

History of atopy or autoimmunity increases risk of alopecia areata

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Background: The association between a history of atopy or autoimmune diseases and risk of alopecia areata (AA) is not well established.

Objective: The purpose of this study was to use the National AA Registry database to further investigate the association between history of atopy or autoimmune diseases and risk of AA.

Methods: A total of 2613 self-registered sporadic cases (n = 2055) and controls (n = 558) were included in this analysis.

Results: Possessing a history of any atopic (odds ratio = 2.00; 95% confidence interval 1.50-2.54) or autoimmune (odds ratio = 1.73; 95% confidence interval 1.10-2.72) disease was associated with an increased risk of AA. There was no trend for possessing a history of more than one atopic or autoimmune disease and increasing risk of AA.

Limitations: Recall, reporting, and recruiting bias are potential sources of limitations in this analysis.

Conclusion: This analysis revealed that a history of atopy and autoimmune disease was associated with an increased risk of AA and that the results were consistent for both the severe subtype of AA (ie, alopecia totalis and alopecia universalis) and the localized subtype (ie, AA persistent). (J Am Acad Dermatol 10.1016/j.jaad.2009.04.031.)

Key words: alopecia areata; atopy; autoimmunity; epidemiology; National Alopecia Areata Registry.

Alopecia areata (AA) is an organ-specific, T cell–mediated autoimmune disease that targets anagen-stage hair follicles. It affects

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Abbreviations used:

AA:	alopecia areata
AAP:	alopecia areata persistent
AT:	alopecia totalis
AU:	alopecia universalis
IFN:	interferon
IL:	interleukin
NAAF:	National Alopecia Areata Foundation
NAAR:	National Alopecia Areata Registry
OR:	odds ratio
Th1:	T helper 1
Th2:	T helper 2

both sexes equally, can occur early in life or present in adulthood, and has a prevalence of approximately 0.1% in the United States with a lifetime risk of 1.7%.¹ Disease severity subtypes range from one or more local patches of hair loss to total loss of scalp hair (alopecia totalis [AT]) or total scalp and body hair loss (alopecia universalis [AU]).² Little is currently known about risk factors for AA, but studies have suggested that AA is a complex multigenetic trait with an inherited predisposition component.³ Discordance in identical twins suggests that

presentation of AA could be triggered by environmental factors in a susceptible host.⁴ The majority of AA cases are sporadic and the reported frequency of a positive family history varies from 3% to 42%.^{5,6}

Previous studies have provided evidence that a history of atopy and autoimmune diseases are also risk factors for AA.⁶⁻¹⁰ Atopic diseases, such as asthma, atopic dermatitis, and hay fever, have been reported in 10% to 60% of patients with AA.^{7,8} However, these studies do not specify whether atopy was diagnosed before or after onset of AA. Previous studies have shown that approximately 12% of individuals with AA go on to develop an autoimmune disease.¹ Several studies have also shown an increased frequency of thyroid disorders, pernicious anemia, psoriasis, and vitiligo in patients with AA.⁸⁻¹⁰ In contrast, Wang et al¹¹ found that a history of type 1 diabetes mellitus was less frequent in probands with AA but significantly more common in their relatives. A previous study that used the National AA Registry (NAAR) database found an association between self-reported autoimmune diseases (Hashimoto thyroiditis, vitiligo, and diabetes mellitus [types 1 and 2 combined]) and risk of AA.¹² However, this previous study was a cross-sectional analysis and did not take into account whether the autoimmune disease was diagnosed before or after AA.

To shed more light on the role of history of atopy and autoimmune diseases for risk of AA, we used data from the NAAR database and performed a case-comparison analysis. We hypothesized that a self-reported history of atopy or autoimmune disease was associated with an increased risk of AA.

METHODS

Study participants and data collection

Study participants were recruited through the NAAR, which includes The University of Texas M. D. Anderson Cancer Center in Houston (database and central repository), the University of California in San Francisco, the University of Colorado in Denver, the University of Minnesota in Minneapolis, and Columbia University in New York City.¹³ The NAAR is a World Wide Web-based registry (<http://www.AlopeciaAreataRegistry.org>)

that collects data on patients with AA and non-blood-related control participants who live in the United States. There were no age, sex, or ethnicity restrictions for participation. NAAR provides resources for self-registration of patients with AA whose diagnosis was confirmed by a dermatologist. The study was conducted according to the Declaration of Helsinki Principles.

NAAR participants are classified by disease subtype according to the severity and duration of AA. Case patients with patchy AA are classified as having AA transient if the duration is less than 1 year, and AA persistent (AAP) if the duration is longer than 1 year; the AT subtype includes patients with total scalp hair loss for more than 1 year, and the AU subtype, those with entire body hair loss. Case patients who have more than one family member with AA were excluded from this analysis of sporadic cases, and case patients with AA transient (ie, patients with patchy AA for <1 year) were also

excluded because it is difficult to predict whether patients with AA transient will progress to AAP or AT/AU after 1 year. Thus, the final analysis only included sporadic cases of AA with AAP, AT, or AU.

Control subjects were unaffected by AA, had never been given the diagnosis of AA at the time of recruitment, were non-blood related to patients with AA, and had no known family history of AA. These individuals were recruited by NAAR from one of the 4 following sources: (1) volunteers who were notified through Internet advertisements from sources such as the National Institutes of Health or National Alopecia Areata Foundation (NAAF); (2) volunteers identified at the Annual NAAF International Conferences; (3) members of the research team who were involved in NAAR or NAAF; or (4) unaffected, non-blood-related family members or friends of patients who had participated in NAAR.

The data collected included age of AA onset, extent of disease, and self-reported history and age of onset of atopy and autoimmune diseases. Atopy included asthma, atopic dermatitis, and hay fever. The autoimmune diseases in this analysis included irritable bowel syndrome, psoriasis, and any thyroid disorder. Because few individuals reported having rheumatoid arthritis, systemic lupus erythematosus,

CAPSULE SUMMARY

- This case-control study examined the association between self-reported history of atopy and/or autoimmunity with alopecia areata (AA).
- A total of 2055 patients with sporadic AA and 558 nonaffected control subjects were analyzed from the National Institute of Arthritis and Musculoskeletal and Skin Diseases—funded AA registry.
- Self-reported atopy, specifically atopic dermatitis (odds ratio = 1.70; 95% confidence interval 1.13-2.56) and autoimmunity, specifically hypothyroidism (odds ratio = 2.96; 95% confidence interval 1.43-6.15) were associated with an increased risk of AA.

Table I. Population characteristics by alopecia areata subtype

Characteristics	AAP	AT	P value for AAP vs AT	AU	P value for AAP vs AU
	N = 852	N = 343		N = 860	
Age of recruitment, y, mean (SD)	37.5 (16.0)	33.2 (17.3)	<.001	41.6 (19.1)	<.001
Age of onset, y, mean (SD)	21.8 (15.7)	14.9 (13.7)	<.001	20.8 (16.5)	.232
Sex, N (%)					
Female	627 (73.6)	268 (78.1)		581 (67.6)	
Male	225 (26.4)	75 (21.9)	.101	279 (32.4)	.006
Ethnicity, N (%)					
African American	60 (7.0)	29 (8.4)		32 (3.7)	
Hispanic	52 (6.1)	16 (4.7)		38 (4.4)	
Caucasian	740 (86.9)	298 (86.9)	.462	790 (91.9)	.002
Any hx of atopy, N (%)					
No hx of dx*	550 (71.9)	200 (67.6)		513 (67.9)	
dx Before AA [†]	215 (28.1)	96 (32.4)	.165	243 (32.1)	.086
Asthma, N (%)					
No hx of dx	734 (91.3)	291 (88.5)		725 (88.5)	
dx Before AA	70 (8.7)	38 (11.5)	.139	94 (11.5)	.064
Atopic dermatitis, N (%)					
No hx of dx	705 (86.8)	257 (82.6)		725 (86.4)	
dx Before AA	107 (13.2)	54 (17.4)	.073	114 (13.6)	.518
Hay fever, N (%)					
No hx of dx	657 (82.4)	250 (81.4)		628 (80.1)	
dx Before AA	140 (17.6)	57 (18.6)	.697	156 (19.9)	.235
Any hx of autoimmune disease, N (%)					
No hx of dx	726 (94.8)	291 (95.4)		704 (93.5)	
dx Before AA	40 (5.2)	14 (4.6)	.670	49 (6.5)	.286
Irritable bowel syndrome, N (%)					
No hx of dx	820 (97.9)	329 (99.1)		830 (99.3)	
dx Before AA	18 (2.1)	3 (0.9)	.148	6 (0.7)	.014
Psoriasis, N (%)					
No hx of dx	827 (99.2)	332 (98.2)		828 (98.3)	
dx Before AA	7 (0.8)	6 (1.8)	.166	14 (1.7)	.130
All hyperthyroidism, N (%)					
No hx of dx	846 (99.8)	342 (100)		846 (99.7)	
dx Before AA	2 (0.2)	0 (0)	.369	3 (0.3)	.655
All hypothyroidism, N (%)					
No hx of dx	776 (98.1)	311 (98.1)		762 (96.6)	
dx Before AA	15 (1.9)	6 (1.9)	.997	27 (3.4)	.059
Any hx of atopy or autoimmune disease, N (%)					
No hx of dx	501 (68.5)	182 (64.5)		439 (61.9)	
dx Before AA	230 (31.5)	100 (35.5)	.224	270 (38.1)	.008

AA, Alopecia areata; AAP, alopecia areata persistent; AT, alopecia totalis; AU, alopecia universalis; dx, diagnosis; hx, history.

P values were derived from Chi-square test or Fisher exact for categorical variables and Student t test for continuous variables. All P values are two-sided.

*dx of disease before dx with AA.

†dx of disease after dx with AA.

or vitiligo associated with AA, it was not possible to analyze the risk of these diseases for AA. Patients with either hypothyroidism or hyperthyroidism were included whether identified by general classification or specific diagnosis (eg, Hashimoto or Graves

disease). Patients whose diagnosis of AA preceded onset of atopy or other autoimmune diseases were excluded. In addition, self-identified Asian and Native American patients were excluded because of the small numbers of individuals available.

Table II. Population characteristics of patients with alopecia areata and control subjects

Characteristics	AA+	Controls	P value*
	N = 2055	N = 558	
Age of recruitment, y, mean (SD)	38.5 (17.8)	40.8 (14.7)	.005
Sex, N (%)			
Female	1476 (71.8)	361 (64.7)	.001
Male	579 (28.2)	197 (35.3)	
Race, N (%)			
African American	121 (5.9)	31 (5.5)	<.001
Hispanic	106 (5.2)	55 (9.9)	
Caucasian	1828 (88.9)	472 (84.6)	
Any hx of atopy, N (%)			
No hx of dx [†]	1263 (69.5)	442 (79.2)	<.001
dx Before AA [‡]	554 (30.5)	116 (20.8)	
Asthma, N (%)			
No hx of dx	1750 (89.7)	515 (92.3)	.064
dx Before AA	202 (10.3)	43 (7.7)	
Atopic dermatitis, N (%)			
No hx of dx	1646 (85.7)	515 (92.3)	<.001
dx Before AA	275 (14.3)	43 (7.7)	
Hay fever, N (%)			
No hx of dx	1535 (81.3)	479 (85.8)	.013
dx Before AA	353 (18.7)	79 (14.2)	
Any hx of autoimmune disease, N (%)			
No hx of dx	1721 (94.4)	522 (93.5)	.478
dx Before AA	103 (5.6)	36 (6.5)	
Irritable bowel syndrome, N (%)			
No hx of dx	1979 (98.7)	545 (97.7)	.097
dx Before AA	27 (1.3)	13 (2.3)	
Psoriasis, N (%)			
No hx of dx	1987 (98.7)	549 (98.4)	.628
dx Before AA	27 (1.3)	9 (1.6)	
Hyperthyroidism, N (%)			
No hx of dx	2034 (99.8)	554 (99.3)	.093
dx Before AA	5 (0.2)	4 (0.7)	
Hypothyroidism, N (%)			
No hx of dx	1849 (97.5)	547 (98.0)	.449
dx Before AA	48 (2.5)	11 (2.0)	
Any hx of atopy or autoimmune disease, N (%)			
No hx of dx	1122 (65.2)	420 (75.3)	<.001
dx Before AA	600 (34.8)	138 (24.7)	

AA, Alopecia areata; AA+, all 3 clinical subtypes (alopecia areata persistent + alopecia totalis + alopecia universalis); dx, diagnosis; hx, history.

*P values were derived from Chi-square test or Fisher exact for categorical variables and Student *t* test for continuous variables. All P values are two-sided.

[†]No hx of autoimmune or atopic disease.

[‡]dx of disease before dx with AA in cases and history of presence of disease in controls.

Statistical methods

Analyses were performed using a statistical software package (Intercooled Stata 10.0, Stata Corp, College Station, TX). Where appropriate, Pearson Chi-square test or Fisher exact test was used to test for differences between cases and controls and between AA subtypes in terms of sex, ethnicity, and history of atopy or autoimmune diseases. Student *t* test was used to test for differences in mean age and mean age of AA onset. Odds ratios (OR) and 95% confidence intervals were calculated as an estimate of the relative risk. Multivariable logistic regression analysis was performed to control for potential confounding by age, age of onset for cases, sex, ethnicity, and history of atopy or autoimmune diseases, where appropriate. With 95% power and a two-sided significance level of 5%, this analysis had statistical power to detect a statistically significant OR of 1.75 when the prevalence of atopy or autoimmune disease was rare (5%) and an OR of 1.38 when the prevalence of atopy or autoimmune disease was more common (40%). Therefore, with this analytic sample size we are powered to detect a modestly sized OR even when the prevalence of atopy or autoimmune disease is rare.

RESULTS

A total of 2055 patients with self-registered sporadic AA and 558 control subjects were included in the analysis. Table I contains the demographic characteristics for the alopecia clinical subtypes: 852 (41%) had AAP, 343 (17%) had AT, and 860 (42%) had AU. Compared with patients with AAP, patients with AT were younger ($P < .001$) and had younger age of onset of AA ($P < .001$). There were no statistically significant differences between patients with AAP and AT for self-reported history of atopic or autoimmune diseases other than a borderline association with atopic dermatitis ($P = .073$). Compared with patients with AAP, those with AU were older ($P < .001$). Caucasians represented approximately 92% of AU and 87% of both the patients with AT and AAP; 26% of the patients with AAP, 22% of the patients with AT, and 33% of patients with AU were male. Any history of atopic or an autoimmune disease ($P = .008$), irritable bowel syndrome ($P = .014$), and hypothyroidism ($P = .059$) were more common in patients with AU than AAP.

Table II contains the demographic characteristics for all combined alopecia clinical subtypes (ie, AA+) and control subjects. Because the registry is ongoing, perfect case-control matching has not yet been achieved. Patients were younger than the control subjects ($P = .005$). There was a predominance of female registrants and Caucasians; approximately 72%

Table III. Association between history of atopy and autoimmune disease and risk of severe alopecia subtypes among patients with alopecia areata

Characteristics	AAP	AT + AU	Crude OR (95% CI)	mOR* (95% CI)	mOR [†] (95% CI)
	N = 852	N = 1203			
Any hx of atopy					
No hx of dx [‡]	550	713			
dx Before AA [§]	215	339	1.22 (0.99-1.50)	1.27 (1.03-1.56)	1.24 (1.01-1.53)
Asthma					
No hx of dx	734	1016			
dx Before AA	70	132	1.36 (1.00-1.85)	1.39 (1.02-1.89)	1.23 (0.89-1.70)
Atopic dermatitis					
No hx of dx	705	941			
dx Before AA	107	168	1.18 (0.91-1.53)	1.24 (0.95-1.61)	1.14 (0.86-1.51)
Hay fever					
No hx of dx	657	878			
dx Before AA	140	213	1.14 (0.90-1.44)	1.20 (0.95-1.53)	1.10 (0.85-1.43)
Any hx of autoimmune disease					
No hx of dx	726	995			
dx Before AA	40	63	1.15 (0.76-1.73)	1.43 (0.94-2.19)	1.34 (0.87-2.06)
Irritable bowel syndrome					
No hx of dx	820	1159			
dx Before AA	18	9	0.35 (0.16-0.79)	0.42 (0.19-0.95)	0.38 (0.17-0.86)
Psoriasis					
No hx of dx	827	1160			
dx Before AA	7	20	2.04 (0.86-4.84)	2.28 (0.95-5.45)	2.11 (0.88-5.06)
Hypothyroidism					
No hx of dx	776	1073			
dx Before AA	15	33	1.60 (0.86-2.95)	2.05 (1.09-3.85)	2.00 (1.06-3.76)
Any hx of atopy or autoimmune disease					
No hx of dx	501	621			
dx Before AA	230	370	1.30 (1.06-1.59)	1.39 (1.13-1.71)	N/A ^{//}

AA, Alopecia areata; AAP, alopecia areata persistent; AT, alopecia totalis; AU, alopecia universalis; CI, confidence interval; dx, diagnosis; hx, history; mOR, multivariable odds ratio; N/A, not applicable; OR, odds ratio.

Numbers in bold type indicate statistically significant odds ratio.

*Multivariable model adjusted for race, sex, age of onset.

[†]Multivariable model adjusted for race, sex, age of onset, other autoimmune or atopic diseases.

[‡]No hx of autoimmune or atopic disease.

[§]dx of disease before dx with AA.

^{//}Any hx of atopy or autoimmune disease represents all diseases associated with AA, thus, could not be adjusted for other diseases.

of the patients were female and 89% were Caucasian ($P < .001$). There were no differences between the cases and controls in terms of history of irritable bowel syndrome, psoriasis, and thyroid diseases.

Multivariable logistic regression analyses were performed to assess the association between a history of atopy or autoimmune disease and AA. For these analyses (Tables III to V), two separate multivariable models were assessed. The first model adjusted for demographic information, specifically age, sex, and ethnicity, whereas the second model included the demographic covariates in addition to adjusting for a history of any atopy or autoimmune disease. The category of having any history of atopy was adjusted for having any history of autoimmune

disease and vice versa. The category of having both any history of atopy or autoimmune disease was not adjusted for other diseases because it included all types of atopic or autoimmune diseases.

Patients with a history of AT and AU (ie, the severe subtypes of AA) were combined and compared with patients with AAP (ie, the localized subtype of AA) (Table III). After adjusting for the demographic covariates and history of atopy or autoimmune disease, history of atopy and history of hypothyroidism were each associated with an increased risk of AT or AU. We excluded hyperthyroidism from this analysis because there were so few individuals with this particular disease (ORs and confidence intervals are provided in Tables III to VI).

Table IV. Association between history of atopy and autoimmune disease and risk of alopecia among all alopecia cases and controls

Characteristics	AA+	Controls	Crude OR (95% CI)	mOR* (95% CI)	mOR [†] (95% CI)
	N = 2055	N = 558			
Any hx of atopy					
No hx of dx [‡]	1263	442			
dx Before AA [§]	554	116	1.67 (1.33-2.10)	2.19 (1.68-2.83)	2.00 (1.50-2.54)
Asthma					
No hx of dx	1750	515			
dx Before AA	202	43	1.38 (0.98-1.95)	1.45 (0.9-2.14)	0.76 (0.50-1.17)
Atopic dermatitis					
No hx of dx	1646	515			
dx Before AA	275	43	2.00 (1.43-2.80)	2.61 (1.78-3.83)	1.70 (1.13-2.56)
Hay fever					
No hx of dx	1535	479			
dx Before AA	353	79	1.39 (1.07-1.82)	1.97 (1.46-2.66)	1.31 (0.95-1.81)
Any hx of or autoimmune disease					
No hx of dx	1721	522			
dx Before AA	103	36	0.87 (0.5-1.28)	2.08 (1.34-3.23)	1.73 (1.10-2.72)
Irritable bowel syndrome					
No hx of dx	1979	545			
dx Before AA	27	13	0.57 (0.29-1.12)	1.40 (0.67-2.91)	1.03 (0.50-2.22)
Psoriasis					
No hx of dx	1987	549			
dx Before AA	27	9	0.83 (0.39-1.77)	1.35 (0.58-3.15)	0.92 (0.39-2.21)
Hypothyroidism					
No hx of dx	1849	547			
dx Before AA	48	11	1.29 (0.67-2.50)	3.30 (1.60-6.77)	2.96 (1.43-6.15)
Any hx of atopy or autoimmune disease					
No hx of dx	1122	420			
dx Before AA	600	138	1.63 (1.31-2.02)	2.34 (1.82-3.01)	N/A ^{//}

AA, Alopecia areata; AA+, all 3 clinical subtypes (alopecia areata persistent + alopecia totalis + alopecia universalis); CI, confidence interval; dx, diagnosis; hx, history; mOR, multivariable odds ratio; N/A, not applicable; OR, odds ratio.

Numbers in bold type indicate statistically significant odds ratio.

*Multivariable model adjusted for race, sex, age of onset.

[†]Multivariable model adjusted for race, sex, age of onset, other autoimmune or atopic diseases.

[‡]No hx of autoimmune or atopic disease.

[§]dx of disease before dx with AA in cases and hx of presence of the disease in controls.

^{//}Any hx of atopy or autoimmune disease represents all diseases associated with AA, thus, could not be adjusted for other diseases.

A case-control analysis comparing the combined alopecia clinical subtypes (ie, AA+) with the control subjects was also performed (Table IV). After adjusting for the demographic covariates and history of atopy and autoimmune disease, where appropriate, statistically increased risks were found for any history of atopy, atopic dermatitis, hay fever, any history of autoimmune disease, hypothyroidism, and any history of atopy or autoimmune disease.

Separate case-control analyses were performed using patients with AAP only and the combined patients with AT and AU (Table V). Possessing any history of atopy was associated with an increased risk of AAP. When the model included only the demographic covariates, statistically elevated risks

for AAP were also observed for history of atopic dermatitis, hay fever, any history of autoimmune disease, irritable bowel syndrome, hypothyroidism, and any history of atopy or autoimmune disease. For combined AT and AU, statistically significant effects were found among individuals with any history of atopy, atopic dermatitis, any history of autoimmune disease, and hypothyroidism. By comparison, the reduced multivariable model yielded statistically significant effects for history of asthma, hay fever, any history of autoimmune disease, and any history of atopy or autoimmune disease for AT or AU.

The impact of possessing a history of one or more atopic or autoimmune diseases (Table VI) was assessed by patients with no history of atopy or

Table V. Association between history of atopy and autoimmune disease and risk of alopecia among alopecia areata subtypes and control

Characteristics	AAP vs controls		AT + AU vs controls	
	mOR* (95% CI)	mOR [†] (95% CI)	mOR* (95% CI)	mOR [†] (95% CI)
Any hx of atopy				
No hx of dx [‡]				
dx Before AA [§]	1.85 (1.37-2.49)	1.58 (1.16-2.16)	2.52 (1.88-3.37)	2.31 (1.72-3.11)
Asthma				
No hx of dx				
dx Before AA	1.08 (0.69-1.70)	0.56 (0.34-0.93)	1.76 (1.15-2.70)	0.88 (0.55-1.41)
Atopic dermatitis				
No hx of dx				
dx Before AA	2.36 (1.52-3.67)	1.51 (0.93-2.46)	2.98 (1.95-4.55)	1.81 (1.15-2.85)
Hay fever				
No hx of dx				
dx Before AA	1.78 (1.26-2.51)	1.23 (0.84-1.79)	2.20 (1.58-3.08)	1.37 (0.95-1.97)
Any hx of autoimmune disease				
No hx of dx				
dx Before AA	2.02 (1.19-3.43)	1.65 (0.96-2.84)	2.23 (1.36-3.67)	1.90 (1.14-3.17)
Irritable bowel syndrome				
No hx of dx				
dx Before AA	2.47 (1.10-5.51)	1.96 (0.86-4.47)	0.65 (0.24-1.74)	0.48 (0.17-1.34)
Psoriasis				
No hx of dx				
dx Before AA	1.05 (0.35-3.13)	0.70 (0.23-2.11)	1.55 (0.63-3.82)	1.00 (0.39-2.54)
Hypothyroidism				
No hx of dx				
dx Before AA	2.39 (1.00-5.70)	1.94 (0.80-4.69)	4.72 (2.16-10.33)	4.29 (1.94-9.50)
Any hx of atopy or autoimmune disease				
No hx of dx				
dx Before AA	1.84 (1.38-2.47)	N/A ^{//}	2.83 (2.13-3.77)	N/A ^{//}

AA, Alopecia areata; AAP, alopecia areata persistent; AT, alopecia totalis; AU, alopecia universalis; CI, confidence interval; dx, diagnosis; hx, history; mOR, multivariable odds ratio; N/A, not applicable.

Numbers in bold type indicate statistically significant odds ratio.

*Multivariable model adjusted for race, sex, age of onset.

[†]Multivariable model adjusted for race, sex, age of onset, other autoimmune or atopic diseases.

[‡]No hx of autoimmune or atopic disease.

[§]dx of disease before dx with AA in cases and hx of presence of the disease in controls.

^{//}Any hx of atopy or autoimmune disease represents all diseases associated with AA, thus, could not be adjusted for other diseases.

autoimmune diseases as the referent. There was no evidence of a trend for individuals possessing one or more atopic or autoimmune disease and increased risk of AA.

DISCUSSION

The main findings of this analysis are that individuals with a history of atopy or any autoimmune disease have a statistically significant elevated risk of AA. In addition, there was evidence that a history of atopic dermatitis or hypothyroidism is also associated with an increased risk of AA. There was no evidence of a trend for having a history of more than one atopic or autoimmune disease and an increased risk of AA.

A case-comparison analysis, among all case patients with AA, was first explored by comparing the different AA severity subtypes with the less severe subtype (ie, AAP). Case-only analyses are used for a variety of reasons including generating hypotheses, such as studies of gene-environmental interactions when both factors are completely independent, or when control subjects are not available. Because AA presents as a spectrum of disease severity on which we have imposed clinical subtypes, we decided to explore the association between the clinical subtypes using AAP as the referent. Furthermore, because little is known about the association among atopy, autoimmune diseases, and AA, this approach was more comprehensive and allowed us to further

Table VI. Number of atopy of autoimmune diseases and risk of severe alopecia subtypes among patients with alopecia areata

No. of atopic or autoimmune diseases	AAP	AT + AU	Crude OR* (95% CI)	mOR† (95% CI)
	N (%)	N (%)		
0	622 (73.0)	833 (69.3)	Referent (1.00)	Referent (1.00)
1	137 (16.1)	219 (18.2)	1.19 (0.94-1.51)	1.31 (1.03-1.67)
2	60 (7.0)	99 (8.2)	1.23 (0.88-1.73)	1.35 (0.96-1.91)
≥ 3	33 (3.9)	52 (4.3)	1.18 (0.75-1.84)	1.34 (0.85-2.12)
	AA+	Control		
0	1455 (70.8)	420 (75.3)	Referent (1.00)	Referent (1.00)
1	356 (17.3)	81 (14.5)	1.27 (0.97-1.65)	2.09 (1.54-2.85)
2	159 (7.8)	35 (6.3)	1.31 (0.90-1.92)	1.87 (1.21-2.88)
≥ 3	85 (4.1)	22 (3.9)	1.12 (0.69-1.80)	2.12 (1.22-3.67)

AA+, All 3 clinical subtypes (alopecia areata persistent + alopecia totalis + alopecia universalis); AAP, alopecia areata persistent; AT, alopecia totalis; AU, alopecia universalis; CI, confidence interval; mOR, multivariable odds ratio; OR, odds ratio.

Numbers in bold type indicate statistically significant odds ratio.

*Multivariable model adjusted for race, sex, age of onset of AA.

†Multivariable model adjusted for race, sex, age of onset of AA for cases and age of recruitment for controls.

explore the association and to assess whether the results of the case-control analyses were consistent with the case-only analyses.

The prevalence of atopy among patients with AA in this study population was 39%, compared with 60.7% and 46% reported for AA by Tan et al⁸ and Goh et al,⁶ respectively. The prevalence of asthma, atopic dermatitis, and hay fever among patients with AA was 15%, 20%, and 25% compared with 3.8%, 17.1%, and 20.9% previously reported in the general population.¹⁴⁻¹⁶ The 3.8% prevalence of asthma in the general population was based on asthma occurring within 12 months whereas our study considered self-reported asthma at anytime before the study. We observed that patients with a history of any atopy have a 2-fold greater risk of having AA, and individuals with a history of atopic dermatitis specifically have a 70% increased risk of having AA. Patients with any history of atopy were at a 24% increased risk of having AT or AU rather than AAP, which confirms the findings of Goh et al.⁶ Similar to the previous study, we observed that the risk of having any subtype of AA was almost double among those with a history of atopic dermatitis and the risk was almost 3 times greater for AT or AU (Tables IV and V).

The association of AA with other autoimmune diseases has been previously reported.^{17,18} The prevalence of having any type of autoimmune disease among our study population with AA was 16% compared with the 12% to 25% observed in previous studies.^{1,6} History of hyperthyroidism ($P = .093$) and history of irritable bowel syndrome ($P = .097$) were found to be less frequent in patients with AA than in control subjects but were only of borderline association. Of note, a history of any autoimmune disease

was found to increase the risk of having AA by 73% similar to the 70% increase with atopic dermatitis. Most striking is that a history of hypothyroidism increased the risk of having AA by 3-fold; and a history of atopy, or any history of autoimmune diseases, increased the risk by 2.5-fold, confirming the findings of Goh et al.⁶ Goh et al⁶ also found that atopic dermatitis ($P = .021$) and thyroid disease ($P = .012$) were significantly associated with AT or AU. In the current analysis, a history of any atopic disease, specifically atopic dermatitis, or hypothyroidism were each found to be statistically significantly associated with AA. Furthermore, a history of atopic dermatitis or history of hypothyroidism was statistically significantly associated with AT or AU. A possible explanation for the difference in results is that Goh et al⁶ combined all patients with AA with hypothyroidism and hyperthyroidism whereas we performed separate analyses for each. Moreover, our multivariable logistic regression models included age, sex, ethnicity, and other atopic or autoimmune diseases whereas Goh et al⁶ only adjusted for age and sex.

Currently, the mechanisms explaining an association among atopy, autoimmunity, and AA are not fully understood. Our study suggests that AA has features of both atopic and autoimmune-mediated skin diseases. AA is considered to be an autoimmune disease caused by CD4⁺ and CD8⁺ T cells invading immune-privileged anagen-stage hair follicles causing a loss of tolerance.¹⁹ The ability to transfer AA with either CD4⁺ or CD8⁺ T cells in the severe combined immunodeficiency mouse model, and by bone-marrow transplantation in an unaffected HLA-matched healthy individual, support the fact that T

Autoimmunity		Alopecia Areata		Atopic dermatitis
Th1: IFN-gamma ⁵¹		Th1: IFN-gamma, IL-12 ^{24,42,46}		Th1: IFN-gamma (chronic) ⁴¹
HLA Class II associations: ^{32,33}		Th2: IL-4, IL-10 ^{24,42}		Th2: IL-4 (acute) ⁴¹
-Hashimotos thyroiditis	→	RANTES ⁴⁶	←	RANTES ^{41,47}
(DQB1*03, DRB1*04),		HLA Class II associations ²⁸⁻³⁰		HLA class II associations ³¹
-Graves disease		(DQB1*0301, DQB1*0202,		(DRB1*1302, DQB1*0604)
(DRB1*03)		DRB1*1104, DQA1*0501)		IgE auto-antibodies against
		Antibodies against hair follicle		keratinocytes, ^{49,50} Filaggrin
		keratin, melanocytes, dermal		(keratin cytoskeleton) ⁴⁴
		papilla ^{22,23}		IgE, histamine, mast cells,
		IgE, mast cells, eosinophils ³⁸⁻⁴⁰		eosinophils ³⁷

Fig 1. Alopecia areata shares common cytokines and HLA associations with both autoimmune and atopic conditions. *HLA*, Human leukocyte antigen; *IgE*, immunoglobulin; *IFN*, interferon; *IL*, interleukin; *RANTES*, regulated upon activation, normal T-cell expressed and secreted; *Th1*, T helper 1; *Th2*, T helper 2.

cells mediate AA.^{20,21} The significance of autoantigens, such as hair follicle keratins, trichohyalin,²² and melanocyte-associated autoantigens,²³ is still unclear. It has been reported that both T helper 1 (Th1) and T helper 2 (Th2) cytokine responses are involved in animal models of AA,²⁴ which could explain the association of AA with both antibody-mediated (ie, systemic lupus erythematosus and autoimmune thrombocytopenic purpura) and T cell-mediated autoimmune diseases (ie, Hashimoto thyroiditis and vitiligo).^{6,25}

Support for AA as an antigen- or autoantigen-driven disease is its association with HLA antigens. Major histocompatibility genes on chromosome 6p21 encoding HLA antigens have been shown to be a major determining loci for autoimmune diseases including AA.^{26,27} HLA-DQB1*0301, DQB1*0202, DRB1*1104, and DQA1*0501 are strongly associated with AA.²⁸⁻³⁰ HLA associations, including HLA-DRB1*1302 and DQB1*0604 with atopic dermatitis and HLA-DQB1*03 and HLA-DRB1*04 with autoimmune hypothyroidism (ie, Hashimoto thyroiditis), have been also reported.^{31,32} HLA-DQB1*03 has positive associations with both AA and autoimmune hypothyroidism. HLA-DRB1*03 has a positive association with Graves disease and a negative association with AA.^{30,33} These associations might explain the protective effect of hyperthyroidism and the predisposing effect of hypothyroidism with AA observed in

this study. The association of AA with HLA class II antigens and with autoimmune diseases, and the response to immunosuppressive treatments, support the autoimmune mechanism of AA (Fig 1).³⁴⁻³⁶

AA and atopy share a Th2 cytokine pattern and increased levels of IgE antibodies, mast cells, and eosinophils.³⁷⁻⁴⁰ In addition, a biphasic pattern of T-helper response in both AA and atopic dermatitis has been observed. There is a Th2 (interleukin [IL]-4) response in localized AA versus a Th1 (interferon [IFN]- γ) response in generalized AA. Similarly, there is a Th2 response in acute phase atopic dermatitis (IL-4) versus a Th1 response (IFN- γ) in chronic phase.^{41,42} It has been reported that histamine, which is secreted by mast cells, up-regulates Th1 cytokine and down-regulates Th2 cytokine responses by increasing IFN- γ and decreasing IL-4 and IL-13.⁴³ Th2 cytokines (IL-4 and IL-13) also influence epidermal barrier function by down-regulating the filaggrin gene expression, encoding a protein of the keratin cytoskeleton.^{44,45} The up-regulation of RANTES (regulated upon activation, normal T-cell expressed and secreted), a chemo-attractant for eosinophils, is increased in both AA and atopic dermatitis.^{46,47} An up-regulation of Th1 serum cytokines (ie, IL-12, tumor necrosis factor- α) is found in patients with atopic AA and in all patients with AA (ie, IL-2, IL-12, IFN- γ), regardless of their atopic status.⁴⁶ These findings also support a common

pathway between AA and atopic dermatitis (Fig 1). The complexity and interaction of immune cells in the pathogenesis of atopic and autoimmune diseases raise the following question: Is AA an atopic condition, an autoimmune disease, or both? Likewise, in atopy the association of HLA antigens, the response to immunosuppressive therapy,⁴⁸ the Th1 cytokine response in the chronic phase, and the presence of IgE autoantibodies against keratinocytes in patients with atopic dermatitis^{49,50} suggest that atopy also may be an IgE-mediated *autoimmune* disease.

Limitations and biases that should be considered in this study include recall bias, reporting bias, recruiting bias, and limited power because of multiple comparisons. In addition, history of atopy and autoimmune diseases were self-reported and not confirmed by a physician. The higher frequency of female patients in this study might be a result of recruiting bias, because even a mild form of AA is generally more devastating for a female patient compared with a male patient and may lead to a higher participation rate in the NAAR.

In summary, overall we observed that a history of either or both atopy and autoimmune disease, especially hypothyroidism and atopic dermatitis, are associated with increased risk of AA. Both the most severe subtypes of AA (AT and AU) and the localized subtype (ie, AAP) were similarly associated. However, because history of atopy and autoimmune disease were based on self-reported data, we caution against any overinterpretation of these findings pending confirmation of our results in hypothesis-driven, prospective studies. In addition, further studies are necessary to elucidate the underlying mechanisms of and the common pathways involved in atopy, autoimmune diseases, and AA.

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