Genetics of chronic pancreatitis and pancreatic cancer

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Chronic Pancreatitis - Etiology

Alcohol        Idiopathic           Metabolic        Anatomical        Hereditary        Autoimmune (?)
Hereditary Pancreatitis

- Hereditary pancreatitis is clinically indistinguishable from other forms and varieties of pancreatitis.

14 year old girl with chronic pancreatitis and R122H-mutation

48 year old women with chronic pancreatitis and R122H-mutation
Identification of the pancreatitis gene

1. Family

2. Genetic Mapping

3. Mutation

4. Mechanism

Hereditary Pancreatitis gene

Recruitment

Chromosom 7

ccaccaccagtcagg

cacactctaccaccAT

GAATCCACTCC

TGATCCTTACCT

TTGTG

G/ACAG

CTGGCTgtaagtat

catgccctgcctcagg

ccccaaccaccccccc

cgttcctggccga

Point Mutation in the Trypsinogen Gene

Trypsinogen

Functional Meaning?

Whitcomb et al. Nature Genetics 1996
Today, restriction enzyme digest with BstU I represents the most extensive initial screening test for hereditary pancreatitis.
Cationic trypsin

Activation site

C139F  D100H  L104P
K92N  R116C  V123M  R122H/C
P36R
K23R  N29I/T
D22G  G83E  E79K
1952: Comfort and Steinberg reported for the first time an autosomal dominant trait for a family with chronic pancreatitis.

1985: The first German family was reported.

1996: Whitcomb et al. discovered the first mutation associated with chronic hereditary pancreatitis in the cationic trypsinogen gene (PRSS1).
Sporadic point mutations in the PRSS1-Gen in idiopathic chronic Pancreatitis

In 5 of 50 Patients with idiopathic Pancreatitis (10%) mutations in the cationic Trypsinogen gene were found.

Affected Patients represented 35% of all patients under 25 years.

Pancreatic Cancer in Hereditary Pancreatitis

50-70% increased risk for pancreatic cancer in patients with hereditary pancreatitis. 40% cumulative risk until age of 70 years.

Elimination/Treatment of causal factors:
- Smoking
- Alcohol
- Hyperlipidemia
- Hypercalcemia
- Gallstones
- Duct stricture
- Drugs and Medications

Pancreatic secretory Trypsin Inhibitor (PSTI, SPINK-1)

Mutations in 23% of children with idiopathic chronic Pancreatitis

◇ autosomal-recessive disorder

Pfützer et al, (Gastroenterology, 2000)
Mutations in idiopathic chronic Pancreatitis (25%), hereditary Pancreatitis and in the healthy population (2%).

◇ Modifier - Gene, risk of pancreatitis < 1%

Bhatia et al, Schneider et al, (Gastroenterology, 2002)
Mutations in tropical calcifying pancreatitis (up to 44%) and in ‘Fibrocalculous Pancreatic Diabetes mellitus‘ (55%).

◇ Risk factor for tropical Pancreatitis and Diabetes mellitus
SPINK1 Mutations (N34S) are found among Pancreatitis patients as well as among healthy carriers of Trypsinogen mutations.

SPINK1 Mutations in Hereditary Pancreatitis

Cumulative Incidence of Pancreatitis

SPINK1 Mutations have no influence on the severity or clinical disease course of hereditary pancreatitis

One third of patients (n=27) with idiopathic pancreatitis carry CFTR-Mutations (Risk x 80).


CFTR Mutations represent a risk factor for chronic pancreatitis in patients without a history of alcohol abuse (19% of n = 60), but not for those with alcoholic pancreatitis (8.5% of n = 72).

## Frequency of CFTR-mutations in patients with idiopathic chronic pancreatitis – review of the literature

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>affected patients</th>
<th>%</th>
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</thead>
<tbody>
<tr>
<td>Choudari et al., 1998</td>
<td>19/96 patients</td>
<td>19,8%</td>
</tr>
<tr>
<td>Sharer et al., 1998</td>
<td>11/60 patients</td>
<td>18,3%</td>
</tr>
<tr>
<td>Cohn et al., 1998</td>
<td>7/27 patients</td>
<td>25,9%</td>
</tr>
<tr>
<td>Ockenga et al., 2000</td>
<td>5/20 patients</td>
<td>25%</td>
</tr>
<tr>
<td>Maire et al., 2003</td>
<td>11/64 patients</td>
<td>17,1%</td>
</tr>
<tr>
<td>Weiss et al., 2005</td>
<td>12/66 patients</td>
<td>16,7%</td>
</tr>
<tr>
<td>Sharer et al., 1998</td>
<td>32/600 Control cohort</td>
<td>5,3%</td>
</tr>
<tr>
<td>Cohn et al. 2005</td>
<td>15/52 patients</td>
<td>17,3%</td>
</tr>
</tbody>
</table>
Prevalence of gene mutations in chronic pancreatitis

- Idiopathic pancreatitis: 45.5%
- Trypsinogen mutations: 10%
- SPINK-1 mutations: 15.2%
- T5 Allels: 12.1%
- CFTR mutations: 18.2%
Genetics in pancreatic cancer - incidence

- Genetic factors are responsible for 17% of all cases of pancreatic carcinoma. 1.4 per 100,000 populations in Germany.

- 10% of patients with sporadic pancreatic carcinoma have a positive family history for pancreatic cancer.

- **Prospective trial in pancreatic cancer families:**
  Risk to develop pancreatic cancer: increased 9-times.
  If more than 3 family members are affected: 32-times
  Klein AP et al Cancer Research 2004; 64: 2634-2638

- **Retrospective trial in pancreatic cancer families to identify additional risk factors**
  Smoking. (87% (HPC) versus 66% (SPC) p = 0.006%)
25% of all patients suffering from ‘Familial Atypical Multiple Mole Melanoma’ Syndrome develop pancreatic cancer.

This disease is associated with mutations in the CDKN2A Gene (coding for the Cyclin dependent Kinase 2A = p16\(^{\text{ink4a}}\)) [analogous p53 bei Li-Fraumeni]

Penetrance of these mutations is variable. The inheritance pattern follows a autosomal dominant trait.

Tumors are observed synchronous or metachronous.

Carrier of mutations in the CDKN2A gene have an 13- to 22-times increased risk for pancreatic cancer.

The Cumulative risk to develop pancreatic cancer until the age of 75 is estimated with 17%.

Hereditary Pancreatic Cancer Syndromes – Peutz-Jeghers-Syndrome

Autosomal dominant cancer syndrome with an incidence of 1:25 000.

Characterised by skin and mucosa pigmentation as well as multiple hamartous polyps.

Closely associated to mutations in the Serine/Threonine Kinase 11 (STK11), which belongs to the family of DNA-Repair genes.

Patients suffering from Peutz-Jeghers-Syndrome have a 132-times increased risk to develop pancreatic cancer.

The cumulative lifetime risk is 36% until the age of 75.

Hereditary Pancreatic Cancer Syndromes – BRCA1 and BRCA2

- Retrospective cohort study in patients (11,847 from 699 families) with a BRCA1 Mutations. Risk of pancreatic cancer: 2.26-times increased

- 10% of all cases with sporadic pancreatic carcinoma (SPC) in Jews (Ashkenazim) are associated with BRCA2 mutations (6174delT). The prevalence of the 6174delT mutation in Jews is (Ashkenazim) 1%.

- The prevalence of BRCA2 mutations in Americans with SPC is 17.2%. The prevalence in Europe in patients with Familial Pancreatic cancer (FPC) is 19%. No 6174delT mutations were detected in this cohort.

BRCA2 is the most frequent mutation associated with familial pancreatic cancer so far identified.

## Hereditary Pancreatic Cancer Syndromes – Conclusion

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Gene</th>
<th>Risk</th>
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<tbody>
<tr>
<td>HBOC</td>
<td>BRCA1, BRCA2</td>
<td>?</td>
</tr>
<tr>
<td>HP</td>
<td>PRSS1</td>
<td>40%</td>
</tr>
<tr>
<td>PJS</td>
<td>STK11/LKB</td>
<td>36%</td>
</tr>
<tr>
<td>FAMMM-PC</td>
<td>CDKN2A</td>
<td>17%</td>
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###gene descriptions:

- **HBOC**: Hereditary Breast- and ovary-carcinoma Syndrom
- **HP**: Hereditary Pancreatitis
- **PJS**: Peutz-Jeghers-Syndrome
- **FAMMM-PC**: Familial multiple mole melanoma – pancreatic cancer syndrome

Genetics in pancreatic disease

- Hereditary chronic and idiopathic chronic pancreatitis are associated with mutations in the Trypsinogen gene, the SPINK-1 Gene, and the CFTR gene. More genes to be evaluated.

- Somatic mutations of proteins which influence tumor progression are closely associated with the development of pancreatic cancer (p53, k-ras, p16ink, DPC-4). Transgenic animal models have proven the relevance of these genes.

- Familial pancreatic cancer syndromes are caused by germline mutations in gene regulatory proteins and are burdened with a significantly increased lifetime risk of pancreatic cancer.
Gene mutations in hereditary pancreatitis:


Pancreatic cancer develops in an adenoma to carcinoma sequence.

Different genetic defects characterise the degree of dysplasia.

Early genetic changes in pancreatic cancer – **kras**^{G12D}

Tuveson DA et al. Cancer Cell 2003; 4: 437

- K (irsten) ras oncogene

- Pancreatic cancer is burdened with the highest incidence of k-ras mutations (55-95% of all investigated cancer samples).

- 79.1% of all mutations are found in Codon 12 (at the position 71-79). **Lüttges J et al, Cancer 2000; 88: 2495-2504**

This suggests kras as key regulator in the tumorigenesis of pancreatic cancer.

PanIN Lesions
90% in 6 Mo
20% cancer
p53 encodes a transcription factor which is regarded as the “Guardian of the Genome“. p53 is induced by DNA-damage or activation of oncongenes.

- Inactivation of p53 leads to the progression of the cell cycle via G1/S-Phase what results in cell proliferation.

- 60% of all pancreatic carcinomas display mutations in the p53 gene and the gene is closely associated with the Li-Fraumeni- Cancer-Syndrom.


- $\text{kras}^{G12D}/\text{Trp53}^{R172H}$ transgenic animal

- 90% of those animals die of pancreatic cancer
- Median survival app. 5 months

Tuveson AD et al Cancer Cell 2005; 7: 469
Pancreatic cancer is best studied for genetic alterations (somatic mutations) of all cancers.

Detection of these genetic lesions are so far of no diagnostic or prognostic value.

Studying transgenic animal models will help us to understand the tumorigenesis in pancreatic cancer.