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Original Research Article

The association of cytosine-adenine-guanine repeat polymorphism in the androgen receptor gene with nodulocystic acne in Egyptian patients

Nehal M. Zuelfakkar[1]*, Nader F. Ragab[1], Abeer Shehab[2], Moemena Nagy[3]

[1]Department of Dermatology, Venereology and Andrology, [2]Department of Clinical Pathology, [3]Faculty of Medicine, Ain Shams University, Cairo, Egypt

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***Correspondence:**
Dr. Nehal M. Zuelfakkar,
E-mail: nehalzf@hotmail.com

ABSTRACT

Background: The role of androgens in acne pathophysiology has been supported by long-standing clinical and experimental observations.
Methods: Genotyping for the androgen receptor gene was performed by PCR-based fragment length analysis, aiming to investigate cytosine-adenine-guanine (CAG) repeat polymorphism in Egyptian nodulocystic acne patients to clarify its relevance to the pathogenesis. Detailed frequency of CAG repeats number in patients and control groups, in 25 males and 25 females and Comparison of CAG repeat number regarding demographic and clinical characteristics was performed.
Results: It was found that females had a higher frequency of longer CAG repeats compared to males, while in control group there was an even distribution of CAG number repeats in both females and males. Male and female acne patients had significantly lower number of CAG repeats compared to controls with statistically significant difference ($p \leq 0.05$). Comparison of CAG repeat number regarding demographic and clinical characteristics revealed no significant correlation or association with patients' age, duration of acne, onset or course of the disease.
Conclusions: These findings support the hypothesis that CAG repeats number affects AR activity, therefore, acne development and severity. Moreover, analysis of CAG repeats number in acne patients can be of considerable importance in the treatment strategy, indicating the role of antiandrogen therapy in acne patients.

Keywords: Androgen receptors, CAG repeat, Nodulocystic acne

INTRODUCTION

Acne vulgaris (AV) is a multifactorial, inflammatory disease of the pilosebaceous unit. It usually starts at puberty.[1] Hormones play a major role in the pathogenesis of acne. However, severe acne can also be seen without evidence of hyperandrogenism. In this case, hypersensitivity of the androgen receptor gene (ARG) encoded in the X chromosome, which is the only receptor for androgens, can be considered. ARG encodes a protein of 910 amino acids and is highly polymorphic.[2]

The role of androgens in sebaceous glands and acne pathophysiology has been supported by long-standing clinical and experimental observations. Dehydroepiandrosterone (DHEA) levels in the circulation during the adrenarche is known to be related to the onset of microcomedonal acne in prepubertal children.[3] The absence or the rarity of acne in men who have undergone premature castration before puberty or people with androgen insensitivity syndrome, reveals the role of androgens in acne etiology.[4]

The androgen receptor (AR) gene, located on Xq11.2–12, is composed of eight exons and is known to show more frequent sequence variation than other steroid receptor genes.[5] AR protein is composed of three major functional domains, including the N-terminal domain (NTD), the

DNA- binding domain (DBD) and the ligand-binding domain (LBD). There is also a small hinge region between the DBD and LBD. The N-terminal region of the AR comprises of a polyglutamine sequence encoded by repeats of polymorphic cytosine-adenine-guanine (CAG) of variable length. It has been shown that changes in repeat lengths in CAG trinucleotide are associated with fine modulation of the AR wide expression.[6]

Androgens activate the receptor when bound to the hormone binding site, leading to nuclear translocation of the ligand-receptor complex and a number of molecular events leading to transactivation of genes regulating androgen function. ARG contains a polymorphic CAG triple repeat encoding the polyglutamine pathway at the 5'end of exon 1. The number of polyglutamine repeats is inversely proportional to the transcriptional activity of AR. Hence, inversely proportional to AR activity.[7]

In the normal allele range, there appears to be an inverse correlation between the CAG repeat length and the androgen wide expression; shorter alleles exhibit higher activity.[8] The CAG repeat count polymorphism has been related to several diseases associated with low or high androgenic activity in both men and women. In males, shorter CAG tracts, have been associated with increased prostate cancer risk and higher cancer grade at diagnosis.[5] In females, acne may be associated with polycystic ovary (PCOS) and ovarian tumors.[9] Studies support a modulating role of the genetic AR polymorphism in PCOS; more active receptors (short CAG repeats) can cause a hyperandrogenic phenotype in absence of markedly elevated androgens, while patients with a decreased receptor's activity (long CAG repeats) will develop the disorder in the presence of distinctly elevated androgens.[10] Although the clinical expression of this syndrome is highly variable, androgenic effects constitute the common mechanism responsible for its phenotype. Androgens transport the characteristic features of PCOS, e. g., acne, hirsutism, polyfollicular ovarian morphology and menstrual cycle disorders.[11]

The aim of this study was to investigate CAG repeat polymorphism in the ARG in Egyptian nodulocystic acne male and female patients to clarify its relevance to the pathogenesis of the disease.

METHODS

This case-control study included 25 patients with nodulocystic acne (11 males and 14 females) with mean age (22.3±4.7 ranged 16-27 years), in addition to 25 apparently healthy control subjects of age and sex matched participants (11 males and 14 females) with mean age (22.9±4.7 ranged 18-28 years). All patients were selected from the outpatient clinic of dermatology, venereology and andrology department of Ain shams University Hospitals in the period between January and August 2021. After the approval of ethics committee of the faculty of medicine, Ain Shams University, all participants signed an informed consent after explaining for them the objective of the study.

Inclusion criteria were patients with severe and very severe nodulocyctic acne according to the global acne grading system (Table 1).

Table 1: Global acne grading system.[12]

Location	Factor X grade (0-4)=local score	
Forehead	2	Global score 0= None 1-18= Mild 19-30=Moderate 31-38=Severe >39=Very severe
Right cheek	2	
Left cheek	2	
Nose	1	
Chin	1	
Chest and upper back	3	

Exclusion criteria were patients below 12 years old and above 40 years old and patients with hormonal changes. Females with hirsutism and menstrual irregularity, hypertrichosis or seborrheic skin structure were also excluded. Pregnant and lactating women and any patient under steroid or any other treatment that affects their hormonal levels were not included in the study.

All the included participants were subjected to the following.

Full history taking

The age and sex of the patients, the age of onset, course, and disease duration. Moreover, drug and menstrual history, history of chronic medical conditions and family history of acne were reported.

Clinical examination

General examination to exclude any systemic disease that may affect the hormonal levels of the patients or that may lead, either by itself or its treatment, to acne development. Severity of nodulocystic acne is assessed according to GAGS score.[12]

Genetic analysis

2 ml of peripheral venous blood samples were collected under complete aseptic conditions in tubes with EDTA anticoagulant from all participants, and DNA was isolated from the samples. Genotyping for the polymorphisms was performed by polymerase chain reaction (PCR)-based fragment length analysis using ABC 3590 DNA sequencer. CAG gene locus is present on the X chromosome, therefore, males have one gene locus (Allele) while females have 2 gene loci.

To analyze CAG repeat number and size in studied groups, gender correction was considered to eliminate gender factor before analysis.

DNA extraction

It was done using QIAamp® DNA Blood Genomic DNA Purification Kit (Qiagen, Cat. No. 51104), according to the following protocol: 200 ul of whole blood was pipetted into 1.5 ml micro centrifuge tube. 20 ul of proteinase K and 5 ul of RNase A solution was added onto the sample tube and gently mixed. 200 ul of buffer BL into upper sample and mixed thoroughly. The lysate was incubated at 56 ºC for 10 minutes and then briefly centrifuged to remove drops from the inside of the rid. 200 ul of absolute ethanol was added into the lysate and mixed gently and then centrifuged briefly. The mixture from the previous step was applied into the spin column, then centrifuged at 13000 rpm for 1 min. The filtrate was discarded and the spin column was placed into a new 2 ml collection tube. 700 ul of buffer WA was added to the spin column and centrifuged for 1 min at 13000 rpm. The filtrate was discarded and the spin column was placed into a new 2 ml collection tube. Then again centrifuged for 1 min at 13000 rpm and the filtrate was discarded. The spin column was placed into 1.5 ml tube and 50 ul of buffer CE was added onto the membrane. The tube was incubated for 1 min at room temperature and then centrifuged for 1 min at 13000 rpm.

PCR

Samples were processed according to the instructions of Go Taq G2 Colorless Master Mix (Promega, Ref. No. M7832). PCR set up: reaction set up was optimized with locus specific primers. Primer sequences: FAM labelled forward primer: 5′-FAM AGT TAG GGC TGG GAA GGG TC-3′ reverse primer: 5′-TAC GAT GGG CTT GGG GAG A-3′ and finally, PCR was processed as follows: for 35 cycles.

Reaction mixture (25 ul total volume)

It included the following components: Promega colorless PCR Master Mix (2X) 12.5 µl. Upstream Primer (10 pmol) 0.7 µl. Downstream Primer (10 pmol) 0.7 µl. Nuclease free water 4.1 µl. DNA template: 7.0 ul of each sample in the corresponding tube.

Reaction tubes were loaded in thermal cycler and programmed as follows: 94 °C for 4 min. 94 °C for 1 min 64 °C for 45 sec, 72 °C for 45 sec, 72 °C for 7 min.

Gel electrophoresis

Preparation of 50x stock solution of tris-acetate-EDTA (TAE) buffer in 1000 ml of distilled H_2O: 242 g of tris base was weighed in a chemical balance and then transferred to a 1000 ml beaker. Preparation of EDTA solution (pH 8.0, 0.5 M) was done by weighing 9.31 g of EDTA and dissolving it in 40ml distilled water. EDTA is insoluble and it can be made soluble by adding sodium hydroxide pellets. The pH was checked using pH meter. 57.1 ml of glacial acetic acid was pipetted out and mixed with the tris base and EDTA solution. Distilled water was added to make the volume to 1000 ml.

Preparation of electrophoresis buffer (usually 1x TAE) to fill the electrophoresis tank and to cast the gel: 2 ml of TAE stock solution was transferred in a flask and the volume was completed to 100 ml by adding 98 ml of distilled water.

Preparation of a solution of agarose in electrophoresis buffer at an appropriate concentration by addition of 2 grams of agarose to 100 ml of electrophoresis buffer. The flask was plugged and then heated in a boiling-water bath until the agarose dissolved. The flask was transferred into a water bath at 55°C. When the molten gel has cooled, 0.5 µg/ml of ethidium bromide was added and mixed. Preparation of ethidium bromide by addition 1 g of ethidium bromide to 100 ml of H_2O. The container was wrapped in aluminum foil stored at room temperature. The warm agarose solution was added into the mold after applying suitable comb. The gel was allowed to set completely (30 minutes at room temperature), then a small amount of electrophoresis buffer was poured on the top of the gel, and the comb was removed.

Electrophoresis buffers were added to cover the gel to a depth of approximately 1 mm. DNA samples were mixed with 0.20 volumes of 6x gelloading buffer.The sample mixture was loaded into the slots of the submerged gel using a disposable micropipette. Size standards were loaded into slots on both the right and left sides of the gel. The electrical leads were attached so that the DNA will migrate toward the positive anode. A voltage of 1-5 V/cm was applied. The gel was run until the tracking dye (bromophenol blue and xylenecyanol FF) had migrated an appropriate distance through the gel. The gel tray was removed and placed directly on a trans illuminator to visualize the DNA bands (Figure 1).

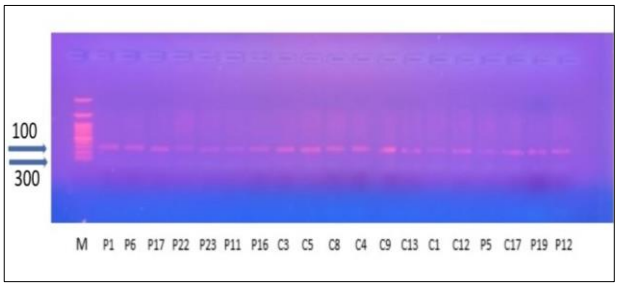

Figure 1: 2% Agarose gel electrophoresis showing some patient's samples (P) and some control samples (C) against 100 base pair (100 bp) size marker (M), electrophoresed bands are nearly located at 280 bp.

Fragment analysis

After electrophoresis, the amplified material of each sample was loaded into ABI-3500c (xl) DNA sequencer to assess number of CAG repeats. 0.7 µl PCR of the amplified material were mixed with 0.2 µl LIZ GS500 size

standard and 9 µl of HiDi formamide. This mixture was heated for 3 min at 86°C and then placed on ice for 2 min followed by sample loading.

Data analysis

Resulted fragment files were uploaded to Thermofisher cloud and analyzed using the microsatellite analysis plugin. The CAG repeat number was calculated using the following formula [CAG repeat number=fragment of amplification -228/3] (Figures 2 and 3).

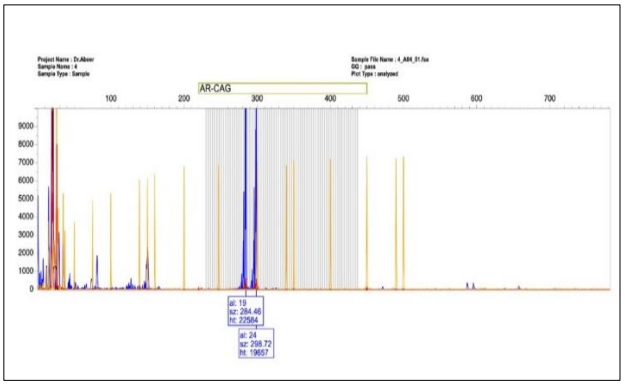

Figure 2: Gene sequencing of the (CAG) in androgen receptor gene with a polymorphic sequence of 19 and 24-repeat lengths (represented by the 2 peaks in the figure) (female patient with 2 different alleles).

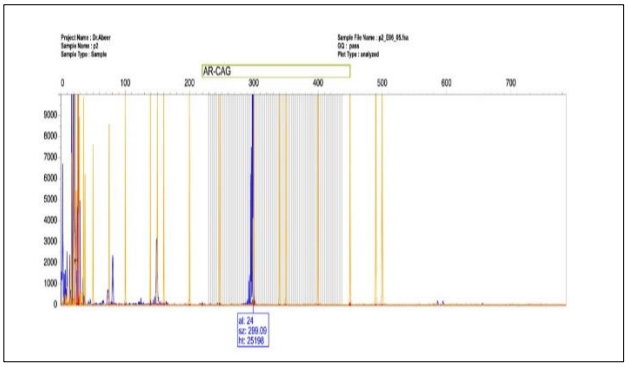

Figure 3: Gene sequencing of the (CAG) androgen receptor gene with a polymorphic sequence of 24-repeat length (male patient).

Statistical analysis

The collected data were revised, coded and tabulated using statistical package for social science (SPSS) (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.). Data were presented and suitable analysis was done according to the type of data obtained for each parameter. Kolmograv-Smirov test was done to test the normality of data distribution. Significant data was considered to be nonparametric.

Descriptive statistics

Mean, standard deviation (±SD) for numerical data. Frequency and percentage of non-numerical data.

Analytical statistics

Independent t test was used to assess the statistical significance of the difference between two study group means, Correlation analysis (using Pearson's method): to assess the strength of association between two quantitative variables and Chi-square test: was used to examine the relationship between two qualitative variables. For p value, $p>0.05$: non-significant, $p\leq0.05$: significant while $p\leq0.01$: highly significant.

RESULTS

Demographic data

The current study included 25 acne patients (11 males (22%) and 14 females (28%)) with mean age (22.3±4.7), and 25 control subjects (11 males (22%) and 14 females (28%)) with mean age (22.9±4.7). There was no statistically significant difference between the two groups regarding age or gender (Table 2).

Table 2: Age and gender of included subjects.

Variables	Mean	SD	Range	T test value	P value
Age (years)					
Acne patients	22.3	4.7	16-27	0.447*	0.657
Control subjects	22.9	4.7	18-28		
Gender	Male	Females	Test value		
Acne patients	11 (22%)	14 (28%)	0.001#		0.999
Control subjects	11 (22%)	14 (28%)			

*Using independent t test, #using Chi square test, p value ≤0.05 is significant

Clinical characteristics of acne patients

Duration of acne in patients' group had a mean of 31.7±31.1 and range 3-120 months. 17 patients (68%) had gradual onset of acne while 8 (32%) had sudden onset. The disease course was progressive in 22 patients (88%) and stationery in 3 patients (12%) (Table 3). Table 4 revealed that in patients group females had a higher frequency of longer CAG repeats compared to males in allele 1. On the other hand, in control group there was an even distribution of CAG number repeats in both females and males in allele 1 (Table 5).

Table 3: Clinical characteristics of acne patients.

Mean	SD	Range
Duration		
31.7	31.1	3-120
Onset of acne		
Gradual	17 (68%)	
Sudden	8 (32%)	
Course of acne		
Progressive	22 (88%)	
Stationary	3 (12%)	

Analysis of CAG number repeats in males and females revealed that male and female acne patients had significantly lower number of CAG repeats compared to control males and females with statistically significant difference in both males and females (p=0.040 and 0.010 respectively) (Table 6).

Genetic analysis of CAG repeats with gender correction

Considering gender correction of CAG repeat numbers, since we have males and females in our study group and males are hemizygous (have a single X chromosome), so we duplicated male results to compensate for the chromosomal difference between males and females. Genetic analysis of CAG repeats numbers in both groups revealed statistically significantly lower number of CAG repeats in acne patients compared to control subjects (p=0.001) (Table 7).

Table 4: CAG repeat numbers in acne patients.

Allele I			Allele II		
Repeat number	**Male frequency**	**Female frequency**	**Repeat number**	**Male**	**Female**
10	-	1	10	-	-
11	-	1	11	-	-
12	1	1	12	-	1
13	3	-	13	-	1
14	2	4	14	-	5
15	5	1	15	-	2
16	-	2	16	-	2
17	-	3	17	-	2
18	-	-	18	-	-
19	-	-	19	-	-
20	-	1	20	-	-
21	-	-	21	-	-
22	-	-	22	-	1
Total	11	14	Total	-	14

Table 5: CAG repeat numbers in control subjects.

Allele I			Allele II		
Repeat number	**Male frequency**	**Female frequency**	**Repeat number**	**Male**	**Female**
9	1	-	9	-	-
10	-	1	10	-	-
11	-	1	11	-	-
12	-	-	12	-	-
13	1	1	13	-	-
14	-	-	14	-	1
15	2	3	15	-	1
16	-	3	16	-	1
17	2	1	17	-	4
18	2	-	18	-	2
19	-	2	19	-	2
20	2	1	20	-	1
21	1	1	21	-	2
22	-	-	22	-	1
23	-	-	23	-	-
24	-	-	24	-	1
Total	11	14	Total		14

Comparison of CAG repeat number regarding demographic and clinical characteristics revealed no significant correlation or association of CAG number repeats with patients' age, duration of acne, onset or course of acne, (Tables 8 and 9).

Table 6: Analysis of CAG repeat number in both groups according to gender.

Variables	Mean	SD	Range	Test value	P value
Males					
Acne patients	14	1.1	12-15	2.208*	0.040
Control subjects	16.7	3.8	9-21		
Females					
Acne patients	15	1.7	10-22	2.766*	0.010
Control subjects	17.2	2.6	10-24		

*Using independent t test, p value ≤0.05 is significant

Table 7: Analysis of CAG repeat number in both groups.

Variables	Mean	SD	Range	Test value	P value
Acne patients	14.6	1.5		10-22	0.001
Control subjects	17	3		9-24	

*Using independent t test, p value ≤0.05 is significant

Table 8: Correlation of CAG repeat number with patients' age and duration of acne.

Variables	Pearson correlation	P value
Age	0.123	0.559
Duration of acne (months)	-0.244	0.262

*Using Pearson correlation test, p value ≤0.05 is significant

Table 9: Comparison of CAG repeat number with acne onset and course in patients' group.

Parameters	Acne onset		Acne course	
	Grad-ual	Sudden	Progre-ssive	Statio-nary
Mean	14.6	14.4	14.0	14.5
SD	1.6	1.2	1.5	1.3
Test value	0.276		0.073	
P value	0.785		0.943	

DISCUSSION

Nodulocystic acne is a severe form of acne that can cause considerable skin damage and has a negative influence on one's quality of life. In the absence of hyperandrogenism, hypersensitivity of the ARG can be regarded as a potent effector of acne pathogenesis.[6]

ARG contains a polymorphic CAG triple repeat that controls the expression of the gene and rate of receptor synthesis and turnover.[13] In the current study we aimed to investigate CAG repeat polymorphism in the ARG in Egyptian nodulocystic acne patients to clarify its relevance to nodulocystic acne.

In our study, genetic analysis of CAG repeats in male and female participants revealed that male and female acne patients had a significantly lower number of repeats compared to control males and females. Study of allelic distribution of allele 1 in both male and female acne patients revealed higher frequency of larger CAG repeats in female patients compared to male patients. The current study results were in accordance with previous studies on CAG repeats number in acne patients.

Demirkan et al investigated CAG repeat polymorphism in the ARG in nodulocystic acne patients in Turkish population.[6] They mentioned that female acne patients had a significantly lower number of CAG repeats compared to control subjects which is similar to the results presented in our study. However, allelic distribution of CAG repeat number was different from our study because their patients had higher frequency of low CAG repeat number compared to that of our study.

Similar results were obtained by Pang et al, as regard the CAG repeat number in their patients however, they have found that the low number of CAG repeat had been associated with higher risk for developing acne vulgaris.[5]

On the other hand, Yang et al investigated the relationship between CAG repeat polymorphism in the AR gene and acne susceptibility from the Han ethnic group in China and reported different results.[14] A total of 206 acne patients and 200 healthy controls were included in the study. The study discovered a link between CAG repeat length and male acne, with male patients having a much lower number of CAG repeats. There was no discernible difference between female patients and their controls. This contradictory results with our study can be explained by the hypothesis that different ethnic groups have different distribution of CAG repeat numbers.

The relevance of CAG repeat number in the etiology of acne vulgaris is explained by its role in regulating ARG expression and, as a result, the synthesis and turnover of its receptor product. Androgens stimulate keratinocyte proliferation in the ductus seboglandularis and the acroinfundibulum, as well as increasing the size of sebaceous glands and promoting sebum production.[15] On the contrary, anti-androgens (for example, flutamide) reduce the synthesis of lipids in the sebaceous glands and participate in decreasing the evolvement of acne.[16]

The AR number and sensitivity are ligand-dependent and are regulated by skin fibroblasts and sebocytes.[17] The role of androgen/AR in the etiology of nodulocystic acne has been linked to a number of processes. AR might boost the activity of the fibroblast growth factor receptor 2 (FGFR2), which has been linked to sebaceous gland development and homeostasis. AR may increase the expression of sterol-regulatory elementbinding proteins in sebocytes, hence lipogenesis (SREBPs). In addition, androgens may interact with the functions of insulin-like growth factor-1 (IGF-1) stimulating SREBP-1 expression and lipogenesis.

Moreover, it has been proposed that androgen/AR can boost macrophage and neutrophil inflammatory responses.[18] As a result, androgen/AR may increase the inflammation that promotes the formation and advancement of nodulocystic acne. Other hypotheses that explain the role of androgens/AR in the pathogenesis of nodulocystic acne is through mammalian target of rapamycin complex 1 (mTORC1), which is a protein complex that functions as a nutrient/energy/redox sensor and controls protein synthesis. After androgens bind to AR localized to cell nucleus, the phosphorylation of mTOR increased. It has been reported that there are a higher cytoplasmic and nuclear expression of mTOR in inflammatory sebaceous glands in acne lesion, which promotes lipogenesis by activating SREBP-1.

Androgen also negatively regulates endogenous Wnt/β-catenin signaling pathway. As a result, the expression of Wnt/β-catenin target genes such as c-MYC is upregulated, inducing sebocyte differentiation.[19] Differentiating sebocytes exhibit a high level of nuclear AR and peroxisome proliferator-activated receptors (PPARs). During this process, lipids gradually accumulate with evolvement of nodulocystic acne.

Our findings that short CAG repeats increase the risk of acne have been previously reported by other authors.[20] In fact, short CAG repeats have been associated with an increased risk of prostate cancer, ovarian hyperandrogenism and benign prostatic hyperplasia.[21-23] Short CAG repeats have been associated with higher AR mRNA and protein levels and also with elevated transcriptional activation activity. These findings support the idea that CAG repeat length and the AR trans-activation potential are inversely correlated.[24]

Nieuwerburgh et al analyzed CAG repeat lengths in 97 women with ultrasound features of PCOS.[25] They reported that patients with shorter CAG repeats had higher PCO activity, comparable to our severe form of acne. Moreover, the highest percentage of patients with acne and/or hirsutism had a significantly lower number of CAG repeats. These results are in accordance with our results that shorter and lower number of CAG repeats are relevant to the development of acne and more specifically the severe nodulocystic ones.

On the contrary, Skrgatic et al studied the association of the AR gene CAG repeat length polymorphism with PCOS and reported that there was no significant difference in the mean CAG repeat number between the PCOS patients and controls in Croatian population.[26] This contradicting results from our study can be explained by either larger number of included patients in the mentioned study or due to ethnic variations.

Predicting the treatment protocol in acne according to the CAG repeats number was also reported in other dermatological diseases as in female pattern hair loss (FPHL). Keene and Goren stated that finasteride would be more effective in the treatment of FPHL patients with CAG repeats number smaller than 24 (comparable to our study) in a randomized clinical trial in Caucasians.[27] They also suggested predicting the sensitivity of the patient response to finasteride in correlation with CAG repeats number, which can also be used as an anti- androgen in the treatment of acne.

It has been shown that changes in repeat lengths in the case of CAG repeats are associated with fine modulation of the AR wide expression and that various downstream targets result in a modified transcriptional activity. In the normal allele range, there appears to be an inverse correlation between the CAG repeat length and the androgen wide expression; shorter alleles exhibit higher activity.[5]

Previous studies reported that a long polyglutamine chain (>30 repeats) in the AR gene is associated with androgen insensitivity and reduced AR activation. Genetic knockout of the polyglutamine chain results in elevated transcriptional activities of AR mRNA.[28] It seems that the decreased length of the CAG repeat is associated with the increased AR activities and the enhanced androgen actions. Therefore, decreased length of the CAG repeats can be considered as a direct enhancer of the pathogenesis of the severe form of nodulocystic acne in our study.

Precise mechanisms by which CAG repeat influences DNA transcription are not clear and hypotheses have been raised. Tirabassi et al reported that opposite association has been found between CAG repeat length and DNA transcriptional activity, they stated that the glutamine residues may contact another protein and inhibit interactions of the activation domain with its target protein, also glutamine residues could interact with a specific repressing protein, thus determining inhibition.[29] That inverse relation could be also explained by producing structural changes inside the transactivation domain and the polyglutamine tract may have an indirect effect on AR function.[30]

This genetic background opens the field of future target therapies of acne. Gene therapy involving knocking out the hyperactive shorter CAG repeats can be performed by blocking its gene transcription or translation via interfering with mRNA transcription and ribosomal machinery. This will decrease androgen receptor responsiveness to effects

of androgen and consequently may antagonize the pathogenic role of androgens in nodulocystic acne.

Our study as well as the above-mentioned ones open the field of new target therapy of acne like mTORC1 and others. Topical anti-androgen could be also a target of therapy in acne. Kircik found that Clascoterone, is the first topical AR antagonist approved by FDA in treatment of acne vulgaris and severe variants as nodulocystic acne.[16] Phase III study results confirmed the safety and efficacy of Clascoterone in the treatment of severe acne with improvement of 20.8% of acne lesions greater than controls. This novel topical line of therapy and the possible systemic ones support our results and reflect the role of AR in the pathogenesis of acne and consequently the pivotal role of targeting AR in treatment guidelines.

Limitations

The limitation of our study was the number of patients and controls, that may be the reason why there was a difference in the results with some of the previous studies. Furthermore, the study of CAG repeat polymorphism in different types of acne to compare if it got a role only in sever types of acne or all the types.

CONCLUSION

We conclude from the findings of our study and the previous studies that androgen receptor gene CAG repeat polymorphism has a role in the development of acne, hence nodulocyctic acne, in the Egyptian population in both males and females.

Based on the current study results we recommend; Further studies with larger number of included patients to elucidate the exact role of CAG repeat numbers in acne vulgaris, moreover, separate studies involving male and female acne patients are recommended. Study of CAG repeat numbers in other dermatological diseases that are predisposed by increased androgen activity as androgenetic alopecia is also needed. Drug trials involving gene therapy to silence the hyperactive, short CAG repeats of AR genes in patients with severe cases of nodulocystic acne is a promising target. Knocking out the hyperactive short CAG repeats will decrease androgen receptor responsiveness to effects of androgen and this may decrease the role of androgen in the pathogenesis of nodulocystic acne. Further studies are recommended on larger number of included patients with separate study of male and female acne patients to elucidate role of AR CAG gene polymorphism in the pathogenesis of acne. Moreover, further studies of AR CAG gene polymorphism in association with androgen receptor blockers are necessary to reveal the true effect of androgens in acne patients.

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