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Association between single nucleotide polymorphisms in non-coding regions of the insulin gene and schizophrenia

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Introduction: Schizophrenia is a psychotic disorder with high heritability [1]. A variety of genes, each with small or moderate effect, have been suggested to be involved, and to date 270 such genetic loci associated with schizophrenia have been reported [2]. Of all these genetic loci reported, it is the gene region encompassing the major histocompatibility complex (MHC) on chromosome 6p22.1 playing an important role in the immune system that is the most significant and consistent [2]. However, a substantial proportion of the heritability for schizophrenia is still unknown [2,3]. There are also indications that an autoimmune-mediated process in the central nervous system, and to some extent in peripheral organs, underlies the development of a core group of schizophrenia cases and that the insulin receptor A and insulin like growth factor 1 receptor and their ligands insulin, connecting peptide (C-peptide) and insulin like growth factor 1 may constitute antigen targets [4]. The insulin gene codes proinsulin that is cleaved into equivalent amounts of insulin and C-peptide before being released from the pancreatic ß-cells to the portal circulation [5]. However, this gene has – as yet – not been studied in schizophrenia.

Aim: The aim of this study was therefore to investigate the involvement of the insulin gene in schizophrenia susceptibility.

Methods: For identification of single nucleotide polymorphisms (SNPs) of interest, the whole insulin gene and parts of its promoter region were first DNA sequenced by the Sanger method in two subgroups of the study population (i.e. 37 schizophrenia patients with heredity for schizophrenia or related psychosis, and 25 controls), and mapped to the reference sequence. Then, 7 identified SNPs of potential interest were typed by TaqMan® SNP Genotyping Assays in the whole study population, consisting of 94 patients with schizophrenia and 60 controls. To summarize categorial data frequency counts and percentages were used. Associations between genotype or allele frequencies and disease (schizophrenia versus controls) were analyzed with Chi-square test or Fisher's exact test. The same statistical methods were used to investigate associations between the variable diabetes mellitus (DM) (type 1 or 2) and/ or heredity for DM (type 1 or 2) in combination with schizophrenia or controls on one hand, and the groups of genotype or allele on the other. A p-value of less than 0.05 was considered statistically significant.

Results: Tendencies towards significant differences in allele frequencies between patients and controls were found for two of the 7 SNPs, rs5505 and rs3842749 ($p=0.077$ and $p=0.078$, respectively), whereas subgroup analyses of DM (type 1 or 2) and/ or heredity for DM (type 1 or 2) in patients and controls showed overall significant differences in genotype and allele frequencies solely for rs5505 ($p=0.021$ and $p=0.023$, respectively).

Conclusion: These findings are of interest, as the two SNPs – rs5505 and rs3842749 – may have regulatory function on the coding of insulin and C-peptide, against which increased antibody reactivity has been previously reported in schizophrenia.

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Gene and environmental risk factors: interplay between CNR1 genetic variants cannabis use, childhood trauma and psychosis

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Background: Cannabis use and childhood trauma have been proposed as environmental risk factors for psychosis and its known that gene-environment (G×E) interactions increase the risk of psychosis [1]. In particular, a recent finding suggests a link between genetic variants in the cannabinoid receptor type 1 (CNR1) gene, which encodes CB1 receptors and is expressed widely in the central and peripheral systems, and cannabis playing a role in the multifactorial pathogenesis of psychosis [2]. However, how the genetic variants interact with lifetime cannabis use and other environmental risk factors, such as childhood trauma, underlying psychosis remains challenging.

Objective: To investigate whether there are associations of gene and environmental factors with psychosis, as well as G×E interactions in the relationship between lifetime cannabis use, childhood trauma, and single nucleotide variants (SNVs) of CNR1 and psychosis in a Brazilian sample.

Methods: In a population-based case-control study nested in an incident study (STREAM, Brazil) [3], part of the WP2 EU-GEI consortium, 143 first-episode psychosis patients (FEPp) and 286 community-based controls of both sexes, aged between 16 and 64 years, were included over a period of three years. Thirteen SNVs of CNR1 gene (rs806380, rs806379, rs1049353, rs6454674, rs1535255, rs2023239, rs12720071, rs6928499, rs806374, rs7766029, rs806378, rs10485170, rs9450898), were genotyped from peripheral blood DNA using a custom Illumina HumanCoreExome-24 BeadChip genotyping arrays (GWAS Cardiff chip). Environmental adversities were evaluated using the Cannabis Experience and the Childhood Trauma Questionnaires. Data were analysed using a binary logistic regression model (Adj OR, 95% CI), including a binary outcome (community-based controls and FEPp), adjusted by sex, age, skin colour, years of education and tobacco smoking. Genotype frequencies were analysed under the dominant model (homozygous ancestral x heterozygous + homozygous variant). The significance level was set at $\alpha \leq 0.05$.

Results: Lifetime cannabis use and childhood trauma increased the risk for psychosis (OR=3.7; 2.6-6.195% CI, $p<0.001$; OR=3.0; 1.9-4.7 95% CI, $p<0.001$,

respectively). We also showed that the presence of CNR1 rs12720071-T-allele moderated the association between lifetime cannabis use and psychosis (OR=6.0; 2.0-17.5 95% CI; p=0.001). Moreover, the combination of CNR1 rs12720071-T-allele carriers with childhood trauma also suggests a change in the risk of psychosis (OR=3.6; 1.4-9.0 95% CI; p=0.006). No significant associations between the environmental factors and other SNVs were found.

Conclusions: We demonstrated a significant interaction between CNR1 rs12720071 SNV and two important environmental risk factors in their association with psychosis. T allele carriers of CNR1 rs12720071 had a higher risk of psychosis when lifetime cannabis use or childhood trauma were present. Our results suggest a G×E interaction involving the CNR1 gene, trauma and cannabis in psychosis. We will explore the associations between genetic and epigenetic markers of the CNR1 gene with environmental factors in larger and longer follow-up cohorts to better understand the mechanisms of endocannabinoid system dysfunction in the etiology of psychosis.

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Quality of life in patients with schizophrenia and their primary caregivers

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Background: Quality of life (QoL) is commonly regarded as one of the most important outcomes to be considered in the treatment of schizophrenia. However, there are still no accurate predictors for poor QoL in this patient group. Current research suggests that sociodemographic factors are significantly associated with the domains traditionally assessed in the study of QoL: physical health, psychological health, social relationships and environmental health. Among these, social relationships is the most impacted domain [1]. Moreover, personal and social functioning, as well as the severity of psychiatric symptoms, are widely considered to play a significant role in determining QoL [2]. Nonetheless, the correlation strength of different types of symptoms and their influence on each of the four QoL domains is still being debated. In the case of caregivers, the observed low QoL might be associated with financial burden, lack of social support and family relationship issues [3].

Objective: Our objective is to evaluate: (a) the sociodemographic and psychopathological characteristics that predict QoL in patients with schizophrenia, and (b) the elements that affect the primary caregiver's QoL, in relation to the patient.

Methods: In our ongoing hospital-based cross-sectional study, we intend to evaluate patients with schizophrenia admitted to the Psychiatry Clinic of Cluj County Emergency Hospital, Cluj-Napoca, Romania, alongside with their available caregivers. Each participant will complete the World Health Organization Quality of Life Instrument - Short Form (WHOQOL-BREF), whilst patients will also be evaluated using the Positive and Negative Syndrome Scale (PANSS), the Brief Assessment of Cognition in Schizophrenia (BACS), as well as the Global Assessment of Functioning (GAF) scale. Statistical significance will be ascertained by multiple linear regression analysis, Pearson correlation coefficients and the independent t-test, as appropriate.

Results: Although the positive symptoms were those which concerned the patients and their families, preliminary results indicate that the negative and depressive symptoms were significantly more linked to poor QoL. So far, better functioning and cognition were associated with higher QoL ratings in patients, as expected. In terms of sociodemographic factors, younger and married patients also had higher QoL scores. Overall, patients and their caregivers had significantly lower QoL when compared to controls. However, when comparing patients and their respective caregivers, we have yet to find a correlation between decrements in either global QoL or each of the four particular domains.

Conclusion: Low levels of functioning, poor cognition, negative and depressive symptoms, alongside social factors such as older age and single status might be key indicators predicting an overall decrease in the QoL. The current study may add to the growing body of evidence demonstrating the relevance of family and community involvement in the treatment of people with schizophrenia. Thus, it may emphasize once again the importance of going beyond symptom-reduction techniques to improve patients' QoL.

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The stress-vulnerability model on the path to schizophrenia – interaction between BDNF methylation and schizotypy on the resting-state brain network

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Background: The interplay between schizophrenia liability and environmental influences has been considered to be responsible for the development of schizophrenia. Recent neuroimaging studies have linked aberrant functional connectivity (FC) between the default-mode network (DMN) and the fronto-parietal network (FPN) in the resting-state to the underlying neural mechanism of schizophrenia. By using schizotypy as the proxy for genetic-based liability to schizophrenia and methylation of brain-derived neurotrophic factor (BDNF) to represent environmental exposure, this study investigated the impact of the interaction between vulnerability and the environment on the neurobiological substrates of schizophrenia.

Methods: Participants in this study included 101 healthy adults (HC) and 46 individuals with ultra-high risk for psychosis (UHR). All participants were tested at resting-state by functional magnetic resonance imaging, and group-independent component analysis was used to identify the DMN and the FPN. The Perceptual Aberration Scale (PAS) was used to evaluate the schizotypy level. The methylation status of BDNF was measured by pyrosequencing. For moderation analysis, the final sample consisted of 83 HC and 32 UHR individuals.

Results: The UHR group had higher PAS scores than the HC group after controlling for age, sex, and level of education [n: HC = 93, UHR = 41; mean (SD): HC = 3.4 (3.7), UHR = 9.3 (7.5); $F(1,132) = 26.2$, $P < 0.001$]. Regarding BDNFm, UHR individuals showed lower percentages of BDNF methylation than HCs after controlling for age, sex, and level of education [n: HC = 83, UHR = 32; mean (SD): HC = 3.9 (0.7), UHR = 3.6 (0.7); $F(1,113) = 4.6$, $P = 0.033$]. Compared to HCs, UHR individuals showed reduced DMN-FPN network FC [$F(1,145) = 9.4$, $P = 0.003$]. PAS scores moderated the relationship between BDNFm and the DMN-FPN network FC after controlling for age, sex, and level of education ($P = 0.031$, f2=0.047, LLCI/ULCI = -0.0193/-0.0009). BDNFm had an effect on the DMN-FPN FC when PAS scores were one SD below the mean ($\beta = 0.11$, $P = 0.008$) and at the mean ($\beta = 0.09$, $P = 0.017$), but not at one SD above the mean ($\beta = 0.03$, $P = 0.319$). Therefore, as the level of schizotypy (PAS score) increased, the strength of the positive relationship between BDNFm and the network FC decreased.

Conclusions: The main findings of this study support the hypothesis that the impact of schizotypy on the candidate network FC, the putative underlying