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In a world of chronic pain, individual treatment possible, research shows

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An investigation into the molecular causes of a debilitating condition known as "Man on Fire Syndrome" has led Yale researchers to develop a strategy that may lead to personalized pain therapy and predict which chronic pain patients will respond to treatment.

More than a quarter of Americans suffer from chronic pain and nearly 40 percent do not get effective relief from existing drugs. In many common conditions such as diabetic neuropathy, no clear source of pain is found.

The new study published in the Nov. 13 issue of *Nature Communications* used sophisticated atomic modeling techniques to search for mutations found in a rare, agonizing, and previously untreatable form of chronic pain called erythromelagia, commonly referred to as "Man on Fire Syndrome." Researchers discovered that one of those mutations seem to predicted whether a patient would respond positively to drug treatment.

"Hopefully we can use this knowledge to help chronic pain patients in more systematic ways, and not depend upon trial and error," said Yang Yang, postdoctoral research associate in the Department of Neurology and lead author of the paper.

Under the leadership of Stephen Waxman, the Bridget Marie Flaherty Professor of Neurology, professor of neurobiology and of pharmacology, and senior author of the new paper, Yale has been a leader in identifying the sodium channel Nav1.7 at the base nerve cells

as the regulator of several forms of chronic pain. The members of the Waxman lab were intrigued when it was reported the anti-seizure medicine carbamazepine relieved pain in members of a family suffering from erythromelagia, apparently by working on the Nav 1.7 sodium channel.

Yale researchers conducted an exhaustive genetic analysis and discovered that a specific variant—a difference of a single amino acid among 1,800—in the sodium channel explained why this family responded to the drug. In this new paper, the Yale team developed a three-dimensional structural model of human Nav1.7 channel and systemically looked at different erythromelagia mutations at the atomic level. The Yale team found an additional, second mutation that was sensitive to carbamazepine treatment. In theory, chronic pain patients with this mutation should respond to treatment with carbamazepine.

"This work shows us that the goal of personalized, genomically-guided drug treatment for pain is not unrealistic," Waxman said.

Provided by Yale University