Hereditary pancreatitis and mutation of the trypsinogen gene

P Weber, V Keim, K P Zimmer

Abstract

Hereditary pancreatitis is a rare form of chronic recurrent pancreatitis. A family, in which 11 members had chronic pancreatitis, five had diabetes, and two had pancreatic cancer, was studied, and hereditary pancreatitis was diagnosed in all patients by demonstrating the mutation in exon 3 of the cationic trypsinogen gene (R117H). The clinical implications of genotypic analysis in hereditary pancreatitis are discussed.

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Hereditary pancreatitis is defined as recurrent or episodic pancreatitis in two or more members of several generations of one family. Analysis of hereditary pancreatitis in large families shows that it is inherited as an autosomal dominant trait with 80% penetration.^{1,2} It is the second most common cause of chronic pancreatitis in the young and the first symptoms usually appear in childhood or adolescence.

Until 1996, when Whitcomb and colleagues linked hereditary pancreatitis to chromosome 7q35³ and then identified the mutation in exon 3 of the cationic trypsinogen gene with a substitution of arginine to histidine at residue 117,⁴ other known factors of recurrent pancreatitis had to be excluded before diagnosing the condition.

Case report

We report the case of a 13 year old girl who had suffered from severe recurrent abdominal pain and attacks of vomiting and mild fever (38°C) two or three times each year since she was 3 years old. She was of normal height (164.4 cm, 75th centile), but her weight was low for her age

(41.1 kg, 10th centile). Her serum amylase and lipase concentrations were raised from 1000 U/l to 2000 U/l during attacks of pancreatitis, and pancreatic elastase 1 was diminished (81 µg/g stool), indicating severe pancreatic insufficiency.⁵ Diagnostic investigation excluded metabolic and endocrinological diseases—for example, cystic fibrosis, hypertriglyceridaemia, hyperlipoproteinaemia, haemochromatosis, hypercalcaemia, and hyperparathyroidism. She showed no signs of systemic inflammatory diseases. Endoscopic retrograde cholangiopancreatography (ERCP) excluded congenital malformation, but demonstrated that recurrent inflammation had caused dilatation and narrowing of the pancreatic duct.

Family history showed that 11 members of the patient's family had recurrent pancreatitis, one had a pancreatic pseudocyst requiring surgical intervention, three had pancreatic stones, and two had developed pancreatic carcinomas in their teens. Five family members had also developed insulin dependent diabetes (fig 1).

We tested for the presence of the described mutation of the trypsinogen gene using restriction fragment length polymorphism for polymerase chain reaction amplification. Digestion with a restriction enzyme showed the presence of the G to A transition of exon 3 of the cationic trypsinogen gene, which was also confirmed by the sequence of the corresponding DNA. As indicated in the pedigree (fig 1), our patient, her mother, and her grandmother were all affected. In addition, the mutation was confirmed in all family members examined with recurrent pancreatitis or pancreatic stones and in obligate carriers. The mutation was also found in one woman who was affected by diabetes only, but not in her diabetic son. One woman without symptoms tested negative.

Discussion

Hereditary pancreatitis is a common cause of chronic recurrent pancreatitis in childhood.

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Figure 1 Pedigree of family members with hereditary pancreatitis. Black symbols indicate recurrent clinical symptoms of pancreatitis; D, diabetes; S, pancreatic stones. Mutation R117H positive in family members: II 4; III 2, 4, 15, 18, 20, 22; IV 2, 4, 11, 17, 21, 23, 24; mutation R117H negative in family members: III 24; IV 1.

Inheritance is autosomal dominant with variable penetration and expressiveness. Clinical symptoms are similar to those in patients with idiopathic recurrent pancreatitis, but have a higher complication rate.² The high carcinoma incidence (3% to 50%) in hereditary pancreatitis makes the condition remarkable.

Until 1996, hereditary pancreatitis was diagnosed by showing positive anamnestic features after the exclusion of other causes. Then, Whitcomb revealed a mutation of the trypsinogen gene in patients with hereditary pancreatitis.⁴ Autosomal dominant inheritance and 80% penetration were confirmed. We analysed a large family with this new diagnostic tool. Of the 11 family members suffering from chronic pancreatitis that we studied, nine were affected with a high risk haplotype (R117H) in exon 3 of the cationic trypsinogen. Examination of six of 12 possible gene carriers of generation III revealed that five were also carriers of the haplotype. Two of the generation III family members who were not analysed had pancreatic cancer. One of these patients died in their 20s and the other has two children with clinical symptoms of hereditary pancreatitis. This indicates the relevance of radiological screenings—for example, ultrasound, and, in unclear cases, computed tomography or in future magnetic resonance cholangiopancreatography⁶—in patients who test positive for this mutation.

Whitcomb's data⁴ suggest that the R117H mutation of trypsinogen prevents the autolysis of trypsin activated within the pancreas by the serin proteases mesotrypsin and enzyme Y. Therefore, these data confirm the pathophysi-

ological concept of autodigestion as a cause of hereditary pancreatitis. A second mutation in exon 2 of the cationic trypsinogen gene has recently been identified.^{7,8}

In an analysis based on one large family, Sossenheimer *et al* showed that clinical features alone are not sufficient for identification of all persons with high risk haplotype.⁹ This is confirmed by our findings which revealed four individuals in one family who carried the haplotype without clinical symptoms. The two family members who developed pancreatic cancer were not initially symptomatic.

Finally, mutational analysis of the trypsinogen gene allows some patients with so called idiopathic pancreatitis to be identified as hereditary pancreatitis sufferers.

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