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Update on the Genetics of Androgenetic Alopecia, Female Pattern Hair Loss, and Alopecia Areata: Implications for Molecular Diagnostic Testing

Pedram Yazdan, MD

Androgenetic alopecia, female pattern hair loss, and alopecia areata are among the most common forms of nonscarring hair loss encountered in clinical practice. Although the exact pathogenesis of these forms of alopecia remains to be clarified, genetic factors appear to have a significant contribution to their pathogenesis. Current treatment strategies are limited and their effectiveness remains modest at best. This review summarizes the current purported pathogenesis and recent genetic discoveries relating to these forms of alopecia. The role of molecular diagnostic testing is also discussed in relation to its future clinical utility for the prediction of developing hair loss, the diagnosis of the type of alopecia, prediction of disease severity, development of novel therapeutic and preventative targeted treatments, as well as determination of response to therapy.
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Hair loss is a common clinical problem in dermatologic practices, yet complex in etiology. Patients are often anxious about the clinical diagnosis and whether effective treatments exist. Among the various forms of alopecia, androgenetic alopecia ([AGA] also known as male pattern hair loss), female pattern hair loss (FPHL), and alopecia areata (AA) are among the most common forms of nonscarring hair loss encountered by clinicians. Additionally, there are significant psychosocial burdens faced by many patients with these forms of alopecia.[1,2] Despite their high prevalence, effective treatment that halts the progression of hair loss and allows for substantial hair regrowth remains a challenge for many patients because our current knowledge of the full spectrum of biomolecular mechanisms underlying these conditions remains modest at best.[3,4] To date, the etiology of these alopecias is unclear and genetic factors appear to play a significant role in their pathogenesis.

Remarkable advances in genomic discovery along with the ever growing usage of molecular diagnostic testing for enhanced diagnosis, prognosis, and treatment of many other diseases are made every day. However, the diagnosis and classification of alopecia is still currently based on the correlation of clinical history, examination, and when necessary scalp biopsy for histopathologic evaluation. Moreover, in certain cases, the clinical and histopathologic features may be ambiguous, making it difficult to render a definitive diagnosis.[5-9] Currently, there are limited ancillary techniques available to allow for more accurate diagnoses in such cases as well as accurately predicting the severity, natural coarse, and treatment response of alopecias. Therefore, reliance on clinical and histopathologic features in this regard has been unpredictable.[5,10,11]

The aim of this article is to review the current understanding of the genetics of these 3 forms of nonscarring alopecias and to discuss how this information and future molecular advancements may allow for the development of ancillary molecular diagnostic testing for patients with hair loss. Such tests will ultimately allow for the prediction of risk of developing alopecia, accurate diagnosis and classification, prognosis of disease severity, development of novel therapeutic and preventative targeted treatments, as well as determination of response to therapy.

Androgenetic Alopecia and Female Pattern Hair Loss

Pathophysiology

The most common form of hair loss affecting men is AGA. As many as 50% of Caucasian men are affected by age 50[12-14]

Department of Dermatology, Feinberg School of Medicine, Northwestern University, Chicago, IL.
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Correspondence Author: Pedram Yazdan, MD, Department of Dermatology, Northwestern University, 676 North St. Clair Street, Suite 1600, Chicago, IL 60611. E-mail: p-pouryazdanparast@fsm.northwestern.edu

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and up to 80% by age 70.[15] The use of the medical term AGA reflects the current knowledge regarding the important role of both androgens and genetic inheritance in this form of alopecia.[16] The association between androgens and AGA was first noted in 400 BC by Hippocrates, who observed that eunuchs never developed patterned baldness. In the 1940s, Hamilton[16] showed that AGA did not develop in men who were castrated before puberty or in early adolescence, or those with severe testicular insufficiency. When testosterone was administered, baldness could be induced in those who were genetically predisposed (ie, family history of baldness), and when testosterone was discontinued, the alopecia did not progress, however, neither did the hair loss reverse. These observations support androgens as a prerequisite for the development of AGA in genetically susceptible men.

Testosterone is the major circulating androgen in men and is metabolized to dihydrotestosterone (DHT) in tissues. DHT is thought to be the key androgen required for the induction of AGA.[17] The conversion of testosterone to DHT in hair follicles is predominately mediated by the enzyme 5α-reductase, which exists as 2 isoforms, types I and II. Both isoforms are found in scalp follicles; however, the conversion of testosterone to DHT in hair follicles is predominately mediated by type II 5α-reductase, and it has been shown that men who are genetically deficient in type II 5α-reductase do not experience AGA.[18] On the scalp, androgen sensitivity and the distribution of androgen receptors are region specific, and this may explain why the occipital scalp is resistant to the effects of androgens and is usually spared even in the most severe case of AGA.

FPHL is somewhat less common than AGA, affecting up to 25% of women under age 50[19] and up to 40% of women by age 70.[20] Although the androgen-dependent nature of AGA in men is well established, the relationship of androgens to the development of FPHL is more complex. Although women with hyperandrogenism certainly have a high incidence of FPHL (up to 86%), many women with FPHL do not have the elevated blood level of androgen hormones.[19] Women without circulating androgens may also develop FPHL,[21] which raises the possibility for nonandrogen-dependent mechanisms and could explain why some women with FPHL do not respond to androgen inhibition therapy.

The role of estrogens in scalp hair growth has not been as extensively studied as that of androgens, and there are different views on whether estrogens are stimulatory or inhibitory to hair growth. Clinically, the increased prevalence of FPHL after menopause implies a possible stimulatory role for estrogens in hair growth.[22] High-systemic estrogen levels in pregnancy are speculated to partially account for the prolongation of anagen, whereas plummeting estrogen levels in the postpartum period may in part account for the simultaneous conversion of hair follicles into the telogen phase, resulting in the condition telogen gravidarum.[23] Lower estrogen levels because of aromatase inhibitor therapy have also been observed to induce hair loss. Topical estrogen applications have been widely used in some European countries as hair-growth stimulants in FPHL. Conversely, other studies show that estrogens are inhibitory to hair growth. In mouse models, the administration of estrogen agonists has been shown to produce a profound and prolonged inhibition of hair growth through telogen arrest, whereas estrogen antagonists stimulated hair growth through the initiation of anagen.[24,25] Additional evidence for an inhibitory role of estrogen in FPHL is the finding of an aromatase gene variant associated with circulating estrogen levels that occur at higher frequencies in women with FPHL when compared with unaffected women (discussed in more detail later in the text).[26]

Both AGA and FPHL are indistinguishable on a histologic level and result from altered hair follicle cycling and progressive miniaturization of the hair follicles. In both conditions, the duration of the anagen phase shortens, whereas the duration of the telogen phase remains the same or lengthens, causing a reduction in the anagen to telogen ratio from around 10-12:1 to 5:1. Because hair length is determined by the anagen phase, each passage through the cycle causes the length of the new anagen hair to be shorter than its predecessor. Eventually, the anagen phase becomes so short that it does not allow time for the new hair to acquire enough length to reach the skin surface. Telogen hairs, which now make up an increasing percentage of the total hairs, are more loosely anchored to the follicle than anagen hairs, leading to increased hair shedding. In addition, the latency period between telogen hair shedding and anagen regrowth becomes longer, ultimately leading to a reduction in the number of hairs present on the scalp. Follicular miniaturization also occurs in both AGA and FPHL, where the size of the follicle is reduced with each consecutive cycle leading to hairs that are narrower and shorter and of smaller diameter over time. Thus, a proportion of the large terminal follicles become miniaturized, making hair significantly finer and more susceptible to falling out. Although the pathophysiology of AGA and FPHL remains to be fully established, the alterations that occur within the hair follicle appear to some extent to be androgen mediated in AGA, and in some cases of FPHL, with androgen-independent mechanisms, possibly contributing to hair loss in both conditions as well.

Genetics of Androgenetic Alopecia and Female Pattern Hair Loss With Implications for Molecular Diagnostic Testing

AGA and FPHL are associated with strong heritability; however, the exact mode of inheritance of AGA and FPHL remains to be fully elucidated. Twin studies have shown that the development of hair loss is predominately determined by genetic predisposition.[27] However, because of the high prevalence of AGA and FPHL, the increased risk of developing alopecia with increasing numbers of affected relatives, the wide distribution of age at onset, and the range of severity of the alopecia among affected individuals strongly suggest that this condition is not controlled by 1 gene (single gene traits rarely occur with a frequency $>$ 1 in 1000), rather follows a polygenic mode of inheritance.[27,28] Like many polygenic human disorders, the ultimate phenotypic expression of AGA and FPHL is likely dependent on the complex interplay between a number of genes throughout the genome. Each of

these genes may contribute variably to the risk of hair loss in one's lifetime and may determine the age of onset, progression, patterning, and severity of the alopecia.

The genetic predisposition of AGA and FPHL and the role of androgens in its pathogenesis lead early genetic association studies to focus on chromosomes 2 and 5, which are the sites of the 5α-reductase enzyme genes, *SRD5A2* and *SRD5A1*, respectively. However, it has been determined that no significant difference in allele, genotype, or haplotype frequencies exists between young bald men and older nonbald male controls, suggesting no association with the genes encoding the 2 5α-reductase isozymes and AGA.[29] Attention was then turned to the androgen receptor gene (*AR*) located on the X-chromosome (Xq11-12) and belonging to a family of nuclear transcription factors whose aminoterminal domain (exon 1) is required for transcriptional activation. Ellis et al[30] demonstrated the polymorphism in the *AR* gene and its association with susceptibility to the development of AGA in men. Specifically, a particular single-nucleotide polymorphism (SNP) in exon 1, known as StuI (rs6152, restriction fragment length polymorphism [RFLP], E211 G > A), is strongly associated with AGA in Caucasian men. The StuI RFLP in exon 1 was found to be present in 98% of young balding men and 92% of older balding men but was also found in 77% of nonbalding older men. As a large proportion of nonbald men carry this marker, it has been postulated that these men must lack other necessary causes of AGA, hence supporting a polygenic pathogenesis for this condition.[30] This particular SNP also cannot account for father-to-son transmission of AGA because it is located on the X-chromosome and men inherit this chromosome maternally. Additionally, the StuI RFLP marker is flanked by 2 highly polymorphic triple-repeat sequences: a polyglutamine triplet repeat (CAG) that lies proximally and a polyglycine triplet repeat (GGN) that lies distally to StuI. Studies have found shorter CAG triplet repeats to be associated with the development of male AGA,[30,31] with conflicting data regarding the role of GGN repeats. Hillmer et al[32] have suggested an association between shorter GGN repeats and AGA; however, Ellis et al[33] found that the *AR* GGN repeat polymorphism did not independently confer susceptibility to AGA.

Interestingly, the StuI RFLP is noncoding and does not appear to lead to the phenotypic consequence of AGA by itself. However, the strong association of this marker with AGA may be explained if it acts as a marker for the inheritance of another functional SNP migrating together with it throughout generations via linkage disequilibrium (LD). Multiple comprehensive studies of SNPs[34-37] and copy number variations[38] of the *AR* gene region by various groups have thus far failed to identify a functional variant in LD that could be responsible for this strong association. Although the highly polymorphic CAG and GGN triplet repeats in exon 1 of the *AR* gene may possibly be in LD with the StuI RFLP, they are not thought to be functional variants responsible for this association.[33] Currently, it has been hypothesized that the association between the *AR* gene and AGA involves variation in regulatory elements of noncoding DNA that may reside upstream or downstream of the *AR* gene region.[10] Recently, 2 independent loci containing SNPs located in the upstream and downstream intergenic regions of the *AR* gene were mapped and each were found to be independently associated with AGA.[39] However, further studies are needed to identify functional variants in the noncoding regions around the *AR* gene that contribute to AGA.

It has been estimated that the genetic variations in the *AR* gene may account for up to 40% of the heritability of AGA.[32] The fact that the vast majority of men with premature hair loss have the predisposing *AR* gene variant suggests that inheriting this variant seems to be a necessary prerequisite for developing AGA. However, because the same predisposing copy of the *AR* gene variant is seen so commonly in older men without AGA, it is unlikely to be sufficient by itself to cause hair loss. In addition, up to 60% of the genetic predisposition remains unexplained, indicating that there are likely other genes contributing to the risk profile of AGA. In contrast to candidate gene methods, genome-wide genetic studies survey the entire genome in a nonbiased way for evidence of genetic contributions to disease. This methodology identifies genes on the basis of their position in the genome and does not depend on understanding the functionality of those genes. Therefore, these types of studies are particularly powerful methods for evaluating disease mechanisms when much remains unknown about how or why the disease occurs.

With the recent advent of the genome-wide association studies (GWAS) and in keeping with the purported polygenic transmission of this condition, several other susceptibility loci have been found to be associated with AGA. Prodi et al[36] recently identified a locus near the androgen receptor at Xq11-12 containing the ectodysplasin A2 receptor gene (*EDA2R*), which was found to be independently and strongly associated with AGA. It has been postulated that *EDA2R* could influence the onset of AGA through the activation of the *NF-κB* pathway or by *c-Jun*, which has been shown to be critical for *AR* transactivation.[40] However, the association of *EDA2R* with AGA could not be replicated in an Australian population.[39] A possible explanation for the inability to replicate this association may be attributable to population stratification. In 2 other GWAS, a significant correlation was found between 5 SNPs on chromosome 20p11 and the development of early onset AGA (< 40 years of age), suggesting that this locus may play a role in a yet to be identified androgen-independent pathway.[34,37] The SNPs identified in these studies lie adjacent to the paired box 1 gene, which is expressed in skin, hair, and scalp, and is, therefore, a good candidate gene for AGA. In the studied populations, it was also determined that 1 in 7 men who harbored the AGA-associated SNPs at both chromosome 20p11 and *AR* had a 7-fold increased risk of developing AGA.[37] However, because this susceptibility locus is located within a gene-poor region, the significance of these findings in relation to AGA are yet unknown. An AGA susceptibility locus has also been mapped to chromosome 3q26 in a population of German men; however, no known genes in this region are involved in hair biology.[35]

A more recent GWAS has demonstrated a potentially new susceptibility locus among German and Australian men, re-

vealing 2 SNPs located at 7p21.1 within the histone deacetylase 9 (*HDAC9*) gene that are associated with AGA.[41] One of these SNPs demonstrated a strong association, especially among men who were severely affected by AGA. In general, members of the histone deacetylase gene family modulate the chromatin structure thereby acting as key regulators of gene transcription. It has been postulated that HDAC9 may interact with the *AR* gene, thereby regulating its transcriptional activity, possibly in a tissue-specific manner.[41] However, caution should be exercised in considering *HDAC9* as a true causative gene for AGA because no direct effects of the associated variants have been demonstrated to date. It is possible that the associated variants or unidentified true causative variant(s) may be located in a regulatory element of a more distant gene. Further studies are necessary to investigate these hypotheses.

There are fewer reported genetic association studies for FPHL in comparison with AGA. The genetic association studies for FPHL have not been able to reproduce the same strong association with the *AR* gene as found with AGA. Therefore, it is not clear whether the *AR* gene is also similarly pathogenic for FPHL. Whether an association between FPHL and the *AR* gene exists is difficult to interpret because of its location on the X-chromosome rendering 1 of the 2 gene copies prone to X-chromosome inactivation. The analyses of the association of FPHL to the *AR* gene using samples of peripheral blood from patients in certain studies make drawing a direct comparison with the changes occurring at the level of the hair follicle tissue difficult because X-chromosome inactivation is tissue specific.

One study did examine the relationship between the StuI RFLP in exon 1 of the *AR* gene; however, no association was found between this SNP and FPHL.[42] In another study, a weak association was found between FPHL and the AGA-associated susceptibility locus at chromosome 20p11.[37] The implications of these findings are unknown at this time, and the authors of the study concluded that it is necessary to investigate this possible association in larger and carefully-phenotyped cohorts. The CAG repeat-length polymorphism in exon 1 in the *AR* gene has been linked with the development of androgen-related skin disorders, including acne, hirsutism, and FPHL in women with elevated androgen levels.[31,43] However, in these studies, peripheral blood was used as the tested sample in the analyses rather than scalp hair follicles. The results generated from these studies do not take into consideration the effects of tissue-specific X-chromosome inactivation thereby limiting the strength of association of CAG repeat-length polymorphism and FPHL.

There has been recent evidence for the role of the aromatase gene (*CYP19A1*) in FPHL. The *CYP19A1* gene encodes the enzyme aromatase that is responsible for the conversion of androgens to estrogens, thereby regulating the balance of sex steroid hormone levels within the hair follicles. Yip et al[26] found a nonfunctional SNP (rs4646) located in the 5'-untranslated region of the *CYP19A1* gene. The frequency of this SNP was found to be higher in women (particularly in younger women) affected by FPHL and, in an unrelated study, was found to be associated with higher circulating estrogen levels in women.[44] The same group demonstrated that variation involving SNPs in the gene encoding for the estrogen receptor beta 2 (*ESR2*) may be associated with developing FPHL. *ESR2* is the predominant estrogen receptor within the hair follicle and thought to be the principle mediator of estrogenic effects in hair growth.[45] These findings support the view that estrogens may be involved in the pathogenesis of FPHL. However, measurement of sex steroid levels within the hair follicles would be necessary for future verification of these results.

As a result of the advancement of genetic data for AGA, there are additional studies to determine if associations exist with treatment response and specific genetic findings. The current mainstay of therapy for AGA is finasteride, which is a potent synthetic inhibitor of 5α-reductase type II. There are a limited number of studies that have postulated a genetic basis for the variable response to finasteride therapy for AGA. In a small study of 9 men with AGA, the messenger RNA expression of several cytokines believed to regulate hair growth was analyzed in follicular dermal papillae before and after finasteride therapy.[46] A positive response to finasteride therapy was found to be associated with increased expression of the insulin-like growth factor 1. Wakisaka et al[47] demonstrated a possible association between the *AR* gene CAG/GGC triplet repeats and response to finasteride among Japanese men. In this study, a sum of $\leq$ 40 CAG plus GGC triplet repeats in the *AR* gene was associated with improved response to finasteride despite the test group presenting with more severe AGA. These results were verified in a second study whereby 70% of men with a marked response to finasteride had CAG repeat lengths $<$ 22, whereas 70% of those with only minimal drug response had CAG repeat lengths $>$ 22.[48] There are limited numbers of similar studies with respect to FPHL. A recent study by Yamazaki et al[49] was not able to show differences in CAG repeat numbers in association with finasteride therapy. However, in a 6-month pilot of 13 patients, Keene and Goren[50] demonstrated that women with greater androgen sensitivity ($<$ 24 cytosine, adenine, and guanine [CAG] repeats) were likely to have a significant response to finasteride compared with patients treated with placebo, and also compared with patients with normal androgen sensitivity ($\geq$ 24 CAG repeats) based on epigenetic-weighted evaluation of the CAG alleles. Currently, additional studies are necessary to firmly establish the possible genetic associations in regard to the efficacy of finasteride therapy in both AGA and FPHL as well as the applicability of this test for clinical use.

The results of the genetic studies described previously in the text have been incorporated into the clinical evaluation and treatment of AGA and FPHL. Based on the information gleaned from these studies, screening tests have been developed for AGA and FPHL by a California based company, HairDx LLC (Irvine, California, USA), and are designed to provide patients with a risk estimate for developing AGA or FPHL. The end goal is to allow for earlier detection because long-term treatment with finasteride has been demonstrated to decrease the likelihood of developing further visible hair loss in some patients.[51] This test uses a cheek swab and evaluates for the StuI SNP in the *AR* gene in men. Reports from

this company indicate that when integrating the family history of AGA from a patient's father, it can help improve the predictive value of the HairDx test. It is claimed that those with a father having a history of AGA who test positive for the *AR* variant have a > 80% chance of developing AGA, and those with a father without any history who test negative for the *AR* variant have > 90% chance of not developing AGA.[52] For young patients concerned about hair loss, this test may help to define the value of early treatment initiation.

For women, there is a different genetic test that evaluates for the number of CAG repeats within the *AR* gene and is used to predict a woman's risk of developing FPHL.[52] The company references the study by Sawaya et al,[31] which found that < 2% of women with > 23 CAG repeats developed FPHL, whereas approximately 98% of women with < 16 CAG repeats had FPHL. In women with intermediate numbers of CAG repeats between 16 and 23, the association with FPHL was not as apparent. According to HairDx LLC, this test could be used to reassure a woman whose CAG repeats are > 23 that she is unlikely to develop FPHL, and those with < 16 CAG repeats may be considered as candidates for initiating therapy for FPHL.

Although these genetic tests are currently available for patients, it is important to be aware of their limitations. To date, only a relatively small portion of the heritability of AGA and FPHL has been explained by variation in the *AR* gene, which makes the clinical relevance of such tests uncertain at this time. Because genetic testing for AGA and FPHL relies predominately on the *AR* gene variation, the tests do not take into consideration the polygenic contributions from other causative genes and the possible role of epigenetic mechanisms.[4] Genetic testing for AGA is based on genotyping for the StuI SNP in the *AR* gene, which is a nonfunctional SNP. This particular *AR* gene SNP does not lead to any alteration in gene protein or function, nor has it been linked to a functional SNP that does produce functional alterations. Additionally, a positive gene test result can be found in a high percentage of men ≥ 50 years of age who have no evidence of hair loss as well as in the majority of balding men, leading to an uncertain clinical significance of a positive test result and ambiguity regarding whether to initiate treatment. By contrast, a negative test should not change the treatment offered to a patient. Therefore, for young patients concerned about hair loss, this test may have some potential in helping to define the value of early treatment initiation. However, it must be noted that because only a portion of AGA heritability can be explained by *AR* gene variation, testing the *AR* genetic variation alone does not accurately predict risk for developing AGA. Genetic testing for FPHL risk estimates are currently based on CAG repeat polymorphism in exon 1 of the *AR* gene, and the strength of this association with FPHL risk is also uncertain at this time.

Alopecia Areata

Pathophysiology

AA is the most frequent cause of inflammatory hair loss, affecting an estimated 4.5 million people in the United States.[53] The prevalence of AA in the United States is approximately 0.1% to 0.2% of the population with an average lifetime risk of developing AA estimated at 2%.[54] Additionally, 1 patient in 5 with AA has reported another family member with the disease. AA affects both children and adults and hair of all colors.[55] The disease is uncommon in children < 3 years of age; however, most patients are relatively young, up to 66% are younger than 30 years of age, and only 20% are older than 40 years of age with no significant sex predilection.

AA is also among the most prevalent autoimmune disorders leading to disfiguring hair loss and is associated with an increased overall risk of other autoimmune disorders (16%).[56,57] The likely mechanism of this disease is probably because of the collapse of the immune privilege of the hair follicle and subsequent autoimmune defect.[58] From a clinical perspective, the natural course of AA is unpredictable. Approximately 30% to 50% of patients with AA will recover their hair loss within 1 year; and 15% to 25% will progress to total loss of scalp hair (alopecia totalis) or loss of the entire scalp and body hair (alopecia universalis), from which full recovery is uncommon (10%).[11] Despite the high prevalence and the psychosocial burden of AA, there are currently no evidence-based treatments with only a few available therapies that have been tested in placebo-controlled trials.[59] Additionally, there are no therapies that are approved by the Food and Drug Administration for the treatment of AA, and treatments are considered "off label." Current treatment choices are frequently based on the age of the patient as well as the extent and duration of their disease. Treatments include a variety of topical, intralesional, and systemic agents.[60] An analysis of 17 trials by the Cochrane Skin Group, published in the online *Cochrane Database of Systematic Reviews*, concluded that "overall, none of the interventions showed significant treatment benefit in terms of hair growth when compared with placebo."[59] The current limited information about the underlying genetics and complete pathomechanism of the disease presents a major challenge in identifying novel effective treatments.

The purported pathomechanism of AA is the collapse of the immune privilege of a previously healthy hair follicle.[61,62] AA can occur in genetically predisposed individuals when proinflammatory signals (including substance P and interferon-γ) that are known to upregulate major histocompatibility complex class Ia expression in the hair follicle expose previously sequestered hair-follicle–associated autoantigens to preexisting autoreactive CD8+ T-cells.[62-64] The lymphocytic infiltrate can then attack the hair follicle if costimulatory signals and interaction with others cells, such as CD4+ T-cells and mast cells, occurs.[61,62] Because only anagen hair follicles are attacked in AA, the autoantigens may be formed and presented only during this phase of the hair cycle.[65] In acute AA, histologic examination reveals a characteristic dense perifollicular lymphocytic inflammatory infiltrate around the terminal bulb portion of the anagen hair follicle.

There are numerous examples from murine-derived models of AA supporting this hypothesized pathomechanism.[58,66-69] Recent studies have also implicated other pro-

inflammatory factors as well as natural killer (NK) cells, NK-cell–stimulating ligands, and NK-cell receptors (NKG2D) in the pathogenesis of AA.[65,70] Hair follicles in AA have also been shown to overexpress the major histocompatibility complex class I polypeptide-related sequence A (MICA) protein, an important NKG2D agonist, whereas MICA expression in the normal hair follicle is much more limited.[65,71] Increased NKG2D-mediated signaling contributing to the pathogenesis of AA is highlighted by the genetic association between AA and NKG2D-activating ligands from the MICA family, specifically the cytomegalovirus UL16-binding protein 3, which is upregulated around the affected hair follicles in AA.[70]

Genetics of Alopecia Areata With Implications for Molecular Diagnostic Testing

The development of AA has a strong genetic component supported by the observation of heritability among first-degree relatives,[72] twin studies,[73] and studies on murine models.[74] Additional support for a genetic component of AA comes from the fact that a history of atopy and autoimmune disease is associated with an increased risk of developing a severe subtype of AA.[56,75] Familial cases of AA are also often characterized by a poorer prognosis with more rapid disease progression, more frequent relapses, and greater resistance to therapy in comparison with sporadic cases.[75,76]

The first genetic studies in AA were candidate-gene association studies, usually testing for a single gene that was chosen on the basis of a previous hypothesis about its function (typically in another autoimmune disease), tested for association in a small sample of cases and controls, and being biased by choices of candidate genes. Before GWAS, as with most autoimmune diseases, candidate gene studies have implicated associations of AA to genes residing in the human leukocyte antigen (HLA) region, including HLA-DQB1, HLA-DRB1, NOTCH4, and MICA, in addition to genes outside of the HLA region, including protein-tyrosine-phosphatase nonreceptor type 22, involved in negative regulatory effects on T-cell activation.[58]

One of the most promising areas of AA research has emerged from several recent large GWAS, which have identified a number of susceptibility loci associated with AA, in the form of SNPs, across several regions of the genome and implicating genes of the immune system as well as genes that are unique to the hair follicle itself.[70,77] Specifically, the key genes found in the GWAS include those linked to T-cell proliferation and hair follicle genes that activate the NKG2D ligand, which can trigger autoimmunity. Interestingly, the risk loci revealed in the GWAS share associations with other forms of autoimmunity, including rheumatoid arthritis, type I diabetes, celiac disease, Crohn disease, systemic lupus erythematosus, multiple sclerosis, and psoriasis.[78,79]

A GWAS of 20 families by Martinez-Mir et al[77] identified at least 4 susceptibility loci on chromosomes 6, 10, 16, and 18. On chromosome 6, 1 susceptibility locus was found at 6p that corresponds to the HLA locus, whereas the region on chromosome 16 overlaps with a region near a susceptibility locus for Crohn disease. The susceptibility locus for AA on chromosome 18p also contains a psoriasis-susceptibility region. In a major recent GWAS, Petukhova et al[70] evaluated 1054 patients and 3278 control subjects and identified 139 SNPs significantly associated with AA. The genomic regions not only encompassed the HLA region but also included genes that control the activation and proliferation of regulatory T-cell, cytotoxic T-lymphocyte-associated antigen 4 (CTLA4), interlukin (IL), IL-2/IL-21, IL-2 receptor A (IL-2RA; CD25) and Eos (known to play a crucial role in regulatory T-cell development). A strong association to AA was also found within the cytomegalovirus UL16-binding protein gene cluster on chromosome 6q25.1, encoding a class of ligands for activating NKG2D, which is highly expressed on NK cells and some CD8+ cells, and stimulates their activity. Previous studies have demonstrated excessive activity of NKG2D-expressing cells in the peripheral blood and lesional skin of AA patients as well as strong upregulation of MICA in lesional AA hair follicles.[65,70]

CTLA4 is a costimulatory molecule that is involved in the negative regulation of T-cell activation. The high expression of CTLA4 in patients with AA by GWAS has also been found in other autoimmune diseases, underscores the fact that AA shares pathways with other autoimmune conditions, and supports the concept of a strong autoimmune component to AA.[80,81] Two GWAS intrafollicularly expressed genes, peroxiredoxin 5 and syntaxin 17, were found to be associated with AA,[70] which points to the potential of follicular autoantigens playing a role in the pathobiology of the AA.

In the most recent GWAS, an intronic region of spermatogenesis-associated protein 5 has been suggested as yet another novel susceptibility loci for AA,[82] as well as *IL-13* and *KIAA0350/CLEC16A*.[83] IL-13 is a member of the cytokine group and is synthesized by activated T helper 2 cells. It is an essential effector in the recruitment of inflammatory cells and is thought to activate immunoglobulin E as well as the production and secretion of mucin. The variant rs20541, which achieved genome-wide significance, has been reported to be associated with autoimmune diseases, such as psoriasis, arthritis, and asthma.[84-86] *KIAA0350/CLEC16A* is located on chromosome 16p13 and encodes a protein without a presently known function. It is mainly expressed in immune cells and assumed to be of crucial importance in the immune-modulating processes.[87] Recent studies have shown that specific genetic variants of the *KIAA0350/CLEC16A* gene confer susceptibility to certain autoimmune disorders, such as multiple sclerosis and type 1 diabetes,[88,89] providing further evidence that certain autoimmune disorders and AA may have shared etiologies.

Although recent advancements have been made in our understanding of the genetic changes associated with AA, there are currently no molecular tests available for the diagnosis, prognosis, and treatment of patients with this disease. Although translational research in the study of AA is in its infancy, there have been several recent studies using molecular techniques that may have important clinical utility in the

future. Lueking et al[90] have combined protein microarray technology with the use of large cDNA expression libraries to profile the autoantibody repertoire of sera from AA patients against a human protein array consisting of 37,200 redundant recombinant human proteins. Eight autoantigens were identified among the AA patients by protein chip technology and were successfully confirmed by Western blot analysis. These proteins included SCG 10, GLCDAC05, α-endosulfine, NOL8, FGFR3, dematin, signal recognition particle subunit 14, and endemic pemphigus foliaceus autoantigen. FGFR3 is known to be expressed in the superbasal layers and the inner layers of hair follicles, and is strongly related to hair disorders. However, the possible pathophysiologic roles of the other detected proteins in AA remain to be defined. The 8 autoantigens were arrayed on protein microarrays to generate a disease-associated protein chip, purported to facilitate the detection of potential autoantigens in AA and in the discrimination of AA from other inflammatory skin disorders, making it potentially suitable for fast diagnosis. With the use of this disease-associated protein chip, the authors reported accurate identification of AA in 90% of their cases when compared with sera from patients with psoriasis or hand-and-foot eczematous dermatitis.

To date, there have been 2 studies examining peripheral blood and lesional skin samples from AA patients. These studies have demonstrated distinct gene expression patterns, suggesting that gene expression profiling could potentially be used to determine transcriptional signatures related to genetic susceptibility to the disease, phenotypic expression of the disease, and disease severity.[91,92] Additionally, Coda et al[93] integrated the findings from the recent GWAS with their transcriptional microarray data from the blood and skin of AA patients. The goal was to find potential molecular links connecting the putative AA susceptibility loci to phenotypic expression and clinical heterogeneity of the disease. This group found several differentially-expressed genes encoded within putative AA genetic loci, suggesting that distinct genetic loci with statistically significant altered gene expression are apparent in the peripheral blood and skin of patients with AA. This finding may have useful clinical application relevant to disease classification and variable expression of the disease. John et al[94] have confirmed that genetic variants in *CTLA4* are strongly associated with AA, and their findings also suggest that it has the strongest effect in patients with a severe form of the disorder. Therefore, *CTLA4* may be a potentially useful clinical marker for disease severity in the future.

The recent advances achieved in understanding the genetic basis of AA have also opened new avenues for development of new therapies based on the underlying purported mechanism of AA. Potential future therapeutic opportunities may involve targeting key inducers of hair-follicle immune-privilege collapse, such as substance P receptor antagonists and interferon-γ antagonists.[95] There may also be a role for treatments targeting NK cells, NK and CD8+ T cell-activating receptors (NKG2D), and their endogenous ligands (MICA, UL16-binding protein 3).[95] Additionally, by virtue of the common molecular pathways shared by AA and other autoimmune diseases, new therapies for AA may also involve classes of drugs and biologics currently under development or being used for other autoimmune diseases. The genetic data implying *CTLA4* in the pathogenesis of AA has an interesting correlate to a study by Carroll et al,[96] which revealed that monoclonal antibodies against CTLA4 were effective in preventing AA in a mouse model of the disease. As anti-CTLA4 antibodies deserve exploration as a potential new therapeutic approach in AA, clinical trials are pending to test the efficacy of the safety of abatacept (a fusion protein with the extracellular domain of CTLA4 fused with human immunoglobulin 1).[60] Abatacept is a medication approved by the Food and Drug Administration currently in clinical use for rheumatoid arthritis, and it selectively modulated the co-stimulatory signal required for full T-cell activation. It is hypothesized that abatacept may block the T-cell activation in AA.

Conclusions

The future of molecular diagnostic testing for AGA, FPHL and AA will likely play a prominent role in the prediction and diagnosis of hair loss, severity of disease, determination of response to therapy, and in identifying candidate targets for novel therapeutic approaches. However, genetic testing for these conditions currently remains limited. The current gold standard in diagnosis of these alopecias is by clinical history, examination, and, when necessary, scalp biopsy for histopathologic evaluation. Although in most cases the diagnosis of these alopecias can be ascertained by these modalities, there are cases whereby the clinical and histopathologic features may be ambiguous, making a definitive diagnosis difficult.[6-8] Additionally, the course and severity of the hair loss is unpredictable in most cases, and currently, there are no reliable and validated clinical or histologic features that can provide patients with prognostic information. It is conceivable that once the underlying genetic risk profiles of these forms of hair loss are more fully established, this information can potentially be used to aid in more definitively elucidating the pathogenesis of the hair loss. This would likely open more avenues for the development of molecular diagnostic testing that could be used as adjunctive tools to clinical and histopathologic examination, allowing for a more accurate and timely diagnosis. The establishment of molecular diagnostic testing for alopecia will also allow for the risk stratification of patients with respect to the development and severity of hair loss. Finally, molecular diagnostic testing will advance the field of pharmacogenetics for alopecia aiding in the development of therapeutic and preventative targeted therapies as well as determination of the treatment response allowing for personalization of treatment for patients with hair loss.

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