Phenotypic and Genetic Overlap Between Autistic Traits at the Extremes of the General Population

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ABSTRACT

Objective: To investigate children selected from a community sample for showing extreme autistic-like traits and to assess the degree to which these individual traits—social impairments (SIs), communication impairments (CIs), and restricted repetitive behaviors and interests (RRBIs)—are caused by genes and environments, whether all of them are caused by the same genes and environments, and how often they occur together (as required by an autism diagnosis). **Method:** The most extreme-scoring 5% were selected from 3,419 8-year-old pairs in the Twins Early Development Study assessed on the Childhood Asperger Syndrome Test. Phenotypic associations between extreme traits were compared with associations among the full-scale scores. Genetic associations between extreme traits were quantified using bivariate DeFries-Fulker extremes analysis. **Results:** Phenotypic relationships between extreme SIs, CIs, and RRBIs were modest. There was a degree of genetic overlap between them, but also substantial genetic specificity. **Conclusions:** This first twin study assessing the links between extreme individual autistic-like traits (SIs, CIs, and RRBIs) found that all are highly heritable but show modest phenotypic and genetic overlap. This finding concurs with that of an earlier study from the same cohort that showed that a total autistic symptoms score at the extreme showed high heritability and that SIs, CIs, and RRBIs show weak links in the general population. This new finding has relevance for both clinical models and future molecular genetic studies. *J. Am. Acad. Child Adolesc. Psychiatry,* 2006;45(10):1206–1214. **Key Words:** twins, genetics, autism, autistic traits.

Autism spectrum disorders (ASDs) are defined by a triad of features: social impairments (SIs), communication impairments (CIs), and restricted repetitive behaviors and interests (RRBIs). Historically, this has also been referred to as the "triad of impairments," although a more neutral descriptor simply refers to this as the "triad" because it is not necessarily the case that RRBIs are impairments (e.g., Baron-Cohen and Wheelwright, 1999). A study more than 25 years ago attempted to identify all individuals who met criteria for any part of the triad (Wing and Gould, 1979). The authors report evidence of a "marked tendency for these problems to occur together." However, it was also reported that some children showed SIs but not RRBIs, and vice versa, suggesting some splintering of the autism phenotype. Since this study, there have been changes in the definition of ASDs, and the sample in the Wing and Gould study was selected from a psychiatric/learning difficulties register, "enriching" it with children with greater severity and comorbidity (Caron and Rutter, 1991).

In terms of causal influences, twin studies have shown that autism and the broader manifestation of the autism phenotype are highly heritable (Bailey et al., 1995; Folstein and Rutter, 1977; Steffenburg et al., 1989). Broader autism phenotype family studies have

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reported that some relatives of individuals with autism show only some of the traits that are characteristic of autism, suggesting segregation of the phenotype among relatives (Bailey et al., 1998; Bishop et al., 2004; Pickles et al., 2000; Piven, 1999; Szatmari et al., 2000). These observations hint that different causal influences may affect the three domains and that it may be fruitful to consider whether there are different genetic influences on the various aspects of the autism phenotype.

Indeed, two recent twin studies have reported only modest genetic overlap between SIs and RRBIs measured as traits in the general population, despite the fact that they are both highly heritable individually (Ronald et al., 2005, 2006). These results can be contrasted to a recent family study of autistic traits that reported high "genetic" overlap between social motivation and range of interest/ flexibility (Sung et al., 2005). However, these studies used different samples: more than 3,000 7- and 8-year-old twin pairs in a representative community sample versus 201 nuclear families ascertained through the existence of at least two children affected with an ASD (average IQ 80; mean age 10.0; SD = 5.1 years).

One way to reconcile these findings is to consider the possibility that there may be genetic heterogeneity in the etiology of autistic traits in the general population, but that at the extreme, different autistic traits have common genetic origins. This would explain why the study with a community sample found genetic heterogeneity between SIs and RRBIs (Ronald et al., 2005, 2006), but the study with a clinical sample (Sung et al., 2005) did not. The best way to compare the etiology of extreme traits and traits in the general population is to select children who score at the extreme end of the distribution from a general population twin sample. One of the previous twin studies reported high heritability of a total autistic symptoms score at the extreme (Ronald et al., 2006), but this approach has not been used before for individual autistic traits. Selecting the sample in this way provides a large enough extreme-scoring sample to have power to detect effects, as well as the ability to disentangle genetic and shared environmental influences (not possible in family studies). A useful tool for this is DeFries-Fulker (DF) extremes analysis (DeFries and Fulker, 1988), a type of analysis used with twin data. Furthermore, the bivariate extension of DF can reveal the genetic overlap between two different extreme traits by considering the quantitative "impairment" on one trait of probands selected as behaviorally extreme on a second trait.

The present study used bivariate DF analysis in the first twin study to investigate the links between extreme individual autistic-like traits: SIs, CIs, and RRBIs. The extreme-scoring sample was selected from the same community sample used by Ronald et al. (2006). The characteristics of these extreme groups, such as overlap across the triad, sex ratio, and their verbal/nonverbal ability, academic ability, and behavior problems, were also studied.

METHOD

Participants

Participants were a subsample of the Twins Early Development Study (TEDS), a United Kingdom–based community sample of twins contacted from birth records (Trouton et al., 2002). Questionnaires were sent to 7,687 families when the twins were age 8 (mean = 8.09, SD = 0.48). A total of 3,807 families (49.5%) returned completed questionnaires. The questionnaires were sent to all families on whom TEDS had details who had not formally withdrawn from the study, regardless of whether families had provided data at age 7 and earlier. Families were not pushed to respond, and so the 7,687 families include a proportion of inactive families, which accounts in part for the modest response rate.

The TEDS sample that did provide data at age 8 was reasonably representative of the U.K. population. Comparing this sample to data from the General Household Survey (Office for National Statistics, 2005), 94% versus 93% were white, 48% versus 50% were male, 37% versus 32% of mothers had one or more A levels (U.K. advanced educational qualification), and 4% of children had a statement of special educational needs versus 3% of children in England (Department for Education and Skills, 2002). Comparing participating families and families invited to participate but who did not send back data, using data collected when the twins were 12 months old: 94% versus 90% were white, 49% versus 50% were male, and 38% versus 32% of mothers had at least A levels as their highest educational qualification.

Exclusions were made for the following reasons: no consent signature (40 families), unclear zygosity (86 families), less than half of the items completed (13 individuals), specific medical syndrome (not including suspected ASDs) such as Down syndrome or chromosomal anomalies (33 families), extreme pregnancy or perinatal difficulties (60 families), or no first contact data available (73 families).

The final sample with data after exclusions, from which the children in this study were selected, was 3,419 pairs. Children who scored in the top 5% of the distributions of autistic traits were defined as extreme. This cutoff was chosen as a compromise between the need for a sample size large enough to provide adequate power versus the desire to study extreme groups.

Existing information about suspected ASD diagnoses comes from using the Social Communication Questionnaire (Rutter et al., 2003) on children whose parents alerted TEDS that they had an ASD. Thirty-one suspected autism cases (based on Social Communication Questionnaire scores that were above the cutoff) provided Childhood Asperger Syndrome Test (CAST) data at age 8. A full diagnostic study of all children with possible ASDs in TEDS is under way.