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Case Report

A GALNT3 mutation causing Hyperphosphatemic familial Tumoral calcinosis

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ABSTRACT

AimHyperphosphatemic Familial Tumoral Calcinosis (HFTC) is an autosomal recessive disorder. This study investigates the etiology of HFTC in offspring from consanguineous parents.
Methods: Clinical assessment, imaging, and direct sequencing were utilized to elucidate the condition. Previously reported cases were also reviewed.
Result: We identified a consanguineous Chinese family with HFTC caused by an interesting homozygous G to A substitution in GALNT3 (c.1626 + 1G > A). The parents were carriers.
Conclusion: This study represents the first report of HFTC in a consanguineous Chinese family due to an interesting GALNT3 mutation. We reviewed known GALNT3 variants and associated clinical features of calcification disorders. The phenotypic difference between homozygous and complex heterozygous mutations is not clinically significant. Gene mutations affect the function of proteins mainly by affecting their binding to polyvalent ligands.

1. Introduction

Phosphorus is crucial for human bone mineralization and metabolism [1]. The lack of phosphate regulators can induce the destabilization of phosphorus homeostasis, which is related to the occurrence and prognosis of various diseases. Dysregulation of phosphate homeostasis, mediated in part by fibroblast growth factor 23 (FGF23) [2,3] and parathyroid hormone (PTH), underpins various diseases. *N*-acetylgalactosaminyltransferase 3 (GALNT3) on chromosome 2 plays a pivotal role in O-glycosylation of FGF23, influencing its stability [4,5]. Lack of O-glycosylation makes FGF23 susceptible to proteolysis [5]. It is involved in the biosynthesis of O-linked glycosylation, a type of post-translational modification of proteins. O-linked glycosylation is an important process in the regulation of many cellular processes, including cell adhesion, signal transduction, and protein folding. GALNT3 is a key enzyme in the O-linked glycosylation pathway [4], and its activity is essential for the proper functioning of many cellular processes. Mutations in GALNT3 impair this process, leading to increased proteolysis of FGF23 and subsequent phosphate imbalance [6,7].

Hyperphosphatemic Familial Tumoral Calcinosis (HFTC) (OMIM 211900) manifests as ectopic calcifications in periarticular soft tissues and hyperostosis in long bones, potentially severe and life-threatening [8,9]. Clinical presentation of HFTC varies widely, from asymptomatic to debilitating, necessitating a diagnosis based on elevated serum phosphate levels, radiographic evidence of calcifications, and genetic testing. Treatment strategies aim to manage symptoms and prevent complications, including surgical excision of calcifications and phosphate binders. Most reports on GALNT3-related HFTC originate from African and Middle-Eastern populations, highlighting geographic variability in disease prevalence and manifestation. Their elevated calcium phosphate crystals are mostly found in limbs, teeth[10], or eyelids [7].

2. Methods

2.1. Patient

The patient was diagnosed in the outpatient department of West China Hospital. Thank this patient for agreeing to report her images and other clinical information in the journal. The patient understands that her name will not be published and will make appropriate efforts to conceal her identity, but anonymity cannot be guaranteed. Written informed consent was obtained from this study participant.

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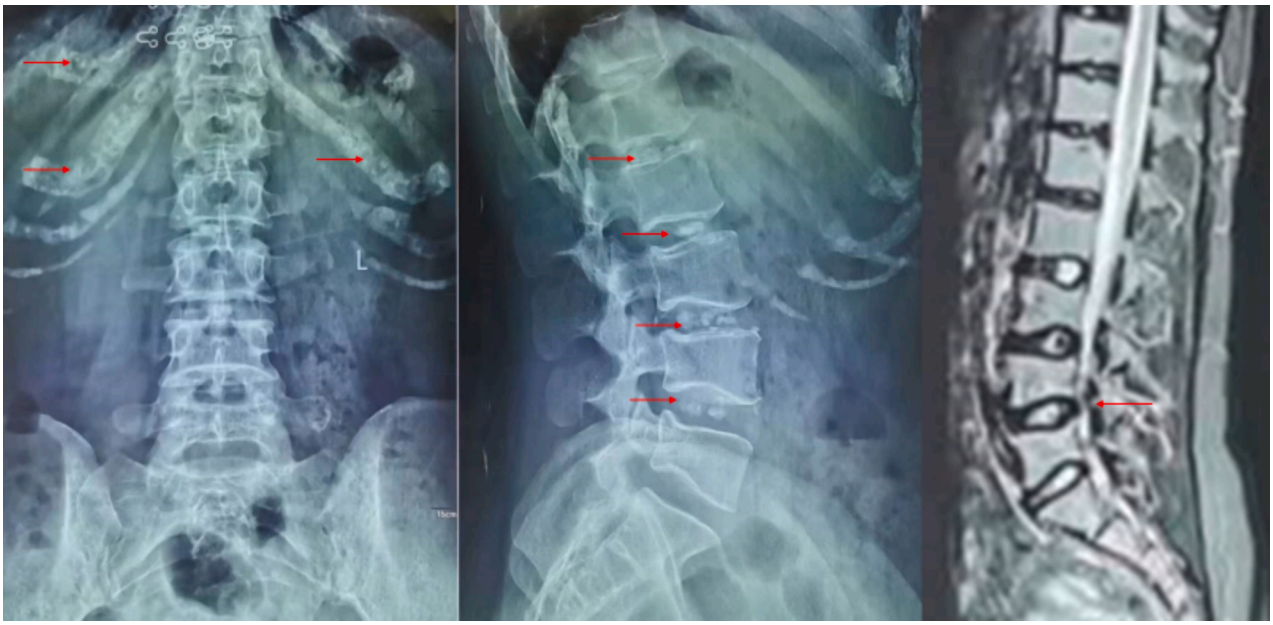

Fig. 1. Imaging data of the patient. a-b Computed tomography (CT) showed round, small calcifications in the ribs and disk spaces of L1–2、L2–3、L3–4、L4-5c Magnetic resonance imaging showed disc herniation of L3–4.

Table 1
Biochemical profiles of proband in the diagnosis phase.

Biochemical parameters/(unit)	Proband	Normal range
Serum calcium(mmol/L)	2.47	2.11–2.52
Serum phosphate(mmol/L)	2.02	0.85–1.51
Serum creatinine(umol/L)	61	48–79
PTH(pmol/L)	3.88	1.60–6.90
25-(OH) vit D(nmol/L)	34.7	47.7–144
Bone alkaline phosphatase(ug/L)	8.93	11.4–24.6
β-CTX(ng/ml)	0.247	0.556–1.008
t-P1NP(ng/ml)	35.9	8.53–64.32
Urine calcium(mmol/24 h)	2.21	2.5–7.5
Urine creatinine(mmol/24 h)	2.91	7.0–18.0
Urine phosphate(mmol/24 h)	5.22	22–48

2.2. Biochemical parameters

Blood samples were collected after an overnight fast to measure serum phosphorus levels, 25-D3, and bone-specific alkaline phosphatase (bone-ALP).

2.3. Genetic analysis

Trio-based exome sequencing was performed by Beijing Full Spectrum Medical Laboratory/Zhiyin Oriental Company to identify genetic mutations.

2.4. The strategy of the literature review

PubMed and Embase databases were searched using keywords “hyperphosphatemic neoplastic calcinosis,” “GALNT3 mutation,” and related terms to identify relevant case reports. Inclusion criteria focused on genetic diagnosis and pedigree information. Exclusion criteria include case reports without a pedigree or genetic diagnosis. Some case reports complement the genetic diagnosis of the same families that previously described only the early clinical presentation and progression, without duplicating the inclusion of the same information.

2.5. Protein structural modeling

Homology modeling of GALNT3 protein was conducted using SWISS-MODEL(https://swissmodel.expasy.org/interactive). Nucleotide sequence or amino acid sequence was obtained by NCBI(https://www.ncbi.nlm.nih.gov/). The model of homologous GALNT3 protein and gene mutation induced by 5 base substitution were constructed. PyMOL (www.pymol.org/2/) was used for sequence comparison and structural analysis of mutant proteins.

3. Results

3.1. Case report

The proband was a 26-year-old woman suffering from a recurrent backache for over 10 years. Initial symptoms included progressive back pain and lower limb paralysis following lumbar disc surgery a decade ago. However, the formation mechanism of new organisms was not traced. In recent years, the symptoms repeated. Her general appearance was that of a normal female without dysmorphic features. Her parents are cousins. No medication was taken during the period.

She underwent radiographic, biochemical, and genetic testing. Radiographic evaluation revealed small round calcifications in the disk spaces of multiple lumbar vertebrae (L1–5) (Fig. 1). Biochemical analysis indicated elevated serum phosphorus (2.02 mmol/L), vitamin D

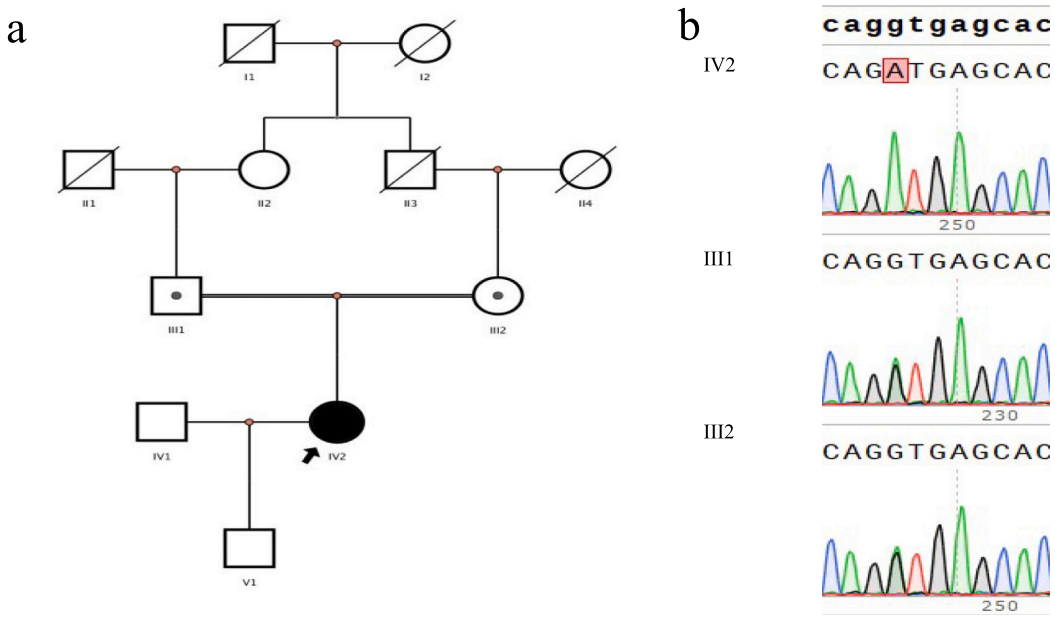

Fig. 2. Family pedigree and genotypes. a family pedigree: the proband were the offspring of two consanguineous parents. b genotypes of individuals for the variant in GALNT 3 gene. The patient were homozygous c.1626 + 1G > A mutation and her parents were carriers.

Table 2
The result of WES in the family.

Test results								
Object	Gene	Chr-location	Res-seq	Nucleic acid alteration	Amino acid alteration	Mutation location	Zygosity	Prediction result
Proband	GALNT3	Chr 2	NM_004482	c.1626 + 1G > A	splicing error	IVS8	Hom	Disease causing
Parents	GALNT3	Chr 2	NM_004482	c.1626 + 1G > A	splicing error	IVS8	Het F(62/103);M(55/120)	–

(25-D3) deficiency (34.7 nmol/L), and increased bone-specific alkaline phosphatase (bone-ALP) levels (8.93 μg/L). Renal phosphate threshold (TmPO4/GFR) was elevated. The biochemical analysis results are shown in Table 1.

3.2. Genetic analysis

Genomic DNA analysis identified a homozygous c.1626 + 1G > A mutation in GALNT3 as causative. Both parents were confirmed as carriers through genetic testing. More details and her family pedigree are shown in Fig. 2 and Table 2.

3.3. Review of case reports

A total of 24 eligible papers were searched, in which 21 heterozygous mutations as well as 10 compound heterozygous mutations were reported (Table 3) [4,7,9,11–13,15–35]. In the previous HFTC reports, most HFTC patients are associated with GALNT3 gene mutations. At present, including the case we reported, a total of 24 case reports with 31 mutation types have been reported. All reported cases were characterized by hyperphosphatemia. Low circulatory integrity FGF23 appears to be the primary cause of all phenotypes. Interestingly, phenotypic variation is significant among patients with the same genotype in the same mutant family. Both homozygous and complex heterozygous mutations have heterogeneous phenotypes, and the gender difference is not obvious, which does not rule out the influence of dietary phosphorus in daily life. In clinical features, ocular and oral involvement data were mostly missing, and their statistical analysis values were of low significance. More details are summarized in Table 4. The included results of all literature and the results of patients' clinical characteristics and biochemical indicators are shown in Table S1.

3.4. Protein structural modeling

The structure of GALNT3 enables us to examine the structural roles of reported FTC mutations. We used PyMOL to mark the locations of five mutation sites on GALNT3 protein (Fig. 3). We constructed the protein structures of seven base substitut-induced missense mutations and sequenced them with the homologous GALNT3. PyMOL was used to compare their sequences, and RMSD was used to quantify their structural difference indexes. The specific results are shown in Table 5.

4. Discussion

We describe an interesting homozygous c.1626 + 1G > A mutation in the GALNT3 gene in a Chinese patient with Hyperphosphatemic Familial

Table 3
Spectrum of GALNT3 variants related to calcification disorders in the case reports.

Nucleotide change	Protein	Exon	Author &Year	References
c.41_58del	p.R14fs21X	1	Holly J et al. 2006	34
c.260_266del	p.R87QfsX2	1	Ramnitz et al. 2016	29
c.484C > T	p.R162X	1	Demellawy DE et al. 2015 Vieira AR et al. 2015	16,35
c.485G > A	p.R162Q	1	Ichikawa et al. 2010	17
c.254_255delCT	P85Rfs*6	2	Kışla Ekinci RM et al. 2018	21
c.516-2A > T	p.C173Vfs*4	2	Laleye et al.2008	19
c.516-2A > G	–	2	Masi L et al. 2015	20
c.677delC	p.A226VfsX3	2	Ichikawa et al. 2010	17
c.767G > T	p.G256V	3	Rafaelsen S et al.2014	15
c.782G > A	p.R261Q	4	Mahjoubi F et al. 2020	22
c.803–804insC	p.T269NfsX3	4	Pallone SG et al. 2022	13
c.1102_1103insT	p.S368Ffs*8	5	Garringer HJ et al. 2007	23
c.1245 T > A	p.H415Q	6	Yancovitch et al.2011	24
c.1312 T > C	p.R438C	6	Yancovitch et al.2011	24
c.1313G > A	p.R438H	6	Olauson et al. 2008	25
c.1387 A > T	p.K463X	6	Campagnoli et al. 2006	26
c.1392 + 1G > A	Splicing error	Splicing error	Ichikawa et al. 2010	17
c.1460G > A	p.W487X	7	Garringer HJ et al. 2007	23
c.1524 + 1G > A	p.K465_Y508del	7	Topaz et al. 2004 Frishberg Y et al. 2005	4,27
c.1584-1585insA	p.P529TfsX17	8	Ramnitz et al.2016	29
c.1626 + 1G > A	splicing error	Splicing error	Present study	
c.1720 T > G	p.C574G	9	Ichikawa et al. 2010	17
c.1774C > T	p.Q592X	9	Spector et al. 2006	11
c.2 T > A	p.M1?	2	Gok et al. 2009	30
c.839G > A	p.C280Y	4		
c.484C > T c.1524 + 5G > A	p.R162X pK465_y508del	1 7	Topaz et al. 2004 Carmichael et al. 2009 Baldursson 1969 Slavin et al. 1993 Clarke et al.1984 Viegas et al.1985	4,31
c.516-2A > T c.260_266del	p.C173Vfs*4 p.R87QfsX2	2 1	Ramnitz et al.2016	29
c.516-2A > T c.1524 + 5G > A	p.C173Vfs*4 splice site	2 7	Ramnitz et al.2016	29
c.746-749del c.892delT	p.R250TfsX2 p.Y298SfsX5	3 4	Ramnitz et al.2016	29

Table 3 (*continued*)

Nucleotide change	Protein	Exon	Author &Year	References
c.1076C > A	p.E281G p.T359K	7 5	Ichikawa et al. 2006	7
c.1392 + 1G > A	p.T269NfsX3 Splicing error	4 Splicing error	Ichikawa et al.,2007	9
c.842 A > G c.1097 T > G	p.E281G p.L366R	4 5	Joseph et al. 2010	32
c.966 T > G c.1441C > T	p.Y322X p.Q481X	4 8	Barbieri et al. 2007	33
c.1312C > T c.1774C > T	p.R438C p.Q592X	6 9	Dumitrescu et al. 2009	12

Table 4
Review of the literature.

Phenotype	Total	Genotype		Sex		NA
		Hom	Het	Male	Femal	
Total	48	31	17	23	25	/
Male	23	17	6	/	/	/
Female	25	14	11	/	/	/
Hyperphosphatemia	48	31	17	23	25	/
Diaphysitis/hyperostosis	28	17	11	11	17	0
Calcific tumors	23	23	12	16	7	1
Dental involvement	19	10	9	11	8	17
Eye involvement	6	5	1	3	3	32
Vascular calcification	4	2	2	0	4	39

Tumoral Calcinosis (HFTC), presenting with recurrent ectopic calcium deposition in the intervertebral space. Previously reported in Africa and other areas [11]. This case underscores the clinical variability and diagnostic challenges associated with HFTC, particularly in regions with lower disease prevalence and awareness [12]. Ectopic calcium deposits have been reported in the extremities. In the case we reported, the clinical manifestations were relatively mild, but the clear diagnosis was difficult and easy to misdiagnose. The clinical presentation of HFTC in our patient, characterized by progressive back pain and paralysis, highlights the importance of considering rare genetic disorders in differential diagnoses of musculoskeletal symptoms. Radiographic findings of calcifications in multiple lumbar discs further emphasize the need for thorough imaging studies in suspected cases of HFTC. This can lead to delayed diagnosis and a lack of awareness of the complications of the disease. Moreover, in HFTC, there is usually a long asymptomatic interval. It is likely that this is not related to phosphate-lowering therapy, but is a feature of the disease.

Our genetic analysis revealed a homozygous GALNT3 mutation, consistent with previous reports linking GALNT3 mutations to impaired FGF23 glycosylation and subsequent hyperphosphatemia. This finding supports the role of GALNT3 in phosphate homeostasis and underscores its significance in the pathogenesis of HFTC. Surgical excision of calcification foci and phosphate binders has been reported as the main method. Niacinamide therapy is associated with greater cardiac risk. The efficacy of anti-osteoclasts such as bisphosphonate [7,11] and denosumab and osteogenic promoters such as teriparatide [13] still needs to be further verified. Gene therapy is still an area that needs further exploration.

Future research should explore targeted therapies aimed at restoring normal FGF23 glycosylation and mitigating hyperphosphatemia in GALNT3-related HFTC.

In this patient, calcium deposits were found at specific sites, mainly in the ribs and vertebral space. Only one case of costal cartilage calcification and intervertebral space calcification has been reported. There was no specific correlation among the three patients, such as gene mutation site and age of onset.

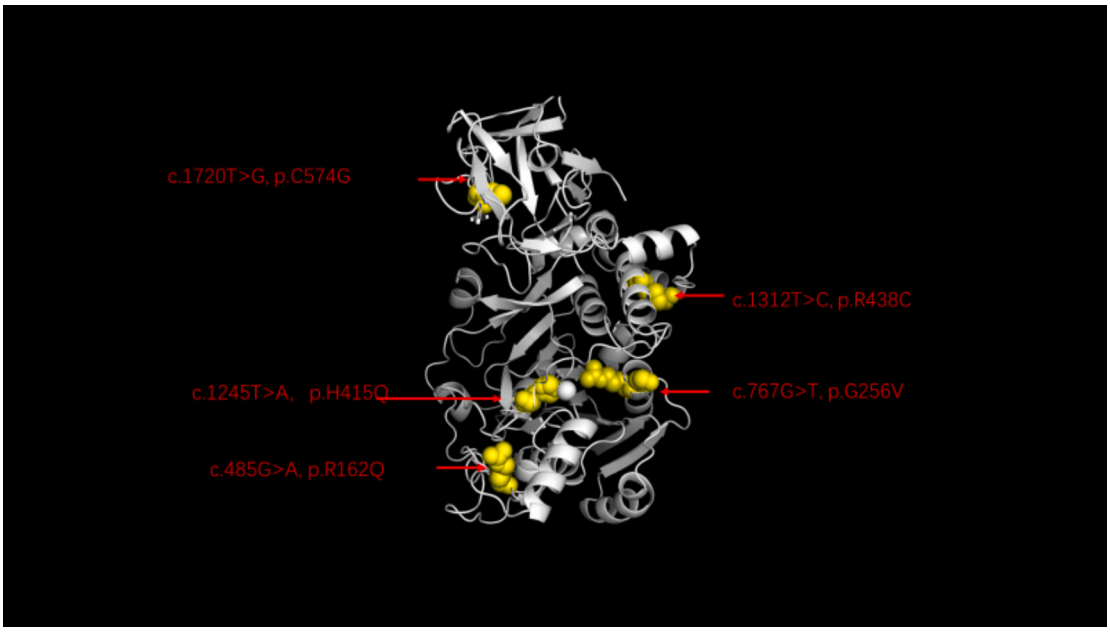

Fig. 3. Overview of GALNT3 protein structure with R162, G256, R415, R438, C574 yellow spheres.

Table 5
The structural comparison of mutant proteins.

Genetic mutation		RMSD					
		All	Cycle1	Cycle2	Cycle3	Cycle4	Cycle5
c.485G > A	p.R162Q	0.005	0.02	0.01	0.01	0.01	0.01
c.767G > T	p.G256V	0.011	0.05	0.02	0.01	0.01	0.01
c.782G > A	p.R261Q	0.023	0.04	0.03	0.02	0.02	0.02
c.1245 T > A	p.H415Q	0.004	0.03	0.01	0.00	0.00	0.00
c.1312 T > C	p.R438C	0.009	0.04	0.01	0.01	0.01	0.01
c.1313G > A	p.R438H	0.003	004	0.01	0.01	0.01	0.01
c.1720 T > G	p.C574G	0.006	0.01	0.01	0.01	0.01	0.01

5. Conclusion

We reported an interesting GALNT3mutation in Chinese patient. It was found that there was no significant correlation between calcification site and mutation type and site. We constructed seven mutant proteins and measured the differences in their skeleton atoms. We found the similarity to be extremely high. Based on the reported GALNT3 tri ligand structure of *Taeniopygia guttata* (Tg) [14], we found point missense mutations located in the catalytic domain, lectin domain, and UDp-Galnac-binding site, affecting GALNT3's functionality.

In summary, we identified one mutation in the GALNT3 gene in a patient with tumoral calcinosis and hyperostosis-hyperphosphatemia syndrome. A review of the literature shows all reported GALNT3 mutation phenotypes.

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CRediT authorship contribution statement

Aijia Wu: Writing – review & editing, Writing – original draft, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Bangxiang Yang:** Writing – review & editing, Writing – original draft, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Xijie Yu:** Validation, Supervision, Funding acquisition.

Declaration of competing interest

The authors declare no conflicts of interest.

Data availability

Data will be made available on request.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ymgmr.2024.101128.

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