The *Fbn1*<sup>C1039G/+</sup> mouse model of Marfan Syndrome has altered bone microstructure and whole-bone morphology, but similar lacunar properties to littermate control mice.

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**INTRODUCTION:** Marfan syndrome (MFS) is a connective tissue disorder resulting from mutations in the FBN1 gene encoding the ECM protein fibrillin-1. Individuals with MFS exhibit a range of skeletal symptoms including long bone overgrowth, low bone mass<sup>1</sup> and increased bone fracture rates<sup>2</sup>. However, it remains unknown if the MFS bone phenotype is caused by alteration of fibrillin-1’s structural function or distortion of its interactions with bone cells. To assess the structural effects of the fibrillin-1 mutation, we characterized bone curvature, microarchitecture, and porosity, including osteocyte lacunar properties in the *Fbn1*<sup>C1039G/+</sup> mouse model of MFS.

**METHODS:** Tibiae of 26-week-old female *Fbn1*<sup>C1039G/+</sup> (MFS) and litter-mate control (LC) mice had bone microstructure as well as whole-bone morphology and curvature assessed with micro computed tomography (8µm voxel size). Bones were then scanned using synchrotron computed tomography (0.728µm voxel size). Lacunar Density, volume surface area, stretch, oblateness, sphericity, and angle were calculated as well as vascular thickness, spacing, number, volume, and surface area. Porosity of the vessels, lacunae and overall porosity were also evaluated.<sup>3</sup> ANOVA followed by Tukey’s post hoc testing were performed with a significance level set to *p*<0.05. All studies were approved by an ethics committee.

**RESULTS:** *Fbn1*<sup>C1039G/+</sup> mice exhibited long bone overgrowth. While trabecular bone microarchitecture was similar between genotypes, the tibial metaphyseal and diaphyseal cortical bone was as well as the whole bone medial-lateral curvature were significantly different in MFS compared to LC mice. For cortical bone, the Fbn1C1039G/+ mice had a lower Imax in the diaphysis and greater CtAr/TtAr in metaphysis than LC mice (Fig. 1). The largest anterior-posterior convexity occurred at 34-39% of tibial length (*C<sub>Ap</sub>* = 0.89 ± 0.06 mm WT; *C<sub>Ab</sub>* = 0.80 ± 0.07 mm *Fbn1*<sup>C1039G/+</sup>) (Fig. 2). The largest medial-lateral convexity (*C<sub>Mb</sub>* = -0.48 ± 0.11 mm WT) appeared at 30-34% of the tibial length from the proximal end WT mice, while this location was shifted (*C<sub>Mb</sub>* = -0.29 ± 0.06 mm 26w *Fbn1*<sup>C1039G/+</sup>) to 22% of the tibial length in *Fbn1*<sup>C1039G/+</sup>. Both the MFS and LC mice had regional differences in lacunar parameters and porosity between the regions of newly formed bone vs quiescent bone, as well as between the major quadrants of the bone. However, there was no significant differences in these lacunar parameters between genotypes (Fig. 3).

**CONCLUSIONS:** The *Fbn1*<sup>C1039G/+</sup> mice displayed long bone overgrowth, deficits in cortical bone structure, and altered curvature in the medial-lateral direction. However, there were no differences in the orientation or number of osteocyte lacunae within the matrix, or in the overall porosity of the bone between genotypes.

**SIGNIFICANCE/CLINICAL RELEVANCE:** This mouse model of Marfan syndrome may provide insight into the skeletal phenotype observed in individuals with MFS.


*Fig. 1:* Cancellous and cortical bone microarchitecture in the left tibiae of 26-week-old female *Fbn1*<sup>C1039G/+</sup> and LC mice. Student t-tests between genotypes *, *p* ≤ 0.05.

*Fig. 2:* Left) Medial-Lateral curvature; Right) Anterior-Posterior Curvature. Tukey post-hoc test *; genotype. Data from left tibiae are shown.

*Fig. 3:* Lacunar parameters of cortical bone in mid diaphysis and metaphyseal bone. Student t-tests between genotypes *, *p* ≤ 0.05.