



RESEARCH

Immunogenetic and metabolic risk factors in male androgenetic alopecia: the role of HLA-DRB1 alleles and vitamin D3 deficiency

Erkek tipi androgenetik alopeside immünogenetik ve metabolik risk faktörleri: HLA-DRB1 allelleri ve D3 vitamini eksikliğinin rolü

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Abstract

Purpose: Androgenetic alopecia (AGA) is the most common cause of hair loss in men. Although medically benign, it has a significant psychosocial impact on patients. The high rate of family history suggests polygenic inheritance. The current study aims to investigate HLA-DR B1 allele positivity in patients with AGA and evaluate the relationship with metabolic and dermatologic diseases that may accompany this disease and vitamin D3 deficiency.

Materials and Methods: The medical records of 85 male patients diagnosed with AGA based on clinical history and physical examination were retrospectively reviewed. Patients with stage II or higher AGA according to the Hamilton-Norwood classification were included in the study. Retrospective data were analyzed and recorded through chart review. Demographic characteristics, clinical findings, laboratory results, HLA-DRB1 allele profiles, and serum vitamin D3 levels were evaluated. Additionally, concomitant metabolic and dermatological conditions were assessed in all patients.

Results: In the distribution of HLA-DRB1 allele frequencies, HLA-DRB101, HLA-DRB104, and HLA-DRB111 positivity were observed more frequently. When the specific allele subtypes were analyzed, DRB104 11 was positive in 6.4%, DRB111 11 in 11.2%, and DRB111 13 in 6.4% of cases. Vitamin D3 levels were found to be low in 82% of patients with AGA.

Conclusion: This study shows that AGA is associated with immunogenetic factors and vitamin D3 deficiency. Screening these parameters may guide clinicians in early diagnosis and treatment.

Keywords: Androgenetic alopecia, HLA-DRB1, metabolic syndrome, vitamin D3, immunogenetics

Öz

Amaç: Androgenetik alopesi (AGA), erkeklerde görülen saç dökülmesinin en yaygın nedenidir. Tıbbi olarak benign bir durum olmasına rağmen, hastalar üzerinde önemli psikososyal etkileri vardır. Bu çalışma, AGA hastalarında HLA-DR B1 alel pozitifliğini araştırmayı, bu hastalığa eşlik edebilecek metabolik ve dermatolojik hastalıklarla ilişkisini değerlendirmeyi ve bu hastaların erken teşhisini sağlamayı amaçlamaktadır.

Gereç ve Yöntem: Öykü ve fizik muayene bulgularına dayanarak AGA tanısı konulan 85 erkek hastanın tıbbi dosyaları retrospektif olarak tarandı. Hamilton-Norwood sınıflamasına göre evre II ve üzeri AGA tanısı alan hastalar çalışmaya dahil edildi. Dosya incelemesiyle hastalara ait retrospektif veriler analiz edilerek kaydedildi. Hastaların demografik özellikleri, klinik bulguları, laboratuvar sonuçları, HLA-DRB1 alel profilleri ve serum vitamin D3 düzeyleri değerlendirildi. Ayrıca tüm hastalarda eşlik eden metabolik ve dermatolojik hastalıklar da analiz edildi.

Bulgular: HLA-DRB1 alel frekanslarının dağılımında, HLA-DRB101, HLA-DRB104 ve HLA-DRB111 pozitifliği daha sık gözlenmiştir. Alellerin spesifik alt tipleri incelendiğinde, DRB104 11 %6,4, DRB111 11 %11,2 ve DRB111 13 %6,4 oranında pozitif bulunmuştur. D3 vitamin seviyeleri, AGA hastalarının %82'sinde düşük saptanmıştır.

Sonuç: Bu çalışma, AGA'nın vitamin D eksikliği ve immünogenetik faktörler gibi sistemik etkenlerle ilişkili olduğunu göstermektedir. Yaygın D3 vitamini eksikliği ve metabolik bozukluklar, kapsamlı sistemik değerlendirme gerekliliğine işaret etmektedir.

Anahtar kelimeler: Androgenetik alopesi, HLA-DRB1, metabolik sendrom, vitamin D3, immünogenetik

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INTRODUCTION

Androgenetic alopecia (AGA) is a common dermatological condition characterised by progressive loss of terminal hair in a specific pattern. Hair loss typically begins after puberty and is more common in men than in women. The prevalence of AGA increases with age in both sexes, and it is the most common form of hair loss in men. It is associated with many factors, primarily genetic predisposition and androgen sensitivity. Although medically considered benign, AGA can significantly impact quality of life and psychological well-being, particularly in young men, thereby creating a significant social and emotional burden^{1,2}.

AGA is characterised by a miniaturisation process resulting from increased sensitivity of hair follicles to androgens, particularly dihydrotestosterone (DHT) formed from testosterone via the 5- α reductase enzyme. In this process, the anagen phase duration in the scalp gradually shortens, while the proportion of hairs in the telogen phase increases. Over successive hair growth cycles, hair follicles shrink; shorter, finer, lighter-coloured, and more superficially located terminal hairs are replaced by vellus hairs. As a result, hair density decreases and a distinct clinical pattern of hair loss emerges. This change is commonly observed in the frontotemporal and vertex regions in men, while in women it is more frequently seen in the parietal region^{3,4}.

Although the pathogenesis of AGA is not fully understood, hormonal imbalances, 25-hydroxy vitamin D3 deficiency, and immune-related genetic markers, particularly human leukocyte antigens (HLA), are among the possible factors involved in the development of the disease. Recent studies have highlighted potential associations between AGA and various systemic conditions such as metabolic syndrome (MetS), cardiovascular diseases (CVD), and hypertension (HT). In this context, it has been suggested that HLA-DRB1 allele diversity and vitamin D3 levels may serve as biomarkers associated with susceptibility to AGA and disease severity⁵⁻⁷.

This study provides a novel contribution to the literature by simultaneously evaluating HLA-DRB1 allele distribution, vitamin D3 status, and systemic comorbidities in male patients with AGA. While previous studies have largely examined these factors individually, our research integrates immunogenetic, metabolic, and dermatological perspectives to

investigate their combined impact on AGA susceptibility and severity. We hypothesize that specific HLA-DRB1 alleles, low vitamin D3 levels, and the presence of metabolic disorders are associated with an increased risk of developing AGA and may correlate with disease severity. This comprehensive approach aims to enhance early detection and support holistic management strategies for patients with AGA.

MATERIALS AND METHODS

Participants

A total of 85 male patients aged between 18 and 65 years who presented to the Dermatology Outpatient Clinic and were clinically diagnosed with AGA were included in the study. The procedure was accepted by Clinical Research Ethics Committee of Mersin University (approval no: 2018/ 442).

A total of 85 male patients aged between 18 and 65 years who presented to the Dermatology Outpatient Clinic of Mersin University Faculty of Medicine and were clinically diagnosed with AGA were included in the study. This research was conducted at Mersin University, Department of Dermatology, where all clinical evaluations, patient follow-up, and laboratory analyses were carried out by dermatologists, clinical researchers, and certified laboratory technicians.

All participants were diagnosed with AGA at stages II to VII based on the Hamilton-Norwood classification and had not received any prior treatment for hair loss. Patients were included if they were male, aged 18–65 years, clinically diagnosed with AGA at stage II–VII according to the Hamilton-Norwood classification, and had complete retrospective medical records available. Patients were excluded if they had incomplete records, prior treatment for hair loss, concomitant scalp disorders, or systemic diseases potentially affecting hair growth. Out of 102 patients initially screened, 17 were excluded: 8 due to incomplete records, 5 for prior hair loss treatment, and 4 for concomitant scalp or systemic conditions, resulting in a final sample of 85 patients. The sample size of 85 patients was determined based on the retrospective availability of complete patient records during the study period. A post-hoc power analysis performed using the G*Power software confirmed that this sample provided more than 80% statistical power to detect significant associations at the $p < 0.05$ level.

Procedure

The study procedure was approved by the Mersin University Clinical Research Ethics Committee (approval no: 2018/442, dated 07.11.2018). Demographic and clinical data were retrieved from medical records, including age, family history of AGA, comorbid systemic conditions (HT, CVD, diabetes mellitus (DM), hyperlipidemia (HL)), presence of dermatological disorders (psoriasis vulgaris, atopic dermatitis, alopecia areata (AA) history, and nail pitting), waist circumference, alcohol and tobacco use, and the severity of hair loss. AGA severity was categorized into three groups: mild (stages II–III), moderate (stages IV–V), and severe (stages VI–VII).

AGA severity was assessed according to the Hamilton–Norwood classification, which grades male pattern hair loss from stages I to VII^{8,9}. Patients were stratified into early-onset and late-onset groups based on <35 or ≥35 years, as previously described in dermatological epidemiological studies¹⁰. Metabolic syndrome was defined according to the NCEP ATP III-2001 criteria¹¹.

Laboratory evaluations

Laboratory evaluations included thyroid function tests (TFT), fasting blood glucose, serum lipid profile, vitamin D3, immunoglobulin E (IgE) levels, and HLA-DRB1 typing. Serum vitamin D3 levels <30 ng/ml were considered low, and ≥30 ng/ml were considered normal. Laboratory analyses were conducted using standardized methods: Beckman Coulter (USA) for biochemical parameters, Luminex (Life Match, USA) for HLA-DRB1 typing, and blood group determination via the Across OctoM OM96-1057 2017 Türkiye protocol.

HLA-DRB1 typing was retrospectively evaluated only for patients whose typing results were available. DNA samples had been previously collected during routine molecular laboratory procedures and stored at –80°C. HLA-DRB1 typing was performed in the Biochemistry Laboratory of Mersin University by experienced biochemists using PCR-based Sequence-Specific Oligonucleotide Probe (SSOP) methods. HLA allele frequencies were calculated via direct counting, and all related data were retrieved retrospectively from patient records and laboratory archives. MetS was defined according to the NCEP ATP III-2001 criteria, with patients meeting at least

three of the diagnostic criteria classified as having MetS¹¹.

Statistical analysis

Continuous variables were presented as mean ± standard deviation (SD), while categorical variables were expressed as frequencies and percentages (%). The associations between AGA severity, waist circumference, and metabolic syndrome were evaluated using the Chi-square test. The normality of continuous variables was assessed using the Shapiro-Wilk test. For normally distributed variables, Student's t-test or one-way analysis of variance (ANOVA) was applied, while for non-normally distributed variables, the Mann-Whitney U test or Kruskal-Wallis test was used. The relationship between HLA-DRB1 allele frequencies and AGA severity was analyzed using the Chi-square test. All statistical analyses were performed using SPSS version 25.0, and p-values <0.05 were considered statistically significant.

RESULTS

The mean age of the patients was 37.81 ± 10.04 years (range: 20–64 years). Of the total, 36.5% (n=31) were under 35 years of age. According to the Hamilton–Norwood classification, the distribution of alopecia severity among patients was as follows: stage II in 25.9% (n=22), stage III in 20% (n=17), stage IV in 15.3% (n=13), stage V in 14.1% (n=12), stage VI in 14.1% (n=12), and stage VII in 10.6% (n=9). Based on severity grouping, 45.9% (n = 39) of patients were classified as mild (stages II–III), 29.4% (n = 25) as moderate (stages IV–V), and 24.7% (n = 21) as severe (stages VI–VII).

A family history of AGA was reported in 85.9% (n = 73) of patients among first- and second-degree relatives. Comorbidities were present in 22.4% (n = 19) of patients: DM in 3.5% (n = 3), HT in 8.2% (n = 7), and HL in 8.2% (n = 7). Psoriasis vulgaris was observed in 1.2% (n = 1), and AA in 4.7% (n = 4). No cases of atopic dermatitis were noted, and nail pitting was found in 1.2% (n = 1) of patients. Smoking was reported by 36.5% (n = 31), with 18.6% (n = 16) having a history of ≥20 pack-years. Alcohol consumption was reported by 42.4% (n = 36).

MetS was present in 36.5% but showed no association with AGA severity (p=0.606). Biochemical analyses showed mean —is not a biochemical analysis of 99.89 ± 10.20 cm, fasting

glucose of 102.70 ± 23.07 mg/dL, TG of 200.29 ± 138.35 mg/dL, HDL of 44.20 ± 14.71 mg/dL, TSH of 1.44 ± 0.73 mIU/L, and vitamin D3 level of 22.11 ± 7.85 ng/mL.

Table 1. Analysis findings related to clinical measurements (n = 85).

Variable	Category	Frequency (n)	Percentage(%)
MetS	None	54	63.5
	Present	31	36.5
Waist circumference	<102 cm	46	54.1
	≥102 cm	39	45.9
Blood pressure	<130/85 mmHg	75	88.2
	≥130/85 mmHg	10	11.8
Fasting blood glucose	<100 mg/dL	48	57.1
	≥100 mg/dL	36	42.9
TG	<150 mg/dL	37	43.5
	≥150 mg/dL	48	56.5
HDL	<40 mg/dL	29	34.1
	≥40 mg/dL	56	65.9
IgE	Low	7	12.7
	Normal	37	67.3
	High	11	20.0
TSH	Low	2	2.4
	Normal	82	96.5
	High	1	1.2
sT4	Normal	82	96.5
	High	3	3.5
Vit D3	Low	50	82.0
	Normal	11	18.0

MetS: metabolic syndrome; TG: triglycerides; HDL: high-density lipoprotein; IgE: immunoglobulin E; TSH: thyroid-stimulating hormone; sT4: free thyroxine; Vit D3: vitamin D3 n.s.: not significant

HLA-DRB1*01, *04, and *11 were the most common alleles. Subtypes *04 11, *11 11, and *11 13 were more prevalent but without significant

differences ($p=0.779$). Vitamin D3 deficiency was significantly associated with AGA ($p=0.045$).

Table 2. Findings related to the frequency distribution of HLA-DRB1 allele subtypes of the patients.

HLA-DRB1 Allele Frequency	Frequency (n)	Percentage (%)
DRB1* 01	01	1.6
	07	1.6
	11	3.1
	13	1.6
	14	1.6
	15	3.1
	16	3.1
DRB1* 03	04	3.1
	09	1.6
	11	3.1
	13	3.1
DRB1* 04	04	3.1
	07	1.6
	11	6.4
	13	4.8
	14	1.6
	15	4.8
	16	1.6

DRB1* 07	07	2	3.2
	10	1	1.6
	11	2	3.2
	14	1	1.6
	15	1	1.6
DRB1* 08	13	1	1.6
DRB1* 09	10	1	1.6
DRB1* 10	10	1	1.6
DRB1* 11	11	7	11.2
	13	4	6.4
	14	2	3.1
	15	2	3.1
	16	1	1.6
DRB1* 13	13	1	1.6
	14	1	1.6
	15	1	1.6
	16	2	3.1
DRB1* 15	15	1	1.6

HLA: human leukocyte antigen

DISCUSSION

AGA is the most common form of non-scarring hair loss in men, characterized by the progressive miniaturization of terminal hairs into vellus hairs in a defined distribution. While historically regarded as a purely cosmetic condition, recent studies have increasingly suggested that AGA may serve as a clinical marker for systemic health risks. Although AGA occurs across all ethnic groups, its prevalence and clinical presentation can vary widely depending on population and geographic region^{12,13}.

While age is a major risk factor for AGA, genetic predisposition appears to have a particularly strong influence in the 25–45 age group. In this demographic, a family history of AGA especially on the paternal side substantially elevates the likelihood of developing the condition. Research has demonstrated that individuals whose fathers exhibit hair loss are significantly more likely to develop AGA themselves. The condition is thought to follow a complex polygenic inheritance pattern, likely involving paternal alleles^{14–16}. Recent genome-wide association studies have identified multiple susceptibility loci, including variants on the X-chromosomal AR/EDA2R region and chromosome 20p11, further supporting the role of paternal and polygenic inheritance in AGA¹⁷. In a study by Chumlea et al, individuals with a history of AGA in their father or maternal grandfather had a nearly twofold increased risk of hair loss¹⁵. A similar trend was noted in a Korean cohort, where over 70% of

both male and female patients with AGA reported a positive family history, most commonly paternal¹⁸. In our study, the mean age of participants was 37.81 ± 10.04 years, which aligns with prior studies. A notable 85.9% of patients had a positive family history, underscoring the significant role of genetic factors in AGA.

Although numerous studies have explored the associations between blood group antigens and various diseases, the exact pathophysiological mechanisms underlying these relationships remain unclear. It has been suggested that certain antigenic structures and cell adhesion molecules expressed on the surface of erythrocytes may play a role in the development of some diseases¹⁹. There are studies in the literature demonstrating significant associations between blood groups and certain dermatological conditions. According to our findings, the majority of patients (47.6%) had the A Rh(+) blood type. Although the severity of AGA appeared to be higher among individuals with this blood group, the difference was not statistically significant. However, the absence of a control group in our study limits the ability to compare the distribution of the A Rh(+) blood type with that of the general population, making it difficult to determine whether this represents a true association. In accordance with our study, a case-control study including 207 AGA patients and 642 controls reported no statistically significant difference in the distribution of ABO and Rh blood groups between patients and healthy individuals²⁰.

The association between AGA and MetS was first proposed in 1972 and has since been supported by numerous studies. It is suggested that androgen excess may underlie the pathophysiology of both conditions^{21,22}. A case-control study from Thailand reported a 3.48-fold increased risk of MetS in individuals with early-onset AGA²³. In our cohort, 36.5% of patients met the NCEP-ATP III criteria for MetS—an incidence higher than the average in the general male population in Turkey (28%). Furthermore, the mean age of patients diagnosed with MetS was significantly higher than that of patients without MetS ($p < 0.05$). Moreover, a previously published meta-analysis further supports this relationship by showing that individuals with AGA have a 2.3–3.46 times higher risk of developing MetS compared to healthy controls²⁴.

The association between AGA and CVD was first reported in the 1970s, and subsequent studies have demonstrated that the risk of CVD increases with the severity of alopecia. Although there are no specific screening guidelines for individuals with AGA, current evidence supports the evaluation of MetS and cardiovascular risk factors in this patient population^{25,26}. In line with this, we assessed our patients for MetS according to the NCEP-ATP III criteria. Hirsso et al. reported higher body mass index (BMI) and waist circumference in young men with severe alopecia²⁷. Recent large-scale studies have further confirmed this association, showing a markedly higher prevalence of MetS in men with early-onset and severe AGA²⁸. However, in our study, the majority of patients had a waist circumference below 102 cm, which does not fully align with the findings in the literature.

The relationship between AGA and HT has also been demonstrated in numerous studies. This association is thought to be related to the binding of androgens to mineralocorticoid receptors, leading to increased blood pressure or contributing to hyperaldosteronism. Arias-Santiago et al. reported significantly higher aldosterone levels and a greater prevalence of HT in women with early-onset AGA compared to controls. Similarly, Ahouansou et al. found a strong association between AGA and HT^{29,30}. Nevertheless, recent evidence indicates that even in patients with initially normal blood pressure, early-onset AGA may predispose to later development of hypertension, highlighting the importance of longitudinal follow-up²⁸. However, in our study, 88.2% of the patients had blood pressure

values within normal limits, which contrasts with some previous reports.

The association between AGA and glucose metabolism disorders is also noteworthy. Hirsso et al. reported a diabetes prevalence of 21% among individuals with AGA²⁷. Matilainen et al. noted an increased risk of hyperinsulinemia in men with early-onset AGA³¹. Although Gopinath et al. did not find a significant difference in plasma glucose levels, they reported higher HOMA-IR and fasting insulin levels in the AGA group³². These findings suggest that insulin resistance may be a key pathophysiological mechanism underlying MetS³³. Similarly, in our study, 42.9% of patients had fasting blood glucose levels ≥ 100 mg/dL. Recent observational data have also demonstrated that, even in the absence of overt hyperglycemia, insulin resistance indices are significantly higher in male patients with AGA compared to controls. This suggests that glucose metabolism begins to deteriorate at an early stage³⁴.

When lipid profiles were evaluated, elevated triglyceride (TG) levels were observed in 56.5% of the patients, while high HDL levels were found in 65.9%. Although androgens are known to reduce HDL levels, the elevated HDL levels observed in our study are noteworthy. However, due to the lack of a control group, it remains unclear whether these findings significantly differ from those in the healthy population.

Another important finding in our cohort was the high prevalence of vitamin D3 deficiency. More than 80% of patients exhibited suboptimal levels of vitamin D3, and this finding was statistically significant ($p = 0.045$). However, since there was no control group in our study, this result cannot conclusively establish a direct relationship between AGA and vitamin D3 deficiency. Therefore, these data should be interpreted only as an observational indicator. Nonetheless, this observation aligns with a recent meta-analysis showing that serum 25(OH)D concentrations were significantly lower in patients with non-scarring alopecia, including AGA, compared to healthy controls³⁵. Recent research indicates that vitamin D3 not only plays a role in hair follicle cycling but also modulates autoimmune and inflammatory pathways implicated in alopecia. Given its established role in dermatological and systemic health, routine screening of vitamin D3 status in patients with AGA may be justified³⁶.

Recent data suggest a potential role of HLA gene expression in the pathogenesis of AGA. Notably, Class II HLA genes such as HLA-DPB1, HLA-DQA1, HLA-DRB3, and HLA-DRB4 have been reported to be significantly overexpressed in scalp samples obtained from patients with AGA.⁶ These findings parallel previous studies in AA, where keratinocytes in the hair follicle bulb were shown to express HLA Class II antigens³⁷. This suggests that in AGA, as in AA, the expression of Class II HLA antigens by hair follicle keratinocytes may be associated with mononuclear cell activation and potentially trigger an autoimmune response. In our study, we evaluated HLA-DRB1 allele frequencies. Although the 01, 04, and 11 alleles particularly the 04 11, 11 11, and 11 13 subtypes were observed more frequently, no statistically significant association was found between these alleles and AGA severity.

This study has several limitations that should be acknowledged. The retrospective design, absence of a control group, and inclusion of only male participants restrict the generalizability of the findings and limit causal interpretations. Additionally, HLA-DRB1 typing was retrospectively evaluated only in patients with available results, lifestyle factors (such as diet, physical activity, and sunlight exposure) were not considered, and laboratory measurements were performed at a single time point, which further limits the interpretation of the results.

In conclusion, our findings reinforce the previously reported associations between AGA and genetic predisposition, metabolic disturbances, vitamin D3 deficiency, and potential HLA-DRB1-related immunogenetic susceptibility. These results underscore that AGA should not be regarded merely as a cosmetic issue, but may serve as a clinical indicator of underlying systemic conditions. The retrospective design, lack of a control group, and inclusion of only male participants are notable limitations, emphasizing the need for caution in generalizing these results. Future multicenter, prospective studies with larger and more diverse cohorts are warranted to clarify the causal relationships, explore the mechanistic role of HLA alleles, and evaluate the benefits of routine metabolic and vitamin D3 screening in patients with AGA. Such studies could inform personalized preventive and therapeutic strategies, ultimately improving patient management and outcomes.

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