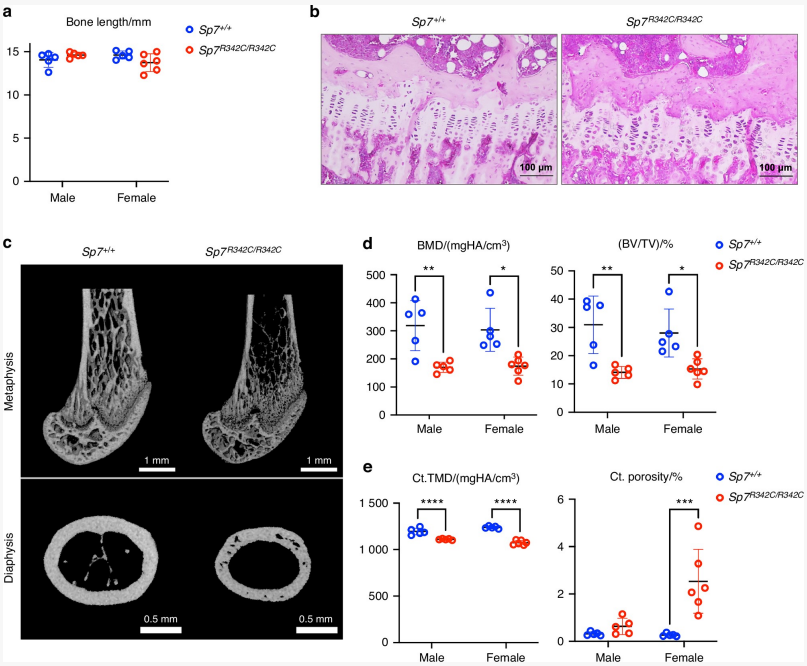
Genetically Engineered Mouse Model Provides Insights on Genetic Bone Disorders

Researchers develop a genetically modified mouse model to uncover the links between dendrite defects in osteocytes and impaired bone remodeling

CHINA, August 12, 2025 /EINPresswire.com/ -- Osteogenesis imperfecta (OI) refers to a group of bone disorders in which certain genetic mutations affect the formation of healthy bones. In a new study, researchers have developed a novel mouse model bearing a substitution mutation at position 342 in the specificity protein 7 (Sp7) gene. Utilizing this model, they investigated the role of mature bone cells called osteocytes in OI and clarified the associations between impaired bone remodeling and osteocyte dendrite defects.



By introducing an amino-acid variant at position 342 in the mouse specificity protein 7 (Sp7) gene, researchers used an animal model to study osteogenesis imperfecta. Increased cortical porosity, lower mineral density and reduced bone volume fraction was observed.

Osteogenesis imperfecta (OI) refers to a group of rare genetic bone disorders that results in the formation of fragile bones. In patients with OI, the matrix that makes up the bone has been found to be abnormal, leading to an increased risk of fractures. Genetic mutations affecting collagen matrix protein biosynthesis in osteoblasts, or bone-forming cells, have been implicated in OI. However, the role of osteocytes—mature bone cells derived from osteoblasts—in OI pathogenesis remains unclear.

Specificity protein 7 (Sp7), encoded by Sp7 gene is an important transcription factor that regulates the formation of healthy bones. Recent studies in patients with OI have revealed that rare SP7 mutations, such as the substitution of arginine with cysteine (R316C), can result in lower number of osteocytes or abnormal osteocyte morphology within bone tissue.

To shed light on the underlying mechanisms involved in OI, caused by Sp7 R316C mutation, a team of researchers led by Dr. Jialiang S. Wang from the University of Texas Southwestern Medical Center, USA and Dr. Marc N. Wein from the Endocrine Unit of Massachusetts General Hospital, Harvard Medical School, USA has conducted an in-depth study using a novel mouse model. In their study, they developed a genetically modified mouse model containing the Sp7 R342C mutation (the arginine amino acid is located at position 342 in mice). Their research findings were published online on July 19, 2025 in Volume 13 of the journal Bone Research.

Initially, the scientists employed an advanced gene editing technique called iGONAD to generate mice with the Sp7R342C mutation. Examination of the femur bone of mutant mice via micro-computed tomography (micro-CT) revealed reduced bone mineral density, a lower trabecular bone volume fraction, and increased cortical porosity-pores or channels in the outer layer of the bone. “These findings are consistent with skeletal phenotypes observed in patients with homozygous Sp7 R316C mutation,” says Dr. Wang, explaining the advantages of using this mutant mouse model for studying OI.

Subsequently, the research team delved into the bone-remodeling process in Sp7R342C mice. Bone remodeling typically involves the degradation of mature and mineralized bone tissue by osteoclasts (special cells that dissolve damaged and old bone tissue) followed by formation of new bone matrix by osteoblasts. Interestingly, in mice with the Sp7R342C mutation, an abnormal bone-remodeling process with increased intracortical bone resorption and formation was observed.

Furthermore, the number of osteocyte dendrites—elongated structures that help in regulation of bone remodeling—was reduced in the mutant mice. Additional genomic analysis of cells obtained from the outer layer of the humerus bone revealed that tumor necrosis factor superfamily member 11 (Tnfsf11) gene, important for osteoclast formation and bone-resorption activity, was highly expressed in mutant mice. Alarmingly, apoptosis (programmed cell death) of osteocytes was elevated in these mutant mice.

The scientists then turned their attention to ribonucleic acid sequencing (RNA-seq) to identify the specific genes that were dysregulated by the R342C mutation. Comprehensive RNA-seq analysis of bone cells isolated from the humerus of female mutant mice showed that 1,079 genes were up-regulated and 920 genes were down-regulated. Notably, 22 osteocyte-related genes were dysregulated in the mutant mice.

Finally, to clarify the relationship between osteocyte dendrite defects and abnormal bone resorption in Sp7R342C mice, the researchers injected mutant mice with osteoprotegerin-Fc (OPG-Fc). Sharing further details about the study, Dr. Wein says, “It is not known whether osteocyte morphology defects and apoptosis drive bone resorption, or whether increased osteoclast activity drives osteocyte morphology defects”. Following treatment with OPG-Fc to inhibit the bone-resorption process, cortical porosity was reduced in mutant mice, but the

osteocyte dendrite defects could not be repaired.

In summary, the development of this mutant mouse model to study OI provides an experimental platform to investigate the molecular mechanisms involved in bone defects and can help facilitate the discovery of novel therapeutic approaches for treating bone disorders.

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Reference
Title of original paper: Osteoclast-independent osteocyte dendrite defects in mice bearing the osteogenesis imperfecta-causing Sp7 R342C mutation
Journal: Bone Research
DOI: 10.1038/s41413-025-00440-1

About Massachusetts General Hospital, Harvard Medical School, USA
Massachusetts General Hospital was established in 1811 to provide care to Boston's general public, and in its first year of operation became the first teaching hospital of Harvard University's new medical school. At present, Massachusetts General Hospital is at the forefront of medical research, and has more than 30 clinical departments and centers on campus. With medical pioneers, dedicated staff and faculty, and state of the art equipment, endocrine Unit at Massachusetts General Hospital, affiliated with Harvard Medical School, is a premier clinical and research department dedicated to diagnosing, treating, and investigating disorders related to bone and mineral metabolism, as well as thyroid diseases and general endocrine conditions. As part of Harvard Medical School, the Endocrine Unit benefits from a rich academic environment that integrates clinical excellence with leading biomedical research.

Website: https://www.massgeneral.org/

About Dr. Jialiang S. Wang from the University of Texas Southwestern Medical Center, Dallas, TX, USA
Dr. Jialiang S. Wang currently serves as an assistant professor at the Charles and Jane Pak Center for Mineral Metabolism and Clinical Research at the University of Texas Southwestern Medical Center in Dallas, USA. Her primary research interests include multi omics, osteocytes, osteoporosis, osteosarcoma, and transcriptional regulation. She completed her postdoctoral training in Dr. Marc N. Wein's laboratory at Massachusetts General Hospital, Harvard Medical School, USA. In addition to receiving several awards for research excellence, Dr. Wang is also a recipient of the prestigious NIH□(NIAMS) Pathway to Independence Award. Furthermore, she is affiliated with professional organizations such as the Orthopaedic Research Society (ORS) and Advances in Mineral Metabolism (AIMM).

About Dr. Marc N. Wein from Harvard Medical School, Boston, MA, USA
Dr. Marc N. Wein serves as an Associate Professor of Medicine at the Massachusetts General Hospital, Harvard Medical School, USA. He has published approximately 86 papers in high-impact factor journals, which have been cited over 3,200 times. His primary research interests include endocrinology, metabolic bone disease, parathyroid disease, and osteoporosis. Additionally, he leads the Wein laboratory in the endocrine unit, part of the Endocrine Division at Massachusetts General Hospital, USA. The Wein laboratory focuses on studying the molecular mechanisms that control osteocyte differentiation and function.

Funding information
The National Institute of Health (K99AR081897, R00AR081897, P01DK011794, and R01DK116716), the Smith Family Foundation Odyssey Award, and the Chen Institute Massachusetts General Hospital Research Scholar (2024-2029) award. μCT and bone histomorphometry were performed by the Center for Skeletal Research at Massachusetts General Hospital, a NIH-funded program (P30AR066261 and AR075042) led by Mary Bouxsein and Marie Demay).

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