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Oxidative stress – A promising candidate in explaining the neurobiology of autism spectrum disorders

M. Bækgaard Thorsen [1,2,*], N. Bilenberg [3], E. Benedikz [4], Å. Fex Svenningsen [4], P. Munk-Jørgensen [1], T. Sheldrick-Michel [2]
[1] *Psychiatric Hospital and University of Southern Denmark, Psychiatric Research Academy Odense, Odense, Denmark*
[2] *Psychiatric Hospital and University of Southern Denmark, Research Unit of Psychiatry Odense, Odense, Denmark*
[3] *Psychiatric Hospital and University of Southern Denmark, Research Unit of Child, and Adolescent Psychiatry Odense, Odense, Denmark*
[4] *Institute of Molecular Medicine, University of Southern Denmark, Department of Neurobiology Research, Odense, Denmark*
* *Corresponding author.*

Introduction The diagnoses of autism spectrum disorders (ASDs) are based on a phenotype, characterized by impaired social interaction and communication and by repetitive and restricted interests. However, this might not represent a single clinical entity, but a behavioral manifestation of different neurodevelopmental deficits with a multifactorial etiology. Small studies have shown elevated levels of oxidative stress and lower levels of anti-oxidants in patients with ASD, and correlations with the severity of ASD. Therapies targeting oxidative stress have shown improvements regarding behavior, social interaction and verbal communication in patients with ASD, supporting the oxidative stress theory.
Objectives To evaluate the importance of oxidative stress in the neurobiology of adults with ASD.
Aims There is a need to understand the neurobiology of ASD, therefore this study analyzes the level of oxidative stress in a larger cohort of patients with ASD and compares to controls.
Methods The study includes 350 patients over 18 years of age diagnosed with ICD-10 diagnoses F84.0, F84.1, F84.5 or F84.8 and compared to gender and age matched neurotypical controls. The included probands will have their serum and plasma analyzed for levels of oxidative stress (superoxide dismutase 1 and 2, catalase, glutathioneperoxidase, malonialdehyde, thiobarbituric acid reactive substances and xanthinoxidase).
Results The preliminary results will be presented at the EPA in March 2016 in Madrid.
Conclusion With this study we aim to elucidate some of the neurobiology in ASD. This could lead to new potential targets for treatment and prevention of the disorders.
Disclosure of interest The authors have not supplied their declaration of competing interest.

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Plasma micro-RNA profiles in patients with major depressive disorder (MDD)

V.R. Enatescu [1,*], I. Papava [1], I. Enatescu [2], M. Antonescu [3], A. Anghel [3], E. Seclaman [3], I.O. Sirbu [3], R. Romosan [1], C. Marian [3]
[1] *"Victor Babes" University of Medicine and Pharmacy Timisoara, Department of Psychiatry, Timisoara, Romania*
[2] *"Victor Babes" University of Medicine and Pharmacy Timisoara, Department of Neonatology and Puericulture, Timisoara, Romania*
[3] *"Victor Babes" University of Medicine and Pharmacy Timisoara, Department of Biochemistry, Timisoara, Romania*
* *Corresponding author.*

Introduction Micro-RNAs (miRs) are involved in processes associated with MDD such as neural plasticity, neurogenesis, synaptogenesis and stress response. MiRs are detectable in biological fluids; however, no data is available regarding the use of plasma circulating miRs as markers of MDD, only whole blood or serum being reported so far.
Objectives We investigated plasma miR profiles as potential markers for MDD in patients treated with antidepressants.
Aims To detect and characterize differentially expressed miRs in the plasma of MDD patients, before and after treatment with escitalopram.
Methods Blood was collected from patients with MDD before and after 12 weeks of treatment. Plasma profiles of 1008 miRs were measured by real time PCR. The fold change of expression between time points was calculated and a paired *t* test was used for statistical significance. Gene targets and pathways were assessed in miRWalk2.0.
Results From 222 plasma miRs expressed, 40 were significantly different after treatment. Upregulated miRs (23) belonged to 43 pathways, down-regulated miRs (17) belonged to 46 pathways; the top 5 significant pathways identified being pathways in cancer, Wnt signalling, endocytosis, axon guidance and MAPK signalling. Six of these miRs are common to all five pathways: miR-146a-5p, miR-146b-5p, miR-221-3p, miR-24-3p, miR-26a-5p.
Conclusions Our analysis of significant changes in plasma miRs after escitalopram treatment of MDD might open new avenues for the understanding of its mode of action and its side effects. To our knowledge, this is the first study to assess miRs affected by antidepressant treatment in plasma of MDD patients.
Disclosure of interest The authors have not supplied their declaration of competing interest.

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Characterizing rare mis-sense variations of CACNA1I identified in a Swedish schizophrenia cohort

J. Pan[*], A. Allen, L. huang, D. Daez
Broad Institute of Harvard and MIT, Stanley Center for Psychiatric Research, Cambridge, USA
* *Corresponding author.*

CACNA1I (hCa$_V$3.3) encodes the α1 pore-forming subunit of human voltage-gated T-type calcium channels. Ca$_V$3.3 is expressed in a limited subset of neurons including GABAergic neurons of the thalamic reticular nucleus (TRN) where they support oscillatory activity essential for sleep spindle generation. *CACNA1I* is implicated in schizophrenia risk by emerging genetics including genome-wide association studies (PGC, 2014), and exome sequencing of trio samples (Gulsuner et al., 2013). In order to understand the impact of disease-associated sequence variation on the function of Ca$_V$3.3, we set out to analyze a complete set of rare mis-sense coding variations in *CACNA1I* in a Swedish cohort, including 15 variations identified in patients, 20 identified in control subjects, and 23 in both. We established a heterologous expression system of isogenic cell lines, each carrying single-copy inducible cDNA variants of hCa$_V$3.3, and evaluated their functional impact on channel function by electrophysiology, calcium imaging, and biochemistry. We found at least five coding variations impaired overall channel protein abundance, as well as whole cell current density. In addition, we identified hCa$_V$3.3 variants with altered voltage-dependence of channel activation and inactivation. Overall, we found that reduced calcium influx through hCa$_V$3.3 is associated with the group of variants identified in patients, compared to those in both patients and controls. Our findings suggest that patient-specific rare variations of *CACNA1I* may influence channel-dependent functions, including rebound bursting in TRN neurons, with potential implications for schizophrenia pathophysiology.

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Polymorphism neuropeptide receptor gene S (NPSR1) and sleep disturbances

V. Gafarov [1,*], M. Voevoda [2], E. Gromova [1], V. Maximov [2], D. Panov [1], I. Gagulin [1], A. Gafarova [1]

[1] *FSBI Institute of Internal and Preventive Medicine, Collaborative Laboratory of cardiovascular disease epidemiology, Novosibirsk, Russia*
[2] *FSBI Institute of Internal and Preventive Medicine, Laboratory of molecular and genetic study, Novosibirsk, Russia*
* *Corresponding author.*

Objective   To study the association gene of candidate NPSR1 rs324981 with sleep disorders in the open population of men 45–64 years of Novosibirsk.

Materials and methods   The study of the association candidate gene polymorphisms with sleep disorders was carried out during the examination of a random representative sample of men 45–69 years ($n = 1770$). The response rate was 61%. The median age is 56.5 year. Every 12 a man was selected for genotyping ($n = 147$). To assess the level of sleep was used a questionnaire which was filled with self-test. Statistical analysis was performed using SPSS-11.5.

Results   The level of sleep disorders in the male population of 45–64 years was 79.9%. The frequency of homozygous C/C genotype of neuropeptide S (gene *NPSR1* rs324981) was 19.4%, T/T genotype occurs in 27.8%, C/T genotype −52.8%. Men dominated the T allele of −54.2%, and the C allele −45.8% growth trend Fnd dissatisfaction with the quality of their sleep among men. Men T-allele carriers, most evaluated their sleep as "satisfactory" in 69% of cases, ($\chi^2 = 15,713$ df = 8, $P < 0.05$).

Conclusion   Association found men carrier T-allele of neuropeptide S (gene *NPSR1* rs324981), a sleep disorder.

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Borderline personality disorder and childhood maltreatment: A genome-wide methylation analysis

L. Stenz [1,*], J. Prados [2], P. Courtet [3], P. Prada [4], R. Nicastro [4], W. Adouan [5], S. Guillaume [3], E. Olié [3], J.M. Aubry [4], A. Dayer [6], N. Perroud [4]

[1] *Switzerland*
[2] *Geneva university, departement of psychiatry, Geneva, Switzerland*
[3] *Centre Hospitalier Régional Universitaire de Montpelier, Department of Emergency Psychiatry, Montpellier, France*
[4] *University Hospitals of Geneva, Department of Mental Health and Psychiatry, Geneva, Switzerland*
[5] *University of Geneva, Department of Psychiatry, Geneva, Switzerland*
[6] *Geneva Unviersity, Department of Psychiatry, Geneva, Switzerland*
* *Corresponding author.*

Early life adversity plays a critical role in the emergence of borderline personality disorder (BPD) and this could occur through epigenetic programming. In this perspective, we aimed to determine whether childhood maltreatment could durably modify epigenetic processes by the means of a whole-genome methylation scan of BPD subjects. Using the Illumina Infinium® Human Methylation 450 Bead Chip, global methylation status of DNA extracted from peripheral blood leucocytes was correlated to the severity of childhood maltreatment in 96 BPD subjects suffering from a high level of child adversity and 93 subjects suffering from major depressive disorder (MDD) and reporting a low rate of child maltreatment. Several CpGs within or near the following genes (IL17RA, miR124-3, KCNQ2, EFNB1, OCA2, MFAP2, RPH3AL, WDR60, CST9L, EP400, A2ML1, NT5DC2, FAM163A and SPSB2) were found to be differently methylated, either in BPD compared with MDD or in relation to the severity of childhood maltreatment. A highly relevant biological result was observed for cg04927004 close to miR124-3 that was significantly associated with BPD and severity of childhood maltreatment. miR124-3 codes for a microRNA (miRNA) targeting several genes previously found to be associated with BPD such as NR3C1. Our results highlight the potentially important role played by miRNAs in the etiology of neuropsychiatric disorders such as BPD and the usefulness of using methylome-wide association studies to uncover such candidate genes. Moreover, they offer new understanding of the impact of maltreatments on biological processes leading to diseases and may ultimately result in the identification of relevant biomarkers.

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Effect of Disrupted-in-Schizophrenia 1 gene on treatment response in patients with a first episode of psychosis

J. Vázquez Bourgon [*], R. Ayesa Arriola , P. Suarez Pinilla , R. Roiz Santiañez , D. Tordesillas Gutierrez , V. Ortiz-García de la Foz , B. Crespo-Facorro

University Hospital Marqués de Valdecilla-IDIVAL, CIBERSAM, Psychiatry, Santander, Spain
* *Corresponding author.*

Introduction   There is substantial evidence suggesting that individual variability in antipsychotic treatment response could be genetically determined. Disrupted-in-Schizophrenia 1 (DISC1) gene has been previously associated to the illness and to treatment response in a sample of patients suffering from psychosis. However, there is a lack of studies on the effect of DISC1 on treatment response in samples of first episode psychosis.

Objectives   The aim of this study was to explore the relation between variations in DISC1 gene and treatment response to antipsychotics in a sample of drug-naïve patients with a first episode of psychosis.

Methods   Two hundred and twenty Caucasian drug-naive patients experiencing a first episode of non-affective psychosis were genotyped for rs821616 (Ser704Cys), rs6675281 (Leu607Phe) and rs1000731. Early (6 weeks) response to antipsychotic treatment was assessed with the Brief Psychiatric Rating Scale, the Scale for the Assessment of Positive Symptoms, and the Scale for the Assessment of Negative Symptoms. Other clinical and socio-demographic variables were recorded to eliminate potential confounding effects.

Results   We found a significant association between rs1000731 and treatment response. Thus, those patients homozygous for the G allele of rs1000731 were more frequently non-responders, measured with SANS, after 6 weeks of treatment, than those carrying the A allele ($X^2 = 4.019$; $P = 0.032$). Moreover, when analysing the clinical improvement longitudinally, we observed that those patients carrying the A allele for the rs1000731 presented a greater improvement in positive symptoms dimension (F = 8.905; $P = 0.003$).

Conclusions   Our results suggest a minor contribution to antipsychotic drug response of genetic alterations in the DISC1 gene.