Genetic and molecular aspects of androgenetic alopecia

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Abstract
Androgenetic alopecia is the most common form of progressive hair loss in humans. A genetic predisposition and hormonal status are considered as major risk factors for this condition. Several recent advances in molecular biology and genetics have increased our understanding of the mechanisms of hair loss in androgenetic alopecia. We review these advances and examine the trends in the genetic and molecular aspects of androgenetic alopecia.

Key words: Androgenetic alopecia, molecular analysis, genetics

Introduction
Androgenetic alopecia is the most common form of hair loss in humans affecting 80% of Caucasian men and 50% of Caucasian women.¹ Hair loss typically begins with bitemporal recession of the frontal hairline, followed by diffuse hair thinning at the vertex, and eventual complete loss of hair at the center of the vertex. The bald patch at the vertex subsequently joins the frontal receding hairline, leaving an island of hair on the frontal scalp. This island finally disappears leaving hair only in the parietal and occipital zones. Other less common patterns include more rapid hair loss over the vertex than the frontal area, frontal hairline loss before the vertex bald patch develops and also, a Ludwig-type pattern with preservation of the frontal hair line.² The Hamilton–Norwood scale is used to assess the extent and severity of androgenetic alopecia in men,³ whereas the Ludwig scale is preferred for women.

Both men and women have higher levels of androgen receptors and alpha-reductase type I and II activities in the frontal area of the scalp as compared to hair follicles located in the occipital area which have higher aromatase levels. The alpha-reductase type I and II activity in frontal hair follicles is three times greater in men than in women.⁴ Thus, male androgenetic alopecia is considered an androgen dependent condition, but the role of androgen signaling in women remains uncertain.⁵

Efforts have been made to elucidate the molecular mechanisms of androgenetic alopecia. Different expression profiles have been proposed in the areas affected by androgenetic alopecia, and various loci have been shown to be associated with this condition, suggesting that nonandrogen-dependent pathways may be involved in the pathophysiology of androgenetic alopecia.

This review focuses on the recent trends in the molecular and genetic aspects involved in the pathogenesis of androgenetic alopecia.

Etiology
Each hair originates in a hair follicle, and a cyclic process known as the hair growth cycle defines its individual and asynchronous growth. This cycle consists of four phases: (1) the anagen or growth phase, which is the longest and lasts 2 to 7 years, (2) the catagen or transition phase, which lasts approximately 2 weeks and includes hair follicle involution due to apoptosis, (3) the telogen or resting phase, which lasts 12 weeks when old hair is removed and (4) the exogen phase, which is the release phase of the telogen hair.¹² Miniaturization of...
the hair follicle is the hallmark of androgenetic alopecia. It occurs at some point between the late catagen or early anagen phase, affecting the dermal papilla and the dermal sheath, resulting in a smaller follicle and a reduced anagen phase. This anomaly is usually irreversible, although partial regrowth and some reversal of miniaturization is possible in some instances.

The different processes involved in the pathogenesis of androgenetic alopecia are shown in Figure 1. The condition is clearly associated with the activity of androgenic hormones and genetic predisposition. It demonstrates a pattern of familial aggregation, but can occur in several individuals within a family without monogenic inheritance, and is therefore considered a complex phenotype. Twin studies have demonstrated a heritability of 0.81, suggesting that genetics plays an important role in its presentation and progression.

It has been assumed that androgenetic alopecia is the result of the abnormal sensitivity of hair follicles of the scalp to circulating androgens, owing to an increase in the number of androgen receptors. The enzyme 5-alpha reductase has two isoforms, types 1 and 2, which catalyze the conversion of testosterone to 5-alpha–dihydrotestosterone. It is believed that both isoforms play a role in the metabolism and action of androgen, and their expression varies depending on the site of the body. Liu and Yamauchi found a higher expression of 5-alpha reductase type 1 in hair follicles, suggesting that they play a key role in androgen-regulated hair growth.

Androgens alter mesenchyme-epithelial cell interactions within the follicle, thus affecting hair growth, dermal papilla size, dermal papilla cells, and keratinocyte and melanocyte activities. The Wnt signaling pathway regulates cells in the dermal papilla and may play a pivotal role in the action of androgen on hair growth. However, the underlying molecular mechanisms of androgen-related actions remain largely unknown.

The replacement of terminal hair by vellus hair (vellus hair is defined as hair <30 µm in diameter and <30 µm in length; transitional hair width between 30 and 40 µm; terminal hair >40 µm) and a reduction in the total hair density (hair/square centimeter) are the major clinical features of androgenetic alopecia. The replacement of terminal follicles by vellus follicles is seen histologically too, along with a perifollicular infiltrate of macrophages, an increase in the size of sebaceous glands and dermal thinning.

Whether follicle miniaturization occurs mainly due to the activity of androgens is still a matter of debate. Whiting showed that miniaturization can be reversed in a single hair cycle in patients treated with finasteride, supporting the involvement of androgens in androgenetic alopecia. It is hypothesized that the miniaturization seen in patterned hair loss may be the direct result of reduction in the cell number and, hence, in the size of the dermal papilla. Yazdabadi et al. suggested that the arrector pili muscle serves as a source of stem cells to maintain the follicle, stimulating stem cell populations in the bulge or dermal sheath. The loss of contact in miniaturized follicles between the arrector pili muscle and the bulge produces miniaturization by disrupting the function of stem cells residing in the follicle.

The stem cells of the hair follicle are located in the bulge where they periodically alternate between activated and quiescent phases to maintain the stem cell population and produce new hair follicles. Wang et al. noted that when murine hair follicle stem cells were active, the FOXC1 gene was highly expressed, maintaining stem cell adhesion and promoting transition to the quiescent state. FOXC1 is a transcription factor involved in the regulation of embryonic development and the eye. It also activates the signaling of Nfatc1 and bone morphogenetic proteins, which play a role in the maintenance and development of hair follicles.

The arrector pili muscle plays an important role in maintaining follicle integrity by holding together each of the hair follicles in a follicular unit at the isthmus level. Torkamani et al. found that the arrector pili muscle degenerates and is replaced by adipose tissue in androgenetic alopecia. It is not clear how arrector pili muscle degeneration and fat infiltration are mechanistically related to follicle miniaturization and hair loss. It has been speculated that adipocytes derived from the aberrant differentiation of the remaining progenitor cells in the arrector pili muscle can cause follicle miniaturization. Mesenchymal progenitor cells in muscle tissue with ectopic fat deposition suggest that the loss of myofiber-derived inhibitory signals in degenerating muscles permits cellular adipose differentiation. Rushon et al. have proposed the existence of growth restricted (dormant/kenogen) nonvellus hair follicles that are re-activated by medical treatments in FPHL and MPHL. All these findings support the role of follicle miniaturization in the pathogenesis of androgenetic alopecia. Further studies are needed to define the role of follicle miniaturization in androgenetic alopecia more completely.

The role of microinflammation in the pathogenesis of androgenetic alopecia has been investigated by Jaworsky et al. who showed that the inflammatory cell infiltrate in the follicular bulge produces a progressive fibrosis of the perifollicular zone resulting in injury to follicular stem cells, impairment of normal hair cycling and finally, hair loss.

Genetics and Androgenetic Alopecia

Although androgenetic alopecia is mediated by androgens, genetic predisposition plays an important role in its etiology. The genetics of androgenetic alopecia is complex. The AR and 5-alpha reductase genes are attractive candidates for androgenetic alopecia.

Several studies have focused on genes related to the sex-steroid pathways guided by reports of differential levels of sex-steroid receptor expression and metabolizing enzymes between balding and
occipital regions of the scalp. There is evidence that both 5-alpha reductase enzymes and the androgen receptor are highly expressed in balding follicles as compared with nonbalding follicles on the same scalp\(^{23}\) which is due to the different genes that encode 5-alpha reductase type I and II and androgen receptors being expressed in these locations.\(^{24}\)

Recent genome-wide association studies in AGA have identified strong association signals in the X chromosome. Both the \(AR\) gene and the ectodysplasin A2 receptor (\(AR/EDA2R\) locus in Xq11-q12) showed strong signals for AGA.\(^{25}\)

It has been estimated that the \(AR\) gene may confer up to 40% of the total genetic risk, which is considered a high level of risk for a single gene.\(^{26}\) There have been several efforts to determine whether the \(AR\) gene is associated with male pattern baldness. Single nucleotide polymorphisms, copy number variations and triplet repeats are among the polymorphisms that have been studied in relation to AGA. Ellis \textit{et al.} compared the allelic frequencies between two polymorphisms in exon 1 of the \(AR\) gene, the Stul restriction site and CAG and GGC triplet repetition polymorphisms. This study found that the Stu restriction polymorphism was present in 98.1% of younger and 92.3% of older men with androgenetic alopecia as compared to 76.6% of non-bald controls. The combination of fewer trinucleotide repeats was more common in men with baldness (\(P = 0.03\)) suggesting that these markers are a close functional variant involved in the polygenic determination of male pattern baldness.\(^{27}\) In 2005, Hillmer \textit{et al.} replicated this work and showed that the leading candidate for AGA was the polyglycine GGN triplet repeat.\(^{27}\) However, Ellis \textit{et al.} found that these polyglycine repeats do not confer susceptibility to AGA\(^{28}\) and analyses of copy number variations in \(AR\) also suggest that polyglycine repeats are not implicated in AGA.\(^{29}\)

Prodi \textit{et al.} showed that the \(AR\) and \(EDA2R\) genes on the X chromosome were strongly associated with AGA. SNP rs1385699, which is located in \(EDA2R\), displayed the best association signal (\(P = 3.9 \times 10^{-9}\)), while the variant located in \(AR\) rs6152 showed lower significance (\(P = 4.17 \times 10^{-12}\)). Although the role of \(EDA2R\) in androgenetic alopecia is not clear, statistical analyses show that the association of markers in \(EDA2R\) and \(AR\) appear to be the result of linkage disequilibrium.\(^{27}\) The location of \(AR\) on the X chromosome and the strong association signal of \(EDA2R\) highlight the importance of the maternal lineage in androgenetic alopecia inheritance.\(^{27}\)

These findings emphasize the importance of the androgen receptor gene responsible for the increased risk of androgenetic alopecia in males which have been confirmed in multiple independent studies.\(^{27}\) However, a gene effect has not been demonstrated in women.

**Genome-Wide association Studies and Risk Loci for Androgenetic Alopecia**

Genome-wide association studies and meta-analysis have been used to evaluate the complex inheritance of androgenetic alopecia. Genome-wide association studies involve scanning markers across a complete set of genomic DNA of many cases and controls to determine genetic variations associated with a particular trait or disease. These studies use microarray technology to identify genetic markers or candidate genes.\(^{30}\) Meta-analyses are a powerful tool used to combine the results of genome-wide association studies from studies with similar designs across different populations to demonstrate a more significant association.\(^{31}\)

Heilmann \textit{et al.} suggested a polygenic component to androgenetic alopecia that may be part of the complex biological pathways associated with androgenetic alopecia.\(^{32}\) They identified four risk loci for androgenetic alopecia located in 2q35, 3q25.1, 5q33.3 and 12p12.1. The strongest association signal was observed in 2q35 (\(P = 3.33 \times 10^{-13}\)). This locus contains the \(WNT10a\) gene, which is expressed in the bulge during the anagen phase of the hair growth cycle and has been shown to have a genotypic effect on hair follicle expression.\(^{25}\)

A meta-analysis by Li \textit{et al.} identified 6 new risk loci for androgenetic alopecia in 1p36.22, 2q37, 7p21.1, 7q11.22, 17q21.31 and 18q21.1 and a strong association for androgenetic alopecia in 20p11 and the \(AR\) gene (rs2497938: \(OR = 2.20, P = 2.40 \times 10^{-9}\)).\(^{32}\) The risk locus for androgenetic alopecia at 20p11 had earlier been identified by Liang \textit{et al.} in a Chinese population.\(^{33}\) A risk locus at 3q26 was identified in a German population\(^{34}\) and a polymorphism in the \(APCDD1\) gene located in 18p11.2 has been also been associated with androgenetic alopecia (rs3185480). This latter polymorphism is interesting because \(APCDD1\) is a Wnt signaling inhibitor.\(^{35}\) The identification of a new susceptibility autosomal gene in these autosomal loci suggests that nonandrogen-dependent pathways are also involved in androgenetic alopecia pathogenesis.\(^{36}\)

**Pathways Signaling Related to Androgenetic Alopecia**

Relatively few studies have used expression analyses because of difficulties in obtaining scalp biopsies. Various genes such as \(BMP2, ephrinA3, PGDS, PGD2, BDNF, neurotrophin-3 protein, neural growth factor-\(\beta\), ASS1\) and \(GDNF\) have been found to be differentially expressed in dermal papilla cell culture and scalp biopsy samples from patients with androgenetic alopecia. These genes may be involved in the development of androgenetic alopecia as either hair growth promoters or inhibitors, although more studies are needed to confirm these results.\(^{37,38}\)

Mirmirani \textit{et al.} identified 38 differentially expressed genes between the scalp vertex and frontal regions of 16 patients with androgenetic alopecia. Among the overexpressed genes were \(MSL3, L2, CD209, MUC7, SLC6A14\) and \(ANKRD20B\). The subexpressed genes included \(DUSP1, FOS, FOSB, CYR61, HBB, EGR1, ZFP36, MSA1, IGL13, ATF3, PSG3, EFCAB4B, KRTAP\) as well as various noncoding RNAs. These authors suggest a specific expression signature for these two regions.\(^{39}\)

Garza \textit{et al.} conducted a microarray global expression analysis with biopsies from the balding and occipital regions of 5 patients with androgenetic alopecia and found 250 differentially expressed transcripts. However, only the overexpression of prostaglandin synthase (\(PGDS\)) was relevant to the region of baldness and concluded that the \(PGDS\) product prostaglandin D2 (\(PGD2\)) inhibits hair growth by inducing a premature catagen phase.\(^{37}\)

Heilmann \textit{et al.} however, felt that there is no genetic evidence for the contribution of prostaglandins to the etiology of androgenetic alopecia as genome-wide association studies have not shown any association signals near these genes (\(PGDS\) and \(PGD2\)).
and suggested the role of the Wnt pathway because of the genotypic effect of WNT10A expression. The involvement of Wnt was also proposed by Leirós et al. who found that androgen action inhibits the canonical Wnt/B-catenin, leading to follicle miniaturization [Figure 2a-c].

The Notch signaling pathway is also involved in androgenetic alopecia. Midorikawa et al. found that increased androgen levels resulted in a negative feedback of gene expression of the Notch pathway, leading to miniaturization of the hair follicle and overexpression of the AR gene. Both the Notch and the Wnt pathways are directly affected by androgen expression in androgenetic alopecia.

Epigenetic Changes in Androgenetic Alopecia

It has been demonstrated that epigenetic mechanisms involved in histone or DNA methylation modulate the accessibility of genes to the transcriptional machinery and are involved in gene regulation activities in which genomic DNA sequences remain unchanged. However, few studies have evaluated the role of epigenetics on hair follicle physiology and androgenetic alopecia etiology.

Recent studies have focused on methylation patterns of specific genes such as the AR gene. Cobb et al. investigated methylation patterns on the AR gene in occipital hair follicles and affected follicles and observed an increase in AR gene methylation in occipital follicles, suggesting that increased AR gene methylation protects the occipital follicles against miniaturization and hair loss. Another study demonstrated that mice lacking the expression of DNA methyltransferase 1 (DNMT1) in the skin produced a baldness phenotype. DNMT1 is involved in the establishment and regulation of methylation patterns for tissue-specific cytokines, suggesting that the activity of this gene may be relevant for the development of androgenetic alopecia.

Conclusion

Androgenetic alopecia is a multifactorial dermatological condition with a complex genetic inheritance. Miniaturization of the hair follicles is the hallmark of androgenetic alopecia. Microinflammation in the follicular bulge plays an important role in the disruption of stem cells resulting in fibrosis of the perifollicular zone and irreversible miniaturization.

Maternal inheritance in androgenetic alopecia may largely be explained by the locus AR in the X chromosome. Androgens are crucial in androgenetic alopecia as they inhibit the expression of Wnt/B-catenin and produce a negative feedback in Notch signaling, both leading to miniaturization of the hair follicle. The discovery of overexpression of the prostaglandin synthase gene (PGDS) and overproduction of prostaglandin D2 (PGD2) is being explored for future potential therapies.

More studies of androgenetic alopecia at the molecular level are necessary as studies performed to analyze epigenetics are gene-specific. It will be relevant to know the global methylation profile of patients with androgenetic alopecia to identify other
genes involved in this condition. Despite these important recent contributions, there is still much to learn about androgenetic alopecia molecular pathophysiology.

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Conflicts of interest
There are no conflicts of interest.

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