

Association between A-1438G polymorphism in the 2A (5-HT2A) serotonin receptor gene and impulsivity in suicidal behaviour

BEGOÑA PAREDES¹, PILAR ALEJANDRA SÁIZ², M.^a PAZ GARCÍA-PORTILLA², BLANCA MORALES³, MERCEDES PAJÍN¹, IGNACIO FERNÁNDEZ¹, IVÁN GARCÍA¹, VICTORIA ÁLVAREZ³, ELIECER COTO³, MARÍA TERESA BASCARÁN², MANUEL BOUSOÑO², JULIO BOBES²

¹Emergency Department, Hospital San Agustín, Avilés, Spain. ²Dept. of Psychiatry, Faculty of Medicine, University of Oviedo, Spain. ³Laboratory of Molecular Genetics, Hospital Central de Asturias, Oviedo, Spain.

CORRESPONDENCE:

Begoña Paredes
Emergency Department
Hospital San Agustín
Camino de Heros 4
33400 Avilés, Spain
E-mail: frank@uniovi.es

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None

Objective: To determine the association between four serotonergic polymorphisms (A-1438G (rs6311) and T102C (rs6313) of the 5-HT2A receptor gene, and STin2 VNTR and 5-HTTLPR of the SLC6A4 gene) and impulsivity in suicide attempts (SA).

Methods: 180 suicide attempters from Asturias (Northern Spain) were assessed using the Suicidal Intent Scale (SIS) and genotyped by standard methods. According to the SIS definition SA were divided into two subgroups (impulsive and non-impulsive). A score of 6 on the planning subscale was used to classify attempts as impulsive or non-impulsive.

Results: Mean age (SD) was 35.6 (12.5) years and about 63.3% of cases were female. Most of patients (95.6%) had at least one psychiatric diagnosis. More prevalent diagnoses were affective disorders (36.7%), schizophrenia and other psychosis (18.3%), anxiety disorders (12.2%), and personality disorders (11.1%). Previous SA was found in 49.4% of cases. About 64.4% of SA patients were classified as impulsive SA. A-1438G and T102C polymorphisms were in complete linkage disequilibrium in our population. We found an excess of -1438GG genotype and -1438G allele when compared impulsive SA with the non-impulsive group (34.5% vs 14.1%, $\chi^2(2) = 11.5$, corrected $P = 0.012$; 0.59% vs 0.41%, $\chi^2(1) = 11.2$, corrected $P = 0.004$, OR = 2.11 (1.36-3.27), respectively). No differences in genotypic or allele frequencies of the SLC6A4 gene polymorphisms were found.

Conclusions: Our findings suggest that polymorphic variants on the 5-HT2A gene may predispose for impulsive suicidal behaviour. [Emergencias 2008;20:93-100]

Key words: Genetic polymorphism. Suicide, attempted polymorphisms.

Introduction

Suicidal behaviour is one of the main public healthcare problems in all countries. The extent of this problem is well reflected in the World Health Organisation (WHO) statistics¹, which reveal suicide as being responsible for 2% of deaths worldwide.

Several lines of research have suggested the existence of family transmission in suicidal behaviour and that this heritability cannot only be explained by transmission of the psychiatric disorders most frequently associated with suicidal behaviour^{2,3}.

Molecular studies carried out in recent years have suggested that the serotonergic system could be involved in the pathogenesis of suicidal behaviour, impulsivity and aggressivity^{4,6}, and numerous studies have shown an association between certain polymorphic variants of the triptophan hydroxylase gene (TPH) (rate-limiting enzyme in serotonin synthesis), of the serotonin transporter (5-HTT, SERT or SLC6A4) and of the 2A (5-HT2A) serotonin receptor and suicidality and impulsivity^{5,7,8}.

In relation to suicidal behaviour, impulsivity can be approached from two angles: that of the individual (trait) and that of the suicide attempt

(SA) (state). In the first instance, we consider an individual's personality trait, defined as a predisposition toward swift and unpremeditated reactions to external or internal stimuli, without taking into account the negative consequences of such reactions for the impulsive individual himself or others⁹. On the other hand, SA impulsivity can be regarded in terms of the absence/presence of planning said SA. In other words, a SA may or may not be impulsive, and the suicidal individual may or may not have impulsive characteristics. In this regard, studies indicate that an individual's impulsivity is not a good prognostic factor for the impulsivity of a SA¹⁰. This study focuses exclusively on measuring the impulsivity of a SA.

SLC6A4 is a key protein in the regulation of serotonergic neurotransmission, responsible for the synaptic reuptake of serotonin (5-HT) and the locus of action of numerous anti-depressants. The SLC6A4 gene is located in the long arm of chromosome 17 (17q11.1-12). Two polymorphic variants of interest have been described for this gene. The first (5-HTTLPR) is located at the 5' tip of the exon 1A promoter region consisting of the insertion/deletion (I/D) of 44 base pairs, giving way to two possible alleles "S" (deletion) and "L" insertion. This polymorphism affects the functionality of SLC6A4 and an association of the "short" variant (S) with a reduction in the degree of transcription of the SLC6A4 gene and fewer uptake loci have been shown¹¹. The second polymorphic variant involves the presence of a variable number of repetitions (9,10 or 12 repetitions) of 17 base pairs (STin2 VNTR) located at intron 2. Previous studies have suggested that short variants of this polymorphism reduce SLC6A4 gene transcription and protein concentration and functionality^{12,13}.

The 5-HT_{2A} receptor is mainly located in cerebral cortex postsynaptic neurons. The gene of this receptor is located in the long arm of chromosome 13 (13q14.1-14.2). Two very frequent polymorphisms have been described in this gene, A-1438G (rs6311) and T102C (rs6313). Recent findings suggest that A-1438G polymorphism could have functional effects on the expression of this receptor in the brain¹⁴.

Despite numerous studies on the aforementioned polymorphisms in relation to suicidal behaviour, their role in the impulsivity of this behaviour remains to be determined. The aim of this study was to determine the possible association between 4 serotonergic polymorphisms (A.1438G and T102C of the 5-HT_{2A} gene and 5-HTTLPR and STin2 VNTR of the SLC6A4 gene) and impulsivity in suicide attempts.

Method

Patients

This study included a total of 180 patients consecutively presenting to the Emergency Department of the San Agustín Hospital (Avilés- Asturias) following a suicide attempt (SA) according to the WHO definition¹⁵. Patients refusing to participate in the study had similar gender and age characteristics as those included therein. All the patients were evaluated in the Emergency Department by Family and Community Medicine Specialists trained in the standardised psychometric tools commonly used within the first 24 hours after the SA.

The impulsivity of the SA was evaluated using the planning subscale¹⁶ of the Suicide Intent Scale (SIS)¹⁷. SA impulsivity has traditionally been measured on the basis of two specific items of the SIS (item 6=active preparation for attempt and item 15=degree of premeditation)¹⁸⁻²⁰. However, considering the fairly limited definition of SA impulsivity based only on two items, we used the definition of SA impulsivity described by Díaz et al¹⁶, based on the scores of 8 SIS items which we believe yields a more complete definition of impulsivity in an SA and shows a marked correlation with the traditional measurement based on 2 items (Spearman's rho = 0.72; $p < 0.001$)¹⁰. The presence or absence of psychiatric diagnoses was determined using the Mini-International Neuropsychiatric Interview-MINI (DSM-IV)²¹ and a full clinical history of the patients. In the event of discrepancies between the MINI diagnoses and the clinical history, a consensus team made up of Psychiatric Specialists made a final diagnosis using DSM-IV criteria after reviewing both sources. The lethality of the SA was evaluated using the Medical Damage Rating Scale (MDS)²². A MDS score ≥ 4 was considered as high lethality. Lastly, SA violence was established using the Apter and Wasserman²³ classification, that classifies suicidal methods as active (including such methods as hanging, strangulation or suffocation, jumping from a height, throwing oneself or lying before a moving object, submersion, firearm etc) and non-violent (or passive) including methods such as overdose, poisoning or gas.

Written informed consent was obtained from all the patients included in the study and all aspects set forth by current legislation regarding clinical research were observed throughout. Likewise, the study has been subjected for approval by the Regional Committee of Ethics and Clinical Research.

Genotyping

Genomic DNA was obtained from polymorphonuclear leukocytes of all the subjects with 10ml of peripheral blood using ethylenediaminetetraacetic acid (EDTA) as an anticoagulant and following the method proposed by Miller et al²⁴. The various polymorphisms were identified in accordance with previously published methods²⁵.

Statistical Analysis

The Hardy-Weinberg equilibrium calculation was performed using the χ^2 test. The SAs were divided into two subgroups: impulsive and non-impulsive according to the SA definition suggested by Díaz et al¹⁶ based on the SIS. According to these authors, a score of 6 in the planning subscale was used to classify attempts as impulsive (scores under 6) or non-impulsive (6 or more points on subscale). Possible genotypical and allelic differences between the groups were analysed using the χ^2 test. Likewise, the different odds ratios (ORs) and respective confidence intervals (CIs) of 95% were calculated. The statistical analysis package SPSS (version 14.0) was used to perform the aforementioned statistical calculations. Finally, the Genecounting Program²⁶ was used to determine the linkage imbalance between all marker pairs as well as to compare the haplotypic frequencies in patients and controls and determine possible differences using the likelihood ratio test (LRT). A Bonferroni correction coefficient of 4 (4 genetic markers included in the study) was applied to all p values reported for multiple comparison control.

Results

An impulsive type SA was carried out by 64.4% (n = 116) of the study subjects (< 6 points in the SIS planning subscale), whereas the remaining 35.6% undertook a non-impulsive SAs (\geq 6 points of the SIS planning subscale). Tables 1 and 2 respectively show the main sociodemographic and clinical characteristics of both the whole sample and both subgroups. As shown in Table 1, both SA groups (impulsive and non-impulsive) were similar in terms of mean age [impulsive SAs: 35.15 (13.5); non-impulsive SAs: 36.22 (10.6); t = 0.55; df = 178; p = 0.583] and gender [impulsive SAs: male = 39 (33.6%); non-impulsive SAs: males = 29 (43.8%); $\chi^2 = 1.81$; df = 1; p = 0.178]. No significant statistical differences were obtained between the groups in relation to other sociodemographic variables such as racial distribution, marital status, educational level or work situation (Table 1). From a clinical point of view, both groups showed a similar prevalence of concomitant psychiatric disorders [110 patients (94.8%) in the impulsive SA group and 62 patients (96.9%) in the non-impulsive SA group; $\chi^2 = 0.41$; df = 1; p = 0.523]. With regard to specific psychiatric diagnoses, no statistically significant differences were observed between the two groups of patients ($\chi^2 = 3.32$; df = 6; p = 0.767) (Table 2). The percentage of non-violent SAs was higher in patients who had carried out impulsive SAs compared to those with non-impulsive SAs (89.7% vs. 78.1%; $\chi^2 = 4.44$; df = 2; p = 0.035). Previous SAs had been carried out by 49.4% of the study sam-

Table 1. Sociodemographic characteristics of the whole sample and both subgroups of suicide attempts (impulsive and non-impulsive)

Characteristic	Total (n = 180)	Impulsive SAs (n = 116)	Non-impulsive SAs (n = 64)	χ^2 (gl)	p
Age [mean (SD)]	35.6 (12.5)	35.15 (13.5)	36.22 (10.6)	-0.55 (178)*	0.583
Sex [n (%)]					
Men	66 (36.7)	39 (33.6)	28 (43.8)	1.81 (1)	0.178
Women	114 (63.3)	77 (66.4)	36 (56.3)		
Racial distribution [n (%)]					
Spaniards of Caucasian origin	173 (96.1)	112 (96.6)	61 (95.3)	0.17 (1)	0.681
Hispanics	7 (3.9)	6 (3.4)	3 (4.7)		
Marital status [n (%)]					
Single	80 (44.4)	53 (45.7)	27 (42.2)	0.92 (3)	0.820
Married/partner	69 (38.3)	45 (38.8)	24 (37.5)		
Separated/divorced	25 (13.9)	14 (12.1)	11 (17.2)		
Widowed	6 (3.3)	4 (3.4)	2 (3.1)		
Educational level [n (%)]					
Primary	89 (49.4)	56 (48.3)	33 (51.6)	2.33 (2)	0.312
Secondary	75 (41.7)	52 (44.8)	23 (35.9)		
Higher	16 (8.9)	8 (6.9)	8 (12.5)		
Professional status [n (%)]					
Employed	112 (62.2)	68 (58.6)	44 (68.8)	2.06 (2)	0.358
Unemployed	34 (18.9)	25 (21.6)	9 (14.1)		
Retired	34 (18.9)	23 (19.8)	11 (17.2)		

*Student-Fisher t test for independent groups. SD: standard deviation; SA: suicide attempt; df: degree of freedom.

Table 2. Clinical characteristics of total sample and both subgroups of suicide attempts (impulsive and non-impulsive)

Characteristic	Total (n = 180)	Impulsive SAs (n = 116)	Non-impulsive SAs (n = 64)	χ^2 (gl)	<i>p</i>
Psychiatric diagnosis (DSM-IV criteria) [n (%)]	172 (95.6)	110 (94.8)	62 (96.9)	0.41 (1)	0.523
Alcohol/substance dependence	6 (3.3)	3 (2.7)	3 (4.8)	3.32 (6)	0.767
Schizophrenia and other psychoses	33 (18.3)	24 (21.8)	9 (14.5)		
Affective disorders	66 (36.7)	43 (39.1)	23 (37.1)		
Anxiety disorders	22 (12.2)	15 (13.6)	7 (11.3)		
Adaptation disorders	19 (10.6)	11 (10.0)	8 (12.9)		
Eating disorders	6 (3.3)	3 (2.7)	3 (4.8)		
Personality disorders	20 (11.1)	11 (10.0)	9 (14.5)		
Non violent SAs (overdose, poison, gas) [n (%)]	154 (85.6)	104 (89.7)	50 (78.1)	4.44 (1)	0.035
Previous SAs [n (%)]	89 (49.4)	56 (48.3)	33 (51.6)	0.18 (1)	0.673

DSM-IV: Diagnostic and statistical manual of mental disorders – DSM-IV. SA: suicide attempt; df: degree of freedom.

ple (n = 89), although no statistically significant differences were observed with regard to repetition percentage in both sub-samples [n = 56 (48.3%) repetitions in impulsive SA subgroup vs. n = 33 (51.6%) in the non-impulsive group; $\chi^2 = 0.18$; df = 1; *p* = 0.673] (Table 2). Low lethality was considered in 52.8% (n = 95) of the SAs in accordance with the MDS. Impulsivity in the SA was correlated with the clinical lethality thereof, detecting a higher number of patients with a MDS < 4 score (low lethality) in this group [68 patients (71.6%) vs. 48 patients (56.5%); $\chi^2 = 4.47$; df = 1; *p* = 0.035].

Consumption of drugs and/or alcohol before the SA and its possible relationship thereto was assessed using the pertinent SIS items (item 19: alcohol consumption and item 20: consumption of other substances). Twenty-eight patients (15.5% of the total) admitted to alcohol intake in relation to the SA. Of these 28, 4 admitted to having drunk enough alcohol to diminish their judgement and the remaining 24 admitted to having intentionally drunk to carry out the SA. No statistically significant differences were observed between the two SA groups (impulsive and non-impulsive) with regard to previous consumption of alcohol [15 patients (12.9%) vs. 13 patients (20.3%), respectively; $\chi^2 = 1.71$; df = 1; *p* = 0.191]. Consumption of other drugs in relation to the SA was admitted to by 5 (2.8% of total) patients (4 reported intentional intake to facilitate SA). No statistically significant differences were observed between the two SA groups in terms of drug intake before or during the SA [2 patients (1.7%) vs. 3 patients (4.7%), respectively; $\chi^2 = 1.34$; df = 1; *p* = 0.247].

All the polymorphisms studied were in Hardy-Weinberg equilibrium. In our sample, A-1438G and T102C polymorphisms were in total linkage disequilibrium (LD) [R (Cramer's V) = 1.00, *p* = 0] that is, -1438AA homozygotes were 102TT homozygotes, the -1438AA heterozygotes were 102TC heterozygotes and homozygotes -1438GG

were 102CC homozygotes. A certain degree of LD was detected between the STin2 VNTR and 5-HTTLPR polymorphisms [R (Cramer's V) = 0.275, *p* < 0.00001] but was not complete enough to guarantee genotyping of a single polymorphism.

Given that the A-1438G and T102C polymorphisms were in full LD, all the statistical analyses were only performed in the A-1438G polymorphism. Table 3 shows the genotypic and allelic frequencies of both patient subgroups.

As shown in Table 3, the 1438GG genotype (or 102CC) was more frequent among patients that carried out impulsive SAs (34.5% vs. 14.1%; $\chi^2 = 11.5$; df = 2; corrected *p* = 0.012) and likewise, allele -1438G (or 102C), of this polymorphism was more prevalent among patients who carried out impulsive SAs [0.59 vs. 0.41; $\chi^2 = 11.2$; df = 1; corrected *p* = 0.004; OR = 2.11 (1.36-3.27)]. No statistically significant differences were found in the genotypic or allelic distribution of the polymorphisms of the SLC6A4 gene.

No haplotypic analyses were performed in the 5-HT2A gene, as these were in full LD in our sample. With regard to haplotypic comparisons within the SLC6A4 gene, a total of 6 different haplotypes were detected, although no statistically significant differences were detected in the frequency of these haplotypes between the two patient subgroups (LRT = 2.20; df = 5; *p* = 0.821).

Discussion

An excess of the 1438GG genotype (or 102CC) and of the 1438G allele (or 102C) was detected in patients who carried out an impulsive SA vs. those who carried out a non-impulsive SA. On the other hand, the 1438A and 102T alleles (and -1438G and 102C) were in full LD in our sample. A similar LD has been previously described for both polymorphisms both among Spanish samples^{25,27,28} and in other Caucasian and non-Caucasian populations²⁹⁻³³.

Table 3. Genotypic and allelic frequencies of the polymorphism of the serotonin transporter gene and the 2A serotonin receptor

	A-1438G/T102C	5HTTLPR	STin2 VNTR
Genotypes			
Impulsive SAs [n (%)]	19 (16.4) AA/TT 57 (49.1) AG/TC 40 (34.5) GG/CC	34 (29.3) LL 52 (44.8) LS 30 (25.9) SS	43 (37.1) 1212 54 (46.5) 1210 17 (14.7) 1010 2 (1.7) Otros
Non-impulsive SAs [n (%)]	21 (32.8) AA/TT 34 (53.1) AG/TC 9 (14.1) GG/CC	14 (21.9) LL 36 (56.2) LS 14 (21.9) SS	30 (46.9) 1212 21 (32.8) 1210 12 (18.7) 1010 1 (1.6) Otros
χ^2 (gl)	11.46 (2)	2.22 (2)	4.01 (4)
non corrected <i>p</i>	0.003	0.329	4.01 (4)
corrected <i>p</i>	0.012	> 1	> 1
Alleles			
Impulsive SAs [n (%)]	95 (0.41) A/T 137 (0.59) G/C	120 (0.52) L 112 (0.48) S	141 (0.61) 12 89 (0.38) 10 2 (0.01) 9
Non-impulsive SAs [n (%)]	76 (0.59) A/T 52 (0.41) G/C	64 (0.50) L 64 (0.50) S	82 (0.64) 12 45 (0.35) 10 1 (0.1) 9
χ^2 (gl)	11.23 (1)	0.10 (1)	0.38 (2)
non corrected <i>p</i>	0.001	0.754	0.828
corrected <i>p</i>	0.004	> 1	> 1
OR (95% IC)	2.11 (1.36-3.27)	1.07 (0.70-1.65)	

SA: Suicide attempt; df: degree of freedom.

An excess of the 102C allele has been previously described for depressed patients carrying out suicidal acts³⁴ and in depressed patients with suicidal ideation⁴. Furthermore, more recently Giegling et al³⁵ observed an over-representation of the C allele of the rs6311 polymorphism in non-violent SAs and in patients with impulsive SAs, which would support our findings, especially if we bear in mind that most of the impulsive SAs in our sample (89.7%) were of the non-violent type.

We must however take into account that several association studies have failed to find any relationship between these polymorphisms and SAs³⁶⁻³⁹ and these findings have been subsequently supported by recent meta-analytical evidence^{40,41}. Nevertheless, such studies compare patients who have carried out an SA with healthy controls, as opposed to our study in which SA patient subgroups are compared.

The present study did not find any association between polymorphisms of the SLC6A4 gene and SA impulsivity similar to previous reports by other authors who failed to find any association between SA and these polymorphisms⁴²⁻⁴⁶. However, two recent meta-analyses concluded that the S allele of the 5-HTTLPR polymorphism is associated with a higher susceptibility to committing suicidal acts^{40,47}. On the other hand, other studies have reported an association between the S allele and violent suicidal behaviours⁴⁸⁻⁵⁰ and have indicated the possible effect of this allele on the number

and severity of the SAs⁵¹⁻⁵³. The fact that most of the cases included in our sample were non-violent SAs may explain, in part, the discrepancies with the foregoing studies.

Among the possible limitations of this study is the possible bias in the election of the patients included given that, except for sex and age, no other comparison between patients accepting and rejecting participation in the study was carried out and thus, the total homogeneity of both groups cannot be guaranteed from a sociodemographic and clinical perspective. Moreover, the statistical force of the study may be insufficient to detect the possible involvement of some of the genes of lesser effect. Lastly, another limitation may lie in the inclusion of patients with different psychiatric diagnoses. With regard to this point, however, we are in complete agreement with the findings of other authors^{2,3} who found that hereditary transmission of suicidal behaviours is a trait that is independent of other psychiatric disorders.

In summary, our data suggest that polymorphic variations of the 5-HT2A gene may predispose toward an impulsive-type SA. Nevertheless, replication studies are necessary to confirm such findings as well as determine the clinical implications thereof.

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Asociación entre el polimorfismo A-1438G del gen del receptor de serotonina 2A (5-HT2A) e impulsividad del comportamiento suicida

Paredes B, Sáiz PA, García-Portilla MP, Morales B, Pajín M, Fernández I, García I, Álvarez V, Coto E, Bascarán MT, Bousoño M, Bobes J

Objetivos: Investigar la posible asociación entre cuatro polimorfismos serotoninérgicos (A-1438G (rs6311) y T102C (rs6313) del gen del receptor 5-HT2A y STin2 VNTR y 5-HTTLPR del gen SLC6A4) e impulsividad de la tentativa suicida (TS).

Método: 180 pacientes (Asturias – Norte de España) que habían realizado una tentativa suicida fueron evaluados utilizando la *Suicidal Intent Scale* (SIS) y, posteriormente, genotipados utilizando métodos estándar. Las TS fueron divididas en dos subgrupos: impulsivas (puntuaciones inferiores a 6 puntos) o no impulsivas (6 o más puntos), utilizando la subescala de planificación suicida de la SIS.

Resultados: Edad media (SD) de la muestra total = 35,6 (12,5) años; mujeres: 63,3%. La mayoría de los pacientes (95,6%) tenían al menos un diagnóstico psiquiátrico. Los diagnósticos más prevalentes fueron: trastornos afectivos (36,7%), esquizofrenia y otras psicosis (18,3%), trastornos de ansiedad (12,2%) y trastornos de la personalidad (11,1%). En un 49,4% se constató la existencia de TS previas. Un 64,4% de las TS fueron de tipo impulsivo. Los polimorfismos A-1438G y T102C estaban en completo desequilibrio de ligamiento en nuestra población. El genotipo -1438GG y el alelo -1438G fueron más prevalentes entre los pacientes que realizaron TS impulsivas [34,5% vs 14,1%, χ^2 (2) = 11,5, p corregida = 0,012; 0,59 vs 0,41; χ^2 (1) = 11,2, p corregida = 0,004, OR = 2,11 (1,36-3,27), respectivamente]. No se encontraron diferencias en las distribuciones genotípicas o alélicas de los polimorfismos del gen SLC6A4.

Conclusiones: Variaciones polimórficas del gen 5-HT2A podrían predisponer hacia la realización de TS de tipo impulsivo. [Emergencias 2008;20:93-100]

Palabras clave: Asociación genética. Comportamiento suicida. Polimorfismos 5-HT2A. Polimorfismos SLC6A4.