### METHODS

- Formalin-fixed femora obtained from mice were dissected free of soft tissue and analyzed by a high-resolution microcomputed tomography (µCT) imaging system, with a voltage of 55 kilovolt peak (kVp) and a current of 109 µA.
- 6-month-old TGF-βR2 (G357W) mutated mice (8).
- Age- and sex-matched wild-type mice (4).
- Cortical morphometric parameters were assessed in a subset of the diaphysis.
- Bone volume, bone surface area, and cortical thickness.
- Trabecular morphometric parameters were assessed in a subset of the metaphysis.
- Bone surface density, proportion of bone volume in intramedullary canal, trabecular thickness, and trabecular number.

### RESULTS

**Figure 1. Coronal and sagittal µCT images of femora showing alterations in bone architecture.** Each pair of images is representative slices from 2 wild-type (A, B) and 2 LDS (C, D) animals. In the LDS femora, the trabeculated areas at the distal end (top) appear denser and span a greater portion of the intramedullary canal moving proximally compared to the wild-type femora. The LDS femora appear more irregular along the vertical axis compared to the relatively straight wild-type femora.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Wild-type</th>
<th>LDS</th>
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</thead>
<tbody>
<tr>
<td>Bone surface density</td>
<td>0.25 ± 0.01</td>
<td>0.30 ± 0.02</td>
</tr>
<tr>
<td>Bone Volume (mm³)</td>
<td>1.5 ± 0.3</td>
<td>2.0 ± 0.4</td>
</tr>
<tr>
<td>% Bone Volume</td>
<td>25 ± 5</td>
<td>28 ± 6</td>
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<tr>
<td>Cortical thickness</td>
<td>0.50 ± 0.02</td>
<td>0.55 ± 0.03</td>
</tr>
<tr>
<td>Trabecular thickness</td>
<td>0.60 ± 0.03</td>
<td>0.65 ± 0.04</td>
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</tbody>
</table>

**Figure 2. LDS increases trabecular bone surface density.** Bone surface density is the ratio of segmented bone surface to the total volume of bone in the region of interest. Trabecular number, and trabecular thickness were statistically increased between LDS and wild-type mice.

**Figure 3. LDS increases the proportion of trabecular bone in the intramedullary canal.** Bone volume fraction (%) is the ratio of segmented bone volume to total volume of the region of interest. Trabecular parameters were statistically increased between LDS and wild-type mice.

### CONCLUSIONS

- LDS mice exhibit heterogeneous bone microarchitecture compared to wild-type mice.
- LDS mice possess thicker, denser trabeculae that could be attributed to disorganized bone remodeling.
- TGF-βα play a significant role in orchestrating bone remodeling.
- An uncoupling of remodeling might account for increased fractures and osteoporosis reported in LDS patients.

### FUTURE DIRECTIONS

- Confirm/compare findings in 8-week-old mice.
- Perform double-tetracycline labeling studies to determine rate of bone formation.
- Studies to determine the effect of LDS on TGF-βR activation and subsequent signaling pathways.

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**BACKGROUND**

- Loeys-Dietz syndrome (LDS) is a recently recognized autosomal dominant connective tissue disorder caused by mutations in transforming growth factor-β receptor 1 or 2 (TGF-βR1 or TGF-βR2) genes.
- Given the phenotypic overlap with other connective tissue disorders such as Ehlers-Danlos syndrome, Marfan’s syndrome, Shprintzen-Goldberg syndrome, and familial thoracic aortic aneurysms and dissections, the diagnosis of LDS can be challenging.
- Clinically, these patients present with a triad of arterial tortuosity with aneurysm and dissection, hypertelorism, and bifid uvula/clut palate.
- Most research to date has examined the vascular manifestations of LDS, but as awareness has grown, many orthopaedic manifestations have been identified.
- Scoliosis
- Arachnodactyly
- Joint laxity
- Pectus carinatum/excavatum
- Club feet
- Recent case reports suggest LDS patients may develop early osteoporosis with increased fracture incidence and delayed bone healing.
- The TGF-β superfamily of cytokines are ubiquitous secreted polypeptides implicated in a number of physiologic processes of the body.
- The role of TGF-βR mutations in the pathogenesis of these musculoskeletal manifestations remains unclear.

**HYPOTHESIS**

- LDS interferes with bone remodeling.
- Altered bone remodeling effects bone morphology and microarchitecture in a TGF-βR2 mutated murine model.

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**Figure 4. LDS increases trabecular number.** Trabecular number is a measure of the average number of trabeculae per unit length.

**Figure 5. LDS increases trabecular thickness.** Trabecular thickness is a measure of the mean trabecular thickness.

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**Figure 6. Axial µCT images of femora from wild-type mice.**

**Figure 7. Axial µCT images of femora from LDS mice.**

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**Figure adapted from** Dencker S, Gourmand M-J, ten Dijke P. Transforming growth factor β signal transduction. J. Leukoc. Biol. 71:731-740, 2002.