

Hunting the genes in male-pattern alopecia: how important are they, how close are we and what will they tell us?

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Abstract: Androgenetic alopecia (AGA) is a highly heritable condition, and the most common form of hair loss in men. The phenotype is characterized by an androgen-dependent, progressive loss of hair from the scalp, which may commence during puberty. Up to 80% of European men experience some degree of androgen-dependent hair loss during their lifetime. Current treatment options for AGA have limited efficacy, and improved understanding of the underlying biological causes is required to facilitate novel therapeutic approaches. To date, molecular genetic studies have implicated 12 genomic regions in AGA and identified a number of candidate genes. The latter include those encoding the androgen receptor (AR), the histone deacetylases

(HDAC) 4 and 9, and the WNT molecule *WNT10A*. However, the majority of contributing genetic risk factors still await identification. This review describes the current status of AGA genetic research. We discuss the strength of the genetic approach and anticipated developments in the field, and how these will facilitate the systematic unravelling of AGA pathobiology, a process which may lead to the identification of new therapeutic targets.

Key words: androgenetic alopecia – gene identification – hair loss – male-pattern baldness

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Introduction

Androgenetic alopecia (AGA) is the most common form of hair loss in humans. In males, AGA is characterized by a distinct pattern of androgen-dependent progressive hair loss from the scalp (male-pattern alopecia). Typically, male AGA commences with a bi-temporal recession of the frontal hair line. This is followed by a thinning of the frontal and vertex scalp areas. This process eventually leads to complete baldness of the top of the scalp (Fig. 1) (1). AGA may commence during puberty, and up to 80% of European men experience some degree of AGA during their lifetime (2).

Although no conclusive data are available, clinical experience suggests that the prevalence of AGA among women is lower than in men (4,5). As in men, affected women experience a progressive loss of hair. However, this typically presents in a more diffuse pattern (female-pattern alopecia). The earliest stages of female-pattern alopecia are subtle, and refined screening and assessment techniques are therefore required (6). Furthermore, the relationship between female-pattern alopecia and androgens is less clear than in males (7,8). Given the lack of robust data on these sex differences, and the fact that the significant findings generated by recent genetic studies relate exclusively to male patients, the present article will focus on male AGA only.

The following describes the current status of AGA genetic research and anticipated developments in the field. Researchers hope that knowledge of the involved genes will lead to both a deeper understanding of the pathobiology of AGA, and the identification of new therapeutic targets. One additional consequence of this research will be an increase in knowledge of the biological basis of normal human hair growth. Furthermore, genetic AGA

research has already revealed, and is likely to continue to reveal, totally unexpected correlations with other characteristics and illnesses, thus placing the biology of hair growth within a broader biological context.

Why is AGA considered to be heritable?

The familial occurrence of AGA is well documented, and monozygotic twins display a striking phenotypic resemblance (4,9,10). To date, two twin studies of AGA have been performed. These generated heritability estimates of 0.81 [95% confidence interval (CI) 0.77–0.85] in early-onset AGA families (25–36 years) and 0.79 (95% CI 0.4–0.85) in elderly males (>70 years), respectively (11,12). However, the true heritability may even be higher, as any random misclassification of AGA severity, for example in studies involving self-assessment, would lead to an underestimation of the heritability. The issue of whether environmental factors – in some instances mediated through epigenetic mechanisms (13–15) – are involved in AGA remains unclear (16–18).

What does the identification of genetic factors offer in terms of causal research?

Each associated genetic locus indicates a position in the human genome at which genetic variation correlates with phenotypic variance (e.g. the occurrence of illness) (19). This genetic variation is likely to influence a critical stage of the complex biological cascade that ultimately results in the phenotype. In recent years, numerous molecular genetic studies have been performed to identify genes that contribute to AGA (see below). The main aim of these studies was to generate novel insights into the biological basis of the following key pathophysiological features of AGA: (i) the strict androgen dependency of the AGA phenotype; (ii) the stringent restriction of AGA to defined subpopulations of scalp hair follicles; (iii) progressive anagen shortening and premature entry into

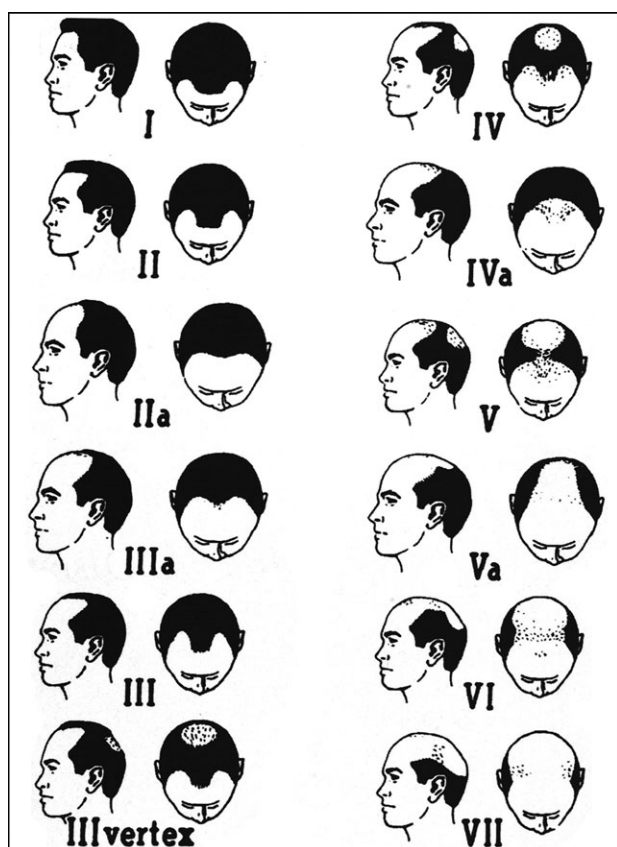


Figure 1. Phenotypic classification of androgenetic alopecia (AGA) according to the Hamilton-Norwood scale. I, no hair loss; II, mild regression of the frontal hairline; III, further frontal hair loss; III-vertex, frontal hair loss coupled with mild hair loss in the vertex area of the scalp; IV, formation of a bald vertex area; V–VII, confluence of the affected areas until only the occipital area maintains significant amounts of hair (3).

the catagen stage; and (iv) the abnormal transformation of terminal into vellus hair follicles (20–23).

How many genes are involved and what is the allelic architecture?

In general, the more complex the underlying biology of a human trait, the greater the number of contributory genes (25). When numerous biological pathways are involved, the contribution to the total variance of genetic variation within an individual gene is relatively limited, and the observed effect sizes are small. As a consequence, larger samples sizes are required to detect these associations. The fact that genomewide association studies (GWAS) have generated the first genomewide significant findings in limited samples of affected individuals (~600 affected individuals) (26,27), suggests that the biology of AGA, is less complex than that of other human traits, such as height or body mass index (28). However, researchers assume that the true number of involved genes significantly exceeds the number of currently known loci (24).

Another important aspect of the genetic architecture of a complex trait is the nature of the genetic variants within a given susceptibility gene. In general, two hypotheses exist: (i) the common disease/common variants hypothesis, which assumes that variants with high population frequency but low penetrance explain the

majority of the genetic disease susceptibility; and (ii) the common disease/rare variants hypothesis, which assumes that rare variants with relatively high penetrance are the major contributors (29,30). Which of these two hypotheses applies to a particular disease is mostly dependent on whether selective pressure acts on the associated phenotype. If strong selective pressure is present, the phenotype leads to reduced reproduction rates, and the associated variants are thus rapidly eliminated from the population. In this case, a higher prevalence of the phenotype in the population is only possible through the repeated occurrence of new (rare) mutations. If a phenotype is not associated with a major reduction in fitness, as is assumed for AGA, no selection against susceptibility variants occurs, and the variants can therefore obtain high frequencies in the population (31). Researchers therefore assume that the majority of the genetic variants that contribute to AGA phenotypic variance are common variants with low-to-moderate individual effect sizes. However, the contribution of rare variants with higher effect sizes cannot be excluded, and may be involved in some cases.

Which genomic regions have been associated with AGA to date and what do they tell us about the biology of AGA?

To date, GWAS of AGA identified 12 genomic regions of interest ($P < 5 \times 10^{-8}$; Fig. 1; Table 1) (26,27,32–34). The most strongly associated genomic region is located on the long arm of the X-chromosome. This region is flanked by two genes, which encode for the androgen receptor (AR) and the ectodysplasin A2 receptor (EDA2R), respectively. In view of the androgen dependency of the AGA phenotype, the AR is presumed to be the most plausible candidate gene for AGA and has previously been studied in this context (35–40). The second candidate gene in this region is EDA2R (41), which has been reported to activate JNK and NF- κ B signaling, the latter being implicated in anagen maintenance (42). While AR expression has mainly been observed in dermal papilla cells and sebaceous gland (22), EDA2R expression has been demonstrated in the mouse hair bulb and in differentiating hair matrix cells (43).

However, follow-up analyses conducted to date could neither confirm nor exclude the AR or EDA2R as the true causative gene, or lead to the identification of the causal variant(s) (35,44). Moreover, no plausible explanation has yet been provided for why a genetically determined overall functional effect on AR signaling should result in hair cycle abnormalities and abnormal terminal-to-vellus transformation in specific skin regions only, whereas the growth of hair follicles elsewhere remains normal and is in fact stimulated by the same ligand (dihydrotestosterone) (22,23). Further studies are warranted to elucidate the connection between genetic variation at the AR/EDA2R-locus and the androgen-dependent development of the AGA phenotype.

The remaining 11 associated regions are located on the autosomes. This is of particular interest, as in males, the X-chromosome is inherited from the maternal side. Thus, the association at the X-chromosomal AR/EDA2R-locus – as for any association at an X-chromosomal locus – does not explain the resemblance in AGA patterns observed between affected fathers and their sons (11,45). Thus, this resemblance is either conferred through genetic variation of the Y-chromosome, which is inherited from the paternal side, but contains very few genes, or through genetic variation

Table 1. Details of genomic regions associated with AGA

Locus	Lead SNP	P-value	OR (95% CI)	Context	Study
Xq12	rs2497938	1.9×10^{-10}	6.1 (3.3–11.1)	<i>AR</i> – <i>EDA2R</i>	Hillmer et al. (2008) (26)
	rs6625163	5.0×10^{-11}	3.3 (2.3–4.7)		Richards et al. (2008) (27)
	rs2497938	3.1×10^{-22}	6.5 (4.3–9.8)		Brockschmidt et al. (2011) (32)
	rs2497938	2.4×10^{-91}	2.2 (2.0–2.4)		Li et al. (2012) (34)
20p11	rs2180439	1.4×10^{-9}	2.2 (1.7–2.8)	<i>PAX1</i> – <i>FOXA2</i>	Hillmer et al. (2008) (26)
	rs1160312	1.1×10^{-14}	1.6 (1.4–1.8)		Richards et al. (2008) (27)
	rs2180439	3.9×10^{-17}	2.1 (1.8–2.5)		Brockschmidt et al. (2011) (32)
	rs6047844	1.2×10^{-39}	1.6 (1.5–1.7)		Li et al. (2012) (34)
7p21.1	rs2249817	9.1×10^{-8}	1.6 (1.4–2.0)	<i>HDAC9</i>	Brockschmidt et al. (2011) (32)
	rs2073963	1.1×10^{-12}	1.3 (1.2–1.9)		Li et al. (2012) (34)
	rs12565727	9.1×10^{-11}	1.3 (1.2–1.5)		Li et al. (2012) (34)
1p36.22	rs9287638	1.0×10^{-12}	1.3 (1.2–1.4)	<i>HDAC4</i>	Li et al. (2012) (34)
2q37.3	rs6945541	1.7×10^{-9}	1.3 (1.2–1.4)	<i>AUTS2</i>	Li et al. (2012) (34)
7q11.22	rs12373124	5.1×10^{-10}	1.3 (1.2–1.5)	<i>IMP5</i>	Li et al. (2012) (34)
17q21.31	rs10502861	2.6×10^{-9}	1.3 (1.2–1.4)	<i>SETBP1</i>	Li et al. (2012) (34)
18q12.3	rs4679955	1.8×10^{-10}	1.2 (1.1–1.2)	<i>SUCNR1</i> – <i>MBNL1</i>	Heilmann et al. (2013) (33)
3q25.1	rs929626	2.1×10^{-11}	0.8 (0.8–0.9)	<i>EBF1</i>	Heilmann et al. (2013) (33)
5q33.3	rs7349332	3.6×10^{-15}	1.3 (1.3–1.4)	<i>WNT10A</i>	Heilmann et al. (2013) (33)
2q35	rs9668810	1.1×10^{-10}	1.2 (1.2–1.3)	<i>SSPN</i> – <i>ITPR2</i>	Heilmann et al. (2013) (33)
12p12.1					

AGA, androgenetic alopecia; SNP, single nucleotide polymorphism; OR, odds ratio; 95% CI, 95% confidence interval.

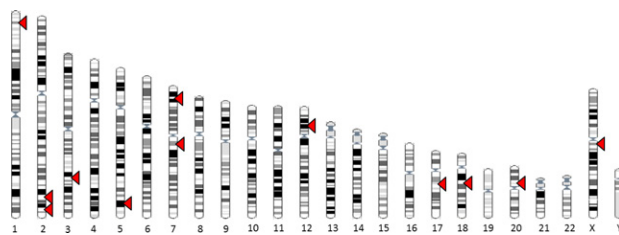


Figure 2. Overview of genomic regions associated with androgenetic alopecia (AGA). Arrows indicate the chromosomal localization of genetic association findings for AGA, as listed in Table 1. The strongest association signal is observed on chromosome X (*AR/EDA2R*-locus). The remaining risk loci are located on the autosomes (chromosomes 1, 2, 3, 5, 7, 12, 17, 18 and 20).

of the autosomes, which are inherited in equal measure from the father and the mother. The latter contain the vast majority of all human genes, including some already implicated in AGA (Table 1).

The strongest finding on the autosomes is for the intergenic region between paired box 1 (*PAX1*) and forkhead box A2 (*FOXA2*) on chromosome 20. Further associated regions are located on chromosomes 1, 2, 3, 5, 7, 12, 17 and 18. Two of these regions are located in the vicinity of genes that encode histone deacetylase class II molecules, that is *HDAC4* on chromosome 2q37 and *HDAC9* on chromosome 7p21.1. Both *HDAC4* and *HDAC9* have been found to be expressed in human hair follicle (32,34) and are known to act as transcriptional repressors via the deacetylation of histone proteins and nuclear compaction of the chromatin (46). Research has shown that both HDACs play a role in the regulation of AR signaling via direct or indirect interaction with the AR protein (32,47–49). Thus, both may contribute to the AGA-specific androgen-induced miniaturization of hair follicles.

The above-mentioned AGA risk loci also contain two members of the TWIST basic helix–loop–helix (bHLH) transcription factors family, that is *TWIST2* (2q37) and *TWIST1* (7p21.1). Interestingly, experiments in dermal papilla cells from adult mice have shown that *TWIST1* is implicated in hair cycle regulation, where it plays a crucial role in the control of anagen-to-catagen transition (50).

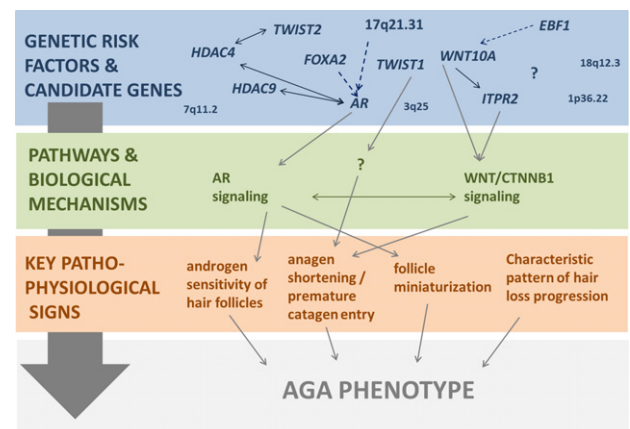


Figure 3. Potential contribution of known genetic risk factors to key pathophysiological characteristics of the androgenetic alopecia (AGA) phenotype. Molecular genetic AGA research has identified a total of 12 genomic risk loci. Some of these loci contain plausible candidate genes, such as the androgen receptor (*AR*); the WNT molecule *WNT10A*; the histone deacetylases *HDAC4* and *HDAC9*; and the twist genes *TWIST1* and *TWIST2*. For the remaining loci, knowledge of the function of neighbouring genes is sparse, and the genes and mechanisms that underlie these association signals are a matter of speculation. These genes contribute to signaling pathways such as the AR pathway, the WNT pathway, and other as-yet-unknown pathways with an impact on human hair follicle homeostasis. Deregulation of these pathways leads to key pathophysiological changes, such as follicle miniaturization, anagen shortening and androgen sensitivity of specific hair follicle subpopulations. In turn, these changes lead to the characteristic progressive hair loss observed in AGA. (Solid lines indicate interactions described in the literature. Broken lines indicate potential interactions. '?' indicates as-yet-unknown genetic factors and pathways.)

The second Twist gene, *TWIST2*, has been implicated in the development of mesenchymal cell lineages (51). Intriguingly, the Twists and the HDACs appear to interact on a functional level in the regulation of the expression of their target genes (52,53). This renders a functional interaction between *HDAC4*, *HDAC9*, *TWIST1* and *TWIST2* during AGA development likely, which may contribute to (i) the androgen-induced follicle miniaturization and (ii) the observed anagen shortening and premature catagen entry (Fig. 3).

Another region of interest is located on chromosome 2q35. Here, the most strongly associated single nucleotide polymor-

phism, that is rs7349332, is located intronically in *WNT10A* (wingless-type MMTV integration site family member 10A). Research has shown that *WNT10A* is expressed during hair morphogenesis and in inner root sheet precursors within the hair matrix of mouse anagen follicles and shows expression in the human hair follicle (33,54). Notably, numerous publications have implicated WNT signaling in the development of the hair follicle and the control of hair follicle cycling, particularly in telogen to anagen transition and the maintenance of anagen characteristics (54–58). This is of particular interest, as changes in hair follicle dynamics are one of the key pathophysiological features of AGA. Indeed, allele-specific expression analyses in human hair follicle tissue have revealed a regulatory effect of the AGA risk variant rs7349332 on *WNT10A* expression. Here, AGA risk allele carriers (T) showed a significant reduction in expression.

This suggests that *WNT10A* plays a specific role in anagen induction and maintenance and that the genetic risk allele at this locus may contribute to the observed premature catagen entry and a prolonged latency period between catagen and anagen re-entry in balding hair follicles (33). Moreover, the association finding on 2q35 revealed an unexpected link between AGA and hair morphology. Here, the AGA risk allele for rs7349332 was associated with increased hair curl in two independent GWAS (59,60). Subsequent analyses of an association between additional AGA risk loci and hair curl identified no further shared loci. This suggests the specific involvement of WNT signaling in the overlapping aetiology of these traits.

The potential role of WNT signaling in AGA development is supported by the fact that additional WNT signaling-related genes are located at other known risk loci, for example *WNT3* on 17q21.31 and *ITPR2* on chr12p12.1. The latter is expressed in the human hair follicle (33) and might act downstream of WNT signaling as a receptor for inositol 1,4,5-triphosphate (IP3) (61). Supportive evidence for *ITPR2* has been generated by Sato-Miyaoka et al. (62) who suggested a role for *ITPR3*, another member of the IP3 receptor family, in the active regulation of hair shedding. Notably, evidence is emerging for the existence of cross-talk between WNT and AR signaling. This may partly explain the androgen-dependent induction of the biological mechanisms and hair cycle changes that lead to the AGA phenotype (22,63).

The remaining loci are located intronically within, or in the vicinity of, genes such as *TARDBP* (1p36.22), *SUCNRI* and *MBNL1* (3q25), *EBF1* (5q33), *AUTS2* (7q11.22), *IMP5* (17q21.31) and *SETBP1* (18q12.3). However, few data are available concerning their expression pattern in the human hair follicle, and current knowledge of the function of these genes suggests no straightforward explanation for an involvement of their protein products in any of the four key AGA pathomechanisms (Fig. 3).

As is typical for the genetic analysis of common phenotypes, the majority of the identified genetic risk loci are located in non-coding, and mostly intergenic, regions of the genome (64).

It is likely that these variants exert a regulatory effect on phenotypically relevant genes, for example by influencing promoter or enhancer activity. This eventually leads to a deregulation of the tightly orchestrated processes necessary for hair follicle cycling and growth.

This hypothesis is supported by the observation of a regulatory effect of an AGA-associated genetic variant on the expression of

the candidate gene *WNT10A* (33). Although the functional annotation of non-coding regions is becoming increasingly detailed (65), in many cases, further experiments are required to explain their often tissue- and cell-specific biological contexts. This is particularly important in male AGA, where the clinical balding phenotype is only seen in selected, androgen-sensitive hair follicle subpopulations in stringently defined regions of scalp skin (23). This phenomenon may be attributable to developmental priming of the hair follicle mesenchyme in these selected skin regions during cutaneous embryogenesis (23,66). Some of the associated genetic variants may exert their functional effects very specifically during this early developmental phase (67).

Another difficulty faced in AGA research is that gene expression profiles and phenotypes of isolated hair follicle cells – in particular dermal papilla cells – change rapidly after extraction from their natural tissue habitat (68,69). This may hamper the detection of regulatory interactions between genetic variants and gene expression in these *in vitro* models. The cultivation of dermal papilla cells in 3D assays that ensure the maintenance of their hair-inducing capacities is therefore considered the method of choice for more detailed AGA cell biology research (68). To demonstrate the effects of AGA-associated genetic variants, common genotypes must be represented. Therefore, these cultivated dermal papilla cells must be established from a number of individuals.

Molecular genetic findings support the hypothesis that AGA is not an isolated trait

Epidemiological studies have shown that AGA patients are at increased risk for benign prostate hyperplasia (70,71), prostate cancer (72,73), cardiovascular disease (e.g. hypertension, coronary heart disease and myocardial infarction) and metabolic syndrome (74–83). However, no shared genetic factors for AGA and these associated diseases have yet been identified, and the overlapping biological mechanisms and common pathophysiological mechanisms remain unknown.

Due to the availability of genome-wide genetic data for these phenotypes, it is now possible to perform a systematic search for shared genetic determinants to explain the disease associations observed in epidemiological studies. The feasibility of such studies has already been demonstrated for a variety of common diseases, such as rheumatoid arthritis and psychiatric disorders (84–88).

Importantly, the identification of AGA-associated genes may also indicate aetiological correlations with diseases for which no connection to AGA has yet been suspected.

In this context, a meta-analysis published in 2012 (34) found an association with a locus on the long arm of chromosome 17q21.31. This locus had previously been associated with Parkinson's disease (89–91). The region contains the gene microtubule-associated protein tau (*MAPT*). This encodes the tau protein, which is of key importance in the development of Parkinson's disease. Subsequent investigations demonstrated tau expression in hair follicles. Furthermore, analysis of data from the 23andMe cohort revealed a significantly higher risk of Parkinson's disease among AGA cases compared with unaffected controls (OR = 1.28, 95% CI 1.06–1.55), a finding which had not been reported in the previous epidemiological literature. The association became even stronger when the analysis was restricted to individuals aged >70 years (OR = 1.94, 95% CI 1.31–2.88, $P = 6.5 \times 10^{-4}$) (34). This suggests that AGA and Parkinson's disease share a common

biological mechanism. Interestingly, research has shown that the tau locus makes only a small contribution to this association, and thus, other genes must be implicated in the association between AGA and Parkinson's.

In addition to this unexpected association between AGA and Parkinson's disease, the 17q21.31 locus finding suggests an association between AGA and fertility. The AGA risk allele is located on the H1 haplotype of a common inversion polymorphism that is under negative selection pressure in Europeans and that has been linked to decreased fertility in women in the Icelandic population (92). This is of particular interest, as polycystic ovary syndrome (PCOS), which is one of the leading causes of decreased fertility in women, is more frequently observed in female relatives of men with early-onset AGA (93,94). Furthermore, both PCOS and AGA are promoted by increased androgen levels. Thus, the overlapping association between AGA and decreased fertility in women may point towards a regulatory interaction of the 17q21.31 locus and AR signaling.

This meta-analysis also identified an AGA-associated region on chromosome 1p36, which is located upstream of the amyotrophic lateral sclerosis (ALS)-gene TAR DNA-binding protein (*TARDBP*). A follow-up analysis of a potential association between early-onset AGA and ALS in a large US cohort ($n = 51\,529$ men) revealed an up to 2.7-fold increase in ALS risk in AGA cases compared with unaffected controls (95).

The identification of associations between AGA and other clinical phenotypes/diseases through genetic AGA research is a promising strategy to gain deeper insights into common pathophysiological mechanisms and may ultimately demonstrate that AGA is not an isolated trait but rather an early prognostic marker for later onset disorders, such as severe neurological or cardiovascular disease.

Can currently available genetic data be used to predict the development of AGA in younger males?

Young men may wish to know their specific risk for AGA, and knowledge of the associated genes is of potential value in terms of prediction. However, the genes identified to date explain only a limited proportion of the genetic variance, and thus, the prediction accuracy remains limited (96,97). Furthermore, it remains uncertain whether commencing treatment before the visible onset of balding (e.g. with finasteride, minoxidil or any other more recently proposed agents) (98,99) is beneficial. This is now a highly pertinent issue, as 5- α -reductase inhibitor therapy has recently been shown to have long-term adverse effects ('postfinasteride syndrome') (100,101).

Conclusions and perspectives

The identification of genetic risk loci for common phenotypes via molecular genetic studies allows systematic mapping of the underlying biological pathways. Although the first loci for AGA have been identified, systematic investigations of the underlying biological pathways are still lacking. This is due to the following reasons: (i) the limited number of loci identified to date; and (ii) the fact that the associated genetic variants tend to reside in non-coding regions of the human genome, for which no clear functional effect, for example on gene regulation, has yet been identified. It is therefore not surprising that researchers remain far from having established firm relationships between identified gene associations and particular biological characteristics in affected hair follicles.

Future molecular genetic AGA research will focus on two general lines of enquiry. First, further gene associations must be identified to provide a more complete overview of the biological factors involved. Second, detailed functional studies are required to allow the stepwise elucidation of the underlying molecular mechanisms and pathways and thereby define the biological bridge between genotype and phenotype. The identification of further genetic risk loci will be accelerated by expanding GWAS cohorts to increase power. This has been achieved for other common phenotypes, and there is no reason to believe that AGA will be an exception to this rule.

Beside the identification of additional genetic risk factors for early-onset AGA, further studies are warranted to clarify whether early- and late-onset AGA share the same genetic basis, or whether age of onset in AGA is determined by distinct genetic risk factors rather than an individual's genetic load for AGA risk alleles. Here, the identification of protective factors and mechanisms that counteract these AGA risk increasing factors may be a promising strategy to further elucidate the biological mechanisms of disease onset in AGA. In this context, the analysis of elderly men who show no signs of AGA may be a promising strategy. The increasing use of new sequencing methods will demonstrate the full extent of AGA genetic variability, including the presence of rare genetic variants. Beyond standard statistical tests for genetic association with individual variants, the performance of advanced bioinformatic analyses of genetic data (such as gene-, pathway- and network-based analyses) will maximize the extraction of information from the genetic data and thus facilitate the identification of the responsible genes.

As a note of caution, the effort involved in progressing from the initial association findings to the identification of the responsible genes, and then ultimately to the functional effects of genetic variation, should not be underestimated. This typically requires laborious and extensive experimental investigations. On the other hand, the functional annotation of the human genome is becoming increasingly detailed (102), and genomewide data on the effects of genetic variants on gene expression are now becoming available for various tissues and stages of development (103–106). In addition, the development of new methods will facilitate the functional follow-up of single variants and their complex interplay in the living organism. These developments include the use of designer nucleases or the CRISPR/Cas technology, which enable the introduction of specific genetic variants into model systems (107,108). Newly generated hypotheses concerning the biological mechanisms of AGA will need to be examined in human hair research models. These models include scalp hair follicle organ cultures (68,69,109–112), and normal, as well as AGA-affected, scalp skin or human hair follicle transplants in immunocompromised mice (113,114).

Researchers hope that systematic mapping of the biological pathways underlying AGA will identify novel drug targets. Although the initial hype around the genomics revolution and its impact on the development of new drugs has undergone a critical re-evaluation in recent years (115,116), the wealth of genetic data now being generated in large-scale GWAS is making the impact of the genomic approach more apparent (116). For example, GWAS for several diseases have confirmed known drug targets and thereby provided a proof of principle for this approach (117–119).

Moreover, recent research has shown that the proportion of drug mechanisms with direct genetic support increases significantly across the drug development pipeline, from 2.0% at the preclinical stage to 8.2% for approved drugs. The authors estimate that selecting genetically supported targets could double the success rate in clinical development (120). There is therefore good reason to believe that the development of new drugs for AGA will profit from the generation of genetic data, although the fact that development from a gene target to an approved marketed drug generally takes more than a decade must be borne in mind.

The genetic findings are also likely to set AGA in a broader context of related phenotypes. In particular, they will elucidate whether male-pattern balding shares common pathways with female-pattern balding and identify pathways that distinguish these distinct AGA entities (7,8,121). In addition, the identification via genetic AGA research of shared disease mechanisms for

AGA and other clinical phenotypes/diseases is an exciting prospect. As with the mapping of biological pathways, the aim of such research is to achieve the extensive mapping of phenotypic correlation networks. Systematic analysis of pleiotropic effects at AGA risk loci, as well as the identification of shared genetic determinants for epidemiologically associated phenotypes such as prostate hyperplasia/cancer or cardiovascular disorders, will free AGA from the prevalent misconception of being a mainly cosmetically and psychologically important phenotype and place it within a wider medical and biological context.

Author contribution

SHH and MMN performed the literature research and prepared the manuscript. SHH and LMH prepared the tables and figures. RP critically revised the manuscript.

Conflict of interests

The authors have declared no conflicting interests.

References

- Qi J, Garza L A. Cold Spring Harb Perspect Med 2014; **4**: a013615.
- Hamilton J B. Ann N Y Acad Sci 1951; **53**: 708–728.
- Norwood O T. South Med J 1975; **68**: 1359–1365.
- Küster W, Happle R. J Am Acad Dermatol 1984; **11**: 921–926.
- Olsen E A, Messenger A G, Shapiro J et al. J Am Acad Dermatol 2005; **52**: 301–311.
- Harries M, Tosti A, Bergfeld W et al. J Eur Acad Dermatol Venereol 2015; doi:10.1111/jdv.13455. [Epub ahead of print].
- Langan E A, Paus R. Br J Dermatol 2010; **163**: 1140–1141; author reply 1141–1142.
- Messenger A G. Br J Dermatol 2011; **165**(Suppl 3): 2–6.
- Davis H. Proc R Soc Med 1913; **6**: 6.
- Osborn D. J Hered 1916; **7**: 347–355.
- Nyholt D R, Gillespie N A, Heath A C et al. J Invest Dermatol 2003; **121**: 1561–1564.
- Rexbye H, Petersen I, Iachina M et al. J Gerontol A Biol Sci Med Sci 2005; **60**: 1077–1082.
- Andl T, Botchkareva N V. Exp Dermatol 2015; **24**: 821–826.
- Cobb J E, Wong N C, Yip L W et al. Br J Dermatol 2011; **165**: 210–213.
- Kilpinen H, Dermizakis E T. Hum Mol Genet 2012; **21**: R24–R28.
- Koyama T, Kobayashi K, Wakisaka N et al. Eur J Dermatol 2013; **23**: 113–115.
- Mosley J G, Gibbs A C. BMJ 1996; **313**: 1616.
- Severi G, Sinclair R, Hopper J L et al. Br J Dermatol 2003; **149**: 1207–1213.
- Beckmann J S, Antonarakis S E. Lessons from the genome-wide association studies for complex multifactorial disorders and traits. In: Speicher M R, ed. Vogel and Motulsky's Human Genetics: Problems and Approaches. Berlin, Heidelberg: Springer Verlag, 2010: 287–297.
- Hamilton J B. Am J Anat 1942; **71**: 451–480.
- Paus R, Cotsarelis G. N Engl J Med 1999; **341**: 491–497.
- Inui S, Itami S. Exp Dermatol 2013; **22**: 168–171.
- Randall V A. Semin Cell Dev Biol 2007; **18**: 274–285.
- Heilmann S, Brockschmidt F F, Hillmer A M et al. Br J Dermatol 2013; **169**: 927–930.
- Clark A G. Formal genetics of humans: multifactorial inheritance and common diseases. In: Speicher M R, ed. Vogel and Motulsky's Human Genetics: Problems and Approaches. Berlin, Heidelberg: Springer Verlag, 2010: 263–286.
- Hillmer A M, Brockschmidt F F, Hanneken S et al. Nat Genet 2008; **40**: 1279–1281.
- Richards J B, Yuan X, Geller F et al. Nat Genet 2008; **40**: 1282–1284.
- Visscher P M, Brown M A, McCarthy M I et al. Am J Hum Genet 2012; **90**: 7–24.
- Schork N J, Murray S S, Frazer K A et al. Curr Opin Genet Dev 2009; **19**: 212–219.
- Reich D E, Lander E S. Trends Genet 2001; **17**: 502–510.
- Mitchell K J. Genome Biol 2012; **13**: 237.
- Brockschmidt F F, Heilmann S, Ellis J A et al. Br J Dermatol 2011; **165**: 1293–1302.
- Heilmann S, Kiefer A K, Fricker N et al. J Invest Dermatol 2013; **133**: 1489–1496.
- Li R, Brockschmidt F F, Kiefer A K et al. PLoS Genet 2012; **8**: e1002746.
- Brockschmidt F F, Hillmer A M, Eigelshoven S et al. Br J Dermatol 2010; **162**: 899–903.
- Ellis J A, Stebbing M, Harrap S B. J Invest Dermatol 2001; **116**: 452–455.
- Hayes V M, Severi G, Eggleton S A et al. Cancer Epidemiol Biomarkers Prev 2005; **14**: 993–996.
- Hillmer A M, Hanneken S, Ritzmann S et al. Am J Hum Genet 2005; **77**: 140–148.
- Levy-Nissenbaum E, Bar-Natan M, Frydman M et al. Eur J Dermatol 2005; **15**: 339–340.
- Sawaya M E, Shalita A R. J Cutan Med Surg 1998; **3**: 9–15.
- Prodi D A, Pirastu N, Maninchedda G et al. J Invest Dermatol 2008; **128**: 2268–2270.
- Klopper J E, Ernst N, Krieger K et al. J Invest Dermatol 2014; **134**: 2036–2038.
- Botchkarev V A, Fessing M Y. J Invest Dermatol Symp Proc 2005; **10**: 247–251.
- Cobb J E, White S J, Harrap S B et al. PLoS One 2009; **4**: e5081.
- Birch M P, Messenger A G. Eur J Dermatol 2001; **11**: 309–314.
- Martin M, Kettmann R, Dequiedt F. Oncogene 2007; **26**: 5450–5467.
- Halkidou K, Cook S, Leung H Y et al. Eur Urol 2004; **45**: 382–389; author reply 389.
- Jeong B C, Hong C Y, Chattopadhyay S et al. Mol Endocrinol 2004; **18**: 13–25.
- Suh J H, Shong M, Choi H S et al. Mol Endocrinol 2008; **22**: 33–46.
- Xu Y, Xu Y, Liao L et al. Am J Pathol 2013; **183**: 1281–1292.
- Li L, Cserjesi P, Olson E N. Dev Biol 1995; **172**: 280–292.
- Gong X Q, Li L. J Biol Chem 2002; **277**: 12310–12317.
- Lee Y S, Lee H H, Park J et al. Nucleic Acids Res 2003; **31**: 7165–7174.
- Reddy S, Andl T, Bagasra A et al. Mech Dev 2001; **107**: 69–82.
- Andl T, Reddy S T, Gaddapara T et al. Dev Cell 2002; **2**: 643–653.
- Fuchs E. Nature 2007; **445**: 834–842.
- Millar S E, Willert K, Salinas P C et al. Dev Biol 1999; **207**: 133–149.
- Shimizu H, Morgan B A. J Invest Dermatol 2004; **122**: 239–245.
- Eriksson N, Macpherson J M, Tung J Y et al. PLoS Genet 2010; **6**: e1000993.
- Medland S E, Nyholt D R, Painter J N et al. Am J Hum Genet 2009; **85**: 750–755.
- Wang H Y, Malbon C C. Science 2003; **300**: 1529–1530.
- Sato-Miyaoka M, Hisatsune C, Ebisui E et al. J Invest Dermatol 2012; **132**: 2137–2147.
- Kretschmar K, Cottle D L, Schweiger P J et al. J Invest Dermatol 2015; **135**: 2753–2763.
- Maurano M T, Humbert R, Rynes E et al. Science 2012; **337**: 1190–1195.
- Schaub M A, Boyle A P, Kundaje A et al. Genome Res 2012; **22**: 1748–1759.
- Mikkola M L. Semin Cell Dev Biol 2007; **18**: 225–236.
- Lim X, Nusse R. Cold Spring Harb Perspect Biol 2013; **5**: pii: a008029. doi:10.1101/cshperspect.a008029.
- Higgins C A, Chen J C, Cerise J E et al. Proc Natl Acad Sci U S A 2013; **110**: 19679–19688.
- Higgins C A, Richardson G D, Ferdinando D et al. Exp Dermatol 2010; **19**: 546–548.
- Arias-Santiago S, Arrabal-Polo M A, Buendia-Eisman A et al. J Am Acad Dermatol 2012; **66**: 401–408.
- Oh B R, Kim S J, Moon J D et al. Urology 1998; **51**: 744–748.
- Giles G G, Severi G, Sinclair R et al. Cancer Epidemiol Biomarkers Prev 2002; **11**: 549–553.
- Hawk E, Breslow R A, Graubard B I. Cancer Epidemiol Biomarkers Prev 2000; **9**: 523–527.
- Ahouansou S, Le Toumelin P, Crickx B et al. Eur J Dermatol 2007; **17**: 220–222.
- Gonzalez-Gonzalez J G, Mancillas-Adame L G, Fernandez-Reyes M et al. Clin Endocrinol (Oxf) 2009; **71**: 494–499.
- Ford E S, Freedman D S, Byers T. Am J Epidemiol 1996; **143**: 651–657.
- Herrera C R, D'Agostino R B, Gerstman B B et al. Am J Epidemiol 1995; **142**: 828–833.
- Hirso P, Laakso M, Matilainen V et al. Cent Eur J Public Health 2006; **14**: 78–81.
- Lesko S M, Rosenberg L, Shapiro S. JAMA 1993; **269**: 998–1003.
- Lotufo P A, Chae C U, Ajani U A et al. Arch Intern Med 2000; **160**: 165–171.

- 81 Matilainen V, Koskela P, Keinanen-Kiukkaaniemi S. *Lancet* 2000; **356**: 1165–1166.
- 82 Schnohr P, Lange P, Nyboe J *et al.* *Am Heart J* 1995; **130**: 1003–1010.
- 83 Trieu N, Eslick G D. *Int J Cardiol* 2014; **176**: 687–695.
- 84 Andreassen O A, Djurovic S, Thompson W K *et al.* *Am J Hum Genet* 2013; **92**: 197–209.
- 85 Lee S H, Ripke S, Neale B M *et al.* *Nat Genet* 2013; **45**: 984–994.
- 86 Mahurkar S, Moldovan M, Suppiah V *et al.* *PLoS One* 2013; **8**: e57655.
- 87 Menon R, Farina C. *PLoS One* 2011; **6**: e18660.
- 88 Zhernakova A, Stahl E A, Trynka G *et al.* *PLoS Genet* 2011; **7**: e1002004.
- 89 Edwards T L, Scott W K, Almonte C *et al.* *Ann Hum Genet* 2010; **74**: 97–109.
- 90 Lill C M, Roehr J T, McQueen M B *et al.* *PLoS Genet* 2012; **8**: e1002548.
- 91 Nalls M A, Plagnol V, Hernandez D G *et al.* *Lancet* 2011; **377**: 641–649.
- 92 Stefansson H, Helgason A, Thorleifsson G *et al.* *Nat Genet* 2005; **37**: 129–137.
- 93 Carey A H, Chan K L, Short F *et al.* *Clin Endocrinol (Oxf)* 1993; **38**: 653–658.
- 94 Starka L, Duskova M, Cermakova I *et al.* *Endocr Regul* 2005; **39**: 127–131.
- 95 Fondell E, Fitzgerald K C, Falcone G J *et al.* *Am J Epidemiol* 2013; **178**: 1146–1149.
- 96 Liu F, Hamer M A, Heilmann S *et al.* *Eur J Hum Genet* 2015; doi:10.1038/ejhg.2015.220. [Epub ahead of print].
- 97 Marcinska M, Pospiech E, Abidi S *et al.* *PLoS One* 2015; **10**: e0127852.
- 98 Jain R, De-Eknamkul W. *Expert Opin Ther Targets* 2014; **18**: 787–806.
- 99 Valente Duarte de Sousa I C, Tosti A. *Expert Opin Investig Drugs* 2013; **22**: 573–589.
- 100 Cecchin E, De Mattia E, Mazzon G *et al.* *Int J Biol Markers* 2014; **29**: e310–e316.
- 101 Ganzer C A, Jacobs A R, Iqbal F. *Am J Mens Health* 2015; **9**: 222–228.
- 102 The Endcode Project Consortium. *Nature* 2012; **489**: 57–74.
- 103 The GTEx-Consortium. *Science* 2015; **348**: 648–660.
- 104 Westra H J, Peters M J, Esko T *et al.* *Nat Genet* 2013; **45**: 1238–1243.
- 105 Yang J, Huang T, Petralia F *et al.* *Sci Rep* 2015; **5**: 15145.
- 106 Gerrits A, Li Y, Tesson B M *et al.* *PLoS Genet* 2009; **5**: e1000692.
- 107 Kim H, Kim J S. *Nat Rev Genet* 2014; **15**: 321–334.
- 108 Urnov F D, Rebar E J, Holmes M C *et al.* *Nat Rev Genet* 2010; **11**: 636–646.
- 109 Fischer T W, Herczeg-Lisztes E, Funk W *et al.* *Br J Dermatol* 2014; **171**: 1031–1043.
- 110 Havlickova B, Biro T, Mescallchin A *et al.* *J Invest Dermatol* 2009; **129**: 972–983.
- 111 Kloepper J E, Sugawara K, Al-Nuaimi Y *et al.* *Exp Dermatol* 2010; **19**: 305–312.
- 112 Langan E A, Philpott M P, Kloepper J E *et al.* *Exp Dermatol* 2015; **24**: 903–911.
- 113 Gilhar A, Keren A, Shemer A *et al.* *J Invest Dermatol* 2013; **133**: 844–847.
- 114 Oh J W, Kloepper J, Langan E A *et al.* *J invest Dermatol* 2016; **136**: 34–44.
- 115 Collins F. *Nature* 2010; **464**: 674–675.
- 116 Evans J P, Meslin E M, Marteau T M *et al.* *Science* 2011; **331**: 861–862.
- 117 Kathiresan S, Melander O, Guiducci C *et al.* *Nat Genet* 2008; **40**: 1384.
- 118 Okada Y. *Clin Genet* 2014; **86**: 432–440.
- 119 Ripke S, Neale B M, Corvin A *et al.* *Nature* 2014; **511**: 421–427.
- 120 Nelson M R, Tipney H, Painter J L *et al.* *Nat Genet* 2015; **47**: 856–860.
- 121 Nuwaihdy R, Redler S, Heilmann S *et al.* *Arch Dermatol Res* 2014; **306**: 413–418.