Published in final edited form as:
*Psychiatr Clin North Am*. 2008 June ; 31(2): 247–269. doi:10.1016/j.psc.2008.01.005.

# Stress, Genes and the Biology of Suicidal Behavior

**Dianne Currier, PhD** and **J. John Mann, MD**
Division of Molecular Imaging and Neuropathology, Department of Psychiatry, Columbia Univeristy, NYSPI Unit #42, 1051 Riverside Drive, New York, NY 10032, (212) 543-5571

Dianne Currier: ; J. John Mann: jjm@columbia.edu

## Abstract

Suicidal behavior is in part heritable. Studies seeking the responsible candidate genes have examined genes involved in neurotransmitter systems demonstrated to have altered function in suicide and attempted suicide. These neurotransmitter systems include the serotonergic, noradrenergic and dopaminergic systems and the HPA axis. With some exceptions, most notably the serotonin transporter promotor HTTLPR polymorphism, replication of candidate gene association studies findings has proven difficult. This chapter reviews what is known of specific gene effects and gene-environment interactions that influence risk for suicidal behavior. Effects of childhood stress on development and how that influences adult responses to current stress will be shown to be relevant for mood disorders, aggressive/impulsive traits and suicidal behavior.

### Keywords

Suicide; Mood Disorders; Genetics; Stress; Serotonin; HPA axis

## Suicidal Behavior and Genetics

Family, twin, and adoption studies provide evidence of the heritability of suicide and attempted suicide, in part independent of the familial transmission of major psychiatric disorders (see Brent & Mann for a review [1]). From twin studies, based on case and register studies, estimates of heritability for suicide range between 21-50%, and 30-55% for a broader phenotype of suicidal behavior (attempts, thoughts, plans) based on general population studies.[2] Identifying the relevant genes and the neurobiological pathways through which they contribute to the etiology of suicidal behavior is important for designing and implementing preventative strategies. The first wave of genetic studies sought to identify genes involved in suicide and/or attempted suicide by linkage studies or specific single nucleotide polymorphisms (SNPs) in association studies. Emerging approaches aim to investigate functional genomics using microarray technologies to profile expression of thousands of genes simultaneously (see Mirnics et al [3] for a review) or doing a genome wide array for hundreds of thousands of SNPs.

Candidate genes for association studies have been generally selected based on evidence from neurobiological studies in suicide. Consequently, the serotonergic system has been most extensively investigated, with other target systems including the dopaminergic and

Correspondence: Dianne Currier, Division of Molecular Imaging and Neuropathology, Department of Psychiatry, Columbia University, 1051 Riverside Drive, Unit 42., New York, NY. 10032, Ph: 212 543 6846, E-mail: dmc2111@columbia.edu.

noradrenergic systems, neurotrophins such as brain derived neurotrophic factor (BDNF) and, more recently, genes related to the hypothalamic-pituitary-adrenal (HPA) axis. Association studies have been the commonest design but replication of findings has proven difficult for individual SNP association studies for a number of reasons, including differences in study sample size and composition with respect to diagnosis, different definitions of suicidality including suicide, nonfatal attempts or suicidal ideation, the effects of ethnicity/race-related stratification, and the effect of, or interactions with, environmental factors. Environment, particularly during childhood developmental periods, can influence the effect of genetic variants on neurobiological function. Another factor contributing to the disparity in results from association studies may be the complexity of the suicidal behavior phenotype, although this may be less of a problem as suicide, nonfatal suicide attempts and suicidal ideation are all partly heritable and perhaps involve many of the same genes. Nevertheless, there are probably many genes, as well as epigenetic factors, involved in the diathesis for suicidal behavior. Moreover, the rarity of completed suicide means that studies may be underpowered to detect the effect of a single SNP or gene. To address the matter of a low base rate for suicide, one approach is to focus on endophenotypes for suicidal behavior that are more prevalent and can often be more narrowly and specifically defined and measured. These may include clinical traits such as impulsive-aggression, cognitive function, or neurobiological functioning such as amygdala responsivity.

Much remains unknown regarding which genes have the most influence in suicidal behavior and the neurobiological mechanisms through which genetic variants act to affect the risk for suicidal behavior. Here we review published findings that together begin to elucidate a picture of the genes, their functional effects, and their involvement in endophenotypes that are putative pathways to suicidal acts.

## Serotonergic System

About thirty years of research documents abnormalities in the serotonergic system in suicide and non-fatal suicidal behavior (see Mann [4] for a review). Thus, it is not surprising that the serotonergic system has been most scrutinized regarding genetic variants potentially contributing to serotonergic system dysfunction and thereby to suicidal behavior. Candidate genes from the serotonergic system that have been examined with respect to suicidal behavior include SNPs in genes for the serotonin transporter, serotonin receptors including 5-HT2A, 5-HT1A and 5-HT1B, tryptophan hydroxylases I and II (the rate limiting enzymes in serotonin synthesis), as well as monoamine oxidase A, which is involved in the breakdown of monoamines including serotonin.

### Serotonin Transporter

Postmortem studies of depressed suicides report fewer serotonin transporters in prefrontal cortex (suicide or major depression), hypothalamus (suicide), occipital cortex (major depression) and brainstem (suicide and major depression) [5]. Of relevance in identifying the responsible brain circuitry in suicides, this prefrontal cortex deficit appears localized to the ventromedial prefrontal cortex (a brain region involved in willed action and decision-making), whereas major depression is associated with lower binding throughout the prefrontal cortex.[6]

The cause of lower transporter binding has been the target of inquiry. The serotonin transporter gene is located on chromosome 17 and has a common, functional promotor polymorphism (5-HTTLPR). Initially a short variant (S allele) of the polymorphism was found to have lower transcriptional efficiency and less transporter expression, binding, and 5-HT uptake in lymphoblasts [7]. The so-called long or L variant was subsequently found to comprise low-expressing ($L_G$) and higher-expressing ($L_A$) variants.[8,9] In healthy volunteers, two PET studies, using the high affinity ligand [$^{11}$C} DASB, resported altered serotonin transporter

binding in midbrain[10] and putamen [11] associated with 5-HTTLPR genotype, however, these and other imaging studies find no evidence of geneotype effect on serotonin transporter binding in the amygdala, thalamus, prefrontal cortex, or anterior cingulate[6,12-14].

Multiple studies in healthy adults have reported that individuals with the lower expressing SS genotype show increased amygdala activity when exposed to angry or fearful faces, negative words, or aversive pictures (reviewed in Brown & Hariri [15]). Two recent studies examine whether genotype has an effect on resting amygdalar activity, that is, when exposed to neutral rather than negative stimuli.[16,17] These studies use spin labeled perfusion fMRI methods, which qualifies absolute cerebral blood flow rather than the BOLD method which is only informative in comparing changes in state. Both report that, compared with the l/l group, the s/s group or s/s & s/l combined group had significantly higher resting CBF in the amygdala.[16,17] This suggests that the presence of the low-expressing allele may contribute to a more generalized alteration in amygdala function that may underlie the observed increased sensitivity to emotional stimuli. Canli et al also noted that life stress interacted with genotype with respect to amygdala function, whereby amygdala activation at rest correlated positively with life stress in short variant carriers, but correlated negatively with life stress in noncarriers.[16] A similar effect was noted in the hippocampus. The amygdala is densely innervated by serotonergic neurons and 5-HT receptors are abundant [18-20] and thus the serotonergic abnormalities seen in suicides may indicate altered amygdala function.

**5-HTTLPR and suicidal behavior—**More than 20 studies have examined the 5-HTTLPR polymorphism with respect to suicidal behavior with both negative and positive findings. Meta-analyses of 12 studies comprising 1599 subjects found a significant association of the 5-HTTLPR low expressing S allele and suicidal behavior.[21] Another meta-analysis found the S allele more frequent in suicide attempters within individual diagnostic categories, and that the S allele was associated with violent rather than non-violent suicide attempts.[22]

The 5-HTTLPR lower expressing alleles have been associated with violent behavior.[23-25] The relationship between impaired serotonergic function and aggression is well established.[26] One potential pathway by which the 5-HTTLPR gene is related to impulsivity and aggression is through observed alterations in amygdala function as the amygdala, along with the prefrontal cortex and orbital cortex, is thought to play a role in the emergence of violent behavior via faulty regulation of negative emotion.[27]

## Serotonin Receptors

Greater postmortem 5-HT2A receptor binding was observed in the prefrontal cortex of suicides compared with non-suicides in some studies.[28-32] Youths who died by suicide had increased protein levels and gene expression, which may partially explain observed higher binding.[32] Higher 5-HT2A binding has also been reported in the amygdala in depressed suicides[33], and in suicide victims with and without depressive diagnoses there is evidence that 5-$HT_{2A}$ receptors are up-regulated in the dorsal prefrontal cortex (areas 8 and 9) but unchanged in the rostral pole of the prefrontal cortex (area 10) (see Stockmeier [34] for a review). Not all studies concur, and several observe no difference in 5-$HT_{2A}$ receptors in the prefrontal cortex in depressed suicides compared to controls.[35-42]

In non-fatal suicide attempts, multiple platelet studies of 5-$HT_{2A}$ receptors, serotonin reuptake sites, and serotonin second messenger systems have reported higher platelet 5-$HT_{2A}$ receptor numbers in suicide attempters compared with nonattempters and healthy controls[43], indications of impaired 5-$HT_{2A}$ receptor mediated signal transduction in the prefrontal cortex of suicides[44], and blunted 5-$HT_{2A}$ receptor in major depression patients who made high-lethality suicide attempts compared to those who made low-lethality suicide attempts.[45] The

implications of such a defect in signal transduction, if present in the brain, would be that although there may be greater density of 5-$HT_{2A}$ receptors, the signal which is transduced by 5-$HT_{2A}$ receptor activation may be blunted, which would compound deficient serotonergic activity as seen in the lower levels of brainstem serotonin and/or 5-HIAA in suicide victims.[35,36,46-50]

### 5-HT receptor genes and suicidal behavior

Studies of 5-HT2A receptor gene and suicidal behavior have largely focused on the T102C SNP. The T102C SNP was not associated with suicide in post mortem studies but sample sizes are small.[51-54] Positive association have been reported with suicide attempt in depressed individuals[55] and with suicidal ideation[56], however there are multiple negative studies in varied populations and diagnostic groups for both ideation and attempt.[57-61] Metaanalysis of 9 studies found no association of the T102C polymorphism with suicide attempt or suicide[21] and a recent expaned metaanalysis of 25 studies confirmed the lack of association.[62]

Huang et al reported decreased 5-HT1B binding in the prefrontal cortex of suicides and non-suicides associated with the C allele of C129T and G allele of G861C SNPs.[63] Multiple studies of the common G861C SNP in the 5-$HT_{1B}$ receptor gene coding region report no association of genotype and suicide[63-65] or suicide attempt.[66-68] The observation that 5-$HT_{1B}$ knockout mice exhibit aggressive behavior[69], suggested that this gene may be involved in the aggressive/impulsive endophenotype of suicidal behavior. Investigations of the two common SNPs in this gene have examined association with aggression and/or impulsive traits as well as with suicide directly. The G861C SNP was shown to be involved in aggression and impulsivity, with increased C allele frequency in antisocial alcoholics[70], although a German study of alcoholics found lower C allele frequency in those with antisocial and conduct disorders.[71]

Other serotonin receptors have been less studied with respect to genetic involvement in suicidal behavior. An overrepresentation of 5-$HT_{1A}$ 1018G allele in suicides compared to controls has been reported by some[72], but others find no association.[73-75] Studies of the 5-$HT_{2C}$ [76], 5-$HT_6$ receptor[77] and a study of 7 other serotonin receptor genes[78] all report no indication of association with suicidality.

The 5-$HT_{1B}$ receptor gene and aggression aside, there have been few other studies of 5-HT receptor polymorphisms for associations with endophenotypes. Giegling et al examined multiple 5-$HT_{2A}$ SNPs, and found that CC-homozygotes for the functional SNP rs6311 reported more anger and aggression related behavior, and that the C allele, as well as the G–C haplotype combination of rs594242–rs6311,. was related to nonviolent and impulsive suicidal acts.[79] A study of multiple SNPs in the 5-HT2C and 5-HT1A genes found no effect of measures of state and trait anger or aggression in Caucasian suicides or in suicide attempters with various psychiatric diagnosis or in healthy volunteers.[80]

## Tryptophan Hydroxylase

Tryptophan hydroxylase is the rate limiting enzyme in the synthesis of serotonin. Two isoforms of TPH have been identified, TPH1 and TPH2, the latter expressed primarily in the brain, and their genes are on different chromosomes. Postmortem studies comparing depressed suicides to controls, report greater density and number of TPH-immunoreactive (TPH-IR) neurons in the DRN[81] and higher TPH IR in the dorsal raphe nucleus, but not in the median raphe nucleus, in depressed suicides[82], although others find less TPH IR in the DRN of depressed alcoholics suggesting common mechanism in major depression.[83] Depressed alcoholic suicides had 46% higher TPH immunoreactivity in the dorsal subnucleus, but no other dorsal raphe subregion, compared to controls.[84] Higher levels of TPH2 mRNA and protein were found in the dorsal

raphe nucleus of drug free suicides.[85] This over-expression may be due to a stress response as it has been reported to occur in animal models of stress.

There are two common polymorphisms on intron 7 of TPH1: A218C and A779C (originally classified as U and L for upper and lower band) that are in very high linkage disequilibrium. A218C has been linked to altered 5-HT function. In a postmortem study, the AA genotype was associated with higher TPH immunoreactivity and lower 5-HT2A binding in the prefrontal cortex compared to other genotypes in both suicides and non-suicides while another TPH1 polymorphism, A-1438, had no effect on either serotonergic marker.[86] Manuck et al found an attenuated prolactin response to fenfluramine in C allele of A779C relative to LL homozygotes in healthy volunteers[87], but New et al observed no relationship between genotypes and prolactin response to fenfluramine in male personality disorder patients with respect to this polymorphism[88]. Jonnsen et al [89] reported a relationship to CSF 5-HIAA in male healthy volunteers but not females, however, we did not find such a relationship in mood disorder subjects (Galfalvy, in preparation). The differences in study population may account for the lack of replication

## TPH genes and suicidal behavior

There have been multiple reports of both positive and negative associations with suicide and suicide attempt and the intron 7 A128C SNP. Initially meta-analysis, found no association with suicide or suicide attempt[90], however subsequent expanded metaanalyses did find an association of this polymorphism with suicidal behavior in Caucasian[91,92] and mixed populations.[93] There have also been positive associations reported for the A779C SNP C allele and suicidal behavior in alcoholic offenders[94] and surviving monozygotic twins of suicides[95], however another study reported an opposite result, with the A allele more frequent in depressed suicide attempters than in non-attempters.[96]

The A allele of the TPH1 A779C polymorphism has been associated with higher scores for state and trait anger and angry temperament in suicide attempters, and suicide attempters and controls combined[97], with higher aggressive hostility in healthy volunteers[98], and aggression and outwardly expressed anger in healthy volunteers[87] compared to CC homozygotes. Another study in schizophrenic males failed to replicate this finding. [99] Rujescu et al also found the TPH1 A allele of the 218C SNP associated with higher anger scores in a combined sample of suicide attempters and controls[97], which is not surprising as the two SNPs are in strong linkage disequilibrium. A study of nonpsychotic inpatients and nonimpulsive controls found no difference in A218C genotype between the groups although the patient group had a number of behavioral tendencies associated with the C allele.[100]

Haplotype and association studies of different SNPs suggest the involvement of the TPH2 gene with suicide[101] and suicide attempt[102,103], however again not all studies agree.[104-106] There are almost no reports of functional consequences of TPH2 gene variation. One recent study in healthy volunteers found evidence of a frequent functional cis-acting polymorphism in the TPH2 gene that affected mRNA expression. In that study, low levels of TPH2 mRNA expression in the pons were associated with the CTGTG combination of alleles and high levels of expression with the TAAGA combination of alleles for the SNPs re2171363, re4760815, rs7305115, rs6582076, and rs9325202.[107] This specific haplotype has yet to be investigated with respect to suicidal behavior.

TPH2 has been little studied with respect to endophenotypes of suicidal behavior, although studies in healthy volunteers found an effect of the TPH2 -703 G/T SNP on amygdala responses to emotional stimuli[108], and the TT genotype of this SNP was associated with more errors in the attention network test, a possible indicator of impaired impulse control, and decreased

performance in executive control, explaining more than 10% of the variance in these two indicators of attention.[109]

## Monoamine Oxidase A

Monoamine oxidase (MAO) A plays a key role in metabolism of amines. Low MAO A activity (about 80% reduced in activity is required to get a detectable effect) results in elevated levels of serotonin, norepinephrine and dopamine in the brain. The MAO A gene has a 13 −30bp uVNTR (variable number tandem repeat) in the promoter region, in which alleles with 3.5 or 4 repeats (referred to alleles 2 and 3) transcribed 2-10 times more efficiently than those with 3 or 5 repeats (referred to alleles 1 and 4).[110] The 2 and 3 alleles were associated lower prolactin responses to fenfluramine challenge in males[111] and higher levels of CSF 5-HIAA in healthy females[112], and healthy males.[113] Meyer-Lindenberg et al, in an fMRI study in healthy volunteers, showed the low expression variant was associated with limbic volume reductions and hyper-responsive amygdala during emotional arousal, as well as diminished reactivity of the regulatory prefrontal regions compared with the higher expressing alleles. [114] Thus a potential pathway for genetic involvement in suicidal behavior is through altered affect and behavioral regulation in part resulting from partially genetically related alterations in serotonergic system function.

### MAO genes and suicidal behavior

MAOA uVNTR is mostly found to be unassociated with suicide or suicide attempt.[115,116, 116-118] One study did find an association with history of suicide attempt, particularly in women with bipolar disorder[119], but not in major depressive disorder. Courtet et al, in a sample of European Caucasian suicide attempters with mixed psychiatric diagnoses and controls, found no association with suicidality, although they did observe a higher frequency of higher expressing alleles in males who made a violent suicide attempt compared to males who made a non-violent attempt.[120]

Human and rodent studies provide evidence of the involvement of MAO A in aggression.[121,122] The MAO A uVNTR has been examined for associations with aggression and violence. In a study of multiple domains of aggressive and disruptive behavior in personality disorder patients, aggression and other domains of disruptive, outward-bound behavior traits were associated with MAOA u-VNTR.[123] Meyer-Lindenberg et al [114] used fMRI study and found the low expressing alleles to be associated with increased risk of violent behavior, and alterations in the corticolimbic circuitry involved in affect regulation, emotional memory, and impulsivity, and thought to be involved in the emergence of aggressive behavior.[27] Moreover, two fMRI studies observed an effect of MAOA genotype during response tasks indicative of impulsivity.[124,125]

## Stress, Genes and Serotonin

Caspi et al observed that life events predicted onset of depressive episode only in individuals with the low expressing 5-HTTLPR S allele. This finding has been replicated multiple times, although not in every case (see Uher & McGuffin[126] for a review). Moreover, Caspi et al found that childhood maltreatment predicted adult depression that appeared to be triggered by stress but more so in individuals with the S allele[127], a finding which has also been replicated in some and not others[126]. With respect to suicidal behavior, Caspi et al found the same relationship between life events, the S allele, and suicide attempt and ideation, however did not report on suicidality with respect to childhood maltreatment/genotype interaction. Childhood adversity-genotype interactions and suicidal behavior are reported in mixed diagnosis inpatients[128] and abstinent African American substance dependent patients.[129]

Gene*environment interactions for the 5-HTTLPR have been investigated with respect to behavioral and putative biological endophenotypes for suicidal behavior, including aggression, amygdala responsivity. Reif et al found that an interaction effect of childhood environment and 5-HTTLPR genotype on violent behavior, whereby high adversity in childhood was associated with later-life violence if the short promoter alleles were present.[130] Gene and early-life environment effects on later life aggressive/violent traits have also been sought for the MAOA uVNTR. Adverse child-rearing in combination with a lower expressing variant of the MAO A gene was also found to contribute, in males only, to the development of antisocial behavior and more impulsivity, both of which may contribute to suicidal behavior.[115,131] In other studies of the MAOA uVNTR, Foley et al found the low expressing alleles more frequent in conduct disorder in the presence of an adverse childhood environment[132], and Nilsson et al found that the short allele interacted with adverse psychosocial risk factors, including adverse living environment and violent victimization, in adolescent boys to increase violent behaviors.[133] Another study reported that for women with a history of childhood sexual abuse, the low-expressing allele was associated with alcoholism and particularly antisocial alcoholism, while in non-abused women there was no relation between genotype and antisocial personality disorder or alcoholism.[134] Not all studies observed a moderating effect of MAOA genotype on childhood/adolescent maltreatment and antisocial or violent behavior.[135,136]

Elucidating the neurobiological underpinnings of this type of gene*early-life environment interactions is a complex task. Both animal and human studies show that early-life stress has an effect on the development and functioning of the serotonergic system in adulthood. Adult rats exposed to maternal separation in early life show evidence of autoreceptor super-sensitivity indicative of enduring alteration in 5-HT transporter and 5-HT1A autoreceptors.[137] In humans, a history of childhood abuse has been associated with blunted prolactin response to different serotonergic agonists in depressed children[138], boys in juvenile detention[139], and adult borderline personality women.[140] Prolactin release is mediated via 5-$HT_{1A}$ and 5-$HT_{2A}$ receptors, and these findings suggest sensitization of these receptors due to early-life stress.

The detrimental effect of early-life stress on the development and function of the serotonergic system may in and of itself confer increased risk for suicidal behavior, for example thorough increased aggression and impulsivity. Moreover, given that there may be underlying genetic differences in level of serotonergic system function, as described earlier, those with low function genotypes may be more vulnerable to the detrimental effects of early-life stress on 5-HT function. Animal studies have observed such effects. Monkeys exposed to maternal deprivation in infancy and having the 5-HTTLPR lower expressing S allele manifest a lowering of CSF 5-HIAA that persists into adulthood, while monkeys exposed to maternal deprivation in infancy with the higher expressing alleles do not show any such alterations.[141] It would be instructive to undertake similar studies in human samples.

Another pathway between genes, stress, and suicidal behaviors may be via the effects of impaired serotonergic function on stress response regulation later in life. Studies in animals and humans demonstrate that the serotonergic system is involved in the regulation of stress response via the HPA axis, and that impairments in the serotonergic system may deteriorate HPA function (for a review see Firk[142]). Thus individuals with lower 5-HT function, due to genes and/or early environment effects, would demonstrate altered HPA axis function. A recent study reports that the low expressing S allele was associated with higher levels of waking cortisol in non-depressed older adults[143], however others found no association of 5-HTTLPR genotype and plasma cortisol.[144,145] Early life experience is likely to mediate this relationship, and animal studies have examined this. In, six month old macaque monkeys exposed to social stress, peer-reared animals with the S allele had a higher ACTH response, an HPA axis hormone related to stress response, compared with peer-reared animals without that allele and to S allele animals who were maternally-reared.[146] Thus, studies of the

serotonergic system suggest that elucidating the genetics of suicidal behavior involves examing not justgenes, but also early-life environment, biologic and behavioral endophenotypes, and interactions between biologic systems.

## Other Systems

### Noradrenergic system

The noradrenergic system has been investigated with respect to suicidal behavior as it is involved in the regulation of stress response. Post mortem studies of suicides have reported ewer noradrenergic neuron in the locus coeruleus of suicide victims with major depression[147] increased brainstem levels of tyrosine hydroxylase.[148] Binding to alpha2 adrenergic receptors in brains of suicides have been reported variously as increased, decreased, or unchanged (see Pandeyand Dwivedi [149] for a review).

There have been few studies of genes related to the noradrenergic system. $\alpha 2_A$adrenoceptors located in the locus coeruleus exert a tonic inhibitory modulation on the firing activity of noradrenergic cells and the release of norepinephrine in projecting areas.[150] Sequiera, et al examining the $\alpha_2$-adrenergic receptor gene in Canadian suicides, found the rare allele of N251K functional SNP that results in an asparagines to lysine amino acid change, present only in suicide victims, but only in 3 cases.[151] A subsequent study could not replicate this finding, failing to detect the polymorphism is a large sample of 214 suicides and 176 controls.[152]

Tyrosine hydroxylase is the rate limiting step for catecholamine synthesis and Persson et al observed a non-significant tendency for low incidence TH-KI allele among suicides compared to controls, although there was a significant association of the K3 allele in subgroup adjustment disorders and suicide attempt.[153] Other studies report a trend for association[154] or no association.[155]

Catechol-O-methyltransferase (COMT) enzyme metabolizes the noradrenaline that diffuses in synaptic cleft. COMT has a common functional polymorphism, val158met, that results in the substitution of valine by methionine. The Val allele has relatively high COMT activity compared to the Met allele.[156,157] Recent metaanalysis of 6 studies with 519 cases and 933 controls found suggestive evidence of an association between COMT val158met polymorphism and suicidal behavior, perhaps related to the lethality of suicide attempt.[158] Supporting this, are reports of association in schizophrenia between the low functioning met allele and impulsive aggression[159-161], violent suicide attempts[162], and of the Met/Met genotype and outward directed aggression in suicide attempters of varied psychiatric diagnosis.[163] Other studies find no relationship between aggression and the Met allele[164-167] or the opposite direction.[168-170] A post mortem study found the Val allele less prevalent and the heterozygote Val/Met more prevalent in male suicides than in controls.[171]

There have been no studies of the effect of early-life environment gene interaction on suicidal behavior with respect to genes related to the noradrenergic system. Given that early life stress has been shown to modify noradrenergic system function in adulthood[172], examining possible genetic factors that play a role in this would be of interest.

### Dopaminergic system

Abnormality of the dopaminergic systems has been reported in depressive disorders (see Dailly [173] for a review) however the role of the dopaminergic system in suicidal behavior is unclear. Reduced dopamine turnover was observed in the caudate, putamen and nucleus accumbens in a postmortem study of depressed suicides.[174] However, no differences in number or affinity of the dopamine transporters was found in depressed suicides compared to controls.[175] Depressed suicide attempters had lower CSF homovanillic acid (HVA), a dopamine

metabolite[176], and lower urinary HVA, DOPAC and dopamine[177], however other studies find no evidence that CSF HVA levels predict suicide or correlate with clinical factors related to suicide, such as aggression or impulsive traits.[178-180] In studies of violent offenders significant correlations between CSF HVA/5-HIAA ratio and psychopathic traits of aggression and violence are reported, suggesting dysfunction in the relative activity of the two systems rather than in dopaminergic system alone may be important.[181,182]

There have been few studies of dopaminergic system genes with respect to suicidal behavior. In studies of dopamine receptor genes, the del allele of the of 141C Ins/Del polymorphism the D2 receptor gene was not associated with suicide attempt, but was found in excess in alcoholics with suicidality.[183] An A-G polymorphism in the 3′utr of exon 8 of the D2 receptor gene was associated with increased number of suicide attempts in alcoholics.[184] No differences between Swedish suicide attempters of mixed psychiatric diagnoses and controls[185] or between Israeli adolescent suicide attempters and controls[186] was found in the dopamine receptor subtype 4 (DRD4) gene exon III 48 bp repeat polymorphism.

## HPA Axis

HPA axis function may be involved in suicidal behavior in the context of acute stress response to life events preceding a suicidal act in which impaired stress response mechanisms contribute to risk. It may also be involved in suicidal behavior if increased activity of stress response to adversity during development has deleterious effects on the development of other systems and brain structures implicated in suicidal behavior.

One measure of abnormal HPA axis function in non-suppression of cortisol in response to dexamethasone administration (DST). Over a 15 year follow-up period, DST cortisol nonsuppressors had an approximately 14 fold higher risk of suicide compared to suppressors[187], and our recent meta-analysis found that for mood disorder individuals, DST nonsuppressors had a 4.5 fold risk of dying by suicide.[188] There have been fewer neuroanatomical studies of HPA axis with respect to suicide, however reported anomalies include larger pituitary and larger adrenal gland volumes found post mortem and using MRI in vivo in depressed suicide victims[189-192], and fewer CRH binding sites in the prefrontal cortex of depressed suicide victims.[193]

For non-fatal suicidal behavior the DST results are inconclusive[194-200], however there are reports that DST nonsuppression may be characteristic of more serious attempts that result in high medical damage[199,201] or the use of violent method in the suicide attempt.[198] In other indices of HPA axis function, depressed adolescents who attempted suicide during a 10 year follow-up period had elevated pre-sleep cortisol compared to depressed non-attempters and healthy controls.[202] Depressed suicide attempters have attenuated plasma cortisol responses to fenfluramine[203-205], and CSF CRH is lower in previous attempters compared to non-attempters[206,207], though not all studies agree[177]

### HPA axis gene and suicidal behavior

There have been comparatively few genetic studies of the HPA axis function, and fewer still in relation to suicidal behavior. In studies of healthy volunteers, there is some evidence that genes play a role in basal HPA axis function, and limited and conflicting reports on the genetic role in HPA axis activity in response to various challenges or stressors (see Wust et al[208] for a review). There have been almost no studies of HPA axis genes with regards to suicidal behavior. Recently the CRH receptor has been examined. One study reported linkage and association between SNP rs4792887 and suicide attempt among depressed males exposed to low lifetime levels of stress, but not in males exposed to high-stress levels.[209] The authors suggest this may indicate increase in risk for suicidal behavior resulting from an overactive

stress response system. Another recent study found the I allele of the ACE I/D polymorphism to be more frequent in completed suicides than in controls.[210]

Studies in animals[211-214], and humans[215-218] have demonstrated that early-life stress results in abnormal HPA axis function in adulthood. There have, as yet, been no studies published examining early-life stress, genes and suicidal behavior with respect to the HPA axis, however preliminary data show an early-life stress gene interaction of the CRH R1 gene and early life stress on severity of depression.[219] Another study reported an interaction effect of a CRH R1 polymorphism and negative life stress on alcohol use behavior in adolescents.[220] Clearly studies investigating the genetic and gene/environment influences on basal HPA axis function and to response to stressors are necessary for elucidating the genetic contributions to suicidal behavior.

## Conclusion

With respect to the genes and biology of suicidal behavior, stress can be considered from two perspectives. Firstly, exposure to stress in early life has lasting detrimental effects on the development and function of neurobiological systems thought to be involved in suicides including those that regulate behavior, affect, and cognitive function. Secondly, impairments in stress response systems may be directly involved in suicidal behavior. In both contexts genes may contribute to altered neurobiological function. Increasingly sophisticated association studies that include an examination of early-life stress, markers of biological function, and/or intermediate phenotypes of suicidal behavior will shed further light on the complexities of the relationship between stress, genes, and suicidal behavior.

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