Study Finds Genetic Component To Chronic Pain

Ed. Note: *The following is a press release from the National Institutes of Health.*

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A new NIH-funded study shows that a specific gene variant in humans affects both sensitivity to short-term (acute) pain in healthy volunteers and the risk of developing chronic pain after one kind of back surgery. Blocking increased activity of this gene after nerve injury or inflammation in animals prevented development of chronic pain.

The gene in this study, GCH1, codes for an enzyme called GTP cyclohydrolase. The study suggests that inhibiting GTP cyclohydrolase activity might help to prevent or treat chronic pain, which affects as many as 50 million people in the United States. Doctors also may be able to screen people for the gene variant to predict their risk of chronic post-surgical pain before they undergo surgery. The results appear in the October 22, 2006, advance online publication of Nature Medicine.*

"This is a completely new pathway that contributes to the development of pain," says Clifford J. Woolf, M.D., of Massachusetts General Hospital and Harvard Medical School in Boston, who led the research. "The study shows that we inherit the extent to which we feel pain, both under normal conditions and after damage to the nervous system."

Dr. Woolf carried out the study in collaboration with Mitchell B. Max, M.D., of the National Institute of Dental and Craniofacial Research (NIDCR) in Bethesda, Maryland, and colleagues at the National Institute on Alcoholism Abuse and Alcoholism (NIAAA) and elsewhere. Dr. Woolf's work was funded by the National Institute of Neurological Disorders and Stroke (NINDS). The research team also received funding from NIDCR, NIAAA, and other organizations.

The researchers originally identified GCH1 by preclinical screening for genes that undergo significant changes in expression after sciatic nerve injury. GCH1 is one of several genes that code for enzymes needed to produce a chemical called tetrahydrobiopterin (BH4). Previous studies have shown that BH4 is an essential ingredient in the process that produces dopamine and several other nerve-signaling chemicals (neurotransmitters). It also plays other important roles in the body. However, this study is the first to show that GCH1 and BH4 play a role in pain.

The investigators tested the effects of GTP cyclohydrolase and BH4 in several animal models of pain. They found that rats with neuropathic pain (pain caused by nerve damage) had greatly increased levels of GCH1 gene activity and BH4, and that injecting a GTP cyclohydrolase inhibitor called 2,4-diamino-6-hydroxypyrimidine (DAHP) alleviated hypersensitivity to pain in animal models of both neuropathic pain and inflammatory pain. In contrast, injecting BH4 greatly increased pain sensitivity.

Next, the researchers looked for GCH1 gene variations in people. They found that a specific variant of the gene, identified by combinations of one-base-pair changes in the DNA called single nucleotide polymorphisms or SNPs, protected against development of chronic post-surgical pain in people who had participated in a study of surgical diskectomy for back pain. About 28 percent of the people in the surgical study had at least one copy of the pain-protective variant of the gene (people have two copies of every gene). The researchers found that people with two copies of the protective version of GCH1 had the lowest risk of developing chronic pain, while those with just one copy had an intermediate risk and those with no copies of the variant had the highest risk.

The researchers then found that the gene variant also appeared to reduce sensations of acute pain in normal volunteers, who had been tested by NIH-supported scientists Dr. William Maixner at the University of North Carolina and Dr. Roger Fillingim at the University of Florida. Normal volunteers with two copies of the protective gene variant were less sensitive to temporary pain induced by pressure and other stimuli than those with one or no copies.

Analysis of blood cells from the people who had undergone back surgery showed that, under normal conditions, the amounts of GTP cyclohydrolase and BH4 were not significantly different in people with and without the gene variant. When the cells were subjected to a chemical that increases GCH1 gene activity, however, the amount of gene activity increased much less in people with the pain-protective variant of the gene than it did in other people.

The variation that affects pain sensitivity is in a region of the gene that may control when the gene is switched on. This, coupled with the results of the blood study, makes the researchers suspect that the protective version of the gene is less likely to be switched on during stressful conditions such as nerve damage and inflammation. "We often hear about gene mutations that are harmful, but here is a mutation that's actually protective," says Dr. Woolf.

The GTP cyclohydrolase inhibitor used in this study, DAHP, is not very strong and is unlikely to be useful as a human drug, Dr. Woolf says. Researchers are now looking for other substances that might work as GTP cyclohydrolase inhibitor drugs in humans.

Screening people for the pain-protective gene variant could allow doctors to identify people at high risk of developing chronic pain before they undergo surgery, Dr. Woolf says. Doctors might then be able to reduce the risk of chronic pain by providing more aggressive pain relief or choosing less invasive surgical procedures for people at high risk of chronic pain. Several studies have suggested that specific pain drugs or combinations of drugs can reduce the risk of chronic pain after surgery.

Dr. Woolf and his colleagues are now planning studies to define exactly how GCH1 is switched on by nerve injury and inflammation and

how it regulates pain. They also hope to identify other gene variants that affect pain sensitivity and the risk of chronic pain. "We think this gene accounts for some of the inherited differences in pain, but other genes may also play a role," Dr. Woolf says.

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Disclosure: Dr. Woolf has an equity holding in a company, Solace Pharmaceuticals, which has licensed technology from the Massachusetts General Hospital related to this research.

*Tegeder I, Costigan M, Griffin RS, Abele A, Belfer I, Schmidt H, Ehnert C, Nejim J, Marian C, Scholz J, Wu T, Allchorne A, Diatchenko L, Binshtok AM, Goldman D, Adolph J, Sama S, Atlas SJ, Carlezon WA, Parsegian A, Lotsch J, Fillingim RB, Maixner W, Geisslinger G, Max MB, Woolf CJ. "GTP cyclohydrolase and tetrahydrobiopterin regulate pain sensitivity and persistence." Nature Medicine, Advance Online Publication, October 22, 2006, doi: 10.1038/nm1490.