

## **Genetics of Chronic Pancreatitis**

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Chronic pancreatitis (CP) is characterized by irreversible morphological and functional alterations of the pancreas, clinically presenting with upper abdominal pain as well as exocrine and endocrine insufficiencies. CP is morphologically characterized by pancreatic head enlargement, calcifications of the parenchyma, cystis and pancreatic stones. Unlike hereditary pancreatitis which is an autosomal dominant disease with 80% penetrance and variable expression, several etiologic risk factors and mechanisms underlying chronic pancreatitis have been proposed: calcification and obstruction within pancreatic ductules due to protein plugs, alcohol consumption which induces an intrapancreatic lipid deposition in the cytoplasm of acinar cells and generation of free radicals by oxidative stress, tobacco smoking through inhibition of pancreatic bicarbonate secretion, hypercalcemia through trypsinogen activation and trypsin stabilization, and hyperlipidemia [1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11].

In approximately one-third of chronic pancreatitis patients, no etiologic factor can be found and these patients are classified as having idiopathic disease; there are several reasons why it is believed that molecular and genetic factors are important in the predisposition to chronic pancreatitis [12, 13, 14, 15].

Since 1952, numerous studies have described cases of familial chronic pancreatitis. The attacks were characterized by severe abdominal pain, fever, and marked elevation of serum amylase. Except for the last symptom, differentiation from familial Mediterranean fever, also called "familial paroxysmal peritonitis", might be difficult. The aminoaciduria was almost certainly an incidental finding since family members without pancreatitis showed it and also because other families with pancreatitis have not had this feature [16]. In 1967, Robeck described a family with five affected people [17]. He suggested that hypertrophy of the sphincter of Oddi together with a common ampulla of the biliary and pancreatic ducts may be the inherited factor. A number of important manuscripts pointed out the different features of the familial form of chronic pancreatitis; Mann and Rubin [18] described the occurrence of hyperparathyroidism in the multiple endocrine adenomatosis syndrome; McElroy and Christiansen [19] pointed out that thrombosis in the portal or splenic vein occurs with significant frequency, and Sibert [20] identified penetrance of the disease at about 80%; the mean age of onset was 13.6 years with two peaks, one at five years and one at 17 years. In 1982, Sarles *et al.* showed that "stone protein" could inhibit in vitro calcium

carbonate nucleation and decrease the rate of crystal growth acting as a physiologic inhibitor of spontaneous calcium carbonate formation in supersaturated pancreatic juice [21].

In 1996, Le Bodiac [22] analyzed the genomic segregation of highly informative microsatellite markers in a French family of 147 individuals, 47 of whom had hereditary pancreatitis. Linkage was found between the disease and 6 chromosome 7q markers. That locus was found to encode carboxypeptidase A1 which is a pancreatic exopeptidase. In 1996 Whitcomb *et al.* carried out a genome wide linkage analysis on a family extensively affected by hereditary pancreatitis. Using genetic linkage studies, the hereditary pancreatitis locus was narrowed to the long arm of chromosome 7 [22, 23, 24]. Two main mutations in the cationic trypsinogen gene (PRSS1) have been identified in patients with hereditary pancreatitis: Arg->117His (R122H, originally called R117H) and Asn->21Ile (N29I, originally called N21I).

Trypsinogen is an inactive proenzyme for trypsin, which becomes active when an 8-amino acid N-terminal peptide is removed.

It has been proposed that the Arg->117His mutation eliminates a trypsin-sensitive cleavage site on trypsin and leads to pancreatitis by rendering prematurely activated trypsin resistant to inactivation through autolysis or proteolysis by trypsin-like enzymes [25, 26, 27, 28, 29, 30, 31, 32]. The Asn->21Ile mutation, instead, could decrease autoactivation and autocatalytic zymogen degradation without affecting trypsin stability or activity [33]. Other less common mutations of the same gene were observed: K23R, -28delTCC in the promotor region of the try4 gene, A16V and D22G. The effect of K23R could be to cause an alteration of the tertiary structure of the protein and of the trypsin inhibitor binding site while the effect of -28delTCC is only speculative at present; moreover, they do not result in the high-penetrance, autosomal dominant pancreatitis as seen with codon 29 and 122 mutations [34]. These findings suggest that prematurely activated trypsinogen is a critical

molecular step in the initiation of acute pancreatitis and links multiple episodes of acute pancreatitis developing into chronic pancreatitis. However, PRSS1 mutations cannot account for all mutations causing hereditary pancreatitis or idiopathic pancreatitis (60% of hereditary and less than 20% of idiopathic pancreatitis); mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) were also found to be associated with chronic pancreatitis [35, 36, 37, 38, 39, 40].

CFTR functions as a chloride channel. CFTR, expressed in pancreatic tissue and mutations or particular polymorphisms of this gene, together with other genetic and environmental factors, could be risk factors for chronic pancreatitis, by altering the pancreatic flow and composition. In 1998, Sharer studied 134 consecutive patients with chronic pancreatitis [35]. DNA was examined for 22 mutations and the noncoding sequence of thymidines in intron 8 of the CFTR gene. None of the patients had a mutation on both copies of the CFTR gene. Thirteen percent had a CFTR mutation on 1 chromosome, as compared with a frequency of 5.3% among 600 local unrelated partners of people with a family history of cystic fibrosis ( $P < 0.001$ ). A total of 10.4% of the patients had the 5T allele in intron 8, which is twice the expected frequency ( $P = 0.008$ ). Patients with a CFTR mutation were younger than those with no mutations ( $P = 0.03$ ). None had the combination of sinopulmonary disease, high sweat electrolyte concentrations, and low nasal potential-difference values which is diagnostic of cystic fibrosis.

Similarly, Cohn *et al.* studied 27 patients (mean age at diagnosis, 36 years), who had been referred for an evaluation of idiopathic pancreatitis [36]. Their DNA was tested for 17 CFTR mutations and for the 5T allele in intron 8. They found that 10 patients with idiopathic chronic pancreatitis (37%) had at least one abnormal CFTR allele. In 3 patients both alleles were affected.

The cystic fibrosis gene can cause idiopathic pancreatitis when present in the heterozygous state in association with the variable number

of thymidines in intron 8 of the CFTR gene, specifically the 5T allele.

In 2000, a correlation between serine protease inhibitor (SPINK1) mutations and the disease was found [39, 40, 41, 42]. SPINK1 is a peptide which specifically inhibits trypsin (about 20% of potential trypsin) by physically blocking the active site. Because gain of function trypsin mutations cause acute and chronic pancreatitis, it was hypothesized that loss of the trypsin inhibitor function would have similar effects and indeed, the role of SPINK1 N34S and P55S mutations in chronic pancreatitis emerged. Witt *et al.* [39] studied 96 children and adolescents with chronic pancreatitis and found a nonsense mutation in the SPINK1 gene in 18; in 6 of these patients, the mutation was homozygous. Only 1 out of 279 healthy controls was heterozygous and no homozygous individuals were found. The same group found a heterozygous mutation destroying the translation initiation codon of SPINK1 in a patient with hereditary pancreatitis; the mutation was also found in the affected grandfather and in the unaffected father. However, because N34S and P55S mutations are common in the general population (2%) while idiopathic chronic pancreatitis is rare, SPINK1 mutations appear to act as disease modifiers and the disease mechanism is more complex than an autosomal recessive one. However, mutations in SPINK1 or in PRSS1 could lead to an imbalance of proteases and their inhibitors within the pancreatic parenchyma, resulting in an inappropriate conversion of pancreatic zymogens to active enzymes with autodigestion and inflammation [41, 42].

A growing body of data supported the association of SPINK1 and CFTR mutations with chronic pancreatitis and in 2002, Audrezet *et al.* systematically analyzed the entire coding sequence and exon/intron junctions of the PRSS1, SPINK1, and CFTR genes in 39 white French patients with idiopathic chronic pancreatitis [40]. One patient had a nonsense mutation (R122H) in the PRSS1 gene; four patients had the same nonsense mutation in the SPINK1 gene, three in heterozygosity and one in homozygosity

(N34S) and eight patients carried one of the most common mutations of the CFTR gene. A trans-heterozygous state with sequence variations in the SPINK1/CFTR genes was found in three patients. The results demonstrated that about one-third of the patients labeled as having idiopathic chronic pancreatitis had, in fact, a genetic defect.

Immunologic events are also believed to be involved in the pathogenesis of chronic pancreatitis [43]; T-lymphocytic infiltration of the exocrine pancreas in patients with chronic pancreatitis has suggested that cell-mediated immune mechanisms may play a part in the pathogenesis of this disease [44, 45]. Normal pancreatic epithelial cells did not express HLA-DR antigens but abnormal expression, by exocrine epithelial cells, of either class I or class II major histocompatibility complex (MHC) determinants or both has been found in chronic pancreatitis. In general, MHC class I present antigens derived from intracellular proteins (self and nonself) to CD8+ T cells. Class II molecules present antigens derived from endocytosed extracellular proteins to CD4+ T cells, which may stimulate both B- and T-cell-mediated immune responses [46, 47, 48, 49].

Among HLA-DRB1 genes, DRB\*04 was shown to be significantly higher in chronic pancreatitis patients than in controls.

HLA DRB1\*0401 contains the QKRAA amino acid sequence in its third hypervariable region and the QKRAA sequence is also expressed by several human pathogens. T cells may be triggered in the pancreatic tissue upon exposure to foreign peptides similar enough to cross-react and to break immunological tolerance [50].

Cytokines and chemokines of the MHC play critical roles in the pathogenesis of autoimmune disease. Among these, tumor necrosis factor-alpha, derived from monocytes or lymphocytes, is a proinflammatory cytokine with pleiotropic biological effects. A growing body of data [51] has demonstrated a significant association of TNF-alpha polymorphism at position -308 with susceptibility to or severity

of autoimmune and infectious disease [52, 53]. Moreover, recent studies on cultured epithelial cells deficient in keratin 8 (K8) and keratin 18 (K18), have demonstrated an increased sensitivity (nearly 100 times) to tumor necrosis factor-alpha (TNF-alpha) acting both as a grow factor and an apoptotic stimulus. This finding addressed the increased sensitivity of K8-cells to TNF, as fundamental in the resistance of epithelia to apoptosis during common inflammatory responses and in the persistence of K8 and K18 expression in carcinoma cells [54].

Important information regarding keratin function was also obtained by the overexpression of mutant or ectopic keratins; the overexpression of human K8 in transgenic mice resulted in significant pancreatic acinar cell atrophy, dysplasia and progressive exocrine dysfunction [55]. Furthermore, a report from Omary *et al.* [56], demonstrated that G61C and Y53H mutations in keratin 8 gene may account for cryptogenetic liver disease by interfering with the normal organization of keratin filaments. The results from Casanova *et al.* and from Omary *et al.* uncovered a possible role as intermediate filaments for K8 in the pathogenesis of chronic inflammatory diseases of tissue containing K8. Moreover, hepatocytes and pancreatic epithelial cells are unique in that they express cytoplasmatic K8/K18 exclusively.

Indeed, the G61C heterozygous mutation of the keratin 8 gene was found in six patients with chronic pancreatitis (P=0.006); none of the normal controls presented the mutation. No Y53H mutation was detected in any subject [57]. Mutations in the keratin 8 gene, together with other environmental factors (alcohol intake, smoking habits) and/or genetic factors, could predispose to chronic pancreatitis by interfering with the normal organization of keratin filaments.

Cytochrome P450IIE1 (CYP2E1) is an ethanol-inducible enzyme; several novel polymorphisms in the CYP2E1 gene have been identified. CYP2E1 is one of the possible mechanisms for ethanol-induced oxidative stress in the pancreas, and the

associated oxidative stress may play a role in the pathogenesis of alcohol-induced pancreatitis. Analysis of the four CYP2E1 gene polymorphisms (-35{G(-35)T}, -1019{C(-1019)T}, 4808{G(4808)A}, and 7668{T(7668)A}), did not show any correlation with the susceptibility and pathogenesis of alcoholic pancreatitis [58].

Apart from alcohol abuse, chronic pancreatitis and pancreatic adenocarcinoma are associated with smoking and environmental aromatic hydrocarbon exposure. Uridine 5'-diphosphate glucuronosyltransferases are phase II detoxifying enzymes capable of tobacco-borne toxicant inactivation and cellular protection. Uridine 5'-diphosphate glucuronosyltransferases A7 (UGT1A7) gene polymorphisms in pancreatic diseases were analyzed [59] as candidate polymorphisms in association with pancreatic disease. Alterations of UGT1A7 functional properties may indeed potentially influence the risk of oxidative injury and therefore of chronic inflammation and cancer initiation. An association of chronic pancreatitis and pancreatic adenocarcinoma with low-activity polymorphisms of the xenobiotic-detoxifying enzyme gene UGT1A7 was seen.

Association studies between a disease and a marker locus are the best method for identifying susceptibility genes for complex diseases, such as chronic pancreatitis. Moreover, chronic pancreatitis has also a threshold character; therefore several genetic backgrounds could lead to the same clinical picture. Genetic analyses will become important in the diagnosis and classification of chronic pancreatic disorders in order to better define the etiology, the progression and the prognosis of the disease. Several attempts have been made to identify clinical, biochemical and histological parameters capable of predicting the prognosis of such diseases. However, all these prognostic scores rely on biochemical or clinical parameters which can be modified only in the very advanced phases of the disease. Therefore, at the time of diagnosis, they are unable to discriminate the patients who will undergo a rapidly progressive course from those who

will never have their quality and expectancy of life reduced by the disease.

New biological markers are therefore needed to identify genetic markers able to identify patients at risk of disease progression. Such new markers need to be identified on "pedigreed patients" carefully selected according to their pattern of disease progression. Moreover, molecular classification will help to provide identification of pancreatitis-associated genes and gene-environmental interactions in the pathogenesis of the disease.

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**Keywords** Cystic Fibrosis Transmembrane Conductance Regulator; Cytochrome P-450 Enzyme System; Genetics; Glucuronosyltransferase; Keratin; Major Histocompatibility Complex; Mutation; Pancreatitis; Polymorphism, Genetic; Trypsinogen

**Abbreviations** CP: chronic pancreatitis; CYP2E1: cytochrome P450III<sub>E1</sub>; K18: keratin 18; K8: keratin 8; MHC: major histocompatibility complex, UGT1A7: uridine 5'-diphosphate glucuronosyltransferases A7

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### References

1. Lowenfels AB, Maisonneuve P, Cavallini G, Ammann RW, Lankisch PG, Andersen JR, et al. Pancreatitis and the risk of pancreatic cancer. International Pancreatitis Study Group. *N Engl J Med* 1993; 328:1433-7. [PMID 8479461]

2. Bansal P, Sonnenberg A. Pancreatitis is a risk factor for pancreatic cancer. *Gastroenterology* 1995; 109:247-51. [PMID 7797022]
3. Steer ML, Waxman I, Freedman S. Chronic pancreatitis. *N Engl J Med* 1995; 332:1482-90. [PMID 7739686]
4. Cavallini G, Frulloni L, Pederzoli P, Talamini G, Bovo P, Bassi C, et al. Long-term follow-up of patients with chronic pancreatitis in Italy. *Scand J Gastroenterol* 1998; 33:880-9. [PMID 9754738]
5. Mergener K, Baillie J. Chronic pancreatitis. *Lancet* 1997; 350:1379-85. [PMID 9365465]
6. Moreira V, Martin-de-Argila C, Aller R, Merono E. Chronic pancreatitis. *Lancet* 1998; 351:67 [PMID 9433447]
7. Lankisch PG. Diagnosis of chronic pancreatitis. *Lancet* 1998; 351:599-600 [PMID 9492808]
8. Ala A, van Someren N. Chronic pancreatitis. *Lancet* 1998; 351:67-8. [PMID 9433448]
9. Talamini G, Bassi C, Falconi M, Sartori N, Salvia R, Rigo L, et al. Alcohol and smoking as risk factors in chronic pancreatitis and pancreatic cancer. *Dig Dis Sci* 1999; 44:1301-1. [PMID 10489910]
10. Adler G, Schmid RM. Chronic pancreatitis: still puzzling? *Gastroenterology* 1997; 112:1762-5. [PMID 9136860]
11. Kleeff J, Friess H, Korc M, Buchler MW. Chronic pancreatitis: pathogenesis and molecular aspects. *Ann Ital Chir* 2000; 71:3-10. [PMID 10829517]
12. Etemad B, Whitcomb DC. Chronic pancreatitis: diagnosis, classification, and new genetic developments. *Gastroenterology* 2001; 120:682-707. [PMID 11179244]
13. Whitcomb DC. Genetic predisposition to acute and chronic pancreatitis. *Med Clin North Am* 2000; 84:531-47. [PMID 10872412]
14. Whitcomb DC. Hereditary pancreatitis: new insights into acute and chronic pancreatitis. *Gut* 1999; 45:317-22. [PMID 10446089]
15. Whitcomb DC. Genes means pancreatitis. *Gut* 1999; 44:150-1. [PMID 9895368]
16. Davidson P, Costanza D, Swieconeck JA, Harris JB. Hereditary pancreatitis: a kindred without gross aminoaciduria. *Ann Intern Med* 1968; 68:88-96. [PMID 5635333]
17. Robeck PJ. Hereditary chronic relapsing pancreatitis. A clue to pancreatitis in general? *Am J Surg* 1967; 113:819-24. [PMID 6023921]
18. Mann TP, Rubin J. Familial pancreatic exocrine dysfunction with pancreatic calcification. *Proc Roy Soc Med* 1969; 62:326. [PMID 5811932]

19. McElroy R, Christiansen PA. Hereditary pancreatitis in a kinship associated with portal vein thrombosis. *Am J Med* 1972; 52:228-41. [PMID 5062005]
20. Sibert JR. Hereditary pancreatitis in England and Wales. *J Med Genet* 1978; 15:189-201. [PMID 671483]
21. Sarles H, de Caro A, Multinger L, Martin E. Giant pancreatic stones in teetotal women due to absence of the 'stone protein'? *Lancet* 1982; 2:714-5. [PMID 6126647]
22. Le Bodic L, Bignon J, Raguene O, Mercier B, Georgelin T, Schnee M, et al. The hereditary pancreatitis gene maps to long arm of chromosome 7. *Hum Mol Genet* 1996; 5:549-54. [PMID 8845851]
23. Whitcomb DC, Preston RA, Aston CE, Sossenheimer MJ, Barua PS, Zhang Y, et al. A gene for hereditary pancreatitis maps to chromosome 7q35. *Gastroenterology* 1996; 110:1975-80. [PMID 8964426]
24. Pandya A, Blanton SH, Landa B, Javaheri R, Melvin E, Nance WE, Markello T. Linkage studies in a large kindred with hereditary pancreatitis confirms mapping of gene to a 16-cm region on 7q. *Genomics* 1996; 38:227-30. [PMID 8954806]
25. Whitcomb DC, Gorry MC, Preston RA, Furey W, Sossenheimer MJ, Ulrich CD, et al. Hereditary pancreatitis is caused by a mutation in the cationic trypsinogen gene. *Nat Genet* 1996; 14:141-5. [PMID 8841182]
26. Gorry MC, Gabbazedeh D, Furey W, Gates LK, Preston RA, Aston CE, et al. Mutations in the cationic trypsinogen gene are associated with recurrent acute and chronic pancreatitis. *Gastroenterology* 1997; 113:1063-8. [PMID 9322498]
27. Nishimori I, Kamakura M, Fujikawa-Adachi K, Morita M, Onishi S, Yokoyama K, et al. Mutations in exons 2 and 3 of the cationic trypsinogen gene in Japanese families with hereditary pancreatitis. *Gut* 1999; 44:259-63. [PMID 9895387]
28. Creighton J, Lyall R, Wilson DI, Curtis A, Charnley R. Mutations of the cationic trypsinogen gene in patients with chronic pancreatitis. *Lancet* 1999; 354:42-3. [PMID 10406366]
29. Creighton J, Lyall R, Wilson DI, Curtis A, Charnley R. Mutations of the cationic trypsinogen gene in patients with chronic pancreatitis. *Br J Surg* 2000; 87:170-5. [PMID 10671922]
30. Witt H, Luck W, Becker M. A signal peptide cleavage site mutation in the cationic trypsinogen gene is strongly associated with chronic pancreatitis. *Gastroenterology* 1999; 117:7-10. [PMID 10381903]
31. Ferec C, Raguene O, Salomon R, Roche C, Bernard JP, Guillot M, et al. Mutations in the cationic trypsinogen gene and evidence for genetic heterogeneity in hereditary pancreatitis. *J Med Genet* 1999; 36:228-32. [PMID 10204851]
32. Truninger K, Kock J, Wirth HP, Muellhaupt B, Arnold C, von Weizsacker F, et al. Trypsinogen gene mutations in patients with chronic or recurrent acute pancreatitis. *Pancreas* 2001; 22:18-23. [PMID 11138965]
33. Sahin-Toth M. Human cationic trypsinogen. Role of Asn-21 in zymogen activation and implications in hereditary pancreatitis. *J Biol Chem* 2000; 275:22750-5. [PMID 10801865]
34. Teich N, Ockenga J, Hoffmeister A, Manns M, Mossner J, Keim V. Chronic pancreatitis associated with an activation peptide mutation that facilitates trypsin activation. *Gastroenterology* 2000; 119:461-5. [PMID 10930381]
35. Sharer N, Schwarz M, Malone G, Howarth A, Painter J, Super M, Braganza J. Mutations of the cystic fibrosis gene in patients with chronic pancreatitis. *N Engl J Med* 1998; 339:645-52. [PMID 9725921]
36. Cohn JA, Friedman KJ, Noone PG, Knowles MR, Silverman LM, Jowell PS. Relation between mutations of the cystic fibrosis gene and idiopathic pancreatitis. *N Engl J Med* 1998; 339:653-8. [PMID 9725922]
37. Malats N, Real FX. Correction: mutations of the cystic fibrosis gene in patients with chronic pancreatitis. *N Engl J Med* 1999; 340:1592-3. [PMID 10336360]
38. Taylor CJ. Chronic pancreatitis and mutations of the cystic fibrosis gene. *Gut* 1999; 44:8-9. [PMID 9862818]
39. Witt H, Luck W, Hennies HC, Classen M, Kage A, Lass U, et al. Mutations in the gene encoding the serine protease inhibitor, Kazal type 1 are associated with chronic pancreatitis. *Nat Genet* 2000; 25:213-6. [PMID 10835640]
40. Audrezet MP, Chen JM, Le Marechal C, Ruzsniwski P, Robaszkiwicz M, Raguene O, et al. Determination of the relative contribution of three genes--the cystic fibrosis transmembrane conductance regulator gene, the cationic trypsinogen gene, and the pancreatic secretory trypsin inhibitor gene--to the etiology of idiopathic chronic pancreatitis. *Eur J Hum Genet* 2002; 10:100-6. [PMID 11938439]
41. Chen J, Mercier B, Audrezet M, Ferec C. Mutational analysis of the human pancreatic secretory trypsin inhibitor (PSTI) gene in hereditary and sporadic chronic pancreatitis. *J Med Genet* 2000; 37:67-9. [PMID 10691414]
42. Pfutzer RH, Barmada MM, Brunskill AP, Finch R, Hart PS, Neoptolemos J, et al. SPINK1/PSTI polymorphisms act as disease modifiers in familial and idiopathic chronic pancreatitis. *Gastroenterology* 2000; 119:615-23. [PMID 10982753]

43. Cavallini G, Frulloni L, Di Francesco V, Bovo P, Filippini M, Vaona B. Autoimmunity and chronic pancreatitis. *Gut* 1995; 36:799-800. [PMID 7797137]
  44. Demols A, Le Moine O, Desalle F, Quertinmont E, van Laethem JL, Deviere J. CD4+ cells play an important role in acute experimental pancreatitis in mice. *Gastroenterology* 2000; 118:582-90. [PMID 10702210]
  45. Bedossa P, Bacci J, Lemaigre G, Martin E. Lymphocyte subsets and HLA-DR expression in normal pancreas and chronic pancreatitis. *Pancreas* 1990; 5:415-20. [PMID 1974351]
  46. Jalleh RP, Gilbertson JA, Williamson RC, Slater SD, Foster CS. Expression of major histocompatibility antigens in human chronic pancreatitis. *Gut* 1993; 34:1452-7 [PMID 8244120]
  47. Forbes A, Schwarz G, Mirakian R, Drummond V, Chan CK, Cotton PB, Bottazzo GF. HLA antigens in chronic pancreatitis. *Tissue Antigens* 1987; 30:176-83. [PMID 3686517]
  48. Anderson RJ, Dyer PA, Donnai D, Klouda PT, Jennison R, Braganza JM. Chronic pancreatitis, HLA and autoimmunity. *Int J Pancreatol* 1988; 3:83-90. [PMID 3162507]
  49. Bovo P, Mirakian R, Merigo F, Angelini G, Cavallini G, Rizzini P, et al. HLA molecule expression on chronic pancreatitis specimens: is there a role for autoimmunity? A preliminary study. *Pancreas* 1987; 2:350-6. [PMID 3498162]
  50. Cavestro GM, Frulloni L, Neri TM, Seghini P, Nouvenne A, Zanetti A, et al. Association of HLA-DRB1 \*0401 Allele with chronic pancreatitis. *Pancreas* 2003; 26:388-91. [PMID 12717273]
  51. Ruuls SR, Sedgwick JD. Unlinking tumor necrosis factor biology from the major histocompatibility complex: lessons from human genetics and animal model. *Am J Hum Genet* 1999, 65:294-301. [PMID 10417271]
  52. Wilson AG, di Giovine FS, Blakemore AI, Duff GW. Single base polymorphism in the human Tumor Necrosis Factor alpha (TNF-alpha) gene detectable by NcoI restriction of PCR product. *Hum Mol Genet* 1992; 1:353. [PMID 1363876]
  53. O'Reilly DA, Sargen KD, Dunlop S, Demaine AG, Kingsnorth AN. Association of tumor necrosis factor microsatellite haplotypes with chronic pancreatitis. *Br J Surg* 2000; 87:365-6. [PMID 10718810]
  54. Caulin C, Ware CF, Magin TM, Oshima RG. Keratin-dependent, epithelial resistance to tumor necrosis factor induced apoptosis. *J Cell Biol* 2000; 149:17-22. [PMID 10747083]
  55. Casanova ML, Bravo A, Ramirez A, Morreale de Escobar G, Were F, et al. Exocrine pancreatic disorders in transgenic mice expressing human keratin 8. *J Clin Invest* 1999; 103:1587-95. [PMID 10359568]
  56. Ku NO, Gish R, Wright TL, Omary MB. Keratin 8 mutation in patients with cryptogenic liver disease. *N Engl J Med* 2001; 344:1580-7. [PMID 11372009]
  57. Cavestro GM, Frulloni L, Nouvenne A, Neri TM, Calore B, Ferri B, et al. Association of keratin 8 gene mutation with chronic pancreatitis. *Dig Liver Dis* 2003; 35:416-20. [PMID 12868678]
  58. Yang B, O'Reilly DA, Demaine AG, Kingsnorth AN. Study of polymorphisms in the CYP2E1 gene in patients with alcoholic pancreatitis. *Alcohol* 2001; 23:91-7. [PMID 11331106]
  59. Ockenga J, Vogel A, Teich N, Keim V, Manns MP, Strassburg CP. UDP glucuronosyltransferase (UGT1A7) gene polymorphisms increase the risk of chronic pancreatitis and pancreatic cancer. *Gastroenterology* 2003; 124:1802-8. [PMID 12806614]
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