Genetic polymorphisms of *NFκB1 -94 del/ins ATTG, NFκB1A 2758 A>G* and *SUMO rs237025 G>A* in psoriasis

Abdullateef A. Alzolibani, [1] Ahmed Settin, [2] Ahmed Ali Ahmed, [2] Hisham Ismail, [3] Noor Elhefni, [3] Ahmad A. Al Robaee [1]

[1] Department of Dermatology, [2] Research Centre, [3] Department of Medicine, College of Medicine, Qassim University, Saudi Arabia

Abstract

Background: Nuclear factor-κB (*NF-κB*) and small ubiquitin-like modifier (*SUMO4*) are key transcription factors involved in the regulation of immune responses and apoptosis. The aim of this study is to test for the association of *NF-κB and SUMO* gene polymorphisms with the susceptibility and severity of psoriasis among Saudi cases.

Subjects and Methods: This is a case controlled study including 85 Saudi psoriasis patients in addition to 92 matched healthy unrelated controls from the same locality. For all participants, DNA was analyzed by PCR for characterization of *NF-κB1 -94 del/ins ATTG, NF-κB IA 2758 A>G and SUMO rs237025 G>A* gene polymorphisms.

Results: Compared to controls, psoriasis patients showed a non-significant difference for all frequencies of genotypes and alleles of *NF-κB1 ins/del, NF-κB1A A>G and SUMO4 G>A polymorphisms (p>0.05)*. However, cases with the plaque type had significantly higher frequency of the *SUMO4 A allele* carriage *(GA+AA* genoytpes) than the guttate type (78.6% vs. 21.4%, p=0.02). The PASI score was also significantly higher among cases with the *NF-κB1A AA* genotype than other cases (*p*=0.00).

Conclusion: Genetic polymorphisms of NF-*κB1-94 ins/del ATTG, NF-κB IA 2758 A>G* and *SUMO4 rs237025 G>A* were not associated with the susceptibility to psoriasis vulgaris in Saudi patients. However, it might be associated with the expressivity of the disease in terms of its clinical type and severity.

Keywords: Psoriasis; Gene polymorphism; Psoriasis; *NF-κB*; *SUMO4*.

Correspondence:

Abdullateef A. Alzolibani, MD.
Department of Dermatology
College of Medicine
Qassim University
P.O. Box 30109, Buraidah 51477
Saudi Arabia
Tel.: +966-505319854
E-mail:azolibani@yahoo.com

Introduction

Psoriasis vulgaris is a common chronic inflammatory skin disease characterized by red scaly plaques with various degrees of severity. [1] The pathogenesis of psoriasis has been speculated to be due to factors originating in the skin, immune system or in the human genome. [2-4] The immune basis of psoriasis was manifested by the presence of the activated type 1 T cells (Th1) and their cytokines in psoriatic lesions. [5-8] 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. [9, 10] Thus, *NFκB* activation might induce resistance to apoptosis of peripheral blood mononuclear cells in patients with autoimmune diseases. [11] *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.* [5-8, 12-14] *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. [15] *NFκB 1* maps to chromosome 4q23–q24 and consists of 24 exons, [16, 17] and its inhibitory gene *NFκBIA* (encoding for IkB) is located on chromosome 14q13 and is including six exons. **[18.19]** Genetic studies have identified single nucleotide polymorphisms (SNPs) in *NFκB1* and *NFκBIA.* [20, 21] Recently, a common insertion/deletion (-94 insertion/deletion *ATTG rs28362491*) polymorphism in the *NFκB1* promoter region and a 39 –untranslated region (*39UTR*) polymorphism *2758 A>G (rs696*) in *NFκBIA* were observed to be significantly correlated with inflammatory bowel disease [22, 23] and cancers. [24, 25] On the other hand, *SUMO* family (*SUMO*1, 2, 3 and 4) was found to act as a negative regulator of *NF-κB* through the inhibition of *IκBα* degradation. [26, 27] The SNP *rs237025 A>G* in *SUMO*4 gene (methionine/valine, M55V) was shown to enhance *NF-κB* transcriptional activity and some its dependent genes. [28, 29]

Previous studies have verified that this polymorphism was strongly associated with type1 diabetes, [30] rheumatoid arthritis (RA), [31, 32] systemic lupus erythematosus (SLE), [33] Behcet's disease [34, 35] and Vogt–Koyanagi–Harada syndrome (VKH). [36] Therefore, it was also speculated to be associated with psoriasis. [37- 42]

This study is aiming to test for the association between polymorphisms in *NF-κB1, NFκB IA* and the *SUMO4* with psoriasis vulgaris susceptibility and clinical pattern among Saudi patients.

Subjects and methods

Eighty five Saudi psoriasis patients were enrolled into the study. They included 45 males and 40 females with a mean (± SD) age of onset of the disease of 23.6 (±11.4) years. Controls were in the form of 47 males and 45 females of a mean (± SD) age of 26 (±11.3) years. Cases were recruited from the Dermatology Clinic affiliated to Qassim University, Saudi Arabia. All the patients were diagnosed as typical cases of psoriasis by a consultant dermatologist. For all patients, data related to their age, sex, age of onset, family history of psoriasis, consanguinity pattern, clinical presentation in terms of the area involved and severity index (PASI) score were recorded. The controls were selected from healthy blood donors with no past or family history of immune or dermatologic disorders. The work started after obtaining an authorized approval from the local health authorities as well as an informed consent from all participants.

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 59-CTGGAGCCGGTAGGGAAG-39 (reverse). PCR was run at 94°C for 3 min followed by 30 cycles of 94°C for 30 s, 56°C for 30 s, and 72°C for 60 s with a final extension at 72°C for 10 min. The PCR products (281/285 bp in size) were digested with PfIMI (Fermentas, Vilnius, Lithuania) at 37°C overnight followed by 2% agarose gel electrophoresis. [43] For determination of the *NFκB IA G/A* substitution in 3' untranslated region (rs696) polymorphism, the SNP containing fragment was amplified using the following primers: *5'-*

GGCTGAAAGAACATGGACTTG-3' (forward) and 5'- *GTACACCATTTACAGGAGGG -39* (reverse). The PCR was run at 94°C for 5 min followed by 32 cycles of 94°C for 30 s, 54.3°C for 45 s and 72°C for 60 s with a final extension at 72°C for 10 min. The amplified fragments were digested with HaeIII (Fermentas, Vilnius, Lithuania) overnight at 37°C followed by 2% agarose gel electrophoresis. [43] On the other hand for characterization of the *SUMO rs237025 G>A* gene polymorphism was carried out through the real time PCR using a readymade light mix prepared by TibMolBiol company (Berlin, Germany). This method is actually a modification of the RFLP- PCR that was performed using primers: *5'-ATT GTG AAC CAC. GGG GAT TGT TA-3'; 5'-CAGCGTTCTGGAGTAAAGAAG-3'* and restriction enzyme MseI. [34, 36]

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.

Results

Comparing cases to controls regarding the frequencies of their *NF-κ B1-94 ins/del ATTG*, *NF-κB1A A>G* and *SUMO4 G>A* polymorphic variants (Table 1) showed no statistical significance (p>0.*05*) both in the recessive and dominant models. Although statistically non-significant (p>0.05), cases had higher frequencies of certain genotypes compared to controls as *SUMO4 GG* genotype *(25% vs. 19.6%), NF-κ B1 ins/del (48.8% vs. 41.3%) and NF-κB1A GG* genotype *(*29.8*% vs.* 23.8*%).* Both cases and controls were conforming to the Hardy-Weinberg equilibrium manifested by of a non-significant difference (p>0.05) between the observed and expected genotype frequencies of all three studied polymorphisms (Table 1). Comparison of the genotype frequencies among cases-subgroups related to their age of onset, gender, consanguinity, family history, PASI score and type of lesion is shown in Table 2. All subgroups showed a non-significant difference (*p*>0.05) in their genotypic frequencies except for cases with the plaque type that showed significantly increased frequency of *SUMO4* A allele carriage (*GA+AA* genotypes) than cases with the guttate type that showed a higher frequency of the GG genotype (*p*=0.02). The PASI score was also found significantly higher among cases with *NF-κB1A AA* genotype (*p*=0.00).

Table 1. Polymorphism of *NF-κ B1-94 ins/del ATTG,* NF-*κB1A A>G* and *SUMO4 rs 237025 G>A* among cases of psoriasis compared to controls

Genotypes	Cases n (%)	Controls n (%)	*p*	*OR (95% CI)*
NF-κ B1-94 ins/del				
ins/ins	30 (35.7)	33 (41.2)	Ref	
ins/del	41 (48.8)	33 (41.3)	*0.46*	*1.4(0.7-2.7)*
del/del	13 (15.5)	14 (17.5)	*0.85*	*1.0(0.4-2.5)*
ins/del+ del/del	54 (64.3)	47 (58.8)	*0.57*	*1.3 (0.7-2.4)*
ins allele	*101(60.1)*	*99 (61.9)*	Ref	
del allele	*67(39.9)*	*61(38.1)*	*0.83*	*1.1(0.7-1.7)*
HWE	*χ2=0.03, p>0.05*	*χ2=1.3, p>0.05*		
NF-κB1A A>G				
AA	7 (8.3)	12 (15.0)	Ref	

AG	52 (61.9)	49 (61.2)	0.36	*1.8(0.7-5.0)*
GG	25 (29.8)	19 (23.8)	*0.24*	*2.3(0.8-6.7)*
AG+GG	77 (91.7)	68 (85.0)	*0.89*	*1.2(0.5-2.6)*
A allele	*66 (39.3)*	*73(45.6)*	Ref	
G allele	*102 (60.7)*	*87(54.4)*	*0.29*	*1.3 (0.8-2.0)*
HWE	*χ2=0.03, p>0.05*	*χ2=1.3, p>0.05*		
SUMO4 rs 237025 G>A				
GG	21 (25.0)	18 (19.6)	Ref	
GA	45 (53.6)	46 (50.0)	*0.73*	*0.84 (0.4-1.8)*
AA	18 (21.4)	28 (30.4)	*0.26*	*0.6(0.2-1.3)*
GA+AA	63(75.0)	74 (80.4)	*0.47*	*0.7(0.4-1.5)*
G allele	87 (51.8)	82 (44.6)	Ref	
A allele	81 (48.2)	102 (55.4)	*0.21*	*0.75(0.5-1.1)*
HWE	*χ2=0.40, p>0.05*	*χ2=0.01, p>0.05*		

HWE: Hardy-Weinberg equilibrium, OR(95%CI): odds ratio (95% confidence interval)

Discussion

This study is an attempt to shed a light on the genetic background of psoriasis among Saudi subjects which is obviously supported by the finding of a positive consanguinity and family history of the disease among about 1/5 of patients. To the best of our knowledge, this is the first study testing for the association between polymorphisms in *NF-κB1, NF-κB1A* and the *SUMO4* genes with psoriasis vulgaris susceptibility and clinical pattern among Saudi patients. Although statistically non-significant, cases had higher frequencies of certain genotypes compared to controls as *NF-κ B1 ins/del, NF-κB1A GG and SUMO4 GG* genotypes. This in fact might attract our attention to the potential effect of the relatively small sample size of the study on the power and significance of results. In this respect we would recommend undertaking another large scale study testing for these genetic polymorphisms along with their expression pattern in the psoriatic skin cells. Regarding the clinical pattern and severity of psoriasis, we have observed that *NF-κB1A GG* was associated with higher PASI score while *SUMO4 AA+AG* genotypes were more associated with the plaque type.

The majority of Saudi psoriasis cases were carriers of the insertion allele while about 15% were homozygous for the deletion allele of *NF-κ B1* gene which was found to result in relatively decreased *NF-κB1* transcript levels and hence decreased p50/p105 *NF-κB1* protein production. [22] In this respect, we speculate that the balance between the expressions of the 3 genes might be responsible for the increased expression of *NF-κB* in the psoriatic lesions as was previously reported. [44] Similarly, in a study conducted among Chinese psoriatic patients ***Li et al.,*** reported only a marginal association 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. [45] On the other hand, **Butt *et al*.,** did not observe an association between *NF-κB1-94 ins/del ATTG* promoter polymorphism in patient with psoriatic arthritis (PsA) from Newfoundland. [46] Comparing the distribution of *NF-κB1 -94del/ins ATTG* polymorphisms among Saudi controls to the controls in other studies, we could observe some variations related to ethnicity. The frequencies of the del/del, del/ins, and ins/ins genotypes of the *NF-κB1* among Saudi controls were 17.5%, 41.3% and 41.2% respectively that was somewhat similar to the frequencies among German (15.6%, 45.9%, and 38.4%, respectively); but different to the frequencies among Han Chinese (18.5%, 51.9%, and 29.6%, respectively) and other Chines (17%, 58%, and 24%, respectively). [43, 47, 48] **Salim *et al*.** have also recently reported a negative association of the allelic and genotype distribution of the *NF-κB* promoter polymorphism with the susceptibility, clinical pattern and laboratory features of systemic sclerosis among Brazilians. [49] However,

several studies have reported that the *NF-κB1* and *NF-κBIA* polymorphisms is related to the development of inflammatory and other diseases including ulcerative colitis, Graves' disease, and diabetes mellitus, and susceptibility to tumors including melanoma, bladder cancer and colorectal cancer in different ethnic groups. [22, 50-54]

Table 2. Demographic and clinical data of studied cases of psoriasis related to their genotypic polymorphisms

	NF-κ B1-94 ins/del			***NF-κB1A A>G***			***SUMO4 G>A***		
	II %	***ID +DD*** %	***P***	***AA*** %	***AG +GG*** %	***p***	***GG*** %	***GA +AA*** %	***P***
Gender									
Male (n=45)	38.6	61.4	*0.98*	12.0	88.0	*0.87*	22.3	77.7	*0.99*
Female (n=38)	38.8	61.3		11.3	88.8		22.2	77.8	
Type									
Plaque (n=70)	32.9	67.1	*0.19*	8.6	91.4	*0.15*	21.4	78.6	*0.02**
Guttate (n=9)	44.4	55.6		0.0	100.0		66.7	33.3	
Family History									
Negative (n=68)	36.2	63.8	*0.97*	10.1	89.9	*0.21*	24.6	75.4	*0.76*
Positive (n=14)	35.7	64.3		.0	100.0		28.6	71.4	
Consanguinity									
Negative (n=64)	32.0	68.0	*0.70*	10.0	90.0	*0.95*	26.0	74.0	*0.67*
Positive (n=19)	36.8	63.2		10.5	89.5		21.1	78.9	
PASI Score									
Mean ±SD	5.9±5.1	4.4±3.1	*0.27*	11.87±3.69	4.3±3.2	*0.00**	5.31±3.02	4.7±4.1	*0.66*
Age of onset									
Mean ±SD	23.6±11.9	24.0±10.9	*0.87*	25.71±7.95	23.7±11.5	*0.66*	23.7±10.3	23.9±11.6	*0.93*

Similar to our finding, **Li *et al*.,** did not detect an association of the *SUMO4 rs237025* ***A>G*** polymorphism with the susceptibility and clinical pattern of psoriasis vulgaris among Chinese patients. [45] In contrast, another study has confirmed the association between this *SNP* of *SUMO* polymorphism and psoriatic patients in USA. [41] A meta-analysis study has demonstrated the association of *SUMO4* M55V polymorphism with other autoimmune and inflammatory diseases, especially in Asian population. [55] Researchers have also reported a weak association of *SUMO4* with type 1 diabetes that was noted in the Caucasian populations, [56-58] while a strong association was found with type1 diabetes in Asian populations. [30, 59] An association was also reported between the *SUMO4* polymorphism with RA and autoimmune thyroid disease (Graves' disease and Hashimoto disease) in the Japanese population; [31] and with BD in Chinese patients; [34] although this association was negative with SLE, [33] RA, [60] BD in Korean patients [35] and with Graves' disease [61] in English patients. **Hou *et al*.,** have also reported a non-association of the *SUMO4* polymorphisms with Vogt-Koyanagi-Harada (VKH) syndrome among Chinese Han population. [36]

In conclusion, Genetic polymorphisms of *SUMO4 rs237025 G>A, NF-κB1-94 ins/del ATTG* and *NF-κB IA (2758 A>G)* were not associated with the susceptibility of psoriasis vulgaris in Saudi patients. However, they might

have an association with the clinical type and severity of the disease.

Acknowledgement

Authors are grateful to King AbdulAziz City for Science and Technology for totally sponsoring this scientific work. Authors also show their appreciation and gratitude for the staff of The Ministry of Health, BuraydahCentral Health Hospital, Al-Qassim, KSA for their help and cooperation.

References:

1. Bowcock AM, Cookson WO. The genetics of psoriasis, psoriatic arthritis and atopic dermatitis. *Hum Mol Genet*. 2004 Apr 1; 13 Spec No 1:R43-55.
2. Peters BP, Weismann FG, Gill MA. Pathophysiology and treatment of psoriasis. *Am J Health-Sys Pharm*. 2000; 57: 645–659.
3. Weedon D. Skin pathology, 2nd edn. Churchill Livingstone London NF- kappa B and I kappa B-gamma: implications for NF-kappa B-mediated signal transduction. *Genomics.* 2002; 30:493–505.
4. Woodley DT, Kim GH. Potential new insight into the pathogenesis of psoriasis. *Arch Dermatol*. 2009 Jun; 145(6):713-4.
5. Galadari I, Sharif MO, Galadari H. Psoriasis: a fresh look. *Clin Dermatol*. 2005 Sep-Oct; 23(5):491-502.
6. Landgren E, Bråbäck L, Hedlin G, Hjern A, Rasmussen F. Psoriasis in Swedish conscripts: time trend and association with T-helper 2-mediated disorders. *Br J Dermatol.* 2006 Feb; 154(2):332-6.
7. Lee MR, Cooper AJ. Immunopathogenesis of psoriasis. *Australas J Dermatol* .2006; 47:151–159.
8. Pérez-Lorenzo R, Núñez-Oreza LA, Garma-Quen PM, López-Pacheco E, Bricaire-Bricaire G. Peripheral blood mononuclear cells proliferation and Th1/Th2 cytokine production in response to streptococcal M protein in psoriatic patients. *Int J Dermatol*. 2006 May; 45(5):547-53.
9. Maldonado V, Meléndez-Zajgla J, Ortega A. Modulation of NF-kappa B, and Bcl-2 in apoptosis induced by cisplatin in HeLa cells. *Mutat Res*. 1997 Nov 19; 381(1):67-75.
10. Mayo MW, Wang CY, Cogswell PC, Rogers-Graham KS, Lowe SW, Der CJ, Baldwin AS Jr. Requirement of NF-kappaB activation to suppress p53-independent apoptosis induced by oncogenic Ras. *Science.* 1997 Dec 5; 278(5344):1812-5.
11. Todaro M, Zerilli M, Triolo G, Iovino F, Patti M, Accardo-Palumbo A, di Gaudio F, Turco MC, Petrella A, de Maria R, Stassi G. NF-kappaB protects Behçet's disease T cells against CD95-induced apoptosis up-regulating antiapoptotic proteins. *Arthritis Rheum*. 2005 Jul; 52(7):2179-91.
12. Johansen C, Flindt E, Kragballe K, Henningsen J, Westergaard M, Kristiansen K, Iversen L Inverse regulation of the nuclear factor-kappaB binding to the p53 and interleukin-8 kappaB response elements in lesional psoriatic skin. *J Invest Dermatol*. 2005 Jun; 124(6):1284-92.
13. Ouyang W, Ma Q, Li J, Zhang D, Liu ZG, Rustgi AK, Huang C. Cyclin D1 induction through I kappa B kinase beta/nuclear factor-kappaB pathway is responsible for arsenite-induced increased cell cycle G1-S phase transition in human keratinocytes. *Cancer Res*. 2005 Oct 15; 65(20):9287-93.
14. Shaker OG, Moustafa W, Essmat S, Abdel-Halim M, El-Komy M. The role of interleukin-12 in the pathogenesis of psoriasis. ClinBiochem. 2006; 39:119–125.
15. Chen F, Castranova V, Shi X, Demers LM. New insights into the role of nuclear factor-kappaB, a ubiquitous transcription factor in the initiation of diseases. *Clin Chem*. 1999 Jan; 45(1):7-17.
16. Mathew S, Murty VV, Dalla-Favera R, Chaganti RS. Chromosomal localization of genes encoding the transcription factors, c-rel, NF-kappa Bp50, NF-kappa Bp65, and lyt-10 by fluorescence in situ hybridization. *Oncogene*. 1993 Jan; 8(1):191-3.
17. Héron E, Deloukas P, van Loon AP. The complete exon-intron structure of the 156-kb human gene NFKB 1, which encodes the p105 and p50 proteins of transcription factors NF-kappa B and I kappa B-gamma: implications for NF-kappa B-mediated signal transduction. *Genomics*. 1995 Dec 10; 30(3):493-505.
18. Le Beau MM, Ito C, Cogswell P, Espinosa R 3rd, Fernald AA, Baldwin AS Jr. Chromosomal localization of the genes

encoding the p50/p105 subunits of NF-kappa B (NFKB 2) and the I kappa B/MAD-3 (NFKB I) inhibitor of NF-kappa B to 4q24 and 14q13, respectively. *Genomics*. 1992; 14:529–531.

19. Duerr RH, Barmada MM, Zhang L, Pfützer R, Weeks DE. High-density genome scan in Crohn disease shows confirmed linkage to chromosome 14q11-12. *Am J Hum Genet.* 2000 Jun; 66(6):1857-62.
20. Ota N, Nakajima T, Shirai Y, Emi M. Isolation and radiation hybrid mapping of a highly polymorphic CA repeat sequence at the human nuclear factor kappa-beta subunit 1 (NFKB 1) locus. *J Hum Genet*. 1999; 44(2):129-30.
21. Glavac D, Ravnik-Glavac M, O'Brien SJ, Dean M. Polymorphisms in the 3'vuntranslated region of the I kappa B/MAD-3 (NFKBI) gene located on chromosome 14. *Hum Genet*. 1994 Jun; 93(6):694-6.
22. Karban AS, Okazaki T, Panhuysen CI, Gallegos T, Potter JJ, Bailey-Wilson JE, Silverberg MS, Duerr RH, Cho JH, Gregersen PK, Wu Y, Achkar JP, Dassopoulos T, Mezey E, Bayless TM, Nouvet FJ, Brant SR. Functional annotation of a novel NFKB 1 promoter polymorphism that increases risk for ulcerative colitis. *Hum Mol Genet*. 2004 Jan 1; 13(1):35-45.
23. Klein W, Tromm A, Folwaczny C, Hagedorn M, Duerig N, Epplen JT, Schmiegel WH, Griga T. A polymorphism of the NFKB IA gene is associated with Crohn's disease patients lacking a predisposing allele of the CARD15 gene. *Int J Colorectal Dis*. 2004 Mar; 19(2):153-6.
24. Campbell KJ, Perkins ND. Regulation of NF-kappaB function. *Biochem Soc Symp*. 2006 ;(73):165-80.
25. Zhou B, Rao L, Li Y, Gao L, Wang Y, Chen Y, Xue H, Song Y, Peng Y, Liao M, Zhang L. A functional insertion/deletion polymorphism in the promoter region of NFKB 1 gene increases susceptibility for nasopharyngeal carcinoma. *Cancer Lett*. 2009 Mar 8; 275(1):72-6. [26] Karin M, Ben-Neriah Y. Phosphorylation meets ubiquitination: the control of NF-[kappa] B activity. *Annu Rev Immunol*. 2000; 18:621-63.
26. Victor FC, Gottlieb AB, Menter A. Changing paradigms in dermatology: tumor necrosis factor alpha (TNF-alpha) blockade in psoriasis and psoriatic arthritis. *Clin Dermatol*. 2003 Sep-Oct; 21(5):392-7.
27. Bohren KM, Nadkarni V, Song JH, Gabbay KH, Owerbach D. A M55V polymorphism in a novel *SUMO* gene (*SUMO*-4) differentially activates heat shock transcription factors and is associated with susceptibility to typeI diabetes mellitus. *J Biol Chem*2004; 279:27233–8.
28. Guo D, Li M, Zhang Y, Yang P, Eckenrode S, Hopkins D, Zheng W, Purohit S, Podolsky RH, Muir A, Wang J, Dong Z, Brusko T, Atkinson M, Pozzilli P, Zeidler A, Raffel LJ, Jacob CO, Park Y, Serrano-Rios M, Larrad MT, Zhang Z, Garchon HJ, Bach JF, Rotter JI, She JX, Wang CY. A functional variant of *SUMO*4, a new I kappa B alpha modifier, is associated with type 1 diabetes. *Nat Genet*. 2004 Aug; 36(8):837-41.
29. Noso S, Ikegami H, Fujisawa T, Kawabata Y, Asano K, Hiromine Y, Tsurumaru M, Sugihara S, Lee I, Kawasaki E, Awata T, Ogihara T. Genetic heterogeneity in association of the *SUMO*4 M55V variant with susceptibility to type 1 diabetes. *Diabetes* 2005; 54:3582-6.
30. Tsurumaru M, Kawasaki E, Ida H, Migita K, Moriuchi A, Fukushima K, Fukushima T, Abiru N, Yamasaki H, Noso S, Ikegami H, Awata T, Sasaki H, Eguchi K. Evidence for the role of small ubiquitin-like modifier 4 as a general autoimmunity locus in the Japanese population. J *Clin Endocrinol Metab* 2006; 91:3138-43.
31. Fakhfakh K. E, Bendhifallah I, Zakraoui L, Hamzaoui K. Association of small ubiquitin-like modifier 4 gene polymorphisms with rheumatoid arthritis in a Tunisian population. *Clin Exp Rheumatol.* 2011 Jul-Aug; 29(4):751.
32. Orozco G, Sánchez E, Gómez LM, González-Gay MA, López-Nevot MA, Torres B, Ortego-Centeno N, Jiménez-Alonso J, de Ramón E, Sánchez Román J, Anaya JM, Sturfelt G, Gunnarsson I, Svennungsson E, Alarcón-Riquelme M,

González-Escribano MF, Martín J. Study of the role of functional variants of SLC22A4, RUNX1 and *SUMO*4 in systemic lupus erythematosus. *Ann Rheum Dis*. 2006 Jun; 65(6):791-5.
33. Hou S, Yang P, Du L, Zhou H, Lin X, Liu X, Kijlstra A. *SUMO*4 gene polymorphisms in Chinese Han patients with Behcet's disease. *ClinImmunol*. 2008 Oct; 129(1):170-5.
34. Park G, Kim HS, Choe JY, Kim SK. *SUMO*4 C438T polymorphism is associated with papulopustular skin lesion in Korean patients with Behçet's disease. *Rheumatol Int*. 2012 Oct; 32(10):3031-7.
35. Hou S, Yang P, Du L, Zhou H, Lin X, Liu X, Kijlstra A. Small ubiquitin-like modifier 4 (*SUMO*4) polymorphisms and Vogt-Koyanagi-Harada (VKH) syndrome in the Chinese Han population. *Mol Vis*. 2008; 14:2597-603.
36. Bos JD, de Rie MA, Teunissen MB, Piskin G. Psoriasis: dysregulation of innate immunity. *Br J Dermatol*. 2005 Jun; 152(6):1098-107.
37. Bos JD. Psoriasis, innate immunity, and gene pools. *J Am Acad Dermatol*. 2007 Mar; 56(3):468-71.
38. Devendra D, Liu E, Eisenbarth GS. Type 1 diabetes: recent developments. *BMJ*. 2004 Mar 27; 328(7442):750-4.
39. Lambert AP, Gillespie KM, Thomson G, Cordell HJ, Todd JA, Gale EA, Bingley PJ. Absolute risk of childhood-onset type 1 diabetes defined by human leukocyte antigen class II genotype: a population-based study in the United Kingdom. *J Clin Endocrinol Metab*. 2004 Aug; 89(8):4037-43.
40. Liu Y, Krueger JG, Bowcock AM. Psoriasis: genetic associations and immune system changes. *Genes Immun,* 2007; 8:1–12.
41. Yoon JW, Jun HS. Autoimmune destruction of pancreatic beta cells. *Am J Ther*. 2005 Nov-Dec; 12(6):580-91.
42. Song S, Chen D, Lu J, Liao J, Luo Y, Yang Z, Fu X, Fan X, Wei Y, Yang L, Wang L, Wang J. NFκB1 and *NFκBIA* polymorphisms are associated with increased risk for sporadic colorectal cancer in a southern Chinese population. *PloS One*.2011; 6(6):e21726.
43. Danning CL, Illei GG, Hitchon C, Greer MR, Boumpas DT, McInnes IB. Macrophage-derived cytokine and nuclear factor kappaB p65 expression in synovial membrane and skin of patients with psoriatic arthritis. *Arthritis Rheum*. 2000 Jun; 43(6):1244-56.
44. Li H, Gao L, Shen Z, Li CY, Li K, Li M, Lv YJ, Li CX, Gao TW, Liu YF. Association study of NFKB 1 and *SUMO*4 polymorphisms in Chinese patients with psoriasis vulgaris. *Arch Dermatol Res*. 2008 Sep; 300(8):425-33.
45. Butt C, Sun S, Peddle L, Greenwood C, Hamilton S, Gladman D, Rahman P. Association of nuclear factor-kappaB in psoriatic arthritis. *Rheumatol*. 2005 Sep; 32(9):1742-4.
46. Riemann K, Becker L, Struwe H, Nückel H, Dührsen U, Alakus H, Winde G, Neuhäuser M, Rübben H, Schmitz KJ, Wohlschlaeger J, Schmid KW, Siffert W. No association of the NFKB 1 insertion/deletion promoter polymorphism with survival in colorectal and renal cell carcinoma as well as disease progression in B-cell chronic lymphocytic leukemia. *Pharmacogenet Genomics*. 2006 Nov; 16(11):783-8.
47. Sun XF, Zhang H. NFKB and NFKB I polymorphisms in relation to susceptibility of tumour and other diseases. Histol Histopathol, 2007; 22: 1387–1398.
48. Salim PH, Jobim M, Bredemeier M, Chies JA, Brenol JC, Jobim LF, Xavier RM. Interleukin-10 gene promoter and NFKB 1 promoter insertion/deletion polymorphisms in systemic sclerosis. *Scand J Immunol*. 2013 Feb; 77(2):162-8.
49. Bu H, Rosdahl I, Sun XF, Zhang H. Importance of polymorphisms in NfkappaB1and NF-kappa B Ialpha genes for melanoma risk, clinicopathological features and tumor progression in Swedish melanoma patients. *J Cancer Res ClinOncol*, 2007; 133: 859–866.
50. Gao J, Pfeifer D, He LJ, Qiao F, Zhang Z, Arbman G, Wang ZL, Jia CR, Carstensen J, Sun XF. Association of NFKB IA polymorphism with colorectal cancer risk and prognosis in Swedish and Chinese populations. *Scand J Gastroenterol*. 2007 Mar; 42(3):345-50.

51. Kurylowicz A, Miskiewicz P, Bar-AndziakE, Nauman J, Bednarczuk T. Association of polymorphism in genes encoding kappaB inhibitors (IkappaB) with susceptibility to and phenotype of Graves' disease: a case-control study. *Thyroid Res*, 2009; 2: 10.
52. Miller MR, Zhang W, Sibbel SP, Langefeld CD, Bowden DW, Haffner SM, Bergman RN, Norris JM, Fingerlin TE. Variant in the 3' region of the IkappaBalpha gene associated with insulin resistance in Hispanic Americans: The IRAS Family Study. *Obesity (Silver Spring).* 2010 Mar; 18(3):555-62.
53. Riemann K, Becker L, Struwe H, Rübben H, Eisenhardt A, Siffert W. Insertion/deletion polymorphism in the promoter of NFKB 1 as a potential molecular marker for the risk of recurrence in superficial bladder cancer. *Int J Clin Pharmacol Ther*. 2007 Aug; 45(8):423-30.
54. Zou YF, Feng XL, Tao JH, Zhu JM, Pan FM, Su H, Ye DQ. Association of *SUMO*4 M55V polymorphism with susceptibility to autoimmune and inflammatory diseases: a meta-analysis. *Int J Immunogenet*. 2010 Oct; 37(5):345-54.
55. Qu H, Bharaj B, Liu XQ, Curtis JA, Newhook LA, Paterson AD, Hudson TJ, Polychronakos C. Assessing the validity of the association between the *SUMO*4M55Vvariant and risk of type 1diabetes. *NatGene*t, 2005; 37:111–112; author reply 112–113.
56. Smyth DJ, Howson JM, Lowe CE, Walker NM, Lam AC, Nutland S, Hutch-ings J, Tuomilehto-Wolf E, Tuomilehto J, Guja C, Ionescu-Tirgoviste C, Undlien DE, Ronningen KS, Savage D, Dunger DB, Twells RC, McArdle WL, Strachan DP, Todd JA. Assessing the validity of the association between the *SUMO*4 M55V variant and risk of type 1 diabetes. *Nat Genet*, 2005; 37:110–111; author reply 112–113.
57. Wang CY, Podolsky R, She JX. Genetic and functional evidence sup-porting *SUMO*4 as a type 1 diabetes susceptibility gene. Ann NY *Acad Sci,* 2006; 1079:257–267.
58. Park Y, Park S, Kang J, Yang S, Kim D. Assessing the validity of the association between the *SUMO*4 M55V variant and risk of type 1 diabetes. *Nat Genet*, 2005; 37:112; author reply 112–113.
59. Gibbons LJ, Thomson W, Zeggini E, Worthington J, Barton A, Eyre S, Donn R, Hinks A. The type 1 diabetes susceptibility gene *SUMO*4 at IDDM5 is not associated with susceptibility to rheumatoid arthritis or juvenile idiopathic arthritis. *Rheumatology* (Oxford). 2005 Nov; 44(11):1390-3. .
60. Jennings CE, Owen CJ, Wilson V, Pearce SH. No association of the codon 55 methionine to valine polymorphism in the *SUMO*4 gene with Graves' disease. *Clin Endocrinol* (Oxf). 2005 Mar; 62(3):362-5.