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Chapter V

The Genetic Basis of Alopecia Areata

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Abstract

Alopecia areata (AA) is a common autoimmune disorder, characterized by circle patches of hair loss, in which genetic and environmental factors influence the disease development and progression. In this chapter, we will focus on the genetic loci that have been associated with AA. Some of these loci contain genes involved in innate and adaptive immunity and are shared with other autoimmune diseases, suggesting an overlap of the genetic mechanisms involved in the development of such disorders. Linkage and association studies underline the major region of AA susceptibility coming from the *HLA* system (6p21.32), specifically *HLA-DQB1*03* alleles coding for DQ7 heterodimers. Modern technological innovations have advanced our understanding of the genetic basis of AA. Genome wide association

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studies have recently identified new chromosomal regions linked to AA liability in 2q33.2 (*CTLA4*), 4q27 (*IL-2/IL-21*), 6q25.1 (*ULBP*), 10p15.1 (*IL-2RA*) and 12q13 (*IKZF4*). A significant association was also evident for single-nucleotide polymorphisms in 9q31.1 and 11q13, harboring genes expressed in the hair follicle (*STX17* and *PRDX5*, respectively), and in an intronic region of *SPATA5* gene. These association studies may provide mechanistic insights into the AA pathogenesis and can improve the predictive models of the genetic risk. Follow-up of individuals with a high genetic risk of AA could also help to elucidate the role of environmental factors (such as stressful events, diet, infections etc) with the general aim to develop novel clinical approaches for AA treatment.

Introduction

Alopecia Areata (AA) is a common tissue-specific autoimmune disease which is characterized by the sudden appearance of areas of hair loss on the scalp and other hair-bearing areas. AA has a prevalence of 1-2% among Caucasians and affects genetically predisposed individuals [1-3]. Indeed, as for many autoimmune disorders, AA is not inherited in a Mendelian way but has a multifactorial etiology in which environmental as well as genetic factors are involved, each acting in an additive fashion to generate the disease clinical manifestations [4, 5]. Infection, nutritional deficiencies and psychological stress have been suggested as triggering factors of AA onset and/or exacerbation [6-9]. The importance of the genetic component is supported by the epidemiological indication that AA shows a familial aggregation, with 10-47% of patients having a positive family history, and the recurrence risk is greater among close relatives [10-13]. The incidence of AA in the offspring, siblings and parents of severely affected probands has been reported as 2%, 3% and 7% respectively, with an estimated lifetime risk of 6% for children [4, 11]. The observation of a significantly higher concordance rate among monozygotic than in dizygotic twins (42-55% vs. 0-10%) also points to a genetic influence on AA occurrence [6, 14]. Moreover, an increased prevalence of autoimmune conditions, such as psoriasis, vitiligo, type 1 diabetes mellitus, celiac disease, thyroid disorders, has been reported in AA cases and their relatives, mainly first-degree individuals, suggesting that common genetic determinants for autoimmunity are likely shared [15, 16]. Traditional approaches such as family-based linkage studies and population-based candidate gene association studies have been extensively used to identify multiple loci and alleles that contribute to AA liability [2]. Recently,

genome-wide association studies (GWASs), based on the identification of single nucleotide polymorphisms (SNPs) determining susceptibility to common diseases, have been applied to a large cohort of AA patients and controls allowing to increase our acknowledgement of the genetic markers involved in the phenotypic expression of this complex disorder [17-19]. This chapter summarizes the current findings of the Alopecia Areata genetic architecture.

Alopecia Areata and HLA Genes

Alopecia Areata pathogenesis is likely related to the activation of CD4+ and CD8+ cells that infiltrate around and inside anagen hair follicles, providing a link between AA development and the Human Leukocyte Antigen (HLA) class I and class II genes. Moreover, aberrant expression of HLA heterodimers has been reported in AA affected scalp tissues [20, 21]. HLA genes map on human chromosome 6p21.3 and code for cell surface glycoproteins important in the antigen presentation and self-recognition by lymphocyte immune cells. HLA class I molecules, specifically recognized by CD8+ T cells, are encoded by the *HLA-A*, *B* and *C* loci while HLA class II heterodimers, bound by CD4+ T cells, are specified by genes in the *HLA-D* region that comprehends the *HLA-DP*, *DQ* and *DR* genes [22].

The genetic load of the HLA region in Alopecia Areata was initially noted in the late 1970s and since that time hundreds of studies have been performed in order to more precisely understand the role of HLA in the disease. As regarding HLA class I, some studies have indicated an association with AA that was not confirmed in other reports [23, 24]. The results on the investigated antigens were different in different ethnic groups, as HLA-B12 in Finnish patients and B18 in Jerusalem [25, 26]. HLA-A1, A2, A28, B40, B62, Cw3 and Cw7 associations have also been described but not replicated [27-30]. Conversely, various *HLA-DQB1* and *-DRB1* alleles have been recurrently suggested to confer a high risk of developing disease by both case-control and family-based studies [4]. The first analyses, performed at serological levels, indicated that DR4, DR5, DR6, DR7 and DQ3 were at-risk heterodimers for AA development [28, 31-36]. More recent studies, performed at molecular level, have shown a significant increased frequency of *DRB1*11:04* allele in patients with AA [32, 33, 35], mainly linked to the early-onset form and to a higher familial recurrence risk [35, 37]. The genetic association analyses

between extension of the disease and particular *DRB1* alleles have generated different results with *DRB1*11:04* variant being strongly correlated to AA totalis (AT) or universalis (AU) phenotypes in some population [38] but not in others [37], and *DRB1*04:01* variant (DR4 molecules) generally associated with the more aggressive clinical manifestations [35]. Among the *HLA-DQ* genes, the *DQB1*03* variants, serologically related to DQ7 heterodimers, have been extensively analyzed and confirmed as the major risk allele for AA onset in different population studies. DQ7-positive status is known to confer the greatest genetic effect in Caucasians with a prevalence of up to 85% in patients compared with 46% in the general population [36]; moreover, the strongest associations have been found between *DQB1*03(DQ7)* allele and severe AA phenotypes [32, 35, 39, 40]. Interestingly, only the *DQB1*03 (DQ7)* variants encode a beta-chain carrying a glutamic acid at position 45 in one of the two extracellular domains which might display an increased binding affinity with hair follicle antigens and, therefore, explain the molecular mechanisms underlying the DQ7-mediated AA genetic suscepti-bility [40, 41].

In addition, an increased frequency of the *DQB1*02:02* allele, frequently co-inherited with *DRB1*07* variant, has been observed in DQ7-negative AA patients [38, 40]. Furthermore, certain HLA class II variants, such for *HLA-DRB1*03:01*, *DRB1*13* and *DQB1*06* alleles, have been described as protective against the development of AA [38-40]. Differences highlighted in the various studies are likely attributable to the different ethnic characteristics of the analyzed populations and the study design.

Overall, it is difficult to determine with certainty if the numerous HLA associations are due to the disease heterogeneity or are casual effects owing to the strong linkage disequilibrium (LD) across the *HLA* region. Literature data give evidence that different populations have characteristic frequencies not only for individual alleles but also for preferential allelic combinations. Among Caucasians, *DQB1*03:01* variant (DQ7 in serology) is almost always found in DR11/12 haplotypes and less frequently with DR4 so that the *DRB1*11:04* association with the risk of AT/AU might be due to the tight LD with *DQB1*03:01* allele [33, 38]. Even if all these variants are common in the healthy population, the *DQB1*03(DQ7)* allele involved in the risk haplotype is over-represented in cases compared to controls suggesting that HLA-DQ status is primarily associated with AA.

The strong correlation between variants in the HLA region and AA has also been confirmed by recent genome-wide genetic analyses [17, 19, 42]. In particular, the AA associated SNPs are physically close to the *DRB1* and *DQB1* loci and are highly correlated with the *HLA-DQB1*03* allele,

serologically corresponding to the HLA-DQ7 glycoprotein. Hence, GWAS findings are consistent with the very early AA associations with classical HLA alleles.

Alopecia Areata and Non-HLA Genes

Particular HLA alleles have been widely established as AA at-risk factors even if they are not sufficient to explain the entire genetic susceptibility of the disease. Classical linkage and case-control analyses have led to the identification of several non-HLA linked chromosomal regions and candidate genes that might have a role in the AA pathogenesis [2].

Starting from the observation that Alopecia Areata is more common in Down syndrome and in autoimmune polyglandular syndrome type I than in general population, many studies have been focused on chromosome 21q22.3 as the more likely susceptibility region for AA. Indeed, a significant association between AA and the intronic polymorphism +9959 in the *MX1* gene has been reported and the impact of *MX1* in the disease onset has been also supported by the observation of a strong expression of the MX1 protein only in patients' lesional hair follicles but not in normal scalp [43].

The investigation of different SNPs in the *AIRE* gene at chromosome 21q22.3 has identified specific alleles and haplotypes that strongly predispose to AA [44, 45]. Since AIRE transcription factor controls expression and presentation of self-antigens in the thymus, its deregulation may impair the central tolerance and contribute to the autoimmune processes in AA.

However, many classical genetic studies are limited by relatively small sample size, candidate-driven selection bias, low statistical power and resolution for variants of modest effect.

GWASs, in which a large number (10^4-10^6) of SNPs across the entire genome are examined in thousands of individuals, have rapidly increased our understanding of the AA genetic background by the identification of novel at-risk loci outside the HLA region showing a consistent association with the disease [17-19]. Most of these candidate non-HLA genes, such as *IL-2/IL-21*, *IL-2RA*, *IKZF4*, *ERBB3* and *ULBP* [17], are localized in genomic blocks that are in moderate linkage disequilibrium and are involved in distinct signaling networks comprising cytokine production and activation/proliferation of regulatory T cells which play an essential role in the control of the immune response and in the maintenance of self-tolerance [46]. ULBP proteins are also

able to bind the natural killer (NK) cell receptor NKG2D and to favor the development of NK-acquired dysfunction. Indeed, NK cell depletion in C3H/HeJ mice, a well-established animal model of AA, significantly accelerated the onset of the disease highlighting the potential involvement of NK cells in autoimmune skin-diseases [47]. Altogether these genetic factors overlap with those for other autoimmune diseases and support that both innate and adaptive immune responses are involved in the AA etiology. In this regard, a high-resolution association analysis of the cytotoxic T lymphocyte-associated antigen 4 (CTLA4) locus has recently shown that specific polymorphisms (rs12990970, rs231775, rs3087243 and rs1427678) significantly influence the risk of AA in a large set of patients from the Central Europe [18], being mainly correlated with the more aggressive forms of the disease. CTLA4 molecules play a key role in the fine tuning of T-cell immunity by negatively interfering with intracellular signal transduction events, so that genetic variants able to modulate CTLA4 activity are likely to be a link between dysregulated T-cell response and AA disease onset. Interestingly, particular SNPs located in DNA sequences encompassing *PRDX5* and *STX17*, two genes that are expressed in the hair follicles [17], and in the *SPATA5* gene, coding for a protein with an acid ATPase domain likely involved in the regulatory subunit of the 26S protease, also achieved the genome-wide statistical significance for AA association [19].

Several papers have revealed oxidative status to be affected in AA patients, rendering the antioxidant enzyme PRDX5 a relevant molecule in the pathogenesis and progression of AA [48].

Replication studies of the identified SNP markers in different populations and expression/functional analysis of candidate genes are needed to establish their weight in the genetic background of AA and the precise role in the disease pathogenesis.

Conclusion

Alopecia Areata is a complex genetic condition caused by genetic and environmental interactions (Figure 1). Several genes have been correlated so far with AA liability, however, when examined individually each of these loci only confer modest disease risk. Efforts in future studies should be addressed to a clear definition of the AA genetic heritability in order to better understand

the pathogenesis and to develop novel laboratory tests and therapeutic treatments for the AA clinical management [49].

Currently, the only available molecular test for AA susceptibility may be the HLA-DQB1 typing since most AA patients are positive for DQB1*03 alleles coding for DQ7 heterodimers. However, considering that many healthy subjects in the general population also carry these alleles, HLA test may be an important marker only in the identification of individuals who belong to at-risk groups such as first-degree relatives of AA patients.

Moreover, the strong relationship between DQB1*03(DQ7) and the disease severity seems to suggest the prognostic value of this genetic test in patients with Alopecia areata.

One goal is, therefore, to design a DNA analysis that combines the individual effects of different and well-validated loci of susceptibility into a global genetic risk able to accurately discriminate individuals with a very high likelihood of developing AA as well as to give important information on the onset and aggressiveness of the disease. This will also help the clinicians to decide on patient-specific monitoring and appropriate treatments.

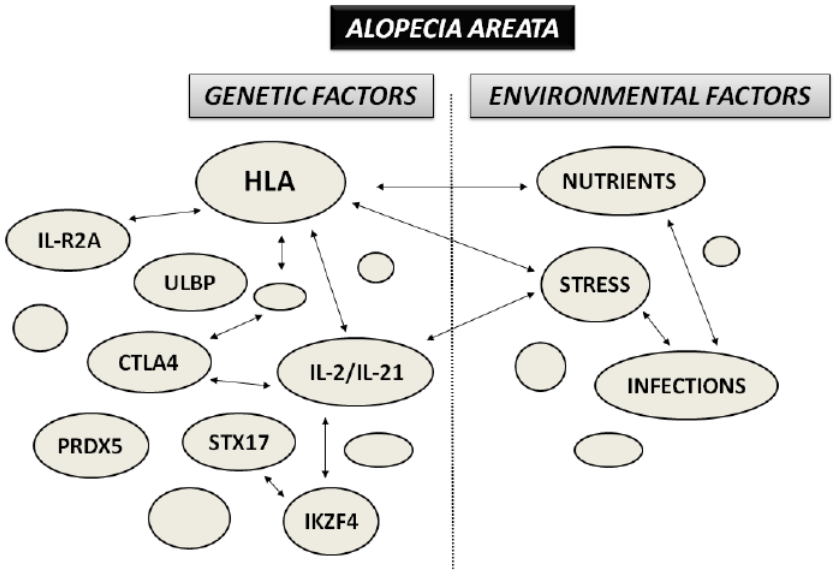

Figure 1. Multifactorial etiology of Alopecia Areata. Gene-gene and gene-environmental interactions among known factors are depicted.

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