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Molecular Biology of Muscle Development

W 331 GENETIC MAPPING AND PATHOLOGY OF THE NEUROMUSCULAR DISEASE IN KYPHOSCOLIOTIC (KY) MICE. Coulton. G.R.'. Skynner. M.J.'. Barrett. M.'. Moss. J. Gangadharan. U.'. Entwhistle. A 4 Beckers-Bleukx, G.' Marechal, G.' Brown. S.D.M.'. van Mier. P. & Mason R.M. Dept. Biochemistry' & Dept. Histopathology'. Charing Cross and Westminster Medical School. London. UK. Dept. Biochemistry. St. Mary's Hospital Medical School, London. UK[3]. Ludwig Institute of Cancer Research. London. UK[4]. Dept. des Physiologic. Universite Catholique de Louvain. Brussels. Belgium'. Dept. Anatomy and Neurobiology, Washington University. St. Louis. USA'.

Ky mutants exhibit a bilateral neuromuscular disease where predominantly slow twitch muscles undergo extensive post-natal necrosis and regeneration but regenerated fibres are smaller and weaker than normal. The most striking feature of ky is the extensive motornerve sprouting and complete loss to normal endplate structure. Pre- and post-synaptic abnormalities have been analysed by *in vitro* and *in vivo* (See van Mier et al.. This meeting) visualisation of junction-associated proteins (JAPs: eg. AChR and 43kD) by immunohistochemistry or u-bungarotoxin-FITC. Expression of a several JAPs was analysed by northern blot. There appears to be continual expression to the -:-AChR subunit in adult ky muscles. Both AChR and 43kD protein were abnormally distributed but were always in close association, suggesting that loss of AChR clustering *per se* is not the primary ky lesion. However. our data suggests that the ky mutation is in a protein which maintains junction integrity and function. Chronic remodelling of ky muscles is associated with sole expression of the slow myosin heavy chain in muscles such as soleus. The ky lesion appears to precipitate succession of changes in cell function resulting in progressive pathology Culminating in spinal deformity.

An interspecific backcross segregating the ky mutation maps the ky locus to a small region of chromosome 9. ky is non-recombinant with the microsatellite marker D9Mit24 and lies in a conserved linkage group that encompasses human chromosome 3. It is striking that ky maps close to, but is recombinant with, a group of genes coding for junction-associated proteins including, s-laminin. collagen 7 and dystroglycan. Having identified the map position of ky we have eliminated all the obvious candidates for the ky gene. The ky mutation appears to lie in a gene coding for an as yet unidentified nmj-associated protein which Causes the death of muscle fibres and massive neural sprouting.