Study provides new insights into cause of human neurodegenerative disease

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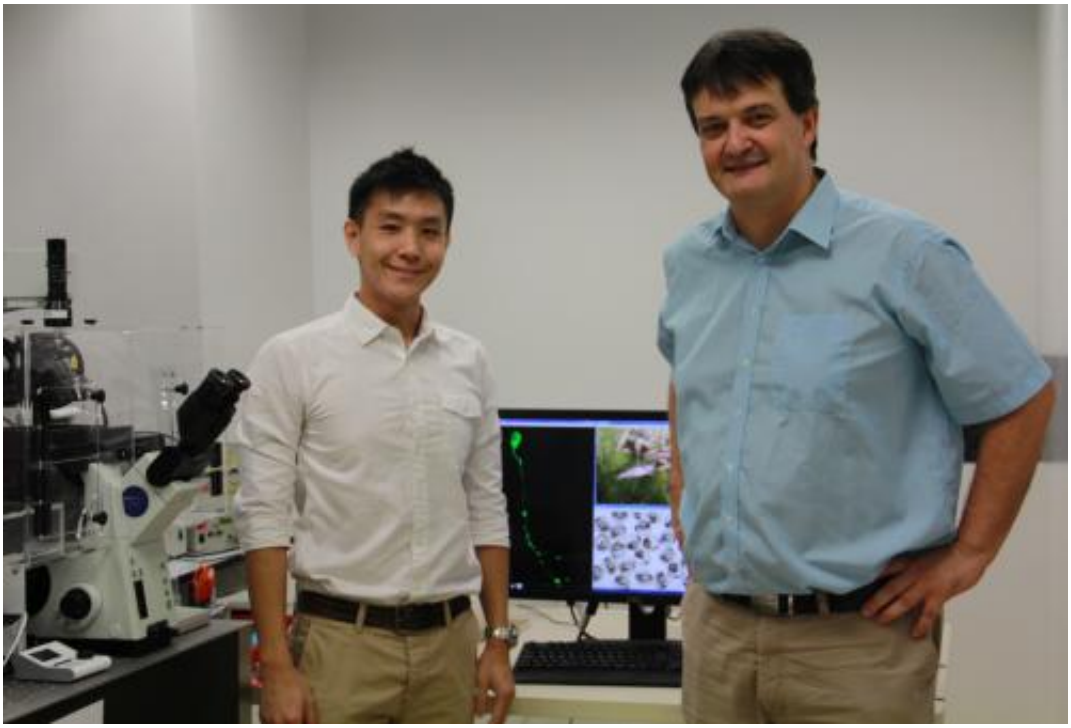

A research team led by Assoc Prof Christoph Winkler (right) and Dr Kelvin See (left) identified Neurexin2 as a novel target for potential therapy of neurodegeneration in Spinal Muscular Atrophy patients. Credit: Yu Tingsheng

A recent study led by scientists from the National University of Singapore (NUS) opens a possible new route for treatment of Spinal Muscular Atrophy (SMA), a devastating disease that is the most common genetic cause of infant death and also affects young adults. As

there is currently no known cure for SMA, the new discovery gives a strong boost to the fight against SMA.

SMA is caused by deficiencies in the Survival Motor Neuron (SMN) gene. This gene controls the activity of various target genes. It has long been speculated that deregulation of some of these targets contributes to SMA, yet their identity remained unknown.

Using global genome analysis, the research team, led by Associate Professor Christoph Winkler of the Department of Biological Sciences at the NUS Faculty of Science and Dr Kelvin See, a former A*STAR graduate scholar in NUS who is currently a Research Fellow at the Genome Institute of Singapore (GIS), found that deficiency in the SMN gene impairs the function of the Neurexin2 gene. This in turn limits the neurotransmitter release required for the normal function of nerve cells. The degeneration of motor neurons in the spinal cord causes SMA. This is the first time that scientists establish an association between Neurexin2 and SMA.

Preliminary experimental data also showed that a restoration of Neurexin2 activity can partially recover neuron function in SMN deficient zebrafish. This indicates a possible new direction for therapy of neurodegeneration.

Collaborating with Assoc Prof Winkler and the NUS researchers are Dr S. Mathavan and his team at GIS, as well as researchers from the University of Wuerzburg in Germany. The breakthrough discovery was first published in scientific journal *Human Molecular Genetics* last month.

SMA is a genetic disease that attacks a distinct type of nerve cells called motor neurons in the spinal cord. The disease has been found to be caused by a defect in the SMN gene, a widely used gene that is

responsible for normal motor functions in the body.

To study how defects in SMN cause neuron degeneration, the scientists utilised a zebrafish model, as the small fish has a relatively simple nervous system that allows detailed imaging of neuron behaviour.

In laboratory experiments, the researchers showed when SMN activity in zebrafish was reduced to levels found in human SMA patients, Neurexin2 function was impaired. This novel disease mechanism was also discovered in other in vivo models, suggesting that it is applicable to mammals and possibly human patients.

When the scientists measured the activity of nerve cells in zebrafish using laser imaging, they found that nerve cells deficient for Neurexin2 or SMN could not be activated to the same level as healthy nerve cells. This impairment consequently led to the reduction of muscular activity. Interestingly, preliminary data showed that a restoration of Neurexin2 activity can partially recover neuron function in SMN deficient zebrafish.

Assoc Prof Winkler, who is also with the NUS Centre for Biolmaging Sciences, explained, "These findings significantly advance our understanding of how the loss of SMN leads to neurodegeneration. A better understanding of these mechanisms will lead to novel therapeutic strategies that could aim at restoring and maintaining functions in deficient nerve cells of SMA patients."

Dr See added, "Our study provides a link between SMN deficiency and its effects on a critical gene important for neuronal function. It would be interesting to perform follow up studies in clinical samples to further investigate the role of Neurexin2 in SMA pathophysiology."

Moving forward, the team of scientists will conduct further research to

determine if Neurexin2 is an exclusive mediator of SMN induced defects and hence can be used as a target for future drug designs. They hope their findings will contribute towards treatment of neurodegeneration.

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