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Genetic abnormalities in pancreatic cancer

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Abstract

The incidence and mortality of pancreatic adenocarcinoma are nearly coincident having a five-year survival of less than 5%. Enormous advances have been made in our knowledge of the molecular alterations commonly present in ductal cancer and other pancreatic malignancies. One significant outcome of these studies is the recognition that common ductal cancers have a distinct molecular fingerprint compared to other nonductal or endocrine tumors. Ductal carcinomas typically show alteration of K-*ras*, *p53*, $p16^{INK4}$, *DPC4* and *FHIT*, while other pancreatic tumor types show different aberrations. Among those tumors arising from the exocrine pancreas, only ampullary cancers have a molecular fingerprint that may involve some of the same genes most frequently altered in common ductal cancers. Significant molecular heterogeneity also exists among pancreatic endocrine tumors. Nonfunctioning pancreatic endocrine tumors have frequent mutations in *MEN-1* and may be further subdivided into two clinically relevant subgroups based on the amount of chromosomal alterations. The present review will provide a brief overview of the genetic alterations that have been identified in the various subgroups of pancreatic tumors. These results have important implications for the development of genetic screening tests, early diagnosis, and prognostic genetic markers.

Review

Pancreatic cancer incidence and mortality virtually coincide having a five-year survival of less than 5%. Surgical intervention is possible in only about 10% of cases and adjuvant therapies are virtually ineffective. An improved understanding of pancreas cancer genetics is the only means to provide new markers for early diagnosis and to identify potential targets for therapeutic intervention. Molecular analyses of pancreatic cancer have been hindered by the low cancer cellularity of this neoplasm, due to the characteristic host desmoplastic reaction. This has been overcome in large part to the application of various enrichment techniques such as xenografting, cryostat-enrichment, and laser capture microdissection of primary lesions. Consequently, enormous advances have recently been made in our knowledge of the molecular alterations in commonly present pancreatic ductal adenocarcinoma. Not unsurprisingly, as for other cancers, both activation of oncogenes and inactivation of tumor suppressor genes play key roles in pancreatic cancer.

Ductal adenocarcinoma is by far the most common pancreatic neoplasm, comprising around 90% of all pancreatic malignancies. However, other types of tumors arise from both the exocrine or endocrine cellular components. A dissection of the assortment of genetic anomalies has allowed for the important distinction at the molecular level that common ductal carcinoma has a distinct molecular fingerprint compared to other nonductal exocrine or endocrine tumors. Moreover, while endocrine tumors have

Table 1: Summary of Known Chromosomal/Gene Alterations in Pancreatic Tumors

	Chromosomal	Gene
Ductal	9p, 17p, 18q	K-*ras*, *p53*, *p16*, *DPC4*
Acinar	1p, 4q, 17p	*APC*/β-catenin
Serous Cystic	3p, 10q	*VHL*
Mucinous Cystic	undescribed	*p53*,*DPC4*
IPMT	undescribed	K-*ras*
Solid papillary	undescribed	β-catenin
Ampullary	undescribed	K-*ras*, *p53*, *p16*, *DPC4*
NF-PET	6q, 11, 20q, 21	*MEN1*

been traditionally grouped together as a single class of neoplasms, significant molecular heterogeneity exists even among this broad faction of tumors. Accordingly, the present review will give a brief overview of the genetic alterations that have been identified in the various subgroups of pancreatic lesions. The known chromosomal/genetic alterations commonly present in pancreatic tumors are presented in Table 1.

Ductal adenocarcinoma

At present, the well-established molecular events that have been correlated with the pathogenesis of ductal neoplasms include activation of the K-*ras* oncogene in about 80% of cases and inactivation of the tumor suppressor genes $p16^{INK4a}$, *p53*, and *DPC4* in about virtually all, 60%, and 50% of primary cancers, respectively [1,2]. In addition, anomalies in *FHIT* gene expression have been shown in about half of cases [3]. The coexistent inactivation of *p16*, *p53*, and *DPC4* is also common [1,2]. Telomerase activity has been detected in up to 95% of cases and undetectable in benign tumors [4].

The inactivation of additional genes has been implicated in pancreatic cancer albeit at lower frequencies. These include *MKK4*, part of a stress-response signaling pathway, in 4% of cases; a *TGF-beta receptor* in 1% of cases;*BRCA2* in nearly 7% and LKB1/STK11 in about 5% of cases [5–9]. Microsatellite instability of the type associated with mutation of DNA repair genes has been observed in a small proportion of ductal cancers and has been associated with an improved prognosis [10,11]. Microsatellite instability has also been found in a limited number of the rare medullary carcinoma [12].

The knowledge of gene alterations involved in transformation has also allowed for the identification and classification of morphological precursor lesions (PanIN), which has permitted the construction of a model for disease progression [13]. Whereas mutation of K-*ras* and overexpression of *Her2/neu* are initial events, alteration of *p16* has been associated with progression of malignancy. It is also apparent that mutation of *p53* and *DPC4* are events that occur relatively late in the transformation process [14,15]. These are not trivial points as a model of genetic progression forms the basis of our understanding of cancer transformation and progression of malignancy. Telomere shortening has also been recently observed to be a frequent event in PanINs, which is highly suggestive that this genetic event plays an early role in neoplastic progression [16]. The fact that p16 is also methylated in PanINs gives further support to this idea [17,18]. Such a model has important implications for the development of genetic screening tests, early diagnosis, prognostic genetic markers and chemoprevention.

It is becoming increasingly apparent that the role of DNA methylation has in pancreatic cancer. About 50% of all human genes have 5' CpG islands, which are typically associated with the 5' regulatory regions of genes. Methylation at these 5' CpG islands generally inactivates gene expression, while demethylation has the opposite effect. While part of normal developmental and aging processes, when deregulated, these events may also inactivate tumor suppressor genes or activate otherwise silenced genes. Promoter methylation is implicated in the transcriptional silencing of several tumor suppressor and mismatch repair genes (*e.g.*, *p16*, *Rb*, *VHL*, *hMLH1*) in many cancers. In pancreatic cancer, de novo methylation of a number of genes has been reported [19]. Among these, *ppENK*, a gene with known growth suppressive properties, has been associated with transcriptional silencing in over 90% of cases [20]. Larger pancreatic cancers and those from older patients possessed more methylated loci compared to smaller tumors and those from younger patients. The identification of larger numbers of genes controlled by methylation has been undertaken and should provide a larger number of genetic targets, which will be invaluable for diagnosis, prognosis, and therapy [19,20].

The quantitative and comprehensive analysis of cellular gene expression profiles has been performed using serial analysis of gene expression (SAGE) and DNA microarrays.

These expression profiling studies and SAGE studies have already allowed for the identification of several candidate genes which may be useful as potential diagnostic/prognostic markers as well as therapeutic targets [21–31]. Nonetheless, these studies are far from complete and are just beginning to unravel the enormous complexities that underlie pancreatic cancer.

One hallmark of pancreatic ductal cancers is the characteristic host desmoplastic reaction that has hindered genetic studies on this neoplasm. Several reports have examined in detail this interaction. Recently, the stromal reaction has been investigated by DNA array analysis using normal pancreas, bulk pancreatic tumor tissues and pancreatic tumor aspirates that contain more than 95% tumor cells. In fact, fine needle aspiration of cancer provides a fast and efficient way of obtaining samples highly enriched in tumor cells with sufficient yields of RNA. Altered expression of genes not previously associated with pancreatic adenocarcinoma was found, including rac1, GLG1, NEDD5, RPL-13a, RPS9 and members of the Wnt5A gene family [25].

Little is known about the genetic factors responsible for familial pancreatic cancer, although familial aggregation and genetic susceptibility may play a role in as many as 10% of pancreatic ductal adenocarcinomas. Germline mutations have been reported in *BRCA2* and *p16*, although these account for only a fraction of cases [32–34].

Other tumors arising from the exocrine pancreas

Less is known about the molecular abnormalities in the more rare epithelial neoplasms of the exocrine pancreas. This heterogeneous group of neoplasms includes tumor entities with distinct clinicopathologic and prognostic features that comprise the acinar cell carcinomas, the serous cystic tumors, mucinous cystic tumors, intraductal papillary-mucinous tumors, the solid-pseudopapillary tumors, and ampullary cancers. In general, the available data suggests that these neoplasms have molecular pathogenetic pathways that are different from those occurring in common pancreatic adenocarcinoma.

Acinar cancers

In these neoplasms, mutations in K-*ras* are exceedingly rare and *p53* mutations have not been found [2,35]. Likewise, alterations in *p16* or *DPC4* are absent [2]. A recently performed genome wide allelotyping of these tumors has shown a high degree of allelic loss [36]. Chromosomes 1p, 4q, and 17p show LOH in >70% of cases and chromosomes 11q, 13q, 15q, and 16q show allelic loss in 60–70% of cases. The resulting allelotype of acinar carcinoma is markedly different from that of either ductal or endocrine tumors of the pancreas and the involvement of chromosome 4q and 16q seems characteristic of this tumor type. Interestingly, alterations in the APC/β-catenin pathway have been found in 4 of 17 cases of acinar carcinoma studied [37].

Serous cystic tumors

These lesions may present as sporadic forms or in association with von Hippel Lindau syndrome. A molecular characterization of these tumors consisting in genome-wide allelic loss analysis, assessment of microsatellite instability, and mutational analysis of the *VHL*, K-*ras* and *p53* genes has been recently reported [38]. While no case showed microsatellite instability, a relatively low fractional allelic loss of 0.08 was found. The allelotype demonstrated that losses on chromosome 10q were the most frequent event, observed in about 50% of cases, followed by allelic losses on chromosome 3p, found in almost 40% of cases. The *VHL* gene was found to possess somatic inactivating mutations in two of nine (22%) cases analyzed, while no mutations were found in either K-*ras* or *p53*. Thus, involvement of chromosome 10q is characteristic of serous cystic tumors and the *VHL* gene is involved in a subset of sporadic cases.

Mucinous cystic tumors

K-*ras* mutations have been reported in a variable proportions among mucinous cystic tumors. The expression of p53 and Dpc4 has been reported as frequently altered and is likely to be related to progression in this malignancy [39,40].

Intraductal papillary-mucinous tumors

To date, K-*ras* mutations have been found in intraductal papillary-mucinous tumors (IPMT) at varying frequency, while no alterations of *p16*, *p53* or *DPC4* have been found [2,41]. There is also a low frequency of LOH found on chromosomal arms 9p, 17p, and 18q further substantiating the supposition that these are entities separate from ductal cancers. IPMT have also been recently studied by cDNA microarray analysis, which led to the observation that several genes are differentially expressed both in IPMTs and pancreatic carcinomas. This suggests that they may be involved at an early stage of pancreatic carcinogenesis [42].

Solid-pseudopapillary tumors

These neoplasms are generally low-grade malignancies primarily affecting girls and young women and characteristically show progesterone receptor immunostaining [39]. Neither alterations in *ras*-family genes, p53 gene/protein, *p16, or DPC4* have been found. Similarly, allelic losses on chromosomal arms 9p, 17p, or 18q have not been detected in these tumors [2]. Immunohistochemistry showed positive staining for Dpc4, as expected from microsatellite analysis [2]. Recently, it has been shown that the vast majority of cases harbor mutations in β-catenin [43,44].

Ampullary cancers

Compared with other exocrine pancreatic tumors, only ampullary cancers have a molecular fingerprint that may involve some of the same genes most frequently altered in common ductal cancers. In fact, alterations have been found in K-*ras*, *p53*, *p16*, and *DPC4*, with *p53* inactivation being the most frequent event (60%) [45]. K-*ras* mutations are seen in about one-half of cases [46,47]. Inactivation of *DPC4* was found in about 50% of cases as shown by negative staining for the protein by immunohistochemistry [2]. There is however, no correlation between the lack of expression of Dpc4 and survival [48]. However, allelic losses on chromosomal arm 17p (63%) have been previously found to be an independent prognostic factor among ampullary cancers at the same stage [49]. Taken together, this data reinforces the hypothesis that ductal tumors and ampullary cancers share common molecular pathways related to tumorigenesis and, possibly, progression of malignancy. Mutations in the *APC* gene have also been found in a proportion of these cancers [50]. Unlike ductal carcinoma however, about 10% of ampullary tumors show microsatellite instability, a feature that significantly correlates with increased survival [51].

Pancreatic endocrine tumors

Much progress has been made in the understanding of pancreatic endocrine tumors (PETs). Nonfunctioning (NF) PETs do not lead to clinical symptoms due to hormonal hypersecretion by the neoplasm, while functioning PETs are in fact a heterogeneous group of malignancies that give rise to clinical symptoms due to hormonal hypersecretion by the neoplasm. To date, nine distinct functional PETs have been designated, although detailed molecular studies of these neoplasms are lacking, in contrast to NF-PETs.

In reality, the elucidation of the molecular events involved in PET carcinogenesis has in part been hindered by the fact that these neoplasms have been considered a single disease entity. The emergence of novel molecular characterization strategies has made it apparent however that these lesions exhibit diverse molecular fingerprints (see [52] for review). Studies involving the genes most frequently altered in exocrine pancreatic tumors (i.e., *p53*, K-*ras*, *p16* and *DPC4*) have confirmed that PETs arise from distinctly different molecular pathways and are unrelated to ductal cancers [2]. Mutations in K-*ras* and *p53* are extremely rare and *p16* and *DPC4* alterations are virtually absent [2,53]. The rare involvement of Dpc4 in either primary or metastatic PETs has also been confirmed by immunohistochemistry [54], but reinforces the fact that these tumors have pathogenetic pathways distinct from ductal adenocarcinoma.

To date, mutation of *MEN-1* is the most common genetic alteration found in PETs, but with markedly different frequencies among insulinomas (7%), other functioning PETs (44–67%) NF-PETs (27%), giving the first genetic clue that PETs might be divided into the three above-mentioned subgroups (see [55]). The fact that mutations in *MEN-1* are found in NF-PETs is not surprising when considering that NF-PETs are fairly common in MEN1 patients. Mutations in *VHL* are extremely rare in sporadic PETs [55,56].

A recent high resolution allelotype for NF-PET has suggested the existence of two subgroups: those showing frequent, large allelic deletions and those showing a small number of random losses, designated high or low FAL, respectively [57]. Chromosomes 6q and 11, 20q, and 21 show frequent LOH. The allelotype of NF-PET is moreover markedly different from that of ductal, acinar, or serous tumors of the pancreas as well as from that of functional PETs [57–61]. Moreover, the two genetic phenotypes also show correlation with ploidy status: high-FAL tumors are aneuploid, while low-FAL neoplasms are diploid. When utilized in conjunction with the Ki-67 cellular proliferation index, ploidy status provides powerful, independent statistically significant information that predicts long-term survival, even among metastatic cases [57]. It is likely that the eventual separation of PETs into distinct clinical and pathological groups will facilitate an even more precise delineation of PET prognosis, histopathology, and carcinogenesis.

More recently, the study of sex chromosome abnormalities in PETs by both microsatellite and FISH analysis identified different frequencies of loss and gain of sex chromosomes in female and male cases [62]. The loss of a sex chromosome significantly correlated with the presence of local invasion, metastasis, and higher proliferation status. Moreover, sex chromosome loss is significantly associated with poor survival and increases the risk of death by approximately two-fold [62].

Conclusion

The demonstration and realization that ductal adenocarcinoma has a distinct molecular fingerprint compared to other nonductal or endocrine tumors has important implications for the development of desperately needed genetic screening tests, as well as for markers for early diagnosis and prognosis. Unfortunately, the results of genetic studies have not yet been translated into significant clinical applications that show either diagnostic or therapeutic benefit for patients with pancreatic malignancies. Much promise is held for the use of new technologies such as expression profiling and proteome analysis.

Authors' contributions

PSM drafted the parts regarding ductal and ampullary cancers, SB drafted the part regarding the exocrine nonductal cancers, GZ drafted the part on endocrine neoplasms and AS finalized the manuscript.

All authors read and approved the final manuscript.

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References

1. Rozenblum E, Schutte M, Goggins M, Hahn SA, Panzer S, Zahurak M, Goodman SN, Sohn TA, Hruban RH and Yeo CJ **Tumor-suppressive pathways in pancreatic carcinoma.** *Cancer Res* 1997, **57:**1731-4
2. Moore PS, Orlandini S, Zamboni G, Capelli P, Rigaud G, Falconi M, Bassi C, Lemoine NR and Scarpa A **Pancreatic tumours: molecular pathways implicated in ductal cancer are involved in ampullary but not in exocrine nonductal or endocrine tumorigenesis.** *Br J Cancer* 2001, **84:**253-62
3. Sorio C, Baron A, Orlandini S, Zamboni G, Pederzoli P, Huebner K and Scarpa A **The FHIT gene is expressed in pancreatic ductular cells and is altered in pancreatic cancers.** *Cancer Res* 1999, **59:**1308-1314
4. Hiyama E, Kodama T, Shinbara K, Iwao T, Itoh M, Hiyama K, Shay JW, Matsuura Y and Yokoyama T **Telomerase activity is detected in pancreatic cancer but not in benign tumors.** *Cancer Res* 1997, **57:**326-31
5. Villanueva A, Garcia C, Paules AB, Vicente M, Megias M, Reyes G, de Villalonga P, Agell N, Lluis F and Bachs O **Disruption of the antiproliferative TGF-beta signaling pathways in human pancreatic cancer cells.** *Oncogene* 1998, **17:**1969-78
6. Su GH, Hilgers W, Shekher MC, Tang DJ, Yeo CJ, Hruban RH and Kern SE **Alterations in pancreatic, biliary, and breast carcinomas support MKK4 as a genetically targeted tumor suppressor gene.** *Cancer Res* 1998, **58:**2339-42
7. Goggins M, Shekher M, Turnacioglu K, Yeo CJ, Hruban RH and Kern SE **Genetic alterations of the transforming growth factor beta receptor genes in pancreatic and biliary adenocarcinomas.** *Cancer Res* 1998, **58:**5329-32
8. Su GH, Hruban RH, Bansal RK, Bova GS, Tang DJ, Shekher MC, Westerman AM, Entius MM, Goggins M and Yeo CJ **Germline and somatic mutations of the STK11/LKB1 Peutz-Jeghers gene in pancreatic and biliary cancers.** *Am J Pathol* 1999, **154:**1835-40
9. Goggins M, Hruban RH and Kern SE **BRCA2 is inactivated late in the development of pancreatic intraepithelial neoplasia: evidence and implications.** *Am J Pathol* 2000, **156:**1767-71
10. Yamamoto H, Itoh F, Nakamura H, Fukushima H, Sasaki S, Perucho M and Imai K **Genetic and clinical features of human pancreatic ductal adenocarcinomas with widespread microsatellite instability.** *Cancer Res* 2001, **61:**3139-44
11. Nakata B, Wang YQ, Yashiro M, Nishioka N, Tanaka H, Ohira M, Ishikawa T, Nishino H and Hirakawa K **Prognostic value of microsatellite instability in resectable pancreatic cancer.** *Clin Cancer Res* 2002, **8:**2536-40
12. Wilentz RE, Goggins M, Redston M, Marcus VA, Adsay NV, Sohn TA, Kadkol SS, Yeo CJ, Choti M and Zahurak M **Genetic, immunohistochemical, and clinical features of medullary carcinoma of the pancreas: A newly described and characterized entity.** *Am J Pathol* 2000, **156:**1641-51
13. Hruban RH, Adsay NV, Albores-Saavedra J, Compton C, Garrett ES, Goodman SN, Kern SE, Klimstra DS, Kloppel G and Longnecker DS **Pancreatic intraepithelial neoplasia: a new nomenclature and classification system for pancreatic duct lesions.** *Am J Surg Pathol* 2001, **25:**579-86
14. Luttges J, Galehdari H, Brocker V, Schwarte-Waldhoff I, Henne-Bruns D, Kloppel G, Schmiegel W and Hahn SA **Allelic loss is often the first hit in the biallelic inactivation of the p53 and DPC4 genes during pancreatic carcinogenesis.** *Am J Pathol* 2001, **158:**1677-83
15. Klein WM, Hruban RH, Klein-Szanto AJ and Wilentz RE **Direct correlation between proliferative activity and dysplasia in pancreatic intraepithelial neoplasia (PanIN): additional evidence for a recently proposed model of progression.** *Mod Pathol* 2002, **15:**441-7
16. van Heek NT, Meeker AK, Kern SE, Yeo CJ, Lillemoe KD, Cameron JL, Offerhaus GLA, Hicks JL, Wilentz RE and G MG **Telomere shortening is nearly universal in pancreatic intraepithelial neoplasia.** *Am J Pathol* 2002, **161:**1541-1547
17. Fukushima N, Sato N, Ueki T, Rosty C, Walter KM, Wilentz RE, Yeo CJ, Hruban RH and Goggins M **Aberrant methylation of preproenkephalin and p16 genes in pancreatic intraepithelial neoplasia and pancreatic ductal adenocarcinoma.** *Am J Pathol* 2002, **160:**1573-81
18. Sato N, Ueki T, Fukushima N, Iacobuzio-Donahue CA, Yeo CJ, Cameron JL, Hruban RH and Goggins M **Aberrant methylation of CpG islands in intraductal papillary mucinous neoplasms of the pancreas.** *Gastroenterology* 2002, **123:**365-72
19. Ueki T, Toyota M, Sohn T, Yeo CJ, Issa JP, Hruban RH and Goggins M **Hypermethylation of multiple genes in pancreatic adenocarcinoma.** *Cancer Res* 2000, **60:**1835-9
20. Ueki T, Toyota M, Skinner H, Walter KM, Yeo CJ, Issa JP, Hruban RH and Goggins M **Identification and characterization of differentially methylated CpG islands in pancreatic carcinoma.** *Cancer Res* 2001, **61:**8540-6
21. Gress TM, Muller-Pillasch F, Geng M, Zimmerhackl F, Zehetner G, Friess H, Buchler M, Adler G and Lehrach H **A pancreatic cancer-specific expression profile.** *Oncogene* 1996, **13:**1819-30
22. Michl P, Buchholz M, Rolke M, Kunsch S, Lohr M, McClane B, Tsukita S, Leder G, Adler G and Gress TM **Claudin-4: a new target for pancreatic cancer treatment using Clostridium perfringens enterotoxin.** *Gastroenterology* 2001, **121:**678-84
23. Weber CK, Sommer G, Michl P, Fensterer H, Weimer M, Gansauge F, Leder G, Adler G and Gress TM **Biglycan is overexpressed in pancreatic cancer and induces G1-arrest in pancreatic cancer cell lines.** *Gastroenterology* 2001, **121:**657-67
24. Wallrapp C, Hahnel S, Muller-Pillasch F, Burghardt B, Iwamura T, Ruthenburger M, Lerch MM, Adler G and Gress TM **A novel transmembrane serine protease (TMPRSS3) overexpressed in pancreatic cancer.** *Cancer Res* 2000, **60:**2602-6
25. Crnogorac-Jurcevic T, Efthimiou E, Capelli P, Blaveri E, Baron A, Terris B, Jones M, Tyson K, Bassi C and Scarpa A **Gene expression profiles of pancreatic cancer and stromal desmoplasia.** *Oncogene* 2001, **20:**7437-46
26. Friess H, Ding J, Kleeff J, Liao Q, Berberat PO, Hammer J and Buchler MW **Identification of disease-specific genes in chronic pancreatitis using DNA array technology.** *Ann Surg* 2001, **234:**769-78
27. Argani P, Rosty C, Reiter RE, Wilentz RE, Murugesan SR, Leach SD, Ryu B, Skinner HG, Goggins M and Jaffee EM **Discovery of new markers of cancer through serial analysis of gene expression: prostate stem cell antigen is overexpressed in pancreatic adenocarcinoma.** *Cancer Res* 2001, **61:**4320-4
28. Argani P, Iacobuzio-Donahue C, Ryu B, Rosty C, Goggins M, Wilentz RE, Murugesan SR, Leach SD, Jaffee E and Yeo CJ **Mesothelin is overexpressed in the vast majority of ductal adenocarcinomas of the pancreas: identification of a new pancreatic cancer marker by serial analysis of gene expression (SAGE).** *Clin Cancer Res* 2001, **7:**3862-8
29. Ryu B, Jones J, Hollingsworth MA, Hruban RH and Kern SE **Invasion-specific genes in malignancy: serial analysis of gene expression comparisons of primary and passaged cancers.** *Cancer Res* 2001, **61:**1833-8
30. Rosty C, Ueki T, Argani P, Jansen M, Yeo CJ, Cameron JL, Hruban RH and Goggins M **Overexpression of S100A4 in Pancreatic Ductal Adenocarcinomas Is Associated with Poor Differentiation and DNA Hypomethylation.** *Am J Pathol* 2002, **160:**45-50
31. Crnogorac-Jurcevic T, Efthimiou E, Nielsen T, Loader J, Terris B, Stamp G, Baron A, Scarpa A and Lemoine NR **Expression profiling of microdissected pancreatic adenocarcinomas.** *Oncogene* 2002, **21:**4587-94

32. Murphy KM, Brune KA, Griffin C, Sollenberger JE, Petersen GM, Bansal R, Hruban RH and Kern SE **Evaluation of candidate genes MAP2K4, MADH4, ACVR1B, and BRCA2 in familial pancreatic cancer: deleterious BRCA2 mutations in 17%.** *Cancer Res* 2002, **62:**3789-93
33. Moore PS, Zamboni G, Falconi M, Bassi C and Scarpa A **A novel germline mutation, P48T, in the CDKN2A/p16 gene in a patient with pancreatic carcinoma.** *Hum Mutat* 2000, **16:**447-8
34. Goggins M, Kern SE, Offerhaus JA and Hruban RH **Progress in cancer genetics: lessons from pancreatic cancer.** *Ann Oncol* 1999, **10:**4-8
35. Pellegata N, Sessa F, Renault B, Bonato M, Leone B, Solcia E and Ranzani G **K-ras and p53 mutations in pancreatic cancer: ductal and non-ductal tumors progress through different genetic lesions.** *Cancer Res* 1994, **54:**1556-1560
36. Rigaud G, Moore P, Zamboni G, Taruscio D, Paradisi S, Falconi M, Klöppel G and Scarpa A **Allelotype of pancreatic acinar cell carcinoma.** *Int J Cancer* 2000, **88:**772-777
37. Abraham SC, Wu TT, Hruban RH, Lee JH, Yeo CJ, Conlon K, Brennan M, Cameron JL and Klimstra DS **Genetic and immunohistochemical analysis of pancreatic acinar cell carcinoma: frequent allelic loss on chromosome 11p and alterations in the APC/beta-catenin pathway.** *Am J Pathol* 2002, **160:**953-62
38. Moore P, Zamboni G, Brighenti A, Lissandrini D, Antonello D, Capelli P, Rigaud G, Falconi M and Scarpa A **Molecular characterization of pancreatic serous microcystic adenomas: evidence for a tumor suppressor gene on chromosome 10q.** *Am J Pathol* 2001, **158:**317-321
39. Zamboni G, Scarpa A, Bogina G, Iacono C, Bassi C, Talamini G, Sessa F, Capella C, Solcia E and Rickaert F **Mucinous cystic tumors of the pancreas: clinicopathological features, prognosis, and relationship to other mucinous cystic tumors.** *Am J Surg Pathol* 1999, **23:**410-22
40. Iacobuzio-Donahue CA, Wilentz RE, Argani P, Yeo CJ, Cameron JL, Kern SE and Hruban RH **Dpc4 protein in mucinous cystic neoplasms of the pancreas: frequent loss of expression in invasive carcinomas suggests a role in genetic progression.** *Am J Surg Pathol* 2000, **24:**1544-8
41. Sessa F, Solcia E, Capella C, Bonato M, Scarpa A, Zamboni G, Pellegata N, Ranzani G, Rickaert F and Klöppel G **Intraductal papillary-mucinous pancreatic tumors are phenotypically, genetically and behaviorally distinct growths. An analysis of tumor cell phenotype, K-ras and p53 genes' mutations.** *Virchows Archiv* 1994, **425:**357-367
42. Terris B, Blaveri E, Crnogorac-Jurcevic T, Jones M, Missiaglia E, Ruszniewski P, Sauvanet A and Lemoine NR **Characterization of gene expression profiles in intraductal papillary-mucinous tumors of the pancreas.** *Am J Pathol* 2002, **160:**1745-54
43. Tanaka Y, Kato K, Notohara K, Hojo H, Ijiri R, Miyake T, Nagahara N, Sasaki F, Kitagawa N and Nakatani Y **Frequent beta-catenin mutation and cytoplasmic/nuclear accumulation in pancreatic solid-pseudopapillary neoplasm.** *Cancer Res* 2001, **61:**8401-4
44. Abraham SC, Klimstra DS, Wilentz RE, Yeo CJ, Conlon K, Brennan M, Cameron JL, Wu TT and Hruban RH **Solid-pseudopapillary tumors of the pancreas are genetically distinct from pancreatic ductal adenocarcinomas and almost always harbor beta-catenin mutations.** *Am J Pathol* 2002, **160:**1361-9
45. Scarpa A, Capelli P, Zamboni G, Oda T, Mukai K, Bonetti F, Martignoni G, Iacono C, Serio G and Hirohashi S **Neoplasia of the ampulla of Vater: Ki-ras and p53 mutations.** *Am J Pathol* 1993, **142:**1163-1172
46. Scarpa A, Zamboni G, Achille A, Capelli P, Bogina G, Iacono C, Serio G and Accolla R **Ras-family gene mutations in neoplasia of the ampulla of Vater.** *Int J Cancer* 1994, **59:**39-42
47. Howe JR, Klimstra DS, Cordon-Cardo C, Paty PB, Park PY and Brennan MF **K-ras mutation in adenomas and carcinomas of the ampulla of vater.** *Clin Cancer Res* 1997, **3:**129-33
48. Beghelli S, Orlandini S, Moore PS, Talamini G, Capelli P, Zamboni G, Falconi M and Scarpa A **Ampulla of vater cancers: T-stage and histological subtype but not Dpc4 expression predict prognosis.** *Virchows Arch* 2002, **441:**19-24
49. Scarpa A, Di Pace C, Talamini G, Falconi M, Lemoine N, Iacono C, Achille A, Baron A and Zamboni G **Cancer of the ampulla of Vater: chromosome 17p allelic loss is associated with poor prognosis.** *Gut* 2000, **46:**842-848
50. Achille A, Scupoli M, Magalini A, Zamboni G, Romanelli M, Orlandini S, Biasi M, Lemoine N, Accolla R and Scarpa A **APC gene mutations and allelic losses in sporadic ampullary tumours: evidence of genetic difference from tumours associated with familial adenomatous polyposis.** *Int J Cancer* 1996, **68:**305-312
51. Achille A, Biasi MO, Zamboni G, Bogina G, Iacono C, Talamini G, Capella G and Scarpa A **Cancers of the papilla of Vater: mutator phenotype is associated with good prognosis.** *Clin Cancer Res* 1997, **3:**1841-1847
52. Gumbs AA, Moore PS, Falconi M, Bassi C, Beghelli S, Modlin I and Scarpa A **Review of the clinical, histological, and molecular aspects of pancreatic endocrine neoplasms.** *J Surg Oncol* 2002, **81:**45-53
53. Beghelli S, Pelosi G, Zamboni G, Falconi M, Iacono C, Bordi C and Scarpa A **Pancreatic endocrine tumours: evidence for a tumour suppressor pathogenesis and for a tumour suppressor gene on chromosome 17p.** *J Pathol* 1998, **186:**41-50
54. Scarpa A, Orlandini S, Moore P, Lemoine N, Beghelli S, Baron A, Falconi M and Zamboni G **Dpc-4 is expressed in virtually all primary and metastatic pancreatic endocrine tumors.** *Virchows Arch* 2002, **440:**155-159
55. Moore PS, Missiaglia E, Antonello D, Zamo A, Zamboni G, Corleto V, Falconi M and Scarpa A **Role of disease-causing genes in sporadic pancreatic endocrine tumors: MEN1 and VHL.** *Genes Chromosomes Cancer* 2001, **32:**177-81
56. Chung DC, Smith AP, Louis DN, Graeme-Cook F, Warshaw AL and Arnold A **A novel pancreatic endocrine tumor suppressor gene locus on chromosome 3p with clinical prognostic implications.** *J Clin Invest* 1997, **100:**404-10
57. Rigaud G, Missiaglia E, Moore PS, Zamboni G, Falconi M, Talamini G, Pesci A, Baron A, Lissandrini D and Rindi G **High resolution allelotype of nonfunctional pancreatic endocrine tumors: identification of two molecular subgroups with clinical implications.** *Cancer Res* 2001, **61:**285-92
58. Hahn SA, Seymour AB, Hoque AT, Schutte M, da Costa LT, Redston MS, Caldas C, Weinstein CL, Fischer A and Yeo CJ **Allelotype of pancreatic adenocarcinoma using xenograft enrichment.** *Cancer Res* 1995, **55:**4670-5
59. Rigaud G, Moore PS, Zamboni G, Orlandini S, Taruscio D, Paradisi S, Lemoine NR, Kloppel G and Scarpa A **Allelotype of pancreatic acinar cell carcinoma.** *Int J Cancer* 2000, **88:**772-7
60. Moore PS, Zamboni G, Brighenti A, Lissandrini D, Antonello D, Capelli P, Rigaud G, Falconi M and Scarpa A **Molecular characterization of pancreatic serous microcystic adenomas: evidence for a tumor suppressor gene on chromosome 10q.** *Am J Pathol* 2001, **158:**317-21
61. Chung DC, Brown SB, Graeme-Cook F, Tillotson LG, Warshaw AL, Jensen RT and Arnold A **Localization of putative tumor suppressor loci by genome-wide allelotyping in human pancreatic endocrine tumors.** *Cancer Res* 1998, **58:**3706-11
62. Missiaglia E, Moore PS, Williamson J, Lemoine NR, Falconi M, Zamboni G and Scarpa A **Sex chromosome anomalies in pancreatic endocrine tumors.** *Int J Cancer* 2002, **98:**532-8