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PERSONAL REVIEW

Genetics of alopecia areata

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SUMMARY

Alopecia areata is a common disorder with a genetic predisposition where interaction with environmental factors leads to episodes of terminal hair loss. In this review article, we examine the evidence for a genetic basis to this disorder and discuss the prospects for future research into genetic susceptibility areas and the problems that are likely to be encountered in such research.

Key words: familial, genes, hair loss, review.

INTRODUCTION

Alopecia areata (AA) is hypothesized to be an organ-specific autoimmune disease with genetic predisposition and an environmental trigger.[1] It is characterized by discrete, well-demarcated areas of non-scarring terminal hair alopecia and its clinical presentation is most often multifocal.

Alopecia areata is a disorder with a complex genetic aetiology with, most likely, polygenic susceptibility and severity loci interacting with environmental factors. However, the extent to which this disorder causes morbidity and its incidence warrant investigation for the genes underlying alopecia areata, despite the hazards this research is likely to encounter.

EVIDENCE FOR A GENETIC AETIOLOGY

The aetiology of alopecia areata remains unclear and although there is much evidence for a genetic component to its aetiology, this is not the only factor. Evidence for non-genetic factors include reports of identical twins being non-concordant for this disease[2] and a report of several workers at the same water and effluent plant, all with exposure to acrylamide, developing alopecia areata.[3]

Evidence for a genetic factor to this disorder include a strong family history in, on average, 20% of patients with this disorder, consistent reports of association with class II HLA, associations with other diseases which have a genetic basis (e.g. Down syndrome and mucocutaneous candidiasis), and with polymorphisms of certain cytokine alleles. There have even been reports of associations with dermatoglyphic patterns.[4] Several animal models of alopecia areata also demonstrate the genetic basis to this disorder.

Familial associations of alopecia areata

Most cases of alopecia areata appear to be sporadic. However, there are many case reports of more than one family member suffering this disorder.[5,6] Many studies have described a positive family history of this disorder and the rate ranges from a low of 3% to a high of 42% (Table 1).

These studies cover several populations. Although, it is difficult to compare the incidence of AA among ethnic groups, interestingly, no cases of AA have been seen in Australian Aboriginal patients of non-mixed race (AC Green, pers. comm., 1999). Descriptions of familial AA rarely have more than three affected members in a single family. A study of 880 northern Indian patients reported a comparatively low incidence of 8.7% having at least one other family member affected (70 patients) and in only nine of these families was AA found in three or more individuals.[20]

However, there have been some reports of AA occurring in multiple family members with a report of six affected members with alopecia universalis (AU) over three generations in a non-consanguineous Northern Italian family,[21] and two reports of families with seven affected members[18,22]

In one of the few studies to subclassify the information on the incidence of AA according to specific family relationships, a series of 348 severely affected patients (minimum scalp involvement of 40%) found that 16% had a first-degree relative affected (51 had one affected and five had two affected relatives). Of these, in 7% one of the parents was affected. The rate of AA in siblings was 3% and among children of those affected it was 2%. The lifetime risk for children of severely affected parents was calculated as 6% for any AA and 2% for severe forms. The degree of involvement observed in the patients was not shown to influence the frequency and type of AA present in their first-degree relatives.[17]

Other reports describe an association between a positive family history and the age of onset. A study of 131 patients found that 37% of patients who developed their first patch of AA by age 30 years had a positive family history, while only 7.1% of patients who had their first patch after the age of

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Table 1 Rate of familial alopecia areata

Author	Year	Place	No. patients	Family history (%)
Brown[7]	1929	London, England	135	20
Anderson[8]	1950	Sheffield, England	114	19
Muller and Winkelman[9]	1963	Rochester, USA	736	10
Cunliffe *et al.*[10]	1969	Newcastle, England	76	25
Gip *et al.*[11]	1969	Stockholm, Sweden	269	17
Sauder *et al.*[12]	1980	Cleveland, USA	98	27
De Weert *et al.*[13]	1983	Ghent, Belgium	100	11
Friedmann[14]	1985	Newcastle, England	151	28
de Waard *et al.*[15]	1989	Rotterdam, The Netherlands	209	17
Gollnick and Orfanos[16]	1990	Berlin, Germany	149	11.4
van der Steen *et al.*[17]	1992	Nijmegen The Netherlands	348	16
Shellow *et al.*[18]	1992	USA	800	42
Puavilai *et al.*[19]	1994	Bangkok, Thailand	152	4.6
Sharma *et al.*[20]	1996	Northern India	880	8.7

Adapted, with the permission of Blackwell Science Ltd, from Messenger R, Simpson N. Alopecia areata. In: Dawber R (ed.). *Diseases of the Hair and Scalp,* 3rd edn. © 1997.

30 years had a family history of AA. Early onset of the disorder was also associated with greater severity and long duration. The authors concluded that there were two groups of AA with the early-onset form associated with greater severity, long duration and a positive family history; and a late-onset form associated with less-severe disease, shorter duration and low family incidence.[23] Subclassifying AA into groups that display different degrees of severity has been attempted previously.[24]

There have also been several reports of AA in identical twins.[25] A recent study of 114 families noted 11 sets of monozygotic twins with a concordance rate of 55%.[2] There are also reports of monozygotic twins with concordance for AA and with simultaneous hair loss in similar areas.[17,26,27]

Animal models of alopecia areata

Further evidence for a genetic basis to AA comes from animal models. Alopecia areata has been described in a variety of other mammals including dogs, cats, horses, cattle and non-human primates,[28] but the most useful model to date is the rodent.

Although rodents with genetic defects causing hair loss have been used in experiments for many years to study a wide spectrum of diseases and pharmacotherapies, until 1991 none of these rodents had hair loss that displayed the typical clinical or histological features of AA.

In 1991, the Dundee Experimental Bald Rat (DEBR)was described.[29] Histology from the areas of hair loss showed a mononuclear cell infiltrate surrounding and penetrating the hair follicles, which is a characteristic histopathological finding of AA in the human.

In 1994, the C3H/HeJ mouse was described, a strain which develops the features of AA spontaneously at a low frequency. Cross breeding set up between affected male and female C3H/HeJ mice has not lead to a significant increase in incidence. In addition, crosses with related strains known not to develop alopecia and with unrelated mice have yielded mice with AA. This indicates that this disease is controlled by at least one dominant or semidominant gene with reduced penetrance.[28,30] A recent report has described the identification, on mouse chromosome six, of a region that appears to contain one or more genes involved in the pathogenesis of AA in the C3H/HeJ mouse. The homologous regions of the human chromosome 2p11–p13 have not been investigated to date.[31]

Defining the location of AA susceptibile genes in the mouse and rat may help to predict the location of homologous genes in humans using comparative maps, since humans and rodents share 80% or more gene homology.[28]

Disease associations of alopecia areata

Many large studies have described an association with various types of thyroid disease, including simple goiter, myxoedema, Grave's disease and Hashimoto's thyroiditis. One large American study reported a rate of 8% compared with a rate of 2% in the general population.[9] Most[18,20,32] but not all[1] studies have confirmed this association.

Several studies demonstrate an association of AA with Down syndrome. A comparison of 1000 Down syndrome patients with 1000 intellectually subnormal controls found an AA rate of 60, compared with one, respectively.[33] A subsequent random survey of 214 institutionalized patients with Down syndrome, found a similar incidence of this disorder.[34]

There are many reports of increased frequency of atopy in patients with AA, as well as an association with more severe disease; however, there is much conflict regarding this issue in the literature. Some series report a low incidence of 1% atopics among AA patients.[11] However, other papers report much higher rates of atopy, some as high as 52%.[35] A study of 736 patients found a difference in the rate of atopy in children (18%) compared with adults (9%), and a higher rate in the more severe forms.[9] One investigator thought the association with atopy so significant that she labelled one of the four categories she created after its association. Patients in this group had a worse prognosis.[24] This has been confirmed by other studies.[16] Unfortunately, different studies have used different criteria to define atopy, which makes comparisons

difficult. Atopy has been associated with a gain-of-function mutation in the α subunit of the interleukin(IL)-4 receptor on chromosome 16 at p12.1–p11.2.[36]

Association with other dermatological diseases

Vitiligo has consistently been reported in association with AA, with rates of approximately 3–4%.[9,18] Systemic lupus erythematosus (SLE) has been linked with AA. A report of 39 SLE patients found a frequency of AA of 10% compared with 0.42% of general dermatologic patients.[37] Evidence also exists for an association with lichen planus with a relative risk of 2.7 of the development of this skin disorder in AA sufferers.[38]

Mucocutaneous candidiasis (also known as candida–endocrinopathy syndrome, polyglandular autoimmune syndrome type I or polyendocrinopathy-candidiasis-ectodermal dystrophy) presents with chronic candidal infection in association with functional failure of one or more endocrine glands. A review of 42 cases described in the literature revealed a rate of 30% of AA.[39] Several allelic variants have now been found for this disorder on chromosome 21 at q22.3.[40]

Other associations

Other disease associations of AA include coeliac disease,[41] ulcerative colitis,[38,42] rheumatoid arthritis[9,18] pernicious anaemia[1] and Addison's disease.[1]

Interestingly, AA appears to be protective for type 1 diabetes mellitus. A study of 517 individuals with AA and almost 3000 of their first-degree relatives found that type 1 diabetes was more prevalent in the siblings (1.2%) than in the probands (0.2%) who had the same rate as the general population. In contrast, there was no difference in the rate of type 2 diabetes.[32] This has been confirmed by others.[18]

Many case reports also exist of associations with other diseases, including pili annulati[43,44] with Legionnaires' disease[45] and some ocular and testicular abnormalities.[46]

Cytokine/immunoglobulin associations of alopecia areata

Interleukin 1

Intron 2 of the gene for the interleukin (IL)-1 receptor antagonist (IL-1ra), which is located on the long arm of chromosome 2 (2q14-q21), has five alleles corresponding to two, three, four, five and six copies of an 86-base pair repeat sequence.[47]

In a study comparing 90 AA patients with 261 healthy controls, an association of *severity* of AA with allele 2 of the IL-1ra gene polymorphism was reported. This severity association was similar to that found in other epithelial-related diseases, such as lichen sclerosus and SLE. But the association did not extend to this allele being a *susceptibility factor*; in that there was no significant difference between the gene carriage of allele 2 between controls and those patients with patchy AA.[48,49] This fits with the theory that aberrant expression and activity of IL-1 within the scalp mediates cessation of hair growth and reversible hair loss.[50] Recently, allele 2 of the IL-1ra has been shown to also be associated with low production of IL-1 receptor antagonist protein.[51]

Tumour necrosis factor-α

Tumour necrosis factor-α (TNF-α) is a pro-inflammatory cytokine that has been implicated in the pathogenesis of several chronic inflammatory diseases with an autoimmune component.[52] The gene for TNF-α lies within the major histocompatibility complex (MHC) and there has been some speculation that a polymorphism within the gene for TNF-α may play a part in the genetic association of MHC haplotypes with inflammatory diseases. Different TNF-α phenotypes have been associated with AA, as they have been with other inflammatory disorders, such as dermatitis herpetiformis, systemic lupus erythematosis (SLE) and coeliac disease.[49] However, given the proximity of the TNF-α gene to the MHC, these altered TNF-α allele frequencies in AA may just reflect linkage disequilibrium with HLA haplotypes associated with AA.[49] Furthermore, some investigators have discovered differences in TNF-α allelic expression when comparing patchy AA with alopecia totalis (AT) or AU. This could be evidence of genetic heterogeneity between these forms of the disorder.[52]

Immunoglobulins

A study of 52 patients with AA found that the immunoglobulin light chain Km1 allotype on chromosome 2 was significantly higher than a control population. It was also associated with the absence of detectable serum thyroid autoantibodies. The authors suggest that this is due to a linkage disequilibrium with a disease-susceptibility gene on chromosome 2. Another possibility was that the Km1 allotype itself has a direct influence on susceptibility to the disease, through a yet to be defined immunological mechanism.[53]

Another study of 42 patients with AT found a significant increase in frequency of the immunoglobulin heavy chain allotype, Gm 1,2,3,17; 5,12,21 ($P < 0.001$) and a significant decrease in frequency of Gm 1,3,17; 5,13,21 ($P = 0.009$).[54]

Human leucocyte antigens associations

Human leucocyte antigens (HLA) are located in the major histocompatibility complex on the short arm of chromosome 6. Associations with specific HLA class I and class II antigens have been shown for many diseases, including rheumatoid arthritis, insulin-dependent diabetes mellitis (IDDM) and psoriasis.[55] One needs to be cautious when studying HLA associations because some HLA antigens exist in a state of linkage disequilibrium in that they occur together on haplotypes more often than would be expected randomly with genetic cross-over. This particularly occurs with reference to the ethnicity of the subjects in a study.

Associations have been reported with HLA class I alleles B12[56] and B18[57] but these have not been reproduced.

Results with HLA class II alleles have, however, been more consistent, even though these studies have been performed on different populations. Several researchers have found a significantly increased frequency of DR5 in either all subgroups of AA with relative risk ratio (RR) of 4.7[58,59] or just in AU of early onset (RR 3.14), not finding significant results for other groups.[60] Association with DR4 has also been found by several groups.[58,61–63]

With molecular subtyping of HLA class II alleles and division of patient groups into mild-patchy disease and more-severe disease, much higher relative risk ratios have been obtained. One study reported an association with DQB1*0301 with an RR of 6.1, and 10.4 when combined with DPA1*0103, and also found an association with DQA1*0501, RR 3.6.[64]

Another report[25] has also found associations in a subgroup with AT/AU with DQB1*0301(DQ7) RR of 3.5, DRB1*0401, RR 3.4, DRB1*1104 (DR11) RR 30.2 (also with patchy disease more recently)[65] and also with DQB1*0301 in patchy disease and AT/AU. Others have obtained significant associations after dividing patients into different severity groups: DRB1*1104 RR 16.25 in patchy disease and DQB1*301 RR 12.14 for more severe disease.[66]

Negative associations have also been found with DRw52a RR 0.19[59] and with DQB106, RR 0.37.[66]

Until recently, linkage studies with familial AA and HLA alleles had been unsuccessful.[21,67,68] However, a recent report of 81 extended pedigrees, including 192 AA patients, supported a linkage between AA and class II loci with a maximal logarithm of the odds of linkage (LOD) score of 2.42 to HLA-DQB at 5% recombination and with a maximal LOD score of 2.34 to HLA-DR at 0% recombination.[69]

LITERATURE DISCUSSION OF THE GENETICS OF ALOPECIA AREATA

In their landmark paper reporting their evaluation of 736 patients seen at the Mayo Clinic, Muller and Winkelman stated that the capacity of hair to react in patterns recognized clinically as AA is probably inherited, although the mode of inheritance, penetrance and expressivity of the genes must be highly variable.[9]

A later opinion was expressed that, by virtue of the pedigree of some examples of familial AA, an argument existed for concluding an autosomal dominant inheritance with variable penetrance.[70] A large series of 800 patients concluded that the significant number of patients with affected relatives (42% in this study) also suggests an autosomal dominant mode of inheritance.[18]

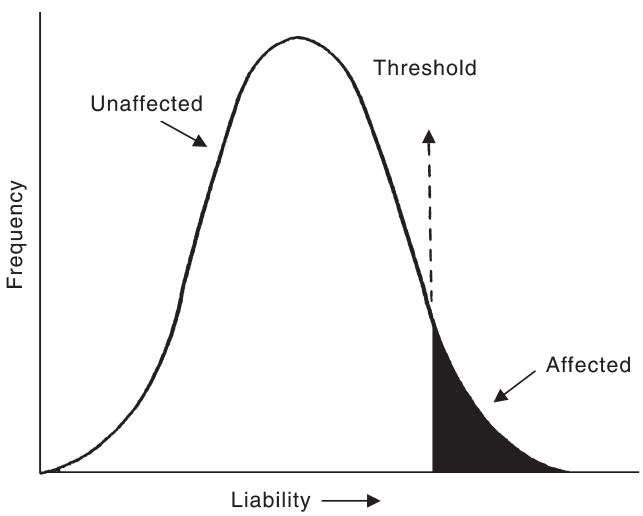

Figure 1 The multifactorial threshold model. Susceptibility to a trait has a normal distribution with a threshold dividing the population into unaffected and affected groups. Reproduced with permission of Wiley-Liss, Inc. (a subsidiary of John Wiley & Sons, Inc.) from: Farrer L, Cupples L. Determining the genetic component of a disease. In: Haines J, Pericak-Vance M (eds). *Approaches to Gene Mapping in Complex Human Disease*, 1998.

In a study of three generations of a non-consanguinous Italian family in which there were six members affected with AU, the authors were of the opinion that it displayed dominant Mendelian inheritance.[21]

In view of the rodent models studied in the last decade, it is now believed that susceptibility to AA is polygenic[28] and, like other complex genetic diseases, its inheritance can be explained by the multifactorial threshold model (Fig. 1).[71]

PROSPECTS FOR FUTURE GENETIC RESEARCH

Genetic loci related to AA can be divided into susceptibility genes that relate to the risk an individual has of developing AA and severity genes that relate to the extent to which an individual displays the clinical features of AA (Table 2). Before the genes can be discovered, a number of hurdles must be overcome. This includes gaining a consistent classification of both the type and severity of hair loss experienced in AA so that a reliable method of defining the phenotype of AA (i.e. the disease expression, as compared with the genotype) can be used to facilitate genetic studies using consistent criteria.

Alopecia areata has been plagued by problems with defining both the type and severity of the disease. Many examples illustrate the differences in categorization of AA among different studies. With regard to severity, one author[13] used five bald patches as their demarcation zone between mild and severe disease, another author divided patients into 'alopecia areata' (referring to patchy disease, which can be confusing but has been common practice), AT and AU, but fails to mention the criteria used to define these groups.[72]

Yet another study defines 'alopecia areata' (patchy disease) as less than 75% of scalp loss and AT as greater than 75% scalp loss, with AU being complete loss of scalp and body hair; there is no assessment of the duration of the illness.[59]

Colombe and colleagues divided AA into three groups: The first is a group of newly diagnosed AA of any type of less than 6 months' duration; a second group of patchy disease is hair loss of greater than 18 months' duration and affecting at least 25% of the scalp. The terms AT and AU are combined to create a third group defined as 100% scalp loss with variable

Table 2 Candidate gene susceptibility and severity areas for alopecia areata

Human chromosome	Candidate area	Severity factor	Susceptibility factor
Two	IL-1 receptor antagonist	+	
	Km1 light chain		+
	Homologue of C3H/HeJ mouse chromosome 6		+
Six	HLA	±	±
	TNF	±	
Fourteen	Gm allotypes		±
Sixteen	Atopy	+	?
Twenty-one	Down syndrome	+	+
	Mucocutaneous candidiasis		+

IL-1, Interleukin one; HLA, human leucocyte antigen; TNF, tumour necrosis factor; Km1, an immunoglobulin κ light-chain determinant; Gm, IgG immunoglobulin heavy-chain allotypes.

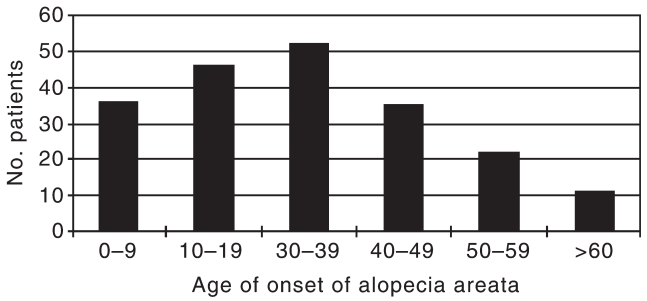

Figure 2 Age at onset of alopecia areata in 269 patients. Data source: Gip L, Lodin A, Molin L. Alopecia areata: A follow-up investigation of outpatient material. *Acta Derm. Venereol. (Stockh.)* 1969; **49**: 180–8.

amounts of body terminal hair loss, and of at least 2 years' duration. Using these definitions, very high RR have been derived for some HLA alleles with more severe forms of the disease.[23]

The Alopecia Areata Investigational Guidelines were published last year and will hopefully lead to consistency amongst researchers regarding defining subgroups of this disease.[73] These guidelines have adopted Colombe's classification of severe disease because AT and AU were felt to too narrowly define disease severity. Also, guidelines on how to calculate the area of hair loss with the use of diagrams will probably lead to greater accuracy in defining the extent of disease activity and, thus, response to treatment. An '*S, B, N* system' has also been created which refers, respectively, to *S*calp hair loss, *B*ody hair loss and *N*ail involvement.[73]

Another difficulty in the genetic study of AA relates to its age-dependent penetrance. Over 30% of people who will get AA develop their first patch of hair loss after age 40[11,17] (Fig. 2).[11] This means that younger members of the families studied will be less informative than those who are older, which makes it difficult to perform linkage studies in families over several generations.

Another potential confounding problem is that those people who only develop AA on inconspicuous body sites, or who experience short-lived patchy disease with spontaneous resolution, either may not realize that they have had AA or may not present to a medical practitioner.

CONCLUSION

Given that AA is likely a polygenic disorder with unidentified environmental triggering of the disease, and given the aforementioned hurdles to be overcome, investigating the genes underlying this disorder will be a difficult task.

Options for investigating genes associated with both severity and susceptibility to the disease include parametric family linkage studies with candidate gene analysis and genome-wide scanning in those families that manifest a high penetrance with an autosomal dominant-like mode of inheritance; or non-parametric studies where a genetic model is not assumed, using sibling pairs or other relative-pair studies. The disadvantage of the latter method is that large numbers of individuals (in the order of hundreds) need to be enrolled in such studies to generate statistical significance. This would necessitate a collaborative effort among research groups.

Using some of the candidate areas outlined would make an obvious starting point in the search for the genes underlying AA.

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