people with highly active MAOA-H alleles hostility was most often absent - 72.1%. It was revealed that in persons with low-active alleles of the MAOA-L gene (allele 2 and 3) a high level of hostility was more common - 50.9%. An analysis of the pattern of hostile behavior showed that people with low-activity MAOA-L alleles are more likely to agree with the statement that “people disappoint them more often”, as well as with the sentence “I think most people have to lie to “go uphill” and “I often felt that strangers look at me critically" that "people envy my good thoughts because they did not think about it first" than carriers of the highly active MAOA-H gene. In youth, the majority of individuals with low-activity MAOA-L alleles considered themselves “definitely assertive and competitive” (53.3%) than men with the presence of MAOA-H alleles (46.7%) ($\chi 2 = 10.080$ $df = 3$, $p = 0.023$). The results of a logistic regression model showed that the presence of low-active alleles (2; 3) of the MAOA gene increases the likelihood of hostility OR = 2,103 (95% CI 1,137-3,889, $p = 0.018$).

Conclusions: Our findings suggest that the low-active allele of the MAOA-L gene is associated with hostility. In our population, the most represented was the allele with 4 repeats - in 57.1% of men and with 3 repeats - in 37.2% of men, which is consistent with world data covering Caucasoid samples. The particular importance of uVNTR polymorphism is due to its functional nature: an allele with 3 repeats, and, to an even greater extent, an allele with 2 repeats, is associated with low transcriptional efficiency of the MAOA promoter, which leads to lower enzyme activity than the variant with 4 repeats [1]. The presence of low-activity alleles (2; 3) increases the risk of hostility by 2.103 times. Persons with low-activity MAOA-L alleles more often believed that “people disappoint them more often”, suspected people of lies, especially if it was related to career growth, more often felt critical views of other people on themselves, believed that others were envious of them. Also, people with low-activity MAOA-L alleles were more often considered “definitely assertive and competitive” by people.

No conflict of interest

Reference

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Genetic overlap between somatic insulin-related and neuro-psychiatric disorders

G. Fanelli[1], F. Barbara[2], W. De Witte[2], N.R. Mota[2], G. Poelmans[2], J. Bralten[2]

[1] *University of Bologna, Department of Biomedical and NeuroMotor Sciences, Bologna, Italy*

[2] *Radboud University Medical Center- Donders Institute for Brain- Cognition and Behaviour, Department of Human Genetics, Nijmegen, The Netherlands*

The prevalence of mental disorders is increased among patients suffering from insulin-related somatopathies, including metabolic syndrome (MetS), obesity and type-2 diabetes (T2D). Dysregulation of insulin signalling has also been implicated in the pathogenesis of some neuropsychiatric conditions, such as Alzheimer’s disease (AD), autism spectrum disorders (ASDs), and obsessive-compulsive disorder (OCD) [1-3], which are highly heritable and heterogeneous conditions and are characterised by a complex genetic architecture. Shared genetic mechanisms may in part underlie the comorbidity of neuropsychiatric diseases and insulin-related somatopathies. In this study, we aim to explore and quantify the extent of (potential) genetic overlap between somatic insulinopathies and the brain disorders AD, OCD and ASDs, by using the summary statistics of the largest GWASs (genome-wide association studies) that have been conducted to date.

Linkage Disequilibrium Score Regression (LDSC) bivariate analyses were performed to estimate the genetic correlation (rg) ascribed to genome-wide common variants between AD, ASDs, OCD and T2D, metabolic syndrome, obesity. Secondary analyses were carried out to further test the genetic overlap between AD, ASDs, OCD and other insulin-related traits (i.e., 2-hour glycemia, body mass index (BMI), fasting glycemia and insulinemia, glycated hemoglobinemia (HbA1c)). Summary statistics of the largest available GWASs, including up to ~900k individuals, were used as input datasets for the analyses. Bonferroni multiple testing correction was applied, correcting for the number of analyses performed (α=0.05/9=0.006 and α=0.05/24=0.002, for the primary and secondary analyses respectively).

After correcting for multiple testing, we found a positive genetic correlation between MetS and ASDs (rg=0.115, P=0.002), as well as negative genetic correlations between MetS, obesity, T2D and OCD (rg= from -0.38 to -0.17, P= from 3e-4 to 3.9e-8). Our analyses did not reveal significant genetic overlap between any of the considered somatic phenotypes and AD. The secondary analyses further identified a negative genetic correlation between OCD and BMI (rg=0.284, P=2.57e-11).

Our findings shed lights on the existence of genetic pleiotropy between insulin-related somatopathies and OCD, and to a lesser extent ASDs. Although our analyses did not reveal genome-wide genetic sharing between AD and any of the considered glyco-lipidic traits, and between ASDs and somatic insulin-related traits other than MetS, we could not rule out that the cross-trait genetic overlap may be limited to specific gene-sets (e.g., insulin signalling gene-sets). This hypothesis will be tested through GNOVA (GeNetic COVariance Analyzer), a tool that allows estimating genetic covariance across traits while stratifying it by functional annotations [4]. Gene-set analyses will also contribute to identifying specific pathways that may contribute to the comorbidity between insulin-related somatic and neuropsychiatric conditions. Overall, our findings contribute to increasing our knowledge of the role of genetic factors in insulin-related somatic and neuropsychiatric

multimorbidity. Functional genetic investigations will be important to enable better stratification of neuropsychiatric patients having higher underlying metabolic risk and to develop better-tailored treatment strategies that minimise metabolic side effects. Genetic correlation analyses will be extended to other psychiatric disorders in order to identify other potential novel brain-based insulinopathies.

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Polymorphisms of serotonergic system genes and their association with remission in patients with depression

N. Vyalova [1], G. Simutkin [2], N. Bokhan [3], S. Ivanova [1]

[1] *Mental Health Research Institute- Tomsk National Research Medical Center- Russian Academy Of Sciences-Tomsk- Russia, Laboratory Of Molecular Genetics And Biochemistry, Tomsk, Russia*
[2] *Mental Health Research Institute- Tomsk National Research Medical Center- Russian Academy Of Sciences-Tomsk- Russia, Department Of Affective Disorders, Tomsk, Russia*
[3] *Mental Health Research Institute- Tomsk National Research Medical Center- Russian Academy Of Sciences-Tomsk- Russia, Department Of Addictive Disorders, Tomsk, Russia*

Background: In patients with major depressive disorder (MDD) during antidepressant pharmacotherapy, an important aspect is the prognosis of the effectiveness of therapy due to the fact that a pronounced antidepressant effect occurs by 3-4 weeks of use [1]. The development of therapeutic resistance significantly increases the duration of hospitalization and the cost of treatment, affects the quality of life of patients. The key pathogenic mechanisms of MDD are associated with dysregulations of the serotonergic system [2, 3]. The main treatment for MDD is the use of antidepressant drugs with high selectivity for a number of neurotransmitters, in particular selective serotonin reuptake inhibitors (SSRIs) [4]. Knowledge of the patient's genetic profile, the carriage of a certain genotype of the studied genes associated with the probability of remission during antidepressant pharmacotherapy, can be the basis for the development of methods that allow an individualized approach to the choice of a drug and its dosage regimen [5].
Objectives: Search for associations of polymorphic variants of serotonin receptor genes and genes for the synthesis and metabolism of the neurotransmitter serotonin with the presence of remission in patients with MDD.
Methods: Two hundred twenty-two patients with MDD were examined (F32-F33according to ICD-10), aged 20 to 60 years. The severity of depressive symptoms was assessed using the HDRS-17 and CGI-S scales before and on the 14th and 28th days of therapy. Remission was assessed using the HDRS-17 and CGI-S scales on the 28th day of therapy. Patients with MDD were given the average therapeutic dose of antidepressants, most patients received SSRIs.

DNA genotyping was carried out using the equipment of the Core Facility "Medical Genomics", Tomsk NRMC: QuantStudio™ 5 Real-Time PCR System (Applied Biosystems, United States) using TaqMan1 Validated SNP Genotyping Assay (Applied Biosystems, USA) and MassARRAY® System (Agena Bioscience™) using the SEQUENOM Consumablesi PLEXGold 384 kits. The results were statistically processed using the SPSS 23.0.
Results: Was studied the frequency of occurrence of genotypes and alleys of 29 polymorphic variants of serotonin receptors genes: HTR1A (rs6295, rs1364043, rs1800042, rs10042486, rs749099), HTR1B (rs6298, rs6296, rs130058), HTR2A (rs6311, rs6312, rs6313, rs6314, rs7997012, rs1928040, rs9316233, rs222472), HTR2C (rs6318, rs5946189, rs569959, rs17326429, rs4911871, rs3813929, rs1801412, rs12858300), HTR3A (rs1062613, rs33940208, rs1176713), HTR3B (rs1176744), HTR6 (rs1805054) and 9 polymorphic variants of genes for the synthesis and metabolism of the neurotransmitter serotonin: MAO-A (rs6323, rs1137070), TPH1 (rs1800532, rs7933505, rs684302), TPH2 (rs7305115, rs4290270, rs13887278, rs14887278) in groups of remitters and non-remitters.

Carriage of C/C genotype rs6298 HTR1B (OR=0.52, 95%Cl=0.28-0.95, p=0.040) and A/A genotype rs130058 HTR1B (OR=0,42, 95%Cl=0.19-0.95, p=0.049), as well as T/T genotype rs3813929 (OR=2.22, 95%Cl=1.24-4.33, p=0.020) and A/A genotype rs17326429 (OR=2.06, 95%Cl =1.04-4.07, p=0.040) of the HTR2C gene in women is a factors that impedes the timely formation of remission in patients receiving antidepressant therapy.
Conclusions: We obtained data on the carriage of certain genotypes of polymorphic variants rs6298 and rs130058 of the HTR1B gene, rs3813929 and rs17326429 of the HTR2C gene in women as factors that impede the timely formation of remission in patients receiving antidepressant therapy.

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