

Factor XII gene missense mutation Thr328Lys in an Arab family with hereditary angioedema type III

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A novel type of hereditary angioedema—HAE type III—was described in the year 2000 (1). Symptoms are similar to those of types I and II (2, 3). However, patients show normal plasma C4 and C1 inhibitor levels and activity.

With few exceptions, all reported patients are women exposed to high estrogen levels. Therefore, estrogens are considered an important precipitating factor.

In patients with HAE type III, we can identify a homogeneous group of individuals with a missense mutation located in exon 9 in the gene of the coagulation factor XII gene (*F12*) (4). This mutation leads to increasing activity of factor XII. To date, this mutation has only been described in Caucasian patients.

We report a non-atopic 27-year-old Arab woman from Morocco who

attended our Allergy Department with a history of episodes of facial edema that were not associated with pruritus, urticarial lesions, upper respiratory tract involvement, or abdominal pain. The angioedema always affected the face (except on one occasion when it affected the little finger of the right hand). She had her first episode at age 20 and, since then, has had at least two episodes per year. These episodes occurred only during the periods she was taking oral contraceptives (OCs) and were sometimes induced by local pressure or stress. She attended the emergency department on two occasions after taking a double dose of OC and was treated with corticosteroids and antihistamines, although no response was observed.

Her mother experienced three episodes of facial angioedema over a 5-month period 35 years ago while taking OCs. She has not presented new episodes to date, even though she has had five pregnancies and undergone several surgical procedures. She has not taken OCs since her last episode. The patient's sister also experienced recurrent attacks of facial edema, sometimes with respiratory distress because of upper

airway edema, also when taking OCs. The rest of the family was asymptomatic.

We recommended the patient and her sister to avoid OCs. They have been symptom-free for the last 2 years and 23 months, respectively. Icatibant was prescribed in case of further episodes of angioedema.

Biochemical parameters and a complete blood count were within the normal range. Total IgE was 376 kU_A/l. Complement factors C3 (123 mg/dl) and C4 (17.6 mg/dl), as well as C1 inhibitor level (22.1 mg/dl) and function (92.1%), were also normal.

A heterozygote missense mutation was identified in exon 9 of the *F12* gene (p.Thr328Lys). This mutation was identified in the patient, her mother, her symptomatic sister, and her 18-year-old half-brother (Fig. 1).

We report the first family of Arab origin with a clinical diagnosis of hereditary angioedema type III and the p.Thr328Lys mutation. Therefore, it is important to investigate this mutation in all populations with this condition.

Pregnancy is a clear risk factor in most cases of HAE type III. However, our patient's mother did not experience

This is the first case of hereditary angioedema type III, associated with a *F12* gen mutation described in a family of Arab origin.

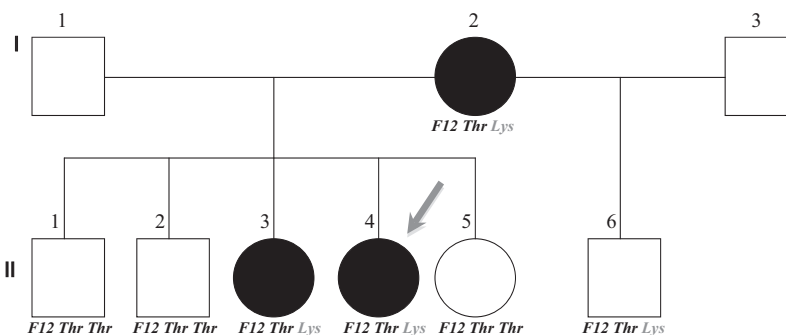


Figure 1 Pedigree demonstrating co-segregation of the mutation and the disease phenotype. Filled symbols indicate individuals affected by recurrent angioedema. The arrow indicates the index patient.

episodes of angioedema during her five pregnancies, in contrast with previously reported cases (5).

The most effective treatment is to avoid exposure to estrogens. Acute episodes of HAE type III have traditionally been treated with a C1-INH concentrate, corticosteroids, antihistamines, and adrenaline, but the effectiveness of this treatment in HAE type III is limited. Icatibant, which blocks bradykinin-related symptoms (6), and ecallantide, a novel, specific, and potent inhibitor of plasma kallikrein (7), have recently been approved in Europe and the USA, respectively, as the elective treatment for HAE types I and II. We prescribed icatibant for compassionate use, as it is not yet approved for patients with HAE type III. Clinical trials with icatibant and ecallantide will be necessary to prove their efficacy and safety profile in this type of angioedema.

Every author contributed to the manuscript. None of the authors have any conflict of interests.

Clinical implications: Angioedema Type III, related to the *F12* gene mutation, should be looked even in non-Caucasian patients.

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