Original Article

Peroxisome Proliferator-Activated Receptor-\( \gamma \) Gene Polymorphism in Psoriasis and Its Relation to Obesity, Metabolic Syndrome, and Narrowband Ultraviolet B Response: A Case-Control Study in Egyptian Patients

Iman Seleit, Ola Ahmed Bakry, Eman Abd El Gayed, Mai Ghanem

Abstract

Background: Psoriasis is a common dermatologic disease with multifactorial etiology in which genetic factors play a major role. Peroxisome proliferator-activated receptor (PPAR)-\( \gamma \) is expressed in keratinocytes and is known to affect cell maturation and differentiation in addition to its role in inflammation. Aim: To study the association between PPAR-\( \gamma \) gene polymorphism and psoriasis vulgaris in Egyptian patients to explore if this polymorphism influenced disease risk or clinical presentation. Methods: Forty-five patients with psoriasis vulgaris and 45 age, sex and body mass index matched healthy volunteers who have no present, past or family history of psoriasis as a control group were enrolled. Selected cases included obese and nonobese participants. Detection of PPAR-\( \gamma \) gene polymorphism was done with restriction fragment length polymorphism polymerase chain reaction. Narrow-band ultraviolet B (NBUVB) was given for every case three times/week for 12 weeks. Results: Homopolymorphism, heteropolymorphism, and Ala allele were significantly associated with cases (\( P = 0.01 \), \( P = 0.01 \), and \( P = 0.004 \), respectively) and increased risk of occurrence of psoriasis by 5.25, 3.65, and 3.37 folds, respectively. Heteropolymorphism was significantly associated with nonobese cases compared to obese ones (\( P = 0.01 \)). Ala allele was significantly associated with obese cases (\( P = 0.001 \)) and increased risk of occurrence of psoriasis in obese participants by 1.14 folds. Homopolymorphism, heteropolymorphism, and Ala allele were more prevalent among obese cases without metabolic syndrome (MS) than obese cases with MS but without statistical significance. Percentage of decrease of mean Psoriasis Area and Severity Index score before and after 3 months of treatment with NBUVB was higher in cases with heteropolymorphism with no significant difference between homo- and heteropolymorphism. Conclusion: PPAR-\( \gamma \) gene polymorphism is associated with and increased the risk of psoriasis and its associated obesity in Egyptian patients. It has no role in NBUVB response in those patients. Future large-scale studies on different populations are recommended.

Key Words: Gene polymorphism, metabolic syndrome, obesity, peroxisome proliferator-activated receptor-\( \gamma \), psoriasis

Introduction

Psoriasis is a common erythrosquamous skin disorder with varying clinical presentations.[1] Psoriasis is a common dermatologic disease that affects >125 million people worldwide and its incidence seems to be increasing over time.[1] The prevalence of psoriasis in Egypt ranges between 0.19% and 3%.[1]

The exact disease pathogenesis is not yet settled, but most reports postulate that disease develops as a result of interaction between metabolic, environmental, and genetic factors.[4]

Genetic factors play a fundamental role in the etiopathogenesis of psoriasis. There is evidence for at least eight psoriasis susceptibility loci, termed PSORS1-7 and PSORS9.[5]

Obesity and metabolic syndrome (MS) are among the most important comorbidities of psoriasis.[6-8] This may be due to lifestyle factors, shared inflammatory pathways, and genetic factors.[9]

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Peroxisome proliferator-activated receptors (PPARs): PPAR-α, PPAR-β/δ, and PPAR-γ are nuclear hormone receptors that act as key transcriptional regulators of lipid and glucose metabolism. In addition, they have been shown to regulate cell proliferation and differentiation, tumor promotion, apoptosis, and immune reactions.

PPAR-γ acts against psoriasis development by several ways. Psoriasis is a Th-1 inflammatory disease such as obesity, MS, diabetes, atherosclerosis, and myocardial infarction. PPAR-γ activation requires the presence of a Th2 cytokine profile and downregulation of Th-1 response. Thereby, PPAR-γ acts as anti-inflammatory combating against psoriasis and its comorbidities. It also suppresses interleukin (IL)-17 gene transcription, inhibits vascular endothelial growth factor with subsequent inhibition of angiogenesis required for psoriasis development. It inhibits nuclear factor-kβ and activating protein, signal transducer and activator of transcription, IL-2 production as well as tumor necrosis factor-α by T-lymphocytes. PPAR-γ enhances the production of adiponectin which was proved to be deficient in psoriasis. It also protects against oxidative stress and induces apoptosis and death of immune cells, especially T-lymphocytes.

Therefore, reduced PPAR-γ activity leads to subsequent severe psoriasis and high susceptibility to its comorbidities.

In skin, PPAR-γ is expressed in suprabasal keratinocytes, hair follicles, and sebaceous glands. It was found to induce keratinocyte maturation, inhibit proliferation, induce apoptosis and modulate filaggrin expression.

The gene encoding for PPAR-γ is located on chromosome 3p25.2, contains 9 exons and spans more than 100 kb.

A polymorphism is a genetic variant that appears in at least 1% of the population. A gene is said to be polymorphic if more than one allele occupies that gene's locus within a population. Sources of gene polymorphism include single-nucleotide polymorphisms, sequence repeats, insertions, deletions and recombination. It may result from chance processes or may have been induced by external agents such as viruses or radiation.

Accumulating evidence indicated that both common and rare polymorphisms of PPAR-γ gene play key roles in the regulation of lipid and glucose metabolism. Genetic variants in the PPAR-γ gene have been reported to be associated with obesity and with severe insulin resistance.

Although PPAR-γ locus is distant from currently accepted psoriasis susceptibility loci, this does not exclude the possibility that it may have effects on certain aspects of the disease.

The most prevalent PPAR-γ polymorphism is a variant that replaces alanine with proline at codon 12 (Pro12Ala). When both alleles are replaced, this is called homopolymorphism (Ala/Ala). When only one allele is replaced, this is called heteropolymorphism (Pro/Ala). Pro12Ala polymorphism has been associated with reduced transcriptional and receptor activity of PPAR-γ.

Based on the putative role of PPAR-γ in the maintenance of skin homeostasis, and in inflammatory processes, we speculated that genetically determined alterations in its functional activity may contribute to the pathogenesis of psoriasis. Therefore, we aimed at investigating PPAR-γ Pro12Ala polymorphism in Egyptian psoriatic cases searching for its role in disease occurrence and increased disease risk.

Methods

This case–control study was conducted on 45 patients with psoriasis vulgaris and 45 age, sex, and body mass index (BMI)-matched healthy volunteers, who have no present, past, or family history of psoriasis, as a control group.

Cases were selected from the dermatology outpatient clinic during the period from June 2016 to December 2016. Control participants were selected from the healthy staff of Menoufyia University Hospital. Laboratory part of the study was done at the Biochemistry Department at Menoufyia Faculty of Medicine.

Written consent form approved by the Local Ethical Research Committee was obtained from every participant before the study initiation. This was in accordance with the Helsinki Declaration of 1975 (revised in 2000).

Cases were either newly diagnosed with no history of treatment or stopped treatment for at least 3 months before sample taking.

Clinical data describing patients' demographics (age and gender) as well as the clinical variables (site of lesion[s], age of onset, disease duration, nail involvement, joint involvement, mucosal affection, itching, Koebnerization, and family history of psoriasis) were all documented.

The severity of the disease was assessed by Psoriasis Area and Severity Index (PASI) score.

Narrow-band (312 nm) ultraviolet B treatment

It was scheduled as follows for every case:

1. The starting dose – the initial radiation dose was determined according to the patient’s skin type. Included cases had skin Types III or IV and were initially treated with 0.5 mJ/cm².
2. Dose increments – dose increment was done every session according to the degree of erythema as follows: if no erythema, dose increment was 20%; if minimal erythema, dose increment was 10%; and if intense

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erythema or erythema and edema or erythema, edema and blisters, no dose increment was done[33]

• Dose frequency – sessions were given three times weekly for 12 weeks
• The machine used – ultraviolet (UV-100 L Waldman (Germany) lighting, equipped with UVB lamps (TL01 lamp), which have physical irradiance values of 7–10 mW/cm² and biological effective (erythematous) irradiance of 0.4–0.6 mW/cm²
• Assessment – percentage of decrease in the mean PASI score after the treatment period.

Exclusion criteria
Any case or control participant with dermatological diseases other than psoriasis, polycystic ovarian syndrome, coronary artery disease, breast cancer, and/or blood transfusion in the last 6 months was excluded from the study.

Every case and control participant underwent the following steps
1. Determination of BMI[34] Selected cases and controls included obese and nonobese participants
2. Evaluation for the presence of MS whose criteria were identified according to the National Cholesterol Education Program Adult Treatment Panel III[35]
3. Detection of PPAR-γ gene polymorphism by restriction fragment length polymorphism polymerase chain reaction (PCR).

DNA extraction from the whole blood was done using the GeneJET whole blood genomic DNA purification Mini Kit (Thermo Scientific Lithuania). DNA eluted in buffer AE was stored at −20°C for further PCR procedure.

Determination of peroxisome proliferator-activated receptor-γ gene polymorphism
PCR for PPAR-γ gene polymorphism was carried out to a total volume of 25 µl, containing 10 µl genomic DNA, 1 µl of each primer, 12.5 µl of Master Mix (Genecraft, Germany and Stratagene, USA), and 1.5 µl distilled water.[34]

Peroxisome proliferator-activated receptor-γ gene

It was analyzed using the following designed primers (Midland, Texas)
Forward: 5’-CCAAATTCAAGCCAGTCCTTTTC-3’
Reverse: 5’-CAGTGAGGAATCGGTTCCTGG-3’

Polymerase chain reaction amplification of peroxisome proliferator-activated receptor-γ gene

It was done using Applied Biosystems 2720 thermal cycler (Singapore). PCR condition consisted of one cycle of amplification at 94°C for 3 min, followed by 30 cycles at 94°C for 1 min, 55°C for 1 min, 72°C for 1 min, and one final cycle of extension at 72°C for 10 min. The amplification products were separated by electrophoresis through 3% agarose gel stained with ethidium bromide and visualized with positive band at 244 bp.

Peroxisome proliferator-activated receptor-γ genotyping using restriction fragment length polymorphism polymerase chain reaction technique

About 15 µl of the PCR products of PPAR-γ gene was mixed with 1 µl (1 unit) of FastDigest® BstUI restriction enzyme (provided by Fermentas) with 6.5 µl nuclease-free water and 2.5 µl of 10X FastDigest® Buffer.[37]

The mixture was mixed well and incubated at 60°C for 30 min, then 10 µl of the product was loaded into a 3% agarose gel containing ethidium bromide for electrophoresis. The uncut fragment was 244 bp and digestion products were 223 bp and 21 bp.

Statistical analysis

Data were collected, tabulated and statistically analyzed using a personal computer with SPSS version 11 program (SPSS Inc., Chicago, IL, USA). Fisher’s exact test was used for comparison of qualitative variables in 2 × 2 tables when expected cell count of more than 25% of cases was <5. Chi-square test ($\chi^2$) was used to study the association between two qualitative normally distributed variables. Mann-Whitney U-test was used for comparison between two groups not normally distributed having quantitative variables. Odds ratio (OR) was used to describe the probability that people who are exposed to a certain factor will have a disease compared to people who are not exposed to the factor. Differences were considered statistically significant with P < 0.05.

Results

Selected cases included 25 nonobese and 20 obese participants. Among obese cases, 6 participants fulfilled the criteria of MS and 14 had no MS. Clinical data of patients are shown in Table 1.

Prevalence of peroxisome proliferator-activated receptor-γ genotypes and alleles in studied groups

Cases and controls

Homopolymorphism (Ala/Ala genotype) was significantly associated with cases (P = 0.01), and it increased risk of occurrence of psoriasis by 5.25 folds. Heteropolymorphism (Pro/Ala genotype) was more prevalent in cases (P = 0.01), and it increased risk of occurrence of psoriasis by 3.65 folds [Figure 1a].

Ala allele was significantly associated with cases (P = 0.004). It increased risk of occurrence of psoriasis by 3.37 folds [Figure 1b].
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3.65 [Figure 1c]. Ala allele was significantly associated with obese cases (P = 0.001) and increased risk of occurrence of psoriasis in obese participants by 1.14 folds [Figure 1d].

Nonobese cases and nonobese controls
Heteropolymorphism was significantly associated with nonobese cases (P = 0.001), and it increased risk of occurrence of psoriasis by 12 folds [Figure 1e]. Ala allele was significantly associated with nonobese cases (P = 0.006). It increased risk of occurrence of psoriasis by 3.76 folds [Figure 1f].

Obese cases and obese controls
Normal genotype has equal prevalence among obese controls and obese cases (2%). Homopolymorphism was more prevalent among obese cases (60% vs. 25%), and heteropolymorphism was more prevalent among obese controls (62% vs. 30%) but without significant difference between both groups (data not shown in tables or figures).

Ala allele was more prevalent among obese controls (57.5% vs. 38%), and Pro allele was more prevalent among obese cases (62% vs. 42.5%) without significant difference between both groups (data not shown in tables or figures).

Obese cases with and without metabolic syndrome
Homopolymorphism and heteropolymorphism were more prevalent among obese cases without MS than obese cases with MS (64.3% vs. 50% and 35.7% vs. 16.7%, respectively) but without significant difference between the groups (data not shown in tables or figures).

Ala allele was more prevalent among obese cases without MS (57.5% vs. 38%), and Pro allele was more prevalent among obese cases with MS (62% vs. 42.5%) without significant difference between both groups (data not shown in tables or figures).

Relationship between peroxisome proliferator-activated receptor-γ genotypes and clinical data of selected cases
Homopolymorphism and Ala allele were significantly associated with higher BMI (P = 0.001 for both) [Figure 2a and b].

Relationship between genotypes and narrow-band ultraviolet B response in selected cases
Percentage of decrease of mean PASI score before and after 3 months of treatment with narrow-band ultraviolet B (NBUVB) was higher in cases with heterolymorphism with no significant difference between homo- and heteropolymorphism [Table 2].

Discussion
The current study showed significant difference between psoriatic cases and healthy controls, regarding PPAR-γ
Pro12Ala gene polymorphism. Homopolymorphism (Ala/Ala) and heteropolymorphism (Pro/Ala) were associated with psoriatic patients and increased risk of occurrence of psoriasis by 5.25 and 3.65 folds, respectively.

Figure 1: (a) The prevalence of peroxisome proliferator-activated receptor-γ genotypes in cases and control participants. (b) The prevalence of peroxisome proliferator-activated receptor-γ alleles in cases and control participants. (c) Significant association between heteropolymorphism and nonobese cases. (d) Significant association between Ala allele and obese cases. (e) Significant association between heteropolymorphism and nonobese cases. (f) Significant association between Ala allele and nonobese cases.

Figure 2: Significant association between (a) homopolymorphism and higher body mass index and (b) Ala allele and higher body mass index.
These different findings could be explained by different clinical criteria, and ethnic background of studied populations as a single genetic mutation may result in conflict outcomes in different ethnic groups.\(^{[18]}\)

As mentioned earlier, PPAR-\(\gamma\) can affect keratinocyte maturation and inflammatory mediators, inhibit proliferation, and induce apoptosis.\(^{[22]}\) As PPAR-\(\gamma\) gene polymorphism will decrease its transcriptional activity,\(^{[21]}\) the association demonstrated here may be explained by loss of PPAR-\(\gamma\) biological effects on keratinocytes, angiogenesis, inflammatory mediators, and immune cells; a postulation that needs further research.

In the current work, Ala allele was significantly associated with obese cases compared with nonobese ones and increased risk of occurrence of psoriasis in obese patients by 1.14 folds.

The association between Ala12 and high BMI is a matter of debate. While some studies confirmed it,\(^{[19-42]}\) others denied such association.\(^{[43-56]}\)

PPAR-\(\gamma\) is proadipogenic. The decreased transactivation function by polymorphism will lead to decreased lipoprotein lipase activity and decreased plasma free fatty acids\(^{[37]}\) which adversely affect insulin action on skeletal muscles.\(^{[51]}\)

In addition, activators of PPAR-\(\gamma\) have been shown to promote differentiation of preadipocytes to small adipocytes.\(^{[52]}\) In small adipocytes, lipolysis is more insulin sensitive than in large adipocytes (insulin action is already impaired by the polymorphism as mentioned above).\(^{[63]}\)

In humans, PPAR-\(\gamma\) expression in visceral adipose tissue relative to subcutaneous adipose tissue is increased in obese participants.\(^{[54]}\) Because visceral adipose tissue is metabolically more harmful,\(^{[55]}\) the Ala allele would be expected to have an even greater impact in obese participants.\(^{[64]}\)

Lifestyle changes and weight reduction lead to improvement or complete remission of psoriasis.\(^{[54]}\) However, based on the current results, these measures may go side by side with genetic interference in cases of polymorphism.

In the present study, homopolymorphism and heteropolymorphism were more prevalent among cases without MS than cases with MS.

Several studies identified a higher prevalence of MS in psoriatic patients compared to nonpsoriatic controls.\(^{[57,58]}\) PPAR-\(\gamma\) activity protects against components of MS. PPAR-\(\gamma\) agonists have been reported to reduce blood pressure in human diabetic participants and in animal models\(^{[59,60]}\) and loss of functional mutations in PPAR-\(\gamma\) leads to severe early-onset hypertension in addition to metabolic abnormalities.\(^{[81]}\) Furthermore, PPAR-\(\gamma\) is associated with improved insulin sensitivity, lower BMI, increased high-density lipoprotein (HDL) levels, and a reduced risk of developing type 2 diabetes mellitus.\(^{[62]}\)

The functional Pro12Ala mutation has also been reported to be associated with MS in several reports as this polymorphism can modulate the association between dietary fat intake and components of the MS.\(^{[63,64]}\)

It was previously reported that reduction in the PPAR-\(\gamma\) expression goes hand in hand with elevation of the PASI score, blood glucose, blood pressure and cholesterol levels as well as reduction of the HDL levels (components of the MS), pointing to the common influence induced by reduced PPAR-\(\gamma\) levels on both psoriasis and MS.\(^{[65]}\)

However, some studies found no association between Pro12Ala polymorphism of PPAR-\(\gamma\) and MS.\(^{[66,67]}\)

Zhang et al. reported that epidermal PPAR-\(\gamma\) signaling is also a target for UV-induced inflammatory response. UV irradiation of human keratinocytes produces potent PPAR-\(\gamma\) agonistic activity in these cells.\(^{[68]}\) Hence, we studied the relationship between PPAR-\(\gamma\) gene polymorphism and the response of NBUVB in psoriatic patients.

Unexpectedly, no association was detected between NBUVB response and PPAR-\(\gamma\) genotypes or alleles. Large-scale studies are needed to confirm or deny such finding.

### Table 2: Relationship between peroxisome proliferator-activated receptor genotypes and narrowband ultraviolet B response in studied cases

| NBUVB response | Homopolymorphism | Heteropolymorphism | \(P\) |
|----------------|------------------|--------------------|------|
| Mean difference of PASI score before and after 3 months | 15.6±12.8 | 16.3±6.40 | 0.232 |
| Range | 4–60.2 | 9–27.3 | |
| Percentage of decrease | 82.3±7.56 | 83.2±17.3 | 0.956 |

NBUVB: Narrow-band ultraviolet B, PASI: Psoriasis Area and Severity Index, SD: Standard deviation.
Studying the relationship between genetic background of psoriatic patients and their response to phototherapy is needed as it may decrease refractory cases and improve treatment outcome.

**Conclusion**

PPAR-γ gene polymorphism is associated with and increases the risk of psoriasis in Egyptian patients. However, it has no role in NBUVB response in those patients.

Future large-scale studies on different populations are needed for firmer conclusion. Investigating gene polymorphism in other clinical varieties of psoriasis and investigating the association between psoriasis and other PPAR-γ polymorphisms are also needed.

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**Conflicts of interest**

There are no conflicts of interest.

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