

Male androgenetic alopecia

Keywords

Androgenetic alopecia

Common baldness

Patterned hair loss

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Abstract

Male pattern hair loss is the most common cause of balding. The pathogenesis involves androgen, and in particular dihydrotestosterone, binding to androgen receptors in the dermal papilla of sensitive hair follicles. Hair follicle sensitivity is genetically determined and shows regional specificity. Androgen stimulation of scalp dermal papilla cells induces transforming growth factor beta (TGF- β) and results in cyclical miniaturization of the entire hair follicle. The resulting hair produced from that follicle is shorter and finer and provides less complete scalp coverage. In contrast androgen stimulation of beard dermal papilla cells produces insulin growth factor -2 (IGF-2) and results in cyclical enlargement of the entire hair follicle. The resulting hair produced from that follicle is longer and thicker and provides more complete facial skin coverage. Some degree of androgenetic alopecia is universal among ageing men, especially bitemporally, however less than half become bald in the Hippocratic sense. Although scalp hair coverage has little functional importance, it has cosmetic significance. Baldness changes the facial appearance of affected men. When that change is perceived as adverse it has the potential to produce emotional morbidity. © 2004 WPMH GmbH. Published by Elsevier Ireland Ltd.

Introduction

Androgenetic alopecia, also known as common baldness, hereditary baldness and androgenic alopecia is the most common cause of hair loss in men. It is distinctive due to the pattern of progression of the scalp hair loss. Genetically predisposed men initially develop bitemporal recession. Next they develop diffuse frontal loss and thereafter a bald patch over the vertex of the scalp. Ultimately all the hair over the crown is lost. The pathogenesis involves androgen-induced miniaturisation of terminal hairs into vellus hairs in affected regions of the scalp. Some degree of follicular miniaturisation and consequential hair loss is universal and is considered to be a physiological secondary sexual characteristic. Androgenetic alopecia only becomes a medical problem when the hair loss is excessive, premature and distressing to the patient. A number of medical treatments aimed at arresting the progression of the hair loss have become

available in recent years, and surgical treatments are constantly being refined. Substantial research into the biology of androgenetic alopecia has been conducted in recent years in a number of centres around the world and is continuing.

Cause

Alopecia means hair loss. The adjective androgenetic describes the two dominant causal factors, namely genetic susceptibility and androgens.

Genetic susceptibility

A familial tendency to androgenetic alopecia is well recognized as is racial variation in the prevalence of balding [1,2]. Genetic factors modify the magnitude of the hair follicle response to circulating androgens. Those with a strong predisposition bald in their teens, and

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those with a weak predisposition may not bald until they are in their 60s or 70s. Fewer than 15% of men have little or no baldness by the age of 70 [3]. Osborne, in 1916 suggested that the baldness gene behaved in an autosomal dominant manner in men and an autosomal recessive fashion in women [4]. A study in 1984 failed to show the bimodal distribution of phenotypes with clearly unaffected and clearly affected men and women as usually indicative of autosomal dominant disorders [5]. In contrast a range of phenotypes was observable that seemed to follow a normal distribution. This, together with the finding that baldness risk increases with the number of affected family members is more consistent with polygenic inheritance. Furthermore, inherited traits due to a single gene defect rarely have an incidence greater than 1:1000, whereas polygenic diseases are much more common, as in androgenetic alopecia.

A polygenic inheritance is supported by a recent Australian study that examined the frequency of baldness in the fathers of balding men [6]. Of the 54 father-son relationships, 81.5% of balding sons had fathers who had cosmetically significant balding. This figure greatly exceeded the proportion expected of an autosomal dominant pattern of inheritance. The same authors also recently described an association of male pattern baldness with a polymorphism of the androgen receptor gene on the X chromosome [7]. The androgen receptor gene *Stu1* restriction fragment length polymorphism was found in almost all (98.1%) young bald men, most older bald men (92.3%), but only in 77% of non-bald men. This polymorphism appears to be necessary for the development of androgenetic alopecia, but its presence in non-bald men indicated it is not sufficient for the development of androgenetic alopecia [6]. In addition several shorter triplet repeat haplotypes were found in higher frequency in bald men than in normal control subjects. These restriction fragment length polymorphism appear to be associated with a functional variant of the androgen receptor gene that is part of the polygenic inheritance of male common baldness. Of note, the androgen receptor gene is located on the X chromosome, which is passed on from mother to a male child.

Current modeling suggests the involvement of at least four genes that combine to modify

the age of onset, pattern of loss and rate of progression of androgenetic alopecia [1]. Other candidate gene and chromosomal regions have been examined. They include *SRDA1* and *SRDA5* coding for the two variants of the 5 α -reductase enzymes [7], the insulin gene [8], the aromatase gene, the gene for the E α oestrogen receptor, the non-recombinant area of the Y chromosome, and the type II insulin-like growth factor genes [1]. To date, no association has been found between any of the above-mentioned genetic areas and the tendency to go bald.

Hormonal influences

Systemic hormonal effects

The effect androgens have on follicles is site specific. Under the influence of androgens during puberty, small vellus hair follicles in the pubic, axillary, beard and chest enlarge into large terminal hairs. The same androgens miniaturize pigmented terminal scalp hairs into non-pigmented vellus hairs, but seem to have no effect on eyebrow or occipital scalp hair [9]. There is no satisfactory explanation for these discordant events.

The evidence that eunuchs [10], patients with androgen-insensitivity syndrome [11], and 5 α -reductase deficiency [12] do not bald suggests that androgenetic alopecia is induced by activation of follicular androgen receptors by dihydrotestosterone. Increased levels of dihydrotestosterone have been found in balding scalp compared with non-balding scalp [13] and androgen receptors have been found in hair follicle dermal papillae. However, the specific mechanism of the androgen effect on the hair follicle is not known.

Intrafollicular overactivity may be the result of local or systemic factors. Possible local factors include an increased number of androgen receptors, functional polymorphisms of the androgen receptor, increased local production of dihydrotestosterone, or reduced local degradation of dihydrotestosterone. Possible systemic factors are increased circulating androgens providing increased substrate for the conversion to dihydrotestosterone, or increased systemic production of dihydrotestosterone at distant sites such as the prostate gland.

Dihydrotestosterone binds the androgen receptor with five times the avidity of testos-

terone and is more potent in its ability to cause downstream activation [14]. The conversion of testosterone is catalysed by 5 α -reductase to dihydrotestosterone [9]. Two 5 α -reductase isoenzymes have been characterized, based on their different pH optima [15].

Type 1 5 α -reductase is found immunohistochemically in sebaceous glands, epidermis, eccrine sweat glands, apocrine sweat glands, and hair follicles (outer root sheath, dermal papilla, matrix), as well as in the endothelial cells of small vessels and the Schwann cells of cutaneous myelinated nerves.

In the skin the activity of the type 1 5 α -reductase is concentrated in sebaceous glands and is considerably higher in sebaceous glands from the face and scalp than in non-acne-prone areas. Northern blot studies revealed most abundant type 1 mRNA in neonatal foreskin keratinocytes, followed by adult facial sebocytes, and stronger expression in dermal papilla cells from occipital hair cells than from beard [16]. Type 1 is also found in the liver, adrenals and kidneys.

The type 2 enzyme has been found by immunohistochemistry to be in the dermal papilla, the inner layer of the outer root sheath, the sebaceous ducts and proximal inner root sheath of scalp hair follicles [17]. Regional studies showed the type 2 mRNA present in beard dermal papillae, but absent from occipital scalp and axillary dermal papillae. The type 2 isoenzyme in beard dermal papillae has three times higher activity than the type 1 5 α -reductase present in the occipital scalp and axillary dermal papillae.

The specific activity of 5 α -reductase in the hair dermal papillae exceeded those in other hair follicle compartments (connective tissue sheaths and outer root sheath) by a factor of at least 14 in the scalp and at least 80 in the beard. The beard dermal papilla cells appeared to generate more 5 α -dihydrotestosterone than those from non-balding scalp hair follicles. However, the individual freshly isolated intact dermal papilla was shown to possess considerably different levels of ex vivo enzyme activities [16].

Type 2 isoenzyme is also found in the prostate, testis, and liver. The effect of subtype-specific 5 α -reductase inhibitors on serum dihydrotestosterone levels has been studied. Type 2 5 α -reductase accounts for about 80% circulating dihydrotestosterone [14].

The relative contribution of circulating and locally produced dihydrotestosterone to activation of hair follicle androgen receptors in the balding scalp remains to be established. Furthermore, the evidence for a link between levels of circulating androgens and androgenetic alopecia remains inconclusive, with very few studies finding any association [18–20].

The severity of androgenetic alopecia cannot be correlated with the presence or density of terminal hairs on the trunk and limbs. There is also no correlation with libido or masculinity as defined by sebum excretion rate, body hair density, bone, skin and muscle thickness [21]. Thus it is likely that the normal levels of systemic androgens is adequate for the maximum production of dihydrotestosterone.

Local hormonal effects

Beard dermal papilla cells are known to secrete growth-inducing autocrine growth factors in response to testosterone, leading to an increase in dermal papilla size and enlargement of the hair follicle and hair cortex. This response is not seen with occipital scalp hair follicles when subjected to the same testosterone challenge [20,22]. Insulin-like growth factor-1 has been identified as a major component of secreted cytokines [23]. Similar investigations on dermal papilla cells from the balding scalp of the stump-tailed macaque show that testosterone inhibited the growth and proliferation of keratinocytes [24].

Studies examining distribution and expression of androgen receptors have shown varying results. Two studies show that androgen receptors are only found in the nuclei of dermal papilla cells [20,25]. Another study found more extensive follicular distribution of receptors including the hair bulb [26]. Comparing different anatomical sites, there appear to be higher numbers of androgen receptors in the pubic hair follicles and beard dermal papilla cells, with occipital scalp follicles expressing lower levels [27]. Further research is required to explain the seemingly paradoxical effect androgens have on different types of hair follicles.

Hair loss on the scalp progresses in an orderly and reproducible pattern, and is a function of factors intrinsic to each hair follicle. In vitro experiments have shown that the hair follicles are able to self-regulate their

response to androgens by regulating the expression of 5 α -reductase and androgen receptors [27-29]. This self-regulation is postulated to produce the quantifiable difference in androgen receptor numbers [27,30] and 5 α -reductase activity [28,31] that is observed between balding and non-balding areas of the scalp. This intrinsic regulation is best seen in hair transplantation experiments: occipital hairs maintain their resistance to androgenetic alopecia when transplanted to the vertex, and scalp hairs from the vertex transplanted to the forearm miniaturise at the same pace as hairs neighbouring the donor site [32].

Pathogenesis

The three key features of androgenetic alopecia pathogenesis are alteration of hair cycle dynamics, follicular miniaturisation and inflammation.

Hair cycle dynamics

Hair growth is cyclical. The hair cycle has three phases (Figure 1): anagen growth phase, catagen involutinal phase and the telogen resting phase [33]. Anagen lasts for 3–5 years, catagen 2 weeks and telogen 3 months. Thus the anagen to telogen hair count is usually in the order of 12:1. Hair shedding (exogen) occurs within the

telogen phase and the sub-phase of telogen that follows exogen is called the latent phase [34].

In androgenetic alopecia, the duration of anagen decreases with each cycle, whereas the length of telogen remains constant or is prolonged. This results in a reduction of the anagen to telogen ratio [1]. Balding patients often describe periods of excessive hair shedding, most noticeable while combing or washing. This is due to the relative increase in numbers of follicles in telogen.

As the hair growth rate remains relatively constant the duration of anagen growth determines hair length. Thus, with each successively foreshortened hair cycle, the length of each hair shaft is reduced. Ultimately, anagen duration becomes so short that the growing fails to achieve sufficient length to reach the surface of the skin, leaving an empty follicular pore.

In androgenetic alopecia, the latent phase is prolonged, reducing hair numbers, further contributing to the balding process [34].

Hair follicle miniaturisation

Hair follicles consist of mesenchymal and ectodermal components. The ectodermal part consists of an invagination of epidermis into the dermis and subcutaneous fat. The hair bulb contains the hair matrix which produces the hair shaft. The mesenchymal component is the dermal papilla, a small collection of specia-

Hair-Growth Cycle

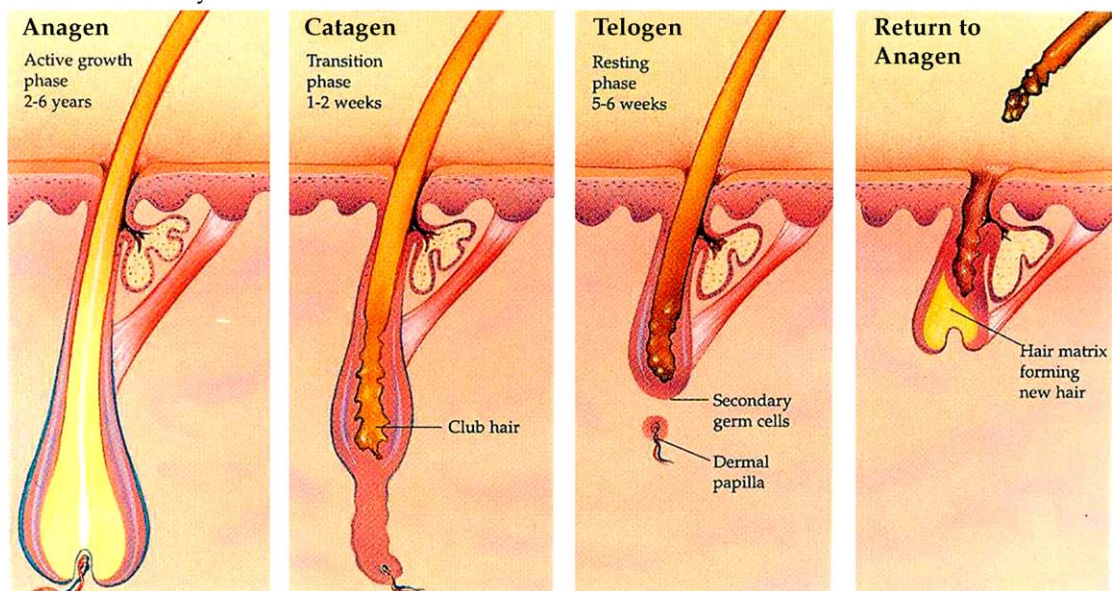


Figure 1 The normal hair growth cycle.

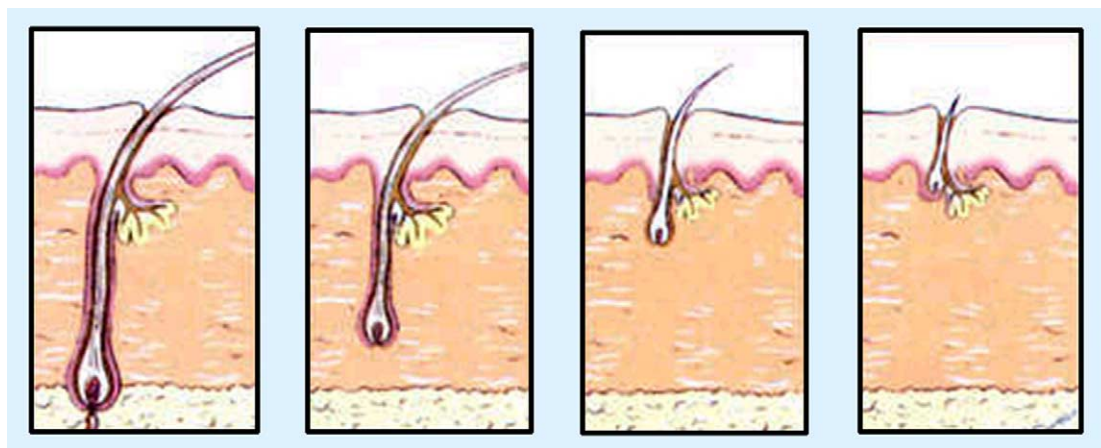


Figure 2 Androgenetic alopecia involves progressive, stepwise miniaturization of the entire hair follicle.

lised fibroblasts that is totally surrounded by the hair bulb. In association with the changes in hair cycle dynamics, there is progressive, stepwise miniaturisation of the entire follicular apparatus (Figure 2). As the dermal papilla is central in the maintenance and control of hair growth, it is likely to be the target of androgen-mediated events leading to miniaturisation and hair cycle changes [35-37]. The constant geometric relation between the dermal papilla size and the size of the hair matrix [38] suggests that the size of the dermal papilla determines the size of the hair bulb and ultimately the hair shaft produced [39].

A greater than tenfold reduction in overall cell numbers is likely to account for the decrease in hair follicular size [40]. The mechanism by which this decrease occurs is unexplained, and may be the result of either apoptotic cell death, decreased proliferation of keratinocytes [41], cell displacement with loss of cellular adhesion leading to dermal papilla fibroblasts dropping off into the dermis, or migration of dermal papilla cells into the dermal sheath associated with the outer root sheath of the hair follicle [39].

In overall volumetric terms, change in the follicular extracellular matrix is unlikely to greatly affect follicular size. However, being a potential source of biologically active molecules, small changes in its volume may affect hair follicular function [40].

Smaller follicles result in finer hairs. The caliber of hair shafts reduces from 0.08 mm to less than 0.06 mm. This is also followed by a reduction in pigment production. On the balding scalp, transitional indeterminate hairs are

the bridge between full-sized and miniaturised terminal hairs [42].

Traditional models of androgenetic alopecia show follicular miniaturization occurring in a stepwise fashion. This has recently been contested, and it is now believed that the transition from terminal to vellus hair occurs as an abrupt, large step process [43]. Either way the cross-sectional area of individual hair shafts remains constant throughout fully developed anagen [42], indicating that the hair follicle, and its dermal papilla, remain the same size. Therefore follicular miniaturization occurs between anagen cycles rather than within anagen.

This short window of androgen effect may also explain the lengthy delay experienced between clinical response and the commencement of therapy, as any pharmacological intervention will only have effect at the point of miniaturization [42]. Follicular miniaturisation leaves behind stellae as dermal remnants of the full-sized follicle. These stellae, also known as fibrous tracts or streamers, extend from the subcutaneous tissue up the old follicular tract to the miniaturised hair and mark the formal position of the original terminal follicle [44]. Arao-Perkins bodies can be seen with elastic stains within the follicular stellae. An Arao-Perkins body begins as a small cluster of elastic fibres in the neck of the dermal papilla. These are clumped in catagen and remain situated at the lowest point of origin of the follicular stellae. With the progressive shortening of anagen hair seen in androgenetic alopecia, multiple elastic clumps can be found in a stella, like the rungs of a ladder [45].

Inflammation

A moderate perifollicular, lymphohistiocytic infiltrate, perhaps with concentric layers of perifollicular collagen deposition, is present in 40% of cases of androgenetic alopecia, but only 10% of normal control subjects [44]. Occasional eosinophils and mast cells can be seen. The cellular inflammatory changes also occur around lower follicles in some cases and occasionally involve follicular stellae. The diagnostic and prognostic significance of the degree of the inflammation is not known [44].

Epidemiology in association with other disease

An estimated 30% of men developed androgenetic alopecia by the age of 30 and 50% by the age of 50 [46]. In Australia a study of 1390 men between the ages of 40 and 69 was conducted to determine the prevalence and risk factors for androgenetic alopecia. The prevalence of vertex or full baldness (Figure 3) increase with age from 31% (age 40–55) to 53% (age 65–69). A receding frontal hairline was found in 25% of men aged 40–55 and 31% aged 65–69. The factors found to be associated with baldness using unconditional logistic regression analysis were a higher weight and BMI at age 21, an early pubertal growth spurt and obesity as evidenced by waist size being in the fourth quartile at age 21 (more than 86 cm) compared with men in the first quartile (78 cm or less).

Androgenetic alopecia has, at various times, been associated with ischaemic heart disease [47–50]. These statistically significant, though weak, associations were discovered by epidemiological, cohort and case control studies. In general, severe early onset of androgenetic alopecia in young subjects before their 30s

have a higher risk for ischaemic heart disease [49]. A study found that men with higher grades of androgenetic alopecia (vertex balding) have a higher risk of developing ischaemic heart disease, especially among men with hypertension or high cholesterol levels [50]. However, most of these studies were conducted by non-dermatologists and no dermatologic expertise was included for confirmation of the accuracy of these studies.

Prostate cancer has also been found to be positively associated with androgenetic alopecia in various studies [51,52]. A recent large-scale Australian case-control study found that vertex balding was associated with a 50% increase in risk of prostate cancer [52]. No increased risk was seen for frontal balding or frontal concurrent with vertex balding. However, associations with high-grade prostate cancer were found in all patterns of androgenetic alopecia with the greatest statistically significant association found in men aged 60–69 years.

No clear mechanistic link between these diseases has been found. High androgen levels have been postulated to cause both androgenetic alopecia as well as atherosclerosis and thrombosis, however other data has shown no association between baldness and established coronary risk factors [53]. An association and a pathophysiological mechanism for the link between androgenetic alopecia and prostate cancer also remains to be established but may involve the dual dependence of these conditions on dihydrotestosterone [54].

Histopathology

Histological diagnosis is rarely necessary for male androgenetic alopecia. In patients where the diagnosis is equivocal, 4 mm punch biopsies are the ideal specimen, taken from the

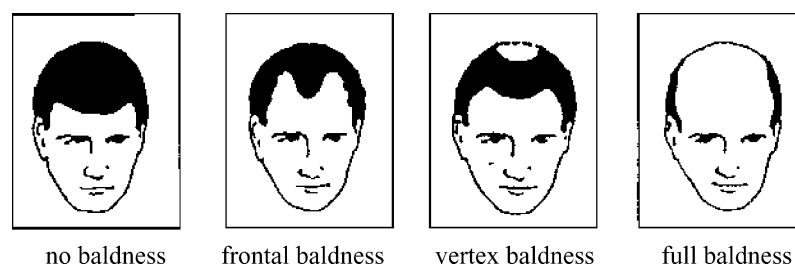


Figure 3 Patterns of hair loss in male androgenetic alopecia.

vertex of the scalp. Two biopsies should be taken and one sectioned horizontally and the other vertically. Horizontal sectioning yields much information on the number and types of follicles seen, facilitating more accurate diagnosis.

The prime feature found in scalp biopsies is the reduction in the terminal anagen hair count. The apparent reduction in the number of terminal hairs is due to progressive replacement of terminal hairs with secondary pseudo-vellus hairs with residual angiofibrotic tracts [55]. Horizontal sections reveal numerous pseudo-vellus hair follicles in the papillary dermis reflecting a miniaturisation process. Hairs are not destroyed. The presence of arrector pili muscle and angiofibrotic streamers distinguishes them from true vellus hairs. There is a change in the ratio of terminal to vellus hairs from greater than 6:1 to less than 4:1. Also, the anagen to telogen hair ratio reduces from 12:1 to 5:1 [45].

Others features that may be seen include follicular fibrosis and perifollicular inflammation. The fibrosis can be seen in around 10% of cases. However, fibrosis is seen in a small

number of normal scalp biopsies as well. The inflammation consists of a mild to moderate peri-infundibular lymphohistiocytic inflammatory infiltrate. It is present in up to two-thirds of biopsies [56], but is a non-specific feature that is also found in up to one-third of normal scalp biopsies [45].

Clinical syndrome

The clinical appearance of male androgenetic alopecia is universally and instantly recognizable in most cases. The progression of the hair loss occurs in an orderly manner and has been well documented [46,56] (Figure 4).

The main relevance of hair relates to socialization. Hair is an essential part of a person's self-image and the consequences of androgenetic alopecia are predominantly psychological. Several studies show that the negative self-perception of balding patients is consistent between Western [57,58] and Asian cultures [59]. The negative effect of androgenetic alopecia is often trivialized or ignored by unaffected people [60]. However, there is evidence that

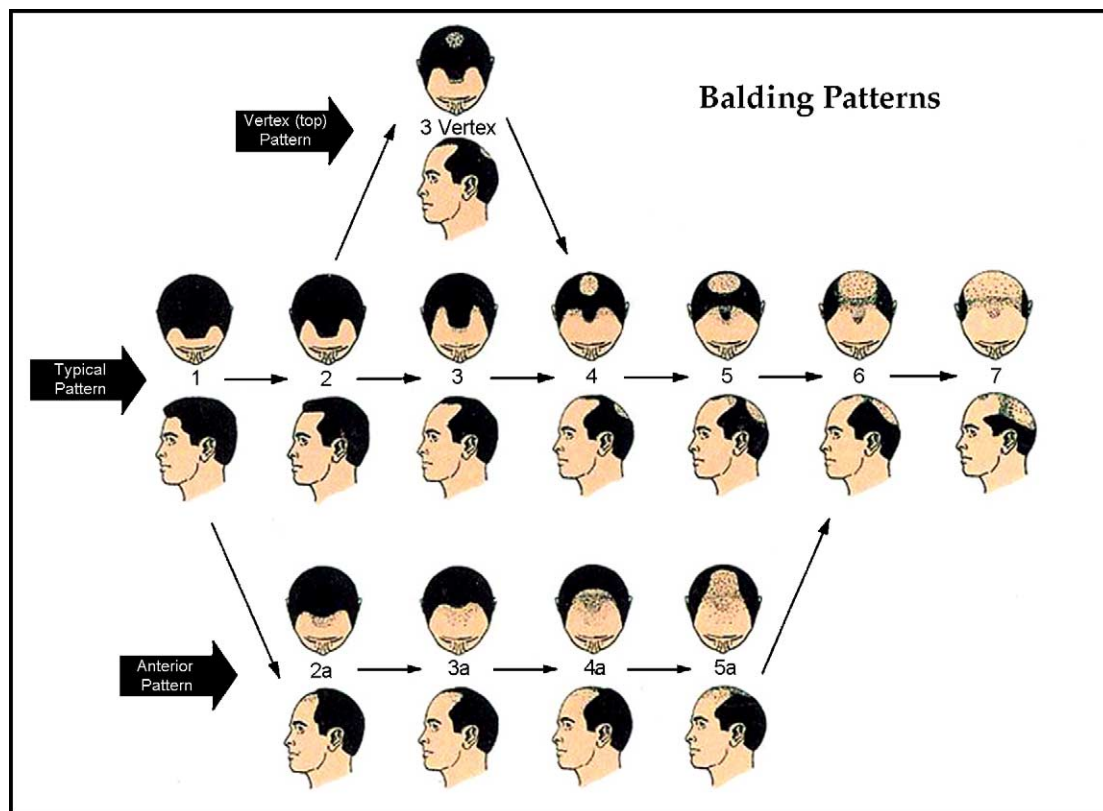


Figure 4 The Hamilton Norwood clinical grading scale for staging male androgenetic alopecia.

perception by others compounds the psychological problems suffered by balding men. A Korean study of the perception of balding men by women and non-balding men found that their negative perception of men with androgenetic alopecia was similar to the psychosocial effects reported by the patients themselves [59]. Of note a perception of bald men looking less attractive was found in more than 90% of subjects surveyed. Importantly, this view was more common in women than non-balding men. Such negative perceptions may further impair the social functioning of balding men.

It is important to note however, that most affected men cope well with androgenetic alopecia, without detriment to their psychosocial function. Thus those who do seek help are likely to be in greater emotional distress and have been dissatisfied with any treatment they have received to date.

The most distressed balding men are those with more extensive hair loss, those who have very early onset and those that deem their balding as progressive, often arising from observation of their father [57].

- Male androgenetic alopecia is inherited as a complex polygenic trait
- Androgens and in particular dihydrotestosterone are necessary for the development of hair loss in predisposed men
- The type 2 isoenzyme of 5 α -reductase converts testosterone into dihydrotestosterone
- Oral inhibitors of 5 α -reductase arrest progression of androgenetic alopecia in over 90% of men and partially reverse it in over 65%
- Hair follicle response to androgens shows regional specificity, with vertex scalp follicles miniaturizing and beard follicles enlarging
- Androgen stimulation of scalp dermal papilla cells induces TGF- β and androgen stimulation of beard dermal papilla cells produces IGF-2 as a second messenger

This review article is the first part of a two-part review series. The second part will be printed in the next issue of jmhg and will cover treatment of male androgenetic alopecia.

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