A Tryptophan Hydroxylase Gene Marker for Suicidality and Alcoholism

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Background: Tryptophan hydroxylase (TPH) is the rate-limiting enzyme in the synthesis of serotonin. Low turnover rate of this monoamine neurotransmitter is associated with impaired impulse control. We previously reported that, in Finns, TPH genotype was associated with suicidality, a pathophysiological mechanism that may involve impaired impulse control.

Methods: Association and sib-pair linkage analyses of a polymorphism in intron 7 of the TPH gene with suicidality, alcoholism, and the Karolinska Scales of Personality were conducted in 804 Finnish alcoholic offenders, controls, and their relatives, in a sample that included 369 sib pairs.

Results: The association of the TPH I779C (L) allele to suicidality in impulsive offenders reported previously was replicated in a new group of Finnish offenders (P = .001, n = 122). The intron 7 variant in the TPH gene showed significant evidence for linkage to suicidality (P = .006 in unaffected sib pairs), severe suicide attempts (P = .006 in unaffected sib pairs; regression: P = .01), alcoholism (P = .003 in unaffected sib-pairs; regression: P = .02), and Karolinska Scales of Personality socialization score (regression: P = .002).

Conclusions: The status of the TPH A779C allele as a marker for suicidality was replicated and linkage with alcoholism and Karolinska Scales of Personality socialization score was also observed. A functional variant(s) in or close to the TPH gene may predispose individuals to suicidality and other behaviors thought to be influenced by serotonin.

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Family, adoption, and twin studies have demonstrated heritability and familial transmission of suicidality and alcoholism. In fact, suicidality and alcoholism may share common genetic vulnerability variables. A major risk factor for suicidality is alcoholism. Compared with the general population, alcoholism increases the risk of suicide 60- to 120-fold when comorbid with a mental disorder. Furthermore, alcoholism is diagnosed ante mortem in 25% of suicide victims.

Low cerebrospinal fluid (CSF) 5-hydroxyindoleacetic acid (5-HIAA) concentrations have been detected in patients with suicidal behavior and early-onset alcoholism, indicating a lower rate of serotonin turnover. Genetic variation may play a role in the control of serotonin turnover rate. Many genes involved in serotonin metabolism have allelic variants including monoamine oxidase A, tryptophan hydroxylase (TPH), cyclohydroxylase, the serotonin transporter, and the serotonin 5-HT1A, 5-HT1D, 5-HT1D, 5-HT1F, 5-HT2A, 5-HT2C, and 5-HT3 receptors.

Several serotonergic variants alter the expression or the properties of the gene product and may modify behavior. A 5-HT2A variant lowers agonist-mediated receptor down-regulation rate and desensitization, and a 5-HT2A variant diminishes serotonin-mediated intracellular calcium release. In 1 kindred, a monoamine oxidase A variant produced a truncated protein that led to an X-linked syndrome characterized by increased impulsive behavior. A serotonin transporter promoter variant attenuates transcription and accounts partially for the variance in anxiety-related personality traits. These findings, like most in psychiatric genetics, remain unreplicated or uncertain.

Inherited variants of TPH, the rate-limiting enzyme in serotonin biosynthesis in the neurons of the raphe nuclei, could influence serotonin metabolism in the brain. We previously observed...
SUBJECTS AND METHODS

SUBJECTS

The Finnish sample consisted of 268 male alcoholic violent offenders and fire setters who were ordered to undergo forensic psychiatric examination by a district court, 256 controls, 274 relatives of violent offenders, and 6 relatives of controls (Table 1). The controls were chosen to roughly match the patients for age, sex, and social class. All controls were recruited by advertisements placed in trade schools, in police and fire stations, and on the docks in Helsinki. The violent offenders and fire setters were classified as impulsive (n = 168) or nonimpulsive (n = 87) on the basis of the characteristics of the crime for which they were remanded to the forensic psychiatric examination. Crimes classified as impulsive were unpreamted and unprovoked, whereas those classified as nonimpulsive were clearly premeditated. The classification was made by one of us (M.V.), blind to the biochemical and genetic data, by analyses of police records, which included interviews of the offender and witnesses to the index crime. All subjects were asked to participate in the study by a physician who was not an investigator. All signed a written informed consent. The study was approved by the National Institute of Mental Health Intramural Research Program Institutional Review Board and the Office of Protection From Research Risks, Bethesda, Md, in the United States and by the University of Helsinki Central Hospital and Department of Psychiatry Institutional Review Boards in Finland.

PSYCHIATRIC DIAGNOSIS

A total of 192 violent offenders, 219 controls, and 269 relatives of controls were interviewed by a research psychiatrist (M.E.) using the Structured Clinical Interview for DSM-III-R. The interviews were independently blind-rated for DSM-III-R diagnoses by 2 research psychiatrists. Discrepancies were resolved in a consensus conference with a senior research psychiatrist (G.L.B.). For this study, intermittent explosive disorder was diagnosed according to DSM-III-R criteria to replicate the methods of our previous studies. Antisocial personality (ASP) is defined herein as having a diagnosis of either ASP disorder or intermittent explosive disorder. Alcoholism was defined as DSM-III-R alcohol abuse (n = 58) or alcohol dependence (n = 252). The Karolinska Scales of Personality (KSP) were administered by a social worker to all subjects. The KSP were developed to measure dimensions of personalities and are derived from theories of biologically based temperament dimensions. The KSP have 135 questions grouped into 15 scales that measure a subject’s habitual behaviors and feelings. The scales are normalized for the Swedish population and measure relatively stable personality traits. The KSP is the most commonly used psychological test in genetic studies on offenders in Scandinavia. The socialization scale consists of questions from the California Psychological Inventory, which, in turn, was derived from the Delinquency Scale.

All 804 subjects were studied for a history of suicide attempts by review of their medical records and responses to the Brown-Goodwin and family history questionnaires that were administered by a social worker. Suicidal gestures were suicidal acts in which the wrist was superficially cut so as to require only suturing. All other attempts were classified as severe. Severe suicide attempts included attempts by violent methods and large overdoses with tricyclic depressants or sedatives. Attempts characterized by low doses of sedatives resulting in somnolence only were excluded.

To use our current clinical data on the Finns, the data on the subjects used in our 1994 study were updated if in the interim a subject had a suicide attempt or if an offender committed a new index crime. One control who was previously free of any suicide attempts made 3 attempts. In addition, 7 impulsive offenders, 1 nonimpulsive offender, and 3 relatives who were previously free of suicide attempts attempted suicide. One nonimpulsive offender was reclassified as impulsive and 11 impulsive offenders were reclassified as nonimpulsive on the basis of the characteristics of the most recent violent crime committed after the release from prison.

GENOTYPE ANALYSIS

The TPH genotype was determined in 804 subjects by single-strand conformational polymorphism analysis. All genotype analyses were performed by individuals unaware of the diagnosis, biochemical, or clinical status of the subjects.

STATISTICAL AND LINKAGE ANALYSIS

Population associations were analyzed by CHI analysis of variance, and Fisher exact tests (StatView, version 4.51; Abacus Concepts Inc, Berkeley, Calif). Significance was obtained when P < .05. The SIBPAL module of the SAGE package was used to evaluate linkage in sib pairs by means of identity by descent (IBD) sib-pair and Haseman-Elston regression analyses. The IBD sib-pair method evaluates the inheritance of alleles inherited identical by descent in discordant sib pairs and in concordant unaffected and affected sib pairs. Evidence for linkage can be obtained from any of the 3 sib-pair groups. In the Haseman-Elston method, the squared trait difference between siblings is regressed on the estimated proportion of marker alleles shared identical by descent. Numerical values were assigned to the presence of the behavior (either suicidality or alcoholism) with 0 indicating the absence of the behavior and 1 indicating its presence. A negative slope is supportive of linkage. Since the accuracy of sib-pair linkage analysis depends on large sampling approximations, P values were empirically determined by computer simulations. Simulations were performed by holding the phenotype, family structures, and population allele frequencies constant. The TPH alleles were randomly assigned to the founders of the pedigrees on the basis of their population frequency. A random allele from each parent was subsequently transmitted to offspring and analyzed for linkage of the phenotype by means of the SAGE SIBPAL module. By replicating this procedure 12,000 times, a simulated distribution was created that was used to obtain the simulation-derived P values.

QUANTIFICATION OF CSF 5-HIAA

Cerebrospinal fluid was obtained by lumbar puncture between 8 and 9 AM after overnight bed rest. The 5-HIAA in the first 12-mL aliquot of CSF was quantitated by high-performance liquid chromatography with electrophysical detection. The CSF 5-HIAA concentration was determined in 79 offenders and 33 controls.
found in the polypyrimidine stretch preceding the 3′ acceptor splice site, no alteration in splicing was identified when complementary DNAs from both alleles were sequenced. It is hypothesized that the I7 A779C polymorphism could be a marker for a nearby, unidentified functional variant(s).

Two other polymorphic nucleotides in the TPH gene have been reported. An A-to-C transversion at nucleotide 218 of intron 7 is in tight disequilibrium with the A779C polymorphism. Another TPH variant has been reported by Abbar et al; however, the nature and location of this AvaII restriction fragment length polymorphism remains unpublished.

Although alcoholism and suicidality represent complex phenotypes, it may be possible to identify genetic variants that have quantitative influences on these behaviors. Toward this goal, we investigated the role of TPH in predisposing individuals to suicidality, alcoholism, and the development of personality traits in a large Finnish cohort. Using association and linkage analyses, we replicated the previous association of a TPH genetic marker to suicidality and extend this finding to related behavioral phenotypes.

RESULTS

DEMOGRAPHIC VARIABLES

The demographics of the replication and combined groups used in this study are listed separately in Table 1. The replication group was used to directly test our earlier finding of an association of TPH genotype to suicidal behavior and includes all unrelated subjects who were not in our previous study. A significant association of TPH genotype to suicidality was observed in the replication group.

ASSOCIATION OF TPH GENOTYPE TO SUICIDALITY IN A NEW GROUP OF OFFENDERS

To replicate our previous finding of an association of TPH genotype to suicidal behavior, we performed a population association analysis on a new sample of Finnish offenders and controls who were not used in our previous study.
impulsive offenders group (P = .001, Cramer V = 0.34). Genotypes containing the 779C allele (L allele)33 were associated with a higher incidence of suicidality in the impulsive group (72% for the 779A/779C genotype, 59% for the 779C/779C genotype, and 31% for the 779A/779A genotype). However, in the nonimpulsive group, a significant association of TPH genotype to suicidality was observed in the opposite direction (P = .03, Cramer V = 0.33). Genotypes with the 779C allele were associated with a lower incidence of suicidality (32% for the 779A/779C genotype, 56% for the 779A/779A genotype, and 80% for the 779C/779C genotype).

We investigated whether there was a stronger association of TPH genotype to the more medically damaging, severe suicide attempts (Table 3). The association of TPH genotype to severe suicide attempts was highly significant (P < .001, Cramer V = 0.39), indicating that the strength of the previous results in Table 2 derive primarily from the severe suicide attempts.

The TPH genotype was analyzed in relation to CSF 5-HIAA level in the new group of Finns (Table 4). However, we were unable to replicate the previously observed association of TPH genotype to CSF 5-HIAA level in the impulsive offenders. The only major difference between subjects with and without CSF 5-HIAA measurements (Table 5) was that subjects with CSF 5-HIAA measurements included a larger proportion of suicide attempters.

### ASSOCIATION OF TPH GENOTYPE TO SUICIDALITY IN THE COMBINED GROUP

When the replication group was combined with the subjects used in our 1994 study,32 the association of TPH genotype and suicidality was strengthened (Table 6). In this combined analysis, a highly significant association (P < .001, Cramer V = 0.34) was observed in the impulsive offender group. The nonimpulsive group did not have the increased frequency of suicides in subjects with 779A/779A genotypes that was observed in Table 2 with the replication group. In fact, in the combined sample a lower 779A allele frequency was found in the suicide attempters group in both the nonimpulsive (0.42 vs 0.48) and impulsive (0.41 vs 0.57) groups. When the offenders were combined, the association remained significant (P = .01, Cramer V = 0.18). As mentioned above, the presence of the 779C allele was associated with an increase in the presence of suicide attempts in the impulsive group (75% for the 779A/779C genotype, 67% for the 779C/779C genotype, and 32% for the 779A/779A genotype) and in the total offender group (60% for the

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**Table 3. Population Association Between Tryptophan Hydroxylase Genotype and History of Severe Suicide Attempts in the Replication Group**

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Impulsive With, No. (%)</th>
<th>Nonimpulsive With, No. (%)</th>
<th>All Offenders With, No. (%)</th>
<th>Controls With, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>779A/779A†</td>
<td>6 (21)</td>
<td>8 (80)</td>
<td>14 (36)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>779A/779C</td>
<td>42 (69)</td>
<td>12 (35)</td>
<td>54 (55)</td>
<td>44 (3)</td>
</tr>
<tr>
<td>779C/779C</td>
<td>16 (50)</td>
<td>9 (56)</td>
<td>25 (52)</td>
<td>23 (1)</td>
</tr>
<tr>
<td>Total</td>
<td>64 (52)</td>
<td>58 (8)</td>
<td>93 (30)</td>
<td>92 (2)</td>
</tr>
</tbody>
</table>

| P‡              | <.001                   | .02                         | .12                         | .44                    |
| 779A allele frequency | 0.42                  | 0.56                        | 0.48                        | 0.44                  |

*a Number of subjects who attempted suicide. The percentage of suicide attempters to total subjects is given in parentheses.
†779A corresponds to the U allele.33
‡ Probabilities were calculated with the χ² test.

**Table 4. Lack of Association Between Tryptophan Hydroxylase Genotype and 5-Hydroxyindoleacetic Acid (5-HIAA) Concentration in the Replication Group**

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Impulsive Mean ± SEM (nmol/L)</th>
<th>Nonimpulsive Mean ± SEM (nmol/L)</th>
<th>Controls Mean ± SEM (nmol/L)</th>
<th>Total Mean ± SEM (nmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>779A/779A†</td>
<td>56 ± 8 (8)</td>
<td>97 ± 14 (7)</td>
<td>66 ± 10 (8)</td>
<td>72 ± 7 (23)</td>
</tr>
<tr>
<td>779A/779C</td>
<td>60 ± 4 (23)</td>
<td>87 ± 6 (19)</td>
<td>79 ± 8 (12)</td>
<td>74 ± 4 (54)</td>
</tr>
<tr>
<td>779C/779C</td>
<td>64 ± 11 (13)</td>
<td>75 ± 11 (9)</td>
<td>72 ± 7 (13)</td>
<td>70 ± 5 (35)</td>
</tr>
<tr>
<td>P‡</td>
<td>.80</td>
<td>.32</td>
<td>.60</td>
<td>.81</td>
</tr>
<tr>
<td>Overall 5-HIAA concentration</td>
<td>60 ± 4 (44)</td>
<td>86 ± 5 (35)</td>
<td>73 ± 5 (33)</td>
<td>72 ± 3 (15)</td>
</tr>
<tr>
<td>779A allele frequency</td>
<td>0.44</td>
<td>0.47</td>
<td>0.42</td>
<td>0.45</td>
</tr>
</tbody>
</table>

*a Mean±SEM concentrations were determined as described by Scheinin et al.49 Numbers in parentheses are numbers of subjects.
†779A corresponds to the U allele.33
‡ Probabilities were calculated with the analysis of variance test.
779A/779C genotype, 64% for the 779C/779C genotype, and 39% for the 779A/779A.

There was a significant difference in the TPH I7 779A allele frequency between offenders who had not attempted suicide and controls (Table 6) in the combined group. The offenders with suicidality had essentially the same I7 779A allele frequency as controls without suicidality (0.41 vs 0.43; Fisher exact P = .66). However, offenders who had not attempted suicide had a significantly higher I7 779A allele frequency than controls (0.53 vs 0.43, Fisher exact P = .002) or suicide attempters (0.53 vs 0.41, Fisher exact P = .01).

An analysis of the association of TPH genotype to severe suicidal behavior was performed in the combined sample. As seen in Table 7, the association of TPH to suicidality was strengthened when only the severe suicide attempts were examined in the impulsive (P < .001, Cramer V = .37), nonimpulsive (P = .03, Cramer V = .29), and all (P = .007, Cramer V = .20) offenders groups.

**LINKAGE OF TPH GENOTYPE TO SUICIDALITY IN FINNISH FAMILIES**

Analysis of linkage to suicidality was conducted by means of the IBD sib-pair and Haseman-Elston methods.6 Analyses were performed with 243 unaffected, 102 discordant, and 21 affected sib pairs. The demographics of the subjects used in the sib-pair analyses are presented in Table 8. These families included subjects from both the previous study33 and the replication sample. Linkage of suicidality to TPH is presented in Table 9. The IBD sib-pair analysis demonstrated significant evidence of linkage in the concordant unaffected sib pairs (simulation-derived P = .006). The deviations from expectation for the alleles IBD in the unaffected and discordant sib pairs are consistent with linkage. A trend toward evidence of linkage was observed by the Haseman-Elston method (Table 10).

When the sib pairs were analyzed for linkage to severe suicides (Table 9), the support for linkage in the IBD analysis again was derived from the unaffected sib pairs (simulation-derived P = .006). The deviations from expectation for the alleles IBD were also consistent with linkage. Haseman-Elston regression analysis reached significance (simulation-derived P = .01), providing further evidence of linkage (Table 10). Therefore, it appears that the strength of the linkage of TPH to suicidality was derived primarily from the severe suicide attempts.

**LINKAGE OF TPH GENOTYPE TO ALCOHOLISM IN FINNISH FAMILIES**

Linkage analysis of TPH genotype to alcoholism was performed with the 158 unaffected, 87 discordant, and 124...
affected sib pairs available (Table 1) who were diagnosed by DSM-III-R criteria. The IBD sib-pair analysis demonstrated significant evidence of linkage in the unaffected sib pairs (simulation-derived \( P = .003 \)). Consistent with linkage is the deviation from expectation of alleles IBD. Significant linkage was also observed by Hase-man-Elston regression analysis (simulation-derived \( \chi^2 \)).

Because of the convergence of alcoholism with ASP traits with the type 2 alcoholism subtype, which has been shown to have a greater heritability than type 1 alcoholism,\(^4\) we investigated linkage of TPH to alcoholism with or without ASP. The unaffected and discordant sib pairs in the IBD sib-pair analysis provided evidence of linkage (Table 11, simulation-derived \( P < .001 \) and \( .006 \), respectively). Deviation from expectation of alleles IBD was also observed, consistent with linkage. Evidence of

**Table 7. Population Association Between Tryptophan Hydroxylase Genotype and History of Severe Suicide Attempts in the Combined Group**

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Impulsive</th>
<th>Nonimpulsive</th>
<th>All Offenders</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>With, No. (%)</td>
<td>Without, No.</td>
<td>With, No. (%)</td>
<td>Without, No.</td>
</tr>
<tr>
<td>779A/779A‡</td>
<td>8 (24)</td>
<td>26</td>
<td>9 (53)</td>
<td>8</td>
</tr>
<tr>
<td>779A/779C</td>
<td>63 (70)</td>
<td>26</td>
<td>13 (29)</td>
<td>32</td>
</tr>
<tr>
<td>779C/779C</td>
<td>27 (60)</td>
<td>18</td>
<td>15 (60)</td>
<td>10</td>
</tr>
<tr>
<td>Total</td>
<td>98 (58)</td>
<td>70</td>
<td>37 (43)</td>
<td>50</td>
</tr>
</tbody>
</table>

\( P^\S \)  
779A allele frequency 0.40 0.56 0.42 0.48 0.41 0.52 0.40 0.43

\( P^\S < .001 \)  
\( P^\S .03 \)  
\( P^\S .007 \)  
\( P^\S .27 \)

\( * \) Only unrelated offenders and controls were included in this analysis.  
\( \dag \) Number of subjects who attempted suicide. The percentage of suicide attempters to total subjects is given in parentheses.  
\( \ddagger \) Significant linkage was not detected in our combined group. In 1995 Abbar et al\(^3\) reported a study whose meaning is difficult to interpret. No association was found between an undefined TPH variant whose linkage disequilibrium to the TPH I7 A779C polymorphism is unknown and suicidal-
ity in French psychiatric patients of mixed ethnicity including few alcoholics. In the Abbar et al study, a nonsignificant trend toward association between TPH and suicidality was observed in the antisocial personality group, the group most resembling the impulsive offenders we have studied.

The strength of the TPH linkage to suicidality was derived from the severe suicide attempts. These attempts included those that met the violent suicide classification used by others. Previous studies have differentiated violent and nonviolent suicide groups on the basis of CSF 5-HIAA, platelet monoamine oxidase activity, urinary cortisol level, and norepinephrine-epinephrine ratio. Presumably, linkage of suicidality to TPH indicates that a gene in the vicinity of the TPH marker is influencing biochemical variables that affect suicidality.

The observed P values in our linkage analysis were verified with computer simulations to control for type I errors. This is important because we have observed (data not shown) that sib-pair linkage analysis can yield inflated P values when the trait is infrequent or sample size is small.

Suicidality was highest among offenders with either 1 or 2 I7 779C alleles in the combined study, similar to our original findings. Individuals with either 1 or 2 I7 779C alleles had an increased odds ratio (5.5 times for the impulsive group, 2.4 times for the all-offenders group; Table 6) of having attempted suicide or severe suicide (6.6 times for the impulsive group, 2.7 times for the all-offenders group; Table 7) indicating that the I7 779C allele was associated with increased vulnerability to suicidality. The higher 779A allele frequency among offenders without suicide attempts could be caused by this allele having a protective effect within a group at high risk for suicide.

Surprisingly, the strength of the linkage of TPH to alcoholism was derived from alcoholics without ASP. Cloninger et al defined 2 classes of alcoholics: type 1 and type 2. Type 1 alcoholics are characterized by a late age at onset and anxious personality traits. Type 2 alcoholics are male, have an early age at onset, and exhibit antisocial traits. However, the alcoholics without ASP comorbidity in the present sample had other personality disorders, particularly borderline personality disorder, confounding the classification of these alcoholics as type 1 or 2. Because of the recruitment of this sample through alcoholic offenders, this sample may be atypical in having a serotonin-associated risk factor, or this may be a typical feature of type 1 alcoholics. Such a result could be consistent with a recent report that a functional serotonin transporter polymorphism, 5HTTLPR, was associated with anxiety-related traits.

Finally, a linkage of TPH genotype to KSP socialization score was observed. Low socialization scores are the result of general dissatisfaction, poor family and school adjustment, and negative childhood experiences. The genetic influences that lead to suicidality and alcoholism may also affect KSP socialization scores. Nordstrom et al have shown that suicide attempters have significantly lower KSP socialization scale scores than controls. Since TPH was linked and associated with suicidality, linkage of TPH to KSP socialization score was not unexpected.

Previous studies have identified several genes associated with alcoholism. Asian alcoholics have significantly lower frequencies of a variant aldehyde dehydrogenase (ALDH2) and alcohol dehydrogenase (ADH2, ADH3) alleles. Although several reports demonstrated an association between the D2 dopamine receptor and alcoholism, a meta-analysis demonstrated no significant association.

This Finnish cohort has proved useful for the study of behavioral traits. Advantages of this group are that Finns are a population isolate more genetically homogeneous than most other Western populations. Their suicide rate is the third highest among industrialized nations, and their alcoholism rate is relatively low. The offenders are a violent, behaviorally extreme sample consisting primarily of murderers, violent sexual offenders, and fire setters. More

### Table 9. IBD Sib-Pair Analysis of Suicidality/Severe Suicide Attempts and TPH I7 A779C Variant

<table>
<thead>
<tr>
<th>Sib-Pair Type</th>
<th>No. of Pairs</th>
<th>Alleles IBD</th>
<th>SEM</th>
<th>P</th>
<th>Simulation-Derived P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unaffected</td>
<td>243</td>
<td>0.535</td>
<td>0.014</td>
<td>.005</td>
<td>.006</td>
</tr>
<tr>
<td>Discordant</td>
<td>102</td>
<td>0.495</td>
<td>0.022</td>
<td>.41</td>
<td>.40</td>
</tr>
<tr>
<td>Affected</td>
<td>21</td>
<td>0.489</td>
<td>0.045</td>
<td>&gt;.50</td>
<td>&gt;.50</td>
</tr>
</tbody>
</table>

### Table 10. Haseman-Elston Regression Analysis of Suicidality/Severe Suicide Attempts and TPH I7 A779C Variant

<table>
<thead>
<tr>
<th>Variable</th>
<th>Suicidality</th>
<th>Severe Suicide Attempts</th>
</tr>
</thead>
<tbody>
<tr>
<td>df</td>
<td>165</td>
<td>165</td>
</tr>
<tr>
<td>T</td>
<td>−1.45</td>
<td>−2.22</td>
</tr>
<tr>
<td>Intercept</td>
<td>0.362</td>
<td>0.303</td>
</tr>
<tr>
<td>Slope</td>
<td>−0.160</td>
<td>−0.214</td>
</tr>
<tr>
<td>P</td>
<td>.07</td>
<td>.01</td>
</tr>
<tr>
<td>Simulation-derived P</td>
<td>.07</td>
<td>.01</td>
</tr>
</tbody>
</table>

*IBD indicates identity by descent; TPH, tryptophan hydroxylase.

*TPH indicates tryptophan hydroxylase.
than half have attempted suicide, and all but 3 of the psychiatrically interviewed offenders were alcoholic.

If the linkage and association results reflect an effect of TPH on behavior, it is highly likely that the effect is not caused by the TPH I7 A779C polymorphism itself but, rather, by another functional variant within the TPH gene or a nearby gene. Association of a trait with a marker generally indicates that the functional variant(s) is nearby, whereas linkage can occur over much greater distances. Tryptophan hydroxylase is located on the short arm of chromosome 11 at p15.4-15.5. Tyrosine hydroxylase and D4 dopamine receptor genes are located nearby and are involved in neurotransmitter metabolism. However, the tyrosine hydroxylase gene has been shown to exert no influence on alcoholism, and no association was found between D4 dopamine receptor and alcoholism or monoamine metabolite concentrations.

The linkage and association results presented herein indicate that the TPH intron 7 polymorphism, or another mutation(s) nearby, is involved in suicidality, alcoholism, and socialization. No other specific genetic components of suicidality have been identified, although the recent report of familial transmission of suicidal behavior is consistent with our findings. Since suicidality and alcoholism are likely to be complex, multifactorial phenotypes, TPH may turn out to be one of several genes involved.

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