INVESTIGATION OF REELIN RS7341475, RS362691 AND RS12705169 GENE POLYMORPHISMS IN CASES A WITH SUICIDE ATTEMPT

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ABSTRACT

***Background**: Suicidal ideations and behavior is one of the most serious conditions among psychiatric emergencies. Neurobiology and genetics of suicide attracted more interest in subsequent period. Today, studies focus on identification of related genes and polymorphisms at chromosomal level as a result of advances in molecular genetics. In this study, we aimed to investigate possible effects of reelin gene polymorphism on the pathogenesis of suicide attempts.*

***Methods**: This study included 106 patients with a suicide attempt and 90 healthy controls. Cases with a suicide attempt were assessed and classified by a clinician regarding the reason for a suicide, whether a suicide attempt was planned. The patients attempted to suicide by firearm or ingestion of toxic drug doses were considered as serious suicidal attempt. Reelin rs326691 (G/C), rs734147 (A/G) and rs12705169 (T/G) gene polymorphisms were examined by Real-PCR between patient and control groups. Homozygous mutant, heterozygous and homozygous normal genotypes were identified based on allele discrimination.*

***Results**: Of 106 patients with a suicide attempt, 23.6% were men and 76.4% were women. Median age was 20 years (12-52). In our study, it was demonstrated there was a significant difference in genotype and allele distribution of rs734147 gene polymorphism between the patient and control groups (p=0.004 and p=0.003). In addition, it was shown that both rs734147 and rs12705169 gene mutations were significantly more common in cases with serious suicidal attempts intending death when compared to those with suicide attempts seeking attention (p<0.001 and p=0.025).*

***Conclusions**: Our results indicated genetic variation of rs734147 and rs12705169 in reelin is significantly associated with the development of suicide attempt.*

***Key words**: Suicide attempt, reelin, reelin gene polymorphism.*

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Introduction

The act of intentionally causing individual's own death is termed as suicide. Suicidal ideations and behavior are one of the most serious conditions among psychiatric emergencies[(1)]. Based on the data of World Health Organization (WHO), suicide appears as a social problem, which is among the ten leading causes of death in developed countries and the leading cause of death in young adults. Although the rate of suicide attempts varies among countries, it is more frequently observed in developed countries. In the USA, suicide is the fourth leading cause of death among children of all ages, while the third leading cause of death among adolescents aged 15-19 years[(2)]. Annually, suicide causes 37,000 deaths in the USA and approximately 1 million deaths worldwide[(3)]. The fact that suicide is one of the most important causes of death in society caused greater interest in suicidal behavior, prompting several studies on this topic. Preliminary studies regarding suicide and suicidality focused on clinical problems and descriptive statistics.

After 1940s, studies on suicide became more comprehensive and the concept that suicidal behavior appeared as a neurobiological entity involving various factors emerged. The main rational underlying this hypothesis was the fact that all individuals sharing suicidal risk factors such as comorbid psychiatric disease, chronic health issues, substance abuse, sexual abuse or violence instead of suicide attempt[4].

Neurobiology and genetics of suicide attracted more interest in the subsequent period. Initially, studies investigating genetic predisposition to suicidal behavior were conducted on monozygotic twins, families and adopted children[5]. Today, studies focus on identification of related genes and polymorphisms at chromosomal level as a result of the advances in molecular genetics.

Recently, some candidate genes that are thought to be associated with suicidal behavior have been identified including tryptophan hydroxylase (TPH), serotonin transporter receptor (SERT), some serotonin receptors (5HT1A, 5HT1B), monoamine oxidase (MAO) and tyrosine hydroxylase (TH) genes. Previous studies demonstrated a significant relationship between suicidal behavior and the above-mentioned genes[6]. To the best of our knowledge, there is no study on reelin gene and suicidal behavior.

Reelin gene localized at chromosome 7 (7q22) in humans synthesizes an extracellular matrix protein that plays a major role in the development of central nervous system[7]. Reelin has positive influences on neurogenesis process during both developmental and adult periods. Activation of reelin signaling has significant effects on long-term potentialization, regulation, cell proliferation, cell migration, brain development such as dendritic spine morphogenesis and adult neurogenesis. It is known that any mutation or altered expression in reelin gene has an essential role in neuronal development process predisposes to neuropsychiatric diseases. To the best of our knowledge, there is no study on suicidal behavior and reelin gen polymorphism. In this study, we aimed to investigate the possible effects of reelin gene polymorphism on the pathogenesis of suicide attempts in patients with suicide attempts.

Subjects and methods

Study Population

This study included 106 patients presented to Internal Medicine, Child Psychiatry and Emergency Medicine Departments of Mugla Sitki Kocman University, Medicine School with suicide attempts. The study protocol was reviewed and approved by an internal ethical review board. The patients with mental retardation, those with dementia and those with a history of substance abuse were excluded. Psychiatric examination was performed by a psychiatrist in adult patients, while it was performed by a child and adolescent psychiatrist in patients younger than 18 years according to DSM-IV criteria. Cases with suicide attempts were assessed and classified by a clinician regarding the reason for the suicide, whether the suicide attempt was planned, the presence of personal or family history of psychiatric disease, and whether the suicidal attempt existed. The patients attempting to suicide by firearm or ingestion of toxic drug doses were considered as serious suicidal attempts.

Age and sex-matched 90 healthy controls without psychiatric disease who presented to the internal medicine outpatient clinic were employed as control group. All controls were evaluated by a psychiatrist. All patients gave informed consent before participation. Parental informed consent was obtained in patients younger than 18 years.

Genotyping

Blood samples (2ml) were drawn to EDTA (ethylenediaminetetraacetic acid) tubes from all patients and controls. Samples were stored at -20°C until DNA analysis. DNAs were isolated by using DNA isolation protocols (PureLink ® Genomic DNA Mini Kit, Invitrogen, Carlsbad, CA, USA) and target polymorphisms were screened by ABI Prism StepOnePlus Real Time system (Applied Biosystems, Foster City, CA, USA) using SNP ID rs7341475, rs362692 and rs12705169 Tagman probes. Overall, 8 μl mix was prepared for each PCR reaction: Tagman Genotyping Master Mix, 5 μl; Tagman genotyping assay (40 X), 0.25 μl, DNase-free, RNase-free water, 2.75 μl. PCR program (40 cycles) was executed on StepOnePlus Real Time device;30 seconds at 60°C, 10 minutes at 95°C, 15 seconds at 60°C, 1 minute at 60°C, 30 seconds at 60°C. Homozygous mutant, heterozygous and homozygous normal genotypes were identified based on allele discrimination, by using software.

Statistical analysis

All statistical analyses were performed by

using SPSS software version 20.0 for Windows (SPSS Inc., Chicago, Illinois, USA). Genetic distribution fitting to Hardy-Weinberg was analyzed by using chi-square goodness-of-fit test. The differences in genotype and allele distributions were assessed by using $\chi 2$ test. One-way ANOVA was used to assess differences in genotype and allele gene distributions of variables with normal distribution. Kruskal-Wallis test was used to assess the differences in genotype and allele gene distributions of skewed variables such as age, duration of education and the number of suicidal attempts despite the use of logarithmic transformation. $p<0.05$ was considered as statistically significant in all tests.

Results

Of 106 patients with suicide attempt, 23.6% were men and 76.4% were women. Median age was 20 years (12-52 age range). When suicide attempt pattern was evaluated, it was seen that 26 patients (27.7%) attempted to serious suicide with intention of death. In addition, suicide attempts were planned in 8 patients (8.5%).

It was found that there was a history of previous suicide attempts in 28 patients (29.8%). Median number of suicide attempts was calculated as 2(1-4).

Demographic characteristics		n (%)
Age	<18	44 (41,1)
	>18	62 (58,9)
Marital status	Married	34 (32,5)
	Single	72 (67,5)
Educational status	Primary school	36 (38,2)
	Secondary school	44 (41,6)
	College	26 (20,2)
Type of suicidal attempt	Serious	29 (27,7)
	Non-serious	77 (72,3)
Type of suicide	Planned	9 (8,5)
	Sudden	97 (91,5)
History of suicidal attempt	Positive	32 (29,8)
	Negative	74 (70,2)
History of psychiatric disorder	Positive	52 (48,9)
	Negative	54 (51,1)
Number of suicidal attempts (median)	2 (1-4)	

Table 1: Demographic characteristics of patients.

Table 1 presents demographic characteristics of the patients.

It was found that there was a difference between the patient and control groups regarding reelin rs734147 gen polymorphism (p=0.04). When the patients with suicidal attempts were assessed according to their ages, genders, duration of education and the number of suicide attempts, no significant difference was detected between the groups regarding reelin rs326691 (G/C), rs734147 (A/G) and rs12705169 (T/G) gene polymorphisms (Table 2).

	Genotype rs362691 % (n)			x^2	P	Genotype rs734147 % (n)			x^2	P	Genotype rs12705169 % (n)			x2	P
	GG	GC	CC			AA	AG	GG			TT	TG	GG		
Case	83 (88)	15.1 (16)	1.9 (2)	1.786	0.409	57.5 (61)	32.1 (34)	10.4 (11)	10.905	**0.004**	64.2 (68)	31.1 (33)	4.7 (5)	1.363	0.506
Control	82.6 (71)	17.4 (15)	-			71.1 (64)	28.9 (26)	-			61.1 (55)	36.7 (33)	2.2 (2)		
Male	87 (20)	13 (3)	-	0.871	0.647	60.9 (14)	26.1 (6)	13 (3)	0.595	0.734	65.2 (15)	34.8 (8)	-	1.716	0.424
Female	80.6 (58)	16.7 (12)	2.8 (2)			54.2 (39)	34.7 (25)	11.1 (8)			62.5 (45)	30.6 (22)	6.9 (5)		
Age (year)	82.1 (78)	15.8 (15)	2.1 (2)	1.141	0.565	55.8 (53)	32.6 (31)	11.6 (11)	0.047	0.977	63.2 (60)	31.6 (30)	5.2 (5)	0.140	0.933
<18 age	79.5 (31)	17.9 (7)	2.6 (1)	0.317	0.854	56.4 (22)	33.3 (13)	10.3 (4)	0.114	0.944	61.5 (24)	30.8 (12)	7.7 (3)	0.783	0.676
>18 age	83.9 (47)	14.3 (8)	1.8 (1)			55.4 (31)	32.1 (18)	12.5 (7)			64.3 (36)	32.1 (18)	3.6 (2)		
Education duration (year)	82.1 (73)	15.7 (14)	2.2 (2)	0.389	0.823	57.3 (51)	31.4 (28)	11.3 (10)	2.698	0.259	61.8 (55)	33.7 (30)	4.5 (4)	0.153	0.927
Number of suicide attempts	24	4		2.649	0.104	21	6	1	1.121	0.571	19	8	1	1.283	0.526

Table 2: Reelin gene polymorphism according to groups.
A: Adenine C: Cytosine G: Guanine T: Thymine

	Genotype Allele	Patient (n=106)	Control (n=90)	X^2	p
rs362691	**GG**	91 (0.858)	74 (0.826)	2,556	0,278
	GC	13 (0.123)	16 (0.174)		
	CC	2 (0.019)	-		
	G	0.92	0.913	0,061	0,804
	C	0.08	0.087		
rs734147	**AA**	61 (0.575)	64 (0.711)	**10.905**	**0.004**
	AG	34 (0.321)	26 (0.289)		
	GG	11 (0.104)	-		
	A	0.736	0.856	**8.432**	**0.003**
	G	0.264	0.144		
rs12705169	**TT**	68 (0.642)	55 (0.611)	2.276	0.25
	TG	33 (3.311)	34 (0.378)		
	GG	5 (0.047)	1 (0.011)		
	T	0.797	0.800	0.004	0.944
	G	0.203	0.200		

Table 3: Genotype and allele distributions of reelin rs362691, rs734147 and rs12705169 gene polymorphisms.
A: Adenine C: Cytosine G: Guanine T: Thymine

Table 3 summarizes genotype and allele distributions of reelin rs326691 (G/C), rs734147 (A/G) and rs12705169 (T/G) gene polymorphisms in the patient and control groups. No significant differences were detected in genotype and allele distributions of reelin rs326691 and rs12705169 gene polymorphisms, while significant differences were detected in the genotype and allele distributions of rs734147 gene polymorphism between the patient and control groups (p=0.004 and p=0.003, respectively).

	Patient	Control	X^2	P
C A T*	5.45(0.026)	6.10(0.036)	0.328	0.566
G A G*	26.19(0.124)	23.42(0.138)	0.163	0.686
G A T*	118.61(0.559)	111.76(0.657)	4.022	0.044
G G G*	7.73(0.036)	4.86(0.029)	0.187	0.665
G G T*	42.47(0.200)	14.96(0.088)	9.468	**0.002**

Table 4: Haplotype analysis among patient and control groups.
All those frequency<0.03 will be ignored in analysis. A: Adenine C: Cytosine G: Guanine T: Thymine

Table 4 shows five haplotypes that are most frequently observed in the haplotype analysis for 3 single nucleotide polymorphism by using SNP analyze software. Although guanin-adenin-thymin (GAT) haplotype was the most frequent in both patient and control groups, no significant difference was observed between the groups. However, there was significant difference between the patient and control groups regarding guanin- guanin -thymin (GGT) haplotype (p=0.002).

When the patient group was stratified according to the presence of suicide attempt history, it was seen that rs734147 gene mutation was significantly higher in the patients with first suicide attempt when compared to those with repeated suicide attempts (Table 5). It was also found that there were significant differences between groups regarding the genotype and allele distributions of reelin rs734147 gene polymorphisms (p=0.035 and p=0.005). It was found that there were serious suicide attempts with intention of death in 72.3% of the cases with the first suicide attempt, while this rate was 28.9% in those with repeated suicidal attempts.

It was found that rs734147 gene mutation was significantly higher in the patients with serious suicide attempts when compared to those with suicide attempts seeking attention (Table V). It was found that there was a significant difference in genotype (p<0.001) but not in the allele distribution of reelin rs734147 gene polymorphism between the groups (p=0.115).

When rs734147 gene polymorphism was assessed according to their ages, genders, family history of suicide attempts and suicide patterns (whether planned or not), no significant difference was observed between the groups regarding the genotype and allele distributions of reelin rs734147 gene polymorphism (Table 5).

It was found that rs12705169 gene mutation was considerably higher in the patients with serious suicide attempts intending death when compared to those with suicide attempts seeking attention. It was found that there were significant differences in the

		n	Genotype Distribution			X^2	p	Allele Distribution		OR	95% CI	p
			AA	AG	GG			A	G			
Gender	**Male**	25	16(0.640)	6(0.240)	3(0.120)	0.984	0.611	118(0.728)	44(0.272)	0.846	0,405-1.767	0,657
	Female	81	45(0.556)	28(0.346)	8(0.09)			38(0.760)	12(0.240)			
Age	**<18**	39	22(0.564)	13(0.333)	4(0.103)	0.114	0.944	57(0.731)	21(0.286)	0.921	0.482-1.758	0.803
	>18	56	31(0.554)	18(0.321)	7(0.125)			80(0.714)	32(0.286)			
Psychiatric disorder	+	46	31(0.674)	11(0.239)	4(0.08)	5.314	**0.07**	73(0.793)	19(0.207)	0.474	0.246-0.914	**0.024**
	-	48	21(0.750)	20(0.417)	7(0.146)			62(0.646)	34(0.354)			
History of suicide	+	28	21(0.750)	6(0.214)	1(0.03)	6.658	**0.035**	48(0.857)	8(0.143)	0.322	0.140-0.739	0.005
	-	66	31(0.470)	25(0.379)	10(0.152)			87(0.659)	45(0.341)			
Family history	+	27	18(0.667)	6(0.222)	3(0.111)	2.222	0.329	42(0.788)	12(0.222)	0.648	0.309-1.357	0.248
	-	67	34(0.507)	25(0.373)	8(0.119)			93(0.694)	41(0.306)			
Intent of suicide	**Death**	26	15(0.577)	3(0.115)	8(0.308)	16.212	0.000	33(0.635)	19(0.365)	1.727	0.870-3.421	0.115
	Attention	68	37(0.544)	28(0.412)	3(0.044)			102(0.750)	34(0.250)			
Planned suicide?	**Yes**	7	5(0.714)	1(0.143)	1(0.143)	1.237	0.538	11(0.786)	3(0.214)	0.704	0.188-2.635	0.601
	No	86	47(0.547)	30(0.349)	9(0.105)			124(0.721)	48(0.279)			

Table 5: Genotype and allele distributions of reelinrs734147 gene polymorphisms in cases with suicidal attempt.
A: Adenine G: Guanine, OR = odd ratio; 95% CI =confidence interval at 95%.

genotype and allele distributions of reelin rs12705169 gene polymorphism between the groups (p=0.025 and p=0.049).

When rs362691 gene polymorphism was assessed according to their ages, genders, history of psychiatric disorders, patterns of suicide (whether planned or not), intention of suicidal attempts, and personal and family history for suicide attempts in the patient group, no significant differences were observed between the groups regarding the genotype and allele distributions of reelin rs362691 gene polymorphism.

Discussion

In our study, a significant relationship was detected between rs734147 gene polymorphism and suicide attempt. It was demonstrated there was a significant difference in the genotype and allele distribution of rs734147 gene polymorphism between the patient and control groups. In addition, it was shown that both rs734147 and rs12705169 gene mutations were significantly more common in cases with serious suicidal attempts intending death when compared to those with suicide attempts seeking attention and that distributions of rs734147 and rs12705169 gene polymorphisms differed significantly between the groups.

The fact that suicide emerging as an important public health issue is the leading cause of death especially in younger and adult populations has prompted a greater interest in this topic and brought forward the need for studies on this topic. Suicidal behavior is inherited to subsequent generations through a complex inheritance process involving interplay between various environmental factors and several genes. In some studies on genetic predisposition to suicidal behavior, it has been reported that genetic characteristics have an influence on suicidal behavior by 30-50% independently from other psychiatric disorders and psychological stressors[8].

Preliminary studies on genetic predisposition to suicidal behavior were conducted on monozygotic twins, families and adopted children. Monozygotic twin studies are important to demonstrate the contribution of genetic characteristics to suicidal behavior. In twin studies, it was shown that the likelihood of suicidal behavior was higher in monozygotic compared to dizygotic twins[9].

In subsequent years, studies attempting to identify related genes and polymorphisms at chromosomal level were conducted with the advances in molecular genetics. Approximately 2 decades ago, in the preliminary study on suicidal behavior and genetics by Nielsen et al., it was shown that a genetic variant of tryptophan hydroxylase gene polymorphism could cause predisposition to suicide attempt by influencing 5-hydroxyindoleacetic acid concentration in cerebrospinal fluid[10].

Today, some candidate genes thought to be related to suicidal behavior has been identified. In recent years, several studies have been conducted, addressing the relationship between single nucleotide polymorphisms (SNPs) in these candidate genes and suicidal behavior. Genetic predisposition studies have begun to include a wide spectrum of different SNPs in recent years[11]. However, to the best of our knowledge, there is no study investigating the relationship between suicidal behavior and reelin gene polymorphism.

Reelin gene localized at chromosome 7 (7q22) synthesizes an extracellular matrix protein that plays a major role in the development of central nervous system[7]. Reelin proteins are released from different areas of cerebral cortex and spinal, mainly from Cajal-Retzius cells localized at cortex and marginal zone of hippocampus. Reelin play a role in several important processes such as cortical lamination and positioning as well as regulation of neural migration.

It was shown that reelin modulates neurogenesis not only during the development process but also at adult age. In adult age, reelin is released from GABAergic interneurons of hippocampus which play an important role in neuroplasticity. In addition, reelin proteins bind to alpha3 subunits of integrin receptors expressed on neuronal cell surface such as apolipoprotein E receptor 2 (poER2) and very-low density lipoprotein receptor (VLDL-R). This induces phosphorylation cascade by activating tyrosine kinase pathway. The activation of reelin signaling has significant effects on long-term potentialization, regulation, cell proliferation, cell migration, brain development such as dendritic spine morphogenesis and adult neurogenesis[12]. It is known that any mutation or altered expression in reelin gene that has an essential role in neuronal development process predisposes to neuropsychiatric diseases[13]. It was shown that reelin deficit is a common phenomenon that serves to cognitive deficit in many disorders including schizophrenia, bipolar disorders, autism, major depression, lizencephaly, alzheimer disease and epilepsy[14-16].

Mutations in reelin gen can result in either the reduction or absence of reelin expression. It is thought that alterations in expression due to mutations developed via methylation of reelin gene promoter or unknown mechanism are the main factor predisposing neuropsychiatric diseases. In studies, it has been shown that there is reduced reelin expression in different brain regions in some disorders such as schizophrenia and major depression[17]. Given its important roles in the brain development, it was evaluated as a major marker for autism, demonstrating a significant relationship between autism and reelin gene mutation and expressions[18].

In our study, it was observed that there were significant differences between the patient and control groups regarding the genotype and allele distributions of rs734147 gene polymorphism. Moreover, it was shown that genotype and allele distributions of both rs734147 and rs12705169 gene polymorphisms differed significantly in the patients with serious suicide attempts. However, lack of reelin gene expression studies; thus, failure to address the relationships between reelin gene polymorphisms and expression, is considered as the main limitation of the present study.

This study detected a significant difference in rs734147 gene polymorphism between the patients with the first suicide attempt and those with repeated suicidal attempt for the first time. Higher rs734147 gene mutation rate in the patient with the first suicide attempt is explained by the fact that majority of these patients (72.3%) had serious suicidal attempt.

In conclusion, our results indicated a significant relationship between reelin gene mutation and suicidal behavior. It is mostly impossible to establish genetic components underlying suicidal behavior that has a complex inheritance process under the influence of several risk factors, mainly psychiatric disorders, and the interaction of various genes. Therefore, more comprehensive studies are needed to identify direct effects of reelin gene on suicidal behavior.

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