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REVIEWS
AND THEORETICAL ARTICLES

Epigenetics of Aggressive Behavior

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Abstract—Multiple studies demonstrating the association of aggressive behavior with allelic variants of neurotransmitter system genes appear to be controversial, while "risk" alleles have no effect on impaired gene expression and functioning of encoded proteins. To explain these associations, we suggested the role of deregulated epigenetic processes caused by the changes in the spatial configuration of transcribed proteins owing to the impaired interaction with noncoding RNAs, which results in modified functioning of genetic networks. Stressful life events occurring during the pre- and postnatal period causing changes in DNA methylation and histone modifications, which disrupt expression of neurotransmitter genes with a long-lasting effect, represent the key factors causing the manifestation of aggressive behavior. The role of stressful life events in epigenome modifications is assumed to be caused by stress-sensitive transposable elements (TEs), whose processing results in the formation of noncoding RNAs probably affecting histone modifications and methylation of certain genomic loci. Transposable elements represent the key sources of sites of binding to transcription factors and regulate genome expression, while their ability to locus-specific transpositions under the stress and self-regulation by noncoding RNAs can explain both the long-term effect of behavioral impairments and their transgenerational transfer. Prevention of behavioral impairments and phenotypic manifestations of genetic liability to aggressive behavior requires the examination of the individual nature of epigenetic modifications for the further targeted action and their correction.

Keywords: aggressive behavior, microRNA, methylation, histone modifications, transposable elements, epigenetic factors

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Interpersonal violence represents a significant cause of disability and mortality worldwide [1], which promotes an intensive study of etiological mechanisms of aggressive behavior (**AB**) by specialists of various fields [2]. Aggressive behavior is a serious social problem, since AB individuals are characterized by cognitive impairment, hyperactivity, and a tendency to drug addiction and social maladaptation, thus complicating the possibility of their working ability and resulting in dissatisfaction with life [3]. According to the results of longitudinal epidemiological studies, aggressive behavior, which is highly manifested and identified in adolescence, is actually observed in the first 12 months after birth and reaches its maximum in 2–4 years followed by a decrease in its level to adulthood. However, about 3–7% of children are characterized by an increased frequency of aggressive behavior in adolescence, which causes the problems in social adaptation later in adulthood [4]. It should be noted that AB development is sex-specific; in particular, the risk of developing aggression is higher in men [5]. Moreover, it should be considered that AB is comorbid with severe psychopathologies with different frequency, including autism spectrum disorders (AB is observed in 68% of patients), bipolar disorder (25%), schizophrenia (13.9%), and attention deficit hyperactivity disorder (ADHD) (5.7%) [6].

According to the results of longitudinal and twin studies, the level of heritability of aggressive behavior in humans is 0.37–0.72 [4, 7] and orthologous genes involved in developing aggressive behavior were identified in humans and animals [8]. The molecular-genetic studies conducted to date demonstrated associations of polymorphic variants of genes of the neurotrophic and monoaminergic systems (including monoamine oxidase A (*MAOA*) [9], D2 receptor (*DRD2*), and dopamine (*SLC6A3*) [10] and serotonin transporter (*SLC6A4*) genes [11]) with aggressive behavior. However, the results of different research groups are contradictory, which may be explained by

significant role of environmental factors, including stressful life events in childhood [12], toxic substances, and a number of hormones during the prenatal development [13–15], in AB manifestation later in ontogenesis. Current hypotheses of the influence of environmental factors on the formation of long-term phenotypic behavioral effects are based on the changes in epigenetic parameters such as structural modifications of chromatin, post-translational modifications of histones, DNA methylation, and expression of noncoding RNAs (ncRNAs) [12].

ENVIRONMENTAL RISK FACTORS OF AGGRESSIVE BEHAVIOR

Phenotypic diversity of a trait is known to be formed via both genetic and epigenetic mechanisms programming tissue-specific patterns of gene expression. Cells, including neurons, are subjected to massive epigenetic reprogramming, sensitive to environmental influences during development, which results in the formation of stable changes in the phenotype. It should be noted that environmental factors may account for more than 20% of phenotypic variance in aggressive behavior in boys and girls older than 7 years [16]. In turn, epigenetic modifications associated with development of aggressive behavior are caused by many environmental factors, including unfavorable family conditions, low income, premature birth, low weight at birth, young maternal age, antisocial behavior of parents, childhood abuse, maternal depression and smoking, and other stressful events during prenatal development [3, 13, 14, 17, 18]. Unfavorable conditions, especially in infancy and childhood, may result in changes in epigenetic regulation of genes involved in stress response, behavioral disinhibition, impulsivity control, and impaired social behavior [19]. Childhood stress causes long-term epigenetic reprogramming, which alters the expression of many genes in both the brain and other systems, including neuroendocrine and immune, thus affecting behavior in adulthood [20].

According to the literature, great importance is given to the factors affecting the individual during prenatal development and early childhood in the study of the etiology of aggressive behavior [21]. Stressful effects during pregnancy may lead in the long term to development of behavioral problems in childhood owing to their influences on the epigenetic mechanisms regulating fetal development, since the placenta is particularly sensitive to stress-caused hormonal fluctuations [22]. The association of aggressive behavior in children with exposure to toxic substances during prenatal development due to administration of psychoactive substances by their mothers was reported [3, 13, 14, 17]. Maternal smoking or administration of some pharmaceuticals (for instance, paracetamol) during pregnancy is associated with developing aggressive behavior later in their children [13, 14, 23], which is explained by methylation of selective genomic regions, which was observed in children with attention deficit hyperactivity disorder (**ADHD**), in particular [24, 25]. The mechanisms of developing ADHD and aggressive behavior may have similar biological pathways, since children with AB are characterized by increased hyperactivity and decreased language capacity [3].

Prenatal stress can affect fetal development by an impaired negative feedback mechanism of response to stress causing overactivation of the hypothalamic-pituitary-adrenal system (**HPA**), producing high levels of stress hormone cortisol penetrating through the placental barrier. For instance, prenatal stress caused by the partner's violence predisposes the children at the age of one year to greater behavioral problems and higher cortisol level [26]. On the other hand, the regulation of the neuroendocrine system under stress is caused by the changes in the glucocorticoid receptor gene (*NR3C1*) expression. Both over- and underactivation of the stress response system associated with changes in the expression of the glucocorticoid receptor (*NR3C1*) gene may promote development of aggressive behavior [27]. In particular, maternal depression during pregnancy was revealed to increase DNA methylation in the promoter region of the *NR3C1* gene in children [28]. Similar data were demonstrated in older children (10 years), indicating the existence of a long-term effect of epigenetic programming [29]. Experiments conducted with model animals also detected that stress-induced excessive maternal glucocorticoid levels are produced during pregnancy, which may cause aggressive behavior in their offspring owing to epigenetic modifications in genes of the HPA system. Notably, chronic stress might induce inherited changes in gene expression patterns owing to DNA methylation or histone modifications [15], while DNA methylation levels in stress response genes and in other stress-sensitive genomic structures (mobile genetic elements) has minor fluctuations in normal placental development [22].

THE ROLE OF DNA METHYLATION AND HISTONE ACETYLATION IN AGGRESSION

The peculiarities of methylation of genes in neurotransmitter systems [4, 30, 31–33] and acetylation of histones responsible for regulation of expression of genes of neurotransmitter systems modified under a stress-induced environment [34] affect behavioral reactions. One of the first studies describing changes in DNA methylation in response to stress at an early age was conducted by Weaver et al. (2004) in rats [35]. As a result of this study, the pattern of DNA methylation in the promoter region of the glucocorticoid receptor (*NR3C1*) gene involved in stress response regulation was shown to be modified under maternal care in the postnatal period. In particular, an increased level of DNA methylation and decreased

histone acetylation resulting in a reduced expression of exon 17 (exon 1F in humans) in the *NR3C1* gene were detected in the hippocampus of rat pups treated with less care during the first week of their postnatal development [35]. The data obtained demonstrated the relationship between changes in the methylation of the *NR3C1* gene, its expression, and response to stress in offspring. Moreover, the epigenetic pattern of the *NR3C1* gene is influenced by maternal behavior and is potentially reversible [35]. Changes in the methylation of the *NR3C1* gene were also detected in the hippocampus of children who were subjected to abuse and committed suicide [36]. Notably, childhood maltreatment caused changes in the pattern of DNA methylation in multiple genomic loci [37], which remained stable throughout adulthood [36].

According to published data, maternal separation stress within 1–14 days after birth resulted in changes in DNA methylation in promoters of several brain-expressed candidate genes, including methyl-CpG-binding protein 2 (*MeCP2*), corticotropin-releasing factor (*CRFR2*), and cannabinoid receptor (*CB1*) gene in mice [30]. Stress exposure of rats within the first week after birth also caused changes in the methylation of the *BDNF* gene in the prefrontal cortex, and these epigenetic changes were transgenerationally transmitted [31].

The epigenetic modulation of genes of the serotoninergic system under environmental factors was observed in a longitudinal analysis of monozygotic twins discordant for aggressive behavior. Twins with enhanced aggression demonstrated both reduced cortisol reaction to stress and elevated methylation of the *SLC6A4* gene (resulting in decreased expression of the *SLC6A4* gene) compared to siblings without aggression. The data obtained indicate the relationship in the epigenetic regulation of the serotoninergic and HPA systems [38], which is congruent to empirical data revealed in birds [15] and mammals [39, 40]. Long-term hypermethylation of the *SLC6A4* gene was identified in women subjected to sexual abuse in childhood [33] and in men characterized by delinquent behavior in childhood [41].

Multiple molecular-genetic studies were focused on the study of a functional VNTR polymorphism in the promoter region of the monoamine oxidase A (*MAOA*-uVNTR) gene encoding the enzyme involved in oxidative deamination of neurotransmitters. Moreover, a low-activity allele was associated with an increased risk of developing aggressive behavior [42]. These associations can be explained by the fact that allelic variants of this polymorphic locus are associated with differential methylation of the *MAOA* gene, which, in turn, causes differential liability to aggressive behavior [43]. Further analysis of the sequence in the promoter region of the *MAOA* gene showed the presence of another CpG-rich VNTR locus containing tandem repeats 10 bp in length 1.5 kb distant from the transcription start codon, whose methylation was associated with aggressive behavior in women [44]. Together with association of allelic variants of the VNTR locus and differential methylation in the *MAOA* gene, the involvement of mobile genetic elements in such epigenetic regulation appears to be possible, since nonautonomous *Alu* elements are involved in the occurrence and dynamics of VNTR repeats [45]. Another possible mechanism of epigenetic regulation of the *MAOA* gene expression includes acetylation of histone H3 in the promoter region of the *MAOA* gene observed in animals subjected to peripubertal stress causing subsequent excessive aggressive behavior [32].

Large-scale longitudinal studies of DNA methylation conducted in more than 20 000 promoter regions of genes and 400 microRNAs in adults revealed associations of aggressive behavior with methylation levels in promoters of 448 candidate genes, including genes of the dopaminergic (*SLC6A3*, *DAT1*), serotonergic (*HTR1D*), glutamatergic (*GRM5*), and arginine-vasopressinergic (*AVPR1A*) systems together with the pathways of inflammatory and immune response [4]. A recent epigenome-wide association study (EWAS) based on a large sample of twins identified the association of increased risk of developing aggressive behavior and DNA methylation in genomic regions close to genes of transcription repressor (*TRPS1*), antisense PARD6G RNA1 (*PARD6G-AS1*), RAS family oncogene (*RAB39*), family of immunoglobulins (*SIGLEC10*), and prolyl-endopeptidase (*PREP*) [46]. According to the results of another large-scale study, aggressive behavior was associated with differential DNA methylation in 744 CpG sites in genomic regions of boys and girls aged 6–12 years [47], which may indicate the existence of specific epigenetic changes manifesting themselves at certain periods of ontogenesis. Single studies demonstrated the association of aggressive behavior with an increased methylation level of genomic regions containing cytokine genes (*IL-1α*, *IL-6*, *IL-4*, *IL-10*, *IL-8*) and their transcription factors (*NF-κB1*, *NFAT5*, *STAT6*) [48].

THE ROLE OF NONCODING RNAs IN AGGRESSION

One of the mechanisms of epigenetic regulation of gene expression is changes in binding of noncoding RNAs (ncRNAs) to target mRNA and/or expression of genes of ncRNAs themselves (including microRNAs). Therefore, microRNAs are involved in regulation of behavior, mediating the influence of environmental stimuli on gene expression. In particular, one of the studies conducted in patients with schizophrenia demonstrated the association of miR-21 expression with aggression as a response to drug therapy [49]. On the other hand, the changes in the nucleotide sequence in the 3'-untranslated mRNA regions result

in lower binding of microRNAs to mRNA and, hence, in a decrease or repression of protein translation.

Regulation of serotoninergic neurotransmission plays an important role in developing aggressive behavior [50, 51], while ethnic-specific serotoninergic functioning is known [52]. In particular, the analysis of the untranslated region in the serotonergic system gene (serotonin receptor 1B, *HTR1B*) revealed the presence of an insertion (so-called *A* element) resulting in the formation of the miR-96 binding site [53]. Interestingly, the repressor activity of the *A* element is reduced by the presence of the *G* allele (*G* element) causing a decreased binding of miR-96 to HTR1B mRNA. In addition, a high aggression level was observed in homozygous individuals by the ancestral *A* allele compared to carriers of the *G* allele [53]. The examination of SNPs located in the site of binding of miR-510 to the serotonin receptor 3E gene (*HTR3E*) mRNA is also of interest in study of aggressive behavior. Despite the correlation of expansion of CGG repeats, which was previously associated with clinical manifestations of fragile X chromosome syndrome, with enhanced miR-510 expression [54], no studies on the relationship between the aggression level and SNPs in the *HTR3E* gene region target for miR-510 binding were published to date. The expression of another important gene of the serotonergic system (serotonin transporter gene, *SLC6A4*) responsible for the regulation of aggressive and depressive behavior [50, 55] is controlled by miR-16 and miR-545 [56].

A possible component of aggressive behavior regulation is the wolframine 1 gene (*WFS1*) encoding a protein involved in calcium homeostasis in the endoplasmic reticulum (**EPR**), whose deregulation causes the development of stress, apoptosis, and the Wolfram syndrome characterized by a progressive neurodegeneration and diabetes mellitus [57]. The analysis of *rs1046322* in the 3'-untranslated region of the *WFS1* gene located in miR-668 binding site demonstrated its association with AB. Notably, the functional significance of *rs1046322* was demonstrated in luciferase reporter assay with miR-668 coexpression: the *A* allele was associated with a reduced repression of translation of the *WFS1* gene compared to the *G* allele [58]. Moreover, a direct target of miR-668 is the *NF-kB* gene encoding a transcription factor involved in the regulation of various biological functions, whose activation depends on enhanced miR-668 expression [59].

According to the published data, allelic variants of the *SNAP-25* gene (*rs3746544* and *rs1051312*) located in the miR-641 binding site are responsible for impulsive-related traits [60]. In addition, luciferase reporter assay revealed that the change in ancestral alleles in the haplotype resulted in increased SNAP-25 translation. A synaptosomal-associated protein of 25 kDa (SNAP-25) is known to be one of the components of the SNARE complex, whose impaired formation together with a decreased activity of SNAP-25 caused a deficit in release of neurotransmitters, impaired regulation of calcium channels, and synaptic plasticity [61].

Together with the study of SNPs residing in microRNA binding sites, the analysis of changes in the nucleotide sequence in genes encoding microRNAs is of interest. In particular, one study was focused on the association of *rs531564* located in the *MIR124-1* gene (encodes miR-124) with aggressive behavior in the Colombian population [1]. A brain-specific mir-124 appears to be a key regulator of neuronal plasticity, while the brain-derived neurotrophic factor (*BDNF*) and dopamine receptor D4 (*DRD4*) genes are its targets [1]. Notably, published studies indicate the involvement of differential expression of the *BDNF* [62] and *DRD4* [63] genes in the manifestation of aggressive behavior. In turn, the level of aggression is controlled by individual serotoninergic system functioning, which also affects miR-124 genesis and interacts with the proteins encoded by the *BDNF* and *DRD4* genes [56].

THE ROLE OF MOBILE GENETIC ELEMENTS IN AGGRESSION

Despite the data on the role of epigenetic factors in developing aggressive behavior under the influence of environmental factors, the way that they may modulate methylation, locus-specific modifications of histones, and expression of certain ncRNAs remains unestablished. One of the explanations of the mechanisms of phenotype inheritance in response to environment may be due to the presence of mobile genetic elements (**MGEs**)—genomic structures encoding hidden genetic variations highly sensitive to stress in humans [64]. A stress perception and response being the universal conservative trait of MGEs is used for dynamic regulation of gene networks in ontogenesis [65], which explains genome plasticity and maintenance of MGEs in eukaryotes, where they compose a significant part (up to 60% in animals and up to 90% in plants). MGEs represent the sources of long ncRNAs [66, 67], miRNAs [68–72], regulatory elements [73, 74], transcription factors [75, 76], and TF binding sites [77, 78]. The possible factors affecting peculiarities of aggressive behavior development may include age-specific parameters of activation of MGEs regulating ontogenetic functioning of the brain and other tissues [79].

Interrelation between MGEs and epigenetic factors can explain the phenomenon of long-lasting changes in behavior under stressful life events [64, 80–82]. Actually, the brain represents the central organ of stress response, whose action specifically changes DNA methylation and histone modifications, thus affecting plasticity in the prefrontal cortex, amygdala, and hippocampus [83]. The effects of stress-related changes in DNA methylation may be caused both by a direct effect of MGEs capable of locus-specific transpositions [84–87] and by ncRNAs formed during the

processing of transcripts of transposable elements and involved in RNA-dependent DNA methylation [42, 88] and modification of histones [9, 89].

MGEs are known to be used in embryogenesis for both maintenance of the pluripotent state (LTR-containing retroelements) and control of cell differentiation (LINE elements), whereas they preserve their activity in adult stem cells [90]. In turn, the long-lasting effect of changes and transfer of epigenetic changes affecting the development of aggressive behavior occurring in the embryonic period [39] may also be explained by the ability of MGEs for locus-specific transposition during their activation, which results in persistent and inherited changes in regulation of genes [84–87]. Interestingly, stress-induced epigenetic changes in the fetal genome during pregnancy can be transmitted to one or two future generations [39], which explains transgenerational transmission of behavioral traits (AB, in particular).

Together with the influence of stress, hormonal levels may cause locus-specific transfer of MGEs [91–93]. Since MGEs are epigenetic regulators of the genome in ontogenesis [94], it can be assumed that changes in epigenetic regulation of genes of neurotransmitter systems under MGEs activated by certain hormones represent one of the mechanisms of hormonal influence on behavior.

FUTURE EPIGENETIC STUDIES OF AGGRESSIVE BEHAVIOR

Epigenetic studies of aggressive behavior are urgent for the design of diagnostic algorithms in each individual case with the possibility of directed action, thus representing the basis for personalized therapy. Animal studies are indicative of the prospects of such research directed to identify the etiology of aggressive behavior. In particular, the efficacy of pharmacological correction of impaired behavior in rats caused by changes in epigenetic regulation of genes encoding glucocorticoid receptors in prenatal development was observed. Another experiment demonstrated the successful administration of MAOA inhibitors in aggressive behavior caused by stress-induced epigenetic upregulation of the *MAOA* gene [32]. Immune system genes represent one of the targets of action of pharmaceutical drugs, since cytokine-dependent regulation of aggressive behavior via modulating serotonin signaling is known [95].

On the other hand, nutrition together with pharmaceuticals can also directly affect the genome structure by changes in epigenetic programming. A number of nutrients and food components affect epigenetic regulation in various human organs and systems including the brain [96]. In particular, administration of trichostatin-A and L-methionine affecting methylation of genes of neurotransmitter systems in the brain to adults with impaired behavior resulted in its normalization, which indicates the efficacy of nutrition correction in epigenome regulation. Such mechanisms of nutrition-mediated behavioral regulation via changes in epigenetic programming may also exist in humans; thus, their identification is particularly significant for developing effective nutrient therapy for the treatment of aggressive behavior [97]. Thus, in 2017, an association analysis of nutrition quality and aggressive behavior was carried out in a multiethnic sample of adolescents. Adolescents with poor nutrition quality demonstrated an increased AB risk compared to those with a high-quality diet [98]. The study of patients in forensic psychiatric hospitals revealed the association of aggressive behavior with the level of consumed fatty acids and suggested the use of vitamin D and omega-3 in food to correct behavioral deviations [99]. Animal experiments showed that Gottingen minipigs fed a diet with high fat and low carbohydrates were less aggressive compared to the animals consuming food with low fat and high carbohydrates [100]. It was proposed to use these data for the development of nutrition therapy in individuals with an increased risk of AB.

The analysis of nutrients appears also to be promising for the development of diet therapy in pregnancy to prevent impaired behavioral manifestation in their children in the postnatal period. During embryogenesis, DNA methylation in the developing fetus is highly dynamic and is influenced by a variety of maternal factors, including unbalanced nutrition. In turn, the effect of the latter is associated with modified DNA methylation [101] and expression of certain microRNAs [102]. Moreover, the maternal organism significantly affects fetal development via stress response mechanism of the HPA axis. In rodents, a high-fat perinatal diet was shown to cause epigenetic reprogramming of the HPA axis (increased expression of the glucocorticoid receptors in the amygdala and hippocampus), which resulted in increased anxiety in response to stress later in ontogenesis [103, 104]. Moreover, nutrition of pregnant females with a high-fat diet causes DNA hypomethylation, thus demonstrating a long-term effect on functioning of the opioid and dopaminergic systems in developing embryos, which results in behavioral problems in the subsequent postnatal development [105].

Together with the use of diet therapy in the prevention and correction of aggressive behavior, the use of microRNA-targeted therapy with minimal side effects is relevant, since there is evidence of the association of aggressive behavior with microRNA-mediated regulation of the expression of genes of neurotransmitter systems [53, 56, 58, 60]. At present, microRNA-based approaches are being developed and empirically tested for active implementation in clinical practice. Thus, miR-135 interaction with serotonin receptor and transporter transcripts made it possible to propose this microRNA for application an endogenous antidepressant [106]. Other potential targets include miR-96,

miR-545, and miR-668, which previously were involved in the expression regulation of serotonin receptor 1B [53], serotonin transporter [56], and wolframin 1 genes [58], respectively, in aggressive behavior cases. It should be noted that the use of certain pharmaceuticals may trigger changes in the activity and level miRNAs, which should be considered in miRNA-targeted AB therapy. In particular, one study reported that fluoxetine promoted miR-16 biogenesis, thus resulting in translational repression of serotonin transporter [56].

Another approach resulting in epigenetic changes causing AB development includes the use of histone deacetylase inhibitor to repair stress-induced overmethylated DNA marks. This effect is caused by demethylation of DNA sites to a normal level corresponding to methylation level in unstressed animals [35].

Despite the developing approaches of the potential action on epigenetic modifications in aggressive behavior therapy, a long-term effect of maltreatment as the most consistently detected predictor of AB in children has to be considered. Accordingly, together with the genetic factor, aggressive behavior is influenced by the family environment as a powerful adaptive system opposing or promoting the development of delinquent behavior [107]. According to above-mentioned data, nowadays the psychological techniques developed for the prevention and correction of AB in combination with advances in epigenetics, such as the use of microRNAs for targeted action on imbalance in the expression of genes of neurotransmitter systems, can make a significant contribution as a part of complex therapy.

CONCLUSIONS

According to the published findings, the genes involved in hormonal regulation and neurotransmission are responsible for the development of aggressive behavior. Expression of these genes can be regulated by epigenetic mechanisms such as structural modification of chromatin, posttranslational modifications of histones, DNA methylation, and expression of noncoding RNAs (including microRNAs). Moreover, the influence of environmental factors in the pre- and postnatal periods, including stress, nutrition, and stress-related social conditions, via epigenetic mechanisms affects the expression of AB-associated genes [108]. Mobile genetic elements highly sensitive to stressors and changes in microenvironment conditions (including nutrients) are the possible mediators of stressors and nutrients. The mechanism of involvement of MGEs in epigenetic changes in genes of neurotransmitter systems affected by environmental factors is explained by the role of MGEs as sources of microRNAs regulating the expression of genes encoding the proteins necessary for normal brain functioning. Various microRNAs interacting with genes actively expressed in the brain are associated with AB development: miR-96—with the *HTR1B* gene, miR-510—with the *HTR3E* gene, miR-545—with the *SLC6A4* gene, miR-668—with the *WFS1* gene, miR-124—with the *BDNF* and *DRD4* genes, and miR-641—with the *SNAP-25* gene. The study of the role of microRNAs in developing AB is promising both for the detection of pharmacodynamic effects of drugs used in aggression therapy and for targeted action on genes of neurotransmitter systems to normalize their expression. Moreover, the analysis of expression of specific microRNAs under the effect of certain nutrients is promising, since it provides an identification of specific targets of action and possible side effects. Therefore, the study of the individual epigenetic changes for subsequent targeted action and correction is significant for the prevention of impaired behavior and phenotypic manifestations of genetic predisposition to aggressive behavior.

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COMPLIANCE WITH ETHICAL STANDARDS

The present study contains no data on research involving animals as the objects of the study.

The present study contains no data on research involving humans as the objects of the study.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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