Press Release

Important novel insights into neurodegenerative diseases

A NEW VARIANT OF JUVENILE HUNTINGTON'S DISEASE HAS BEEN DISCOVERED. POTENTIAL FUTURE THERAPEUTIC APPLICATIONS TO BE IMPLEMENTED AS EARLY AS CHILDHOOD OR EVEN BEFORE BIRTH.

Rome, 20 September 2018 – Revolutionary new insights for Huntington's disease (HD) describe the rarest and more aggressive pediatric variant: this pediatric form of HD starts very early in life and shows genetic and brain abnormalities that were so far unknown. The study was lead by **Dr Ferdinando Squitieri**, Head of the Huntington and rare Diseases Research Unit at Fondazione IRCCS Casa Sollievo della Sofferenza Research Hospital, Italy, in collaboration with other international institutes*.

This research – published in the Lancet Neurology - identifies and describes for the first time the most aggressive variant of HD. HD is a rare, severe, neurodegenerative disease affecting about 100-150.000 people worldwide, characterized by relentless progression of physical, cognitive and functional disability, presenting at all ages but most commonly in middle-aged people after a clinically dormant period, is caused by an increased number of CAG repeats ('CAG repeat expansion mutation') in the huntingtin (*HTT)* gene. Juvenile onset HD refers to patients with onset of manifest disease before 20 years of age. Juvenile onset HD, which may affect also very young children, represents about 6-10% of all HD patients.

This first longitudinal (i.e. clinical observations for many years) study ever, conducted on the world's largest population of 36 juvenile onset HD and 197 adult onset HD patients, revealed that the rarest and more aggressive pediatric form impairs brain and nervous system development, causing psychomotor developmental delay as early as 1.5 years of age, more rapid disease progression and shorter lifespan in very young children. This finding may pave the way for future experimental studies, with the aim of understanding how and if it is possible to influence disease progression already at a very early age.

This pediatric variant is the consequence of a genetic 'anomaly' that makes the gene products responsible for pathogenesis even more toxic and dangerous for the normal development of specific areas of the brain, altering the normal growth of the central nervous system. Researchers discovered that the CAG expansion mutation in very early onset patients is particularly mosaic, meaning many *HTT* gene variants with different expanded CAG repeat lengths are present in the same individual. "This is the largest and most detailed study of juvenile HD ever performed, combining genetic analysis, imaging data, and longitudinal clinical data on a multinational set of patients", stated **Dr. Martha Nance**, one of the world experts of juvenile HD and Director of the Huntington Disease Center of Excellence at Hennepin County Medical Center, Minnesota, USA.

"Our study identifies the most aggressive juvenile-pediatric variant, that affects children, with clinical manifestations and brain damage characteristics in which a deep part of the brain, called striatum, does not seem to develop properly, starting the neurodegeneration process much later during life", said lead author **Dr. Ferdinando Squitieri**, head of Huntington and Rare Diseases Unit

of Fondazione IRCCS Casa Sollievo della Sofferenza Research Hospital and of CSS-Mendel and Scientific Officer at Fondazione Lega Italiana Ricerca Huntington e malattie correlate (LIRH). "Our hope, therefore, is to act on the malfunction of nerve cells, even before their death, to prevent the onset and progression of the disease", Squitieri continued.

This important result may open the door to new therapeutic strategies against such a rare and devastating variant of HD, which causes an even greater and more dramatic impact on the quality of life, already immediately after birth. "We trust this will finally give renewed hope to juvenile HD families, whose voice have the right to be heard as well as the adult patients' voice. JHD is a very rare disease and it is therefore important to expand the focus. The International Huntington Association (IHA) will contribute to this with a JHD development program. Barbara D'Alessio, Rome Italy, Vice President of the European Huntington Association, will lead this work on behalf of IHA in close collaboration with the Board" states **Svein Olaf Olsen**, the newly elected president of the organization.

Dr. Sarah Tabrizi, Director of the UCL's Huntington's Disease Centre and IONIS-HTTRx Global Chief Investigator, commented: "Juvenile onset HD is devastating, far more aggressive than the adult disease, with a rapidly progressive course. Currently treatment options for juvenile onset HD are very limited – in the future, lowering mutant huntingtin with agents such as antisense oligonucleotides for example, may for the first time offer possible treatments for patients suffering from juvenile onset HD. In order to design such future interventions, a better understanding of the natural history based on observational studies and large case series is a critical requirement; the paper by Fusilli et al paves the way to such future therapies".

Patients and researchers, stronger together, against juvenile HD.

Reference: Biological and clinical manifestations of juvenile Huntington's disease: retrospective analysis **-** *The Lancet Neurology. Sept. 2018.*
http://www.thelancet.com/journals/laneur/article/PIIS1474-4422(18)30294-1/fulltext

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