
بسم الله الرحمن الرحیم

Genetics of Hereditary Angioedema

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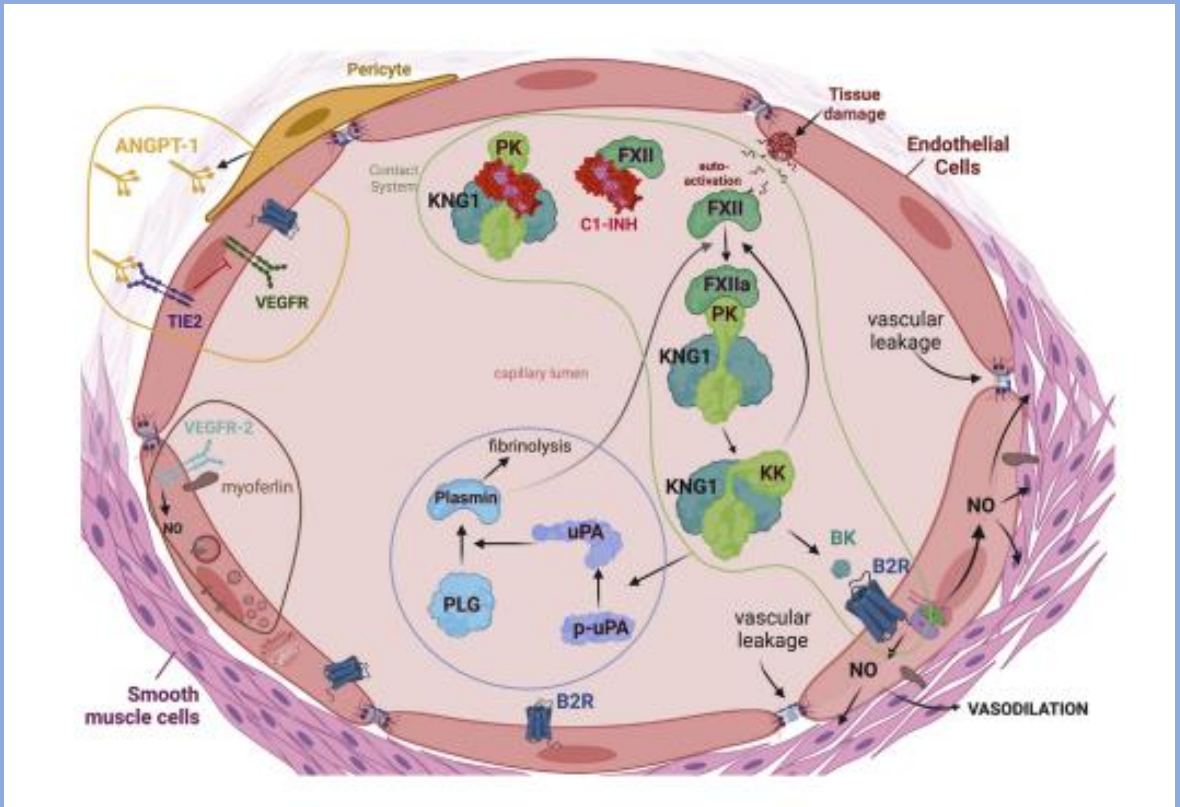
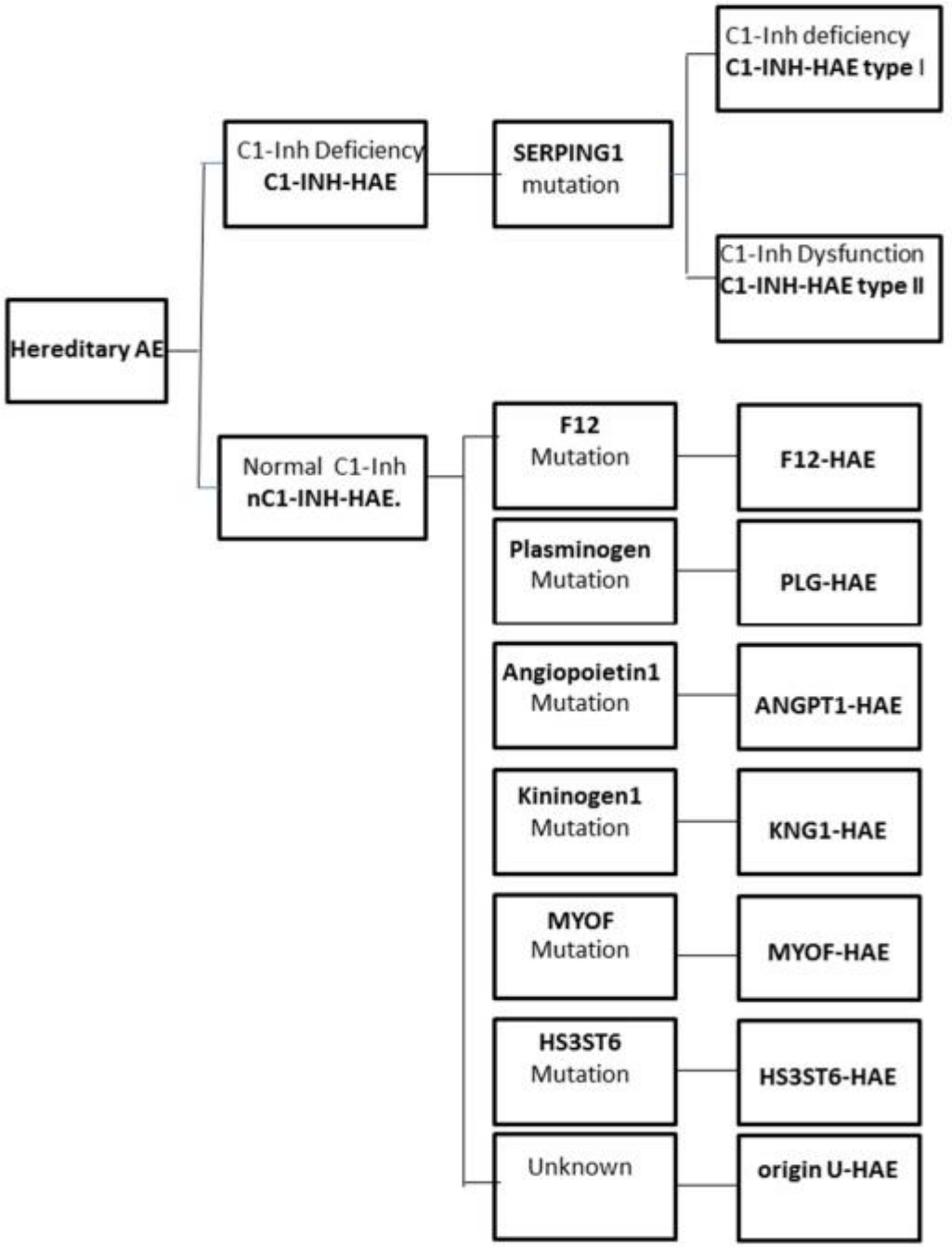
Intravascular mechanisms of permeability regulation involved in HAE



In the Contact System (green), C1-INH regulates factor XII (FXII) autoactivation, which activates plasma prokallikrein (PK). Activated kallikrein (KK) cleaves high-molecular-weight KNG1, generating bradykinin (BK). BK activates the B2-receptor (B2R), releasing nitric oxide (NO) and causing vasodilation. Deficiency of C1- INH, or specific mutations in the genes encoding FXII or KNG1, cause the release of an excess of BK, leading to HAE. Angiopoietin-1 (ANGPT-1) and myoferlin control vascular permeability by regulating VEGF signaling through tyrosine kinase receptor-2 (TIE2) and VEGF receptor-2 (VEGFR-2). Specific mutations in the genes encoding ANGPT-1 (yellow) or myoferlin (brown) disturb these regulatory mechanisms and are associated with HAE. A specific mutation in the gene encoding PLG, a key enzyme in the fibrinolytic system (blue) and associated with the Contact System, is also known to cause HAE by unclear mechanisms. p-uPA, Proeurokinase plasminogen activator; uPA, urokinase plasminogen activator.

Classification of the different forms of hereditary angioedema



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Genetic Study of Hereditary Angioedema Type I and Type II (First Report from Iranian Patients: Describing Three New Mutations)

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ABSTRACT

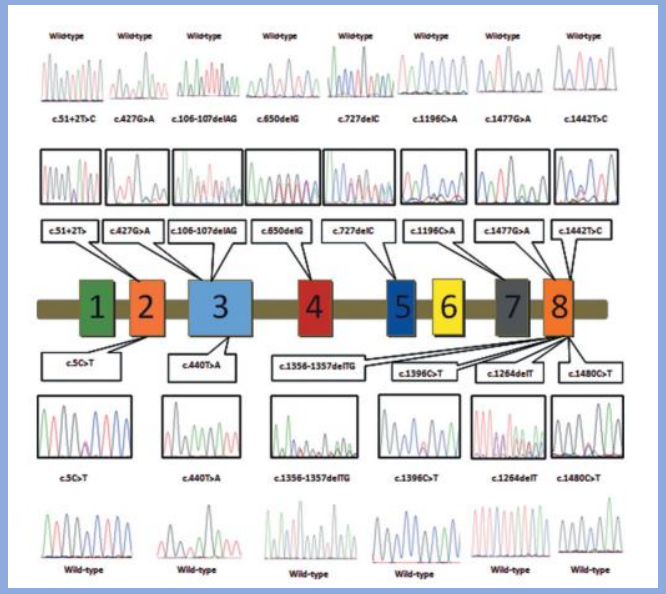
Background: Hereditary Angioedema (HAE) is a rare autosomal dominant immunodeficiency disease with mutation in C1 inhibitor gene (*SERPING1*) which deficient and dysfunction of C1-INH protein result in HAE type I or type II, respectively. The present study aimed to define the genetic spectrum of HAE type I and type II among Iranian patients.

Methods: Thirty-four patients with clinical phenotype of recurrent edematous attacks in face, upper and lower limbs, hands, and upper airway entered the study. Mutations in *SERPING1* were analyzed using PCR and Sanger Sequencing. In addition, Multiplex Ligation-dependent Probe Amplification (MLPA) was performed to discover large deletions or duplications in negative screening samples by Sanger.

Results: Twenty-three patients were diagnosed with HAE type I and 11 with HAE type II. Fourteen distinctive pathogenic variations including five frameshift (p.G217Vfs*, p.V454Gfs*18, p.S422Lfs*9, p.S36Ffs*21, p.L243Cfs*9), seven missense (p.A2V, p.G493R, p.V147E, p.G143R, p.L481P, p.P399H, p.R466C), one nonsense (p.R494*), and one splicing defect (C.51 + 2 T>C), which three of these mutations were identified novel. However, no mutation was found in seven patients by Sanger sequencing and MLPA.

Conclusion: Final diagnosis with mutation analysis of HAE after clinical

KEYWORDS
Sequencing; mutation; C4; SERPING1; C1 Inhibitor



Type 1 are dispersed throughout the entire SERPING1. Type 2 mutations map around the protein reactive center loop (RCL), with the single exception of a mutation in the amino acid residue Lys251, which affects functionality after protein folding.

More than 748 mutations reported

High variability in clinical expression between patients with the same mutation

- **Other related genes could be potential**

p.Y244C, p.G354R, and p.T916M in the ACE gene; p.C548Y in the KLKB1 (kallikrein) gene; and p.D287N in the NOS3 (nitric oxide synthase) gene

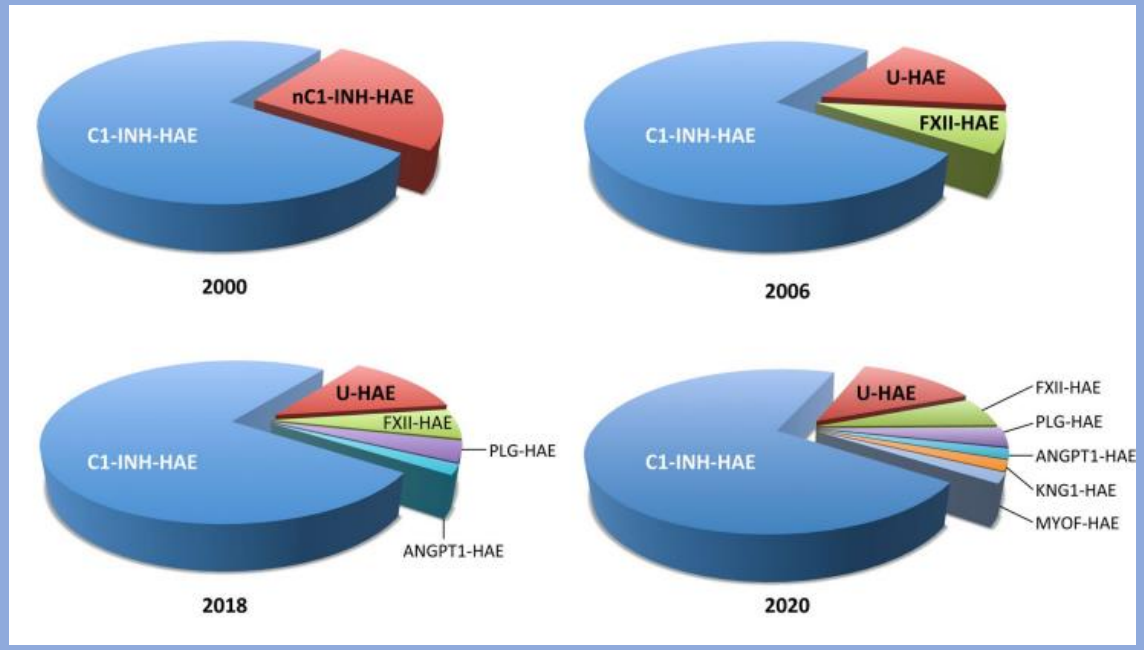
- **Epigenetics and environmental factors**

Do epigenetic changes in H19 locus by hormones offer an explanation for some of the notoriously unexplained variability in angioedema attacks or C4 levels in HAE patients?

- **The higher cortisol (due to GR polymorphism) level observed during attacks may reflect the effect of a stressful situation (such as of the attack itself), on the patients' neuroendocrine system.**

Gut microbiome in patients with HAE and explored the possible role of bacteria in the etiology of edema episodes, which may provide new clues for the prediction of disease course, clinical treatment, and therapeutic evaluation.

The evolution of HAE taxonomy



Identification of new genes and families with HAE with normal C1-INH will facilitate the diagnosis of additional patients and the study of the mechanisms of pathogenesis.

International consensus on the use of genetics in the management of hereditary angioedema
(14 experts)

Statement 1	Ordinarily, genotyping is not necessary for the diagnosis of C1-INH-HAE with rare exceptions, like inconclusive measurements of C4 and/or C1-INH antigenic or functional levels, and the diagnosis of the disease in newborns and children or in asymptomatic relatives.
Statement 2	Genotyping is required for the diagnosis of FXII-HAE, PLG-HAE and ANGPT1-HAE.
Statement 3	*SERPING1* genotyping should cover all exonic, 5'- and 3'-UTR regions and exon-intron boundaries for SNVs, MNVs and large defects.
Statement 4	Segregation study of novel *SERPING1* variants with the disease in multiple family members can provide key evidence of their pathogenicity and penetrance, and should be performed where possible.
Statement 5	Exon 9 of *F12* is the only region of the gene that is recommended to be analyzed as a routine molecular diagnosis of FXII-HAE.
Statement 6	HGVS nomenclature should be used in the reports.
Statement 7	Clinical laboratories and researchers should submit all detected variants to ClinVar.
Statement 8	The constitution of an approved by ClinGen HAE Variant Curation Expert Panel is recommended to help evaluate the pathogenicity of individual genetic variants submitted to ClinVar, to design and validate gene-optimized rules for variant classification.
Statement 9	Laboratories performing and reporting results of HAE genetic testing are encouraged to incorporate the adapted ACMG-AMP guidelines.
Statement 10	There is an urgent need to establish and implement clinical practice guidelines, standardized procedures for gene testing and EQA programs to provide a framework for best laboratory practice and reporting on the genetic diagnosis of HAEs.
Statement 11	It is recommended to implement genetic counseling –placed within the legal framework of each country– in collaboration with experts specialized

The importance of HAE genetic diagnosis

First-degree relatives of patients with HAE patients are at risk for having the disease. So, screening of family members, including individuals who were asymptomatic, is the key for earlier diagnosis and effective treatment.

Precision Medicine and pharmacogenomics era in HAE management is ready. Disease endotypes are expected to be uncovered and specifed targets for therapeutic intervention will be detected, promising a more efective, individualized management of the disease.

با سپاس از توجه
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