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## Psychogenetics of Human Spatial Abilities

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### Abstract

**Introduction.** This scientific review aims to understand the etiology of human spatial abilities. Spatial thinking is a complex combination of cognitive abilities related to recognizing, transforming, and storing information about objects and predicting the transformation of interactions among them under the influence of other factors. In this work we tend to provide the most complete description of spatial abilities as a specific type of mental activity that underlies practical and theoretical problem-solving in the framework of psychology and genetics to emphasize the importance of synthesizing the experimental data and psychological foundations of spatial intelligence.

**Theoretical Basis.** This review presents the results of genetically informative studies of human spatial abilities. Since the ability to orientate in space is an integral characteristic of all living organisms, spatial abilities are of evolutionary and adaptive importance. In cognitive psychology, spatial skills are understood as the ability to operate with mental spatial images, schemes, and models of reality. Moreover, these abilities vary widely among individuals. The analysis of the etiology of these individual differences showed a significant contribution (69 %) of hereditary factors in the formation of spatial abilities. The results of twin studies indicate the need for searching specific polymorphic variants in genes involved in the development of spatial skills. Large-scale longitudinal studies have shown that spatial abilities are a reliable predictor of individuals' achievements in science, technology, engineering, and mathematics (STEM). Therefore, studying their molecular-genetic mechanisms merits special attention.

**Results and Discussion.** Various experimental studies on the psychogenetics of human spatial abilities first reported very interesting findings confirming their hereditary nature. Thus, spatial intelligence is a moderately heritable trait, which development involves a wide range of genetic

factors causing the activation of various signaling pathways of the metabolism of the human organism.

## Keywords

intelligence, spatial abilities, behavioral genetics, cognitive traits, gene, polymorphic variant, individual differences, predictor, correlation, heritability

## Highlights

- ▶ Spatial abilities represent a complex combination of cognitive components that ensure the integrity of the intellectual development of an individual.
- ▶ Spatial abilities are of evolutionary and adaptive importance for all individuals, as they provide a more productive interaction with the environment.
- ▶ Spatial intelligence is a moderately heritable cognitive trait (30–50 %). Various genetic factors contribute to 69 % of individual differences in spatial abilities.
- ▶ Spatial thinking is an effective predictor of individuals' academic success in advanced scientific areas – STEM disciplines (Science, Technology, Engineering, and Mathematics).

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## Introduction

Large-scale longitudinal studies involving both normative and gifted samples have shown that spatial ability is a reliable predictor of success in STEM disciplines (Super & Bachrach, 1957; Shea, Lubinski, & Benbow, 2001; Webb, Lubinski, & Benbow, 2007; Wai, Lubinski, & Benbow, 2009; Lubinski, 2016). It is not surprising that the study of these abilities has recently gained considerable attention of researchers in the field of cognitive psychology. Spatial abilities are of evolutionary and adaptive importance because any living organism must be able to navigate in its surrounding environment to survive (Newcombe & Frick, 2010).

Spatial abilities represent a combination of several cognitive components, including *spatial visualization* (complex multi-stage manipulations of spatial information), *mental rotation* (mentally rotating spatial forms), *spatial relationships* (perception of relationships among objects), *closing speed* (understanding a spatial form in the presence of distracting content, e.g., integration of visual stimuli into a meaningful whole), *flexibility of closure* (search for a visual field to find a specific spatial form), and also *spatial scanning*, *motion detection*, *mechanical reasoning*, *length estimation*, *directional thinking*, *spatial memory*, etc. (Carroll, 1993; Colom, Contreras, Shih, &

Santacreu, 2003; Uttal, Miller, & Newcombe, 2013; Weisberg, Schinazi, Newcombe, Shipley, & Epstein, 2014; Rimfeld et al., 2017).

In cognitive psychology, spatial intelligence is regarded as an important characteristic of the general intellectual development of an individual. Linear theories of multiple intelligences and their structural-hierarchical models pay special attention to the phenomenon of human spatial thinking (Ananyev & Rybalko, 1964).

Several studies have analyzed the impact of spatial abilities on individuals' mathematical skills (Snow, 1999; Stanley, 2000; Colangelo, Assouline, & Gross, 2004). Currently, global cognitive psychology recognizes the critical role of the development of spatial thinking as a predictor of an individual's academic success in advanced scientific areas – STEM disciplines (Science, Technology, Engineering, and Mathematics) (Lobanov, Radchikova, & Semenova, 2013; Wai et al., 2009; Khine, 2017). Results from large-scale studies of spatial abilities demonstrate that they play a key role in structuring educational and professional outcomes among both the general population and talented individuals (Shea et al., 2001; Webb et al., 2007; Wai et al., 2009).

Russian studies also recognize the role of spatial abilities in cognitive development of a child. Thus, it is noted that insufficient degree of spatial orientation affects school performance of students (Semago & Semago, 2005). Subsequent studies on the ability of students to operate with mental images showed that adolescence is a sensitive period for the development of spatial intelligence (Panfilov & Panfilova, 2015).

The results of the studies carried out by I. S. Yakimanskaya also provide evidence for the role of spatial intelligence in determining the success of academic training in natural sciences and mathematics, associated with graphic arts and engineering design activities (Yakimanskaya, 2008).

## **Theoretical Basis**

### ***The role of hereditary factors in the development of spatial abilities***

The cognitive abilities vary in the degree of expression in the population. Despite the high heritability of these traits (30–80 %), the involvement of genetic factors in cognitive functioning remains poorly understood (Kovas, Haworth, Dale, & Plomin, 2007; Lee, Henry, Trollor, & Sachdev, 2010; Deary, 2012; Malykh et al., 2019). Perhaps the insufficient information content of the research data is explained by the fact that a high percentage of the contribution of hereditary factors to the development of traits is provided through a cumulative genetic effect. This makes it very difficult to obtain a more detailed picture of the processes of heritability of intellectual abilities. The discovery of the genes involved in the formation of a particular cognitive function is of particular interest (Deary, Johnson, & Houlihan, 2009; Knowles et al., 2014; Knowles, Viar-Paxton, Riemann, Jacobi, & Olatunji, 2016). Therefore, the identification of genetic markers associated with human mental health in combination with psychological aspects is one of the primary objectives of the interdisciplinary academic field – psychogenetics.

Today, there are only few genetically informative studies of human spatial abilities, which increases the degree of their relevance for researchers. The genetically informative studies of spatial abilities by using various diagnostic techniques, have shown that spatial intelligence is moderately heritable (30–50 %) (Kan, Wicherts, Dolan, & van der Maas, 2013; Knopik, Neiderhiser, De Fries, & Plomin, 2017).

Similar results were obtained in a large-scale twin study of spatial abilities (Shakeshaft et al., 2016; Rimfeld et al., 2017). The results of analysis showed that genetic factors explain 69 % of

individual differences in spatial abilities (Rimfeld et al., 2017). These same genetic factors partially coincide with genetic factors involved in the formation of individual differences in general intelligence (Rimfeld et al., 2017).

Another study showed that the presence of a moderate correlation between mathematical and spatial abilities is largely determined by the contribution of heredity. However, we should note that the analysis was carried out using a relatively small sample size ( $n = 278$  pairs of twins) with a wide age range (6–12 years), which somewhat reduces its statistical power (Thompson, Detterman, & Plomin, 1991). Nevertheless, the stated hypothesis was confirmed in other works. Thus, the study of spatial skills in their correlation with mathematical abilities on the sample of 4174 pairs of 12-year-old twins showed that genetic factors explained ~60 % of the observed correlations between spatial and mathematical abilities, while a significant part of these correlations was characterized by environmental influences (Tosto et al., 2014). The results of another experimental study (involving 1250 pairs of twins and 413 twins without pairs at the age of 20) assessing spatial intelligence also demonstrated a significant contribution of hereditary factors (~56 %) to individual differences (Shakeshaft et al., 2016).

In addition, according to the literature, there is evidence of a partial genetic correlation between spatial abilities and general intelligence ("g") (Robinson et al., 2015). As a rule, general intelligence ("g") accounts for more than half of individual differences in cognitive abilities. However, there are also domain-specific areas responsible for the manifestation of various types of intellectual traits (Plomin & Spinath, 2002). This view is largely consistent with findings from cognitive neuroscience, which suggest that certain domains are associated with relatively different brain circuits (Lenartowicz, Kalar, Congdon, & Poldrack, 2010). The identification of genes involved in specific cognitive domains may be more effective than the search for genetic markers associated with the development of general intelligence, especially since the specifically focused approach is, in fact, multivariate and statistically more powerful than one-dimensional analysis of general neuropsychological tasks (Bearden & Freimer, 2006; van der Sluis, Verhage, Posthuma, & Dolan, 2010).

Thus, the results of twin studies offer a challenge for finding specific polymorphic variants in genes involved in the development of spatial abilities.

## **Results and Discussion**

### ***Molecular-genetic aspects of the mechanism of the development of human spatial abilities***

The first results of molecular-genetic studies on spatial thinking were obtained in research projects devoted to studying the morphology/physiology of the human nervous system. The development of methods of biomedicine (GWAS – Genome-wide association studies), the analysis of transcriptome, exome, and proteome) has significantly improved the quality of analysis of endogenous correlates involved in the development and functioning of tissues and divisions of the central nervous system (CNS). These studies showed the impact of genetic factors on various kinds of complex neurological diseases and psychiatric disorders (temporal lobe epilepsy, vascular dementia, Alzheimer's disease, depressive pathologies, bipolar disorder, autism spectrum diseases, etc.) (Thompson et al., 2004; Kim et al., 2015; Hibar et al., 2016). However, along with work on the pathophysiology/pathogenetics of the central nervous system, research groups are currently interested in the study of normal brain functioning.

Thus, several studies noted that the formation of the hippocampus, optimal synaptic plasticity in the cells of the cerebral cortex play an important role in the development and formation of spatial intelligence. The hippocampus is a part of the limbic system of the brain and hippocampal formation, involved in the development of mechanisms for memory consolidation, spatial navigation, and the manifestation of emotions. The navigation in the environment can be achieved by using either of two systems of memory, each with a different strategy (Hartley & Burgess, 2005). The 'spatial' strategy involves the establishment of associations among guiding lines in the environment to develop a cognitive map and is associated with increased gray matter and activity in the hippocampus. The 'response' strategy involves the analysis of stimulus-response relationships such as a series of turns from certain points in space. The response strategy is associated with increased gray matter levels and increased brain activity in the caudate nucleus of the striatum (Iaria, Petrides, Dagher, Pike, & Bohbot, 2003; Bohbot, Lerch, Thorndyraft, Iaria, & Zijdenbos, 2007). The studies showed that humans spontaneously use one of these two alternative navigation strategies with almost equal frequency to solve a navigation task. This choice correlates with activity of functional magnetic resonance imaging (fMRI) and density of gray matter (Banner, Bhat, Etchamendy, Joober, & Bohbot, 2011).

The study of structural changes of the gene of brain-derived neurotrophic factor (*BDNF*) has also demonstrated the importance of the hippocampal system in the formation of human spatial intelligence. The polymorphic variant *rs6265* (*c.196G>A*), which leads to the replacement of valine (Val) by methionine (Met) at codon 66 of the *BDNF* gene, causes a decrease in the level of secretion of the brain-derived neurotrophic factor involved in the survival and differentiation of nerve cells during their development (Bath & Lee, 2006). Subsequently, the low expression of *BDNF* protein can lead to the impairment of hippocampal-dependent cognitive functions, such as episodic and spatial memory and recognition. Individuals with one or two copies of the allele of Met have a decrease in fMRI of the hippocampus and gray matter, compared to individuals homozygous for Val (Hariri et al., 2003; Bueller et al., 2006). In addition, as discovered in further analysis by Banner et al., the polymorphic variant *rs6265* is associated with the choice of the spontaneous navigation strategy by an individual. Thus, Met carriers showed a reduced likelihood of using the hippocampus-dependent spatial strategy. The obtained data enable us to conclude that the *BDNF* gene can be considered as a candidate gene involved in the spontaneous strategy of navigation choice (Banner et al., 2011).

A subsequent study of genetic determinants and products that provide normal synaptic plasticity of cells of the limbic system of the brain and its basal nuclei of the hemispheres, coupled with the study of the above navigation paradigm of virtual reality in groups of young/elderly people, showed the presence of an association of the polymorphic variant *rs17070145* (*c.1185-3222C>T*) of the *KIBRA* gene with the degree of manifestation of spatial thinking in individuals, depending on age differences (Schuck et al., 2013; Piras et al., 2017). We should note that Piras et al. (2017) also analyzed the association of the polymorphic variant *rs17070145* of *KIBRA* with both an improvement in episodic memory in the elderly and a reduced risk of late-onset Alzheimer's disease. However, the mechanism of this protective effect is still not fully understood.

The study by Mueller et al. (2014) demonstrates the involvement of the gene of monoamine oxidase A (*MAOA*) localized at X chromosome in the development of spatial skills. The *MAOA* gene have a repeat of 30 bp in the promoter region (*MAOA-LPR*), which affected efficiency of transcription *in vitro*. Individuals with long alleles (3.5 repeats and 4 repeats) demonstrated



greater transcriptional activity than carriers of short alleles (3 repeats) (Sabol, Hu, & Hamer, 1998). According to the literature, the differences in the variable of number of tandem repeats of the *MAOA* gene are associated with the development of a variety of mental disorders, including anxiety, depression, and schizophrenia, due to cognitive impairments such as spatial learning and memory dysfunction (Dannlowski et al., 2009; Mueller et al., 2009). Neurobiological studies also support the involvement of MAOA protein in the normal functioning of spatial intelligence, but mainly by measuring the levels of MAOA enzyme activity in mice (Steckler et al., 2001).

A study carried out by S. C. Mueller and colleagues to assess the levels of transcription of the *MAOA* gene in the formation of spatial thinking in 69 adolescents, preferably males, showed that high activity of the enzyme monoamine oxidase A contributes to more effective spatial learning and better memory of an individual. It is noteworthy that after the identification of the gene of brain-derived neurotrophic factor (*BDNF*) as a possible marker of normal development and functioning of episodic memory and spatial navigation, the obtained data on the *MAOA* gene significantly expand the understanding of the mechanisms of deamination of neurotransmitters involved in the activity in the prefrontal cortex, such as dopamine, serotonin, and norepinephrine. Perhaps, *BDNF* can modulate spatial navigation through the hippocampus, whereas MAOA can modulate spatial navigation at the prefrontal level (Spiers, 2008). Presumably, the level of production of MAOA protein may indirectly influence spatial cognition by affecting the function of catecholamines in the prefrontal cortex/striatum. The higher transcription of the highly active *MAOA* gene in men provides greater production of the enzyme, followed by increased deamination of catecholamines and, in turn, faster clearance of neurotransmitters, which provides a faster turnover of available monoamines. This is consistent with the idea that individuals with a low-activity variant may have higher level of homovanillic acid, the main metabolite of catecholamines in the CNS, but exhibit poorer performance on executive tasks (Ducci et al., 2006). However, these results should be clarified at the behavioral level, given the conflicting evidence that individuals with the low level of expression of *MAOA* make better financial decisions and achieve higher educational attainment at a similar IQ and given the small sample size of respondents as well (Mueller et al., 2014).

In addition to the involvement of the limbic system of the brain, the functioning of spatial thinking, as it turned out, involves the parahippocampal regions, the transverse occipital sulcus, and the retrosplenial cortex (RSC) localized in the parietal-occipital sulcus, which cells process and store information about objects (Maguire, 2001; Grill-Spector, 2003; Dilks, Julian, Paunov, & Kanwisher, 2013). Neuroimaging studies showed that these areas of the brain respond more strongly when viewing navigation-relevant 'events' compared to responses to stimuli that are not related to navigation (e.g., objects), and play a key role in the development of human spatial skills (Aguirre, Zarahn, & D'Esposito, 1998; Epstein & Kanwisher, 1998; Nakamura et al., 2000; Hasson, Harel, Levy, & Malach, 2003; Epstein, 2008). The electrophysiological studies *in vivo* in the rats prove this fact, demonstrating that spatial learning enhances stimulation of the RSC cells (Smith, Barredo, & Mizumori, 2012). The study of architectonics of the retrosplenial cortex *in vivo* in mice by using two-photon imaging showed that spatial navigation in objects is largely determined by the optimal level of the expression of the *c-Fos* gene, mediated by the activation of the factor of *CREB* transcription (*cAMP-responsive element-binding protein*) (Czajkowski et al., 2014). The nature of this transcriptional response depends on the type and strength of stimulation of the nerve cells. The CREB-dependent expression of genes has been previously shown to

be involved in many different aspects of nervous system function, from embryonic development to neuronal survival, as well as synaptic, structural, and intrinsic plasticity (Barco & Marie, 2011; Barry & Commins, 2011).

The genetic factor *c-Fos* itself is a member of the *Fos* family (leucine zipper proteins, regulators of cell proliferation, differentiation, and transformation), belonging to the vast group of early response genes (*Immediate Early Genes, IEG*), which also includes the *Zif268* and *Arc* genes. All these immediate early response genes act as markers of the consolidation of the mechanisms of neural activity during the restoration of spatial memory. The consolidation of systems is a process involving the stabilization of memory traces in the neocortex over time. The medial prefrontal cortex becomes increasingly important over time in retrieving old memories, but the timing of its involvement is unclear, and little attention has been paid to the contribution of other areas of the neocortical brain to distant memory. Studies of the levels of *Zif268*, *Arc*, and *c-Fos* transcripts in the hippocampus, medial prefrontal and entorhinal, perirenal, retrosplenial and parietal cortex of the brain of Wistar rats during navigation in the Morris water maze showed that the systemic interaction of all the above factors provides normal cognitive function in animals (Barry, Coogan, & Commins, 2016).

Several studies assessing the expression of levels of *Fos* proteins in neurons demonstrate their interaction with *SATB2* protein. *SATB2* is a highly conserved nuclear protein that is expressed in embryonic brain cells – namely, in the superficial cortical layers – and determines the identity of the corpus callosum and subcortical projection neurons (FitzPatrick et al., 2003). During the ontogenesis of the CNS, the expression of *SATB2* protein shifts towards the deep cortical layers, and, ultimately, the most significant levels of *SATB2* production in the adult brain are observed in the pyramidal cells of the brain and in the *CA1* region of the hippocampus, which indicates its involvement in cognition (Huang et al., 2013). Patients with defects in the gene *SATB2* usually suffer from moderate to severe mental retardation, but the mechanism of intellectual disability in individuals remains understudied. However, in the study by Li et al. with the use of model animals showed that in heterozygous mice and mice with *SATB2* conditional KO (*SATB2 cKO*) spatial and working memory were considerably disrupted. The low expression of immediate early genes (IEG), including *Fos*, *FosB*, and *Egr1*, was also noted, especially in animals with a deleted gene. In addition, it was found that the product of the *SATB2* gene can regulate the expression of *FosB* protein by directly binding to its promoter. Thus, we may conclude that *SATB2* plays an important role in the development of spatial/working memory mechanisms, regulating the indirect activation of IEG and synaptic plasticity of the hippocampus (Li et al., 2017; Cera et al., 2019).

Other experimental studies on the analysis of spatial navigation in animals described the importance of polymorphic variants of the *S100B* gene located on chromosome 21 and encoding a protein of member family of the *S100*  $\text{Ca}^{2+}$  – binding signal proteins which are actively produced in cells of the immune system, astrocytes, Schwann cells, melanocytes, chondrocytes, and adipocytes (Donato et al., 2009; Donato et al., 2013). It was noted that increased levels of expression of *S100B* in mouse cells contributed to the deterioration of the mechanisms of orientation in rodents and their behavior in general, by reducing post-tetanic excitatory postsynaptic potentials in the hippocampus and impairing spatial learning. This may be explained by the fact that *S100B* protein secreted by astrocytes has different (trophic, toxic) effects on neurons and microglia, which depends on the level of production (Van Eldik & Wainwright, 2003; Donato et al., 2009; Sorci et al., 2010). Moreover, several studies emphasize that transgenic mice at *S100B* exhibit an

increased susceptibility to perinatal hypoxia-ischemia, and overexpression of S100B accelerates pathology similar to Alzheimer's disease, with increased astrogliosis and microgliosis (Wainwright et al., 2004; Mori et al., 2010). In contrast, S100B knockout mice show enhanced spatial skills, fear stimulus memorization, and increased long-term potentiation in the CA1 region of the hippocampus (Nishiyama, Knöpfel, Endo, & Itohara, 2002). This indicates that the extracellular expression of S100B protein may be a regulator of synaptic plasticity, although the mechanism underlying this activity is not yet clear (Donato et al., 2013).

Subsequent molecular-genetic analysis of *S100B* gene in a cohort of respondents from China and an assessment of the levels of expression of its product in human post-mortal brain tissue showed an association of polymorphic variants *rs3788266* and *rs11542311* with the development of spatial intelligence in an individual, and also indicated that the degree of production of S100B protein does not correlate only with pathological conditions of the brain, but also with its normal functioning in healthy individuals, ensuring the stability of neuronal plasticity and conduction (Epstein & Vass, 2014; Kong, Song, Zhen, & Liu, 2017). Previously, it was found that *rs3788266* is a marker of the risk for bipolar affective disorder, and *rs11542311* is a marker of the risk for schizophrenia (Liu et al., 2005; Roche et al., 2007). Additionally, it was noted that overexpression of S100B in blood serum negatively influenced the course of these types of neurological diseases (Andreazza et al., 2007; Schroeter & Steiner, 2009).

There is evidence that the product of the *DCDC2* gene, a member of the doublecortin family (*DCX*), can also be involved in the mechanism of the development of the spatial type of thinking (Wang et al., 2011). The *DCX* gene is required for normal neuronal migration in the cerebral cortex. To date, structural abnormalities in *DCX* have been found to cause abnormal neuronal migration, leading to the development of human pathologies – lissencephaly and double cortex syndrome (Gleeson, Lin, Flanagan, & Walsh, 1999). Regarding the impact of the product of the *DCDC2* gene on the development of cognitive abilities, the functions of protein *DCDC2* were first described in studies on dyslexia in children, a reading disorder characterized by retardation in academic performance and everyday life (American Psychiatric Association, 1999; Gabel, Gibson, Gruen, & LoTurco, 2010).

In the context of studying the etiology of speech retardation, several theories have been put forward considering the reasons for this defect, including impaired visual perception of objects, spatial orientation in the text among them, and attention mechanisms in general (Hari & Renvall, 2001; Smith-Spark & Fisk, 2007; Ruffino et al., 2010; Vidyasagar & Pammer, 2010). Assessment of visual attention, visuospatial learning and memory in *DCDC2* knock-out mice showed that deletion of the gene impairs the visual perception of an object and reduces task performance in visuospatial learning and memorization, while not affecting the learning ability of the animal. We should note that mice with genotypes *dcdc2<sup>wt</sup> / del2*, *dcdc2<sup>del2</sup> / del2* lost the ability to retain visual information for a long period of time, which considerably impaired the Hebb–Williams maze performance. The constant deficit in task performance (average speed and accuracy) made it possible to conclude that mice are not able to improve their performance over time due to the knockout of *DCDC2* (Gabel et al., 2011).

Experimental studies on the genetics of human spatial skills have expanded the range of analysis of neurogenetic factors involved in the development of cognitive processes, and, as a result, identified several other organ systems. The cerebellum is known to control movement coordination, fine motor skills, and motor learning. However, there is growing evidence for its contribution to



cognitive and motivational processes in the central nervous system (Ito, 2006). Dysfunction of the cerebellum is associated not only with motor conditions, but also with disorders such as autism spectrum disorders, attention deficit hyperactivity disorder (ADHD), and the fragile X syndrome, phenotypes ranging from motor to higher brain functions (including cognitive processes and social behavior) (Rogers et al., 2013; Wang, Kloth, & Badura, 2014). In most studies the analysis of the malfunction of cerebellar cells and neural development focused on the Purkinje cells. However, in the present, the study of Golgi cells is currently of great interest, because inhibitory GABAergic/glycergic interneurons in the cerebellar cortex may mediate a number of signalings of granular cell with subsequent innervation of Purkinje fiber (Kalmbach, Voicu, Ohyama, & Mauk, 2011; Rössert, Dean, & Porrill, 2015).

Tantra et al. (2018) suggested that the expression of the *CDH13* gene in Golgi cells affects the motor/cognitive behavior of mice. The *CDH13* gene (*16q23.3*) encodes atypical cadherin lacking transmembrane and cytoplasmic domains, attached to the cell membrane via a glycosylphosphatidylinositol anchor that regulates cell migration and neurite outgrowth (Ranscht & Dours-Zimmermann, 1991). Many members of the cadherin superfamily are produced in the nervous system with various spatial and temporal expression patterns and are associated with neurological disorders. The results of GWAS, exome sequencing, indicate the presence of association of polymorphic variants of *CDH13* with the development of ADHD, dependence on the use of psychotropic drugs, depression, aggressive behavior, bipolar disorder, autism, and schizophrenia (Treutlein et al., 2009; Terracciano et al., 2010; Lionel et al., 2011; Sanders et al., 2015). In addition, a number of polymorphic variants of the *CDH13* gene have shown associations with the cognitive skills – namely, with working memory in patients with ADHD (Arias-Vasquez et al., 2011). Both excitatory and inhibitory synaptic functions in the hippocampus depend on the expression of *CDH13*, and its complete deletion leads to impairments of spatial learning and conditional place preference. In addition to synaptic formation, *CDH13* controls neuronal migration and axon specificity targeting the developing cortex of the brain and spinal cord (Redies, Hertel, & Hübner, 2012; Rivero et al., 2015). Tantra et al. found that mice with deleted of the *CDH13* gene show reduced cognitive flexibility and loss of preference for contacts, which is accompanied by increased reciprocal social interactions. At the behavioral level, the loss of function of *CDH13* in the cerebellum, piriform cortex, and endopyriform claustrum does not affect overall locomotor coordination, but leads to a deficit in the animal's cognitive and social abilities (Tantra et al., 2018).

Subsequent literature data also demonstrate an important role of the gene of cadherin 13 in the regulation of social behavior, learning mechanisms, and visual-spatial memory in animals. The obtained results are very useful, since they are of fundamental importance in the study of cognitive function in violation of the development of the nervous system (Forero et al., 2020).

Subsequently, the GWAS were carried out to identify genetic factors involved in the genesis of the human nervous system, optimal synaptic plasticity, survival, neuronal proliferation, which revealed several additional genes: *CADM2*; *SLC4A10*; *DPP450*; *DPP4*; *AKAP6*; *APOE/TOMM40*; *NPAS3*; *FNBP1L* involved in the development of intelligence (Thomas, Akins, & Biederer, 2008; Davies et al., 2011; Davies et al., 2015; Davies et al., 2016; Davies et al., 2018). It is noteworthy that certain of the above genetic factors are involved in the genesis of human spatial thinking (visualization of objects, analysis of relationship among them, etc.).

Thus, researchers have emphasized the impact of the polymorphic variant *rs17518584* of the *CADM2* gene on the speed of information processing in groups of individuals of various

ages (Ibrahim et al., 2018). The *CADM2* gene encodes a protein of the SynCAM group, molecules of adhesion of synaptic cells, also known as nectin-like molecules (*NECL*) or molecules of cell adhesion (*CADM*), which represent a subgroup of the immunoglobulin superfamily (*IgSF-CAM*) (Biederer et al., 2002). Publications devoted to the analysis of the functional activity of the *CADM2* gene demonstrate that its polymorphic variants and mutations are associated with the formation of human intellectual and behavioral traits, development of metabolic mechanisms, physical activity, obesity, the level of the consumption of alcohol and cannabinoid derivatives (Davies et al., 2016; Amare, Schubert, Klingler-Hoffmann, Cohen-Woods, & Baune, 2017; Clarke et al., 2017; Ouakinin, Barreira, & Gois, 2018). In particular, *CADM2*-knockout mice have a reduced degree of obesity, significantly low systemic glucose levels, hypersensitivity to insulin, and increased motor activity, which indicates an important role of *CADM2* protein in the energy homeostasis (Yan et al., 2018). The analysis of endogenous factors involved in the development of physical activity in a group of subjects from the United States aged 45–64 years showed the presence of associations of polymorphic variants of *CADM2* with this trait (Klimentidis et al., 2018).

In addition, as previously reported, molecules of cell adhesion (*CADM*) are involved in the regulation of synaptic plasticity in relation to spatial learning of the object (Robbins et al., 2010). In psychogenetics, some works are mentioned that assess the levels of expression of the product of the *CADM2* gene in the onset and formation of attention deficit/hyperactivity disorder and various types of mental disorders (neuroticism, bipolar disorder, mood instability, depression, and risky behavior) in correlation with metabolic syndrome, due to the use of psychotropic drugs (Morris et al., 2019).

The functional importance of the region of *APOE/TOMM40* genes in cognitive genomics was originally studied in patients with Alzheimer's disease. Later, it was shown that the region of *APOE/TOMM40* is closely associated with general cognitive function in middle-aged and elderly people (Davies et al., 2015). It is well known that apolipoprotein E is a genetic marker for sporadic forms of late-onset Alzheimer's disease. The type of the inherited allele may determine the time of disease onset, the severity of its course, and the degree of decline in cognitive function (Caselli et al., 2009). Recent studies have shown that the *poly-T* of polymorphic variant *rs10524523* ('523') of the *TOMM40* gene can accelerate the course of Alzheimer's pathology. A functional analysis of the genetic factors *APOE* and *TOMM40* showed that multiple cis-regulatory elements of *APOE* affect the activity of both the promoter of apolipoprotein E itself and translocase 40. The study of *rs10524523* in individuals with homozygous apolipoprotein E genotype  $\epsilon 3/\epsilon 3$  with amnesic mild cognitive impairments, which are considered the most common and 'neutral' in relation to the progression of the disease, showed the presence of an association of '523' with a deterioration in allocentric spatial navigation and a decrease in cortical thickness in certain brain areas in elderly subjects (Laczó et al., 2015). The data of brain pathology of individuals with *APOE*  $\epsilon 3/\epsilon 3$  indicate that '523' long allele (poly-T repeats  $\geq 20$ ) may increase the burden of disease (Yu et al., 2017).

Luoma & Berry (2018) presented interesting data on the analysis of the function of *NPAS3* (*Neuronal PAS (period-ARNT-single minded) domain containing 3*) in model animals. The authors have demonstrated that the loss of the function of this gene in the cells of mice leads to a change in behavioral responses due to dysfunction of the hippocampus and a deterioration in task performance. It was previously established that *NPAS3* encodes a transcription factor, which is mainly involved in the regulation of the mechanisms of ontogenesis of the nervous system, since it activates the processes of cell proliferation and apoptosis (Kamnasaran, Muir, Ferguson-Smith, &

Cox, 2003; Pickard, Malloy, Porteous, Blackwood, & Muir, 2005). Interestingly, *NPAS3* has been originally identified as a candidate gene in patients with bipolar disorder and schizophrenia from Scotland (Piccione et al., 2012; Erbel-Sieler et al., 2004).

Several experimental studies demonstrate the involvement of nicotinamide mononucleotide adenylyltransferase 2 (*NMNAT2*) in the mechanisms of the development of intelligence and spatial abilities in human. The *NMNAT2* is a key factor in maintaining stability and neuronal activity and in protecting the nervous system from stressful influences, which has been demonstrated in numerous preclinical models of neurological disorders. *NMNAT2* protein itself is a member of the family of enzymes of nicotinamide mononucleotide adenylyltransferases (*NMNAT*), which synthesize nicotinamideadeninedinucleotide (NAD), an important cofactor of many cellular processes, as well as acting as chaperones (D'Angelo et al., 2000; Ali, Li-Kroeger, Bellen, Zhai, & Lu, 2013). Thus, it was found that in humans the levels of the transcript of *NMNAT2* positively correlate with the cognitive function of the brain, while low expression of nicotinamide mononucleotide adenylyltransferase 2 is noted in Alzheimer's, Huntington's, and Parkinson's diseases (Lin & Koleske, 2010; Ali et al., 2016).

In pharmacogenetics, several studies examine the stabilization of multiple clusters of cell signalings with the participation of the gene of nicotinamide mononucleotide adenylyltransferase 2 (*NMNAT2*) with using chemical modulators at certain concentrations (ziprasidone, cantharidin, wortmannin, retinoic acid, and caffeine), which have different effects on the viability of the cortical layers of the brain in a mouse model of tauopathy. These associations suggest that the levels of *NMNAT2* protein can be regulated by an increase in cAMP or by a mechanism of excitatory neurotransmission. As a result, caffeine compounds had a beneficial effect on the production of *NMNAT2* enzyme. Here with, systemic injection of caffeine restored expression of *NMNAT2* to control levels in a mouse model of tauopathy (Ali, Bradley, & Lu, 2017). Previously, Laurent et al. (2014) showed that chronic caffeine treatment in a mouse model of tauopathy reduces hyperphosphorylation of Tau protein (Tubulin binding protein) and improves memory function. While ziprasidone, cantharidin, wortmannin, and retinoic acid reduce the synaptic conductivity of neurons by decreasing their survival. Interestingly, the use of these negative modulators in therapy with vincristine further reduces nerve cell viability by dramatically decreasing the expression of *NMNAT2* (Ali et al., 2017). These experimental studies have prognostic value in health care, as they make it possible to assess the therapeutic effect of various chemicals on cognitive skills in defects in the functioning of the nervous system and to consider them in health and disease.

An associative study assessing psychiatric and cognitive characteristics associated with a hereditary component carried out by Bi et al. (2017) demonstrated the association of the polymorphic variant *rs10494561* of *NMNAT2* with manifestations of the severity of an individual's professional functioning as a prodrome of psychosis. The same work also assessed the association of genetic factor *IFT122*, encodes intraflagellar transport 122 protein which is important for the formation of a neuronal pattern, with spatial abilities. Namely, the association of the polymorphic variant *rs2285351* of *IFT122* with the formation of such a cognitive skill as orientation in space. Interestingly, structural impairments in the *IFT122* gene contribute to the emergence of a rare hereditary disease – cranioectodermal dysplasia (Walczak-Sztulpa et al., 2010; Bi et al., 2017). The GWAS analysis of cognitive functions in 7600 middle-aged and elderly Hispanic Americans ( $\geq 45$  years) similarly confirmed the possible involvement of protein *IFT122* in the normal function of cognition (Jian et al., 2020).

The identification of genetic determinants associated with the development of intellectual and spatial abilities made it possible to discover other possible participants in the cognition process: *SIRT1*, *CNTNAP2*, *FOXP2*, *ZNF711*, *KIAA0319*, and *DYX1C1*. All the above genetic factors are involved in the mechanisms of nerve cell migration, ensuring the growth of axons and neurites (Michán et al., 2010; Mascheretti et al., 2017; van der Werf et al., 2017). Animal studies have shown that RNA-interference of the expression of patterns of these genes *in utero* is associated with deficits in spatial memory, learning ability, impaired visual discrimination, visual and auditory information processing, and long-term memory (Kurt, Fisher, & Ehret, 2012; Centanni et al., 2014; Rodenas-Cuadrado, Ho, & Vernes, 2014; Rendall, Tarkar, Contreras-Mora, LoTurco, & Fitch, 2017).

In neurogenetics, researchers pay attention to the change in the internal parameters of an individual depending on the lifestyle and nutrition. For example, Bahrami et al. assessed the impact of the dosage degree of vitamin D on intelligence in adolescents and investigated associations of polymorphic variant *rs10766197* of the *CYP2R1* gene with the effectiveness of high doses of vitamin D3. The authors note that the dosage of cholecalciferol improves cognitive skills and varies greatly depending on the mental activity of the individual. The role of vitamin D derivatives, functional gene variants involved in signaling pathways of activation, has previously been characterized in correlation with the development of neurodegenerative diseases (Bahrami et al., 2019). In addition to the results described above, studies of the effects of vitamin D on normal spatial function have been reported in the literature. For example, Taghizadeh, Talaei, & Salami (2013) noted that impaired vitamin D intake resulted in significantly lower spatial orientation of rats. Kueider et al. (2016) described the critical role of a decrease in vitamin D levels in elderly people with a high level of education in correlation with impaired speech and visual-spatial abilities, as well as psychomotor development.

We should emphasize that the study of the development of human spatial abilities in the framework of psychogenetics seems to be one of the most interesting areas in experimental science today. It is well known that physiological capabilities and cognitive abilities are individual and not very predictable. This explains an increasing interest in the issues of their internal regulation, and individual spatial features are no exception. The search for candidate genes which products are involved in spatial intelligence, neuroimaging of the mechanisms of generation of this type of thinking in the nervous tissue, modeling the activation of endogenous factors in the cognitive function of space in animals, and analysis of the characteristics of the body metabolism associated with the manifestation of this type of mental activity contribute to the accumulation of useful knowledge about the formation and development of spatial skills, which makes it possible to more fully characterize the very concept of 'human spatial abilities', to look at them from the inside, to provide a clear comprehensive description of the foundations for the development of these cognitive traits.

### **Conclusion**

Spatial abilities play an important role in cognitive development and represent a reliable predictor of success in STEM disciplines. At the same time, genetic factors contribute to the formation of individual differences in spatial abilities. It is not surprising, since spatial abilities are of evolutionary and adaptive importance for living organisms, including humans. This review provides a brief description of the phenomenon of human spatial intelligence. The analysis of experimental studies indicates the important role of genetic factors in its development. Thus, we found that spatial skills are moderately inherited, and works on functional genetics describe

in more detail genetic determinants, which structural changes cause a variation in the level of generation of spatial thinking.

This obtained scientific groundwork can be used in fundamental research carried out in cognitive psychology, neurogenetics, and evolutionary biology, and also as an applied component in the development of educational and training programs to improve and effectively use spatial skills by individuals of different ages in various spheres of life.

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**E. Kh. Khusnutdinova, S. B. Malykh** performed comprehensive consulting, supervised the publication, and edited the manuscript.

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