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REVIEWS
AND THEORETICAL ARTICLES

Genetic Mechanisms of Cognitive Development

R. N. Mustafin[a], *, A. V. Kazantseva[b], S. B. Malykh[c], and E. K. Khusnutdinova[b, c]

[a] *Bashkir State Medical University, Ufa, 450008 Russia*
[b] *Institute of Biochemistry and Genetics, Ufa Federal Research Centre, Russian Academy of Sciences, Ufa, 450054 Russia*
[c] *Moscow State University, Moscow, 119991 Russia*
**e-mail: ruji79@mail.ru*

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Abstract—The results of large-scale meta-analyses of GWAS and genetic association studies demonstrated the role of allelic variants of a large number of genes in the development of cognitive abilities. Many of the identified genes are expressed in the brain and are involved in the pathogenesis of nervous system diseases. It has been shown that the summarized genetic effect for various cognitive abilities is no more than 50%. For certain genes, such as *BDNF*, *DRD2*, *FNBP1L*, *PDE1C*, *PDE4B*, and *PDE4D*, related to the regulation of neurogenesis and synaptic plasticity, associations with specific cognitive abilities were revealed. We assume the prospect of using the obtained results for the targeted effect in order to improve human cognitive abilities. This review describes DNA methylation, histone acetylation, expression of specific noncoding RNAs during brain functioning, and the development of individual differences in cognitive abilities. The revealed epigenetic mechanisms suggest the methods of reversible correction of cognitive functioning both in nonclinical forms and pathological states.

Keywords: genetic associations, genetic predisposition, brain, cognitive abilities, g factor
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INTRODUCTION

Human cognitive characteristics include praxis (acquisition and use of motor skills), attention, speech, gnosis (information perception), memory, and intelligence [1]. The general intelligence factor ("g" factor) is one of the best predictors of important life indicators, including educational attainment, professional activity, mental and physical health, morbidity [2], and life expectancy [3]. The g factor is a key construct in differential psychology, behavioral genetics, and cognitive neuroscience [2]. Twin, family, and adoption studies demonstrated that the g factor was highly inherited and genetically stable throughout life [3, 4].

The impact of inherited factors in intelligence development increases from 20% in infancy to 80% in late adulthood. At the same time, other cognitive abilities differ significantly within early postnatal human development. Their level increases significantly from birth to puberty, while it decreases in adulthood [5]. The coefficient of phenotypic correlation between various cognitive abilities is known to be on average 0.30, while the coefficient of genetic correlation is about 0.60 [2]. Different cognitive abilities are characterized by a specific distribution of the impact of the genetic and environmental factors. For example, an estimate of phenotypic covariance demonstrated that the heritability coefficient of reading ability was 0.66, while the impact of the general environment was 0.14. At the same time, the coefficient of inheritance of mathematical abilities was 0.51 with the role of the general environment of 0.21 [6]. In 2018, Tosto et al. examined more than 3000 twins aged 8 to 16 and revealed about 57 to 98% of genes associated with both mathematical and reading abilities. In addition, comorbid genetic factors explain about 70% of the covariance between general intelligence and mathematical abilities [7].

Variations in the normal cognitive functioning are caused by different factors; however, the sum of all genetic effects is no more than 50% for different cognitive abilities, which indicates a small impact of each of multiple genes involved in cognitive performance. Several basic approaches in genetic analysis (candidate gene association study, genome-wide association study, etc.) are used to estimate a potential role of distinct genes in cognitive processes. Association analysis determines the degree of relation between alleles of genes and features of cognitive performance. A positive association with cognitive characteristics can be observed if the gene variant is a causative factor and is in linkage disequilibrium with an unexamined allele, or in the case of false-positive association [8].

Another approach (GWAS—genome-wide association study) appeared to be more effective in the estimate of inheritance of cognitive characteristics based on simultaneous analysis of hundreds of thousands of

single nucleotide polymorphisms (SNPs) with subsequent GWAS to predict individual cognitive phenotypes in independent samples. However, they appeared to be less precise to detect specific genetic variants affecting cognitive differences [9]. Although even if genetic variants are significantly associated with cognitive characteristics, the size effects are small. Therefore, the study of neurocognitive phenotypes required the use of polygenic risk scores (PRS) to predict differential genetic liability to the formation of individual differences in cognitive performance. According to the conducted GWAS of intelligence, several associations were detected, while PRS estimates constituted only 1% of variance in intelligence [2]. According to GWAS data, the differences in cognitive abilities were shown to be associated with genes involved in neurotransmission and formation of neuronal networks necessary for brain functioning and for adaptation to changing physical and social conditions [10]. Molecular-genetic studies of cognitive abilities in healthy individuals and pathological states confirm the "generalist genes hypothesis" proposed by R. Plomin [11], which suggests that the same set of genes may be responsible for the formation of various cognitive abilities [12].

MOLECULAR-GENETIC STUDIES OF COGNITIVE ABILITIES

In recent years, multiple large-scale studies of the molecular-genetic mechanisms of cognitive development have been conducted. Namely, in 2019, Gurney published the data from a large-scale GWAS study of 1.1 million healthy respondents examining different cognitive characteristics. The association of genetic variants of phosphodiesterase genes (*PDE1C*, *PDE4B*, *PDE4D*) and brain-derived neurotrophic factor gene (*BDNF*) with such cognitive abilities as self-estimated mathematical ability, the number of years of mathematical education, educational level, and combined normalized scores on cognitive tests was reported [13]. In 2018, Lee et al. [14] examined 1.1 million individuals and identified 1271 independent SNPs involved in differential level of learning success with a mediating role of environmental factors. The associated SNPs reside in the genes associated with brain development and neuronal communication. A combined multiphenotypic analysis of educational level and three related cognitive phenotypes made it possible to obtain a polygenic risk score explaining 11–13% of differences in educational level and 7–10% of differences in cognitive performance. Such forecast accuracy significantly increases the efficacy of polygenic risk scores as a predictive tool [14].

The study of the role of the genetic component in individual differences in intelligence are focused on the genes belonging to the family of neurotrophins (*BDNF*), oxidative stress (*LTF*, *PRNP*), and adrenergic (*ADRB2*, *CHRM2*) and dopaminergic systems (*DRD2*, *DRD4*, *COMT*, *SLC6A3*, *DAT*, *CCKAR*). The associations with allelic variant c.957C>T in the *DRD2* gene, c.472G>A in the *COMT* gene, c.46A>G in the *ADRB2* gene, c.1890A>T in the *CHRM2* gene, and c.472G>A in the *BDNF* gene were detected [4]. The allelic variants of the genes encoding cholinergic receptor nicotinic alpha 7 subunit (*CHRNA7*, 15q14), dopamine receptor type 4 (*DRD4*, 11p15.5), dopamine transporter (*SLC6A3*, 5p15.33), and monoamine oxidase A (*MAOA*, Xp11.3) were associated with attention. Episodic memory demonstrated association with allelic variants of genes encoding *BDNF* and type 2A serotonin receptor (*5-HT2A*, 13q14.2), while prefrontally-based executive functions were associated with catechol-O-methyltransferase gene (*COMT*, 22q11.21) [8]. In turn, allelic variants located in promoter region of the serotonin transporter gene (*SLC6A4*, 17q11.2) were related to individual differences in cognitive abilities [15].

Executive functioning and information processing speed were associated with allelic variants of rs17518584 (results in the formation of alternative splicing site in the first exon) of the *CADM2* gene encoding the cellular adhesion molecule [16]. The study of various cognitive abilities, including verbal-numerical, memory, reaction time, and educational level, identified associations of genetic loci located in the *ATXN2L* (encodes a protein of the spinocerebellar ataxia family associated with the development of neurodegenerative diseases), *CYP2D6* (encodes cytochrome P450, which metabolizes hydroxytryptamines (such as serotonin) and neurosteroids), *APBA1* (the gene product interacts with amyloid Alzheimer's disease precursor protein), and *CADM2* genes (encodes a synaptic cell adhesion molecule, which plays an important role in maintaining synaptic contacts in the CNS) [9].

Several studies were performed to examine the role of genetic predisposition to cognitive performance in certain age groups, which indicates peculiarities of cognitive functioning at different stages of ontogenesis. The study of intelligence in 17989 children (aged 6–18) via GWAS approach reported the association of the *FNBP1L* gene with intelligence. This gene encodes formin binding protein 1 like interacting with CDC42 and N-WASP and involved in the pathways binding cell surface signals with actine cytoskeleton [3]. The association of the *FNBP1L* gene with intelligence was also observed in adults [17]. The reading ability in children at the age of 12 was associated with rs807701 in the *DCDC2* gene responsible for neuronal development [6].

The involvement of the genetic component in altered cognitive performance was also demonstrated in adults and elderly individuals in several studies. In particular, GWAS conducted by Debette et al. [18] involving 29076 healthy individuals without dementia or stroke from 19 cohorts (above the age of 45) reported the role of the genes related to the immune

system and ubiquitin pathways in memory formation. Namely, rs4420638 neighboring the apolipoprotein E gene (*APOE*) was associated with a decline in executive functioning (delayed response), while rs11074779 (HS3ST4) and rs6813517 (SPOCK3) located within immune response genes also demonstrated the involvement in variations of certain cognitive abilities. A *cis*-association of the *WDR48* and *CLDN5* genes involved in ubiquitin metabolism with increased risk for developing dementia and gene expression in hippocampus was observed [18]. The role of immune system genes, proinflammatory cytokines, in particular, in cognitive performance was reported by Sasayama et al. [19]. Namely, the analysis of the functional SNP (Asp358Ala) in the interleukin 6 receptor gene (*IL-6R*) demonstrated that enhanced IL-6 and soluble IL-6R levels in 358Ala-allele carriers could negatively affect verbal cognitive performance, which requires long-term memory resources [19].

THE ROLE OF GENES INVOLVED IN NERVOUS AND PSYCHIATRIC PATHOLOGY IN COGNITIVE DEVELOPMENT

Intellectual and emotional activity is believed to be caused by functioning of about 5000 genes. Many of them, including the nBAF subunit gene, have an indirect impact. A number of genes which function as the components of the genetic network of normal intelligence are responsible for the frequency of intellectual disability (ID). The analysis of the OMIM database revealed that one half of existing human genetic disorders have a neurological component, frequently including various aspects of intellectual impairments. This observation is indicative of the involvement of multiple genes in intellectual and emotional functioning [20]. The GWAS conducted in 2016 based on data from 293723 individuals made it possible to detect 74 loci associated with the number of years of education. The detected candidate genes are predominantly expressed in nervous tissue especially during prenatal period and are involved in the processes necessary for brain development. The association was observed for gene variants also involved in developing intellectual disability, autism spectrum disorders, and schizophrenia: rs4500960 in the *TBR1* gene, rs7277187 in the *MEF2C* gene, rs61160187 in the *ZSWIM6* gene, rs2457660 in the *BCL11A* gene, rs11712056 in the *CELSR3* gene, rs192818565 in the *MAPT* gene, rs7306755 in the *SBNO1* gene, rs12987662 in the *NBAS* gene, rs9544418 in the *NBEA* gene, rs1871109 in the *SMARCA2* gene, rs11712056 in the *MAP4* gene, rs10061788 in the *LINC00461* gene, rs9320913 in the *POU3F2* gene, rs11712056 in the *RAD54L2* gene, and rs2964197 in the *PLK2* gene [21].

In 2017, Sniekers et al. [22] conducted GWAS involving 78308 individuals from 13 cohorts for the purpose of detecting the genes affecting cognitive abilities. They identified 336 SNPs from 18 genomic regions, half of which are located in the genes predominantly expressed in brain tissue. They include the *SHANK3* (responsible for formation of synapses), *DCC* (encodes netrin 1 receptor involved in axonal guidance), *ZFHX3* (regulates neuronal differentiation), *APBA1*, *PRR7*, *HCRTR1*, *NEGR1*, *MEF2C*, and *ATXN2L* genes. Association was reported for the *CSE1L* gene involved in apoptosis and cell proliferation. Other genes are responsible for the development of psychopathologies, including schizophrenia (*CYP2D6*, *NAGA*, *NDUFA6*, *TCF20*, *SEPT3*, *FAM109B*, and *MEF2C*), and neurodegenerative disorders, such as Alzheimer's disease (*EXOC4*, *MEF2C*) [22].

A study of 107207 healthy individuals identified 70 independent genomic loci associated with the g factor and educational level. The results obtained demonstrated the enrichment in the genes specifically expressed in neurons and causing monogenic disorders with comorbid intellectual disability (*AFF3*, *AMT*, *ARFGEF2*, *BCL11A*, *C12orf65*, *CLN3*, *DPYD*, *ERCC8*, *FOXP1*, *GMPPB*, *KANSL1*, *KCNH1*, *KMT2D*, *LARGE*, *MEF2C*, *NFIX*, *PDE4D*, *SHANK3*, *ST3GAL3*, *SUOX*, *TCF4*, *THRB*, and *UBA7*) [23]. An association of the g factor with the *TOMM40*, *APOE*, *MEF2C*, and *ABCG1* genes, nucleotide substitutions in which are responsible for Alzheimer's disease, was detected [24]. As a result of meta-analysis of genetic and cognitive data from GWAS of the CHARGE, COGENT, and UK Biobank consortia ($N = 300486$), the association of 709 genes with the g factor was confirmed. Moreover, novel genetic loci which were also associated with nervous system development, formation of brain structures, and development of neurodegenerative and psychiatric diseases were identified. In total, the identified genetic loci explain up to 4.3% of variance in the g factor in independent samples. The common genetic loci associated with individual variance in the g factor, reaction time, and multiple individual somatic characteristics, including vision, arterial pressure, and life expectancy, were observed. The associations were reported for the *GATAD2B* (mutations were revealed in cases of intellectual disability), *SLC39A1* and *TTBK1* (associated with Alzheimer's disease), *ATXN1* and *CWF19L1* (associated with spinocerebellar ataxia type 1), *DCDC2* (associated with dyslexia), *AUTS2* (associated with autism spectrum disorders), *RBFOX1* (associated with nervous system pathology), and *RAI1* (associated with schizophrenia) genes. Six genomic regions associated with the g factor were detected: the gene *NMNAT2* (substitutions were detected in Wallerian degeneration), the gene of noncoding RNA (ncRNA) *ENSG00000271894*, the *SLC4A10* (associated with schizophrenia), *DPP4* (associated with hippocampus volume), *FOXO3* (associated with longevity), *MAPT*, *WNT3*, *CRHR1*, *KANSL1*, and *NSF* genes (related to the infant's head circumference, subcortical volume of the brain and intracranial volume, Alzheimer's and Parkinson's diseases) [25]. The meta-analysis based on 300 studies of

spatial memory in knockout mice was conducted in accordance with the Allen Brain Atlas and Enrichr (gene enrichment) databases. It was demonstrated that the *PDF* genes (post-deletion "forgetfulness" genes), deletions in which result in memory deficit, encoding G-protein-coupled receptors could be involved in regulation of synaptic functioning and have an increased expression in ventral structures of the brain, especially in the hypothalamus [8, 26].

SPECIFIC METHODS FOR THE STUDY OF GENETICS OF COGNITIVE ABILITIES

Another approach for the identification of genetic effects involves the analysis of individuals with extreme levels of cognitive abilities. It can be suggested that an extremely high level of intelligence is caused by the presence of many "positive" alleles and a lower number of "negative" alleles. It is assumed that a large group with extremely high intelligence would be enriched in the alleles associated with the level of intelligence. At the same time, an extremely low intelligence is caused by the presence of variants of genes unrelated to the variance in intelligence level. On the basis of this hypothesis, a "case-control" GWAS involving 1238 individuals with an extremely high intelligence (average IQ was 170) and 8172 individuals of control group was conducted. It succeeded in detecting three loci in the *ADAM12* gene, which were in close linkage disequilibrium (rs4962322, rs496520, and rs1079407). This gene encodes a member of the ADAM metallopeptidase domain family, which is involved in multiple biological processes, including cell-matrix and intercellular interactions during fertilization, muscular development, and neurogenesis [2]. Accordingly, the *ADAM12* gene polymorphisms are also responsible for the development of individual differences in intelligence.

The study of cognitive abilities is also based on the proxy-phenotype approach, which represents a two-stage method for the identification of general genetic variations associated with various cognitive characteristics. The first stage included GWAS of educational level in a sample of 106736 individuals, which identified 69 associated SNPs. The second stage based on the independent sample of 24189 responders included the association analysis of these loci with cognitive abilities. After the correction for multiple comparisons, only three loci survived the significance level: rs1487441, rs7923609, and rs2721173. A polygenic risk score based on SNPs previously associated with memory and the absence of dementia was detected in an independent sample of 8652 elderly individuals. Convergent data obtained as a result of bioinformatics analysis demonstrated the role of four specific genes (*KNCMA1*, *NRXN1*, *POU2F3*, and *SCRT*) involved in neurotransmitter pathways and regulating synaptic plasticity as the main cellular mechanism of learning and memory [27].

Another study performed by Trampush et al. [29] consisted of two stages; the first one involved the identification of genetic loci associated with education level as a result of GWAS. The second stage examined the relation of these genetic loci to the variance in the g factor in an independent sample of 20495 healthy individuals from the Cognitive Genomics Consortium (COGENT). Subsequent meta-analysis of results obtained on a sample of 24189 individuals with neurocognitive data based on the educational level and 53188 individuals from GWAS results of cognitive abilities was conducted. The association of rs1906252 (6q16.1), which previously correlated with the number of years of education [28], together with rs76114856 in the *CENPO* (2p23.3) gene and rs6669072 in close proximity to *LOC105378853* (1p22.2) [29], was reported with the g factor.

LONGITUDINAL STUDIES OF COGNITIVE ABILITIES

Owing to heterogeneity of cognitive characteristics and to identify their changes during ontogenesis caused by environmental and hereditary factors, longitudinal studies are conducted, which allows us to identify more significant relations. Longitudinal studies are carried out on a group of individuals examined within a certain period with mandatory reevaluation of the phenotype of interest [30]. Such studies result in the improved accuracy in obtained experimental data and detected interindividual differences [31]. According to the results of 15 independent longitudinal studies, heredity affects cognitive performance in adolescence and adulthood to a large extent [5]. The meta-analysis of longitudinal data obtained from the studies examining the role of genetic factors in the development of cognitive abilities demonstrated that the impact of heredity increased from 55 to 70% at the age of 13–25 years [32], while other findings indicated its increase from 41% in 9-year-olds to 66% in 17-year-olds [33]. The data obtained can be explained by the greater effect of innovative adaptation effects in children as a response to novel environmental factors compared to adolescence and adults, when genetic factors appear to be predominant [34].

Longitudinal studies can determine the effect of both genetic and environmental factors determining the changes in cognitive characteristics within normal development. Namely, longitudinal studies of cognitive abilities in elderly individuals from the Asian population reported the involvement of education and employment levels along with vascular disorders [35], sleep quality [36], vitamin D levels [37], smoking, diet, obesity, and high glucose consumption [38]. Longitudinal studies demonstrate the significance of cognitive activity [39] and regular physical [40] and social activity in the elderly to maintain cognitive abilities in physiological aging [41].

Longitudinal studies of cognitive characteristics made it possible to determine the causes of changes in intelligence level during aging. According to the results of a longitudinal study conducted for 20 years, it was reported that features of a profession did not affect cognitive functioning in individuals aged 60–80 years, which points to the role of other environmental and genetic processes in the preservation of intelligence upon aging [42]. Specific features of cognitive characteristics (such as reaction time) in the elderly were associated with the alleles of the *COMT* (encodes catechol-O-methyltransferase) and *BDNF* (encodes brain-derived neurotrophic factor) genes [43]. One of the longitudinal studies demonstrated the association of alleles of the *CBP* gene (encodes CREB-related protein) with unchanged high levels of cognitive abilities during aging [44], while the *KIBRA* gene was associated with both maintained cognitive performance and hippocampal volume [45]. A longitudinal study of elderly individuals revealed an association of progressive cognitive decline with a variant of the *VDR* gene (encodes the vitamin D receptor) [46] and with an increased expression of the gene encoding interleukin 6 (IL-6) [47]. Vitamin D functions as a hormone and regulates the expression of 300 genes in humans. Unsurprisingly, longitudinal studies demonstrated an association of vitamin D deficiency with cognitive impairment and depression [48].

Longitudinal studies identify a significant role of epigenetic factors in development of cognitive abilities and their specificity. The epigenetic factors represent mediators of the long-term effect of the environmental factors on formation of cognitive performance in ontogenesis. For instance, a longitudinal study of children subjected to toxic substances within the early postnatal period demonstrated a preserved effect of this action later in ontogenesis at 1, 2, 3, 4.5, and 8.5 years, which represented a decreased IQ compared to the control group of children [49]. Longitudinal studies of children whose mothers were exposed to stressors at early stages of pregnancy reported cognitive delay [50] and pronounced differences in methylation of 2872 CpG islands involved in regulation of immune reactions [51]. The data obtained are congruent with the findings on the involvement of immune system genes in cognitive development [18, 19]. A differential DNA methylation in promoter regions of the genes of serotonin transporter (*SLC6A4*), dopamine D4 receptor (*DRD4*), and monoamine oxidase A (*MAOA*), which were also previously associated with individual differences in cognitive performance, was reported in longitudinal studies conducted in twins [52].

During the postnatal development, individual cognitive characteristics significantly differ within both the period of active growth and aging. Information processing speed and memory, as well as conceptual reasoning, gradually decrease, while vocabulary volume remains almost unchanged during aging. These processes are accompanied by gray matter hypotrophy mainly in the prefrontal cortex [53]. At the genomic level, the changes are caused by modifications in DNA methylation, which indicates the prospects of research in this field aimed at affecting functioning of genes during aging [54]. Therefore, the analysis of the results from multiple longitudinal studies made it possible to conclude that ontogenetic changes in cognitive abilities were caused by complex interaction between environmental, genetic, and epigenetic factors.

THE ROLE OF DNA METHYLATION AND MODIFICATION OF HISTONES IN DEVELOPMENT OF COGNITIVE CHARACTERISTICS

The development of cognitive abilities is mediated by epigenetic factors involved in the formation of brain structures and functioning and providing specific regulation of gene expression depending on the age and type of cells [55]. Previously, it was reported that environmental factors demonstrated a more significant effect in DNA methylation in children compared to adults [56]. The neuroepigenetic landscape may significantly differ between brain regions, while changes in the regulation of chromatin-modifying enzymes may significantly affect cognitive characteristics.

These enzymes directly interact with such transcription factors as nuclear factor NF-κB, Nanog, and Oct4, providing site-specific epigenetic regulation [57]. The optimal performance in cognitive tasks depends on a precise tuning between neuronal activation and inhibition, which is maintained by strictly regulated initiation and repression of genes. An important significance in these processes belongs to histone deacetylases, which modulate the expression of genes related to synaptic plasticity and involved in regulation of cognitive functioning. Namely, murine studies demonstrated that stress early in life could affect future cognitive development via changes in expression in genes encoding histone deacetylases [58]. In addition, changes in chromatin modifications as a response to learning were reported to be caused by acetylation, phosphorylation, and methylation of histones [59]. In order to estimate the mechanism of environmental impact on cognitive functioning, in 2019, Lewis et al. [60] conducted an analysis of the role of epigenetic regulation of dopaminergic system genes in variation of cognitive abilities. The use of a microarray to detect the methylation profile of CpG sites neighboring six dopaminergic system genes helped to analyze differences in response inhibition and memory performance in monozygotic twins. Between twins, differences in *DRD4* gene methylation related to differentiation in short-term memory capacity were revealed, while differences in methylation of the *DRD1*, *DRD2*, *COMT*, *DBH*, and *DAT1* genes caused individual differences in inhibition of cognitive reactions. The data obtained point to a significant impact of epigenomic modifications in the mainte-

nance of complex cognitive characteristics and to a dissociative effect of methylation of dopaminergic genes in some of them [60].

Alterations in epigenetic regulation of cognitive abilities were detected in cognitive aging. These variations are caused by modifications in DNA methylation, expression of noncoding RNAs (ncRNAs), and post-translation modifications of histones [61]. In particular, analysis of DNA methylation in the frontal and temporal cortex, pons, and cerebellum demonstrated age-dependent changes in more than 27000 CpG sites related to differences in cognitive characteristics [62]. Systematization of published data made it possible to identify 55 genes involved in epigenomic regulation and associated with cognitive impairments. These genes were divided into four categories: (1) involved in DNA methylation (*DNMT1*, *DNMT3B*, and *FTO*); (2) involved in histonal modification (*CREBBP*, *CUL4B*, *EHMT1*, *EP300*, *EZH2*, *HLCS*, *HUWE1*, *KAT6B*, *KMT2A*, *KMT2D*, *KMT2C*, *NSD1*, *WHSC1*, and *UBE2A*); (3) necessary for deletion of side groups of histones (*HDAC4*, *HDAC8*, *KDM5C*, *KDM6A*, and *PHF8*); (4) involved in chromatin remodeling (*ACTB*, *ARID1A*, *ARID1B*, *ATRX*, *CHD2*, *CHD7*, *CHD8*, *SMARCA2*, *SMARCA4*, *SMARCB1*, *SMARCE1*, *SRCAP*, and *SS18L1*) [10]. Moreover, epigenetically caused differences in cognitive abilities may be related to the changes in the *HMGN1* gene previously reported to be associated with developing neuropsychiatric phenotypes. The *HMGN1* gene (high mobility group nucleosome-binding domain 1) encodes the nucleosome-binding protein affecting chromatin activity. The changes in *HMGN1* gene expression are responsible for neurological functions and were detected in such pathologies as X-linked cognitive impairment (Fragile X syndrome), autism spectrum disorders, and Down syndrome. The *HMGN1* gene negatively regulates methyl-CpG-binding protein 2 (MeCP2), mutations in which are observed in Rett syndrome cases [24].

THE ROLE OF NONCODING RNAs IN COGNITIVE DEVELOPMENT

At least 85% of the whole human genome is transcribed (i.e., information from DNA is transferred into RNA), but only 1.2% is translated into proteins. The majority of produced molecules are registered as noncoding RNAs (ncRNAs), including microRNAs and long ncRNAs, which represent epigenetic factors and play a functional role in controlling the genome [63]. Some evidence on the role of microRNAs in the development of cognitive characteristics was obtained. In neurons, several microRNAs enrich synaptic regions and can directly bind to more than 90% of synaptic proteins. Cognitive processes such as learning and memory share cellular and molecular mechanisms, which frequently comprise experience-dependent changes in the strength of synaptic connections. This process is called synaptic plasticity [64]. Neurons are able to change the set of synaptic connections and the relative strength of each of these connections in time as a response to sensory experience and other environmental signals. Such plasticity characteristics underlie learning, memory, and other cognitive abilities and the ability of the brain to recover from injuries and stroke. Therefore, molecular pathways regulating synaptic plasticity are also involved in the development of cognitive characteristics and their changes. Long ncRNAs such as *KCN2AS* and *BC1/200* are actively involved in these mechanisms [65].

About 40% of all ncRNAs are expressed in the brain, where they exhibit precise temporal and spatial patterns of expression [65]. Antisense long ncRNAs were reported to locally regulate mRNA stability of protein-encoding genes involved in synaptic plasticity such as *BDNF*, *GDNF*, *EPHB2*, and *KCNA2* [66]. In addition, activation of the long ncRNA MEG3 improved cognitive performance via inhibition of the PI3K/Akt-signaling pathway. Interestingly, up to 80% of proteins encoding loci in mammalian genomes express several forms of antisense transcripts together with corresponding mRNAs. These antisense ncRNAs can affect the regulation of associated protein encoding genes and demonstrate an additional trans-effect [67]. The expression of many long ncRNAs in the brain depends on the type of neurons and their localization in specific neuroanatomic formations and on the expression of protein-encoding genes involved in the functioning of these structures [68]. It was observed that long ncRNAs had an expression pattern similar to neurogenesis genes, which proves their role in CNS development via regulating the expression of protein-encoding genes [69]. Long ncRNAs play a key role in brain development and the formation of higher cognitive abilities. For instance, long ncRNA Malat1 is involved in synapse formation and regulation of alternative splicing in neurons; Gomafu affects alternative splicing in neurons depending on their activity. Moreover, long ncRNAs can be considered as precursors of piRNAs (Piwi-interacting RNAs), siRNAs (small interfering RNAs), and microRNAs. Thus, miR-675 is formed from exon 1 of the long ncRNA H19. Long ncRNAs can also directly bind to microRNAs to affect the transcriptional landscape and to compete with them for binding sites. For example, BACE1, which is involved in development of Alzheimer's disease, physically blocks the binding of miR-485-5p to the target BACE1mRNA binding site. Therefore, long ncRNAs represent "sponges" for microRNAs, thus suppressing their function [70].

MicroRNAs have different expression patterns in the brain depending on the region, cell type, and stage of development. Their expression profile changes under neuronal activation as a response to behavior and chemical/electrical stimulation. The dynamic changes in microRNA levels regulate the expression of genes involved in such cognitive processes as learning

and memory. Moreover, cognitive decline (i.e., dementia) is accompanied by an impaired expression of many microRNAs not only in the affected regions of the brain but also in the cerebrospinal fluid and plasma. This makes it possible to use microRNAs as biomarkers for early detection and assessment of cognitive dysfunction. Since microRNAs target many genes and pathways, they can represent key molecular signs that allow us to understand the mechanisms of cognitive impairments and to develop potential therapeutic agents [64]. The vast diversity of neurons in the brain comes from a limited pool of neuronal stem cells processed through different gene expression programs to acquire specific phenotypes. MicroRNAs are involved in the regulation of neuronal differentiation via changing the expression profiles of genes important for functioning of temporal and spatial cells [71]. Differential expression of specific microRNAs depending on neuronal type [72] and function was proved. Moreover, the accumulation of distinct microRNAs in axons, dendrites, and synapses was detected [73]. MicroRNAs are ideal candidates controlling complex processes, including cognitive characteristics, in the brain owing to their abundance and regulated temporal and spatial expression [74].

In 2010, Gao et al. [75] published data on the role of brain-specific miR-134 in regulation of memory and synaptic plasticity. This microRNA affects SIRT1 via posttranscriptional regulation of CREB expression. In turn, SIRT1 modulates synaptic plasticity and memory formation [75]. Experiments conducted in mice demonstrated the impact of another microRNA (miR-128b) in the transfer from retrieval of the initial fear memory to the formation of the novel fear extinction memory [76]. The experiments conducted in rats reported the role of miR-182 expressed in amygdala in suppression of long-term fear memory (without affecting short-term memory of auditory fear). A suppression of miR-182 level induced by learning promotes the formation of long-term memory in amygdala via derepression of the key actin-regulating proteins [77]. Various stressful stimuli may result in impaired cognitive functioning. In particular, the use of three different models of stress was demonstrated in these processes of stress-induced increase in miR-132 and, hence, in a decrease in its target—acetylcholinesterase. Within a moderate model of predator-induced anxiety, a long-term increase in miR-132 in the hippocampus accompanied by a reduced acetylcholinesterase activity was demonstrated, which resulted in a cognitive deficit [78]. Empirical data from another research group which studied the effect of stress on microRNA-mediated cognitive changes indicate that the level of mature miR-132 in the hippocampus significantly increases 30 min after formation of fear memory (time-related type of learning) and returns to its initial value after 2 h. The mice knockdown by miR-132 expression proved an impaired acquisition of fear memory [79]. The miR-132 interacting with CREB influences synaptogenesis via its effect on dendrite branching and spinogenesis (formation of spines). In a mature nervous system, an impaired miR-132 regulation plays a role in several neurocognitive disorders characterized by aberrant synaptogenesis. In addition, the role of miR-132 under normal physiological cognitive development was studied. The presentation of a spatial memory task in murine experiments caused a 1.5-fold increase in miR-132 expression in the CA1, CA3, and GCL layers of hippocampal excitatory cells in these animals. It should be noted that miR-132 expression has to be maintained in a limited range to provide normal learning and memory formation [80]. The study of specific activity of miR-132 demonstrated its effect on integration of novel neurons in the hippocampus [81].

Several cognitive characteristics such as learning and memory are affected in a dose-dependent manner by the IQGAP1 scaffold protein (IQ motif containing GTPase activating protein 1), whose expression is regulated via miR-124 binding to the 3'UTR of the corresponding mRNA. Notably, this region contains rs1042538, whose allelic variants were shown to alter microRNA binding to IQGAP1 mRNA. The rs1042538* T-allele carriers demonstrated an increased expression of the *IQGAP1* gene compared to those bearing the rs1042538*A allele, together with better performance in the haptic sensory test (which relates the object's shape with its position) [82]. The role of miR-124 in the regulation of learning and memory was also reported by Malmevik et al. [83] while examining the role of specific microRNAs in neuronal processes in the hippocampus. Inhibition of miR-124 results in improved spatial learning and working memory by change in the expression of genes associated with synaptic plasticity and neuronal transmission. In contrast, inhibition of miR-9 (affects genes related to endocytosis, adhesion, and cell death) and miR-34 (affects transcription of genes related to transduction of neuroactive ligand receptors and cell communication) results in impaired spatial learning and memory prior to learning [83]. Another microRNA, miR-23b, is involved in the recovery of injury-induced cognitive deficit via binding to the 3'UTR region of *ATG12* mRNA, causing inhibition of neuronal autophagy [84].

Genome-wide association studies and their systematization also point to a significant role of certain microRNAs in cognitive functioning. For instance, meta-analysis of GWAS conducted in 2017 [85] identified two loci in the *MIR2113* (encodes miR2113) and *AKAP6* genes associated with cognitive abilities. Moreover, elderly individuals without dementia were examined in detail for the association of the variants of these genes with episodic and working memory, vocabulary, speed of perception, and reaction time. As a result of this study, an association of rs17522122T-allele in the *AKAP6* gene with reduced episodic and working memory, vocabulary, and reaction speed was reported. At the same time, the rs10457441*T-allele in

the *MIR2113* gene was associated with an accelerated decrease in episodic memory [85]. In 2018 [86], a study of 90 elderly monozygotic twins (aged 73–95) involved the analysis of 754 plasma-circulating microRNAs and their association with the cognitive parameters assessed with the Mini-Mental State Examination (MMSE) and Cognitive Component Score (CCS). Both individual and pairwise analyses were performed to assess cognitive abilities. Twenty-three microRNAs were observed to be nominally associated with MMSE and CCS levels in pairwise analyses. Elderly individuals with reduced cognitive levels were characterized by an increased expression of several microRNAs compared to those with better cognitive performance. The miR-151a-3p, miR-212-3p, and miR-1274b were associated with CCS levels in both pairwise and individual analyses [86].

The role of several environmental factors in altered binding of microRNAs to mRNA targets should be noted. In particular, listening to music was observed to affect the regulation of several genes, many of which are activated as a response to the singing of songbirds. Therefore, the presence of microRNA-related epigenetic regulation of gene expression caused by listening to music is assumed. In particular, the effect of listening to classical music for two hours on microRNA expression in peripheral blood in professional musicians was compared to other activities of the same duration. A pronounced activation of five miRNAs, namely, hsa-miR-3909, hsa-miR-30d-5p, hsa-miR-92a-3p, hsa-miR-222-3p, and hsa-miR-30a-5p, was observed, while two miRNAs (hsa-miR-6803-3p and hsa-miR-1249-3p) demonstrated reduced levels. These microRNAs play a critical role in cell differentiation, activation of CREB and dopamine signaling, and the regulation of apoptosis. It is assumed that hsa-miR-222-3p and hsa-miR-92a-3p target the *FOXP2* gene, whose expression is suppressed by microRNA binding during listening to songbirds. The reaction of miR-30d and miR-222 was confirmed in experiments on birds. The miR-222 is induced by the ERK cascade, which plays an important role in functioning of motor neurons and neuron plasticity. Moreover, miR-222 is activated by FOSL1, encoded by the gene of the FOS family of transcription regulators stimulated by motor-auditory stimuli. The miR-222 and miR-92 provide neurite growth via negative regulation of neuronal growth inhibitor, PTEN, and via activating CREB expression and phosphorylation [87]. The analysis of published data also demonstrated the role of epigenetic factors in development of depressive disorders [88], aggressive behavior [89], and aging [90]. This indicates the necessity of studying noncoding RNAs within brain functioning owing to the possibility of affecting both cognitive abilities and socially significant deviations in behavior and mental health.

CONCLUSIONS

To date, published findings have accumulated the results of large-scale studies on the role of genetic factors in the development of individual cognitive abilities. The data on associations of many genes with various cognitive characteristics were obtained. The pathogenetic pathways based on the effect of allelic variants of these genes on altered cognitive abilities were proved. It is suggested that the results obtained will both expand our knowledge on the molecular mechanisms resulting in individual differences in cognitive performance and provide the possibility to determine the ways of their potential improvement via targeting of specific genes. In this regard, the study of epigenetic factors that can be used for reversible and safe regulation of the functions of specific genes in the brain is prospective. The scientific literature has accumulated data on the role of specific noncoding RNAs and their involvement in different mechanisms of cognitive performance, and we assume that the use of microRNAs and their derivatives will make it possible to correct cognitive decline in the very near future. Moreover, the analysis of environmental factors as regulators of epigenetic mechanisms in cognitive performance will facilitate the use of various environmental factors for the correction of cognitive impairment.

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COMPLIANCE WITH ETHICAL STANDARDS

The authors declare that they have no conflict of interest. This article does not contain any studies involving animals or human participants performed by any of the authors.

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