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Gene Expression and Single Nucleotide Polymorphisms of CYP19A1 gene as markers for Female pattern hair loss in Egyptians

(1)N.E.Ahmedm ,(1)O.A.Abdullah ,(2)G.M.abd El Khalek ,(1)A.F.El Kholy,(1) S. Abd El Rahman ,(1)M.G.Abd EL-Razik
1Lecturer of Medical Biochemistry &Molecular Biology ,Dept., Faculty of Medicine, Benha Univ., Benha, Egypt
2Lecturer of Dermatology, Venereology and Andrology ,Dept., Faculty of Medicine, Benha Univ., Benha, Egypt
E-mail: manargadhaz@yahoo.com

Abstract

Female pattern hair loss, or FPHL, is a disorder that affects millions of women worldwide and may be emotionally and psychologically taxing in addition to being visually disconcerting. A successful result can only be achieved with a timely diagnosis and treatment. Diffuse thinning of hair on the crown and front of the scalp, with the hairline remaining unaffected, characterises female pattern hair loss (FPHL), the most frequent kind of hair loss in women. It becomes more common as people become older and is linked to serious mental health issues. It seems that there are several factors involved in FPHL's pathogenesis, which remains poorly understood. Although androgens have been suspected, the absence of clinical or biochemical indicators of hyperandrogenism in afflicted women suggests that other, androgen-independent processes are at play. Increasing evidence suggests that genetic variants affecting the androgen and oestrogen receptors have a significant role in both its aetiology and the ability to predict response to anti-androgen therapy. The purpose of this research was to examine whether or not FPHL is associated with single-nucleotide polymorphisms (SNPs) in the CYP19A1 gene among Egyptian women.

Keywords: Female pattern hair loss, CYP19A1 gene, polymorphism

1.Introduction

One of the most prevalent hair diseases, female pattern hair loss (FPHL) has been linked to negative psychological outcomes, such as diminished self-esteem and increased rates of anxiety and despair, particularly in young women [1]. While the exact cause of FPHL is uncertain, most theories revolve on androgens and other hormones [2]. Most individuals with FPHL have normal testosterone levels in their sera, despite the fact that biochemical tests are often conducted to establish a hyperandrogenic state as the aetiology of FPHL. Hair follicles have the enzyme machinery essential for androgen metabolism in situ, suggesting that they depend less on circulating androgens than was previously thought [4]. Because of this, a number of studies have employed invasive techniques (such as scalp biopsies) to collect samples in order to measure androgen levels [5] and pinpoint the location of androgen-metabolizing enzymes inside the hair follicle [6].

The most powerful androgen, dihydrotestosterone (DHT), controls the expression of genes that cause hair follicles to shrink over time [7] and proteins that shorten the hair growth cycle [8]. Dermal papilla senescence and hair's transition into telogen phase are triggered by DHT's elevation of cytokine production [9]. By influencing the Wnt signalling pathway, DHT may potentially disrupt the follicular cycle [10].

There is significant inconsistency in the published statistics on the prevalence of FPHL, which may be attributable to the difficulties in categorising moderate cases. Yet, they all seem to become more common as people become older. White European American, British, and Australian women show a 3%-12% prevalence in their thirties, a 14%-28% prevalence in their sixties, and a 29%-56% prevalence in their seventies, according to studies. Prevalence rates are lower among East Asian women, reported at between 12 and 25 percent in the over 70 age range. [14] Pattern hair loss may occur as early as age 6, however it often begins during puberty [15].

By converting C19 precursor androgens to aromatic C18 oestrogens, the aromatase enzyme in the sex steroid pathway controls the amounts of androgens and oestrogens in scalp tissue.[16].

There is some evidence that oestrogen levels in the scalp have a role in controlling hair loss, while the precise mechanism of this regulation is unknown. Aromatase expression is localised to the dermal papilla cells and the outer root sheath keratinocytes of hair follicles in the scalp. [17] Chromosome 15q21.1 is home to the CYP19A1 gene, which provides instructions for making aromatase. CYP19A1 is regulated by tissue-specific promoters and covers about 123 kb of DNA, which includes 10 coding exons and numerous alternative, untranslated first exons. [18] The coding region of CYP19A1 is located only at the 3′

end of the gene, while the remaining 93 kb in the 5′ end function as the regulatory unit. [19] Circulating hormone levels, the pathogenesis of breast and endometrial malignancies, and the response to therapy have all been linked to genetic variation in and around CYP19A1. [20] As a result, CYP19A1 genetic variation may contribute to the equilibrium of sex steroid concentrations in the scalp, and hence play a role in the development of FPHL.

2.Subject and Methods

This study was carried out between March 2021 and August 2022 after approval of the study scheme by the research ethical committee of Benha Faculty of Medicine and obtaining informed consent from the included subjects.

This study included 60 subjects of females which were selected from Department of Dermatology, Faculty of Medicine, Benha University Hospital. FPHL group gathered 40 female patients and the control group had 20 healthy females.

Blood samples: Blood was gathered on ethylene diamine tetra-acetic acid (EDTA) tube. The blood sample was aliquoted in 2 Eppendorf tubes and kept at -20°C.

3.Statistical analysis

The collected data will be tabulated and analyzed using SPSS version 16 software (SpssInc, Chicago, ILL Company). Categorical data were presented as number and percentages while quantitative data were expressed as mean ± standard deviation, median and range. P-value 0.05 was considered statistically significant, while P-value > 0.05 was considered statistically non-significant. Analysis is performed using the Statistics Program for Social Sciences (SPSS) and Microsoft Office Excel is used for the data processing and data analysis.

4.Results

The ages of Patients ranged from 21 to 40 years with mean± SD= 29.13± 5.33 years while the ages of controls ranged from 16 to 38 years with mean± SD= 26.9± 6.26 years. Comparing the mean values of ages between the two groups revealed non-significant difference (P= 0.08); Table (1).

Table (1) Demographic data of the studied groups

Group	Patients group		Control group		P-value
Age (years)	(n=40)		(n=20)		
	Mean	S.D	Mean	S.D	
Mean± SD	29.13	5.33	26.90	6.26	0.08
Range	21-40		16-38		

SD: Standard deviation, P 0.05 ≤ significant, P > 0.05 non-significant, analysis done by independent samples Student T test.

The number of married female in patients is 33 with percentage of (82.5%) and The number of unmarried females in patients is 7 with percentage of (17.5%), while The number of married female in controls is 13 with percentage of (65.0%) and The number of unmarried females in controls is 7 with percentage of (35.0%). Comparing these values of marital status between the two groups revealed non-significant difference (P= 0.1); Table (3).

Table (2): Marital status of the study groups.

Group	Patients group		Control group		P-value
Marital status	(n=40)		(n=20)		
	No.	%	No.	%	
Married	33	82.5%	13	65.0%	0.1
Unmarried	7	17.5%	7	35.0%	

In the rs6493497 patient group, the arginine (A) and guanine (G) frequencies (A = 12 and G = 68) were significantly different from those of the control group (A = 24 and G = 16, p p<0.001). Similarly, in the rs7176005 patient group, the thymine (T) and cytosine (C) frequencies (T = 12 and C = 68) were significantly different from those of the control group (T = 24 and C = 16, p<0.001) Table (3).

Table (3): Allele frequencies in SNPs of CYP19A1 gene

SNP	Allele	patients	controls	χ2/p
rs7176005	C	68	16	25.7/<0.001*
	T	12	24	
rs6493497	A	12	24	17.8/<0.001*
	G	68	16	

Furthermore, in the rs6493497 patient group, the A and G genotype distributions (AA = 1, AG = 10, and GG = 29) were significantly different from those of the control group (AA = 8, AG = 8, and GG = 4, p <0.001). The same was true for the rs7176005 patient group, T and C distributions (TT = 1, CT =

10, and CC = 29) relative to the control group (TT = 8, CT = 8, and CC = 4, p <0.001), as shown in table 4.

Table (4): Distribution of SNP genotypes of the CYP19A1 gene

SNP	Genes	Patients	Controls	χ2/p
rs7176005	CC	29	4	
	CT	10	8	20.2/<0.001*
	TT	1	8	
rs6493497	AA	1	8	
	AG	10	8	20.2/<0.001*
	GG	29	4	

5.Discussion:

The vertex, as well as the frontal and parieto-temporal areas, saw a decrease in hair shaft density in FPHL patients. Contrarily, the frontal region exhibited a less degree of decrease than the other regions. The vertex terminal hair shafts of the FPHL patient group were narrower than those of the control group. Consistent with these results is the fact that FPHL is characterised by a reduction in HF volume with time, most noticeably in the vertex and parieto-temporal scalp [21].

Female pattern hair loss (FPHL) is also known as female androgenetic alopecia due to its association with a change in androgen metabolism and its hereditary nature. A feminine counterpart to the MAGA movement. While MAGA is known to be androgen dependent, this is not the case with FPHL. Even though hyperandrogenism is what triggers pattern hair loss and hirsutism, the majority of women who suffer from FPHL actually have normal androgen levels. Hypopituitarism and the absence of measurable androgens in FPHL imply that the condition may have other causes. Therefore, 'female pattern hair loss' is preferred over 'female androgenetic alopecia' A smaller number of genetic association studies have been conducted for FPHL compared to MAGA [22].

Widespread differences in circulating estrogenic steroid levels have been associated with the CYP19A1 gene. Women receiving aromatase inhibitor medication for breast cancer have a quick beginning of female pattern hair loss (FPHL) [23], which supports the hypothesis that oestrogens may speed up hair growth.

Evidence suggests the opposite, despite widespread assumption to the contrary. Treatments with topical oestrogen on mouse skin greatly reduced hair growth by keeping hair follicles in the dormant telogen phase, whereas treatments with topical oestrogen antagonists switched hair follicles from telogen to the actively growing anagen phase. Also, oestrogens have been shown to interrupt the hair cycle clock in telogen, preventing the hair follicle from transitioning into anagen [24].

According to our findings, there was no statistically significant difference in age between cases and controls (mean SD= 29.13 5.33 years vs. 26.9 6.26 years; P=0.08).

While the density and diameter of women's hair shafts peaked in their 20s and 30s, then progressively fell as they aged, a significant connection between age and early beginning of FPHL was found in a research by Kim et al. (2013). This study's case group was significantly younger than the control group (p 0.015), suggesting that genetic susceptibility rather than either age or environmental factors may play a larger role in the development of eFPHL [21].

Our data showed that rs6493497 expression differed significantly between FPHL patients and controls (P0.001).

SNPs rs6493497 and rs7176005 are located in the CYP19A1 promoter sequence, just before exon 1. Exon 1 expression is tightly correlated with aromatase activity. Promoter structure affects its affinity with the RNA polymerase, which in turn increases gene expression, making transcription initiation a critical step in the expression of a gene. More functional investigations are needed to determine the effect these 2 SNPs have on CYP19A1 gene transcription, as was suggested in a recently published research on breast cancer [25].

6.References

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