

Single Nucleotide Polymorphisms within the 8Q24 Region are Not Associated with the Risk of Intraductal Papillary Mucinous Neoplasms of the Pancreas

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ABSTRACT

Background & Aims: Intraductal papillary mucinous neoplasms (IPMNs) of the pancreas have been reported to be associated with an increased risk of developing extra-pancreatic malignancies. A common genetic background has been hypothesised to be responsible for such an association. Human chromosomal region 8q24 has been associated with many types of cancer. The majority of these associations lie at approximately 128 Mb on chromosome 8. We conducted a study in order to examine the association between IPMN and single nucleotide polymorphisms (SNPs) from the 8q24 region, namely rs10505477, rs6983267, rs7014346, rs6993464, previously reported to influence general cancer susceptibility.

Methods. The study was performed on 117 IPMN cases and 231 controls. Cases were enrolled at the Digestive Endoscopy Unit, Policlinico Agostino Gemelli from January, 2010 to June, 2011, with either a prevalent or incident IPMN diagnosis. Status of SNPs was determined using a StepOne Real-time PCR system (Applied Biosystems) and TaqMan SNP Genotyping Assay™ 40X. Unconditional multiple logistic regression models were used to estimate odds ratios and 95% confidence intervals for the association of selected SNPs and IPMNs.

Results. Cases were more likely to report a 1st degree family history of cancer ($p < 0.001$), as well as heavy smoking ($p = 0.001$) and heavy drinking habits ($p < 0.001$). No significant association was observed between IPMN and selected SNPs. The results were confirmed also when stratified according to any 1st-degree family history of cancer.

Conclusion. Patients with IPMN do not have a higher prevalence of SNPs in the human chromosomal region 8q24 in respect to the control population.

Key words: pancreas – intraductal papillary mucinous neoplasms – single nucleotide polymorphisms.

Abbreviations: CASC8: cancer susceptibility candidate 8; CRC: colorectal cancer; ENPP2: ectonucleotide pyrophosphatase/phosphodiesterase 2; EPM: extra-pancreatic malignancy; eQTLs: expression quantitative trait loci; IPMN: intraductal papillary mucinous neoplasm; MYC: myelocytomatosis viral oncogene homolog gene; NOV: nephroblastoma over-expressed gene; PCR: polymerase chain reaction; POU5F1P1: POU class 5 homeobox 1 pseudogene 1 gene; S-MRCP: magnetic resonance cholangiopancreatography with secretin stimulation; SNP: single nucleotide polymorphism; TCF4: transcription factor 4.

INTRODUCTION

Intraductal papillary mucinous neoplasms (IPMNs) of the pancreas have been reported to be associated with an increased risk of developing extra-pancreatic malignancies (EPM) [1]. The most frequent EPM consistently found in IPMN patients is colorectal cancer (CRC) [1, 2]. Nevertheless, IPMN patients are also reported to be at higher risk of other

cancers such as gastric, lung, breast, kidney and thyroid cancers [1]. Although the biological mechanism behind this association is still unknown, it can be hypothesized that a common genetic background may be responsible.

The human chromosomal region 8q24 has been associated with many types of cancer [3-5]. The majority of these associations lie at approximately 128 Mb on chromosome 8. Among them, one prominently associated single nucleotide polymorphism (SNP), rs6983267, has been shown to interact with the myelocytomatosis viral oncogene homolog gene (MYC) [6]. The region contains several other genes which could be functionally related to cancer development, including nephroblastoma over-expressed gene (NOV), which encodes a regulatory protein from the CCN family that has been

associated with cancer development [7]. Furthermore, as several studies suggest the possibility that some loci within 8q24 influence more than one type of cancer per locus [8] it could be a case that this region contains loci that affect general cancer susceptibility. Knowing this it can be hypothesized that the presence of SNPs in the 8q24 region could be responsible for the increased propensity of IPMN patients to develop EPMS.

We conducted a genetic association study in order to examine the relationship between pancreatic IPMN and selected SNPs within the 8q24 region of human genome.

METHODS

The study was conducted at the Digestive Endoscopy Unit of the Università Cattolica del Sacro Cuore, Rome, Italy. Prevalent cases of patients with either a new diagnosis of IPMN or those seen during follow-up at the participating units during an 18-month period (January, 2010 to June, 2011) were enrolled. The criteria for the IPMN diagnosis have been previously described [9]. The diagnosis of IPMN was considered as certain in the presence of either a histological diagnosis obtained by EUS or surgical specimen, or a cytologic diagnosis obtained by EUS. A highly probable diagnosis of IPMN was based on the presence of one or several main pancreatic duct and/or branch duct dilatation(s) and/or pancreatic cystic lesions communicating with pancreatic ducts at CT, magnetic resonance cholangiopancreatography with secretin stimulation (S-MRCP), ERCP or EUS. Patients were excluded if they had cystic lesions other than IPMN. The controls included patients from the same hospital with a broad range of diagnoses, enrolled during the same time period. Around 50% of the controls were outpatients, and the remaining were patients undergoing surgical interventions (laparoscopic cholecystectomy, appendicitis, inguinal hernia) or admitted for a wide spectrum of other non neoplastic diseases. Controls were matched to each IPMN case by gender and age (± 5 years). Written informed consent was obtained from all study subjects. The study was conducted according to the Declaration of Helsinki and was approved by the Ethical Committee of the Università Cattolica del Sacro Cuore. Both cases and controls were interviewed by trained physicians using a structured questionnaire and data on demographics, lifestyle habits (alcohol consumption, cigarette smoking), prior medical history, cancer family history were collected.

SNPs genotyping

The SNPs rs10505477, rs6983267, rs7014346 and rs6993464 within the 8q24 region of human genome have been selected to be tested in the study. Among all the SNPs within the 8q24 region, these have been most frequently reported to be significantly associated with cancer susceptibility in general.

Genomic DNA from whole blood samples was extracted by using a salting out protocol. This method uses lysis buffer that contains detergent and salts and creates a hypertonic condition resulting in lysis of cells. The DNA concentration was measured by the spectrophotometer. The working solutions were obtained at a final concentration of 10 ng/ μ l and stored at -20°C . All SNPs were performed using a StepOne Real-time PCR system (Applied Biosystems) and commercial kits TaqMan SNP Genotyping Assay™ 40X (Assay

IDs: C__29809139_20, C__29086771_20, C__29086780_10, C__2149241__10, Applied Biosystems). PCR reactions were done according to the manufacturer's protocol with a final volume of reaction 15 μ l per well. The program used considered an initial step of 10 minutes at 95°C , followed by 40 cycles at 95°C of 15 seconds each, and one minute at 60°C . Allelic discrimination was determined by the Step One software applying the fluorescence probes. The fluorescence values were detected in the FAM channel for the allele 1 and VIC channel for the allele 2. The dye used as the passive reference was ROX.

Statistical analysis

Hardy-Weinberg equilibrium (HWE) was tested for the controls. Descriptive analysis using proportions and means \pm standard deviation was computed for categorical and quantitative variables. Differences between groups were calculated using chi-squared and two-sample *t*-tests.

Association of IPMN with named SNPs was assessed by fitting unconditional multiple logistic regression models both to investigate departure from the multiplicative model and to identify the effect model best fitting the data. We started by modelling the relationship between IPMN and the genetic markers to try to underpin the transmission inheritance model. We fitted the regression model at a genotype level by assuming the following genetic models: not assuming any model, a dominant, a recessive and multiplicative. A Likelihood Ratio test was used to check the departure from a multiplicative model. Finally, odds ratios (OR) of IPMN and corresponding 95% confidence intervals (CI) according to analysed polymorphisms were derived from unconditional multiple logistic regression models using the multiplicative model, including terms for age and sex.

We also examined the possible confounding effect of smoking, alcohol, and cancer family history. However, models including these covariates yielded very similar results. Thus, given the small numbers in some strata, only the age- and sex-adjusted estimates were presented. Finally, the results were stratified according to any 1st-degree family history of cancer.

RESULTS

A number of 117 IPMN cases and 231 controls were included in the study. Among the included IPMNs, 91 (77.8%) had a histological diagnosis obtained by surgical or EUS specimen, 12 had a cytologic diagnosis obtained by EUS (10.3%), and 14 (11.9%) had the diagnosis set according to CT/MRCP/ERCP or EUS findings.

The demographics of 117 IPMN cases and 231 controls are reported in Table I. There was no difference in age and gender structure among cases and controls.

Table I. Demographics of the 117 intraductal papillary mucinous neoplasm (IPMN) cases and 231 controls included in study

	IPMN cases	Controls	P value
Age (years) mean \pm SD	63.5 \pm 11.8	63.8 \pm 12.5	0.81
Gender N (%)			
Male	70 (59.8)	135 (58.4)	0.80
Female	47 (40.2)	96 (41.6)	

Table II reports the cancer family history and lifestyle habits of the 117 IPMN cases and 231 controls included. Cases were more likely to report any 1st degree family history of cancer than controls ($p < 0.001$). There were significantly more heavy smokers ($p = 0.001$) and heavy drinkers ($p < 0.001$) among the cases (Table II).

Table II. Distribution of the 117 intraductal papillary mucinous neoplasm (IPMN) cases and 231 controls according to lifestyle habits and cancer family history

	IPMN cases	Controls	P value
	N (%)	N (%)	
Age (years) mean \pm SD	63.5 \pm 11.8	63.8 \pm 12.5	0.81
Gender			
Male	70 (59.8)	135 (58.4)	0.80
Female	47 (40.2)	96 (41.6)	
Any 1 st degree family history of cancer*	71 (62.3)	65 (30.1)	<0.001
1 st degree family history of CRC*	15 (13.2)	16 (7.5)	0.10
Smoking*			
Never	47 (41.0)	138 (59.7)	0.001
Ex-smoker	15 (12.9)	32 (13.9)	
Current-smoker	8 (6.9)	15 (6.5)	
>20 pack/years	46 (39.3)	46 (20.0)	
Alcohol g/day			
< 12 g/day	51 (43.6)	147 (63.6)	<0.001
12-23 g/day	13 (11.1)	47 (20.4)	
> 23 g/day	53 (45.3)	37 (16.2)	

CRC: colorectal cancer; *the sum does not add up to the total because of missing values.

Table III reports the distribution of cases and controls, the ORs and 95% CIs for IPMN according to the selected SNPs. No significant association was observed between the selected SNPs and IPMN. The results were confirmed also when stratified according to any 1st-degree family history of cancer (data not shown).

DISCUSSION

The genetic association study we conducted did not find any of the named SNPs (rs6983267, rs6993464, rs7014346, rs10505477) in the human chromosomal region 8q24 to be associated with IPMN.

SNPs in the human chromosomal region 8q24 are reported to be associated with cancer in general, and particularly CRC [8]. The majority of these associations lie at approximately 128 Mb on chromosome 8. Some of the SNPs in 8q24 have been shown to interact with the proto-oncogene MYC [6]. MYC is an important protooncogene, over-expressed in numerous tumors, including CRC. The region contains several other genes which could be functionally related to cancer development, including NOV and ectonucleotide pyrophosphatase/phosphodiesterase 2 (ENPP2). NOV encodes a regulatory protein from the CCN family that has been associated with cancer development [7]. ENPP2 encodes a phospholipase which stimulates tumor cell motility and proliferation [10]. In addition, it has been reported that both NOV and ENPP2 are indirectly regulated by the 8q24 proto-oncogene MYC [11], via p53 (for NOV) [12, 13] and ESR2 (for ENPP2) [14, 15], which makes their potential involvement in a pathway for cancer susceptibility plausible. In light of the named facts, it can be hypothesized that this region contains a locus for general cancer susceptibility. Recent studies have identified

Table III. Distribution of the 117 intraductal papillary mucinous neoplasm (IPMN) cases and 231 controls, according to studied single-nucleotide polymorphisms (SNPs) and their association with intraductal papillary mucinous neoplasms (IPMNs)

	IPMN cases (N=117)		Controls (N=231)		p-value*	OR (95% CI)
	N	%	N	%		
rs10505477					0.29	
wt/wt	26	23.01	60	30.45		1
wt/mt	61	53.98	113	51.36		1.30 (0.93-1.82)
mt/mt	26	23.01	40	18.18		1.69 (0.86-3.31)
rs6983267					0.28	
wt/wt	21	18.58	57	25.91		1
wt/mt	68	60.18	115	52.27		1.16 (0.82-1.62)
mt/mt	24	21.24	48	21.82		1.35 (0.67-2.62)
rs7014346					0.57	
wt/wt	37	32.74	85	38.46		1
wt/mt	61	53.98	111	50.23		1.20 (0.85-1.70)
mt/mt	15	13.27	25	11.31		1.44 (0.72-2.89)
rs6993464					0.57	
wt/wt	30	26.55	71	32.13		1
wt/mt	61	53.98	111	50.23		1.09 (0.88-1.37)
mt/mt	22	19.47	39	17.65		1.19 (0.77-1.88)

*chi square test; OR: odds ratio; 95% CI: 95% confidence interval; wt:wild-type allele; mt:variant-type allele

and confirmed the associations of several SNPs within the region with CRC [4, 16, 17], breast [18, 19] and prostate cancer [20-22]. Additional associations have been found for kidney, thyroid, and larynx cancer [23], as well as cancers of the upper aerodigestive tract [24].

The SNP within 8q24 that showed highest significance for carcinogenesis was rs6983267. Several reports provided the insights into the functional role of the rs6983267 [6, 25]. Tuupanen et al. [25] reported that the risk allele G of rs6983267 demonstrated a copy number increase during CRC development. They also showed that the SNP is located in a transcriptional enhancer and that the G allele has increased affinity for binding the transcription factor 4 (TCF4) [25], which is important in activating the transcription of Wnt target genes. Furthermore, they showed that the rs6983267 region physically interacts with the MYC promoter region [25]. Thus, it can be concluded that the biological mechanisms associating the rs6983267 to cancer risk includes an impact on Wnt signalling and MYC expression [6, 25]. Several studies have reported SNP rs698267 to be associated with an increased risk of CRC [5, 8, 17, 26-28]. The findings have been confirmed in meta-analyses conducted by Hunter et al. [29] and Brisbin et al. [30]. However, Brisbin et al. reported rs698267 to be associated not only with CRC but also with prostate cancer [30].

Another SNP from the 8q24 region reported to be significantly associated with cancer risk is rs6993464 [30]. This SNP lies in the region between NOV and ENPP2. Several of the significant SNPs in this region are identified as expression quantitative trait loci (eQTLs) for different genes throughout the genome, that modify the risk for various cancer types [31]. Among them rs6993464 has been shown to be an eQTL for POLR2F, a gene on chromosome 22 which is up-regulated in CRC [32]. Furthermore, the T allele of the rs6993464 has been reported to be associated with an increased risk for breast and pancreatic cancer [30].

The SNP rs7014346 is another SNP on chromosome 8q24, associated with increased risk to CRC [3, 26, 29]. It is located on the POU class 5 homeobox 1 pseudogene 1 gene (POU5F1P1) [33]. It has been suggested that the deregulated expression of POU genes could repress the expression of a tumor suppressor and activate the expression of an oncogenic growth factor [34].

The rs10505477 from 8q24 has so far been associated with the risk of CRC and breast cancer (4, 17, 35-37). It is located in the intron of Cancer Susceptibility Candidate 8 (CASC8), a long non-coding RNA (lncRNA), which overlaps the POU5F1B gene [38]. It has been hypothesized that rs10505477 may disrupt the key regulatory region of CASC8, resulting in its miss-expression [38]. Miss-expressed CASC8 may modulate the recruitment of general transcription factors on the promoter of its cognate gene, POU5F1B, which was found to be a putative cancer susceptibility gene [39]. By altering the fine tuning interactions between the CASC8 and POU5F1B, the rs10505477 could influence cancer susceptibility [38].

These findings gave a strong rationale for the named SNPs to be tested for the association with IPMN. However, the results of our study show that none of the selected SNPs from 8q24 regions was significantly associated with IPMN, even when stratified according to the 1st-degree family history of cancer. Nevertheless, in interpreting the results, it should be taken

into consideration that due to the relatively small number of included IPMN cases our study had limited power to identify weak associations. Future larger studies are required in order to confirm our findings. Although we offer negative results, this is the first study addressing the genetic background of an association between IPMN and EPMS. Our finding should help other researchers to point their research in the right direction, in order to further enlighten this subject.

CONCLUSION

The patients with IPMN do not have a higher prevalence of SNPs rs10505477, rs6983267, rs7014346, rs6993464 in the human chromosomal region 8q24 in respect to the control population.

Conflicts of interest: The authors have no conflicts of interest to disclose.

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Authors' contribution: N.P. and S.B. designed the study. A.L. enrolled the patients. R.A. performed PCR analyses. R.O. conducted statistical analysis. N.P. wrote the manuscript. S.B., A.L., M.B. and G.C. revised the manuscript.

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Polimorfismele mononucleotidice în regiunea 8q24 nu se asociază cu risc crescut de neoplasm intraductal papilar mucinos al pancreasului

ABSTRACT / REZUMAT

Premize și Scop: S-a constatat că neoplasmul intraductal papilar mucinos al pancreasului (IPMN) se asociază cu un risc crescut de dezvoltare a tumorilor maligne extrapancreatice. S-a emis ipoteza unui fond genetic comun ca fiind responsabil pentru această asocieră. Regiunea cromozomială 8q24 a fost asociată cu numeroase tipuri de cancer. Majoritatea acestor asocieri se află la aprox. 128 Mb pe cromozomul 8. Am efectuat un studiu pentru a evalua asocieră dintre IPMN și polimorfismele mononucleotidice (single nucleotide polymorphism, SNP) din regiunea 8q24, respectiv rs10505477, rs6983267, rs7014346, rs6993464, care au fost raportate a influența susceptibilitatea generală la cancer.

Metodă: Studiul a fost efectuat la 117 pacienți cu IPMN și la 231 martori. Cazurile au fost recrutate în Departamentul de Endoscopie Digestivă, Policlinico Agostino Gemelli în perioada ianuarie 2010 – iunie 2011, pacienți care aveau diagnosticul principal sau incidental stabilit de IPMN. Statusul SNP a fost determinat utilizând sistemul StepOne Real-time PCR (Applied Biosystems) și TaqMan SNP Genotyping Assay™ 40X. Modele de regresie multiplă au fost utilizate pentru a stabili riscul (Odds Ratio) și intervalele de confidență 95% pentru asocieră SNP-urilor selectate cu prezența IPMN.

Rezultate. Pacienții cu IPMN au raportat mai frecvent decât martorii un istoric familial de cancer la rudele de gradul 1 ($p < 0.001$), și au fost mai frecvent mari fumători ($p = 0.001$) și mari consumatori de alcool ($p < 0.001$). Nu au fost constatate asocieri semnificative între IPMN și polimorfismele SNP selectate. Rezultatele au fost confirmate și după stratificarea în funcție de istoricul familial de cancer la rudele de gradul 1.

Concluzie. La pacienții cu IPMN nu s-a constatat o prevalență mai ridicată decât la populația de control a polimorfismelor mononucleotidice studiate în regiunea cromozomială 8q24.