Abstract

Background: Psoriasis is a chronic inflammatory skin disorder, which is characterized by a heightened immunological response. Although the immunogenetics of this chronic inflammatory disorder is poorly understood, its expression is known to be dependent on proinflammatory cytokines. It is known that two distinct subtypes of chronic plaque psoriasis: Early-onset psoriasis (EOP) before the age of 40 years and late-onset psoriasis after the age of 40 years. Forkhead box class O3A (FOXO3A) is a transcription factor, which plays an important role in cell-cycle regulation, apoptosis, oxidative stress, and DNA repair. The silent information regulator (SIRT) is thought to have a role in skin disorders, including psoriasis, that are characterized by hyperproliferation and inflammation. Aim: The aim of this study was to investigate FOXO3A and SIRT1 gene polymorphisms in EOP. Methods: The study group consisted of 142 EOP patients and 123 unrelated healthy controls. FOXO3A polymorphisms were determined using the polymerase chain reaction (PCR)-restriction fragment length polymorphism method. SIRT1 gene polymorphisms were determined by PCR-confronting two-pair primers methods. Results: The FOXO3A rs4946936 and SIRT1 rs7069102 gene polymorphisms were positively correlated with EOP and disease severity. The GG genotype frequency of SIRT1 rs7069102 gene polymorphisms was increased in severe EOP. The CC frequency of FOXO3A rs4946936 was increased in EOP with nail disorders. Conclusion: The rs7069102 gene polymorphism of SIRT1 and rs4946936 polymorphism of FOXO3A are associated with early onset psoriasis; this may be responsible for increased keratinocyte proliferation in the pathogenesis of psoriasis and disease severity.

Key words: Forkhead box class O3A, gene polymorphism, psoriasis, silent information regulator T1
oxidative stress and a reduced antioxidant capacity may play a role in the development or aggravation of psoriasis.[7,8] Silent information regulator (SIRT1), a member of the sirtuin family, and FOXOs are evolutionary conserved regulators of aging, metabolic processes, and the response to oxidative stress.[9]

Forkhead box class O (FOXO) proteins are a subclass of the FOXO family of transcription factors and include FOXO1, FOXO3A, FOXO4, and FOXO6. FOXO proteins play crucial roles in diverse cellular processes, such as cell-cycle regulation, apoptosis, scavenging of reactive oxygen species, and DNA repair.[10-13] A recent study reported that FOXO proteins suppressed tumor formation, tumor angiogenesis, and possibly, metastasis.[10] FOXO1 and FOXO3A are the most abundant FOXO isoforms in mature endothelial cells.[11] Studies have demonstrated that overexpression of constitutively active FOXO1 or FOXO3A significantly inhibited endothelial cell migration and tube formation in vitro.[15] In addition, inhibition of Ras/MEK/ERK and PI3K/AKT pathways was shown to activate FOXO transcription factors.[13] A number of studies suggested that the activation of FOXO transcription factors may have physiological significance in diabetic retinopathy, rheumatoid arthritis, psoriasis, cardiovascular diseases, and cancer.[10-13]

Members of the SIRT family of genes are NAD+-dependent Class III deacetylase enzymes. There are seven known isoforms (SIRT1-7), which differ in their subcellular localization, substrate specificities, and functions.[14,15] SIRT1, which has a predominantly nuclear localization, has received the most research attention, and its impact on other proteins is relatively well understood.[16,17] Studies have confirmed that it plays a critical role in the regulation of numerous cellular processes, such as cell-cycle progression, nutrient metabolism, cellular ageing, and cell apoptosis.[18] In addition, research has suggested that SIRT1 may have a role in skin disorders, such as psoriasis, that are characterized by hyperproliferation and inflammation.[14] A gene expression microarray analysis data supported a role of SIRT1-induced inhibition of the proliferation of keratinocytes.[14] SIRT1 was shown to deacetylate nonhistone proteins, including transcription factors, signaling proteins, tumor suppressors, FOXO1, FOXO3A, and FOXO4.[13] Studies also demonstrated that the regulation of chromatin dynamics was involved in oxidative stress and transcription in many diseases, including cancer, as well as in glucose homeostasis and cell life.[14] Another study showed that SIRT1 regulated FOXO3A functions, including cell-cycle arrest, resistance to oxidative stress, and the induction of cell death.[19]

There have been no previous studies of the potential roles of SIRT1 and FOXO3A gene variants in psoriasis. Elucidating the underlying genetic mechanisms and the role of oxidative stress in psoriasis might help to shed light on potential therapeutic modalities for this skin disorder. Based on the aforementioned literature on the role of oxidative stress and inflammation in the pathophysiology of psoriasis, this study hypothesized that polymorphisms of FOXO3A and SIRT1A genes might be linked to psoriasis. This study investigated the role of SIRT1 gene polymorphisms (rs7895833, rs7069102, and rs2273773) and FOXO3A gene polymorphisms (rs2253310 and rs4966936) in EOP.

**Methods**

**Study population and design**

This study was approved by the Ethics Committee for Clinical Studies of the Mugla Sitki Kocman University Faculty of Medicine and was performed in accordance with the guidelines of the Declaration of Helsinki. The study consisted of 142 patients (<40 years) with EOP psoriasis and 123 age-and gender-matched healthy volunteers (control group) without first-degree, second-degree, or third-degree relatives with psoriasis. The patients were recruited from the Department of Dermatology at Mugla Sitki Kocman University Hospital and the Department of Dermatology of Bulent Ecevit University Hospital in 2016.

Patients with psoriasis and healthy volunteers who were older than 18 year and received no systemic treatment in the last 6 months were included in the study. The exclusion criteria were LOP patients, pregnancy, lactation, malignancies, active liver disease, renal disorders, infections, alcohol use, and medication use for the condition. The characteristics of patients and control groups are shown in Table 1. Written informed consent

| Table 1: Clinical characteristics of early-onset psoriasis patients and healthy controls |
|-----------------------------------------------|-------------------|-----------------|
| **Clinical characteristics** | **Mean±SD EOP** | **Mean±SD Control** | **P** |
| Age (years) | 34.52±10.42 | 32.68±9.73 | >0.05 |
| Gender, n (%) | | | |
| Male | 76 | 71 | >0.05 |
| Female | 66 | 52 | |
| Psoriatic nail | | | |
| Yes | 75 | | |
| No | 67 | | |
| Family history | | | |
| Yes | 82 | | |
| No | 60 | | |
| BMI | 23.88±0.71 kg/m² | 23.61±0.83 | >0.05 |
| PASI <3 | 60 | | |
| PASI (3-10) | 54 | | |
| PASI >10 | 28 | | |

EOP: Early-onset psoriasis, BMI: Body mass index, PASI: Psoriasis Area Severity Index
was provided by all the patients and controls before the study. The severity of the skin disorder was assessed by the psoriasis area severity index (PASI).

**Genotyping**

Venous blood samples from the subjects were collected into vacutainer plastic tubes containing sodium/potassium EDTA. The polymerase chain reaction (PCR) with confronting two-pair primers genotyping method was employed for genotyping SIRT1 gene polymorphisms (rs7895833, rs7069102, and rs2273773), and the PCR-restriction fragment length polymorphism method was used to determine FOXO3A gene variants (rs2253310 and rs4966936). DNA was extracted using a GeneJet Genomic DNA purification kit (Thermo K0772, USA). The primers, annealing temperatures, and fragments of these polymorphisms are shown in Table 2. The PCR was performed in a 25 µl volume containing 50 ng of DNA, 100 µM dNTPs, 20 pmol of each primer, 1.5 mM MgCl$_2$, 1xPCR buffer with (NH$_4$)$_2$SO$_4$, and 1U Taq DNA polymerase. Amplification was performed on an automated thermal cycler (Roche, Swiss). The PCR products were directly analyzed by electrophoresis on 3% agarose gel. Each allele was identified according to its size. The SNPs of the FOXO3A and SIRT1 genes, primer sequences, annealing temperatures, restriction enzymes, and allele sizes are shown in Table 2.

**Statistical analysis**

The allelic and genotypic frequencies of the polymorphisms were calculated both in the cases and in controls. The Hardy–Weinberg equilibrium was verified using the Chi-square test ($\chi^2$) and estimating the expected genotypic frequencies on the basis of the square of the binomial for these polymorphisms. The $\chi^2$ test was used to compare the genotypic and allelic frequency of all the genotypes. The association between the polymorphisms and psoriasis was modeled using a binary logistic regression analysis. Odds ratios (ORs) and their 95% confidence intervals (CIs) were calculated to compare the risk of EOP associated with the genotypes. In addition, a haplotype analysis was conducted to determine the effect of the genetic correlation between two polymorphic regions.

**Results**

The mean age of the 142 patients with psoriasis was 34.52 ± 10.42 years, and the mean age of the 123 age-matched healthy volunteers was 32.68 ± 9.73 years. Males accounted for 43% of the study population. There was no significant difference in the mean age of psoriasis and control groups ($P$>0.05). The demographic characteristics of the patients are given in Table 1. There were no between-group differences in

| Primer | Annealing temperature | Restriction enzymes | Allele Size (bp) |
|--------|-----------------------|---------------------|-----------------|
| **FOXO3A (PCR-RFLP)** | | | |
| rs2253310 | 53°C | DpnI | GG: 321, GC: 321, 127, 194, CC: 127, 194 |
| rs4966936 | 53°C | Sfcl | TT: 224, TC: 224, 152, 72, CC: 152, 72 |
| **SIRT1 (PCR-CTPP)** | | | |
| rs7895833 | 64°C | AA: 320, 241 bp, AG: 320, 241, 136 bp, GG: 320, 136 bp |
| rs7069102 | 64°C | CC: 391, 277 bp, CG: 391, 277, 167 bp, GG: 391, 167 bp |
| rs2273773 | 63°C | CC: 314, 228 bp, CT: 314, 228, 135 bp, TT: 314, 135 bp |

PCR: Polymerase chain reaction, RFLP: Restriction fragment length polymorphism, FOXO3A: Forkhead box class 0 3A, SIRT: Silent information regulator.
age and gender (P>0.05). The distribution of the FOXO3A and SIRT1 polymorphism genotypes in the control group showed no deviation from the Hardy–Weinberg equilibrium. The frequencies of the genotypes and alleles of the FOXO3A and SIRT1 genes are shown in Tables 3 and 4. In addition, we have analyzed the association between PASI and SIRT1 variant [Table 5]. In the result of our rs7069102 gene polymorphism analysis of SIRT1, we have found that GG genotype frequency is in severe EOP (P=0.043). In addition, the other variants of SIRT1 gene have not related with PASI level in EOP (P>0.05). We have tried to understand the association between nail retention and SIRT1 gene variants in EOP. We have not found any significant relationship between nail retention and SIRT1 gene variants in EOP (not shown in table, P>0.05). We have not found any significant association between family history of EOP patient, and SIRT1 rs7895833, rs7069102, and rs2273773 gene polymorphisms (not shown in table, P>0.05).

There was a significant association between the genotypic and allelic frequencies of the FOXO3A gene rs4946936 polymorphism in EOP patients (P=0.010). The CC allele of the FOXO3A gene rs4946936 polymorphism seemed to be a risk factor for EOP (OR=1.66; 95% CI: 1.14-2.42; P=0.010). There were no significant differences between the genotypic and allelic frequencies of the FOXO3A rs2253310 polymorphism of the EOP patients compared with those of the healthy controls (P=0.275). We have found significant relationship between rs4946936 polymorphism and EOP patients with nail retention (not shown in table, P=0.014). We also found that CC frequency is significantly higher in nail retention of EOP. In addition, we have shown the association between family history in EOP and rs4946936 gene (not shown in table, P=0.007). We have determined an association between PASI score of EOP and rs4946936 gene polymorphism (not shown in table, P=0.007). In addition, there was no relation between rs2253310 gene polymorphism and nail retention, family history, and PASI (not shown in table, P>0.05).

The result of the haplotype analysis of the FOXO3A gene polymorphisms (rs4946936, rs2253310) revealed no significant association in EOP patients (not shown in table, P>0.05).

The results also revealed an association between the rs7069102 polymorphism of the SIRT1 gene and EOP (OR=2.24, 95% CI: 0.864–5.828, P=0.027, Table 4). The findings revealed no association between the rs7895833 and rs2273773 polymorphisms of the SIRT1 gene and EOP (P=0.811 and P=0.565, respectively, Table 4). The haplotype analysis of the SIRT1 gene polymorphisms (rs7895833 and rs2273773) revealed no significant differences between the EOP patients and controls (not shown in Table, P>0.05).

**Discussion**

This study is the first to report a significant association between genetic polymorphisms of SIRT1 and FOXO3A and psoriasis. The findings indicated that the FOXO3A rs4946936 and SIRT1 rs7069102 gene polymorphisms were associated with EOP. We especially have shown that these polymorphisms are also associated with disease severity in EOP. Psoriasis is an inflammatory disorder, which is characterized by a heightened immunological response by immunological cells, thereby disrupting immunoregulation. Although the complex immunogenetics of chronic plaque psoriasis are poorly understood, it is known to be a chronic inflammatory disorder, the expression of which is dependent on proinflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α), nuclear factor-kB (NF-kB) Th1 cytokines, and natural killer cells.[2] It was reported that activation and DNA binding of NF-kB because of the degradation of inhibitory proteins (IkBa) induce the transcription of target genes responsible for immune response and inflammatory functions.[20]
Omentin also has an anti-inflammatory effect that works through the NF-κB. It was shown that omentin inhibits TNF-alpha-induced IkBα degradation and NF-κB activity in human umbilical vein endothelial cells. In a previous study, the omentin gene was examined with regard to Val109Asp polymorphism, and no difference was found between the psoriasis and the control. Theodorakopoulou et al. [3] drew attention to the presence of distinct immunocytochemical differences between psoriatic skin in cases of LOP and EOP. According to the study, LOP was characterized by greater cutaneous inflammatory infiltrates and the dermis in LOP contained twice as many CD4+ cells and consequently a higher CD4:CD8 ratio as in the dermis in EOP. The study also reported significant differences in the distribution of T-cell subtypes in EOP and LOP. Hébert et al. [22] detected an association between the IL-1B-511 × 1 homozygous genotype and LOP. The same study found that a polymorphic variation of the IL-1b gene (IL-1B) was not associated with EOP but that rs16944 and rs2853550 (polymorphisms of the IL-1B gene) were associated with LOP. In addition, the study revealed that the mobilization of epidermal Langerhans cells was degraded in response to IL-1b in uninvolved skin of EOP patients but not LOP patients. Other studies detected an association between cytokine polymorphisms (TNF-α [A-238], vascular endothelial growth factor [G405C], and IL-1b) and EOP. Thus, to date, the evidence indicates that psoriasis is a complex polygenic disorder.

Table 4: Genotype and allele frequencies of silent information regulator 1 gene variants in early-onset psoriasis and healthy controls, and their association with risk of early-onset psoriasis compared to healthy controls

| SIRT1 gene | Healthy control (%) | EOP (%) | χ² | OR (95% CI) |
|------------|---------------------|---------|----|-------------|
| rs7895833  |                     |         |    |             |
| A          | 169 (68.7)          | 196 (69.09) | 0.1 | Reference    |
| G          | 77 (31.3)           | 88 (31.0)  | 0.985 (0.682-1.425) |
| AA         | 58 (47.2)           | 70 (49.3)  | 0.811 Reference    |
| GA         | 53 (43.0)           | 56 (39.4)  | 0.875 (0.525-1.461) |
| GG         | 12 (9.8)            | 16 (11.3)  | 1.105 (0.484-2.522) |
| rs7069102  |                     |         |    |             |
| C          | 135 (54.9)          | 143 (50.4) | 0.337 Reference    |
| G          | 111 (45.1)          | 141 (49.6) | 1.119 (0.851-1.689) |
| CC         | 21 (17.1)           | 26 (18.4)  | 0.027 Reference    |
| CG         | 93 (75.6)           | 91 (63.8)  | 0.782 (0.411-1.488) |
| GG         | 9 (7.3)             | 25 (17.7)  | 2.244 (0.864-5.828) |
| rs2273773  |                     |         |    |             |
| C          | 128 (52)            | 150 (52.8) | 0.862 Reference    |
| T          | 118 (48)            | 134 (47.2) | 0.969 (0.688-1.364) |
| CC         | 5 (4.1)             | 8 (5.6)    | 0.565 Reference    |
| TC         | 118 (95.4)          | 134 (94.4) | 0.710 (0.226-2.229) |
| TT         | -                   | -         |    |             |

EOP: Early-onset psoriasis, OR: Odds ratio, CI: Confidence interval, SIRT: Silent information regulator

Table 5: Genotype and allele frequencies of silent information regulator 1 gene variants in early-onset psoriasis with Psoriasis Area Severity Index level

| SIRT1 gene | Healthy control (%) | PASI <3 (%) | χ² | OR (95% CI) | PASI <10 (%) | χ² | OR (95% CI) | PASI >10 (%) | χ² | OR (95% CI) |
|------------|---------------------|-------------|----|-------------|--------------|----|-------------|--------------|----|-------------|
| rs7895833  |                     |             |    |             |              |    |             |              |    |             |
| A          | 169 (68.7)          | 85 (70.8)   | 0.718 | 0.904       | 76 (70.4)    | 0.803 | 0.924     | 35 (62.5)    | 0.429 | 1.317     |
| G          | 77 (31.3)           | 35 (29.2)   | (0.561-1.456) | 32 (29.6)    | (0.564-1.513) | 21 (37.5) | (0.720-2.410) |
| AA         | 58 (47.2)           | 30 (50.0)   | 0.916 NS | 27 (50.0)    | 0.941 NS     | 13 (46.4) | NS         |
| GA         | 53 (43.0)           | 25 (41.7)   | 22 (40.7) | 9 (32.1)    | 6 (21.4)    |
| GG         | 12 (9.8)            | 5 (8.3)     | 5 (9.3)   |
| rs7069102  |                     |             |    |             |              |    |             |              |    |             |
| C          | 135 (54.9)          | 60 (50.8)   | 0.501 | 1.176       | 55 (50.9)    | 0.563 | 1.172     | 27 (48.2)    | 0.377 | 1.306     |
| G          | 111 (45.1)          | 58 (49.2)   | (0.757-1.825) | 53 (49.1)    | (0.745-1.844) | 29 (51.8) | (0.731-2.336) |
| CC         | 21 (17.1)           | 9 (15.3)    | 0.416 NS | 10 (18.5)   | 0.163 NS     | 7 (25.0)  | NS         |
| CG         | 93 (75.6)           | 42 (71.2)   | 35 (64.8) | 13 (46.4)  | 8 (28.6)    |
| GG         | 9 (7.3)             | 8 (13.6)    | 9 (16.7)  |
| rs2273773  |                     |             |    |             |              |    |             |              |    |             |
| C          | 128 (52)            | 65 (54.2)   | 0.739 | 0.918       | 57 (52.8)    | 0.909 | 0.971     | 28 (50.0)    | 0.882 | 1.085     |
| T          | 118 (48)            | 55 (45.8)   | (0.593-1.422) | 51 (47.2)    | (0.617-1.527) | 28 (50.0) | (0.607-2.938) |
| CC         | 5 (4.1)             | 5 (8.3)     | 0.300 NS | 3 (5.6)     | 0.701 NS     | 0 (0.0)   | 0.585 NS  |
| TC         | 118 (95.4)          | 55 (91.7)   | 51 (94.4) | 28 (100.0) |

PASI: Psoriasis Area Severity Index, OR: Odds ratio, CI: Confidence interval, NS: Not significant, SIRT: Silent information regulator
Recently, studies have identified the pathophysiological functions of SIRT1 and FOXO3A in various biological processes (e.g., cell-cycle regulation, apoptosis, and oxidative stress), and they have demonstrated the interaction between SIRT1 and FOXO1 in different studies.\[9,10,26\] These studies showed that FOXO3A exerted its effects on biological processes by controlling the expression of the target genes.\[10,26\] A number of studies demonstrated that oxidative stress and genetic proclivity were important in various dermatological disorders, such as vitiligo and psoriasis.\[8,11\]

Ozel Turkcu et al. revealed an association between vitiligo and FOXO3A gene variants. In the study, the authors determined that decreased serum FOXO3A levels and catalase activity in vitiligo patients.\[11\] In addition, the authors showed that increased superoxide dismutase antioxidant enzyme activities in vitiligo patients. They suggested that low FOXO3A levels might be associated with increased oxidative stress and that FOXO3A might regulate superoxide dismutase and catalase antioxidant enzyme activity through the removal of superoxide anions and H$_2$O$_2$. Furthermore, they suggested that the rs4946936 polymorphism of the FOXO3A gene might be associated with susceptibility to vitiligo. Until now, there have been no studies of the association between psoriasis and FOXO3A gene variants.

Brunet et al.\[19\] suggested that the TT genotype and T allelic frequencies in the rs4946936 polymorphism of the FOXO3A gene were associated with the risk of vitiligo. The present study found an association between the FOXO3A gene variant rs4946936 and psoriasis but no relationship with the rs2253310 polymorphism. Previous studies of polymorphisms of FOXO3A confirmed the association of FOXO3A with inflammatory diseases, such as chronic obstructive pulmonary disease, rheumatoid arthritis, and inflammatory bowel disease.\[27-29\]

Previous studies suggested that SIRT1–SIRT7 may play roles in skin aging and autoimmune skin disorders characterized by hyperproliferation and inflammation, including psoriasis, as well as cutaneous fungal infections, inherited dermatological diseases, and skin cancer.\[14,18\] It was reported that omentin-1 promotes apoptosis through regulating SIRT1-dependent p53 deacetylation in hepatocellular carcinoma cells and an adipocyte-derived hormone would contribute to the therapeutic strategies for hepatocellular carcinoma.\[30\]

Research also demonstrated that SIRT1 enhanced the ability of FOXO3 to induce resistance to oxidative stress and cell-cycle arrest by inhibiting the ability of FOXO3 to induce cell death.\[19\] Gene expression data were shown to support a role for SIRT1 inhibition of keratinocyte proliferation, and the data were confirmed by in vitro assays using human epidermal keratinocytes.\[18\] Furthermore, studies demonstrated that the regulation of SIRT1 or SIRT6 appeared to result in downregulation of the activity of TNF-α.\[31-33\] The TNF-α pathway is known to be involved in a number of inflammatory skin disorders, including psoriasis.\[34\] Although, it has detected that many cytokines play role in the proliferation of keratinocytes in psoriasis, the major mediator in the pathogenesis of this disease is TNF-α.\[8\] Reactive oxygen species play a basic role in the transformation of signals into transcription factors and activation of transcription factors. It was shown that TNF-α increased proinflammatory cytokine expression by the effect of reactive oxygen species.\[12\] Ludikhuizeet et al.\[18\] showed that modulation of the function of SIRT directed at inhibition of TNF-α. Investigations of the potential utility of modulation of SIRT in the treatment of hyperproliferative skin disorders are ongoing. The finding of the present study of an association between the rs7069102 gene polymorphism and psoriasis can aid these investigations.

**Conclusion**

To the best of our knowledge, this is the first study to investigate the association with genetic polymorphisms of SIRT1 and FOXO3A in EOP. The results indicate that the rs4946936 and rs7069102 polymorphisms of the FOXO3A and SIRT1 genes, respectively, might be associated with susceptibility to psoriasis, especially EOP. We especially have shown that these polymorphisms are important for disease severity in EOP. Further studies with larger samples are required to elucidate the molecular mechanism underlying the association of FOXO3A and SIRT1 with psoriasis. In our study, although the sample size is not too small overall, it might be inadequate for the subcategories. Therefore, the results obtained in this study should be supported by other studies conducted with larger patient groups including LOP and by assessing other gene polymorphisms. It may be a study that could shed light on the pathogenesis of psoriasis in the future.

**Financial support and sponsorship**

Nil.

**Conflicts of interest**

There are no conflicts of interest.

**What is new?**

FOXO3A and SIRT1 gene variants may play a role in the pathogenesis of early-onset psoriasis.

**References**

1. Lebwohl M. Psoriasis. Lancet 2003;361:1197-204.
2. Donn RP, Plant D, Jury F, Richards HL, Worthington J, Ray DW, et al. Macrophage migration inhibitory factor gene polymorphism is associated with psoriasis. J Invest Dermatol 2004;123:484-7.
3. Theodorakopoulou E, Yiu ZZ, Bundy C, Chularrajanantonti L, Gittins M, Jamieson LA, et al. Early- and late-onset psoriasis: A cross-sectional clinical and immunocytochemical investigation. Br J Dermatol 2016;175:1038-44.

4. Henseleit T, Christophers E. Psoriasis of early and late onset: Characterization of two types of psoriasis vulgaris. J Am Acad Dermatol 1985;13:450-6.

5. Allen MH, Ameen H, Veal C, Evans J, Ramrakha-Jones VS, Marsland AM, et al. The major psoriasis susceptibility locus PSORS1 is not a risk factor for late-onset psoriasis. J Invest Dermatol 2005;124:103-6.

6. Holgate MC. The age-of-onset of psoriasis and the relationship to parental psoriasis. Br J Dermatol 1975;92:643-8.

7. Di Meglio P, Villanova F, Nestle FO. Psoriasis. Cold Spring Harb Perspect Med 2014-4; pii: a015354.

8. Emre S, Demirseren DD, Alisik M, Aktas A, Neselioglu S, Erel O, et al. Dynamic thiol/disulfide homeostasis and effects of smoking on homeostasis parameters in patients with psoriasis. Cutan Ocul Toxicol 2017;36:393-3.

9. Kedenko L, Lamina C, Kedenko I, Kollerits B, Kiesslich T, Iglèsies B, et al. Genetic polymorphisms at SIRT1 and FOXO1 are associated with cutaneous attherosclerosis in the SAPHIR cohort. BMC Med Genet 2014;15:112.

10. Furuwaka-Hibi Y, Kobayashi Y, Chen C, Motoshima N. FOXO transcription factors in cell-cycle regulation and the response to oxidative stress. Antioxid Redox Signal 2005;7:752-60.

11. Ozel Turkcu U, Solak Tekin N, Godkolgan Edgunlu T, Karakas Celik S, Oner S. The association of FOXO3A gene polymorphisms with serum FOXO3A levels and oxidative stress markers in vitiligo patients. Gene 2014;536:129-34.

12. Srivastava RK, Unterman TG, Shankar S. FOXO transcription factors and VEGF neutralizing antibody enhance antiangiogenic effects of resveratrol. Mol Cell Biochem 2010;337:201-12.

13. Klotz LO, Sánchez-Ramos C, Prieto-Arroyo I, Urbánek P, Serravallo M, Jagdeo J, Glick SA, Siegel DM, Brody NI. Sirtuin 1 (SIRT1): The misunderstood protein kinase. J Biol Chem 2011;286:269-82.

14. Stünkel W, Campbell RM. Sirtuin 1 (SIRT1): The misunderstood transcription factor in cell-cycle regulation and the response to oxidative stress. Antioxid Redox Signal 2005;7:752-60.

15. Brunet A, Bonni A, Zigmond MJ, Lin MZ, Juo P, Hu LS, et al. Akt promotes cell survival by phosphorylating and inhibiting a forkhead transcription factor. Cell 1999-96:857-68.

16. Calamia S, Edgulun TG, Turkcu UO, Ketin ES, Zeybek A, Candan H. FOXO3a gene polymorphism and serum FOXO3a levels in patients with chronic obstructive pulmonary disease and healthy controls: Effects of genetic polymorphism in chronic obstructive pulmonary disease. Smyrna Med J 2014;1:1-5.

17. Ludikhuize J, de Launay D, Grob D, Smeets TJ, Vinkenoog M, Sanders ME, et al. Inhibition of forkhead box class 0 family member transcription factors in rheumatoid synovial tissue. Arthritis Rheum 2007;56:2180-91.

18. Snoeks L, Weber CR, Wasland K, Turner JR, Vainder C, Qi W, et al. Tumor suppressor FOXO3 regulates the expression of murine ferritin in breast cancer cell lines. Mol Cancer 2005;4:pii: a015354.

19. Zhong X, Li X, Liu F, Tan H, Shang D. Omentin inhibits TNF-α-induced expression of adhesion molecules in endothelial cells via ERK/NF-κB pathway. Biochem Biophys Res Commun 2012;425:401-6.

20. Hébert HL, Bowes J, Smith RL, McHugh NJ, Barker JN, Griffiths CE, et al. Polymorphisms in IL-1B distinguish between psoriasis of early and late onset. J Invest Dermatol 2014;134:1459-62.

21. Reich K, Mössner R, König IR, Westphal G, Ziegler A, Neumann C, et al. Promoter polymorphisms of the genes encoding tumor necrosis factor-alpha and interleukin-1beta are associated with different subtypes of psoriasis characterized by early and late disease onset. J Invest Dermatol 2002;118:155-63.

22. Young HS, Summers AM, Bhushan M, Brenchley PE, Griffiths CE. Single-nucleotide polymorphisms of vascular endothelial growth factor in psoriasis of early onset. J Invest Dermatol 2004;122:209-15.

23. Capon F, Munro N, Barker J, Trembath R. Searching for the major histocompatibility complex psoriasis susceptibility gene. J Invest Dermatol 2002;118:745-51.

24. Brunet A, Bonni A, Zigmond MJ, Lin MZ, Juo P, Hu LS, et al. Akt promotes cell survival by phosphorylating and inhibiting a forkhead transcription factor. Cell 1999-96:857-68.

25. Kadenko L, Lamina C, Kedenko I, Kollerits B, Kiesslich T, Iglèsies B, et al. Genetic polymorphisms at SIRT1 and FOXO1 are associated with cutaneous attherosclerosis in the SAPHIR cohort. BMC Med Genet 2014;15:112.

26. Furuwaka-Hibi Y, Kobayashi Y, Chen C, Motoshima N. FOXO transcription factors in cell-cycle regulation and the response to oxidative stress. Antioxid Redox Signal 2005;7:752-60.

27. Ozel Turkcu U, Solak Tekin N, Godkolgan Edgunlu T, Karakas Celik S, Oner S. The association of FOXO3A gene polymorphisms with serum FOXO3A levels and oxidative stress markers in vitiligo patients. Gene 2014;536:129-34.

28. Srivastava RK, Unterman TG, Shankar S. FOXO transcription factors and VEGF neutralizing antibody enhance antiangiogenic effects of resveratrol. Mol Cell Biochem 2010;337:201-12.

29. Klotz LO, Sánchez-Ramos C, Prieto-Arroyo I, Urbánek P, Steinbrenner H, Monsalve M, et al. Redox regulation of Fox0 transcription factors. Redox Biol 2015;6:51-72.

30. Serravallo M, Jagdeo J, Glick SA, Siegel DM, Brody NI. Sirtuins in dermatology: Applications for future skin and therapeutic. Arch Dermatol Res 2013;305:269-72.

31. Vaziri H, Dessain SK, Ng Eaton E, Imai SI, Frye RA, Pandita TK, et al. Sirtuin 1 (SIRT1): The misunderstood transcription factor in cell-cycle regulation and the response to oxidative stress. Antioxid Redox Signal 2005;7:752-60.

32. Zhang YY, Zhou LM. Omentin-1, a new adipokine, promotes apoptosis through regulating Sirt1-dependent p53 deacetylation in hepatocellular carcinoma cells. Eur J Pharmacol 2013;698:137-44.

33. Kalmeci S, Edgulun TG, Turkcu UO, Ketin ES, Zeybek A, Candan H. FOXO3a gene polymorphism and serum FOXO3a levels in patients with chronic obstructive pulmonary disease and healthy controls: Effects of genetic polymorphism in chronic obstructive pulmonary disease. Smyrna Med J 2014;1:1-5.

34. Vinkenoog M, Sanders ME, et al. Inhibition of forkhead box class 0 family member transcription factors in rheumatoid synovial tissue. Arthritis Rheum 2007;56:2180-91.

35. Snoeks L, Weber CR, Wasland K, Turner JR, Vainder C, Qi W, et al. Tumor suppressor FOXO3 regulates the expression of murine ferritin in breast cancer cell lines. Mol Cancer 2005;4:pii: a015354.

36. Zhang YY, Zhou LM. Omentin-1, a new adipokine, promotes apoptosis through regulating Sirt1-dependent p53 deacetylation in hepatocellular carcinoma cells. Eur J Pharmacol 2013;698:137-44.

37. Kalmeci S, Edgulun TG, Turkcu UO, Ketin ES, Zeybek A, Candan H. FOXO3a gene polymorphism and serum FOXO3a levels in patients with chronic obstructive pulmonary disease and healthy controls: Effects of genetic polymorphism in chronic obstructive pulmonary disease. Smyrna Med J 2014;1:1-5.