Title: Pancreatitis Overview *GeneReview* – Supplemental Gene Information: *SPINK1*, *CFTR*, and *CTRC*
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Note: The following information is provided by the authors listed above and has not been reviewed by *GeneReviews* staff.

Supplemental Gene Information: *SPINK1*, *CFTR*, and *CTRC*

SPINK1, encoding the serine protease inhibitor, Kazal type 1 (which is a pancreatic secretory trypsin inhibitor).

One to three percent of populations worldwide have disease-associated loss of function *SPINK1* variants. *SPINK1* variants have been identified in approximately 20% of families with hereditary pancreatitis who do not have a *PRSS1* germline mutation. The most common variant, p.Asn34Ser, is in exon 2 and has no demonstrated effect on protein expression or function. Debate exists as two whether the pAsn34Ser is functional, or linked to a non-coding pathologic variant. Homozygosity or compound heterozygosity for these variants confers a high risk for familial chronic pancreatitis. The variant p.Asn34Ser is associated with early onset disease and/or rapid disease progression with found with other pathogenic variants.

Heterozygous mutations appear to modify disease severity regardless of primary etiology.

SPINK1 mutations have also been associated with recurrent acute pancreatitis. They are, however, not associated with an increased risk of an initial attack of acute pancreatitis, presumably because basal expression levels are of SPINK1 low, and SPINK1 becomes highly expressed as an acute phase reactant after the onset of inflammation to inhibit ongoing trypsin activity [Khalid et al 2006].

Mutations that disrupt protein expression or function that have been identified in affected individuals, but are rare include: c.27delC, p.Asp50Glu, p.Tyr54His, and p.Arg67Cys.

Only two large genomic deletions in *SPINK1* have been reported among families with hereditary pancreatitis, making gene deletion a confirmed, but exceptionally rare, etiology for pancreatitis [Chen et al 2008].

See Table 3 *SPINK1* Allelic Variants

Table 3. *SPINK1* Allelic Variants

Class of Variant Allele	DNA Nucleotide Change	Protein Amino Acid Change	Reference Sequences
Pathogenic	c.101A>G	p.Asn34Ser	NM_003122.3 NP_003113.2
	c.194+2T>C [1]		
	c.150T>G	p.Asp50Glu	
	c.160T>C	p.Tyr54His	
	c.199C>T	p.Arg67Cys	
	c.163C>T	p.Pro55Ser	

1. A T to C mutation at the +2 position of intron 3 causes exon 3 skipping [Kume et al 2006]

CFTR, encoding the cystic fibrosis transmembrane conductance regulator.

CFTR mutations have been identified in approximately 25% of families who do not have a *PRSS1* mutation. All *CFTR* mutations that cause cystic fibrosis (CF) are also risk factors for pancreatitis, but mutations that do not cause classic CF may still be risk factors for pancreatitis. The prototype *CFTR* variant that predisposes to hereditary pancreatitis is p.Arg75Gln which impairs the function of conductance of bicarbonate, but not chloride [Schneider et al 2011]. Additional mutations disrupting this function are believed to exist, but have not yet been reported.

Although direct sequencing of all 27 *CFTR* exons is expected to identify 90-95% of deleterious mutations in persons with CF, this has not been calculated these data are not available for chronic pancreatitis.

Deep intronic mutations and deletion/duplications are missed by direct sequencing, which may account for up to 10% of disease-causing mutations.

Mutations that cause classic CF are expected to be risk factors for pancreatitis, due to loss of CFTR function (similar to p.Phe508del) but most mutations have not been statistically proven in a pancreatitis cohort.

CFTR mutation panels in use today are those designed for the diagnosis of the monogenic disorder cystic fibrosis (CF). The North American ACMG 23 mutation panel includes the most common CF-causing mutations covering 85% of alleles in CF patients (for North American non-Jewish Caucasians only, alternative panels are available for different ethnicities). More extensive panels have been designed to increase the coverage for CF diagnosis, probing 40, 50 or 100 of the 1600+ known *CFTR* mutations. The most common CF-causing mutation, p.Phe508del, is present in 70% of individuals with CF and currently accounts for approximately 40% of identified *CFTR* variants in persons with hereditary pancreatitis. The detection rate of CF panels for pancreatitis has not been established and mutations that are not CF-causing may still confer risk for pancreatitis.

The frequency of *CFTR* deletions in hereditary pancreatitis has not been investigated. *CFTR* deletions = occur rarely in cystic fibrosis (~1%). Specific exonic deletions (del_exon2, 3 and del_exon22, 23) account for the majority of *CFTR* deletions.

A single mutation in *CFTR* is not considered disease causing, but may increase the risk of pancreatitis 2-5 fold. This risk is increased in the presence of a heterozygous *SPINK1* mutation, reflecting a double heterozygous or digenic trait [Schneider et al 2011, Cohn et al 2005].

See Table 4 *CFTR* Allelic Variants

Table 4. *CFTR* Allelic Variants

Class of Variant Allele	DNA Nucleotide Change (Alias [1])	Protein Amino Acid Change	Reference Sequences
Benign	c.1408A>G	p.Met470Val	NM_000492.3 NP_000483.3
	c.3870A>G	p.Pro1290Pro	
	c.1584G>A	p.Glu528Glu	
Pathogenic	c.1521_1523delCTT	p.Phe508del	
	c.224G>A	p.Arg75Gln	
	c.1652G>A	p.Glu551Asp	
	c.1624G>T	p.Glu542Ter	
	(del_exon 2,3) [2]		
	(del_exon 22,23) [2]		

1. Variant designation that does not conform to current naming conventions
2. Large deletion mutations of multiple exons in CFTR c.54-5940_273+10250del21kb (del_exon2,3) and c.3963-78_4242+577del (del_exon22,23)

CTRC encodes for an enzymatic trypsin inhibitor, mutations have been identified in a small number of persons with idiopathic chronic pancreatitis. The most commonly reported mutations, p.Ala73Thr, p.Arg254Trp, and p.Lys247_Arg254del, may account to up to 3% of families with hereditary pancreatitis [Masson et al 2008]. This has not been confirmed in North American populations in which mutation carriers were not significantly overrepresented in patients compared to healthy controls [LaRusch et al 2011].

A common synonymous variant p.G60G is overrepresented in North American chronic pancreatitis as well as familial chronic pancreatitis in European populations [Masson et al 2008]. This mutation is also associated with risk factors such as smoking, alcohol, and mutations in *CFTR* and *SPINK1* [LaRusch et al 2011] and is representative of a frequent mild pathogenic mutation that may contribute to progression in complex disease but is not a diagnostic risk factor.

See Table 5 *CTRC* Allelic Variants

Table 5. ***CTRC*** **Allelic Variants Discussed in This** ***GeneReview***

Class of Variant Allele	DNA Nucleotide Change	Protein Amino Acid Change	Reference Sequences
Pathogenic	c.760C>T	p.Arg254Trp	NM_007272.2 NP_009203.2
	c.738_761del24	p.Lys247_Arg254del	
	c.164G>A	p.Trp55Ter	

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