

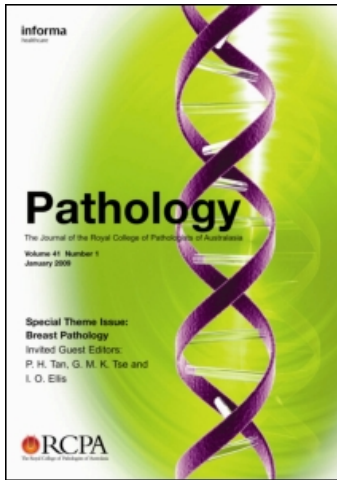
This article was downloaded by: [Macquarie University]

On: 17 April 2009

Access details: Access Details: [subscription number 908812114]

Publisher Informa Healthcare

Informa Ltd Registered in England and Wales Registered Number: 1072954 Registered office: Mortimer House, 37-41 Mortimer Street, London W1T 3JH, UK



Pathology

Publication details, including instructions for authors and subscription information:

<http://www.informaworld.com/smpp/title~content=t713440474>

First molecular confirmation of an Australian case of type III hereditary angioedema

Christopher G. Bell ^a; Edward Kwan ^a; Richard C. Nolan ^b; Karl W. Baumgart ^a

^a Sonic Clinical Institute, North Ryde, Sydney, New South Wales ^b Allergy, Immunology and Respiratory Medicine, Alfred Hospital, Melbourne, Victoria, Australia

Online Publication Date: 01 January 2008

To cite this Article Bell, Christopher G., Kwan, Edward, Nolan, Richard C. and Baumgart, Karl W. (2008) 'First molecular confirmation of an Australian case of type III hereditary angioedema', *Pathology*, 40:1, 82 — 83

To link to this Article: DOI: 10.1080/00313020701716433

URL: <http://dx.doi.org/10.1080/00313020701716433>

PLEASE SCROLL DOWN FOR ARTICLE

Full terms and conditions of use: <http://www.informaworld.com/terms-and-conditions-of-access.pdf>

This article may be used for research, teaching and private study purposes. Any substantial or systematic reproduction, re-distribution, re-selling, loan or sub-licensing, systematic supply or distribution in any form to anyone is expressly forbidden.

The publisher does not give any warranty express or implied or make any representation that the contents will be complete or accurate or up to date. The accuracy of any instructions, formulae and drug doses should be independently verified with primary sources. The publisher shall not be liable for any loss, actions, claims, proceedings, demand or costs or damages whatsoever or howsoever caused arising directly or indirectly in connection with or arising out of the use of this material.

CORRESPONDENCE

First molecular confirmation of an Australian case of type III hereditary angioedema

Sir,

We describe the first identification of the molecular genetic cause of an Australian case of type III hereditary angioedema (MIM #610618) in a 36-year-old Caucasian woman, who had recurrent angioedema, usually four times per year since the age of 20. She had numerous episodes of subjective throat swelling with objective angioedema elsewhere. Episodes often occurred after dental visits but also without any obvious provoking stimulus. She was not atopic and was not responsive to treatment with anti-histamines and adrenaline. She commenced an oral contraceptive at the age of 17 years. Her C3, C4, and C1 inhibitor (quantitative and qualitative) levels have always been normal.

The syndrome of hereditary angioedema (HAE) (MIM #106100) is classically associated with episodes of well-circumscribed, non-pitting, subcutaneous, and submucosal oedema.¹ More than half the cases are diagnosed following a first attack in the first decade of life, which may be precipitated by trauma, insect stings, food, or stress. Symptoms predominantly involve the upper respiratory tract. Laryngeal oedema is potentially life-threatening (previously with mortality rates of up to 30%²). Gastro-intestinal angioedema can mimic an acute abdomen, often leading to unnecessary laparotomy. Prevalence levels have been estimated to be 1 in 50 000.³ No significant ethnic predisposition has been identified.³

Mutations in the *SERPING1* gene, which encodes the C1 inhibitor protein result in HAE.¹ C1 inhibitor functions to regulate activation of the complement, contact and intrinsic coagulation systems.¹ The causative role of *SERPING1* mutations has enabled the categorisation of the disease at the molecular level into either type I or II on the basis of either a truncating deletional or non-sense mutation leading to a quantitative reduction in levels (type I) or missense mutations producing a dysfunctional protein (type II).⁴

The inheritance pattern is autosomal dominant, and haploinsufficiency of the C1 inhibitor protein is deemed to be the pathogenic cause.¹

Due to the occurrence of phenotypically identical HAE in individuals with normal C1 inhibitor levels and function, the involvement of further loci was suspected.⁵ These phenocopies were exclusively females, whose symptoms became more severe with increasing oestrogen levels (e.g., during pregnancy or treatment with oral contraceptives) and were consequently described as oestrogen-related (sensitive) HAE.⁶ Subsequently this has been renamed HAE type III.⁵ In 2006, Dewald and Bork discovered a single nucleotide transversion mutation [c.1032C → A (p.Thr328Lys)] in the coagulation factor XII (Hageman factor) gene (*F12*), located in the chromosome 5q33-qter region, was found to be responsible for these non-classical HAE cases in three German families and one French family.⁷ Factor XII acts on the same physiological pathway as C1 inhibitor, leading to the production of the potent vasodilator bradykinin. This mutation is hypermorphic, with increased enzymatic activity leading to enhanced kinin production resulting in angioedema.⁸ Substitution of a neutral threonine by a positively charged lysine located in the proline-rich region domain (amino acids 296–349) has been hypothesised to increase activation by more effective binding to negatively charged surfaces.⁸ Factor XII also possesses oestrogen-responsive elements in the promoter region of the gene,⁹ thus leading to a possible explanation of the observed female preponderance.⁸

We subsequently designed a real-time PCR assay to detect this *F12* c.1032C → A (p.Thr328Lys) variant. Two fluorescently labelled FRET probes complementary to the mutant and wild-type variant, respectively, were designed to distinguish between these alleles. Screening of 11 mutation negative females in a previous HAE cohort examined for *SERPING1* mutations, as well as one additional sample clinically diagnosed with type III HAE, found only the *F12* mutation in the latter patient. This mutation was subsequently confirmed by bidirectional sequencing (Fig. 1).

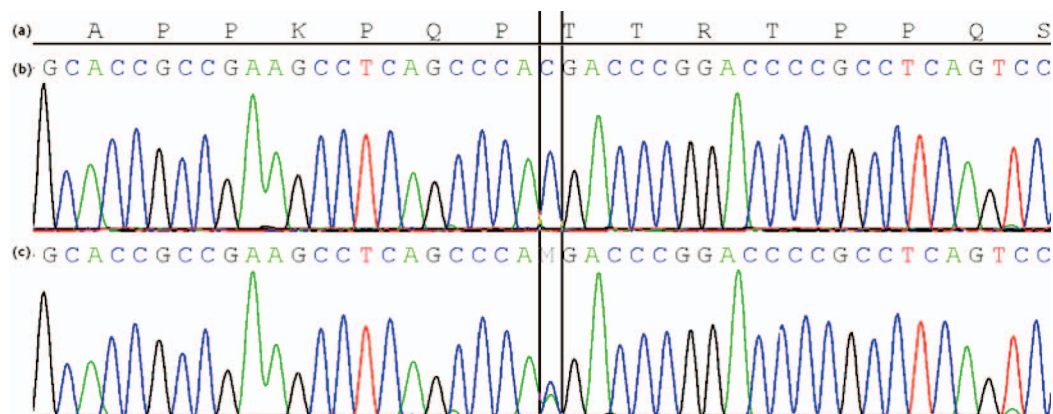


FIG. 1 (a) Single letter code amino acid sequence. (b) Normal electropherogram *F12* c.1032C (p.Thr328). (c) Heterozygote electropherogram *F12* c.1032C → A (p.Thr328Lys).

Cichon *et al.* performed haplotype analysis in the four families in which the c.1032C → A (p.Thr328Lys) were identified suggesting a common founder. They estimated the date of most recent common ancestor (MRCA) to be in the 11th century (95% CI, AD 720–1510).⁸ Unfortunately, we were unable to determine the phased haplotypes in our subject without further pedigree samples. However, due to her Caucasian ancestry (mother 50% English, 50% Scottish; father defined as Australian Caucasian) and the significant time period since MRCA, common descent is possible.

The prevalence of type III HAE is unknown. In the initial paper to describe HAE type III, an examination of persons with recurrent lone angioedema (angioedema without urticaria) with upper airway or gastrointestinal symptoms, found approximately 20% of affected pedigrees had only women with normal C1 inhibitor concentrations and function.⁵ The availability of a simple molecular diagnostic test will now hopefully enable diagnosis in women suffering from lone angioedema and collection of type III HAE prevalence data.

Christopher G. Bell*
Edward Kwan*
Richard C. Nolan†
Karl W. Baumgart*

*Sonic Clinical Institute, North Ryde, Sydney, New South Wales, and †Allergy, Immunology and Respiratory Medicine, Alfred Hospital, Melbourne, Victoria, Australia

Contact Dr C. G. Bell.
 E-mail: christopher.bell@swahs.health.nsw.gov.au

1. Davis AE 3rd. The pathophysiology of hereditary angioedema. *Clin Immunol* 2005; 114: 3–9.
2. Frank MM, Gelfand JA, Atkinson JP. Hereditary angioedema: the clinical syndrome and its management. *Ann Intern Med* 1976; 84: 580–93.
3. Fay A, Abinun M. Current management of hereditary angioedema (C1 esterase inhibitor deficiency). *J Clin Pathol* 2002; 55: 266–70.
4. Zuraw BL, Herschbach J. Detection of C1 inhibitor mutations in patients with hereditary angioedema. *J Allergy Clin Immunol* 2000; 105: 541–6.
5. Bork K, Barnstedt SE, Koch P, Traupe H. Hereditary angioedema with normal C1-inhibitor activity in women. *Lancet* 2000; 356: 213–7.
6. Binkley KE, Davis A, 3rd. Clinical, biochemical, and genetic characterization of a novel estrogen-dependent inherited form of angioedema. *J Allergy Clin Immunol* 2000; 106: 546–50.
7. Dewald G, Bork K. Missense mutations in the coagulation factor XII (Hageman factor) gene in hereditary angioedema with normal C1 inhibitor. *Biochem Biophys Res Commun* 2006; 343: 1286–9.
8. Cichon S, Martin L, Hennies HC, *et al.* Increased activity of coagulation factor XII (Hageman factor) causes hereditary angioedema type III. *Am J Hum Genet* 2006; 79: 1098–104.
9. Farsetti A, Misiti S, Citarella F, *et al.* Molecular basis of estrogen regulation of Hageman factor XII gene expression. *Endocrinology* 1995; 136: 5076–83.

Metastatic renal cell carcinoma masquerading as a primary gastric carcinoma associated with synchronous early gastric carcinoma

Sir,

Metastatic renal cell carcinoma in the stomach is rare and usually associated with widely disseminated neoplasm and diagnosed during necropsy.^{1,2} We recently experienced a synchronous metastatic renal cell carcinoma and adenocarcinoma in the stomach. As metastatic renal cell carcinoma in our case was endoscopically and pathologically similar to ordinary gastric carcinoma, accurate diagnosis was difficult.

A 60-year-old woman was transferred from outside hospital after diagnosis of multiple gastric carcinoma in the mid-body of the stomach. The patient's symptoms included loose stools, dyspepsia, and abdominal pain. Endoscopy revealed diffuse mucosal atrophy on the antrum. At the posterior wall of the low body, an approximately 1.0 cm ill-defined nodular lesion was noted. The centre of this lesion was slightly depressed with a punctate haemorrhagic spot (Fig. 1A). Histological examination of the biopsy specimen revealed typical moderately differentiated tubular adenocarcinoma (Fig. 1B). Two approximately 0.5 cm ovoid elevated lesions were also noted at the anterior wall and greater curvature side of the midbody (Fig. 2A). The centres of each lesion had hyperaemic round erosion surrounded by white exudates. Endoscopic diagnosis was multiple early gastric carcinomas. In the gastric biopsy specimens from these lesions, nests of clear cells mimicking signet ring cells were noted (Fig. 2B). The morphology of clear cells was somewhat different from signet ring cells although very similar. For differential diagnosis of metastatic renal cell carcinoma and signet ring cell carcinoma, immunohistochemical staining for vimentin and cytokeratin (AE1/AE3) was performed, and these clear tumour cells were positive for both antibodies (Fig. 3). After pathological diagnosis, her medical history revealed removal of the right kidney because of renal cell carcinoma 8 years ago, and she has been healthy without any further treatment. Pathological review of the previous renal specimen confirmed diagnosis of metastatic renal cell carcinoma with Fuhrman's nuclear grade I. After pathological diagnosis, abdominal CT scan showed no demonstrable gastric lesion and non-specific small lymph node in the left gastric area. PET scan showed mildly increased FDG uptake in the mid- and lower-body area of the stomach. The patient had undergone subtotal gastrectomy and an 0.8 × 0.8 cm early gastric carcinoma confined in the mucosa of the posterior wall of the lower body, and up to 0.5 cm metastatic renal cell carcinoma in the mucosa and submucosa of the anterior wall of the mid-body were confirmed.

Metastatic involvement of the stomach is usually considered as an extraordinary event and accounts for only 0.2% of gastric neoplastic diseases.³ Because of their rare occurrence, the possibility of gastric involvement of metastatic carcinoma has usually been relegated to a bare possibility.

Renal cell carcinoma spreads haematogenously and is known for its ubiquitous metastatic patterns. However, the