DRD2, BDNF AND SLC6A3 SEQUENCE VARIANTS AND LEVODOPA INDUCED DYSKINESIA

N. Kaplan[1,3], A. Vituri[4], A.D. Korczyn[5], O.S. Cohen[1,3], R. Inzelberg[1,3], G. Yahalom[1], E. Friedman[2,3], S. Rosset[4], S. Hassin-Baer[1,3]

[1]*The Parkinson Disease and Movement Disorders Clinic, Sagol Neuroscience Center and Department of Neurology; Chaim Sheba Medical Center, Tel-Hashomer, Ramat Gan, Israel*

[2]*The Susanne-Levy Gertner Oncogenetics Unit, The Institute of Human Genetics; Chaim Sheba Medical Center, Tel-Hashomer, Ramat Gan, Israel*

[3]*The Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel*

[4]*The School of Mathematical Sciences, Tel Aviv University, Tel Aviv, Israel*

[5]*The Sieratzki Chair of Neurology; Tel Aviv University, Tel Aviv, Israel*

Background: Levodopa-induced dyskinesias (LID) are a common treatment limiting adverse effect of levodopa therapy in Parkinson's disease (PD) patients. The precise mechanisms and genes affecting LID latency are elusive.

Methods: In order to identify genetic factors associated with LID latency, 352 (213 males) levodopa-treated Israeli PD patients, were genotyped for 34 polymorphisms within 3 candidate genes affecting dopaminergic activity and synaptic plasticity: SLC6A3 [DAT1] (14 SNPs and 40bp VNTR), DRD2 (11 SNPs and dinucleotide CA STR) and BDNF (7 SNPs).

The hazard rate for LID over time was evaluated using survival analyses [Cox proportional hazards and accelerated failure time (AFT) lognormal models].

Results: The mean age at PD motor symptoms onset (± SD) was 59.4 (±13.4) years and mean PD duration until LID occurrence or last follow-up was 7.0 (±4.7) years. Overall, 192 (54.5%) of participants developed LID, with a mean latency of 5.0 (±4.5) years. After adjusting for the confounding effects of gender, age at disease onset, symptoms duration to levodopa exposure, and multiple testing, 2 SNPs in the SLC6A3 gene were significantly associated with LID latency: rs393795, a protective "C" allele extending expected time to LID, TR= 4.91 (95% CI, 2.24-10.74; p=6.7*10-5) and rs2617605 with an "A" additive, risk-increasing allele, HR=1.88 (95% CI, 1.368-2.585; p=9.98*10-5) limited to Ashkenazi patients (n=217).

Conclusions: Sequence variants in the SLC6A3 gene were associated with LID latency in Israeli PD patients mostly of Ashkenazi Jewish origin. These preliminary results should be validated in larger, ethnically diverse PD populations.