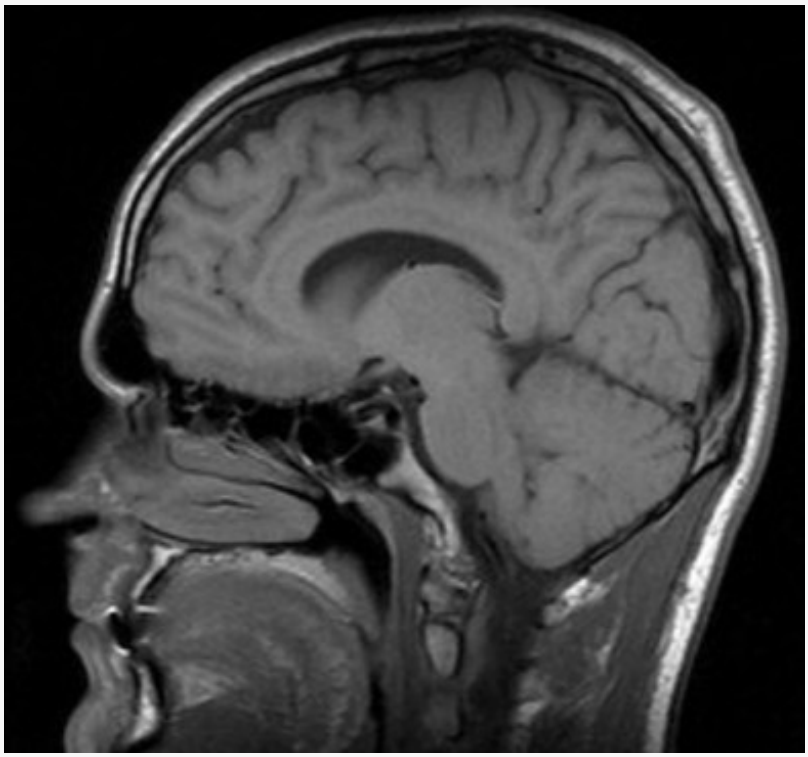
Time-Dependent Premature Suture Fusion in Craniosynostosis

Study uncovers a critical developmental window linking FGFR2 signaling to premature coronal suture fusion



Study identifies a critical postnatal window in which excessive FGFR2 signaling activates the P38–retinoic acid pathway, disrupting GLI1+ progenitor cells and promoting premature coronal suture fusion in mice.

CHENGDU, CHINA, August 28, 2026 /EINPresswire.com/ -- Craniosynostosis occurs when the skull's cranial sutures fuse prematurely, disrupting brain development. While the condition may begin with a genetic mutation, what happens afterward could be just as important. Researchers from the University of Southern California explored this idea by examining the postnatal coronal suture in FGFR2-associated craniosynostosis. By tracking GLI1+ progenitor cells and their interactions with the dura mater, the team investigated the biological events that may set premature suture fusion in motion.

Craniosynostosis is a congenital developmental disorder in which the skull's cranial sutures fuse prematurely. Although genetic mutations can drive the condition, new research suggests that timing may determine when these abnormalities emerge. During early life, cranial sutures must remain open to accommodate rapid brain growth. When these flexible joints fuse too early, they can restrict skull growth, increase intracranial pressure (ICP), and impair neurocognitive development. Gain-of-function mutations in fibroblast growth factor receptor 2 (FGFR2) are a major cause of syndromic craniosynostosis. Yet how excessive FGFR2 signaling triggers postnatal suture fusion, and why it becomes harmful during a specific developmental window, have remained unclear.

To address this, researchers from the University of Southern California investigated how and when FGFR2 signaling disrupts postnatal coronal suture development and identified the

downstream mechanisms driving craniosynostosis. Lead author Prof. Yang Chai explains, “We focused on GLI1+ progenitor cells, which help maintain suture patency, and on interactions between the coronal suture mesenchyme and underlying dura mater.” The team also examined whether retinoic acid (RA) signaling acts downstream of FGFR2 and whether restoring this pathway could prevent or reverse disease-associated changes. The study was published in the International Journal of Oral Science on August 17, 2026.

Researchers used genetically engineered mice to selectively overactivate FGFR2 in GLI1+ progenitors at different postnatal stages, allowing them to identify the critical developmental window. Histology, microCT, ICP measurements, and reporter models were used to assess suture fusion and changes in progenitor cells. RNA sequencing identified altered signaling pathways, while co-culture experiments, P38 inhibition, and Aldh1a3 reduction were used to investigate the FGFR2–P38–RA pathway. Suture regeneration and behavioral testing further assessed whether restoring suture patency or RA signaling could rescue structural and neurocognitive abnormalities.

The study identified a critical postnatal window in which excessive FGFR2 signaling drives coronal craniosynostosis. FGFR2 overactivation at P3.5, but not P7.5, caused premature suture fusion by reducing GLI1+ progenitors and promoting their differentiation into osteoblasts. RNA sequencing revealed RA signaling as a key downstream pathway, with increased Rbp1 and Aldh1a3 expression sustaining RA production. Prof. Chai explains, “Mechanistically, FGFR2 activated P38 MAPK, which enhanced RA synthesis in the dura mater and suture mesenchyme. Reducing Aldh1a3 restored GLI1+ progenitors, prevented abnormal osteogenesis, and rescued suture patency, skull morphology, and ICP.” Suture regeneration or RA restoration also improved neurocognitive deficits in mutant mice.

The study also helped explain the neurocognitive consequences of craniosynostosis. Although FGFR2 was expressed in the brain, regenerating the coronal suture restored skull structure and normalized ICP, while rescuing deficits in memory, sociability, spatial working memory, and motor learning. Similarly, restoring RA signaling improved neurocognitive performance in mutant mice. These findings suggest that the observed impairments primarily result from restricted skull growth and elevated ICP rather than direct neural effects of the FGFR2 mutation.

Overall, the study identifies a time-specific FGFR2–P38–RA pathway linking dura mater–suture interactions to GLI1+ progenitor fate and coronal suture integrity. The findings highlight RA signaling as a potential therapeutic target and emphasize the importance of early, time-sensitive intervention. Future studies should determine how P38-regulated transcription factors control RA synthesis genes and assess whether targeting this pathway can safely prevent or treat FGFR2-associated craniosynostosis.

Reference

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Yang Chai is Dean and the G. Donald and Marian James Montgomery Professor of Dentistry at the Herman Ostrow School of Dentistry, University of Southern California (USC), and University Professor of Otolaryngology–Head and Neck Surgery at the Keck School of Medicine. Internationally recognized for his research on craniofacial development, genetics, and cellular signaling, he investigates the causes and prevention of craniofacial disorders. Prof. Chai chairs the National Institute of Dental and Craniofacial Research Board of Scientific Counselors and was elected to the National Academy of Inventors in 2024.

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