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ARTICLE

Personality Traits as Intermediary Phenotypes in Suicidal Behavior: Genetic Issues

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A genetic contribution to the risk of suicidal behavior is now supported by many studies. It probably involves specific factors acting on their own, independently of the genetic transmission of associated psychiatric disorders. A history of childhood maltreatment, adverse events, psychosocial stress, psychological traits and major psychiatric disorders all appear to contribute to the global risk of suicide attempt or completion. The interplay between previously identified risk factors, different as they are in nature and degree of complexity, still remains to be clarified. A stress-diathesis model has been proposed, where trait-like genetic and developmental risk factors (the diathesis) interact through still unknown mechanisms with actual (stress-related) factors to create the conditions for a suicidal gesture. Disentangling the effects of these risk factors, and specifically the effects of the genetic factors influencing these different pathological conditions, appears to be a difficult task. Indeed the results of candidate gene association studies suggest that genetic vulnerability factors for various related psychiatric phenotypes (major psychiatric disorders and personality traits) partly overlap with more specific factors predisposing to suicidal behavior. Personality traits are partly under genetic control and may be closer to the genetic effects than psychiatric syndromes. We review here the available data on the genetics of personality traits presumably involved in suicidal behavior, focusing on the association studies carried out with serotonin-related genes. We suggest that future studies on the genetic vulnerability to suicidal behavior should include the investigation of endophenotypes, with the aim of deciphering the mechanisms underlying the genetic susceptibility to these closely associated phenotypes.

KEY WORDS: suicide; personality traits; genetics; serotonin

INTRODUCTION

Family, twin, and adoption studies have been concordant in suggesting the implication of genetic factors in suicide [Roy et al., 1997; Brent and Mann, this issue], and there is now strong evidence that these factors could act independently of the genetic background of associated psychiatric disorders. The existence of a genetic component for suicide independent of the genetic transmission of any associated psychiatric disorder raises new questions in the field. What is the nature of the specific vulnerability factors for suicidal behavior and how do they increase the risk? This review examines the possibility that genes contributing to the shaping of personality traits are involved in the transmission of vulnerability factors for suicidal behavior. Indeed, studies of identical and fraternal twin pairs reared together [Eaves et al., 1989] and apart [Tellegen et al., 1988; Bouchard et al., 1990], as well as studies of adoptees and their relatives [Loehlin et al., 1981], have produced results that support an important genetic contribution to personality differences in adults. Thus suicidal behavior and personality traits appear to be influenced to some extent by genetic factors and these phenotypes possibly share some common genetic vulnerability factors.

Suicidal behavior and personality traits possibly share some common genetic vulnerability factors.

We first discuss the relationship between personality disorders (PDs) and suicidal behavior, highlighting some specific aspects of suicide attempts in these disorders. Then we review the main personality dimensions associated with suicidal behavior and the molecular genetic studies carried out on particular traits, as far as they relate to suicide.

COMORBID PSYCHIATRIC-PERSONALITY DISORDERS AND SUICIDAL BEHAVIOR

PDs are widely recognized as increasing the risk of suicide attempt or completion, independently of the presence of any Axis I diagnosis (for a recent review, see Mehlum [2001]). The presence of a comorbid Axis I disorder, mainly major depressive disorder (MDD) and substance use disorder, increases the risk of suicide attempts (or completions) still more [Yen et al., 2003]. In fact, at the time of a suicidal act, comorbid Axis I disorders are very often, if not always, present in PD patients [Isometsa et al., 1996].

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In a recent work by Hawton et al. [2003], patients hospitalized after a suicide attempt were assessed for the presence of psychiatric and PDs according to ICD-10 criteria (PDs were diagnosed at a follow-up interview, 12–20 months after study inclusion, with the self-report version of the Personality Assessment Schedule). Subjects with comorbid psychiatric and PDs (44%) had a greater frequency of multiple attempts and showed a trend for more parental suicidal behavior.

In a follow-up study, a comorbid PD was found to be associated with an increased suicidal vulnerability in major depressed patients, particularly those presenting the non-melancholic subtype of depression [Hansen et al., 2003].

Major Axis I psychiatric disorders (anxiety, mood, eating, disruptive, and substance use disorders), PDs, suicidal ideation, and behavior were assessed in a prospective study on a community sample of 717 youths when they were adolescents and some years later when they were young adults. Adolescents with PDs were at elevated risk for major mental disorders and suicidal ideation or behavior during early adulthood [Johnson et al., 1999a].

Among the different categories of DSM-IV PDs, borderline personality disorder (BPD) and antisocial personality disorder (APD) are the most frequently associated with attempted and completed suicide. A comorbidity with major depression and/or addiction is frequently found in BPD and APD patients, substantially increasing the risk of suicide. Indeed, some, but not all, of the studies examining the issue of comorbidity of MDD and PD reported an increased mortality rate of suicide [McGlashan, 1986] and an increase in the seriousness and frequency of suicide attempts [Corbitt et al., 1996] among BPD patients.

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BPD and APD patients are both characterized by a high rate and wide diversity of impulsive behaviors. Indeed, impulsivity is a core psychopathological feature of BPD [Links et al., 1999] and has been identified as a risk factor for suicidal behavior in BDP patients [Soloff et al., 1994]. Another study found impulsivity to be the only BPD characteristic associated with a higher number of suicide attempts, after controlling for diagnoses such as depression and substance abuse [Brodsky et al., 1997]. The latter work also found an association between childhood abuse and the number of lifetime suicide attempts.

Soloff et al. [2000] compared the characteristics of suicide attempts in patients with BPD, MDD, and comorbid BPD plus MDD, with the aim of determining if specific aspects of core psychopathology predicted the number or the characteristics (lethality, planning, violence of the method) of the attempts. The authors found no difference in the characteristics of the suicidal gesture, but BPD patients with comorbid MDD had an increased number of suicide attempts and the highest level of planning. They conclude that MDD-BPD comorbidity increases the number and seriousness of suicide attempts, and also that hopelessness and impulsive aggression independently increase the risk of suicidal behavior in both groups of patients. Although objective planning seems at first sight inconsistent with impulsivity, the authors rightly highlighted that these characteristics are not mutually exclusive. In fact, a planned suicide can be acted on impulsively.

In contrast with the abovementioned study, a work by Horesh et al. [2003] showed marked differences in the characteristics of suicidal behavior in adolescent inpatients according to their diagnosis. BPD patients had more anger, aggression, and impulsiveness than those with MDD. Moreover, suicidal BPD adolescents were more impulsive than non-suicidal BPD adolescents. Impulsiveness and aggression correlated significantly and positively with suicidal behavior in the subjects with BPD, but in MDD adolescents, no such correlations were found.

Psychosis, and particularly schizophrenia, is known to be associated with a high rate of suicide attempt and completion, but the role PDs could play to increase the risk of suicide in these conditions is a complex topic. Worth mentioning here that a prospective study by Moran et al. [2003] purporting that comorbid PD—assessed by administration of the PAS-R, a rapid screening instrument focusing on pre-morbid personality—was independently associated with an increased risk of suicidal behavior in a sample of community-dwelling patients with psychosis. This association was independent of the effects of other risk factors.

Personality disorder may also create a suicide risk when co-occurring with disorders that do not by themselves comport a serious risk, as seems to be the case according to a study on panic-agoraphobia patients with cluster B and C PDs [Starcevic et al., 1999].

Finally, alcohol abusers or alcohol-dependent subjects, who are at elevated risk of suicidal behavior (for a recent review, see Hufford [2001]), frequently show PDs, mainly APD [Mulder, 2002]. Although the intricate relationships and the causal links between alcohol abuse and/or dependence, personality traits and suicidal behavior are not clearly understood and still a matter of debate, impulsive and aggressive traits are probably key common predisposing factors [Koller et al., 2002; Sher et al., 2003; Conner and Duberstein, 2004].

PERSONALITY TRAITS RELATED TO SUICIDAL BEHAVIOR

Categorical (DSM-IV or ICD-10) PDs, particularly cluster B PDs, appear to significantly increase the risk of suicide attempts or completions through the behavioral or psychological effects of particular personality traits or dimensions.

Indeed, some personality-related characteristics have hypothetically been related to suicidal behavior. Among the most studied are aggressive-impulsive traits, neuroticism and anxiety-related traits, and anger-related traits, which are all partly under genetic control. Other studies suggest that the personality dimensions or behavioral traits of hopelessness, self-esteem, problem-solving, and decision-making play a role in increasing the risk for suicide, but until now a genetic component for these traits has not been demonstrated (with the possible exception of a few works suggesting a genetic basis for self-esteem). Nevertheless, decision-making capacity, which has been shown to strongly depend on emotional information processes implemented in the orbitofrontal cortex [Bechara et al., 2000; Bechara, 2004] and to be affected in violent suicide attempters [Jollant et al., 2005], could well prove to have a heritable component through the genetic make-up of the prefrontal cortex.

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Impulsivity

Impulsivity is a partly heritable personality trait, as revealed by numerous family, twin, and adoption studies. Indeed, behavior-genetic studies have assessed genetic and environmental influences on measures of impulsivity and found discrepant values (heritability estimates for impulsivity varied from 0.30 to 0.45) according to the methods used (twins reared together and apart, family or adoption studies [Seroczynski et al., 1999]). Genetic and environmental influences on the phenotypic relationship between impulsivity and aggression (assessed with the Barratt Impulsiveness Scale and the Buss-Durkee Hostility Inventory) were studied in MZ and DZ pairs [Seroczynski et al., 1999]. The authors concluded that there are more overlapping genetic and environmental influences accounting for the relationship between irritability and impulsivity than between direct assault and impulsivity, and that the genetic and environmental influences contributing to impulsivity are shared with those contributing to reactive (or irritable) aggression.

Impulsivity is a complex and probably heterogeneous trait [Evenden, 1999; Moeller et al., 2001; Swann et al., 2002]. For instance, a study on the biological parents of adolescent inpatients with disruptive behavior disorders (oppositional defiant disorder, conduct disorder, and attention-deficit/hyperactivity disorder) investigated two models of laboratory impulsivity, rapid response impulsivity (the inability to conform responses to environmental context), and reward-delay impulsivity (the inability to delay reward) and found the former more strongly related to impulsivity as a personality characteristic [Swann et al., 2002]. Evenden [1999] highlighted that a behavioral pattern develops through different stages—preparation, evaluation, and outcome—involving various cognitive and behavioral processes and probably also different brain anatomical areas and neurotransmitter systems. Hence impulsivity is probably a multifactorial construct with a complex biological basis.

In spite of the uncertainties on the concept, impulsivity and/or impulsive aggression have been strongly associated with central 5-HT activity. Correlations have repeatedly been found between impulsive/aggressive traits and various indices of 5-HT functioning. Indeed cerebrospinal fluid 5-hydroxyindoleacetic acid (CSF 5-HIAA) concentrations, 5-HT pharmacological challenges, platelet 5-HT receptor, and 5-HTT binding studies have stressed the role of a dysfunctional 5-HT activity in aggressive and impulsive traits, in suicide attempters as well as in violent offenders [Coccaro et al., 1989; Linnoila and Virkkunen, 1992]. A study by Coccaro et al. [1989] demonstrated that impulsive aggression correlates with a low serotonergic activity in PD patients, particularly in those having made a suicide attempt. More precisely, a reduced central 5-HT function was present in a subgroup of patients with MDD and/or PD, and associated with a history of suicide attempt in patients with either disorder, but with impulsive aggression in patients with personality disorder only.

A recent study on BPD inpatients [Hansenne et al., 2002] showed a blunted prolactin (PRL) response to flesinoxan (a more specific 5-HT agent than fenfluramine) challenge, even after controlling for MDD comorbidity. Notably, these responses were still lower in BPD inpatients with a history of suicide attempts.

Studies more specifically devoted to suicide attempts have also associated impulsive behaviors with indices of altered 5-HT functioning. The low CSF 5-HIAA level found in suicide attempters was related to their impulsiveness, assessed by interview-based rating [Cremniter et al., 1999]; in homicide offenders, it was associated with impulse control disorder and suicide attempts [Lidberg et al., 2000]. Another study found that among suicide attempters, subjects described as "impetuous, desperate, and ambivalent" had lower whole blood 5-HT content than those described as "appealing" [Rilke et al., 1998]. In alcohol-dependent subjects, impulsive and aggressive traits might contribute significantly to the risk of suicide attempts [Koller et al., 2002]. A recent study by Brent et al. [2003] on high-risk subjects, comparing mood disorder patients with and without suicide attempts and considering the existence of suicide attempts in siblings, suggests that the familial transmission of impulsive aggression should mediate the rate of transmission and age of onset of suicidal behavior.

Thus impulsivity has been widely investigated in relation to suicidal behavior and there is now much evidence to

consider that it is an important predisposing trait in at least a subgroup of suicidal subjects. However, some important questions are still being debated, notably if impulsivity is more closely related to suicide attempts than to suicide completions, and if it could increase the risk of suicidal behavior independently of aggressive traits.

Neuroticism and Anxiety-Related Traits

There is a well-established association between the personality trait neuroticism and negative affectivity [Costa and McCrae, 1980; Larsen and Ketelaar, 1991], and although the overlap between neuroticism and depressive symptoms makes it difficult to determine whether it represents a vulnerability trait for depressive illness or the consequence of past depressive episodes, family studies suggest that elevated neuroticism scores may be a vulnerability factor for MDD [Duggan et al., 1995].

A substantial proportion of the variation in neuroticism scores is accounted for by genetic effects. Estimates of the heritability of neuroticism are usually between 40% and 45% [Loehlin, 1992], and the concordance of monozygotic twins reared apart is much less (0.38 vs. 0.46) than that of monozygotic twins reared together, indicating a strong environmental component [Goldberg, 2001]. The heritability of individual differences in neuroticism (emotional instability) has been supported by twin studies, and a recent work based on a large sample (n = 45,850) of members of extended twin kinships unambiguously demonstrated that a simple genetic structure underlies familial resemblance for this personality trait [Lake et al., 2000].

Quantitative genetic analysis of personality has also revealed a complex relationship between gender and neuroticism [Fullerton et al., 2003]: some studies found evidence of gender-specific genetic factors for neuroticism [Eaves et al., 1989; Martin et al., 2000; Fanous et al., 2002], while others did not [Lake et al., 2000]. Indeed, in a clinical population, neuroticism as assessed by the NEO-PI-R was positively related to suicidal ideation in females (particularly the *angry hostility* and *depression* facets) but not in males (in the same study in males the *conscientiousness* factor of the FFM was negatively associated with suicidal ideation, more specifically the *self discipline* facet) [Velting, 1999].

Roy tested the hypothesis that inherited personality vulnerability may be a way in which patients with a family history of suicide are at increased risk for suicidal behavior. In a study [Roy, 2002] comparing patients with or without a family history of suicide, the difference for Eysenck Personality Questionnaire (EPQ) neuroticism scores became significant when the personal history of suicide attempts was also taken into account: patients with such a history scored higher for neuroticism.

The anxiety-related temperamental dimension of harm avoidance, as measured by the Temperamental and Character Inventory [Cloninger et al., 1993], shows considerable overlap with neuroticism [Heath et al., 1994; De Fruyt et al., 2000]. Harm avoidance is a partly heritable temperamental dimension (50% of the total variance is from genetic origin) measuring anxiety proneness and hypothetically related to central 5-HT system activity. This functional link has been supported by a number of neurochemical studies, and a substantial work has been devoted to association studies between harm avoidance and 5-HT-related genes, providing inconsistent and controversial results.

Since Lesch et al. [1996] first reported an association between the short variant of the promoter region of the *5-HTT* gene and anxiety-related traits, numerous candidate gene association studies, with either the same gene or other *5-HT*-related genes, have provided conflicting results, raising complex methodological issues. A recently published meta-analysis of 26 studies on the association between trait anxiety and the *5-HTT* gene-linked polymorphic region (*5-HTTLPR*) does not provide support for a relationship between the short allele of the *5-HTTLPR* and trait anxiety. Interestingly this work revealed the importance of the instrument used to measure personality traits: a small positive effect of 5-HTTLPR appeared when anxiety-related traits are characterized with the neuroticism scale of the FFM, but not with the harm avoidance construct of the TCI [Schinka et al., 2004]. Another recent work indicates that taking into account the categorical Axis II diagnosis could help clarify these apparently contradictory results. Indeed, the association between anxiety-related traits and 5-HTTLPR does not appear to be a general one, but to be more pronounced within a subgroup of patients with a cluster C PD, as opposed to cluster B patients [Jacob et al., 2004].

A genome-wide scan for personality traits carried out by Cloninger et al. [1998] detected significant linkage between the HA dimension and a locus on chromosome 8p21-23, as well as other epistatic loci. This result was recently confirmed in an independent sample of 384 sibling pairs of Ashkenazi and non-Ashkenazi Jews [Zohar et al., 2003], which found evidence for a linkage to HA at locus 8p21-23.

Aggression and Anger-Related Traits

Aggression and anger-related traits are considered risk factors for suicidal behavior [Mann et al., 1999]. Anger can be conceptualized as a core construct of related traits or variables inwardly and/or outwardly expressed such as aggression, rage, and hostility [Spielberger et al., 1985]. A twin study [Cates et al., 1993] on hostility-related emotions, attitudes, and behaviors found evidence of significant heritability on the measure of trait anger. Studies with suicidal and non-suicidal psychiatric patients suggest that anger traits and high impulsivity synergistically contribute to increase the risk of suicide [Horesh et al., 1997]. Few molecular genetic studies have been conducted on anger-related traits either in control or in clinical populations.

In a non-patient sample of community-derived volunteers, persons possessing one of the two alleles of an intronic polymorphism in the *TPH* gene (the A218C U-allele) scored significantly

higher on measures of aggression and unprovoked anger than individuals homozygous for the L-allele. Additionally, they more often reported expressing their anger outwardly [Manuck et al., 1999]. Aggression and anger traits were assessed with the Life History of Aggression Scale (LHA), the Buss-Durkee Hostility Inventory (BDHI), and the State-Trait Anger Expression Inventory (STAXI). The same group also found an association between a VNTR regulatory polymorphism in the promoter region of the gene for monoamine oxidase A (MAO-A), inter-individual variability in aggressiveness, and impulsivity and central nervous system 5-HT response in a non-patient sample of 110 men [Manuck et al., 2000].

Another study on adult males derived from a non-patient community sample assessing fenfluramine-induced prolactin (PRL) responses, LHA scores, and a functional polymorphism in the promoter region of the *MAO-A* gene found greater LHA scores (reflecting a higher rate of aggression) and diminished central 5-HT responsive among men possessing "high transcription" alleles compared with "low transcription" alleles [Manuck et al., 2002].

The association of aggression, irritability, and anger-related traits with two single nucleotide polymorphisms (SNPs) located on the *TPH* gene (A218C and A779C) was studied in a group of community-derived volunteers without mental disorders and compared with a group of suicide attempters [Rujescu et al., 2002]. A218 and A779 alleles (U-allele in the study) carriers in both groups showed higher scores for state anger, trait anger and angry temperament, and an interactive effect of genotype and diagnosis was found, the U-allele having a greater effect on anger in the group of suicide attempters.

We studied the same SNP (*TPH* A218C) in two different populations of suicide attempters and a control group and did not replicate these results. Among the different subscales of the STAXI, we only found an effect of *TPH1* genotype on the "anger out" factor (outwardly expressed anger) (unpublished results).

Aggressive and anger-related traits in suicide attempters and control subjects have also been investigated in relation to a functional COMT polymorphism [Rujescu et al., 2003a]. As the low-activity genotype (LL) was over-represented in violent suicide attempters, the authors speculate that this polymorphism may modify the phenotype of suicidal behavior rather than the susceptibility to suicidal behavior itself. Furthermore, they suggest that the COMT genotype could differentially affect outwardly and inwardly directed aggressive behavior.

Hopelessness and Helplessness

Suicidal behavior is associated with hopelessness (more than with the severity of depression) [Pollock and Williams, 2004]. In elderly patients, a high degree of hopelessness persisting after remission of depression is associated with a history of suicidal behavior and may also lead to future suicide attempts or completions [Rifai et al., 1994]. In schizophrenic patients, hopelessness was found to be the principal predictor of suicidality [Kim et al., 2003].

Higher levels of hopelessness, higher scores on the TCI dimensions harm avoidance, and self-transcendence (and lower scores on self-directedness and cooperativeness) were reported in suicide attempters when compared with normal controls [van Heeringen et al., 2003]. In this study, prefrontal 5-HT2A receptor binding correlated negatively with harm avoidance and hopelessness, and the level of hopelessness correlated positively with the score on harm avoidance.

Self-Esteem

Low scores on self-esteem, defined as the affective and evaluative appraisal of the self, have been associated with depression and suicidality, as well as with personality functioning [Daskalopoulou et al., 2002; Neiss et al., 2002].

Behavioral genetic studies (reviewed in Neiss et al. [2002]) suggest that genetic influences on self-esteem are very substantial, and shared environmental influences minimal. Roberts and Kendler [1999] found that the covariance between self-esteem, neuroticism, and depression could be entirely explained by genetic influences common to all three and they concluded that the personality construct *neuroticism* was a better index of risk for depression in women than low self-esteem. Analyzing data from the National Comorbidity Survey to determine associations among neuroticism, self-esteem, sociodemographic variables, and depression disorder, Schmitz et al. [2003] found that both traits were strongly associated with past-year depression disorders, and concluded that their assessment may shed some light on the understanding of the relationships between personality and depression.

To our knowledge, no molecular genetic studies on self-esteem have been published, and there are no data on candidate genes in suicidal studies taking self-esteem into account.

Problem-Solving and Decision-Making

Studies on cognitive processes in suicide attempters suggest that ineffective problem-solving is linked to altered autobiographical recall, leading to difficulties in finding solutions to problematic interpersonal situations. [Pollock and Williams, 2001]. Until now, this cognitive psychological component of suicidal behavior has not been linked with a neuroanatomical or neurobiological basis.

Decision-making in suicidal behavior has been studied with the gambling test. A complex pattern emerged from a first study between 5-HT genes and the scores for this task exploring orbital prefrontal function [Jollant et al., in press].

Childhood Trauma, PDs, and Suicidal Behavior

Among the various stress-related factors increasing the risk of suicidal behavior, a history of childhood abuse or neglect appears to play an important role.

In many clinical and community studies, childhood abuse or neglect has

been associated with PDs and with elevated PD symptoms in early adulthood. Some of these studies have suggested the possibility of specific and differential associations between the type of maltreatment (physical abuse, sexual abuse, affective or physical neglect) and PD symptoms or diagnosis [Johnson et al., 1999b, 2000; Battle et al., 2004]. Indeed, the strong association between BPD and childhood sexual abuse is now well documented. The severity of sexual and other forms of abuse may play a role in the symptomatic severity and psychosocial impairment characteristic of BPD [Zanarini et al., 2002]. Roy [2001] suggested that a history of childhood trauma might be determinant of the personality dimension "hostility" in abstinent cocaine or opiate dependent patients.

Nevertheless many questions subsist on the nature of the mechanisms behind the associations between personality traits and childhood maltreatments, particularly on the role played by biological diatheses in the development of PDs in abused or neglected children.

Childhood physical and sexual abuse also dramatically increase the risk of suicide and suicide attempts in adolescents and adults [Dube et al., 2001]. In a community sample of women meeting criteria for MDD (n = 347), a close association was found between a history of childhood physical abuse and suicidal ideation, but not with suicide attempts, which were more strongly linked to psychiatric comorbidity [McHolm et al., 2003]. Childhood trauma may be a determinant of the age of onset of suicidal behavior and of the number of suicide attempts [Roy, 2004], and abuse in childhood may constitute an environmental risk factor for the development of trait impulsivity and aggression as well as suicide attempts in depressed adults [Brown et al., 1999; Brodsky et al., 2001]. It is worth mentioning here that childhood abuse often leads to the development of a persistent stress reactivity [Heim et al., 2000].

If maltreated children are at higher risk to develop antisocial behavior and to become violent offenders, large differences exist, nevertheless, among children in their response to maltreatment: the majority do not become delinquents or criminals. An interesting work by Caspi et al. [2002] demonstrated that genetic factors can moderate the effects of maltreatment: a functional polymorphism in the *MAO-A* gene modifies the influence of maltreatment on children's development of antisocial behavior. Such a study design is able to reveal the interplay between genetic risk (or protective) factors and developmental and environmental hazards.

SYNTHESIS AND DISCUSSION

The contribution of genetic factors to psychiatric disorders, to personality and temperamental traits, and to suicidal behavior is now well established by many convergent studies, although the precise links between any particular gene variant and each of these multi-determined clinical traits are still to be discovered. Today there is no clear picture convincingly explaining how an altered serotonergic activity could influence such complex behavior as attempted or completed suicide. Disentangling the relationships between genetic factors for psychiatric disorders, for suicidal behavior, and for personality and temperamental traits appears to be a difficult challenge. Each of these disorders or traits is uniquely related to various genetic influences, some of them being linked to inter-individual variations in the genetic control of the serotonin general turnover and local neuroanatomical 5-HT activity. How can we decipher the intricate overlap of these variables?

Personality traits or dimensions are among the main risk factors influencing vulnerability to suicidal behavior (together with a family history of suicide, a personal history of childhood maltreatment or sexual abuse, and a comorbid Axis I disorder, particularly MMD and addiction). According to different models of personality description, traits are diversely associated with a small number of (super)factors. Neuroticism (one of the three main factors in Eysenk's model or one of the five factors in the FFM) and harm avoidance (one of the four heritable temperamental dimensions in Cloninger's model) are among the most widely investigated personality dimensions in relation to suicidal behavior, and their genetic basis is the subject of a growing number of studies in both clinical and control populations. As these two largely overlapping dimensions influence the vulnerability to Axis I disorders (particularly affective disorders and substance use disorders) and to suicidal behavior, their specific role still remains elusive.

As clinical phenotypes, personality traits or dimensions are less complex than psychiatric disorders or integrated behaviors, and thus, in some ways, they are easier to operationally define and characterize. That is to say, neuroticism, anger traits, harm avoidance and anxiety-related traits, impulsivity, and/or impulsive aggression can be perceived as intermediary phenotypes, possibly predisposing through various mechanisms to suicidal behavior. Indeed, personality traits or related constructs are certainly constituted of a smaller number of functional elements than psychiatric disorders or complex behaviors, and therefore easier to deconstruct into their basic components. They are probably phenotypically less complex and more homogenous than syndromal disorders, but their genetic transmission, at least when globally characterized by self-report procedures, still remains a complex one.

In studies on the genetics of suicide and personality dimensions, impulsivity was until now almost exclusively investigated by means of self-report questionnaires, which may confound different constructs of varying influence on personality traits and/or behavioral patterns. Impulsivity being a heterogeneous construct, its characterization in future studies will require laboratory investigations in addition to the use of self-report questionnaires. In fact, psychophysiological measures and/or cognitive assessments may well become endophenotypes for personality traits and suicidal behavior.

In the process of deciphering the genetic underpinnings of neuropsychiatric diseases or complex behaviors,

investigating endophenotypes has emerged as a promising strategy, with the aim of reducing the complexity of phenotype and genetic analyses [Gottesman and Gould, 2003] by decomposing complex behaviors into more fundamental components. Endophenotypes have been proposed in the genetic study of schizophrenia (P50 suppression, eye-tracking dysfunction, prepulse inhibition, working memory deficits) and possibly in bipolar disorder (circadian rhythms, behavioral responses to psychostimulants, and other medications such as lithium, response to sleep deprivation) [Lenox et al., 2002]. In BPD, the "go/no go" versions of the Continuous Performance Task (CPT) and the Point Subtraction Aggression Paradigm (PSAP) are laboratory paradigms discriminating aggressive individuals from comparison groups, but proof of their heritability is still required before they can be introduced in endophenotypic approaches [Siever et al., 2002].

Candidate endophenotypes for personality traits are information processing speed in relation to impulsivity and inhibitory control and the above-mentioned measures for BPD (CPT and PSAP) in relation to anger-trait and aggression dyscontrol.

A paradigm in which genetic factors would influence the development of personality traits or dimensions, which in turn might predispose to suicidal behavior at times of stress or when individuals are suffering from an Axis I psychiatric disorder, could be a heuristic one.

From a genetic perspective, categorical (DSM-IV or ICD-10) PDs are no simpler than any Axis I disorder, and thus they are not of much help in dissecting the complex biological pathways leading from a genetic vulnerability to the multifaceted phenotypic picture of suicidal behaviors. In contrast, personality traits can hypothetically be conceived of as constructs closer to the effects of genes, thus serving as intermediary phenotypes susceptible to shed some light on the process of discovering true endophenotypes.

There are still few studies investigating genetic factors for suicidal behavior in relation with associated (underlying) personality traits or behavioral dimensions such as impulsivity, neuroticism, anger, hopelessness, and self-esteem.

Future studies aiming to identify the genetic factors (candidate genes or other genes of interest) influencing suicidal behavior should be prospective in nature and include a large array of assessments and investigations on personality traits or dimensions as well as adverse developmental events. A great deal of work remains to be done at the phenotypic level to decipher the multiple intermingled constructs, which probably overlap to a large extent. Interactions between genes and between different phenotypic constructs are in the scope of future work.

Future studies aiming to identify the genetic factors influencing suicidal behavior should include a large array of assessments and investigations on personality traits or dimensions.

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