Update on the Pathogenesis, Genetics and Medical Treatment of Patterned Hair Loss

Eric S. Schweiger MD,[a,b] Olga Boychenko DO,[a,c] Robert M. Bernstein MD[a,d]

[a]Bernstein Medical-Center for Hair Restoration, New York, NY
[b]Department of Dermatology, Mount Sinai Medical Center, New York, NY
[c]Philadelphia College of Osteopathic Medicine, Philadelphia, PA
[d]Department of Dermatology, Columbia University, College of Physicians and Surgeons, New York, NY

ABSTRACT

Androgenic alopecia (AGA), or pattern hair loss, is a common condition that affects both men and women has been gradually increasing. The discovery of the androgen receptor (AR) gene and related genes has expanded the knowledge on the genetics of hair loss. These basic science studies, combined with more recent clinical studies, have led to a better understanding of the pathogenesis of AGA in both men and women. These genetic advances have also led to the development of a new screening test for AGA. Recently, in addition to the two currently approved U.S. Food and Drug Administration (FDA) medications (minoxidil and finasteride), a novel device was FDA-approved for the treatment of hair loss, the laser hair comb. Further studies are needed to verify the accuracy and validity of the genetic screening test and the efficacy of the laser hair comb.

INTRODUCTION

Androgenic alopecia (AGA) is the most common form of hair loss, affecting both men and women. In men with AGA (also known as male pattern baldness) hair is lost in defined patterns that have been described by the Hamilton and Norwood scales.[1,2] Female pattern hair loss (FPHL) is characterized by more diffuse thinning.

The prevalence of AGA in both sexes increases with age. In Caucasians, 30 percent of males over age 30 and 50 percent of males over age 50 are affected.[2] By age 80, 80 percent of Caucasian males will experience signs of AGA.[3] The prevalence of male AGA also varies by race.[4–6] Caucasian males are four times more likely to develop premature balding compared African-American males.[6]

FPHL is estimated to affect 21 million women worldwide and, while more common in older women, can have a relatively early onset.[7] FPHL affects 6–12 percent of women by age 20–30 years and up to 40–55 percent above age 70. Prevalence may vary by race.[8]

The purpose of this paper is to review several major advances in the study of AGA that have occurred over the past decade. These include identifying several key features in the pathogenesis of AGA; the discovery of the AR gene and related genes; further study of pharmacotherapy; the development of a new device for the treatment of AGA and the development of a novel genetic screening test for AGA.

METHODS

To review the current pathogenesis and treatment of androgenic alopecia, a literature review was performed between the dates January 1, 1942 and December 31, 2008. The following keywords were used for the PubMed search: "female androgenic alopecia," "male androgenic alopecia," "pathogenesis of female AGA/male AGA," "AR variants," "genetics in AGA," "Antigen Receptor variants in AGA," "mesenchyme-epithelial interactions" and "pathological molecular mechanisms in AGA." In total, over 65 original articles and expert reviews from major journals were reviewed.

RESULTS

The Hair Growth Cycle

The average human head has approximately 100,000–150,000 hair follicles, with each follicle growing approximately 20 individual hairs in a person's lifetime by way of the hair growth cycle. This cycle consists of three main phases: anagen, catagen and telogen. The anagen phase is the growth phase and the determinant of hair length. It is followed by a short transition stage called the catagen, which signals the end of the active growth of a hair. Finally, the telogen phase is the resting phase of the hair follicle. The club hair, which is a dead fully keratinized hair is the final product of a hair follicle in the telogen stage.[9]

Pathogenesis of Male Pattern Hair Loss (MPHL)

Genetically pre-programmed scalp follicles progress through long growth (anagen) cycles and short resting (telogen) cycles. Normally, 85–90 percent of the hair follicles are in anagen phase, 10–14 percent are in telogen and 1–2 percent in catagen. But, with each passage through the hair cycle, the duration of the anagen phase decreases whereas the telogen phase increases.[10] Hair loss occurs when there is a significant increase in the number of telogen hairs compared to anagen hairs, and it is marked by several key features which include alteration in hair cycle dynamics, follicular miniaturization and local hormonal factors such as androgens.

Alteration of Hair Cycle Dynamics

In males with androgenic alopecia, the duration of the anagen phase decreases whereas the telogen phase increases causing a reduction in the anagen to telogen ratio from around 12:1 to 5:1.[11] Since hair length is determined by the anagen phase, each passage through the cycle causes the length of the new anagen hair to be shorter than its predecessor. Eventually, the anagen phase being so short does not allow any time for the new hair to acquire enough length to reach the skin surface. Telogen hairs, which now make up an increasing percent of the total hair, are more loosely anchored to the follicle than anagen hairs, which explains the increased hair shedding. In addition, the latency period (kenogen phase) between telogen hair shedding and anagen regrowth becomes longer, ultimately leading to a reduction in the number of hairs present on the scalp.

Follicular Miniaturization

Follicular miniaturization is another phenomenon that accompanies hair loss, where the size of the follicle is reduced with each consecutive cycle. Thus, a proportion of the large (terminal) follicles become miniaturized (vellus) making hair significantly finer and more susceptible to falling out. In this process, the dermal papilla, the matrix and, ultimately, the hair shaft are affected.[11]

Androgens

In the first half of the twentieth century, androgens were recognized as a contributor to MPHL.[12] More recently certain androgens, in particular dihydrotestosterone (DHT) and testosterone, as well as the androgen receptor, have been shown to play a major role in MPHL. In a non-balding scalp, testosterone enters the follicular cell and is converted to DHT via the enzyme 5-alpha-reductase which exists in two forms, types I and II. Both isomers are found in scalp follicles.[11] While the precise physiologic function of type I 5-alpha-reductase is unknown, there is strong evidence that type II 5-alpha-reductase is a significant contributor to MPHL. It has been shown that men who are genetically deficient in type II 5-alpha-reductase do not experience MPHL.[12] In addition, treatment with finasteride, a selective inhibitor of type II slows the progression of MPHL and produces regrowth of hair in up to 66 percent of men.

After its conversion, DHT binds to the androgen receptor, a member of the steroid thyroid hormone nuclear super family, and acts as a transcription factor for androgen dependent genes.[13] In a balding scalp, the concentration of 5-alpha-reductase is increased; therefore, there is an increase in production of DHT. The concentration of androgen receptor is also increased, which leads to an over abundance of androgen dependent genes.[14]

Until recently, the location of action of androgen in the hair follicle has been uncertain, but recent research suggests that it occurs in the dermal papilla. The dermal papilla is critical for hair growth. All hair follicles are formed in utero and their spatial relationship is determined by follicle inducing/repressing molecules. Hair shaft production in the follicle is regulated by signals from both the dermal papilla as well as lateral signaling between the epithelial cell. Changes in hair size cause changes in dermal papilla volume and follicle cell number, but the relationship between hair and dermal papilla size remains constant. This suggests that alterations within the dermal papilla itself are the target for androgen medicated changes within the hair cycle and miniaturization of the follicle. In addition, dermal papilla cells from non-balding scalps produce soluble factors which stimulate the growth of human scalp cells (in vitro). On the contrary, human balding dermal papilla cells cause a significant reduction in human scalp cell growth (in vitro). Therefore, balding dermal papilla cells probably produce inhibitory factors, which cause the formation of smaller dermal papillae as well as smaller hairs in MPHL.[15]

Pathogenesis of FPHL

FPHL is a common form of hair loss affecting approximately 21 million women world wide.[7] Clinically it presents as a diffuse reduction in scalp hair density which mostly affects the crown and frontal scalp and is staged by the Ludwig scale system.[16] FPHL appears to be age dependent with both prevalence and severity increasing with age. Approximately 40–55 percent of women are affected above age 70. However, it can have a relatively early onset; with an estimated 6–12 percent of women affected between the ages of 20–30 years.[17]

It is important to differentiate FPHL from FPHL due to other medical problems. Iron deficiency anemia, fatty acid deficiency and thyroid disease are examples of conditions that can also lead to hair loss in women. In these conditions, hair loss occurs by a different mechanism than FPHL, and usually resolves after the underlying condition has been treated.[18–20]

Until recently, FPHL had been regarded as the female counterpart of male pattern hair loss (MPHL). FPHL resembles MPHL in that there is an alteration of the hair cycle with gradual reduction in the duration of the anagen phase, and progressive follicular miniaturization. There is also increased emphasis on the prolongation of the latent (kenogen) phase, (a period of persistent suspension of growth of the follicle after the hair shaft has been shed).

A study by Guarrera et al.[21] showed that the number of kenogen phases increased in parallel with vellus hairs and diminished the number of normal hair cycles, features that mark the progression of female AGA. Miniaturization is suggested by reduction in terminal to vellus ratio on scalp biopsies.[22] As the severity of FPHL increases the number of vellus follicles increases, demonstrating that miniaturization does occur. Interestingly, the terminal/vellus ratio also falls but only to a certain

grade in FPHL after which it begins to plateau. This suggests that miniaturization does not stop with vellus follicle formation, but actually progresses to follicular deletion.[23]

Androgens

It is now thought that the differences between male and female AGA are related to different androgenic affects. In the past, female AGA was believed to be associated with increased DHT levels by way of the same mechanism as in the males; however, recent studies have shown that, unlike men with MPHL, women with FPHL are characterized by increased production rates of testosterone, but not of DHT, suggesting that the concentration of 5-alpha-reductase is not crucial.[24]

While hormones do affect the hair growth cycle in females, the actual mechanism of this is unclear. In certain cases, female hair loss does seem to occur with hyperandrogenism and is accompanied by other signs such as hirsutism or polycystic ovarian syndrome (or PCOS).[9] However, not all women with hair loss show biochemical evidence of hyperandrogenism.[61] At this point in time, FPHL appears to be a multifactorial, genetically determined trait, with both androgen-dependent and androgen-independent mechanisms contributing to the phenotype.

The Genetics of Androgenic Alopecia

The increased concentration of the ARs in balding scalps has encouraged a surge of research that looked at differences in the DNA sequence of the genes encoding the receptor as well as AR regulatory sequences. Recently, patients with particular variants in the AR gene, were shown to have an increased risk of developing AGA.[27]

The AR gene is located on the X-chromosome and belongs to a family of nuclear transcription factors. The amino-terminal domain of the AR gene, which contains a region encoded by CAG repeats, is required for transcriptional activation. It has been hypothesized that an inverse relationship exists between repeat number and AR activity, whereby tracts of shorter size display greater activity than tracts of longer size.[28] In humans, the number of CAG repeats is polymorphic and expansion of this trinucleotide sequence has been shown to have clinical implications for human disease, such as PCOS, hirsutism and acne.[29,30]

One of the first studies to look at the clinical implications of AR gene variants was a study by Sawaya et al.[31] This study specifically looked to see if variations in number of CAG repeats within the AR gene had any clinical significance in the development of AGA. Normal lymphatic genomic DNA of 48 men and 60 women was analyzed and CAG repeats within the AR gene was amplified via PCR. After careful analysis, the study concluded that the number of CAG repeats correlates inversely with androgen levels and is associated with female hirsutism, acne and male balding. This conclusion opened up the door for a number of studies which aimed to identify the significance of certain genetic sequences in both male and FPHL.

MPHL

Ellis et al.[3] looked at whether polymorphism of the AR gene is associated with MPHL. This was accomplished by comparing allele frequencies of the AR gene polymorphisms in both an experimental group (n=446) and a control group (n=107). The experimental group was composed of men with cosmetically significant baldness. The majority (n=392) was over age 50, while a small subset (n=54) was between ages 18–30. The control group was composed of men over 50 years old with no indication of baldness. There were three AR gene polymorphisms of particular interest: (1) the StuI restriction fragment, (2) the CAG triplet repeat length and (3) the GCC triplet repeat lengths.

The study found that 98 percent of all balding men and 92.3 percent of older balding men had the StuI restriction fragment present in their DNA, compared to 76 percent of the non-balding control group. In addition shorter CAG and GCC triplet repeat lengths were more prevalent in the balding experimental group. The study concluded that that the AR gene StuI restriction fragment and shorter CAG and GCC triplet repeat lengths were associated with MPHL.

A more recent study by Prodi et al.[32] aimed at identifying more genes associated with male AGA. Subjects were pooled from remote villages in Central Sardinia in order to keep a small gene pool. Initially the researchers were looking to see if a particular section of the X-chromosome (Xq11-q12) was associated with AGA. The DNA from 200 subjects with AGA was compared to 200 controls. This was done by taking individual single nucleotide polymorphisms (SNP) within the region and using them as markers. Several SNPs were found to be associated with AGA, in particular SNP rs1352015. This SNP is located in close proximity to the EDA2R gene as well as the AR gene. This realization led to the second part of the study, in which the researchers looked at EDA2R in its relation to AGA.

In the second part of the study, 492 male subjects and 492 male controls were taken from the same region in Sardinia. Their DNA was inspected using similar methods as before, and the results showed that SNP rs 1385694 within the EDA2R gene was linked with AGA. The researchers concluded that the EDA2R gene is also associated with AGA.

FPHL

The initial study by Sawaya et al.[31] also encouraged researchers to examine if CAG repeat length had significance in the development of FPHL.

Westeberg et al.[33] showed that pre-menopausal women with relatively few CAG repeats in the AR gene had higher transcriptional activity of the receptor and displayed higher levels of serum androgens, than those with longer CAG repeat sequences. In addition, the study showed that short CA repeat regions of the ERb gene was associated with higher levels of androgens and lower SHBG levels than regions with many CA repeats. They concluded that serum levels of androgens in pre-menopausal women may be influenced by variants of both the AR gene and the ERb gene.

Ali et al.[34] looked at the role of CAG polymorphism as well as X-chromosome inactivation in women with varying degrees of hair loss. In this study, 235 post-menopausal women over age 45 with varying degrees of AGA were selected for genetic analysis. Their DNA was analyzed for CAG repeat length as well as X-inactivation status (X-inactivation refers to one X-chromosome becoming inactive in every female cell).[35] The study concluded that FPHL and facial hirsutism positively correlated with shorter CAG repeat length in post menopausal women over age 65. The study also demonstrated that X-inactivation showed skewing toward the shorter allele in this age group, meaning that the longer allele was expressed. In conclusion these findings support a role for the CAG repeat polymorphism of the AR gene in the development of post-menopausal facial hirsutism and FPHL.

Table 1 summarizes the findings of various studies on the genetics of AGA.[3,11,27,31–38]

Screening Test for Androgenetic Hair Loss

Findings from the above have led to the development of the Hair Genetic Test (hairdx.com), a screening test for predicting hair

TABLE 1.

Genes Involved in MPHL and FPHL

Study	Population	# Subjects	Gene Studied	Primary Findings
Sawaya et al. 1998	Male and Female	108 subjects	AR	CAG repeat length in AR may affect androgen mediated gene expression in hair follicles and sebaceous glands in men and women.
Ellis et al. 2001	Male	54 young subjects 392 older subjects 107 control	AR (particularly StuI restriction site)	Functional mutation in or near AR gene may explain the reported high levels of expression of this gene in balding scalp.
Westeberg et al. 2001	Female	1137 subjects	AR ERb	Serum levels of androgens in pre-menopausal women may be influenced by variants of both the AR gene and the ERb gene.
Hillmer et al. 2005	Male (who had at least two first degree relatives with early onset AGA)	391 subjects (201 subjects with AGA)	AR	Genetic variability in the AR gene is associated with early onset AGA.
Levy-Nissenbaum et al. 2005	Male	41 subjects 39 controls	AR (particularly StuI restriction site)	AR gene polymorphism is strongly associated with AGA.
Ellis et al. 2001	Male	1200 subjects (father/son)	AR	The identification of functional non-coding variants surrounding AR may have significance.
Hillmer et al. 2008	Male who had at least two first degree relatives with early onset AGA (same as Hilmer et al. 2005)	391 subjects (201 subjects with AGA)(same as Hilmer et al. 2005)	3q26 locus on X-chromosome	3q26 locus strongly linked to AGA.
Richards et al. 2008	Male	1125 men	20p11.22 locus on X-chromosome	One out of seven men who harbors risk alleles at AR and 20p11.22 will develop AGA.
Prodi et al. 2008	Sardinians	200 subjects 200 controls	EDA2R	EDA2R gene, (located on Xq11-q12, in close proximity to AR gene) is strongly associated with AGA
Ali et al. 2008	Female	235 subjects (post-menopausal aged >45 years)	AR gene	CAG repeat polymorphism of the AR gene plays a role in the development of post-menopausal facial hirsutism and FPHL.

loss. The goal of the test is to identify people who are at risk for AGA before they start developing any significant symptoms.

Due to the difference in pathogenesis in male and female AGA, the Hair Genetic Test is different for men and women. For men, the test examines a total of eight variants of the AR gene, including variants located on Chromosome 20. One of the most important variants of the AR gene is located at the StuI site, also known as rs6152. This variant is associated with changes in the hair follicle response to dihydrotestosterone leading to alterations in hair growth cycle. A man who tests positive for the variant has a 70 percent chance of developing AGA.[7,19,31,52] However, those who test negative have a 70 percent likelihood of not developing AGA.

In women of all ethnicities and in Asian males, the Hair Genetic Test measures the length of CAG and GGC repeats within the AR gene. Shorter CAG and GGC repeats are associated with a significant risk of developing AGA. For example, the percentage of female population with a CAG repeat length of 15 or less who suffer from Ludwig II or Ludwig III grade female FPHL is as high as 97.3 percent.

Treatment of AGA

There are several treatments available for AGA. Below is a brief summary of these therapies.

Minoxidil

Minoxidil is an arteriolar vasodilator acting specifically to open potassium channels. It was first introduced in 1970s as an oral antihypertensive agent but, after hypertrichosis was observed as a side effect, was made into a topical agent to stimulate hair growth.[39]

There is still a debate over the mechanism of action of minoxidil on hair growth. Some of the proposed mechanisms include vasodilatory and angiogenic properties, enhanced cell proliferation and DNA synthesis, potassium channel opening, antiandrogenic and immunosuppressive effects, and suppression of collagen synthesis. While the exact mechanism may not yet be elucidated, several randomized, double-blind, placebo-controlled trials have proven that minoxidil is efficacious.[22,40–50]

One study compared the efficacy of topical 5% solution with topical 2% solution and showed that men in the 5% group experienced 45 percent more hair growth in 48 weeks than the 2% group.[51] Another randomized double blind controlled trial of 5% minoxidil foam formula versus placebo showed a statistically significant increase in hair counts as well as a notably better subjective assessment of overall hair growth in the treatment group.[52]

Studies have also confirmed the efficacy of minoxidil in women. A randomized, double-blind, placebo-controlled trial comparing topical 5% solution with topical 2% and placebo in woman demonstrated statistically significant increased hair growth in both the 2% and 5% groups as compared to placebo.[53]

Most experts agree that the more recent the hair loss, the more success patients will have with the drug, especially if patients have a large number of partially miniaturized hairs. Unfortunately, significant hair loss is much more difficult to reverse. In addition, it is important to note that if patients discontinue using minoxidil, all its benefits will be lost.[39]

Finasteride

Finasteride is a potent 5-alpha-reductase type II inhibitor which lowers serum and scalp levels of DHT while increasing scalp levels of testosterone. It increases the growth rate and thickness of hair more than the actual hair count.[54] Finasteride was approved in 1997 for treatment of androgenic alopecia in men after large, double-blind, randomized, placebo-controlled studies showed it effectiveness. In total, 1,553 men with mild-to-moderate alopecia were randomized to receive 1 mg of oral finasteride per day or placebo for one year.[55] In addition, 1,215 men continued in blinded extension studies for a second year. Efficacy was evaluated by scalp hair counts, patient and investigator assessments and review of photographs by an expert panel. Finasteride treatment improved scalp hair by all evaluation techniques at both one and two years. In 51 percent of the patients, the hair loss stabilized, and 48 percent regrew hair. Several subsequent studies have validated the efficacy and safety of finasteride for males with androgenic alopecia.

In current practice, it is suggested that finasteride be taken for at least 12 months to evaluate its full effects; however, some response to finasteride may be seen as soon as four months. If successful, finasteride should be taken indefinitely or hair loss will resume.

The success of finasteride in treating MPHL is not seen in FPHL. Since finasteride is a category X drug, studies have thus far been conducted with post-menopausal women. In this population, finasteride does not appear to be effective at the 1 mg dose.[56] However, finasteride was found to benefit four women with hyperandrogenism, which suggests that not all FPHL has the same mechanism.[57] In the future, it may be learned that finasteride is successful for a subset of patients with FPHL or that it may be effective at higher doses.

Dutasteride

Dutasteride is an inhibitor of both type I and type II 5-alpha-reductase. It has enhanced efficacy compared to finasteride and in vitro is three times more potent in inhibiting type II and 100 times more potent in inhibiting the type I isomer. Dutasteride was approved in 2002 for treatment of symptomatic BPH at 0.5 mg daily, but has been used off-label by some physicians to

treat AGA. However, there have been few studies to assess its safety and efficacy for this indication. One study has compared dutasteride to finasteride. This study demonstrated that dutasteride 2.5 mg was superior to finasteride 5 mg at both 12 and 24 weeks at increasing target hair growths.[58]

Interestingly, dutasteride might prove to be efficacious in women. A case report has been published that describes a 46-year-old woman who had only limited improvement from finasteride, and was then placed on dutasteride (0.5 mg) and an oral contraceptive daily.[59] After six months she had thickening of hair shafts, and after nine months, the clinical diagnosis of AGA could not be made.

Fluridil

Fluridil is a topical antiandrogen used for treatment of hyperandrogenic skin syndromes. It is widely used through out Europe, but is still awaiting FDA approval in the U.S. A study by Kucerova et al.[60] tested the efficacy of 2% solution of fluridil in anhydrous isopropanol (Eucapil). This was an open clinical study consisting of female patients with mild-to-moderate AGA. Hair growth was evaluated at six and nine months using phototrichograms. The anagen to telogen ratio showed no significant statistical changes but after nine months there was no AGA progression. The anagen hair stem diameter was measured as well and did show a statistically significant increase after both six and nine months. With regards to safety, no changes in biochemical and hematological values were found. Overall, Eucapil may be an attractive alternative for treatment of female AGA.

Cyproterone Acetate

Cyproterone acetate is an oral antiandrogen. It acts by blocking androgen receptors and suppresses LH release which decreases testosterone levels.[61] It is currently not available in the U.S., but it is approved for use in the European Union as a treatment for hirsutism, acne and female alopecia, but is used less commonly for the latter indication.

Several studies have suggested that cyproterone, with or without ethinyl estradiol and spironolactone, can ameliorate female androgenic alopecia in women with normal hormone levels. A study by Rushton et al.[20] compared the efficacy of cyproterone (with ethynil estradiol) to placebo in 40 Caucasian pre-menopausal women and found that the experimental group had greater improvement of their alopecia over controls. The greatest improvement was in patients who had serum ferritin levels over 40 ug/l.

In another study, a 12-month, randomized trial looked at the effects of minoxidil 2% versus cyproterone acetate treatment on females with androgenic alopecia.[61] The study consisted of 66 women, half of whom received minoxidil 2% plus combined OCP, the other half received cyproterone acetate plus ethylene estradiol. The patients in the minoxidil arm had a mean increase in hair and those in the cyproterone group had a mean reduction on hair after the 12 months. The authors concluded that minoxidil is a superior treatment when there are no signs of hyperandrogenism, whereas cyproterone acetate treatment is effective when signs of hyperandrogenism are present.[26]

Laser Hair Comb

The HairMax® laser comb is non-invasive device that has been approved by the FDA for male AGA since 2005. While the exact mechanism of action is unknown, it is believed that this handheld device works by improving the scalp's blood circulation and stimulating the growth of individual hair follicles.

There has been one double-blinded study evaluating this device. In the study, male subjects who received treatment with the laser comb had a significantly greater increase in mean terminal hair density than subjects in the control group (P<0.0001). The treatment group also had significantly better subjective assessments of overall hair growth compared with subjects in the controls (P=0.010). No subject experienced any serious adverse events in either group.

The laser hair comb is designed to be used like a regular comb, three times a week in 15-minute sessions. If efficacious, results are expected to see results in eight to 16 weeks. Currently, the laser comb is only approved for men; however, the company has recently filed with the FDA for permission to market the device for females with pattern baldness and is awaiting their review. Further studies, especially long-term trials, are needed to verify the efficacy of this device in both men and women.

CONCLUSION

AGA is a common condition that affects both men and women. In recent years, new research has provided us with a better understanding of the pathogenesis and genetics of AGA. This knowledge is necessary for developing more effective treatment modalities and has led to the invention of a novel genetic test that may be able to predict which patients may develop AGA in the future. In addition to the current pharmacotherapy options, a novel hand held laser device has been FDA-approved to treat males with AGA. Continued research should reveal the clinical usefulness of new screening tests, the true efficacy of laser devices, the ideal dosing of currently available medications and, hopefully, bring a new array of medical therapies that are not yet under the radar.

DISCLOSURES

The authors have no relevant conflicts of interest to disclose.

REFERENCES

1. Hamilton JB. Patterned loss of hair in man: Types and incidence. *Ann NY Acad Sci.* 1951;53:708-728.

2. Norwood OT. Male pattern baldness: Classification and incidence. *South Med J*. 1975;68:1359-1365.
3. Ellis J, Stebbing M, Harrap SB. Polymorphism of the androgen receptor gene is associated with male pattern baldness. *J Invest Dermatol*. 2001;116:452-455.
4. Muller SA. Alopecia. Syndromes of genetic significance. *J Invest Dermatol*. 1973;60:475-492.
5. Hamilton JB. *Age, sex, and genetic factors in the regulation of hair growth in man: A comparison of Caucasian and Japanese populations. Montaaqna W, Ellis RA, editors. The Biology of Hair Growth*. New York: Academic Press; 1958:399-433.
6. Setty LR. Hair patterns of the scalp of white and Negro males. *Am J Phys Antropol*. 1970;33:49-55.
7. Leavitt M. Understanding and management of female pattern alopecia. *Facial Plast Surg*. 2008;24:414-427.
8. Paik JH, Yoon JB, Sim WY, et al. The prevalence and types of androgenetic alopecia in Korean men and women. *Br J Dermatol*. 2001;145(1):95-99.
9. Kligman A. The human hair cycle. *J Invest Dermato*l 1959l33:307-316.
10. Paus R, Cotsarelis G. The biology of hair follicles. *New Engl J Med*. 1999;341:491-497.
11. Ellis JA, Sinclair R, Harrap SB. Androgenetic alopecia: Pathogenesis and potential for therapy. *Expert Rev Mol Med*. 2002;4:1-11.
12. Jenkins EP, Andersson 5, Imperato-McGinley J, et al. Genetic and pharmacological evidence for more than one human steroid 5-alpha-reductase. *J Clin Invest*. 1992;89:293-300.
13. Janne OA. Androgen receptor and mechanism of androgen action. *Ann Med*. 1993;25:83-89.
14. Sawaya ME, Price VH. Different levels of 5alpha-reductase type I and II, aromatase, and androgen receptor in hair follicles of women and men with androgenetic alopecia. *J Invest Dermatol*. 1997;109:296-300.
15. Hamada K, Randall VA. Inhibitory autocrine factors produced by the mesenchyme-derived hair follicle dermal papilla may be a key to male pattern baldness. *Br J Dermatol*. 2006;154:609-618.
16. Ludwig E. Classification of the types of androgenetic alopecia (common baldness) occurring in the female sex. *Br J Dermatol*. 1977;97:247-254.
17. Birch MP, Messenger JF, Messenger AG. Hair density, hair diameter and the prevalence of female pattern hair loss. *Br J Dermatol*. 2001;144:297-304.
18. Hard S. Non-anemic iron deficiency as an etiologic factor in diffuse loss of hair of the scalp in women. *Acta Derm Venereol*. 1963;43:562-569.
19. Freinkel BK, Freinkel N. Hair growth and alopecia in hypothyroidism. *Arch Dermatol*. 1972;106:349-352.
20. Rushton DH, Ramsay ID. The importance of adequate serum ferritin levels during oral cyproterone acetate and ethinyl oestradiol treatment of diffuse androgen-dependent alopecia in women. *Clin Endocrinol*. 1992;36:421-427.
21. Guarrera M, Rebora A. Kenogen in female androgenetic alopecia. A longitudinal study. *Derm*. 2005;210:18-20.
22. Whiting DA. Scalp biopsy as a diagnostic and prognostic tool in androgenetic alopecia. *Dermatol Ther*. 1998;8:24-33.
23. Messenger AG, Sinclair R. Follicular miniaturization in female pattern hair loss: Clinicopathological correlations. *Br J Dermatol*. 2006;155;Iss 5;926-930.
24. Vierhapper H. Production rates of testosterone and of dihydrotestosterone in female pattern hair loss. *Metabolism*. 2003;52:927-929.
25. Futterweit W, Dunaif A, Yeh H-C, Kingsley P. The prevalance of hyperandrogenism in 109 consecutive female patients with diffuse alopecia. *J Am Acad Dermatol*. 1988;19:831-836.
26. Vexiau P , Chaspoux C, Boudou P, et al. Effects of minoxidil 2% vs. cyproterone acetate treatment on female androgenetic alopecia: a controlled, 12-month randomized trial. *Br J Dermatol*. 2002;146(6):992-999.
27. Hillmer AM. Genetic variation in the human androgen gene is the major determinant of common early-onset androgenetic alopecia. *Am J Human Genet*. 2005:140-148.
28. Hicky T, Chandy A, Norman RJ. The androgen receptor CAG repeat polymorphism and X-chromosome inactivation in australian Caucasian women with infertility related to polycystic ovary syndrome. *J Clin Endocrinol Metabol*. 2002; 87:161-165.
29. M, Nicolas MH, Craves JC, et al. Androgens in polycystic ovarian-syndrome. *Ann NY Acad Sci*. 1993;687:124-135.
30. Futterweit W. Polycystic ovary syndrome: Clinical perspectives and management. *Obstet Gynecol Surv*. 1999;54:403-413.
31. Sawaya ME, Shalita AR. Androgen receptor polymorphisms (CAG Repeat Lengths) in Androgenetic Alopecia, Hirsutism, and Acne. *J Cutan Med Surg*. 1998;3:9-15.
32. Prodi DA. EDA2R is associated with androgenetic alopecia. *J Invest Dermatol*. 2008;128:2268-2270.
33. Westeberg. Polymorphisms of the androgen receptor gene and the estrogen receptor beta gene are associated with androgen levels in women. *J Clin Endocrinol Metabol*. 2001; 86(6):2562-8.
34. Ali I, Dawber RPR, Wojnarowska FT. The role of the androgen receptor gene CAG repeat polymorphism and X-chromosome inactivation pattern in postmenopausal female pattern hair loss: O-16. *Br J Dermatol*. 2008:159(Suppl 1):8-9.
35. Lyon MF. The William Allan memorial award address: X-chromosome inactivation and the location and expression of X-linked genes. *Am J Hum Genet*. 1988;42:8-16.
36. Levy-Nissenbaum E. Confirmation of the association between male pattern baldness and the androgen receptor gene. *Eu J Dermatol*. 2005;15:339-340.
37. Hillmer AM. Genome-wide scan and fine-mapping linkage study of androgenetic alopecia reveals a locus on chromosome 3q26. *Am J Human Genet*. 2008;82(3):737-43.
38. Richards BJ. Male-pattern baldness susceptibility locus at 20p11. *Nature Genet*. 2008;40:1282-1284.
39. Rogers NE, Avrum MR. Medical treatments for male and female pattern hair loss. *J Am Acad Dermatol*. 2008;59):547-566.
40. Wester RC, Maibach HI, Guy RH, Novak E. Minoxidil stimulates cutaneous blood flow in human balding scalp: Pharmacodynamics

measured by laser Doppler velocimetry and photopulseplethysmography. *J Invest Dermatol*. 1984;82:515-7.
41. Galbraith GM, Thiers BH. In vitro suppression of human lymphocyte activity by minoxidil. *Int J Dermatol*. 1985;24:249-251.
42. Bunker CB, Dowd PM. Alterations in scalp blood flow after the epicutaneous application of 3% minoxidil and 0.1% hexylnicotinate in alopecia. *Br J Dermatol*. 1987;117:668-669.
43. Murad S, Pinnell SR. Suppression of fibroblast proliferation and lysyl hydroxylase activity by minoxidil. *J Biol Chem*. 1987;262:11973-11978.
44. Nuck BA, Fogelson SL, Lucky AW. Topical minoxidil does not act as an antiandrogen in the flank organ of the golden Syrian hamster. *Arch Dermatol*. 1987;123:59-61.
45. Pinnell SR, Murad S. Effects of minoxidil on cultured human skin fibroblasts. *Dermatologica*. 1987;175(Suppl 2):12-18.
46. Kvedar JC, Baden HP, Levine L. Selective inhibition byminoxidil of prostacycline production by cells in culture. *Biochem Pharmacol*. 1988;37:867-874.
47. O'Barr TP, Swanson EW, Fitzpatrick JE, Corby DG. Effect of minoxidil on platelet function and the synthesis of prostaglandins in platelets. *J Lab Clin Med*. 1989;114:575-578.
48. Mori O, Uno H. The effect of topical minoxidil on hair follicular cycles of rats. *J Dermatol*. 1990;17:276-281.
49. Buhl AE, Waldon DJ, Conrad SJ, et al. Potassium channel conductance: A mechanism affecting hair growth in vitro and in vivo. *J Invest Dermatol*. 1992;98:315-319.
50. Lachgar S, Charveron M, Gall Y, Bonafe JL. Minoxidil upregulates the expression of vascular endothelial growth factor in human hair dermal papilla cells. *Br J Dermatol*. 1998;138:407-411.
51. Olsen EA, Dunlap FE, Funicella T, et al. A randomized clinical trial of 5% topical minoxidil versus 2% topical minoxidil and placebo in the treatment of androgenetic alopecia in man. *J Am Acad Dermatol*. 2002;47:377-385.
52. Olsen EA, Whiting D, Bergfeld W, et al. A multicenter, randomized, placebo-controlled double-blind clinical trial of a novel formulation of 5% topical minoxidil topical foam vs. placebo in the treatment of androgenetic alopecia in men. *J Am Acad Dermatol*. 2007;57:767-774.
53. Lucky AW, Picquadio DJ, Ditre CM, et al. A randomized, placebo-controlled trial of 5% and 2% topical minoxidil solutions in the treatment of female pattern hair loss. *J Am Acad Dermatol*. 2004;50:541-553.
54. Price VH, Menefee E, Sanchez M, Kaufman KD. Changes in hair weight in men with androgenetic alopecia after treatment with finasteride (1 mg daily): Three- and 4-year results. *J Am Acad Dermatol*. 2006;55:71-74.
55. Kaufman KD. Finasteride in the treatment of men with androgenetic alopecia. Finasteride Male. *J Am Acad Dermatol*. 1998;39:578-89.
56. Price VH, Menefee E, Sanchez M, et al. Changes in hair weight and hair count in men with androgenetic alopecia after treatment with finasteride, 1 mg, daily. *J Am Acad Dermatol*. 2002;46:517-523.
57. Shum KW, Cullen DR, Messenger AG. Hair loss in women with hyperandrogenism: Four cases responding to finasteride. *J Am Acad Dermatol*. 2002;47:733-739.
58. Olsen EA, Hordinsky M, Whiting D, et al. The importance of dual 5-alpha reductase inhibition in the treatment of male pattern hair loss: results of a randomized placebo-controlled study of dutasteride vs.finasteride. *J Am Acad Dermatol*. 2006;55:1014-1023.
59. Olszewska M, Rudnicka L. Effective treatment of female androgenic alopecia with dutasteride. *J Drugs Dermatol*. 2005;4:637-640.
60. Kucerova R, Bienova M, Novotny R, et al. Current therapies of female androgenetic alopecia and use of fluridil, a novel topical antiandrogen. *Scripta Medica (Brno)*. 2006;79:35-48.
61. Neumann F. The antiandrogen cyproterone acetate: Discovery, chemistry, basic pharmacology, clinical use and tool in basic research. *Exp Clin Endocrinol*. 1994;102;1-32.

ADDRESS FOR CORRESPONDENCE

Eric S. Schweiger, MD
Bernstein Medical-Center for Hair Restoration
110 East 55th Street, Fl 11
New York, NY 10022
Phone: .....(212) 826-2400
E-mail:..... eric.schweiger@gmail.com