

Possible Association of a Polymorphism of the Tryptophan Hydroxylase Gene With Suicidal Behavior in Depressed Patients

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Objective: This study was designed to test the hypothesis that serotonin-system-related genes may be correlated with suicide risk. *Method:* Fifty-one unrelated Caucasian inpatients with major depression, with or without a history of suicidal acts, were genotyped for a biallelic polymorphism at the tryptophan hydroxylase locus. *Results:* The less common tryptophan hydroxylase U allele occurred with greater frequency in the patients who had attempted suicide. A logistic regression analysis confirmed an association between tryptophan hydroxylase genotype and lifetime history of suicide attempts. *Conclusions:* Serotonergic-system-related genes may influence the risk of suicide in persons with major depression.

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Alterations in the serotonergic system occur in persons who commit suicide (1) and in persons with major depression (2), schizophrenia (3), and personality disorders (4) who attempt suicide compared with those who do not attempt suicide. Genetic factors contribute to the risk of suicidal behavior or suicide (5). Because serotonergic activity is partly under genetic control, reduced serotonergic function may be one mechanism whereby genetic factors can influence suicide risk. The rate-limiting biosynthetic enzyme tryptophan hydroxylase regulates levels of serotonin. The tryptophan hydroxylase gene has a biallelic polymorphism (A-to-C transversion) in intron 7 (6). The alleles

are designated "U" and "L." We examined the association of tryptophan hydroxylase genotype with suicidal behavior in major depression.

METHOD

We studied 51 inpatients aged 18-80 years who had a current major depressive episode confirmed by the Structured Clinical Interview for DSM-III-R (7). Axis II diagnoses were made with the International Personality Disorder Examination (8). All patients were Caucasians from western Pennsylvania, were of European origin, were without unstable medical illness, and had been drug free for at least 2 weeks before the study. Written informed consent was obtained as approved by the institutional review board at Western Psychiatric Institute and Clinic, Pittsburgh, where the patients were hospitalized for major depression.

Attempted suicide was defined as a self-destructive act, with some intent to end one's life, resulting in medical damage sufficient to require a physician's evaluation. The nonattempter group (N=22) had no lifetime history of an attempted suicide. The group who had attempted suicide (N=29) had made an average of 2.2 attempts during their lifetime. Suicidal ideation was rated for the most recent suicide attempt (9). Depressive symptoms were rated with the 17-item Hamilton Depression Rating Scale.

DNA was extracted from blood (10), and 50 ng of genomic DNA was amplified with use of the polymerase chain reaction (11). Lumbar punctures were performed in a subgroup of the subjects (N=11), and their CSF 5-hydroxyindoleacetic acid (5-HIAA) concentrations were assayed by high-performance liquid chromatography (12).

All tests of significance were two-tailed. An analysis of variance was performed for comparison of continuous variables in the three genotypes. Logistic regression analysis and chi-square tests were carried out when dichotomous variables were included.

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TABLE 1. Demographic and Clinical Characteristics of Patients Who Had and Had Not Attempted Suicide

Variable	Patients Who Had Attempted Suicide (N=29)		Patients Who Had Not Attempted Suicide (N=22)	
	N	%	N	%
Sex				
Male	13	45	6	27
Female	16	55	16	73
Family history of suicide or suicide attempt	16	55	8	36
	<i>Mean</i>	<i>SD</i>	<i>Mean</i>	<i>SD</i>
Age (years)	35.3	14.0	41.0	16.6
Hamilton Depression Rating Scale score	26.8	9.8	28.4	9.1
Scale for Suicide Ideation score ^a	17.8	11.9	14.4	10.8

^aN=26 for patients who had attempted suicide; N=16 for patients who had not attempted suicide.

RESULTS

The group who had attempted suicide and the group who had not were comparable in severity of depression and suicidal ideation, age, and sex ratio at the index episode (table 1), and they had similar numbers of past episodes of major depression (data not shown). The cumulative period of risk—based on age at the time of the study and onset of the first lifetime episode of major depression—was similar in the two groups. The rarer tryptophan hydroxylase U allele was found with a higher frequency in the group who had attempted suicide (41%) than in the group who had not (20%) ($\chi^2=6.8$, $df=1$, $p<0.009$).

To determine whether the association of the U allele with attempted suicide was independent of depression and comorbid borderline personality disorder, we conducted a logistic regression analysis in which the dependent variable was attempter status and the independent variables were genotype (UU, UL, or LL), Hamilton depression score, and presence or absence of comorbid borderline personality disorder. The results for the overall model were significant ($\chi^2=9.6$, $df=4$, $p<0.05$). The analysis for the UU versus the LL genotype distinguished the patients who had attempted suicide from those who had not (odds ratio=12.5, 95% confidence interval=1.6–142.9; $\chi^2=5.1$, $df=1$, $p=0.02$). Severity of depression and comorbid borderline personality disorder were not statistically significant predictors ($\chi^2=1.3$, $df=1$, $p=0.23$, and $\chi^2=3.5$, $df=1$, $p=0.07$, respectively). Treating genotype as a continuous variable (i.e., UU=2, UL=1, and LL=0) generated similar results for the overall model ($\chi^2=9.6$, $df=3$, $p=0.02$), the likelihood ratio test for genotype ($\chi^2=6.0$, $df=1$, $p=0.01$; Wald $\chi^2=5.2$, $df=1$, $p=0.02$), and the odds ratio of genotype predicting suicide attempter status (12.0).

Severity of depression differed across genotypes ($F=3.31$, $df=2$, 48 , $p=0.04$). Greater severity was found in the LL and UL groups relative to the UU group (for UU

versus LL, $p<0.0001$; for UU versus UL, $p<0.0007$; Dunn post hoc tests with Bonferroni correction).

No difference in CSF 5-HIAA between the groups with the three possible genotypes was found.

DISCUSSION

The less common U allele of the tryptophan hydroxylase genotype was associated with suicidal behavior in these subjects with major depression. Since all of the subjects had major depression, the finding appears related to suicidal behavior in the context of major depression and not to major depression itself. The genetic or familial liabilities for depression and for suicide attempts

are separate (13, 14); our results refer to the liability for suicide attempts.

Serotonergic function is under genetic regulation (15). Serotonergic dysfunction is associated with a past suicide attempt and can predict future suicide and attempted suicide (3, 16). An association between tryptophan hydroxylase genotype and suicidal behavior supports the hypothesis that genetic factors can modulate suicide risk by influencing serotonergic activity.

Nielsen and colleagues (17) reported an association of the L allele with suicide attempts in impulsive alcoholic offenders. They found that the L allele was not associated with suicide attempts in a nonimpulsive offender group (D.A. Nielsen et al., personal communication). Our results and those reported earlier (17) may be partly explained by differences in subject phenotype and ethnicity. Abbar and colleagues (18) reported no association between an uncharacterized polymorphism at the tryptophan hydroxylase locus and suicidal behavior. Thus, the significance of their results with respect to ours and those of others (17) is uncertain. Nevertheless, association studies have methodological limitations and need replication in large homogeneous populations.

An association between tryptophan hydroxylase alleles and suicidal behavior suggests a mutation of physiological significance at or very close to the tryptophan hydroxylase locus. An intronic mutation is unlikely to convey this effect directly. The tryptophan hydroxylase intronic polymorphism might be in linkage disequilibrium with another mutation elsewhere in the tryptophan hydroxylase coding region or in a regulatory sequence.

This study provides the first evidence linking a genotype involving a serotonin-related gene to suicidal behavior in major depression. Further studies of the tryptophan hydroxylase gene and immediately neighboring genes on chromosome 11 may yield insights into neurobiological genetic mechanisms associated with suicidal behavior.

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