Genes and Environment in Psychiatry

Winner's Curse or Cure?

IT HAS BECOME A CLICHÉ TO say that individuals are predisposed to psychiatric illnesses by a gene × environment interaction, yet we cannot say with certainty which genes or environments account for illness risk. Although the 2 major psychiatric illnesses, schizophrenia and bipolar disorder, are familial (ie, they cluster within families), it has proven extremely difficult to dissect any clear genetic cause.[1] Many potential reasons for this difficulty exist. One often cited is that the disorders are too heterogeneous because they are defined by symptom clusters, many of which

See also pages 444 and 457

overlap concurrently and longitudinally (ie, the phenotype problem). Although this factor likely contributes to the complexity of analysis, it is unlikely to be the major reason researchers are unable to find genetic loci because the diagnoses themselves are clearly familial and, therefore, affected individuals would be expected to share alleles. Another possible reason is that the clear familiality has led to an overestimate of the genetic, as opposed to the shared family environmental, risk. This could be a partial explanation because the precise quantification of genetic load is performed in twin and adoption studies, each of which has its own problems and biases.[2] A third suggested reason for the lack of consistent observations is that to find and quantify the genetic risk loci, we need to factor in relevant environmental risk factors. This third approach is the topic of an article in this issue of the *Archives*.[3]

In 2003, Caspi and colleagues,[4] in an article already cited 3000 times according to Google Scholar, reported that genetic variability in the serotonin transporter (*5-HTT*) gene (OMIM *182138) was associated with clinical depression only in individuals who were experiencing life stress. This remarkable finding had a beguiling and seductive plausibility: the role of serotonin pharmacology in the treatment of clinical depression is well understood, the polymorphism of *5-HTT* (5HTTLPR) appears to be functional (http://www.ncbi.nlm.nih.gov/gene/6532), and the *5-HTT* gene association with clinical depression had been previously tested with inconsistent results. The original article appeared to reconcile these issues neatly. Its findings were consistent with the general tendency to think gene × environment interactions are sensible and reasonable and that they form the long-sought-after explanation for the lack of consistent genetic findings in this area. However, the statistical analyses in the study depended on remarkably small numbers in key analytic cells (the starting population was 847, there are 3 possible genotypes, as many as 14 stressful life events, and male and female subjects): this yields 84 possible combinations (of 3 genotypes × 2 sexes × 14 events) and, therefore, an average of 10 possible subjects per combination (847 in the cohort yields 84 outcomes). More important, the significance threshold (*P* value) was set to .05, a decision typically based on specific a priori hypotheses and the strength of previous studies (which was sparse for an interaction effect leading to the novelty of the study). The reported *P* value for the gene × environment interaction was .02. In other words, the statistical analysis only reached significance if the a priori hypotheses, including the definitions, timing, and exposures of stressful life events regarding clinical depression, were accurate and, therefore, not subject to any type of significance threshold correction (Bonferroni or otherwise).

Not surprisingly, given the putative importance of the observation and the slimness of the statistical evidence, the article has attracted considerable controversy. In such a circumstance, researchers should use replication and meta-analysis for a field to reach a definitive conclusion. Replication is the mainspring of the scientific method. Unfortunately, unlike simple genetic studies in which the methods are standardized, large epidemiologic studies are difficult to replicate exactly. Although genotyping is easy, every epidemiologic study uses a unique sample with limits of generalizability and has measured and used different definitions of stressful life events and clinical depression. Two meta-analyses, which had strict study inclusion criteria, reported failures to replicate the gene × environment interaction.[5,6] The current study, which included every study that purported to attempt replication, reports a confirmation of the original finding, albeit with a smaller effect size.[3]

The reader is therefore entitled to ask, "What should I believe? Which explanation is true?" Unfortunately, the answer is unclear, and a long time will pass before questions can be resolved because all the studies so far can be interpreted in opposing ways. Furthermore, an exact replication study would take more than 20 years to conduct because the original study relied on a 23-year follow-up of a birth cohort. Seemingly, no established consensus exists, a state with which scientists inherently struggle. We are left only with the choice of whether to believe the assertions of Caspi et al, depending on how we weigh the strength of the prior evidence for an

interaction between stressful life events and the serotonin system in clinical depression (see Rutter et al[7] for an optimistic view of this problem and Zammit et al[8] for a pessimistic one). However, the seemingly never-ending and expensive efforts regarding replication vs nonreplication are not only limited to this specific gene × environment interaction. Innumerable other gene × environment interaction studies have been conducted in psychiatry with inconsistent findings and replication track records. Psychiatry is especially prone to these unsettling outcomes because of the lack of illness-validating biological markers. Our wish to find the "truth," that is, the cause of these illnesses after years of symptom-based treatments, is driven by the frustration of researchers and health care professionals, as well as the suffering and despair of patients and their families.

What lies ahead regarding this story? Only time will tell. Let us hope the results of our efforts will not be similar to those said to possess the *winner's curse*.[9] This term was coined to describe the initial genetic studies that report large odds ratios between the genetic variant and disease but that, with increasing time and replication attempts, converge to null.

John Hardy, PhD
Nancy C. Low, MD, MS, FRCPC

Author Affiliations: Rita Lilla Weston Laboratory, Department of Molecular Neuroscience, University College London Institute of Neurology, London, England (Dr Hardy); and Department of Psychiatry, McGill University, Montreal, Quebec, Canada (Dr Low).
Correspondence: Dr Hardy, Department of Molecular Neuroscience, University College London Institute of Neurology, Queen Square House, Queen Square, London WC1N 3BG, England (j.hardy@ion.ucl.ac.uk).
Financial Disclosure: None reported.

REFERENCES

1. Hardy J, Low N, Singleton A. Whole genome association studies: deciding when persistence becomes perseveration. *Am J Med Genet B Neuropsychiatr Genet*. 2008;147B(2):131-133.
2. Tishler PV, Carey VJ. Can comparison of MZ- and DZ-twin concordance rates be used invariably to estimate heritability? *Twin Res Hum Genet*. 2007; 10(5):712-717.
3. Karg K, Burmeister M, Shedden K, Sen S. The serotonin transporter promoter variant (5-HTTLPR), stress, and depression meta-analysis revisited: evidence of genetic moderation. *Arch Gen Psych*. 2011; 68(5):444-454.
4. Caspi A, Sugden K, Moffitt TE, Taylor A, Craig IW, Harrington H, McClay J, Mill J, Martin J, Braithwaite A, Poulton R. Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. *Science*. 2003;301(5631):386-389.
5. Risch N, Herrell R, Lehner T, Liang K-Y, Eaves L, Hoh J, Griem A, Kovacs M, Ott J, Merikangas KR. Interaction between the serotonin transporter gene (*5-HTTLPR*), stressful life events, and risk of depression: a meta-analysis. *JAMA*. 2009;301(23): 2462-2471.
6. Munafò MR, Durrant C, Lewis G, Flint J. Gene × environment interactions at the serotonin transporter locus. *Biol Psychiatry*. 2009;65(3):211-219.
7. Rutter M, Thapar A, Pickles A. Gene-environment interactions: biologically valid pathway or artifact? *Arch Gen Psychiatry*. 2009;66(12):1287-1289.
8. Zammit S, Owen MJ, Lewis G. Misconceptions about gene-environment interactions in psychiatry. *Evid Based Ment Health*. 2010;13(3):65-68.
9. Kraft P. Curses—winner's and otherwise—in genetic epidemiology. *Epidemiology*. 2008;19(5): 649-658.