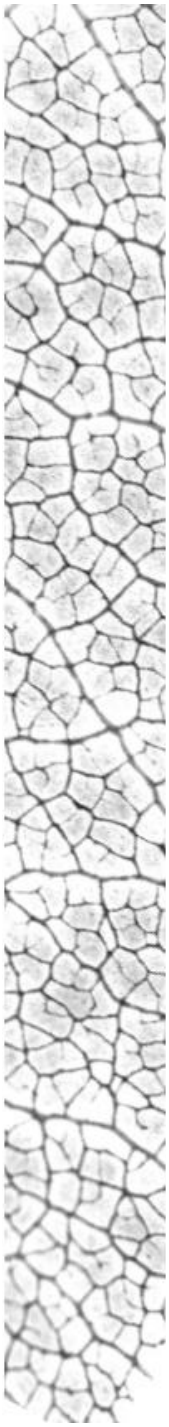

EurAsian Journal of BioSciences
Eurasia J Biosci 14, 671-676 (2020)

Role of IL-18 and caspas-9 polymorphism in disease susceptibility in prostate cancer

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Abstract

Backgrounds: Prostate cancer (PCa) is the 2nd utmost global prevalent male cancer and major cancer in economically developed countries. Environmental factors and person having genetic polymorphism might have a function in prediction and consequently treatment strategies for a particular disease in a particular or a group of patients. This emerging approach has the potential to improve prediction of susceptibility to prostate cancer and disease progression, thereby minimizing the development of metastatic disease and allowing the ability to tailor therapeutic intervention. **Objective:** The present study aimed to examine whether the prostate cancer, and benign prostatic hyperplasia (BPH) patients have distinctive IL-18 and capsase 9 single nucleotide polymorphism (SNP) that could have an effect on disease susceptibility. **Material and Methods:** A case control study has been steered to attain this goal which is based on three groups include 50 patients with PCa (group 1), 50 patients with BHP (group 2) and 50 healthy (non BHP & non prostate) volunteers (group 3, control). Patients were under observation in the Thi Qar Oncology Center from the period of January 2018 till February 2019. Moreover, the supervision of specialists of oncology was also incorporated in this research. For the extraction of DNA, 2mL blood was directly collected to the EDTA comprising sterile tube. Then, amplification refractory mutation-PCR system (ARMS-PCR) technique is used to study interleukin-18 (IL-18) and caspase 9 polymorphism. **Results:** there was no significant difference among the BHP patient's mean age and patients with prostatic cancer (P=0.093; 60.04±10.47 vs. 63.04±8.35 years, respectively); however, patients in both BPH and cancer groups were found to be significantly older as compared to the subjects of control group (P<0.001). IL-18 genotypes homozygous CC and heterozygous GC genotypes were significantly more frequent in patients with prostatic carcinoma in comparison with control group (P=0.002) and in comparison with BPH group (P=0.030). Caspase genotypes homozygous GG and heterozygous AG genotypes were significantly more frequent in patients with prostatic carcinoma in comparison with control group (P=0.003) and in comparison with BPH group (P=0.018); however, there was no significant difference in caspase 9 genotype frequency distribution between control and BPH groups (P=0.842). **Conclusions:** We can speculate that population who have AC, CC genotype for IL-18, and AG, GG genotype for caspase 9 could be at risk for malignant tumor formation, and this could emerging an approach which has the potential to improve prediction of susceptibility to prostate cancer and disease progression.

Keywords: IL-18, caspas-9, polymorphism, prostate cancer

Altamemi IA, Aubaid AH, Hussein TA (2020) Role of IL-18 and caspas-9 polymorphism in disease susceptibility in prostate cancer. Eurasia J Biosci 14: 671-676.

INTRODUCTION

Interleukin-18 (IL-18) primarily termed as IFN-g inducing factor is a pro-inflammatory systemic cytokine which is synthesized through activated macrophages, keratinocytes, osteoblasts, epithelial cells and even cancer cells as well (Nakanishi et al. 2001). The administration of IL-18 led to noteworthy tumor growth suppression in the models of animals (Golab 2000), which signified this cytokine's function in the defense of host against cancer. Furthermore, the anti-tumor activity of the IL-18 is exerted by enhancing the production of IFN-g mostly in the existence of IL-12. Accordingly, increasing the CD8 lymphocytes and NK cell's cytotoxic activities (Nakanishi et al. 2001), inhibiting angiogenesis, encouraging cancer cell apoptosis (Golab 2000). The two single nucleotide polymorphisms (SNPs) at the gene's promotor region's -137 (G/C) and -607 (C/A) positions regulate the IL-18 expressions. A protein element-binding site of potential responsive cAMP is disrupted by an alteration at -607 position from C to A.

Received: March 2019
Accepted: September 2019
Printed: March 2020

The human histone H4 gene specific transcription factor-1 (H4TF-1) is abolished by a change from G to C at nuclear factor binding site's -137 position (Giedraitis et al. 2001). The variations in the binding of transcription factors indicate the mechanisms that affect the gene activity of IL-18 by two promoter polymorphisms.

Several studies have been suggested that some differences in the pathways of apoptosis are related to the various different cancer's susceptibility. This research examined the relationship amongst caspase 7 and caspase 3 polymorphism &the risk of cancer (Yan et al. 20113). Due to the fundamental role of caspases, we have considered an SNP (rs12108497) of caspase 3 (related to common two-way executable caspases), which has been proven to be related to various cancers (Yan et al. 20113).

MATERIAL & METHODS

Patient Group and Sample Collection

The study of case control was established on the basis of three groups. 1st group comprised of 50 PC patientswho were under observation at the Thi Qar Oncology Center. Patients were being supervised for a time period of January 2018- February 2019 by specialists of oncolog. Second group was 50 patients who have benign hyperplaisa (BHP), this group has been collected from uro-surgical department.

Third group was include 50 healthy volunteers (non prostate cancer and non BHP). Blood sample were collected by venipuncture from these groups. For DNA extraction, 2 milliliter blood was directly collected to sterile EDTA tubes, then uses Amplification refractory mutation-PCR system (ARMS-PCR) technique application to study polymorphism of IL-18 and caspase 9, after that samples were frozen at -20°C instantaneously.

Genomic DNA Extraction

Geneaid's (Frozen Blood) Genomic DNA mini extraction kit (USA) was used to extract the genomic DNA from samples of blood conferring to the instruction of company. Moreover, the Nano-drop spectrophotometer (THERMO, USA) was utilized to extract the genomic blood DNA.It further checked the purity of DNA through absorbance reading at 260/280nm and calculated the concentration of DNA in (ng/µL).

ARMS-PCR Primers

ARMS-PCR Primers for detection of caspase9 gene polymorphism (rs4645978) (A/G) were designed in this study using (Web-Based Allele-specific primers of SNPs- Genome Institute, National Center for Genetic Engineering and Biotechnology (BIOTEC) PathumThani, Thailand). Likewise, the primers were delivered from Macrogen Company, Korea as below:

Primer		Sequence	Amplicon
caspase9 gene (rs4645978) (A/G)	A allele Reverse primer	CAGTCTTCCATTCCCTCTTCCCTAT	150bp
	G allele Reverse primer	CAGTCTTCCATTCCCTCTTCCCTAC	150bp
	Common Forward Primer	TGCTCAGTAAACAGAAACGA	

Whereas, ARMS-PCR Primers for detection of Interleukin-18 Gene polymorphism –137 (G/C) were designed by Web-Based Allele-specific primers of SNPs- Genome Institute, National Center for Genetic Engineering and Biotechnology (BIOTEC) Pathum Thani, Thailand). These primers were provided from (Macrogen company, Korea) as following:

Primer		Sequence	Amplicon
Interleukin-18 Gene –137 (G/C)	G allele forward primer	CCCCAACTTTTACGGAAGAAAAG	261bp
	C allele forward primer	CCCCAACTTTTACGGAAGAAAAC	261bp
	common reverse primer	AGGAGGGCAAAATGCACTGG	446bp
	common forward primer	CCAATAGGACTGATTATTCCGCA	

RESULTS

The Frequency Distributions of Patients and Control Subjects according to Age

Table 1 illustrated the control subjects and patient's frequency distributions according to the comparison of mean age & age. No patient with prostatic cancer was bellow 40 years, 19 (38 %) of patients with prostatic cancer were between 40 to 59 years and most of cases (62 %) were 60 years or older, **Table 1** and **Fig. 1**. There was also no patient with benign prostatic hyperplasia (BPH) bellow 40 years, 24 (48 %) between 40 to 59 years and majority of BPH patients (52 %) were 60 years or older, **Table 1** and **Fig. 1**. However, no difference of significance was observed amongst the mean age of BPH patients & patients with prostatic cancer (P = 0.093), 60.04 ±10.47 years versus 63.04 ±8.35 years, respectively; however, patients in both BPH and cancer groups were found to be considerably older in comparison to the control P<0.001 subjects as presented in **Table 1**.

Table 1. Comparison of mean age among study groups

Age (years)	Control *n* = 50	BPH *n* = 50	Prostatic cancer *n* = 50
< 40	7 (14 %)	0 (0%)	0 (0 %)
40-59	38 (76 %)	24 (48 %)	19 (38 %)
≥ 60	5 (10 %)	26 (52 %)	31 (62 %)
Mean ±SD	48.26 ±7.57	60.04 ±10.47	63.04 ±8.35
Range	36 -64	43 -83	48 -83
	***P*-value**		
Control vs BPH	<0.001 † HS		
Control vs Carcinoma	<0.001 † HS		
BPH vs Carcinoma	0.093 † NS		

n: number of cases; BPH: benign prostatic hyperplasia; SD: standard deviation; †: Independent samples t-test; HS: highly significant at $P \leq 0.01$; NS: not significant at $P > 0.05$

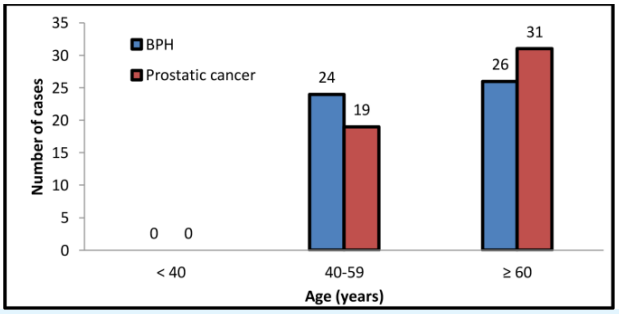

Fig. 1. Bar chart showing the frequency distribution of patients BPH and prostatic carcinoma according to age

Table 2. IL-18 genotype frequency distribution in patients and control subjects

IL-18 gene	Control *n* = 50	BPH *n* = 50	Prostatic cancer *n* = 50
GG	38 (76 %)	35 (70 %)	22 (44 %)
GC	5 (10 %)	11 (22 %)	19 (38 %)
CC	7 (14 %)	4 (8 %)	9 (18 %)
*P*1	0.203 NS		
*P*2	0.002 HS		
*P*3	0.030 S		

n: number of cases; BPH: benign prostatic hyperplasia, *P*1: Control versus BPH; *P*2: Control versus carcinoma; *P*3: BPH versus carcinoma; HS: highly significant at $P \leq 0.01$; NS: not significant at $P > 0.05$; S: significant at $P \leq 0.05$

IL-18 SNP

IL-18 genotypes GG, GC and CC were expressed as 38 (76 %), 5 (10 %) and 7 (14 %) in control group, as 35 (70 %), 11 (22 %) and 4 (8 %) in BPH group and as 22 (44 %), 19 (38 %) and 9 (18 %) in prostatic carcinoma group; therefore, homozygous CC and heterozygous GC genotypes were significantly more frequent in prostatic carcinoma patients when compared to the BPH group of significance P= 0.030 & control group (P= 0.002). Conversely, no significance variance was observed in the genotype IL-18 frequency distribution among BPH and control group (P= 0.203), as given in **Table 2**. In order to calculate the risk of homozygous CC and heterozygous GC genotypes in association with prostatic cancer, both control group and BPH group were combined into a single group and the results were outlined in table 3GC genotype had an odds ratio of 3.94 and an etiologic fraction of 0.41; whereas, genotype CC had an odds ratio of 2.71 and an etiologic fraction of 0.28, as shown in **Table 3**.

Table 3. IL-18 genotype and allele frequency distribution in patients and control subjects with risk estimation

IL-18 gene	BPH and Normal *n* = 100	Carcinoma *n* = 50	*P*	OR	95 % CI	EF
GG	73 (73 %)	22 (44 %)	Reference			
GC	16 (16 %)	19 (38 %)	0.001 HS	3.94	1.74 -8.93	0.41
CC	11 (11 %)	9 (18 %)	0.002 HS	2.71	1.00 -7.39	0.28
Allele	**BPH and Normal *n* = 200**	**Carcinoma *n* = 100**	***P***	**OR**	**95 % CI**	**EF**
G	162 (81 %)	63 (63 %)	Reference			
C	38 (19 %)	37 (37 %)	<0.001 HS	2.50	1.46 -4.29	0.30

n: number of cases; BPH: benign prostatic hyperplasia, OR: odds ratio; CI: confidence interval; EF: etiologic fraction; HS: highly significant at $P \leq 0.01$

Table 4. Caspase genotype frequency distribution in patients and control subjects

Caspase gene	Control *n* = 50	BPH *n* = 50	Prostatic cancer *n* = 50
AA	33 (66 %)	30 (60 %)	16 (32 %)
AG	12 (24 %)	14 (28 %)	22 (44 %)
GG	5 (10 %)	6 (12 %)	12 (24 %)
*P*1	0.824 NS		
*P*2	0.003 HS		
*P*3	0.018 S		

n: number of cases; BPH: benign prostatic hyperplasia, *P*1: Control versus BPH; *P*2: Control versus carcinoma; *P*3: BPH versus carcinoma; HS: highly significant at $P \leq 0.01$; NS: not significant at $P > 0.05$; S: significant at $P \leq 0.05$

Caspase 9 SNP

Caspase genotypes AA, Ag and GG were expressed as 33 (66 %), 12 (24 %) and 7 5 (10 %) in control group, as 30 (60 %), 14 (28 %) and 6 (12 %) in BPH group and as 16 (32 %), 22 (44 %) and 12 (24 %) in prostatic carcinoma group; therefore, homozygous GG and heterozygous AG genotypes were significantly more frequent in prostrate carcinoma patients as compared to the group of controls ($P = 0.003$) and in comparison with BPH group ($P = 0.018$); however, the BPH & control group expressed no significant difference in the frequency distributions of caspase genotype ($P = 0.842$), as shown in **Table 4**. In order to calculate the risk of homozygous GG and heterozygous AG genotypes in association with prostatic cancer, both control group and BPH group were combined into a single group and the results were outlined in **Table 5** AG genotype had an odds ratio of 3.33 and an etiologic fraction of 0.32; whereas, genotype GG had an odds ratio of 4.30 and an etiologic fraction of 0.40, as shown in **Table 5**.

DISCUSSION

The current research agreed to the former studies which stated that the evident rises in the BPH prevalence are due to the increase in age. The studies of autopsy have perceived the histological occurrence of

Table 5. Caspase genotype and allele frequency distribution in patients and control subjects with risk estimation

Caspase gene	BPH and Normal *n* = 100	Carcinoma *n* = 50	*P*	OR	95 % CI	EF
AA	63 (63 %)	16 (32 %)	Reference			
AG	26 (26 %)	22 (44 %)	0.045 S	3.33	1.51 -7.34	0.32
GG	11 (22 %)	12 (24 %)	0.003 HS	4.30	1.60 -11.50	0.40
Allele	**BPH and Normal *n* = 200**	**Carcinoma *n* = 100**	***P***	**OR**	**95 % CI**	**EF**
A	152 (76 %)	54 (54 %)	Reference			
G	48 (24 %)	46 (46 %)	< 0.001 HS	2.70	1.62 -4.49	0.31

n: number of cases; BPH: benign prostatic hyperplasia, OR: odds ratio; CI: confidence interval; EF: etiologic fraction; HS: highly significant at $P \leq 0.01$

80%, 50% and 8% in of 9th, 6th, and 4th life decades, correspondingly (Berry et al. 1984). Moreover, the Asia, US and Europe's observational studies have confirmed the factor of onset clinical BPH & its progression to be the older age (Kok 2017). Also, the upsurge in the volume of prostrate with age depended on the longitudinal aging study of Krimpen & Baltimore which suggested the 2.0- 2.5% per year rate of growing prostrate in older men (Kok 2017, Loeb et al. 2009).

As the prostate cancer is aging related ailment, about 70% of all United States' prostate cancers are identified in men of age 65 years (American Cancer Society 2003). Comparatively, it is uncommon for the PC to be diagnosed in 50 years old men, however, later this age, the rates of mortality occurrence exceptionally increase (Haas and Sakr 1997).Rate of the possibility of prostate cancer development intensifies to 0.005%amongst the 39 years old individuals to 2.2% (1 in 45) for 40-59 years older persons, whereas, 60-79 years older persons showed 13.7% ratio of 1 in 7. Generally, 16.7% (1 in 6) is the lifetime risk of prostate cancer development. The outcomes of autopsy researches proposed the even higher rates of mounting histological evidence of prostate cancer. Carter et al. (1990) exposed that 50% of 70-8- years old while 20% of 50-60 years aged men had histological indication of malignancy (Carter et al. 1990). Further, estimation exhibited that 50 years aged men have 42% lifetime risk of evolving histological confirmation of PC (Crawford 2003). Therefore, all stated studies supported the recent research regarding age of the prostate cancer patients.

According to a universal phenomenon, all men above age 45 years are susceptible to BPH. Several factors are liable to the disease of prostate most specifically in older men (Christudoss et al. 2011). Hence, 40 years old men with a family history of this cancer and 50 years elder males or above without any history of cancer essentially undertake the DRE (digital rectal examination). Likewise, levels of PSA must be examined annually as per recommendation of Food & Drug Administration (FDA) and American Urological Association (AUA) (Shahana et al. 2017).

Moreover, present study demonstrated that, IL-18 genotypes homozygous CC and heterozygous GC genotypes were significantly more frequent in patients with prostatic carcinoma in comparison with control group ($P = 0.002$) and in comparison with BPH group ($P = 0.030$); though, no significant variance was observed in the frequency distribution of IL-18 genotype amongst BPH group and control group (P= 0.203) (**Table 2**).

The five single nucleotide polymorphic positions make up the promotor region of *IL-18* while merely (rs1946518) & (rs187238) have inveterate the effect on the expression and activity of *IL-18* in tissues (Giedraitis et al. 2001). Apart from this, various polymorphisms of *IL-18* haplotypes lead to different *IL-18* mRNA's expression levels (Zhou et al. 2001).

Genetic variants are considered to be the chief risk factors contributing to the prostate cancer. Although, significant understanding is available about the substantial association of several chromosome segments and genes with the risks of PCa in a multinational population, for instance *PCA3* (Liu et al. 2013, Zhou et al. 2001). Prostate cancer risk for IL-18 was investigated in similar study. They found that poor prognosis causes the G/C GG genotype signifying the importance of IL-18's polymorphism G/C as a probable prognostic marker in the patients of the cancer of prostate. Though, their research indicated no significant relationship with the prostate cancer's liability in two SNPs. Which specified that distinctive *IL-18*'s expression might not have any contribution to the tumor occurrence. All these data differed from the current study's data and potential cause of such contraversary might be related to the difference in the genotype and disease susceptibility of Iraqi population and such difference give a clear breakthrough and originality of present study (Sicramaz et al. 2016).

Conversely, due to the prostate cancer's multifocal growth and high heterogeneity, the endocrine therapy's reaction in between various patients differs extensively. Therefore, prognostic molecular markers' identification might impact the therapeutic effect and substitute of treatment modality as well.

In formerly directed study, GG genotype -137G/C polymorphism was related to the shorter yet development free survival period. The level of expression for IL-18 mRNA was greater at for G at position -137 showing that IL-18 may function as a pro-tumor factor in the tumor progression.

In summary, recent data verified the contribution of IL-18-G/C, CC polymorphism to the incidence and proneness of disease in the patients of prostate. In future, other forthcoming studies with greater samples, comprehensive medical data and longer term follow ups are required to further approve our conclusions.

In addition to that, Caspase genotypes homozygous GG and heterozygous AG genotypes were significantly more frequent in patients with prostatic carcinoma in

comparison with control group (*P* = 0.003) and in comparison with BPH group (*P* = 0.018); however, there was no significant difference in caspase genotype frequency distribution between control and BPH groups (*P* = 0.842), as shown in **Table 3**.

In a study by Deng et al. (2016) on caspase-3 polymorphism, it was reported that rs12104897 SNP is more prevalent among smokers with HCC in Chinese population. A little earlier, Li and colleagues revealed that rs4647693, rs12104897, rs4647610 alleles have a statistically significant difference in distribution between healthy and patient with gastric cancer individuals (Mohammad et al. 2017). On the other hand, in a study on Non-Small cell lung cancer by Yoo and colleagues, it seemed that Caspase 3 polymorphisms did not have any effect on cancer predisposition (Yoo et al. 2009). Wu et al. in an investigation about the association of caspases 3, 8, and 9 genes polymorphisms with colorectal cancer (CRC) progression also achieved similar results (Wu et al. 2013).

Moreover, polymorphisms in this area may provide useful markers for predicting prognosis in patients undergoing surgery (Mittal et al. 2012). In a study by Jang and his colleagues in 2008 on lung cancer, it was shown that caspase 3 polymorphism (928A>G, 77G>A, and 17532A>C) reduced the risk of lung cancer (Jang et al. 2008). The results of the current study indicate that caspase 3 gene GG Homozygous, and AG heterozygous is associated with prostate cancer disease susceptibility. This finding can also be useful for determining the appropriate therapeutic approaches to increase longevity and improve the quality of life of patients with prostate cancer. It should be noted that this result is limited to the population studied and more studies are needed on a larger number of individuals to confirm the association of rs12108497 polymorphism with prostate cancer.

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