



## Research article

## AVPR1A main effect and OXTR-by-environment interplay in individual differences in depression level

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## ARTICLE INFO

## Keywords:

Oxytocin  
Arginine vasopressin  
Serotonin  
Depression  
Family environment  
GxE interaction  
Behavioral neuroscience  
Molecular neuroscience  
Mental disorder  
Genomics  
Polymerase chain reaction  
Human genetics  
Biological psychiatry  
Mental health  
Psychological disorders

## ABSTRACT

**Background:** Multiple studies of depression indicated a significant role of gene-by-environment interactions; however, they are mainly limited to the examination of modulating effect of recent stressful life events. Other environmental factors occurring at different stages of ante- and postnatal development may affect the association between multiple genes and depression. The study aimed to analyze the main and haplotype-based effect of serotonergic system and HPA-axis gene polymorphisms on depression and to detect gene-by-environment interaction models explaining individual variance in depression in mentally healthy young adults from Russia.**Methods:** Depression score was assessed using Beck Depression Inventory (BDI) in 623 healthy individuals (81% women; 17-25 years) of Caucasian origin (Russians, Tatars, Udmurts) from Russia. The main- and gene-based effects of 12 SNPs in *SLC6A4* (5-HTTLPR, rs1042173), *HTR2A* (rs7322347), *OXTR* (rs7632287, rs2254298, rs13316193, rs53576, rs2228485, rs237911), *AVPR1A* (rs3803107, rs1042615), and *AVPR1B* (rs33911258) genes, and gene-by-environment interactions were tested with linear regression models (PLINK v.1.9) adjusted for multiple comparisons.**Results:** We observed ethnicity-specific main effect of the *AVPR1A* rs3803107 ( $P = 0.003$ ;  $P_{FDR} = 0.047$ ) and gene-based effect of the *OXTR* gene ( $P = 0.005$ ;  $P_{perm} = 0.034$ ) on BDI-measured depression, and modifying effect of paternal care on *OXTR* rs53576 ( $P = 0.004$ ;  $P_{FDR} = 0.012$ ) and birth order on *OXTR* rs237911 ( $P = 0.006$ ;  $P_{FDR} = 0.018$ ) association with depression level.**Limitations:** A hypothesis driven candidate gene approach, which examined a limited number of genetic variants in a moderately large sample, was used.**Conclusions:** Our preliminary findings indicate that familial environment may play a permissive role modulating the manifestation of *OXTR*-based depression variance in mentally healthy subjects.

## 1. Introduction

Major depression (MD) and depressive-like behavior represent important public health issues due to their high prevalence and incidence in the population (Mandelli and Serretti, 2013). Considering high economic costs of depression to society and a high frequency of depression-like behavior in non-clinical forms in population (10-15% of the general population experience a clinical depressive episode in their lifetime), the study of etiology of depression in population is of high relevance. According to family, twin, epidemiological, and molecular

studies, depression is a multifactorial illness showing a highly complex genetic architecture with a large number of loci, each contributing a very small effect size to the phenotype (Gonda et al., 2018). Genetic factors account for ~30% in childhood increasing to ~40% in adolescence, while shared environmental influences decrease from 70% to 48% in the same period and individual environment accounts for a significant proportion of the association in adolescence only (~12%) in depression etiology (Hannigan et al., 2017).

During the past decades manifold biological factors and candidate genes have been examined in major depression. Although recent

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advances in this field such as consortium-based cohorts for GWAS of major depressive disorder (MDD) identified distinct SNPs at genome-wide significance level in case-control studies (Coleman et al., 2020; Howard et al., 2019; Mullins and Lewis, 2017), GWAS unconsidered gene-environment interaction (GxE) effects except for two research groups, which have applied a genome-wide by SLEs (stressful life events) interaction studies (GWEIS) to improve the percent of variance explained in depression liability in Scotland-UK cohort (Arnao-Soler et al., 2019), African Americans and Hispanics/Latinas (Dunn et al., 2016). However, together with recent SLEs other environmental factors occurring during antenatal and childhood periods of development were reported to modulate genetic liability to depression (Brummett et al., 2008; Kendler et al., 2018; Lahat et al., 2017; Lin and Tsai, 2019; Starr and Huang, 2019).

Candidate gene association studies represent another approach, which can deal with GxE interaction involving individual differences in manifold environmental factors. In particular, such studies have been mainly focused on the involvement of childhood adversity in later depression development. For instance, childhood trauma and maltreatment positively correlate with the strength of GxE interactions involving low-activity serotonergic system associated with low-expressing *SLC6A4* and *HTR2A* gene variants (for review see (Lin and Tsai, 2019; Starr et al., 2019)). The genes belonging to hypothalamic-pituitary-adrenal (HPA) system (*FKBP5*, *CRHR1*, *CRHBP*) were also shown to significantly interact with traumatic life events, physical abuse and childhood maltreatment to affect depression (Lin and Tsai, 2019; Starr and Huang, 2019). However, other researchers failed to detect such effects (Culverhouse et al., 2018; Van der Auwera et al., 2017). Between study heterogeneity may be attributed to inherited epigenetic patterns (Jiang et al., 2019) and environmental factors other than childhood trauma, which cause induced differential health outcomes via epigenetic reprogramming (Jiang et al., 2019). Therefore, some scientists have focused on other psychosocial factors including peculiarities of child-parent relations, familial support, parenting behavior (Cao et al., 2018; Van Assche et al., 2016), and peer relationships with respect to depressive symptomatology; however, such attempts are scarce. One of recent large-scale studies evidence in the parent-offspring resemblance in MD and an additive effect of genetic factors and rearing experiences (Kendler et al., 2018). Functional studies suggested that parenting behaviors affected the neural correlates of emotion processing in children. Specifically, an interactive effect of parenting behaviors and HPA axis-related genes on amygdala activity and connectivity during emotion processing, and, in turn, on internalizing symptoms in children was reported (Pozzi et al., 2019). Together with parenting style, a significant effect of birth order (Easey et al., 2019), socioeconomic status (SES) (Brummett et al., 2008), season of birth (Kazantseva et al., 2015), gestational age (preterm birth) (Johns et al., 2019) and/or extremely low birth weight (ELBW, less than 1000 g) (Lahat et al., 2017; Mathewson et al., 2017) interacting with genetic factors on depressive symptoms was also established. Prenatal factors such as maternal nutrition (House et al., 2018), inflammatory response to infection, maternal depression (Nemoda and Szyf, 2017), maternal age at birth (Miller et al., 2019), and smoking (Kuja-Halkola et al., 2014) during gestation have been examined for their impact on offspring's behavioral problems under GxE interactions. These observations can be partially explained by differential methylation in genes involved in HPA-axis and immune functions, which may cause later mental health problems in children (Kantake et al., 2014; Nemoda and Szyf, 2017). In addition, a significant effect of addictive behavior (smoking, alcohol abuse/dependence) during adulthood on developing depression in a predictive framework based on interactions of multiple functional genetic variants has been reported (Schmitz et al., 2019; Tylee et al., 2018; Wong et al., 2012). In turn, increased exposure to smoking may significantly affect epigenetic changes in HPA-axis (Dogan et al., 2016) and serotonergic genes (Smolka et al., 2019).

Although the abovementioned research evidence in a significant role of family environment in stress and depression sensitivity, the GxE

studies have been mainly focused on the role of the *SLC6A4* and HPA-axis genes (*NR3C1*, *NR3C2*, *CRHR1*, *FKBP5*) in clinical manifestation of depression. Moreover, there is a controversy in GxE effect of the most examined 5-HTTLPR (*SLC6A4*) and SLEs (Coventry et al., 2010; Gonda et al., 2018; Mandelli and Serretti, 2013) thus indicating the possibility of moderating effect of other SNPs in stress-related depression liability (Kazantseva et al., 2008). Recently, several studies in the field of psychopathology have been focused on the analysis of rs1042173 located in the 3'-UTR regulatory region of the *SLC6A4* (Resnick et al., 2015; Wang et al., 2018), since differential expression of the *SLC6A4* gene caused by rs1042173 variants was reported (Seneviratne et al., 2009). A functional rationale to examine the role of another serotonergic system gene (*HTR2A*) in depressive traits involves the data on differential *HTR2A* level detected in neocortex of individuals with depression and suicidal behavior varying on childhood adversity (Underwood et al., 2018). The most widely studied genetic variant of the *HTR2A* gene (rs6311) have been implicated in depression development (Dressler et al., 2009; Gonda et al., 2018; Jokela et al., 2007). However, other genetic variants located in regulatory gene regions may be relevant to individual differences in depression. For instance, the main effect of rs7322347 in the *HTR2A* gene on increased aggression (Banlaki et al., 2015) and GxE effect of rs7322347×physical assault in childhood/adolescence on suicidal attempts (Ben-Efraim et al., 2013) were reported.

It should be noted that studies examining interaction between family environment and other HPA-axis genes (*AVPR1A*, *AVPR1B*) promoting individual sensitivity to stressors and, therefore, depression liability are absent to date. However, it is known that stress reaction causes enhanced cortisol release, which is regulated by the HPA axis and influenced by oxytocin (OXT) and arginine vasopressin (AVP) (Holmqvist Jämsen et al., 2017). Since activation of AVP and OXT receptors oppositely affects fear and anxiety-related behaviors, we can suggest that variations in *AVPR1A* and *AVPR1B* genes associated with their upregulation and lower *OXT* gene expression may result in higher depressive-like behavior. To date multiple studies have focused on *AVPR1A* VNTR polymorphisms (RS1 and RS3) located in the 5'-flanking region and their relation to anxiety and social behavior (Procyshyn et al., 2017; Tansey et al., 2011; Yang et al., 2017). However, the studies on other regulatory regions (for instance, 3'-UTR) in the *AVPR1A* gene remain scarce. Namely, just few attempts to find relations between *AVPR1A* rs1042615 and rs3803107 and stress sensitivity were performed (Bernhard et al., 2016; Holmqvist Jämsen et al., 2017). Although studies dedicated to the involvement of *AVPR1B* SNPs in mood states (Gonzalez et al., 2019), emotional empathy and prosociality (Wu et al., 2015), MDD (Ben-Efraim et al., 2013; Szczepankiewicz et al., 2013) and personality traits (Kazantseva et al., 2014) were published, a pervasive modulating effect of environmental factors on *AVPR1B* gene variants has to be explored.

The presence of prominent sex-specific differences in depression (Labonté et al., 2017) dictates the analysis of genes encoding sex hormones including oxytocin receptor gene (*OXT*) under GxE paradigm. Since oxytocin was shown to regulate different social behaviors including social recognition, affiliation and response to threat (Meyer-Lindenberg et al., 2011; Skuse and Gallagher, 2009) via regulation of HPA axis and attenuate amygdala's response to stress (Bernhard et al., 2016), the *OXT* gene became explored with respect to depressive mood, stress reactivity, antisocial behavior, emotional loneliness (Inoue et al., 2010; Kang et al., 2017; Kawamura et al., 2010; LoParo et al., 2016; Lucht et al., 2009; Thompson et al., 2011). Congruent with a suggestion that variations in the *OXT* gene may differentially affect oxytocin regulation moderated by the effect of family environment, several studies clarified the effect of gene-by-environment interactions based on the *OXT* gene variants in clinical samples (Asherin et al., 2019; Choi et al., 2019; Elwood et al., 2019; Park et al., 2019; Parris et al., 2018). However, no findings of *OXT*-by-environment effect on depressive-like behavior in non-clinical cohort were published to date.

Given that multiple common gene variants together with environmental factors are associated with clinical forms of depression, we sought

to investigate the association of the serotonergic (*SLC6A4*, *HTR2A*) and HPA-axis genes (*AVPR1A*, *AVPR1B*, *OXTR*) with depression level in mentally healthy young adults from the Russian population. We aimed to analyze the main and haplotype-based effect of candidate gene polymorphisms on depression within the framework of stress-diathesis and plasticity gene models and to detect gene-by-environment interactions explaining individual variances in depression level. We hypothesized that: 1) sex and ethnicity modulate main/gene-based effect on depression; 2) environmental factors occurring within ante- and postnatal development may modulate the association between gene variants and depression score.

## 2. Materials and methods

### 2.1. Subjects

In total, 623 healthy individuals (81% women) from Russia comprised the sample. All participants were young adults (mean age  $\pm$ SD: 19.53  $\pm$  1.75 years, age range: 17-25 years), enrolled at the Universities in Russia. All participants were of Caucasian origin, from the Russian population (Slavic group of the Indo-European language family) (N = 225), Tatar population (Turkic group of the Altaic language family) (N = 141), Udmurt population (Finno-Ugric group of the Finn-Permian Branch of the Uralic language family) (N = 218) and individuals of mixed ethnicity (N = 39). Exclusion criteria were a self-reported individual or family history of any psychiatric disorder. Socio-demographic data including sex, ethnicity (by 3 generations), place of residence, birth order, number of children in the family (sibship size), family income, rearing in a full family (yes/no), maltreatment in childhood, bilingual rearing, the presence of severe chronic disease, smoking, weight at birth, mother age at birth were obtained from the participants. The study was approved by the Biological Ethics Committee at the Institute of Biochemistry and Genetics – Subdivision of the Ufa Federal Research Centre of Russian Academy of Sciences (Ufa, Russia), and written informed consent was obtained from all the participants after they were acquainted with all the procedures. All participants were informed about the voluntary and confidential nature of their participation. All procedures performed were in accordance with the Helsinki Declaration as revised 1989.

### 2.2. Psychological measures

Depression score was assessed using the Russian version of self-report Beck Depression Inventory (BDI) representing 21 multiple-choice questionnaire, which measures the severity of depression and consists of a cognitive-affective and somatic depression subscales. To assess the style of parental rearing, Parental Bonding Instrument (PBI) (Parker et al., 1979) was used, which consists of 25 items and estimates two bipolar scales (care and protection) with respect to maternal and paternal style of parenting.

Involved individuals were residents of the Republic of Bashkortostan (population = 4.072 million of citizens, 60.4% of urban status) and the Udmurt Republic (population = 1.517 million of citizens, 65% of urban status) of Russia. Place of childhood residence was determined as urban/rural. Urban status was given to individuals from medium and large metropolitan regions with a population between 60 000 and 1 100 000; while individuals from the localities with a population lower than 60 000 were recognized of rural status.

### 2.3. SNPs selection and genotyping

Genomic DNA was isolated from the whole blood using a standard phenol-chloroform technique. In total, 12 SNPs with a minor allele frequency above 5% (rs7632287, rs2254298, rs13316193, rs53576, rs2228485, rs237911 in the *OXTR* gene, rs3803107 and rs1042615 in the *AVPR1A* gene, rs33911258 in the *AVPR1B* gene, rs7322347 in the

*HTR2A* gene, and 5-HTTLPR (rs4795541), rs1042173 in the *SLC6A4* gene) were selected based on their relation to depression and anxiety-related behavior in previously published studies or due to their location in functional gene regions (5'-UTRs, 3'-UTRs) for their possible involvement in the regulation of gene expression. Six SNPs in the *OXTR* gene were genotyped for the better gene coverage to perform the haplotype-based association analysis to obtain higher statistical power. All SNPs demonstrated sufficient call rates and no deviation from Hardy-Weinberg equilibrium except for *OXTR* rs13316193 ( $P < 0.01$ ) was detected.

Genotyping of examined SNPs was performed using a real-time PCR based on TaqMan technology using oligonucleotide probes with chemical modifications of locked nuclear acids (TaqMan-LNA) with subsequent fluorescent detection via a fluorescent resonance energy transfer approach (TestGen, Russia). DNA samples were amplified in a total volume of 10  $\mu$ l with 20–50 ng of genomic DNA, Taq polymerase and Master Mix (TestGen, Russia) containing two DNA probes (to two alleles of the SNP) marked with different fluorescent labels and fluorescence absorbers. Alleles' assignment was conducted via fluorescence end-point analysis using CFX96 Touch™ Real-Time PCR Detection System (BioRad, USA).

### 2.4. Statistical analysis

Genotype and allele frequencies of investigated SNPs as well as the Hardy-Weinberg equilibrium calculations were performed in a total sample (Table 1) using PLINK v.1.9 (Purcell et al., 2007). Haplotype blocks were delineated using the confidence interval method of Gabriel et al. (2002), and measures of linkage disequilibrium (LD, standardized  $D'$ ) between markers were obtained using Haploview 4.2. Haplotypes with a frequency less than 1% were excluded from the further analysis.

To test for the normality of distribution of the quantitative data (depression score, age, weight at birth and mother age at birth), Kolmogorov-Smirnov's test was used (SPSS v.23). Due to deviation of the depression score from normality, the Mann-Whitney U test and Kruskal-Wallis H test was used to estimate the influence of stress-related environmental factors, sex and ethnicity on depression (SPSS v.23). For independent categorical variables with a number of categories higher than two, a matrix of binary dummy variables was constructed with PLINK v.1.9, which were later used in the linear regression analysis. The main effects of the individual genotypes and haplotypes on depression were investigated using linear regression models adjusted for sex and ethnicity as covariates in a total sample followed by sex- and ethnicity-stratified analysis with PLINK v.1.9. The best statistical model (among additive, dominant, recessive, and dominance deviation from additivity ones) was selected based on Akaike information criterion (AIC). Multiple linear regression models controlled for sex and ethnicity were analyzed to estimate gene-by-environment interactions to test for the modulating effects of stress-related environmental factors and PBI scores on depression in healthy individuals. For the interaction effects, those with P-value less than 0.05 were considered for stratification analysis. Three gene-by-environment models were constructed: (1) Model 1 containing the main effect of SNP, sex and ethnicity, together with SNP-by-sex and SNP-by-ethnicity interaction terms; (2) Model 2 containing the main effect of SNP, sex, ethnicity and environmental factor together with SNP-by-environment interaction term; and (3) Model 3 containing the main effect of SNP, sex, ethnicity and environmental factor together with SNP-by-environment, SNP-by-sex and SNP-by-ethnicity interaction terms. For the models demonstrating an interaction effect of a specific SNP and environmental stress-related factor on depression score, we conducted stratification analysis to clarify the direction of the effect.

As multiple positive findings were expected, correction for multiple testing was performed via false discovery rate (FDR) procedure (Benjamini and Hochberg, 1995) for genotype-based effect, while permutation (10000) test was used for haplotype-based associations. Corrected P-values ( $P_{FDR}$ ,  $P_{perm}$ ) are shown in the present study. Effect sizes were

**Table 1.** The investigated SNPs.

Gene	SNP	Chromosomal position, bp*	Location in gene	Minor allele/Major allele	Genotype frequency			P <sub>HWE</sub>
AVPR1A	rs3803107	63147054	3'-UTR	A/G	0.025	0.280	0.695	0.775
	rs1042615	63150429	exon 1	A/G	0.156	0.486	0.358	0.798
AVPR1B	rs33911258	206118034	5'-UTR	G/A	0.020	0.293	0.687	0.201
OXTR	rs7632287	8749760	3'-UTR	A/G	0.041	0.318	0.642	0.901
	rs2254298	8760542	intron 1	A/G	0.003	0.164	0.833	0.299
	rs13316193	8761057	intron 1	C/T	0.255	0.401	0.344	<0.01
	rs53576	8762685	intron 1	A/G	0.213	0.498	0.290	1
	rs2228485	8768017	exon 1	C/T	0.042	0.283	0.674	0.149
	rs237911	8768322	5'-UTR	G/A	0.030	0.264	0.706	0.559
HTR2A	rs7322347	46835968	intron 2	A/T	0.095	0.473	0.432	0.108
SLC6A4	5-HTTLPR (rs4795541)	30237299	5'-UTR	L/S	0.235	0.490	0.275	0.635
	rs1042173	30197993	3'-UTR	T/G	0.206	0.493	0.301	0.936

\* according to NCBI36 genome build 36.3. P<sub>HWE</sub> – P-value for Hardy-Weinberg equilibrium test. UTR - untranslated region.

calculated for all statistical models. The effect sizes were reported as  $r^2$ , which describes the proportion of variance in BDI-measured depression that is accounted for the differences in genotype or haplotype controlling for sex and ethnicity.

### 3. Results

#### 3.1. Sample characteristics

Since depression score in our sample didn't coincide with the Gaussian distribution ( $P < 0.05$ ), non-parametric tests (Mann-Whitney-Wilcoxon U test and Kruskal–Wallis H test) were used to estimate the association between stress-related and socio-demographic parameters and depression level in mentally healthy individuals. The descriptive statistics of the examined sample is shown in Table 2. Thus, sex ( $P = 0.019$ ), ethnicity ( $P = 0.001$ ) together with such socio-demographic factors as birth order ( $P = 0.017$ ), sibship size ( $P = 0.017$ ), maltreatment in childhood ( $P = 0.004$ ), a presence of severe chronic disorders ( $P = 0.033$ ), maternal care ( $P < 0.001$ ) and protection ( $P = 0.002$ ), as well as paternal care ( $P = 0.010$ ) significantly affected depression score (Table 2). In particular, significantly higher depression level was more likely observed in women and/or in individuals who were the only child in a family and/or those reported childhood maltreatment or severe chronic disease. At the same time, a decreased mean depression score was significantly more prominent in third-born individuals. Congruent with previous research, participants with low maternal care and over-protection together with low paternal care scored significantly higher on depression compared to those, who reported the opposite style of parenting. A linear regression analysis conducted to estimate the influence of individual age, weight at birth (1500–4950 g) and maternal age at birth (16–44 years) on depression level revealed statistically significant effect of age ( $\beta = -0.408$ ,  $P = 0.010$ ), whereas weight at birth ( $\beta < 0.001$ ,  $P = 0.863$ ) and maternal age at birth ( $\beta = -0.508$ ,  $P = 0.309$ ) failed to affect individual's variance in depression.

#### 3.2. Genotype-based association analysis

No statistically significant differences in allele and genotype frequencies distribution in all examined loci were detected between individuals of different ethnicity and sex ( $P > 0.05$ ). Hence, the main effect estimate was carried out in both total sample and certain ethnic groups (Russians, Tatars, and Udmurts) and men and women separately. While testing for the main effects of the examined gene polymorphisms on BDI-measured depression, we detected associations between the rs3803107 A-allele of the AVPR1A gene and increased depression in the dominant model (AA + AG vs GG) in both total sample ( $\beta = 1.241$ ;  $P = 0.046$ ;  $P_{FDR} = 0.644$ ;  $r^2 = 0.005$ ), women ( $\beta = 1.468$ ;  $P = 0.035$ ;  $P_{FDR} = 0.415$ ;  $r^2 =$

0.008), and individuals of Russian ethnicity ( $\beta = 3.596$ ;  $P = 0.003$ ;  $P_{FDR} = 0.047$ ;  $r^2 = 0.031$ ) (Table 3). However, only the last association remained statistically significant after FDR-correction for multiple comparisons. We also detected a trend for sex-specific effect of 5-HTTLPR in the SLC6A4 gene and rs2228485 in the OXTR gene on depression level. Namely, men bearing 5-HTTLPR LL genotype under recessive model scored significantly higher on this trait compared to other genotype carriers ( $\beta = 3.798$ ;  $P = 0.009$ ;  $P_{FDR} = 0.135$ ;  $r^2 = 0.044$ ), while men ( $\beta = -2.684$ ;  $P = 0.035$ ;  $P_{FDR} = 0.491$ ;  $r^2 = 0.036$ ) or individuals of Tatar ethnic origin ( $\beta = -2.411$ ;  $P = 0.019$ ;  $P_{FDR} = 0.139$ ;  $r^2 = 0.029$ ) with rs2228485 C-allele demonstrated reduced depression level under dominant statistical model (Table 3). However, these associations became non-significant after FDR-correction.

#### 3.3. Haplotype-based association analysis

The analysis of pair-wise linkage disequilibrium revealed the presence of haplotype block in the AVPR1A gene (rs3803107, rs1042615) ( $D' > 0.73$ ) and in the OXTR gene (rs53576, rs2228485, rs237911) ( $D' > 0.70$ ), while no LD was detected between rs4795541 and rs1042173 in the SLC6A4 gene ( $D' < 0.088$ ) in all examined groups. Three haplotypes in the AVPR1A gene and eight haplotypes in the OXTR gene with haplotype frequencies above 1% have been observed (Table 4, Figure 1).

Haplotype analysis revealed association of OXTR GTG haplotype (based on rs53576, rs2228485, rs237911, respectively) and enhanced depression level in the total sample ( $\beta = 4.96$ ;  $P = 0.005$ ;  $P_{perm} = 0.034$ ;  $r^2 = 0.013$ ) and among women ( $\beta = 5.25$ ;  $P = 0.006$ ;  $P_{perm} = 0.028$ ;  $r^2 = 0.015$ ), which survived correction for multiple testing (Figure 1). At the same time, ethnicity-specific haplotype-based association of OXTR GCA haplotype in Russians ( $\beta = -3.30$ ;  $P = 0.039$ ;  $P_{perm} = 0.187$ ;  $r^2 = 0.019$ ) and GCG haplotype in Tatars ( $\beta = -2.32$ ;  $P = 0.021$ ;  $P_{perm} = 0.106$ ;  $r^2 = 0.038$ ) underachieved the level of statistical significance after FDR correction (Figure 1). In addition, a trend for carriers of AVPR1A AG haplotype (based on rs3803107 and rs1042615) to score higher on depression was observed in the total group ( $\beta = 1.23$ ;  $P = 0.034$ ;  $P_{perm} = 0.084$ ;  $r^2 = 0.008$ ) and among Russians ( $\beta = 0.127$ ;  $P = 0.015$ ;  $P_{perm} = 0.059$ ;  $r^2 = 0.027$ ).

#### 3.4. Gene-environment interaction analysis

The analysis of gene-by-environment interactions was based on the inclusion of 16 different socio-demographic parameters and examined SNPs in linear regression models as main effects and interaction terms controlled for sex and ethnicity.

While examining gene-by-environment interactions with sex and ethnicity inclusion as covariates in linear regression models, we succeeded to detect a modifying effect of a sibship size (i.e. the number of



**Table 2.** The sample structure according to examined socio-demographic parameters, mean depression score and Mann-Whitney U-test on depression score.

Parameter	N (%)	Mean score $\pm$ SD	Mann-Whitney test (p) <sup>a</sup>
<b>Sex</b>			
Men	118 (18.90)	7.23 $\pm$ 6.62	<b>0.019</b>
Women	505 (81.10)	8.63 $\pm$ 6.98	
<b>Ethnicity</b>			
Russians	225 (36.11)	8.78 $\pm$ 7.71	0.814
Tatars	141 (22.63)	6.61 $\pm$ 5.60	<b>0.001</b>
Udmurts	218 (35.00)	8.55 $\pm$ 6.36	0.134
Others (mixed ethnicity)	39 (6.26)	11.54 $\pm$ 8.38	0.014
<b>Residence</b>			
Urban	329 (52.81)	8.28 $\pm$ 7.53	0.589
Rural	294 (47.19)	8.03 $\pm$ 6.02	
<b>Order of birth</b>			
1	367 (58.91)	8.32 $\pm$ 7.01	0.976
2	195 (31.30)	8.69 $\pm$ 6.65	0.123
>3	61 (9.79)	6.50 $\pm$ 6.44	<b>0.017</b>
<b>Number of children in family</b>			
1	130 (20.87)	10.17 $\pm$ 8.20	<b>0.017</b>
2	302 (48.47)	7.41 $\pm$ 6.01	0.116
>3	191 (30.66)	7.88 $\pm$ 6.69	0.685
<b>Family income</b>			
lower than average	78 (12.52)	9.38 $\pm$ 8.41	0.379
average	503 (80.74)	7.99 $\pm$ 6.59	0.322
higher than average	42 (6.74)	8.09 $\pm$ 5.64	0.689
<b>Rearing in full family</b>			
yes	510 (81.86)	8.18 $\pm$ 6.78	0.974
no	113 (18.14)	8.37 $\pm$ 7.06	
<b>Maltreatment</b>			
yes	81 (13.00)	10.58 $\pm$ 8.00	<b>0.004</b>
no	542 (87.00)	7.70 $\pm$ 6.74	
<b>Bilingual</b>			
yes	326 (52.33)	7.16 $\pm$ 5.61	0.498
no	297 (47.67)	8.25 $\pm$ 7.48	
<b>Chronic disease</b>			
yes	172 (27.61)	9.27 $\pm$ 7.68	<b>0.033</b>
no	451 (72.39)	7.64 $\pm$ 6.64	
<b>Smoking</b>			
yes	42 (6.74)	9.22 $\pm$ 8.37	0.796
previously	58 (9.31)	10.39 $\pm$ 8.42	0.064
no	523 (83.95)	7.93 $\pm$ 6.49	0.096
<b>Maternal care</b>			
high	452 (72.55)	7.26 $\pm$ 6.10	<b>&lt;0.001</b>
low	171 (27.45)	11.48 $\pm$ 9.01	
<b>Maternal protection</b>			
high	361 (57.95)	9.39 $\pm$ 7.75	<b>0.002</b>
low	262 (42.05)	7.06 $\pm$ 6.28	
<b>Paternal care</b>			
high	331 (53.13)	7.41 $\pm$ 6.42	<b>0.010</b>
low	292 (46.87)	9.60 $\pm$ 7.87	
<b>Paternal protection</b>			
high	282 (45.27)	8.89 $\pm$ 8.23	0.854
low	341 (54.73)	7.95 $\pm$ 6.15	
Age (17–25 years)	623 (100)	19.53 $\pm$ 1.75	<b>0.010<sup>b</sup></b>
Weight (1500–4950 g)	623 (100)	3381 $\pm$ 533	<b>0.863<sup>b</sup></b>
Mother Age (16–44 years)	623 (100)	25.61 $\pm$ 5.43	<b>0.309<sup>b</sup></b>

<sup>a</sup> Mann-Whitney U-test was performed for dummy variables (one variable vs others) in the case of a number of categorical variables higher than 2.

<sup>b</sup> Linear regression analysis was performed for quantitative data instead of non-parametric Mann-Whitney test. SD - standard deviation. Statistically significant P-values are marked in bold.

**Table 3.** Main effect of examined SNPs on depression score in different groups based on linear regression analysis\*.

Gene	SNP (MiA/MaA)	Model <sup>a</sup>	Total (N = 623)		Women (N = 504)		Men (N = 117)		Russians (N = 225)		Udmurts (N = 218)		Tatars (N = 141)	
			β	P-value	β	P-value	β	P-value	β	P-value	β	P-value	β	P-value
AVPR1A	rs3803107 A/G	dominant	1.241	0.046	1.468	0.035	0.763	0.570	3.596	<b>0.003<sup>b</sup></b>	-0.059	0.948	0.080	0.941
AVPR1B	rs1042615 A/G	additive	-0.139	0.748	0.091	0.850	-1.330	0.164	-0.929	0.225	0.056	0.929	-0.466	0.602
	rs33911258 G/A	domdev	0.711	0.238	0.634	0.294	0.832	0.532	0.041	0.971	1.456	0.426	2.101	0.047
OXTR	rs7632287 A/G	additive	-0.013	0.980	0.199	0.728	-0.544	0.588	0.030	0.973	0.027	0.981	-1.177	0.180
	rs2254298 A/G	additive	-0.808	0.273	-1.016	0.226	0.290	0.850	-1.192	0.378	-0.855	0.530	0.016	0.989
	rs53576 A/G	additive	-0.053	0.894	0.189	0.675	-0.875	0.305	-0.141	0.853	0.411	0.522	0.950	0.146
	rs2228485 C/T	dominant	-0.679	0.258	-0.081	0.905	-2.684	0.035	-0.834	0.444	-0.243	0.800	-2.411	0.019
	rs237911 G/A	domdev	0.498	0.427	0.459	0.465	-2.055	0.131	3.419	0.085	0.224	0.882	-2.141	0.048
HTR2A	rs7322347 A/T	additive	0.741	0.094	0.779	0.105	0.588	0.602	0.257	0.746	0.995	0.199	0.475	0.550
SLC6A4	rs4795541 L/S	recessive	0.520	0.441	-0.199	0.790	3.798	0.009	1.358	0.298	0.066	0.958	-0.312	0.792
	rs1042173 T/	additive	-0.069	0.863	-0.023	0.957	0.588	0.602	-0.218	0.767	0.308	0.662	-0.734	0.248

\* Sex, ethnicity and age were included as covariates in linear regression models.

<sup>a</sup> SNP model (additive, dominant, recessive, or dominance deviation from additivity) best explaining variance in depression score (based on AIC criterion) is reported. In the case of non-significant association between SNP and depression level in any examined group the values for additive model are shown.

<sup>b</sup> P<sub>FDR</sub> = 0.047. domdev - dominance deviation from additivity model (A1A2 vs A1A1+A2A2). MiA/MaA – Minor allele/major allele. Statistically significant P-values after FDR correction are marked in bold.

**Table 4.** Haplotype frequencies in the AVPR1A gene (based on rs3803107 and rs1042615) and haplotype-based linear regression analysis in the examined groups.

Group	N	Haplotype								
		G*A			A*G			G*G		
		Freq	β	P	Freq	β	P	Freq	β	P
Total	623	0.394	-0.21	0.628	0.163	1.23	<b>0.034</b>	0.439	0.55	0.206
Women	504	0.364	-1.33	0.164	0.206	0.58	0.612	0.430	1.00	0.313
Men	117	0.400	-0.002	0.996	0.153	1.52	0.023	0.441	-0.88	0.067
Russians	225	0.393	-1.07	0.162	0.127	2.90	<b>0.015</b>	0.472	-0.25	0.743
Udmurts	218	0.401	0.09	0.881	0.219	-0.002	0.998	0.379	-0.09	0.879
Tatars	141	0.358	-0.46	0.602	0.128	1.71	0.135	0.514	-0.53	0.539

Statistically significant P-values before correction for multiple comparisons are marked in bold. Haplotypes with the frequencies less than 1% are not shown.

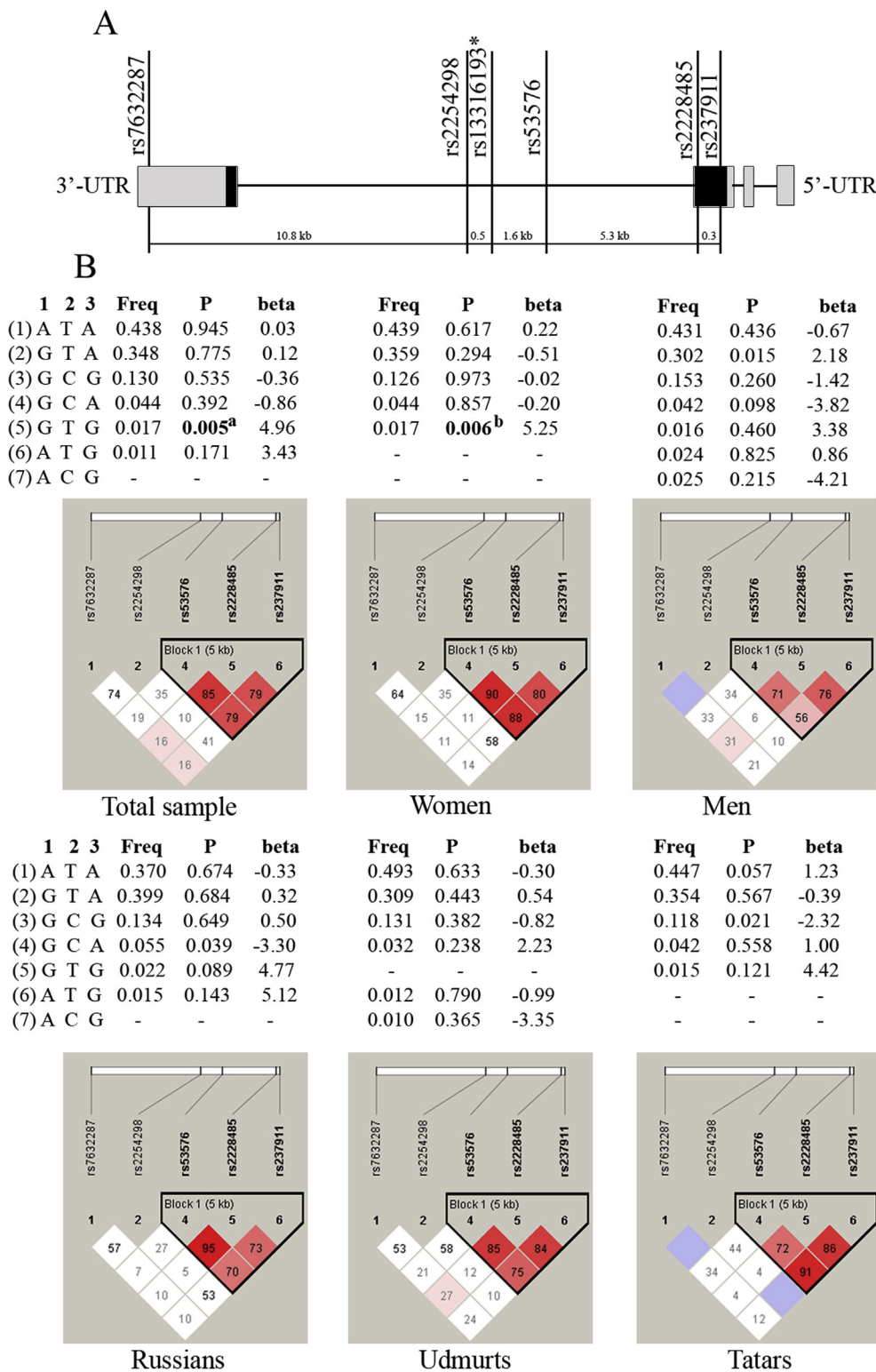
children in a family) on the association of SLC6A4 rs1042173 and BDI-measured depression (Table 5) (Model 2, β = 2.89; P = 0.017; r<sup>2</sup> = 0.100). The inclusion of sex and ethnicity as interaction terms with rs1042173 weakened the rs1042173-by-sibship size interaction model (Model 3, β = 2.66; P = 0.040; r<sup>2</sup> = 0.116). Subsequent post hoc analyses revealed a trend for individuals bearing rs1042173 major GG genotype to score lower on depression while rearing in a large family (more than 3 children in a family) compared to those with less than two siblings, however, it was under the level of statistical significance (Z = -2.027; P = 0.043; P<sub>FDR</sub> = 0.129).

Next, we revealed a modifying effect of parenting style (namely, a degree of paternal care) on the association between the OXTR gene rs53576 and depression (Table 5) (Model 2, β = -2.52; P = 0.017; r<sup>2</sup> = 0.089). While including rs53576-by-sex and rs53576-by-ethnicity interaction terms in the model, the rs53576-by-paternal care interaction remained statistically significant (Model 3, β = -2.49; P = 0.020; r<sup>2</sup> = 0.104). The following stratified analysis revealed that carriers of rs53576 minor AA genotype demonstrated lower depression while rearing under the conditions of high paternal care compared to those, which reported

low paternal interest in their rearing (Z = -2.898; P = 0.004; P<sub>FDR</sub> = 0.012) (Figure 2, a).

Another GxE model explaining individual differences in depression included the OXTR rs237911-by-birth order interaction term (Table 5) (Model 2, β = -2.74; P = 0.031; r<sup>2</sup> = 0.049), which remained significant, however, attenuated after controlling for rs237911-by-sex and rs237911-by-ethnicity interaction (Model 3, β = -2.71; P = 0.035; r<sup>2</sup> = 0.073). Subsequent post-hoc analysis revealed that second-born individuals with rs237911 AA genotype scored significantly higher on depression compared to first- and third-borns (Z = -2.756; P = 0.006; P<sub>FDR</sub> = 0.018) (Figure 2, b).

Finally, an interaction effect of previous smoking and AVPR1B rs33911258 on depression was established (Table 5) (Model 2, β = 5.87; P = 0.007; r<sup>2</sup> = 0.057), while inclusion of rs33911258-by-sex and rs33911258-by-ethnicity facilitated GxE interaction model (Model 3, β = 6.13; P = 0.005; r<sup>2</sup> = 0.064). A stratified analysis by previous smoking demonstrated that rs33911258 G-allele carriers (GG + GA vs AA under the dominant statistical model), which reported previous smoking,



**Figure 1.** The structure of the *OXTR* gene and association analysis of *OXTR* gene haplotypes (based on rs53576, rs2228485, rs237911) and depression level in healthy individuals. A. A schematic structure of the *OXTR* gene, examined SNPs and distance between them (kb). \*rs13316193 was excluded from analysis due to deviation from the Hardy-Weinberg equilibrium. UTR – untranslated gene region. B. Haplotype frequencies of the *OXTR* gene in the examined groups (in total sample, women, men, individuals of Russian, Udmurt, and Tatar ethnic origin). 1 – rs53576, 2 – rs2228485, 3 – rs237911. Freq – haplotype frequency, P – P-value before correction for multiple comparisons. <sup>a</sup>R<sup>2</sup> = 0.013, P<sub>perm</sub> = 0.034, <sup>b</sup>R<sup>2</sup> = 0.015, P<sub>perm</sub> = 0.028. Statistically significant P-values after 10000 permutations are marked in bold. Haplotypes with the frequencies less than 1% are not shown or marked with dashes. Constructed haplotype blocks of linked SNPs in the examined groups based on Lewontin's criterion (D') are marked with triangles (Haploview v.4.2).

tended to have higher depression level compared to non-smoking individuals (Z = -2.327; P = 0.020; P<sub>FDR</sub> = 0.060).

**4. Discussion**

In the present study, ethnicity-specific main effect of the *AVPR1A* rs3803107 and gene-based effect of the *OXTR* gene on BDI-measured depression, as well as a modulating effect of paternal care and birth order on gene-based association with depression has been observed.

More specifically, an increased depression level was reported in individuals bearing *OXTR* rs53576 AA genotype while reported low level of paternal care and/or *OXTR* rs237911 AA genotype being the second-born individuals.

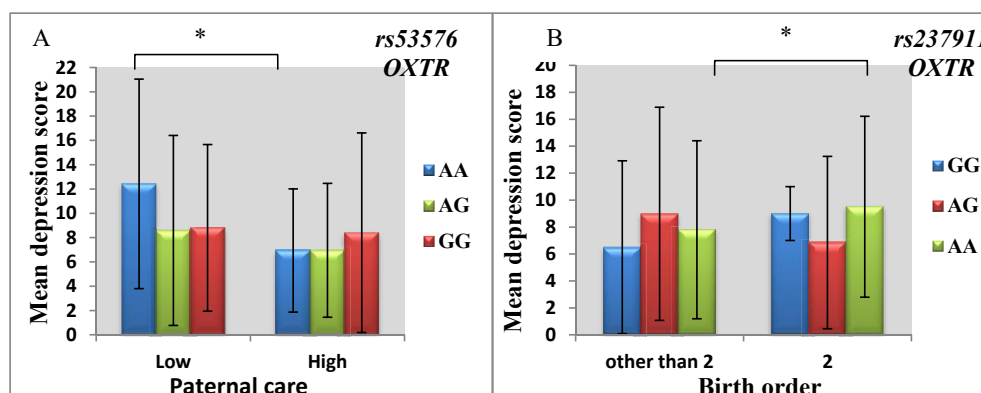
**4.1. Serotonergic system genes (*SLC6A4*, *HTR2A*)**

Given that changes in serotonergic system functioning have been largely implicated in the etiology of depression and 5-HTT is a master

**Table 5.** Significant multiple linear regression models (with GxE interaction) explaining variation in depression score controlled for sex and ethnicity.

Items in linear regression model	Ref. group	Model 1			Model 2			Model 3		
		$\beta$	T	P	$\beta$	T	P	$\beta$	T	P
rs1042173 ( <i>SLC6A4</i> )	T-allele	-0.16	-0.08	0.936	-0.72	-1.12	0.263	1.00	0.37	0.710
Sex	Women	1.33	1.12	0.263	2.23	2.4	0.015	2.20	1.46	0.143
Ethnicity	Russians	-0.41	-0.37	0.706	-1.65	-1.60	0.109	-1.15	-0.62	0.530
	Tatars	-1.79	-1.56	0.119	-4.07	-4.20	<0.001	-1.85	-1.11	0.266
rs1042173 x sex	T*women	0.11	0.10	0.915	-	-	-	-0.13	-0.10	0.916
rs1042173 x ethnicity	Russians	0.17	0.18	0.855	-	-	-	-0.68	-0.40	0.683
	Tatars	-0.71	-0.68	0.491	-	-	-	-2.57	-1.66	0.097
Sibship size	$\geq 3$	-	-	-	-3.01	-2.17	0.030	-2.76	-1.90	0.057
rs1042173 x sibship size	T* $\geq 3$	-	-	-	2.89	2.39	<b>0.017</b>	2.66	2.05	<b>0.040</b>
rs53576 ( <i>OXTR</i> )	A-allele	-2.68	-1.42	0.154	4.33	2.52	0.012	2.27	0.79	0.431
Sex	Women	0.28	0.23	0.815	1.05	1.10	0.270	0.28	0.18	0.855
Ethnicity	Russians	-0.71	-0.66	0.508	-0.11	-0.12	0.904	-1.27	-0.86	0.392
	Tatars	-3.97	-3.18	0.001	-3.13	-3.35	<0.001	1.09	0.84	0.404
rs53576 x sex	A*women	1.17	1.18	0.234	-	-	-	0.72	0.57	0.571
rs53576 x ethnicity	Russians	0.35	0.37	0.708	-	-	-	1.21	0.91	0.362
	Tatars	1.53	1.48	0.139	-	-	-	1.09	0.83	0.404
Paternal care	High	-	-	-	0.29	0.23	0.810	0.25	0.20	0.841
rs53576 x paternal care	A*high	-	-	-	-2.52	-2.38	<b>0.017</b>	-2.49	-2.33	<b>0.020</b>
rs237911 ( <i>OXTR</i> )	G-allele	-3.45	-1.55	0.121	0.55	0.79	0.427	-1.99	-0.78	0.435
Sex	Women	0.63	0.73	0.466	1.25	1.60	0.108	0.56	0.60	0.547
Ethnicity	Russians	-0.62	-0.80	0.423	-0.06	-0.09	0.925	0.12	0.14	0.886
	Tatars	-2.27	-1.59	0.112	-2.67	-3.48	<0.001	-1.88	-2.18	0.030
rs237911 x sex	G*women	2.18	1.73	0.084	-	-	-	2.04	1.46	0.144
rs237911 x ethnicity	Russians	0.83	0.68	0.494	-	-	-	-0.87	-0.63	0.526
	Tatars	-2.27	-1.59	0.112	-	-	-	-2.78	-1.87	0.062
OB	2	-	-	-	1.59	2.02	0.043	1.59	2.03	0.042
rs237911 x OB	G*2	-	-	-	-2.74	-2.15	<b>0.031</b>	-2.71	-2.12	<b>0.035</b>
rs33911258 ( <i>AVPR1B</i> )	G-allele	0.80	0.28	0.778	0.16	0.26	0.790	0.82	0.27	0.789
Sex	Women	1.58	1.77	0.075	1.59	2.09	0.036	1.78	1.89	0.058
Ethnicity	Russians	-0.13	-0.16	0.866	-0.36	-0.51	0.603	-0.37	-0.44	0.659
	Tatars	-2.74	-3.16	0.002	-2.26	-3.01	0.002	-2.80	-3.18	0.001
rs33911258 x sex	G*women	-0.41	-0.28	0.777	-	-	-	-0.62	-0.39	0.692
rs33911258 x ethnicity	Russians	-0.27	-0.22	0.823	-	-	-	0.06	0.04	0.961
	Tatars	1.04	0.71	0.477	-	-	-	1.87	1.21	0.225
Smoking	Previous	-	-	-	0.48	0.40	0.689	0.47	0.38	0.701
rs33911258*smoking	G*previous	-	-	-	5.87	2.70	<b>0.007</b>	6.13	2.78	<b>0.005</b>

Additive effect of SNPs on depression score is shown while controlled for sex and ethnicity (Models 1, 2, 3). Smoking – previous smoking. OB – order of birth. Ref. group – reference group. Statistically significant P-values after FDR-correction for GxE interaction are shown in bold. Ethnicity was encoded as a set of dummy variables for the inclusion in the models. The number of children higher than three in the family is included in the model. Previous smoking is included in the model.



**Figure 2.** Stratification analysis demonstrating a modulating effect of level of paternal care - on association of *OXTR* rs53576 (A), birth order - on association of *OXTR* rs237911 (B) gene variants and individual differences in depression under GxE paradigm while controlling for sex and ethnicity. The charts demonstrate medians and standard deviations. Statistically significant differences in depression score between stratified groups detected in non-parametric models are marked by brackets. \* $P_{FDR} < 0.05$ .



regulator of the fine-tuning of 5-HT signaling, an extensive literature reported that attenuated *SLC6A4* level caused by enhanced methylation of the *SLC6A4* gene and associated with 5-*HTTLPR* S-allele (Bleys et al., 2018) was an elevated risk of depressive pathology (Dell'Osso et al., 2016). However, we failed to detect any association of the *SLC6A4* gene polymorphisms (5-*HTTLPR* and rs1042173) with depression variance while considering either main effect or GxE interaction in healthy young adults. The most recent and methodologically different study, which have imputed and examined the effects of several highly explored VNTRs in a large GWAS dataset, also failed to confirm a significant effect of 5-*HTTLPR* in depression liability even at a liberal significance threshold ( $3.13 \times 10^{-3}$  vs.  $5 \times 10^{-8}$ ) (Border et al., 2019). Congruent with our results several researchers were unable to detect an interaction between 5-*HTTLPR* and stressful life events (SLEs) on increased depression risk in a community sample (Coventry et al., 2010) or MD patients (Gonda et al., 2018; Mandelli and Serretti, 2013). Such observation can be explained by recent conclusion that *SLC6A4* gene expression is not only attributed to a classic assignment of S and L as low- and high-expressing alleles but is also affected by modulating polymorphisms such as rs25531, rs25532, intronic and 3'-UTR variations together with epigenetic regulatory mechanisms (Iurescia et al., 2016). Probably, a precise analysis of gene-based effect of the *SLC6A4* gene has to be conducted in the study of depression etiology.

Recent findings reported the involvement of another gene belonging to the serotonergic system functioning (*HTR2A*, rs6311) in developing depressive symptoms while dealing with gene-by-environment interactions including smoking, chronic disease (Gonda et al., 2018) and urban/rural residency (Dressler et al., 2009; Jokela et al., 2007). The rs7322347 examined in the present study moderated the effect of place of residency (rural/urban areas) (Mandelli and Serretti, 2013) on depression level and physical assault in childhood/adolescence on suicidal attempts (Ben-Efraim et al., 2013). Our findings indicate the absence of *HTR2A* rs7322347 effect on individual differences in depression level under the dialogue with environmental factors. Congruent with the present results, Mandelli and Serretti (2013) unobserved an interactive effect between lifetime SLEs or childhood trauma and *HTR2A* SNP on developing MD. It was suggested that the effect of stress exposure severity on depression might be mediated by partially different pathways and mechanisms of serotonergic functioning (Gonda et al., 2018).

#### 4.2. Oxytocin receptor gene

In the present study we observed a haplotypic effect on depression with the *OXTR* GTG haplotype (based on rs53576, rs2228485, rs237911, respectively) carriers scoring higher on this trait, which was both true for the total sample and women group. The rationale behind the use of gene-based tests instead of analyzing the effects of SNPs individually is based on the suggestion that gene is a functional unit of the genome; thus, simultaneous analysis of gene SNPs increases the statistical power (Holmqvist Jämsen et al., 2017). Previously *OXTR* rs53576 has been associated with empathy and stress reactivity (Rodrigues et al., 2009), interaction with stress-protective effects such as social support (Chen et al., 2011), and responses to acute stressors (Moons et al., 2014). The attempts to find associations between rs2228485 (c.171C > T) and eating behavior (Kim et al., 2015), autism spectrum disorders (Kelemenova et al., 2010) and social recognition (Lucht et al., 2013) were undertaken. However, to date no findings depicting gene-based haplotypes including the same SNPs as in the present study were reported. Nevertheless, in methodologically similar study a specific haplotype in the *OXTR* gene (rs53576, rs2254298 and rs2228485) was associated with affectivity, emotional loneliness and cognitive functioning in mentally healthy individuals (Lucht et al., 2009). It should be noted that rs237911 has been unexamined for the association with psychological and psychiatric phenotypes before.

To date multiple efforts to unravel GxE interactions affecting depression-like behavior have been conducted, which demonstrated the

interrelation of stress-related factors occurred at pre- and postnatal levels of development and *OXTR* gene polymorphisms. These studies reported a modulating effect of childhood adversity experienced by responders (Park et al., 2019) or by their mother in childhood (Elwood et al., 2019; Mileva-Seitz et al., 2013), maternal postnatal depression (Choi et al., 2019), and even their child's *OXTR* genotype (Asherin et al., 2019). Previously, an interaction between *OXTR* rs2254298 and the quality of the parental environment was reported to affect symptoms of depression and anxiety in female adolescents (Thompson et al., 2011). In the present study we also clarified the modulating effect of parenting style as GxE interaction between another SNP in the *OXTR* gene (rs53576) and paternal style of parenting. Interestingly, statistically significant differences in depression level were identified in individuals with a differential level of paternal care, which was demonstrated only in respondents bearing low-activity minor A-allele (AA + AG vs GG) of rs53576 (Parris et al., 2018). We suggest that modulating effect of enhanced level of paternal care on a reduced depression-like behavior is observed only under the conditions of *OXTR* deficit related to the presence of rs53576 A-allele. This effect was reported to be caused by a reduced methylation of exon 2 in the *OXTR* gene in the carriers of rs53576 GG genotype and, hence, elevated *OXTR* expression (Reiner et al., 2015). Together with allele-related association of *OXTR* gene expression, stressful life events are also known to result in differential *OXTR* methylation. Since an interaction between childhood maltreatment and *OXTR* methylation at multiple CpG sites predicted depressive symptoms later in ontogenesis (Misra et al., 2019; Smearman et al., 2016), it was suggested that *OXTR* methylation might moderate, rather than mediate, the association between childhood abuse and depression (Park et al., 2019). According to previous research consistent with a diathesis-stress model (Augustine et al., 2018), rs53576 A-allele was frequently associated with psychopathologies correlated with an increased sensitivity to stress (Saphire-Bernstein et al., 2011; Choi et al., 2019). Despite the suggestion that individuals homozygous for the G-allele may exhibit greater sensitivity to social experiences (Asherin et al., 2019), the present findings oppositely demonstrated that A-allele carriers appeared to be more sensitive to parenting style (presumably, to the level of paternal interest in their lives) compared to those with GG genotypes. Therefore, together with the "plasticity genes model" the data obtained allow to hypothesize that A-allele is a plasticity marker, contributing to a greater sensitivity to both positive and negative environmental influences. One of the possible mechanisms of the involvement of family environment in emotions processing is probably based on changes in neurobiological pathways (related to distinct gene variants) triggered by a specific family environment (Little et al., 2015; Pozzi et al., 2019).

Moreover, our findings indicate that the effect of rs237911 (c.-135C > T, located in the 5'-UTR of the *OXTR* gene) on depression score was modified by birth order controlling for sex and ethnicity. In particular, being the second-order of birth child in a family facilitated higher depression only among those with a major AA genotype of the rs237911 compared to first-born individuals. One of the probable explanations of this observation might be based on the "resource depletion theory", which suggests that each subsequent child requires an amount of parental resources higher than they can provide (Härkönen, 2014). From another side, the middle position in a siblingship was shown to be related to specific unfavorable rearing patterns resulting in psychiatric prevalence (Richter et al., 1997). Accordingly, in the case of limited parental resources (i.e., if the individual is the middle sibling in a family), the differences in emotional processing would be associated with stress sensitivity depending on the presence of a certain rs237911 variant in the *OXTR* gene. As observed in the present study (mean depression score for the first-borns was  $8.32 \pm 7.00$ , for the second-borns was  $8.69 \pm 6.65$ , for the third-borns was  $6.50 \pm 6.44$ ), in multiplex families birth order has V-shaped effects on several psychopathologies (for instance, ASD) with middle births being at high risk (Turner et al., 2011). From another side, our findings might be explained by differential methylation of depression-related genes caused by differences in birth order and several

other predictors, which were shown to explain 75% of variably methylated regions (Teh et al., 2014). According to bioinformatics resources, rs237911 resides the region of intronic circular RNA (circRNA), which represents a class of small non-coding RNAs functioning as microRNA sponges, regulators of splicing and transcription, modifiers of parental gene expression, and interacting with RNA binding proteins (Qu et al., 2017). Moreover, due to circRNAs high expression in the brain, their role in early brain development and other brain-related processes (Zhuo et al., 2020) including depression-like behavior (Zhang et al., 2018) have been recently reported. In addition, birth order might have an indirect effect on depressive-like behavior via changes in intrauterine environment caused by previous delivery, which plays a key role in shaping offspring DNA methylation of genes related to “Nervous system development and function” pathway (Li et al., 2017).

The involvement of the *OXTR* gene in anxiety-related traits (BDI-measured depression) on the gene-based and SNP-by-environment interaction level is unsurprising, since oxytocin receptors might buffer stress reactivity associated with a reduced cortisol secretion (Cardoso et al., 2014). In turn, cortisol represents one of the primary stress hormones activating the body during a stress reaction and is regulated by the HPA axis together with oxytocin (Holmqvist Jämsen et al., 2017). It was previously suggested that the effect of *OXTR* SNPs on stress-related symptoms could be realized via either direct effects of SNPs on *OXT* function influencing cortisol levels or indirect effects of SNPs on social traits, which promote seeking of peer support during stress and hence could reduce stress symptoms and lower cortisol levels (Holmqvist Jämsen et al., 2017). In the present study there was an interaction between *OXTR* rs53576 and paternal care, as well as rs237911 and birth order, thus demonstrating the possibility of the influence of parental style and birth order on HPA axis reactivity with direct effect on *OXTR* functioning. Thus, the presence of high level of paternal care may attenuate HPA-axis activity caused by diminished *OXTR* level (rs53576 AA genotype) related to enhanced anxiety and stress (Landgraf and Neumann, 2004).

#### 4.3. Arginine vasopressin receptor genes

Since arginine vasopressin receptor is a potential regulator of stress response, we succeed to demonstrate the main effect of *AVPR1A* rs3803107 on individual liability to increased depression-like behavior. Although a correlation between *AVPR1A*-related differences in circulating levels of AVP and emotional responses to an acute stressor was revealed (Moons et al., 2014), we failed to detect any moderating effect of stressful childhood conditions on *AVPR1A*-related association with depression. Recently it was predicted that miR-375 and miR-186 target regions were located at the rs3803107 locus and an increased *AVPR1A* mRNA was detected in the case of A-allele (GA/AA genotypes) compared to GG genotypes at rs3803107 (Zhang et al., 2019). In the present study we reported the association of rs3803107 A-allele and higher depression score in one ethnic group (Russians), which seems to be congruent with published data on association between lower *AVPR1A* level and reduced anxiety (Barrett et al., 2013) and the presence of rs3803107 GG genotype (Zhang et al., 2019). According to the literature, miR-375 is relevant to psychiatric conditions and psychological phenotypes (Bhinge et al., 2016; Dulcis et al., 2017), while chronic unpredictable stress can cause miR-375 increase thus affecting expression of relevant genes (Lotan et al., 2018). In turn, the role of miR-186 in synaptic scaling as a degree of stable neuronal activity affected by developmental processes was demonstrated (Silva et al., 2019). Therefore, future research on the connection between rs3803107 variations and depression liability via miR-375 and miR-186 binding appears to be promising. From the other side, observed association was ethnicity-specific, which can be explained by the existence of cross-cultural differences in depression and anxiety level (Zhao and Zhang, 2018). Previously we also demonstrated the involvement of another SNP located in 3'-UTR of the *AVPR1A* gene (rs11174811) in individual variation in personality traits in ethnicity-specific manner (Kazantseva et al., 2014). Moreover, the

impact of maternal ethnicity on placental gene expression (HPA-axis genes, in particular) may mediate differences in depressive behavior (Capron et al., 2018). Although previous findings indicated the involvement of *AVPR1B* rs33911258 in manifestation of specific behavioral pattern (Self-transcendence measured with TCI-125) (Kazantseva et al., 2014), which resembles with a decreased depression, we failed to observe any impact of this SNP in depression level in the present study.

#### 4.4. Strengths and limitations

The present study has a number of methodological strengths including homogeneity of the sample in respect to age and education. To our best knowledge, the present study is the first one to explore a modulating effect of multiple early postnatal factors occurring in childhood on genetic association of oxytocin and arginine-vasopressin receptor genes with individual liability to depression in a community sample of young adults. The majority of previously conducted studies sought to unravel genetic effect on depression under case-control paradigm, while the present study involved mentally healthy subjects based on the hypothesis of depression as a subtherapeutic continuum of affective disorders. Moreover, correction for multiple testing was used to decrease the possibility of false positive results under the false discovery rate (FDR) procedure (Simes procedure), since multiple independent hypotheses have been tested.

However, the present investigation study suffers from a number of limitations that should be reported. First, the study used a hypothesis driven candidate gene approach, which examined a limited number of genetic variants in a moderately large sample. Second, although we sought to conduct our study on the subjects of approximately the same age group (18-25 years) to protect against confounding by age, the findings may not generalize to younger or older ages. Third, we could not control for the type of parental transmission due to the absence of parental DNA samples; however, a type of allele inheritance (maternal/paternal) was described so far to affect liability to psychiatric phenotypes (Ben-Efraim et al., 2013). Although the analyses included multiple stress-related environmental factors occurring during childhood as modifiers between candidate genes and individual depression level, it is possible that we missed some other important environmental factors, such as maternal depression, recent and *in utero* stressful life events, social adversity.

#### 5. Conclusion

This is a preliminary study, which indicates that specific interaction of alleles with environmental risk may be relevant to individual sensitivity in depression variance in non-clinical sample of healthy young adults. Congruent with the differential susceptibility model of depression, we demonstrated that distinct genetic context (based on *OXTR* rs53576, rs237911) modulated sensitivity to both positive and negative environmental influences thus resulting in plasticity-related individual differences in depression level in mentally healthy subjects. Future psychogenetic research of depression should seek to replicate and extend the present research by examining other stress-related environmental factors of ante- and postnatal development under gene-by-environment paradigm involving more biologically interacting pathways and to involve not only clinical forms of depression (for instance, MDD) but also population-based samples.

#### Declarations

#### Author contribution statement

A. Kazantseva: Conceived and designed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Yu. Davydova: Conceived and designed the experiments; Performed the experiments; Contributed reagents, materials, analysis tools or data.

R. Enikeeva, M. Lobaskova, S. Malykh: Conceived and designed the experiments; Contributed reagents, materials, analysis tools or data.

R. Mustafin: Performed the experiments; Contributed reagents, materials, analysis tools or data.

Z. Takhirova: Analyzed and interpreted the data.

E. Khusnutdinova: Conceived and designed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data.

### Funding statement

This work was supported by the state task of the Ministry of education of the Russian Federation (project no. AAAA-A16-116020350032-1), the Program of collections of biological resources of FASO of Russian Federation (project no. 007-030164/2) and partially supported by the grant of the Russian Foundation for Basic Research (project no. 17-29-02195\_ofi\_m) and by the grant of the Bashkortostan Republic to young scientists in 2020 (to Yu. Davydova, state contract no. 9GR).

### Competing interest statement

The authors declare no conflict of interest.

### Additional information

Supplementary content related to this article has been published online at <https://doi.org/10.1016/j.heliyon.2020.e05240>.

### Acknowledgements

We are grateful to Dr. I. Gilyazova, Dr. N. Ekomasova, Dr. A. Nurgaliev, Prof. A. Karunas, and Dr. M. Dzhaubermezov for their assistance with samples collection.

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