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ORIGINAL ARTICLE

Association between Single-nucleotide Polymorphism of miR-146a and Psoriasis

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ABSTRACT

Background: *Micro-RNAs (miRNAs) play important roles in the development of different inflammatory conditions of the skin. However, few studies investigated the association between miR-146a and psoriasis.* ***Aim of the work:*** *This work aimed to study the association between miR-146a single-nucleotide polymorphism (SNP) rs2910164 and the risk of psoriasis and to study the association between levels of skin expression of miR-146a and the response to treatment.* ***Methodology:*** *The study was carried out on 120 patients with psoriasis and 60 control subjects. The miR-146a rs2910164 SNP was detected by using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) analysis. Levels of skin expression of miR-146a were detected by Real Time PCR before and 3 months after treatment with PUVA therapy.* ***Results:*** *Non significant association could be found between combined (CG+GG) genotypes and risk of psoriasis [OR (95% CI) = 0.81 (0.41-1.60)], (P=0.52). The level of miR-146a expression was significantly increased in patients compared to controls, with the highest level recorded in patients with CC genotype. There was a significant decrease in the miR-146a levels after treatment in both CC (P<0.001) & CG (P=0.01) genotypes but not in GG genotype (P=0.29). MiR-146a levels were higher in patients responding to treatment than non-responders (P<0.001). Also, there was significantly higher response to PUVA treatment in CC genotype (100%) than in CG genotype (50%) and GG genotype (20%) (P<0.001).* ***In conclusion,*** *no significant association could be found between combined rs2910164 genotypes (CG + GG) and risk of psoriasis. Moreover, measuring miR-146a level and knowing patients' genotype could be useful predictors of therapeutic response.*

INTRODUCTION

Psoriasis is a chronic inflammatory condition affecting the skin, resulting from an interplay between the immune system, susceptibility genes, and environmental factors [1].

Micro-RNAs (miRNAs) are small, noncoding RNA molecules that regulate expression of genes post-transcriptionally via binding to complementary sequences in the coding region or 3' untranslated region of target messenger RNAs (mRNAs)[2].

Huang et al.[2] found that miRNAs function as regulators of different biological processes like cell proliferation, development, apoptosis, haematopoiesis and, importantly, tumourigenesis.

Different miRNAs have been found to be abnormally expressed in psoriatic patients. One of the highly upregulated miRNAs in psoriasis is miR-146a [3]. MiR-146a is an essential negative regulator of inflammation, autoimmunity, and the innate immunity [4]. This miRNA promotes resolution of the immune response by negatively regulating nuclear factor kappa-light-chain enhancer of activated B cells (NF-kB)-dependent inflammatory signals through direct targeting of IL-1 receptor associated kinase 1 (IRAK1) and TNF receptor associated factor 6 [5]. TNF receptor associated factor 6 and IRAK1 are key signaling mediators involved in the secretion of pro-inflammatory cytokines (e.g., IL-6 and TNF-a) after toll-like receptor and IL-1 receptor activation [4].

A single-nucleotide polymorphism (SNP) called rs2910164 located within the miR-146a precursor. This SNP has been found to affect the miR-146a level and related to the risk of different inflammatory diseases and cancers [6].

However, there is no enough data about the contribution of rs2910164 to the development of psoriasis. This work aimed to study the relation between a functional miR-146a rs2910164 SNP and the risk of psoriasis and to study the association between the levels of skin expression of miR-146a and the treatment response according to genotypes in patients with psoriasis, in Benha University Hospital, Egypt.

METHODOLOGY

This observational case–control study was carried out during the period from January 2015 to December

2017 in Benha University, Egypt. The work was approved by Ethics Committee for Human Research of Benha University. It was carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments in humans. Informed consent was obtained from all participants or their guardians.

Study participants

The study involved 120 Egyptian psoriatic patients and 60 sex and age matched healthy individuals served as control group. The study included patients who had active plaque psoriasis, psoriasis involving ≥10 % of surface area of the body and a baseline Psoriasis Area and Severity Index (PASI) ≥ 10, were candidates for systemic therapy or photochemotherapy [7]. Patients who received any treatments for psoriasis and patients having any other autoimmune disorders, cancers, chronic illnesses or comorbidities were excluded from the study.

Patients received 12 weeks of PUVA (psoralen and ultraviolet A) treatment, three sessions per week in the phototherapy unit in the Dermatology, Andrology and Venereology Department in Benha University hospital. Psoralen was given two hours before UVA exposure. The UVA dose followed the guidelines published by the American Academy of Dermatology [7].

A standard questionnaire was used to collect demographic data (e.g., age, sex, disease onset, course, duration and family history). PASI score of each patient was assessed by dermatologists. The patients were assessed before PUVA treatment and 12 weeks after treatment. The response to treatment is evaluated by decrease in PASI score by > 75%.

Method

Genotyping:

The miR-146a rs2910164 SNP was detected by using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) analysis. DNA isolation kit (QIAGEN, Germany) was used to extract genomic DNA from the peripheral blood. PCR amplification was done using DreamTaq Green PCR Master Mix (2X) (Thermo-Scientific, Lithuania). Amplification was generated by using the miR-146a gene primers (Invitrogen, Germany) which gives a product of 147 bp, forward 5'-CATGGGTTGTGTCAGTGTCAGAGCT-3', reverse 5' TGCCTTCTGTCTCCAGTCTTCCAA- 3'.

PCR was performed under the following conditions: 95°C for 5 min.; 32 cycles of 95°C for 30 sec., annealing temperature of 56°C for 30 sec. and 72°C for 40 sec.; and final extension step at 72°C for 10 min [8]. The amplified product was digested by SacI restriction enzyme (ThermoScientific, Lithuania) which cuts only the C allele, resulting in 125- and 22-bp fragments (Figure1), and all products of PCR were electrophoresed and visualized using UV transilluminator.

Relative Quantitation of miR-146a expression:

A 3-mm punch biopsy was taken from lesional area of each psoriatic patient (before and after PUVA treatment) and from equivalent area of each control subject and immediately stored in RNA later solution (RNA stabilizing reagent) (QIAGEN, Germany) at -80°C for further processing. Total RNA was extracted by use of miRNeasy Mini Kit (QIAGEN, Germany). cDNA was synthesized from miRNA by use of miScript II RT Kit (QIAGEN, Germany) according to manufacturer's protocol. Quantitative real time PCR: it was done following the SYBR Green PCR protocol by use of miScript SYBR Green PCR Kit (QIAGEN, Germany) with the StepOne real-time PCR. Each reaction mix contained 2x Quanti- Tect SYBR Green PCR Master Mix, 10x miScript Universal Primer, 10x miScript Primer Assay specific for miR-146a (hsa-miR-146a-5p), template cDNA, and RNase-free water in a total volume of 25 µl. The real time PCR instrument Rotor-Gene Q (QIAGEN, Germany) was used with the following instrument settings: enzyme activation at 95 ˚C for 15 min, followed by 45 cycles of denaturation at 94 ˚C for 15 s annealing at 55 ˚C for 30 s and extension at 70 ˚C for 30 s. Primer sequence of miR-146a was: 5'UGAGAACUGAAUUCCAUGGGUU. Primer sequence of Glyceraldehyde Phosphate Dehydrogenase (GAPDH) as internal control (housekeeping gene) was: Forward 5' GAAATCCCATCACCATCTTCCAGG -3' Reverse 5′ GAGCCCCAGCCTTCTCCATG- 3′. Because the relative quantities of the miR-146a gene are normalized against the relative quantities of the endogenous control (GAPDH) gene fold expression changes are calculated using the equation $2^{-\Delta\Delta ct}$ [9].

Statistical analysis:

The collected data were summarized in terms of mean ± Standard Deviation (SD) for quantitative data and frequency and percentage for qualitative data. The study groups were compared using the Chi-square (χ^2) and Fisher's Exact Test (FET) to compare proportions as appropriate. The odds ratio (OR) and 95% Confidence Interval (95% CI) were also calculated.

The student t-test (*t*) was used for comparing two groups regarding parametric data. While, one-way Analysis Of Variance (ANOVA; F) was used for comparing more than two groups followed by post hoc test, using the Bonferroni method to detect differences in pairs. The Pearson correlation coefficient (r) was used to assess the correlation between miRNA levels and some estimated parameters. Genotype frequencies were tested for the deviation from Hardy–Weinberg equilibrium and compared for statistical differences with the Cochrane test. The accepted level of significance in this work was stated at 0.05 ($P < 0.05$ was considered significant). All statistical analyses were done using STATA/SE version 11.2 for Windows (STATA Corporation, College Station, Texas) Receiver Operating Characteristics (ROC) analysis was carried

out to evaluate the diagnostic performance of miRNA skin levels for response to treatment among studied cases.

RESULTS

The psoriasis patients were 66 males and 54 females with mean age (range) of 39.55±18.72; (8-70), while the healthy control group were 36 males and 24 females with mean age (range) of 34.8±18.06; (3-65).

Out of the 120 psoriasis patients, 36 (30%) had +ve family history of psoriasis. 50% of patients had disease with duration more than 12 months and 65% of them recorded PASI score above 20.

Results of genotyping of polymorphic restriction sites in the miR-146a gene were shown in Figure 1. The frequencies of the CC, CG and GG genotypes for the miR-146a gene polymorphism were illustrated in Table 1. The CC genotype had the highest frequency of 45% in cases and 40% in controls, respectively. No significant differences could be found between patients and controls as regards CC, CG, GG genotypes distribution (P=0.39, 0.26 and 0.80, respectively).

Compared with the wild miR-146a rs2910164 CC genotype, there was no significant relation between combined rs2910164 genotypes (CG + GG) and risk of psoriasis (OR (95% CI) =0.81 (0.41-1.60) (P= 0.52), Table 1.

Table 1: Alleles and genotypes frequencies distribution of rs2910164 miR-146a SNP in psoriasis patients and controls

Genotype	Psoriasis (no.=120)		Controls (no.=60)		Chi-square test	P value	OR (95% CI)
	no.	%	no.	%			
CC	54	45.0	24	40.0	1.86	0.39	1.00 (reference)
CG	36	30.0	24	40.0	1.27	0.26	0.67 (0.31-1.43)
GG	30	25.0	12	20.0	0.06	0.80	1.11 (0.45-2.80)
CC	54	45.0	24	40.0	0.41	0.52	0.81 (0.41-1.60)
CG + GG	66	55.0	36	60.0			
Allele C	144/240	60.0	72/120	60.0	0.00	1.00	1.00 (0.62-1.61)
Allele G	96/240	40.0	48/120	40.0			

OR: Odds ratio. 95% CI: 95% Confidence Interval. Significant P <0.05.

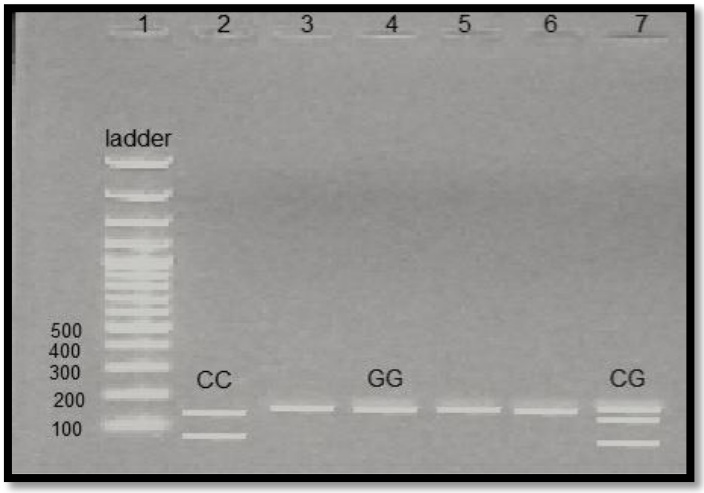

Fig. 1: The SacI restriction profiles of the C/G polymorphic site of miR-146agene.

- Lane 1: DNA ladder (100-1000bp).
- Lane 2: CC genotype (homozygous wild) 125 bp, 22 bp PCR products.
- Lane 4: GG genotype (homozygous polymorphic) 147 bp PCR product.
- Lane 7: CG genotype (heterozygous polymorphic) 147 bp, 125 bp, 22 bp PCR products.

The level of miR-146a expression was increased in psoriasis patients by 3.1 folds when compared with controls.

There were significant differences in the miR-146a levels among patients and controls with different genotypes. The highest levels detected in patients and controls with CC genotype (Table 2).

Table 2: The levels of miR-146a expression among different genotypes in psoriasis patients and controls

Genotypes	miR-146a expression levels (Fold change)		Test	P Value
	Patients (no.) Mean ± SD	Controls (no.) Mean ± SD		
CC	(no. = 54) 4.70 ±1.3	(no.= 24) 1.62 ± 0.47	t =15.46	**<0.001**
CG	(no. = 36) †2.02 ± 0.49	(no.= 24) †0.72 ± 0.12	t= 15.73	**<0.001**
GG	(no.=30) †1.92 ± 0.53	(no. = 12) †0.55 ± 0.06	t=8.64	**<0.001**
Test	F=40.12	F=22.72		
P value	**<0.001**	**<0.001**		

F: One way Analysis Of Variance (ANOVA). t: student t-test.
†: Significant differences compared to genotype CC. Significant P <0.05.

No significant relation could be found between level of skin expression of miR-146a and each of age, gender, family history, onset, duration, or PASI score (P = 0.78, 0.94, 0.77, 0.14, 0.82, 0.37, respectively) (Table 3).

There was significant reduction in the mean levels of miR-146a after 3 months of PUVA therapy (from 3.2±1.66 to 2.15± 1.05, t=6.59; P<0.001, Table 3).

Table 3: Variations in levels miR-146a expression by different variables

Variable		no.	miR-146a levels Mean ± SD	Test	P value
Sex	Female	54	3.22±1.73	t= 0.07	0.94
	Male	66	3.18±1.64		
Family history	No	84	3.25±1.61	t= 0.29	0.77
	Yes	36	3.08±1.85		
Duration	≤12 months	60	3.14±1.63	t= 0.22	0.82
	>12 months	60	3.26±1.73		
Onset	≤40 years	102	3.03±1.65	t= 1.51	0.14
	>40 years	18	4.13±1.5		
PASI	≤20	42	3.53±1.91	t= 0.91	0.37
	>20	78	3.02±1.52		
Before treatment		120	3.2±1.66	t=6.59	<0.001
After treatment		120	2.15±1.05		
Age (years)				r=0.04	0.78

t: Paired t-test. r: Pearson correlation coefficient. Significant P <0.05.

The reduction was significant in both CC (P<0.001) & CG (P=0.01) genotypes but not in GG genotype (P=0.29, Table 4).

Table 4: The expression levels of miR-146a among different genotypes in psoriasis patients before and after treatment

Genotype	no.	miR-146a expression levels (Fold change)		Test	P value
		Before treatment Mean ± SD	After treatment Mean ± SD		
CC	54	4.70 ±1.3	2.87 ± 1.02	t= 9.89	**<0.001**
CG	36	†2.02 ± 0.49	†1.35 ± 0.52	t =3.3	**0.01**
GG	30	†1.92 ± 0.53	†1.84 ± 0.71	t=1.12	0.29
Test		F=40.12	F=13.10		
P value		**<0.001**	**<0.001**		

F: One way Analysis Of Variance (ANOVA) Significant (p < 0.05).
†: Significant differences compared to genotype CC

Baseline miR-146a expression was compared between responders (78 patients) and non-responder (42 patients). The level was significantly higher in patients responding to treatment (3.87±1.7) than those not responding to treatment (1.96 ± 0.43, P<0.001, Figure 2). Also, there was significantly higher response in CC genotype (100%) than in CG genotype (50%) and GG genotype (20%), P<0.001.

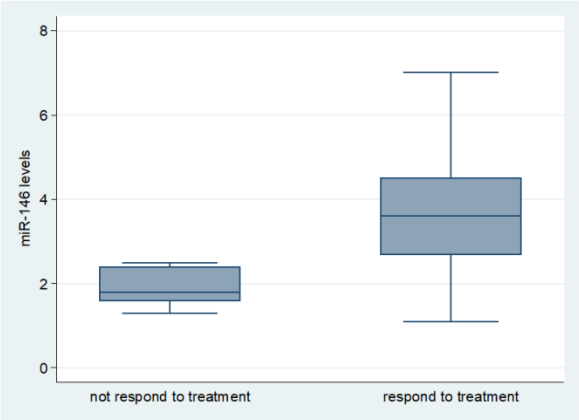

Fig. 2: miR-146a expression (Fold change) and the treatment response in psoriasis patients

The role of each of miR-146a level and genotyping as a predictor for treatment response was determined and Receiver-operating characteristic (ROC) curves were constructed. The ROC analysis which represents the predictive ability of miR-146a for the treatment response showed the best cut off ≥1.9, and the corresponding sensitivity, specificity, PPV, NPV and AUC were 84.62%, 57.14 %, 78.57 %, 66.67% and 0.8626, respectively (Figure 3). The ROC analysis which represent the predictive value of genotyping for the treatment response showed the corresponding sensitivity, specificity, PPV, NPV and AUC were 69.2%, 100 %, 100 %, 63.6% and 0.8462 (Figure 4).

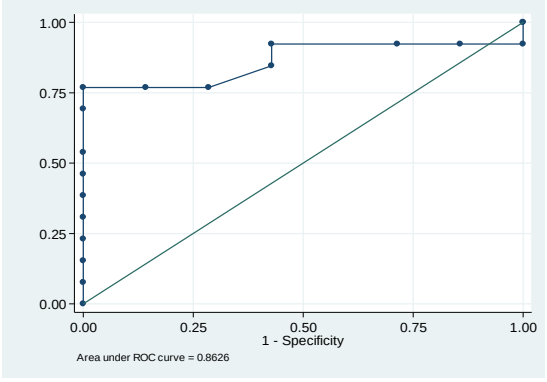

Fig. 3: ROC analysis for miR-146a expression levels as predictors for the treatment response in psoriasis patients.

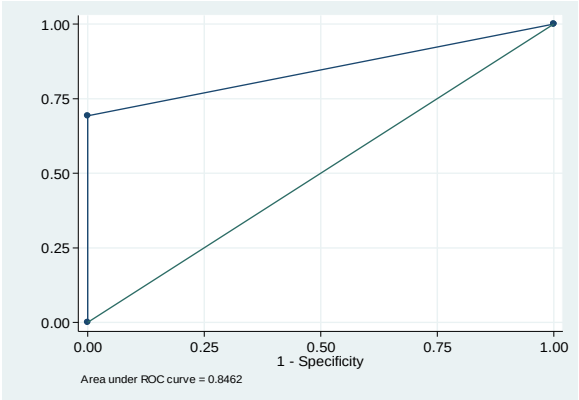

Fig. 4: ROC analysis for CC genotypes vs. CG and GG as a predictor for the treatment response in psoriasis patients.

DISCUSSION

An area of considerable interest is whether a single miRNA or a group of miRNAs can act as biomarkers of psoriasis. Several miRNAs have been found aberrantly expressed in psoriatic tissues [10]. One of the up-regulated miRNAs in skin of psoriatic patients is miR-146a [3].

In the present study, levels of skin expression of miR-146a was increased in psoriasis patients by 3.1 folds when compared with controls. These results come in agreement with that reported by other studies [3, 8, 11]. Also, in certain study, [12] the authors reported that the miR-146a expression in PMBCs from psoriasis patients was significantly up-regulated compared to healthy controls (the fold changes were 2.08 vs. 0.61, respectively).

Several studies [13,14] implicated that miR-146a is increased in psoriatic lesions. However, whether miR-146a serves as a disease promoter or a protective factor in psoriasis is not clear.

In one report [3], the authors reported that increased miR-146a with impaired function failed to supress the expression of IRAK1, thus inducing IL-17 persistence in psoriatic skin lesions, which an increasingly important cytokine in psoriasis pathogenesis.

In another study [8], it is proved that miR-146a can inhibit the epidermal growth factor receptor (EGFR) and hence, the proliferation of keratinocytes. Considering the fact that EGFR is over-expressed in psoriasis, the up-regulation of miR-146a may be a protectively negative feedback factor in psoriasis.

Indeed, Srivastava et al., [15] identified a protective role of miR-146a in psoriasis, as they found that the genetic deletion of miR-146a lead to alteration of the disease course, with delayed healing and earlier onset in the mouse model of psoriasis.

Although, skin samples from psoriasis patients with a GG or CG genotypes showed significant lower-

expression levels of miR-146a than those with a CC genotype, the results of this study demonstrated that, compared with the wild miR-146a rs2910164 CC genotype, there was non-significant association between combined (CG + GG) genotypes and risk of psoriasis (OR (95% CI) =0.81 (0.41-1.60) (p= 0.52).

These results come in accordance with the results of a work [16] that studied the association between psoriatic arthritis in patients from Greece and SNP found in miR-146a (rs2910164). They found no association between the rs2910164 miR-146a variant and psoriatic arthritis susceptibility.

In contrast to these results, Zhang et al., [8] reported that the rs2910164 miR-146a was associated with increased susceptibility to psoriasis in Han Chinese patients specifically; the rs2910164G allele which result in reduction in miR-146a levels and impaired its ability to regulate EGFR. They explained the protective role of the CC genotype, which has found to be accompanied by increased miR-146a levels by less sensitivity to IL-17–mediated inflammation of skin in these subjects, however, the reduced levels of skin miR-146a in subjects of GG/CG genotype rendering them more susceptible to the disease as a result of increased inflammatory processes caused by insufficient feedback suppression of the IL-17A signaling pathway**.**

In the white population, the protective allele is a minor allele, in which the psoriasis prevalence is much higher (3% to 4%) [(17)], than in the Chinese Han population (<1%) [8]**,** in which it represents the major allele. In the present study the CC genotype represent (45%, 40%) while CG + GG represent (55%, 60%) among patients and control group, respectively. The different frequencies in rs2910164 alleles might be the basis of differences in the psoriasis prevalence among patients of different ethnicities, in addition to other environmental and genetic factors.

As regards the relation between miR-146a levels and disease severity, the results of this study found no significant relation between miR-146a levels and PASI score (p= 0.37). This result comes in agreement with another study in Egypt [18] as they reported no significant positive relation with PASI scores in their patients. In contrast to this result, Yang et al., [12] reported that the miR-146a levels were highly correlated with severity of psoriasis, suggesting that miR-146a is a good marker for disease activity.

The effect of systemic therapies on specific psoriasis related miRNAs has been explored. The effect of PUVA therapy is variable on different miRNAs. The current work studied the impact of PUVA therapy on miR-146a and the result found a significant decrease of miR-146a levels after PUVA therapy (p<0.001). However, another study [19] found that miR-4516 is upregulated after PUVA therapy as it mediates down-regulation of STAT3 and apoptosis in keratinocytes exposed to PUVA therapy**.**

The alteration of miRNAs expression after systemic treatments of psoriasis is, for some degree, specific to each treatment, thus they can be used as predictors of treatment efficacy [11,20].

The present work studied the predictive ability of miR-146a levels for the treatment response and the results showed statistically significant relation between miR-146a skin levels and the treatment response being higher in the patients who showed response to treatment. ROC curve was constructed and AUC was 0.8626. This result supports the ability of miR-146a level to be used as a predictor of treatment response to PUVA therapy. Also, Yang et al., [12] suggested that miR-146a may serves as a good biomarker for the response to Zhuhuang Granule treatment which is used traditionally in China for the treatment of psoriasis.

Our results showed a significantly higher response to treatment in CC genotype (100%) than in CG genotype (50%) and GG genotype (20%). This may be explained by the higher levels of the protective miR-146a in CC genotype than in CG and GG genotypes. ROC curve, which represent the predictive value of genotyping for the response to treatment, was constructed, the corresponding sensitivity, specificity, PPV, NPV and AUC were 69.2%, 100 %, 100 %, 63.6% and 0.8462, respectively.

So, measuring the of miR-146a levels and knowing the genotype of miR-146a gene before treatment with PUVA is recommended by this work, as the physicians can predict treatment response in psoriasis patients.

CONCLUSION

No significant association could be found between a functional miR-146a rs2910164 SNP and the risk of psoriasis. The levels of skin expression of miR-146a were decreased after PUVA therapy in different genotypes. Baseline measuring of the miR-146a levels and knowing the genotype of miR-146a gene, can predict PUVA response in psoriasis patients.

Conflict of Interest: The authors have declared no conflicting interest.

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