## EPP0453

## The role of miRNA in diagnosing and clarifying the pathomechanisms in major depressive disorder

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**Introduction:** There are currently no diagnostic or treatment-guiding biomarkers for major depressive disorder (MDD). Micro-ribonucleic acids (miRNA) may facilitate understanding the reorganisation of gene expression networks in MDD. Identifying miRNA and target mRNA pathways that contribute to MDD may open new therapeutic avenues, such as inhibiting endogenous miRNA or administering exogenous miRNA.
**Objectives:** This study investigates how miRNAs can clarify the molecular mechanisms of MDD by comparing the miRNA levels in the blood serum of patients with MDD and healthy individuals. The study also investigates the discriminative ability of miRNAs to distinguish between depressed patients and healthy controls.
**Methods:** Sixty depressed patients were matched with 60 healthy controls based on age, gender, ethnicity, and years of education. The severity of depression was measured using the Hamilton Depression Rating Scale, and venous blood was collected for miRNA profiling. Using the QIAGEN Ingenuity Pathway Analysis, networks were constructed to identify the biological pathways associated with MDD influenced by the differentially expressed miRNAs. Analyses of the receiver operating characteristic (ROC) were performed to examine the capacity of miRNAs to distinguish between depressed and healthy individuals.
**Results:** Six miRNAs (miR-542-3p, miR-181b-3p, miR190a-5p, miR-33a-3p, miR-3690, and miR-6895-3p) were significantly down-regulated in untreated depressed patients compared to healthy controls. miR-542-3p has experimentally validated mRNA targets predicted to be associated with MDD. ROC analyses determined that a panel containing miR-542-3p, miR181b-3p, and miR-3690 distinguished between depressed and healthy individuals with an area under the curve value of 0.67.
**Conclusions:** Specific miRNAs, including miR-542-3p, miR181b-3p, and miR-3690, may be biomarkers with targets implicated in the pathophysiology of depression. They could also be used to distinguish accurately between depressed and healthy individuals.

**Disclosure of Interest:** None Declared

## EPP0454

## Association of rs11644461 GRIN2A with clinical phenotype of schizophrenia

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**Introduction:** The glutamatergic system plays an important role in the neurobiology of schizophrenia. A lot of number of variants in the GRIN genes have been found in patients with various neuropsychiatric disorders (Myers et al. F1000Res 2019; 8(F1000 Faculty Rev) 1940). GluN2A, encoded by the GRIN2A gene, is the most abundant of the GluN2 NMDA receptor subunits in the mammalian CNS. Clinical symptoms of schizophrenia vary among individuals. The GRIN2A gene has previously been shown to be associated with early onset schizophrenia (Poltavskaya et al. Life (Basel) 2021; 11(10) 997).
**Objectives:** The aim of the study was to identify associations of the GRIN2A gene rs11644461 polymorphism with features of the course of schizophrenia.
**Methods:** This study was carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki 1975). 805 patients with schizophrenia (ICD-10: F20) were included. Clinical examination and diagnostic evaluation were performed using the Positive and Negative Syndrome Scale (PANSS). From the general group of patients, 2 subgroups were distinguished according to the PANSS survey: 391 patients with leading negative symptoms and 414 patients with leading positive symptoms. Also 2 subgroups were distinguished from the general group of patients: 398 patients with a continuous course of schizophrenia and 257 patients with episodic schizophrenia. Genotyping was performed by real-time PCR.
**Results:** An association of the C rs11644461 GRIN2A allele with the continuous course of schizophrenia was revealed (p<0,047). The rs11644461 polymorphism was not associated with the leading symptoms of the disease (positive or negative). At the same time, the values of the total score on the PANSS scale differed statistically significantly in carriers of different genotypes for this polymorphism. The sum of PANSS scores (Me [Q25 – Q75]) in carriers of the TC rs11644461 genotype was statistically significantly higher (106 [92–113]) than in carriers of the CC genotype (101 [87–108]) (p=0.006).
**Conclusions:** According to the results obtained, carriers of the TC rs11644461 GRIN2A genotype have a higher severity of schizophrenia symptoms according to the PANSS scale than carriers of the CC genotype. Also in the present study, it was shown that the C allele rs11644461 GRIN2A is associated with the continuous course of schizophrenia, which indicates the contribution of this locus to the formation of the course of the disease.

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## EPP0455

## Noncoding de novo mutations contribute to autism via long-range chromatin interactions

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**Introduction:** Three-dimensional chromatin interactions regulate gene expressions. The significance of de novo mutations (DNMs) in chromatin interactions remains poorly understood for autism spectrum disorder (ASD).
**Objectives:** To investigate the genomic architecture of ASD in terms of non-coding de novo mutations and 3-dimensional chromatin interactions
**Methods:** We generated 813 whole-genome sequences from 242 Korean simplex families to detect DNMs, and identified target genes which were putatively affected by non-coding DNMs in chromatin interactions.
**Results:** Non-coding DNMs in chromatin interactions were significantly involved in transcriptional dysregulations related to ASD risk. Correspondingly, target genes showed spatiotemporal expressions relevant to ASD in developing brains and enrichment in biological pathways implicated in ASD, such as histone modification. Regarding clinical features of ASD, non-coding DNMs in chromatin interactions particularly contributed to low intelligence quotient levels in ASD probands. We further validated our findings using two replication cohorts, Simons Simplex Collection (SSC) and MSSNG, and showed the consistent enrichment of non-coding DNM-disrupted chromatin interactions in ASD probands. Generating human induced pluripotent stem cells in two ASD families, we were able to demonstrate that non-coding DNMs in chromatin interactions alter the expression of target genes at the stage of early neural development.
**Conclusions:** Taken together, our findings indicate that non-coding DNMs in ASD probands lead to early neurodevelopmental disruption implicated in ASD risk via chromatin interactions.

**Disclosure of Interest:** None Declared

## EPP0456

## Emotionally Unstable Personality Disorder and Severity of Suicide Attempt are related to Epigenetic Hypermethylation of Brain-Derived Neurotrophic Factor in Women

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**Introduction:** Brain-derived neurotrophic factor (BDNF) has been associated with both emotionally unstable personality disorder (EUPD) and suicidal behavior. No study has yet investigated BDNF-associated epigenetic alterations in severely impaired EUPD and suicidal patients.
**Objectives:** The main goal of the present study was to investigate whether epigenetic dysregulation in BDNF, CRP, IL-1, IL-2 and IL-6 were associated with EUPD and severity of suicidal behavior.
**Methods:** The discovery cohort consisted of 97 women with emotionally unstable personality disorder (EUPD) with at least two serious suicide attempts (SA) and 32 healthy women. The genome-wide methylation pattern was measured by the Illumina EPIC BeadChip and analyzed by robust linear regression models to investigate mean BDNF methylation levels in a targeted analysis conditioned upon severity of suicide attempt. The validation cohort consisted of 60 female suicide attempters, stratified into low-(n=45)and high-risk groups (n=15) based on degree of intent-to-die and lethality of suicide attempt method, and occurrence of death-by-suicide at follow-up.
**Results:** Mean BDNF methylation levels exhibited hypermethylation in relation to EUPD(p=0.0343, percentage mean group difference ~3.8%). Similarly, this locus was confirmed as hypermethylated in an independent cohort of women with severe suicidal behavior (p=0.0469). Results were independent of age and BMI.
**Conclusions:** This study elicits emerging evidence of epigenetic dysregulation of BDNF in relation to phenotypes known to increase risk of suicide (lethality of suicide-attempt method and presence of EUPD diagnosis with history of recent SA). Further studies investigating epigenetic and genetic effects of BDNF on severe suicidal behavior and EUPD are needed to elucidate the role of epigenetic regulatory mechanisms and neurotrophic factors in relation to suicide risk.

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## EPP0457

## BDNF expression in brain regions of Anorexia Nervosa mouse model, a biomarker of diagnostic and prognostic?

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**Introduction:** Anorexia nervosa (AN) is a complex mental disorder mainly characterized by a voluntary food restriction and excessive physical activity resulting in dramatic weight loss. Changes in the brain-derived neurotropic factor (BDNF) have been reported in AN patients compared to controls. According to meta-analysis, functional variant rs6265 Val66Met of the *BDNF* gene has been found genetically associated to AN. We also reported an association of this functional variant and electrodermal response to images of thinness suggesting an association between rs6265 and a reward effect of weight loss in AN. In animal models, BDNF modulates negatively the central control of food intake and its injection in rodents induces weight loss and anorexia. Thus, besides its function on neuronal survival, synaptic plasticity and mood, BDNF was also reported to have a metabolic effect via both central nervous system and peripheral organs, which makes BDNF a good candidate for AN diagnosis biomarker.
**Objectives:** Our study investigates the levels of expression of Bdnf, gene and protein, taking advantage of the mouse AN-like model by measuring Bdnf levels in specific brain areas and blood in food-restricted and refeed animals.
**Methods:** We used a mouse AN-like model combining a phase of chronic food restriction (50%) during 15 days followed by an *ad libitum* refeeding period of one week. Female mice have or not access to a running with wheel to create a similar metabolic environment that those patients suffering from AN during restriction and recovery once hospitalised. The Bdnf mRNA and protein levels were measured in samples of blood and brain regions (prefrontal