

Chronic pancreatitis resulting from genetic mutations in trypsin and trypsin inhibitors

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Chronic pancreatitis (CP) is a rare condition characterised by progressive and irreversible inflammatory changes that potentially leads to exocrine and endocrine damage of the pancreas. Alcohol abuse is an important cause of CP, but other factors such as anatomical changes, metabolic disease and autoimmunity are also implicated. On the other hand, genetic factors clearly underlie a substantial portion of CP cases.^{1,2} The pace of developments in this field has been very rapid, making it appropriate to review some of the key advances. Trypsin and trypsin inhibitors are thought to be central to the pathogenesis of CP. Trypsinogen is produced in the pancreas, secreted into the small intestine, and converted to trypsin. Trypsin hydrolyses proteins into smaller peptides or amino acids. Premature pancreatic activation of trypsin and subsequent pancreatitis is the central concept in CP and documented by recent experimentation. The effect of genetics is most obvious in a familial form of pancreatitis. Here, CP is inherited in an autosomal dominant trait. Patients develop CP early, and the clinical profile is similar to that of non-inherited CP, but the lifetime risk for pancreatic cancer is very high. Mutations in cationic trypsinogen (PRSS1) cause familial CP. Two mutations, R122H and N29I, are very common and account for almost all familial cases assessed so far.³ Functional analysis of these mutants demonstrated enhanced autoactivation, pointing to a gain of function. This seems to support the concept that enhanced intrapancreatic trypsin causes pancreatic inflammation and autolysis. A second isoform of trypsinogen, anionic trypsinogen (PRSS2) is also involved in CP. A recent study showed that one PRSS2 mutant, G191R, actually protects against CP, as it was found in 3.4% of controls, but in 1.3% of affected individuals.⁴ It appeared that this mutant encoded non-functional trypsinogen, a severe loss of function. So far, disease enhancing PRSS2 mutants have not been found. The clinical implications are limited, though G191R carriers developed the disease at a significant later age.

One of the best-known trypsin inhibitors is serine protease inhibitor, Kazal type 1 (SPINK1). It appears that one specific mutation (N34S) is enriched in CP patients. Many case control studies show that N34S is found mostly in patients without a clear underlying cause for CP, as 15-40% of patients with

so-called idiopathic CP carry N34S on one allele or on both alleles.^{5,6} Though it is logical to assume that N34S decreases the inhibitory effect of SPINK1, functional analysis does not show any effect. However, N34S is coinherited with other, nearby located SPINK1 variants. It is conceivable that these variants cause the effect. The last, and most recent development is the discovery of trypsin-degrading enzyme chymotrypsin C (CTRC) variants. Similar to SPINK1 it inhibits trypsin and serves as a protective mechanism against pancreatitis. Using a very large European CP cohort it was shown that two CTCRC mutants were significantly overrepresented in CP patients compared to controls (3.5 vs. 0.7%).⁷ Functional assays demonstrated that these mutants reduce CTCRC activity and/or impair secretion. Again, the results accord with the common theme that loss of function of a trypsin inhibitory enzyme predisposes to CP, apparently by diminishing its protective trypsin degrading activity. All in all, these studies provide support for the central role of trypsin in the pathogenesis of CP. Without doubt future studies will identify other players in this pathway that modify the risk for CP.

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