Type II osteogenesis imperfecta: an exemple of abnormality handled at ONAB

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Osteogenesis imperfecta (OI): at least 15 genetic disorders, with bone deformity and fragility and various degrees of severity (possible addition of other symptoms)

In humans, two genes account for 77% of cases : alpha 1 and alpha 2 chains of collagen type I : *COL1A1* and *COL1A2,* the rest being caused by at least 17 other genes

In cattle, three independent cases of OI have been characterized at the molecular level, all caused by COL1A1 mutations.

Frozen specimen - descendant of « Ly. »

Anamnesis

17 purebred Normande calves (9 m, 8 f) with skeletal abnormalities received at ONAB were born in different farms from the same AI bull "Ly.", suggesting an autosomal dominant determinism with mosaicism.

Clinical symptoms consistent with the clinical features of the most severe form of OI: type II

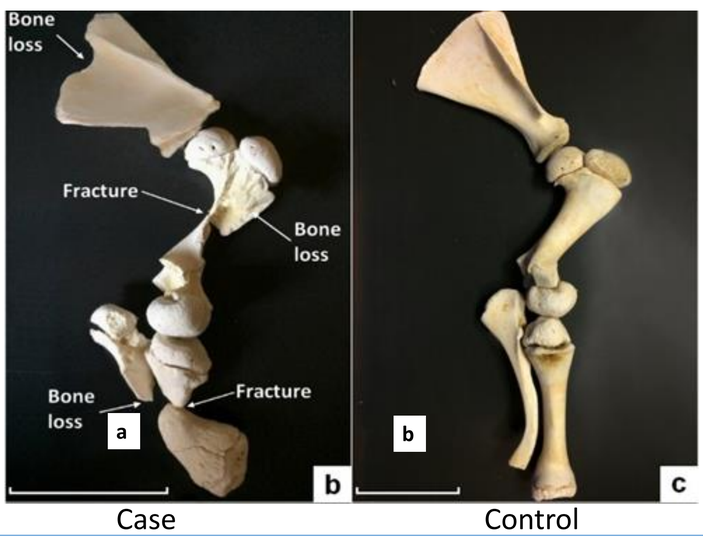
Necropsy findings:

- Eyes: light blue sclerae / Teeth: dentinogenesis imperfecta

CT scan and preparation of the skeleton :

- ancient fractures with bone loss or abnormal repair
- recent limb and rib fractures due to calving
- arthrogryposis and thickening of the joint capsule

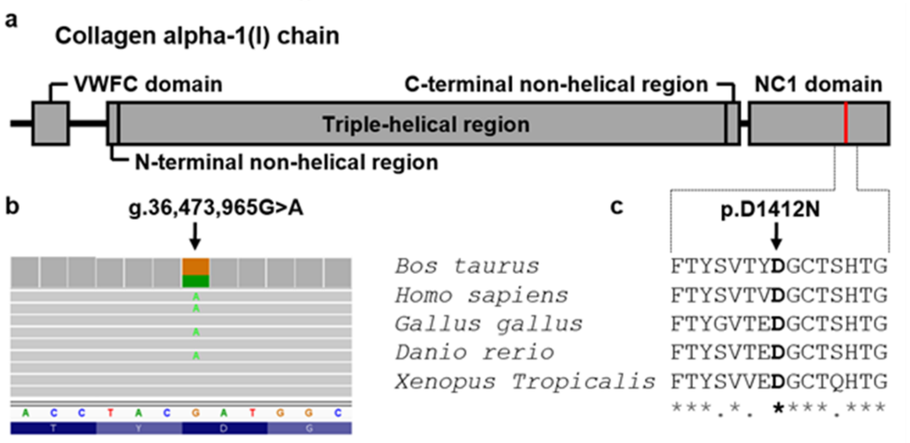
X-ray analysis : generalized osteopenia



Case Control

Genetic Analysis

- Genotyping (ILLUMINA) followed by Paternal phasing
- One region mapped on BTA19 (35.4Mb - 41.9Mb)
- WGS of one case: only 1 deleterious htz. mutation, absent from 5116 controls, and affecting *COL1A1*



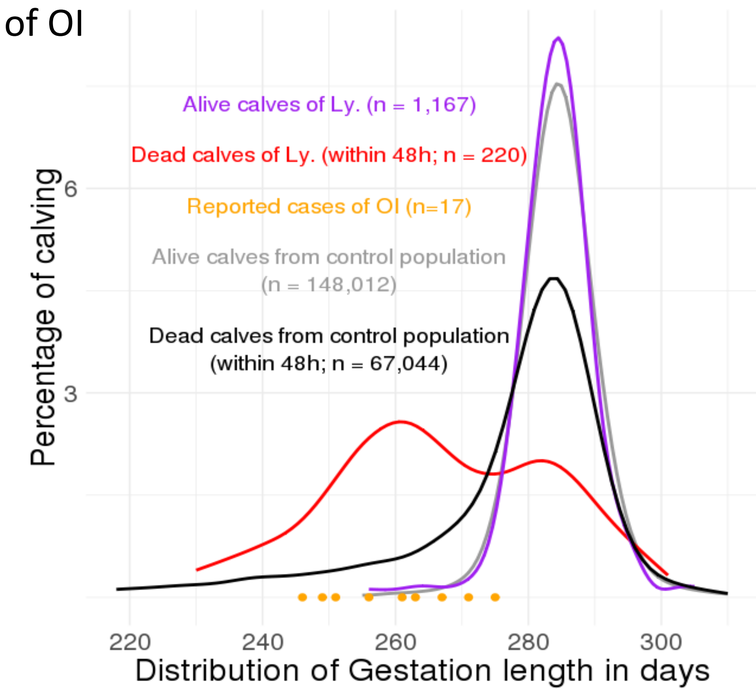
- NC1 domain necessary for triple helix formation
- Substitution conserved among vertebrates
- Reported 3 times as causal in type II OI in human
- Validated as "de novo" by PCR-Sanger sequencing

Shorter gestation length in agreement with premature rupture of membranes leading to preterm delivery

Dates of birth, survival within 48h after delivery, and gestation lengths recovered for:

- 1,387 progeny of "Ly."
- 161,413 Normande calves from 63 control bulls born the same year as "Ly." (mean = 2,400 progeny/bull)

Gestation lengths of dead calves of "Ly." showed a bimodal distribution: additional subpopulation around 260 days, comprising the cases of OI



Underreporting of defects

- Ly.", the worst Normande bull for perinatal mortality: 15.9% of calves dead within 48h Vs 8.2% for controls
- Estimation of the proportion of affected calves: 7.7% (107 cases) contrasting with the only 17 reported to ONAB

→ underreporting of congenital defects, even for textbook genetic syndromes

Deviation of the 1:1 ratio of paternal haplotype

- 84 "Ly." phased calves: haplo1: 40 healthy- 4 cases
  haplo2: 44 healthy

→ proportion of affected calves estimated: 4.5% consistent with the 7.7% estimated on the excess of perinatal mortality

Conclusion

17 cases of skeletal malformations in the progeny of a mosaic bull allowed us to identify a *de novo* deleterious substitution in COL1A1 previously described in human patients, responsible for a preterm delivery in association with classical symptoms of OI type II
This study highlights the interest of large data sets available in livestock species to characterize genetic defects and raises the concern of underreporting of cases to dedicated observatories