

# Germline Aberrations in Pancreatic Cancer

Subjects: **Oncology**

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Pancreatic ductal adenocarcinoma (PDAC) has an extremely poor prognosis and represents a major public health issue, as both its incidence and mortality are expecting to increase steeply over the next years. Effective screening strategies are lacking, and most patients are diagnosed with unresectable disease precluding the only chance of cure. Therapeutic options for advanced disease are limited, and the treatment paradigm is still based on chemotherapy, with a few rare exceptions to targeted therapies. Germline variants in cancer susceptibility genes—particularly those involved in mechanisms of DNA repair—are emerging as promising targets for PDAC treatment and prevention.

germline

pancreatic cancer

BRCA

PARP inhibitors

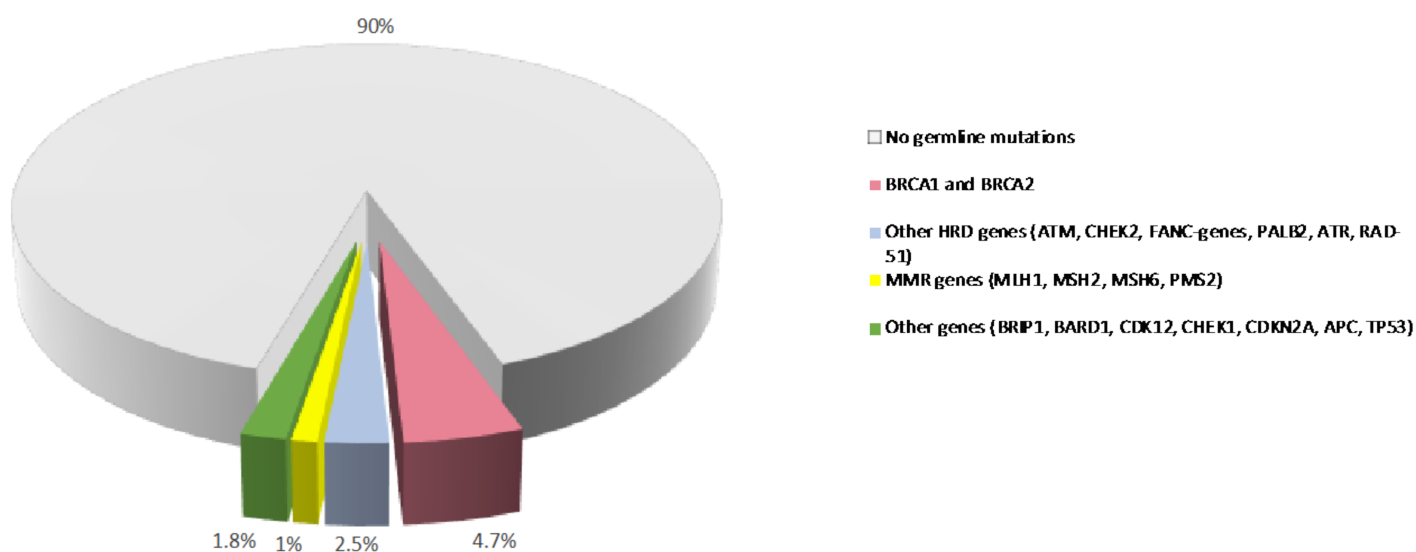
## 1. Introduction

Pancreatic ductal adenocarcinoma (PDAC) is a malignant disease with an extremely poor prognosis <sup>[1][2]</sup>. Both incidence and mortality continue to rise, and PDAC is predicted to soon become the second leading cause of cancer-related death <sup>[3][4]</sup>. Major efforts in improving surgical outcomes and progress in therapeutic development have only marginally increased the 5-year overall survival (OS) rate of patients with PDAC over the past 5 decades, and is still less than 10% <sup>[3]</sup>. Much still needs to be improved to impact the burden of this disease. Currently, most patients (up to 80%) are diagnosed with unresectable disease due to non-specific symptoms and a lack of effective screening strategies. Earlier diagnosis may potentially improve outcomes since surgical resection is the only chance of cure <sup>[5]</sup>. As a consequence, the identification of biomarkers for early detection is an urgent priority. Patients with advanced tumors are treated with chemotherapy with an unselected approach, either in the neoadjuvant or metastatic setting. The most effective combinatorial regimens, based on phase III clinical trials, i.e., FOLFIRINOX (5-fluorouracil, leucovorin, irinotecan, and oxaliplatin) and nab-paclitaxel plus gemcitabine, only marginally improve the OS of patients, which rarely exceeds one year <sup>[6][7][8][9][10][11][12][13]</sup>. After progression, less than 50% of patients are eligible for further treatments due to the rapid clinical deterioration typical of this disease. Second-line treatments have a very limited impact on clinical and survival outcomes, and clinical trials remain the optimal therapeutic choice in this setting <sup>[14]</sup>.

## 2. Germline Variants and PDAC Susceptibility

In contrast to somatic mutations, which are acquired during life and arise specifically in tumors, germline variants can be passed from parents to offspring and are associated with hereditary cancer syndromes. Germline

pathogenic/likely-pathogenic variants in cancer predisposing genes are prevalent molecular alterations in PDAC (**Figure 1**) [15][16]. Several studies have shown that 3.8% to 9.7% of patients with PDAC carry a pathogenic germline mutation in genes that predispose them to hereditary cancer syndromes, including familial atypical multiple mole melanoma (*CDKN2A*), Peutz-Jeghers (*STK11*), hereditary breast and ovarian cancer (*BRCA1*, *BRCA2*, *PALB2*, *ATM*), Lynch (*MLH1*, *MSH2*, *MSH6*), and Li-Fraumeni (*TP53*) syndromes [17][18][19][20][21][22][23][24]. In some large single-center datasets, the prevalence of these alterations is as high as 19.8% [25]. Germline deleterious variants in the hereditary pancreatitis genes *PRSS1* and *SPINK1* also confer an increased risk of PDAC [26].



**Figure 1.** Prevalence of germline variants in PDAC. Prevalence of germline mutations in PDAC patients from published studies. MMR: mismatch repair. HR: homologous recombination.

Compared with a risk of about 1.5% in the general population, carriers of pathogenic variants in *CDKN2A* and *STK11* have a higher lifetime risk of developing PDAC, which is estimated to be more than 15%. Carriers of pathogenic variants in the breast cancer genes *BRCA2*, *ATM*, and *PALB2* have a moderate lifetime risk, ranging from 5% to 10%, whereas pathogenic variants in *BRCA1* are estimated to confer a lower risk (less than 5%) [27]. More recently, data from a large international consortium of families with hereditary cancer syndromes associated with *BRCA* germline mutations demonstrated that the relative risk (RR) of PDAC was 2.36 (95% CI, 1.51–3.68) for *BRCA1* and 3.34 (95% CI, 2.21–5.06) for *BRCA2*. The absolute risk of PDAC to age 80 was approximately 2.5% (for both *BRCA1* and *BRCA2* carriers) [28]. Pathogenic variants in Lynch syndrome genes and *TP53* are estimated to confer a moderate pancreatic cancer lifetime risk of about 5–10% [29].

A family history of PDAC also confers an increased risk. Patients with one or more first-degree relatives affected by PDAC are considered familial pancreatic cancer (FPC) cases [30]. In general, in the presence of a first-degree relative family history, the risk of developing PDAC increases with the number of affected relatives (by up to 4, 6, and 32 times for 1, 2, and 3 or more affected relatives, respectively) [31]. Overall, 80–90% of FPC cases are not

attributable to a known genetic cause, suggesting the presence of additional genetic factors involved in PDAC susceptibility that have not yet been identified.

The recent broad use of cancer predisposing gene panel testing in clinical practice has allowed for the identification of pathogenic variants in a larger number of candidate cancer susceptibility genes, and also in patients without a family history, the so-called sporadic cases, with mutation rates varying among studies [15][32][33][34]. These findings have supported the current National Comprehensive Cancer Network (NCCN) recommendation of performing extended genetic testing on all patients with a diagnosis of PDAC, regardless of family history or age of onset. Genetic testing should be performed with a comprehensive multi-gene panel, including, at a minimum, the genes *ATM*, *BRCA1*, *BRCA2*, *CDKN2A*, *MLH1*, *MSH2*, *MSH6*, *EPCAM*, *PALB2*, *STK11*, and *TP53* [29].

The opportunity for extended and universal genetic testing as a standard of care or in the research setting is expanding the probability of identifying clinically actionable germline variants in many genes, but their association with increased risk of PDAC is still uncertain. Indeed, a limited number of proposed candidate susceptibility genes have been consistently associated with an increased risk of PDAC, both in familial and sporadic cases [35][36]. For instance, there is no robust evidence suggesting a significant increased risk of PDAC in mutation carriers of *CHEK2* pathogenic variants [36], although these variants are frequently observed in PDAC patients [15]. Overall, the rarity of pathogenic variants makes it very challenging to define reliable population-based risk estimates, and much larger studies are warranted. Targeted sequencing using comprehensive cancer gene panels may represent the best way to accumulate data to improve the genetic risk assessment for known-candidate genes. On the other hand, a broader genomic approach using whole exome sequencing or whole genome sequencing in selected high-risk families may help define “missing heritability” in PDAC.

As for most complex diseases, the role of low-penetrance common single nucleotide polymorphisms (SNPs) has been investigated in PDAC using genome-wide association studies (GWAS). According to the GWAS catalogue (accessed May 2021), a total of 200 associations with pancreatic risk were reported; however, few loci reached GWAS statistical significance at a  $p$ -value threshold of  $5 \times 10^{-8}$  and was consistently replicated among many studies (reviewed elsewhere [37]). To date, GWAS-identified loci have been estimated to explain about 4% of the phenotypic variation of PDAC; however, more associated SNPs (up to 1750) are expected to be discovered using larger study populations [25][38]. Since each common variant has a small impact on cancer risk, a polygenic architecture, in which many variants that confer low risk individually act in combination to confer much larger risk in the population, has been suggested as a model of cancer susceptibility. Polygenic risk scores (PRS), developed including GWAS identified loci, and multifactorial risk scores (MRS), developed combining genetic and non-genetic risk factors, were recently shown to improve risk prediction in patients with PDAC [39][40][41]. However, the clinical implementation of these models has yet to be established and deserves further assessment.

### **3. Preclinical and Translational Research in Hereditary PDAC**

Preclinical and translational research is essential to improve the understanding of PDAC susceptibility and to facilitate the development of therapeutic strategies for patients with germline mutations. While approximately 10%

of PDAC patients may harbor germline mutations, only a few pre-clinical models are commercially available in this field. CAPAN1 is the most commonly used BRCA2-deficient PDAC cell line, harboring *BRCA2* c.6774delT truncating mutation [42]. In addition, PL11 and Hs766T harbor genetic alterations in the Fanconi anemia pathway genes *FANCC* (null mutation) and *FANCG* (nonsense mutation), respectively [43]. There are no detailed genomic annotations associated with commercially available PDAC cell lines or other preclinical models, and this hampers the preclinical usage of PDAC cell lines in the context of FPC. Genetically engineered mouse models have been critical for basic PDAC research and the preclinical evaluation of therapeutic strategies. One of the representative PDAC GEMM is the KPC mouse model, which harbors oncogenic *KRAS* G12D and a gain-of-function *p53* R172H or R270H mutation (equivalent to human *TP53* R175H or R273H) or *p53* null mutation specifically in pancreatic epithelial cells driven by a Pdx1-Cre or Ptf1-Cre transgenic allele [44][45]. Since *KRAS* and *TP53* mutations are the most common genetic alterations in PDAC, putative tumor suppressors or oncogenes have been modeled in the *Kras* mutant background or *Kras/Trp53* double mutant background (reviewed by Guerra and Barbacid [46]). Although many genes are associated with hereditary PDAC, a few genes have been experimentally shown to contribute to PDAC progression in vivo using GEMM. Among cancer predisposing genes, mutations in *BRCA2* and *ATM* play a role in PDAC progression [47][48], whilst the role of other genes remains to be defined. One of the challenges in modeling hereditary PDAC with GEMM is that the generation of conditional knockout alleles for individual cancer predisposing genes is time-consuming. In addition, PDAC mouse models need to be crossed with multiple oncogenic alleles, such as *Kras* mutations and pancreas-specific Cre alleles. Another critical issue related to hereditary PDAC is that genetic mutations are introduced at the embryonic development stage, which complicates the question of whether cancer predisposing genes play a role in the inception of key driver mutations, such as oncogenic mutations in *KRAS* in other tumor suppressors. Available GEMMs only allow us to address whether these mutations in cancer predisposing genes can cooperate with oncogenic *Kras* mutations or other driver mutations for PDAC progression.

In conclusion, various preclinical models of human PDAC are available for basic and translational research, including PDAC cell lines, patient-derived xenografts (PDXs), and patient-derived organoids (PDOs) [49]. Each preclinical model has its own advantages and disadvantages. Thus, the optimal model for each study should be determined based on specific scientific and clinical questions. To evaluate the efficacy of PARPi and other therapies for PDAC patients, a lack of detailed genomic annotations in the currently existing preclinical models is an issue that needs to be addressed. The use of isogenic cell lines or other preclinical models with CRISPR or other genetic engineering approaches is ideal for addressing a mutation-specific drug response in hereditary PDAC. In this way, the possibility of confounding effects that may come from other genetic mutations or other backgrounds can be excluded. In addition, the use of preneoplastic cells (e.g., PanIN-derived organoids) could be useful to address the effect of cancer predisposing gene mutations in the early stage of PDAC progression without generating new GEMM for hereditary PDAC [50].

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