Genome-Wide Allelotypes of Familial Pancreatic Adenocarcinomas and Familial and Sporadic Intraductal Papillary Mucinous Neoplasms

Tadayoshi Abe,1 Noriyoshi Fukushima,1 Kieran Brune,1 Corinne Boehm,4 Norihiro Sato,1 Hiroyuki Matsubayashi,1 Marcia Canto,3 Gloria M. Petersen,5 Ralph H. Hruban,1, 2 and Michael Goggins1, 2, 3

Abstract

Purpose: Most familial cancer susceptibility genes are tumor suppressor genes that are biallelically inactivated in familial neoplasms through somatic deletion of the wild-type allele. Identifying the genomic losses that occur in pancreatic neoplasms, particularly those that occur in familial and precursor neoplasms, may help localize the genes responsible for pancreatic cancer susceptibility.

Experimental Design: Normal and neoplastic tissue DNA was isolated from fresh-frozen surgically resected tissues from 20 patients with primary familial pancreatic adenocarcinoma (defined as having at least one first-degree relative with pancreatic cancer), 31 with sporadic intraductal papillary mucinous neoplasms (IPMN), and 7 with familial IPMNs using laser capture microdissection. Microdissected DNA was whole genome amplified using multiple strand displacement. Genome-wide allelotypes were determined using 391 microsatellite markers. The accuracy of microdissection and fidelity of the whole genome amplification were determined by comparing the genotypes of microdissected primary pancreatic cancers to the genotypes of xenografts derived from these cancers and by comparing the results of amplified to nonamplified specimens.

Results: The concordance of genotypes between LCM whole genome amplified primary pancreatic cancers and their corresponding pancreatic cancer xenograft DNAs was 98%. Among the 20 primary familial pancreatic adenocarcinomas, we found a high prevalence of loss of heterozygosity (LOH) with an average fractional allelic loss (FAL) of 49.9% of an aggregate of 2,378 informative markers. The level of FAL in the IPMNs (10%) was significantly lower than in the pancreatic adenocarcinomas. The most common locus of LOH in the IPMNs was at 19p (LOH at 24% of markers). The regions of frequent allelic loss observed in the familial pancreatic cancers were similar to those found in sporadic pancreatic cancers.

Conclusions: The allelic loss patterns of familial and sporadic pancreatic cancers and IPMNs provide clues as to the genomic locations of tumor suppressor genes inactivated in these neoplasms.

It is estimated that 10% to 20% of patients that develop pancreatic ductal adenocarcinoma have a familial predisposition to their disease (1). By convention, familial pancreatic cancer is defined as a family having at least two first-degree relatives with pancreatic cancer that does not fulfill the criteria of another hereditary cancer syndrome (2). Healthy individuals from families with familial pancreatic cancer are at an increased risk of developing pancreatic cancer, and their risk rises with the increasing number of affected relatives (3). Known genetic factors, including germ line mutations in the BRCA2, p16/CDKN2A, PRSS1, STK11, hMLH1, and FANCC genes explain only a portion (<20%) of this familial clustering (4–11), making it likely that additional genes that increase a person’s risk of developing pancreatic cancer remain to be discovered. Recently, Brentnall et al. have identified a germ line mutation in the PALLD gene on chromosome 4q32-34 in Family X, a family with an unusual phenotype of early-onset pancreatic insufficiency, diabetes mellitus, and familial pancreatic cancer typically before age 40 (12). This locus does not seem to be a site of linkage in most pancreatic cancer families (13, 14), although additional mutational studies of PALLD in other kindreds are awaited (15).

The National Familial Pancreas Tumor Registry was established at the Johns Hopkins University in 1994. Detailed segregation analysis of 287 families enrolled in this registry suggested the existence of a rare dominant gene that increases...
the risk of pancreatic cancer (16). However, the identification of the gene or genes responsible for familial pancreatic cancer susceptibility has been elusive in large part because DNA for genetic studies such as linkage analysis is unavailable from most affected individuals in pancreatic cancer families due to the rapidly lethal nature of this cancer (2).

Neoplasms obtained from patients with familial pancreatic cancer are a unique resource for the study of familial pancreatic cancer (17). Analyses of these neoplasms may not only help localize genomic loci likely to contain tumor suppressor genes, they may also facilitate the design of diagnostic assays that detect allelic losses in clinical samples (18–21). Although the patterns of allelic loss have been well characterized for sporadic pancreatic cancers (22), such information is not available for familial pancreatic cancers or familial or sporadic intraductal papillary mucinous neoplasms (IPMN). That neoplasms from familial pancreatic cancer kindreds have not been subject to extensive genetic analysis reflects the fact that it is difficult to obtain sufficient neoplastic tissue from large numbers of patients with familial pancreatic neoplasms. Indeed, because only ~5% to 10% of patients have a family history of pancreatic cancer and only ~20% of patients with pancreatic ductal adenocarcinoma currently undergo surgical resection (23) only ~1% to 2% of all patients that undergo a surgical resection for pancreatic cancer have a familial form of the disease. For a large-volume, tertiary referral center performing 100 pancreatic cancer resections, this would be 1 to 2 cases a year. Interestingly, patients with familial pancreatic neoplasia may be predisposed to developing IPMNs based on the results of screening studies of this risk group (24, 25). However, this observation may reflect an ascertainment bias because these screenings lead to the detection and treatment of IPMNs. There are no population-based epidemiologic studies of the prevalence of IPMNs in patients with a family history of pancreatic cancer.

Stromal contamination and small samples are significant challenges when studying any pancreatic neoplasm (26). Careful laser capture microdissection (LCM) of neoplastic cells can prevent contamination by the abundant stromal reaction associated with the infiltrating cancer cells, and whole genome amplification (WGA) techniques can accurately copy small starting amounts of DNA, thereby enabling the detailed analysis of DNA available from LCM tissues (27). Isothermal WGA using the strand-displacing ø29 polymerase has been developed and successfully applied to amplify small amounts of DNA. This method, also termed “whole genome multiple strand displacement amplification,” provides a highly accurate representation of genomes and typically yields amplifications of >1,000-fold (28). In this study, we have used ø29 polymerase–based isothermal WGA to amplify DNA from LCM tissues to obtain genome-wide allelotypes of familial and sporadic pancreatic adenocarcinomas and IPMNs.

Materials and Methods

**Patients and samples.** Fresh frozen neoplastic tissue was obtained from 20 patients with primary familial pancreatic cancer, 5 with primary sporadic pancreatic cancer, and 11 independent neoplasms from 7 patients with familial pancreatic IPMN, and 33 pancreatic IPMNs from 31 patients with a sporadic IPMN who had undergone surgical resection of their neoplasms at the Johns Hopkins Hospital (Baltimore, MD) and the Mayo Clinic (Rochester, MN) between 1994 and 2004. The inherited genetic basis for the pancreatic cancer susceptibility in the 27 patients with familial pancreatic neoplasms was not known. For this study, we did not want to characterize allelotypes of patients with a known genetic predisposition. Patients with pancreatic cancer were defined as familial if they reported at least one first-degree relative with pancreatic cancer. Patients with familial IPMN were defined as individuals with an IPMN and a family history of either pancreatic cancer or an IPMN. We chose this definition of familial IPMN, i.e., one that did not require affected individuals to have a first-degree relative with pancreatic cancer or an IPMN because IPMN is a rarer neoplasm than pancreatic cancer, and we believe that such a definition reflects an inherited predisposition to pancreatic neoplasia in the family. Of the seven subjects in this study with a familial IPMN, five had a first-degree, and two had a second-degree relative with pancreatic cancer. A total of 3 of the 11 familial IPMNs and 25 of 33 of the sporadic IPMNs had an associated infiltrating pancreatic adenocarcinoma. Among the 28 patients whose IPMNs had an associated infiltrating adenocarcinoma, in 26, the IPMN component had high-grade dysplasia (carcinoma in situ) and 2 had moderate dysplasia (borderline). Because the allelotypes of sporadic pancreatic ductal adenocarcinomas have been previously well characterized, only the IPMN component was microdissected and genotyped (22). Of the remaining familial IPMNs, two had moderate dysplasia (borderline), and five had low-grade dysplasia (IPMN adenoma). Of the remaining sporadic IPMNs, six had low-grade dysplasia, and two had moderate dysplasia. The histologic subtype of IPMNs analyzed included 20 intestinal type IPMNs, 15 pancreaticobiliary type, 2 mixed type, 1 gastric, and 6 that were not classified. The nine familial IPMNs that were classified were all of the intestinal type. As a way to determine the accuracy of genotypes obtained from microdissected tissues, five sporadic infiltrating ductal adenocarcinomas of the pancreas were included for analysis, and their genotypes were compared with the genotypes of pancreatic cancer xenografts that were derived from these corresponding primary cancers. These studies were done under Institutional Review Board–approved protocols.

**Laser capture microdissection.** Fresh-frozen samples were embedded in optimal controlled temperature (OCT) media; 8-µm-thick sections were cut in a cryostat at -20°C and mounted on glass slides. Every second section was stained with H&E and covered with a glass coverslip for diagnostic purposes. Tissue section slides that underwent LCM were fixed with 75% ethanol for 30 s, rinsed in distilled water for 30 s, and stained in HistoGene Staining Solution (Arcturus Engineering Inc.) for 20 s. After rinsing with distilled water for 30 s, the slide was treated with 75% ethanol for 30 s, 95% ethanol for 30 min, 100% ethanol for 3 min, and xylene for 5 min and allowed to air dry for 5 min. The stained slides were microdissected within 2 h using the Pincell II LCM system (Arcturus Engineering Inc.) using the CapSure HS LCM Caps (Arcturus Engineering Inc.). For those IPMNs that had an associated infiltrating pancreatic ductal adenocarcinoma, only the IPMN component was microdissected for LOH analysis. Approximately 2,000 to 5,000 cells were microdissected per lesion from one or more slides.

**DNA isolation.** DNA was isolated from the LCM tissues, as well as normal pancreas, duodenal or lymphocyte tissues using the DNaseasy Tissue Kit (Qiagen). One of the neoplasms from a patient with familial pancreatic cancer was cultured as a xenograft, and this xenograft was used as a source of DNA. As described above, DNA was also available from xenografts of five other surgically resected sporadic pancreatic cancers (29). Frozen tissue from the five primary pancreatic cancers that was used to create these pancreatic cancer xenografts was microdissected to compare the genotypes of microdissected whole genome amplified primary pancreatic cancers to their corresponding xenografts. We also compared genotypes obtained from microdissected frozen normal pancreatic tissue from five individuals and lymphocyte DNA from five individuals to whole genome amplified DNA from these tissue sources.

**Whole genome amplification.** WGA was done using the GenomiPhi WGA kit (Amersham, Inc.) according to kit instructions. About 1 µL of
DNA solution from LCM cells was added to 9 µl of sample buffer, heated at 95°C for 3 min, and then cooled on ice for 5 min. Approximately 10 µl of reaction mix (9 µl of reaction buffer plus 1 µl of α-29 polymerase) was added, and the resulting samples were incubated at 30°C for 16 h. After heat inactivation at 65°C for 10 min, each sample was purified by alcohol precipitation according to the manufacturer’s protocol, and its DNA concentration was measured by spectrophotometry. Typically, 4 to 7 µg of amplified DNA product was obtained from a 20-µl reaction mixture. Amplified DNA products were diluted to 20 ng/µl for microsatellite analysis.

Microsatellite DNA analysis. Microsatellite DNA analysis was done using a panel of 391 microsatellite DNA markers that span the human genome (average spacing 10 cM; Center for Inherited Disease Research (CIDR) Fall 2004 panel). Further information about the microsatellite DNA markers is available from the CIDR. Microsatellite PCRs were done using 40 ng of genomic DNA in a final reaction volume of 5 µl. Forward primers were labeled with fluorescent dyes FAM and HEX (obtained from Life Technologies, Inc.) and NED (obtained from Applied Biosystems). PCR products were electrophoresed at CIDR (obtained from Life Technologies, Inc.) and NED (obtained from Applied Biosystems). PCR products were electrophoresed at CIDR using an ABI 3730 DNA analyzer. Reverse primers were obtained from MWG. ABI Genescan software was used for image analysis of each gel containing fluorescence-labeled PCR products. Each marker was reviewed for quality and marker size, and the size of each allele as defined by the area of the peak. The ratio of the size of the tumor to normal alleles was determined for each marker. Because laser capture microdissected DNA was likely to be almost pure with respect to neoplastic cellularity, we defined loss of heterozygosity (LOH) as ≥75% loss of the size of one allele in the neoplastic DNA compared with corresponding normal DNA.

Statistical analysis. Statistical analysis was done using the Stat View 5.0 statistical software package (SAS Institute Inc.). Unpaired t tests were used to test differences of genomic fractional allelic loss (FAL) in pancreatic neoplasms between pancreatic cancers and IPMNs. A P value of <0.05 was considered statistically significant.

FAL was defined as the number of markers with LOH divided by all informative markers/neoplasm in aggregate. For each chromosomal arm, we also determined allelic loss as the number of markers with LOH divided by number of informative loci on each chromosomal arm.

Results

Reliability of whole genome amplified laser capture microdissected DNA. To assess the accuracy of genotypes from whole genome amplified laser capture microdissected DNA, we analyzed DNA from five individuals, comparing the genotypes of DNA from lymphocytes and frozen normal tissues to the genotypes of DNA from these tissues after WGA. The microsatellite marker concordance rate among the informative paired whole genome amplified and unamplified samples was 98% (Table 1). We also compared genotypes of five primary sporadic pancreatic cancers to the genotypes of their corresponding pancreatic cancer xenografts that were generated from these primary cancers (Fig. 1A). Concordance between the informative markers for primary pancreatic cancers and their pancreatic cancer xenograft was 99%. Xenografting pancreatic cancers for genetic analysis is known to be an excellent way to provide large amounts of cancer DNA for analysis and to remove the problem of contaminating stromal cells when analyzing pancreatic cancer cells for mutations. These results show that primary pancreatic cancers and pancreatic cancer xenografts are almost identical genetically. With large-scale genetic analysis of cancer genomes becoming a reality, there is a need for abundant and reliable sources of pure cancer DNA. Our results show that xenografted cancers are an appropriate source of DNA for such genetic profiling.

Table 1. Concordance of microsatellite markers before and after WGA

<table>
<thead>
<tr>
<th></th>
<th>Matching heterozygote alleles</th>
<th>Loss of an allele</th>
<th>Matching homozygous alleles</th>
<th>Discordant alleles</th>
<th>Concordance rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal pancreatic tissue (n = 5)</td>
<td>312</td>
<td>13</td>
<td>167</td>
<td>8</td>
<td>96.0</td>
</tr>
<tr>
<td>Xenograft (n = 5)</td>
<td>294</td>
<td>2</td>
<td>261</td>
<td>9</td>
<td>99.3</td>
</tr>
<tr>
<td>Normal lymphocyte (n = 5)</td>
<td>484</td>
<td>0</td>
<td>164</td>
<td>1</td>
<td>100</td>
</tr>
</tbody>
</table>

NOTE: Overall concordance rate of 98.5%.

Allelotypes of familial pancreatic cancers and familial and sporadic IPMNs. We used a genome-wide panel of 391 microsatellite DNA markers to analyze the tumor and normal genotypes of 20 patients with familial pancreatic cancer (10 males; mean age, 67 years; range, 45-83 years), 7 patients with 11 familial IPMNs (5 males; mean age, 70 years; range, 48-82 years), and 31 patients with 33 sporadic IPMNs (15 males; mean age, 68 years; range, 31-83 years). Figure 1 illustrates examples of genotypes with LOH detected in microdissected primary pancreatic cancer samples before versus after WGA and in their corresponding pancreatic cancer xenograft DNA.

Among the 20 familial pancreatic cancers, LOH was found in 1,291 out of 2,587 aggregate informative markers. A total of 4 of the 20 FPCs yielded limited genotyping information (genotypes obtained from <100 of the microsatellite markers in the panel). The overall FAL of the familial pancreatic cancers was 49.9% of informative markers (Fig. 2). This is similar to the percentage of FAL reported recently in pancreatic cancer cell lines using oligonucleotide arrays (43.2%; ref. 30), but higher than the 25.4% mean allelic loss previously reported in a study of 82 sporadic pancreatic cancer xenografts (22). Among the familial pancreatic cancers, the FAL ranged widely from 89.2% to 13.0%. There was no relationship between FAL and histologic grade. The chromosomal arms with loci showing the highest levels of allelic loss in the familial pancreatic cancers were 19p (67% of informative markers), 17p (65%), 7q (61%), Xp (61%), 18q (59%), 2p (58%), 5p (58%), 6q (58%), 9p (56%), 15q (57%), 4q (56%), and 1p (54%; Fig. 2). For comparison, the previously reported chromosomal loci with high levels of allelic losses among sporadic pancreatic cancers...
were in descending order: 9p (~88%), 17p (82%), 18q (82%), 6q (57%), 8p (53%), 21p (50%), 21q (50%), 3p (45%), 17q (50%), 18p (45%), 22q (45%), Xp (40%), 6p (40%), 19p (35%), and 1p (~35%; ref. 22). Other regions of loss on chromosomal arms in sporadic pancreatic cancers include 4q (28%) and 2p (10%; ref. 22). The familial pancreatic cancers seemed to have higher levels of LOH compared with sporadic pancreatic cancers at most chromosomal arms, but particularly of certain chromosomal arms such as 2p and 19p.

Allelic loss was much less common in the familial IPMNs than in the invasive familial pancreatic cancers, with an average FAL of 9.5% ($P < 0.0001$). Similarly, the FAL among the sporadic IPMNs was 11% ($P < 0.0001$ compared with FPCs). The range of FAL in the IPMNs varied from 0% to 52%. There was no relationship between an IPMN’s histologic grade and its level of FAL.

Among the familial IPMNs, allelic loss was found in 24% of the informative markers on 19p, 19% on 17p, 17% on 8p, 16% on 6p, 16% on 17q, and 16% on 22q (Fig. 3). Among the sporadic IPMNs, the highest level of allelic loss was found at Xp (27%), 19p (23%), 10q (16%) 17p (15%), 12p (15%) 6p (15%), and 20q (15%; Fig. 4). In the combined group of sporadic and familial IPMNs, 19p had the highest level of LOH (24%). There were no significant differences identified in the patterns of allelic loss patterns between the familial and sporadic IPMNs, although our sample size limited such comparisons. Most of the allelic losses identified in IPMNs involved isolated microsatellite markers rather than extensive regions of LOH. We examined IPMNs at chromosomal loci known to harbor tumor suppressor genes commonly targeted for losses in pancreatic ductal adenocarcinomas. A total of 24% of the IPMNs with informative markers at the $TP53$ locus showed allelic loss of one or more adjacent markers. For $p16/CDKN2a$, the corresponding figure was 18%, and for $SMAD4$, it was 22%. Other chromosomal regions with allelic losses of consecutive adjacent markers in IPMNs included 19p (D19S591-D19S586; 21% of informative markers), 6q (D6S494-1009; 21%), and 2p (D2S1400-1360; 21%).

Because the $PALLD$ locus on 4q32 is the only genomic region thus far proposed as a familial pancreatic cancer susceptibility
locus, we examined LOH at this locus in our neoplasms. The hCDC4 tumor suppressor gene is also located in this region and is inactivated in a small percentage of pancreatic cancers (31). A total of 47% of the tumors from patients with familial pancreatic cancer, 30% from patients with familial IPMN, and 12% from patients with sporadic IPMN with informative markers showed LOH of at least one of the markers in this region (12). Of note, the mutated PALLD gene reported by Brentnall et al. was reported to have oncogenic functions. Other regions of interest included the CDKN1C locus, which showed LOH in four of nine (44%) familial pancreatic cancers with informative markers at this locus, but not in any of the IPMNs.

Discussion

We report the genome-wide allelic loss patterns of familial pancreatic adenocarcinomas and familial and sporadic IPMNs. Overall, we find that familial pancreatic cancers usually display high levels of chromosomal losses with an average FAL of 49.9%. Previous studies have reported that the average FAL in sporadic pancreatic adenocarcinomas ranged from 25% to 43% (22, 30). We also find that the chromosomal arms targeted for loss in familial pancreatic adenocarcinomas correspond closely to those of sporadic pancreatic adenocarcinomas. For example, we find a high prevalence of LOH in familial pancreatic adenocarcinomas at the loci of tumor suppressor genes commonly inactivated in sporadic pancreatic adenocarcinomas, such as p16/CDKN2A, TP53, and SMAD4 (22, 30).

An important potential benefit of knowing the patterns of chromosomal loss in familial neoplasms is that when integrated together with linkage information of pancreatic cancer families, they could be helpful in localizing familial cancer susceptibility genes. Investigators searching for the MEN1 gene examined the patterns of chromosomal loss in multiple MEN1-associated neoplasms within a previously identified linkage region to narrow the genomic region that contained the MEN1 gene (17). Similarly, chromosomal loss patterns of sporadic pancreatic adenocarcinomas have also been used to help prioritize candidate genes for genetic analysis, and this approach has helped identify many of the genes known to be somatically mutated in pancreatic cancer (9, 31 – 34).

One of the big challenges in analyses of infiltrating pancreatic adenocarcinomas is that they are genetically very complex. To overcome this problem, we also studied precursor neoplasms. Because precursor neoplasms have undergone much fewer genetic alterations than invasive carcinomas, the genetic alterations that do occur in precursor neoplasms may be more likely to occur at sites of tumor suppressor gene loci, particularly if the tumor suppressor gene has a gatekeeper function (35). In addition, early chromosomal loss events in precursor neoplasms may occur before chromosomal losses associated with genomic instability have had a chance to manifest. For example, precursor neoplasms such as adenomatous polyps of

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**Fig. 2.** Genome-wide allelic loss patterns in familial pancreatic cancers.

**Fig. 3.** Genome-wide allelic loss patterns in familial IPMNs.
the colon show low levels of LOH in their genomes, but the most common site of chromosomal loss is at the *APC* locus (36). We analyzed the chromosomal loss patterns of familial and sporadic IPMNs to understand better the earlier genetic alterations that arise in pancreatic neoplasms. IPMNs are a recognized precursor neoplasm to pancreatic ductal adenocarcinoma (37); they are large neoplasms and are therefore amenable to genetic analysis, and IPMNs are a frequently identified precursor neoplasm in patients with a family history of pancreatic cancer (24, 25). In this study, we identified several regions of frequent allelic loss in familial IPMNs. Among the IPMNs, the locus with the most allelic loss was chromosome 19p (24%). Although the IPMNs analyzed in this study had much less chromosomal loss than the infiltrating pancreatic adenocarcinomas, our results show that even low-grade IPMNs are characterized by multiple loci of loss. The fact that chromosomal loss occurs in IPMN neoplasms probably reflects the fact that genomic instability begins early in the neoplastic process. Indeed, as has been found for PanINs (38), telomere shortening occurs in some IPMNs and probably contributes to the development of genomic instability. Interestingly, the extent of allelic loss in IPMNs seems to be less than has been described in PanINs. Because of their small size, PanINs have not been extensively characterized for their allelic loss patterns, but Hahn et al. investigating allelic losses at the loci of *p16/CDKN2a*, *TP53*, and *SMAD4* found that the majority of PanIN-3 lesions have allelic loss at these loci (39). It is possible that regions of prevalent chromosomal loss in IPMNs are loci of undiscovered tumor suppressor genes. For example, the chromosomal region with the highest level of LOH in the familial IPMNs was 19p (24%). 19p13.3 is the location of *STK11*, the gene for Peutz-Jeghers syndrome, but this gene is only mutated in a small fraction of sporadic pancreatic cancers and IPMNs (33, 40). In addition, other regions of frequent LOH in invasive pancreatic adenocarcinomas where tumor suppressor genes have not been identified such as 2p and 6q are regions where further investigation could be fruitful. Another target of chromosomal loss in the familial pancreatic cancers, although not in the IPMNs, was 11p15. This region contains the imprinted gene *CDKN1C/Ip57KIP2*. Mutations of *CDKN1C* are implicated in sporadic cancers and in the development of the Beckwith-Wiedemann syndrome (41). Because only one allele of an imprinted gene is expressed, one hit such as by chromosomal loss is sufficient to inactivate the gene. Indeed, we have previously shown that the *CDKN1C* gene is commonly down-regulated in pancreatic ductal neoplasms through a combination of promoter hypermethylation, histone deacetylation, and genetic loss of the paternal allele (42). LOH at *SMAD4* was found in 22% of IPMNs, but LOH alone is not sufficient to inactivate the gene, as evidenced by the fact that ~80% to 90% of pancreatic cancers show LOH at the *SMAD4* locus, but only ~50% have biallelic inactivation of *SMAD4*. For reasons that are not well understood, unlike advanced PanINs, based on immunohistochemical studies, IPMNs rarely completely inactivate *SMAD4* (43). Interestingly, we find that the chromosome 4q32 locus identified by Brentnall et al. as a locus of familial pancreatic cancer susceptibility (12) is a frequent site of chromosome loss in familial pancreatic neoplasms. Further studies are required to determine if mutations in these or other genes in the 4q32 region contribute to familial pancreatic cancer development.

Knowledge of the chromosomal loss patterns of noninvasive and invasive pancreatic neoplasms may also be useful in the design of diagnostic tests. For example, the detection of LOH in clinical biopsy samples is being evaluated as a way of differentiating malignant from nonmalignant pancreatic masses and neoplastic from non-neoplastic pancreatic cystic lesions (18–21). The markers that detect LOH in these studies represent a limited number of chromosomal regions and include chromosomal regions that are not frequent targets of LOH (such as 5q) either in pancreatic cancers or in IPMNs (22). Hopefully, our description of genome-wide allelic loss patterns in IPMNs will help in the selection of the markers most likely to be lost in these neoplasms.

In summary, we describe the chromosomal loss patterns of familial pancreatic adenocarcinomas and familial and sporadic IPMNs. This information may be helpful both for designing diagnostic tests to detect allelic loss in pancreatic samples and for identifying familial pancreatic cancer susceptibility genes in conjunction with other genetic studies of familial pancreatic cancer kindreds (2). The discovery of familial pancreatic cancer susceptibility genes will not only provide important information about the mechanisms of pancreatic tumorigenesis, it would also allow for the better identification of individuals who are most at risk of developing pancreatic cancer who can benefit from genetic counseling and pancreatic cancer screening (3, 24, 25, 44).
References

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