An FGF23 missense mutation causes familial tumoral calcinosis with hyperphosphatemia.

Familial tumoral calcinosis (FTC) is an autosomal recessive disorder characterized by ectopic calcifications and elevated serum phosphate levels. Recently, mutations in the GALNT3 gene have been described to cause FTC. The FTC phenotype is regarded as the metabolic mirror image of hypophosphatemic conditions, where causal mutations are known in genes FGF23 or PHEX. We investigated an individual with FTC who was negative for GALNT3 mutations. Sequencing revealed a homozygous missense mutation in the FGF23 gene (p.S71G) at an amino acid position which is conserved from fish to man. Wild-type FGF23 is secreted as intact protein and processed N-terminal and C-terminal fragments. Expression of the mutated protein in HEK293 cells showed that only the C-terminal fragment is secreted, whereas the intact protein is retained in the Golgi complex. In addition, determination of circulating FGF23 in the affected individual showed a marked increase in the C-terminal fragment. These results suggest that the FGF23 function is decreased by absent or extremely reduced secretion of intact FGF23. We conclude that FGF23 mutations in hypophosphatemic rickets and FTC have opposite effects on phosphate homeostasis.