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# Whole genome sequencing revealed novel *ANO5* mutation c.1067G>T (p.C356F) in a big family with atypical gnathodiaphyseal dysplasia

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## Abstract

**Background:** Gnathodiaphyseal dysplasia (GDD) is a rare skeletal disorder that has not been well studied.

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Conflicts of interest

All authors have reported no conflicts of interest.

**Methods:** Sanger sequencing, whole-genome sequencing, and bioinformatics and structural modeling analyses were performed.

**Results:** A family with patients with fibro-osseous lesions of the jawbones were initially diagnosed with cherubism. Sequencing of *SH3BP2*, which is the causal gene of cherubism, revealed no pathogenic mutation. Through whole-genome sequencing, we identified a novel mutation c.1067G>T (p.C356F) in *ANO5*, and bioinformatics analyses and structural modeling showed that the mutation was deleterious. Because *ANO5* is the gene responsible for GDD, we reappraised the clinical data of the patients, and the diagnosis was corrected to atypical GDD. A review of the literature showed that 67% of GDD cases confirmed by molecular testing were initially misdiagnosed.

**Conclusions:** The novel mutation c.1067G>T (p.C356F) in *ANO5* is responsible for the atypical GDD observed in our patients. GDD should be included in the differential diagnosis for patients with fibro-osseous lesions.

### Keywords

gnathodiaphyseal dysplasia; cherubism; *ANO5* ; *SH3BP2* ; whole-genome sequencing

## Introduction

In 2001, the name gnathodiaphyseal dysplasia (GDD) was given to a skeletal syndrome characterized by fibro-osseous lesions of jaw bones, long bone bowing and bone fragility.[1] Riminucci et al. considered GDD to be a distinct entry different from fibrous dysplasia and other diseases with fibro-osseous lesions.[1] They reported that the histopathological characteristics of GDD were cemento-ossifying fibroma, psammomatoid bodies and aberrant mineralization within the walls of blood vessels. The inheritance pattern of GDD is autosomal dominant. In 2004, GDD was found to be caused by missense mutations in the *ANO5* gene (also known as TMEM16E).[2] A few recent studies identified six different *ANO5* missense mutations in patients with GDD, suggesting an important role of *ANO5* missense mutations in the onset of GDD.[3–6] However, some clinical overlap between GDD and other diseases, such as polyostotic fibrous dysplasia, was found in some patients, indicating that the full spectrum of the GDD phenotype may still remain to be explored.[4] GDD is rare, and no prevalence rate data is available.

Cherubism is characterized by swelling of the maxilla and mandible. The name cherubism was designated due to the cherubic appearance of the patients, including full round cheeks and upward cast of the eyes.[7] The onset of cherubism is usually in early childhood, and it generally progresses until puberty.[8] Histopathologically, cherubism lesions show as fibro-osseous lesions containing many multinucleated giant cells.[9] Chomette and colleagues classified cherubism lesions into three stages: the osteolytic stage, the reparative stage and the bone-formation stage. The latter stage is characterized by the presence of more newly formed bone matrix and fewer multinuclear giant cells.[10] The inheritance pattern of cherubism is autosomal dominant. Mutations in the *SH3BP2* gene have been reported to result in cherubism.[11, 12] Cherubism was estimated to have a prevalence of 1:180,000 in Norway.[13]

In this study, we used Sanger sequencing, whole-genome sequencing, and bioinformatics and structural modeling analyses to investigate the genetic basis of a family with fibro-osseous lesions of the jawbones. The identification of a novel mutation, c.1067G>T (p.C356F), in *ANO5* helped us correct the diagnosis.

## Materials and Methods

### Subjects

Seven patients and four healthy individuals were recruited from a Chinese family with cherubism at the Department of Oral and Maxillofacial Surgery, Sun Yat-sen Memorial Hospital. Detailed clinical, radiological and histological examinations were performed. The study was approved by the Ethical Review Committee of Sun Yat-Sen Memorial Hospital, Sun Yat-sen University. Informed consent was obtained from all the subjects who participated in this study. The principles outlined in the Declaration of Helsinki were followed.

### Mutation analysis of *SH3BP2*

The pedigree of the family is shown in Figure 1A. Two patients (IV:9 and IV:11) were selected to be evaluated for pathogenic mutations in *SH3BP2*. Genomic DNA was extracted and then subjected to PCR and Sanger sequencing. The methods used for DNA extraction, PCR and Sanger sequencing have been described in our previous studies.[14, 15] The primer sequences that were used are shown in Supplemental Table 1. The sequencing results were compared to the gene sequence obtained from the UCSC Genome Browser.

### Whole-genome sequencing, variant selection and co-segregation analysis

Genomic DNA was extracted from the peripheral blood of two individuals (IV:9 and V:3). DNA libraries of 300-bp inserts were constructed and sequenced using an Illumina HiSeq 2000 platform (Illumina, San Diego, CA, USA) to generate 100-bp paired-end reads. The reads were aligned to GRCh37 using Burrows-Wheeler Aligner (BWA) software. SNPs, InDels, CNVs and SVs were identified using SOAPsnp, SAMtools, CNV-Detection and BreakDancer, respectively. The identified variants were annotated using ANNOVAR. The variants were analyzed in the autosomal dominant inheritance mode. Variants that were homozygous, presented in population databases with a minor allele frequency (MAF) > 1%, or did not affect exons were excluded. We included missense mutations that were predicted by two or more functional prediction tools to be pathogenic. We designed primers (Supplemental Table 2) and performed Sanger sequencing to validate the variants that passed the WGS filtering selection. We tested another five patients (III:5, IV:4, IV:11, V:2 and V:4) and four healthy individuals (IV:1, IV:8, IV:12 and V:1) in the study family for candidate variants.

### Bioinformatics analyses

The methods used for bioinformatics analyses have been described in previous studies. [14, 15] Briefly, we obtained the population frequencies of variants from the 1000 Genomes, NHLBI Exome Sequencing Project and Exome Aggregation Consortium (ExAC) datasets. We used SIFT, PolyPhen2, Mutation Taster and Mutation Assessor to predict the mutational effects of

the variants. The conservation of amino acids was assessed using cross-species alignments of multiple amino acid sequences.

### Structural modeling

Structural modeling of the wild-type and mutant ANO5 proteins was performed using Swiss PdbViewer v4.1 (http://spdbv.vital-it.ch/). We used the PDB file 4wis as the homology model to construct the proteins. The 3D structures were visualized using PyMol v1.5.0.3 (http://www.pymol.org/). To analyze the distributions of ANO5 mutations in the individuals with muscle and skeletal diseases, we retrieved ANO5 missense mutations from the public version of the Human Gene Mutation Database (HGMD, http://www.hgmd.cf.ac.uk/ac/index.php, accession date: 15 March 2017) and from the literature using PubMed (https://www.ncbi.nlm.nih.gov/pubmed/).

## Results

### Clinical report

The pedigree of the family is shown in Figure 1A. The proband (IV:9) was a 14-year-old girl who was referred to the Department of Maxillofacial Surgery because of apparent hypertrophy of the jaw bones. The deformation was first noted when she was 2 years old and continued to progress with age. An intraoral examination revealed that several anterior teeth were displaced or absent. The mandible showed apparent hypertrophy from the labial to lingual areas. The patient had no history of bone fractures, and her long bones were not different from those of a normal person (Supplemental Figure 1).

A panoramic radiograph and CT showed extensive lesions throughout the maxilla and the mandible body, with no condyle involvement. The lesions were composed of radiolucencies and radiopacities, with an imperceptible border. The bony cortex was expanded and discontinuous. Some teeth were located at the inferior margin of the mandible. The roots of the teeth were dysplastic or absent (Figure 2A–C). A subtotal mandibulectomy was performed, and this was followed by reconstruction of the mandible with a titanium plate and fibular grafting. The postoperative course was uneventful in this patient. No postoperative recurrence was found at 12 months (Supplemental Figure 2). The histological examination results showed that the bone matrix had been replaced by fibrous connective tissue. The bone trabecula was poorly formed. There were some multinucleated giant cells in the fibrous tissue. Most of the vessels were normal, with the exception of a few vessel walls that showed aberrant calcification (Figure 3).

Patient IV:11 was a 7-year-old boy with clinical features that were similar to but milder than those of patient IV:9. The anterior region of his mandible showed apparent hypertrophy. A panoramic radiograph and CT revealed radiopacities in the maxilla and the anterior region of the mandible. Several teeth were dislocated in the nasal side of the maxillary sinus and the inferior margin of the mandible (Figure 2D–F). In addition to patients IV:9 and IV:11, 11 more individuals in the family were affected, and in these individuals, the condition manifested as apparent hypertrophy of the jaw bones. Information on the 7 patients is summarized in Table 1.

Based on the family history, clinical, radiological and histopathological characteristics of the patients, they were initially diagnosed with cherubism.

### Whole-genome sequencing (WGS) results for *HRPT2, GNAS* and *NF1*

We performed Sanger sequencing to detect mutation of *SH3BP2*, but no pathogenic mutation was identified. We then performed WGS for patients IV:9 and V:3. A summary of the WGS results is provided in Supplemental Table 3. Other conditions that may be mistaken for cherubism include hyperparathyroidism, giant cell lesions, Noonan/multiple giant cell lesion syndrome and fibrous dysplasia. We inspected the variants that might have affected the genes that cause these diseases, including *HRPT2*, *GNAS* and *NF1*. No pathogenic mutation was found.

### Whole-genome sequencing, variant filtering and co-segregation analysis results

Because we found no pathogenic mutations in known candidate genes, we continued to search for a novel candidate gene. The filtering process used for this analysis is shown in Table 2. A total of 44 variants met the criteria, and we tested whether these 44 variants co-segregated with cherubism in this family. Thirteen of the variants were carried by patients III:5, IV:4, IV:11, V:2 and V:4. Finally, two candidate variants that were not carried by four healthy individuals (IV:1, IV:8, IV:12 and V:1) in the family were identified.

The two candidate variants were c.1067G>T (p.C356F, NM_213599) in *ANO5* and rs148471178 (c.G865T, p.D289Y, NM_174902) in *LDLRAD3*. The rs148471178 variant in *LDLRAD3* was recorded in the ExAC, 1000 Genomes and ESP with MAF of 0.003, 0.004 and 0.0002, respectively. According to the ExAC database, the MAF of rs148471178 is higher in East Asian (0.0095) and Latino (0.023) populations. Its allele frequency is too high to account for cherubism, which is associated with extremely low morbidity.[13] Therefore, the rs148471178 variant in *LDLRAD3* was determined to represent a population variant rather than a pathogenic mutation for cherubism.

The mutation c.1067G>T (p.C356F) in *ANO5* (Figure 1B) describes the substitution of a cysteine by a phenylalanine at the 356th amino acid of the encoded protein. This amino acid, p.Cys356, was found to be evolutionarily conserved through a cross-species amino acid sequence alignment (Figure 1C). It was predicted to be “deleterious”, “probably damaging”, “disease-causing” and “medium” by SIFT, PolyPhen2, Mutation Taster and Mutation Assessor, respectively, and was not reported in dbSNP, ExAC, 1000 Genomes, ESP and the public version of HGMD. We therefore considered that c.1067G>T in *ANO5* is the mutation that led to the onset of the disease in the study family.

Interestingly, *ANO5* mutations have been reported in patients with GDD, which is also characterized by fibro-osseous lesions of the jawbones. We reevaluated all data from our patients. The clinical and histopathological manifestations of the patients were not fully consistent with previous studies (these differences are carefully discussed in the Discussion section). The diagnosis was changed to “gnathodiaphyseal dysplasia (atypical)”.

### Structural modeling results

We used the PDB file 4wis as the template to determine the structure of the 79-883 amino acids of the ANO5 protein with a coverage of 0.68. The results of structural modeling suggested that Cys356 is located in the extracellular region of ANO5. The Cys356Phe mutation introduced substantial changes to the 3D structure of the extracellular region of the mutated protein (Figure 4A and B). The mutation also led to significant changes in the electrostatic characteristics in this region (Figure 4C and D). These results indicate that the mutation is pathogenic in nature.

In the public version of the Human Gene Mutation Database and the literature in PubMed, we identified nine bone diseases and 19 muscle diseases associated with ANO5 mutations (Supplemental Table 4 and 5). Interestingly, there was no overlap between the bone disease-related and muscle disease-related mutations. The patients with ANO5-associated muscle diseases did not have bone defects, and those with ANO5-associated bone diseases did not present with muscle defects (Supplemental Table 4 and 5). The locations of the mutated amino acids are marked on the 3D structure of the wild-type ANO5 protein. We found that the bone disease-associated ANO5 mutations were located predominantly in or near the extracellular region of the protein, whereas the muscle disease-associated ANO5 mutations were located throughout the protein (Figure 4E and F).

## Discussion

The awareness of pathologists and clinicians regarding GDD is relatively low, even though GDD was histologically defined in 2001.[1] Including this paper, there are only eight articles reporting 12 families with GDD confirmed by molecular testing (Table 3). Importantly, 67% (8/12) of the GDD patients were initially misdiagnosed as polyostotic fibrous dysplasia, gigantiform cementoma, suspected malignancy, cementoma, osteopenia or cherubism (Table 3). This finding demonstrates a need for increased awareness of GDD among pathologists and clinicians.

There are three articles reporting the histological features of GDD.[1, 3, 6] All agreed that the pathology shows fibro-osseous lesions with scattered psammomatoid bodies. Riminucci et al. reported aberrant calcification and thickening of vessel walls and narrowing of the lumens.[1] However, these findings were not reported in the other two articles.[3, 6] In our study, the bone trabeculae were poorly formed and cementum-like. There were some osteoblasts in the cementum-like trabeculae, in contrast to the acellular features reported by Riminucci et al.[1] We also did not observe psammomatoid bodies, thickening of vessel walls and narrowing of lumen in the lesions. We found a few vessel walls with calcification, which aligned with Riminucci et al. However, we observed some multinucleated giant cells in the fibrous tissue, which was not reported by other researchers. Due to the limited information from these patients, further studies investigating the histological features of GDD are needed.

Variations in clinical manifestations also exist. Bowing of the long bones was not reported in four articles.[3, 5, 6, 16] Jin et al. reported a patient who did not experience a bone fracture, although gross thickening of the diaphyseal cortices of long bones was shown

by radiograph.[6] In this study, the patients did not show long bone abnormality, and bone fracture did not occur. Hence, patients with GDD may not inevitably suffer from diaphyseal dysplasia.

The diagnosis of fibro-osseous lesions is a challenge for pathologists and clinicians.[17] There are partial clinical and pathological overlaps among fibrous dysplasia, ossifying fibroma and cemento-ossifying fibroma.[18] The variability of clinical and pathological features makes it challenging to diagnosis, as evidenced by the high misdiagnosis rate (67%, Table 3). Molecular diagnosis might serve as the gold standard in the diagnosis of GDD. We suggest that for diseases with fibro-osseous lesions, if no mutation is identified in *GNAS* and *SH3BP2*, mutations in *ANO5* should be screened.

*Anoctamin 5* (*ANO5*, Gene ID: 203859) encodes anoctamin 5 (ANO5), which is a protein of unknown function. The anoctamin family has ten members, all of which possess eight transmembrane regions.[19] ANO1 and ANO2 are $Ca^{2+}$-dependent $Cl^{-}$ channels, and ANO3, ANO4, ANO6, ANO7 and ANO10 are $Ca^{2+}$-dependent lipid scramblases.[20] Gyobu *et al.* reported that ANO5 possesses a segment that is homologous to the ANO6 scrambling domain. When this segment of ANO1 was replaced with the homologous ANO5 segment, the chimeric ANO1 protein gained the $Ca^{2+}$-dependent lipid scrambling function of ANO5.[21] Therefore, ANO5 may function as a $Ca^{2+}$-dependent lipid scramblase, but further evidence is needed to support this claim.

Although its function is unclear, mutations in *ANO5* have been reported to cause GDD and three muscle diseases (limb girdle muscular dystrophy (LGMD2L), Miyoshi-type distal myopathy (MM3) and asymptomatic hyperCKemia).[2, 22] To increase our understanding of the effects of *ANO5* mutations, we constructed a 3D model of the protein to identify differences between the structures of the wild-type and mutated proteins. The Cys356Phe mutation caused substantial changes to the structure and electrostatic characteristics of the extracellular region of the mutated protein. Even with a putative $Ca^{2+}$-dependent lipid scramblase domain, the mutated ANO5 protein might not be able to respond to the molecular signal that controls its activation. Our investigation of the distribution of *ANO5* mutations in individuals with bone diseases and muscle diseases led us to view the extracellular region of the ANO5 protein as being important to the onset of *ANO5*-associated bone diseases because most of the bone disease-associated mutations are located in or near the extracellular region of ANO5. However, we cannot yet explain why some of the mutations led to bone disease, while others led to muscle disease.

To investigate the function of the ANO5 protein *in vivo*, three research teams generated three different *ANO5*-knockout mouse lines. Gyobu *et al.* deleted exon 2 of *ANO5* and found that these $ANO5^{-/-}$ mice had no apparent skeletal muscle abnormalities. However, males showed impaired sperm motility and consequently reduced fertility.[21] Xu *et al.* disrupted exon 1 and approximately 1.6 kb of the region upstream of *ANO5*. These *ANO5*-knockout mice did not exhibit overt skeletal or cardiac muscle pathology.[23] Griffin *et al.* generated a gene trap between exons 8 and 9 of *ANO5*, and these *ANO5*-deficient mice displayed defective membrane fusion and repair abilities.[24] None of the three research groups reported whether the *ANO5*-knockout mice exhibited deformities in the jaw or

tubular bones. However, in our opinion, a knockout strategy is not sufficient to simulate a disease condition. We suggest that in the future, researchers should construct *ANO5*-knockin mice because different *ANO5* mutations produce different mutation effects in humans. An additional reason to include knock-in mice is that most reported mutations are missense mutations, with a possible a gain-of-function effect.

Surgery is the primary treatment for GDD. Subtotal mandibulectomy and bilateral partial maxillectomy can be used to remove the jawbone lesions.[6, 25] Extraction of the involved teeth, surgical revision of the site, and a graft of autologous bone can be helpful for the treatment of osteomyelitis of the jawbone.[26] The malignant transformation risk of GDD is unknown.[25] Recurrence of jawbone lesions has been reported in some patients, and the patients underwent secondary excisions of the lesions.[25] In a few cases, complications of GDD may lead to patient mortality.[6] In this study, subtotal mandibulectomy, followed by reconstruction of the mandible with a titanium plate and fibular grafting, was performed to the proband. The lesions did not recur one year after the surgery.

In summary, we investigated the genetic basis of a family with fibro-osseous lesions of the jawbones. The identification of a novel *ANO5* mutation, c.1067G>T (p.C356F), helped us diagnose the patients with GDD. This study also extended the clinical and pathological spectrum of GDD. In fact, GDD should be considered when diagnosing patients with fibro-osseous lesions in the jawbone.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgments

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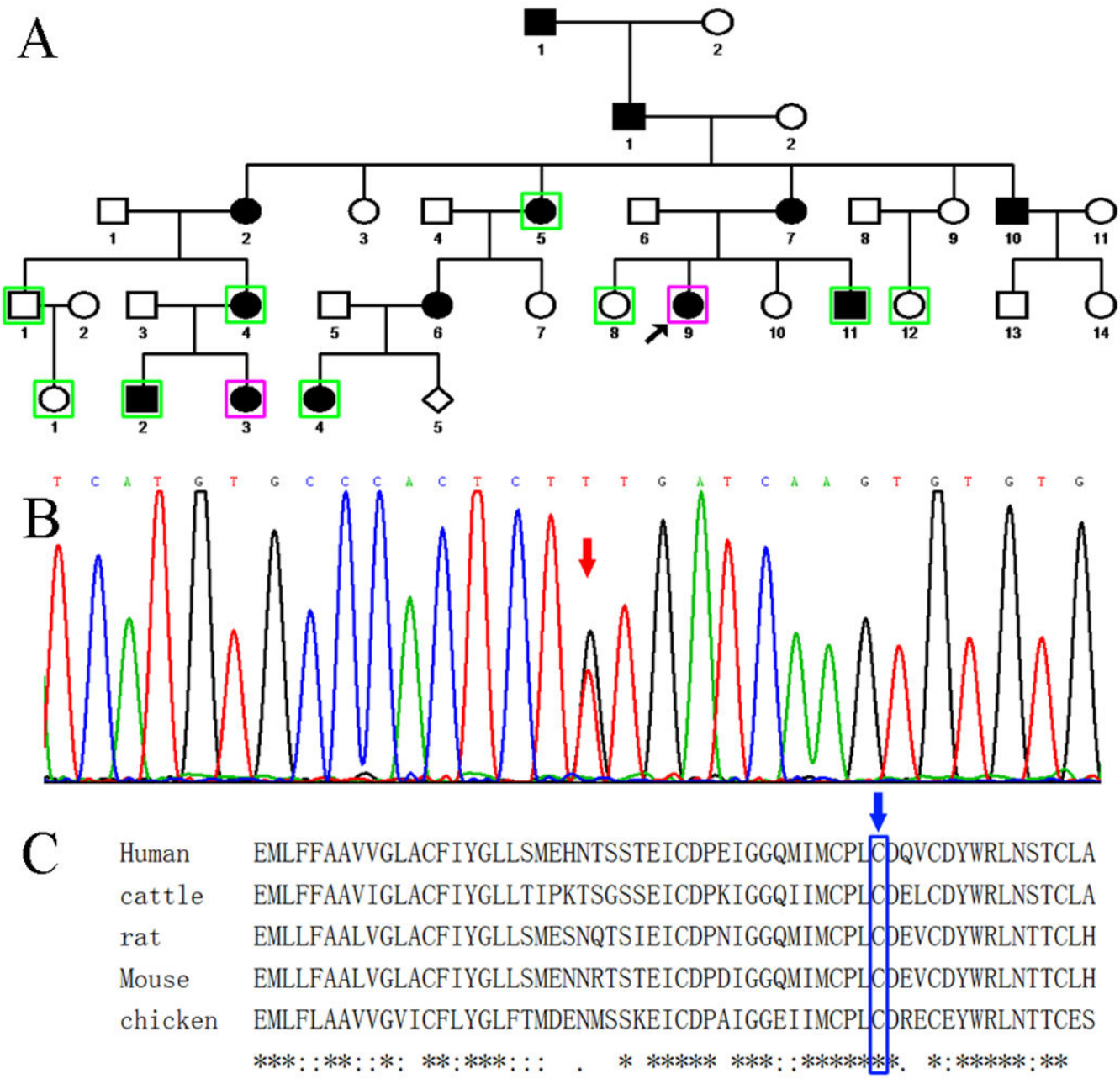


**Figure 1.**

(A) Pedigree of the family. The squares and circles filled in black indicate the subjects with gnathodiaphyseal dysplasia. The black arrow indicates the proband. The purple squares indicate the patients for whom whole-genome sequencing was performed. The green squares indicate the individuals who were submitted for mutation analysis using Sanger sequencing. (B) Partial sequence of the *ANO5* gene. The red arrow indicates the location of the c.1067G>T mutation. (C) Cross-species alignment of the amino acid sequence of ANO5. p.C356 (in the blue box) was conserved across the five tested species.

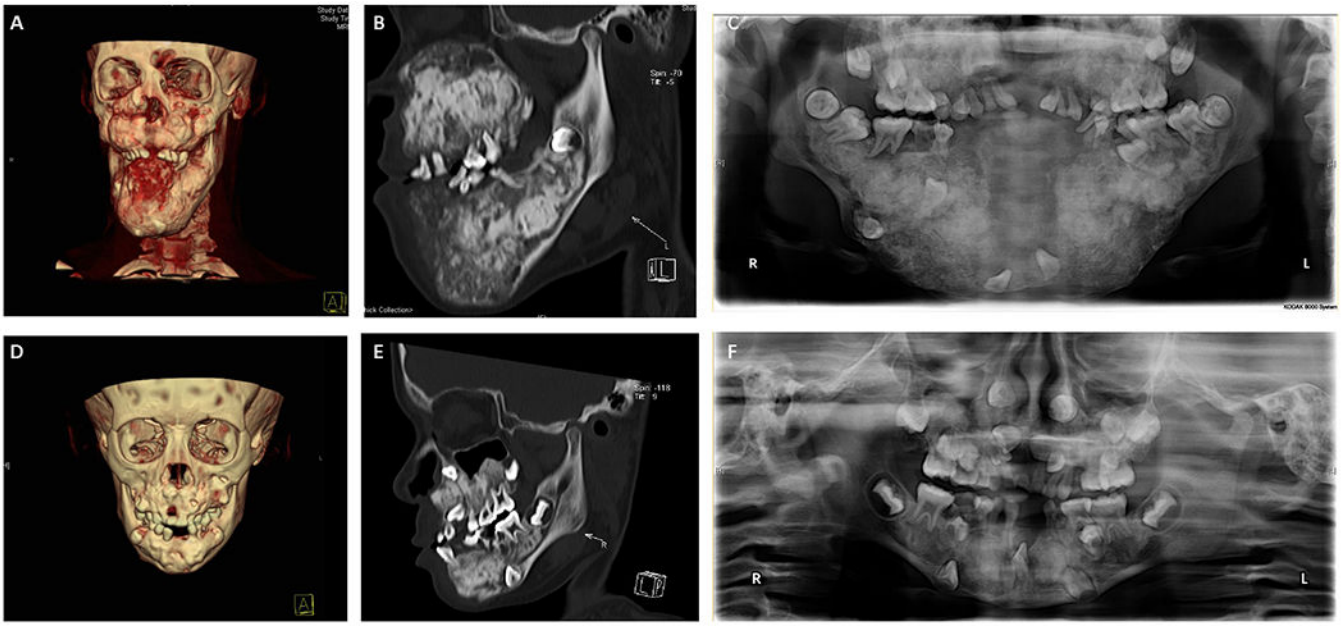


**Figure 2.**

Radiological images of patient IV:9 (A-C) and patient IV:11 (D-F). (A) CT reconstruction image showing a lesion involving the bilateral mandibular body and the entire maxilla. (B and C) CT sagittal section and panoramic radiograph showing that the lesion was composed of radiolucencies and radiopacities. The bony cortex was expanded and discontinuous. Some teeth were dislocated at the inferior margin of the mandible. The roots of the teeth were dysplastic or absent. (D-F) CT and panoramic radiographs reveal radiopacities in the maxilla and the anterior region of the mandible. Several teeth were dislocated at the nasal side of the maxillary sinus or at the inferior margin of the mandible.

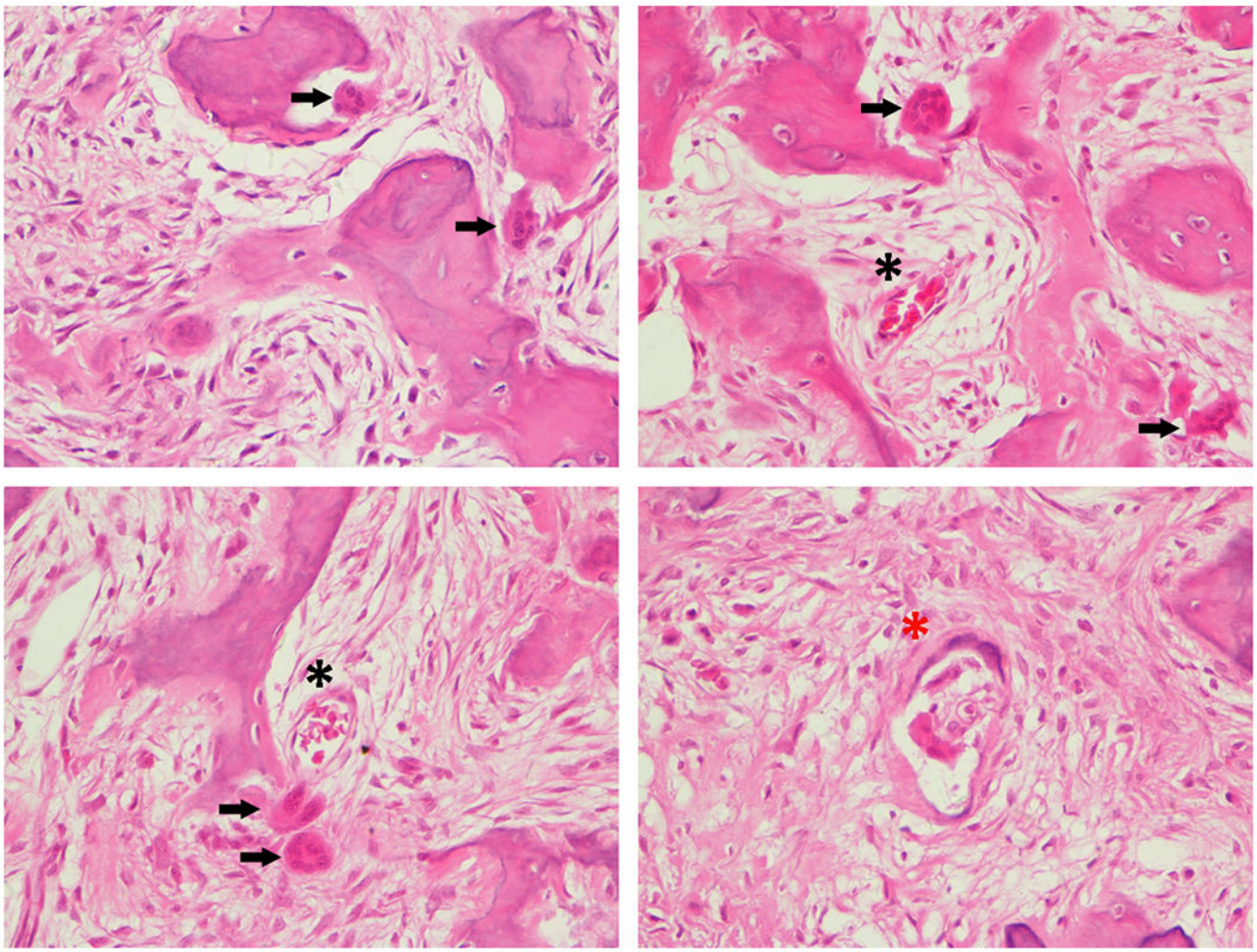

**Figure 3.**

Histological images of the jawbone lesions in patient IV:9. The lesion was composed of fibrous connective tissue, poorly newly formed bone trabeculae and multinucleated giant cells (black arrows). Most vessels (black *) were normal, except for a few vessel walls (red *) that showed aberrant calcification.

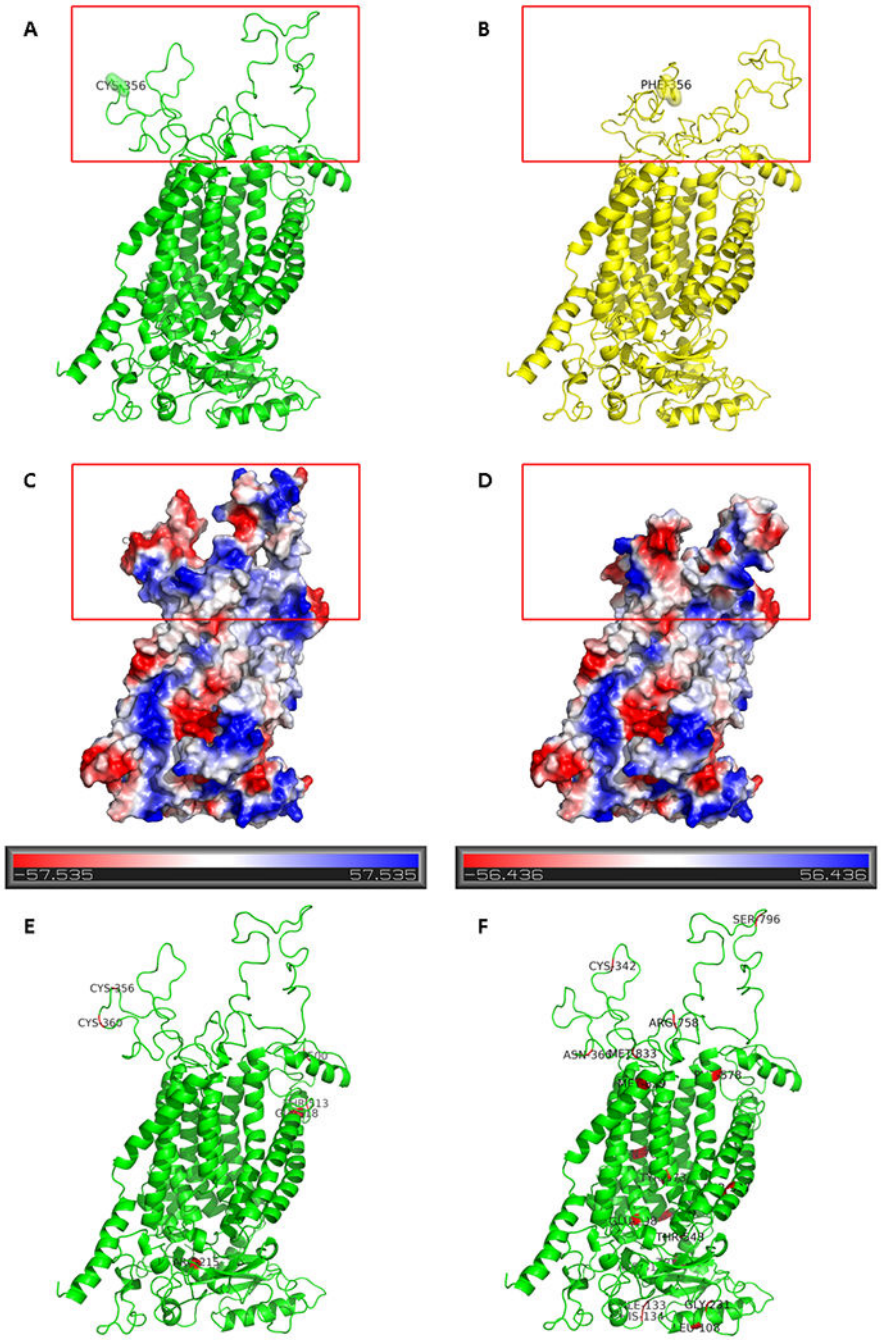


**Figure 4.**

Structural modeling of the wild-type and mutant ANO5 proteins. (A and B) Illustrations of the (A) wild-type ANO5 and (B) Cys356Phe-mutated ANO5. The Cys356Phe mutation resulted in substantial changes to the extracellular region of the mutated protein. (C and D) Surface electrostatic images of (C) wild-type ANO5 and (D) Cys356Phe-mutated ANO5. The mutation led to significant changes in the electrostatic characteristics of the extracellular region. (E) Bone disease-associated ANO5 mutations were predominantly located in or

near the extracellular region of the ANO5 protein. (F) Muscle disease-associated ANO5 mutations were located throughout the protein.

**Table 1.**

Clinical characteristics of seven affected members

| Patient | Age and gender | Mutation c.1067G>T | Features of jawbones | Fracture | long bone bowing | Treatment |
|---|---|---|---|---|---|---|
| III:5 | 59y, F | Yes | Radiolucent and radiopaque fibro-osseous lesions throughout the maxilla and the mandible body. The teeth were missing or impacted. | No | No | No |
| IV:4 | 36y, F | Yes | Radiolucent and radiopaque fibro-osseous lesions throughout the maxilla and the mandible body. Some teeth were missing. Some teeth were impacted in the nasal side of the maxillary sinus and the inferior margin of the mandible.. | No | No | No |
| IV:9 | 14y, F | Yes | Radiolucent and radiopaque fibro-osseous lesions throughout the maxilla and the mandible body. Some teeth were located at the inferior margin of mandible. The roots of the teeth were dysplastic or absent. | No | No | Subtotal mandibulectomy, reconstruction of the mandible with a titanium plate and fibular grafting |
| IV:11 | 7y, M | Yes | Radiopaque fibro-osseous lesions in the maxilla and the anterior region of the mandible. Several teeth were dislocated in the nasal side of the maxillary sinus and the inferior margin of the mandible. | No | No | Subtotal mandibulectomy, reconstruction of the mandible with a titanium plate and fibular grafting |
| V:2 | 13y, M | Yes | Radiolucent and radiopaque fibro-osseous lesions throughout the maxilla and the mandible body. Some teeth were dysplastic and located at the inferior margin of mandible. | No | No | Subtotal mandibulectomy, reconstruction of the mandible with a titanium plate |
| V:3 | 9y, F | Yes | Radiolucent and radiopaque fibro-osseous lesions in the maxilla and the anterior region of the mandible. Some teeth were dislocated in the nasal side of the maxillary sinus and the inferior margin of the mandible. | No | No | Subtotal mandibulectomy, reconstruction of the mandible with a titanium plate |
| V:4 | 5y, F | Yes | Radiolucent and radiopaque fibro-osseous lesions in the maxilla and the anterior region of the mandible. Several teeth were dislocated in the nasal side of the maxillary sinus and the inferior margin of the mandible. | No | No | Subtotal mandibulectomy, reconstruction of the mandible with a titanium plate and fibular grafting |

**Table 2.**

Filtering process and genetic analyses of WGS data

| Criteria | Number of remaining variants |
|---|---|
| Variations shared by IV:9 and V:3 | 2015140 |
| Exonic variations | 5716 |
| MAF[a] <0.01 in 1000 genomic and ESP[b] | 506 |
| Heterozygous variations | 401 |
| Variations predicted to be pathogenic by more than one prediction software[c] | 155 |
| MAF <0.01 in ExAC[d] | 44 |
| Co-segregation analysis | 2 |
| Critical bioinformatics and structural modeling analyses | c.1067G>T (p.C356F) in *ANO5* |

Notes:

[a] MAF: minor allele frequency

[b] ESP: Exome Sequencing Project

[c] prediction software packages: SIFT, PolyPhen 2, Mutation Taster and Mutation Assessor

[d] ExAC: Exome Aggregation Consortium.

**Table 3.**

67% of molecular testing confirmed GDD cases were initially misdiagnosed

| References | Gene | Mutations | Initial diagnose | Final diagnose |
|---|---|---|---|---|
| Tsutsumi et al. 2004 [1] | ANO5 | p.Cys356Arg | GDD | GDD |
| | ANO5 | p.Cys356Gly | GDD | GDD |
| Marconi et al. 2013 [2] | ANO5 | p.Thr513Ile | GDD | GDD |
| Vengoechea et al. 2015 [3] | ANO5 | p.Cys356Tyr | polyostotic fibrous dysplasia | GDD |
| Andreeva et al. 2016 [4] | ANO5 | p.Cys356Tyr | gigantiform cementoma | GDD |
| Duong et al. 2016 [5] | ANO5 | p.Cys356Tyr | GDD | GDD |
| Rolvien et al. 2017 [6] | ANO5 | p.Ser500Phe | suspected malignancy | GDD |
| Jin et al. 2017 [7] | ANO5 | p.Cys356Tyr | polyostotic fbrous dysplasia | GDD |
| | ANO5 | p.Cys360Tyr | cementoma | GDD |
| | ANO5 | p. Gly518Glu | osteopenia | GDD |
| | ANO5 | p.Arg215Gly | polyostotic fbrous dysplasia | GDD |
| This study | ANO5 | p. Cys356Phe | cherubism | GDD |

References:

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