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Interaction of Polymorphisms in Mitotic Regulator Genes With Cigarette Smoking and Pancreatic Cancer Risk

Ji-Hyun Jang[1,2], **Michelle Cotterchio**[2], **Ayelet Borgida**[3], **Geoffrey Liu**[4], **Steven Gallinger**[3,5], and **Sean P. Cleary**[5,6,*]

[1]Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada

[2]Prevention and Cancer Control, Cancer Care Ontario, Toronto, Ontario, Canada

[3]Dr. Zane Cohen Digestive Diseases Clinical Research Centre, Mount Sinai Hospital, Toronto, Ontario, Canada

[4]Division of Medical Oncology, Princess Margaret Hospital, University Health Network, Toronto, Ontario, Canada

[5]Department of Surgery, University Health Network, University of Toronto, Toronto, Ontario, Canada

[6]Prosserman Center for Health Research, Samuel Lunenfeld Research Institute, Toronto, Ontario, Canada

Abstract

Mitotic regulator genes have been associated with several cancers, however little is known about their possible association with pancreatic cancer. Smoking and family history are the strongest risk factors for this highly fatal disease. The main purpose of this study was to determine if polymorphisms of mitotic regulator genes are associated with pancreatic cancer and whether they modify the association between cigarette smoking and pancreatic cancer risk. A population-based case-control study was conducted in Ontario with 455 pathology-confirmed pancreatic cancer cases and 893 controls. Cigarette smoking history was collected using questionnaires and DNA obtained from blood samples. Genotypes were determined by mass-spectrometry. Odds ratio estimates were obtained using multivariate logistic regression. Interactions between genetic variant and smoking were assessed using stratified analyses and the likelihood ratio statistic (significance $P < 0.05$). Variants of *MCPH1*, *FYN*, *APC*, *PRKCA*, *NIN*, *TopBP1*, *RIPK1*, and *SNW1* were not independently associated with pancreatic cancer risk. A significant interaction was observed between pack-years and *MCPH1*-2550-C > T ($P = 0.02$). Compared to never smokers, individuals with 10–27 pack-years and *MCPH1*-2550-CC genotype were at increased risk for pancreatic cancer (MVOR = 2.49, 95% confidence interval [95% CI]: 1.55, 4.00) as were those with >27 pack-years and *MCPH1*-2550-TC genotype (MVOR = 2.42, 95% CI: 1.45, 4.05). A significant interaction was observed between smoking status and *TopBP1*-3257-A > G ($P = 0.04$) using a dominant model. Current smokers with the *TopBP1*-3257 A allele were at increased risk for pancreatic cancer (MVOR = 2.55, 95% CI: 1.77, 3.67). *MCPH1*-2550-C > T and

*Correspondence to: 10EN212 Toronto General Hospital, 200 Elizabeth St., Toronto, ON, Canada M5G 2C4.

TopBP1-3257-A > G modify the association between smoking and pancreatic cancer. These findings provide insights into the potential molecular mechanisms behind smoking-associated pancreatic cancer.

Keywords

pancreatic neoplasms; smoking; polymorphism; single nucleotide; mitosis; case-control studies

INTRODUCTION

Mitotic regulators operate at various points in the cell cycle to maintain genomic integrity and cell division control. Given the uncontrolled, proliferative nature of cancer, it is not surprising that mutations in these regulatory genes may be associated with cancer [1,2].

Genetic variants of mitotic regulators have previously been investigated in cancer. Polymorphisms of *adenomatous polyposis coli (APC)* and *receptor-interacting serine/threonine-protein kinase 1 (RIPK1)* have been associated with increased colorectal cancer risk [3] and poorer colorectal cancer survival [4], respectively. Polymorphisms of *tyrosine protein kinase Fyn (FYN)* have been associated with breast cancer risk with odds ratios ranging from 1.38 to 1.45 [5]. A higher frequency of the *topoisomerase 2-binding protein 1 (TopBP1)*-1010-C > T polymorphism was reported among familial breast and/or ovarian cancer cases compared to controls [6]. Individuals with the TC genotype of *protein kinase C alpha (PRKCA)* (rs734287) have been found to have a 30% risk reduction for breast cancer compared to wildtypes [7].

A recent study [8] suggests an association between polymorphisms of mitotic regulator genes, cigarette smoking, and pancreatic cancer risk with smokers carrying polymorphisms of *TopBP1*, *polo-like kinase 2 (PLK2)*, and *microcephalin (MCPH1)* at significantly increased pancreatic cancer risk, while those with polymorphisms in *FYN*, *ninein (NIN)*, *SNW domain-containing protein 1 (SNW1)*, and *PRKCA* showed decreased risk.

To further explore and validate these pancreatic cancer findings, we investigated the potential interactions between variants of mitotic regulator genes *MCPH1*, *FYN*, *APC*, *PRKCA*, *NIN*, *TopBP1*, *RIPK1*, and *SNW1*, cigarette smoking and pancreatic cancer risk.

MATERIALS AND METHODS

Study Design

A population-based case–control study was conducted with cases obtained through the Ontario Pancreas Cancer Study (OPCS), one of six study sites of the Pancreatic Cancer Genetic Epidemiology (PACGENE) Consortium [9]. Control subjects were obtained from the accompanying Ontario Familial Colorectal Cancer Registry (OFCCR), one of six sites of the Colon Cancer Family Registry (C-CFR) [10]. Detailed methodologies of the OPCS, the OFCCR and the current study design have previously been described [11–14]. Key methodological details pertinent to the present study are included below.

Participants

Cases are Ontario residents with a primary pathology-confirmed adenocarcinoma of the pancreas or metastasis diagnosed between April 2003 and July 2009. Cases completed three self-administered questionnaires (Family History Questionnaire [FHQ], Personal History [epidemiology] Questionnaire [PHQ], and Clinical Patient Questionnaire [CPQ]), and provided consent for blood samples, medical records, and tumor specimens. 455 cases were included in this study with a median age of diagnosis of 65 yr (range: 20–89 yr), and 54% of them being male. 8/455 cases (1.76%) had a proxy respondent (e. g., spouse) complete the questionnaires on their behalf.

Population-based controls in the study were originally recruited as controls for the OFCCR. All controls in this study do not have a personal history of colorectal or pancreatic cancer. Controls were recruited by random-digit dialing and the Ministry of Finance Property Assessment Database. They also completed self-administered questionnaires. Cases and controls are frequency-matched by age and sex. In total, 893 controls were included with the median age of questionnaire completion (recruitment) being 64 yr (range: 29–79 yr), and 53% of them being male.

Data Collection

Three cigarette smoking variables were derived from data collected using the PHQ: (1) Smoking status (classified as never smoker, former smoker for those who regularly smoked cigarettes >2 yr prior to pancreatic cancer diagnosis for cases and >2 yr prior to questionnaire completion for controls, and current smoker for those who reported regularly smoking cigarettes ≤2 yr prior to pancreatic cancer diagnosis for cases and ≤2 yr prior to questionnaire completion for controls); (2) pack-years defined as the number of packs of cigarettes smoked per day multiplied by the number of smoking years reported at questionnaire completion. Categories were based on tertiles of controls who were ever-smokers; and (3) years smoked defined as the number of years participants reported of smoking cigarettes at questionnaire completion. Categories were based on tertiles of controls who were ever-smokers.

DNA Collection and Genotyping

Sequence variants in genes regulating the mitotic process were identified through literature searches and the National Center for Biotechnology Information dbSNP database [15]. Variants with a published minor allele frequency >5% were selected for analysis. After reviewing the findings reported by Couch et al. [8] we further selected SNPs of genes that Couch et al. [8] reported to be significant in their study. Given the limited sample size and consequent power of the present study, all possible mitotic regulator gene polymorphisms could not be investigated. Genetic variants that were tested in the present study are listed in Table 1.

Genotyping of variants was performed using the SequenomiPLEX genotyping assay and MassARRAY-MALDI-TOF Mass Spectrometry system (Sequenom, San Diego, CA). Primers for amplification of each variant were designed using the MassARRAY Workstation 3.0 (Sequenom) software into three multiplex PCR reactions. Samples were

then randomly ali-quoted onto 384-well plates and blinded by disease status. All plates included positive and negative controls for each variant as well as a 10% repeat samples for quality control. The concordant rate of 10% repeat samples for quality control was >99% in agreement. Genotypes were analyzed using the MassARRAY Workstation 3.0 software and confirmed by visual assessment of the data.

Statistical Analysis

Multivariate unconditional logistic regression analysis was conducted to obtain age-, sex-adjusted odds ratio (ASOR) and multivariate-adjusted odds ratio (MVOR) estimates. Pancreatic cancer risk factors (ethnicity, body mass index, alcohol consumption, personal history of diabetes mellitus diagnosis, aspirin use, non-steroidal anti-inflammatory drug use, and family history of pancreatic cancer) were evaluated as potential confounders in the associations between pancreatic cancer and all three types of cigarette smoking variables. To build the most parsimonious multivariate models, only potential confounding variables that changed the ASOR by >10% [16] were deemed to be confounding variables, and were subsequently adjusted for in multivariate models. As ethnicity was the only confounding variable that changed the ASOR >10%, it was the only additional variable (plus age and sex) that was adjusted for in multivariate models. Caucasians were heavily represented in both our cases and controls at 85% and 96%, respectively.

Main genetic effects were investigated with multivariate unconditional logistic regression investigating the effect of each genetic genotype on pancreatic cancer risk as well as a dominant model for genes if such a trend was suggested when analyzed by genotype.

Stratified analyses and the likelihood ratio statistic (LRS) comparing models with and without the interaction term at a statistically significant result set at $P < 0.05$ were used to investigate effect modification between each genetic variant and smoking.

All statistical analyses were conducted using SAS (SAS Institute, Cary, NC).

Deviation from Hardy–Weinberg equilibrium (HWE) was tested for each polymorphism on a subset of control participants only using HWE.test in the genetics package [17] of R [18] with the statistically significance level set at $P = 0.05$.

Ethics Approval

This project was approved by the research ethics boards of University Health Network and Mount Sinai Hospital, Toronto, Ontario, Canada.

RESULTS

A previous report using the same cases and controls as in the present study has described this study sample's distribution of risk factors and smoking variables in detail [14].

Testing of HWE was completed for all polymorphisms showed in Table 1. *APC* (rs2431238; $P = 0.003$), and *NIN* (rs10145182; $P = 0.049$) deviated from HWE. All other genetic variants described in this study were within HWE ($P > 0.05$). *P* values of HWE. test [17,18]

for *MCPH1* (rs1057091), *FYN* (rs1465061), *PRKCA* (rs7342847), *TOPBP1* (rs10935070), *RIPK1* (rs12209182), and *SNW1* (rs1477261) were 0.34, 0.43, 0.57, 0.82, 0.84, and 0.07, respectively.

Table 2 illustrates genotype frequencies for cases and controls, and ASOR estimates for the association between each genotype and pancreatic cancer risk. None of the genetic variants investigated were significantly associated with pancreatic cancer risk.

Potential interactions between smoking and genetic variants listed in Table 1 were investigated, and only the statistically significant and marginally significant results are presented in Table 3. A significant interaction was observed between pack-years and *MCPH1*-2550-C > T (rs1057091; $P = 0.02$). Compared to never smokers, individuals with 10–27 pack-years and the *MCPH1*-2550-CC genotype were at increased risk for pancreatic cancer (MVOR = 2.49, 95% confidence interval [95% CI]: 1.55, 4.00) =as were those with >27 pack-years and the *MCPH1*-2550-TC genotype (MVOR = 2.42, 95% CI: 1.45, 4.05). A marginally significant interaction was observed between smoking status and *TopBP1*-3257-A > G ($P = 0.07$), with the trend of MVORs suggesting an interaction; our study may have been underpowered to detect a statistically significant interaction. However, when those with the A allele of *TopBP1*-3257 were grouped together, again current smokers were at increased risk for pancreatic cancer (MVOR = 2.55, 95% CI: 1.77, 3.67), and a statistically significant interaction was observed ($P = 0.04$).

DISCUSSION

Couch et al. [8] conducted the only previous study that evaluated the potential interaction between smoking, polymorphisms of mitotic regulator genes, and pancreatic cancer risk. In contrast to this earlier study that reported an increased risk associated with *APC* (rs2431238) [8], we did not find such association with *APC*. However, it is important to consider this finding with consideration that in our study, *APC* (rs2431238) deviated from HWE, while this polymorphism was in HWE in the previous report [8]. Consistent with the previous study [8], we found that *NIN* AA genotype was associated with a non-significant reduced risk for pancreatic cancer (ASOR = 0.83, 95% CI: 0.58, 1.19). No significant associations were found between pancreatic cancer and *MCPH1*, *FYN*, *PRKCA*, *TopBP1*, *RIPK1*, and *SNW1*. Congruent with previous finding [8] of *TopBP1* (rs10935070) being significantly associated with increased pancreatic cancer risk among current smokers, we report current smokers with the *TopBP1*-3257-AA and *TopBP1*-3257-GA genotypes are at increased risks with MVOR estimates of ~2.50. Furthermore under a dominant model, current smokers with the *TopBP1*-3257 AA and GA genotypes are at increased risk for pancreatic cancer (MVOR = 2.55, 95% CI: 1.77, 3.67), and a statistically significant interaction was observed between smoking and *TopBP1*-3257 using a dominant model ($P = 0.04$). A significant interaction between *MCPH1* and pack-years ($P = 0.02$) was observed, with individuals with 10–27 pack-years and the *MCPH1*-2250-CC genotype and those with *MCPH1*-2250-TC and >27 pack-years being at a particularly high risk for pancreatic cancer with MVORs of ~2.50. It is unclear why significantly increased risk for pancreatic cancer was only observed among *MCPH1*-2250-CC carriers with 10–27 pack-years, but not among those with >27 pack-years, and similarly why only smokers with >27 pack-years and the *MCPH1*-2250-TC

genotype were at increased risk. It is possible that we were underpowered to detect a statistically significant effect for those with >27 pack-years and the *MCPH1*-2250-CC genotype and/or there is a dose-dependent effect where individuals with one copy of the C allele require higher exposure to cigarette smoking to have a statistically significant increased risk. Similarly Couch et al. [8] reported that *MCPH1* (rs2433149) is associated with increased pancreatic cancer risk among ever and former smokers. It is important to note that *MCPH1* (rs1057091) in our study, and *MCPH1* (rs2433149) in the previous study [8] are in high linkage disequilibrium.

The MCPH1 protein has been shown to regulate the expression of *CHK1* and *BRCA1* [19] and mitotic checkpoints [20]. Specifically in relation to cancer, it has been demonstrated that cytoplasmic MCPH1 is only found in cultures of high-grade epithelial ovarian cancer cells [21]. Meanwhile, *in vitro* studies have demonstrated that TopBP1 plays a role in cell cycle regulation and responding to DNA damage [22,23]. Mutations of *TopBP1* [24] have been observed in tumor cells and in relation to p53 [25]. Epidemiologically, previous studies report *TopBP1* variants being associated with breast cancer [6]. In summary, there is growing biological evidence that *MCPH1* and *TopBP1* may be contributors to carcinogenesis, supporting our hypothesis that the combination of cigarette smoking and polymorphisms of mitotic regulators can increase pancreatic cancer risk.

Limitations of the present study are that despite a relatively large sample size for a pancreatic cancer study, we were still limited in statistical power for certain calculations, particularly interactions. Specifically compared to Couch et al.'s [8] study ours was relatively underpowered with a total sample size of 1348 compared to Couch et al.'s [8] 2240. Similar to other retrospective pancreatic cancer studies, our study is susceptible to survival bias given the poor prognosis of pancreatic cancer. Given the modest response rates of our cases and controls at ~30% [11] and ~61% [13], respectively, response bias is possible. Data on smoking and potential confounding variables were collected using self-administered questionnaires, hence recall bias cannot be excluded. HWE testing for genetic variants demonstrated that two variants deviated from HWE (*APC* [rs2431238], *NIN* [rs10145182]) and, genotyping errors in these variants cannot be excluded.

Strengths of the study are that as a population-based study, our findings are not limited by biased sampling frames (e.g., hospital-based). As the OPCS and OFCCR collect extensive epidemiological data, we were able to adjust for pancreatic cancer risk factors, reducing the possibility of our findings being biased by uncontrolled confounding.

This is the first study to investigate mitotic regulator gene variants and pancreatic cancer risk in a Canadian population. While we did not find significant independent associations between the variants that we investigated and pancreatic cancer risk, we report that the *MCPH1*-2550-C > T variant significantly modifies the association between smoking and pancreatic cancer. These results validate earlier findings [8] indicating a potentially significant role of *MCPH1* in modifying the risk of pancreatic cancer associated with cigarette smoking. As few results are replicated in genetic epidemiology, these findings are particularly noteworthy. While the modification of *TopBP1* on cigarette smoking and pancreatic cancer failed to reach statistical significance initially, a statistically significant

interaction was observed using a dominant model of grouping individuals with the A allele versus without.

Future studies are necessary to elucidate the mechanism by which *MCPH1* and *TopBP1* influence the pathogenesis of pancreatic cancer, and replications of our findings are needed to validate our report.

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Abbreviations

APC	adenomatous polyposis coli
RIPK1	receptor-interacting serine/threonine-protein kinase 1
FYN	tyrosine protein kinase Fyn
TopBP1	topoisomerase 2-binding protein 1
PRKCA	protein kinase C alpha
MCPH1	microcephalin
NIN	ninein
SNW1	SNW domain-containing protein 1
PACGENE	pancreatic cancer genetic epidemiology
OFCCR	Ontario Familial Colorectal Cancer Registry
OPCS	Ontario Pancreas Cancer Study
CPQ	Clinical Patient Questionnaire
ASOR	age-, sex-adjusted odds ratio
MVOR	multivariate-adjusted odds ratio
HWE	Hardy–Weinberg equilibrium
95% CI	95% confidence interval
C-CFR	Colon Cancer Family Registry
FHQ	Family History Questionnaire
LRS	Likelihood ratio statistic

OR	odds ratio
PHQ	Personal Health Questionnaire
PLK2	Polo-like kinase 2

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Table 1

List of Genes and National Center for Biotechnology Information (NCBI) Single Nucleotide Polymorphisms Database Number (dbSNP) Tested in Cases and Controls

Gene	NCBI dbSNP no.	Minor allele frequency	Allele change	Amino acid change
MCPH1	rs1057091	0.22	C > T	p.Pro 828 Ser
FYN	rs1465061	0.37	A > G	N/A
APC	rs2431238	0.26	C > T	N/A
PRKCA	rs7342847	0.45	C > T	N/A
NIN	rs10145182	0.23	A > T	N/A
TopBP1	rs10935070	0.18	A > G	p.Asn1042Ser
RIPK1	rs12209182	0.33	C > T	N/A
SNW1	rs1477261	0.19	A > T	N/A

NCBI db SNP, National Center for Biotechnology Information Single Nucleotide Polymorphisms Database Number; minor allele frequency, Global minor allele frequency from NCBI db SNP; *MCPH1*, *microcephalin; FYN*, *tyrosine protein kinase Fyn*; N/A, not available; *APC*, *adenomatous polyposis coli; PRKCA*, *protein kinase C alpha; NIN*, *ninein; TopBP1*, *topoisomerase 2-binding protein; RIPK1*, *receptor-interacting serine/threonine-protein kinase 1; SNW1*, *SNW domain-containing protein*.

Table 2

Distribution of Pancreatic Cancer Cases, Controls, and Age-, Sex-Adjusted Odds Ratio (ASOR) Estimates for Selected Genetic Polymorphisms

	Cases (*n* = 455)		Controls (*n* = 893)			
Genetic polymorphism	**No.**	**%**	**No.**	**%**	**ASOR**	**95% CI**
MCPH1 (rs1057091)						
CC	215	48	419	47	1.00 (referent)	
TC	201	45	389	44	1.00	0.78, 1.27
TT	31	7	77	9	0.80	0.51, 1.26
FYN (rs1465061)						
GG	158	35	341	39	1.00 (referent)	
AG	224	50	424	48	1.17	0.91, 1.51
AA	68	15	116	13	1.28	0.89, 1.83
FYN (rs1465061)						
AG +þ AA	292	65	540	61	1.00 (referent)	
GG	158	35	341	39	0.84	0.66, 1.07
APC (rs2431238)						
CC	207	47	403	46	1.00 (referent)	
CT	184	41	353	40	0.98	0.76, 1.26
TT	53	12	120	14	0.89	0.62, 1.29
PRKCA (rs7342847)						
CC	181	40	349	40	1.00 (referent)	
CT	208	46	406	46	1.00	0.78, 1.29
TT	62	14	128	15	0.96	0.67, 1.38
NIN (rs10145182)						
TT	161	36	336	38	1.00 (referent)	
TA	224	50	394	45	1.18	0.92, 1.53
AA	66	15	152	17	0.83	0.58, 1.19
TopBP1 (rs10935070)						
AA	213	47	407	46	1.00 (referent)	
GA	193	43	381	43	0.95	0.74, 1.21
GG	45	10	93	11	0.95	0.64, 1.41

Genetic polymorphism	Cases (*n* = 455) No.	%	Controls (*n* = 893) No.	%	ASOR	95% CI
RIPK1 (rs12209182)						
TT	157	35	292	33	1.00 (referent)	
CT	205	46	437	49	0.88	0.68, 1.14
CC	87	19	158	18	1.02	0.73, 1.42
SNW1 (rs1477261)						
TT	284	71	593	68	1.00 (referent)	
AT	107	27	263	30	0.85	0.65, 1.11
AA	11	3	18	2	1.31	0.61, 2.83

No., numbers may not add to total due to missing values; ASOR, age, sex-adjusted odds ratio; 95% CI, 95% confidence interval; *MCPH1, microcephalin; FYN, tyrosine protein kinase fyn; APC, adenomatous polyposis coli; PRKCA, protein kinase C alpha; NIN, ninein; TopBP1, topoisomerase 2-binding protein; RIPK1, receptor-interacting serine/threonine-protein kinase 1; SNW1, SNW domain-containing protein.*

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Table 3

Multivariate-Adjusted Odds Ratio (MVOR) Estimates and 95% Confidence Interval (95% CI) for Smoking Status Stratified by Genotypes Selected Based on Significance

	Genetic variant							
	MVOR	95% CI	MVOR	95% CI	MVOR	95% CI		
	***MCPH1* 2550 C > T (rs1057091)**							
	CC (*n* = 634)		TC (*n* = 590)		TT (*n* = 108)		df	$P_{interaction}$
Smoking pack-years								
Never smoker	1.00 (referent)		1.00 (referent)		1.00 (referent)			
≤9	1.00	0.58, 1.73	1.26	0.76, 2.07	0.99	0.23, 4.29		
10–27	2.49	1.55, 4.00	1.00	0.59, 1.70	1.09	0.31, 3.81		
>27	1.40	0.87, 2.26	2.42	1.45, 4.05	1.75	0.54, 5.74	6	0.02

	Genetic variant							
	MVOR	95% CI	MVOR	95% CI	MVOR	95% CI		
	***TopBP1* 3257 A > G (rs10935070)**							
	AA (*n* = 620)		GA (*n* = 574)		GG (*n* = 138)		df	$P_{interaction}$
Smoking status								
Never	1.00 (referent)		1.00 (referent)		1.00 (referent)			
Former	1.38	0.91, 2.11	0.82	0.53, 1.25	0.94	0.40, 2.20		
Current	2.79	1.66, 4.70	2.32	1.39, 3.88	0.55	0.13, 2.34	4	0.07

	Genetic variant							
	MVOR	95% CI	MVOR	95% CI	MVOR	95% CI		
	***TopBP1* 3257 A > G (rs10935070)**							
	AA + GA (*n* = 1194)		GG (*n* = 138)				df	$P_{interaction}$
Smoking status								
Never	1.00 (referent)		1.00 (referent)					
Former	1.05	0.78, 1.42	0.94					
Current	2.55	1.77, 3.67	0.55	0.13, 2.34			2	0.04

MVOR, multivariate-adjusted odds ratio; adjusted for age, sex, ethnicity; 95% CI, 95% confidence interval; df, degrees of freedom; $P_{interaction}$, *P*-value for interaction; *MCPH1, microcephalin; TopBP1, topoisomerase 2-binding protein*.