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Clinical and Molecular Characterization of a Unique Familial Disorder: Proximal Myopathy, Paget disease of Bone and Frontotemporal dementia. *V.E. Kimonis[1], J. Wymer[1], S. Mumm[2], S. Mehta[1], A. Pestronk[3], M. Whyte[2], G. Watts[1]*. 1) Genetics, CHB, Harvard Medical School, Boston, MA; 2) Division of Bone and Mineral Diseases, Washington University, St Louis, MO; 3) 3Dept. of Neurology, Washington Univ. School of Med., St Louis, MO.

We have delineated a new limb-girdle myopathic disorder associated with Paget disease of bone (PDB) and frontotemporal dementia (FTD. Of 87 affected individuals in 13 families, 75 (86%) had progressive proximal limb girdle type of muscle weakness resulting in early demise from respiratory failure. EMG and muscle biopsy revealed myopathic changes, with 25% of individuals showing rimmed vacuolar muscle fibers suggestive of 'inclusion body myopathy'. Paget disease of the bone caused by overactive osteoclasts in 45 (52%) individuals was associated with trabecular coarsening,and cortical thickening, with pain primarily of the spine and hip, elevated alkaline phosphatase, and elevated urine pyridinoline/ deoxypyridinoline levels. Frontotemporal dementia associated with relative sparing of memory and impairment of executive skills occurred in 25 (29 %) individuals at a mean age of 54 y. We have previously demonstrated linkage to 9p 13.3-p12 in 4 families (Kovach et al 2001) and have confirmed a critical locus of 3.5 Mb by haplotype analysis in 12/13 families analyzed. We have identified five missense mutations occurring in a critical domain within the VCP gene (Valosin Containing Protein) in 10/13 families. VCP, is widely expressed, and encodes a 806 amino acid protein. It has two AAA ATPase domains, and has been implicated in two distinct and crucial cell pathways, namely membrane biogenesis and targeted protein degradation. Previous studies have shown that a ATPase D2domain mutant induced cytoplasmic vacuoles and accumulation of polyubiquitinated protein in the nuclear and membrane fractions in neurons, these findings resembling the rimmed vacuolar muscle fibers seen in this disease. It is hoped that identification of the gene for this complex disorder will help in understanding the pathogenetic mechanisms and developing new therapeutic target.