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The gene for autosomal dominant Limb-Girdle Muscular Dystrophy and Paget Disease of Bone in a large family maps to a unique locus on 9p22.3-q12. *M.J. Kovach[1], V.E. Kimonis[1], S. Leal[2], B. Waggoner[1], A. Salam[2], R. Khadori[3], D. Gelber[4].* 1) Dept Pediatrics, Southern Illinois Univ Sch Med, Springfield, IL; 2) Lab Statistical Genetics, Rockefeller University, NY, NY; 3) Dept Internal Medicine, Southern Illinois Univ Sch Med, Springfield, IL; 4) DeptNeurology, Southern Illinois Univ Sch Med, Springfield, IL.

The limb-girdle muscular dystrophies (LGMDs) encompass a large family of clinically and genetically heterogeneous neuromuscular disorders. We have identified a large family with autosomal dominant LGMD and Paget disease of bone (PDB) with Alzheimer disease in two individuals. Muscle biopsy shows non-specific changes and vacuolar myopathy in the oldest male. The existence of these two pathologically distinct phenotypes co-segregating among affected individuals within a single family is a rare occurrence. To date, only three other families with a similar phenotype have been reported.

Molecular studies have previously identified 4 chromosomal loci for autosomal dominant LGMD and 2 loci for autosomal dominant PDB. Preliminary linkage studies have excluded these loci, leading to a hypothesis that a unique gene is involved in the pathogenesis of the disease in this family. A genome-wide scan of 39 family members including 9 affected individuals, indicated linkage to chromosome 9p21-q21 with marker D9S301 (max LOD=3.64). Haplotype analysis with a high density of markers flanking D9S301 mapped the disease locus to a 30.94 cM region on chromosome 9p22.3-q12 flanked by markers D9S1869 and D9S1118. The autosomal recessive locus for vacuolar myopathy, IBM2, which maps within 1 cM of D9S1791 may be within the critical region, however recombinations distal to D9S1118 exclude the LGMD2H locus mapped to chromosome 9q. Linkage analysis of additional families is being performed towards narrowing the critical region for LGMD/PDB.

Immunocytochemistry of muscle biopsy material with antibodies specific for components of the dystrophin-sarcoglycan complex showed a complete absence of staining for a-sarcoglycan in affected individuals.