Вавиловский журнал генетики и селекции. 2018;22(6):716-725
DOI 10.18699/VJ18.415

Recent advances in genetics of aggressive behavior

J.D. Davydova[1] ✉, S.S. Litvinov[1], R.F. Enikeeva[1], S.B. Malykh[2], E.K. Khusnutdinova[1, 3]

[1] Institute of Biochemistry and Genetics, Ufa Federal Research Centre of RAS, Ufa, Russia
[2] Psychological Institute, Russian Academy of Education, Moscow, Russia
[3] Department of Genetics and Fundamental Medicine, Bashkir State University, Ufa, Russia

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 serotonergic (*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 (*OXT*, *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.

Современные представления о генетике агрессивного поведения

Ю.Д. Давыдова[1] ✉, С.С. Литвинов[1], Р.Ф. Еникеева[1], С.Б. Малых[2], Э.К. Хуснутдинова[1, 3]

[1] Институт биохимии и генетики, Уфимский федеральный исследовательский центр Российской академии наук, Уфа, Россия
[2] Психологический институт Российской академии образования, Москва, Россия
[3] Кафедра генетики и фундаментальной медицины, Башкирский государственный университет, Уфа, Россия

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 (*OXT*, *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 нерецепторной тирозинкиназы *FYN*, трансмембранного белка 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.

HOW TO CITE THIS ARTICLE:
Davydova J.D., Litvinov S.S., Enikeeva R.F., Malykh S.B., Khusnutdinova E.K. Recent advances in genetics of aggressive behavior. Vavilovskii Zhurnal Genetiki i Selektsii = Vavilov Journal of Genetics and Breeding. 2018;22(6):716-725. DOI 10.18699/VJ18.415

Received 29.03.2018
Accepted for publication 02.07.2018

✉ e-mail: julia.dmitrievna@list.ru

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).

Neurophysiological 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 (Ragozinskaya, 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 promotor (*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*L* 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/*L_G, *S/*L_A 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 (Hemmings 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 *5R 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 5 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 *rs279858*A* allele carriers (Kiive 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 *AVPR1A* (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 *AVPR1A* 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 *AVPR1B* gene in AB development. In particular, mice with *AVPR1B* (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 *rs35369693* 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 neurotoxic 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 *Val66Met* (*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 specifics 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 $[TA]_n$ 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 (Vaillancourt 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 polylutamine 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 $[CAG]_n$-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 (Bragin 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 (Ilchibaeva 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 periaqueductal gray (Bragin 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 of 3–7 years and primary school/teenage of 8–15 years. The analysis performed revealed the most significant association both in general sample ($p = 5.30 \cdot 10^{-8}$) and preschool age ($p = 1.27 \cdot 10^{-5}$) and primary school/teenage ($p = 6.32 \cdot 10^{-7}$) 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 (*rs10170138*, $p = 9.27 \cdot 10^{-7}$) (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*, *rs1176317*, *rs12613157*, *rs1542677*, and *rs1542678* are discovered in the vicinity of this gene, differences by which reached significant levels both in general sample ($p < 1.02 \cdot 10^{-6}$), and samples of preschool-aged and primary school/teenage children ($p < 2.90 \cdot 10^{-6}$) (Pappa et al., 2015). In turn, *SNAR-H* is a gene that belongs to the family of small RNA associated with the NF90 nuclear factor involved in transcription regulation and expressed in neurons (Parrott, Mathews, 2007). However, its role in behavior regulation is not fully studied and requires further research.

It is well-known that individuals with attention deficit and hyperactivity disorder (ADHD) often demonstrate hostility and aggression traits, in addition to inattentiveness and increased impulsiveness, which is why these traits are often analyzed together. When AB was investigated in 1060 adults with ADHD, the strongest association was observed with *rs10826548* locus (lncRNA transcript; $p = 1.07 \cdot 10^{-6}$), as well as with *rs35974940* in *NTM* neurotrimin gene ($p = 1.26 \cdot 10^{-6}$) involved in cell adhesion and neurite growth in neurons (Brevik et al., 2016).

In addition, several GWAS studies were performed for individual AB phenotypes. The sample of 8747 people aged 45–64 in one of these studies showed the *rs2148710* polymorphic locus ($p = 2.9 \cdot 10^{-8}$) to be associated with anger manifestations, according to Spielberger's STAXI scale. It was found that this locus was located in the 6q21 chromosome region in the *FYN* gene that encodes non-receptor tyrosine kinase, whose activity may be related to mood dysregulation. Since postsynaptic linkage of brain-derived neurotrophic factor BDNF with tyrosine kinase receptor B activates non-receptor tyrosine kinase responsible for phosphorylation of NDMA receptors and inositol-1,4,5-triphosphate-linked channels, these signaling pathways, through which intracellular calcium homeostasis is regulated (which is particularly important for CNS functioning and neuron survival), may be involved in formation of emotional traits in humans, including anger traits (Mick et al., 2014).

When genetic foundations of antisocial behavior were 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* ($p = 1.6 \cdot 10^{-9}$) and *rs9471290* ($p = 2.9 \cdot 10^{-7}$) 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, Tiihonen J. et al. used the same sample to establish a significant association with *rs11649622* polymorphism ($p = 4.19 \cdot 10^{-6}$) 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*; $p = 6.2 \cdot 10^{-7}$) and **G/*G/*A/*A* (*rs12919501*, *rs4075942*, *rs11649622* and *rs7190768*; $p = 7.0 \cdot 10^{-6}$) haplotypes with extremely violent behavior in criminals (Tiihonen 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 ($p = 4.8 \cdot 10^{-8}$) on chromosome 1 and with *rs11215217* ($p = 2.1 \cdot 10^{-8}$) on chromosome 11 are found in females. Association analysis in males with antisocial behavior showed the strongest signal for *rs41456347* ($p = 2.0 \cdot 10^{-8}$) on chromosome X (Tielbeek et al., 2017). Earlier, the same author noted the association of antisocial behavior with the *rs12106331*, *rs2835702*, and *rs2835771* loci ($p = 8.7 \cdot 10^{-5}$) in the *DYRK1A* (21q22.13) 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 neuropeptides 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.

Acknowledgements

The work was supported by the Russian Foundation for Basic Research under ofi-m project "Genomics of Aggressive and Depressive Behavior in Humans", no. 17-29-02195.

Conflict of interest

The authors declare no conflict of interest.

References

Albaugh M.D., Harder V.S., Althoff R.R., Rettew D.C., Ehli E.A., Lengyel-Nelson T., Davies G.E., Ayer L., Sulman J., Stanger C., Hudziak J.J. COMT Val158Met genotype as a risk factor for problem behaviors in youth. J. Am. Acad. Child Adolesc. Psychiatry. 2010;49(8):841-849. DOI 10.1016/j.jaac.2010.05.015.

Avinun R., Davidov M., Mankuta D., Knafo-Noam A. Predicting the use of corporal punishment: Child aggression, parent religiosity, and the BDNF gene. Aggress. Behav. 2018;44(2):165-175. DOI 10.1002/ab.21740.

Baron R., Richardson D. (Eds.) Human Aggression. New York: Plenum Publ., 1994. Russ. ed.: Baron R., Richardson D. Aggression. St. Petersburg: Piter Publ., 2001. (in Russian)

Beden O., Senol E., Atay S., Ak H., Altintoprak A.E., Kiyan G.S., Petin B., Yaman U., Aydin H.H. TPH1 A218 allele is associated with suicidal behavior in Turkish population. Leg. Med. (Tokyo). 2016;21:15-18. DOI 10.1016/j.legalmed.2016.05.005.

Bereczki E., Branca R.M., Francis P.T., Pereira J.B., Baek J.H., Hortobágyi T., Winblad B., Ballard C., Lehtiö J., Aarsland D. Synaptic markers of cognitive decline in neurodegenerative diseases: a proteomic approach. Brain. 2018;141(2):582-595. DOI 10.1093/brain/awx352.

Blanco E.A., Duque L.M., Rachamallu V., Yuen E., Kane J.M., Gallego J.A. Predictors of aggression in 3.322 patients with affective disorders and schizophrenia spectrum disorders evaluated in an emergency department setting. Schizophr. Res. 2018;195:136-141. DOI 10.1016/j.schres.2017.10.002.

Bragin A.O., Saik O.V., Chadaeva I.V., Demenkov P.S., Markel A.L., Orlov Yu.L., Rogaev E.I., Lavrik I.N., Ivanisenko V.A. Role of apoptosis genes in aggression revealed using combined analysis of ANDSystem gene networks, expression and genomic data in grey rats with aggressive behavior. Vavilovskii Zhurnal Genetiki i Selektsii = Vavilov Journal of Genetics and Breeding. 2017; 21(8):911-919. DOI 10.18699/VJ17.312. (in Russian)

Brevik E.J., van Donkelaar M.M., Weber H., Sánchez-Mora C., Jacob C., Rivero O., Kittel-Schneider S., Garcia-Martínez I., Aebi M., van Hulzen K., Cormand B., Ramos-Quiroga J.A., Lesch K.P., Reif A., Ribasés M., Franke B., Posserud M.B., Johansson S., Lundervold A.J., Haavik J., Zayats T. Genome-wide analyses of aggressiveness in attention-deficit hyperactivity disorder. Am. J. Med. Genet. B Neuropsychiatr. Genet. 2016;171(5):733-747. DOI 10.1002/ajmg.b.32434.

Butovskaya M.L., Lazebny O.E., Vasilyev V.A., Dronova D.A., Karelin D.V., Mabulla A.Z., Shibalev D.V., Shackelford T.K., Fink B., Ryskov A.P. Androgen receptor gene polymorphism, aggression, and reproduction in tanzanian foragers and pastoralists. PLoS One. 2015;10(8):e0136208. DOI 10.1371/journal.pone.0136208.

Calcagnoli F., de Boer S.F., Beiderbeck D.I., Althaus M., Koolhaas J.M., Neumann I.D. Local oxytocin expression and oxytocin receptor binding in the male rat brain is associated with aggressiveness. Behav. Brain Res. 2014;261:315-322. DOI 10.1016/j.bbr.2013.12.050.

Cherepkova E.V., Aftanas L.I., Maksimov N., Menshanov P. Frequency of 3′ VNTR polymorphism in the dopamine transporter gene *SLC6A3* in humans predisposed to antisocial behavior. Bull. Exp. Biol. Med. 2016;162(1):82-85. DOI 10.1007/s10517-016-3551-7.

Cherepkova E.V., Maksimov V.N., Aftanas L.I., Menshanov P.N. Genotype and haplotype frequencies of the DRD4 VNTR polymorphism in the men with no history of ADHD, convicted of violent crimes. J. Crim. Justice. 2015;43(6):464-469. DOI 10.1016/j.jcrimjus.2015.10.002.

Cicchetti D., Rogosch F.A., Thibodeau E. The effects of child maltreatment on early signs of antisocial behavior: genetic moderation by tryptophan hydroxylase, serotonin transporter, and monoamine oxidase-a-genes. Dev. Psychopathol. 2012;24(3):907-928. DOI 10.1017/S0954579412000442.

Dmitrieva T.B., Shostakovich B.V. Aggression and Mental Health. St. Petersburg: Yuridichesky Center Publ., 2002. (in Russian)

Gansler D.A., McLaughlin N.C., Iguchi L., Jerram M., Moore D.W., Bhadelia R., Fulwiler C. A multivariate approach to aggression and

the orbital frontal cortex in psychiatric patients. Psychiatry Res. 2009;171(3):145-154. DOI 10.1016/j.pscychresns.2008.03.007.

Georgiev A.V., Klimczuk A.C.E., Traficonte D.M., Maestripieri D. When violence pays: a cost-benefit analysis of aggressive behavior in animals and humans. Evol. Psychol. 2013;11(3):678-699.

Gorodetsky E., Carli V., Sarchiapone M., Roy A., Goldman D., Enoch M.A. Predictors for self-directed aggression in italian prisoners include externalizing behaviors, childhood trauma and the serotonin transporter gene polymorphism 5-HTTLPR. Genes Brain Behav. 2016;15(5):465-473. DOI 10.1111/gbb.12293.

Guan X., Dong Z.Q., Tian Y.Y., Wu L.N., Gu Y., Hu Z.Q., Zhang X. Lack of association between brain-derived neurotrophic factor Val66Met polymorphism and aggressive behavior in schizophrenia. Psychiatry Res. 2014;215(1):244-245. DOI 10.1016/j.psychres.2013.10.017.

Gurskaya I.Y. Methodological problems in the research of aggressive behavior. Uchenye Zapiski Pedagogicheskogo Instituta Saratovskogo Gosudarstvennogo Universiteta. Ser. Psychologiya. Pedagogica = Scientific Reports of the Chernyshevskiy Pedagogical Institute, Saratov State University, Ser: Psychology. Pedagogics. 2008;1(3-4):13-17. (in Russian)

Gusev E.I., Konovalova A.N., Skvortsova V.I., Geht A.B. Neurology: The National Guide. Moscow: GJeOTAR-Media Publ., 2009. (in Russian)

Gutzler S.J., Karom M., Erwin W.D., Albers H.E. Arginine-vasopressin and the regulation of aggression in female Syrian hamsters (*Mesocricetus auratus*). Eur. J. Neurosci. 2010;31(9):1655-1663. DOI 10.1111/j.1460-9568.2010.07190.x.

Hemmings S.M.J., Xulu K., Sommer J., Hinsberger M., Malan-Muller S., Tromp G., Elbert T., Weierstall R., Seedat S. Appetitive and reactive aggression are differentially associated with the STin2 genetic variant in the serotonin transporter gene. Sci. Rep. 2018;8:6714. DOI 10.1038/s41598-018-25066-8.

Holz N., Boecker R., Buchmann A.F., Blomeyer D., Baumeister S., Hohmann S., Jennen-Steinmetz C., Wolf I., Rietschel M., Witt S.H., Plichta M.M., Meyer-Lindenberg A., Schmidt M.H., Esser G., Banaschewski T., Brandeis D., Laucht M. Evidence for a sex-dependent *MAOA* × Childhood stress interaction in the neural circuitry of aggression. Cereb. Cortex. 2016;26(3):904-914. DOI 10.1093/cercor/bhu249.

Hong C.J., Liou Y.J., Tsai S.J. Effects of BDNF polymorphisms on brain function and behavior in health and disease. Brain Res. Bull. 2011;86(5-6):287-297. DOI 10.1016/j.brainresbull.2011.08.019.

Hovey D., Lindstedt M., Zettergren A., Jonsson L., Johansson A., Melke J., Kerekes N., Anckarsäter H., Lichtenstein P., Lundström S., Westberg L. Antisocial behavior and polymorphisms in the oxytocin receptor gene: findings in two independent samples. Mol. Psychiatry. 2016;21(7):983-988. DOI 10.1038/mp.2015.144.

Hygen B.W., Belsky J., Stenseng F., Lydersen S., Guzey I.C., Wichstrøm L. Child exposure to serious life events, COMT, and aggression: Testing differential susceptibility theory. Dev. Psychol. 2015;51(8):1098-1104. DOI 10.1037/dev0000020.

Ilchibaeva T.V., Tsybko A.S., Kozhemyakina R.V., Naumenko V.S. Expression of apoptosis genes in the brain of rats with genetically defined fear-induced aggression. Molecular Biology (Moscow). 2016;50(5):719-724. DOI 10.1134/S0026893316030079.

Jager A., Amiri H., Bielczyk N., van Heukelum S., Heerschap A., Aschrafi A., Poelmans G., Buitelaar J.K., Kozicz T., Glennon J.C. Cortical control of aggression: GABA signalling in the anterior cingulate cortex. Eur. Neuropsychopharmacol. 2017. DOI 10.1016/j.euroneuro.2017.12.007.

Kazantseva A.V., Khusnutdinova E.K. Genes vs Environment, or What Controls Our Behavior. Ufa: Bashkirian State University, 2017. (in Russian)

Kiive E., Laas K., Vaht M., Veidebaum T., Harro J. Stressful life events increase aggression and alcohol use in young carriers of the *GABRA2* rs279826/rs279858 A-allele. Eur. Neuropsychopharmacol. 2017;27(8):816-827. DOI 10.1016/j.euroneuro.2017.02.003.

King A.R., Ratzak A., Ballantyne S., Knutson S., Russell T.D., Pogalz C.R., Breen C.M. Differentiating corporal punishment from physical abuse in the prediction of lifetime aggression. Agress. Behav. 2018;44(3):306-315. DOI 10.1002/ab.21753.

Koh K.B., Kim C.H., Choi E.H., Lee Y.J., Seo W.Y. Effect of tryptophan hydroxylase gene polymorphism on aggression in major depressive disorder and undifferentiated somatoform disorder. J. Clin. Psychiatry. 2012;73(5):e574-e579. DOI 10.4088/JCP.11m07342.

Kretschmer T., Vitaro F., Barker E.D. The association between peer and own aggression is moderated by the BDNF Val-Met polymorphism. J. Res. Adolesc. 2014;24(1):177-185. DOI 10.1111/jora.12050.

Laas K., Kiive E., Mäestu J., Vaht M., Veidebaum T., Harro J. Nice guys: Homozygocity for the TPH2 –703G/T (rs4570625) minor allele promotes low aggressiveness and low anxiety. J. Affect Disord. 2017;215:230-236. DOI 10.1016/j.jad.2017.03.045.

Lee R., Ferris C., Van de Kar L.D., Coccaro E.F. Cerebrospinal fluid oxytocin, life history of aggression, and personality disorder. Psychoneuroendocrinology. 2009;34(10):1567-1573. DOI 10.1016/j.psyneuen.2009.06.002.

Lopez-Castroman J., Jaussent I., Beziat S., Guillaume S., Baca-Garcia E., Genty C., Olié E., Courtet P. Increased severity of suicidal behavior in impulsive aggressive patients exposed to familial adversities. Psychol. Med. 2014;44(14):3059-3068. DOI 10.1017/S0033291714000646.

MacKenzie A., Quinn J. A serotonin transporter gene intron 2 polymorphic region, correlated with affective disorders, has allele-dependent differential enhancer-like properties in the mouse embryo. Proc. Natl. Acad. Sci. USA. 1999;96(26):15251-15255.

Malik A.I., Zai C.C., Berall L., Abu Z., Din F., Nowrouzi B., Chen S., Beitchman J.H. The role of genetic variants in genes regulating the oxytocin-vasopressin neurohumoral system in childhood-onset aggression. Psychiatr. Genet. 2014;24(5):201-210. DOI 10.1097/YPG.0000000000000044.

Meyer-Bahlburg H.F.L. Sex chromosomes and aggression in humans. In: Brain P.P., Benton D. (Eds.) The Biology of Aggression. Rockville: MD, 1981;109-123.

Mick E., McGough J., Deutsch C.K., Frazier J.A., Kennedy D., Goldberg R.J. Genome-Wide Association Study of proneness to anger. PLoS One. 2014;9(1):e87257. DOI 10.1371/journal.pone.0087257.

Miczek K.A., de Almeida R.M., Kravitz E.A., Rissman E.F., de Boer S.F., Raine A. Neurobiology of escalated aggression and violence. J. Neurosci. 2007;27(44):11803-11806. DOI 10.1523/JNEUROSCI.3500-07.2007.

Nagata T., Kobayashi N., Shinagawa S., Yamada H., Kondo K., Nakayama K. Plasma BDNF levels are correlated with aggressiveness in patients with amnestic mild cognitive impairment or Alzheimer disease. J. Neural. Transm. (Vienna). 2014;121(4):433-441. DOI 10.1007/s00702-013-1121-y.

Pappa I., St Pourcain B., Benke K., Cavadino A., Hakulinen C., Nivard M.G., Nolte I.M., Tiesler C.M., Bakermans-Kranenburg M.J., Davies G.E., Evans D.M., Geoffroy M.C., Grallert H., Groen-Blokhuis M.M., Hudziak J.J., Kemp J.P., Keltikangas-Järvinen L., McMahon G., Mileva-Seitz V.R., Motazedi E., Power C., Raitakari O.T., Ring S.M., Rivadeneira F., Rodriguez A., Scheet P.A., Seppälä I., Snieder H., Standl M., Thiering E., Timpson N.J., Veenstra R., Velders F.P., Whitehouse A.J., Smith G.D., Heinrich J., Hypponen E., Lehtimäki T., Middeldorp C.M., Oldehinkel A.J., Pennell C.E., Boomsma D.I., Tiemeier H. A genome-wide approach to children's aggressive behavior: *The EAGLE consortium*. Am. J. Med. Genet. B Neuropsychiatr. Genet. 2015;171(5):562-572. DOI 10.1002/ajmg.b.32333.

Pardini D.A., Raine A., Erickson K., Loeber R. Lower amygdala volume in men is associated with childhood aggression, early psychopathic traits, and future violence. Biol. Psychiatry. 2014;75(1):73-80. DOI 10.1016/j.biopsych.2013.04.003.

Parrott A.M., Mathews M.B. Novel rapidly evolving hominid RNAs bind nuclear factor 90 and display tissue-restricted distribution. Nucleic Acids Res. 2007;35(18):6249-6258. DOI 10.1093/nar/gkm668.

Popova N.K., Ilchibaeva T.V., Naumenko V.S. Neurotrophic factors (BDNF and GDNF) and the serotonergic system of the brain.

Biochemistry (Moscow). 2017;82(3):308-317. DOI 10.1134/S0006297917030099.

Qadeer M.I., Amar A., Mann J.J., Hasnain S. Polymorphisms in dopaminergic system genes; association with criminal behavior and self-reported aggression in violent prison inmates from Pakistan. PLoS One. 2017;12(6):e0173571. DOI 10.1371/journal.pone.0173571.

Ragozinskaya V.G. Features of EEG spectral power in autoaggression. Izvestiya Vysshih Uchebnykh Zavedenij. Uralskij Region = Proceedings of Higher Educational Institutions. Ural Region. 2015; 2:97-104. (in Russian)

Rajender S., Pandu G., Sharma J.D., Gandhi K.P., Singh L., Thangaraj K. Reduced CAG repeats length in androgen receptor gene is associated with violent criminal behavior. Int. J. Legal Med. 2008; 122(5):367-372. DOI 10.1007/s00414-008-0225-7.

Rautiainen M.R., Paunio T., Repo-Tiihonen E., Virkkunen M., Ollila H.M., Sulkava S., Jolanki O., Palotie A., Tiihonen J. Genome-wide association study of antisocial personality disorder. Transl. Psychiatry. 2016;6(9):e883. DOI 10.1038/tp.2016.155.

Rosstat: Russian Federal State Statistics Service. 2017. Available at: http://www.gks.ru/wps/wcm/connect/rosstat_main/rosstat/ru/statistics/population/ (in Russian)

Rujescu D., Giegling I., Mandelli L., Schneider B., Hartmann A.M., Schnabel A., Maurer K., Möller H.J., Serretti A. NOS-I and -III gene variants are differentially associated with facets of suicidal behavior and aggression-related traits. Am. J. Med. Genet. B Neuropsychiatr. Genet. 2008;147B(1):42-48. DOI 10.1002/ajmg.b.30569.

Schlomer G.L., Cleveland H.H., Vandenbergh D.J., Feinberg M.E., Neiderhiser J.M., Greenberg M.T., Spoth R., Redmond C. Developmental differences in early adolescent aggression: a gene × environment × intervention analysis. J. Youth Adolesc. 2015;44(3):581-597. DOI 10.1007/s10964-014-0198-4.

Schlüter T., Winz O., Henkel K., Eggermann T., Mohammadkhani-Shali S., Dietrich C., Heinzel A., Decker M., Cumming P., Zerres K., Piel M., Mottaghy F.M., Vernaleken I. MAOA-VNTR polymorphism modulates context-dependent dopamine release and aggressive behavior in males. Neuroimage. 2016;125:378-385. DOI 10.1016/j.neuroimage.2015.10.031.

Siddiqui T.J., Tari P.K., Connor S.A., Zhang P., Dobie F.A., She K., Kawabe H., Wang Y.T., Brose N., Craig A.M. An LRRTM4-HSPG complex mediates excitatory synapse development on dentate gyrus granule cells. Neuron. 2013;79(4):680-695. DOI 10.1016/j.neuron.2013.06.029.

Singh J.P., Volavka J., Czobor P., Van Dorn R.A. A meta-analysis of the Val158Met COMT polymorphism and violent behavior in schizophrenia. PLoS One. 2012;7(8):e43423. DOI 10.1371/journal.pone.0043423.

Stochholm K., Bojesen A., Jensen A.J., Juul S., Gravholt C.H. Criminality in men with Klinefelter's syndrome and XYY syndrome: a cohort study. BMJ Open. 2012;2:e000650. DOI 10.1136/bmjopen-2011-000650.

Takeuchi H., Tomita H., Taki Y., Kikuchi Y., Ono C., Yu Z., Sekiguchi A., Nouchi R., Kotozaki Y., Nakagawa S., Miyauchi C.M., Iizuka K., Yokoyama R., Shinada T., Yamamoto Y., Hanawa S., Araki T., Hashizume H., Kunitoki K., Sassa Y., Kawashima R. Cognitive and neural correlates of the 5-repeat allele of the dopamine D4 receptor gene in a population lacking the 7-repeat allele. Neuroimage. 2015; 110:124-35. DOI 10.1016/j.neuroimage.2015.01.053.

Tielbeek J.J., Johansson A., Polderman T.J.C., Rautiainen M.R., Jansen P., Taylor M., Tong X., Lu Q., Burt A.S., Tiemeier H., Viding E., Plomin R., Martin N.G., Heath A.C., Madden P.A.F., Montgomery G., Beaver K.M., Waldman I., Gelernter J., Kranzler H.R., Farrer L.A., Perry J.R.B., Munafò M., LoParo D., Paunio T., Tiihonen J., Mous S.E., Pappa I., de Leeuw C., Watanabe K., Hammerschlag A.R., Salvatore J.E., Aliev F., Bigdeli T.B., Dick D., Faraone S.V., Popma A., Medland S.E., Posthuma D. Genome-Wide Association Studies of a broad spectrum of antisocial behavior. JAMA Psychiatry. 2017;74(12):1242-1250. DOI 10.1001/jamapsychiatry.2017.3069.

Tielbeek J.J., Medland S.E., Benyamin B., Byrne E.M., Heath A.C., Madden P.A., Martin N.G., Wray N.R., Verweij K.J. Unraveling the genetic etiology of adult antisocial behavior: a genome-wide association study. PLoS One. 2012;7(10):e45086. DOI 10.1371/journal.pone.0045086.

Tiihonen J., Rautiainen M.R., Ollila H.M., Repo-Tiihonen E., Virkkunen M., Palotie A., Pietiläinen O., Kristiansson K., Joukamaa M., Lauerma H., Saarela J., Tyni S., Vartiainen H., Paananen J., Goldman D., Paunio T. Genetic background of extreme violent behavior. Mol. Psychiatry. 2015;20(6):786-792. DOI 10.1038/mp.2014.130.

Tkachenko O.N. Genetic correlations of a person's aggression: literature review. Socialno-Ecologicheskie Tekhnologii = Environment and Human: Environmental Studies. 2016;3:68-86. (in Russian)

Tuvblad C., Narusyte J., Grann M., Sarnecki J., Lichtenstein P. The genetic and environmental etiology of antisocial behavior from childhood to emerging adulthood. Behav. Genet. 2011;41(5):629-640. DOI 10.1007/s10519-011-9463-4.

Tyuzikov I.A., Kalinchenko S.Yu., Vorslov L.O., Tishova Yu.A. Vasopressin: nonclassical effects and the role in the development of age-related diseases. Effectivnaya Pharmacotherapiya = Effective Pharmacotherapy. 2015;26:38-50. (in Russian)

United Nations Office on Drugs and Crime "UNODC": Reports on world crime trends. 2017. Available at: https://www.unodc.org/documents/data-and-analysis/statistics/crime/reports-on-world-crime-trends.html

Vaillancourt K.L., Dinsdale N.L., Hurd P.L. Estrogen receptor 1 promoter polymorphism and digit ratio in men. Am. J. Hum. Biol. 2012; 24(5):682-689. DOI 10.1002/ajhb.22297.

Van Donkelaar M.M.J., Hoogman M., Pappa I., Tiemeier H., Buitelaar J.K., Franke B., Bralten J. Pleiotropic contribution of *MECOM* and *AVPR1A* to aggression and subcortical brain volumes. Front. Behav. Neurosci. 2018;12:61. DOI 10.3389/fnbeh.2018.00061.

Van Ijzendoorn M.H., Belsky J., Bakermans-Kranenburg M.J. Serotonin transporter genotype 5HTTLPR as a marker of differential susceptibility? A meta-analysis of child and adolescent gene-by-environment studies. Transl. Psychiatry. 2012;2:e147. DOI 10.1038/tp.2012.73.

VanNess S.H., Owens M.J., Kilts C.D. The variable number of tandem repeats element in *DAT1* regulates *in vitro* dopamine transporter density. BMC Genet. 2005;6:55. DOI 10.1186/1471-2156-6-55.

Vermeersch H., T'sjoen G., Kaufman J.M., Van Houtte M. ESR1 polymorphisms, daily hassles, anger expression, and depressive symptoms in adolescent boys and girls. Horm. Behav. 2013;63(3):447-453. DOI 10.1016/j.yhbeh.2012.11.017.

Viding E., Blair R.J., Moffitt T.E., Plomin R. Evidence for substantial genetic risk for psychopathy in 7-year-olds. J. Child Psychol. Psychiatry. 2005;46(6):592-597. DOI 10.1111/j.1469-7610.2004.00393.x.

Wagner S., Baskaya Ö., Dahmen N., Lieb K., Tadić A. Modulatory role of the brain-derived neurotrophic factor $Val^{66}Met$ polymorphism on the effects of serious life events on impulsive aggression in borderline personality disorder. Genes Brain Behav. 2010;9(1):97-102. DOI 10.1111/j.1601-183X.2009.00539.x.

Waleewong O., Laslett A.M., Chenhall R., Room R. Harm from others' drinking-related aggression, violence and misconduct in five Asian countries and the implications. Int. J. Drug Policy. 2018;56:101-107. DOI 10.1016/j.drugpo.2018.03.015.

Waller R., Corral-Frías N.S., Vannucci B., Bogdan R., Knodt A.R., Hariri A.R., Hyde L.W. An oxytocin receptor polymorphism predicts amygdala reactivity and antisocial behavior in men. Soc. Cogn. Affect Neurosci. 2016;11(8):1218-1226. DOI 10.1093/scan/nsw042.

Wendland J.R., Martin B.J., Kruse M.R., Lesch K.P., Murphy D.L. Simultaneous genotyping of four functional loci of human *SLC6A4*, with a reappraisal of *5-HTTLPR* and rs25531. Mol. Psychiatry. 2006;11(3):224-226. DOI 10.1038/sj.mp.4001789.

Wersinger S.R., Ginns E.I., O'Carroll A.M., Lolait S.J., Young W.S. Vasopressin V1b receptor knockout reduces aggressive behavior in male mice. Mol. Psychiatry. 2002;7:975-984. DOI 10.1038/sj.mp.4001195.

Willour V.L., Seifuddin F., Mahon P.B., Jancic D., Pirooznia M., Steele J., Schweizer B., Goes F.S., Mondimore F.M., Mackinnon D.F., Bipolar Genome Study Consortium, Perlis R.H., Lee P.H., Huang J., Kelsoe J.R., Shilling P.D., Rietschel M., Nöthen M., Cichon S., Gurling H., Purcell S., Smoller J.W., Craddock N., DePaulo J.R., Schulze T.G., McMahon F.J., Zandi P.P., Potash J.B. A genome-wide association study of attempted suicide. Mol. Psychiatry. 2012;17(4):433-444. DOI 10.1038/mp.2011.4.

Willour V.L., Zandi P.P., Badner J.A., Steele J., Miao K., Lopez V., MacKinnon D.F., Mondimore F.M., Schweizer B., McInnis M.G., Miller E.B., Depaulo J.R., Gershon E.S., McMahon F.J., Potash J.B. Attempted suicide in bipolar disorder pedigrees: evidence for linkage to 2p12. Biol. Psychiatry. 2007;61(5):725-727. DOI 10.1016/j.biopsych.2006.05.014.

Yang L., Wang F., Wang M., Han M., Hu L., Zheng M., Ma J., Kang Y., Wang P., Sun H., Zuo W., Xie L., Wang A., Yu D., Liu Y. Association between oxytocin and receptor genetic polymorphisms and aggression in a northern Chinese Han population with alcohol dependence. Neurosci. Lett. 2017;636:140-144. DOI 10.1016/j.neulet.2016.10.066.

Yoon H.K., Lee H.J., Kim L., Lee M.S., Ham B.J. Impact of tryptophan hydroxylase 2 G-703T polymorphism on anger-related personality traits and orbitofrontal cortex. Behav. Brain Res. 2012;231(1):105-110.

Young S.E., Smolen A., Corley R.P., Krauter K.S., DeFries J.C., Crowley T.J., Hewitt J.K. Dopamine transporter polymorphism associated with externalizing behavior problems in children. Am. J. Med. Genet. 2002;114(2):144-149.

Zai C.C., Muir K.E., Nowrouzi B., Shaikh S.A., Choi E., Berall L., Trépanier M.O., Beitchman J.H., Kennedy J.L. Possible genetic association between vasopressin receptor 1B and child aggression. Psychiatry Res. 2012;200(2-3):784-788. DOI 10.1016/j.psychres.2012.07.031.

Zhang Y., Ming Q., Wang X., Yao S. The interactive effect of the *MAOA*-VNTR genotype and childhood abuse on aggressive behaviors in Chinese male adolescents. Psychiatr. Genet. 2016;26(3):117-123. DOI 10.1097/YPG.0000000000000125.

ORCID ID

J.D. Davydova orcid.org/0000-0003-3508-4710

S.S. Litvinov orcid.org/0000-0002-5999-149X

R.F. Enikeeva orcid.org/0000-0002-4301-5283

S.B. Malykh orcid.org/0000-0002-3786-7447

E.K. Khusnutdinova orcid.org/0000-0003-2987-3334