Genetic Polymorphisms Involved in Mitochondrial Metabolism and Pancreatic Cancer Risk

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ABSTRACT

Background: The mitochondrial metabolism has been associated with pancreatic ductal adenocarcinoma (PDAC) risk. Recent evidence also suggests the involvement of the genetic variability of the mitochondrial function in several traits involved in PDAC etiology. However, a systematic investigation of the genetic variability of mitochondrial genome (mtSNP) and of all the nuclear genes involved in its functioning (n-mtSNPs) has never been reported.

Methods: We conducted a two-phase association study of mtSNPs and n-mtSNPs to assess their effect on PDAC risk. We analyzed 35,297 n-mtSNPs and 101 mtSNPs in up to 55,870 individuals (12,884 PDAC cases and 42,986 controls). In addition, we also conducted a gene-based analysis on 1,588 genes involved in mitochondrial metabolism using Multi-marker Analysis of GenoMic Annotation (MAGMA) software.

Results: In the discovery phase, we identified 49 n-mtSNPs and no mtSNPs associated with PDAC risk ($P < 0.05$). In the second phase, none of the findings were replicated. In the gene-level analysis, we observed that three genes (*TERT*, *SUGCT*, and *SURF1*) involved in the mitochondrial metabolism showed an association below the Bonferroni-corrected threshold of statistical significance ($P = 0.05/1588 = 3.1 \times 10^{-5}$).

Conclusions: Even though the mitochondrial metabolism might be involved in PDAC etiology, our results, obtained in a study with one of the largest sample sizes to date, show that neither n-mtSNPs nor mtSNPs are associated with PDAC risk.

Impact: This large case–control study does not support a role of the genetic variability of the mitochondrial function in PDAC risk.

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Introduction

Overwhelming evidence suggests a central role for mitochondria in cellular metabolism and tumorigenesis. The mitochondrial metabolism, genetic variability and content have been associated with pancreatic ductal adenocarcinoma (PDAC) risk (1, 2). Statistically significant associations were identified between SNPs in the mitochondrial genome (mtSNP), as well as SNPs situated in the nuclear genome but involved in mitochondrial metabolism (n-mtSNPs), and seven metabolic traits (3). Several of these traits, such as body mass index and type-2 diabetes, are strongly associated with PDAC risk.

A comprehensive study of the mitochondrial genome and n-mtSNPs in relation to PDAC has not been reported, therefore we analysed the involvement of 101 mtSNPs and 35,297 n-mtSNPs in PDAC susceptibility in a study comprising almost 50,000 individuals.

Materials and Methods

Study design and populations

We employed a two-step approach. In the first phase we used the genotypes of 7,843 PDAC cases and 7,719 controls from the Pancreatic Cancer Cohort Consortium (PanScan) I (4), PanScan II (5), and the Pancreatic Cancer Case–Control Consortium (PanC4; ref. 6) downloaded from dbGaP (study accession numbers phs000206.v5.p3 and phs000648.v1.p1; project reference #12644). Quality controls are reported in the original publications (4–6). We imputed the mitochondrial and nuclear genome as described in detail in (3) and (7) respectively, obtaining 101 SNPs for the mitochondrial and 7,509,345 SNPs for the nuclear genomes.

In the second phase (validation) we genotyped 3,638 PDAC cases and 3,332 controls of European descent from the PANcreatic Disease ReseArch (PANDoRA; ref. 8) consortium and used the publicly available summary statistics of the Japan Pancreatic Cancer Research (JaPAN) consortium for an additional 2,039 PDAC cases and 32,592 controls of Asian descent (9).

Nuclear gene and SNP selection

We identified 1,588 genes encoding for a mitochondrial localized protein, using two databases: Human MitoCarta 2.0 (https://www.broadinstitute.org/mitocarta/mitocarta30-inventory-mammalian-mitochondrial-proteins-and-pathways) and Integrated Mitochondrial Protein Index (http://www.mrc-mbu.cam.ac.uk/impi). For each gene we identified tagging SNPs (tSNP) using Haploview software, for a total of 67,960 tSNPs.

Data analysis

Out of 67,960 tSNPs, 34,007 were found in the PanScan I–II and PanC4 dataset. Additionally, 1,290 proxies (linkage disequilibrium $r^2 \geq 0.80$) were included, for a total of 35,297 n-mtSNPs. All 101 mtSNPs were included. In the first phase logistic regression, adjusted for sex, age, and the eight first principal components, was performed. In the second phase we selected for replication SNPs fulfilling the following criteria: minor allele frequency (MAF) > 0.05, $P < 5 \times 10^{-4}$ considering all dbGaP data together, $P < 0.05$ in each individual dataset and no linkage disequilibrium with known PDAC risk loci. Genotyping in PANDoRA was performed with TaqMan technology (ThermoFisher Applied Biosystems). The genotype quality control of PANDoRA, consisted of 8% duplicated samples (99.13% concordance rate), Hardy–Weinberg equilibrium check (no significant deviation) and computation of call rate (average 97%). PANDoRA data were analysed by logistic regression adjusted for sex, age, and country of origin. Finally, we conducted a meta-analysis on 55,870 individuals from all datasets with either a fixed or a random effect model. We also conducted a gene-level analysis using the Multi-marker Analysis of GenoMic Annotation (MAGMA) software (10), and pathway enrichment analysis using the gProfiler g:GOSt tool (https://biit.cs.ut.ee/gprofiler/gost).

Results

In the first phase, we observed 49 independent n-mtSNPs showing an association with PDAC risk with $P < 0.05$ in both PanScan I–II and PanC4 and in their pooled dataset. None of the mtSNPs met our criteria for replication and therefore we did not advance them to the following steps. Five n-mtSNPs (rs7676303, rs11717398, rs3845970, rs11130833, rs802933) were genotyped in the replication phase in PANDoRA and analyzed in JaPAN but none showed a concordant association. In the meta-analysis we observed no significant results (**Table 1**).

In the MAGMA analysis of all the 1,588 genes performed in the European population, 110 genes showed an association at $P < 0.05$, with 3 (*TERT*, *SUGCT*, and *SURF1*) below the Bonferroni-corrected threshold ($P = 0.05/1{,}588 = 3.1 \times 10^{-5}$) and 3 more (*MRPS25*, *HSCB*, and *PNPO*) if using FDR (as described in the **Table 2**). We did not observe statistically significant association in JaPAN. A pathway enrichment analysis with gProfiler g:GOSt tool on these 110 genes showed that they are involved mainly in the mitochondrial metabolism without overlap with pancreatic or tumorigenic pathways.

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Table 1. Case–control analysis of the five candidate SNPs selected after the discovery phase of the study.

SNP	Chromosome	Position (hg38)	Gene	Alleles (M/m)	Phase	Total controls\ cases	Additive model		
							OR (95% CI)	*P* value	*P*-value Het[a]
rs7676303	4	123,169,108	*SPATA5*	A/G	PanScan+PanC4	6,953\7,070	**0.83 (0.74–0.92)**	**3.84×10^{-4}**	—
					PANDoRA	3,298\3,465	0.97 (0.83–1.12)	0.635	—
					JaPAN	—	—	—	—
					Meta-analysis 1[b]	10,251\10,535	**0.88 (0.80–0.96)**	**3.20×10^{-3}**	0.990
					Meta-analysis 2[c]	—	—	—	—
rs11717398	3	15,060,934	*MRPS25*	G/C	PanScan+PanC4	7,058\7,198	**1.11 (1.05–1.16)**	**1.25×10^{-4}**	—
					PANDoRA	3,295\3,454	0.95 (0.87–1.02)	0.168	—
					JaPAN	32,592\2,039	1.02 (0.90–1.14)	0.715	—
					Meta-analysis 1[b]	10,353\10,652	1.03 (0.89–1.19)	0.690	**0.001**
					Meta-analysis 2[c]	42,945\12,691	1.03 (0.94–1.13)	0.524	**0.004**
rs3845970	3	60,014,810	*FHIT*	C/A	PanScan+PanC4	7,063\7,207	**0.92 (0.87–0.96)**	**8.84×10^{-4}**	—
					PANDoRA	3,238\3,418	**1.12 (1.03–1.22)**	**0.006**	—
					JaPAN	32,592\2,039	0.98 (0.91–1.06)	0.682	—
					Meta-analysis 1[b]	10,301\10,625	1.01(0.84–1.22)	0.903	**8.23×10^{-5}**
					Meta-analysis 2[c]	42,893\12,664	0.99 (0.89–1.12)	0.990	**4.11×10^{-4}**
rs11130833	3	61,229,668	*FHIT*	C/T	PanScan+PanC4	7,059\7,198	**0.91 (0.87–0.96)**	**6.15×10^{-4}**	—
					PANDoRA	2,786\3,359	0.97 (0.89–1.05)	0.407	—
					JaPAN	32,592\2,039	0.98 (0.91–1.06)	0.664	—
					Meta-analysis 1[b]	9,845\10,557	**0.93 (0.89–0.97)**	**3.23×10^{-4}**	0.193
					Meta-analysis 2[c]	42,437\12,596	**0.94 (0.90–0.97)**	**6.81×10^{-4}**	0.187
rs802933	3	60,211,757	*FHIT*	A/G	PanScan+PanC4	6,987\7,136	**0.92 (0.88–0.97)**	**9.99×10^{-4}**	—
					PANDoRA	2,703\3,384	1.06 (0.99–1.15)	0.105	—
					JaPAN	32,592\2,039	1.03 (0.93–1.13)	0.552	—
					Meta-analysis 1[b]	9,690\10,520	0.98 (0.86–1.13)	0.818	**0.002**
					Meta-analysis 2[c]	42,282\12,559	0.99 (0.91–1.09)	0.925	**0.003**

Note: All analyses of PanScan and PanC4 data were adjusted by age, sex, and the first eight principal components; analysis of PANDoRA data was adjusted for sex, age, and country of origin; and JaPAN results were adjusted for the first two principal components. Statistically significant results ($P < 0.05$) are in bold. The specific number of controls and cases for each polymorphism in the JaPAN consortium is not available in the publicly available data; therefore, the ones indicated in the table are the overall numbers of cases and controls in the original publication for the study (9). The meta-analysis was performed applying the fixed-effects model, or random-effects model for SNPs showing heterogeneity. The polymorphism rs7676303 was not present in JaPAN, and therefore the meta-analysis was not conducted.

Abbreviations: CI, confidence interval; M, major allele; m, minor allele.

[a]*P* value for the heterogeneity test.

[b]Meta-analysis of PanScan+PanC4 and PANDoRA.

[c]Meta-analysis of PanScan+PanC4, PANDoRA and JaPAN.

Discussion

The mitochondrial metabolism and content have been associated with PDAC risk, but a systematic investigation of the genetic variability of mitochondrial genome and of all the genes involved in its functioning has never been attempted. After conducting a meta-analysis, we did not observe any statistically significant finding at individual SNP level. We had more than 80% statistical power to observe objective response (OR) ≥ 1.14 for frequent SNPs (MAF 40%) and OR ≥ 1.23 for less frequent ones (MAF 10%) using an alpha of 1.42×10^{-6} and only the discovery phase. In the European population, aggregating the SNPs in a multi-marker model, we observed associations with 2 known PDAC risk genes (*TERT*, *SUGCT*) and a novel one (*SURF1*) that is involved in the biogenesis of the cytochrome c oxidase complex. However, the association was significant only with the model that relies on the most significant SNP, thus not adding much to what has been previously observed with the individual variants. Pathway enrichment analysis showed overlap only with mitochondrial pathways.

Table 2. Significant results of the analysis performed with MAGMA.

Gene	Chromosome	No. SNPs	$P_{SNPWiseMean}$	$P_{SNPWiseTop1}$	P_{Multi}	FDR adj. *P* value
TERT	5	18	1.75×10^{-6}	7.94×10^{-7}	6.10×10^{-8}	9.24×10^{-5}
SUGCT	7	894	1.60×10^{-3}	9.17×10^{-7}	2.64×10^{-6}	2.00×10^{-3}
SURF1	9	13	3.22×10^{-3}	1.21×10^{-5}	9.35×10^{-5}	4.72×10^{-2}
MRPS25	3	47	1.10×10^{-4}	1.74×10^{-3}	1.29×10^{-4}	4.90×10^{-2}
HSCB	22	44	5.50×10^{-4}	2.80×10^{-4}	1.80×10^{-4}	4.99×10^{-2}
PNPO	17	20	1.05×10^{-4}	1.26×10^{-3}	1.97×10^{-4}	4.99×10^{-2}

Note: The three models used are (i) SNP-wise Mean, (ii) SNP-wise Top 1, and (iii) Multi model. The two SNP-wise models examine the individual SNPs present in the gene and subsequently combine the resulting *P* values of the SNPs into a gene-test statistic, while the Multi model runs the basic models (SNP-wise) and combines the resulting *P* values into an aggregated *P* value for the gene. *TERT*, *SUGCT*, and *SURF1* are significant after the Bonferroni correction ($P \le 0.05/1{,}588 = 3.15 \times 10^{-5}$), while all six genes are significant after Benjamini–Hochberg correction (FDR adjusted $P < 0.05$). In the table are reported only the results using the data of PanScan I–II and PanC4. No statistically significant associations were observed in JaPAN.

A possible limitation is the exclusion of rare variants (MAF < 0.05), considering the lack of power to observe modest effect sizes typically associated with germline variants.

In conclusion, our results suggest no effect of the common genetic variability in mitochondrial metabolism in relation to PDAC susceptibility, while larger studies may nonetheless find significant associations, albeit with small effect sizes.

Authors' Disclosures

No disclosures were reported.

Authors' Contributions

G. Peduzzi: Data curation, formal analysis, writing–original draft, writing–review and editing. **M. Gentiluomo:** Data curation, formal analysis, writing–original draft, writing–review and editing. **F. Tavano:** Data curation, writing–review and editing. **P. Arcidiacono:** Data curation, writing–review and editing. **S. Ermini:** Data curation, writing–review and editing. **P. Vodicka:** Data curation, writing–review and editing. **U. Boggi:** Data curation, writing–review and editing. **G.M. Cavestro:** Data curation, writing–review and editing. **G. Capurso:** Data curation, writing–review and editing. **L. Morelli:** Data curation, writing–review and editing. **A.C. Milanetto:** Data curation, writing–review and editing. **R. Pezzilli:** Data curation, writing–review and editing. **R.T. Lawlor:** Data curation, writing–review and editing. **S. Carrara:** Data curation, writing–review and editing. **M. Lovecek:** Data curation, writing–review and editing. **P. Souček:** Data curation, writing–review and editing. **F. Guo:** Data curation, writing–review and editing. **T. Hackert:** Data curation, writing–review and editing. **F.G. Uzunoğlu:** Data curation, writing–review and editing. **M. Gazouli:** Data curation, writing–review and editing. **A. Párniczky:** Data curation, writing–review and editing. **J. Kupcinskas:** Data curation, writing–review and editing. **M.F. Bijlsma:** Data curation, writing–review and editing. **B. Bueno-de-Mesquita:** Data curation, writing–review and editing. **R. Vermeulen:** Data curation, writing–review and editing. **C.H.J. van Eijck:** Data curation, writing–review and editing. **K. Jamroziak:** Data curation, writing–review and editing. **R. Talar-Wojnarowska:** Data curation, writing–review and editing. **W. Greenhalf:** Data curation, writing–review and editing. **D. Gioffreda:** Data curation, writing–review and editing. **M.C. Petrone:** Data curation, writing–review and editing. **S. Landi:** Data curation, writing–review and editing. **L. Archibugi:** Data curation, writing–review and editing. **M. Puzzono:** Data curation, writing–review and editing. **N. Funel:** Data curation, writing–review and editing. **C. Sperti:** Data curation, writing–review and editing. **M.L. Piredda:** Data curation, writing–review and editing. **B. Mohelnikova-Duchonova:** Data curation, writing–review and editing. **Y. Lu:** Data curation, writing–review and editing. **V. Hlaváč:** Data curation, writing–review and editing. **X. Gao:** Data curation, writing–review and editing. **M. Schneider:** Data curation, writing–review and editing. **J.R. Izbicki:** Data curation, writing–review and editing. **G. Theodoropoulos:** Data curation, writing–review and editing. **S. Bunduc:** Data curation, writing–review and editing. **E. Kreivenaite:** Data curation, writing–review and editing. **O.R. Busch:** Data curation, writing–review and editing. **E. Małecka-Panas:** Data curation, writing–review and editing. **E. Costello:** Data curation, writing–review and editing. **F. Perri:** Data curation, writing–review and editing. **S.G.G. Testoni:** Data curation, writing–review and editing. **G. Vanella:** Data curation, writing–review and editing. **C. Pasquali:** Data curation, writing–review and editing. **M. Oliverius:** Data curation, writing–review and editing. **H. Brenner:** Data curation, writing–review and editing. **M. Loos:** Data curation, writing–review and editing. **M. Götz:** Data curation, writing–review and editing. **K. Georgiou:** Data curation, writing–review and editing. **B. Erőss:** Data curation, writing–review and editing. **E. Maiello:** Data curation, writing–review and editing. **A. Szentesi:** Data curation, writing–review and editing. **F. Bazzocchi:** Data curation, writing–review and editing. **D. Basso:** Data curation, writing–review and editing. **J.P. Neoptolemos:** Data curation, writing–review and editing. **P. Hegyi:** Data curation, writing–review and editing. **V. Kiudelis:** Data curation, writing–review and editing. **F. Canzian:** Conceptualization, resources, data curation, formal analysis, supervision, funding acquisition, writing–original draft, writing–review and editing. **D. Campa:** Conceptualization, resources, data curation, formal analysis, supervision, funding acquisition, writing–original draft, writing–review and editing.

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