An update on the genetics and pathogenesis of hereditary angioedema

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Abstract
Hereditary angioedema (HAE) is an uncommon genetic disorder characterized by recurrent episodes of edema involving subcutaneous tissue and submucosa. The pathogenesis of HAE reflects an intricate coordinated regulation of components of complement, kinin and hemostatic pathway. Till date, mutations in 4 different genes have been identified to cause HAE which includes serine protease inhibitor G1 (SERPING1), factor XII (F12), plasminogen (PLG) and angiopoietin 1 (ANGPT1). These mutations lead to increased bradykinin 2 receptor mediated signalling via increased production of bradykinin except mutations in ANGPT1 gene that disturbs the cytoskeletal assembly of vascular endothelial cells. In this review we aim to summarize the recent advances in the pathogenesis and genetics of HAE. We also provide an overview of possible future prospects in the identification of new genetic defects in HAE.

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Introduction
Hereditary angioedema (HAE) is a genetic disorder that predisposes an individual to develop vasogenic edema. Prevalence of HAE has been reported to be 1 in 10,000 to 1 in 150,000.1 The pathogenesis of HAE involves accumulation of extravascular fluid in various tissues via a non-inflammatory and non-allergic mechanism. Clinical manifestations include abrupt onset swelling around eyes, face and extremities; pain abdomen (as a result of bowel edema) and laryngeal edema leading to hoarseness of voice, breathing difficulty and occasionally death.2,3 Awareness and recognition of this disease is important as HAE is often misdiagnosed as allergic angioedema or acute abdomen (especially acute appendicitis).4 This may often lead to inappropriate use of antihistamines, corticosteroids, adrenaline and sometimes even surgical interventions.4

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Identification of defects in \textit{SERPING1} gene and several other recently identified genes have added significantly to the understanding of pathophysiology of HAE. This disease was initially believed to be a disorder of complement pathway caused by deficiency of C1-inhibitor (C1-INH). However, identification of novel genetic defects (other than \textit{SERPING1} gene) has expanded the spectrum of this disease beyond complement pathway. Genetic defects in some of the intermediate pathway components that may be possible cause HAE are yet to be identified. These advances may bring new therapeutic modalities for the management of HAE. In this review, we aim to update about current understanding in the pathogenesis and recent advances in the genetics of HAE.

**Pathophysiology of HAE**

Elevated serum levels of bradykinin in the blood are responsible for clinical manifestations seen in patients with HAE. Bradykinin is generated in the body via a complex interaction of various molecules involved in kinin, complement, hemostatic and fibrinolytic pathways (Fig. 1). Factor XII is activated at first by negatively charged surfaces. Activated FXII subsequently activates prekallikrein to kallikrein (prekallikrein may also be activated by enzyme prolylcarboxypeptidase). Kallikrein is capable of directly converting plasminogen to plasmin and also with the help of urokinase type plasminogen activator. Plasmin and kallikrein in turn augment Factor XIIa generation thereby creating an auto-activation loop. Kallikrein generates bradykinin, a nonapeptide, from kininogen (high molecular weight form (HMWK)). Kallidin, a decapetide with an additional lysine residue at the amino-terminal end of bradykinin, is generated preferentially from low molecular weight kininogen (LMWK). Kallidin, a decapeptide with an additional lysine residue at the amino-terminal end of bradykinin, is generated preferentially from low molecular weight kininogen (LMWK). Kallidin, a decapeptide with an additional lysine residue at the amino-terminal end of bradykinin, is generated preferentially from low molecular weight kininogen (LMWK).7 Bradykinin can also be generated from kallidin by the action of aminopeptidases. Kininase I generates active metabolites from kallidin and bradykinin, whereas, angiotensin-converting enzyme, ACE (also known as Kininase II), and aminopeptidases both inactivate bradykinin and kallidin (Fig. 1).

Most cases of hereditary angioedema result from mutations in the gene encoding for C1 esterase inhibitor (C1-INH) protein. C1-INH belongs to serine protease inhibitor (serpin) protein superfamily. This superfamily also includes other proteins such as \( \alpha \)-antitrypsin, antithrombin III, \( \alpha \)-antichymotrypsin, protein C inhibitor and heparin cofactor II. Genetic defects in these proteins have also been referred to as serpinopathies. As defects in these genes lead to conformational change in protein, its dimerization and loss of function, hence these defects may also be

![Figure 1](image-url)  
A simplified summary of the kinin metabolism and the mutual interactions between the kinin, complement, hemostatic and fibrinolytic pathways. (The blue arrows represent the augmentation of the enzymatic reactions shown in brown arrows). The sites of action of C1 esterase inhibitor (C1-INH) are represented in green chevron shapes). Abbreviations: FXII — Factor XII, a as a suffix indicates the active form; pK — prekallikrein; K (in bold) — kallikrein; HMWK — high molecular weight kininogen; LMWK — low molecular weight kininogen; BK — bradykinin; KD — kallidin (lysine-bradykinin: K-BK), BK2-9 — bradykinin with its first amino acid cleaved off; BK1-7 — bradykinin with its last two amino acids cleaved off; Des-R BK — bradykinin with its ninth arginine residue cleaved off; meaning of subscripts in case of kallidin (K-BK) is the same as that for bradykinin derivatives; ACE (also called kininase II) — angiotensinogen converting enzyme, AP — aminopeptidase, K I — kininase I.
labeled as conformational disorders.\(^9,10\) Mutation in \textit{SERPING1} gene leads to either decreased levels or functionally abnormal C1-INH protein. This results in loss of regulation of factor XIIa and kallikrein enzymes thereby leading to excess production of bradykinin. Bradykinin is the key molecule that mediates all clinical manifestations of HAE by acting on BR2 receptors leading to increased vascular permeability and edema.\(^11\) Other than C1-INH, defects in many other molecules involved in this pathway may lead to excess production of bradykinin and similar clinical manifestations.

### Genetics of HAE

Mutations in the \textit{SERPING1} gene are responsible for majority of cases of hereditary angioedema. In addition, various genetic defects have also been found to result in HAE phenotype (Fig. 2). \textit{SERPING1} gene mutations (that lead to type 1 and type 2 HAE), constitute more than 95\% of all cases of HAE. Clinical manifestations of C1-INH deficiency HAE are highly variable and depends upon the location of mutation in \textit{SERPING1} gene. This gene is characterized by a remarkable allelic heterogeneity and approximately 450 different mutations have been reported as per the Human Gene Mutation Database (HGMD)\(^12\) and a similar database specifically dedicated for HAE (HAEdb, hae.enzim.hu).\(^13\) Mutations in \textit{SERPING1} gene may be classified as shown in Fig. 3. This gene is located on chromosome 11 band position 11q12-q13.1 and has an unusual promoter devoid of TATA box. It rather contains TdT-like initiator and poly purine pyrimidine tract.\(^14\) \textit{SERPING1} gene consists of 8 exons and 7 introns. Various exonic mutations and mutations at intron/exon junctions have been identified in this gene and these mutations are transmitted with an autosomal dominant mode of inheritance. However, approximately a quarter of all C1-INH deficiency HAE patients are sporadic in nature (i.e. they are caused by de-novo mutations in \textit{SERPING1} gene).\(^15\) Since the availability of various mutations reported in \textit{SERPING1} gene, it has become easier to predict the structural and functional attributes of this gene thereby explaining the phenomena of allelic heterogeneity.\(^16,17\)

\textit{SERPING1} gene is an example of mutagenic liability and various theories have been postulated for the same: 1) \textit{SERPING1} gene is located near centromeric region; 2) Presence of 17 Alu repeats on intron 7 of the gene makes it a hotspot for non-homologous recombination and causes partial deletions or duplication in the gene,\(^18\) characterized by absence of protein product accounting for approximately 15–20% of all cases of C1-INH deficiency HAE; 3) Presence of CpG sites in the coding part of the gene predisposes it for mutations due to spontaneous deamination.
The 466th residue of gene encodes for the arginine amino acid (CGC) that forms the reactive center of CI-INH and CpG is a natural target for recurrent amino acid substitution. Missense mutations constitute approximately 30–40% of all mutations in SERPING1 gene. Various nonsense and indel mutations lead to addition of premature stop codon and frame-shift mutations that eliminate protein synthesis via nonsense mediated mRNA decay.

Single Nucleotide Polymorphisms (SNPs) in SERPING1 gene have also been found to be associated with some non-HAE disease conditions; e.g. rs4926 [c.1438G>A, p.V480M] polymorphism is a missense variant in the coding region and has been found to be associated with staphylococcal carriage of the anterior nares. In Caucasian populations, presence of intron 6 SNP (rs2511989) in SERPING1 gene has been found to be associated with age related macular degeneration.

**Factor XII gene**

In the year 2000, Bork et al described another type of HAE with a quantitatively and qualitatively normal C1-INH (labeled as nlC1-INH-HAE). In this rare type of HAE, clinical manifestations were found to be similar to classical type 1 and 2 HAE but no mutation was detected in the SERPING1 gene. The genetic defect for this type of HAE was discovered in the year 2006 when two missense mutations (p.Thr309Lys and p.Thr309Arg) in F12 gene were detected for the first time in a German family (Table 1). Over the next few years after discovery of mutations in F12 gene, researchers found out that these mutations lead to increased production of activated Factor XII (Factor XIIa) via plasmin. This also provides an insight into the effect of anti-fibrinolytic medications in this type of HAE. Around 300 patients with F12 gene mutations have been reported till date (OMIM#610619). F12 gene has a size of 12 kb and comprises of 14 exons. The promoter of the F12 gene is similar but not identical to the promoter of the estrogen responsive elements (EREs) gene. Because of this similarity, estrogen also enhances the concentration of FXII in the plasma and may produce manifestations similar to this type.

### Table 1 Summary of the mutations described in F12, plasminogen (PLG) and angiopoietin (ANGPT1) genes resulting in HAE.

| S no | Gene name | Variant observed in HAE |
|------|-----------|-------------------------|
| 1.   | F12       | Exon 9 missense variants (p.Thr328Lys) and (p.Thr328Arg) Exon 9/intron 9 boundary large deletion of 72 bp (c.971_1018 + 24del72) duplication of 18 bp (c.892_909dup) |
| 2.   | Plasminogen (PLG) | Exon 9 missense variant (c.988 A>G), (p.Lys330Glu) |
| 3.   | Angiopoietin (ANGPT1) | Missense mutation c.807G>T, (p.Ala119Ser) |

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of HAE.\textsuperscript{30} F12 gene mutation associated with HAE is a gain of function mutation and is transmitted in an autosomal dominant mode of inheritance.\textsuperscript{31} Four most common pathogenic mutations in this gene have been identified so far. These include 2 missense variants in exon 9 (p.Thr328Lys and p.Thr328Arg); 72 bp deletion (c.971_1018 +24del72) in two unrelated families from Turkey; mutation at the exon 9/intron 9 junction\textsuperscript{12,32} and 18 bp duplication (c.892_909dup) in a Hungarian family causing repetition of 6 amino acids (p.298-303) at the same locus.\textsuperscript{33} The clinical phenotype of HAE caused by mutations in F12 gene is similar to C1INH deficiency HAE except that there is higher female predominance, more aggravation during pregnancy and more estrogen dependency.\textsuperscript{34} Complement C4 and C1-INH activity is often normal except occasionally during the attack. Assessment of activity of coagulation factor XII is not reliable for diagnosis.

Plasminogen gene

Plasminogen is inactive precursor protein of the enzyme plasmin. Plasmin plays its role in bradykinin production via activation of factor XII. A newly identified missense mutation in exon 9 of plasminogen (PLG) gene, c.988A>G (or named as c.1100A>G depending upon the assembly used), describes glutamic acid replacing lysine at position 330 (p.Lys330Glu) (or named as p.Lys311Glu depending on the numbering scheme used).\textsuperscript{35,36} Interestingly, the same mutation has been described by various groups in about 25 families from different countries with affected individuals numbering more than 100 (Table 1).\textsuperscript{37} The mutation leads to change in the kringle 3 domain which alters the structure of the wild-type protein. The mutant protein leads to the increased production of the bradykinin thereby resulting in HAE. Clinical profile of patients with plasminogen mutation is different from C1INH deficiency HAE. Patients with plasminogen gene mutation present usually in adulthood as compared to pediatric onset in majority of patients with C1-INH deficiency HAE. In addition, these patients tend to have higher chances of head and neck swellings (tongue, face, laryngeal edema) and relatively less chances of extremity edema or swelling of the genitals. ACE inhibitors and Angiotensin 1 receptor blockers tend to precipitate the attacks. Icatibant, tranexamic acid seem to be the most effective drugs.\textsuperscript{35,36–40}

Angiopoietin 1 gene

A novel mutation was identified in angiopoietin 1 (ANGPT1) gene using whole exome sequencing (WES) in patients with normal C1-INH HAE (Table 1).\textsuperscript{41} This was an unusual mutation as this gene has not been shown to be associated with hemostatic system or kinin pathway. It has also been shown that p.Ala119Ser mutation reduces the plasma levels of ANGPT1 protein and further hampers its ability to form multimers. Deficiency of ANGPT1 protein leads to reduced ability of mutant protein to bind to its cognate receptor tunica interna endothelial cell kinase 2 (TIE2). This signaling cascade is involved instabilizing vasculature and diminishing vascular permeability. ANGPT2 protein, on the other hand, antagonizes ANGPT1 protein leading to enhanced vascular permeability. The ratio of ANGPT1/ANGPT2 was found to be decreased in patients with p.Ala119Ser mutation.\textsuperscript{42} A simplified summary of the pathogenic mechanism involved in HAE caused by ANGPT1 gene mutation is shown in Fig. 4.\textsuperscript{43} Discovery of novel pathways in the pathogenesis of HAE have remarkably opened new frontiers in understanding and managing this disease.

Laboratory evaluation of patients with a clinical suspicion of HAE

The initial laboratory workup for hereditary angioedema is shown in Fig. 5. For genetic testing of HAE, molecular analysis is to be carried out for the genes associated with HAE. In the classical form of type 1 and type II HAE SERPING1 gene is the prominent target. Initially all the eight exons of SERPING1 gene with intronic/exonic junctions are amplified using oligonucleotides. Using MLPA kit, probe amplification depending on Multiplex Ligation can be done\textsuperscript{44,45} when all the eight exons data of SERPING1 gene is clear than one
might expect some large gene rearrangements like insertion/deletions. For other genes like F12, plasminogen and angio-
poietin diseases associated exons are amplified with oligo-
nucleotides and checked for the variants using Sanger
sequencing. In addition, next generation sequencing (NGS)
panel including all genes known to cause HAE and several
other genes that may potentially lead to HAE may be utilized
for diagnosis with an additional advantage of identifying
newer genetic defects.

**Treatment**

Treatment of HAE has evolved with advancement in understanding the pathogenesis of this disease and is either directed towards replacing the defective protein or blocking various molecules involved in the production of bradykinin or the bradykinin receptor (Fig. 6). In addition to various preparations of C1-INH analogues, other therapeutic options available include icatibant, a parenterally administered bradykinin receptor type 2 antagonist; ecallantide, a parenterally administered kallikrein inhibitor; Land-
elumb, a monoclonal antibody targeting kallikrein and a novel molecule BCX7353, an oral kallikrein inhibitor. Other management options include fresh frozen plasma (FFP)/single donor plasma (SDP) [aimed at replacing the defective or insufficient C1-INH]; attenuated androgens and tranexamic acid. Androgens act by augmenting bradykinin inactivation via aminopeptidase enzyme and by increasing the production of C1-INH. Tranexamic acid limits the production of plasmin by blocking the cleavage of its proenzyme plasminogen (Table 2).

**Future perspectives**

HAE is a heterogeneous disease with complex pathophys-
iology that has been studied extensively. Despite detailed research and identification of novel defects, a proportion of patients with HAE are still labeled as HAE-Unidentified (HAE-UI) wherein the genetic defect has not yet been identified. There are several molecules involved in the pathway for production of bradykinin and mutations in genes encoding these molecules may be potential genetic etiology for HAE-UI. These could include activating mutations in Kallikrein gene; activating mutations in Bradykinin gene or its receptor; activation mutations in Kininase 1 gene and loss of function mutations in gene encoding aminopeptidase and ACE enzymes. There is a possibility that mutations in these and other related genes could be potential modifiers in the clinical phenotype of patients with known genetic causes of HAE. A recent study analyzed polymorphisms in 15 such genes and their effect on the clinical phenotype of patients with C1-INH HAE/FXII-HAE. Amongst several variants that were identified in this study, 5 were classified as probably pathogenic. These included
The effect of these mutations on the final clinical phenotype was found to be rather complex. In patients with c.-22-2A>G mutations in C1-INH gene, p.Y244C resulted in infrequent attacks as compared to p.T916M. However, in patients with c.889G>A mutation in C1-INH gene, the clinical phenotype was very different even with the same variant p.G354R in the ACE gene. Identification of these novel polymorphisms in several genes leading to modification in the clinical phenotype of HAE is a relatively recent phenomenon. This needs more research work and needs to be studied in several other populations.

In addition, the recent discovery of ANGPT1 gene mutation in an Italian family with HAE-UI phenotype has expanded our understanding about this disease beyond the complement, kinin cascade. This discovery has also raised several questions for researchers that in the process of finding out novel genes for HAE, they not only need to work on above mentioned potential genes involved in pathway of bradykinin synthesis but several other pathways as well. Increasing number of novel mutations in the ANGPT1 gene are now being reported to be associated with the HAE phenotype [c.23C>T (p.A8V) and c.1110G>C (p.Q370H)].

Apart from this, several novel mutations are likely to be discovered in populations wherein the genetic etiology of HAE has not been evaluated till date. In our experience, we analyzed our cohort of pediatric HAE patients and found novel mutations in SERPING1 gene from 3 families (unreported data). Discovery of new genetic etiologies is likely to bring new therapeutic options in the management of patients with HAE.

### Conflict of interest
The authors declare no conflict of interest.

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