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INVESTIGATION OF THE ASSOCIATION OF LEPTIN (LEP) –2548G/A (RS7799039) AND LEPTIN RECEPTOR (LEPR) 668A/G (RS1137101) GENE POLYMORPHISMS WITH CLINICAL PARAMETERS AND DISORDER SUBTYPES IN INDIVIDUALS WITH PANIC DISORDER

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BACKGROUND AND AIM: Panic disorder (PD) is a clinically heterogeneous anxiety disorder characterized by recurrent and unexpected panic attacks accompanied by persistent concern about having additional attacks and avoidance behaviors related to these attacks (1). Although family and twin studies indicate that PD has a substantial genetic component, the biological determinants of the disorder and the specific genetic factors associated with disease subtypes have not yet been clearly identified (2). In recent years, the effects of metabolic hormones on the central nervous system have attracted increasing interest in the biology of anxiety disorders. Leptin, a neuropeptide involved in energy homeostasis, has been suggested to exert regulatory effects on brain regions associated with anxiety and affective processes (2). However, the number of studies directly investigating the relationship between leptin (LEP) and leptin receptor (LEPR) gene polymorphisms and PD and its subtypes remains limited. In this study, the associations of LEP –2548G/A and LEPR 668A/G gene polymorphisms with PD, clinical characteristics, and disease subtypes were investigated.

METHODS (Ethics Committee Approval must be obtained and the number should be specified.): The study was approved by the Basaksehir Cam and Sakura City Hospital Ethics Committee (Protocol no: 2025.06.251). This study included 102 patients diagnosed with PD according to DSM-5 diagnostic criteria and followed at Basaksehir Cam and Sakura City Hospital, as well as 102 healthy control individuals without any psychiatric diagnosis. Diagnostic assessments were conducted using the Structured Clinical Interview for DSM-5 (SCID-5-CV). Sociodemographic and clinical characteristics of the participants were recorded, and the Panic Disorder Severity Scale, Panic Agoraphobia Scale, Hamilton Depression Rating Scale, and State–Trait Anxiety Inventory were administered. PD subtypes were classified based on clinical characteristics (respiratory subtype, nocturnal subtype, and agoraphobia). For genetic analyses, DNA was isolated from peripheral blood samples, and LEP –2548G/A and LEPR 668A/G gene polymorphisms were analyzed using polymerase chain reaction (PCR) and restriction fragment length polymorphism (RFLP) methods. Group comparisons and association analyses were performed for statistical evaluation.

RESULTS: With respect to the LEP 2548G/A polymorphism, the frequency of the AA genotype was significantly higher in the patient group compared with the control group, and similarly, the A allele frequency was also higher in the patient group. Regarding the LEPR 668A/G polymorphism, the AG genotype frequency was significantly higher and the AA genotype frequency was significantly lower in the patient group compared with the control group. While no statistically significant association was detected between the presence of agoraphobia and the LEP –2548G/A gene polymorphism, the AA genotype and A allele frequency distributions of the LEPR –668A/G gene polymorphism were found to be significantly higher in the group with agoraphobia compared with the group without agoraphobia. In addition, no significant differences were observed in LEP and LEPR gene polymorphisms according to the presence of the respiratory subtype or nocturnal panic attacks. Mean scores on the State–Trait Anxiety Inventory–Trait (STAI-2), Panic Disorder Severity Scale, and Panic Agoraphobia Scale were found to be significantly higher in patients with panic disorder accompanied by agoraphobia compared with patients without agoraphobia.

CONCLUSIONS: In our study, the frequency of the AA genotype for the LEP 2548G/A polymorphism was significantly higher in the patient group compared with the control group. Similarly, the higher frequency of the A allele in the patient group suggests that the A allele may confer susceptibility to PD. Although serum leptin levels were not measured in this study, previous studies have reported an association between lower leptin levels and increased anxiety symptoms (3).

While no statistically significant association was found between the presence of agoraphobia and the LEP –2548G/A gene polymorphism, the AA genotype and A allele frequency distributions of the LEPR –668A/G gene polymorphism were significantly higher in patients with agoraphobia compared with those without agoraphobia. This finding suggests that leptin signaling at the receptor level, rather than leptin production itself, may play a more prominent role in agoraphobia. While the LEP –2548G/A polymorphism primarily affects leptin expression, the LEPR –668A/G polymorphism directly influences receptor function and downstream signaling in brain regions involved in anxiety and fear regulation. Consequently, LEPR variation may

have a stronger impact on agoraphobia susceptibility by altering central leptin receptor–mediated signaling, whereas variation in LEP alone may be insufficient to produce behavioral effects in the absence of receptor-level dysfunction (4).

Overall, our results highlight the potential importance of leptin receptor–mediated signaling in PD and agoraphobia. Future studies integrating genetic, biochemical, and functional approaches are needed to elucidate the role of leptin pathways in anxiety disorders.

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Table 1. Comparison of LEP and LEPR Genotype and Allele Frequency Distributions Between Patients with Panic Disorder and the Control Group

Gene	Model	Patients (n = 102)	Controls (n = 102)	OR	95% CI	p value
LEP	Dominant AA GA+GG	25 (24,5) 77 (75,5)	12 (11,8) 90 (88,2)	2,435	1,147-5,168	0,018*
	Over-dominant GA AA+GG	49 (48,0) 53 (52,0)	55 (53,9) 47 (46,1)	0,790	0,456-1,369	0,401
	Recessive GG AA+GA	28 (27,5) 74 (72,5)	35 (34,3) 67 (65,7)	0,724	0,399-1,316	0,289
	Additive AA GG	25 (47,2) 28 (52,8)	12 (25,5) 35 (74,5)	2,604	1,114-6,087	0,025*
	Alel A G	99 (48,5) 105 (51,5)	79 (38,7) 125 (61,3)	1,492	1,007-2,211	0,046*
LEPR	Dominant AA AG+GG	44 (43,1) 58 (56,9)	67 (65,7) 35 (34,3)	0,396	0,225-0,698	0,001*
	Over-dominant AG AA+GG	48 (47,1) 54 (52,9)	29 (28,4) 73 (71,6)	2.238	1,253-3,996	0,006**
	Recessive GG AA+AG	10 (9,8) 92 (90,2)	6 (5,9) 96 (94,1)	1,739	0,608-4,979	0,298
	Additive AA GG	44 (81,5) 10 (18,5)	67 (91,8) 6 (8,2)	0,394	0,134-1,162	0,084
	Alel A G	136 (66,7) 68 (33,3)	163 (79,9) 41 (20,1)	0,503	0,321-0,789	0,003**

*Data are presented as n (%). In the additive model, percentages were calculated based only on the AA and GG genotypes. OR = Odds Ratio; CI = Confidence Interval. *p < 0.05, p < 0.01.*

Table 2. Comparison of Clinical Parameters and Scale Scores According to the Presence or Absence of Agoraphobia in Patients with Panic Disorder

Variable	No Agoraphobia (n = 52)	Mean ± SD / Median (Min–Max)	Agoraphobia Present (n= 50)	Mean ± SD / Median (Min–Max)	Test	p value
Age (years)	38,65 ± 11,63	38,00 (20,00-65,00)	34,78 ± 11,00	34,00 (19,00-62,00)	t	0,087
Body Mass Index (BMI, kg/m²)	25,68 ± 4,26	25,77 (16,65-35,19)	26,71 ± 4,73	27,22 (17,63-37,18)	t	0,252
Age at Disease Onset (years)	35,97 ± 10,56	37,00 (20,00-64,79)	33,13 ± 10,84	32,87 (15,50-60,00)	t	0,182
Duration of Illness (months)	32,20 ± 48,75	12,00 (0,03-228,00)	19,86 ± 33,32	8,00 (0,03-156,00)	MWU	0,235
STAI-1	39,14 ± 13,16	37,00 (20,00-68,00)	38,76 ± 10,87	35,00 (20,00-61,00)	MWU	0,986
STAI-2	44,66 ± 10,44	44,00 (20,00-67,00)	49,56 ± 9,00	47,00 (30,00-65,00)	t	0,016*
HAM-D	4,56 ± 3,35	4,00 (0,00-12,00)	5,46 ± 3,23	5,00 (0,00-14,00)	MWU	0,157
PDSS	9,67 ± 5,25	10,00 (1,00-22,00)	12,80 ± 5,54	12,50 (0,00-26,00)	t	0,004**
PAS	18,47 ± 10,64	17,00 (2,00-41,00)	23,74 ± 11,41	23,00 (4,00-52,00)	MWU	0,024*

*Mean = Mean; SD = Standard Deviation; Min = Minimum; Max = Maximum; t = Independent samples t-test; MWU = Mann–Whitney U test; BMI = Body Mass Index; STAI-1 = State Anxiety Inventory; STAI-2 = Trait Anxiety Inventory; HAM-D = Hamilton Depression Rating Scale; PDSS = Panic Disorder Severity Scale; PAS = Panic and Agoraphobia Scale. *p < 0.05, p < 0.01.*