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Association between the SAT-1 Gene and Suicidal Behavior in Mexican Population

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Abstract

Objective: The gene coding for spermidine/spermine N1-acetyltransferase 1 (SAT-1) participates in the metabolic pathways of polyamines as a rate-limiting enzyme; this gene is involved in regulating polyamine levels and it has been considered a candidate gene for suicidal behavior. The aim of this study was to determine the association between SAT-1 polymorphism A-1537C (rs6526342) and suicidal behavior, in a sample of suicide attempt patients in the Mexican population.

Methods: To observe the association between rs6526342 and suicidal behavior, we evaluated 169 unrelated suicide attempters and compared them to 218 non-suicidal individuals. Patients were evaluated by a trained psychiatrist or clinical psychologist. SAT-1 rs6526342 genotypes were analyzed using the polymerase chain reaction end-point method.

Results: No significant association was observed between cases and comparison group for allele frequency (p=0.40, df=1, p=0.69). However, a significant association between rs6526342 and suicidal behavior was observed in the male group for allele distribution (χ^2=4.0, df=1, p=0.04, OR 0.48; 95% CI: 0.24-0.98), whereas in the female group, no association was found by genotype (χ^2= 2.85, df=2, p=0.23) or allele (χ^2=0.01, df=1, p=0.91) frequency.

Conclusion: Our results showed an association between allele C of the polymorphism in the promoter region of SAT-1 A-1537C (rs6526342) and suicidal behavior in Mexican males. This suggests that the SAT-1 gene may contribute to the risk for suicidal behavior among the Mexican population.

Keywords: Suicide; Mexican population; SAT-1 gene; Polymorphism

Introduction

Suicidal behavior is a serious public health problem. An increase in suicides has been observed in both developed and developing countries [1,2]. Worldwide, one suicide is completed every 40 seconds, leading to approximately one million deaths every year [3]. Also, it is well known that there are populations that show an increased rate of suicides as it has been reported in the native Alaskan population with a rate of 38.5 per 100000 persons [4]. In Mexico the literature suggests that from 1970 to 2007 suicides increased 275% [5]. Also, suicides have been reported as the second cause of death in Mexican teenagers between 15 to 19 years old [6]. The spectrum of suicidal behavior includes suicide ideation, suicide attempt and completed suicide [7,8]. However, there is another definition in suicidal behavior known as parasuicide which cover behaviors that may vary from an exclusively manipulatory attempt to an intentional suicidal gesture and a serious act which was not fatal by chance [9]. It is known that the etiology of suicidal behavior has multiple genetic and environmental influences throughout life, as well as in their in-between interactions, as conceptualized in a stress-vulnerability model [10,11]. The literature has shown evidence for a genetic contribution in suicidal behavior [12-14]. To date there is strong neurobiological evidence showing that serotonergic dysfunction is implicated in suicidal behavior, in particular, the genes coding for tryptophan hydroxylase-1 (TPH-1), tryptophan hydroxylase-2 (TPH-2) and 5-hydroxytryptamine receptor 1A (HTR1A). However, the association of genes in this neurobiological system and suicidal behavior remains controversial [15-17]. Furthermore, the possible contributions of specific genes and their different allelic variants are still in the process of ongoing studies [10]. The same is observed in the literature concerning studies of genome-wide association of suicidal behavior, in which new loci and genes are being reported [18-20]. Recent evidence suggests the involvement of changes in the polyamine stress response system in suicidal behavior [21], through a dysregulation of the polyamine system in the pathogenesis of this behavior [22]. The polyamines- putrescine, spermidine, and spermine-are naturally occurring polycations essential for cell proliferation [23,24]; they regulate cellular activities at transcriptional, translational, and post-translational levels [24,25]. Spermidine/spermine N1-acetyltransferase 1 (SSAT1 or SAT1) is a key enzyme in the metabolism of polyamines. Furthermore, it is decreased in the cortex of suicide completers [21,26]. It has become increasingly evident that this mechanism is involved in suicidal behavior [22]. The gene coding for SAT-1 is located on chromosome Xp22.1 (cloned by Xiao et al. [27]). Several polymorphisms in this gene have been reported as functional Single Nucleotide Polymorphisms (SNPs) such as A-1537C (rs6526342). This

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polymorphism has been associated with SAT-1 transcript levels, since allele A itself has been linked to higher SAT-1 expression, suggesting that this SNP could be a predictor of SAT-1 expression; hence the importance given to the study of this polymorphism [26,28-31].

The SAT-1 gene has been previously studied in relation to other diseases such as lung carcinoma and other cancers [32,33]. In 2006, Sequeira et al. reported the association between the SAT-1 gene and suicidal behavioral [26]; since then many studies have associated SAT-1 with other psychiatric diagnoses including schizophrenia [34], anxiety disorder [35,36], and mood disorders [36]. To date there are only few reports that have evaluated the association between the SAT-1 A-1537C (rs6526342) polymorphism and suicidal behavior [28,37-40], mostly in Caucasian populations. Therefore, it is necessary to explore the involvement of the SAT-1 gene in other ethnic communities. Therefore, the aim of this study was to determine a possible association between A-1537C (rs6526342) and suicide attempt patients in a Mexican population.

Materials and Methods

Sample

We performed a case-control study with a total of 169 patients consecutively recruited from the outpatient service of the General Hospital of Comalcalco in the state of Tabasco, Mexico. These patients had attempted suicide between January 2011 and February 2012 in the municipality of Comalcalco, in the state of Tabasco, Mexico. In addition, 218 unrelated persons were consecutively recruited from the Blood Donor Center of the same hospital to be used as the comparison group. The comparison group consisted of physically healthy subjects after a medical evaluation, with no manifested psychiatric problems when interviewed by a psychiatrist. To reduce ethnic variation and stratification effects, only Mexican subjects descending from Mexican parents and grandparents were included.

Ethics Statement

All subjects signed an informed consent to participate in the study after they were given a verbal and written explanation of the research objectives; they did not receive any economical remuneration. This study complied with the principles convened in the Helsinki Declaration. In addition, this study was approved by the DAMC-UJAT Ethics and Research Committee (UJAT-DAMC-2012-02).

Clinical Evaluation

Each patient was diagnosed based on the Structured Clinical Interview for DSM-IV Axis in the Spanish version. Trained psychiatrists or clinical psychologists with at least a master's degree evaluated all patients. Subjects with self-injury behavior, undetermined suicide attempt, or suicide ideation were excluded from the study. Of the 169 patients, 22 (13.0%) were diagnosed with schizophrenia spectrum disorders, 52 (30.1%) with mood disorders, 63 (37.3%) with stress-related disorders, 32 (18.9%) with substance-related disorders and 1 person with organic disorder.

Patients were excluded when the suicide attempt was determined not to have any suicidal intention or ideation using the Scale for Suicide Ideation in the Spanish version [41]. Also, subjects who were determined to have other concomitant medical or neurological illness were excluded. The presence of self-injury was evaluated only subject with self-injury was excluded.

In the comparison group, each individual was interviewed using systematic forms to obtain a detailed medical and psychiatric history in order to exclude subjects who had relatives with a lifetime history of mental disorder or suicidal behavior (as seen in other reports) [42].

Genotype Assay

Peripheral blood samples were taken from every subject to extract the DNA, using the Wizard Genomic DNA Purification Kit (Promega). SAT-1 A-1537C (rs6526342) genotypes were analyzed in all patients using the polymerase chain reaction (PCR) end-point method. The assay for rs6526342 is available in TaqMan SNP Genotyping Assay (Applied Biosystems). We followed the manufacturer's genotyping protocol. All genotyping was performed blind to patient outcome; as a quality control in our genotyping analyses we used random blind duplicates and checked for genotype concordance (the concordance rate was 100%).

Statistical Analysis

The information is presented as numerical values and percentages for the categorical variables (gender, marital status, socio-economic level), also we used the mean ± standard deviation for continuous variables (age, years of schooling). The chi-squared test was used to compare: i) categorical variables, ii) genotype and allele frequencies between groups. We used Student's t-test to compare continuous variables. The level of significance was set at 0.05. In this report suicidal behavior (dependent variable) was associated with genotype and allele frequencies of SAT-1 in subjects with suicidal behavior (independent variable). The fitness of genotype frequency distribution to the Hardy-Weinberg equilibrium was tested using the Finetti software (http://ihg.gsf.de/cgi-bin/hw/hwa1.pl). Genotype frequencies of the rs6526342 polymorphism were not in Hardy-Weinberg equilibrium in the female group ($p<0.05$). The power to detect associations was analyzed with the Quanto 1.2 software [43]. The power of the analysis was 0.44 (minor allele frequency =0.3170; genetic odds ratio=1.5; overall disease risk in the general population=0.01).

Results

Socio-demographic features of suicide attempters are summarized in Table 1. In the comparison group (n=218) the mean age was 31.77 years (± 12.68; range 16-60 years old) and the mean of education was 13.28 years of schooling (± 4.75; range 0-22 years).

Genotype and allele frequencies of A-1537C (rs6526342) of the SAT-1 polymorphism are shown in Table 2. No significant association was observed between cases and comparison group for allele (p=0.40, df=1, p=0.69). Given that the SAT-1 gene is located on chromosome X, separate analyses were performed for males and females. When we analyzed by gender, the A allele was significantly more frequent in males of the comparison group than in male cases (χ^2= 4.0, df=1, p=0.04, OR 0.48; 95% CI: 0.24-0.98). However, in the female group, no significant differences were observed in genotype (χ^2= 2.85, df=2, p=0.23) or allele (χ^2= 0.01, df=1, p=0.91) distribution (Table 2).

Discussion

In this study, we explored the association between the SAT-1 A-1537C (rs6526342) polymorphism and suicidal behavior. Initially, we analyzed the association in the population as a whole. Subsequently, we investigated whether gender differences were observed. The polyamine stress response has been studied in relation to suicidal behavior, mainly because this system may participate in physiological responses

	Cases group		Comparison group		χ^2	df	p value
Socio-demographic features	**Number**	**Percent**	**Number**	**Percent**			
Gender							
Male	60	35.5	76	65.1	0.01	1	0.89
Female	109	64.5	142	34.9			
Marital status	85	50.2	100	45.8	8.97	2	0.01
Married	82	48.5	101	46.4			
Single	2	1.3	17	7.8			
Widowed							
Socio-economic level							
High	12	7.2	5	2.3	10.80	2	0.004
Middle	88	52.0	145	66.5			
Low	69	40.8	68	31.2			
	Average (SD)	**Range**	**Average (SD)**	**Range**	**t**	**df**	
Age (years)	28.45(10.42)	14-57	33.12(13.08)	14-73	3.77	381	<0.001
Education (years of schooling)	8.67 (3.46)	0-22	12.21 (4.87)	0-22	6.59	329	<0.001

χ^2=Chi-squared test, df=Degree of freedom, t=Student's t-test, SD=Standard deviation.

Table 1: Socio-demographic features of a Mexican population sample contrasting suicidal (cases group) and non-suicidal individuals (comparison group).

	Cases (n=169)		Comparison group (n=218)	
Genotype	**Female (n=142) n(%)**	**Male (n=76) n(%)**	**Female (n=109) n(%)**	**Male (n=60) n(%)**
AA	62 (43.7)		43 (39.6)	
AC	31 (21.8)		34 (31.1)	
CC	49 (34.5)		32 (29.3)	
Allele				
A	155 (54.6)	37 (48.7)	120 (55.1)	19 (31.7)
C	129 (45.4)	39 (51.3)	98 (44.9)	41 (68.3)
Total	284	76	218	60

Female genotypes: χ^2=2.85, df=2, p=0.23
Female alleles: χ^2=0.01, df=1, p=0.91
Male alleles: χ^2=4.0, df=1, p=0.04, OR=0.48 (95% CI: 0.24-0.98)

Table 2: Genotype and allele distribution of SAT-1 (rs6526342) in suicidal behavior in patients and comparison group.

to physical, emotional and hormonal stressors [21]. Spermidine/spermine N1-acetyltransferase 1 is the rate-limiting enzyme of this system. A major interest was established when this enzyme was observed decreased in prefrontal profiles of gene expression in subjects with consummated suicide [44]. As a result, SAT-1 could be used as a possible peripheral biomarker [26].

In this Mexican population, we found no association between SAT-1 A-1537C and suicidal behavior by allele when the sample was taken as a whole. Finally, we did not observe any significant differences between female groups. However, male subjects presented a different scenario. We found a higher prevalence of allele C in patients who had attempted suicide. To our knowledge, this is the first study addressing the genetic association between SAT-1 A-1537C (rs6526342) and suicidal behavior in a Mexican population, which confirms our working hypothesis that SAT-1 gene genotype may confer a vulnerability to attempt suicide in Mexicans. Our results are similar to previous reports such as in Sequeira et al. [26], where these authors compared 181 male suicide completers (post-mortem) and 80 male controls (patients of French-Canadian origin). As a result, they also found a higher frequency of allele C in suicidal completers, and propounded that allele C may increase the predisposition to suicide. Gender-specific differences have also been observed in SAT-1 expression, possibly because this gene is located on the X chromosome [31]. Furthermore, differences by gender have been observed in polyamines and their metabolic enzymes [31,45,46]. The positive evidence in the literature and our genetic association study suggest a possible role for SAT-1 in suicidal behavior. Conversely, there is a report that did not encounter any association of either allele A or C in rs6526342 of SAT-1; this study was performed in Geneva and Montpellier in Swiss and French populations. These authors analyzed suicide attempters (n=449) and suicide completers (n=88) vs. a comparison group (n=224) and did not observe statistical significant differences [28]. Therefore, more studies are necessary for the replication of positive results.

There are several possible explanations for the discrepancies observed in the four populations analyzed regarding this association, as proposed by Fiori et al. [47]. They may be due to sample heterogeneity and the differences in allele frequency and properties among populations. However, our sample was selected from a relatively homogenous Mexican population, since only individuals of the state of Tabasco with parents and grandparents born in this state were included (only the Chontalpa City region of Tabasco was considered).

Finally, we recognize four weaknesses in our study: 1) the sample size is small in comparison with other studies. Statistical tests normally require larger samples to ensure a representative distribution of the population in order to generalize outcomes. On other hand, there are several association studies of suicidal behavior that have analyzed different gene variants which may play a role in this pathology. In consequence, our second limitation is that we only studied one polymorphism, because there have not been other SAT-1 polymorphisms associated with suicidal behavior. Third, no scales to measure clinical symptomatology were used (specifically for depression and anxiety), which may be considered as risk factors involved in the pathology of suicidal behavior. Fourth, our results may be influenced by an association between the studied SNP and any underlying psychiatric condition in the case group. Finally, we did not correct for multiple testing because only one polymorphism was included in this study. In contrast, a positive point to consider is that suicidal behavior is the leading cause of mortality in psychiatric patients; our results contribute to understand how the polyamine stress response system could be involved in suicide attempt.

In conclusion, our results found that in men allele C of the A-1537C (rs6526342) polymorphism of the SAT-1 gene exhibited an association with suicidal behavior in a Mexican population sample. However, more

comprehensive studies and larger samples are necessary to determine conclusively the association of SAT-1 with suicidal behavior.

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Disclosure

The authors declare not to have any competing interests.

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