Erythermalgia / Paroxysmal extreme pain disorder / Small fiber neuropathy / Congenital insensitivity to pain (SCN9A)

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 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]

Test Methods:
Using genomic DNA from the submitted specimen, the coding regions and splice junctions of the requested gene are PCR amplified and capillary sequencing is performed. Bi-directional sequence is assembled, aligned to reference gene sequences based on NCBI RefSeq transcript and human genome build GRCh37/UCSC hg19, and analyzed for sequence variants. Concurrent deletion/duplication testing is performed for most, if not all, of the coding exons using exon-level oligo array CGH (ExonArrayDx), and data analysis is performed using gene-specific filtering. Probe sequences and locations are based on human genome build GRCh37/UCSC hg19. Reported clinically significant variants are confirmed by an appropriate method. Sequence and copy number variants are reported according to the Human Genome Variation Society (HGVS) or International System for Human Cytogenetic Nomenclature (ISCN) guidelines, respectively. Reportable variants include pathogenic variants, likely pathogenic variants and variants of uncertain significance. Likely benign and benign variants, if present, are not routinely reported but are available upon request.

References:

1. Drenth et al., (2005) J Invest Dermatol 124:1233-1238.
2. Fertleman et al., (2006) Neuron 52;767-774.
3. Faber et al., (2012) Ann Neurol 71 :26-39.
4. Goldberg et al., (2007) Clin Genet 71:311-319.
5. Dabby R., (2012) Curr Neurol Neurosci Rep 12 :76-83.
6. Fischer, T.Z. and Waxman, S.G., (2010) Ann NY Acad Sci 1184:196-207.
7. Dib-Hajj et al., (2008) Adv in Genet 63:85-11.