

Letter to the Editor

Hereditary angioedema with normal C1 inhibitor gene in a family with affected women and men is associated with the p.Thr328Lys mutation in the *F12* gene

To the Editor:

Hereditary angioedema (HAE) is an autosomal dominant condition with recurrent, potentially life-threatening, swelling attacks in the skin, abdomen, and upper respiratory tract. Edema formation is a result of excessive release of bradykinin. Most cases of HAE are attributable to mutations in the *SERPING1* gene, resulting in defective serpin C1 inhibitor (C1Inh; HAE types I and II, Mendelian Inheritance in Man #106100).¹ We and others have described an etiologically distinct form of HAE, with women exhibiting HAE but normal plasma C1Inh function (so-called HAE type III, Mendelian Inheritance in Man #610618).²⁻⁴ Most affected women experienced angioedema attacks in the setting of estrogen overload, such as pregnancy or contraceptive pill intake. We have recently demonstrated that part of these autosomal dominant HAEs is attributable to a missense mutation in *F12* that encodes the Hageman factor protease (FXII).⁵ We also showed that some pedigrees with HAE type III are not linked to the *F12* locus, strongly suggesting the presence of locus heterogeneity.⁵ The mutation p.Thr328Lys results in increased FXII activity in patients' plasma, enhanced kinin production, increased vascular permeability, and edema.⁵ Interestingly, HAE type III seemed to affect exclusively women in the families reported to date.²⁻⁴ We hypothesized that this sex specificity may be explained by the fact that the expression of FXII is positively regulated by estrogens.⁶

Here, we report a novel French pedigree with HAE in which our first diagnosis was idiopathic nonhistaminergic angioedema (INAE) as proposed by Cicardi et al.⁷ Indeed, attacks were present in both sexes (Fig 1). Attacks in

women were most often related to estrogen intake or pregnancy, but sometimes occurred independently and despite prophylactic treatment with tranexamic acid (individual III6). Attacks were clearly present in 1 man, but were less frequent and less severe. This patient had not taken any drug affecting hormonal balance, including testosterone blockers. According to the disease stage, disease severity class⁸ was 4 or 5 in men versus 1 or 2 in women. Several male carriers younger than 50 years were symptomless (III2, 3, 5). No prophylactic treatment was given in any man. All affected patients had C1Inh antigenic level and function within normal ranges. Plasma C4 levels were always found within the normal range during and in between attacks. After informed consent, DNA was extracted from peripheral blood, and the *SERPING1* gene was found normal after exhaustive analysis according to a previously described strategy.⁹ Because of phenotype similarity between INAE and HAE type III, we sought to investigate whether mutations in *F12* might also be associated with INAE. Indeed, we could identify in all affected family members (Fig 1) the same *F12* mutation (c.1032C>A resulting in p.Thr328Lys) previously reported by us in families with HAE type III.⁵ Kininogenase plasma activity was measured in patient III6 and in her parents by using the *para*-nitroanilide Arg substrate as previously described,⁵ and reported in percentage of both enzyme and proenzyme converted in the presence of 25 µg/mL dextran sulfate on ice. Amidolytic activity was found dramatically increased in the patient sample in comparison with those measured in her father (who only experienced a single facial attack in his life and displayed a discrete increase of the enzymatic activity) and her unaffected mother (Fig 1). Interestingly, only patient III6 displayed a slight decrease in C1Inh function level at the time of attacks. The anti-C1Inh immunoblot performed on 7.5% SDS-PAGE (nonreducing conditions) demonstrated proteolyzed circulating C1Inh (Fig 1).

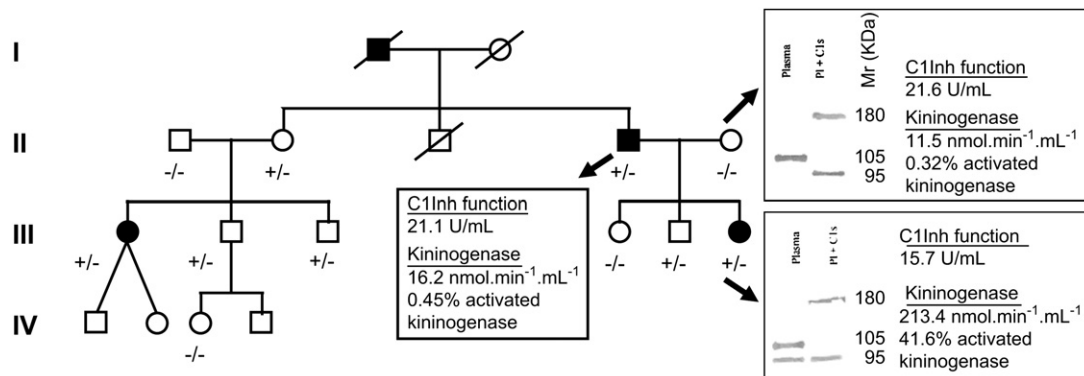


FIG 1. HAE type III pedigree. Affected individuals are indicated in black. The *F12* genotype is given as +/- for mutation carriers and -/- for wild-type individuals. Plasma C1Inh function (reference values 22.3 ± 5.1 U/mL), kininogenase activity (5.2 ± 3.1 and 3.6 ± 1.1 nmol·min⁻¹·mL⁻¹, for female and male individuals, respectively), and the proportion of active enzyme (0.15 ± 0.07 and 0.11 ± 0.04%, for female and male subjects, respectively) are indicated for individuals II4, II5, and III6. Anti-C1Inh immunoblot analyses are added for II5 and III6.

Collectively, these data allowed us to give the diagnosis of HAE type III and provide some comments about the condition. It seems indisputable now that men can be affected with HAE type III. Given that a clinical diagnosis of HAE type III now can be extended to both sexes, it will be interesting to consider to what extent previously reported families may be reclassified. For instance, Cicardi et al⁷ first described familial cases of the so-called "idiopathic non-histaminergic angioedema." Among their patients, some were male, including brothers, and male-to-male transmission was present in 1 family. More recently, Bork et al¹⁰ reported a pedigree with 8 affected members in 4 successive generations. Three patients were male, and male-to-male transmission was also noticed. Gupta et al¹¹ reported 3 brothers with angioedema and normal C1Inh function. It is not clear, however, whether the latter patients had HAE type III because the occurrence of their condition was compatible with recessive inheritance, whereas HAE type III is described to have an autosomal dominant mode of inheritance. Autosomal dominant inheritance in this family, however, might still be present assuming reduced penetrance in one of the parents. In addition, we have had the opportunity to observe that the father of the female index case of our first French family with HAE type III⁴ unequivocally developed attacks of genital and laryngeal angioedema. Interestingly, in all those male cases, attacks were less severe and less frequent. Further, the average age of onset (in the sixth decade) was older than that of females. Strikingly, kininogenase activity was found highly elevated and C1Inh defective to some extent in the female case III6, but not in her affected father, II4. C1Inh function was slightly lower (drop of 10% to 40%) than normal in patient III6, a situation observed in most female patients with HAE type III (C. Drouet, unpublished data, May 2007). This was related to the cleavage of the serpin from 105 to 95 kd without development of serpin-protease association (Fig 1), suggesting that the factor XII mutant escaped control by C1Inh. Whether clinical severity is only or closely related to plasma kininogenase activity in HAE type III is still unknown. In our experience, however, kininogenase activity in male carriers is always far below the female values (C. Drouet, unpublished data, May 2007), and consistent with limited disease expression in male patients. Further studies are needed to shed light on the biological reasons for these findings.

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REFERENCES

- Agostoni A, Aygoren-Pursun E, Binkley KE, Blanch A, Bork K, Bouillet L, et al. Hereditary and acquired angioedema: problems and progress: proceedings of the Third C1 Esterase Inhibitor Deficiency Workshop and beyond. *J Allergy Clin Immunol* 2004;114:S51-131.
- Bork K, Barnstedt SE, Koch P, Traupe H. Hereditary angioedema with normal C1-inhibitor activity in women. *Lancet* 2000;356:213-7.
- Binkley KE, Davis A. Clinical, biochemical, and genetic characterization of a novel estrogen-dependent inherited form of angioedema. *J Allergy Clin Immunol* 2000;106:546-50.
- Martin L, Degenne D, Toutain A, Ponard D, Watier H. Hereditary angioedema type 3: an additional French pedigree with autosomal dominant transmission. *J Allergy Clin Immunol* 2001;107:747-8.
- Cichon S, Martin L, Hennies HC, Müller F, van Driesche K, Karpushova A, et al. Increased activity of coagulation factor XII (Hageman factor) causes hereditary angioedema type III. *Am J Hum Genet* 2006;79:1098-104.
- Farsetti A, Misiti S, Citarella F, Felici A, Andreoli M, Fantoni A, et al. Molecular basis of estrogen regulation of the Hageman factor XII gene expression. *Endocrinology* 1995;136:5076-83.
- Cicardi M, Bergamaschini L, Zingale LC, Gioffré D, Agostoni A. Idiopathic nonhistaminergic angioedema. *Am J Med* 1999;106:650-4.
- Cicardi M, Zingale L. Clinical manifestations of HAE. *J Allergy Clin Immunol* 2004;114:S55-61.
- Drouet C, Blanch A, Roche O, Monnier N, Duponchel C, Kalmar L, et al. HAE: genetic investigations. *J Allergy Clin Immunol* 2004;114:S65-74.
- Bork K, Gül D, Dewald G. Hereditary angioedema with normal C1-inhibitor in a family with affected women and men. *Br J Dermatol* 2005;154:542-5.
- Gupta S, Yu F, Klaustermeyer WB. New variant hereditary angioedema in three brothers with normal C1 esterase inhibitor level and function. *Allergy* 2004;59:557-8.

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