

Chronic Pancreatitis – an Overview

Disease Summary

It is estimated that between 1 and 2 out of every 4000 individual suffer from chronic pancreatitis, which is defined as relapsing or chronic inflammation of the pancreas leading to irreversible morphological changes that can result in impaired exocrine and/or endocrine pancreatic function (1,2). Consequences include maldigestion and bile duct or duodenal obstruction and insulin-dependent diabetes, respectively.(2) In addition, the risk of pancreatic cancer is increased. About 75-80% of CP is estimated to be alcohol induced, about 1-3% is familial, and the remainder idiopathic (3). About 50% of familial and 60% of idiopathic forms of CP have been associated with mutations in the genes *PRSS1*, *SPINK1*, or *CFTR* (3). Gain-of-function mutations in *PRSS1*, which codes for the serine protease cationic trypsinogen, and loss-of-function mutations in *SPINK1*, which codes for a serine protease inhibitor, Kazal type 1, both lead to increased intrapancreatic trypsin activity and autodigestion of pancreatic tissue (2,4). Loss-of-function mutations in *CFTR*, which codes for a membrane ion channel, prevent appropriate dilution and alkalization of acinar secretions, increasing the risk of protein plugs in pancreatic ducts (4). Compared to alcohol-induced CP, genetic CP shows earlier onset (in late childhood or adolescence rather than adulthood), slower disease progression, and a somewhat higher risk of pancreatic cancer (2-3). Early detection of genetic risk factors for CP can help physicians inform patients of their increased risk of CP.

Genetic CP typically follows an autosomal dominant inheritance pattern, but penetrance is highly variable and depends on the exact underlying genetic cause.(2-3) Gain-of-function variants in *PRSS1* are a highly penetrant cause of

CP (2,4). Rare variants in *SPINK1* can also cause CP with high penetrance (30-75%), while the common risk variant N34S, if heterozygously present, shows below 1% penetrance, conferring about 20fold increased risk of CP (4). Penetrance of N34S is higher if the variant is present in the homozygous state, or if it co-occurs with pathogenic variants in *CFTR* (4). Variants in *CFTR* are recessively associated with cystic fibrosis (CF), an often life-limiting multisystem disease affecting the respiratory, digestive, and male reproductive systems (5). While most CF patients suffer from pancreatic insufficiency, about 10% of CF patients demonstrate pancreatic sufficiency, which is correlated with a milder clinical course (non-classic CF) and an approximately 40fold increased risk of CP (4,5). In carriers of heterozygous severe variants in *CFTR*, who are not affected with CF, the risk of CP is increased about sixfold (4).

CP is usually diagnosed through pancreatic function tests and imaging methods.(2) However, non-invasive function tests cannot detect moderate pancreatic insufficiency, and imaging methods are not useful for diagnosing early-stage CP (2). Genetic testing can confirm a suspected diagnosis of CP and clarify disease etiology in a patient.(2) Once the exact mutation or mutations underlying CP in an individual patient have been identified, genetic testing can also detect mutation carriers among the patient's relatives and alert them to their increased genetic susceptibility for CP(2).

For additional information, see Tables 1-2 below and references 2-4.

Table 1: Disease Facts about CP (based on references 2-4, unless otherwise noted)

Disease Fact	Chronic Pancreatitis
MIM* number	167800
Estimated Prevalence	1-2:4000 (1,2)
Average Age at Diagnosis	Adulthood (alcohol-induced CP)
Typical Symptoms Pulmonary	Nausea and vomiting Maldigestion Diabetes Pancreatic pseudocysts Bile duct and duodenal obstruction Pancreatic cancer (rare)
Therapy Pulmonary	Pancreatic exocrine replacement therapy Pain management Surgery for pseudocysts, bile duct or duodenal obstruction, or pancreatic duct dilation Pancreatic endocrine replacement therapy

*MIM: Mendelian Inheritance in Man, see <http://www.ncbi.nlm.nih.gov/omim>

Table 2: Molecular Genetics of CP (based on references 2-4, unless otherwise noted)

Gene (Protein)	Transmission	Mutation type	Penetrance	Comments
<i>PRSS1</i> (protease, serine 1)	Autosomal dominant	Gain-of-function	50-80%	R122H and N29I account for the majority of <i>PRSS1</i> -related CP; gene triplication is the next common cause; loss-of-function mutations in <i>PRSS1</i> are associated with protection from CP
<i>SPINK1</i> (serine protease inhibitor, Kazal type 1)	Autosomal dominant Increased risk	Loss-of-function	30-75% <1%	Rare pathogenic variants in <i>SPINK1</i> About 20fold increased risk of CP for heterozygous occurrence of N34S, higher if variant is homozygously present (500fold) or co-occurs with non-classic CF (900fold)
<i>CFTR</i> (cystic fibrosis transmembrane conductance regulator)	Autosomal recessive Increased risk	Loss-of-function	10% in patients with non-classic CF; 0.5% in patients with classic CF (5) ND	About 40fold increased risk of CP, higher if co-occurring with N34S in <i>SPINK1</i> (900 fold) About 6fold increased risk of CP in presence of heterozygous severe CF mutation

NOTE: Specimens must be accompanied by a completed consent form. In the case of family tests (ie, known mutations) a copy of the result of the first patient tested in the family (the index case) must be submitted if the test was not performed at Correlagen. Other family members are subsequently tested for the specific mutation found in the first patient tested.

References

1. Levy P, Barthelet M, Mollard BR, Amouretti M, Marion-Audibert A-M, Dyard F (2006) Estimation of the prevalence and incidence of chronic pancreatitis and its complications. *Gastroenterol Clin Biol* 30:838-44.
2. Rosendahl J, Bodeker H, Mossner J, Teich N (2007) Hereditary chronic pancreatitis. *Orphanet Journal of Rare Diseases* 2:1-10.
3. Keim V (2008) Role of genetic disorders in acute recurrent pancreatitis. *World J Gastroenterol* 14:1011-5.
4. Chen J-M, Ferec C (2009) Chronic Pancreatitis: Genetics and Pathogenesis. *Annu Rev Genom Human Genet* 10:63-87.
5. Moskowitz SM, Chmiel JF, Sternen DL, Cheng E, Cutting GR. *CFTR-Related Disorders*. GeneReviews. <http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=gene&part=cf>. Accessed 022110.