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A Sex-Related Genetic Difference in Bipolar Disorder: Tryptophan Hydroxylase 1 Gene 218 A>C Polymorphism

İkiuçlu Bozuklukta Cinsiyetler Arası Genetik Bir Farklılık: Triptofan Hidroksilaz Gen Polimorfizmi

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ABSTRACT

Objective: Considering the suggested association of tryptophan hydroxylase gene 1 (TPH1) polymorphism with some psychiatric disorders and studies concerning serotonin's effect on TPH 1 gene, brain and the neurotransmitter monoamines, as well as the studies performed on the serotonin levels in cerebrospinal fluid of bipolar patients, we aimed to investigate the frequencies and distribution of TPH 1 gene 218 A>C (rs1800532) polymorphism; A/A, A/C and C/C genotypes in bipolar patients and healthy control subjects for the first time in Turkish population (1-2).

Methods: One hundred and sixteen adult patients who applied to the Mood Disorders Unit of Psychiatry Department, Medical School of Gaziantep University, and diagnosed with bipolar disorder (BD) according to DSM-IV diagnostic criteria were included in the study. One hundred and fifty healthy volunteers, a hospital staff at Gaziantep University, were involved as the control group.

Results: In female patients, the frequency of A/A genotype was found to be higher than in the females in the control group. No significant difference was detected between patient and control groups in terms of age and gender distribution. The distribution of A/A, A/C and C/C genotypes were similar in patient and control groups.

Conclusion: The distribution of TPH1 gene 218 A>C polymorphism was found to be significantly different between female patients and females in the control group. This result can be explicated as being one of the possible reasons for different course of bipolar disorder in male and female patients. *(Archives of Neuropsychiatry 2010; 47: 96-100)*

Key words: Bipolar disorder, tryptophan hydroxylase, genetic, gender

ÖZET

Amaç: Triptofan hidroksilaz (TPH 1) gen polimorfizminin bazı psikiyatrik bozukluklarla ilişkili olduğunun iddia edilmesi ve serotoninin üretiminde önemli bir rolü olan TPH 1 geninin beyne ve beyindeki nörotransmitter monoaminlere etkisi ve ikiuçlu hastalarda BOS serotonin düzeyi ile ilgili çalışmalar göz önüne alarak, Türk ikiuçlu hastalarda ve sağlıklı kontrol örneklerinde daha önce çalışılmamış bulunan TPH 1 geni 218 A>C (rs1800532) polimorfizmini; A/A, A/C ve C/C genotiplerinin sıklık ve dağılımını araştırmayı amaçladık.

Yöntemler: Gaziantep Üniversitesi Tıp Fakültesi Psikiyatri Anabilim Dalı Duygudurum Bozuklukları Birimi'ne tedavi amacıyla başvuran hastalardan ve DSM-IV tanı ölçütlerine göre ikiuçlu bozukluk tanısı alan toplam 116 erişkin hasta ile çalışmanın yapıldığı Gaziantep Üniversitesi Tıp Fakültesi hastanesi çalışanlarından psikiyatrik açıdan sağlıklı olan gönüllüler arasından 150 kişi kontrol grubu olarak alınmıştır.

Bulgular: Kadın hastalarda A/A genotipi kadın kontrol vakalarına göre daha yüksek oranda görüldü. Hasta ve kontrol grubu arasında yaş ve cinsiyet dağılımı bakımından anlamlı farklılık bulunamadı. Hasta ve kontrol gruplarında A/A, A/C ve C/C genotipleri benzer oranlarda dağılmaktaydı.

Sonuç: TPH 1 geni 218 A>C polimorfizmi dağılımının hasta olan ve olmayan kadınlar arasında anlamlı farklılık ortaya çıkmıştır. Bu bulgu ikiuçlu bozukluğun erkek ve kadınlarda farklı seyretmesinin olası nedenlerinden biri olarak yorumlanabilir. *(Nöropsikiyatri Arşivi 2010; 47: 96-100)*

Anahtar kelimeler: İkiuçlu bozukluk, triptofan hidroksilaz, genetik, cinsiyet

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Introduction

Bipolar disorder (BD) is a chronic condition with onset in the late adolescence and early adulthood, with relapsing symptoms afterwards, and in which genetic predisposition is thought to be the principal etiological factor. BD is seen equally among males and females, and its incidence varies between 0.5 and 1.5% in the general population (1).

Genetic predisposition is accepted to be the basis of the disease, although infectious agents, labour trauma and environmental factors are also suggested in the etiology of the disorder (2).

Studies on families, twins and adopted children have suggested significantly increased risk of the disease in biological relatives of the patients. However, the type of genetic linkage is yet to be identified. Genetic predisposition was related with the effects of more than one susceptibility gene (2,3). Various chromosomal disorders, gene locus and abnormalities associated with BD were identified; however, all of the studies are controversial (2,4).

Tryptophan hydroxylase 1 (TPH1) is the enzyme that catalyzes the initial step in the biosynthesis of serotonin (5-hydroxytryptamine, 5-HT). Pharmacologically, 5-HT is the most active indoleamine. However, it rapidly loses its biological activity when bounded to platelets or tissue cells. Availability of tryptophan hydroxylase is the rate-limiting step of serotonin synthesis. The enzyme TPH1 is encoded by gene localized to 11p15.3-p14. Polymorphism of this gene area causes regional increase in tryptophan density and decrease in serotonin density. TPH1 gene, which has a length of 29 kilobase (kb), involves 11 exons of a single promotor and a single transcriptional initiation sequence (5). In the studies on TPH gene, 12 polymorphisms have been identified (6).

Neurobiological and genetic studies in patients with BD suggest that this disease has a genetic basis. Catechol-O-methyl transferase (COMT), 5-hydroxytryptamine transporter (5HTT) and finally TPH1 genes were studied for this purpose. Serretti et al., in a review of 169 patients with BD (103 type I, 66 type II) who have suffered from a previous severe mania or hypomania episode at least once, demonstrated that patients and controls were comparable in respect to serotonin transporter (SERT), TPH1, COMT and 5HT2A gene polymorphisms (7). Besides, depressive patients cycling to mania/hypomania were shown not to be different regarding the same gene polymorphisms. In their study on SERT gene polymorphism in BD, Barlas et al. (8) did not report a difference between patients and controls.

Serotonin level and activity in brain and cerebrospinal fluid (CSF) are directly affected by the polymorphisms of TPH1 gene (9,10). The influence of TPH1 gene polymorphisms on psychiatric diseases has also been studied. Among studies investigating the association of TPH1 gene polymorphism with BD (5,11,12), impulsive-aggressive behaviors (13), activity alterations by antidepressant treatment (14), suicidal behavior (15-17), schizophrenia (18), nicotine addiction and smoking behavior (19) and migraine (20,21), those on BD and TPH1 gene gave contradictory results. Bellivier et al. made a comparison between 152 BD patients and 94 healthy controls regarding TPH1 gene alleles and despite the predisposition of TPH1 gene to BD, they concluded that such kind of predisposition was not present in case of suicidality (11). Rietschel et al. reported that 218 A>C polymorphism was not associated with this disease in their 95 patients with BD (12). Serretti et al. compared 1424 patients with major psychoses, defined according to DSM IV diagnostic criteria, with 380 healthy controls and investigated TPH 1 gene 218 A>C gene variants (5). While TPH 1 gene variants were not found to be associated with major psychoses, it was observed that patients with BD had a high predisposition to TPH1 gene A/A genotype. According to symptomatology, male patients with TPH1 gene A allele were found to have lower depressive symptoms compared to patients with TPH1 C allele, although TPH1 gene 218 A>C variants did not exhibit a significant difference. They suggested that TPH1 gene 218 A>C variants were not the basic sensitivity factors for psychoses at least in their sample, however, they determined that for male patients TPH1 gene A allele containing variants might be a protective factor for depressive symptoms or might be a subtype of mood disorder associated with manic symptoms of this genotype. Possible factors, such as current age and disease onset, age were not found to be affecting the observed results. In summary, BD exhibits a genetic inheritance pattern involving more than one gene (polymorphic-polygenic) and multiple factors (multifactorial) (22,23).

Considering the studies concerning serotonin's effect on TPH1 gene, brain and the neurotransmitter monoamines in addition to the studies concerning the serotonin levels of CSF in bipolar patients (BD), we aimed with the present study to investigate the frequencies and distribution of A/A, A/C and C/C genotypes for the TPH1 gene 218 A>C (rs1800532) polymorphism among patients with BD and healthy controls for the first time in Turkish population.

Methods

a) Selection of Patient and Control Groups

One hundred and sixteen patients, diagnosed with BD, according to DSM-IV diagnostic criteria, in the Mood Disorders Unit, Psychiatry Department, Gaziantep University Medical School, and 150 healthy subjects, a hospital staff at Gaziantep University Medical School, were included as patient and control groups, respectively. Informed written consents were obtained from the patients and their relatives. Diagnosis was established by at least two specialists. Venous blood samples (5 ml) were drawn into ethylenediaminetetra acedic acid (EDTA) tubes from all patients and control subjects, and kept under -20 °C until DNA isolation. The patients, who were followed on treatment for BD, and with recent onset of the disease, were included in the study. Patients with mental retardation and chronic physical disability were excluded from the study.

b) Molecular Genetic Analysis

DNA Extraction and Analysis

With written informed consent, a blood sample was drawn from each individual. Venous blood samples were collected in EDTA-containing tubes. DNA was extracted from whole blood by salting-out procedure (24).

Genotypic Analysis of the TPH1 Gene 218 A>C (rs1800532) Polymorphism

Polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) assays were used to determine TPH1 gene 218 A>C (rs1800532) polymorphism.

The oligonucleotide primers used to determine the TPH1 gene 218 A>C (rs1800532) polymorphism within the TPH1 gene have been previously described (25). The primers, forward 5'-TTCCATCCGTCCTGTGGCTGGTTA-3'; reverse 5'-TTTGAACAGCCTCCTCTGAAGCGC-3', were used to amplify the TPH1 gene. PCR was performed in a 25 µl volume with 50 ng DNA, 100 µm dNTPs, 20 pmol of each primer, 1.5 mM $MgCl_2$, 1x PCR buffer with $(NH_4)SO_4$ (Fermentas, Vilnius, Lithuania,) and 1U Taq DNA polymerase (Fermentas, Vilnius, Lithuania). Amplification was performed on an automated Thermal Cycler (Techne Flexigene, Cambridge, UK). PCR conditions were 3 min for initial denaturation at 95°C; 35 cycles at 95°C for 45 s for denaturation, 45 s at 68°C for annealing and 1 min at 72°C for extension, followed by 7 min at 72°C for final extension. After amplification, PCR products were digested by restriction endonuclease 10 U NheI (Fermentas, Vilnius, Lithuania) for 14 h at 37°C; the genotyping of the TPH1 gene was determined by fragment separation at 120 V for 40-50 min on a 2.5% Agarose gel containing 0.5 µg/ml ethidium bromide. A 100 bp marker (100 bp DNA Ladder, Fermentas) was used as a size standard for each gel lane. The gel was visualized under UV light using visualization system for gel electrophoresis (Vilber Lourmat). The NheI restricted products of TPH1 gene 218 A>C; A/A, A/C and C/C genotypes had band sizes of 1024bp, 1024bp/660bp/364bp and 660bp/364bp, respectively. Genotyping was based upon independent scoring of the results obtained by two reviewers, who were unaware of case/control status.

c) Statistical Analysis

Distribution differences of TPH1 genotypes and alleles between patients and controls were determined using chi-square test and Fischer's exact test. In calculation of average of quantitative variables such as age distribution and education time in subgroups of patients, student-t test was used in their paired groups comparisons and ANOVA analysis was used in the multigroup comparisons. Genotype distribution was compared using Hardy-Weinberg equilibrium. P 0.05 was considered as statistically significant.

Results

Patient group consisted of 116 subjects (52 females, 64 males) and control group consisted of 150 subjects (62 females, 88 males). The mean age of the patient group was 36.62±12.98 with age range of 20-73 years. The mean age of the control group was 34.65±11.24 years. Age and gender distributions were not significantly different between patients and the control group (p>0.05).

The distribution of TPH1 genotypes in patients with BD was as follows: A/A: 18 (15.5%), A/C: 49 (42.2%), C/C: 49 (42.2%). The distribution in the control group was: A/A: 20 (13.3%), A/C: 69 (46.0%), C/C: 61 (40.6%) (Table 1). The distribution of A/A, A/C and C/C genotypes in patient and control groups was comparable (15.5%, 13.3%; 42.2%, 42.2%; 46%, 40%) (χ^2=0.46, df=2, p>0.05). Genotype distribution among the groups was in Hardy-Weinberg equilibration.

Among patients with BD, A allele was found in 85 (36.6%) and C allele in 147 (63.3%) patients, whereas in the control group, A allele was found in 109 (36.3%) and C allele in 191 (63.6%) subjects (χ^2=0.00, df=1, p>0.05).

When both groups were divided into two new groups according to the presence and absence of C allele (C/C and A/C genotype versus A/A genotype), 58 patients (90.6%) and 72 control subjects (82.7%) had C allele, whereas 6 patients (9.3%) and 15 control subjects (17.2%) did not have C allele (χ^2=9.37, df=8, p>0.05).

When the subjects in both groups were divided into two groups according to the presence and absence of A allele (A/A and A/C genotype versus C/C genotype), 35 patients (54.6%) and 51 control subjects (58.6%) had A allele, whereas 29 patients (45.3%) and 36 control subjects (41.3%) did not have A allele (χ^2=0.23 df=1, p>0.05).

The distribution of genotypes in male patients and male controls were as follows: A/A (6: 9.3%; 16: 18.1%), A/C (29: 45.3%; 36: 40.9%) and C/C (29: 45.3%; 36: 40.9%) (p>0.05). The distribution of genotypes in female patients and female controls were as: A/A (23.0%; 6.4%), A/C (38.4%; 53.2%) and C/C (38.4%; 40.3%) (p>0.05). A/A genotype had the lowest frequency in patient and control groups. The frequency of A/A genotype was the lowest among female controls (Table 2). The frequency of A/A genotype in female patients was significantly higher compared to female controls (χ^2=6.92, df=2, p<0.05).

Table 1. Genotype distribution in BD and control samples

	A/A (%)	A/C (%)	C/C (%)	Total (%)
BD	18 (15.5)	49 (42.2)	49 (42.2)	116 (100.0)
Control	20 (13.3)	69 (46.0)	61 (40.6)	150 (100.0)
Total	38 (14.2)	118 (44.3)	110 (41.3)	266 (100.0)

(χ^2=0.46, df=2, p>0.05)

Table 2. Genotype distribution in female patients and female controls

	A/A (%)	A/C (%)	C/C (%)	Total (%)
Patient	12 (23.0)	20 (38.4)	20 (38.4)	52 (100.0)
Control	4 (6.4)	33 (53.2)	25 (40.3)	62 (100.0)
Total	16 (14.0)	53 (46.4)	45 (39.4)	114 (100.0)

(χ^2=6.92 df=2 p=.031)

Discussion

The influence of TPH gene polymorphisms on psychiatric diseases has been studied. Zill et al. suggested an association between TPH2 gene variants and major depression (26). Eley et al. studied gene-environment interactions, 5HTT, 5HTR2A, 5HTR2C, monoamine oxidase subtype A (MAOA) and TPH1 genes in depressions during adolescence (27). They suggested that among depressive patients, particularly females, environmental risks together with SERT gene are important. HTR2A and TPH1 genes were important predictors independent of the effects and interactions of environmental risk and gender factor. Rotondo et al. reported that the distribution of TPH1 polymorphism was different in bipolar patients with panic disorder compared to bipolar patients without panic disorder (28). They also supported the hypothesis, which suggests that patients with accompanying panic disorder would be a separate subtype of BD.

Cusin et al. reported that there is no difference in the frequency of TPH1 gene among patients with unipolar depressions, BD and rapid-cycling BD (29). Serretti et al. reported less depressive symptoms in male patients with TPH1 A allele compared to patients with TPH1 gene C allele, although TPH1 gene 218 A>C gene variant was not different between groups (5). They suggested that variants containing TPH1 gene A allele might be a protective factor for depressive symptoms in male patients or this genotype might be related to a subtype of mood disorders characterized by manic symptoms.

Furlong et al. could not find a significant difference between patients with affective disorder with or without suicide attempts in respect to TPH1 gene polymorphism (30). Sourey et al. reported no difference in TPH1 218 A>C polymorphism in patients with unipolar or bipolar mood disorder, however, the frequency of C/C genotype was higher among patients with unipolar mood disorder having history of suicide attempt compared to the controls (31). Serretti et al. reported that bipolar and depressive patients having TPH1 A/A genotype had poor response to lithium therapy (32).

Serretti et al. reported poor response to therapy with serotonin reuptake inhibitors in depressive and bipolar depressive patients having TPH1 A/A genotype (24).

Mizuno et al. demonstrated a lack of relationship between smoking and TPH1 218 A>C gene polymorphism in Japanese population, but confirmed the early onset of smoking in patients with A/A genotype (33). Sekizawa et al. suggested a two-fold increased risk of early onset schizophrenia in children with TPH1 A/A genotype compared to the other genotypes (34).

The major evidence in our study is the observation of A/A genotype at higher frequency in female patients than female controls. Neither genotype nor allele distribution differences were present between patient and control groups with regard to the other variables. Also according to gender, no difference was established regarding genotype and allele distributions among patients.

Yıldız et al. reported a gender-specific relationship between rapid cycling and use of antidepressants, prior to the first episode of mania/hypomania in patients with BD (35). They suggested that the use of antidepressants would be associated with an increased risk of rapid cycling in female patients compared to males. This suggests that gender factor and serotonergic system should be considered in the context of BD.

We herein report different distribution of TPH1 gene 218 A>C gene polymorphism between patients and healthy controls which could be explained by different clinical presentation and course in male and female patients with BD. Furthermore, this gene polymorphism would be a contributing factor in female patients for the development of the disease. This is the first study demonstrating the female gender-related difference in TPH1 gene polymorphism among patients with BD.

In conclusion, the relation between BD and TPH1 gene 218 A>C polymorphism demands further investigations. Studies are required containing independent samples with higher number of patients. Focusing on the phenotypic subtypes of the disease would enable us to conduct studies on a relatively homogenous population and would give us the opportunity to identify the genes influencing a complex disease. Possible important subtypes of TPH gene polymorphism are: BD with or without suicidal behavior, early or late onset, rapid cycling, responsiveness/irresponsiveness to lithium therapy. Future studies on the association of genes with the clinical signs and symptoms, and the course of the disease (number and type of attacks, etc) would open up new horizons.

References

1. Meiser B, Mitchell PB, McGirr H et al. Implications of genetic risk information in families with a high density of bipolar disorder: an exploratory study. Soc Sci Med 2005; 60:109-8. [Abstract] / [PDF]
2. Belmaker RH. Bipolar disorder. N Engl J Med 2004; 351:476-86. [Abstract] / [Full Text] / [PDF]
3. Savaş HA. İki uçlu bozuklukta genetik polimorfizm çalışmaları. 3P Dergisi 2004; 12:39-48. [Abstract]
4. Porteous DJ, Evans KL, Millar JK et al. Blackwood DH. Genetics of schizophrenia and bipolar affective disorder: strategies to identify candidate genes. Cold Spring Harb Symp Quant Biol 2003; 68:383-94. [Abstract] / [PDF]
5. Serretti A, Lilli R, Lorenzi C et al. Tryptophan hydroxylase gene and major psychoses. Psych Res 2001; 103:79-86. [Abstract] / [Full Text] / [PDF]
6. Shen P, Buchholz M, Sung R et al. Population genetic implications from DNA polymorphism in random human genomic sequences. Human Mutat 2002; 20:209-217. [Abstract] / [PDF]
7. Serretti A, Cusin C, Rossini D et al. Further evidence of a combined effect of SERTPR and TPH on SSRIs response in mood disorders. Am J Med Genet 2004; 129:36-40. [Abstract] / [Full Text] / [PDF]
8. Barlas O, Savaş HA, Arslan A ve ark. "İki uçlu bozuklukta Serotonin Taşıyıcı Gen Polimorfizmi" 38. Ulusal Psikiyatri Kongre Kitabı, Marmaris. 2002, 35.
9. Hoogendoorn B, Coleman SL, Guy CA et al. Functional analysis of polymorphisms in the promoter regions of genes on 22q11. Hum Mutat 2004; 24:35-42. [Abstract] / [PDF]
10. Kelsoe JR, Niculescu AB 3rd. Finding genes for bipolar disorder in the functional genomics era: from convergent functional genomics to phenomics and back. CNS Spectr 2002; 7:215-26. [Abstract] / [PDF]
11. Bellivier F, Leboyer M, Courtet P et al. Association Between the Tryptophan Hydroxylase Gene and Manic-depressive illness. Arch Gen Psychiatry 1998; 55:33-7. [Abstract] / [Full Text] / [PDF]
12. Rietschel M, Schorr A, Albus M et al. Association Study of the Tryptophan Hydroxylase Gene and Bipolar Affective Disorder Using Family-Based Internal Controls. Am J Med Gen (Neuropsych Gen) 2000; 96:310-1. [Abstract] / [Full Text] / [PDF]

13. Staner L, Uyanık G, Correa H et al. A Dimensional Impulsive-Aggressive Phenotype Is Associated With the A218C Polymorphism of the Tryptophan Hydroxylase Gene: A Pilot Study in Well-Characterized Impulsive Inpatients. Am J Med Gen (Neuropsych Gen) 2002; 114:553-7. [Abstract] / [Full Text] / [PDF]
14. Serretti A, Zanardi R, Cusin C et al. Tryptophan hydroxylase gene associated with paroxetine antidepressant activity. Eur Neuropsychophar 2001; 11:375-80. [Abstract]
15. Nielsen DA, Jenkins GL, Stefanisko KM et al. Sequence, splice site and population frequency distribution analyses of the polymorphic human tryptophan hydroxylase intron 7. Mol Brain Res 1997; 45:145-8. [Abstract] / [PDF]
16. Zalsman G, Frisch A, King RA et al. Case Control and Family-Based Studies of Tryptophan Hydroxylase Gene A218C Polymorphism and Suicidality in Adolescents. Am J Med Gen (Neuropsych Gen) 2001; 105:451-7. [Abstract] / [Full Text] / [PDF]
17. Bellivier F, Chaste P, Malafosse A. Association Between the TPH Gene A218C Polymorphism and Suicidal Behavior: A Meta-Analysis. Am J Med Gen Part B (Neuropsych Gen) 2004; 124:87-91. [Abstract] / [Full Text] / [PDF]
18. Hong CS, Tsai SJ, Wang YC. Association between tryptophan hydroxylase gene polymorphism (A218C) and schizophrenic disorders. Schizophrenia Research 2001; 49:59-63. [Abstract] / [Full Text] / [PDF]
19. Lerman C, Caporaso NE, Bush A et al. Tryptophan Hydroxylase Gene Variant and Smoking Behavior. Am J Med Gen (Neuropsych Gen) 2001; 105:518-20. [Abstract] / [Full Text] / [PDF]
20. Estevez M, Estevez AO, Cowie RH et al. The voltage-gated calcium channel UNC-2 is involved in stress-mediated regulation of tryptophan hydroxylase. J Neurochem 2004; 88:102-13. [Abstract] / [Full Text] / [PDF]
21. Erdal N, Erdal ME, Çamdeviren H ve ark. Bir Grup Sağlıklı Gönüllüde Katekol-O-Metiltransferaz (COMT) Gen Polimorfizmi. Klinik Psikofarmakoloji Bülteni 2004; 20:14:2. [Abstract] / [PDF]
22. Sourney D, Masat I, Mendlewicz J. Genetics of bipolar disorders. Acta Neuro Psychiatrica 2000; 12:65-68.
23. Berettini WH, Ferraro TN, Goldin LR. A linkage study of bipolar illness. Arch Gen Psychiatry 1997; 54:27-35. [Abstract] / [PDF]
24. Miller SA, Dykes, DD, Polesky HF. A simple salting out procedure for extracting DNA from human nucleated cells. Nucleic Acids Research 1988; 16:1215. [Abstract] / [PDF]
25. Nielsen DA, Jenkins GL, Stefanisko KM et al. Sequence, splice site and population frequency distribution analyses of the polymorphic human tryptophan hydroxylase intron 7. Brain Res Mol Brain Res 1997; 45:145-8. [Abstract] / [PDF]
26. Zill P, Baghai TC, Zwanzger P et al. SNP and haplotype analysis of a novel tryptophan hydroxylase isoform (TPH2) gene provide evidence for association with major depression. Mol Psychiatry 2004; 9:1030-6. [Abstract] / [Full Text] / [PDF]
27. Eley TC, Sugden K, Corsico A et al. Gene-environment interaction analysis of serotonin system markers with adolescent depression. Mol Psychiatry 2004; 9:908-15. [Abstract] / [Full Text] / [PDF]
28. Rotondo A, Mazzanti C, Dell'Osso L et al. Catechol o-methyltransferase, serotonin transporter, and tryptophan hydroxylase gene polymorphisms in bipolar disorder patients with and without comorbid panic disorder. Am J Psychiatry 2002; 159:23-9. [Abstract] / [Full Text] / [PDF]
29. Cusin C, Serretti A, Lattuada E et al. Influence of 5-HTTLPR and TPH variants on illness time course in mood disorders. J Psychiatr Res 2001; 35:217-23. [Abstract] / [PDF]
30. Furlong RA, Ho L, Rubinsztein JS et al. No association of the tryptophan hydroxylase gene with bipolar affective disorder, unipolar affective disorder, or suicidal behavior in major affective disorder. Am J Med Genet 1998; 81:245-7. [Abstract] / [PDF]
31. Sourey D, Van Gestel S, Massat I et al. Tryptophan hydroxylase polymorphism and suicidality in unipolar and bipolar affective disorders: a multicenter association study. Biol Psychiatry 2001; 49:405-7. [Abstract] / [Full Text] / [PDF]
32. Serretti A, Lilli R, Lorenzi C et al. Tryptophan hydroxylase gene and response to lithium prophylaxis in mood disorders. J Psychiatr Res 1999; 33:371-7. [Abstract] / [PDF]
33. Mizuno S, Ito H, Hamajima N et al. Association between smoking habits and tryptophan hydroxylase gene C218A polymorphism among the Japanese population. J Epidemiol 2004; 14:94-9. [Abstract] / [PDF]
34. Sekizawa T, Iwata Y, Nakamura K et al. Childhood-onset schizophrenia and tryptophan hydroxylase gene polymorphism. Am J Med Genet 2004; 128:24-6. [Abstract] / [Full Text] / [PDF]
35. Yildiz A, Sachs GS. Do antidepressants induce rapid cycling? A gender-specific association. J Clin Psychiatry 2003; 64:814-8. [Abstract] / [PDF]