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Association between the HLA-DQA1 rs1391371 Risk Allele and Chronic Rhinosinusitis

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INTRODUCTION

Chronic rhinosinusitis (CRS), an extremely common chronic condition, is defined as symptomatic and objective inflammation of the sinonasal mucosa lasting more than 12 weeks.[1,2] Treatment for CRS remains a challenge despite our evolving understanding of the underlying mechanisms.

Genes implicated in CRS are involved in cytokine expression, eicosanoid production, cell growth, cellular proliferation, and reduced apoptosis, among others.[3,4] HLA genes play a crucial role in antigen presentation, and HLA gene variations are associated with inflammatory diseases. Multiple HLA loci have been implicated in genetic susceptibility to CRS[4,5] and nasal polyps (NP).[6,7]

A large meta-analysis of genome-wide association studies (GWAS) of NP (n=4366 cases) and CRS (n=5608 cases) using Icelandic and UK data sets found a statistically significant association between the HLA-DQA1 polymorphism rs1391371 (chr6:32636021) and these disease processes, with an odds ratio (OR) of 1.47 for NP and 1.22 for CRS.[8] We aimed to replicate their results in a US population.

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Conflict of interest:

D.R.R. and N.A.C. have a patent for Therapy and Diagnostics for Respiratory Infection (61/697,652 [filed December 6, 2012] WO2013112865). All authors declare that they have no relevant conflicts of interest.

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METHODS

With institutional review board approval, from May 2010 to June 2018 we enrolled adult patients from the Rhinology and Allergy Clinics, Perelman Center for Advanced Medicine, who met Academy of Otolaryngology–Head and Neck Surgery guidelines for CRS[1,2,9] and control subjects with no current symptoms or history of treatment for CRS. Results from a subset of these data have been previously published.[10]

Patients with CRS were subcategorized into those with NP (CRSwNP) or without NP (CRSsNP) based on endoscopy. Basic demographic data were collected from self-report and chart review. Subjects completed questionnaires collecting background information including demographic information and smoking status. Saliva samples from all subjects were collected and genotyped for the HLA-DQA1 SNP rs1391371 using PCR-based methods. Alleles were genotyped with allele-specific Taqman probes and primers purchased from Life Technologies in the Step One RealTime PCR System.

Subject groups were compared for demographic and clinical variables using the Fisher's exact test for categorical variables and *t* tests for continuous variables. CRSwNP and CRSsNP groups were compared with controls. The χ^2 test evaluated Hardy–Weinberg equilibrium (HWE) in allele and genotype frequencies and general characteristics between CRS and control groups. Multivariate ORs and 95% CIs were calculated using binomial logistic regression to assess potential associations between rs1391371 and CRS risk, controlling for age, sex, smoking status, and comorbid asthma within each study group compared to controls, with a nominal p-value of 0.05 (95% confidence level). Statistical analyses were conducted in R (version 4.0.5) and R Studio (version 1.4.1106).

RESULTS

The 550 patients comprised 317 CRS patients (208 CRSwNP, 109 CRSsNP) and 233 controls (Tables 1), all self-identified as white/Caucasian and middle-aged. The control and CRS groups were similar in ethnicity ($p = 0.18$) but differed by sex ($p < 0.001$), age ($p < 0.001$), and smoking history ($p < 0.01$). CRS patients had higher SNOT-22 scores ($p < 0.001$).

CRS patients and controls had similar distribution of rs1391371 diplotypes (homozygous dominant AA; heterozygous AT; and homozygous recessive TT) ($p = 0.14$) (Table 1), with similar results between CRS subgroups and controls. rs1391371 genotype frequencies showed significant deviations from HWE in both groups (CRS: $\chi^2 = 43.21$, $p < 0.05$; controls: $\chi^2 = 53.18$; $p < 0.05$).

The heterozygous AT genotype exhibited a strongly positive and significant OR in susceptibility for patients with CRS (OR=2.81, p<0.01) and CRSwNP (OR=3.03, p<0.05), indicating an association between the genotype and risk of developing CRS and NP, but a positive, nonsignificant OR for patients with CRSsNP (OR=2.62, p=0.228) (Figure 1). Patients homozygous for either allele were not more likely to have CRS than controls (p>0.05) (Figure 1).

DISCUSSION

We replicated the association between the HLA-DQA1 polymorphism rs1391371 and CRS with nasal polyps in the original GWAS study,[8] although our result was significant only for heterozygotes. The AT genotype exhibited a strongly positive and significant OR in susceptibility for CRS as a whole, indicating an association between the genotype and risk of developing CRS, a relationship replicated for patients with CRSwNP but with CRSsNP, suggesting the AT genotype is associated with increased susceptibility for CRSwNP.

Our chi-squared analysis showed that (a) genotype and allele frequencies of rs1391371 deviated from HWE and (b) the AT genotype conveyed the most risk for CRS, an association probably driven by the CRSwNP effect—results not mentioned in the original GWAS report.[8] Thus, although we have replicated the association in the CRSwNP group, how the rs1391371 polymorphism, and especially its heterozygosity, contributes to the development of disease remains unexplained. Further genetic and molecular analyses need to be done to investigate how this polymorphism may contribute to CRSwNP. As noted by Kristjansson et al. (2019), the rs1391371 SNP is a common intergenic (i.e., non-coding) variant upstream of the *HLA-DQA1* gene that correlates most strongly with *HLA-DQA1*03:01:01,* which is highly correlated with four coding variants (rs9272785, rs1048023, rs12722061 and rs1064944). These variants had similar odds ratios for NP and CRS in the Icelandic and UK data sets as rs1391371. Further work could focus on investigating the role of these genes in inflammation and immunity associated with CRS and their interplay with rs1391371.

In summary, we have determined that heterozygous carriers of the rs1391371 T allele are at significantly increased risk for developing CRSwNP, which further supports the potential contribution of this HLA region to CRS.

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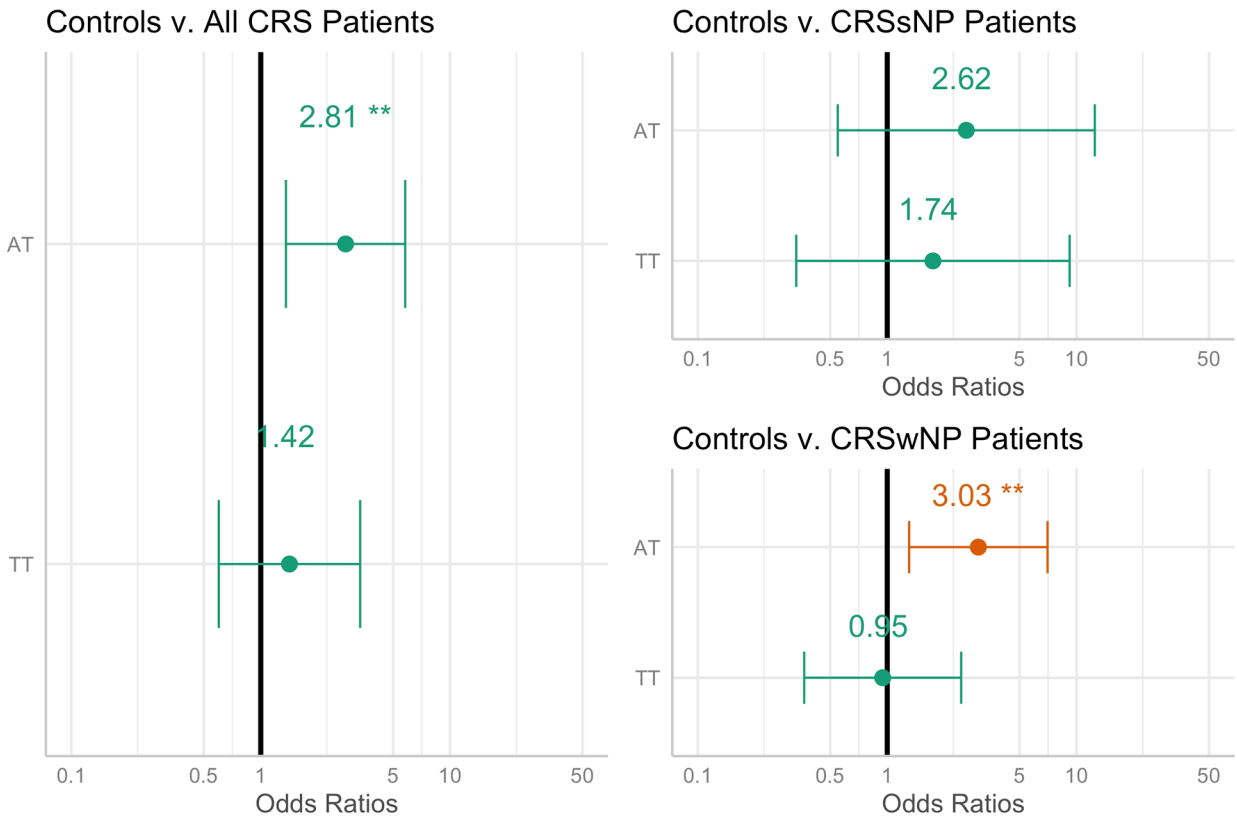

Figure 1.

Estimated Odds Ratios from Linear Regressions. Forest plots showing estimated odds ratios for rs1391371 heterozygote (AT) and homozygous recessive (TT) diplotypes. '*' indicates statistical significance at the 5% level ($p<0.05$), '**' indicates statistical significance at the 1% level ($p<0.01$), '***' indicates statistical significance at the 0.01% level ($p<0.001$).

Table 1.

Subject Characteristics

Characteristic	Control (n = 233)	CRS (n = 317)	p-value	CRSsNP (n = 109)	CRSwNP (n = 208)	p-value
Age (years, mean ± SD)	45.24 ± 14.95	57.35 ± 13.91	<0.001 ***	58.4 ± 15.2	56.8 ± 13.2	<0.001 ***
Gender (male), n (%)	95 (40.8)	187 (59.0)	<0.001 ***	52 (47.7)	135 (64.9)	<0.001 ***
Ethnicity (Non-Hispanic, Non-Latino), n (%)	231 (100.0)	312 (98.4)	0.144	109 (100.0)	203 (97.6)	0.016 *
Race (White/Caucasian), n (%)	233 (100.0)	317 (100.0)		109 (100.0)	208 (100.0)	
Ever smoker, n (%)	47 (20.3)	83 (32.7)	0.003 **	30 (34.1)	53 (31.9)	0.008 **
Comorbid Asthma, n (%)	44 (19.0)	161 (50.8)	<0.001 ***	37 (33.9)	124 (59.6)	<0.001 ***
rs1391371 diplotype, n (%)			0.276			0.302
AA	158 (67.8)	194 (61.2)		68 (62.4)	126 (60.6)	
AT	46 (19.7)	74 (23.3)		21 (19.3)	53 (25.5)	
TT	29 (12.4)	49 (15.5)		20 (18.3)	29 (13.9)	

Note:

'' indicates statistical significance at the 5% level (p<0.05),

*'**'* indicates statistical significance at the 1% level (p<0.01),

*'***'* indicates statistical analysis at the 0.01% level (p<0.001).