

Serotonin transporter gene and threatening life events are associated with depressive phenotype

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Although heritability of affective disorders is well accepted, several questions are still unsolved. The phenotype associated with the disorder is still uncertain, e.g., different disorders of the affective spectrum could be observed in the family of the patient. Furthermore, genetic studies failed to provide exact explanation for these questions either. We reported first that the role of the promoter region variant (*5-HTTLPR*) is not exclusive, and the middle region (tagged by the SNP *rs140700*) of the gene has also a significant role in the G x E model. Furthermore, we discovered a significant Gene x Gene x Environment interaction between *5-HTTLPR*, *rs140700* and threatening life events. Haplotype analyses of the serotonin transporter gene suggested that the majority of the S allele carriers for *5-HTTLPR* with multiple threatening life events expressed high depression score, however, a subgroup with much lower depression score was also identified. In another study, interaction of *5-HTTLPR* with the cannabinoid receptor 1 gene promoter was significantly associated with anxious phenotype. These results suggest that extremely high or low synaptic serotonin concentration could be associated with a high anxiety score. These findings call attention to the serotonergic dysfunction in the vulnerability for affective disorders.

Keywords: 5-HTTLPR, gene-environment interaction, threatening life events, cannabinoid receptor, affective disorders

The fact that the same threatening life events provoke serious depression only in a part of the population while minimal affective instability can be observed in other subjects, and that depression aggregates in families suggest that a genetically determined vulnerability may play a role in the background of depression, which may influence the reaction to environmental effects. There is growing body of evidence showing that not depression as a syndrome is heritable, but rather some kind of general vulnerability for affective disorders. Akiskal (2005) proposed a model of affective temperaments for the description of this affective instability. However, data are not available on the association between affective temperaments and affective family history of depressive symptoms. Genetic studies focused on the heritability of depression also yielded heterogeneous results so far. Pharmacological evidence suggests that the serotonin

transporter plays an important role in the pathomechanism of depression. The association studies investigating the direct effect of a functional polymorphism (*5-HTTLPR*) located in the promoter region of the serotonin transporter gene on depression did not provide unambiguous results. Although, Caspi et al. (2003) reported that *5-HTTLPR* is associated with depression only in those persons who experienced a high number of threatening life events (Gene-environment interaction, G x E model), not all replication studies confirmed this relationship (Eley et al., 2004; Grabe et al., 2005; Kendler et al., 2005; Sjöberg et al., 2006; Wilhelm et al., 2006; Cervilla et al., 2007; Surtees et al., 2004; Chipman et al., 2005; Risch et al., 2009). Several explanations can be given for these conflicting data: 1. Gene-gene interaction (G x G): there are other genes or other polymorphisms within the gene of 5-HTT in interaction with *5-HTTLPR* on

depression; 2. Gene-gene-environment interaction (G x G x E): Multiple genetic markers in different combinations are in interaction with the environmental factor on depression; 3. Case-control design can lead to false results due to stratification effects (e.g. individuals carrying vulnerability for depression can be included in the control group if they do not show the symptoms of depression at the time of investigation). Therefore we designed our studies on depression considering these points.

OBJECTIVES OF OUR RESEARCH

The aim of our studies was to investigate the heritable components of depression through analyses of affective temperaments, serotonin transporter gene and threatening life events in a large scale Hungarian general population. Since the gene-environment interaction on depression was investigated earlier only with *5-HTTLPR* we measured the effect of the whole serotonin transporter gene with tagging polymorphisms in interaction with threatening life events. Single marker associations of the polymorphisms tagging different gene regions and also the combinations of different allele variants (haplotypes) of the serotonin transporter gene were analysed. Genetically determined trait anxiety may also play role in the development of depression. Thus, we investigated the effect of *5-HTTLPR* and gene-gene interaction between *5-HTTLPR* and the gene variants of cannabinoid receptor 1 (*CNR1*) which has intensive relationship with the serotonergic system on state, trait and temperament of anxiety.

Our aims were as follows:

1. Is there an association between the affective temperaments and affective family history on depressive symptoms?
2. Are there any effects of the serotonin transporter gene promoter variant (*5-HTTLPR*) and other polymorphisms tagging different parts of the gene on the depressive score? (single marker associations, SMA)
3. Is there any significant interaction between *5-HTTLPR* and threatening life events on depressive symptoms? (G x E model)
4. Is there any significant interaction between other gene regions apart from the promoter and threatening life events on depressive symptoms? (G x E model)
5. Do the polymorphisms show any interaction with each other and with threatening life events on the depressive score? (G x G; G x G x E model)
6. What is the cumulative effect of the haplotypes of the serotonin transporter gene and of threatening life events on depressive phenotype? (haplotype analyses, G x E model)
7. Are there any significant individual effects of *5-HTTLPR* and *CNR1* promoter variants on state, trait and temperamental level of anxiety? (SMA)
8. Is there any significant promoter-promoter interaction on state, trait and temperamental level of anxiety? (G x G model)
9. Can the transcription binding profile based on haplotype analyses give a functionally explicable model for genetic results?

METHODS

Subjects and measures

We recruited 800 Hungarian volunteers (age 18-60 year old) in our study. Data on subjects are summarized in table 1. Detailed background information was obtained from all participants. The background questionnaire was adapted from the version developed by the Epidemiology Unit of the University of Manchester. This well-structured self-rating questionnaire consists of 22 items and collects detailed information about medical history including psychiatric history and medications, family psychiatric history and socio-economic background. Affective family history was measured by this background questionnaire. In the family medical history topic, subjects had to indicate if depression, bipolar disorder/manic episode/manic depression or suicide was present in their families. We coded this information as a combined binary variable indicating whether any of the above indicators of affective-related positive family history was present or not (AFH1 and AFH0). Suicide was also included because of the strong evidence on the relationship between depression and suicide and because it has been described previously that relatives of persons with mood disorder who attempt suicide are at a significantly greater risk for mood disorder (Mann et al., 2005).

The Zung Self-Rating Depression Scale (ZDS) was used to measure symptoms of depression. ZSDS is a valid, reliable instrument used in several studies in order to measure depressive symptoms. Higher scores correspond to more frequent symptoms, thus this qualitative scale provided the dependent variable representing the depressive phenotype in the total sample.

Table 1. Basic characteristics of the study population

	1st study	2nd study	3rd study
Σ n	501	567	706
Gender			
Females	350 (69.9%)	447 (78.8%)	572 (81.0%)
Males	150 (30.1%)	120 (21.1%)	134 (19.0%)
Mean Age ± S.D.	33± 3.2	30.96 ± 10.66	30.26 ± 10.62

Affective temperaments were measured by the TEMPS-A (Temperament Evaluation of the Memphis, Pisa, Paris and San Diego-Autoquestionnaire; Akiskal et al., 2005). Subjects were characterized by average values of each subscales and also extreme forms of each affective temperaments, namely dominant temperaments (DTs) based on a z-score (mean of TEMPS-A score + 2 S.D.) according to previously published methods (Kesebir et al., 2005; Vahip et al., 2005; Vazquez et al., 2007). Persons carrying and not carrying any dominant affective temperament based on any subscale score were grouped separately (DT₁ or DT₀).

We used the depressive (BSI-D) and anxiety (BSI-ANX) subscales of Brief Symptom Inventory in our investigations. In the third study cut-off point was the median + 2SD of the anxious subscale score. Subjects with BSI-ANX score higher than 1.8 were grouped in the high anxiety subgroup. Adverse life event experience was assessed by the List of Threatening Life Events (TLE) developed by Brugha et al. in 1985.

Besides the anxious temperament (TEMPS-Anx) and symptoms of anxiety (BSI-Anx) anxious phenotype was measured by The State-Trait Anxiety Inventory (STAI; Spielberger, 1970).

Genotyping

Buccal mucosa samples were collected from each subject and genomic DNA was extracted using conventional phenol-chloroform extraction protocol. For genotyping 5-HTTLPR, the genomic region containing the polymorphism was amplified using

PCR and Taqman method. Single nucleotide polymorphisms (SNPs) were genotyped (in case of serotonin transporter gene for rs2020942, rs140700, rs3794808, rs104217; in case of CNR1 gene for rs2180619, rs806379, rs1535255 and rs2023239) with Sequenom® MassARRAY technology. From our laboratory dr. Gabriella Juhász and Krisztina Mekli contributed to the extraction, genotyping and coordination of work in Manchester.

Statistic methods

We used chi-square tests, Pearsons' correlation, Mann-Whitney-U, ANOVA tests and linear regression models for descriptive statistics. Hardy-Weinberg equilibrium (HWE), minimal allele frequencies (MAF) and linkage disequilibria (LD) were computed by Haploview 4.0 software. Phenotypes were measured as continuous variables and they were adjusted for age and gender in all analyses. Gene-gene interactions were tested log-likelihood ratio tests (LRT), and generalized linear models (GLM) with 'SNPassoc' R package software.

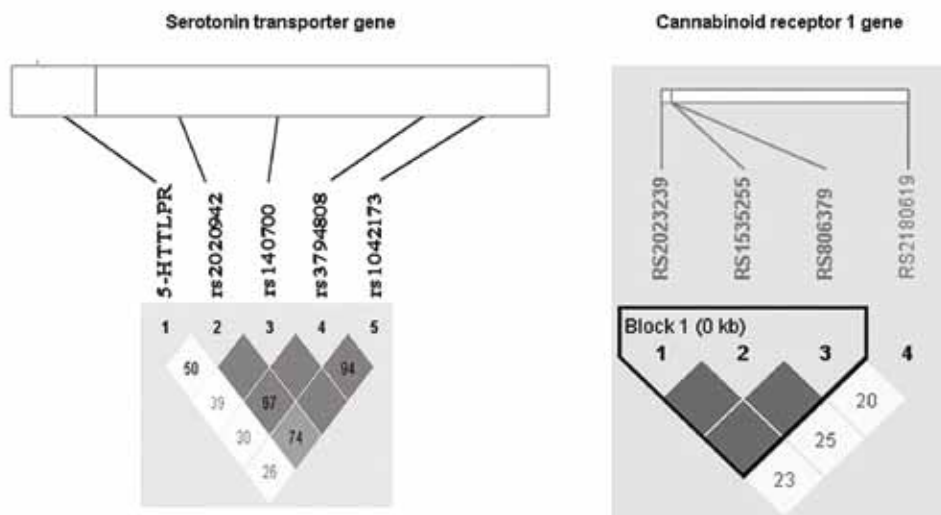
Score tests and GLM were used for haplotype analyses with UNPHASED 3.0.11, and THESIAS softwares.

RESULTS

Association between affective family history and depressive phenotype is mediated by affective temperaments

Three temperaments had a significant effect on depressive phenotype measured by ZDS and BSI-D in a linear regression model: anxious, cyclothymic and depressive temperaments ($p < 0.005$ in all cases), while irritable and hyperthymic temperament had no significant effect. Subjects with a positive affective family history scored significantly higher on the anxious ($p = 0.028$), cyclothymic ($p = 0.020$) and depressive ($p = 0.037$) subscale of TEMPS-A compared to negative family history. The significant association between depressive phenotype and positive affective family history was eliminated when the model was adjusted for affective temperaments. Carrying any dominant temperament was dependent on positive affective family history in a logistic linear model ($p = 0.003$). In case of a positive affective family history the chance to have a dominant temperament was twofold (OR=2.33) compared to those without family history.

Figure 1. Location and linkage disequilibrium of investigated polymorphisms in serotonin transporter gene and cannabinoid receptor 1 gene



Association of the serotonin transporter gene, threatening life events and depressive phenotype

Single marker associations between serotonin transporter gene polymorphisms and depressive phenotype

Individuals with the S allele of the 5-HTTLPR scored significantly higher on the ZDS compared to SL and LL genotype carriers ($p=0.0056$, adjusted $R^2=0.012$). Apart from promoter variants (represented by 5-HTTLPR) different gene region variants tagging by 4 other SNPs had no significant individual effect on depressive score.

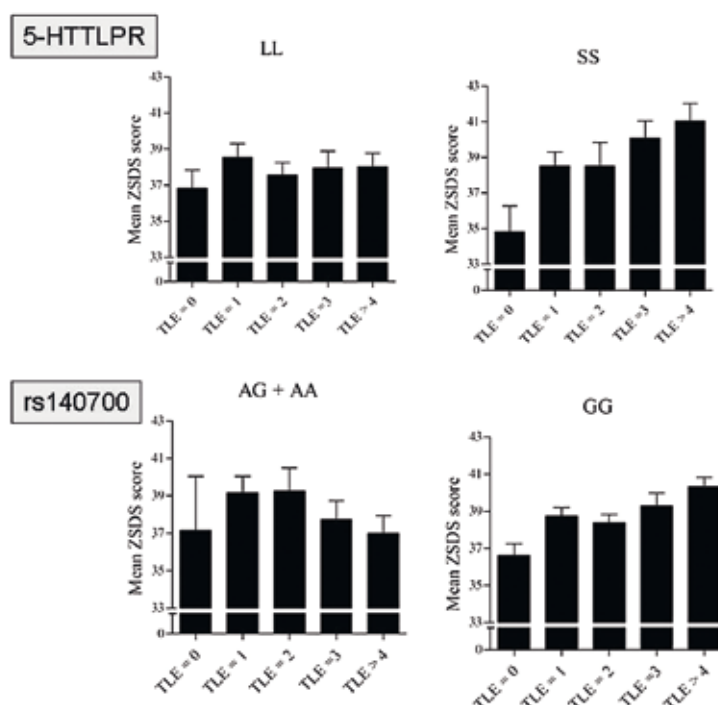
Interaction of the serotonin transporter gene and threatening life events (TLE) on depressive phenotype

Significant interaction was observed between the 5-HTTLPR and TLE on ZDS score in a linear regression model ($p=0.0049$) where the explained variance represented by the adjusted R^2 was 0.042. We revealed another significant G x E interaction between the rs140700 polymorphism and TLE on ZDS score ($p=0.0036$). In this case the adjusted R^2 was 0.040. The effect of TLE on ZDS score was significant in individuals with homozygous GG genotype of the rs140700 polymorphism ($p<0.0001$, adjusted $R^2=0.045$), and A allele carriers did not show this association ($p=0.245$).

Gene-gene and gene-gene-environment interactions on depressive phenotype were also tested between the 5-HTTLPR, rs140700 and TLE. No significant interaction between 5-HTTLPR and rs140700 was found, but the effect of the three-way model (5-HTTLPR x rs140700 x TLE) was significant ($p=0.0005$) on ZDS score. Explained variance was the highest in the latter case (adjusted $R^2=0.059$).

Haplotype analyses of the serotonin transporter gene in interaction with threatening life events on depressive phenotype

The most common haplotype (SGGAG) containing the S allele of the 5-HTTLPR polymorphism was associated with a high ZDS score, while two less frequent haplotypes (SGAGT, LGAGT), one of which also contains the S allele of the 5-HTTLPR, were significantly associated with low ZDS score testing the effect of threatening life events. The difference between the two haplotypes containing the S allele (SGGAG and SGAGT) was significant ($\text{Khi}^2=9.8$; $\text{df}=1$; $p<0.005$). The difference between the LGAGT-associated ZDS score and SGGAG-associated ZDS score was significant ($\text{chi}^2=10.1$; $\text{df}=1$; $p<0.005$), although the haplotype-related phenotype score did not differ significantly between the LGAGT and SGAGT haplotypes ($\text{Khi}^2=1.1$; $\text{df}=1$; $p>0.25$) suggesting that S allele carriers had two subgroups: one with more members associating with high depression score

Figure 2. Significant interaction between threatening life events (TLE) and 5-HTTLPR and rs140700 on ZSDS score

and another containing fewer subjects but associated with as low depression score as the L allele carriers.

Association of the 5-HTTLPR and cannabinoid receptor 1 gene promoter variants on anxious phenotype

Effect of single marker associations of 5-HTTLPR and CNR1 promoter variants on anxious phenotype

5-HTTLPR and CNR1 promoter polymorphisms (*rs2180619*, *rs806379*, *rs1535255* and *rs2023239*) did not show any significant effects on anxious scales if studied separately.

Interactions between SLC6A4 gene promoter and CNR1 gene promoter variants on anxious phenotype

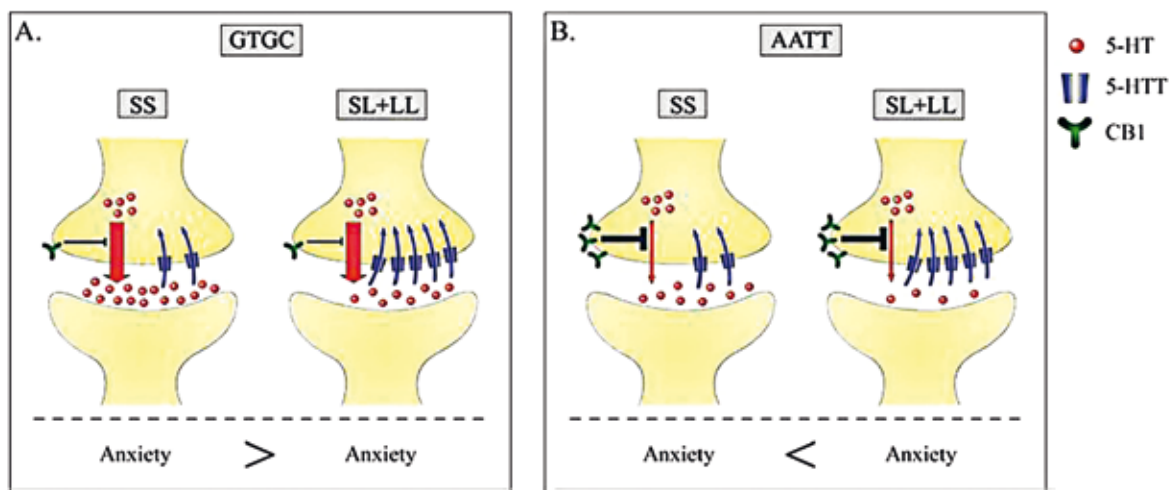
A significant interaction was demonstrated between the 5-HTTLPR and the *rs2180619* polymorphism in the CNR1 promoter on STAI-T, TEMPS-Anx and BSI-Anx measured by likelihood ratio tests and a regression model. The homozygous GG genotype for *rs2180619* polymorphism in interaction with homozygous SS genotype for 5-HTTLPR was associated with the highest STAI-T (mean±S.E.M.=

46.35±3.262; $p=0.0006$) and highest TEMPS-ANX (mean±S.E.M.=0,394±0,05; $p=0.0013$) scores compared to the A allele carriers for *rs2180619* and L allele carriers for 5-HTTLPR polymorphisms. The chance to have a high anxiety phenotype as measured by the BSI-ANX score was more than 4-fold (OR=4.64) in case of the homozygous GG genotype of *rs2180619* in interaction with SS genotype carriers of 5-HTTLPR compared to complementary allele carriers (OR=1), respectively. Carriers of the GG genotype of *rs2180619* and L allele of 5-HTTLPR were protected against high anxiety phenotype (OR=0.36).

Effect of CNR1 gene promoter haplotypes in interaction with 5-HTTLPR on anxious phenotype

First we analysed the haploblock constructed by 3 SNPs (*rs806379*, *rs1535255*, *rs2023239*) located in the 1st intron previously described as the alternative promoter region (Zhang et al., 2003). In our investigation this haplotype did not show any significant association with anxious phenotype nor by itself, nor in interaction with 5-HTTLPR.

Second, we analyzed a four-marker haplotype model in which the *rs2180619* polymorphism located in the conventional promoter was also involved.

Figure 3. Association of CNR1 haplotypes, 5-HTTLPR, synaptic serotonin concentration and anxiety

Based on putative transcription factor binding profile analysis two haplotypes showed possible functional interaction with 5-HTTLPR. In this model high anxiety was associated with extremely elevated and low synaptic serotonin concentration.

We found that the GTGC haplotype was associated with the highest estimated phenotype mean (EPM) of the STAI-T (GTGC haplotype-related $EPM_{STAI-T} = 26.23$ in case of SS and 19.47 in case of SL+LL carriers, $p_{G \times G} = 0.005$) and a trend for TEMPS-ANX score ($p_{G \times G} = 0.085$) in case of the SS genotype of 5-HTTLPR. However, another haplotype, namely AATT, was also significantly associated with a high STAI-T score in L allele carriers for 5-HTTLPR (AATT haplotype-related $EPM_{STAI-T} = 18.35$ in SS and 21.73 in SL+LL carriers, $p_{G \times G} = 0.009$) and TEMPS-Anx (AATT haplotype related $EPM_{TEMP-Anx} = 0.010$ in SS and 0.176 in SL+LL allele carriers, $p_{G \times G} = 0.009$).

CONCLUSION

Our results suggest that association between affective family history and depressive phenotype is mediated by affective temperaments. Since affective family history was determined by heterogeneous affective disorders (major depression, bipolar disorder, manic episode etc.) our results suggest that heritable components of mood disorders predispose to a general mood instability not to an exact clinically defined disorder. This affective instability can be described by affective temperaments.

The well known polymorphism in the serotonin transporter gene promoter, 5-HTTLPR in itself has a significant effect on depressive phenotype in the

general Hungarian population. Other serotonin transporter gene regions tagged by our 4 SNPs do not show any significant individual effect on depressive scores. We replicated for the first time the gene-environment interaction presented by Caspi et al. (2003) in large scale Hungarian general population. We found that S allele carriers of the 5-HTTLPR had higher depressive score in the presence of higher number of threatening life events. We reported first time that *rs140700* polymorphism located in the middle region of serotonin transporter gene had a significant effect in interaction with threatening life events on depressive phenotype. Our analyses revealed for the first time a significant gene-gene-environment interaction effect between 5-HTTLPR, *rs140700* and threatening life events on depressive phenotype. Moreover, our results suggest that this model was the strongest in terms of the explained variance of depressive phenotype among the presented models. Our haplotype analyses showed that the presence of the S allele of 5-HTTLPR was associated with a high depressive score in general but a small group of S allele carriers showed a significantly lower depression score depending on the carrier status of *rs140700*. These results suggest a possible explanation for previous contradictory findings, since S allele carriers might had different allele frequencies for *rs140700* and thus, different association with life events and depression. Our results confirmed the significant role of the serotonin transporter

gene in the gene-environment model in association with depression but in a more sophisticated model than suggested earlier.

Our further results suggest that *5-HTTLPR* in interaction with the cannabinoid receptor gene promoter polymorphism is associated with trait and temperamental level anxiety. These results provide further evidence for the separation of state and trait anxiety. As both *CB1* receptor and serotonin transporter influence the synaptic serotonin concentration and we could identify the functional consequence of the *CNR1* promoter haplotypes based on transcriptional factor binding profiles, we created a biologically relevant model to explain our association findings. Based on this model we concluded that high anxiety scores could be associated with either extremely high or low synaptic serotonin concentration as well. Thus, our data suggest that not only the direction of the alteration but also the imbalance of serotonergic function lead to pathological anxiety states.

The previously raised theory about the shared background of depression and anxiety was based on pharmacological and clinical evidence (eg., therapeutic use of SSRIs in both disorders; anxiety is one of the most common symptoms of depression; high comorbidity of anxiety disorders and depression etc.). Based on our studies *5-HTTLPR* is a significant genetic factor in the background of depressive and anxious phenotype as well.

Our results suggest that *5-HTTLPR* may play a significant role in the development of vulnerability for depression which can be manifested also as trait or temperamental type of anxiety. Certain combination of genetic and/or environmental factors lead to a vulnerability for different psychiatric disorders.

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A szerotonin transzporter gén és a negatív életesemények hatása a depresszióra való hajlamra

A hangulatzavarok öröklődésével kapcsolatban számos kérdés tisztázatlan. Az sem eldöntött, hogy a betegség milyen fenotípus része és hogyan öröklődik, hiszen ismert tény, hogy egy adott klinikai zavarban szenvedő beteg családjában más típusú affektív betegség is előfordulhat. Ugyanakkor a hangulatzavarokra vonatkozó genetikai vizsgálatok sem adnak egyértelmű választ. Elsőként írtuk le, hogy a szerotonin transzporter gén középső szakaszát jelölő *rs140700* polimorfizmus a súlyos életeseményekkel interakcióban szignifikáns összefüggést mutat a depressziós tünetekkel. Szintén elsőként mutattunk ki szignifikáns gén x gén x környezet interakciót az *5-HTTLPR* és az *rs140700*, valamint a súlyos életesemények között a depressziós tünetek megjelenésének hátterében. A szerotonin transzporter gén haplotípus elemzése azt mutatta, hogy az *5-HTTLPR* S allélját hordozók körében a súlyos életeseményt átélt személyek zömmel magas depresszió pontszámot mutatnak, ugyanakkor azonosítottunk ugyanebben a csoportban egy depresszió ellen védő haplotípust is. Eredményeink szerint az *5-HTTLPR* a Kannabinoid receptor 1 génnel interakcióban a szorongásra való hajlam kialakulásában is részt vesz. Vizsgálataink alapján arra következtethetünk, hogy akár a szélsőségesen magas, akár az alacsony szinaptikus szerotonin koncentráció magas szorongás pontszámmal jár együtt, ami a szerotonerg diszfunkció hangulati labilitás kialakulásában játszott szerepére hívja fel a figyelmet.

Kulcsszavak: 5-HTTLPR, gén-környezet interakció, súlyos életesemények, cannabinoid receptor 1 gén, hangulatzavarok