Genetics of Suicide: An Overview

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Risk for suicide may have heritable contributions. Evidence supporting this hypothesis includes strong and consistent findings from more than 20 controlled family studies indicating nearly 5-fold greater relative risk of suicidal acts among relatives of index cases with suicidal behavior compared to relatives of nonsuicidal controls. Relative risk was greater for completed suicide than for attempts. Contributions of genetic instead of environmental factors are indicated by a higher average concordance for suicidal behavior among co-twins of suicidal identical twins compared to fraternal twins or to relatives of other suicidal subjects, in at least seven studies. Three studies indicate significantly greater suicidal risk, particularly for completed suicide, among biological versus adoptive relatives of suicidal or mentally ill persons adopted early in life. Molecular genetics studies have searched inconclusively for associations of suicidal behavior with genes mainly for proteins required for central serotonergic neurotransmission. Complex interactions of environmental with heritable risk and protective factors for suicide and psychiatric illnesses or vulnerability traits are suspected, but specific intervening mechanisms remain elusive. Familial or genetic risks for psychiatric factors strongly associated with suicide, such as major affective illnesses and alcohol abuse, as well as impulsive or aggressive traits, have not consistently been separated from suicidal risk itself. (HARV REV PSYCHIATRY 2004;12:1–13.)

adoption, attempts, family studies, genetics, mood disorders, serotonin, suicide, twins

Suicide is a prevalent outcome of many psychiatric illnesses, particularly in association with major depressive, bipolar, psychotic, substance use, and some personality disorders.1–8 In persons with such conditions, risk of suicide is 10 to 20 times higher than in the general population.2 New interest in the psychobiology of suicide, including exploration of possible genetic contributions, and in the possibility of reducing suicidal risk by specific psychopharmacological treatments has recently emerged.1,4,5 Attempting to clarify the heritability of a complex behavior like suicide, and to separate a putative inheritance of suicidal behavior from major risk factors or protective factors associated with suicide, are daunting challenges.

Relevant risk factors for suicide include specific psychiatric disorders—particularly major depressive and bipolar disorders, and highly comorbid substance use disorders, all of which are heritable.9 Potentially heritable risk factors for suicide may also include particular behavioral traits, including forms of aggression or impulsivity, and perhaps psychic anxiety.1,3,4,7 Currently, there is uncertainty as to whether “suicidality” itself, particular vulnerability-producing behavioral traits, or specific psychiatric illnesses are the most relevant phenotypes to investigate. Moreover, research on suicide often assumes close associations among completed suicides, potentially lethal attempts, relatively minor suicidal or self-injurious acts, and even suicidal ideation. Not
only is this basic premise unproved, but inconsistency or incomparability of research findings can arise from variance in the definitions of suicidality selected to define cases. Finally, the relative rarity of completed suicides, the tendency toward under- or misreporting them, and even greater difficulties in ascertaining suicide attempts all add to the technical challenges of research aimed at defining heritable or genetic factors relevant to suicide.3–4,8

Despite this potential complexity, there is a substantial and growing body of evidence pertinent to the hypothesis that risk of suicide has a heritable, and presumably genetic, contribution. Available findings derive mainly from epidemiological or clinical studies that, in essence, indicate that close biological relationship to probands or index cases identified by their suicidal behavior is associated with increased risks for such behavior in persons so related. Family studies strongly and consistently report increased risks of suicidal behavior among relatives of suicidal index cases compared to relatives of nonsuicidal controls. Efforts to refine the contributions of inheritance, and to separate those from shared environmental factors, have produced consistent findings of closer concordance for suicidal behavior between identical than fraternal twins or other relatives, and rare adoption studies have indicated greater risk of suicidal behavior among biological than adoptive relatives of suicidal index cases.9–12 Some efforts have also been made to associate particular molecular genetic markers with suicidal behavior.1–4,12 This body of research is the topic of this overview.

METHODS

The following overview was based on systematic searching of MEDLINE, from the mid-1960s through mid-2003, for reports pertaining to the genetics of suicidal risk. Various combinations of the following key words were used: suicide, suicidal, family, twin, adoption, gene, genetic. We also considered references cited in reports so identified, as well as citations in recent reviews on the topic of suicide.1,4,9–12 We concentrated on studies of families, twins, and adoptions, and particularly on data pertaining to suicide as the index outcome, when available, or to suicide attempts, as an alternative. Since available studies are limited in number, we made no effort to select or rate them based on quality standards. In order to be included in formal meta-analyses, however, studies were required to report numerical values for numerators and denominators for all rates, so as to permit quantitative pooling and weighting. Data were pooled across individual study reports in order to estimate an overall risk ratio and its 95% confidence interval (95% CI). These calculations were made in two ways: (1) using a weighted-average risk ratio procedure, with weights equal to the study sample size, and (2) using standard meta-analytic methods based on random-effects modeling. The first procedure was used because it provides an intuitively suitable estimate of the overall risk ratio, and the second procedure was used because interstudy variance (Q-test) was found to be high in preliminary testing. The 95% confidence interval for the first method was obtained using bootstrap methods. All of these meta-analytic methods are described in detail elsewhere.13–15

FAMILY STUDIES

The most extensive evidence for a familial, and possibly heritable, risk for suicidal behavior arises from studies that typically (but not always; see Table 1) compare risks of suicides or of serious attempts among close relatives of index cases with suicidal behavior, with such risks among relatives of nonsuicidal or normal controls. Such evidence arises from 21 reports16–36 providing 22 controlled comparisons involving a total of nearly 25,000 suicidal subjects and their family members (Table 1). In aggregating risk estimates across studies, we elected to include data from studies encompassing both first- and second-degree relatives together with data from studies of only first-degree relatives. There are too few studies available to permit carrying out these analyses separately.

The overall crude pooled risk ratio in close relatives of suicidal probands compared to relatives of controls, weighted by the number of subjects in each study, was 5.01 (95% CI, 2.76–8.23), indicating a 5-fold increased risk of suicidal behavior (suicides and attempts) among relatives of suicidal versus nonsuicidal control subjects (Table 1). A more rigorous estimate, based on meta-analytic, random-effects regression modeling with weighting for study size and interstudy variances,13–15 is 2.86 (95% CI, 2.32–3.53). Study-specific and pooled risk ratios and their variances are illustrated in Figure 1. The relative risk for suicidal behavior was consistently greater than the null value of 1.0 in all 22 comparisons analyzed (Figure 1).

Nevertheless, it is important to emphasize that reported risks of suicidal behavior vary greatly among studies (Table 1), ranging from 1.4%19 to 90%21 among relatives of suicidal probands, and from 1.1%17 to 24%33 among relatives of controls. Studies involving small numbers of subjects or relatives probably generate especially unreliable risk estimates for suicidal behavior. These estimates may vary further with the ages of those assessed, since time at risk for suicidal acts will be greater in older persons, further compromising the reliability of risk estimates. The observed variation also may depend on the type of behavior required (usually serious attempts, completed suicides, or both) and the method of case identification (direct interviews or medical records vs. family history acquired from subjects or secondary informants), as well as the closeness of relationships.
<table>
<thead>
<tr>
<th>Study</th>
<th>Proband samples (cases)</th>
<th>Events/cases</th>
<th>Comparison subjects (controls)</th>
<th>Events/controls</th>
<th>Suicidal behavior</th>
<th>Ascertainment method</th>
<th>Crude risk ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Woodruff et al. (1972)</td>
<td>Psychiatric patients</td>
<td>13/71</td>
<td>Nonsuicidal psychiatric patients</td>
<td>39/429†</td>
<td>Attempts</td>
<td>FH</td>
<td>2.01</td>
</tr>
<tr>
<td>Roy (1983)</td>
<td>Psychiatric inpatients, family suicide</td>
<td>118/243†</td>
<td>Inpatients without family suicide</td>
<td>1225/560†</td>
<td>Attempts</td>
<td>MR (I + II)</td>
<td>2.22†</td>
</tr>
<tr>
<td>Tsuang (1983)</td>
<td>Suicides</td>
<td>9/193</td>
<td>Nonsuicidal psychiatric patients</td>
<td>46/375†</td>
<td>Suicides</td>
<td>FH (I)</td>
<td>3.81†</td>
</tr>
<tr>
<td>Tsuang (1983)</td>
<td>Suicides</td>
<td>55/947†</td>
<td>Surgical patients</td>
<td>3/140†</td>
<td>Suicides</td>
<td>FH (I)</td>
<td>9.78</td>
</tr>
<tr>
<td>Linkowski et al. (1985)</td>
<td>Major depressives with attempts</td>
<td>52/239†</td>
<td>Major depression, no attempts</td>
<td>71/474†</td>
<td>Attempts</td>
<td>FH (I + II)</td>
<td>1.45</td>
</tr>
<tr>
<td>Shafi et al. (1985)</td>
<td>Suicides</td>
<td>18/20</td>
<td>Normals</td>
<td>4/17†</td>
<td>Suicides + attempts</td>
<td>DI</td>
<td>3.83</td>
</tr>
<tr>
<td>Wender et al. (1986)</td>
<td>Biorelatives of suicidal adoptees</td>
<td>28/387†</td>
<td>Relatives of nonsuicidal adoptees</td>
<td>20/693†</td>
<td>Suicides + attempts</td>
<td>MR (I)</td>
<td>2.51</td>
</tr>
<tr>
<td>Mitterauer (1990)</td>
<td>Major depressives, suicidal family</td>
<td>100/342†</td>
<td>Depressives, nonsuicidal family</td>
<td>9/80†</td>
<td>Attempts</td>
<td>FH (I + II)</td>
<td>2.60</td>
</tr>
<tr>
<td>Pfleger et al. (1994)</td>
<td>Child attempters</td>
<td>8/25 (approx.)†</td>
<td>Other psychiatric disorders</td>
<td>1/16 (approx.)†</td>
<td>Attempts</td>
<td>FH (I)</td>
<td>5.12</td>
</tr>
<tr>
<td>Malone et al. (1995)</td>
<td>Major depressives with attempts</td>
<td>7/51†</td>
<td>Depressives, no attempts</td>
<td>1/49†</td>
<td>Attempts</td>
<td>FH (I)</td>
<td>6.72</td>
</tr>
<tr>
<td>Brent et al. (1996)</td>
<td>Adolescent suicides</td>
<td>10/58†</td>
<td>Normals</td>
<td>2/55†</td>
<td>Suicidal acts + thoughts</td>
<td>DI (I)</td>
<td>4.73</td>
</tr>
<tr>
<td>Gould et al. (1996)</td>
<td>Adolescent suicides</td>
<td>20/120†</td>
<td>Community sample</td>
<td>7/147†</td>
<td>Suicides + attempts</td>
<td>DI (I)</td>
<td>3.51</td>
</tr>
<tr>
<td>Bridge et al. (1997)</td>
<td>Adolescents with attempts</td>
<td>8/37†</td>
<td>Nonsuicidal adolescents</td>
<td>8/465</td>
<td>Attempts</td>
<td>DI (I + II)</td>
<td>12.6</td>
</tr>
<tr>
<td>Johnson et al. (1998)</td>
<td>Adolescent attempters</td>
<td>36/62†</td>
<td>Normals</td>
<td>20/70†</td>
<td>Suicides + attempts</td>
<td>DI (I)</td>
<td>2.03</td>
</tr>
<tr>
<td>Foster et al. (1999)</td>
<td>Suicides</td>
<td>19/115†</td>
<td>Community sample</td>
<td>10/115†</td>
<td>Suicides</td>
<td>FH</td>
<td>1.90</td>
</tr>
<tr>
<td>Vijayakumar &amp; Rajkumar (1999)</td>
<td>Suicides</td>
<td>12/210†</td>
<td>Community sample</td>
<td>4/100†</td>
<td>Suicidal acts</td>
<td>FH (I)</td>
<td>3.00</td>
</tr>
<tr>
<td>Cheng et al. (2000)</td>
<td>Suicides</td>
<td>20/113†</td>
<td>Matched controls</td>
<td>13/226†</td>
<td>Suicides + attempts</td>
<td>FH (I)</td>
<td>3.05</td>
</tr>
<tr>
<td>Potash et al. (2000)</td>
<td>Bipolar alcoholic attempters</td>
<td>11/27 (approx.)†</td>
<td>Bipolar not a koholic or suicidal</td>
<td>7/39 (approx.)†</td>
<td>Attempts</td>
<td>DI (I + II)</td>
<td>2.27</td>
</tr>
<tr>
<td>Powell et al. (2000)</td>
<td>Suicides</td>
<td>12/94†</td>
<td>Matched psychiatric nonsuicides</td>
<td>3/89†</td>
<td>Suicides</td>
<td>MR (I)</td>
<td>3.77</td>
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<tr>
<td>Roy (2000)</td>
<td>Alcoholics</td>
<td>19/124†</td>
<td>Alcoholics nonsuicidals</td>
<td>9/209†</td>
<td>Suicides + attempts</td>
<td>FH (I + II)</td>
<td>3.56</td>
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<tr>
<td>Glowinska et al. (2001)</td>
<td>Adolescent female twins with attempts</td>
<td>N/A</td>
<td>Twins without attempts</td>
<td>N/A</td>
<td>Attempts</td>
<td>FH (I + II)</td>
<td>5.60</td>
</tr>
<tr>
<td>Total (n = 22)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Suicides + attempts</td>
<td></td>
<td>5.01</td>
</tr>
</tbody>
</table>

DI, direct interviews of relatives; FH, family history based on secondary reports, not interviews; MR, review of medical records; N/A, not available; I and II, first- and second-degree relatives. The pooled crude risk ratio (5.01; 95% CI, 2.76–8.23) is based on data from 24,701 total subjects (6,811 proband relatives, 14,474 control relatives, and a minimum of 3,416 relatives in Glowinski et al.) in the 22 reported comparisons of high-risk probands versus controls, and is weighted by the number of subjects per study; a more robust pooled risk ratio, based on meta-analytic, random-effects regression modeling with weighting for study size and interstudy variances, is 2.86 (95% CI, 2.32–3.53). Tsuang et al included two studies, and Wender et al included comparisons of risks of suicidal acts among biological relatives of 71 suicidal adoptees versus both biological and adoptive relatives of 71 nonsuicidal adoptee controls. The overall crude risk among relatives (column 3) was 612/6811, or 8.98%.

†Suicidal risk among relatives.

‡Reverse risk of suicide attempts among probands with a family history of suicide versus controls with no such family history, or among depressive probands with versus without such family histories.

§Glowinski et al. considered suicide attempts among relatives of 3,416 female twins (suggesting at least 1,708 subjects in suicidal and control groups), with familial risk ratios averaging 5.60 among co-twins and other relatives, but did not report attempt and sample numbers.
FIGURE 1. Meta-analysis of 22 studies of familial risk of suicidal behavior summarized in Table 1, based on random-effects modeling of relative risk (shaded squares, of size reflecting approximate weighting by sample size and variance measures) among families of suicidal probands vs. controls and their 95% confidence intervals (CI; horizontal bars), with a pooled risk ratio and its CI (black diamond). All 22 studies found increased familial risk associated with suicidal probands. The pooled risk ratio (vertical dotted line) is 2.86 (CI, 2.32–3.53), which is highly significantly ($p < 0.0001$) greater than the null of 1.0 (vertical line).

(first-degree relatives including parents, siblings, and children, with or without second-degree relatives, including grandparents, aunts, and uncles).

In order to illustrate such methodological sources of variance, we carried out further analyses of the data summarized in Table 1. In those studies in which suicidality included attempts, the average risk ($\pm$SD) among relatives of probands and controls was $18.0 \pm 13.3\%$, which was 4.6 times higher than the rate of $3.92 \pm 3.72\%$ when only completed suicides were considered ($F [1; 19 df] = 3.15; p = 0.09$). Similarly, ascertaining suicidal relatives by direct interviews or medical records yielded a 1.8-times greater average risk than did indirect estimates of family history based on reports by identified cases or family members ($21.0 \pm 1.72\%$ vs. $11.4 \pm 6.4\%$; $F [1; 19 df] = 2.98; p = 0.10$). When only first-degree relatives were included, the average risk of suicidal behavior was somewhat lower than with second-degree relatives included ($10.9 \pm 11.9\%$ vs. $18.6 \pm 10.9\%$; $F[1; 16 df] = 2.10; p = 0.17$). Surprisingly, however, mean rates of suicidal behavior among relatives of psychiatric and nonpsychiatric controls were similar ($8.1 \pm 7.0\%$ vs. $7.7 \pm 8.7\%$; $F [1; 19 df] = 0.02$;
situating that definitions of suicidality and methods of case ascertainment may have mattered more than the degree of kinship or the nature of the controls employed.

Given the high variance encountered among family studies and the lack of simple means of accounting or controlling for it, comparisons across studies are best done using study-specific ratios of relative risk, reflecting the differential suicide experience of subgroups exposed to the same within-study risk factors. The merit of this suggestion is supported by our finding that within-study risk estimates were closely congruent (Spearman nonparametric rank correlation, $r_s = 0.860; p < 0.001$). Nevertheless, the estimated ratios of relative suicidal risks within studies also varied considerably from one study to another (coefficient of variation, or SD/mean = 65%), from a low of 1.45 in a study comparing rates of suicide attempts among first- and second-degree relatives of patients with major depressive illness, with versus without a history of suicide attempts,26 to a high of 12.6 in a large study comparing risks of suicide attempts among first- and second-degree relatives of adolescents with suicide attempts versus others without.28 These strikingly dissimilar estimates of relative risk may, at least in part, reflect covariance of suicidality and major affective illness in the first comparison, and a possibly unreliably low estimate of risks of attempts among relatives of adolescent controls in the second.

It is also worth noting that among studies summarized in Table 1, the mean crude risk ratio was nonsignificantly higher in the 4 studies with the more stringent outcome criterion of completed suicide, compared to the 18 studies that involved suicide attempts only or attempts plus suicides (risk ratio $= 3.43$ [95% CI, 1.90–6.17] vs. 2.77 [95% CI, 2.22–3.48]). This trend may reflect a more heterogeneous or less familial basis for attempts than for completed suicides. The mean risk ratio also was nonsignificantly lower (2.45 [95% CI, 1.78–3.39] vs. 3.25 [95% CI, 2.41–4.38]) in the 11 studies with psychiatrically ill, but nonsuicidal, comparison groups than in the 11 studies with nonsuicidal, nonpsychiatric, or normal controls—which may perhaps be a reflection of covariance of suicidality and psychiatric illness in some studies. Moreover, familial risks among psychiatric controls averaged 4.63 times higher than among relatives of nonpsychiatric controls (1.416/11,183, or 12.7%, vs. 90/3291, or $p = 0.90$), suggesting that definitions of suicidality and methods of case ascertainment may have mattered more than the degree of kinship or the nature of the controls employed.

TWIN STUDIES

A powerful method of separating risks due to shared environments from specifically genetic factors is to compare concordance rates for a condition-of-interest between identical, or monozygotic (MZ), twins and fraternal, or dizygotic (DZ), twins.9–12 We identified seven twin studies of suicidal behavior, with required concordance data in identical versus fraternal twins (Table 2).9,39–44 None has involved samples of twins reared separately from early life, so as to avoid potential contributions of shared postnatal environments. Moreover, the size and presumed statistical power of these studies varies markedly, from an analysis involving only a single pair of MZ twins42 to a massive recent study of an entire national twin registry in Australia involving 1,538 MZ and 1,199 DZ twin pairs.44 The studies summarized in Table 2 are those that include concordance data for both MZ and DZ twins (not provided in the studies by Glowinski,46 Fu,47 and their colleagues).

When data from seven studies providing concordance rates and numbers of twins at risk were pooled, the overall concordance for suicides or attempts, weighted for the number of subjects involved, was 401/1,704, or 23.5%, for MZ twin pairs versus only 2/1,486, or 0.135%, for DZ twin pairs. These concordance rates yield an extraordinarily high pooled relative risk that appears to be 175 times higher among identical twins (Table 2). However, the observed incidence of suicidal behavior among fraternal co-twins in these studies was
TABLE 2. Summary of Twin Studies of Suicidal Risk

<table>
<thead>
<tr>
<th>Study</th>
<th>Reported co-twin suicidal rates</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Identical (MZ)</td>
</tr>
<tr>
<td>Kallman &amp; Anastasio (1947)9**</td>
<td>0/11</td>
</tr>
<tr>
<td>Haberlandt (1967)48††</td>
<td>14/51</td>
</tr>
<tr>
<td>Juel-Nielsen &amp; Videbach (1970)41‡</td>
<td>4/15</td>
</tr>
<tr>
<td>Zair (1981)45</td>
<td>1/1</td>
</tr>
<tr>
<td>Roy et al. (1991)36,‡</td>
<td>7/62</td>
</tr>
<tr>
<td>Statham et al. (1998)44,‡</td>
<td>365/1,538</td>
</tr>
<tr>
<td>Roy et al. (1999)β†</td>
<td>10/26</td>
</tr>
<tr>
<td>Total (7 studies)</td>
<td>401/1,704</td>
</tr>
<tr>
<td>Twin rates</td>
<td>23.5%</td>
</tr>
<tr>
<td>Family risk</td>
<td>Not applicable</td>
</tr>
</tbody>
</table>

CI, confidence interval; DZ, dizygotic; MZ, monozygotic. The estimated risk (concordance) among DZ co-twins (0.135%) is 67 times lower than the average rate (8.98%) among the combined pool of first- and second-degree relatives in family studies summarized in Table 1, suggesting a more plausible estimate of the MZ/DZ risk ratio of 2.62 (23.5%/8.98%; $\chi^2$ [1 df] = 276; $p < 0.0001$). Even with DZ and family rates pooled, the MZ/DZ risk ratio would be 23.5%/7.40%, or 3.18. For most studies, CIs are not provided since zero values appear in several numerators.

*Based on rate of suicides.
† Based on rate of suicides plus attempts.
‡ Based on rate of attempts only.
§ Overall, Fisher's exact $p < 0.0001$ for the $n = 7$ studies.
** Based on raw data pooled from Table 1, column 3 (612/6811, or 8.98%).

extraordinarily low, with only 2 suicides among 1,486 fraternal twin pairs (with none identified in five of the studies). We therefore suggest that the high resulting pooled MZ/DZ twin risk ratio is probably unstable and unreliable.

This impression is further supported by the marked disparity between the rates for DZ twins and rates reported in the preceding family studies summarized on Table 1. DZ rates, other things equal, should be similar to risks found among other first-degree family members. Based on reported family rates (8.98%) as a surrogate estimate of expected risk among DZ twins, one would expect a MZ/DZ risk ratio of 2.62 (Table 2). Instead, the observed risk ratio among identical twins of 175 (Table 2) is more than 66 times greater (175/2.62 = 66.8).

Similar findings of modest MZ/DZ differences in suicidal risk were also reported in another large study of 3,416 adolescent female twin pairs in Missouri by Glowinski and colleagues, with a crude MZ/DZ risk ratio of only 25.0%/12.8%, or 1.95. Of note, the risk among identical twins was nearly the same as that reported in earlier studies (25.0% vs. 23.5%), whereas the concordance among fraternal twins was 95 times higher (12.8% vs. 0.135%; Table 2), and much closer to the pooled family rate of 8.98%. Such a difference again suggests incomplete case ascertainment among DZ twin pairs in the earlier studies. This study also estimated zygosity-based odds ratios for suicidal behavior, corrected statistically for the contributions of specified psychiatric risk factors. These corrected rates differed remarkably little between MZ (5.60 [95% CI, 1.75–17.8]) and DZ twin pairs (4.00 [95% CI, 1.10–14.7]), suggesting little evidence for specific heritability of suicidal behavior itself.

For comparison, the large Australian national twin study by Statham and colleagues also provided sufficient statistical power (with a total of 2,737 twin pairs) to support corrections for contributions of depressive and other forms of psychiatric morbidity commonly associated with suicide. Even with this critical correction, a highly significant, 4-fold excess of risk for suicidal behavior (at least for attempts) in identical twins remained. This observation may suggest heritability of suicidal risk separate from the heritability of other important risk factors (in particular, mood disorders). The estimated genetic contribution to suicidal risk (heritability) per se in the Australian study was substantial, at 45%. The remaining variance (55%) suggests that contributions of nongenetic factors, including shared environments, also were substantial. To paraphrase, the authors proposed that risk for suicidality (defined as thoughts and attempts, not fatalities) is the result of complex interactions of psychiatric history, neuroticism, and traumatic life experiences; genetic vulnerability specific to suicidal behavior; and underlying sociocultural risk factors and protective factors.

Very recently, Fu and colleagues used a large military registry of 3,372 twin pairs and employed multiple regression analytic techniques to estimate contributions of separate factors on twin concordance for suicidal ideation and...
attempts (again, not deaths). Their analysis also supported the conclusion that suicidality may have heritability separate from that of psychiatric illnesses. Surprisingly, however, genetic factors accounted for a higher proportion of variance for suicidal ideation (36%) than for suicide attempts (17%). These results again suggest the biological non-equivalence of suicidal thoughts and behaviors, and indicate that non-genetic factors contribute importantly to risk of suicidality among twins.

These three recent studies—of Glowinski, Statham, Fu, and their colleagues—illustrate the difficulty of obtaining substantial numbers of completed suicides for analysis, even in unusually large samples involving thousands of twin pairs. It would be of great interest if these and other investigators involved would pool their resources and focus particularly on the separability of risk for completed suicides or life-threatening attempts, from risk of major affective and other psychiatric disorders highly associated with suicide.

**ADOPTION STUDIES**

Another, less commonly employed technique aimed at separating genetic from shared environmental factors among close relatives is to study persons adopted very early in life. For suicide, there have been only three such studies to date, each making use of the same Danish health and vital statistics registers pertaining to 5,483 adoptions in greater Copenhagen between 1924 and 1947. Critical findings for contrasting the risk of suicidal behavior among biological versus adoptive relatives of index cases are summarized in Table 3. For simplicity, additional data for relatives of normal controls are omitted from Table 3 (although some are included in Table 1 as a family study of risk among first-degree biological relatives of suicidal probands and nonsuicidal, but otherwise matched, controls).

In the earliest of the three studies—by Kety and colleagues—suicide was not a specific predefined outcome; the study was aimed primarily at determining risk of "psychotic spectrum" disorders among relatives of probands diagnosed with broadly defined schizophrenia. Nevertheless, reports of suicide were included, and the post hoc analysis indicated a nearly 3-fold greater risk among biological over adoptive relatives of psychiatrically ill index adoptees, although this difference was not significantly different from the null value of 1.0 (risk ratio = 2.67; 95% CI, 0.32–22.4; Fisher’s exact p = 0.67; Table 3A).

In a subsequent study, Schulsinger and colleagues identified 57 completed suicides among early-adopted Danish citizens defined as index cases. Suicides were matched with control adoptees lacking evidence of suicide or psychiatric illnesses, by sex, age at the time of index suicide, time spent with biological mothers, and socioeconomic class of the adopting families. For both groups, larger panels of (biological) first-degree relatives (n = 269, including parents,

<table>
<thead>
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<th>Groups</th>
<th>Biological</th>
<th>Adoptive</th>
<th>Risk ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Kety et al. (1968)</td>
<td>5/156 (3.20%)</td>
<td>1/83 (1.20%)</td>
<td>2.67 (0.32–22.4)†</td>
</tr>
<tr>
<td>B. Schulsinger et al. 1979</td>
<td>12/269 (4.6%)</td>
<td>0/148 (0.00%)</td>
<td>4.46‡</td>
</tr>
<tr>
<td>C. Wender et al. 1986</td>
<td>28/387 (7.24%)</td>
<td>8/180 (4.44%)</td>
<td>1.63 (0.76–3.50)</td>
</tr>
<tr>
<td>D. Pooled data from studies A &amp; C</td>
<td>20/543 (3.68%)</td>
<td>2/263 (0.76%)</td>
<td>4.84 (1.14–20.6)</td>
</tr>
</tbody>
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CI, confidence interval. Note that all three studies are based on a single Danish database. Study A data are for rates of suicides or attempts in biological or adoptive first-degree relatives of early-adopted probands who were diagnosed with schizophrenia-like disorders (n = 33), committed suicide (n = 57), or were diagnosed with an affective disorder (definite or probable DSM-III major depression or bipolar disorder; n = 71), compared to early-adopted controls matched for number, sex, socioeconomic class of adoptive parents, age at adoption, current age compared to proband age at suicide, and time living with biological mother. Study B data (involving suicidal adopted probands), though complementary to other analyses, are probably not independent and are therefore not included in D (pooled data from studies A and C).

†Schizophrenia-like probands.
‡Mood-disordered probands.
§Fisher’s exact p = 0.0056.
†Suicidal probands.
‡CI is indeterminate because of zero numerator.
siblings, and half-siblings) of the suicidal probands and of the nonsuicidal matched controls (n = 148) were identified, and evidence of suicides among them was sought, again through the excellent public health and death records available in Denmark. There were several suicides among the biological relatives (4.46%), but in none of the adoptive relatives of suicidal index cases (because of a zero value in one numerator, a risk ratio was not calculated; Fisher’s exact \( p = 0.0056 \); Table 3B). When biological relatives of cases versus controls were compared, the identified risk of suicide was 12/269, or 4.6%, for relatives of suicidal probands, versus only 2/269, or 0.74%, for relatives of matched, nonsuicidal controls; this 6.03-fold difference is statistically significant (Fisher’s exact \( p = 0.012 \); data not included in Table 1 owing to probable sample overlap with the earlier study by Wender and colleagues\(^2\) that is included in Table 1). A major limitation of this study is that it did not consider the possible coincident heritability of clinical risk factors for suicide, such as major affective, psychotic, and substance use disorders. Moreover, identification of suicides from public health records may lead to underestimates.\(^7\)

Later, the same international collaborators, led by Wender,\(^2\) considered as index cases (against matched normal control adoptees) all Danish adoptees identified as having “affective-spectrum” disorders (for each group, \( n = 71 \)), with likely sampling overlap with the earlier study by Schulzinger and colleagues.\(^47\) The index disorders included not only DSM-III major depression and bipolar disorder, but also milder “neurotic” depressions and a condition (“affect reaction”) marked by affective instability that may represent a personality disorder or trait. In a critical comparison of rates of suicides plus attempts among biological versus adoptive relatives of affectively ill adopted probands, the risks differed only moderately (1.63-fold; 95% CI, 0.76–3.50) and nonsignificantly (7.24% vs. 4.44%; Fisher’s exact \( p = 0.27 \); Table 3C).

However, for completed suicides considered separately among the biological versus adoptive relatives of index cases, the risk was 6.93 times greater (95% CI, 1.03–52.4) among the biological relatives (3.88% vs. 0.56%; Fisher’s exact \( p = 0.028 \); Table 3C). Moreover, when data for suicides among affectively\(^2\) and psychotically ill probands\(^46\) were pooled, there was a 4.84-fold greater risk (95% CI, 1.14–20.6) among biological than adoptive relatives (3.68% vs. 0.76%; Fisher’s exact \( p = 0.019 \); Table 3D). Further comparison of rates of completed suicides for biological relatives of probands versus biological relatives of controls (not shown) also yielded a highly significant, 13.3-fold difference (15/387, or 3.88%, vs. 1/344, or 0.29%; 95% CI, 1.78–100; Fisher’s exact \( p = 0.0006 \).\(^2\)

In striking contrast, when suicide attempts were considered separately in the study by Wender and colleagues,\(^2\) there was, contrary to expectations, a nonsignificant, but slightly lower, risk (risk ratio = 0.86; 95% CI, 0.35–2.13) in biological versus adoptive relatives of affectively ill adopted probands (3.36% vs. 3.89%; Fisher’s exact \( p = 0.86 \); Table 3C). A similar comparison for attempts alone provided rates of 13/387, or 3.36%, in biological relatives of index cases versus 4/344, or 1.16%, for biological relatives of matched, but not affectively ill, controls (not shown), indicating a modest, 2.89-fold difference (95% CI, 0.95–8.78; Fisher’s exact \( p = 0.053 \)). Overall, these adoption studies indicate greater risk of completed suicides, but not of attempts, among biological, compared to adoptive, relatives of probands, and among biological relatives of probands versus controls. These results are consistent with the hypothesis that some aspect of suicidality is heritable and, again, that attempts and completed suicides probably differ in risk factors and contributing mechanisms. The heritability of suicide attempts may well be much less than for completed suicides in that the severity and lethality of attempts are exceedingly diverse and likely to include environmentally or situationally determined actions in many cases.\(^38\)

Among first-degree adoptive relatives, the risk of suicides and attempts was smaller and virtually identical among adoptive relatives of both affectively ill index adoptees and their matched controls (8/180, or 4.44%, vs. 7/169, or 4.14%, indicating a risk ratio of only 1.07, which does not differ significantly from the null value of 1.00; 95% CI, 0.40–2.89; Fisher’s exact \( p > 0.99 \).\(^2\) For suicides alone, the risk was, paradoxically, somewhat lower among adoptive relatives of affectively ill index cases (1/180, or 0.56%) than in adoptive relatives of controls (2/169, or 1.18%). This 2.13-fold difference was not statistically significant (95% CI, 0.19–23.3; Fisher’s exact \( p = 0.61 \)), however, and the very small numerators involved suggest that these risk estimates may be unstable. The average near-lifetime suicidal risk among adoptive relatives (3/349, or 0.86%) is what would be expected in the general population (0.93%, based on an international average of approximately 0.0155%/year over about 60 years of risk exposure),\(^6,7\) suggesting that suicidal behavior among adoptees probably was not mediated by the behavior of adoptive relatives.

It is curious that the difference in risk for affective illness among biological relatives of affectively ill adoptees and of matched, nonaffectively ill, adopted controls\(^2\) was much less robust than for suicide, at 20/387, or 5.17%, and 8/344, or 2.33%, in relatives of affectively ill index cases versus controls, respectively (a 2.22-fold difference; 95% CI, 0.99–4.98; Fisher’s exact \( p = 0.054 \)). This weaker evidence of heritability of affective illness than of completed suicide (involving 2-fold vs. 7- to 13-fold risk ratios) may reflect inclusion of neurotic depression and affective instability along with major affective syndromes. Such broad inclusion criteria probably also diluted the nearly 3-fold average increase in suicidal risk expected from the family studies.
considered above that involved major mood disorders (Table 1; Figure 1).

Similarly, when only DSM-III major affective disorders were considered in relatives,\(^2\) the respective rates for major mood disorder among biological and adoptive relatives of broadly affectively ill index cases were 20/387, or 5.17%, versus 5/180, or 2.78%, again yielding a low risk ratio of 1.86 (95% CI, 0.71–4.88; Fisher’s exact \(p = 0.272\)). The relatively low rate of major mood disorders found among adoptive relatives of affectively ill index cases (5/180, or 2.78%) was similar to their risks in biological (8/344, or 2.33%) and adoptive (3/169, or 1.78%) relatives of nonaffectively ill controls (pooled rate = 16/693, or 2.31%, which is moderately, though significantly, below the rate of 5.17% in the biological relatives of affectively ill probands; \(\chi^2 [1 \text{ df}] = 6.35, p = 0.012\)). This modest contrast in risks for familial major mood disorders may again reflect selection of the index cases by broad criteria for “affective illness.” Taken together, findings from the small number of adoption studies appear to indicate a stronger heritability for suicide than for attempts or for mood disorder. Nevertheless, they leave considerable uncertainty about the potentially confounding effects and interactions of the inheritance of affective illness and suicidality, as well as their relative heritability.

**MOLECULAR GENETIC STUDIES**

In keeping with remarkable advances in molecular genetics in recent years, there has been intense interest in seeking associations of specific candidate genes with risk of suicide. Since the findings remain largely preliminary and sometimes inconsistent or inconclusive, the interested reader is referred elsewhere to recent reviews on this topic:\(^1\)\(^,\)\(^4\)\(^10\)\(^,\)\(^12\) only selected highlights are considered here. Most molecular studies have searched for associations with genes of the enzymes, transporters, and receptor proteins required for synaptic neurotransmission mediated by serotonin (5-hydroxytryptamine [5-HT]). This focus has been encouraged by considerable biochemical evidence of relatively low biochemical production and metabolic turnover of 5-HT among persons with a history of violent behavior, including suicide attempts. This association rests largely on assays of the primary metabolite of serotonin, 5-hydroxyindoleacetic acid (5-HIAA), in cerebrospinal fluid (CSF).\(^10\) There is also evidence of reduced expression of some 5-HT receptor types in postmortem brain tissue of suicide victims. In addition, most antidepressants facilitate serotonergic neurotransmission;\(^48\) the ability of antidepressants to reduce risk of suicide is unproved, however, and the available data do not indicate a selective antisuicide effect of serotonin reuptake inhibitor antidepressants, in particular (Baldessarini RJ, Hennen J, Kwok KW, Ioanitescu DO, Ragade J, Tondo L, Simhandl C, unpublished manuscript).\(^1\)\(^,\)\(^5\)\(^–\)\(^50\)

Most molecular studies related to suicide have involved genes for L-tryptophan hydroxylase, the rate-limiting enzyme required for neuronal biosynthesis of serotonin.\(^4\)\(^10\)\(^,\)\(^12\)

The significance of the reported findings remains uncertain, however. In some studies, polymorphisms of the gene for this critical enzyme, including A-779C (selectively associated with low CSF concentrations of 5-HIAA and so implicated in suicide) and A-218C, have been associated with suicide\(^51\)–\(^53\) or suicide attempts.\(^54\)–\(^58\) In other studies, these same polymorphisms were not associated with suicide\(^59\)–\(^61\) or were associated with alcoholism, violence, impulsivity, and anger,\(^59\) but not, interestingly, with major depression.\(^4\)\(^12\)\(^53\) Also, the gene sequences involved in the reported associations usually involved introns, which are generally considered “nonfunctional” gene components (although they can exert regulatory influences on gene expression), in contrast to exons, which are required to produce peptide sequences of final product proteins. Some genetic findings regarding L-tryptophan hydroxylase seem to predict deficient activity of this critical enzyme, and so may be consistent with the low CSF and postmortem cerebral tissue levels of 5-HIAA that have repeatedly been associated with violence and suicide.\(^10\) This inference remains unproved, however, and the available findings are inconsistent and inconclusive.\(^4\)\(^10\)\(^,\)\(^12\)\(^63\) Moreover, the recent identification of a brain-specific form of tryptophan hydroxylase (TPH2) complicates genetic analysis of this enzyme even further since previous analyses considered only the molecular form TPH1, which is not characteristic of brain tissue.\(^64\)

Fewer, and still preliminary, studies have also suggested associations between suicidal risk and genes for particular serotonin (5-HT) receptors, including types 1A, 2A, and the 5-HT autoreceptors 1B/1D. Despite some preliminary, encouraging results pertaining to one or more of three polymorphisms of genes controlling expression of the serotonin 5-HT\(_{2A}\) receptor,\(^56\)\(^65\)\(^,\)\(^66\) the few positive findings have been inconsistent and poorly replicated.\(^4\)\(^12\)\(^61\)\(^,\)\(^65\)\(^,\)\(^67\)\(^,\)\(^68\)

There has also been some tentative exploration of genes controlling proteins involved in the inactivation of monoamine neurotransmitters.\(^12\) Components of genes for the serotonin transporter membrane protein found uniquely in the cell membranes of serotonergic neurons—in particular, either long\(^69\) or short\(^70\)\(^,\)\(^71\) promoter regulatory regions of the gene sequence—also have been associated with suicides or attempts. These findings have been inconsistent,\(^68\)\(^72\) however, and show overlapping associations with depression, bipolar disorder, alcoholism, and, perhaps, violence traits,\(^73\) all of which are important risk factors for suicide.\(^12\) Finally, genes that control expression of type A monoamine oxidase (MAO-A)—which is found in the membranes of mitochondria
in monoaminergic nerve terminals and is considered important in regulating neurotransmitter availability at the synapse—also have been tentatively associated with suicide and other forms of violent and impulsive behavior, particularly in men.⁴,¹²,⁷⁴

In general, the molecular genetic approach, while promising and technically compelling, has not yielded consistent, specific, and unambiguous evidence of genetic factors associated with suicidal behavior. Emerging applications of gene-array and protein-array analyses to evaluate associations of thousands of genes and gene products simultaneously may eventually yield useful information.⁴ Moreover, like the epidemiological genetic studies, the reported molecular genetics studies of suicide have not yet clearly separated genetic contributions to important clinical risk factors for suicide, such as depression, substance abuse, and impulsivity, as opposed to suicidal behavior itself.

COMMENTS AND CONCLUSIONS

This brief overview indicates strong support for familial risk of suicide. More than 20 studies indicate consistently that risks of suicidal behavior (completed suicides and attempts) were increased in all comparisons, by nearly three times overall, among close relatives of persons who themselves have been suicidal, depressed, or otherwise mentally ill, compared to relatives of unaffected controls (Table 1; Figure 1). These findings are, however, quantitatively variable and ambiguous as to their specific association with suicide rather than psychiatric risk factors, and fail to distinguish environmental from specifically genetic risk factors. The findings of family risk studies also appear to be affected by variance in defining “suicidal” outcomes (thoughts, attempts, fatalities), by case-finding methods, and by the degree of kinship involved.

Efforts to separate genetic from environmental factors have included several twin studies that appear to establish a greater risk for suicidal behavior among identical versus fraternal co-twins of index twins identified by suicidal behavior (Table 2). Most reported rates for fraternal co-twins are remarkably low, however, and there are only two studies with suicidal cases among both MZ and DZ co-twins. This numerical circumstance is likely to yield unreliable estimates of risk, especially among fraternal co-twins, whose reported rates are far lower than those reported among other first-degree relatives of suicidal persons in family studies (Table 1). These results suggest limitations related to case identification. Moreover, the twin studies are very limited in number and inconsistent in defining index behaviors (completed suicides vs. attempts of varying severity). Three recent twin studies suggest that heritable risk factors specific to suicidal behavior may be separable from psychiatric and other risk factors.⁸,¹⁰,⁴⁴,⁴⁵

To date, only one database, derived mainly from public health records, has been used to study adoptions for the purpose of separating nature and nurture in risk for suicidal behaviors. Findings from three studies based on these data are suggestive, but less than compelling, in documenting an increased risk of suicidal behaviors, and especially completed suicides, among biological relatives over adoptive families of mentally ill or suicidal index cases adopted early in life (Table 3).

Molecular genetic studies have focused almost entirely on plausible candidate genes for enzymes and other proteins involved in the synthesis, metabolism, or actions of serotonin, for which there is suggestive evidence of deficient availability or activity in violent behavior, including suicide. This emerging research remains, however, tentative and inconclusive.

Although polygenic inheritance of unspecified factors in suicide is widely suspected, there is no established mode of inheritance and no coherent genetic model.¹⁴,¹⁰ Moreover, specifically what may be inherited is not clear. It may include suicidal behavior itself; closely related (and probably partly genetically determined) psychiatric risk factors (notably, depressive and other psychiatric illnesses, substance use disorders, or traits of impulsivity or aggression); and perhaps also factors that may be protective against suicide. Recent family and genetic studies employing multivariate analytical methods suggest that estimates of the heritability of suicidal behavior and major psychiatric risk factors may be separable.

In general, progress in this challenging area of research on genetic factors related to suicide is encouraging, but more tantalizing than definitive and conclusive. Evidence for familial risk is particularly abundant, consistent, and strong. There are some indications from twin and adoption studies, moreover, that an imprecisely defined degree of heritability of suicidal behavior, and especially completed suicide, seems to be involved, but also that undefined, shared, and independent clinical and environmental risk factors are important. This situation is hardly unique to suicide; it is characteristic of the current status of knowledge about heritability in many of the complex clinical syndromes in psychiatry. It is a major research challenge to clarify the relative heritability of the risk for suicide, in particular, as separate from the heritability of disorders or traits that are strongly associated with suicidal risk—notably major affective and substance use disorders, as well as aggressive or impulsive traits.¹–⁴

Some of this material was developed for a 2003 task force on suicide prevention for the American Psychiatric Association.¹
REFERENCES


