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Syndrome Scale (PANSS). There were no significant correlations between chlorpromazine equivalent dosage or treatment duration and the level of HERV-K methylation.

Summary of results: There was no significant difference in the level of HERV-K methylation between first-episode schizophrenia patients and healthy controls (40.33 ± 4.85 vs. $40.95 \pm 4.10\%$, $p = 0.192$). However, there was a negative correlation between the level of HERV-K methylation and PANSS positive symptoms score ($r = -0.352$, $p = 0.017$). Linear regression analysis revealed that HERV-K methylation level was a negative predictor of the severity of positive symptoms ($B = -0.378$, $t = -2.688$, $p = 0.010$) after co-varying for chlorpromazine equivalent dosage. HERV-K methylation level was not associated with scores of other PANSS subscales.

Conclusion: Our results provide preliminary evidence that HERV-K methylation is not related to schizophrenia susceptibility. However, the level of HERV-K methylation might be associated with the severity of positive symptoms. Future studies in larger samples are required to confirm results of this study.

Reference

- [1] Leboyer, M., Tamouza, R., Charron, D., Faucard, R., Perron, H., 2013. Human endogenous retrovirus type W (HERV-W) in schizophrenia: a new avenue of research at the gene-environment interface. *The World Journal of Biological Psychiatry* 14 (2), 80–90.

P.1.a.025 Dopamine receptors genes polymorphisms in Parkinson patients with levodopa-induced dyskinesia

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Introduction: Long-term levodopa treatment of Parkinson's disease (PD) is frequently complicated by spontaneously occurring involuntary muscle movements called levodopa-induced dyskinesia (LID). LID are a substantial barrier to effective symptomatic management of Parkinson's disease (PD), as up to 45% of L-DOPA users develop LID within 5 years [1]. The exact pathological mechanism of this complication has not yet been elucidated. A lot of studies nowadays which approved complex genetic nature of LID. And these genes are involved not only for oxidative stress, but in drug metabolism too [2–4].

Objective: This study aimed to investigate a possible contribution of polymorphic variants of DRD1, DRD2, DRD2/ANKK1, DRD3, DRD4 genes in the development of LID in PD patients.

Methods: 212 patients with Parkinson's disease on levodopa therapy were investigated. Dyskinesia was measured by using Abnormal Involuntary Movement Scale (AIMS). DNA extraction and fluorogenic 5'-exonuclease TaqMan genotyping assays were conducted according to standard protocols and blind to clinical status of the subjects. Genotyping was carried out on 28 SNPs of dopamine receptors (rs4532, rs936461, rs6275, rs1801028,

rs4245147, rs134655, rs6277, rs1076560, rs2283265, rs179997, rs6279, rs1076562, rs2734842, rs2734849, rs11721264, rs167770, rs3773678, rs963468, rs7633291, rs2134655, rs9817063, rs324035, rs1800828, rs167771, rs6280, rs1587756, rs3758653, rs11246226) on the MassARRAY® Analyzer 4 (Agena Bioscience™) using the set SEQUENOM Consumables iPLEX Gold 384. SPSS software was used for statistical analysis. Statistical significance of the association testing was established using permutations. P-value <0.05 after permutations was considered statistically significant.

Results: Patients in our cohort demonstrated typical PD demographics, with a mean age of onset of 60.04 ± 9.46 years, a mean disease duration of 9.79 ± 5.57 years. Dyskinesia was reported in 57 (26.9%) patients. The distribution of genotypes of studied genes corresponded to the Hardy-Weinberg equilibrium. We found that 5 polymorphisms (rs4245147, rs6275, rs2734842, rs6279, rs1076562) are significantly associated with LID. All these polymorphisms are located in DRD2 gene. In logistic regression models adjusted for the covariates, such as age, gender and duration of disease only one of the studied markers was associated with LID (rs4245147). Odds ratio for carriers of the genotype TT is 1.73 [95% CI: 1.12–2.70], which indicates the predisposing effect of this genotype on the development of dyskinesia. Polymorphisms in the dopamine receptors genes play significant role in the therapy response to L-DOPA as well as in various of its adverse effects. We hypothesized that single nucleotide polymorphisms in DR genes may result in a clinical phenotype contributing to an increased risk of LID. This appears to be especially true for rs4245147 of the DRD2 gene. Hence, this gene polymorphism is a good candidate for studying (genetic) biomarkers predicting the risk of developing this movement disorder.

Conclusion: Rs4245147 polymorphism of the DRD2 gene is a putative component of a set of biomarkers predicting the vulnerability to develop dyskinesia.

References

- [1] Rascol, O., Brooks, D.J., Korczyn, A.D., et al., 2000. Study Group: A five-year study of the incidence of dyskinesia in patients with early Parkinson's disease who were treated with ropinirole or L-DOPA. *N Engl J Med* 342, 1484–1491.
- [2] Ivanova, S.A., Fedorenko, O.Y., Freidin, M.B., et al., 2016. Dissimilar mechanistic background of peripheral and orofacial hyperkinesia in patients with Parkinson's disease and levodopa-induced dyskinesia. *Physiology and Pharmacology* 19, 216–221.
- [3] Kaplan, N., Vituri, A., Korczyn, A.D., et al., 2014. Sequence variants in SLC6A3, DRD2, and BDNF genes and time to levodopa-induced dyskinesias in Parkinson's disease. *J Mol Neurosci* 53 (2), 183–1880.
- [4] Rieck, M., Schumacher-Schuh, A.F., Altmann, V., et al., 2012. DRD2 haplotype is associated with dyskinesia induced by levodopa therapy in Parkinson's disease patients. *Pharmacogenomics* 13 (15), 1701–1710.

P.1.a.026 Association between polymorphisms of the PCDH15 gene and schizophrenia in Korean population

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Objective: Protocadherin 15 (PCDH15) gene, which encodes a member of the cadherin superfamily that plays a crucial role in hair cell sensory transduction and contributes to neural development