 0.33)	0.22 (0.20-0.24)
ACE Fix DZOS covariance								
Male estimates	18 802.83	11 925	11	0.00 (1)	–3.68	0.72 (0.68-0.76)	0.04 (0.02-0.08)	0.24 (0.22-0.26)
Female estimates						0.53 (0.44-0.62)	0.25 (0.17-0.33)	0.22 (0.20-0.24)
P value				>.99				
AE males; ACE females								
Male estimates	18 822.11	11 926	10	19.28 (2)	+13.60	0.77 (0.78-0.79)		0.23 (0.21-0.26)
Female estimates						0.65 (0.57-0.73)	0.14 (0.05-0.22)	0.22 (0.20-0.23)
P value				<.001				
AE								
Male estimates	18 832.37	11 927	9	29.54 (3)	+21.86	0.77 (0.74-0.79)	. . .	0.23 (0.21-0.26)
Female estimates						0.79 (0.77-0.80)	. . .	0.21 (0.20-0.23)
P value				<.001				
AE; equate males and females	18 837.93	11 929	7	35.10 (5)	+23.42	0.78 (0.76-0.79)	. . .	0.22 (0.21-0.24)
P value				<.001				
E	21 586.95	11 930	6	2784.12 (6)	+2770.44	. . .	. . .	1.00 (1.00-1.00)
P value				<.001				

Abbreviations: A, additive genetic influences; AIC, Akaike Information Criterion; C, shared environmental influences; D, nonadditive genetic influences; E, nonshared environmental influences; LRT(*df*), likelihood ratio χ^2 test with Δ*df* comparing model to first model listed within group (eg, LRT for the ACE submodels is calculated through comparison with the Scalar ACE); par, parameters; –2LL, log likelihood fit.

[a] Sex-limited ACE/ADE = ACE/ADE model permitting both qualitative and quantitative sex effects; ACE/ADE fix DZOS covariance = ACE/ADE model permitting only quantitative sex effects (no qualitative sex effects); AE males, ACE females = model in which C term has been dropped for males only, quantitative sex effects estimated, no qualitative sex effects; AE = model with A and E terms only, quantitative sex effects estimated, no qualitative sex effects.

the general population for both males and females. This study therefore presents the strongest evidence to date that genetic and environmental influence is stable in the population with increasing levels of autistic traits.

Phenotypic analyses showed there was an etiologic relationship between extreme scores in probands and subthreshold trait variation in their cotwins. Very extreme (>99%) scores were associated with both continuous shifts in cotwin autistic trait liability and increases in the categorical probability of lesser higher-scoring values, suggesting shared etiology between scores above and below the top 1% threshold. Given both that the liability shifts were much greater for MZ than DZ twins and that variation in autistic traits across the range of impairment was predominantly genetic, these data are consistent with shared genetic influence on autism-like behavior across a clinically significant threshold. Analyses of the molecular structure of genetic risk for ASD will be the ultimate test of consistent genetic etiology: we predict that some genes associated with ASD will also be associated with autistic traits across the distribution, a hypothesis that has now begun to be tested.[37,46-48]

Evidence for etiologic continuity across the clinical threshold carries substantial implications for gene-finding studies. For common disorders with polygenic liability, statistical power for genome-wide association studies can be greatly improved by examining the entirety of a trait distribution. Dichotomized approaches become less powerful as the control group includes more individuals who nearly meet case status.[29] Control group contamination is likely a problem in most case-control studies of common, complex neuropsychiatric phenomena. However, empirical evidence for the risk continuum that underlies the contamination is very rare. This study is unique in that its size allowed for direct examination of etiologic consistency up to a clinically relevant extreme.

The primary limitation of this study was its reliance on parent report. Although the highest scoring group in this analysis had a symptom *count* similar to that of children with ASD, the degree to which their symptom clustering or severity is comparable is unknown. The analyses of parent response were also limited by both individual item missingness (<2% per item) and the yes-no re-

sponse structure that reduced the degree of symptom variability that could be measured.

The comparison between etiologic structure in the general population and at the extremes was impeded by lack of power to consider sex differences within the extreme scoring groups. The extremes analyses were underpowered to test the significance of either the modest shared environmental effects (25% for females and 4% for males) or quantitative sex difference in heritability (19% difference in additive heritability) noted in the general population models. This, however, is a limitation inherent to the goal of testing etiologic continuity between regular variation and extremely high trait scores. The problem of small extreme groups is amplified in this case by male preponderance among individuals with high autistic trait scores.

The analysis was additionally limited by the methodological challenges inherent to twin-only designs. Measured environmental variables and multigenerational designs, in conjunction with molecular genetic studies, would clarify the degree to which twin-only assumptions hold in the general population.

In conclusion, this study found that parent-rated autistic traits are moderately to highly heritable in the general population at age 12. There was evidence for equivalent heritability within normal variation and the extremes, suggesting a consistent etiology of strong genetic and modest nonshared environmental influences across different autistic trait concentrations. Phenotypic analyses suggested shared etiology between extremely severe autism-like impairment and both less extreme impairment and regular variation. These data accordingly provide support for a continuous risk hypothesis, which argues that inherited genetic risk sets are associated with both subthreshold autistic traits and the clinical ASD phenotype. Furthermore, continuous genetic liability implies that clinical thresholds are etiologically arbitrary because clinical disorders exist as the quantitative extreme of a continuum.

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