



Letter

Idiopathic angioedema with F12 mutation: is it a new entity?

In recurrent angioedema attacks without concomitant urticaria or pruritus, bradykinin-mediated angioedema (hereditary and acquired) and angioedema induced by angiotensin-converting enzyme inhibitor are considered. In patients with normal C1 inhibitor (C1-INH) level and function and those with normal C1q antibodies, hereditary angioedema (HAE) with normal C1-INH, angioedema induced by angiotensin-converting enzyme inhibitor, and idiopathic angioedema are possible diagnoses. Idiopathic angioedema is a diagnosis of exclusion and should be considered after a detailed evaluation.¹

Hereditary angioedema with normal C1-INH was described in 2013 by Sher and Davis-Lorton.¹ This type of HAE is more common in women in their 30s and is related to menstruation, pregnancy, estrogen-containing oral contraceptive drugs, or other high-estrogen conditions. It also can include rare multiorgan attacks and abdominal swelling. Although its etiology is not completely understood, there is evidence showing an association with *F12* gene mutations, which is present in up to 25% of patients in European cohorts and similarly extremely rare in US patients.¹ To be diagnosed as HAE with normal C1-INH, a patient must meet the following criteria: recurrent angioedema without urticaria or a causative medication and with normal or near normal C1-INH antigen and function. The patient also must have normal complement C4 levels during attacks and a positive family history of angioedema and evidence that chronic high-dose antihistamine therapy is ineffective or a disease-associated mutation in the *F12* gene.²

Idiopathic angioedema is defined as at least 3 episodes of swelling within 6 to 12 months without a clear etiology after a thorough evaluation. In patients presenting with recurrent swelling without urticaria, the diagnosis is made after the exclusion of acquired angioedema and HAE. In addition, all known causative entities of angioedema should be ruled out. The treatment of idiopathic angioedema remains largely empiric and often is based on the control of clinical symptoms.¹

We present 2 cases of recurrent angioedema attacks without urticaria, initially considered idiopathic angioedema. However, further evaluation demonstrated mutations in the *F12* gene, suggesting a diagnosis of HAE with normal C1-INH.

A 50-year-old man was referred for recurrent edema attacks on his face, especially on his lips. His attacks began 2 years before the referral and occurred at 15-day intervals with a duration of at least 2 days. He was not taking angiotensin-converting enzyme inhibitors or any other suspicious drugs and attacks were unresponsive to high doses of antihistamines or steroids. C1-INH, C4, C1q levels, F12 levels, and C1-INH function were within normal limits. His initial diagnosis was non-histaminergic idiopathic angioedema and a twice-daily 250-mg dose of tranexamic acid was

started. He did not report any angioedema attacks at his 6-month follow-up. Although he did not report a positive family history, an *F12* gene mutation analysis was performed.

A 35-year-old woman was admitted with a 7-year history of recurrent episodes of isolated edema in various locations on her body, including her face and extremities, and laryngeal mucosa in 2 of these episodes. These attacks did not respond to antihistamines or steroids and were not accompanied by itching or urticaria. She also had abdominal pain and was misdiagnosed with familial Mediterranean fever, although she did not respond to colchicine. Various nonsteroidal anti-inflammatory drugs and her menstrual period seemed to trigger her attacks. C1-INH, C4, C1q levels, F12 levels, and C1-INH function were within normal limits. Despite the lack of family history, a diagnosis of HAE with normal C1-INH was considered and 100 mg of danazol was started as prophylaxis. At her follow-up, she reported less severe attacks, although she had to use a 1,000-mg C1-INH extract for 1 laryngeal attack. She recovered within 2 hours after the infusion. Thereafter, prophylactic treatment with danazol was continued at the lowest effective dose.

DNA was isolated for genetic analysis from blood cells of case 1, case 2, and the healthy parents and sibling of case 2 after obtaining informed consent. All 14 exons, including the flanking regions of the *F12* gene (NM_000505.3), were amplified and sequenced using the Sanger technique.

Analysis of the electropherograms showed that case 1 carried heterozygous c1681-1G→A in intron 13 and case 2 carried c1027G→C, altering alanine to proline (pAla343Pro; former nomenclature, pAla324Pro) in exon 10 (Fig 1). The inheritance pattern of case 1 could not be defined because his parents did not give consent for a genetic test. Analysis of the family members of case 2 showed that none carried this mutation, thus supporting a de novo occurrence.

Until recently, 4 different missense mutations in the proline-rich region of factor XII (FXII) have been described.^{3–5} Currently, all known mutations in HAE with normal C1-INH have occurred in the proline-rich linker peptide between the Kringle and trypsin-like serine protease (Tryp-SPc) domains of the FXII protein (Thr328Arg, pThr328Lys, 72-bp deletion at c971_1018+24 and c894_911dup18).^{3–5} These mutations are considered to increase bradykinin generation by enhancing *F12* activation and thus causing angioedema attacks.² The pAla343Pro identified in case 2 also occurs at the proline-rich linker domain and c1681-1G→A alters the evolutionally conserved splicing acceptor region, which is strongly predicted to interfere with the correct splicing of the transcript, furthering intron retention or exon skipping. This leads to the disruption of the function of the proline-rich linker peptide and Tryp-SPc domain. These 2 mutations have been identified in association with FXII deficiency, but neither was reported with angioedema.^{6–8} The pAla343Pro was identified in a Japanese male patient in compound heterozygous with pGly550Glu. This case

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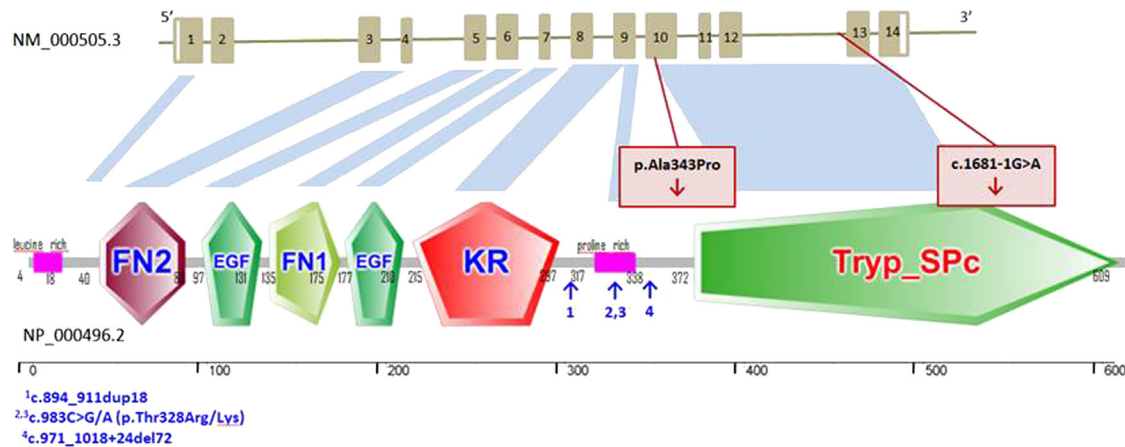


Figure 1. Genomic layout of the *F12* gene with exons reflecting amino acid numbering of coding domains (light blue arrays), scaled from the SMART database for human P00748. Mutations associated with hereditary angioedema and factor XII (blue arrows) are described in the footer. Mutations identified in case 1 and case 2 are indicated with red arrows. EGF, epidermal growth factor-like; FN1, fibronectin type 1; FN2, fibronectin type 2; KR, Kringle; Tryp_SPc, trypsin-like serine protease domains.

presented with a cross-reactive material positive for FXII deficiency with partially impaired FXII activity.⁶ The c1681-1G→A mutation was described in association with FXII deficiency and was recently implicated in atypical hemolytic uremic syndrome in a targeted genetic screening of 794 patients with atypical hemolytic uremic syndrome for the coding sequence and splice sites of all genes in the complement and coagulation pathways.^{7–9}

Although the present cases did not have a family history and family members lacked the same mutation, there is a probability that the detected alterations are de novo mutations as seen in 25% of patients with HAE type I and type II. These mutations are supposed to have an *F12* lowering effect, contrary to previous research indicating a gain of function mutations in patients with HAE with normal C1-INH. As a result, the causative nature of such a finding is tentative. Nevertheless, we question whether the association of idiopathic angioedema with an *F12* gene alteration is coincidence.

In conclusion, idiopathic non-histaminergic angioedema seems to overlap with HAE with normal C1-INH. Further genetic and functional analyses are needed to elucidate this dilemma.

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