**CASE REPORT**

Novel cationic trypsinogen (PRSS1) N29T and R122C mutations cause autosomal dominant hereditary pancreatitis

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Hereditary pancreatitis (HP) is usually caused by mutations in the cationic trypsinogen (PRSS1) gene, especially R122H or N29I. We sequenced the PRSS1 gene in the proband of families without these common mutations. Novel R122C and N29T mutations were detected in independent families that segregated with the disease in an autosomal dominant fashion. The R122C mutation eliminates the arginine autolysis site as with R122H mutations. The N29T mutation may also enhance intrapancreatic trypsin activity as has been demonstrated in vitro. Identification of these new mutations requires special attention as commonly used detection methods may fail.

**RESULTS**

**Pedigree No 1**

The 25 year old index patient, with symptoms from age five years, was diagnosed with pancreatitis at age 18 years (fig 1A).

Her paternal grandmother (deceased) was diagnosed with chronic pancreatitis at age 34 years and one of her two daughters had pancreatitis at age five years. A C to T transition mutation at position 133282 (Genbank accession U66061) resulted in a R122C amino acid substitution. This mutation was detected in the father and symptomatic daughter but not in 58 PRSS1 R122H/N29I mutation negative HP patients, 66 patients with familial or idiopathic pancreatitis, or 130 healthy controls. The $A_{III}$III digestion failed to detect the novel R122C mutation.

**Pedigree No 2**

The 23 year old proband, his father, and grandfather all had symptoms of pancreatitis (fig 1B). An A to C transition mutation at position 131945 (Genbank accession U66061) resulted in a N29T amino acid substitution. This mutation was present in the affected father but not other groups, as described above. $B_{III}$III digest detected the N29T mutation.

**DISCUSSION**

Two novel mutations alter the “hot spot” codons 29 and 122 where previously gain of function mutations associated with hereditary pancreatitis were found. Several novel N29I mutations.

**Figure 1** Pedigrees demonstrating an autosomal dominant inheritance pattern of pancreatitis. (A) Pedigree of the family with a R122C mutation. The arrow points to the index case. (B) Pedigree of the family with a N29T mutation. The arrow points to the index case.

**Abbreviations:** HP, hereditary pancreatitis; RFLP, restriction fragment length polymorphism; PCR, polymerase chain reaction.
an autosomal dominant inheritance pattern were found. Sahin-Toth has recently expressed mutants in human cationic trypsin at codon 29 (that is, N29I and N29T) and completed in vitro studies comparing them with wild-type human cationic trypsinogen. In vitro, the N29T mutation markedly enhanced autoactivation and also decreased autolysis. The R122 site is critical for initiating autolysis in humans, and any amino acid substitution (R122H or R122C) would eliminate that site. Finally, RFLP analysis and similar mutation specific screening strategies may miss important mutations that clearly predispose some individuals to pancreatitis.

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REFERENCES