



The Search for a Chronic Pain Gene

By Roger Chriss, Columnist

The book **“Chasing Men on Fire: The Story of the Search for a Pain Gene”** by Yale University neuroscientist Stephen Waxman, MD, describes the hunt to understand and treat a rare neuropathic disorder called erythromelalgia – also known as burning man syndrome.

Inherited erythromelalgia is a rare painful neuropathy that causes severe burning pain and skin redness. Attacks are periodic and commonly triggered by heat, pressure, mild activity, exertion, insomnia or stress. The burning pain occurs in small fiber sensory nerves.

The book includes 13 research papers by Waxman and his team that illustrate the process of discovering that the gene SCN9A is responsible for erythromelalgia, as well as idiopathic small fiber neuropathy. Waxman shows considerable understanding of the plight of people with these disorders.

“Since their neurological examinations were often normal, the complaints of patients with small fiber neuropathy -- which occurred without physical signs of disease of the nervous system that can be seen by the physician -- were, in the past, often dismissed as being of little consequence, or as having a psychological origin,” he wrote.

But the disorders are genetic. And understanding them has wide-ranging potential value. These mutations, once identified in families with rare inherited diseases, can teach us important lessons about other medical conditions.

Waxman cites the famous example of familial hypercholesterolemia, a rare metabolic dysfunction whose understanding led to the development of statin drugs.

Waxman’s work suggests that similar advances may be possible for other neuropathic pain disorders. Waxman and his research team found that “neuropathic pain reflects dysfunction of the nervous system and can occur when DRG [dorsal root ganglion] neurons take on a life of their own and generate pain signals even in the absence of a noxious stimulus or inflammation.”

Eventually, Waxman was able to show that one change in the genetic code for this gene was responsible. In other words, erythromelalgia and inherited small fiber neuropathy are

the result of genetic mutations – debunking the theory that patients with these disorders have psychological issues.

“Surprisingly, despite their history of chronic pain, on psychological testing we found that only two subjects displayed signs of moderate anxiety and depression,” Waxman explains.

Rigorous clinical testing confirmed these ideas. Waxman and his team began by doing human studies on erythromelalgia, then moved on to small fiber neuropathy in 2010. They found evidence that genetic mutations may contribute to disorders of pain signaling. Understanding the exact pathophysiology of these painful neuropathies opens the door to new and more effective treatments.

“Identification of specific molecules that play key roles in axonal injury might provide a basis for therapies that would prevent, or slow, the degeneration of axons, thus halting or slowing the progression of peripheral neuropathy,” Waxman wrote.

The first drug tried was the sodium channel blocker carbamazepine. Pre-clinical studies in people confirmed that it does have a protective effect. Additional work using a research drug nicknamed “771” shows similar promise.

Research into leveraging this hard-won knowledge is ongoing. This work could ultimately lead to new treatments for a wide range of neuropathic disorders, including trigeminal neuralgia, diabetic neuropathy, and phantom limb pain.

The book “Chasing Men on Fire” amply illustrates the challenges of medical research and the importance of even seemingly small genetic variations in chronic neuropathic disorders. And it reminds us that rare disorders often provide invaluable insight into human disease and dysfunction that can benefit us all.



*Roger Chriss lives with Ehlers Danlos syndrome and is a proud member of the **Ehlers-Danlos Society**. Roger is a technical consultant in Washington state, where he specializes in mathematics and research.*

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