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Alpha-2-Macroglobulin (*A2M*) and Dopamine Receptor D2 (*DRD2*) expression analysis and influence of separation from parents in childhood on the suicide and self-injury behavior and psychological adjustment in adolescence

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ABSTRACT

To explore the influence of separation from parents in childhood on suicide and self-injury behavior and psychological adjustment in adolescence. A total of 880 subjects were selected, including 197 students who were separated from their parents in childhood and 683 students who were not separated from their parents in childhood. The scores of psychological resilience, self-compassion, forgiveness and suicide and self-injury were investigated and analyzed. Logistic regression analysis was made on the relationship between suicide and self-injury behavior and psychological adjustment in adolescence. The scores of psychological resilience, self-compassion, forgiveness and suicide and self-injury were statistically significant between children who were separated from their parents and those who were not separated. The students who were not separated had better psychological adjustment abilities and a lower rate of suicide and self-injury ($P<0.05$). There was a positive correlation between separation from parents in childhood and suicide and self-injury behavior and psychological adjustment in adolescence ($P<0.05$). The separation from parents in childhood is closely related to psychological resilience, forgiveness, self-compassion, and suicide-related psychological behavior and self-injury behavior in adolescence. Suicide and self-injury behavior can be reduced by reducing separation from parents in childhood and improving self-psychological adjustment ability in adolescence. During the past years, genetics, heritability, and genes' contribution to depression disorders have been well established. Alpha-2-Macroglobulin (*A2M*) and Dopamine Receptor D2 (*DRD2*) genes are very effective in behavioral and mood disorders. The results of this study showed the expression of these genes in different organs, especially in connection with the cerebrospinal system, so investigating the mechanism of their effect is very effective and promising, and it is hoped that they will be used in other research.

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Introduction

Separation from parents in childhood will have a negative impact on the psychological and physiological development in childhood and adolescence and may last until adulthood and even the whole life cycle. This is because childhood is the most critical period for the development of the human nervous system, and the living environment at this stage plays a vital role in the cognition and recognition ability of the brain. A positive environment can guide children's positive and optimistic emotions(1, 2). According to the survey data, suicide has become an important cause of death among Chinese teenagers. Non-suicidal self-injury behavior can be used to predict adolescent suicide behavior. Whether teenagers themselves have good psychological adjustment ability can generally be comprehensively responded by psychological resilience, forgiveness and self-compassion, among which psychological resilience refers to the ability to actively recover to a good state when in trouble. Good psychological resilience can play a positive role in protecting students in trouble(3-5). In this study, 197 students separated from their parents in childhood and 683 students not separated from their parents in childhood were selected as the research subjects, so as to study the influence of separation from parents in childhood on suicide and self-injury behavior and psychological adjustment in adolescence and provide a theoretical basis for formulating preventive measures to prevent suicide and self-injury behavior in adolescence.

Suicide is the cause of more than 700,000 deaths per year and is the fourth leading cause of death among people aged 15 to 29 (6). Through genomic analysis of blood samples, the researchers identified several genes that were evident among participants with documented cases of suicidal thoughts or actions (regardless of their ancestral background). Meanwhile, Alpha-2-Macroglobulin (*A2M*) and Dopamine Receptor D2 (*DRD2*) genes showed the strongest link with suicide attempts. In this research, we investigate *DRD2* and *A2M* genes, which are effective in mental disorders (7,8).

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Materials and Methods

General data

A total of 887 junior middle school students from grade two and grade three in Chengdu, Sichuan Province were selected by convenient sampling, and they were organized to fill out questionnaires. 880 questionnaires were collected, and the effective recovery rate was 99.21%, including 467 boys and 413 girls. Among them, 197 students were separated from their parents in childhood, and 683 students were not separated from their parents in childhood. The average age of all students was (15.43±0.54) years.

Inclusion criteria: male or female, aged 12-16 years; students have no history of mental illness and their data are complete and accurate; both the students and their parents have signed the informed consent form.

Exclusion criteria: students younger than 12 or older than 16; students have a history of mental illness; students have communication difficulties and poor understanding ability; students are unable to cooperate with the completion of this test.

Ethical considerations: A. patients and their families sign informed consent; B. the trial followed the Ottawa Working Group's Statement on Clinical Trial Registration;C. the subjects' right to privacy is protected.

Method

Among the 880 students have completed the questionnaire, 197 students who were separated from their parents in childhood were set as the separation group in this experiment, and 683 students who were not separated from their parents in childhood were set as the non-separation group in this experiment. All students were investigated and analyzed by the psychological resilience scale, self-compassion scale, Heartland forgiveness scale, suicide-related psychological behavior and self-injury behavior investigation

Quality control in the investigation process: all data collectors participating in the research are trained uniformly to ensure the uniformity of the scoring standards.

Observation indicators

Scores of psychological resilience of students in the two groups

The adjustment ability and psychological resilience of the two groups of students were compared. Psychological resilience was investigated by psychological resilience scale, including 25 items and 3 dimensions, namely strength, tenacity and optimism. The score of each item is 0-4 points. The higher the scores of students are, the better the psychological resilience of students is(9).

Scores of self-compassion of two groups of students

The adjustment ability and self-compassion of the two groups of students were compared and analyzed. Self-compassion was investigated by a self-compassion scale, including 26 items and 3 dimensions, namely mindfulness, self-friendliness and universal humanity. The score of each item is 1-5 points. The higher the students' scores are, the higher the students' self-compassion level is (10).

Scores of forgiveness of two groups of students

The forgiveness of the two groups of students was compared and analyzed. Forgiveness was investigated by the Heartland Forgiveness Scale, including 24 items and 2 dimensions, namely, self-forgiveness and forgiving others. The score of each item is 1-7 points. The higher the students' scores are, the higher the forgiveness level of students is(11, 12).

Suicide and self-injury behavior of two groups of students

For the suicide-related psychological behavior, it is mainly to test the number of suicidal behaviors of students in the last 6 months. Suicide behaviors mainly include suicidal ideation, planning, preparation and action, etc. When the number of occurrences is ≥1, it can be judged that the student has suicidal psychological behavior; for self-injury behavior, it is mainly to investigate the frequency of self-injury behavior of students in the last 6 months, including cutting, injuring and attacking oneself, taking too much medicine, etc.

Logistic regression analysis of the effect of separation from parents in childhood on suicide and self-injury behavior and psychological adjustment in adolescence

According to the analysis results of items 1.3.1-1.3.5, the single-factor and multi-factor Logistic regression analysis were used to analyze the influence of separation from parents in childhood on suicide and self-injury behavior and psychological adjustment in adolescence.

Statistical methods

SPSS20.0 statistical analysis software was adopted; the measurement data were expressed by "mean ± standard deviation" χ , and the comparison was tested by independent sample t; the counting data were expressed by percentage (%), and comparison was analyzed by x^2. $P < 0.05$ indicated a statistically significant difference.

Bioinformatics analysis

First, the sequences of *DRD2* (NM_000795.4) and *A2M* (NM_000014.6) genes were obtained from the NCBI database. The lengths of these proteins were 443 and 1474 amino acids, respectively. The exact location of these genes was then determined using the UCSC database. The molecular weight and isoelectric point of the proteins were determined using the ProtScale database. Then, the comparison of the expression profile of *DRD2* and *A2M* genes was analyzed by the OMIM Human Protein Atlas database (13).

Results

Comparison of the psychological resilience scores of two groups of students

The scores of strength, tenacity and optimism of the students separated from their parents in childhood were (18.53 ± 3.23), (27.34 ± 4.32) and (8.79 ± 2.01) respectively, with a total score of (54.66 ± 9.56), while scores of psychological resilience of the students who were not separated from their parents were (21.92 ± 2.74), (32.74 ± 5.23) and (9.43 ± 1.44) respectively, with a total score of (64.09 ± 9.41). The students who were not separated from their parents had better psychological resilience than students who were separated from their parents ($P < 0.05$) as shown in Table 1 and Figure 1.

Table 1. Comparison of psychological resilience scores of two groups of students.

Group	Case (n)	Strength	Tenacity	Optimism	Total score
Separation	197	18.53±3.23	27.34±4.32	8.79±2.01	54.66±9.56
Non-separation	683	21.92±2.74	32.74±5.23	9.43±1.44	64.09±9.41
t value		-14.674	-13.246	-4.993	-12.347
P value		<0.001	<0.001	<0.001	<0.001

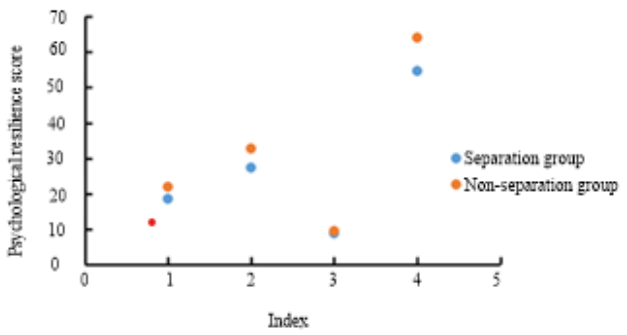

Figure 1. Scattered map of psychological resilience scores of two groups of students. 1 for strength score, 2 for tenacity score, 3 for optimism score and 4 for a total score.

Comparison of self-compassion scores of two groups of students

The scores of mindfulness, self-friendliness and universal humanity of the students separated from their parents in childhood were (22.42 ± 3.13), (28.01 ± 5.73) and (23.83 ± 6.92) respectively, with a total score of (74.27 ± 15.78), while those of students who were not separated from their parents were (26.79 ± 4.01), (32.53 ± 4.99) and (26.53 ± 3.44) respectively, with a total score of (85.85 ± 12.44). Students who were not separated from their parents had better psychological resilience than those who were separated from their parents $P < 0.05$ as shown in Table 2.

Comparison of forgiveness scores of students' psychological adjustment ability between the two groups

The scores of self-forgiveness and forgiving others of students who were separated from their parents in childhood were (48.23 ± 4.23) and (46.12 ± 5.72) respectively, with a total score of (94.35 ± 9.95), while those of students who were not separated from their parents were (53.92 ± 8.21) and (52.74 ± 3.42) respectively, with a total score of (106.66$_{P<0.05}$11.63). Students who were are not separated from their parents had better forgiveness than those who were separated from their parents $P < 0.05$ as shown in Table 3.

Comparison of suicide and self-injury behavior of two groups of students

For students separated from their parents in childhood, 17.26% and 28.43% of them had suicide-related psychological behavior and self-injury behavior respectively. For students not separated from their parents in childhood, 0.30% and 0.63% of them had suicide-related psychological behavior and self-injury behavior respectively. Students who were not separated from their parents had a lower probability of committing suicide and self-injury than students who were separated from their parents $(P < 0.05)$ as shown in Table 4 and Figure 2. Note: Figure 2 is the mechanism diagram of the relationship between the separation from parents in childhood and suicide and self-injury behavior and psychological adjustment in adolescence.

Table 2. Comparison of self-compassion scores of two groups of students.

Group	Cases (n)	Mindfulness	Self-friendliness	Universal humanity	Total score
Separation	197	22.42±3.13	28.01±5.73	23.83±6.92	74.27±15.78
Non-separation	683	26.79±4.01	32.53±4.99	26.53±3.44	85.85±12.44
t value	-	-14.105	-10.882	-7.488	-10.800
P value	-	<0.001	<0.001	<0.001	<0.001

Table 3. Comparison of forgiveness scores of psychological adjustment ability between two groups of students.

Group	Cases (n)	Self-forgiveness	Forgiving others	Total score
Separation	197	48.23±4.23	46.12±5.72	94.35±9.95
Non-separation	683	53.92±8.21	52.74±3.42	106.66±11.63
t value	-	-9.373	-20.220	-13.498
P value	-	<0.001	<0.001	<0.001

Table 4. Comparison of suicide and self-injury behavior between two groups of students [*n*(%)].

Group	Cases (n)	Suicide-related psychological behavior	Self-injury behavior
Separation	197	34(17.26)	56(28.43)
Non-separation	683	2(0.30)	5(0.63)
x^2 value		14.234	18.634
P value		0.001	0.001

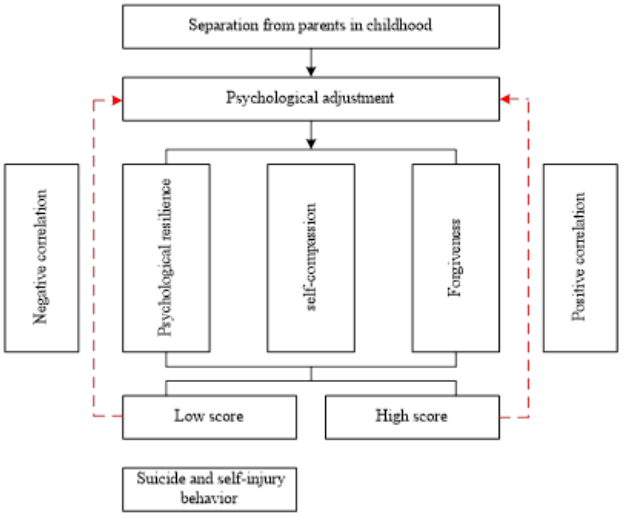

Figure 2. The mechanism diagram of the relationship between the separation from parents in childhood and suicide and self-injury behavior and psychological adjustment in adolescence.

Logistic regression analysis of separation from parents in childhood on suicide and self-injury behavior in adolescence

Multivariate Logistic regression analysis was conducted. The dependent variable is whether there is suicide and self-injury behavior, and the independent variable is psychological adjustment ability, including strength, resilience, optimism, mindfulness, self-kindness, universal humanity, self-forgiveness and forgiving others. The analysis found that the independent influencing factors of suicide and self-injury behavior included: strength (OR=1.629, $P<0.05$), tenacity (OR=1.653, $P<0.05$), optimism (OR=1.341, $P<0.05$), mindfulness (OR=0.742, $P<0.05$), self-friendliness (OR=0.815, $P<0.05$), universal humanity (OR=1.706, P), self-forgiveness (OR=1.113, $P<0.05$) and forgiving others (OR=0.927, $P<0.05$), separating or not (OR=1.867, $P<0.05$), psychological resilience (OR=0.611, $P<0.05$), self-compassion (OR=0.532, $P<0.05$) and forgiveness (OR=1.958, $P<0.05$) as shown in Table 5.

Logistic regression analysis of separation from parents in childhood on suicide and self-injury behavior and psychological adjustment in adolescence

Multivariate Logistic regression analysis was performed. The dependent variable was whether there was suicide and self-injury behavior in adolescence, and the independent variables include whether separated from parents in childhood, psychological resilience, self-compassion, and forgiveness. And it was found that the independent influencing factors of suicide and self-injury behavior and psychological adjustment in adolescence included separating or not (OR=1.867, $P<0.05$), psychological resilience (OR=0.611, $P<0.05$), self-compassion (OR=0.532, $P<0.05$) and forgiveness (OR=1.958, $P<0.05$) as shown

Table 5. Logistic regression analysis of separation from parents in childhood on suicide and self-injury behavior and psychological adjustment in adolescence.

Item	*P*value	SE	WaldX² value	*P* value	OR value	95%CI
Separating or not	0.713	0.295	6.427	0.018	1.867	1.129~3.547
Psychological resilience	-0.652	0.273	5.892	0.019	0.611	0.366~0.937
Self-compassion	-0.745	0.311	11.769	0.011	0.532	0.315~0.834
Forgiveness	0.814	0.309	6.143	0.028	1.958	1.102~4.217
Strength	0.461	0.128	17.427	0.021	1.629	1.249~2.024
Tenacity	0.415	0.082	35.724	0.012	1.653	1.294~1.837
Optimism	0.273	0.126	4.687	0.019	1.341	1.105~1.728
Mindfulness	-0.341	0.118	10.148	0.029	0.742	0.579~0.911
Self-friendliness	-0.231	0.093	7.012	0.023	0.815	0.675~1.033
Universal humanity	0.468	0.135	19.672	0.026	1.706	1.314~2.093
Self-forgiveness	0.224	0.019	79.513	0.018	1.113	1.064~1.238
Forgiving others	-0.125	0.024	30.047	0.011	0.927	0.847~1.058

Note: reasons and methods of controlling demographic variables: A. Reasons for controlling demographic variables: because the results of controlling demographic variables in the process of Logistic regression analysis are more robust and the inference range of conclusions is wider, this study has implemented measures to control basic demographic variables. B. Method of controlling demographic variables: constant method is to take certain measures to keep some irrelevant variables constant in the whole research process. It is also the most basic method to control irrelevant variables. In educational research, many variables cannot be eliminated, such as age, sex, height, weight, etc. In this case, it is necessary to adopt the constant method to control their influence by fixing their effects. In this study, the demographic variables were controlled by the constant method. That is, the included subjects were strictly controlled in terms of age. Their ages were from 12 to 16 years old, and the average age was (15.43 ± 0.54) years old; at the same time, the gender ratio was controlled to 1: 1.

Table 6. Logistic regression analysis of separation from parents in childhood on suicide and self-injury behavior and psychological adjustment in adolescence.

	β value	SE	WaldX² value	*P* value	OR value	95%CI
Separating or not	0.713	0.295	6.427	0.018	1.867	1.129~3.547
Psychological resilience	-0.652	0.273	5.892	0.019	0.611	0.366~0.937
Self-compassion	-0.745	0.311	11.769	0.011	0.532	0.315~0.834
Forgiveness	0.814	0.309	6.143	0.028	1.958	1.102~4.217

Table 7. Characteristics of DRD2 and A2M genes.

Name	*DRD2*	*A2M*
ORGANISM	Homo sapiens (Human)	Homo sapiens (Human)
Accession number nucleotide	NM_000795.4	NM_000014.6
Accession number protein	NP_000786.1	NP_000005.3
Gene ID	1813	2
Chromosome	11	12
Cytogenetic location	11q23.2	12p13.31
Chromosome location bp	113409605-113475398	9067708-9116229
nucleotide length	2808 bp	4610bp
protein length	443aa	1474aa
Molecular weight (Da)	50619.43	163291.00
Isoelectric point	9.55	6.03
Total Exon	8	36

in Table 6.

Alpha-2-Macroglobulin (*A2M*) gene analysis

Alpha-2-Macroglobulin gene with accession number (NM_000014.6) is located on chromosome 12 (12p13.31), which synthesizes a protein with a molecular weight (Da) of 163291 and 1474 amino acids and 36 exons (Table 7). Studies have shown that the *A2M* gene leads to significant emotional, physical, and sexual reactions. Therefore, it seems necessary to investigate this gene in suicide attempts and psychiatric studies. The alpha-2-Macroglobulin gene inhibits inflammatory cytokines and disrupts inflammatory cascades. An important paralog of this gene is *PZP*.

Dopamine Receptor D2 (*DRD2*) gene analysis

DRD2 gene with accession number (NM_000795.4) is located on chromosome 11 (11q23.2), which synthesizes a protein with a molecular weight (Da) of 50619.43 and 443 amino acids and 8 exons (Table 7). *DRD2* gene encodes the dopamine receptor; this receptor inhibits adenylyl cyclase activity through binding with the G protein. A missense mutation in this gene leads to myoclonus dystonia; other mutations are associated with schizophrenia. The important paralog of this gene is *ADRA2A*.

Examining the expression of *A2M* and *DRD2* genes in different body organs

As can be seen in figure 3 and ', *DRD2* gene expression is very high in cerebrospinal tissue, especially the Basal ganglia, and Pituitary gland, and it has low expression in other organs. On the other hand, *A2M* gene expression is present in all organs and it is more in the lungs and liver than in other organs of the body. As shown in the expression profile of these genes, the *DRD2* gene is more expressed in cerebrospinal tissues. Considering that the expression of this gene in the pituitary gland is also high and the pituitary gland plays an effective role in traumatic brain injuries, therefore this gene may lead to problems with memory, communication, or behavioral disorders (Figure 3,4).

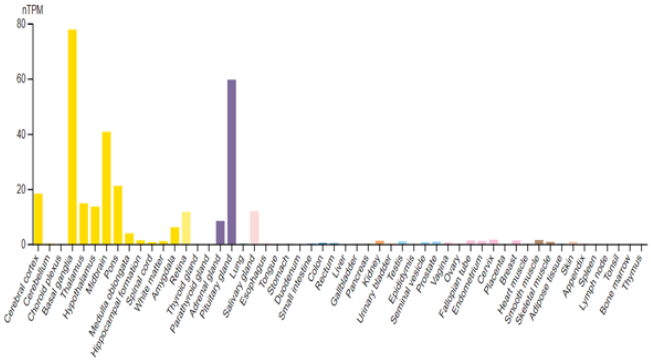

Figure 3. Results of the study of *DRD2* gene expression.

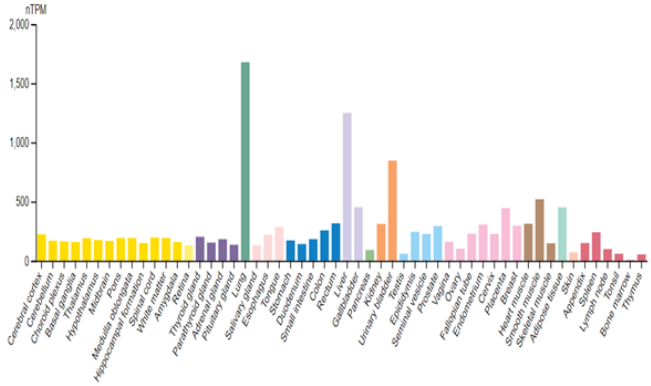

Figure 4. Results of the study of *A2M* gene expression.

Discussion

The early stage of life is the most important and critical period. From infancy to adolescence, the individual's physiology and psychology are in an important stage of rapid development, so a good growth environment is particularly important (14-16). If children suffer from more unfavorable conditions for physical and mental development, such as separation from parents. The research found that (17) family is the most important environment for children's growth, and parents' care, education and emotional connection with children cannot be replaced. However, if parents are away from home for a long time due to various reasons, not only the distance between parents and children will be widened, but also the emotion between parents and children will be weakened due to certain changes in family structure (18, 19). The results of this experiment showed that the psychological adjustment of the students who were not separated was better, and the total score of

psychological resilience is (64.09 ± 9.41), while the score of psychological resilience of the students who were separated from their parents was only (54.66 ± 9.56) and the probability of committing suicide and self-injury was higher. Through Logistic multiple regression, it was found that separation from parents in childhood had a great negative impact on psychological adjustment in adolescence, leading to suicide and self-injury among teenagers.

Childhood, especially the early stage, is the most critical and important stage of growth and development in one's life. A positive growth environment can promote the healthy development of children's psychology, while an early bad environment or aggressive experience will seriously affect children's physical development and social-psychological development (20). The strength, tenacity and total score in the results of the psychological resilience survey are closely related to suicide and self-injury behavior in adolescence(21). The incidence or risk of suicide-related psychological behavior of students with better psychological resilience will be significantly reduced; on the contrary, students with poor psychological resilience have a higher risk of self-injury behavior. Related studies have confirmed that psychological resilience will play a positive role in protecting against suicide and self-injury. In an adverse environment, students with better psychological resilience can better adjust their psychological state, turn negative emotions into positive energy, and increase the growth and happiness level caused by trauma, so as to successfully survive adversity (22). In addition, students with better psychological resilience have better interpersonal relationships and self-acceptance ability at the same time. When faced with greater pressure, they can better seek help from friends such as classmates through their own harmonious interpersonal relationships and at the same time, they will also relieve stress through various protective factors, such as entertainment(23-25). Some foreign researchers have found that teenagers with good psychological resilience in an unfavorable environment can overcome difficulties better, get through difficulties smoothly, and get better growth and experience in the process. Many studies show that there is a significant negative correlation between psychological resilience and suicide and self-injury behaviors and there is a negative correlation between forgiveness level and suicide, which indicates that the higher the forgiveness score is, the lower the suicide and self-injury behavior is. It can be seen that forgiveness, as a kind of positive psychology, can help individuals face setbacks actively, maintain a good psychological state and reduce the negative impact caused by negative life events (26).

Therefore, to avoid and alleviate the negative impact of separation from parents in childhood on the physical and mental health of children and adolescents, it is necessary to give priority to raising and educating children by their mothers or grandparents; if it is truly necessary to choose others for care, priority should be given to families that have a close relationship with the original family of children and have more interactions to support and educate them (27). During the separation, parents should keep more contact with their children through various contact methods. When contacting, they should not only pay attention to their children's material needs but also pay attention to their spiritual needs. On the basis of comforting their children, the parents should make their children subjectively feel their concern and support, and try to reduce the situation of multiple separations (28). In addition, schools should regularly carry out mental health education, so that students can understand and master psychological adjustment skills to better cope with difficulties or setbacks and avoid self-injury behavior (29).

Suicide is a complex and multifaceted behavioral phenotype that occurs under the influence of multiple and bipolar mood disorders. But this disorder can also have a genetic origin. Family studies and investigation of depression disorders show the genetic contribution and heritability of 30 to 40 percent of genes and genetic and environmental interaction in suicide. Most of the candidate genes in suicide are registered in the SBGAS genetic association database. Meanwhile, the serotonin neurotransmission system has attracted the most attention in genetic studies related to suicidal behaviors, which is mainly related to the role of serotonin in suicide victims and the change in cerebrospinal fluid concentration in 5-hydroxyindoleic acid (5HIAA) metabolites (30).

D2 receptors are members of the G protein-coupled dopamine receptor family, which also includes D1, D3, D4, and D5. They play a role in regulating movement, reward, reinforcement, memory, and learning. Diseases associated with DRD2 include cocaine dependence and substance dependence, which play an important role in suicidal behavior (31).

The protein encoded by this gene (Alpha-2-Macroglobulin) A2M is a protease inhibitor and cytokine transporter that uses a bait-and-trap mechanism to inhibit a wide range of proteases including trypsin, thrombin, and collagenase. Thus, when a proteinase cleaves the prey region, a conformational change occurs in the protein that traps the proteinase. The entrapped enzyme remains active against low molecular weight substrates (activity is greatly reduced against high molecular weight substrates). After cleavage in the prey region, a thioester bond is hydrolyzed, mediating the covalent attachment of the protein to the proteinase. Mutations in this gene cause alpha-2-macroglobulin deficiency. This gene is the main component of beta-amyloid deposits due to its great ability to clear and destroy A-beta and is involved in Alzheimer's disease (AD). Diseases associated with A2M include alpha-2-macroglobulin deficiency and mastitis. Among the pathways related to it, we can mention the defects of the contact activation system (CAS) and kallikrein/kinin system (KKS) and response to elevated platelet cytosolic Ca2+. Gene Ontology (GO) descriptions related to this gene include signaling receptor binding and serine-type endopeptidase inhibitory activity (32). In general, these genes are related to suicide attempts, mood disorders, high-risk behaviors, and alcohol consumption disorders, and since these genes are involved in many psychiatric disorders, it is necessary to be very specific when analyzing markers (33).

To sum up, the separation from parents in childhood is closely related to psychological resilience, forgiveness and self-compassion in adolescence and suicide-related psychological behaviors and self-injury behaviors. The occurrence of suicide and self-injury behaviors can be reduced by reducing the separation from parents in childhood and improving self-psychological adjustment in adolescence.

Data Availability

All the data pertaining to this article is available in the

article will give on special request by readers.

Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

Author Contributions

All the authors have equal contributions in this research study and article drafting.

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