Zebrafish study paves the way for new treatments for genetic disorder

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Scientists from the University of Sheffield have paved the way for new treatments for a common genetic disorder thanks to pioneering research on zebrafish – an animal capable of mending its own heart.

Charcot Marie Tooth disease (CMT) is the most common genetic disorder affecting the nervous system. More than 20,000 people in the UK suffer from CMT, which typically causes progressive weakness and long-term pain in the feet, leading to walking difficulties. There is currently no cure for CMT.

A research project conducted at the Sheffield Institute for Translational Neuroscience (SITraN) and the MRC Centre for Developmental and Biomedical Genetics (CDBG) by Dr Andrew Grierson and his team has revealed that zebrafish could hold the key to finding new therapeutic approaches to treat the condition.

Dr Grierson said: "We have studied zebrafish with a genetic defect that causes CMT in humans. The fish develop normally, but once they reach adulthood they start to develop difficulties swimming.

"By looking at the muscles of these fish we have discovered that the problem lies with the connections between motor neurons and muscle, which are known to be essential for walking in humans and also swimming in fish."

CMT represents a group of neurodegenerative disorders typically

characterised by demyelination (CMT1), a process which causes damage to the myelin sheaths that surround our neurons, or distal axon degeneration (CMT2) of motor and sensory neurons. The distal axon is the terminal where neurotransmitter packages within neurons are docked.

The majority of CMT2 cases are caused by mutations in mitofusin 2 (MFN2), which is an essential gene encoding a protein responsible for fusion of the mitochondrial outer membrane. Mitochondria are known as the cellular power plants because they generate most of the supply of adenosine triphosphate (ATP), which is used as a source of chemical energy.

Dr Grierson said: "Previous work on this disorder using mammalian models such as mice has been problematic, because the mitofusin genes are essential for embryonic development. Using zebrafish we were able to develop a model with an adult onset, progressive phenotype with predominant symptoms of motor dysfunction similar to CMT2.

"Motor neurons are the largest cells in our bodies, and as such they are highly dependent on a cellular transport system to deliver molecules through the long nerve cell processes which connect the spinal cord to our muscles. We already know that defects in the cellular transport system occur early in the development of diseases such as Alzheimer's disease, Motor Neuron Disease and spastic paraplegia. Using our zebrafish model we have found that similar defects in transport are also a key part of the disease process in CMT."

Dr Grierson and his team are now seeking funding to identify new treatments for CMT using the zebrafish model. Because of their size and unique biology, zebrafish are ideal to be used in drug screens for the identification of new therapies for untreatable human conditions.

More information: dx.plos.org/10.1371/journal.pone.0067276