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Clinical and Molecular Studies in a large unique family with Limb-Girdle Muscular Dystrophy and Paget Disease of Bone. *V.E. Kimonis[1], M.J. Kovach[1], S. Leal[4], B. Waggoner[1], R. Khardori[2], D. Gelber[3]*. 1) Dept Ped, Div Gen & Metabolism, Southern Illinois Univ Sch Med, Springfield, IL; 2) Dept of Internal Medicine, Southern Illinois Univ Sch Med, Springfield, IL; 3) Dept of Neurology, Southern Illinois Univ Sch Med, Springfield, IL; 4) Lab of Statistical Genetics, Rockefeller University, NY, NY.

A large Central Illinois family with Limb-Girdle Muscular Dystrophy (LGMD) and Paget disease of bone (PDB) includes 11 affected individuals (8 M, 3 F) ranging in ages from 33 y to 64 y. Onset of PDB is at a mean age of 41 y with pain in the hips, shoulders and back. Onset of the LGMD is at a mean age of 45.6 y. with weakness of the girdle muscles, and absent/reduced tendon reflexes. Affected individuals have elevated alkaline phosphatase (mean 455 (normal 30-130 mg/dl)), and CPK levels (mean 273 (20-222 mg/dl)). High-resolution karyotype is normal. Muscle biopsies in 5 individuals reveals non-specific myopathy with vacuolar changes seen in the oldest male. Individuals die prematurely from progressive muscle weakness, cardiomyopathy and cardiac failure in the forties to sixties. There are three previous reports of PDB and neuromuscular disease. Caughey et al. (1957) described familial dominant dystrophia myotonica, Tucker et al. (1982) identified a family with dominant amyotrophic lateral sclerosis, and McBride et al. (1966) found recessive LGMD in four of six siblings in addition to PDB. Linkage analysis in this family excluded all the 22 candidate loci for LGMDs, myopathy, PDB and cardiomyopathy. A genome wide search (Marshfield)indicated linkage to a unique locus on 9p21-q21 with D9S301 (max LOD=3.64) which includes the locus for recessive vacuolar myopathy, IBM2, however excludes the LGMD2H locus. Identification of the specific gene mutation may permit understanding the pathogenesis and permit development of specific treatment protocols in this unusual disorder.