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ORIGINAL ARTICLE

Association between angiotensin-converting enzyme gene insertion deletion polymorphism and androgenetic alopecia susceptibility among Egyptian patients: A preliminary case-controlled study

Amany Ibrahim Mustafa MD[1,2] | Samah Ezzat Ibrahim MD[1] | Yasser Mostafa Gohary MD[3] | Naglaa Fathy Al-Husseini MD[4] | Eman Fawzy PhD[5] | Ola Samir El-Shimi MD[6]

[1]Department of Dermatology, Venereology and Andrology, Faculty of Medicine, Benha University, Benha, Egypt

[2]Department of Dermatology, Venereology and Andrology, Faculty of Medicine, October 6 University, Giza Governorate, Egypt

[3]Department of Dermatology, Venereology and Andrology, Faculty of Medicine, Beni-Suef University, Beni Suef, Egypt

[4]Department of Medical Biochemistry and Molecular Biology, Faculty of Medicine, Benha University, Benha, Egypt

[5]Department of Laboratory Medicine, Mansoura Fever Hospital, Mansoura, Egypt

[6]Department of Clinical and Chemical Pathology, Faculty of Medicine, Benha University, Benha, Egypt

Correspondence
Amany Ibrahim Mustafa, Department of Dermatology, Venereology and Andrology, Faculty of Medicine, Benha University, Benha 13511, Egypt.
Email: amanyibrahim26@yahoo.com

Abstract

Background: Androgenetic alopecia (AGA) is a prevalent condition with a complex etiopathogenesis. Angiotensin-converting enzyme (ACE) gene located on the chromosome 17q23 contains an insertion (I) and deletion (D) polymorphism in the intron 16. This gene polymorphism plays a role in multiple inflammatory disorders. However, there are no studies investigating its association with AGA susceptibility.

Objectives: In this work, we aimed at exploring the association of *ACE* gene I/D polymorphism in AGA susceptibility in a group of Egyptian patients.

Methods: This study included 100 AGA patients, and 100 apparently healthy controls. The *ACE* gene I/D polymorphism was analyzed by polymerase chain reaction.

Results: The DD, ID genotypes, and D allele showed higher frequent distribution among studied AGA patients than controls ($p < 0.05$ each). Positive family history and *ACE* gene I/D polymorphism were considered AGA susceptibility predictors in both uni- and multivariable analyses [$p < 0.05$ each (OR (95% CI)] on applying logistic regression analysis for risk factors prediction.

Conclusions: This study highlights the possible contribution of the suspected genetic polymorphism as a susceptibility indicator for AGA development in the examined group of patients.

KEYWORDS
androgenetic alopecia, insertion/deletion, polymorphism

1 | INTRODUCTION

Androgenetic alopecia (AGA), is hair loss disorder, characterized by hereditary hair thinning induced by androgen in genetically predisposed individuals and has an onset in late adolescence.[1,2] The incidence and prevalence of AGA vary depending on age and ethnicity. It affects about 50%–70% of Caucasian males and 40% of Caucasian women by the age of 70, but Chinese, Japanese, and African Americans have a lesser incidence.[3,4]

Androgenetic alopecia is a multifactorial disease linked to interplay between genetic and environmental factors.[5] The implication of inflammation activators in its etiopathogenesis has progressively emerged

This research was conducted in: Dermatology, Venereology & Andrology Department and Department Medical Biochemistry and Molecular Biology, Faculty of Medicine, Benha University, Egypt.

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from various independent studies.[6-10] There is also an evidence of oxidative stress presence in dermal papilla cells (DPC) in AGA patients.[11]

Angiotensin-converting enzyme (ACE) gene on chromosome17q23 includes an insertion (I) and deletion (D) polymorphism within intron 16. Of the three potential genotypes (DD and II homozygotes and ID heterozygotes), DD genotype carriers have greater serum ACE concentrations, than II genotype carriers.[12,13] Angiotensin I is converted to angiotensin II (Ang II) by ACE, which acts as a pro-inflammatory modulator and activates the enzyme nicotinamide adenine dinucleotide phosphate (NADPH) oxidase thus inducing reactive oxygen species (ROS) generation.[14,15]

The association between this gene polymorphism with inflammatory skin conditions had been evaluated before.[15-21] In the current study, we attempted to explore its association with AGA development in a group of Egyptian population.

2 | MATERIALS AND METHODS

2.1 | Study population

One hundred patients diagnosed with AGA from both sexes, different disease duration, clinical presentation, and different grades of severity along with 100 apparently healthy control subjects were included in the current work that was carried out between September 2020 and March 2021. This research was approved by the local ethical committee on research including human subjects of Benha Faculty of Medicine, and an informed consent was obtained from all subjects enrolled in this study.

2.2 | Exclusion criteria

Patients with inflammatory, autoimmune disorders such as systemic lupus erythematosus, sarcoidosis, vitiligo, or psoriasis, hypertension, diabetes mellitus, females complaining of menstrual disturbances, or with history of polycystic ovaries and patients with other hair loss disorders were excluded from the present work.

2.3 | Methods

Androgenetic alopecia diagnosis was based on the detailed history, typical clinical, and trichoscopy findings. Patients were classified according to Hamilton-Norwood classification system[22] for the male pattern hair loss (MPHL) and Ludwig grading system[23] for the female pattern hair loss (FPHL). Patients in the current study gave a detailed history and underwent full general and local clinical assessment. On the basis of a routine health check, control participants were chosen.

2.4 | Laboratory work

Venous blood samples (3 ml) were drawn from participants in EDTA-containing tubes under strict aseptic conditions. The DNA was extracted using Gene JET Whole Blood Genomic DNA Purification Mini Kit (Cat.# K0781, Thermo Fisher Scientific), according to the manufacturer's protocol. The DNA quality and quantity were determined by NanoDrop^{TM} 2000 (Thermo Fisher Scientific). DNA target amplification was carried out on Vereti thermal cycler (Applied Biosystems). Polymerase chain reaction (PCR) was performed in a final volume 25 µl using1 ng genomic DNA, 20 p moles of the primer pair; forward 5′–CTG GAG ACC ACT CCC ATC CTT TCT–3′ and reverse 5′–GAT GTG GCC ATC AAT TCG TCA GAT–3′ (*metabion* International AG), 0.5 µl *i*-StarTaq^{TM} DNA polymerase (Cat.# 25161, iNtRON Bio), 2 µl 10× PCR buffer, 2 µl dNTP Mixture and nuclease-free sterile water up to 20 µl. PCR was done with an initial denaturation for2 min at 94°C. Then, the DNA was amplified for 35 cycles with denaturation at 94°C for 20 s, annealing at 58°C for 30 s, and extension at 72°C for l min. This was followed by final extension at 72°C for 5 min. The PCR products were visualized directly under UV light using ethidium bromide-stained 2.0% agarose gel after electrophoresis. The amplification product is 190 bp fragments in the presence of the deletion (D) allele and a 490 bp fragment in the presence of the insertion (I) allele. Thus, the possible genotypes were the DD genotype (190 bp band), the II genotype (490 bp band), and the ID genotype (490 and 190 bp band) (Figure 1).

2.5 | Statistical tests

The collected data were analyzed using SPSS Version 20. Student (*t*) and one-way analysis of variance (ANOVA) tests were used to detect the statistical differences between two or more means respectively. Chi-square (χ^2) and Fisher's exact (FET) tests were used to determine the relation between qualitative variables.

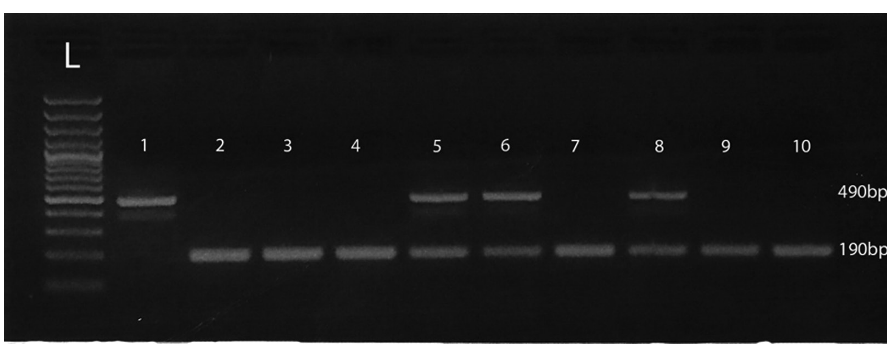

FIGURE 1 Gel electrophoresis showing II, ID, and DD genotypes of *ACE* gene polymorphism. The genotyping resulting by 2.0% agarose gel electrophoresis

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Logistic regression analysis was applied for risk factors prediction. Deviations from Hardy-Weinberg equilibrium were assessed by the goodness of fit test. The power of the study was calculated using CaTS-Power Calculator software.[24] Calculated power was 98%, using disease allele frequency 0.52, disease prevalence 0.1%, odds ratio 2.26, and level of significance of 0.05. *p* Value is considered significant if ≤0.05.

3 | RESULTS

3.1 | Demographic and clinical data

Study groups were age and sex matched (*p* 0.421 and 0.450 respectively). Demographic, clinical, and family history data are shown in Table 1.

3.2 | Genotypic and alleles distribution frequency

The revealed frequencies of the investigated genotypes in control subjects did not deviate from Hardy-Weinberg equilibrium (HWE) (*p* 0.0774 for control group and 0.236 for patients). Considering II genotype and I allele as references (wild type), studied patients showed significantly higher frequencies of ID, DD, total polymorphism (ID + DD genotypes), and D allele than control groups (*p* 0.048, <0.001, 0.003 and <0.001; OR (95% CI) 1.478 (1.004–2.175), 2.673 (1.576–4.533), 1.740 (1.215–2.492), 2.260 (1.496–3.414) respectively) (Table 2).

3.3 | Relation between genotypes distribution and studied parameters

Male patients, patients with longer disease duration, and those with higher Hamilton-Norwood classification system grades showed significantly higher distribution frequency of ID, DD, and total polymorphism (ID + DD genotypes)than II genotypes ($p < 0.05$ each) (Table 3).

3.4 | Prediction of risk factors for AGA among the studied patients

Risk factors were predicted in the investigated patients using logistic regression analysis. In both uni- and multivariable models, positive family history and the ACE gene I/D polymorphism were considered AGA susceptibility factors (p < 0.001, <0.001 0.003, 0.032; OR (95% CI) 2.339 (1.687–9.226), 1.958 (1.426–8.685), 1.740 (1.215–2.492), and 1.893 (1.389–2.183) respectively) (Table 4).

TABLE 1 Demographic and clinical data in both studied groups

Variable		Patients *N* = 100	Control *N* = 100	*p* Value
Age (Years)	Mean ± SD	37.9 ± 8.8	36.9 ± 8.3	0.421
Sex				
Male	*N*, %	70 (70%)	65 (70%)	0.450
Female	*N*, %	30 (30%)	35(35%)	
Family history				
Positive	*N*, %	74 (74%)	–	–
Negative	*N*, %	26 (26%)		
Onset				
Early	*N*, %	46 (46%)	–	–
Late	*N*, %	54 (54%)		
Duration (years)	Mean ± SD	9.1 ± 3	–	–
Hamilton-Norwood Grading (No. = 70)				
III	*N*, %	16 (22.9%)	–	–
IV	*N*, %	22 (31.4%)		
V	*N*, %	22 (31.4%)		
VI	*N*, %	6 (8.6%)		
VII	*N*, %	4 (5.7%)		
Ludwig Grading (No. = 30)				
I	*N*, %	18 (60%)	–	–
II	*N*, %	12 (40%)		

Hamilton-Norwood grading frequency was calculated out of total males, while Ludwig grading frequency was calculated out of total females.

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TABLE 2 Comparison between patients and control groups regarding *ACE* I/D genotypes and alleles distribution frequency

Genotype	Control N = 100 N (%)	Patients N = 100 N (%)	p	OR	95% CI
II	51 (51%)	26 (26%)		Reference	
ID	40 (40%)	44 (44%)	0.048	1.478	1.004–2.175
DD	9 (9%)	30 (30%)	<0.001	2.673	1.576–4.533
ID + DD	49 (49%)	74 (74%)	0.003	1.740	1.215–2.492
Allele					
I	71 (71%)	29 (29%)		Reference	
D	52 (52%)	48 (48%)	<0.001	2.260	1.496–3.414
HW*p*	0.774	0.236			

CI, confidence interval; HW*p*, Hardy-Weinberg *p* value; OR, odds ratio.

TABLE 3 Comparison of *ACE* I/D genotypes distribution frequency regarding different studied parameters

Variable		II N = 26	ID N = 44	DD N = 30	Total polymorphism (ID + DD) N=74	p1	p2
Age (years)	Mean ± SD	24.9 ± 6.6	29.1 ± 8.3	26 ± 8.7	27.7 ± 8.4	0.205	0.091
Age groups							
20–30	N, %	12 (40%)	20 (45.5%)	14 (53.8%)	34 (48.6%)	0.458	0.295
30–40	N, %	14 (60%)	24 (54.5%)	16 (46.2%)	40 (51.4%)		
Sex							
Male	N, %	14 (53.8%)	38 (86.4%)	18 (60%)	52 (74.3%)	**0.005**	**0.043**
Female	N, %	12 (40%)	6 (13.6%)	12 (46.2%)	22 (25.7%)		
Duration (years)	Mean ± SD	6.4 ± 1.9	10.6 ± 2.2	9.8 ± 2.7	10.3 ± 2.4	**0.002**	**0.001**
Onset							
Early onset	N, %	16 (53.3%)	22 (50%)	16 (61.5%)	38 (54.3%)	0.643	0.930
Late onset	N, %	14 (46.7%)	22 (50%)	10 (38.5%)	32 (45.7%)		
Family history							
Negative	N, %	10 (33.3%)	12 (27.3%)	4 (15.4%)	16 (22.9%)	0.301	0.274
Positive	N, %	20 (67%)	32 (72.7%)	22 (84.6%)	54 (77.1%)		
Hamilton-Norwood Grading (No. = 70)							
N (III + IV)	N, %	14 (46.7%)	16 (36.4%)	8 (30.8%)	24 (34.3%)	**0.042**	**0.020**
N (V + VI + VII)	N, %	4 (13.3%)	22 (50%)	6 (23.1%)	28 (40%)		
Ludwig Grading (No. = 30)							
L I	N, %	6 (20%)	2 (4.5%)	10 (38.5%)	12 (17.1%)	0.082	0.458
L II	N, %	6 (20%)	4 (9.1%)	2 (7.7%)	6 (8.6%)		

p1, comparison between II, ID, and DD genotypes distribution frequency. *p2*, comparison between patients carrying ID + DD genotypes vs. those carrying II genotypes. Hamilton-Norwood grading frequency was calculated out of total male patients; while Ludwig grading frequency was calculated out of total female patients. Bold indicates significant *p* value.

4 | DISCUSSION

Although the pathogenesis of AGA is debated, genetic predisposition and sex steroid hormones are well-established prerequisites for its development.[25] Histological studies illustrated perifollicular inflammation in AGA affected hair follicles.[26,27] Moreover, oxidative stress was found to be evident in the DPCs of AGA patients.[11]

The present results revealed significantly higher distribution frequencies of ID, DD, and total polymorphism (ID + DD genotypes) in AGA patients than controls (*p* 0.048, <0.001, and 0.003 respectively). Also, the D allele was distributed significantly among AGA patients than healthy controls ($p < 0.001$). This implies that the D allele has been linked to a considerably increased risk of AGA development. Previous researches revealed that DD genotypes carriers have high serum and tissue levels of ACE, causing excess angiotensin II (Ang II) production which is a potent pro-inflammatory modulator.[28] Higher plasma ACE concentration is involved in ovarian endothelium angiogenesis in vitro,

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TABLE 4 Logistic regression analysis for prediction of AGA susceptibility

Risk factors	Univariable			Multivariable		
	B	p	OR (95% CI)	B	p	OR (95% CI)
Age	0.008	0.387	1.001 (0.983–1.017)			
Gender	0.143	0.948	1.132 (0.739–1.353)			
Positive family history	2.428	**<0.001**	2.339 (1.687–9.226)	2.395	**<0.001**	1.958 (1.426–8.685)
ACE gene POLYMORPHISM (*ID + DD*)	0.782	**0.003**	1.740 (1.215–2.492)	0.500	**0.032**	1.893 (1.389–2.183)

B, regression coefficient; CI, confidence interval; OR, odds ratio.
Bold indicates significant *P* value.

steroidogenesis and inflammation.[29] Also, it increases adrenal steroidogenesis that may have a role in AGA development through induction of follicular miniaturization.[30] Furthermore, Ang II is a potent activator of NAD(P)H oxidase thus inducing reactive oxygen species (ROS) generation.[31] Current findings propose that the DD genotype is linked with high risk for AGA. This also was the condition in other inflammatory diseases in which the same polymorphism was investigated previously.[16-21]

The present study results revealed that male patients, patients with longer disease duration, and those with higher Hamilton-Norwood classification grades showed significantly higher distribution frequencies of ID, DD, and total polymorphism (ID + DD genotypes) than II genotypes ($p < 0.05$ each) supporting the hypothesized relation between the investigated genetic polymorphism and MPHL severity.

Angiotensin-converting enzyme takes part in unfavorable fibrous remodeling. Collagen deposition, dermal sheath thickening, and perifollicular fibrosis were found to be involved in AGA pathology.[32-34] Over abundance of extracellular matrix deposition leads to depressed tissue vascularity in balding scalp tissues that might induce follicular miniaturization.[35-37]Collagen filaments are nearly four times as abundant in the vertex and temple regions, and this could be related to disease progression in these areas.[38,39]

Our results provided a relation between *ACE* I/D gene polymorphism as vulnerability factor in both uni- and multivariable analyses when regression analysis was performed to predict the risk factors for disease development among the studied patients.

The limitations of the current study are the relative small sample size owing to the higher expense of molecular studies with the limited self-funded research and the recruitment of subjects from one center. Furthermore, our findings could be the result of genetic-environmental interactions that were not examined in our study.

5 | CONCLUSIONS

Despite these breakthroughs in AGA genetics understanding, a notewosrthy part of the overall heritable risk still needs clarification. The current findings pointing to the assignment of *ACE* gene I/D polymorphism to the genetic background of this inflammatory skin disorder. Future large-scale multi-centers studies along with functional studies are required to confirm our findings.

6 | COMPLIANCE WITH ETHICS GUIDELINES

The study was approved by the local ethics committee on research involving human subjects in the faculty of Medicine; Benha University in agreement with the Declaration of Helsinki. An informed consent was obtained from each subject prior to participation.

ACKNOWLEDGMENTS

We are extremely grateful to all volunteers who took part in this study and the research team who collected the data.

CONFLICT OF INTEREST

The authors have declared no conflicting interests.

ETHICAL APPROVAL

This research was approved by the local ethical committee on research including human subjects of Benha Faculty of Medicine, and an informed consent was obtained from all subjects enrolled in this study.

AUTHORS' CONTRIBUTIONS

Amany Ibrahim Mustafa, Samah Ezzat Ibrahim, Yasser Mostafa Gohary, designed the research study. Amany Ibrahim Mustafa and Ola Samir El-Shimi performed the research. Naglaa Fathy Al-Husseini contributed essential reagents or tools. Eman Fawzy analyzed the data. Amany Ibrahim Mustafa and Ola Samir El Shimi wrote the paper.

DATA AVAILABILITY STATEMENT

Data available on request due to privacy/ethical restrictions.

ORCID

Amany Ibrahim Mustafa https://orcid.org/0000-0003-3877-5787
Ola Samir El-Shimi https://orcid.org/0000-0001-8276-8352

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