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Major Association of Vitiligo with *HLA-A*02:01* in Japanese

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To the Editor,

Recently, genome-wide association studies (GWAS) have been particularly successful in identifying vitiligo susceptibility loci in populations of European-derived white, Chinese, and Indian subcontinental ancestry (Spritz, 2013). The strongest genetic associations of vitiligo are in the major histocompatibility complex (MHC) on chromosome 6, both in terms of statistical significance and magnitude of effect (odds ratio; OR). However, the specific associated MHC loci and alleles differ among different world populations. In European-derived whites, vitiligo is associated with both MHC class I (*HLA-A*) and class II loci. On the Indian subcontinent, vitiligo is associated with MHC class II loci. In Han Chinese, vitiligo is associated with the class III region (Spritz, 2013).

Here, we describe a detailed genetic association study of vitiligo with the MHC in the Japanese population. To test for association between vitiligo and the MHC region, we compared the allele frequencies of 1649 genotyped SNPs spanning the extended MHC in chr6p21.3 (chr6:25,895,575-33,421,577; de Bakker et al., 2006) in 177 Japanese vitiligo cases with those from 932 Japanese pseudocontrols, generated using data from the Japanese Single Nucleotide Polymorphism database (JSNP; http://snp.ims.u-tokyo.ac.jp/; Appendix S2). Genome-wide association analyses of this case-control dataset indicate minimal inflation of test statistics due to population stratification or other sources of bias (Appendix S1). As shown in Figure 1 and Table 1, we observed significant association of vitiligo with

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Conflict of interests

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multiple SNPs in the MHC class I region; specifically, six SNPs located downstream of *HLA-A* (chr6:29,942,083-30,064,562). Most significant was rs9261394 ($P = 4.49 \times 10^{-5}$, OR = 1.60), while greatest OR was observed for rs3823375 ($P = 5.91 \times 10^{-5}$, OR = 1.67) (Table 1). There was no significant association of vitiligo with SNPs in the MHC class II or class III regions (Figure 1 and data not shown).

Corrrelation of *HLA-A* subtype

(http://www.inflammgen.org/index.php?ption=com_content&task=view&id=25&Itemid=42) and corresponding genotype (http://hapmap.ncbi.nlm.nih.gov/) data for rs3823375, the SNP with the greatest OR in the MHC class I region, for 44 Japanese controls showed that the rs3823375-C allele tags *HLA-A**02 ($r^2 = 0.80$, D' = 1.0) (data not shown). To define the specific *HLA-A**02 subtype associated with vitiligo in Japanese, we carried out next-generation DNA sequencing of *HLA-A, HLA-B, and HLA-C* exons 2, 3, and 4, which contain the sequence variations that define HLA subtypes (http://www.ebi.ac.uk/imgt/hla/). We sequenced 20 unrelated Japanese vitiligo patients selected on the basis of carrying the rs3823375 high-risk C allele: 11 homozygotes and 9 heterozygotes. As shown in Table S2, of the 22 *HLA-A* alleles among the 11 rs3823375-C homozygotes, 15 (68.2%) were *HLA-A**02:01, 6 (27.3%) were *HLA-A**02:06, and 1 (4.5%) was a non-*HLA-A**02 allele. Similarly, among the rs3823375-C heterozygotes, 5 alleles were *HLA-A**02:01, 3 were *HLA-A**02:06, and the remainder were non-*HLA-A**02; whereas phase in the heterozygotes is uncertain, assuming maximum parsimony this distribution is not different than among the homozygotes (P = 0.72). Thus, unlike in European-derived whites, in which the vitiligo-associated *HLA-A* region SNPs tag only *HLA-A**02:01 (Jin et al., 2012), in Japanese the vitiligo-associated *HLA-A* region SNPs tags both *HLA-A**02:01 and *HLA-A**02:06, and also occasional non-*HLA-A**02 alleles, but do not tag specific alleles of *HLA-B* or *HLA-C* (Table S2).

To determine whether *HLA-A**02:01, *HLA-A**02:06, or both, are associated with vitiligo in Japanese, we imputed genotypes for SNPs that specifically tag *HLA-A**02:01 and *HLA-A**02:06 in Japanese (de Bakker et al., 2006), using data from the 177 Japanese vitiligo cases and 89 Japanese controls from the 1000 Genomes Project (1KGP; (http://www.1000genomes.org/); imputation could not be performed for the JSNP control data used for the GWAS. Principal components analysis of genome-wide genotype data for these 266 subjects using EIGENSOFT (Price et al., 2006) identified one Japanese case as an outlier, which was therefore excluded. The remaining Japanese cases and controls matched well, with genomic inflation factor (Devlin et al., 2001) 1.018 based on genome-wide statistics for 428,762 autosomal SNPs (data not shown). The six MHC class I region SNPs that showed association with vitiligo in the initial comparison of 177 Japanese cases and 932 controls (Table 1) likewise showed association in the comparison of 176 Japanese cases and 89 controls (Table S3). *HLA-A**02:01 is tagged ($r^2 = 1$) by the T-A haplotype of SNPs rs9348834-rs6457110, whereas *HLA-A**02:06 is tagged ($r^2 = 1$) by the T-C haplotype of SNPs rs892666-rs2517699 (de Bakker et al., 2006). As shown in Table 2, the rs9348834-rs6457110 TA haplotype showed significant association with vitiligo (P = 4.26E-03, OR = 2.31), whereas the rs892666-rs2517699 TC haplotype showed no association (P =0.435, OR

= 0.73). These results demonstrate that vitiligo is specifically associated with *HLA-A**02:01 in Japanese.

Of the 177 Japanese vitiligo patients, 24 (13.6%) had other concomitant autoimmune diseases including autoimmune thyroid disease, rheumatoid arthritis, psoriasis, adult-onset autoimmune diabetes, and pernicious anemia (Table S1), as observed previously (Narita et al., 2011). To test whether association of vitiligo with the MHC class I region is direct, versus is indirectly driven by these other autoimmune diseases, we compared the case-control datasets of the 24 Japanese vitiligo patients with other autoimmune diseases versus the 153 patients without other diseases, both versus the 932 Japanese pseudocontrols, finding that only the vitiligo patients without other autoimmune diseases contributed to the significant P values of the 6 SNPs (data not shown). This indicates that association of vitiligo with the MHC class I region in Japanese is direct. In other analyses, we found no significant association of MHC class I region SNPs with vitiligo age of onset (Table S1) or gender (data not shown) in Japanese.

Our findings in Japanese vitiligo patients closely parallel those we have reported for the MHC class I region in European-derived white vitiligo patients, in whom MHC class I association derives from *HLA-A*; specifically, *HLA-A**02:01 (Jin et al., 2010, 2012). HLA-A*02:01 presents peptide antigens on the surfaces of all cells. In melanocytes, HLA-A*02:01 presents the major vitiligo autoimmune antigen, tyrosinase (TYR), which in turn activates and recruits anti-melanocyte autoreactive cytotoxic T lymphocytes to the skin, within then target and destroy melanocytes (Birlea et al., 2012). In European-derived whites, we have shown that vitiligo is strongly associated with two common *TYR* missense variants, S192Y and R402Q, which are protective (Jin et al., 2010, 2012). These protective variants are prevalent only in European-derived whites, and are not genetically associated with vitiligo in other populations, including Japanese (data not shown). Nevertheless, it seems likely that TYR functions as a major vitiligo autoimmune antigen in all populations, presented by HLA-A*02:01 in at least European-derived whites and Japanese.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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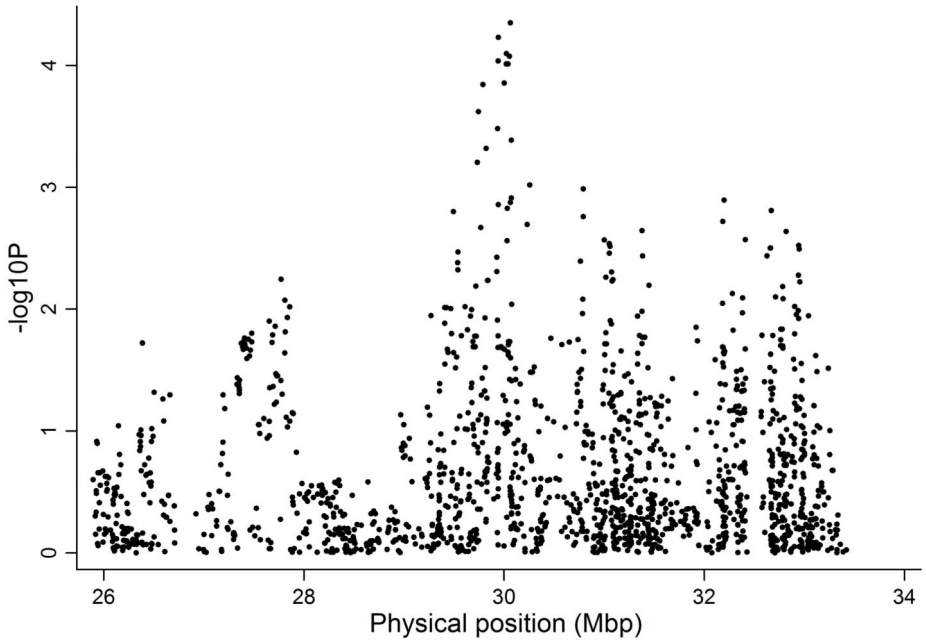

Figure 1.

Major histocompatibility complex association results for vitiligo in Japanese. Results of association of 1649 MHC region single-nucleotide polymorphisms (SNPs; black dots). SNPs are ordered by physical genomic position (GRCh37/hg19) versus −Log10(P value).

Table 1

Most significant associations between 6 MHC class I region SNPs and vitiligo in Japanese

				177 cases, 932 controls	
Chromosome	**SNP**	**Nucleotide**	**Allele**	**OR**	**P-value**[1]
6p21.3	rs3823355	29,942,083	T	1.64	9.22×10^{-5}
	rs6904029	29,943,067	A	1.64	9.22×10^{-5}
	rs3823375	29,944,158	C	1.67	5.91×10^{-5}
	rs9366752	30,024,677	T	1.65	8.02×10^{-5}
	rs6909253	30,055,643	G	1.57	8.45×10^{-5}
	rs9261394	30,064,562	A	1.60	4.49×10^{-5}

[1] P-values from the Cochran-Armitage trend test.

Table 2

Association analysis of haplotypes tagging *HLA-A*02:01* and *HLA-A*02:06* in 176 Japanese cases and 89 controls

Haplotypes defined by rs9348834 and rs6457110			
Haplotype	**Frequency**	**OR (95% CI)**	**P-value**[1]
CA	0.21	(−ref-)	(−ref-)
TT	0.06	|	|
CT	0.57	|	|
TA (tags *HLA-A*02:01*)	0.16	2.31 (1.26-4.23)	4.26E-03
Haplotypes defined by rs892666 and rs2517699			
Haplotype	**Frequency**	**OR (95% CI)**	**P-value**[1]
CC	0.31	(−ref-)	(−ref-)
CT	0.02	|	|
TT	0.61	|	|
TC (tags *HLA-A*02:06*)	0.06	0.73 (0.34-1.59)	4.35E-01

Abbreviations: OR, odds ratio; 95% CI, 95% confidence interval.

[1] P-value from the likelihood ratio test