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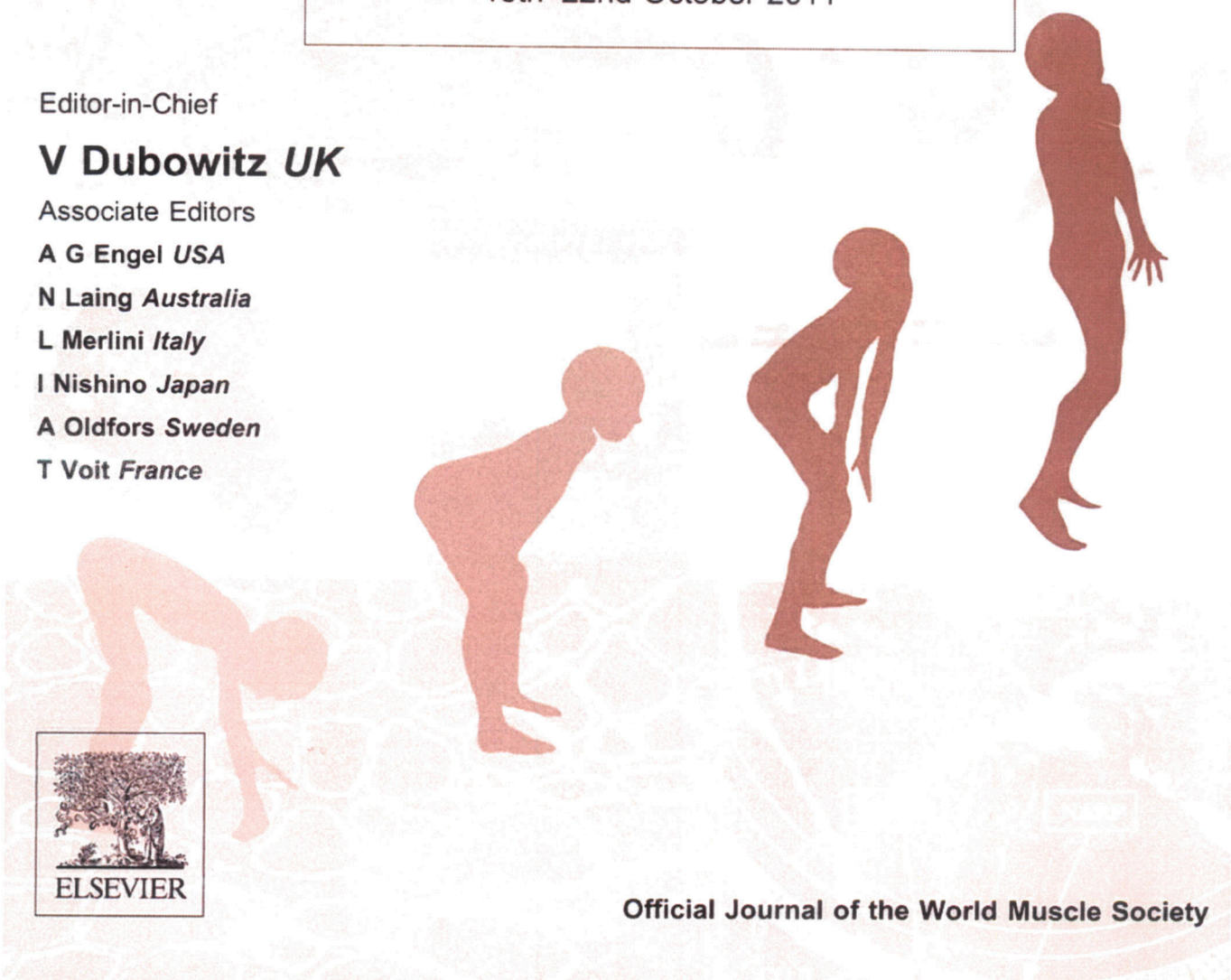

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Mutations in myostatin lead to a massive increase in muscle mass suggesting potential relevance of myostatin inhibition for therapeutic treatment of muscle wasting. Contradictory data in mdx and laminin a2 deficient mice have been published debating on the effect of myostatin inhibition in case of muscular dystrophies. Mutations in dysferlin cause limb girdle muscular dystrophy 2B due to defects in muscle membrane repair. We asked whether myostatin knock-out in a dysferlin deficient mouse model leads to improved muscle performance and a decrease in histopathological alterations. We crossed myostatin null mutant mice with the dysferlin deficient mouse model B6.A/J-Dysf^{prmd}. Mstn $^{-/-}$/ B6.A/J-Dysf^{prmd} (DKO) were compared to Mstn$^{-/-}$, B6.A/J-Dysf^{prmd} and C57BL/6 mice ($n = 8$/group). Individual muscle mass was determined and body composition was performed. Treadmill performance was assessed for three weeks and grip strength was tested. We histologically analyzed Quadriceps and Tibialis muscle of untrained and trained mice at three months of age. Mstn$^{-/-}$ and DKO mice equally gained muscle mass but differed significantly in physiological muscle function. In treadmill analysis B6.A/J-Dysf^{prmd} slowly worsened over time (weeks) compared to WT and Mstn$^{-/-}$ while DKO already showed a significantly reduced running distance and a higher rate of drop backs during the first training days. Grip strength was mostly reduced in DKO, but was also significantly diminished in B6.A/J-Dysf^{prmd} and Mstn$^{-/-}$ compared to WT. The histological analysis reflects the impaired muscle function of B6.A/J-Dysf^{prmd} and especially DKO mice with significantly increased numbers of central nucleated, necrotic and regenerating fibers. Like in Mstn$^{-/-}$ mice muscle fiber diameter was increased in DKO mice but showing additional atrophic fibers. These results indicate that permanent myostatin knock-out aggravates the course of disease in dysferlinopathy and that this is not a promising therapeutic option.

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P2.56

Migration of an ancestral dysferlin splicing mutation from the Iberian peninsula to South America

L. Vernengo[a], J. Oliveira[b], M. Krahn[c], E. Vieira[b], R. Santos[b], L. Carrasco[d], L. Negrão[e], L. Panuncio[f], F. Leturcq[g], V. Labelle[c], E. Bronze-da-Rocha[b], R. Mesa[h], C. Pizzarossa[h], N. Lévy[c], M.M. Rodriguez[a]

[a] *Faculty of Medicine, University of the Republic, Clinical Unit, Department of Genetics, Montevideo, Uruguay;* [b] *Centro de Genética Médica Jacinto Magalhães, Instituto Nacional de Saúde Ricardo Jorge, Unidade de Genética Molecular, Porto, Portugal;* [c] *Hôpital d'Enfants de la Timone, Département de Génétique Médicale, Marseille, France;* [d] *Hospital Maciel, Servicio de Neurología, Montevideo, Uruguay;* [e] *Centro Hospitais da Universidade de Coimbra, Serviço de Neurologia, Coimbra, Portugal;* [f] *Faculty of Medicine, University of the Republic, Electron Microscopy Unit, Pathology Department, Montevideo, Uruguay;* [g] *CHU Cochin, Department of Genetic Biochemistry, Paris, France;* [h] *Hospital de Clínicas, University of the Republic, Laboratory of Neuromuscular Pathology, Montevideo, Uruguay*

Miyoshi myopathy, LGMD2B and DMAT are primary dysferlinopathies that belong to a group of muscular dystrophies inherited in an autosomal recessive mode. Additional presentations range from isolated hyperCKemia to severe functional disability. LGMD2B involves predominantly the proximal muscles of the lower limbs whereas in Miyoshi myopathy the muscles involved are those of the posterior muscle compartment of the calf. DMAT is characterized by anterior tibial muscle weakness which rapidly progresses to the lower and upper proximal muscles. Onset is usually in young adults, but congenital and late-onset forms have also been reported. We present the first Uruguayan patient to have been diagnosed with Miyoshi myopathy and four Portuguese patients that carry a novel mutation in exon12/intron12 boundary: c.1180_1180 + 7delAGTGCGTG (r.1054_1284del) in the DYSF gene. Evidence of a founder effect due to a common ancestral origin of this mutation was detected in heterozygosity in four patients and in homozygosity in one patient. The homozygous patient has no proven inbreeding so it can be inferred that the mutation is identical by descent. All patients shared a common haplotype block identical in state between markers Cy172-H32 and D2S211. We believe that it derives from a common mutational event which is ancestral because of the recombination between the mutated gene and the telomeric flanking marker D2S2113. As this haplotype is not common among the Portuguese population, it is very unlikely that these mutated DYSF alleles represent recurrent events. This is the sixth founder effect of the DYSF gene to be found in the world so far.

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P2.57

First dysferlinopathy patients in Egypt: Clinical, pathological and genetic characteristics

N. Fahmy[a], A. Abd El-Hady[a], A. Abd El-Naser[a], S. Ashour[a], A. El-Etribi[a], I. Nonaka[b], M. Narihiro[b], S. Naoki[c], T. Toshiaki[c], M. Aoki[c]

[a] *Ain Shams University, Neuropsychiatry, Cairo, Egypt;* [b] *National Center of Neurology and Psychiatry, DNA Laboratory, Tokyo, Japan;* [c] *Tohuku University, Neurology, Sendai, Japan*

Dysferlinopathy is caused by mutations of the dysferlin gene (DYSF) on chromosome 2p13. To study the clinical, pathological and genetic characteristics of dysferlinopathy in Egypt. Patients were selected from those with progressive muscular dystrophy referred to Muscle and Nerve Research Laboratory, Cairo, Egypt. We studied 77 patients with dystrophic muscle biopsy. Patients had neurological assessment, family pedigree study, Serum Creatine Kinase, ECHO cardiography, electromyography and Dystrophin gene testing. A battery of histochemical tests, immunohistochemistry using both fluorescent and automated methods against a panel of antibodies were done. Mini-multiplex Western Blotting was also done. Genetic study of Dysferlin gene was done for some patients. We found 40 patients with limb-girdle muscular dystrophy, 12 with dysferlinopathy, 6 with calpainopathy, 6 with sarcoglycanopathy and 16 with non-specified limb-girdle muscular dystrophy. Dysferlinopathy patients showed 3 patients with proximal type, 3 patients with Miyoshi myopathy and 6 patients with anterior compartment myopathy. Weakness was asymmetrical in 5 patients and symmetrical in 7 patients. Some muscles were uniformly affected in most patients: gluteus maximus, hamstrings, gastrocnemius, tibialis anterior and deltoids. Pathological study showed dystrophic changes of all biopsies, mitochondrial changes in 2 biopsies and inflammatory changes in 3 biopsies. Dysferlin gene analysis was done for only 6 patients of 4 families, showed homozygous mutations in two families, one heterozygous mutation in one family, and no mutation (only polymorphisms) in one family. Dysferlinopathy is a common condition in Egypt. Many clinical, pathological and genetic characteristics are found and help in its diagnosis.

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P2.58

Dissecting the interactions of proteins constituting the dysferlin complex

B. Flix[a], C. De la Torre[a], J. Castillo[a], C. Casal[b], I. Illa[c], E. Gallardo[a]

[a] *Institut de Recerca de l'Hospital de Sant Pau, Experimental Neurology, Barcelona, Spain;* [b] *Institut de Recerca de l'Hospital de Sant Pau, Core Facilities IRHSCSP, Barcelona, Spain;* [c] *Hospital de Sant Pau, Neurology, Barcelona, Spain*

Dysferlinopathies are a group of progressive muscular dystrophies characterized by mutations in the gene DYSF causing a severe reduction or complete absence of the protein dysferlin. It is expressed mainly in skel-