

# Hereditary Angioedema



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## Introduction

Hereditary angioedema (HAE) affects approximately 1 in 50,000 of the population and does not show ethnic variation in frequency. HAE is inherited in an autosomal dominant manner and results in unpredictable episodic swellings which can affect the face, peripheries, genitals, abdomen and airway. Laryngeal swellings can result in death. As with many rare conditions, there is unfortunately often a delay to diagnosis during which time patients do not receive appropriate treatment.

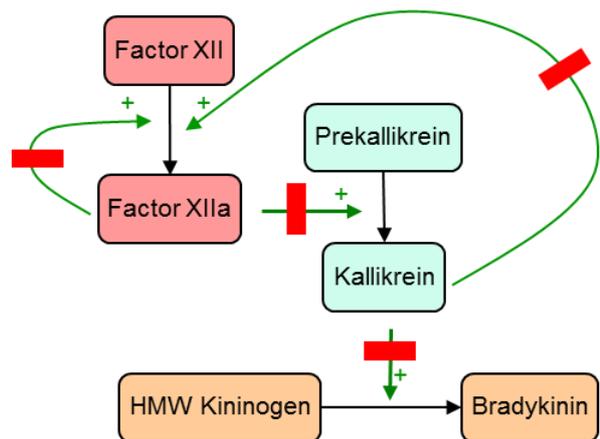
The vast majority of cases result from mutations affecting SERPING1 which encodes C1 esterase inhibitor (C1INH). Mutations can result in either low levels of C1INH (approx. 85% of cases) or normal levels of C1INH but with decreased function (approx. 15% of cases). When measuring C1INH, it is important that both levels and function are measured as otherwise cases will be missed.

HAE with normal C1INH is rare and makes up less than 1% of cases of HAE. In some cases mutations in Factor XII are responsible, and mutations of ANGPT1 leading to HAE have also been described. In the remaining cases the gene is not known.

## Bradykinin

HAE results in increased generation of bradykinin. Bradykinin mediates vasodilation through binding to the bradykinin type 2 receptor (BK2R).

**Figure 1** shows the pathways involved in bradykinin formation. While in some patients particular triggers such as infection or mild trauma may result in angioedema, in most cases the episodes of swelling are unpredictable.



**Figure 1** Pathways leading to the production of bradykinin  
HMW = high molecular weight  
Points of action of C1INH indicated by red bars

## Treatments

Androgenic steroids increase liver production of C1INH. However, some patient suffer with side effects especially with long term use.

Plasma derived and recombinant C1INH are available for both emergency and prophylactic treatment of HAE.

Icatibant is a selective competitive antagonist of BK2R and ecallantide inhibits the action of kallikrein. Potential future treatments under development include an oral kallikrein inhibitor and an injected monoclonal targeting kallikrein.

Patients should also receive genetic counseling and be offered sequencing of C1INH or factor XII.

Advice should be given to avoid angiotensin converting enzyme (ACE) inhibitors and oestrogen containing contraception and hormone replacement therapy.

## Further research

Poor phenotype/genotype correlation is a hallmark of HAE. For example some family members with an identical mutation have very rare episodes of angioedema, whereas other family members have frequent attacks. Potential disease modifying genes or pathways have been suggested to include BK2R, kallikrein, factor XII, ACE and oestrogen .

The role of bradykinin in other conditions such as anaphylaxis and acquired andioedema is a topic of ongoing research.