The FASEB Journal / Volume 35, Issue S1

Anatomy | Free Access

Assessing Gene Expression Patterns in Mouse Models to Test Hypotheses About Human Head Evolution

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First published: 14 May 2021
https://doi.org/10.1096/fasebj.2021.35.S1.03594

Marie Curie Fellowship FP7-PEOPLE-2012-IIF 327382, National Institutes of Health grants NICHD P01HD078233 and NIDCR R01DE02298, and a Burroughs-Welcome Fund 2013 Collaborative Research Travel Grant.

Abstract

Continuous fossil discoveries and recent analysis of genomic data are revealing that anatomically modern traits evolved following a complex evolutionary path. Our current understanding of human evolution considers that the skull likely evolved as a mosaic of correlated traits whose development is in turn integrated with other organs, such as the brain. However, we still know little about the complexity of the genetic networks supervising these processes and the developmental mechanisms underlying observed patterns of morphological evolution. To further understand the integrated evolution of the human skull and brain, it is crucial to characterize the gene expression patterns that provide detailed instructions to organize cell behavior, tissue growth, and organ patterning and to investigate how development translates genetic variation into phenotypic variation. We propose that developmental biology analyses using mouse models can enable the experimental test of hypotheses about how craniofacial morphological diversification occurred across the human lineage. Here, we combine molecular (Whole-Mount *in situ* Hybridization), 3D imaging (Optical Projection Tomography), and morphometric techniques to assess changes in the space, time, and intensity of gene expression patterns during embryonic development. We used *Fgfr2*$^{+/P253R}$ Apert syndrome mouse models, in which an *Fgfr2* mutation is associated with midfacial hypoplasia, brachycephaly, and macrocephaly. These pathological phenotypes

provide a practical model of processes similar to those involved in the evolution of a large globular braincase and a small, retracted face in modern humans. We compared the expression patterns of two downstream targets of *Fgfr2*, *Dusp6* and *Hand2*, that are relevant for brain and craniofacial development, in 25 mice carrying the *Fgfr2* mutation and 27 littermates collected between E10.5 and E11.5. Qualitative comparisons revealed that both genes are co-expressed in the brain and face with variable intensity depending on developmental time and genotype. Results suggest that the FGF signaling pathway participates in brain and face morphogenesis and that changes in the location and timing of gene expression can induce correlated changes in brain and craniofacial systems. This supports the hypothesis that facial retraction and encephalization likely evolved as direct and correlated responses to common signaling pathways. We are testing high throughput methods to produce objective quantifications of gene expression patterns that can be used in future analyses to reveal the complex genotype-phenotype correspondence in the evolution of modern human traits.