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The use of genetic risk score approach to predict higher depression risk in young adults

Kazantseva A.[1, 2, 3]*, Davydova Yu.[1, 2], Enikeeva R.[1, 2], Mustafin R.[4], Malykh S.[5, 6], Lobaskova M.[5], Kosareva A.[2], Mikhailova A.Y.[2], Khusnutdinova E.[1, 2, 6]

[1] *Institute of Biochemistry and Genetics – Subdivision of the Ufa Federal Research Centre, RAS, Ufa, Russia*

[2] *Bashkir State University, Ufa, Russia*

[3] *Ufa State Petroleum Technological University, Ufa, Russia*

[4] *Bashkir State Medical University, Ufa, Russia*

[5] *Psychological Institute of Russian Academy of Education, Moscow, Russia*

[6] *Lomonosov Moscow State University, Moscow, Russia*

* *Kazantsa@mail.ru*

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Motivation and Aim: Various genetic risk score (GRS) studies reported a genetic overlap between different affective psychopathologies. However, GRS studies of depression simultaneously based on both genetic and environmental factors remain scarce. Suggesting that depression should be viewed on a continuum [1], individuals with elevated depression scores in early adulthood may be at risk for developing clinical forms of depression later in ontogenesis [2]. Since previous studies implicated deregulation in monoaminergic [3, 4], HPA-axis [5, 6], inflammatory system [7], functioning in liability to depression and related phenotypes, the present study aimed to examine whether a GRS of depression-related traits based on genetic and environmental parameters predicts higher depression risk in the testing sample of age- and ethnicity-similar individuals.

Methods and Algorithms: The study included 1067 mentally healthy individuals (79 % women; 18.85 ± 4.85 years) - students at the Universities of Russia of Caucasian origin (357 Russians, 341 Tatars, 234 Udmurts, and 135 of mixed ethnicity). The sample was divided into training (N = 767) and testing sets (N = 300). Depression score was assessed via self-report Beck Depression Inventory (BDI), while style of parental rearing – via Parental Bonding Instrument (PBI). Genotyping of examined SNPs in the *SLC6A4* (rs4795541, rs1042173), *MAOB* (rs6651806), *DRD4* (rs1800955), *AVPR1A* (rs1042615, rs3803107), *AVPR1B* (rs33911258, rs28632197), *OXTR* (rs53576, rs237911, rs7632287, rs2254298, rs2228485, rs13316193), *CRP* (rs3093077), *IL1B* (rs16944), *TNF* (rs1041981), *MIR124* (rs531564), *MIR135* (rs10459194), *MIR2113* (rs10457441), *MRAS* (rs9818870), *HTR1B* (rs13212041), *HTR2A* (rs7322347), *FYN* (rs2148710), *PCLO* (rs2715157) genes was performed using PCR-based KASP genotyping. Statistical analysis included multiple linear regressions with genotypes and environmental parameters as predictors for the training sample. GRS assessment at different P-values ($P < 0.05$, $P < 0.1$, $P < 0.2$, $P < 0.3$) was conducted in the testing sample with linear regression (PLINK v.1.09). The study was approved by the Biological Ethics Committee at the Institute of Biochemistry and Genetics.

Results: A series of linear regression analysis of depression score as dependent variable and SNPs and environmental factors as independent predictors were conducted. We succeeded to identify the best GRS model at P<0.1 significance level (P = 0.001, β = 1.099) in the testing sample, which explained 13.4 % of variance in depression score in mentally healthy young adults. This GRS model included the minor alleles of *AVPR1B* rs28632197 (β = 1.23; P = 0.010), *MRAS* rs9818870 (β = 0.90; P = 0.089), *PCLO* rs2715157 (β = 0.81; P = 0.025), *AVPR1A* rs3803107 (β = 0.96; P = 0.055), *MIR135A2* rs10459194 (β = 0.91; P = 0.020) gene variants together with such environmental factors as a decreased income level (β = 4.02; P = 0.007), the presence of chronic disorders (β = 1.68; P = 0.049), low level of paternal care (β = –2.03; P = 0.013), paternal overprotection (β = 2.53; P = 0.002).

Conclusion: Our findings established the best GRS model, which simultaneously assessed genetic and environmental factors and successfully predicted an increased depression level in the testing sample of the similar-age individuals from the same geographic region of Russia. Notably, the GRS model confirmed the involvement of genes encoding for arginine vasopressin receptors, hsa-miR-135a2 together with its target MRAS in individual variance in depression-related traits. In addition, the data obtained confirmed a significant effect of parental style of rearing and income level on individual differences in depression-related traits.

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