of Centres of Excellence (Canadian Allergy and Immune Diseases Advanced Training Initiative) and the Canadian Institutes of Health Research (Sir Frederick Banting and Charles Best Canada Graduate Scholarship and Michael Smith Foreign Study Supplement Award). The aforementioned funding sources had no involvement in the study design, in the collection, analysis, and interpretation of data, in the writing of the report, and in the decision to submit the article for publication.

Disclosure of potential conflict of interest: D. S. Postma's institution has received consultancy fees from AstraZeneca, Chiesi, Boehringer Ingelheim, GlaxoSmithKline, TEVA, and Takeda; she has received or has grants pending from Chiesi, from which she has also received payment for delivering lectures. G. Pershagen's institution has received funding from the Swedish Research Council and the Swedish Environmental Protection Agency. M. Brauer's institution has received funding from AllerGen Networks of Centres of Excellence, as has E. Fuertes, who has also received funding from the Canadian Institutes of Health Research. G. H. Koppelman's institution has received funding from the Dutch Lung Foundation. The rest of the authors declare that they have no relevant conflicts of interest.

## REFERENCES

1. Moffatt MF, Kabesch M, Liang L, Dixon AL, Strachan D, Heath S, et al. Genetic variants regulating ORMDL3 expression contribute to the risk of childhood asthma. Nature 2007;448:470-3.
2. Ferreira MAR, Matheson MC, Tang CS, Granell R, Ang W, Hui J, et al. Genome-wide association analysis identifies 11 risk variants associated with the asthma with hay fever phenotype. J Allergy Clin Immunol 2014;133:1564-71.
3. Tomita K, Sakashita M, Hirota T, Tanaka S, Masuyama K, Yamada T, et al. Variants in the 17q21 asthma susceptibility locus are associated with allergic rhinitis in the Japanese population. Allergy 2013;68:92-100.
4. Andiappan AK, Wang DY, Anantharaman R, Parate PN, Suri BK, Low HQ, et al. Genome-wide association study for atopy and allergic rhinitis in a Singapore Chinese population. PLoS One 2011;6:e19719.
5. Ramasamy A, Curjuric I, Coin LJ, Kumar A, McArdle WL, Imboden M, et al. A genome-wide meta-analysis of genetic variants associated with allergic rhinitis and grass sensitization and their interaction with birth order. J Allergy Clin Immunol 2011;128:996-1005.
6. Hinds DA, McMahon G, Kiefer AK, Do CB, Eriksson N, Evans DM, et al. A genome-wide association meta-analysis of self-reported allergy identifies shared and allergy-specific susceptibility loci. Nat Genet 2013;45:907-11.
7. Verlaan DJ, Berlivet S, Hunninghake GM, Madore A-M, Larivière M, Moussette S, et al. Allele-specific chromatin remodeling in the ZPBP2/GSDMB/ORMDL3 locus associated with the risk of asthma and autoimmune disease. Am J Hum Genet 2009;85:377-93.
8. Hao K, Bossé Y, Nickle DC, Paré PD, Postma DS, Laviolette M, et al. Lung eQTLs to help reveal the molecular underpinnings of asthma. PLoS Genet 2012;8:e1003029.
9. Ha SG, Ge XN, Bahaie NS, Kang BN, Rao A, Rao SP, et al. ORMDL3 promotes eosinophil trafficking and activation via regulation of integrins and CD48. Nat Commun 2013;4:2479.

Available online September 26, 2014.
http://dx.doi.org/10.1016/j.jaci.2014.08.016

## Increased noneosinophilic nasal polyps in chronic rhinosinusitis in US second-generation Asians suggest genetic regulation of eosinophilia

*To the Editor:*

Chronic rhinosinusitis (CRS) with nasal polyps (CRSwNP) is an inflammatory disease with a high impact on quality of life and is characterized by the presence of polyps in an individual with diagnosis of CRS. Although most of the nasal polyps (NPs) in patients with CRSwNP seen in Western countries are eosinophilic,[1,2] noneosinophilic NPs comprise a significant percentage of CRSwNP seen in East Asian countries including China, Korea, Japan, and Malaysia.[3-8] Studies comparing polyps in Chinese and Belgian patients have shown significantly lower eosinophil numbers[3,9] and lower eosinophil cationic protein (ECP) levels[9] in NPs in Chinese patients.

In the last decade, there has been a trend toward increasing eosinophilic nasal polyposis in Asian populations.[5,10] A Korean study has shown that eosinophilic NPs have increased from 24% of the total NPs resected in 1993-1994 to 50.9% in 2010-2012.[5] However, recent studies still show that about half of the CRSwNP cases in East Asian countries have a noneosinophilic pathology.[4-8] This raises the possibility that this type of NPs are influenced by different pathogenesis elements that are more common in that area and/or that genetic factors play a role in the level of eosinophilia in NPs in Asian populations.

In an attempt to test whether the propensity of Asian populations to manifest noneosinophilic polyps is due to genetic factors, we evaluated the eosinophilic marker ECP and evidence for eosinophilia in the pathology report of polyp and sinus tissue collected during functional endoscopic surgery in a group of second-generation Asian patients with CRS in Illinois and compared them with those in patients of other ethnicities in Illinois. We focused on study patients with both parents from Asian countries who were born and raised in the United States. Such patients come from the same genetic pool as their parents but have presumably been exposed to environmental factors present in the United States. Our findings demonstrated reduced eosinophilia in Asian patients with CRSwNP who were born and raised in the United States.

A consecutive series of 296 patients with CRSwNP who underwent surgery at Northwestern University from 2005 to 2013 were included. Patients with self-reported Asian ancestry and born in the United States were identified as second-generation Asian. Twenty-three patients had identified themselves as Asian (including Chinese, Korean, Japanese, and Malaysian), out of which 11 were second generation and were included. The rest were excluded from the study. Original pathology reports of polyp and sinus tissue obtained during surgery were reviewed for reported eosinophilia. The tissue would have been reported as eosinophilic by the pathologists if eosinophils comprised more than 10% of inflammatory cells in the studied area. Furthermore, in 161 of the enrolled cases, tissue homogenates of polyp and/or uncinate tissue (UT) were available in a prospectively collected biorepository and were analyzed for ECP. UT was used as representative of sinus and upper nasal tissue. Previous studies have shown that NPs and UT of patients with CRSwNP from the United States have a significantly higher number of eosinophils than does control UT.[2] ECP levels were measured by ELISA using the Mesacup ECP Test Kit from MBL (Woburn, Mass). The ECP concentration was measured as ng/μL. The level was adjusted to total protein concentration in each sample, which was measured as mg/μL. All ECP levels were reported as ng/mg of total protein. Physician diagnosis of asthma and atopy was recorded as part of the study and was double-checked by using chart review. Atopy was defined by evidence of allergic sensitization to aeroallergens by using skin prick test or Immunocap testing. The study was approved by the Northwestern University institutional review board.

Comparisons among groups in terms of ECP levels were assessed by using Kruskal-Wallis and Dunn's multiple comparisons tests. Comparisons between groups in terms of eosinophilic polyps, asthma, and atopy were done by using Fisher exact test. Adjusting for age and sex for the above analyses was performed by logistic regression. These statistical analyses were performed using IBM SPSS, version 22. A $P$ value of less than .05 was considered statistically significant.

Levels of ECP in polyp (mean, 179.4 vs 1256 ng/mg; $P < .001$) and UT samples (mean, 133.6 vs 838.6 ng/mg; $P < .001$) were significantly lower in tissue from second-generation Asian versus

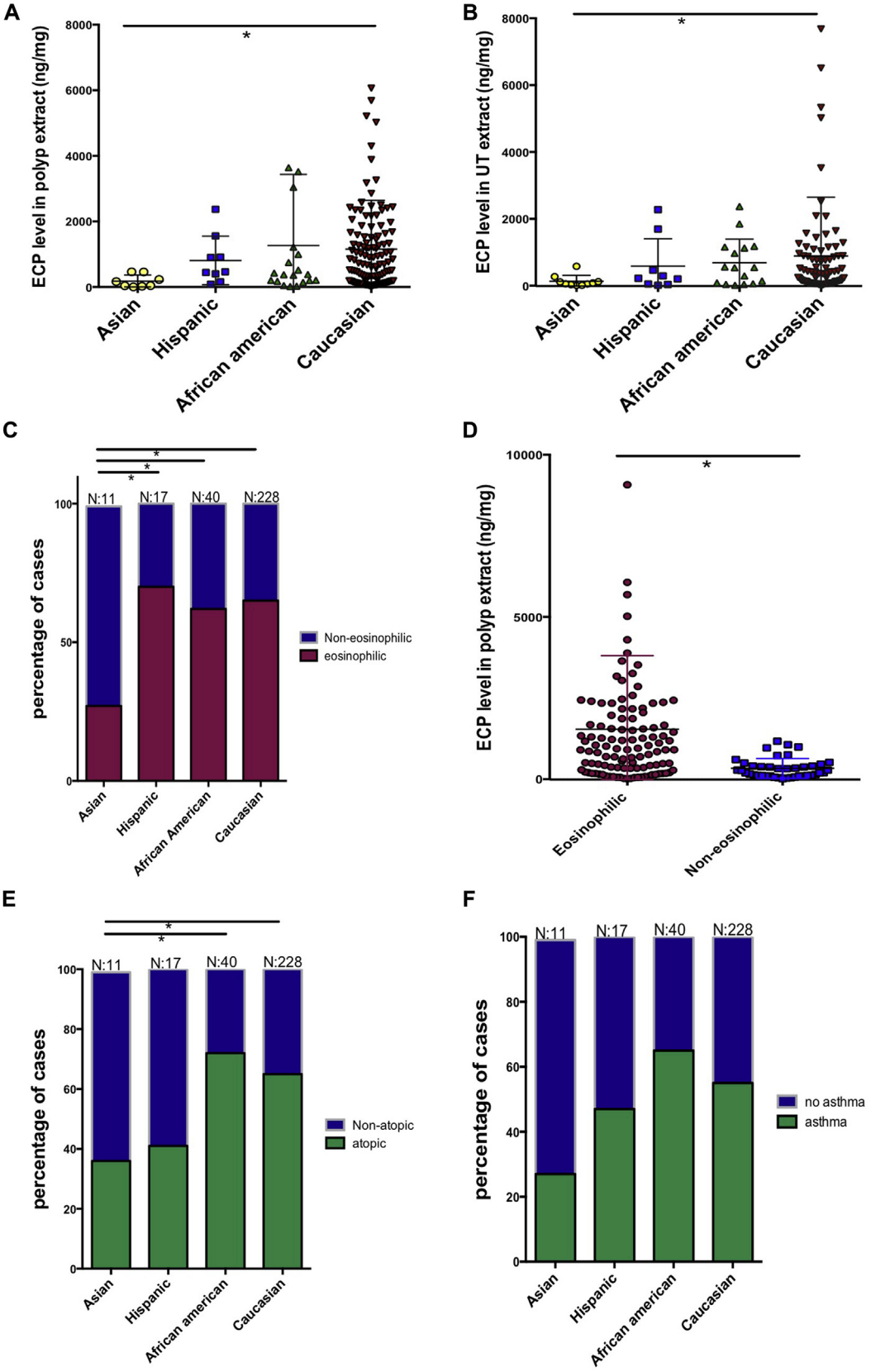


**FIG 1.** **A,** The ECP level in polyp tissue homogenates was significantly lower in samples from Asian patients than in samples from white patients. **B,** Also, the ECP level in UT of Asian cases was significantly lower than the ECP level in UT extracts of both white and black patients. **C,** Asian patients had a significantly lower frequency of pathology-reported eosinophilic sinusitis than did patients of other ethnicities. **D,** The ECP level in polyp extracts was significantly lower in cases reported in the surgical pathology examination as noneosinophilic than in those reported as eosinophilic. Asian patients with CRS and nasal polyposis had a significantly lower frequency of atopy **(E)** and a trend toward lower frequency of asthma compared with white and black patients. (*$P < .05$).