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RAPID COMMUNICATION

A Novel Mutation in Fibroblast Growth Factor 23 Gene as a Cause of Tumoral Calcinosis

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Context: Tumoral calcinosis is a disease characterized by ectopic calcification and hyperphosphatemia due to enhanced renal tubular phosphate reabsorption. Fibroblast growth factor (FGF)23 was identified as a responsible factor in hypophosphatemic diseases caused by renal phosphate leak.

Objective: The objective of the study was to analyze the involvement of FGF23 in the development of tumoral calcinosis.

Design: Serum FGF23 level was evaluated in a patient with tumoral calcinosis by two kinds of ELISA: full-length assay that detects only full-length FGF23 with phosphate-lowering activity and C-terminal assay that measures full-length as well as C-terminal fragment of FGF23. FGF23 gene was analyzed by direct sequencing of PCR products, and mutant FGF23 was analyzed by Western blotting after expression in mammalian cells.

Patients: A family of tumoral calcinosis patients were studied.

Results: Serum FGF23 was extremely high when measured by C-terminal assay. In contrast, it was low normal by full-length assay. Analysis of FGF23 gene detected a serine to phenylalanine mutation in codon 129. No wild-type allele of this codon was found in the patient. The brother of the proband showed the same base change. When this mutant FGF23 was expressed *in vitro*, full-length and N-terminal fragments were barely detectable by Western blotting, whereas C-terminal fragment with the same molecular weight as that from wild-type FGF23 could be detected.

Conclusion: The production and serum level of C-terminal fragment of FGF23 are increased in this patient with tumoral calcinosis. Together with the recent similar report of FGF23 mutation, impaired action of full-length FGF23 seems to result in tumoral calcinosis. (***J Clin Endocrinol Metab* 90: 5523–5527, 2005**)

TUMORAL CALCINOSIS IS a disease characterized by ectopic calcification especially around large joints and hyperphosphatemia due to enhanced renal tubular phosphate reabsorption (1). Serum 1,25-dihydroxyvitamin D [1,25$(OH)_2$D] level was reported to be normal or high despite high serum phosphate level (2). These features are mirror images of several hypophosphatemic diseases such as X-linked hypophosphatemic rickets/osteomalacia, autosomal dominant hypophosphatemic rickets/osteomalacia, and tumor-induced rickets/osteomalacia (TIO). In these diseases, hypophosphatemia caused by renal phosphate leak and rather low serum 1,25$(OH)_2$D level are reported (3). Because serum calcium and PTH levels are usually normal in these hyper- and hypophosphatemic diseases, it is postulated that there is another mechanism(s) for regulating serum phosphate level than PTH.

Recently fibroblast growth factor (FGF)23 was shown to play important roles in the development of several hypophosphatemic diseases. FGF23 was positionally cloned as a responsible gene for autosomal dominant hypophosphatemic rickets/osteomalacia (4). In addition, FGF23 was identified as a causative factor for TIO (5). Furthermore, it has been shown that serum FGF23 level is increased in most patients with X-linked hypophosphatemic rickets/osteomalacia (6, 7). *In vivo* studies indicated that FGF23 causes renal phosphate leak, hypophosphatemia, and low 1,25$(OH)_2$D level when injected into mice (8). These results indicate that excess action of FGF23 results in phosphaturia, hypophosphatemia, and rather low serum 1,25$(OH)_2$D level. In contrast, knockout mice of FGF23 were shown to exhibit hyperphosphatemia associated with high serum 1,25$(OH)_2$D level, indicating that FGF23 is physiologically working as a regulatory factor of phosphate and vitamin D metabolism at least in mice (9, 10).

Recently, mutations in the uridine diphosphate-*N*-acetyl-α-D-galactosamine-polypeptide *N*-acetylgalactosaminyltransferase 3 (GalNAc transferase 3 or *GALNT3*) gene were identi-

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Abbreviations: FGF, Fibroblast growth factor; *GALNT3*, uridine diphosphate-*N*-acetyl-α-D-galactosamine-polypeptide *N*-acetylgalactosaminyltransferase 3 (GalNAc transferase 3); 1,25$(OH)_2$D, 1,25-dihydroxyvitamin D; TIO, tumor-induced rickets/osteomalacia.

fied to be responsible for familial tumoral calcinosis (1). In addition, a mutation in FGF23 gene was also reported as a cause of tumoral calcinosis (11, 12). We here show another mutation in FGF23 gene as a cause of tumoral calcinosis. These results underscore the important role of FGF23 in phosphate and vitamin D metabolism in human.

Subjects and Methods

A case presentation

A 28-yr-old man (V-3, Fig. 1) from consanguineous Arabian parents had had sc nodules with occasional white discharge from childhood. Laboratory tests showed hyperphosphatemia of 5–10 mg/dl (1.62–3.2 mmol/liter; normal 3–5 mg/dl; 0.97–1.62 mmol/liter), hypophosphaturia with tubular reabsorption of phosphate of 96–100% (80–95) normocalcemia of 8.4–10.0 mg/dl (2.10–2.50 mmol/liter; normal 8.0–10.4 mg/dl; 2.00–2.59 mmol/liter), normal creatinine of 0.9–1.2 mg/dl (80–106 μmol/liter; normal 0.8–1.3 mg/dl; 71–115 μmol/liter), and high serum 1,25-dihydroxyvitamin D levels of 59–89 pg/ml (152–231 pmol/liter; normal 15–55 pg/ml; 39–143 pmol/liter). Serum alkaline phosphatase and pH were normal. Two brothers and a cousin with consanguineous parents from the same family also had a similar syndrome, and he was diagnosed as having tumoral calcinosis (Fig. 1). The family tree suggested the autosomal recessive inheritance of the disease.

Measurement of serum FGF23

Serum FGF23 levels were determined by two kinds of commercially available sandwich ELISAs. The ELISA for the full-length FGF23 was developed to detect only the uncleaved peptide using the combination of two monoclonal antibodies that recognize the N-terminal and the C-terminal portions, respectively, of the processing site of FGF23 (Kainos, Tokyo, Japan) (6). The second ELISA for the C-terminal portion of FGF23 (Immutopics, San Clemente, CA) detects both the full-length and processed C-terminal fragment of FGF23 (7).

Analysis of FGF23 gene

The following study was approved by the Ethical Committee of the University of Tokyo Hospital. After informed consent was obtained, genomic DNA was extracted from peripheral leukocytes using QIAamp blood kit (QIAGEN, Hilden, Germany). FGF23 gene was composed of three coding exons. All the coding exons of FGF23 gene were PCR amplified using the following primers and directly sequenced using PRISM ready reaction dye deoxyterminator cycle sequencing kit and ABI model 373S-36 autosequencer (PerkinElmer, Chiba, Japan). Primers used were as follows: 5′-GCAAGGGAGAAGGAAAAGGC-3′ and 5′-TTAGCCCTCCAGTCTAGTCCCC-3′ for exon 1, 5′-CAGGAGGTGCTTGAAGGTGG-3′ and 5′-CCCAGCTATTAAACGTGAGCATT-3′ for exon 2; 5′-AGGCTCAACGCCCTAAGAACT-3′ and 5′-ATGGGGGTGTTGAAGTGAATTAG-3′ for 5′ portion of exon 3; and 5′-CTCTCCTCAGTATCACTTCCTGGT-3′ and 5′-TCGGAACGTCAAGGGACCT-3′ for the 3′ portion of exon 3.

Western blotting and measurement of FGF23 in the conditioned medium

Complementary DNA coding for the mutant FGF23 was created by *in vitro* mutagenesis using QuickChange site-directed mutagenesis kit (Stratagene, La Jolla, CA) and expressed in peak rapid cells (Edge Biosystems, Gaithersburg, MD) as described (5). Primers used for construction of cDNA for mutant FGF23 were 5′-GTACGACGTCTACCACTTTCCTCAGTATCACTTCC-3′ and 5′-GGAAGTGATACTGAGGAAAGTGGTAGACGTCGTAC-3′ for S129F; 5′-GTACGACGTCTACCACGCTCCTCAGTATCACTTCC-3′ and 5′-GGAAGTGATACTGAGGAGCGTGGTAGACGTCGTAC-3′ for S129A; 5′-GTACGACGTCTACCACACTCCTCAGTATCACTTCC-3′ and 5′-GGAAGTGATACTGAGGAGTGTGGTAGACGTCGTAC-3′ for S129T; and 5′-GTACGACGTCTACCACTGGCCTCAGTATCACTTCC-3′ and 5′-GGAAGTGATACTGAGGCCAGTGGTAGACGTCGTAC-3′ for S129W. Conditioned medium and cell lysate were subjected to SDS-PAGE followed by Western blot analysis using two kinds of monoclonal antibodies that recognize N- and C-terminal portion of the processing site of FGF23, which reacts with amino acids 148–163 and 244–251 of FGF23, respectively. The results were visualized by enhanced chemiluminescence detection system (Amersham Pharmacia Biotech, Little Chalfont, UK). The amount of FGF23 in the conditioned medium was measured by ELISA for full-length FGF23.

Results

Measurement of FGF23 levels in sera by two ELISA methods repeatedly produced discrepant results. Although the full-length assay showed rather low FGF23 levels (11.0 and 15.0 pg/ml with reference range of 10–50 pg/ml), C-terminal assay indicated extremely high FGF23 levels (2948 and 5875

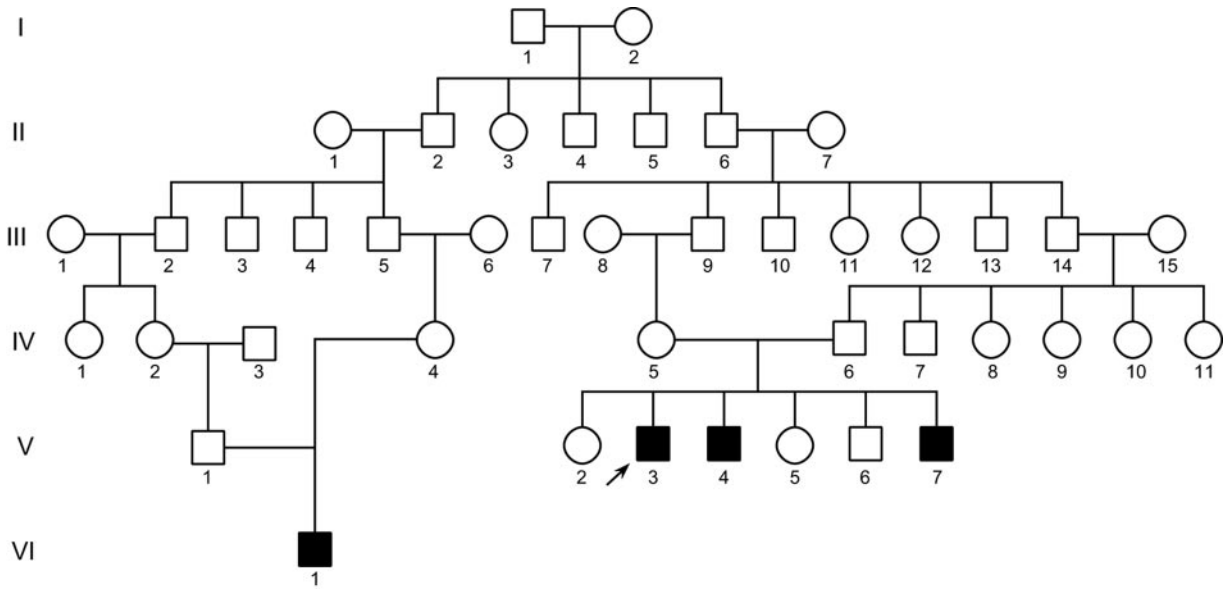

FIG. 1. Family tree of the patients. Four affected patients were found in the family. DNA samples could be obtained from only two patients (V-3 and V-4).

RU/ml with reference range of < 150 RU/ml). These results suggested that there is only a small amount of full-length FGF23 in the patient's sera, whereas the processed C-terminal fragment is accumulated. To clarify the mechanism of this discrepant FGF23 levels, we then analyzed the FGF23 gene in this patient. As shown in Fig. 2, direct sequencing of all the coding exons of FGF23 gene revealed that this patient has serine to phenylalanine substitution at codon 129 (S129F) and no wild-type allele of this codon was detected. His brother (V-4 in Fig. 1) also showed the same base substitution (data not shown).

To examine the effect of this mutation on protein form of FGF23, we expressed the mutant FGF23 *in vitro* and conditioned medium and cell lysate were analyzed by Western blotting. As shown in Fig. 3, when wild-type FGF23 was expressed and conditioned medium was analyzed by Western blotting using antibodies against N- and C-terminal portion of FGF23, both full-length and processed fragments could be observed. However, when the mutant FGF23 with S129F substitution was expressed, full-length and N-terminal fragment of FGF23 could be barely detectable, whereas a small amount of C-terminal fragment could be observed. These results are similar to those obtained by S71G mutation of FGF23 (11) and suggested that proper maturation of FGF23 protein is impaired by these mutations. We further analyzed the importance of serine at codon 129 by introducing several mutations. As shown in Fig. 3, less amount of full-length and processed fragments, compared with those of wild-type, could be observed in conditioned medium of S129A. However, S129T and S129W mutations resulted in loss of full-length and N-terminal fragment in the conditioned medium as in S129F. Analysis of FGF23 levels in the conditioned medium also supported the notion that secretion of full-length FGF23 is impaired from cells expressing these mutant FGF23 proteins (mock < 3 pg/ml, wild-type 14562 pg/ml, S129F 5 pg/ml, S129A 2529 pg/ml, S129T 144 pg/ml, S129W 19 pg/ml). In addition, when cell lysate was analyzed by Western blotting, immunopositive bands around 30 kDa could be observed in cells expressing wild-type as well as all the mutant FGF23 proteins. Although the precise nature of

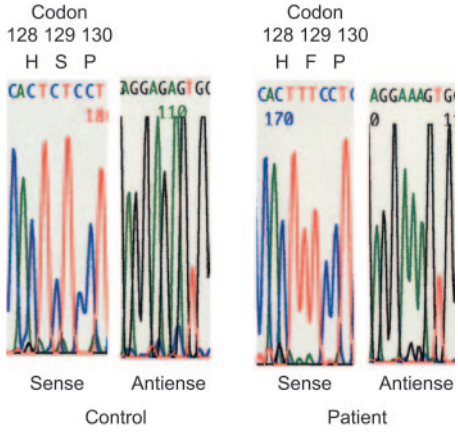

FIG. 2. A mutation in the FGF23 gene. All the coding exons of FGF23 were analyzed by direct sequencing of PCR products. A cytosine to thymine substitution at codon 129, which converts serine to phenylalanine, was identified, and no wild-type allele was found in the patient.

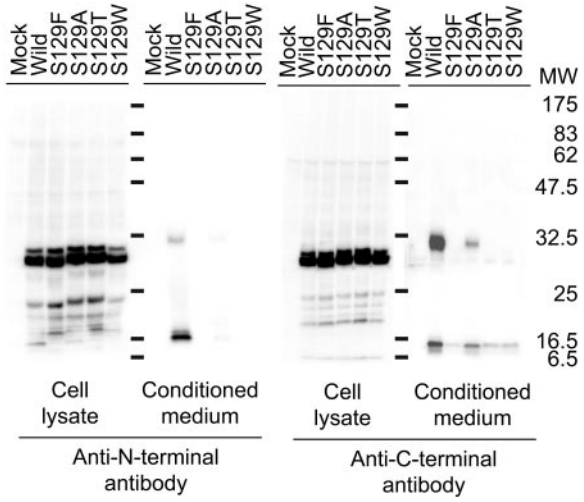

FIG. 3. Western blotting for FGF23 protein. Conditioned medium and cell lysate of peak rapid cells expressing wild-type or mutant FGF23 were analyzed by Western blotting. Whereas full-length and processed N-terminal and C-terminal fragments were observed when wild-type FGF23 was expressed, neither full-length nor N-terminal fragments was barely detectable in conditioned medium of cells expressing S129F mutant FGF23. S129T and S129W mutations produced similar results, whereas smaller amounts of full-length and processed fragments could be detected in S129A FGF23, compared with those of wild-type FGF23. MW, Molecular weight.

these bands is not clear at the moment, it is likely that these bands represent immature FGF23 protein. Collectively, these results indicate that serine at codon 129 is indispensable for the maturation and secretion of full-length FGF23.

Discussion

We have shown discrepant FGF23 levels in a patient with tumoral calcinosis measured by two ELISAs. Whereas intact assay indicated low normal value of FGF23, it was extremely high by C-terminal assay that detects both full-length and C-terminal fragment of FGF23. FGF23 was shown to be cleaved between arginine179 and serine180 by subtilisin-like endopeptidase (13), and only full-length FGF23 demonstrated the activity to cause hypophosphatemia *in vivo* (14). These results suggest that production and the serum level of C-terminal fragment of FGF23 are increased in this patient. There are several lines of evidence that the physiological production of FGF23 is tightly regulated. First, heterozygous knockout mice for FGF23 show the same phosphate and FGF23 levels as those of wild-type mice (9). In addition, FGF23 became undetectable just after removal of the responsible tumor for TIO, indicating suppression of its production by normal tissues under condition of phosphate wasting (15). Furthermore, FGF23 level increases with high phosphate diet associated with hyperphosphatemia in rodents (16). It was also shown that phosphate restriction and loading change serum FGF23 in human (17). Therefore, enhanced production of FGF23 in the present case seems to be a physiological response to hyperphosphatemia or other accompanying metabolic changes associated with hyperphosphatemia.

When the mutant FGF23 with S129F substitution was expressed *in vitro*, neither full-length nor N-terminal fragment was barely detectable. In contrast, C-terminal fragment with

the same molecular size to that from wild-type FGF23 could be observed. These results are identical with those described in another mutant FGF23 protein associated with tumoral calcinosis (11). In the report by Benet-Pages *et al.* (11), it was shown that the mutant FGF23 is retained in the Golgi complex, although the precise mechanism of secretion of C-terminal fragment is unknown at the moment. We have also examined the importance of serine at codon 129 by creating several mutant FGF23 proteins including S129A, S129T, and S129W. This serine residue is well conserved among FGF families as that in codon 71. Although some differences in the pattern of FGF23 protein were observed, the amount of full-length FGF23 was lower, compared with that of wild-type FGF23, in all these mutant proteins. In addition, S129T and S129W as well as S129F mutation prevented the secretion of full-length FGF23, indicating that serine rather than amino acid containing hydroxide ion or simple amino acid is essential for secretion and activity of full-length FGF23.

DNA analysis showed that this patient has a base change in codon 129 of the FGF23 gene, and no wild-type allele could be observed. Because we could not obtain samples from parents of this patient, it is possible that this patient has heterozygous mutation and a deletion of one allele of FGF23 gene rather than homozygous for this mutation. However, clinical data together with *in vitro* analysis indicate that lack of wild-type allele of FGF23 results in disordered phosphate metabolism.

The *GALNT3* gene was identified as a responsible gene for familial tumoral calcinosis. GALNT3 is an enzyme that transfers *N*-acetylgalactosamine from the sugar donor uridine diphosphate-*N*-acetylgalactosamine to serine or threonine residues and is responsible for the initiation of O-linked glycosylation. The initial report indicated high FGF23 levels measured by C-terminal assay in patients with mutations in *GALNT3* gene and thus ruled out the involvement of FGF23 in the development of hyperphosphatemia (1). However, as shown in this report, FGF23 levels measured by C-terminal and full-length assay can be discrepant. Actually, intact FGF23 was shown to be rather low in patients with mutations in *GALNT3* gene (18). FGF23 actually has several O-linked glycosylation sites (14). Therefore, it is possible that FGF23 is one of the targets of GALNT3, and O-linked glycosylation affects the processing of FGF23 between arginine179 and serine180. However, serine 129 as well as serine 71 are considered to be solvent inaccessible (19), and a computer program suggests that it is unlikely that these serine residues are glycosylated (http://www.cbs.dtu.dk/services/NetOGlyc/). FGF23 protein may need these serine residues for proper posttranslational folding rather than these amino acids being glycosylated by themselves.

Western blotting using cell lysate indicated that there is immunopositive protein for FGF23 with molecular mass of 25–30 kDa. Although we could not determine the precise nature of this protein because of difficulty of obtaining enough material, it is possible that this band represents FGF23 protein with less glycosylation considering the molecular mass of FGF23 polypeptide chain of about 28 kDa. This band could be observed in both wild-type and mutant FGF23 proteins and fully glycosylated FGF23 with molecular mass of 32 kDa was not found in cell lysate. Therefore, it is suggested that glycosylated FGF23 is not stored in cells and is rapidly secreted. During this secretion process, a part of glycosylated FGF23 seems to be processed between arginine 179 and serine 180. In the case of FGF23 with mutation in codon 129, it is possible that the mutation prevents glycosylation of FGF23 by misfolding, and the processing of FGF23 protein is enhanced in a less glycosylated form. Furthermore, the mutation may make N-terminal fragment of FGF23 more fragile by modification of the structure, and the N-terminal fragment could not be observed in the conditioned medium. Further studies are necessary to clarify the precise mechanism of glycosylation, processing, and secretion of FGF23.

Collectively, recent studies indicate that there are at least two causal genes for tumoral calcinosis, *GALNT3* and *FGF23*. Mutations in both genes are associated with extremely high FGF23 levels by C-terminal assay and rather low intact FGF23. These results, together with several hypophosphatemic diseases caused by excess actions of FGF23, underscore the importance of full-length FGF23 in phosphate and vitamin D metabolism in humans.

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