Medical Xpress

Zebrafish help unlock mystery of motor neurone disease

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Scientists from the University of Sheffield have successfully created zebrafish that carry the complex genetic change known to cause the most common genetic form of motor neurone disease (MND).

The breakthrough will help to accelerate pioneering research and experimental drug trials to tackle the degenerative disease.

Until now, research to better understand how the disease occurs and the trial of experimental drugs has been conducted on fruit flies or mice models. This has had limited success due to the difference between the human brain and the fruit fly brain, and the time and cost implications of using mice models.

For the first time, researchers from the University of Sheffield's Institute of Translational Neuroscience (SITraN) have successfully created the complex aspects of human C9-ALS/FTD pathobiology in zebrafish models.

This pioneering breakthrough is essential for studying the underlying mechanisms of MND and frontotemporal dementia (FTD).

MND, also known as Amyotrophic Lateral Sclerosis (ALS), is a devastating neurogenerative disorder that affects the nerves—motor neurones—in the brain and spinal cord that tell your muscles what to do.

The messages from these nerves gradually stop reaching the muscles,

leading them to weaken, stiffen and eventually waste. The progressive disease affects a patient's ability to walk, talk, eat and breathe. MND affects 5,000 adults in the UK and there is currently no cure.

Approximately 10 per cent of MND cases are inherited but the remaining 90 per cent of MND cases are caused by complex genetic and environmental interactions which are currently not well understood—this is known as sporadic MND.

The most common known genetic cause of MND and FTD is a hexanucleotide expansion within the first intron of the C9orf72 gene. In this gene there are hundreds and thousands of repetitions of the sequence GGGGCC in patients with MND. This mutation is the largest genetic cause of MND and also the most predominant form of sporadic ALS.

Dr. Tennore Ramesh, from SITraN at the University of Sheffield, said: "Using zebrafish models for MND research means that we can accelerate studies and our understanding of the devastating disease and other neurological conditions.

"Because zebrafish are transparent you can record results of studies much quicker and easier—the research is much less invasive.

"Trialing 1,000 drugs on mice models would take more than 10 years, however trialling 1,000 drugs on zebrafish would take only a couple of months.

"This will enable us to accelerate research into clinical trials in humans quicker than ever before."

The four year project, which was led by Dr. Ramesh in collaboration with leading researchers from SITraN including Professor Dame Pamela Shaw, Vice-President and Head of the Faculty of Medicine, Dentisry

and Health at the University of Sheffield, is published in the journal *Acta Neuropathologica Communications*. The study was funded by the MND Association.

More information: Matthew P. Shaw et al, Stable transgenic C9orf72 zebrafish model key aspects of the ALS/FTD phenotype and reveal novel pathological features, *Acta Neuropathologica Communications* (2018). DOI: 10.1186/s40478-018-0629-7

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