**RESEARCH TOPIC DASMEN7**

# Same germinal DNA but different outcomes: dissecting Parkinson's disease pathogenesis by integrated omics analyses of discordant monozygotic twins

**Curriculum DASMEN Standard**

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**Abstract**
Parkinson's disease (PD) is a chronic progressive disorder for which there is no cure. The loss of dopaminergic neurons that leads to disability develops slowly over many years, so that, by the time the disease is diagnosed, it is already extensive and irreversible. Both genetics and environmental factors play a role in determining the susceptibility and clinical presentation of PD. Among the environmental factors the immune system and in particular inflammation certainly play an important role. Our present understanding of the pathogenesis of PD and the available therapies remain limited. Therefore, there is an urgent need to develop early disease biomarkers and neuroprotective treatments.

Monozygotic (MZ) twins have been widely exploited to study the relative contributions of genetics and environment in human diseases. In PD the large discordance in MZ twins has been interpreted to indicate a stronger impact of the environment in disease pathogenesis, particularly when PD occurs later in life. However, multiple reports suggest that MZ twins are not genetically identical: in particular, a recent paper showed that MZ twins differ on average by 5.2 early developmental (somatic) mutations. Even more importantly, twins accumulate over years a number of epigenetic differences, which are due to environmental agents, aging and stochastic phenomena that might affect the gene-expression portrait and the risk to develop diseases. Therefore, beyond the analysis of environmental factors, discordant MZ twin pairs are an excellent resource to discover crucial genetic and epigenetic factors that determine the phenotypic expression of a disease. Moreover, twin studies represent a unique experimental design to point out disease-specific biomarkers.

In this project, we are proposing an approach that will take advantage of the peripheral blood and detailed medical information collected from a large group (85 individuals) of MZ twins (couples or

triplets) discordant for PD. By comparing the genome (length of telomeres, early somatic developmental mutations, somatic recombination events mediated by repetitive regions), epigenome (RNAseq methylation analysis), transcriptome (differential gene expression, repertoire of BCR and TCR receptors, circRNA and alternative splicing profiles), and inflammatory profile of the diseased twin with the one of the healthy sibling/s we expect to unravel important aspects of disease etiology and to identify early peripheral disease biomarkers.

The different sets of data will be integrated by multi-OMICS data analysis by Bayesian unsupervised methods or by artificial intelligence (AI) approaches, and combined with deep phenotyping. Our work is expected to pinpoint peripheral disease markers, hopefully providing a tool for the early identification of individuals who will eventually develop the disease. Moreover, we expect to leverage the power of genetically identical twin comparison to identify subtle molecular disease-related changes at the genetic/epigenetic/transcriptomic/metabolomic level that could provide important clues on disease pathogenesis.

Importantly, data on the genome, exome, and transcriptome have already been collected, and those on the epigenome and on the inflammatory (proteome) profile are currently in the process of collection.

**Main technical approaches**

It is preferable, but not mandatory, that the candidate has already acquired experience in bioinformatics (use of bioinformatics pipelines for analysis of omics data).

**Scientific references**

1. Straniero L, Rimoldi V, Monfrini E, Bonvegna S, Melistaccio G, Lake J, Soldà G, Aureli M, Shankaracharya, Keagle P, Foroud T, Landers JE, Blauwendraat C, Zecchinelli A, Cilia R, Di Fonzo A, Pezzoli G, Duga S, Asselta R. Role of Lysosomal Gene Variants in Modulating GBA-Associated Parkinson's Disease Risk. Mov Disord. 2022 Jun;37(6):1202-1210. doi: 10.1002/mds.28987.

2. Straniero L, Asselta R, Bonvegna S, Rimoldi V, Melistaccio G, Soldà G, Aureli M, Della Porta M, Lucca U, Di Fonzo A, Zecchinelli A, Pezzoli G, Cilia R, Duga S. The SPID-GBA study: Sex distribution, Penetrance, Incidence, and Dementia in GBA-PD. Neurol Genet. 2020 Oct 20;6(6):e523. doi: 10.1212/NXG.0000000000000523.

3. Straniero L, Rimoldi V, Melistaccio G, Di Fonzo A, Pezzoli G, Duga S, Asselta R. A rapid and low-cost test for screening the most common Parkinson's disease-related GBA variants. Parkinsonism Relat Disord. 2020 Nov;80:138-141. doi: 10.1016/j.parkreldis.2020.09.036.

4. Straniero L, Rimoldi V, Samarani M, Goldwurm S, Di Fonzo A, Krüger R, Deleidi M, Aureli M, Soldà G, Duga S, Asselta R. The GBAP1 pseudogene acts as a ceRNA for the glucocerebrosidase gene GBA by sponging miR-22-3p. Sci Rep. 2017 Oct 5;7(1):12702. doi: 10.1038/s41598-017-12973-5.

5. Cilia R, Tunesi S, Marotta G, Cereda E, Siri C, Tesei S, Zecchinelli AL, Canesi M, Mariani CB, Meucci N, Sacilotto G, Zini M, Barichella M, Magnani C, Duga S, Asselta R, Soldà G, Seresini A, Seia M, Pezzoli G, Goldwurm S. Survival and dementia in GBA-associated Parkinson's disease: The mutation matters. Ann Neurol. 2016 Nov;80(5):662-673. doi: 10.1002/ana.24777.

**Brief description of the coherence of the project in relation to the PNRR objectives**
Our project proposal will be in line with the major objectives of the 2021-2027 National Research Programme, including:

**Consequences and challenges of ageing.** PD affects over 1% of the population over the age of 60. As the second most common age-related neurodegenerative disease after Alzheimer's disease, the health, social and economic impact resulting from PD will continue to increase alongside the longevity of the population. In Western Europe the annual cost per PD patient is 6000-17000 euro and age is inversely correlated with costs.

**Advanced diagnostics and precision medicine.** The P4 medicine (personalized, predictive, preventive, participatory) implies a deep understanding of inter-individual differences in health/disease that are due to genetic and environmental factors. As for PD, we are only approaching to this side of medicine (the only notable example being the GBA gene and the current clinical trials specifically developed for FBA mutation carriers). Our project will dissect genetic and epigenetic mechanisms behind PD , to reach the ultimate goal of changing treatment paradigms by taking into account both genetic and epigenetic factors.

In compliance with the principles of **open science and FAIR data policy**, all the data produced with this project will be deposited in ad-hoc data repository with dedicated accession numbers and associated with detailed metadata. The analysis pipeline(s) will also be available to allow reuse and replication of the main findings. The results of this project will be presented at national/international congresses and published in peer-reviewed open-access journals.
In addition, the proximity and full integration among Humanitas University, Humanitas Hospital and Humanitas Research Center, with access to state-of-the -art technologies (e.g. omics and bioinformatics), will provide the ideal environment for the successful completion of the PhD program.

All participants to this project will completely endorse and will be fully committed to PNRR priorities.

**N. of months abroad**
6 months, at Institute of Neuropathology, University Hospital Zurich and UZH Rämistrasse 100 - 8091 - Zurich

**Type of contract**
PhD scholarship of € 18.000 gross per year awarded by Humanitas University on institutional funds and cofounded with PNRR funds under M.D.M. D.D. N. 118/2023.
This sum is exempt from IRPEF income tax according to the provisions of art. 4 of Law no. 476 of 13th August 1984, and is subject to social security contributions according to the provisions of art. 2, section 26 and subsequent sections, of Law no. 335 of 8th August 1995 and subsequent modifications.

Borsa di dottorato pari a € 18.000 annui lordi erogata da Humanitas University su fondi istituzionali e fondi da D.M. 118/2023. Importo non soggetto a tassazione IRPEF a norma dell'art. 4

della L. 13 agosto 1984 n. 476 e soggetto, in materia previdenziale, alle norme di cui all'art. 2, commi 26 e segg., della L. 8 agosto 1995, n. 335 e successive modificazioni.