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

Nadja Fratzl-Zelman1*, Kenneth M. Kozloff2, Jeff Meganck2, Adi Reich3, Paul Roschger1, Wayne Cabral3, Klaus Klaushofer1, Joan Marini3
1Ludwig Boltzmann Institute of Osteology at Hanusch Hospital of WGKK and AUVA Trauma Centre Meidling, 1st Med. Dept. Hanusch Hospital, Vienna, Austria
2Orthopaedic Research Laboratories, Department of Orthopaedic Surgery, University of Michigan, Ann Arbor, MI, USA
3Bone and Extracellular Matrix Branch, NICHD, NIH, Bethesda MD, USA

Introduction:

Classical Osteogenesis imperfecta (OI) is caused by mutations in one of 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

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 24-month-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

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

**Heterozygous Mov13/+ mutants have**
- a null COL1A1 allele (haploinsufficiency)
- 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 ?

**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.

nadja.fratzl-zelman@osteologie.at

---

**Notes:**

- 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.