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ORIGINAL ARTICLE

Single nucleotide polymorphisms in 5-HT receptors in the etiology of premature ejaculation

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KEYWORDS
Premature ejaculation;
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Abstract
Introduction and objectives: Premature ejaculation (PE) is characterized by shorter intravaginal ejaculation latency time than it is acceptable for the patient or partner. It is thought that lifelong PE is a neurobiological dysfunction associated with genetic predisposition and with central serotonin neurotransmission dysfunction in receptors. To contribute to the understanding the genetic etiology of lifelong PE, it was planned to compare the 5-HT2C receptor gene rs3813929, rs518147, 5-HT1A receptor gene rs6295, 5-HT1B receptor gene rs11568817 of lifelong PE patients to healthy controls.
Materials and methods: For this purpose, 100 patients with premature ejaculation and 100 healthy controls were included in the study. Blood samples for DNA extraction were obtained. Appropriate procedures were applied to the probes (rs3813929, rs518147, rs6295, rs11568817) suitable for the DNA studied.
Results: A statistically significant relationship was found between the rs11568817 polymorphism ($p = 0.019$) in the 5-HT1B receptor gene and the rs518147 polymorphism ($p = 0.016$) in the 5-HT2C receptor gene. Also, no statistically significant relationship was found between 5-HT1A receptor gene rs6295 polymorphism and 5-HT2C receptor gene rs3813929 polymorphism and lifelong PE.
Conclusions: The relationship between rs3813929 and rs11568817 polymorphisms with lifelong PE was confirmed. Repeating the study in larger sample groups could be useful in determining the genetic etiology of PE.

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PALABRAS CLAVE
Eyaculación precoz;
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Polimorfismo

Polimorfismos de nucleótido único en receptores 5-HT en la etiología de la eyaculación precoz

Resumen
Introducción y objetivos: La eyaculación precoz (EP) se caracteriza por un tiempo de latencia de eyaculación intravaginal más corto de lo que es aceptable para el paciente o para la pareja. Se cree que la EP de por vida es una disfunción neurobiológica asociada con la predisposición genética y con la disfunción central de la neurotransmisión de serotonina en los receptores. Para contribuir a la comprensión de la etiología genética de la EP de por vida, se planificó comparar el gen del receptor 5-HT2C rs3813929, rs518147, el gen del receptor 5-HT1A rs6295 y el gen del receptor 5-HT1B rs11568817 de pacientes con EP de por vida con controles sanos.
Materiales y métodos: Para este propósito, se incluyeron en el estudio 100 pacientes con eyaculación precoz y 100 controles sanos. Se obtuvieron muestras de sangre para extracción de ADN. Se aplicaron procedimientos apropiados a las sondas (rs3813929, rs518147, rs6295, rs11568817) adecuadas para el ADN estudiado.
Resultados: Se encontró una relación estadísticamente significativa entre el polimorfismo rs11568817 (p = 0,019) en el gen del receptor 5-HT1B y el polimorfismo rs518147 (p = 0,016) en el gen del receptor 5-HT2C. Además, no se encontró una relación estadísticamente significativa entre el polimorfismo del gen del receptor 5-HT1A rs6295 y el polimorfismo del gen del receptor 5-HT2C rs3813929 y la EP de por vida.
Conclusiones: Se confirmó la relación entre los polimorfismos rs3813929 y rs11568817 con EP de por vida. Repetir el estudio en grupos de muestra más grandes podría ser útil para determinar la etiología genética de la EP.

Introduction

Premature ejaculation (PE) has been reported to be the most common male sexual dysfunction, with an estimated global prevalence of approximately 30%.[1] PE is characterized by shorter intravaginal ejaculation latency time (IELT) than it is acceptable for the patient or partner.[2]

While the psychological, environmental, and situational risk factors for the etiology of PE are still important, recent research has focused on the neurobiological and genetic explanatory frameworks of PE.[3] Bernard Schapiro first investigated the genetic component of the etiology of PE in his familial prevalence study in 1943, and it was found that PE was common in male family members of patients.[4] Waldinger et al. confirmed this study by finding 88% of first-degree relatives of men with PE's IELT was less than 1 min.[5]

Serotonin or 5-hydroxytryptamine (5-HT) is the most widely studied neurotransmitter associated with mediating ejaculation in men.[6] Waldinger et al. described PE as a neurobiological dysfunction with a genetic susceptibility to short IELT associated with reduced central 5-HT neurotransmission and/or 5-HT receptor dysfunction.[5,7]

In the first deoxyribonucleic acid (DNA) based study on the genetic etiology of lifelong PE, it was aimed to determine the effect of serotonin transporter promoter region (5-HTTLPR) polymorphism.[8] Later, the same gene polymorphisms were researched in Turkey, Iran, China, Italy, Finland, and in Egyptian populations; conflicting results were obtained.[9–15]

In the literature, there are a limited number of studies investigating serotonin receptor polymorphisms in lifelong PE. In 2010, Luo et al. investigated 5-HT2C receptor polymorphisms; and found that men with the −759T or −697C genotype had an increased lifelong PE.[2] In the study of Jern et al., the effects of a total of 6 single gene nucleotide polymorphisms on 5-HT1A, 1B and 2C receptor genes on IELT were investigated in 1399 men, and only 5-HT1B related polymorphisms were found to be significant.[16] Janssen et al., who investigated the effect of 5-HT1A receptor C (1019) G polymorphism on IELT in PE patients, showed that individuals with CC genotypes shorter ejaculation times.[17] The same single nucleotide polymorphism (SNP) was studied in the Egyptian patient group, and the authors stated that GG genotype and G allele were found to be significantly higher in the control group.[18]

Considering the insufficient data on the genetics of lifelong PE, it is essential to determine which genetic polymorphisms contribute to the etiology of PE. For this purpose, in this study, 5-HT2C receptor gene rs3813929, rs518147, 5-HT1A receptor gene rs6295, 5-HT1B receptor gene rs11568817 in the patients of lifelong PE is planned to be compared to the healthy control group in terms of single nucleotide polymorphisms.

Materials and methods

The study was approved by Eskişehir Osmangazi University Clinical Research Ethics Committee on 21.06.2018 with a decision number 45425468-25 and supported by Eskişehir

Osmangazi University Scientific Research Project Unit with the project code 2018-2223.

Study group

The study group included patients who applied to Eskişehir Osmangazi University Faculty of Medicine psychiatry and urology outpatient clinics with premature ejaculation, met the inclusion criteria, and agreed to participate in the study. For the healthy control group, couples who applied to urology and infertility clinics were evaluated, males with no urological or psychiatric disorders detected, and who are willing to participate included. The participants were evaluated according to DSM-5 lifelong premature ejaculation diagnostic criteria.

The inclusion criteria for the patient group were being male between the ages of 18 and 65, being literate, having a regular sexual partner for at least six months, willing to participate in the study, in all or almost all (75–100%) sexual activity, having the experience of a pattern of ejaculation occurring during partnered sexual activity within 1 minute after vaginal penetration, occurring from first sexual activity; not occurring situational. Inclusion criteria for the control group were being male between the ages of 18–65 and being literate.

The exclusion criteria were, currently having a psychiatric diagnosis, use of antidepressants or antipsychotics, history of a head trauma, having any neurological disorder, having diagnosed with diabetes, cardiovascular disease, and having a urological disease other than premature ejaculation for the patient group, having a urological disease for the control group.

The selection of the participants was made between 22.06.2018 and 04.08.2019. In determining the study sample for the power analysis, the PASS-II program was used. Using one-way analysis of variance, 0.85 power and type 1 error was calculated as 0.05. Summary values used in power analysis were obtained from the study titled ''Association between polymorphisms in the serotonin 2C receptor gene and premature ejaculation in Han Chinese subjects''.[2] As the result of the power analysis, a total of 200 people, 100 people per group was considered appropriate.

All candidates were informed about the study, and their written consent was obtained. A psychiatrist evaluated the participants. Sociodemographic Data Form was applied to the participants; age, education level, working status, marital status, and ejaculation times were questioned. In order to evaluate IELT, we asked the participants, ''In the most of the sexual activities (75–100% of sexual activities), after entering the vagina, when does the ejaculation occur?''. 10 cc venous blood samples were collected from the participants.

DNA extraction and analysis

Venous blood sample taken from the participants was sent to the laboratory for a short period to obtain DNA in tubes containing EDTA. DNA has extracted from the blood in accordance with the kit (Thermo Scientific GeneJET Genomic DNA Purification, USA) procedure. For the PCR amplification mixture, 10 μl Master Mix TaqProb 2× (Abmgood, Canada), 1 μl probe (Applied Biosystems, Thermo Fisher Scientific, USA), 5 μl d H_2O and 4 μl DNA samples were completed, and the total volume was completed by 20 μl. PCR was performed by setting the PCR mixture, the amplification program automatic heat cycle device (Step One Plus, Applied biosystems, Thermo Fisher Scientific, USA) to the specified program.

Appropriate procedures were applied to the probes (rs3813929, rs518147, rs6295, rs11568817) suitable for the DNA studied. After completion of DNA amplification in PCR, the temperature was raised very slowly, creating a melting curve for each sample. During the elevation of the temperature, single nucleotide polymorphisms were determined by separating the typical sequence and the sequence containing polymorphism.

Statistical analysis

The continuous data were given as mean ± standard deviation. Categorical data were given as a percentage (%). We used Pearson Chi-Square analysis for the analysis of the cross tables. Odds ratio (OR) was used as the disease risk ratio. Logistic regression analysis was performed. The power of the study was 0.80. IBM SPSS Statistics 21.0 (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.) was used for the analyses. A p-value of <0.05 was considered as statistically significant.

Results

In the patient group, 23 of the patients had elementary school education, 19 had a middle school education, 31 had a high school education and 27 had a university education. Whereas in the healthy control group, these numbers were 7, 12, 38 and 43 respectively. There was a statistically significant difference in the patient and healthy control groups in terms of educational level ($p = 0.002$, $\chi^2 = 14.49$). As for employment status, 87 were employed in the patient group, while 97 were employed in the healthy control group. There was a statistically signifcant difference between the groups in terms of employment status ($p = 0.016$, $\chi^2 = 6.79$). Lastly, 89 patients were living together or married, while 80 healthy controls were livng together or married, and there was no statistically significant difference ($p = 0.079$, $\chi^2 = 3.09$).

The ejaculation time of all participants in the control group was over 60 s after vaginal intercourse. Of 100 patients with PE, 2 of them reported ejaculation before contact, 8 reported ejaculation within 15 s after contact, 17 were within 15–30 s, and 73 reported ejaculation in between 30 and 60 s.

5-HT2C receptor gene rs518147 polymorphism

In order to investigate the rs518147 polymorphism, sufficient DNA could not have been obtained in 19 participants. rs518147 polymorphism was analyzed in a total of 181 participants, 87 in the patient group, and 94 in the control group. As a result of statistical analysis, it was found that lifelong PE was 2.15 times higher in individuals carrying C allele than those carrying G allele (OR = 2.152, 95% CI = 1.149, 4.029, $p = 0.017$).

5-HT2C receptor gene rs3813929 polymorphism

In order to investigate the polymorphism of rs3813929, sufficient DNA could not have been obtained in 16 participants. The rs3813929 polymorphism was analyzed in a total of 186 participants, 91 from the patient group, and 93 from the control group. There was no statistically significant difference between the two groups ($p = 0.092$). Since the 5HT2C receptor gene is located on the X chromosome, males carry only one allele for this gene. Therefore, no Hardy-Weinberg Equilibrium (HWE) calculation was made for rs518147 and rs3813929.

5-HT1B receptor gene rs11568817 polymorphism

In order to investigate the polymorphism of rs11568817, sufficient DNA could not have been obtained in 14 participants. The rs11568817 polymorphism was analyzed in a total of 186 participants, 92 in the patient group, and 94 in the control group.

The most common genotype in both groups was GT genotype, which was 42% in the patient group and 46% in the control group. There was a 2.55-fold increase in the likelihood of lifelong PE in individuals with TT genotype compared to individuals with GG genotype (OR = 2.557, 95% CI = 1.160–5.636, $p = 0.019$). Genotype distributions for 5-HT1B receptor gene rs11568817 polymorphism are shown in Table 1.

In terms of rs11568817 polymorphism, the genotyping results of the participants were distributed within HWE ($\chi^2 = 0.01$, degree of freedom = 2, $p = 0.995$).

Allele frequencies for rs11568817 polymorphism were also analyzed. It was found that the lifetime probability of PE in individuals with T allele was 1.68 times higher than those with G allele (OR = 1.68, 95% CI = 1.116–2.533, $p = 0.013$).

5-HT1A receptor gene rs6295 polymorphism

In order to investigate the rs6295 polymorphism, sufficient DNA could not have been obtained in 12 participants. The rs6295 polymorphism was analyzed in a total of 188 participants, 93 from the patient group and 95 from the control group. The most common genotype was GC (43% and 40%) in the patient and control groups. There was no statistically significant difference between the two groups ($p > 0.05$). Genotype distributions of 5-HT1A receptor gene rs6295 polymorphism of the participants are shown in Table 2.

In terms of rs6295 polymorphism, the genotyping results of the participants were distributed in HWE ($\chi^2 = 0.03$, degree of freedom = 2, $p = 0.985$).

Allele frequencies for rs6295 polymorphism were also evaluated in patient and control groups. C and G alleles were 52.7% and 47.3%, respectively, in the patient group, and 52.6% and 47.4% were in the control group. There was no statistically significant difference between the groups ($p = 0.991$).

Allele distributions for 5-HT2C receptor gene rs518147, 5-HT2C receptor gene rs3813929, 5-HT1B receptor gene rs11568817, 5-HT1A receptor gene rs6295 polymorphisms are shown in Table 3.

When two SNPs, which were found to be statistically significantly correlated with lifelong PE, added to logistic regression analysis as an independent variable, it was found that in the rs518147 (C/G reference) polymorphism, individuals with C allele had a probability of lifelong PE 1.99 times higher than those with G allele. (OR = 1.990, 95% CI OR: 1.049–3.776, $p = 0.035$). For the rs11568817 (TT/GG reference) polymorphism, the probability of disease was found to be 2603 times higher in individuals with TT genotype than GG genotype (OR = 2.603, 95% CI OR: 1.139–5.946, $p = 0.023$). Logistic regression analysis is shown in Table 4.

Discussion

This study aimed to investigate the role of SNPs in serotonergic receptor protein genes in the etiology of lifelong PE. As a result of our study, we found a relationship between rs3813929 and rs11568817 polymorphisms and lifelong PE.

In our study, the education level of the control group was higher than the patient group. Several authors state that as the level of education in PE increases, concerns about satisfaction of the partner increase, so the admittance to the doctor may increase.[8] In our study which is investigating the genetic etiology in lifelong PE, we believe that the environmental factors have a low role and thus the results are not affected by the educational and occupational status.

The rs11568817 polymorphism, which is one of the polymorphisms in which we found a significant difference in genotype and allele distributions between the patient group and healthy control group, is located on the 5-HT1B receptor gene. It was found that the probability of lifelong PE was 2.56 times higher in individuals with TT genotype than those with GG genotype (OR = 2.557, 95% CI = 1.160–5.636, $p = 0.019$). When allele frequencies were analyzed, it was found that individuals with T allele had 1.68 times higher risk of PE than individuals with G allele (OR = 1.68, 95% CI = 1.116–2.533, $p = 0.019$). This SNP occurs in the promoter region of the 5-HT1B receptor gene and affects the expression of the gene. G allele transport has been shown to cause a 2.3-fold increase in gene expression when compared with the T allele.[19] It is difficult to fully understand the role of the 5-HT1B receptor in the physiology of ejaculation, as this is a 5-HT receptor subtype. This G protein-bound receptor inhibits adenylate cyclase, it can be both a presynaptic autoreceptor and postsynaptic heteroreceptor.[20] Studies in rats and mice have shown that systemic or local injection of selective 5-HT1B receptor agonists delays ejaculation, and this effect can be reversed by 5-HT1B receptor antagonists.[21–23] The mechanism by which 5-HT1B receptors inhibit ejaculation has not yet been demonstrated, but the role of 5-HT1B autoreceptors does not seem to be possible, as these receptors cause a reduction in the serotonin release, which is expected to reduce the ejaculation threshold. The effect of 5-HT1B on ejaculation physiology is not only through serotonin release. 5-HT1B heteroreceptor activation may also inhibits the release several chemicals, which are thought to facilitate the ejaculation, e.g. acetylcholine, glutamate and galanin.[7]

In the light of these data, having T allele may decrease the expression of 5-HT1B receptor gene and thus receptor activity; theoretically, it may result in shortening of

Table 1 Genotype distributions of rs11568817 polymorphism in patient and control groups.

rs11568817 genotypes	Patient (*n*)/(%)	Healthy control (*n*)/(%)	OR	%95 CI	*p*
GT	39 (42%)	43 (46%)	1.40	0.691	0.346
GG	20 (22%)	31 (33%)		−2.858	
TT	33 (36%)	20 (21%)	**2.557**	1.160	**0.019***
GG	20 (22%)	31 (33%)		−5.636	
TT	33 (36%)	20 (21%)	1.819	0.899	0.095
GT	39 (42%)	43 (46%)		−3.680	

G: guanine, T: thymine, OR: odds ratio, CI: confidence interval.
* $p < 0.05$.

Table 2 Genotype distributions of rs6295 polymorphism in patient and control groups.

rs6295 genotypes	Patient (*n*)/(%)	Healthy controls (*n*)/(%)	OR	%95 CI	*p*
GG	24 (26%)	26 (27%)	0.876	0.430	0.717
GC	40 (43%)	38 (40%)		−1.784	
GG	24 (26%)	26 (27%)	0.986	0.465	0.972
CC	29 (31%)	31 (33%)		−2.091	
GC	40 (43%)	38 (40%)	1.125	0.573	0.731
CC	29 (31%)	31 (33%)		−2.206	

C: cytosine, G: guanine, OR: odds ratio, CI: confidence interval.

Table 3 Allele distributions of rs518147, rs3813929, rs11568817, rs6295 polymorphisms in patient and control groups.

	Patient *n* (%)	Healthy controls *n* (%)	OR	%95 CI	*p*
rs518147					
C allele	64 (74%)	53 (56%)	**2.15**	1.149	**0.017***
G allele	23 (26%)	41 (44%)		−4.029	
rs3813929					
T allele	71 (78%)	72 (77%)	0.135	0.517	0.092
C allele	20 (22%)	21 (23%)		−2.073	
rs11568817					
T allele	105 (57%)	83 (44%)	**1.68**	1.116	**0.013***
G allele	79 (43%)	105 (56%)		−2.533	
rs6295					
C allele	98 (52.7%)	100 (52.6%)	1.002	0.67	0.991
G allele	88 (47.3%)	90 (47.4%)		−1.51	

C: cytosine, G: guanine, T: thymine, OR: odds ratio, CI: confidence interval.
* $p < 0.05$.

Table 4 Results of logistic regression analysis.

	β	S.E.	Wald	dof	*p*	OR	%95 OR	
							Lower	Higher
rs518147 (C/G reference)	0.688	0.327	4.437	1	**0.035***	**1.990**	1.049	3.776
rs11568817			5.393	2	0.067			
rs11568817 (GT/GG reference)	0.333	0.378	0.779	1	0.378	1.396	0.666	2.926
rs11568817 (TT/GG reference)	0.957	0.422	5.150	1	**0.023***	**2.603**	1.139	5.946
Constant value	−1.641	0.609	7.276	1	0.007	0.194		

β: coefficient, S.E.: standart error, dof: degree of freedom.
* $p < 0.05$. OR: odds ratio.

IELT. The increased risk of PE in individuals with TT genotype or T allele supports this hypothesis. In the literature, the relationship between rs11568817 polymorphism and PE was previously examined in a Finnish community-based study, and it was found that GG genotype was associated with shorter IELT.[16] In the study, 33 (2.4%) of 1399 participants reported IELT in less than 1 minute. However, in this community-based study, participants were grouped according to their IELT time; it is not specified whether those who have short IELT have this complaint since the first sexual activity (lifelong PE) or not. This may be the reason why our findings are not in the same direction.

The 5-HT2C receptor protein gene rs518147, rs3813929 SNPs are both located in the promoter region of the gene, close to the significant transcription starting site.[24] Their proximity to the transcription starting site makes these SNPs good candidates for regulating gene expression. Regarding promoter activity, there have been studies suggesting that the T allele of rs3813929 polymorphism increases the transcription rates,[25,26] but there are also studies contradicting these results.[27] There are also studies suggesting having T or C alleles does not alter gene expression.[28] The C allele of the rs518147 polymorphism is thought to increase gene transcription.[25,27] Systemic injection of the non-selective agonist of the 5-HT2 receptor increased ejaculation latency in rats, and this effect was shown to be reversed with the 5-HT2 receptor antagonist.[29,30] Systemic administration of 5-HT2C agonist meta-chlorophenylpiperazine dose-dependently reduced the number of those capable of ejaculation in rats and rhesus monkeys.[31] In our study, there was no relationship between rs3813929 polymorphism and lifelong PE. Among the variants of rs518147 polymorphism, the risk of PE was found to be 2.15 times higher in individuals carrying the C allele than in individuals carrying the G allele (OR = 2.152, 95% CI = 1.149, 4.029, $p = 0.016$). This finding does not support the hypothetical 5-HT2C receptor hypofunction that is thought to be in PE,[5] but it is consistent with the results of Luo et al.[2] The mechanism of how 5-HT2C receptor activation increases the ejaculation threshold has not yet been established. One of the reasons why the hypothesis are not parallel with the findings may be that polymorphisms cause changes in receptor expression as well as changes in agonist binding activity, down regulation, and desensitization. To our knowledge, there is no study that clearly demonstrates the functional consequences of the SNPs we investigated, and this interpretation can be made on the basis of some other in vivo receptor gene polymorphism studies.[32]

Another serotonin receptor that plays a role in the pathophysiology of PE is 5-HT1A. The most studied polymorphism of the 5-HT1A receptor gene is the C(-1019) G polymorphism, which is designated as rs6295. The G allele variant of this SNP is associated with higher 5-HT1A receptor activity and decreased 5-HT release via autoreceptors. In our study, no statistically significant difference was found between the groups in terms of genotype and allele distributions of rs6295 polymorphism ($p > 0.05$). Janssen et al. investigated the relationship between GG genotype and IELT, and contradictory to their hypothesis, they found that individuals with CC genotypes had significantly shorter IELTs.[17,18] In another study, no significant difference was found between the groups.[16]

The polymorphisms rs11568817 and rs 3813929 that we found to be associated with lifetime PE, were previously found to be also associated with suicidal ideation, alcohol and drug dependence, obesity and attention deficit hyperactivity disorder.[33–37] PE, which is thought to be multifactorial, cannot be wholly associated with a single nucleotide polymorphism, and a single nucleotide polymorphism can play a role in the etiology of more than one clinical condition. In individuals with rs11568817 and rs 3813929 polymorphisms, lifelong PE and other mental illnesses may coexist, or a clinical situation may begin first and cause or contribute to other diseases later on. Identifying and distinguishing other diseases in individuals with these polymorphisms in a structured interview will shed more light on the effect of genetic polymorphisms on psychopathologies.

In our work, the diagnostic evaluation was made by a face-to-face interview. In the field of sexuality, which can be seen as a taboo in Turkish society, obtaining reliable information from participants before the opportunity to develop a reliable patient-physician relationship has difficulties in clinical practice. However, there is no study validating the reliability of the lifelong diagnosis of PE in Turkish. Scales such as Premature Ejaculation Profile, Index of Premature Ejaculation, Premature Ejaculation Diagnostic Tool developed for PE are available in the international literature; however, it is emphasized that these scales may be insufficient to diagnose the PE subtypes and that the scales should not replace the face-to-face patient-physician evaluation when working on PE.[38]

IELT was determined based on the self-report of the participants. IELT, which defines the period between vaginal entry and ejaculation in sexual intercourse, can be measured by two methods, based on self-report or with a stopwatch.[39] IELT data were obtained based on self-report since it was difficult for the participants to use a stopwatch in clinical practice, and our study was a cross-sectional design with a one-time interview. Although authors are stating that using stopwatches is necessary, there are also studies reporting that IELT values measured by self-report and stopwatch show interrelated levels.[40]

To our knowledge, our study is the first to have the quality of work being done in this field in Turkey. As a result of our study, which was carried out on four polymorphisms that were previously made in various countries and found to be associated with lifelong PE, the relationship of rs3813929 and rs11568817 polymorphisms to lifelong PE was confirmed. Repeating the study in larger sample groups in other populations could be useful in determining the genetic etiology of PE. As with the similar studies in the field, our study's patient group consisted of individuals with lifelong PE because it is reported that the role of genetics are higher in the etiology of PE.[5] However, non-genetic factors may play a role in the etiology of PE in this group. Accordingly, future studies should include lifelong PE participants with a familial history of PE, in order to evaluate the role of the genetics more clearly.

The presence of patients who have been diagnosed with lifelong PE and have not benefited from the current treatments suggests that there may be unclear points in the etiology. As in our study, the data obtained from research in this field may shed light on the development of new

screening, diagnostic tools, or pharmacological treatment methods in the future.

Conclusions

In conclusion, a statistically significant relationship was found between lifelong PE and the rs11568817 polymorphism ($p = 0.019$) in the 5-HT1B receptor gene and the rs518147 polymorphism ($p = 0.016$) in the 5-HT2C receptor gene. Also, no statistically significant relationship was found between 5-HT1A receptor gene rs6295 polymorphism and 5-HT2C receptor gene rs3813929 polymorphism and lifelong PE. As a result, the relationship between rs3813929 and rs11568817 polymorphisms with lifelong PE was confirmed. Repeating the study in larger sample groups could be useful in determining the genetic etiology of PE.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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Conflict of interest

The authors declare no conflict of interest.

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