A new genetic discovery suggests that most forms of ALS may have a common final cause—inability to recycle damaged proteins and cell structures. The accumulation of these worn-out bits of cell “junk” may be toxic to motor neurons, the cells that die in ALS.

The discovery was made by Teepu Siddique, M.D., and colleagues. Dr. Siddique is the Les Turner ALS/Herbert C. Wenske Foundation Professor in Neuromuscular Medicine at the Northwestern University Feinberg School of Medicine in Illinois. Dr. Siddique, who outlined his findings in a recent ALS Association webinar, “is very well known in the ALS research field,” said host and ALS Association Chief Scientist Lucie Bruijn, Ph.D., as he was the lead investigator in the discovery of SOD1, the first ALS gene, in 1993. He was also the first recipient of the Sheila Essey Award, given by The Association in conjunction with the American Academy of Neurology for leadership in the field of ALS research. “His contributions have been long and significant,” Bruijn continued, “and this new gene discovery adds to his distinguished list of achievements.”

The new gene is called UBQLN2, which encodes the protein ubiquilin-2. The gene resides on the X chromosome. In many X-linked diseases, women are protected from the disease because they possess two X chromosomes, and a good gene on one can overcome the effects of a mutated gene on the other. However, with UBQLN2, both males and females are affected. Dr. Siddique noted, “Some women never get the disease. This is a sign of hope because even if you have the mutation, there could be a mechanism that can keep you disease-free.”

While the gene mutation accounts for only a small fraction of familial ALS (probably less than 2%), its discovery points strongly to a cellular pathway that may link many forms of ALS.

There are two major routes through which worn-out or damaged cellular components are degraded and recycled, Dr. Siddique said. Short-lived proteins are tagged with a protein called ubiquitin, which marks them for destruction in a barrel-shaped structure called the proteasome. Longer-lived proteins and larger cell components are swallowed up in sac called the lysosome, which contains digestive enzymes, in a process called autophagy (aw-TOFF-a-jee). In both cases, ubiquilin-2 helps induce the damaged cell parts to enter the recycling stream.

“You need a recycling mechanism to keep the system healthy,” Siddique said. Without a functioning recycling mechanism, these damaged components build up in the cell, where they can cause damage themselves or interfere with critical cell functions. Understanding the details of those toxic mechanisms is an active area of research in ALS and other neurodegenerative diseases, including Alzheimer’s disease and Parkinson’s disease, which also appear to be linked to defects in protein recycling.
Other genes responsible for ALS may also cause defects in the recycling system, Dr. Siddique said. “There is a divergence of causes of ALS, but it all converges onto misfolded and damaged proteins.” The protein accumulations, or aggregates, in motor neurons contain TDP-43, FUS, optineurin, and ubiquilin-2, along with another protein called p62, which may also be involved in ALS pathogenesis. “We think ubiquilin-2 and p62 are major players” in a pathway involving many forms of ALS, he said. “We have proof of principle that this system of recycling organelles and proteins is at the heart of the problem. Now we have to figure out what this pathway is composed of, and what is the best way to intervene,” in order to develop treatments aimed at correcting the problem and slowing disease progression.

“The discovery of ubiquilin’s role in ALS pathogenesis presents exciting opportunities for understanding more about what causes the disease,” Dr. Bruijn said. “We look forward to learning more about the disease and how we can intervene.” This discovery, along with the other recent gene discoveries, including TDP-43, FUS, and C9orf72, “will make a tremendous impact on how fast we can move to develop treatments for ALS.”

To view the entire presentation, please visit: https://alsa.webex.com/alsa/ldr.php?AT=pb&SP=MC&rID=64214042&rKey=32d3200d726dbebf