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RESEARCH ARTICLE

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Prevalence of MMP-1 rs1799750 Polymorphism in Androgenetic Alopecia: A Cross-Sectional Study in an Indonesia Population

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Background: Matrix metalloproteinase-1 (MMP-1) is an enzyme responsible for degrading extracellular matrix (ECM) components, particularly collagen. Overexpression of MMP-1 can accelerate ECM degradation, contributing to various pathological conditions. The most studied polymorphism in the promoter region of the MMP-1 gene is rs1799750, which has been linked to several diseases in previous studies. Androgenetic alopecia (AGA) is a condition characterized by the progressive miniaturization of hair follicles, influenced by androgen signaling and ECM remodeling. This study aimed to investigate the prevalence of MMP-1 gene polymorphism and its potential association with AGA..

Materials and methods: This study included 50 subjects diagnosed with AGA and 50 subjects without AGA. All subjects completed a questionnaire that included gender, age, BMI, and ethnicity. DNA was extracted from blood samples for genotyping of the MMP-1 rs1799750 gene. Genotyping was performed using the PCR-RFLP method with AluI as the restriction enzyme. For validation, several samples were sequenced at Apical Scientific Laboratory, Malaysia.

Results: Among the 50 subjects with AGA, 9 had the 1G/1G genotype, 26 had the 1G/2G genotype, and 15 had the 2G/2G genotype. Similarly, among the 50 subjects without AGA, 8 had the 1G/1G genotype, 27 had the 1G/2G genotype, and 15 had the 2G/2G genotype. The allele frequencies of 1G and 2G in the AGA group were 0.44 and 0.56, respectively, while in the non-AGA group, they were 0.43 and 0.57, respectively. Chi-square analysis of AGA and MMP-1 genotype yielded a p-value of 0.96, indicating no significant association between AGA and the MMP-1 genotype.

Conclusion: In this study, the association between the MMP-1 gene polymorphisms rs1799750 with AGA was not observed.

Keywords: *androgenetic alopecia, matrix metalloproteinase-1, polymorphisms, rs1799750*

Introduction

Matrix metalloproteinases (MMPs) are calcium- and zinc-dependent enzymes essential for extracellular matrix (ECM) degradation and remodeling. Among them, collagenase-1, or MMP-1, is one of the most extensively studied. MMP-1 plays a key role in cleaving fibrillar collagen, specifically targeting collagen types I, II, and III, which are the predominant components of the ECM.[1,2]

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The MMP-1 gene is located in chromosome 11q22, and its expression is low in normal conditions. However, in pathological conditions such as osteoarthritis and cardiovascular diseases, the MMP-1 gene is expressed at a high level.[3,4] High expression of the MMP-1 gene can also result from a single nucleotide polymorphism (SNP) in the promotor region of the gene. One of the most studied MMP-1 SNPs in the promotor area is rs1799750. This mutation can lead to the insertion of one guanine at -1607 bp, thus making two different alleles, 1G allele and 2G allele. This insertion mutation increases the MMP-1 gene expression and might lead to pathological diseases.[5,6] Several other polymorphic variants, such as rs498186 A/G and rs1144393 T/C, also affect MMP-1 enzyme activity. The rs498186 variant creates a protein binding site for the p300 protein, which can enhance transcription, while the rs1144393 variant affects the promoter region of the gene that regulates transcriptional activity.[7]

Androgenetic Alopecia (AGA) is the most common form of hair loss, which is caused by progressive miniaturization of hair follicles and is driven mainly by androgenic signaling and ECM remodeling.[8] The dermal papilla, a key regulator of hair follicle cycling, is rich in collagen and ECM components. MMP-1 upregulation may contribute to collagen breakdown, weakening follicular support, and hair loss.[9] Given the role of MMP-1 in collagen degradation, its overexpression due to genetic mutations, such as rs1799750, could play a potential role in AGA pathogenesis by altering the hair follicle microenvironment and enhancing the effects of androgens on follicular miniaturization.[10]

Given the potential significance of this polymorphism, mapping the prevalence of the rs1799750 genotype would be relevant to observe its association with pathological diseases. Therefore, this study aimed to observe the prevalence of the rs1799750 genotype in the population of Jakarta, Indonesia, and its relation to AGA.

Materials and methods

Subjects Recruitment

Ethical approval was obtained from the Universitas Tarumanagara Human Research Ethics Committee, under the Institute of Research and Community Engagement, with the assigned project number 002-UTHREC/UNTAR/I/2024. Prior to participation, all subjects provided written informed consent, ensuring adherence to autonomy, beneficence, and justice. In this study, the subjects were patients from Nataliani Mawardi Clinic with specific inclusion and exclusion criteria. Participants were eligible for inclusion if they were aged 18 to 60 years, male or female, had signed informed consent and were willing to complete the study questionnaire. For the AGA group, participants were required to have been diagnosed with androgenetic alopecia by the attending physician. For the non-AGA group, participants had to exhibit no clinical signs of AGA or any other form of hair loss. Exclusion criteria applied to all participants such as diagnosis of other types of alopecia, such as alopecia areata and telogen effluvium, as well as history of hair transplant surgery. Individuals who were unable or unwilling to provide informed consent or complete the questionnaire were also excluded. A total of 100 subjects were recruited, comprising 50 subjects with AGA and 50 without androgenetic abnormalities (non-AGA). Each subject completed a questionnaire collecting data on age, gender, ethnicity, and body mass index (BMI).

DNA Extraction and Genotyping

A physician drew blood from subjects for genomic DNA extraction, which was then used for DNA extraction. DNA was extracted using a column-based kit (Genomic DNA Midi Kit, Geneaid, Taiwan). The extracted DNA samples were stored at -20°C until further use. The PCR amplification was performed by the following primers (Table 1).

The PCR reaction was performed in a total volume of 20 µL, consisting of 10 µL MyTaq HS Red Mix (Bioline, UK), 4 µL nuclease-free water, 1 µL of each 10 µM primer, and 4 µL of a 50 ng/µL DNA template. The PCR cycling conditions were set as follows: initial denaturation step of 95°C for 5 minutes, the denaturation step of 95°C for 30 s, the annealing step of 56°C for 45 s, the extension step of 72°C for 1 minute, and the final extension step of 72°C for 10 minutes. These cycles were repeated for 35 cycles using conventional PCR (Thermal Cycles T100, Biorad, California, USA). After amplification, the PCR product was visualized by agarose gel electrophoresis. According to the manufacturer's instruction, the RFLP was done with FastDigest AluI (Thermo Fisher Scientific, USA) restriction enzyme for 1 hour at 37°C.[11]

Table 1. Primer sequence for MMP-1 genotyping.

Primer	Sequence (5'-3')	Product Size
Forward	TCTTGGATTGATTTGAGATAAGTCATAGC	269 bp
Reverse	GACTTTTAAAACATAGTCTATGTTCA	

After incubation, digestion products were visualised using 2.5% agarose gel electrophoresis. Genotype was determined as 1G/1G, homozygote wild-type genotype (241, 28), 2G/2G homozygote mutant genotype (269), and 1G/2G, heterozygote genotype (269, 241, 28). A total of five representative samples, one homozygous 1G, two homozygous 2G, and 2 heterozygous were selected and sent to Apical Scientific Laboratory, Malaysia, for validation.

Statistical Analysis

Collected data were analyzed using R software (version 4.3.1), and data visualizations were created with ggstatplot and ggbarplot packages. Chi-square analysis, Hardy-Weinberg equilibrium testing, and allele frequency comparisons between MMP-1 genotypes were performed, with $p< 0.05$ to be considered statistically significant.

Results

Demographic and MMP-1 Genotyping by PCR-RFLP of Subjects

One hundred subjects participated in the study, comprising 50 subjects diagnosed with AGA and 50 subjects without AGA (Table 2). Among the 50 subjects with AGA, 9 had the 1G/1G genotype, 26 had the 1G/2G genotype, and 15 had the 2G/2G genotype. Similarly, among the 50 subjects without AGA, 8 had the 1G/1G genotype, 27 had the 1G/2G genotype, and 15 had the 2G/2G genotype. The median BMI in the AGA and non-AGA group was 23.82 and 24.16, respectively. The median age in the AGA group was 36 years, compared to 28.5 years in the non-AGA group. Based on statistical analysis, a significant association was found between age and AGA (p=0.012).

The 2G/2G genotype displayed a single band at 269 bp, the 1G/1G genotype shows a single band at 241 bp, and the 1G/2G genotype shows two bands at 241 bp and 269 bp (Figure 1). The smallest band (28 bp), present in the 1G/1G and 1G/2G genotypes, was not visible on the gel due to its small size.

MMP-1 Sequence

Among the 5 sequenced samples, 2 were heterozygous, 2 were homozygous for 2G, and 1 was homozygous for 1G, all of which were consistent with the PCR-RFLP results. The 1G/1G genotype has 1 guanine peak, the 1G/2G genotype has 2 guanine peaks, one of which coincides with the cytosine peaks indicating an insertion, and the 2G/2G genotype showed 2 distinct guanine peaks (Figure 2).

Table 2. Demographic data and genotyping results.

Characteristic	AGA n=50[1]	Non-AGA n=50[1]	*p*-value[2]
Genotype			> 0.9
1G/1G	9 (18%)	8 (16%)	
1G/2G	26 (52%)	27 (54%)	
2G/2G	15 (30%)	15 (30%)	
Age	36.00 (28.00-51.00)	28.50 (24.00-40.00)	0.012
BMI	23.82 (22.29-25.80)	24.16 (20.70-26.53)	> 0.9
Ethnic			0.058
Acehnese	2 (4.0%)	2 (4.0%)	
Ambonese	1 (2.0%)	0 (0%)	
Balinese	1 (2.0%)	0 (0%)	
Batak	2 (4.0%)	4 (8.0%)	
Betawi	7 (14%)	9 (18%)	
Buginese	0 (0%)	1 (2.0%)	
Chinese	11 (22%)	1 (2.0%)	
Jawanese	17 (34%)	16 (32%)	
Mixed	4 (8.0%)	9 (18%)	
NTB	0 (0%)	1 (2.0%)	
Sumatran	2 (4.0%)	2 (4.0%)	
Sundanese	2 (4.0%)	5 (10%)	
Torajan	1 (2.0%)	0 (0%)	
Gender			< 0.001
Female	20 (40%)	42 (84%)	
Male	30 (60%)	8 (16%)	

[1]n (%); Median (Q1-Q3). [2]Pearson's Chi-squared test; Wilcoxon rank sum test; Fisher's exact test.

Chi-Square Analysis of MMP-1 Genotype and Androgenetic Alopecia

The results showed no significant association (p=0.96) between MMP-1 rs1799750 genotype and AGA (Figure 3).

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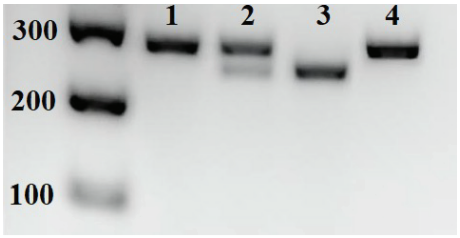

Figure 1. PCR-RFLP result of of MMP-1 rs1799750 gene polymorphism. Lanes 1 and 4 represent the 2G/2G genotype, lane 2 represents the 1G/2G genotype, and lane 3 represents the 1G/1G genotype.

Hardy-Weinberg Equilibrium of MMP-1 rs1799750 Genotype

The Hardy-Weinberg equilibrium test was applied to assess genotype distribution (Figure 4). The *p*-value was 0.736, this results indicates no significant deviation between the observed and expected genotype frequencies.

Allele Frequency of MMP-1

The allele frequency of the 1G allele was 0.435, and the allele frequency of the 2G allele was 0.565 (Table 3).

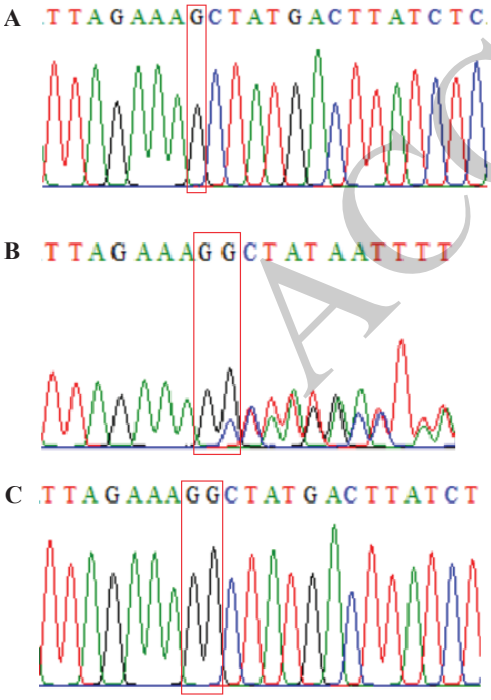

Figure 2. Sequence analysis of the MMP-1 rs1799750 gene polymorphism. A: sequence electropherogram for the 1G/1G genotype. B: sequence electropherogram for the 1G/2G genotype C: sequence electropherogram for the 2G/2G genotype.

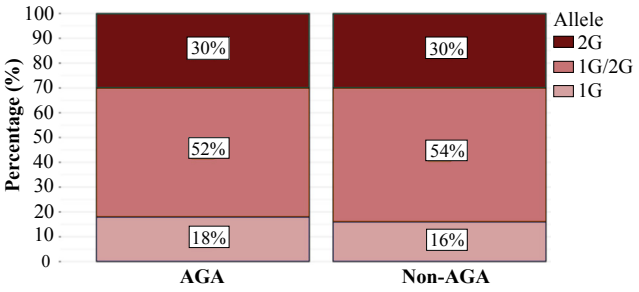

Figure 3. Chi-square analysis MMP-1 rs1799750 between AGA and Non-AGA.

Further analysis of allele frequency in relation to AGA status showed no significant association (Figure 5; chi-square analysis, p=1).

Discussion

This study investigated the prevalence of MMP-1 gene polymorphism rs1799750 in Jakarta, Indonesia. The rs1799750 polymorphism involves the insertion or deletion of a single guanine at position -1607 bp in the gene promoter. The insertion of one guanine (2G allele) at this site creates a binding motif (5′-AAGGAT-3′) for the Erythroblast Transformation-Specific (ETS) family of transcription factors, which enhances the transcription of the MMP-1 gene, thereby increasing plasma MMP-1 levels. Elevated plasma MMP-1 has been associated with various pathological conditions, suggesting that the rs1799750 polymorphism may contribute to disease susceptibility.[5] Therefore, a downregulation of MMP-1 gene expression and a reduction in its enzymatic activity are anticipated. Previous studies have demonstrated that natural compounds such as chlorogenic acid derived from snake fruit (Salacca zalacca) and tocopherol and β-carotene present in red fruit oil (Pandanus conoideus) are capable of suppressing MMP-1 gene expression and inhibiting its enzymatic activity.[12,13]

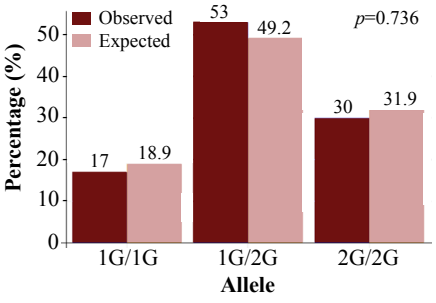

Figure 4. Hardy-Weinberg Equilibrium analysis of MMP-1 rs1799750 genotype.

Table 3. Allele frequency of MMP-1 rs1799750.

Allele	Frequency	Allele Frequency
1G	87	0.435
2G	113	0.565

In this study, the allele frequencies of 1G and 2G were similar to those found in a previous study conducted on the Greek population.[6] However, this study did not find a significant association between MMP-1 rs1799750 polymorphism and AGA, despite previous suggestions that MMP-1 overexpression could contribute to hair follicle miniaturization and ECM remodeling.[14,15] It is likely that gene-gene interactions involving androgen receptor (AR) polymorphisms, Wnt signaling, and inflammatory pathways could substantially influence AGA progression more than MMP-1 alone.[16-19] Additionally, other MMP-1-related polymorphisms, such as rs498186 and rs1144393, which also regulate gene expression, warrant investigation for their potential roles in AGA.[6]

Another explanation is that AGA is a polygenic condition influenced by multiple molecular pathways beyond MMP-1 and ECM remodeling. Androgen metabolism, DHT sensitivity, oxidative stress, and inflammatory cytokines have been implicated in follicular miniaturization, making it possible that other ECM-related genes, such as MMP-2, MMP-9, COL1A1, and TIMPs may have a more pronounced effect on the progression of hair loss.[20,21] Given that MMP-1 is primarily involved in collagen degradation, its genetic variations alone may not be sufficient to drive AGA pathogenesis, mainly if compensatory ECM regulatory mechanisms are active.

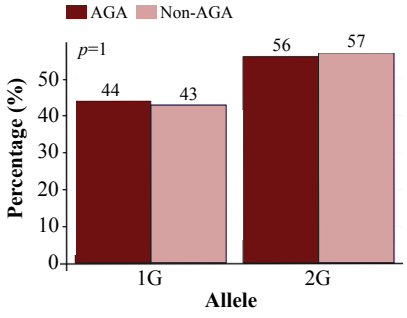

Figure 5. Distribution of allele frequency of MMP-1 rs1799750 based on AGA status.

Furthermore, environmental and epigenetic factors may play a significant role in AGA. MMP-1 expression can be influenced by external stimuli such as UV radiation, oxidative stress, smoking, and hormonal imbalances. This suggests that gene-environment interactions override the direct genetic influence of rs1799750, potentially masking any association with AGA in our study population.[22-24] However, this study demonstrated a significant association between age and AGA. This correlation has been well-documented in populations from India and Nigeria.[25-27] As age increases, dermal papilla cells undergo progressive degeneration, contributing to follicular miniaturization. The levels of reactive oxygen species (ROS) tend to rise with age, potentially exacerbating hair follicle damage.[28,29]

Despite the lack of a significant association, our study provides valuable insights into the genetic landscape of MMP-1 rs1799750 in an Indonesian population. This study examines the prevalence of this polymorphism in AGA subjects, contributing important population-specific data to the field of hair loss genetics. The findings highlight the importance of considering polygenic interactions and environmental influences when studying AGA susceptibility. Moreover, our study underscores the need for future research integrating genomic, transcriptomic, and functional analyses to unravel the complex interplay of ECM remodeling and androgen signaling in AGA. Expanding the research to include other MMP genes, TIMP inhibitors, and DHT-related pathways could offer a more comprehensive understanding of the molecular mechanisms driving hair follicle miniaturization. Lastly, this study also shows the importance of regional genetic research and the need for caution when interpreting commercial genetic testing results from foreign databases. Given that allele frequencies and genetic risk factors can vary significantly across ethnic groups, relying on genetic data from outside the country could lead to misinterpretation of disease risk or ineffective personalized treatments.

Conclusion

The investigation of allele frequencies for the MMP-1 rs1799750 polymorphism in Jakarta, Indonesia, revealed a frequency of 0.435 for the 1G allele and 0.565 for the 2G allele. No significant difference was observed between the AGA and non-AGA groups. This study did not find any

association between the MMP-1 rs1799750 polymorphism and AGA. This lack of association may be due to population-specific genetic variation, the polygenic nature of AGA, compensatory ECM regulatory mechanisms, or environmental influences.

Although no significant association was found, further studies on MMP-1 gene polymorphisms are warranted. Other variants, such as rs1144393 and rs498186, have not yet been examined in relation to AGA in the Indonesian population and may provide additional insights into its genetic basis.

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Authors' Contributions

ES contributed to the conception and planning of the research, performed the experimental calculations, and drafted the manuscript. DS was responsible for recruiting respondents and diagnosing AGA cases. ICA conducted the experiment and also contributed to drafting the manuscript.

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