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# Familial aggregation of alopecia areata

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**Background:** Familial aggregation of alopecia areata (AA) has been previously described, but systematic studies with information obtained directly from family members have yet to be undertaken.

**Objective:** We sought to study the pattern of familial aggregation of AA by assessing the affection status of patients' relatives. The study included 206 index patients with a total of 1029 first-degree and 2625 second-degree relatives.

**Methods:** First-degree relatives were directly interviewed, whereas information on second-degree relatives was obtained by interviewing the index patients and their first-degree relatives.

**Results:** Estimated lifetime risks were 7.1% in siblings, 7.8% in parents, and 5.7% in offspring. The risk in second-degree relatives was slightly higher than the reported population risk. Age at onset in index patients and first-degree relatives was significantly correlated.

**Limitations:** Using patients drawn from specialized hair clinics may have produced results showing a higher proportion of early onset and severe cases.

**Conclusion:** The familial aggregation of AA supports the role of genetic factors in the development of the disease. In addition, our data indicate genetic factors might contribute to the age at onset of AA. (J Am Acad Dermatol 2006;54:627-32.)

**A**lopecia areata (AA) is a common dermatologic disorder. The cause remains unclear, but there is strong evidence indicating that it is a tissue-specific autoimmune disease with a

#### *Abbreviations used:*

AA: alopecia areata  
AT: alopecia totalis  
AU: alopecia universalis

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genetic predisposition. AA clinically manifests as a sudden onset of patchy, nonscarring hair loss, which may be diffuse or complete.

Familial aggregation of AA has been previously described in numerous studies. However, few of these studies have systematically obtained information regarding family history from a larger number of patients with AA and reported the affection rates of their relatives.<sup>1-3</sup> These previous studies suffered from reporting bias because of the reliance on obtaining family history information from interviews and questionnaires completed by the patients. We report here the first family study of AA to systematically examine first-degree relatives by direct interview and to obtain information on the affection status of second-degree relatives by interviewing index patients and first-degree relatives.

## METHODS

The patients came from hair clinics at 3 university departments of dermatology in Belgium (Antwerp and Gent) and Germany (Düsseldorf). Patients in Antwerp and Gent were recruited on the basis of a systematic review of patient records. Patients in Düsseldorf were recruited from consecutive admissions. Inclusion criterion was the diagnosis of AA by standard criteria.<sup>4</sup> Exclusion criterion was the presence of Down syndrome in a patient. Patients were asked to participate regardless of family history or age at onset. All participating index patients signed an informed consent that was approved by the institutional review board.

All patients with living relatives were asked to obtain consent from first-degree relatives allowing us to contact them. First-degree relatives were then contacted by telephone for a structured interview after having obtained consent. Information on second-degree relatives was obtained by interviewing index patients and first-degree relatives. Relatives who had at least one episode of AA during their lifetime were considered affected.

Age at onset was defined as the age when patchy hair loss was first noticed, regardless of whether a diagnosis of AA was made at that time or a later date. The severity of alopecia was assessed according to published guidelines<sup>4</sup> and patients were categorized as having patchy alopecia ( $S_1$ - $S_4$ ), alopecia totalis (AT), AT/alopecia universalis (AU), or AU. Patchy alopecia includes the stages  $S_1$  (<25% hair loss) to  $S_4$  (75%-99% hair loss). AT was defined as 100% scalp terminal hair loss without body hair loss. AT/AU was defined as 100% scalp hair loss with variable body hair loss. AU was defined as 100% scalp and body hair loss. The detailed severity categorization proved difficult when no medical records or direct clinical examination data were available. We simplified the severity groups to two categories, mild patchy alopecia ( $S_1$ - $S_4$ ) and severe (AT, AT/AU, and AU) for first- and second-degree relatives.

### Statistical analysis

Time was specified as the age at onset for the affected individuals and the age at last contact or death for the unaffected individuals. The lifetime risk for the different relatives was estimated, assuming the Cox proportional hazard model as the cumulative risk, at 79 years of age, the highest age at onset in our data. The Cox proportional hazard model was introduced to analyze survival data in circumstances where not for all persons the date of death could be ascertained. In this model it is assumed that the risk to decrease is variable over time but proportional with fixed factors between the different analyzed

groups. We decided to use this model instead of estimating different risk distributions for the diverse groups because of the small number of affected persons in several groups.

Age at onset was compared using the Wilcoxon two-sample rank test. The number of affected first- and second-degree relatives was compared between male and female index patients with the Cochran-Mantel-Haenszel test to control for the degree of relationship. The degree of affection and sex of the index patient was compared with the familial and nonfamilial cases using Fisher's exact test. The same test was also used to compare the number of mildly affected index patients and mildly affected first- and second-degree relatives. Linear regression analysis was used to investigate the dependency between the age at onset of patients and the age at onset of their relatives. To investigate the dependency of the degree of hair loss between index patients and their affected relatives we used alternating logistic regression. This was done to adjust for a possible correlation of the degree of hair loss between the relatives in one family.

All analyses were performed using software (SAS 8.02, SAS Institute Inc, Cary, NC).

## RESULTS

A total of 206 index patients were studied; 134 female (65%) and 72 male (35%), with a female to male ratio of 1.9:1. The age of the patients ranged from 7 to 80 years, with a mean age of 39.0 years (female = 41.3 years, male = 34.3 years). Information regarding ethnicity was obtained by documenting the origin of the patients' grandparents. In all, 162 patients had grandparents from Belgium; 9 had grandparents from Germany; 32 had at least one grandparent from a neighboring country, but not from a more distant country; one patient had two English grandparents; and one patient had an Italian grandparent.

The age at onset ranged from 1 to 72 years with a mean age at onset of 23.4 years (SD  $\pm$  16.0 years). The mean age at onset was 23.9 years (SD  $\pm$  16.6 years) in female patients and 22.6 years (SD  $\pm$  14.8 years) in male patients ( $P = .791$ ). The first episode of AA before the age of 20 years occurred in 50.3% of patients and 83.8% had the first symptoms within the first 4 decades of life. Fig 1 shows the distribution by age at onset and sex of the patients with AA. The degree of hair loss ranged from 89 patients (43.2%) having  $S_1$  to  $S_4$  (45 female and 44 male), 19 (9.2%) having AT (14 female and 5 male), 7 (3.4%) having AT/AU (7 female), and 91 (44.2%) having AU (68 female and 23 male).

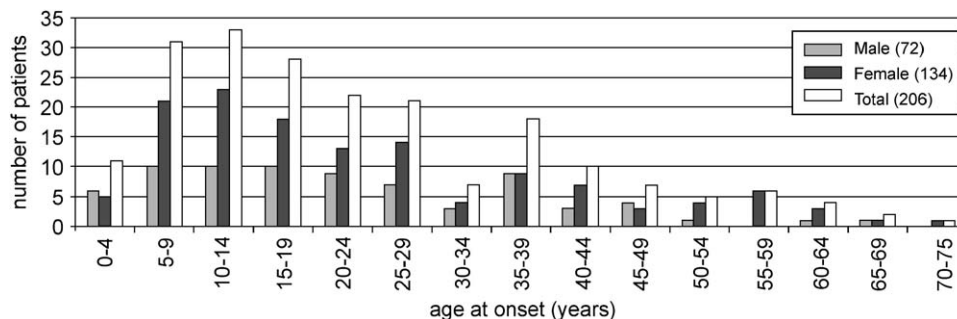


Fig 1. Distribution of onset age in patients with alopecia areata.

Table I. Frequency of alopecia areata and degree of affection among first- and second-degree relatives

Relation	No.	No. with AA	Frequency, %	Mild (%)	Severe (%)
Parents	406	30	7.4	22/30 (73.3)	8/30 (26.7)
Mother	205	18	8.8		
Father	201	12	6.0		
Siblings	404	22	5.5	16/22 (72.7)	6/22 (27.3)
Brother	200	14	7.0		
Sister	204	8	3.9		
Children	219	5	2.3	5/5 (100)	0/5 (0)
Son	114	4	3.5		
Daughter	105	1	1.0		
<b>Total first-degree</b>	<b>1029</b>	<b>57</b>	<b>5.5</b>	<b>43/57 (75.4)</b>	<b>14/57 (24.6)</b>
Grandparents	785	12	1.5	8/12 (66.7)	4/12 (33.3)
Uncle/aunt	1262	17	1.4	12/17 (70.6)	5/17 (29.4)
Nephew/niece	518	9	1.7	8/9 (88.9)	1/9 (11.1)
Grandchildren	60	0	-	-	-
<b>Total second-degree</b>	<b>2625</b>	<b>38</b>	<b>1.5</b>	<b>28/38 (73.7)</b>	<b>10/38 (26.3)</b>

AA, alopecia areata.

The 206 index patients had a total of 1029 first- and 2625 second-degree relatives. The median number was 66 first- and second-degree relatives per pedigree. In all, 630 first-degree relatives were directly interviewed. A total of 399 first-degree relatives could not be questioned for various reasons, such as too young or too advanced an age, mental retardation, no longer living, or no known contact details. Information concerning first-degree relatives who were unavailable for interview was gathered by questioning the index patient and other first-degree relatives. One female index patient had been adopted and had no available information about her biologic family. Therefore, she was excluded from the calculation of recurrence risks. One index patient had a monozygotic affected twin brother. No dizygotic twins appeared in the sample.

In all, 57 (5.5%) of the first-degree and 38 (1.5%) of the second-degree relatives were affected with alopecia (Table I). In all, 45 (21.8%) index patients had at least one first-degree relative with AA and

69 (34.0%) index patients had at least one first- or second-degree relative with AA. There were 19 families with more than one affected relative. Two relatives were affected in 16 families; 6 families with two affected first-degree relatives, 7 families with one affected first-degree and one affected second-degree relative, and 3 families with two affected second-degree relatives. One family had 3 affected relatives; two affected first-degree and one affected second-degree relative. Two families had more than 3 affected relatives; one family with one affected first-degree and 3 affected second-degree relatives and one family with 4 affected first-degree and one affected second-degree relative. The distribution of affected family members among different categories of first- and second-degree relatives and their degree of affection is shown in Table I. The majority of first- (75.4%) and second- (73.7%) degree relatives were mildly affected. The frequency of severe disease was lower among affected relatives than among index patients ( $P < .011$  for first-degree

**Table II.** Comparison of patients with and without familial alopecia areata

	Familial AA (%)	Nonfamilial AA (%)	<i>P</i>
No. of patients	69 (34.0)	136 (66.0)	
Mean age at onset	22.4 y (SD 15.0)	21.1 y (SD 16.5)	.676
Degree of affection			
Mild	28 (40.6)	59 (43.4)	.766
Severe	41 (59.4)	77 (56.6)	
Sex			
Male	24 (34.8)	48 (35.3)	1.000
Female	45 (65.2)	88 (64.7)	

AA, alopecia areata.

**Table III.** Number of affected relatives in relation to the degree of affection of the index patient

Patients' no. of affected relatives	Mild		Severe	
1	19		31	
2	8		8	
3	1		-	
4	-		1	
5	-		-	
6	1		-	

relatives,  $P = .051$  for second-degree relatives). This probably reflected a higher ascertainment probability in severely affected cases.

No differences were found when the degree of affection, sex, and median age at onset between patients with and without familial AA were compared (Table II). The majority of patients with familial AA had just one affected relative, regardless of the degree of affection (Table III). More than one affected relative occurred in 34% (10 of 29) of mildly affected patients and 22.5% (9 of 40) of severely affected patients with a familial history ( $P = .290$ ).

We also tested whether the relatives' age at onset was influenced by the age at onset of the index patient. We included only information on first-degree relatives for this because age at onset information of second-degree relatives was considered less reliable. Children of the index patients were excluded from this analysis because they were biased toward lower onset ages. A positive correlation was found between the age at onset of index patients and their first-degree relatives ( $r = 0.284$ ,  $P = .043$ , linear regression:  $\text{aorel} = 21.8 + 0.272^* \text{aoid}$ ). We found that male index patients had 26 affected first-degree (7.6%) and 11 affected second-degree (1.3%) relatives, and female index patients had 31 affected first-degree (4.5%) and 27 affected

**Table IV.** Lifetime risks in first- and second-degree relatives of patients with alopecia areata

Relation	No.	No. with AA	Lifetime risk (95% CI)
First-degree relatives			
Parents	406	30	7.8% (5.0-10.5)
Siblings	403	22	7.1% (4.0-10.1)
Children	219	5	5.7% (0.0-11.1)
Second-degree relatives			
Grandparents	785	12	1.6% (0.7-2.5)
Uncle/aunt	1265	17	1.2% (0.6-1.9)
Nephew/niece	518	9	3.5% (1.0-5.8)

AA, alopecia areata; CI, confidence intervals.

second-degree (1.5%) relatives. Affection rates of relatives were similar between male and female index cases ( $P = .189$ ).

We ascertained the number of affected and unaffected first- and second-degree relatives of our index patients, excluding the adopted index patient (as there was no knowledge about the relatives) and the affected monozygotic twin brother of one index patient from the analyses, to calculate lifetime risks for relatives. Lifetime risks according to the type of family relationship are given in Table IV.

We analyzed if there was a relation between the degree of hair loss in the index patient and his first-degree relatives. However, no such relation was observed in our data. A total of 21 mildly affected index patients had 23 mildly and 5 severely affected first-degree relatives and 25 severely affected index patients had 20 mildly and 9 severely affected first-degree relatives ( $P = .463$ ). Looking at first- and second-degree relatives we found for 28 mildly affected index patients 34 mildly affected and 9 severely affected relatives. In all, 40 severely affected index cases represented 37 mildly affected and 15 severely affected relatives. There was no significant association between severity of disease in index patients and severity of disease in relatives ( $P = .279$ ).

## DISCUSSION

This study estimated the risks of AA in first- and second-degree relatives of patients with AA from Belgium and Germany. It was the first family study to systematically contact the first-degree relatives directly and to collect reliable information regarding second-degree relatives through the interview of first-degree relatives.

A familial occurrence of AA has been previously reported.<sup>1-3,5-23</sup> The previous reports of AA familiarity were often highlighted with a statement concerning the number of patients with affected family members. In our study 21.8% of the patients had a positive

family history of AA defined by the affection of at least one first-degree relative. A positive family history was noted in 34.0% of our patients when information on second-degree relatives was included. The studies were difficult to compare because the declaration of a positive family history was, among other things, dependent on family size, severity of affection, the thorough ascertainment of relatives, and age distribution. The fraction of familial cases ranges from 5.7% to 19.3% if we only consider those studies that examined at least 100 patients and where the allegation of familiarity was made because of the affection of first-degree relatives.<sup>2,5,7-9,11</sup> Two large studies showed the rate of affected first-degree relatives,<sup>1,3</sup> but it is not apparent from their data how often the affected relatives were observed in independent families. The high number of familial cases (21.8% as defined by the affection of at least one first-degree relative) we observed was probably predominantly a result of obtaining direct information from interviewed first-degree relatives and, thereby, avoiding a reporting bias.

In our study population, the frequency of AA was greatest in parents (7.4%), followed by siblings (5.5%) and children (2.3%). This was consistent with previous findings<sup>1-3</sup> and likely reflects differences in mean ages of the 3 groups. The highest frequency of AA within the second-degree relatives can be seen among nephews and nieces (1.7%), followed by grandparents (1.5%) and aunts and uncles (1.4%). The lack of affected grandchildren could be explained by the young age of this group. It would be expected that the number of affected persons would increase with age. We also estimated the lifetime risks for first- and second-degree relatives of probands with AA to account for differences in mean ages among the different groups. The lifetime risk was higher among first-degree relatives than among second-degree relatives. Among first-degree relatives the risk was highest in parents (7.8%). The recurrence risk for children was estimated at 5.7%, a figure that will provide valuable information for genetic counseling procedures. However, it is worth noting that this figure also contains mildly affected cases and that the recurrence risk for severe cases will be substantially lower.

One measure of the magnitude of the genetic contribution to the development of AA would be the sibling risk ratio ( $\lambda_s$ ). Alteration in the population prevalence directly influences the risk ratio (sibling risk/population prevalence). The only study to date to provide a reliable estimate of the lifetime population prevalence of AA reported a figure of 1.7% in a US population, which was greater than 90% white.<sup>24</sup> No estimate of the lifetime population prevalence of

AA is available for the European population. The  $\lambda$  was estimated using the data obtained from the US population and determined to be 4.2. Based on the estimation of lifetime risk for the US population, it seems appropriate to assume that the recurrence risk for second-degree relatives in our sample was only slightly higher than the population risk. The dramatic dilution of the genetic material with more distant degrees of genetic relatedness could be explained by assuming a multifactorial mode of inheritance as the most likely method of inheritance for AA.

Controversial studies exist concerning the possible influence of familiarity on onset age and severity of the disease.<sup>2,3,11,13,20,22</sup> We could not detect such influence in our study. The onset age and severity of the disease were similar in patients with or without a positive family history. It has also been suggested, on the basis of a nonsignificant trend, that more severely affected index patients among familial cases have a greater number of affected relatives.<sup>2</sup> However, we did not observe this effect in our sample. In contrast, we actually observed an opposite tendency that showed a higher percentage of mildly affected index patients having at least two affected relatives (34%, 10 of 29) as opposed to the severely affected index patients (23%, 9 of 40). Based on our data, we found no evidence in support of an early age at onset or severe expression of the phenotype being associated with genetic load in AA. Clearly, much larger samples are needed to convincingly address this issue and to confirm or refute smaller effects.

There has been anecdotal evidence from studies of families and monozygotic twins that onset age correlates with families.<sup>7,25-28</sup> However, the only large twin study showed less conclusive results. Similarities and differences in age at onset were observed among concordant monozygotic twins.<sup>29</sup> We were able to demonstrate a positive correlation between the age at onset of index patients and their first-degree relatives in our sample.

We also investigated the presence of a Carter effect,<sup>30</sup> defined as a higher incidence in relatives when the index case is the least commonly affected sex, because we observed that the sex ratio of our patients was unbalanced. The numbers of affected first- and second-degree relatives were comparable between male and female index patients. Thus, the presence of the Carter effect was unlikely.

A limitation of our study was the use of patients from specialized hair clinics. Thus, there was the likelihood that they may have contained a higher proportion of early onset and severe cases than would normally be the case for patients drawn from the general population, which might also affect the lifetime risks. Therefore, the results cannot be

generalized until confirmed using population-based studies.

In conclusion, we provided additional support for the role of genetic factors, probably acting in a polygenic fashion, in the contribution to the susceptibility of AA. It will be a matter for future studies to systematically identify disease-associated genes to determine the molecular mechanism that causes AA. In addition, our data indicated that familial factors influence the age at onset of AA, which was evidenced by the correlation of age at onset between index patients and first-degree relatives. The lifetime risks calculated in our study will be of practical value in the genetic counseling of patients and family members.

We are grateful to all of the individuals who cooperated in this study.

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