Jurnal 20 Scopus Q2 The Association between a Genetic Polymorphism in the 196-1589975371

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Submission date: 08-Apr-2022 02:46PM (UTC+0700)
Submission ID: 1805094354
File name: ciation_between_a_Genetic_Polymorphism_in_the_196-1589975371.pdf (179.4K)
Word count: 3016
Character count: 16331

Sys Rev Pharm 2020; 11(5): 288 – 292
A multifaceted review journal in the field of pharmacy
E-ISSN 0976-2779 P-ISSN 0975-8453

The Association between a Genetic Polymorphism in the Promoter Region of the CYP17 Gene and Sebum Level on Acne Vulgaris

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Article History: Submitted: 20.02.2020 Revised: 12.04.2020 Accepted: 05.05.2020

ABSTRACT

Introduction: Generally Acne vulgaris (AV) is considered as a multifactorial disease, and many arguments have been raised on the role of heredity in the etiology of acne, the relevant genetic elements in the pathogenesis of the disease are not well established.

Objective: The aim of our study was to explore the association between a genetic polymorphism in the promoter region of the CYP17 gene and sebum level on mild and severe the development of acne patients.

Methods: There were total 43 samples, consisted of 22 severe AV and 21 mild AV patients. sebum level were measured using Sebumeter. Blood samples were taken from all patients as much as 1 µL. Polymerase Chain Reaction-Sequencing (PCR- sequencing) was used to detect existence of CYP17 gene polymorphism, genome group was observed and the results of the genotype and allele frequencies were compared with sebum level. genotype distribution group was compared with previous researches.

Results: Proportion of T gene CYP17 allele frequency is higher than alel C, indicated that T gene CYP17 allele may serve as a risk factor for severe AV cases in Makassar. The genotype frequency towards increase of sebum level revealed that TC is two times larger than TT genotype and five times larger than CC genotype.

Conclusion: The study shows that polymorphisms of CYP 17 gene and the interaction polimorphisms of CYP 17 gene was considered as a risk factor for higher sebum level.

Keywords: Acne vulgaris, Gene CYP17 Polymorphism, Sebum level

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DOI: 10.31838/srp.2020.5.42

INTRODUCTION

Acne vulgaris (AV) is a chronic inflammation disease on human's follicle sebaceous gland. Clinical descriptions of AV are papules, pustules, nodules and cystics which commonly affects the face, neck, chest and back. Acne vulgaris may also be in the form of non- inflammatory lesions, such as comedones.[1,2] Etiology of AV has not been conclusively identified. Nevertheless, most experts assume that AV is a multifactorial disease, characterized by disorder in differentiation and increase keratinization of sebaceous gland follicles, increase activity of sebaceous gland and hyperseborrhea, as well as increase colonization of Propionicbacterium Acnes.[3]

A lot of research indicate that genetic is one of influential factors on acne cases. Incidence of AV is higher on twins, especially the homozygote ones. Even the grade and severity is similar. The interesting fact is identification of relationship between acne, androgen hormones and disruption of lipid production. Neonatal acne relates with familial hyperandrogenism. Activity disorder of steroid 21-hydroxylase and CYP21 gene mutation were reported to have a correlation with pathogenesis of acne. On homozygotic twins, the sebum excretions is identical, while heterozygotic is not. Moreover, levels of essential fatty acids on sebaceous fluid ester and levels of epidermis acyceramide on homozygotic twins of acne sufferers are lower than non-acne twins.[4]

Enzyme 17α-hydroxylase/17.20-lyase, which is coded by CYP17 gene is a substantial enzyme for androgen production in adrenal gland as well as in testicles. CYP 17 is a gene located on chromosome 10q24.3. Correlation of polymorphism CYP17 with endocrinopathy, especially on the increase of androgen hormones has been widely reported. Research regarding correlation between polymorphism of CYP17 gene and acne vulgaris has not been considerably conducted. During his study, He et al, found that polymorphism of CYP17 correlate with severe acne. On severe acne men group, frequency of homozygote CC increased significantly compared to homozygote TT group. In addition, it also found that increase of allele C was occured in acne women group from mild to severe.[5] However, the research did not identify correlation of polymorphism of CYP17 with target organ phenotype of the sebaceous glands particularly the function of sebum production. Therefore, in this study we will explore the correlation of polymorphism of CYP17 gene with increase sebum level on acne vulgaris. The mutation found from the DNA's sequence will be confirmed with the sebum level of acne vulgaris patients.

RESEARCH METHOD

Location and research design

This research was conducted at the Department of Dermatology and Venereology of Dr. Wahidin Sudirohusodo General Central Hospital and networking hospitals. The examination was conducted at Microbiology Laboratory of Faculty of Medicine Hasanuddin University Makassar. The research used explorative research design.

Subjects of Research

The research was an explorative research aimed to explore relationship between polymorphism of CYP17 gene and the increasing of sebum level on mild to severe AV patients. The number of samples was calculated using Mann Whitney, with the total amount of 43 subjects. After obtaining approval from the Ethical Committee, 43 subjects which met the criteria of the research were collected and listed in this study. The research samples were all AV patients which fulfilled the inclusion criteria with both mild or severe grade that had been clinically diagnosed. The inclusion criteria of this research were: severe AV patient based on Combined Acne Severity Classification evaluated by one dermatology and venerology specialist doctor, both mild and severe AV patients had approved and signed informed consent. The exclusion criteria were mild and severe AV patients who have: received retinoid, antibiotic and anti-inflammatory medications in the last one month, used hormonal contraceptives, and mild and severe AV sufferers who were pregnant and breast-feeding. The research was conducted at the Departments of Dermatology and Venerology of Dr.Wahidin Sudirohusodo General Central Hospital and Microbiology Laboratory of the Faculty of Medicine of Hasanuddin University.

Method

All the subjects who have met the research criteria were required to fill out a personal questionnaire and history of disease. Photographs of lesion location on face were taken using digital camera.

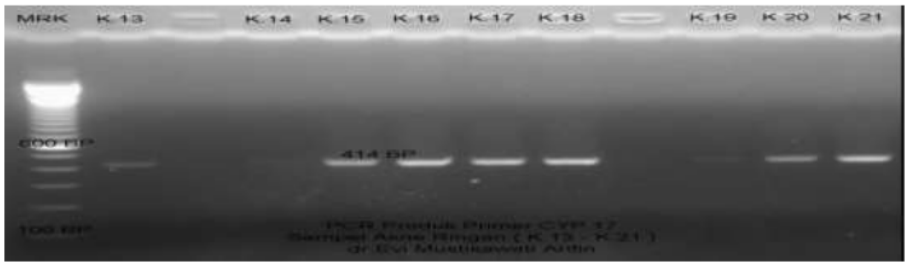
Statistical Analysis

The data was processed and presented in the forms of table, graphic and narration. The statistic analysis was conducted using Odd Ratio Test and X2 Test.

RESULT AND DISCUSSION

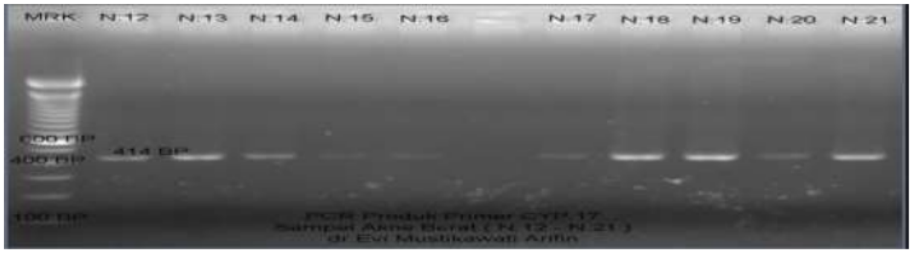
The total amount of research samples were 43 patients, consisted of 21 mild AV and 22 severe AV patients. On molecular examination results using PCR Method to see the DNA band from sample groups of severe and ,mild AV cases, continued by PCR sequencing to determine nucleotide sequence in a DNA fragment, and confirmed with sebum measurement results using sebumeter. Electrophoresis product of PCR on group samples of mild and severe AV patients showed that positive domination was detected on target band 414bp (Picture 1,2,3,4)

Picture 1: Result: Positive (K.01-K.12/Mild AV)



Picture 2: Result: Positive (K.13-K.21/Mild AV)

Picture 3: Result: Positive (N.01-N.11/Severe AV)

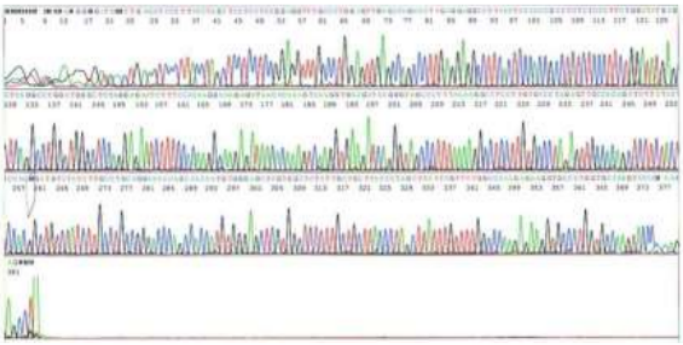


Picture 4: Result: Positive (N.12-N.21/Severe AV)

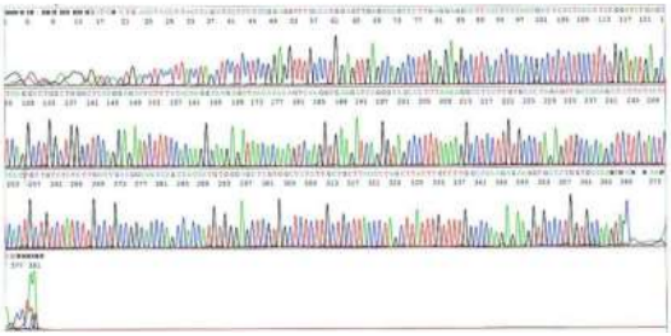
The sequencing result of gene CYP17 is demonstrated on picture 5,6,7. On mild AV cases, it was identified that frequency of genotype homozygote CC were 4 samples and genotype homozygote TT were 9 samples. While on the group of severe AV cases, it was identified that frequency of genotype homozygote CC, TC, and TT were 5, 5 and 12 samples, consecutively. (Table 1 and Picture 5,6,7).

Table 1: Genotype Distribution of Severe and Mild AV Cases

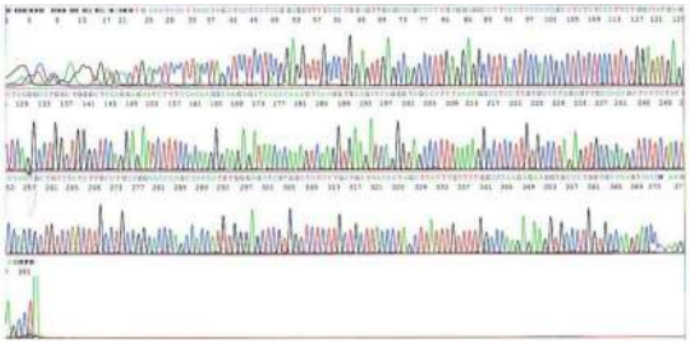
Group	Genotype Frequency			
	CC	TC	TT	Total
Heavy	5	5	12	22
% within GENOM	38.5%	55.6%	57.1%	51.2%
Light	8	4	9	21
% within GENOM	61.5%	44.4%	42.9%	48.8%
Total	13	9	21	43
% within GENOM	100.0%	100.0%	100.0%	100.0%



Picture 5: Sequencing Result of PCR Product. AV: homozygote TT



Picture 6: Sequencing Result of PCR Product. AV: heterozygote T/C



Picture 7: Sequencing Result of PCR Product. AV: homozygote CC

The measurement result of sebum level on the samples showed that sebum level of severe AV patients was two times higher than the mild AV (Table 2).

Table 2: Distribution of Sebum Level on AV Samples

GROUP	N	MEAN	STD. DEVIATION	STD. ERROR MEAN
Sebum 1.00	22	167.9545	49.76753	10.61047
2.00	21	87.4286	40.85042	8.91429

P=0.00

This research used CYP17 gene based on research conducted by He et al, which was the first research regarding correlation of CYP17 with AV and stated that frequency of homozygote allele C CYP17 gene in severe AV group (men) was significantly higher than control group. It indicated that homozygote CYP17-34C/C may increase risk of developing severe acne on men.[5] Another research was conducted by Anwar et al, which was the second research that identified correlation between polimorfism of CYP17-34T/C and severe acne using sequencing method in Makassar and obtained frequency result of CC homozygote higher in severe AV than control.[6]

Until recently, there has been no literature review on research regarding polymorphism of CYP17 gene and sebum level on AV in Indonesia. In this research, CYP17 gene was detected on position of 414 bp, T allele reflected more towards severe AV and relation of genotype frequency with increase of sebum level identified that TC 2 genotype was twice higher than TT genotype and five times higher than CC genotype, which showed a different result with the previous research. In our research, we did not apply statistic test since the research was only descriptive.

The previous evidence showed that acne is a congenital disease. Several researches indicated that pattern of acne inheritance is polygenic. A research towards 458 monozygote pairs and 1,099 pairs of female twins indicated that 81% disease variants associated with additive genetic effects and the rest 19% related to environmental factor.[7] Another research on 204 acne cases and 144 control volunteers who were not acne sufferers showed that familial factor is substantial in determining individual vulnerability towards AV.[8]

Several reports on identical twins who were almost at about the same time suffering severe acne nodulocystis or acne fulminans indicated implication of genetic elements to the disease.[9] The research conducted by Walton et.al, stated that sebum excretion rate is almost similar in identical twins.[10] It showed that sebum excretion is controlled by genetics. However, there are still limited acne candidate genes which have been proposed such as human cytochrome P4501A1 gene, sterpoid 21- hydroxylase gene (CYP21), epithelial mucin genes (MUC1) or androgens reseptor. In this research, we presented first research regarding exploration of CYP17 gene polymorphism and increase of sebum level on AV.

The result of sebum level measurement demostrated that there were a difference between severe and mild AV groups, in which severe AV had sebum level twice higher than the mild AV group. This result proves the statement that sebum playsan important part on acnegenesis process which was supported by several facts such as comedogenicity and the data indicated that production of sebum level is higher on severe acne sufferers.[3,11] Pappas et al., conducted a research by comparing lipid level of facial skin on acne sufferer and non-acne individual.[12] It was made possible by the role of androgens. The research carried out by Kurokawa et al., stated that production of sebum was stimulated by androgen hormones and androgen has a key role on pathogenesis of acne. Nevertheless, apparently the acne severity is not parallel with serum androgen levels. The serum androgen level on acne sufferers is generally within normal limits. Therefore, it was assumed that local androgen play a role on skin and/or raised amount of androgen receptors were occurred.[13,14,15,16] Androgen have an important role on pathogenesis of acne and androgen therapy is exceptionally successful in the treatment of the disease. The CYP17 genes has coded the human's P450 17- hydroxylase cytochrome which catalyzes two consecutive oxidation reactions on Leydig cell of adrenal gland: convertion of progesterone or pregnenolone to become 17α- hydroxilated product and the next oxidation into androstenedione. In the 5'-UTR CYP17 gene promoter

area, when T is substituted with C, changes in base pairs result in additional CCACC sequences.[4,17,18,19,20]

It has been suggested that the number of these elements is correlated with promoter activity which result in increased amount of gene product, that in this case ultimately leads to higher serum androgen level . Thus, the elevation of androgen level result in increasing sebum production and acne risk. In severe acne group, this may become one of genetic factors which affects the development of AV.

CONCLUSION

The study shows that polymorphisms of CYP 17 gene and the interaction polimorphisms of CYP 17 gene was considered as a risk factor for higher sebum level.

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