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Clinical delineation and localization to chromosome 9p13.3-p12 of a unique dominant disorder: Hereditary inclusion body myopathy, Paget disease of bone and frontotemporal dementia in four families. *V.E. Kimonis[1], M. Kovach[1], B. Waggoner[1], S.M. Leal[2], Z. Simmons[3], R. Khardori[4], M.P. Whyte[5], A. Pestronk[6].* 1) Div of Genet. & Metab., Dept. of Ped., Southern Illinois Univ. Sch. Med, Springfield, IL; 2) Rockefeller Univ., New York, NY; 3) Pennsylvania State Univ., Hershey, PA; 4) Dept. of Med., Southern Illinois Univ. Sch. Med., Springfield, IL; 5) Div of Bone and Mineral Dis, Washington Univ. Schl. of Med., St Louis, MO; 6) Dept. of Neurology, Washington Univ. Schl of Med., St Louis, MO.

The clinical, biochemical, radiological and pathological characteristics of 49 affected (23 M, 26 F) individuals from 4 unrelated families with this unique autosomal dominant disorder(MIM 605382) are reported. Of these individuals 44/49 (90 %) have myopathy, 21/49 (43 %) have PDB and 18/49 (37 %) frontotemporal dementia. Muscle histology reveals myopathic changes with blue rimmed vacuoles. Ultrastructural examination reveals filaments of phosphorylated tau, b-amyloid precursor protein epitopes and apolipoprotein E. PDB caused by overactive osteoclasts primarily involves the spine and hip, causes pain, elevated alk. phosphatase, and urine pyridinoline/ deoxypyridinoline and is responsive to bisphosphonates. Frontotemporal dementia occurs at a mean age of 54 y and contributes to the early demise from respiratory and cardiac failure secondary to the progressive muscle weakness. A genome-wide screen in the large Illinois family revealed linkage to chromosome 9 with a maximum LOD score of 3.64 with marker D9S301. Linkage analysis with a high density of chromosome 9 markers generated a maximum two-point LOD score of 7.62 for D9S1791, with a maximum multipoint LOD score of 12.24 between markers D9S304 and D9S1788. Subsequent identification and evaluation of three additional families demonstrating similar clinical features has allowed for localized to a 1.08-6.46 cM critical interval on 9p13.3-12 in the region of autosomal recessive IBM2. Identification of the putative gene is in progress and will no doubt provide insight into the common pathogenesis of this unusual combination of disorders.