

Intergenerational Transmission of Subthreshold Autistic Traits in the General Population

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Background: *Autistic disorder (AD) is a disabling oligogenic condition characterized by severe social impairment. Subthreshold autistic social impairments are known to aggregate in the family members of autistic probands; therefore, we conducted this study to examine the intergenerational transmission of such traits in the general population.*

Methods: *The Social Responsiveness Scale (SRS), a quantitative measure of autistic traits, was completed on 285 pairs of twins (by maternal report) and on their parents (by spouse report).*

Results: *Correlation for social impairment or competence between parents and their children and between spouses was on the order of .4. In families in which both parents scored in the upper quartile for social impairment on the SRS, mean SRS score of offspring was significantly elevated (effect size 1.5). Estimated assortative mating explained approximately 30% of the variation in parent SRS scores.*

Conclusions: *Children from families in which both parents manifest subthreshold autistic traits exhibit a substantial shift in the distribution of their scores for impairment in reciprocal social behavior, toward the pathological end. As has been previously demonstrated in children, heritable subthreshold autistic impairments are measurable in adults and appear continuously distributed in the general population.*

Key Words: Assortative mating, autism, family studies, genetics, pervasive developmental disorder, twins

According to recent epidemiologic studies, autism spectrum conditions have reached a prevalence of .5% of all children (Fombonne 2003). Twin, family and adoption studies are all compatible with autism being highly heritable (Cook 2001; Pickles et al 1995; Spiker et al 2002), with the vast majority of cases of autism attributable to the interactive effects of multiple genetic loci, variously estimated to be between 3 and 20 (Pickles et al 1995; Risch et al 1999). Autism is characterized by extreme deficiency in the capacity for reciprocal social behavior (RSB), a trait that may be continuously distributed in nature (Constantino and Todd 2003; Spiker et al 2002). Autistic traits of severity that falls below the threshold for a diagnosis of autism have been shown to aggregate in the family members of autistic probands (Pickles et al 2000; Piven et al 1997); such traits constitute potential markers of family genetic liability to autism.

In this study, we examined the transmission of subthreshold autistic impairments across generations in a general population sample. Several goals motivated the study. First, given the possibility that there might be changes in the phenotypic expression of genetic liability to autistic impairment over the life course, we were interested in whether phenotypic manifestations of this genetic liability are actually identifiable in parents. Specifically, we were interested in whether aggregation of such traits in parents results in a shift in the distribution of autistic traits in their children, toward the pathological end. It is conceivable that if categorically defined autistic spectrum disorders (such as DSM-IV-defined pervasive developmental disorders) represent the extreme end of a continuous distribution of social impairments in nature, then factors that shift that distribution toward more

impairment could result in an increase in the prevalence of categorically defined cases (at the severe end of the distribution).

Second, we attempted to extend previous findings on the heritability of subthreshold autistic impairment in twins (Constantino et al 2003b; Constantino and Todd 2000) to patterns of intergenerational transmission to explore possible parent-of-origin effects (which are not resolvable in single-generation twin samples) and to examine whether heritability estimates for autistic traits in parents are consistent with those derived from observations of children. Finally, to make optimal use of the intergenerational data involving twins, we conducted an initial exploration of possible effects of assortative mating on the genetic structure of subthreshold autistic traits. Assortative mating can substantially influence genotype frequencies related to complex traits (i.e., those that are a function of additive or epistatic effects of multiple genetic susceptibility loci). When present, but not accounted for, in genetic studies, assortative mating can confound heritability estimates, especially when social or cultural influences also affect transmission of the trait in question.

Methods and Materials

For the biological parents of 285 epidemiologically ascertained twin pairs (subjects of the ongoing Missouri Twin Study; Constantino and Todd 2003), we obtained spouse-report parent assessments (mother reporting about father and father reporting about mother) and maternal-report assessments of twins using the Social Responsiveness Scale (SRS), a quantitative measure of autistic traits (Constantino et al 2000). All of the families had been participants in a previous study (Constantino and Todd 2003) in which the twins were assessed with the SRS, an average of 18 months before the current assessment. The previous study involved 788 twin pairs aged 7–15 years, randomly ascertained from Missouri birth records.

Sample

The primary inclusion criteria for this follow-up study were 1) prior enrollment in the previously mentioned study (Constantino and Todd 2003) and 2) marital status of parents (biological parents still married and living in the same household, which was the case for 65% of the original sample). The primary exclusion

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Table 1. Social Responsiveness Scale Means and Standard Deviations for Male and Female twins at Baseline and at Follow-Up

	Baseline			Follow-Up		
	Mean	SD	N	Mean	SD	N
Female Twins	27.75	18.27	898	25.94 ^a	16.58	443
Male Twins	35.22	21.58	714	30.09 ^b	21.77	127
Female Subgroup Not Followed Up	29.46 ^a	19.62	455	—	—	—
Male Subgroup Not Followed Up	36.33 ^b	21.40	587	—	—	—

Mean for males was significantly higher than that for females, as reported by Constantino and Todd (2003).

^a $t = 2.90, df = 896, p = .004.$

^b $t = 2.97, df = 712, p = .003.$

criterion was simultaneous involvement in a competing research study involving the Missouri Twin sample. An oversight committee ensures that families in the Missouri Twin Study are not overburdened with research requests and therefore severely limits the number of research contacts per family per year. Because of concomitant research studies involving male twins, none of the 219 male–male twin pairs from the prior study were available to be contacted for the current follow-up study. In addition, a small number of previously assessed female–female twin pairs ($n = 25$) and male–female pairs ($n = 17$) were unavailable at the time that this study was conducted.

Thus, the target follow-up sample consisted of 342 families in which the biological parents were married and both were known to reside within the same household at the time of previous research contact. Recontact of the families (including a written informed consent procedure) was conducted entirely by mail after approval of the protocol by the Washington University Human Studies Committee. We received responses from 305 families, including complete sets of data (mother-report SRS on father, father-report SRS on mother, and mother-report SRS on the twins) from 285 of the families, for an effective response rate of 83%. There were no differences between 1) responders, 2) nonresponders, or 3) families unavailable for follow-up with respect to age, urban or rural residency, race, or ethnicity.

Mean SRS scores of twins at baseline and at follow-up are presented in Table 1. Male and female twins had slightly higher SRS scores than those of twins from the original sample who were not followed up; the differences in means were statistically but not clinically significant, as shown in the table. In general, twins with higher levels of psychopathology tend to be more actively recruited into competing research studies (because of the nature of their respective inclusion criteria). This fact, coupled with the slight phenotypic overlap observed between SRS scores and ratings for other dimensions of psychopathology (Constantino et al 2003b), could account for the finding of a slightly lower SRS scores in the available follow-up sample.

The sample for this study included 89 monozygotic female–female twin pairs and their parents, 69 dizygotic female–female twin pairs and their parents, and 127 dizygotic male–female twin pairs and their parents. Parents ranged in age from 30 to 55 years (average 44 years for both mothers and fathers). Twins ranged in age from 8 to 17 years, with an average age of 12.5 years. The sample was predominantly European American, with 12.5% African American and <1% other ethnicity by self-report.

Comparison of the previous and current SRS ratings of twins revealed a high degree of stability of SRS scores over 18 months of time (time 1–time 2 correlation, Pearson r , was .85 for boys, .72 for girls $p < .0001$).

Measures

The Social Responsiveness Scale. The SRS is a 65-item quantitative measure of autistic social impairment that has been extensively tested in both clinically ascertained and population-based samples of subjects. The instrument is completed by an adult informant who has regularly observed the subject in naturalistic social contexts over a period of at least 2 months. Each item is rated on a scale from 0 (not true) to 3 (almost always true); the instrument requires 15–20 min to complete. Scores on the SRS are highly heritable (Constantino et al 2003b), generally unrelated to IQ (Constantino et al 2003a), and continuously distributed in the general population (Constantino and Todd 2003); they distinguish patients with autism spectrum disorders from those with other child psychiatric conditions (Constantino et al 2000; Constantino and Todd 2003). The SRS inquires about a subject's ability to engage in emotionally appropriate reciprocal social interaction, which is believed to be the core domain of deficiency in all autism spectrum disorders. Reciprocal social behavior (RSB) requires an individual to be cognizant of the emotional cues of others, to interpret those cues appropriately, to respond appropriately to what he or she interprets, and to be motivated to engage in social interactions with others.

Items on the SRS are not exclusively limited to assessment of RSB per se; items representing the other domains of autistic symptomatology (6 items for deficits in social communication and language and 12 items representing restricted and stereotypic behaviors or interests) are also included in the measure. Factor analysis, cluster analysis, and latent class analysis of SRS data in both clinical and population-based samples (Constantino et al 2000, 2004; Constantino et al 2003b) have failed to demonstrate the existence of separable categories of deficiency for the three DSM-IV criterion domains for autism (social deficits, language deficits, and stereotypic behaviors and restricted range of interests). Rather, deficits across all three domains appear attributable to a singular underlying continuously distributed variable, characterized by general impairment in RSB, for which a single index score is generated by the SRS.

Normative SRS data involving over 2500 children and adolescents (age 4–18 years) has been previously published (Constantino et al 2000, 2003a; Constantino and Todd 2000, 2003; Ho et al, in press); SRS scores are unrelated to age in the range from 7 years to 18 years and do not vary as a function of race, ethnicity, or rater's level of education (Constantino and Gruber, in press; Ho et al, in press). Psychometric properties of the SRS have been described extensively in previous research reports. Current understanding of the specificity of the SRS for measuring autistic social impairment is derived from clinical studies in which elevated SRS scores are highly associated with clinical

Table 2. Listing of Items for Which There Are Substantive Wording Changes Between Child and Adult Versions of the Social Responsiveness Scale (SRS)

Item	SRS, 4- to 18-year-old version	SRS, Adult Version
9	Clings to adults, seems too dependent on them	Seems too dependent on others for help with meeting basic needs
15	Is able to understand the meaning of other people's tone of voice and facial expressions	Perceives and appropriately responds to changes in other people's tone of voice and facial expressions
20	Shows unusual sensory interests (such as mouthing or spinning objects) or strange ways of playing with toys	Shows unusual sensory interests (such as smelling his/her fingers frequently) or strange repetitive ways of handling or manipulating small items within reach
21	Is able to imitate others' actions	Is able to imitate others' actions and demeanor when being prompted to do so for the sake of social appropriateness
23	Does not join group activities unless told to do so	Does not join group activities or social events unless forced to do so
36	Has difficulty "relating" to adults	Has difficulty "relating" to family members
37	Has difficulty "relating" to peers	Has difficulty "relating" to other adults
43	Separates easily from caregivers	Enjoys and is competent with "small talk" (casual conversation with others)
45	Focuses his/her attention to where others are looking or listening	Generally gets interested in what others around him/her are interested in
49	Does extremely well at a few tasks, but does not do as well at most other tasks	Does extremely well at a few intellectual or computational tasks, but does not do as well at most other tasks
57	Gets teased a lot	Isolative; tends not to leave his/her home
58	Concentrates too much on parts of things rather than "seeing the whole picture" (for example, if asked to describe what happened in a story, child may talk about the kind of clothes the characters were wearing)	Concentrates too much on parts of things rather than "seeing the whole picture"
63	Touches others in an unusual way (for example, child may touch someone just to make contact and then walk away without saying anything)	Touches or greets others in an unusual way

Selected portions of the Social Responsiveness Scale (SRS) were reproduced from Constantino (in press) with permission from Western Psychological Services.

diagnoses of autism spectrum conditions, but not with other child psychiatric conditions (Constantino et al 2000, 2003a). Bivariate genetic analyses have revealed that the additive genetic influences on SRS scores are independent from the genetic influences responsible for other major domains of child psychopathology measurable on the Child Behavior Checklist (Constantino et al 2003b).

SRS scores range from 0 (highly socially competent) to 195 (severely socially impaired). Scores in the range from 60 to 80 indicate deficiencies in reciprocal social behavior that are clinically significant and result in mild to moderate interference in everyday social interactions (Constantino and Gruber, in press). These scores indicate deficiencies in social relatedness, which might be observed in children with the very mildest variants of pervasive developmental disorder not otherwise specified (PDD-NOS) or Asperger disorder (mean SRS scores for children with those diagnoses are on the order of 100 ± 20). Scores in this range are associated with descriptions from peers or caregivers that the child is "odd," "socially inept," or "very nerdy." Scores above 80 suggest a more severe interference in everyday social interactions. In this sample, six male twins and one female twin (representing 7 different families) had SRS scores greater than 80 by parent report. When scores for 4- to 18-year-old children above 85 are obtained by both parent and teacher report, there is 98% specificity for a clinical diagnosis of a specific pervasive developmental disorder (PDD-NOS, Asperger disorder, or autistic disorder; Constantino and Gruber, in press).

An adult version of the SRS was also used in this study; it corresponds item-by-item to the child and adolescent version, but a number of items differ moderately in wording or content; descriptions of specific behaviors are modified in accordance with what would be most developmentally appropriate for adults. A listing of items for which there are substantive wording differ-

ences between child and adult versions of the SRS is provided in Table 2. Among the parents in this sample, the mean scores were in close keeping with what has been observed in population-based samples of children and adolescents: for fathers the mean was 31.7 ± 21.1 ; for mothers the mean score was 30.7 ± 20.0 (Figure 1); 10 mothers and 11 fathers (representing a total of 18 families) scored above 80 on the adult SRS by spouse report. Internal consistency of the adult version of the SRS was calculated separately for fathers and mothers and was found to be highly acceptable (Cronbach's alpha of .95 and .94, respectively) and entirely congruent with SRS data from children and adolescents.

Data Analysis. Intraclass correlations were calculated for each respective pairing of family member types (fathers and sons, fathers and daughters, mothers and sons, mothers and daughters, mothers and fathers). Next, we segregated offspring

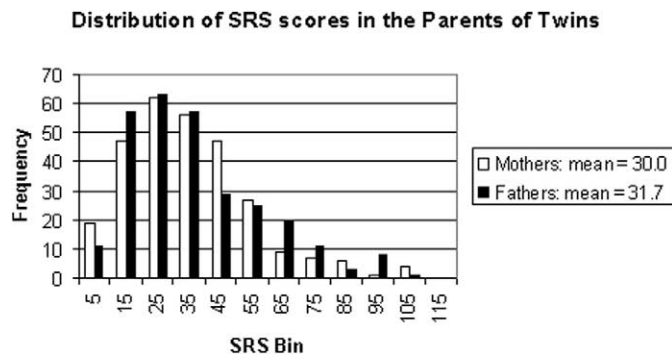


Figure 1. Distribution of Social Responsiveness Scale (SRS) scores in the parents of twins who participated in this follow-up study.

on the basis of whether their parents fell in either the upper or lower quartile for SRS assessments in the distribution for this parent sample and examined mean offspring (twin) SRS scores as a function of parental SRS status.

Finally, a separate set of analyses involving structural equation modeling (SEM) explored the genetic structure of all of the SRS data collected in this study. To quantify the degree of “fit” between observed data (in this case, separate variance and covariance statistics for members of the families of monozygotic and dizygotic twins) and what would be expected from a given mathematical model of causality, the maximum likelihood method was implemented using the statistical software program Mx (Neale and Cardon 1992). Variance–covariance statistics were computed from square-root-transformed SRS scores of the various pairings of family members (see results section). In constructing the mathematical models to be tested, we assumed the presence of causal influences on twins demonstrated in our previous research (Constantino and Todd 2003): 1) additive genetic (male and female subjects), 2) common environmental (female subjects only), and 3) unique environmental (male and female subjects). We tested the goodness of fit of three separate models to the data: 1) an assortative mating model, 2) a model without effects of assortative mating, and 3) a rater bias model in which similarity between twins and their fathers was in part a function of reporting bias on the part of the mother (who rated all three).

Results

SRS scores were unrelated to parental age and were continuously distributed in both mothers and fathers (Figure 1). Intraclass correlations for pairings of family members were highly statistically significant (in all cases $p < .00001$): mother–daughter .41, mother–son .38, father–daughter .49, father–son .58. Intraclass correlation between mothers and fathers was .38, suggestive (at the simplest level of analysis) of the presence of assortative mating.

Figure 2 depicts variation in offspring SRS score as a function of SRS profile of parents. Elevation in the SRS score of either parent was associated with elevation in mean SRS score of offspring; there were no parent-of-origin effects observed for this association nor were there differential associations as a function of offspring gender. As shown in Figure 2, mean SRS scores for the offspring ($n = 64$ twins) of parents whose SRS scores both fell in the top quartile of their respective distributions (for parents in this sample) were substantially higher (by approximately 1.5 standard deviations) than those whose parents fell in any other SRS profile. Of these 64 children, 4 (from 4 different families) had SRS scores at or above 80 (i.e., within or above 1 standard deviation of the mean SRS score for children with PDD-NOS, in comparison to 3 such children (from 3 different families) in the entire remainder of the sample ($n = 506$ twins; Fisher’s exact $p = .004$). Only 3 of the parents of these clinical-level-affected offspring had SRS scores at or above 80.

Results of structural equation modeling applied to this intergenerational data extended previous findings (obtained from analysis of the twin generation; see Constantino and Todd 2003) regarding the genetic structure of social impairments measured by the SRS in males and females. Table 3 displays fit statistics for the path models fit to the data. The best fitting model was an assortative mating model, which is depicted in Figure 3, in which covariance statistics for the data are summarized. Consideration and testing of a rater bias model resulted in significantly poorer fit to the data. For the best fitting model, standardized parameter

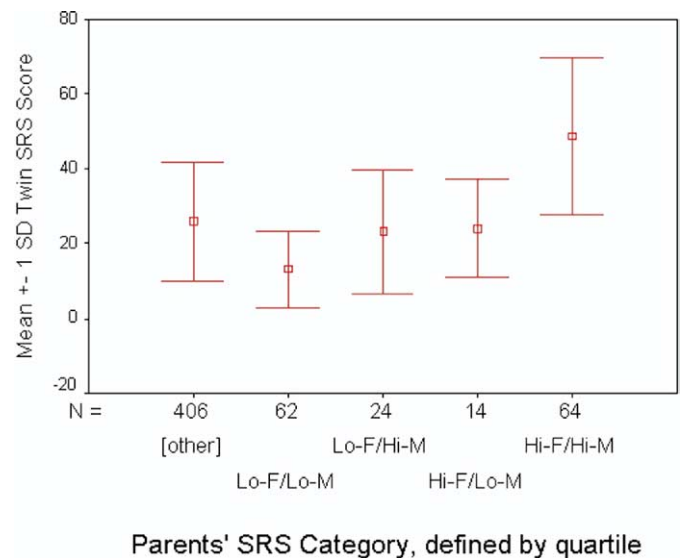


Figure 2. Mean Social Responsiveness Scale (SRS) score of offspring, stratified by SRS scores of parents. F, father; Hi, upper quartile of sample distribution of respective gender; Lo, lower quartile of sample distribution of respective gender; M, mother. Analysis of variance: $F = 16.2$; $df = 3$; $p < .001$. For high/high offspring versus all others: Twin 1: $t = 8.73$, $df = 283$, $p < .0001$; Twin 2: $t = 7.20$, $df = 283$, $p < .0001$. For low/low offspring versus all others: Twin 1: $t = -4.570$, $df = 283$, $p < .0001$; Twin 2: $t = -4.673$, $df = 283$, $p < .0001$.

estimates (with 95% confidence intervals) for additive genetic (a_2), shared (c_2), and unique (e_2) environmental influences on both the twins and their parents were as follows: for male subjects (fathers and sons), $a_2 = .87$ (.85–.89); $c_2 = .12$ (.01–.25); $e_2 = .0$ (–.11 to .11); for female subjects (mothers and daughters) $a_2 = .73$ (.68–.77); $c_2 = .10$ (.01–.20); $e_2 = .17$ (.01–.25). The parameter estimate for assortative mating, m , from this model was $.29 \pm .12$.

Discussion

Data from this intergenerational study of autistic traits confirmed previous findings of substantial genetic influence on subthreshold autistic traits (Constantino and Todd 2003) and extends our heritability estimates to adults. The condition of having both parents within the top quartile of their respective distributions for degree of autistic social impairment resulted in a substantial pathologic shift in the distribution of scores for autistic social impairment in offspring, with an effect size of 1.5 (on the mean), and an 11-fold increase in prevalence of children falling above an SRS clinical cutoff for PDD-NOS. This may be a conservative estimate of the magnitude of such intergenerational effects, because the offspring sample was predominantly female, and girls may be relatively protected from phenotypic manifestation of genetic susceptibility to autistic social impairment (Constantino and Todd 2003). There were no parent-of-origin effects observed in this sample.

Our results also support the presence of assortative mating, which explained nearly 30% of the variation in subthreshold autistic traits in parents. Because mother–father SRS scores were positively correlated, it is possible that mate selection occurs on the basis of social impairment, social competence, or other characteristics that closely correlate with SRS scores. Although it is conceivable that qualities of the relationship perceived by both members of a married couple could contribute to correlations

Table 3. Results of Structural Equation Modeling

Model	ML χ^2	<i>p</i>	<i>df</i>	RMSEA	AIC	μ
Assortative Mating	43.2	.006	23	.076	−2.7	.29 (.17–.42)
No Assortative Mating	89.2	.000	24	.167	41.2	—
Rater Bias	89.2	.000	23	.172	43.2	—

AIC, Akaike’s information criterion; μ , parameter estimate for assortative mating; RMSEA: root mean square error approximation; ML, maximum likelihood.

between the SRS ratings of parents, it is unlikely that such shared perceptions could explain the strong associations with heritable traits of their offspring unless the qualities of the marital relationship itself were directly affected by such heritable traits in the parents. Furthermore, the SRS does not inquire about a specific relationship, but about behaviors that an individual exhibits in a broad array of social contexts.

Although the assortative mating model provided the best fit to these data, the sampling design that was used (and the fact that the analyses pertained exclusively to a single outcome variable, without the availability of data pertaining to potential mediating or moderating variables) made it impossible to resolve mathematically more complex models, such as ones that might additionally incorporate the direct effects of gene–environment interaction or the indirect effects of parental genotypes on child phenotypes (mediated by the social environment).

There were other advantages and disadvantages of the study design. The fact that this study involved a population-

based sample was advantageous in that it was less prone to biases inherent in clinically ascertained samples. Coupled with the fact that the study used quantitative measurements (of a trait which is continuously distributed in the population), the intergenerational findings have relevance not only to understanding the causes of social impairment in children, but also to the development of social competence. The disadvantage of utilizing a population-based sample was that it included few individuals affected at clinical levels of symptomatology; the significant increase in the prevalence of offspring affected at clinical levels of social impairment (when both parents fall in the upper quartile of the SRS distribution) will require replication in future research. Such studies should incorporate confirmatory clinical assessments for individuals presumed to be substantially affected on the basis of elevated quantitative trait (SRS) scores and should include large enough numbers of individuals affected at a clinical level to confirm that the overall pattern of intergenerational transmission observed

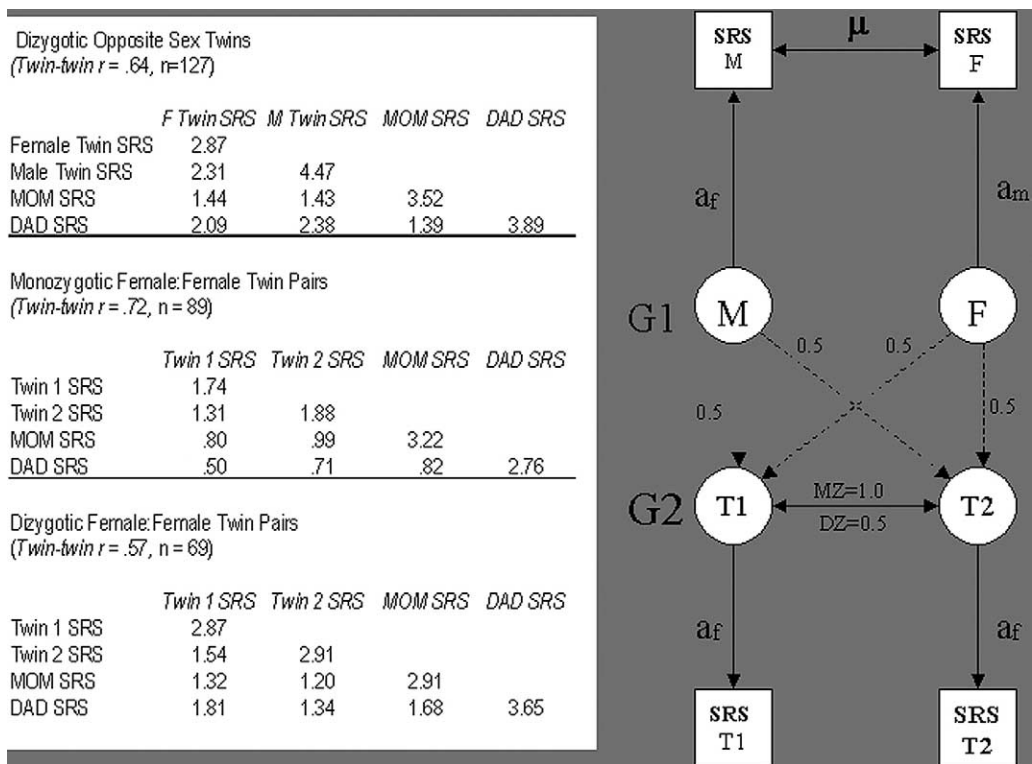


Figure 3. Structural equation modeling of parent–twin data. The variance–covariance matrices shown here were mathematically fit to path models such as the assortative mating model shown on the right (in this case, illustrating genetic influences on female–female twin pairs and their parents). Common and unique environmental influences incorporated into the actual mathematical model are excluded from this figure for the sake of clarity of the illustration. For each triangular variance–covariance matrix, the diagonal values represent variances, and the off diagonal values represent covariances; “*r*” refers to Pearson’s coefficient of correlation. At the time of ascertainment for this study, male–male twin pairs were unavailable because of extended involvement in other research protocols. *a_m*, additive genetic influences on SRS scores in male subjects (fathers and sons); *a_f* = additive genetic influences on SRS scores in female subjects (mothers and daughters); SRS M, observed SRS score of mother (by spouse report); SRS F, observed SRS score of father (by spouse report); SRS T1 and SRS T2, observed SRS scores of twins by maternal report; μ , parameter estimate for magnitude of effect of assortative mating.

here holds true at greater levels of severity of autistic symptomatology.

Because our goal was to estimate the genetic effects of parental SRS scores on offspring, we restricted spousal reports to biological parents who were still married. This may have biased against the inclusion of parents with extreme scores (but may have protected from artificially inflated scores from disgruntled divorced parents).

Another important limitation of the study was the fact that male–male twin pairs were not available for inclusion in the sample. This makes it difficult to identify possible gender discrepancies in the extent to which subthreshold autistic traits in offspring are related to such traits in parents. In comparison to previously published analyses of SRS assessments in the offspring generation only (Constantino et al 2003b; Constantino and Todd 2003), which involved prior assessments of the twins and additionally included male–male twin pairs), the inclusion of intergenerational data and the incorporation of a parameter for assortative mating into the causal model resulted in increases in the proportion of variance attributed to additive genetic influences for both male and female subjects. For male subjects, there was a concomitant reduction in the proportion of variance attributed to unique environmental influences (including measurement error); for female subjects, there was a concomitant reduction in the proportion of variance attributed to common environmental influence. These shifts occurred despite the fact that twin–twin correlations in the follow-up offspring data were nearly identical to those observed in the baseline assessments on which the previously published analyses were conducted.

Possible contributing factors to this discrepancy across studies include the fact that strong parent–offspring correlations observed in this sample (and incorporated into the structural equation model) might substantially influence parameter estimations for familial influence on parent SRS scores, without being “balanced,” as it were, with information from grandparent reports on the parents (which were not available). Alternatively, the lack of incorporation of parent data (and specifically a parameter for assortative mating) in the previously published analyses, involving exclusively the offspring generation, may have resulted in overestimation of the proportion of variance attributable to common environmental influences (observed among female subjects in our previously published report). Either way, both sets of findings strongly support the notion that subthreshold autistic traits are highly heritable in male offspring and moderate to highly heritable in female offspring.

From these data, we conclude that the condition of having two parents with elevated scores for subthreshold autistic symptomatology may substantially raise offspring risk for both subthreshold and clinical-level symptomatology. Although the dividing line between these outcomes is arbitrary (based on the continuous distribution of autistic social impairments in the general population), it is important to keep in mind that subthreshold autistic symptomatology is not necessarily pathological. Such traits may, in fact, be adaptive under many circumstances, and the nature of those circumstances may provide clues to understanding underlying mechanisms in the maintenance of

(or rise in) genotype frequencies associated with susceptibility to autism spectrum conditions over successive generations. Future genetic studies of autism spectrum conditions may benefit from quantitative approaches that consider the extent to which subthreshold autistic traits mediate the intergenerational transmission of autism and that control for the possible effects of assortative mating.

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