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Association of single nucleotide polymorphisms with renal cell carcinoma in Algerian population

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Abstract

Background: Renal cell carcinoma (RCC) is a common malignant tumor of the urinary system. The etiology of RCC is a complex interaction between environmental and multigenetic factors. Genome-wide association studies have identified new susceptibility risk loci for RCC. We examined associations of genetic variants of genes that are involved in metabolism, DNA repair and oncogenes with renal cancer risk. A total of 14 single nucleotide polymorphisms (SNPs) in 11 genes (*VEGF, VHL, ATM, FAF1, LRRIQ4, RHOBTB2, OBFC1, DPF3, ALDH9A1 and EPAS1*) were examined.

Methods: The current case–control study included 87 RCC patients and 114 controls matched for age, gender and ethnic origin. The 14 tag-SNPs were genotyped by Sequenom MassARRAY® iPLEX using blood genomic DNA.

Results: Genotype CG and allele G of *ATM rs1800057* were significantly associated with RCC susceptibility ($p = 0.043$; OR = 8.47; CI = 1.00–71.76). Meanwhile, we found that genotype AA of *rs67311347* polymorphism could increase the risk of RCC ($p = 0.03$; OR = 2.95; IC = 1.10–7.89). While, genotype TT and T allele of *ALDH9A1 rs3845536* were observed to approach significance for a protective role against RCC ($p = 0.007$; OR = 0.26; CI = 0.09–0.70).

Conclusion: Our results indicate that *ATM rs1800057* may have an effect on the risk of RCC, and suggest that *ALDH9A1* was a protective factor against RCC in Algerian population.

Keywords: Renal cell carcinoma, Polymorphism, Sequenom MassARRAY® iPLEX, *ATM*, *ALDH9A1*

1 Background

Kidney cancer is predicted to be the 15th most common cancer worldwide, with approximately 403,000 new cases and 175,000 deaths from the disease in 2018 [1]. Renal cell carcinoma (RCC) is the predominant form of kidney malignancy, although there has been an increased incidence of RCC globally, with higher incidences and mortality rates reported in men and Caucasian populations. Several occupational and lifestyle factors may affect the risk of RCC such as smoking, obesity, hypertension and socioeconomic status. Furthermore, knowing well the related factors can contribute to make successful prevention possible for a disease [2, 3]. With the aim of prevention, we should take into account the fact that RCC consists of different types with specific genetic molecular characteristics, although most RCCs are sporadic and 2–4% have a hereditary cause. Several genetic diseases are associated with RCC, including *VHL* syndrome, hereditary papillary renal carcinoma (*HPRCC*), hereditary leiomyomatosis RCC, Birt–Hogg–Dube (*BHD*) syndrome, chromosome 3 translocation, and tuberous sclerosis (*TCS1*, *TCS2*) [4]. The most common type of RCC, clear cell renal cell carcinoma (ccRCC), is closely associated with *VHL* gene mutations that lead to stabilization of hypoxia inducible factors (*HIF-1a* and *HIF-2a*, also known as *HIF1A* and *EPAS1*) in both sporadic and familial forms [5]. An overaccumulation of

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HIFs increased transcription of their downstream genes, considered to be important in cancer, including vascular endothelial growth factor (*VEGF*) [6]. The *VHL/HIF/VEGF* is a functional pathway that plays a major role in the development and progression of RCC. Therefore, in the present study, we investigate the association of three functional SNPs (–2578C/A [rs699947], –460T/C [rs833061] and +405C/G [rs2010963]) in *VEGF* gene, and two SNPs (rs1642742 and rs779805) in the *VHL* gene with RCC risk. Furthermore, other new loci may also be involved in genetic predisposition to RCC.

Recently, several genome-wide association studies (GWAS) were conducted in the aim to identify additional new risk loci for RCC. Here, we investigate nine risk loci identified by previous GWAS [7–9] to be related with RCC risk, within European population, at chromosome bands 1p32.3, 3p22.1, 3q26.2, 8p21.3, 10q24.33- q25.1, 14q24.2, 11q22, 1q24.1 and 2p21.

Our study aimed to investigate the role of fourteen genetic polymorphisms (SNPs) in RCC Algerian patients. The selected variants were chosen on the basis of their positive correlation with renal carcinoma (*VEGF, VHL*) or on the basis of their identification as new loci in the latest GWAS studies [7–9]. It should be mentioned that these selected SNPs were considered for the first time in our study in Algerian RCC cases.

2 Methods

2.1 Study population

This case–control study included 87 patients diagnosed with RCC at the Uro-Nephrology Hospital "The Department of Urology and Renal Transplantation", Constantine, Algeria, between 2015 and 2017. All patients had undergone radical or partial nephrectomy, with histopathologically confirmed RCC. Patients were excluded from our study if they had a prior history of other tumors. Before recruitment, a standard questionnaire was administered through face-to-face interviews to collect demographic and clinico-pathological characteristics data of patients.

The control group included 114 healthy volunteers (48 women and 66 men) who were free of any chronic diseases and having no history of any cancer. All patients and controls were from North of Algeria and all of them signed informed consent to participate in this study, which was approved by the ethics committee of our hospital.

2.2 Blood samples and genotyping

Genomic DNA was extracted from the peripheral blood leukocytes using standard NaCl method according to the protocol suggested by Miller and co-workers [10]. DNA quality and concentration were evaluated by Nanodrop spectrophotometer. The selected 14 tag-SNPs were genotyped using the Sequenom MassARRAY® iPLEX Platform from Agena Bioscience. The iPLEX workflow begins by using Assay Design Suite (ADS) software to design polymerase chain reaction (PCR) and iPLEX extension primers for each SNP, which are available upon request. SNP amplification assays were performed according to the manufacturer's instructions. Briefly, 2 µl of sample DNA was placed in 3 µl of reaction solution containing: 0.4 µl of 25 mM MgCl2, 0.1 µl of 25 mM dNTP, 0.5 µl of 10 × buffer, 1 µl of primer mix and 0.4 µl of 5 U Platinum *Taq* DNA polymerase in 0.8 µl of nuclease-free water. The PCR cycling conditions were: 95 °C for 2 min and 45 cycles of 95 °C for 30 s, 56 °C for 30 s and 72 °C for 1 min. The PCR product was purified using the shrimp alkaline phosphatase (SAP) method, which included 0.17 µl of 10 × SAP buffer, 1.7 µl SAP enzyme, 1.53 µl ddH2O and 5 µl PCR product, beginning at 37 °C for 40 min and then 85 °C for 5 min. The iPLEX extension reaction was carried out in a 9-µl volume containing 2 µl of reaction Mix (MassARRAY®), 7 µl PCR products and performed in 40 cycles of 95, 52 and 80 °C for 5 s, respectively. The iPLEX reaction products were also cleaned up using the Resin method (clean resin) and transferred from 384-well microtiter plate on 384-sample SpectroCHIP® using Nanodispenser. The genotype of each sample was attributed by MALDI-TOF mass spectrometry using sequenom supplies software (SpectroTyper 4.0) that automatically translates the mass of the observed primers into a genotype for each reaction. About 10% of the samples were randomly selected for repeated assays, and the results were all concordant.

2.3 Statistical analysis

The genotype distributions of all these SNPs were in Hardy–Weinberg equilibrium using Pearson Chi-square test. χ^2 test was used to compare genotype frequencies between cases and controls, and to evaluate the relationships of SNPs genotypes with histologic type of our patients. Odds ratios (ORs) and p values were also calculated. $p < 0.05$ was considered statistically significant. All analysis were done using R software version (3.5.2).

3 Results

3.1 Subjects characteristics

The demographic and clinical characteristics of the study subjects are shown in Table 1. A total of 201 participants were included, 87 patients with RCC and 114 age-and gender matched healthy controls. The mean ages of the cases and controls were 56.27 ± 13.91 (range, 25–88 years old) years and 51.71 ± 13.64 (range, 23–84 years old) years, respectively. Of the 87 RCC patients, 30 (34.5%) had pT3 stage of RCC, 39 (44.8%) had grade II of RCC,

Table 1 Demographic and clinical characteristics of RCC cancer cases and controls

Characteristics	Cases	Controls
Age (mean ± SD), yr	56.27 ± 13.91	51.71 ± 13.64
Gender (%)		
Male	51 (58.6)	66 (58)
Female	36 (41.4)	48(42)
Tumor size (%)		
> 7	47(54.0)	
≤ 7	35 (40.2)	
Unknown	5 (5.7)	
Tumor stage (%)		
pT1	28 (32.2)	
pT2	21 (24.1)	
pT3	30 (34.5)	
PT4	5 (5.7)	
Unknown	3 (3.4)	
Tumor grade (%)		
I	1 (1.1)	
II	39 (44.8)	
III	28 (32.2)	
IV	13 (14.9)	
Unknown	6 (6.9)	
Location (%)		
Left	47 (54)	
Right	40 (46)	
Histopathology (%)		
Clear-cell carcinoma	54 (62.1)	
Chromophobe cell carcinoma	14 (16.1)	
Papillary renal cell carcinoma	12 (13.7)	
Bellini-duct carcinoma	2 (2.3)	
Renal mucinous tubular carcinoma	2 (2.3)	
Primary renal lymphoma (PRL)	2 (2.3)	
Renal neuroendocrine tumor (NET)	1 (1.15)	

Table 2 Genotypic and allelic frequencies of 14 tag-SNPs in the RCC cases and controls

	P1[a]	OR (95% CI)[a]	P2[a]	HWE
VEGF				
rs2010963	0.775	1.16 (0.77–1.73)	0.47	0.51
rs699947	0.416	1.31 (0.87–1.95)	0.21	0.91
rs833061	0.475	1.27 (0.85–1.89)	0.26	0.96
VHL				
rs1642742	0.663	0.88 (0.59–1.31)	0.61	0.82
rs779805	0.691	0.88 (0.59–1.32)	0.61	0.88
FAF1				
rs4381241	0.417	1.27 (0.85–1.89)	0.26	0.40
rs67311347	0.086	1.49 (0.99–2.25)	0.05	0.20
LRRIQ4				
rs10936602	0.248	0.69 (0.39–1.20)	0.21	0.70
RHOBTB2				
rs2241261	0.604	0.89 (0.60–1.33)	0.61	0.91
OBFC1				
rs11813268	0.869	0.89 (0.59–1.34)	0.60	0.07
ATM				
rs1800057	0.034	10.93 (1.35–88.31)	0.01	0.53
DPF3				
rs49030664	0.979	1.04 (0.69–1.55)	0.91	0.93
ALDH9A1				
rs3845536	0.015	0.62 (0.41–0.93)	0.02	0.76
EPAS1				
rs7579899	0.977	1.02 (0.69–1.52)	0.91	0.64

[a] χ^2 test or Fisher's exact test. P1: Genotypic frequencies *p* value. P2: Allelic frequencies p value. OR: Odds Ratio. CI: Confidence Interval

and approximately 47 (54%) have larger tumors (> 7 cm). The majority of patients 54 (62.1%) had the conventional clear-cell carcinoma. Fourteen patients (16.1%) had chromophobe carcinoma. Twelve patients (13.7%) had papillary carcinoma and other rare subtypes of RCC were also found including Bellini–duct carcinoma, mucinous tubular carcinoma, primary renal lymphoma (PRL) accounted for (2.3%), respectively, and renal neuroendocrine tumor (NET) for (1.15%) of all the carcinoma.

3.2 Genotypic and allelic frequencies of selected 14 tag-SNPs in the RCC cases and controls

Table 2 shows the genotypic and allelic distributions of the 14 tested polymorphisms in cases and controls with estimated ORs. The selected 14 tag-SNPs were all conformed to Hardy–Weinberg equilibrium. Similar frequencies in the distribution of *rs1642742A/G* and *rs779805A/G* polymorphisms of *VHL* were found between healthy controls and RCC patients ($p = 0.66$ and $p = 0.69$, respectively) for genotypic frequencies, and ($p = 0.61$ and $p = 0.61$, respectively) for allelic frequencies. No significant differences in genotypic and allelic frequencies of VEGF polymorphisms were also observed between RCC patients and controls ($p = 0.771$, 0.416, and 0.475 for *+405C/G*, *−2578C/A* and *−460T/C*, respectively).

Regarding the polymorphisms (*rs1800057C/G, rs4381241T/C, rs10396602T/C, 2241261C/T, 11813268C/T, 49030664T/C, 3845536C/T, rs7579899A/G and rs67311347G/A)* in *ATM, FAF1, LRRIQ4, RHOBTB2, OBFC1, DPF3, ALDH9A1* and *EPAS1* genes, respectively, an association with RCC was found in *ATM rs1800057and ALDH9A1 rs3845536* polymorphisms ($p = 0.034$ and $p = 0.015$ for genotypic frequencies, respectively).

As shown in Table 3, the patients with CG genotype of *ATM P1054R* variant, had significantly higher risk

Table 3 Association between SNPs *rs67311347*, *ATM rs1800057* and *ALDH9A1 rs3845536* and risk of RCC

Polymorphisms	Cases *n* %	Controls *n* %	*P*[a]	OR (95% CI)[a]	*P*[a]
rs67311347					
GG (ref)	29 (33.33%)	49 (42.98%)			
GA	44 (50.57%)	57 (50.00%)	0.08	1.30 (0.71–2.38)	0.44
AA	14 (16.09%)	8 (7.02%)		2.95 (1.10–7.89)	0.03
G allele (ref)	102 (58.62%)	155 (67.98%)			
A allele	72 (41.38%)	73 (32.02%)		1.49 (0.99–2.25)	0.05
ATM rs1800057					
CC (ref)	80 (91.95%)	113 (99.00%)			
CG	6 (6.90%)	1 (0.88%)	0.03	8.47 (1.00–71.76)	0.04
GG	1 (1.15%)	0 (0.00%)		Inf (Inf–Inf)	0.41
C allele (ref)	166 (95.40%)	227 (100.00%)			
G allele	8 (4.60%)	1 (0.44%)		10.93 (1.35–88.31)	0.01
ALDH9A1 rs3845536					
CC (ref)	35 (40.23%)	36 (32.43%)			
CT	46 (52.87%)	51 (45.95%)	0.01	0.92 (0.50–1.71)	0.87
TT	6 (6.90%)	24 (21.62%)		0.25 (0.09–0.70	0.007
C allele	116 (66.67%)	123 (55.41%)			
T allele	58 (33.33%)	99 (44.59%)		0.62 (0.41–0.93)	0.02

[a] χ^2 test or Fisher's exact test. OR: Odds Ratio. CI: Confidence Interval

of developing RCC than patients with *ATM* CC genotype (CG Vs. AA OR = 8.47; CI = 1.00–71.76; $p = 0.043$). Only one mutated GG genotypes among cases have been observed in our study (1.15%). Moreover, the difference of G allele frequency was statistically significant in the two groups (OR = 10.93; IC = 1.35–88.31; $p = 0.012$).

Genotypic distributions of *rs67311347* polymorphism had no obvious discrepancies between cases and controls ($p > 0.05$), while mutated genotype AA frequency showed statistically significant difference between case and control groups (OR = 2.95; IC = 1.10–7.89; $p = 0.03$).

Interestingly, in our population, the TT variant of the rs3845536 *ALDH9A1* polymorphism was observed to approach significance for a protective role against RCC (OR = 0.26; IC = 0.09–0.70; $p = 0.007$). Likewise, the *ALDH9A1* T allele was also observed to be significantly reduced in RCC (and OR = 0.62; IC = 0.41–0.94; $p = 0.02$).

Also, ATM rs1800054 and ALDH9A1 rs3845536 polymorphisms did not provide evidence of an association with RCC histologic subtype (clear cell, other) ($p = 1$ and $p = 0.18$ for genotypic frequencies, respectively) (Table 4).

Table 4 Association of the ATM rs1800057 and ALDH9A1 rs3845536 genotypes with RCC histologic type

Genotype	Histopathology		OR (95%CI)	*P*[a]
ATM rs1800057	Clear cell (*n*)	Other (*n*)		
CC (ref)	50	30		
CG	3	3	1.65 (0.2–13.2)	0.67
CG + GG	4	3	1.25 (0.17–7.9)	1
C allele (ref)	103	63		
G allele	5	3	0.98 (0.14–5.24)	1
ALDH9A1 rs3845536				
CC (ref)	25	10		
CT	26	20	1.9 (0.69–5.53)	0.24
TT	3	3	2.44 (0.28–21.50)	0.36
CT + TT	29	23	1.97 (0.73–5.57)	0.18
C allele	76	40		
T allele	32	26	1.54 (0.77–3.1)	0.19

[a] χ^2 test or Fisher's exact test. OR: Odds Ratio. CI: Confidence Interval. [b]Due to the small number of homozygous variant alleles, the combined results for the heterozygous and homozygous variant alleles are shown

4 Discussion

In the present study, we evaluated the association between 14 SNPs including *VEGF* (-2578C/A [rs699947], -460T/C [rs833061] and +405C/G [rs2010963]), *VHL* (rs1642742 and rs779805), *FAF1* (rs4381241), *LRRIQ4* (rs10936602), *RHOBTB2* (rs2241261), *OBFC1* (rs11813268), ATM (rs1800057), DPF3 (rs49030664), ALDH9A1 (rs3845536), EPAS1 (rs7579899) and rs67311347 and the risk of RCC. Only *ATM* (rs1800057) was found to be significantly correlated to RCC risk. Interestingly, the rs3845536 *ALDH9A1* polymorphism shows a protective effect. To the best of our knowledge,

the present study is the first that investigated the association of these polymorphisms and RCC risk in Algerian population.

In clear-cell renal carcinoma, the *VHL* tumor suppressor gene is frequently inactivated leading to *VEGF* overexpression [1]. −2578C/A, +460T/C, +405C/G polymorphisms were among the most common of all the SNPs of *VEGF* gene investigated. The previously published data have reported that these polymorphisms might be risk factors for RCC especially in Asian population [11, 12] (Table 5), although our results showed that no significant associations were found between the *VHL* and *VEGF* functional polymorphisms and RCC susceptibility. Similarly to our results Sáenz-López and al [13] reported that −2578C/A, −460T/C, −405C/G, −936C/T *VEGF* polymorphisms do not appear to exert a significant effect on RCC risk in Spanish population. Regarding *VHL* gene polymorphisms (rs1642742 and rs779805), numerous studies have examined the association with development and/or prognosis of RCC but with inconclusive results [14, 15] (Table 5). It has reported that the existence of G allele at both rs1642742 and rs779805 may play an important role in tumorigenesis of RCC through methylation of CpG island to suppress gene expression [15]. These discrepancies might depend on ethnicity or the different carcinoma types. Therefore, the *VEGF* gene polymorphisms may possibly be associated with overproduction of this cytokine that might influence tumor progression in RCC. Moreover, many studies indicated that −2578C/A, −460T/C, −405C/G polymorphisms may have an effect on progression and behavior of this cancer [16–18].

Recently, several genome-wide association studies have been interested on renal cell carcinoma, in the aim

Table 5 List of recent studies and meta-analysis regarding the 14 tag-SNPs investigated

Cene	1st Author, Year	Population	Case/Control	SNP	*P* value
VEGF					
Meta-analyses (8 studies)	Gong M, 2016	Asian/Caucasian	1.397/2.094	*rs699947*	*
			262/477	*rs2010963*	NA
			677/1.299	*rs833061*	NA
Meta-analyses (14 studies)	Tang J, 2017	Asian/Caucasian	1588/2470	*rs699947*	*
			1086/1460	*rs2010963*	*
			677/1299	*rs833061*	NA
Meta-analyses (9 studies)	Hou Q, 2017	Asian/Caucasian	1588/2470	*rs699947*	*
			2315/3552	*rs2010963*	*
VHL					
	Qin C, 2011	China	620/632	*rs779805*	NA (0.96)
	Wang W, 2014	China	19/616	*rs779805*	*
				rs1642742	*
	Lv C, 2015	China	81/80	*rs779805*	* (0.01)
EPAS1					
GWAS	Purdue MP, 2011	European	2278/3719	*rs7579899*	* (2.3×10^{-9})
	Cao Q, 2011	China	710/760		NA (0.46)
	Su T, 2013	China	400/806		NA (0.43)
	Purdue MP, 2014	African Americans	255/375		NA (0.86)
	Melkonian SC, 2014	Texas	659/699		* (0.02)
ALDH9A1					
GWAS	Henrion MYR, 2015	Western-European	2.215/8.566	*rs3845536*	* (2.30×10^{-8})
ATM					
GWAS	Scelo G, 2017	European	10.784/20.406	*rs1800057*	* (9.0×10^{-9})
FAF1	/			*rs4381241*	* (3.1×10^{-10})
LRRIQ4	/			*rs10936602*	* (8.8×10^{-9})
RHOBTB2	/			*rs2241261*	* (5.8×10^{-9})
OBFC1	/			*rs11813268*	* (3.9×10^{-8})
DPF3	/			*rs49030664*	* (2.2×10^{-24})
–	/			*rs67311347*	* (2.5×10^{-8})

*Significant association between SNP and RCC, NS: not significant

to indentify additional RCC common risk loci and new prognostic biomarker for this cancer. We therefore investigated some of these loci and detected that *ATM P1054R* variant is likely to directly affect the risk of malignancy. Our data indicate that homozygous carries of the P1054R variant and heterozygous present a significant association with RCC compared with carriers of homozygous wild-type genotype, SNPs in *ATM* predicted to be deleterious. The *ATM* missense substitution *P1054R* can be a genuine *ATM* mutation seems the rarity of this polymorphism (MAF = 0.02) [19], and because it causes a significant amino acid change in a conserved part of the protein (nonpolar to polar), and it was demonstrated that the presence of such variant may have a functional consequences on an in vitro cellular phenotype [20]. Heterozygous for *P1054R* has been reported to be associated with decreased *ATM* expression in CLL [19], also increased prostate cancer risk [21]. Furthermore, recent studies are reported the implication of *ATM* mutations and variants in several other cancers likely oral [22], lung [23] and breast cancer [24]. To the best of our knowledge, there have been no published reports on *ATM* gene variants and RCC risk. So further understanding of the function of the ATM protein and it's implication in carcinogenesis may explain the known genetic susceptibility to this disease. *ATM* plays a critical role in maintenance of genomic integrity. Is activated primarily in response to double-strand breaks, leads to *ATM*-dependent phosphorylation of variety of proteins including P53, BRCA1, c-Abl and CHEK2 involved in checkpoint function, transcription activation and DNA repair [25]. Thus, gene–gene interaction of the *ATM* gene with *CHEK2* was reported to predispose to chronic lymphocytic leukemia (CLL) [26], and breast cancer [27]. Knowing that, *CHEK2* has been also associated with increased risk of colon, prostate and kidney cancer [28]. The major cytotoxic lesion induced DNA damage caused by ionizing radiation. Furthermore, it has been reported that *ATM* genetic polymorphisms interacted with radiation exposure, resulting an effect in carcinogenesis [29, 30]. Indeed, the linked heterozygous *F858L* and *P1054R* variants are documented to confer an increased radiosensitivity in cell lines from breast cancer [20]. Knowing well, that obviously the radiotherapy is not the treatment adopted for renal cancer. We can suggest that this variant may increase the risk of RCC independently of radiotherapy treatment, highlighting that this SNP may have a role in modifying the *ATM* gene function and consequently altering DNA repair mechanisms.

The mutated genotype AA of *rs67311347* polymorphism, appear to exert a significant effect on RCC risk in our population. This SNP has previously been definitively associated with RCC in a large GWAS [7]. The risk associated allele of *rs67311347* was associated with a higher expression of *ZNF620*. This gene encodes the Zinc finger protein 620, but the function of this protein has not been well described [7].

rs3845536 ALDH9A1 is a new common variant on chromosome 1q24.1 reported in a genome-wide meta-analysis study as a potential risk for renal cancer [8]. The aldehyde dehydrogenase (ALDH) superfamily of enzymes comprises 19 human isozymes involved in detoxification of specific endogenous and exogenous aldehydes substrates [31, 32]. The ability of the ALDH family members to metabolise reactive aldehydes represents a major underlying cytoprotective mechanism, whereas mutations in *ALDH* genes that lead to a defective aldehyde metabolism are the molecular basis for several diseases, and may contribute to the etiology of cancer [32]. *ALDH9A1* encodes γ-trimethylaminobutyraldehyde dehydrogenase that participates in the metabolism of γ-aminobutyraldehyde and aminoaldehydes derived from polyamines, with high levels expression are observed in kidney [8, 33]. Interestingly, in our study rs3845536 *ALDH9A1* polymorphism was associated with a reduced risk of RCC. This variant is intronic to *ALDH9A1*, and the transition C → T is silent [34]. Although a SNP in intronic region would not influence the protein sequence, it might generate splice variants of transcripts and promote or disrupt binding and function of long noncoding RNAs (lncRNAs) [35]. However, Henrion et al. have reported that variation at 1q24.1 represents a potential risk locus for RCC. But they didn't observe any association between rs3845536 genotype and *ALDH9A1* expression. Also no association was detected for any other cancers [8]. This polymorphism was mentioned only in three publications all of them examined the association of SNPs with RCC [7, 8, 36].

Table 5 shows an overall view of the results of different studies evaluated the association between the 14 test SNPs and RCC.

The present study suggests an eventual association between ATM rs1800057 and ALDH9A1 rs3845536 variants and RCC. These SNPs were first discovered in GWAS in cases of European ancestry [7, 8]. There have been six risk loci identified for renal cell carcinoma, all of which were identified in GWAS in European ancestry population [37]. There is only one GWAS conducted among African Americans population; where, they observed an association of the 11q13.3 variant rs7105934 with reduced RCC risk, consistent with European ancestry GWAS findings; However, the association did not reach genome-wide significant [37, 38]. The identification of disease-associated SNPs by GWAS tends to have low concordance when different populations are compared. This is seen with prostate cancer, which is the most cancer studied by GWAS in diverse populations

[37, 39]. Most large-scale GWAS have been carried out in European populations, but there have been studies investigating common risk variants in other ethnic groups and population-specific differences have been reported [39]. Moreover, genome scan study of prostate cancer in Arabs, demonstrated differences between Tunisians and Arab ancestry living in Qatar and Saudi Arabia by the identification of three genomic regions with multiple prostate cancer susceptibility loci in Tunisians [40]. It was also observed that the established markers do not necessarily replicate among inter-Arabic population groups. For example, Mtiraoui et al. illustrated differences between the North African Arabs (from Tunisia) and Levant Arabs (from Lebanon) by demonstrated differential contributions of T2DM susceptibility loci [41]. Population structure in North Africa is particularly complex, and disease or phenotypic studies should carefully [42, 43]. Within the North African context, the genetic composition of the Algerian population is an amalgam of different ancestral component coming from the middle East, Europe, sub-Saharan Africa and autochthonous to North Africa (Maghrebi) [43]. For this, it's not evident to compare populations of North Africa with only Arab and/or European populations. Additional functional studies are required to have a good investigation specific to the North African population.

Our study has some limitations. First, our sample size may not have enough statistical power to explore the real association and, as such, significant finding should be interpreted cautiously. Data on RCC and rare diseases in Algeria and North Africa remain scarce because of the limited resources in biomedical research. Moreover, the lack of biological sample collection structure has driven researchers to focus much more on the most prevalent diseases. Another limitation association with this investigation is that the increase in family wise error rate across the reported statistical analyses was not controlled. Overall, we consider this research relatively preliminary and encourage replication.

5 Conclusion

Our findings suggest that the *ATM rs1800057* polymorphism may contribute to influence development of renal cancer. Thus, the possible role of the *ATM* gene in cancer predisposition in the general population makes this gene a potential target for screening. Our study suggests also that the *ALDH9A rs3845536* polymorphism was associated with reduced risk of RCC in Algeria. Specifically, TT mutated homozygous is associated with a lower risk of RCC than CC or CT genotype. In silico and subsequent RT-PCR analyses are needed to predict the effect of the *rs3845536 ALDH9A1* variant on the efficiency of splicing. Further genotyping studies are warranted in a larger number of patients and controls.

Abbreviations

RCC: Renal cell carcinoma; SNP: Single nucleotide polymorphism; GWAS: Genome-wide association study; VHL: Von Hippel–Lindau; VEGF: Vascular endothelial growth factor; ATM: Ataxia telangiectasia mutated; ALDH9A1: Aldehyde dehydrogenase 9 family member A1.

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Authors' contributions

FZB gave idea protocol/project development, data collection or management, data analysis, and manuscript writing/editing. DR helped in protocol/project development, manuscript writing/editing and final correction of the manuscript; MAG and NC helped in data analysis; NA helped in protocol/project development; AD was thesis advisor; D.S helped in protocol/project development and final correction of the manuscript. Allauthors read and approved the final manuscript.

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Availability of data and materials

The data sets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The ethics committee of the Dr BENBADIS – Constantine University Hospital Centre has approved the study. The use of human blood sample and the protocol in this study strictly conformed to the principles expressed in the Declaration of Helsinki. We work in accordance with the Declaration of Helsinki (1964): Ethical principles applicable to medical research on human subjects and in accordance with the recommendations of the Algerian national council for ethics in health sciences. Informed consent (written) was obtained from all participants.

Consent for publication

All patients included in this research gave written informed consent to publish the data contained within this study.

Competing of interests

The authors declare that they have no competing interests.

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