Genetics of Bipolar Disorder: Where Do We Stand?

Fall down seven times; stand up eight times.

—Japanese proverb, attributed to Daruma Daishi

Hell, there are no rules here. We're trying to accomplish something.

— Thomas Edison

In this issue are several articles on bipolar disorder. As a cause of human suffering and lives disrupted or lost, the importance of bipolar disorder is very well established, as is its underrecognition, undertreatment, and associated high costs (1–3). The practical benefits of successfully identifying the genes underpinning bipolar disorder could be in making its diagnosis surer and faster and its treatment rational and much more effective.

"For complex phenotypes like bipolar disorder... hypothesis-driven departures from the conventional assumptions are essential."

So, 17 years after the first map of the human genome was published (4), where do we stand in terms of the genetics of bipolar disorder? The primary strategy for locating genes in diseases of unknown etiology has been linkage analysis, employing data from genome maps and DNA samples from families with multiple affected members. Studies of common diseases of unknown etiology, including asthma, diabetes mellitus, and most psychiatric disorders, have proven that this is a difficult exercise. On the other hand, recent genetic discoveries in schizophrenia that began with linkage analyses of genome scans are so encouraging that we have every reason to expect that the identities of genes underlying bipolar disorder will follow.

Where are the bipolar disorder genes? There are many positive linkage findings, although only five of these have met the stringent criteria set years ago for significant linkage (5). Nonetheless, debates have continued about whether any of these linkages are proven and whether our current linkage and association study paradigms will work to find genes for bipolar disorder. There are about 16 favored chromosomal regions of the genome, but the 1,000 or so original reports and the more than 40 review papers plus two published meta-analyses (6, 7) reach sometimes overlapping but also differing conclusions about the location of bipolar disorder genes. The greatest surprise for psychiatric genetics as a whole has been the remarkable success in locating and identifying genes associated with schizophrenia (8, 9) while simultaneously debating the linkage results. In the bipolar disorder studies, a truly notable surprise has been the overlap of genomic regions linked to or associated with both schizophrenia and bipolar disorder (10).

Despite the linkage debates and admitting that further studies are needed, evidence is now mounting for declaring the gene complex G72/G30 as the first confirmed gene related to bipolar disorder. Statistically significant associations of single nucleotide polymorphism (SNP) alleles in this gene complex with bipolar disorder have been observed in four independent samples (11–13). The gene was first isolated in DNA on chromosome 13q33 (14), where there was an early linkage finding in schizophrenia (15) that was patented to a French company (Genset S.A.) 3 years ago. This result has directed our attention to the other genes associated with schizophrenia, especially those

residing in chromosomal regions where both bipolar disorder and schizophrenia pedigrees show evidence favoring linkage (8p22, 10p14, 18p11, and 22q11), old paradigms not withstanding (16).

How should we proceed? From the 17-year perspective, the scientific resources produced by the Human Genome Project (large, publicly available genetic databases, mass genotyping services, etc.) and by the NIMH Human Genetics Initiative (DNA and clinical datasets for disease-specific clinical samples [17]) are moving our field forward, albeit in fits and starts. Call these "Big Science" resources.

For complex phenotypes like bipolar disorder, the "Big Science" resources are necessary but not sufficient. Hypothesis-driven departures from the conventional assumptions are essential. Since these usually come from individual or small groups, call them "Boutique" innovations. The departures (innovations) might be changing the operational definition of bipolar disorder (i.e., the phenotype) by clinical or by laboratory means. Familial rather than individual phenotype approaches, devised 40 years ago to divide the mucopolysaccharidoses (18), are now being tested in bipolar disorder studies. Studies of families in which there is clustering of milder bipolar disorder forms point with linkage evidence to one chromosomal region 18q22 (19), whereas studies of families with clustering of psychotic or severe forms of bipolar disorder point to chromosomes 13q31 and 22q11 (20).

Creating new statistical methods for finding genes is also a work in progress. Linkage statistics combine the phenotype and genotype data to predict where genes reside. Association statistics combine the data to predict which DNA sequence variation (in a gene or its regulatory components) contributes to the risk of disease. Quantitative Trait Loci analyses are powerful linkage methods that use more information than the standard binary phenotype. They have helped to identify the genes responsible for the size of tomatoes and are currently being adapted to human studies.

In this issue, Faraone and colleagues employ "Big Science" resources and test an innovative (dimensional) definition of the bipolar disorder phenotype in a linkage study of bipolar disorder. Their study sample, derived from the NIMH Genetics Initiative Bipolar collection, is the largest publicly available bipolar disorder sample in existence. Their genotype data was generated at the NIH Center for Inherited Disease Research. Their boutique innovations were 1) the use of the age at onset of bipolar disorder, not the diagnosis of bipolar disorder itself, as the phenotype and 2) the use of a new statistical method that favors a quantitative rather than categorical definition of the phenotype (21). Their tantalizing results point to 12p, 14p, and 15p as chromosomal regions that could harbor genes related to bipolar disorder. The three chromosomal regions cannot be proclaimed confidently as established sites for bipolar disorder genes. Rather, these regions must stand in line, like the other 16 "favored regions," for attempts at replication or refutation using other samples. With persistence and innovative approaches, several of these regions will yield important genes. The studies exploring the age at onset, familial phenotypes, and the overlapping schizophrenia and bipolar disorder findings also have the attractive potential to redefine the scourge that, at least for today, we call bipolar disorder.

References

1. Lopez A, Murray C: The global burden of disease, 1990–2020. Nature Med 1998; 4:1241–1243
2. Lish JD, Dime-Meenan S, Whybrow PC, Price RA, Hirschfeld RM: The National Depressive and Manic-depressive Association (DMDA) survey of bipolar members. J Affect Disord 1994; 31:281–294
3. Coryell W, Scheftner W, Keller M, Endicott J, Maser J, Klerman GL: The enduring psychosocial consequences of mania and depression. Am J Psychiatry 1993; 150:720–727
4. Donis-Keller H, Green P, Helms C, Cartinhour S, Weiffenbach B, Stephens K, Keith TP, Bowden DW, Smith DR, Lander ES: A genetic linkage map of the human genome. Cell 1987; 51:319–337
5. Lander E, Kruglyak L: Genetic dissection of complex traits: guidelines for interpreting and reporting linkage results. Nat Genet 1995; 11:241–247
6. Badner JA, Gershon E: Meta-analysis of whole-genome linkage scans of bipolar disorder and schizophrenia. Mol Psychiatry 2002; 7:405–411

7. Segurado R, Detera-Wadleigh SD, Levinson DF, Lewis CM, Gill M, Nurnberger JI Jr, Craddock N, DePaulo JR, Baron M, Gershon ES, Ekholm J, Cichon S, Turecki G, Claes S, Kelsoe JR, Schofield PR, Badenhop RF, Morissette J, Coon H, Blackwood D, McInnes LA, Foroud T, Edenberg HJ, Reich T, Rice JP, Goate A, McInnis MG, McMahon FJ, Badner JA, Goldin LR, Bennett P, Willour VL, Zandi PP, Liu J, Gilliam C, Juo SH, Berrettini WH, Yoshikawa T, Peltonen L, Lonnqvist J, Nothen MM, Schumacher J, Windemuth C, Rietschel M, Propping P, Maier W, Alda M, Grof P, Rouleau GA, Del-Favero J, Van Broeckhoven C, Mendlewicz J, Adolfsson R, Spence MA, Luebbert H, Adams LJ, Donald JA, Mitchell PB, Barden N, Shink E, Byerley W, Muir W, Visscher PM, Macgregor S, Gurling H, Kalsi G, McQuillin A, Escamilla MA, Reus VI, Leon P, Freimer NB, Ewald H, Kruse TA, Mors O, Radhakrishna U, Blouin JL, Antonarakis SE, Akarsu N: Genome scan meta-analysis of schizophrenia and bipolar disorder, part III: bipolar disorder. Am J Hum Genet 2003; 73:49–62
8. Harrison PJ, Owen MJ: Genes for schizophrenia? Recent findings and their pathophysiological implications. Lancet 2003; 361:417–419
9. Owen MJ, Williams NM, O'Donovan MC: The molecular genetics of schizophrenia: new findings promise new insights. Mol Psychiatry 2004; 9:14–27
10. Berrettini WH: Evidence for shared susceptibility in bipolar disorder and schizophrenia. Am J Med Genet 2003; 123C:59–64
11. Hattori E, Liu C, Badner JA, Bonner TI, Christian SL, Maheshwari M, Detera-Wadleigh SD, Gibbs RA, Gershon ES: Polymorphisms at the G72/G30 gene locus, on 13q33, are associated with bipolar disorder in two independent pedigree series. Am J Hum Genet 2003; 72:1131–1140
12. Chen YS, Akula N, Detera-Wadleigh SD, Schulze TG, Thomas J, Potash JB, DePaulo JR, McInnis MG, Cox NJ, McMahon FJ: Findings in an independent sample support an association between bipolar affective disorder and the G72/G30 locus on chromosome 13q33. Mol Psychiatry 2004; 9:87–92
13. Schumacher J, Abon Jamra R, Freudenberg J, Becker T, Ohlraun S, Otte A, Tullius M, Kovalenko S, Van Den Bogaert A, Maier W, Rietschel M, Propping P, Nothen M, Cichon S: Examination of G72 and D-amino-acid oxidase as genetic risk factors for schizophrenia and bipolar affective disorder. Molecular Psychiatry 2004; 9: 203-207
14. 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, Picard FP, Maurice K, Essioux L, Millasseau P, Grel P, Debailleul V, Simon AM, Caterina D, Dufaure I, Malekzadeh K, Belova M, Luan JJ, Bouillot M, Sambucy JL, Primas G, Saumier M, Boubkiri N, Martin-Saumier S, Nasroune M, Peixoto H, Delaye A, Pinchot V, Bastucci M, Guillou S, Chevillon M, Sainz-Fuertes R, Meguenni S, Aurich-Costa J, Cherif D, Gimalac A, Van Duijn C, Gauvreau D, Ouellette G, Fortier I, Raelson J, Sherbatich T, Riazanskaia N, Rogaev E, Raeymaekers P, Aerssens J, Konings F, Luyten W, Macciardi F, Sham PC, Straub RE, Weinberger DR, Cohen N, Cohen D, Ouelette G, Realson J: 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
15. Blouin JL, Dombroski BA, Nath SK, Lasseter VK, Wolyniec PS, Nestadt G, Thornquist M, Ullrich G, McGrath J, Kasch L, Lamacz M, Thomas MG, Gehrig C, Radhakrishna U, Snyder SE, Balk KG, Neufeld K, Swartz KL, DeMarchi N, Papadimitriou GN, Dikeos DG, Stefanis CN, Chakravarti A, Childs B, Pulver AE: Schizophrenia susceptibility loci on chromosomes 13q32 and 8p21. Nat Genet 1998; 20:70–73
16. Kraepelin E: Psychiatry: A Textbook for Students and Physicians, 6th ed. Leipzig, Barth Verlag, 1899
17. Moldin S: The NIMH Human Genetics Initiative. Am J Psychiatry 2003; 160:621-622
18. McKusick VA: The genetic mucopolysaccharidoses. Circulation 1965; 31:1-4
19. McMahon FJ , Simpson SG, McInnis MG, Badner JA, MacKinnon DF, DePaulo JR: Linkage of bipolar disorder to chromosome 18q and the validity of bipolar II disorder. Arch Gen Psychiatry 2001; 58:1025–1031
20. Potash JB, Zandi PP, Willour VL, Lan TH, Huo Y, Avramopoulos D, Shugart YY, MacKinnon DF, Simpson SG, McMahon FJ, DePaulo JR Jr, McInnis MG: Suggestive linkage to chromosomal regions 13q31 and 22q12 in families with psychotic bipolar disorder. Am J Psychiatry 2003; 160:680–686
21. Blangero J, Williams JT, Almasy L: Variance component methods for detecting complex trait loci. Adv Genet 2001; 42:151–181

J. RAYMOND DEPAULO, JR., M.D.

Address reprint requests to Dr. DePaulo, Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, MD 21287-7413; jrd@jhmi.edu (e-mail).