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Case Report

# A case of hyperphosphatemic familial tumoral calcinosis due to maternal uniparental disomy of a *GALNT3* variant

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## Highlights

- We report the first case of HFTC caused by maternal UPD of the *GALNT3* variant.
- A novel *GALNT3* variant was predicted as an alteration of the acceptor site.
- *GALNT3* mRNA analysis confirmed the deletion of exon 11.

**Abstract.** Hyperphosphatemic familial tumoral calcinosis (HFTC) is a rare, inherited autosomal recessive disorder caused by fibroblast growth factor-23 (*FGF23*), N-acetylgalactosaminyltransferase 3 (*GALNT3*), or Klotho (*KL*) gene variants. Here, we report the case of a Japanese boy who presented with a mass in his left elbow at the age of three. Laboratory test results of the patient revealed normocalcemia (10.3 mg/dL) and hyperphosphatemia (8.7 mg/dL); however, despite hyperphosphatemia, serum intact FGF23 level was low, renal tubular reabsorption of phosphate (TRP) level was inappropriately increased, and 1,25-dihydroxyvitamin $D_3$ ($1,25(OH)_2D_3$) level was inappropriately normal. Genetic analysis revealed maternal uniparental disomy (UPD) of chromosome 2, which included a novel *GALNT3* variant (c.1780-1G>C). Reverse transcription-polymerase chain reaction (RT-PCR) analysis of *GALNT3* mRNA confirmed that this variant resulted in the destruction of exon 11. We resected the mass when the patient was five years old, owing to its gradual enlargement. No relapse or new pathological lesions were observed four years after tumor resection. This is the first case report of a Japanese patient with HFTC associated with a novel *GALNT3* variant, as well as the first case of HFTC caused by maternal UPD of chromosome 2 that includes the *GALNT3* variant.

**Key words:** tumoral calcinosis, hyperostosis–hyperphosphatemia syndrome, hyperphosphatemic familial tumoral calcinosis, N-acetylgalactosaminyltransferase 3 (*GALNT3*), uniparental disomy

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## Introduction

Hyperphosphatemic familial tumoral calcinosis (HFTC) (OMIM#211900) is a rare autosomal recessive disorder caused by variants in the genes encoding fibroblast growth factor-23 (*FGF23,* 12p13.3), N-acetylgalactosaminyltransferase 3 (*GALNT3,* 2q24-q31), or Klotho *(KL,* 13q12). These variants result in a relative deficiency of or resistance to intact FGF23 (iFGF23), thereby leading to hyperphosphatemia due to increased renal tubular reabsorption of phosphate and abnormally normal or high 1,25-dihydroxyvitamin $D_3$ production, which promotes gastrointestinal absorption of phosphorus (P) and calcium (Ca). The resulting increase in calcium–phosphorus products leads to ectopic calcification (1, 2).

Uniparental disomy (UPD) is a rare condition in which both homologous chromosomal regions or segments are inherited from a single parent. UPDs have been reported to cause some recessive disorders (3). To date, most cases of UPDs have been reported in imprinting diseases, such as Prader–Willi syndrome. The incidence of UPDs of any chromosome is estimated to be 1 per 3,500 live births (4–6). However, only a limited number of UPD cases that induce recessive diseases have been reported. To date, we lack reports of HFTC accompanied by UPDs.

Herein, we report the case of a Japanese boy with HFTC. This is the first report of a Japanese patient with a novel *GALNT3* variant and the first case of HFTC caused by maternal UPD of chromosome 2, which includes the *GALNT3* variant.

## Patient and Methods

### Case description

The patient was a 3-yr-old boy who presented with a mass on his left elbow that had been present for 6 mo. He was born uneventfully (delivered at 41 wk and 1 d of gestation, with a birth weight of 3,034 g and a body length of 50.0 cm). He was healthy until the onset of symptoms and had no history of medications or nutritional supplements. His parents and sibling were also healthy, with no family history of calcified masses, mineral disorders, or cardiovascular events. His parents were not in a consanguineous marriage. His height and weight were 99.9 cm (+ 0.2 SD score) and 15.3 kg (+ 0.0 SD score), respectively, on presentation. Physical examination revealed a hard, tender, irregular mass measuring approximately 5 cm on the left elbow. The tumor limited extension movements, and no lymphadenopathy was detected. The remaining physical examination findings were normal.

Laboratory data revealed hyperphosphatemia (8.7 mg/dL; reference: 4.1–5.3 mg/dL); however, the iFGF23 level was low (13 pg/mL; reference:14–68 pg/mL), and the TRP level was inappropriately high (96.1%; reference: 84.3–90.3%), and $1,25(OH)_2D_3$ level was inappropriately normal (59 pg/mL; reference: 20–60 pg/mL) (**Table 1**). The levels of blood urea nitrogen, creatinine, alkaline phosphatase, growth hormone, and thyroid function were normal. Radiography and magnetic resonance imaging revealed a calcified mass around the left elbow (**Figs. 1A, B**). Histopathological examination of the needle biopsy specimen revealed calcified deposits with multinucleated giant cell formation (data not shown). Based on these findings, the patient was diagnosed with HFTC. Both head CT and ultrasonography confirmed no calcification in the basal ganglia, kidney, urinary tract, or vessel

**Table 1.** Laboratory data

| Age (yr) | Patient 3 (at first visit) | Father 36 | Mother 34 | Sister 2 | Reference range |
|---|---|---|---|---|---|
| Serum | | | | | |
| Ca (mg/dL) | 10.3 (9.4–10.8) | 8.9 (9.1–10.2) | 8.9 (8.8–10.0) | 9.9 (9.4–10.8) | age-specific normal range |
| P (mg/dL) | 8.7 (4.5–6.2) | 3.1 (2.4–4.5) | 3.3 (2.4–4.5) | 5.7 (4.5–6.2) | age-specific normal range |
| ALP (IU/L) | 516 (420–1,200) | 250 (150–410) | 164 (120–340) | 824 (410–1,150) | age-sex-specific normal range |
| Intact PTH (pg/mL) | 18 | 34 | 55 | 33 | 10–65 |
| iFGF23 (pg/mL) | 13 | 31 | 34 | 24 | 14–68 |
| 25(OH)D (ng/mL) | 21 | 15 | 15 | 13 | >25 |
| $1.25(OH)_2D_3$ (pg/mL) | 59 | 22 | 43 | 48 | 20–60 |
| Urine | | | | | |
| Ca/Cre | 0.07 | 0.12 | 0.07 | 0.11 | <0.21 |
| TRP (%) | 96.1 (60–90) | 86.5 (80–96) | 92.9 (80–96) | 96.8 (60–90) | age-specific normal range |
| TmP/GFR (mg/dL) | 8.36 | 2.68 | 3.07 | 5.52 | 2.3–4.3 |

Ca, calcium; P, phosphorus; ALP, alkaline phosphatase; Intact PTH, intact parathyroid hormone; iFGF23, intact fibroblast growth factor 23; 25(OH)D, 25-hydroxyvitamin D; $1.25(OH)_2D_3$, 1,25-dihydroxyvitamin $D_3$; Ca/Cre, calcium-creatinine ratio; TRP, renal tubular reabsorption of phosphate; TmP/GFR, maximal tubular reabsorption of phosphorus per GFR.


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walls. Fundoscopic findings were normal. Furthermore, the parents and sister of the patient had no biochemical abnormalities (**Table 1**).

### *FGF23* and *GALNT3* gene analyses

Genomic DNA was extracted from the peripheral blood leukocytes of the patient, his parents, and his sister. PCR-based direct sequencing of *FGF23* (exon 1–3) and *GALNT3* (exon 2–11) genes, which are known to cause HFTC, was performed. To examine the structure of mRNA using reverse-transcription polymerase chain reaction (RT-PCR), total RNA was extracted from leukocytes and resected tumors using an RNeasy Mini Kit (Qiagen, Hilden, Germany). Subsequently, cDNA was synthesized from total RNA using ReverTra Ace qPCR RT Master Mix (Toyobo, Osaka, Japan), according to the manufacturer's instructions. All the primer sets used in this study are listed in Supplementary Table 1.

### Single nucleotide polymorphism (SNP) genotyping and analysis

We performed genome-wide SNP analysis. The patient and his parents were genotyped using Genome-Wide Human SNP Array 6.0 (Affymetrix, Santa Clara, CA, USA) in accordance with the manufacturer's instructions. In addition to data from the patient and his parents, we used data from 418 Japanese individuals from previous reports to ensure reliable genotype calling (6, 7). Genotyping Console v4.2 software was used for genotype calls and loss of heterozygosity (LOH) analysis. The average quality control call rate of the three individuals was 95.8% (95.2–96.4%), and the average call rate was 97.3% (97.1–97.7%).

### Ethical consideration

This study was approved by the Ethics Committees of Osaka University (IRB No. 700-12) and Aichi Children's Health and Medical Center (IRB No. 2017010). All procedures involving human participants were performed in accordance with the ethical standards of

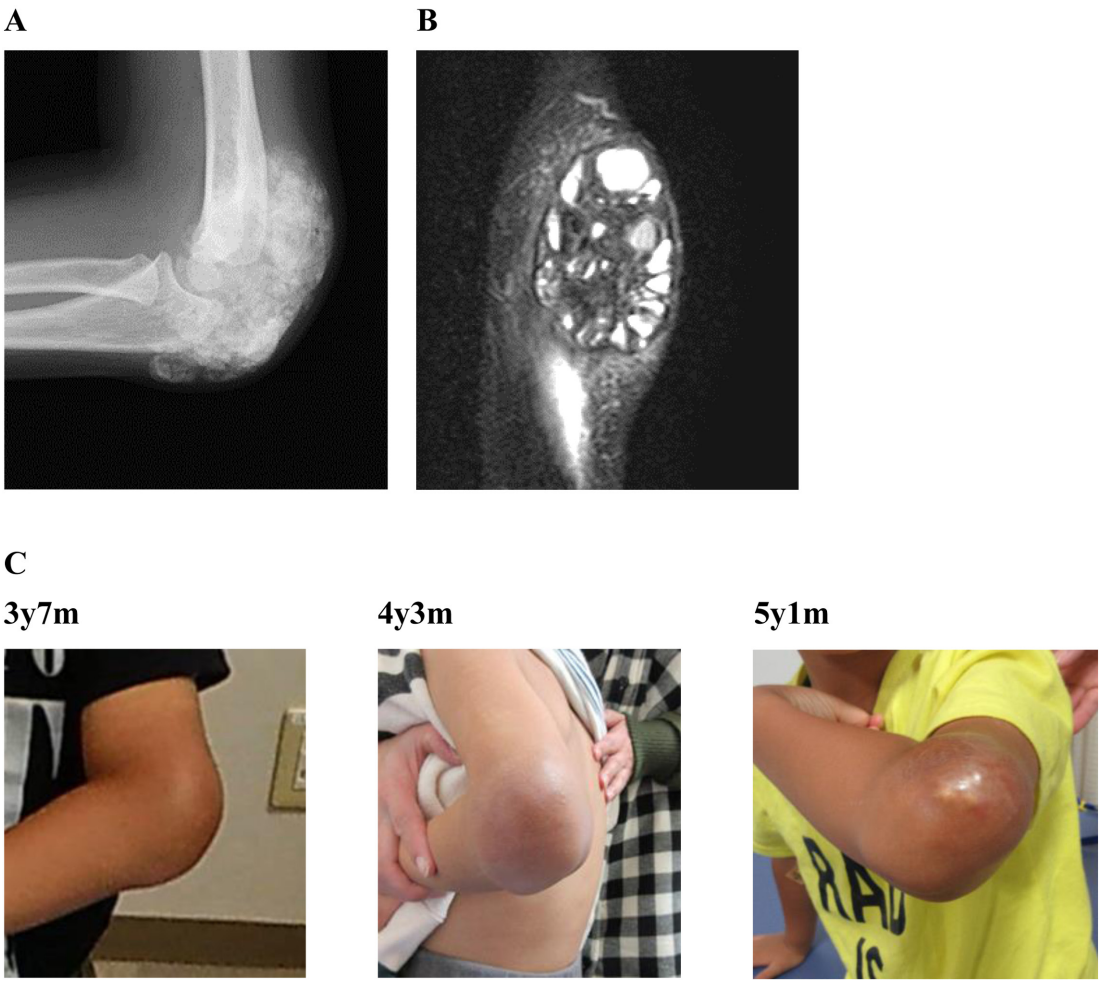


**Fig. 1.** Ectopic multilocular calcification in the patient. A: X-ray and B: coronal T2-weighted magnetic resonance images of the left elbow at the first visit (3 yr and 7 mo old). The tumor enlarged and caused self-destruction of the skin at 5 yr (y) and 1 mo (m) of age.


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the institutional and/or national research committee and the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The parents of the patient provided written informed consent for genomic DNA collection and analysis.

## Results

### Detection of a novel *GALNT3* variant

Genetic analysis revealed no pathogenic variants in *FGF23* but a novel homozygous variant in intron 10 (c.1780-1G>C) affecting the splice site in *GALNT3* (**Figs. 2A, B**). The asymptomatic mother and sister of the patient were heterozygous carriers of this variant, whereas the father was not (**Fig. 2C**). Further analysis of the *GALNT3* mRNA in the patient confirmed that this variant resulted in the deletion of exon 11 (**Fig. 2D**). G-banding karyotype analysis and high-resolution chromosome banding techniques of the proband revealed a normal 46,XY karyotype without monosomy 2q24.3.

### Detection of UPD using genome-wide SNP array

The genome-wide SNP array revealed 68,942 SNPs on chromosome 2, of which 23,490 SNPs multiple genotypes in the samples from the proband and his mother and father. The proband had 7,673 homozygous SNPs from the mother and six homozygous SNPs from the father (**Fig. 3**). Therefore, we considered that the proband had a maternal UPD on chromosome 2.

### Clinical course

We initiated a low phosphate diet to reduce the risk of arteriosclerosis. Despite avoiding phosphate-rich foods for four months, the hyperphosphatemia did not improve (Ca 9.8 mg/dL, P 7.2 mg/dL, iFGF23 10 pg/mL, TRP 98.7%). Thus, we administered phosphate-binding therapy with 500 mg bixalomer thrice daily (approximately 100 mg/kg/d), which resulted in a decrease in serum phosphorus levels (P 6.1 mg/dL, TRP 96.03%). However, the tumor in the elbow was enlarged (**Fig. 1C**). Therefore, tumor resection was performed after considering the possibility of recurrence owing to the risk of self-destruction of the skin. Histopathological examination of the resected tissue indicated diffuse multinodular and map-like ectopic calcinosis. We also observed foreign body giant cells, histiocytic infiltrates, fibrosis, and lymphocyte and plasma cell infiltrates, consistent with HFTC. We confirmed that the mRNA extracted from the tumor did not express *GALNT3* mRNA (data not shown).

Subsequently, the patient was maintained on a low-phosphate diet and administered bixalomers, and we observed no signs of relapse or new pathological lesions.

## Discussion

HFTC is a rare autosomal recessive disorder caused by variants in *FGF23*, *GALNT3*, or *KL*. *GALNT3* is the most prevalent genetic cause of HFTC (80%) (8, 9). Most cases were identified in patients of African or Middle Eastern origin, with a few cases of Caucasian or Asian origin (10). To our knowledge, this is the first report of a *GALNT3* variant in Japan. Furthermore, *GALNT3* are typically missense homozygous variants rather than compound heterozygotes (1, 8, 10–12). Our findings confirmed the deletion of exon 11, indicating that the identified *GALNT3* mRNA variant is pathogenic. Based on the guidelines published by The American College of Medical Genetics and Genomics (13), this variant is "pathogenic", predicted to be VS1 (null variant) + PM2 (absent from controls) + PM3 (for recessive disorders) and detected in trans with a pathogenic variant.

We excluded the gross deletion of chromosome 2 in our patient using subsequent G-band karyotyping and confirmed the presence of complete maternal isodisomy of chromosome 2 using a genome-wide SNP array. The current reports on a few complete paternal UPD cases and a partial maternal UPD case confirmed the lack of clinically conspicuous phenotype. This suggests the likelihood of few or no paternal imprinted genes in chromosome 2, which majorly affect growth and development (14–17). In contrast, maternal UPD of chromosome 2 causes a variable phenotype (18, 19). To the best of our knowledge, this is the first Japanese report of HFTC owing to maternal UPD of a *GALNT3* variant. Furthermore, we did not observe apparent differences in the symptoms between our patient and previously reported cases of the *GALNT3* variant without UPD.

HFTC is caused by the dysfunction of FGF23, a phosphorus-regulating hormone (20). FGF23 is synthesized by osteocytes and undergoes O-linked glycosylation by GALNT3, thereby limiting its cleavage into inactive forms. FGF23 is secreted into the blood as a stable structure less susceptible to splicing. Subsequently, FGF23 binds to the αKlotho–FGF receptor complex on the nephron, leading to decreased expression of sodium-dependent phosphate co-transporters type IIa and IIc (NPT2a and NPT2c, respectively) in the proximal tubule, thereby increasing urinary phosphate and decreasing serum phosphate levels. Increased serum calcium phosphate levels can lead to ectopic calcifications (1, 2, 8, 9, 20). Currently, we lack reports on the genotype–phenotype correlations between HFTC and *GALNT3* variants. However, Ramnitz *et al.* reported that vascular calcifications appear to be more frequent in individuals with biallelic *FGF23* loss-of-function variants (5 of 27; 18.5%) than in those with biallelic *GALNT3* loss-of-function variants (5 of 37; 13.5%) (1, 9).

Standard treatment procedures have not been established for HFTC owing to the lack of randomized clinical trials; studies on the treatment of HFTC only include case reports or case series. In most cases, a combination of a low-phosphate diet and phosphate

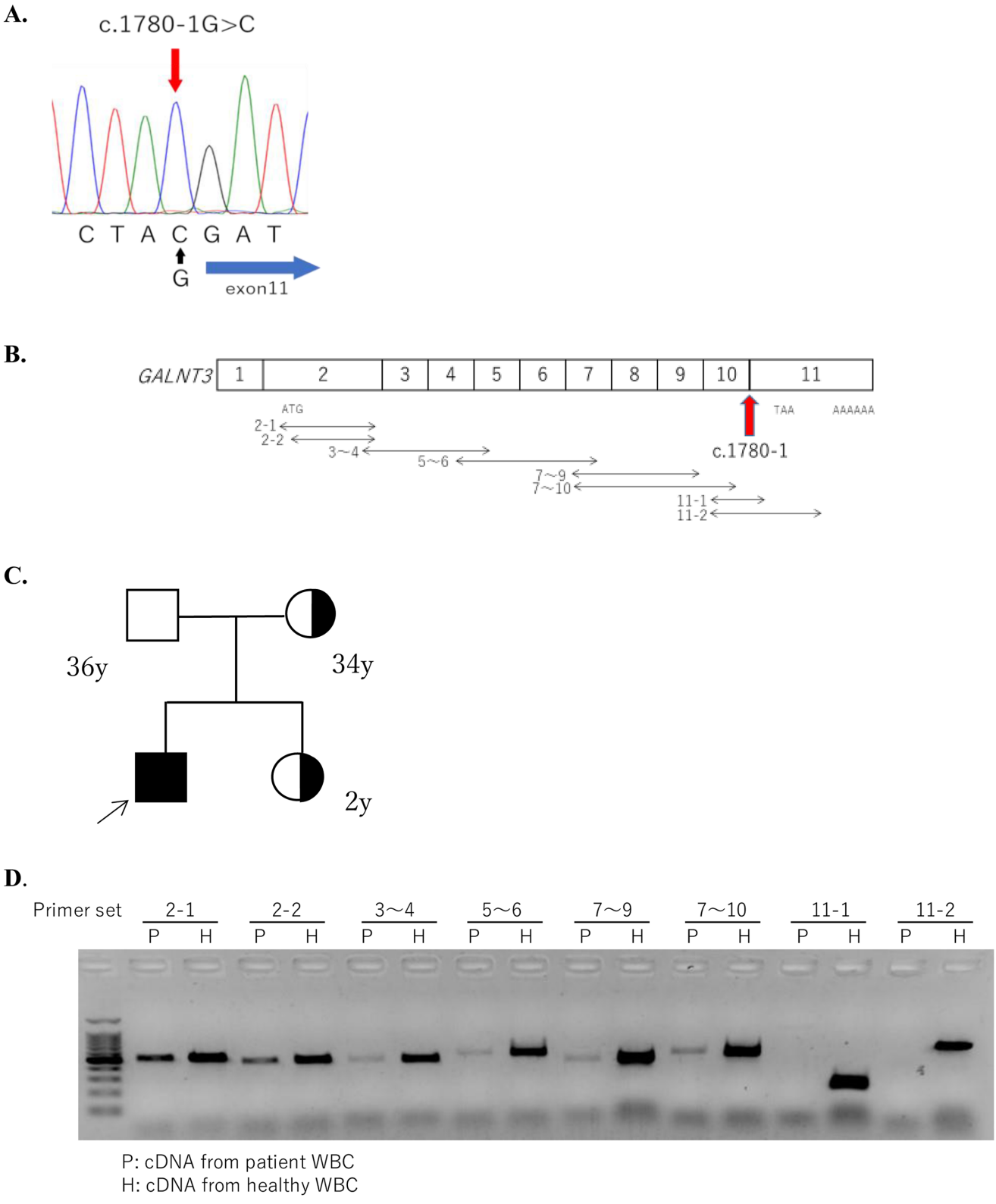


**Fig. 2.** *GALNT3* variant identified in our patient. A: The DNA sequence analysis of our proband revealed a splice site-affecting homozygous variant in intron 10 (c.1780-1G>C). B: Schematic design of *GALNT3* mRNAs and PCR products. We designed a primer set to amplify each exon as mapped below the *GALNT3* mRNA model. C: The asymptomatic mother and sister of the proband had the same variant (heterozygous), whereas his father did not. D: PCR analysis confirmed the deletion of exon 11 in the *GALNT3* mRNA of the patient. As described in panel C, the primer sets 11-1 and 11-2 were designed to amplify exons 10 and 11. The PCR products amplified from the cDNA of healthy donors were of the expected size, whereas these bands were absent in the cDNA of the patient (D). WBC, white blood cell.


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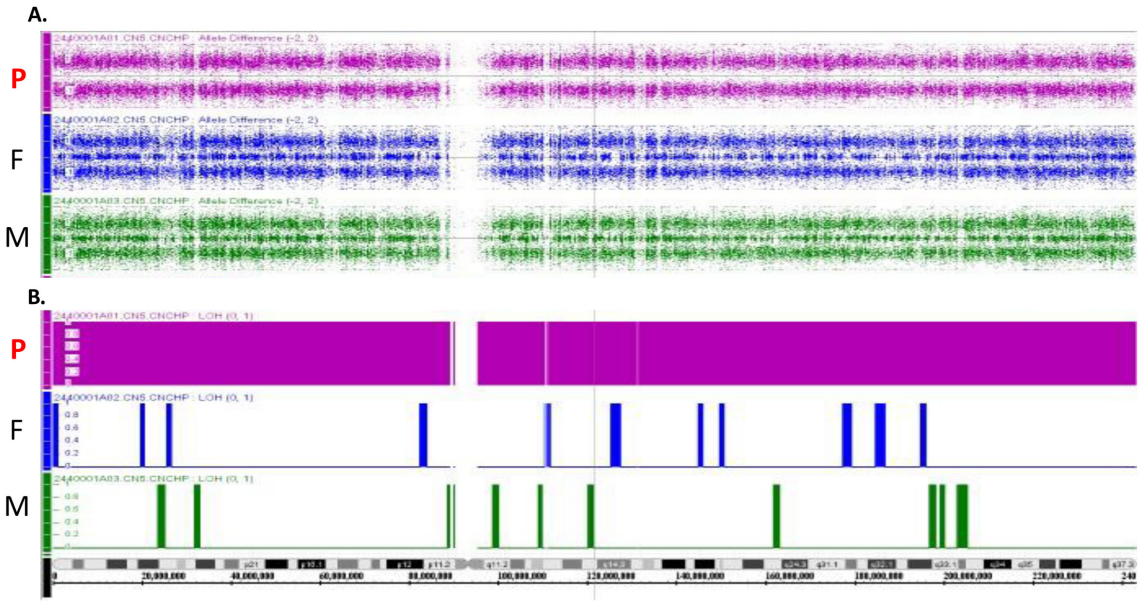


**Fig. 3.** Genome-wide SNP array indicating maternal isodisomy of chromosome 2. A: Differences in the alleles of genotyped SNPs on chromosome 2 in the proband (P), his father (F), and his mother (M) are displayed. B: Loss of heterozygosity (LOH) on chromosome 2. LOH represents the loss of allelic differences, and the LOH state is either 0, representing no LOH or 1, representing LOH. Allele segregation in the proband comprised homozygotes and LOH; however, parental (F and M) allele segregation exhibited a heterozygous pattern on chromosome 2. The proband had 7,673 homozygous SNPs from the mother and six homozygous SNPs from the father.

binders, such as sevelamer and aluminum hydroxide, are used to lower serum phosphorus levels (9). Ramnitz *et al.* reported a case of tumor shrinkage without resection owing to the administration of anti-inflammatory drugs and suggested that inflammation may play a role in the pathogenesis of this disorder (1, 2). In contrast, Dauchez *et al.* demonstrated that anti-IL-1 therapy effectively suppressed inflammatory flares but did not prevent the extension of calcification (21). However, the efficacy of anti-inflammatory therapies remains to be elucidated. Surgical resection is often performed for patients with HFTC with tumoral calcinosis lesions. Some patients exhibit complete remission of the lesion by surgical resection, whereas others require multiple surgeries owing to lesion recurrence. The clinical response to treatment varies depending on the case (1, 2, 8, 22), we lack treatment regimens that effectively decrease lesion size consistently or universally or prevent the progression or recurrence of lesions post-surgery (9). In our patient, despite proper control of serum phosphate concentration with diet and phosphate binders, the elbow tumor enlarged gradually, with a risk of self-destruction of the skin. Therefore, we performed surgical resection after considering the risks of recurrence and poor wound healing.

HFTC develops typical symptoms within the first 20 years of life (9). The natural course of HFTC remains poorly elucidated. The age of the patient at onset was three years. We observed no tumor recurrence or other complications four years after resecting the tumor from the elbow. Hyperphosphatemia is an independent risk factor for arteriosclerosis; therefore, we recommend continuing the low-phosphate diet and phosphate-binding therapy.

Our study has some limitations. Despite attempting to determine the precise structure of mutant *GALNT3* mRNA with homozygous c.1780-1G>C using primer sets, we could not amplify any fragments of exon 11 and determine the sequence of the mutant mRNA. We also could not evaluate the pathogenesis of the novel variant owing to the lack of functional analyses. RT-PCR analysis indicated that the *GALNT3* mRNA levels in the white blood cells were decreased (data not shown). Although these data suggest that the lack of stability in the mutant mRNA contributes to pathogenesis, further investigation is required to obtain more mechanistic insights into its pathogenesis.

## Conclusion

Herein, we report the first case of a novel *GALNT3* variant observed in Japan. This is also the first case of HFTC caused by maternal UPD of chromosome 2, which includes the *GALNT3* variant.

**Conflict of interests:** The authors have no conflict of interest to declare.

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