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The PANcreatic Disease ReseArch (PANDoRA) consortium: Ten years' experience of association studies to understand the genetic architecture of pancreatic cancer

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ABSTRACT

Pancreatic cancer has an incidence that almost matches its mortality. Only a small number of risk factors and 33 susceptibility loci have been identified. so Moreover, the relative rarity of pancreatic cancer poses significant hurdles for research aimed at increasing our knowledge of the genetic mechanisms contributing to the disease. Additionally, the inability to adequately power research questions prevents small monocentric studies from being successful. Several consortia have been established to pursue a better understanding of the genetic architecture of pancreatic cancers. The Pancreatic disease research (PANDoRA) consortium is the largest in Europe. PANDoRA is spread across 12 European countries, Brazil and Japan, bringing together 29 basic and clinical research groups.

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In the last ten years, PANDoRA has contributed to the discovery of 25 susceptibility loci, a feat that will be instrumental in stratifying the population by risk and optimizing preventive strategies.

1. Pancreatic cancer epidemiology

Pancreatic neoplasms are hard to be diagnosed at early stages and have limited treatment options (Milella et al., 2022). Pancreatic ductal adenocarcinoma (PDAC), the most common form of exocrine pancreatic cancer, was estimated to have been diagnosed in almost 500,000 individuals and to have been responsible for approximately 470,000 deaths in 2020 worldwide (https://gco.iarc.fr/today/home) (Sung et al., 2021). It is the fourth leading cause of cancer related mortality in Europe, and the 5-year survival rate after diagnosis approaches 10% and only small progress in terms of treatment has been achieved in the last decades (Siegel et al., 2022). Reasons for this poor outcome are the lack of early specific symptoms, the lack of strong established environmental risk factors, the aggressiveness of the disease, the very limited knowledge on the genetic basis of its susceptibility with only 30 risk loci identified so far (Gentiluomo et al., 2020a; Klein et al., 2018). A further reason is the lack of a curative treatment with the exception of surgery which is suitable for only 20% of patients (Park et al., 2021; Stott et al., 2022).

Pancreatic neuroendocrine neoplasms (pNENs) are much rarer and usually have a less aggressive phenotype compared to PDAC. Knowledge of pNEN risk factors is limited (Valente et al., 2017) and no genetic risk loci have been identified yet. The relative rarity of both diseases (worldwide crude incidence of 6.4 per 100,000 per year) (Sung et al., 2021) implies that their genetic determinants can be addressed with reasonable statistical power only in the context of large multicentric studies. Several consortia dedicated to the study of PDAC have been established across the world. By contrast, none exists where the focus is entirely on pNEN. The Pancreatic Disease Research (PANDoRA) consortium is the largest European consortium focusing on the genetic susceptibility of pancreatic diseases and has contributed to the discovery of the majority of the known PDAC risk loci.

2. Description of the consortium

PANDoRA was established 10 years ago with the goal of improving our knowledge of pancreatic cancer susceptibility and prognosis mainly by focusing on the genetic contribution to both outcomes. The driving force behind the PANDoRA consortium was to amass the expertise of many researchers across the world in order to build a large bio- and data banks.

Over the last ten years, PANDoRA has greatly increased in size, considering both data and collected specimens, and centers and researchers involved in the consortium. To date, PANDoRA brings together 29 basic and/or clinical research groups with a wide spectrum of expertise and spreads across 12 European countries (Czech Republic, Denmark, Germany, Greece, Hungary, Italy, Lithuania, The Netherlands, Poland, Spain, Ukraine, United Kingdom), Brazil and Japan. Fig. 1 shows the current composition of PANDoRA in terms of centers and countries involved. The PANDoRA members have a very broad range of expertise as the consortium is composed by basic scientists (biologists, molecular biologists, geneticists), epidemiologists and clinicians (surgeons, gastroenterologists, pathologists, oncologists). The multidisciplinary nature of PANDoRA is one of its strengths, especially considering that pancreatic diseases have complex phenotypes that can be unraveled only by a multi-pronged approach.

The cases included in the consortium are defined by a confirmed diagnosis. For each patient, information about sex and age at diagnosis was collected. In addition, information concerning overall survival (OS) is registered, to investigate the role of genetic variants in the disease prognosis. Controls have been recruited among hospitalized individuals (excluding oncological patients), blood donors and the general population. Patients with PDAC make up for the bulk of the cases enrolled, but there are also a smaller number of other pancreatic conditions including rarer entities and precancerous lesions. For all individuals a biologic

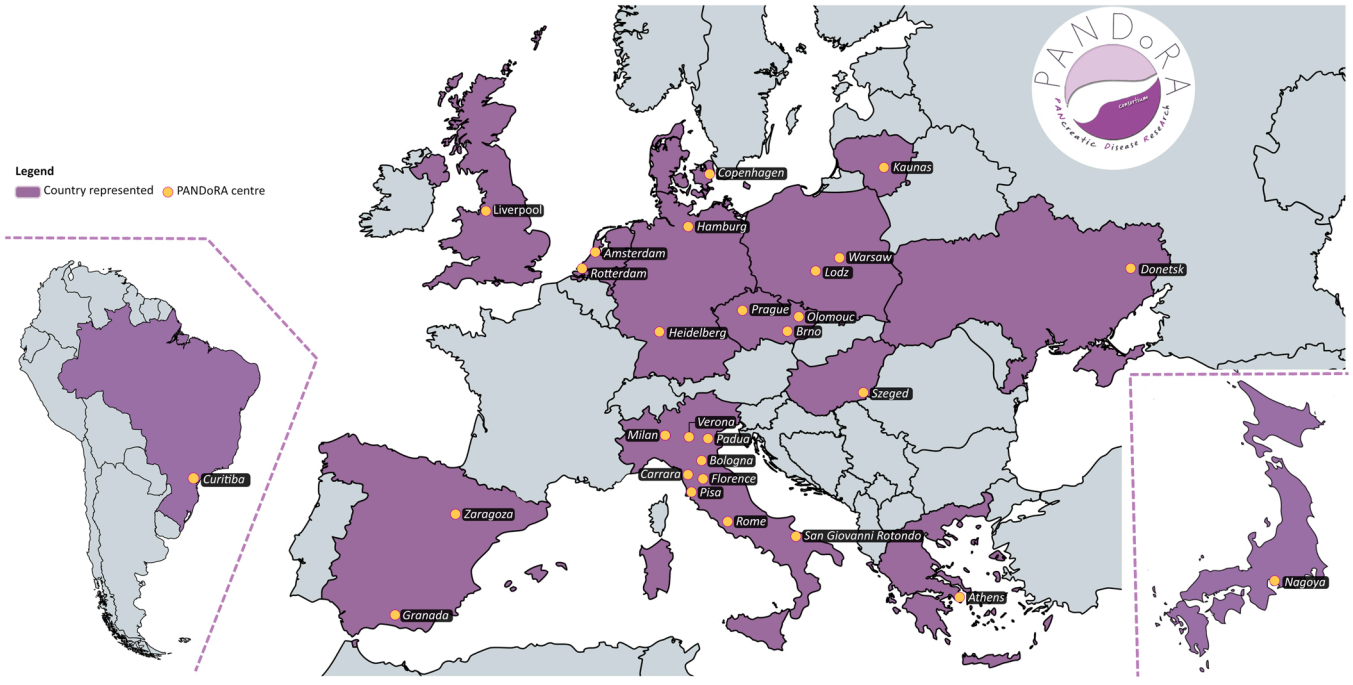

Fig. 1. List of PANDoRA centres. Czech Republic: Brno; Olomouc; Prague | Denmark: Copenhagen Germany: Hamburg; Heidelberg | Greece: Athens | Hungary: Szeged | Italy: Bologna; Carrara; Florence; Milan; Padua; Pisa; Rome; San Giovanni Rotondo; Verona | Lithuania: Kaunas | Poland: Warsaw; Lodz | Spain: Zaragoza; Granada Netherlands: Amsterdam; Rotterdam | Ukraine: Donetsk United Kingdom: Liverpool | Brazil: Coimbra | Japan: Nagoya.

sample (blood for the vast majority of patients, tumor material for some) has been obtained and DNA has been extracted. Table 1 shows the current composition of cases and controls for whom there is a biospecimen available and for whom detailed clinical and epidemiologic data have been collected.

3. Overall aim of the consortium

The focus of PANDoRA has been, and will be in the foreseeable future, the identification of pancreatic cancer risk loci. To achieve this goal several approaches will be employed following the strategies implemented so far and developing new ones, as detailed below. Other topics of interest for the consortium, that are already being actively investigated, are represented by the identification of germline variants associated with 1) PDAC prognosis and response to treatments; 2) progression of preneoplastic precursors towards malignancy; 3) neuroendocrine neoplasms risk and response to treatments; 4) chronic pancreatitis risk.

4. What has been accomplished so far by the consortium in the field of pancreatic cancer genetics?

4.1. PDAC susceptibility loci

In the past ten years PANDoRA has contributed to the discovery of several polymorphisms that individually or grouped in a score contribute to pancreatic cancer susceptibility and prognosis. The main strategies employed have been candidate gene/region approaches, genome-wide association studies (GWAS), secondary analyses of GWAS data, and polygenic (PRS) and multifactorial (MRS) risk score analysis.

4.2. Genome wide association studies

Currently, five GWAS (or meta-analyses of existing GWAS) on PDAC risk have been conducted in individuals of European descent (Amundadottir et al., 2009; E. J. Childs et al., 2015a, 2015b; Klein et al., 2018; Petersen et al., 2010; B. M. Wolpin et al., 2014a, 2014b). PANDoRA has been involved in three of these studies, that in total identified 18 variants associated with the risk of developing PDAC. Fig. 2 and Table 2 show the known PDAC risk loci found in GWAS, highlighting those discovered through PANDoRA. As for other cancer types, these single nucleotide polymorphisms (SNPs) show a modest increase in risk for carriers of the effect allele (ORs between 1.12 and 1.46) but are very frequent in the population with a minor allele frequency (MAF)$>$ 0.05 and an average MAF$=$ 0.43. The majority are situated in non-protein coding regions (15 loci) and therefore their mechanistic link with the disease still needs to be completely understood. Additionally, two GWAS focused on early onset cases where also performed, but the low number of patients involved limited the power and only suggestive associations where identified (Campa et al., 2020; Nodari et al., 2023).

4.3. Candidate gene approach

PANDoRA has contributed to establishing several pleiotropic regions (i.e., regions associated with multiple traits) as risk loci for PDAC. Table 3 shows the SNPs identified by PANDoRA using the candidate gene approach.

The *ABO* locus, on chromosome 9, was identified by a previous GWAS and validated in PANDoRA, confirming that individuals with non-O genotype have an increased risk of developing the disease (Amundadottir et al., 2009; Rizzato et al., 2013). This locus has also been reported to increase the risk of progressing from intraductal papillary mucinous neoplasms (IPMNs) to PDAC, although the associations have some degrees of uncertainty (Capurso et al., 2020).

Moreover, the *TERT* locus on chromosome 5 showed several independent SNPs contributing to the disease onset (Campa et al., 2015). The *TERT* locus is characterized by a very low linkage disequilibrium (LD), at least in Europeans, explaining why multiple independent alleles are associated with the disease. This region is involved in telomere length (TL) regulation and maintenance and TL is associated with pancreatic cancer risk, among several other human phenotypes (Campa et al., 2019; Gaspar et al., 2018; Gentiluomo et al., 2022; Giaccherini et al., 2022b).

Another pleiotropic region of interest is on chromosome 9 around the *CDKN2A/CDKN2B* locus that harbors rare high penetrance mutations as well as frequent low penetrance mutations associated with PDAC risk. In PANDoRA, an association of the *CDKN2A/CDKN2B* locus was reported for both PDAC and pNEN (Campa et al., 2016). A study was also performed to compare if SNPs associated with PDAC risk were associated with pNEN, but only a very partial overlap was found between the genetic variants(Ofure Obazee et al., 2018a, 2018b; O. Obazee et al., 2018a, 2018b).

PANDoRA compared polymorphisms associated with risk of chronic pancreatitis and risk of developing PDAC and observed no effect. (Daniele Campa et al., 2018a, 2018b).

In addition, considering that the rather large sample size of the consortium offers suitable statistical power, a replication of previously identified SNPs was attempted for PDAC and pNEN. While for PDAC essentially all associations replicated, for pNEN almost none did (Campa et al., 2017; Rizzato et al., 2011). The difference was probably due to the fact that the PDAC SNPs previously reported in the literature were identified through large collaborative GWAS studies while the pNEN

Table 1
PANDoRA participants.

Country	*Age Avg (min-max)*	*Controls*	*PDAC*	*PNEN*	*IPMN*	*CP*	*Other*	*N*	*Female/Male*
Czech Republic	55 (18–94)	1737	649	33	5	48	34	2506	1155/1351
Denmark	66 (19–89)	0	1345	13	41	37	97	1533	681/852
Germany	60 (18–92)	1747	1245	145	769	283	87	4276	2141/2135
Greece	55 (18–95)	301	373	97	10	7	0	788	337/451
Hungary	47 (18–90)	975	430	10	1	180	3	1599	591/1008
Italy	63 (18–100)	1975	1662	454	621	146	284	5142	2294/2848
Lithuania	59 (19–92)	493	377	16	6	55	0	947	488/459
Netherlands	66 (31–86)	102	176	3	20	3	16	320	170/150
Poland	53 (18–98)	424	185	29	5	145	19	807	434/373
Spain	66 (40–85)	0	230	0	0	0	0	230	112/118
Ukraine	37 (18–72)	200	0	0	0	102	0	302	123/179
United Kingdom	65 (25–89)	176	146	54	0	0	0	376	152/224
Brazil	54 (18–88)	326	70	4	10	0	4	414	243/171
Total		8456	6888	858	1488	1006	544	19,240	8921/10319

N: total number of individuals considering all pancreatic conditions and controls. Age-avg: average age. PDAC: pancreatic ductal adenocarcinoma. PNEN: Pancreatic neuroendocrine neoplasms. IPMN: intraductal papillary mucinous neoplasm. CP: chronic pancreatitis; Other: other pancreatic diseases. The numbers reported in this table represent the total of cases and controls recruited since the beginning of PANDoRA, and are not necessarily all currently available, due to sample depletion.

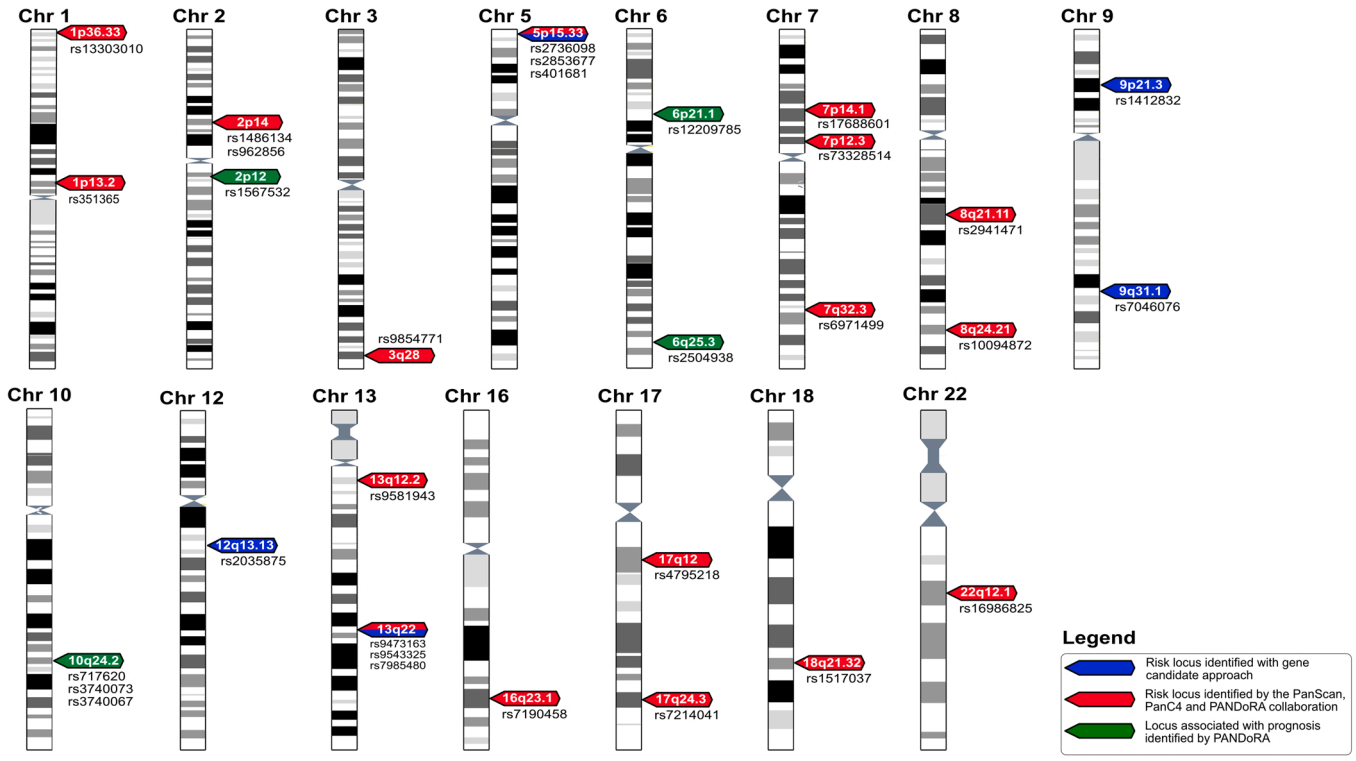

Fig. 2. Known loci associated with PDAC risk and prognosis discovered through PANDoRA consortium.

Table 2
GWAS PDAC risk loci identified by the PanScan, PanC4 and PANDoRA collaboration.

Chromosome	Closest gene (s)	Best SNP[a]	Risk allele	RAF[b]	OR (95% CI)[c]	P-value
13q12.2	*PDX1-AS1-PDX1*	rs9581943	**A**/G	0.43	1.15 (1.12–1.19)	5.1×10^{-14}
13q22.1	*KLF5 and KLF12*	rs9543325	**C**/T	0.61	1.23 (1.18–1.30)	4×10^{-14}
16q23.1	*BCAR1/CTRB1/CTRB2*	rs7190458	**A**/G	0.05	1.46 (1.30–1.65)	1×10^{-10}
17q12	*HNF1B*	rs4795218	**G**/A	0.76	1.14 (1.09–1.19)	1×10^{-8}
17q24.3	*LINC00673*	rs7214041	**T**/C	0.11	1.25 (1.19–1.30)	9×10^{-15}
18q21.32	*GRP*	rs1517037	**C**/T	0.19	1.16 (1.10–1.25)	3×10^{-8}
1p13.2	*WNT2B*	rs351365	**C**/T	0.77	1.12 (1.08–1.18)	7×10^{-7}
1p36.33	*NOC2L*	rs13303010	**G**/A	0.9	1.26 (1.19–1.35)	8×10^{-14}
22q12.1	*ZNRF3*	rs16986825	**T**/C	0.16	1.15 (1.10–1.20)	1×10^{-8}
2p14	*ETAA1*	rs962856	**C**/T	0.63	1.12 (1.08–1.17)	2×10^{-8}
2p14	*ETAA1*	rs1486134	**G**/T	0.73	1.14 (1.09–1.19)	3×10^{-9}
3q28	*TP63*	rs9854771	**G**/A	0.39	1.12 (1.08–1.18)	2×10^{-8}
5p15.33	*TERT*	rs2736098	**C**/T	0.23	1.25 (1.18–1.32)	9×10^{-14}
7p12.3	*TNS3*	rs73328514	**A**/T	0.1	1.18 (1.11–1.25)	1×10^{-7}
7p14.1	*SUGCT*	rs17688601	**C**/A	0.25	1.14 (1.09–1.19)	1×10^{-8}
7q32.3	*LINC-PINT*	rs6971499	**T**/C	0.13	1.27 (1.19–1.35)	3×10^{-12}
8q21.13	*HNF4G*	rs2941471		0.58	1.12 (1.08–1.18)	7×10^{-10}
8q24.21	*MIR1208,PVT1*	rs10094872	A/T	0.35	1.15 (1.10–1.20)	3×10^{-9}

[a] SNP showing the lowest p-value for association with PC risk at each locus.
[b] RAF: risk allele frequency in the populations where the original study has been performed.
[c] OR: odds ratio; CI: confidence interval.

Table 3
Susceptibility SNPs identified by PANDoRA using the gene candidate approach.

SNP	Chromosome	Closest gene (s)	Risk allele	RAF[a]	OR (95% CI)[b]	P-value
rs2035875	12q13.13	*KRT8*	G/**A**	0.49	1.11 (1.08–1.15)	7.14×10^{-10}
rs7046076	9q31.2	*(lnc-SMC2–1)*	T/**C**	0.33	1.13 (1.09–1.18)	9.73×10^{-9}
rs7985480	13q22.2	*LMO7*	T/C	0.73	1.12 (1.07–1.17)	3.03×10^{-6}
rs2853677	5p15.33	*CLPTM1L/TERT*	A/**G**	0.43	0.85 (0.80–0.0	8.3×10^{-8}
rs401681	5p15.33	*CLPTM1L/TERT*	C/**T**	0.43	1.37 (1.24–1.42)	1.9×10^{-9}
rs1412832	9p21.3	*CDKN2B-AS1/ANRIL*	**C/T**	0.70	1.11 (1.07–1.15)	5.25×10^{-9}

[a] RAF: risk allele frequency in the populations where the original study has been performed.
[b] OR: odds ratio; CI: confidence interval.

SNPs were reported by candidate gene studies, usually undertaken in only one center with limited sample size. Also, GWAS hits identified in other ethnicities were investigated (Chinese and Japanese), but none replicated in PANDoRA, highlighting the importance of cross validating GWAS results across multiple populations (Campa et al., 2013).

4.4. Secondary analysis of GWAS data

GWAS have been extremely useful for identifying many genetic variants associated with human traits, however they suffer from the penalization of reporting only the top findings (i.e., usually the SNPs with a p value of association lower than 5×10^{-8}) due to the very high number of tests performed, and therefore are plagued by false negatives. Additionally, it is usually difficult to link the statistical association with a function of the variant. GWAS results may be illustrated with an analogy of a fruit tree, with GWAS hits represented by the low-hanging fruits that have already been picked (Fig. 3) and many more loci that still need to be picked. A very successful way to overcome these limitations, and to reach the more difficult branch of the tree, is to use the data produced by the GWAS and test only a limited number of SNPs (selected by an a priori hypothesis) and to then replicate the significant association in an independent dataset. A particularly useful way is to combine functional databases (where hundreds of thousands of SNPs have been functionally annotated) with genotyping data. PANDoRAs has used this approach to uncover several regulatory polymorphisms. The GWAS data used were downloaded by the dbGaP database and originated from four studies (Pancreatic Cancer Cohort Consortium (PanScan) I, PanScan II, PanScan III, and the Pancreatic Cancer Case-Control Consortium (PanC4)) carried out in populations of mostly European descent.

For example, Pistoni and colleagues identified an expression quantitative trait locus (eQTL, i.e., a SNP whose alleles regulate the expression of a nearby gene), rs2035875, that increases PDAC risk, likely by modulating the expression of genes *KRT8* and *KRT18* (Pistoni et al., 2021).

In recent years the importance of the genetic variability in non-coding RNA such as long noncoding RNA (lncRNA) and microRNA (miRNA) has been shown by several publications and databases annotating lncRNA, miRNAs and their genetic variability that are continuously updated. Corradi and colleagues found a SNP in a lncRNA (rs7046076) to be associated with PDAC risk, while Lu et al. reported a polymorphic variant (rs7985480) situated in a miRNA (Corradi et al., 2021; Y. Lu et al., 2021a, 2021b).

The secondary approach was also attempted to identify variants considering pathways or functions/mechanisms such as inflammation, estrogen metabolism and taste perception, but no association was identified (Gentiluomo et al., 2019b, 2019c; Peduzzi et al., 2022).

Considering that mitochondrial copy number have been associated with the risk of developing multiple cancer types (Blein et al., 2014; D. Campa et al., 2018a, 2018b; Gentiluomo et al., 2020b; Giaccherini et al., 2021; Hosnijeh et al., 2014), the genes and SNPs involved in the mitochondrial metabolism were analyzed also in PANDoRA (Peduzzi et al., 2021). Even though no significant association was observed analyzing the SNPs individually, a gene-wise test (i.e., adding together all SNPs of a gene) suggested associations of the *TERT*, *SUGCT*, and *SURF1* genes with PDAC risk.

Finally, two additional GWAS were also performed, one using a recessive model of inheritance and another one considering only early onset cases (Campa et al., 2020; Ye Lu et al., 2021a, 2021b). Both studies reported three and four SNPs respectively associated with their respective phenotype but neither showed a p-value lower than the threshold for statistical significance computed considering the number of tests performed.

Moreover, Giaccherini et al. identified a polymorphic variant in the *CDKN2B-AS1/ANRIL* analyzing the common genetic variability in genes that have been reported to harbor rare, high penetrance mutations in pancreatic cancer kindreds (Giaccherini et al., 2022a).

Finally, Obazee et al. also investigated two rare variants in BRCA2 and CHECK2 using PANDoRA samples, with interesting results, however additional rare mutations have been identified (Fujitani et al., 2023) for PDAC and PANDoRA could be used as a replication set(Obazee et al., 2019).

4.5. Polygenic risk scores and multifactorial risk scores

Individually SNPs are responsible for small increases in risk, therefore recently a lot of attention has been given to adding the effect of the SNPs together in polygenic risk scores to achieve an increased effect of the estimate (expressed as ORs/betas) and stratify the population by risk (Lewis and Vassos, 2020; Mavaddat et al., 2019). In more common cancer types, for which many risk loci have been identified, this approach has given very encouraging results (Dixon et al., 2022; Roberts et al., 2023). In PANDoRA two PRSs were computed and analyzed: one considering the SNPs in the loci associated with PDAC and combining them with non-genetic risk factor in a multifactorial risk score (Galeotti et al., 2021). The results were very promising with an OR of 14.37 (95% C.I 5.57–37.09) comparing the highest quintile with the lowest quintile for the MRS with genetic and non- genetic variables, although this value must be taken with caution, because the multifactorial score analysis

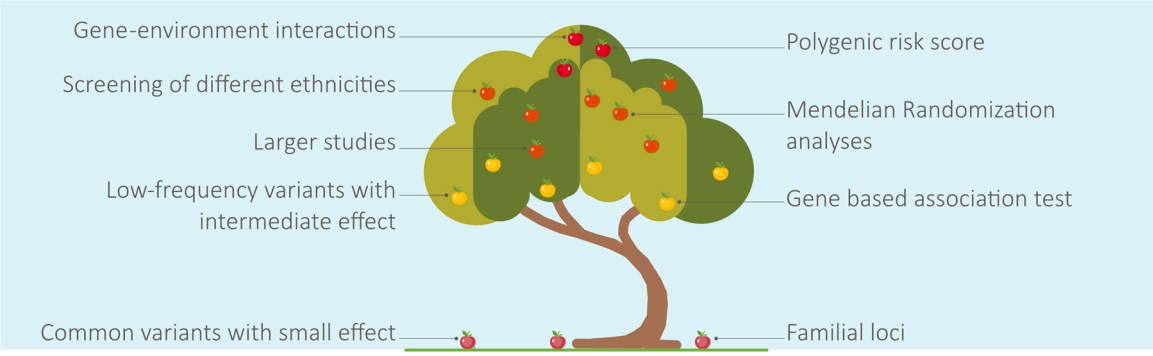

Fig. 3. The low hanging fruits analogy of pancreatic cancer genetic knowledge. In the low hanging fruits analogy the low-hanging fruit has been picked and represents the genetic discoveries on pancreatic ductal adenocarcinoma (PDAC) done so far. Familial loci were identified with family studies, and common risk variants were identified principally through genome-wide studies in relatively limited Caucasian populations. The remaining pancreatic cancer hereditability (low-frequency risk variants) is a difficult to reach fruits and is included between the high penetrant mutations and the common variants. The identification of these variants will be possible through a change of study approaches. First, increasing the study population size, analysing populations with different ancestry, and adopting an approach of region-based test. Finally, an increment of knowledge of the genetics of PDAC will allow the development of a tool for personalised risk prediction, such as polygenic risk scores and permit the application of mendelian randomization analyses and gene-environmental interaction investigation that is still challenging but will be extremely beneficial in the understanding of PDAC aetiology.

was performed on a small number of PDAC cases and controls. Additionally, considering that TL is a risk factor for pancreatic cancer (Campa et al., 2014; Giaccherini et al., 2021), a score based on the SNPs associated with TL (teloscore) was tested in PDAC and pNEN (Campa et al., 2019; Gentiluomo et al., 2022). The score was associated with PDAC risk, supporting an association between shorter telomere length and PDAC risk. For pNEN an association between genetically determined long telomeres and the risk of developing pNEN was observed.

4.6. Studies on PDAC survival

Although the main focus of the PANDoRA consortium is to identify variants associated with risk of developing pancreatic diseases, an effort has also been undertaken to identify variants associated with survival of pancreatic cancer patients. SNPs associated with risk (those identified via the first published GWAS) were tested to uncover their potential effect on survival since this has been observed for several other cancer types (Sartor et al., 2020; Summers et al., 2020; Theodoratou et al., 2018). We observed that rs8028529 had a weak association with PDAC survival, However, the study was carried out in a relatively small number of individuals and therefore it is not possible to exclude that it was due to random statistical fluctuation (Rizzato et al., 2011). Considering the capricious nature of association studies, a replication of a PDAC survival GWAS was attempted in PANDoRA and two SNPs, rs1567532 and rs12209785, were validated (Rizzato et al., 2016).

Recently Dimitrakopoulos et al. (2019) proposed two SNPs to be associated with survival in resected pancreatic cancer patients, but in PANDoRA the association was not confirmed, highlighting the importance of large studies and of replication efforts (Gentiluomo et al., 2021).

PANDoRA also analyzed genes associated with chemotherapeutic drugs transport and observed that four SNPs were associated with patient survival, rs3740067, rs3740073, rs717620 in the ATP Binding Cassette Subfamily C Member 2 (*ABCC2/MRP2*) gene (Gentiluomo et al., 2019a), and rs2504938 in the *SLC22A3* gene (Mohelnikova--Duchonova et al., 2017). The contribution of germline genetic variability is certainly a central point for achieving personalized medicine strategies, however for pancreatic cancer the road is still very long. All the associations are reported in Table 4.

5. What is the future direction of the consortium?

In these last ten years, PANDoRA has strengthened its relationship with several large consortia in Europe and in the United States, such as PanGenEU, PanC4, and PanScan. These collaborations are essential to uncover the disease etiology and to run powerful and meaningful studies (Campa et al., 2015; Erica J. Childs et al., 2015a, 2015b; B.M. Wolpin et al., 2014a, 2014b). As an example, the possibility of collaborations with other consortia will enable PANDoRA to study rarer entities such as cholangiocarcinoma, or bile duct cancers.

In addition, pooling together the resources of all the consortia and therefore dramatically increasing the sample size will enable the study of rare variants and allow also to attempt gene-by-gene and gene-by-environment interaction studies which would be extremely difficult for just PANDoRA or any other consortium alone.

5.1. IPMNs

An additional aim for the future is to study IPMNs, since our knowledge is very limited on what drives the risk of developing IPMN and, more importantly, progression from IPMN to carcinoma and the identifications of biomarkers and risk factors is sorely needed. From a genetic point of view there is a very limited knowledge on the process with only 2 loci suggested so far. One is *ABO* (Capurso et al., 2020), which is particularly interesting since it is also associated with PDAC (Rizzato et al., 2013). The other is in the PX Domain-Containing Protein Kinase-Like Protein (*PXK*) gene that is involved in telomere maintenance (Giaccherini et al., 2022b). However, both loci have been investigated in IPMN to PDAC transition, in relatively small samples while no loci have been identified for IPMN development.

5.2. Chronic pancreatitis risk

Chronic pancreatitis (CP) is a pathological condition that increases the risk of developing PDAC, with a relative risk of 13.3 (6.1–28.9) (Raimondi et al., 2010). The etiology of CP is extremely heterogeneous, but a genetic component is present, with different degrees in the majority of the clinical representations (Wertheim-Tysarowska et al., 2021). In PANDoRA we have collected 1006 cases of CP and many centers are actively recruiting cases, with the idea of performing a PANDoRA CP GWAS and/or of contributing to existing studies.

5.3. Mendelian randomization approaches

The growing availability of GWAS data and the progression of new mathematical algorithms have paved the way for the development of Mendelian Randomization (MR) approaches in the study of the directionality of the relationship between outcome and exposure (Burgess et al., 2013; Davey Smith and Hemani, 2014). The MR approach uses the genetic variants as proxies to explain non-genetic exposures (for example the SNPs associated with height in place of the direct measure expressed in cm). MR is a powerful tool, especially when the direct measure of interest is difficult to obtain or is not present in a dataset or when it can be confounded by other factors. For a more comprehensive explanation of the methods and its possible use please see Sanderson et al. (2022). For PDAC, three MR studies have been published so far and they supported a causative role of BMI on the risk of developing the disease (Carreras-Torres et al., 2017; Langdon et al., 2019; Lu et al., 2020). Genome wide genotyping is currently ongoing in PANDoRA, and MR will be a priority when data become available.

5.4. Pharmacogenetics

Studies on PDAC pharmacogenetics have been very limited so far across the world, mainly due to the low percentage of patients that undergo chemotherapy and the even lower number of individuals that respond to the therapy. In PANDoRA we focused so far on survival studies considering progression-free survival and overall survival as outcomes. However, new therapeutic regimens are showing progress and we plan to collect data and samples to investigate how the genetic

Table 4
SNPs associated with prognosis identified by PANDoRA.

SNP	Chromosome	Closest gene (s)	Effect allele	EAF[a]	HR (95% CI)[b]	P-value
rs1567532	2p12	*CTNNA2*	T	0.23	1.75 (1.19–2.58)	0.005
rs12209785	6p21	*RUNX2*	G	0.25	0.88 (0.80–0.98)	0.014
rs3740067	10q24.2	*ABCC2*	G	0.37	3.29 (1.56–6.97)	0.002
rs3740073	10q24.2	*ABCC2*	T	0.39	3.11 (1.52–6.38)	0.002
rs717620	10q24.2	*ABCC2*	T	0.20	2.90 (1.41–5.95)	0.004
rs2504938	6q25.3	*SLC22A3*	T	0.78	1.40 (0.95–2.05)	0.089

[a] EAF: risk allele frequency in the populations where the original study has been performed.
[b] HR: hazard ratio

variability will influence the individual response. A similar approach could be employed for pNEN treated with different regimens.

5.5. Identifying biomarkers for risk prediction

One of the main aims of the search for genetic risk factors for PDAC and the other clinical entities studied in PANDoRA is to facilitate risk stratification, i.e., assigning people in the general population or specific subgroups to classes of risk. The work performed by us and others on PRS/MRS clearly shows that efficient risk stratification will not be achieved by these tools alone. Their usefulness will be in assisting risk-adapted screening, where people will be classified in risk classes and screening measures and frequency will be calibrated to each class (Guo et al., 2023). Effective screening does not exist for PDAC, and given the relative rarity of the disease, it is probably not recommended in the general population. However, it could make sense in subgroups who are known to be at increased risk, such as people with family history of PDAC, new-onset diabetics patients with chronic pancreatitis and IPMN patients. There is an urgent need to discover and validate biomarkers to be potentially used for both risk stratification and screening. Recently several new biomarkers have been proposed and (Bunduc et al., 2022; Levink et al., 2023; Wang et al., 2023), while this work has very little relation with the activities done so far in PANDoRA, the consortium is uniquely well placed to perform validate them. Indeed, with the support of a COST action (https://www.cost.eu/actions/CA21116), we have established the TRANSPAN network, of which PANDoRA is the backbone, with, among others, the aim of doing biomarkers studies. Biological material of various types (whole blood, serum, plasma, urine, stool, pancreatic juice, cyst fluid, non-affected and tumoral pancreatic tissues) already collected by the PANDoRA/TRANSPAN clinical collaborators is being assessed for the suitability to do joint biomarkers studies. In parallel, standard operating procedures are being defined to prospectively collect additional biological material and data for studies to be performed in the coming years. Additionally, the centralization of the data could be used to test novel approaches such as machine learning or genetic ancestry inference from cancer-derived molecular data (Belleau et al., 2023).

6. Critical aspects of association studies

There are several critical issues in association studies that need to be considered and several aspects in which PANDoRA is well positioned to give meaningful contributions in the future. Like for most cancers, it is clear that the heritability of PDAC is explained only to a very limited extent, estimated to be 4.1% for the loci identified so far by GWAS (Chen et al., 2019). The simplest way to expand the number of known genetic risk loci is to perform larger GWAS, as shown successfully by groups studying breast and prostate cancer (Conti et al., 2021; Zhang et al., 2020). This can only be achieved by joining resources of multiple consortia, and it is currently ongoing in a large-scale GWAS on PDAC risk led by the National Cancer Institute of the USA, where the data of all the published GWAS will be included, in addition to a number of newly genotyped patients/samples from various resources, including PANDoRA. It is expected that the final sample size will include about 25,000 PDAC cases of European ancestry, about 8000 of East Asian ancestry, and similar numbers of controls.

One critical point is that in association studies it is often difficult to link the function of the variant identified with a function. In PANDoRA we have attempted to use functional data produced by other projects and consortia to scan the human genome for functional variants that affect gene expression and/or that are situated in non-coding RNA. One resource that has been successfully used is the Genotype-Tissue Expression (GTEx) project where data on genotyping produced with arrays, whole exome sequencing (WES) and whole genome sequencing (WGS) are correlated with gene expression primarily obtained with RNA sequencing. The use of this resource has tremendously helped in understanding if a given SNP regulates the expression of a nearby gene and therefore functionally characterize the association identified. These data are not in silico simulations or predictions but derive from wet lab experiments carried out on around 1000 individuals across 54 organs and tissues and therefore allow the identification of specific regulation in the specific tissues, including the pancreas. This not only has been useful to link novel loci to their function, but also to better understand the biologic function of known GWAS hits. Additionally, databases on non-coding RNA function are continuously updated and linking the position in the genome of genetic variants and non-coding RNA has been useful to better characterize the associations of several established PDAC risk loci such as *NR5A2* (chromosome 1q32.1), *ETAA1* (2p14), *TERT-CLPTM1L* (5p15.33), *ABO* (9q34.2) and BCAR (16q23.1). All these resources are continuously growing and therefore it would be easier in the future to better understand why a given SNP is associated with PDAC risk.

Another point on which PANDoRA will improve is that the collection of somatic material is ongoing in some of the centers and therefore it would be possible, also considering the lowering of the prices of NGS techniques, to explore not only the involvement of common germline variants but also of rarer high penetrance somatic mutations. In this respect only one study, with a limited number of cases has been published with PANDoRA samples (Rachakonda et al., 2013).

A point of weakness of PANDoRA, that is shared with all retrospective case-control studies, is the lack of extensive data on environmental and lifestyle exposure such as smoking, alcohol drinking and diet. To partially overcome this limitation when the PANDoRA GWAS data are available we will use the genotyping data to carry out MR analyses and possibly further our knowledge on the impact of various factors on disease susceptibility, to the extent that the genetic component of those factors captured by the MR approach is sufficiently representative of their variation.

Finally, another limitation of genetic association studies is that individually each identified SNP explains a modest proportion of the variance of the phenotype of interest and therefore they are still of moderate use in clinical use. However, new risk loci are being identified faster than in the past and better algorithms and statistical methods have been developed to sum the effects of the SNPs in PRSs. The use of PRSs is getting a lot of attention because it has been clearly shown that adding up an adequate number of risk alleles it is possible to reach predictive estimates that are similar to high penetrance mutations (Roberts et al., 2023). It is plausible that in the future the combination of PRS with environmental and lifestyle variables will improve the possibility of stratifying the population and identifying high risk individuals.

7. Conclusion

In conclusion, in the last decade PANDoRA has brought together 29 centers across the world and has been instrumental in the discovery of 22 PDAC susceptibility SNPs. Recently the consortium has been awarded a COST action (https://www.cost.eu/actions/CA21116), that will certainly be of enormous help in strengthening even more the collaboration between the institutions involved in it.

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