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Association of Variants in IL6-Related Genes with Lung Cancer Risk in Moroccan Population

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Abstract

Purpose Lung cancer is known to be a complex multifactorial disease, involving both genetic and environmental factors. The study of the different signaling pathways and the identification of the genes involved, will contribute to further understanding the pathogenesis of the disease, thus allowing the development of appropriate targeted treatments. Recently, the link between cancer and inflammation has become more evident and inflammation has been proposed as the seventh hallmark of cancer. Previous studies have suggested that key cytokines involved in inflammation may have an important role in the etiology of lung cancer. The aim of this study was to investigate whether common variants in inflammation-related genes: IL-6, IL6-R, and IL6-ST, influence lung cancer risk in Moroccan population.

Materials and Methods Single nucleotide polymorphisms (SNPs) in IL-6, IL6-R, and IL6-ST genes were assessed in 120 controls and 120 patients with confirmed lung cancer diagnosis. Genotyping analysis was performed with the TaqMan® allelic discrimination technology. The results were analyzed using SPSS 24.0 software.

Results Among the studied SNPs, we found a significant association for the IL-6 (rs2069840) (OR = 1.63; 95% confidence interval 1.08–2.47; $p = 0.01$). No significant association was observed for the remaining SNPs of IL-6R (rs2228145) and IL-6ST (rs2228044) genes.

Conclusion Our results suggest the IL-6 (rs2069840) polymorphism may influence the occurrence of lung cancer in Moroccan patients.

Keywords Lung cancer · Inflammation · Cytokines · Polymorphisms · Risk · Moroccan population

Abbreviations

IL-6	Interleukin 6
IL-6R	IL6 receptor
IL-6ST	IL6 receptor subunit
IL-11	Interleukin 11
LIF	Leukaemia inhibitory factor
OSM	Oncostatin M
CNTF	Ciliary neurotrophic factor
CT-1	Cardiotrophin-1
CLC	Cardiotrophin-like cytokine
SNPs	Single nucleotide polymorphisms
ADK	Adenocarcinoma
SCC	Squamous cell carcinoma
SCLC	Small cell lung cancer

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Introduction

According to the recent statistics, lung cancer still constitutes the leading cause of cancer mortality worldwide, with 1.8 million deaths, representing 18.4% of the total cancer deaths. In Morocco, the incidence rates remain generally

high (31.9 per 100,000) comparing to others countries in Africa [1].

Lung cancer represents a multifactorial disease, resulting of complex interactions between environmental, genetic, and other factors [2, 3]. The study of different signaling pathways and identification of the genes involved, will contribute to further understand the pathogenesis of the disease, thus allowing the development of appropriate targeted treatments and prevention strategies.

Interleukin 6 (IL-6) is a member of the IL-6 type cytokines family, comprising also IL-11, LIF (leukaemia inhibitory factor), OSM (oncostatin M), CNTF (ciliary neurotrophic factor), CT-1 (cardiotrophin-1), and CLC (cardiotrophin-like cytokine). Having both the pro- and anti-inflammatory properties, IL-6 plays a major role in hematopoiesis process including immune responses, inflammation, bone metabolism, as well as in acute-phase and immune responses of the organism [4, 5].

Signal transduction of IL-6 is mediated by the interaction with two important elements: membrane-bound IL-6-receptor (IL-6R) and the ubiquitously expressed transmembrane receptor subunit IL6 signal transducer (IL-6ST), also known as glycoprotein 130. For cells not expressing membrane-bound IL-6R, signal transduction is mediated by formation of complexes between IL-6 and soluble IL-6Rs, and subsequent binding of the complexes to membrane-bound IL-6ST [6].

IL-6 plays critical roles in the activation of several important signaling pathways, including the JAK-STAT [7], the Ras-MAP kinase (MAPK), and the Phosphatidylinositol 3-kinase-AKTmammalian target of rapamycin (PI3K-AKT-mTOR) pathways. All those signaling pathways regulate a variety of important biological processes, such as proliferation, apoptosis, survival, and invasion that are crucial in tumorgenesis [8, 9].

Several case–control studies have been conducted to determine the association between IL-6 polymorphisms and lung cancer risk, and several single nucleotide polymorphisms in the IL-6 gene have been described in association with its transcriptional regulation in several populations [10–13].

The aim of this study was to investigate if common variants in IL6-related genes; IL-6 (rs2069840), IL-6R (rs2228145), and IL6ST (rs2228044) influence lung cancer risk in Moroccan patients.

Material and Methods

Study Population

One hundred twenty patients diagnosed with lung cancer at the Mohammed VI Center for Cancer Treatment, CHU Ibn Rochd (Casablanca, Morocco) were recruited between 2017 and 2018. Samples from 120 blood donors were used as ethnically matched controls.

SNP Genotyping Analysis

Genomic DNA was isolated from peripheral blood samples using Phenol/Chloroform standard procedure. SNPs in the genes encoding interleukin 6 (IL6), its receptors (IL6R), and receptor subunit (IL6ST) were analyzed: IL-6 rs2069840, IL-6R rs2228145, and IL6ST rs2228044. All the SNPs were genotyped using TaqMan allelic discrimination assay on a 7500 Fast Real time PCR system (Applied Biosystems—Thermo Fisher Scientific). Information about the SNPs analyzed in our study is represented in Table 1.

Statistical Analysis

All statistical calculations were performed using SPSS 24.0 for Windows software. Continuous variables were represented as arithmetic means and standard deviations, whereas group categories were expressed as percentages. The genotypes and alleles frequencies' distribution was compared between patients and controls using the χ^2 test or Fisher's test. ORs with a CI of 95% were calculated to measure the strength of association. A p value < 0.05 was considered statistically significant. The Hardy–Weinberg equilibrium (HWE) was tested for all SNPs using χ^2 test.

Table 1 Information about the SNPs analyzed in our study

SNPs ID	Gene	Chromosome	MAF	Allele	Position
rs2069840	IL6	chr7:22728953	G = 0.2706/33980 (TOPMED)	C/G	6807C > G
rs2228145	IL6 R	chr1:154454494	C = 0.33024 (41467/125568, TOPMED)	A/C	Intron, Asp358Ala 1073A > C
rs2228044	IL6ST (GP130)	chr5:55968325	G = 0.21240 (26671/125568, TOPMED)	C/G	755C > G Gly148Arg

SNPs single nucleotide polymorphisms, *chr* chromosome, *MAF* minor allele frequency

Results

Clinical Characteristics of the Study Population

This study included a total of 120 lung cancer cases and 120 healthy controls. All participants were genotyped for the IL-6 rs2069840, IL-6R rs2228145, and IL6-ST rs2228044 gene polymorphisms. The mean age (±SD) of patients was 60.76 ± 8.55 years, ranging between 36–81 years of age. According to gender distribution, the majority of our patients were males (92.5%) compared to (7.5%) of females. The most histological type observed was adenocarcinoma (64.2%) and 20.2% of patients had squamous cell carcinoma. Furthermore, our cohort consisted of 93.3% smokers and 6.7% non-smokers. The main clinicopathological characteristics and environmental factors of our study population are given in Table 2.

With regard to genotype frequencies, the homozygous mutant genotype GG was frequent among lung cancer patients compared to controls (OR = 6.02; 95% confidence interval 1.94–18; $p = 0.0018$). Analysis for the IL6 rs2069840 polymorphism indicated that the distribution of mutant allele G was significantly different between patients and controls groups with a higher frequency in lung cancer cases compared to healthy subjects (OR = 6.73; 95% confidence interval 1.94–18; $p = 0.01$). In addition, patients carrying at least one copy of C allele (recessive model) were 6.73 times more likely to develop lung cancer than healthy subjects (OR = 1.72; 95% CI 2.2–20.35; $p = 0.0007$). The minor IL6 rs2069840 G allele conferred an increased lung cancer risk than the major C allele in our population (Table 3).

Table 2 Clinicopathological characteristics of the study population

Clinicopathological characteristics	All patient ($N = 120$), *n*, %
Age	
Mean (±SD)	60.76 ± 8.55
Average	36–81
Gender	
Men	111 (92.5%)
Women	9 (7.5%)
Smoking status	
Smokers	112 (93, 3%)
Non-smokers	8 (6, 7%)
Cannabis intoxication	
Yes	16 (13, 3%)
No	104 (86, 7%)
Alcohol	
Yes	11 (9, 2%)
No	109 (90, 8%)
Hystological type	
NSCLC	111 (92.5%)
Adenocarcinoma	81 (67, 5%)
Squamous cell carcinoma	24 (20, 0%)
Other subtype	6 (5.0%)
SCLC	9 (7, 5%)

NSCLC non-small cell lung cancer, *SCLC* small cell lung cancer

IL-6R rs2228145, IL6ST rs2228044 Polymorphisms

The IL6R (rs2228145) and IL-6ST (GP130) (rs2228044) polymorphisms were not associated with lung cancer risk in our population. The distribution of alleles and genotypes of, IL6R rs2228145 and IL6ST (GP130) rs2228044 in patients and controls groups is shown in Table 3.

Genotypic and Allelic Distribution According to the Clinical Characteristics

In this study, we considered potential gene–environment interactions. We evaluated the possible effect of IL-6 rs2069840, IL-6R rs2228145, and IL6-ST rs2228044 SNPs genotypes on Lung cancer risk. Results were sorted by age, gender, histological type, and smoking status. We found a significant effect of IL6-ST rs2228044 SNP genotype on lung cancer risk when adjusting by histological type. However, the obtained results showed no statistically significant difference for IL-6 rs2069840 and IL6 ST rs 2228044 SNPs genotypes (Table 4).

Discussion

It is well known that inflammatory responses play a major and crucial role in carcinogenesis [14]. Previous studies have proved that at least 20% of all cancers are associated with persistent infections and chronic inflammation, and for those cancers that do not develop as a consequence of chronic inflammation, they present extensive inflammatory infiltrates, referred to as 'tumor-elicited inflammation', accompanied with high cytokine expression in the tumor microenvironment [15, 16]. Several cytokines were found to serve as growth and survival factors playing crucial roles on premalignant cells, they stimulate angiogenesis, tumor progression, and metastasis, and also maintain tumor-promoting inflammation [17, 18].

In inflammation, the IL-6 is mainly involved in controlling important process of target cells as differentiation, proliferation, migration, and apoptosis [19, 20]. This pleiotropic cytokine has also implication in several others biological functions as in metabolism [21, 22], neural function [23, 24], and embryonic development processes. Thus, any

Table 3 The distribution of genotypes and allele frequencies for the IL-6 rs2069840, IL-6R rs2228145, and IL6 ST rs2228044 gene polymorphisms

Gene SNPs	Genotypes/models	Cases (%)	Controls (%)	OR (95% CI)	*p* Value
IL6 rs2069840	CC	51.0%	60.8%	1	
	CG	28.4%	29.2%	1.16 (0.63–2.13)	0.6
	GG	20.6%	10%	2.45 (1.11–5.43)	0.02*
	Recessive model				
	CC + CG	79.4%	90%	1	
	GG	20.6%	10%	2.33 (1.08–5.01)	0.03*
	Dominant model				
	CC	51.0%	60.8%	1	
	CG + GG	49.0%	39.2%	1.49 (0.87–2.54)	0.1
	Allele				
	C	65.2%	88.8%	1	
	G	34.8%	11.2%	1.63 (1.08–2.47)	0.01*
χ^2 (HWE)		14.23	3.42		
p value (HWE)		< 0.05	0.064		
IL6ST rs2228044	Genotypes				
	CC	3.1%	3.1%	1	
	GC	37.5%	40.6%	0.9 (0.12–7.077)	0.9
	GG	59.4%	56.3%	1.05 (0.14–7.89)	0.9
	Recessive model				
	CC + GC	40.6%	43.7%	1	
	GG	59.4%	56.3%	1.13 (0.56–2.29)	0.7
	Dominant model				
	CC	3.1%	3.1%	1	
	GG + GC	96.9%	96.9%	1 (0.13–7.32)	1
	Allele				
	C	21.88%	23.44%	1	
	G	78.12%	76.56%	1.09 (0.60–1.96)	0.76
χ^2 (HWE)		0.60	1.11		
A *p* value (HWE)		0.44	0.3		
IL6R rs2228145	Genotypes				
	AA	47.9%	41.1%	1	
	AC	39.7%	43.8%	0.77 (0.38–1.56)	0.47
	CC	12.3%	15.1%	0.70 (0.25–1.91)	0.48
	Recessive model				
	AA + AC	87.7%	84.9%	1	
	CC	12.3%	15.1%	1.2 (0.48–3.25)	0.63
	Dominant model				
	AA	44.9%	41.1%	1	
	AC + CC	52.1%	58.9%	0.75 (0.39–1.45)	0.4
	Allele				
	A	67.8%	63.01	1	
	C	32.2%	36.98%	0.80 (0.49–1.31)	0.38
χ^2 (HWE)		0.6	0.26		
A *p* value (HWE)		0.44	0.61		

Genotype and alleles distribution of IL-6, IL-6R, and IL-6ST polymorphisms are represented as percent

IL-6 Interleukin 6, SNPs single nucleotide polymorphisms, OR Odds ratio, CI confidence interva, HWE Hardy–Weinberg equilibrium

*p value < 0.05 significant

Table 4 Clinicopathological relevance of IL6 (rs2069840), IL-6R (rs2228145), and IL-6ST (rs2228044) polymorphisms in non-small lung cancer

Clinicopathological parameters	Genotype IL6 (rs2069840)			*p* value	Genotype IL6R (rs2228145)			*p* value	Genotype IL6st (rs2228044)			*p* value
	CC	CG	GG		AA	AC	CC		CC	GC	GG	
Age				0.99				0.77				0.60
< 50	50.0%	30.0%	20.0%		33.3%	50.0%	16.7%		0.0%	20.0%	80.0%	
> 50	51.1%	28.3%	20.7%		48.5%	39.7%	11.8%		3.4%	39.%	57.6%	
Gender				0.90				0.16				0.12
Male	50.5%	28.4%	21.1%		50.7%	37.3%	11.9%		3.4%	33.9%	62.7%	
Female	57.1%	28.6%	14.3%		14.3%	71.4%	14.3%		0.0%	80.0%	20.0%	
Hystological type				0.62				0.80				0.003**
Adk	55.4%	26.2%	18.5%		50.0%	36.0%	14.0%		0.0%	37.8%	62.2%	
Scc	45.5%	31.8%	22.7%		33.3%	53.3%	13.3%		0.0%	38.5%	61.5%	
Sclc	22.2%	44.4%	33.3%		50.0%	50.0%	0.0%		33.3%	33.3%	33.3%	
Other	66.7%	16.7%	16.7%		60.0%	40.0%	0.0%		33.3%	33.3%	33.3%	
Smoking status				0.10				0.67				0.12
Smokers	51.0%	30.2%	18.8%		94.1%	96.6%	88.9%		3.4%	33.9%	62.7%	
Non-smokers	50.0%	0.0%	50.0%		5.9%	3.4%	11.1%		0.0%	80.0%	20.0%	

Genotype distribution of IL6 (rs2069840), IL-6R (rs2228145), and IL-6ST (rs2228044) according to clinicopathological parameters polymorphisms is represented as percent

ADK adenocarcinoma, *SCC* squamous cell carcinoma, *SCLC* small cell lung cancer

*p value < 0.05 significant

dysfunction of the complex regulatory of this cytokine network might lead to crucial disorders.

Several variants in IL6 gene have been investigated for their association with a pathogenesis of several type of cancer, especially the IL6 -174 G/C (rs1800795) and -634 C/G (rs1800796) polymorphisms in the promoter region that are well studied and has been reported to be biologically and clinically important. Previous studies have reported an association of IL-6-174G/C and IL-6-634 C/G SNP with various cancers, including pancreatic, prostate, gastric, colorectal, multiple myeloma, ovarian and lung cancer [25–34].

The presented study, conducted for the first time in Morocco, explores three polymorphisms (IL-6 rs2069840, IL-6R rs2228145, and IL-6ST rs2228044) within three candidate genes encoding key inflammatory factors IL-6, IL-6R, and IL-6ST for association with lung cancer risk. The selection of these SNPs was based on their involvement in inflammatory responses and lung development. Previous studies have investigated the implication of these polymorphisms in the pathogenesis in several type of diseases and cancer [35–44]. However, to our knowledge, no previous genetic studies have investigated the association between any of these SNPs and lung cancer susceptibility.

In our study, the analysis of IL-6 (rs2069840) polymorphism demonstrated a significant association with lung cancer risk in our population (OR = 1.63; 95% confidence interval 1.08–2.47; $p = 0.01$). We found that the distribution of the homozygous mutant genotype (GG) was more frequent in lung cancer patients (20.6%) compared to controls (10%); patients carrying the mutant genotype were 2.45 times more likely to develop lung cancer than those with normal genotype (OR = 2.45; 95% confidence interval 1.11–5.43; $p = 0.02$). When genetic models were assessed, significant association was observed under the recessive genetic model (GG vs. CC + CG) (OR = 2.33; 95% CI 1.08–5.01; $p = 0.03$) for lung cancer patients. These findings were confirmed by the distribution of the mutant allele (G), more frequently observed in lung cancer patients (34.8%) than healthy controls (11.2%); consequently, the minor allele (G) conferred an increased lung cancer risk than the major (C) allele in our population. However, when the Hardy–Weinberg equilibrium (HWE) was tested, the genotype deviation in the patients group was departed. The most plausible causes of the deviation from HWE could the population admixture; the Moroccan population is a mixture of three different ethnical groups (Arab, Berber and Sahrawi) which contribute to the genetic diversity in our population.[45]. Besides, the small sample size analyzed in the study may also explain the deviation found in cases results.

In 2017, a study conducted in a Chinese population investigated the association of IL-6 (rs2069840) polymorphism and other SNPs in several genes with the risk of lung adenocarcinoma among never-smoking patients with different Epidermal Growth Factor Receptor (EGFR) mutation status. As results, they found that IL-6 rs2069840 conferred

susceptibility to EGFR mutant lung adenocarcinoma in a Hong Kong and Macau never smoking patients [46].

To further establish the potential role of gene polymorphisms implicated in the IL-6 pathway, we assessed functional polymorphisms influencing IL-6R and IL-6ST. For this purpose, we selected the IL6R rs2228145 as this single nucleotide polymorphism located in the proteolytic cleavage site of IL-6Rα, resulting in an aspartic acid to alanine substitution (Ala358Asp), plays an important role in the signal transmission leading to abnormal soluble receptor levels. Additionally, there is a common non-conservative functional polymorphism within the IL6ST/gp130 gene (IL6ST/gp130 rs2228044), that leads to an arginine to glycine (Gly148Arg) change, and which modifies the stability and functional properties of the gp130 molecule. In the present investigation, no significant association of the IL-6R (rs2228145) and IL6ST (rs2228044) gene polymorphisms with lung cancer risk was found, suggesting that genetic variants of these genes have potentially no effect on lung cancer risk in our patients. However, being the first study to investigate the association of these polymorphisms with lung cancer risk, we couldn't compare our results with other studies findings. However, previous study conducted in the Chinese population has investigated the IL6ST gene mutations in lung cancer patients. They identified a germline missense c.599C>G mutation in exon 6 that they considered as a new SNP [47].

IL-6 plays a crucial role in carcinogenesis process including stimulation of angiogenesis, promotion of cell proliferation and increased survival of malignant cells, besides of inhibition the apoptosis of cancer cells [48]. Previous studies results have suggested that the tumorigenic role of IL-6 in lung cancer can be biologically mediated through enhanced host susceptibility via SNPs. The localization of the polymorphism rs2069840 in the regulatory region of the IL-6 gene, can lead to a direct functional role in lung cancer disease mediated via IL-6 signaling pathway.

For these reasons, IL6 have represented a potential target for lung cancer treatment [49]. Clinical studies demonstrated that IL-6 antibody, siltuximab, could inhibit STAT3 tyrosine phosphorylation in NSCLC cells, and it's combination with erlotinib could result in dual inhibition of lung cancer growth [50]. Another study conducted by Yao et al. illustrated that adjunctive therapies designed to either control inflammation and/or decrease the bioavailability of IL-6 may provide an effective means to improve response to EGFR TKI treatment in lung cancer [51].

Conclusion

In conclusion, this is the first study investigating the association of polymorphisms in genes encoding IL-6 cytokine, its receptor IL6R and receptor subunit IL6ST with lung cancer risk. Our results suggest that the rs2069840 polymorphism in IL-6 gene may modulate the susceptibility to develop lung cancer in Moroccan population. However, further studies including more participants, with additional functional investigations, evaluating IL6 transcriptional and cytokine production levels, are required to confirm our findings.

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Compliance with Ethical Standards

Conflict of interest The authors declare no conflict of interest.

Ethical Approval The study was approved by the local Ethical Committee of Hassan II University, Faculty of Medicine and Pharmacy, Casablanca, Morocco and all procedures performed were in accordance with the 1964 Helsinki Declaration and its later amendments.

Informed Consent Informed written consents were obtained from all participants taking part in the research.

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