*Medical Xpress*

# No pain and extreme pain from one gene

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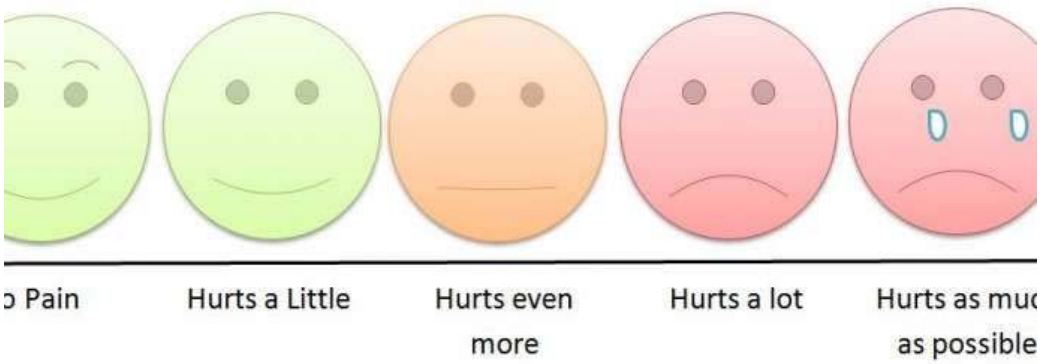



The family from northern Pakistan is one of the strangest to appear in the scientific literature. At its center is a 10-year-old, a street performer who walked on hot coals and inserted daggers through his arms before astonished crowds – feeling absolutely no pain. He died at age 13 from jumping off of a roof, considering himself impervious to all injury.

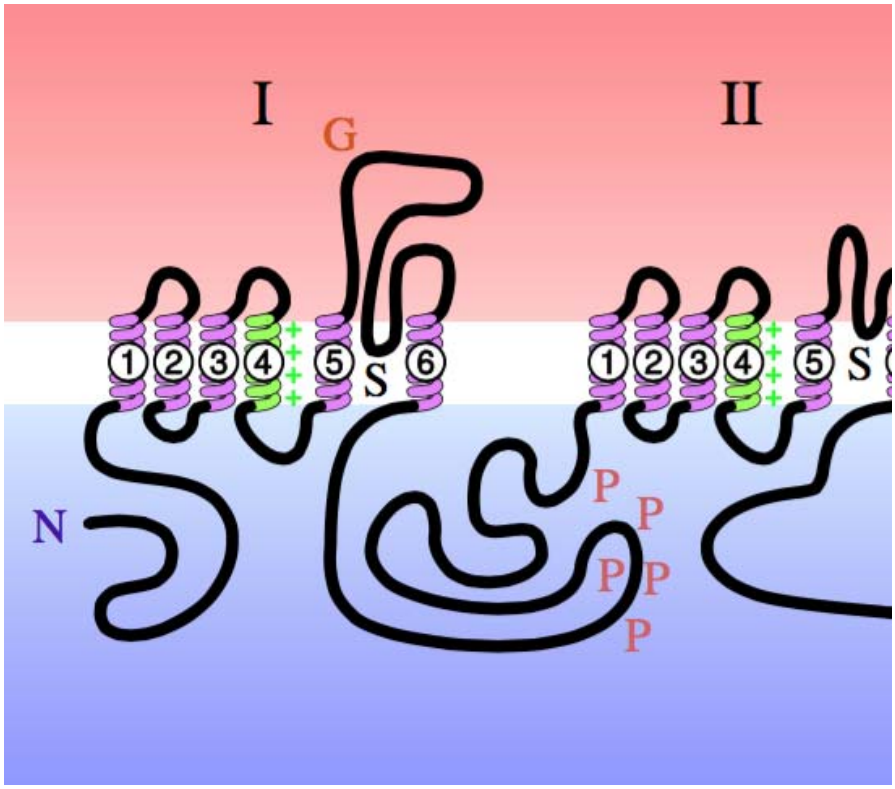
I've included this story in my textbooks for so long that I recently began to wonder if I'd been perpetuating an urban legend. Then a study in this week's Science Translational Medicine led me back to the Pakistani boy. He was real. And it turns out that different mutations in the same gene can cause complete absence of pain, or attacks of pain so severe that sufferers compare the sensation to dipping one's feet into hot lava. In these extremes lie clues to developing new painkillers.

**From Hot Coals to a Channelopathy**

In 2006, James Cox at University College London and Frank Reimann of the University of Cambridge and their colleagues pinpointed a mutation in the gene SCN9A, which encodes a sodium channel, as the likely cause of the Pakistani boy's inability to feel pain.

The team focused on 3 families from the same area of Pakistan, a nation where about 60% of marriages are between cousins. Six members of the 3 families, all age 14 or younger, also were curiously unable to feel pain.

Life without pain is dangerous. Babies chew off their tongues and lips, become scalded from hot food and drink, and without the feedback of pain toddlers bruise and even break bones. Older children learn from observation and context when to grimace so as to appear normal.



Sodium channels

Results of the study from a decade ago were intriguing. The 6 youngsters could feel touch, warmth and cold, pressure and tickles, and had a sense of where their body parts were in space, called proprioception. Many signs of nervous system function were just fine: the kids could move body parts when requested, and gagged, sweat, cried, and didn't pee unless the urge and facilities were present. Nerve biopsies were normal. But pain was different. Strong prodding, poking, and even withdrawing blood elicited no response.

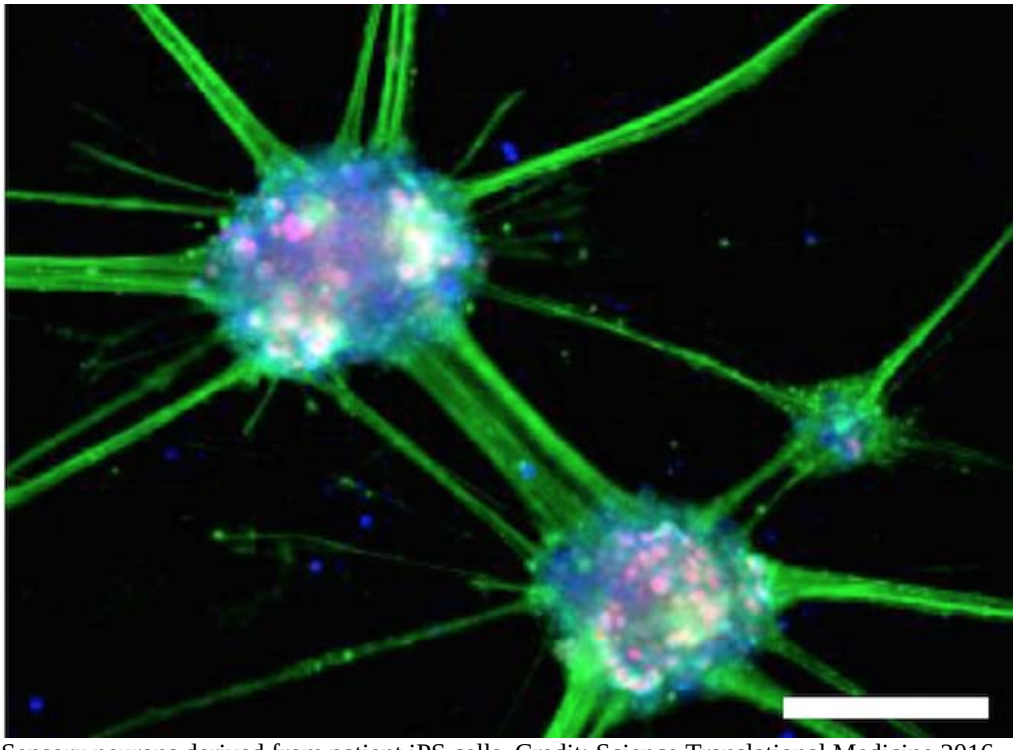
Only a handful of similar cases had ever been reported, and the nomenclature was confusing and overlapping. So the researchers named the condition from Pakistan 'channelopathy-associated insensitivity to pain' and identified the mutation in the sodium channel gene. But this was in the olden days of 2006. Instead of sequencing the children's genomes in under a day, as the researchers might today, they used painstaking positional cloning and linkage to narrow down chromosome sections that the families shared, leading them to the same part of chromosome 2. Each family had its own nonsense mutation, turning a DNA triplet that encodes an amino acid into one that encodes "stop." The result: a stunted protein.

The SCN9A gene encodes a subunit of a sodium channel, called Nav1.7, that festoons the tips of dorsal root ganglion neurons that function as nociceptors – sensing pain from the body's periphery. The sodium channel is one of ten types, distinguished by its binding tetrodotoxin. That's the stuff in pufferfish, a delicacy that makes one's lips tingle when one eats it, and which I wrote about in 2002 when its genome was sequenced.

**Burning People Syndrome**

The mutations in the children who couldn't feel pain are "loss-of-function" – their nociceptors can't generate the action potentials that provoke the sensation. Mutations in the same gene that introduce a "gain-of-function" cause something quite different—inherited erythromelalgia (IEM), aka "burning man syndrome." These people suffer episodes of acute pain upon warmth or mild exercise. Yet another variation is "paroxysmal extreme pain disorder," which causes intense pain in the face and around the rectum.

Stephen Waxman from Yale and co-author of the new paper wrote an editorial that accompanied the 2006 paper on the Pakistani families who couldn't feel pain. In a paper from 2007, he described a 15-year-old who'd suffered the burning episodes to his hands, feet, and ears since early childhood. Each attack lasted minutes to hours, he had several a day, and it was induced by exercise as well as alcohol, caffeine, or "sometimes melon." He wore open-toed shoes and fought the urge to plunge his searing feet into buckets of ice, for doctors told him this would kill the tissue. An extensive pedigree revealed 36 burning people over 6 generations of his family – classic autosomal dominant inheritance consistent with a gain-of-function mutation.



Sensory neurons derived from patient iPS cells. Credit: Science Translational Medicine 2016

The paper published yesterday in Science Translational Medicine also addresses the inappropriate pain of IEM in five people with different mutations in SCN9A, but with an intriguing side experiment: recapitulating the disease in sensory neurons derived from induced pluripotent stem (iPS) cells. The group is from the Pfizer Neuroscience and Pain

Research Unit, and includes Lishuang Cao, Anja Nitzsche, Edward Stevens, and James Bilsland.

**Enter Stem Cells**

The researchers were assessing efficacy of a drug candidate that blocks the sodium channels by inducing attacks in the participants with hot probes, and results were promising. But at the same time, they derived induced pluripotent stem (iPS) cells from the blood of four of the patients. The iPS route was necessary because neurons don't divide and therefore are not sustainable in cell culture. But the researchers could watch what happens as iPS cells from patients divide and spawn daughter cells that differentiate as sensory neurons.

Indeed, the sensory neurons coaxed from the iPS cells showed overenthusiastic firing that the drug dampened. In vitro echoed in vivo, in sync to the drug concentration. And the cells illuminated a physiological basis to the differing severities associated with the different mutations.

The iPS approach might seem a step backward, starting a preclinical investigation when a clinical one is already going well, but it's not. Identifying how a drug works can have all sorts of repercussions.

I've never been comfortable with widely-prescribed drugs whose mechanisms aren't well understood. For decades, for example, people have taken selective serotonin reuptake inhibitors (SSRIs) to treat depression. But the keeping of serotonin in synapses longer was more mantra than known mechanism, until very recently. Not many people seemed to mind, or even know, that an entire class of drugs could be marketed for years, even going generic, without the mechanism firmly established.

**Painkillers and Precision Pain Scales?**

Other aspects of the SCN9A sodium channels suggest they're a good painkiller target. The channels are not on neurons in the heart or of the central nervous system, and the children in whom the channels don't work do not have any symptoms other than their painlessness. The possibility of adverse effects seems low.

Modulating pain is critical in the practice of medicine, not just in controlling it in disease and in chronic pain, and avoiding reliance on opiates, but during surgery. A precision medicine approach to pain control might implement ion channel mutation screening to more objectively assess pain sensation than pointing to cartoon faces or assigning a number from 1 to 10.

Of course sodium channel genotypes would probably help to assess sensation, but not perception, which overlays feelings and experience on those firing pain neurons. Differences in perception explain why one woman can bear the pain of childbirth easily while another can't, why my husband can get cavities filled without Novocain and I can't,

and why my friend Linda can go back to zumba class a week after major surgery when everyone else takes weeks. Clearly, we bring more to our sense of pain than our gene variants dictate.

Pairing of the drug clinical trial with the use of iPS cells to view the condition's beginnings – the very reason for making these cells – is ingenious. Perhaps the work will lead to new painkillers that will enable all of us to experience pain at a level somewhere between that of the boy who walked on hot coals and the burning people who easily feel like they are.