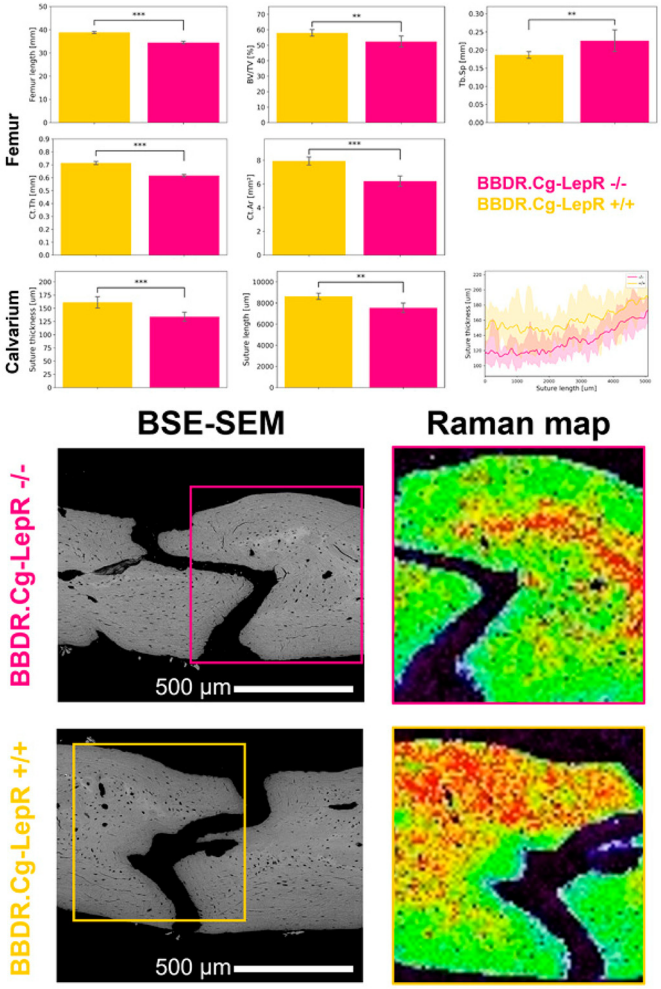

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Variants in STAT4 and TMEM151B identified as potential causal factors in Early-Onset Familial Osteoporosis

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Objective: Osteoporosis is a bone disease with a strong genetic background. The aim of the study was to identify the underlying genetic cause of early-onset osteoporosis in a Maltese pedigree.

Methods: A 3-generation family of 9 relatives aged 21-76 years was recruited. Osteoporosis was defined by lumbar and hip T-scores or Z-scores derived from BMD measurements by dual X-ray absorptiometry. The proband, a 52-year-old female, was diagnosed with osteoporosis at the hip (T-score FN -3.4; TH -2.7). Whole genome sequencing was performed on 6 relatives (including 4 affected relatives) and the shortlisted variants were tested using Competitive Allelic Specific PCR in the Malta Osteoporotic Fracture Study (MOFS), a case-control collection of 1,045 Maltese postmenopausal women.

Results: Variant filtering following a dominant inheritance pattern identified a novel missense variant *STAT4* c.1309C>T (p.Leu437Pro) in affected relatives. The conserved variant is located in the DNA-binding domain affecting the binding of enhancer region of IFN-γ activated sequence (GAS) family genes. The variant is predicted to be deleterious by most *in silico* tools, and is classified as 'pathogenic' per ACMG guidelines. A second novel missense variant *TMEM151B* c.545A>G (p.Tyr182Cys) was identified and is classified as deleterious by most pathogenicity prediction tools. This variant is located in the transmembrane domain involved in the transport of substances across the cell membrane. Both shortlisted variants were not identified in the MOFS, and are therefore monomorphic.

Conclusion: Our findings postulate that the identified novel variants, alone or in combination, might play a role in the pathogenesis of familial osteoporosis. STAT4 is a transcription activator of the AMPK pathway which promotes osteoblast differentiation and bone formation. TMEM151B is predicted to interact with proteins involved in bone physiology, including NFκBIE and MMP19. Further testing in a larger collection could potentially lead to a better understanding of the variants' association with osteoporosis.

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Paralogs of human parathyroid hormone encoding gene

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Generally speaking, parathyroid hormone (PTH) is one of the most important hormones that with vitamin D (a secosteroid hormone) play crucial role in bone growth and development, and additionally it is one of major regulators of mineral metabolism involved in calcium and phosphate homeostasis. Moreover, there is some evidence from animal model studies that PTH is involved in mandible and mandibular condyle development and mineralization. Thus, the most important factor related with craniofacial growth and development seems to be hormones, genetic, and molecular mechanisms. However, the role of PTH and genes associated with this hormone in the human mandibular retrognathism, which is a common skeletal malocclusion in humans, is still unclear. Therefore, it was important to study, evaluate and trace the intraspecific evolution of the PTH encoding gene, so the aim of this work was to detect paralogs and order of duplication of human PTH encoding gene (*PTH*).

Methods: Nucleotide sequences of human *PTH* were taken from the database (https://www.genome.jp). By mechanism of "SSDB Paralog Search" the paralogs of human *PTH* were detected. The evolutionary history was inferred by using the Maximum Likelihood method based on the Tamura Nei model. Evolutionary analyses were conducted in MEGA6. The reliability of the inferred tree was detected by bootstrap test. Reliable result was considered at 70 and more.

Results: The analysis involved seven nucleotide sequences. Paralogs of human ATP are PTHR1 (parathyroid hormone receptor 1), PTHR2