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LETTER TO THE EDITOR

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# The role of genetics in the current diagnostic workup of idiopathic non-histaminergic angioedema

To the Editor,

Angioedema (AE) is a clinical syndrome characterized by recurrent episodes of swelling mainly of skin, subcutaneous and submucosal tissues and/or the upper respiratory tract.

Angioedema can occur along with wheals in urticaria and as result of exposure to specific agents in allergic reactions. Non allergic angioedema without wheals is defined as primary angioedema.[1] The Hereditary Angioedema International Working Group (HAWK)/EAACI classification in 2014 recognized hereditary (HAE) and acquired (AAE) forms of angioedema.[2]

In this classification, hereditary forms include those caused by a deficiency of complement component 1 (C1) esterase inhibitor HAE (C1-INH-HAE), the form with coagulation factor XII (FXII) mutations (FXII-HAE), and those with an unknown genetic cause (U-HAE). For the latter, a higher age at onset of disease is reported when compared to C1-INH-HAE and FXII-HAE.[3]

Among the acquired forms, ACE-inhibitor related (ACEI-AAE), acquired C1 deficiency (C1-INH-AAE), idiopathic histaminergic (IH-AAE) and non-histaminergic angioedema (InH-AAE) can be recognized, the latter being identified by clinical features, absence of an identifiable cause of angioedema, and failure to prevent symptoms with high-dose antihistamine prophylaxis.

In the HAWK/EAACI classification, the etiopathogenesis of one hereditary (U-HAE) and one acquired (InH-AAE) form of angioedema still remains undefined. Considering HAE with normal C1-INH (U-HAE and FXII-HAE), the proportion of unknown is about 2/3.[4] Within InH-AAE cases, about 10% are bradykinin-mediated and the remaining 90% is an heterogenous group of disorders for which there is still uncertainty on origin and pathophysiology. In these patients, the swelling could be mediated by either mast cell mediators, in particular histamine, bradykinin, or by other mediators.[2]

Owing to the limited biomarkers available for distinguishing primary angioedema with normal C1-INH, diagnosis of InH-AAE relies on an exclusion process; however, genetics could play a fundamental role.

In FXII-HAE, disease-causing mutations of *F12* gene are transmitted as an autosomal dominant trait with incomplete penetrance, and the proportion of asymptomatic carriers is >90% in males, while it is around 40% in females. Such an incomplete penetrance and variable clinical presentation hinder diagnosis of FXII-HAE.[3]

Recently, a large study of Lopes Veronez and colleagues highlighted the usefulness of *F12* genetic testing to diagnose patients presenting with HAE with normal C1-INH, including male patients, even in the absence of a family history or without clear estrogen influence.[5] So far, a number of studies showed that a proportion of patients initially diagnosed as InH-AAE was affected by FXII-HAE with lack of family history, with a prevalence varying from 12% to 100% across different centers (Table 1), whose data derive from different study designs and by patients' ancestry.[3-6]

However, in several HAE patients presenting with normal C1-INH, no mutations in FXII gene are detectable and these patients have been previously classified as U-HAE. Within this latter subset of patients, we recently discovered a causal mutation in the Angiopoietin 1 (*ANGPT1*) gene.[7] While in the index ANGPT1-HAE family, all A119S mutation carriers were symptomatic and the trait clearly followed an AD pattern; we also found another unrelated female patient classifiable as InH-AAE (recurrent angioedema with non-histaminergic features, lack of response to high-dose antihistamine prophylaxis and steroids, negative family history) but bearing the same recently described A119S ANGPT1 mutation. Although we did not have yet the opportunity to examine the family members of this new subject, there is an apparent lack of family history for angioedema or related symptoms.

Furthermore, Bork's group recently found a previously unreported variant of the plasminogen (PLG) gene K330E, segregating with the clinical phenotype as an AD trait among four families with HAE and normal C1-INH and the index patients of nine further families, not bearing *F12* mutations.[8] Although the pathogenicity has been not yet fully demonstrated by functional studies, Germenis and colleagues found the same K330E PLG variant in 6 individuals.[9] Further five families coming from France and Japan with HAE with normal *C1-INH* and the *PLG* gene mutation have been described in this Journal.[10,11] Interestingly, in both the Bork's and Germenis' cohorts of PLG-mutated patients the clinical expression of disease ranged from asymptomatic to highly symptomatic subjects and Germenis describes that two out of three PLG-HAE index patients did not have family history and had been initially identified as InH-AAE.

Thus, for both the newly identified ANGPT1-HAE and PLG-HAE, the preliminary data show that the genetic background of the disease may at first not be overt similarly to FXII-HAE. Data in Table 1 summarize the studies with available data on the occurrence of FXII-HAE, PLG-HAE, and ANGPT1-HAE diagnosis in patients with initial diagnosis of InH-AAE.

Taking into account these recent data and the current definition of InH-AAE by exclusion of other diseases, we underscore that the screening of HAE-associated mutations in *F12*, *PLG*, and *ANGPT1* is important in patients with angioedema of uncertain etiopathogenesis. For *F12* and *PLG* mutations, the ascertainment can be easily performed in most laboratories by amplification and Sanger sequencing of a single exon of each gene. As the number of reported patients for *ANGPT1* is still quite small,

**TABLE 1** Patients with mutations in HAE disease-causing genes initially mislabeled as InH-AAE

| Mutated gene | Mutation type | Patient no. (% female) | Symptomatic patients no. (% female) | Unrelated families no. | Case index without family history of angioedema no. (% of families) | Study |
|---|---|---|---|---|---|---|
| *F12* | Thr328Lys | 35 (77%) | 29 (90%) | 13 | 4 (31%) | *Marcos* et al *Ann Allergy Asthma Immunol, 2012* |
| | Thr328Lys | 20 (80%) | 14 (100%) | 4 | 1 (25%) | *Firinu* et al *Clin Immunol, 2015* |
| | Thr328Lys | 35 (88%) | 22 (91%) | 9 | 3 (33%) | *Pinegro-Saavedra* et al *Ann Allergy Asthma Immunol, 2016* |
| | Thr328Lys | 6 (84%) | 3 (100%) | 3 | 3 (100%) | *Mansi* et al *J Inter Med, 2014* |
| | Thr328Lys c.971-1018 + 24del72 | 134 (78%) | 102 (80%) | 42 | 5 (12%) | *Veronez* et al *J Allergy Clin Immunol Pract, 2017* |
| | Thr328Lys | 118 (70%) | 80 (90%) | 40 | 12 (30%) | *Charignon* et al *Allergy, 2014* |
| | Thr328Lys Thr328Arg c.971_1018 + 24del72 | 104 (76%) | 69 (100%) | 23 | 5 (22%) | *Bork* et al *Allergy, 2015* |
| *PLG* | Lys330Glu | 6 (83%) | 4 (100%) | 3 | 2 (67%) | *Germenis* et al *Allergy, 2017* |
| | Lys330Glu | 32 (53%) | 18 (72%) | 4 | 1 (25%) | *Dewald* et al *Biochemical and Biophysical Research, 2018* |
| *ANGPT1* | Ala119Ser | 1 (100%) | 1 (100%) | 1 | 1 (100%) | *In this paper* |

ANGPT1, Angiopoietin 1; F12, Coagulation Factor XII; HAE, Hereditary Angioedema; InH-AAE, idiopathic non-histaminergic angioedema; PLG, Plasminogen.

a complete analysis of the gene should be performed. Of note, novel techniques such as the applications of next-generation sequencing may be employed in this field in the near future.

In conclusion, we propose that the diagnosis of InH-AAE should be established only after genetic analysis of *F12*, *PLG*, and *ANGPT1* is made. A better definition of InH-AAE diagnosis on this basis is fundamental for a precise definition of outcomes, evaluation of safety, and efficacy of treatments in these subgroups of patients.

## CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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