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Candidate Endophenotypes for Genetic Studies of Suicidal Behavior

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Abstract

Twin, adoption, and family studies have established the heritability of suicide attempts and suicide. Identifying specific suicide diathesis-related genes has proven more difficult. As with psychiatric disorders in general, methodological difficulties include complexity of the phenotype for suicidal behavior and distinguishing suicide diathesis-related genes from genes associated with mood disorders and other suicide-associated psychiatric illness. Adopting an endophenotype approach involving identification of genes associated with heritable intermediate phenotypes, including biological and/or behavioral markers more proximal to genes, is an approach being used for other psychiatric disorders. Therefore, a workshop convened by the American Foundation for Suicide Prevention, the Department of Psychiatry at Columbia University, and the National Institute of Mental Health sought to identify potential target endophenotypes for genetic studies of suicidal behavior. The most promising endophenotypes were trait aggression/impulsivity, early-onset major depression, neurocognitive function, and cortisol social stress response. Other candidate endophenotypes requiring further investigation include serotonergic neurotransmission, second messenger systems, and borderline personality disorder traits.

Keywords

Endophenotype; genetics; suicide

Suicidal behavior is an important preventable cause of injury, disability, and death worldwide. In most countries, the vast majority of suicides and nonfatal suicide attempts are associated with psychiatric disorders. Twin and adoption studies find that the predisposition to suicidal behavior is partly heritable; however, the genes responsible are mostly unknown. Recently, there have been substantial advances in knowledge of the pathophysiology of suicide and nonfatal suicide attempts; recognition of behavioral components of the diathesis for suicidal behavior including aggressive/impulsive traits and neurocognitive deficits;

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development of methods for imaging relevant neural circuitry of the brain; finer grained single nucleotide polymorphism (SNP) maps of the human genome; improved statistical approaches; and greater appreciation of the role of gene-environment interactions. This article is based on a workshop convened by the National Institute of Mental Health, the American Foundation for Suicide Prevention, and the Department of Psychiatry at Columbia University that addressed the biological and behavioral diathesis for suicidality for the purpose of identifying promising clinical, cognitive, and biological intermediate phenotypes for finding candidate gene studies.

Suicidal Behavior Phenotypes

There are multiple levels of severity and injury burden within the construct of suicidality, ranging from suicidal ideation without a specific plan, suicidal ideation with a specific plan, low-lethality suicide attempts, high-lethality but nonfatal suicide attempts, and death by suicide. In 2005, the U.S. suicide rate was 11 per 100,000 persons (1). In the general population, prevalence of suicide attempt is .4 % to .6%, and suicidal ideation 2.8% to 3.3% (2).

Comparison of findings between studies is limited by lack of uniform definitions of suicidal ideation and behaviors. The Columbia Classification Algorithm of Suicidal Assessment is being widely adopted and provides operational definitions of suicide and suicide attempt that set two minimal requirements: 1) a suicidal act must be a self-directed act; and 2) it must be characterized by some intent to die (for detailed definitions, see Posner, *et al.*) (3).

Suicidal Behavior and Genetics

Heritability

The contribution of additive genetic factors is estimated to be 30% to 50% for a broad phenotype of suicidality that includes ideation, plans, and attempts and is largely independent of the inheritance of psychiatric disorder (4). There is a higher concordance rate for suicide in monozygotic than dizygotic twins (24.1% vs. 2.8%) (4) and a 2.0 to 4.8 times greater prevalence of suicide in the relatives of individuals who die by suicide, even after adjusting for psychiatric disorder. Adoption studies document fourfold to sixfold higher rates of suicide in the biological relatives of adoptees who die by suicide compared with adoptive relatives (see Brent and Melhem [5] for a review).

Nonfatal suicide attempts have heritability estimates of 17% to 45%, even after controlling for psychiatric disorder, and family studies consistently report higher rates of suicide attempt in relatives of suicide attempters compared with relatives of nonattempters. However, an adoption study did not find higher rates of suicide attempt in the biological parents than in the adoptive parents of suicide attempters (5). Data on suicidal ideation are sparser. Twin studies report 36% to 43% heritability, and family studies have documented transmission of suicidal ideation (5). However, familial transmission of ideation, in contrast to transmission of behavior, appears to be related to the transmission of psychiatric disorder (5).

Genes and Suicidal Behavior

Whole-genome linkage studies seek to identify genetic loci and ultimately candidate genes associated with disease phenotypes. Such studies have reported linkage of suicide attempt and chromosome 2p11, 2p12, and 2p, 5q, 6q, 8p, 11q, and Xq in varied psychiatric disorder pedigrees (6). A study of suicide deaths in bipolar pedigrees reported linkage at chromosome 6q25.2 (6).

Microarray technology enables expression profiling of thousands of genes in the brains of suicides and may also aid in identification of candidate genes, as well as extending the understanding of neurobiological pathways in suicide. Studies comparing suicides and control subjects report higher expression of serotonin 2A receptor (5-HT2A) genes in Brodmann area 11 in depressed suicides (7) and lower expression of the spermine/sperminidine N1-acetyltransference gene in the dorsolateral prefrontal cortex and motor cortex in both depressed and nondepressed suicides (8).

To date, candidate genes for suicidal behavior have been selected largely on the basis of established biological correlates of suicidal behavior and thus have focused primarily on the serotonergic system. Genes for the serotonin transporter, serotonin 1A (5-HT1A), serotonin 1B (5-HT1B), and 5-HT2A receptors; monoamine oxidase A (MAOA) (an enzyme responsible for the degradation of serotonin); and tryptophan hydroxylase (tryptophan hydroxylase 1 [TPH1], tryptophan hydroxylase 2 [TPH2] isoforms), the rate-limiting biosynthetic enzyme for serotonin, have been investigated with respect to suicidal behavior with suggestive but inconclusive results (see [6] for a review). Preliminary studies of the recently identified TPH2 gene link an intronic polymorphism to suicide and depression (9), although others find an association only with mood disorder and not independently with suicide (10). Meta-analysis of 14 5-HT2A receptor gene and 12 serotonin transporter promoter (*5-HTTLPR*) gene association studies found an association between the low-expressing alleles of the *5-HTTLPR* and suicide but no association for the 5-HT2A receptor 102T/C polymorphism (11). The noradrenergic and dopaminergic systems, hypothalamic-pituitary-adrenal (HPA) axis, and brain-derived neurotrophic factor have also been examined for candidate genes, with no consistent associations identified as yet (6).

Pharmacogenetic studies have examined the effect of genetic variants on treatment-emergent suicidal ideation, and a large multicenter treatment trial of major depression reported associations with *GRIK2* and *GRIA3* (encode ionotropic glutamate receptors), *IL28R* (encodes an interleukin receptor), and *PAPLN* (encodes a protoglycan-like sulfated glycoprotein) (12).

Association studies suggest that interaction between genetic vulnerability and environmental conditions increases risk for suicidal behavior. The lower-expressing allele of the *5-HTTLPR* appears associated with increased risk for depression and suicidality in response to stressful life events, though others have failed to replicate those findings (see [6] for a review). Adverse childhood experiences in conjunction with a lower-expressing variant of the *MAOA* gene contributed to the development of antisocial behavior and greater impulsivity (risk factors for suicidal behavior) in male subjects (13).

No single gene will explain complex multidetermined behaviors such as suicide and nonfatal suicide attempt. Thus, given likely gene-gene relationships, gene-environment interactions, and the multiple pathways resulting in suicidal acts, a more productive approach is to identify biological and clinical endophenotypes.

Defining Endophenotypes for Suicidal Behavior

Gottesman and Gould (14) have described an endophenotype as an internal phenotype between gene and disease. They stipulate five criteria for an endophenotype: 1) association with illness in population; 2) heritable (20% or greater); 3) primarily state-independent; 4) illness and endophenotype co-segregate within families (linkage of trait to gene variant); and 5) found in nonaffected family members more frequently than in the general population (14).

Proposed endophenotypes for suicidal behavior include impulsive-aggressive traits, early onset of major depression, neurocognitive function, and heightened cortisol response to social stress.

Impulsive and Aggressive Traits

Behavioral dysregulation is thought to characterize suicidal behavior, with traits of impulsivity and aggression being particularly salient because impulsiveness favors acting on emotions including anger and suicidal ideation. Psychological autopsy studies have found higher levels of aggression in individuals who die by suicide than in living psychiatric control subjects ([15] and [16]). Greater lifetime aggression is associated with nonfatal suicide attempts in prospective and cross-sectional studies (17), particularly attempts with higher medical lethality (18). The heritability of aggressive traits has been demonstrated, with studies of adult twins, using a variety of measures, reporting heritability of 40% to 47% ([19] and [20]). Aggression has a trait dimension (21). Family studies demonstrate co-segregation of the aggressive/impulsive endophenotype and suicidal behavior in families ([22] and [23]). Associations have been reported between aggressive/violent behaviors and genes related to the serotonergic system, including *5-HT1B* and *5-HT2A* receptors and *MAOA* ([24], [25] and [26]). Violent suicidal behavior and/or medical seriousness of suicide attempts are correlates of trait aggression and possibly associated with *5-HTTLPR* genotype and *TPH1* (6). There are no direct data available regarding frequency of trait aggression in nonsuicidal relatives compared with the general population, although the finding of higher levels of aggression in first-degree relatives of suicide completers than in first-degree relatives of control subjects (27) is suggestive.

Impulsivity has been associated with suicidal behavior in prospective and retrospective studies (see [16] for a review). Twin and family studies support the heritability of impulsivity, assessed using various personality trait scales ([28] and [29]) and laboratory behavior measures (30), with estimates of heritability between 30% and 45% ([28] and [29]). Impulsivity is understood to be a trait but is a multifaceted construct and likely the outcome of different underlying deficits. Impulsivity assessed using the Barratt Impulsivity Scale (BIS) has been associated with the *5-HT2A* gene in alcohol-dependent subjects (31) but not with *5-HTTLPR* (32). Behavioral indices of impulsivity, such as response initiation, response inhibition, and consequence sensitivity, may be more suitable endophenotypes, as they are more basic constructs and more reliably quantified through laboratory-based neuropsychological testing than self-report impulsivity scales that depend on recall and the nature of stressful events in the patient's life. Single nucleotide polymorphism studies have detected associations with measures of neuropsychological performance but not self-report scale scores (33) or with the hyperactive/impulsive clinical subtype in attention-deficit/hyperactivity disorder (ADHD) (34). Response initiation can be assessed by commission errors and has been shown to be related to suicide attempt history (35) and severity of attempt (36). Response inhibition can be measured with go-stop tests and has not yet been linked to suicidal behavior, although deficits in response inhibition appear to be associated with particular subtypes of impulsive aggression, for example, fighting in conduct disorder (37). Consequence sensitivity can be assessed with the delayed reward test and differentiates suicide attempters from nonattempters in self-injury patients (38).

There is some evidence of heritability and genetic association for behavioral measures of impulsivity. Commission errors have been shown to be heritable in family studies ([30] and [39]). Higher rates of commission errors were associated with the T allele in the *5-HT2A* T102C SNP (39) and the lower-expressing allele of the *5-HTTLPR* (M.A. Dawes, *et al.*, unpublished data, 2008). Polymorphisms in the dopamine D4 receptor gene have been associated with response inhibition, assessed by the stop task in healthy adults (33) and stop task and go/no-go in ADHD children (40). Dopamine transporter genotype has been

associated with response inhibition assessed by the Opposite World test in boys aged 6 to 11 (41) and the stop-signal task in healthy adults (33). Stop task scores varied by *TPH2* genotype in healthy college-age adults (42). Delayed reward, a measure of consequence sensitivity, is associated with a polymorphism in the dopamine receptor D2 subtype (DRD2) gene but not with clinical scale measures of impulsivity in healthy adults (43). Unaffected relatives, compared with control subjects, affected siblings, and unaffected siblings of ADHD patients, have response inhibition deficits in the stop-signal task (44). Unaffected relatives of obsessive-compulsive disorder (OCD) probands showed the same response inhibition deficits in the stop-signal task as probands compared with individuals with no family history of OCD (45). Thus, impulsivity appears to meet all five criteria for an endophenotype, assessed either using clinical instruments or neuropsychological tasks; however, additional studies are necessary to reproduce these findings in study samples ascertained based on suicidal behavior.

Early-Onset Major Depression

The association of early-onset major depression and suicidal behavior has been documented in clinical (46) and community (47) samples. In the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) treatment trial cohort, individuals with onset of major depressive disorder (MDD) before age 18 were three times more likely to report a suicide attempt than those with an onset after age 18, adjusted for duration of illness, current age, and gender (46). Family studies have shown early-onset major depression to be heritable (46), and a study of male twins estimated heritability of early-onset MDD (<age 30) at 47% (48). Early-onset MDD is a subtype characterized by a more severe course with greater chronicity and psychiatric comorbidity and poorer psychosocial function (49), thus meeting the trait criterion. Genome-wide linkage studies in affected family pedigrees or relative pairs with early-onset recurrent major depression identified linkage to chromosomes 15q, 17p, 8p, and 6p (50). The endophenotype criterion of greater frequency in unaffected relatives has not been investigated.

Neurocognitive Function

Suicidal behavior has been associated with altered neurocognitive function in multiple domains, including executive function, attention, verbal fluency, and decision making (see [50] for a review). Attentional deficits, such as impaired selective attention leading to difficulty in shifting attention from inappropriate stimuli and the inability to generate new solutions, may underlie the clinical observations of cognitive rigidity in suicidal individuals ([51] and [52]). Poorer performance in the Stroop Interference Test, which assesses selective attention, is found in high-lethality depressed suicide attempters compared with depressed low-lethality attempters, depressed nonattempters, and healthy control subjects (51). Moreover, selective attention toward suicide-relevant cues is demonstrated in suicidal individuals in a modified Stroop task ([53] and [54]). Attentional fixation is a related information-processing bias, characterized by agitation, narrowing of attention on suicide-specific cues, and a preoccupation with suicide as the only solution to one's problems (55). Twin studies in children and adults ([56] and [57]) indicate 39% to 50% heritability in Stroop Interference Test performance. In healthy subjects, the *DRD2* gene and the catechol-*O*-methyltransferase (*COMT*) valine (val)/methionine (met) polymorphism had an interaction effect on Stroop Interference Test performance (58). Other gene association studies of dopamine receptor genes and *COMT* in schizophrenia and/or ADHD subjects report genetic associations with various domains of cognitive function, including executive function, verbal and working memory, attention, and performance monitoring ([59] and [60]). Bipolar disorder individuals and their unaffected relatives exhibit impaired performances on tests of cognitive flexibility compared with healthy control subjects (61), and attention deficits (Stroop) are seen in schizophrenia (62) and bipolar disorder (63)

individuals and their unaffected relatives compared with healthy control subjects. Thus, attentional deficits meet the endophenotype criteria of association with illness, heritability, gene association, and greater frequency in unaffected relatives.

There is evidence of the persistence of cognitive deficits, including attention, verbal fluency, memory, and learning, after remission of depressive symptoms, indicative of trait status (64), although one study found executive dysfunction in suicide ideators to be state-related (65). For other domains of neurocognitive function, including memory, verbal fluency, and problem solving, association with suicidal behavior is suggested, but data regarding heritability and familial co-segregation are lacking.

Cortisol Response to Psychosocial Stress

Hypothalamic-pituitary-adrenal axis dysfunction is associated with suicide death, with dexamethasone nonsuppression of cortisol increasing risk for suicide more than fourfold in major depression (66). Disturbances in HPA axis function have been observed in suicide attempters using various indices, including cerebrospinal fluid (CSF) corticotrophin-releasing hormone (CRH), postdexamethasone cortisol, and urinary cortisol, though not all agree (67). Twin studies of cortisol levels in blood, urine, and saliva indicate approximately 60% heritability (68). A twin study of cortisol response to psychosocial stress (Trier Social Stress Test [TSST]) estimated heritability of cortisol response with repetition of the stressor between 56% to >97% (69). Altered HPA axis stress responsivity is a trait influenced by genes and adversity in early life (70). Cortisol response to psychosocial stress (TSST) appears associated with polymorphisms in the mineralocorticoid and glucocorticoid receptor genes (71), the *5-HTTLPR* (72), and the gamma-aminobutyric acid (GABA) A alpha 6 receptor gene (73). Studies are necessary to establish if the same deficits in cortisol response are more frequent in unaffected relatives of suicidal individuals compared with the general population.

Candidate Endophenotypes

Other biological and clinical factors associated with suicidal behavior are candidate endophenotypes. These meet the criteria of association with the disease but more work is needed to establish heritability, trait status, co-segregation in families, and gene variant associations.

Serotonergic System Alterations in Suicide and Nonfatal Suicide Attempt

Alterations in various indices of serotonergic function have been associated with suicide attempt and suicide (reviewed in Mann [74]). Studies of postmortem brain tissue of suicides may yield molecular endophenotypes for genetic studies of suicide death. Postmortem studies comparing suicides with nonsuicides have found death by suicide associated with low serotonin transporter binding in orbital prefrontal cortex and anterior cingulate, higher 5-HT1A and 5-HT2A receptor binding in the dorsolateral prefrontal cortex and 5-HT1A binding in the brainstem dorsal raphe nucleus, and higher transcript level, protein expression, and number of TPH2 expressing neurons in the brainstem (74). Evidence of genetic association with serotonergic alterations observed postmortem in suicides is sparse and inconclusive. Studies are necessary to establish if serotonergic alterations observed in suicides meet criteria of heritability, state-independence, and presence in nonaffected family members.

The level of CSF 5-hydroxyindoleacetic acid (5-HIAA) is a potential endophenotype, as lower levels have been associated with suicide attempt and suicide death across psychiatric disorders (75). In nonhuman primates, CSF 5-HIAA levels have shown trait characteristics (76). Heritability estimates in humans and nonhuman primates range from 25% to 50% ([77]

and [78]). Animal studies show CSF 5-HIAA is under genetic regulation (77), and in humans, studies of gene association and CSF 5-HIAA have been both positive (79) and negative (80). Further studies are necessary in humans to establish if nonaffected family members exhibit this anomaly more than the general population.

Imaging studies support the association of altered serotonergic function and suicidal behavior, reporting lower serotonin transporter binding in the frontal and midbrain regions in impulsive violent subjects (81). An inverse correlation between 5-HT1A binding in the orbital frontal cortex and aggression scale scores has been reported (82). Lower C-α-methyl-L-tryptophan trapping in the orbital and ventromedial prefrontal cortex was observed in high-lethality suicide attempters with a negative correlation with suicide intent (83). Serotonin 2A receptor binding also correlated negatively with levels of hopelessness, a correlate of suicide and suicide attempt (84). There have been no studies of heritability in imaging studies of serotonin (5-HT) and genetic association studies involving brain imaging are few and negative (85). The state-independent status of these indices is yet to be established, as is the frequency in nonaffected relatives.

Brain Structure and Function In Vivo

Alterations in resting condition brain blood flow and/or glucose metabolism have been associated with suicidal behavior and related clinical traits. Relative hypometabolism in high-lethality compared with low-lethality suicide attempters in ventral, medial, and lateral prefrontal cortex become more marked with administration of the serotonergic agonist fenfluramine (86). Impulsivity correlates with bilateral hypometabolism in the medial frontal cortex (87) and reduced perfusion in the right side frontotemporal cortex (88). Likewise, impaired frontal perfusion and metabolism are consistent with cognitive deficits, including reduced executive function, and verbal fluency correlates positively with regional cerebral glucose metabolic rates (rCMRGlu) in the same brain regions that differ between high-lethality and low-lethality suicide attempters (86). Blunted prefrontal perfusion is related to poorer verbal fluency in suicide attempters compared with control subjects (89). The heritability of altered brain structure and function has not been investigated in imaging paradigms nor has state-independence, co-segregation in families, or frequency in nonaffected family members.

Second Messengers

Alteration in markers of second messenger function is another potential biological endophenotype for suicide death. Several markers have been shown to be altered in teenagers and/or adults who died by suicide, including glycogen synthase kinase-3β (GSK-3β), an important component of the Wnt signaling pathway (90); protein and messenger RNA (mRNA) expression of protein kinase C (PKC) isozymes, protein kinase PKCα, PKCβ, and PKCγ (91); transcription factors, including cyclic adenosine monophosphate (cAMP) response element binding (CREB) and brain-derived neurotrophic factor (BDNF) ([92] and [93]); and lower tyrosine receptor kinase B (TrkB) mRNA and protein levels have been found in prefrontal cortex and hippocampus of suicides (94). It remains to be determined whether these alterations meet the other criteria for endophenotype, as there are no data available as yet regarding their heritability, trait status, co-segregation in families, or frequency in nonaffected relatives.

Borderline Personality Disorder

Borderline personality disorder (BPD) is characterized by a high rate of suicide, suicide attempt, and other self-harm behavior. In twin studies, the heritability of BPD is reported in the range of 35% to 60% (95) and family studies also provide support of heritability of both the diagnosis and of symptom clusters (96).

Three main BPD symptom clusters that may yield useful endophenotypes are 1) disturbances in interpersonal relatedness, characterized by interpersonal deficits and dysfunction and an overreliance on others to maintain a sense of self; 2) behavioral dysregulation, characterized by impulsivity, self-injury, and suicidal behavior; and 3) affective dysregulation, characterized by affect lability and intense emotional reactions. For the first cluster, a potential endophenotype is interpersonal reactivity, which can be assessed by measures of rejection sensitivity or in functional magnetic resonance imaging (fMRI) paradigms assessing trust but has not yet been investigated with respect to the five criteria for an endophenotype. The second cluster is behavioral dysregulation, described earlier as the impulsive aggression endophenotype. For the third cluster, affect dysregulation, emotional or pain sensitivity is a potential endophenotype that can be assessed though social stress paradigms, including examining biological indices such as HPA axis dysfunction, opioid dysfunction, and/or autonomic dysfunction. Higher cortisol response to the Trier Social Stress Test was observed in comorbid BPD and MDD suicide attempters compared with MDD-only suicide attempters (Barbara Stanley, Ph.D., unpublished data, 2008). Twin studies of borderline personality traits report a 45% heritability of affective lability (96), but there are no data on co-segregation in families or frequency in nonaffected relatives.

A summary of proposed and candidate endophenotypes for suicidal behavior appears in Table 1.

Genetic Studies–Other Considerations

Epigenetics

Genetic impact on suicidality may not just be a matter of a direct generation-to-generation transmission of vulnerability genes. Familial transmission may also occur in the context of early-life environment effects on epigenetic mechanisms resulting in altered neurobiological function. Evidence that epigenetic factors play a role in psychiatric disorders includes discordance in monozygotic (MZ) twins and discordance for psychiatric illness in twins being associated with differential DNA methylation (97). Epigenetic events alter expression for different copies of the same gene in a given cell nucleus. Methylation of parts of DNA mostly blocks transcriptional factors from gaining access to the gene and thus effectively silences expression of the gene. This is a stable epigenetic modification that is maintained after cell division and is the means by which cellular differentiation occurs during development. Microarray SNP chips allow for whole-genome DNA methylation profiling in human tissues, including brain, and can provide data on total and allele-specific methylation that can then be examined for disease-related aberrations.

Animal studies can examine environmental, genetic, and behavioral circuitry, and in rodents there is clear evidence for the effects of early environment on gene expression (98). For example, differences in maternal behavior (licking and grooming) result in alterations in HPA axis response to stress, one of the candidate endophenotypes, in offspring (99) and in differential methylation of the noncoding glucocorticoid receptor promotor region 1_7 in hippocampal tissues in adult offspring (100).

Methodological Issues

Identifying endophenotypes for suicidal behavior may address some difficulties related to heterogeneity and complexity of the phenotype; however, there remain substantial methodological challenges in identifying relevant genes and elucidating their causal pathways.

Gene expression array data sets are enormous. False discovery rate corrections are often too stringent, and real findings can be missed (type 2 error). Verifying positive findings by a

second assay method such as in situ hybridization histochemistry is one safeguard, and better statistical methods offer another approach. Type 2 error is also an issue in SNP association studies, even where polymorphisms have established functional effects, i.e., val/met in COMT, where the small difference in frequencies between affected and nonaffected groups means large sample sizes are required to detect any effect. Even in relatively large homogenous samples, it can be difficult to detect an effect; for example, a Finnish study of 2000 families with schizophrenia found heritability of 54%, but despite examining 317,000 SNPs and characterizing the genome so precisely that individuals could be identified by village of origin, no locus was significant for schizophrenia (101).

Conclusions

Given the heritability of suicidal behavior, more knowledge of the risk and/or protective genes would be valuable in the identification of high-risk individuals and the development of treatment interventions. Discovering the relevant genes and their biological role in complex and multidetermined phenotypes such as suicide and attempted suicide is a challenge. However, advances in clinical and biological understanding of suicide and attempted suicide and methodological and technical developments in genetic studies assist in this task. Moving from broad end point phenotypes to more specific narrower endophenotypes is one approach. Several promising endophenotypes that largely meet the criteria of Gottesman and Gould (14) include impulsive-aggressive traits, early-onset major depression, neurocognitive function, and increased cortisol response to social stress. Systematic genetic studies of these endophenotypes are proposed using genome-wide structural and expression arrays and superimposed mapping of methylation sites. Other potential candidate biological and clinical endophenotypes have been identified, based largely on association with the phenotype. For these, studies are needed to establish that they can fulfill the criteria for endophenotype. The heritability of suicidal behavior is comparable with major psychiatric disorders and warrants a comparable effort to identify the responsible genes. Such studies will require large sample sizes, and the National Institute of Mental Health (NIMH) Center for Collaborative Genetic Studies is an important resource (http://nimhgenetics.org/).

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Table 1

Proposed and Candidate Endophenotypes for Suicidal Behavior

	Endophenotype Criteria				
	Association with Suicidal Behavior	**Heritability (>20%)**	**State- Independent**	**Cosegregate in Families (Gene Association)**	**More Frequent in Nonaffected Relatives**
Endophenotypes					
Aggression/impulsivity	YES	YES	YES	YES	YES
Early-onset major depression	YES	YES	YES	YES	No data
Neurocognitive function	YES	YES	YES	YES	YES
Cortisol stress response	YES	YES	YES	YES	No data
Candidate Endophenotypes					
5-HT in postmortem brain	YES	No data	No data	Insufficient data	No data
CSF 5-HIAA	YES	YES	YES[a]	Insufficient data	No data
5-HT in vivo (imaging)	YES	No data	No data	No data	No data
Brain imaging (rCMRGlu)	YES	No data	No data	No data	No data
Second messengers	YES	No data	No data	No data	No data
BPD					
Interpersonal reactivity	No data	YES	YES	No data	No data
Affect dysregulation	YES	YES	YES	No data	No data

BPD, borderline personality disorder; CSF, cerebrospinal fluid; 5-HIAA, 5-hydroxyindoleacetic acid; 5-HT, serotonin; rCMRGlu, regional cerebral glucose metabolic rates.

[a]Animal studies.

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