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Researchers uncover source of mystery pain

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An estimated 20 million people in the United States suffer from peripheral neuropathy, marked by the degeneration of nerves and in some cases severe pain. There is no good treatment for the disorder and doctors can find no apparent cause in one of every three cases.

An international team of scientists headed by researchers from Yale University, the Veterans Affairs Medical Center in West Haven and the University Maastricht in the Netherlands found that mutations of a single gene are linked to 30 percent of cases of unexplained neuropathy. The findings, published online June 22 in the *Annals of Neurology*, could lead to desperately needed pain treatments for victims of this debilitating disorder.

"For millions of people, the origin of this intense pain has been a frustrating mystery," said Stephen Waxman, the Bridget Marie Flaherty Professor of Neurology and professor of neurobiology and of pharmacology and a senior co-author of the paper. "All of us were surprised to find that these mutations occur in so many patients with neuropathy with unknown cause."

The study focused upon mutations of a single gene – SCNA9 – which is expressed in sensory nerve fibers. Waxman's group had discovered that mutations in this gene's product – the protein sodium channel Nav1.7 – cause a rare disorder called "Man on Fire Syndrome," characterized by excruciating and unrelenting pain. Colleagues in the Netherlands carefully scrutinized neuropathy patients to rule out all known causes of the neuropathy, such as diabetes, alcoholism, metabolic disorders and

exposure to toxins. Researchers then did a genetic analysis of 28 patients with neuropathy with no known cause. They found 30 percent of these subjects had mutations in the SCN9A gene. The researchers found that the mutations cause nerve cells to become hyperactive, a change they believe eventually leads to degeneration of nerve fibers.

"These findings will help us as clinicians to a better understanding of our patients with small fiber neuropathy and could ideally have implications for the development of future specific therapies," said Catharina G. Faber, who is a lead author of the study along with Ingemar Merkies of the Netherlands.

Provided by Yale University