Probing the Genome to Understand Suicide

Suicidal behavior, including completed and attempted suicide, is among the most tragic events psychiatrists encounter in their practice and requires separate attention in diagnosis and research (1). In spite of efforts of generations of researchers, suicidal behavior remains disturbingly common and hard to predict. The fact that suicide runs in families has been highlighted in eminent families with multiple completed suicides, like those of Ludwig Wittgenstein and Ernest Hemingway, and has been confirmed in systematic studies (2). Risk of suicide is shared by biological but not adoptive relatives, prompting the conclusion that familiality of suicide is due to genes rather than family environment or culture (3). However, no associations with specific genetic variants have been identified to date (4).

In this issue of the *Journal*, Perlis et al. report on the most comprehensive attempt to find genetic predictors of suicidal behavior (5). They tested nearly 2 million genetic variants for association with a history of suicide attempt among 5,815 individuals with bipolar disorder and 2,922 individuals with major depression. Several aspects of this study merit discussion before we turn to the results and their implications. First, Perlis et al. focused on attempted rather than completed suicide. This is a choice of convenience, since it is easier to assemble large, representative samples of suicide attempters than of completed suicides. It is reasonable to assume that genetic determinants of attempted and completed suicide overlap, since attempted suicide in a relative increases the risk of completed suicide in the proband and vice versa (2, 6). Second, the authors explored genetic correlates of suicide within a group of subjects with mood disorders. This approach is justified, since in high-income countries suicide usually occurs in the context of mental illness and mood disorders account for the largest share. In addition, genetic predilection for suicide appears to be independent of genetic liability to mental illness, meaning that findings from individuals with mood disorders can be cautiously generalized to other populations (2, 6). Third, they explored a large number of genetic variants covering all known human genes and noncoding DNA sequences. Since our knowledge of the neurobiology of suicide is imperfect, this approach represents a substantial advance on previous studies of selected genes (4). However, Perlis et al. focused on genetic variants that are carried by at least several percent of individuals (i.e., common variants). There are even more individual differences in the genome that are carried by less than one in one hundred humans. These rare variants have not been tested in the present study.

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Perlis et al. first tested association with suicide attempts separately in bipolar and major depression samples. One finding in the major depression group appeared compelling, as it was detected with a high level of statistical certainty and was in a gene that could plausibly be involved in relevant brain function, the *ABI3BP*. This association was not confirmed in a replication sample of a larger group of subjects with major depression. A meta-analysis of all 8,737 subjects with mood disorders found some evidence suggestive of genetic variants in other genes, including *PRKCE*, the encoding protein kinase C-epsilon. However, none of these associations was at a level of statistical certainty that would inspire confidence that they are genuine associations. None of the 19 genes implicated in previous literature received strong evidence of association (4, 5).

The meager results of such major effort are sobering. What do they mean? First, it is certain that there is no single suicide gene and that no genetic test would be useful in

predicting risk of suicidal behavior at present. Second, some of the genes implicated by Perlis et al. are worth pursuing, since determinants of suicidal behavior may be heterogeneous and nonreplicated due to differences between samples. For example, *ABI3BP* was associated with history of suicide attempts in a sample of treatment-seeking outpatients but was not replicated in a population-based sample. Suicidal behavior was not a major focus of either study and was assessed with different questions asked by different professionals in each study. Causal pathways into suicide may differ substantially in such diverse groups.

Is the lack of replicable associations between common genetic variants and suicidal behavior surprising? Suicide often occurs in young people before or during their reproductive age. If a genetic variant is directly predisposed to suicide, it would be less likely to be passed on to the next generation and would no longer be common (7). As a result, the genetic determination of suicide is more likely to involve rare genetic variants or genetic effects that are conditional on aspects of environment (7). This framework may help us determine what should be the next steps toward understanding the genetic components in the etiology of suicidal behavior. One avenue of exploration will involve rare genetic variants. Whole-genome sequencing and even larger samples will be required to overcome the challenges associated with searching for rare and heterogeneous determinants of suicidal behavior. Another avenue will be to explore the genetic determinants of suicidal behavior among individuals exposed to the same environmental factors or treatment.

Finding genetic predictors of the emergence or worsening of suicidal risk during treatment could have a considerable impact on clinical practice. Candidate gene studies of treatment-emergent or worsening suicidality have brought some tentative findings. For example, in the same sample explored by Perlis et al., variants in genes encoding ionotropic glutamate receptors were associated with emergence of suicidal ideation during treatment with citalopram (8). Another study found that variants in the gene encoding the brain-derived neurotrophic factor (*BDNF*) and an interaction between *BDNF* and the gene encoding its receptor (*NTRK2*) predicted emergence or worsening of suicidality during treatment with escitalopram or nortriptyline (9). A first comprehensive genome-wide exploration of suicidality during treatment has implicated the guanine deaminase (*GAD*) among other genes (10), and results of other similar studies are expected in the near future. While the power and applicability of these studies is enhanced through inclusion of subjects receiving the same treatment, there are other challenges to overcome. Pharmacogenetic studies are typically carried out in smaller samples and, due to the relative rarity of completed or attempted suicide during treatment, have to focus on suicidal ideation in addition to attempts. Their eventual success will depend on the role of common genetic variants in the treatment-related changes in suicidality and the overlap between genetic determinants of suicidal ideation and suicidal behavior during treatment.

In conclusion, the most important genetic study of suicidal behavior has not brought up any genetic variant that could be used as a predictor of suicide risk. This does not weaken the robust conclusion of family, twin, and adoption studies that liability to attempted and completed suicide is heritable. Since the study did not include rare genetic variants, environmental exposures or treatment, the results do not exclude an important role of genetic variants in suicidal behavior. In the absence of a genetic test, personal and family history of suicidal behavior remain the best indicators of liability to suicide. Advance in knowledge about the genetics of suicidal behavior can be expected from studies including rare variants and studies of suicidality during specific treatment.

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