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Polymorphism Study of Nuclear Factor Kb and Psorisis In Egypt.

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ABSTRACT

Nuclear factor-κB (NF-κB) is a key transcription factor involved in the regulation of immune responses and apoptosis. The aim of this study is to test for the association of NF-κB gene polymorphisms with the susceptibility and severity of psoriasis among Egyptian cases. This is a case controlled study including 100 Egyptian psoriasis patients in addition to 100 matched healthy unrelated controls from the same locality. For all participants, DNA was analyzed by RFLP- PCR for characterization of NF-κB194-ATTG del/ins and NF-κB IA 2758 A>G gene polymorphisms. Compared to controls, psoriasis patients showed a significant difference for all frequencies of genotypes and alleles of NF-κB1 ins/del and NF-κB1A A>G Genetic polymorphisms of NF-κB1-94 ins/del ATTG, NF-κB IA 2758 A>G were associated with the susceptibility to psoriasis in Egyptian patients.

Keywords: NFkB, psoriasis ,autoimmune disease, Egypt.

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INTRODUCTION

Psoriasis is a common immune-mediated inflammatory skin disorder affecting 2–3% of the population. It is characterized by infiltrating leukocytes that release growth factors, cytokines, and chemokines affecting epidermal keratinocyte proliferation and differentiation (Miyoshiet al., 2011; Perera et al., 2012). The pathogenesis of psoriasis has been speculated to be due to factors originating inthe skin, immune system or in the human genome. (Peters et al; 2000, Weedon, 2002 and Woodley, Kim, 2009) The immune basis of psoriasis was manifested by the presence of the activated type 1 T cells (Th1) and their cytokines in psoriatic lesions. (Galadari et al , 2005, Landgren ,et al; 2006, Lee , Cooper , 2006, Pérez-Lorenzo et al; 2006). As an important transcription factor, NFκB mediates the ;'.survival response by inhibiting p53-dependent apoptosis and up-regulating anti apoptotic members of the Bcl-2 family and caspase inhibitors. (Maldonado, et al., 1997, Mayo et al; 1997) Thus, NFκB activation might induce resistance to apoptosis of peripheral blood mononuclear cells in patients with autoimmune diseases. (Todaro,et al;2005) NF-κB was found to augment the transcription of crucial genes in the activated Th1 cells which were involved in the pathogenesis of psoriasis such as TNF-α, IL-8, IL-12 and cyclin D. (Galadari et al , 2005, Landgren ,et al; 2006, Lee , Cooper , 2006, Pérez-Lorenzo et al; 2006, Johansen et al; 2005, Ouyang et al; 2005 and Shaker, et al; 2006) NF-κB designates a group of critical transcription factors, the major form of which is a heterodimer of the p50 and p65/Rel A subunits, encoded by the genes NF-κB1 and NF-κB2, respectively. (Chen, et al; 1999). NFκB 1 maps to chromosome 4q23–q24 and consists of 24 exons, (Mathew, et al; 1993, Héron et al; 1995) and its inhibitory gene NFκB1A (encoding for IkB) is located on chromosome 14q13 and is including six exons.(Le Beau, et al; 1992, Duerr et al; 2000) Genetic studies have identified single nucleotide polymorphisms (SNPs) in NFκB1and NFκB1A. (Ota, et al; 1999, Glavac, et al; 1994) Recently, a common insertion/deletion (-94 insertion/deletion ATTGrs28362491) polymorphism in the NFκB1promoter region and a 39 –un translated region(39UTR) polymorphism 2758 A>G (rs696) in NFκB1A were observed to be significantly correlated with inflammatory bowel disease (Karban et al; 2004,Klein, et al; 2004) and cancers (Campbell et al; 2006, Zhou, et al; 2009).

SUBJECTS AND METHODS

One hundred egyptian psoriasis patients selected from dermatology clinic, mansoura university hospital, Egypt. They included (42) males and (58) females . All the patients were diagnosed as typical cases of psoriasis by a consultant dermatologist. For all patients, data related to their age, sex, family history of psoriasis, consanguinity pattern. 100Controls were in the form of (42)males and (58) females. The controls were selected fromhealthy blood donors with no past or family history of immune or dermatologic disorders.For all patients and controls, DNA was extracted from peripheral blood samples and purified using the MagNa Pure purification system (Roche, Berlin, Germany). For determination of the NFκB 1 promoter(rs28362491) polymorphism, the SNP containing fragment was amplified using the following primers: 5’-TGGGCACAAGTCGTTTATGA-3’ (forward) and 5' CTGGAGCCGGTAGGGAAG-3'(reverse).PCR was run at 94oC for 3 min followed by 30cycles of 94oC for 30 s, 56oC for 30 s, and 72oC for 60 s with a final extension at 72oC for 10min. The PCR products (281/285 bp in size) were digested with PFIMI (Fermentas, Vilnius, Lithuania) at 37oC overnight followed by 2% agarose gel electrophoresis. (Danning et al; 2000) For determination of the NFκB IA G/A substitution in3’ un translated region (rs696) polymorphism, the SNP containing fragment was amplified using the following primers: 5’-GGCTGAAAGAACATGGACTTG-3’ (forward) and 5’-GTACACCATTTACAGGAGGG -3'(reverse). The PCR was run at 94oC for 5 min followed by 32 cycles of 94oC for 30 s, 54.3oC for 45 s and 72oC for 60 s with a final extension at 72oC for 10 min. The amplified fragments were digested with HaeIII (Fermentas, Vilnius, Lithuania) overnight at 37oC followed by 2%agarose gel electrophoresis. (Danning et al; 2000).

Statistical analysis

All data were analyzed using SPSS version 12.0.1 software. To test for the association of the studied genetic variants and susceptibility to psoriasis, the chi-square, Fisher exact and odds ratio tests were used to compare genotype and allele frequencies of psoriasis patients and controls. Association of genetic variants to the clinical pattern and severity of psoriasis was carried out by comparing the frequency of genotypes of case-subgroups regarding their age of onset, gender, family history, clinical type and PASI score. Hardy Weinberg equilibrium was tested separately for patient and control groups comparing the observed vs. expected frequencies of genotypes. All statistical tests were two-sided, and statistical significance was considered positive at a p value <0.05.

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RESULTS

Comparing psoriasis cases to controls regarding the frequencies of their NF-κB1-94 ins/del ATTG. variants (Table 1) showed the recessive form (ID+DD vs. II), dominant form (DD vs. II+ID.) and over dominant(ID vs. II+DD) had higher significant frequency among cases compared to that of controls (P= <0.0001, 0.00085and 0.006102) respectively). Also, the frequency of D allele was significantly higher among psoriasis cases compared to controls.

Comparing cases to controls regarding the frequencies of their NF-κB1A A>G variants table (2) showed that the recessive form (AG+GG vs. AA),dominant form (GG vs. AA+AG) and over dominant (AG vs. AA+GG) had higher significant frequency among cases compared to that of controls (P=<0.0001, 0.002685, 0.006136 respectively).Also the G allele was significantly higher among psoriasis cases compared to controls).

No significant differences were found by comparing cases according to sex, psoriasis type, complications, family history and consanguinity regarding the distribution of genotypes and alleles of NF-KB1(-94 ins/del ATTG) (rs28362491) and NF-KB1A(3' UTR A→G) (rs696) genes polymorphisms (Table 3).

Table (1): Genotypes and alleles distribution of NF-κB1-94 ins/del gene polymorphism among psoriasis cases compared to controls.

NFKB1	**Cases n = 100 (%)**	**Controls n = 100 (%)**
II	16 (16%)	57 (57%)
ID	34 (34%)	13 (13%)
DD	50 (50%)	30 (30%)
HWE	χ2= 5.34 p<0.05*	χ2=51.78,p<0.001
Allele I	66(33%)	127 (63.5)
Allele D	134(67%)	73 (36.5%)
II + ID	50 (50%)	70 (70%)
ID +DD	84 (84%)	43 (43%)
II+ DD	66 (66%)	87(87%)
Statistics	**P**	**OR, 95% C.I**
DD vs. ID vs. II (Genotypic)	**0.004****	
ID+DD vs. II (Recessive)	**<0.0001*****	3.961(2.04-7.70)
ID vs. II+DD (over dominant)	**0.00085*****	3.448(1.68-7.05)
DD vs. II+ID (dominant)	**0.006102****	2.33(1.31-4.17)
D allele vs. I allele	**<0.0001*****	3.5322(2.34-5.33)

Table (2):Genotypes and alleles distribution of NF-κB IA 2758 A>G gene polymorphism among psoriasis cases compared to controls.

NFKB1A	**Cases n = 100 (%)**	**Controls n = 100 (%)**
AA	26 (26%)	64 (64%)
AG	33 (33%)	14 (14%)
GG	41 (41%)	22 (22%)
HWE	χ2= 10.6 p<0.005**	χ2=43.56,p<0.001**
Allele A	85(24.5%)	142(71)
Allele G	115(75.5%)	58(29%)
AG+AA	59 (59%)	78 (78.0%)
AG +GG	74 (74%)	36 (36.0%)
GG+AA	67 (67%)	86 (86.0%)
Statistics	**P**	**OR, 95% C.I**
GG vs. GA vs. AA (Genotypic)	**0.000***	
AG+ GG vs. AA (Recessive)	**<0.0001*****	5.0598(2.76-9.27)
AG vs. GG + AA (over dominant)	**0.002685****	3.0256(1.499-6.105)
GG vs. AA + AG (dominant)	**0.006136****	2.4638(1.327-4.574)
G allele vs. A allele	**<0.0001*****	3.3124(2.19-5.014)

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Table (3): Genotypes distribution of NF-κB1-94 ins/del and NF-κB IA 2758 A>G among sub groups of psoriasis cases.

	NFkB1-94 ins/del			NFkB1A A>G		
	II	ID+DD	P	AA	AG+GG	P
Gender						
Male	8	34	0.599	11	31	0.610
Female	8	50		10	48	
Psoriasis type						
Vulgaris	10	58	0.824	15	53	0.286
Scalp	2	10		4	8	
Guttate	4	8		5	7	
Plaque	0	5		1	4	
Pustular	0	2		1	1	
erythrodermic	0	1		0	1	
Family history						
Positive	4	12	0.484	5	11	0.832
Negative	12	72		21	63	
Consanguinity						
Positive	3	9	0.626	6	6	0.095
Negative	13	75		20	68	
Diabetes mellitus						
Diabetic	3	12	0.939	4	11	0.997
Non diabetic	13	72		22	63	
Complicomplication						
No	14	64	0.772	21	57	0.903
Psychological	0	4		0	4	
Hcv	3	4		3	4	
Hcv+renal	1	0		0	1	

DISCUSSION

This study illustrated the association of NF-KB1(-94 ins/del ATTG) (rs28362491) and NF-KB1A(3' UTR A→G) (rs696) genes polymorphisms with psoriasis among Egyptian cases. Participants were in the form of a cohort sample of 100 (100%) cases of psoriasis patients were genotyped and compared to 100(100%) healthy unrelated controls. Our results revealed that there was an increased association between NF-KB1(-94 ins/del ATTG) and psoriasis as the recessive form (ID+DD vs. II), dominant form (DD vs. II+ID.) and over dominant(ID vs. II+DD) had higher significant frequency among cases compared to that of controls (P= <0.0001, 0.00085and 0.006102) respectively). Also, the frequency of D allele was significantly higher among psoriasis cases compared to controls,P<0.0001.

Also there was an increased association between NF-KB1A (3' UTR A→G) polymorphism and psoriasis as the recessive form (AG+GG vs. AA),dominant form (GG vs. AA+AG) and over dominant (AG vs. AA+GG) had higher significant frequency among cases compared to that of controls (P=<0.0001, 0.002685, 0.006136 respectively).Also the G allele was significantly higher among psoriasis cases compared to controls, p<0.0001). No significant differences by comparing cases according to sex, psoriasis type, complications, family history and consanguinity regarding the distribution of genotypes and alleles of NF-KB1(-94 ins/del ATTG) (rs28362491) and NF-KB1A(3' UTR A→G) (rs696) genes polymorphisms.

The same results was found in other studies that had shown that NF-KB1 (-94 ins/del ATTG) (rs28362491) and NF-KB1A (3' UTR A→G) (rs696) polymorphisms were associated with increased risk of autoimmune inflammatory diseases. It was found that in the Hungarian patients with UC(Ulcerative colitis) , the 3'UTR GG genotype associated with extensive colitis (55.3 vs. 29.4%, odds ratio 2.97, 95% confidence interval 1.45-6.08) (Szamosi et al,. 2009).

Also, it was shown that NFKB has been activated in rheumatoid arthritis synovium and resembled in inflammation mediators from rheumatoid arthritis (RA), suggesting a role in the control of inflammation (Miagkov et al.,1998).The -94del ATTG association with Ulcerative Collits (UC) was replicated in a second set of

258 unrelated, non-Jewish UC cases and 653 new, non-Jewish controls (P=0.021). Nuclear proteins from normal human colon tissue and colonic cell lines, but not ileal tissue, showed significant binding to -94ins ATTG but not to -94delATTG containing oligonucleotides. NFKB1 promoter/exon 1 luciferase reporter plasmid constructs containing the -94 del ATTG allele and transfected into either HeLa or HT-29 cell lines showed less promoter activity than comparable constructs containing the -94 ins ATTG allele (Karban et al., 2004).Also, NFKB1-94ATTGins/del polymorphism had an increased risk of rheumatoid arthritis(RA) among Spain population (López et al., 2012).The study of Yalcin and his colleges provided evidence that the -94 ins/del ATTG promoter polymorphism of NFKB1 have functional consequences in Behçet's Disease (BD) (Yalcin et al., 2008).It was demonstrated that the frequencies of the del/del (DD) genotype and del (D) allele were significantly higher in coronary artery disease (CAD) Chinese patients than in controls. CAD patients carrying mutant DD genotype had worse stenosis of diseased coronary arteries compared to those carrying ins/ins (II) or ins/del (ID) genotype. So, it can be concluded that mutant DD genotype of NFKB1 gene was associated with the risk and severity of CAD (Luo et al., 2017).also, it was indicated that NFKB1-94 ins/del ATTG polymorphism may play a role in CAD susceptibility in Chinese Uygur population and was functionally associated with IL-6 expression, suggesting a mechanistic link between NFKB1-94 ins/del ATTG polymorphism and CAD susceptibility (Lai et al., 2015).By genotyping the Graves Disease (GD) Turkish patients from the point of NFKB1-94ins/del ATTG, it has been noticed that ins/del genotype was a risk factor for Graves Disease (GD). But by genotyping these GD patients from the point of NFKBIA 3'UTR (rs696), there was no differences was reported (Niyazoglu, et al., 2014).

On the other hand, Other studies had shown negative association between nfkb1 and nfkb1a polymorphisms and autoimmune diseases. NFKB1 -94ins/del ATTG SNP (rs28362491) did not play a role in the development of rheumatoid arthritis(RA) and systemic lupus erythematosus(SLE) among Spain population (Orozco et al. 2005). No evidence was found for association of the –94ins/del ATTG NFKB1 polymorphism with ulcerative colitis among British population (Mirza MM, et al 2005). By analyzing the distribution of -94ins/del ATTG NFKB1 in 258 ulcerative colitis patients and 264 healthy controls from southern Spain by, a polymerase chain reaction-fluorescent method, it was found that the genotype and allele frequencies of -94ins/del ATTG did not significantly differ between patients and controls, as the frequency of the -94delATTG allele was almost identical in both groups (Oliver J ,et al 2005).No association was found between NFKBAI 2758 A>G and psoriatic arthritis in Newfoundland (Butt et al., 2005).No significant association between the -94ins/del ATTG NFKB1 polymorphism with Crohn's disease (CD) or ulcerative colitis(UC) in a population of German origin was detected (Glas ;et al 2006). The results of Martin and his colleges study did not support a role for -94ins/del ATTG NFKB1 promoter polymorphism in susceptibilityand clinical expression of Giant cell artheritis (GCA) in a Northwestern Spanish population (Martin , et al., 2006). There was no difference in A and a G allele frequency of NFKBIA gene between the control group and patients of autoimmune diabetes mellitus (Katarina et al., 2007).It was found that The NFKBAI A>G is not strong factor for crohn's disease (CD) in NewZealand (Hong J.2007). By evaluating the effect of a single polymorphism in the 3′ -UTR of NFKBIA on disease susceptibility and phenotype in Israeli Crohn's disease cohort , no association was found between NFKBIA genotype and CD susceptibility as the case–control frequencies were similar for both cohorts (E. Leshinsky-Silver et al; 2007).No association was found between NF-KB1A (3′ UTR A→G) and Graves disease among polish population (Kurylowicz et al., 2009)Also, in a meta-analysis study, no significant difference for NFkB1 was found in inflammatory bowel disease (IBD) patients (343 with Crohn's disease [CD] and 306 with ulcerative colitis [UC] (Latiano A, et al;2007). Also, Szamosi and his colleges found that the NFKBIA 3'UTR and NFKB1-94ins/del ATTG genotypes and allele frequencies were not significantly different among IBD (inflammatory bowel disease) and controls (Szamosi et al., 2009). Also, in a meta;-analysis study, no association of NFKBIA gene 2758A/G polymorphism with autoimmune and inflammatory diseases was detected (Guo-Long Zhang et al., 2010).A negative association of the allelic and genotype distribution of the NF-κB promoter polymorphism was reported with the susceptibility, clinical pattern and laboratory features of systemic sclerosis among Brazilians (Salim et al. ,2013). There was no considerable differences in the frequency of genotypes and alleles of the two variants (rs28362491 and rs696 in NFKB1 and NFKBIA genes) individually among patients with Hashimoto's Thyroiditis (HT) (Sultuybek ,2014). Comparing psoriasis vulgaris cases to controls regarding the frequencies of NF-κ B1-94 ins/del ATTG and NF-κB1A A>G polymorphic variants in Saudi Arabia showed no statistical significance (p>0.05) both in the recessive and dominant models. Genetic polymorphisms of NF-κB1-94 ins/del ATTG and NF-κBIA 2758 A>G were not associated with the susceptibility to psoriasis vulgaris in Saudi patients (Abdullateef et al., 2015).By analyzing the distribution of NFKB1 -94ins/del ATTG and NFKBIA 3'UTR A→G polymorphisms in 120 Hashimoto Thyroiditis(HT) patients and 190

healthy controls in Turkish population. Although, there was no statistical significant difference in distribution of the genotypes and alleles of NFKB1-94ins/del ATTG or NFKBIA 3'UTR A→G polymorphisms in patients and control subjects as single, ins/ins/GG combined genotype had protective effect on the disease when compared to ins/ins/AG combined genotype as combined genotypes of both polymorphisms (Koc A, et al. 2014).There was no significant difference in the distribution of genotypes (AA, AG or GG), and alleles (A, G) of NFKBIA3'UTR A/G polymorphism between CADChinese Uygur cases and controls between sexes (for total participants, males, and females, all P>0.05) (Lai et al., 2015). Genotype distributions of rs28362491 NFkB1SNPwere similar between rheumatoid arthritis (RA) patients and controls. Thus the rs28362491 NFkB1 polymorphism was not found to be associated with predis position to RA(Bogunia-Kubiket al., 2016).By analyzing both rs28362491 NfkB1 and rs696 NfkBI polymorphisms among Turkish patients with atherosclerosis , the data revealed no significant differences in the distribution of the genotype and alleles of rs28362491 ,whereas AA genotype of rs696 lead to a higher risk for atherosclerotic patients (Oner et al., 2017).

On the other hand, it was reported that the activation of NFKB is decreased in systemic lupus erythematosus (SLE) patients but not in rheumatoid arthritis(RA) patients (Wong et al., 1999). Also, in the study by Gao and his colleges, it was found a decreasing risk for systemic lupus erythematosus(SLE) in 224 SLE patients and 256 control subjects in Chinese population (Gao et al.,2012).

In a study conducted among Chinese psoriatic patients, only a marginal association was reported between the NF-κB1-94 ins/del ATTG Ins/Ins genotype and the increased risk of psoriasis vulgaris in the cases-subgroups of onset age <or=40, PASI >20, male patients and sporadic (non-familial) patients (Li et al.,2008).

In comparison to controls, it was found that the A allele and the AA genotype frequencies of the single nucleotide polymorphisms in the 3'-UTR were significantly increased only in patients with Crohn's disease (CD) (Klein et al., 2004).Also, in a study conducted among Turkish population with Behçet's Disease(BD), by examining both single and combined genotype analysis of NFKB1-94ins/del ATTG (rs28362491) and NFKBIA 3'UTR(rs696) polymorphisms, it was indicated that ins/ins and AA genotypes and ins/ins/AA combined genotype are strongly associated with enhanced risk of BD (Yenmis et al., 2015).-94 ATTG ins/ins polymorphism might be associated with increased risk of developing nephropathy in Asian Indian subjects with diabetes mellitus. This SNP may be considered as genetic markers for susceptibility to develop nephropathy in patients with T2DM (Gautam et al., 2017).

These wide variations in genetic associations might be due to genomic diversity in subjects of different ethnicities, nonetheless it can also arise from biased selection criteria and low power studies. However, we can safely come to the conclusion that NF-KB1(-94 ins/del ATTG) (rs28362491) and NF-KB1A(3' UTR A→G) (rs696) polymorphic rare alleles are associated with increased risk of psoriasis among Egyptian patients and can be considered as risk factors of psoriasis.

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Conflict of Interest: The authors state that this study is completely free from all issues related to interest conflict.

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