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Male pattern baldness: current treatments, future prospects

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Male pattern baldness affects up to half of the male Caucasian population by middle age, and almost all Caucasian men by old age. Especially in younger men, this heritable form of hair loss can have significant psycho-social consequences. Although approved pharmacological agents exist to manage the condition, none of the currently available options are highly efficacious. New treatments under development, and acceleration in our understanding of the underlying molecular genetic aetiology of this condition provide increased hope for future targeted treatment strategies.

Male pattern baldness (MPB), also known as androgenetic alopecia, affects up to half of the Caucasian male population by middle age. By age 80, over 95% of Caucasian males are affected to some degree [1]. This high prevalence in older men suggests that this form of hair loss may be considered a normal consequence of ageing. However, particularly in younger men, hair loss can have significant psycho-social manifestations [2,3]. Consequently the baldness treatment industry is worth billions of dollars worldwide annually [4]. A large proportion of this expenditure funds a section of the industry that preys on the eagerness of sufferers to halt their hair loss by pushing untested and usually worthless treatments [5]. However, there are now several approved pharmacological options shown by proper rigorous scientific processes to assist with the halting of hair loss and, in some men, may encourage renewed hair growth. Several more are currently being trialled for efficacy. These advancements are coupled with a growing understanding of the hair loss process and, in particular, the molecular mechanisms through which the process acts, furthering future potential for targeted therapeutic options based on disease aetiology.

Pathophysiology

Common patterned hair loss occurs in men and in women. In men, the pattern of loss follows the scale developed by Hamilton [6], and later extended by Norwood [7] (Fig. 1). The Hamilton–Norwood baldness scale defines seven distinct categories, beginning with type I representing no hair loss and a normal (prepubertal) frontal hairline. Type II demonstrates some mild frontal recession, but this category is not considered cosmetically significant. Types III–VII represent noticeable balding, incorporating frontal, and as the loss progresses, vertex hair loss. Even in the most severe categories, hair is retained on the occipital region of the scalp. Although this review focuses on MPB, it is worth pointing out to readers that the pattern of loss experienced by women is diffuse, manifesting itself as a widening of the central part, and is defined by the Ludwig scale [8]. The commonality of aetiology of these two conditions is a current topic of debate, thus the commonly used term for females is female pattern hair loss (FPHL) [9,10] (Table 1).

The process of hair loss is a progressive one, and is dependent on changes to the normal cycling of the hair follicle (Fig. 2). Follicles undergo a period of growth, known as anagen. In the normal state, this phase can last several years and result in scalp hair of some length. The anagen phase is followed by a brief transition phase, called catagen, where involution of the hair follicle occurs. Following this structural transition, the follicle enters telogen. This phase is hallmarked by a resting state, where the follicle appears dormant, followed by shedding of the hair from the follicle. Following telogen, the follicle returns to the anagen phase, and a new hair is grown [11,12]. In MPB, a perturbation of this cycle causes a progressive shortening of the anagen phase, coupled with a lengthening of the telogen phase. Over time, as the follicle moves through several cycles, the length of the hair that can be grown

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1359-6446/06/$ - see front matter doi:10.1016/j.drudis.2008.05.010

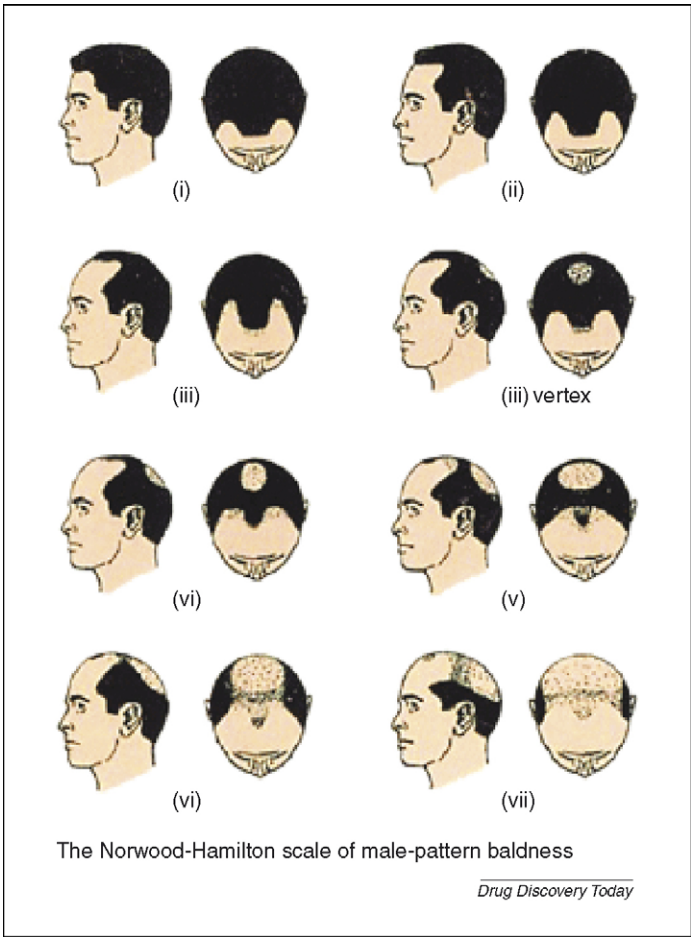

FIGURE 1

Hamilton–Norwood male pattern baldness scale. Reproduced from Norwood, O.T. (1973) *Hair Transplant Surgery* (1st edn), courtesy of Charles C. Thomas Publisher Ltd., Springfield, IL, USA.

shortens. This process is married with a miniaturisation of the follicle itself, the result of which is that with each hair cycle, the hair is shorter, finer and less pigmented. Eventually, the follicle becomes incapable of producing a hair that reaches the skin surface, and the region is recognised as bald [13].

The pattern on hair loss indicates that hair follicles undergo this balding process in a pre-programmed fashion. Loss initially occurs bitemporally, usually followed by vertex loss, with the eventual joining of the two balding regions. It is worth noting that the speed with which frontal and vertex loss occurs can vary, producing some variation in the usually recognised pattern types [14]. The lack of such programming of follicles in the occipital region of the scalp, and the fact that, if transplanted to balding regions, occipital follicles retain their non-balding characteristics, is a fascinating aspect of the biology of the balding process that has been exploited in follicle transplant techniques [15]. Defining the differences in the follicle biology between balding and occipital regions is also likely to unlock clues to MPB aetiology.

Aetiology

The use of the medical term androgenetic alopecia to describe MPB reflects current knowledge regarding the important role of both androgens and genes in MPB aetiology. It has long been known that the presence of testosterone in hair follicles is a pre-requisite for MPB. Common balding is not observed in eunuchs [16]. The more specific role of androgen is also demonstrated by a lack of MPB in pseudohermaphrodites who lack a functional 5α-reductase type II enzyme [17]. This enzyme, along with its isozyme, 5α-reductase type I, is responsible for the conversion of testosterone (T) to dihydrotestosterone (DHT) [18]. Both T and DHT bind to the androgen receptor (AR) and effect transcription of androgen-dependent genes [19]. The importance of AR in the balding process is further demonstrated by reduced prevalence of MPB in individuals with Kennedy's Disease in whom partial androgen insensitivity is caused by the loss of receptor function [20].

The crucial role of genes in MPB is also well-recognised. The observation that baldness runs in families was made in the early 1900s by Osborn [21]. Initially an autosomal dominant mode of inheritance was postulated. However, MPB is now recognised as a genetically multifactorial trait, with a complex underlying genetic architecture [22,23]. Interestingly, many such multifactorial human diseases and traits are usually hallmarked by a complex interplay of genetic and environmental risk factors. By comparison, twin studies of MPB have demonstrated that risk of developing MPB is determined almost exclusively by genetic predisposition [24].

Little was known as to the genetic architecture of MPB until the late 1990s. Candidate gene association studies focused on genes related to the sex-steroid pathways, and were guided by reports of

TABLE 1

Summary of currently approved, and developing pharmacological agents for the treatment of male pattern baldness

Drug	Action	Status	Refs
Minoxidil	Unknown Vasodilation? Cell proliferation? Prostaglandin synthesis?	A	[4,36–40]
Finasteride	5α-reductase type II inhibition	A	[41–48]
Dutasteride	Dual 5α-reductase inhibition	D	[49–51]
Latanoprost	Prostaglandin analogue possible hair cycle regulator?	D	[52–55]
Ketoconazole	Anti-fungal Inhibition of inflammation? Anti-androgenic?	AO	[56–58]

A, approved for use in treating MPB; D, under development, not approved; AO, approved for the treatment of other conditions.

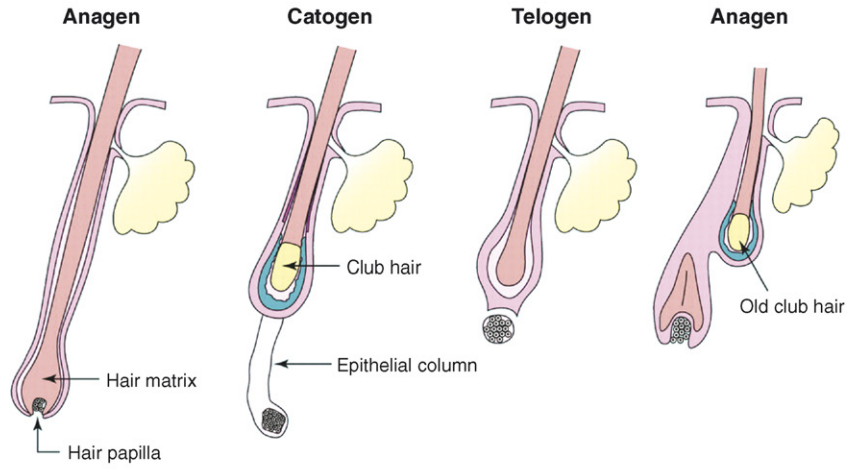

FIGURE 2

Phases of the hair follicle cycle. Growth of the hair occurs during anagen. The hair is shed at the end of telogen, and the follicle returns to anagen. In follicles undergoing the baldness process, anagen shortens and the follicle miniaturises. Reproduced from [14] with permission.

differing levels of expression of sex-steroid receptors and metabolising enzymes between balding and occipital regions of scalp. In relation to androgens, evidence emerged that both the 5α-reductase enzymes and the androgen receptor were more highly expressed in balding follicles compared to non-balding follicles on the same scalp [25,26]. Thus, the genes encoding 5α-reductase type I (*SRD5A1*) and type II (*SRD5A2*) [23] and *AR* [27] were examined. It was demonstrated that sequence variation in *AR* differed significantly between young balding men (high genetic predisposition) and older men with full heads of hair (low genetic predisposition). This finding earmarked *AR* as a gene responsible for increased risk of MPB [27], and has subsequently been confirmed in multiple independent studies [28–30]. Neither *SRD5A1* or *SRD5A2* were found to be associated with MPB [23]. However, advances in methodology used to more accurately identify genetic associations that include comprehensive consideration of sequence variants throughout the gene coding and non-coding regions in large sample sizes [31] provide impetus to return to these genes to further assess their involvement.

It has been estimated that AR may confer up to 40% of total genetic risk for MPB [29]. This is a high level of risk for a single gene involved in a multifactorial trait [32]. Even so, this estimation indicates that there are likely to be several as-yet unidentified genes that contribute to the remaining 60% of genetic predisposition. These genes may be involved, for example, in the sex-steroid pathways; they may be genes controlling hair follicle cycling, or they may include genes not yet known to be involved in hair growth and loss. Genome-wide association analyses, a hypothesis-free approach to gene discovery that has recently harvested several new genes for multifactorial diseases and traits such as diabetes and obesity [33,34], may be the best approach to identifying the remaining genes. It will not be until such genes are identified, and the function of important variation within them is understood, that we will achieve a proper understanding of the molecular mechanisms underlying MPB [35]. Such an understanding is crucial for targeted, effective development of pharmacological treatment regimes.

Currently approved treatments

The progressive, pre-programmed nature of MPB means that unless a therapeutic intervention occurs to halt the process, hair loss will become continually more severe. Particularly in younger men where hair loss is premature in comparison to the general population, the psycho-social consequences of this progressive baldness can be significant. Research-based and anecdotal evidence suggests significant decreases in self-esteem, and a higher incidence of anxiety, depression, aggressiveness and hostility in men with hair loss, often manifesting as social, personal and work-related difficulties [2,3]. Thus there is high motivation by sufferers to seek a cure for their hair condition that has led to an entire industry devoted to the sale of treatment products where the only proof of efficacy lies in manufacturer's claims. These include various herbal remedies [5]. However, there are government-approved treatments that have been shown in scientifically rigorous double-blind placebo-controlled trials to halt, and sometimes reverse the hair loss progress in a significant number of sufferers. Interestingly, these treatments are not based on knowledge of the underlying molecular aetiology of the hair loss process, but rather hair regrowth was identified as a beneficial side effect when these pharmaceutical agents were used to treat other conditions.

Minoxidil

The vasodilator minoxidil was initially approved as a drug to control hypertension [4]. Following observations that hypertensive patients taking minoxidil showed increases in hair growth, a 2% topical solution, and later a 5% topical solution of minoxidil was approved by the US Food and Drug Administration (FDA) for use as a treatment for MPB. In approximately half of men using minoxidil solution, the hair loss process is arrested by minoxidil.

In addition, a small percentage of men experience mild to moderate degrees of hair regrowth [36].

Minoxidil appears to halt hair shedding; however, the biological basis for this effect remains unknown. It was originally thought that the vasodilatory properties of this compound that served to increase blood supply to the scalp provided the mechanism through which minoxidil may exert its effects [4], perhaps by removing locally produced androgens from the follicles, but this has since been shown to be improbable [37]. Other proposed actions of minoxidil include stimulation of cell proliferation, and of prostaglandin (PG) synthesis [38]. It is not immediately clear how these properties might promote hair growth. It is known, however, that minoxidil does not permanently inhibit hair loss processes; cessation of minoxidil treatment is quickly followed by rapid shedding of hairs returning the scalp to an untreated state [39]. Despite these factors, minoxidil has become a mainstay in clinical management of MPB.

A recent advancement in the use of minoxidil as a hair loss treatment is the development of a 5% topical foam [40]. Efficient delivery of topical pharmaceuticals to relevant structures in the hair follicle in a cosmetically acceptable fashion is challenging. The traditional topical solution consists of a liquid vehicle with a tendency to spread beyond the intended site of treatment, and that takes time to dry. It also contains a high concentration of propylene glycol, a potential irritant. The newly developed topical hydroalcoholic foam is propylene glycol-free, and has been shown to be more easily applied specifically to target areas. Placebo-controlled double-blind trials have demonstrated that the hydroalcoholic foam is efficacious, safe and well accepted cosmetically by patients [40].

Finasteride

Finasteride is a synthetic azo-steroid that selectively inhibits the actions of the type II 5α-reductase enzyme [41]. Type II 5α-reductase is the predominant isozyme in prostate, and a 5 mg daily oral dose is approved for the treatment of benign prostatic hyperplasia (BPH) [42]. On the basis of the observed lack of balding in pseudohermaphrodites, who are naturally deficient in type II 5α-reductase, it was predicted that finasteride would also affect male pattern balding [43]. Dose ranging studies favoured a 1 mg daily dose [44]. The FDA-approved daily oral dose of 1 mg for the treatment of MPB has been demonstrated to reduce concentrations of DHT in scalp significantly, where type II 5α-reductase is also the predominantly (but not exclusively) expressed isozyme [45]. In many, but not all, men, hair loss is halted by finasteride treatment and in some men, there is noticeable hair regrowth within two years of treatment uptake [46]. The 1 mg daily oral treatment is well tolerated by patients, with rare side effects that may include some loss of libido and erectile function [47]. As for minoxidil, cessation of treatment recommences the balding process, indicating that the effects of finasteride are not curative [48].

Thus, neither of the approved MPB treatments is based firmly on an understanding of the molecular aetiology of the condition, or the pharmacological mechanism of action. The individual variability in efficacy, and the rapid return to the balding state when treatments are ceased, are therefore not surprising. However, there are treatments under development that are more firmly based on aetiological understanding that provide hope for more well targeted and more highly efficacious pharmacological options.

Treatments in development

Dutasteride

Dutasteride is a dual type I and type II 5α-reductase inhibitor that is approximately 3 times as potent as finasteride at inhibiting type II enzyme action, and 100 times as potent at inhibiting type I enzyme action [49]. It is capable of decreasing serum DHT by up to 90%, about a 20% greater reduction compared to finasteride. Dutasteride is approved at the 0.5 mg level as a treatment for BPH. This dual inhibitor has recently been tested for improved efficacy over finasteride in promoting hair growth [49]. Although type II 5α-reductase is the predominant 5α-reductase enzyme expressed in scalp, expression of the type I enzyme occurs in scalp also. Type I 5α-reductase is the principally expressed isozyme in scalp sebaceous glands [50], and many studies have also demonstrated expression of this isozyme within the hair follicle itself [51]. Both enzymes metabolise T to DHT, and therefore it is probable that type I 5α-reductase acts as a source of DHT in hair follicles. In a treatment regime that aims to block DHT production, therefore, a dual 5α-reductase inhibitor should be preferable to a selective inhibitor. In a randomised placebo-controlled study, Olsen *et al.* assessed target area hair counts in patients receiving placebo, finasteride 5 mg and dutasteride 2.5 mg over 24 weeks of treatment. Both 5α-reductase inhibitors increased hair counts over placebo, and dutasteride 2.5 mg was shown to be more rapid and superior to finasteride 5 mg in promoting hair growth [49]. Thus, the further development of a dual 5α-reductase inhibitor for the treatment of MPB appears warranted.

Latanoprost

Latanoprost is a prostaglandin analogue that was originally introduced as a treatment for glaucoma and ocular hypertension to reduce intraocular pressure. Soon after, the stimulatory effects of this compound on eyebrow and eyelash hair growth and pigmentation in high numbers of patients were reported. Thus the potential for the use of latanoprost as a hair growth stimulant was swiftly touted [52,53]. The expression of PG receptors was examined in mouse skin hair follicles, and mRNA was identified in dermal papilla and outer root sheath follicular structures during anagen. However, this expression was found to be absent on follicles in the telogen phase. Depilation, which forced the follicles back into anagen, resulted in re-expression of the PG receptors. Other studies have demonstrated the ability of PG to stimulate movement from telogen to anagen in mice [54]. These results suggest that, in least in rodents, PG may be important in regulating the hair follicle cycle. Studies of the application of high doses of latanoprost to the scalp of the stump-tailed macaque, an animal model of human common baldness, demonstrated the ability of this PG analogue to stimulate marked hair regrowth [55].

Taken together, the above studies provide strong evidence to suggest that further investigation of the efficacy of PG as a hair growth agent may have significant merit. As previously mentioned, one proposed action of minoxidil that may be relevant to hair regrowth is stimulation of PG synthesis [38]. If this is correct, it would seem sensible to consider the direct application

of a PG analogue such as latanoprost to the hair follicle, rather than to indirectly stimulate PG synthesis *via* minoxidil [52].

Ketoconazole

The anti-fungal agent ketoconazole is used topically for the treatment of seborrheic dermatitis and dandruff [56]. There is some evidence, both in humans [57] and in rodents [56], that this agent may stimulate hair growth. The mechanism is unknown, but may involve inhibition of inflammation, or anti-androgenic properties of the agent [58]. To date the evidence is based on small sample sizes and does not include clinical trials. Thus, further research is required to determine its efficacy.

Future treatment potential

The approved and developing treatments for MPB are largely based upon accidental observations of hair regrowth side-effects of drugs developed for other purposes. As our understanding of the molecular genetic aetiology of MPB gains pace, it is reasonable to expect that development of more targeted pharmaceuticals based on new knowledge will similarly accelerate. In this section we examine probable new directions for hair loss treatment based on current and developing molecular genetic understanding.

Androgen receptor blockers

Knowledge of the important role of androgen, particularly increased ARs, in genetically predisposed individuals leads to the idea that blockage of response to androgen by hair follicles through the use of AR blockers may halt or reverse hair loss. The use of AR blockers has been investigated as a treatment of MPB for some time. However, systemic anti-androgen treatments cannot be used in men, owing to the potential risks of development of gynaecomastia, feminisation and impotence [59]. The key to exploiting this approach will lie in the development of AR blockers that block AR selectively in scalp hair follicles and not elsewhere in the body. Interestingly, there is no evidence of perturbation of sex-steroid action in other tissues outside the scalp in carriers of the MPB-relevant *AR* variant. This suggests that the effect of the variant *AR* may be site-specific, possibly through alteration of a scalp-specific *AR* transcription factor-binding site. It should be noted that whilst the existence of a variant *AR* that predisposes to MPB is well established, the exact functionally relevant variation(s) within this gene has not yet been identified [60]. Indeed, there is little known regarding the regulation of expression of *AR*; however, it is known that the gene is flanked by large non-coding regions harbouring stretches of sequence that are highly conserved across species [61]. These characteristics are hallmarks of the presence of functionally important and often tissue-specific regulatory elements, sequence variation within which may hold the key to altered scalp *AR* expression levels in variant *AR* carriers. Identification of such elements may hold the key to MPB disease pathogenesis, and provide opportunities for pharmacological treatment development that is targeted to the molecular mechanisms underlying the hair loss process.

Identification of other predisposing genes, and use of such findings for treatment development

As previously mentioned, other candidate genes have been investigated in relation to MPB risk, and have mostly focused upon genes relevant to sex-steroid pathways. These include *SRD5A1*, *SRD5A2* [23] and the gene encoding aromatase (*CYP19A1*) [62]. Aromatase metabolises T to estrogens, and has been shown to be expressed in reduced quantities in balding scalp [25]. Presumably aromatase may serve to reduce the amount of T available for conversion to DHT in the hair follicle. None of these genes were shown to be associated with MPB. However, the more successful contemporary gene-hunting strategies of today demonstrate that these previous studies lacked both statistical power through small sample sizes, and comprehensive evaluation of sequence variation in each of these gene regions [31]. It is now clear that to identify genes contributing moderate to low increases in risk of complex multifactorial traits like MPB, genetic association studies must be performed in hundreds, to thousands, of cases and controls to achieve adequate statistical power. Additionally, sequence variation such as single nucleotide polymorphisms (SNPs) relevant to multifactorial disease risk may be located in both protein coding and non-coding regions of the genome. Such variation within a gene locus must be considered comprehensively using panels of tens to hundreds of SNPs [31]. This process is augmented by a more thorough understanding of human genetic architecture that demonstrates common co-inheritance of closely lying groups of SNPs, termed haplotypes, across the genome at a population level. The advantage of this is that only a single representative of such co-inherited SNPs needs to be examined to identify genetic association of that haplotype with disease [63]. On the basis of these new approaches, SNP panels to comprehensively evaluate the involvement of sequence variation in and around *SRD5A1*, *SRD5A2* and *CYP19A1* are currently being designed and validated (Ellis, unpublished), with the future intention of thorough investigation of the role of these genes in MPB.

There are a myriad of other genes that could justifiably be considered candidate genes for MPB both within and outside the sex-steroid pathway, and therefore the identification of MPB-relevant genes might best be achieved by a genome-wide analysis of SNP sequence variation. Technological advances now allow genotyping of up to one million SNPs throughout the genome in a single experiment for less than $1000 per DNA sample. Highly significant differences in SNP allele frequency between case and control groups points to possible involvement in disease. Interestingly, genome-wide association analyses of other multifactorial conditions have both confirmed the involvement of genes previously identified *via* candidate gene approaches, and identified new and replicable association with sequence variants both within and outside known gene loci [33]. Application of this approach to large MPB case–control populations will probably provide similar new knowledge of the underlying genetic architecture of common hair loss and open up considerable new avenues for targeted pharmacological intervention in the hair loss process. Such interventions might include application of follicle-specific synthetic analogues of molecules suffering genetically moderated reduced expression, or blockers of molecules whose expression is upregulated. The key to efficacious treatment based on molecular mechanisms will probably be the development of vehicles that specifically and efficiently deliver drugs to follicles.

Another important future aspect to targeted drug therapy for any multifactorial condition will be the consideration of the underlying unique genetic makeup of each patient. The complexity of common

diseases suggests that in conditions that are determined by many genes that confer a range of risk levels, the expression of the condition will be dependent upon the individual mix of genes inherited. Prior studies have suggested that AR may be necessary, but not sufficient, to cause baldness, at least in prematurely balding young men [27]. A combination of other risk genes will therefore work with *AR* to determine overall risk of hair loss, and the number of predisposing genes inherited might determine age of onset and baldness severity [23]. The genetic combination is therefore likely to be different across different individuals. Therefore, truly targeted pharmaceutical therapies will need to be matched to the underlying genetic combination. This growing field of research has been termed pharmacogenomics [64], and provides great promise for future personalised treatment strategies in multifactorial disease.

Conclusions

Despite the potential market for effective targeted treatments for MPB, pharmacological approaches to the prevention of hair loss and to hair regrowth are in their infancy. This is underpinned by a paucity in understanding the underlying molecular mechanisms that contribute to the pathogenesis of baldness. It is known that, in the presence of sufficient androgen, hair loss is determined almost entirely by genetic predisposition. However, gene-hunting research, to date, has uncovered only one replicable genetic association, with *AR*. The utilisation of this finding in treatment development is hampered by a lack of understanding of the relevant sequence variation in this gene that leads to upregulation of *AR* in balding follicles, and the fact that methods to very specifically direct androgen-blockers to follicular target tissues to avoid systemic effects are not yet available. The currently approved MPB treatments, minoxidil and finasteride are variably effective, and hair regrowth is achieved in only a small subset of patients. Some developing treatment options including dutasteride and latanoprost, hold increased promise, but are still not based on a full understanding of disease aetiology. Increased understanding of the underlying MPB genetic architecture, which may be gleaned from comprehensive candidate gene and/or genome-wide association studies, will provide a pathway to the development of more efficacious, personalised future pharmacological treatment options.

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