TNFAIP3 and *TNIP1* polymorphisms confer psoriasis risk in South Indian Tamils

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ABSTRACT

Psoriasis is a chronic inflammatory skin disease with genetic and environmental factors having an important role in its aetiology. Several genome-wide association studies have reported the association of the genes of the TNFα signalling, tumour necrosis factor alpha-induced protein 3 (TNFAIP3), TNFAIP3-interacting protein 1 (TNIP1) with psoriasis in Western and Chinese populations. The aim of this study is to demonstrate whether the *TNFAIP3* and *TNIP1* genes contribute to the risk of psoriasis in the ethnically distinct South Indian population. 360 psoriatic subjects and 360 healthy controls were recruited in this case control study. *TNFAIP3* (rs610604) and *TNIP1* (rs17728338) polymorphisms were typed by using TaqMan 5 allele discrimination assay. The results demonstrated that the SNPs rs610604 and rs17728338 of the *TNFAIP3* and *TNIP1* genes, respectively, were associated with psoriasis in our population at both allelic and genotypic levels. Thus, our results suggest that *TNFAIP3* (rs610604) and *TNIP1* (rs17728338) polymorphisms confer increased risk of psoriasis and may play a vital role in its pathogenesis in our ethnic South Indian Tamils.

KEY WORDS: India.
Polymorphism, genetic.
Psoriasis.

Introduction

Psoriasis is a complex, inflammatory, immunologically mediated, multifactorial and hyper-proliferative skin disease with genetic and environmental factors having an important role in its aetiology, affecting about 1–3% of the population worldwide.[1] Psoriasis is found worldwide, though its prevalence differs widely among different ethnic descents, indicating inter-ethnic variations in psoriasis susceptibility. Linkage studies have identified the psoriasis susceptibility 1 locus (PSORS 1), closely linked to HLA-Cw6, within the major histocompatibility complex on chromosome 6q21 as major genetic predispositions to the development of psoriasis.[2] However, there are additional susceptibility loci, identified by several genome-wide association studies, suggesting that several biologically relevant non-HLA candidate genes also contribute to the development of psoriasis.[3,4] Recent genome-wide association studies reported significant associations of around 40 psoriasis susceptibility genes in different ethnicities.[3–6]

Of these, variants involved in tumour necrosis factor-α (TNFα) signalling, tumour necrosis factor-α induced protein 3 (TNFAIP3) and TNFAIP3-interacting protein 1 (TNIP1) were identified as risk factors of psoriasis in the Caucasian and Chinese populations.[5,7–11] *TNFAIP3*, a TNF-inducible gene, acts as a negative feedback inhibitor of TNF signalling.[12] *TNFAIP3* encodes A20, a TNFα inducible zinc-finger protein, acts at multiple steps in the nuclear factor-kappa light chain-enhancer of activated B cells (NF-κB) signalling pathway by inhibiting NF-κB activation and terminating NF-κB mediated responses.[13] A20 binds to A20-binding inhibitor of NF-κB (ABIN-1), a protein encoded by the *TNIP1* gene, and these proteins interact with each other and participate in the ubiquitin-mediated destruction of inhibitor of kappa B kinase gamma subunit/NF-κB essential modifier (IKKg/NEMO), thereby regulating a key nexus of NF-κB signalling.[14]

As many events in the immunological milieu of psoriatic skin such as maturation, activation and function of the macrophages and dendritic cells are NF-κB-dependent, genetic variation in *TNFAIP3* and *TNIP1* could influence the increased susceptibility to psoriasis. With the increasing evidence of the important role of the *TNFAIP3* and *TNIP1* genes in psoriasis susceptibility, through various genome-wide association studies performed on cohorts of Caucasians and Han Chinese descents, we were interested to investigate the influence of these genes on the psoriasis risk in our South Indian Tamil ethnic population.

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Materials and methods

Study subjects

Three hundred and sixty patients with psoriasis and psoriatic arthritis, who were diagnosed and classified according to International Psoriasis Council Consensus Classification of psoriasis vulgaris[15] and by Classification Criteria for Psoriatic Arthritis (CASPAR) criteria,[16] respectively, at the Department of Dermatology of Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry, India, were included in the study.

A total of 360 age and gender matched healthy individuals of Tamil ethnicity, without any skin and infectious diseases and without a family history of autoimmune or systemic

Table 1. Allele and genotypic frequencies of *TNFAIP3* and *TNIP1* genes in patients with psoriasis and controls.

Gene and SNP	Genotype/allele	Psoriasis cases (n=360)	Healthy controls (n=360)	P value	OR (95% CI)
TNFAIP3	TT *vs.* GG+GT	207	169	0.006	1.53 (1.14–2.05)
	GG	53	33	0.006	2.01 (1.24–3.25)
	GT	154	136	0.037	1.41 (1.03–1.94)
	TT	153	191		
	G	260	202	0.001	1.45 (1.16–1.81)
	T	460	518		
TNIP1	GG *vs.* AA+AG	168	131	0.007	1.53 (1.14–2.06)
	AA	34	16	0.004	2.54 (1.36–4.73)
	AG	134	115	0.050	1.39 (1.02–1.90)
	GG	192	229		
	A	202	147	0.001	1.52 (1.19–1.94)
	G	518	573		

diseases were recruited as healthy controls, in case:control ratio of 1:1 in this case-control immunogenetic study. The clinical characteristics including disease severity as assessed by psoriasis area severity index (PASI) scoring,[17] duration of psoriasis, past therapies, associated co-morbidities and the detailed family history were recorded.

The JIPMER Institute Ethics Committee (Human Studies) approved the study. The participants had the study procedure explained in detail and written informed consent was obtained from all of them. The study was performed according to the Declaration of Helsinki ethical principles for medical research involving human subjects.

Determination of genotype

Genomic DNA extraction from peripheral venous blood was performed by the standard phenol-chloroform method[18] and the DNA extracted was diluted to 100 ng/μl and was stored at –20°C. The single nucleotide polymorphisms (SNPs) rs610604 and rs17728338 in the *TNFAIP3* and *TNIP1* genes were genotyped using TaqMan 5'allele discrimination assay. Allele specific fluorogenic probes (customised and designed by Helini Biomolecules, India) amplified the target genes in a CFX96 Touch real-time polymerase chain reaction (PCR) detection system (Bio-Rad Laboratories, Berkeley, California). Homozygous wild, mutant and heterozygous mutant genotypes were distinguished based on the fluorescence emission from the corresponding fluorescent dyes (FAM and CAL GOLD 540). 30% of the randomly selected samples were replicated to ensure validation and to rule out technical or observational error.

Statistical analysis

Statistical analysis was performed by Graph Pad Instat 3 (Graph Pad Software Inc., San Diego, CA, USA). The observed allele frequencies in cases and controls were compared with expected frequencies to check for the Hardy-Weinberg equilibrium by χ^2 method. The frequency of genotypes and alleles were determined by the direct gene counting method. Within patient group, the frequency of genotypes and the alleles were correlated with subphenotypes such as clinical manifestations, family history and disease activity. Odds ratio (OR) and confidence intervals (CIs) were calculated by χ^2 test. To reduce the chances of obtaining type I errors when multiple pair wise tests were performed on a single set of data, Bonferroni correction was used. A two-sided P value <0.05 was considered as significant. However for multiple pair wise comparisons, $P<0.005$ was considered statistically significant.

Results

Study subjects

We recruited 292 male and 68 female subjects with psoriasis. Similarly, we recruited 288 male and 72 female healthy volunteers as controls. The average age of the patient group at the time of recruitment was 43.1±14.1 years, with a mean age of disease onset at 35.7±14.9 years. The mean disease activity score (PASI) observed in the patient group was 9.3±8.8, indicating an active disease at the time of enrollment.

Of the 360 psoriasis patients recruited, 338 were of chronic plaque type (93.9%), 11 patients were of guttate type (3.1%), five of pustular psoriasis (1.4%), six were of psoriatic erythroderma type (1.7%). 140 patients had psoriatic arthritis and 173 patients had abnormalities in nails such as pitting, distal onycholysis, subungual hyperkeratosis, longitudinal ridging, salmon patch and thickening of nails. Among the 173 patients who had nail abnormalities, 147 patients had pitting of nails. 58 patients had their first degree relatives affected with psoriasis, showing a strong family history of psoriasis.

The allele and genotype frequencies of *TNFAIP3* (rs610604) and *TNIP1* (rs17728338) for psoriasis patients versus controls are tabulated in Table 1.

Frequencies of the allele and genotypes of rs610604 are associated with psoriasis

The frequency of the minor allele G was 36% in psoriasis patients and 28% in healthy controls.

The comparison of allele distributions revealed that there was a significant association (P=0.001) of the G allele with the risk of psoriasis (OR [95% CI] = 1.45 [1.16–1.81]). The frequency of wild type (TT) genotype was 42.5% and 53.1% in patients and controls, respectively. The heterozygous combination GT was found in 154 psoriasis patients and in

136 controls with $P=0.037$ and OR (95% CI) 1.41 (1.03-1.94). The homozygous mutant (GG) genotype was found in 14.7% of patients and 9.2% of controls and the comparison of the genotype distributions showed a significant $P=0.006$ and OR (95% CI) 2.01 (1.24–3.25), thus showing an extremely significant association of *TNFAIP3* (rs610604) polymorphism with susceptibility to psoriasis. The dominant model genotype (GG+GT) had a frequency of 57.5% in patients and 46.9% in controls. In the dominant model genotype analysis, rs610604 was associated with the risk of psoriasis ($P=0.006$, OR=1.53; 95% CI –1.14–2.05).

When we performed genotype-phenotype analysis of rs610604 by comparing cases having a particular subphenotype with cases that did not have the subphenotype, we found that both the GT and GG+GT genotype had a significant difference between patients with family history of psoriasis compared to patients without the family history ($P=0.04$, OR=2.07 and $P=0.02$, OR=2.12, respectively). However, with a conservative estimate, we failed to observe statistically significant difference for family history with this SNP. We did not find any significant differences in the other subphenotypes of age of onset, gender, severity, nail involvement, psoriatic arthritis development, chronic plaque type, past history of systemic therapy between patients positive and those negative for a particular phenotype (Table 2).

Table 2. Influence of *TNFAIP3* polymorphism on the phenotypic profile of psoriasis.

S. No.	Heading	TNFAIP3	No. of positives	No. of negatives	*P* value*	OR	95% CI
1	Females	TT *vs.* GG+GT	40	167	0.91	1.07	0.63–1.83
		GG	8	45	0.75	0.79	0.34–1.87
		GT	32	122	0.69	1.17	0.67–2.06
		TT	28	125			
2	Early-onset type	TT *vs.* GG+GT	126	81	0.91	0.98	0.64–1.50
		GG	34	19	0.85	1.12	0.59–2.15
		GT	92	62	0.85	0.93	0.59–1.47
		TT	94	59			
3	Psoriatic arthritis involvement	TT *vs.* GG+GT	77	130	0.51	0.85	0.55–1.30
		GG	19	34	0.60	0.80	0.42–1.53
		GT	58	96	0.61	0.86	0.55–1.37
		TT	63	90			
4	Nail involvement	TT *vs.* GG+GT	102	114	0.68	0.89	0.59–1.37
		GG	19	34	0.11	0.56	0.29–1.07
		GT	83	80	0.96	1.04	0.66–1.63
		TT	72	72			
5	Chronic plaque	TT *vs.* GG+GT	184	13	0.86	0.93	0.39–2.17
		GG	44	5	0.51	0.58	0.19–1.77
		GT	140	8	0.97	1.14	0.44–2.98
		TT	153	10			
6	Pure skin changes	TT *vs.* GG+GT	130	77	0.51	1.18	0.77–1.81
		GG	34	19	0.60	1.25	0.66–2.39
		GT	96	58	0.60	1.16	0.73–1.83
		TT	90	63			
7	Family history	TT *vs.* GG+GT	41	166	0.02	2.12	1.14–3.93
		GG	11	42	0.09	2.24	0.97–5.21
		GT	30	124	0.04	2.07	1.08–3.98
		TT	16	137			
8	Severity	TT *vs.* GG+GT	122	85	0.45	0.83	0.54–1.27
		GG	26	27	0.09	0.56	0.30–1.05
		GT	96	58	0.94	0.96	0.60–1.52
		TT	97	56			
9	Past history of systemic therapy	TT *vs.* GG+GT	93	114	0.59	0.87	0.57–1.32
		GG	20	33	0.24	0.65	0.34–1.23
		GT	73	81	0.96	0.96	0.61–1.51
		TT	74	79			

*$P<0.005$ statistically significant.

Frequencies of the allele and genotypes of rs17728338 are associated with psoriasis

The frequency of the minor allele A was 28% in psoriasis patients and 20% in healthy controls.

The comparison of allele distributions revealed that there was a significant association (P=0.001) of the A allele with the risk of psoriasis (OR [95% CI] = 1.52 [1.19 –1.94]). The frequency of wild type (GG) genotype was 53.3% and 63.6% in patients and controls, respectively. The heterozygous combination AG was found in 134 psoriasis patients and in 115 controls with P=0.05 and OR (95% CI) 1.39 (1.02–1.90). The homozygous mutant (AA) genotype was found in 34 patients and 16 controls and the comparison of the genotype distributions showed a significant P value of 0.004 and OR (95% CI) 2.54 (1.36–4.73), thus showing an extremely significant association of *TNIP1* (rs17728338) polymorphism with susceptibility to psoriasis. The dominant model genotype (GG+GT) had a frequency of 46.7% in patients and 36.4% in controls. In the dominant model genotype analysis, rs17728338 was associated with the risk of psoriasis (P=0.007, OR=1.53; 95% CI –1.14–2.06).

When we performed genotype-phenotype analysis of rs17728338 by comparing cases having a particular subphenotype with cases that did not have the subphenotype, we found that the homozygous mutant AA genotype had a significant difference between patients with severe psoriasis

Table 3. Influence of *TNIP1* polymorphism on the phenotypic profile of psoriasis.

S. No.	Heading	TNFAIP3	No. of positives	No. of negatives	*P* value*	OR	95% CI
1	Females	GG *vs.* AA+AG	31	137	0.95	0.95	0.56–1.61
		AA	7	27	0.86	1.09	0.44–2.69
		AG	24	110	0.87	0.91	0.52–1.62
		GG	37	155			
2	Early-onset type	GG *vs.* AA+AG	104	64	0.86	1.07	0.70–1.63
		AA	18	16	0.53	0.74	0.35–1.53
		AG	86	48	0.57	1.17	0.74–1.85
		GG	116	76			
3	Psoriatic arthritis involvement	GG *vs.* AA+AG	66	102	0.97	1.03	0.67–1.58
		AA	7	27	0.07	0.41	0.17–1.00
		AG	59	75	0.38	1.25	0.80–1.96
		GG	74	118			
4	Nail involvement	GG *vs.* AA+AG	81	87	1.00	0.99	0.65–1.50
		AA	19	15	0.54	1.35	0.65–2.81
		AG	62	72	0.78	0.92	0.59–1.43
		GG	93	99			
5	Chronic plaque	GG *vs.* AA+AG	159	9	0.59	1.39	0.59–3.30
		AA	31	3	0.75	0.81	0.22–3.00
		AG	128	6	0.42	1.68	0.63–4.49
		GG	178	14			
6	Pure skin changes	GG *vs.* AA+AG	102	66	0.97	0.97	0.63–1.48
		AA	27	7	0.07	2.42	1.00–5.84
		AG	75	59	0.38	0.80	0.51–1.25
		GG	118	74			
7	Family History	GG *vs.* AA+AG	23	145	0.37	0.74	0.41–1.31
		AA	1	33	0.05	0.14	0.02–1.07
		AG	22	112	0.87	0.91	0.51–1.64
		GG	34	158			
8	Severity	GG *vs.* AA+AG	107	61	0.35	1.25	0.82–1.92
		AA	28	6	0.01	3.33	1.32–8.43
		AG	79	55	0.91	1.02	0.66–1.61
		GG	112	80			
9	Past history of systemic therapy	GG *vs.* AA+AG	86	82	0.11	1.44	0.95–2.18
		AA	17	17	0.51	1.37	0.66–2.85
		AG	69	65	0.12	1.46	0.93–2.27
		GG	81	111			

*P<0.005 statistically significant.

compared to patients with mild psoriasis ($P=0.01$, OR=3.33, 95% CI=1.32–8.43). However, after adjusting for multiple comparisons, we failed to observe statistically significant difference for severity of psoriasis with this SNP. We did not find any significant differences in the other subphenotypes of age of onset, gender, family history, nail involvement, psoriatic arthritis development, chronic plaque type, past history of systemic therapy between patients positive and those negative for a particular phenotype (Table 3).

Discussion

Several genome-wide studies have identified psoriasis susceptibility loci within the TNFα signalling pathway, tumour necrosis factor-α induced protein 3 (TNFAIP3) and TNFAIP3-interacting protein 1 (TNIP1) as risk factors of psoriasis. In the present study, we investigated whether the single nucleotide polymorphisms in *TNFAIP3* (rs610604) and *TNIP1* (rs17728338) genes are associated with psoriasis in the hitherto unexplored genetically distinct South Indian Tamil population.

Our results confirmed that both the *TNFAIP3* (rs610604) and *TNIP1* (rs17728338) polymorphisms contributed to psoriasis risk in the South Indian population. Also we found that the rs610604 of *TNFAIP3* was associated with the family history of psoriasis and the SNP rs17728338 of *TNIP1* was associated with clinical severity of psoriasis in the genotype-phenotype analysis. However, with a conservative estimation after adjustment for multiple comparison, the association of rs610604 of *TNFAIP3* with family history and rs17728338 of *TNIP1* with clinical severity did not reach statistical significance ($P<0.005$).

There are several studies reporting association of the variants of these two genes of the TNFα signalling with psoriasis, in Caucasians and Chinese populations.[5,7–11] Hasse *et al*.[19] confirmed a psoriasis association of the SNP rs610604, lying in the intronic region of the *TNFAIP3* gene in an Egyptian cohort. Li *et al*.[20] reported that *HCP5*, *TNIP1* and *TNFAIP3* genes were associated with Chinese population at both allelic and genotypic level which is in line with our results. A study from the University of Manchester also confirmed that *IL23A*, *TNIP1*, *TNFAIP3*, *TSC1* and *RNF114* genes are associated with susceptibility to psoriatic arthritis (PsA) as well as psoriasis in the western race.[21] A meta-analysis of the *TNFAIP3* region revealed that psoriasis risk haplotype is distinct from other *TNFAIP3* risk variants observed in autoimmune diseases such as systemic lupus erythematosus, rheumatoid arthritis and chronic dermatitis and thus highlighted the complex genetics of the *TNFAIP3* locus in autoimmune susceptibility.[22] A study from Michigan demonstrated that polymorphisms in *TNFAIP3* are associated with response to anti-TNF agents in a Michigan psoriasis cohort.[23] Recently, a Chinese study highlighted that rs610604 in the *TNFAIP3* gene plays an important role in the susceptibility of psoriasis vulgaris and also contributes to the clinical severity and complex phenotypes of psoriasis vulgaris.[24]

Jiang *et al*. described TNFAIP3 mRNA expression levels in peripheral blood mononuclear cells from 44 patients with psoriasis vulgaris were negatively correlated with the psoriatic area and severity index.[25] Another similar study suggested that TNFAIP3 mRNA was highly expressed in patients with mild psoriasis vulgaris and not with severe disease, thus indicating that TNFAIP3 may contribute to the primary defence reactions which are involved in the pathogenesis of psoriasis vulgaris.[26]

In conclusion, our results demonstrate the association of the *TNFAIP3* and *TNIP1* polymorphisms with psoriasis susceptibility in the hitherto genetically unexplored ethnically distinct South Indian Tamil psoriatic population, which is in parallel to the previously reported findings in different ethnicities as discussed above.

The limitation of our study is that we did not look into the expression levels of protein products of *TNFAIP3* and *TNIP1* genes, A20 and ABIN-1, respectively, which would have explained the possible mechanisms of the genotype-phenotype association in our study, which may contribute to the pathogenesis of psoriasis. □

References

1 Gudjonsson JE, Elder JT. Psoriasis: epidemiology. *Clin Dermatol* 2007; **25** (6): 535–46.

2 Nair RP, Stuart PE, Nistor I *et al*. Sequence and haplotype analysis supports HLA-C as the psoriasis susceptibility 1 gene. *Am J Hum Genet* 2006; **78** (5): 827–51.

3 Zhang XJ, Huang W, Yang S *et al*. Psoriasis genome-wide association study identifies susceptibility variants within LCE gene cluster at 1q21. *Nat Genet* 2009; **41** (2): 205–10.

4 Genetic Analysis of Psoriasis Consortium & the Wellcome Trust Case Control Consortium, Strange A, Capon F, Spencer CC *et al*. A genome-wide association study identifies new psoriasis susceptibility loci and an interaction between HLA-C and ERAP1. *Nat Genet* 2010; **42** (11): 985–90.

5 Nair RP, Duffin KC, Helms C *et al*.; Collaborative Association Study of Psoriasis. Genome-wide scan reveals association of psoriasis with IL-23 and NF-kappaB pathways. *Nat Genet* 2009; **41** (2): 199–204.

6 Tsoi LC, Spain SL, Knight J *et al*. Identification of 15 new psoriasis susceptibility loci highlights the role of innate immunity. *Nat Genet* 2012; **44** (12): 1341–8.

7 Capon F, Bijlmakers MJ, Wolf N *et al*. Identification of *ZNF313/RNF114* as a novel psoriasis susceptibility gene. *Hum Mol Genet* 2008; **17** (13): 1938–45.

8 Duffin KC, Krueger GG. Genetic variations in cytokines and cytokine receptors associated with psoriasis found by genome-wide association. *J Invest Dermatol* 2009; **129** (4): 827–33.

9 Elder JT. Genome-wide association scan yields new insights into the immunopathogenesis of psoriasis. *Genes Immun* 2009; **10** (3): 201–9.

10 Liu Y, Helms C, Liao W *et al*. A genome-wide association study of psoriasis and psoriatic arthritis identifies new disease loci. *PLoS Genet* 2008; **4** (3): e1000041.

11 Sun LD, Cheng H, Wang ZX *et al*. Association analyses identify six new psoriasis susceptibility loci in the Chinese population. *Nat Genet* 2010; **42** (11): 1005–9.

12 Werner SL, Kearns JD, Zadorozhnaya V *et al*. Encoding NF-kappaB temporal control in response to TNF: distinct roles for the negative regulators IkappaBalpha and A20. *Genes Dev* 2008; **22** (15): 2093–101.

13 Vereecke L, Beyaert R, van Loo G. The ubiquitin-editing enzyme A20 (TNFAIP3) is a central regulator of immunopathology. *Trends Immunol* 2009; **30** (8): 383–91.

14 Mauro C, Pacifico F, Lavorgna A *et al*. ABIN-1 binds to

NEMO/IKKgamma and co-operates with A20 in inhibiting NF-kappaB. *J Biol Chem* 2006; **281** (27): 18482–8.

15 Griffiths CE, Christophers E, Barker JN *et al*. A classification of psoriasis vulgaris according to phenotype. *Br J Dermatol* 2007; **156** (2): 258–62.

16 Taylor W, Gladman D, Helliwell P *et al*. Classification criteria for psoriatic arthritis: development of new criteria from a large international study. *Arthritis Rheum* 2006; **54** (8): 2665–73.

17 Langley RG, Ellis CN. Evaluating psoriasis with Psoriasis Area and Severity Index, Psoriasis Global Assessment, and Lattice System Physician's Global Assessment. *J Am Acad Dermatol* 2004; **51** (4): 563–9.

18 Miller SA, Dykes DD, Polesky HF. A simple salting out procedure for extracting DNA from human nucleated cells. *Nucleic Acids Res* 1988; **16** (3): 1215.

19 Haase O, Mosaad H, Eldarouti MA *et al*. *TNFAIP3* and *IL12B* gene polymorphisms associated with psoriasis vulgaris in an Egyptian cohort. *J Eur Acad Dermatol Venereol* 2015; **29** (7): 1297–301

20 Li XL, Yu H, Wu GS. Investigating the genetic association of *HCP5*, *SPATA2*, *TNIP1*, *TNFAIP3* and *COG6* with psoriasis in Chinese population. *Int J Immunogenet* 2014; **41** (6): 503–7.

21 Bowes J, Orozco G, Flynn E *et al*. Confirmation of *TNIP1* and *IL23A* as susceptibility loci for psoriatic arthritis. *Ann Rheum Dis* 2011; **70** (9): 1641–4.

22 Nititham J, Taylor KE, Gupta R *et al*. Meta-analysis of the *TNFAIP3* region in psoriasis reveals a risk haplotype that is distinct from other autoimmune diseases. *Genes Immun* 2015; **16** (2): 120–6.

23 Tejasvi T, Stuart PE, Chandran V *et al*. *TNFAIP3* gene polymorphisms are associated with response to TNF blockade in psoriasis. *J Invest Dermatol* 2012; **132** (3 Pt 1): 593–600.

24 Zhang C, Zhu KJ, Liu H *et al*. The *TNFAIP3* polymorphism rs610604 both associates with the risk of psoriasis vulgaris and affects the clinical severity. *Clin Exp Dermatol* 2015; **40** (4): 426–30.

25 Jiang X, Tian H, Fan Y *et al*. Expression of tumor necrosis factor alpha-induced protein 3 mRNA in peripheral blood mononuclear cells negatively correlates with disease severity in psoriasis vulgaris. *Clin Vaccine Immunol* 2012; **19** (12): 1938–42.

26 Zhang X, Xia P, Zhang L, Zhang Z. Upregulation of tumor necrosis factor alpha-induced protein 3 mRNA in mild psoriasis vulgaris. *Clin Vaccine Immunol* 2013; **20** (8): 1341.