Mitochondrial Genetic Polymorphisms and Pancreatic Cancer Risk

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Abstract

The role of genes that influence the risk of developing pancreatic cancer (PC) has not been well studied. The mitochondrion, conventionally thought to be an organelle specific to energy metabolism, is in fact multifunctional and has been implicated in many diseases, including cancer. To evaluate whether single nucleotide polymorphisms in mitochondrial DNA (mtSNP) are associated with increased risk of PC, we screened Caucasian cases diagnosed or seen at the Mayo Clinic with primary pancreatic adenocarcinoma (n = 955), and healthy clinic-based Caucasian controls (n = 1,102). A total of 24 mtSNPs, including 10 of the most common tagSNPs, 7 non-tagSNPs in the coding region, and 7 common SNPs in the regulatory region were genotyped. For analysis, these samples were grouped into two phases, the "testing" set (474 cases and 615 controls), and the "validation" set (481 cases and 487 controls). In the testing set, one mtSNP (SNP11719) suggested an association in single SNP analysis, with an odds ratio of 1.34 (95% confidence intervals, 1.05-1.72; P = 0.020), but did not remain statistically significant after correction for multiple testing. In the validation set, none of the 24 variants indicated any association with PC. For haplogroup analysis, 10 core SNPs that form common haplogroups in Caucasians (1719, 4580, 7028, 8251, 9055, 10398, 12308, 13368, 13708, and 16391) were evaluated. No significant associations with PC were identified either by analyzing the two sets separately or combined (combined global P = 0.17). Overall, these results do not support a significant involvement of mitochondrial DNA variation in the risk of developing PC. Investigation of other mitochondrial genetic variations (i.e., nuclear-encoded mitochondrial proteins) would be necessary to elucidate any role of mitochondrial DNA variation in PC. (Cancer Epidemiol Biomarkers Prev 2007;16(7):1455–9)

Introduction

Pancreatic cancer (PC) will affect ∼37,170 individuals in the U.S. in 2007, and lead to 33,370 deaths, making PC the fourth leading cause of cancer death in the U.S. (1). Five-year survival rates for patients suffering from this cancer are a dismal 5%, emphasizing the need for a detailed understanding of the molecular changes underlying this disease and the application of this knowledge to early diagnosis and therapeutic intervention. Several etiologic factors for PC have been suggested, including both genetic and environmental factors. These risk factors include age, smoking, diabetes, gender, race/ethnicity, family history, and chronic and hereditary pancreatitis. PC is rare before the age of 40 years, but incidence increases sharply with increasing age; most patients are diagnosed between the ages of 60 and 80.

The mitochondrion, an organelle specific to energy metabolism, is in fact multifunctional, having roles in cell signaling, apoptosis, and cellular homeostasis. Mitochondria can activate apoptosis, during which reactive oxygen species are generated that on one hand serve as crucial proapoptotic factors, but on the other hand, function in both the initiation and promotion of carcinogenesis. Mitochondrial dysfunction is a common feature of cancer cells. Somatic mutations of mitochondrial DNA have been reported in a variety of cancers, including PC (2-9). Intragenic deletions (10), missense and chain-terminating point mutations (3), and alterations of homopolymeric sequences (11) have been identified in nearly every type of tumor studied.

Recently, several reports have shown that mitochondrial enzymes are directly implicated in hereditary cancer syndromes (12). For example, complex II of the mitochondrial respiratory chain is composed of four nuclear-encoded subunits and is localized in the mitochondrial inner membrane. Germ line heterozygous mutations in three of the four subunits (SDHB, SDHC, and SDHD) cause the inherited syndromes that feature phaeochromocytoma and paraganglioma (13). Another example is the nuclear-encoded mitochondrial enzyme, fumarase (FH). The protein is an enzymatic component of the tricarboxylic acid cycle and catalyzes the formation of L-malate from fumarate. Mutations in the FH gene cause a predisposition to cutaneous and uterine leiomyomas, as well as to kidney cancers (14). More recent studies showed that single nucleotide polymorphisms in the mitochondrial genome (mtSNP) were associated with increased risk of several types of cancers, including invasive breast cancer in African American women (15), and poor outcome of PC (6). These findings provide evidence that DNA variation in mitochondria may play an important role in developing PC, a hypothesis recently emphasized in a conference report (16). To systematically test the role of mtSNPs in PC risk, we genotyped 24 common variants, including 10 of the most common tagSNPs and 7 non-tagSNPs in the coding region, as well as 7 common SNPs in the regulatory region. We compared allele and haplogroup frequencies in a total of 955 cases with primary pancreatic adenocarcinoma and 1,102 healthy clinic-based controls.

Materials and Methods

Patients with PC. PC index cases were adult persons with a histologically confirmed primary adenocarcinoma of the pancreas seen at Mayo Clinic between October 1, 2000 and

Table 1. Characteristics of PC cases and controls

	Testing set			Validation set		
	Control (N = 615)	PC case (N = 474)	P	Control (N = 487)	PC case (N = 481)	P
Age	59.8 ± 12.2	65.8 ± 10.4	<0.001	65.3 ± 10.5	66.3 ± 10.9	0.16
Gender			0.018			0.50
Female	292 (47%)	191 (40%)		217 (45%)	204 (42%)	
Male	323 (53%)	283 (60%)		270 (55%)	277 (58%)	
Smoking history			0.011			<0.001
Never smoker	297 (49%)	193 (41%)		216 (50%)	167 (35%)	
Smoker	315 (51%)	280 (59%)		216 (50%)	304 (65%)	
Questionnaire completed						
No				50 (10%)	149 (31%)	
Yes				437 (90%)	332 (69%)	
Body mass index		28.2 ± 5.6		27.2 ± 4.6	27.9 ± 5.0	0.06
Diabetes mellitus (>2 y)						<0.001
No		329 (90%)		418 (96%)	287 (86%)	
Yes		35 (10%)		17 (4%)	45 (14%)	

June 1, 2006. Eligible Mayo pancreatic adenocarcinoma cases were identified through an ultra-rapid patient identification system. Study coordinators identified potential patients from the electronic patient schedule system and daily pathology reports. All eligible patients were contacted either in the clinic at the time of their appointment, or later by mail or phone if clinic contact was not possible. If contacted at the clinic, a research nurse obtained informed consent, arranged a venipuncture for 40 mL of blood, and asked the participant to complete the study questionnaire. If mail contact was required (~28% of the cases were approached by mail), the study coordinator mailed an invitation letter to the patient's home address. A follow-up telephone call was made if the sample or forms were not received after 1 month. Approximately 74% of all eligible patients were enrolled in this study. The characteristics of the Caucasian subjects used in this study are listed in Table 1. We included 474 patients in the testing set and 481 patients in the validation set.

Controls. The 615 healthy Caucasian controls in the testing set were individuals who were identified through a colon cancer screening study between June 1, 2000 and May 31, 2004. These subjects were recruited after completion of a routine screening colonoscopy which was negative for colon cancer. This control group was a convenience sample and therefore was not selected to match the pancreas cancer cases. Self-reported height, weight, and diabetes status were not available on these individuals. The 487 healthy Caucasian controls in the validation set were from a Mayo Clinic–based control sample of primary care patients having routine check-up visits (general medical exam) between May 1, 2004 and August 31, 2006. Controls were frequency-matched on age (±5 years), race, sex, and state/region of residence distribution of the cases. Controls had no previous diagnosis of cancer (except non–melanoma skin cancer) at the time of enrollment. Prior to their appointment, potential controls were mailed an information brochure describing the study and a letter of invitation. On the day of the appointment, a study assistant approached the subject, confirmed eligibility criteria, and obtained informed consent. Each participant completed study questionnaires (which included a self-report of height, weight, and diabetes status) and provided 30 mL of research blood sample. Approximately 70% of all approached controls participated in this study.

SNP Selection. To date, thousands of mtSNPs have been reported.[4] However, the majority are rare (allele frequency

< 1%). Based on allele frequency and published literature (17), we selected a total of 24 SNPs distributed across the mitochondrial genome for genotyping (Table 2). Ten of the 24 SNPs define common haplogroups in the Caucasian population (18). For the mitochondrial coding region, Saxena et al. (17) identified 144 SNPs with minor allele frequencies $\geq$ 1% and 64 tagSNPs to capture them with $r^2 \geq 0.8$. By considering sample sizes, we selected the top 10 most common tagSNPs and 7 non-tagSNPs (necessary for haplogroup analysis) in the coding region. Because a non-tagSNP may have high correlation with multiple tagSNPs (e.g., non-tagSNP1719 is correlated with tagSNPs 709, 12007, and 12705 with $r^2 = 0.84$), the 7 non-tagSNPs actually capture 13 extra tagSNPs with $r^2 > 0.8$. Altogether, our 17 SNPs in the coding region captured 23 of 64 tagSNPs with minor allele frequencies $\geq$ 1%, 10 of 15 tagSNPs with minor allele frequencies $\geq$ 5%, and 10 of 10 tagSNPs with minor allele frequencies $\geq$ 7%. For the regulatory region (displacement loop or D-loop), we selected 7 SNPs based on higher allele frequency or necessity for haplogroup analysis.

SNP Genotyping. We used the Beckman SNPstream system for genotyping. Two 12 plex panels of primer sets were designed using the Web-based Autoprimer. For each 12 plex panel, 2 ng of DNA isolated from peripheral blood lymphocytes was amplified with the pooled primer sets (50 nmol/L each) under universal PCR conditions (5 mmol/L MgCl$_2$, 75 µmol/L of deoxynucleotide triphosphates, 0.1 unit of AmpliTaq Gold; Applied Biosystems) in a final volume of 5 µL. After initial denaturation at 94°C for 1 min, 34 cycles were done at 94°C for 30 s, 55°C for 30 s, and 72°C for 1 min. The amplified materials were then cleaned by incubating with SBE Clean-up (shrimp alkaline phosphatase and exonuclease I) at 37°C for 30 min and 96°C for 10 min. After 9 µL of extension mixes for each panel (C/T or G/A) were added to 7 µL of cleaned PCR product, the plates were thermocycled at 96°C for 3 min, then 45 cycles of 94°C for 20 s and 40°C for 11 s. SNPware array plates were prepared (washing with buffers I and II). Eight microliters of hybridization solution was added to each well of the plate following primer extension reaction, and 10 µL of this was added to the corresponding well in the SNPware tag plate, incubated at 42°C at 100% humidity for 2 h. The tag arrays were then washed and vacuum-dried and imaged on the scanner. The SNPstream software was used for image data analysis and genotype calls.

Single SNP Analysis. Although there are multiple mitochondrial DNA copies per cell, there is generally only a single allele for any given individual (maternal inheritance). The mtSNP allele frequency was used to assess the difference between the cases and controls using standard contingency

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Table 2. Analysis of 24 mtSNPs in patients with PC and controls

Position and variant	Location	Accession no., if known	Testing set			Validation set			Combined set		
			Control (N = 615)	PC case (N = 474)	P*	Control (N = 487)	PC case (N = 481)	P*	Control (N = 1,102)	PC case (N = 955)	P*
73G/A	D-loop	–	338/248	255/212	0.32	258/222	248/229	0.59	596/470	503/441	0.24
152T/C	D-loop	–	427/102	358/95	0.51	364/112	358/105	0.76	791/214	716/200	0.77
489C/T	D-loop	–	59/519	52/407	0.56	43/424	48/412	0.53	102/943	100/819	0.41
709A/G	12S rRNA	–	88/483	21/126	0.73	68/417	61/417	0.57	156/900	825/43	0.35
1189C/T	12S rRNA	–	44/541	33/431	0.80	32/455	35/441	0.63	76/996	68/872	0.90
1719A/G	16S rRNA	–	34/560	28/442	0.87	26/460	15/465	0.09	60/1,020	43/907	0.29
3010G/A	16S rRNA	–	401/119	321/127	0.05	365/121	363/114	0.72	766/240	684/241	0.26
4580A/G	ND2	–	24/558	19/451	0.95	18/467	20/460	0.72	42/1,025	39/911	0.85
7028T/C	COI	rs2015062	356/223	265/203	0.11	275/210	271/206	0.97	631/433	536/409	0.24
8251A/G	COII	rs3021089	31/567	21/450	0.58	26/455	21/438	0.56	57/1,022	42/888	0.43
9055G/A	ATPase 6	–	535/56	426/43	0.86	438/48	430/47	0.99	973/104	856/90	0.91
10398G/A	ND3	rs2853826	118/464	95/365	0.88	98/385	97/374	0.91	216/849	192/739	0.85
11719A/G	ND4	rs2853495	322/239	234/233	0.02	248/232	231/244	0.35	570/471	465/477	0.016
11812G/A	ND4	rs16822406	46/539	33/433	0.63	33/453	21/456	0.11	79/992	54/889	0.14
12308A/G	tRNA	rs2853498	148/437	99/365	0.13	109/376	109/369	0.90	257/813	208/734	0.30
12372A/G	ND5	rs2853499	151/429	103/368	0.12	112/372	111/369	1.00	263/801	214/737	0.24
12705T/C	ND5	rs2854122	47/541	37/432	0.95	35/451	34/444	0.96	82/992	71/876	0.91
13368G/A	ND5	rs3899498	526/58	424/44	0.77	440/47	439/38	0.36	966/105	863/82	0.38
13708A/G	ND5	–	71/497	59/409	0.96	69/418	56/422	0.26	140/915	115/831	0.46
14798T/C	Cytb	–	484/100	399/69	0.30	406/78	400/80	0.82	890/178	799/149	0.56
16126C/T	D-loop	–	119/427	91/375	0.38	101/385	85/393	0.24	220/812	176/768	0.14
16189T/C	D-loop	–	476/86	395/73	0.90	419/63	419/56	0.55	895/149	814/129	0.70
16391G/A	D-loop	–	572/16	458/11	0.70	473/13	467/10	0.56	104/529	925/21	0.49
16519C/T	D-loop	–	367/204	303/159	0.66	307/180	296/180	0.78	674/384	599/339	0.94

*P values were estimated prior to statistical adjustment for covariates (age, gender, and smoking history).

table methods. Unconditional logistic regression models, which treated case/control status as the outcome, were used to test the association between PC risk and SNP carrier status adjusting for covariates (age, gender, and smoking history). Odds ratios (OR) and 95% confidence intervals (95% CI) were used to quantify any significant associations. Similar analyses were done on the validation set. Additional analyses which included body mass index and history of diabetes exceeding 2 years as covariates were also investigated in the validation set. To account for multiple testing, Bonferroni correction was used. Analyses were done using SAS version 9.1.3.

Haplogroup Analysis. Genotypes for the multiple mtSNPs were combined to construct mitochondrial haplogroups. Haplogroups are specific combinations of nucleotides on the same mitochondrial genomes. To test for an association between the haplogroup and case/control status, we calculated a score statistic using a modified version of the haplo.stats program (19) which implements an expectation-maximization algorithm to infer missing haplogroups. Analyses using the haplo.stats software were run using S-plus version 7.0.6. We then obtained estimates of ORs and 95% CIs

for haplogroups using unconditional logistic regression models in SAS version 9.1.3.

Results

We genotyped 24 SNPs distributed across the mitochondrial genome. We first examined quality control samples to assess the reliability of genotyping. There were 44 positive (same anonymous DNA) and 44 negative (no DNA) controls in the entire data set. There were also control spots embedded within each of the wells of the tag array plate for each homozygous allele, one heterozygous and one negative control. Final analysis revealed no sign of contamination or other technical problems associated with the genotype call. Except for mtSNP709, which failed quality control in some cases in the testing set, the overall median call rate for each of the groups ranged from 94.6% to 99.6%. The frequencies of the mtSNPs are shown in Table 2, organized by the testing set, the validation set, and the combined set. In our initial unadjusted analysis, we did not detect any significant association between cases and controls in 23 of the 24 mtSNPs. The only SNP that

Table 3. Analysis of 10 haplogroups in PC cases and controls

Haplogroup	Testing set			Validation set			Combined set		
	Controls (N = 615)	Cases (N = 474)	OR* (95% CI)	Controls (N = 487)	Cases (N = 481)	OR* (95% CI)	Controls (N = 1,102)	Cases (N = 955)	OR* (95% CI)
H	210	197	1 (–)	206	191	1 (–)	416	388	1 (–)
I	12	10	0.888 (0.375-2.102)	13	9	0.747 (0.312-1.787)	25	19	0.815 (0.442-1.503)
J	51	40	0.836 (0.529-1.321)	49	43	0.946 (0.601-1.491)	100	83	0.890 (0.645-1.228)
K	40	31	0.826 (0.497-1.373)	31	33	1.148 (0.677-1.947)	71	64	0.966 (0.671-1.392)
T	54	39	0.770 (0.488-1.214)	44	416	0.858 (0.528-1.394)	98	74	0.810 (0.581-1.128)
U	95	64	0.718 (0.495-1.042)	77	70	0.980 (0.671-1.432)	172	134	0.835 (0.641-1.089)
V	23	18	0.834 (0.437-1.593)	18	20	1.198 (0.615-2.334)	41	38	0.994 (0.626-1.578)
W	8	5	0.666 (0.214-2.071)	9	7	0.839 (0.306-2.297)	17	12	0.757 (0.357-1.605)
X	10	8	0.853 (0.330-2.205)	6	2	0.360 (0.072-1.803)	16	10	0.670 (0.300-1.494)
Com[†]	22	24	1.163 (0.632-2.141)	16	32	2.157 (1.147-4.057)	38	56	1.580 (1.023-2.440)

*ORs were estimated prior to statistical adjustment for covariates (age, gender, and smoking history).
[†]A composite group of two less frequent haplogroups.

showed an association was mtSNP11719 (accession no. rs2853495). The minor allele frequencies (C allele) for this SNP in the testing set was 50% in PC and 43% in controls. The OR was 1.34 with 95% CI between 1.05 and 1.72 ($P = 0.02$). However, mtSNP11719 did not show an association with PC in the validation set (OR, 1.13; 95% CI, 0.87-1.46). After adjustment for age, gender, and smoking history, two additional mtSNPs (mtSNP3010 and mtSNP1719) showed an association with PC. The association for mtSNP3010 (OR, 1.45; 95% CI, 1.07-1.96) was observed in the testing set and the association for mtSNP1719 (OR, 2.03; 95% CI, 1.02-4.03) was observed in the validation set. Additional analyses which also adjusted for body mass index and history of diabetes exceeding 2 years were done in the validation set and provided consistent results (data not shown).

Rather than just leaving persons with missing data out of the analysis, we also conducted a sensitivity analysis to determine the effect of missing information on covariates. Because the questionnaires were available for all cases and only for the controls in the validation set, we did our sensitivity analysis using only the validation set. We evaluated minimally adjusted ORs, and then adjusted for the additional covariates on the reduced data set. Similar results were observed when persons were removed with missing information.

To analyze mitochondrial haplogroups, we used 10 core mtSNPs that defined common haplogroups in Caucasians (18): SNPs 1719, 4580, 7028, 8251, 9055, 10398, 12308, 13368, 13708, and 16391. Haplogroups were constructed using an expectation-maximization algorithm to allow for missing data. Eleven haplogroups with frequencies of at least 1% were included in the analysis. The analysis was based on global score statistics that compare all 11 haplogroups between cases and controls. This approach, which controls for multiple testing, did not identify a significant association with PC (combined global $P = 0.17$). Two haplogroups that occurred less frequently (0.011 and 0.042) seemed to be driving the global P value in the combined analysis. These two less frequent haplogroups were combined into a composite (Com) group. The final analyses were done in 10 haplogroups (Table 3). When haplogroups were examined individually, however, haplogroup Com showed a positive association with PC in the validation set only, and its frequency was 0.07 in cases and 0.03 in controls (OR, 2.16; 95% CI, 1.15-4.06). The combined set did show a similar pattern for association of the haplogroup Com with PC risk (Table 3). This association also remained significant in the validation set after adjusting for age, gender, and smoking history (OR, 2.26; 95% CI, 1.15-4.42). However, the association did not remain significant in the combined set after adjusting for age, gender, and smoking history.

Discussion

In this study, we genotyped and compared 24 mtSNPs and 11 common haplogroups in Caucasian PC cases and clinic-based healthy controls. Although the overall statistical analysis did not reveal significant differences for these mtSNPs/haplogroups between controls and PC cases, some individual SNP or haplogroup combinations did show weak associations. The mtSNP11719 was the only SNP that showed an association before statistical adjustment, and is located in the coding region of the ND4 gene. As this variant does not cause an amino acid change (synonymous change), it is unlikely to be causal if it indeed is associated with PC risk. However, the recent report of altered *in vivo* protein folding for a synonymous *MRD1* variant (20) does indicate that synonymous variants should not *a priori* be assumed to be nonfunctional. After adjustment for covariates (age, gender, and smoking history), two additional mtSNPs (3010 and 1719) showed associations with PC. The mtSNP3010 is located at the coding

region of 16S rRNA and the mtSNP1719 is also located at the coding region of 16S rRNA. Therefore, both may potentially cause functional changes. However, these associations were observed in only one of our two data sets, suggesting that these associations should be interpreted carefully and may require further evaluation.

Navaglia et al. recently tested four mtSNPs (73, 152, 16189, and 16519) in the D-loop region for association with PC risk using 99 cases with PC and 87 controls, and found that none were correlated with the disease (6). Our current study strengthens their observation that these mtSNPs do not predispose to PC (Table 2). However, Navaglia et al. also reported a significant association of the mtSNP16519 with PC-associated diabetes mellitus and prognosis (6). In our preliminary analysis of 654 non–surgery patients and 366 surgery patients (separately assessed), we observed no correlation of this mtSNP with PC survival. Clearly, detailed analysis is needed to elucidate the potential prognostic role of this SNP in PC patients.

When considering each haplogroup individually, we observed an association between haplogroup Com and PC risk in both the validation set and the combined set (Table 3). Studies have shown that inherited polymorphisms are functionally different. For example, different mitochondrial haplogroups are qualitatively different from each other. Haplogroups H and T displayed a significant difference in the activity of complexes I and IV of oxidative phosphorylation (21). Individuals selected for longevity (male centenarians) had a significantly higher frequency of the European haplogroup J than sex-matched younger subjects having the same ethnic and geographic origin (22, 23). Therefore, although our observation may be a chance association, haplogroup-specific effects on PC risk and rate of aging may merit further study.

Recent data suggest that inherited variation of mitochondrial DNA could affect the occurrence of mutations (24). The acquired mutations are not randomly distributed across the mitochondrial genome, and the rate of mutation accumulation seems to vary with different genetic background. Yeh et al. (25) have shown that the distribution and spectra of germ-line mitochondrial gene variants seemed to differ between individuals with thyroid cancer compared with normal controls, with complex I variants favored among cancer cases. Maximo et al. (26) reported that germline polymorphisms of the mitochondrial *ATPase 6* gene were associated with the occurrence of mitochondrial DNA common deletion in thyroid tumors. Because *ATPase 6* may have a role in mitochondrial DNA maintenance, these polymorphisms in *ATPase 6* could lead to a less efficient mitochondrial DNA replication and to mitochondrial DNA abnormalities that could contribute to the occurrence of mitochondrial DNA common deletions and tumorigenesis.

Overall, our results do not support a significant involvement of mtSNPs or haplogroups in PC risk. Much larger numbers will be needed to achieve the power required to confirm the suggestive associations we have observed, which could also be due to chance. Because this study did not represent an exhaustive investigation of mitochondrial genetic variation (especially for nuclear-encoded mitochondrial proteins), additional work would be necessary to fully elucidate the role of mitochondrial genetic variation in PC.

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Mitochondrial Genetic Polymorphisms and Pancreatic Cancer Risk

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