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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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Plasminogen gene mutation with normal C1 inhibitor hereditary angioedema: Three additional French families

To the Editor

Hereditary angioedema should be divided into 2 forms according to the function of C1 inhibitor: HAE with C1 inhibitor deficiency (C1-INH-HAE)¹ and HAE with normal C1 inhibitor level (nC1-INH-HAE). Within this second form, some mutations have been described, such as *F12* gene mutation.² A missense variant in angiotensin-converting enzyme 1 gene (*ANGPT1*, c.807G > T, p.Ala119Ser) seems also to be associated with nC1-INH-HAE.³ However, in many cases, no mutation was found in nC1-INH-HAE patients.

Recently, Bork et al⁴ described a new mutation associated with nC1-INH-HAE with variable penetrance. This mutation affected the plasminogen (*PLG*, NM_000301.3) gene and corresponded to the mutation c.988A > G in exon 9. This mutation led to the missense mutation p.Lys330Glu (K330E) in the kringle 3 domain of the PLG protein. It was identified in 60 patients belonging to 13 different German families. The phenotype of PLG-HAE in this cohort seemed to have some particularities: Patients preferentially developed face and tongue swelling. Oral contraceptive did not seem to be a frequent

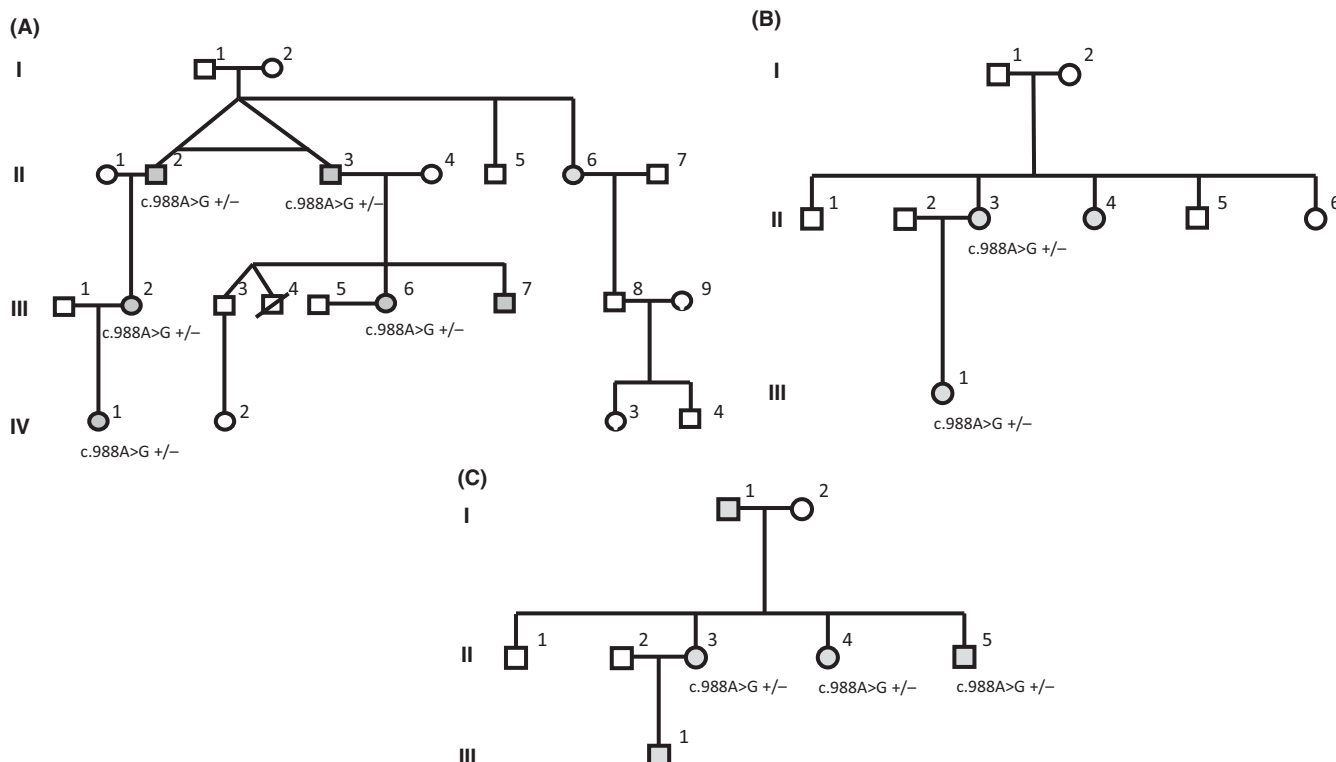


FIGURE 1 Families with mutation in the gene encoding for plasminogen. A, Family O1; B, family O2; C, family O3

trigger as it was described in HAE-FXII patients. Finally, some therapy like icatibant as attack treatment and tranexamic acid (TXA) as long-term prophylaxis could be efficient. After this report, another medical team found this same mutation in 3 large German families.⁵ We also assessed the PLG mutation in nC1-INH-HAE patients without F12 mutation in our French cohort. Selected families had ≥ 2 symptomatic patients with nC1-INH-HAE and no F12 gene mutation. Three index cases were found mutated among 15 different families tested (20%). After familial investigations around these 3 cases, we found 10 patients with this mutation (Figure 1). Clinical and biological characteristics of 8 patients are presented in Table 1. The majority of our cohort were women (7/10). The median age of the first angioedema attack was 23 years (range 6-64) with a median delay in diagnosis of 24 years (range 5-47 years). The median annual number of attacks was 5 (range 0-12). Four of them developed severe attacks. The median duration of attacks was 2 days with a broad range: 3 hours-7 days. Most of them described attacks affecting the tongue (7), the ENT region,⁶ the face,⁵ the lips,⁵ and the abdominal region.⁴ No patient developed attacks in extremities. C1Inh antigen and function were normal in all patients; plasminogen activity was normal in all but 1 patient. Angiotensin-converting-enzyme inhibitor (ACEi) and angiotensin II receptor blocker (ARA) were trigger factors for 4 patients (one male and 3 women). This has not been reported in the previous studies.^{4,5} Oral contraception exacerbated the frequency and/or

intensity of attacks in 2 patients. TXA long-term prophylaxis was used for 2 patients and was efficient for both of them. Icatibant also improved attacks for these 2 patients. In conclusion, patients with PLG mutation seemed to have a particular clinical phenotype. Attacks seem to be preferentially located on tongue, face, and laryngeal area confirming the results observed in other studies.^{4,5} Prophylactic treatment with TXA seems to be effective. Interestingly, our work suggests that ACEi/ARA can be trigger factors. This has not been reported in previous studies.^{4,5} Recently, a patient with F12 mutation developed an angioedema after ACEi exposure.⁶ In this case, F12 mutation was found to be likely responsible for FXII-HAE triggered by ACEi. These cases could underline a potential role of genetic mutation to ACE inhibitor-induced angioedema. This deserves further studies, as it could have an impact on the assessment and treatment of ACEi-induced angioedema.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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TABLE 1 Clinical and biological characteristics of the 8 patients with PLG mutation

	8 patients
Sex: female/male	6/2
Median age of 1st attack (years)	23 ^a (6-64) ^a
Median diagnosis delay (years)	24 ^a (5-47)
Median annual number of attacks (years)	5 (0-12)
Trigger factors	
Oral contraception	2
ACEi/ARA	4
Attacks localization	
Face	5
Tongue	7
Lips	5
ENT	6
Abdomen	4
Extremities	0
C1Inh antigen, mg/L (reference values: 206-358 mg/L)	354 ^a (246-477) ^a
C1Inh function, U/mL (reference values: 17.2-27.4 U/mL)	26.9 ^a (18.6-35.2)
Plasminogen activity, % (reference values: 80%-120%), n = 5	96 (71-112)

ACEi, angiotensin-converting-enzyme inhibitor; ARA, angiotensin II receptor blocker; C1Inh, C1 inhibitor; ENT, ear, nose, and throat; PLG, plasminogen gene.

^aAll values are median unless otherwise stated (minimum and maximum values are indicated between brackets).

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slgE and slgG to airborne atopic allergens: Coupled rather than inversely related responses

To the Editor,

Specific IgG (slgG) to allergens has been suggested to indicate a healthy immune response, as opposed to the pathological IgE response.¹ This is true for some antiallergen responses, such as to insect stings and to many foods, as well as for allergen-specific immunotherapy (AIT). The situation in relation to low-dose airborne allergens, such as allergens from the prototypical atopic allergen sources pollen and mites, is still unresolved. Recently, an analysis was published on the influence of geographical variability and route of exposure on allergen-specific IgG and IgE. The study was based on the data obtained by an allergen microarray in sera from the French Epidemiological study of the Genetics and Environment of Asthma (EGEA, for details, see² and the Electronic Supplement). Based on an alternative way of analyzing the same data set, we want to argue that the level of IgG to the clinically most relevant airborne allergens is strikingly low in subjects with slgE < 0.3 ISAC standardized units (IgE⁻). This is important, because it may substantially change our views on the initial phase of allergic sensitization (as will be discussed below).

Methodological details on the selection of sera, allergens, and data analysis procedure, as well as a discussion on the important but insufficient contribution of exposure, age, and gender, are presented in the Electronic Supplement. The values shown in the Figures are (a) the prevalence of high slgG, that is, IgG higher than the median of slgG in subjects with slgE > 0.3 ISAC standardized units (ISU) to the same allergen (IgE⁺); and (b) the relative prevalence (RP), which is the prevalence of high slgG in the IgE⁻ population compared to prevalence of high IgG in the IgE⁺ population. In the present context, high slgG corresponds to a modest slgG level (in the µg/L range) compared to the IgG level following a full-blown antibody response

originating in a mature GC (typically in the mg/L range). The scope of the presented analysis is exploratory: We want to show a phenomenon. For such an exploratory data analysis, the use of 95% confidence intervals, as used in the figures, is appropriate.

The evidence presented in favor of our main message (slgG is low in IgE⁻ subjects) is strong. For the two major allergens (mite group 1 and grass group 1), the analysis shown in Figure 1 confirms preliminary results published almost 40 years ago.^{3,4} Those results were not well noticed, possibly because of small sample sizes and the use of the currently unpopular radioisotope technology (a quantitative RadioImmunoAssay, RIA, see the Electronic Supplement). Moreover, conflicting results were obtained by ELISA.⁵

Our data show that the effect size for some, but not all, allergens is big, with a relative prevalence of high slgG in the IgE⁻ population that is often 10- to 100-fold below the statistical no-effect level (ie, RP = 1), with 95% confidence levels mostly well below 1, (Figure 2, Electronic Supplement Table E1). For allergens from 8 families (Amb a 1, Art v 1, tree group 1, Ole e 1, grass group 2, mite group 2, Alt a 1, and Can f 1), the prevalence of high slgG was more than 10 times lower in IgE⁻ than in IgE⁺ subjects. For grass group 1 and mite group 1, the difference was substantially smaller when measured by the microarray than by RIA. The RP was close to 1 for 7 allergens (Pla a 2; mite group 1 and 5; and Der p 4, 7, 21, and 23).

If we accept that lack of allergen exposure is an insufficient explanation for the low IgG response in IgE⁻ subjects (see the Electronic Supplement Figure E1), another explanation is needed. One possible explanation is that atopic allergens are poorly immunogenic and fail to induce a B-cell response in all but the most genetically predisposed subjects.⁶ Even in these most reactive subjects, the immune response is incomplete, germinal centers (GCs) fail to mature, and the absolute amount of IgG produced is modest. However, some IgE-switched B cells become long-lived plasma cells. Upon subsequent exposure, mucosal TH2 inflammation is induced, in which the IgE response diversifies and expands via indirect switching. Recently, it has been established that a fully matured GC effectively prevents the development of long-lived IgE-switched B cells in several mouse models (reviewed in 7,8).

Abbreviations: AIT, allergen immunotherapy; Aln g 1, Bet v 1, Ole e 1, Pla l 1, Pla a 2, tree pollen allergens; Der p 1, 2, 4, 5, 7, 21, 23; Der f 1, 2; Blo t 5, mite allergens; EGEA, epidemiological study of the genetics and environment of asthma; Fel d 1, cat allergen; GC, germinal center of a lymph node follicle; IgE⁺, IgE > 0.3 ISU; IgE⁻, IgE < 0.3 ISU; ISAC, immuno solid-phase allergen chip; ISU, ISAC standardized units; Lol p 1, Phl p 1, 2, 5, 6, 11; Amb a 1, Art v 1, grass and weed pollen allergens; MeDALL, mechanisms of the development of allergy; RIA, radioimmunoassay; RP, relative prevalence; slgE, slgG, allergen-specific IgE, allergen-specific IgG.