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Review

Suicide-Related Genes

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ABSTRACT

Suicide is a health problem in which the individual ends his/her life voluntarily. It is a phenotype composed of environmental and genetic factors. The suicidal tendency of the individual is due to bipolar disorder, schizophrenia, stress, etc. It is associated with psychological ailments. These are known as environmental factors. The suicidal tendency of the individual also depends on genetic factors. Serotonin and dopamine are neurotransmitters that directly affect human mood. The serotonergic system and dopaminergic system regulate serotonin and dopamine, respectively. The hypothalamic-pituitary-adrenal (HPA) axis is a neuroendocrine structure that regulates stress responses in the body and has a great impact on human psychology. The BDNF protein, also known as a brain-derived neurotrophic factor, provides neuronal development and growth and has an important role in the nervous system. n this article, the function of 5-HTT, TPH-1 and MAOA genes, which are some of the genes belonging to the serotonergic system, the COMT gene, which is one of the genes of the dopaminergic system, the FKBP5 and CRHBP genes belonging to the HPA axis, and the BDNF gene encoding the BDNF relationship has been examined.

Keywords: Brain-derived neurotrophic factor, dopaminergic system, genetics of suicide, HPA axis, serotonergic system, suicide.

Approximately 1 million people end their own lives by suicide within a year. The proportion of suicide among all deaths is 1.5% and it enters the list at the 10th place in causes of death. Many environmental factors cause suicide to occur. Important factors such as stress, schizophrenia, bipolar disorder, depression, alcohol and substance addiction, including childhood trauma, cause the individual to commit suicide. It is not possible to explain and understand suicide only with environmental factors. To truly understand the etiology and pathophysiology of suicide, it is necessary to examine the genetic factors that may cause suicide, and scientists have made their research on suicide based on genetic factors.[1,2] Many families, twin and patient-control studies were conducted in which comparative genotypes were examined. The general purpose of these studies is to observe whether there is a difference between the genotypes of individuals with suicidal tendencies and individuals who do not. Although negative and positive results were obtained in studies, generally positive results were obtained in studies in which environmental factors, bipolar disorder, stress, etc. were included. While investigating the genetic factors underlying suicide, scientists especially benefited from the genetic factors underlying the development of psychological disorders. Serotonin and Dopamine systems in which neurotransmitter substances, which are involved in the neural activities of humans and can directly affect the mental state of the human, and the genes that regulate the activity and activity of these substances were used for research purposes. The serotonergic system is one of the oldest known neurotransmission systems. Besides, serotonin is a monoamine neurotransmitter and due to the regulatory role of serotonin in human mood, candidate genes of this system that may be associated with suicide have been the most used genes in suicide studies. In this study, the genes that are related to suicide and belong to the serotonergic system are TPH-1, MAOA and 5-HTT genes.[1,3] Dopaminergic system is an important system that studies investigating

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the relationship of another suicide with genetics. The dopaminergic system provides the synthesis and secretion of dopamine, a neurotransmitter. Dopamine has a very effective role, especially in the brain part of the body. Dopamine underlies pleasure and motivational behavior. The gene under the dopaminergic system and examined in this article is the COMT gene.[1,4] The HPA axis has been another system that has attracted the attention of studies conducted to examine the genetic background of suicide. The HPA axis regulates the homeostatic systems, immune system and metabolic system in the body and is a neuroendocrine system that secretes hormones depending on the stress level in the body. It regulates the cortisol level in the body. The genes of the HPA axis examined in this article are FKBP5 and CRHBP genes.[1,5,6] Another gene examined in the article is the Brain-derived neurotrophic factor (BDNF) gene, which encodes the hormone BDNF. BDNF hormone is particularly effective in the development and function of neurons. It has an important place in the efficiency of learning and memory actions in the brain.[1,7,8] In this article, the functions of BDNF, FKBP5, CRHBP, TPH-1, MAOA, 5-HTT and COMT genes, their relationship with other psychological disorders and suicidal tendency, and important studies questioning the existence of this relationship are reviewed.

TPH-1 GENE

The TPH-1 gene is located on human chromosome 11, containing 11 exons in situ and encoding Tryptophan Hydroxylase.[9] It acts as a regulation in the serotonergic system and synthesizes serotonin. Serotonin is a neurotransmitter with a monoamine structure. It is known that when it is secreted in the human brain, it creates a feeling of happiness and vitality. Also, low serotonin activity can lead to mental and psychological disorders such as depression, fatigue, and stress.[3,10] Since the TPH-1 gene synthesizes serotonin, research has been carried out on its association with psychological disorders. Serotonin directly affects the mental states of people. The TPH-1 gene synthesizing serotonin has led to the idea that this gene is associated with psychological disorders. For this reason, studies have been conducted to find a relationship between the TPH-1 gene and suicidal tendency. In a study conducted on 51 Caucasian individuals, it was observed whether the TPH-1 gene was associated with suicidal tendency. Analyzes have shown that there is a strong relationship between the TPH-1 gene and suicidal tendency. In other words, it has been observed that genes involved in the serotonergic system such as the TPH-1 gene increase the risk of suicide in individuals with depression.[11] In another study, the effect of the TPH-1 gene on suicidal tendency was examined on 343 Caucasian, African-American and Spanish individuals. The results showed that the TPH-1 gene may play a role, but not necessarily.[12] The results of the meta-analysis including 37 articles examining the relationship between TPH-1 and TPH-2 genes suicidal tendency showed that there is a positive correlation between TPH-1 gene and suicidal tendency.[13]

In a study conducted on 810 Chinese individuals (329 non-suicidal individuals, 297 suicidal individuals and 184 healthy individuals), it was investigated whether the haplotypes of the TPH-1 gene affected suicidal tendency. The results of research conducted in Han Chinese have shown that the TPH-1 gene and its haplotypes may play an effective role in the etiology of their psychological disturbances.[10] In contrast to these studies, a study in the Mexican population did not observe an effective association between variants of the TPH-1 gene and suicidality.[14]

MAOA GENE

The MAOA gene is the gene that encodes the mitochondrial enzyme complex MAO-A (Monoamine Oxidase), which is located on the X chromosome and catalyzes structures such as dopamine and serotonin belonging to the amine group.[15,16] The effect of the MAOA gene and its polymorphisms on substances such as serotonin and dopamine, which directly affect psychological and biological events, has led to the idea that this gene may play a role in the etiology and genetic infrastructure of psychological disorders. For example, antisocial and aggressive behaviors are alcohol and nicotine addiction.[17] Besides, mutations that may occur in the MAOA gene also lead to Brunner syndrome, whose effects such as mental retardation are observed.[18]

Changes in the activity of the MAOA gene are associated with psychological disturbances. Low levels of MAOA gene activity result in high levels of serotonin secretion. This situation leads to nicotine and alcohol addictions and can cause mood disorders, aggressive and antisocial behaviors, etc.[19] Genotypes of 96 women and 95 men were studied to investigate whether the methylation of the MAOA gene is associated with nicotine and alcohol addiction. The results showed that there is a positive correlation between nicotine and alcohol addiction in women and the MAOA gene, but not in men. There are many reasons for the effect of sexual difference on the results, but the most striking one

is that the epigenetic regulation that occurs in men and women may be different.[15] Also, it has been observed that MAOA activity is low in cigarette addicts.[20] According to a study of transgenic mice, it was observed that male mice with the low and insufficient activity of the MAOA gene exhibited changes in serotonin metabolism and a high degree of aggressiveness.[16] In contrast to these studies, the relationship of the MAOA gene with alcohol addiction and antisocial personality was investigated in 129 Han Chinese individuals. (Among 129 individuals, 41 have alcoholic and antisocial personality, 50 have antisocial personality but not alcoholic and 38 are control group who do not show both ailments). According to the results of the study, no significant relationship was observed between the MAOA gene and polymorphisms and alcohol addiction and antisocial personality.[21]

After the MAOA gene is associated with psychological disorders, many studies have been conducted to examine its relationship with suicidal tendency. In summary, these studies could not observe a direct and effective relationship between the MAOA gene and suicidal tendency. For example, in a study of 199 Italian individuals, no relationship was found between the MAOA gene and suicidal tendency.[22] In another example, research on Japanese suicide victims showed that the MAOA-uVNTR polymorphism did not affect suicide.[23] Although a weak relationship was found in some studies, this relationship was considered insufficient to show the relationship between the MAOA gene and suicidal tendency.[24]

There has been a study in which Du et al.[25] Group experimented with 44 suicide victims and showed positive results in this regard. Overall, studies have not shown a sufficient association between the MAOA gene and suicidality.

5-HTT GENE

The 5-HTT gene is located on human chromosome 17, encodes the 5-HTT or SERT protein, also known as the serotonin transporter, and regulates the activity of serotonin found in synapses. Neurons communicate with each other with neurotransmitter substances such as serotonin and dopamine. The 5-HTT protein constantly regulates serotonin and regulates the reuptake of serotonin (5-HT). Many studies have shown that changes in serotonin metabolism can have an impact on psychological disorders. For example, the 5-HTTLPR variant, a variant of the polymorphism found in the promoter region of the 5-HTT gene and the 5-HTT gene, has been associated with many psychological disorders.[26-28]

The research was conducted on 191 Japanese patients, 142 of whom were bipolar and 49 of whom were unipolar, to see if there was a positive correlation between 5-HTTLPR polymorphism and bipolar disorder. 212 healthy Japanese individuals were used as a control group in the study. In the results, no effective relationship was observed between the 5-HTTLPR polymorphism and bipolar disorder.[29] The results of the study conducted by Collier and his group to investigate the role of the activity of the 5-HTT gene in emotional disorders and in which 454 patients with bipolar and unipolar disorder were used as the patient group and 570 healthy individuals as the control group, the results of the study that the 5-HTT gene and polymorphism (5-HTTLPR) affected emotional disorders. showed.[30] The results of a study conducted in Japan showed that there is no relationship between 5-HTTLPR polymorphism and alcohol addiction.[31] The results of the meta-analysis conducted by Feinn et al.[32] Including 17 studies have shown that alcohol dependence and the short variant of the 5-HTTLPR polymorphism are associated with it.

After the role of serotonin in other psychological disorders and the important role of serotonin in mental disorders have been demonstrated in general, studies have been conducted to question whether the 5-HTT gene will also affect suicidal tendency. It was observed whether there is a relationship between 5-HTTLPR polymorphism and suicidal tendency in 306 substance-addicted African-American males. 132 healthy male individuals were used as the control group. In the results, it was observed that 5-HTTLPR interacts with childhood traumas and increases the risk of suicide.[33] Childhood trauma can be considered an environmental factor. Decreases in 5-HTT expression levels are effective in suicidality.[34] In a meta-analysis including 39 studies, an effective relationship between the 5-HTT gene and 5-HTTLPR polymorphism and suicide was observed.[26] Arató et al.[35] Conducted the first study to observe the displacement of 5-HTT attachment sites in suicide victims. In another study, the L allele of the 5-HTT gene was observed to be higher in suicide victims. [36] Chong et al.[37] Examined the relationship between 5-HTTLPR polymorphism and suicide attempts on individuals with schizophrenia and could not observe an effective relationship. In the results of the meta-analysis of Lin and his group including 18 studies, no relationship was observed between 5-HTTLPR and suicidal tendency. A relationship was observed

between the S allele of the 5-HTT gene and suicidal tendency.[38]

As a result, the 5-HTT gene and its variants have been associated with psychological disturbances and suicidal tendencies according to many studies, but many studies are required for strong results.

COMT GENE

The COMT gene is located on human chromosome 22 and encodes the enzyme Catechol-o-methyltransferase. COMT is responsible for the catabolism of dopamine and noradrenaline in the brain.[39] COMT inactivates catecholamines. Abnormalities in catecholamine transmission are thought to cause alcohol and substance addiction and schizophrenia.[40]

COMT gene has val and met alleles, and the activation of these alleles can affect the human mental state. For example, a meta-analysis including 17 studies of 2,370 individuals was conducted to observe whether there is a relationship between Val158Met, which is the polymorphism of the COMT gene, and the tendency to violence in individuals with schizophrenia. 15 of 17 studies were used in the study. The results showed a tendency to violence in men with schizophrenia who had a low activity of the Met allele. This relationship was not found in women.[39] Schizophrenia is a genetic disorder based on an imbalance of neurotransmitters and catecholamines (dopamine, epinephrine). It has been suggested that schizophrenia is caused by the inability of dopamine communication between cells to function. The results of the study conducted by the Genetics Department of Delhi University to examine the relationship between the COMT gene and schizophrenia on North Indian individuals with schizophrenia could not detect an effective relationship between the pair, but it was emphasized that the COMT gene could have an effect on schizophrenia and that more studies should be conducted.[41] In a study based on families, an effective increase in transmission of the Val allele was observed in individuals with schizophrenia. Therefore, it has been concluded that the efficiency of the Val allele of the COMT gene increases the risk of schizophrenia.[42] In a study examining whether the COMT gene has a relationship with schizophrenia, haplotype analysis of the COMT gene was performed. In haplotype analyzes, 7 COMT haplotypes were associated with schizophrenia.[43] The relationship of the COMT gene with alcohol addiction has been supported by the study of Tiihonen and his group. It has been reported that the L allele is more common in individuals with alcohol dependence.[44]

After the COMT gene has been found to affect serious psychological disorders such as schizophrenia, many studies have been conducted to observe the relationship between the COMT gene and suicidal tendency. In a study conducted with schizophrenic individuals, an effective interaction was observed between the L allele of the COMT gene and suicidal tendency. It has been observed that the L allele of the COMT gene is common in schizophrenic individuals who have attempted suicide, but these results have been observed effectively in men. This is not the case for women.[45] In the results of the meta-analysis including 14 studies (2353 suicidal individuals and 2593 healthy individuals), no effective relationship was observed between COMT Val158Met, which is the polymorphism of the COMT gene, and suicidal tendency. There is an interesting detail presented by the results of this study. An effective relationship has been observed between COMT Val158Met and suicidal tendency in women. The relationship between COMT Val158Met and suicidal tendency investigated in the study may differ depending on the gender factor.[46] A study was conducted to question whether there is a relationship between COMT val158met, a polymorphism type of the COMT gene, and suicidal tendency in 105 Mexican patients. 236 Mexican healthy individuals were also used as a control group. No effective relationship was found between the two in the results. Also, no correlation was found in the results of the meta-analysis including 12 studies.[47] Another study aimed to find the relationship between the COMT gene and suicidal tendency. The study was conducted on 258 individuals with emotional disorders and childhood maltreatment was used as an environmental factor. Results revealed a relationship between the COMT gene and suicidal tendency. It was thought that childhood maltreatment and traumas, which are considered as an environmental factor of suicide, interact with the COMT gene and increase the risk of attempting suicide in the following years.[48]

CRHBP GENE

CRHBP is a gene located on the human 5th chromosome and encodes corticotropin-secreting factor binding protein. It is involved in the regulation of the HPA axis and plays a role in the synthesis and secretion of proopiomelanocortin derived peptides. Changes in the HPA system are thought to play a role in the development of psychological disorders

such as schizophrenia, aggression and stress. The fact that the CRHBP gene is a gene belonging to the HPA system makes it reasonable to associate the changes in the expression level of this gene with psychological disturbances.[49-51] For example, a study was conducted to answer the question of why male mice tolerate stress more than female mice. This difference in behavior is striking because the same number of cells with the same functions have been found in male and female brains. When the CRHBP gene was observed to reduce the stress levels in the brain of mice, this gene and related hormones were investigated. It has been observed that neurons associated with the oxytocin hormone stimulate the production of CRHBP. Subsequently, CRHBP has been observed to increase the stress level in the body by stimulating the CRH hormone. To examine the neuronal activities of the oxytocin hormone, the stress levels of the mice were examined through the responses of the associated neurons in the mice brain. The results provided a logical answer to the question posed. The answer lies in the low CRH level in males and high CRH levels in females. Since the CRH level in females is very high, the CRH level cannot be effective enough to cause a change in the stress level, but the efficiency of CRHBP may be more effective because the CRH level in males is low. While this answer explains why men can tolerate stress more, it also answers the difference in behavior between the two genders.[52,53]

The direct relationship of the CRHBP gene with stress has led scientists to answer the question of whether the activity of this gene is associated with suicidality. According to the results of the study conducted among 231 individuals with schizophrenia, 81 of who attempted suicide, and which is the first study investigating the role of the HPA axis in suicidal tendency; An effective relationship was observed between the CRHBP gene and suicidal tendency. It was also observed whether the relationship of the CRHBP gene with other genes of the HPA system affects the suicidal tendency. This research has shown that the combination of CRHBP and CRHR1 genes may play a role in suicidality and that future studies should be on this duo. Also, a positive correlation was observed between the CRHBP gene and suicidal tendency when the genotypic comparison of individuals with and without suicidal tendencies was made between the CRHBP gene and suicidal tendency.[49] The research of Merali and his group observed that the mRNA expression of CRHBP did not change in the frontal complex regions of individuals who killed themselves by suicide.[54]

It has been observed that the activity of the CRH gene is high in depressive suicide victims.[55] Besides, Roy and the group observed that the relationship between the FKBP5 gene and the CRHBP gene interacted with childhood trauma and increased the risk of suicide.[56] It has also been revealed that epigenetic changes in the CRH gene are associated with suicide. Research conducted among 88 people who attempted suicide showed that these epigenetic changes showed a positive correlation between the methylation and expression of the CRH gene and suicidal tendency.[50]

FKBP5 GENE

FKBP5 gene is located on the human 5th chromosome. The FKBP5 gene encodes and regulates glucocorticoids, which are steroid hormones secreted in the body during stress. The largest example of glucocorticoids is cortisol. The mechanism takes place as follows; Cortisol is secreted in the body in response to stress in case of stress. Cortisol enters the cell and binds to GR, also known as the Glucocorticoid receptor. NR3C1 gene encodes GR and FKBP5 protein regulates GR. Glucocorticoids can thus show their effects in the body and develop a response. The FKBP5 gene also plays a role in immunoregulation. High levels of FKBP5 mRNA expression and high levels of cortisol production in the body have been associated with psychological disturbances.[57,58]

The FKPB5 gene has been associated with many stress-related neuropsychiatric disorders. For example, in studies on why aging-related diseases develop worse in depressed and stressed individuals, it has been observed that the expression level of the FKBP5 gene is higher because aging decreases the methylation level of the FKBP5 gene. Childhood traumas have a large and long-lasting effect on the activity of the FKBP5 gene. Epigenetic regulation of this gene is worse in depressed and stressed individuals.[60] Childhood traumas were thought to cause changes in the HPA axis. For this reason, it is thought that the FKBP5 gene and its variants may change the effects of childhood trauma on humans, and the results of the study showed that this inference may be correct.[58] A study was conducted to examine the relationship between the methylation level of the FKBP5 gene and childhood maltreatment. Research has shown that low-level methylation of the FKBP5 gene is associated with childhood maltreatment. Also, this study may lead to the explanation of disorders in the HPA axis and dysfunction of the neuroendocrine.[61] In a study

conducted to investigate the relationship of the FKBP5 gene with post-traumatic mental disorders and including 237 Han Chinese individuals who lost their children, a positive correlation was observed between the FKBP5 gene and post-traumatic mental disorders.[62]

According to the meta-analysis including 14 studies on the relationship between the FKBP5 gene and its variants with depression until 2017, it has been explained that an effective relationship was observed between the FKBP5 gene and depression. In addition, it was thought that the FKBP5 gene could lead not only to depression but also to many behavioral disorders.[63] Research has been conducted on patients with schizophrenia and bipolar disorder to examine whether rs3800373, a variant of the FKBP5 gene, is associated with schizophrenia and bipolar disorder. An adequate relationship was not observed in the study.[63] Research conducted to examine the association of variants of the FKBP5 gene with bipolar disorder in patients with bipolar disorder with variants of the FKBP5 gene (rs4713902, rs7757037, rs9296158, rs3800373, and rs9380525) has provided very strong evidence of the existence of the association.[64]

After the relationship with psychological disorders was observed, the possibility of the FKBP5 gene's effect on suicidal tendency was seen as a great potential, and many studies have been conducted. For example, a study was conducted on 219 Japanese suicide victims to find out whether the genes involved in FKBP5 and HPA axis affect the suicidal tendency. 228 Japanese healthy persons were taken as the control group. The victims killed themselves in many ways. For example, excessive medication use, jumping from a height and burning yourself. In the results, an effective interaction was observed between the haplotypes of the FKBP5 gene and suicidal tendency, but the study could not detect the effect of polymorphisms of the FKBP5 gene on the suicidal tendency.[65] One of the biggest factors affecting suicidal tendencies is childhood trauma and the FKBP5 gene has a significant effect on childhood trauma. Due to this notion, it is thought that the FKBP5 gene may affect suicidal tendency. In this study, the FKBP5 gene and childhood trauma were taken together as gene-environment interaction and its effect on suicidal tendency was investigated. Substance addicts attempted suicide, and the results of a study conducted on patients who were not addicted but in need of treatment showed that the FKBP5 gene interacted with childhood traumas and increased the risk of suicide.[66] A review article supported the relationship between the FKBP5 gene and its variants with suicidal tendencies.[67]

BDNF GENE

The BDNF gene belongs to the neurotrophin growth factor family and is located on the 11th chromosome of the human and encodes the protein-BDNF. Neurotrophins are growth factors and also adjust the strength of synaptic connections and neurotransmission. It also regulates the plasticity structure of the brain, which means the ability to make connections.[68] The BDNF gene plays a role in physiological and neuronal functions and synaptic plasticity in the brain. Since increases and decreases in the expression level of the BDNF gene are directly related to physiological functions in the brain, it has been thought to be related to psychological disorders.[68] For example, it has been observed that the transfer of the recombinant BDNF gene to the brain of mice results in an antidepressant effect in the brain. In addition, the activity of the BDNF gene has been associated with stress and depression, according to studies.[69]

Stress and depression are among the important reasons why suicidal individuals show this action. Therefore, studies have been conducted to show that the BDNF gene may be associated with suicidality. In a study, BDNF gene levels in the blood cells of depressed individuals who had attempted suicide and BDNF gene levels in the blood cells of healthy individuals who were depressed and taken as a control group were examined.[67] They observed that BDNF gene levels in Kim and her group blood cells were significantly lower in individuals who had attempted suicide.[70]

Autopsy studies are available on the brain tissues of individuals who have committed suicide. The general purpose of these studies was to examine the expression levels of the BDNF gene in the prefrontal cortex (PFC) and hippocampus of individuals who committed suicide. It was found that individuals who killed themselves by suicide had low mRNA levels of the PFC and BDNF gene in the hippocampus. These findings showed that there is a correlation between the low-level BDNF gene and suicidal tendency.[68] A similar study to these studies was conducted by Karege et al.,[71] But no change was found in the entorhinal cortex.[68] These results may indicate that the decrease in the BDNF gene may only be related to brain regions related to cognition and emotion.

Another issue is whether the sex change will have an impact on the BDNF gene level. According to the results of the study of Kozicz and his group, it was observed that the expression level of the BDNF gene was low in males who had a suicidal tendency and high in females.[68,72]

The Val66Met polymorphism of the BDNF gene regulates human cortical plasticity.[68] In a study conducted on individuals with Chinese bipolar disorder, the Val66Met polymorphism of the BDNF gene could not be found to be associated with suicidal tendency.[70] According to the study conducted by Kim and his group on Korean individuals, a correlation was observed between the Val/Val genotype between Val/Val, Val/Met and Met/Met genotypes and suicidal tendency in bipolar patients.[68,70,73] Many studies supporting the role of the BDNF gene in suicidal tendencies were observed. has been made. These studies have shown that there is a positive correlation between the BDNF gene and suicidal tendency.

In conclusion, studies have been conducted to examine the relationship between many genes thought to be associated with suicide and suicidal tendency. Most of the studies confirm the efficacy of candidate genes on the suicidal tendency. It has been observed that studies involving environmental factors have achieved more successful results. Based on this, it is suggested that future studies examine the effectiveness of a candidate gene on suicidal tendencies include environmental factors, childhood trauma, schizophrenia, bipolar disorder, alcohol and substance abuse. Finally, besides examining the effect of variants and polymorphism of a gene on suicidal tendency, studies that examine the effects of the interaction of that gene with another gene on suicidal tendency are also recommended.

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