

# Osteosclerotic Metaphyseal Dysplasia: A novel homozygous LRRK1 mutation in two siblings

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## BACKGROUND

Osteosclerotic metaphyseal dysplasia (OSMD, OMIM 615198) is an extremely rare autosomal recessive disorder, within the family of sclerosing bone dysplasias. It is a distinctive type of osteopetrosis characterised by a unique pattern of osteosclerosis predominantly involving the metaphyseal margins of the long tubular bones.

OSMD is characterised by skeletal deformity and multiple fractures and associated clinically with developmental delay, hypotonia, seizures and osteonecrosis of the jaw.

To date, only eight families with ten affected individuals have been reported. Three homozygous sequence variants in the leucine-rich repeat kinase 1 (LRRK1) gene have been identified to cause OSMD in four of the above individuals.

We present two male siblings with OSMD with a novel LRRK1 mutation.

## SIBLING 1

- 9 month old male
- Incidental finding of diffuse sclerosis of the ribs and vertebral bodies, suggestive of osteopetrosis on a chest radiograph done for suspected lower respiratory tract infection.
- Parents were consanguineous (first cousins).
- Clinical assessment revealed developmental delay, significant genu valgus deformity and nystagmus.
- Further evaluation showed bilateral optic nerve hypoplasia with severe visual impairment and an abnormal bone texture indicative of osteopetrosis.

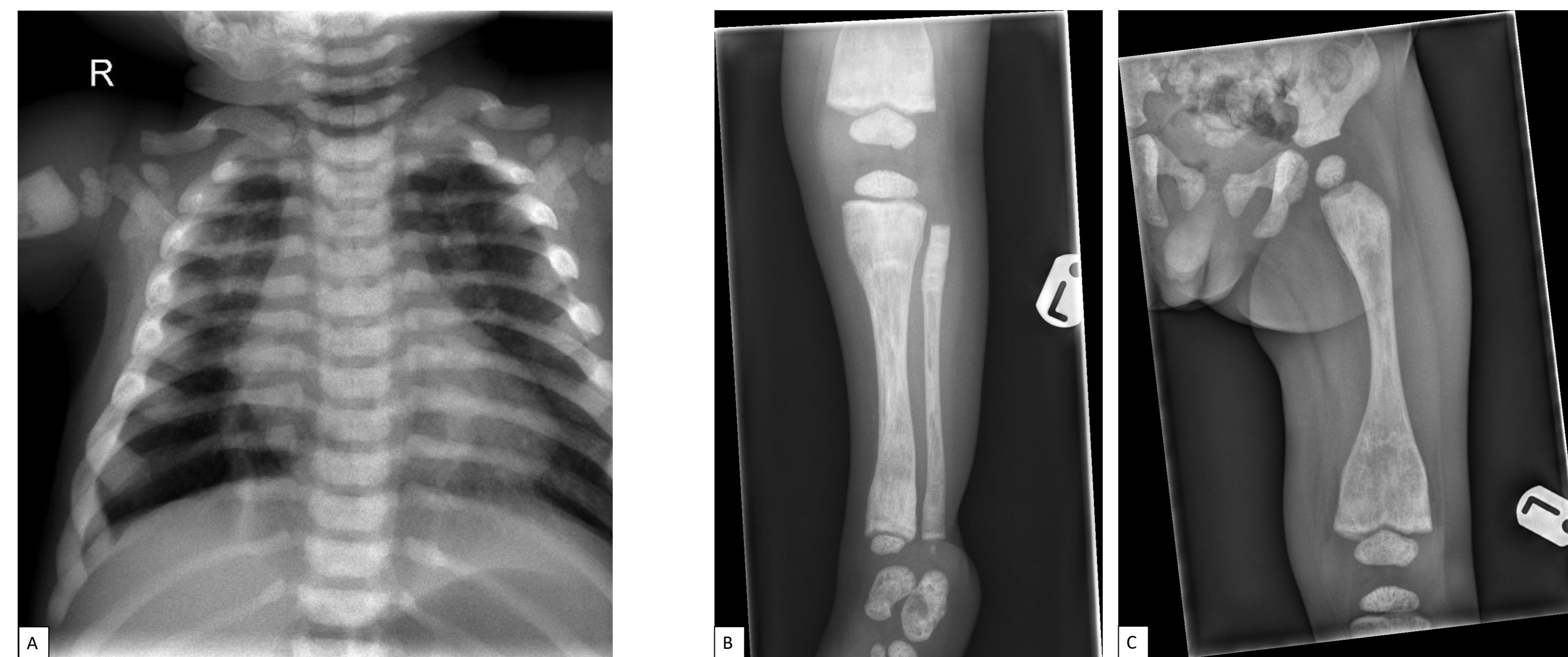


Fig 1. Sibling 1. Diffuse sclerosis of the ribs and vertebrae on chest radiography (A) and long bones on skeletal survey (B, C).

## SIBLING 2

- 7 year old male
- Similar clinical course with recurrent respiratory infections in infancy, nystagmus with bilateral visual impairment and significant valgus deformity
- No apparent developmental delay or hypotonia.
- Chronic osteomyelitis of the left mandible that required debridement, debulking and long-term antibiotics. Dense bones confirmed at the time of operation.
- A skeletal survey revealed widespread diffuse sclerosis with Erlenmeyer flask deformity of the femurs, similar to previous reports.
- Unlike previous reports suggesting sparing of the skull, our patient had scaphocephaly with evidence of osteosclerosis on CT scan.
- Neither sibling had significant skeletal fractures or cytopenia.



Fig. 2A Sibling 2. CT Skull demonstrating osteomyelitis of the left mandible.

Fig. 2B Sibling 2. Erlenmeyer flask deformity of the left femur with evidence of osteopetrotic bone (black arrow) and under-tubulation of the distal diaphysis (white arrow).

## GENETIC TESTING

Negative for the common autosomal recessive and dominant pathogenic variants of osteopetrosis.

Whole Exome Sequencing (WES) followed by Sanger sequencing, identified a **homozygous LRRK1 c.2506C>T p.(Gln836Ter) nonsense variant** which is predicted to result in premature truncation of LRRK1 transcript.

## DISCUSSION

Our cases confirm and expand the spectrum of clinical and radiological features of OSMD reported in the literature.

Increasing reports of LRRK1 mutation in this phenotype raises the question of whether LRRK1 gene should be included in targeted osteopetrosis panels. Bone histology in previous cases has shown this to be an osteoclast rich form of osteopetrosis and therefore bone marrow transplantation may be an appropriate treatment modality.

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