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Contact: A'ndrea Elyse Messer
aem1@psu.edu
814-865-9481
[Penn State](#)

3-D imaging sheds light on Apert syndrome development

Three dimensional imaging of two different mouse models of Apert Syndrome shows that cranial deformation begins before birth and continues, worsening with time, according to a team of researchers who studied mice to better understand and treat the disorder in humans.

Apert Syndrome is caused by mutations in *FGFR2* -- fibroblast growth factor receptor 2 -- a gene, which usually produces a protein that functions in cell division, regulation of cell growth and maturation, formation of blood vessels, wound healing, and embryonic development. With certain mutations, this gene causes the bones in the skull to fuse together early, beginning in the fetus. These mutations also cause mid-facial deformation, a variety of neural, limb and tissue malformations and may lead to cognitive impairment.

Understanding the growth pattern of the head in an individual, the ability to anticipate where the bones will fuse and grow next, and using simulations "could contribute to improved patient-centered outcomes either through changes in surgical approach, or through more realistic modeling and expectation of surgical outcome," the researchers said in today's (Feb. 28) issue of *BMC Developmental Biology*.

Joan T. Richtsmeier, Distinguished Professor of Anthropology, Penn State, and her team looked at two sets of mice, each having a different mutation that causes Apert Syndrome in humans and causes similar cranial problems in the mice. They checked bone formation and the fusing of sutures, soft tissue that usually exists between bones in the skull, in the mice at 17.5 days after conception and at birth -- 19 to 21 days after conception.

"It would be difficult, actually impossible, to observe and score the exact processes and timing of abnormal suture closure in humans as the disease is usually diagnosed after suture closure has occurred," said Richtsmeier. "With these mice, we can do this at the anatomical level by visualizing the sutures prenatally using micro-computed tomography -- 3-D X-rays -- or at the mechanistic level by using immunohistochemistry, or other approaches to see what the cells are doing as the sutures close."

The researchers found that both sets of mice differed in cranial formation from their littermates that were not carrying the mutation and that they differed from each other. They also found that the changes in suture closure in the head progressed from 17.5 days to birth, so that the heads of newborn mice looked very different at birth than they did when first imaged prenatally.

Apert syndrome also causes early closure of the sutures between bones in the face. Early fusion of bones of the skull and of the face makes it impossible for the head to grow in the

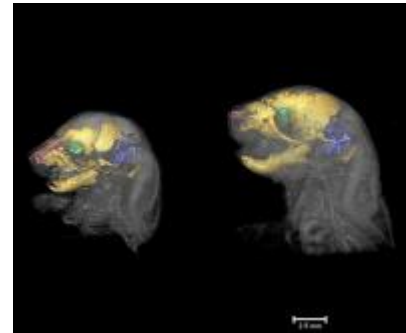


IMAGE: This image shows craniofacial growth patterns in mouse models for Apert syndrome. Apert syndrome is caused by two neighboring mutations on Fibroblast growth factor receptor 2 (*FGFR2*). Multimodal imaging and...

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typical fashion. The researchers found that the changed growth pattern contributes significantly to continuing skull deformation and facial deformation that is initiated prenatally and increases over time.

"Currently, the only option for people with Apert syndrome is rather significant reconstructive surgery, sometimes successive planned surgeries that occur throughout infancy and childhood and into adulthood," said Richtsmeier. "These surgeries are necessary to restore function to some cranial structures and to provide a more typical morphology for some of the cranial features."

Using 3-D imaging, the researchers were able to estimate how the changes in the growth patterns caused by either of the two different mutations produced the head and facial deformities.

"If what we found in mice is analogous to the processes at work in humans with Apert syndrome, then we need to decide whether or not a surgical approach that we know is necessary is also sufficient," said Richtsmeier. "If it is not in at least some cases, then we need to be working towards therapies that can replace or further improve surgical outcomes."

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Other Penn State researchers on this project include Susan M. Motch Perrine, post doctoral research assistant, and Neus Martínez-Abadías, former post doctoral fellow, now at Center for Genomic Regulation, Barcelona, Spain. Other researchers include Theodore M. Cole III, associate teaching professor, University of Missouri-Kansas City School of Medicine; Kristina Aldridge, former post doctoral fellow at Penn State and currently assistant professor, University of Missouri-Columbia; and Ethylin Wang Jabs, professor, Icahn School of Medicine at Mount Sinai.

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