# Genetics of Suicide in Depression

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Evidence is mounting that genetic factors may be included in the many determinants of suicide. Clinical studies of psychiatric patients have suggested that risk of suicidal behavior is increased by the presence of family history of suicidality, a claim that is also supported by findings of twin and adoption studies. In addition, molecular genetic studies have reported polymorphisms in the tryptophan hydroxylase gene that is involved in the synthesis of serotonin. The genetic susceptibility to suicide, however, tends to affect individuals only in association with stress or psychiatric illness.

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Suicide is a multidetermined act. The importance of psychiatric, social and biological factors, psychodynamics, and physical illness as determinants of suicide is well-established. However, increasing data suggest that genetic factors may also play a part in suicidal behavior. This paper will examine this possibility by reviewing relevant clinical, twin, and adoption studies, as well as recent molecular genetic studies, with an emphasis on suicide in depression.

## CLINICAL STUDIES

A family history of suicide has been noted to be associated with suicidal behavior at all stages of the life cycle. Clinical studies documenting this association in adolescents, adults, and the elderly have been extensively reviewed elsewhere.[1–3] Studies in psychiatric patients show that a family history of suicide raises the risk of suicidal behavior.[4]

### Clinical Studies in Depressed Patients

Pitts and Winokur[5] found that among 748 consecutive inpatients, 37 (4.9%) reported a possible or definite suicide in a first-degree relative. In 25 (68%) of these 37 cases, the diagnosis was an affective disorder. Roy[4,6–8] reported studies of 5845 consecutively admitted psychiatric patients. Of these patients, 243 inpatients had a family history of suicide (4.2%). More than half (56.4%) had a primary diagnosis of an affective disorder. A family history of suicide was found to significantly increase the risk for an attempt at suicide in a wide variety of diagnoses. Almost half (48.6%) of those with a family history of suicide had themselves attempted suicide.

Similarly, among depressed patients, Mitterauer[9] found that 100 of 342 patients with major depression who had a family history of suicide had themselves attempted suicide compared with only 9 of 80 depressed patients without such a history ($p < .001$). Also, Malone et al.[10] found that parents of depressed patients who attempted suicide were more likely than parents of nonattempters to have attempted suicide themselves (7/51 vs. 1/49, $p < .02$).

### Type of Suicide Attempt

A family history of suicide is often associated with a violent suicide attempt. For example, Roy[11] reported that a family history of suicide was found significantly more among depressed patients who had made a violent suicide attempt in comparison with either patients who had made a nonviolent attempt (3/6 vs. 1/21, $\chi^2 = 7.56$, df = 1, $p < .006$) or in comparison with all patients who had not made a violent attempt (3/6 vs. 5/38, $\chi^2 = 4.73$, df = 1, $p < .03$).

Linkowski et al.[12] reported similar results. They found that 123 (17%) of 713 depressed patients had a first- or

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*This paper is dedicated to the memory of Markku Linnoila, M.D., Ph.D., who died prematurely on February 25, 1998. He made landmark contributions to the biology and genetics of suicide.*

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second-degree relative who had committed suicide. A family history of suicide significantly increased the probability of a suicide attempt among the depressed women, especially the risk for a violent suicide attempt. Among the depressed male patients, a family history of suicide significantly increased the risk only for a violent suicide attempt. Linkowski et al.[12] concluded that "a positive family history for violent suicide should be considered as a strong predictor of active suicidal attempting behavior in major depressive illness."(p237)

### Confounds

However, confounds do exist in the interpretation of the results of family studies of suicidal behavior. First, the familial aggregation of suicidal behavior may involve nongenetic factors such as exposure to family violence, hostility and discord, low parental involvement, or imitation of suicidal behavior in a family member.[13] Second, a higher rate of suicidal behavior in the families of individuals who have exhibited suicidal behavior may simply be due to the genetic transmission of the psychiatric disorders associated with suicide, i.e., depression, alcoholism, and schizophrenia. This potential confound was addressed in a recent study by Brent et al.[14] of adolescent suicide victims. They found, as expected, that the rate of suicide attempts was higher in the first-degree relatives of suicide probands compared with the relatives of adolescent controls. However, Brent and colleagues also found that this significant difference remained even after adjusting for differences in the rates of proband and familial Axis I and II psychiatric disorders. In addition, they reported that among suicide probands, higher ratings of aggression were associated with higher familial loading for suicide attempts. They therefore concluded that the liability to suicidal behavior might be familially transmitted as a trait independent of Axis I and II psychiatric disorders.

## THE AMISH STUDY

Egeland and Sussex[13] reported on the 26 suicides that occurred over 100 years among the Old Order Amish community of Lancaster County, in southeastern Pennsylvania. Twenty-four of the 26 suicide victims met criteria for a major affective disorder. Almost three quarters of the 26 suicides were found to cluster in 4 family pedigrees, each of which contained a high prevalence for affective disorders and suicide. The converse was not true, as there were other family pedigrees with high prevalence for affective disorder but without suicides. Thus, a familial prevalence for affective disorders was not in itself a predictor for suicide. Egeland and Sussex concluded: "Our study replicates findings that indicate an increased suicidal risk for patients with a diagnosis of major affective disorder and a strong family history of suicide."(p917)

## TWIN STUDIES

Kallman and Anastasio[15] stated: "If hereditary factors play a decisive role we should find a concordant tendency to suicide more frequently in 1-egg than in 2-egg pairs regardless of ordinary differences in environment."(p41) Recently, we reported 176 twin pairs in which 1 twin had committed suicide.[16] In 9 of these 176 twin pairs, both twins had committed suicide. Seven of these 9 twin pairs concordant for suicide were found among the 62 monozygotic twin pairs, whereas only 2 were found among the 114 dizygotic twin pairs. This twin group difference for concordance for suicide (11.3% vs. 1.8%) is statistically significant ($p < .01$).

The combination of our 176 twin pairs with the other suicide twin pairs in the literature yields a total of 399 twin pairs: 129 monozygotic twin pairs (17/129 [13.2%] concordant for suicide) and 270 dizygotic twin pairs (2/270 [0.7%] concordant for suicide).[16] These combined data demonstrate that monozygotic twin pairs show significantly greater concordance for suicide, relative to dizygotic twin pairs ($p < .001$).

In a second study[17] we examined attempts at suicide among living co-twins whose twin had committed suicide. Among 35 twins for whom 1 twin had committed suicide, we found that 10 of the 26 living monozygotic co-twins had themselves attempted suicide, compared with 0 of the 9 living dizygotic co-twins ($p < .04$). We concluded that, although monozygotic and dizygotic twins may have some differing developmental experiences, studies show that monozygotic twin pairs have significantly greater concordance for both suicide and attempted suicide.

A confound in the interpretation of the results of twin studies of suicidal behavior is that monozygotic twins are also more highly concordant for the psychiatric disorders associated with suicide than are dizygotic twins. However, that possible confound was addressed by a recent study of 5995 Australian twins by Statham et al.[18] These twin pairs were a community sample and not selected on the basis of suicidal behavior. Nonetheless, controlling for a history of psychopathology in the statistical analysis, a significant association with the co-twins' history of suicidal thoughts and behavior remained, stronger in monozygotic than in dizygotic twin pairs.

## MODE OF INHERITANCE

Papadimitriou et al.[19] used the computational model of Slater to investigate possible modes of transmission of suicidal behavior, i.e., whether a single dominant gene or polygenic inheritance might be involved. Their sample consisted of 549 depressed patients with a lifetime history of attempting suicide. One relative per subject, whenever possible, was interviewed with a semistructured interview about suicidal behavior in his or her family. Fifteen patients

had 2 or more first- or second-degree relatives who had committed suicide. However, the results did not show a significant excess of unilateral pairs of suicides in the family, as would be expected in a transmission with a single dominant gene. Therefore, the authors concluded that their results were most compatible with polygenic inheritance.

## ADOPTION STUDIES

Adoption studies of suicide were carried out in Denmark by Schulsinger et al.[20] and Wender et al.[21] Individuals separated at birth, or shortly afterwards, share their genes, but not subsequent environmental experiences, with their biological relatives. In contrast, adoptees share their environmental experiences through childhood and adolescence with their adopting relatives, but share no genes. Thus, familial aggregation of suicide in adoption studies cannot be attributed to the earlier discussed confound of familial nongenetic factors.

The Psykologisk Institut has a register of the 5483 adoptions in greater Copenhagen between 1924 and 1947. A screening of the register of causes of death revealed that 57 of these adoptees eventually committed suicide. They were matched with adopted controls. Searches of the causes of death revealed that 12 of the 269 biological relatives of these 57 adopted suicides had themselves committed suicide, compared with only 2 of the 269 biological relatives of the 57 adopted controls ($p < .01$). None of the adopting relatives of either the suicide or control group had committed suicide. Schulsinger et al.[20] therefore proposed that there may be a genetic predisposition for suicide independent of, or additive to, the major psychiatric disorders associated with suicide.

Wender et al.[21] went on to study the 71 adoptees identified by the psychiatric case register as having suffered from an affective disorder. They were matched with 71 control adoptees without affective disorder. Not unexpectedly, and as hypothesized, significantly more of the adoptees with affective disorder than controls had committed suicide. However, it was particularly adoptee suicide victims with the diagnosis of "affect reaction" who had significantly more biological relatives who had committed suicide than controls. This diagnosis describes an individual who has affective symptoms accompanying a situational crisis—often an impulsive suicide attempt. The overall findings led Kety[22] to suggest that one genetic factor in suicide may be an inability to control impulsive behavior that has its effect independently of, or additively to, a psychiatric disorder.

## MOLECULAR GENETIC STUDIES

Nielsen et al.[23] were the first to report an association between suicidal behavior and a molecular genetic variant. Tryptophan hydroxylase (TPH) is the enzyme involved in the biosynthesis of serotonin. It catalyzes the oxygenation of tryptophan to 5-hydroxytryptophan, which is decarboxylated to serotonin.[24] Nielsen et al.[23] had earlier identified a polymorphism in an intron and mapped TPH to the short arm of chromosome 11. Two alleles—U and L—were identified.

**Table 1. Population Association Between Tryptophan Hydroxylase (TPH) Genotype and History of Suicide Attempts***

| | History of Suicide Attempts, All Violent Offenders | |
|---|---|---|
| Variable | With | Without |
| Genotype | | |
| UU, N (%) | 2 (17) | 10 |
| UL, N (%) | 19 (53) | 17 |
| LL, N (%) | 15 (65) | 7 |
| p Value | .02 | |
| Total N | 36 | 34 |
| U allele frequency | 0.32 | 0.54 |

*Adapted from Nielsen et al.[23]

Low concentrations of the serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) have been associated with suicidal behavior. Thus, Nielsen et al.[23] examined TPH and suicide attempts in a relatively homogeneous group of Finnish alcoholics in whom cerebrospinal fluid (CSF) 5-HIAA concentrations had been determined. Nielsen et al.[23] found a population association between TPH genotype and CSF 5-HIAA concentrations in the impulsive alcoholics. Furthermore, the impulsive alcoholics with the LL or UL genotype had the lowest CSF 5-HIAA.

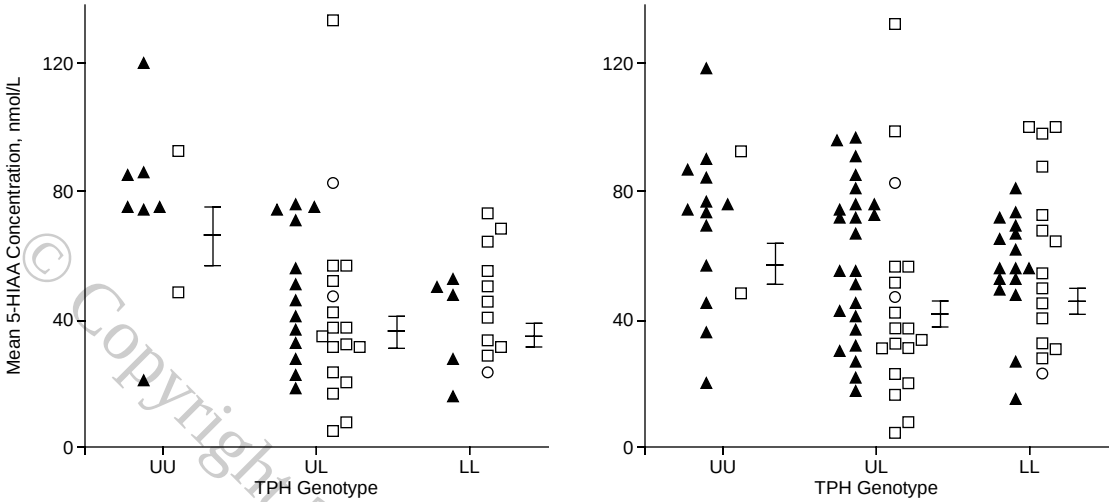
A history of suicide attempts was significantly associated with TPH genotype in all of the alcoholic offenders ($p = .016$) (Table 1; Figure 1). In fact, 34 of the 36 subjects who attempted suicide had either the UL or LL genotype. Thus, Nielsen and colleagues concluded that the presence of the L allele was associated with an increased risk of suicide attempts.

When Nielsen and colleagues examined multiple suicide attempts, they found that such a history was present most in offenders with the LL genotype and to a lesser extent among those with the UL genotype (Figure 2). Thus, they concluded that the L allele was associated with repetitive suicidal behavior.

Overall, Nielsen et al.[23] suggested that the presence of one TPH L allele may indicate a reduced capacity to hydroxylate tryptophan to 5-hydroxytryptophan in the synthesis of serotonin, producing low central serotonin turnover and thus low CSF 5-HIAA concentrations.

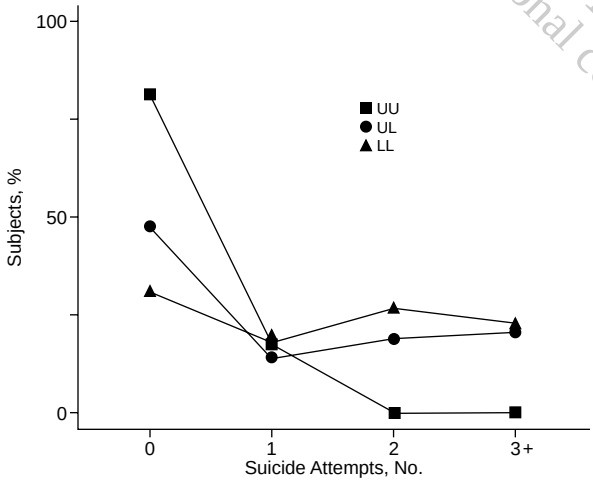
Nielsen et al.[25] went on to carry out further association and sibling pair linkage analyses of this TPH polymorphism in 804 Finnish alcoholic offenders, controls, and their relatives in a sample that included 369 sibling pairs. They replicated their earlier finding of the association of the TPH allele to suicidality in a new group of 122 Finnish offenders. The most highly significant association was with severe suicide attempts. In addition, the sibling pair analy-

**Figure 1. Relationship Between TPH Genotype, 5-Hydroxindoleacetic Acid (5-HIAA) Concentrations, and History of Suicide Attempts***




*From reference 23. Symbols: ▲ = subjects who had never attempted suicide, □ = subjects who had attempted suicide, ○ = subjects who had committed suicide. The 5-HIAA concentrations of the subjects are plotted against their TPH genotypes for impulsive subjects (left) and all subjects (right).

**Figure 2. Relationship Between TPH Genotype and Lifetime History of Multiple Suicide Attempts***




*From reference 23. For each genotype, the fraction of subjects having each genotype is plotted against the number of suicide attempts they have made in their lives.

sis revealed that this TPH allele showed significant linkage to suicidality, severe suicide attempts, alcoholism, and socialization scores on the Karolinska Scales of Personality.

### TPH in Living Co-Twin of Monozygotic Suicide Victim

Among the 17,370 monozygotic twin pairs in the Swedish Twins Register, there are 36 pairs for which 1 twin is alive and the other has died from suicide. They were contacted and asked whether they would consider participating in a study. Twenty-eight remaining twins were interviewed in their homes by 1 of the authors (G. R.). Venous blood was sampled and cell lines were established. So far, genotypes for the TPH polymorphism have been established for 17 twins. Seven had the LL genotype, 9 the UL genotype, and only 1 the UU genotype.[2,3] Thus, these monozygotic twin data also suggest that the L allele is associated with suicidal behavior.

### TPH Studies in Depressed Patients

Bellivier et al.[26] recently examined the TPH intron 7 A218C polymorphism in DNA samples from 152 patients with bipolar disorder and 94 normal controls. They found that there was a significant association between TPH genotype and bipolar disorder. However, there was no significant difference for A allele frequency between patients with (N = 52) and without (N = 100) a suicide attempt (0.56 vs. 0.48). Furthermore, there was no significant difference in frequency between bipolar patients who had made violent (N = 14) suicide attempts or those who had made nonviolent attempts (N = 38) (0.57 vs. 0.55). Bearing in mind the data of Nielsen et al.,[23] Bellivier et al. concluded that TPH intron 7 polymorphism might be associated with a trait related to violence and bipolar disorder rather than directly to these phenotypes themselves.

Mann et al.[27] reported that the less common TPH U allele occurred with significantly greater frequency among depressed patients who had attempted suicide compared with those who had not.

### TPH Studies in Personality Disordered Patients

It is possible that molecular genetic abnormalities may predispose an individual to suicidal behavior, at times of

stress, through an effect on personality. For example, the personality traits of impulsivity and aggression are associated with suicidal behavior. Furthermore, impulsivity/aggression is associated with decreased central serotonin (low CSF 5-HIAA and reduced prolactin response to challenge with serotonergic agents like fenfluramine or *m*-CPP [*m*-chlorophenylpiperazaine]).

A first link between the molecular genetics of the serotonergic system and impulsivity/aggression has been reported by New et al.[28] They measured impulsivity/aggression in 40 personality disordered patients with the Buss-Durkee Hostility Inventory (Buss-Durkee). Male patients with the LL genotype had significantly higher total Buss-Durkee scores compared with males with the UL or UU genotype ($45.3 \pm 9.8$ vs. $32.9 \pm 13.5$, $p < .03$). They also scored significantly higher on the Buss-Durkee irritability subscale. Also, the Buss-Durkee assault plus irritability subscales correlated negatively with prolactin responses to fenfluramine ($r = -0.70$, $N = 16$, $p < .01$) and patients with the LL genotype had a lower prolactin response, though not significantly so.

### Serotonin Transporter Studies

The human platelet serotonin transporter (SERT) is found presynaptically and has attracted renewed interest since Lesch et al.[29] demonstrated that it is identical with the human brain serotonin transporter. Both human brain and platelet serotonin transporter proteins are encoded by a gene on chromosome 17.[30] Polymorphic regions in the second intron and transcriptional control region have been associated with unipolar depression and neuroticism.[31,32]

Postmortem studies of suicide victims have reported changes in the serotonin transporter,[33] and Mann et al.[34] found that platelet serotonin content was significantly lower in depressed patients who had attempted suicide. A recent study suggests that the affinity of the serotonin uptake protein for serotonin may be decreased in patients who exhibit suicidal behavior.[35] Thus, it is noteworthy that significant differences in human platelet serotonin uptake Km values between different polymorphisms of the human SERT gene have been reported.[36] Although Bellivier et al.[37] found no relationship between an allele of the SERT gene and suicide attempts in bipolar patients, preliminary data have suggested an association between a 10-repeat allele of the SERT gene and clinical measures related to impulsive aggression.[38] This is noteworthy as impulsivity/aggression is a heritable personality dimension associated with low CSF 5-HIAA and suicidal behavior (reviewed in references 39 and 40).

### Monoamine Oxidase Studies

Buchsbaum et al.[41] found that significantly more college students with low blood platelet monoamine oxidase (MAO) levels had a family history of suicidal behavior compared with students with high platelet MAO levels. This is relevant, as MAO is involved in the metabolism of serotonin. Recently, a Dutch family was described whose members exhibited violent behavior and had a mutation in the gene for MAO A.[42]

### Serotonin Receptors

Zhang et al.[43] reported a slight association between a 5-$HT_{2A}$ receptor polymorphism and suicide attempts in depressed patients.

## CONCLUSION

In summary, a large body of clinical data from family, twin, and adoption studies now show that there is a genetic susceptibility to suicide. However, this susceptibility is only likely to manifest itself in an individual at times of severe stress or when ill with a major psychiatric disorder. The first molecular genetic studies have reported polymorphisms in the TPH gene involved in the synthesis of serotonin. Further replications are needed of this and the other molecular genetic findings reviewed above. It seems likely that further polymorphisms will be found in other genes controlling different parts of the pathways involved in the synthesis and metabolism of serotonin. It is also possible that polymorphisms in other neurotransmitter systems may play a part in the multidetermined act of suicide.

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