Researchers isolate first 'neuroprotective' gene in patients with amyotrophic lateral sclerosis

May 12 2009

A genetic variant that substantially improves survival of individuals with amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig's disease, has been indentified by a consortium of researchers led by John Landers, PhD, Associate Professor of Neurology and Robert Brown, MD, DPhil, Chair and Professor of Neurology at the University of Massachusetts Medical School. Discovery of the KIFAP3 gene variant is reported in the *Proceedings of the National Academy of Sciences*.

"This report is the first to describe genetic factors that determine rate of progression in ALS," said Brown. "The finding reflects a truly international collaboration in which physicians and scientists from nearly 20 teams in several countries worked together to use new methods in genetics to understand ALS."

ALS is a progressive, neurodegenerative disorder affecting the motor neurons in the central nervous system. As motor neurons die, the brain's ability to send signals to the body's muscles is compromised. This leads to loss of voluntary muscle movement, paralysis and eventually death from respiratory failure. In 1993, a team of researchers led by Dr. Brown discovered the first gene linked to familial ALS, a protein anti-oxidant known as superoxide dismutase, or SOD1. Earlier this year, Dr. Brown and his colleagues discovered a mutation in the FUS/TLS gene which is estimated to account for 5 percent of inherited ALS cases. There are only four genes known, that when mutated, cause familial

ALS. The KIFAP3 gene variant is the first to be linked with the rate of progression in ALS.

To isolate the KIFAP3 gene variant, a consortium of researchers from the U.S., Mexico, Israel and Europe examined more than 300,000 genetic variants in over 1,800 people with ALS and nearly 2,200 unaffected controls. The approach is based on the assumption that naturally occurring gene variations can influence both disease susceptibility and the way a disease runs its course once underway. During their search, the consortium detected a beneficial variant of the KIFAP3 gene which was associated with an increase in survival time of 40 to 50 percent.

Because survival with ALS is normally only three to five years, patients with the KIFAP3 gene variant experience a substantial improvement. In fact, the impact of this genetic variant is comparable to the effect of the only drug (Riluzole) now approved for use in the United States. More importantly, this genetic variant may potentially point the way to future drug development efforts.

While it's still unclear how the KIFAP3 gene variant alters the progression of ALS, researchers know that it is involved with a number of cellular processes, including the transport of essential molecules throughout the nerve cell.

"The favourable gene variant decreases levels of a motor protein complex in nerves," said Landers. "This complex transports substances through different parts of nerve cells. If we can understand the biological basis for the beneficial effect in ALS, it will potentially provide a target for the development of new ALS treatments."

Ammar Al-Chalabi, PhD, co-senior author of the study and Professor of Neurology and complex disease genetics at King's College, London

added, "Treatments can now be directly designed to exploit the effect of this gene variation."

Source: University of Massachusetts Medical School (news : web)