Case Report
Olgu Sunumu

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A new *HLA* susceptibility haplotype defined in three familial cases of frontal fibrosing alopecia

Üç ailevi frontal fibrozan alopesi vakasında tanımlanan yeni bir HLA duyarlılık haplotipi

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Abstract

Frontal fibrosing alopecia (FFA) is a scarring alopecia that primarily affects postmenopausal women. Although its etiology remains unknown, familial cases suggest a genetic basis. In this case report, we present the findings of three sisters with familial FFA, aged 55, 60, and 62 years, from Türkiye. Genetic analysis revealed that all three sisters shared the *human leukocyte antigen (HLA)-A*11:01; B*35:01; C*04:01* haplotypes. Two sisters had *HLA-DRB1*03:01* and *HLA-DQB1*02:01*, while the third had *HLA-DRB1*01:01; HLA-DQB1*05:01*. The shared *HLA-A*11:01*, *B*35:01*, and *C*04:01* haplotype has not been previously associated with familial FFA. This finding marks the first familial FFA report from Türkiye and suggests a new genetic susceptibility haplotype for FFA in the Turkish population. The variation in *HLA-DRB1* and *HLA-DQB1* alleles among the sisters indicates complex genetic influences on the familial FFA. Further research is required to determine the role of these genetic variations in disease progression and to identify potential therapeutic approaches.
Keywords: Familial frontal fibrosing alopecia, *HLA* haplotypes, genetic susceptibility, scarring alopecia

Öz

Frontal fibrozan alopesi (FFA), genellikle menopoz sonrası kadınları etkileyen skatrisyel bir alopesidir. Etiyolojisi bilinmemekle birlikte, ailesel olgular genetik bir bileşen öne sürmektedir. Bu olgu raporunda, Türkiye'den 55, 60 ve 62 yaşlarındaki üç kız kardeşle ilgili ailesel FFA bulgularını paylaşıyoruz. Genetik analiz, üç kardeşin de insan lökosit antijeni *(HLA)-A*11:01; B*35:01; C*04:01* haplotipini paylaştığını ortaya koydu. İki kardeş *HLA-DRB1*03:01; HLA-DQB1*02:01*, diğer kardeş ise *HLA-DRB1*01:01; HLA-DQB1*05:01* alellerine sahipti. Paylaşılan *HLA-A*11:01; B*35:01; C*04:01* haplotipi, literatürde daha önce ailesel FFA ile ilişkilendirilmemiştir. Bu bulgular, Türkiye'den bildirilen ilk ailesel FFA olgusunu oluşturmaktadır ve FFA için yeni bir genetik yatkınlık haplotipini öne sürmektedir. Kız kardeşler arasındaki *HLA-DRB1* ve *HLA-DQB1* alel varyasyonları, ailesel FFA üzerindeki karmaşık genetik etkileri vurgulamaktadır. Bu genetik varyasyonların hastalık progresyonu ve potansiyel terapötik yaklaşımlar üzerindeki rolünü belirlemek için daha fazla araştırmaya ihtiyaç vardır.
Anahtar Kelimeler: Ailesel frontal fibrozan alopesi, *HLA* haplotipleri, genetik yatkınlık, skatrisyel alopesi

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Introduction

Frontal fibrosing alopecia (FFA) belongs to the group of primary cicatricial alopecias, most commonly presents as progressive recession of the frontotemporal hairline accompanied by bilateral eyebrow loss, particularly among postmenopausal women[1,2]. Since its initial description by Kossard[3] in 1994, there has been a marked global rise in FFA incidence, and it is now recognized as the most frequently reported form of cicatricial alopecia in numerous studies[3,4].

The precise pathogenesis of FFA remains to be elucidated; however, multiple factors, such as hormonal changes, immune system dysregulation, and environmental influences have been proposed[1]. Although sporadic cases are the norm, the presence of familial clusters suggests an underlying genetic and/or epigenetic component[5-12]. A positive family history has been reported in as many as 8% of cases, raising the possibility of an autosomal dominant mode of inheritance with incomplete penetrance[2,13].

FFA is considered a clinical subtype of lichen planopilaris. Although the two conditions display distinct clinical features, they both fall under the category of lymphocytic primary scarring alopecias and share similar immune and inflammatory mechanisms[14]. The disease process likely begins with the collapse of immune privilege at the level of the hair follicle (HF) bulge, where epithelial HF stem cells (eHFSCs) reside. This disruption enables T cell-mediated inflammatory responses, resulting in eHFSC apoptosis and subsequent irreversible alopecia[15]. The immune privilege of HF protects eHFSCs from autoimmune attacks by suppressing the expression of major histocompatibility complex (MHC) class I and II molecules[16,17]. Aberrant expression of *human leukocyte antigen (HLA)* class I and II molecules, which are components of MHC, within eHFSCs may compromise this immune privilege[15]. While *HLA* class I molecules (A, B, and C) are present on all nucleated cells, *HLA* class II molecules (such as *DRB1, DQB1,* and *DPB1*) are typically expressed on immune-activated cells. Variants within *HLA* genes have been implicated in altering susceptibility to a wide range of infectious, inflammatory, and autoimmune diseases[18].

Few studies have reported shared *HLA* haplotypes in familial FFA cases. To date, three distinct susceptibility haplotypes have been documented across different patient cohorts[19-21]. Furthermore, *HLA* class II polymorphisms previously linked to conditions such as Lassueur-Graham-Little-Piccardi syndrome and both familial and sporadic forms of lichen planus were not associated with familial FFA[9,22-25].

In this report, we present a newly identified *HLA* susceptibility haplotype in three sisters affected by familial FFA, representing the first such case reported in Türkiye. Our findings contribute to the growing body of evidence that genetic predisposition plays a pivotal role in FFA pathogenesis. By analyzing the genetic profiles of affected individuals, we aimed to enhance our understanding of the hereditary factors involved in this disease.

Case Report

Three sisters, aged 62, 60, and 55 years, presented with progressive frontotemporal hair loss and lateral eyebrow alopecia (Figures 1, 2, and 3). All patients' symptoms began after menopause and gradually worsened. None of the patients experienced body hair loss or facial pain. They had no other siblings. Their personal and family medical histories were unremarkable, with no evidence of dermatologic or autoimmune conditions. They lived in the same city but resided in different neighborhoods. They did not work in regular jobs and mostly stayed at home. They did not regularly use cosmetic products, such as sunscreen. None of the patients were smokers. Trichoscopy revealed loss of hair follicular openings in the affected hairline and perifollicular hyperkeratosis in all patients (Figure 4). Histopathological examination was compatible with FFA. We addressed the *HLA-A, HLA-B, HLA-C, HLA-DRB1, and HLA-DQB1* genetic variabilities in this family. Haplotype analysis was performed using the sequence-specific oligonucleotide method. Haplotype analysis revealed *HLA-A*11:01; B*35:01; C*04:01* shared among all sisters. Two sisters had *HLA-DRB1*03:01 and HLA-DQB1*02:01*, while the other sister had *HLA-DRB1*01:01; HLA-DQB1*05:01*. We were unable to do genetic analysis on the patient's mother and father since they were deceased, and on their offspring because they were unable to attend the hospital.

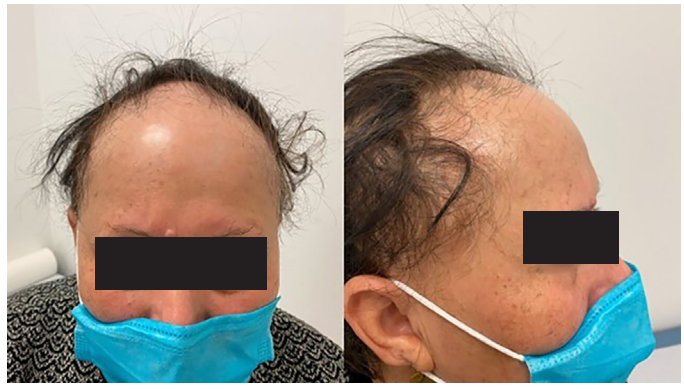

Figure 1. Oldest sister

Figure 2. Middle sister

Figure 3. Youngest sister

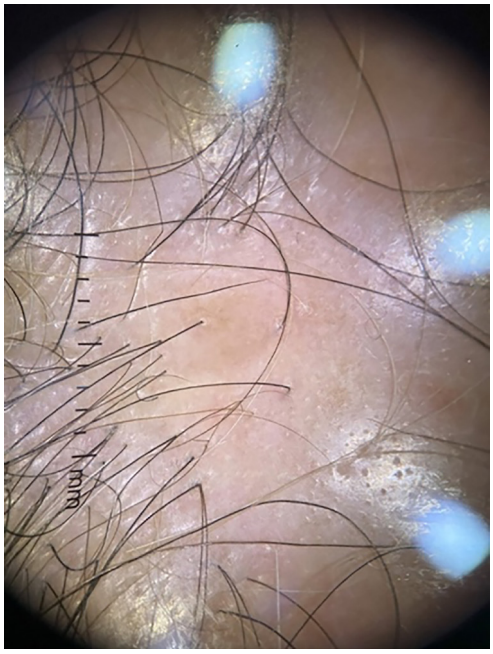

Figure 4. Trichoscopic examination showing loss of hair follicular openings in the affected hairline and perifollicular hyperkeratosis

Discussion

In this family with FFA, a shared *HLA-A*11:01, B*35:01*, and *C*04:01* haplotype was identified across all three sisters. To date, this specific HLA class I haplotype has not been linked to FFA in the literature. Furthermore, this report is the first to identify familial FFA in the Turkish population.

Earlier studies have highlighted several other HLA haplotypes that are potentially associated with FFA. A genome-wide association study by Tziotzios et al.[19] conducted in British and Spanish cohorts revealed four genomic regions implicated in FFA, one of which included the *HLA-B*07:02* allele. Additionally, this study highlighted the associations of genetic variants involved in xenobiotic metabolism, T-cell regulation, and antigen presentation across four susceptibility loci. The *HLA-B*07:02* allele demonstrated the strongest single-locus association, conferring an approximate four-fold increase in FFA risk among women. Rayinda et al.[26] subsequently confirmed the significant contribution of this allele to FFA risk in men. Despite the limited number of familial cases included, these findings from large cohort studies underscore the role of genetic predisposition in FFA.

Porriño-Bustamante et al.[21] described an alternate susceptibility haplotype- *HLA-A*33:01; B*14:02; C*08:02*-in 13 Spanish familial FFA cases. The study also reported a link between the *HLA* class I haplotype *F16A* and the *CYP21A2 p.V281L* mutation in affected individuals, suggesting that this mutation, previously associated with congenital adrenal hyperplasia, may serve as a genetic marker for familial FFA.

Additionally, Ramos et al.[20] analyzed a Brazilian cohort of both familial and sporadic FFA cases and identified two potential susceptibility haplotypes: *HLA-B*07:02:01:01; C*07:02:01:03* and *HLA-B*42:01:01:01; C*17:01:01:02*[20]. The first haplotype had not been previously associated with FFA, and both were found in certain unaffected relatives, implying that environmental or epigenetic factors may influence disease expression.

Conclusion

Our identification of the *HLA-A*11:01, B*35:01,* and *C*04:01* haplotypes in this Turkish family provides further evidence supporting the genetic contribution to FFA pathogenesis. While prior studies have described various *HLA* haplotypes associated with FFA, our findings suggest possible ethnic and regional differences in genetic susceptibility. The variation in *HLA-DRB1* and *HLA-DQB1* alleles observed among the siblings further underscores the complex genetic architecture underlying the expression of this disease. Familial cases such as this one offer valuable insights into the genetic mechanisms driving FFA. Ongoing research is required to elucidate how these genetic factors interact with additional risk elements to inform the development of targeted therapeutic strategies.

Ethics

Informed Consent: Written consent was obtained from all patients for the use of their images and genetic material.

Footnotes

Authorship Contributions

Surgical and Medical Practices: A.K.Ö., Y.H., F.Ö., M.G.K., S.K.Ç., Concept: A.K.Ö., Y.H., F.Ö., M.G.K., S.K.Ç., Design: A.K.Ö., Y.H., F.Ö., M.G.K., S.K.Ç., Data Collection or Processing: A.K.Ö.,Y.H., F.Ö., M.G.K., S.K.Ç., Analysis or Interpretation: A.K.Ö., Y.H., F.Ö., M.G.K., S.K.Ç., Literature Search: A.K.Ö., Y.H., F.Ö., M.G.K., S.K.Ç., Writing: A.K.Ö., Y.H., F.Ö., M.G.K., S.K.Ç.

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