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HUMAN GENETICS

A Replication Study of GWAS-Associated Variants in the *TUFM*, *SH2B1*, *ZNF638*, *NEGR1*, *ATP2A1*, *EXOC4*, and *CSE1L* Genes and Cognitive Abilities

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Abstract—A large number of genome-wide association studies (GWASs) of cognitive abilities (i.e., intelligence, educational level, executive functions, etc.) have been conducted in European populations. A replication analysis of GWAS-associated variants of the general factor of intelligence in the development of spatial (3D) abilities in the individuals from Russia is relevant. In order to estimate the main effects of the most significant GWAS loci on spatial abilities in the Russian cohort ($N = 1011$, 18–25 years old) a set of seven "top" SNPs ($p < 10^{-13}$) was formed: *TUFM* rs7187776, *SH2B1* rs7198606, *ZNF638* rs2287326, *NEGR1* rs12128707, *ATP2A1* rs8055138, *EXOC4* rs1362739, and *CSE1L* rs6063353. Statistically significant differences ($p < 0.05$) in the genotype frequency distribution of *ATP2A1* rs8055138, *NEGR1* rs12128707, and *ZNF638* rs2287326 between Russians, Tatars, and Udmurts have been observed. As a result of analysis of genotype-by-environment interactions we revealed the ethnicity-specific character of associations: in Russians maternal age at delivery ($\beta_{ST} = 0.84$, $p = 0.005$) and in Tatars bilingual/unilingual rearing ($\beta_{ST} = 0.44$, $p = 0.020$) modulated association of *ZNF638* rs2287326 with spatial abilities. Moreover, urban/rural residency in childhood modulated the association of *TUFM* rs7187776 with 3D abilities ($\beta_{ST} = 0.41$, $p = 0.009$). The data we obtained indicate the involvement of the *ZNF638*, *TUFM*, *SH2B1*, and *EXOC4* genes, which are related to adipogenesis, in the manifestation of cognitive abilities, and, therefore, confirms the relationship between cognitive and metabolic disorders. Nevertheless, the ethnicity-specific character of demonstrated associations and differences in genotype frequencies of analyzed GWAS-SNPs point to the specific pattern of associated genetic loci characteristic for the Russian cohort and to the complexity of replication of data reported for the combined samples of Europeans.

Keywords: genome-wide association study, spatial abilities, SNP, Alzheimer's disease, replication, *ZNF638*

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INTRODUCTION

The individual level of cognitive abilities determines both successful professional self-realization and the quality of life at different stages of development. The dynamic development of an IT society requires the training of highly qualified individuals with effectively developed mathematical abilities. Their successful development to a certain extent is related to the formation of mathematical fluency or the ability to quickly and accurately perform elementary mathematical operations [1], which correlates with the development of spatial (3D) abilities and spatial memory [1, 2]. Spatial abilities are defined as the creation, recoding, and operation of spatial images to solve practical problems [1]. Moreover, spatial thinking plays a significant role in achievements in both mathematical, humanities and natural sciences [3]. Moreover, a significant link exists between highly developed spatial abilities and educational achievements, which can be observed even within years of schooling [3]. The results of twin research show a moderate inheritance (30–50%) of spatial abilities caused by the cumulative effects of multiple genetic loci, which together are

involved in both development of spatial intelligence and other cognitive abilities (for review see [4]).

A large number of published findings from studies of the role of the genetic component in developing cognitive abilities [5–10] and impairments [11, 12] allow one to select certain genes/genetic variants and gene ontology processes. In particular, the apolipoprotein E (*APOE*) gene [5] and a neighboring region comprised of the *TOMM40*, *APOC1*, and *NECTIN2* genes [11, 12] are the most examined ones toward the specificity of cognitive functioning. Moreover, the genes involved in neurogenesis and synaptic plasticity regulation (*NGF*, *NRXN1*, *KIBRA*, *NRG1*, *BDNF*, *GRIN2B*, *SNAP25*, *SORL1*, and *CLSTN2*) [5, 6, 8, 9] and inflammatory system genes (*CRP*, *IL1A*, *IL1B*, *TNF/LTA*, and *P2RX7*) [7] are being actively studied. Nevertheless, the value and direction of the effect of some genetic locus differs between the examined samples depending on age, the cognitive state of respondents, ethnic background, and sex.

Multiple genome-wide association studies (GWAS) of various cognitive traits (including intelligence, educational level, and executive functions) have been conducted on Europeans [13–16]. In addition to the existing GWAS findings, meta-analyses aimed at systematizing the data on the effect of each statistically significant single nucleotide polymorphism (SNP) and summarizing the findings obtained from millions of individuals have been published [17]. Nevertheless, the unique specificity of the distribution of genotype and allele frequencies in different populations requires the performance of replication studies that assume an ethnicity-specific component. No findings from published GWAS data reporting associations of genetic variants with cognitive abilities in ethnical groups from Russia have been published. Moreover, the data from twin and family research show the presence of severe genetic correlations between various cognitive domains [18], which points to the involvement of the same genes in the development of various cognitive parameters. In this regard, the assessment of the effect of GWAS-detected SNPs of general factors of intelligence (*g*) of individual variance of spatial abilities in the Russian cohort remains highly relevant. Together with the role of the genetic component, individual variance in spatial thinking is attributed to the specificity of the micro- and macroenvironment during ontogenesis [5].

The present study aimed to determine the association of GWAS-significant SNPs residing the *TUFM*, *SH2B1*, *ZNF638*, *NEGR1*, *ATP2A1*, *EXOC4*, and *CSE1L* genes with spatial abilities in individuals from Russia considering the effect of genotype-by-environment interactions.

MATERIALS AND METHODS

The study was conducted using an existing DNA collection of mentally healthy volunteers without a family burden of mental illness, who were absent in the Psychiatric and Narcological Registry ($N = 1011$, 80% women). The collection was described in detail in our previous studies [5, 7]. The respondents were students at the Universities in Russia (aged 18–25 years), including Russians, 535; Tatars, 231; Udmurts, 160; and individuals of mixed ethnicity, 85. Ethnicity was determined by self-response questionnaires up to three generations. Voluntary consent to participate in the study was received from all the participants. This study was approved by the Bioethical Committee at the Institute of Biochemistry and Genetics of the Ufa Federal Research Centre of the Russian Academy of Sciences. The assessment of spatial (3D) abilities was carried out using a test battery consisting of questions on mental rotation of 3D figures (shape rotation), and was assessed as the number of correct answers (on the psychodiagnostic platform of the Russian Academy of Education). Potential affecting environmental factors included the child–parent relationship (parenting style, rearing in a complete/incomplete family, and episodes of abuse in childhood), family income, place of residence, the number of children in the family (sibship size) and birth order, maternal and paternal age at childbirth, child weight at birth, bilingual rearing for individuals of nonRussian ancestry, the presence of chronic diseases, and smoking.

We searched for the most significant genetic variants ($p < 10^{-13}$), which have been identified in one of the recent meta-analyses of cognitive traits, and formed the following set of seven top SNPs: *TUFM* rs7187776, *SH2B1* rs7198606, *ZNF638* rs2287326, *NEGR1* rs12128707, *ATP2A1* rs8055138, *EXOC4* rs1362739, and *CSE1L* rs6063353. The criteria for the inclusion of polymorphic loci were the following: the lowest statistical significance level; residence in different protein encoding genes; a minor allele frequency (MAF) above 0.05 in European populations; a high regulatory effect of SNP according to the CADD (Combined Annotation Dependent Depletion, https://cadd.gs.washington.edu) and RDB (Regulome Database, https://regulomedb.org/regulome-search) databases. The CADD database contains information on the most destructive effects of SNPs on protein translation (a higher CADD score indicates more destructive effects). At the same time, the RDB score reflects the possible regulatory effect of SNPs (a lower score indicates a higher regulatory effect). Genotyping of genetic loci was carried out using real-time PCR with KASP kits (Maxim Medical LLC, LGC Genomics, UK) and endpoint fluorescence analysis was carried out on a CFX96 DNA Analyzer (BioRad, United States).

The statistical analysis included the test for the normality of distribution of quantitative values of spa-

tial abilities (Shapiro–Wilk *W*-test, $p > 0.05$). A comparison of the genotype frequencies distribution was based on calculation of the Pearson χ^2 criterion (adjusted for Yates continuity) and the significance level. Linear regression analysis with inclusion of spatial ability scores as a dependent factor and genotypes of examined GWAS-related SNPs as independent predictors was used to estimate the association of each of the examined SNP in the total sample, controlling for sex and ethnicity and in ethnically homogenous subgroups. Social/lifestyle factors were also included in the linear regression model as an independent variables, together with genotypes while conducting a genotype-by-environment interaction analysis in each of ethnic groups. Regression analysis was carried out based on various statistical models (additive, dominant, and recessive) in PLINK v1.09. For observed statistically significant models of genotype-by-environment interactions, we performed a regression analysis to determine statistically significant differences in 3D abilities between the groups stratified by the environmental factor (SPSS 23.0). The level of statistical significance was set at $p < 0.05$.

RESULTS

The analysis of genotypes distribution of the studied genetic loci in the *TUFM*, *SH2B1*, *ZNF638*, *NEGR1*, *ATP2A1*, *EXOC4*, and *CSE1L* genes conducted in various ethnic groups (Russians, Tatars, and Udmurts) demonstrated statistically significant differences ($p < 0.05$) in genotype frequencies in the *ATP2A1* rs8055138, *NEGR1* rs12128707, and *ZNF638* rs2287326 (Table 1). A comparison of genotype frequencies of the examined ethnic groups from the Volga-Ural region with European populations (according to the 1000 Genomes Project) revealed a similar character of distribution between analyzed groups and residents of Northern and Western European ancestry and Finns (representatives of the Finno-Ugric group of peoples). The distribution of allele and genotype frequencies of all examined SNPs corresponded to the Hardy–Weinberg equilibrium ($p > 0.05$) (Tables 1, 2).

In order to replicate the association of the *TUFM*, *SH2B1*, *ZNF638*, *NEGR1*, *ATP2A1*, *EXOC4*, and *CSE1L* gene SNPs with spatial abilities, we carried out a linear regression analysis in the total sample controlling for ethnicity and sex as covariates (for SNPs that were characterized by similar genotype frequencies between ethnic groups) and in ethnically homogenous groups (Table 2). As a result of the analysis we failed to confirm an association of analyzed polymorphic loci with 3D abilities in both the total sample and ethnically homogenous groups ($p > 0.05$) (Table 2). Nevertheless, a trend to score higher on spatial ability was observed for *ZNF638* rs2287326**T*/*T* genotype carriers compared to those carrying the major *G* allele ($p = 0.057$, $\beta_{ST} = 0.01$).

The conducted analysis of genotype-by-environment interactions, which considered the effect of all possible social predictors together with genetic variants, revealed that in Russians the maternal age at delivery modulated the association of *ZNF638* rs2287326 with 3D abilities ($\beta_{ST} = 0.84$, $p = 0.005$) (Fig. 1a). In Tatars we observed that bilingual rearing had a modulating effect on association of rs2287326 with the analyzed cognitive trait ($\beta_{ST} = 0.44$, $p = 0.020$). A subsequent stratified analysis, which has been performed in each group split by bilingual/monolingual rearing, demonstrated a linear dependence between a number of minor *T* alleles in rs2287326 and greater spatial ability only in individuals with monolingual rearing ($\beta_{ST} = 0.34$, $p = 0.023$) (Fig. 1b). Moreover, in Tatars urban/rural residency modified the association of the *TUFM* rs7187776**G* allele with 3D abilities ($\beta_{ST} = 0.41$, $p = 0.009$). The subsequent stratified analysis revealed that a statistically significant decline in mental rotation was associated with the rs7187776 minor *G* allele compared with the *A*/*A* genotype in individuals who were reared in a rural area ($\beta_{ST} = -0.30$, $p = 0.007$) (Fig. 1c). In Udmurts no statistically significant genotype-by-environment interactions related to individual differences in spatial abilities were detected.

DISCUSSION

Within the framework of the present replication study we confirmed the effects of the GWAS-related SNPs rs2287326 (in the *ZNF638* gene) and rs7187776 (in the *TUFM* gene) on the development of spatial abilities in Russians and Tatars from Russia, while controlling for environmental factors. According to the meta-analysis [17], the *ZNF638* minor *T* allele was associated with lower general intelligence ($\beta = -0.02$, $p = 2.4 \times 10^{-13}$) in a combined sample of Europeans. In contrast, the results obtained from the FinnGen database (https://r8.finngen.fi), which contains the data from genome-wide association analyses of various traits and multifactorial diseases performed on 500000 participants from Finland, indicated a reduced risk of dementia in carriers of the rs2287326 minor *T* allele ($\beta = -0.30$, $p = 4.1 \times 10^{-2}$). Other GWASs also support the association of different SNPs in the *ZNF638* gene with education attainment and intelligence [14–16]. The present study demonstrated a differential association of rs2287326 genotypes with spatial abilities caused by differences in maternal age at delivery (in Russians) and childhood rearing in a bilingual family (in Tatars). In particular, in Russians a tendency to develop higher spatial skills in rs2287326**T*/*T* genotype carriers was observed in individuals with older mothers (above 25–30 years), which can be partially explained by conscious motherhood. The published findings indicate a positive correlation between maternal age at child delivery and the

Table 1. The genotype frequencies of examined SNPs and the differences in their distribution between Russians, Tatars, and Udmurts

SNP	Genotype	Russians ($N = 535$)	Tatars ($N = 231$)	Udmurts ($N = 160$)	CEU	FIN
TUFM rs7187776	*G/G*	0.20	0.21	0.21	0.16	0.11
	A/G	0.47	0.49	0.48	0.41	0.55
	A/A	0.34	0.30	0.31	0.42	0.34
	$\chi 2$ (*p*)	0.9 (0.64) (Russians vs. Tatars) 0.5 (0.76) (Russians vs. Udmurts) 0.1 (0.98) (Tatars vs. Udmurts)				
SH2B1 rs7198606	*G/G*	0.23	0.23	0.17	0.15	0.08
	G/T	0.53	0.51	0.54	0.42	0.57
	T/T	0.25	0.26	0.29	0.42	0.35
	$\chi 2$ (*p*)	0.2 (0.92) (Russians vs. Tatars) 2.6 (0.27) (Russians vs. Udmurts) 2.5 (0.29) (Tatars vs. Udmurts)				
ATP2A1 rs8055138	*T/T*	0.13	0.22	0.23	0.15	0.08
	T/C	0.49	0.49	0.39	0.42	0.57
	C/C	0.38	0.29	0.38	0.42	0.35
	$\chi 2$ (*p*)	12.4 (**0.002**) (Russians vs. Tatars) 9.8 (**0.007**) (Russians vs. Udmurts) 4.8 (0.09) (Tatars vs. Udmurts)				
NEGR1 rs12128707	*G/G*	0.09	0.07	0.09	0.05	0.06
	A/G	0.40	0.37	0.51	0.49	0.39
	A/A	0.52	0.56	0.40	0.46	0.55
	$\chi 2$ (*p*)	1.2 (0.52) (Russians vs. Tatars) 7.4 (**0.02**) (Russians vs. Udmurts) 9.5 (**0.008**) (Tatars vs. Udmurts)				
CSE1L rs6063353	*A/A*	0.21	0.19	0.14	0.16	0.25
	A/G	0.50	0.48	0.59	0.45	0.45
	G/G	0.29	0.33	0.27	0.39	0.30
	$\chi 2$ (*p*)	1.4 (0.50) (Russians vs. Tatars) 5.1 (0.08) (Russians vs. Udmurts) 5.1 (0.08) (Tatars vs. Udmurts)				
EXOC4 rs1362739	*A/A*	0.18	0.21	0.21	0.28	0.23
	A/C	0.49	0.50	0.49	0.46	0.51
	C/C	0.33	0.28	0.30	0.26	0.26
	$\chi 2$ (*p*)	1.9 (0.38) (Russians vs. Tatars) 0.8 (0.67) (Russians vs. Udmurts) 0.2 (0.91) (Tatars vs. Udmurts)				
ZNF638 rs2287326	*T/T*	0.17	0.26	0.24	0.16	0.21
	T/G	0.46	0.52	0.53	0.48	0.58
	G/G	0.36	0.23	0.23	0.36	0.21
	$\chi 2$ (*p*)	16.2 (**<0.001**) (Russians vs. Tatars) 10.7 (**0.005**) (Russians vs. Udmurts) 0.1 (0.96) (Tatars vs. Udmurts)				

The data from several European populations are shown (1000 Genomes Project): CEU, Utah residents with Northern and Western European ancestry, FIN, Finns. Statistically significant differences are shown in bold.

Table 2. The results of linear regression association analysis of GWAS-loci with spatial ability in the total sample and among Russians, Tatars, and Udmurts

SNP	Alleles[a]	P_{HWE}	MAF_{GWAS}	β_{GWAS}	P_{GWAS}	Total sample			Russians			Tatars			Udmurts		
						β_{ST}	p	MAF	β_{ST}	p	MAF	β_{ST}	p	MAF	β_{ST}	p	MAF
TUFM rs7187776	*G/A*	0.496	0.393	–0.08	2.4×10^{-24}	0.06	0.082	0.447	0.09	0.068	0.429	0.01	0.880	0.452	0.12	0.156	0.453
						0.06	0.084		0.09	0.087		0.09	0.189		0.02	0.815	
SH2B1 rs7198606	*G/T*	0.157	0.381	–0.09	2.7×10^{-24}	–	–	–	–0.04	0.401	0.488	0.12	0.104	0.487	0.11	0.223	0.441
						–	–		<0.01	0.901		0.12	0.081		–0.01	0.863	
ATP2A1 rs8055138	*T/C*	0.676	0.381	–0.09	2×10^{-24}	–0.02	0.552	0.409	0.01	0.810	0.375	0.02	0.712	0.467	–0.04	0.683	0.422
						<0.01	0.812		0.02	0.659		0.05	0.435		–0.05	0.568	
NEGR1 rs12128707	*G/A*	0.934	0.260	0.08	4.2×10^{-18}	<0.01	0.925	0.284	0.06	0.211	0.284	–0.08	0.263	0.255	0.04	0.650	0.343
						–0.02	0.540		0.09	0.078		–0.13	0.071		0.06	0.458	
CSE1L rs6063353	*A/G*	0.456	0.427	–0.06	9.4×10^{-17}	–0.01	0.730	0.460	–0.05	0.330	0.460	–0.04	0.567	0.431	–0.05	0.533	0.434
						–0.01	0.629		–0.05	0.313		–0.08	0.265		–0.09	0.279	
EXOC4 rs1362739	*A/C*	0.945	0.468	0.06	1.8×10^{-14}	–	–	–	–0.05	0.283	0.428	0.08	0.221	0.465	0.03	0.750	0.456
						–	–		–0.08	0.115		0.08	0.250		–0.01	0.898	
ZNF638 rs2287326	*T/G*	0.277	0.447	–0.02	2.4×10^{-13}	–	–	–	0.03	0.525	0.405	0.05	0.496	0.514	0.05	0.587	0.503
						–	–		0.07	0.175		0.01	0.057		<0.01	0.979	

P_{GWAS}, p-value in GWAS meta-analysis of cognitive abilities [17]; P_{HWE}, p-value for the Hardy–Weinberg test; β_{GWAS}, regression coefficient from the meta-analysis [17]; MAF, minor allele frequency; MAF_{GWAS}, minor allele frequency in the meta-analysis [17]; β_{ST}, standardized regression coefficient; p, p-value; [a] minor/major alleles. The values of additive model parameters are shown in the upper row, of recessive model, in the lower row. Dashes in the total sample are marked for the *SH2B1*, *EXOC4,* and *ZNF638* genetic loci due to the absence of regression analysis caused by absent statistically significant differences in genotype frequencies between the examined ethnic groups.

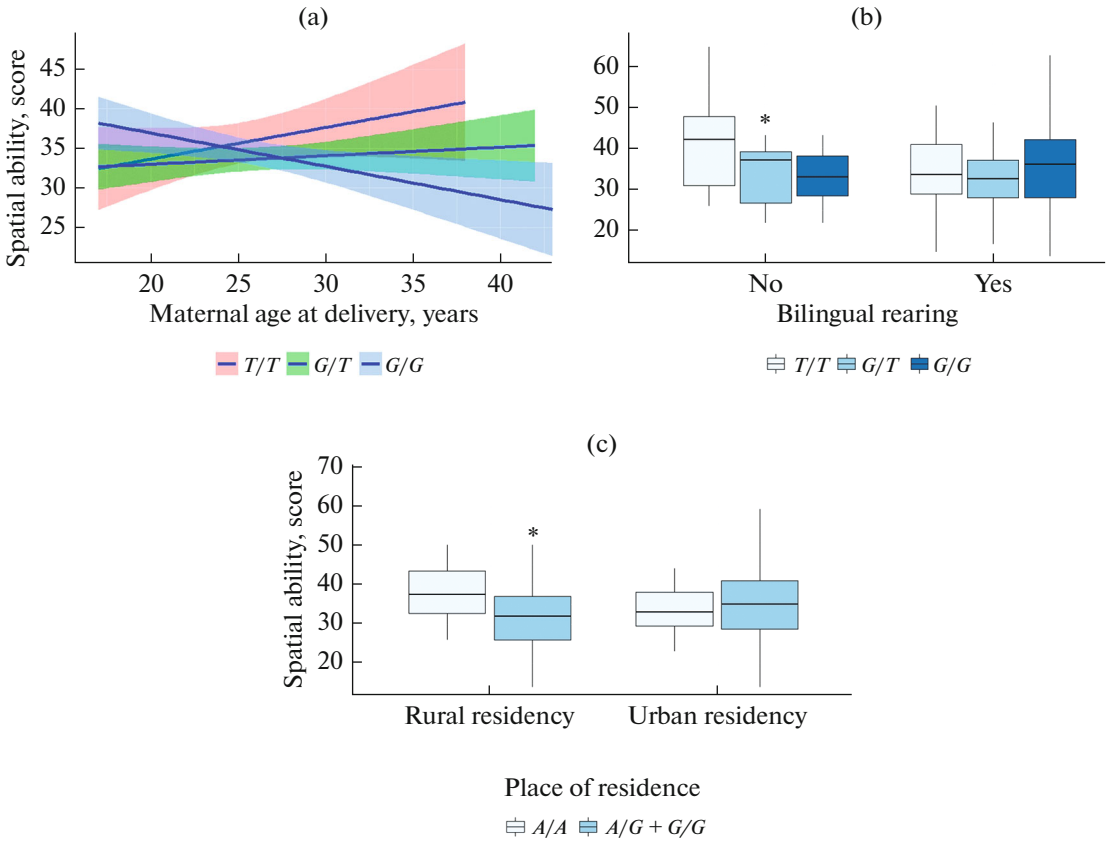

Fig. 1. The mean values of spatial ability scores in carriers of different genotypes of *ZNF638* rs2287326 in Russians with respect to maternal age at delivery (a), in Tatars with respect to bilingual/monolingual rearing (b), *TUFM* rs7187776 in Tatars with respect to place of residence (c). * Statistically significant differences among the groups are marked ($p < 0.05$).

cognitive characteristics of their children in the longitudinal perspective including short-term memory and executive functions [19]. At the same time, Russian *G/G* genotype carriers who were reared by mothers older than 25–30 showed a decline in 3D abilities. Therefore, maternal age represents a factor that modulates differences in spatial abilities related to the presence of certain genotype in the *ZNF638* gene; this relationship was more pronounced for rearing by older mothers. A similar association pattern (higher 3D abilities in rs2287326**T/T* genotype carriers) was observed in Tatars who reported monolingual rearing, whereas such an association in bilingual Tatars (freely speaking native Tatar language) was not observed. Data exist on the stressor effect of bilingual rearing, which affects cognitive development negatively [20]. In this regard, association of the *ZNF638* gene variants with cognitive ability in Russians and Tatars is observed only under favorable rearing conditions (in our study, a positive effect of rearing by older mothers without bilingual rearing as a stressor).

The *ZNF638* gene encodes zinc finger protein 638, which is highly expressed in the brain. Functional and association studies show the role of the *ZNF638* gene in human height [21] and differentiation of adipocytes [22]. Recently, it has been reported that enhanced expression of the *ZNF638* gene is characteristic for adipocytes that overexpress the FoxP4 (Forkhead box protein) protein, which belongs to the family of transcription factors [23]. Despite the absence of published functional studies pointing to a direct effect of ZNF638 on cognitive abilities or their decline, its role may be attributed to an indirect effect of interaction with FoxP family proteins, which has been repeatedly studied for a relationship with cognitive phenotypes. Nucleotide substitutions in heterozygotes in the *FoxP1*, *FoxP2*, and *FoxP4* genes are related to impaired language abilities [24], autism spectrum disorders and cognitive abnormalities [25, 26], and apraxia of speech [27]. It should be noted that these genes are highly expressed in different brain regions including the prefrontal cortex, hippocampus, amygdala, basal ganglia, thalamus, and cerebellum, and regulate molecular processes related to brain development and functioning [28]. Manipulations with the expression of FoxP family genes in model animals also indicate their association with developing spatial perception. In particular, *FoxP1* knockout mice demonstrated that impaired striatum functioning caused a decrease in the number

of correct spatial tests and a decline in object recognition [25, 29].

Another interesting finding obtained by our group is the association between the 3D mental rotation level and rs7187776, which is located in the promoter region of the *TUFM* gene, in Tatars, which was statistically significant only in individuals who were the residents of a rural area in childhood. The data reported by our group are congruent with meta-analysis results, which demonstrated the association of the *TUFM* rs7187776**A* allele with higher cognitive domains in a combined sample of Europeans [17]. Functional studies also show the correlation between a reduced expression of the *TUFM* gene and cognitive decline and accumulation of amyloid β and β-secretase [30]. Other GWASs linked the major rs7187776**A* allele with a reduced hip circumference corrected by the body mass index (BMI), especially in women [31]. The pleiotropic effect of the rs7187776 on cognitive abilities, hip circumference, and BMI is not surprising, since a negative genetic correlation was reported between intelligence level, BMI ($rg = -0.11$), and waist/hip circumference ($rg = -0.10$) [17]. In turn, a two-times TUFM decrease in obese mice and an enhanced protein level in mice with higher physical activity compared to the control group [32] coincide with a hypothesis linking metabolic impairments to developing Alzheimer's disease. Contradictory findings have been revealed for the effect of *TUFM* rs7187776 in children from rural Chinese regions [33]. Namely, the frequency of the rs7187776 *G* allele was statistically significantly higher in individuals characterized by a higher IQ level compared to children with lower IQs, which seems to be contrary to our results. Such an opposite effect may be attributed to the differences in genotype frequencies between individuals of Tatar and Chinese ethnicity (0.21 for the *G/G* genotype in Tatars and 0.11 in Han Chinese), and by cultural specificity of rearing.

The *TUFM* gene encodes the mitochondrial translation elongation factor Tu, whose reduced level causes an impaired mitochondrial respiratory chain and enhanced level of reactive oxygen species in various cell lines [34]. Our findings show that the association between allelic variants of the *TUFM* gene and 3D abilities in Tatars is only observed under favorable rearing conditions (i.e., rural residency in childhood). A positive effect of "green" territory in surrounding neighborhood on improved cognitive parameters was reported previously in children even within 1 year [35], while a prolonged residence in green location correlated with memory improvement due to increase in the gray matter in the prefrontal cortex [36]. In contrast, a negative effect of residency in an urban area accompanied by the effect of fine dispersed particles leading to a reduced efficiency of mitochondria exists [37]. Although there are no published findings on the link between the rs7187776 polymorphism and differential expression of the *TUFM* gene, our data demonstrate a differential character of association of the rs7187776 genotypes with 3D abilities, which is observed under the conditions of reduced allostatic load (in particular, rearing in a rural area [38]).

The present replication study of GWAS genetic loci, which has been initially associated with general intelligence factor in Europeans, confirmed the association of the *ZNF638* and *TUFM* genes in developing spatial abilities within a genotype-by-environment interaction framework in young adults from Russia of Russian and Tatar ethnicity. Interestingly, such an association was detected only under favorable rearing conditions, including rearing by older mothers, the absence of a bilingual childhood, and rural residency. Nevertheless, we could not completely replicate the association of the studied SNPs in the *TUFM*, *SH2B1*, *ZNF638*, *NEGR1*, *ATP2A1*, *EXOC4*, and *CSE1L* genes with 3D mental rotation ability in ethnic groups of Tatars, Russians, and Udmurts from the Volga-Ural region of Russia. The necessity to perform a statistical analysis in each ethnic group separately is attributed to the differences in genotype frequencies distribution in the *ATP2A1* rs8055138, *NEGR1* rs12128707, and *ZNF638* rs2287326 gene polymorphisms between examined ethnic groups. Accordingly, negative findings to a certain extent may be caused by differences in allele and genotype frequency distributions in these SNPs between examined ethnic groups and a combined sample of Europeans, which was used in a GWAS meta-analysis, by moderate sample size, and by differences in the analyzed cognitive domains used as phenotypes. Nevertheless, the data we obtained show the role of genes involved in adipogenesis in the development of cognitive abilities, which coincides with a hypothesized link between cognitive and metabolic impairments. The number of GWASs devoted to the examination of neuropsychological and cognitive phenotypes in the Russian cohort is low. However, they also point to the pattern of associated genetic variants, which is specific to the Russian cohort, and to the complexity of result replication in other ethnic groups [39]. Future research in the field of genetics of cognitive abilities using the GWAS approach is needed to unravel related genetic variants specific for individuals from Russia.

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COMPLIANCE WITH ETHICAL STANDARDS

Conflict of interest. The authors declare that they have no conflicts of interest.

Statement of compliance with standards of research involving humans as subjects. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants involved in the study.

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