Hereditary pancreatitis

Richard M Charnley, DM FRCS, Consultant Surgeon, Freeman Hospital, Newcastle upon Tyne, NE7 7DN, UK

Correspondence to: Richard M Charnley, DM FRCS, Consultant Surgeon, Freeman Hospital, Newcastle upon Tyne, NE7 7DN, UK.

Richard.charnley@nuth.northy.nhs.uk

Received: 2002-11-30 Accepted: 2002-12-08

Abstract

Hereditary pancreatitis is an autosomal dominant condition, which results in recurrent attacks of acute pancreatitis, progressing to chronic pancreatitis often at a young age. The majority of patients with hereditary pancreatitis express one of two mutations (R122H or N29I) in the cationic trypsinogen gene (PRSS1 gene). It has been hypothesised that one of these mutations, the R122H mutation causes pancreatitis by altering a trypsin recognition site so preventing deactivation of trypsin within the pancreas and prolonging its action, resulting in autodigestion. Families with these two mutations have been identified in many countries and there are also other rarer mutations, which have also been linked to hereditary pancreatitis.

Patients with hereditary pancreatitis present in the same way as those with sporadic pancreatitis but at an earlier age. It is common for patients to remain undiagnosed for many years, particularly if they present with non-specific symptoms. Hereditary pancreatitis should always be considered in patients who present with recurrent pancreatitis with a family history of pancreatic disease. If patients with the 2 common mutations are compared, those with the R122H mutation are more likely to present at a younger age and are more likely to require surgical intervention than those with N29I. Hereditary pancreatitis carries a 40% lifetime risk of pancreatic cancer with those patients aged between 50 to 70 being most at risk in whom screening tests may become important.

Charnley RM. Hereditary pancreatitis. World J Gastroenterol 2003; 9(1): 1-4

http://www.wjgnet.com/v1007-9327/9/1.htm

INTRODUCTION

Hereditary pancreatitis (HP) is an autosomal dominant condition characterised by recurrent attacks of acute pancreatitis and progressing to the development of chronic pancreatitis over a variable period of time. Symptoms usually begin in childhood or adolescence and with time, exocrine and/or endocrine insufficiency may develop. The clinical spectrum of hereditary pancreatitis was first reported in 1952[1]. Mutations causing HP have been identified in the PRSS1 gene which encodes cationic trypsinogen[2-4]. This article discusses the genetics of HP, its pathophysiology and clinical spectrum.

THE GENETICS OF HEREDITARY PANCREATITIS

HP is an autosomal dominant condition with 80% penetrance. The specific mutations responsible for HP were identified in 1996 when it was confirmed that the hereditary pancreatitis gene could be mapped to chromosome 7q35[5,6]. Whitcomb et al demonstrated that a mutation in these patients existed in the third exon of the cationic trypsinogen gene (PRSS1)[7]. This mutation, a guanine (G) to adenine (A) transition, alters arginine (CGC) to histidine (CAC) at codon 117 (using the chymotrypsin numbering system) and was originally known as R117H. This first mutation is easily identified because it creates a novel recognition site for the restriction endonuclease AflIII. More recently, it has been shown that a neutral polymorphism within this enzyme recognition site may produce a false negative result[8]. A second mutation in the cationic trypsinogen gene was subsequently discovered, which was found to be a single A to thiamine (T) transversion mutation in exon 2 resulting in an asparagine (ACC) to isoleucine (ATC) substitution at amino acid 21[9]. These two mutations (R117H and N21I) have now been identified in families with hereditary pancreatitis from many countries including France[10], Germany[9], United Kingdom[10], Japan[11] and the USA[12,13]. A further mutation, which appears to be much less common, is the A16V mutation, which was originally identified in three patients with idiopathic pancreatitis and in one patient with HP[12]. There is also evidence that mutations in genes other than the cationic trypsinogen gene might be associated with HP[13]. Since the discovery of the cationic trypsinogen gene mutations, a new nomenclature system for human gene mutations has been devised and accepted. This has changed the names of the common mutations from R117H to R122H and N21I to N29I[14].

PATHOPHYSIOLOGY

The mechanism by which mutations of the cationic trypsinogen gene cause hereditary pancreatitis is important for several reasons. Firstly, the cellular mechanisms of acute pancreatitis and progression to chronic pancreatitis are poorly understood. Secondly it is not known why the pancreas of one individual is susceptible to alcohol whilst the pancreas of another is not. Thirdly, focusing on the link between genetics and pancreatitis might provide a clue to the etiology of pancreatic cancer which can occur as a complication in sporadic and hereditary pancreatitis. Trypsinogen is secreted by the pancreatic acinar cell[15]. It is activated to trypsin within the duodenum by enterokinase, which cleaves an 8-aminoacid N-terminal peptide. Trypsin then activates a cascade of digestive enzyme precursors. A number of mechanisms exist to prevent inappropriate activation of trypsin within the pancreas before its secretion into the duodenum. It is hypothesised that the R122H mutation alters a trypsin recognition site, which would prevent deactivation of trypsin within the pancreas, thus prolonging its action[12]. The mechanism whereby the N29I mutation causes pancreatitis is unclear. It has been speculated, however, that the N29I mutation would enhance autoactivation of trypsinogen, altering the binding of pancreatic secretory trypsin inhibitor (PSTI)[16] or impairing trypsin inactivation by altering the accessibility of the initial hydrolysis site to trypsin. Predicted molecular conformational changes in the structure of trypsin support this[16]. The pathogenic mechanism whereby the A16V mutation causes pancreatitis is speculative but it is thought to alter the cleavage site of the signal peptide[12]. Because the two common mutations, R122H and N29I produce such a similar
Clinical picture, it has been speculated that these mutations, rather than being the cause of hereditary pancreatitis, simply represent markers for a number of linked pancreatic defects. There appears no doubt, however, that inappropriate prevention of the deactivation of trypsin within the pancreas is responsible for HP in the majority of cases.

The penetrance of cationic trypsinogen gene mutations remains at approximately 80% in the majority of studies. To investigate factors contributing to this, a study of monozygotic twins with HP was carried out[17]. Of 11 sets of twins, seven were suitable for this study. Whereas four of these seven sets were concordant for pancreatitis, three of the seven sets of twins (43%) were discordant for phenotypic expression of pancreatitis. The overall penetrance in the seven pairs of twins was 78%. The conclusion from this study was that genetic and/or environmental factors contribute to the expression and age of onset of HP. As yet the mechanism of non-penetrance remains unclear.

**CLINICAL PRESENTATION IN HEREDITARY PANCREATITIS**

The initial presentation of a patient with HP is usually indistinguishable from a case of sporadic pancreatitis. The clinical presentation is variable but typical patients present with recurrent attacks of acute pancreatitis in childhood, progressing to chronic pancreatitis with time[18,19]. The presentation during an acute attack is identical to an attack of gallstone-induced, alcoholic or idiopathic, acute pancreatitis. The presentation of chronic pancreatitis in these patients is likewise indistinguishable from alcoholic, idiopathic or other forms of chronic pancreatitis[18-20]. Pediatric patients with HP have a similar presentation to idiopathic juvenile chronic pancreatitis[21]. It is however very common for these patients to remain undiagnosed for many years having often suffered from chronic symptoms since childhood. We have found that recognition of the disease within a family often results in several relatives being newly diagnosed with pancreatitis whereas previously they had been labelled as “peptic ulcer” or “chronic abdominal pain”. In Newcastle upon Tyne, UK, the pancreatic clinic now has individuals belonging to thirteen families with hereditary pancreatitis. Data on nine of these families has been previously published[20]. The R122H (R117H) mutation was identified in three families and the N29I (N21I) mutation was demonstrated in a further five families. In a remaining family, no mutations were demonstrated in any of the five exons of the PRSS1 gene. The families and patients belonging to the R122H group were compared with those belonging to the N29I group. Comparison of clinical details including complications of pancreatitis was carried out. The mean age at onset of symptoms of pancreatitis was lower in the R122H group at 8.4 vs 6.5 years, (P=0.007) and more patients with the R122H mutation had developed symptoms by the age of 20 years (89 vs 64%). More patients with the R122H mutation required surgical intervention (8 of 12 vs 4 of 17, P=0.029) and this occurred at an earlier age. There was also a tendency for more patients with the R122H mutation to develop exocrine failure but the incidence and age of onset of exocrine failure (as measured by the development of insulin dependent diabetes mellitus) was similar in both groups. Patients in both groups identified alcohol as a provoking factor for the symptoms. These observations were also noted in the original description of the N21I mutation in 1997[19] and have also been noted by the European Registry of Hereditary Pancreatitis and Pancreatic Cancer (EUROPAC)[22]. It is also clear that as well as hereditary pancreatitis being identical to other forms of pancreatitis in terms of the mode of clinical presentation, radiological and histopathological features are also identical[23]. Apart from earlier onset and delay in diagnosis, hereditary pancreatitis has been found to have a natural history similar to that of chronic alcoholic pancreatitis in terms of a similar prevalence of pancreatic calcification, a similar amount of pancreatic insufficiency both endocrine and exocrine but a higher prevalence of pseudocysts[24].

**CATIONIC TRYPsinogen GENE MUTATIONS IN NON-HEREDITARY PANCREATITIS**

Taking a family history is very important in all patients with pancreatitis because the majority of patients with cationic trypsinogen gene mutations have a clear cut family history of pancreatitis. It is, however, common for patients to be referred to a pancreatic specialist with so-called idiopathic pancreatitis without a reliable family history having been obtained[25]. It has also been considered whether idiopathic chronic pancreatitis might be due to PRSS1 gene mutations. An investigation of patients with chronic alcoholic pancreatitis showed no evidence of the R122H or N29I mutation in 21 patients[26] but a much larger and important study investigated 221 patients with idiopathic chronic pancreatitis and no family history. The entire PRSS1 gene was sequenced in these patients. Only three patients had mutations, one with R122H and two patients with A16V[27]. A genetic background has also been investigated in patients with idiopathic juvenile chronic pancreatitis, a disease which closely mimics the clinical pattern of hereditary pancreatitis[28]. The R122H mutation was detected in one patient with idiopathic juvenile chronic pancreatitis and the A16V mutation was also found in one patient. It is clear from these studies that new mutations do occur and that screening of individuals with idiopathic pancreatitis for cationic trypsinogen gene mutations is worthwhile. It is, therefore, our policy in patients with idiopathic pancreatitis, after exclusion of other causes, to perform genetic counselling and genetic testing. We have found that patients are keen to know their genetic status in relation to this disease.

**RISK OF CANCER IN HEREDITARY PANCREATITIS**

Sporadic chronic pancreatitis carries a significantly increased risk of pancreatic cancer. This has been clearly demonstrated by a multi-centre historical cohort study of over 2000 patients[29]. The standardized incidence ratio, i.e. the ratio of observed to expected pancreatic cancers was 16.5. This study may have been subject to detection bias in that increased surveillance of chronic pancreatitis patients may have increased the number of cancers diagnosed compared with the general population. A study of Swedish patients, however, confirmed an increased risk of pancreatic cancer in sporadic chronic pancreatitis but with a standardised incidence ratio of 3.8[30]. Patients with HP have not been included in either of these studies but have since been examined for the risk of developing pancreatic cancer by the International Hereditary Pancreatitis Study Group. A cohort of 246 patients with hereditary pancreatitis was identified from ten countries with a mean follow-up period of over 14 years[31]. Eight patients with pancreatic adenocarcinoma were identified yielding a standardized incidence ratio of 53.3. The estimated cumulative risk of pancreatic cancer developing in these patients was nearly 40% and was greater for patients with a paternal inheritance pattern. These figures have been confirmed by the Midwest Multicentre Pancreatic Study Group[32]. The conclusions from these cancer studies are that, firstly chronic pancreatitis is a risk factor for pancreatic cancer and secondly hereditary pancreatitis puts patients at an even higher risk of developing cancer than the sporadic disease. Although it is not absolutely clear whether the risk of cancer is due to prolonged inflammatory change or whether it is related to the presence of a cationic trypsinogen mutation per se, the evidence available at present indicates that those patients with HP who
develop cancer, are those with a prolonged history of chronic pancreatitis\[32\]. The number of cancers, which have developed in HP patients have so far not allowed an investigation into which mutation(s) might predispose to cancer more than another. This data, however, will be available with time. A study of pancreatic tissue from 34 patients with sporadic ductal adenocarcinoma has shown no specific relationship between the R122H mutation and pancreatic cancer\[33\]. Further such studies are expected as tissue from patients with hereditary pancreatitis becomes available for analysis.

**MANAGEMENT DILEMMAS IN HEREDITARY PANCREATITIS**

When faced with a patient or a family with a possible diagnosis of HP, three questions are commonly asked. Firstly, what can be done about the patient with pancreatitis? Secondly, are other relatives likely to be affected? Thirdly, what can be done to reduce the risk of cancer?

**Management of the pancreatitis**

There are no specific medical therapies recommended in patients with HP. The management of acute attacks of pancreatitis are the same as for the sporadic disease that is, rehydration, analgesia and careful monitoring. Severe necrotising pancreatitis is rare in HP but pseudocysts seem to be relatively common. It has been suggested that antioxidant therapy may be helpful to prevent acute attacks but there is no evidence to support this and it is not recommended. Chronic pancreatitis should be treated as for any other patients. Enzyme supplements are likely to be required and analgesics as necessary. If diabetes mellitus occurs it is likely to require insulin therapy. Surgical treatment is for complications such as pseudocyst, biliary obstruction or duodenal obstruction. In older patients requiring surgery, a total pancreatectomy should be considered in order to abolish the cancer risk (see below).

**Genetic counselling of relatives**

Relatives should be told that although the majority of HP cases are revealed by the age of 18, the disease may not manifest itself until the age of 30 or older. In these unaffected individuals, genetic testing confers no advantage and should be discouraged. Since unaffected (non-carrier) individuals and unaffected carriers do not have pancreatitis, they carry no increased risk of developing cancer.

**Screening of hereditary pancreatitis patients for cancer**

Since patients with this disease exhibit a 53-fold increased risk of pancreatic cancer with a cumulative risk of 40% by the age of 70, an attempt at screening would appear to be essential. Unfortunately, no adequate screening test exists. The measurement of tumor markers, endoscopic techniques and radiological imaging lack the sensitivity and specificity for early diagnosis. Tumors are particularly difficult to detect on a background of chronic pancreatitis. It is thought therefore that molecular based strategies are likely to offer the best opportunities for the screening of these high risk patients for pancreatic ductal adenocarcinoma\[34\]. It has been suggested that the banking of blood and pancreatic juice samples should be mandatory in any screening protocol and that imaging of the pancreas should be carried out by endoscopic ultrasound\[35\]. One such protocol for the secondary screening of patients with HP has been established by EUROPCR (European Registry of Hereditary Pancreatitis and Pancreatic Cancer). As part of a research program only, affected individuals over the age of 30 are offered imaging by CT and endoscopic ultrasound (EUS), followed after genetic counselling, by genetic analysis of pancreatic juice obtained at ERCP for K-ras mutations. Patients negative for K-ras continue with repeat screening at 3 yearly intervals by CT, EUS and K-ras analysis of pancreatic juice. Patients who are K-ras positive undergo further genetic analysis in the form of p53, p16 and aberrant methylation. If positive, these patients may be at risk of pancreatic ductal carcinoma and an attempt should be made to obtain cells for cytology by ERCP brushing of the pancreatic duct. The ultimate preventative measure in these patients would be a total pancreatectomy but this is a relatively high morbidity operation with the certainty of becoming diabetic. Certainly any patient with HP aged 30 or over, who requires surgery for relief of symptoms should undergo a total pancreatectomy in order to abolish the cancer risk rather than a lesser procedure. This is not, however, appropriate in patients who are well unless there is clear evidence that they possess cellular atypia or a focal abnormality suspicious of cancer.

**CONCLUSIONS**

Hereditary pancreatitis is a fascinating condition which has provided new insights into the pathophysiology of pancreatitis. There are however many unanswered questions particularly in relation to the ways in which these mutations relate to pancreatitis and cancer. Management of these patients should be carried out by a team of experienced pancreatic specialists who are also able to provide genetic counselling. Registration of patients with one of the large Hereditary Pancreatitis Registries is essential if management strategies are to be improved and genetic research to be continued.

**REFERENCES**

1 Comfort MW, Steinberg AG. Pedigree of a family with hereditary chronic relapsing pancreatitis. Gastroenterology 1952; 21: 54-63
2 Whitcomb DC. Hereditary pancreatitis: new insights into acute and chronic pancreatitis. Gut 1999; 45: 317-322
3 Gorry MC, Gabbaiadeh D, Furey W, Gates LK Jr, Preston RA, Aston CE, Zhang Y, Ulrich C, Ehrlich GD, Whitcomb DC. Mutations in the cationic trypsinogen gene are associated with recurrent acute and chronic pancreatitis. Gastroenterology 1997; 113: 1063-1068
4 Ferre C, Ragueneau O, Salomon R, Roche C, Bernard JP, Guillot M, Quere I, Faure C, Mercier B, Audrezet MP, Guillausseau PJ, Dupont C, Munlich A, Bignon JD, Le BodiC. Mutations in the cationic trypsinogen gene and evidence for heterogeneity in hereditary pancreatitis. J Med Genet 1999; 36: 228-232
5 Whitcomb DC, Preston RA, Aston CE, Sossenheimer MJ, Barua PS, Zhang Y, Wong-Chong A, White GJ, Wood PG, Gates LK Jr, Ulrich C, Martin SP, Post JC, Ehrlich GD. A gene for hereditary pancreatitis maps to chromosome 7q35. Gastroenterology 1996; 110: 1975-1980
6 Pandya A, Blanton SH, Landa B, Javaheery R, Melvin E, Nance WE, Markelio T. Linkage studies in a large kindred with hereditary pancreatitis confirms mapping of the gene to a 16-cM region on 7q. Genomics 1996; 38: 227-230
7 Whitcomb DC, Gorry MC, Preston RA, Furey W, Sossenheimer MJ, Ulrich GD, Martin SP, Gates LK Jr, Amann ST, Toskes PP, Liddle R, McGrath K, Uomo G, Post JC, Ehrlich GD. Hereditary pancreatitis is caused by a mutation in the cationic trypsinogen gene. Nat Genet 1996; 14: 141-145
8 Howes N, Greenhalf W, Rutherford S, O’Donnell M, Mountford R, Ellis I, Whitcomb D, Imrie C, Drumm B, Neoptolemos JP. A new polymorphism for the R122H mutation in hereditary pancreatitis. Gut 2001; 48: 247-250
9 Teich N, Mossner J, Keim V. Mutations of the cationic trypsinogen in hereditary pancreatitis. Hum Mutat 1998; 12: 39-43
10 Creighton JE, Lyall R, Wilson DI, Curtis A, Charney RM. Mutations of the cationic trypsinogen gene in patients with hereditary pancreatitis. Br J Surgery 2000; 87: 170-175
11 Nishimori I, Kamakura M, Fujikawa-Adachi K, Morita M, Onishi S, Yokoyama K, Makino I, Ishida H, Yamamoto M, Watanabe S, Ogawa M. Mutations in exons 2 and 3 of the cationic trypsinogen gene in Japanese families with hereditary pancreatitis. Gut
tinction in the cationic trypsinogen gene is strongly associated with chronic pancreatitis. Gastroenterology 1999; 117: 7-10

13 Bartness MA, Duerr RH, Ford MA, Zhang L, Aston CE, Barnada M. Potential linkage of a pancreatitis associated gene to chromosome 12. Pancreas 1998; 17: 426

14 Antonarakis SE. Recommendations for a nomenclature system for human gene mutations. Nomenclature Working Group. Hum Mutat 1998; 11: 1-3

15 Scheele G, Kern H. The exocrine pancreas. In: Desnuelle P, Sjöström H, Norén O, eds. Molecular and Cellular Basis of Digestion. Amsterdam: Elsevier 1986: 173-194

16 Whitcomb DC. Hereditary pancreatitis: new insights into acute and chronic pancreatitis. Gut 1999; 45: 317-322

17 Amann ST, Gates LK, Aston CE, Pandya A, Whitcomb DC. Expression and penetrance of the hereditary pancreatitis phenotype in monozygotic twins. Gut 2001; 48: 542-547

18 Perrault J. Hereditary pancreatitis. Gastroenterol Clin North Am 1994; 23: 743-752

19 Konzen KM, Perrault J, Moir C, Zinsmeister AR. Long-term follow-up of young patients with chronic hereditary or idiopathic pancreatitis. Mayo Clinic Proc 1993; 68: 1993

20 Kattwinkel J, Lapey A, Di Sant`Agnese PA, Edwards WA. Hereditary pancreatitis: three new kindreds and a critical review of the literature. Pediatrics 1973; 51: 55-69

21 DuBay D, Sandler A, Kimura K, Bishop W, Eimen M, Soper R. The modified Puestow procedure for complicated hereditary pancreatitis in children. Journal of Pediatric Surgery 2000; 35: 343-348

22 Howes N, Rutherford S, McDonald F, Ellis I, Whitcomb DC, Mountford R, Neoptolemos JP. For the UK and Ireland Consortium of EUROPAC. Trypsinogen mutations in families with Hereditary Pancreatitis in the UK and Ireland. Int J Pancreatol 1999; 25: 237

23 Sossenheimer MJ, Aston CE, Preston RA, Gates LK Jr, Ulrich CD, Martin SP, Zhang Y, Gorry MC, Ehrlich GD, Whitcomb DC. Clinical characteristics of hereditary pancreatitis in a large family, based on high-risk haplotype. The Midwest Multi-Centre Pancreatic Study Group (MMPCG). Am J Gastroenterol 1997; 92: 1113-1116

24 Paolini O, Hasler P, Buckley M, Maes B, Demarquay JF, Staccini P, Bellow S, Caroli-Bosch FX, Dumas R, Delmont J. The natural history of hereditary chronic pancreatitis: a study of 12 cases compared to chronic alcoholic pancreatitis. Pancreas 1998; 17: 226-271

25 Creighton J, Lyall R, Wilson DI, Curtis A, Charnley R. Mutations of the cationic trypsinogen gene in patients with chronic pancreatitis. Lancet 1999; 354: 42-43

26 Teich N, Mossner J, Keim V. Screening for mutations of the cationic trypsinogen gene are they of relevance in chronic alcoholic pancreatitis? Gut 1999; 44: 413-416

27 Chen JM, Piepoli Bls A, Le Bodic L, Ruszniewski P, Robaszkiewicz M, Deprez PH, Raguenes O, Ouere I, Andriulli A, Ferec. Mutation screening of the cationic trypsinogen gene in a large cohort of subjects with idiopathic chronic pancreatitis. Clinical Genetics 2001; 59: 189-193

28 Truninger K, Kock J, Wirth HP, Muelhaupt B, Arnold C, von Weizsacker F, Seifert B, Ammann RW, Blum HE. Trypsinogen gene mutations in patients with chronic or recurrent acute pancreatitis. Pancreas 2001; 22: 18-23

29 Lowenfels AB, Maisonneuve P, Cavallini G, Ammann RW, Lankisch PG, Andersen JR, Dimagno EP, Andren-Sandberg A, Domelof L. Pancreatitis and the risk of pancreatic cancer. International Hereditary Pancreatitis Study Group. J Natl Cancer Ins 1994; 86: 625-627

30 Ek bom A, McLaughlin JK, Karlsson BM, Nyren O, Gridley G, Adami HO, Fraumeni JF Jr. Pancreatitis and pancreatic cancer: a population-based study. J Natl Cancer Ins 1994; 86: 625-627

31 Lowenfels AB, Maisonneuve P, DiMagno EP, Elitsur Y, Gates LK Jr, Perrault J, Whitcomb DC. Hereditary pancreatitis and the risk of pancreatic cancer. International Hereditary Pancreatitis Study Group. J Natl Cancer Ins 1997; 89: 442-446

32 Whitcomb DC, Applebaum S, Martin SP. Hereditary pancreatitis and pancreatic carcinoma. Ann NY Acad Sci 1999; 880: 201-209

33 Hengstler JG, Bauer A, Wolf HK, Bulitta CJ, Tanner B, Oesch F, Gebhard S, Boettger T. Mutation analysis of the cationic trypsinogen gene in patients with pancreatic cancer. Anticancer Research 2000; 20: 2967-2974

34 Howes N, Greenhalf W, Neoptolemos J. Screening for early pancreatic ductal adenocarcinoma in hereditary pancreatitis. Med Clinics North Am 2000; 84: 719-738

35 Martin SP, Ulrich CD. Pancreatic cancer surveillance in a high-risk cohort. Is it worth the cost? Med Clinics North Am 2000; 84: 739-747

Edited by MajY