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Association between polymorphisms of *FKBP5* gene and suicide attempt in a Mexican population: A case-control study

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ABSTRACT

Five polymorphisms (rs4713916, rs4713902, rs1360780, rs9296158 and rs3800373) of *FKBP5* gene were analyzed in a case–control study comprising 423 Mexican individuals (146 individuals with suicide attempt and 277 controls). The SNP's were genotyped using the TaqMan-allelic assay. Genotype and allele frequencies were compared between the two groups, then the association between *FKBP5* gene polymorphisms and suicide attempt was analyzed. We found a significant association of rs1360780 T minor allele (All, OR = 1.80, 95 % CI = 1.35–2.41, P = 0.0005; Males, OR = 2.25, 95 % CI = 1.44–3.50, P = 0.0002) as a suicide behavior risk factor. Conversely, rs3800373 C minor allele (All, OR = 0.61, 95 % CI = 0.46–0.83; P = 0.0013; Females, OR = 0.33, 95 % CI = 0.22–0.50; P = 0.0001) and the A-C-T-A-C haplotype (OR = 0.06, 95 % CI = 0.01–0.36; P = 0.002) were significantly associated as protective factors. No association was observed with the other SNP's. Our study suggests that SNP's in *FKBP5* gene contribute to suicide behavior pathogenesis.

1. Introduction

Suicide behavior is a major health problem worldwide. It has been suggested that there are almost one million deaths by suicide in the world per year. However, it should be noted that suicide rates vary depending on the geographic region. For example, the Eastern Mediterranean region has a suicide rate of 3.8, in the African region is 8.8, the Americas 9.6, the Western Pacific region 10.8, in the South East Asia is 12.9, while that in Europe is 14.1 per 100,000 inhabitants (Bachmann, 2018). Nowadays, it has been observed that suicide behavior also differs by gender. Men are highly likely to use more lethal methods when attempting suicide than the methods used by women (Bridge et al., 2006; Nock et al., 2008); nevertheless, more women attempt suicide than men, what is known as the gender paradox of suicide behavior.

The etiology of suicide behavior has not been fully described. It has been suggested that cortisol secretion alterations are causally related to the development of suicide behavior (Velders et al., 2011). When stress is detected, the hypothalamus-pituitary-adrenal (HPA) axis is activated, secreting cortisol as well as the FK506 binding protein 51 (FKBP51) (Zannas et al., 2016).

On the other hand, the FKBP51 is a 51 kDa protein encoded by *FKBP5* gene, which is located on the short arm of chromosome 6 (chromosome 6p21.31) and spans around 155 kb (Mahon et al., 2013). The FKBP51-bound glucocorticoid receptor (GR) complexes have low cortisol affinity with reduced nuclear translocation@ the *FKBP5* gene is strongly upregulated by stress and this creates an ultrashort negative feedback loop of cortisol release and thus prolonged elevations of cortisol following a stressor. This maladaptive prolonged stress response may render individuals to be more vulnerable to suicide. On a circuit level, the upregulation of *FKBP5* gene impacts the structure and brain regions that are implicated in suicide, including the amygdala and the hippocampus (Nicolaides et al., 2014; Zannas et al., 2016).

Due to the function of FKBP51 protein, there is an increasing interest of the possible association between single-nucleotide polymor-

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phisms (SNP's) in *FKBP5* gene and suicide (Hernandez-Diaz et al., 2019). Several genetic association studies have suggested that SNP's in *FKBP5* gene are associated with suicide attempt, including rs4713916, rs4713902, rs1360780, rs9296158 and rs3800373, as well as their haplotypes in populations of different origins (Brent et al., 2010; Leszczynska-Rodziewicz et al., 2014; Supriyanto et al., 2011). In this idea, the rs1360780 T allele has been associated with a greater induction of *FKBP5* mRNA, which is mediated by allele-specific differences observed in the three-dimensional DNA conformation. The DNA conformation differences are likely promoted by the fact that the T allele sequence interacts with the TATA-box binding protein (TBP), which leads into direct contact with the transcription start site and RNA polymerase II, resulting in a transcriptional activation of *FKBP5* (Klengel et al., 2013; Zannas and Binder, 2014). Haplotypes in *FKBP5* gene have also been associated with completed suicide (Supriyanto et al., 2011); nevertheless, the role of these SNP's and suicide behavior remains unknown in the Mexican population.

In order to determine the possible association of *FKBP5* gene in suicide risk, we first evaluated the association of *FKBP5* gene polymorphisms rs4713916, rs4713902, rs1360780, rs9296158 and rs3800373 with suicide attempt, in a Mexican population through a case-control study. Then, we assessed whether these SNP's were associated with the risk of suicide attempt using different genetics models (co-dominant, dominant, recessive and over-dominant) and we stratified by gender. Finally, we explored whether the haplotypes of the five SNP's in *FKBP5* would modify the risk of suicide attempt.

2. Materials and methods

2.1. Selection of case and control groups

We performed a two-center study that included two regions in Mexico. We recruited 146 unrelated Mexican individuals who had attempted suicide (cases) and 277 unrelated healthy Mexican individuals (controls). All participants in the case-group were diagnosed by a psychiatrist using a structured interview following the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) criteria. They were recruited from the General Hospital of Comalcalco "Dr. Desiderio G. Rosado Carbajal" in Tabasco State, Mexico, and from the Psychiatric Hospital "Dr. Juan N. Navarro" in Mexico City, Mexico. In every case, suicide attempt was confirmed by family members as well as through medical records. Since suicidal behavior may be multifactorial, we focused on a homogenous sample of individuals with suicide attempt. The inclusion criteria were: individuals who had had at least one suicide attempt, whose parents and grandparents were Mexican. The exclusion criteria were: younger than 10 or older than 60 years of age; current substance abuse; history of substance dependence; concomitant medical or neurological illness. Control individuals were volunteer blood donors at the Psychiatric Hospital "Dr. Juan N. Navarro" in Mexico City and the Regional Hospital "Dr. Gustavo A. Rovirosa Perez" in Tabasco State. They were selected, interviewed and determined to have no psychiatric illnesses through the psychiatric interview, as well as no family history of psychiatric disorders; their parents and grandparents had to be all Mexican.

2.2. Ethical criteria

This study was approved by relevant ethics committees and all participants were given a complete description of the study before they signed a written and informed consent. The study methodology adhered to the tenets of the Declaration of Helsinki.

2.3. Single-nucleotide polymorphism genotyping of FKBP5 gene

Each participant provided 2 ml of peripheral venous blood. Blood samples were placed in vacuum tubes containing preservative and anticoagulant, ethylenediamine tetraacetic acid (EDTA). Peripheral blood leucocyte genome DNA was extracted using the Gentra Puregene Blood Kit (Qiagen; Hilden, Germany) following the manufacturer's instructions, and then stored at −20 °C for standby application. Procedures were performed under standardized conditions to prevent variation in DNA quality. Five SNP's were selected due to their previously described association with suicide attempt: rs4713916, rs4713902, rs1360780, rs9296158 and rs3800373. The five SNP's were genotyped through allelic discrimination using TaqMan SNP Genotyping Assays (Applied Biosystems; Foster City, CA) (Table 1).

2.4. Statistical analysis

Data were expressed as mean ± SE (continuous variables) or as percentages (categorical variables); intergroup significance was assessed by chi-square goodness of-fit test (χ^2) or *t*-student.

When applying the Kolmogorov–Smirnov test ($P < 0.05$), we found that the variables followed a normal distribution, so we proceeded to use the *t*-student test. Genotypic frequencies were tested for Hardy-Weinberg equilibrium (HWE) and analyzed using X^2 online, freely, and available at https://ihg.gsf.de/cgi-bin/hw/hwa1.pl. Differences in genotype and allele frequencies of the SNP's were compared between cases and controls by X^2. Odds ratio (OR) and 95 % confidence intervals (CI) were used to assess the effect of each SNP and suicide attempt risk using a logistic regression analysis. All association analyses were conducted under four genetic models: codominant, dominant, recessive and over-dominant model using the SPSS 22.0 software.

Linkage disequilibrium (LD) and haplotypes between *FKBP5* polymorphisms were analyzed through Haploview 4.2 software. For the gene-sex interaction analysis, joint effects between SNP genotypes and gender in suicide attempt risk were assessed with a multivariate general linear model (MANOVA). The SPSS 22.0 was used for statistical analyses. A two-tailed $P < 0.05$ was considered statistically significant. Due to the number of SNP´s studied and to the high risk of false positive results due to the high number of comparisons, Bonferroni's corrections were applied and set at $P < 0.006$ ($P_{correction} = 0.05/8 = 0.006$).

A power analysis was performed using Quanto V.1.2.4 software with an allelic frequency of 0.43 additive mode of inheritance, assuming a disease prevalence of 0.05, at 0.006 significant level. We obtained a power of 0.91 (n = 146) with odds ratio of 2.

3. Results

3.1. Sample characteristics

A total of 146 cases and 277 controls were evaluated in this study. The case group included 57 males and 89 females, their age ranged from 11 to 56 years, (average 19.63 ± 9.09 years). Whereas the control group included 148 men and 129 women; their average age was 37.74 ± 11.98 years, ranging from 19 to 70 years. All parameters showed statistically significant differences between cases and controls for age ($P = 0.000$) and gender ($P = 0.006$).

Table 1
Characteristics of the SNP's studied.

SNP's	Alleles	Position	Location	Assay ID
rs4713916	G/A	6:35702206	Intron	C_1979246_10
rs4713902	T/C	6:35646249	Intron	C_30559929_10
rs1360780	C/T	6:35639794	Intron	C_8852038_10
rs9296158	G/A	6:35599305	Intron	C_1256775_10
rs3800373	A/C	6:35574699	3´UTR	C_27489960_10

Risk alleles are indicated in bold.

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3.2. Allele frequencies and genotype distribution of FKPB5 polymorphisms

No deviation from HWE was found for any SNP studied (P = 0.838 for rs4713916, P = 0.783 for rs4713902, P = 0.846 for rs1360780, P = 0.145 for rs9296158, P = 0.091 for rs3800373).

Table 2 shows the frequency of genotypes and alleles of five SNP's in *FKBP5* gene evaluated in cases and controls. Statistically significant differences regarding the distribution of genotypes between cases and controls were observed for rs1360780 (P = 0.0002) and rs3800373 (P = 0.0016). When we stratified the analysis by gender, genotype frequencies also exhibited a significant difference in males for rs1360780 (P = 0.0002) and in females for rs3800373 (P = 0.0001) (Table 2). Nonetheless, for rs4713916, rs4713902 and rs9296158 no statistically significant differences were observed in genotypes or alleles distribution when stratified by gender (Table 2).

The alleles analysis only showed that the T allele of rs1360780 was correlated with an increased risk of suicide attempt, compared with the C allele (All, OR = 1.80, 95 % CI = 1.35–2.41, P = 0.0005; Males,

Table 2
Genotype and allele distributions for SNP's in FKBP5 gene.

		All				Males				Females			
SNP	Genotype or allele	Cases(%)	Control(%)	*P*	OR (95 % CI)	Cases(%)	Control(%)	*P*	OR (95 % CI)	Cases (%)	Control(%)	*P*	OR (95 % CI)
rs4713916													
	G/G	63 (43)	143 (52)	0.223		22 (39)	81 (55)	0.111		41 (46)	62 (48)	0.627	
	G/A	72 (49)	113 (41)			29 (51)	57 (38)			43 (48)	56 (43)		
	A/A	11(8)	21 (7)			6 (10)	10 (7)			5 (6)	11 (9)		
	G	198 (68)	399 (72)	0.201	1.22 (0.89–1.66)	73 (64)	219 (74)	0.047	1.59 (1.00–2.53)	125 (70)	180 (69)	0.824	0.95 (0.62–1.44)
	A	94 (32)	155 (28)		1.00 (Ref)	41 (36)	77 (26)		1.00 (Ref)	53 (30)	80 (31)		1.00 (Ref)
rs4713902													
	T/T	48 (33)	89 (32)	0.452		22 (39)	47 (32)	0.174		26 (29)	42 (33)	0.867	
	T/C	65 (44)	138 (50)			22 (39)	78 (53)			43 (48)	60 (46)		
	C/C	33 (23)	50 (18)			13 (22)	23 (15)			20 (23)	27 (21)		
	T	161 (55)	316 (57)	0.595	1.08 (0.81–1.43)	66 (58)	172 (58)	0.952	1.00 (0.65–1.56)	95 (53)	144 (56)	0.614	1.10 (0.75–1.61)
	C	131 (45)	238 (43)		1.00 (Ref)	48 (42)	124 (42)		1.00 (Ref)	83 (47)	114 (44)		1.00 (Ref)
rs1360780													
	C/C	39 (27)	113 (41)	**0.0002**		15 (26)	67 (45)	**0.0002**		24 (27)	46 (36)	0.225	
	C/T	67 (46)	129 (46)			27 (47)	71 (48)			40 (45)	58 (45)		
	T/T	40 (27)	35 (13)			15 (26)	10 (7)			25 (28)	25 (19)		
	C	145 (50)	355 (64)	**0.0005**	**1.80 (1.35–2.41)**	57 (50)	205 (69)	**0.0002**	**2.25 (1.44–3.50)**	88 (49)	150 (58)	0.073	1.42 (0.96–2.08)
	T	147 (50)	199 (36)		1.00 (Ref)	57 (50)	91 (31)		1.00 (Ref)	90 (51)	108 (42)		1.00 (Ref)
rs9296158													
	G/G	55 (38)	103 (37)	0.958		24 (42)	52 (35)	0.336		31 (35)	51 (40)	0.331	
	G/A	75 (51)	141 (51)			24 (42)	79 (53)			51 (57)	62 (48)		
	A/A	16 (11)	33 (12)			9 (16)	17 (12)			7 (8)	16 (12)		
	G	185 (63)	347 (63)	0.836	0.96 (0.72–1.30)	72 (63)	183 (62)	0.803	0.94 (0.60–1.47)	113 (63)	164 (64)	0.985	1.00 (0.67–1.49)
	A	107 (37)	207 (37)		1.00 (Ref)	42 (37)	113 (38)		1.00 (Ref)	65 (37)	94 (36)		1.00 (Ref)
rs3800373													
	A/A	61 (42)	92 (33)	**0.0016**		24 (42)	62 (42)	0.384		37 (42)	30 (23)	**0.0001**	
	A/C	71 (48)	119 (43)			23 (40)	70 (47)			48 (54)	49 (38)		
	C/C	14 (10)	66 (24)			10 (18)	16 (11)			4 (4)	50 (39)		
	A	193 (66)	303 (55)	**0.0013**	**0.61 (0.46–0.83)**	71 (62)	194 (65)	0.536	1.15 (0.73–1.80)	122 (69)	109 (42)	**0.0001**	**0.33 (0.22–0.50)**
	C	99 (34)	251 (45)		1.00 (Ref)	43 (38)	102 (35)		1.00 (Ref)	56 (31)	149 (58)		1.00(Ref)

The significance is shown in bold. *P*-value adjusted for age and gender.

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OR = 2.25, 95 % CI = 1.44–3.50, P = 0.0002). On the other hand, a protective effect was observed with the C allele of rs3800373 (C vs. A, All, OR = 0.61, 95 % CI = 0.46–0.83; P = 0.0013; Females, OR = 0.33, 95 % CI = 0.22–0.50; P = 0.0001).

3.3. Association between FKBP5 polymorphisms and suicide attempt susceptibility

Four genetic models were used to further identify the associations between the SNP's in *FKBP5* gene and the risk of suicide attempt. Table 3 shows the results. When the Bonferroni correction was applied, we found that rs1360780 TT genotype was statistically associated with an increased risk of suicide attempt in the overall population, this association remained significant among males using three genetic models ($P < 0.006$). Additionally, the rs3800373 CC genotype was observed to have a protective effect in the overall population; when it was stratified by gender, this association was positive only in the female group using the co-dominant, dominant and recessive models ($P < 0.006$) (Table 3). Table 3 shows the results of interaction gene-sex. Significant interactions were observed for rs1360780 ($P_{interaction\ for\ recessive\ model} = 0.035$) and rs3800373 ($P_{interaction\ for\ co\text{-}dominant\ model} = 0.023$ and $P_{interaction\ for\ recessive\ model} = 0.007$) but there were no statistically significant associations after Bonferroni correction were applied.

3.4. Haplotype analysis of FKBP5 polymorphisms and suicide attempt susceptibility

We explored whether the haplotypes of five SNP's of *FKBP5* gene would modify the risk of suicide attempt (Fig. 1). Five-marker-haplotype showed an effect on the risk of suicide attempt: A-C-T-A-C, their frequency is shown in Table 4. The haplotype may confer protection effect against suicide attempt (Table 4).

4. Discussion

Suicide attempt has been identified as a serious health problem and eventual death by suicide; this situation can increase the degree of stress in patients and their families. The understanding of molecular mechanisms of suicide attempt as well as the identification of genes that underlie its development are highly necessary in order to determine the individual's susceptibility to suicide. It has been suggested that HPA axis dysregulation plays a key role in developing suicide attempt; therefore, in this study we focused on five SNP's (rs4713916, rs4713902, rs1360780, rs9296158 and rs3800373) in *FKBP5* gene, that have been implicated with suicide in previous publications. These polymorphisms have been associated positively with suicide attempt in Caucasian (Fudalej et al., 2015), African-American (Yeo et al., 2017) and Asian (Supriyanto et al., 2011) populations. To our knowledge, this is the first study that has evaluated the unique and combined influence of the five most common SNP's in *FKBP5* on suicide attempt in a Mexican population.

Table 3
Associations between SNP's and risk of suicide attempt under genetic models.

	Genotypes	All		Males		Females		$P_{interaction}$
Model		OR (95 % CI)	*P*	OR (95 % CI)	*P*	OR (95 % CI)	*P*	
rs4713916								
Co-dominant	AA vs. GA	0.82 (0.37–1.80)	0.626	1.15 (0.38–3.50)	0.794	0.60 (0.19–1.86)	0.379	0.620
	AA vs. GG	1.18 (0.54–2.61)	0.667	2.18 (0.71–6.66)	0.171	0.69(0.22–2.15)	0.533	
Dominant	AA vs. GA/GG	1.13 (0.45–2.81)	0.793	0.65 (0.15–2.71)	0.561	0.92 (0.25–3.35)	0.904	0.350
Recessive	GA/AA vs. GG	1.50 (0.91–2.46)	0.109	2.16 (0.88–5.26)	0.090	1.17 (0.62–2.21)	0.628	0.660
Over-dominant	GA vs. AA/GG	1.63 (0.99–2.67)	0.051	3.11 (1.28–7.55)	0.012	1.15 (0.61–2.18)	0.646	0.460
rs4713902								
Co-dominant	CC vs. TC	1.40 (0.82–2.37)	0.212	1.95 (0.85–4.47)	0.114	1.06 (0.53–2.12)	0.853	0.830
	CC vs. TT	1.22 (0.69–2.14)	0.482	1.20 (0.51–2.81)	0.663	1.19 (0.56–2.55)	0.642	
Dominant	CC vs. TC/TT	1.19 (0.70–2.00)	0.506	1.71 (0.77–3.79)	0.185	0.78 (0.38–1.59)	0.498	0.560
Recessive	TC/CC vs. TT	1.06 (0.67–1.67)	0.799	0.82 (0.40–1.66)	0.593	1.1.4 (0.60–2.15)	0.682	0.950
Over-dominant	TC vs. CC/TT	0.79 (0.52–1.21)	0.293	0.68 (0.35–1.33)	0.272	0.98 (0.55–1.74)	0.952	0.720
rs1360780								
Co-dominant	TT vs. CT	**2.20 (1.28–3.78)**	**0.004**	**3.88 (1.55–9.71)**	**0.004**	1.47 (0.74–2.92)	0.266	0.640
	TT vs. CC	**3.31 (1.85–5.92)**	**0.000**	**6.60 (2.48–17.53)**	**0.000**	1.95 (0.93–4.10)	0.075	
Dominant	TT vs. CT/CC	**4.07 (2.20–7.52)**	**0.000**	**5.22 (1.99–13.65)**	**0.001**	3.43 (1.39–8.47)	0.007	0.770
Recessive	CT/TT vs. CC	**2.66 (1.53–4.64)**	**0.001**	3.04 (1.20–7.68)	0.018	1.79 (0.84–3.80)	0.129	**0.035**
Over-dominant	CT vs. TT/CC	0.72 (0.42–1.24)	0.241	0.82 (0.33–2.02)	0.670	0.57 (0.27–1.20)	0.141	0.760
rs9296158								
Co-dominant	AA vs. GA	0.91 (0.47–1.76)	0.783	1.72 (0.68–4.35)	0.252	0.54 (0.20–1.41)	0.210	0.600
	AA vs. GG	0.90 (0.46–1.79)	0.781	1.12 (0.43–2.88)	0.806	0.73 (0.27–1.98)	0.542	
Dominant	AA vs. GA/GG	0.90 (0.40–2.03)	0.802	0.93 (0.29–2.94)	0.914	1.06 (0.24–4.65)	0.933	0.337
Recessive	GA/AA vs. GG	0.76 (0.42–1.37)	0.373	0.27 (0.10–0.73)	0.010	1.94 (0.83–4.53)	0.124	0.960
Over-dominant	GA vs. AA/GG	0.92 (0.55–1.55)	0.772	0.52 (0.23–1.18)	0.121	1.59 (0.76–3.32)	0.210	0.320
rs3800373								
Co-dominant	CC vs. AC	**0.35 (0.18–0.67)**	**0.002**	1.84 (0.73–4.64)	0.191	**0.85 (0.02–0.25)**	**0.000**	**0.023**
	CC vs. AA	**0.32 (0.16–0.62)**	**0.001**	1.61 (0.64–4.05)	0.307	**0.65 (0.02–0.20)**	**0.000**	
Dominant	CC vs. AC/AA	**0.22 (0.10–0.46)**	**0.000**	1.41 (0.47–4.19)	0.532	**0.04 (0.01–0.16)**	**0.000**	0.260
Recessive	AC/CC vs. AA	**0.44 (0.25–0.76)**	**0.004**	0.86 (0.36–2.05)	0.733	**0.22 (0.10–0.48)**	**0.000**	**0.007**
Over-dominant	AC vs. CC/AA	1.32 (0.83–2.11)	0.230	0.72 (0.31–1.66)	0.444	0.88 (0.46–0.93)	0.035	0.430

The significance is shown in bold. *P*-value adjusted for age and gender.

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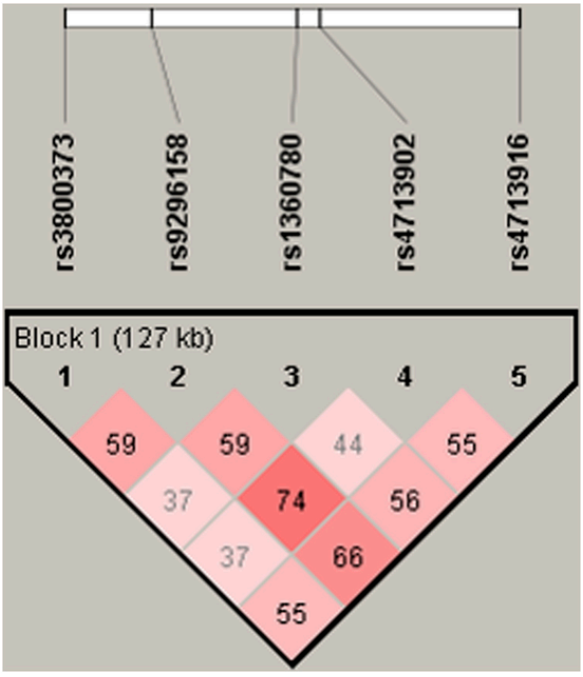

Fig. 1. Linkage disequilibrium (LD) map of SNP's in *FKBP5* genotyped by Haploview. Pairwise linkage disequilibrium is expressed as *D'* (different colors) and r^2 (numbers). This was based on *D´*, that is, normalized linkage disequilibrium measure or *D* divided by the theoretical maximum for the observed allele frequencies, multiplied by 100. Values close to zero indicate no LD, while values approaching 100 indicate full LD. Red squares represent varying degrees of LD; darker shades indicate stronger LD.

First, our results suggest that the T allele of rs1360780 could increase the susceptibility to suicide attempt. The *FKBP5* gene transcription is regulated predominantly by the intronic steroid hormone response elements (GRE); rs1360780 is located in intron 2 in a functional enhancer region and 488 bp away from a GRE in which it has been reported that the T allele can alter the *FKBP5* transcription (Klengel et al., 2013).

Several studies have observed high and long-lasting cortisol responses and anxiety symptoms in healthy individuals carrying the T allele after being exposed to psychosocial stressors. Moreover, our results agree with previous reports where the TT genotype has been significantly associated with suicidal behavior, including a recent meta-analysis on *FKBP5* rs1360780 and suicide risk, in which they found a statistical association between TT genotype and suicidal behavior (Brent et al., 2010; Buchmann et al., 2014; Hernandez-Diaz et al., 2019; Hohne et al., 2014).

Evidence suggests that polymorphisms of *FKBP5* gene may have functional effects on baseline transcription or on stimulated transcription of this gene. FKBP51 protein interacts intracellularly with multiple proteins; it is also a cochaperone and modulator of the glucocorticoid receptor in the HPA axis (Binder, 2009; Matosin et al., 2018). Altered GR activity leads to neuroendocrine dysregulation, perturbations in brain circuitry, specific behavioral and cognitive symptoms that may predispose to the development of stress related disorders (Binder, 2009; Criado-Marrero et al., 2018; Fries et al., 2017; Matosin et al., 2018). GR has an important role in stress responses, its activation directly induces the *FKBP5* transcription, after a rapid induction of FKBP51 protein, this binds to the GR reducing its affinity for cortisol; FKBP51 protein also decreases the translocation of GR to the nucleus where it binds target DNA sequences as a positive or negative transcription factor (Binder, 2009; Tatro et al., 2009; Vermeer et al., 2003; Zannas and Binder, 2014). Alterations in the balance of these steroid receptor systems, particularly in brain regions related to the presence of *FKBP5* polymorphisms may lead to the expression of psychiatric phenotypes.

Second, our study also shows a statistically significant difference in the distribution of rs3800373 genotypes and alleles between patients and controls suggesting a protective role for the genetic polymorphism, which was consisted in four genetic models. The association between this SNP with suicide susceptibility has been replicated in several independent studies and a meta-analysis (Hernandez-Diaz et al., 2019; Roy et al., 2010, 2012; Zobel et al., 2010). Literature suggest that *FKBP5* rs3800373 minor allele reduces the ability of microRNA miR-320a to bind *FKBP5* by altering the RNA secondary structure of the *FKBP5* 3´UTR (Linnstaedt and Riker, 2018).

Third, there is a notable linkage disequilibrium in these loci; five-marker-haplotype in this study showed a decreased suicide attempt risk. Genetic markers used in this study have been replicated in previous researches in different populations who presented suicidal behavior (Breen et al., 2016; Leszczynska-Rodziewicz et al., 2014; Roy et al., 2010). The expression of *FKBP5* gene is moderated by common genetic variants that are part of a haplotype that is commonly tagged by rs3800373, rs9296158, rs1360780 and rs9470080, and spans the whole *FKBP5* locus (Binder et al., 2004; Klengel et al., 2013). For suicide is a multifactorial disease that is not caused by a single mutation, our results indicate that these polymorphisms and haplotypes might well be genetic markers for suicide attempt.

Fourth, a sex-specific association of rs1360780 and rs3800373 SNP's were observed. In Mexico, suicide affects more men than women. In recent years, the suicide rate in men increased from 5.95 to 8.50 (per 100,000 inhabitants) and from 1.06 to 2.00 in women; nevertheless, women attempt suicide 2–3 times more often than men (Borges et al., 2010; Fernández-Niño et al., 2016). A possible explanation for the gender differences observed may be that modifiable factors such as diet or environment and sex-specific hormone levels (testosterone and androgens) could differentially influence epigenetic modifications of these variants and neighboring loci (Lee et al., 2018). Additional studies are needed in order to clarify the mechanisms underlying these gender differences. It is important to identify gender-specific risk and

Table 4
Haplotype analysis of SNP's in FKBP5 gene in occurrence of suicide attempt.

Haplotypes					Frequencies			OR (95 % CI)	*P*
rs4713916	rs4713902	rs1360780	rs9296158	rs3800373	All	Cases	Control		
G	C	C	G	A	0.252	0.203	0.278	1	–
A	T	T	A	C	0.152	0.134	0.162	1.03 (0.44–2.45)	0.94
G	C	C	G	C	0.070	0.032	0.090	2.29 (0.72–7.29)	0.16
G	C	T	G	A	0.046	0.110	0.012	0.41 (0.12–1.35)	0.14
G	T	T	G	A	0.037	0.080	0.014	0.20 (0.05–0.83)	0.027
G	T	C	G	C	0.034	0.027	0.038	0.15 (0.03–0.85)	0.032
A	C	T	A	C	0.021	0.042	0.010	0.06 (0.01–0.36)	0.002

The significance is shown in bold.

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protective factors for suicidal behaviors to develop and/or improve prevention programs and treatment.

Our results are particularly relevant for the Mexican population. Genetic studies on suicide in Mexico may contribute to the development of biomarkers in order to target intervention strategies to individuals with an increased risk.

There are some limitations in our study. First, the key limitation of our study is the small sample size, which may also have a significant effect on observed statistical significance; nevertheless, a recently meta-analysis indicated that there are only few studies about the association of SNP's in *FKBP5* gene and suicide attempt, and those have shown a positive association (Hernandez-Diaz et al., 2019). Although in Mexico the prevalence of suicide behavior is high, only a few individuals accepted to participate in this study; this could be the reason why other studies in Mexican population have been performed in groups that included around 166 cases and 235 controls (Genis-Mendoza et al., 2017; Molina-Guzman et al., 2017; Sarmiento-Hernandez et al., 2019). Therefore, it is necessary to increase size samples in future studies, as well as to replicate our study in order to validate whether these SNP's are reproducibly associated with suicide attempt. Second, the age of the participants in our comparison group did not match our cases group, with a big difference of average age between groups. Mainly because the control group were volunteer blood donors whereas the case group was formed by individuals who were attending medical consultations after a suicide attempt. A better statistical outcome may be achieved with age-matched groups.

Third, gene-gene interaction analysis or functional analysis were not included in the present study. Fourth, this study reflects only the genetic characteristics of Mexican individuals from two particular regions; nevertheless, each region has a different ancestral component, for Mexico is a country formed by a heterogenous population (Ramírez-Bello et al., 2019). Therefore, our results should be taken with caution. Additionally, future studies should include individuals from other regions in Mexico in order to minimize the effect of population stratification; ethnicity matched cases and controls should also be performed to verify the results obtained in this study.

In conclusion, our findings show that SNP's in *FKBP5* gene could be associated with suicide attempt in Mexican population. The T allele of rs1360780, C allele of rs3800373 and the A-C-T-A-C haplotype were found to be risk or protective factors for suicide attempt. Moreover, our results provide evidence of sex-related differences for rs1360780 and rs3800373 SNP's. This is a preliminary study and data obtained will be used in future studies in order to better understand suicide susceptibility and suicide risk factors.

CRediT authorship contribution statement

Yazmín Hernández-Díaz: Conceptualization, Methodology, Writing - review & editing. **Thelma Beatriz González-Castro:** Data curation, Writing - original draft. **Carlos Alfonso Tovilla-Zárate:** Conceptualization, Methodology, Software, Validation, Writing - review & editing. **Isela Esther Juárez-Rojop:** Data curation, Writing - original draft. **María Lilia López-Narváez:** Data curation, Writing - original draft. **Nonanzit Pérez-Hernández:** Visualization, Investigation. **José Manuel Rodríguez-Pérez:** Visualization, Investigation. **Alma Delia Genis-Mendoza:** Supervision.

Declaration of Competing Interest

The authors declare that they do not have any conflict of interest.

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