

A NOVEL RECESSIVE MUTATION IN FIBROBLAST GROWTH FACTOR-23 (FGF-23) IN TUMORAL CALCINOSIS

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Tumoral calcinosis (TC) is a rare genetic disorder characterized by periarticular cystic and solid tumoral calcifications. Biochemical markers of disorder include hyperphosphatemia and an elevated serum of calcitriol concentration in every patients. The hyperphosphatemia results from an increase in capacity of renal tubular phosphate reabsorption. The identification of phosphatonin family hormones suggest that mutations of these molecules could be involved in the pathogenesis of TC. One of these molecules is represented by FGF-23. Recently, biallelic mutation on the GalNAc transferase 3 or GALNT3 gene has been established as the molecular cause of recessive forms of TC. In the present study we described a new FGF-23 mutation in a subject affected by TC without mutations of GALNT3 gene.

A Caucasian woman (years 67) was examined for a history of ectopic calcification. Biochemical exams showed hyperphosphatemia and hyperphosphaturia with normal value of PTH and 1-25(OH)₂ D₃. The patient presented a shoulder calcification and also a calcification of femoral artery.

The family tree history revealed that parents were consanguineous. Hystologically the mass was characterized by calcium deposition and granulomatous reaction around the mass. Genomic DNA was extracted from blood collected from the patient, her daughter and her grandchild by standard procedure. DNA was not available from her parents. All three FGF-23 coding exons, as well as conserved splice sites, were amplified by standard PCR procedure. Nucleotide sequences were determined by direct sequencing with a DNA kit and an automated DNA sequencer (ABI PRISM 3100 - Perkin-Elmer Corp).

We discovered a new homozygous codon 41, His/Gln (CAC-CAA) substitution in exon 1 of FGF-23 gene in the affected patient. A heterozygous substitution was present in the daughter. No mutation were found in the two children. FGF-23 gene mutation was not found in the SNP database (www.ncbi.nih.gov/snp). In summary, a recessive mutation in FGF-23 causes TC. Understanding the functional significance and molecular physiology of this novel mutation will reveal critical information regarding the role of FGF-23 in states of normal and of disorder of phosphate homeostasis.