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Gene variants found that increase pain sensation after common childhood surgery

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In the first genome-wide analysis of postsurgical pain in children, pediatric researchers identified variations in genes that affect a child's need for pain-control drugs. The findings suggest that at some point physicians may calibrate pain-medication dosages according to a child's individual genetic makeup.

"Although this research is only a first step for our team, it provides tremendous new insight into the biological mechanisms and brings us a little closer to personalizing medicine for pain control," said Scott D. Cook-Sather, M.D., a pediatric anesthesiologist at The Children's Hospital of Philadelphia (CHOP). He is co-first author with CHOP statistician Jin Li, Ph.D., and is the corresponding author of the study.

Cook-Sather and colleagues published the study online June 9 in the journal *Pain*. He collaborated with Hakon Hakonarson, M.D., Ph.D., director of CHOP's Center for Applied Genomics, and the senior author of the study.

The study team performed a genome-wide association study (GWAS) of more than 600 children between ages 4 and 18 who had tonsils and adenoids removed in day surgery procedures. The retrospective study analyzed whether gene variants were associated with the need for higher or lower than average dosages of morphine for pain control. The researchers also analyzed genetic links to postoperative pain scores.

The GWAS identified one gene location linked to increased morphine

requirement: the TAOK3 locus, a site not previously linked to morphine sensitivity. Genes within the TAOK3 locus carry the code for a protein with a key role in signal transduction for many cell types, including neurons involved with transmitting the sensation of pain.

"It makes sense that genes related to signaling systems would modify how patients feel pain and respond to analgesics," said Cook-Sather. "Follow-up studies are necessary to identify the fundamental neurobiology and details of the mechanisms involved."

"While scientists already know that morphine works by binding to specific opioid receptors in the nervous system," added Cook-Sather, "we don't know exactly why there is, in this setting, a tenfold variation in how much morphine patients require for pain relief." The study team found that two single-base gene variants at the TAOK3 locus were associated with approximately 8 percent of that tenfold variance in morphine requirement, comparable to that portion of the variance associated with age, body mass and overall health status combined.

Cook-Sather explained that multiple genes are assumed to contribute to these analgesic effects, and that further investigations, with larger numbers of patients, are needed to understand and prioritize the full array of genes that modify morphine response.

Within their initial sample of 617 children, the researchers found that the association between the variants in TAOK3 and the morphine dose needed for pain relief held up for children of European ancestry but not for African-American children. In both groups, however, the gene variants correlated with increased postoperative pain. "Future investigations," said Cook-Sather, "may help us predict which patients will need more pain medicine than the standard dose. We could customize an appropriate dose while the child is still under anesthesia in order to minimize the pain when the child regains consciousness."

"We have identified a novel biological pain target, and even though the variants we identified in this study explain only about 8 percent of the difference in pain sensation between individuals, they give us a strong lead in developing new therapies," said Hakonarson. "This proof-of-concept study may advance the process of individualizing pain therapy in children."

Since its launch in 2007, the Center for Applied Genomics at CHOP has published hundreds of studies revealing genomic contributions to over 50 pediatric and childhood-onset disorders, including asthma, type 1 and type 2 diabetes, autism, obesity, food allergies, attention-deficit hyperactivity disorder, inflammatory bowel disease, anorexia and pediatric cancers.

The Children's Hospital of Philadelphia supported this study with funding from the Department of Anesthesiology and Critical Care Medicine and from the Center for Applied Genomics. Co-authors with Cook-Sather, Hakonarson and Li were Theodora K. Goebel, R.N.; Emily Sussman, B.A.; and Mohamed A. Rehman, M.D., all from CHOP. Cook-Sather is an associate professor of Anesthesiology and Critical Care in the Perelman School of Medicine at the University of Pennsylvania. Hakonarson is an associate professor of Pediatrics at Penn Medicine,

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