

Muscular Dystrophies: Other**P21**

Poster

The relationship between syntrophins and syntrophin-binding sites (SBSs) in the dystrophins and dystrobrevinsS.V. Böhm¹, R.N. Sewduth¹, L.L. Zhuo¹, P. Constantinou¹, R.G. Roberts¹. ¹Department of Medical & Molecular Genetics, King's College London, UK

Duchenne muscular dystrophy (DMD) is a lethal multisystem disorder that results from defects in dystrophin and the consequent disruption of the dystrophin glycoprotein complex (DGC). Although the basic function of the DGC remains unclear, attempts have been made to explain many aspects of the DMD phenotype in terms of the loss of proteins normally recruited to the DGC by the syntrophin proteins. Syntrophins are adaptors which bind to multiple modular sites (SBSs) in the core DGC proteins dystrophin, utrophin, DRP2 and α - and β -dystrobrevin. Syntrophins have also been implicated in long QT syndrome and multiple sclerosis.

Alternative splicing is used to modulate the number of SBSs in dystrophin, and we have recently shown it can also modulate not only the number but also the type of SBSs in α -dystrobrevin. This raises the possibility that there is significant specificity of interaction between syntrophins and SBSs, and therefore that both the stoichiometry and "flavour" of DGC syntrophins can be modulated.

The human genome encodes five syntrophins and eleven SBSs. We here describe the preliminary characterisation (using quantitative interaction studies, mutagenesis and comparative biology) of the extent and determinants of their specificity of interaction, and discuss the implications for DGC function in various tissues.

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Poster

Clinical and pathological heterogeneity in partial merosin deficiencyS. Rajakulendran¹, M. Parton¹, J.L. Holton¹, M.G. Hanna¹. ¹MRC Centre for Neuromuscular Diseases, UCL Institute of Neurology, London WC1N 3BG, UK

Background: Recessive mutations in the *LAMA2* gene leading to complete laminin $\alpha 2$ deficiency underlie a severe phenotype of congenital muscular dystrophy type IA (MDC1A), a disorder characterised by muscle weakness and white matter changes on brain MRI. We describe a family with a syndrome characterized by slowly progressive myopathy, cortical white matter changes and epilepsy.

Case report: The proband presented with a history of epilepsy and progressive proximal muscle weakness. Her one affected brother exhibited a slowly progressive myopathy but not epilepsy. An MRI scan of her brain revealed diffuse white matter changes consistent with leukodystrophy. Histology of her affected muscle from both affected individuals demonstrated a reduction in laminin $\alpha 2$ staining. In addition, there were features suggestive of inclusion body myopathy including rimmed vacuoles and inclusion bodies. Genetic studies of the *LAMA2* gene identified two new pathogenic heterozygous point mutations (c.2749+1G>A; p.Cys393Gly) in both individuals. Her two unaffected siblings were carriers for the splice site change but not the missense mutation.

Conclusions: The presence of compound heterozygous mutations in *LAMA2* together with a reduction in laminin $\alpha 2$ staining confirms the diagnosis of partial merosin deficiency in the two affected individuals. The presence of epilepsy in the proband and its absence in the affected brother suggests that other genes are also likely to determine the phenotype. In addition, the finding of features typical of inclusion body myopathy on muscle histology in both affected patients suggests that merosin deficient muscular dystrophy is associated with a wide spectrum of clinical and pathological features.

Mouse Models of Neuromuscular Diseases**P23**

Poster

Assessing the effects of exercise-induced stress on the Fiona mouse modelA. Bareja¹, R.J. Fairclough¹, A. Potter¹, D. Powell¹, S. Squire¹, K.E. Davies¹. ¹University of Oxford, MRC Functional Genomics Unit, Department of Human Anatomy and Genetics, South Parks Road, Oxford, OX1 3QX, UK

Background and Aim: Characterized by the severe progressive wastage of skeletal muscle, Duchenne muscular dystrophy is a crippling disease that is caused by the absence of the cytoskeletal protein dystrophin. *Utrophin* is a paralogue of *dystrophin*. The Fiona mouse is an *mdx* (dystrophin-deficient) transgenic mouse that over-expresses the full-length utrophin protein in skeletal muscle. Various studies have shown that it is completely rescued and does not display any of the dystrophic characteristics of *mdx* mice. However, these studies have only been performed on sedentary mice. Our aim was to see if Fiona mice continue to display this rescued phenotype after an extended period of sustained exercise-induced stress, or whether they revert to the dystrophic phenotype.

Methods: 4-week-old C57BL/6, *mdx*, and Fiona mice were divided into two groups – 'sedentary' and 'run'. Those in the 'run' group were made to run on a treadmill at 12 m·min⁻¹ for 30 minutes, twice a week, for 8 weeks. After the end of the trial, muscle samples were dissected out and subjected to a range of tests.

Results: Muscle physiology tests show a significant decrease in maximum isometric force produced by the extensor digitorum longus (EDL) muscle caused by exercise in *mdx* and Fiona but not C57BL/6 mice. Leftward shifts in the force-frequency curves were seen for all groups. Increased centronucleation was seen in muscle sections of *mdx* mice but not of C57BL/6 and Fiona. These data indicate that utrophin's protective effect is partially diminished after a sustained period of exercise-induced stress.

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Poster

Blocking calcium influx with streptomycin worsens myocardial pathology in the *mdx* mouse model of muscular dystrophyA. Blain¹, E. Greally¹, L. Jørgensen¹, S. Laval¹, K. Bushby¹, G. MacGowan¹, H. Lochmüller¹, V. Straub¹. ¹Institute of Human Genetics, Newcastle University, UK

There is evidence to suggest that abnormal calcium influx is involved in the pathology of Duchenne muscular dystrophy (DMD) and short term treatment with the nonselective calcium channel blocker has been shown to ameliorate muscle pathology in the *mdx* mouse model of the disease. We have investigated whether early (in utero) and long term (until 6 months of age) treatment with streptomycin can prevent/ameliorate muscle and heart pathology in *mdx* mice. We present histological and functional MRI data to suggest that long term treatment with streptomycin does not improve heart pathology. On the contrary, treated animals showed evidence of increased myocardial sarcolemmal damage, necrosis and fibrosis. Treated mice showed no evidence of improved left ventricular function with overall trends toward reduced cardiac function. Treated C57/BL10 mice had significantly reduced left ventricular mass and cardiac output suggesting that the treatment had negative effects on healthy controls that showed no histological evidence of myocardial damage. The potential for non-selective calcium channel blockers as a therapy for DMD is therefore questionable.

Alison Blain, Elizabeth Greally and Louise Jørgensen contributed equally.