Researchers discover genetic mutation behind serious skull disorder

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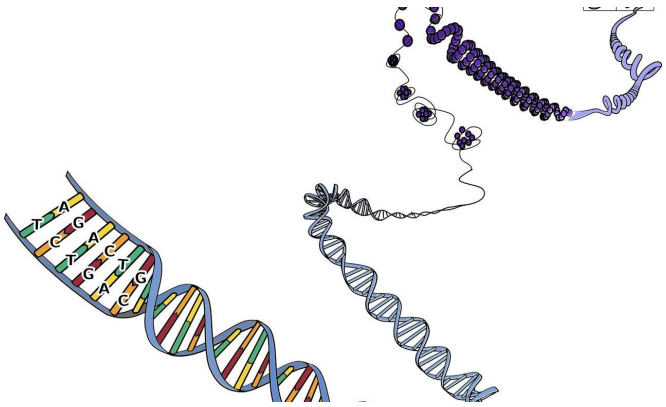

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A collaboration led by scientists at Oregon State University, the University of Oxford in the United Kingdom and Erasmus University in The Netherlands has identified a new genetic mutation behind the premature fusing of the bony plates that make up the skull.

The findings are a key step toward preventing a serious cranial condition that affects roughly one child in 2,250, and also toward understanding how the protein the gene encodes works in the development and function of other organ systems such as skin, teeth and the immune system.

In the skull, when one or more of the fibrous joints, called skull sutures, between cranial bones close too soon—a condition known as craniosynostosis—the resulting early plate fusion disrupts proper growth of the skull and brain.

Pressure inside the cranium can lead to a variety of medical problems including impaired vision, respiration and mental function, as well as abnormal head shape. Males are affected at slightly higher rates, and most cases are termed "sporadic"—meaning they occur by chance.

"As an individual grows, sutures are supposed to close gradually, with complete fusion taking place in the third decade of life," said Oregon State researcher Mark Leid. "Proper suture formation, maintenance and ossification require an exquisitely choreographed balance—stem cells and their progeny need to proliferate and differentiate at just the right time."

Leid, professor and interim dean of the OSU College of Pharmacy, and scientists Stephen Twigg of Oxford and Irene Mathijssen of Erasmus University in Rotterdam performed whole-genome sequencing on a male craniosynostosis patient and found a mutation in a gene known as BCL11B.

Neither of the patient's parents had symptoms of craniosynostosis, a family history of the condition, or carried the mutation, which generated a single amino acid change in the BCL11B protein.

The international research group proved that the human patient's mutation was causative for craniosynostosis by utilizing a mouse model harboring the same mutation. Like the human patient, the genetically modified mouse exhibited craniosynostosis at birth.

"Our data demonstrate that the identified amino acid substitution caused craniosynostosis in the patient we studied," Leid said. "The mouse model that we created should be useful in dissecting the mechanisms behind the role of the BCL11B protein in keeping sutures open, as well as the role of the protein in the development and function of other organ systems."

More information: Jacqueline A C Goos et al, A de novo substitution in BCL11B leads to loss of interaction with transcriptional complexes and craniosynostosis, *Human Molecular Genetics* (2019). DOI: 10.1093/hmg/ddz072

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