A novel homozygous variant in exon 10 of the GALNT3 gene causing hyperphosphatemic familial tumoral calcinosis in a family from North India

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SUMMARY

Hyperphosphatemic familial tumoral calcinosis (HFTC) is an extremely rare autosomal recessive disorder caused by variants in the GALNT3 (N-acetylgalactosaminyltransferase 3), FGF23 (Fibroblast Growth Factor-23) and αKL (α-Klotho) genes, which results in progressive calcification of soft tissues. We describe the case of a 9-year-old girl who presented with recurrent hard nodular swellings on her feet and knees which intermittently discharged chalky white material. Her younger brother also had a similar condition. Both siblings showed hyperphosphatemia, but the parents’ biochemical parameters were normal. The histological features of the material aspirated from a skin lesion were consistent with tumoral calcinosis. Sanger sequencing identified a novel homozygous non-synonymous sequence variant in exon 10 of the GALNT3 gene (NM_004482.3:c.[1681T>A];[1681T>A], NP_004473.2:p.[Cys561Ser];[Cys561Ser] in the proband and her affected brother. The parents were heterozygous carriers for the same sequence variant. In conclusion, we report a new variant in the GALNT3 gene that caused HFTC in a North Indian family.

Keywords

hyperphosphatemic familial tumoral calcinosis, calcinosis cutis, GALNT3 gene, novel variant, Indian family

Hyperphosphatemic familial tumoral calcinosis (HFTC) is a rare disorder of phosphate metabolism caused by mutations in genes related to Fibroblast Growth Factor-23 (FGF23), which include FGF23 itself, an FGF23-glycosylating enzyme, N-acetylgalactosaminyltransferase 3 (GALNT3), and the FGF23 co-receptor α-Klotho (αKL) (1). The altered gene function decreases FGF23 synthesis or activity and causes increased renal tubular reabsorption of phosphate, thereby increasing blood calcium-phosphate product, which leads to predisposition for soft-tissue calcification (2). The most common manifestation of HFTC is calcinosis cutis, which appears clinically as firm, otherwise asymptomatic, white, yellowish or flesh-colored papules, plaques, or nodules. The clinical course is often associated with excretion of chalky material, pain, itching, ulceration, or infection of the lesions (1).

Only about 75 patients of genetically confirmed HFTC have been reported (1). The majority (about 80%) have mutations in the GALNT3 gene followed by the FGF23 gene (about 20%) and the KL gene (1). Most described patients were of African or Middle East origin, with few cases in Caucasians and Asians (1-6). Of about 60 patients reported with the GALNT3 gene mutations, there is one report of two siblings from India (7).

A 9-year-old girl presented with recurrent hard nodular swellings that intermittently discharged chalky white material. The first lesion was noticed at age 4 years on the left knee, which gradually increased in size and ruptured spontaneously. Similar lesions appeared on the right knee and both feet over the next year. At age 5 years, she underwent excision of foot lesions, and was subsequently referred to us for repeated recurrences. There were no dental problems, and pain or redness at the site of lesions. She belonged to a hilly hamlet of the North-Indian state of Himachal Pradesh and was born to non-consanguineous parents. There was no family history of such skin lesions.

Examination showed multiple, small, hard, non-tender masses on the feet and knees, along
with an incision scar on the left foot. Her dental, ophthalmological, and systemic examinations were normal. The results of laboratory investigations are shown in Table 1. The younger sibling also showed abnormal serum biochemical parameters (phosphorus 8.1 mg/dL, calcium 8.7 mg/dL, alkaline phosphatase 202 U/L) but normal parathyroid hormone levels (44.94 pg/mL). The parents’ biochemistry was normal. Cytological examination of the thick cheese-like material aspirated from one of the skin lesions showed extensive amorphous calcified deposits with granular calcification and clusters of benign epithelial cells of adnexa.

All relevant ethical guidelines have been followed for data collection and reporting. We obtained consent and assent from parents and children respectively, and approval from the Departmental Review Board for reporting data. Genomic DNA was extracted from leucocytes in the peripheral blood of the children and their parents. The 10 coding exons (exons 2-11) of the GALNT3 gene were amplified by using PCR. Sanger sequencing identified a novel homozygous non-synonymous sequence variant in exon 10 of the GALNT3 gene. The parents were heterozygous carriers.

### Table 1. Results of laboratory investigations of the index patient

| Parameter                  | Patient’s value | Reference range |
|----------------------------|-----------------|-----------------|
| Serum phosphorus           | 7.5 mg/dL       | 4.5-5.6 mg/dL   |
| Serum calcium              | 9.0 mg/dL       | 9-11 mg/dL      |
| Alkaline phosphatase       | 216 U/L         | 50-160 U/L      |
| Serum creatinine           | 0.5 mg/dL       | 0.3-0.8 mg/dL   |
| Parathyroid hormone        | 23.77 pg/mL     | 10-65 pg/mL     |
| Plasma c-FGF23             | 2612.7 RU/mL    | Upto 125 RU/mL  |
| 25-hydroxyvitamin D        | 11.9 ng/mL      | 20-100 ng/mL    |
| 1, 25-dihydroxyvitamin D   | 68 mmol/L       | 50-150 mmol/L   |
| Total leucocyte count      | 8,800/mm³       | 4,000-11,000/mm³|
| ESR                        | 10 mm/hr        | 0-20 mm/hr      |
| C-reactive protein         | 1.2 mg/dL       | < 0.5 mg/dL     |
| Renal TRP                  | 88%             | > 85%           |
| TmP/GFR ratio              | 3.0 mg/dL       | 2.9-6.5 mg/dL   |

**c-FGF23**, c-terminal fibroblast growth factor 23; **ESR**, erythrocyte sedimentation rate; **TmP/GFR**, tubular maximum reabsorption of phosphorus/glomerular filtration rate; **TRP**, tubular reabsorption of phosphate.

The mutation is indicated above the electropherograms. The affected patients are homozygous for a non-synonymous sequence variant in exon 10 of the GALNT3 gene. The parents are heterozygous carriers.

### Figures

**Figure 1. Mutations analysis of the GALNT3 gene in two affected siblings and their parents.** The mutation is indicated above the electropherograms. The affected patients are homozygous for a non-synonymous sequence variant in exon 10 of the GALNT3 gene. The parents are heterozygous carriers.
variation in disease severity and clinical course (4). The younger sibling of our proband showed milder manifestations and disease course.

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