Biogenetics plays an important role in the pathogenesis of adolescent depression and the study of gene polymorphisms has updated the understanding of adolescent depression. However, under the influence of gene-environment interaction and adolescent developmental age factors, the impact of gene polymorphisms on adolescent depression is intricate. Studying and elucidating the relationship between depression-related gene polymorphisms and adolescent depression contributes to the study of the pathogenesis of depression and provides new clues for the prevention and treatment of depression in adolescents. This article reviews the related gene polymorphisms around adolescent depression.

Keywords: Depressive Disorder; Gene polymorphism; Adolescent; Pathogenesis

Depressive disorder is a common mental illness, mainly characterized by depression of mood (loss of interest, anhedonia) as the core manifestation, accompanied by psychological symptoms such as anxiety, slow thinking, suicide attempt, sleep disorders, and anorexia (1). According to the 2022 Global Burden of Disease report, depressive disorders are one of the reasons for the increase in the absolute number of disability-adjusted life years, ranking the fourth among the reasons for the increase in the absolute number of disability-adjusted life years in the 10-24-year-old group (2).

During adolescence, due to heavy academic pressure, poor parent-child family relationship and other reasons, the incidence of depression increases sharply. Different from adult depressive disorder, adolescent depressive disorder is slow and insidious, which not only causes poor academic performance and social function impairment, but also leads to substance dependence behaviors such as smoking and drinking, and even suicide behavior (3, 4). Depression has become one of the public health problems that seriously affect the physical and mental health of adolescents (5). In addition, studies have found that depressive disorder is the result of the interaction of social, psychological, and biological factors, and is a complex mental illness (6). Abnormal gene expression or single nucleotide polymorphisms (SNPs) are closely related to the occurrence and development of depressive disorders, suggesting that depressive disorders have complex genetic mechanisms (7). This paper summarizes the research on the genetic polymorphisms related to adolescent depression.

5-HTT Gene-Linked Polymorphic Region Gene Polymorphism

The 5-hydroxytryptamine (5-HT) system is one of the most extensively studied systems. The downregulation of 5-HT in the human brain plays an important role in the pathogenesis of af-
ffective disorders, and compared with adult depression, behavioral and social-emotional problems are more prominent in adolescent depression (8), so the 5-HT system dysfunction is a key factor in the pathogenesis of adolescent depressive disorder.

The level of 5-HT in the synaptic cleft of the brain is mainly regulated by 5-hydroxytryptamine transporter (5-HTT). 5-HTT is distributed in the presynaptic membrane, and the 5-HT in the synaptic cleft is recycled to the presynaptic nerve endings through reuptake, thereby reducing the level of 5-HT in the synaptic cleft. 5-HTT can control 5-HT in terms of quantity and receptor action time and realize fine regulation of neuronal information transmission (9). The gene encoding 5-HTT is located on chromosome 17q11.1-q12, and there are multiple gene polymorphisms, and the most common variation is located in the 5-HTT gene linked polymorphism region of the 5-HTT gene promoter region (5-HTT gene-linked polymorphic region, 5-HTTLPR) (10). The variable number tandem repeat sequence (5-HTTLPR-VNTR) present in the 5-HTTLPR gene polymorphism is located on chromosome 17q11.2 and is biallelic. If a 44 base pair tandem repeat element is deleted or inserted in the 5' lateral promoter region of the 5-HTTLPR gene, a short (S) or long (L) allele results, with the S allele being the active, its presence reduces the transcriptional efficiency of the 5-HTT promoter gene, resulting in reduced 5-HTT production, reduced 5-HT reuptake and higher 5-HT levels in the synaptic cleft (11). Studies have found that the S allele is a susceptibility gene for depression. The 5-HTTLPR gene polymorphism is mainly composed of three genotypes: S/S, S/L and L/L (12). The expression level of 5-HTT in individuals with L/L genotype is twice the expression level of L/S and S/S individual genotype (13), in the single nucleotide polymorphism rs25531 variation of 5-HTTLPR-VNTR, the heterozygous L/S genotype is the most common (14), while L/S, carriers of the S/S genotype are more prone to major depressive disorder (15).

Extensive research has been carried out on the relationship between 5-HTTLPR gene polymorphism and adolescent depression. Xia et al. screened and determined 26 studies on 5-HTTLPR polymorphisms for analysis, 24 of which showed a positive correlation between 5-HTTLPR polymorphisms and adolescent depression (16). In a study of Mexican adolescents, researchers found that the S allele and S/S genotype in the 5-HTTLPR polymorphism were associated with adolescent depression and a history of suicide attempts (17). Rao et al. conducted 5-HTTLPR gene sequencing and biological analysis on Chinese adolescents, and the results showed that rare mutations in the 5-HTTLPR gene may lead to an increased risk of major depressive disorder in adolescents with suicidal ideation (18). However, some studies are contrary to the above conclusions, multiple studies pointing out the relationship between major depressive disorder and 5-HTTLPR polymorphism are contradictory, some studies show a positive relationship between the two, while others do not confirm its correlation.

In view of the above research differences, consider the role of gene-environment interaction between the two. Rocha et al. followed up 3,558 adolescents and showed that child abuse and 5-HTTLPR gene polymorphisms interacted in the development of adolescent depression, and 5-HTTLPR could reduce the link between child abuse and adolescent depression (19). Research on depression related to stress and 5-HTTLPR allelic variation is controversial, a meta-analysis supports that 5-HTTLPR can mediate the relationship between depression and stress (20), another meta-analysis shows that 5-HTTLPR There is no strong relationship between genotype and stress leading to the development of depression, and the interaction of 5-HTTLPR with stress and depression can only be observed in stressed individuals (21). Studies have shown that 5-HTTLPR can enhance the impact of environmental stress on adolescents, the onset of depression (22). Sleep disturbance is one of the major risk factors for depression and there is a strong genetic association with depressive disorders. Van Dalsen et al. studies have shown that sleep disorders may play an important role in the interaction between 5-HTTLPR and depression (23).

Therefore, the S allele or S/S genotype plays a key role in the relationship between 5-HTTLPR and adolescent depression, and the 5-HTTLPR gene polymorphism can affect the risk of adolescent depression, but it exists under different gene-environmental factors.

### Brain-Derived Neurotrophic Factor Gene Polymorphism

Brain-derived neurotrophic factor (BDNF) is an important regulator of early neuronal development and survival. BDNF plays an essential role in the process of neurodevelopment, synapse formation and synaptic plasticity, and participates in the work of brain stress system and brain reward incentive system and is related to emotional and cognitive functions. The reduction of BDNF in serum is one of the biomarkers of depressive disorder (24). The BDNF gene is located on human chromosome 11q14 and contains 11 exons and 9 promoters. Val66Met (rs6265) is a typical SNP of BDNF gene, which is a mutation from G to A at the 196th position of the nucleotide coding region, resulting in the occurrence of valine (val) to methionine (met) at codon 66 amino acid substitution (25). Val66Met polymorphism has been shown to impair BDNF secretion, thereby reducing hippocampal volume and impairing memory (26).

Evidence supports that the Met allele, Val/Met or Met/Met genotype is common in adult depressive disorders, and the Met allele is associated with an increased risk of depressive disorders (27). Studies on the relationship between BDNF gene polymorphisms and depressive disorders in adolescents showed that the Met allele and depression-related amygdala-cortical connections is more significant, and it is associated with an increase in depressive disorders in adolescent females. Mikhailova et al. found that among adolescents with conduct disorder, Met allele carriers showed more cortical dysfunction than Val allele carriers, and adolescents carrying Met alleles Antisocial behavior was significantly increased (28). Rimay et al. showed that the Val allele would affect the development of depressive disorder in early adolescence, and Val/Val and Val/Met genotypes were common in adolescent female patients with depressive disorder (29).

There are also studies that do not support the association between BDNF polymorphisms and depressive disorders. Terracciano et al. found that BDNF Val66Met variation has nothing to do with serum BDNF through meta-analysis and genome-wide association analysis (30). Zhang et al. used tar-
geted sequencing to detect the BDNF gene variation Chinese adolescents, and the results showed that Val66Met was not significantly associated with major depressive disorder (31). Kishi et al. did not find that Val66Met polymorphisms can cause major depressive disorder (32).

The formation of the above differences may be related to the gene-environment interaction. Gene polymorphisms and environmental factors play an essential role in the development of adolescent depression. Studies on the genes of 5-HTTLPR and BDNF Val66Met polymorphisms found that the cumulative effect of different parenting styles on adolescent depressive disorder, the results show that cumulative gene polymorphisms increase the susceptibility to adolescent depressive disorder in a positive parenting environment. Val66Met polymorphism plays a regulatory role in life stress and the occurrence of depressive disorders. When predicting adolescent depressive disorders, Val66Met polymorphism interacts with environmental stress (33, 34). At the same time, BDNF Val66Met polymorphism can affect a person’s susceptibility to environmental stressors, such as stressful events, childhood adversity and trauma (35, 36).

Although studies have documented the role of gene-environment interactions in depressive disorders, studies of this cohort of adolescents have not been extensively studied. The influencing factors of depressive symptoms in adolescents may be different in different stages, and BDNF may play different roles in different stages of neurodevelopment. Therefore, the specific mechanism between BDNF Val66Met gene polymorphism and adolescent depressive disorder needs further study.

**Catechol-O-Methyltransferase Gene Polymorphism**

Catechol-O-methyltransferase (COMT) is a dopamine-degrading enzyme that plays a key role in the metabolism of dopamine, norepinephrine, and epinephrine in the prefrontal cortex (PFC). When dopamine metabolism in PFC dopaminergic neurons is dysregulated, it results in cognitive dysfunction, lack of motivation, and loss of interest (37, 38). Therefore, COMT is a regulator of cognition and emotion, and the COMT gene is one of the candidate genes for depressive disorders. The human COMT gene is located on chromosome 22q11.21, the polymorphism of the COMT gene will cause Val at position 158 to be replaced by Met, and the enzymatic activity of the Val allele is 3 to 4 times higher than that of the Met allele, so the mutation at this site will cause the activity of the enzyme being reduced, and the degradation of dopamine is reduced (39).

COMT Val158Met gene polymorphism can regulate the association between environment, emotion, and cognition. Studies have shown that the COMT gene is a regulator of dopamine function in environmental responses. Environmental factors have a significant impact on the association between Val158Met gene polymorphisms and adolescent depression. Hygen et al. demonstrated that COMT genotype interacts with serious life events, and Val/Val at the age of 4-5 who experienced severe life events Children with the genotype were more likely to display aggressive behavior, and Val/Val carriers who had not experienced serious life events showed lower aggressiveness scores than Met carriers, suggesting the importance of gene-environment interactions for psychosis-related behaviors (40). Abraham et al. showed that adolescents with at least one Met allele genotype are more susceptible to early life adversity and exhibit symptoms of hyperactivity and impulsiveness (41). Cao et al. demonstrated that adolescents with Val/Val homozygous genotype may benefit more from parental parenting practices supported by positive responsiveness and autonomy than Met allele carriers, reducing the incidence of depressive disorders (42).

The basic dopamine level of adolescents has the characteristics of changing with development (43), and the influence of Val158Met polymorphism also changes with the development of adolescents (44). Therefore, in addition to environmental factors, the role of COMT Val158Met in adolescent depression, developmental age may also be an important factor between the two. Kant et al showed that Met homozygous genotype carriers under the age of 13 and Val genotype carriers over the age of 13 were more likely to exhibit psychotic features (45). Studies have also shown that among children aged 7-10, the risk of Met allele carriers developing disruptive behaviors of depressive disorders increases, but the results are different in children before the age of 7 (46, 47).

**Other Gene Polymorphisms**

Oxytocin receptor (OXTR) SNPs, multiple epidermal growth factor-like domains protein 9 (MEGF9), and DRD2 gene Taq1A polymorphism may also be closely related to the onset of depression in adolescents. OXTR is widely distributed in the amygdala, hippocampus, hypothalamus, and striatum, and its activity and distribution density may affect the social behavior of individuals. Strauss et al. showed that there is no direct link between OXTR SNPs and adolescent depression and anxiety, but the mutation of OXTR SNP (rs53576) can increase the risk of depression and disruptive behavior disorders in adolescents and is associated with social psychology (48). MEGF9 is a transmembrane protein containing several epidermal growth factor-like repeats that functions in the development, maintenance, and injury response of the nervous system. Recent studies have shown that MEGF9 is a new candidate key gene related to adolescents, and MEGF9 may become a specific biological marker for adolescent depression (49). Taq1A polymorphism is the most commonly studied polymorphism site of DRD2 gene, which plays an important role in depressive disorders (50). DRD2 gene Taq1A polymorphism interacts with environmental factors on adolescent depression, and physical aggression and relationship aggression can predict the level of depression in boys carrying the A2A2 genotype (51).

**Conclusion**

Genetic factors are a pivotal part of the pathogenesis of depression in adolescents, and studies on gene expression and gene polymorphism have updated the progress of related theories of depression. 5-HTTLPR, BDNF Val66Met and COMT Val158Met polymorphisms are closely related to adolescent depression. Because specific environmental factors (such as childhood abuse, stress trauma, and life adversity) and genetic factors are involved in the occurrence and development of adolescent depression, a variety of depression-related genes have synergistic or antagonistic effects during adolescent develop-
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