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The role of tyrosine hydroxylase gene variants in suicide attempt in schizophrenia

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HIGHLIGHTS

- Association between suicide attempt in schizophrenia and rs11564717 and the TH tetranucleotide repeat.
- Association between the TH haplotype A-A-A-G and suicide attempt.
- Strong association between suicide attempt and high number of hospitalization.

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ABSTRACT

Evidence has shown that attempted suicide in psychiatric disorders is a complex interplay of genes and environment. Noradrenergic dysfunction due to abnormalities in the tyrosine hydroxylase (TH) gene has been implicated in the pathogenesis of suicidal behavior in mood disorders. However, suicide is a leading cause of mortality in schizophrenia too. Recent evidence suggests that TH gene variants may also increase the risk of suicide attempts in schizophrenia patients, although the interaction with established clinical risk factors is unclear. This study aimed to identify TH gene variants conferring risk for suicide attempt in schizophrenia while accounting for the interaction between this gene and clinical risk factors. We performed analysis on four TH SNPs (rs11564717, rs11042950, rs2070762, rs689) and the common TCAT repeat (UniSTS:240639) for 234 schizophrenia patients (51 suicide attempters and 183 non-attempters). Clinical risk factors and ethnic stratification were included as covariates. Single marker analysis identified the SNP rs11564717 ($p = 0.042$) and the $TCAT_{(6)}$ ($p = 0.004$) as risk variants for suicide attempt. We also identified the haplotype A-A-A-G as a risk factor for suicide attempt ($p = 0.0025$). In conclusion, our findings suggest that TH polymorphisms may contribute to the risk of attempted suicide in schizophrenia even after accounting for established clinical risk factors and ethnic stratification. Further larger scale studies are needed to confirm these findings and to understand the mechanisms underlying the role of TH gene variants in suicide attempt in schizophrenia.

1. Introduction

Suicide attempt is a common phenomenon among patients with schizophrenia in which 20–40% of these patients reported to have had attempted suicide [17]. A history of attempted suicide is a robust clinical predictor of suicide [3], one of the leading causes of mortality in schizophrenia [2]. Genetic predisposition has been shown to contribute to the multifactorial risk model of suicidal behavior in schizophrenia. Most studies have focused on genes involved in the serotonergic pathway, although definitive genetic predictors have remained elusive [3]. A review by Souery et al. [20] highlighted that tyrosine hydroxylase (TH) may be a promising candidate gene for suicidal behavior. Tyrosine hydroxylase is the rate-limiting enzyme in the synthesis of noradrenaline. The finding of increased TH immunoreactivity in the locus coerulus of post-mortem brains of violent suicides has led to the postulated mechanism of noradrenergic dysfunction due to abnormalities in the TH gene as a vulnerability factor for suicidal behavior [9].

Persson et al. [16] found an association between suicide attempt and a gene variant of the tyrosine hydroxylase gene. The authors showed that the TH-K3 allele of the tetranucleotide short-tandem repeat of the TH gene was significantly higher among suicide attempters with adjustment disorders. The TH-K1 allele also had a marginally lower trend among all suicide attempters.

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The relationship between the TH gene and suicidal behavior in schizophrenia is less well defined. Giegling et al's study [10], which included schizophrenia spectrum disorders, showed preliminary evidence of an interaction effect between the TH gene (rs3842727) and personality traits in suicide attempters compared to healthy controls. However, the authors did not show any association between TH gene variants (rs3842727, rs6356) and suicidal behavior per se. A knowledge gap still exists in terms of the interaction between the TH gene and well-established clinical predictors of suicidal behavior in schizophrenia such as younger age [18], earlier age of onset and longer duration of untreated psychosis [1], gender [15], higher number of hospitalizations and comorbid drug abuse [21]. In terms of protective factors of suicidal behavior, clozapine has been demonstrated to have anti-suicidal effect in patients with schizophrenia [22].

Further research into the possible gene-environment interactions between the TH gene and known risk factors of suicidal behavior in schizophrenia would potentially improve the clinical utility of genetic predictors of suicidal behavior in schizophrenia. Therefore, the objective of this study is to investigate the association between polymorphisms in the TH gene and suicide attempt in schizophrenia while taking into account the interaction effect of clinical risk factors for suicidal behavior.

2. Materials and methods

Study participants were recruited at the Center of Addiction and Mental Health (CAMH, Toronto, Canada) from 1991 to 2008. Exclusion criteria included age <18 or >65, history of major neurological disorders, head injuries, major substance abuse and intellectual disabilities. A study population consisting of 234 unrelated patients with a DSM-IV diagnosis of schizophrenia were included in the molecular genetics study. Research ethics approval was obtained from CAMH. Written informed consent was obtained from all participants prior to the interview and blood sample collection.

The Structured Clinical Interview for Psychiatric Diagnosis (SCID-I) was administered to all subjects by trained clinical interviewers. The occurrence of a suicide attempt was assessed according to the Mood module of the SCID-I [8] and more aggressive attempts were classified as violent attempts [6]. The SCID assessment was retrospective.

2.1. Genetic analysis

Genomic DNA was obtained from peripheral leukocytes, using high salt extraction methods [13]. For genotype analysis, we selected the following single nucleotide polymorphisms, SNPs: rs11564717, rs11042950, rs2070762, rs689; and the short tandem repeat, STR tetranucleotide: UniSTS:240639, all of which are located within the TH gene on chromosome 11. All genotyping was done using a customized Illumina Chip (San Diego, US). The chromosome positions were as follows: rs689 at 2122224 (3′ TH gene flanking), rs2070762 at 2126335 (3′ untranslated region of the TH gene), rs11564717 at 2126889 (10th intron of TH gene) and rs11042950 at 2129718 (2nd intron of the TH gene). The STR tetranucleotide TCAT repeat (UniSTS:240639) is located at 2132220.2132381 (1st intron of the TH gene).

To analyze the presence of population stratification, the STRUCTURE software (version 2.3.4; [13], [101]). was used to identify the population substructure and estimate the geographic ancestry of the study participants. Inferred clusters of ancestry were calculated from Structure and included in the statistical analysis [12]. We selected 190 SNPs that were successfully genotyped in the study participants ($n = 234$). Corresponding HapMap [4] markers in the 3 reference populations:112 North/Western Europeans (CEU), 113 Yorubans from Nigeria (YRI), and 84 Han Chinese from Beijing (CHB) were utilized in the genetic analysis with the number of cryptic populations being set at 3.

2.2. Statistical analysis

All statistical analyses were carried out using the Statistical Package for the Social Sciences (SPSS) software, version 19.0. For the analysis of suicide attempt, bivariate logistic regression tests were performed with age, gender, self-reported ethnicity, age of onset of illness, duration of illness, high number (more than three) of lifetime hospitalizations and history of substance abuse as independent variables. Allele and genotype analyses were performed with UNPHASED and linkage disequilibrium analysis was done with Haploview. Multivariate logistic regression was used to estimate predictive models of TH gene variants at risk for suicide attempt after controlling for clinical covariates. Haplo-stats [19] was used to predict risk or protective TH haplotypes after controlling for clinical covariates.

3. Results

3.1. Clinical variables

The median age of the total sample population ($n = 234$) participants was 36 years (range = 16–65). For the age of onset, the median was 19.5 years (range = 7–40) while the median for duration of illness was 15 years (range = 1–41). This study population consisted of mainly male participants, $n = 167$ (66.2%). According to self-reported ethnicity, there were 183 (71.4%) White European participants. The mean age of onset of illness was 20.7 years (S.D. = 5.9) and mean duration of illness was 15.6 years (S.D. = 10). Fifty-one (21.8%) study participants had attempted suicide and nearly half of which ($n = 21$) were violent attempters.

Patients with schizophrenia who had more than 3 lifetime hospitalizations were 3 times more likely to attempt suicide compared to those who had 3 or less lifetime hospitalizations (Table 1). The following demographic and clinical factors were not significantly associated with suicide attempt: age, age at onset, male gender, self-reported ethnicity, duration of illness, illicit drug or alcohol use (Table 1).

3.2. Structure analysis

We inferred three genetic clusters in our samples and in the HapMap reference populations. The inferred ancestry in the White-European group in our sample was 92.1% European, 5.1% Asian and 2.8% African, consistent with CEU HapMap reference population: 92.1%, 5.8% and 2.1% respectively. The inferred ancestry in the Non-White European group was mixed (59.3% European, 28.7% Asian and 12% African). The three inferred clusters were incorporated as covariates in the analysis.

3.3. Allelic association

When we analyzed the SNP markers (Table 2), we found that rs11564717 showed significant allelic associations. Allele A was significantly associated with suicide attempt ($p = 0.043$). This risk allele was a rare variant with a frequency of 4% among suicide attempters and 1% among non-attempters. The other SNP markers, rs11042950, rs2070762 and rs689 were not significant (p-values of 0.072, 0.119 and 0.899 respectively). When we analyzed the TCAT repeat polymorphism (Table 3), the common allele (wild type) in our sample was $TCAT_{(9)}$ (frequency 28.21%). There was a trend in the global p-value (chi-square = 10.4051,