Heritability of Autism Spectrum Disorder in a UK Population-Based Twin Sample

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**IMPORTANCE** Most evidence to date highlights the importance of genetic influences on the liability to autism and related traits. However, most of these findings are derived from clinically ascertained samples, possibly missing individuals with subtler manifestations, and obtained estimates may not be representative of the population.

**OBJECTIVES** To establish the relative contributions of genetic and environmental factors in liability to autism spectrum disorder (ASD) and a broader autism phenotype in a large population-based twin sample and to ascertain the genetic/environmental relationship between dimensional trait measures and categorical diagnostic constructs of ASD.

**DESIGN, SETTING, AND PARTICIPANTS** We used data from the population-based cohort Twins Early Development Study, which included all twin pairs born in England and Wales from January 1, 1994, through December 31, 1996. We performed joint continuous-ordinal liability threshold model fitting using the full information maximum likelihood method to estimate genetic and environmental parameters of covariance. Twin pairs underwent the following assessments: the Childhood Autism Spectrum Test (CAST) (6423 pairs; mean age, 7.9 years), the Development and Well-being Assessment (DAWBA) (359 pairs; mean age, 10.3 years), the Autism Diagnostic Observation Schedule (ADOS) (203 pairs; mean age, 13.2 years), the Autism Diagnostic Interview–Revised (ADI-R) (205 pairs; mean age, 13.2 years), and a best-estimate diagnosis (207 pairs).

**MAIN OUTCOMES AND MEASURES** Participants underwent screening using a population-based measure of autistic traits (CAST assessment), structured diagnostic assessments (DAWBA, ADI-R, and ADOS), and a best-estimate diagnosis.

**RESULTS** On all ASD measures, correlations among monozygotic twins (range, 0.77-0.99) were significantly higher than those for dizygotic twins (range, 0.22-0.65), giving heritability estimates of 56% to 95%. The covariance of CAST and ASD diagnostic status (DAWBA, ADOS and best-estimate diagnosis) was largely explained by additive genetic factors (76%-95%). For the ADI-R only, shared environmental influences were significant (30% [95% CI, 8%-47%]) but smaller than genetic influences (56% [95% CI, 37%-82%]).

**CONCLUSIONS AND RELEVANCE** The liability to ASD and a more broadly defined high-level autism trait phenotype in this large population-based twin sample derives primarily from additive genetic and, to a lesser extent, nonshared environmental effects. The largely consistent results across different diagnostic tools suggest that the results are generalizable across multiple measures and assessment methods. Genetic factors underpinning individual differences in autismlike traits show considerable overlap with genetic influences on diagnosed ASD.
Twin studies of autism,1-6 conducted from 1977 onward, provided the first clear evidence that genetic factors were etiologically important. Recent reviews of this literature6-9 show general agreement across studies that concordance for autism in monozygotic (MZ) twin pairs is typically at least double that in dizygotic (DZ) twin pairs, resulting in high heritability estimates (60%-90%)10-14 and suggesting little influence of shared environmental factors. Two twin studies15,16 stand in contrast and reported only moderate heritability (21%-38%), with a substantial shared environmental component explaining 58% to 78% of the variance in liability to autism spectrum disorder (ASD). In comparison, 1 recent twin study did not confirm significant shared environmental effects and reported heritability of 95%.7 In addition, a large population study of extended families (approximately 2 million individuals)16 reported estimates of 50% for heritability and nonshared environmental factors. Most recently, in the same population, molecular genetic analysis19 indicated that 95% of variance in ASD is accounted for by common allelic variants, supporting a polygenic model. This finding contrasts markedly with heritability estimates of around 0 derived from single-nucleotide polymorphism data (GCTA) in an arguably underpowered sample.20 Given the interest in possible environmental factors in the etiology of autism, these contradictory findings have reopened the discussion of high heritability and the possibility that findings may be biased by sample selection and screening. The first aim of the present study was to examine the relative importance of genetic and environmental factors in liability to ASD in a large systematically screened, population-based twin sample.

Twin and family studies21,22 have also shown that the genetic liability to autism confers a risk for a broader range of impairments in social communication, restricted and repetitive behaviors, and behaviors that extend beyond the traditional diagnostic boundaries for autism.9,23,24 These pioneering studies contributed to the revision and broadening of diagnostic criteria and to the conceptualization of autism as a spectrum encompassing subtypes of pervasive developmental disorders, such as Asperger syndrome, atypical autism, and subатель presentations.25,26 Research27-31 has explored autismlike traits in community samples and provided evidence of a genetic correlation between autismlike traits at the extremes and in the rest of the population. Our second aim was therefore to quantify the genetic and environmental relationship between dimensional trait measures and the categorical diagnostic constructs of ASD (from criterion-standard instruments), which, to our knowledge, has not been tried before.

To provide a more definitive picture that addresses these 2 aims and incorporates current diagnostic concepts, we used rigorous approaches and screened an age-specific epidemiologic sample of twins to ascertain all twins with possible ASD. We then undertook independent, in-depth evaluations using an additional screening instrument and well-established diagnostic assessment tools. The purpose was to minimize methodological artifacts and provide results that can be used as a benchmark for comparison in future research.

Our approach is novel and contrasts with those of other recent twin and family studies in sample ascertainment and analytic methods. Previous studies35-36 have identified their twin samples through clinical services. Such a strategy could result in sampling bias; if registration or participation is influenced by concordance, probandwise concordance rates in DZ twin pairs might be increased, resulting in inflated estimates of common environmental influence. In addition, sole reliance on clinical ascertainment could result in underidentification of cases with high levels of functioning.32 Investigators should include these cases and define the genetic liability as a continuous distribution that extends beyond stringent diagnostic categories. Our study is novel in using criterion-standard, in-person, clinical diagnostic tools with a population-based (vs a clinic-based) sample in which ascertainment was good (62.1% response rate from the eligible sample compared with 17% in the study by Hallmayer et al19).

In summary, our first aim was to estimate heritability of the liability to ASD using a population-based sample that was selected using several screening instruments sent to all twins in a 3-year birth cohort. The second aim was to study the genetic/environmental relationship between dimensional trait measures and categorical diagnostic constructs of ASD. In contrast to previous approaches,15,18 we assumed a continuous liability distribution underlying ASD and a more broadly defined phenotype with high-level autism traits that fell short of thresholds for an ASD diagnosis. We predicted a strong genetic overlap between dimensional and diagnostic measures in keeping with previous twin analyses based on extreme cases.29-33

Methods

Participants

The participants were recruited from the Twins Early Development Study,33 a longitudinal study of twin pairs ascertained from population records of twin births in England and Wales from January 1, 1994, through December 31, 1996. The Twins Early Development Study sample is considered representative of the population of the United Kingdom in terms of maternal ethnicity (92.8% white) and educational level (40.1% with A level qualifications or higher, the equivalent of some college education in the United States). Ethical authorization, including authorization to work with children, was given by the Institute of Psychiatry ethics committee. Parents were given a letter describing the general purpose of the study, and written parental consent was required. Participation was voluntary and participants could withdraw from the study whenever they wished.

The ASD and co-twin sample were selected after a 2-stage screening process outlined in Figure 1 and section 1 of eAppendix 1 in the Supplement. Of the 412 eligible families for the Social Relationship Study at stage 1, 80.1% completed the Development and Well-being Assessment (DAWBA) interview.34,35 At stage 2, 62.1% of the 235 eligible families underwent diagnostic evaluations. Two researchers worked with each family. One researcher administered the Autism Diagnostic Interview–Revised (ADI-R)36 and the other administered the Autism Diagnostic Observation Schedule (ADOS)37 for the first twin;
the researchers then swapped assessments for the second twin. This design meant that different assessors administered the ADI-R and ADOS assessments within each pair to minimize any effects of rater bias.

Within the final sample, participants with ASD were broadly comparable to those eligible for participation (score of ≥15 on the Childhood Autism Spectrum Test [CAST]) or with suspected ASD but who did not take part (zygosity, χ² = 1.5 [P = .23]; socioeconomic status, t₁₉₇ = −1.2 [P = .25, independent t test with 2-tailed significance]; and CAST result, t₄₂₀ = −1.5 [P = .14, independent t test with 2-tailed significance]), with the exception of sex (χ² = 20.1 [P < .001]). Among the group with high CAST scores or suspected ASD, 36.4% were female compared with 16.6% of the final sample.
Measures

**Childhood Autism Spectrum Test**

The CAST is an informant-completed questionnaire based on behavioral descriptions of ASD as delineated in the *International Statistical Classification of Diseases, Tenth Revision (ICD-10)* and the *DSM-IV*. The 31 items are scored yes or no and summed; a cutoff score of 15 or greater is reported to have 100% sensitivity, 97% specificity, and a positive predictive value of 50% for a diagnosis of ASD.

The CAST data from at least 1 twin were available from 6423 pairs (MZ pairs, 2261; DZ same-sex pairs, 2097; and DZ opposite-sex pairs, 2065), with a mean (SD) age of 7.9 (0.5) years. Of these, 289 pairs (4.5% of all pairs; 317 pairs, 2097; and DZ opposite-sex pairs, 2065), with a mean (SD) age of 7.9 (0.5) years. Of these, 289 pairs (4.5% of all pairs; 317 individuals) had scores greater than the cutoff value.

**Development and Well-being Assessment**

Telephone interviews using the ASD module of the DAWBA were performed at the second stage and included 15 questions about social difficulties; 14 questions about repetitive, restricted behaviors and interests; and 3 questions about developmental language milestones. The same parent rated both twins during a telephone call with a single interviewer. A child received a DAWBA diagnosis of autism when the operational criteria in the *DSM-IV* and *ICD-10* were met. A diagnosis of Asperger syndrome was given when parent reports indicated that all autism criteria were met but the child’s early language development was not delayed and the child’s intellectual ability was in the normal range. A diagnosis of ASD (other) was assigned if the parents reported a minimum of 3 probable or 2 definite symptoms from the social difficulties domain, 2 probable or 1 definite symptom from the communication domain, and 2 probable or 1 definite symptom from the repetitive, restricted behaviors and interests domain. The measure used in analysis was a 3-category diagnosis of ASD, where 0 indicates no ASD/controls; 1, ASD (other); and 2, Asperger syndrome or autism.

**Autism Diagnostic Interview–Revised**

The ADI-R is a well-established diagnostic tool for the assessment of autism. It consists of a semistructured caregiver interview inquiring about current function and developmental history (93 items) and is administered by a trained investigator. We used criteria from the Autism Genetics Resource Exchange (http://agree.autismspeaks.org/site/c.lWlZKNhLRh/b.532889/k.B473/AGRE.htm) to assign cases to 1 of the following 3 categories: ASD (consisting of Autism Genetics Resource Exchange categories *autism* and *not quite autism*), broad-spectrum disorder, and unaffected (operational definitions are given in eAppendix 2 in the Supplement). The measure used in the analysis was a 3-category diagnosis of ASD, where 0 indicates no ASD/controls; 1, broad-spectrum disorder; and 2, ASD.

**Autism Diagnostic Observation Schedule**

TheADOS is a well-validated, semistructured observational assessment designed to accompany the ADI-R in the diagnosis of ASD. The present study used recent updates to the ADOS algorithm (Catherine Lord, PhD, written communication, 2008; described in eAppendix 2 in the Supplement) to yield scores for communication, social interaction, and restricted behaviors and interests. Clinical cutoffs were available for ASD and autism, and these diagnostic groups were combined to create a single ASD category. An additional broad-spectrum category included individuals who scored just below the cutoff (~2 points) to correspond to the broad-spectrum category on the ADI-R. The measure used in the analysis was a 3-category diagnosis of ASD, where 0 indicates no ASD/controls; 1, broad-spectrum disorder; and 2, ASD.

**Best-Estimate Diagnosis**

Diagnoses were assigned with investigators blinded to zygotypes and co-twin diagnostic status after review of all available information (ADI-R, ADOS, and DAWBA assessments and clinical reports). When all available sources of information were in agreement, cases were assigned to that category. In 89 cases, the diagnostic classifications across instruments were inconsistent. In these cases, all available data were assessed by expert clinicians (E.C., S.R.C., and/or P.B.), and best-estimate diagnoses (BeDs) were assigned based on this review. Additional details are given in eAppendix 2 in the Supplement. Best-estimate diagnosis was used in the analysis as a 3-category measure of ASD, where 0 indicates no ASD/controls; 1, broad-spectrum disorder; and 2, ASD.

**Data Analysis**

**Twin Correlations**

Twin data analysis was performed in the structural equation modeling program OpenMx. We used the full information maximum likelihood estimation to jointly analyze the continuous (CAST) and ordinal (ADI-R, ADOS, and DAWBA assessments and clinical reports). When all available sources of information were in agreement, cases were assigned to that category. In 89 cases, the diagnostic classifications across instruments were inconsistent. In these cases, all available data were assessed by expert clinicians (E.C., S.R.C., and/or P.B.), and best-estimate diagnoses (BeDs) were assigned based on this review. Additional details are given in eAppendix 2 in the Supplement. Best-estimate diagnosis was used in the analysis as a 3-category measure of ASD, where 0 indicates no ASD/controls; 1, broad-spectrum disorder; and 2, ASD.

**The Bivariate Genetic Model**

With the use of biometrical genetic theory, the covariance of the CAST score and each ASD diagnosis was modeled as the effects of additive genetic (A), shared environmental (C), and nonshared environmental and measurement error (E) factors. Because the order of traits is immaterial, we interpreted the standardized solution in which the paths from the A factor to the CAST score and the A factor to ASD are the square roots of their respective heritabilities, and the correlation between A and A is the genetic correlation between them (r_A). The same logic applies to the nonshared environmental effects (Figure 2). Shared environmental factors were modeled on ASD
Results

Probandwise Concordance Rates

Probandwise concordance rates were calculated as \( \frac{[2 \times \text{number of concordant pairs}] - \text{discordant pairs}}{[2 \times \text{number of concordant pairs}]} \) (Table 1). These calculations express the probability that the co-twin of a proband (affected twin) is also affected and are commonly used as an index of twin resemblance. The high MZ (0.62-0.94) and low DZ (0.05-0.61) concordances suggest substantial genetic influence. For example, MZ concordances are 0.87 for ASD and 0.94 for BeD, in contrast to 0.22 and 0.46, respectively, for DZ concordances. However, concordance rates cannot be used to estimate genetic and environmental parameters because they do not take population prevalence rates into account.

Diagnostic Agreement

Agreement of classification of individuals into the 3 categories (unaffected, broad-spectrum disorder, and ASD) for different diagnostic measures was calculated by means of weighted \( \kappa \) coefficients (Stata software; StataCorp) with predefined weights used so that the 0-2 cells get a full weight of 1 and the 0-1 and 1-2 cells only a weight of 25% in calculating disagreement. These values (-1 to 1) represent the observed agreement between 2 diagnostic tests relative to the expected agreement between tests occurring by chance alone. We found moderate \( \kappa \) agreement for DAWBA and the ADOS assessment (0.58) and substantial agreement for DAWBA and the ADI-R assessment and for DAWBA and BeD (both 0.72), for the ADI-R and ADOS assessments (0.67), and for the ADOS assessment and BeD (0.79). Agreement for the ADI-R assessment and BeD was almost perfect (0.91).

Twin Correlations

The 2:1 MZ:DZ ratio of the cross-twin within-trait correlations for the ADOS assessment and BeD suggest a significant contribution of genetic effects, with the remainder explained by nonshared environmental effects (Table 2). This contribution is not the case for DAWBA, for which the DZ correlation is less than half that of the MZ pairs, pointing to nonadditive genetic effects. For the ADI-R assessment, the DZ correlation is more than half the MZ correlation, indicating genetic and shared environmental effects. The MZ:DZ ratio of the cross-twin cross-trait correlations for the CAST score and each diagnosis indicates mainly genetic and nonshared environmental influences on their overlap.

Bivariate Genetic Model

Table 3 reports the standardized results of the bivariate ACE models. Variance in the CAST score (age and sex regressed) resulted from genetic influences (78% [95% CI, 77%-79%]) and
nonshared environmental effects (22% [95% CI, 21%-23%]), as reported previously.30 Genetic influences were significant for all clinical measures with the highest heritability reported for BeD (95% [95% CI, 74%-98%]) and shared environments significantly explaining the variance of the ADI-R assessment only (30% [95% CI, 8%-47%]). The correlations between the CAST score and each of the ASD variables ($r_{ph}$) is the sum of the paths via the additive genetic and nonshared environmental factors (A and E) connecting the 2 variables ($r_{ph,A}$ and $r_{ph,E}$). The phenotypic correlations were moderate to high (0.52-0.65), and genetic factors accounted for 77% to 100% of the covariance. The genetic correlations, that is, the extent to which the same genetic factors influence the CAST score and clinical measures independent of their heritabilities, are substantial (0.52-0.89). The remainder of the covariance was explained by nonshared environmental factors ($r_{ph,E}$), although nonsignificant for the overlap between the CAST score and the ADI-R or the ADOS assessment. Figure 2 depicts the path diagram with standardized estimates of the reduced bivariate AE model (in which no shared environmental influences are found) for the CAST score and BeD, BeD being the best diagnostic estimate of ASD in our study. The findings indicate strong and overlapping genetic influences on dimensional and categorical measures.

### Discussion

The present study examines the genetic and environmental contributions to ASD in a large systematically screened population-based twin sample and the genetic/environmental overlap between a continuous measure of autistic traits and categorical diagnostic assessments. Our study was novel in including twins with high subclinical levels of traits and selected low-risk twins as well as those with diagnosed ASD to capture the full range of liability. The probandwise concordance rates and liability threshold model analyses reassert the
The importance of genetic factors in the etiology of ASD. Analyses partitioning liability into genetic and shared and nonshared environmental components indicate that most liability could be attributed to additive genetic influences and a smaller proportion attributed to nonshared environmental influences. This finding held across a number of different measures. We found very little evidence of shared environmental effects overall, which is contrary to the findings of Hallmayer et al., although the wide CIs in their results for additive genetic and shared environmental effects overlap with some of the present estimates. In our study, only the ADI-R parent-reported developmental history measure showed significant shared environment effects. Because the ADI-R assessment was completed by the same parent for both twins, the estimated influence of shared environment may be inflated by rater bias. However, the wide CIs (0.08–0.47) warrant caution in interpretation.

Our findings also confirm that the heritability of the liability to ASD is high when incorporating subclinical cases with high trait scores into the model, extending support for the notion that the genetic liability to autism confers a risk for a broader autism phenotype. Indeed, the relationship between the CAST score and diagnostic assessments indicated a substantial genetic correlation and a significant correlation in the nonshared environmental factors that influence variations in both traits. This result indicates common etiologic underpinnings for individual differences in autistic traits across the whole spectrum and in our 3 clinically meaningful categories (ASD, high subclinical trait level, and low risk/trait level). This result provides support for examining broader autistic traits in the general population as a complementary strategy for identifying the genetic risk factors for ASD.50–52 Our findings are broadly in line with those of recent twin and family studies and point toward strong genetic effects in ASD and no strong influence from shared environmental factors. The strengths of the present study add validity to these conclusions because previous research has often lacked the rigor and systematic approach to the sample selection used herein. The population-based sampling in the present study, the 2-stage systematic screening methods used, and the inclusion of individuals with subclinical disorders ensured the capture of a more complete picture of genetic risk (additive and nonadditive) for ASD than in previous studies. A novel contribution is the strong evidence that the same genetic influences are largely responsible for the overlap between dimensional trait measures and categorical diagnostic constructs of ASD. In addition, to the best of our knowledge, this study is one of the largest screened population-based twin studies yet reported.

The limitations of this study include the fact that few of the potentially eligible twin pairs did not enroll in the study. Second, although one of the largest twin studies, the sample size was insufficient to allow any meaningful analyses of the basis for sex differences in ASD. In addition, twin study methods assume that the environments of MZ and DZ twins are equal and that twins are not at especially high risk for the disorder under investigation. The available evidence indicates that both assumptions are justified in this study.54 Another issue is that genetic modeling assumes that no gene-environment interactions or correlations exist; if they exist, the estimates of environmental and genetic effects may be inflated.55 Heritability estimates are also population specific and depend on the dynamic interaction with the current environment. Our analysis took a liability threshold approach, but other types of analyses (eg, continuous data modeling, DeFries-Fulker quantile regression56) are possible and may be warranted by future developments in the molecular genetics of ASD. Recent findings lend support to a polygenic trait approach.19

Conclusions

The present study combines the strengths of previous studies and provides a more complete picture than any of them individually by being nationally representative and incorporating dimensional and categorical measures using a systematic repeated screening method. We conclude that liability to ASD and a more broadly defined high-level autism trait phenotype in UK twins 8 years or older derives from substantial genetic and moderate nonshared environmental influences. Genetic influences on diagnosed ASD are shared with those on autistic traits in the general population.