Title
Clinical and genetic heterogeneity in familial dominant muscular dystrophy with pathological fractures

Authors
Mehta, S
Watts, GDW
Wymer, J
et al.

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Clinical and genetic heterogeneity in familial dominant muscular dystrophy with pathological fractures. *S. Mehta[1], G.D.J. Watts[1], J. Wymer[1], S.J. Hamilton[1], B. McGillivray[2], V.E. Kimonis[1]*. 1) Division of Genetics and Metabolism, Childrens Hospital, Harvard Medical School, 300 Longwood Avenue, Fegan 5, Boston, MA 02115; 2) Provincial Medical Genetics Programme, Children's and Women's Health Centre of British Columbia C234, 4500 Oak Street, Vancouver, British Columbia, Canada.

We have previously reported the unusual combination of autosomal dominant Paget disease of the bone (PDB) with a limb-girdle/inclusion body myopathy associated with dementia (IBMPFD). This disorder has been mapped to chromosome 9p22.3-q12 (Kovach et al, 2001). This present study describes an unrelated family previously reported by Henry et al. (1958) with an autosomal dominant progressive limb girdle muscular dystrophy, early onset of fracturing with poor healing, osteomyelitis and limb amputations. Some members also have herniae, premature greying, and a Von Willebrand type haematological picture.

Informed consent was obtained. Clinical, biochemical and radiological features have been documented in 9 males and 4 females. The average age of onset of the limb girdle myopathy was 29 y. occurring in 77% of affected individuals. The average age of onset of fractures was 20 y. occurring in 69% of affected individuals. Biochemical analysis showed a low normal alkaline phosphatase of 60 U/L (Normal 30-120) and high creatinine phosphokinase of 236.5 U/L (Normal 0-150). Radiographs show coarse trabeculation, sclerosis, cortical thickening, and narrowing of the medullary cavity. They were not suggestive of Pagets however there were features of fibrous dysplasia. Muscle biopsies and electromyograms showed myopathic changes. Nerve conduction studies were normal. Collagen studies were normal. Linkage analysis was undertaken for markers for the chromosome 9p22.3-q12 locus. This family does not map to this locus suggestive of a unique locus.

Screening of candidate genes and genome wide genotyping is in progress to identify the gene involved in the pathogenesis of this unique disorder. We report a unique autosomal dominant disorder with the combination of muscular dystrophy and bone fragility.