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An Investigation of Genetic Polymorphism In The Rs35521 Serotonin Transporter Gene In Allergic Rhinitis

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Abstract

Objective: Allergic rhinitis (AR) is one of the most frequently encountered allergic disorders and has a typical prevalence of between 18 and 40%. The factors which underlie allergic disorders may vary since they are linked to climate, geography, different social conditions and genetic makeup. The objective of our research was to investigate any connections between polymorphism in the serotonin transporter gene and allergic rhinitis.

Methods: This study involved the participation of two groups aged between 15 and 60 years of age who attended the ENT clinic of the Medical Faculty at Erzincan University: 100 individuals with allergic rhinitis plus a control group of 200 individuals who lacked the condition. The AR cases were established on the basis of history, physical examination and skin prick testing. Peripheral blood samples were taken from both groups and subjected to genetic analyses. The analysis utilised a 5-HTT Taqman® primer as genetic probe. The Chi-squared method was utilised for statistical analysis.

Results: 129 of the participants were female (64.5%) and 71 (35.5%) male. The average age of those participating was 34.5 ± 14.6 (range: 20-65) years. In reference to the sex distribution of the patients, 79% of the patients were female. There was a significant difference between the groups according to sex ($p < 0.01$). No significant differences were noted between the patient and control groups when compared according to genetic polymorphism or place of residence. In 61% of the allergic rhinitis sufferers, their symptoms were seasonal. The incidence of AR was higher in both females and in those living in an urban rather than rural setting. When the polymorphism is examined in both the patient and control groups, the most common type is the mutant type. In both the cases and controls, when the polymorphism was investigated, the most frequently seen type was the Mutant variety and no signi0cant difference in frequency was noted according to sex or place of residence.

Conclusion: In this study, when the cases and controls were compared in terms of the polymorphism in the rs35521 serotonin transporter gene, there was no difference at the level of statistical significance between the frequency of occurrence of the mutant or heterozygote form of the gene.

Keywords: Allergic rhinitis, serotonin, serotonin transporter, genetic polymorphism

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Introduction

Allergic rhinitis (AR) is characterised by signs such as sneezing, nasal congestion and rhinorrhoea. It is one of the most frequently encountered of the atopic conditions. In clinical terms, it is a type of hypersensitivity reaction dependant on specific IgE (immunoglobulin E) caused by the nasal mucosa coming into contact with an allergen. It is defined as a symptomatic inflammatory disorder affecting the nose. IgE acts upon basophils and eosinophils to stimulate the release of chemical mediators, resulting in mucosal oedema, increased secretion of mucus, vasodilation and increased vascular permeability. These events lead to symptoms such as nasal congestion, serous discharge and sneezing, which negatively impact the quality of life of AR sufferers.[1]

Whilst the precise aetiology of asthma, allergic reactions and other atopic disorders remains unknown, it is generally accepted that these diseases occur as a result of an interaction between genetic and environmental factors.[2] Although the role of genetic factors in allergic disorders is controversial, the existence of environmental aetiological factors has been known about for a considerable period. Infections, exposure to cigarette fumes, air pollution and allergens both within and outside the home, and encountering proteins of extraneous origin, principally cow's milk, at an early age, are some of the known risk factors.[3,4]

AR is a significant clinical problem, since it is a disorder of high prevalence which demonstrates a low rate of remission in spite of treatment, and because of its co-occurrence with asthma. In the majority of industrialised populations, it is found to be a hypersensitivity to environmental allergens in over 25% of cases. The prevalence of allergic disorders is reported to have gone up within the last 50 years.[5]

In individuals with a genetic predisposition, sensitisation takes place following contact with an allergen. At that point, there is nothing in the patient's clinical condition to indicate the existence of allergic rhinitis. Only if contact with the same allergen is maintained do symptoms develop. The allergen initiates the immune response by entry into the mucosa followed by binding to the specific IgE carried on mast cells. The initial release of histamine and serotonin by mast cells is followed by other chemical messengers, such as tryptase and kinase.[6]

It has been demonstrated that chemical mediators such as histamine and serotonin (5-HT) have a prominent role in the development of AR. Serotonin is involved in a multiplicity of physiological roles within the body and exerts its effects through 14 types of receptor specific to particular tissues. It plays a role in allergic inflammation as it is stored in basophils, platelets and mast cells. 5-HT is released into the synapse by cerebral neurons, then effectively cleared from the synaptic gap by the sodium and chloride ion-dependent high-affinity serotonin transporter (5-hydroxytryptamine transporter, 5-HTT, SERT) protein, which is localized to the presynaptic neuronal membrane and is encoded by the SLC6A4 gene.[7] Thus the synaptic activity of serotonin is terminated by the transporter protein and neurotransmitter is returned to the pool for re-use. In other words, the 5-HTT molecule has a key role in serotonin reuptake and regulating serotonergic function. The level of unbound serotonin circulating in the plasma is controlled by SERT located on cell membranes. Abnormal function of this protein may produce pathophysiological alterations as a result of fluctuations in the level of unbound serotonin.[8]

Given the vital part it plays in serotonergic function, in this research we aimed to clarify whether there is a relationship between the polymorphic variants of the 5-HTT molecule and the aetiology of AR.

Methods

Location and sampling method

The research was undertaken at the ENT polyclinic attached to the Medical Faculty of the Binali Yildirim University in Erzincan, Turkey. There were two groups, each consisting of 100 individuals aged above 15 years. The cases group had a diagnosis of AR, whilst the controls were healthy.

Ethical approval to proceed was obtained from the Ethics Committee of the University Medical Faculty. Genetic analyses were supported by a grant from the Erzincan University Scientific Projects Commission.

The cases consisted of patients who were attending the ENT Clinic attached to the Medical Faculty of Erzincan University with a complaint of rhinitis. These individuals had their history taken using a form as well as undergoing nasal endoscopy and a detailed ENT physical examination. If rhinitis was clinically apparent and hypersensitivity to at least one allergen was apparent on skin prick testing, the diagnosis of AR was assigned and the individual joined the cases group. Circulating venous blood samples (2mL) were then taken in an FBC tube from both the cases and control individuals, to be sent for genetic analysis. Whilst the samples were being transported to the biochemical

laboratory of the hospital, they were kept at minus 20 Celsius.

Skin prick testing

Skin prick testing was performed on all the individuals involved in the study, from both the control and cases groups.

The skin prick testing was carried out on individuals who had no history of using antihistamines, local or systemic corticosteroids, any immunosuppressive agent or any acute infection within the previous ten days. The same researcher carried out all the tests and they were done at the same time each day.

Allergopharma allergen extracts were utilised for the test. Prior to the test, the skin was disinfected in an appropriate fashion and the areas to test demarcated using a pen at 2-3cm intervals. To administer the test, the upper layer of skin was pierced using a device with a sharp tip. The skin was penetrated to a depth of 1mm at an angle of approximately 45 degrees, which produced a scratch in the upper layer of the skin when the epidermis was punctured. This was the method used to ensure contact between the epidermis and the antigen. A solution containing antigen was then dripped onto the area overlying the skin puncture. After waiting for 15-20 minutes, the results could be interpreted. To prevent the possibility of cross-contamination, a separate lancet was used for each application. The evaluation depended on whther an indurated area was produced and if so, what its diameter was.

Molecular DNA analysis

1) 20 microlitres of proteinase K was pipetted into a 1.5mL or 2mL microcentrifuge tube. Then 5-10 microlitres of uncoagulated blood from the samples were added to the tube. The total volume of liquid within the microcentrifuge tube was made up to 220 microlitres by adding PBS solution. In order to obtain material for DNA free isolation, 4 microlitres of a solution of 100mg/mL RNase A were added and the contents vortexed. Following this the tubes were incubated at room temperature for 2 minutes.
2) After adding 200 microlitres of AL buffer minus ethanol the tubes were again vortexed and incubated for 10 minutes at +56 Celsius.
3) 200 microlitres of ethanol (96-100%) were mixed in, using the vortex mixer.
4) The mixture produced by the third step in the procedure was then transferred using a pipette to a 2 mL capacity DNeasy mini spin column. It was spun at above 6000g (8000 rpm) for one minute. The leftover material from centrifugation was then discarded.
5) The DNeasy mini spin column contents were transferred to a new 2mL capacity test tube and 500 microlitres of AW1 buffer added. Again it was centrifuged at above 6000g (8000 rpm) for one minute. The leftover material from centrifugation was then discarded.
6) The DNeasy mini spin column contents were transferred to a new 2mL capacity test tube and 500 microlitres of AW2 buffer added. Again it was centrifuged at above 20000g (14000 rpm) for three minutes. The leftover material from centrifugation was then discarded.
7) The DNeasy mini spin column contents were transferred to a new 2mL capacity test tube. 200 microlitres buffer was added using an AETNAeasy membrane pipette. After incubating the prepared material at room temperature for one minute, it was centrifuged at greater than 6000g (8000 rpm) for one minute.
8) The samples for research were then stored at minus 20 Celsius until needed.

Quantitative measurement of the concentration of DNA isolated by means of spectrophotometry.

1) The DNA samples were then diluted to a level of 1/600 and the values for absorbance at the wavelengths of 260nm (for DNA) and 280nm (for protein) were measured using the ultraviolet spectrophotometer.
2) The DNA concentration of the samples was calculated from the absorbance value at 260nm. The DNA needs to be at an appropriate level of purity for a satisfactory PCR result to be obtained.
3) To prepare the DNA samples for the polymerase chain reaction, the DNA was diluted using DNA hydration solution at a strength of 50ng/μL. For each sample, the readings were taken twice and in this way the DNA purity level was checked and the result quantified.
4) In samples where the concentration of DNA was low, the procedure was repeated up to the point where an acceptable level had been obtained.

5-HTT genetic polymorphism study

Specifically optimised primers were prepared for the study. The NCBI (National Center for Biotechnology Information) database was consulted regarding the 5-HTT rs35521 protein and information sought on G>A

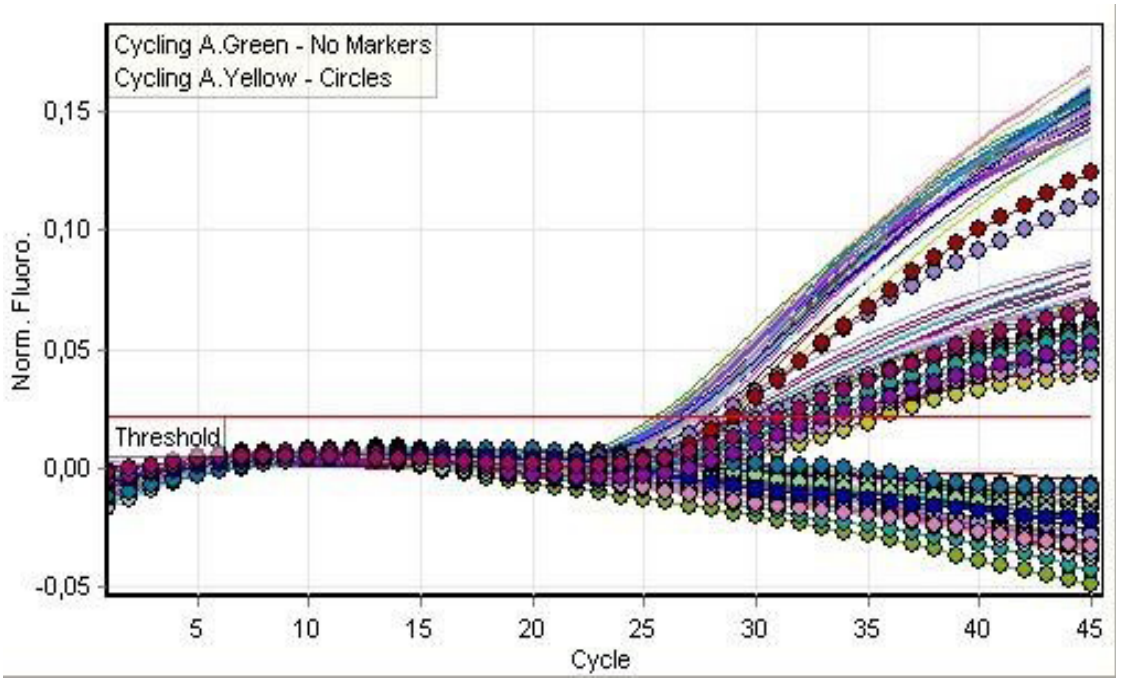

Figure 1. Analysis of the samples for 5-HTT Gene Polimorphism

single nucleotide polymorphisms using the reference NC_000005.10:107745777 and the GRCh38.p7 software version. Primers were constructed as follows: for the forward direction - 5'ATGCCAGCACCTAACCCCTAATGT3' and the reverse - 5'GGACCGCAAGGTGGGCGGGA3'.

One 0.2 mL PCR tube was labelled for each individual. A total volume of 20 µL was set aside for the polymerase chain reaction. Heterozygous and mutant control DNA samples were used in this study. The primers and heterozygous / mutant controls were diluted with 500 microlitres of RNase-free water before use. The primer / probes were diluted with 65 microlitres of RNase-free water. The samples were incubated for 5 min then vortexed. The heterozygous / mutant controls were diluted 1/10 before use.

Analysis of results

The wild probe (GG genotype) is labeled in the ROX (orange) channel and the mutant probe (AA genotype) is labeled in the VIC (yellow) channel. If the sequence is a wild type, a strong amplification graph is detected in the ROX channel and no signal or only a very low level one is detected in the VIC channel. The mutant type produces the opposite. In heterozygotes (GA genotype), an average signal level is determined in both (ROX and VIC) channels.

Statistical analysis

The data gathered were evaluated and analysed using the SPSS for Windows statistical application version 21.0. Numerical variables were expressed as mean and standard deviation, whilst categorical variables were expressed as absolute values and percentages. In the statistical evaluation of the data, the chi-squared test was utilised for categorical variables. A p value of less than 0.05 was set as the level needed to achieve statistical significance.

Results

The sample consisted of 100 cases and 100 controls (200 individuals in total), of whom 129 (64.5%) were female and 71 (35.5%) were male. The average age of those taking part was 34.5 ± 14.6 (range: 20-65) years.

The sex distribution between the groups is presented in table 1. When the sex distribution is examined in the cases group, it can be seen that 79% of the sample consisted of women. The sex difference between the groups reached statistical significance ($p<0.01$).

Table 1. Age and sex distribution of groups

	Female n (%)		Male n (%)	
Patient	79	(79)	21	(21)
Control	50	(50)	50	(50)
Total	129	(64.5)	71	(35.5)

$\chi 2=18,3$ $p<0,01$

When the age distribution between the two groups were compared, it was noted that the average age of the cases was 41.5 years, whilst that of the controls was 27.5 years.

When both groups are compared in terms of their usual place of residence, it was observed that 72% and 70% of the cases and controls were living in an urban setting, respectively. There was no statistically significant difference between the groups in this regard. For the cases group, 61% had symptoms with a seasonal pattern and 39% were perennial, it was noted.

In the cases group, there was a higher frequency of AR symptoms in females compared to males, as is evident in table 2, and those living in the urban setting were found to be more symptomatic than those living in the countryside.

Table 2. Distribution of symptoms according to sex

	Female n (%)		Male n (%)	
Sneezing	60	(75.9)	19	(24.1)
Nasal Discharge	33	(78.6)	9	(21.4)
Nasal stiffness	15	(75)	5	(25)
Itching	46	(82.1)	10	(17.9)
Eye symptoms	6	(66.7)	3	(33.3)
Post nasal discharge	27	(90)	3	(10)

A comparison of the two groups in terms of the genetic polymorphism in the rs35521 gene revealed that 875 of the cases and 78% of the controls carried the mutant genotype, but the difference between the groups in this respect did not reach the level of statistical significance (see table 3).

Table 3. rs35521 polymorphism in patient and control groups

	Mutant (GG→AA)		Heterozygous (GG→AG)		Statistical Analysis
Group	n (%)		n (%)		
Patients	87	87	13	13	$\chi 2=2.85$
Control	78	78	22	22	p=0.09
Total	165	82.5	35	17.5	

Table 4 lists specific details of the patient group in terms of the rs35521 genetic polymorphism. As can be seen in the table, the most frequently observed variant was the homozygous mutant type, in both males and females.

Table 4. Analysis of various parameters of our patients.

	Mutant (GG→AA)	Heterozygous (GG→AG)	Statistical Analysis	
Sex	N (%)	N (%)	p	$\chi 2$
Female	71 (89.9)	8 (10.3)		
Male	16 (76.2)	5 (23.8)	0.09	2.74
Location				
City Center	64 (88.9)	8 (11.1)		
Village	23 (82.1)	5 (17.9)	0.36	0.81
Symptom Period				
Seasonal	51 (83.6)	10 (16.4)		
Perennial	36 (92.3)	3 (7.7)	0.2	1.59
Symptoms				
Sneezing	67 (84.8)	12 (15.5)	0.2	1.59
Nasal discharge	38 (90.5)	4 (9.5)	0.37	0.77
Nasal stiffness	19 (17.4)	1 (5)	0.23	1.14
Itching	51 (91.1)	5 (8.9)	0.17	1.86
Eye symptoms	7 (77.8)	2 (22.2)	0.33	0.74
Post nasal drainage	29 (96.7)	1 (3.3)	0.1	3.54
Wheezing	5 (100)	0		
Cough	24 (87)	2 (13)	0.5	0.87

There was no statistically significant difference according to sex in this variable. Neither was there any statistically significant difference according to place of residence for the genetic polymorphism. In both rural and urban dwellers, the most frequent genotype was the mutant variant.

Within the cases group, the most frequently observed genotype was the mutant variant, which had a frequency of 83.6% in those with seasonal and 92.3% in those with perennial symptoms. There was no statistically significant difference in terms of genotype when examined from the point of view of timing of symptoms.

In the cases group, when the frequency of symptoms was examined, the mutant genotype was the one most frequently encountered, but this difference was not statistically significant.

Within the control group, when the genetic polymorphism was compared between men and women, the most frequently occurring type was the mutant type, found in 84% of women and 72.5% of men. This difference lacked statistical significance. The mutant type was also the most common regardless of whether the individuals were urban or rural dwellers, and there was no statistically significant difference in this regard (see table 5).

Table 5. Distribution of rs35521 polymorphism according to sex and location.

	Mutant (GG→AA)		Heterozygous (GG→AG)		Statistical Analysis
Group	n	(%)	n	(%)	
Male	36	(72.5)	14	(11.1)	$\chi 2=2.09$
Female	42	(84)	8	(16)	p=0.14
Location					
City Center	56	(80)	14	(20)	$\chi 2=0.54$
Village	22	(73.3)	8	(26.7)	p=0.46
Total	78	(78)	22	(22)	

The frequency of asthma in those taking part in the trial was observed to be 12%. Some 91.7% of these asthma sufferers carried the mutant variant of the genetic polymorphism. There was no statistically significant difference observable in the asthmatic group in terms of the genetic result (see table 6).

Table 6. Distribution of rs35521 polymorphism according to concomitant asthma presence

	Mutant (GG→AA)		Heterozygous (GG→AG)		Total		Statistical analysis
Asthma	N	(%)	N	(%)	N	(%)	
+	11	(91.7)	1	(8.3)	12	(6)	$\chi 2=0.74$
-	154	(81.9)	34	(18.1)	188	(94)	p=0,69
Total	165	(82.7)	35	(17.5)	200	(100)	

Discussion

Allergic rhinitis (AR) is the most common amongst atopic disorders and is a somewhat common disease worldwide. It is known to affect 10-25% of the world's population and its prevalence shows an increasing tendency, especially in the last 10 years [9]. AR typically starts before the age of 40 and the mean age of onset is between 12 and 15.[10] In our study, the average age of participants was 34.5 ± 14.6 (range: 20-65) years. This corresponds to what would be expected from the literature.

When the sex distribution of the cases and control groups was investigated, it was seen that 79% of the cases were female, and there was a statistically significant difference between cases and controls in this regard. In research carried out by Öztürk et al [1], of 180 patients receiving a provisional diagnosis of AR, 105 were female and 75 male. The female to male ratio was found to be 1.4 to 1. Nihlen et al [11] reported that the women in their study were more troubled than the men by AR symptoms. In the research that has been carried out so far, AR has been found to be more common in women, and in our study, too, AR was more common amongst females, a result that was significant.

Asthma was found in 12% of the AR cases in the present study, but there was no statistically significant result observable in the genetic analysis with regard to whether the patients were asthmatic or not. Bousquet et al [12] carried out research which looked at the frequency of occurrence of asthma in individuals with AR. Their control group contained 502 individuals, whilst there were 591 AR cases. 2% of the controls and 24% of AR sufferers were asthmatic

The results they obtained are comparable with those seen in the present study.

Serotonin is a key molecule in the body, with 14 different receptors and with various physiological functions within different tissues. The research to date has produced important findings, particularly in reference to the effects of serotonin on the central nervous system. Catalano [7] reported how serotonin, once it has been released into the synaptic gap is effectively cleared by the serotonin transporter protein located on the presynaptic neuronal membrane. In research undertaken by Lesch et al, it is supposed that polymorphism of the serotonin transporter gene may possibly affect the regulation of serotonin-linked behaviours, in particular certain psychiatric disorders such as anxiety, depression, schizophrenia, autism, bipolar affective disorder and seasonal affective disorder.[13] However, a significant relationship was not observed in all of these disorders. In a study undertaken by Özkaya et al [14] a group of 76 individuals suffering from Parkinson's disease was compared with 54 healthy individuals. Both groups were genotyped for the serotonin transporter protein. The relationship between disease and observed frequencies of the L and S alleles were investigated. The alleles were found to be present at similar rates in both cases and controls. No statistically significant relationship was reported from the statistical analysis.

Erdal et al. performed a study on 121 healthy, unrelated volunteers, which looked at the polymorphism within intron 2 of the variable number tandem repeat sequence in the 5-HTT protein and polymorphism of insertion/ deletion type in the transcriptional control region of the gene (5-HTTLPR). Using PCR to genotype the polymorphic regions of this gene, they looked at genetic frequencies. The following results were obtained: 63 individuals (52.07%) had the genotype 12/12; 51 individuals (42.15%) had the genotype 12/10; and 7 individuals had the genotype 10/10. These results were not found to be statistically significant. In a German study carried out by Collier et al [16], the frequency of the L allele of the 5-HTT gene was found to be 0.60, the S allele having a frequency of 0.40.

Karakülah [17] researched genetic frequencies in the 5-HTTLPR genetic polymorphism in case and control groups. For the L allele, the control group frequency was 49.3% and the case group frequency 50%; for the S allele, the controls had a frequency of 50.7% and the cases a frequency of 50%.No statistically significant difference was observed (p=0.835). For the smokers in the sample, the S/S genotype was found in 27.8%, the S/L genotype in 45% and the L/L genotype in 27%. For the control group, 26.9% of individuals had the genotype S/S, 47.8% the genotype S/L and 25.4% the genotype L/L. There was no statistically significant difference between these groups (p=0.861). Possession of the L allele was 72.1% in the group of smokers and 73.7% in the control group, a result that lacked statistical significance (p>0.05). For possession of the S allele, the group of smokers had the gene at a frequency of 73% and it was present in 74% of the controls. This result also lacked statistical significance (p=0.368).

The rs35521 polymorphism was examined in our study and the homozygous mutant form discovered in 87% of the cases group and 78% of the controls, a result that was not found to show difference at the level of statistical significance. In the literature we reviewed there is no previous study investigating the serotonin transporter gene and AR.

Farjadian et al [18] investigated 100 cases of asthma alongside a control group of 100 individuals. When they compared the groups for the same rs35521 polymorphism we examined, they found no relationship with asthma of mild or moderate degree beginning in childhood.

In both the control and cases groups involved in our research, when the polymorphism is compared in men and women, the most frequently occurring genotype in bothe sexes is the homozygous mutant variant. There was no significant difference observable between the sexes. When the frequency of rs35521 was compared in rural and urban dwellers, the homozygous mutant type was again the most frequently occurring in both groups and there was no signifcant difference between groups. Considering the symptomatic course in the individuals comprising the cases group, we find that the homozygous mutant form is the most common variant, being found in 83.6% of cases with a seasonal pattern and 92.3% of the perennial cases. There was no significant difference in gene occurrence according to pattern of symptoms.

When the case and control groups were examined with regard to whether they were homozygous or heterozygous mutant gene carriers for the 5-HTT gene, no significant differences were observed. Further studies involving greater numbers of patients will supply more information on the effects of the transport protein.

Conclusion

Allergic rhinitis is a disorder with a generally high prevalence and a genetic basis. It has a connection with asthma. For these reasons it is a significant clinical problem.

In the present study, there was no statistically significant difference observable in the genotype of the rs35521 gene on the basis of sex, place of residence or duration of symptoms. We believe further studies involving greater numbers of patients are now required.

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