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Authors
Watts, GDJ
Thorne, M
Kovach, MJ
et al.

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Clinical and Molecular Studies in 5 families with Limb Girdle Muscular Dystrophy/Hereditary Inclusion Body Myopathy, Paget disease of Bone and Frontotemporal dementia. *G.D.J. Watts[1], M. Thorne[1], M.J. Kovach[2], A. Pestronk[3], V.E. Kimonis[1]*. 1) Department of Genetics, Children's Hospital Boston, Harvard Medical School, Boston, MA; 2) Department of Biological and Environmental Sciences, University of Tennessee at Chattanooga, Chattanooga, TN; 3) Dept. of Neurology, Washington Univ. School of Med., St Louis, MO.

We have previously demonstrated linkage to 9p 13.3-p12 in a large family with Limb Girdle Muscular dystrophy and Paget disease of bone and an additional 3 families with autosomal dominant inclusion body myopathy (HIBM), Paget disease of bone (PDB) and frontotemporal dementia (Kovach et al 2001). Linkage in these families and an additional one with this unique combination identifies a critical locus on 9p 13.3-p12 spanning 4-6 MB.

Clinical features in 57 affected individuals in 5 families indicate that 51 had muscle weakness in variable patterns involving proximal, and, occasionally, distal muscles. With disease progression, the weakness became more generalized, often resulting in respiratory failure.

Muscle histology reveals myopathic changes and rimmed vacuoles. PDB caused by overactive osteoclasts was present in 51/57 primarily involving the spine and hip, causing pain, elevated alkaline phosphatase, and urine pyridinoline/ deoxypyridinoline and is responsive to bisphosphonates. Frontotemporal dementia associated with relative sparing of memory and impairment of executive skills occurred in 21/57 at a mean age of 54 y.

Recently mutations in the GNE (UDP-N-acetylglucosamine 2-epimerase) gene which maps to 9p13-p12 have been found in IBM2, an autosomal recessive inclusion body myopathy associated with quadriceps sparing. No mutations were found in the GNE gene in affected individuals in our families indicating that LGMD/HIBM/PDB/FTD is not allelic with IBM2. Candidate gene tropomyosin 2, NDUFB6 and SMU1 were also not implicated. Identification of the genes for this complex disorder is a priority in understanding these common pathways/ pathogenetic mechanisms.