Mechanism underlying Alzheimer-like damage in the brain of patients with Down syndrome elucidated

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Life expectancy for individuals with Down syndrome has grown in recent decades, thanks in large part to progress in patient care and

treatment. But with survival into the fifth and sixth decades of life now possible, increasing numbers of these individuals are affected by conditions linked to aging, among them impairments in thinking that are associated with the accumulation in the brain of atypical proteins better known for their involvement in Alzheimer's disease.

Precisely why Alzheimer-like changes—marked by the build-up of harmful amyloid and tau proteins—occur in the brain in Down syndrome has been unclear. But now, in new research, scientists at the Lewis Katz School of Medicine at Temple University show that reduced efficiency of a key protein transport system is partly to blame. In analyses of human brain tissue collected post-mortem, the researchers found that the so-called retromer complex system, which plays a critical role in clearing damaged and degraded proteins from neurons in the brain, operates at only about 50 percent of its usual efficiency in Down syndrome patients. The reduction was linked specifically to the accumulation of pathogenic tau protein.

"The decline in protein transport via the retromer system is a lot like a traffic jam, with the transporter stalling out and causing a major back-up in the clearance of pathologic tau proteins, leaving them to accumulate over time," explained Domenico Praticò, MD, Scott Richards North Star Foundation Chair for Alzheimer's Research, Professor in the Department of Neural Sciences, Director of the Alzheimer's Center at Temple, and senior investigator on the new study.

"We also found that a major factor underlying tau accumulation is diminished activity of the cathepsin-D enzyme, which resides within the retromer complex," Dr. Praticò added. Cathepsin-D normally acts like a pair of scissors, cutting up tau to facilitate its digestion and removal.

The study, published online in the journal *Annals of Neurology*, is the first to connect reductions in retromer system efficiency and cathepsin-

D activity to the accumulation of pathogenic tau in Down syndrome. The findings are significant because they suggest that Alzheimer-like changes are not strictly modulated by the extra copy of human chromosome 21 that is characteristic of Down syndrome. Even though the extra chromosome provides an additional copy of a gene known as amyloid precursor protein (APP), which increases the risk of amyloid plaque formation, not all Down syndrome patients develop dementia, implicating the involvement of factors beyond genetics.

Dr. Praticò and colleagues first measured the extent of tau pathology in brain tissue from patients with Down syndrome and then assessed the relationship between the retromer core protein levels and the amount of pathologic tau protein in young and aged individuals with Down syndrome. They further compared the activity of cathepsin-D with the amount of tau pathology in the same individuals.

The team's analyses uncovered an inverse relationship between the emergence of tau pathology in Down syndrome and the levels of retromer proteins and activity of cathepsin-D. Moreover, the team's observations suggest that reduced levels of retromer proteins in young Down syndrome subjects sets the stage for the development of tau pathology later in life.

"Overall, our data identify the retromer complex as a key regulator of pathogenic tau in Down syndrome, with evidence for the development of tau pathology at a relatively young age," Dr. Praticò said.

The results also identify the retromer system as a promising new target for the treatment of Alzheimer's disease pathology in Down syndrome patients. Drugs that target the retromer system, such as small chaperones, have already been developed. In future work, Dr. Praticò and colleagues plan to explore these potential treatments in animal models that reproduce most of the aspects of Down syndrome observed

in humans.

"Using these existing therapeutics, we want to see if it is possible to reverse amyloid plaque and pathological tau accumulation in animal models," Dr. Praticò added. "If we are successful, we will have created an exciting opportunity to explore treatments in human patients with Down syndrome."

More information: Mary Elizabeth Curtis et al, Association of Retromer Deficiency and Tau Pathology in Down Syndrome, *Annals of Neurology* (2022). DOI: 10.1002/ana.26321

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