Brain-Derived Neurotrophic Factor (BDNF) Polymorphism and Depression-Suicide

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ABSTRACT

Brain-derived neurotrophic factor (BDNF) is a member of the neurotrophin family that has significant roles in neuron regulations, such as proper functioning of the brain and nervous system. Brain-derived neurotrophic factors response to stress, neural plasticity, behavior, mood, and in addition to these, the decrease in plasma levels in cases of depression, completed suicide and suicidal tendency have associated this gene with the pathophysiology of suicide and depression. Val66Met (valin 66 methionine), which is a single nucleotide polymorphism (SNP), results in Met replacing the Val at the 66th codon. It was found that this polymorphism, which has various genotypes, is mostly seen in cases of depression and suicide, with the Val/Met genotype and the frequency of the Met allele. In this context, it has been tried to explain how and in what way it affects the cases, what should be considered in future studies.

Keywords: Brain-derived neurotrophic factor (BDNF), depression, single nucleotide polymorphism (SNP), Val66Met polymorphism.

Suicide and depression have become an increasing public problem around the world. Genetic and environmental factors affect the risk of depression and suicide. One of these genetic factors is brain-derived neurotrophic factor (BDNF), which is found in the 11p14.1 chromosomal region and is mostly expressed in the brain. BDNF is one of the most abundant neurotrophin families in the brain. Its function is to provide flexibility and development of the nervous system, to regulate some types of neurons, in other words, to play an important role in the growth, functioning, survival, and development of neurons. Val66Met, which is a SNP due to these tasks that are significant for functioning of the brain, has also been studied in the last 15 years; It caught the attention of researchers who found that people who were depressed, had a stressful life, or were suicidal had lower serum BDNF levels compared to normal and healthy people. Other reasons for BDNF and its polymorphism being the focus of research include the inseparable relationship between suicide and stress, that both suicide and depression regulate BDNF expression, and depression is an important component of suicide. The Val66Met polymorphism is caused by the conversion of the amino acid valine at the 66th codon into the methionine. This Val66Met polymorphism has been studied on a population basis and genotyped.

BDNF GENE

Brain-derived neurotrophic factor, a nerve growth factor, a member of the neurotrophin family, it is liable for the growth, development, change, and survival of neuronal cells and populations.¹ It is responsible for neurite growth, phenotypic maturation, protein synthesis, differentiated functioning of neurons, and morphological plasticity to ensure synaptic functioning.² In other words, BDNF is the main regulator for various neuron types such as certain cholinergic neurons, sensory neurons, some

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dopaminergic neurons, retinal ganglion cells, and spinal motor neurons.\textsuperscript{[3]} This gene is located in the 11p14.1 chromosome region.\textsuperscript{[4]}

In addition to guiding neurons, this gene, which is found in large amounts in the brain, is responsible for brain flexibility by being overexpressed in the adult brain and plays an important role in the neuronal cells' survival by binding to receptors of the same origin. Furthermore, it is responsible for the structural integrity of the adult brain and nerve regeneration, including neurotransmitter synthesis and regulation of synaptic activity.\textsuperscript{[5]} BDNF regulates mRNA (messenger RNA) from nerve terminals at many levels, including activity-dependent release and transcriptional regulation. Decreased BDNF expression can reduce neurogenesis and neuroplasticity in the hippocampus after chronic and acute stress, and it has been found to be related to depressive symptoms in clinical research.\textsuperscript{[6]} Therefore, ordinary antidepressant treatment increases BDNF's mRNA expression in the cortical and hippocampus region.\textsuperscript{[6]} In addition, it increases blood levels in patients with depression.\textsuperscript{[5]}

The BDNF gene consists of a main 3' exon, five alternatively spliced exons, and a total of 11 exons. It also has 9 functional promoters specific to tissue and brain regions.\textsuperscript{[8]} This generation results in the ability to produce at least 34 mRNA transcripts that give rise to three preproprotein isoforms of different signal peptide lengths and respond to a variety of stimuli.\textsuperscript{[9]} Therefore, sequence variations in BDNF can create variations in protein metabolism or gene expression that cause selective neuronal sensitivity. In addition, the pathological changes of BDNF not only lead to structural abnormalities in the brain by causing problems in neural regeneration and care but also may impair the ability of the person to adapt in a crisis situation by reducing neural flexibility.\textsuperscript{[11]}

Transcription of this gene causes the manufacture of a precursor molecule called proBDNF, which, thanks to plasmin activators, can be converted into its mature form called mBDNF (mature BDNF). mBDNF and proBDNF bind to different receptors and thus affect neuronal function by activating various signaling pathways. For example, mBDNF, which is a mature form of the BDNF, binds with high affinity to trkB (tropomyosin receptor kinase B) expressed by BDNF. After activation of trkB, MAPK (mitogen-activated protein kinase) activates downstream signaling mediators, including PLC-\(\gamma\) (phosphoinositide phospholipase C gamma) and PI3-K (phosphoinositide 3-kinases), thereby helping the formation of dendritic spines, cell growth and ensuring the survival of different serotonergic neurons.\textsuperscript{[10]} On the other hand, suppression of trkB blocks dendritic spine growth. proBDNF binds to p75, an NGFR (nerve growth factor receptor) that causes apoptotic cascade, long-term depression (LTD), and dendritic retraction.\textsuperscript{[11]}

Although p75NTR (p75 neurotrophin receptor) does not include any catalytic motif, it interacts with various proteins such as Trk receptors and increases the ligand affinity of these proteins.\textsuperscript{[12]} It also induces apoptosis of dendritic spines by activating NF-\(\kappa\)B (nuclear Factor kappa B) and JNK (c-Jun N-terminal kinase) with which it interacts.\textsuperscript{[13]} On the other hand, in the absence of trk (tropomyosin receptor kinase) in the p75NTR cell, it can lead to hippocampal neuronal death caused by neurotrophins. Other pathways including BDNF include Ras signaling, MAPK signaling, PI3K-Akt signaling, cAMP (cyclic adenosine monophosphate) signaling, Huntington's disease, neurotrophin signaling pathway, neurodegenerative pathways, alcoholism, and cocaine addiction.\textsuperscript{[14]}

Brain-derived neurotrophic factor protein exists at high rates in the hypothalamus, hippocampus region, cerebellum, cortex, and also it is located in the soma, dendrites, and terminals in these regions.\textsuperscript{[15,16]} Although protein and mRNA levels overlap in most areas of the brain, it is a protein that can be transported to other regions such as retrograde and anterograde, stored in vesicles, and released instantly when necessary.\textsuperscript{[17]}

**VAL66MET: BDNF POLYMORPHISM**

Val66Met, a single gene polymorphism found in 25-30% of humans (c.196Guanine>Adenine, dbSNP: rs6265) explains the conversion of the amino acid valine in the 66th codone in the 5'pro-region to the Met amino acid.\textsuperscript{[18]} In the BDNF Met/Met homozygous and the Met variant forms, which are Val/Met heterozygous, the foreground structure of this gene has been modified. Although this alteration will not always alter the biological activity of the mature BDNF protein, it may contribute to a decrease in the affinity of mature BDNF to trkB, resulting in damage to the hippocampal volume and function, and improper folding of the protein.\textsuperscript{[19]}

In addition to the decreased hippocampal volume of the Val66Met polymorphism, the Val/Met genotype also affects the gray matter volume in the cerebral neocortex. It decreases the brain volume especially
in the part of lateral convexity of the prefrontal cortex region. Moreover, the Met allele was found to be associated with decreased gray matter in the thalamus, amygdala, and fusiform gyrus in the midfrontal region of the brain.

The Val66Met polymorphism can change the localization, protein-protein interactions, conformational stability, and binding affinity of the BDNF protein. In this context, translin, the RNA (ribonucleic acid) transport molecule that binds to the region where the polymorphism occurs, is degraded. Thus, it is seen that the traffic of BDNF mRNA transcripts to dendrites decreases, and the processing of these transcripts in dendrites is weakened. In other words, the Met allele disrupts the synaptic position and intracellular traffic of mature BDNF. On the other hand, this polymorphism prevents the decomposition of BDNF into secretory granules and reduces the activity-related induction of BDNF up to 30%. It is thought that BDNF-containing vesicles disrupt the interaction of BDNF with intracellular transport molecules such as sortilin, which are involved in the release of regulators, and thus affect to emit of BDNF at the synapse. Additionally, the 66Met endamages N-methyl-D-acetate (NMDA) receptor mediated plasticity and neurotransmission found at CA1-CA3 synapses in the hippocampal region of the brain.

When Met allele carriers exposed to early life stress or trauma are exposed to childhood distress, hippocampal volume changes occur and individuals are also at critical risk for depression. In other words, a meta analysis by scientists showed that there does not exist any relationship between Val66Met and hippocampal volume in patients who have neuropsychiatric disease. When looking at the results of an amino acid change disrupting the secretion and neuroplastic effect of mBDNF protein in primary hippocampal neurons and changing the intracellular monitoring of pro-BDNF, it was seen that BDNF polymorphism was not only linked to suicide and depression. Studies have also been conducted to be associated with Alzheimer's disease, Parkinson's disease, bipolar disorder, eating disorder, obsessive-compulsive disorder. In addition, it has been observed that people heterozygous for Met have memory impairment.

When the Val66Met polymorphism was examined on a population basis, it was observed that the Met allele had a prevalence of 19.9% in Europeans, 55% in Africans, and 43.6% in Asian people. In the Asian population, the Met/Met homozygous genotype was determined as 23.4%, the Val/Val genotype as 30.7%, and the Val/Met genotype as 45.9%. Considering the Caucasian population, Val/Met is seen at 30.5-32.4%, and the Val/Val genotype is seen at 64.2-65%.

The most widely used method for BDNF genotyping in studies is PCR-RFLP (polymerase chain reaction/restriction fragment length polymorphism). Enzymatic digestion is performed by treating PCR products with specific restriction enzymes, and then the individual's genotype can be determined by gel electrophoresis. In addition, the enhanced refractory mutation system has been shown to be as cost-effective, reliable, and efficient as PCR-RFLP. In addition, genotyping approaches such as TaqMan test, pyroscence, fluorescence polarization, SNP (single nucleotide polymorphisms) gene chip based test, mass spectrometer based test are also used to identify SNPs.

**VAL66MET AND SUICIDE**

Suicide is a primary public matter for the whole world and a primary cause of death. According to the World Health Organization (WHO), suicide accounts for approximately 2% of deaths in the world. Roughly 800,000 people commit suicide in a year. In addition, suicide cases occur every 40 seconds. Completed suicide rate is less than attempted suicide. The prevalence of suicide attempts is 3.5%, and it is generally suggested that 10% of the people who attempted will commit suicide within 10 years. Although the rate of suicide for both men and women increases as age increases, young people commit more suicide numerically in many geographies. Genetic factors, as well as environmental factors such as religion, social and political systems, climate, behavior, regional and national differences, also affect suicide. Although the destructive effect of suicide on life is known, there are still unknown issues about the pathological mechanism that pushes the person to suicide. Considering the importance of BDNF functions in the brain, more than 1100 studies have been investigated for Val66Met polymorphism in the last 15 years. By reason of BDNF; it is regulated by stress, plays a role in differentiation during development, and is linked to the pathophysiology of major mental disorders. In this context, BDNF is a candidate molecule that can mediate the risk of suicide.
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There are many studies in the literature investigating whether the BDNF level affects the pathogenesis of suicide. For example, in a study using 27 suicide cases and 21 control subjects, less BDNF existed in the prefrontal cortex hippocampus regions of suicide subjects compared to control subjects. In another study, it was observed that the amount of plasma BDNF was importantly lower in depressive patients who attempted suicide compared to the non-suicidal depressive patient group and the control group. Interestingly, BDNF levels were determined to be similar between non-fatal and fatal suicide attempts. In another study, it was observed that the amount of plasma BDNF was importantly lower in depressive patients who attempted suicide compared to the non-suicidal depressive patient group and the control group. Interestingly, BDNF levels were determined to be similar between non-fatal and fatal suicide attempts.

In one study, this polymorphism was genotyped in a total of 560 DNA samples taken from 201 Caucasian control subjects and 359 Caucasian suicide victims. 560 subjects; the suicide method was divided into subgroups according to the effect of gender and childhood difficulties. As a result, a similar frequency of Val66Met variant was determined between the control group and suicide victims. Frequencies of Met/Val, Met/Met, and Val/Val genotypes; among the female control group and female suicide victims, the female control group using the violent suicide method, and the female victims, they were significantly different from the other people included. Especially, Met/Val and Met/Met genotypes contributed significantly to this genotype frequency. Therefore, these genotypes may be a significant risk factor for victims of childhood trauma and female subjects using violent suicide methods. In this context, Val66Met polymorphism can make the person vulnerable to stress, emotional disorders, and suicide.

In another study, 170 depressive patients were examined in terms of suicide attempt and polymorphism. As a result of the genotyping of Val66Met, it was found that the suicidal behavior in depressive patients with Val/Met variant significantly increased. Among them, it was observed that those who were physically, sexually, and emotionally abused in childhood had a higher risk of a suicide attempt. In consequence of this data, it was determined that Val66Met wild-type variant of Val66Met polymorphism affected suicidal behavior.

In a study conducted with a population of 251 control groups and 169 bipolar patients, it was observed that allelic distributions did not differ importantly from the control group and the bipolar patient’s group. On the other hand, a significant difference was found in suicide attempts between the Met/Met (38.9%), Val/Met (28.8%) and Val/Val (11.3%) genotypes. As a result of this study; people with the Met/Met genotype were found to be 4.9 times more prone to suicide attempts than people with the Val/Val genotype. It has also been found that the Val/Met genotype triggers suicidal behavior in bipolar patients.

A study with the Japanese population included the Val66Met polymorphism, 154 gender and age matched control subjects, and 154 major depressive disorder (MDD) patients. The results show that the Val66Met does not affect the development of MDD, but is related to the clinical features of MDD. Considering that MDD is the most common psychiatric disorder in suicide victims, it is seen that Val66Met polymorphism is significantly related to suicidal behavior.

A meta-analysis study was conducted in which only the BDNF gene was analyzed, it was shown that there does not exist any link between suicidal behavior and Val66Met polymorphism in the general population. However, it has been reported that this polymorphism may be a risk factor in Caucasian people.

In a study using a sample of 813 Caucasian suicide attempts, approaching the subject from a different perspective, the impact of the Val66Met polymorphism on the severity, number, and onset of suicidal behavior in childhood maltreatment was investigated. It has been observed that those who were sexually abused in childhood resorted to violent suicide attempts in adulthood, and that childhood abuse was linked to more suicide attempts at a younger age. In addition, when the fatality of the suicide methods used was evaluated, it was concluded that the Val66Met polymorphism is not...
able to influence the severity of suicidal behavior, the age of onset, and the number of suicide attempts of those who experienced childhood sexual abuse.\[49\]

In another study, when the sample of 120 depressive patients admitted to the hospital due to suicide attempts were examined, the relationship between Val66Met polymorphism and high lethality in attempted suicide was found.\[50\]

There are also studies reporting otherwise. For example, in a brain study conducted after the death of people who suffered suicide, it was observed that the Val/Met genotype was not associated with suicide. It has been estimated that attempted suicide and suicide may have different genetic components.\[51\]

**VAL66MET AND DEPRESSION**

Depression is a prevalent psychiatric disorder, impacting more than 264 million people of all ages, throughout the world. Depression, which has turned into a global public problem, is one of the most important causes of suicide-related premature deaths. Morbidity in depression is thought to be 10-15%. According to the results obtained from twin studies, 37% of depression is a complex disease that is hereditary. Although heritability is important evidence in its pathogenesis, it is difficult to identify specific gene variants in the disease. Genome-wide association studies (GWAS) are carried out to solve this. Another difficulty is that it is a heterogeneous disease. In other words, individuals affected by depression may have different combinations of risk alleles, and moreover, unaffected individuals will have many of these variants. Early onset depressions or recurrent depressions may be more inherited.\[52\] Major depression risk arises as a result of the interaction of hereditary factors with environmental factors. In addition, it has been proven that women are affected by depression 2 times more than men.\[53\]

The relationship between the change in BDNF level and depression has drawn attention with some studies. 11 studies examining the divergences in serum BDNF levels of 748 individuals without and with depression; in addition, in a study that made a meta-analysis of 8 studies involving 220 people comparison the change in serum BDNF before and after antidepressants; BDNF levels in the serum were appointed to be significantly less lower in patients with major depression disorder. Moreover, it has been proven that the BDNF levels in the serum of individuals increase post-antidepressant treatment.\[54\] In another similar study, 218 individuals, including 111 patients with major depression and 107 controls, were included. As a result of analytical analysis, low serum BDNF amount was determined in depression patients in comparison with controls. It was observed that antidepressant treatment significantly increased serum BDNF levels.\[55\]

The relationship between depression and the Val66Met polymorphism has emerged in animal studies. Chen et al.\[24\] Produced a mouse with methionine instead of valine in both alleles. This mouse demonstrated human phenotypic characteristics with its variant allele. Although BDNF (Met) is expressed at a normal level in the brains, its secretion from neurons has been found to be impaired. When mice containing Met/Met allele were inserted in a stressful environment, they began to exhibit raised anxiety-associated behaviors that could not be normalized by fluoxetine, the antidepressant. Therefore, it has been concluded that this variant may play an important role in the genetic dimension of depressive illness and anxiety.

In the previous section, Egan et al.\[19\] study showed that BDNF secretion induced by depolarization was decreased in Val66Met transfected neurons. Therefore, individuals with the Met/Met allele can be said to have less BDNF activity than Val carriers. In a study based on this, it was observed that raised Met/Met frequency in depression was associated with decreased BDNF level and activity in major depression.\[56\]

In a meta-analysis study consisting of a sample of 21,060 people and including 31 studies, the Val66Met polymorphism was determined to be related to life stress in the depression. It is seen that environmental factors are significant in depression and BDNF makes the person deteriorated to stress. In addition, this polymorphism interacts with childhood distress and stressful life events. This interaction varies according to ethnicity. In the study, the mentioned interaction was not observed in the Asian population, but it was found that this interaction was quite strong in Caucasians.\[57\]

14,233 participants and 22 studies were incorporated in another meta-analysis. Eight of the 22 studies are studies that prove the link between Val66Met and life stress on depression behavior. This analysis also confirms the interaction between life
stress that causes depression and the Val66Met. Based on this, it is thought that Val66Met is sensitive to late and early environmental determinants and has an important role in the etiology of depression.[58]

In a study conducted with 284 depressed Mexican-Americans and 331 Mexican-American controls who were matched in terms of gender and age, it was found that the Val66Met polymorphism, which exists in behavioral and also functional impacts, is related to MDD. In this ethnic group, it has been found that patients with major depression especially have the major allele, G/G (guanine/guanine).[59]

Another study included 110 aged Chinese patients diagnosed with MDD, 171 Chinese gender and age compatible control groups. The link between the Val66Met and the severity and susceptibility of depression, cognitive function, age of onset, and history of suicide attempt was investigated. Consequently, an important difference was realized in depressive patients in comparison to the healthy control group in terms of excess Met allele. On the other hand, it was found that this polymorphism did not affect the severity of depression, history of suicide attempt, cognitive function, or age of onset. In this context, it was concluded that Val66Met is a risk agent for senile depression.[60]

In this study conducted by Hong et al.,[61] which is the first study to survey that the relationship between Val66Met and mood disorders may be related to ethnic origin, the Chinese population was evaluated as a sample group. For the Val66Met polymorphism, no significant difference was found when genotype and allele frequencies were compared between the MDD or bipolar disorder groups and control groups. In addition, it was observed that this polymorphism did not affect the suicide history and age of onset in patients with mood disorders. Considering these results, it has been suggested that Val66Met does not contribute to genetic predisposition in mood disorders.

In a research investigating the impact of Val66Met on amygdala and hippocampal region volumes in 60 control subjects and 60 patients with MDD, the polymorphism was genotyped. As a result, the hippocampal volume was significantly smaller in Met carriers and patients in comparison with subjects carrying the homozygous Val allele. No effect of Val66Met polymorphism was found on amygdala volumes. In other words, it has emerged that those with the Met may develop smaller hippocampal volume, thus making the person more susceptible to major depression.[62]

A similar study was conducted with Caucasian subjects. The fusiform gyrus, several parts of the thalamus and frontal gyri were found to have smaller volumes in humans carrying the 66Met allele. It has also been shown that the Val66Met does not only penetrate the hippocampus region, but also extends to the amygdala and parahippocampal gyrus region. The fact that this polymorphism affects the size of the amygdala and parahippocampal in healthy people expose them to a genetic risk factor that increases the likelihood of depression.[63]

BDNF levels in the dorsolateral prefrontal cortex, caudal brainstem, rostral brainstem, and frontal cingulate cortex were found by the Western Blot technique in a study conducted in 2018 with 53 people who did not commit suicide and 37 people who committed suicide. As a consequence of the research, it was found that the risk of depression increased in subjects with the Met. These individuals were observed to have lower BDNF levels in the caudal brainstem and cingulate cortex than non-depressed individuals. The allele genotype has not been found to have an effect on early life difficulties and suicidal death. However, when the subjects who had early life difficulties and who committed suicide and the subjects who did not commit suicide were compared, a low level of BDNF was found in the anterior cingulate cortex of those who committed suicide.[64]

Conclusion

Brain-derived neurotrophic factor, a type of neurotrophin, is liable for synaptic activation, nerve regeneration, regulation of various neurons, and morphological plasticity of neurons. Located in the 11p14.1 chromosomal region in humans, this factor turns into the form of mBDNF after it is produced as proBDNF. This transforming mBDNF firstly provides the activation of trkB and then various downstream signaling mediators and thus acts on dendrite and serotonergic neurons. The decrease in the level of such an important factor reduces neurogenesis and neuroplasticity in the hippocampus region, which is associated with depression. In this context, the antidepressant treatment offered increases BDNF mRNA transcription in the relevant region. Under normal conditions, more than 34 mRNA transcripts that respond to stimuli can be produced.
This transcript diversity may result in variations that lead to neuronal sensitivity. One of the variations mentioned in the Val66Met polymorphism, which is formed by replacing the valine in the 66th codon with methionine. The Val66Met polymorphism has been shown to cause problems in hippocampal volume and function, decreased gray matter in some parts of the brain, and even reduced brain volume. Moreover, this polymorphism can alter the binding affinity for the related gene or proteins in the signaling pathways in which the BDNF protein is located, and also affect the conformational stability and synaptic position of the protein. In addition, the Met allele causes a decrease in BDNF secretion, impairment of mBDNF synaptic release and neurotransmission. When this polymorphism is examined epidemiologically, it is mostly seen in Africans, Asians and Caucasians. On the basis of genotype, the most common Val/Met genotype is found in Asians and Val/Val genotype is found in Caucasians.

When suicidal behavior and the connection with BDNF were examined, it was observed that the functioning and expression of BDNF in suicidal patients decreased and was downregulated as a result of posthumous brain researches of people who committed suicide, and those who attempted suicide and had suicidal thoughts. When examined in more detail, it was concluded that the Val66Met polymorphism makes the person more vulnerable to suicide in general. The Met allele (especially the Val/Met genotype) reduces the amount of gray matter in the cerebral neocortex, the thalamus, amygdala, fusiform gyrus in the mid-frontal region, and decreases the hippocampal volume, as well as the intracellular traffic, synaptic localization and expression of BDNF. It is estimated that it leads the person to suicidal behavior and depression due to disruption. In addition, the regulation of BDNF by stress can also make Val66Met polymorphism more dangerous in the context of suicide and depression risk. In addition, despite depression is a significant agent in suicide, suicidal behavior and the risk of depression could be differentiated in terms of Val66Met polymorphism. Studies have shown that depressive patients with suicidal tendencies have less plasma BDNF and more frequent Val/Met genotype than patients who are depressed but do not have suicidal tendencies. In this context, it is seen that the Val/Met genotype increases suicidal behavior in depressives. It has even been determined that the Val/Met genotype is an important genetic determinant for suicide in bipolar patients. Although there are a few studies reporting that the Val/Met genotype is not related to suicide, in general, this polymorphism appears to be important for suicide. Among the populations, it has been found that the Val66Met poses a risk for suicide, especially in the Caucasus. It is estimated that the Val66Met polymorphism does not generally affect the suicide severity, age of onset and the number of attempts of those who experienced childhood sexual abuse.

It was mentioned that plasma BDNF levels of depression patients decreased and increased after antidepressant treatment. In addition, it was observed that the Val66Met and especially the increased Met allele decreased the BDNF activity and made the individual more susceptible to depression as it decreased the volume of not only the hippocampus but also the amygdala and parahippocampal gyrus. Moreover, it has been suggested that it may be a risk agent for senile depression. To evaluate on the basis of race, it has been found that the relationship between depression and Val66Met is very tight in Mexican-Americans, Chinese and Caucasians. On the other hand, Val66Met polymorphism is thought to have no effect on depression onset age, severity, or cognitive function.

When studies on the Val66Met polymorphism and the relationship between depression and suicide are examined, it can be said that in general, those with this polymorphism have a high tendency to suicide and depression, and the Met allele increases suicide in depressive patients.

**DISCUSSION**

As a result of the review of many researches, it was determined that the BDNF levels decreased in cases of the suicide and depression, and the Val66Met polymorphism contributed to vulnerability to these conditions. If we talk about the limitations of the studies, the studies generally used a small sample. It will be healthier to demonstrate this effect by increasing the number of healthy individuals and patients in the control group.

Only a certain time point of the patients was evaluated in the relevant cases. Therefore, it could not be predicted how the Val66Met polymorphism affects the person and BDNF expression in terms of depression and suicidality in other disease stages. To solve this, it would make sense to conduct large-scale, comprehensive and longitudinal patient follow-up with a well-characterized larger sample.
Another limitation is that studies have examined the relationship between the amount of either plasma or serum or blood BDNF levels and the Val66Met polymorphism and the reflection of this relationship on suicide/depression. Examining the effect of polymorphism in these three positions separately will contribute to the literature.

Conducting some studies using the retrospective method subjects the study to recall bias. In addition to the patient’s ability to remember, it is necessary to minimize prejudice and eliminate inadequate recall by making use of the information obtained by interviewing with close relatives and all the available medical answers.

Almost all the investigations have focused on Val66Met SNP. Given the complex relationship between the brain and the Val66Met polymorphism, it can be seen that this polymorphism affects suicide and depression in conjunction with another yet unidentified functional polymorphism. In other words, Val66Met, which is seen as a risk factor, may be affecting suicide/depression as it may be in connection to imbalance with another risk factor polymorphism of BDNF or with the risky allele of polymorphism in another gene. If there are other polymorphisms or alleles of other gene polymorphisms that mediate these conditions, they should be identified and their relationship with Val66Met should be determined. It should also be determined whether not only polymorphism but also the BDNF gene interacts with another gene to affect suicide and depression. In this context, it may be useful to conduct more research on neurotrophins such as neurotrophin-3 or NGF, and to examine the interactions of more than one gene at the same time to examine in detail how this polymorphism affects depression and suicide. For example, the importance of p75 and pro-BDNF expression, the possible feature in p75NTR-mediated apoptotic signaling in the improvement of suicidal behavior, how trkB affects BDNF and polymorphism in the context of suicide and depression, and the effect of polymorphism should be better elucidated.

Considering that environmental factors are also important in addition to genetic factors in suicide and depression, it is lacking to examine the effect of only a genetic factor such as polymorphism in studies. In this context, future studies should be done by including the polymorphism-environmental factor relationship. Environmental factors can become more important, especially if the patient has been exposed to depression or suicidal behavior for a long time.

The effect of polymorphism has been investigated by considering certain populations in studies, so there is a possibility that ethnic differences may affect the result. In order to prevent this, it would be better to conduct a wide-ranging research in terms of correct results. The same can be seen in studies where unequal control and patient subjects were used in terms of criteria such as culture level and education. Therefore, while conducting the research, it should be considered whether such criteria guide the result or not.

The biological risk factor, Val66Met polymorphism, will contribute to the definition of the pathophysiology and etiology of suicidal behavior and depression by clarifying how and why it affects suicide-depression. In this context, it will allow for therapeutic interventions specific to the region and variant. The use of the Val66Met polymorphism as a predictor of suicide and depression may enable early diagnosis of high-risk patients. It can also be seen as a tool in the clinical care of patients in the future.

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