Scientists identify mutation in SIGMAR1 gene linked to juvenile ALS

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Researchers from the Kingdom of Saudi Arabia have identified a mutation on the SIGMAR1 gene associated with the development of juvenile amyotrophic lateral sclerosis (ALS). Study findings published today in *Annals of Neurology*, a journal of the American Neurological Association and the Child Neurology Society, show the gene variant affects Sigma-1 receptors which are involved in motor neuron function and disease development.

ALS, also referred to as Lou Gehrig's disease, is a progressive neurodegenerative disorder that attacks brain and spinal cord nerve cells (neurons) responsible for controlling voluntary muscle movement. The degeneration of upper and lower motor neurons gradually weakens the muscles they control, leading to paralysis and eventual death from respiratory failure.

Studies report an annual incidence of 1-3 per 100,000 individuals, with 90% of cases not having a family history of the disease (sporadic ALS). In the remaining 10% of cases there is more than one affected family member (familial ALS). Juvenile ALS-characterized by age of onset below 25 years-is a rare and sporadic disorder, making it difficult to determine incidence rates. One of the more prominent juvenile ALS patients is renowned physicist, Professor Stephen Hawking, who was diagnosed at the age of 21.

Previous research found that mutation of the superoxide dismutase 1 (SOD1) gene accounts for 20% of familial and 5% of sporadic ALS cases; gene mutations of ALS2 and SETX have been reported in juvenile ALS cases. The present study led by Dr. Amr Al-Saif from the King Faisal Specialist Hospital and Research Center in Riyadh, KSA performed genetic testing on four patients from an ALS family who were diagnosed with juvenile ALS to investigate mutations suspected in disease development.

Researchers performed gene mapping on the DNA of study participants and used direct sequencing to detect the genetic variant. The team identified a shared homozygosity region in affected individuals and gene sequencing of SIGMAR1 revealed a mutation affecting the encoded protein, Sigma-1 receptor. Those cells with the mutant protein were less resistant to programmed cell death (apoptosis) induced by stress to the endoplasmic reticulum.

"Prior evidence has established that Sigma-1 receptors have neuroprotective properties and animal models with this gene inactivated have displayed motor deficiency," explains Dr. Al-Saif. "Our findings emphasize the important role of Sigma-1 receptors in motor neuron function and disease. Further exploration is warranted to uncover potential therapeutic targets for ALS. "

More information: "A Mutation in Sigma-1 Receptor Causes Juvenile Amyotrophic Lateral Sclerosis"; Amr Al-Saif, Futwan Al-Mohanna and Saeed Bohlega. *Annals of Neurology*; Published Online: August 12, 2011. DOI:10.1002/ana.22534

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