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A novel p.Gly775Glu missense *COL1A2* mutation causes severe osteogenesis imperfecta in a prepubertal girl.

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Background

Osteogenesis imperfecta (OI) due to *COL1A1* and *COL1A2* mutations is the most common cause of primary osteoporosis.

Case presentation

We present a 10-year-old girl with a history of skeletal fragility, starting in the perinatal period.

Family & Perinatal History

- Patient was the the first offspring of two healthy non-consanguineous parents.
- No family history of early osteoporosis was retrieved.
- She was delivered full term with caesarean section in excellent condition.
- Birth anthropometry was symmetrical for gestational age with birth weight 2630 gr (Z-score: -1.4), length 48 cm (Z-score: -0.62) and head circumference 32 cm (Z-score: -1.59).

Personal History

- The first sign of skeletal fragility was apparent at the age of 7days when she presented with a left femoral fracture.
- At one year of age, four more fragility fractures of her long bones had been recorded.
- Up to now, she has sustained nineteen low-energy, long bone fractures in total.

Physical Examination

- On examination, blue sclerae & grey teeth were noted.
- Cardiac function, renal function and hearing were normal.
- She presented
  - normal auxology in all anthropometric parameters
  - normal achievement of developmental milestones.
- Gradually, multiple fractures resulted in significant skeletal deformities including
  - leg length discrepancy,
  - genu varum,
  - scoliosis.

Investigations

- During infancy, a full diagnostic investigation for secondary osteoporosis (inborn errors of metabolism, hematological and endocrine disorders) did not reveal any pathology.
- Baseline bone mineral density at the age of 2.5 years was low (Z-score L2-L4= -3.4).
- Initial *COL1A1/COL1A2* Sanger sequence analysis was reported as negative.
- At the age of 4 years, IV pamidronate (0.5 mg/kg x 3 days, every 2 months, annual dose: 9 mg/kg/year) was initiated.
- Bone mineral density was normalized during bisphosphonate treatment.

Orthopaedic management

- Her orthopaedic management has been challenging, including right tibial osteotomies.
- While on IV pamidronate right tibial pseudarthrosis (figures 1, 2) was diagnosed and two Ilizarov's procedures were performed.
- Additionally, she underwent femoral fractures treatment with flexible intramedullar nails and double open osteotomies of bowed femoral bones with expandable Duvet Fassier nails (figure 3).
- Currently she is on a weight bearing procedure after the union of her femoral osteotomies.

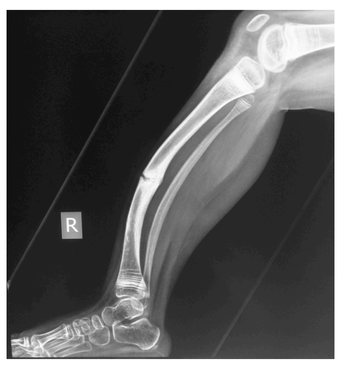

Figure 1

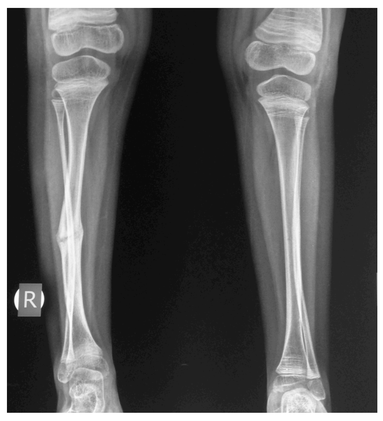

Figure 2

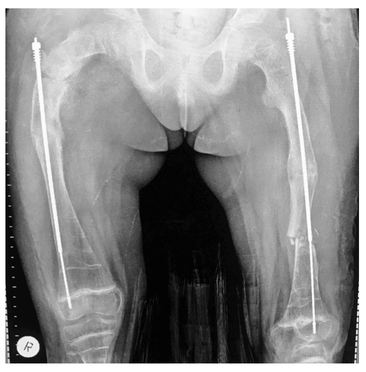

Figure 3

Figure 1, 2. Right tibial pseudarthrosis. Figure 3. Femoral fractures treatment with expandable Duvet Fassier nails

Methods

- Whole-genome sequencing was performed on the index patient, healthy parents and her brother to identify the genetic cause of the disease.

Results

- A novel missense mutation in exon 38 of *COL1A2*, NM_000089.3: **c.2324G>A (p.Gly775Glu)** was revealed in whole-genome sequencing analysis and confirmed by Sanger sequencing (figure 4).

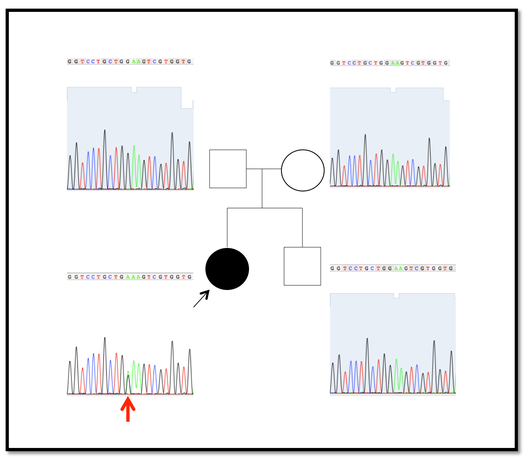

Figure 4. Sanger sequencing validation of the 2324G>A (p.Gly775Glu) mutation in exon 38 of COL1A2 in index and family members

Conclusion

- This case provides more insight into the molecular background of OI and the association between genotype-phenotype of the disease.
- The possibility of pseudarthrosis in OI under treatment, a relatively uncommon, poorly described complication of the disease, is highlihted.
- The possibility of falsely reassuring genetic results should always be taken into account and should lead to further investigations when the clinical suspicion is strong.