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Androgenetic alopecia: pathogenesis and potential for therapy

Justine A. Ellis, Rodney Sinclair and Stephen B. Harrap

Androgenetic alopecia occurs in men and women, and is characterised by the loss of hair from the scalp in a defined pattern. Determining factors appear to be genetic predisposition coupled with the presence of sufficient circulating androgens. The prevalence of this condition is high (up to 50% of white males are affected by 50 years of age) and, although there are no serious direct health consequences, the loss of scalp hair can be distressing. Knowledge of the pathogenesis of androgenetic alopecia has increased markedly in recent years. Pre-programmed follicles on the scalp undergo a transformation from long growth (anagen) and short rest (telogen) cycles, to long rest and short growth cycles. This process is coupled with progressive miniaturisation of the follicle. These changes are androgen dependent, and require the inheritance of several genes. To date, only one of these genes, which encodes the androgen receptor (*AR*), has been identified. Of the many treatments available for androgenetic alopecia, only two (finasteride and minoxidil) have been scientifically shown to be useful in the treatment of hair loss. However, these therapies are variable in their effectiveness. Discovery of the involvement of the *AR* gene, and the identification of other genes contributing to the condition, might lead to the development of new and more effective therapies that target the condition at a more fundamental level.

Justine A. Ellis (corresponding author)
Research Fellow, Department of Physiology, The University of Melbourne, Victoria 3010, Australia. Tel: +61 3 8344 0243; Fax: +61 3 9349 4519; E-mail: justine@unimelb.edu.au

Rodney Sinclair
Senior Lecturer, University of Melbourne Department of Dermatology, St Vincent's Hospital, Victoria Parade, Melbourne, Victoria 3065, Australia. Tel: +61 3 9288 3293; Fax: +61 3 9288 3292; E-mail: sinclair@svhm.org.au

Stephen B. Harrap
Professor and Head, Department of Physiology, The University of Melbourne, Victoria 3010, Australia. Tel: +61 3 8344 5836; Fax: +61 3 9349 4519; E-mail: s.harrap@unimelb.edu.au

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Androgenetic alopecia, which in men is often referred to as male-pattern baldness, is a common form of scalp hair loss that affects most males by old age (Ref. 1). The condition can also affect females; however, this is less well characterised and it remains controversial as to whether the two conditions are the same (Ref. 2). Certainly, the pattern of hair loss is different in women and the prevalence is lower than that in men (Ref. 3). Therefore, in this review article we will focus specifically on male androgenetic alopecia.

The onset of androgenetic alopecia is extremely variable, and appears to be determined by the presence of sufficient circulating androgens and the degree of genetic predisposition (Ref. 4). The condition is not a serious one from a medical perspective; however, the loss of hair is often an unwanted and stressful event for the patient (Refs 5, 6), and therefore might have considerable psychosocial consequences. Effective treatments are being developed and current research efforts, including the search for genes, are yielding much promising new information.

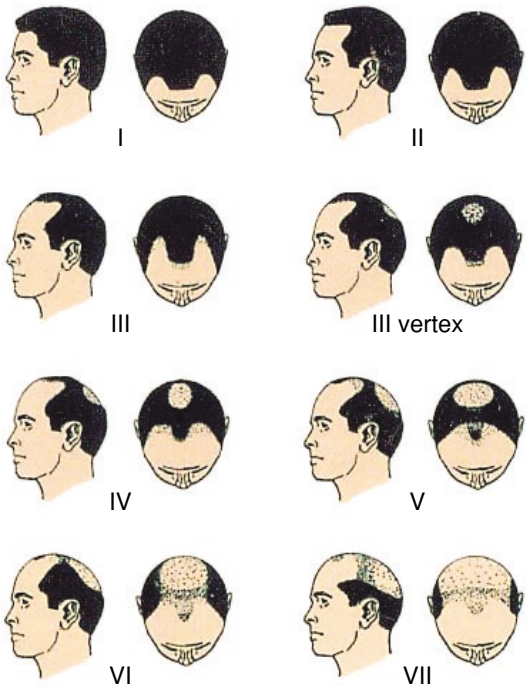
Another common form of alopecia is alopecia areata, which is an inflammatory form of hair loss that is thought to be autoimmune in origin. Both genetic predisposition and environmental influence lead to episodes of patchy terminal hair loss. The loss might completely reverse without leaving any scarring; alternatively, it might progress and result in the total loss of scalp hair (alopecia totalis) or the total loss of body hair (alopecia universalis). Alopecia areata occurs equally in males and females, and does not appear to be androgen dependent (Refs 7, 8).

Prevalence and clinical features of androgenetic alopecia

By 30 years of age, ~30% of white males have androgenetic alopecia; by 50 years of age, 50% are affected (Ref. 1). White males are four times more likely to develop androgenetic alopecia than are males of African origin (Ref. 9).

Hair loss follows a defined pattern, as described by the Hamilton–Norwood scale (Refs 1, 10) (Fig. 1), beginning with bitemporal recession of the frontal hairline. This is followed by diffuse thinning over the vertex (top) of the scalp, eventually leading to complete hair loss in this region. The bald patch progressively enlarges and eventually joins the receding frontal hairline. Ultimately, marginal parietal and occipital hair remains, and this might also continue to thin and be lost.

Although this pattern is typical of most cases of androgenetic alopecia, the rate of hair loss in the various scalp regions can produce visual



The Norwood—Hamilton scale of male-pattern baldness

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Figure 1. The Norwood–Hamilton scale of male-pattern baldness. The typical pattern of hair loss is divided into seven categories. No hair loss is termed 'type I'. Minor recession of the frontal hairline is termed 'type II'. Type III indicates further frontal loss, and is considered 'cosmetically significant'. The subset of type III, termed 'III vertex', shows significant frontal recession coupled with hair loss from the vertex region of the scalp. Types IV–VI show further frontal and vertex loss, culminating in type VII, in which only the occipital scalp region maintains significant amounts of hair. Reproduced from Norwood, O.T. (1973) Hair Transplant Surgery (1st edition), courtesy of Charles C. Thomas, Publisher, Ltd, Springfield, Illinois, USA **(fig001jem)**.

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variation. For instance, rapid vertex loss coupled with slower frontal regression can appear different from faster frontal, and slower vertex, loss. Less commonly, the frontal hairline can be preserved (Ref. 11).

Associations with other conditions

There is some evidence to support the hypothesis that male-pattern hair loss imparts an increased risk of cardiovascular disease (CVD). It would appear that men with androgenetic alopecia are more likely to develop CVD (Ref. 12); however, there is no evidence of an increase in conventional risk factors such as blood pressure and cholesterol concentrations (Ref. 13). Recent studies have also demonstrated an increased risk of benign prostatic hyperplasia (Ref. 14) and prostate cancer (Ref. 15) in those with male-pattern baldness; however, the molecular basis for this link has yet to be evaluated.

Pathogenesis of androgenetic alopecia

Androgenetic alopecia is the result of step-wise miniaturisation of the hair follicle and alteration of the hair-cycle dynamics (Ref. 16). The three phases of the normal hair cycle (Ref. 17) are shown in Figure 2. Pre-programmed follicles on the scalp progress through long growth (anagen) cycles and short rest (telogen) cycles. With each passage through the hair cycle, the duration of the anagen phase decreases whereas the telogen phase elongates. Because the duration of the anagen phase is the main determinant of hair length, the maximum length of the new anagen hair is shorter than that of its predecessor. Eventually, the anagen phase is so short that the emerging hair does not reach the skin surface and the only testimony to the presence of a functioning follicle is a pore. In addition, the latency period between telogen hair shedding and anagen regrowth becomes longer, leading to a reduction

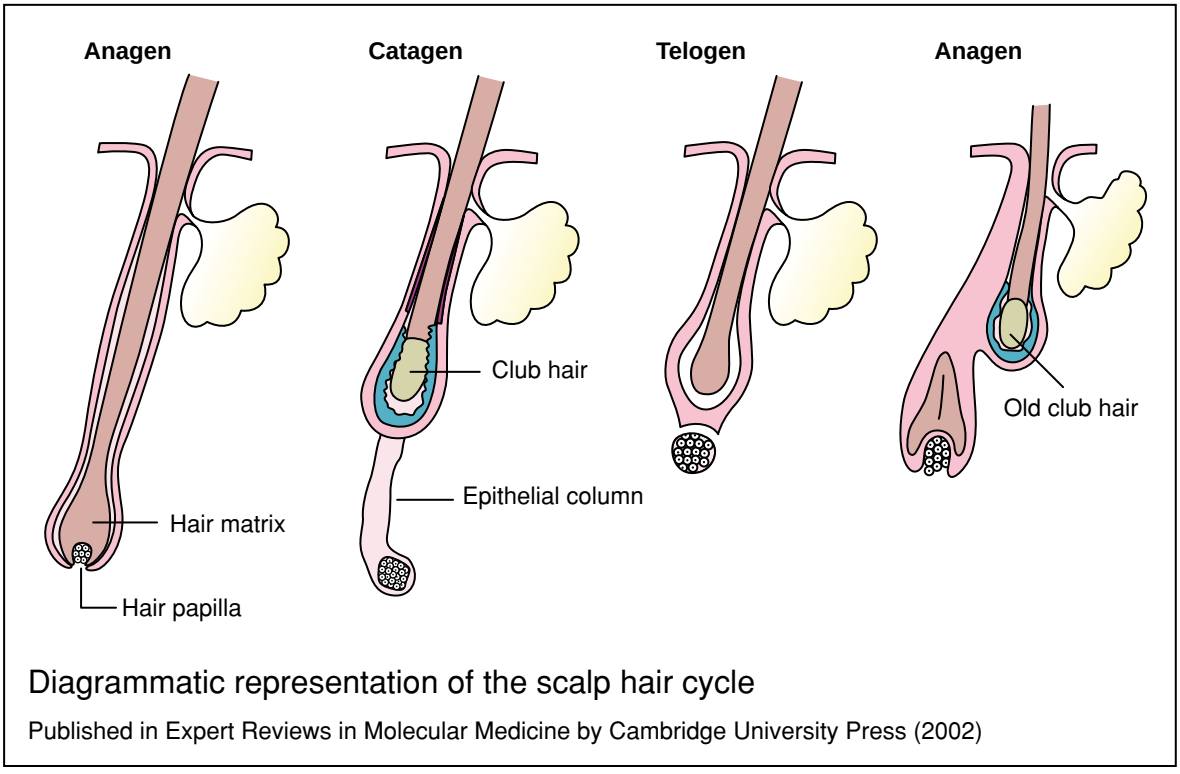

Figure 2. Diagrammatic representation of the scalp hair cycle. (a) During the normal hair cycle, the active growth phase (anagen) can last from 2 years up to 6 years. This is followed by a short transition phase (catagen), which lasts 1–2 weeks, and then by a resting phase (telogen), lasting 5–6 weeks. The hair is then shed, the anagen phase begins again, and a new hair is grown. In the altered hair cycle of the balding scalp (not shown), the phases of the cycle remain unchanged. However, the anagen growth phase becomes shorter and the telogen resting phase becomes longer with each passage through the hair cycle, resulting in diminishing hair length. Reproduced, with permission of the BMJ Publishing Group, from Sinclair, R. (1998) Male pattern androgenetic alopecia, BMJ 317, 865-869 **(fig002jem)**.

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in the number of hairs present on the scalp (Ref. 16). The follicular miniaturisation that accompanies these hair-cycle changes is global, affecting the papilla, the matrix and ultimately the hair shaft. The dermal papilla is fundamental to the maintenance of hair growth (Ref. 18) and is probably the target for androgen-mediated changes in the hair cycle and miniaturisation of the follicle (Refs 19, 20) (see below).

Involvement of androgen and the androgen receptor

Two predominant, naturally occurring androgens are the sex steroids testosterone and 5α-dihydrotestosterone (DHT). Testosterone is converted to DHT by the enzyme 5α-reductase (Fig. 3a), which exists as two isozymes: type I and type II (Ref. 21). Although the tissue distribution of the isozymes does vary, both are found in scalp follicles (Ref. 22). Androgens mediate their activities by binding to the human androgen receptor, a member of the steroid-thyroid hormone nuclear receptor superfamily. The structure of the androgen receptor includes a ligand-binding domain and a DNA-binding domain. Both testosterone and DHT can bind to the ligand domain, which activates the DNA-binding domain. The receptor–ligand complex then acts as a transcription factor, regulating the expression of androgen-sensitive genes (Fig. 3a) (Ref. 23). The androgen receptor is required for male development and, throughout adult life, for the normal functioning of organs such as the reproductive system, testes, muscles, liver, skin, nervous system and immune system (Refs 24, 25). The androgen receptor plays a role in several diseases and hereditary traits including prostate cancer, androgen insensitivity syndrome (Ref. 26) and spinal and bulbar muscular atrophy (Kennedy disease) (Ref. 27).

The involvement of androgens in androgenetic alopecia has been established for some time, and is well accepted. Eunuchs, who lack androgens, do not bald (Ref. 4). Individuals who lack a functional androgen receptor are androgen insensitive and develop as females; again, these individuals do not bald (Ref. 28). Similarly, no baldness is seen in pseudohermaphrodites, who lack 5α-reductase, the enzyme that converts testosterone to the potent androgen DHT (Ref. 29). The concentration of DHT has been shown to be higher in the balding scalp than in the non-balding scalp (Fig. 3b) (Ref. 30). In addition, increased concentrations of both 5α-reductase and the androgen receptor have been detected in the balding scalp (Ref. 31), suggesting that such changes contribute to hair loss. The exact mechanism(s) through which androgens act to cause baldness remain unclear; however, given that the complex formed between the androgen receptor and androgen acts as a transcription factor, it is likely that genes controlling follicle cycling are regulated by androgen. The expression of such genes will therefore be dependent on the concentrations of androgen and androgen receptor in the follicle (Fig. 3b).

Genetic models of androgenetic alopecia

Androgenetic alopecia – an autosomal dominant disorder?

The nature of the inheritance of genetic predisposition to androgenetic alopecia is unresolved. Although it is a popular belief that baldness is inherited from the maternal grandfather, the mode of inheritance is usually cited in the scientific literature as autosomal dominant, suggesting that the inheritance of only one autosomal gene conveys full genetic predisposition. However, there appears to be only one published comprehensive familial analysis of androgenetic alopecia, conducted by Dorothy Osborn in 1916 (Ref. 32). In this study of 22 families, it was concluded that a single autosomal gene, termed 'B', could account for genetic predisposition to baldness, acting in an autosomal dominant manner in men, and in an autosomal recessive manner in women. In other words, men are predisposed to baldness if they inherit either 'BB' or 'Bb'; however, women are predisposed only if they inherit 'BB'. The inheritance of androgenetic alopecia remains listed as autosomal dominant in such respected references as Victor McKusick's Online Mendelian Inheritance in Man (OMIM: http://www.ncbi.nlm.nih.gov/Omim; entry number 109200). However, the first real test of Osborn's hypothesis appeared in 1984, when Kuster and Happle re-assessed the inheritance of androgenetic alopecia (Ref. 33). They presented a strong argument for a more complex polygenic mode of inheritance of androgenetic alopecia, as described below.

The polygenic hypothesis

A trait determined by a single gene would be more likely to display two or more distinct phenotypes,

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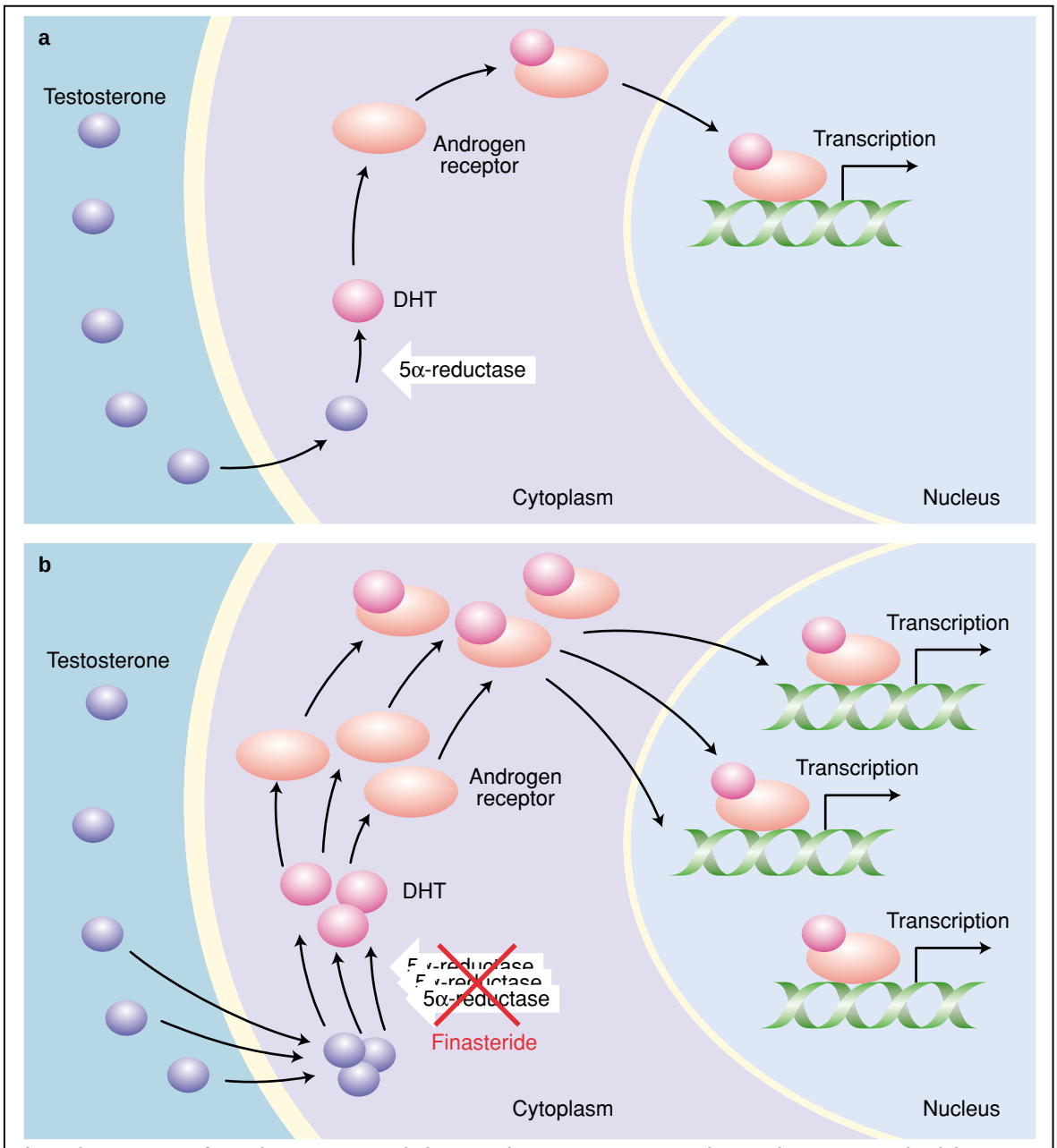

Involvement of androgens and the androgen receptor in male-pattern baldness

Figure 3. Involvement of androgens and the androgen receptor in male-pattern baldness. (a) In the non-balding scalp, testosterone enters the cell and is reduced to 5α-dihydrotestosterone (DHT) by 5α-reductase. DHT binds to the androgen receptor, and the complex moves into the nucleus, where transcription control of androgen-dependent genes occurs. (b) In the balding scalp, the concentration of 5α-reductase is increased, resulting in the increased production of DHT. Because the concentration of the androgen receptor also appears to be increased, more complexes are formed between androgen receptors and DHT, augmenting the regulation of androgen-dependent genes in the nucleus. The androgen-responsive genes that are involved in male-pattern baldness are yet to be identified. Finasteride, a type-II 5α-reductase inhibitor, reduces the production of DHT by blocking the action of the type II enzyme, thereby slowing the action of the androgen receptor. The site of action of minoxidil is yet to be determined. Future therapies might involve the prevention of the binding of DHT to the androgen receptor **(fig003jem)**.

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rather than a continuous distribution (Ref. 34). In Kuster and Happle's analysis, the distribution of androgenetic alopecia followed a normal distribution, representing the full range of phenotypes, from no evidence of hair loss, to fully developed baldness. This distribution is more consistent with a polygenic trait. In addition, Kuster and Happle pointed out that hereditary traits determined by a single gene rarely occur at a frequency greater than 1 in 1000. Although the exact frequency of androgenetic alopecia is difficult to ascertain, it has been estimated to be between 40% and 60% in men, further supporting a more pervasive mode of inheritance (Ref. 33).

The characteristics of a polygenic trait can be illustrated using a simplified four-gene model (Ref. 35). Consider a scenario whereby predisposition to androgenetic alopecia is determined by four distinct genes, each contributing 25%. Inheritance of none of these genes obviates genetic predisposition to androgenetic alopecia. Inheritance of one gene predisposes to some hair loss later in life. Inheritance of two or three of these genes predisposes to hair loss during middle age, whereas inheritance of all four genes predisposes to hair loss at a young age. In reality, androgenetic alopecia might depend on more or fewer than four genes, each of which might contribute variably to predisposition.

Father-to-son transmission

A recent study of the inheritance of baldness examined fathers and sons who had participated in the Victorian Family Heart Study (VFHS) – a study of 3000 healthy Caucasian individuals belonging to 828 family groups living in the state of Victoria, Australia (Ref. 36). The VFHS was designed to examine risk factors associated with CVD that might include androgenetic alopecia. Males were surveyed for degree of baldness, and concordance was examined between 54 balding adult sons and their fathers. Under a model of autosomal dominant inheritance, sons might be expected to inherit baldness equally from their mothers and fathers. However, 81.5% of balding sons were found to have fathers with cosmetically significant baldness (type 3 or greater on the Hamilton–Norwood scale), considerably exceeding the autosomal dominant expectation (Ref. 36). These findings are consistent with a polygenic mode of inheritance, which includes a paternally inherited gene, and this polygenic model remains the most likely basis of androgenetic alopecia.

Genes involved in androgenetic alopecia

The identification of genes that are involved in androgenetic alopecia has been hindered by difficulties geneticists have faced when using classical genetic analysis techniques to study the condition. In general, these techniques compare the DNA sequences of unaffected and affected individuals, either from large family groups in which the presence or absence of baldness is known for all family members, or from large groups of unrelated affected and unaffected individuals. In both cases, it is vitally important that the presence or absence of baldness is correctly diagnosed. This is difficult given the variable age of onset of the condition. For example, is a 30-year-old man with a full head of hair guaranteed not to carry genetic predisposition?

In recent studies, the sequences of several candidate genes were compared between groups of individuals who were considered to be most and least genetically predisposed to androgenetic alopecia (Refs 36, 37, 38). These are, respectively, young males who have a significant degree of baldness and older males who have no indication of hair loss. Candidate genes for androgenetic alopecia were chosen because of their relevance to the hypothesis that androgens are involved in this form of hair loss.

Candidate genes

The 5α-reductase genes

As mentioned earlier, the concentrations of both DHT and 5α-reductase are increased in the balding scalp (Refs 33, 31), whereas the concentration of testosterone remains the same (Ref. 39). The involvement of DHT, rather than testosterone, in the hair-loss process implicates the genes that encode the 5α-reductase enzymes, *SRD5A1* and *SRD5A2*, in male-pattern baldness because 5α-reductase converts testosterone to DHT. However, analyses of these genes using case–control association and familial linkage studies have shown that it is unlikely that they contribute to androgenetic alopecia (Refs 36, 40).

The aromatase gene

The enzyme aromatase converts androgens, such as testosterone, to oestrogens, and appears to be present at decreased concentrations in the balding

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scalp (Ref. 31). The autosomal gene encoding aromatase, *CYP19*, was compared between cases and controls but no differences were detected (Ref. 37), suggesting that it is unlikely that the aromatase gene is involved in determining predisposition to androgenetic alopecia.

The Y chromosome

The observed father-to-son transmission of androgenetic alopecia raises the hypothesis that a gene on the Y chromosome might contribute to the condition. In addition, the Y chromosome determines sex and the concentrations of sex steroids such as testosterone and DHT (Ref. 41). However, examination of the non-recombining region of the Y chromosome has demonstrated that it is unlikely that causative mutations occur in any genes contained in this region (Ref. 37). Although most of the Y chromosome does not recombine, it remains possible that mutations that contribute to predisposition to androgenetic alopecia occur in genes that are contained on the ends of the Y chromosome, in the so-called pseudoautosomal regions, which recombine with the X chromosome. Further study will be required to determine if this is the case.

Discovery of the first gene associated with androgenetic alopecia: the *AR* gene

Because an increased concentration of androgen receptor is associated with the balding scalp (Ref. 31), differences in the DNA sequence of the gene encoding the androgen receptor, or in the *AR* regulatory sequences, might lead to differences in the concentration or activity of the receptor. Such differences might increase sensitivity to DHT in balding individuals, leading to hair loss at an earlier age.

On comparing the *AR* gene sequence found in case and control individuals, a significant difference was found between the two groups in the frequency of a single base change in the coding region (exon 1) of the gene. This polymorphism does not alter the amino acid sequence of the protein and is therefore unlikely to be functional. However, it is likely that the polymorphism is tightly linked to other functional sequence changes. All but one of the 54 young, bald men studied carried the non-functional variant of the *AR* gene (Ref. 38). Interestingly, 77% of non-bald men also carried this version of *AR*, suggesting that *AR* is necessary but not sufficient for causing baldness (Ref. 38). To date, *AR* functional mutations that are associated with androgenetic alopecia have not been located. However, the results of this study nevertheless provide good evidence for the involvement of the *AR* gene in androgenetic alopecia. The likely functional difference(s) will be those in the sequence of the regulatory regions that cause relatively subtle increases in androgen-receptor production and activity in the cell (Ref. 38).

Further genetic research

If the *AR* gene is necessary but not sufficient for causing baldness (Ref. 38), it is possible that other genes might be acting in conjunction with *AR*. For example, genes other than *SRD5A1* and *SRD5A2* that control DHT production remain candidates. Given that the concentration of 5α-reductase is increased in the balding scalp, candidate genes might include those encoding transcription factors that regulate the production of 5α-reductase. Such genes have yet to be identified. The many other genes, known and unknown, that are involved in androgen production, regulation and responses might also be involved.

In addition to androgen-related genes, genes that are involved in patterning, signalling and hair-follicle morphogenesis are attracting much attention from researchers. All hair follicles are formed in utero. The spatial relationship of hair follicles is determined by the competing influences of follicle-inducing and follicle-repressing molecules. Interaction between the epidermis and dermis is required. Epidermal signals trigger the formation of the dermal papilla, and subsequent dermal signals direct epidermal downgrowth into the dermis that envelopes the dermal papilla and creates the hair follicle. Hair-shaft production from the follicle is regulated by signals from both the dermal papilla and lateral signalling between epithelial cells. These signalling pathways have been recently reviewed (Ref. 42). Important candidate areas include fibroblast growth factor, WNT proteins, β-catenin, LEF1, FOXN1, noggin, bone morphogenic protein 2 and 4, sonic hedgehog and its cognate receptor patched, platelet-derived growth factor A, follistatin and epidermal growth factor.

Therapeutic management of androgenetic alopecia

Without treatment, androgenetic alopecia is a progressive condition. Hairs decrease in number at a rate of ~5% per year (Ref. 43). Apart from

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various camouflage and surgical options (which are reviewed in Refs 44, 45), currently only two pharmaceutical treatments exist for the treatment of androgenetic alopecia in males: topical minoxidil and oral finasteride, both approved by the US Food and Drug Administration.

Minoxidil, a vasodilator, was originally used to treat high blood pressure (Ref. 46). However, following observations that patients treated with this drug showed increased hair growth, a topical formulation was developed that arrested the progression of hair loss and promoted the regrowth of a small amount of hair in ~40% of men (4% experienced medium-to-dense regrowth) (Ref. 47). Minoxidil appears to prolong the anagen growth phase by an as yet unknown mechanism, leading to a decrease in hair shedding, but it does not inhibit the biological process. Hence, once treatment is stopped, hair shedding rapidly resumes, with the loss of all minoxidil-stimulated hair growth (Ref. 48).

Finasteride is a synthetic azo-steroid that has been used for the treatment of androgenetic alopecia in males since 1997. It is a potent and highly selective 5α-reductase type-2 inhibitor (Ref. 49). It binds irreversibly to the 5α-reductase type-2 enzyme and inhibits the conversion of testosterone to DHT. Thus, although the pharmacological half-life is in the order of 8 h, the biological half-life is substantially greater. The administration of a daily dose of 1 mg reduces concentrations of scalp DHT and serum DHT by 64% and 68%, respectively (Ref. 50). The dose–response curve is non-linear, and therefore higher doses do not lead to significantly increased suppression of DHT or clinical benefit (Ref. 51). After 24 months of continuous use, 66% of patients experienced ~10–25% regrowth of their hair (Ref. 52). Most of the remainder showed no further hair loss, and only a few continued to lose hair. Continued use beyond 2 years does not appear to promote continued hair regrowth; instead the hair density stabilises with the retention of the newly acquired hairs (Ref. 52). If successful, the treatment should be continued indefinitely because the balding process continues once treatment ceases (Ref. 53).

Future potential for therapy

The importance of the elucidation of androgenetic alopecia genes

The discovery of the genes that are involved in predisposition to androgenetic alopecia will dramatically enhance our knowledge of the mechanisms both at the molecular and cellular level that result in hair loss. For example, identifying the functional sequence change in or around the *AR* gene will lead to the determination of the exact differences in androgen-receptor proteins between bald and non-bald men. With this knowledge, treatments can be designed that target and reverse these differences, thereby blocking specific hair-loss mechanisms. Current pharmaceutical treatments for androgenetic alopecia do not target specific cellular mechanisms in this way. Rather, they inhibit enzymes involved in the increase of androgens in the balding scalp; thus, they are suppressive rather than curative, with variable rates of success.

The use of androgen-receptor blockers

Although the involvement of the *AR* gene in androgenetic alopecia is a recent finding, the idea of blocking the action of the androgen receptor in an attempt to prevent the action of excess DHT in the scalp is not new. However, androgen-receptor antagonists that act systemically cannot be used to treat men, owing to the potential risks of gynaecomastia (an excessive development of the male mammary glands), feminisation and impotence. Therefore, methods must be developed that block the action of the androgen receptor only in scalp follicles.

Knowledge of the sequence differences between the *AR* gene in balding and non-balding men would allow the possibility of gene-therapy techniques that could selectively deliver the non-balding *AR* gene to hair follicles, preventing hair loss without any systemic effects. This possibility has been advanced by the development of a topical cream containing liposomes to deliver entrapped DNA selectively to hair follicles in mice (Ref. 54). In this study, the *lacZ* reporter gene was successfully targeted to the hair follicles in mice after topical application of the gene entrapped in liposomes, demonstrating the feasibility in the future of the selective and safe targeting to the hair follicles of genes relevant to androgenetic alopecia. In addition, the variability in the age of onset and severity of baldness among individuals indicates that it is likely that various numbers and combinations of predisposing genes will be identified. Assuming this proves to be the case, such treatments could be designed on a case-by-case basis to target precisely those genes involved in each individual.

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Conclusions

Despite the recent research efforts aimed at elucidating the mechanisms behind hair loss in androgenetic alopecia, there is some way to go before a thorough understanding of this condition is achieved. Given that androgenetic alopecia is heritable, identification of the genes involved should lead to a thorough understanding of the causes of this condition. Only on the acquisition of such knowledge will it be possible to design treatments that target the causes. Current pharmaceutical treatments are suppressive rather than curative, and success is variable. The recent association of the gene encoding the androgen receptor with androgenetic alopecia might provide an incentive for the development of better treatments; however, completely effective treatments are unlikely to be developed until a thorough understanding of this condition is achieved at the genetic and molecular level.

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References

1 Hamilton, J.B. (1951) Patterned loss of hair in man: types and incidence. Annal NY Acad Sci 53, 708-728
2 Norwood, O.T. and Lehr, B. (2000) Female androgenetic alopecia: a separate entity. Dermatol Surg 26, 679-682, PubMed Label: 20345216
3 Norwood, O.T. (2001) Incidenc□e of female androgenetic alopecia (female pattern alopecia). Dermatol Surg 27, 53-54, PubMed Label: 21143619
4 Hamilton, J.B. (1942) Male hormone stimulation is a prerequisite and an incitant in common baldness. Am J Anat 71, 451-480
5 Cash, T.F. (1999) The psychosocial consequences of androgenetic alopecia: a review of the research literature. Br J Dermatol 141, 398-405, PubMed Label: 20050124
6 Cash, T.F. (1992) The psychological effects of androgenetic alopecia in men. J Am Acad Dermatol 26, 926-931, PubMed Label: 92299711
7 Green, J. and Sinclair, R.D. (2000) Genetics of alopecia areata. Australas J Dermatol 41, 213-218, PubMed Label: 20556991
8 Randall, V.A. (2001) Is alopecia areata an autoimmune disease? Lancet 358, 1922-1924, PubMed Label: 21615388
9 Setty, L.R. (1970) Hair patterns of scalp of white and Negro males. Am J Phys Anthropol 33, 49-55, PubMed Label: 70241751
10 Norwood, O.T. (1975) Male pattern baldness: classification and incidence. South Med J 68, 1359-1365, PubMed Label: 76055283
11 Sinclair, R. (1998) Male pattern androgenetic alopecia. BMJ 317, 865-869, PubMed Label: 98421435
12 Lotufo, P.A. et al. (2000) Male pattern baldness and coronary heart disease: the Physicians' Health Study. Arch Intern Med 160, 165-171, PubMed Label: 20112280
13 Ellis, J.A, Stebbing, M. and Harrap, S.B. (2001) Male pattern baldness is not associated with established cardiovascular risk factors in the general population. Clin Sci (Lond) 100, 401-404, PubMed Label: 21157301
14 Oh, B.R. et al. (1998) Association of benign prostatic hyperplasia with male pattern baldness. Urology 51, 744-748, PubMed Label: 98272118
15 Hawk, E, Breslow, R.A. and Graubard, B.I. (2000) Male pattern baldness and clinical prostate cancer in the epidemiologic follow-up of the first National Health and Nutrition Examination Survey. Cancer Epidemiol Biomarkers Prev 9, 523-527, PubMed Label: 20273121
16 Courtois, M. et al. (1994) Hair cycle and alopecia. Skin Pharmacol 7, 84-89, PubMed Label: 94271589
17 Kligman, A. (1959) The human hair cycle. J Invest Dermatol 33, 307-316
18 Oliver, R. and Jahoda, C. (1989) The dermal papilla and the maintenance of hair growth. In The Biology of Wool and Hair (Rogers, G. et al, eds), pp. 51-67, Chapman and Hall, London, UK
19 Obana, N. and Uno, H. (1996) Dermal papilla cells in macaque alopecia trigger a testosterone-dependant inhibition of follicular cell proliferation. In Hair research in the next millennium (van Neste, D. and Randall, V, eds), pp. 307-310, Elsevier, UK
20 Randall, V.A. (1996) The use of dermal papilla cells in studies of normal and abnormal hair follicle biology. Dermatol Clin 14, 585-594, PubMed Label: 97380961
21 Jenkins, E.P. et al. (1992) Genetic and pharmacological evidence for more than one human steroid 5 alpha-reductase. J Clin Invest 89, 293-300, PubMed Label: 92105396
22 Eicheler, W. et al. (1995) Immunohistochemical

Accession information: (02)00511-2a.pdf (short code: txt001jem); 19 November 2002
ISSN 1462-3994 ©2002 Cambridge University Press

evidence for differential distribution of 5 alpha-reductase isoenzymes in human skin. Br J Dermatol 133, 371-376, PubMed Label: 96142562
23 Janne, O.A. et al. (1993) Androgen receptor and mechanism of androgen action. Ann Med 25, 83-89, PubMed Label: 93168417
24 Hiort, O, Holterhus, P.M. and Nitsche, E.M. (1998) Physiology and pathophysiology of androgen action. Baillieres Clin Endocrinol Metab 12, 115-132, PubMed Label: 99106738
25 McPhaul, M.J. and Young, M. (2001) Complexities of androgen action. J Am Acad Dermatol 45, S87-94, PubMed Label: 21402866
26 Avila, D.M, Zoppi, S. and McPhaul, M.J. (2001) The androgen receptor (AR) in syndromes of androgen insensitivity and in prostate cancer. J Steroid Biochem Mol Biol 76, 135-142, PubMed Label: 21278907
27 Butler, R. et al. (1998) Truncated forms of the androgen receptor are associated with polyglutamine expansion in X-linked spinal and bulbar muscular atrophy. Hum Mol Genet 7, 121-127, PubMed Label: 98046015
28 Griffin, J.E. and Wilson, J.D. (1989) The resistance syndromes: 5alpha-reductase deficiency, testicular feminisation and related disorders. In The Metabolic Basis of Inherited Disease (Scriver, C.R. et al, eds), pp. 1919-1944, McGraw Hill, New York, USA
29 Imperato-McGinley, J. et al. (1974) Steroid 5alpha-reductase deficiency in man: an inherited form of male pseudohermaphroditism. Science 186, 1213-1215, PubMed Label: 75048319
30 Schweikert, H.U. and Wilson, J.D. (1974) Regulation of human hair growth by steroid hormones. II. Androstenedione metabolism in isolated hairs. J Clin Endocrinol Metab 39, 1012-1019, PubMed Label: 75041332
31 Sawaya, M.E. and Price, V.H. (1997) 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 109, 296-300, PubMed Label: 97427905
32 Osborn, D. (1916) Inheritance of baldness. J Heredity 7, 347-355
33 Kuster, W. and Happle, R. (1984) The inheritance of common baldness: two B or not two B? J Am Acad Dermatol 11, 921-926, PubMed Label: 85080828
34 Harrap, S.B. (1994) Hypertension: genes versus environment. Lancet 344, 169-171, PubMed Label: 94293688
35 Harrap, S.B. and Watt, G.C. (1992) Genetics and the risk of coronary heart disease. Med J Aust 156, 594-596, PubMed Label: 92326669
36 Ellis, J.A, Stebbing, M. and Harrap, S.B. (1998) Genetic analysis of male pattern baldness and the 5alpha-reductase genes. J Invest Dermatol 110, 849-853, PubMed Label: 98281598
37 Ellis, J.A. and Harrap, S.B. (2001) The genetics of androgenetic alopecia. Clin Dermatol 19, 149-154, PubMed Label: 21290794
38 Ellis, J.A, Stebbing, M. and Harrap, S.B. (2001) Polymorphism of the androgen receptor gene is associated with male pattern baldness. J Invest Dermatol 116, 452-455, PubMed Label: 21154100
39 Dallob, A.L. et al. (1994) The effect of finasteride, a 5 alpha-reductase inhibitor, on scalp skin testosterone and dihydrotestosterone concentrations in patients with male pattern baldness. J Clin Endocrinol Metab 79, 703-706, PubMed Label: 94358066
40 Sreekumar, G.P. et al. (1999) Serum androgens and genetic linkage analysis in early onset androgenetic alopecia. J Invest Dermatol 113, 277-279, PubMed Label: 99399303
41 Capel, B. (1998) Sex in the 90s: SRY and the switch to the male pathway. Annu Rev Physiol 60, 497-523, PubMed Label: 98219165
42 Cotsarelis, G. and Millar, S.E. (2001) Towards a molecular understanding of hair loss and its treatment. Trends Mol Med 7, 293-301, PubMed Label: 21319691
43 Rushton, D.H. et al. (1991) Natural progression of male pattern baldness in young men. Clin Exp Dermatol 16, 188-192, PubMed Label: 92035679
44 Unger, W.P. (1996) What's new in hair replacement surgery. Dermatol Clin 14, 783-802, PubMed Label: 97380979
45 Sinclair, R.D. (1999) Androgenetic alopecia. In Handbook of Diseases of the Hair and Scalp (Sinclair, R.D, Banfield, C. and Dawber, R.P.R, eds), pp. 49-63, Blackwell Science, Oxford, UK
46 Devine, B.L, Fife, R. and Trust, P.M. (1977) Minoxidil for severe hypertension after failure of other hypotensive drugs. Br Med J 2, 667-669, PubMed Label: 78001076
47 Savin, R.C. (1987) Use of topical minoxidil in the treatment of male pattern baldness. J Am Acad Dermatol 16, 696-704, PubMed Label: 87166914
48 Olsen, E.A. and Weiner, M.S. (1987) Topical minoxidil in male pattern baldness: effects of discontinuation of treatment. J Am Acad Dermatol 17, 97-101, PubMed Label: 87280920
49 Olsen, E. (1997) Finasteride (1mg) in the

Accession information: (02)00511-2a.pdf (short code: txt001jem); 19 November 2002
ISSN 1462-3994 ©2002 Cambridge University Press

treatment of androgenetic alopecia in men (abstract). Aust J Dermatol 38, A316
50 Drake, L. et al. (1999) The effects of finasteride on scalp skin and serum androgen levels in men with androgenetic alopecia. J Am Acad Dermatol 41, 550-554, PubMed Label: 99426900
51 Roberts, J.L. et al. (1999) Clinical dose ranging studies with finasteride, a type 2 5alpha-reductase inhibitor, in men with male pattern hair loss. J Am Acad Dermatol 41, 555-563, PubMed Label: 99426901
52 Whiting, D.A. (2001) Advances in the treatment of male androgenetic alopecia: a brief review of finasteride studies. Eur J Dermatol 11, 332-334, PubMed Label: 21292784
53 Sinclair, R.D. (2001) Management of male pattern hair loss. Cutis 68, 35-40, PubMed Label: 21373494
54 Li, L. and Hoffman, R.M. (1995) The feasibility of targeted selective gene therapy of the hair follicle. Nat Med 1, 705-706, PubMed Label: 96071536

Further reading resources and contacts

Olsen, E.A. (1994) Disorders of Hair Growth. Diagnosis and Treatment. Macgraw Hill, New York, NY, USA

Sinclair, R.D, Banfield, C. and Dawber, R.P.R. (1999) Handbook of Diseases of the Hair and Scalp. Blackwell Science, Oxford, UK

Dawber, R.P.R. (1996) Diseases of the Hair and Scalp. Blackwell Science, Oxford, UK

Founded in 1996, the Australasian Hair and Wool Research Society is a not-for-profit organisation that aims to disseminate accurate, ethical, information on all diseases of the hair and scalp to the public. The Society's website provides detailed information, including patient brochures, on various hair conditions, and should be of interest to the medical profession as well as to patients.

http://www.alopecia.com.au

Features associated with this article

Figures

Figure 1. The Norwood–Hamilton scale of male-pattern baldness (fig001jem).
Figure 2. Diagrammatic representation of the scalp hair cycle (fig002jem).
Figure 3. Involvement of androgens and the androgen receptor in male-pattern baldness (fig003jem).

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