



## REVIEW ARTICLE

# 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. Copyright © 2019, Chongqing Medical University. Production and hosting by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

## 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.<sup>1</sup> 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.<sup>2,3</sup> Awareness and recognition of this disease is important as HAE is often misdiagnosed as allergic angioedema or acute abdomen (especially acute appendicitis).<sup>4</sup> This may often lead to inappropriate use of antihistamines, corticosteroids, adrenaline and sometimes even surgical interventions.<sup>4</sup>

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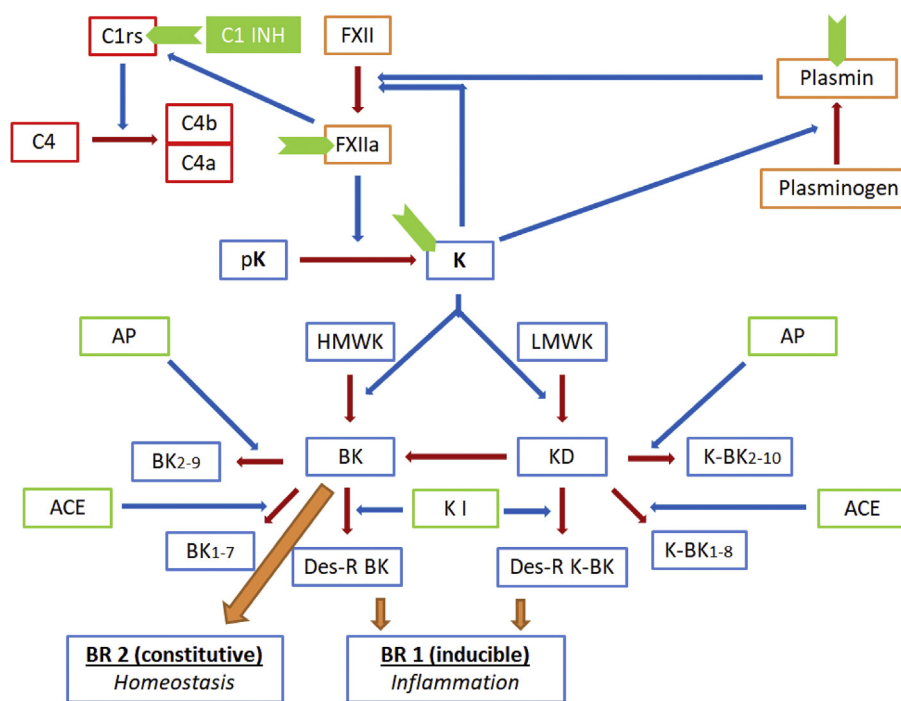
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## Pathophysiology of HAE

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)).<sup>6</sup> Kallidin, a decapeptide with an additional lysine residue at the amino-terminal end of bradykinin, is generated preferentially from low molecular weight kininogen (LMWK).<sup>7</sup> 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).<sup>8</sup>

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  $\alpha_1$ -antitrypsin, antithrombin III,  $\alpha_1$ -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** 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), BK<sub>2-9</sub> – bradykinin with its first amino acid cleaved off; BK<sub>1-7</sub> – 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.



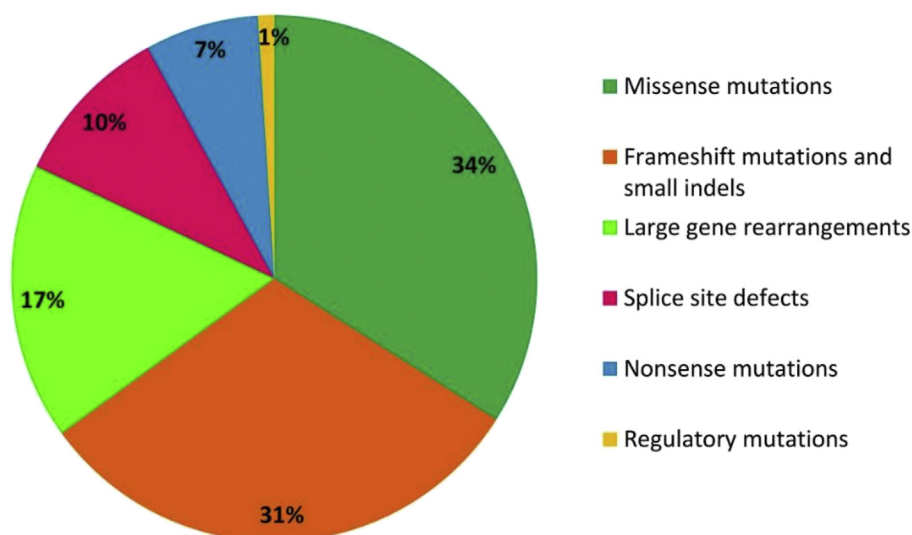
**Figure 2** Summary of the genetic defects leading to the phenotype of hereditary angioedema. HAE-1 (Type 1) is due to mutations leading to a quantitative defect of C1 esterase, whereas HAE-2 (Type 2) represents qualitative defects of C1-INH function. HAE-FXII and HAE-PLG pertains to defects in factor XII and plasminogen respectively. HAE-ANGPT1 corresponds to the recently described defects in the angiopoietin-1 gene leading to a hereditary angioedema like phenotype, whereas HAE-UI represents still unidentified mutations.

labeled as conformational disorders.<sup>9,10</sup> Mutation in *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.<sup>11</sup> 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 *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).

*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 *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)<sup>12</sup> and a similar database specifically dedicated for HAE (HAEdb, hae.enzim.hu).<sup>13</sup> Mutations in *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.<sup>14</sup> *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 *SERPING1* gene).<sup>15</sup> Since the availability of various mutations reported in *SERPING1* gene, it has become easier to predict the structural and functional attributes of this gene thereby explaining the phenomena of allelic heterogeneity.<sup>16,17</sup> *SERPING1* gene is an example of mutagenic liability and various theories have been postulated for the same: 1) *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,<sup>18</sup> 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.



**Figure 3** Various mutations reported in *SERPING1* gene.

The 466th residue of gene encodes for the arginine amino acid (CGC) that forms the reactive center of C1-INH and CpG is a natural target for recurrent amino acid substitution.<sup>19</sup>

Missense mutations constitute approximately 30–40% of all mutations in *SERPING1* gene.<sup>20,21</sup> 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.<sup>22</sup>

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.<sup>23</sup> In Caucasian populations, presence of intron 6 SNP (rs2511989) in *SERPING1* gene has been found to be associated with age related macular degeneration.<sup>24</sup>

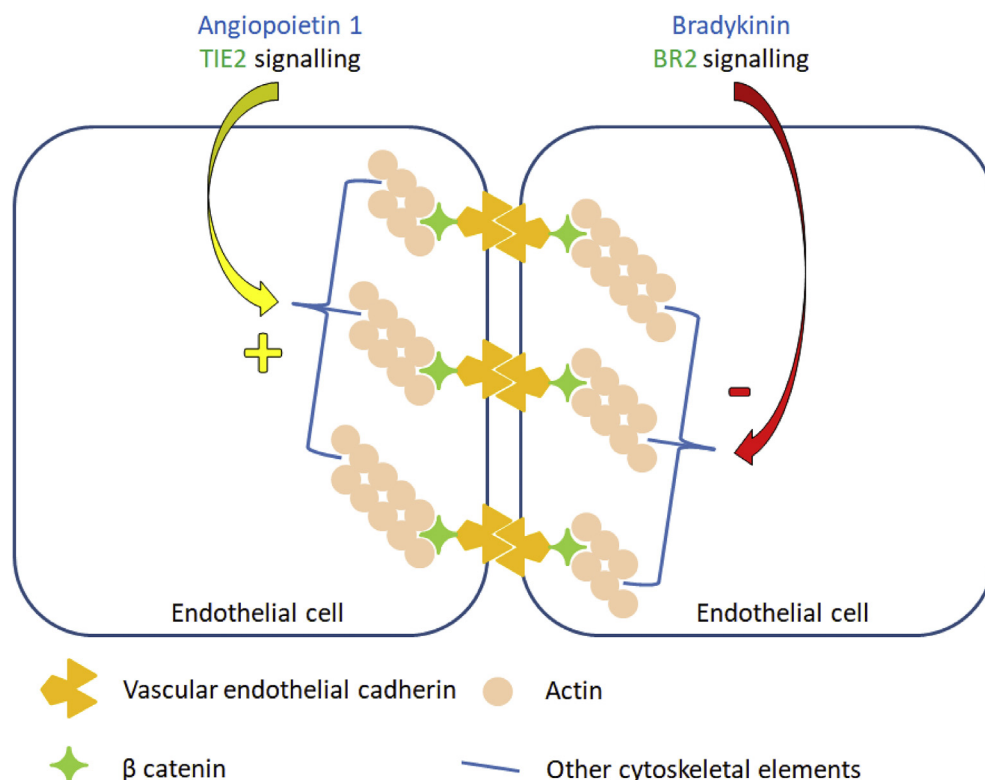
## Factor XII gene

In the year 2000, Bork et al described another type of HAE with a quantitatively and qualitatively normal C1-INH (labeled as nC1-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).<sup>25,26</sup>

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

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

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.<sup>27,28</sup> 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.<sup>29</sup> 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



**Figure 4** Counteracting influences of angiotensin 1 and bradykinin on vascular endothelial cells. Angiotensin 1 acting via TIE 2 receptor reinforces the cell cytoskeletal arrangements and decreases the vascular permeability. While, bradykinin disrupts this orderly arrangement leading to increased vascular permeability.

of HAE.<sup>30</sup> *F12* gene mutation associated with HAE is a gain of function mutation and is transmitted in an autosomal dominant mode of inheritance.<sup>31</sup> 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<sup>22,32</sup> and 18 bp duplication (c.892\_909dup) in a Hungarian family causing repetition of 6 amino acids (p.298–303) at the same locus.<sup>33</sup> 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.<sup>34</sup> 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).<sup>35,36</sup> 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).<sup>37</sup> 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.<sup>35,38–40</sup>

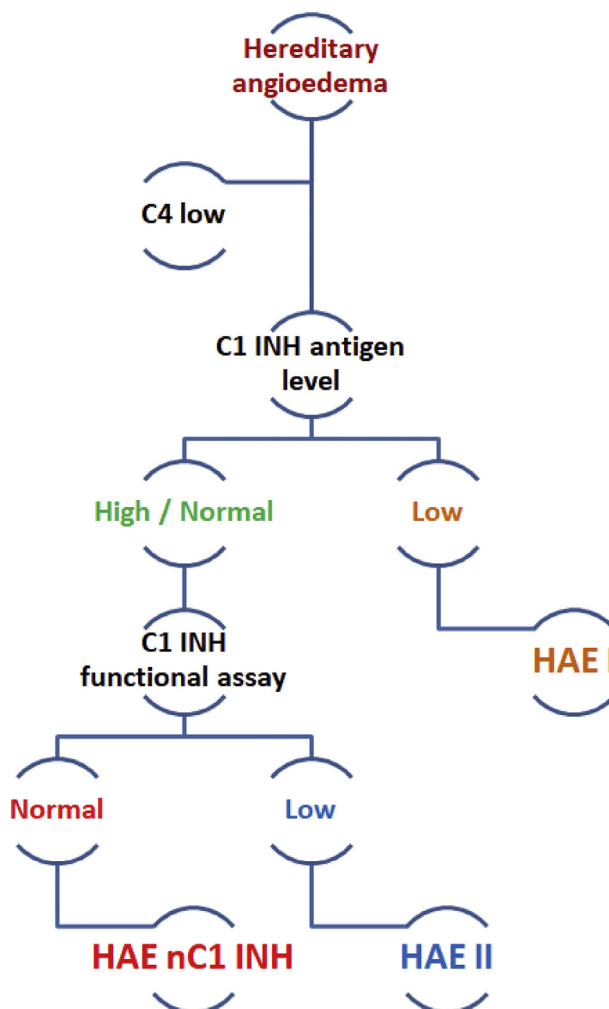
### Angiopietin 1 gene

A novel mutation was identified in angiotensin 1 (*ANGPT1*) gene using whole exome sequencing (WES) in patients with normal C1-INH HAE (Table 1).<sup>41</sup> 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 in stabilizing vasculature and diminishing vascular permeability. ANGPT2 protein, on the other hand, antagonizes ANGPT1 protein leading to

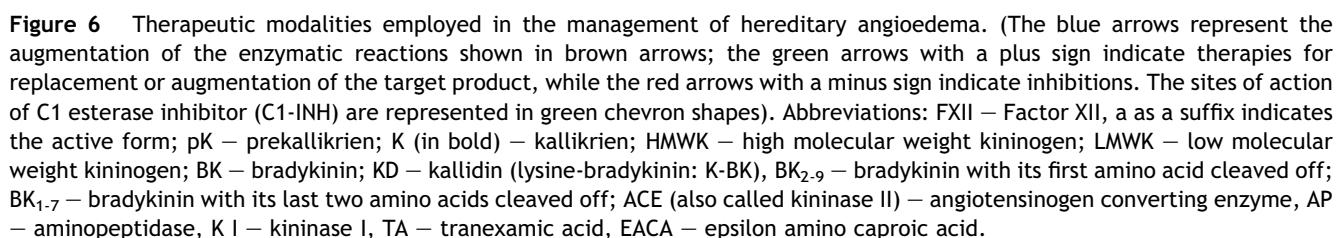
enhanced vascular permeability. The ratio of ANGPT1/ANGPT2 was found to be decreased in patients with p.Ala119Ser mutation.<sup>42</sup> A simplified summary of the pathogenic mechanism involved in HAE caused by *ANGPT1* gene mutation is shown in Fig. 4.<sup>43</sup> Discovery of novel pathways in the 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<sup>44,45</sup> when all the eight exons data of *SERPING1* gene is clear than one



**Figure 5** Proposed diagnostic algorithm for evaluation of a suspected case of hereditary angioedema (HAE with normal C1 inhibitor function requires genetic analysis for diagnosis).



via aminopeptidase enzyme and by increasing the production of C1-INH.<sup>50,51</sup> Tranexamic acid limits the production of plasmin by blocking the cleavage of its proenzyme plasminogen (Table 2).<sup>52,53</sup>

## Future perspectives

HAE is a heterogeneous disease with complex pathophysiology 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

**Table 2** Summary of effective treatment options for hereditary angioedema.

| Therapeutic options                                          | Uses                                                                                                                                                                                           | Suggested doses                                                                                                                                                                                                                                                        | Remarks                                                                                                                                    |
|--------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------|
| Danazol<br>Stanozolol<br>Oxandrolone<br>(Weak androgens)     | Short term &<br>Long term prophylaxis                                                                                                                                                          | Danazol - STP: 2.5–10 mg/kg/day (maximum 600 mg/day). LTP: 2.5–5 mg/kg/day (maximum 200 mg/day).                                                                                                                                                                       | Easily available. Undesirable virilising effect, weight gain, acne, headaches, menstrual irregularities, depression.                       |
| Tranexamic acid<br>Epsilon aminocaproic acid                 | Short term &<br>Long term prophylaxis                                                                                                                                                          | Tranexamic acid: 20–50 mg/kg/day in 2 or 3 divided doses (maximum 3–6 g/day).                                                                                                                                                                                          | Can be used in pregnancy if benefits outweigh risk (category B)                                                                            |
| FFP (fresh frozen plasma)/<br>SDP (solvent detergent plasma) | Short term prophylaxis<br>Acute treatment                                                                                                                                                      | 10 ml/kg/dose                                                                                                                                                                                                                                                          | Easily available, inexpensive. Concern of infections with regular use.                                                                     |
| C1 esterase inhibitors                                       | pdC1-INH <sub>Be</sub> for short term prophylaxis, acute treatment<br>pdC1-INH <sub>Cl</sub> for long term prophylaxis, acute treatment<br>rhC1-INH for acute treatment, long term prophylaxis | pdC1-INH <sub>Be</sub> 15–30 units/kg/dose IV.<br>pdC1-INH <sub>Cl</sub> 10–20 units/kg/dose once or twice weekly (initial maximum dose 1000 units).<br>rhC1-INH 50 units/kg/dose and is given by intravenous injection. Subcutaneous preparations are also available. | Expensive, currently unavailable in many Asian countries. One unit parallels the amount of C1INH in 1 ml of plasma of a normal individual. |
| Ecallantide                                                  | Acute treatment                                                                                                                                                                                | 30 mg/dose subcutaneous injection                                                                                                                                                                                                                                      | Expensive, risk of anaphylaxis. Not available in many Asian countries.                                                                     |
| Icatibant                                                    | Acute treatment                                                                                                                                                                                | 30 mg/dose subcutaneous injection (maximum three doses/day)                                                                                                                                                                                                            | Expensive. Not available in many Asian countries. Local reactions.                                                                         |
| Lanadelumab                                                  | Long term prophylaxis                                                                                                                                                                          | Dose range 150–300 mg every 2–4 weeks.                                                                                                                                                                                                                                 | Pediatric dosing yet to be established.                                                                                                    |
| BCX7353                                                      | Long term prophylaxis                                                                                                                                                                          | Minimum effective dose used: 125 mg/day                                                                                                                                                                                                                                |                                                                                                                                            |

p.Y244C, p.G354R, p.T916M in the ACE gene; p.C548Y in KLKB1 (kallikrein) gene and p.D287N in NOS3 (nitric oxide synthase) gene. However, 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.<sup>54</sup> 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)].<sup>55</sup>

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 *SERPINE1* 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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