

## **Role of Hereditary Pancreatitis and CFTR Gene Mutations in the Aetiology of Acute Relapsing Pancreatitis of Unknown Origin. How Are They Important ?**

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### **Introduction**

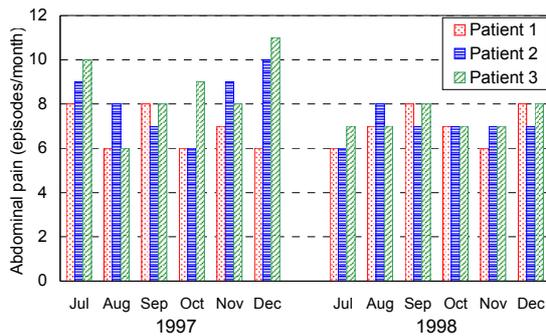
From the clinical standpoint, the causes of acute relapsing pancreatitis (ARP) are either immediately identifiable by their history and a few standard investigations, less obvious and requiring more detailed investigations or obscure and even conjectural. When no immediate cause is found, the recurrent episode is classified as "idiopathic ARP", accounting for 10 to 30% of all recurrences [1]. Over the last few years this so-called idiopathic pancreatitis has been decreasing as a result of increased recognition of causes such as biliary sludge or microlithiasis, sphincter of Oddi dysfunction, autoimmune diseases, and genetic disorders.

This contribution will attempt to determine the role of the two most important hereditary pancreatic diseases, namely, hereditary pancreatitis (HP) and cystic fibrosis (CF), in the etiology of ARP of unknown origin.

### **Recurrent Attacks in Hereditary Pancreatitis**

Patients with HP develop repeated episodes of acute pancreatitis that are indistinguishable from pancreatitis associated with gallstones, acute alcohol ingestion, drugs, or other causes. In the follow-up, recurrent acute bouts lead to the subsequent development of chronic pancreatic damage with morphological, functional, and clinical findings similar to those of the classic forms of chronic pancreatitis [2]. A single molecular

defect that predisposes affected individuals to the disease was suggested by a clear autosomal dominant inheritance pattern. Using genetic linkage studies the HP locus was narrowed to the long arm of chromosome 7 and, finally, the gene responsible was identified by Whitcomb *et al.* [3]. The mutation was identified in the third exon of the gene that transcribes cationic trypsinogen (Protease-Serine-1 gene, PRSS-1); this mutation resulted in an arginine to histidine substitution (R122H "classic" mutation). Subsequently, other family members with a similar phenotype tested negative for this mutation and were associated with other less frequent mutations, namely the N91I and the A16V mutation [4]. In normal individuals, one of the mechanisms preventing pancreatic autodigestion appears to involve competitive inhibition of the trypsin catalytic site by the pancreatic secretory trypsin inhibitor; this event emphasizes the role of trypsin in the activation of the pancreatic enzyme cascade, changing all of the other pancreatic proenzymes to their active form. The suggested patho-mechanism involved in the HP classic mutation and responsible for pancreatic damage is related to the block of the physiological mechanism of intracellular trypsin autolysis which prevents pancreatic autodigestion. In short, the PSSR-1 mutation eliminates the initial hydrolysis site thus preventing destruction of trypsin prematurely activated in the pancreas and, in turn, leading to generalized zymogen activation, autodigestion and pancreatitis [5].

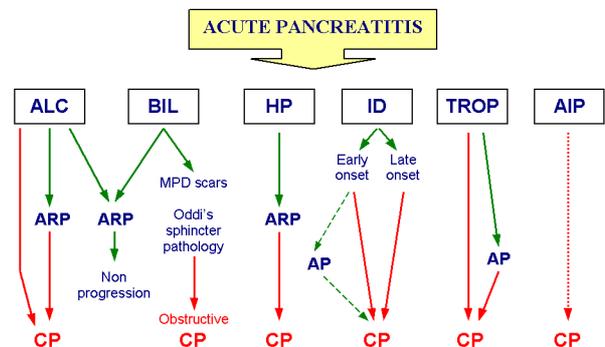


**Figure 1.** Recurrence of abdominal pain in three young patients affected by hereditary pancreatitis (classic R122 H mutation of the cationic trypsinogen gene); the number of abdominal pain episodes per month requiring analgesic treatment is shown on the y axis and the period (months) of observation on the x axis. (See reference [6])

Analysis of data obtained by the European Registry of Hereditary Pancreatitis and Pancreatic Cancer (EUROPAC), including 342 affected individuals coming from 13 European countries over a four-year period (1997-2000) [4], showed that the median age of symptom onset was 12 years with no difference between patients presenting different PSSR-1 mutations. Furthermore, the median number of attacks of acute pancreatitis was 2.0 per year with a duration greater than 2 days in nearly 80% of the patients; more hospital admissions were registered in mutation negative patients. Nearly 30% of these patients had surgery at a median age of 24 years and 15 years after the onset of symptoms; the risk of pancreatic surgery was significantly greater in patients presenting the N9I mutation [4]. Recurrent attacks of mild or severe acute pancreatitis are associated with disabling pain that constitutes the most challenging symptom of HP, mainly during the first years of the disease [6] and in patients with the N9I mutation [4]. Figure 1 shows episodes of recurrent abdominal pain requiring analgesic treatment in three young patients with HP (R122H mutation of PSSR-1) who were followed up over the last year.

HP is certainly a rare form of pancreatitis. Nevertheless, the disease should be investigated in families with at least two first-degree relatives or three or more second-degree relatives, over two or more

generations, having ARP and/or chronic pancreatitis for which there were no causative or precipitating factors. In the USA, it is estimated that at least 1,000 individuals are affected with HP [5]. The clue which arouses suspicion is basically the result of a carefully performed anamnesis. The importance of the identification of HP is also related to the knowledge of its natural history (Figure 2). As a rule, these patients develop pancreatic endocrine and exocrine failure during their lives, undergo one or more surgical procedures and present an increasingly high risk of pancreatic cancer after the age of 40 years [4]. The intermittent nature of acute episodes suggests the involvement of triggering factors (such as diet, stress, drugs and duct obstruction) which initiate the attack [7]. In this setting, Matew and co-workers [8] showed that, within a family having HP, members who developed the disease had lower serum vitamin E and selenium levels and higher activities of the antioxidant enzyme superoxide dismutase than did their asymptomatic relatives or unrelated controls. No specific or proven therapy is yet available for HP; during ARP episodes, the treatment is the same as that utilised in the other forms of acute pancreatitis [9]. Analgesics, often in large doses, are required to counteract recurrent abdominal pain without pancreatitis. A recent promising experience involving three young HP patients [6] showed that an orally administered antioxidant treatment,



**Figure 2.** Progression from acute (AP) to chronic pancreatitis (CP).

ALC: alcoholic; BIL: biliary; HP: hereditary pancreatitis; ID: idiopathic; TROP: tropical; AIP: autoimmune; ARP: acute recurrent pancreatitis; MPD: main pancreatic duct.

based upon sulphadenosyl-methionine, vitamin C, E, A, and selenium, is able to significantly reduce the period of abdominal pain and thus the consumption of analgesics.

### **Cystic Fibrosis and Relapsing Pancreatitis**

CF, inherited as an autosomal-recessive, is by far the most common inherited disease of the exocrine pancreas [10] and consists of a generalised disorder of the secretory epithelia of all exocrine glands. The suggested underlying pathogenetic mechanism involves a defect in the regulation of the apical membrane-chloride channels of epithelial cells, resulting in highly viscous secretions with an inability to maintain luminal hydration. The basic defect of impaired salt and water transport leads to secondary alterations of the pancreas and the gastrointestinal, hepatobiliary and respiratory tracts. A deletion of 3 base pairs of the *Cystic Fibrosis Transmembrane Conductance Regulator*- gene (CFTR-gene), resulting in the loss of phenylalanine residue (mutation  $\Delta F508$ ), has been shown to be responsible for the disease in approximately 70% of patients [11, 12]. Many other mutations have been reported and as of 1998 more than 800 disease-causing lesions had been identified in the CFTR-gene [13], thus verifying the severity of the disease. The CFTR-gene is located on chromosome 7q3.1, existing as a single copy in the human genome, and encoding a 170,000 molecular-weight glycoprotein. The mutated CFTR-gene protein product is able to determine the specific defect of chloride ion transport. In addition to its transport function, CFTR is involved in the trafficking between the trans-Golgi network and the apical membrane; it influences protein secretion, exo- and endocytosis of vesicles, pH in endosomal compartments, cell growth and apoptosis [11]. From the clinical standpoint, CF is the only hereditary disease in which pancreatic involvement can be expressed by both exocrine insufficiency (without pancreatic inflammatory disease) and pancreatitis [14]. Exocrine pancreatic insufficiency occurs in

the vast majority of the patients (80-85%) while ARP is more rare [12, 13, 14]. In addition, some CF patients without pancreatic insufficiency may have elevated serum levels of pancreatic isoamylase in the absence of gastrointestinal symptoms and morphological (ultrasound/computed tomography) pancreatic abnormalities.

The ability to detect CFTR-gene mutations has led to the recognition that the clinical spectrum of the disease is broader than previously thought. The association between the CFTR mutation phenotype and the clinical manifestations of the disease in an individual organ depends on the susceptibility of the organ to CFTR mutations and the impact of environmental and other genetic factors on the manifestation of the disease [12]. Recent studies showed that the frequency of CFTR-gene mutations is underestimated and, more interesting, these mutations may prove important from the aetiological and pathogenetic standpoint in so-called "idiopathic" ARP and chronic pancreatitis. Research at Duke University in Durham, NC, USA, conducted the genetic analysis of 27 patients with idiopathic pancreatitis and found that 37% showed abnormalities in the CFTR-gene [15]. The frequency of a single CFTR mutation and two mutant alleles resulted 11 and 80 times the expected frequency, respectively. In a similar study, researches from the Manchester Royal Infirmary in England examined 134 pancreatitis patients, including alcoholics, and found that 13.4% had the genetic mutation with a frequency of nearly 2.5 times greater than expected [16]. Other studies confirmed these results [17, 18]. The question arising from all these studies is: why are people with CFTR mutations susceptible to pancreatitis?. Symptoms of ARP or chronic pancreatitis develop in approximately 2% of patients with cystic fibrosis diagnosed on clinical grounds, first occur in adolescence or adulthood, and occur only in patients with pancreatic sufficiency. Presumably, patients with pancreatic insufficiency are free of ARP because functional acinar tissue is lost in *utero* or soon after birth [19]. In patients with pancreatic

sufficiency, the presence of functional acinar cells is a prerequisite for pancreatitis; a change in ductal and acinar function, induced by loss of CFTR function or its dysfunction, could represent the precipitating event or, in turn, could increase the risk of an acute attack after exposure to alcohol, fatty meals or certain drugs [13].

From the practical clinical standpoint, one can affirm, at this time, that it is probably premature to "routinely" test ARP patients for CFTR mutations. Inasmuch as basic research and clinical series will undoubtedly improve our understanding of the relationship between CFTR and ARP, guidelines will be developed in the near future for the use of this genetic testing in patients with this and other pancreatic diseases. At the same time, future research will show how the great potential of genetic engineering and gene therapy can be utilized in the treatment of pancreatic manifestations of cystic fibrosis.

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**Key words** Cystic Fibrosis; Cystic Fibrosis Transmembrane Conductance Regulator; Hereditary Diseases; Pancreatitis, Acute Necrotizing; Trypsinogen

**Abbreviations** ARP: acute relapsing pancreatitis; CF: cystic fibrosis; CFTR: cystic fibrosis transmembrane conductance regulator; EUROPAC: European Registry of Hereditary Pancreatitis and Pancreatic Cancer; HP: hereditary pancreatitis

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