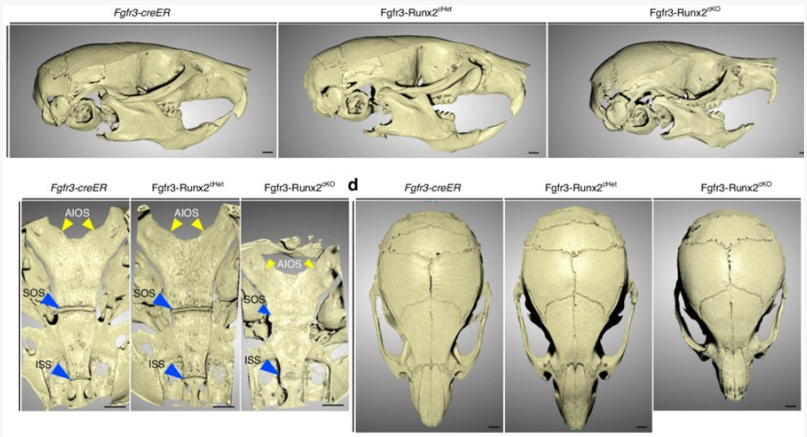
New Study Reveals How RUNX2 Regulates Skull Development

Researchers uncover how a key protein controls cranial base growth, revealing complex pathways that could inform future therapies



These 3D renderings of mouse skulls clearly show the effects of RUNX2 deficiency. Fgfr3-creER mice, which were the control group, and Fgfr3-Runx2cHet mice, which had a working copy of the Runx2 gene, exhibited normal cranial development. In contrast, Fgfr

CHENGDU, SICHUAN, CHINA, June 23, 2025 /EINPresswire.com/ -- Problems with cranial base growth, which supports the skull's structure, can lead to several chronic conditions of the face and upper airway. However, the molecular mechanisms regulating this process remain poorly understood. In a recent study, researchers from the United States use a sophisticated mouse model to understand the role of RUNX2, a master regulator protein, in cranial base growth. Their findings offer new insights into craniofacial malformations and may contribute to identifying potential therapeutic targets.

The cranial base, which forms the floor of the skull, is essential for supporting the brain and upper airway. This structure grows through specialized cartilage structures called synchondroses, composed of neatly arranged layers of cells known as chondrocytes. These cells gradually transform into bone, driving the skull's lengthening from front to back. When this process is impaired, it can lead to malformations in the skull, such as skeletal Class III malocclusion (an underbite) or foramen magnum stenosis (narrowing of the opening at the base of the skull). Such conditions often affect essential processes such as breathing, chewing, and speaking, resulting in prolonged challenges.

Despite the importance of proper cranial base growth, many aspects of the molecular mechanisms governing this process remain unclear. Previous research suggests that RUNX2, a master regulator protein essential for bone formation, plays a crucial role in skull development. Individuals with RUNX2 deficiency develop cleidocranial dysplasia, a condition marked by

underdeveloped facial features and deficient skull base growth. However, the specific functions of RUNX2 protein in cranial base synchondrosis chondrocytes—and its interactions with other bone-related molecular pathways—remain largely unknown.

To address these gaps, a research team from the University of Texas Health Science Center at Houston School of Dentistry (UTHealth Houston) and the University of Michigan School of Dentistry, USA, conducted an in-depth study. Led by Professor Noriaki Ono from UTHealth Houston, the team employed a specialized mouse model to selectively remove RUNX2 from specific cells after birth, allowing them to study its precise role in cranial growth. Their findings were published in Bone Research on May 29, 2025. Highlighting the focus of their study, Prof. Ono explains," Many studies show that RUNX2 is important for osteoblasts in the skull and chondrocytes in the limb. Also, FGFR3 is known to regulate RUNX2 expression through downstream MAPK signaling in vitro. However, how RUNX2 regulates chondrocytes in the skull and FGFR3 activities in vivo has yet to be determined."

The researchers employed a sophisticated genetic approach using tamoxifen-inducible mice, enabling them to turn off the Runx2 gene in Fgfr3-expressing synchondrosis chondrocytes upon administration of tamoxifen. They tracked these cells over time using fluorescent markers to observe how the loss of RUNX2 affected their differentiation into other cell types, as well as their organization, proliferation, survival, and appearance. The team analyzed skull growth in these mice using high-resolution micro-CT scans and examined tissue samples under the microscope to understand the cellular changes occurring in the synchondroses. Notably, they also investigated changes in the expression of Fibroblast Growth Factor Receptor 3 (Fgfr3), a gene known to be involved in skull growth, and its downstream signaling components.

Their findings revealed that mice lacking Runx2 in synchondrosis chondrocytes exhibited severe skeletal dwarfism and reduced cranial base growth. This was directly linked to the premature ossification of the synchondroses. At the cellular level, the absence of RUNX2 caused disorganization of the chondrocyte layers, hindered chondrocyte proliferation, increased apoptosis, and increased higher cartilage resorption. Interestingly, through lineage tracing experiments, the team showed that Runx2-deficient cells failed to differentiate into osteoblasts, which are essential for bone formation.

Moreover, the researchers observed significantly elevated levels of FGFR3 protein and its downstream signaling molecules in Runx2-deficient chondrocytes. This suggests that RUNX2 normally acts to suppress FGFR3 activity in these cells. "This study unveils a new role of Runx2 in cranial base chondrocytes, identifying a possible RUNX2-FGFR3 signaling axis that may control cranial base growth," highlights Prof. Ono.

Overall, these results provide a fundamental understanding of how critical bone growth processes are regulated during skull formation. By understanding the complex interplay between RUNX2 and FGFR3, they shed light on how their dysregulation results in the craniofacial defects seen in various genetic disorders. Most importantly, by clarifying the precise roles of

these proteins in cranial base growth, this research opens new avenues for developing therapies. “Our findings may provide novel therapeutic targets to address cranial base skeletal defects,” concludes Prof. Ono.

With further research, these insights could help improve the diagnosis, prevention, and treatment of craniofacial malformations in both children and adults.

Reference
Titles of original papers: RUNX2 is essential for maintaining synchondrosis chondrocytes and cranial base growth

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