LRP5 mutation in a boy with osteopetrosis and normal stature despite low IGF-I levels


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Background
Osteopetrosis is a genetic disorder characterized by increased bone mass due to defective osteoclast formation and function. The genetic basis of this disease has been largely uncovered. Osteopetrosis is commonly associated with short stature but serum IGF-I and spontaneous or provocative GH levels are usually within the normal range. Thus, GH/IGF-I deficiency is unlikely to be the cause of the short stature of these patients. Aim: to study the underlying genetic mechanisms and the GH/IGF-I axis of a tall patient with radiological features of osteopetrosis.

Methods
A 19 year-old male patient with osteopetrosis was studied. His final height was 179cm (0.43 SDS), above family target height. The patient was first seen in the clinic at the age of 14yr due to delayed puberty (GIP1). Bone-age investigation showed increased bone mass and bone densitometry was performed. Blood samples were obtained for molecular analysis and laboratory tests for pituitary function were carried out.

Results
Lumbar spine bone mass (Hologic) was increased (Z-score=-5.1). Calcifications were present within the skull base but the brain MRI was normal. At the age of 16yr, the patient had a femoral fracture with abnormal consolidation. Heterozygous mutation of LRP5 gene was detected: A1330V [GCG>GCT](C/T). Serum IGF-I levels were consistently low (<-2SDS) for his age and pubertal stage. Provocative tests (Glucagon) performed after priming with sexual steroids (15 and 16yr) or testosterone replacement (19yr) resulted in undetectable GH but normal cortisol levels.

Exome analysis

Conclusion
This patient represents an uncommon case of osteopetrosis, with final height above the target height and very low GH/IGF-I concentrations. A de novo mutation was present in the LRP5 gene, which causes autosomal dominant Type I osteopetrosis. However, further studies are necessary to evaluate the relationship between these molecular findings and the normal growth rate observed in spite of the extremely low serum GH and IGF-I levels.