Genetic testing of the SCN9A Gene in Inherited Pain Syndromes

**Disorder also known as:** Inherited erythromelalgia (IEM); Paroxysmal extreme pain disorder (PEPD); Small fiber neuropathy (SFN); Congenital indifference to pain (CIP)

**Clinical Features:**
Pathogenic variants in the SCN9A gene cause several distinct clinical disorders associated with increased pain sensitivity or indifference to pain, in some cases associated with autonomic or other symptoms.

Inherited erythromelalgia (IEM) is characterized by recurrent attacks of bilateral, symmetric intense pain accompanied by redness, warmth, and swelling. Onset is typically in childhood or adolescence. Symptoms are noted first in the feet, followed by the hands, and in later stages can also involve the legs, arms, face, and ears. Episodes are often triggered by warmth, exercise, alcohol, or other vasodilating agents and may eventually occur multiple times per day or become constant.

Paroxysmal extreme pain disorder (PEPD), previously called familial rectal pain, is characterized by episodes of burning pain in the rectal, ocular, and mandibular pain in association with autonomic symptoms such as skin flushing, tonic-nonepileptic seizures, bradycardia, or apnea. Symptoms are typically noted at birth and are triggered by bowel movements. Over time, the episodes of rectal pain decrease, but ocular and mandibular pain becomes more prominent and may be triggered by temperature changes, eating, or emotional stress. Many individuals with PEPD respond well to treatment with carbamazepine.

Small fiber neuropathy (SFN) results in neuropathic pain that is often described as burning, tingling, or stabbing and typically begins in the distal extremities. Pain is often associated with autonomic symptoms such as orthostatic dizziness, palpitations, dry eyes, and dry mouth. Some individuals report that episodes are triggered by heat or exercise. The onset is typically in adulthood. Individuals with SFN have thinly myelinated and unmyelinated small diameter nerve fibers, and the clinical diagnosis is confirmed by demonstrating reduced intraepidermal nerve fiber density (IENFD) and/or abnormal quantitative sensory testing (QST) in the presence of normal nerve conduction studies.

Congenital indifference to pain (CIP) is characterized by the inability to experience inflammatory, heat, or visceral pain sensations. All other sensory, motor, and autonomic functions are normal. Affected individuals have typically exhibited bone deformities and neuropathic joints secondary to untreated injuries, self-mutilating oral and extremity lesions.
from biting, and a history of burn-related injuries. They also experience anosmia or hyperosmia but have normal blood pressure, tear formation, sweating, and body temperature regulation.

**Inheritance Pattern/Genetics:**
Variants in the SCN9A gene causing IEM, PEPD, and SFN are inherited in an autosomal dominant manner, while variants causing CIP follow autosomal recessive inheritance.

**Test Methods:**
Analysis is performed by bi-directional sequencing of the 26 coding exons and the exon/intron splice junctions of the SCN9A gene. Any variant identified is confirmed by repeat analysis using sequencing, restriction fragment analysis, or other methods as appropriate.

**Test Sensitivity:**
The likelihood of detecting a variant in the SCN9A gene depends on an individual’s clinical phenotype, and, to date, the clinical sensitivity of SCN9A sequencing has only been evaluated in a small number of patients. An SCN9A variant was identified in 5/6 (83%) probands with IEM, 8/13 (62%) probands with PEPD, and 8/28 (29%) probands with idiopathic SFN.\(^1,2,3\) Additionally, homozygous or compound heterozygous variants in SCN9A were detected in 9/9 (100%) probands from multiple ethnicities with CIP.\(^4\)

**References:**