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Genetic mutation associated with a developmental disorder could be a treatment target

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The discovery of a rare genetic mutation associated with a devastating developmental disorder called arthrogryposis multiplex congenita could also provide researchers with a new treatment target for a group of related neurodegenerative diseases, including multiple sclerosis, in adults.

Arthrogryposis multiplex congenita is a common birth defect, affecting around 1 in 3,000 live births. Babies with the disorder have stiff joints and their limbs become locked into awkward positions because of a lack of movement in the womb.

The disorder can be caused by crowding in utero—for example with twin pregnancies—but it also occurs when genetic mutations affect the normal development of muscles and nerves.

A study led by researchers from A*STAR looked at a group of families affected by a severe form of arthrogryposis that resulted in several fetuses dying before birth or soon after.

"We knew that it was probably going to be genetic because many of these families had multiple individuals with this condition," says Shifeng Xue from the A*STAR Institute of Molecular and Cell Biology.

But when the researchers looked at the families' genomes, they couldn't

find any of the known mutations associated with arthrogryposis.

Instead they discovered a new mutation in the gene coding for a molecule called LGI4. This molecule is secreted by Schwann cells, which produce the fatty sheath called myelin that covers and insulates nerve cells, and enables them to conduct electrical impulses quickly and effectively. It suggests that LGI4 plays a key role in the myelination process.

LGI4 and Schwann cells operate in the peripheral nervous system—the parts that don't include the brain and spinal cord—which controls movement and sensory function.

This new mutation stopped the LGI4 gene from functioning altogether, so those affected by it didn't have any myelin on their peripheral nerve cells. This caused severe malformation of their limbs and also affected the muscles of the diaphragm so their lungs didn't develop properly.

The discovery means the mutation could be screened for in the early stages of pregnancy, and people with a family history of the disease could be offered genetic counseling before pregnancy. It also opens the door to research that could help adults with degenerative diseases such as multiple sclerosis, where the immune system attacks and destroys myelin.

"We're hoping that by identifying LGI4 as being important for Schwann cell development, differentiation and myelination, we can possibly develop it as a therapeutic biologic to stimulate myelination," says Bruno Reversade, research director at the A*STAR Institute of Medical Biology.

More information: Shifeng Xue et al. Loss-of-Function Mutations in LGI4 , a Secreted Ligand Involved in Schwann Cell Myelination, Are

Responsible for Arthrogryposis Multiplex Congenita, *The American Journal of Human Genetics* (2017). DOI: 10.1016/j.ajhg.2017.02.006