Novel severe skeletal dysplasia with under-mineralisation associated with *in utero* calcium transport and *TRPV6* compound heterozygous variants

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Clinical Case
- Antenatal skeletal abnormalities and recurrent polyhydramnios
- Postnatal severe thoracic insufficiency with significant skeletal and biochemical abnormalities
- Normal parental biochemistry
- Treatment included pamidronate, cinacalcet, calcium and Vitamin D supplementation
- Required tracheostomy and long term ventilation strategies

Initial Genetic Investigations
- No abnormality on antenatal CGH array and UDP14 testing
- 1:1: Initial postnatal calcium/alcium.
- Bowen Institute of Biochemistry and Clinical Science, University of Exeter, UK.
- Molecular genetic analysis excluded Neonatal Severe Hyperparathyroidism (CASR, GNA11, APS21)
- Mucolipidosis Type II excluded biochemically and genetically (GNPTG)
- Whole exome sequencing (WES) using 336 gene skeletal dysplasia panel detected no abnormalities

Relevance of *TRPV6*
- Fetal skeletal development and mineralisation depends on placental calcium transfer
- *TRPV6* (Transient Receptor Potential Vanilloid family 6th member) functions in tetramer form and has been recently identified in calcium transport2
- Not previously linked with skeletal development disorders

Parathyroid Hormone (PTH) 53.4-101 pmol/L
Corrected Calcium 2.43 mmol/L
Alkaline Phosphatase (ALP) 289 IU/L
Urinary Ca/Creat Ratio 1.05
Vitamin D 29 nmol/L

Figure 1: Clinical and radiological findings. (a) Bell-shaped chest was associated with respiratory distress. (b–i) Skeletal survey aged 2 weeks showed generalised under-mineralisation, short, thin, and fractured ribs, absence of Worianer bones and normal vertebrae. The long bones showed a similar pattern of metaphyseal irregularities with corner fractures and periosteal reaction, especially diaphyses of femora, tibiae and humeri. (j, k) Chest and femur X rays aged 10 weeks showed broader, longer ribs, improved bone mineralisation and improved metaphyseal lesions2

Figure 2: Initial postnatal biochemistry
- Markedly elevated PTH
- Predominantly normocalcaemia
- Normal ALP
- Normal calcium/creatine ratio
- Vitamin D insufficiency

Figure 3: Resolution of biochemical abnormalities - Prompt PTH normalisation with ongoing normocalcaemia, including following cinacalcet cessation

Figure 4: Human TRPV6 tetramer structure. (a) Structure in open form, complex oriented to show view in the plane of the membrane (represented by the grey bar) with the cytoplasmic region at the top. (b) As (a), but rotated to show the view from the cytoplasm; the ion channel lies at the centre of the tetramer2

Figure 5: Location of Gly660 and effect of p.(Gly660Arg) substitution. (c) Detail of the interface between the C-terminal hook of subunit A and the N-terminal helix of subunit B, the position of the Gly660 backbone is indicated, and side chains shown in stick format. (d) As (c), but showing detail of the p.(Gly660Arg) variant6

Conclusion
- First reported case of *TRPV6* compound heterozygous variants in a novel skeletal dysplasia
- Astute clinical interpretation remains valuable in complex calcium and bone pathophysiology and helps inform whole exome sequence interpretation1

References