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Authors
Waggoner, B
Kimonis, VE
Kovach, MJ
et al.

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Heterogeneity in Familial Autosomal Dominant Paget Disease of Bone and Muscular Dystrophy. *B. Waggoner[1], V.E. Kimonis[1], M.J. Kovach[1], D.A. Gelber[2], R. Khardori[3].* 1) Dept. Pediatrics, Division of Genetics and Metabolism, Southern Illinois University, Springfield, IL; 2) Dept. of Neurology, Southern Illinois University, Springfield, IL; 3) Dept. of Internal Medicine, Southern Illinois University, Springfield, IL.

Autosomal dominant muscular dystrophy with the association of early onset Paget disease of bone (PDB) is an unusual disorder. We recently mapped the disorder in a large family from central Illinois with proximal limb girdle muscular dystrophy and PDB to a unique locus on chromosome 9p23.3-q12 (Kovach et al., 2000). We have identified a new 10-member family with dominant PDB and muscular dystrophy. The father, age 70 y., had onset of myopathy at age 41 y. Progression of the disorder began with foot drop in addition to PDB in the L knee. Presently, he has a severe, generalized, distal>proximal weakness and severe PDB causing deformity of his extremities. He is bedridden and requires a tracheostomy and gastrostomy. EMG and muscle biopsy are compatible with a primary dystrophy. His creatine phosphokinase (CPK) levels are currently 40 U/L (normal range 52-336 U/L), however, these levels have been elevated in the past to 776 U/L. Additionally, alkaline phophatase levels (530 U/L, normal range 98-250)and osteocalcin levels(140 U/L, normal range 2-10) are markedly elevated.

Of his 8 children, a 41 y. old son has a similar muscular dystrophy with onset at age 37 y. His CPK level is 662 U/L. Two daughters, age 43 y. and 40 y, developed PDB at mean age of 39y. with distribution in the pelvis, arms, spine, and tibia. All of the affected children have elevated alkaline phosphatase levels at a mean of 282 U/L.

Haplotype analysis of nine members (4 affected, 4 unaffected, 1 spouse) with a high-density of markers excluded the critical region on chromosome 9p23.3-q12, thus providing evidence for genetic heterogeneity among families with autosomal dominant PDB and muscular dystrophy.