Young Adult Male and Female +/G610C Mice as an Animal Model of Osteogenesis Imperfecta

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Introduction
Human Osteogenesis Imperfecta (OI) is a group of genetic disorders that results in heterogeneous symptoms ranging from low bone mass and occasional fractures to perinatal lethality. Most cases of OI are caused by autosomal dominant mutations in type I collagen genes (COL1A1 and COL1A2) and are classified into subtypes I to IV. Accordingly, most animal models of OI are gene-modified mice mimicking genetic disorders observed in human patients. One model is Female vitamin D mouse with a dominant negative G610C mutation in Col1a2 gene. Heterozygous mice (+/G610C) mimic human type IV OI with mild-to-moderate severity and suffer from low bone mineral density (BMD) and bone strength.

Materials and Methods
Materials and methods are detailed in a separate section. Briefly, young adult male and female heterozygous +/G610C and wild-type (+/+) mice were used. X-ray images were acquired using PharoSoft I orthopaedic x-ray system. Tibial and femoral bone were harvested at sacrifice, decalcified, embedded in methyl methacrylate, then sectioned at different levels and stained with haematoxylin and eosin. Bone mineral content (BMC) and bone mineral density (BMD) were determined using µCT software. Bone strength was determined using 3-point bending test and mechanical testing of 4-month-old mice.

Statistical analysis: All data presented as mean ± standard deviation. Differences in bone parameters were adjusted using parametric Kruskal-Wallis and Mann-Whitney tests.

Results
Young male and female +/G610C mice were lighter and had smaller tibiae than their +/+ controls at 2 and 4 months (Figs. 1A-B, 2A-B). Both male and female +/G610C mice had less trabecular bone and thinner trabecular in tibial metaphysis at 2 months (Figs. 1C-D). Both male and female +/G610C mice had less trabecular bone, fewer trabecular, impaired mechanical properties predicted from trabecular bone distribution, and decreased total trabecular bone (BMD) in femoral metaphysis, and decreased total and trabecular BMD in lumbar vertebral body at 4 months (Figs. 2C-4). Both male and female +/G610C mice had less cortical bone and impaired mechanical properties predicted from cortical bone distribution in femoral diaphysis at 4 months (Figs. 3A-B). Both male and female +/G610C mice had increased total and cortical BMD in femoral diaphysis at 4 months (Figs. 3C-D). Both male and female +/G610C mice had smaller maximum load and work-to-fracture in femoral neck, and post-yield displacement and work-to-fracture in tibial diaphysis at 4 months (Figs. 4A-D).

Bone OI phenotype seemed to be more prominent in females than in males in the present cohort.

Conclusions
Young adult male and female +/G610C mice are smaller and exhibit less trabecular and cortical bone, impaired biomechanical bone properties, and increased cortical BMD when compared with their +/+ controls. These +/G610C mice are an excellent animal model of mild-to-moderate OI.

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References

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