The Genetics of Schizophrenia: Chromosomal Deletions, Attentional Disturbances, and Spectrum Boundaries

The scientific study of the genetics of schizophrenia began in 1916 (1, 2). The last year has seen several potential watershed events in the identification of a number of possible susceptibility genes (3–6) and replication of at least two of them (7, 8). This issue of the *Journal* has three articles devoted to schizophrenia genetics that examine an intriguing chromosomal deletion syndrome and explore attentional abnormalities in and the boundaries of the schizophrenia spectrum.

The search for genetic subtypes of schizophrenia began in the earliest days of psychiatric genetics, with the initial finding that the Kraepelinian subtypes "breed true" within families (9–11). It is unfortunate that modern studies, using superior methods, have been unable to confirm this finding (12–14). The article by Bassett et al. in this issue takes a different approach to this problem, proposing that the schizophrenic syndrome associated with microdeletions of chromosome 22q11 reflect such a distinct "genetic subtype." The 22q11 deletion syndrome (22qDS)—which has variously and confusingly been called the velocardiofacial syndrome, the DiGeorge syndrome, or the Shprintzen syndrome—is the second most common human chromosomal anomaly (after trisomy 21) and occurs in approximately one out of every 4,000 births. Individuals with 22qDS have excess rates of psychopathology, although the precise nature of the psychiatric conditions overrepresented in these individuals is a subject of debate (15–17).

"If some of these 'gene discoveries' for schizophrenia turn out to be true...we will have a new set of particularly exciting tasks before us."

In their report, Bassett and colleagues address the question of whether the schizophrenic syndrome occurring in 22qDS subjects is clinically similar to typical schizophrenia. Across nearly all historical and symptomatic variables examined, including negative symptoms, the two groups do not significantly differ. They conclude that 22qDS subjects with schizophrenia constitute a valid genetic subtype of the disorder.

While their conclusion is likely to be correct, at least two methodologic issues are noteworthy. The 22qDS subjects with schizophrenia whom they studied were probably not a representative sample, since most were selected because they were first diagnosed with schizophrenia and only later shown to have the deletion. This selection process probably biases toward more typical schizophrenic presentations. A prior study that ascertained most of their 22qDS schizophrenic subjects through medical genetics clinics found that they had significantly lower levels of negative symptoms than a typical schizophrenia comparison group (15). If 22qDS individuals with more typical or more disabling schizophrenic symptoms were more likely referred to psychiatric care and to then receive a diagnosis of schizophrenia, this could explain the discrepancy in these two results.

Second, 22qDS is usually associated with diminished intellectual functioning. IQ scores were available on the 22qDS subjects in this study but not on the comparison group of typical patients with schizophrenia. The authors' approach to this problem was to exclude 22qDS subjects with overt mental retardation. However, it remains unclear how well the resulting group of 22qDS subjects was matched to the comparison group. Since intelligence can influence both symptoms of schizophrenia and global functioning, the lack of matching of the two groups could have influenced their findings.

Nonetheless this present work, along with other studies showing that brain structural abnormalities in 22qDS schizophrenic patients are similar to that seen in more typical schizophrenia, suggests that much might be learned by studying this rare group of patients. The study of potential chromosomal abnormalities in schizophrenia has now moved from a relatively unproductive examination of gross alterations (18) to subtler abnormalities typified by the 22qDS patients and the analysis of translocations (19, 20).

The second paper related to schizophrenia genetics in this issue by Hazlett et al. explores attentional abnormalities in individuals with schizotypal personality disorder. A large research literature suggests abnormalities in sensory gating and attention abnormalities in individuals with schizophrenia. In this study, Hazlett et al. examine the degree to which the startle response elicited by a short burst of loud noise is altered by prior auditory tones. While the interested reader should consult the paper for details, previous research had shown a particular pattern of abnormalities in the modulation of the startle response in patients with schizophrenia. The question posed in this report was whether similar findings would be seen in individuals recruited from the general population meeting criteria for schizotypal personality disorder.

The results were clear-cut. The pattern of differences seen in the schizotypal personality disorder and comparison subjects were very similar to those previously observed in schizophrenic subjects. Along with prior results of their group and others, these results suggest that schizotypal personality disorder and schizophrenia share common dysfunctions in the modulation of sensory input. This startle paradigm, along with a number of other promising "endophenotypes" or "intermediate phenotypes," may prove of substantial value in clarifying the etiologic pathway leading to schizophrenia and the schizophrenia spectrum condition.

One modest methodologic concern deserves mention. Experimental design usually dictates that a control group be matched to the experimental group on all variables *except* the one isolated for study. Here that variable was having schizotypal personality disorder. However, the authors have followed a rather common practice and obtained "supernormal" subjects who not only did not have schizotypal personality disorder but also had no other psychiatric illness *and* had no family history for psychiatric illness. The problem with this approach is that it prevents us from isolating the source of the between-group differences. While the major source of the effect probably results from one group having and the other not having schizotypal personality disorder, the differences in the startle response in the two groups could have been influenced by the differing rates of other psychopathology or differences in the psychiatric family history of the two groups.

In the third schizophrenia genetics paper in this issue, Tienari and colleagues present a definitive analysis of the boundaries of the schizophrenia spectrum in their large-sample Finnish adoption study. Although Kety and colleagues, in their analyses of the Danish Adoption Studies of Schizophrenia (21, 22), are widely and justly credited with having stimulated modern interest in the schizophrenia spectrum, in fact, empirical studies of this issue also go back to the first systematic family studies of schizophrenia conducted in Germany in the first half of the 20th century (23).

In a time-tested approach, Tienari et al. operationalized the schizophrenia spectrum as those disorders that were significantly more common in the genetic high-risk group (here adopted away offspring of the schizophrenic or schizophrenia spectrum mothers) versus those in the control group (here adopted-away offspring of mothers without schizophrenia spectrum disorders). In addition to schizophrenia, they found significant evidence that both schizotypal personality disorder and other nonaffective psychoses belong within the spectrum. They found little evidence that other putative spectrum disorders, particularly schizoid, paranoid, and avoidant personality disorders and affective psychoses, belonged within the spectrum. They also found no indication that

nonpsychotic affective illness, anxiety disorders, or alcohol abuse were genetically related to schizophrenia.

This study has three noteworthy strengths. First, their sample was nationally representative. Second, they employed careful diagnostic procedures, utilized multiple sources of information, and had an 18-year follow-up interview on most subjects. Furthermore, the median age of the adoptees at their last evaluation was in their mid-40s, suggesting that most had passed through their age of risk of illness. Third, because this was an adoption study, the authors could examine the impact of genetic factors, unconfounded by possible effects of the rearing environment. The sample, however, has one limitation. Although quite large by the standards of adoption studies, the sample size of relatives studied (total N=364) was substantially smaller than a number of recent family studies of schizophrenia that examined the boundaries of the schizophrenia spectrum (e.g., references 24–26). Thus, their study would have limited power to detect the aggregation of the rarer disorders in relatives of schizophrenic subjects.

Nonetheless, the pattern of findings in this study is reassuringly similar to that found in the prior literature. A meta-analysis of three independent family studies of schizophrenia demonstrated significant familial aggregation for schizotypal personality disorder (odds ratio=5.0) and other nonaffective psychoses (odds ratio=4.0) in relatives of schizophrenic probands, with the results being statistically homogeneous across studies (27). A recent review noted 11 family and adoption studies that have examined the risk for schizophrenia-spectrum personality disorders (mostly schizotypal but also in some studies paranoid personality disorder) in first-degree relatives of schizophrenic and control probands (28). In all studies, the risk for these spectrum personality disorders was higher in relatives of schizophrenic probands (unweighted relative risk=5.9), and the difference was significant in all but two of the studies. A controlled family study of childhood-onset schizophrenia also demonstrated significant aggregation of schizotypal personality disorder in relatives of schizophrenic probands (29).

Whether the schizophrenia spectrum extends to other personality disorders—especially schizoid and avoidant—as suggested by some studies (26, 29) is less certain, probably for two reasons. First, these are relatively rare disorders, and large sample sizes might be needed to reliably demonstrate that they belonged within the spectrum. Second, differences in results across research groups may derive from distinct approaches toward the diagnosis of cases commonly seen in these samples that present with a mixture of schizotypal, schizoid, paranoid, and avoidant traits.

Much controversy remains about the genetic relationship between schizophrenia and affective illness (30, 31). It is therefore noteworthy that the prevalence rates of total affective illness (psychotic and nonpsychotic forms) in this large adoption study were nearly identical in the adopted-away offspring of the schizophrenic (mean=6.6% [SD=2.1]), schizophrenia spectrum (mean=7.4% [SD=1.9]), and control (mean=7.3% [SD=1.9%]) mothers. These results are inconsistent with the hypothesis that these two forms of psychiatric illness share genetic risk factors.

In conclusion, these three papers provide good examples of the range of research questions in the vibrant field of the genetics of schizophrenia. We have reason to be proud of the advances we have made, although we have very far to go. If some of these "gene discoveries" for schizophrenia turn out to be true, as evidence is increasingly suggesting (32), we will have a new set of particularly exciting tasks before us. Two of them are directly relevant to papers in this issue: 1) clarify the set of disorders to which variants in these genes predispose, and 2) begin the critical and long-term goal of tracing the pathway from DNA variants to the complex and still rather enigmatic clinical syndrome we call schizophrenia.

References

1. Rudin E: Studien uber Vererbung und entstehung geistiger Storungen, I: Zur vererbung und neuentstehung der Dementia praecox (Studies on the Inheritance and Origin of Mental Illness, I: The Problem of the Inher-

itance and Primary Origin of Dementia Praecox): Monographien aus dem Gesamtgebiet der Neurologie und Psychiatrie, Number 12. Berlin, Springer, 1916
2. Kendler KS, Zerbin-Rudin E: Abstract and review of "Studien uber Vererbung und Entstehung geistiger Storungen, I: Zur Vererbung und Neuentstehung der dementia praecox." Am J Med Genet Neuropsychiatr Genet 1996; 67:338–342
3. Liu H, Heath SC, Sobin C, Roos JL, Galke BL, Blundell ML, Lenane M, Robertson B, Wijsman EM, Rapoport JL, Gogos JA, Karayiorgou M: Genetic variation at the 22q11 PRODH2/DGCR6 locus presents an unusual pattern and increases susceptibility to schizophrenia. Proc Natl Acad Sci USA 2002; 99:3717–3722
4. Chumakov I, Blumenfeld M, Guerassimenko O, Cavarec L, Palicio M, Abderrahim H, Bougueleret L, Barry C, Tanaka H, La Rosa P, Puech A, Tahri N, Cohen-Akenine A, Delabrosse S, Lissarrague S, et al: Genetic and physiological data implicating the new human gene G72 and the gene for D-amino acid oxidase in schizophrenia. Proc Natl Acad Sci USA 2002; 99:13675–13680; correction, 99:17221
5. Stefansson H, Sigurdsson E, Steinthorsdottir V, Bjornsdottir S, Sigmundsson T, Ghosh S, Brynjolfsson J, Gunnarsdottir S, Ivarsson O, Chou TT, Hjaltason O, Birgisdottir B, Jonsson H, Gudnadottir VG, Gudmundsdottir E, et al: Neuregulin 1 and susceptibility to schizophrenia. Am J Hum Genet 2002; 71:877-892
6. Straub RE, Jiang Y, MacLean CJ, Ma Y, Webb BT, Myakishev MV, Harris-Kerr C, Wormley B, Sadek H, Kadambi B, Cesare AJ, Gibberman A, Wang X, O'Neill FA, Walsh D, Kendler KS: Genetic variation in the 6p22.3 gene DTNBP1, the human ortholog of the mouse dysbindin gene, is associated with schizophrenia. Am J Hum Genet 2002; 71:337–348
7. Stefansson H, Sarginson J, Kong A, Yates P, Steinthorsdottir V, Gudfinnsson E, Gunnarsdottir S, Walker N, Petursson H, Crombie C, Ingason A, Gulcher JR, Stefansson K, St Clair D: Association of neuregulin 1 with schizophrenia confirmed in a Scottish population. Am J Hum Genet 2003; 72:83–87
8. Schwab SG, Knapp M, Mondabon S, Hallmayer J, Borrmann-Hassenbach M, Albus M, Lerer B, Rietschel M, Trixler M, Maier W, Wildenauer DB: Support for association of schizophrenia with genetic variation in the 6p22.3 gene, dysbindin, in sib-pair families with linkage and in an additional sample of triad families. Am J Hum Genet 2003; 72:185–190
9. Schulz B: Zur Erbpathologie der Schizophrenie (On the hereditary pathology of schizophrenia). Z Gesamte Neurol Psychiatrie 1932; 143:175–293
10. Kendler KS, Zerbin-Rudin E: Abstract and review of "Zur erbpathologie der Schizophrenie." Am J Med Genet Neuropsychiatr Genet 1996; 67:343–346
11. Kendler KS, Davis KL: The genetics and biochemistry of paranoid schizophrenia and other paranoid psychoses. Schizophr Bull 1981; 7:689–709
12. Kendler KS, Gruenberg AM, Tsuang MT: A family study of the subtypes of schizophrenia. Am J Psychiatry 1988; 145:57–62
13. Ungvari G: Validity of the ICD-9 schizophrenia classification: a blind family history study. Acta Psychiatr Scand 1983; 68:287–296
14. Kendler KS, McGuire M, Gruenberg AM, Walsh D: Outcome and family study of the subtypes of schizophrenia in the west of Ireland. Am J Psychiatry 1994; 151:849–856
15. Murphy KC, Jones LA, Owen MJ: High rates of schizophrenia in adults with velo-cardio-facial syndrome. Arch Gen Psychiatry 1999; 56:940–945
16. Gothelf D, Frisch A, Munitz H, Rockah R, Laufer N, Mozes T, Hermesh H, Weizman A, Frydman M: Clinical characteristics of schizophrenia associated with velo-cardio-facial syndrome. Schizophr Res 1999; 35:105–112
17. Bassett AS, Chow EW: 22q11 deletion syndrome: a genetic subtype of schizophrenia. Biol Psychiatry 1999; 46:882–891
18. Delisi LE, Reiss AL, White BJ, Gershon ES: Cytogenetic studies of males with schizophrenia: screening for the fragile X chromosome and other chromosomal abnormalities. Schizophr Res 1988; 1:277–281
19. Millar JK, Wilson-Annan JC, Anderson S, Christie S, Taylor MS, Semple CA, Devon RS, Clair DM, Muir WJ, Blackwood DH, Porteous DJ: Disruption of two novel genes by a translocation co-segregating with schizophrenia. Hum Mol Genet 2000; 9:1415–1423
20. MacIntyre DJ, Blackwood DH, Porteous DJ, Pickard BS, Muir WJ: Chromosomal abnormalities and mental illness. Mol Psychiatry 2003; 8:275–287
21. Kety SS, Rosenthal D, Wender PH, Schulsinger F: The types and prevalence of mental illness in the biological and adoptive families of adopted schizophrenics. J Psychiatr Res 1968; 6:345–362
22. Kety SS, Wender P, Jacobsen B, Ingraham LJ, Jansson L, Faber B, Kinney DK: Mental illness in the biological and adoptive relatives of schizophrenic adoptees: replication of the Copenhagen study in the rest of Denmark. Arch Gen Psychiatry 1994; 51:442–455
23. Zerbin-Rudin E, Kendler KS: Ernst Rudin and his genealogic-demographic department in Munich: an introduction to their family studies of schizophrenia. Am J Med Genet Neuropsychiatr Genet 1996; 67:332–337
24. Baron M, Gruen R, Rainer JD, Kane J, Asnis L, Lord S: A family study of schizophrenic and normal control probands: implications for the spectrum concept of schizophrenia. Am J Psychiatry 1985; 142:447–455
25. Maier W, Minges J, Lichtermann D, Heun R, Franke P: Personality variations in healthy relatives of schizophrenics. Schizophr Res 1994; 12:81–88
26. Kendler KS, McGuire M, Gruenberg AM, O'Hare A, Spellman M, Walsh D: The Roscommon Family Study, III: schizophrenia-related personality disorders in relatives. Arch Gen Psychiatry 1993; 50:781–788
27. Kendler KS, Gardner CO Jr: The risk for psychiatric disorders in relatives of schizophrenic and control probands: a comparison of three independent studies. Psychol Med 1997; 27:411–419

28. Kendler KS: Schizophrenia: genetics, in Kaplan and Sadock's Comprehensive Textbook of Psychiatry, 7th ed. Edited by Sadock BJ, Sadock VA. New York, Williams & Wilkins, 2000, pp 1147–1158
29. Asarnow RF, Nuechterlein KH, Fogelson D, Subotnik KL, Payne DA, Russell AT, Asamen J, Kuppinger H, Kendler KS: Schizophrenia and schizophrenia-spectrum personality disorders in the first-degree relatives of children with schizophrenia: the UCLA Family Study. Arch Gen Psychiatry 2001; 58:581–588
30. Weissman MM, Fink M, Endicott J, Taylor MA, Kendler KS, Winokur G, Gershon ES: Discussion of debate: is there a genetic Kraepelinian dichotomy for manic-depressive illness and schizophrenia? in Genetic Approaches to Mental Disorders. Edited by Gershon ES, Cloninger CR. Washington, DC, American Psychiatric Press, 1994, pp 193–202
31. Berrettini WH: Are schizophrenic and bipolar disorders related? a review of family and molecular studies. Biol Psychiatry 2000; 48:531–538
32. Harrison PJ, Owen MJ: Genes for schizophrenia? recent findings and their pathophysiological implications. Lancet 2003; 361:417–419

KENNETH S. KENDLER, M.D.

Address reprint requests to Dr. Kendler, Department of Psychiatry, Medical College of Virginia of Virginia Commonwealth University, P.O. Box 980126, Richmond, VA 23298-0126; kendler@hsc.vcu.edu (e-mail).