Clinical and Experimental Health Sciences

Determining Expression Profile of Leucine-Rich Repeating Transmembrane Protein4 (LRRTM4) in Suicide Cases

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Received: 08.05.2024 **Accepted:** 24.09.2024

ABSTRACT

Objective: Suicide is important in forensic medicine. Studies conducted to determine the etiology of suicide have shown that genetic factors have a critical role along with neuroendocrine changes occurring in the brain. It has been shown that dysregulation in the glutamatergic signaling pathway plays an essential role. One of the glutamatergic genes that causes suicide is the leucine-rich repeating transmembrane protein4 (LRRTM4). In our study, unlike previous studies, we planned to investigate LRRTM4 gene expression levels at mRNA and protein levels by taking samples from the dorsolateral prefrontal cortex (DLPFC) of the brain from autopsy cases. It was aimed to determine whether there is a statistically significant difference in LRRTM4 gene expression levels between suicide and non-suicide cases.

Methods: The study group consisted of 38 suicides. The control group consisted of 30 non-suicidal cases. Samples were taken from the DLPFC in the brain from these cases at autopsy. In the tissue samples obtained LRRTM4 gene expressions were analyzed at the mRNA and protein level using quantitative PCR and western blot methods.

Results: LRRTM4 gene expression values of suicides and non-suicide cases were compared. It was found to be 1.6 times higher in the study group than in the control group.

Conclusion: It has been determined that there is a statistically significant positive relationship between suicide and the LRRTM4. Our findings will contribute positively to the pre-detection of risk factors in suicidal individuals and the medicolegal evaluation. Furthermore, our study will guide further research on the role of genetic factors in the etiology of suicide.

Keywords: Gene expression, leucine-rich repeating transmembrane protein4, glutamate, suicide.

1. INTRODUCTION

Glutamate is the most abundant excitatory neurotransmitter in the central nervous system. It is responsible for memory, learning, and cognitive functions. It also acts as a signal molecule in peripheral tissues and organs and takes part in various steps such as cell migration, cell differentiation, synapse induction. Glutamate exerts its effects through AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid/kainate) and NMDA (N-Methyl-D-Aspartate) receptors located on presynaptic and postsynaptic cell membranes. When glutamate receptors are activated in the postsynaptic cell, some events occur inside the cell, such as activation/inhibition of some enzymes and secondary messengers, and expression/regulation of Ca^{+2}-dependent genes (1).

Gene expression and epigenetic studies have shown that dysregulation of the glutamatergic signaling pathway plays an important role in suicidal behavior (2,3). Genome-wide association studies (GWAS) are the most common approach used to identify genetic risk factors for suicide. According to these studies, one of the glutamatergic genes involved in suicide is the leucine-rich repetitive transmembrane protein4 (LRRTM4) (4).

The leucine-rich repetitive transmembrane protein (LRRTM) gene family is located on chromosome 2p12 and encodes neuronal leucine-rich repetitive transmembrane protein (4). These genes are expressed in the hippocampus, cerebral cortex, and striatum. LRRTM proteins are synaptic adhesion molecules located on postsynaptic membranes. These molecules form synaptic connections between the presynaptic and postsynaptic membranes and stabilize the membranes. Moreover,

DOI: 10.33808/clinexphealthsci.1480334

these proteins facilitate the recognition of targets at synapses, determine the specificity of presynaptic and postsynaptic regions, and contribute to synaptic plasticity. LRRTM proteins act as initiators at selectively excitatory synapses but have no effect on inhibitory synapses (5,6). LRRTM proteins perform their functions through three mechanisms: direct association with AMPARs, indirect association with AMPARs by binding to postsynaptic density protein 95 (PSD-95), and transsynaptic interaction with their presynaptic ligand neurexins (7).

The LRRTM gene family is composed of four members: LRRTM1, LRRTM2, LRRTM3, and LRRTM4. LRRTM4 is more similar to LRRTM3, while LRRTM1 is more similar to LRRTM2 (6). Genome-wide association studies have revealed a significant correlation between LRRTM4 and suicide attempts (4). Different studies have linked variations on chromosome 2p12 to suicide attempts in bipolar disorder, alcoholism, or major depression (8,9,10,11).

In our study, we planned to investigate LRRTM4 gene expression levels at mRNA and protein levels by taking samples from the dorsolateral prefrontal cortex of the brain from autopsy cases. It was aimed to determine whether there is a statistically significant difference in LRRTM4 gene expression levels between suicide and non-suicide cases. In our study, unlike previous studies, LRRTM4 gene expressions were investigated at mRNA and protein levels in samples taken directly from the dorsolateral prefrontal cortex localization of the brain.

2. METHODS

Prior to commencing the study, we submitted an application to the Pamukkale University Faculty of Medicine Clinical Research Ethics Committee and obtained approval with decision number 60116787-020/53631 dated 09/09/2020 Our study was supported by Pamukkale University Scientific Research Projects Coordination Unit under project number 2021TIPF007.

2.1. Samples Set

Our study included 68 autopsy cases performed between 10/09/2020 and 09/09/2021 in the Department of Forensic Medicine at Pamukkale University Faculty of Medicine.

The study group consisted of 38 suicide cases, 31 male and 7 female. The causes of death in suicide cases were hanging, oral drug intake, parenteral drug intake, gunshot wounds, strangulation, and jumping from a height. The control group consisted of 30 cases, 27 male and 3 female, whose cause of death was not suicide. The control group included sudden cardiac deaths, firearm injuries, traffic accidents, murders, and other accidents (work accidents, drowning in water).

During the autopsy, we took 1 cm^3 brain tissue samples from the BA9 (Brodmann Area9) area of the dorsolateral prefrontal cortex (DLPFC) from the cases. We stored tissue samples in cryotubes in RNA later solution at – 80°C.

2.2. RNA Isolation and cDNA Synthesis

We isolated total RNA from brain tissue samples using the Hybrid-R RNA isolation kit (Geneall Biotechnology). Then, we synthesized cDNA using the High Capacity cDNA Reverse Transcription Kit (Applied Biosystems/Life Technologies). We stored these cDNAs at – 20°C until PCR.

2.3. Determination of Expressions by Real-Time Quantitative PCR

We used cDNAs synthesized from RNAs obtained from tissue samples for the analysis of LRRTM4 gene expression. We performed relative quantitation analysis for LRRTM4 (target gene) and β-actin (reference gene) using the real-time PCR system (LightCycler 480 Real-time PCR System, Roche Diagnostics). We used the Primer-BLAST program (NCBI) to select the primer sets for expression analysis of the target gene and reference gene at the mRNA level.

To evaluate the relative expression of the LRRTM4 gene at the mRNA level in the study and control groups, we prepared a real-time PCR mix with the 2X qPCR SYBR-Green Mastermix (Without Rox) kit (Applied Biosystems/Life Technologies). We applied this protocol for the target gene LRRTM4 and the reference gene β-actin. We performed the real-time qPCR reaction of the reaction mixture on the Applied Biosystems 7500 Real-time PCR system (Applied Biosystems, Foster City, CA, USA).

We performed analyses with negative control reaction mixtures containing PCR-grade water instead of DNA. We calculated quantification of LRRTM4 mRNA expression levels based on the quantification cycle (Cq) for each well and normalized it to β-actin as endogenous controls in both study and control groups. We processed raw data using LightCycler 480 software (Roche Diagnostics GmbH, Mannheim, Germany). We calculated the expression of LRRTM4 mRNA using the ΔΔCq method and compared it with the expression in the control group. We considered the difference significant when the ρ value was <0.05. We represented the value as the mean fold of RNA expression compared with the controls (We calculated the ΔCT value for each case by subtracting the CT beta-actin (reference gene expression) from the CT LRRTM4 (target gene expression), which gave us the ΔCT (normalized gene expression). We calculated mean ΔCT values for both the study group and control group to compare their expression levels. We also calculated the mean “fold change” value of the LRRTM4 gene expression for the study group by determining the Δ/Δ Ct value.).

2.4. Western Blotting

We obtained total protein extracts from cells using ProtinEx Total Protein Extraction Solution (GeneAll, Cat No: 701-001). We performed protein quantification using Qubit® Protein Assay Kits (Thermo Fisher Scientific, Cat No: Q33211) and Qubit® 3.0 Fluorometer (Thermo Fisher Scientific, Cat No: Q33216). Then we started the electrophoresis step.

We prepared the mixture using a 100 µg protein sample, 4X NuPAGE LDS Sample Buffer (Thermo Fisher Scientific, Cat No: NP0004), and 10X NuPAGE Sample Reducing Agent (Thermo Fisher Scientific, Cat No: B0004), and performed protein denaturation. We placed samples in the Buffer core vertical gel system tank (XCell SureLock, Invitrogen). We loaded a 5 µl marker (Prime-Step™ Prestained Broad Range Protein Ladder, Biolegend, Cat No: 773301) to the top and bottom of the wells in the gel cassette and performed the execution process. Then we performed blotting using the Iblot Gel Transfer System. We added 5% BSA (Bovine Serum Albumin) to the PBS-T solution containing 0.1% Tween-20 and performed the blocking process with the prepared solution. After this process, we washed it and applied Anti-LRRTM4 at a dilution rate of 1/50000 and Anti-beta actin antibodies at a dilution rate of 1/500. After applying the primary antibody, we applied a secondary antibody using the Secondary Goat-Anti-Rabbit IgG H&L (HRP) antibody (ab205718) blocking solution (5%BSA-PBST). Then we washed it again. We took membranes in 6 ml of ECL Solution (NZY Supreme ECL HRP Substrate, Nzytech, Cat No: Mb19301) and placed them in the imaging device (ChemiDoc-It2, UVP), and performed imaging. We analyzed band intensities of cases in the control and study groups using the Image J program.

2.5. Statistical Analysis

We analyzed the data obtained in the study using the SPSS (Statistical Package for Social Sciences) for Windows 25.0 statistical package program. We expressed continuous variables as mean±standard deviation and median (minimum-maximum values), while categorical variables were expressed as numbers and percentages. We evaluated the conformity of the data to the normal distribution using the Shapiro-Wilk and Kolmogorov Smirnov tests. In independent group reviews, we used the Independent groups t-test when parametric test assumptions were provided. When parametric test assumptions were not met, we used the Mann-Whitney U test. We used chi-square and Fisher exact chi-square tests to examine differences between categorical variables. We used Pearson and Spearman's correlation analyses to examine relationships between numerical variables. We considered a p-value of <0.05 statistically significant in all analyses.

3. RESULTS

3.1. Evaluation of LRRTM4 Expression at the mRNA (Transcript) Level

Our study included 68 cases, with 38 cases in the study group and 30 cases in the control group.

The mean ΔCT value for the study group was 9.39±3.32, while the mean ΔCT value for the control group was 5.78±4.27. We found a statistically significant difference between these two groups (p< .001)(Table 1). The Δ/ΔCt value of the Study/Control group was calculated as 1.6. In other words, we found that LRRTM4 gene expression was 1.6 times higher in the study group than in the control group.

3.2. Evaluation of LRRTM4 Expression at Protein Level-WB Band Intensity Values

The mean of LRRTM4 expression band intensity values for the cases in the study group was 14238907.18±3427656.35, while the mean for the control group was 11779693.87±3919453.19. We found a statistically significant difference between the study and control groups (p< .01)(Table 1).

When all the cases included in the study were evaluated together, we observed a statistically significant, positive and strong correlation between the normalized expression values(ΔCT) of the LRRTM4 gene and the WB band intensity values (n=68; r=0.798; p< .001).

When the cases in the study and control groups were evaluated within their groups, we observed a statistically significant, positive, and strong correlation between the normalized expression values(ΔCT) of the LRRTM4 gene and the WB band intensity values (Table 2).

When the brain weights of the cases were evaluated, we found that the mean brain weight of the study group was 1412±146 g, while the mean brain weight of the control group was 1478±147 g. In the control group, we found that there was a statistically significant, positive weak correlation between the normalized expression values(ΔCT) of LRRTM4 and brain weight, but this relationship was not found in the study group cases (Table 3).

The mean age of the study group was 42±16, with the youngest case being 18 and the oldest being 84 years old. The mean age of the control group was 40±12, with the youngest case being 21 and the oldest being 58 years old. When the cases were evaluated in terms of age groups, we found that most cases in the study group were in the 30-44 age group with 15(39.5%) cases, and a few were in the group over 60 years old with 5(13.2%) cases. In the control group, we found that most cases were in the 30-44 and 45-60 age groups, with 11(36.7%) cases. When we compared the study and control groups according to age distribution, we found no statistically significant difference between the two groups (p> .01). We also found that there was a statistically significant, negative, and weak correlation between WB band intensity values and age in the study group, but this correlation was not found in the control group (Table 3).

When the groups were compared in terms of weight, we found that in the control group, there was a statistically significant, positive, weak correlation between normalized expression values(ΔCT) and weight, but this relationship was not found in the study group (Table 3).

In the study group, 81.6%(n=31) of the cases were male, and 18.4%(n=7) were female. However, 90%(n=27) of the cases in the control group were male, and 10%(n=3) were female. When we compared the study and control groups according to sex distribution, we found no statistically significant difference between the two groups (p> .05). When we evaluated the WB band intensity values and normalized expression values(ΔCT) of the cases in the study and control groups according to sex, we found no statistically significant difference between sex and WB band intensity values or normalized expression values(ΔCT)(Table 4).

Table 1. *Comparison of age, height, weight, BMI, brain weight, ΔCT values, and WB band intensity values of study and control groups.*

		Mean±S.D.	Med (min-max)	p
Age	Study	42±16	39 (18-84)	.533*
	Control	40±12	40 (21-58)	
Height (cm)	Study	169±10	170 (146-190)	.373*
	Control	171±6	170 (157-185)	
Weight (kg)	Study	77±20	73 (49-160)	.354**
	Control	78±13	77 (53-101)	
BMI (kg/m^2)	Study	27±5	26 (19-45)	.795**
	Control	27±4	26 (19-35)	
Brain weight (g)	Study	1412±146	1375 (1200-1740)	.063**
	Control	1478±147	1503 (1155-1900)	
Δct (normalized expression values)	Study	9.39±3.32	8.96 (3.38–18.2)	.0001*
	Control	5.78± .27	5.75 (-3.09-17.83)	
WB Band intensity	Study	14238907.18±3427656.35	14249577 (6882.870.23140406)	.008*
	Control	11779693.87±3919453.19	11900844.5 (2157.870.17417406)	

** Independent Samples T Test was performed. **Mann Whitney U Test was performed. *** p< .05 was considered significant. BMI: Body Mass Index*

Table 2. *The relationship between the normalized expression values (ΔCT) of the LRRTM4 gene and the WB band intensity values of the study and control groups.*

Groups			WB Band Intensity Values
Control	Normalized Expression Values (ΔCT)	r	.753**
		p	.000*
Study	Normalized Expression Values (ΔCT)	r	.796**
		p	.000*

** p< .05 was considered significant. **r: The Pearson correlation coefficient.*

Table 3. *Comparison of age, height, weight, BMI, brain weight of study and control groups.*

		Control		Study	
		Normalized Expression Values (ΔCT)	WB Band Intensity Values	Normalized Expression Values (ΔCT)	WB Band Intensity Values
Brain Weight	r	*.398**	.226	.175	.221
	p	.029	.230	.294	.183
Age	r	.132	.230	-.287	*-.325**
	p	.488	.222	.080	.046
Height	r	.179	.078	.092	.129
	p	.343	.683	.584	.441
Weight	r	*.384**	.227	.133	.088
	p	.036	.228	.427	.599
BMI	r	.286	.183	.103	.043
	p	.126	.334	.537	.800

** p< .05 was considered significant. *r: Spearman correlation coefficient. BMI: Body Mass Index*

Table 4. *The relationship between the sex of the cases in the study and control groups, WB band intensity values, and normalized expression values (ΔCT).*

		Sex	Mean±S.D.	Med (min – max)	p
Control	Normalized Expression Values (ΔCT)	male (n=27)	6.24±4	5.96 (-0.71-17.83)	.074
		female (n=3)	1.61±5.26	0.6 (-3.09-7.3)	
	WB Band Intensity Values	male (n=27)	12111135.93±3361932.97	11991991 (4327.284.17417406)	.540
		female (n=3)	8796715.33±7809395.7	6831163 (2157.870.17401113)	
Study	Normalized Expression Values (ΔCT	male (n=31)	9.35±3.46	9.03 (3.38-18.2)	.882
		female (n=7)	9.57±2.82	8.21 (6.32-13.45)	
	WB Band Intensity Values	male (n=31)	14374560.1±3674634.08	14375991 (6882.870.23140406)	.614
		female (n=7)	13638158.57±2102451.94	14246870 (11368.991.16426113)	

**Independent Samples T Test was performed, p< .05 was considered significant.*

4. DISCUSSION

The frontal and prefrontal cortex play an important role in suicidal behavior as they are involved in the regulation of mood and cognitive functions. Activation of the prefrontal cortex ends the inhibition of impulsive behaviors and increases the risk of suicide (12). In a study, glutamatergic signaling pathways, especially localized in the dorsolateral prefrontal cortex, were found to be associated with neuropsychiatric disorders and suicide risk (13).

With the advent of molecular techniques, recent extensive research has focused on the genetic risk factors underlying the behavioral patterns associated with suicide. Transcription of messenger mRNAs encoded by glutamatergic genes is induced by calcium-mediated activation of specific genes. The mRNA level is a significant measure of the function of the relevant gene, as it shows the amount of transcription (14). Genome-wide association studies on suicide attempts have revealed a significant relationship between suicide attempts and the LRRTM4 gene, which is involved in glutamatergic pathways (15). When previous studies are examined, it can be seen that LRRTM4 gene expression has not been analyzed at the tissue level before. Therefore, our study investigated LRRTM4 gene expressions at the mRNA and protein levels in samples taken from the brain's dorsolateral prefrontal cortex for the first time. Our data analysis revealed a statistically significant positive correlation between LRRTM4 gene expression levels and suicide. These findings were also confirmed by the western blotting method.

LRRTM4 has an intron-3 region containing HREs (hormone response elements), which are the binding sites for the hormone-receptor complex. Studies have shown that variations in HREs may cause changes in the binding of hormones to receptors and the activation of receptors. It has been demonstrated that changes in gene expression may lead to an increased risk of disease (16,17). The data indicate that hormones affect the LRRTM4 gene and provide an understanding of genetic factors in sex-specific differences in suicide. In a genome-wide association study of patients with bipolar disorder, the LRRTM4 gene was found to be associated with the risk of suicide attempts in women (4). Similarly, in a study performed on bipolar disorder cases with and without suicide attempts, five male-specific haplotypes and one female-specific haplotype were detected in the LRRTM4 gene analysis in the intron-3 region. These haplotypes were thought to be associated with gender-specific risk of suicide attempts in bipolar disorder (15). When the LRRTM4 gene expression level in suicide cases in our study was evaluated according to gender, no statistically significant difference was found between both genders. The reason for this result may be the presence of the majority of male cases in the study. It can be concluded that there is a significant relationship between the LRRTM4 gene and sex in studies with a balanced and sufficient sample size for sex.

In our study, the median age of suicide cases was 39(18-84), while the median age of the control group was 40(21-58). In Zhao et al.'s (18) study on the expression of glutamatergic genes in the DLPFC, the median age of suicide cases with major depressive disorder was 40(24-63), while the median age of the control group without psychiatric disorders was 47(24-63). In our study, we observed a weak negative correlation between LRRTM4 protein density values and age in the study group. However, this relationship was not observed in the control group. We found no statistically significant relationship between age and LRRTM4 expression values. When we reviewed gene expression studies in the literature, we didn't find any studies that obtained similar data to our study (18,19).

In our study, the median brain weight of suicide cases was 1375 g, while the median brain weight of the control group was 1503 g. In Zhao et al.'s (18) study on the expression of glutamatergic genes in the DLPFC, the median brain weight of suicide cases with major depressive disorder was 1480 g. The median brain weight of the control group without psychiatric disorders was 1444.83 g. In our study, we observed a weak positive correlation between the LRRTM4 gene expression level and brain weight of the control group. However, this relationship was not observed in the study group. We found no statistically significant correlation between brain tissue weight and protein density values. When we examined gene expression studies in the literature, we didn't find any studies that obtained similar data to our study (18,19).

5. CONCLUSION

In conclusion, in our study, it was found that LRRTM4 gene expression was increased in samples taken from the dorsolateral prefrontal cortex in suicide cases. Our study is pioneering as it is the first study to analyze the mRNA and protein levels of the LRRTM4 gene directly in brain tissue.

Our study will contribute positively to the early detection of risk factors in suicidal individuals, establishing of treatment-prevention protocols, and the forensic medicine evaluation process. We also believe that the studies evaluating the localization, function and interactions of LRRTM4 in various central nervous system circuits will lead to a holistic understanding of the synaptic mechanisms underlying the etiology of suicide.

Acknowledgements: *The authors express their gratitude to the staff of the Medical Genetics Laboratory at İzmir Tınaztepe University and Ass. Prof. Hande ŞENOL for her statistical contributions.*

Funding: *This work was supported by Pamukkale University Scientific Research Projects Coordination Unit under project number 2021TIPF007. The funding body had no involvement in study design or the collection, analysis and interpretation of data or writing of the report.*

Conflicts of interest: *The authors declare that they have no conflict of interest.*

Ethics Committee Approval: *Helsinki Declaration rules were followed to conduct this study. The study was approved by Pamukkale University Medical School Ethics Committee (60116787-020/53631 09.09.2020).*

Peer-review: *Externally peer-reviewed.*

Author Contributions:
Research idea: HKAO, SK, VZ, KA.
Design of the study: HKAO, SK
Acquisition of data for the study: HKAO
Analysis of data for the study: HKAO, SK, VZ
Interpretation of data for the study: HKAO, SK, VZ
Drafting the manuscript: HKAO, KA.
Revising it critically for important intellectual content: HKAO, SK, VZ, KA.
Final approval of the version to be published: HKAO, SK, VZ, KA.

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How to cite this article: Ata Öztürk HK, Zeybek V, Kesan S, Acar K. Determining Expression Profile Of Leucine-Rich Repeating Transmembrane Protein4 (LRRTM4) In Suicide Cases. Clin Exp Health Sci 2024; 14: 1042-1047. DOI: 10.33808/clinexphealthsci.1480334