Table 19-3 Somatic Molecular Alterations in Invasive Pancreatic Adenocarcinoma

Gene	Chromosomal Region	Percentage of Carcinoma with Genetic Alteration	Gene Function
Oncogenes			
KRAS	12p	90	Growth factor signal transducer
AKT2	19q	10-20	Growth factor signal transducer
MYB	6q	10	Transcription factor
NCOA3/AIB1	20q	10	Chromatin regulator
MAP2K4/MKK4	17p	5	Growth factor signal transducer
Tumor Suppressor and DNA Repair Genes			
p16/CDKN2A	9p	95	Negative cell-cycle regulator
TP53	17p	50-70	Response to DNA damage
SMAD4	18q	55	TGFβ pathway
GATA-6	18q	10	Transcription factor
RB	13q	5	Negative cell-cycle regulator
STK11	19p	5	Regulation of cellular metabolism
ATM	11q	5	DNA damage response
ARID1A	1p	4	Chromatin regulator
TGFBR1	9q	2	TGFβ pathway
TGFBR2	3p	2	TGFβ pathway

KRAS, which is a small, GTP-binding protein that normally participates in signaling events downstream of growth factor receptors with intrinsic tyrosine kinase activity (Chapters 1 and 7). KRAS signaling activates a number of downstream pathways that augment cell growth and survival, most notably the MAPK and PI3K/AKT pathways (Chapter 7).

CDKN2A. The *CDKN2A* gene (chromosome 9p) is inactivated in 95% of pancreatic cancers, making it the most frequently inactivated tumor suppressor gene in these tumors. This complex locus encodes two tumor suppressor proteins (Chapter 7): p16/INK4a, a cyclin-dependent kinase inhibitor that antagonizes cell cycle progression, and ARF, a protein that augments the function of the p53 tumor suppressor protein.

SMAD4. The *SMAD4* tumor suppressor gene (chromosome 18q) is inactivated in 55% of pancreatic cancers. *SMAD4* encodes a protein that plays an important role in signal transduction from the TGF-β family of cell surface receptors. *SMAD4* is only rarely inactivated in other cancer types.

TP53. Inactivation of the *TP53* tumor suppressor gene (chromosome 17p) occurs in 70% to 75% of pancreatic cancers. This gene encodes p53, a nuclear DNA-binding protein that can respond to DNA damage by arresting cell growth, inducing cell death (apoptosis) or causing cellular senescence (Chapter 7).

Other Genes. A growing number of less common, but nonetheless important, genetic loci have been reported to be damaged in pancreatic cancer (Table 19-3).

DNA Methylation Abnormalities. Several DNA methylation abnormalities also occur in pancreatic cancer. Hypermethylation of the promoter of several tumor suppressor genes, including *CDKN2A*, is associated with transcriptional silencing of these genes and loss of their function.

Gene Expression. In addition to DNA alterations, global analyses of gene expression have identified several pathways that seem to be abnormally active in pancreatic cancers. These pathways and their downstream consequences are potential targets for novel therapies and may form the basis of future screening tests. For example, the Hedgehog signaling pathway has been shown to be activated in pancreatic cancer and represents a potential therapeutic target.

Epidemiology and Inheritance. Pancreatic cancer is primarily a disease of older adults, with 80% of cases occurring in people aged 60 to 80 years. It is more common in blacks than in whites, and it is slightly more common in individuals of Ashkenazi Jewish descent.

The strongest environmental influence is *cigarette smoking*, which is believed to double the risk of pancreatic cancer. Even though the magnitude of this increased risk is not great, the impact of smoking on pancreatic cancer is significant because of the large number of people who smoke. Consumption of a diet rich in fats has also been implicated, but less consistently. Chronic pancreatitis and diabetes mellitus are both risk factors for, and complications of, pancreatic cancer. In an individual patient it can be difficult to sort out whether chronic pancreatitis is the cause of pancreatic cancer or an effect of the disease, since small pancreatic cancers may block the pancreatic duct and produce chronic pancreatitis. A similar argument applies to the association of diabetes mellitus with pancreatic cancer, in that diabetes may develop as a consequence of pancreatic cancer and new-onset diabetes mellitus in an older patient may be the first sign that the patient has pancreatic cancer.

Familial clustering of pancreatic cancer has been reported, and a growing number of inherited genetic defects are recognized to increase pancreatic cancer risk (Table 19-4). Germline *BRCA2* mutations account for approximately 10% of pancreatic cancer cases in Ashkenazi Jews. Patients with these mutations may not have a family history of breast or ovarian cancers. Germline mutations in *CDKN2A* are associated with pancreatic cancer and are almost always observed in individuals from families with an increased incidence of melanoma, which also frequently harbors *CDKN2A* loss-of-function mutations.

MORPHOLOGY

Approximately 60% of cancers of the pancreas arise in the head of the gland, 15% in the body, and 5% in the tail; in 20% the neoplasm diffusely involves the entire gland. Carcinomas of the