Genetics of Pancreatic Neoplasms and Role of Screening

Venkata S. Katabathina, MD[a], Omid Y. Rikhtehgar, MD[a], Anil K. Dasyam, MD[b], Rohan Manickam, BS[c], Srinivasa R. Prasad, MD[c,*]

KEYWORDS

• Genomics • Pancreatic ductal adenocarcinoma • Neuroendocrine neoplasm
• Solid-pseudopapillary tumor • Serous cystadenoma • Screening

KEY POINTS

- A diverse group of histobiologically and genetically distinct tumors arise from the exocrine and endocrine components of the pancreas.
- Pancreatic adenocarcinoma, the most common and most lethal pancreatic malignancy, originates from microscopic and macroscopic precursors that are mainly characterized by *KRAS* mutations.
- Pancreatic neuroendocrine neoplasms are primarily characterized by germline or somatic mutations involving *MEN-1*, *TSC 1/2*, *ATRX*, and *DAXX* genes. Activating somatic mutations in *CTNNB1* occur in 95% of solid-pseudopapillary neoplasms.
- Detailed studies of hereditary pancreatic tumor syndromes have thrown fresh light on the frequency/relevance of genetic abnormalities, tumor pathways, tumor biology, and prognostic significance of the more common sporadic tumors.
- Current recommendations for screening of pancreatic neoplasms pertain to high-risk individuals, primarily patients with a familial and hereditary predisposition to early and frequent tumor development.

INTRODUCTION

The broad spectrum of pancreatic neoplasms may be classified based on the direction of cellular differentiation into exocrine and endocrine tumors. Pancreatic ductal adenocarcinoma (PDAC), the most lethal pancreatic cancer, comprises 90% of all malignant neoplasms. Pancreatic neuroendocrine tumors (PanNET) account for 5% of pancreatic tumors, and rarer solid pseudopapillary neoplasms (SPNs) and acinar cell carcinomas (ACC) constitute 1% to 2% of tumors. Although most tumors are sporadic in nature, up to 10% of tumors occur in the setting of hereditary syndromes that predispose to early onset development of characteristic tumor phenotypes. For example, although patients with Lynch syndrome (LS) show an increased propensity to develop the rare medullary variant of PDAC, PanNET tumors occur more frequently in patients with multiple endocrine neoplasia (MEN)-1 syndrome, von Hippel-Lindau (VHL) disease, type 1

[a] Department of Radiology, University of Texas Health Science Center at San Antonio, 7703 Floyd Curl Drive, San Antonio, TX 78229, USA; [b] Department of Radiology, University of Pittsburgh Medical Center, 200 Lothrop Street, Pittsburgh, PA 15213, USA; [c] Department of Radiology, The University of Texas MD Anderson Cancer Center, 1400 Pressler street, Unit 1473, Houston, TX 77030, USA
* Corresponding author. Department of Radiology, MD Anderson Cancer Center, 1400 Pressler Street, Unit 1473, Houston, TX 77030.
E-mail address: sprasad2@mdanderson.org

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neurofibromatosis (NF-1), and tuberous sclerosis complex (TSC). Patients with VHL disease develop serous cystadenomas and PanNET tumors. This article provides a broad overview of the genetic landscape of a diverse spectrum of pancreatic tumors (**Table 1**), a synopsis of characteristic hereditary syndromes with specific pancreatic tumors (**Tables 2** and **3**), and current recommendations for screening in high-risk individuals (**Box 1**).

PANCREATIC DUCTAL ADENOCARCINOMA

PDAC, the most common pancreatic malignant neoplasm, is the most lethal pancreatic malignancy

Table 1
Summary of epidemiology and genomic landscape of pancreatic neoplasms

Tumor (Prevalence, Comments)	Gene (Prevalence)	Comments	Average Number (Mutations)
Ductal adenocarcinoma (90%; mean age, 66 y; M:F, 3:2)	*KRAS* (95%) *P16/CDKN2A* (95%) *TP53* (75%) *SMAD4/DPC4* (55%)	Marker of PanIN Marker of high-grade dysplasia Marker of high-grade dysplasia	26–63
IPMN (median age, 66 y; more common in men; 25%–50% of resected cystic pancreatic lesions; two-thirds of tumors in the head region)	*KRAS* (80%) *GNAS* (60%) *RNF43* (60%) *p16/CDKN2A* *TP53* *SMAD4/DPC4* *PIK3CA* (10%) *STK11/LKB1* (5%)	 Intestinal type, colloid *p16* loss (10% noninvasive; 100% invasive) SMAD4 loss (one-third invasive)	26
Mucinous cystic neoplasm (perimenopausal women; 40–60 y; F:M, 20:1; 95% in pancreatic body/tail; low malignant potential in cyst <4 cm)	*KRAS* (80%) *RNF43* (40%) *p16/CDKN2A* *TP53* *SMAD4/DPC4*	 Marker of late cancer Marker of late cancer	16
Serous cystadenoma (predominantly women, 75%; mean age, 62 y; 16% resected cystic tumors; 10% oligocystic/macrocystic)	*VHL* (50%: somatic mutations; LOH: 90%) Loss of *10q* (50%)		10
Solid-pseudopapillary tumor (1%–2%; mean age, 29 y; M:F, 9:1; low malignant potential; 8% with metastatic disease)	*CTNNB1* (95%)		3
Acinar cell carcinoma (1%–2%; mean age, 56 y; M:F, 2:1)	*SMAD4*, *JAK1*, *BRAF*, *RB1*, *TP53* (up to 30%) *RAF* rearrangements (25%)		131
Pancreatoblastoma (<1%; mean age, 5 y; M:F, 2:1)	*CTNNB1* (55%) *APC* (10%) *11p* loss (85%)		18
Neuroendocrine tumors (5%; mean age, 58 y; M:F, 3:2)	*MEN1*, *ATRX*, *DAXX*, *TSC2* (*KRAS* [30%] *Rb* [70%], *p53* [60%] in NECs)	45% in *MEN1*, 45% in *ATRX/DAXX*, 15% *mTOR* pathway	16

Abbreviations: IPMN, intraductal papillary mucinous neoplasm; LOH, loss of heterozygosity; NEC, neuroendocrine carcinoma; PanIN, pancreatic intraepithelial neoplasia.