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## Genetics and other factors in the aetiology of female pattern hair loss

**Running Head:** Genetics of female pattern hair loss

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### Abstract

Pattern hair loss is the most common form of hair loss in both women and men. Male pattern hair loss, also termed male androgenetic alopecia (M-AGA), is an androgen-dependent trait that is predominantly genetically determined. Androgen-mediated mechanisms are probably involved in

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FPHL in some women but the evidence is less strong than in M-AGA; and other non-androgenic pathways, including environmental influences, may contribute to the aetiology. Genome-wide association studies (GWASs) have identified several genetic loci for M-AGA and have provided better insight into the underlying biology. However, the role of heritable factors in female pattern hair loss (FPHL) is largely unknown. Recently published studies have been restricted to candidate gene approaches and could not clearly identify any susceptibility locus/gene for FPHL but suggest the aetiology differs substantially from that of M-AGA. Hypotheses about possible pathomechanisms of FPHL as well as the results of the genetic studies performed to date are summarized.

### **Key words**

female pattern hair loss, pathomechanism, molecular genetics, genetic complex disorder, clinics

### **Introduction**

Female pattern hair loss (FPHL) is the most common hair loss disorder in women. Currently available therapies for FPHL are unsatisfactory, and there is a demand for new treatment strategies. FPHL typically presents as a diffuse reduction in hair density that mainly affects the mid and frontal regions of the scalp with preservation of the frontal hairline (Fig 1). Some women show a more pronounced frontal accentuation (the Christmas tree pattern) (1) and some have a more global reduction in hair density involving the sides and back of the scalp. Deep recession of the fronto-temporal hairline and true vertex balding, as seen in men, occasionally occur in women but are uncommon. Nevertheless, the regressive changes that occur in hair follicles in FPHL are similar if not identical to those that occur in male balding. It is well-established that male balding is a genetically determined androgen-dependent trait (male androgenetic alopecia, M-AGA) and it has long been assumed that FPHL shares the same aetiology, hence the term female androgenetic alopecia is often applied to this condition. However, the role of androgens in causing FPHL is less clear than in men. The genetic studies performed so far have not led to any firm conclusions but rather suggest different pathways for M-AGA and FPHL.

In this review, we summarize what is known about the aetiology of FPHL and its relationship to M-AGA. Our main focus is on the results of genetic studies performed within the last decade. We also discuss the role of endocrine and other factors in the pathogenesis.

## **Prevalence**

Published data on the prevalence of FPHL show some variation between studies, perhaps reflecting the difficulty in classifying mild forms of the condition. However, all show an increasing prevalence with age. Studies in women of white European ethnicity in the USA,(2) UK(3) and Australia(4) record a prevalence of 3-12% in the third decade, rising to 14-28% in the sixth decade and 29-56% in women aged 70 and over. Reported prevalence rates in East Asian women are lower, reaching 12-25% in over 70 group.(5-7) Although the onset is after puberty in the great majority of cases pattern hair loss has been reported in children as young as 6 years of age.(8)

## **Pathophysiology**

### *Pathology*

The pathologic changes in pattern hair loss appear identical in men and women. There is a reduction in the duration of anagen and prolongation of telogen.(9) The time to exogen is unchanged but there is an increasing delay in the onset of the next anagen phase leading to prolongation of the latent phase (kenogen) where the follicle is not producing a hair and is 'empty'.(10) Follicles then undergo a process of miniaturisation, possibly ending in follicular deletion.(11) The precise cause for this process of follicular regression is unclear.

### *Arrector pili muscle degeneration*

In a recent study of eight scalp biopsies from patients with AGA degeneration of the arrector pili muscle (APM) and replacement by fat tissue was observed.(12) The precise mechanism remains unclear but the authors speculated that degeneration of APM might be related to depletion of follicular stem or progenitor cells. The authors did not state whether samples were from men or women.

### *Inflammation/immunity/apoptosis of hair follicle*

A role for inflammation in the pathogenesis of androgenetic alopecia was proposed by Jaworsky et al.(13) Later, Whiting reported the presence of inflammation in 37% of biopsy samples from patients with FPHL compared with 12% of control subjects.(14) Scalp biopsies from 17 women with FPHL and five healthy females were included in the study of Ramos et al.(15) They observed a higher apoptosis index and prominent mononuclear microinflammation among the miniaturized follicles. Furthermore, they reported a positive correlation between apoptosis and perifollicular inflammation. Kolivras et al.

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reported presence of T-cells in tissue samples of a total of 28 patients with AA but not in the tissue samples of 31 cases with “pattern hair loss”.(16) Mahé et al. studied the level of interleukin (IL)-1 alpha production in plucked human anagen hair and suggested that IL-1 has a negative effect on hair growth in patients with AGA.(17)

Whether inflammation plays a causative role in pattern hair loss is unclear although treatment with anti-inflammatory agents or immunosuppressive drugs is not conspicuously associated with its reversal.

## **Aetiology**

### *Sex steroid hormones*

The term “*female androgenetic alopecia*” was introduced in 1977 by the dermatologist Ludwig,(18) implying an androgen-dependent mechanism underlying FPHL. There is little doubt that severe hyperandrogenism, such as occurs due to androgen-secreting adrenal or ovarian tumours, does cause scalp hair loss in women, and was recognised prior to Hamilton’s seminal publication on the causative role of testosterone in M-AGA.(19) Some studies have found elevated androgen levels or an elevated androgen/oestrogen ratio in women with FPHL,(20, 21) though generally of minor degree, and one ultrasound study has reported an increased frequency of polycystic ovaries.(22) Alopecia is frequently mentioned as a feature of polycystic ovary syndrome (PCOS) though it is less common than hirsutism. Two studies from Turkey and the USA reported the prevalence of FPHL in women diagnosed with PCOS as 34.8% and 22% respectively.(23, 24) However, not all studies have found evidence of hyperandrogenism in FPHL(25) and in all studies there is a variable proportion of subjects without clinical or biochemical signs of androgen excess. FPHL has been reported in complete androgen insensitivity syndrome,(26) and in the absence of circulating androgens.(27) Although antiandrogens are used in the treatment of FPHL the evidence of benefit from controlled trials is lacking. Finasteride 1 mg daily had no effect in a controlled trial in postmenopausal women with FPHL(28) although two uncontrolled case series using higher doses of finasteride have reported improvement.(29, 30) In a one-year trial comparing cyproterone acetate with topical minoxidil hair loss progressed in women taking cyproterone acetate (but improved in the minoxidil group).(31) Paradoxically, a questionnaire study in women receiving testosterone implants for symptoms of androgen deficiency reported an improvement in hair growth (although almost all developed hirsutism).(32) Androgen levels in women

decline progressively from early in the 4<sup>th</sup> decade(33) and this parallels the gradual reduction in scalp hair density and hair diameter in the female population that occurs with advancing age.(3) It was suggested that testosterone may have an anabolic effect on hair growth that is distinct from a virilising effect via the 5 $\alpha$ -reductase pathway.

The possible role of oestrogen in FPHL is similarly uncertain. The oestrogen receptor beta is expressed in human hair follicles(34) and oestrogens exhibit stimulating effects on the generation of the hair shaft and the proliferation of keratinocytes of the hair matrix, with prolongation of the anagen phase, in cultivated male hair follicles.(35) Indirect evidence for a protective effect of oestrogens on human hair growth comes from the increasing prevalence of FPHL following the menopause, the prolongation of anagen during pregnancy(36) and reports of hair loss in women taking tamoxifen or aromatase inhibitors for treatment of breast cancer.(37) One study found lower oestrogen:androgen ratios in premenopausal women with FPHL compared to a control group, suggesting a protective effect of oestrogen on hair loss, although the number of subjects was quite small.(38) Interestingly, androgen levels were slightly lower in the FPHL subjects than in controls though the difference was not significant. On the other hand there is no clear effect of oestrogen supplements on human hair growth and several studies have shown an inhibitory effect of oestrogens on hair growth in other species.(39-41)

#### *Prostaglandins*

Prostaglandins have been implicated in the pathogenesis of male balding.(42) Garza et al. showed elevated levels of prostaglandin D2 synthase (PTGDS) mRNA and protein in bald compared to haired scalp. The product of its activity, prostaglandin D2 (PGD2) was also elevated in bald scalp, and inhibited hair growth in explanted human follicles and when applied topically to mice. K14-Ptgs2 transgenic mice, which show elevated PGD2 in the skin, developed alopecia and miniaturisation of hair follicles. Further experiments in transgenic mice and cultured human follicles indicated the inhibitory effect of PGD2 on hair growth was via the GPR44 receptor. It is not yet known whether these results are applicable to FPHL.

### *Iron stores, Vitamin D*

The place of low iron stores in the aetiology of FPHL is controversial. Both lower (43, 44) and similar (45) serum ferritin levels compared to control groups have been reported in women with FPHL. There are no controlled trials that have tested the hair growth response to iron supplementation in women with FPHL. One study reported a response to antiandrogen therapy in women with serum ferritin levels above 40 µg/l but not in those with serum ferritins below this level.(46)

Recently, Banihashemi et al. found lower vitamin D<sub>3</sub> levels in a sample of 45 women with FPHL than in 45 control subjects.(47) Rasheed et al. reported significantly decreased serum ferritin and serum vitamin D<sub>2</sub> levels in 80 women with either chronic telogen effluvium or FPHL compared to 40 age-matched healthy females.(48) Fawzi *et al* observed decreased serum and tissue levels of vitamin D receptors (VDRs) in 20 patients with AGA.(49) VDR levels were significantly higher in female patients with AGA than in males. There are no published studies on the hair growth response to vitamin D supplementation in women with FPHL and vitamin D deficiency.

### *Dickkopf-1/ WNT signalling pathway*

In a sample of 24 patients with AGA (including either M-AGA or FPHL) and 31 patients with alopecia areata (AA) and 33 healthy controls of Egyptian origin, a significantly higher concentration of tissue DKK-1 (Dickkopf 1) levels was detected in AGA patients compared to controls.(50) DKK-1, a secreted glycoprotein, is an antagonist of the Wnt signaling pathway.(51) Wnt, itself a proto-oncoprotein, can promote cell proliferation and transformation when mutated or overexpressed. Of note, in M-AGA, genome-wide significance was found for the variant rs7349332 on chr2q35, which is located intronically in WNT10.(52) Expression studies in human hair follicle tissue suggest that WNT10A has a functional role in M-AGA etiology. Interestingly, Tosti et al. applied methyl vanillate (MV), an activator of the WNT/β-catenin signalling to 20 female patients with FPHL. They demonstrated increase of hair count and hair mass index in the patients as well as increased WNT10B mRNA expression levels in affected scalp skin.(53)

## Comorbidities

A number of studies have reported an increased frequency of features of metabolic syndrome in women with FPHL including obesity, insulin resistance, hypertension, hyperprolactinaemia and raised aldosterone levels.(54-58) An increased risk of carotid and coronary artery disease has also been reported.(55, 59, 60) Birch et al. reported a significantly raised BMI in women with hirsutism, both with and without FPHL, but BMI levels were not raised in non-hirsute women with FPHL.(61) A study from Turkey found an association between FPHL and insulin resistance that appeared to be independent of hyperandrogenaemia.(62)

Although research points to comorbidity, current studies are limited by i) small sample sizes, ii) small control groups, iii) lack of population-based data (Berkson's bias) and iv) lack of homogeneous, standardized examination methods. To further elucidate the comorbidity profile in FPHL and to shed light on a possible influence of comorbidity on disease severity, systematic studies in larger population-based samples are a necessary step.

## Heritable Factors - the present status of FPHL genetic research

### *Mode of inheritance*

Two twin studies from Australia and Denmark have shown that M-AGA is largely determined by genetic factors, with heritability in the region of 80-95%.(63, 64) In the first published family study, Dorothy Osborn concluded that pattern hair loss is due to a single gene and is inherited as an autosomal dominant trait in men and autosomal recessive in women.(65) This idea was subsequently questioned by Küster and Happle who proposed a polygenic model of inheritance,(66) although, like Osborn, they assumed that male and female pattern hair loss are the same entity. The polygenic hypothesis for M-AGA is now generally accepted and supported by results of GWAS. Less is known about the role of genetic factors in FPHL. Smith and Wells reported that balding was more common in first-degree male relatives of 56 women with hair loss than women without hair loss, suggesting a common genetic influence.(67) On the other hand, a twin study in older women found no evidence of a genetic component to hair thinning although there was a strong heritable influence on fronto-temporal recession.(68) Clinical observation suggests that early-onset FPHL is inherited but it is notable that this study was performed in similarly aged subjects and drawn from the same population as the Danish study that demonstrated strong heritability in male balding.(64)



### *Molecular genetic studies*

To understand the complex biological cascades behind polygenic disorders, such as M-AGA, genome-wide association studies (GWAS) are suitable for the identification of genetic variants on a given locus which will help in the elucidation of the biological function behind the disease. This has recently been exemplified in M-AGA.(69) No genome-wide linkage or association studies of FPHL have been reported to date. Only a few candidate gene studies, primarily focussing on genes of the sex steroid hormone pathway and known M-AGA susceptibility loci, have been performed (Table 1); these and others are discussed in the following sections.

### *Sex steroid hormone pathway*

Association studies between the genes for aromatase (*CYP19A1*) and oestrogen receptor 2 (*ESR2*) with FPHL were performed in an Australian group of almost 500 affected women and 500 controls. Nominal significant association was obtained for three variants of each of the two genes; however, these results did not withstand correction for multiple testing.(70, 71) We intended to replicate the reported borderline associations of three SNPs and added an additional SNP within *CYP19A1* in our FPHL sample of 200 patients of German and British origin; however we could not find any association, including for the rs4646 CC genotype which is known to be associated with higher oestrogen levels.(72) Rui et al. chose twelve SNPs in *CYP19A1* and examined them in a cohort of 200 Chinese women with FPHL and a similar number of healthy controls. They found that rs6493497 and rs7176005 were significantly associated with FPHL without applying any multiple testing strategy.(73) In addition, the authors found no association with rs4646, which was among the top SNPs of the study by Yip et al.(70, 73)

In another association study, we attempted to replicate the Australian findings for *ESR2* with markers rs10137185, rs17101774 and rs2022748 in our German/UK FPHL case–control sample. In the German sample, no significant association was found for rs17101774 or rs2022748. However, significant association was found for rs10137185 in the overall sample ( $P_{\text{uncorr.}} = 0.012$ ); and the strongest association was found for rs10137185 in the late-onset FPHL subgroup ( $P_{\text{uncorr.}} = 0.010$ ).<sup>(74)</sup> We had earlier investigated four variants in the *ESR2* gene in our German/UK FPHL sample and found no association.<sup>(75)</sup> However, this may have been attributable to the fact that none of these four variants were in strong linkage disequilibrium with variants showing association in the Australian

sample (max.  $r^2 = 0.149$ ).

The latter study also included variants of other genes implicated in androgen, or other sex steroid, metabolism in women with FPHL: *ESR1* (oestrogen receptor 1), *PGR* (progesterone receptor), as well as *SRD5A1* and *SRD5A2* (steroid-5-alpha-reductase, alpha polypeptide1 and 2); but no association was observed for any of the examined variants.(75) Due to the enormous number of single nucleotide polymorphisms (SNPs) in these genes we did not attempt to cover entirely the genes using a tagging SNP approach; instead we opted to genotype selected variants predicted to have functional effects. The involvement of these genes in the aetiopathogenesis of FPHL cannot, therefore, be completely excluded.

#### *M-AGA susceptibility loci*

To test the hypothesis that M-AGA and FPHL share the same aetiology we examined all gene loci respectively variants in FPHL that had previously been identified for M-AGA. These included *AR/EDA2R*,(76) and the chromosomal regions 1p36.22, 2q35, 2q37.3, 3q25.1, 5q33.3, 7p21.1, 7q11.22, 12p12.1, 17q21.31, 18q21.1, and 20p11.(77-79)

For the *AR/EDA2R* locus, we investigated 25 SNPs, based on their use in a recent fine mapping study of the association signal in M-AGA.(77) Genetic variability at the *AR/EDA2R* locus is thought to enhance the effect of androgens by increasing the number of androgen receptors in affected scalp tissue. We used a sample of 230 British and German women with FPHL. In the overall combined German and British samples no significant differences in allele or genotype frequencies were observed between patients and controls for any of the investigated variants at this locus. Subgroup analysis of British patients with an early age of onset generated nominally significant *P*-values for seven SNPs within *AR/EDA2R*, with the lowest *P*-value being obtained for rs1397631 (*P* = 0.00483, OR 0.16 [CI 0.04-0.69], *P* = 0.047 after adjustment for the testing of multiple SNPs). No association was found after stratification for disease severity.(76) Although the role of the locus *AR/EDA2R* in FPHL remains unclear, our results suggest that it may represent a common genetic factor for early onset FPHL and M-AGA. Further research is warranted in larger FPHL sample sets, as the subgroup of early affected British women (n = 57) was relatively small.(76)

Two other studies have investigated the association between the major M-AGA susceptibility locus, the X-chromosomal locus containing the androgen receptor (*AR*) and ectodysplasin A2 receptor (*EDA2R*) genes, and FPHL. These association studies, carried out in a very small Egyptian sample(80) and the above mentioned sample of Chinese Han women with FPHL,(81) were each

limited to the investigation of the CAG repeat length variant of the *AR* gene and no association between this and FPHL was found.(80, 81) Fine mapping studies of this locus in AGA have indicated that the CAG repeat length variant is unlikely to be the causative variant, and that other variants at this locus show much stronger association with AGA.(77)

### **Susceptibility locus 20p11**

Chromosome 20p11 contains a further major susceptibility locus for M-AGA, for which no candidate gene has yet been identified. We genotyped the top five SNPs from the chromosome 20p11 region that reached genome-wide significance in a recent GWAS of M-AGA(78) in our FPHL sample of 230 women. No significant association was obtained for the five 20p11 variants, in either the overall sample set or in subgroup analyses.(76) Our results do not implicate the 20p11 locus in the aetiology of FPHL.

### **Further susceptibility loci; 1p36.22, 2q35, 2q37.3, 3q25.1, 5q33.3, 7p21.1, 7q11.22, 12p12.1, 17q21.31, 18q21.1**

In larger cohorts of M-AGA a further ten susceptibility loci were identified. (52, 82, 83) We genotyped up to three variants from each of the newly identified loci in our FPHL sample, and were unable to demonstrate a significant association for any of the genotyped variants, in either the overall sample or in subgroup analyses.(84, 85)

### **Melanocortin 4 receptor (MC4R)**

Recent studies suggested an association of metabolic syndrome - including obesity, hyperlipidaemia, hypertension and diabetes mellitus type 2 or abnormally high fasting blood glucose - with FPHL. As mutations in the melanocortin 4 receptor gene (*MC4R*) have been identified in patients with morbid obesity,(55, 86, 87) and about half of the women in our FPHL sample present with obesity, we considered *MC4R* as an interesting candidate gene. Furthermore, this neuropeptide receptor has been detected amongst others in the dermal papilla of the hair follicle.(88) However, none of the six variants examined showed any association with FPHL.(89)

### **Conclusion of the molecular genetic data**

Female pattern hair loss and male balding share a final common pathway of follicular regression but current knowledge suggests the aetiology is not necessarily the same in both sexes. Androgens are a key driver of male balding and are also involved in the aetiology of pattern hair loss in some women. However, it is likely that other non-androgenic factors, as yet unidentified, play a role in causing FPHL.

The idea that the aetiologies of FPHL and M-AGA are not necessarily identical is supported by the results of genetic studies. The predisposition to M-AGA is largely due to heritable factors. Although only some of the loci identified as associated with M-AGA have been examined for FPHL, not even the most significant *AR/EDA2R* locus for M-AGA ( $p = 1 \times 10^{-320}$ ) showed a clear susceptibility for FPHL: other than the association of seven *AR/EDA2R* markers in the small group of 57 British patients with early onset, no clear overlap of susceptibility loci between M-AGA and FPHL could be demonstrated by any of the published studies. These results, therefore, point to distinct risk loci in the two disorders and to different underlying pathomechanisms. Similarly, the attempt to investigate the candidate genes of the sex steroid hormone pathway failed to demonstrate significant association with FPHL. This provides further support to the hypothesis that unexpected disease-causing mechanisms lead to the development of FPHL. Two very recent studies have substantially increased the number of gene loci (>60) that associate with M-AGA.(90, 91) These findings have yet to be investigated or replicated in FPHL. Similar studies employing a GWAS approach are sorely needed in FPHL if we are to clarify the uncertainties over its aetiology and pathophysiology, and potentially to develop new approaches to its treatment.

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**Table 1: Candidate gene studies**

Gene/ Locus	Function	Population	Results	Reference
<b>AR/EDA2R</b>	M-AGA susceptibility locus	UK & Germany	Significant association of seven variants in a subgroup of British women with an early age of onset	Redler et al., <i>Br J Dermatol</i> 2012
<b>AR/EDA2R</b>	M-AGA susceptibility locus	Han Chinese	No significant association	Rui et al., <i>Dermatology</i> 2016
<b>1p36</b>	M-AGA susceptibility locus	UK & Germany	No significant association	Redler et al., <i>J Dermatol Sci</i> 2013
<b>2q35</b>	M-AGA susceptibility locus	UK & Germany	No significant association	Nuwayhid et al., <i>Arch Dermatol Res</i> 2014
<b>2q37</b>	M-AGA susceptibility locus	UK & Germany	No significant association	Redler et al., <i>J Dermatol Sci</i> 2013
<b>3q25.1</b>	M-AGA susceptibility locus	UK & Germany	No significant association	Nuwayhid et al., <i>Arch Dermatol Res</i> 2014
<b>5q33.3</b>	M-AGA susceptibility locus	UK & Germany	No significant association	
<b>7p21.1</b>	M-AGA susceptibility locus	UK & Germany	No significant association	Redler et al., <i>J Dermatol Sci</i> 2013
<b>7q11.22</b>	M-AGA susceptibility locus	UK & Germany	No significant association	
<b>12p12.1</b>	M-AGA susceptibility locus	UK & Germany	No significant association	Nuwayhid et al., <i>Arch Dermatol Res</i> 2014
<b>17q21.31</b>	M-AGA susceptibility locus	UK & Germany	No significant association	Redler et al., <i>J Dermatol Sci</i> 2013
<b>18q21.1</b>	M-AGA susceptibility locus	UK & Germany	No significant association	
<b>20p11</b>	M-AGA susceptibility locus	UK & Germany	No significant association	Redler et al., <i>Br J Dermatol</i> 2012
<b>CYP19A1</b>	Sex steroid hormone pathway	Australia	CC genotype of rs4646 significantly more frequent in cases than controls compared with collapsed AC and AA	Yip et al., <i>Br J Dermatol</i> 2009
<b>CYP19A1</b>	Sex steroid hormone pathway	UK & Germany	No significant association	Redler et al., <i>Br J Dermatol</i> 2011
<b>CYP19A1</b>	Sex steroid hormone pathway	Han Chinese	Association for variants rs6493497, rs7176005	Rui et al., <i>Dermatology</i> 2016
<b>ESR1</b>	Sex steroid hormone pathway	UK & Germany	No significant association	Redler et al., <i>Exp Dermatol</i> 2012
<b>ESR2</b>	Sex steroid hormone pathway	UK & Germany	No significant association	Redler et al., <i>Exp Dermatol</i> 2012
<b>ESR2</b>	Sex steroid hormone pathway	Australia	Nominal significance for the variants rs10137185, rs17101774, rs2022748	Yip et al., <i>Br J Dermatol</i> 2012
<b>ESR2</b>	Sex steroid hormone pathway	UK & Germany	Significant association for rs10137185 in the overall German sample	Redler et al., <i>Brit J Dermatol</i> 2012
<b>PGR</b>	Sex steroid hormone pathway	UK & Germany	No significant association	Redler et al., <i>Exp Dermatol</i> 2012
<b>SRD5A1</b>	Sex steroid hormone pathway	UK & Germany	No significant association	Redler et al., <i>Exp Dermatol</i> 2012
<b>SRD5A2</b>	Sex steroid hormone pathway	UK & Germany	No significant association	Redler et al., <i>Exp Dermatol</i> 2012
<b>MC4R</b>	Melanocortin receptor gene	UK & Germany	No significant association	Mahmoudi & Redler et al., <i>Arch Dermatol Res</i> 2012

**Figure legends**

Figure 1

Female pattern hair loss. Diffuse reduction in hair density affecting the mid and frontal regions of the scalp with retention of the frontal hairline.

