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Potential association between *PSCA* rs2976395 functional variant and pancreatic cancer risk

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Abstract

Correlated regions of systemic interindividual variation (CoRSIV) represent a small proportion of the human genome showing DNA methylation patterns that are the same in all human tissues, are different among individuals, and are partially regulated by genetic variants in *cis*. In this study we aimed at investigating single-nucleotide polymorphisms (SNPs) within CoRSIVs and their involvement with pancreatic ductal adenocarcinoma (PDAC) risk. We analyzed 29,099 CoRSIV-SNPs and 133,615

Chiara Corradi and Giulia Lencioni share the first position.

Federico Canzian and Daniele Campa share the last position.

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CoRSIV-mQTLs in 14,394 cases and 247,022 controls of European and Asian descent. We observed that the A allele of the rs2976395 SNP was associated with increased PDAC risk in Europeans ($p = 2.81 \times 10^{-5}$). This SNP lies in the prostate stem cell antigen gene and is in perfect linkage disequilibrium with a variant (rs2294008) that has been reported to be associated with risk of many other cancer types. The A allele is associated with the DNA methylation level of the gene according to the PanCan-meQTL database and with overexpression according to QTLbase. The expression of the gene has been observed to be deregulated in many tumors of the gastrointestinal tract including pancreatic cancer; however, functional studies are needed to elucidate the function relevance of the association.

KEYWORDS

DNA methylation, pancreatic cancer, risk factors, single-nucleotide polymorphism

What's new?

Correlated regions of systemic interindividual variation (CoRSIV) contain or are near to single-nucleotide polymorphisms (SNPs) that are likely to be associated with disease. Here, CoRSIVs were analyzed for the presence of SNPs and methylation quantitative trait loci effects in relation to pancreatic ductal adenocarcinoma (PDAC) risk in individuals of European or Asian descent. Of 29,099 CoRSIV SNPs identified, only 1—the A allele of *PSCA*-rs2976395—was found to have a possible relationship with PDAC risk. The rs2976395 SNP was associated with increased *PSCA* methylation. Further investigation of *PSCA*-rs2976395 is needed to better elucidate its relevance in PDAC.

1 | INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) is a highly aggressive form of cancer, with a 5-year survival after diagnosis of about 11%.[1] PDAC is expected to become the second leading cause of cancer-related deaths in western countries by 2030.[2] The main reasons for this meagre survival are the absence of specific symptoms, of effective curative treatment and of applicable preventive measures, through risk stratification and early detection.[3] Only a small number of non-genetic risk factors including smoking behavior high body mass index (BMI), pancreatitis and age have been identified.[4] Several others have been suggested, but with limited validation.[4,5] Genetic association studies have identified approximately 30 susceptibility loci through genome-wide association studies (GWAS)[6–13] or large candidate region/gene approaches.[14–20] However, only a very limited proportion of the heritability of the disease has been determined, indicating that many more loci need to be discovered.[21] Recently, secondary analysis of GWAS data (i.e., the re-analysis of large GWAS, using only single-nucleotide polymorphisms [SNPs] belonging to a certain pathway or functional class, followed by a replication in a large cohort for validation) has been used to identify regulatory SNPs associated with PDAC risk, that were not reported by the original GWASs.[22–24] In addition to environmental and genetic components, also epigenetics plays a role in PDAC development.[25] In particular, several studies have shown the importance of aberrant DNA methylation in PDAC pathogenesis.[26–28] However, DNA methylation is tissue-specific and changes over time, which makes impractical to analyze it in an epidemiologic setting. Very recently Gunasekara and colleagues have identified 9926 methylated sequences, called correlated regions of systemic interindividual variation (CoRSIV), that show the same DNA methylation patters in all tissues/organs and do not change over time. Interestingly, the DNA methylation pattern is different among different individuals.[29] CoRSIV regions are 200–300 bp long are randomly distributed in the genome and represent only the 0.1% of the genome. CoRSIV regions are polymorphic, and their DNA methylation status is largely regulated by SNPs acting in *cis* or in *trans*. In addition, CoRSIV regions are often identified as top hits in epigenome-wide association studies (EWAS) and therefore SNPs within their sequence or nearby are likely candidates to be associated with disease risk.[30] The discovery of CoRSIV has prompted the investigation of their effect in various diseases, and they have been found to be associated with several human pathologic phenotypes, including metabolic diseases, cardiovascular diseases, mental disorders and digestive system diseases.[29] Gunasekara and colleagues also tested, within the UK Biobank (UKBB), if CoRSIVs were implicated in four cancers, but surprisingly, they have not identified strong association. However, an analysis for PDAC was not reported, possibly because the number of PDAC cases in UKBB is relatively low.[30] Therefore, considering that CoRSIV-related SNPs regulate the methylation level at the region, the aim of this study was to analyze the germline genetic variability within CoRSIV regions to identify novel susceptibility loci and to colocalize known PDAC risk loci in CoRSIV regions, in order to give a functional explanation, exploiting

existing databases, to variants that have already been reported but for which the biologic mechanism is unclear. The study of CoRSIV SNPs in PDAC is particularly relevant because, as an organ is not easily accessible for epigenetic epidemiology studies and because the unexplained heritability of the disease is still high, suggesting that many loci remain to be discovered.

2 | MATERIALS AND METHODS

2.1 | CoRSIV SNP and CoRSIV-mQTL identification

A total of 9926 CoRSIV regions, as defined by Gunasekara and colleagues, have been selected.[29] In each CoRSIV, all SNPs with minor allele frequency (MAF) higher than 5% in Europeans and East Asians were identified using the data downloaded from the 1000 Genome website (https://www.internationalgenome.org/). In addition, 133,615 SNPs and their proxies ($r^2 > .8$) that have shown a strong methylation quantitative trait locus (mQTL) effect on CoRSIV (CoRSIV-mQTL), have been included in the analysis. These SNPs were identified by a recent work by Gunasekara et al.,[30] as having regulatory effect on CoRSIV methylation and intriguingly are not necessarily situated in CoRSIV regions.

2.2 | Study subjects and workflow

The association between CoRSIV-SNPs, CoRSIV-mQTL, and PDAC risk was tested in individuals of European descent, using four different studies: the Pancreatic Cancer Cohort Consortium (PanScan), the Pancreatic Cancer Case-Control Consortium (PanC4), the FinnGen project as discovery, and the PANcreatic Disease ReseArch (PANDoRA) consortium as replication, for a total of 12,355 PDAC cases and 214,430 controls. Genotype data of PanScan (I–III) and PanC4 studies was downloaded from the NCBI database of genotypes and phenotypes (dbGaP) (study accession numbers phs000206.v5.p3 and phs000648.v1.p1; project reference #12644). Detailed information on the study participants and genotyping arrays used are described in the original publications.[8–12] The PanScan (I–III) and PanC4 datasets were merged. Individuals that did not pass quality control procedures (gender mismatches, call rate <0.98), minimal or excessive heterozygosity (>3 standard deviation from the mean) or cryptic relatedness (PI_HAT >0.2) were excluded from the dataset to be imputed. SNPs with low imputation quality (INFO score $r^2 < .7$, MAF <0.01 or call rate <0.9) were excluded after imputation, and evidence for violation of the Hardy–Weinberg equilibrium ($p < 10^{-6}$) were excluded. Individuals not clustering in the PCA with the 1000 Genomes subjects of European descent were excluded from further analysis. The final dataset comprised 15,772 individuals (8738 cases and 7034 controls).

The FinnGen project GWAS on 881 PDAC cases and 204,070 controls (excluding other cancer types) was used. Summary statistics were downloaded (FinnGen Release R6) from the FinnGen website. More details on genotypes, data and statistical analysis are available at the FinnGen website (https://www.finngen.fi).

Then, CoRSIV-SNPs and CoRSIV-mQTLs with a statistically significant association ($p < .05$) in PanScan+PanC4 and FinnGen were replicated in the PANDoRA consortium. The detailed description of PANDoRA consortium is available elsewhere.[31] Briefly, it is a large multicentric study involving several European countries and Brazil. In this study, a total of 2736 cases and 3326 controls of European descent, and 68 cases and 254 controls from Brazil were used. Controls were blood donors and hospitalized individuals without diagnosis of cancer. Additional German controls from the longitudinal prospective ESTHER study and Dutch controls from the European Prospective Investigation into Cancer and Nutrition (EPIC, epic.larc.fr/), two prospective cohorts with available GWAS data, were included in the study.

The association between CoRSIV-SNPs and PDAC was also tested in an East Asian population sample, consisting of the summary statistics of a meta-analysis including three GWASs (JaPAN, National Cancer Centre and BioBank Japan GWASs). Data were downloaded from the JaPAN consortium website for a total of 2034 PDAC cases and 32,592 controls.[12] The details of the studies used are summarized in Table 1.

2.3 | Data and statistical analysis

For the subjects of European descent, a two-phase association study was performed. The association between CoRSIV-SNPs, CoRSIV-mQTLs, and PDAC risk was tested in the PanScan + PanC4 datasets as discovery phase, with a logistic regression analysis, adjusting for age, sex, and the top eight principal components, and in the summary statistics of FinnGen. SNPs with a p-value lower than .05 in both PanScan + PanC4 and FinnGen were genotyped in PANDoRA. After genotyping, the association with PDAC was tested through a logistic regression analysis, adjusting by age, sex, and country of origin. The analyses were performed including or excluding the Brazilian cases and controls, to verify whether this multiethnic group could alter the results. Then, a meta-analysis was performed between the two phases using a fixed effect model, with the R package meta.[32]

For East Asians, the summary statistics of JaPAN consortium as reported by Lin and colleagues were used.[12]

To account for multiple testing, we considered linkage disequilibrium (LD, $r^2 > .6$) among the SNPs used in the discovery phase (CoRSIV-SNPs + CoRSIV-mQTL) to obtain a list of independent variants ($n = 14{,}898$ for European descent and $n = 12{,}867$ for Asian descent). The resulting Bonferroni-corrected threshold were $0.05/10{,}538 = 3.35 \times 10^{-6}$ and $0.05/12{,}867 = 3.89 \times 10^{-6}$, respectively.

2.4 | Genotyping

DNA of cases and controls within PANDoRA consortium was extracted from whole blood using the QIamp 96 DNA QIAcube HT

TABLE 1 Description of study populations.

Colonna1	PanScan I II III, PanC4	FinnGen	PANDoRA	JaPAN	Total
Diagnosis					
Cases	8,738	881	2,736	2039	14,394
Controls	7,034	204,070	3326	32,592	247,022
Total	15,772	204,951	6062	34,631	261,416
Median age (years)					
Cases	65	–	65	65	
Controls	65	–	57	51	
Sex %					
Male	53%	–	51%	57%	
Female	47%	–	49%	43%	

Note: Information about age and sex is not available in the public data of the FinnGen project.
Abbreviations: PANDoRA, PANcreatic Disease ReseArch; PanScan, Pancreatic Cancer Cohort Consortium; PanC4, Pancreatic Cancer Case-Control Consortium.

Kit (QIAGEN, Hilden, Germany) and genotyped in 384-well plates with TaqMan technology (ThermoFisher Applied Biosystems, Waltham, Massachusetts). Approximately, the same number of cases and controls was placed in each plate; for QC purposes, no-template controls were included. Duplicate samples (around 8% of the samples) were randomly added to the genotyping plates. Genotyping calls were made with QuantStudio 5 Real-Time PCR system (ThermoFisher) and QuantStudio software.

2.5 | Bioinformatics tools

To identify the CoRSIV position on the genome, the supplementary materials of the study by Gunasekara et al. were used. In addition, we used PanCan-meQTL, a database of mQTLs identified through the combination of genotype and DNA methylation data downloaded from TCGA data portal to evaluate the possible effect of the SNPs on CpG site methylation (http://gong_lab.hzau.edu.cn/Pancan-meQTL/).[33] QTLbase was used to check the QTL characteristics, that is, expression QTL (eQTL), splicing QTL (sQTL, http://www.mulinlab.org/qtlbase).[34] QTLbase aggregates data from various data sources, including TCGA, GTEx, Pancan-MNVQTLdb, and DICE. We used also LDlink to evaluate the LD blocks near CoRSIV regions (https://ldlink.nih.gov/).

2.6 | Colocalization and enrichment analyses

The possible involvement of mQTLs in pancreatic cancer risk was also checked with a colocalization analysis performed between the pancreatic cancer mQTL data downloaded from PanCan-meQTL and PanScan I, II, III and PanC4 genotyping datathe coloc.abf function from the Rstudio package "coloc." The estimate for the colocalization was evaluated trough the PP.H4 value, that is, the probability of shared common SNPs affecting both phenotypes. The signal of colocalization was considered positive if PP.H4 was at least 75%.[35] Additionally, an enrichment analysis was carried out using stratified QQ plots comparing all GWAS data, only CoRSIV SNPs and only CoRSIV-mQTL SNPs.[36] The QQ plot was computed with "QQman" Rstudio package.

3 | RESULTS

A total of 29,099 CoRSIV-SNPs (i.e., SNPs situated in the 9926 CoRSIV regions, identified by Gunasekara), and 133,615 CoRSIV-mQTLs (i.e., SNPs identified by Gunasekara as mQTLs or in LD with mQTLs). All SNPs selected were common (MAF >5%) in the Europeans of the 1000 Genomes Project. Fifty CoRSIV-SNPs and 366 CoRSIV-mQTLs showed a nominal significant association ($p < .05$) with PDAC risk in PanScan I-III, PanC4 and in the combined PanScan I-III and PanC4 datasets (Supplementary Table 1). Among them, 12 CoRSIV SNPs and 147 CoRSIV-mQTLs are in LD with known PDAC susceptibility loci (Table 2). Among the remaining variants, 6 CoRSIV-SNPs and 26 CoRSIV-mQTLs showed a nominal significant association with PDAC also in FinnGen. After LD pruning ($r^2 > .6$), one independent CoRSIV-SNP (rs2976395) and four independent CoRSIV-mQTLs (rs4676291, rs2976395, rs2816649, rs56010181) were tested in PANDoRA, but none showed a statistically significant association. Table 3 shows the association of these 5 SNPs with PDAC and their mQTL effect and pvalue. The best result was observed for the A allele of rs2976395, that showed a trend with increased risk, although the association was not statistically significant (odds ratio [OR] = 1.07; 95% confidence interval [CI] 0.90–1.16; $p = .12$). For this variant, a meta-analysis considering all studies together (PanScan I-III, PanC4, FinnGen, and PANDoRA) was carried out. The results showed an increased risk associated with the A allele OR = 1.08 (95% CI 1.04–1.12; $p = 6.21 \times 10^{-5}$), that however was not significant after correction for multiple testing (3.35×10^{-6}) (Table 3). A workflow of the study is shown in Figure 1.

The possible involvement of CoRSIV-SNPs in PDAC risk was tested also in the summary statistics of the JaPAN study. After filtering, a total of 25,629 CoRSIV-SNPs with a MAF greater than 5% were

TABLE 2 SNPs in linkage disequilibrium with known PDAC susceptibility loci and their functional characterization.

Region	No. of SNPs	No. of CoRSIV-SNPs	No. of CoRSIV-mQTLs	No. of mQTL-PDAC[a]	Study
1q32.1	1	1	0	0	Klein et al.[13]
7p12.3	1	1	0	0	Klein et al.[13]
9q31.1	76	1	75	75	Klein et al.[13]
12q14.2	1	1	0	0	Pistoni et al.[24]
12q24.31	19	3	16	16	Klein et al.[13]
17q12	56	0	56	55	Walsh et al.[37]
18q21.32	4	4	0	0	Childs et al.[9]
22q12.1	1	1	0	0	Klein et al.[13]

Note: No. of SNPs = total number of SNPs located in that region. No. of CoRSIV-SNPs = number of CoRSIV-SNPs located in that region. No. of CoRSIV-mQTLs = number of CoRSIV-mQTLs located in that region. No. of mQTL-PDAC = number of SNPs annotated as mQTLs in pancreatic cancer tissue.
[a]Information about the data of functional characterization (mQTL-PDAC) was taken from PanCan-meQTL.
Abbreviations: CoRSIV, Correlated Regions of Systemic Interindividual Variation; mQTL, methylation quantitative trait locus; PDAC, pancreatic ductal adenocarcinoma; SNPs, single-nucleotide polymorphisms.

either genotyped or imputed and 1383 showed a statistically significant association $p < .05$, but none were statistically significant considering the Bonferroni correction for multiple testing.

3.1 | Bioinformatic analysis results

According to PanCan-meQTL, the A allele of *PSCA*-rs2976395 is associated with an increase of DNA methylation level of the *PSCA* gene through a CpG site that is situated in the Exon 2 of the gene ($\beta = .36$, $p = 2.78 \times 10^{-5}$). According to QTLbase, the A allele of PSCA-rs2976395 was also associated with PSCA gene expression increase ($\beta = .553$, $p = 1.21 \times 10^{-21}$).

In addition, the SNP is annotated as an sQTL ($\beta = -.72$, $p = 3.42 \times 10^{-17}$) by QTLbase in pancreatic tumor tissues. This sQTL may cause the inclusion in the transcript of Exon 2.1 instead of Exon 2.2. All the results of the bioinformatic analysis regarding PSCA-rs2976395 are shown in Table 4.

3.2 | Colocalization analysis

The colocalization analysis suggests that PSCA-rs2976395 and the mQTL variants for PSCA do not represent the same association signal (PP.H4 = 25%).

3.3 | Enrichment analysis

We observed that there was a substantial enrichment of mQTLs among SNPs that were associated with PDAC (23.3%; 3703 of 15,873 SNPs) compared to SNPs that were not associated with PDAC (9.8%; 623,689 of 6,377,535 SNPs). This was also explored with stratified QQ plots using all GWAs data, only CoRSIV SNPs and only CoRSIV-mQTL SNPs. The QQ plot considering all GWAS SNPs clearly shows that there is little deviation from the expected $\lambda = 1.05$, while the QQ plot with CoRSIV SNPs ($\lambda = 1.21$), and the one with CoRSIV-mQTL SNPs ($\lambda = 1.23$) suggest that there are more statistically significant associations than expected (Supplementary Figure 1).

4 | DISCUSSION

DNA methylation plays a role in pancreatic cancer carcinogenesis; however, it is difficult to use as a biomarker in an epidemiologic study setting because it is fluid (i.e., it changes due to endogenous and exogenous stimuli) and tissue specific. The identification of the CORSIV regions (i.e., DNA sequences in which methylation is stable over time, but different among individuals) and the following discovery that their DNA methylation pattern is determined by mQTLs has opened the possibility of studying the genetic variability of these regions in relation to human phenotypes. It has already been shown that many CoRSIV regions are located near or within genes involved in several human phenotypes, including neoplasms and diseases of the digestive system.[29]

This is the first study testing the hypothesis that mQTLs in CoRSIV regions are involved in PDAC development. We identified a SNP (*PSCA*-rs2976395), situated in a CoRSIV in the 3′ UTR of the *PSCA* gene that shows a promising association with PDAC risk. This variant, according to Gunasekara, is also a CoRSIV-mQTL, that is, it is associated with the CoRSIV methylation level. The *PSCA* gene encodes a GPI-anchored cell membrane protein that is involved in numerous cellular functions such as signal transduction, growth regulation, proliferation and adhesion.[38–40] The A allele of *PSCA*-rs2976395 shows an association ($p = 2.81 \times 10^{-5}$) with increased risk of PDAC in PanScan I-III, PanC4, and FinnGen, while in PANDoRA the association shows the same trend (i.e., the OR goes in the same direction), but it is not significant ($p = .12$). According to PanCan-meQTL, *PSCA*-rs2976395 is associated with increased DNA methylation of the PSCA gene through a CpG site that is situated in the Exon 2 of the *PSCA* gene. Additionally, QTLbase annotates *PSCA*-rs2976395 as an sQTL ($p = 3.42 \times 10^{-17}$) in pancreatic cancer tissue with the risk allele

TABLE 3 Association of five SNPs (one CoRSIV-SNP and four CoRSIV-mQTLs) with PDAC and their mQTL effect and *p*-value.

	SNP	Position	Cases	Controls	M/m	Phase	OR (95% CI)	*p*-value	I^2	*p*-value Het.	CpG site	mQTL Effect	mQTL *p*-value
CoRSIV-mQTL	rs2976395	8q24.3	8738	7034	G/A	PanScan + PanC4	1.07 (1.02–1.12)	2.80×10^{-3}					
			2668	3072		PANDoRA	1.05 (0.97–1.14)	.23					
			881	204,070		FinnGen	1.15 (1.05–1.26)	4.10×10^{-3}					
			12,287	214,176		Meta-analysis	**1.08 (1.04–1.12)**	$\mathbf{6.21 \times 10^{-5}}$	0%	.37	cg13446199	0.36	2.78×10^{-5}
	rs4676291[a]	2q13	8738	7034	C/T	PanScan + PanC4	1.07 (1.02–1.12)	4.76×10^{-3}					
			2668	3072		PANDoRA	0.99 (0.90–1.10)	.757					
			881	204,070		FinnGen	1.14 (1.03–1.25)	.0126					
			12,287	214,176		Meta-analysis	1.07 (0.99–1.15)	9.68×10^{-2}	49%	.14	NA	NA	NA
	rs2816649[a]	14q32.33	8738	7034	A/G	PanScan + PanC4	1.11 (1.05–1.16)	1.14×10^{-4}					
			2668	3072		PANDoRA	0.99 (0.90–1.1)	.9489					
			881	204,070		FinnGen	1.13 (1.01–1.23)	.0335					
			12,287	214,176		Meta-analysis	1.08 (0.99–1.17)	.0832	51%	.13	cg13114125	−0.62	1.25×10^{-7}
	rs56010181[a]	19q13.32	8738	7034	A/C	PanScan + PanC4	0.89 (0.83–0.95)	6.75×10^{-4}					
			2668	3072		PANDoRA	1.02 (0.89–1.17)	.7457					
			881	204,070		FinnGen	0.84 (0.72–0.98)	.0264					
			12,287	214,176		Meta-analysis	0.91 (0.82–1.02)	.0968	51%	.13	NA	NA	NA
CoRSIV-SNP	rs2976395	8q24.3	8738	7034	G/A	PanScan + PanC4	1.07 (1.02–1.12)	2.80×10^{-3}					
			2287	3072		PANDoRA	1.05 (0.97–1.14)	0.23					
			881	204,070		FinnGen	1.15 (1.05–1.26)	4.10×10^{-3}					
			12,355	214,176		Meta-analysis	**1.08 (1.04–1.12)**	$\mathbf{6.21 \times 10^{-5}}$	0%	.37	cg13446199	0.36	2.78×10^{-5}

Note: Information about the data of functional characterization (mQTL-PDAC) was taken from PanCan-meQTL. SNPs with NA value are not mQTL-PDAC. Results that were statistically significant in the meta-analysis are shown in bold.

Abbreviations: CI, confidence intervals; CoRSIV, Correlated Regions of Systemic Interindividual Variation; eQTL, expression quantitative trait locus; Het, heterogeneity; M, major allele; m, minor allele; mQTL, methylation quantitative trait locus; OR, odds ratio; PANDoRA, PANcreatic Disease ReseArch; PanScan, Pancreatic Cancer Cohort consortium; PanC4, Pancreatic Cancer Case–Control consortium; SNP, single-nucleotide polymorphism.

[a]The meta-analysis was conducted using the random model.

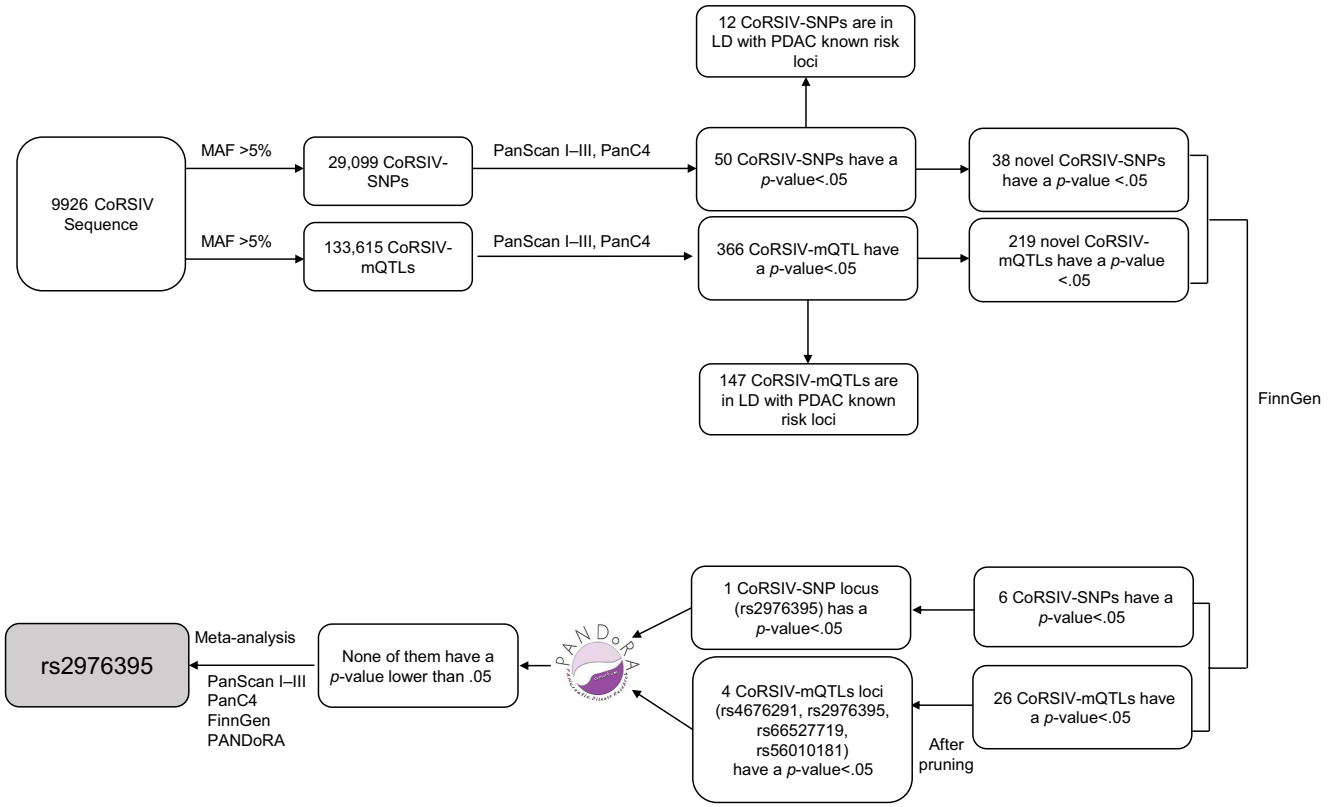

FIGURE 1 Workflow of the study. [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 4 All annotations of the best SNP PSCA-rs2976395.

SNP	QTL	Effect	*p*-value	Tool used	Website	Reference
rs2976395	eQTL	0.5825	1.21×10^{-21}	QTLbase	http://www.mulinlab.org/qtlbase	Zheng et al.[34]
	mQTL-PDAC	0.36	2.78×10^{-5}	PanCan-meQTL	http://gong_lab.hzau.edu.cn/Pancan-meQTL/	Gong et al.[33]
	sQTL	−0.72	3.42×10^{-17}	QTLbase	http://www.mulinlab.org/qtlbase	Zheng et al.[34]

Abbreviations: eQTL, expression quantitative trait locus; mQTL, methylation quantitative trait locus; QTL, quantitative trait locus; SNP, single-nucleotide polymorphism.

associated with the inclusion of Exon 2. However, ad hoc functional studies are needed to test this possibility.

PSCA-rs2976395 is in perfect LD with rs2294008 ($r^2 = 1$, $D' = 1$ in Europeans and $r^2 = .99$, $D' = 1$ in Asians of the 1000 Genomes Project), a pleiotropic SNP associated with risk of multiple cancers. The T allele of rs2294008 (in LD with the A allele of *PSCA*-rs2976395, identified in the present study) has been consistently associated with the development of gastric and bladder cancers in several ethnic groups.[41–43] There is overwhelming evidence that the genetic variability at this locus influences the transcriptional regulation and mRNA stability of the *PSCA* gene in epithelial cells.[44] For example, Fu et al. also reported the association between the T allele of rs22944008 SNP with increased expression of *PSCA* in bladder tissue.[45] Therefore, PSCA-rs2976395 may be involved in PDAC development through the regulation of *PSCA* expression by regulating the DNA methylation status of the gene. However, considering the strong LD pattern at that locus, it is possible to unequivocally determine which SNP may be responsible for the gene expression changes especially considering that the associations between the alleles and the change in expression level are derived from comparing genotypes with expression data obtained from arrays and not by in vitro direct mutagenesis or gene editing technique. Additionally, even though the possibility that the A allele of rs2976395 modifies *PSCA* expression through DNA methylation regulation is intriguing, our colocalization analysis (using as outcomes PDCA risk and methylation level) does not support this hypothesis. Therefore, the functional relevance of the variant needs to be investigated with ad hoc functional studies. An alternative explanation, that seems completely unrelated to methylation, of the casual relation between the SNP (or a SNP in LD with it) and PDAC risk has been proposed by Fu et al. The authors showed that the T allele of *PSCA*-rs2294008 creates a novel translation start site nine amino acids upstream of the regular start site, which extend the *PSCA* leader peptide, that can alter the function or the location of the resulting protein.[45] Interestingly, a difference in the distribution of the

cytoplasmic and membrane expression of this isoform was observed in bladder and prostate cancer tissue compared to normal.[45,46] However also in this case, as the authors state, the functional significance is still under evaluation. It is also interesting to note that the risk allele is the same for all tumor types involved, suggesting that the genetic variability at this locus affect many tumor types in the same way, which is consistent with a regulatory effect either at the transcriptional or translational level that is conserved across multiple organs. Supporting this, an incorrect regulation of the *PSCA* gene has been observed in several tumor types including gastric and bladder cancer.[47,48] For example, in a a very recent report, the downregulation of *PSCA* was associated with gastric cancer proliferation.[47] An increased level of expression has been found in tumor tissue compared with healthy tissue of several cancer types including prostate, bladder, and pancreatic cancer.[39,49,50]

Another interesting point is the fact that seven CoRSIV-SNPs are or are in LD with known PDAC risk loci. Considering that only 30 susceptibility loci are known for PDAC, the enrichment of CoRSIV-related SNPs is clear. This trend was also confirmed by the fact that 23.3% of the statistically significant SNPs ($p < .05$ in PanScan I, II, III, PanC4 and in the combined dataset) was annotated as an mQTL in pancreatic cancer tissue compared to 9.8% of non-significant SNPs. For example, rs1517037, that was identified in the GWAS by Childs et al., is situated around 10 kb upstream of the gastrin releasing peptide (*GRP*) gene.[9] This locus is pleiotropic and is associated with type two diabetes, BMI and Crohn's disease.[51,52] Although the association was validated in an additional study,[13] the functional mechanisms by which this SNP increases PDAC risk is still not clear, and we hypothesize that it could be CoRSIV mediated. Additionally, rs7310409, reported in the same study by Childs et al. is in almost perfect LD ($r^2 = .99$, $D' = 1$ in Europeans) with rs2393776 that is in a CoRSIV. The GWAS SNP is involved in the regulation of the expression of the hepatocyte nuclear factor 1 homeobox A (*HNF1A*) gene that has been associated with PDAC development, through inflammatory response, protein folding, and cell growth.[53,54] According to PanCan-meQTL, both SNPs (rs7310409 and rs2393776) are mQTLs in pancreatic tumor tissue and the G allele of the rs7310409 SNP, which is associated with increased risk, decreases the DNA methylation of cg02403541, a CpG island located in the promoter of the C12orf43 gene. The function of this gene is not yet completely characterized but is involved in the regulation of the Wnt signaling pathway. In addition, the structural maintenance of chromosomes 2 (*SMC2*) locus that showed a strong mQTL effect on CoRSIV was identified associated with PDAC by Klein et al.[13] Taken together, these observations suggest a possible role of CoRSIV variants in PDAC development and merit further investigation also in other cancer types. A clear strength of this study is represented by the large sample size and by the two-phase approach, that limit the chances of reporting spurious associations. Moreover, our study highlights the importance of secondary analysis of GWAS data. GWASs are prone to false negatives considering the very strict threshold of significance that is commonly used due to the large number of comparisons carried out, and therefore secondary analysis are a useful tool for identifying additional loci that have possible functional relevance.

We are aware of the possible limitations of this study, namely the association reported is not statistically significant considering multiple testing and the biological mechanism proposed to explain the association of *PSCA*-rs2976395 with PDAC risk (i.e., the regulation of the expression of *PSCA* by regulating DNA methylation) does not derive from functional data produced in this work but from two widely used SNP databases such as PanCan-meQTL and GTEx and needs to be considered as hypothesis generating. In addition, the pleiotropy of the locus is also a possible indicator of a plausible true association. Another possible limitation of the study is represented by the lack of prior CoRSIV annotations specific for the Asian population that could be the possible cause for the absence of strong associations of CoRSIV-SNPs in JaPAN, suggesting that an appropriate study for this population is needed.

In conclusion, we report a possible new association of the rs2976395 SNP that is situated in the *PSCA* gene and is pleiotropic since it is associated with multiple cancer, but for which a functional causality still needs to be established through gene editing or similar experiments.

AUTHOR CONTRIBUTIONS

The work reported in the paper has been performed by the authors, unless clearly specified in the text. D.C. conceived and designed the study. C.C. and G.L. performed the lab work and the analysis of the data. C.C., A.F., and D.C. wrote the first draft of the manuscript. All authors contributed to the writing and approved of the final version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The PanScan and PanC4 genotyping data are available from the database of Genotypes and Phenotypes (dbGaP, study accession numbers phs000206.v5.p3 and phs000648.v1.p1). The PANDoRA data are available upon reasonable request with approval by the PANDoRA Steering Committee and Ethics Committee of the Medical Faculty of Heidelberg University, Germany. The JaPAN data used in this work are available in the JaPAN consortium website (http://www.aichi-med-u.ac.jp/JaPAN/current_initiatives-e.html). The FinnGen R6 dataset of PDAC cases and controls ("finngen_R6_C3_PANCREAS_EXALLC") is downloadable from the FinnGen official website (https://finngen.gitbook.io/documentation/). Further information is available from the corresponding author upon request.

ETHICS STATEMENT

Each study was approved by the relevant research ethics committee or institutional review board (IRB). The study was conducted in

accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Commission of the Medical Faculty of the University of Heidelberg (project identification code: S-565/2015).

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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