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## Frontal fibrosing alopecia: reflections and hypotheses on etiology and pathogenesis

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**Abstract:** Since it was first described by Kossard in 1994, frontal fibrosing alopecia (FFA) has been something of an enigma. The clinical heterogeneity of FFA, its apparent rarity, and investigators' suboptimal access to phenotypically consistent patient cohorts, may all have had a negative impact on delineating disease pathogenesis. Moreover, there is a relative paucity of epidemiologic interventional and basic research studies, and there have been no advances in translational therapeutics, unlike for other inflammatory dermatoses, such as alopecia areata (AA). Dermatologists anecdotally describe an increasing incidence in FFA over the last decade, which has led to the notion that the disorder may be induced by unknown environmental triggers. On the other hand, segregation of FFA in some families lends support to an unexplored genetic element implicated in disease pathogenesis. We herein review what is known about the pathobiology of FFA and formulate working hypotheses to advance insight into this intriguing hair disorder.

**Keywords:** FFA; frontal fibrosing alopecia; LPP; lichen planopilaris; scarring; cicatricial alopecia

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## Introduction

Cicatricial or scarring alopecias, whether primary or secondary, are a therapeutically challenging problem in clinical practice. Primary cicatricial alopecias (PCA) represent a rather diverse group of inflammatory disorders, where the common denominator, in pathologic terms, is the irreversible destruction of hair follicles. Frontal Fibrosing Alopecia (FFA) is a recently described, predominantly postmenopausal, primary lymphocytic cicatricial alopecia (1) that has been thought to be a variant of lichen planopilaris (LPP) (2). Clinically, the disorder involves the frontotemporal hairline with perifollicular erythema, follicular hyperkeratosis and scarring with evident hairline recession, although clinical signs of inflammation are not always evident (3). Eyebrow loss is recorded in 50%-83% of cases (3-5) but body hair loss has been less commonly reported, as has eyelash volume loss (0%-77%) (5-7). The histology of FFA (**Fig 1**) is similar to that of classic (multifocal) LPP, with the early active stages showing a perifollicular lichenoid inflammatory infiltrate involving the isthmus and infundibulum; later stages are characterized by perifollicular fibrosis with follicular dropout and follicular scars replacing the pilosebaceous units (2, 8). The inflammatory focal point in FFA is the bulge area of the hair follicle (HF) in contrast to alopecia areata (AA),

where the bulb at the lower third of the HF is at the epicentre (9, 10). The identical histological appearance accounts for the widespread acceptance of FFA as clinical sub-variant of (follicular) lichen planus (11).

Dividing PCAs histologically into lymphocytic, neutrophilic and mixed, has guided clinical classification but microscopic characterisation may not reflect upstream differences in pathogenesis. Neither do the histological similarities reflect clinical overlap: the classic pattern of LPP behaves differently clinically and epidemiologically from its rather distinct subvariant FFA: the latter has a striking clinical pattern of ear-to-ear scarring hair loss, often with eyebrow and body hair involvement and much commoner in postmenopausal women (12, 13). Only rarely does FFA affect men whereas LPP does not show a gender or older age predilection. Of note, pediatric cases of LPP have also been reported, whereas FFA is unheard of in the pediatric population (14).

The exact pathogenesis of FFA remains unknown. Its postmenopausal occurrence led to the speculation of a hormone-related triggering mechanism. Moreover, 5-alpha reductase inhibitors have been reportedly used with some success, although it has been argued that the beneficial effect of these may be on any concomitant androgenetic element of hair loss, while the overall evidence-basis for this claim remains poor (12, 15). There have been familial cases of FFA reported in the literature (16–19) but robust genetic analysis of the condition has not been undertaken to date.

### **The case for a genetic basis underlying FFA and the role of the environment**

Genetic exploration has been instrumental in revealing molecular pathways underlying alopecic variants, such as Marie-Unna hypotrichosis (20) and alopecia areata (AA) (21), among other cutaneous disorders. It would therefore be prudent to consider the research question of whether there is genetic basis to be explored and, if so, what method would be more appropriate to employ in doing so.

The notion that FFA is underlain by a genetic element is supported primarily by evidence of disease segregation in first-degree relatives. We and others (16–19) have reported familial cases of FFA, where the observed inheritance is in keeping with an autosomal dominant

mode with incomplete penetrance, lending support to the hypothesis that the trait in question may be Mendelian. The exceptionally rare incidence of the disorder would also be in keeping with the hypothesis that FFA is caused by rare alleles of large effect size. Twin studies can be insightful in discerning whether a trait is strongly genetic and we have undertaken a search in the UK via our network of collaborating clinicians and Twins UK: 3 pairs of monozygotic (MZ) twins affected by FFA have been identified, 2 of which are concordant and 1 discordant (67% concordance vs 33% discordance) in a cohort of just over 12,000 individuals. It should be emphasized that the rare overall incidence of FFA and the small number of twin pairs identified (N=3) warrant caution in interpreting the above observation. Moreover, even strongly genetic conditions, such as systemic lupus erythematosus (SLE), are characterized by higher discordance among MZ twins (22), thereby supporting the suggestion that epigenetics may play a profound role in FFA pathogenesis in addition to genetic predisposition. Nevertheless, case-studying of MZ cases could be insightful when undertaken with robust research methods.

On the other hand, the apparent recent increase in the overall incidence of FFA has sparked interest in 'environmental' triggers (23). The late onset of FFA could imply lower genetic causality, although there are plenty of disorders, which are characterized by late life onset and yet which are known to be genetically predisposed, such as systemic lupus erythematosus (SLE) (24) and hidradenitis suppurativa (HS) (25). It is worth noting that, despite the later-life manifestations of the classic frontal fibrosing pattern of hair loss, individuals affected by FFA report, in our experience, lifelong body hair loss, predated eyebrow and scalp involvement. This diffuse and perhaps unrecognized long-term hair loss would also be in keeping with germline predisposition, enhanced by a more complex interplay of possible hormonal factors postmenopause.

#### **Parallels between FFA and AA**

The concept of immune-privileged anatomical sites has been well-established since Medawar's experiments, which demonstrated that allogeneic skin grafts are not subjected to immunological rejection when transplanted into certain sites, such as the eye or brain (26). Within the skin, the hair follicle (HF) is a site of relative immune privilege (IP), which serves as a protective strategy against autoimmune injury. Protection is achieved by

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downregulation of major histocompatibility complex (MHC) class I and  $\beta 2$  microglobulin in the bulb and bulge of the hair follicle epithelium, besides an augmented expression of a local immunosuppressive milieu. In physiological terms, the exact role of the HF IP remains somewhat unclear, although proposed theories have included the possibility of the crucial evolutionary benefit of ensuring mammals such as polar bears maintained their hair (27–33). Relative IP loss in anagen hair follicular epithelium is postulated to underlie the organ-specific auto-immune disorder AA, where loss of relative IP leads to ectopic MHC class I expression and, as yet elusive, autoantigens trigger a CD8+T cell-mediated inflammatory process, microscopically seen as the classic peribulbar ‘swarm of bees’ (**Fig 2**) (34–36).

The IP-privileged HF bulge is home to epithelial hair follicle stem cells (37). The crucial role of epithelial hair follicle stem cells (eHFSC) in the pathobiology of PCA is well established: destruction of the bulge is detrimental to the HF’s regenerative ability and is seen in permanent, scarring types of alopecia (38, 39). Harries *et al.* studied how proinflammatory events influence eHFSC integrity and postulated that LPP (and variant FFA) represents a T-cell dependent autoimmune disorder, underlain by IFN $\gamma$ -Induced IP collapse at the level of the bulge (40). IP collapse was evidenced by reduced expression of the IP guardians TGF $\beta 2$  and CD200 and enhanced expression of the normally locally down-regulated presence of MHC class I/II and  $\beta 2$  microglobulin, which are thought to limit autoantigen presentation (41). In other words, LPP and variant FFA were postulated to mirror the autoimmune process underlying AA with the difference that IP in AA is centred at the deeper but less catastrophic potential bulb, as opposed to the critical stem cell niche and anatomically more superficial bulge. The observed features were only found to characterise lesional areas of scalp skin in individuals affected by LPP, whereas the previously proposed crucial role of defective PPAR $\gamma$  signalling, which Karnik and colleagues (42) found to underlie both lesional and non-lesional scalp skin, could not satisfactorily explain the pattern of patchy involvement in LPP. On the other hand, as Harries *et al.* pointed out, that study did not allow one to conclude whether IFN $\gamma$  production preceded CD8+ T cell infiltration at the bulge level or whether elusive factors attract T cells, which would subsequently secrete IFN $\gamma$ , thereby causing IP collapse (41).

Genetic determinants in the pathogenesis of AA were revealed with the help of the genome-wide association study led by Christiano and colleagues: a region of strong association within the novel ULBP gene cluster on chromosome 6q25.1 was identified, which encodes activating ligands of the natural killer cell receptor NKG2D (21). When probed, it was demonstrated that ULBP3 was expressed in lesional scalp and upregulated in the HF dermal sheath during active disease stages (21). If we consider LPP and variant FFA to be immunologically analogous to a bulge-affecting AA-like process, it might be anticipated that the causative weak link in LPP and variant FFA could be reminiscent to *ULBP3*: an overexpressed 'danger signal' or a defective 'gate-keeper' at the level of the bulge, responsive to stressors that might impose a breach of the integrity of the follicular unit. Such a locus could be explored using an investigational genomic approach.

#### **Can we get clues about FFA from other fibrotic disorders?**

Fibrotic disorders comprise a multitude of clinical entities, ranging from widespread systemic sclerosis (43, 44), multifocal fibrosclerosis (45, 46), sclerodermatous graft-versus-host disease (47) and nephrogenic systemic fibrosis (48, 49) to more organ-specific disorders such as cutaneous, pulmonary, hepatic, and renal fibrosis (7, 50–52). Whether reactive or reparative, these fibrotic disorders are defined by excessive fibrous connective tissue and aberrant and excessive deposition of extracellular matrix (ECM) in involved tissues. Enhanced expression of genes encoding matrix proteins is a common finding in many of these conditions, where the resulting fibrosis disrupts normal architecture, ultimately leading to organ dysfunction and failure (53–55). A common feature is a dense population of activated fibroblasts or myofibroblasts, which are largely responsible for the hyper-fibrotic response by promoting the production of fibrillar type I and type III collagens and reducing expression of genes encoding extracellular matrix (ECM)-degradative enzymes (56–59). Although the exact origins of the mesenchymal cells leading the aberrant collagen and ECM protein production has not been entirely elucidated, resident fibroblasts, bone-marrow derived fibrocytes, as well as endothelial and epithelial cells undergoing epithelial-to-mesenchymal transition (EMT) are important players in the process (60).

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One immunohistochemical marker of EMT is Snail1 (61) which is expressed in the fibrotic dermis of individuals affected by FFA (62), indicating that profibrotic cells may be derived at least in part by of EMT, where molecules such as TGF $\beta$  could be key. This makes one consider targeting such molecular regulators (or EMT-related miRNA) to arrest or reverse the fibrotic process, whether in skin, liver, lungs or kidneys.

### **Hormones and trauma: true culprits or mere helpers and enemies?**

FFA is known to almost exclusively affect women of postmenopausal age (1, 2). Of the 150 cases that currently are under our care, the vast majority developed the disorder after menopause, whereas the few younger female patients had iatrogenic, syndromic or biochemical estrogen decline prior to developing FFA (namely ovariectomy, Turner's syndrome or early menopause). Of course, disease chronicity is known to be associated with excessive fibrous tissue deposition, altered tissue architecture, and organ dysfunction and fibrosis *per se* increases in all organs with aging (63, 64). Estrogen has been found to exert antifibrotic effects *in vivo* (65) and act as potent immunomodulator by suppressing central, innate and adaptive immunity in certain cell types (66), although its effects are known to be variable (67). Does menopause simply coincide with the profibrotic processes of aging or does the menopausal estrogen decline cause unfavourable immunomodulation, thereby allowing a lifelong condition to declare itself and come to the fore? The latter may be in keeping with our observation that other body regions in people with FFA are hairless from a much younger age, thus predating the more intense manifestations of the disorder that occur much later. Male FFA may also be consistent with the above hypothesis: serum testosterone levels are known to decrease with ageing, as does its aromatase-induced conversion to estrogen (68, 69). In either scenario, hormone replacement following realisation of disease activity would not possibly be capable to reverse the underlying process of immune privilege collapse and autoantigen driven lymphocytic attack.

The observation that hair transplantation and face-lift surgery re-activates the disease process (70–72) may also be in keeping with the above hypothesis: the disordered immune-mediated collapse of the hair-follicle's privileged integrity may well leave local factors, such as memory T-cells in skin stroma. In line with this, when apparently normal autologous hair follicles are transplanted to a region previously involved with FFA, subjects can develop the



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histological hallmarks of the disease (73, 74). Any traumatic or inflammatory insult or merely implanting more antigens by transplanting hairs in that stroma would be germane to stepping into an active but quiet minefield before the ensuing catastrophe becomes macroscopically and clinically noticeable.

#### **Are there potential diagnostic markers or disease biomarkers for FFA?**

MicroRNAs (miRNAs) are relatively recently discovered small, endogenous, non-coding ribonucleic acid molecules (RNAs) that affect various cellular processes underlying health and disease by exerting target gene expression regulatory functions (75, 76). Recent years have seen miRNAs emerging as key determinants of organ phenotypes and potential candidates of prognostic, diagnostic and therapeutic interest in numerous disease processes (77–81). Aberrant expression or function of miRNAs has been implicated in a broad spectrum of human disorders, such as several types of malignancy, neurodegenerative, infectious, metabolic, chronic inflammatory, fibrotic and autoimmune diseases (82–89) and this has led to widespread attention to miRNAomics.

It has recently been discovered that miRNAs can be detected in plasma and serum, where they circulate in a stable form (90–92) mostly because of their encapsulation in serum microvesicles or exosomes (93). There is relative paucity of microRNAomic investigations in cutaneous pathophysiology with the notable exception of psoriasis (94) rendering the prospect of exploring their potential usefulness in FFA and other related alopecic disorders a very attractive one and we are pursuing.

#### **Proposed strategies for advancing insights into FFA**

In order to dissect the molecular etiopathogenesis of FFA, a genomic investigation would need to explore if there is a genetic component underlying any observed heritability (**Table 1**). Whether rare coding alleles of large effect size determine FFA would best be addressed via deep sequencing affected familial cases. By studying related, highly clinically consistent individuals it is anticipated that the shared phenotype is caused by shared genetic variation, an approach that circumnavigates the problem of heterogeneity. Nevertheless, the vast majority of cases are sporadic and it would be important to explore whether common genetic variation or more complex pathways predispose to disease: a genome-wide

association study may be the best research tool in delineating underlying pathways, while also examining gene-environment interactions, an approach we are currently recruiting for. The overall rare incidence argues against an environmental etiology as the sole pathogenic determinant, although carefully designed observational studies could examine this notion, ideally followed by epigenetic exploration.

Identifying a refined genetic or protein micro-entity as a biomarker would be indispensable to disease prognostication and could help optimise therapeutic strategies: circulating microRNA and metabolomic profiling may also be an appropriate approach but may be challenging to validate, given the slowly progressive nature of FFA requiring a prolonged and carefully controlled study.

Appreciation of the normal scalp cutaneous cell demographics and architecture and regional gene expression differences could potentially help understand the pattern of disease: appropriate transcriptomic analysis and suitable functional organ and *in vivo* models would be essential and complementary to genomic investigation. *Sine qua non* to molecular delineation is the necessity for deep phenotyping and understanding the clinical character of FFA. To this end, is it time for Cicatricial Alopecia Registry UK (CAR-UK) or, why not, CAR-EU? We have set the foundation stone by establishing a UK-wide research network via the NIHR UK Rare Disease Research Consortium Agreement and look forward to gaining new momentum in the important but thus far understudied area of rare alopecic, scarring and lichenoid dermatoses.

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### **Author contributions**

CT, DAF, CMS, MAS and JAM take full responsibility of the contents of the manuscript. CT and JAM wrote the paper. CMS contributed to Fig 1 and Fig 2. CT, DAF, CMS, MAS and JAM provided critical revision of the manuscript.

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## Author contributions

Jimenez, Poblet and Izeta take full responsibility of the contents of the manuscript. Jimenez and Izeta wrote the paper. Poblet provided Fig. 1 and Izeta provided Fig. 2. Critical revision of the manuscript for important intellectual content: Jimenez, Poblet and Izeta. Administrative support: Jimenez.

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## Conflicts of interest

None declared

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**Table 1.** A summary of research questions and potential strategies for working and alternate hypothesis

Hypothesis	Proposed Experimental Strategy
1. Familial FFA is determined by rare, large effect size, coding alleles	Whole-exome sequencing
2. Sporadic FFA is due to common genetic variation	Genome-wide association study (GWAS)
3. Sporadic FFA is due to environmental factors	Observational/cross-sectional study; Epigenome-wide association study (EWAS)
4. FFA is a complex trait attributed to interplay between genetic and environmental contribution	Gene-environment interaction across the genome via GWAS and multiple testing correction for each interaction
5. The pattern of FFA may be explained by regional differences conferring immune privilege advantage for follicular units in certain areas of the scalp	Characterization of normal skin for cutaneous cell populations immunohistochemically and for gene and protein expression via RNA sequencing and proteomic analysis



## FIGURE LEGENDS

**Figure 1:** Frontal fibrosing alopecia: Scalp with frontal hairline recession involving the temporal areas bilaterally (A), as well as the eyebrows (B). Histopathology shows perifollicular fibrosis with a moderately dense perifollicular lymphoid cell infiltrate involving several hair follicles X40, (C). Detail showing the different phases of the scarring process in different hair follicles leading to hair loss, 100X (D).

**Figure 2:** Alopecia areata: Retroauricular scalp with a patch of non-scarring alopecia with exclamation hairs (A), which are best appreciated with trichoscopy (B). Histopathology shows an increased number of telogen hair follicles with peribulbar lymphoid cell infiltrate X40(C). Detail of the peribulbar lymphoid cell infiltrate 'swarm of bees' X400 (D).



