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Epidemiologic and genetic characteristics of alopecia areata (part 2)

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Abstract

Alopecia areata (AA) is hypothesized to be an organ-specific autoimmune disease mediated by T cells to the hair follicles. Despite the fact that most cases of AA are sporadic, there is an accumulation of evidence that AA is a complex multigenetic trait with components of inherited predisposition. In the last decade, rapid progress in molecular genetics and biotechnology has led to the identification of many candidate genes in humans that confer susceptibility to AA. The first part of this review focused on the association of HLA genes with the disease. The second part reviews non-HLA and other genes associated with AA, including the autoimmune regulator (AIRE) gene. Recently, the lymphoid-specific protein tyrosine phosphatase, non-receptor type 22 (PTPN22) gene was found to be an additional immunoregulatory gene associated with AA. In addition, alleles of genes coding for cytokines and their receptors, such as the interleukin-1 receptor antagonist (IL1RN) and chemokines (MCP-1), have also been associated with AA. Some studies have hypothesized that filaggrin gene mutations (FLG) may also play a role in AA, particularly in patients with comorbid atopic disease. MX1 is another new candidate gene in AA. Thus, this second part of the review completes the overview of current knowledge about the molecular genetics of AA begun in the first part.

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Non-histocompatibility locus antigen (HLA) and other genes

An enormous number of HLA genes were reviewed in the first part of this series. This part reviews non-HLA and other genes associated with alopecia areata (AA), including the autoimmune regulator (AIRE) gene. Recently, the lymphoid-specific protein tyrosine phosphatase, non-receptor type 22 (PTPN22) gene was found to be an additional immunoregulatory gene associated with AA. In addition, alleles of genes coding for cytokines and their receptors, such as the interleukin-1 receptor antagonist (IL1RN) and chemokines (MCP-1), have also been associated with AA. Some studies have hypothesized that filaggrin gene mutations (FLG) may also play a role in AA, particularly in patients with comorbid atopic disease. MX1 is another new candidate gene in AA; see Table 1.

A: Cytokine genes

The cytokines are produced by multiple diverse cell types and their main function is to regulate the magnitude and nature of immune responses. Cytokine genetic polymorphisms are the subject of disease-association studies that require large-scale human genotyping. Genetic polymorphisms in cytokines affect gene transcription and cause inter-individual variations in cytokine production, thus influencing the outcome of infectious diseases, cancers, and autoimmune diseases. Polymerase chain reaction (PCR)-based custom microarrays and microfluidics systems were used to develop genotyping assays for the following cytokine polymorphisms:

A.1: Interleukin-1 like molecule 1 (IL-1L1)

The novel interleukin-1-like molecule 1 (IL-1L1) is a primary cytokine involved in mediating inflammatory responses. The IL-1L1 has the greatest gene sequence homology with IL1RN, located at 2q14.2 and encoding IL-1RA, another potential IL-1 antagonist. In addition to its fundamental pro-inflammatory role, IL-1 also directly influences hair-growth regulation. In hair follicle organ cultures, IL-1 inhibits growth of hair fiber and brings about morphological changes similar to those seen in AA. The variable number of tandem repeats (VNTR) in intron 2 of the gene IL-1RN has five alleles, comprising 2 to 6 repeats of an 86 bp sequence (1). The IL-1RN*2 allele has been found to be associated with AA severity in two British case-control studies (1, 2). Tarlow et al. found allele 2 in 41% of controls versus 44% in patchy AA patients, 66% in AT affected individuals, and 77% in AU affected individuals (1, 3). A case-control association study found that homozygosity for the rare allele of IL1RN (IL1RN*2) was significantly associated with AA. Similar associations of the allele IL1RN*2 (IL1RN+2018) with AU have been reported in other UK-based studies (1, 3, 4). This association, however, was not confirmed in the U.S. population (5). Composite genotypes including at least three copies of either of the alleles of IL1RN and IL1L1 loci conferred more than a merely additive increase in risk for AA, indicating a synergy between the two genes (4). Galbraith et al. have shown that patients with severe forms of AA have an increased frequency of the IL-1β 1,2 genotypes in conjunction with the immunoglobulin K light chain (KM) genotype (6). Allele 2 of the IL-1β +3953 polymorphism exhibits a strong association with increased production of IL-1β (7). The Galbraith et al. study also found that IL-1β loci along with loci of the immunoglobulin (KM) light chain act synergistically to significantly increase susceptibility to the disease (6). All studies suggested that the polymorphisms within IL1RN and IL1L1 themselves or a gene in linkage disequilibrium with IL1RN and IL1L1 predispose their carriers to the more severe forms of AA. The IL-1 gene polymorphisms may be responsible for exaggerated release of IL-1, leading to rapid and more progressive disease (8). On the other hand, a British family-based sample study demonstrated

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Table 1 | **Overview of genes associated with alopecia areata that have been identified to date as having potentially polymorphism or alleles.**

Gene symbol	Gene name	Chromosomal location	Polymorphism or allele	Function
IL-1L1	Interleukin-1-like molecule 1	2q14.2	IL1RN*2(IL1RN+2018)	Mediates inflammatory responses, directly influences hair-growth regulation
IFN-γ	Interferon gamma	12q23-24	SNP; rs2430561 and rs3138557 within intron 1	Macrophage-activated factor
TNF-α	Tumor necrosis factor alpha	9p13-21	G/A-308 in the promoter region	Plays a pivotal role in inflammation and immune defense
MIF	Macrophage migration inhibitory factor	22q11.2	173 (G to C) in the promoter, –794 and CATT repeat	Lymphokine known to prevent random migration of macrophages, regulates the production of proinflammatory IL-1 and TNF-α
MCP-1	Monocyte chemoattractant protein-1	17q11-21	A/G –2518	It is thought to be responsible for monocyte and lymphocyte T recruitment in acute inflammatory conditions and may be an important mediator in chronic inflammation
AIRE	Autoimmune regulator E	21q22.3	C/G-961 and	Plays a role in the development of organ-specific autoimmune disease with monogenic autosomal recessive inheritance
FLG	Filaggrin	1q21	R501X and 2282del4 alleles	One of the genes within the epidermal differentiation complex
MX1	Myxovirus resistance 1	21q22.3	+9959 within intron 6	Interferon-induced p78 protein
eNOS	Endothelial nitric oxide synthase	7q35-36	27 bp-VNTR within intron 4	Regulates local blood flow and systemic blood pressure, inhibits platelet activation, reduces low-density lipoprotein oxidation, and modulates migration and growth of vascular smooth muscle cells
PTPN22	Protein tyrosine phosphatase nonreceptor 22	1p13	C/T –1858	Important in the negative control of T lymphocyte activation
VDR	1,25-dihydroxyvitamin D3 receptors	12q13-12q14	FokI polymorphism	Plays an important role in the physiology of the hair follicle

that the IL-1RN*2 allele was not associated with alopecia totalis and alopecia universalis. A borderline association was observed between IL-1RN and patchy AA, but it was not statistically significant (p = 0.06). This study reported an observed association between IL1-RN*1 allele and patchy AA (p = 0.045).

A.2: IFN-γ

Interferon gamma (IFN-γ), located on chromosome 12q23-24, encodes IFN-γ protein belonging to a macrophage-activated factor and is known to be abnormally expressed in AA as part of a CD4+ Th1-mediated response. It is synthesized by perifollicular or follicular antigen-presenting cells and through several actions also suppresses dermal papilla cells' ability to maintain anagen hair growth. Highly significant levels of IFN-γ were observed in patients with alopecia totalis or alopecia universalis (9, 10). In addition, Deeths et al. illustrated that antigen-specific T-cells from patients with extensive disease were revealed to have some intrinsic defect in production of IFN-γ (11). Single nucleotide (SNP; rs2430561) and microsatellite (rs3138557) polymorphisms within the first intron of the IFN-γ gene correlate with a high amount of in-vitro production of IFN-γ and are associated with disease severity in various autoimmune diseases (12). This allele is associated with higher or lower risk of a variety of diseases, including autoimmune and chronic inflammatory conditions (13).

Some additional factors are also related to the role of INF-γ. The MIG is a monokine induced by IFN-γ. It is a cytokine that is elevated in human AA, and is considered a useful marker for monitoring the disease status (14). MIG is mostly expressed in mononuclear cells in the peri- and intrabulbar infiltrate and also in the follicular papilla. Another factor is IP-10 (interferon inducible protein-10), a chemokine that leads to recruitment of mononuclear cells in AA (15).

A.3: TNF-α

Tumor necrosis factor alpha (TNF-α) is located on chromosome 9p13-21. TNF-α belongs to a superfamily of ligands that plays a pivotal role in inflammation and immune defense and is described as having an important role in the pathogenesis of AA. TNF-α is produced in epidermal keratinocytes along with numerous other cytokines (16) and is known to greatly inhibit proliferation (17). Galbraith and Pandey demonstrated a significant difference in TNF-α phenotypes between patients with patchy disease and those with alopecia totalis/universalis (18). Two TNF-α phenotype polymorphisms (T1, T2) were determined in 50 patients with AA, and their distribution differed between patients with the patchy form and those with totalis/universalis. The first biallelic TNF-α polymorphism (G, A-308 in the promoter region) was detected in humans and subsequently was shown to be a closely linked locus within the MHC that may play a role in the pathogenesis of the patchy form of the disease. The second TNF-α polymorphism, described by D'Alfonso and Richiardi (19), involves a G to A base change at position –238 of the gene. These data indicated

that TNF-T1, T2 heterozygosity is significantly associated with one form of AA (20).

A.4: Macrophage migration inhibitory factor (MIF)

Macrophage migration inhibitory factor (MIF) is a cytokine produced by lymphocytes and peripheral blood mononuclear cells. It is the first lymphokine known to prevent random migration of macrophages (21). A recent study has demonstrated that MIF molecules regulate the production of proinflammatory IL-1 and TNF-α, and so it is considered an initiator of inflammation and the immune response. The cycle endpoint is an ongoing inhibition of hair growth (22). MIF polymorphism, which may play a key role in the pathogenesis of extensive AA, has been identified in the MIF promoter at position –173 (G to C) and in a tetranucleotide CATT repeat beginning at nucleotide position –794 that confers an increased risk of early onset of an extensive form of AA at ages under 20, as shown in a study by Shimizu et al. (21).

B: Chemokine gene

In general, the directional recruitment of leukocytes is regulated by chemokines and their counteracting chemokine receptors (23). An in-situ hybridization procedure revealed a high expression of lymphocyte-specific chemoattractant (MIG) mRNA, a moderate expression of monocyte chemoattractant protein-1 (MCP-1) mRNA, and a slight expression of IP-10 mRNA, whereas all other chemokines (GROa, MIP-1a, and MIP-1b) were not expressed at significant levels. Experiments in the mouse model of AA show variable expression of intensity in chemokines that may also correspond to distinct stages of inflammation (24).

A β-chemokine protein precursor containing a signal peptide of 23 amino acids and a mature peptide of 76 amino acids with a molecular weight of approximately 13kDa is endcoded by the MCP-1 gene located on chromosome 17q11-21. It is also known as SCYA2 (small inducible cytokine A2) or CCL2 (C-C motif ligand 2). It is thought to be responsible for monocyte and lymphocyte T recruitment in acute inflammatory conditions and may be an important mediator in chronic inflammation. In fact, it has been proposed that MCP-1 may be responsible for tissue inflammation in autoimmune diseases because of its tissue expression in human and experimental autoimmune models (25-28). Thus, genetic polymorphism in the regulatory regions of the MCP-1 gene could be implicated in the susceptibility or progression of autoimmune disease. A biallelic A/G polymorphism at position –2518 of the MCP-1 gene has been described. The polymorphism proved functionally important because peripheral blood mononuclear cells of individuals with G/G and A/G genotypes produced significantly more MCP-1 after stimulation with IL-1β than those with Caucasian wild-type A/A (29, 30). On the other hand, in a case-control study on AA patients among the Korean population, no association existed between the –2518A/G polymorphism of the MCP-1 gene and AA (24).

C: AIRE gene

The autoimmune regulator (AIRE) is a transcription factor composed of 552 amino acids encoded by the AIRE gene, located on chromosome 21q22.3. Recently, it has been identified as playing a role in the development of organ-specific autoimmune disease with monogenic autosomal recessive inheritance (31, 32). In autoimmunity, AIRE expression was found in restricted tissues; for example, medullary thymic epithelial cells and cells of the monocytes' dendritic cell lineage of the thymus (33). Therefore, it has been considered to play a major role in regulating the expression of several mRNA genes of ectopic peripheral proteins in the thymus (34). This response is dosage-dependent (35), such that a slight decrease in AIRE gene function can lead to a consequent decrease in thymic protein expression, allowing delivery of autoreactive T cell clones to the periphery. The investigators have recorded at least 40 mutations of the AIRE gene responsible for this rare autosomal recessive disease. AIRE gene mutations have also been identified in several patients with atypical or incomplete manifestations of the disease. On the other hand, AIRE mutations were not found to be associated with AA in the general population in some studies (36), although two polymorphic alleles of this gene, AIRE916G and T1029C (giving rise to the amino acid changes S278R and V301A), were increased in Caucasian AA patients, particularly in AT cases (37). However, a case-control study of Belgian-German origin did not support the hypothesis that the g.961C>G (S278R) polymorphism of the AIRE gene is associated with an increased risk of AA (36). However, extended determination of association with haplotype analysis, including six SNPs in the AIRE gene (C-103T, C4144G, T5238C, G6528A, T7215C, and T11787C) among the Caucasian population, revealed strong association only between the AIRE 7215C allele and AA. The AIRE haplotypes CCTGCT and CGTGCC showed a highly significant association with AA.

In fact, AIRE mutations are responsible for the development of autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) with monogenic autosomal recessive inheritance. Furthermore, in the general population, AA frequency is increased to more than 30% in the recessive condition APECED and is associated with severe, early-onset disease (38). Finally, a strong association between AA and autoimmune polyglandular syndrome type 1 (APS1), also known as PGA type I caused by mutations in the AIRE gene on chromosome 21, has also been reported in 37% of patients with APS1 (39).

D: FLG gene

Filaggrin (FLG) is one of the genes within the epidermal differentiation complex (EDC), located on chromosome 1q21. It encodes a polyprotein precursor known as profilaggrin (400-kDa) composed of numerous tandem filaggrin repeats. Profilaggrin is a prominent component of the keratohyalin granule in human epidermis. It is proteolytically cleaved into the 37-kDa filaggrin protein during differentiation of the granular cells in the stratum corneum (40). There are multiple known mutations of FLG. About 10% of the European population carries one of the FLG mutations (41). Most FLG gene mutations are considered to be a strong risk factor for atopic dermatitis (AD) (41-45); some investigators have therefore postulated that FLG mutations might also play a role in AA, particularly in patients with comorbid atopic disease. Some investigators have compared the prevalence of R501X and 2282del4 alleles in AA patients with controls (46). The presence of FLG mutations became more significant after the investigators combined the two mutations and performed subset analyses of AA patients with comorbidity of asthma, atopic dermatitis, and allergic rhinitis. Severe forms of AA were significantly present in patients with combined diseases of asthma, atopic dermatitis (AD), and allergic rhinitis; the presence of AD alone, however,

was not associated with severe AA. Based on these findings, it is concluded that the presence of an FLG mutation in AD patients is associated with more severe disease (46).

E: MX1 gene

The myxovirus resistance 1(MX1) gene is a new candidate gene for AA that encodes the interferon-induced p78 protein. It is located on chromosome 21q22.3 and contains 17 exons extending over 33 kb. It is strongly expressed in lesional anagen-hair bulbs from AA patients compared to healthy controls (47). Screening of 4747 bp within the MX1 gene revealed four single nucleotide polymorphisms in intron 6. In a case-control association study, only one polymorphism (+9959) was found to have a highly significant association with AA (48). This finding of genetic association between the MX1 gene and the disease supports the hypothesis that this is a new marker in AA.

F: eNOS gene

Endothelium-derived NO is synthesized by oxidation of L-arginine to L-citruline by endothelial nitric oxide synthase (eNOS), which is encoded by the NOS3 gene located on chromosome 7q35-36, spans 21 kb, and contains 26 exons. The NO is an endothelium-derived relaxing factor (49); it also regulates local blood flow and systemic blood pressure (50), inhibits platelet activation, reduces low-density lipoprotein oxidation, and modulates migration and growth of vascular smooth muscle cells (51, 52). Nitric monoxide was shown to contribute in the pathogenesis of AA. A case-control study of eNOS gene polymorphism in Kuwaiti AA patients showed a significant association between the intron-4 27 bp-VNTR and AA. Genotype (4b/4b) showed a significant association with susceptibility to AA. It has a 22% higher frequency in AA patients than in healthy controls. This finding confirms the association of a polymorphism within the eNOS gene and susceptibility to AA (53).

G: PTPN22 gene

The non-synonymous C1858T substitution in the protein tyrosine phosphatase nonreceptor 22 (PTPN22) gene is located on chromosome 1p13 (54). It encodes lymphoid protein tyrosine phosphatase (LYP), which is important in the negative control of T lymphocyte activation (55). Recently, the missense R620W polymorphism in the PTPN22 gene at nucleotide 1858 (C1858T) in codon 620 (R620W) has been shown to be associated with susceptibility to autoimmune diseases. A case-control study for PTPN22 C1858T (W620) alleles was performed in English patients using a polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) genotyping method. The results indicated that the frequency of the 1858T allele was significantly higher in patients with a severe form of AA as compared to controls. These results provide further evidence for autoimmunity as an etiological factor in this disorder (46, 56).

H: VDR gene

The 1,25-dihydroxyvitamin D3 receptor (VDR) gene is located on chromosome 12q13-12q14. It is expressed in the hair follicle and the lack of it leads to alopecia. It plays an important role in the physiology of the hair follicle. Therefore some investigators examined the role of one of the VDR polymorphisms (the FokI polymorphism) in the translation initiation codon of the VDR gene and hypothesized that the VDR gene could play a role in AA. Some studies have detected the expression of VDR in the epidermis and hair follicles of AA patients (57-59). VDR is expressed in two major cell populations that comprise the hair follicle: the epidermal keratinocytes and the mesenchymal dermal papilla cells (59). Expression of VDR in keratinocytes is necessary for maintenance of the normal hair cycle (60). Lack of VDR is associated with reduced epidermal differentiation and hair follicle growth. In addition, patients with hereditary 1,25-dihydroxyvitamin D3-resistant rickets type II (HVDRR) and VDR knockout mice exhibit a phenotype that includes alopecia totalis (61).

Conclusions

To conclude, we have provided an overview of available current knowledge about the molecular genetics of AA. Various genes that have a role in regulating immunity have been associated with susceptibility to AA including AIRE and certain HLA such as HLA-DRB1*0401 and DQB1*0301. Recently, the PTPN22 gene has been identified as an additional immunoregulatory gene whose alleles may be associated with AA. In addition, alleles of genes coding for cytokines and their receptor (e.g. IL1RN) and chemokines (e.g., MCP-1) have also been associated with AA. Some studies have hypothesized that FLG may also play a role in AA, particularly in patients with comorbid atopic disease. Moreover, the MX1, eNOS, and 1,25-dihydroxyvitamin D3 receptor (VDR) genes are new candidate genes in AA.

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