

# The natural history of hereditary pancreatitis: a national series

V Rebours,<sup>1</sup> M-C Boutron-Ruault,<sup>2</sup> M Schnee,<sup>3</sup> C Férec,<sup>4</sup> C Le Maréchal,<sup>4</sup> O Hentic,<sup>1</sup> F Maire,<sup>1</sup> P Hammel,<sup>1</sup> P Ruzsniwski,<sup>1</sup> P Lévy<sup>1</sup>

<sup>1</sup> Pôle des Maladies de l'Appareil Digestif, Service de Gastroentérologie – Pancréatologie, Hôpital Beaujon, AP-HP, Université Denis Diderot-Paris VII, Clichy, France; <sup>2</sup> Unité nutrition – hormones et cancer E3N, Inserm, Institut Gustave Roussy, Villejuif, France; <sup>3</sup> Service d'Hépatogastro-Entérologie, Centre Hospitalier Départemental, La Roche sur Yon, France; <sup>4</sup> Inserm-U613, Génétique Moléculaire et Génétique Epidémiologique, Etablissement Français du Sang-Bretagne, Université de Bretagne Occidentale, Centre Hospitalier Universitaire, Brest, France

Correspondence to: Professor P Lévy, Pôle des Maladies de l'Appareil Digestif, Service de Gastroentérologie-Pancréatologie, APHP, Hôpital Beaujon, 92118 Clichy Cedex, France; philippe.levy@bjn.aphp.fr

Revised 10 June 2008  
Accepted 5 August 2008  
Published Online First  
28 August 2008

## ABSTRACT

**Background and aims:** The prevalence and natural history of hereditary pancreatitis (HP) remain poorly documented. The aims of this study were to assess genetic, epidemiological, clinical and morphological characteristics of HP in an extensive national survey.

**Methods:** A cohort comprising all HP patients was constituted by contacting all gastroenterologists and paediatricians (response rate 84%) and genetics laboratories (response rate 100%) in France (60 200 000 inhabitants). Inclusion criteria were the presence of mutation in the cationic trypsinogen gene (PRSS1 gene), or chronic pancreatitis in at least two first-degree relatives, or three second-degree relatives, in the absence of precipitating factors for pancreatitis.

**Results:** 78 families and 200 patients were included (181 alive, 6673 person-years, males 53%, alcoholism 5%, smoking 34%). The prevalence was 0.3/100 000 inhabitants. PRSS1 mutations were detected in 68% (R122H 78%, N29I 12%, others 10%). Penetrance was 93%. Median age at first symptom, diagnosis and date of last news, were 10 (range 1–73), 19 (1–80) and 30 (1–84) years, respectively. HP was responsible for pancreatic pain (83%), acute pancreatitis (69%), pseudocysts (23%), cholestasis (3%), pancreatic calcifications (61%), exocrine pancreatic insufficiency (34%, median age of occurrence 29 years), diabetes mellitus (26%, median age of occurrence 38 years) and pancreatic adenocarcinoma (5%, median age 55 years). No differences in clinical and morphological data according to genetic status were observed. 19 patients died, including 10 directly from HP (8 from pancreatic adenocarcinoma).

**Conclusion:** The prevalence of HP in France is at least 0.3/100 000. PRSS1 gene mutations are found in 2/3 with a 93% penetrance. Mutation type is not correlated with clinical/morphological expression. Pancreatic adenocarcinoma is the cause of nearly half the deaths.

Hereditary pancreatitis (HP) is a rare cause of chronic pancreatitis (CP), first described by Comfort and Steinberg in 1952.<sup>1</sup> Descriptions of families suggested an autosomal dominant inheritance pattern with incomplete penetrance (80%).<sup>2</sup> In 1996, an association between HP and the long arm of chromosome 7 (7q35) was found and described by genetic linkage analysis with microsatellite markers by three independent teams.<sup>3–5</sup> Whitcomb *et al*<sup>6</sup> identified a first genetic defect of the cationic trypsinogen gene (PRSS1), ie, the R122H mutation<sup>6</sup> which was independently confirmed by Férec *et al*<sup>7</sup> Other mutations in this gene, such as N29I, A16V, E79K, R122C, R116C, have been described subsequently.<sup>8–13</sup>

HP is a rare entity and its prevalence is unknown. No data concerning the natural history of the disease, based on a complete recruitment in a definite area, have been published. Clinical features of HP patients have been described, but mostly in selected families with a known genetic mutation or only in case reports or in small series of patients ( $n < 15$ ).<sup>14–17</sup> Recently, an important European study recruited several European families with a known PRSS1 mutation or a clear familial history of chronic pancreatitis.<sup>14–20</sup> However, this study relied on a spontaneous declaration by gastroenterology specialists. The results regarding the natural history of HP described the risk of pancreatic adenocarcinoma and the occurrence of exocrine and endocrine insufficiencies. Severity of symptoms was associated with the type of mutation, the R122H mutation being associated with a more severe presentation. Patients with HP are increasingly aware of the disease and frequently ask questions about its long-term evolution including the occurrence of acute pancreatitis, exocrine and endocrine insufficiency. The high risk of pancreatic adenocarcinoma (PA) has been described by several teams including our work issued from the same cohort.<sup>20</sup>

The aims of the present study were to describe epidemiological, clinical and morphological features of HP, to search for a correlation between the main HP manifestations and PRSS1 mutations, in a complete series of HP patients based on a national census. The risk of PA will be briefly addressed, but has been extensively studied elsewhere.<sup>20</sup>

## PATIENTS AND METHODS

### Data source

A systematic registration of patients with a known diagnosis of HP in France (60 200 000 inhabitants in 1999) was set up in 2005. All the genetics laboratories involved in testing PRSS1 and the serine protease inhibitor Kazal type 1 (SPINK1) in France accepted an invitation to participate in this study and provided the names of all the patients with PRSS1 gene mutations. All French paediatricians and gastroenterologists ( $n = 6917$ ) were contacted by mail. The initial letter invited them to join a collaborative study aimed at investigating the natural history of HP. A questionnaire was included in order to determine whether they followed or had followed (or not) at least one patient with HP during the past 30 years. The response rate to the initial mail was 71%. A recall mail was sent 6 months later to the non-responders and an 84% total response rate was obtained. Physicians who followed patient(s) with HP were

subsequently asked to forward clinical and genetic data about their patients. A complete family tree was established with the physician and the patients for all subjects, including at least three generations. All cases with HP criteria (see below) were investigated and included in the data set. Clinical diagnosis reported by patients or family members was verified in all instances by consulting the original medical records. The clinical, biochemical and genetic records were entirely reviewed by one of us (VR) in each medical centre. Special attention was paid to pancreatic pain, acute pancreatitis, diabetes mellitus, smoking status and alcohol consumption in patients by direct contact or by consulting medical files. For deceased patients, we questioned the index cases and their families to confirm data obtained from medical files. A historical cohort was created.

### Inclusion criteria

Patients were included if they met at least one of two criteria.

### Genealogical and clinical criterion

Patients with chronic pancreatitis with a familial history were included in this group. A familial history was defined by recurrent acute pancreatitis or chronic pancreatitis occurring in two first-degree relatives or three or more second-degree relatives, in two or more generations in the absence of precipitating factors. Other causes of chronic pancreatitis were searched for depending on the clinical and anamnestic context in particular alcohol consumption.

### Genetic criterion

Patients were included in this group if they had a detected cationic trypsinogen gene mutation (with or without clinical or radiological manifestations of chronic pancreatitis).

### Definitions

The diagnosis of chronic pancreatitis was based on the presence at least one of the following: pancreatic calcifications as evidenced by plain radiography of the pancreatic area in three projections, computed tomography scan, or endoscopic ultrasonography; moderate to marked pancreatic ductal lesions on pancreatography obtained by endoscopic retrograde or magnetic resonance pancreatography (Cambridge classification)<sup>21</sup> or typical histology of an adequate surgical pancreatic specimen.

Acute pancreatitis was defined by acute abdominal pain with increased serum pancreatic enzyme levels over three times the upper limit of normal values. Pancreatic pain was defined by typical pancreatic pain without elevation of serum pancreatic enzyme or typical pancreatitis lesion at imaging procedure.

Exocrine pancreatic insufficiency was diagnosed in the case of clinical steatorrhea, a need for long-term oral pancreatic enzyme supplements, faecal fat output greater than 6 g per day or faecal elastase 1 concentration lower than 100 µg/g of stools.

Diabetes mellitus was diagnosed if a whole venous blood fasting glucose concentration was recorded  $\geq 126$  mg/dl (6.99 mmol/l) at at least two determinations or  $>11.0$  mmol/l,

**Table 1** Baseline characteristics of the patients

Characteristic	All patients (n = 200)	Patients with PRSS1 mutations (n = 135)	Patients without detected PRSS1 mutation (n = 65‡)	p Value
Age at last news, in years*	30 (1–84)	32 (1–84)	27 (5–79)	NS
Number of men	105	73	32	NS
Number of families	78	50	28	
Number of affected generations in each family*	3 (1–4)	3 (1–4)	2 (1–4)	NS
Number of smokers	66/129†	50/95†	16/34†	NS
Tobacco consumption, (pack-years)*	12 (1–100)	11 (1–100)	15 (1–50)	NS
Chronic alcoholism (n), (md = 5)	10	7	3	NS
PRSS1 mutations (n)	135	135		
R122H	–	105		
N29I	–	16		
R122C	–	3		
E79K	–	3		
K23R	–	2		
A16V	–	1		
R116C	–	1		
K170E	–	1		
Q98K	–	1		
33delTCC	–	1		
667 tc	–	1		
Origin of inheritance (n)				
Maternal	78	70	11	
Paternal	67	37	35	<0.0001
Unknown	55	28	18	
SPINK1 mutations (n), (md = 9)	25§	7	18	<0.0001
CFTR mutations (n), (md = 9)	3¶	2	1	NS

\*Median and (range).

†The influence of smoking habits was assessed only in patients older than 18 years (n = 147). Data were missing in 18. Therefore, the comparison is based on 129 patients.

‡Including nine patients, deceased before 1996, in whom the PRSS1 mutation could not be searched for.

§Twenty patients had the N34S mutation.

¶The mutations were E528E, IVS3+2T/C and ΔF508.

CFTR, cystic fibrosis transmembrane regulator; md, missing data; PRSS1, cationic trypsinogen gene; SPINK1, serine protease inhibitor Kazal type 1.

post-prandially, at one determination. Insulin requirement was defined by the inefficacy of adequate diet (diet without sugar) and oral drugs (biguanids, sulfonylurea, alpha-glucosidase inhibitors) in preventing hyperglycaemia.

Cholestasis was defined as increased alkaline phosphatase levels above the upper limit of normal values associated with a dilated common bile duct.

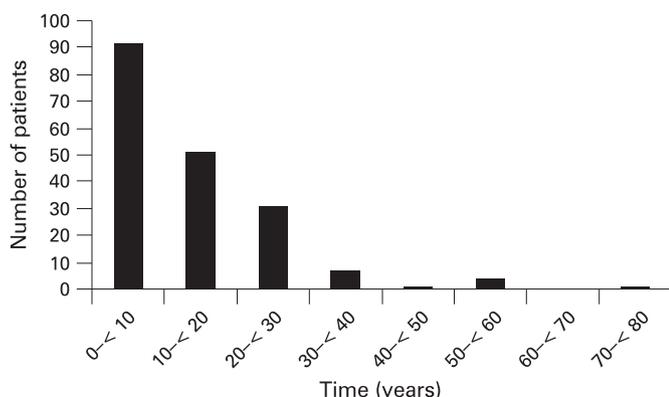
Chronic alcoholism was defined by alcohol intake exceeding 6 units/day in men (60 g of pure alcohol per day) and 4 units/day (40 g of pure alcohol per day) in women for at least 2 years.<sup>22</sup>

Smoking status was defined as “daily smoker” if patients had smoked for at least 2 years (current and ex daily smokers) and non-smokers. The number of cigarettes smoked per day and duration of smoking were recorded and expressed as pack-years (pack-years of smoking were calculated at the baseline examination as number of cigarettes per day multiplied by number of years of smoking divided by 20).

The follow-up period was defined as the delay between the date of the first sign attributable to HP and the date of the last visit or death.

### Genetics data

All known mutations of the cationic trypsinogen gene (PRSS1), ie, R122H, N29I, A16V, D22G, K23R, E79K, Q98K, R122C or R116H were considered. Molecular analyses were shared between three French molecular genetics laboratories. For single point mutations, a screening strategy was chosen by these three laboratories in order to find both known and novel variations located in the five exons of the PRSS1 gene and the four exons of the SPINK1 gene by double-strand direct sequencing (n = 18 patients) or by a screening approach (denaturing gradient gel electrophoresis, DGGE) then replaced by denaturing high-performance liquid chromatography (DHPLC)<sup>23, 24</sup> (n = 173) confirmed by sequencing.<sup>6, 7, 25</sup> In patients deceased before 1996, PRSS1 mutations were not assessed. The parental (maternal or paternal) mode of transmission was recorded. As a result of analyses of the genealogical tree, a PRSS1 mutation was searched for in the first-degree relatives even if they did not have any symptoms. SPINK1 and cystic fibrosis transmembrane regulator (CFTR) mutations were systematically searched for. The most 30 frequent CFTR mutations were screened by using a Cf-OLA kit (CFV3 ASR; Celera Diagnostics, Alameda, California, USA) or an Elucigen kit (Elucigen CF30; Tepnel Diagnostics, Oxon, UK).



**Figure 1** Distribution of the cohort according to the age at onset of the symptoms.

### Treatment of hereditary pancreatitis

Duration and results of medical (ie, chronic use of analgesics defined as at least one period of more than three consecutive months), endoscopic (lithotripsy, endoscopic pancreatic or biliary stenting and pseudocyst drainage) or surgical (pancreaticoduodenectomy, median pancreatectomy, distal pancreatectomy and pancreatic, biliary or pseudocyst drainage) treatment were recorded.

### Diagnosis of pancreatic adenocarcinoma

Patients, physicians in charge of patients and family were questioned about the occurrence of PA. In all cases, data about PA were verified by consulting the original medical records including pathological records. The age at PA diagnosis and the delay between the first sign of HP and diagnosis of PA were recorded.

### Study design and data collection

All data were collected directly by reviewing individual medical files, from questionnaires addressed to the physician in charge of the patients and by direct phone contact with the physicians. In the case of missing data, the patients (or their relatives when patients were deceased) were directly contacted by phone. Information on demographic characteristics and vital status, genetic status, symptoms and complications of HP, and data on the smoking and drinking status were obtained for each patient.

Collected data included genealogical tree, general characteristics (age, gender, smoking status and number of cigarettes smoked per day, alcohol consumption as number of units of alcohol consumed per day), genetic characteristics (status of PRSS1, SPINK1 and CFTR genes, inheritance of the mutation), symptoms (date of the first HP sign, evolution of symptoms, occurrence of diabetes mellitus, exocrine insufficiency, pancreatic adenocarcinoma, date and cause of death), morphological pancreatic features, and treatment (chronic analgesic use, endoscopic or surgical procedures).

In patients without clear clinical pancreatic symptoms, the date of the first imaging procedure showing CP lesions was considered as the date of the first CP sign.

### Statistical analysis

General characteristics were expressed as median and range or percentages. Comparison of general characteristics, clinical manifestations, morphological characteristics and treatment according to the genetic status were performed using the Kruskal–Wallis test for continuous data and the  $\chi^2$  test or Fisher’s exact test for categorical data.

The size of the historical cohort was calculated using person-years. Since HP is a genetic disease and since early symptoms of this disease are easily overlooked, we used the year of birth as the initial date for the accrual of person-years. The end-point was the date of last contact or death (or the date of the diagnosis of PA to assess the risk of PA).

Cumulative rates of patients with exocrine and endocrine pancreatic insufficiency and PA over time were estimated by using the Kaplan–Meier method to account for censored data. Cumulative rates were compared with the log-rank test according to constitutional parameters (gender, PRSS1, SPINK1 and CFTR mutation status, parental inheritance, smoking habits, age at first HP symptoms and history of acute pancreatitis). Drinking status was not tested because too few patients had chronic alcohol use (n = 10). Association between

**Table 2** Clinical and biochemical features

Characteristics	All patients (n = 200)	Patients with PRSS1 mutations (n = 135)	Patients without detected PRSS1 mutation (n = 65 <sup>‡</sup> )	p Value <sup>§</sup>
Age (in years) at first HP symptoms*	10 (1–73)	10 (1–52)	10 (2–73)	NS
Age (in years) at HP diagnosis*	19 (1–80)	19 (1–80)	20 (4–73)	NS
Pancreatic pain (%) (md = 3) <sup>†</sup>	164 (83) <sup>†</sup>	111 (82)	53 (81)	NS
Acute pancreatitis (%) (md = 3)	135 (69)	93 (69)	42 (65)	NS
Admission in intensive care unit (%) (md = 1)	9 (4)	5 (3)	4 (6)	NS
Exocrine pancreatic insufficiency (%) (md = 4)	67 (34)	50 (37)	17 (26)	NS
Age at occurrence of exocrine insufficiency*	29 (1–76)	30 (1–76)	25 (5–46)	NS
Endocrine pancreatic insufficiency (%) (md = 3)	51 (26)	38 (28)	13 (20)	NS
Age (in years) at occurrence of endocrine insufficiency*	38 (14–76)	37 (14–76)	42 (30–68)	NS
Cholestasis (%) (md = 3)	6 (3)	3 (2)	3 (4)	NS

\*Median and (range).

<sup>†</sup>Continuous pain, n = 9 (5%); occasional pain, n = 155 (95%).

<sup>‡</sup>Including nine patients, deceased before 1996, in whom the PRSS1 mutation could not be searched for.

<sup>§</sup>The Kruskal–Wallis test for continuous data and the  $\chi^2$  test or Fisher's exact test for categorical data were used. HP, hereditary pancreatitis; md, missing data; NS, not significant; PRSS1, cationic trypsinogen gene.

risk factors and pancreatic insufficiency were assessed by univariate analysis ( $\chi^2$  test or Fisher's exact test).

Data were analysed with the SAS 9.1 statistical software for Windows. All statistical tests were two-sided. The critical level of statistical significance was set at  $p < 0.05$ .

## RESULTS

### General characteristics of the cohort

The total cohort consisted of 78 families and 200 patients (181 patients alive, males 105 (53%)) accounting for 6673 person-years. The prevalence of HP in France was 0.3/100 000 inhabitants. The median age at inclusion was 30 years (range 1–84 years). The median number of generations with HP was 3 (range 1–4). Non-smokers and daily smokers in the population older than 18 years were 49% and 51%, respectively. Chronic consumption of alcohol was found in 5% of the patients. The general characteristics of the population are summarised in the table 1.

### Genetic characteristics of the cohort

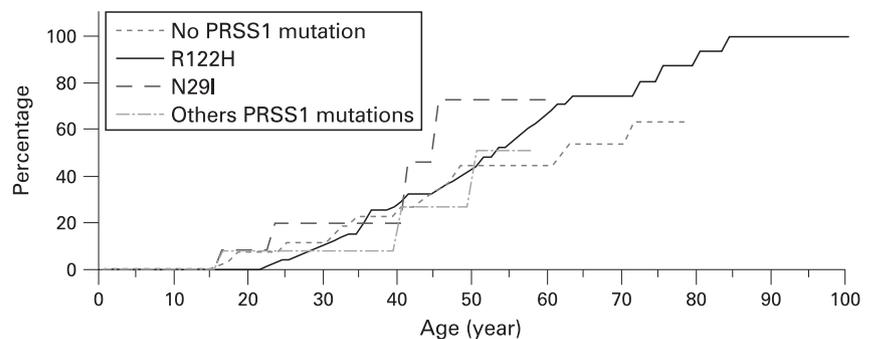
A PRSS1 mutation was searched for in 191 patients and found in 135 patients (68%). PRSS1 mutation status was unknown in 4% because patients were deceased before 1996 and no blood

sample was available. Based on examination of the genealogical tree, inheritance of the mutation was maternal in 78/145 (54%), paternal in 67/145 (46%) and unknown in 55 patients. The types of PRSS1 mutation are provided in table 1. Among the patients with a known mutation, 93% had clinical or morphological signs of HP (penetrance). Patients with or without detected PRSS1 mutations had the same general characteristics (table 1). A SPINK1 or CFTR mutation was found in 13% and 2% of the patients, respectively.

### Clinical characteristics of the patients

The median age at onset of HP symptoms and at diagnosis was 10 (range 1–73) years and 19 (range 1–80) years, respectively. The distribution of the cohort according to the age at the onset of the symptoms is represented by a histogram in the fig 1. The two most frequent clinical symptoms were pancreatic pain (83%) and at least one bout of acute pancreatitis (69%). Severe acute pancreatitis (requiring admission to intensive care units) was noticed in 4%. Exocrine and endocrine pancreatic insufficiency occurred in 34% and 26% at a median age of 29 and 38 years, respectively. Among patients with diabetes mellitus, 60% required insulin and 40% only oral drugs. The presence or the absence of a PRSS1 gene mutation did not influence the

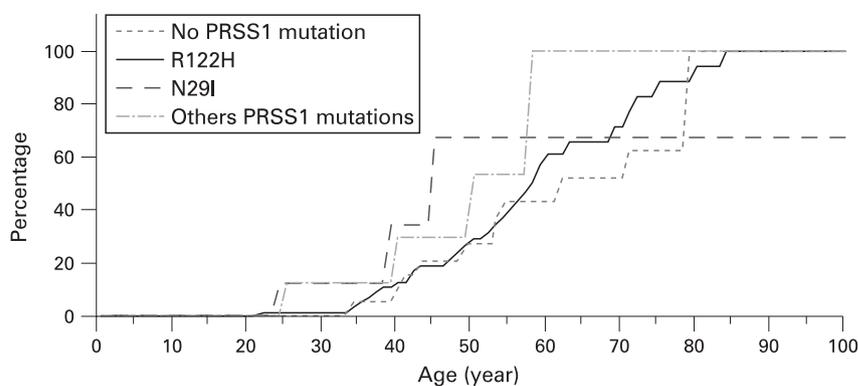
**Figure 2** Cumulative rates of exocrine pancreatic insufficiency in 200 patients with hereditary pancreatitis according to mutation status of the cationic trypsinogen gene (PRSS1). (N291 and R122H are mutations of PRSS1.)



Patients at risk:

No PRSS1 mutation	65	47	31	24	18	11	7	5	0	0
R122H	105	96	79	58	41	28	10	5	2	0
N291	16	14	9	7	3	1	0	0	0	0
Others PRSS1 mutations	14	13	10	5	4	2	0	0	0	0

**Figure 3** Cumulative rates of endocrine pancreatic insufficiency (diabetes mellitus) in 200 patients with hereditary pancreatitis according to mutation status of the cationic trypsinogen gene (PRSS1). (N29I and R122H are mutations of PRSS1.)



Patients at risk:										
No PRSS1 mutation	65	47	31	24	18	11	7	5	0	
R122H	105	96	79	58	41	28	10	5	2	0
N29I	16	14	9	7	3	1	0			
Others PRSS1 mutations	14	13	10	5	4	2	0			

symptoms. Clinical characteristics according to the parental origin of the mutation were analysed. The onset of symptoms was earlier when the inheritance was maternal, 9 years vs 14 years in median ( $p = 0.012$ ). The results are summarised in the table 2. The cumulative risks of exocrine and endocrine pancreatic insufficiency are represented in the figs 2 and 3.

#### Genotype–phenotype correlations

Frequency and nature of clinical manifestations of HP were not significantly different according to genetic status (presence or absence of a PRSS1 mutation, R122H vs N29I vs other mutations, R122H vs other mutations). Patients with maternal inheritance had the first symptoms earlier than those with paternal inheritance (9 vs 14 years of age,  $p = 0.012$ ). Symptoms occurred earlier in females than in males (11 vs 15 years of age,  $p = 0.02$ ). The presence of a SPINK1 gene mutation was not associated with clinical difference.

#### Morphological features

Pancreatic calcifications were diagnosed at a median age of 23 years (table 3). Pancreatic calcifications and ductal abnormalities were diagnosed during lifespan in 61% and 63% of the patients, respectively (fig 3). Pseudocysts and spleno-portal thrombosis were diagnosed in 23% and 3%, respectively. Radiological abnormalities were the sole manifestation of HP in 1% of the patients. Calcifications or ductal changes were not related to genetic status, gender or smoking habits.

#### Treatments

Indications for treatment are summarised in the table 4. At least one period of chronic use of analgesics was necessary in 10% of the patients. Specific treatments, including endoscopic procedures (16%) or surgical interventions (24%) were required in 80 patients (40%). Endoscopic procedures included stenting of the main pancreatic duct ( $n = 18$ ), lithotripsy ( $n = 10$ ), pseudocyst fenestrations ( $n = 7$ ), and stenting of the common bile duct ( $n = 1$ ). Pancreatic resection was performed in 24 patients (pancreaticoduodenectomy ( $n = 4$ ), median pancreatectomy ( $n = 4$ ) and splenopancreatectomy ( $n = 16$ )). Bypass or drainage was performed in 25 patients (pancreatic duct drainage ( $n = 16$ ), biliary bypass ( $n = 6$ ), digestive bypass ( $n = 3$ ) and pseudocyst drainage ( $n = 7$ )). The surgical procedures were performed at the median age of 23 years (range 5–52).

#### Risk of pancreatic adenocarcinoma

A pancreatic adenocarcinoma was diagnosed in ten patients (5%), six males and four females, in eight families. Two patients with pancreatic adenocarcinoma are still alive. The median age at diagnosis of cancer was 55 years (range 39–78). The cumulative risks at age 50, 60 and 75 years were 10.0% (95% confidence interval (CI) 1% to 18%), 18.7% (95% CI, 3% to 32%) and, 53.5% (95% CI, 7% to 76%), respectively.

#### Mortality

Nineteen patients (9.5%) died, 10 directly due to HP consequences including eight from PA (42% of deaths). The median age at death was 60 years (range 24–84). The cause of death was known in all but one of the remaining patients and was not related to HP or pancreatic adenocarcinoma.

#### DISCUSSION

This study is based on a national series of patients with HP. The recruitment was complete, as far as possible, allowing the prevalence of the disease (0.3/100 000 inhabitants) to be calculated. A mutation of PRSS1 was detected in 68%. The penetrance of the mutation was 93%. Symptoms mainly occurred during childhood but the delay for diagnosis was nearly 10 years, emphasising the difficulties in recognising the disease, particularly in paediatric units. Pancreatic pain and acute pancreatitis were the main clinical manifestations but were rarely severe. Pancreatic adenocarcinoma represented the main cause of mortality.

HP patients had never been extensively recruited in an epidemiological study in a definite area. The main series reported collection of HP families based on spontaneous registration by gastroenterologists. In the methods, particular attention was paid to contacting all gastroenterologists and paediatricians and all genetics laboratories involved in PRSS1 gene testing to allow, for the first time, a calculation of the prevalence of this disease and confirmation of its rarity. The risk that patients or families with HP were missed and not included in the present work seems low because chronic pancreatitis in general and HP in particular is associated with pancreatic symptoms and usually requires specialised medical advice. Only patients in whom the diagnosis was not yet performed or with “silent” disease and no familial history would have been undetected. The risk that the 16% non-responder physicians followed HP patients is possible but we tried to reduce this bias

**Table 3** Morphological pancreatic features

Characteristic	All patients (n = 200)	Patients with PRSS1 mutations (n = 135)	Patients without detected PRSS1 mutation (n = 65‡)	p Value§
Ductal lesions (%) (md = 15)	117 (63)	79 (63)	38 (63)	NS
Pancreatic calcifications (%) (md = 14)	113 (61)	78 (62)	35 (59)	NS
Age at diagnosis of pancreatic calcifications*	23 (3–73)	24 (3–57)	23 (6–73)	NS
Venous thrombosis† (%) (md = 3)	11 (6)	9 (7)	2 (3)	NS
Pseudocysts (%) (md = 5)	44 (23)	32 (25)	12 (18)	NS

\*Median and (range).

†Thrombosis of the splenic vein or/and the portal vein.

‡Including nine patients, deceased before 1996, in whom the PRSS1 mutation could not be searched for.

§The Kruskal–Wallis test for continuous data and the  $\chi^2$  test or Fisher's exact test for categorical data were used.

CP, chronic pancreatitis; md, missing data; NS, not significant; PRSS1, cationic trypsinogen gene.

by collecting and analysing all results from the database of genetics laboratories testing for PRSS1 mutations in France.

Clinical features of HP patients have been described, but mostly in selected families with a known genetic mutation or only in case reports or in small series of patients (n<15). In 1978, Sibert<sup>16</sup> reported HP clinical features in seven families (n = 72 patients) in England and Wales. Symptoms began during childhood (mean age of onset, 13 years). Symptoms decreased when patients approached middle age or after a severe attack. Exocrine and endocrine pancreatic insufficiencies were diagnosed in 5.5% and 12.5%, respectively. Keim *et al*<sup>17</sup> reported clinical features in 76 and 25 subjects with either R122H or N29I mutation, respectively. The age at onset of symptoms suggested a bimodal distribution, with peaks at age 6 and 18 years. In the present study, 71% of the patients had first symptoms before 20 years of age and mainly before 10 years of age. In Keim's study, as in the present study, the clinical profile of HP (age at onset, cyst, calcifications, diabetes mellitus, operations) was similar whatever the mutation type.

Recently, one large important European study (EUROPAC) was published dealing with the natural history of HP. Patients (n = 418) were recruited in 14 countries. The study relied on a register in which patients were included after a spontaneous declaration by gastroenterologists. The recruitment of families was not systematic from one country to another. Some of our data are comparable to that of EUROPAC study: age at first symptoms, age at onset of diabetes mellitus, percentage of patients who underwent surgery, percentage of pancreatic cancer. No difference of symptoms was notified according to the mutation type.<sup>14</sup> We did not compare patients according to the chronic alcoholic consumption status because of the very low percentage of patients with chronic alcoholism (5%).

**Table 4** Indications of specific treatment

Characteristic	All patients (n = 200)	Patients with PRSS1 mutations (n = 135)	Patients without detected PRSS1 mutation (n = 65†)	p Value
Chronic use of analgesics (%)* (md = 2)	20 (10)	14	6	NS
Endoscopic treatment (%) (md = 3)	31 (16)	24	7	NS
Surgical treatment (%) (md = 1)	49 (24)	39	10	NS

\*At least one period of chronic use >3 months.

†Including nine patients deceased before 1996, in whom PRSS1 mutation could not be searched for.

md, Missing data; NS, not significant; PRSS1, cationic trypsinogen gene.

The penetrance was higher than in others series. Comfort and Steinberg<sup>1</sup>, Sibert<sup>16</sup> and Le Bodic *et al*<sup>2</sup> reported an estimated penetrance of 80%. These three studies did not make use of genetic analysis to confirm their data because they were published before 1996. The penetrance was calculated by comparison of an estimation of the number of patients with mutations considering autosomal dominant inheritance and the number of those with clinical manifestations. Morphological explorations were not systematic and, therefore, patients with only morphological pancreatic alterations were not taken in account. This may account for the difference. In 2001 Keim *et al*<sup>17</sup> reported an estimated penetrance of 78–80% in a cohort of patients (not recruited on a familial basis) with PRSS1 gene mutations. Considering the usual age at onset, patients older than 30 years and clinically asymptomatic were considered as unaffected. Patients with late-onset (>30 years accounting for 6% in the present study) or with only morphological abnormalities have been categorised as healthy carriers. This may lead to an underestimation of the penetrance. In the present study, patients and first-degree relatives (parents and children) were all genetically tested when it was possible. Morphological data were analysed for each case. The presence of pancreatic lesions (calcifications or ductal lesions), even without clinical manifestations, was sufficient to consider that patients had HP and accounted for penetrance. It probably explains the higher penetrance.

Patients with HP have an increased risk of pancreatic adenocarcinoma. The EUROPAC study estimated the standardised incidence ratio (SIR) adjusted for age and nationality to 67 (95% CI, 50 to 82). In the present cohort, SIR was 87 (95% CI, 42 to 114).<sup>14 18–20</sup> Smoking is a major cofactor increasing the risk of pancreatic adenocarcinoma in all the published series.

By contrast to publications devoted to alcoholic chronic pancreatitis, no series of patients with HP deals with mortality.<sup>22</sup> This is obviously of utmost importance for patients and their families. Sibert<sup>16</sup> reported only one death associated to HP but the cause was not precised. The crude mortality rate was 5%, half due to HP manifestations of whose pancreatic adenocarcinoma was at the first rank. In series of patients with alcoholic chronic pancreatitis, the crude mortality was 33% after 10 years of follow-up and 20% of the deaths were directly due to chronic pancreatitis manifestations and the remaining were related to extra pancreatic consequences of alcohol and tobacco abuse.<sup>22 26</sup>

The present study confirms that the R122H mutation of the PRSS1 gene is the commonest mutation encountered.<sup>14</sup> Thirty-two per cent of patients had no detectable PRSS1 mutation although they had a clear familial history. There was no

difference in gender, clinical or radiological features in the population with or without a detected mutation. The type of the detected mutation had no influence on HP manifestations. In the EUROPAC series, only age at onset of the first symptoms was related to the type of mutation.<sup>14</sup>

In summary, HP is a rare disease, with a long delay between the first manifestation and the diagnosis. Until now, knowledge about the evolution of the disease was extrapolated from that of alcoholic chronic pancreatitis or from series pooling many causes of non-alcoholic chronic pancreatitis.<sup>27</sup> The present study allows, for the first time, a precise description of its natural history. The type of mutation has no influence. The major risk and the main cause of mortality is pancreatic adenocarcinoma. Beside the description of natural history of HP, this study allows answers to the frequent questions about the effects of HP on patients' lives.

**Acknowledgements:** We thank all the patients who participated to our study and the French Association of Patients with Hereditary Pancreatitis (APCH, Issy les Moulineaux, France), especially the President, Madame Meslet. We are grateful to all gastroenterologists and paediatricians who participated in this study, especially J Lamoril, G Lalau and V Dumur, and to all the genetics laboratories.

**Funding:** Supported by grants from Solvay Pharma Pharmaceuticals, Inc.

**Competing interests:** None.

**Ethics approval:** Agreement from the French Department for Computerized Information Security (Commission Nationale de l'Informatique et des Libertés) was obtained on 4 February 2005 before study initiation (no. 04.555).

## REFERENCES

1. **Comfort MW**, Steinberg AG. Pedigree of a family with hereditary chronic relapsing pancreatitis. *Gastroenterology* 1952;**21**:54–63.
2. **Le Bodic L**, Schnee M, Georgelin T, *et al*. An exceptional genealogy for hereditary chronic pancreatitis. *Dig Dis Sci* 1996;**41**:1504–10.
3. **Le Bodic L**, Bignon JD, Raguene O, *et al*. The hereditary pancreatitis gene maps to long arm of chromosome 7. *Hum Mol Genet* 1996;**5**:549–54.
4. **Pandya A**, Blanton SH, Landa B, *et al*. Linkage studies in a large kindred with hereditary pancreatitis confirms mapping of the gene to a 16-cM region on 7q. *Genomics* 1996;**38**:227–30.
5. **Whitcomb DC**, Preston RA, Aston CE, *et al*. A gene for hereditary pancreatitis maps to chromosome 7q35. *Gastroenterology* 1996;**110**:1975–80.
6. **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.
7. **Férec 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.
8. **Gorry MC**, Ghabbaideh D, Furey W, *et al*. Mutations in the cationic trypsinogen gene are associated with recurrent acute and chronic pancreatitis. *Gastroenterology* 1997;**113**:1063–8.
9. **Konzen KM**, Perrault J, Moir C, *et al*. Long-term follow-up of young patients with chronic hereditary or idiopathic pancreatitis. *Mayo Clin Proc* 1993;**68**:449–53.
10. **Paolini O**, Hastier P, Buckley M, *et al*. The natural history of hereditary chronic pancreatitis: a study of 12 cases compared to chronic alcoholic pancreatitis. *Pancreas* 1998;**17**:266–71.
11. **Amann ST**, Gates LK, Aston CE, *et al*. Expression and penetrance of the hereditary pancreatitis phenotype in monozygotic twins. *Gut* 2001;**48**:542–7.
12. **Le Marechal C**, Bretagne JF, Raguene O, *et al*. Identification of a novel pancreatitis-associated missense mutation, R116C, in the human cationic trypsinogen gene (PRSS1). *Mol Genet Metab* 2001;**74**:342–4.
13. **Chen JM**, Mercier B, Ferec C. Strong evidence that the N21I substitution in the cationic trypsinogen gene causes disease in hereditary pancreatitis. *Gut* 1999;**45**:916.
14. **Howes N**, Lerch MM, Greenhalf W, *et al*. Clinical and genetic characteristics of hereditary pancreatitis in Europe. *Clin Gastroenterol Hepatol* 2004;**2**:252–61.
15. **Sibert JR**. A British family with hereditary pancreatitis. *Gut* 1975;**16**:81–8.
16. **Sibert JR**. Hereditary pancreatitis in England and Wales. *J Med Genet* 1978;**15**:189–201.
17. **Keim V**, Bauer N, Teich N, *et al*. Clinical characterization of patients with hereditary pancreatitis and mutations in the cationic trypsinogen gene. *Am J Med* 2001;**111**:622–6.
18. **Lowenfels AB**, Maisonneuve P, DiMaggio EP, *et al*. Hereditary pancreatitis and the risk of pancreatic cancer. International Hereditary Pancreatitis Study Group. *J Natl Cancer Inst* 1997;**89**:442–6.
19. **Lowenfels AB**, Maisonneuve P, Whitcomb DC, *et al*. Cigarette smoking as a risk factor for pancreatic cancer in patients with hereditary pancreatitis. *Jama* 2001;**286**:169–70.
20. **Rebours V**, Boutron-Ruault MC, Schnee M, *et al*. Risk of pancreatic adenocarcinoma in patients with hereditary pancreatitis: a national exhaustive series. *Am J Gastroenterol* 2008;**103**:111–9.
21. **Levy P**, Bernades P. [Influence of bouts of acute pancreatitis on the course of chronic alcoholic pancreatitis in man]. *Gastroenterol Clin Biol* 1989;**13**:1050–4. (In French.)
22. **Levy P**, Milan C, Pignon JP, *et al*. Mortality factors associated with chronic pancreatitis. Unidimensional and multidimensional analysis of a medical-surgical series of 240 patients. *Gastroenterology* 1989;**96**:1165–72.
23. **Le Marechal C**, Chen JM, Quere I, *et al*. Discrimination of three mutational events that result in a disruption of the R122 primary autolysis site of the human cationic trypsinogen (PRSS1) by denaturing high performance liquid chromatography. *BMC Genet* 2001;**2**:19.
24. **Le Marechal C**, Chen JM, Le Gall C, *et al*. Two novel severe mutations in the pancreatic secretory trypsin inhibitor gene (SPINK1) cause familial and/or hereditary pancreatitis. *Hum Mutat* 2004;**23**:205.
25. **Witt H**, Luck W, Hennies HC, *et al*. Mutations in the gene encoding the serine protease inhibitor, Kazal type 1 are associated with chronic pancreatitis. *Nat Genet* 2000;**25**:213–6.
26. **Ammann RW**, Akovbiantz A, Largiader F, *et al*. Course and outcome of chronic pancreatitis. Longitudinal study of a mixed medical-surgical series of 245 patients. *Gastroenterology* 1984;**86**(5 Pt 1):820–8.
27. **Layher P**, Yamamoto H, Kalthoff L, *et al*. The different courses of early- and late-onset idiopathic and alcoholic chronic pancreatitis. *Gastroenterology* 1994;**107**:1481–7.