Leukocyte telomere length as possible biomarker to track Huntington’s disease progression

D. Scarabino¹, E. Mantuano², M. Frontali², R.M. Corbo¹,³ L. Veneziano²

¹IBPM-CNR, Rome; ²IFT-CNR, Rome; ³Department of Biology and Biotechnology, Sapienza University, Rome.

Background: Huntington’s disease (HD), is an autosomal dominant neurodegenerative disease, caused by an expanded CAG repeat stretch in the first exon of the HTT gene. The disease has fully penetrance in individuals with ≥ 40 CAG repeats, and reduced penetrance with 36–39 repeats. Clinical onset commonly occurs at midlife and inversely correlates with the number of CAGs. Therapies for HD are currently in development, and reliable biomarkers, reflecting different factors of physiopathology in the brain, can be used, especially in the early stages of the disease, to predict progression and to monitor effects of novel drug candidates in clinical trials. A recent focus was on easily accessible biomarkers, coming from peripheral leukocytes and plasma.

Aims: The focus of the project is to validate Leukocyte Telomere Length (LTL) as accessible biomarker to track disease progression in HD.

Methods: LTL (T/S ratio) was measured by real-time PCR quantitative analysis (qPCR) in manifest HD (HD n=62), premanifest HD (FP pre-HD n=38) patients with fully penetrant alleles, in subjects with reduced penetrant alleles (RP pre-HD n=23), and age matched controls (n= 76).

Results: Mean LTL values of controls, pre-HD and HD patients were significantly different (p< 0.0001): HD (0.58 ± 0.07)<FP pre-HD (0.78 ± 0.16)< RP pre-HD (0.82± 0.16)< controls (0.92 ± 0.09). In premanifest HD individuals, LTL was examined in relation to the estimated time to clinical diagnosis. A significant linear positive relationship was observed between LTL and estimated years to diagnosis (1).

Conclusions: In pre-HD subjects, LTL gradually shortens according to progression of age and CAG number, up to the low values observed in HD symptomatic patients. LTL measurement seems to possess distinctive features required for a suitable biomarker to detect HD progression: it is easy to obtain, readily quantifiable and reproducible, and closely linked to the inflammatory component of HD physiopathology (2).

Perspectives: In order to validate these results, we are extending the analysis to a larger sample, with a follow-up study design, examining the LTL in pre-HD subjects at different time points, aiming to establish a relationship between LTL values and time to clinical onset, and to measure their predictive potential of disease onset. The study design was approved and DNA samples were provided by Enroll- HD network (https://enroll-hd.org/).

References:

Keywords: Huntington’s Disease; biomarker; Leukocyte Telomere Length.

Grants: European Huntington’s Disease Network (EHDN) 2018 (0942) to LV; Associazione Italiana Còrea di Huntington Roma onlus (AICH) 2019 to LV.

Contacts: daniela.scarabino@cnr.it, liana.veneziano@ift.cnr.it

Other: This project is the result of close collaboration between researchers from two Institutes of the DSB, integrating medical genetics and molecular biology skills.