Table 19-2 Inherited Predisposition to Pancreatitis

Gene (Chromosome Location)	Protein Product	Function
CFTR (7q31)	Cystic fibrosis transmembrane conductance regulator	Epithelial anion channel. Loss-of-function mutations alter fluid pressure and limit bicarbonate secretion, leading to inspissation of secreted fluids and duct obstruction
PRSS1 (7q34)	Serine protease 1 (trypsinogen 1)	Cationic trypsin. Gain-of-function mutations prevent self-inactivation of trypsin
SPINK1 (5q32)	Serine peptidase inhibitor, Kazal type 1	Inhibitor of trypsin. Mutations cause loss-of-function, increasing trypsin activity
CASR (3q13)	Calcium-sensing receptor	Membrane-bound receptor that senses extracellular calcium levels and controls luminal calcium levels. Mutations may alter calcium concentrations and activate trypsin.
CTRC (1p36)	Chymotrypsin C (caldecrin)	Degrades trypsin, protects the pancreas from trypsin-related injury
CPA1 (7q32)	Carboxypeptidase A1	Exopeptidase involved in regulating zymogen activation

cells. Increased calcium flux appears to be another important trigger for inappropriate activation of digestive enzymes. Calcium has a key role in regulating trypsin activation. When calcium levels are low, trypsin tends to cleave and inactivate itself, but when calcium levels are high autoinhibition is abrogated and activation of trypsinogen by trypsin is favored. It is suspected that any factor that causes calcium levels to rise in acinar cells may trigger excessive activation of trypsin, including certain inherited abnormalities that affect calcium levels (Table 19-2).

- **Defective intracellular transport of proenzymes within acinar cells.** In normal acinar cells, digestive enzymes and lysosomal hydrolases are transported in separate pathways. In animal models of acinar injury, the pancreatic proenzymes are inappropriately delivered to the intracellular compartment containing lysosomal hydrolases. Proenzymes are then activated, the lysosomes are disrupted, and the activated enzymes are released. The role of this mechanism in human acute pancreatitis is not clear.

Alcohol consumption may cause pancreatitis through all of these mechanisms. Alcohol consumption transiently increases contraction of the sphincter of Oddi (the muscle at the Papilla of Vater), and chronic alcohol ingestion results in the secretion of protein-rich pancreatic fluid that leads to the deposition of inspissated protein plugs and obstruction of small pancreatic ducts. Alcohol also has direct toxic effects on acinar cells. Alcohol-induced oxidative stress may generate free radicals in acinar cells, leading to membrane lipid oxidation and free radical production, which as already mentioned has been linked to activation of the pro-inflammatory transcription factors AP1 and NF-κB. Oxidative stress also may promote the fusion of lysosomes and zymogen granules and alter intracellular calcium levels, possibly through mitochondrial damage, promoting the intraacinar activation of trypsin and other digestive enzymes. Nevertheless, it should be noted that most drinkers never develop pancreatitis and those who do usually do so after many years of alcohol abuse. Thus, key aspects of the pathophysiology of alcohol-induced pancreatitis remain obscure.

Other proven or suspected triggers of acute pancreatitis in the remaining sporadic cases include the following (Table 19-1):

- **Metabolic disorders,** such as hypertriglyceridemia, and hypercalcemic states, such as hyperparathyroidism
- **Genetic lesions,** described below
- **Medications**. More than 85 drugs have been implicated, including furosemide, azathioprine, 2′,3′-dideoxyinosine, estrogens, and many others. In most cases the mechanism of drug-induced pancreatitis is unknown.
- **Traumatic injury of acinar cells,** either by blunt abdominal trauma or by iatrogenic injury during surgery or endoscopic retrograde cholangiopancreatography
- **Ischemic injury of acinar cells,** caused by shock, vascular thrombosis, embolism, and vasculitis
- **Infections,** including mumps, can lead to acute pancreatitis through direct acinar cell injury

Hereditary factors are increasingly being recognized as a significant cause of pancreatitis. Hereditary pancreatitis is characterized by recurrent attacks of severe acute pancreatitis often beginning in childhood and ultimately leading to chronic pancreatitis. The disorder is genetically diverse, but **the shared feature of most forms is a defect that increases or sustains the activity of trypsin** (Table 19-2). Three genes implicated in hereditary pancreatitis deserve special note: *PRSS1*, *SPINK1,* and *CFTR*. Most hereditary cases are due to gain-of-function mutations in the *trypsinogen* gene (also known as *PRSS1*). Some of these *PRSS1* gene mutations make trypsin resistant to self-inactivation, abrogating an important negative feedback mechanism; other mutations appear to make trypsinogen more prone to proteolytic activation. Hereditary pancreatitis associated with trypsinogen mutation has an autosomal dominant mode of inheritance, as is typically true of disorders associated with gain-of-function mutations.

Hereditary pancreatitis can also be caused by loss-of-function mutations in *SPINK1*, already described as a gene encoding a trypsin inhibitor. As expected, this form of hereditary pancreatitis has an autosomal recessive mode of inheritance.

As discussed in detail in Chapter 5, cystic fibrosis is caused by mutations in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene, and homozygous and even heterozygous *CFTR* gene mutations are associated with pancreatitis, the latter particularly in patients who also have *SPINK1* mutations. Mutations in *CFTR* decrease bicarbonate secretion by pancreatic ductal cells, thereby promoting protein plugging, duct obstruction, and the development of pancreatitis.

Of note, patients with hereditary pancreatitis have a 40% lifetime risk of developing pancreatic cancer, yet another example of the nefarious association of chronic tissue injury and inflammation with neoplasia.