

Methylenetetrahydrofolate Reductase C677T Gene Polymorphism as Risk Factor for Psoriasis in Saudis

Ghaleb Bin Huraib¹, Fahad Al Harthi², Misbahul Arfin³, Ahmad Al Khelaiwi¹, Sadaf Rizvi³ and Abdulrahman Al-Asmari³

¹Medical Services Department of Armed Forces, Riyadh, Saudi Arabia. ²Department of Dermatology, Prince Sultan Military Medical City, Riyadh, Saudi Arabia. ³Scientific Research Center, Medical Services Department of Armed Forces, Riyadh, Saudi Arabia.

Biomarker Insights
Volume 14: 1–5
© The Author(s) 2019
Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/1177271919830973



ABSTRACT: *Methylenetetrahydrofolate reductase (MTHFR)* has been linked with the etiopathogenesis of psoriasis with inconsistent results. *Methylenetetrahydrofolate reductase C677T* polymorphism was evaluated in 106 Saudi psoriasis vulgaris patients and 280 matched healthy controls using PCR-RFLP (restriction fragment length polymorphism) technique. The cardiovascular risk factors were also compared in cases and controls. Allele T and genotypes CT and TT were found to be increased while allele C and genotype CC significantly decreased in psoriasis patients as compared with controls ($P < .001$). These results showed that the T-allele and T-containing genotypes (TT, CT) of *MTHFR C677T* are significantly linked with psoriasis susceptibility while C-allele and CC genotype are protective for it. Body mass index, fasting glucose, total cholesterol, low-density lipoprotein, triglycerides, and C-reactive protein, known markers for cardiovascular diseases, were found to be significantly elevated in the patient group as compared with the controls. It is concluded that the *MTHFR C677T* polymorphism increases psoriasis risk in Saudi patients.

KEYWORDS: Psoriasis, *methylenetetrahydrofolate reductase*, polymorphism, genetic marker, Saudi

RECEIVED: January 13, 2019. **ACCEPTED:** January 20, 2019.

TYPE: Original Research

FUNDING: The author(s) received no financial support for the research, authorship, and/or publication of this article.

DECLARATION OF CONFLICTING INTERESTS: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

CORRESPONDING AUTHOR: Abdulrahman Al-Asmari, Scientific Research Center, Medical Services Department of Armed Forces, PO Box 22454, Riyadh 11495, Saudi Arabia. Email: abdulrahman.alasmari@gmail.com

Introduction

Psoriasis is a chronic inflammatory, immune-mediated disease which affects 120 to 180 million people worldwide.¹ It affects male and female patients equally.^{2,3} Globally 80% of psoriatic patients has psoriasis vulgaris, a subtype of psoriasis.^{4,5} Various factors including race, geographic location, genetics, infection, immunologic, biochemical, psychological, and environmental factors influence the prevalence of psoriasis.⁶ Ethnic variations, ranging from 0% to 12% have been reported in the prevalence of psoriasis worldwide.^{7–11} According to World Health Organization (WHO),¹¹ psoriasis is a serious chronic non-communicable inflammatory skin disease with multifactorial cause.

The pathogenesis of psoriasis is very complex and several different etiological hypotheses including those of the genetic, environmental, and immunologic factors have been suggested.^{12,13} Available literature indicated that genetic variation contributes significantly to the risk of psoriasis and more than 40 genes/loci are associated with the susceptibility to psoriasis in different populations.¹⁴

The *methylenetetrahydrofolate reductase (MTHFR, NM-005957)* has been linked with the etiopathogenesis of psoriasis. The *MTHFR* gene located at chromosome 1 (1p36.3) converts 5, 10-methylenetetrahydrofolate to 5-methylenetetrahydrofolate leading to the remethylation of homocysteine to methionine.^{15,16} This process maintains the methyl donors for DNA methylation which is important for gene regulation and cellular differentiation.^{17,18}

The polymorphism at position 677 in *MTHFR* gene substitutes nucleotide C with T changing Alanine to Valine. This

change results into the reduction of *MTHFR* enzymatic activity and thermostability, leading to the increased homocysteine levels.^{19,20} The hyperhomocysteinaemia has deleterious effects on various systemic and inflammatory diseases.^{21–26} As the psoriasis is associated with multiple diseases and causes high psychological burden in patients, this association of the *MTHFR* gene polymorphism with psoriasis becomes quite significant.^{27–29}

The role of *MTHFR* gene polymorphism in psoriasis has attracted much attention during last 2 decades due to inconsistent results reported in various studies from different regions of the world.^{17,24,30–32} Till date, no report on the association of *MTHFR* gene polymorphism with psoriasis is documented for the Middle Eastern population. In this study, a possible association of *MTHFR C677T* polymorphism with psoriasis vulgaris in Saudi patients has been investigated.

Subjects and Methods

Subjects

Three hundred eighty-six Saudi subjects (106 psoriasis patients and 280 healthy controls matched for age and sex) visiting Dermatology Clinic of Prince Sultan Military Medical City (PSMMC) Riyadh, Saudi Arabia, were recruited. The diagnosis of psoriasis was based on dermatological changes, the location, and condition of plaques. All cases and controls were examined by dermatologists. Patient information including demographic features was collected using a questionnaire. All patients must be diagnosed with plaque psoriasis for at least 1 year. Exclusion



criteria were coexisting inflammatory skin disease, diabetes mellitus, hypothyroidism, systemic lupus erythematosus, rheumatoid arthritis, history of hyperlipidemia, and renal and liver failure. The severity and extend of disease was assessed by Psoriasis Area and Severity Index (PASI) score.³³

Written informed consent from the patients/parent was obtained before their enrolment. We recruited 106 confirmed cases of psoriasis including 42 female and 62 male patients. The patients with mean age of 37 ± 15.5 years (age ranging from 9 to 65 years) and the mean duration of disease 9 ± 4.5 years were recruited. All the cases were adults except 3 children with 9, 12, and 16 years of age. The male to female ratio in patient group was 1.76:1, while the age of onset of disease varied from 8 to 55 years. For control, healthy women ($n=100$) and men ($n=180$) with mean age of 36 ± 10 years were included. The control subjects were also screened using the same questionnaire about the health status and those with the history of autoimmune or inflammatory disorders were excluded. The controls having first or second degree relative with psoriasis or any autoimmune disorders were also excluded from the study to minimize genetic heterogeneity. The protocol of this study was approved by the research and ethical committee of the PSMMC, Riyadh, via No. A/2015-10D.

Venous blood was collected from all selected subjects following 12 hour fasting. Lipid profile of all the subjects was determined following standard procedures in central pathological laboratory of PSMMC.

Genotyping

For genotyping, venous blood samples were collected in the tubes containing ethylenediaminetetraacetic acid (EDTA). Genomic DNA was extracted using DNA extraction kits from Qiagen (USA). *Methylenetetrahydrofolate reductase* C677T genotyping was performed by PCR-RFLP technique following the protocol as described elsewhere.³⁴ We included positive and negative controls in the PCR and repeated genotyping for 25% of the randomly selected samples for quality control.

Statistical analysis

The statistical significance was determined by comparing allele and genotype frequencies in patients and controls using the Fisher's exact test.³⁵ P values $\leq .05$ were considered significant. Hardy-Weinberg Equilibrium (HWE) was calculated using Hardy-Weinberg Equilibrium Calculator for 2 Alleles (<https://www.easycalculation.com/health/hardy-weinberg-equilibrium-calculator.php>).

The strength of the association of disease with respect to a particular genotype/allele are reported with the odds ratio interpreted as relative risk (RR) following the method of Woolf as described by Schallreuter et al.³⁶ RR indicates how many times more frequent a disease is in the positive subjects compared with allele/genotype-negative subjects. The etiologic

Table 1. Basic clinical and laboratory parameters of participants.

PARAMETERS	PSORIASIS	CONTROLS
Age (years)	37 ± 15.5	36 ± 10
Sex (Male: Female)	64:42	60:40
BMI (kg/m ²)	$24.0 \pm 5.5^*$	22.5 ± 2.21
Blood sugar (mmol/L)	$6.405 \pm 2.425^{**}$	5.551 ± 0.665
Total cholesterol (mmol/L)	$5.569 \pm 0.997^*$	4.973 ± 0.909
Triglyceride (mmol/L)	$1.401 \pm 0.776^*$	1.146 ± 0.554
LDL cholesterol (mmol/L)	$3.455 \pm 0.906^*$	2.748 ± 0.569
HDL cholesterol (mmol/L)	1.383 ± 0.310	$1.528 \pm 0.218^*$
TC/HC ratio	4.39 ± 2.1	3.31 ± 1.50
CRP (mg/L)	$6.1 \pm 2.54^{**}$	2.52 ± 0.85

Values are indicated as mean \pm standard deviation. Abbreviations: BMI, body mass index; CRP, C-reactive protein; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TC/HC, total cholesterol/HDL cholesterol. * $P < .05$; ** $P < .01$

fraction (EF) and preventive fraction (PF) were calculated following Svejgaard et al,³⁷ as mentioned elsewhere.³⁸

Results

The basic characteristics of the participants are summarized in Table 1. The fasting glucose, total cholesterol, low-density lipoprotein (LDL cholesterol), triglycerides, and systemic inflammation indicated as C-reactive protein (CRP) were found significantly higher in the patients than the controls. Similarly data for body mass index (BMI) was higher for psoriasis patients than the controls. The PASI scores of patients ranged from 10 to 35 indicating that the patients were with moderate to severe psoriasis.

The frequencies of alleles and genotypes of *MTHFR* C677T polymorphism differed in cases and controls (Tables 2 to 4). The *MTHFR* C677T polymorphism (rs1801133) was in HWE in patients. Contrarily this polymorphism was not in HWE in control group. The frequency of genotype CT was higher (43.40% vs 25%) while that of genotype CC was lower (51.89% vs 75%) in patients than controls. Genotype TT was found in 5 (4.71%) patients while totally absent in the controls ($P = .001$). Higher allele T and lower allele C frequencies were found in psoriasis patients than controls ($P < .001$). Sex stratification of genotyping results within the group (in cases or controls) showed no significant difference. However, when compared across the group (cases vs controls), significant differences were noticed (Table 3). The comparison of results obtained after repeating genotyping for 25% of the random blind samples with the earlier results showed 100% similarity.

The lipid profile of psoriasis patients with respect to genotypes of *MTHFR* polymorphism are shown in Table 4. The significant differences were noticed in the levels of HDL cholesterol, LDL cholesterol, total cholesterol, and triglycerides in

Table 2. Comparison of frequencies of *MTHFR* (C677T) variants in patients and controls.

GENOTYPE/ ALLELE	PSORIASIS (N=106)		CONTROL (N=280)		P	OR/RR†	EF*/PF	95% CI
	N	FREQ. %	N	FREQ. %				
CC	55	51.89	210	75.00	<.001 ^a	0.359	0.269	0.225-0.573
CT	46	43.40	70	25.00	<.001 ^a	2.30	0.223*	1.437-3.679
TT	5	4.71	0	—	.001 ^a	22.812†	—	1.429-16.591
CT+TT	51	48.11	70	25.00	<.001 ^a	2.782	0.269*	1.442- 5.321
C-allele	156	73.58	490	87.50	<.001 ^a	0.239	0.432	—
T-allele	56	26.42	70	12.50	<.001 ^a	2.513	0.267*	1.693-3.729

Abbreviations: CI, confidence interval; EF, etiological fraction; *MTHFR*, methylenetetrahydrofolate reductase; n, number of subjects; OR, odds ratio; PF, preventive fraction; RR, relative risk.

*Statistically significant.

†Indicates RR values as other values in the column are odds ratios (OR).

Table 3. Distribution of *MTHFR* (C677T) variants in male and female psoriasis patients.

GENOTYPE/ ALLELE	MALE PATIENTS (N=64)		FEMALE PATIENTS (N=42)		P	CONTROLS (N=280)	
	N	FREQ. %	N	FREQ. %		N	FREQ. %
CC	35	55.17*	20	47.62*	.552	210	75.00
CT	26	41.38*	20	47.62*	.549	70	25.00
TT	3	3.45*	2	4.76*	1.00	0	0
C-allele	96	75*	60	72.43*	.633	490	87.50
T-allele	32	25*	24	28.57*	.633	70	12.50

Abbreviation: *MTHFR*, methylenetetrahydrofolate reductase.

*Statistically significant difference as compared with controls ($P < .01$).

Table 4. Lipid profile with genotype of the patients.

GENOTYPE	TOTAL CHOLESTEROL (MEAN ± SD)	HDL CHOLESTEROL (MEAN ± SD)	LDL CHOLESTEROL (MEAN ± SD)	TRIGLYCERIDES (MEAN ± SD)
CC	5.46 ± 0.06	1.50 ± 0.04*	3.55 ± 0.05	1.32 ± 0.04
CT	5.72 ± 0.08	1.34 ± 0.05	3.81 ± 0.02	1.41 ± 0.06
TT	5.98 ± 0.09*	1.30 ± 0.04	4.22 ± 0.07*	1.52 ± 0.07*

All values are in mmol/L. Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein.

*Higher than other groups ($P < .0001$, using MedCalc software).

the carriers of different genotypes of *MTHFR* polymorphism. Carriers of CC genotype had lower LDL cholesterol, total cholesterol, and triglycerides but higher HDL cholesterol. Subjects with TT genotype had significantly elevated triglycerides, LDL cholesterol, and total cholesterol but lower HDL cholesterol concentrations.

Discussion

The polymorphism data in controls were not in HWE. This deviation from HWE can be due to genotyping error or genetic factors which include a heterozygous advantage, population

admixture/substructure, inbreeding, or copy number variants.³⁹ However, genotyping error was ruled out by repeating the genotyping for 25% of randomly selected samples and obtaining the same results. Therefore, this deviation could be due to consanguinity and/or an association with the functional locus as the consanguinity in Saudi population is quite high due to being a closed and isolated society with high rate of cousin marriages.

Higher frequencies of T-containing genotypes of *MTHFR* C677T polymorphism in patients as compared with controls indicated that *MTHFR* C677T polymorphism is associated

with susceptibility to psoriasis. These results are in agreement with the earlier published reports from other ethnic groups (Chinese, Czech, Turkish, and Iranians) which consider *MTHFR* C677T polymorphism as a genetic risk factor for susceptibility and/or severity of psoriasis.^{17,31,32,40–42}

Contrarily, the lack of association between *MTHFR* C677T polymorphism and psoriasis was reported in Australian and Malaysian patients.^{24,30} Recent meta-analysis also showed absence of association of this polymorphism with psoriasis susceptibility^{43,44}; however, it was suggested that *MTHFR* C677T polymorphism may affect the severity of psoriasis.⁴⁴

These variations in association reports can be attributed to the ethnic variations as the prevalence of *MTHFR* C677T polymorphism varies among different healthy populations.^{34,45} The frequency of CC genotype varies from 23% to 97%, that of TT genotype from 0% to 28%, except in Mexican population where it is quite high (52%), while heterozygous CT genotype varies from 2.4% to 53% in various healthy populations worldwide as reviewed by Al-Shahrani et al.³⁴ In Saudi healthy population, the frequencies of CC, CT, and TT were 75%, 25%, and 0%, respectively.

Enzyme *MTHFR* is involved in homocysteine and folic acid metabolism and it is responsible for the irreversible conversion to 5-methyl tetrahydrofolate, which is a methyl donor of 5, 10-methylenetetrahydrofolate.⁴⁶ The reduced *MTHFR* enzymatic activity and thermostability due to *MTHFR* C677T polymorphism leads to the increased homocysteine levels.^{19,20} Higher Hcy concentrations in plasma of psoriasis patients than controls have been found.^{17,47,48} Significant differences in Hcy levels have also been reported in carriers of CC, CT, and TT genotypes of *MTHFR* polymorphism.^{17,49,50} *MTHFR* 677TT genotype and resulting hyperhomocysteinemia are known risk factors for cardiovascular diseases, cancer, and chronic idiopathic acrocyanosis.^{24,31,46,51–56} The *MTHFR* C677T polymorphism also decreases folate level in the serum^{57–59} which further increases the risk of hyperhomocysteinemia.⁶⁰ The decrease in folate consumption also influences the production of keratinocytes, consequently affecting the severity of psoriasis as suggested by Baiqiu et al.¹⁷

The elevated CRP levels in Saudi psoriasis patients are in accordance with the earlier report.^{61–65} The increased BMI, fasting glucose, total cholesterol, LDL cholesterol, and triglycerides are similar to those reported in several studies.^{66,67} Various parameters of adiposity like BMI, waist circumference, waist-to-hip ratio, and weight gain have also been associated with increased risk of psoriasis.⁶⁸

Conclusions

It is concluded that C677T polymorphism in *MTHFR* gene increases the risk of psoriasis development in Saudis. Psoriasis patients with T-containing genotypes of *MTHFR* C677T should be followed up for progression of any comorbidity as several comorbidities have been associated with psoriasis.

Acknowledgements

The authors extend sincere thanks to the administration of MSD for providing facilities.

Author Contributions

MA conceived and designed the experiment. GBH, FAH, and AAK performed clinical examinations and collected demographic data. SR extracted DNA and performed genotyping. MA analyzed the data, interpreted the results, and drafted the manuscript. GBH, FAH, AAK, and AA-A agree with the manuscript results and conclusions. AA-A and MA revised, supervised, and approved the final version. All authors read and approved the final manuscript.

REFERENCES

- Icen M, Crowson CS, McEvoy MT, Dann FJ, Gabriel SE, Maradit Kremers H. Trends in incidence of adult-onset psoriasis over three decades: a population-based study. *J Am Acad Dermatol*. 2009;60:394–401.
- Lebwohl M, Menter A, Koo J, Feldman S. Case studies in severe psoriasis: a clinical strategy. *J Dermatolog Treat*. 2003;14:26–46.
- Balta S, Balta I, Mikhailidis DP, et al. Bilirubin levels and their association with carotid intima media thickness and high-sensitivity C-reactive protein in patients with psoriasis vulgaris. *Am J Clin Dermatol*. 2014;15:137–142.
- Chen K, Wang G, Jin H, et al. Clinic characteristics of psoriasis in China: a nationwide survey in over 12000 patients. *Oncotarget*. 2017;8:46381–46389.
- Zangeneh FZ, Shoostary FS. Psoriasis-types, causes and medication. In: Lima H, ed. *Psoriasis-types, Causes and Medication*. Rijeka, Croatia: InTech Publisher; 2013:3–37.
- Al-Harthi F, Huraib GB, Zouman A, Arfin M, Tariq M, Al-Asmari A. Apolipoprotein E gene polymorphism and serum lipid profile in Saudi patients with psoriasis. *Dis Markers*. 2014;2014:239645.
- Schön MP, Boehncke WH. Psoriasis. *N Engl J Med*. 2005;352:1899–1912.
- Dogra S, Yadav S. Psoriasis in India: prevalence and pattern. *Indian J Dermatol Venereol Leprol*. 2010;76:595–601.
- Ding X, Wang T, Shen Y, et al. Prevalence of psoriasis in China: a population-based study in six cities. *Eur J Dermatol*. 2012;22:663–667.
- Michalek IM, Loring B, John SM. A systematic review of worldwide epidemiology of psoriasis. *J Eur Acad Dermatol Venereol*. 2017;31:205–212.
- World Health Organization. Global report on psoriasis, 2016 (WHO Library Cataloging-in-Publication Data), pp. 1–48. Website: https://apps.who.int/iris/bitstream/handle/10665/204417/9789241565189_eng.pdf;jsessionid=D2533C38AE1C9D400B8858B62C82D057?sequence=1.
- Krueger JG, Bowcock A. Psoriasis pathophysiology: current concepts of pathogenesis. *Ann Rheum Dis*. 2005;64:ii30–ii36.
- Boehncke WH. Etiology and pathogenesis of psoriasis. *Rheum Dis Clin North Am*. 2015;41:665–675.
- Zuo X, Sun L, Yin X, et al. Whole-exome SNP array identifies 15 new susceptibility loci for psoriasis. *Nat Commun*. 2015;6:6793.
- Goyette P, Pai A, Milos R, et al. Gene structure of human and mouse methylenetetrahydrofolate reductase (MTHFR). *Mamm Genome*. 1998;9:652–656.
- Rosenberg N, Murata M, Ikeda Y, et al. The frequent 5,10-methylenetetrahydrofolate reductase C677T polymorphism is associated with a common haplotype in Whites, Japanese, and Africans. *Am J Hum Genet*. 2002;70:758–762.
- Baiqiu W, Songbin F, Guiyin Z, Pu L. Study of the relationship between psoriasis and the polymorphic site C677T of methylenetetrahydrofolate reductase. *Chin Med Sci J*. 2000;15:119–120.
- Hustad S, Midttun O, Schneede J, Vollset S, Grotmol T, Ueland P. The methylenetetrahydrofolate reductase 677C-T polymorphism as a molecular of a B vitamin network with major effects on homocysteine metabolism. *Am J Hum Genet*. 2007;80:846–855.
- Frosst P, Blo H, Milos R, et al. A candidate genetic risk factor for vascular disease: a common mutation in methylenetetrahydrofolate reductase. *Nat Genet*. 1995;10:111–113.
- Jacques P, Bostom A, Williams R, et al. Relation between folate status, a common mutation in methylenetetrahydrofolate reductase, and plasma homocysteine concentrations. *Circulation*. 1996;93:7–9.
- Bhargava S, Parakh R, Manocha A, Ali A, Srivastava LM. Prevalence of hyperhomocysteinemia in vascular disease: comparative study of thrombotic venous disease vis-à-vis occlusive arterial disease. *Vascular*. 2007;15:149–153.
- Santos M, Silva F, Gomes K, et al. Mutations in methylenetetrahydrofolate reductase and in cystathionine beta synthase: is there a link to homocysteine levels in peripheral arterial disease? *Mol Biol Rep*. 2010;38:3361–3366.

23. Hamzaoui A, Harzallah O, Klii R, Mahjou S. Hyperhomocysteinaemia in Behcet's disease. *Biochem Res Int.* 2010;2010:361387.
24. Liew SC, Das-Gupta E, Wong SF, Lee N, Safdar N, Jamil A. Association of methylenetetrahydrofolate reductase (MTHFR) 677 C > T gene polymorphism and homocysteine levels in psoriasis vulgaris patients from Malaysia: a case-control study. *Nutr J.* 2012;11:1.
25. Ganguly P, Alam SF. Role of homocysteine in the development of cardiovascular disease. *Nutr J.* 2015;14:6.
26. Keshteli AH, Baracos VE, Madsen KL. Hyperhomocysteinemia as a potential contributor of colorectal cancer development in inflammatory bowel diseases: a review. *World J Gastroenterol.* 2015;21:1081–1090.
27. Miller IM, Ellervik C, Yazdanyar S, Jemec GB. Meta-analysis of psoriasis, cardiovascular disease, and associated risk factors. *J Am Acad Dermatol.* 2013;69:1014–1024.
28. Kwa MC, Silverberg JI. Association between inflammatory skin disease and cardiovascular and cerebrovascular co-morbidities in US adults: analysis of nationwide inpatient sample data. *Am J Clin Dermatol.* 2017;18:813–823.
29. Menter MA, Armstrong AW, Gordon KB, Wu JJ. Common and not-so-common comorbidities of psoriasis. *Semin Cutan Med Surg.* 2018;37:S48–S51.
30. Weger H, Hoffer A, Stanger O, et al. The methylenetetrahydrofolate reductase 677C>T gene polymorphism is not associated with chronic plaque psoriasis. *Exp Dermatol.* 2008;17:748–751.
31. Vasku V, Bienertova-Vasku J, Necas M, Vasku A. MTHFR (methylenetetrahydrofolate reductase) C677T polymorphism and psoriasis. *Clin Exp Med.* 2009;9:327–331.
32. Izmirli M, Sen BB, Rifaoglu E, et al. Methylenetetrahydrofolate reductase (MTHFR) C677T polymorphism in psoriasis in southern Turkey. *An Bras Dermatol.* 2016;91:611–613.
33. Schmitt J, Wozel G. The psoriasis area and severity index is the adequate criterion to define severity in chronic plaque-type psoriasis. *Dermatology.* 2005;210:194–199.
34. Al-Shahrani H, Al-Dabbagh N, Al-Dohayan N, et al. Association of the methylenetetrahydrofolate reductase (MTHFR) C677T polymorphism with primary glaucoma in Saudi population. *BMC Ophthalmol.* 2016;16:156.
35. Khan HA. A Visual Basic software for computing Fisher's exact probability. *J Stat Softw.* 2003;8:1–7.
36. Schallreuter KU, Levenig C, Kühnl P, Löliger C, Hohl-Tehari M, Berger J. Histocompatibility antigens in vitiligo: Hamburg study on 102 patients from northern Germany. *Dermatology.* 1993;187:186–192.
37. Svejgaard A, Platz P, Ryder LP. HLA and disease 1982: a survey. *Immunol Rev.* 1983;70:193–218.
38. Al-Dabbagh NM, Al-Saleh S, Al-Dohayan N, Al-Asmari AK, Arfin M, Tariq M. The role of Apolipoprotein E gene polymorphisms in primary glaucoma and pseudoexfoliation syndrome. In: Shimon R, ed. *Glaucoma—basic and clinical aspects*. Rijeka, Croatia: InTech Publisher; 2013:129–156.
39. Li B, Leal SM. Deviations from Hardy-Weinberg equilibrium in parental and unaffected sibling genotype data. *Hum Hered.* 2009;67:104–115.
40. Karabacak E, Aydin E, Ozcan O, et al. Methylenetetrahydrofolate reductase (MTHFR) 677C>T gene polymorphism as a possible factor for reducing clinical severity of psoriasis. *Int J Clin Exp Med.* 2014;7:697–702.
41. Asefi M, Vaisi-Raygani A, Khodarahmi R, et al. Methylenetetrahydrofolate reductase (rs1801133) polymorphism and psoriasis: contribution to oxidative stress, lipid peroxidation and correlation with vascular adhesion protein 1, preliminary report. *J Eur Acad Dermatol Venerol.* 2014;28:1192–1198.
42. Kilic S, Ozdemir O, Silan F, et al. Possible association between germline methylenetetrahydrofolate reductase gene polymorphisms and psoriasis risk in a Turkish population. *Clin Exp Dermatol.* 2017;42:8–13.
43. Qi JH, Qi JH, Shi N, Chen YJ, Nie G. Association between MTHFR 677C/T polymorphism and psoriasis risk: a meta-analysis. *Genet Mol Res.* 2015;14:3869–3876.
44. Wu D, Shi D, Yang L, Zhu X. Association between methylenetetrahydrofolate reductase C677T polymorphism and psoriasis: a meta-analysis. *J Dermatol.* 2016;43:162–169.
45. Mansoor A, Mazhar K, Ali L, Muazzam AG, Siddiqi S, Usman S. Prevalence of the C677T single-nucleotide polymorphism in the methylenetetrahydrofolate reductase gene among Pakistani ethnic groups. *Genet Test Mol Biomarkers.* 2009;13:521–526.
46. Sampogna F, Camaioni DB, Giampetruzzi AR, et al. Chronic idiopathic acrocyanosis and methylenetetrahydrofolate reductase C677T (p.Ala222Val) and A1298C (p.Glu429Ala) polymorphisms. *Eur J Dermatol.* 2013;23:356–361.
47. Vanizor Kural B, Orem A, Cimsit G, Uydu HA, Yandi YE, Alver A. Plasma homocysteine and its relationships with atherothrombotic markers in psoriatic patients. *Clin Chim Acta.* 2003;332:23–30.
48. Malerba M, Gisondi P, Radaeli A, Sala R, Calzavara Pinton PG, Girolomoni G. Plasma homocysteine and folate levels in patients with chronic plaque psoriasis. *Br J Dermatol.* 2006;155:1165–1169.
49. Engbersen AM, Franken DG, Boers GH, Stevens EM, Trijbels FJ, Blom HJ. Thermolabile 5, 10-methylenetetrahydrofolate reductase as a cause of mild hyperhomocysteinemia. *Am J Hum Genet.* 1995;56:142–150.
50. Harmon DL, Woodside JV, Yarnell JW, et al. The common thermolabile variant of the methylene tetrahydrofolate reductase is a major determinant of mild hyperhomocysteinemia. *QJM.* 1996;89:571–577.
51. Ilhan N, Cucuksu M, Kaman D, Ilhan N, Ozbay Y. The 677 C/T MTHFR polymorphism is associated with essential hypertension, coronary artery disease, and higher homocysteine levels. *Arch Med Res.* 2008;39:125–130.
52. Izmirli M, Inandiklioglu N, Abat D, et al. MTHFR gene polymorphisms in bladder cancer in the Turkish population. *Asian Pac J Cancer Prev.* 2011;12:1833–1835.
53. Holmes MV, Newcombe P, Hubacek JA, et al. Effect modification by population dietary folate on the association between MTHFR genotype, homocysteine, and stroke risk: a meta-analysis of genetic studies and randomized trials. *Lancet.* 2011;378:584–594.
54. Wang W, Hou Z, Wang C, Wei C, Li Y, Jiang L. Association between 5, 10-methylenetetrahydrofolate reductase (MTHFR) polymorphisms and congenital heart disease: a meta-analysis. *Meta Gene.* 2013;1:109–125.
55. Baszczuk A, Kopczyński Z. Hyperhomocysteinemia in patients with cardiovascular disease. *Postepy Hig Med Dosw.* 2014;68:579–589.
56. Wang WM, Jin HZ. Homocysteine: a potential common route for cardiovascular risk and DNA methylation in psoriasis. *Chin Med J(Engl).* 2017;130:1980–1986.
57. Yakub M, Moti N, Parveen S, Chaudhry B, Azam I, Iqbal MP. Polymorphisms in MTHFR, MS and CBS genes and homocysteine levels in a Pakistani population. *PLoS ONE.* 2012;7:e33222.
58. Safarinejad MR, Shafiei N, Safarinejad S. Methylenetetrahydrofolate reductase (MTHFR) gene C677T, A1298C and G1793A polymorphisms: association with risk for clear cell renal cell carcinoma and tumour behavior in men. *Clin Oncol (R Coll Radiol).* 2012;24:269–281.
59. Husemoen LL, Skaaby T, Jørgensen T, et al. MTHFR C677T genotype and cardiovascular risk in a general population without mandatory folic acid fortification. *Eur J Nutr.* 2014;53:1549–1559.
60. Scazzone C, Bono A, Tornese F, et al. Correlation between low folate levels and hyperhomocysteinemia, but not with vitamin B12 in hypertensive patients. *Ann Clin Lab Sci.* 2014;44:286–290.
61. Takahashi H, Inuma S, Honma M, Iizuka H. Increased serum C-reactive protein level in Japanese patients of psoriasis with cardio- and cerebrovascular disease. *J Dermatol.* 2014;41:981–985.
62. Vadakayil AR, Dandekeri S, Kambil SM, Ali NM. Role of C-reactive protein as a marker of disease severity and cardiovascular risk in patients with psoriasis. *Indian Dermatol Online J.* 2015;6:322–325.
63. Vachatoeva S, Andrys C, Krejssek J, et al. Metabolic syndrome and selective inflammatory markers in psoriatic patients. *J Immunol Res.* 2016;2016:5380792.
64. Coimbra S, Oliveira H, Reis F, et al. C-reactive protein and leucocyte activation in psoriasis vulgaris according to severity and therapy. *J Eur Acad Dermatol Venerol.* 2010;24:789–796.
65. Beygi S, Lajevardi V, Abedini R. C-reactive protein in psoriasis: a review of the literature. *J Eur Acad Dermatol Venerol.* 2014;28:700–711.
66. Vanizor Kural B, Orem A, Cimsit G, Yandi YE, Calapoglu M. Evaluation of the atherogenic tendency of lipids and lipoprotein content and their relationships with oxidant-antioxidant system in patients with psoriasis. *Clin Chim Acta.* 2003;328:71–82.
67. Mallbris L, Granath F, Hamsten A, Ståhle M. Psoriasis is associated with lipid abnormalities at the onset of skin disease. *J Am Acad Dermatol.* 2006;54:614–621.
68. Aune D, Snekvik I, Schlesinger S, Norat T, Riboli E, Vatten LJ. Body mass index, abdominal fatness, weight gain and the risk of psoriasis: a systematic review and dose-response meta-analysis of prospective studies. *Eur J Epidemiol.* 2018;33:1163–1178.