Genetic and Radiographic Profile of a Family with Osteopoikilosis

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Abstract

Osteopoikilosis is a rare condition of bones inherited in an autosomal dominant manner caused by mutations in *LEMD3*. It is characterized by sclerotic bone lesions in the epiphyses and metaphyses of long tubular bones, carpal bones, tarsal bones, pelvis, and scapulae (Serdaroglu et al., 2007). Individuals with osteopoikilosis are usually asymptomatic and often diagnosed incidentally through radiographs done for other medical conditions (fractures, joint dislocations, etc). Here we report the case of a 19 years old male with generalized back pain and radiographic evidence of multiple hyperostotic spots throughout the skeleton. The mother of the proband also had similar radiographic findings. A heterozygous pathogenic variant in *LEMD3* is identified to be the cause of osteopoikilosis in them.

Introduction

Osteopoikilosis (MIM #166770) is an autosomal dominant sclerosing bone dysplasia with multiple endostosis. Characteristic circular or ovoid shaped bone lesions in wrist, foot, pelvis, scapula and end of long bones are commonly seen (Ye et al., 2017). Individuals are usually asymptomatic and sometimes may also develop superficial skin lesions/ dermatofibrosis (Baasanjav et al., 2010). They are diagnosed by radiographs done incidentally for other medical conditions such as fractures or joint pain (Mahbouba et al., 2015). Heterozygous variations in *LEMD3* are known to be causative of the osteopoikilosis phenotype (Hellemans et al., 2004).

Case summary

A 19 years old male was referred with persistent lower back pain of one month. His birth and development was unremarkable. In childhood, he had history of recurrent fractures in the left leg on trivial trauma. On examination, the head circumference was 53 cm (-2 SD for age), height was 172 cm (normal for age) and weight was 47 Kg (-2 SD for age). No characteristic skin nodules were observed. His intellect was appropriate for age and he had no other co-morbid conditions. In radiographs, numerous symmetric, hyperostotic, well defined, ovoid spots more localized in the epiphyses and metaphyses of long bones, and in other bones like scapula, spine and pelvis were seen (Figure 1 A-C). The proband's mother was also asymptomatic and had similar radiographic findings. The typical hyperostotic spotted bone lesions were observed in her radiographs (Figure 2 A-B).

Informed consents were obtained and 3ml of peripheral blood was collected from the proband and parents. Genomic DNA was extracted and the coding exons and their flanking intronic regions of *LEMD3* (NM_001167614.1) were PCR amplified with the primers designed for the same. Sanger sequencing of the PCR amplicons and data analysis revealed C-to-T transition in exon 9 (c.2203C>T) in *LEMD3*. This pathogenic variant was predicted to change arginine amino acid to a stop codon (p.Arg753Ter). It is a known pathogenic stop gain variant and is predicted to cause premature termination of translation thus forming a truncated protein. This variant is not observed in population databases like 1000 Genomes Project, Exome Aggregation Consortium and our in-house data of 569 exomes. Multiple *in silico* analysis tools are consistent in predicting that the variant may damage the LEMD3 protein function. Bi-allelic segregation in his parents was performed. The same variant, c.2203C>T was found in his mother who also shared similar radiographic features with the proband and the variant was not observed in the father. Radiographic findings observed in the proband and his mother are in concordance with osteopoikilosis (Figure 3 A-B).

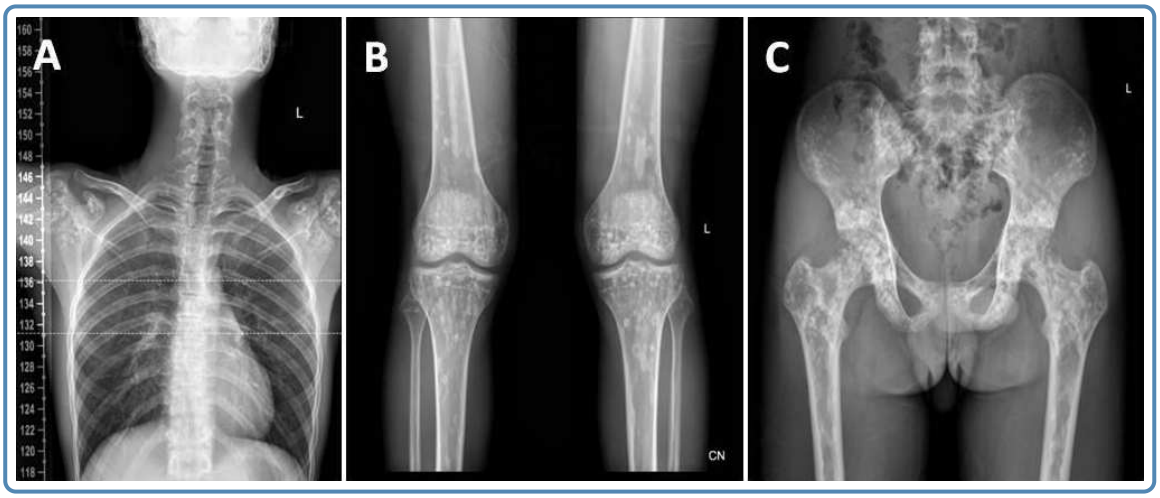

Figure 1 (A) Radiograph of the shoulder joint demonstrating multiple sclerotic foci involving the scapula, epiphysis and metaphysis of humerus in the proband, (B) Knee joint with small discrete sclerotic lesions involving the epiphyseal and metaphyseal regions of femur and tibia, (C) Hyperostotic lesions in pelvis, epiphyseal and metaphyseal regions of femur.

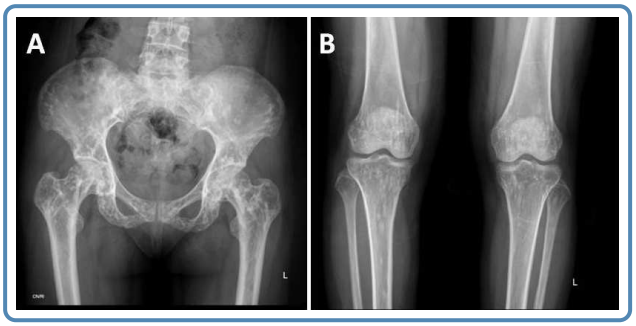

Figure 2 Radiographs of proband's mother shows – (A) Multiple sclerotic foci in pelvis, epiphyseal and metaphyseal regions of femur, (B) Knee joint with small discrete sclerotic lesions involving the epiphyseal and metaphyseal regions of femur and tibia.

Discussion

Osteopoikilosis, also called spotted bone disease, is a rare autosomal dominant bone dysplasia. The overall incidence of osteopoikilosis is 1 in every 50,000 subjects (Mohapatra et al., 2006). This condition is seen in both men and women and can become evident at any age. Both inherited and sporadic forms of this condition have been reported (Hellemans et al., 2004). Typically, the patients are asymptomatic, although as many as 20 % may have mild articular pain and joint effusion (Paraskevas et al., 2009).

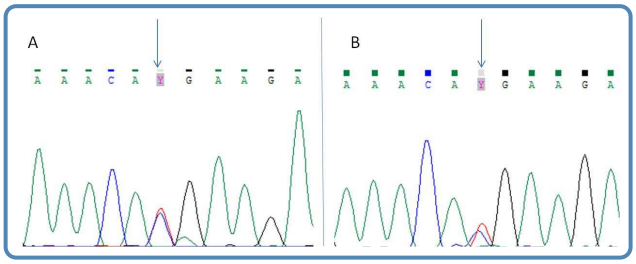

Figure 3 Sequence chromatograms of exon 9 in LEMD3 gene shows – (A) Proband with sequence variant c.2203C>T, in heterozygous state, (B) Mother with sequence variant c.2203C>T, in heterozygous state.

An epidemiological, clinical and radiological study has revealed that a predominance of lesions is seen in the phalanges of hand (100%) followed by carpal bones (97.4%), metacarpals (92.3%), foot phalanges (87.2%), metatarsals (84.4%), tarsal bones (84.6%), pelvis (74.4%), radius (66.7%), ulna (66.7%), sacrum (58.9%), humerus (28.2%), tibia (20.5%) and fibula (12.8%) (Benli et al., 1992). The primary cause of osteopoikilosis is heterozygous *LEMD3* mutations (Hellemans et al., 2004). The exact mechanism by which *LEMD3* mutation leads to bone lesions is not clear (Dheedene et al., 2009).

At present there is no consensus on treatment. Non-steroidal anti-inflammatory drugs (NSAIDs) are often used as an option for the treatment of pain. Analgesics such as acetaminophen and

opioids can also be used. Rare active lesions have been treated with bisphosphonate therapy, but the results are controversial (Woyciechowsky et al., 2012).

In our study, we are providing clinical, radiographic and genetic details of a familial case with osteopoikilosis.

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