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'Gene for speed' linked to severity and progression of Duchenne muscular dystrophy

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Scientists from the Murdoch Childrens Research Institute (MCRI) have discovered that a gene linked to performance in elite athletes also influences disease severity in Duchenne muscular dystrophy (DMD), the most common inherited muscle disease that affects around one in 3,500 boys.

MCRI's Director, Professor Kathryn North, and researchers Dr Marshall Hogarth and Dr Peter Houweling have successfully shown a link between a common variant in the gene, alpha-actinin-3 (ACTN3), and the degree of muscle weakness and rate of disease progression of DMD.

Prof North and her research team are renowned internationally for their previous discovery that ACTN3 variants have a major influence on muscle performance in elite athletes and on muscle mass and strength in the general population. ACTN3 has been dubbed the 'gene for speed' due to its link with sprint performance ability.

As a result of these findings, testing for the ACTN3 gene will likely become a part of a more personalised and targeted approach for the treatment of DMD.

The research was published in *Nature Communications*.

DMD is a genetic disorder characterised by progressive muscle degeneration and weakness. It is caused by changes in the DMD gene, which is responsible for producing a protein called dystrophin, needed

for skeletal and cardiac muscle function. It is linked to the X-chromosome, which means only males are affected.

DMD is usually diagnosed at preschool age due to early signs of muscle weakness, followed by rapid progression of muscle weakness. Without treatment, DMD patients lose their ability to walk between 8-14 years, and can die in their 20s due to respiratory failure.

The problem scientists have encountered when studying the disorder is that the onset and progression varies greatly between patients. Some patients lose their ability to walk years earlier than others with the same disorder, and the rate of decline, making it difficult to determine whether newly developed therapies are making a difference in an individual.

This means that even though many clinical trials are underway to treat DMD, they can often be inconclusive.

The crucial step MCRI's researchers have taken is to look at the influence of the ACTN3 gene on muscle strength and damage in DMD patients

In 1999, Prof North discovered the unique variant in the ACTN3 gene. Around 20 per cent of the world's population have a genetic change that means they no longer produce the ACTN3 protein, which affects fast-twitch skeletal muscle fibres (the cells that are required for rapid, forceful movement, such as sprinting and weight-lifting).

Prof North found the absence of ACTN3 to be detrimental to sprint performance but beneficial in endurance events, and that deficiency in ACTN3 was extremely rare in sprint athletes, suggesting the presence of ACTN3 is essential to peak sprint and power muscle performance at the elite level. This discovery has now been replicated in elite athletes from

around the world.

"Knowing that ACTN3 significantly influences muscle function at one extreme of peak performance led us to hypothesise that it may also influence muscle strength at the other end of the spectrum, in those with muscle weakness caused by muscle disease," Prof North explains.

"Understanding the role ACTN3 plays in the severity and nature of individual cases of DMD will guide the selection of effective interventions for patients, potentially aiding the generation of new treatments to improve muscle metabolism, bulk and strength."

To test the hypothesis, scientists explored the role of ACTN3 in DMD in the laboratory, examining how a deficiency in both ACTN3 and dystrophin protein would manifest.

The resulting analysis showed in disease models of DMD that an absence of ACTN3 and the dystrophin protein contributed to weaker muscles, but was protective against the progressive muscle damage.

"Knowing that ACTN3 contributes to DMD will lead to more controlled clinical trials and more accurate results for standard DMD tests," Dr Houweling says

"We hope in future to be able to personalise treatments for patients as a result, by enrolling them in programs most relevant to their individual needs."

More information: Marshall W. Hogarth et al. Evidence for ACTN3 as a genetic modifier of Duchenne muscular dystrophy, *Nature Communications* (2017). DOI: 10.1038/ncomms14143