

Craniosynostosis, delayed tooth eruption and supernumerary teeth -- one gene in background

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Researchers have described a new, recessively inherited human syndrome featuring craniosynostosis, maxillary hyperplasia, delayed tooth eruption and extra teeth. They also identified causative mutations in a gene IL11RA.

In craniosynostosis, the sutures between skull bones become ossified prematurely, affecting skull shape and limiting space for the growth of the brain. It is observed in 1:2500 and often requires operative surgery. Supernumerary teeth are more common, and in most cases they also require dental surgery.

A combination of these [anomalies](#) was observed in four children of a Pakistani family living in Denmark. Extra teeth developed in positions suggesting that they may represent a third set of teeth, the formation of which is normally prevented in humans.

The parents of the family were first cousins, which made it possible to localize the gene in the [genome](#) (so called homozygosity mapping) and identify the mutation, causing a change of a single amino acid, in a gene for interleukin 11 receptor alpha (IL11RA). This is a [protein](#) on [cell surface](#) that binds the extracellular interleukin 11 and makes possible for the [cells](#) to sense the presence of this factor. When tested in cultured cell lines, the mutation inactivated the function of the receptor.

The researchers also found four other [mutations](#) in IL11RA in patients from Pakistan, England and The Netherlands.

"This is a quite novel discovery as IL11 - or the signaling pathway it belongs to - has not previously been associated with any inherited human disorders", says Dr. Pekka Nieminen, the leader of the study (University of Helsinki). "The results

show that IL11 signaling is essential for the normal development of craniofacial bones and teeth, and that its function is to restrict suture fusion and tooth number."

"We believe that normally IL11 mediates the complex tissue interactions that regulate replacement tooth development in mammals. In skull, IL11 signals are probably needed to regulate a process called bone remodeling in the edges of the skull bones, including site-specific regulation of bone apposition and bone resorption. Eruption of permanent teeth was also delayed in the patients with IL11RA mutations, and it may well be explained by defects in bone resorption that is necessary for teeth to erupt."

Exactly how and why the mutations lead to craniosynostosis may be possible to study in a knockout mouse model as the researchers also registered a peculiar growth anomaly, shortening and skewing of the snout.

"In the future it may be possible to use modulation of IL11 signaling for treatment of craniosynostosis", Dr. Nieminen believes.

Provided by University of Helsinki

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