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Association between *TAP1* gene polymorphisms and alopecia areata in a Korean population

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ABSTRACT. The transporter 1 ATP-binding cassette sub-family B (MDR/TAP) gene (*TAP1*) is located in the major histocompatibility complex class

II region, and forms a heterodimer that plays a key role in endogenous antigen presentation pathways. Investigation of polymorphisms identified in these loci has revealed an association with several autoimmune disorders. Alopecia areata (AA) is a common autoimmune disease resulting from T cell-induced damage to hair follicles. The present study documents for the first time a comparison between the allelic and genotypic frequencies of *TAP1* single nucleotide polymorphisms (SNPs) in patients with AA and those of a control group, using a direct sequencing method. Our results suggest an association between a promoter SNP (rs2071480) and susceptibility to this disease.

Key words: Alopecia areata; Association; Single nucleotide polymorphism; Transporter 1 ATP-binding cassette sub-family B

INTRODUCTION

Alopecia areata (AA), a chronic disorder of the hair follicles and nails, is a disease of unknown etiology with evident autoimmune and genetic components (Rivitti, 2005; Alkhalifah et al., 2010). AA prevalence worldwide is 0.1-0.2% (Safavi, 1992), with a calculated lifetime risk of 1.7% (Safavi et al., 1995). It is thought to be an organ-specific autoimmune disease mediated by either CD4+ or CD8+ T cells, in which inflammation primarily targets the immune-privileged anagen-stage hair follicles (Paus et al., 1993; McDonagh and Tazi-Ahnini, 2002; Lu et al., 2006; Barahmani et al., 2009; Alkhalifah et al., 2010). Genetic susceptibility to AA results in increased concordance rates in family members and twins, and frequent co-diagnosis with other autoimmune disorders, such as vitiligo and autoimmune thyroiditis. Genetic associations have been reported between AA and several human leukocyte antigen (HLA) genes (Colombe et al., 1995; Kavak et al., 2000; Akar et al., 2002; Entz et al., 2006; Petukhova et al., 2010).

The transporter 1 ATP-binding cassette sub-family B (MDR/TAP) gene (*TAP1*) has been localized to the major histocompatibility complex (MHC) class II region, between the *HLA-DQB1* and *HLA-DPA1* loci. The TAP1 protein forms a heterodimer with TAP2, which transports antigenic peptides from the cytosol into the endoplasmic reticulum lumen, prior to assembly of class I molecules (Trowsdale et al., 1990). The HLA class I antigen-peptide complex is transported to the cell surface, where it is recognized by the immune system as a sign of infection and is involved in autoimmune reactions (Spies et al., 1992). Momburg et al. (1994) showed that TAP gene polymorphisms influence the selection of peptide epitopes in animals (Momburg et al., 1994). In addition, it has been shown that polymorphisms in *TAP1* or *TAP2* may affect antigen recognition and presentation (Koch et al., 2004), potentially resulting in low or entirely absent cell surface expression of MHC-I molecules, and an adverse immune response. Specificity can be affected by variation in the structure and/or expression of these genes between individuals. Therefore, different sets of peptides can be derived from presentation of the same antigen to T cells in different people. Thus, TAP genes represent possible susceptibility factors for some autoimmune diseases (Vinasco et al., 1998). Polymorphisms in such genes have been associated with various diseases, such as tuberculosis (Wang et al., 2012), ankylosing spondylitis (Feng et al., 2009), leprosy (Shinde et al., 2013), idiopathic bronchiectasis (Doğru et al., 2007), and cystic fibrosis (Ozbaş-Gerçeker et al., 2002). However, no study has investigated the association between *TAP1* sequence variants and AA. Therefore, we investigated three functional *TAP1* single nucleotide polymorphisms (SNPs),

consisting of two missense mutations (rs1135216 and rs1057141), and one promoter variant (rs2071480) in AA patients and a control group.

MATERIAL AND METHODS

Patients and control subjects

A case-control study was conducted to determine the relationship between *TAP1* SNPs and AA. Patients and control subjects in this study were enrolled from Kyung Hee University Hospital, Gang-dong, Seoul, Republic of Korea. The control subjects were recruited after being determined mentally and physically healthy following a general health check-up. AA patients were diagnosed according to clinical features and a physical examination, including a pull test and microscopic analysis of hair. In some cases, AA diagnosis was confirmed by skin biopsy. A thorough general health history was taken from each patient, including prior AA incidence, triggering factors, occurrence of autoimmunity or atopy, and family history of AA or autoimmune disease. A serologic workup was carried out for all patients, including tests for anemia, venereal disease, antinuclear antibodies, thyroid function, and hormones, such as testosterone, estradiol, and luteinizing and follicle-stimulating hormone. A total of 229 healthy controls were included, comprising 104 men and 125 women, with an average age at survey of 31.4 years. These control subjects had no known diseases or symptoms. Informed consent was obtained from all participants, and this study was approved by the Institutional Review Board of Kyung Hee University Hospital.

SNP genotyping

We searched for *TAP1* SNPs in the National Center for Biotechnology Information databases (www.ensembl.org, www.ncbi.nlm.nih.gov/SNP, and www.hapmap.org). Three were selected for analysis, consisting of two previously described missense variants (rs1135216 and rs1057141; Zhang et al., 2002) and a promoter SNP (rs2071480; Kim et al., 2014). DNA was isolated from peripheral blood using the GenEx B DNA purification kit (GeneAll Biotechnology, Seoul, Republic of Korea), and *TAP1* SNPs were genotyped using a previously reported method (Qian et al., 2013). Polymerase chain reaction products were sequenced using an ABI PRISM 3730xl DNA analyzer (PE Applied Biosystems, Foster City, CA, USA), and sequence data were examined using SeqManII software (DNASTAR Inc., Madison, WI, USA).

Statistical analysis

Hardy-Weinberg equilibrium (HWE) was assessed using SNPStats (http://bioinfo.iconcologia.net/index.php) and SPSS 18.0 (SPSS Inc., Chicago, IL, USA). Associations between SNP genotypes and AA and AA subgroups were estimated by computing odds ratios (ORs) and 95% confidence intervals (CIs) with logistic regression analyses, after controlling for age and sex as covariates. Models assuming co-dominant (where relative disease hazard differs between subjects with one minor allele and those with two minor alleles), dominant (subjects with one or two minor alleles demonstrate the same relative hazard), or recessive inheritance (individuals with two minor alleles are at increased risk of the disease) were used in the logistic regression analysis for each SNP. The chi-square test was used to compare allele frequencies between groups. To avoid chance findings due to multiple testing, the Bonferroni correction was applied by multiplying P values by the number of SNPs analyzed (N = 3).

RESULTS

Clinical and demographic characteristics of the study subjects

Table 1 shows the clinical and demographic attributes of the AA and control subjects. In this study, 231 AA patients were enrolled, comprising 106 men and 125 women with an average age at survey of 28.6 years (Table 1).

Table 1. Clinical and demographic features of alopecia areata and control groups.

	Alopecia areata (N = 231)	Control (N = 229)
Age (years, mean ± SD)	29.32 ± 12.99	31.45 ± 7.80
Gender (male:female)	106:125	104:125
Age at onset		
<30 years	70	
≥30 years	161	
Family history		
(+)	17	
(−)	214	
Type		
Patchy	196	
Totalis or universalis	35	
Involvement of nails		
(+)	31	
(−)	200	
Involvement of body hair		
(+)	32	
(−)	199	

SD = standard deviation.

At the time of onset, 161 patients (70%) were less than 30 years old (early onset), while 70 (30%) were older than this (late onset). Seventeen (7%) had a family history of AA, however, 214 (93%) did not. A total of 196 (85%) exhibited patchy AA, while 35 (15%) suffered alopecia totalis (AT) or alopecia universalis (AU). In addition, 31 patients (13%) had a concomitant nail disorder, but 200 patients (87%) did not. Thirty-two patients (14%) demonstrated involvement of body hair such as eyebrows, axillary hair, or pubic hair, whereas 199 patients (86%) showed no such clinical feature.

Association between *TAP1* SNPs and AA

The genotype distributions of all SNPs were in HWE (P > 0.05). As shown in Table 2, rs2071480 genotype frequency was significantly associated with AA under the co-dominant 2 and log-additive models after Bonferroni correction. For the co-dominant 2 model, the G/T and T/T genotype frequencies of 49.8 and 15.7% in the control group, and 46.8 and 9.5% in the AA group, respectively, were used. The T/T genotype was associated with an increased risk of AA (OR, 0.47; 95%CI, 0.26-0.87; P = 0.014; P-value corrected with Bonferroni mothod, P^c = 0.042). For the log-additive model, the frequencies of genotypes containing the T allele (T/T and G/T) and those lacking it (G/G) were 65.5 and 34.5% in the control group, and 56.3 and 43.7% in the AA group, respectively (OR, 0.71; 95%CI, 0.54-0.94; P = 0.015; P^c = 0.045). rs2071480 allele frequency was also associated with AA (OR, 0.71; 95%CI, 0.54-0.94; P = 0.015; P^c = 0.045). Moreover, frequency

of the T allele was lower in the AA group (32.9%) than in the control group (40.6%). However, the other SNPs tested (rs1135216 and rs1057141) were not found to be associated with development of this disease (Table 2). We also investigated differences between the polymorphisms relating to AA clinical parameters. However, none of the three *TAP1* SNPs demonstrated a significant association with age at onset, family history of AA, disease type (patchy *vs* AU or AT), or nail or body hair involvement (data not shown).

To assess haplotype structure in our study group, we characterized a linkage disequilibrium (LD) block between the three *TAP1* SNPs in the control subjects using pairwise D' values. According to the criteria used by Gabriel et al. (2002), a haplotype block was identified in *TAP1* from the LD data. The D' value from rs1135216 to rs1057141 was 0.978, indicating strong LD between these markers (data not shown). A haplotype-based association analysis was performed between the case and control groups for different combinations of SNPs within *TAP1*. However, no significant associations were detected between the three possible haplotypes (haplotype, frequency: A/A, 0.853; G/G, 0.126; A/G, 0.02) and AA (all P values > 0.05, data not shown).

Table 2. Genotype and allele frequencies of TAP1 single nucleotide polymorphisms in alopecia areata and control groups.

SNP	Genotype/ allele	AA		Control		Model	OR	95%CI		P	PC
		Freq.	%	Freq.	%			LCL	UCL		
rs2071480	G/G	101	43.7	79	34.5	Codominant 1	0.76	0.51	1.13	0.15	0.45
promoter	G/T	108	46.8	114	49.8	Codominant 2	0.47	0.26	0.87	0.014	0.042
	T/T	22	9.5	36	15.7	Dominant	0.69	0.47	1.01	0.05	0.162
						Recessive	0.55	0.31	0.97	0.037	0.111
						Log-additive	0.71	0.54	0.94	0.015	0.045
	G	310	67.1	272	59.4						
	T	152	32.9	186	40.6		0.71	0.54	0.94	0.015	0.045
rs1135216	A/A	173	74.9	178	77.7	Codominant 1	1.14	0.73	1.79	0.57	1.00
Asp697Gly	A/G	53	22.9	48	21	Codominant 2	1.79	0.41	7.73	0.46	1.00
	G/G	5	2.2	3	1.3	Dominant	1.18	0.77	1.82	0.45	1.00
						Recessive	1.74	0.40	7.49	0.45	1.00
						Log-additive	1.19	0.81	1.76	0.38	1.00
	A	399	86.4	404	88.2						
	G	63	13.6	54	11.8		1.18	0.80	1.76	0.40	1.00
rs1057141	A/A	167	72.3	172	75.1	Codominant 1	1.22	0.79	1.89	0.40	1.00
Ile393Val	A/G	58	25.1	50	21.8	Codominant 2	0.93	0.30	2.83	0.87	1.00
	G/G	6	2.6	7	3.1	Dominant	1.18	0.78	1.80	0.43	1.00
						Recessive	0.88	0.29	2.69	0.83	1.00
						Log-additive	1.12	0.78	1.60	0.55	1.00
	A	392	84.8	394	86.0						
	G	70	15.2	64	14.0		1.10	0.76	1.59	0.61	1.00

SNP = single nucleotide polymorphism; AA = alopecia areata; Freq. = frequency; OR = odds ratio; CI = confidence interval; LCL = lower confidence limit; UCL = upper confidence limit; Pc = P value corrected by the Bonferroni method.

We compared our Korean population genotype data to that of other populations using the human SNP database (dbSNP Build 137; www.ncbi.nlm.nih.gov/SNP). This database contains genotype frequencies for rs2071480 (G/G:G/T:T/T, European: 0.316:0.544:0.140; Chinese: 0.455:0.477:0.068; Japanese: 0.439:0.488:0.073; Sub-Saharan African: 0.305:0.508:0.186), rs1135216 (A/A:A/G:G/G, European: 0.796:0.186:0.018; Chinese: 0.605:0.395:0.000; Japanese: 0.756:0.221:0.023; Sub-Saharan African: 0.504:0.460:0.035), and rs1057141 (A/A:A/G:G/G, European: 0.761:0.212:0.027; Chinese: 0.581:0.419:0.000; Japanese: 0.744:0.233:0.023; Sub-

Saharan African: 0.504:0.442:0.053; Table 3). The SNP genotype distributions that we observed in our control group were similar to those in other populations. Thus, our results may be valuable as a case-control study, in that our investigation included only a single population.

Table 3. Genotype frequencies of TAP1 single nucleotide polymorphisms in different populations.

SNP	Genotype	Korean		European	Chinese	Japanese	Sub-Saharan African
		AA	Control				
rs2071480	G/G	0.437	0.345	0.316	0.455	0.439	0.305
promoter	G/T	0.468	0.498	0.544	0.477	0.488	0.508
	T/T	0.095	0.157	0.140	0.068	0.073	0.186
P				0.998	0.975	0.979	0.998
rs1135216	A/A	0.749	0.777	0.796	0.605	0.756	0.504
Asp697Gly	A/G	0.229	0.210	0.186	0.395	0.221	0.460
	G/G	0.022	0.013	0.018	0.000	0.023	0.035
P				0.961	0.904	0.966	0.905
rs1057141	A/A	0.723	0.751	0.761	0.581	0.744	0.504
Ile393Val	A/G	0.251	0.218	0.212	0.419	0.233	0.442
	G/G	0.026	0.031	0.027	0.000	0.023	0.053
P				0.902	0.833	0.897	0.871

SNP = single nucleotide polymorphism; AA = alopecia areata. Data regarding genotype frequencies in other populations were retrieved from www.ncbi.nlm.nih.gov/SNP. We calculated P values based on comparisons between the control group in our study and each population.

DISCUSSION

The purpose of our study was to evaluate the relationship between *TAP1* gene polymorphisms and AA risk. We found that the rs2071480 SNP was associated with AA susceptibility, with the T allele contributing to decreased risk.

Although the role of TAP genes in the pathogenesis of autoimmune diseases such as AA is largely unknown, several studies have reported their direct or indirect participation in the development of autoimmunity. *TAP1* and *TAP2* are involved in MHC class I antigen-mediated processing and presentation to cytotoxic CD8+ T lymphocytes (Glynne et al., 1991; Spies et al., 1992; Kamei et al., 2013). Because of an important role of antigen presentation in the immune response, MHC-encoded antigen-processing genes such as those of the TAP subfamily have been investigated in patients with autoimmune disorders and inflammatory bowel disease (Heresbach et al., 1997; Martín-Villa et al., 1998; Kamei et al., 2013). A previous study from our group identified possible associations between *IL17A*/*IL17RA* polymorphisms and AA (Lew et al., 2012). In this report, we concluded that two different *IL17RA* variants might contribute to increased AA susceptibility and age at onset in a Korean population. Furthermore, Miao et al. (2013) reported that the *IL2RA* rs3118470 SNP may constitute a genetic marker of AA risk in a Chinese population. One of the *TAP1* SNPs (rs1135216) investigated in the present study has previously been associated with increased risk of ankylosing spondylitis (Feng et al., 2009). Thus, we expected that polymorphisms in this gene might be related to AA susceptibility and symptoms.

In conclusion, this is the first study to investigate the potential influence of *TAP1* gene polymorphisms in AA patients. Our results suggest that such SNPs may contribute to AA susceptibility in the Korean population, and that *TAP1* may be one of the many genes confirmed to play a role in polygenic susceptibility to this disease. Specifically, the rs2071480 T allele was found

to be associated with the development of AA. However, our findings must be validated through additional studies using larger sample sizes, due to the relatively small number of subjects enrolled in this investigation.

Conflicts of interest

The authors declare no conflict of interest.

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