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Rare and common genetic variants combine to cause skull-fusion disorder

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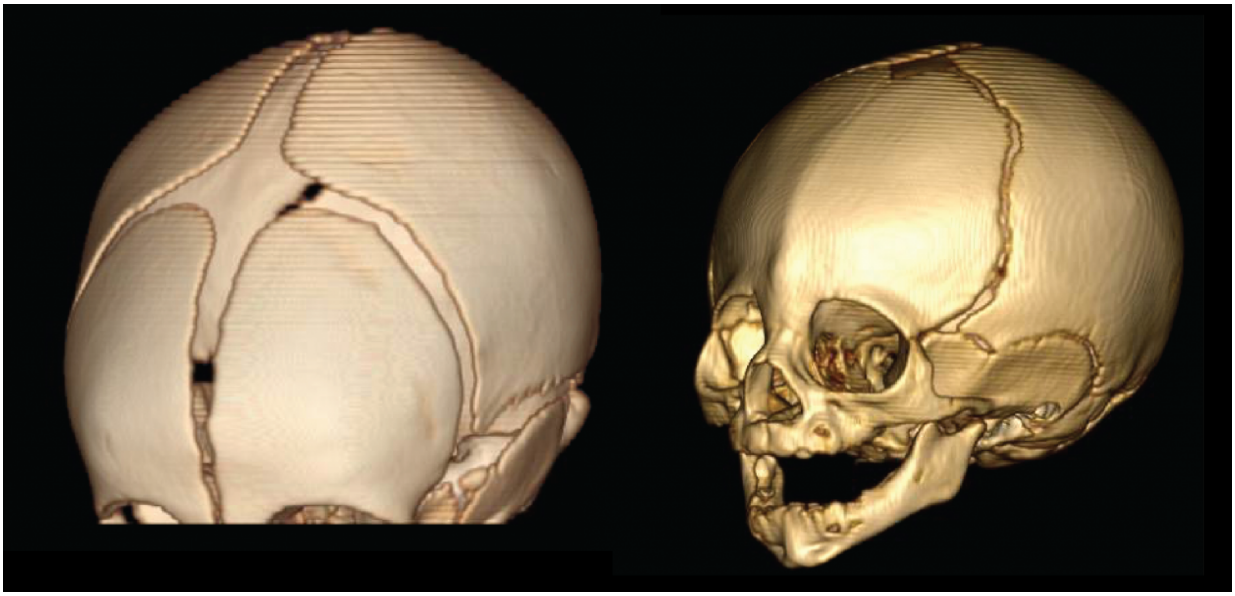

In one type of midline craniosynostosis, the two plates at the front of an infant's head fuse before they should, forming a boney ridge down the forehead. This condition can lead to abnormalities in the growing skull and brain. Credit: The Rockefeller University/eLife

During the first year of life, the human brain doubles in size, and continues growing through adolescence. But sometimes, the loosely connected plates of a baby's skull fuse too early, a disorder known as craniosynostosis. Variants of this disorder can produce facial and skull deformities, and put potentially damaging constraints on a young brain.

A research team led by Rockefeller University President Richard P. Lifton, then at Yale University, has identified mutations responsible for a type of craniosynostosis that affects the suture running along the top of the skull. The results appear in *eLife*.

"While this discovery will immediately help us diagnose and counsel patients, it also has much broader relevance for understanding the genetics of complex traits, including many human diseases," says Lifton, who is head of Rockefeller's Laboratory of Human Genetics and Genomics and was a Howard Hughes Medical Institute investigator prior to moving to Rockefeller.

He and his team at Yale, including John Persing and colleagues in the Section of Plastic and Reconstructive Surgery, found that rare mutations in one gene collaborate with common variants near a second to cause midline craniosynostosis. As such, this disorder is a unique example of how an interaction between genes can contribute to disease.

Sporadic inheritance

Midline craniosynostosis occurs when the suture in front of or behind the soft spot atop a baby's skull closes early, producing a ridge or other distortions and, in some cases, neurological problems. First author Andrew Timberlake, an M.D.-Ph.D. student in Lifton's lab at Yale, used social media to recruit many of the 191 families who participated in this study.

By plotting out the inheritance of the disorder through the families, the team noticed that it showed up unpredictably within them. Clearly, they thought, something more than simple dominant or recessive inheritance was at play. When they sequenced the participants' protein-coding genes, or exomes, mutations in one gene, SMAD6, caught their attention. This made sense; SMAD6 is a protein that inhibits so-called BMP signaling,

which promotes bone formation. But not everyone carrying these rare SMAD6 mutations had midline craniosynostosis. In fact, none of the parents who shared the SMAD6 mutation with their affected children had a history of craniosynostosis—a finding that initially surprised researchers.

A partner in crime

The team then looked to find mutations that might affect the same bone formation pathway. Some previous work implicated common changes near one such gene, BMP2, so they looked for these variations among the families.

"It was amazing to then find that the affected children had inherited both the SMAD6 mutation and the common BMP2 variant. In each case, the SMAD6 mutation came from one parent and the BMP2 risk variant came from the other parent, explaining why neither parent had craniosynostosis," Timberlake says.

The researchers believe that the risk variants near BMP2 increase the levels of the bone-promoting BMP signaling, thereby amplifying the effect of the loss of SMAD6's ability to inhibit the process. The result: The gap between the skull bones fuses ahead of schedule.

Among the families studied, those who carried the rare, damaging SMAD6 mutation plus a common BMP2 risk variant always had midline craniosynostosis, while those with only a SMAD6 mutation, but no BMP2 risk allele, were much less likely to suffer from the disorder. This knowledge should help doctors and genetic counselors better assess the risk within families.

New insight on disease risk

The researchers suggest that a similar dynamic may be at play in other rare genetic disorders that don't appear to follow classical Mendelian inheritance patterns.

"Our results offer a clear demonstration of the interaction between rare and common variants," Lifton says, "offering one explanation to a lingering question in genetics: Why do some individuals with potent rare mutations develop disease, while others with the same mutations do not?"

More information: Andrew T Timberlake et al, Two locus inheritance of non-syndromic midline craniosynostosis via rareand commonalleles, *eLife* (2016). DOI: 10.7554/eLife.20125

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