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Dominant BIN1-related centronuclear myopathy (CNM) revealed by lower limb myalgia and moderate CK elevation

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We report a *BIN1*-related CNM family with unusual clinical phenotype. The proband, a 56-year-old man suffered of lower limbs myalgia since the age of 52. Clinical examination showed short stature, mild symmetric eyelid ptosis without ophthalmoplegia, scapular winging and Achilles tendon retraction. A muscle weakness was not noted. CK levels were up to 350 UI/L. Deltoid muscle biopsy showed nuclear centralization and clustering, deep sarcolemmal invaginations and type 1 fiber hypotrophy. Whole body MRI revealed fatty infiltration of posterior legs compartments, lumbar paraspinal and serratus muscles. Myotonic dystrophy type1 and 2, Pompe disease and *MTM1* and *DNM2*-related CNM were ruled out. By sequencing *BIN1*, we identified a heterozygous pathogenic mutation [c.107C > A (p.A36E)], and we demonstrate that the mutation strongly impairs the membrane tubulation property of the protein. One affected sister carried the same mutation. Her clinical examination and muscle MRI revealed a similar phenotype. Our findings expand the clinical and genetic spectrum of the autosomal dominant CNM associated with *BIN1* mutations.

http://dx.doi.org/10.1016/j.nmd.2015.06.321

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Non-invasive NMR study of the mouse model for centronuclear myopathy with mutation in the dynamin-2 gene

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Centronuclear myopathies are a group of non-dystrophic congenital myopathies characterized by the altered positioning of the nuclei in muscle fibers without extensive muscle degeneration and regeneration. The knock-in KI-Dnm2^{R465W} mouse (Dnm2) models the autosomal dominant centronuclear myopathy with the most frequent mutation in DNM2 in patients. Different from human, this model presents only strength reduction and atrophy, with very few histological alterations. The objective of this study was to non-invasively characterize Dnm2 mice with nuclear magnetic resonance (NMR), comparing NMR results to histological findings. For NMR, 16 Dnm2 and 13 wild-type (WT) mice were evaluated at 3 or 6 months of age, while 4 Dnm2 and 2 WT mice were evaluated histologically. The NMR study included anatomical evaluation and muscle T1 and T2 measurements, performed in a 4.7 T magnet, under isoflurane anesthesia. Despite the similar body weight, atrophy could be detected in Dnm2 mice by comparing the cross-section of the caudal limb normalized by tibia length (CSA/Lt: Dnm2 = 2.7 ± 0.3 mm, WT = 3.0 ± 0.2 mm, $p < 0.001$). No differences were observed for muscle T1 in the comparison between Dnm2 and WT mice, for both ages. Muscle T2 was increased in Dnm2 mice for both ages (T2: Dnm2–3m: 31.8 ± 1.4 ms, WT-3m: 30.2 ± 1.5 ms, $p < 0.05$; Dnm2–6m: 31.5 ± 1.1 ms, WT-6m: 30.3 ± 1.4, $p < 0.05$). Even if this mouse model has a mild phenotype, this non-invasive NMR study could identify muscle atrophy and increased muscle T2 in the heterozygous Dnm2 mice. We hypothesize that the increased muscle T2 was related to altered intracellular organization, due to the absence of pathological alterations usually related to increased muscle T2, such as necrosis and inflammation. These results indicate that NMR, especially T2 relaxometry, is sensitive enough to identify alterations in a pre-clinical stage in the centronuclear myopathy model, the heterozygous Dnm2 mouse.

http://dx.doi.org/10.1016/j.nmd.2015.06.322

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A family with DNM2-related centronuclear myopathy without ophthalmoplegia

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Centronuclear myopathy (CNM) is a rare congenital myopathy characterized by centrally located nuclei in most of its muscle fibers. DNM2 is most commonly found assuming autosomal dominant inheritance pattern. Clinically, DNM2-related CNM typically shows distal dominant muscle atrophy, ptosis, ophthalmoplegia and contracture. Here we report a first Korean family diagnosed as DNM2-related CNM without ocular symptoms. A 48 year old Korean male presented with slowly progressive weakness since 20s. His weakness progressed and at the age of 40 he was unable to climb stairs. His daughter also had a mild myopathic elongated face and she was unable to perform a tip-toe gait. With mild elevation of creatine kinase, the muscle magnetic resonance imaging showed an extensive fatty infiltration in the posterior thigh and distal leg muscles. Muscle biopsy was performed and it illustrated a numerous number of central nuclei in most of the muscle fibers with disrupted myofibril that was compatible with a typical centronuclear myopathy. Genetic analysis of DNM2 revealed a first western prototypic pathogenic mutation in the middle domain of DNM2 (p.R465W). The Caucasian studies reported a high prevalence rate of ptosis and ophthalmoplegia with early onset and it correlated with the severity of the disease. However, Asian reports show a low prevalence of ocular symptoms in DNM2-related CNM patients and patients who had ocular symptoms were of late onset. The p.R465W is one of the most commonly found mutations in the western countries and all of them had ocular symptoms. However our proband and his daughter had no ocular symptoms despite the identical mutation. Therefore clinical findings in DNM2-related CNM can be heterogeneous, probably due to an ethnic difference that needs to be further elucidated. Also, this is the first Korean familial case in comparison to a recent Korean study that reported only sporadic cases.

http://dx.doi.org/10.1016/j.nmd.2015.06.323

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Recessive loss-of-function *SCN4A* mutations associated with a novel phenotype of congenital myopathy

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