Azadeh Arabzadeh[1,2], Tammy-Claire Troy[1] and Kursad Turksen[1,2,3,4]

[1]Department of Chronic Diseases, Ottawa Health Research Institute, Ottawa, Ontario, Canada; [2]Department of Cellular and Molecular Medicine, University of Ottawa, Ottawa Ontario, Canada; [3]Divisions of Dermatology and Endocrinology, Department of Medicine, University of Ottawa, Ottawa Ontario, Canada and [4]Division of Reproductive Endocrinology, Department of Obstetrics, Gynaecology, Faculty of Medicine, University of Ottawa, Ottawa Ontario, Canada
E-mail: kturksen@ohri.ca

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Human Leukocyte Antigen Class II Alleles Are Associated with Risk of Alopecia Areata

Journal of Investigative Dermatology (2008) **128,** 240–243; doi:10.1038/sj.jid.5700973; published online 19 July 2007

TO THE EDITOR

Alopecia areata (AA) is an organ-specific autoimmune disease in which T cells are directed against hair follicles, causing a non-scarring alopecia ranging from patchy AA to total scalp (alopecia totalis (AT)), or scalp and body hair loss (alopecia universalis (AU)) (Gilhar and Kalish, 2006). Previous studies have shown that major histocompatibility complex genes on chromosome 6p21 encoding human leukocyte antigens (HLAs) are major determining loci for T-cell-mediated diseases including AA (Nair *et al.,* 2000; Martinez-Mir *et al.,* 2007). In addition to HLA molecules, major histocompatibility complex class I chain-related gene A (MICA), a stress-inducible antigen, is also associated with several autoimmune diseases including AA (Barahmani *et al.,* 2006). MICA is located about 46.5 kb centromeric to HLA-B, 1.2 Mb telomeric to the HLA-D region with a distance between HLA-DQB1 and DRB1 of about 65 kb (Nair *et al.,* 2000). Whether class I or II HLA genes are more important for susceptibility to AA is not yet known and would have implications for the pathogenesis as a CD8+ or CD4+ T-cell-mediated disease.

We have previously reported that in sporadic AA, HLA-DQB1*03(*0301-*0305) alleles were present in 92% of patients with AT/AU and in 80% of all patients with AA. We also showed that the frequency of the HLA-DRB1*1104 allele increased for all types of AA ((Welsh *et al.,* 1994; Colombe *et al.,* 1995; Duvic *et al.,* 1995; Price and Colombe, 1996), whereas the frequencies of HLA-DR52a (HLA-DRB3*0101) and HLA-DQB1*06 alleles were negatively associated (Duvic *et al.*, 1991; Welsh *et al.,* 1994). These genes (HLA-DQB1 and HLA-DR) were also found to be linked to familial AA (de Andrade

Table 1. Significant HLA class II and MICA association in persistent patchy AA, AT/AU, and overall AA versus controls

	AAP (*n*=99)				AT/AU (*n*=163)				Overall AA[1] (*n*=291)			Controls (*n*=152)
HLA alleles	Frequency[2] *n*, (%)	*P*-value	OR	CI	Frequency *n*, (%)	*P*-value	OR	CI	Frequency *n*, (%)	P-value	OR	CI	Frequency *n*, (%)
DRB1*0301	12, (12)	0.032[3]	0.44	0.21, 0.90	12, (7)	0.000066[4]	0.26	0.13, 0.51	27, (9)	0.000083[4]	0.33	0.19,0.57	36, (24)
DRB1*0701	31, (31)	0.022[3]	2.01	1.12, 3.64	42, (26)	0.136	—	—	78, (27)	0.06	—	—	28, (18)
DRB1*1101	16, (16)	0.063	2.25	1.01, 4.99	28, (18)	0.018[3]	2.4	1.18, 4.95	49, (17)	0.009[3]	2.36	1.21,4.60	12, (8)
DRB1*1104	13, (13)	0.013[3]	3.68	1.35, 10.03	31, (19)	0.000033[4]	5.71	2.31, 14.13	46, (16)	0.00014[4]	4.57	1.90,11.0	6, (4)
DRB1*1501	16, (16)	0.016[3]	0.46	0.24, 0.87	32, (20)	0.049[3]	0.59	0.35, 0.98	55, (19)	0.012[3]	0.55	0.35,0.87	45, (30)
DRB*52b	38, (38)	0.099	—	—	82, (50)	0.000084[4]	2.57	1.61, 4.10	131, (45)	0.0007[3]	2.08	1.36, 3.16	43, (28)
DRB*53	59, (60)	0.053	—	—	100, (61)	0.0096[3]	1.81	1.16, 2.84	175, (60)	0.009[3]	1.2	1.16,2.56	71, (47)
DQA1*0102	32, (32)	0.143	—	—	50, (31)	0.05	0.61	0.38, 0.97	94, (32)	0.05	0.66	0.44,0.98	64, (42)
DQA1*0501	44, (44)	0.238	—	—	82, (31)	0.02[3]	1.74	1.11, 2.72	136, (47)	0.055	—	—	56, (37)
DQB1*0201	11, (11)	0.0015[3]	0.32	0.15, 0.65	15, (9)	0.000018[4]	0.26	0.14, 0.49	31, (11)	0.0000064[4]	0.30	0.18,0.50	43, (28)
DQB1*0202	27, (27)	0.00015[4]	4.01	1.95, 8.24	34, (21)	0.0025[3]	2.81	1.42, 5.58	65, (22)	0.0002[4]	3.08	1.63,5.79	13, (9)
DQB1*0301	45, (45)	0.0045[3]	2.18	1.28, 3.71	97, (60)	0.000000016[4]	3.85	2.40, 6.19	154, (53)	0.0000004[4]	2.95	1.93,4.50	42, (28)
DQB1*0602	20, (20)	0.140	—	—	30, (18)	0.033[3]	0.55	0.32, 0.94	58, (20)	0.043[3]	0.61	0.39,0.96	44, (29)
MICA*5.1	55, (56)	0.030[3]	0.54	0.32, 0.92	106, (65)	0.402	—	—	183, (63)	0.17	—	—	106, (70)

AA, alopecia areata; AT, alopecia totalis; AU, alopecia universalis; CI, confidence interval; HLA, human leukocyte antigen; MICA, major histocompatibility complex class I chain-related gene A; OR, odds ratio.
Corrected α-level: 0.0004=(0.05/(66*2)).
[1]Overall AA includes AAT, AAP, and AT/AU.
[2]Number of individuals with at least one copy of the allele.
[3]$0.0004 < P\text{-value} < 0.05$.
[4]$P\text{-value} < 0.0004$.

et al., 1999). Using these AA families, we also reported a significant association with haplotypes HLA-DQ1-DR6-MICA*5.1 and HLA-DQB1*0201-DR3-MICA*5.1 and AA (Barahmani *et al.,* 2006).

To confirm previous reports, we analyzed DNA samples of sporadic (non-familial) cases of AA in patients with no affected family members. The samples were obtained through the National Alopecia Areata Registry (NAAR), a large, centralized database funded by the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) (Duvic *et al.,* 2003). The study was conducted according to the Declaration of Helsinki Principles. Participants gave written informed consent approved by the institution review board to have blood samples drawn for genotyping. These AA samples were classified into one of two phenotypic and clinical categories: (1) persistent patchy AA (AAP) or (2) AT/AU, defined as total scalp and scalp/body hair loss lasting more than 1 year.

A total of 443 samples were successfully genotyped for 61 HLA-DRB, DQB, and DQA alleles and five MICA alleles using PCR and sequence-specific oligonucleotide probe hybridization (http://www.ihwg.org/tmanual/TMcontents.htm). Ninety-nine patients had AAP, 163 had AT/AU, 29 patients had AAT, and 152 were unrelated controls. The AAT patients (transient AA < 1 year) were not included owing to small numbers. All subjects were American Caucasian. χ^2 test was performed to analyze the association of HLA class II and MICA alleles with risk of AA severity phenotypes. The Bonferroni correction for multiple comparisons was performed. The corrected α-level is 0.0004, equal to 0.05 divided by the total number of alleles (66) times two phenotypes (AAP and AT/AU). If the *P*-value was <0.0004, the allele was considered to have a statistically significant association with AA. If the *P*-value was between 0.05 and 0.0004, the significance was interpreted as tentative (Table 1).

The results of our analyses confirmed the previously reported positive association of HLA-DQB1*0301 with AT/AU (Welsh *et al.,* 1994; Colombe *et al.,* 1995; Price and Colombe, 1996).

Also HLA-DRB1*1104 was found to be strongly associated with risk of AT/AU ($P=0.000033$) but AAP ($P=0.013$) was not significant, possibly due to smaller sample size. The association of DRB1*1104 with risk of AT/AU might be due to linkage disequilibrium of this allele with DQB1*0301 allele (Welsh *et al.,* 1994).

We also previously reported an association of the HLA-DQB1*0201-DR3-MICA*5.1 haplotype in patients with all AA phenotypes ($P=0.009$) and with AAP ($P=0.008$) in multiplex families (Barahmani *et al.,* 2006). In this study, we observed a strong nega-

tive association between the HLA-DQB1*0201 allele and the AT/AU phenotype. A decreased frequency of this allele has also been reported in an Italian population with rheumatoid arthritis (Morozzi *et al.,* 1995).

Another strong negative association was observed between the frequency of HLA-DRB1*0301 (formerly known as HLA-Dw3) and risk of AT/AU. Previous reports also have shown a protective effect of the HLA-DRB1*0301 allele in AA (Akar *et al.,* 2002; Broniarczyk-Dyla *et al.*, 2002; Entz *et al.,* 2006). Of interest, the frequencies of both HLA-DQB1*0201 and HLA-DRB1*0301 alleles were increased in patients with diabetes mellitus type I, whereas the frequency of the HLA-DQB1*0301 allele was decreased (Diaz *et al.,* 2003; Buc *et al.,* 2006). These findings may provide one explanation for the protective role of AA in diabetes mellitus type I in probands (Wang *et al.,* 1994).

Our results demonstrated a new positive association of the HLA-DQB1*0202 allele with risk of AAP. This allele has been reported to have a protective role in fibrocalculous pancreatic diabetes (Chowdhury *et al.,* 2002), but this is the first report on the association of this allele with risk of AA. Of interest, HLA-DQB1*0202 and *0201 alleles only differ by one single amino acid in the membrane-proximal domain, residue 135 and are found on different haplotypes (Olerup *et al.,* 1997).

This study did not confirm a negative association between the HLA-DR52a allele (DRB3*0101) (Duvic *et al.*, 1991), but we did find a positive association of the HLA-DR52b (DRB3*0202) allele with risk of AT/AU. The association of both HLA-DR52a and HLA-DR52b alleles with autoimmune diseases were reported previously: HLA-DR52a with Graves' disease in a Jamaican population (Smikie *et al.,* 2001), and HLA-DR52b allele with multiple sclerosis in Korean children (Oh *et al.,* 2004).

In this study, we found that after a multiple comparison correction, the frequencies of HLA-DRB1*0701, -DRB1*1101, -DRB1*1501, -DR53, -DQA1*0501, DQB1*0602, and MICA*5.1 were not considered to be significantly associated with risk of AA ($0.0004 < P < 0.05$). More studies are indicated to confirm lack of association.

The overall findings in this study support our hypothesis that the HLAs class II are major susceptibility determinants for AA and may be useful in distinguishing among AA severity phenotypes.

CONFLICT OF INTEREST

The authors have no commercial associations or other conflicts of interest.

ACKNOWLEDGMENTS

This study was supported by the NIAMS grant AR45789, the National Alopecia Areata Registry, the National Alopecia Areata Foundation research grant 2004-2005, K24-CA86815, and the Zarrow Foundation. We thank the University of Texas MD Anderson Cancer Center's core-laboratory facility, funded by NCI Grant CA-16672 (DNA analysis Core Facility), for performing tests with the ABI 3100 Genetic analyzer and Dr Fernandez-Vina, Department of Bone marrow transplantation for kindly providing supplementary data.

Nazila Barahmani[1], Mariza de Andrade[2], Joshua P. Slusser[2], Qingyi Wei[4], Maria Hordinsky[5], Vera H. Price[5], Angela Christiano[5], David Norris[5], John Reveille[3] and Madeleine Duvic[1,5]

[1]Department of Dermatology, The University of Texas M.D. Anderson Cancer Center, Houston, Texas, USA; [2]Division of Biostatistics, Mayo Clinic, Rochester, Minnesota, USA; [3]Department of Rheumatology, The University of Texas M.D. Anderson Cancer Center, Houston, Texas, USA; [4]Department of Epidemiology, The University of Texas M.D. Anderson Cancer Center, Houston, Texas, USA; [5]National Alopecia Areata Registry, The University of Texas M.D. Anderson Cancer Center, Houston, Texas, USA
E-mail: nbarahma@mail.mdanderson.org

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Epidemiologic Support for Melanoma Heterogeneity Using the Surveillance, Epidemiology, and End Results Program

Journal of Investigative Dermatology (2008) **128,** 243–245; doi:10.1038/sj.jid.5701028; published online 23 August 2007

TO THE EDITOR

Several studies have used evidence evaluating genetic alterations (Curtin *et al*., 2005) and anatomic location (Whiteman *et al*., 2003) to support theories that melanoma is a heterogeneous disease with differing etiologies. Using data from the large-scale, population-based Surveillance, Epidemiology, and End Results Program (SEER) of the National Cancer Institute, we examined whether age-specific incidence patterns separated by sex and site would reveal distinct melanoma subgroups.

Age, sex, and anatomic site were abstracted for all microscopically confirmed, first invasive cutaneous melanomas among non-Hispanic white adults collected by the SEER 17 Registry Program from 2000 to 2004. Incidence rates, summarized across 5-year age groups, were plotted by age at diagnosis on a log-log scale, and age distribution curves were created. Detailed materials and methods are available in Supplementary Materials and Methods.

After excluding 15 cases missing age at diagnosis, 48,673 cases were available for analysis (Table 1). Fifty-six percent of patients were male, and the mean age at diagnosis was 57.0 years. Forty-one percent of all melanomas occurred among those 40–59 years of age. However, the age-specific incidence rate peaked among people aged 70–79 years, who had an incidence rate 5.9 times higher (95% confidence intervals, 5.6–6.2) than those aged 20–29 years. The incidence rate ratio for females compared to males was 0.7 (95% confidence intervals, 0.7–0.7). Forty-three percent of melanomas were located on the extremities, 34% on the trunk, 12% on the face/ears, 7% on the scalp/neck, and 4% at other/unclassified sites.

The age-specific incidence rate curve and the age distribution for all melanoma cases are shown in Figure 1. Rates for all cases increased rapidly until age 55–59, then continued to rise at slower rates before beginning to decline (Figure 1a). The age distribution plot displayed a multimodal distribution, with distinct early-onset and late-onset peak frequencies of melanoma occurring at ages 54 and 74 years, respectively (Figure 1b).

Melanomas demonstrated different incidence patterns by anatomic site. Age-specific incidence rates among those with trunk melanoma generally increased until age 55–59 years, then plateaued and subsequently declined (Figure 1c). The flattening of rates for trunk melanoma occurred earlier and was more extreme for females than for males. The age distribution of trunk melanoma was predominantly unimodal, with early-onset peak frequencies occurring at age 54 for males and 44 for females (Figure 1d). In contrast, age-specific incidence rates among those with face/ear melanoma increased sharply throughout older age (Figure 1e). The age distribution for face/ear melanoma was unimodal with late-onset peaks at age 77 for males and at age 78 for females (Figure 1f). Incidence rates for melanomas of the extremities, scalp/neck, and other/unclassified sites demonstrated various mixtures of these two patterns and did not show unimodal distributions (data not shown). These distinct patterns for trunk and face/ear melanomas were maintained when the analysis was limited to those classified as superficial spreading melanoma and nodular melanoma histological subtypes (Figure 2).

The multimodal distribution of invasive melanoma might be explained, in part, by divergent patterns for anatomic site. Broken down by site, trunk melanomas displayed an early-onset peak of melanoma incidence, while face/ear melanomas demonstrated a late-onset incidence peak. Comparable divergent incidence rate patterns have been noted for breast cancer, and the bend in age-specific rates near menopause has been termed Clemmesen's hook (Clemmesen, 1948; Anderson *et al*., 2005). Clemmesen's hook on the age-specific incidence rate curve has been shown to correspond to the dip between the bimodal peaks of the age distribution plot (Anderson *et al*., 1950). Our data suggest the existence of a Clemmesen's hook for melanoma.

Bulliard (2000) analyzed age-and surface area-adjusted incidence rates by anatomic site for the non-Maori population of New Zealand using data from 1968 to 1993 and found patterns similar to ours. Elwood and Gallagher

Abbreviations: SEER, Surveillance, Epidemiology, and End Results