A Mutation in Sigma-1 Receptor Linked to Juvenile ALS

In this study, done by three doctors at King Faisal Specialist Hospital and Research Center in Saudi Arabia, homozygosity mapping and direct sequencing were used to detect a genetic variant and to test the effect of this variant of Sigma-1 receptor (SIGMAR1) on NSC34 cells. It is known that these SIGMAR1 receptors play a role in motor neuron function.

SIGMAR1 is a receptor that binds to numerous ligands and is involved in lipid transport. SIGMAR1 is increasingly present in the brainstem and spinal cord. This gene is involved in stress response, chaperon activity, and is implicated in neurodegeneration. Here, the missense mutation of SIGMAR1 and what its effects are in juvenile ALS is researched.

Juvenile ALS is classified as being a progressive neurodegenerative disorder which affects the muscles of those with the disease and is present under the age of 25 years. It is not as rapidly degenerative as normal ALS, but is still a serious disease that is often genetic, therefore inherited. As of now, there is no known cure so researchers, like this team, are continuing to look into mutations and drugs to get closer to a more permanent solution or cure.

In this study, the team had four subjects participate. Their family members had their DNA sequenced using a small sample of blood. This DNA was obtained from the lymphocytes within the blood. After obtaining the DNA, it was mapped, analyzed, and the 4 exons of SIGMAR1 underwent PCR to increase the quantity. The SIGMAR1 samples were then introduced to the E102Q mutation. NSC34 cells were also infected with the mutant type of SIGMAR1. Some cells were also transfected with a red fluorescent protein as a control to serve as a basis for analysis later on in the research. The samples were centrifuged and incubated prior to analyzing the information. When the samples were ready to be read, the researchers found some incredible results.

Results of this study found that NSC34 cells expressing the SIGMAR1 gene enhanced cell apoptosis, or programmed cell death. It was also discovered that there is a shared region in those affected by juvenile ALS—120 kbp on chromosome 9. This then revealed a mutation in the SIGMAR1 gene, which creates an unusual distribution in NSC34 cells, supporting the effect of the mutation on the health of motor neurons. The loss of SIGMAR1 function is discovered to lead to stressed motor neurons that build up unfolded proteins, degenerating them. Through these discoveries, the knowledge of what effects juvenile ALS continues to increase, and researchers are able to move closer to not only a full understanding of the disease, but also towards a cure.

This study is particularly intriguing due to the fact that the parents, not even the actual ALS patients, were the ones giving their DNA. In essence, with the parents’ DNA, the child’s DNA is then obtained. Since this study is examining the SIGMAR1 gene and it is known that this is inherited, it does make sense that this DNA would be as effective. The research on ALS and juvenile ALS has been increasing over the turn of the century as it has become a more prominent disease, gripping the lives of those affected. Research like this helps to push the limits on what we can discover. Now the question is, what to do about this SIGMAR1 flaw?