Protein inhibitor points to potential medical treatments for skull and skin birth defects

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Researchers at Mount Sinai School of Medicine in New York have found new clues in the pathogenesis of skull and skin birth defects associated with a rare genetic disorder, Beare-Stevenson cutis gyrata syndrome (BSS). Using a mouse model, investigators found that by inhibiting the protein p38, previously associated with cancer and certain autoimmune conditions, they were able to interrupt development of specific birth defects associated with it: craniosynostosis, or the premature fusion of certain bones of the skull, and acanthosis nigricans, a hyperpigmentation skin disorder that often makes the skin look dirty and rough.

"We urgently need to identify the molecular mechanisms underlying the development of these disorders so that we can design effective treatment and strategies," said Ethylin Wang Jabs, MD, the study's senior investigator and Professor of Genetics and Genomic Sciences, Developmental and Regenerative Biology, and Pediatrics at Mount Sinai School of Medicine. "What this opens up for the first time are potential targets for treatment."

Results from the study are published in the June 2012 Journal of Clinical Investigation.

Using a mouse model of Beare-Stevenson cutis gyrata syndrome, researchers found that there was an increase in intracellular signaling through p38. When Yingli Wang, DMD, PhD, used intraperitoneal injections of an inhibitor of p38 into the mouse in utero, the skull and

skin defect improved. In a separate experiment, topical application to the skin of a p38 inhibitor helped the skin defect.

The skull disorder, craniosynostosis, has devastating consequences if surgery is not performed within the first 6 months of life. Excessive intracranial pressure prevents normal growth of the head, impairing the brain, the eyes, the ears, and cognitive development. Approximately 1 in 2500 newborns across all groups are born with this birth defect, making it one of the top 10 birth defects. The disorder is listed in birth registries in the United States.

The skin disorder, acanthosis nigricans (AN), causes hyperpigmentation, and there are no standard treatments for it. AN is common. Certain conditions increase the risk for AN, including insulin resistance, obesity, diabetes, and polycystic ovary disease. Some series have shown that as many as 74 percent of obese individuals and 36 percent of people with type 2 diabetes are parents of newborns with AN. The skin disorder is especially common in Native Americans, followed by African-Americans, Hispanics, and Caucasians.

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