Online First

Genetic Heritability and Shared Environmental Factors Among Twin Pairs With Autism

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Context: Autism is considered the most heritable of neurodevelopmental disorders, mainly because of the large difference in concordance rates between monozygotic and dizygotic twins.

Objective: To provide rigorous quantitative estimates of genetic heritability of autism and the effects of shared environment.

Design, Setting, and Participants: Twin pairs with at least 1 twin with an autism spectrum disorder (ASD) born between 1987 and 2004 were identified through the California Department of Developmental Services.

Main Outcome Measures: Structured diagnostic assessments (Autism Diagnostic Interview–Revised and Autism Diagnostic Observation Schedule) were completed on 192 twin pairs. Concordance rates were calculated and parametric models were fitted for 2 definitions, 1 narrow (strict autism) and 1 broad (ASD).

Results: For strict autism, probandwise concordance for male twins was 0.58 for 40 monozygotic pairs (95% conc

Conclusion: Susceptibility to ASD has moderate genetic heritability and a substantial shared twin environmental component.


Autism is a complex neurodevelopmental disorder that interferes with the normal course of social, communicative, and cognitive development. The diagnosis of autism is made in early childhood, with symptoms manifesting within the first 3 years of life. Over the last 3 decades, a substantial increase in the prevalence of autism has been reported, from 4 to 5 per 10,000 in the 1960s to around 40 per 10,000 children today. For autism spectrum disorders (ASDs), prevalence rates have been estimated to be about 1%. This 10-fold increase in prevalence has received considerable attention, with concomitant increases in research funding.

There have been numerous studies designed to characterize the contribution of genetic factors to the development of this disorder. Concordance rates in siblings range from about 3% to 14% and linkage studies are consistent with a polygenic mode of transmission. Three studies of twins ascertained from clinical samples with a total of 36 monozygotic pairs (concordance rate of 72%) and 30 dizygotic pairs (concordance rate of 0%) have estimated the heritability of autism, or proportion of liability attributable to genetic factors, at about 90%. The dizygotic concordance (0%) is substantially lower than the expected rate based on estimates of sibling recurrence rates. More recent twin studies of autism based on either case vignettes or telephone interviews have also yielded high heritability estimates. In addition, a number of twin studies that used dimensional measures of some core features of autism, such as social responsiveness, have yielded a broad...
range of heritability estimates of autism. However, none of these more recent studies included structured clinical assessments by both parental interview and direct child observation, which is the contemporary standard for establishing the diagnosis of autism or ASD.

This report describes the results of a twin study of autism: the California Autism Twins Study. The chief aims were to (1) collect a sample of twins with validated diagnoses of autism (ASD) from a population-based sample; (2) examine sex-specific concordance rates for narrow and broad definitions of autism (ASD); and (3) determine the extent to which genetic and shared environmental factors underlie susceptibility.

## METHODS

### PARTICIPANTS

Twin pairs were identified from the records of the Department of Developmental Services (DDS). The DDS operates a system of 21 regional centers throughout California that coordinate services for persons with autism, mental retardation, and other developmental disabilities. Referral sources for regional centers include primary care providers, educators, public health clinics, other service agencies, and parents. The electronic DDS client files were linked by California Center for Autism and Developmental Disabilities Research and Epidemiology (CADDRE) staff to California live birth records to identify twin births and obtain demographic data. The birth years of the twin pairs included in our study were 1987 to 2004. Twin pairs were considered eligible for the study if they met the following criteria:

1. At least 1 child in the pair had a qualifying diagnosis (see later) in the DDS electronic file or in client records; each twin in a pair who met this criterion was considered a proband.
2. Maternal residence in California at the time of delivery.
3. Both co-twins were alive and residing in California at the time of enrollment.
4. No history among proband(s) of neurogenetic conditions that might account for autism (eg, fragile X syndrome, Down syndrome, tuberous sclerosis, and neurofibromatosis).
5. Proband(s) had a mental age more than 18 months.
6. At least 1 parent with sufficient verbal and reading ability in English or Spanish was able to respond to interviews and checklists.

Using DDS electronic files, CADDRE staff ascertained twins receiving services for autism (DDS autism codes A1 or A2) and twins with a possible ASD based on other recorded information indicating a suspected ASD (DDS autism code A9), DSM-IV diagnosis of ASD (code A4, derived by CADDRE), mental retardation of unknown etiology (MRnOE, derived by CADDRE), or other developmental disability (other, derived by CADDRE). Trained CADDRE staff then abstracted client records to record presence or absence of an ASD diagnosis, criteria used for diagnosis, specific autistic behaviors, and other clinical characteristics. Expert clinical review was then conducted to verify that the children met eligibility based on qualifying diagnosis and other criteria (mentioned earlier). The diagnosis of autism can be most reliably established if a child is at least 4 years or older, so the birth years 1987 to 2004 were included.

A letter from the local regional center and a recruitment package were sent to parents explaining the study and asking their consent to send identifying information to study staff at Stanford University who then contacted them to further describe the study and obtain written consent. The twin pairs described in this article were assessed starting in August 2005 and continuing un-
within 2 points on the other or (3) met full criteria on the ADI-R for autism on all of the domains.

**STATISTICAL ANALYSIS**

**Definition of Probands**

Twin pairs were ascertained through the DDS electronic files and client records, which constituted our sampling frame. In some cases, both twins in the pair were identified as having a high likelihood of autism in these records. In other cases, only 1 twin was so identified. On direct examination of the twins, we determined final diagnoses of strict autism or ASD as described earlier. For the purpose of our concordance and model-fitting analyses, we defined a proband as any individual who was identified in the DDS files or client records with qualifying DDS data and whose diagnosis of autism or ASD was subsequently confirmed by us through expert clinical review of abstracted data. Some individuals were diagnosed by us with autism or ASD but were not ascertained in the DDS file or client records; these individuals were not considered probands. Any individual who was determined by us to be unaffected was not counted as a proband. Also, in the analysis of strict autism, some individuals with a diagnosis of ASD but not strict autism were considered unaffected and not probands, even if they were identified through DDS records. Pairs where neither child met our criteria of strict autism were not included in the concordance analysis of strict autism.

**Calculation of Concordance Rates**

Pairwise concordance is calculated as the proportion of all ascertained pairs with 2 affected individuals and can be impacted by method of ascertainment of the twins. Probandwise concordance is calculated as the proportion affected among the co-twins of probands. Probandwise concordance accounts for ascertainment and represents the recurrence risk to a co-twin of an affected individual. In numerical terms, let \( N \) = total number of twin pairs, \( R \) = number of pairs with 2 affected twins, \( t \) = number of pairs among the \( R \) that have 2 probands, \( S \) = number of pairs among the \( R \) that have 1 proband, and \( U \) = number of discordant pairs (with 1 proband). Then \( S + t = R \) and \( R + U = N \). The pairwise concordance is simply given by \( R/N \). The total number of co-twins of probands (which is the same as the number of probands because each proband has 1 co-twin) is \( 2 \times t + 2 \times S + U = N + t \). The number of these co-twins who are also affected is \( 2 \times t + S + R + t \). In both of these cases, we doubled \( t \) because both affected twins in the pair are co-twins of probands. By contrast, we did not double \( S \) because only 1 affected twin in the pair is the co-twin of a proband. Hence, the probandwise concordance is given by \( (R + t)/(N + t) \).

For opposite-sex dizygotic twin pairs, the pairwise concordance is straightforward to calculate, as described earlier. For the probandwise concordance of opposite-sex twin pairs, we calculated the proportion of female co-twins of male probands who are affected and the proportion of male co-twins of female probands who are affected.

For pairwise concordance, 95% confidence intervals (CIs) were calculated exactly assuming a binomial distribution. For probandwise concordance, 95% CIs were calculated using the modified variance formula given by Davie.

**Examination of Potential Demographic, Ascertainment, or Clinical Biases**

To test for differences (ie, potential biases) across several demographic factors between twin pairs or individuals who were included in the study vs those from the original DDS files who met entry criteria but were not included, a univariate analysis of variance was performed for continuous variables and \( \chi^2 \) tests were used for dichotomous traits. For both analyses, a \( P \) value of .05 for a 2-sided test was considered significant. To determine whether demographic factors influenced the concordance rates of monozygotic and dizygotic twin pairs, we used logistic regression separately for monozygotic and dizygotic pairs, with concordance vs discordance of the twin pair as the dichotomous outcome (dependent) variable. Independent variables included twin type (male or female for monozygotic twins; male, female, or male-female for dizygotic twins), age of mother and father, years of paternal and maternal education, ethnicity of mother and father, difference in birth weight between twin individuals, and gestational age (in completed weeks). For significance, a 2-sided \( P \) value of .05 adjusted for number of tests performed was considered. A critical assumption of the logistic regression is independence of the outcomes (in this case, concordance vs discordance among twin pairs). Because the twin pairs in our study were not related, independence is a reasonable assumption. All study-specific statistical analyses were performed using SPSS Statistics 19 (IBM SPSS, Chicago, Illinois).

To explore possible ascertainment bias, we compared the proportion of twin pairs concordant for being affected according to the qualifying DDS diagnostic categories among the twins included in the final study vs the twins from the original list who were ultimately not included. This analysis was stratified on type of twin pair (male-male, female-female, male-female). We could not stratify on zyosity because zyosity was unknown for pairs not included. For this analysis, we calculated odds ratios and \( \chi^2 \) tests for each of the 3 strata (defined by sex) and then a summary odds ratio and \( \chi^2 \) test across the 3 strata by Mantel-Haenszel analysis. The Mantel-Haenszel \( \chi^2 \) was assumed to have 1 df and was considered significant if greater than 3.84 (\( P < .05 \)).

To determine whether diagnostic shifts may have occurred during the recruitment process, we compared the distribution of DDS diagnostic categories between affected twins included in the study vs those from the original list who were not included using a \( \chi^2 \) test, with \( df \) equal to the number of categories minus 1. Results were considered significant if the \( \chi^2 \) exceeded the threshold corresponding to a \( P \) value of .05.

**Model Fitting**

To determine the relative importance of genetic (heritable) vs shared co-twin environmental factors to the development of autism and ASD, we performed a classic ACE twin analysis and fit parametric models to the twin concordance data using maximum likelihood, incorporating information on proband status of the twins. The model assumes that numeros genic and environmental factors of small effect accumulate into a continuous, normally distributed unobserved trait called liability. Liability values above a given threshold value lead to disease. Hence, this model is usually termed a multifactorial or polygenic threshold model. The critical parameters for this model are the components of variance of liability and the threshold value. The threshold value reflects disease prevalence. We assume different threshold values for males and females, which are denoted by \( T_m \) and \( T_f \), respectively. For the modeling, we assumed a prevalence of 1% for males and 0.3% for females for ASD and 0.5% for males and 0.15% for females for strict autism. Because autism may be more prevalent in twins, we also considered the effect of assuming higher as well as lower prevalence estimates on our results.

Aside from the thresholds, 3 components of liability variance are included, a genetic component, an environmental com-
A total of 1156 pairs fulfilled our initial eligibility criteria. We were unable to establish contact with 384 pairs, primarily because the families had lost contact with the regional center. Of the 772 remaining pairs, 330 declined participation and 10 pairs were ineligible. Of the 432 pairs whose contact information was sent to the Stanford team, 90 pairs declined participation in the study. Of the remaining 333 pairs, we completed the assessments for 202 pairs.

Among the 404 twin individuals, 242 met criteria for ASD (171 of whom also met criteria for strict autism), with the remaining 162 failing to meet criteria for an ASD. Comparing the study-qualifying diagnosis based on the DDS data with the diagnosis based on the ADI-R and ADOS, we calculated the sensitivity for ASD as 229/242 = 94.6% and the specificity as 137/162 = 84.6%. For strict autism, the sensitivity was 166/171 = 97.1% and the specificity, 158/233 = 67.8%. The DDS-based diagnosis was therefore a good predictor of the study ASD diagnosis based on the ADI-R and ADOS. For 10 twin pairs, neither of the twins met study criteria for the broader definition of ASD; these twin pairs were excluded from the genetic analyses.

To consider potential bias or differences among the 192 twin pairs who were included in the genetic analyses, we compared the 2 groups on a number of demographic criteria (eTable 1). The 2 groups were comparable for most variables, except that the age of the twins included in the genetic analyses was on average slightly older, birth weight of males was somewhat higher, and their mothers and fathers were, on average, slightly more educated and more likely to be white and less likely to be African American.

We also examined clinical differences by examining the distribution of DDS categories between the 2 groups (eTable 2). The proportional representation of the 6 diagnostic categories in the included vs nonincluded twins was comparable ($\chi^2$=8.82; $P$ = .12). We also looked to see if there was any correspondence between the 6 DDS diagnostic categories and our research diagnoses of strict autism vs ASD (eTable 2). Most DDS categories showed a similar distribution of strict autism vs ASD vs unaffected with the possible exception of “other,” for which a somewhat higher proportion (50%) was unaffected, although the number of individuals in this group was quite small (n=6).

Of the 192 twin pairs included in the final analysis, 54 were monozygotic (45 male and 9 female) and 138 were dizygotic (45 male, 13 female, and 80 sex-discordant). The monozygotic twins were slightly older and had slightly shorter gestation periods (Table 1). In addition, the mothers of the dizygotic twins were older than the mothers of the monozygotic twins (Table 1), consistent with the known increase in dizygotic twinning with maternal age, and more likely to be white and non-Hispanic.

For strict autism (143 pairs), probandwise concordance rates (Table 2) for monozygotic twins were similar for 40 male pairs (58%; 95% CI, 42%-74%) and 7 female pairs (60%; 95% CI, 28%-90%), comparable with those reported in prior studies. However, probandwise concordance rates for dizygotic pairs were higher than previously reported, with rates of 21% for 31 male pairs (95% CI, 9%-43%) and 27% for 10 female pairs (95% CI, 9%-69%) (Table 2). The probandwise concordance rate for 54 female dizygotic co-twins of male probands was 3.7% (95% CI, 0.5%-13%), which was lower than for sex-concordant pairs, while the rate for male dizygotic co-twins of female probands was 50% (95% CI, 1%-99%). This latter finding was based on small numbers (n = 2).

For ASD (192 pairs), concordance estimates for both monozygotic and dizygotic twin pairs were generally higher. Probandwise concordance for monozygotic twins was 77% (95% CI, 65%-86%) for 45 male pairs and 50% (95% CI, 16%-84%) for 9 female pairs. Concordance rates for dizygotic twins were 31% (95% CI, 16%-46%) and 36% (95% CI, 11%-60%) for 45 male and 13 female pairs, respectively. Probandwise concordance for female dizygotic co-twins of 76 male probands was 5.3% (95% CI, 1.5%-13.0%), while the rate for male dizygotic co-twins of 6 female probands was 50.0% (95% CI, 11.8%-88.2%). Again, these dizygotic concordance rates are higher than previously reported and have a significant impact on the heritability analysis. From logistic regression analysis of concordance, the only factor impacting concordance rates was sex of co-twins in the dizygotic pairs ($P$ value = .045), which was formally not significant if adjusted for multiple testing.
We also considered possible ascertainment bias in terms of concordance. Using the DDS categories to define affected, we examined the proportion of twin pairs concordant among the included pairs vs the nonincluded pairs, stratified by sex (eTable 1). Overall, there was no significant difference in proportion concordant (Mantel-Haenszel odds ratio = 1.17; 95% CI, 0.80-1.70) between the included and nonincluded pairs.

As described in the eAppendix, twin concordance rates were used to obtain parameter estimates for the genetic models; results are presented in Table 3 and likelihood ratio tests of different models, in Table 4. In all models, both genetic and shared environmental components were significant. The best-fitting models for both strict autism and ASD suggest that a large proportion of the variance in liability is due to shared environmental factors in addition to genetic heritability. For strict autism, we could conclude that heritabilities in males and females were equal and that the shared environmental components in males and females were also equal. The best-fitting model had a genetic heritability of 37% (95% CI, 8%-84%) and a shared environmental vari-
ance component of 55% (95% CI, 9%-81%). For the broader ASD phenotype, again we could conclude that heritabilities and shared twin environmental components were equal in males and females. Heritability was estimated to be 38% (95% CI, 14%-67%) and the shared environmental component, to be 58% (95% CI, 30%-80%). The shared environment component was estimated to be larger than the genetic heritability component. The poor fit of a pure heritability model can be attributed primarily to the high dizygotic twin concordance relative to the monozygotic twin concordance and population prevalence.

Table 3. Results of Model Fitting, California Autism Twins Study, 1987-2004 Births

<table>
<thead>
<tr>
<th>Model</th>
<th>Parameter Constraints</th>
<th>τ</th>
<th>A_0</th>
<th>C_m</th>
<th>A_f</th>
<th>C_f</th>
<th>r_mf</th>
<th>−2lnL + C</th>
<th>AIC</th>
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<tr>
<td><strong>Strict Autism (Narrow)</strong></td>
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<tr>
<td>Equal heritability for M and F; no shared twin environment</td>
<td>A_m = A_f; C_m = C_f = 0</td>
<td>0.896</td>
<td>0.931 (0)</td>
<td>0.931 (0)</td>
<td>1.00</td>
<td>7.83</td>
<td>11.83</td>
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<tr>
<td>No shared twin environment</td>
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<tr>
<td>C_m = C_f = 0</td>
<td>0.895</td>
<td>0.926 (0)</td>
<td>0.951 (0)</td>
<td>1.00</td>
<td>7.64</td>
<td>13.64</td>
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<tr>
<td>No heritability, equal twin environment for M and F; perfectly correlated</td>
<td>A_m = A_f; C_m = C_f; r_mf = 1</td>
<td>0.904</td>
<td>0.819 (0)</td>
<td>0.819 (1.0)</td>
<td>19.35</td>
<td>23.35</td>
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<tr>
<td>No heritability, equal twin environment for M and F</td>
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<tr>
<td>A_m = A_f; C_m = C_f</td>
<td>0.902</td>
<td>0.862 (0)</td>
<td>0.862</td>
<td>0.578</td>
<td>9.01</td>
<td>13.01</td>
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<tr>
<td>No heritability; twin environment perfectly correlated for M and F</td>
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<tr>
<td>A_m = A_f; C_m = C_f; r_mf = 1</td>
<td>0.904</td>
<td>0.837 (0)</td>
<td>0.757 (1.0)</td>
<td>18.86</td>
<td>22.86</td>
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<td><strong>ASD (Broad)</strong></td>
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<tr>
<td>Equal heritability for M and F; no shared twin environment</td>
<td>A_m = A_f; C_m = C_f = 0</td>
<td>0.878</td>
<td>0.969 (0)</td>
<td>0.969 (0)</td>
<td>1.00</td>
<td>19.93</td>
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<tr>
<td>No shared twin environment</td>
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<tr>
<td>C_m = C_f = 0</td>
<td>0.879</td>
<td>0.978 (0)</td>
<td>0.930 (0)</td>
<td>1.00</td>
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<td>24.61</td>
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<tr>
<td>No heritability, equal twin environment for M and F; perfectly correlated</td>
<td>A_m = A_f; C_m = C_f; r_mf = 1</td>
<td>0.894</td>
<td>0.864 (0)</td>
<td>0.864 (1.0)</td>
<td>35.00</td>
<td>37.00</td>
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<tr>
<td>No heritability, equal twin environment for M and F</td>
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<tr>
<td>A_m = A_f; C_m = C_f</td>
<td>0.889</td>
<td>0.901 (0)</td>
<td>0.901</td>
<td>0.622</td>
<td>18.73</td>
<td>22.73</td>
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<td>No heritability; twin environment perfectly correlated for M and F</td>
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<tr>
<td>A_m = A_f; C_m = C_f; r_mf = 1</td>
<td>0.892</td>
<td>0.895 (0)</td>
<td>0.723 (1.0)</td>
<td>31.32</td>
<td>35.32</td>
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<tr>
<td><strong>ASD (Broad)</strong></td>
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<tr>
<td>Equal heritability for M and F; no shared twin environment</td>
<td>A_m = A_f; C_m = C_f = 0</td>
<td>0.889</td>
<td>0.905 (0)</td>
<td>0.822</td>
<td>0.822</td>
<td>18.55</td>
<td>24.55</td>
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<tr>
<td>C_m = C_f = 0</td>
<td>0.889</td>
<td>0.513</td>
<td>0.450</td>
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<td>0.450 (1.0)</td>
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<td>11.28</td>
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<tr>
<td>No heritability, equal twin environment for M and F; perfectly correlated</td>
<td>A_m = A_f; C_m = C_f; r_mf = 1</td>
<td>0.888</td>
<td>0.383</td>
<td>0.581</td>
<td>0.383</td>
<td>0.581</td>
<td>0.724</td>
<td>3.28</td>
<td>9.28</td>
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<td>No heritability, equal twin environment for M and F</td>
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<tr>
<td>A_m = A_f; C_m = C_f</td>
<td>0.889</td>
<td>0.633</td>
<td>0.342</td>
<td>0.208</td>
<td>0.682 (1.0)</td>
<td>4.62</td>
<td>12.62</td>
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<tr>
<td>Full model</td>
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Abbreviations: A_0, additive genetic variance for females; AIC, Akaike information criterion; A_m, additive genetic variance for males; ASD, autism spectrum disorder; C_m, twin environmental variance for males; C_f, twin environmental variance for females; F, females; M, males; r_mf, male-female correlation in variance components; ascertainment probability; −2lnL + C, minus twice the natural logarithm of the likelihood plus a constant.

Parameters in parentheses are fixed.


<table>
<thead>
<tr>
<th>Hypothesis Tested</th>
<th>Parameter Constraint</th>
<th>df</th>
<th>τ</th>
<th>A_0</th>
<th>C_m</th>
<th>A_f</th>
<th>C_f</th>
<th>r_mf</th>
<th>−2lnL + C</th>
<th>AIC</th>
<th>χ²</th>
<th>P Value</th>
<th>χ²</th>
<th>P Value</th>
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<tr>
<td>Perfect correlation in liability between M and F</td>
<td>r_mf = 1</td>
<td>2</td>
<td>2.68</td>
<td>.10</td>
<td>4.62</td>
<td>.03</td>
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<tr>
<td>Equal heritability and equal twin environment for M and F</td>
<td>A_m = A_f; C_m = C_f</td>
<td>2</td>
<td>0.81</td>
<td>.67</td>
<td>3.28</td>
<td>.19</td>
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<tr>
<td>Equal heritability and equal twin environment for M and F; perfectly correlated</td>
<td>A_m = A_f; C_m = C_f; r_mf = 1</td>
<td>3</td>
<td>2.98</td>
<td>.40</td>
<td>7.28</td>
<td>.06</td>
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<tr>
<td>No heritability</td>
<td>A_m = A_f = 0</td>
<td>2</td>
<td>8.86</td>
<td>.01</td>
<td>18.55</td>
<td>&lt;.001</td>
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<tr>
<td>No twin environment</td>
<td>C_m = C_f = 0</td>
<td>2</td>
<td>7.64</td>
<td>.02</td>
<td>18.61</td>
<td>&lt;.001</td>
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Abbreviations: A_0, additive genetic variance for females; A_0, additive genetic variance for males; ASD, autism spectrum disorder; C_m, twin environmental variance for males; C_f, twin environmental variance for females; C_m, twin environmental variance for males; F, females; M, males; r_mf, male-female correlation in variance components.
To our knowledge, this study is the largest population-based twin study of autism that used contemporary standards for the diagnosis of autism. All twin individuals underwent a thorough diagnostic and cognitive examination that included a structured interview and observation that allowed differentiation between autism and other delays of development.\textsuperscript{13,14} The results suggest that environmental factors common to twins explain about 55% of the liability to autism. Although genetic factors also play an important role, they are of substantially lower magnitude than estimates from prior twin studies of autism. Nearly identical estimates emerged for ASD, suggesting that ASD presents the same liability spectrum as strict autism.

The California population, as represented in our twin sample, is highly diverse regarding ethnicity, socioeconomic status, and other demographic factors. Hence, our results should be readily generalizeable, especially as compared with previous twin studies, which were based exclusively on individuals from Northern Europe. Even though this study was population based, the participation rate was only about 17% of eligible twin pairs. However, comparison of demographic and clinical characteristics of twins who did and did not participate showed only modest differences, primarily in parental education (eTable 1). Furthermore, concordance rates were not influenced by a range of potential confounding factors.

One possible concern is that a higher proportion of concordant dizygotic pairs participated than concordant monozygotic pairs. Examination of proband status among the monozygotic vs dizygotic pairs suggests this is not the case. Among 28 concordant monozygotic pairs, 24 had 2 probands, while 4 had 1 proband. By contrast, for the same-sex dizygotic pairs, among 13 concordant pairs, 8 had 2 probands and 5 had 1 proband. Thus, if anything, there might have been some underascertainment of concordant dizygotic pairs.

The ACE model we used has several inherent assumptions. First, it assumes no gene × environment interaction. If such a gene × environment effect does exist, it would be confounded with the A parameter in our analysis, implying that as an estimate of pure genetic effect, A may actually be an overestimate. Similarly, a critical assumption in the model is that the shared twin environmental effect is the same for monozygotic and dizygotic twins. If, in fact, monozygotic twins share the relevant environment to a greater degree than the dizygotic twins, some of the effect included in the parameter A would actually be environmental rather than genetic; again, A may actually overestimate the true genetic heritability.

Another potential limitation is the validity of the assumptions regarding prevalence rates of autism and ASD. We therefore compared heritability and shared twin environment estimates obtained by varying assumptions about prevalence. As shown in the eAppendix, we examined the impact of both doubling and halving our prevalence assumptions on derived parameter estimates. The range of heritability (eg, 41%-56% in males; 13%-16% in females) and shared twin environment (eg, 57%-41% in males; 78%-72% in females) estimates were similar. Hence, our conclusions regarding the relative importance of genetic and shared twin environment are quite robust to prevalence assumptions.

Our study provides evidence that the rate of concordance in dizygotic twins may have been seriously underestimated in previous studies and the influence of genetic factors on the susceptibility to develop autism, overestimated. Because of the reported high heritability of autism, a major focus of research in autism has been on finding the underlying genetic causes, with less emphasis on potential environmental triggers or causes. The finding of significant influence of the shared environment, experiences that are common to both twin individuals, may be important for future research paradigms.\textsuperscript{21} Increasingly, evidence is accumulating that overt symptoms of autism emerge around the end of the first year of life. Because the prenatal environment and early postnatal environment are shared between twin individuals, we hypothesize that at least some of the environmental factors impacting susceptibility to autism exert their effect during this critical period of life. Nongenetic risk factors that may index environmental influences include parental age,\textsuperscript{13} low birth weight,\textsuperscript{22} multiple births,\textsuperscript{26} and maternal infections during pregnancy.\textsuperscript{27} Future studies that seek to elucidate such factors and their role in enhancing or suppressing genetic susceptibility are likely to enhance our understanding of autism.\textsuperscript{23}

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REFERENCES


