

## GENETICS

# Unraveling Pain's DNA

The genetics of pain, long overlooked, is now getting attention—but identifying the genes at work isn't an easy task

Neuroscientist Marshall Devor used to judge the aftermath of amputations much like everyone else. Some who have lost an arm or leg perceive a searing pain in the limb that's no longer there, whereas others are untroubled. The going theory was that this so-called phantom pain is psychological: "Some people can accept the loss of the limb, and some can't and spend their lives mourning," says Devor, who works at The Hebrew University in Jerusalem, Israel.

Then, about 2 decades ago, Devor's perspective shifted. He found that the offspring of rats who reacted strongly to a nerve injury in their leg, scratching and nibbling at their toes as if they were in pain, responded to weak stimuli with distress, unlike those born to rats less troubled by the same nerve injury. That research, published in 1990, was among the first to suggest that pain sensitivity has a genetic component.

Pinpointing the genes that predispose to pain, particularly chronic forms caused by nerve injuries, could help guide development of new pain treatments and even prevention. Such clues are desperately needed. Roughly 50 million adults in the United States suffer from persistent pain; it accounts for more than 20% of doctor's visits and 10% of health care dollars. "The solutions offered to patients are not satisfactory, and those that are cost dearly in terms of side effects," says Ze'ev Seltzer, a pain researcher at the University of Toronto in Canada.

But perhaps more than other complex diseases spurred by a mix of problem genes and environmental insults, the pain field has faced an uphill battle in finding relevant genes. The role of a gene identified several years ago as an important key to pain sensitivity is now being questioned, for example. "Even 5 years ago, people really doubted that pain was genetic at all," says Luda Diatchenko, a geneticist at the University of North Carolina, Chapel Hill (UNC-CH), who is exploring the roles of genes in facial pain.

Still, a shortlist of so-called pain genes is emerging, and with a report in *Nature Medicine* this week, scientists tentatively added another. That gene, *GCHI*, is the first to be linked to neuropathic pain, a common, difficult-to-treat chronic condition caused by nerve damage that affects more than 2 million people in the United States.

## A genetic thicket

Without an objective means of measuring pain, and with chronic pain patients exhibiting enormous variability in symptoms, designing human studies that produce lasting results has been challenging. And with hundreds of genes apparently influenced by pain in animal research, knowing which ones to pursue, and how influential they really are, is daunting, say researchers.

**"Even 5 years ago, people really doubted that pain was genetic at all."**

—Luda Diatchenko, University of North Carolina, Chapel Hill



**At risk.** Knowing who's most susceptible to pain could help surgeons take extra precautions when operating near major nerves.

To find *GCHI*, a team led by pain researcher Clifford Woolf at Massachusetts General Hospital in Boston started with what Woolf calls "a fishing expedition." They began by damaging nerves in

rats and assessing how gene expression changed with the injury. The number of genes in nerve cells whose activity shifted was overwhelming—about 1500 in all. To pinpoint those that affected pain sensitivity rather than ones simply reacting to an insult, the researchers looked for altered expression that persisted for 6 weeks following nerve injury. That shrank the number of genes about 10-fold, to roughly 150. That was "still too many to deal with one at a time," says Woolf, so the team examined whether any of those genes were known to work together in a common pathway. That highlighted a trio of genes.

Then Woolf's group turned to Mitchell Max of the National Institute of Dental and Craniofacial Research (NIDCR) in Bethesda, Maryland, who has studied pain genetics in people, including a cohort of 147 people who were followed for 2 years after back surgery to relieve leg pain from a herniated disc. The researchers asked the volunteers to rate their pain every 3 months and also examined their DNA to see whether variations in any of the three genes correlated with the pain ratings. Two showed no effect.

But a version of *GCHI* identified by a combination of 15 single-nucleotide polymorphisms (SNPs) was associated with less neuropathic leg pain in the first 2 years after surgery. People with two copies of that gene variant rated their pain as 0.06 on average, whereas those with no copies rated their pain 0.8 (Those with one copy rated their pain 0.44). *GCHI* controls production of a chemical called BH4, and Woolf's team found that administering it to rodents made sensory neurons more excitable.

It's not clear yet whether the *GCHI* connection will hold up in larger cohorts and those encompassing different types of pain. Still, the genes that have pain researchers most intrigued are those, like *GCHI*, that appear to influence the excitability of neurons. Although some studies, such as the one on facial pain in which Diatchenko is participating, focus on common chronic pain syndromes, other researchers are hoping that inherited pain disorders may be easier to dissect geneti-

cally and shed light on pain in general. At the Society for Neuroscience meeting in Atlanta, Georgia, last week, Stephen Waxman, a neurologist at Yale University, detailed the genetic mutations his group has found in a rare familial neuropathic pain syndrome called erythromelalgia. The people affected experience excruciating pain in their hands and feet when exposed to slight warmth, and abnormal vasculature turns their limbs bright red.

The mutations alter the gene for a sodium channel, a type of molecular gate that controls neural signaling. When this sodium channel has one of the mutations seen in erythromelalgia, it causes sensory neurons to fire with little provocation. “They scream when they should be whispering,” says Waxman. And whereas sodium-channel mutations have not been linked to more prevalent kinds of chronic pain, Waxman’s group and some British scientists have found that the channel appears to play a role in inflammatory pain in animals. “We’re beginning to ask the question, ‘Are there polymorphisms [in this gene] ... that don’t cause disease but are associated with high or low thresholds of pain?’” says Waxman.

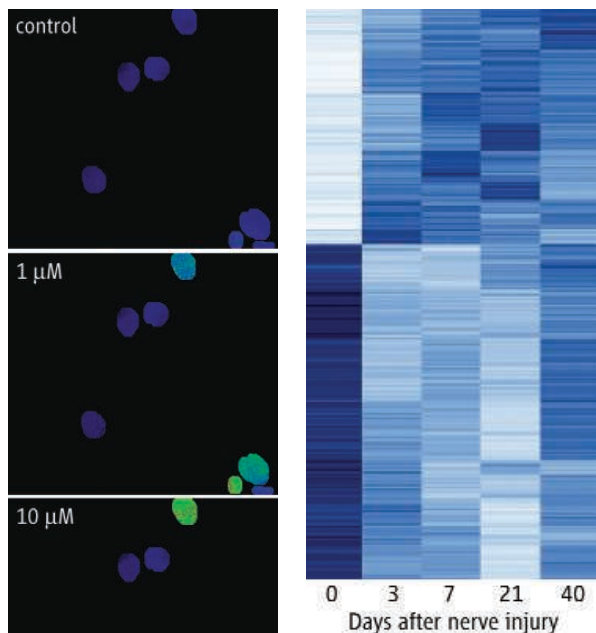
Increasingly, scientists believe that a person’s pain thresholds reflect their risk of developing chronic pain. After all, only 5% to 15% of people wounded in car accidents or by gunshots, or suffering from shingles, will develop chronic neuropathic pain—perhaps because they possess a combination of genetic mutations that increases their sensitivity to pain.

### The face of pain

As the *GCH1* story shows, finding gene variants behind pain is a complex task. The tool typically employed to tease out the genetic component of other complex diseases—twin studies—is nearly impossible to use in chronic pain because few twins will suffer the same environmental insult that leads to pain. “Chronic pain is probably the classic example of gene-environment interaction,” says Jeffrey Mogil, a neuro-

geneticist at McGill University in Montreal, Canada.

Another challenge in pain genetics is knowing whom to study. For example, in 2003, researchers led by Jon-Kar Zubieta of the University of Michigan, Ann Arbor, and David Goldman of the National Institute on Alcohol Abuse and Alcoholism in Bethesda, Maryland, reported in *Science* that among



**Tracking pain genes.** Nearly 1200 genes show expression changes (above) after a rat endures nerve damage. Scientists homed in on one of those genes and found that its protein product boosts calcium (colored dots) in neurons, making them more excitable.

people, a variation in a gene for an enzyme called COMT (catechol-*O*-methyltransferase) modulated the  $\mu$ -opioid system (21 February 2003, p. 1240). That system naturally helps the body control pain. The find initially electrified the research community, because it suggested that the gene influences a person’s pain sensitivity.

But efforts to confirm a broad role for the gene in pain have faltered. One possible explanation, says Woolf, is that various research teams have focused on different “phenotypes”: individuals with different types of pain. A study led by Raymond Dionne of NIDCR reported this summer that the gene for COMT played little role in pain sensitivity following wisdom tooth surgery. The original *Science* study, on the other hand, exposed 29 healthy volunteers to painful injections in jaw muscles. That sample size is

small, note researchers, and it’s still not clear how much overlap exists between genes that govern experimental pain and those guiding chronic pain sensitivity or susceptibility.

Most pain researchers, however, still believe that COMT has a role to play. Last year, Diatchenko and her colleagues found that different combinations of four SNPs in *COMT* affected the risk of developing a form of musculoskeletal facial pain known as temporomandibular joint disorder. Those with one particular combination of SNPs were less than half as likely to suffer from the disease and were much more resistant to pain. “The [COMT] story is probably a lot more complicated than we thought,” says Mogil.

Indeed, Mogil has found in mice that the genes governing hypersensitivity to touch are generally not the same as those influencing hypersensitivity to cold, or to heat. “Our animal studies show very clearly that all these symptoms dissociate from each other,” he says, suggesting that in different pain phenotypes, the genetic combinations at work vary.

In humans, however, various types of pain are often lumped together, and it’s virtually impossible to distinguish between the physical pain cause by overly excited sensory neurons and the patient’s emotional response to pain. Both, says Diatchenko, feed into an individual’s perception of his or her pain.

Diatchenko hopes that the facial pain study she’s involved in, which is led by her colleague William Maixner of UNC-CH, may provide a framework for teasing apart genetic and environmental drivers of chronic pain. The study, which garnered \$19 million from the National Institutes of Health—a remarkable figure, given that only 1% of the agency’s \$28 billion budget goes to pain research—will follow 3200 healthy individuals and 200 who have facial pain. Roughly 5% to 15% of the healthy group is expected to spontaneously develop facial pain as well. The researchers will hunt for both environmental factors and genetic candidates that appear to increase an individual’s susceptibility to such facial pain and other pain conditions.

“The main question is, ‘Can we predict the people who are predisposed to chronic pain conditions?’” both facial pain and beyond, says Diatchenko. Such a skill could allow physicians to take extra care in potentially dicey scenarios—such as offering additional protection to nerves at risk during surgery. Given the complexity and the halting pace of pain genetics research so far, that would be a giant step forward.

—JENNIFER COUZIN

CREDITS (LEFT TO RIGHT): A. BINSHTOCK; R. GRIFFIN AND M. COSTIGAN