

Oral Abstract

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A novel disorder of type I collagen characterised by high bone mass, a mineralization defect and tendon calcification

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The most prevalent forms of osteogenesis imperfecta (OI) arise from mutations in the genes *COL1A1* or *COL1A2*. These conditions are characterized by skeletal fragility, narrow long bones and low bone mass, but normal mineralization of bone.

We describe two siblings - a man aged 41 and his 39 year old sister - with a fracturing bone disease inherited from their late father. By the age of 15 the elder sibling had suffered more than thirty long bone fractures, and developed marked scoliosis. The younger sibling sustained nine major fractures by the age of 16. Their father had started to fracture in infancy and sustained more than fifty fractures. All three subjects had significant hearing loss; audiometry demonstrated a conductive component suggestive of cochlear ossification. Both father and son suffered Achilles tendon rupture that healed with extensive calcification. Stature was normal, the sclerae were white, and there was no dentinogenesis imperfecta.

The radiographs showed osteosclerosis of the axial skeleton. The long bones were not narrow: the z-score for the total width of the second metacarpal was >2. The cortices of the long bones were thick with loss of tubulation. The femoral neck BMD z-score was +0.3 in the elder sibling and +6.2 in the younger. Bone turnover markers were increased. Transiliac bone biopsy specimens showed thick osteoid covering much of the bone surfaces (8-13 osteoid lamellae - normal ≤4).

Sequence analysis of the type I collagen genes identified a mutation (c.3652 G>A) in one allele of *COL1A1* in both affected siblings. The mutation results in an Ala→Thr substitution at position 1218. This mutation disrupts the alanine-aspartic acid site where the C-terminus propeptide of type I procollagen is cleaved by BMP1. The mutation could slow formation of type I collagen fibrils in the extracellular matrix and impair mineralization – as it is in the regions that would be occupied by propeptide extension fibrils that mineral starts to form.

This novel bone disorder extends the phenotype of type I collagen disorders to include features (mineralization defect, high bone mass and tendon calcification) hitherto unrecognized in the OI spectrum.