LETTER TO THE EDITOR

Trypsinogen mutations in hereditary pancreatitis: which nomenclature is convenient?

EDITOR,—In a recent issue (*Gut* 1999;45:317–322), David Whitcomb reviewed the current knowledge on molecular genetics and pathogenetic concepts in hereditary pancreatitis. We were delighted by this review from an expert who has recently published landmark papers in which the most frequent mutations of the cationic trypsinogen in hereditary pancreatitis were described.

However, there is considerable confusion concerning the nomenclature of the identified mutations, as in the literature two different systems were used in parallel: the chymotrypsin system and the trypsinogen system. The two frequent mutations R117H and N21I were reported in the chymotrypsin nomenclature^{1,2} whereas for the other mutations (A16V, K23R) the trypsinogen system was used.^{3,4} By mistake, the N21I mutation could be assumed to be located two amino acids proximal to K23R but is in fact six amino acids distal. Remarkably, in the paper of Gorry and colleagues² the N21I mutation was reported in the chymotrypsin nomenclature whereas for the frequent polymorphism D162D in exon 4 the trypsin nomenclature was used.

The chymotrypsinogen nomenclature favoured in the above review is based on the static alignment of the amino acid sequences at serine 195 of the chymotrypsin molecule, as Ser195 is the catalytic residue of all serine proteases. However, use of this nomenclature for mutations of the cationic trypsinogen has several drawbacks:

- The start codon (Met) is not codon 1.
- The amino acids of the signal peptide as well as five amino acids in the active enzyme are not numbered. Mutations of these amino acids cannot be referred to adequately.
- There are 11 numbers without corresponding amino acids.
- A direct alignment of chymotrypsinogen and trypsinogen to numerate mutations is not useful as homologies are rare.

At summary meetings on "Mutation Databases" in San Francisco, USA and "Locus-specific Mutation Databases" in Heidelberg, Germany, the International Nomenclature Working Group pointed out that the nomenclature of mutations needs to be accurate and unambiguous. A list of clear recommendations for mutation names has been published.⁵

To avoid further confusion in the numbering of trypsinogen mutations, we suggest that the trypsinogen numbering system should be used as this system undoubtedly identifies all amino acids in the sequence of trypsinogen.⁶ This nomenclature also fulfils the criteria proposed by the Nomenclature Working Groups⁷:

- Numbering of the protein starts at methionine (codon 1).
- Each amino acid in the protein can be identified by a unique number.

As a consequence, however, the frequent mutations R117H and N21I will have to be called R122H and N29I whereas the nomenclature of the other mutations (A16V, K23R) can be maintained.

To sequence trypsinogen genes in DNA from patients suspected of having hereditary pancreatitis is a simple task and will probably become a standard diagnostic procedure for early onset chronic pancreatitis. Comparable with cystic fibrosis, which is the most common congenital cause of chronic pancreatitis, more mutations of trypsinogens are expected to be found in the future. The standardised gene based nomenclature of trypsinogen mutations that is proposed here should prevent future confusion and clearly identify all mutations of the molecule.

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- 1 Whitcomb DC, Gorry MC, Preston RA, *et al*. Hereditary pancreatitis is caused by a mutation in the cationic trypsinogen gene. *Nat Genet* 1996;14:141–5.
- 2 Gorry MC, Gabbazadeh D, Furey W, *et al*. Mutations in the cationic trypsinogen gene are associated with recurrent acute and chronic pancreatitis. *Gastroenterology* 1997;113: 1063–8.
- 3 Ferec C, Raguene O, Salomon R, *et al*. Mutations in the cationic trypsinogen gene and evidence for genetic heterogeneity in hereditary pancreatitis. *J Med Genet* 1999;36:228–32.
- 4 Witt H, Luck W, Becker M. A signal peptide cleavage site mutation in the cationic trypsinogen gene is strongly associated with chronic pancreatitis. *Gastroenterology* 1999;117:7–10.
- 5 Antonarakis SE. Recommendations for a nomenclature system for human gene mutations. *Hum Mutat* 1998;11:1–3.
- 6 Teich N, Hoffmeister A, Keim V. Nomenclature of trypsinogen mutations in hereditary pancreatitis. *Hum Mutat* 2000;15(2):197–8.

Reply

EDITOR,—I appreciate the comments of Keim *et al* in response to the leading article on hereditary pancreatitis. It is clear that there is confusion about the proper numbering system for cationic trypsinogen (PRSS1) and that consensus on a uniform numbering system should be adopted.¹ We certainly agree that the numbering systems proposed by the nomenclature working groups are useful and should be adapted, but the chymotrypsinogen numbering system (chy#), at times, is also useful. However, we also suggest that if the original R122H (chy #R117H) and N29I (chy #N21I) mutations are mentioned, that both nomenclatures are given for reasons of clarity and consistency. Alignment of the serine proteases with both numbering systems clarifies this problem.²

We also noted a problem in figure 1 of our review on hereditary pancreatitis³ that reflects our own difficulty with the two systems. The problem occurred when we attempted to align the chymotrypsinogen in exon III with trypsinogen by back numbered from the Calpha backbone of trypsinogen structure in the MAGE image,⁴ which shows a two amino acid numbering deletion (#67 and #68). Inserting the two spaces in trypsinogen sequence resulted in a frame shift of chymotrypsinogen through chy#128 (for example, the aspartic acid (D) at chy#102 should be aligned with trypsinogen), although the numbering of cationic trypsinogen, anionic trypsinogen, and mesotrypsinogen remains correct in the figure (allowing for the various chy# given for the trypsinogen amino acids coded by codons 71 to 73). However, alignment of trypsinogen and chymotrypsinogen using the figure 3 in the pancreatic

elastase chapter of Hartley and Shotton⁵ provides a proper alignment, as recently published by Whitcomb.² We regret any further confusion the frame shift in a portion chymotrypsinogen exon III may have caused.

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- 1 Pfützer, RH, Whitcomb DC. Trypsinogen mutations in chronic pancreatitis (letter). *Gastroenterology* 1999;117:1508–9.
- 2 Whitcomb, DC. Genetic predispositions to acute and chronic pancreatitis. *Med Clin N Am* 2000;84:531–47.
- 3 Whitcomb DC. Hereditary pancreatitis: new insights into acute and chronic pancreatitis. *Gut* 1999;45:317–22.
- 4 Hubbard SJ, Eisenmenger F, Thornton JM. Limited proteolysis sites modeling. Hubbard.kin 3.5 (2PTC, 1TGN, 5RSA). Protein Science [serial online] 1994;3:URL: <http://prosci.org/Kinimage/Hubbard.kin> 3.5.
- 5 Hartley BS, Shotton DM. Pancreatic Elastase. In: RD Boyer, ed. *The Enzymes*. New York: Academic Press, 1971:323–73.

NOTES

7th Southeast European Symposium of Paediatric Surgery: Intestinal Motility Disorders

The 7th Southeast European Symposium of Paediatric Surgery will be held at the University of Graz, Austria, on 2 and 3 June 2000. Further information from: Prof Günther Schimpl, Department of Paediatric Surgery, Auenbruggerplatz 34, A-8036 Graz, Austria. Tel: +43 316 385 3762; fax: +43 316 385 3775; email: kinderchirurgie@kfunigraz.ac.at

Courses from the European Postgraduate Gastro-Surgical School

The Board of Directors of the European Postgraduate Gastro-Surgical School announce the following events for 2000:

- 3rd Course in Endoscopy Live will be held at the Academic Medical Centre, Amsterdam, The Netherlands, on 8 and 9 June 2000. Registration fee: NLG 350.
- 9th Course in Digestive Endoscopy will be held at the Academic Medical Centre, Amsterdam, The Netherlands, from 31 August to 1 September 2000. Registration fee: NLG 500.
- Functional Disorders of the Colon and Rectum will be held at the Academic Medical Centre, Amsterdam, The Netherlands, on 19 and 20 October 2000. Registration fee: NLG 450.
- Diagnostic and Therapeutic Endoscopic Intervention in Paediatric Gastroenterology will be held at the Academic Medical Centre, Amsterdam, The Netherlands, on 16 and 17 November 2000. Registration fee: NLG 450.
- The 3rd Amsterdam International Update on Hepatology will be held at the Academic Medical Centre, Amsterdam, The Netherlands, on 14 and 15 December 2000. Registration fee: NLG 450.

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