Epidemiologic and genetic characteristics of alopecia areata (part 1)

A. A. Alzolibani

KEY WORDS

alopecia areata, human leukocyte antigen genes, cytokine genes, chemokine genes, polymorphism

ABSTRACT

Alopecia areata (AA) is a common, chronic, inflammatory disease resulting in an unpredictable, non-scarring form of hair loss. It affects almost 0.1% of the general population. Although the cause of AA is poorly understood, it is hypothesized to have an autoimmune etiology. Supporting this theory is the fact that activated CD4 and CD8 T lymphocytes have been found in characteristic perifollicular and intrafollicular inflammatory infiltrates of affected individuals' anagen hair follicles. AA provides an excellent opportunity to study the role of immunogenetics. In fact, various genes that have a role in regulating immunity have also been associated with susceptibility to AA. Several reports have indicated a significant association between AA and certain human leukocyte antigens (HLA) genes such as HLA-DRB1*0401 and DQB1*. This review provides an overview of current knowledge about the molecular genetics of AA. The literature review has shown overlapping gene patterns suggestive of common pathogenic mechanisms. However, many questions remain unanswered because data about local gene expression patterns in affected tissues are still scarce.

Epidemiology

Alopecia areata (AA) is a common, chronic, inflammatory disease causing an unpredictable, non-scarring form of hair loss. Alopecia presents with different clinical patterns such as: a) Alopecia areata (AA), or recurrent hair loss with patches on legs, arms, the pubic region, scalp, lashes, or brows (1); b) Alopecia totalis (AT), or complete (or near complete) loss of facial and scalp hair (2); and c) Alopecia universalis (AU), or complete loss of all bodily and scalp hair (2).

Although figures quoted in the literature vary, the approximate prevalence rate of AA is 0.1% worldwide (3). The prevalence rate may be as much as between 0.9 and 6.9% in some ethnicities such as Korean (4). In the United States alone, 14.5 million people (approximately 2%) are affected with AA (5). The disease affects both sexes, all ages, and all ethnic groups (1, 6–8). Although the disease can begin at any time of life, its peak incidence is between 20 and 25 years of age. About 60% of patients present with the first epi-

sode of the disease before age 20 (9–12). Around 70% of cases occur between ages 10 and 25 (9). Although the disease is reported with equal frequency in both sexes, men are afflicted with severe forms of disease more often than women (63% vs. 36%).

Immunogenic factors

Evidence of the non-genetic etiology of AA is limited. Several environmental factors such as infections, stress factors, toxins, and diet have been incriminated, but none confirmed (13). A study has detected cytomegalovirus (CMV) DNA in AA scalp lesions (14), but these findings remained unconfirmed in another study in which PCR analysis of peripheral blood mononuclear cells of patients showed no relation between AA and latent or active CMV infection. (14) Similarly, the association of *Helicobacter pylori* with AA remains inconclusive (13).

Recent studies in humans have led to much evidence in support of an autoimmune etiology. The process appears to be T-cell mediated. Antibodies against anagen stage hair follicle structures have been detected in affected patients and in mouse models (15–17). Using immunofluorescence, antibodies to anagen phase hair follicles were found in as many as 90% of patients with AA, compared to fewer than 37% of control subjects (18). Histological finding of a dense perifollicular and intrafollicular infiltrate of primarily CD4+ and CD8+ lymphocytes is closely associated with dystrophic anagen stage hair follicles (18). The transmission of AA by T lymphocytes cultivated from affected scalp cells and transferred to human scalp explants on a severe combined immunodeficiency mouse model has been demonstrated (19).

Alopecia areata and atopy

Atopic diseases have been associated with 10% to 60% of AA patients (20, 21). Therefore several studies have suggested that a history of atopic diseases such as asthma, atopic dermatitis, and hay fever are risk factors for AA (20–25). Moreover, mutations in certain genes like the filaggrin gene (FLG) have been suggested as a strong risk factor for atopic dermatitis (26–32). Hence, some investigators hypothesize that mutations in these types of genes may also play a role in AA, particularly in the severe form of AA with comorbid atopic disease (22, 33). Moreover, the fact that the prognosis for hair re-growth is worse in atopic patients than in non-atopic ones may be additional evidence that atopic diseases are associated with increased risk of AA (34). The reason for this apparent higher frequency of atopy in AA may be ascribed to the genes involved in the inflammatory component of AA, which also increase the chances of an allergic reaction.

On the other hand, immunoglobulin E (IgE) is a class of immunoglobulin essential for the allergic response that has traditionally been associated with atopic disease. Recently, some studies have shown correlations between AA patients and elevation of IgE levels (35–37). Others have reported that AA and atopic diseases share a Th2 cytokine pattern and increase levels of IgE antibodies, mast cells, and eosinophils (38–41). This association may be caused by a shift from a Th1 response in early AA to a more chronic Th2 immune profile, with secondary B-cell stimulation and possible IgE class switching (42).

Genetic factors

The genetic factors for AA are important. There is a high frequency of a positive family history in AA patients, varying from 10 to 42%, and a lifetime risk of 2% (43–45). Genetic influence is also suggested by the occurrence of AA in twins, with a concordance of 55% in monozygotic twins (46). Similarly, a higher incidence of AA (8.8%) is seen in individuals with Down syndrome compared to the general population (10). Alopecia areata is considered a polygenic disease that depends on the additive action of several major susceptibility genes. In the last decade, the paradigm of a "complex trait" or "multifactorial trait" has become acceptable because genetic and ecological factors seem to contribute in the final phenotype of AA (44, 45, 47, 48). The term "complex trait" is used to describe phenotypes that do not exhibit classic Mendelian inheritance attributable to a single gene locus but do have a genetic component, as demonstrated by twin, adoption, and epidemiological studies (49). There are four separate observations in favor of polygenic inheritance (50): (i) the high prevalence of the trait, typical of complex traits for which the predisposing alleles are more common than the relatively rare mutations identified for Mendelian disorders; (ii) the Gaussian curve of distribution for both the stages of disease progression and the distribution of the disease, with a threshold effect that may be lowered, for example, by the presence of a particular HLA haplotype or autoimmune susceptibility (51); (iii) heritability as defined by both the frequency of affected family members, ranging from 3% to 42% (44), and concordance in twins (52); and (iv) the presence of congenital AA, strongly suggesting the contribution of genetic factors (53–56). Sundberg et al. (57) have reported the identification of potential susceptibility loci for AA phenotype in an experimental mouse model. In an attempt to determine the genetic basis of AA, a number of association studies for suspected genes have been

performed. Several of these studies have suggested a significant association of AA with numerous candidate genes.

Candidate genes

Genetic and proteomics technologies for autoimmune diseases have developed rapidly in the last decade. These technologies have led to the identification of many candidate genes in humans that confer susceptibility to the development of autoimmunity in cases of AA. There are two main approaches to determining the genetic contributions to a disease. The first is to conduct "association studies" in which an individual candidate gene is examined for association with the condition. The disadvantage of this approach is the possibility of false associations as a result of linkage disequilibrium. Therefore, it is necessary to conduct "frequency studies" in multiple populations. The second approach is to perform "genome-wide searches," which have recently started being utilized for identification of chromosomal regions associated with disease risk. This genome-wide approach has the advantage that it is not biased by an initial hypothesis. However, determination of chromosomal regions with genome-wide screens is only the first step, and much additional work is required to map the risk to specific genes. The following candidate genes have been studied.

Histocompatibility locus antigen (HLA) genes

The major histocompatibility complex (MHC) region represents the major susceptibility locus on chromosome 6 within the locus 6p21.3. Most of its genes encode cell-surface antigen-presenting proteins. These are divided into three classes. Human leukocyte antigen class-I (HLA-I), sub-classified as A, B, and C, are expressed on the surface of all nucleated cells and present peptides to CD8+ T cells. The CD8+ lymphocytes have the capacity to recognize cellular antigens presented in association with class I via their T cell receptors. In contrast, class II antigens (DP, DM, DOA, DOB, DQ, and DR) are normally expressed on antigen-presenting cells (APCs), such as macrophages and Langerhans cells, and expression may be induced on other nucleated cells during inflammatory processes such as AA (58, 59). CD4+ lymphocytes may recognize antigen plus class II complexes on APCs (60). The remainder comprises the HLA class III region that encodes components of the complement system, such as complement factors, tumor necrosis factor (TNF), and heat shock protein 70 (HSp70).

The association of AA with HLA-DR and HLA-DQ supports the notion that CD4+ T cells are involved in the disease process. HLA-DR and -DQ molecules are responsible for presenting antigen to CD4+ T cells (1). In addition, tissue histology of affected areas in AA demonstrates the presence of a perifollicular CD4+ lymphocytic infiltrate as well as a CD8+ intrafollicular infiltrate (61).

Early studies on HLA Class I failed to show a consistent linkage with a single antigen, although HLA-A2, B40, Aw32, and B18 alleles have each been reported as being associated with a high prevalence of AA in two families (62). Associations between HLA-B12 in Finnish patients, HLA-B18 in Israelis, and B13 and B27 in Russians have also been suggested (63–65). Kalish et al. have suggested that normal hair epithelium is an immune-privileged site due to its lack of HLA-A, -B, and -C expression (15). T cell recognition of follicular autoantigens may be induced by the increased expression of HLA-A, -B, and -C as well as HLA-DR during inflammatory conditions, resulting in a loss of immune privilege (66).

More consistent associations have been found between AA and Class II haplotypes. Recurrent direct linkage analysis advocates for a link between the HLA class II region and AA, showing an LOD (logarithm of odds) score of 2.42 for HLA-DQB at 5% recombination (6). Recently, a report from the United States stated that HLADQB1*03 (*0301–*0303) alleles were present in 80% of all AA cases regardless of phenotype, and this presence increased to 92% in cases with AT or AU (odds ratio = 12.14, $p = 0.00003$) (67–69). Also, DQB1*0301 (DQ7 by serology) was found to be significantly expressed only in association with AA (totalis and universalis) (67, 68, 70). Other studies implicate other DQB1 alleles in AA, such as DQB1*302, DQB1*601, and DQB1*603 (69). Turkish patients had a higher frequency of HLA-DQ1, HLA-DQ3 (71), and DQB1*03 (72). In the Danish population, subjects with DQA1*0501, DQB1*0301, and DPA1*0103 alleles carried a greater risk of developing AA (73). Analysis of the combined presence of DQB1*0301 and DPA1*0103 in AA suggests that an additive risk effect (synergism or interaction) exists between the DQB1*0301 and DPA1*0103 alleles, which are situated at different HLA class II loci (74). More recently, Han Chinese individuals with AA were found to have a higher frequency of HLA-DQA1*0104, DQB1*0604, and DQA1*0606 (75).

Many genetic analysis studies in AA have primarily focused on the HLA-D genes (MHC class II encoding) as the most likely region for genes that regulate susceptibility, severity of, or resistance to disease (76). The majority of these studies have indicated an increased frequency of DR4, DR5, DR6, and DR7

(76, 77). Earlier studies using serological typing techniques suggested that DR4 and DR5 were associated with severe forms of AA. (51, 76) HLA-DRB1*1104 is associated with patchy AA (51, 67–69), whereas DR4, DR5 (DR11), (7, 12), DR6 (6), and HLA-DRB1*1104 are significantly increased in longstanding AT/AU patients (70). A Turkish study, however, did not reveal associations with DR4 and DR11 (DR5) in AA (71). Another study has demonstrated a predisposing effect of DRB1*04 (DRB1*0401 was most prevalent) in the European population (78).

Certain HLA associations, on the other hand, may provide relative protection from AA, as has been proposed for HLA-DRw52a (76) and HLADRB1* 03 (79). The frequencies of HLA-DR52a (12) and DR16 (71) have been reported to be lower in AA cases. Similarly, a decrease in DR1 was observed among male AA patients (80), possibly suggesting a protective role of DR1. Another study of a Belgian-German population found that DRB1*03 (most suggestive of DRB1*0301) was a protective factor against AA compared to controls (78). However, the results also indicated that the protective effect was frequently present in individuals with a familial history of AA and less commonly among sporadic cases.

In addition, there are several other non-HLA genes that map within the MHC region that may be primary or additional susceptibility loci associated with AA. One possible candidate gene for AA-susceptibility is Notch4, which maps to the centromeric end of the HLA class-III region (335 kb telomeric to DRB1) (81). In mammals, Notch 1–4 genes are known to be involved in angiogenesis, hair growth, and T-cell maturation (82–86). The human Notch4 gene is located on chromosome 6p21.3. In a case-control study, several associations have been reported between Notch4 gene polymorphisms and mild to severe AA, particularly with polymorphisms at positions +1297 and +3063. The initial analyses have shown a significant association of AA in the overall data set with the Notch4 (T+1297C) polymorphism ($p < 0.001$) but not with Notch4 (A+3063G) polymorphism (81, 84).

Conclusion

To conclude, we have provided an overview of available current knowledge about the molecular genetics of AA. Various HLA genes such as HLA-DRB1*0401 and DQB1*0301 that have a role in regulating immunity have been associated with susceptibility to AA.

Table 1. Various HLA genes have been associated with susceptibility to alopecia alopecia areata among several populations. AA - alopecia areata, AU - alopecia universalis, AT - alopecia totalis, USA - United States of America, UK - United Kingdom of Great Britain.

Alopecia	HLA class I	Population	HLA class II	Population
AA	A1	Turkish	DQ3 (DQB1*03)	US
	B13	Russians	DQ7 (DQB1*0301)	Denmark
	B18	Israelis	DR4	US
	B52-Cw*0704	Chinese	DR4	Italy
	B27	Russians	DR4	UK
	B40	Americans	DR4	Denmark
	B44(B12)	Finns	DR5 (DR11)	US
	B62,CW3	Turkish	DPW4	Denmark
AU/AT			DQ3 (DQB1*03)	US
			DR11 (DRB1*1104)	US
			DQ7 (DQR1*0301)	US

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A U T H O R ' S A D D R E S S *Abdullateef A. Alzolibani, MD, Associate Professor of Dermatology, Department of Dermatology, College of Medicine, Qassim University, P.O. Box 30109, Buraidah 51477, Qassim, Saudi Arabia, Tel Office: +966 6 3800050 ext. 2862, Fax: +966 6 3801228, E-mail: azolibani@yahoo.com*