2024 ANNUAL CONFERENCE PESTOLA
PEDIATRIC ENDOCRINE SOCIETY OF TEXAS, OKLAHOMA, LOUISIANA, AND ARKANSAS
SAVE THE DATE | APRIL 5-7, 2024
SAN ANTONIO, TEXAS

An Unusual Case of Brittle Bone Disease

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Introduction

We present the case of a now 21-month-old F with prenatally suspected skeletal dysplasia; subsequent evaluation revealed concern for a form of brittle bone disease that has not been previously described.

Case Presentation

The patient was delivered at an outside facility at 37.0 weeks gestational age via C-section for breech presentation and prenatal concerns for a possible skeletal dysplasia. Family history was negative for skeletal disorders or significant fractures. A skeletal survey done on day-of-life 2 noted generalized demineralization of her bones, shortening/bowing of the long bones, an acute right proximal ulnar fracture, and evidence of multiple discontinuous healed rib fractures. A repeat skeletal survey done at day-of-life 19 demonstrated worsening skeletal findings with a very poorly mineralized skull, shortening of the clavicles and extremities, progressive fractures in all extremities and further bowing of the limbs, progressive rib fractures with callus formation, and multiple vertebral bodies with stature loss concerning for compression fractures. Directed genetic testing for osteogenesis imperfecta was negative, so whole exome sequencing was pursued and identified variants of unknown significance in the *KAT6B* and *WDR35* genes not previously described, noting that the patient was heterozygous for both. She was suspected to be a carrier for the *WDR35* mutation as it is inherited in an autosomal recessive fashion, and parental genetic testing revealed that the patient's father carried the same *KAT6B* mutation and was phenotypically normal. Mutations in these genes have been described in disorders associated with bone abnormalities (such as genitopatellar syndrome and craniectodermal dysplasia 2)[1,2], but with different clinical presentations.

Results and Figures

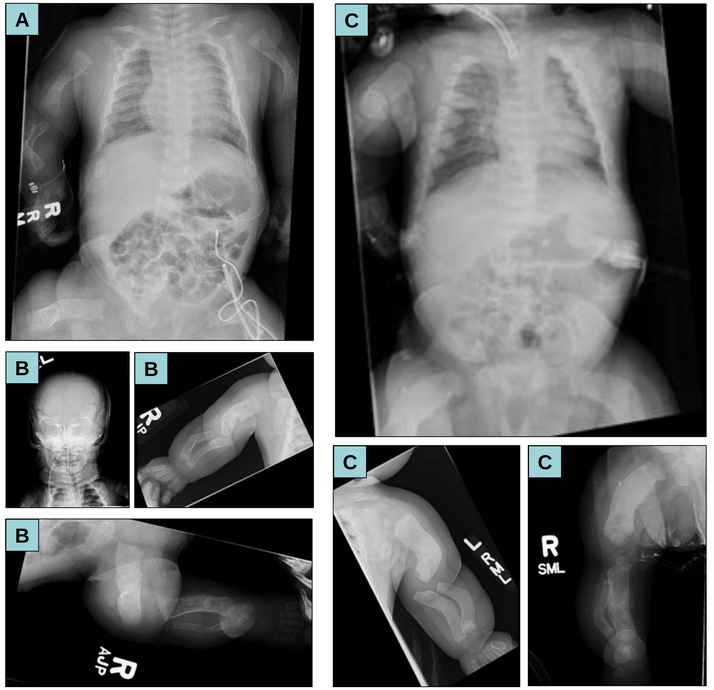
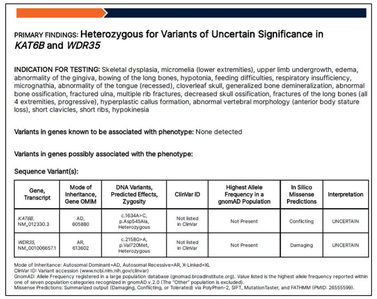


Figure 1: Radiographic Findings at Diagnosis and During Treatment.

A) Imaging done as part of skeletal survey completed on day-of-life 2. Skeletal survey demonstrated generalized demineralization of the osseous structures. Essentially no skull ossification was noted and numerous intrasutural bones were identified. There was additional shortening and bowing of the long bones of the extremities with a crumpled appearance, acute fracture of the right ulna, and other areas suspicious for more subtle acute fractures. The ribs were noted to be shortened and wavy, suggestive of healing fractures. Vertebral bodies were normal.
B) Selected radiographs from repeat skeletal survey on day-of-life 19. Imaging again demonstrated poor mineralization of the skull. There was evidence of progressive fractures of all extremities and worsening bowing of the long bones and callus formation. She was noted to have progressive rib fractures as well and new anterior vertebral body height loss in the lower thoracic and upper lumbar spine.
C) Selected radiographs from repeat skeletal survey at 3.5 months of age. Continued generalized demineralization of the bones. Vertebra noted to have flattening. Continued evidence of extensive healing rib fractures bilaterally. It was reported that the persistent bowing of the bilateral femurs and humeri were consistent with extensive healing fractures.
D) Chest and abdominal imaging obtained during an admission for respiratory distress at 16 months of age, ultimately diagnosed with tracheitis and COVID infection.



PRIMARY FINDINGS: **Heterozygous for Variants of Uncertain Significance in *KAT6B* and *WDR35***

INDICATION FOR TESTING: Skeletal dysplasia, micromelia (lower extremities), upper limb undergrowth, edema, abnormality of the gingiva, bowing of the long bones, hypotonia, feeding difficulties, respiratory insufficiency, micrognathia, abnormality of the tongue (recessed), cloverleaf skull, generalized bone demineralization, abnormal bone ossification, fractured ulna, multiple rib fractures, decreased skull ossification, fractures of the long bones (all 4 extremities, progressive), hyperplastic callus formation, abnormal vertebral morphology (anterior body stature loss), short clavicles, short ribs, hypokinesia

Variants in genes known to be associated with phenotype: None detected

Variants in genes possibly associated with the phenotype:

Sequence Variant(s):

Gene, Transcript	Mode of Inheritance, Gene OMIM	DNA Variants, Predicted Effects, Zygosity	ClinVar ID	Highest Allele Frequency in a gnomAD Population	In Silico Missense Predictions	Interpretation
KAT6B, NM_012330.3	AD, 605880	c.1634A>C, p.Asp545Ala, Heterozygous	Not listed in ClinVar	Not Present	Conflicting	UNCERTAIN
WDR35, NM_001006673	AR, 613602	c.2758G>A, p.Val720Met, Heterozygous	Not listed in ClinVar	Not Present	Damaging	UNCERTAIN

Mode of Inheritance: Autosomal Dominant=AD, Autosomal Recessive=AR, X-Linked=XL
ClinVar ID: Variant accession (www.ncbi.nlm.nih.gov/clinvar)
GnomAD: Allele Frequency registered in a large population database (gnomad.broadinstitute.org). Value listed is the highest allele frequency reported within one of seven population categories recognized in gnomAD v 2.0 (The "Other" population is excluded).
Missense Predictions: Summarized output (Damaging, Conflicting, or Tolerated) via PolyPhen-2, SIFT, MutationTaster, and FATHMM (PMID: 26555590).

Figure 2: Whole Exome Sequencing Results.

Table 1: General Serum Lab Trends

Serum Lab	Range of Values (July 2022-August 2023)
Total Calcium	8.3-10.8 mg/dL (ref. 8.0-11.0 mg/dL)
Ionized Calcium	0.86-1.42 mmol/L (ref. 1.12-1.32 mmol/L)
Phosphorus	2.7-6.1 mg/dL (ref. 3.8-6.5 mg/dL)*
Albumin	3.0-4.0 g/dL (ref. 3.5-4.8 g/dL)
Magnesium	1.5-3.5 mg/dL (ref. 1.7-2.7 mg/dL)
PTH	12.7-16.1 pg/mL (ref. 10.0-65.0 pg/mL)**

*excluded single occurrences of outlying values of 7.6mg/dL and 8.1mg/dL
**obtained with concurrent normal total and ionized calcium

Table 2: Evaluation of Hypophosphatemia

Lab Test	Value
Serum Phosphorus	3.1 mg/dL
Serum Creatinine	0.16 mg/dL
Urine Phosphorus	59.4 mg/dL
Urine Creatinine	5.30 mg/dL
Fractional Excretion of Phosphate	57.9%
Intact FGF23	93pg/mL (ref. ≤52 pg/mL)
Concurrent Medications (at time of above labs)	Pediatric multivitamin with iron 1mL daily Sodium phosphate 7.5 mmol q6 hours (~155 mg/kg/day)
Most Recent Medications (resulting in stable phosphorus levels)	Pediatric multivitamin with iron 1mL daily Sodium phosphate 6mmol q6 hours (~126 mg/kg/day) Calcitriol 0.5 mcg qAM and 0.25 mcg qPM

During her NICU stay she developed respiratory failure and ventilator dependence, so ultimately underwent tracheostomy and G-tube placement before transfer to our facility for inpatient rehabilitation. She received treatment with bisphosphonates, initially with two infusions of pamidronate before transitioning to zolendronate infusions approximately every three months. During her course, she was also identified to have hypophosphatemia shortly after birth and concerns for phosphate wasting; she was noted to have a high fractional excretion of phosphate in the setting of low serum phosphorus despite enteral phosphorus supplementation. She additionally was found to have an elevated FGF23 level at the same time the suspected renal phosphate wasting was identified. Her total calcium remained normal with normal PTH values; her 25-OH vitamin D has also been normal. She has subsequently been successfully managed on sodium phosphate and calcitriol supplementation, as well as regular zolendronate infusions, without recurrence of fractures, and clinically experienced improvements in her respiratory status and overall development.

Conclusion

This patient illustrates a severe case of brittle bone disease that presently does not have a clear etiology, though could represent a novel genetic mutation that has not been described and could subsequently be identified with continued review of her genetic testing in the future. Reporting her case could be beneficial to other patients with similar skeletal disease in helping to identify an underlying cause.

References

1. Zhang LX, Lemire G, Gonzaga-Jauregui C, et al. Further delineation of the clinical spectrum of KAT6B disorders and allelic series of pathogenic variants. *Genet Med*. 2020;22(8):1338-1347.
2. O'Neill MJF, and Kniffin, CL. Craniectodermal dysplasia 2; CED2. OMIM. Available at https://www.omim.org/entry/613610?search=613610&highlight=613610. Accessed February 2, 2024.