

# Genetic polymorphism in CYP1A1 affected susceptibility to acne vulgaris in Pekanbaru Indonesian Population, Desember 2013 - Maret 2014

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**Submission date:** 15-Dec-2020 03:49PM (UTC+0800)

**Submission ID:** 1475609351

**File name:** 1243-4824-1-PB.pdf (649.01K)

**Word count:** 2650

**Character count:** 14353



# Genetic polymorphism in CYP1A1 affected susceptibility to acne vulgaris in Pekanbaru Indonesian Population, Desember 2013 - Maret 2014



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## ABSTRACT

**Background:** Susceptibility to acne vulgaris had seen by modulating devolution of encoding cytochrome P450 1A1 (CYP1A1) gene polymorphism which is involved in bioactivation and detoxification of drugs, chemical agents, and pollutants from the environment. Acne incidence is known different based on ethnic, so that, we did this study in Indonesian acne vulgaris patients.

**Aim:** To characterize cytochrome P450 1A1 (CYP1A1) polymorphism in Indonesian acne vulgaris patients.

**Method:** Multiplex polymerase chain reaction (PCR) dan PCR based restriction fragment length polymorphism (PCR-RFLP) were used to detect polymorphism changes of CYP1A1 by doing a case-control study of 35 acne patients dan 35 controls. All the examination samples were obtained from Pekanbaru, Riau Province, Indonesia.

**Result:** The frequency of CYP1A1 heterozygous variant alleles was higher in case (odds ratio 2.21; 95% Confidence Interval 0.71-6.87).

**Conclusion:** Polymorphism of CYP1A1 allele m1 gene increases susceptibility to acne vulgaris.

**Keywords:** Polymorphism, CYP1A1, acne vulgaris

**Cite this Article:** Darmani, E., Darwin, E., Damayanti, I., Nurdin, A.E. 2019. Genetic polymorphism in CYP1A1 affected susceptibility to acne vulgaris in Pekanbaru Indonesian Population, Desember 2013 - Maret 2014. *Bali Medical Journal* 8(1): 169-172. DOI: [10.15562/bmj.v8i1.1243](https://doi.org/10.15562/bmj.v8i1.1243)

## INTRODUCTION

Acne vulgaris refers to the most frequent disease in various countries in the world and almost 85% of cases occur at 12-25 years old age group.<sup>1</sup> The highest incidence and severity was found between 14-17 years old in female and between 16-19 years old in the male.<sup>2</sup> Based on hospital reports in several big cities in Indonesia, the incidences of acne vulgaris tend to increase every year.

There is a lot of factor that responsible for acne vulgaris, such as genetic factor, diet, hormone, stress, and environment.<sup>3</sup> Cytochrome 450 gene is a gene that has correlations with several metabolic processes. The cleavage of p450 transcription from all exons or most exons were used to produce an enzyme with a new catalyst.<sup>4</sup> The cytochrome 450 is a superfamily of hemoproteins which is important in oxidative, peroxidative, and reductive metabolism process of various endogenous agents. Those agents such as steroids, bile acids, lipids, prostaglandins, leukotrienes, retinoids, lipid hydroperoxide and phytoalexin.<sup>5</sup> CYP also metabolizes exogenous agents such as drugs, chemical agents, and pollutants.<sup>6</sup>

Exogenous stimulations as endogenous regulation factors regulate excretion of specific CYP.<sup>7</sup> CYP1A subfamily has two members; they are CYP1A1 and CYP1A2.<sup>8</sup> Between these families,

CYP1A1 is the most active enzyme which has responsibility for activation and inactivation of metabolism.<sup>9</sup> This is an individual variant on P450 enzyme activity which could increase or decrease susceptibility. The biggest part of a particular variant is explained by P450 gene polymorphism causes metabolic capacity change or expression of encoded enzymes.<sup>10</sup>

CYP1A1 enzyme involves in retinoid, vitamin A, and its natural metabolites endogenous metabolism for sebaceous glands.<sup>11,12</sup> P450 cytochrome isozymes will activate retinol, retinal, and all-trans-retinoic acid to 4-hydroxy and 4-oxo retinoic acid.<sup>13,14</sup> Vitamin A overoxidation causes shrinkage of dynamic nature retinoic on pilosebaceous follicles.<sup>15</sup> It causes abnormal sebocyte differentiation and follicles' canal hyperkeratinization which lead to the vulgaris.<sup>16</sup>

The human CYP1A1 gene is localized on the long arm of chromosome 15 (15q22-q24)<sup>17</sup> and comprises seven exons and six introns with a total length of 5,810 bp.<sup>18</sup> The first polymorphism described for the CYP1A1 gene is m1<sup>19</sup> at position 6235 T>C transition into exon 7<sup>8,20</sup> and generated a cut site for the MspI restriction enzyme, which confers a threefold increase in its catalytic activity. The increase of the cellular oxidative stress is generated by the high CYP1A1 activity.<sup>21</sup>

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Received: 2018-07-17  
Accepted: 2018-11-24  
Published: 2019-4-1

## METHODS

In the present study, a total of 70 study subject comprising 35 acne patient and 35 controls were recruited. All subjects are males, similar in age, BMI and education.

Acne diagnose was established in the Department of Dermatology, Arifin Achmad General Hospital, Pekanbaru Indonesia. Blood samples were collected in EDTA containing tubes and stored at -20°C until further use. Leukocyte DNA was isolated, using an organic protocol with phenol-chloroform extraction after digestion with a proteinase (1 mg/ml) overnight at 37°C and subsequent ethanol precipitation. Electrophoresis was performed on isolated DNA on 1% ethidium bromide-stained agarose gel and photographed. Five dilutions were made of each DNA isolated and stored at 4°C until used. To detect the mutation, genomic DNA was amplified by polymerase chain reaction (PCR) in a 50 µl reaction mixture containing 10 pM of each primer P79 and P80, 1 U Taq DNA polymerase, 0.2 mM of each dNTP at pH 7.0, 50 mM KCl, 10 mM Tris-HCl

at pH 8.3 and 2.4 mM MgCl. The reaction mixture was placed in 9600 thermal cycles and subjected to 32 cycles, DNA denaturation at 92°C for the 30s, primer annealing at 63°C for 1 min, polymerization at 72°C for 1 min. 20 µl of the amplified product were then digested with 40 U restriction endonuclease MspI overnight at 37°C and were analyzed by gel electrophoresis (2.5% agarose).

The samples were sequenced from MacroGen (Korea). The reverse primer was used for sequencing. The sequencing results were made forward complementary before analysis using genious v 7.0 software. Statistical analysis was performed by using SPSS statistic 17.0 software and Graph Pad Prism 5 demo for calculating odds ratio, 95% Confidence Interval.

## RESULT

### CYP1A1 genetic polymorphism

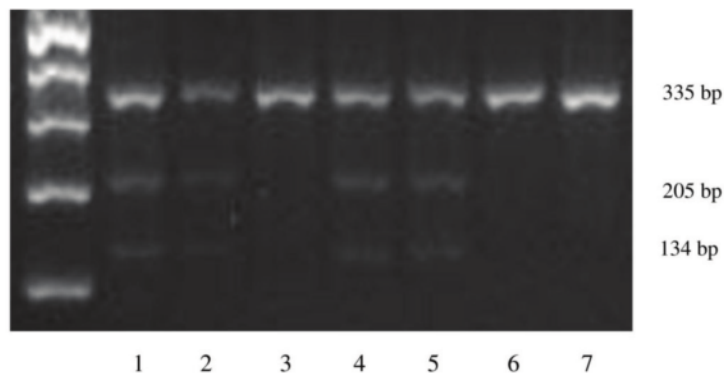
DNA samples subjected to PCR and enzymatic digestion with MspI revealed the expected fragment length and resulted in three genotypes of CYP1A1. The absence of the MspI site in both alleles represents the homozygous wild-type genotype (wt1/wt1) is characterized by a single 335-bp fragment. A homozygous variant genotype (m1/m1) showed MspI restriction site results in two fragments of 206 bp and 129 bp fragment. In addition, a heterozygous variant genotype showed MspI restriction site results in three fragments of 335 bp, 205 bp, and 134 bp fragment.

The RFLPs of PCR-amplified obtained using MspI and subjected to agarose gel electrophoresis. Wild-type without MspI restriction site shows a single 335 bp band (lanes 3, 6, 7) a variant with MspI restriction site shows in three bands of 335 bp, 205 bp and 134 bp (lanes 1, 2, 4, 5). In this study, there is no homozygous variant with MspI restriction in two bands.

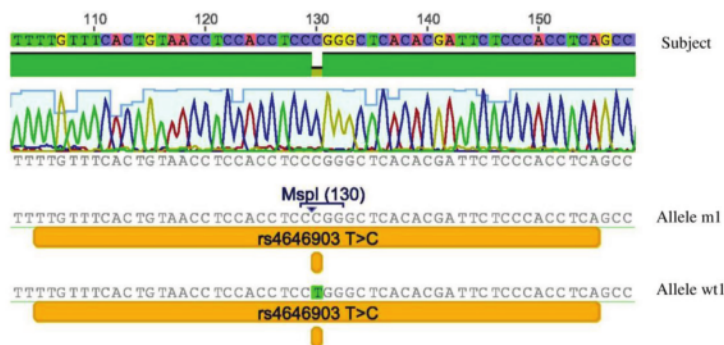
Table 1 shows the distribution of individual genotype CYP1A1 in the study population. The population of homozygous wild-type (wt1/wt1), heterozygous variant (wt1/m1) and homozygous variant (m1/m1) genotype were 6 (17,1%), 29 (82,9%) and 0 (0%) in case. On the other hands, controls showed 11 (31,4%) 24 (68,57%) and 0 (0%) respectively. Evaluation of the CYP1A1 polymorphism analysis shows a tendency of higher risk in heterozygous genotype to suffer acne vulgaris (odd ratio 2,21 95% Confidence Interval 0,71 – 6,87).

## DISCUSSION

There is some research conducted and published about CYP1A1 polymorphism effect to several



**Figure 1** The examples of CYP1A1 polymorphism



**Figure 2** The result of subjects sequences analysis with software genious v 7.0 shows allele m1 as the transition of thymine to cytosine at position 6235 creating an additional cleavage site for MspI in the 3'-flanking region 130 bp downstream of exon 7

**Table 1** Distribution of CYP1A1 genetic polymorphism in acne patients and controls

	Case	Control	OR
Wild-type (wt1/wt1)	6 (17.1%)	11 (31.4%)	
Heterozygous variant (wt1/m1)	29 (82.9%)	24 (68.6%)	2.21
Homozygous variant (m1/m1)	0 (0%)	0 (0%)	

Odds ratio 2.21; 95% CI 0.71 – 6.87

malignancy diseases such as head and neck cancer, lung cancer and colon cancer. Its correlation is by increasing metabolic enzyme activity, but there is a bit of research linked it with skin disease. Research about CYP1A1 gene polymorphism correlation with acne vulgaris had done by Paraskevaidis et al. (1998) in Germany. This research explained that CYP1A1 gene polymorphism increased CYP1A1 enzyme activity on vitamin A metabolism which caused active natural retinoid metabolites changed to an inactive form. Lack of active retinoid-induced abnormal sebocytes differentiation and follicle canal hyperkeratinization so that lead acne.

Polymorphic genes involving metabolic polymorphism almost universally exhibit ethnic and racial variation.<sup>22</sup> It allowed a significant population has a high prevalence of related polymorphism. As regard with the acne incidence is corresponding to the race, a study with a west Indonesian acne patient to asses association between CYP1A1 with the likelihood of development of acne in our population.

In this study, there was a high frequency of CYP1A1 MspI gene polymorphism (wt1/m1). High prevalence of CYP1A1 heterozygous variant genotype was recorded among acne patients compared to controls. Evaluation of the result of CYP1A1 polymorphism analysis showed a tendency of risk enhancement on heterozygous genotype to sustain acne with an OR of 2.21 (95% CI 0.71 – 6.87). The location of polymorphism CYP1A1 allele m1 in the 3' flanking region of the CYP1A1 gene was over presentation in acne patient in Germany.<sup>16</sup>

A CYP1A1 morphogenic enzyme in skins's sebaceous gland takes a role in vitamin A metabolism, all-trans-retinol to all-trans-retinoic acid (AtRA). Furthermore, AtRA will be oxidized to 4-hydroxy-retinoic acid and 4-oxo-retinoic acid.<sup>23</sup> Excessive oxidation process will cause a similar condition like vitamin A deficiency.<sup>6</sup>

Zouboulis had shown the role of AtRA as active retinoid metabolic on sebocyte culture. Deficiency of AtRA induced abnormal sebocyte proliferation and differentiation and also increased direct and indirect lipid synthesis. Retinoid also affected epidermal proliferation.<sup>24</sup> The retinoid (AtRA) tested altered the expression of certain human sebocyte in vitro, forming downregulation of

“hyperproliferative” keratin 6 and 16.<sup>14</sup> Abnormal sebocyte proliferation and differentiation, increased lipid synthesis, and hyperkeratinization led to acne.<sup>16</sup>

## CONCLUSION

Our study showed over-representation of the m1 allele. CYP1A1 polymorphism gene with m1 allele is a sign of changes in the regulatory sites which caused rapid metabolism in naturally occurring retinoid into its inactive form. A decrease in the amount of natural retinoid can lead to acne. Hence it can be concluded that CYP1A1 polymorphism gene with m1 allele could increase the risk of acne vulgaris

## CONFLICT OF INTEREST

The author declares there is no conflict of interest regarding all aspect of the study.

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