The Fbn1[C1039G/+] 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[1] and increased bone fracture rates[2]. 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[C1039G/+] mouse model of MFS.

METHODS: Tibiae of 26-week-old female Fbn1[C1039G/+] (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 for the vessels, lacunae and overall porosity were also evaluated.[3] 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[C1039G/+] mice exhibited long bone overgrowth. While trabecular bone microarchitecture was similar between genotypes, the tibial metaphyseal and diaphyseal cortical bone 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. Trabecular bone volume fraction and thickness were smaller in Fbn1C1039G/+ than LC mice. (Fig 1). The largest anterior-posterior convexity occurred at 34-39% of tibial length ($C_{AP} = 0.89 \pm 0.06$ mm WT; $C_{AP} = 0.80 \pm 0.07$ mm Fbn1[C1039G/+]) (Fig. 2). The largest medial-lateral convexity ($C_{ML} = -0.48 \pm 0.11$ mm WT) appeared at 30-34% of the tibial length from the proximal end WT mice, while this location was shifted ($C_{ML} = -0.29 \pm 0.06$ mm 26w Fbn1[C1039G/+]) to 22% of the tibial length in Fbn1[C1039G/+]. 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[C1039G/+] 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.

REFERENCES: Carter et al. . Rheumatology 2000;39:307–9. 2) Trifirò et al. Bone. 2020. 3) Goff et al. Bone. 2021 Nov 1;152.

Parameters	LC Left	Fbn1[C1039G/+] Left
Diaphyseal cortical bone	n = 5	n = 6
Ct.Ar (mm²)	0.57 ± 0.09	0.53 ± 0.01
Tt.Ar (mm²)	1.00 ± 0.17	0.94 ± 0.03
Ct.Ar/Tt.Ar (mm²/mm²)	0.58 ± 0.02	0.56 ± 0.01
Ct.Th (mm)	0.21 ± 0.02	0.20 ± 0.00
I_{max} (mm⁴) *	0.08 ± 0.02	0.06 ± 0.01
I_{min} (mm⁴)	0.06 ± 0.02	0.05 ± 0.00
Metaphyseal cortical bone	n = 5	n = 6
Ct.Ar (mm²)	0.85 ± 0.12	0.80 ± 0.06
Tt.Ar (mm²)	1.99 ± 0.28	1.79 ± 0.10
Ct.Ar/Tt.Ar (mm²/mm²) *	0.43 ± 0.01	0.45 ± 0.02
Ct.Th (mm)	0.18 ± 0.02	0.18 ± 0.01
I_{max} (mm⁴)	0.30 ± 0.07	0.29 ± 0.05
I_{min} (mm⁴)	0.21 ± 0.05	0.16 ± 0.02
Metaphyseal cancellous bone	n = 5	n = 6
Tb.BV/TV (mm³/mm³) *	0.07 ± 0.02	0.06 ± 0.00
Tb.Th (μm) *	41 ± 2	36 ± 4
Tb.N (1/mm)	1.6 ± 0.4	1.6 ± 0.1
Tb.Sp (μm)	367 ± 16	387 ± 20
	n = 5	n = 6
Bone length (mm) *	17.8 ± 0.7	18.5 ± 0.3

Fig. 1: Cancellous and cortical bone microarchitecture in the left tibiae of 26-week-old female Fbn1[C1039G/+] 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.
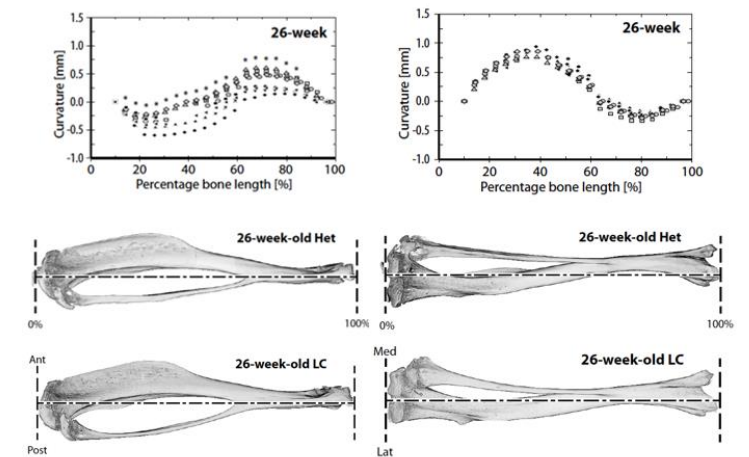
Parameter	Metaphyseal Cortical Bone		Diaphyseal Cortical Bone	
	Fbn1C1039G/+	LC	Fbn1C1039G/+	LC
	n = 6	n = 5	n = 6	n = 5
Lacunar Density (1000/mm³)	39.13 ± 8.2	41.64 ± 10.19	42.5 ± 8.77	48.53 ± 7.41
Average Lacunar Volume (mm³)	170.96 ± 34.76	177.66 ± 54.09	234.16 ± 165.8	306.31 ± 96.12
Average Lacunae Surface Area (mm²)	222.73 ± 74.21	192.98 ± 36.27	225.08 ± 96.39	309.6 ± 91.11
SA/V ratio (1/mm)	1.42 ± 0.19	1.25 ± 0.13	1.18 ± 0.18	1.16 ± 0.14
Lacunar stretch (1)	0.65 ± 0.02	0.66 ± 0.02	0.66 ± 0.04	0.65 ± 0.03
Lacunar Oblateness (1)	-0.39 ± 0.06	-0.39 ± 0.04	-0.36 ± 0.04	-0.38 ± 0.04
Lacunar Sphericity (1)	1.47 ± 0.21	1.27 ± 0.12	1.2 ± 0.16	1.17 ± 0.13
Lacunar Equancy (1)	0.26 ± 0.06	0.25 ± 0.04	0.25 ± 0.06	0.27 ± 0.04
Lacunar Angle (°)	152.09 ± 4.4	150.46 ± 4.88	156.8 ± 1.23	156.13 ± 1.21
Lacunar Porosity (%)	0.007 ± 0.002	0.008 ± 0.004	0.011 ± 0.01	0.016 ± 0.006
Lacunar Total Volume (mm³)	0.0066 ± 0.0022	0.0075 ± 0.003	0.0078 ± 0.006	0.0116 ± 0.0042
Vascular Thickness (mm)	0.006 ± 0.003	0.008 ± 0.001	0.007 ± 0.001	0.006 ± 0.002
Vascular Spacing (mm)	0.18 ± 0.02	0.2 ± 0.04	0.3 ± 0.08	0.23 ± 0.04
Vascular Number (1/mm)	5.59 ± 0.55	5.08 ± 0.94	3.56 ± 1.23	4.46 ± 1.07
Vascular Volume (mm³)	0.006 ± 0.003	0.006 ± 0.003	0.002 ± 0.001	0.003 ± 0.002
Vascular Surface Area (mm²)	1.58 ± 0.478	1.536 ± 0.686	0.611 ± 0.415	0.903 ± 0.522
Vascular Porosity (%)	0.006 ± 0.003	0.007 ± 0.004	0.003 ± 0.002	0.004 ± 0.002
Total Porosity (%)	0.016 ± 0.004	0.019 ± 0.008	0.026 ± 0.037	0.028 ± 0.015

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