# Gnathodiaphyseal dysplasia: Diagnostic clues from two fetal cases and literature review.

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Received: 5 February 2024 | Revised: 13 June 2024 | Accepted: 14 June 2024

DOI: 10.1002/pd.6631

REVIEW

PRENATAL DIAGNOSIS WILEY

# Gnathodiaphyseal dysplasia: Diagnostic clues from two fetal cases and literature review

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## Abstract

This article presents two fetal cases of gnathodiaphyseal dysplasia (GDD), a rare autosomal dominant disorder, and reviews the relevant literature. The cases involved two fetuses exhibiting bone bowing, which led to the diagnosis of GDD. Genetic testing revealed two de novo variants of the *ANO5* gene, confirming the diagnosis. A literature review was conducted to explore GDD's clinical and paraclinical presentation, diagnosis, and management. GDD is a rare but frequently inherited cause of bone fragility and jaw lesions characterized by a gain-of-function variant within the *ANO5* gene. Clinical manifestations range from recurrent dental infections with mild jaw lesions to severe bone fragility with several fractures associated with large jaw lesions requiring disfiguring surgeries. Diagnostic techniques depend on the context and include targeted genetic testing of *ANO5*, untargeted molecular analysis with whole-exome sequencing, or whole-genome sequencing. This case report highlights the importance of recognizing GDD as a novel cause of bone bowing and fractures during pregnancy. By summarizing the literature, this article contributes to healthcare professionals' knowledge and improves the recognition, diagnosis, and care of patients with GDD.

## Key points

**What is already known about this topic**

- Rare Skeletal Disorder: Gnathodiaphyseal dysplasia is a rare genetic condition linked to mutations in the *ANO5* gene characterized by bone fragility and jaw lesions.

**What does this study add**

- Fetal Case Discovery: This review highlights the pioneering diagnosis of the first two fetal cases, expanding the phenotypic spectrum.
- Literature Overview: Providing a literature review, this report synthesizes current knowledge, aiding healthcare professionals in accurate diagnosis and management strategies.

## 1 | INTRODUCTION

Gnathodiaphyseal dysplasia (GDD; OMIM #166260) is a rare autosomal dominant disorder that affects bone, jaw, and tooth development. GDD was first described in 1969 in a large Japanese family comprising 21 individuals with gnathodiaphyseal sclerosis.[1] It was renamed in 2001 as gnathodiaphyseal dysplasia, which is associated with fibro-osseous lesions of the jawbones, bone fragility, and long bone bowing.[2] However, the responsible gene remained unknown until 2004 when linkage analysis and recombination mapping permitted the localization of the *GDD1* (also named *TMEM16*E or *ANO5*) gene on chromosome 11p14.3.[3,4] *ANO5* is involved in bone and muscle functions and is highly expressed in growth plate chondrocytes and muscle cells.[5] Variants implicated in this disorder are considered to be gain-of-function,[6,7] whereas pathogenic biallelic loss-of-function variants of this gene are known to be involved in recessive myopathy with various presentations, such as limb-girdle muscular dystrophy, Miyoshi's muscular dystrophy, metabolic myopathy-like, and asymptomatic hypercalcemia. To date, only one patient has been described with an overlapping phenotype of GDD and a muscular disorder.[8]

Clinically, GDD is characterized by bone fragility and diaphyseal cortical sclerosis. This leads to multiple fractures during childhood, long bone bowing, and cemento-osseous lesions of the jawbones responsible for tooth anomalies and facial deformities. Other findings include generalized osteopenia, recurrent osteomyelitis, and elevated alkaline phosphatase levels. Onset typically occurs during childhood or adolescence with recurrent fractures, which decrease in frequency with age, and is followed by the development of a progressively growing benign tumor of the maxilla, mandible, or both, which usually requires a debulking procedure.

Currently, there is no cure for GDD, and management of the disorder is focused on symptom relief and prevention of complications, such as surgical procedures, dental care, or sometimes the use of bisphosphonate therapy.

Here, we report the first two cases of prenatally diagnosed GDD and review the literature to provide a comprehensive overview of the current knowledge on GDD, including its prenatal and postnatal clinical features, genetic basis, pathophysiology, diagnosis, and treatment options.

## 2 | METHODS

Legal guardians provided written informed consent to participate on behalf of the fetus and for themselves. The two French cases were retrieved through a collaboration between the University Hospital of Lille and the Necker University Hospital of Paris.

The literature review was done on PubMed using « gnathodiaphyseal dysplasia » as the search term for all published data up to December 2023. All articles were manually reviewed, and all clinical and molecular information was extracted.

Ethical approval was not required in accordance with the institutional guidelines and retrospective nature of this study.

## 3 | RESULTS

### 3.1 | Case histories and review of the literature:

#### 3.1.1 | Family 1

The first case involved a female fetus of a non-consanguineous couple. It was their second pregnancy; their first child was noted to have a short femoral length (<1st percentile at 32 weeks of gestational age (GA)) and growth retardation (height was 42 cm (<1st percentile) at birth). There was no family history of bone disease.

Our patient presented with short, bowed, long bones[9] and low estimated fetal weight (380 g, <1st percentile) with preserved head and abdominal circumference (50th percentile) at 22 + 6 weeks of GA (Table 1). The chest circumference was normal. There were no other signs on ultrasound examination.

The array comparative genomic hybridization was normal. Fetal osseous computed tomography (CT) performed at 27 + 6 weeks GA showed homogeneous and normal osseous mineralization, absence of fractures, and non-ossified cranial sutures. The long bones were short and stocky, particularly the femoral bones. Excluding the humerus and fibula, all the tubular bones were bowed. The chest circumference and morphology were normal. No other morphological anomalies were observed (Figure 1).

Trio-based prenatal exome sequencing was then performed and showed a de novo (PS2) heterozygous variant of *ANO5* (NM_213599): c.1533_1535dup; p. (Gln_Ile512insMet). This variant is absent from population (GnomAD, PM2) and patient (ClinVar)

**TABLE 1** Measurements of long bone average values at 22 weeks gestational age (GA).

| | Fetus 1 | 50th percentile at 22 w. of GA (mm)[a] |
|---|---|---|
| Femoral length (mm) | 27.5 (<1st percentile) | 37.6 |
| Humerus length (mm) | 31.3 (<3rd percentile) | 36.3 |
| Radius length (mm) | 21.2 (<1st percentile) | 30.9 |
| Ulna length (mm) | 23.1 (<1st percentile) | 31 |

[a]Data are taken from Chitty LS, 2003(9).

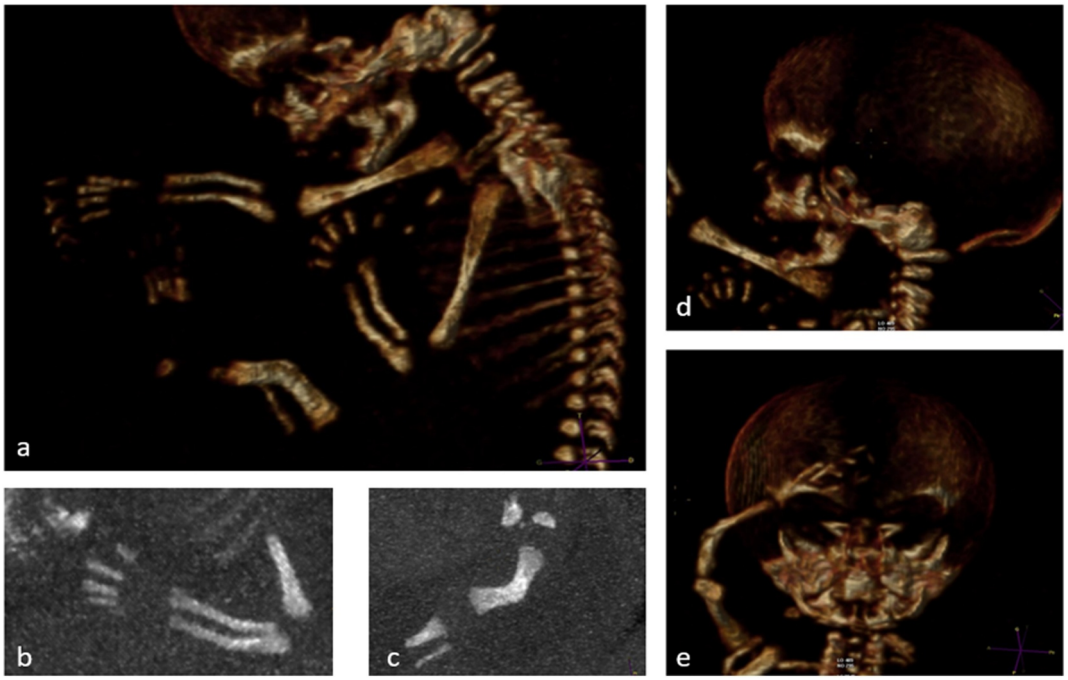


**FIGURE 1** Prenatal osseous tomodensitometry of the proband of Family 1. (A, D, and E) 3-dimensional reconstruction showing bowing of multiple tubular bones, short and stocky femoral bones without abnormalities of the face and the cranium. (B) Bowed bones of the forearm. (C) Bowed, short, and stocky femur. [Colour figure can be viewed at wileyonlinelibrary.com]

databases and results in an in-frame duplication of 3 bp (PM4), which leads to the insertion of methionine at the junction between the 2nd extracellular loop and the 4th transmembrane domain. Sanger sequencing retrieved this variant in the fetus but not in his parents. According to the American College of Medical Genetics (ACMG) guidelines, this variant was classified as probably pathogenic (class 4, PS2 + PM2 + PM4).

Considering this result and the potential severe prognosis, the couple asked for a medical termination of pregnancy, which was performed at 33 weeks of GA. A fetal autopsy showed multiple diaphyseal fractures of the long bones: the right femur, tibia, fibula, bilateral ulna, radius, and humerus, as well as the ribs, right temporal bone, clavicle, and scapula. Some fractures were recent, whereas others were older, with osseous-cartilaginous calluses. No osseous lesions of the jaw were found, but the inferior gingiva was thickened and irregular on an intraoral radiodense radiograph (Figure 2). Microscopic examination revealed diaphyseal cortical sclerosis in the femur and decreased density of the bony tracts (Figure 3).

### 3.1.2 | Family 2

The second case involved the male fetus of a non-consanguineous couple. This was the couple's second pregnancy. The first pregnancy was normal. There was no family history of bone disease.

An ultrasound examination at 12 weeks GA showed marked bowing of both femoral bones. Further ultrasound examination at 16 weeks GA confirmed this anomaly, with shortened femurs and voluminous cysts of the choroidal plexus. No other anomalies were observed.

A diagnosis of constitutional osseous disease was suspected, and the couple asked for medical termination of the pregnancy at 17 weeks GA. A fetal autopsy was performed and showed irregular lower limbs with bowed femoral bones measured at 16.4 and 18.3 mm (the 50th percentile corresponds to 23.3 mm at this GA), a malposed left foot in varus, there were no fractures or jaw lesions, but the vertebral bodies were thin and short. Other bone lengths were within the normal range for GA (corresponding to a GA of 17 weeks).

Genetic analysis of a panel of genes implicated in osseous fragility and osteochondrodysplasia revealed a heterozygous de novo (PS2) variant of *ANO5* (NM_213599): c.1475C > T; p. (Ala492Val). This variant is absent from population (GnomAD (PM2)) and patient (ClinVar) databases and is predicted to be pathogenic by several prediction scores (SIFT, PolyPhen2, Mutation Taster (PP3)). It was not found in either parent. According to the ACMG guidelines, this variant was probably classified as pathogenic (class 4, PS2 + PM2 + PP3).

## 3.2 | Literature

To date, including our cases, 108 individuals from 25 families have been clinically diagnosed with GDD. Among these, 67 cases from 21 families were confirmed by molecular analyses. All clinical and paraclinical signs and surgical histories of these 67 patients were studied (Supplementary Table S1). Some data were lacking and considered absent; therefore, some studied features could be underestimated.

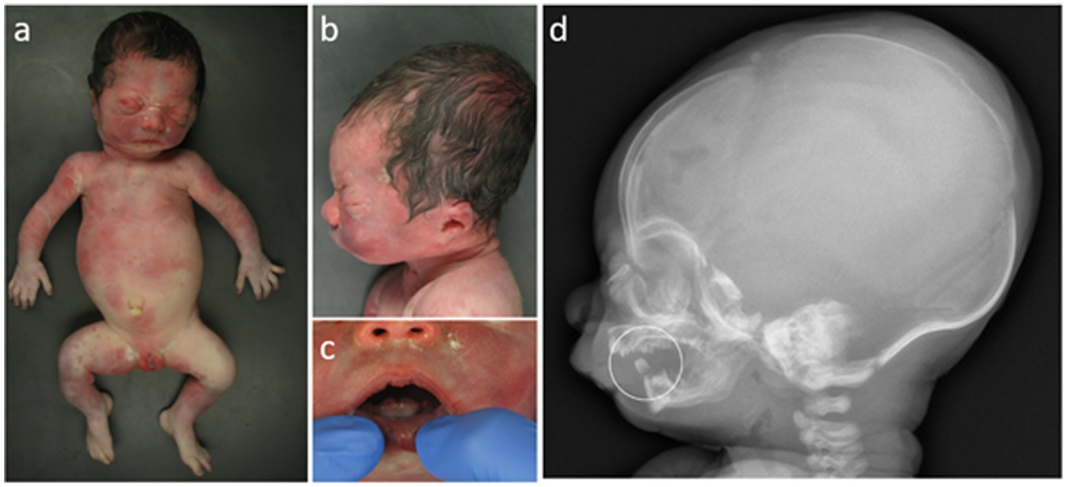


**FIGURE 2** Fetopathologic and radiological examination of the proband of Family 1 (31 weeks of gestation). (A) Fetus with long bone bowing; (B) profile appearance; (C) thickened and irregular inferior gingiva; (D) profile X-ray view of the head of the fetus showing an intraoral radiodense lesion (circle). [Colour figure can be viewed at wileyonlinelibrary.com]

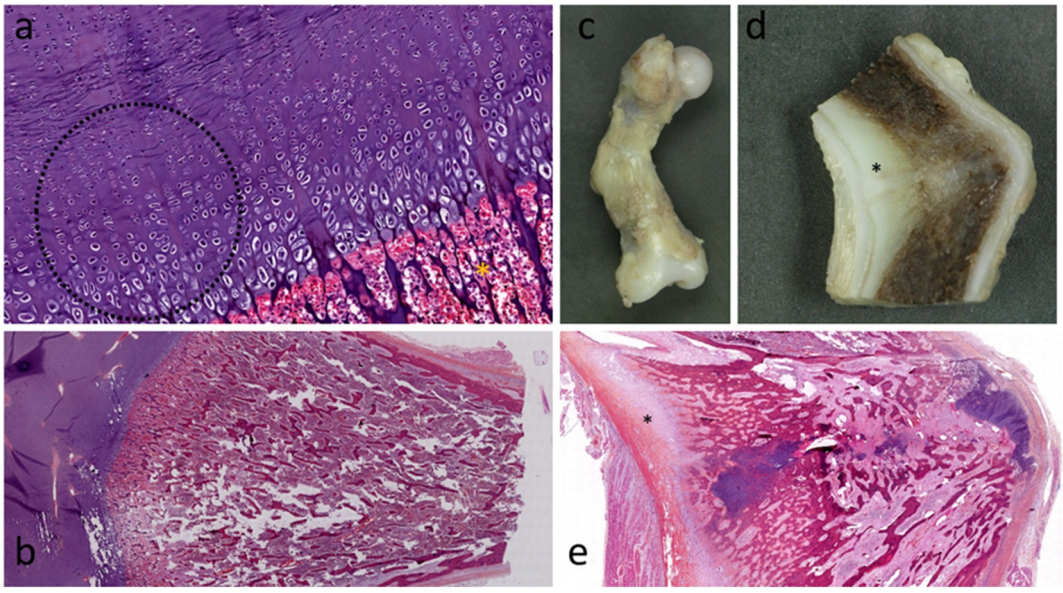


**FIGURE 3** Macroscopic and microscopic examination of the femur. (A) Metaphyseal growth plate with reduced size of pre-hypertrophic and hypertrophic zones (circle) and thin primary bone trabeculae (*); (B) slice showing low bone density; (C) femur with deformity of the greater trochanter and diaphyseal angulation; (D) focus on angulation showing diaphyseal cortical thickening (*); (E) microscopic view of (D), showing cortical sclerosis with zone of fibrosis (*) and cartilage islets (blue). [Colour figure can be viewed at wileyonlinelibrary.com]

Of all the families published to date, only one report described a case that presented prenatally with bowing of the long bones and multiple fractures identified on ultrasonography examination with normal fetal growth. That case was later molecularly diagnosed in childhood.[10] In the two cases reported herein, bowing of the long bones was the presenting feature making bowing of the long bones the recurrent prenatal sign (Table 2).

Concerning the postnatal features, there were multiple findings for the long bones. Fractures were the most frequent, occurring in

**TABLE 2** Prenatal features of gnathodiaphyseal dysplasia (GDD): Literature review and study findings.

| | Bowing | Fractures |
|---|---|---|
| Herman TE, 2014 | Yes | Yes |
| Fetus 1 | Yes | No |
| Fetus 2 | Yes | No |
| Total | 100% | 33% |

45% (30/67) of the patients, and most of these occurred during childhood, with an onset ranging from the prenatal period[10] to 42 years of age.[11] Long bones were the most commonly involved, but any bone could be affected.[8,12–14] Bone bowing was observed in 19% of the individuals (13/67), and diaphyseal thickening was observed in 16% (11/67). Generalized osteopenia was the least frequent sign in 10% (7/67) of the patients. Among those with osteopenia, 71% (5/7) had 25-OH vitamin D deficiency.

Jaw lesions were observed in approximately 67% (45/67) of the patients, most requiring at least one surgery in the following years. Mandibular fractures also occurred with jaw lesions.[11]

The frequency of tooth anomalies was 48% (32/67), including recurrent infections and displaced, impacted, or missing teeth, and anomalies were present only in individuals with jaw lesions (diagnosed or not).

One family was reported to have both muscular and skeletal phenotypes associated with the p. (Thr513Ile) variant.[8] Another individual from a different family was reported to have elevated creatine phosphokinase (CPK) levels with the same previously cited variant.[12] Families with the p. (Cys356Phe) and p. (Leu370_Ala371insDYWRLNSTCL) variants do not display any fractures.[15,16] All patients with a very severe phenotype or early disease onset had a de novo, not previously reported variant (5/67). Some positions seemed to be hotspots for variants, such as Cys356 or Cys360.

## 4 | DISCUSSION

Herein, we report two fetal cases molecularly diagnosed with GDD, expanding our knowledge of this disease during the prenatal period. The major radiological sign of this disease is the bowing of the long bones, which can be suspected early in the pregnancy. Fractures have already been described during pregnancy in another severe case,[10] and this could be another major prenatal sign. Typical jaw lesions have not been described prenatally; however, a thickened and irregular gingiva with a radiodense intraoral lesion in one fetus could potentially represent the primary lesion. With prenatal bowing and fractures, a diagnosis of Osteogenesis Imperfecta (OMIM #166200, OI) may be considered, as well as other rare bone diseases such as Stuve-Wiedemann syndrome (OMIM#601559, STWS). Arguments for these rare diseases should be explored with a reference ultrasound looking for extraskeletal features (for example, cleft palate or micrognathia in campomelic dysplasia, OMIM#114290, and kyphomelic dysplasia, OMIM#211350). A fetal osseous CT should be performed to look for other bone features (e.g., round epiphyses in cartilage hair hypoplasia, OMIM#250250),[17] to refine the diagnosis and mainly evaluate the severity and prognosis of this condition. In parallel, extensive genetic analysis, such as exome or genome sequencing or a large gene panel for osseous diseases, should also be considered for diagnosis and to assess the potential severity of the disease.

GDD is caused by variants localized in a few exons,[7,11,15,16] particularly in regions that encode the cytoplasmic or extracellular domains of *ANO5* (Figure 4). Cysteine residues 356 and 360 are the most frequent variant sites for GDD. There are six other cysteine residues (342, 353, 369, 601, 606, and 804) which are also important for protein folding via intrachain cysteine bonding.[13] These other cysteine residues have not been implicated in human disease.

Among all the molecularly confirmed cases of GDD, de novo variants appear to be associated with a more severe phenotype and earlier onset, while familial variants generally exhibit less phenotypic variability but vary in age of onset, ranging from childhood to adulthood. Interestingly, some variants seem to be correlated with a specific phenotype. The absence of fractures was observed in only two families, the first one with the p. (Leu370_Ala371insDYWRLNSTCL)[16] variant, and the other one with the p. (Cys356Phe)[15] variant. This included a total of 11 individuals who primarily exhibited jaw lesions.

The p.(Thr513Ile) variant is a recurrent variant that was first reported in a family with elevated CPK in one patient but without muscular symptoms,[12] followed by some members of a family with a mixed skeletal and muscular phenotype with a non-classical *ANO5*-related myopathy.[8] Indeed, whereas heterozygous gain-of-function variants of *ANO5* are associated with GDD,[7] biallelic loss-of-function variants are associated with a myopathic spectrum, including limb–girdle muscular dystrophy type R12 (LGMDR12, or formerly known as LGMD2L), Miyoshi distal myopathy type 3 (MMD3), asymptomatic hyperCKemia, and a metabolic myopathy-like (pseudometabolic) phenotype (myalgia or exercise intolerance with or without rhabdomyolysis).[18] Investigations of this variant are needed to explain this phenotype and expand our knowledge of the molecular functions of *ANO5*.

To conclude, GDD is a rare autosomal dominant disorder affecting all life stages. Typically appearing in childhood, it presents with multiple non-traumatic long bone fractures and bowing, even during pregnancy. This condition is characterized by diaphyseal thickening, undertrabeculation, and generalized osteopenia, rendering the bones fragile.[19] Swelling of the jawbones, observed from infancy to adulthood, is prominent. Radiologically, lesions manifest as multiple amorphous, well-defined areas of mixed radiodensity surrounded by a radiolucent halo, predominantly in the tooth-bearing areas of the maxilla and mandible.[19] These lesions require surgical intervention because of their progressive nature and are often composed of fibrous tissue with fibromas and psammomatoid bodies.[13] Dental anomalies and facial dysmorphia can arise from jaw lesions. Bone fragility and fractures should be managed similarly to Osteogenesis Imperfecta.[20,21] Jaw lesions do not seem to be associated with malignancy, and considering their risk of recurrence, we recommend surgery only for a functional problem or aesthetics. GDD is usually inherited from a symptomatic parent, and it is important to provide genetic counseling regarding the disease before pregnancy. The variant has a 50% chance of transmission during each pregnancy. Symptoms can be very severe, even fatal,[13] penetrance is complete with age, and prenatal manifestations are uncommon; therefore, prenatal and pre-implantation diagnosis and medical termination of pregnancy should be

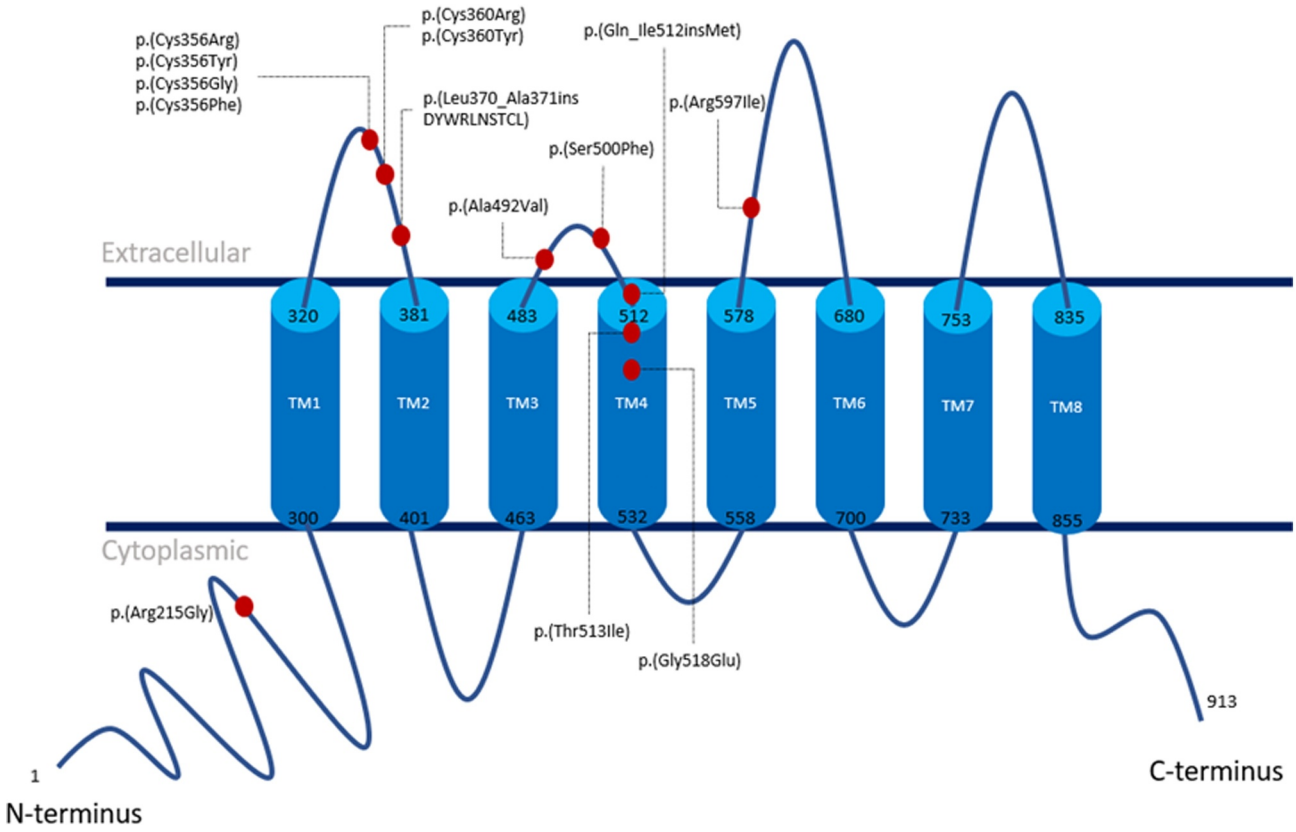


**FIGURE 4** Schematic representation of the ANO5 protein with the relative position of all the variants described as causing gnathodiaphyseal dysplasia (GDD). ANO5 protein is composed of 913 amino acids. Each transmembrane junction is annotated with its corresponding amino acid position. Red dots are the relative position of the GDD-causing variant. [Colour figure can be viewed at wileyonlinelibrary.com]

mentioned to couples. In cases in which the couple requests none of these, pregnancy should be followed with regular monitoring, with particular attention paid to fetal bones (bowing, fractures). If the mother has GDD, and as we do not have any data on these cases, we propose following the recommendations for Osteogenesis Imperfecta: management of pain, vitamin D and calcium supplementation, and discussion of cesarean section according to the severity of the disease in both mother and/or infant.

## ACKNOWLEDGMENTS

We thank the families that participated in this study. This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

## CONFLICT OF INTEREST STATEMENT

All authors have no conflicts of interest.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author.

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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

**How to cite this article:** Cuvelier V, Trost D, Stichelbout M, et al. Gnathodiaphyseal dysplasia: diagnostic clues from two fetal cases and literature review. *Prenat Diagn*. 2024;44(9):1098-1104. https://doi.org/10.1002/pd.6631