Recent advances in genetics of aggressive behavior

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One of the most important problems of modern neurobiology and medicine is an understanding of the mechanisms of normal and pathological behavior of a person. Aggressive behavior is an integral part of the human psyche. However, environmental risk factors, mental illness and somatic diseases can lead to increased aggression to be the biological basis of antisocial behavior in a human society. An important role in development of aggressive behavior belongs to the hereditary factors that may be linked to abnormal functioning of neurotransmitter systems in the brain yet the underlying genetic mechanisms remain unclear, which is due to a large number of single nucleotide polymorphisms, insertions and deletions in the structure of genes that encode the components of the neurotransmitter systems. The most studied candidate genes for aggressive behavior are serotoninergic (TPH1, TPH2, HTR2A, SLC6A4) and dopaminergic (DRD4, SLC6A3) system genes, as well as the serotonin or catecholamine metabolizing enzyme genes (COMT, MAOA). In addition, there is evidence that the hypothalamic-pituitary system genes (OXTR, AVPR1A, AVPR1B), the sex hormone receptors genes (ER1, AR), neurotrophin (BDNF) and neuronal apoptosis genes (CASP3, BAX) may also be involved in development of aggressive behavior. The results of Genome-Wide Association Studies (GWAS) have demonstrated that FYN, LRRTM4, NTM, CDH13, DYRK1A and other genes are involved in regulation of aggressive behavior. These and other evidence suggest that genetic predisposition to aggressive behavior may be a very complex process.

Key words: aggression; aggressive behavior; behavior genetics; neurotransmitter systems; polymorphisms.

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Понимание механизмов нормального и патологического поведения человека представляет собой одну из актуальных проблем современной нейробиологии и медицины. Агрессивное поведение является неотъемлемой частью человеческой психики, однако стрессовые воздействия окружающей среды, предрасполагающие психические расстройства и перенесенные соматические заболевания могут служить причиной развития повышенной агрессивности, которая, в свою очередь, рассматривается как биологическая основа антисоциального поведения в человеческом обществе. Немаловажное значение в развитии агрессивного поведения принадлежит наследственным факторам, среди которых ключевая роль отводится нарушениям нейромедиаторного обмена в головном мозге, однако генетические механизмы, лежащие в его основе, до сих пор не ясны. Это обусловлено большим количеством однонуклеотидных замен, инсерций и делеций в структуре генов, кодирующих компоненты нейромедиаторных систем, каждый из которых привносит лишь небольшой вклад (1–2 %) в формирование признака. Среди ключевых генов-кандидатов развития агрессивного поведения традиционно рассматриваются гены серотонинергической (TPH1, TPH2, HTR2A, SLC6A4) и дофаминергической (DRD4, SLC6A3) систем, а также гены ферментов их метаболизма (COMT, MAOA). Кроме того, имеются данные об участии генов гипоталамо-гипофизарной системы (OXTR, AVPR1A, AVPR1B) и рецепторов половых гормонов (ER1, AR), генов семейства нейротрофинов (BDNF) и нейронального апоптоза (CASP3, BAX) в развитии агрессивности. Результаты полногеномных анализов ассоциаций (GWAS) позволяют говорить о вовлеченности в развитие агрессивного поведения генов нервно-транспортного тирозинкиназы FYN, трансмембранных белков нервной системы LRRTM4, нейротримина NTM, кадгерина CDH13, участвующего в клеточной адгезии, и фермента DYRK1A, участие которого отмечено в пролиферации клеток и синаптической пластичности. Эти и другие литературные данные дают возможность предположить, что формирование генетической предрасположенности к агрессивному поведению – весьма сложный процесс, затрагивающий функционирование большого числа генов. Кроме того, ни один из наиболее изученных генов-кандидатов не объясняет значительной вариабельности по данному признаку, по причине чего в этой области до сих пор существует ряд открытых вопросов.

Ключевые слова: агрессия; агрессивное поведение; генетика поведения; нейромедиаторные системы; полиморфные варианты.
According to recent data, the social, economic, biological, and ecological instabilities of today’s fast-paced society have a significant effect on the psychological state of an individual and may act as precursors for development of a mental pathology of various natures. Aggressive behavior (AB) is a complex trait, which is an indicator of experienced stress and implies actions aimed at inflicting moral, physical, or any other harm to another living being, an object or self (self-aggression or suicidal behavior). A reasonable degree of aggression remains an important component of social life in humans, since it is necessary to achieve one’s stated goals, maintain and increase an individual’s social standing, and overcome interpersonal conflicts (Baron, Richardson, 2001). However, anomalous or increased aggression often becomes the driving cause behind criminal acts of various degrees. The data of the Ministry of Internal Affairs of the Russian Federation show that about 2 mln crimes were committed in Russia in 2017, with murders and intended grievous bodily harm accounting for 9.7 and 24.6 thousand cases respectively (Rosstat, 2017). Similar picture may be observed in most regions, aside from South and Central American, as well as South African countries, where criminal rates are 2–3 times as high (UNODC, 2017). Thus, increased aggression is one of the most important social problems in human society.

Phenomenology of aggressive behavior
Nowadays, all forms of AB of both large and small scale (bullying, criminal behavior, terrorism, etc.) are seen as very complex multi-aspect phenomena, and the body of knowledge available is open to multiple interpretations and classifications. Most of them, however, agree that AB is an action intended to harm individuals who are motivated to avoid such harm (Baron, Richardson, 2001). Hence, AB may be impulsive or well thought-through, intended to harm the victim, or instrumental to achieving specific goals. It may also be considered a response to other person’s negative actions or an attempt to prevent them (Tkachenko, 2016). The ways aggression manifests itself are also different, which may be illustrated by dichotomous classifications, i.e. physical and verbal, active and reactive, direct and indirect aggression. Aggression is often associated with a wide variety of negative emotions (anger or hatred), motives (intentions to insult or harm), and negative mindsets (racial and ethnic prejudices). However, despite the fact that all these factors have a significant part to play in AB, their presence is not a necessary condition for this type of behavior (Baron, Richardson, 2001).

It is worth noting that AB may manifest itself in both mentally healthy people and the ones with mental disorders. Apparently, in the latter category there is the whole series of factors affecting the development of AB and realization of aggression, the predominant one being presence of a specific psychopathological syndrome (Dmitrieva, Shostakovich, 2002). Among those, the researchers emphasize twilight consciousness, bipolar disorder, alcohol addiction, hallucinatory, delusional or affective forms of psychopathy, and schizophrenia (Dmitrieva, Shostakovich, 2002; Blanco et al., 2018; Waleewong et al., 2018). It is also noted that people suffering from schizophrenia have the highest risk of committing violence due to rapidly developing systematized delusions that overcome self-control mechanisms (Dmitrieva, Shostakovich, 2002; Blanco et al., 2018). It is commonly known that AB may also be preceded by short-circuiting depressive response or suicidal tendencies motivated by self-accusation and search for redemption (Dmitrieva, Shostakovich, 2002).

When it comes to healthy individuals, it is necessary to mention the traits making it possible to assume a predisposition towards AB. These primarily include anxiety and fear of social disapproval, hostility attribution bias, excessive irritation and emotional sensitivity (Baron, Richardson, 2001). In addition, AB may be caused by negative nature of child-parent relationships in the upbringing (King et al., 2018). Also of interest are the data implying evolutionary nature of differences in aggression levels in males and females, which encouraged researching the effects of hormonal state on AB (Baron, Richardson, 2001; Georgiev et al., 2013).

Despite significant advancements in AB research, the wide variety of definitions, theories, and factors prevents the researchers from developing an integral approach to describing aggression development and its individual and sex- and age-dependent features. Although there is noteworthy evidence of linkage between psychopathological states, individual and social demographic factors and the risk of AB available, the cause-effect aspect remains to be further studied.

Methods and approaches to studying aggressive behavior
Psychological assessment of aggressive behavior
Nowadays, there are designated sets of methods available to identify the nature of aggressive manifestations in humans, which prioritize experimental approach making it possible to indirectly judge on aggression levels based on independent variables. A multitude of questionnaires dedicated to studying general aggressiveness, AB in particular, and specific aggression phenotypes, such as anger and hostility, have been developed for this purpose.

The most popular of them include: Buss–Durkee Hostility Inventory (BDHI), Buss–Perry Aggression Questionnaire (BPAQ), Spielberger Aggression Expression Scale, Assinger’s Assessment of Aggressiveness in Relationships, a method of personal aggression and conflict by E.P. Ilin and P.A. Kovalev, etc. Projective techniques that are also used to study aggression, include thematic apperception test (TAT) and Rorschach Inkblot Test (Gurskaya, 2008).

Neuropsychiological research of aggressive behavior
Interaction between the designated structures in human brain responsible for providing an adequate response of the body to changes in external and internal environment plays a major part in AB determination within the
neurophysiological approach. Here, the methods, such as positron emission tomography (PET), functional magnetic resonance imaging (fMRI), electroencephalography (EEG), invoked potential technique (IP), etc., are used.

The results obtained show that individuals with high AB levels tend to have reduced amygdaloid complex (Pardini et al., 2014) and grey matter volumes in orbitofrontal cortex (Gansler et al., 2009), deviations in EEG pattern and coherence (Ragozinikaya, 2015), as well as reduced P300 VP component amplitudes, which is also peculiar for schizophrenia patients (Gusev et al., 2009).

Investigation of hereditary factors in aggressive behavior regulation
Numerous twin studies have been performed to date that prove the role of heredity in AB development by comparing monozygotic twins raised under different conditions in their postembryonic period. It was found that heritability factor for aggressiveness is about 50% (from 30 to 81%) for particular aggressiveness phenotypes, including antisocial behavior (Viding et al., 2005; Tuvblad et al., 2011). This scatter in values may be explained by nonuniformity of the studied groups, as well as a wide range of environmental factors taken into account in specific studies. However, the twin method may only provide a general estimate of heritability without identifying specific markers associated with the development of the trait.

One of the earlier hypotheses to explain the hereditary nature of AB was the assumption that aggression level was affected by anomalous sex chromosome count. This hypothesis was considered by Meyer-Bahlburg, who noted that the presence of a redundant Y-chromosome led to increased aggression level (for example, 47XYY syndrome, as it is encountered more often in people in prison confinement), whereas a redundant X-chromosome (for example, 47XXX in females) resulted in reduced aggression level (Meyer-Bahlburg, 1981, quoted after: Baron, Richardson, 2001), however the support for this hypothesis was far from unequivocal. Furthermore, there are the data available that show increased aggression in males with 47XXY karyotype (Klinefelter syndrome) (Stochholm et al., 2012). In addition, the linkage between various chromosome anomalies and AB may be explained by low intelligence or high impulsiveness in the individuals considered, which supposedly resulted in criminal acts (Baron, Richardson, 2001).

In recent decades, molecular-genetic research becomes increasingly important in studying predisposition towards AB. Key studies are the ones focused on search for candidate genes based on their functional significance, which implies investigation of associations between traits and gene alleles involved in functioning of various systems, and genome-wide association studies (GWAS), under which hundreds of thousands of single nucleotide polymorphic (SNP) loci covering the genome are studied. However genetic nature of this trait remains understudied, despite the numerous research results available. There are a number of theories, in which the major part in AB development is attributed to cerebral neurotransmitter system disorders associated with a large number of single nucleotide polymorphisms, insertions, and deletions in the structure of genes that encode the components of the neurotransmitter systems. However, precise identification of genes involved in AB regulation is complicated since each of them only slightly contributes (1–2%) to the development of the trait (Kazantseva, Khusnutdinova, 2017).

Molecular-genetic markers of predisposition towards aggressive behavior
Neurotransmitter system genes
As of today, the genetic role of the serotonergic and dopaminergic systems in AB development in humans has been studied to a significant extent. It was found that increased serotonergic system activity results in lower aggression levels, whereas activation of the catecholaminergic system, in turn, stimulates aggression (Miczek et al., 2007). Thus, genes that encode proteins involved in serotonin and dopamine metabolism are candidate genes for aggressive behavior.

Tryptophan hydroxylase, which catalyzes tryptophan hydroxylation to 5'-hydroxytryptophan with further decarboxylation to serotonin on the first limiting stage, acts as a key serotonin biosynthesis enzyme. There are two typical isoforms for this enzyme, namely tph-1 and tph-2, encoded by the TPH1 (11p15.1) and TPH2 (12q21.1) genes respectively. One of the better studied polymorphic sites in the TPH1 gene is single nucleotide polymorphism 218A > C (rs1800532) in the 7th intron causing reduced gene expression level due to its localization in the GATA transcription factor linkage site. A series of studies show the link between highly active *A allele and/or *A/*A genotype with self-aggression (Beden et al., 2016), and *C/C genotype with high general and verbal aggression levels in people with depressive disorders (Koh et al., 2012). Polymorphism -703G > T (rs4570625) is a widely studied polymorphism in the TPH2 gene, which determines reduction in the gene’s transcription activity. The results of association studies of -703G > T locus alleles in terms of aggressiveness are rather contradictory, because both the data indicating the absence of *T allele association with AB (Yoon et al., 2012) and showing the contrary are available (Laas et al., 2017). Many researchers believe that contradictions like this may be caused by differences in the studied samples associated with sample volumes, ethnogeographic and social and economic factors, as well as psychological states and sex of individuals (Kazantseva, Khusnutdinova, 2017).

Investigations of the polymorphisms of the SLC6A4 (5-HTT or SERT; 17q11.2) serotonin transporter gene, which acts as the main serotonergic neurotransmission regulator in various regions of brain, made it possible to discover a variable 44 base pair-length segment in the gene promoter (5-HTTLPR) associated with presence (*L) or absence (*S) of the considered fragment. In addition, presence of another polymorphism, rs25531 (A > G), is observed in the 5-HTTLPR*S insertion form, which has stimulating effect
on the SLC6A4 gene transcription activity, which allows some researchers to consider them as a single three-allele locus (*L_A*, *L_G*, *S*) (Wendland et al., 2006).

In course of studying self-aggression and violent behavior genetics in male inmates it was found that the *L_A/*L_A, *L_A/*G, *S/*S* genotype carriers demonstrating high and intermediate SLC6A4 gene activity are more prone to self-aggression compared to the low-activity *L_G/*L_G, *S/*L_G, *S/*S genotype carriers (Gorodetsky et al., 2016). At the same time, a confident association between the *S* allele and/or *S/*S genotype and AB, violent and self-aggressive tendencies were shown in a series of papers both in children (Cicchetti et al., 2012) and adults (Lopez-Castroman et al., 2014). It may be explained by cumulative negative effects peculiar for short alleles making the *S*-allele carriers more perceptive to negative environmental effects (van Ijzendoorn et al., 2012).

VNTR polymorphism of Stin2 (17 base pairs) in the 2nd intron is another SLC6A4 gene polymorphism possibly associated with AB. It is noted that presence of 12 repeats (Stin2*12), as opposed to 9 and 10, leads to increased gene transcription activity (MacKenzie, Quinn, 1999), which many researchers believe to be associated with increased aggressiveness in combination with the 5-HTTLPR*S allele (Hemnings et al., 2018).

The DRD4 (11p15.5) receptor gene in the dopaminergic system, along with the SLC6A3 (or DAT; 5p15.33) dopamine transporter gene, is the most commonly studied candidate gene in terms of AB. The DRD4 gene includes in its 3rd exon a variable region with 2 to 11 repeats with 48 base pair length, the highest linking ability of the receptor is observed for 4 repeats, whereas expression level decreases significantly for 7 repeats (VanNess et al., 2005). It was found in course of studying aggressive and antisocial behavior that the *7R* repeats were more often encountered in people convicted for violent crimes (Cherepkova et al., 2016), especially the ones, who experienced stress factors in their childhood (Schlomer et al., 2015). At the same time, it was shown for the Russian sample of inmates that the *7R* allele carriers also demonstrated high aggression levels similar to those of the *7R* allele carriers (Cherepkova et al., 2015), which agrees with the data on identical functional changes in the DRD4 receptor with 5 or 7 repeats (Takeuchi et al., 2015).

Tandem repeat of VNTR40 (from 3 to 11 times) is found in the SLC6A3 gene, however, the presence of a link between the repeat count and gene expression activity remains unconfirmed. Numerous papers show associations between the *10R* allele (Cherepkova et al., 2016), as well as the *9R* allele (Qadeer et al., 2017), and antisocial behavior. Furthermore, the association between the *9R* allele and increased aggressiveness was earlier confirmed by the longitudinal twin study (Young et al., 2002).

Recent studies confirm the role of monoamine oxidase-A (MAOA gene; 11.3 chromosome), i.e. the enzyme that catalyzes oxidative deamination of serotonin, dopamine, and noradrenaline, in AB regulation. Several polymorphisms in human gene MAOA have been identified to date, including VNTR30, for which six repeat patterns were described, the *3R* (or *L*) allele being the least functional, as it ensures transcription 3 times as low compared to *4R* (*H*). Most researchers report the *L* allele to be associated with impulsiveness and AB (Schlüter et al., 2016; Zhang et al., 2016) caused in particular by abusive treatment in childhood (Holz et al., 2016).

Catechol-O-methyl transferase (COMT; 22q11.21) is another enzyme involved in catecholamine degradation. Functional locus Val158Met, which reduces enzyme activity by 40% is found in its gene’s encoding part. The data are available that indicate the *Met* allele to be associated with increased aggression level in individuals aged under 18 (Albaugh et al., 2010), and there is a meta-study assuming that this polymorphism increases the risk of AB in males suffering from schizophrenia by approximately 50% (Singh et al., 2012). In addition, a significant effect of the *Met* allele on aggressiveness in children raised under adverse conditions was shown by Hygen B.W. et al. (2015), however aggressiveness in the allele carriers from functional families was lower than in the *Val* allele carriers.

The role of GABA in AB development, as the main neurotransmitter involved in central nervous system (CNS) inhibition, was initially proven by models, because mice with low GABA levels and increased concentration of GABA-degrading enzyme ABAT demonstrated significantly higher aggressiveness (Jager et al., 2017). The effect on AB in humans was noted via the GABRA2 (4p12) gene polymorphisms, which encoded the α_2 subunit of GABA_A-receptor, specifically increased aggression was observed in the rs279826*A and rs279838*A allele carriers (Kiiv et al., 2017).

**Hypothalamic-pituitary system genes**

The hypothalamic-pituitary system is another critical link in psychic function regulation. Key role in this system is played by oxytocin responsible for birth- and lactation-related functions and vasopressin with antidiuretic and vasopressor effects, which in addition to the classical variety of effects have non-classical ones. For example, it was found that balance between oxytocin and vasopressin concentrations determines various social and emotional reactions, whereas its derangement was described under depression, anxiety, and autism (Tyuzikov et al., 2015).

The effect of oxytocin (OXT gene; 20p13) depends primarily on its interaction with the OXTR receptor (3p25.3). It was found that decreased OXT gene expression, low oxytocin concentration cerebrospinal fluid, as well as the high linking ability of OXTR receptor cause increased aggressiveness in both rodents and humans (Lee et al., 2009; Calcagnoli et al., 2014), however the data on links between polymorphic loci in OXT and OXTR genes and AB were not that decisive. One of the studies dedicated to aggressive tendencies showed the OXT-rs6133010*A/*A × OXTR-rs2254298*G/*G × OXTR-rs53576*A/*G genotypes to be associated with a high level of physical aggression (Yang et al., 2017), however another paper, while not confirming
this association, admitted the role of rs1042778*T/*T genotype in development of antisocial behavior in males (Waller et al., 2016).

In addition, some authors analyzed OXTR gene polymorphisms in children with AB. Hovey D. et al. (2016) showed the rs4564970*C/*C, rs53576*G/*A, and rs7632287*A/*A genotypes to be associated with AB in boys, whereas the rs2254298*G/*G genotype was associated with aggression in girls. Another paper showed the rs237898*A and rs237902*C allele frequencies to be higher in the group of boys with AB, and rs6770632*T – in the group of girls (Malik et al., 2014).

Numerous data indicate that increased AVP1A (12q14.2) vasopressin receptor gene expression in hypothalamic paraventricular nuclei often accompanies anxiety and AB in rodents (Gutzler et al., 2010). Apart from that, additional evidence of the role of AVP1A in aggression regulation was obtained by studying candidate genes (Pappa et al., 2015), as well as in one of the recent meta-analyses (van Donkelaar et al., 2018). Functional model-based studies also indicate an important role of the AVP1B gene in AB development. In particular, mice with AVP1B (1q32) gene knockout showed a significant decrease in aggressiveness in the experiments (Wersinger et al., 2002), while association studies in human populations showed the polymorphic loci of rs55369693 and rs28676508 to be involved in aggression regulation in children (Zai et al., 2012).

Genes of neurotrophic factor system

In addition to classical ways of neurotransmission, genetic research of the enzymes and receptors involved in regulation of neurototoxic and neuroprotective responses to stress seem to be of interest. Neurotrophic factors (neurotrophins) are a large group of polypeptides, which play a critical role in developing and maintaining CNS structures (Popova et al., 2017), the BDNF factor encoded by homonymous BDNF (11p14.1) gene being the most wide-spread in the human brain.

The analysis of BDNF gene structure in human revealed functional locus Val566Met (196G > A; rs6265), which causes reduced neurotrophin protein secretion (Hong et al., 2011). It is shown in several papers that the *Met/*Met genotype carriers are characterized with high aggression level (Kretschmer et al., 2014), whereas other researchers were not able to discover this link (Guan et al., 2014; Nagata et al., 2014). It was also noted that modulating effect of the *Met/*Met genotype was largely defined by interaction with such environmental factors as chronic stress, negative parental upbringing, abusive treatment or sexual violence in childhood, which in turn facilitate development of aggressive phenotype (Wagner et al., 2010; Kretschmer et al., 2014; Avinun et al., 2018).

Role of sex hormone genes and their receptors

It has been mentioned earlier that persuasive evidence exists in favor of evolutionary gender specificity of aggression, which may be validated by global criminal statistics, according to which the vast majority of antisocial acts are committed by males (Baron, Richardson, 2001; Georgiev et al., 2013). Thus, studying sex hormone effects on mental health in humans becomes increasingly popular in psychoendocrinology.

Estrogens are a general group of female sex hormones, whose cerebral activity is determined by their interaction with the ERα and Erβ estrogen receptors encoded by the ESR1 (6q25.1) and ESR2 (14q23.3) genes respectively. Human gene ESR1 includes the [TA] repeat as one of its functional loci, which is imbalanced with −397T > C (rs2234693 or PvuII, for which alternative *P and *p allele designations may be encountered) and −351A > G (rs9340799; XbaI – *X and *x alleles) loci. Rare studies indicate the link between the [TA]n repeat count and physical aggressiveness in males (Vailancourt et al., 2012), as well as the rs2234693*P and rs9340799*X alleles and anger in girls (Vermeersch et al., 2013).

Androgens are male sex hormones potentially involved in CNS activity regulation as well. It was found that lengthy polytamine segments ([CAG]n) in the AR (Xq12) androgen receptor gene reduce its functional activity. In addition, a significant negative link is observed between repeat count and aggressiveness in males (Butovskaya et al., 2015), which was further confirmed by studies in the individuals convicted for violent crimes and rape. For example, average [CAG]−repeat counts in murderers and rapists were 17.59 and 18.44 respectively, whereas in a control group it didn’t exceed 21.19 (Rajender et al., 2008).

Neuronal apoptosis genes

Investigation of neurogenesis as a key phenomenon behind maintaining cell homeostasis in the nervous system becomes increasingly topical due to the rise of mental disorders in the society. It has been established by now that neuronal apoptosis disorders are revealed under ageing and various forms of neuropathology accompanied by changes in the psychological state of individuals. In addition, rare model-based studies are available indicating that neural apoptosis processes are linked to AB, which may be used as a basis for further molecular-genetic research in humans (Brigin et al., 2017).

For example, highly aggressive rats demonstrate increased CASP3 caspase gene expression in hypothalamus and mRNA expression of antiapoptotic BCL-XL gene in suture nuclei, as well as decreased proapoptotic BAX gene expression in hippocampus (Ichibaeva et al., 2016). It was noted in another study that rats with AB had increased expression of hypoxia-inducible factor-3 genes EGLN3, proteoglycan chondroitin sulfate ACAN, tyrosine hydroxylase TH, and NTS neuropeptide, as well as decreased expression of MEF2C and SOX2 transcription factors, ERBB3 tyrosine kinase receptor, EZR actin-linking cytoskeletal protein, VIP casoactive intestinal peptide in ventral tegmental midbrain, whereas increased expression of KIRREL3 protein genes and NOS1 nitric oxide synthase was observed in periaductual gray (Brigin et al., 2017). Meanwhile, NOS1 involvement
in AB development in humans has been proven earlier (Rujescu et al., 2008).

**Genome-wide association study (GWAS)**

Genome-wide association study analyzing thousands of SNPs simultaneously appears to be among the most promising methods for studying complex behavioral traits at the present stage of psychogenetic development. However, only a small number of GWAS have been performed to study AB in humans.

In 2015, a team of scientists within the EAGLE consortium performed GWAS analysis of AB associations in 18,988 children from two age groups, i.e., preschool age (3–7 years) and primary school/teenage of 8–15 years. The analysis performed revealed the most significant association both in general sample ($p = 5.30 \times 10^{-4}$) and preschool age ($p = 1.27 \times 10^{-4}$) and primary school/teenage ($p = 6.32 \times 10^{-4}$) samples being with the rs11126630 polymorphic locus, which, according to the authors, is located in the intergenic region space of LRRTM4 and SNAR-H (Pappa et al., 2015). The data are available indicating that the 2p12 chromosome region, where the LRRTM4 and SNAR-H genes are localized, is associated with self-aggression risk (Willour et al., 2007). It was also confirmed by GWAS analysis of suicidal behavior, in which the LRRTM4 gene was associated with risk of suicidal tendencies in females ($p = 9.27 \times 10^{-7}$) (Willour et al., 2012), which makes it possible to assume that it is involved in mechanisms of outgoing aggression.

The product of LRRTM4 gene belongs to the family of cell adhesion molecules. It is expressed in the dentate gyrus in the hippocampus and is involved in regulation of excitatory synapse development via its interaction with presynaptic heparan sulfate proteoglycans (HSPG) (Siddiqui et al., 2013). In addition to the rs11126630 polymorphic locus, polymorphisms rs10169036, rs11763137, rs12613157, rs1542677, and rs1542678 are discovered in the vicinity of this gene, differences by which reached significant levels both in general sample ($p < 1.02 \times 10^{-4}$), and samples of preschool-aged and primary school/teenage children ($p < 2.90 \times 10^{-4}$) (Pappa et al., 2015). In turn, SNAR-H is a gene that belongs to the family of small RNA associated genes, whose expression was primarily studied using genome-wide analysis in 543 Finnish criminals and 9616 individuals from general population, the strongest signals were discovered in the 6p21.2 chromosome region for rs4714329 ($p = 1.6 \times 10^{-8}$) and rs9471290 ($p = 2.9 \times 10^{-8}$) in the vicinity of the LINC00951 and LRFN2 genes, whose expression was primarily observed in the cerebellum (Rautiainen et al., 2016). Apart from that, functioning disorders in the LRFN2 gene product involved in cellular adhesion and plasticity, as well as in excitatory synapse development, are traditionally attributed to a series of cognitive disorders (Bereczki et al., 2018). It is worth noting that the GWAS analysis performed by Rautiainen M.R. et al. is not the only study of violent and antisocial behavior. For example, Tiibon J. et al. used the same sample to establish a significant association with rs11649622 polymorphism ($p = 4.19 \times 10^{-8}$) located on the long chromosome arm 16 (q23.3) in the intron region of cadherin gene (CDH13) involved in cell adhesion, while additional analysis of gene polymorphisms made it possible to reveal the association of *A/*A (rs11649622, rs7190768; $p = 6.2 \times 10^{-6}$) and *G/*G/*A/*A (rs12919501, rs4075942, rs11649622 and rs7190768; $p = 7.0 \times 10^{-6}$) haplotypes with extremely violent behavior in criminals (Tiibonen et al., 2015).

The study by Tielbeek J.J. et al. (2017), in which the results are presented with gender taken into account, may be considered as another example. Here, the associations with the rs2764450 locus ($p = 4.8 \times 10^{-8}$) on chromosome 1 and with rs11215217 ($p = 2.1 \times 10^{-8}$) on chromosome 11 are found in females. Association analysis in males with antisocial behavior showed the strongest signal for rs41456347 ($p = 2.0 \times 10^{-8}$) on chromosome X (Tielbeek et al., 2017). Earlier, the same author noted the association of antisocial behavior with the rs12106331, rs2835702, and rs2835771 loci ($p = 8.7 \times 10^{-6}$) in the DYRK1A (2q22.13) gene that encodes the enzyme critical for the cell proliferation signaling pathway and linked to synaptic plasticity. In addition, DYRK1A is a candidate gene for studying risks of mental retardation development, since it is localized in the chromosome region critical for Down syndrome development (Tielbeek et al., 2012).
Conclusions
Thus, aggressive behavior is a complex multifactor trait, and its development is affected by both environmental and genetic factors. Most research on studying genetic foundations of AB are limited to candidate gene approach and analysis of linkage between the gene loci primarily involved in the neurotransmitter system. In addition, the results are available for a number of association studies of a series of genes that encode key neupeptides and hormones and are also involved in synaptic plasticity and neuronal apoptosis, which indicates that development of genetic predisposition towards AB is a rather complex process, which includes disruptions in the whole cascade of reactions and in functioning of genes, which individually only slightly contribute (1–2 % of the total variability) to the development of pathological aggressiveness. It is worth noting that the effect of gene-environment interactions, ethnogeographic, social, and cultural factors, as well as sex-dependent peculiarities on the degree of manifestation of the aggressive phenotype is not discarded as well. Thus, taking these characteristics into account in future research may possibly solve the existing contradictions and lead to a deeper understanding of the nature of AB.

Although quite a lot of genetic studies of AB both in normal health and under pathology have been performed in recent decades, the number of genome-wide studies remains small. The GWAS results generalized in this survey are rather contradictory and barely replicated in papers by other authors, however, they agree that cell adhesion, synaptic plasticity, and neurogenesis are key processes in development of aggressive phenotype, while changes in these processes were conventionally considered in the context of main causes of cognitive and neurodegenerative disorders. Hence, the genes involved in these processes may be considered as potential genetic markers for further research of foundations of AB, since they have not been studied using the candidate gene approach before.

Presumably, integrated studies of epigenetic factors, such as methylation and acetylation of DNA and histones, as well as microRNA, involved regulation of target gene expression, may contribute significantly to understanding development mechanisms of AB. In addition, constructing and analyzing gene networks to describe interactions between molecular-genetic markers associated with aggressiveness, which would make it possible to identify new candidate genes for further experimental research of mechanisms of AB appears to be a topical problem.

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Conflict of interest
The authors declare no conflict of interest.

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