Title: Pancreatitis Overview *GeneReview* – Genetic Risk Factors that Predispose to Pancreatitis
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Date: March 2014
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Genetic Risk Factors that Predispose to Pancreatitis

It is critical to note that the phenotype of individuals with the same allelic variant(s) may differ and the majority of individuals heterozygous for a single mutation in one of these genes (other than *PRSS1*) do not have pancreatitis.

Table 1. Molecular Genetic Risk Factors that Predispose to Pancreatitis

Degree of Risk	Inheritance Pattern	Frequency in Control Population	Gene (Variant)	Molecular Consequence of Variant	Other
High	Autosomal dominant	<0.1% (frequency same for all 3 alleles?)	*PRSS1* (gene duplication, R122H,N29I)	-50% increase in protein levels -Protein resistant to degradation	See Table 2
	Autosomal dominant with low penetrance or multigenic		*PRSS1 (*A16V)	Protein partially resistant to degradation	
Moderate	Multigenic or autosomal dominant with low penetrance	<0.1%	*SPINK1* (c.27delC, p.Tyr54His)	Severe loss of protein function	See Table 3
	Multigenic or autosomal dominant with low penetrance	<0.1% 0.4% <0.1%	*CTRC* p.K247_R254del24 p.R254W p.Ala73Thr		
	Autosomal recessive or multigenic	3.0% <0.1% <0.1%	*CFTR* p.F508del c.del_exon2, 3 p.G551D		

Degree of Risk	Inheritance Pattern	Frequency in Control Population	Gene (Variant)	Molecular Consequence of Variant	Other
Mild	Autosomal recessive or multigenic	5-10%	*CFTR (*p.R75Q)	Selective loss of protein function	See Table 4
	Autosomal recessive or multigenic	3-5%	*SPINK1* (p.N34S,no known change)		
Modifiers	Complex	70%	*PRSS1 (*c.-408T>C)	Altered expression of protein	See Table 5
	Complex	26%	*CLDN2* (c.-275-1293G>A)		
	Complex	20%	*CTRC* (c.180C>T)	No known change	

1. This table is provided by the authors of this GeneReview and has not been reviewed by GeneReviews staff.

2. Allelic variants may be described in www.CFTR2.org and www.pancreasgenetics.org/

Table 2. *PRSS1* Allelic Variants

Class of Variant Allele	DNA Nucleotide Change	Protein Amino Acid Change	Reference Sequences
Pathogenic		p.Arg122His	NM_002769.4 NP_002760.1
		p.Arg122Cys	
		p.Ala16Val	
		p.Cys139Ser	
		p.Val39Ala	
		p.Asn29Ile	

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]

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)

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	

Other genes in which mutations or common variants have been implicated as risk factors for chronic pancreatitis include:

- *CASR:* Mutations have either a small effect or have not been studied and/or confirmed in all populations [Felderbauer et al 2003, Muddana et al 2008, Murugaian et al 2008]. *CASR* loss-of-function variants appear to increase the risk of pancreatitis in individuals with *CFTR* mutations, while loss-of-function mutations appear to increase the risk of pancreatitis in heavy users of alcohol.
- *GGT1:* Variation in the gene encoding γ-glutamyltransferase 1 has been recently associated with both pancreatic cancer and chronic pancreatitis [Brand et al 2013].
- Non-coding variants in the *CLDN2* locus and *PRSS1-PRSS2* locus*:* Common variants that do not directly alter amino acid sequence have recently been identified as risk modifiers for chronic pancreatitis in North America, but have not been investigated in families with hereditary pancreatitis [Whitcomb et al 2012]. *CLDN2*-locus haplotypes on the X chromosome is an X-linked-recessive risk factor for alcoholic pancreatitis, while a *PRSS1-PRSS2*-locus haplotype appears

to reduce trypsinogen gene expression and reduces the risk for pancreatitis from multiple causes.

- CPA1: carboxypeptidase 1 is the second most abundant pancreatic digestive enzyme produced by pancreatic acinar cells. Multiple rare mutations increase risk of chronic pancreatitis through protein missfolding and increased endoplasmic reticulum stress response, especially in children [Witt et al 2013].
- Note: Genes in which mutations do not appear to be associated with chronic pancreatitis include: *PRSS3, TGFB1, TNF, TNFRSF1A, IL10, UGT1A7, PDGFB, EPHX1, HFE* (in which mutations cause *HFE*-related hereditary hemochromatosis), *GP2* [Masson et al 2010] and *SERPINA1* (in which mutations cause alpha1 antitrypsin deficiency).

Variants in the secondary trypsinogens. Anionic trypsinogen encoded by *PRSS2* and mesotrypsin encoded by *PRSS3* are generally not considered major risk factors in non-*PRSS1* hereditary pancreatitis, but isolated instances have been described of mutations associated with either disease or healthy controls. For example:

- **Damaging variants**. A double gain-of-function mutation was reported in which a hybrid duplication of exons 1 and 2 of *PRSS2* and exons 3 to 5 of *PRSS1* resulted in a copy number variant (CNV) of trypsin with a damaging Isoleucine at the 29th amino acid [Masson et al 2008].
- **Protective variants**
  - It has been suggested that a rare protective loss-of-function *PRSS2* mutation- p.Gly191Arg -may mitigate risk alleles in other genes [Witt et al 2006, Santhosh et al 2008].
  - Protective mitigation is also seen in the frequent low expression haplotype *PRSS1* characterized by the intronic SNP rs10273639, which is significantly less frequent in persons with pancreatitis than healthy controls [Whitcomb et al 2012].

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