

# Genetics of ALS progression

June 1 2008

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An upcoming paper in the June 1 issue of G&D, from Drs. Hidenori Ichijo and Hideki Nishitoh (University of Tokyo) and colleagues, lends new and valuable insight into the genetics of ALS.

Amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig's disease, is a rapidly progressive, fatal neurological disease involving the degeneration and death of motor neuron cells.

ALS is one of the most common neuromuscular diseases worldwide, affecting as roughly 25,000 Americans, with an estimated 5,000 new diagnoses each year. The life expectancy of ALS patients is usually 3 to 5 years after diagnosis.

5-10 percent of all ALS cases are inherited. About 20% of these familial ALS cases are the result of an inherited genetic mutation on chromosome 21, in the gene encoding for the superoxide dismutase 1 (SOD1) enzyme. SOD1 is an antioxidant that protects the body from DNA damage caused by the accumulation of free radicals within cells. However, several reports have demonstrated that mutated SOD1 toxicity is not due to decreased antioxidant activity, but rather to a 'gain of unknown toxic function'.

In their upcoming paper, Dr. Ichijo and colleagues delineate how mutations in SOD1 lead to motor neuron cell death and the progression of ALS. The researchers characterized a molecular pathway by which mutated SOD1 contributes to the accumulation of malformed proteins inside the endoplasmic reticulum (ER) compartment of motor neuron

cells. Beyond a certain threshold, this ER stress induces cell death.

Interestingly, Dr. Ichijo's team found that the inactivation of certain key factors in this pathway could mitigate neurodegeneration and prolong survival in a mouse model of inherited ALS.

Although not all familial ALS cases are due to the SOD1 mutation (and not all persons with a mutated form of SOD1 develop ALS), further insight into mechanism of the disease will undoubtedly aid in the development of an effective treatment for ALS.

Source: Cold Spring Harbor Laboratory

Citation: Genetics of ALS progression (2008, June 1) retrieved 1 February 2024 from <https://medicalxpress.com/news/2008-06-genetics-als.html>

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