New research model to aid search for degenerative disease cures

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(Medical Xpress)—Efforts to treat disorders like Lou Gehrig's disease, Paget's disease, inclusion body myopathy and dementia will receive a considerable boost from a new research model created by UC Irvine scientists.

The team, led by pediatrician Dr. Virginia Kimonis, has developed a genetically modified mouse that exhibits many of the clinical features of human diseases largely triggered by mutations in the valosin-containing protein.

The mouse model will let researchers study how these now-incurable, degenerative disorders progress in vivo and will provide a platform for translational studies that could lead to lifesaving treatments.

"Currently, there are no effective therapies for VCP-associated diseases and related neurodegenerative disorders," said Kimonis, a professor of pediatrics who specializes in genetics and metabolism. "This model will significantly spark new approaches to research directed toward the creation of novel treatment strategies."

She and her team reported their discovery Sept. 28 online in PLOS ONE , a peer-reviewed, open-access journal.

The UCI researchers – from pediatrics, neurology, pathology and radiological sciences – specifically bred the first-ever "knock-in" mouse in which the normal VCP gene was substituted with one containing the

common R155H mutation seen in humans with VCP-linked diseases. Subsequently, these mice exhibited the same muscle, brain and spinal cord pathology and bone abnormalities as these patients.

VCP is part of a system that maintains cell health by breaking down and clearing away old and damaged proteins that are no longer necessary. Mutations in the VCP gene disrupt the demolition process, and, as a result, excess and abnormal proteins may build up in muscle, bone and brain cells. These proteins form clumps that interfere with the cells' normal functions and can lead to a range of disorders.

Another study carried out by members of this group – and published in August in the journal Cell Death & Disease – made use of these genetically altered mice to examine the development of Lou Gehrig's disease, or ALS. The researchers, led by Dr. Hong Yin and Dr. John Weiss in UCI's Department of Neurology, documented slow, extensive pathological changes in the spinal cord remarkably similar to changes observed in other animal models of ALS as well as in human patients. ALS research is currently limited by a paucity of animal models in which disease processes can be studied.

Genetically modified mice have become important research models in the effort to cure human ailments. Mice bred to exhibit the brain pathology of Alzheimer's disease, for example, have dramatically sped up the race to advance new treatments – one such model was developed at UCI. And many cancer therapies were created and tested using genetically altered mice.

More information: www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0046308