Public Abstract
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Title: The Role of Genetic Background on the Phenotypic Severity of the Osteogenesis Imperfecta Murine (*oim*) COL1A2 Gene Mutation Throughout Postnatal Development

Osteogenesis imperfecta (OI) is a diverse disease of type I collagen, the main structural protein in the body. More than 850 distinct OI-causing mutations have been identified representing a broad range of clinical outcomes. It has been well documented that related individuals harboring the same OI-causing mutation can have very different clinical outcomes. But the relationship between mutation and clinical outcome is unclear.

The goal of this study was to further examine the genotype-phenotype relationship with the long-term goal of identifying possible modifier genes impacting the quality of bone. Modifier genes are those that influence clinical outcome by interacting with genes known to impact bone quality such as the type I collagen genes. As gene expression changes throughout development, we sought to determine if age related changes occurred in our animal model. To this end, we studied the same OI-causing mutation on two genetic backgrounds, one with reduced bone strength (C57) and one with variable bone strength (outbred). Normal, carrier and diseased animals of each background were analyzed at one, two and four months of age to assess quantitative bone parameters such as femoral shape and strength. Total amounts of type I collagen were determined and trace minerals quantitated to asses biochemical parameters while bone turnover was analyzed to determine if an uncoupling of bone formation and resorption occurs.

This work showed background related differences at all ages examined, but the presence of the mutation overrides these differences. Bones from diseased animals of either strain have altered bone geometry and reduced biomechanical strength as compared to normal animals, with animals of the C57 background having a more severe phenotype than outbred animals. Disease animals also exhibit an altered mineral composition as well as reduced amounts of type I collagen, which were background specific. Strain differences in carrier and diseased, but not normal, animals were seen in bone turnover.

Taken together, these data indicate a role for genetic background in determining phenotypic severity, although some parameters are more affected by genetic background than others.