

Sex differences in microRNA expression in levodopa-naïve PD patients

*Maria Claudia Russillo*¹, A. Vallelunga², T. Iannitti³, G. Somma¹, M. Picillo¹, R. De Micco⁴, L. Vacca⁵, R. Cilia⁶, E.C. Cicero⁷, R. Zangaglia⁸, G. Lazzeri⁹, S. Galantucci¹⁰, F.G. Radicati⁵, A. De Rosa¹¹, M. Amboni¹, C.L. Scaglione¹², A. Tessitore⁴, F. Stocchi^{1,3,5}, R. Eleopra⁶, A. Nicoletti⁷, C. Pacchetti⁸, A.B. Di Fonzo⁹, M.A. Volontè¹⁰, P. Barone¹, M.T. Pellecchia¹

¹ Department of Medicine Surgery and Dentistry “Scuola Medica Salernitana”, Neuroscience Section, University of Salerno, Salerno, Italy

² Department of Life Sciences and Biotechnologies, University of Ferrara, Ferrara, Italy

³ Department of Medical Sciences, Section of Experimental Medicine, University of Ferrara, Ferrara, Italy

⁴ Department of Advanced Medical and Surgical Sciences, University of Campania “Luigi Vanvitelli”, Napoli, Italy

⁵ IRCCS San Raffaele, Roma, Italy

⁶ Fondazione IRCCS Istituto Neurologico Carlo Besta, Department of Clinical Neurosciences, Parkinson and Movement Disorders Unit, Milano, Italy

⁷ Neurologic Unit, AOU “Policlinico-San Marco”, Department of Medical, Surgical Sciences and Advanced Technologies, G.F. Ingrassia, University of Catania, Catania, Italy

⁸ Parkinson's Disease and Movement Disorders Unit, IRCCS Mondino Foundation, Pavia, Italy

⁹ IRCCS Ca' Granda Ospedale Maggiore Policlinico, Neurology Unit, Milano, Italy

¹⁰ IRCCS San Raffaele Scientific Institute, Neurology Unit, Milano, Italy

¹¹ Department of Neurosciences and Reproductive and Odontostomatological Sciences, Federico II University, Napoli, Italy

¹² IRCCS Istituto delle Scienze Neurologiche di Bologna, Bologna, Italy

¹³ University San Raffaele, Roma, Italy

Introduction: Parkinson's disease (PD) is the second most common neurodegenerative disorder that affects millions of individuals worldwide. Biological sex is an important factor influencing epidemiological and clinical features of the disease. MicroRNAs (miRNAs) are small non-coding RNAs which regulate gene expression at post-transcriptional level. Several studies have shown that specific panels of miRNAs are dysregulated in PD and other parkinsonian disorders [1,2].

Objective: Our goal was to evaluate gender differences in the expression of a panel of miRNAs (miR-34a-5p, miR-146a, miR-155, miR-29a, miR-106a) possibly involved in the pathophysiology or progression of disease.

Methods: Serum samples were obtained from 104 PD patients (58 men and 46 women) never treated with levodopa. All samples with severe hemolysis were excluded. We measured levels of miRNAs using quantitative PCR. Correlations between miRNA expression and clinical data were assessed using the Spearman's correlation test. We used STRING to evaluate co-expression relationship among target genes.

Results: MiR-34a-5p was significantly upregulated in PD male patients compared with PD female patients (fc: 1.62; $p < 0.0001$). No correlation was found with age, BMI, and disease severity, assessed by UPDRS III scale, in male and female patients. MiR-146a-5p was significantly upregulated in PD female compared with male patients (fc: 3.44; $p < 0.0001$) and a significant correlation was also observed between disease duration and mir-146a-5p. No differences were found in the expression of

miR-29a, miR-106a-5p and miR-155 between genders. Predicted target genes for miR-34a-5p and miR-146-5p and protein interactions in biological processes were reported.

Conclusions: Our study supports the hypothesis that there are sex specific differences in serum miRNAs expression in PD patients, possibly affecting disease progression and response to treatment.

References:

- [1] Zago E, Dal Molin A, Dimitri GM, Xumerle L, Pirazzini C, Bacalini MG, Maturo MG, Azevedo T, Spasov S, Gómez-Garre P, Periñán MT, Jesús S, Baldelli L, Sambati L, Calandra-Buonaura G, Garagnani P, Provini F, Cortelli P, Mir P, Trenkwalder C, Mollenhauer B, Franceschi C, Liò P, Nardini C; PROPAG-AGEING Consortium. Early downregulation of hsa-miR-144-3p in serum from drug-naïve Parkinson's disease patients. *Sci Rep.* 2022 Jan 25;12(1):1330. doi: 10.1038/s41598-022-05227-6. PMID: 35079043; PMCID: PMC8789812.
- [2] Vallelunga A, Iannitti T, Capece S, Somma G, Russillo MC, Foubert-Samier A, Laurens B, Sibon I, Meissner WG, Barone P, Pellecchia MT. Serum miR-96-5P and miR-339-5P Are Potential Biomarkers for Multiple System Atrophy and Parkinson's Disease. *Front Aging Neurosci.* 2021 Jul 26;13:632891. doi: 10.3389/fnagi.2021.632891. PMID: 34381349; PMCID: PMC8350521.