Individual Variance in Human Aaggression: A Combined Effect of Polygenic Score and Social/Lifestyle Factors

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Abstract—To date, the assessment of a simultaneous effect of SNPs on manifesting aggression via polygenic score (PGS) approach has been performed mainly in Western Europeans and is scarce in Russians. In turn, genes belonging to monoaminergic systems, inflammatory response, hypothalamic-pituitary-adrenal axis, telomerase activity, and miRNA regulation have been previously associated with aggressive behavior or affective pathology. Therefore, we aimed to estimate a combined effect of PGS based on 30 SNPs belonging to abovementioned systems and social/lifestyle factors on individual differences in BPAQ-measured aggression in young adults from the Volga-Ural region (VUR) of Russia. Initially, a series of multiple linear regression was carried out in the testing sample ($N = 500$) from VUR with PGS calculated on a basis of effect estimates obtained from the training sample ($N = 565$) from VUR and controlling for sex, ethnicity, and age. The final model was based on a combined effect of PGS of *TERT, TNF, SLC6A4*, smoking and maternal protection ($p = 8.41 \times 10^{-10}$), which explained up to 11.51% of variance in physical aggression. Subsequently, we calculated PGS in the total sample from VUR ($N = 1,065$) based on summary statistics from risky behavior GWAS conducted in UK Biobank (Mbatchou et al., 2021). The best model explaining up to 4.6% of variance in verbal aggression comprised of PGS, sibship size, and childhood adversity ($p = 1.71 \times 10^{-6}$). Revealed findings evidence in a better prognostic ability of models comprising PGS based on summary statistics from ethnically same cohort and the same phenotype.

Keywords: polygenic score, antisocial behavior, single nucleotide polymorphism, neurotransmitter system, hypothalamic-pituitary-adrenal axis, microRNA

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The study of the nature of human aggressive behavior has been undertaken in enormous research conducted by psychologists, neuroscientists, sociologists, physiologists, geneticists, etc. From the evolutionary point of view, aggression is one of essential types of behavior, which gave biological advantages to our ancestors and helped humans to survive [1]. Despite a trend toward a diminished manifestation of aggressive behavior in the contemporary society, a number of criminal behavior cases remains tremendous. Namely, based on official statistics (database of the Ministry of Internal Affairs of the Russian Federation, http://www.crimestat.ru), a number of registered crimes was more than 2.6 million cases in 2022 in Russia with more than 567 thousands representing severe and especially severe cases. It should be also mentioned, that high incidence of domestic violence have aroused during the COVID-19 pandemic [2]. Therefore, the study of factors underlying escalating aggressive behavior is of high relevance.

The analysis of such factors has to be carried out within a framework of interaction between biological and environmental factors (i.e. social/lifestyle parameters, specificity of interfamily relations and the presence of unfavorable environment in childhood). Based on various findings from twin and adoption studies, heritability estimates account for 50 to 80% of variance in aggression [3]. This observation provided a series of attempts aimed to unravel a genetic basis of manifesting aggressive behavior (including antisocial behavior,

violence, conduct disorder, callous-unemotional traits, etc.), which have been focused on the functional roles of molecular networks. Initially, antisocial behavior was linked to a deletion or diminished activity of monoamine oxidase A (*MAOA*) gene [4]. Several hypotheses also relate aggressive behavior to specific functioning of certain molecular pathways, thus depicting genetic variants linked to monoaminergic functioning [5], hypothalamic-pituitary-adrenal (HPA) axis [6]. A high interest was placed toward the examination of the role of inflammatory system and related genes, i.e. proinflammatory cytokines (*TNF, IL1β, IL-6*), in mental states and social behavior [7]. In addition, the role of microRNAs and microRNA target genes in the etiology of antisocial behavior has been established [8]. It should be noted that genome-wide association studies (GWAS) have depicted SNPs associated with aggression-related traits, including rs2148710 in the *FYN* gene [9]. A dearth of these studies is a small proportion of variance in aggressive behavior explained by a single genetic variant, which requires the use of another methodological approach.

During the past decade the association analysis of single nucleotide polymorphisms (SNPs) with a variety of complex diseases and traits have been switched toward the examination of a combined effect of multiple loci on a trait of interest. One of statistical approaches, which enables estimation of such combined effect, is so called polygenic score (PGS) or polygenic index (PGI) technique [10]. This method implements the knowledge on the effect values of certain SNPs (i.e. effect estimates) on disease/trait manifestation in the initial cohort (training sample). Usually odds ratios (ORs) serve as effect estimates in case-control studies, while regression coefficients (betas) are used to calculate PGS for the analysis of quantitative trait as the outcome in a replication cohort (i.e. testing sample). At the second stage the weighted sum of all SNPs represents a polygenic score, which is calculated for each individual in the testing sample. Subsequently, relevant statistical criteria are used to examine the association between the phenotype and PGS based on individual genotypic data. This procedure enables researchers to use the PGS to explain higher proportion of variance in the trait of interest compared to a single-locus effect.

However, several potential challenges occur with the use of PGS approach for prognostic purposes. The most favorable situation is to use PGS based on effect estimates obtained from GWAS of the same phenotype and the same population. However, in comparison to UK Biobank, a number of deposited or "on demand" available GWAS data on the majority of complex traits conducted in individuals from Russia is rather small. Nevertheless, several possibilities exist, which can help to overcome such complications. First, various studies used the effect estimates reported for the SNPs association with one phenotype to examine PGS association with another close phenotype. Such

possibility exists based on a suggestion that biological/genetic factors indirectly affect liability to aggression via probable influence on some aggression-related traits (impulsivity, arousal, self-control). For example, PGS based on effect estimates for risk tolerance was shown to predict antisocial behavior in adolescents [11], while PGS of antisocial behavior (ASB) predicted disruptive behavior in ADHD case-control sample and even amygdala shape alterations [12]. Second, it is possible to use effect estimates obtained from one population (for example, Western Europeans) to calculate polygenic score, which will be tested for a possible prediction of the same phenotype in another close population (for example, Eastern Europeans, including residents of Russia). Some of published findings confirmed such possibility [11]; however, in our recent study we demonstrated the inability to use PGS for trait prediction in another population [13]. Another point is to select a set of SNPs, which combined effect can explain a greater proportion of variance in the examined phenotype. To be more precise, in some cases there is a rationale to include SNPs falling into certain statistical significance level to calculate PGS rather than to use the summary statistics from all 650k SNPs genotyped via GWAS. From another side, various studies have checked a predictive difference for a set of SNPs within a p-value range of 0.1−0.5 [14]. Therefore, a number of SNPs to include in PGS calculation represents another question. In the present study we decided to select variants in the genes belonging to monoaminergic, HPA, inflammatory systems, and miRNA binding pathways, which have previously demonstrated functional relevance to antisocial and aggressive behavior.

Aggressive behavior, as a complex phenotype caused by the interplay between genetic and environmental factors, has been recently considered within the framework of accompanying epigenetic changes [15, 16]. In this regard and assuming our previous data [13], the inclusion of social/lifestyle factors in mathematical models together with a combined effect of SNPs can probably increase a proportion of variance explained in liability to demonstrate aggressive behavior. Existing studies evidence that sex, specificity of rearing and maltreatment, family income, and smoking [1, 6] can also affect individual manifestation of aggression. Although several studies revealed a combined effect of PGS and environmental factors on proclivity toward antisocial traits [11, 17, 18], to date such studies are absent in individuals from Russia.

Therefore, the present study aimed to estimate the effect of PGS based on 30 SNPs on predisposition to develop aggression-related traits in young adults from the Volga-Ural region (VUR) of Russia assuming two approaches. The first includes PGS calculation from the effect estimates of the same population/phenotype training sample, while the second implicates effect estimates from previous GWAS of impulsivity and risk taking of Western Europeans. Moreover, we aimed to

identify social/lifestyle factors that can significantly improve PGS-based prognostic models of aggressive behavior and to determine a proportion of variance explained by a combined effect of genetic and environmental predictors.

MATERIALS AND METHODS

The study sample consisted of 1.065 mentally healthy young adults (79% women, mean age $\pm$ SD: 19.53 $\pm$ 1.75 yr; age range: 18−25 yr), who were randomly enrolled from the Universities of the Republic of Bashkortostan and the Udmurt Republic to participate in the scientific research. All participants were of European ancestry, including Russians − 357, Tatars − 340, Udmurts − 234, and individuals of mixed ethnicity − 134. The present research was approved by the Bioethical Committee at the Institute of Biochemistry and Genetics UFRC RAS (protocol code 15, date of approval, October 12, 2017). A voluntary consent to participate in the study was received from all volunteers after they were given information on the voluntary and confidential nature of their participation.

To evaluate aggression level, we used the Russian version of Buss-Perry Aggression Questionnaire (BPAQ-29) [19], that includes 29 questions and provides the results for four subscales such as physical aggression (9 items), anger (7 items), hostility (8 items), and verbal aggression (5 items). A total aggression score is calculated as a sum of subscale scores. The Russian version of BPAQ has been checked for validity and internal consistency (Cronbach's alpha for all subscales > 0.69).

In order to control for the possible impact of social/lifestyle factors on manifesting aggression, the enrolled volunteers were asked for the questions regarding their interrelations with parents in childhood (maltreatment cases, rearing in a complete/incomplete family, parenting style). The questionnaire also included the items on sibship size, urban/rural residency in childhood, present tobacco smoking. Parenting style was assessed using the Parental Bonding Instrument (PBI, 25 items) [20] separately relative to maternal and paternal styles. The PBI measures a level of "care" (parental warmth toward his/her child) and "protection" (control of decision-making in his/her child), and the best parenting style reflects high "care" and low "protection" levels.

DNA samples were isolated from the peripheral venous blood leukocytes using a phenol-chloroform technique and preceded to subsequent alignment of DNA concentrations. Thirty SNPs with a minor allele frequency (MAF) > 0.05 in Europeans have been selected based on their relevance to the genes belonging to monoaminergic systems, inflammatory response, hypothalamic-pituitary-adrenal axis, telomerase activity, and miRNA regulation, which have been previously associated with aggressive behavior or affective pathology. A complete list of genetic variants is shown in Table 1. SNPs genotyping was conducted via real-time PCR with KASP chemistry (Maxim Medical LLC, LGC Genomics, UK).

At the first stage of statistical analysis, we checked the correspondence of quantitative score on aggression scale and its subscales to the Gaussian distribution (Shapiro-Wilk W-test, $p > 0.05$). To test for the correlation between BPAQ subscales, we carried out a correlation analysis via Spearman's rank correlation coefficient. To determine individual polygenic scores, we randomly split the initial sample into a training sample ($N = 565$) and a testing sample ($N = 500$), which corresponded to each other by sex, age, and ethnicity. Accordingly, training and testing samples consisted of different individuals from the VUR. Initially, we performed linear regression analysis under additive model with sex, age, and ethnicity inclusion as covariates in the training sample ($N = 565$) (PLINK v. 1.09). This step gave us the effect estimates (standardized regression coefficients, β_{ST}), calculated for the total aggression level, physical aggression, anger, hostility, and verbal aggression. Subsequently, we selected several sets of SNPs based on their significance level: 1) all SNPs; 2) $p < 0.1$; 3) $p < 0.2$; 4) $p < 0.3$; 5) $p < 0.5$, which were used for the generation of individual PGS for each aggression subscale in the testing sample ($N = 500$). However, the assumptions for PGS calculation require an inclusion of only one of proxy SNPs. In this regard, we excluded OXTR rs237911 (proxy to rs2228485, $r^2 = 0.44$); FKBP5 rs1360780 (proxy to rs3800373, $r^2 = 0.55$); and TNF rs1041981 (proxy to rs1800629, $r^2 = 0.23$).

Briefly, a polygenic score for each individual was assumed as a weighted sum of the number of effect alleles at each locus multiplied by standardized beta. The PGS calculation was performed in accordance with PGS guide [10]. The effect alleles at each locus were assigned to those linked to higher BPAQ score in the training set. A the following stage, we have tested for the association between generated PGS and BPAQ scores in the testing sample and for a combined effect of PGS and social/lifestyle factors (R v.4.3.0, $p < 0.05$). A stepwise backward elimination procedure implemented in R was used to establish the best social predictors in regression models, which is mainly based on the lowest p-values and Akaike information criterion (AIC), and the highest proportion of variance (r^2) explaining phenotypic variance.

Another part of our study was to estimate whether PGS calculated on the basis of effect estimates from European GWAS of impulsivity [21] and risk taking [22] can also evaluate individual proneness to aggression in Russian cohort ($N = 1065$). The same procedure of PGS generation as described above was used, where the sample of young adults from the Volga-Ural region of Russia was the testing one.

Table 1. Examined genetic variants and parameters of linear regression analysis for aggression and its subscales in the training sample ($N = 565$)

SNP	Gene	EA/NEA	EAF	Direction[b]	Aggression		Physical Aggression		Anger		Hostility		Verbal Aggression	
					β_{ST}	p	β_{ST}	p	β_{ST}	p	β_{ST}	p	β_{ST}	p
rs3093077	*CRP*[b]	G/T	0.079	+/+	0.024	0.564	0.025	0.551	0.011	0.802	−0.005	0.907	0.056	0.182
rs28632197	*AVPR1B*	A/G	0.167	−/−	0.061	0.149	0.049	0.245	0.018	0.672	0.092	0.029	0.011	0.803
rs1800587	*IL1A*	G/A	0.278	−/−	0.024	0.571	0.041	0.334	0.012	0.780	−0.004	0.925	0.027	0.525
rs16944	*IL1B*[b]	A/G	0.378	+/+	0.050	0.236	0.059	0.161	0.044	0.299	0.007	0.870	0.042	0.315
rs7632287	*OXTR*	G/A	0.199	−/−	0.010	0.814	−0.026	0.545	0.030	0.479	0.033	0.437	−0.016	0.705
rs2254298	*OXTR*[b]	A/G	0.095	+/+	0.026	0.531	0.011	0.786	−0.001	0.973	0.042	0.315	0.030	0.471
rs53576	*OXTR*[b]	G/A	0.473	+/−	0.016	0.701	0.003	0.940	0.040	0.339	−0.012	0.779	0.020	0.637
rs237911[a]	*OXTR*	A/G	0.165	−/−	0.015	0.728	0.007	0.873	0.019	0.649	0.035	0.405	−0.018	0.662
rs9818870	*MRAS*[b]	T/C	0.139	+/−	0.004	0.931	0.020	0.643	−0.032	0.453	0.013	0.763	0.015	0.723
rs1317082	*TERC*[b]	G/A	0.341	+/+	0.002	0.969	0.042	0.325	−0.018	0.677	−0.003	0.951	−0.027	0.523
rs7726159	*TERT*[b]	C/A	0.337	+/−	0.090	**0.033**	0.090	**0.033**	0.041	0.337	0.064	0.130	0.082	0.053
rs41423247	*NR3C1*	G/C	0.352	−/−	0.026	0.535	0.051	0.223	−0.025	0.556	0.039	0.358	0.009	0.829
rs1800629[a]	*TNF*[b]	G/A	0.109	+/−	0.103	**0.014**	0.074	0.080	0.096	**0.023**	0.052	0.218	0.096	**0.022**
rs1360780[a]	*FKBP5*	C/T	0.280	−/−	0.050	0.235	0.047	0.263	0.059	0.159	0.031	0.467	0.067	0.111
rs13212041	*HTR1B*	T/C	0.177	−/−	0.044	0.299	0.024	0.572	0.021	0.620	0.040	0.348	0.056	0.185
rs10457441	*MIR2113*[b]	C/T	0.419	+/+	0.026	0.534	0.018	0.663	0.021	0.615	0.011	0.802	0.033	0.428
rs2148710	*FYN*	C/T	0.135	−/+	0.101	**0.017**	0.053	0.206	0.087	**0.038**	0.098	**0.020**	0.057	0.176
rs2715157	*PCLO*	A/G	0.438	−/−	0.105	**0.013**	0.058	0.169	0.100	**0.018**	0.084	**0.047**	0.070	0.099
rs531564	*MIR124*	C/G	0.151	−/+	0.011	0.797	0.041	0.335	0.011	0.801	−0.025	0.555	0.006	0.887
rs2487999	*OBFC1*	T/C	0.087	−/−	0.017	0.692	0.006	0.888	0.012	0.783	0.046	0.280	−0.028	0.507
rs1800955	*DRD4*	T/C	0.402	−/−	0.032	0.453	−0.009	0.829	0.045	0.286	0.031	0.468	0.032	0.451
rs187238	*IL18*[b]	C/G	0.283	+/+	0.028	0.504	0.054	0.203	−0.004	0.919	0.015	0.718	0.019	0.646
rs3803107	*AVPR1A*	T/C	0.176	−/+	0.000	0.994	−0.032	0.448	0.037	0.375	−0.007	0.875	0.004	0.929
rs1042615	*AVPR1A*	G/A	0.403	−/+	0.030	0.471	0.022	0.596	0.029	0.493	0.039	0.358	−0.011	0.799
rs10459194	*MIR135*	T/C	0.302	−/+	0.019	0.658	0.056	0.187	0.005	0.914	−0.038	0.364	0.045	0.287
rs2230912	*P2RX7*	A/G	0.170	−/−	0.063	0.133	0.025	0.557	0.041	0.333	0.091	**0.030**	0.025	0.558
rs1042173	*SLC6A4*	G/T	0.454	−/−	0.021	0.619	0.071	0.091	−0.031	0.462	−0.023	0.588	0.063	0.135

EA/OA — effect allele/other allele; EAF — effect allele frequency; β_{ST} — standardized regression coefficient. Statistically significant allele effects are shown in bold. Sex, ethnicity and age are included in linear regression models as covariates. [a] — the results for only one proxy SNP in LD pair in the *OXTR*, *TNF*, and *FKBP5* genes are shown. [b] — the same direction of SNPs effect alleles as in previous GWAS of risk taking [22]/ impulsivity [21] is shown as "+", while the opposite direction is marked with "−".

RESULTS

A distribution of allele and genotype frequencies was congruent with the Hardy-Weinberg expected one ($p > 0.05$), and no significant differences in them were observed between various ethnic groups comprising the sample. Subsequently, we carried out regression analysis in the training sample ($N = 565$) to establish standardized regression coefficients (β_{ST}) for total aggression score and subscales (Table 1), which have been used as effect estimates to calculate individual PGS in the corresponding testing sample ($N = 500$). It should be noted that a significant effect of *TERT* rs7726159 ($\beta_{ST} = 0.09$, $p = 0.033$ — for total aggression

and physical aggression), *TNF* rs1800629 ($\beta_{ST} = 0.103$, $p = 0.014$ — for total aggression; $\beta_{ST} = 0.096$, $p = 0.023$ — for anger; $\beta_{ST} = 0.096$, $p = 0.022$ — for verbal aggression), *FYN* rs2148710 ($\beta_{ST} = 0.101$, $p = 0.017$ — for total aggression; $\beta_{ST} = 0.087$, $p = 0.038$ — for anger; $\beta_{ST} = 0.098$, $p = 0.020$ — for hostility), *PCLO* rs2715157 ($\beta_{ST} = 0.105$, $p = 0.013$ — for total aggression; $\beta_{ST} = 0.1$, $p = 0.018$ — for anger; $\beta_{ST} = 0.084$, $p = 0.047$ — for hostility), and *P2RX7* rs2230912 ($\beta_{ST} = 0.091$, $p = 0.030$ — for hostility) was shown for the total aggression level, and for several aggression subscales. The effect alleles for examined loci are shown in Table 1. In addition, we observed positive correlations between total aggression

Table 2. The impact of social/lifestyle parameters on BPAQ-measured aggression in the testing sample ($N = 500$)

Parameter	$N,(\%$	Mean aggression score $\pm$ SD	p-value
Sex			
Men	105 (21.0)	75.03 ± 18.62	0.440
Women	395 (79.0)	73.48 ± 17.95	
Ethnicity			
Russians	167 (33.4)	76.15 ± 19.14	0.064
Tatars	160 (32.0)	70.13 ± 18.17	**0.001**
Udmurts	110 (22.0)	75.55 ± 16.31	0.291
Place of residence			
Urban	284 (56.8)	73.77 ± 16.93	0.232
Rural	216 (43.2)	71.71 ± 18.53	
Sibship size			
1	106 (21.2)	74.27 ± 18.81	0.224
2	269 (53.8)	73.01 ± 16.50	0.269
≥3	125 (25.0)	68.02 ± 17.98	**0.015**
Rearing in full family			
yes	419 (83.8)	72.84 ± 17.72	0.310
no	81 (16.2)	75.08 ± 18.19	
Childhood adversity			
yes	49 (9.8)	78.08 ± 16.83	**0.031**
no	451 (90.2)	71.71 ± 17.53	
Present smoking			
yes	40 (8.0)	79.14 ± 23.10	**0.043**
no	460 (92.0)	72.86 ± 17.25	
Maternal care			
high	341 (68.2)	70.91 ± 18.13	**0.002**
low	159 (31.8)	77.20 ± 15.67	
Maternal protection			
high	270 (54.0)	75.24 ± 17.48	**0.002**
low	230 (46.0)	69.64 ± 17.46	
Paternal care			
high	265 (53.0)	71.80 ± 18.94	0.370
low	235 (47.0)	73.52 ± 16.49	
Paternal protection			
high	235 (47.0)	73.81 ± 16.67	0.256
low	265 (53.0)	71.62 ± 18.69	

Mean aggression score and standard deviation (SD) for categorical factors are shown. Statistically significant p-values are marked in bold.

and its subscales ($p < 2.2 \times 10^{-16}$): physical aggression ($r = 0.73$), anger ($r = 0.83$), hostility ($r = 0.76$), and verbal aggression ($r = 0.65$).

In order to enhance a prognostic value of our regression model to evaluate individual differences in aggression, we have also examined whether selected social/lifestyle factors affect BPAQ-measured aggression in young adults. Our findings indicate that statistically significant effect on aggression was attributed to ethnicity ($p = 0.001$), sibship size ($p = 0.015$), childhood adversity ($p = 0.031$), tobacco smoking ($p = 0.043$), maternal care ($p = 0.002$) and protection ($p = 0.002$) (Table 2).
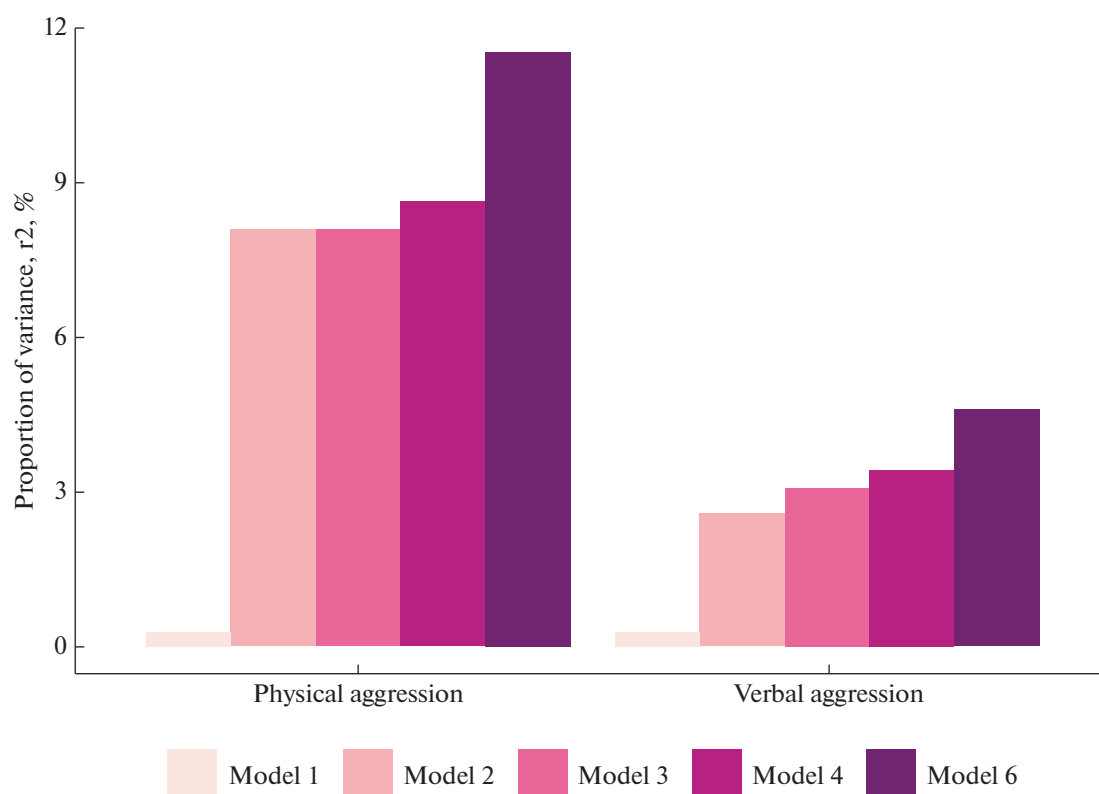
Fig. 1. Proportion of variance (adjusted r^2) in BPAQ-measured physical aggression (testing sample $N = 500$) and verbal aggression (testing sample $N = 1067$) in the Russian cohort explained by predictors under various regression models. The following predictors were included: (Model 1) PGS; (Model 2) PGS and sex; (Model 3) sex, ethnicity, and age; (Model 4) PGS, sex, age, and ethnicity; (Model 5) PGS, sex, tobacco smoking, maternal protection (for physical aggression) and PGS, sex, ethnicity, sibship size, childhood adversity (for verbal aggression). Statistical results for examined predictors are described in details in Table 3.

Within the framework of the present study we tested for several linear regression models with the inclusion of PGS based on different p-value cutoffs for SNPs (0.1, 0.2, 0.3, 0.5, all SNPs) as predictor. The most significant effect of weighted model on physical aggression was shown for PGS based on SNPs falling into $p < 0.1$ ($PGS_{0.1}$), including *TERT* rs7726159, *TNF* rs1800629, and *SLC6A4* rs1042173; however, it was observed only at a trend level ($p = 0.063$, $r^2 = 0.005$) (Table 3). We have failed to confirm the association between total aggression, anger, hostility, verbal aggression and PGS calculated for various p-value cutoffs based on standardized betas from our training sample ($p > 0.05$). In addition, we have tested for a combined effect of $PGS_{0.1}$ and sex, ethnicity, and age, which resulted in a statistically significant model (Model 3, Table 3) ($p = 5.76 \times 10^{-9}$, $r^2 = 0.0862$), mainly due to a valuable impact of sex, ethnicity, and age (Model 2, Table 3) ($p = 9.49 \times 10^{-9}$, $r^2 = 0.0811$). The final regression model, which was selected on the basis of backward elimination procedure, included $PGS_{0.1}$, sex, present smoking, and maternal protection level (Model 5, Table 3) ($p = 8.41 \times 10^{-10}$, $r^2 = 0.1151$), and explained up to 11.51% of variance in physical aggression (Fig. 1).

The second part of our present study was the attempt to establish regression models evaluating a combined effect of social factors and PGS based on effect estimates from previous GWAS of risk taking behavior [22] and impulsivity [21] in Europeans. For this purpose we calculated individual PGS for our total sample of young adults from the Volga-Ural region ($N = 1065$). No association between aggression and its subscales and polygenic score was detected at any p-value cutoff for PGS based on impulsivity effect estimates [21]. However, we succeeded to establish a crude model evaluating verbal aggression, which included PGS based on risk taking effect estimates [22] ($p = 0.044$, $r^2 = 0.0029$) (Table 3). The most significant model comprised of SNPs, which demonstrated the same direction of effects in our sample from the VUR and in GWAS of risky behavior [22]: *CRP* rs3093077, *IL1B* rs16944, *OXTR* rs2254298, rs53576, *MRAS* rs9818870, *TERC* rs1317082, *TERT* rs7726159, *TNF* rs1800629, *MIR2113* rs10457441, and *IL18* rs187238. Subsequently, an addition of sex, ethnicity, age (Model 3, $p = 2.11 \times 10^{-7}$, $r^2 = 0.0338$), sibship size, and childhood adversity (Model 5, $p = 1.71 \times 10^{-6}$, $r^2 = 0.046$) together with PGS improved the model

Table 3. Linear regression models demonstrating the effect of SNP-based PGS and social/lifestyle predictors on Physical and Verbal Aggression in the testing sample

Model	Parameter	Physical aggression ($N = 500$)			Verbal aggression [22] ($N = 1065$)		
		β	SE	p-value	β	SE	p-value
1	PGS	40.25	21.57	0.063	263.94	131.06	**0.044**
	Model p-value	0.063			**0.044**		
	Adjusted r^2	0.0050			0.0029		
2	Sex	−4.77	0.72	$\mathbf{9.58 \times 10^{-11}}$	−1.55	0.30	$\mathbf{3.22 \times 10^{-7}}$
	Ethnicity (Russians)	0.45	0.99	0.64	−0.06	0.43	0.89
	Ethnicity (Tatars)	−1.04	0.98	0.28	−1.07	0.42	**0.013**
	Ethnicity (Udmurts)	−0.09	1.07	0.93	−0.69	0.46	0.13
	Age	0.04	0.16	0.81	0.05	0.07	0.50
	Model p-value	$\mathbf{9.49 \times 10^{-9}}$			$\mathbf{4.0 \times 10^{-7}}$		
	Adjusted r^2	0.0811			0.0312		
3	PGS	40.65	21.13	0.055	259.91	132.59	0.050
	Sex	−4.73	0.72	$\mathbf{1.22 \times 10^{-10}}$	−1.53	0.30	$\mathbf{4.12 \times 10^{-7}}$
	Ethnicity (Russians)	0.71	0.99	0.47	−0.08	0.43	0.84
	Ethnicity (Tatars)	−0.86	0.98	0.47	−1.05	0.43	**0.014**
	Ethnicity (Udmurts)	0.06	1.07	0.95	−0.66	0.46	0.15
	Age	0.03	0.16	0.83	0.04	0.07	0.53
	Model p-value	$\mathbf{5.76 \times 10^{-9}}$			$\mathbf{2.11 \times 10^{-7}}$		
	Adjusted r^2	0.0862			0.0338		
4	PGS	35.73	20.75	0.085	247.87	129.57	0.056
	Sex	−4.59	0.71	$\mathbf{2.19 \times 10^{-10}}$	−1.52	0.29	$\mathbf{3.68 \times 10^{-7}}$
	Model p-value	$\mathbf{3.09 \times 10^{-9}}$			$\mathbf{3.20 \times 10^{-7}}$		
	Adjusted r^2	0.0808			0.026		
5	PGS	38.64	22.86	0.091	301.86	160.21	0.059
	Sex	−4.39	0.81	$\mathbf{9.51 \times 10^{-8}}$	−1.53	0.34	$\mathbf{1.24 \times 10^{-5}}$
	Ethnicity (Russians)	−	−	−	−0.26	0.47	0.57
	Ethnicity (Tatars)	−	−	−	−0.97	0.44	**0.029**
	Ethnicity (Udmurts)	−	−	−	−1.10	0.59	0.065
	Tobacco smoking	2.43	1.16	**0.037**	−	−	−
	Maternal protection	1.86	0.63	$\mathbf{3.13 \times 10^{-3}}$	−	−	−
	Sibship size (two)				−0.64	0.36	0.077
	Childhood adversity				1.31	0.48	**0.007**
	Model p-value	$\mathbf{8.41 \times 10^{-10}}$			$\mathbf{1.71 \times 10^{-6}}$		
	Adjusted r^2	0.1151			0.046		

The PGS for evaluate physical aggression was based on effect estimates obtained from VUR training sample ($N = 565$) for SNPs falling into $p < 0.1$, including *TERT* rs7726159, *TNF* rs1800629, and *SLC6A4* rs1042173 (see Table 1 for effect alleles). The PGS for verbal aggression was based on effect estimates reported in recent GWAS of risk taking behavior [22] and included SNPs with the same direction of effect as in the VUR sample: *OXTR* rs53576, rs2254298, *MIR2113* rs10457441, *IL1B* rs16944, *CRP* rs3093077, *MRAS* rs9818870, *TERC* rs1317082, *TERT* rs7726159, *TNF* rs1800629, and *IL18* rs187238. The best social/lifestyle predictors according to stepwise backward elimination procedure are included in the Model 4. *P*-values < 0.05 are marked in bold. Dashes stand for non-included parameters.

and gave the possibility to explain up to 4.6% of variance in verbal aggression level (Fig. 1).

DISCUSSION

Within the framework of the present study we succeeded to evaluate a combined effect of genetic variants and social/lifestyle factors on aggression types including PGS calculation based on effect estimates from: BPAQ aggression in VUR training sample and risk taking GWAS in Europeans [22]. The main finding is that designed prognostic models can explain up to 11.5% of variance in physical aggression and 4.6% — in verbal aggression in examined young adults from Russia. A proportion of variance attributed to the impact of assessed genetic variants is expectedly small (up to 0.5%), which is congruent with other PGS-based studies reporting 3.4% [23] and 2.1% [14] of variance in ASB comprising of SNPs effect at a genome-wide level. Therefore, observed findings evidence in more pronounced impact of such social predictors as tobacco smoking, specificity of rearing and child-parent relationships at younger age compared to the effect of 30 selected genetic variants related to monoaminergic, HPA, inflammatory systems, miRNA binding pathways, and telomerase functioning. Although recent studies implementing PGS approach to unravel a genetic component in manifesting aggression-related traits reported that a cumulative effect of SNPs could contribute up to ~2% of variance in childhood ASB and ~4% — in newborn ASB and externalizing behavior [23], the problem of "missing heritability" attributed to SNPs remains unsolved.

Recent studies also demonstrated a significant effect of such social/lifestyle factors as nicotine addiction and parenting style on externalizing problems, antisocial behavior and related phenotypes [17, 24]. A positive relation between smoking and aggression level in the present study can be partially attributed to common genes underlying these traits, since genetic correlation between smoking and antisocial behavior was reported [23]. From another point of view, smoking can promote aggressive behavior due to nicotine impact on CNS resulting in enhanced sensitivity to stress. While occasional smoking can help to overcome exaggerated stress, nicotine addiction causes worsening of aggressive behavior [25]. In turn, nicotine exposure has a detrimental effect on gene expression and behavior via altering epigenetic signaling [24]. Other valuable predictors in our study, which are associated with higher liability to physical and verbal aggression, are an enhanced protection style of maternal parenting and childhood maltreatment, respectively. According to the authors of the PBI [20], high protection level reflects a permanent parental trend to control their offspring in all fields, represents a negative style of rearing and, thus, adversely affects personality development. Moreover, unfavorable parenting together with a genetic predisposition influences a

development of externalizing behavior via a certain molecular mechanism [17]. In turn, an exposure to violence in childhood promoting an exaggerated distress has been repeatedly linked to the development of a negative personality and violence [26]. Another significant predictor determined in the present study is rearing with a sibling, which positively affected individual's behavior compared to a single-reared child and resulted in a diminished level of verbal aggression within a regression model. Some of published findings indicate that rearing in a family with several siblings represents an adaptive rearing strategy, which results in enhanced sociability [27]. However, an excessive number of children in a family correlates with a disruptive behavior even in childhood [28].

Existing literature evidences in a possibility to use effect estimates obtained from a study of certain phenotype to calculate PGS on its basis for subsequent association analysis with a similar phenotype. For example, a successful use of ASB PGS predicted disruptive behavior in ADHD cases [12] and PGS of risky behavior predicted ASB [11]. Since to date there is no published raw genetic data on BPAQ-measured aggression for a selected set of SNPs, we have demonstrated an applicability of PGS models, which used the data from risky behavior [22], i.e. a phenotype frequently correlating with aggression [29], to predict individual variability in BPAQ-measured aggression. However, a proportion of variance explained (0.29%) was lower than in the case of using betas from the same population and same phenotype (0.5%).

Our findings also have stressed the utility to use the data on genetic associations with aggression-related traits, which was obtained for Western Europeans, to evaluate liability to aggression in individuals from Russia. Other recent studies also were able to predict ASB in ethnically mixed cohort, including about 50% of African ancestry individuals [11]. However, our recent study failed to confirm the applicability of effect estimates from UK Biobank GWAS of depression to predict individual variance in depression in our young adults cohort [13].

It should be mentioned that among a set of 30 potential genetic variants only four were significantly associated with aggression and/or its subtypes such as physical and verbal aggression, anger, and hostility. Although these subscales significantly correlate with the total score and each other, they demonstrate a unique pattern of genetic association. To be more precise, a significant effect on aggression was observed for genes involved in inflammatory response (*TNF* rs1800629 and *P2RX7* rs2230912), telomerase activity (*TERT* rs7726159) and those detected as top significant SNPs in previous GWAS of proneness to anger (*FYN* rs2148710) [9] and depression (*PCLO* rs2715157) [30]. In turn, the best predicting model based on risky behavior GWAS included a weighted effect of SNPs related to HPA axis (*OXTR, IL1B, CRP, TNF, IL18*),

microRNA (*MIR2113*), and telomerase activity (*TERC, TERT, MRAS*). Disturbances in inflammatory response [7] and HPA axis functioning including cortisol hyporeactivity to stress [31] are considered as the probable cause of enhanced aggression. In turn, a hypothesis of the role of telomerase activity and telomere length in the liability to some mental disorders has been also discussed [32]. However, our findings also confirm previous results on a small effect of a single genetic locus in manifesting aggressive behavior.

In summary, our results testify in a probability to design a linear regression model implementing a combined effect of SNPs and social predictors to evaluate individual differences in physical and verbal aggression. We failed to demonstrate a combined effect of regression models on such aggression types as anger and hostility at various SNP p-value cutoffs. However, a stronger prognostic ability was characteristic for the model, which was based on input parameters obtained from the same phenotype and ethnically same cohort from the VUR. Recent PGS study of depression also reported that genetic associations in the Russian cohort had a specific pattern differing from other ethnic groups [33]. In this regard, further research based on PGS calculation in behavioral genetics phenotypes has to be carried out in Russian cohorts at a genome-wide association level, which can examine genetic variants specific for individuals from Russia. From the other side, a combined effect of genetic and environmental components evidence in more pronounced impact of examined social/lifestyle factors (including parenting style and smoking) compared to genetic ones on liability to exaggerated aggression (verbal and physical). The present study has several limitations, which include a limited number of SNPs comprising PGS calculation, a moderate sample size, and the absence of GWAS summary statistics of aggressive behavior established for individuals from Russia. However, the present study has several prompts that comprise of the use of the same population and the same phenotype in both training and testing samples; an inclusion of social/lifestyle factors together with the impact of SNPs in mathematical models to enhance prediction ability; the use of the sample homogenous by age and the level of education.

COMPLIANCE WITH ETHICAL STANDARDS

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.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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