Rare muscular dystrophy gene mutations discovered

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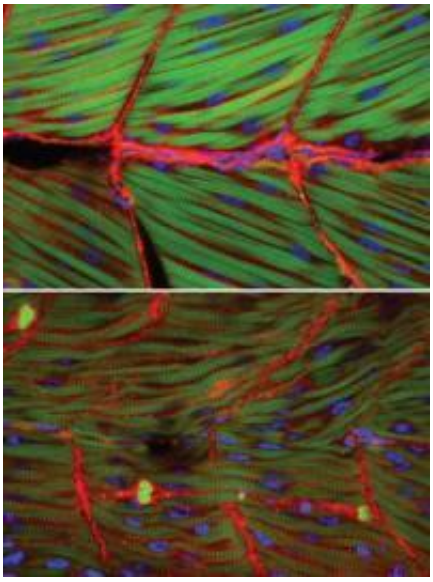

Normal zebrafish muscle [top] compared with muscle where ISPD gene expression has been blocked [bottom]. In the absence of normally functioning ISPD, the muscle fibres are degenerated and disordered. [doi:10.1038/ng.2253]

(Medical Xpress) -- Research co-led by Radboud University Nijmegen Medical Centre and the Wellcome Trust Sanger Institute has revealed gene mutations that account for 15 per cent of all babies born with Walker-Warburg syndrome, a rare congenital muscular dystrophy. The syndrome, which is associated with muscle wasting, brain and eye abnormalities, is fatal and most babies do not live beyond two years. A key symptom is hydrocephalus - having an enlarged brain filled with

excess fluid.

The discovery of the gene mutations in causing the syndrome brings the number of genes linked to the syndrome to seven and now explains 50 per cent of cases of the disease in the patient cohort of Nijmegen Medical Centre. The role of the gene, known as ISPD, in Walker-Warburg syndrome was identified by combining genetic investigation in affected families and their offspring with disease modelling in zebrafish.

"Until now we have only been able to explain the genetic basis of just 35 per cent of this distressing disease," says Professor Hans van Bokhoven from Radboud University Nijmegen Medical Centre and co-senior author of the research. "By discovering the role of ISPD, we have found the second most common causative gene mutation accounting for additional 15 per cent of all babies born with this muscular dystrophy."

The researchers used a genetic mapping strategy in some affected children who did not have mutations in any of the six previously known causative genes. They found an association with the ISPD gene in two children. While this suggested that ISPD was likely to be linked to the syndrome, supporting strong evidence came from an independent approach using next-generation DNA sequencing and stringent filtering of candidate genetic variants. A specific mutation was identified in the ISPD gene. These results led to the discovery of additional mutations in ISPD from another six families with children affected with Walker-Warburg syndrome.

"ISPD was shown to be strongly associated with the syndrome," says co-senior author Dr Yung-Yao Lin from the Sanger Institute. "However, the function of ISPD has not been studied in vertebrates. Experimental evidences from loss of function of the same gene in vertebrate animal models will shed light on the pathological mechanisms underlying Walker-Warburg syndrome."

To do this, the team chose to use zebrafish as a vertebrate animal model because the ISPD gene is evolutionarily conserved between humans and their fish counterparts. They used a gene silencing technique that prevented the ISPD gene from producing its normal protein and found that the fish displayed the same symptoms as babies with Walker-Warburg syndrome. Furthermore, they show that ISPD may have adopted a role involved in the sugar modification of dystroglycan, a central component of a big protein complex governing the integrity of muscle and other tissues.

"The results of silencing the ISPD gene in zebrafish - hydrocephalus, muscular dystrophy and eye abnormalities - provided definitive proof that it plays a role in disease pathogenesis," says Dr Derek Stemple, Head of Mouse and Zebrafish Genetics from the Sanger Institute. "The key questions now are 'What does this gene do regarding the sugar modification of dystroglycan?' and 'How does a mutation of it cause these terrible symptoms?' We are now carrying out further investigations to elucidate the biological pathways involving ISPD in vertebrates."

More information: Mutations in ISPD cause Walker-Warburg syndrome and defective glycosylation of α-dystroglycan. Roscioli T et al. *Nature Genetics* 2012. DOI: 10.1038/ng.2253

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