Bone fragility and matrix hypermineralization are rescued in homozygous OI Brtl mice mutants

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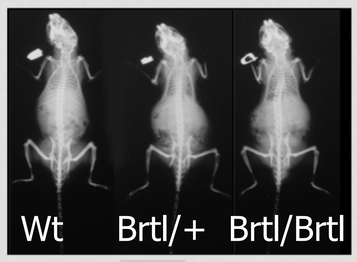
Introduction:

Classical Osteogenesis imperfecta (OI) is caused by mutations in one of the the two genes encoding for type I collagen.
OI is associated with low bone mass and abnormally high bone matrix mineralization.
The Brtl/+ OI mouse is a knock-in mouse model for non-lethal OI type IV caused by a glycine substitution in one COL1A1 allele.

Heterozygous Brtl/+ mutants have:

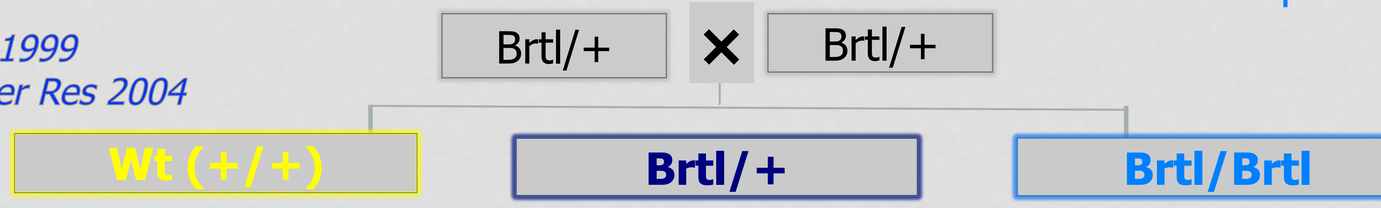
- the glycine substitution in one COL1A1 allele
- 30% perinatal lethality
- small size, decreased BMD and increased bone fragility
  ➔ OI phenotype



Homozygous Brtl/Brtl mutants have:

- the glycine substitution in both COL1A1 alleles
- normal survival rates
- a rescued phenotype with normal bone fragility.
  ➔ minimal OI phenotype

Ref: Forlino, A et al., J Biol Chem 1999
Kozloff, KM et al., J Bone Miner Res 2004



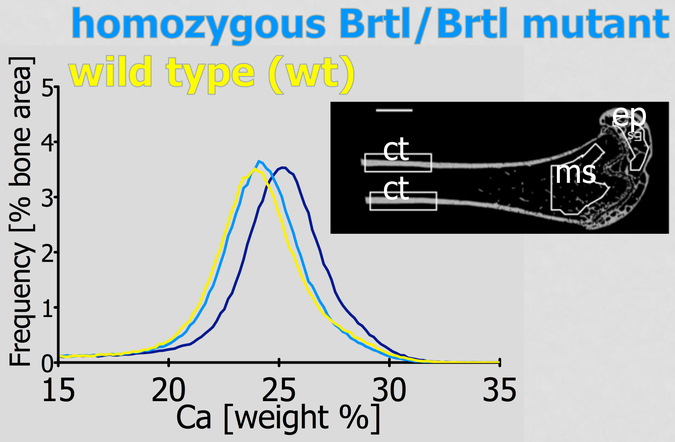
Is the rescued bone fragility in Brtl/Brtl mutants reflected by normalized bone matrix mineralization?

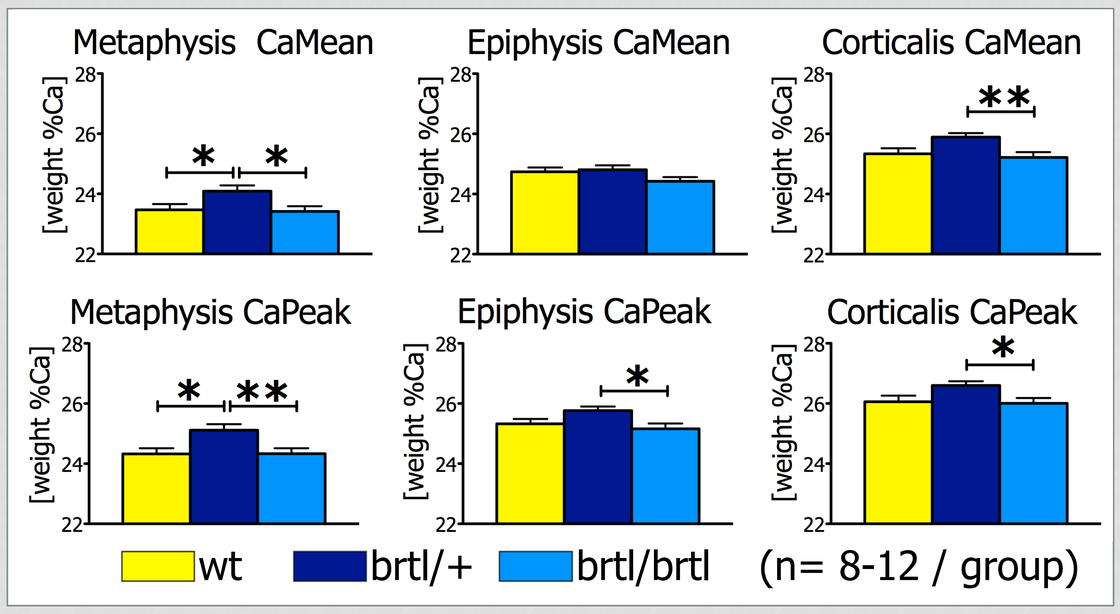
Method: quantitative Back-scattered Electron Imaging (qBEI) to evaluate Bone Matrix Density distribution (BMDD) in femoral bone in 2month-old mutants at the metaphysis, epiphysis & corticalis.
CaMean=mean calcium concentration of the bone matrix
CaPeak=most frequent calcium concentration of the bone matrix

Ref: Roschger, P et al., Bone 2008

BMDD in metaphyseal cancellous bone

heterozygous Brtl/+ mutant
homozygous Brtl/Brtl mutant
wild type (wt)





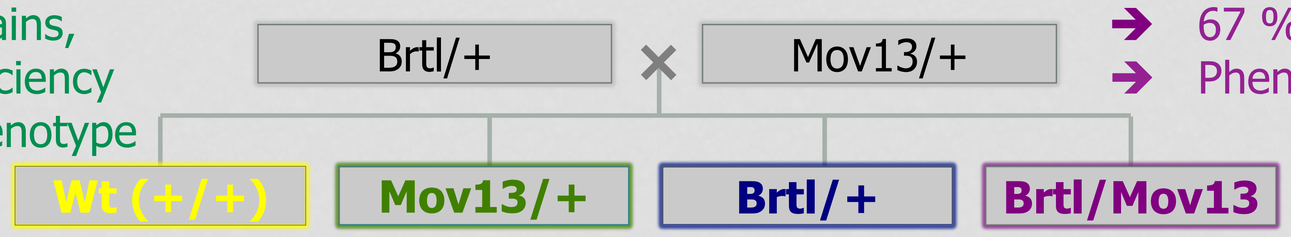
Are bone fragility and BMDD in Brtl/Brtl mutants rescued because of matrix homogeneity?

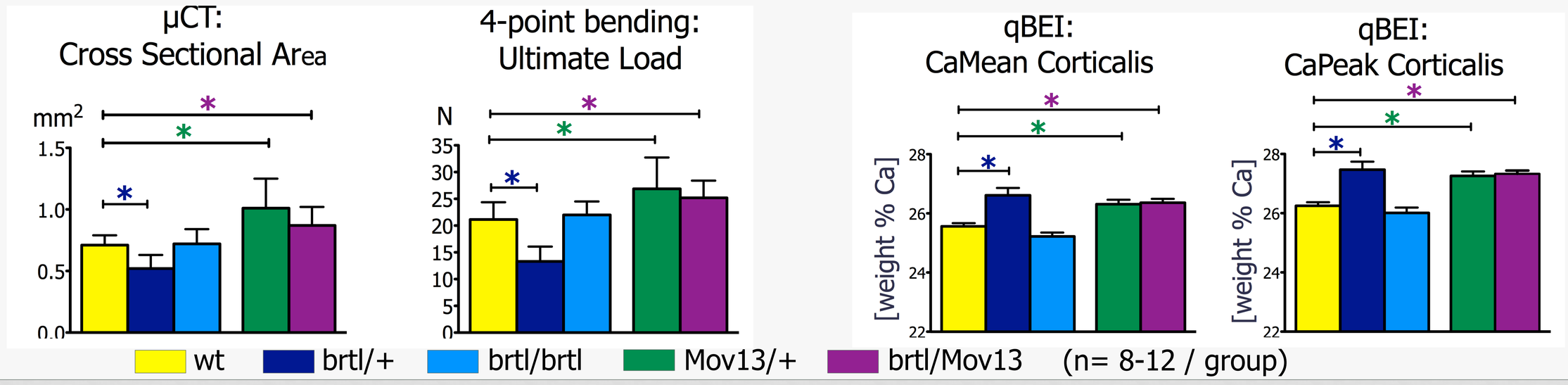
Heterozygous Mov13/+ mutants have

- ➔ a null COL1A1 allele (haploinsufficency)
- ➔ 2 normal α1(I) chains,
- ➔ 50% matrix insufficiency
- ➔ a moderate OI phenotype

Homozygous Brtl/Mov mutants have

- ➔ 2 mutant α1(I) chains
- ➔ 67 % matrix insufficiency
- ➔ Phenotype ?





Cross-sectional area and ultimate load are lower in Brtl/+, similar in Brtl/Brtl and significantly higher in Mov/+ and and Brtl/Mov13. This indicates that the increased load to fracture in Mov13/+ and Brtl/Mov13 is due to altered bone geometry.

CaMean and CaPeak are similar in Brtl/Brtl and WT but significantly higher in all other groups compared. This indicates an OI phenotype of bone material in Brtl/+ Mov13/+ and Brtl/Mov13 but a minimal one in Brtl/Brtl.

Conclusion:

These results indicate that in Brtl/Brtl mice both mechanical properties and hypermineralization of the matrix are rescued by homozygosity, which may be caused by homogeneity of matrix with mutant collagen, while Brtl/Mov13 mutants have increased ultimate load due to increased cross-sectional area compared to WT. However, the hypermineralization associated with severe matrix insufficiency is not normalized despite the bone size adaptation.

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ECTS 2014-Prague – PP17