World Journal of Pharmaceutical Sciences
ISSN (Print): 2321-3310; ISSN (Online): 2321-3086
Published by Atom and Cell Publishers
Available online at: http://www.wjpsonline.org/
Original Article

Genotyping analysis of tumor necrosis factor –alpha and lysyl oxidase- like 1 genes in patients with pseudoexfoliation syndrome

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Received: 27-09-2015 / Revised: 15-10-2015 / Accepted: 25-10-2015

ABSTRACT

Pseudoexfoliation syndrome (PEX) is an age-related systemic disorder characterized by deposition of whitish-gray pseudoexfoliation fibrillogranular amyloid like material in several intraocular and extraocular tissues. The present study was carried out to investigate the association of *Tumor Necrosis Factor-alpha and lysyl oxidase like 1 (LOXL1)* genes variants with pseudoexfoliation syndrome in the Iraqi population. The coding regions of *TNF-α* and *LOXL1*genes were fully sequenced in 45 clinically diagnosed PEX patients and 30 healthy controls. The regions of *TNF-α* and *LOXL1* genes with their single nucleotide polymorphisms (SNPs) were amplified and sequenced. The single nucleotide polymorphism of *Tumor necrosis factor-alpha G 308 A* was not statistically significant (P=0.545), whereas, GG genotype and allele G of *lysyl oxidase-like 1* were statistically significant among PEX patients, (P=0.0003 and P <0.0001, respectively). GG genotype G allele polymorphism of lysyl oxidase like 1 is mainly expressed among PEX patients and susceptibility with disease might be prospected.

Key words: Pseudoexfoliation syndrome, TNF-α, LOXL1, Allele, Genotype, RFLP

INTRODUCTION

Pseudoexfoliation syndrome (PEX) is an age-related, characterized by the deposition of a distinctive fibrillar material in the anterior segment of the eye and it is the most common identifiable cause of open angle glaucoma worldwide [1]. The prevalence of the syndrome demonstrates considerable geographic, ethnic and racial variation and many of studies show that the syndrome is associated with increase age [2].

Although its pathogenesis unclear, there are some evidences suggest that both genetic and non-genetic factors is involved in the PEX syndrome progression. Studies have focused on immunological role and *lysyl oxidase-like protein 1* (*LOXL1)* expression during PEX syndrome pathogenesis. Some advances revealed that cytokines play an important role in the pathogenesis of pseudoexfoliation and may regulate retinal ganglion cell (RGC) survival or death [3]. Tumor necrosis factor -alpha (*TNF-α*) is one of the main proinflammatory cytokines that plays an important role in initiating and regulating the cytokine cascades in the inflammatory procession various diseases [4]. It has been observed that in the retina of glaucomatous eyes, both mRNA and protein levels of tumor necrosis factor -alpha or tumor necrosis factor -alpha receptor-1 are raised as compared to normal eyes, and therefore it was suggested that the cell death mediated by tumor necrosis factor -alpha is a contributing factor in the neurodegeneration in glaucoma [5].

Genetic studies have shown that there is a relationship between *lysyl oxidase-like 1* gene polymorphisms and pseudoexfoliation material production [6]. *The lysyl oxidase-like protein 1* gene is important for elastin metabolism. Defects in elastin metabolism have been postulated to be the causative agent of pseudoexfoliative material synthesis. It has been shown that specific mutations of the *lysyl oxidase-like 1* gene are strongly associated with the development of pseudoexfoliation and secondary glaucoma. The primary aim of this study was to investigate whether SNPs in the *TNF-α* and *LOXL1* genes was associated with the risk of pseudoexfoliation syndrome in the Iraqi population.

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MATERIALS AND METHODS

Subject: The current study was conducted on 45 patients (17 female, 28 male) attended to Al-Diwaniyah Teaching Hospital, for the period from December 2014 to March 2015. The patients were diagnosed clinically by an ophthalmologist via slit lamp biomicroscope, intraocular pressure, visual acuity fundoscopy and visual field assessment as having PEX and Patients were interviewed directly by using an anonymous questionnaire form which covered age, sex, family history and others. Another group consists of 30 apparently healthy individuals (18 female and 12 male) without any history of systemic disease were clinically considered as healthy also included in this study as a control group. Verbal informed consent was obtained from all participants.

***Genotyping*:** The *TNF-α* and *LOXL1* genes were purified by using a AccuPower^{TM} PCR PreMix (Bioneer), and their genotypes were determined by PCR–restriction fragment length polymorphism (RFLP), with special thermocycling condition Table (1), Table (2). Then the PCR products were visualized in an ethidium bromide-stained 1.5% agarose gel using a UV Transilluminator. Following which they were digested with the Nco1 restriction enzymes for *TNF-α*gene & AvaI restriction enzymes for *LOXL1*gene. The digested PCR products were visualized in an ethidium bromide-stained 4% agarose gel using a UV Transilluminator. For *TNF-α*gene, there were an A allele (212 bp) and G allele was digested into two fragments of 192 bp and 20 bp. Whereas PCR products for *LOXL1* were T allele (244 bp) and G allele was digested into two fragments of 162 bp and 82 bp.

Statistical analysis: The data were analyzed using Microsoft excel 2010 and Statistical Package for the Social Sciences version 22 and MedCalc soft ware programs. The Fisher's exact test was applied and p value less than 0.05 was considered statistically significant. Odds ratio (OR) was calculated by MedCalc software programs, that calculate genotypes / alleles are increased or decreased in patients as compared to control group.

RESULT

This study includes 45 patients with mean age64.69 years (SD±8. 62) and 30 control subjects with mean age59.96 years (SD±9. 30) years. The gender distribution was 28 (62.2 %) male and 17 (37.6 %) female; the male to female ratio was (1.64:1) in patients group, and 12 (40%) male and 18 (60%) female; the male to female ratio was (1.5:1) in control group. There were no significant differences in age and gender distribution between cases and control (p=0.57, p=0.31, respectively), Demographic characteristics of the study subjects are shown in table (3).In this study 25 patient was present as PEX with Cataract, 13patients was PEX with Cataract and Glaucoma, 5patients as PEX with Glaucoma and only 2 patients was present as PEX only, table (4).The glaucoma distribution was 18 case from 45 patients, the gender distribution was 7 (15.5%) cases in females, and 11(24.5%) case in males among patients with glaucoma. Bilateral glaucoma was noted in 27.8% of PEX patients and the unilateral glaucoma was noted in 72.2% of patients. The association between unilateral and bilateral glaucoma distribution was not significant (P>0.05). Cataract was detected in 38 patients, 23 (60.5 %) male and 15 (39.5) female. The percentage of bilateral cataract was 34.2% among cases and there was a 65.8% unilaterally cases which are not statically significant, table (5).

Distributions of alleles and genotype frequencies of *TNF-α and LOXL1* genes are shown in table (6). For *TNF-α*gene, there was no significant association with PEX syndrome. The A allele prevalent in the pseudoexfoliation patients was (36.7%) as compared to controls (31.7%) with, [OR=1.25 (95% CI=0.62-2.49), p = 0.601]. Whereas the relative frequency G allele was 63.3 % in PEX patients and 68.3% in control with, [OR=0.80 (95% CI=0.40-1.60), p = 0.601]. Also the genotype frequencies of *TNF-α* gene in patients with PEX were not statistically different from those of control subjects. The AA genotype was present in 13.3 % of the control, whereas 20.0 % of the PEX patients in which the OR=1.62 (95% CI=0.45-5.85),with p=0.545.The GG genotype relative frequency was found as 46.7% in the PEX patients with an odds ratio (OR) was 0.87 (95% confidence interval 0.34-2.20, p=0. 817), and 50.0 % in the control, while heterozygous genotype GA was 33.3 % in patients, while in the control this genotype was present in only 36.7%, with OR=0. 86(95% CI=0.32-2.27, p=0.808).

The genotype distribution of (R141L) *LOXL1SNPs* was significantly associated with PEX syndrome. The G allele was more prevalent in the PEX patients(73.3%) as compared to control (33.3%) and was strongly associated with the disease with OR=5. 50 (95% CI=2. 69-11.20) and p = <0.0001. The difference in distribution of homozygous mutant genotype (GG) between patient and control groups was statistically significant, (P=0. 0003, OR= 19.15, 95%CI 4.059-90.42). Heterozygous genotype TG prevalent was differ between control and patient, and this was (31.1%) in PEX patients and (53.3%) in healthy control, but not statistically

significant in the patient group in comparison with a control group of the SNP R141L OR=0. 395 (95%CI 0.152-1.027 P=0. 091**.**

DISCUSSION

Pseudo-exfoliation syndrome is age-related syndrome, the reported prevalence rate of this syndrome in different populations shows extensive variations. Prevalence rates of as low as 0% in Eskimos [7], and as high as 46.9% in Greece [8] were reported.

This study reported that there was increased PEX prevalence by increasing the age with mean (64.69±8.62), which are in consistence with finding conducted by Emiroglu *et al* [9] study, in which the prevalence of PEX increases among patients mean age (65.9±4.2) years. PEX was more common among males than in females. A similar finding was reported on the prevalence of PEX among patients in the Kashmir population [10]

Association of glaucoma with PEX was studied and was found that 40% of the PEX patients had glaucoma, and was more common in males. A study from Egypt reported that 30.31% of PEX cases had glaucoma [11]. Shafiq *et al* [12] and Metaxaki *et al* [13] study that found the glaucoma in males more than females.

A significant association between PEX and cataract was also conducted in our study and it is compatible with findings in other studies [11]. We found that cataract was unilaterally in the majority of cases (84.4%), comparable to finding revealed by Rasit *et al* [14]. Also, cataract was a high prevalence in males 69.5% than females 39.5%, this finding was similar to Naseem *et al* study [15], in which there was a cataract in 33% among females and 67% among males.

In the last few years, several immunological components believed that to have a role in the evolution of pathogenesis of PEX. And also observed that the role of these components are not usually the primary causative agents, but involved in the progression of the disease [16]. Also, recent studies focused on lysyl *oxidase-like protein 1* (*LOXL1)* role during PEX syndrome pathogenesis.

Mossbock *et al* [17], found that the distribution of *TNF-α*−308 G/A (genotype distributions and allelic frequencies) was not significant in Caucasian patients with primary open-angle glaucoma (POAG). Xin *et al* [18], evaluated that the association of *TNF-α*-308 polymorphism and POAG in Chinese patients, they determined that *TNF-α*−308 G/A showed a strong association with the POAG.

In the present study, we found that the A allele and AA genotype have obviously suggested as an etiology for PEX, with [Etiologic Fraction (EF) =0. 125 and 0.265 respectively], In contrast, to the G allele, GG and GA genotype which it have a rather preventive role as it has [Protective Fraction (PF) =0. 127, 0.079 and 0.086 respectively]. This may indicate that the A allele may increase the pathogenesis of the disease. With the possibility of G allele may be protective. However, By compared with previous studies our findings was coincided with studies in both Iran and Pakistan populations [19,20], which have shown a significant association of the *TNF*-α polymorphism G-308A with PEX, also study by [20], revealed a strong association of GA genotypes with PEXG. Agarwal *et al* [21], compare the patient to normal basal level transcription, they found G to A transition at position −308 in patients, results in a six- to seven fold increase in transcription of *TNF*-α.

These results are in contradiction with Turkish population's study [22], which have shown no significant association between *TNF*-α polymorphism G-308A and PEX patients, they found a high prevalence of the GG genotype in Turkish patients, but their main hypothesis was to determine the high frequency of the GA genotype in PEX patient. And also did not correspond to [23], a study of the Caucasian populations, they found an insignificant odds ratio for PEX in both carriers of the *TNF*-α −238 G-allele and of the *TNF-α* −308 G-allele. Possible explanations for the conflict of these results with previous results may be due to varying genotype distributions among different populations as well as small sample size.

In the initial genome-wide association study, Thorleifsson *et al* [6], explain a strong association between *LOXL1* SNPs and PEX in Icelandic and Swedish populations. This genetic association was confirmed in several different populations, including Asians [24], Europeans [25] and North Americans [26]. However, the type and frequency of allele and genotype, which lead to increased risk for PXF for the *LOXL1*SNPs varied among different ethnic groups. The association of *LOXL1* SNPs (rs1048661) with PEX has now been studied in Caucasian populations in the USA [27], Germany [28], Australia [29], and Finland [30] and in other ethnic groups, including Indian [31], Japanese [32], black South Africans [33] and Chinese [34], the risk for PEX was associated strongly with GG genotype and G allele of rs1048661 in all populations except in the Chinese

[34] and Indian populations [31]. In other studies, the T allele and TT genotype of SNP rs1048661 was reported to increase the risk of PEX in the Chinese [24], Japanese [35] and Korean [36] population.

Moreover, in our study the G allele and GG genotype showed a strong association at genotyping level [OR = 19.15, Etiologic Fraction (EF) =0. 880] as well as in allelic level [OR = 5.50, Etiologic Fraction (EF) =0. 627], which demonstrates that this may be one of the risk factors for PEX. In contrast, the T allele and TT genotype have a rather preventive role [OR=0. 180, Protective Fraction (PF) =0. 635] and [OR =187, Protective Fraction (PF) =0. 561] respectively. This explains the G allele increase susceptibility to PEX. With the possibility of T allele may be protective. A recent report by Kasim *et al* [37] of Turkish and Saudi Arabian [38] patients corroborate the findings of this study, the G and GG was risk allele and genotype for PEX in most population.

Based on the results of *LOXL1* gene polymorphisms in Turkish and Saudi Arabian populations, the allele frequencies of rs1048661 in this study were confirmed similar to patterns within other study, including [39] in Greek Population and [40], and differ from Koreans [41] and Chinese [42] studies that found the G allele is protective.

These diversities in genetic findings between different ethnic groups suggest that changes in *LOXL1* SNPs are not directly responsible for increase PEX; rather, other genetic or environmental factors unidentified of *LOXL1* gene may affect gene expression or protein function, which needs further investigation. The inability to detect statistically significant differences may be due to low frequency of the minor allele in Iraq population. In order to make safe conclusions regarding the former association of the polymorphism, a larger sample is needed because of the found rarity of the A allele in the Iraqi population.

CONCLUSIONS

Our results showed significantly associated between *LOXL1* gene polymorphisms and PEX syndrome in our population. PEX Syndrome increases with the age, and according to gender, there was more prevalence of PXF in male than female. Also show Increase the frequency of the AA genotype and A allele of TNF-α -308 G/A polymorphism in patients with PEX compared to healthy subjects. The sequence variants residing on the *LOXL1*gene, rs1048661 were associated with PEX, the T allele of rs1048661as in the *LOXL1*gene was the most significant risk-modifying factor for PEX in Iraq individuals, but the GG genotype and the G allele in patients with PEX were higher and significantly associated.

Acknowledgement

I thank Al-Qadisiyah Medicine College and Al-Qadisiyah hospital, for all what they provide me of my study requirements.

Table 1: The primer sets and restriction enzymes used for the PCR–RFLP analyses

Gene Variations	Restriction enzymes	Primers used for PCR analysis
TNF-α Gene	NCOI	F: 5 'AGG CAA TAG GTT TTG AGG GCC AT3' R: 5 'GTA GTG GGC CCT GCA CCT TCT3'
LOXL1 Gene	Ava I	F- 5 'GCCA GGCGCGGCACCCAT3' R-5 'GCGGGGTCGTAGTTCTCGTA3'

Table 2: Thermo cycling condition for *TNF-a* and *LOXL1* genes detection

Step	Temperature/0C	Time (second)	Number of cycle
Thermo cycling condition for *TNF-a* gene detection			
Initial denaturation	95	420	1
Denaturation	95	30	35
Annealing	60	30	
Extension	72	45	
Final extension	72	600	1
Thermo cycling condition for *LOXL1* gene detection			
Initial denaturation	94	300	1
Denaturation	94	30	35
Annealing	68	30	
Extension	72	30	
Final extension	72	420	1

Table 3. Demographic characteristics of the study subjects

	Patients	Control	P-value
	No.(%)	No.(%)	
No. sample	45 (100%)	30 (100%)	
Age (years)			0.57
Range	(35 - 84)	(37 - 73)	
Mean	64.69	59.96	
SD	8.62	9.30	
SE	1.28	1.69	
Gander			0.31
Male	28 (62.2%)	12(40%)	
Female	17 (37.8%)	18 (60.0%)	

Table 4. Frequency Distribution of Patients group according to type of Disease.

Type of Disease	NO / n=45	%
PEX only	2	4.4
PEX with Cataract	25	55.6
PEX with Glaucoma	5	11.1
PEX with Cataract+ Glaucoma	13	28.9

Table **5.**Frequency Distribution of Glaucoma and Cataract according to the gender and its appearance in the eyes among Patients with pseudoexfoliation.

	No /n=45	%	P-value
Glaucoma	18	40	P>0.05
Bilateral Glaucoma	5	27.8	P>0.05
Unilateral Glaucoma	13	72.2	
Glaucoma in Male	11	61.1	P<0.05
Glaucoma in Female	7	38.9	
Cataract	38	84.4	P<0.05
Bilateral Cataract	13	34.2	P>0.05
Unilateral Cataract	25	65.8	
Cataract in Male	23	60.5	P>0.05
Cataract in Female	15	39.5	

Table 6.Genotype / Alleles distribution of TNF-α and *LOXL1*in patients and controls

	Patient(n=45)		Control(n=30)						
Genotype	No	%	No	%	P-value	OR	95% CI	EF	PF
TNF-α									
GG	21	46.7	15	50.0	0.817	0.87	0.34-2.20	***	0.079
GA	15	33.3	11	36.7	0.808	0.86	0.32-2.27	***	0.086
AA	9	20.0	4	13.3	0.545	1.62	0.45-5.85	0.265	***
Allele									
G	57	63.3	41	68.3	0.601	0.80	0.40-1.60	***	0.127
A	33	36.7	19	31.7	0.601	1.25	0.62-2.49	0.125	***
LOXL1									
GG	26	57.8	2	6.7	0.0003	19.15	4.059-90.42	0.880	***
GT	14	31.1	16	53.3	0.091	0.395	0.152-1.027	***	0.415
TT	5	11.1	12	40.0	0.004	0.187	0.057-0.611	***	0.561
Allele									
G	66	73.3	20	33.3	<0.0001	5.50	2.69-11.20	0.627	***
T	24	26.7	40	66.7	<0.0001	0.180	0.082-0.37	`***	0.635

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