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Invited review article

The genetics of alopecia areata: New approaches, new findings, new treatments

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ABSTRACT

Alopecia areata (AA) is a common immune-mediated hair loss disorder. Despite its high prevalence, its etiology is still largely unknown, but it is hypothesized to have a strong genetic basis. In the last decade, there has been a major progress in the field of genetic research, leading to novel findings regarding the genetic component of AA. The aim of this review is to summarize the information collected so far in this field, the basic principles of the genetic methods used in previous studies, and new therapeutic strategies that might become available in light of the new findings.

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Fig. 1. Patches of hair loss involving the beard area.

1. Introduction

Alopecia areata (AA) is a common immune-mediated disorder, which targets hair follicles, and presents as a patchy, non-scarring hair loss (Figs. 1 and 2). It affects approximately 2% of the US population, with a lifetime risk of 1.7%, including both men and women of all ages [1]. While most individuals obtain complete remission, some affected patients can have a chronic course of the disease, and might progress toward alopecia totalis (AT), involving the whole scalp, or alopecia universalis (AU), affecting the whole body (Fig. 3) [2]. Histologically, AA is characterized by accumulation of mononuclear cells around the bulb of the affected hair follicles [3].

Despite its prevalence, the etiology of AA is still largely unknown, and currently available treatments are mostly unsatisfactory and inefficient for the more chronic and severe types of the disease [4], and a useful biological marker implicating the disease's activity has not yet been identified [5]. While environmental factors probably contribute to the induction of the disease, there is a strong genetic background, which is believed to stand at the root of the disorder. Until recently, the genetic basis has been largely obscure, but it is thanks to significant advances in genetic methods, and the formation of large patient registries, that this genetic basis starts to unveil.

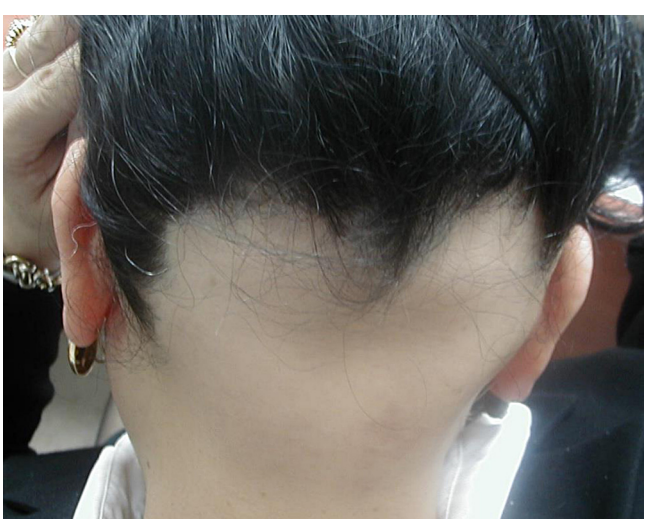

Fig. 2. Two coalescing patches of hair loss affecting the occipital scalp, conforming to the ophiasis pattern of alopecia areata.

Fig. 3. Hair loss from the entire scalp in an alopecia universalis patient.

The aim of this review is to summarize the available knowledge on the genetics of AA, highlighting the recent findings in this field. The review is specifically aimed for the non-geneticists, and therefore gives special emphasis on explaining the different genetic methods which have been used in previous studies. We try to summarize the existing data on the genetic components of AA by forming a unifying pathway, and explain the future treatment modalities that might become available based on this new acquired knowledge.

2. Evidence for a genetic component for AA

The fact that AA has a strong genetic basis was established many years ago, and is based on a large number of studies and observations. Below is a list of key evidence for such a connection [6]:

(1) *Increased risk of disease in first-degree relatives* [7,8]: Observational studies indicated a high incidence rate (10–42%) for AA among first-degree relatives. The results were even more significant when the disease had an early onset [9]. In a large study, conducted among 348 severely affected patients, 7% of the patients had one affected parent. Among the siblings, 3% had developed the disease, and 2% of the children, with a lifetime risk reaching 6% [8]. All of the above, in addition to the equal frequency in males and females, led in the beginning to the assumption that AA is an autosomal dominant genetic disease [9].

(2) *Twins studies* [10,11]: The concordance rate of AA in identical twins supports both genetic and environmental factors, with a rate of 55% for monozygotic twins.

(3) *Studies on murine models* [12]: In a study conducted on C3H/HeJ mice (a strain that spontaneously develops an adult-onset form of AA), four susceptible intervals were identified: on chromosome 8 (Alaa 3), 9 (Alaa 2), 15 (Alaa 4), and 17 (Alaa 1). Alaa1 site is the chromosomal region which matches the HLA locus in humans.

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