F12 Gene Testing in Hereditary Angioedema (HAE) Type III

Clinical Features:
Hereditary angioedema type III is characterized primarily by skin swellings (predominantly facial) and abdominal attacks. Additional symptoms that may occur are tongue swellings, laryngeal edemas and swellings of the soft palate. Affected individuals are predominantly women, though men can be affected, typically at a later age of onset and with less frequency and severity of attacks. Factors that can influence the onset and frequency of angioedemic attacks include trauma and increased estrogen levels. Nearly 60% of women experienced onset of symptoms after initiation of oral contraceptives or during the first pregnancy.[1] Features that distinguish HAE type III from types I and II include: presence of normal C1 inhibitor activity levels, average later age of onset (typically in the 2nd decade of life), predominance of facial swelling as compared to swellings of the extremities and sex bias.

Genetics:
Hereditary angioedema type III has an autosomal dominant with variable expressivity, incomplete penetrance and sex bias.

Test Methods:
Using genomic DNA obtained from the submitted biological material, bi-directional sequence of exon 9 of the F12 gene is obtained using 2 independent sets of primers and analyzed for any variant of codon 328, corresponding to amino acid Thr309 in the mature processed protein. If a sequence change is identified, the variants is confirmed by a second sequence analysis.

Test Sensitivity:
In an early study, approximately 25% of individuals with a clinical diagnosis of HAE type III had a pathogenic variant in the F12 gene at codon Thr328. Nearly 85% of those individuals had the Thr328Lys (T328K) variant, while the remainder had the Thr328Arg (T328R) variant. The method used by GeneDx to screen the F12 gene is expected to identify any variants that occur at this site in the gene with a sensitivity greater than 99%.

Variant Spectrum:
Only two variants have been reported in the F12 gene in association with HAE type III. Both affect codon 328 in exon 9: Thr328Lys and Thr328Arg. In the mature processed protein, this position becomes Thr309, so these variants have also been called Thr309Lys (T309K) and Thr309Arg (T309R).

References:

1. Bork K. et al., Hereditary angioedema caused by missense mutations in the factor XII g ene: Clinical features, trigger factors, and therapy. J Allergy Clin Immunol. 2009 Jul;124(1):129-34.
2. Cichon S. et al., Increased activity of coagulation factor XII (Hageman factor) causes hereditary angioedema type III. Am J Hum Genet. 2006 Dec;79(6):1098-104.
3. Dewald G. and Bork K., Missense mutations in the coagulation factor XII (Hageman factor) gene in hereditary angioedema with normal C1 inhibitor. Biochem Biophys Res Commun. 2006 May 19;343(4):1286-9.
4. Martin L. et al., Hereditary angioedema with normal C1 inhibitor gene in a family with affected women and men is associated with the p.Thr328Lys mutation in the F12 gene. J Allergy Clin Immunol. 2007 Oct;120(4):975-7.