

A coupled Reaction-Diffusion-Strain model predicts cranial vault formation in development and disease

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Abstract How cells utilize instructions provided by genes and integrate mechanical forces generated by tissue growth to produce morphology is a fundamental question of biology. Dermal bones of the vertebrate cranial vault are formed through the direct differentiation of mesenchymal cells on the neural surface into osteoblasts through intramembranous ossification. Here we join a self-organizing Turing mechanism, computational biomechanics, and experimental data to produce a 3D representative model of the growing cerebral surface, cranial vault bones, and sutures. We show how changes in single parameters regulating signaling during osteoblast differentiation and bone formation may explain cranial vault shape variation in craniofacial disorders. A key result is that toggling a parameter in our model results in closure of a cranial vault suture, an event that occurred during evolution of the cranial vault and that occurs in craniofacial disorders. Our approach provides an initial and important step towards integrating biomechanics into the genotype phenotype map to explain the production of variation in head morphology by developmental mechanisms.

Keywords computational morphogenesis · finite volume method · intramembranous ossification · skull growth and evolution · craniosynostosis · brain · mouse model

1 Introduction

The evolutionary emergence of the head is central to the rise of the vertebrates and involves the evolution of key characters including a mineralized skull that protects and supports a cephalic nervous system and sense organs. The vertebrate cranial vault represents the cranial portion of the dermal skeleton that evolved to protect the rostral brain surface (Kawasaki et al. 2004). One of the fundamental questions underlying patterns of cranial vault shape variation across ontogenetic and evolutionary time is how organisms integrate genetic inputs and mechanical forces from growing soft tissues to produce skull morphology. Increase in brain size is evident across the evolution of vertebrates (O’Leary et al. 2007), and persistent loss of skull bones is demonstrated over the approximately 150 million years of synapsid evolution (Sidor 2001), yet remarkable accommodation of brain and skull is evident across living and extinct vertebrates (Richtsmeier and Flaherty 2013). Still, the mechanisms that direct the synchronization of these two tissues in development and in evolution is not understood.

The basic structure of the cranial vault is similar across mammals, consisting of plates of dermal bone that are not preformed in cartilage but form directly through intramembranous ossification, where the action of extracellular molecules (Long 2011; Westendorf et al. 2004; Cheng et al. 2003; Wan and Cao 2005; Aspenberg et al. 2001; Wan et al. 2007) and mechanical

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