ORIGINAL ARTICLE

Genotyping of the rs1800440 Polymorphism in CYP1B1 Gene and the rs9258883 Polymorphism in HLA-B Gene in a Spanish Cohort of 223 Patients with Frontal Fibrosing Alopecia

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The pathogenesis of frontal fibrosing alopecia has been linked to specific genetic variants. CYP1B1 codes for a component of the cytochrome p450 machinery that is involved in the metabolism of xenobiotic oestrogens. The study of the prevalence of polymorphisms in this gene may help to understand their role in the development of frontal fibrosing alopecia. The aim of this study is to describe the frequency of genetic variations in the alleles HLA-B*07:02 and CYP1B1 in patients with frontal fibrosing alopecia. A cross-sectional study was designed to evaluate blood samples from patients with frontal fibrosing alopecia who attended the Dermatology Department at University Hospital Ramón y Cajal (Madrid, Spain), in search of the polymorphisms rs9258883 and rs1800440 in the alleles HLA-B*07:02 and CYP1B1, respectively. A total of 223 patients were included in the study. Among the 83.8% of patients who carried the rs9258883 polymorphism in HLA-B*07:02, 58.7% were heterozygous for this variant and it was not present in 14.8% of the cases. The majority of patients with frontal fibrosing alopecia lacked the protective rs1800440 polymorphism in CYP1B1 (75.2%). This suggests a relevant role of this variant in development of frontal fibrosing alopecia. The genetic approach to this condition might influence patient prognosis and therapy options.

Key words: cicatricial alopecia; genetic loci; hair loss; HLA antigens; pathogenesis; xenobiotics.

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SIGNIFICANCE

The origin of frontal fibrosing alopecia has been linked to 2 genetic variants in CYP1B1 and HLA-B*07:02. CYP1B1 plays a role in the metabolism of xenobiotic oestrogens and HLA-B is related to the aberrant immune response. This study includes 223 patients with frontal fibrosing alopecia and determines how frequent are the genetic variants described. A total of 83.8% of patients with frontal fibrosing alopecia carried the rs9258883 polymorphism in HLA-B*07:02, and the majority of them lacked the protective rs1800440 polymorphism in CYP1B1 (75.2%). The high proportion of both genetic variants in the group of patients in this study suggests a relevant role of genetics in the development of frontal fibrosing alopecia.

Frontal fibrosing alopecia (FFA) is a scarring and inflammatory permanent hair loss condition involving frontotemporal hairline and eyebrows (1–3). FFA primarily affects women, and it has also been linked to various autoimmune illnesses, such as chronic discoid lupus erythematosus, autoimmune thyroid disease, and pernicious anaemia (4, 5). The aetiopathogenesis of FFA, however, is unknown (6, 7). Hundreds of cases of FFA have been documented in the literature since 1994, with a constant increase in its incidence worldwide. Moreover, genetic research has played a key role in identifying molecular pathways underpinning other hair loss disorders, such as alopecia areata (8, 9). FFA has been found among siblings and family members, implying a genetic link and familial disease was studied in detail by Tziotzios et al. (10). Thus, no highly penetrant alleles were identified to segregate in a Mendelian pattern, suggesting that the trait was polygenic or genetically complex (11).

A subsequent genome-wide association study (GWAS) examined common genetic variations in patients with FFA (12). In fact, this study evaluated more than 15 million common variants in 2 large cohorts of female patients with FFA and controls from the UK and Spain. Four causal variants were identified (*HLA-B*07:02*, *CYP1B1*, *SEMA4B* and *ST3GAL1*), with the largest effect size observed for *HLA-B*07:02* and *CYP1B1*. The latter encodes a part of cytochrome P450, which is involved in oestrogen and xenobiotic metabolism, and it may well interact with hormonal exogenous exposures. The presence of these polymorphisms in diverse FFA populations might help us to better understand their impact on the disease's aetiopathogenesis and clinical characteristics.The aim of this study is to determine the

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prevalence of the above variants in a large cohort of patients with FFA at University Hospital Ramón y Cajal and to correlate its genotype with clinical characteristics.

MATERIALS AND METHODS

Patients

The study included men and women over the age of 18 years with a confirmed diagnosis of FFA who attended the Dermatology Department at University Hospital Ramón y Cajalbetween January 2015 and September 2020. FFA was defined as trichoscopy-detected regression of the frontotemporal hairline and loss of follicular openings, as well as histological analysis of a skin biopsy. Samples and data from patients included in this study were provided by the Biobank Hospital Ramón y Cajal-IRYCIS (National Registry of Biobanks B.0000678), integrated in the Platform ISCIII Biobanks and Biomodels (PT20/00045) and they were processed following standard operating procedures with the appropriate approval of the Ethics and Scientific Committees at University Hospital Ramón y Cajal. All participants gave written informed consent allowing a blood sample to be stored. If the blood samples obtained were of low quality or had degraded, the patients were excluded from the study.

Study design

A cross-sectional observational study was conducted to evaluate blood samples for genetic variants at 2 genomic loci: 6p21.1 (gene *HLA-B*) and 2p22.2 (gene *CYP1B1*). The local institutional review board gave their approval to the research (Code: GEN-AFF 04-2019).

Data on epidemiology, comorbidities, personal gynaecological background and clinical presentation were collected. After at least 1 year of treatment, a satisfactory response to treatment was defined as no hair loss progression in the frontal and lateral hairline, according to the Frontal Fibrosing Alopecia Severity Score (FFASS) (13).

Storage and genotyping

The patients' blood samples were collected and processed into 250-µl cell rest aliquots, then stored at –80 °C of the Ramón y Cajal Hospital's Biobank. DNA extraction and genotyping were performed at the Hospital's Central Translational Genomics Support Unit (UCA-GT). The DNA samples extraction was obtained in the first stage using the Qiagen Flexigem DNA Extraction Kit (Qiagen, Hilden, Germany). Next, DNA was quantified with the nanodrop, the Qubit, and the Tape Station 2200 (Thermo Fisher Scientific, Waltham, MA, USA) to check its concentration and quality. The appropriate PCRs were run to amplify the 2 regions of interest containing the 2 polymorphisms. Electrophoresis has been used to confirm PCR amplification. The PCRs were purified using the ExoSAP-IT kit (Thermo Fisher Scientific, Waltham, MA, USA), and Sanger sequencing (Macrogen Inc., Seoul, Republic of Korea) of both fragments was conducted to genotype the 2 single-nucleotide polymorphisms (SNPs) in each patient. For the rs1800440 polymorphism located in the *CYP1B1* gene, the genotypes to be considered would be AA, AG or GG. While for the rs9258883 polymorphism located in the *HLA-B* locus, the possible genotypes would be CC, CT or TT.

Statistical analysis

All analyses were carried out using the statistical software package SPSS 25.0. (IBM SPSS Statistics for Macintosh; IBM Corp., Armonk, NY, USA). For the patients' demographic and clinical features, descriptive statistics were employed (mean and range for continuous measures, and frequency and percentage for categorical variables).

A bivariate analysis was used to compare groups, employing the χ^2 test or, where applicable, the Fisher's exact test. According to the normal distribution of the data, the Student's *t*-test or the Kruskal–Wallis test was utilized to compare quantitative variables.

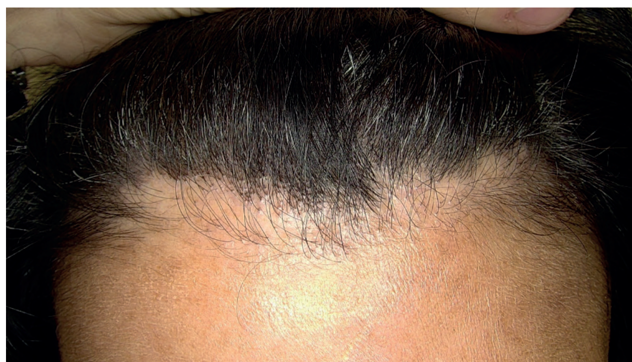

Fig. 1. Clinical presentation of hair loss in a patient with frontal fibrosing alopecia with a pseudo-fringe pattern.

RESULTS

Patients

A total of 223 patients who agreed to participate were enrolled into the study (**Fig. 1**). There were 221 women and 2 men, with a mean age of 61 (range 32–86) years. All patients were Caucasian. Family history was confirmed in 20 patients (9.0%), while in 6 of them there was a first-grade relative with FFA. Thyroid alterations were present in 80.0% of patients, with hypothyroidism being the most frequent condition (Hashimoto's disease

Table I. Baseline characteristics collected from 103 participants out of a total of 223 patients

Baseline characteristics	
Sex, female, *n* (%)	103 (100)
Age (mean, SD)	61.0 (10.6)
Age of onset FFA (mean, SD)	55.8 (10.4)
Autoimmune comorbidities, *n* (%)	
• Hashimoto thyroiditis	11 (10.7)
• Grave's disease	3 (2.9)
• Sjögren's syndrome	1 (1.0)
• Pernicious anaemia	1 (1.0)
• Ankylosing spondylitis	1 (1.0)
• Discoid lupus erythematosus	1 (1.0)
• Rosacea	28 (35.4)
Gynaecological history	
• Postmenopausal women, *n* (%)	82 (79.2)
∘ Age of menopause, years, mean (range)	47.8 (37–58)
• Hysterectomy, *n* (%)	30 (28.8)
• Oophorectomy, *n* (%)	15 (14.4)
∘ Age of oophorectomy, years, mean (range)	45.2 (38–52)
• Breast cancer	8 (7.7)
Hormonal treatments received, *n* (%)	
Oral contraceptives	38 (36.9)
Hormone replacement therapy	15 (14.6)
SERMS (breast cancer)	8 (7.8)
Hormonal IUDs	2 (1.9)

SD: standard deviation; FFA: frontal fibrosing alopecia; SERMS: selective oestrogen receptor modulators; IUD: intrauterine device.

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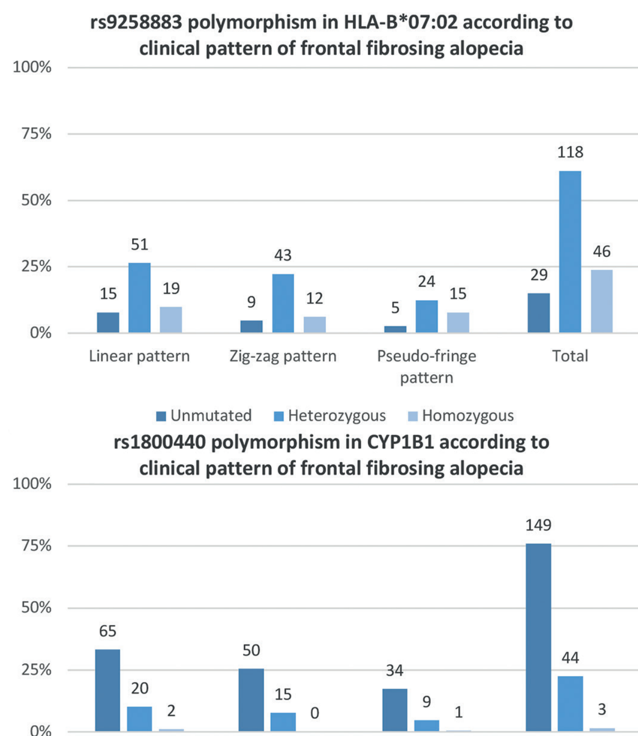

Fig. 2. Distribution of genetic variations on the alleles identified in the genome-wide association study (GWAS) in the current study sample. The prevalence of rs1800440 polymorphism in CYP1B1 is remarkably low and distribution of the rs9258883 variant of HLA-B*07:02 allele is more heterogeneous.

in 10.7%). **Table I** summarizes the medical comorbidities, gynaecological background, and hormonal therapy received by patients.

Clinical patterns in frontal fibrosing alopecia

The clinical characteristics of FFA were analysed in all patients. The 3 patterns of hair loss in FFA were detected among the patients included (**Fig. 2**). Pattern I "linear" was observed in 87/203 patients (42.9%), pattern II "zig-zag" in 65/203 patients (32.0%) and pattern III "pseudo-fringe" in 44/203 patients (21.7%). Seven patients (7/203, 3.4%) had a clinical pattern that was not clearly defined. Loss of eyebrows was total in 78/196 patients (39.8%) and partial in 44/196 patients (22.4%). In contrast, no eyebrows loss was observed in 74/196 patients (37.8%). Facial papules were present in 56/196 cases (28.6%). Inflammatory signs were detected in 92/203 patients (45.3%).

The response to medical treatment was evaluated in 107 patients (47.9%) after a 1-year follow-up. The alopecia was stabilized in 60 of them (56.1%), on the frontal and lateral hairline. All patients underwent the same therapy, including oral dutasteride (3–7 capsules per week), topical clobetasol propionate 0.05% twice weekly, and topical minoxidil 5% 5 nights per week.

Table II. Variations in CYP1B1 and HLA-B*07:02 genes in patients with frontal fibrosing alopecia

rs1800440 (*CYP1B1*)	rs9258883 (*HLA-B*07:02*)			
	Unmutated	Heterozygous	Homozygous	Total
Unmutated, *n* (%)	26 (11.9)	95 (43.4)	45 (20.5)	166 (75.8)
Heterozygous, *n* (%)	6 (2.7)	33 (15.1)	10 (4.6)	49 (22.4)
Homozygous, *n* (%)	1 (0.5)	2 (0.9)	1 (0.5)	4 (1.8)
Total, *n* (%)	33 (15.1)	130 (59.4)	56 (25.6)	219 (100)

The distribution of mutations in both loci was not statistically significant ($p > 0.05$).

Genotyping

Genetic analysis of blood samples was carried out for *HLA-B*07:02* and for *CYP1B1*. The *HLA-B*07:02* allele presented the rs9258883 polymorphism in 187 individuals (83.8%), 56 (25.1%) of whom were homozygous, while 131 (58.7%) were heterozygous. In comparison, 33 individuals (14.8%) lacked the described variant in this locus, and in 3 patients (1.3%) the allele could not be assessed due to the low quality of DNA extracted. Singularly, most FFA patients did not present the protective mutation in *CYP1B1* (167 patients, 75.2%). However, 55 patients (24.8%) showed the rs180040 polymorphism. Fifty-one of them were heterozygous and just 4 patients were homozygous (23.0% and 1.8%, respectively). In only 1 patient the variant could not be studied, also due to the low quality of DNA extracted. The relationship between mutations in both loci is shown in **Table II**.

On the whole, no statistically significant differences were found between the clinical pattern of hair loss and

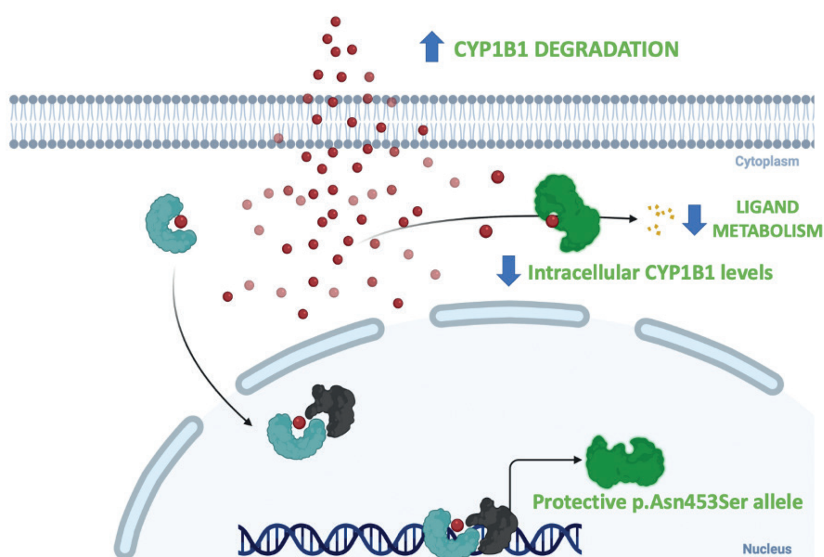

Fig. 3. The protective p.Asn453Ser allele enhances the rate of CYP1B1 degradation, resulting in lower intracellular CYP1B1 levels. Individuals with this allele are protected from developing frontal fibrosing alopecia.

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genetic mutations (**Fig. 3**). Moreover, no other statistically significant associations were observed between the genetic mutations identified and the patients' clinical characteristics or treatment responses.

DISCUSSION

A genetic explanation for FFA has been hypothesized for a decade, and there have been some early attempts to investigate it, particularly in short publications and case reports (14). As an illustration, Navarro-Belmonte et al. (15) identified 4 FFA-affected families and 8 mother–daughter cases, implying that the gene anticipation phenomenon was associated to the onset of FFA in daughters at an earlier age. Furthermore, researchers identified a 67% concordance in 2 pairs of FFA monozygotic twins, which was greater than in comparable disorders, such as systemic lupus erythematosus (16). In these trials, however, the small sample size was deemed insufficient to show a link between the genome and the FFA. But it was not until Tziotzios et al.'s (12) latest study that we observed an in-depth genetic picture in patients with FFA.

Human major histocompatibility complex research in patients with FFA is still in its early stages. In essence, HLA A, HLA B, and HLA C expression is low in the hair follicle bulge area and the outer root sheath. As mentioned at the outset, the identified *HLA-B*07:02* mutation in the GWAS study (HLA class I), has been postulated to assist in the presentation of autoantigens, facilitating the auto-inflammatory lymphocytic death of the epithelial hair follicle stem cells located in the hair follicle bulge. Past reports have suggested that the collapse of hair follicles, the disease's hallmark sign, might be caused by changes in the expression pattern of HLA class I and class II molecules (17). One argument favouring this is the study by Ramos et al., in which 2 susceptible HLA class I haplotypes were identified (*HLA-C*17:01:01:02/B*42:01:01:01* and *C*07:02:01:03/B*07:02:01:01*) in a Brazilian large familiar cluster with FFA (14). Similarly, research in 13 cases of FFA in Spain uncovered a linkage between the F16A HLA class I haplotype and the *CYP21A2* gene p.V281L mutation (4). Chan et al. (18) on the other hand, found no HLA-DR1 association (HLA class II) in 2 siblings with FFA. Nonetheless, these studies have several limitations that make it difficult to draw significant conclusions. As the HLA area is dense and complex, only in-depth genetic research can provide insight into its relevance in this disorder.

The association found in the GWAS study is much more solid than those described in smaller studies. Authors suggested that the variant in the allele *HLA-B*07:02* can induce a 5-fold increase in the risk of FFA. This variant was found in most of the patients in this study, although the most common presentation was a heterozygous mutation in the patients' allele (58.7%). However, this gene mutation was not observed in 14.8% of subjects, raising the question that distinct HLA alleles may be involved in the pathogenesis of the disease.

As previously noted, *CYP1B1* gene variations accounted for the large number of FFA cases in the current study sample. This gene has attracted attention because of its unusual properties and characteristics (19). The *CYP1B1* gene belongs to the *CPYP1* gene family, including the *CYP1A1* and *CYP1A2* genes (20). It is expressed in the liver and extrahepatic tissue and is located on chromosome 2 (21). It does, however, perform xenobiotic metabolism, which includes the metabolic activation of polycyclic aromatic hydrocarbons via the microsomal enzyme cytochrome B450 1B1 (22). This enzyme aids in the conversion of oestradiol and oestrone to their hydroxylated catechol oestrogens through oxidative metabolism (23). Previous research, observed a possible role for intracellular *CY1PB1* levels in the risk of carcinogenity (19, 20). *CYP1B1* is regulated by several key transcription factors, such as the aryl hydrocarbon receptor (AhR) (24). The activation of this signalling pathway suggests that it plays a crucial role in the development of immunological, toxicological, and oncological processes. It is also an important regulator of skin barrier function (25). Interestingly, the interaction between dioxin-like substances and the AhR may be related to the suppression of PPAR-gamma, an aetiopathogenic mechanism that has been described in lichen planopilaris (26). The possible role of AhR on occurrence of FFA is still to be elucidated, although a higher expression of this receptor has been detected in skin biopsies from patients with FFA (27).

Only 4 patients presented a homozygous mutation in the *CYP1B1* gene that was related to a protective allele. In fact, most of the study patients (75.2%) had not the rs180040 polymorphism described, as expected. The presence of the protective allele expressed in homozygous might be an important predictor factor for low-risk of FFA. However, larger studies must corroborate the extremely low prevalence of this genetic variation in FFA population. The FFA protective *p.Asn453Ser* allele enhances the rate of *CYP1B1* degradation, resulting in lower intracellular *CYP1B1* levels, according to functional analysis of allelic variation in *CYP1B1* (28). Considering the importance of *CYP1B1* in sex hormone metabolism, FFA's female preponderance, and its worldwide rise in occurrence, FFA is most likely the consequence of increased female exposure to a *CYP1B1* substrate (**Fig. 3**) (12).

The current study has several limitations. First, we selectively genotype 2 particular SNPs in the sample, excluding additional loci that may well be involved in FFA. The study's major goal, however, was to characterize the genetic variations associated with this type of alopecia that had previously been observed. Secondly, we included only a limited number of particular cases of FFA, comprising 2 males who had been diagnosed with the condition. The actual data could become more

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heterogeneous as a result of this. Future research should focus on the genetic bases of FFA in these patients. We also added 6 relatives, which increased the likelihood of detecting similar mutations in most of them. Thirdly, 139 individuals out of the total of the patients included in the study had already been investigated in the previous GWAS. Despite this, describing the genetic variations in a larger sample of patients with FFA might aid in determining the prevalence of these molecular findings in an ongoing cohort in clinical practice. Lastly, the retrospective design of the study entails some missing clinical data. However, the missing data is few and does not significantly impact the data analysis.

In a nutshell, this is the first description of a large Spanish FFA sample based on the genetic findings in the GWAS study. The above-mentioned aspects suggest that HLA class I mutations, and the *CYP1B1* gene in particular, could play a decisive role in the development of FFA. The genetic approach to this disease may have an impact on prognosis and on future therapies for patients.

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The current study has been approved by an Institutional Review Board at University Hospital Ramón y Cajal (study number: GEN AFF 04-2019). The patients in this study have given written informed consent to publication of their case details.

The authors have no conflicts of interest to declare.

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