Phenotyping the brain, the face, and their genetic interaction over development

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The development of the brain and the face is intimately coordinated through a continuous physical and molecular interaction during morphogenesis. Understanding how dynamic spatio-temporal regulation of gene expression patterns guide this process is crucial to reveal mechanisms that may have contributed to human evolution. Facial retraction and encephalization are modern human traits that may have evolved in response to changes in signaling pathways that are common to the regulation of the development of these systems. Combining methods for visualizing gene expression patterns (Whole-Mount in situ Hybridization) with mesoscopic 3D imaging (Optical Projection Tomography), we are developing methods to quantify changes in the space, time and intensity of gene expression patterns in organ development using mouse models. We analyzed an Apert syndrome mouse model, which carries an FGFR2 mutation that in humans is associated with craniofacial dysmorphology and brain malformations. We compared face and head development in 43 mice (22 wildtype and 21 *Fgfr2+/P253R* mutant) between embryonic days 10.5 and 11.5. We also assessed the differential expression of *Dusp6,* a downstream target of *Fgfr2* that is relevant for both brain and craniofacial development. Geometric Morphometrics successfully detected phenotypic differences between wildtype and mutant embryos. However, traditional landmark-based methods could not be applied to quantify the fuzzy 3D spatial distribution of gene expression domains. We are testing automatic free-landmark methods (auto3Dgm) to produce accurate quantifications of gene expression patterns that can be associated with the observed phenotypic malformations. This knowledge will help reveal genotype-phenotype correspondence in brain/face development driving evolutionary change.

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