Signal Transduction Pathways and Their Impairment in Syndromic Craniosynostosis

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**Abstract**

The cranial sutures act as the growth centers for the flat bones of the skull. They regulate the growth of these bones, but also prevent their premature fusion, known as craniosynostosis, to allow for the growth of the brain. In the past 15 years or so, many of the signaling pathways and transcription factors that regulate cranial suture formation and patency have been identified, largely through the identification of genes that are mutated in syndromic forms of craniosynostosis. While many such genes have been identified as being important in these processes, exactly how these pathways integrate with one another to regulate the formation and morphogenesis of the craniofacial structures is only starting to be understood. In the past few years, functional differences between tissues within the sutures have emerged as critical regulators of suture patency, and several recent studies have begun to determine how changes to this signaling affect these tissues to alter their function and result in craniosynostosis. Here, we review the current literature on the regulation of normal suture growth and patency, and on the events that occur due to changes to these pathways resulting in craniosynostosis.

The skull is composed of 22 separate bones, which are categorized into 2 components, the neurocranium and the viscerocranium. The neurocranium includes the skull vault, which covers the brain and sensory organs, while the viscerocranium comprises the bones of the face. The majority of the cranial bones, especially those of the neurocranium, are known as flat bones and arise from intramembranous ossification, the direct formation of bone from mesenchymal cell precursors. These flat bones of the cranium and face remain separated by openings termed sutures that allow for deformation of the skull during childbirth and absorption of mechanical trauma in childhood. The sutures also function as the growth centers of these bones, allowing growth of the skull during fetal and postnatal development in concert with the expanding brain. With the exception of the metopic suture, which closes during the 2nd or 3rd year of life, the rest of the cranial sutures slowly become more fibrous and interdigitated and eventually ossify during the 2nd or 3rd decade of life. In the mouse, all of the cranial sutures remain patent except for the posterior interfrontal suture, which is equivalent to the metopic suture in humans, and fuses during the first few weeks after birth.

The development of the head and facial structures is a complex interplay between many different signaling pathways, transcription factors, and tissue interactions, and the bones and mesenchyme...