Genetic Susceptibility in Understanding of Pancreatic Ductal Adenocarcinoma Risk: A Decade-Long Effort of the PANDORA Consortium

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ABSTRACT

Pancreatic cancer, a complex disease, emerges as a severe health problem worldwide and it exhibits a poor prognosis and high mortality. Risk factors associated with sporadic pancreatic cancer remain poorly understood, even less is known about disease prognosis due to its rapid progression. The PANcreatic Disease ReseArch (PANDoRA) consortium, of which the authors are members, was established to coordinate the efforts of different research groups to uncover new genetic factors for pancreatic cancer risk, response to treatment, and patient survival. PANDoRA consortium has contributed to the identification of several low-penetrance risk loci for the disease both by candidate variants approach and genome-wide association studies, including those in cell-cycle and DNA damage response, telomere homeostasis, SCL and ABC transporters, *ABO* locus variability, mitochondrial metabolism and it participated on collaborative genome-wide association study approach and implementation of a search for functional-based pancreatic cancer risk loci and long noncoding RNAs. Complex studies covering genetic, environmental and microenvironmental factors in the pancreatic cancer onset, progression and its prognosis are warranted.

Pancreatic Cancer: Importance and Genetics

Pancreatic cancer ranks among frequent malignancies with more than 458,918 new cases in 2018 (http://gco.iarc.fr/today/online-analysis-table) worldwide; it exhibits a poor prognosis and high mortality (1). Pancreatic ductal adenocarcinoma (PDAC), the most common subtype of pancreatic cancer, is anticipated as the second leading cause of cancer death in the United States by 2030 (2). Less than 10% of PDAC cases are familial: germline mutations in *BRCA1/2, ATM, CHEK2, PALB2*, and *CDKN2A* contribute to the mechanisms of malignant transformation. Somatic *KRAS* mutations occur in a majority of tumors and with mutations in *SMAD4, CDKN2A*, and *TP53* represent the most common genetic changes in sporadic PDAC (3). These genetic alterations along with low-penetrance loci and other risk factors (obesity, insulin resistance, type 2 diabetes mellitus, smoking, personal history of pancreatitis, age, family history of PDAC or other cancers, exposure to ionizing radiation, environmental and life-style factors), are underlying pancreatic cancer onset (4). The PANcreatic Disease ReseArch (PANDoRA) consortium, of which the authors are members, was established to coordinate the efforts of different research groups and strives to uncover new genetic factors for pancreatic cancer risk, response to treatment, and patient survival. The goal is to detect pancreatic cancer while the disease is in its earliest and treatable stages (5).

PDAC Genetics and Disease Risk

A decade-long effort of the PANDoRA consortium resulted in the discovery of mild to low risk associations for variants in several genomic regions, modulating PDAC risk and in minor extent, prognosis; significant results of individual studies are given in **Table 1**. Because *TP53* has a fundamental role in cell cycle and apoptosis and is frequently mutated in solid tumors, we studied, in a population from Czech Republic, whether *TP53* polymorphisms modulate the risk of PC. By assessing polymorphisms individually, patients with variant C allele of rs1042522 polymorphism were at an increased risk of PDAC. By comparing with the most common haplotype A1GCG, the A2CCG haplotype was associated with an increased risk and the A1CCG with a reduced risk of PDAC (6). The above haplotypes also affected colorectal and breast cancer risk. In the line of investigating of associations between inherited germline mutations in cancer predisposition genes and the risk of pancreatic cancer a case–control study comprising 3,030 patients with pancreatic cancer is reported by Hu and colleagues (7). The authors observed significant associations between pancreatic cancer and mutations in *CDKN2A*, *TP53*, *MLH1*, *BRCA2*, *ATM*, and *BRCA1*. In this study, mutations in six genes associated with pancreatic cancer were identified in 5.5% of all patients with pancreatic cancer, including 7.9% of those with a family history of pancreatic cancer (7). The manuscript by Amundadottir and colleagues (8) inspired PANDoRA consortium to address the association of pancreatic cancer risk with carriers of the A or B allele of single-nucleotide polymorphisms (SNP). These SNPs ale involved in determining the blood group in comparison with the *O* allele, which encodes a nonfunctional enzyme. *A1* variant carriers were at higher risk of developing PDAC. These data are consistent with higher

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Cancer Epidemiol Biomarkers Prev 2022;31:942–8

doi: 10.1158/1055-9965.EPI-21-1340

Table 1. Gene variants significantly associated with the risk of PDAC.

SNP ID	Gene	Localisation (chr:base, GRCh38.p13)	Consequence	HGVSc	HGVSp	Allele frequency (1000 Genomes database)	OR (95% CI)	N of cases vs. N of controls	Note	Ref.
rs1042522[a]	*TP53*	17:7676154	missense variant	ENST00000269305.9:c.215C>G	ENSP00000269305.4:p.Pro72Arg	0.5429	1.73 (1.26–2.39)	240 vs. 1,827		Naccarati et al. Carcinogen 2010
rs12947788[a]		17:7674109	intron variant	ENST00000269305.9:c.782+72C>T	x	0.1783	NS			
rs17884306[a]		17:7668783	3 prime UTR variant	ENST00000269305.9:c.[a]826G>A	x	0.05711	NS			
rs17878362[a]		x	x	x	x	x	NS			
A2CCG haplotype		x	x	x	x	x	1.39 (1.02–1.88)			
A1CCG haplotype		x	x	x	x	x	0.30 (0.12–0.76)			
rs8176741	*ABO* locus	9:133256074	synonymous variant	ENST00000611156.4:c.654C>T	ENSP00000483265.1:p.His218%3D	0.153	*0.73 (0.58–0.9)*	1,028 vs. 2,257		Rizzato C, et al. Oncol Rep 2013
rs8176746		9:133255935	missense variant	ENST00000611156.4:c.793C>A	ENSP00000483265.1:p.Leu265Met	0.1528	*0.8 (0.65–0.99)*			
rs8176747		9:133255928	missense variant	ENST00000611156.4:c.800G>C	ENSP00000483265.1:p.Gly267Ala	0.1528	*0.77 (0.63–0.95)*			
rs505922		9:133273813	intron variant	ENST00000611156.4:c.28+1349G>A	x	0.650063	1.18 (0.99–1.40)			
rs6971499	*LINC-PINT*	7:130995762	non coding transcript variant	ENST00000647388.1:n.336–11653A>G	x	0.12	0.79 (0.74–0.84)	7,683 vs. 4,397	2 stages of analysis	Wolpin BM, et al. Nat Gen 2014
rs7190458	*BCAR1/CTRB1/CTRB2*	16:75229763	synonymous variant	ENST00000162330.10:c.2361C>T	ENSP00000162330.5:p.Leu787%3D	0.1016	1.46 (1.30–1.65)			
rs9581943	*PDX1*	13:27919860	upstream gene variant	NC_000013.11:g.27919860G>A	x	0.3281	1.15 (1.1–1.2)			
rs16986825	*ZNRF3*	22:28904318	intron variant	ENST00000544604.7:c.300+20252C>T	x	0.2039	1.18 (1.12–1.25)			
rs2736098	*TERT*	5:1293971	synonymous variant	ENST00000310581.10:c.915G>A	ENSP00000309572.5:p.Ala305%3D	0.2656	0.80 (0.76–0.85)			
rs11655237	*LINC00673*	17:72404025	non coding transcript variant	ENST00000648631.1:n.763–2604G>A	x	0.2344	*1.26 (1.19–1.34)*	9,925 vs. 11,569	two-stage genome-wide association study	Childs EJ et al. Nat Genet 2015
rs17688601	*SUGCT*	7:40827064	intron variant	ENST00000335693.9:c.1154–33252C>A	x	0.1673	*0.88 (0.84–0.92)*			
rs9854771	*TP63*	3:189790682	intron variant	ENST00000264731.8:c.325–17590G>A	x	0.2869	*0.89 (0.85–0.93)*			
rs1486134	*ETAA1*	2:67412637	downstream gene variant	NC_000002.12:g.67412637G>T	x	0.7302	*1.14 (*1.09–1.19)			
rs2853677	*TERT*	5:1287079	intron variant	ENST00000310581.10:c.1574–4455C>T	x	0.6124	*0.85 (0.80–0.90)*	5,550 vs. 7,585	2 stages of analysis	Campa et al. Int J Cancer, 2015
rs2736100		5:1286401	intron variant	ENST00000310581.10:c.1574–3777G>T	x	0.5154	1.11 (1.02–1.21)			
rs4583925		5:1248932	downstream gene variant	NC_000005.10:1248931:C>T	x	0.02356	1.31 (1.1–1.55)			
rs2735948		5:1299098	upstream gene variant	NC_000005.10:g.1299098A>G	x	0.7342	1.13 (1.04–1.23)			
rs10936599	*TERC*	3:169774313	synonymous variant	ENST00000349841.10:c.18C>T	x	0.2706	*0.78 (0.69–0.89)*			

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Table 1. Gene variants significantly associated with the risk of PDAC. (Cont'd)

SNP ID	Gene	Localisation (chr:base, GRCh38.p13)	Consequence	HGVSc	HGVSp	Allele frequency (1000 Genomes database)	OR (95% CI)	N of cases vs. N of controls	Note	Ref.
rs3217992	*CDKN2B*	9:22003224	3 prime UTR variant	ENST00000276925.7: c.[a]2763G>A	x	0.3482	ORhet: 1.14 (1.01–1.27) ORhom: 1.30, (1.12–1.51)	2,857 vs. 6,111		Campa D, et.al, Oncotarget 2016
rs2816938	*RNU6–609P*	1:200016240	upstream gene variant	NC_000001.11:g.200016240T>A	x	0.3207	1.23 (1.15–1.31)		GWAS study	Zhang M, et al. Oncotarget 2016
rs10094872	*CASC11*	8:127707639	non coding transcript variant	ENST00000502463.7: n.144–15773T>A	x	0.2806	1.18 (1.11–1.25)		Gene expression study	
rs35226131	*TERT*	5:1295258	upstream gene variant	NG_009265.1:g.4790G>A	x	0.01218	0.71 (0.63–0.80)			
rs10273639	*PRSS1-PRSS2*	7:142749077	upstream gene variant	NG_008307.3:g.4594T>C	x	0.394	ORhom: 1.19 (1.02–1.38)	2,914 PDAC vs. 356 CPT vs. 5,596 controls	rs11988997, rs379742, rs10273639, rs2995271, rs12688220 risk variants for CPT	Campa et al, Int J Cancer 2018
rs78417682	*TNS3*	7:47449305	intron variant	ENST00000311160.14:c.-75–7250C>G	x	0.1214	0.85 (0.80–0.90)	11,537 vs. 17,107	PanScan	Klein A, et al, Nat Com 2018
rs13303010	*NOC2L*	1:959193	intron variant	ENST00000327044.7: c.26+22C>T	x	0.6344	1.26 (1.19–1.35)		PanC4	
rs2941471	*HNF4G*	8:75558169	intron variant	ENST00000396423.4: c.734–349G>A	x	0.5889	0.89 (0.85–0.93)		Pandora	
rs4795218	*HNF1B*	17:37718512	intron variant	ENST00000617811.5: c.1046–7849T>C	x	0.78512	0.88 (0.84–0.92)			
rs1517037	*GRP*	18:59211042	upstream gene variant	NC_000018.10:g.59211042C>T	x	0.2368	0.86 (0.80–0.91)			
rs2736100	*TERT*	5:1286401	intron variant	ENST00000310581.10: c.1574–3777G>T	x	0.5154	1.54 (1.35–1.76)	2,374 vs. 4,326		Campa D, et al. Int J Cancer 2019
rs7675998	*NAF1*	4:163086668	upstream gene variant	NC_000004.12: g.163086668A>G	x	0.8069	0.80 (0.73–0.88)			
rs3740067	*ABCC2*	10:99844024	intron variant	ENST00000647814.1: c.3843+124C>G	x	0.2692	HR: 3.29 (1.56–6.97)	1,415	prognosis	Gentiluomo M, et al. Carcinog 2019
rs3740073		10:99817203	intron variant	ENST00000647814.1: c.2095–105T>C	x	0.6929	HR: 3.11 (1.52–6.38)			
rs717620		10:99782821	5 prime UTR variant	ENST00000647814.1:c.-24C>T	x	0.135	HR: 2.90 (1.41–5.95)			

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Table 1. Gene variants significantly associated with the risk of PDAC. (Cont'd)

SNP ID	Gene	Localisation (chr:base, GRCh38.p13)	Consequence	HGVSc	HGVSp	Allele frequency (1000 Genomes database)	OR (95% CI)	N of cases vs. N of controls	Note	Ref.
rs11571833	*BRCA2*	13:32398489	stop gained	ENST00000380152.8:c.9976A>T	ENSP00000369497.3:p.Lys3326Ter	0.004393	1.78 (1.26–2.52)	2,935 vs. 5,626		Obazee O, et al, IJC 2019
rs17879961	*CHEK2*	22:28725099	missense variant	ENST00000404276.6:c.470T>C	ENSP00000385747.1:p.Ile157Thr	0.000998	1.74 (1.15–2.63)			
rs2328991	*LOC107984587*	13:76822966	non coding transcript variant	ENST00000648060.1:n.229+13015G>C	x	0.0757	1.19 (1.09–1.30)	855 young vs. 4,142 controls	2 stages study	Campa et al. IJC 2020
101 SNPs for mitochondrial and 7,509,345 SNPs for nuclear genomes.							No signif. results	12,884 vs. 42,986	2 stages study	Peduzzi G. et al. CEBP 2021
rs7985480	*LMO7*	13:75627328	non coding transcript variant	ENST00000563635.5:n.704+5460T>C	x	0.7530	1.12 (1.07–1.17)	14,062 vs. 11,261	2 stages study	Ye Lu, Front Genet 2021
rs2035875	*KRT8*	12:52902133	intron variant	ENST00000552551.5:c.325–61T>C	x	0.5669	1.11 (1.08–1.16)	13,713 vs. 43,784	2 stages study	Pistoni L. et al. Carcinog 2021
rs789744	*SRGAP1*	12:64091580	intron variant	ENST00000355086.8:c.1539+202A>G	x	0.8870	0.90 (0.86–0.94)			
rs353630§§	*CD44*	11:35166644	intron variant	ENST00000428726.8:c.68–9931G>A	x	0.2809	HR: 5.01 (1.58–15.88)	1,856	prognosis	Gentiluomo et al. Sci Rep 2021
PRS							2.70 (1.99–3.68)	7,259 vs. 6,929		Galeotti J Med Genet 2021
rs7046076	*lnc-SMC2–1*	9:104024600	non coding transcript variant	NC_000009.12:g.104024600T>C	x	0.4097	1.21 (1.10–1.18)	9,893 vs. 9,969		Corradi et al. Int J Cancer 2021
rs2504938	*SLC22A3*	6:160403722	intron variant	ENST00000275300.3:c.534–3319C>T	x	0.9065	Signif. in discovery, not in validation set	1,518 vs. 3,908		Mohelnikova-Duchonova B, et al. Sci Rep 2017
rs9364554		6:160412632	intron variant	ENST00000275300.3:c.975+1786C>T	x	0.2101				
rs2457571		6:160413796	intron variant	ENST00000275300.3:c.975+2950T>C	x	0.6839				

Abbreviations: CPT, chronic pancreatitis; NS, not significant.

[a]SNPs used for haplotype construction (OR, 1.19; 95% CI, 1.02–1.40).

glycosyltransferase activity for the A1 variant compared with the A2 variant. However, no effect of the genetic variability at the *ABO* locus on pancreatic cancer survival was shown in the study of PANDoRA group (9).

The effort of PanScan/PanC4 has resulted in the identification of eight SNPs that map to three loci on chromosomes 13q22.1, 1q32.1 and 5p15.33 (10). Among these common susceptibility *loci* identified for pancreatic cancer there is rs401681 in the *TERT – CLPTM1 L* gene region (chr5p15.33; ref. 11). Due to the low linkage disequilibrium present in this region, additional SNPs have been identified as independent risk factors for PDAC. An analysis of genetic variability of the telomerase reverse transcriptase (*TERT*) and the telomerase RNA component (*TERC*) genes, conducted within the PANDoRA consortium, revealed a significant association between a variant rs2853677in *TERT* and pancreatic cancer risk (**Table 1**). Three additional SNPs in *TERT*, rs2736100, rs4583925, and rs2735948 reached statistical significance after correction for multiple testing (**Table 1**). The *TERT locus* is associated with pancreatic cancer risk through several independent variants (12). Interestingly, other studies showed that genetically predicted short telomere length is either not associated with PDAC risk (13) or the association is not consistent (14). One option to tackle these inconsistencies may be the direct measurement of telomere length in blood cells and/or in tumor tissue. However, the experience of the authors introduces additional variables, such as target versus surrogate tissue (15) or complex disease phenotype/tumor heterogeneity (16).

Another gene involved in pancreatic cancer etiology is *CDKN2A* (p16). Hence, the PANDoRA consortium focused on the common genetic variability in this region and pancreatic cancer risk by genotyping 13 SNPs. The *A* allele of the rs3217992 SNP was associated with an increased pancreatic cancer risk (**Table 1**), possibly due to changing the binding site of one or more noncoding RNAs. The novel association in this pleiotropic region *CDKN2A/B* could represent a genetic link between diabetes and pancreatic cancer risk (17). The study by Zhang and colleagues, in which PANDoRA was part of, disclosed three new pancreatic cancer risk SNPs: rs2816938 at chromosome 1q32.1 (*NR5A2*), rs10094872 at 8q24.21 (*MYC*), and rs35226131 at 5p15.33 (*CLPTM1L-TERT*; ref. 18). The genetic variability in solute carrier transporter *SLC22A3* was investigated with pancreatic cancer risk. In summary, common genetic variation in the *SLC22A3* gene is unlikely to significantly contribute to pancreatic cancer risk; however, the rs2504938 SNP in *SLC22A3* associates with a prognosis of patients with pancreatic cancer (19). PANDoRA did not observe any specific chronic pancreatitis risk loci that would also contribute to PDAC susceptibility (20). Telomere deregulation is a hallmark of cancer and telomere length in lymphocytes (LTL) may represent a risk marker for several cancers. In a study that analyzed ten SNPs (*ZNF676*-rs409627, *TERT*-rs2736100, *CTC1*-rs3027234, *DHX35*-rs6028466, *PXK*-rs6772228, *NAF1*-rs7675998, *ZNF208*-rs8105767, *OBFC1*-rs9420907, *ACYP2*-rs11125529, and *TERC*-rs10936599) combined in an LTL genetic score, a statistically significant association was found between genetically determined shorter telomere length and PDAC risk (21). Rare truncating *BRCA2* K3326X (rs11571833) and pathogenic *CHEK2* I157T (rs17879961) variants have been tested for the risk of sporadic PDAC within PANDoRA consortium (**Table 1**; ref. 22). Early onset pancreatic cancer (EOPC), a rare disease with a very high mortality rate, has been investigated by genome-wide association study (GWAS) in young patients diagnosed with PDAC. PANDoRA proposed a novel variant rs2328991 to be involved in EOPC risk, despite current difficulty to ascertain a mechanistic link between the variant and the function (23). Since the mitochondrial metabolism has been associated with PDAC risk and a systematic investigation of the genetic variability of mitochondrial genome (mtSNP) and of all the nuclear genes involved in its functioning (n-mtSNPs) is virtually missing, PANDoRA conducted a two-phase association study of mtSNPs and n-mtSNPs to assess their effect on PDAC risk (**Table 1**). In the discovery phase, 49 n-mtSNPs and no mtSNPs associated with PDAC risk were identified, but none replicated in the second phase (24).

GWAS have become a powerful tool for detecting genetic variants associated with complex traits, including pancreatic cancer. The PANDoRA consortium has participated in a multistage GWAS on 7,683 individuals with PC and 4,397 controls of European descent. Four new loci reached GWAS significance: rs6971499 at 7q32.3 (*LINC-PINT*), rs7190458 at 16q23.1 (*BCAR1/CTRB1/CTRB2*), rs9581943 at 13q12.2 (*PDX1*) and rs 16986825 at 22q12.1. (*ZNRF3*, **Table 1**). An independent signal in exon 2 of *TERT* at the region 5p 5.33 (rs2736098) was also identified (25). Three newly associated regions 17q25.1 (*LINC00673*, rs11655237), 7p13 (*SUGCT*, rs17688601), and 3q29 (*TP63*, rs9854771) were identified in a GWAS on cases and controls from North America, Central Europe and Australia (11). Previously reported associations at 9q34.2 (*ABO*), 13q22.1 (*KLF5*), 5p15.33 (*TERT* and *CLPTM1*), 13q12.2 (*PDX1*), 1q32.1 (*NR5A2*), 7q32.3 (*LINC-PINT*), 16q23.1 (*BCAR1*) and 22q12.1 (*ZNRF3*) (25; 11) were also replicated. The study by Klein and colleagues (26) reported the largest GWAS on pancreatic cancer cases of European ancestry. The novel association at rs78417682 (7p12/*TNS3*) was reported. Replication of 10 promising signals in the PANDoRA set of patients yielded new GWAS significant loci: rs13303010 at 1p36.33 (*NOC2L*), rs2941471 at 8q21.11 (*HNF4G*), rs4795218 at 17q12 (*HNF1B*), and rs1517037 at 18q21.32 (*GRP*; **Table 1**). To identify individuals at high risk of developing PDAC a polygenic risk score (PRS) for PDAC risk prediction, combining the effect of known risk SNPs, was computed in the PANDoRA consortium. The scores were significantly associated with increased PDAC risk (**Table 1**). PRS in assessing PDAC risk represents a useful tool for risk stratification in the population (27).

PANDoRA expanded the knowledge of PDAC genetic heritability by focusing on SNPs that modulate miRNA function. Out of SNPs in 3 prime untranslated regions (3′UTRs) of miRNA target genes, only rs7985480 was consistently associated with PDAC risk (**Table 1**). These results, alongside studies considering expression quantitative traits (eQTL) and those on SNPs in long noncoding RNA, proved the usefulness of functional prioritization to identify PDAC risk-associated genetic polymorphisms (28–30).

The analysis of eQTLs in three independent pancreatic datasets provided molecular support of *NOC2 L* as a PDAC susceptibility gene (26). By exploiting functional and GWAS data, the associations between polymorphisms affecting gene function in the pancreas (eQTLs) and PDAC risk was also investigated in PANDoRA. A genome-wide significant association between the *A* allele of the rs2035875 polymorphism and increased PDAC risk was identified (**Table 1**). This allele is often associated with increased expression of the keratin genes *KRT8* and *KRT18* in the pancreas. In addition, the A allele of the rs789744 variant conferred a decreased risk of PDAC. The A allele is associated with higher *SRGAP1* gene expression, which in turn inactivates the cyclin-dependent protein 42 (*CDC42*) gene expression and decreases the risk of PDAC. Significant associations and plausible biological mechanisms may further add

strong candidates to functional-based PDAC risk loci (29). Since long noncoding RNAs (lncRNA) are involved in regulation of key biological processes, by combining GWAS and functional data the genetic variability in all lncRNAs was also investigated and a significant association between the rs7046076 SNP and risk of PDAC (**Table 1**) was observed. This SNP participates in the regulation of several cell cycle genes, such as *CDKN2B*. A possible mode of action could be an imperfect interaction between lncRNA and miRNA (30). Despite the overall effort much of pancreatic cancer heritability remains unexplained (31).

PDAC Genetics and Disease Prognosis

The rs2504938 SNP in solute carrier transporter *SLC22A3* significantly associated with a poor prognosis of patients with pancreatic cancer (19). The ATP binding cassette subfamily C member 2 (ABCC2) protein mediates a response to various drugs and is differentially expressed in gemcitabine sensitive and resistant cells. Moreover, SNPs in the gene have been associated with differential outcomes and prognosis in several malignancies. The associations between SNPs in the *ABCC2* gene and overall survival (OS) in patients with PDAC were analyzed. The results are presented in **Table 1**; briefly: whereas no statistically significant associations in patients with more advanced PDAC were observed, rs3740067, rs3740073 and rs717620 could be promising prognostic markers in patients with stage I PDAC (32). In addition, two SNPs (*CD44*-rs353630 and *CHI3L2*-rs684559), that were suggested as genetic markers of prognosis, were studied within PANDoRA. They did not show, either individually or combined, any statistically significant association, suggesting that their effect cannot be generalized to all patients with pancreatic cancer (33). The study of Wang and colleagues demonstrated that host genetic variant (rs2057482-CC genotype) alters the regulation of the miR-199a/HIF1A regulatory loop, increases susceptibility to PDAC and is associated with worse prognosis (34). A recent study by Lin and colleagues indicated that regional and ethnic differences in gene variant frequencies and, possibly, different impact of risk factors should be given proper consideration (35). Finally, noncoding RNAs have been suggested as putative prognostic biomarkers for pancreatic cancer prognosis and treatment prediction (36). In the recent reviews the potential of cell-free DNA biomarkers in pancreatic cancer and other gastrointestinal cancer prognosis has been discussed (37, 38).

Conclusions and Perspectives

PANDoRA consortium has contributed to the identification of several low-penetrance risk loci for PDAC, including those in cell cycle and DNA damage response, telomere homeostasis, SCL and ABC transporters, *ABO* locus variability and mitochondrial metabolism. It has also participated on GWAS approach and implementation of a search for functional-based PDAC risk loci and long noncoding RNAs. However, risk factors associated with sporadic pancreatic cancer remain poorly understood. PANDoRA's effort in disease prognosis was even less satisfactory due to the rapid progression of the disease. To achieve early detection of pancreatic cancer the consortium will aim at addressing genetics in the new traits (e.g., autophagy), deeper understanding of shared traits between the incident type 2 diabetes mellitus, pancreatic cancer, and chronic pancreatitis, and elucidation of telomeric homeostasis and a role of mitochondria in early development of PC. PANDoRA consortium will dedicate its attention to the identification and role of rare variants in pancreatic carcinogenesis. Further, studies on genetic factors affecting prognosis of pancreatic cancer and its treatment are scarce and an effort has to be dedicated to these aspects. Despite emerging and studied risk factors for pancreatic cancer risk (such as tobacco use, diabetes, chronic pancreatitis, particular nutritional deficits, bacterial infections, and psychosocial factors), a little attention is dedicated to interactions of these risk factors in additive or synergistic mode (39) or to gene–environmental interactions. Complex studies covering genetic, environmental and microenvironmental factors and their interactions in the pancreatic cancer onset, progression and therapy outcomes are warranted.

Authors' Disclosures

No disclosures were reported.

Acknowledgments

P. Vodicka was awarded by Grant Agency of the Ministry of Health of the Czech Republic NU21-07-00247. L. Vodickova and P. Vodicka acknowledge Charles University Research Centre program UNCE/MED/006 and the Charles University Research Fund - Cooperation no. 43- Surgical Disciplines for providing financial support.

Received November 21, 2021; revised February 8, 2022; accepted March 2, 2022; published first May 4, 2022.

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