Mice holding back muscular dystrophy research

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Humans and mice have previously unknown and potentially critical differences in one of the genes responsible for Duchenne muscular dystrophy (DMD). Researchers writing in the open access journal *BMC Biology* have found that two major features of a key DMD gene are present in most mammals, including humans, but are specifically absent in mice and rats, calling into question the use of the mouse as the principal model animal for studying DMD.

Roland Roberts led a team of researchers from King's College London, UK, and was funded by the Muscular Dystrophy Campaign. The team made the discovery while studying α-dystrobrevin, a component of the dystrophin protein complex that is disordered in DMD. Roberts said, "Two previously unrecognized features (a gene switch or promoter and a novel binding site for the adaptor protein syntrophin) are encoded by the α-dystrobrevin gene of almost all four-legged animals except mice. We assume that this tardy recognition of key features of a gene that has been intensively studied since its discovery 13 years ago is due to the predominance of the mouse as the model organism for studying DMD and the specific destruction of these parts of the gene in the mouse".

A major consequence of these findings is that mice (and their rat and hamster relatives) are likely to be particularly poor models in which to study the effects of DMD on the brain. Roberts added, "The brain is the major site of α-dystrobrevin expression and we now know that the mouse is missing more than 50% of the brain α-dystrobrevins. The fact that there are fundamental differences between the brains of mice and

humans potentially limits our understanding of the role of dystrobrevins and DMD-related complexes in this organ. In fact, almost all of our knowledge of the function of α-dystrobrevin has been gleaned from the mouse".

DMD is a fatal skeletal myopathy, causing loss of muscle tissue throughout the body. It is also associated with substantial neurological effects including learning difficulties, night blindness, defective color vision and a suggestion of personality disorders, so studying the mechanisms in the brain underlying these effects is crucial.

More information: Profound human/mouse differences in alpha-dystrobrevin isoforms: a novel syntrophin-binding site and promoter missing in mouse and rat, Sabrina V Boehm, Panayiotis Constantinou, Sipin Tan, Hong Jin and Roland G Roberts, *BMC Biology* (in press), www.biomedcentral.com/bmcbiol/

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