SERPING1 (C1INH) Gene Analysis in Hereditary Angioedema (HAE)

Disorder also known as: Hereditary angioedema Type I or II; Hereditary angioneurotic edema (HANE); C1 esterase inhibitor deficiency; C1 inhibitor; C1-INH

Clinical Features:
Angioedema; episodic non-puritic, non-urticarial, non-pitting edema; laryngeal edema; GI symptoms including pain with visceral edema, nausea, diarrhea and vomiting. Trauma can precipitate or aggravate edema. In Type 1 HAE, C1 esterase inhibitor is quantitatively decreased while in Type II HAE, serum levels of the protein are normal or elevated, but activity is reduced. A third type, HAE III, is associated with variants in a different gene (F12) that is not included in this test.

Genetics:
Hereditary Angioedema (HAE) has an autosomal dominant pattern of inheritance, though de novo variants occur in a minority of cases.

Test Methods:
Analysis is performed by bi-directional sequencing of each of the seven coding exons (exons 2-8) of the SERPING1 gene plus targeted array CGH analysis with exon-level resolution (ExonArrayDx) to evaluate for deletions and duplications of one or more exons. Variants found in the first person of a family to be tested are confirmed by repeat analysis using sequencing, restriction fragment analysis, or another appropriate method.

Test Sensitivity:
Germline pathogenic variants in SERPING1 have been found in nearly all patients with the clinical findings of hereditary angioedema and deficient levels or activity of C1 esterase inhibitor. About 82% of patients have variants that are identifiable by sequencing while ~17% have gross duplications or deletions. Both strategies are employed in this test. Only about 1% of variants are located in the promoter or are otherwise not detectable with this test.[1,2,3]

Variant Spectrum:
Variants are dispersed throughout the SERPING1 gene, and include missense, frameshift, nonsense, splice-site, promoter, and in-frame small deletion/insertion variants. In addition, this gene is predisposed to gross rearrangements due to numerous intragenic Alu repeats.[4]

References:

1. Kalmár, L. et al., HAEdb: A Novel Interactive, Locus-Specific Mutation Database for the C1 Inhibitor Gene. Hum Mutat. 25: 1-5, 2005.
2. Kalmár, L. et al., Mutation Screening for the C1 Inhibitor Gene Among Hungarian Patients With Hereditary Angioedema. Hum Mutat. 22:498, 2003.
3. Bowen, B. et al., A Review of the Reported Defects in the Human C1 Esterase Inhibitor Gene Producing Hereditary Angioedema Including Four New Mutations. Clin Immunol. 98: 157-163, 2001.
4. Stoppa-Lyonnet et al. Recombinational Biases in the Rearranged C1-Inhibitor Genes of Hereditary Angioedema Patients, Am J Hum Genet 49:1055, 1991.