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Rare, lethal childhood disease tracked to failure to degrade nerve cells' filaments

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For the first time, a defective protein that plays a specific role in degrading intermediate filaments (IF), one of three classes of filaments that form the structure of nerve cells, has been discovered by an international team of researchers.

The defective protein, gigaxonin, which was first identified in children with a rare and untreatable genetic disease called giant axonal neuropathy (GAN), according to Saleemulla Mahammad, PhD, of the Northwestern Feinberg School of Medicine in Chicago, who presented the data on Dec. 17 at the American Society for Cell Biology Annual Meeting in San Francisco.

The identification of gigaxonin's specific role explains why a failure in protein degradation would lead to massive aggregations of IF in the neuronal cells of GAN children, said Dr. Mahammad who is in the laboratory of Robert D. Goldman, PhD, and collaborated with Puneet Opal, MD, PhD, at Northwestern along with researchers at INSERM in Montpelier, France and the Université Laval in Quebec, Canada.

The GAN gene was first identified in 2000 by Dr. Pascale Bomont, now at the French INSERM neurological institute in Montpellier, who reported that it encoded for the protein gigaxonin. Based on sequence homology, gigaxonin is involved in the normal turnover of proteins by the well-studied ubiquitin-proteasome system. But it wasn't clear why a failure in protein degradation would lead to massive aggregations of IF in a patient's neuronal cells.

Because it is not possible to study nerve cells experimentally from patients, Dr. Mahammad and collaborators instead used fibroblasts from skin biopsies of children with GAN because previous studies had revealed that other classes of IF are also altered in GAN patients. In particular, the IF vimentin expressed in fibroblasts of children with GAN also forms abnormally large aggregates. These cells can readily be obtained from skin biopsies and grown in lab cultures.

When the researchers introduced the gigaxonin gene into both control and patient fibroblasts, the results were dramatic. In the fibroblasts cultured from GAN patients, the complex network of vimentin filaments and abnormal aggregates disappeared. The vimentin filaments in the control cells also disappeared following the overexpression of the gigaxonin protein. Boosting gigaxonin to higher levels in normal cultured nerve cells also led to a degradation of neuronal forms of IF. However, the cytoskeleton's two other major systems, microtubules and actin filaments, were not affected by this treatment.

These findings point to a central role for gigaxonin in regulating the normal turnover of IF proteins. When gigaxonin is defective, neurofilaments pile up, and eventually the aggregates disrupt the normal functioning of nerve cells in GAN.

Gigaxonin is the first factor to be identified that plays a specific role in the degradation of several types of IF proteins, including neurofilaments, according to Dr. Mahammad. This discovery may have implications for more common types of neurodegenerative diseases that are also characterized by large accumulations of IF proteins, including Alzheimer's disease, Parkinson's disease, dementia with Lewy bodies, Charcot-Marie-Tooth (CMT) disease, neuronal intermediate filament inclusion disease (NIFID), and diabetic neuropathy.

GAN is an extremely rare genetic disorder that strikes at both the

peripheral and central nervous systems of children. The leading GAN disease foundation, Hannah's Hope Fund, currently knows of 31 cases worldwide, 19 in the United States alone. But its rarity doesn't dull its severity in children affected by GAN. There are no symptoms at birth, but by age three the first signs of muscle weakness usually appear and progress slowly but steadily. With increasing difficulty in walking and coordinating hand movements, children with GAN are often wheelchair-bound by age 10. Over time, they become dependent on feeding and breathing tubes. A few will survive into young adulthood. The pathological markers for GAN are swollen (thus "giant") axons, filled with abnormal aggregates of neurofilaments, rich in Ifs.

More information: "Gigaxonin regulates the degradation of intermediate filament proteins: Insights into giant axonal neuropathy," Monday, Dec. 17, 2012, 12:30 – 2 pm, Session: Intermediate Filaments, presentation: 1290, poster: B575

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