Lay Summary

BRAIN UK Ref: 21/018

In-depth characterisation of muscle pathology in female carriers of dystrophinopathy

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Duchenne muscular dystrophy (DMD) is an inherited disease that primarily affects boys. It occurs due to errors (or mutations) in the DMD gene on the X-chromosome, which carries the genetic code for making an essential muscle protein called dystrophin. Lack of dystrophin leads to progressive wasting and weakness of the limb muscles. Later, respiratory and cardiac muscles are also affected. A milder form of the disease is called Becker muscular dystrophy (BMD), where a reduced amount of partially functional protein is made by the muscle cells. Females carry two copies of the X chromosome. As one copy is randomly switched off early in development, females carrying mutations in the DMD gene generally are not clinically affected. However, a smaller group of females (called manifesting carriers) can develop symptoms, from mild muscle weakness to full blown DMD/BMD-like severity. The reasons underlying this variability are not clearly understood. The amount of residual functional dystrophin protein in their muscles is likely to play an important role, as well as additional genetic and environmental factors. It is important to understand the causes underlying the variable clinical severity for proper clinical management, genetic counselling, prenatal testing and developing new treatments. The primary aim of our study is to accurately measure the amount of dystrophin protein in the diagnostic muscle biopsies from a large international cohort of manifesting carriers. We shall also use molecular biology tools and techniques to study additional disease-modifying factors. Correlation of this data with the clinical phenotype should improve our understanding of the disease in manifesting carriers of DMD/BMD.