

# Study reveals new insights into facial birth defects

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Mount Sinai researchers have revealed new insights into how the body regulates craniofacial development in newborns, which can sometimes lead to birth defects such as cleft lip or palate.

The study, published November 12 in *Genes and Development*, focused on fibroblast growth factors (FGFs), a family of growth factors that mediate cellular responses, in mice. The research team studied signaling pathways that influence cell behavior, and also reported that [biological processes](#) beyond just signaling, particularly [cell adhesion](#), might play a pivotal role in how FGFs regulate a host of pathologies.

FGFs bind to and activate four different molecules called [receptor tyrosine kinases](#) (RTKs) on the surface of the cell. These RTKs, in turn, trigger an established signaling [pathway](#) that influences cellular behaviors such as proliferation, death, and migration. Improper activation of these receptors and aberrant signaling within these so-called [signal transduction pathways](#) have been linked to skeletal birth defects of the face and jaw, and to premature bone formation in the sutures, where the fibrous

joints between the bones of a baby's skull fuse before the brain is fully formed, giving the head a misshapen appearance. Deregulation of FGF activity has also been linked to multiple forms of cancer.

"Through our laboratory work with mice we've elucidated for the first time the unique role of signaling pathways that are engaged downstream by the FGF receptors in embryonic development," says Philippe Soriano, Ph.D., Professor of Cell, Development and Regenerative Biology at the Icahn School of Medicine at Mount Sinai, and senior author of the study. "This is revealing because these signaling mechanisms and the phenotypic consequences of their disruption are giving us a better understanding of how FGFs affect mid-face closure and development of the jaw. In the mouse, FGF receptors also affect implantation of the embryo into the uterus." Over the years, Dr. Soriano's laboratory has played a key role in unraveling the mechanism of RTK using genetic approaches in mice as a model system.

The Mount Sinai study also breaks new ground by uncovering how RTKs may function beyond their well-known roles in cell signaling. By engineering mutant mice that express receptors unable to engage the classic signaling pathways, the researchers were able to identify how FGFs regulate cell adhesion, the process by which cells attach to each other or to the extracellular matrix, which provides structural and biochemical support for surrounding cells. "We have always thought that all FGF activities are dependent on the typical established signaling pathways," explains Dr. Soriano. "But we were able to identify new signaling outputs that seem to function in ways independent of FGF signal transduction pathways. One of those outputs is cell adhesion."

Dr. Soriano and his team are continuing to investigate how FGF receptors work not just on the surface of the cell—which is established science—but

within the cell to modulate how [cells](#) stick to each other or to the extracellular matrix. Giving impetus to their work is the fact that knowing precisely how FGFs regulate cell adhesion could open a valuable window for scientists onto a process that is believed to underlie the development of many types of cancer.

"Perhaps most importantly, we've created surprising new investigative channels through our findings with regard to cell adhesion and signaling pathways," says Dr. Soriano. "We now want to know if there are additional biological processes at play that could bring us closer to the development one day of inhibitors of these various pathways that might prevent diseases in which FGFs and their [receptors](#) are believed to be complicit."

Provided by The Mount Sinai Hospital

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