Advances in Our Understanding of Genetic Risk Factors for Autism Spectrum Disorders

It is common knowledge in our field that autism is among the most heritable of psychiatric disorders. Yet the empirical basis for this claim is slender as we have no adoption studies of autism and only a handful of classical twin studies, with small sample sizes, have been conducted. Furthermore, while several large twin studies have clarified genetic relationships among the common psychiatric disorders of adulthood—such as major depressive, anxiety, substance use, and, more recently, personality disorders (1, 2)—we have no comparable comprehensive examination of genetic relationships among the important psychiatric disorders of childhood. Both of these limitations in the literature are addressed by Lichtenstein et al. in this issue (3). The study has several noteworthy methodological strengths: a large sample size (7,982 pairs), representativeness (the target population was the parents of all 9- and 12-year-old twins in Sweden), and high cooperation rates (80%). Diagnostic information came from parental report using a reliable structured interview.

The authors report a heritability estimate of 80% for autism spectrum disorders, confirming much smaller classical twin studies as well as a large U.K. study (4) and a smaller U.S. study (5) of autistic traits in general-population twin samples. These results provide us with considerably firmer footing for our conclusions about the high heritability of autism spectrum disorders.

"As we are seeing with the common psychiatric disorders of adulthood, patterns of underlying genetic liability do not map well onto current DSM categories."

However, the authors went beyond these findings and examined the sharing of genetic risk factors in their sample between autism spectrum disorders and attention deficit hyperactivity disorder (ADHD), developmental coordination disorder, tic disorder, and learning disorders. The sharing was quite substantial. For example, nearly three-quarters of the genetic risk factors for autism spectrum disorders are shared with ADHD. The authors provide us with another way to look at these results via genetic correlations—for example, 0.87 for autism spectrum disorders and ADHD and 0.71 for autism spectrum disorders and developmental coordination disorder. These are quite a bit higher than the correlation observed between, for example, major depression and alcoholism (6) and are in the range of that found between the genetic liabilities to dependence on licit versus illicit drugs (7). As we are seeing with the common psychiatric disorders of adulthood (1, 2), patterns of underlying genetic liability do not map well onto current DSM categories—that is, our genes seem neither to have read DSM-IV nor to particularly respect the diagnostic boundaries it established.

This excellent study is not without limitations. First, although the diagnostic instrument employed had relatively high specificities (e.g., ~95%), when studying traits as rare as autism spectrum disorders in the general population, even specificities this high result in a substantial proportion of false positive diagnoses. Second, even with the quite large sample size, the relative rarity of the disorders examined means that heritability estimates were known with low precision. For autism spectrum disorders, the 95% confidence intervals for their heritability estimates ranged from 29% to 91%. Third, diagnostic information was only from parents. Would the diagnostic overlap between categories and the resultant genetic correlations be lower if diagnoses were provided by mental health clinicians?

Constantino et al., also in this issue (8), examine one similar and one quite different aspect of the genetics of autism spectrum disorders. Using data from parental reports obtained through the Interactive Autism Network, they provide further evidence that a spectrum of autistic traits runs in families of individuals with autism. Of the "unaffected" siblings of individuals with a categorically defined autism spectrum disorder, 8.9% exhibited a history of language delay with autistic speech. As with schizophrenia, the familial liability to autism confers risk to syndromes or traits far broader than the narrowly defined, substantially impairing, full autistic syndrome. More uniquely, the authors compare the distribution of scores on the Social Responsiveness Scale in their "single-incidence families" (where no child but the index case had an autism spectrum disorder or language delay with autistic speech) and "multiple-incidence families" (either with two or more children with an autism spectrum disorder or with one child with an autism spectrum disorder and one or more with a history of language delay with autistic speech). What they found is intriguing. Within the single-incidence families, the number of siblings with abnormal scores on the Social Responsiveness Scale did not exceed population expectations, while a substantial excess of such individuals was seen in the multiple-incidence families. This pattern of findings is suggestive of etiological heterogeneity within the autism spectrum disorders. The sporadic cases within single-incidence families are more likely to result from large effect causes—such as de novo chromosomal rearrangements, now commonly referred to as copy-number variants (CNVs) (9, 10)—that typically produce relatively severe phenotypes. The familial cases, by contrast, are more likely to arise from multiple small genetic risk factors, which in heavy doses produce classical autism spectrum disorder phenotypes but in moderate doses can produce a range of milder autistic-like traits. Consistent with this hypothesis are results from several different studies that found higher rates of CNVs in sporadic than in familial causes of autism spectrum disorders (9). Preliminary evidence suggests that such a pattern of findings might also occur in schizophrenia (10). While exciting, these emerging results in autism spectrum disorders and schizophrenia should be interpreted in the context of the crudity of the familial-sporadic method. The power of this approach varies substantially depending on the size and age structure of the family and the widely variable accuracy of family history information.

Interestingly, a broadly parallel pattern of findings has long been observed with mental retardation (11). The rate of mental retardation among relatives of individuals whose mental retardation resulted from obstetric complications, hydrocephalus, or chromosomal anomalies is much lower than that among individuals whose mental retardation has no clearly identifiable cause and whose impairment probably reflects the lower end of the normal distribution of intelligence (11). It is perhaps a general rule for neurodevelopmental disorders that they can result either from large-effect sporadic causes or from many small genetic and environmental risk factors. These two kinds of cases would, the theory predicts, be differentiated by the pattern of illness within the families.

St. Pourcain et al., in the third autism spectrum disorder-related paper in this issue (12), take a complementary approach to clarifying the phenotypic spectrum of autism spectrum disorder risk genes. In 2009, Wang et al. (13) reported a genome-wide association study of autism spectrum disorders that found, and replicated in two independent samples, a signal from a set of single-nucleotide polymorphisms (SNPs) between two cadherin genes on chromosome 5, the most significant of which was rs4307059. St. Pourcain and colleagues examined variation in this SNP in 7,313 members of the population-based Avon Longitudinal Study of Parents and Children cohort, looking specifically at 29 measures related to social communication assessed between the ages of 3 and 12. Of the 29 traits examined, two—stereotyped conversation and pragmatic aspects of communication, both assessed at age 9—were significant after correction for multiple testing. More interesting, when the authors combined these traits into an autism spectrum disorder-like phenotypic profile, the association with rs4307059 substantially strengthened with communicative, cognitive, and social-interactive traits

playing a particularly strong role in the association. This is an impressive report from a large representative sample, utilizing creative but rigorous statistical methods. Most importantly, the study shows that a genetic variant initially detected in individuals with clinically diagnosed autism spectrum disorders has an impact on functioning in the general population. Again, genes do not seem to respect our diagnostic boundaries. Also noteworthy is that the effect of this variant (which was very small—no more than 0.3% of any individual trait) was more robustly detected by a spectrum of phenotypes than by any one measure alone.

What might we conclude from this rich array of studies on autism spectrum disorders? The syndrome is highly heritable but shares genetic liability with several other childhood syndromes. Two at least partially independent etiological pathways to autism spectrum disorders may exist, reflecting large-effect sporadic and multiple small-effect genetic causes. Finally, genetic variation that has an impact on risk for autism spectrum disorders may also influence variation in autism spectrum disorder-like traits observed in the general population.

References

1. Kendler KS, Prescott CA, Myers J, Neale MC: The structure of genetic and environmental risk factors for common psychiatric and substance use disorders in men and women. Arch Gen Psychiatry 2003; 60:929–937
2. Kendler KS, Aggen S, Knudsen GP, Roysamb E, Neale M, Reichborn-Kjennerud T: The structure of genetic and environmental risk factors for syndromal and subsyndromal common DSM-IV axis I and all axis II personality disorders. Am J Psychiatry (published online Oct. 15, 2010; doi:10.1176/appi.ajp.2010.10030340)
3. Lichtenstein P, Carlström E, Råstam M, Gillberg C, Anckarsäter H: The genetics of autism spectrum disorders and related neuropsychiatric disorders in childhood. Am J Psychiatry 2010; 167:1357–1363
4. Ronald A, Happe F, Price TS, Baron-Cohen S, Plomin R: Phenotypic and genetic overlap between autistic traits at the extremes of the general population. J Am Acad Child Adolesc Psychiatry 2006; 45:1206–1214
5. Constantino JN, Todd RD: Autistic traits in the general population: a twin study. Arch Gen Psychiatry 2003; 60:524–530
6. Kendler KS, Heath AC, Neale MC, Kessler RC, Eaves LJ: Alcoholism and major depression in women: a twin study of the causes of comorbidity. Arch Gen Psychiatry 1993; 50:690–698
7. Kendler KS, Myers J, Prescott CA: Specificity of genetic and environmental risk factors for symptoms of cannabis, cocaine, alcohol, caffeine, and nicotine dependence. Arch Gen Psychiatry 2007; 64:1313–1320
8. Constantino JN, Zhang Y, Frazier T, Abbacchi AM, Law P: Sibling recurrence and the genetic epidemiology of autism. Am J Psychiatry 2010; 167:1349–1356
9. Stankiewicz P, Lupski JR: Structural variation in the human genome and its role in disease. Annu Rev Med 2010; 61:437–455
10. Bassett AS, Scherer SW, Brzustowicz LM: Copy number variations in schizophrenia: critical review and new perspectives on concepts of genetics and disease. Am J Psychiatary 2010; 167:899–914
11. Reed EW, Reed SC: Mental Retardation: A Family Study. Philadelphia, WB Saunders, 1965
12. St Pourcain B, Wang K, Glessner JT, Golding J, Steer C, Ring SM, Skuse DH, Grant SFA, Hakonarson H, Davey Smith G: Association between a high-risk autism locus on 5p14 and social communication spectrum phenotypes in the general population. Am J Psychiatry 2010; 167:1364–1372
13. Wang K, Zhang HT, Ma DQ, Bucan M, Glessner JT, Abrahams BS, Salyakina D, Imielinski M, Bradfield JP, Sleiman PMA, Kim CE, Hou CP, Frackelton E, Chiavacci R, Takahashi N, Sakurai T, Rappaport E, Lajonchere CM, Munson J, Estes A, Korvatska O, Piven J, Sonnenblick LI, Retuerto AIA, Herman EI, Dong HM, Hutman T, Sigman M, Ozonoff S, Klin A, Owley T, Sweeney JA, Brune CW, Cantor RM, Bernier R, Gilbert JR, Cuccaro ML, McMahon WM, Miller J, State MW, Wassink TH, Coon H, Levy SE, Schultz RT, Nurnberger JI, Haines JL, Sutcliffe JS, Cook EH, Minshew NJ, Buxbaum JD, Dawson G, Grant SFA, Geschwind DH, Pericak-Vance MA, Schellenberg GD, Hakonarson H: Common genetic variants on 5p14.1 associate with autism spectrum disorders. Nature 2009; 459:528–533

KENNETH S. KENDLER, M.D.

Address correspondence and reprint requests to Dr. Kendler, Virginia Institute for Psychiatric and Behavioral Genetics, Virginia Commonwealth University School of Medicine, Box 980126, 800 E. Leigh St., Rm. 1-123, Richmond, VA 23298–0126; kendler@vcu.edu (e-mail). *Editorial accepted for publication August 2010 (doi: 10.1176/appi.ajp.2010.10081160).*

Dr. Kendler reports no financial relationships with commercial interests.