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Clinical features in a unique family with Autosomal Dominant Limb-Girdle Muscular Dystrophy and Paget Disease of Bone. *V.E. Kimonis, M. Kovach, R. Khardori, D.A Gelber.* Southern Illinois Univ Sch Med, Springfield, IL.

We have identified a large family with a unique phenotype: Autosomal Dominant Limb-Girdle-Muscular-Dystrophy (LGMD) associated with early onset Paget Disease of Bone (PDB). A large family with autosomal dominant amyotrophic lateral sclerosis and PDB first reported by Tucker et al. in 1982 (MIM 167320) bears some resemblance to this family. Clinical evaluation in eight affected individuals (5M, 3F), mean age 49 y. indicated that 6/8 had both LGMD/PDB with evidence of only PDB in the youngest individual age 34 y. The onset of bone pain leading to a diagnosis of PDB begins early at a mean age of 39.5 y. Muscle weakness and pain begins at a mean age of 41.5 y. Clinical findings include tenderness of the hip, shoulder and spine, muscular weakness and pain, wasting of the shoulder and pelvic girdle muscles, and reduced/absent deep-tendon reflexes. Muscle biopsy in 4 individuals revealed abnormal muscle with evidence of atrophic fibers, fibrosis and mild regeneration and degeneration. Consistent with PDB, X-rays show coarse trabeculation, and sclerosis, particularly of the pelvis, shoulder and skull bones. Bone biopsy in 1 female for suspected neoplasia confirmed PDB. Laboratory evaluation revealed elevated alkaline phosphatase (mean 250 U/L, normal 30-130) in all individuals except one male age 46 y. who only had LGMD. Interestingly this male had the highest creatine kinase level of 264 IU/L (mean of group 121.6, normal 20-260). High resolution karyotype was normal. A male died at age 50 y from muscular dystrophy and cardiomypathy. He also had insulin dependant diabetes mellitus and coronary artery disease. Affected individuals eventually become bedbound; several ancestors died prematurely in their fifties from LGMD/cardiomyopathy. The association of LGMD with Paget disease of bone appears to also be genetically unusual. Linkage analysis excluded the loci for dominant and recessive forms of LGMD, PDB and cardiomyopathy in the family. A genome search is in progress to identify the gene causing these two apparently unrelated disorders. The clinical and molecular data in this unique family will be presented.