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Scientists find genetic clues about pain insensitivity

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A baby who rarely cries is many parents' idea of a "happy" baby. Ashlyn Blocker was that kind of baby.

She never cried at birth, when she was hungry, wet or teething. But when neither a severe diaper rash nor a cut on the surface of her eye caused the tiniest complaint, her parents, Tara and John Blocker, realized it wasn't happiness that kept her quiet.

Ashlyn could not feel pain in a normal way.

Now, researchers at the University of Florida have pinpointed a major clue about her condition, called congenital insensitivity to pain. They identified two genetic mutations that affect how strongly pain signals are sent to the brain.

“This is a gene that, depending on how it is modified, has the ability to affect pain sensitivity to a large degree,” said Dr. Roland Staud, a pain expert and professor in the UF College of Medicine who led the study.

The findings shed light not just on the inability to feel pain, but also, at least potentially, on cases in which people feel unbearable or chronic pain. This knowledge ultimately could guide the development of novel and effective pain therapies.

The work appears in online and upcoming print editions of the *European Journal of Pain*.

Since 2004, Staud has collaborated with geneticists, neurologists, pediatricians and clinical psychologists to better understand Ashlyn's condition. They evaluated the Blocker family, who live in Patterson, Ga., and 10 other individuals who feel pain normally.

"When we found out what gene it was, we were so excited," Tara Blocker said. "It's really nice to be able to say, 'this is why.' It might be little, but to us it's huge. Finding out more about our daughter helps us take better care of her. "

The gene in question, called SCN9A, contains the "message" to produce a molecule that acts as a battery to power pain-signaling nerve cells so they can fire impulses. Mutations that lead to overactivity of that molecule lead to severe pain, whereas those that cause the molecule not to function lead to the inability to feel pain.

"If you don't have this gene it's like a faint whisper in the wind," Staud said. "Nothing much goes up the nerve, and you don't feel anything."

But Ashlyn, now 11, has a condition that is between the two extremes. Staud and colleagues found that the mutations decreased, but did not abolish, sensitivity to pain. Whereas Ashlyn cannot feel what is normally a painful touch or heat or cold, she can sense warmth and feel someone's touch or tickle. But on rare occasions, in cases of very severe illness, she has said she hurts.

"This is an interesting finding — for many families just knowing that there is a physical cause for an abnormality, in this case a mutation that causes blunted ability to feel pain, can be helpful," said Dr. Stephen G. Waxman, the Bridget Marie Flaherty professor of neurology at Yale University, and director of the Center for Neuroscience and Regeneration Research of the VA Connecticut Healthcare System. "Hopefully by studying patients with these mutations, we will more fully

understand the gene's role in pain signaling and in human pain disorders."

Waxman, who was not involved in the study, pioneered research on the affected gene.

Insensitivity to pain is rare, and since the first reported case in 1932, only a few others have surfaced. Pain is a vital survival tool, because it alerts people to damage or potentially harmful situations. It is also a key element of emotional experiences such as empathy. Sickness and premature death occur in greater rates among people who are insensitive to pain.

Pain arises from both sensory and emotional stimuli, and involves various nerves and regions of the brain. Sensations or pain come as a result of contact with an object or other stimulus such as heat, when a signal is generated and transmitted to the brain. Sometimes, as in Ashlyn's case, the signals don't get through to the brain.

For Ashlyn, that has meant many injuries over the years. She has bitten the skin off her finger, chewed her bottom lip, gotten second-degree burns on her hand and broken her ankle in a bicycle accident without feeling any of it.

Her parents have had to watch her closely to make sure she doesn't injure herself while doing the things she enjoys, such as swimming and running. They have also taught her how to look over her body for signs of injury.

While scientists potentially could manipulate genes to allow Ashlyn and others like her to feel pain more readily, they have to weigh the possibility that they might, in the process, set off other conditions such as epilepsy or hypersensitivity to pain, the researchers said. On the other

end, the idea of creating genetic therapies to block pain raises questions about whether doctors should remove a person's capacity to feel pain simply because he or she requests it.

For now, though, the UF researchers are focusing on identifying functional abnormalities associated with the genetic mutations, and ways in which the body compensates.

"It's kind of an experiment of nature that we're observing here," Staud said.

Provided by University of Florida