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A novel homozygous variant in exon 4 of the *GALNT3* gene causing hyperphosphataemic familial tumoural calcinosis in a family from China

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Familial tumoural calcinosis (FTC) is a rare autosomal recessive genetic disorder characterised by the deposition of calcium and phosphorus in the soft tissues surrounding the joints, often leading to pain, limited mobility, and potential secondary infections. It has a low incidence and is primarily found in African and Middle Eastern populations [1, 2]. The clinical diagnosis of HFTC is established by the presence of tumoural calcinosis and/or characteristic laboratory findings of hyperphosphataemia in the setting of inappropriately increased renal tubular reabsorption of phosphorus (TRP), and elevated or inappropriately normal 1,25-dihydroxy-vitamin D levels. One of the clinical features of hyperphosphataemic familial tumoural calcinosis (HFTC) secondary to fibroblast growth factor 23 (FGF23) or polypeptide N-acetylgalactosaminyltransferase 3 (GALNT3) mutations is an elevated level of C-terminal FGF23. When clinical and laboratory findings are inconclusive, the diagnosis can be confirmed through molecular genetic testing to detect biallelic pathogenic variants in FGF23, GALNT3, or KHLOTO (KL) [3]. This paper provides a detailed report on the clinical manifestations, laboratory examinations, and treatment of hyperphosphataemia familial tumour-like calcinosis in a Chinese close family, aiming to offer valuable reference for future clinical practice.

The patient under report is a 49-year-old female from a close-knit family in China. Her parents are in a cousin relationship and she has one daughter. Her height and weight were 155 cm and 58.4 kg, respectively. The patient had no prior medical history of hypertension, diabetes, cardiac disease, or neoplasms. Ten years previously, she had begun to experience the development of nodules and discomfort in both shoulder joints, with nocturnal exacerbation of pain. Over time, the nodules progressed in size, ultimately resulting in restricted range of motion. The shoulder joint masses were surgically excised, followed by administration of phosphorus-lowering medications (sevelamer hydrochloride) to regulate serum phosphate levels. The patient's serological, imaging, and genetic data were systematically gathered.

The serological results showed that the serum creatinine levels of the proband, her father, mother, and daughter were 62.00, 92.00, 89.00, and 58.00 umol/L (reference range: 70.00–106.00 umol/L), glomerular filtration rates (GFR) were 101.85, 71.35, 55.97, and 130.68 ml/min/1.73 m^2, serum phosphorus levels were 1.82, 1.16, 1.01, and 0.96 mmol/L (reference range: 0.85–1.51 mmol/L), serum calcium levels were 2.23, 2.18, 2.05, and 2.33 mmol/L (reference range: 2.15–2.50 mmol/L), and parathyroid hormone levels were 15.80, 17.10, 15.90, and 16.20 (reference range: 15–65 pg/mL), respectively. The levels of 1,25-dihydroxy-vitamin D were 31.20, 32.47, 35.25, and 30.77, respectively (reference range: 30.10-100.00 ng/mL). The 24-hour urinary phosphorus excretion was 5.10, 25.60, 23.70, and 21.80 mmol/L (reference range 13.00–44.00 mmol/L), and the urinary creatinine was 2600.00, 6734.00, 11320.00, and 16735.00 umol/L (reference range 2470.00–19200.00 umol), respectively. The renal tubular reabsorption of phosphate (TmP/GFR) were 2.01, 0.81, 0.83, and 0.88 mmol/L, respectively (reference

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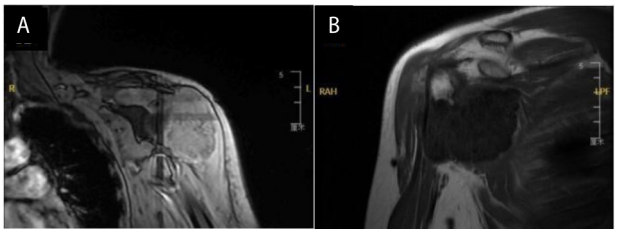

Figure 1AB. *The preoperative magnetic resonance imaging revealed substantial masses in the patient's left and right shoulder joints*

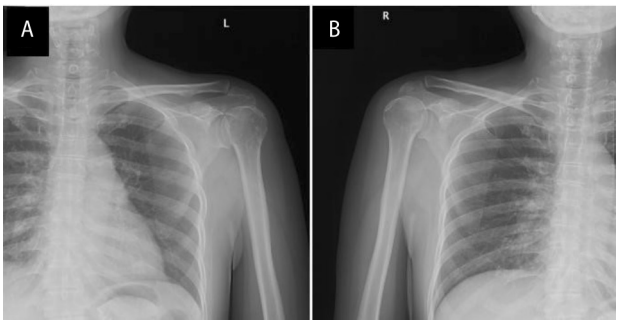

Figure 2AB. *Following surgical resection, the patient's shoulder joint mass was no longer present*

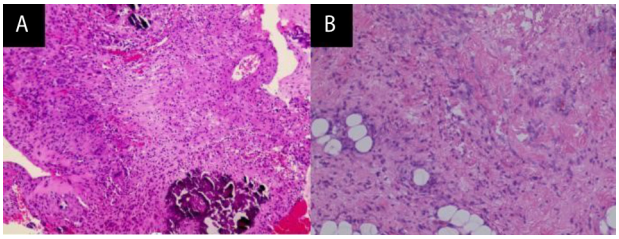

Figure 3AB. *The histological examination revealed interstitial collagen fibrous hyperplasia accompanied by infiltration of lymphocytes and neutrophils, as well as increased calcification*

range: 0.80–1.35 mmol/L). Informed consent was obtained from the subject described in this report.

The magnetic resonance imaging of the patient's shoulder joint revealed clusters of abnormal signals, leading to a diagnosis of tumour-like calcinosis. The surgical resection was successful with no signs of recurrence. The postoperative pathology findings revealed the presence of microscopic synovial tissue, interstitial collagen fibre hyperplasia, small vascular hyperplasia, lymphocyte and neutrophil infiltration, and increased calcification in the focal area, consistent with tumoural calcinosis (Fig. 1–3).

The results of the whole exome gene test revealed that the patient's disease was attributed to a homozygous mutation of c.781C>T (p.Arg261Trp) in exon 4 of the *GALNT3* gene. Both the parents and daughter had heterozygous variants with no phenotype.

The research indicates that, in addition to laboratory tests, a definitive diagnosis can be achieved through molecular genetics. *GALNT3* mutations in HFTC can occur at various loci within the gene [3]. In our study, the proband's disease was attributed to a homozygous mutation of c.781C>T (p.Arg261Trp) in exon 4 of the *GALNT3* gene. Both the parents and daughter had heterozygous variants with no phenotype. We primarily conducted verification through multiple official paper retrieval platforms, and as of now, there are no precedent reports available. In Su's study, both the proband and his sister carried 2 homozygous mutations (R180H and I220N) on exon 2 of the *GALNT3* gene. The clinical phenotype closely resembled the findings reported in this case, demonstrating calcification of the soft tissue mass in the right hip [4].

According to the existing literature, treatment methods primarily encompass low-phosphorus diet, administration of phosphate binders, surgical resection, anti-interleukin-1 therapy, and so on. Following surgical resection of the masses, the patient experienced significant relief in clinical symptoms of pain and joint limitation. The serum phosphorus level remained stable after treatment with sevelamer [5].

In summary, we identified the new novel mutation (c.781C > T; p.Arg261Trp) in exon 4 of the *GALNT3* gene. This case expands the spectrum of genotypic features associated with HFTC and provides a comprehensive overview of its clinical and genetic characteristics.

Authors' contributions

Y.Z. — medical practices, concept, data collection and processing, analysis or interpretation, literature search, writing; H.L. — data collection and processing, analysis; B.G. — medical practices, data collection and processing; G.Z. — medical practices, analysis or interpretation.

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Conflict of interest

The authors report no conflict of interest.

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