Published in final edited form as:

J Allergy Clin Immunol. 2013 April ; 131(4): 977–993.e5. doi:10.1016/j.jaci.2013.01.028.

Genetics of Chronic Rhinosinusitis: State of the Field and Directions Forward

Joy Hsu, MD¹, Pedro C. Avila, MD¹, Robert C. Kern, MD², M. Geoffrey Hayes, PhD³, Robert P. Schleimer, PhD¹, and Jayant M. Pinto, MD⁴

¹Division of Allergy-Immunology, Northwestern University Feinberg School of Medicine;

²Department of Otolaryngology-Head and Neck Surgery, Northwestern University Feinberg School of Medicine

³Division of Endocrinology, Metabolism, and Molecular Medicine, and Center for Genetic Medicine, Northwestern University Feinberg School of Medicine, and Department of Anthropology, Northwestern University

⁴Section of Otolaryngology-Head and Neck Surgery, Department of Surgery, Pritzker School of Medicine, The University of Chicago.

Abstract

The etiology of chronic rhinosinusitis (CRS) remains unclear. Study of the genetic susceptibility to CRS may be a valuable strategy to understand the pathogenesis of this burdensome disorder. The purpose of this review is to critically evaluate the current literature regarding the genetics of CRS in a comprehensive fashion. The most promising findings from candidate gene studies include the Cystic Fibrosis Transmembrane Conductance Regulator gene (*CFTR*), as well as genes involved in antigen presentation, innate and adaptive immune responses, tissue remodeling, and arachidonic acid metabolism. We also review the few hypothesis-independent genetic studies of CRS (i.e., linkage analysis and pooling-based genome-wide association studies). Interpretation of the current literature is limited by challenges with study design, sparse replication, few functional correlates of associated polymorphisms, and inadequate examination of linkage disequilibrium or expression quantitative trait loci for reported associations. Given the relationship of CRS to other airway disorders with well-characterized genetic components (e.g., asthma), study of the genetics of CRS deserves increased attention and investment, including the organization of large, detailed, and collaborative studies to advance knowledge of the mechanisms that underlie this disorder.

Keywords

Genetics; genome; variation; chronic rhinosinusitis; nasal polyposis; single nucleotide polymorphism; polymorphism; candidate gene; linkage; genome wide association study; susceptibility; sinusitis

© 2013 American Academy of Allergy, Asthma and Immunology. Published by Mosby, Inc. All rights reserved.

Corresponding author: JAYANT M. PINTO, M.D. Associate Professor of Surgery Section of Otolaryngology-Head and Neck Surgery The University of Chicago Medicine and Biological Sciences 5841 South Maryland Avenue | Room E-103, MC 1035 | Chicago, Illinois 60637 773-702-6727 (office) 773-702-6809 (fax) jpinto@surgey.bsd.uchicago.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Clinical Implications: We review evidence for a genetic predisposition to chronic rhinosinusitis and discuss future directions for the field. Increased understanding of this topic may provide insights into disease pathogenesis and management.

Introduction

Chronic rhinosinusitis (CRS) is a syndrome associated with persistent inflammation of the nasal and paranasal sinus mucosa.¹ The diagnosis of CRS requires indicative symptoms (e.g., nasal congestion or discharge) of at least 12 weeks duration, and objective confirmation of sinonasal disease (by nasal endoscopy or computed tomography [CT] of the sinuses).¹⁻³ CRS has been estimated to affect 13% of the US population,⁴ and annual direct costs of this disease in the US exceed \$8 billion.⁵ Patients with CRS have demonstrated a lower quality of life, worse than heart failure or back pain in some domains.⁶ Availability of effective therapies for CRS is limited, especially in the most severe cases, and understanding the etiology may be the best way of developing effective therapeutic strategies.⁷

CRS has been under active investigation for the past 25 years, but intense debate continues regarding the etiology of this condition. Many potential contributing factors have been identified—including allergic responses, impaired mucociliary clearance, immune dysfunction, impaired epithelial defense, microbes, and environmental exposures (see Figure 1).^{8,9} One manifestation of this ongoing controversy is the existence of several proposed approaches to dividing CRS into subphenotypes, or endotypes, which may reflect distinct pathogenetic mechanisms or therapeutic responsiveness. CRS is frequently classified as CRS with nasal polyposis (CRSwNP) or CRS without nasal polyposis (CRSsNP) by many clinicians and researchers.^{1,2} Some studies have suggested a T helper(Th) 2 inflammatory profile (e.g. increased levels of eosinophils, interleukin-5 [IL-5], and IL-13 in sinonasal tissue) may be more characteristic of CRSwNP than CRSsNP.^{8,10,11} However, sinonasal Th2 inflammation has not been identified in all patients with CRSwNP, and there is evidence of Th1 and Th2 overlap in both groups.¹² Another suggested approach to subdividing CRS relies on histologic classification: CRS may be categorized as chronic hyperplastic eosinophilic sinusitis (CHES, defined as increased sinonasal tissue eosinophilia or immunohistochemical staining for activated eosinophilic cationic protein) or chronic inflammatory sinusitis (CIS, defined as CRS without evidence for CHES).¹³ By this method, nasal polyposis may be associated with either CHES or CIS. Beyond these general classification systems, distinct subphenotypes of CRS may exist which span or supersede these categories, such as aspirin-exacerbated respiratory disease (AERD) and allergic fungal rhinosinusitis (AFRS).^{1,8,14} Although several major guidelines committees have favored the division of CRS into CRSwNP and CRSsNP for clinical and research purposes^{1,2}, the most appropriate method for cataloguing CRS remains a matter of debate, as does the etiology of CRS itself. Considerable effort will be required to construct a coherent model of cellular and molecular mechanisms underlying the pathogenesis of CRS, toward an ultimate goal of effective therapy for this disease.

There are several obstacles hindering the achievement of this goal. At present, despite some efforts¹⁵⁻¹⁷, there is no widely accepted animal model of CRS. Consequently, most investigations have focused on the examination of nasal secretions, nasal mucosa, nasal polyps, sinus secretions, sinus mucosa, and peripheral blood of human patients who have CRSwNP or CRSsNP. Other major barriers include the variability of classifying CRS subphenotypes, lack of cohort studies, heterogeneous environmental influences, and limited investment of research funding. Though more recent studies have attempted to search for genes related to sinus disease by use of DNA microarrays^{14,18-20} and protein expression analyses²⁰⁻²², we still lack a clear understanding of the underlying molecular pathology. A fundamental problem is essentially all of the published studies have focused on CRS sufficiently advanced enough to require surgical intervention, making it difficult to determine the predisposing genetic and environmental factors that may affect the development of CRS from its onset. Along with our inability to predict which patients will

develop CRS, restricted access to sampling of the sinus cavity limits our ability to provide information on the transformation from a healthy epithelium to an inflamed mucosa. Thus, there is a clear need for novel approaches to understanding the pathophysiology of CRS.

Genetic approaches have provided insight into the etiology of many chronic relapsing and remitting diseases.²³ Study of the genetic susceptibility to CRS may be a valuable path toward understanding the development of this burdensome disorder. Advantages of this strategy include: (1) an ability to examine variation in the human genome that predisposes to disease, thereby avoiding potentially confounding issues associated with CRS advanced enough to require surgery; (2) the opportunity to provide information on not only the mechanism but also the prognosis and response to therapy; and (3) direct applicability to human patients. Furthermore, this approach permits use of modern genetic methods toward greater insight into the disease biology, including: genome-wide association studies (GWAS), in which very large patient sample sizes are required to examine hundreds of thousands or millions of genetic variants to identify associations with disease²⁴; whole genome sequencing, which collects complete genetic information and therefore can detect rare genetic variants associated with disease²⁴; exome sequencing, in which only the coding portions of genes (exons) are sequenced²⁴; RNA sequencing, which explores how variation in RNA transcripts may correlate with disease²⁵; epigenomics, the study of how disease may be associated with biochemical modifications of DNA which affect gene regulation (e.g., DNA methylation or histone acetylation)²⁶; proteomics, the large scale analysis of the structure and function of proteins in cells or tissues²²; and metabolomics, the global analysis of small metabolites involved in cellular processes that may be affected by or predispose to disease.²⁷ One benefit from these unbiased approaches is that novel, clear, and testable hypotheses often emerge for subsequent direct evaluation.

Our purpose in this review is to critically evaluate the current literature on the genetics of CRS and to identify areas of promise for future investigations in this field. In this review, we have utilized standard research classifications for CRS disease, including CRSwNP and CRSsNP.²

Evidence for Genetic Susceptibility to CRS

Classic evidence for a genetic component of a disease is heritability of the condition. Although formal heritability studies are not available for CRS, a genetic basis for CRS has long been suspected.²⁸ One early report documented cases of concordant monozygotic twins who developed CRSwNP despite distinct environmental exposures.²⁹ Similarly, familial aggregation of a disease points to a genetic basis and, indeed, reports of families with an unusually high prevalence of CRSsNP and CRSwNP (with and without AERD) are available.³⁰⁻³⁴ Additionally, patients with CRS are more likely to report a positive family history than those without CRS.^{33, 35, 36} Supportive evidence for a genetic basis of CRS also includes the fact that several syndromes associated with known genetic defects have CRS as a clinical component. This includes primary ciliary dyskinesia³⁷ as well as monogenic diseases such as cystic fibrosis (CF), which is caused by a deficiency in epithelial chloride transport due to mutations in the Cystic Fibrosis Transmembrane Conductance Regulator (*CFTR*) gene.³⁸ Lastly, the inflammatory features of CRS have similarities to those seen in allergic rhinitis and asthma, two complex diseases with well-established genetic components^{24, 39} and strong clinical associations with CRS.^{1, 3} Indeed, studies have demonstrated common molecular and cellular aspects of these disorders, leading to the unified airway concept that postulates the common clinical manifestations of CRS, allergic rhinitis, and asthma suggest a shared etiology.⁴⁰

Genetics of CRS: Current State of the Field and Limitations of the Existing Literature

Approaches for Studying the Genetics of CRS

Investigators from Europe, Asia, and North America have attempted to test whether genetic variation is associated with CRS. The majority of studies have used a candidate gene approach, which compares the allele frequencies of single nucleotide polymorphisms (SNPs) in genes suspected *a priori* to be involved in CRS among patients with CRS and patients without CRS (controls). However, there are several limitations to this strategy, most importantly an inability to generate novel information on disease mechanisms because candidates are selected based on what is already known (or suspected) about its biology. Additional considerations for association studies include the difficulty of achieving adequate power, the potential for confounding by ancestry when subject groups are heterogeneous, and the caveat that an association between CRS and a polymorphism does not necessarily indicate causality. Of course, other approaches share many of these issues as well.

Genome-wide approaches overcome the first limitation because of their ability to interrogate the entire genome in an unbiased, hypothesis-independent fashion. However, to date, such studies are rare in CRS. One linkage analysis has been conducted, although the small sample size limited its utility.⁴¹ Though GWAS have provided useful information for a host of diseases, including related conditions such as asthma (reviewed in ²⁴), there are only two such studies of CRS.^{28, 42} There are several reasons for the paucity of GWAS of CRS, including the need for a large number of well-phenotyped subjects, the expense of high-density genotyping, and the lack of research consortia in this area.²⁴ Although some have criticized GWAS for producing a smaller direct impact on clinical medicine than was initially anticipated or promoted,⁴³ GWAS have proved to be fruitful in a number of diseases for identifying novel pathways and providing new insights into disease biology.^{23, 24}

Phenotype

Rigorous study design is critical to the validity and interpretability of all genetic studies of complex diseases. One of the most important elements of study design is meticulous classification of the disease phenotype.^{2, 23, 24} For CRS this remains a difficult challenge not only for genetic studies, but also in other avenues of investigation including clinical, immunological, pathologic, or radiographic studies. Interpretation of most studies is challenging because of a lack of detailed information about study subjects.^{13, 28, 44-55} For example, few studies provide information on the specific results of sinus CT scans, nasal endoscopy, symptomatology, tissue histology, or related conditions such as atopy, asthma, and other important subphenotypes (e.g., AERD, AFRS). Classification systems for CT scan findings are crude at best, and most studies do not mention issues such as minimal abnormalities (e.g., mucous retention cysts) that are likely inconsequential. Similar problems plague methods of classifying endoscopic findings in CRS, histologic results, and even clinical comorbidities (atopy by report, by skin test, or by serum testing; asthma by self-report, doctor's diagnosis, or pulmonary function testing). Because variants may be associated with subsets of the disease, a more complete evaluation may be necessary for identification of a true genetic signal; conversely, lack of information may dilute such a signal. For example, because CRSwNP and CRSsNP may be distinct in their genetic susceptibility,^{2, 8, 56} combining these groups may obscure genetic associations. Furthermore, subphenotypes of CRS (e.g., CRS associated with asthma, or CRS associated with AERD) may be pathogenetically unique and thus yield a genetic signature distinct from CRS without these comorbidities. Even prior to categorizing CRS into subphenotypes, inadequate inclusion criteria for the primary diagnosis of CRS in a research study (e.g., lack of

endoscopy or adequate imaging⁵⁷⁻⁵⁹) or insufficient scrutiny of ambiguous radiographic findings (e.g., inclusion cysts on sinus CT) may result in incorrect assignment of cases and controls. Additionally, there is real concern for the presence of undiagnosed CRS disease among control subjects (due to difficulties in phenotyping controls with endoscopy and CT imaging). Incorrect or inadequate phenotyping of CRS and control patients diminish study power, but this can be overcome by increasing the sample size of cases, controls, or both. However, no large genetic studies of CRS have been performed to date. Because the etiology of CRS is likely multifactorial, and because genes relevant to CRS are likely to have small effect sizes (similar to other complex multifactorial diseases^{23, 24}), available genetic studies in CRS have been severely limited by small sample sizes and low statistical power to identify genetic determinants of CRS.

Challenges in Finding Causal Variants

Even when a genetic polymorphism is found to be associated with CRS, it is important to consider several possibilities that may account for the association. A SNP may directly cause disease by altering gene regulation or by changing protein function. Alternatively, the identified SNP may be in linkage disequilibrium (LD) with the actual causal variant (i.e., the identified genotyped SNP may be some distance away from the actual causal [ungenotyped] SNP, but because these two SNPs happen to be nonrandomly inherited, the genotyped SNP would predict variation in the ungenotyped, causal SNP). Hence, accounting for LD is critical. An association signal may also be due to allele frequencies caused by unknown or undetected differences between the ancestry proportions of the case and control groups (i.e., population structure), and therefore unrelated to CRS disease. This must be considered if CRS and control subjects are not adequately matched for ancestry (e.g., by assessing polymorphisms that are known to differ in allele frequency between populations).⁶⁰ The associated SNP may be an expression quantitative trait locus (eQTL) for a gene elsewhere in the genome (i.e., the SNP in question affects the transcription of another gene involved in the disease process) that is actually related to the underlying biology of CRS. Finally, the association may be falsely positive, due to a type 1 statistical error, which is a common risk inherent in genetic studies if methodological safeguards (e.g., correction for multiple testing) are not implemented.²⁴ Thus, replication of positive findings lends further credence to the possibility that a positive statistical association represents a true relationship. Existing studies have not been consistent in accounting for alternative possibilities when reporting significant findings.

Here, we review current knowledge on the genetics of CRS. Most published studies consist of candidate gene studies and must be interpreted with the caveats described. Nevertheless, we have attempted to catalogue and discuss the available literature with equanimity, given the limited attention devoted to the field. We have chosen to highlight genes identified in multiple studies and those in molecular pathways implicated by other avenues of research. A list of studies that have reported statistically significant associations between CRS and genetic polymorphisms appears in Table 1. A comprehensive list of studies and their major findings (statistically significant or negative studies) is provided as a Supplementary Table.

CRS and the Cystic Fibrosis Transmembrane Regulator (*CFTR*) locus

The vast majority of CF patients have severe CRS, which is typically CRSwNP.^{61, 62} CF is caused by mutations in the *CFTR* gene, which encodes a chloride channel and regulatory protein found in exocrine glands.⁶¹ The most common *CFTR* mutation in the United States (US) is the F508 mutation, but numerous pathogenic *CFTR* mutations have been identified, and their frequencies vary by racial and ethnic group.⁶³ The high prevalence of CRS among CF patients suggests *CFTR* may contribute to the pathogenesis of CRS, and this relationship may extend beyond patients with clinical features of CF.

Indeed, prior epidemiologic and genetic studies support a relationship between *CFTR* and CRS in patients without other features of CF. To date, these studies have been limited to patients of European ancestry, and have explored primarily known *CFTR* mutations common among CF patients of European ancestry.^{44, 64-66} For example, a landmark study by Wang et al.⁶⁴ of 147 adults with CRS and 123 control subjects (all of European ancestry) found CRS patients were more likely to be *CFTR* carriers compared to controls (7% vs. 2%). Use of objective measures to confirm CRS (i.e., nasal endoscopy or sinus CT) was a strength of this study. The most frequent mutations identified in this study were the F508 and M470V variants, but the study screened only for the most common *CFTR* mutations for this ethnic group.⁶⁴ The absolute difference in prevalence of *CFTR* carriers among CRS patients and controls in this study was small (5%) but significant, and this finding was followed by studies that identified a higher-than-expected prevalence of CF carriers in children with isolated CRS (12% vs. 4%)⁶⁵ and a higher-than-expected prevalence of CRS (36% vs. 13%) among obligate CF carriers (i.e., parents of children with known CF).⁴⁴ Studies of populations outside the US have reported similar associations.^{66, 67} Additionally, results from a linkage study (reviewed in our discussion of linkage analyses and GWAS) support a possible relationship between *CFTR* and CRS.⁴¹

Although most of these studies have identified *CFTR* mutations in only a minority of patients with CRS, some data suggest that gene sequencing may reveal the prevalence of *CFTR* mutations in CRS to be higher than previously reported. A small retrospective US study of patients with CRS who underwent full sequencing of *CFTR* (n=68) found 38% of these patients had mutations in *CFTR* (n=26).⁶⁸ The prevalence of *CFTR* mutations was slightly higher in CRS patients with comorbid asthma (42%, or 16 out of 38 patients), and even higher in their very small sample of patients with CRSwNP (66%, or 4 out of 6 CRSwNP patients in the study).⁶⁸ The authors estimated they would have missed 75% of *CFTR* mutation carriers (i.e., 30 of 41 patients) if they had employed only genetic screening for the 23 most common *CFTR* mutations for CF patients of European ancestry.⁶⁸ As gene sequencing becomes a feasible and inexpensive method for investigation, applying this technology to further study of *CFTR* in CRS may prove worthwhile.

Several mechanisms have been proposed to explain how *CFTR* dysfunction affects sinonasal disease in CF, and these also may apply to *CFTR* mutations associated with CRS without other features of CF. First, decreased mucociliary clearance has been observed in the sinonasal epithelium in CF, which may predispose to recurrent infection and chronic inflammation.³⁸ Susceptibility to recurrent sinusitis in CF may also be due to other alterations in host defense associated with *CFTR* dysfunction, including abnormal sinonasal pH⁶⁹ and decreased transport of thiocyanate (which functions both as an antioxidant and as an antimicrobial) into CF airways.⁷⁰ Moreover, the hyperviscous mucus layer of CF patients contains an abnormally low oxygen tension (attributed to increased oxygen utilization by epithelial cells), and this local hypoxia has been associated with biofilm formation and bacterial proliferation, features that have been implicated in CRS.⁷¹ Insights from the lower airway in CF suggest additional hypotheses for the origin of *CFTR* mutation-induced sinonasal inflammation; for example, increased levels of IL-8 and/or Toll-like receptor (TLR)-2 activity may contribute to self-perpetuating inflammation and airway injury.⁷²⁻⁷⁴

In summary, multiple studies support a relationship between *CFTR* and CRS independent of CF. Given the well-described association between *CFTR* and CRS in patients with CF, the number of highly suggestive candidate gene studies of *CFTR* and patients with CRS, and plausible mechanisms by which *CFTR* dysfunction may underlie sinus disease, further investigation of the importance of *CFTR* in CRS is warranted. Exploring this relationship is not without challenges, including: the large number of mutations to be studied given the size

of this gene, the possibility that only rare *CFTR* variants may cause CRS, and the interethnic variation in allele frequencies of *CFTR* mutations.⁷⁵⁻⁷⁸

CRS and Human Leukocyte Antigen (HLA) genes

Presentation of antigen is an important link between innate and adaptive immunity, and the Human Leukocyte Antigen (*HLA*) genes play a critical role in antigen presentation. The three major HLA class I molecules (HLA-A, HLA-B, and HLA-C) are nearly ubiquitously expressed in the body and primarily present “endogenous” antigens (i.e., antigenic peptides derived from proteins synthesized within the cell); the three major class II molecules (HLA-DR, HLA-DQ, and HLA-DP) are constitutively expressed by B cells, dendritic cells, monocytes, and macrophages (although their expression can be induced in other cells) and mediate presentation of “exogenous” antigens (those from outside the cell).⁷⁹ HLA variation has been strongly associated with several inflammatory diseases (e.g., insulin-dependent diabetes mellitus and ankylosing spondylitis)²³, but the relationship between CRS and HLA variation (both class I and class II) remains unclear. This body of literature is limited by a paucity of replication of these associations. Nevertheless, *HLA* loci remain attractive candidate genes due to the significant immunodysregulation that is characteristic of CRS.

Several groups have examined variation in *HLA* in CRS (primarily CRSwNP) and identified alleles associated with disease (HLA-A*24, HLA-A*74, HLA-B*07, HLA-B*54, HLA-Cw*12, HLA-DR*7, HLA-DR*16, HLA-DQ*8, HLA-DQ*9, HLA-DQA1*0201, HLA-DQB1*03, HLA-DRB1*03, HLA-DRB1*04, HLA-A1/B8 haplotype).^{45, 46, 57, 80-84}

However, there remains no consensus, as few attempts have been made to replicate these associations. To give one example of the complexity of comparing studies, the haplotype *HLA-A1/B8* has been examined in two populations, a case series of 29 CRSwNP subjects from the United Kingdom (UK) by Moloney et al.⁸¹ and an Austrian case-control study of 89 CRSwNP subjects and 1070 controls by Luxenberger et al.⁸⁰ Neither study found *HLA-A1/B8* to be associated with CRSwNP itself.^{80, 81} However, the UK study found *HLA-A1/B8* was present in three of their four CRSwNP patients with AERD.⁸¹ In contrast, the Austrian study found no significant relationship between that particular subphenotype and *HLA-A1/B8* ($P > .05$).⁸⁰ Replication studies are essential to determine whether *HLA-A1/B8* is truly associated with CRSwNP with AERD.

Perhaps the most robust association between CRS and HLA variation is for the *HLA-DRB1*04* allele.^{45, 46} In a study of Mexican Mestizos (defined as having mixed Native American [56%], European [40%], and African [4%] ancestry) involving 34 CRSwNP patients and 99 controls, Ramirez-Anguiano et al.⁴⁵ found the *HLA-DRB1*04* allele was significantly associated with CRSwNP (odds ratio [OR]=2.2, 95% confidence interval [CI]=1.2-4.2, $P = .009$). However, a Turkish study of 66 CRSwNP patients and 100 controls by Keles et al.⁴⁶ did not find *HLA-DRB1*04* to be more frequent in CRSwNP patients compared to controls (allele frequency [AF] in CRSwNP=23.4%, AF in controls=23.4%, $P > .05$). The Turkish study did find that *HLA-DRB1*04* was more frequent in CRSwNP patients with associated asthma or with AERD (AF in CRSwNP with asthma=32.4%, AF in CRSwNP with AERD=44.4%, AF in controls=23.4%, $P < .05$ for both comparisons).⁴⁶ Of note, none of the CRSwNP patients in the study of Mexican Mestizos had AERD, and only four patients (12%) had asthma.⁴⁵ These differences suggest *HLA-DRB1*04* may be associated with distinct CRS phenotypes (e.g., with or without asthma or AERD) in different populations.

CRS and Genes of Innate Immunity

Innate immunity refers to germline-encoded host defense mechanisms, including physical barriers (e.g., the epithelial barrier and mucociliary clearance of pathogens), antimicrobial

molecules (e.g., complement, defensins, and pentraxins), hematopoietic cells (e.g., dendritic cells, eosinophils, and neutrophils), inflammatory mediators, and receptors that recognize highly conserved microbial elements (often referred to as pattern recognition receptors and pathogen-associated molecular patterns, respectively).⁸⁵ A growing body of evidence suggests aberrant innate immunity may underlie the pathogenesis of CRS.⁸⁶⁻⁸⁹ For example, studies have shown decreased levels of the antimicrobial S100 proteins in CRS sinonasal tissue compared to control tissue,^{86, 87} as well as decreased TLR9 expression and increased TLR2 expression.^{88, 89} Recent evidence suggests the bitter taste receptor T2R38 (*TAS2R38*) may influence the ability of upper respiratory tract cells to combat infection.⁹⁰ Thus, innate immunity genes appear worthy candidates for studies of genetic variation in CRS.

Despite multiple attempts to study variation in genes of innate immunity among patients with CRS, definite conclusions regarding this relationship remain elusive. Few reported associations have been replicated. The causality of positive associations (replicated or not) remain unproven: assessment of possible LD and eQTL is inconsistent in these studies⁹¹⁻⁹³, and, to our knowledge, functional assessments of implicated SNPs have not yet been reported.

A candidate gene study from Germany (68 CRSwNP, 51 controls) found no association between CRSwNP and the *TLR2* SNP rs5743708 ($P > .05$)⁴⁸; a subsequent Korean study also reported no association between CRS (subphenotype unspecified) and this SNP, but identified other SNPs associated with CRS in their population (rs3804099: OR, 2.88; 95% CI, 1.17-7.09; $P = .022$; rs3804100: OR, 3.76; 95% CI, 1.42-9.96; $P = .008$).⁴⁹ To our knowledge, these results have not yet been replicated. Studies exploring the role of other TLRs in CRS pathogenesis are not available, although one study has reported no association between serum total IgE levels and *TLR1*, *TLR2*, *TLR3*, *TLR4*, *TLR6*, *TLR9*, and *TLR10* among patients with CRS.⁹⁴ A US study (179 CRSwNP, 153 controls) found no association between CRSwNP and the TLR4 co-receptor CD14 ($P > .05$), but a more recent study from Iran (106 CRSwNP, 87 controls) reported the C allele at rs2569190 was associated with CRSwNP ($P = .04$).^{95, 96} A study of TLR signaling mediators (by Tewfik et al.⁹⁷) from Quebec involved 206 CRS subjects (75% CRSwNP, 13% CRSsNP, and 12% recurrent acute rhinosinusitis [RARS]) and 200 controls, and found no association with genetic variation in the TLR4 signaling molecule MyD88 or interleukin-1 receptor-associated kinase 4 (*IRAK4*), which mediate downstream signaling of multiple TLRs.⁹⁷ The enrollment strategy of this study required cases to have severe sinus disease, and the authors combined (as a single phenotype) patients with CRSwNP, CRSsNP, and RARS. It is possible that a true genetic association signal specific to CRSwNP or CRSsNP may have been diluted by phenotype heterogeneity in this study, although limited power for subgroup analysis may have made finding a signal challenging regardless. Given our lack of knowledge of the specific pathophysiology of this disease, especially regarding genetic effects, this study design may represent one reasonable and practical approach to finding genetic variation involved. In a larger, more recent study of Chinese patients (324 CRSwNP, 341 CRSsNP, 326 controls), significant associations were found between CRS and *IRAK4* polymorphisms (for CRSwNP: rs1461567, $P = .0385$; rs4251431, $P = .0138$; rs4251559, $P = .0497$; rs6582484, $P = .0232$; rs3794262, $P = .0415$; for CRSsNP: rs1461567, $P = .0348$).⁹⁸ Analysis of CRSwNP and CRSsNP separately and a relatively large sample size are strengths of this study, but replication of these findings has not been reported to date.

Other innate immune defense pathway candidate genes implicated in CRS by supportive cell biology data have also been studied. For example, the nitric oxide synthase (NOS) family of genes encodes enzymes that generate the proinflammatory reactive free radical nitric oxide. Studies of human airways have implicated this molecule in allergic disease.^{47, 99, 100} A Quebecois study of 206 patients with severe CRS (75% CRSwNP and 25% CRSsNP) and

196 controls found this phenotype was associated with variation in the *NOS1* gene (rs1483757: OR, 0.62; 95% CI, 0.46-0.85; $P = .0023$; rs9658281: OR, 0.66; 95% CI, 0.48-0.92; $P = .0129$) and the gene for the NOS1 ligand, NOS1 adaptor protein (*NOS1AP*) (rs4657164: OR, 1.66; 95% CI, 1.09-2.53; $P = .0178$).⁹⁹ A separate study of Spanish patients (46 CRSwNP, 98 controls) that examined the relationship between CRSwNP and variable number tandem repeats (VNTR) in the promoter region of the gene encoding NOS2 (*NOS2A*) showed 15 repeats of the pentanucleotide polypyrimidine microsatellite CCTTT correlated with increased risk for CRSwNP (OR, 14.39; 95% CI, 3.02-68.60; $P = .001$) compared to controls.⁴⁷ Results from a more recent Spanish study supported a relationship between *NOS2A* VNTR and certain subphenotypes of CRSwNP: 15 CCTTT repeats were associated with CRSwNP patients with asthma ($n=144$; $P = .034$ compared to 245 controls), as well as CRSwNP with AIA ($n=75$; $P = .005$ vs. controls).¹⁰¹

In addition to identifying associations between CRS, *IRAK4*, and NOS family members, Desrosiers and colleagues have employed candidate gene studies of their Quebecois cohort to demonstrate significant relationships between CRS and the met proto-oncogene (*MET*) locus (a.k.a. hepatocyte growth factor receptor, thought to be involved in epithelial cell proliferation^{1, 93}) and serpin peptidase inhibitor, clade A (alpha-1 antiproteinase, antitrypsin), member 1 (*SERPINA1*)⁹², the molecule that underlies alpha-1 antitrypsin deficiency, a severe lower airway disease. A recent study in a Polish population also supports an association between *MET* and CRSwNP (-14C > G: OR, 2.83; 95% CI, 1.74-4.61; $P < .001$).¹⁰² Additionally, these investigators have reported an association between CRSwNP and genetic variation in the lactoferrin gene, an antimicrobial peptide.¹⁰³ Confirmatory studies are needed.

Pooling-based GWAS (pGWAS) have implicated additional genetic variation in innate immunity in the pathogenesis of CRS.^{28, 42} These findings are reviewed in our discussion of GWAS and linkage studies.

CRS and Genes Involved in Th2 inflammation

Evidence supports a Th2 inflammatory profile for CRSwNP, including increased Th2 cytokine levels (e.g., IL-5, IL-13) and eosinophil numbers in CRSwNP sinonasal tissue.^{8, 10, 11} Furthermore, studies have linked genetic variants in genes encoding Th2 inflammatory mediators to atopic and airway disease. For example, some studies have linked the *IL4* promoter polymorphism rs2243250 to asthma.^{104, 105} Extensive literature exists for the *IL13* promoter polymorphism rs20541, which has been implicated in many disease phenotypes, including atopy, eosinophilia, asthma, and chronic obstructive pulmonary disease.^{24, 39, 106, 107} Thus, investigating the potential relationship between CRS (especially CRSwNP, which may be more associated with Th2 inflammation than CRSsNP^{8, 10, 11}) and genetic variation in Th2 inflammatory mediators may provide insights into the etiology of CRS. Although single studies have not identified significant associations between genetic variation in the Th2-associated chemokines CCL2 (a.k.a. monocyte chemoattractant protein [MCP] 1)⁹⁵ and CCL11 (a.k.a. eotaxin)¹⁰⁸, other research efforts have yielded promising leads linking CRS to variation in Th2-associated genes. However, most reported associations still require replication and determination of functional relevance.

Some evidence has implicated genetic variation in *IL4* in the pathogenesis of CRSwNP.¹⁰⁹ Yea et al.¹⁰⁹ studied 106 patients with CRS (61 CRSwNP, 45 CRSsNP) and 70 controls, and in a subgroup analysis found the T allele at the *IL4* promoter SNP rs2243250 appeared to be protective against CRSwNP (OR for TT genotype compared to CC genotype, 0.529; 95% CI, 0.307-0.912; $P = .028$). The authors acknowledged their finding contrasted with prior reports of increased functional IL-4 expression associated with the T allele (due to enhanced binding of the transcription factor nuclear factor of activated T cells 1 [NFAT1]).¹⁰⁹ The

question of how the T allele at rs2243250 may reduce risk of CRSwNP while increasing IL-4 expression remains unresolved. This investigator group subsequently reported the T allele may be associated with lower expression of 5-lipoxygenase (5-LO) in nasal polyp tissue.¹¹⁰ Both of these studies await successful replication. A recent Chinese study failed to replicate an association between CRSwNP and rs2243250.¹¹¹ This study also was the first to report a statistically significant association between CRSwNP and variation elsewhere in *IL4* (-33 T > C).¹¹¹

Similar to *IL4*, only one study has examined genetic variation in *IL13* in CRS. In a Korean study of 162 patients with aspirin-intolerant asthma (AIA), 111 of whom were diagnosed with CRS (presence or absence of nasal polyps not specified), and 301 patients with aspirin-tolerant asthma (ATA; n=183 with CRS), Palikhe et al.⁵⁸ did not find an association between the *IL13* polymorphism rs20541 and CRS. However, a subgroup analysis of AIA subjects demonstrated that SNPs in the *IL13* promoter (rs1881457 and rs1800925) were significantly associated with CRS ($P = .012$ and $P = .001$, respectively).⁵⁸ These findings must be interpreted with caution for several reasons. First, characterization of CRS in this study relied on paranasal sinus x-rays and rhinoscopy, without mention of nasal endoscopy or the more definitive imaging modality, CT. The possibility of LD or eQTL as alternate etiologies for the positive associations identified in this study (other than causality) were not explored. Also, this study evaluated atopy using aeroallergen skin prick testing, but the analysis did not specify whether the significant association between *IL13* and CRS in AIA patients was confounded by atopy. The *IL13* promoter SNP rs1800925 is particularly interesting, because separate studies have determined that this SNP results in increased transcription of IL-13 by human Th2 cells.¹¹² To our knowledge, no study has replicated this association between *IL13* and CRS.

IL-33 is another cytokine known to induce Th2 immune polarization,²⁴ and genetic variation in *IL33* has been implicated in allergic disease, including a well-replicated association with asthma.²⁴ IL-33 mRNA has been reported to be elevated in epithelial cells from subjects with CRSwNP.¹¹³ To date, only one genetic study of *IL33* and CRS has been reported. In a well-phenotyped study of more than 700 Belgian patients (284 CRSwNP patients and 427 controls) by Buysschaert et al.,¹¹⁴ the risk allele A at the SNP rs3939286 (approximately 32 kilobases proximal to the start codon of *IL33*) was significantly associated with CRSwNP in both a discovery and a replication cohort (discovery cohort: OR, 1.60; 95% CI, 1.16–2.22; $P = .0041$; replication cohort: OR, 1.43; 95% CI, 1.00–2.06; $P = .046$), and remained significantly associated with CRSwNP after accounting for atopy.¹¹⁴ Of course, this SNP may be an eQTL or in LD with the causal variant. Furthermore, the relevance of rs3939286 to *IL33* expression or function remains unclear.

Studies of CRS sinonasal tissue have suggested an association between CRSwNP and abnormal expression of the interleukin-1 receptor-like 1 (IL1RL1, also known as ST2 and IL18RI), which is a receptor for IL-33.¹¹⁵ However, results from genetic studies of *IL1RL1* variation and CRS are inconsistent. A candidate gene study from the Desrosiers group found a SNP (rs13431828) to be associated with CRS in a Quebecois population¹¹⁶, but these investigators did not find a significant association in subsequent study involving Chinese patients.⁹¹ A Belgian study failed to detect an association between another *IL1RL1* SNP (rs1420101) and CRSwNP.¹¹⁴ These disparate results may reflect allele frequency differences among populations, gene by environment interactions that are distinct, or simply a spurious association.⁹¹

CRS and Other Proinflammatory Genes

Although prior studies have suggested Th2 immune deviation may be more characteristic of CRSwNP than CRSsNP,^{8, 10, 11} both Th1 and Th2 inflammatory features are found in

CRSwNP and CRSsNP.^{12, 117} Thus, studies of the genetics of CRS have extended beyond Th2-associated molecules to include other mediators of inflammation and associated processes (e.g., cell adhesion and communication). Results from these investigations have been mixed, yielding little improvement in understanding of the underlying biology of CRS. Significant associations have been reported between CRS and variants in lymphotoxin-alpha (*LTA*, a.k.a. tumor necrosis factor(TNF)-beta, a lymphokine also involved in lymphangiogenesis)⁵⁰, TNF-alpha-induced protein 3 (*TNF-AIP3*, a.k.a. *A20*, which modulates nuclear factor- κ B transcription factor [NFKB] activation)¹¹⁸, interleukin 22 receptor, alpha 1 (*IL22RA1*, involved in production of acute phase reactants and antimicrobial peptides)¹¹⁹, indoleamine 2,3-dioxygenase (*IDO1*, associated with immune tolerance)¹²⁰ and two inhibitory receptors of IL-1 (interleukin 1 receptor antagonist [*IL1RN*], and interleukin 1 receptor, type II [*IL1R2*]).^{51, 120} To our knowledge, replication of these findings has not yet been reported. One Chinese study of 123 CRS patients (subphenotype unspecified) and 239 controls identified an association between CRS and genetic variation in IL-6¹²¹, which supports prior clinical experiments implicating IL-6 in CRSwNP¹²²; a prior US study found no association between CRSwNP and *IL6*⁹⁵, so the results of the Chinese study await replication. Individual studies have failed to show significant association between CRS and the genes *SH2B3* (which encodes SH2B adaptor protein 3, involved in cell signaling in inflammation)¹¹⁴, *SCGB1A1* (which encodes secretoglobin, family 1A, member 1, a.k.a. uteroglobin or Clara cell 10-kDa protein; an anti-inflammatory surfactant molecule implicated in asthma)¹²³ and *GJB2* (which encodes gap junction protein, beta 2) and *GJB6* (gap junction protein, beta 6) (both connexins; involved in cell-cell communication).⁵³ Many of these studies were limited in power.^{53, 95, 114, 123, 124} The generalizability of these negative studies to other populations is uncertain, because subjects in these studies were primarily of European descent.

A SNP in the *TNF* promoter region (rs1800629) has been reported to associate with asthma, autoimmunity, and a myriad of other diseases; very limited data also suggest this SNP may influence expression levels of TNF.¹²⁵ Three studies have suggested the A allele in rs1800629 to be associated with CRSwNP,^{95, 126, 127} including a US study of 179 CRSwNP patients (evaluated by CT, also with nasal polyps visible to “the unaided eye”) and 153 controls that found the A allele associated with an OR of 1.86 (95% CI, 1.14-3.09; $P = .01$)⁹⁵, and a Turkish study (97 CRSwNP, 95 controls) that reported an OR of 3.68 (95% CI, 1.27-10.7; $P = .016$) with the same allele.¹²⁷ Another Turkish candidate gene study reported an association between CRSwNP and patients who were heterozygotes at this SNP (for GA haplotype: OR, 3.2; 95% CI=1.4-71; $P = .004$) but found no significant relationship between CRSwNP and the AA haplotype ($P > .05$)¹²⁶, a finding that remains difficult to interpret. Some (but not all) functional studies of this polymorphism have shown an association between the A allele and elevated TNF production.¹²⁸⁻¹³⁰ Studies of Quebecois (n=206 CRS, 196 controls)¹³¹ and Japanese (38 CRS, 35 controls)⁵⁰ patients found no significant association with CRS for this SNP. Thus, the relationship between CRSwNP and this putative risk allele in the *TNF* promoter remains open to debate. Furthermore, despite numerous reports of disease phenotypes associated with this SNP, a functional correlate has not yet been established. It is possible that these reported associated SNPs are in LD with the causal variant or affect the transcription of the gene of interest (i.e., they are eQTLs).

The SNP rs17561 in the coding region of *IL1A*, which encodes the cytokine IL-1 alpha, has been linked to autoimmunity¹³², in addition to CRS. However, the candidate gene studies of CRS conflict regarding the presumed risk allele for CRS.^{126, 131, 133} Furthermore, these studies have been limited to patients of predominantly European ancestry. Mfuna Endam et al.¹³¹ found the minor allele T of rs17561 to be more frequent among Quebecois CRS patients compared to controls (OR, 1.48; 95% CI, 1.06-2.05; $P = .02$). Similarly, a Turkish study of 82 CRSwNP patients and 106 controls reported a trend for the TT genotype to be

more prevalent among patients with CRSwNP compared to controls (OR, 5.8; 95% CI, 3.1–11.0; $P = .05$).¹²⁶ However, a Finnish study of 35 asthmatics with CRSwNP and 210 asthmatics without CRSwNP found the prevalence of the TT genotype to be virtually identical between patients with and without CRSwNP (8.6% and 8.2% respectively).¹³³ Instead, these investigators found the GG genotype associated with CRSwNP; the GG genotype was identified in 68.6% of asthmatics with CRSwNP, compared to 40.4% of asthmatics without CRSwNP (OR, 2.73; 95% CI, 1.40–5.32; $P = .005$).¹³³ These contradictory results need to be clarified. Additionally, although variation at this SNP is known to influence the amino acid sequence of IL-1 alpha, differential levels of IL1 alpha expression have yet to be associated with this SNP. Studies of polymorphisms in IL-1 beta (*IL1B*) have also yielded conflicting results,^{51, 95, 126, 131, 134, 135}

CRS and Genes Involved in Sinonasal Tissue Remodeling

Aberrant remodeling of sinonasal epithelial tissue has been identified in patients with CRS of varied ancestral origin.^{8, 136–140} For example, sinonasal tissue levels of transforming growth factor-beta (TGF-beta) appear to be higher in CRSsNP and lower in CRSwNP compared to controls.^{8, 136–138} Levels of matrix metalloproteinases (MMPs; which act on extracellular matrix components) and tissue inhibitors of MMPs (TIMPs) also differ in CRSwNP and CRSsNP sinonasal tissue compared to control tissue.^{8, 138, 139} Additionally, fibrinolytic components such as plasminogen activator inhibitor-1 (PAI-1) and tissue plasminogen activator (t-PA) are known to mediate remodeling and fibrosis,^{140–142} and they have been implicated in diseases such as asthma and CRS.¹⁴³

Based on these data, these molecules appear as attractive targets for study of genetic variation in CRS. However, conclusions from this body of literature remain elusive due to heterogeneity of phenotype, sparse replication of positive findings, unclear functional relevance of implicated SNPs, and limited power due to small sample size. MMP9 protein levels are reported to be abnormal in sinonasal tissue¹³⁹ and two candidate gene studies have implicated *MMP9* in CRS pathogenesis.^{144, 145} A Taiwanese study of 203 CRSwNP patients (characterized by history, CT, and endoscopy) and 730 controls by Wang et al.¹⁴⁴ found a functional promoter SNP (-1562 C > T) of *MMP9* (rs3918242) to be associated with CRSwNP (increased risk with minor allele T: OR_{dominant model}, 1.62, $P_{dominant model} = .023$; OR_{additive model}, 1.60, $P_{additive model} = .012$). A Turkish study of 93 CRSwNP patients and 115 controls found this SNP was associated with CRSwNP only among their AIA subgroup ($n=13$, $P = .014$, OR not specified)¹⁴⁵; the proportion of AIA patients in the Taiwanese study was not specified.¹⁴⁴ This ambiguity highlights the importance of rigorous phenotyping in study design, even within a population of well-characterized CRSwNP patients.

Additionally, two studies have examined genetic variation in *TGFB1* among patients with CRS.^{59, 95} A significant association was found between CRSsNP and rs11466315 in a Korean study by Kim et al.⁵⁹ involving 203 AIA patients (including 72 patients with CRSwNP and 59 patients with CRSsNP), 324 ATA patients (including 10 patients with CRSwNP and 179 patients with CRSsNP), and 456 control patients. Confirmation of CRS was limited to rhinoscopy and paranasal sinus x-ray.⁵⁹ In a secondary analysis of the AIA subgroup, CRSsNP was more frequent among patients with the CT or TT genotypes at rs11466315 compared to those with the CC genotype (87.1% vs. 68.2%, $P = .012$).⁵⁹ Although other studies have identified increased expression of local TGF-beta in the sinonasal tissue of patients with CRSsNP,^{8, 136–138} this study found the implicated CT and TT genotypes of rs11466315 associated with lower serum levels of TGF-beta in this study (levels of TGF-beta in the sinonasal tissue of patients in this study were not reported).⁵⁹ In contrast to the positive association between rs11466315 and CRSsNP among patients with AIA in this study, these investigators found no significant association between variation in

TGFB1 and CRSsNP in ATA subjects, nor between *TGFB1* and CRSwNP.⁵⁹ Similarly, Bernstein et al.⁹⁵ found no association between rs11466315 and CRSwNP in their study of 179 CRSwNP patients and 153 controls.

Despite studies of sinonasal tissue suggesting a role for other tissue remodeling components in the development of CRS including MMP2, t-PA, and PAI-1,^{138, 139, 141, 142} studies of *MMP2* and *SERPINE1* (a.k.a. *PAI1*) have not shown associations between CRS and variation in these genes.^{13, 55} The relationship between CRS and genetic variation in *MMP2* has been examined in one Taiwanese study of 136 CRSwNP and 136 control patients, with no significant associations found; the phenotyping of CRS cases in this study was excellent, consisting of history, CT, and endoscopy.⁵⁵ Similarly, in a US study, de Alarcon et al.¹³ found no association ($P > .05$) between *SERPINE1* and the phenotypes of CHES (defined as CRS with evidence of eosinophilia in sinonasal tissue) or CIS (defined as CRS without evidence for CHES). However, this study may have been underpowered (n=51 CHES patients, n=16 CIS patients, n=66 controls), perhaps explaining why a subset analysis of CRSwNP and CRSsNP was not performed.¹³

CRS and Genes Involved in Arachidonic Acid Metabolism

Arachidonic acid metabolism is disrupted in AERD (also known as Samter's triad), in which CRSwNP is one of the diagnostic criteria along with aspirin sensitivity and asthma.^{146, 147} Indeed, recent evidence implicates aberrant arachidonic acid metabolism in CRSwNP even outside the syndrome of AERD.^{148, 149} A few studies have investigated whether genetic variation in the arachidonic acid pathway is associated with CRS. Although this work is noteworthy for its focus on a mechanism known to be relevant in (at least a subset of) patients with CRSwNP, it has been limited by heterogeneity of phenotype, limited study power, and lack of replicated findings. A candidate gene study of CHES and CIS patients in the US reported the minor allele C in a leukotriene C₄ synthase (*LTC4S*) promoter SNP (rs730012) as more frequent in CHES patients than controls (AF for C allele in CHES=0.31, in controls=0.19; $P = .04$).¹³ The frequency of nasal polypsis among patients in this study was not specified, nor was the frequency of nasal polypsis among patients with CHES.¹³ Among patients with CIS in this study, the AF for the C allele at rs730012 was 0.27, but this did not differ significantly from the AF among controls (0.19, $P > .05$).¹³ A Spanish study found the C allele at this SNP was significantly more common among atopic CRSwNP patients compared to controls (atopic CRSwNP, n=74, C allele AF=0.34; controls, n=245, AF=0.24; $P = .033$ for comparison).¹⁰¹ In contrast, Al Shemari et al.¹⁵⁰ failed to replicate the association between *LTC4S* and CRS in Quebecois patients (75% CRSwNP, 25% CRSsNP, 12% RARS); the frequency of CHES among these patients was not examined. Moreover, these authors acknowledged their study lacked power to detect polymorphisms conferring a relative risk of 2.0 or less for disease, a major issue because effect sizes for complex diseases tend to occur in this range.¹⁵⁰ This study also found no significant association between CRS and variation in other genes involved in arachidonic acid metabolism (arachidonate 5-lipoxygenase [*ALOX5*], arachidonate 5-lipoxygenase-activating protein [*ALOX5AP*], cysteinyl leukotriene receptor 1 [*CYSLTR1*] and cysteinyl leukotriene receptor 2 [*CYSLTR2*]), but these results must be interpreted in light of the study's limitations.¹⁵⁰ Findings from a recent Spanish study (241 CRSwNP, 245 controls) support lack of a relationship between *CYSLTR1* and CRSwNP.¹⁰¹ This study did identify a combination of particular genotypes at specific alleles of the gene for the prostaglandin D₂ receptor (*PTGDR*) that was significantly associated with CRSwNP and AERD (Supplementary Table).¹⁰¹ Another recent publication reported an association between the gene encoding cyclooxygenase-2 (*PTGS2*) and CRSwNP (-765G/C: OR, 6.05; 95% CI, 4.15-8.83; $P < .001$) among 195 CRSwNP patients and 200 matched controls.¹⁰²

Other candidate gene studies in CRS

An assortment of other molecules has been examined in genetic studies of CRS subjects, but, as with the work discussed so far, this literature suffers from similar challenges of limited statistical power, few replicated findings, and little knowledge of the functional importance of implicated SNPs. Only one candidate gene study of antioxidant glutathione-S-transferase (GST) enzymes has found a positive association between a null mutation in the gene for glutathione S-transferase T1 (*GSTT1*) and CRSwNP in a Turkish population of 75 CRSwNP patients and 167 controls (OR, 2.03; 95% CI, 1.03-4.011; $P < .05$)⁵⁴; other studies using another Turkish sample (98 CRSwNP, 102 controls) and a German population (69 CRSwNP, 49 CRSsNP, 52 controls) did not find a significant association with variation in this gene.^{52, 151} None of these studies detected an association in CRSwNP or CRSsNP with genetic variation in genes coding for other enzymes in this pathway (glutathione S-transferase M1 [*GSTM1*], glutathione S-transferase π [*GSTP1*]), but these studies were likely underpowered.^{52, 54, 151} A candidate gene approach has identified an association between CRS and variation in the gene for the adrenergic beta-2 receptor (*ADRB2*),¹⁵² which has been linked to AERD, asthma exacerbations, and bronchodilator response among patients with asthma.¹⁵³⁻¹⁵⁵ A recent study of Chinese patients (306 CRSwNP, 332 CRSsNP, 315 controls) has identified an association between CRSwNP, CRSsNP, and Ring1 and YY1 binding protein (*RYBP*) (CRSwNP: OR, 2.76, $P = 3.24 \times 10^{-6}$; CRSsNP: OR, 2.45, $P = 4.12 \times 10^{-5}$); these findings remained significant after correction for multiple statistical testing.⁹¹ RYBP is a pleomorphic molecule that binds transcription factors and apoptotic mediators⁹¹; its direct effect on CRS pathogenesis remains unclear. All these results, while intriguing, require replication.

Insights from Genome-wide Approaches: Linkage Studies and GWAS

Whereas the majority of studies regarding genetic susceptibility in CRS have utilized candidate gene approaches, two groups have employed genome-wide study designs (i.e., linkage analysis and pooling-based GWAS [pGWAS]) to answer this question.^{28, 41, 42} Using a hypothesis-independent approach, these studies have provided additional support for genes previously suspected in CRS (e.g., *CFTR*) and also identified numerous genes heretofore unexplored in CRS. Despite these valuable contributions, the majority of findings await replication and functional studies.

To date, one linkage study of CRS has been published. Pinto et al.⁴¹ investigated the genetics of CRS in a founder population with normalized environmental influences; the largest linkage peak in this study was located at chromosome 7q31.1-7q32.1 ($P = .0023$), a region that includes the *CFTR* locus. However, additional genotyping of 38 mutations in the *CFTR* gene did not reveal any variation accounting for this linkage signal.⁴¹ Thus, this study was unable to determine the causal variant underlying this linkage signal, likely due to the challenges of extensive variation within the *CFTR* gene, as well as the large number of other candidate loci in this region.⁴¹

Two pGWAS of CRS patients have been published.^{28, 42} Unlike traditional GWAS, this approach relies on pooled DNA from multiple subjects for analysis, which reduces the genotyping cost.²⁸ The first pGWAS involved 210 patients with “severe CRS” (including CRSwNP and CRSsNP) and 189 controls from Quebec. This study identified novel associations between CRS and variation in genes involved in basement membrane formation: laminin, alpha 2 (*LAMA2*); laminin, beta 1 (*LAMB1*); and the enzyme acyloxyacyl hydrolase (*AOAH*).²⁸ The *AOAH* gene is particularly interesting because it contributes to host defense against bacterial lipopolysaccharide and has also been linked to asthma.^{156, 157} Subsequently, these investigators have replicated an association between *AOAH* (rs4504543) and CRSsNP in a candidate gene study of Chinese patients (OR, 0.30; P

$= 8.11 \times 10^{-11}$); this association remained statistically significant after correction for multiple statistical testing.⁹¹ There was no association between *AOAH* and CRSwNP.⁹¹

Besides *AOAH*, this pGWAS found CRS was significantly associated with polymorphisms in genes encoding a variety of molecules, including: mitochondrial prolyl-tRNA synthetase 2 (*PARS2*); neuron navigator 3 (*NAV3*); calcium channel, voltage-dependent, T type, alpha 1I subunit (*CACNA1I*); chromosome 8 open reading frame 79 (*KIAA1456*); muscle, skeletal, receptor tyrosine kinase (*MUSK*); thyroid hormone receptor interactor 12 (*TRIP12*); and methionine sulfoxide reductase A (*MSRA*).²⁸

A second pGWAS from Quebec studied 206 CRS patients (CRSwNP and CRSsNP combined) and 196 controls and found an association between CRS and variation in the gene encoding epithelial tumor protein p73 (*TP73*).⁴² In particular, AA homozygotes at the *TP73* SNP rs3765731 had a seven-fold lower risk of CRS compared to GG homozygotes (OR: 0.14).⁴² A possible role for *TP73* in CRS is supported by separate studies that have reported abnormal expression of the p73 protein in the sinonasal tissue of patients with CRSwNP.^{42, 158} The potential relationship between CRSwNP and *TP73* requires additional replication and functional validation of the implicated SNP, as do results from the initial pGWAS from this group.

Future Directions

The existing literature regarding the genetics of CRS has provided preliminary evidence of a role for genetic effects in CRS pathogenesis. To date, the most replicated gene in CRS is *CFTR*; however, research on this gene has been limited primarily to patients of European ancestry, and the majority of studies have investigated only the most frequent mutations associated with the CF phenotype in this population. Future studies utilizing gene sequencing of *CFTR* (and examining populations of other ancestries) may yield additional insights, though the large amount of variation in this gene may prove a challenge to such studies. It is also possible that many rare variants in *CFTR* are involved, in which case a gene-based approach that analyzes all variation within one gene may be required.

There is a need for rigorously designed candidate gene studies of CRS. The ability to draw conclusions from existing candidate gene studies of CRS is hampered by the methodological constraints related to phenotyping and power. For example, many studies that reported negative findings were underpowered, so the genes examined cannot be excluded as candidates for involvement in CRS. Studies that reported positive associations often had limited phenotyping (e.g., the unclear importance of AERD in the association between CRS and *HLA-DRB1*04*^{45, 46}) or included a heterogeneous phenotype (e.g., CRSwNP, CRSsNP, and RARS combined¹⁵⁰). In some sense, this could be an advantage because SNPs identified might be involved in all these disease categories, but there is also no ability to determine SNPs affecting individual disease subphenotypes. Such issues complicate the interpretation of intriguing associations, such as the unspecified role of atopy in the reported association between CRS, AIA, and the *IL13* promoter SNPs rs1881457 and rs1800925.⁵⁸

Additionally, there is a great need for replication studies so we can determine which of these signals are worth investing further effort into understanding and which are spurious. Future efforts to replicate findings might target SNPs of genes implicated in sinonasal and related airways disease (e.g., *TGFB1*, *TP73*, *SERPINA1*, *AOAH*, and members of the *NOS* family).^{8, 92, 100, 136-138, 156-158} Of the few replicated genes in the literature for CRS, *IL33* deserves mention because it was identified through an exceptional study design: among other strengths, this study comprised both a discovery and replication cohort, adjusted for multiple statistical testing in the study, and accounted for atopy, asthma, and aspirin sensitivity in the analysis.¹¹⁴ Remaining to be explored are the functional significance of the

implicated *IL33* SNP (rs3939286) and investigation of the possibility of eQTL or LD as an explanation for the association. However, *IL33* appears worthy of replication in other populations as an exciting candidate gene for CRS. Lastly, unbiased study designs will lead to identification of novel targets that might provide new directions for CRS research.

Accounting for possible gene-environment interactions in the development of CRS remains largely an unexplored frontier. Adequate measurement of (and adjustment for) atopy has not occurred in many published candidate gene studies of CRS. Environmental toxins (e.g., tobacco smoke, particulate air pollutants) may be relevant in CRS, but these relationships remain largely unknown.¹ Several studies have examined the role of tobacco smoke in CRS: for example, CRS may be more prevalent among tobacco smokers, and postoperative outcomes for smokers undergoing sinus surgery may be worse than for nonsmokers.¹ This relationship may be mediated by effects of tobacco smoke on ciliary function or biofilm formation.¹ Although the importance of tobacco smoke (and other environmental toxins) in the development of CRS is uncertain, future genetics studies that account for potential gene-environment interactions in CRS may detect genes pertinent to CRS under certain circumstances.

What are the barriers to progress in CRS genetics? First and foremost, careful, prospective collection of sizable cohorts of well-characterized subjects with disease and controls is needed. The need for expensive, time consuming, and detailed phenotyping will likely require collaboration among multiple centers and the exploitation of clinical data warehouses and linked archived samples, if available. Detailed characterization of phenotypic features (e.g., nasal polypsis) and other potential comorbid conditions (e.g., asthma, atopy, and AERD) that may suggest distinct pathogenic mechanisms is also important. Interdisciplinary research teams (of both clinical and basic scientists) are needed to integrate the complexities of clinical information and the experimental and analytic challenges inherent in complex-trait genetics. Due to the myriad of environmental and other non-genetic influences that likely affect disease expression, approaches that take advantage of cell-culture based intermediate phenotypes for disease may allow for enhanced power to detect relevant effects.

A reluctance of funding agencies to support such large-scale prospective studies has been a major barrier to using traditional GWAS to study CRS. GWAS have proved useful for understanding complex disease traits and have produced a number of novel insights into disease biology (for example, regarding the potential importance of ORM1-like 3 [*ORMDL3*] in asthma²⁴). GWAS are not without shortcomings, including a limited ability to interrogate rare variants, the inability to account for a significant portion of heritability for many traits, and logistical issues related to sample collection and cost.⁴³ However, given the advances produced by GWAS in other disease phenotypes^{23, 24}, this methodology merits attention and funding in the study of CRS.

With the advent of other technologies that are revolutionizing the search for genetic variation underlying complex diseases (e.g., epigenomics, exome and whole genome sequencing, transcriptomics) and which are now feasible in terms of time, analysis, and cost, alternative strategies that supplant GWAS can be employed for identification of genes involved in CRS biology. Epigenomics, the systematic study of epigenetic changes (e.g., DNA methylation, histone modification) may generate new discoveries regarding how gene dysregulation may affect CRS, but investigators are only beginning to utilize this methodology to study CRS.^{159, 160} Whole genome sequencing studies of small kindreds could be performed by identifying families with multiple family members with CRS. Such studies would potentially identify variants that could be the subject of testing for association in larger cohorts. Indeed, whole genome sequencing has proved to be feasible, useful, and

relatively low cost. This approach has the ability to catalogue complete information on genetic variation, thereby enhancing the ability to detect relevant variants. The tools required for analysis of such data are becoming increasingly available.

Lastly, functional analysis of genetic variation associated with CRS is critical and currently lacking. If genetic studies of CRS are to provide mechanistic insight and, ultimately, utility in prevention, risk stratification, or therapeutic target identification, specific knowledge of how variation affects regulatory or protein function is crucial. Given the disease burden of CRS, the translational potential is high and deserves to be a research priority. Greater investment in research in this area would create a climate for the study of CRS comparable to the quality and advancement of related diseases such as asthma and atopy.

Conclusions

We have attempted to comprehensively review the current literature regarding the genetics of CRS, and have identified what we believe to be the most promising associations, albeit with caveats in the available data. Studies suggest genetic variation in *CFTR*, *HLA* genes, innate immune genes, inflammatory mediators (including *IL13* and *IL33*), and genes involved in tissue remodeling and arachidonic acid metabolism may contribute to the pathogenesis of CRS. However, interpretation of existing results is limited by the many challenges inherent to this line of inquiry including study design issues, sparse replication, few functional correlates, and minimal consideration of LD and eQTL as alternative explanations for reported associations. We believe there is a critical need for large, well-designed studies of the genetic susceptibility to CRS. We may be able to glean relevant information from genetic studies of related diseases of the airway, both in terms of methodological approaches and in terms of candidate genes implicated in other airway pathology. Combining creative approaches with recent advances in genetic technologies (e.g., exome sequencing, whole genome sequencing, or epigenomics) will set the stage for great progress in understanding CRS in the near future.

Acknowledgments

JMP was supported by K23 AG036762 and T35 AG029795 from the National Institute on Aging, the Institute for Translational Medicine (KL2RR025000, UL1RR024999) at The University of Chicago, the Allergy, Asthma and Immunology Education and Research Trust (ARTrust™) and the McHugh Otolaryngology Research Fund. JH was supported by the Ernest S. Bazley Trust and the Allergy, Asthma and Immunology Education and Research Trust (ARTrust™). PCA was supported by AI082984 from the National Institute of Allergy and Infectious Diseases and the Ernest S. Bazley Trust. RPS was supported by R37 HL068546 and R01 HL078860 from the National Heart, Lung, and Blood Institute, and the Ernest S. Bazley Trust. MGH received institutional support from Northwestern University. The authors declare no conflicts of interest relevant to this work. We thank Carole Ober, Ph.D., Blum-Riese Professor, Interim Chair, Departments of Human Genetics and Obstetrics and Gynecology at The University of Chicago for useful comments.

Abbreviations

ADRB2	gene that encodes adrenergic beta-2 receptor
AERD	Aspirin-exacerbated respiratory disease
AF	Allele frequency
AFRS	Allergic fungal rhinosinusitis
AIA	Aspirin-intolerant asthma
AOAH	gene that encodes acyloxyacyl hydrolase
ATA	Aspirin-tolerant asthma

CHES	Chronic hyperplastic eosinophilic sinusitis
CIS	Chronic inflammatory sinusitis
CF	Cystic fibrosis
CFTR	Cystic Fibrosis Transmembrane Conductance Regulator
CFTR	gene that encodes Cystic Fibrosis Transmembrane Conductance Regulator
CI	Confidence interval
CRS	Chronic rhinosinusitis
CRSsNP	Chronic rhinosinusitis without nasal polyps
CRSwNP	Chronic rhinosinusitis with nasal polyps
CT	Computed tomography
eQTL	Expression quantitative trait locus
GST	Glutathione-S-transferase
GWAS	Genome-wide association study
HLA	Human Leukocyte Antigen
IL	Interleukin
IL1A	gene that encodes interleukin-1 alpha
IL1B	gene that encodes interleukin-1 beta
IL1RL1	Interleukin-1 receptor-like 1
IL1RL1	gene that encodes interleukin-1 receptor-like 1
IRAK4	Interleukin-1 receptor-associated kinase 4
IRAK4	gene that encodes interleukin-1 receptor-associated kinase 4
LD	Linkage disequilibrium
LTC4S	gene that encodes leukotriene C ₄ synthase
MCP	Monocyte chemoattractant protein
MET	met proto-oncogene
MET	gene that encodes met proto-oncogene
MMP	Matrix metalloproteinase
MMP2	gene that encodes matrix metalloproteinase 2
MMP9	gene that encodes matrix metalloproteinase 9
NFAT1	Nuclear factor of activated T cells 1
NFKB	Nuclear factor- κ B transcription factor
NOS	Nitric oxide synthase
NOS1	gene that encodes nitric oxide synthase 1 (neuronal)
NOS2A	gene that encodes nitric oxide synthase 2, inducible
NOS1AP	gene that encodes nitric oxide synthase 1 (neuronal) adaptor protein
OR	Odds ratio

PAI-1	Plasminogen activator inhibitor-1
PAI1	gene that encodes plasminogen activator inhibitor-1
pGWAS	Pooling-based GWAS
RARS	Recurrent acute rhinosinusitis
RYBP	Ring1 and YY1 binding protein
RYBP	gene that encodes Ring1 and YY1 binding protein
SERPINA1	gene that encodes serpin peptidase inhibitor, clade A (alpha-1 antiproteinase, antitrypsin), member 1
SNP	Single nucleotide polymorphism
t-PA	Tissue plasminogen activator
TGF-beta	Transforming growth factor-beta
TGFB1	gene that encodes transforming growth factor-beta
Th	T helper
TIMP	Tissue inhibitor of matrix metalloproteinase
TLR	Toll-like receptor
TNF	Tumor necrosis factor
TNF	gene that encodes tumor necrosis factor
TP73	gene that encodes tumor protein p73
US	United States
UK	United Kingdom
VNTR	variable number tandem repeats

References

1. Fokkens WJ, Lund VJ, Mullol J, Bachert C, Alobid I, Baroody F, et al. European Position Paper on Rhinosinusitis and Nasal Polyps 2012. *Rhinol Suppl.* 2012; 3:1–298. p preceding table of contents.
2. Meltzer EO, Hamilos DL, Hadley JA, Lanza DC, Marple BF, Nicklas RA, et al. Rhinosinusitis: developing guidance for clinical trials. *J Allergy Clin Immunol.* 2006; 118:S17–61. [PubMed: 17084217]
3. Slavin RG, Spector SL, Bernstein IL, Kaliner MA, Kennedy DW, Virant FS, et al. The diagnosis and management of sinusitis: a practice parameter update. *J Allergy Clin Immunol.* 2005; 116:S13–47. [PubMed: 16416688]
4. Pleis JR, Ward BW, Lucas JW. Summary health statistics for U.S. adults: National Health Interview Survey, 2009. *Vital Health Stat.* 2010; 10:1–207.
5. Bhattacharyya N. Incremental health care utilization and expenditures for chronic rhinosinusitis in the United States. *Ann Otol Rhinol Laryngol.* 2011; 120:423–7. [PubMed: 21859049]
6. Gliklich RE, Metson R. The health impact of chronic sinusitis in patients seeking otolaryngologic care. *Otolaryngol Head Neck Surg.* 1995; 113:104–9. [PubMed: 7603703]
7. Meltzer EO, Hamilos DL. Rhinosinusitis diagnosis and management for the clinician: a synopsis of recent consensus guidelines. *Mayo Clin Proc.* 2011; 86:427–43. [PubMed: 21490181]
8. Hsu J, Peters AT. Pathophysiology of chronic rhinosinusitis with nasal polyp. *Am J Rhinol.* 2011; 25:285–90.

9. Kern RC, Conley DB, Walsh W, Chandra R, Kato A, Tripathi-Peters A, et al. Perspectives on the etiology of chronic rhinosinusitis: an immune barrier hypothesis. *Am J Rhinol.* 2008; 22:549–59. [PubMed: 18786300]
10. Bachert C, Gevaert P, Holtappels G, Johansson SG, van Cauwenberge P. Total and specific IgE in nasal polyps is related to local eosinophilic inflammation. *J Allergy Clin Immunol.* 2001; 107:607–14. [PubMed: 11295647]
11. Van Zele T, Claeys S, Gevaert P, Van Maele G, Holtappels G, Van Cauwenberge P, et al. Differentiation of chronic sinus diseases by measurement of inflammatory mediators. *Allergy.* 2006; 61:1280–9. [PubMed: 17002703]
12. Van Crombruggen K, Zhang N, Gevaert P, Tomassen P, Bachert C. Pathogenesis of chronic rhinosinusitis: inflammation. *J Allergy Clin Immunol.* 2011; 128:728–32. [PubMed: 21868076]
13. de Alarcon A, Steinke JW, Caughey R, Berekzi E, Hise K, Gross CW, et al. Expression of leukotriene C4 synthase and plasminogen activator inhibitor 1 gene promoter polymorphisms in sinusitis. *Am J Rhinol.* 2006; 20:545–9. [PubMed: 17063752]
14. Orlandi RR, Thibault SL, Ferguson BJ. Microarray analysis of allergic fungal sinusitis and eosinophilic mucin rhinosinusitis. *Otolaryngol Head Neck Surg.* 2007; 136:707–13. [PubMed: 17478202]
15. Jacob A, Faddis BT, Chole RA. Chronic bacterial rhinosinusitis: description of a mouse model. *Arch Otolaryngol Head Neck Surg.* 2001; 127:657–64. [PubMed: 11405864]
16. Lindsay R, Slaughter T, Britton-Webb J, Mog SR, Conran R, Tadros M, et al. Development of a murine model of chronic rhinosinusitis. *Otolaryngol Head Neck Surg.* 2006; 134:724–30. discussion 31–2. [PubMed: 16647523]
17. Kim DW, Khalmuratova R, Hur DG, Jeon SY, Kim SW, Shin HW, et al. Staphylococcus aureus enterotoxin B contributes to induction of nasal polypoid lesions in an allergic rhinosinusitis murine model. *Am J Rhinol Allergy.* 2011; 25:e255–61. [PubMed: 22185735]
18. Payne SC, Han JK, Huyett P, Negri J, Kropf EZ, Borish L, et al. Microarray analysis of distinct gene transcription profiles in non-eosinophilic chronic sinusitis with nasal polyps. *Am J Rhinol.* 2008; 22:568–81. [PubMed: 19178793]
19. Platt M, Metson R, Stankovic K. Gene-expression signatures of nasal polyps associated with chronic rhinosinusitis and aspirin-sensitive asthma. *Curr Opin Allergy Clin Immunol.* 2009; 9:23–8. [PubMed: 19532090]
20. Seshadri S, Lin DC, Rosati M, Carter RG, Norton JE, Suh L, et al. Reduced expression of antimicrobial PLUNC proteins in nasal polyp tissues of patients with chronic rhinosinusitis. *Allergy.* 2012; 67:920–8. [PubMed: 22676062]
21. Zander KA, Saavedra MT, West J, Scapa V, Sanders L, Kingdom TT. Protein microarray analysis of nasal polyps from aspirin-sensitive and aspirin-tolerant patients with chronic rhinosinusitis. *Am J Rhinol Allergy.* 2009; 23:268–72. [PubMed: 19490800]
22. Upton DC, Welham NV, Kuo JS, Walker JW, Pasic TR. Chronic rhinosinusitis with nasal polyps: a proteomic analysis. *Ann Otol Rhinol Laryngol.* 2011; 120:780–6. [PubMed: 22279949]
23. Cho JH, Gregersen PK. Genomics and the multifactorial nature of human autoimmune disease. *N Engl J Med.* 2011; 365:1612–23. [PubMed: 22029983]
24. Ober C, Yao TC. The genetics of asthma and allergic disease: a 21st century perspective. *Immunol Rev.* 2011; 242:10–30. [PubMed: 21682736]
25. Martin JA, Wang Z. Next-generation transcriptome assembly. *Nat Rev Genet.* 2011; 12:671–82. [PubMed: 21897427]
26. Ku CS, Naidoo N, Wu M, Soong R. Studying the epigenome using next generation sequencing. *J Med Genet.* 2011; 48:721–30. [PubMed: 21825079]
27. Johnson CH, Gonzalez FJ. Challenges and opportunities of metabolomics. *J Cell Physiol.* 2011
28. Bosse Y, Bacot F, Montpetit A, Rung J, Qu HQ, Engert JC, et al. Identification of susceptibility genes for complex diseases using pooling-based genome-wide association scans. *Hum Genet.* 2009; 125:305–18. [PubMed: 19184112]
29. Drake-Lee A. Nasal polyps in identical twins. *J Laryngol Otol.* 1992; 106:1084–5. [PubMed: 1487667]

30. Grunberg H. The inheritance of a disease of the accessory nasal cavities. *J Genetics*. 1934; 29:367–74.
31. Cohen NA, Wideltitz JS, Chiu AG, Palmer JN, Kennedy DW. Familial aggregation of sinonasal polyps correlates with severity of disease. *Otolaryngol Head Neck Surg*. 2006; 134:601–4. [PubMed: 16564380]
32. Delagrang A, Gilbert-Dussardier B, Burg S, Allano G, Gohler-Desmonts C, Lebreton JP, et al. Nasal polyposis: is there an inheritance pattern? A single family study. *Rhinology*. 2008; 46:125–30. [PubMed: 18575014]
33. Qu SH, Li TY, Li M, Shi JB, Wen WP, Wen WH. [Genetic epidemiologic study on nasal polyps]. *Zhonghua Er Bi Yan Hou Tou Jing Wai Ke Za Zhi*. 2007; 42:608–11. [PubMed: 17944211]
34. Lockey RF, Rucknagel DL, Vanselow NA. Familial occurrence of asthma, nasal polyps and aspirin intolerance. *Ann Intern Med*. 1973; 78:57–63. [PubMed: 4682309]
35. Nakamura O. Pediatric chronic sinusitis and genetic factors. *Oto-Rhino-Laryngology (Tokyo)*. 1974:25–43.
36. Greisner WA 3rd, Settipane GA. Hereditary factor for nasal polyps. *Allergy Asthma Proc*. 1996; 17:283–6. [PubMed: 8922148]
37. Noone PG, Leigh MW, Sannuti A, Minnix SL, Carson JL, Hazucha M, et al. Primary ciliary dyskinesia: diagnostic and phenotypic features. *Am J Respir Crit Care Med*. 2004; 169:459–67. [PubMed: 14656747]
38. Armengot M, Escribano A, Carda C, Sanchez C, Romero C, Basterra J. Nasal mucociliary transport and ciliary ultrastructure in cystic fibrosis. A comparative study with healthy volunteers. *Int J Pediatr Otorhinolaryngol*. 1997; 40:27–34. [PubMed: 9184975]
39. Davila I, Mullol J, Ferrer M, Bartra J, del Cuvillo A, Montoro J, et al. Genetic aspects of allergic rhinitis. *J Investig Allergol Clin Immunol*. 2009; 19(Suppl 1):25–31.
40. Braunstahl GJ. The unified immune system: respiratory tract-nasobronchial interaction mechanisms in allergic airway disease. *J Allergy Clin Immunol*. 2005; 115:142–8. [PubMed: 15637561]
41. Pinto JM, Hayes MG, Schneider D, Naclerio RM, Ober C. A genomewide screen for chronic rhinosinusitis genes identifies a locus on chromosome 7q. *Laryngoscope*. 2008; 118:2067–72. [PubMed: 18622306]
42. Tournas A, Mfunu L, Bosse Y, Filali-Mouhim A, Grenier JP, Desrosiers M. A pooling-based genome-wide association study implicates the p73 gene in chronic rhinosinusitis. *J Otolaryngol Head Neck Surg*. 2010; 39:188–95. [PubMed: 20211107]
43. Goldstein DB. Common genetic variation and human traits. *N Engl J Med*. 2009; 360:1696–8. [PubMed: 19369660]
44. Wang X, Kim J, McWilliams R, Cutting GR. Increased prevalence of chronic rhinosinusitis in carriers of a cystic fibrosis mutation. *Arch Otolaryngol Head Neck Surg*. 2005; 131:237–40. [PubMed: 15781764]
45. Ramirez-Anguiano J, Yamamoto-Furusho JK, Barquera R, Beltran O, Granados J. Association of HLA-DR3 and HLA-DR4 with sinonasal polyposis in Mexican Mestizos. *Otolaryngol Head Neck Surg*. 2006; 135:90–3. [PubMed: 16815190]
46. Keles B, Cora T, Acar H, Arbag H, Inan Z, Ozturk K, et al. Evaluation of HLA-A, -B, -Cw, and -DRB1 alleles frequency in Turkish patients with nasal polyposis. *Otolaryngol Head Neck Surg*. 2008; 139:580–5. [PubMed: 18922348]
47. Pascual M, Sanz C, Isidoro-Garcia M, Davila I, Moreno E, Laffond E, et al. (CCTTT)n polymorphism of NOS2A in nasal polyposis and asthma: a case-control study. *J Investig Allergol Clin Immunol*. 2008; 18:239–44.
48. Sachse F, Becker K, Rudack C. Incidence of staphylococcal colonization and of the 753Q Toll-like receptor 2 variant in nasal polyposis. *Am J Rhinol Allergy*. 2010; 24:e10–3. [PubMed: 20109309]
49. Park CS, Cho JH, Park YJ. Toll-like receptor 2 gene polymorphisms in a Korean population: association with chronic rhinosinusitis. *Otolaryngol Head Neck Surg*. 2011; 144:96–100. [PubMed: 21493395]
50. Takeuchi K, Majima Y, Sakakura Y. Tumor necrosis factor gene polymorphism in chronic sinusitis. *Laryngoscope*. 2000; 110:1711–4. [PubMed: 11037831]

51. Cheng YK, Lin CD, Chang WC, Hwang GY, Tsai SW, Wan L, et al. Increased prevalence of interleukin-1 receptor antagonist gene polymorphism in patients with chronic rhinosinusitis. *Arch Otolaryngol Head Neck Surg.* 2006; 132:285–90. [PubMed: 16549749]
52. Arbag H, Cora T, Acar H, Ozturk K, Sari F, Ulusoy B. Lack of association between the glutathione-s-transferase genes (GSTT1 and GSTM1) and nasal polyposis. *Rhinology.* 2006; 44:14–8. [PubMed: 16550944]
53. BuSaba NY, Cunningham MJ. Connexin 26 and 30 genes mutations in patients with chronic rhinosinusitis. *Laryngoscope.* 2008; 118:310–3. [PubMed: 17989577]
54. Ozcan C, Tamer L, Ates NA, Gorur K. The glutathione-S-transferase gene polymorphisms (Gstt1, Gstm1, and Gstp1) in patients with non-allergic nasal polyposis. *Eur Arch Otorhinolaryngol.* 2010; 267:227–32. [PubMed: 19701760]
55. Wang LF, Chien CY, Kuo WR, Tai CF, Juo SH. Matrix metalloproteinase-2 gene polymorphisms in nasal polyps. *Arch Otolaryngol Head Neck Surg.* 2008; 134:852–6. [PubMed: 18711060]
56. Meltzer EO, Hamilos DL, Hadley JA, Lanza DC, Marple BF, Nicklas RA, et al. Rhinosinusitis: establishing definitions for clinical research and patient care. *J Allergy Clin Immunol.* 2004; 114:155–212. [PubMed: 15577865]
57. Takeuchi K, Majima Y, Shimizu T, Ukai K, Sakakura Y. Analysis of HLA antigens in Japanese patients with chronic sinusitis. *Laryngoscope.* 1999; 109:275–8. [PubMed: 10890778]
58. Palikhe NS, Kim SH, Cho BY, Choi GS, Kim JH, Ye YM, et al. IL-13 Gene Polymorphisms are Associated With Rhinosinusitis and Eosinophilic Inflammation in Aspirin Intolerant Asthma. *Allergy Asthma Immunol Res.* 2010; 2:134–40. [PubMed: 20358028]
59. Kim SH, Park HS, Holloway JW, Shin HD, Park CS. Association between a TGFbeta1 promoter polymorphism and rhinosinusitis in aspirin-intolerant asthmatic patients. *Respir Med.* 2007; 101:490–5. [PubMed: 16916603]
60. Barnes KC. Ancestry, ancestry-informative markers, asthma, and the quest for personalized medicine. *J Allergy Clin Immunol.* 2010; 126:1139–40. [PubMed: 21134571]
61. Ramsey B, Richardson MA. Impact of sinusitis in cystic fibrosis. *J Allergy Clin Immunol.* 1992; 90:547–52. [PubMed: 1527348]
62. DeMarcantonio MA, Han JK. Nasal polyps: pathogenesis and treatment implications. *Otolaryngol Clin North Am.* 2011; 44:685–95. ix. [PubMed: 21621054]
63. Watson MS, Cutting GR, Desnick RJ, Driscoll DA, Klinger K, Mennuti M, et al. Cystic fibrosis population carrier screening: 2004 revision of American College of Medical Genetics mutation panel. *Genet Med.* 2004; 6:387–91. [PubMed: 15371902]
64. Wang X, Moylan B, Leopold DA, Kim J, Rubenstein RC, Togias A, et al. Mutation in the gene responsible for cystic fibrosis and predisposition to chronic rhinosinusitis in the general population. *JAMA.* 2000; 284:1814–9. [PubMed: 11025834]
65. Raman V, Clary R, Siegrist KL, Zehnbauser B, Chatila TA. Increased prevalence of mutations in the cystic fibrosis transmembrane conductance regulator in children with chronic rhinosinusitis. *Pediatrics.* 2002; 109:E13. [PubMed: 11773581]
66. Irving RM, McMahon R, Clark R, Jones NS. Cystic fibrosis transmembrane conductance regulator gene mutations in severe nasal polyposis. *Clin Otolaryngol Allied Sci.* 1997; 22:519–21. [PubMed: 9466061]
67. Kuchynkova Z, Macek M Jr, Holcat M, Macek M. [Detection of the G551D mutation in a patient with nasal polyps]. *Cas Lek Cesk.* 1995; 134:212–3. [PubMed: 7538905]
68. Meth MJ, Serota M, Rosenthal DW, Santiago MT, Cavuoto MA. High Frequency of CF Transmembrane Conductance Regulator (CFTR) Mutations in a Population with Persistent Asthma and/or Chronic Rhinosinusitis. *J Allergy Clin Immunol.* 2009; 123:S159.
69. Cho DY, Hwang PH, Illek B, Fischer H. Acid and Base Secretion in Freshly Excised Nasal Tissue From Cystic Fibrosis Patients with DeltaF508 Mutation. *Int Forum Allergy Rhinol.* 2011; 1:123–7. [PubMed: 22034590]
70. Moskwa P, Lorentzen D, Excoffon KJ, Zabner J, McCray PB Jr, Nauseef WM, et al. A novel host defense system of airways is defective in cystic fibrosis. *Am J Respir Crit Care Med.* 2007; 175:174–83. [PubMed: 17082494]

71. Worlitzsch D, Tarran R, Ulrich M, Schwab U, Cekici A, Meyer KC, et al. Effects of reduced mucus oxygen concentration in airway Pseudomonas infections of cystic fibrosis patients. *J Clin Invest.* 2002; 109:317–25. [PubMed: 11827991]
72. Strieter RM. Interleukin-8: a very important chemokine of the human airway epithelium. *Am J Physiol Lung Cell Mol Physiol.* 2002; 283:L688–9. [PubMed: 12225944]
73. Shuto T, Furuta T, Oba M, Xu H, Li JD, Cheung J, et al. Promoter hypomethylation of Toll-like receptor-2 gene is associated with increased proinflammatory response toward bacterial peptidoglycan in cystic fibrosis bronchial epithelial cells. *FASEB J.* 2006; 20:782–4. [PubMed: 16478769]
74. Li J, Johnson XD, Iazvovskaia S, Tan A, Lin A, Hershenson MB. Signaling intermediates required for NF-kappa B activation and IL-8 expression in CF bronchial epithelial cells. *Am J Physiol Lung Cell Mol Physiol.* 2003; 284:L307–15. [PubMed: 12388360]
75. Rohlfes EM, Zhou Z, Heim RA, Nagan N, Rosenblum LS, Flynn K, et al. Cystic fibrosis carrier testing in an ethnically diverse US population. *Clin Chem.* 2011; 57:841–8. [PubMed: 21474639]
76. Maria Ciminelli B, Bombieri C, Ciccacci C, Belpinati F, Pompei F, Maselli R, et al. Anthropological features of the CFTR gene: Its variability in an African population. *Ann Hum Biol.* 2011; 38:203–9. [PubMed: 20812883]
77. Sugarman EA, Rohlfes EM, Silverman LM, Allitto BA. CFTR mutation distribution among U.S. Hispanic and African American individuals: evaluation in cystic fibrosis patient and carrier screening populations. *Genet Med.* 2004; 6:392–9. [PubMed: 15371903]
78. Alper OM, Wong LJ, Young S, Pearl M, Graham S, Sherwin J, et al. Identification of novel and rare mutations in California Hispanic and African American cystic fibrosis patients. *Hum Mutat.* 2004; 24:353. [PubMed: 15365999]
79. Chaplin DD. Overview of the immune response. *J Allergy Clin Immunol.* 2010; 125:S3–23. [PubMed: 20176265]
80. Luxenberger W, Posch U, Berghold A, Hofmann T, Lang-Loidolt D. HLA patterns in patients with nasal polyposis. *Eur Arch Otorhinolaryngol.* 2000; 257:137–9. [PubMed: 10839486]
81. Moloney JR, Oliver RT. HLA antigens, nasal polyps and asthma. *Clin Otolaryngol Allied Sci.* 1980; 5:183–9. [PubMed: 7408219]
82. Zhai L, Sun Y, Tang L, Liu H. Polymorphism between loci for human leukocyte antigens DR and DQ in patients with nasal polyps. *Ann Otol Rhinol Laryngol.* 2007; 116:66–8. [PubMed: 17305280]
83. Fajardo-Dolci G, Solorio-Abreu J, Romero-Alvarez JC, Zavaleta-Villa B, Cerezo-Camacho O, Jimenez-Lucio R, et al. DQA1 and DQB1 association and nasal polyposis. *Otolaryngol Head Neck Surg.* 2006; 135:243–7. [PubMed: 16890076]
84. Molnar-Gabor E, Endreffy E, Rozsasi A. HLA-DRB1, -DQA1, and -DQB1 genotypes in patients with nasal polyposis. *Laryngoscope.* 2000; 110:422–5. [PubMed: 10718431]
85. Turvey SE, Broide DH. Innate immunity. *J Allergy Clin Immunol.* 2010; 125:S24–32. [PubMed: 19932920]
86. Tieu DD, Peters AT, Carter RG, Suh L, Conley DB, Chandra R, et al. Evidence for diminished levels of epithelial psoriasin and calprotectin in chronic rhinosinusitis. *J Allergy Clin Immunol.* 2010; 125:667–75. [PubMed: 20226301]
87. Richer SL, Truong-Tran AQ, Conley DB, Carter R, Vermeylen D, Grammer LC, et al. Epithelial genes in chronic rhinosinusitis with and without nasal polyps. *Am J Rhinol.* 2008; 22:228–34. [PubMed: 18588753]
88. Lane AP, Truong-Tran QA, Schleimer RP. Altered expression of genes associated with innate immunity and inflammation in recalcitrant rhinosinusitis with polyps. *Am J Rhinol.* 2006; 20:138–44. [PubMed: 16686375]
89. Ramanathan M Jr, Lee WK, Dubin MG, Lin S, Spannhake EW, Lane AP. Sinonasal epithelial cell expression of toll-like receptor 9 is decreased in chronic rhinosinusitis with polyps. *Am J Rhinol.* 2007; 21:110–6. [PubMed: 17283572]
90. Lee RJ, Xiong G, Kofonow JM, Chen B, Lysenko A, Jiang P, et al. T2R38 taste receptor polymorphisms underlie susceptibility to upper respiratory infection. *J Clin Invest.* 2012; 122:4145–59. [PubMed: 23041624]

91. Zhang Y, Endam LM, Filali-Mouhim A, Zhao L, Desrosiers M, Han D, et al. Polymorphisms in RYBP and AOA1 Genes Are Associated with Chronic Rhinosinusitis in a Chinese Population: A Replication Study. *PLoS One*. 2012; 7:e39247. [PubMed: 22723975]
92. Kilty SJ, Bosse Y, Cormier C, Endam LM, Desrosiers MY. Polymorphisms in the SERPINA1 (Alpha-1-Antitrypsin) gene are associated with severe chronic rhinosinusitis unresponsive to medical therapy. *Am J Rhinol Allergy*. 2010; 24:e4–9. [PubMed: 20109307]
93. Castano R, Bosse Y, Endam LM, Filali-Mouhim A, Desrosiers M. c-MET pathway involvement in chronic rhinosinusitis: a genetic association analysis. *Otolaryngol Head Neck Surg*. 2010; 142:665–71. e1–2. [PubMed: 20416453]
94. Tewfik MA, Bosse Y, Lemire M, Hudson TJ, Vallee-Smejda S, Al-Shemari H, et al. Polymorphisms in interleukin-1 receptor-associated kinase 4 are associated with total serum IgE. *Allergy*. 2009; 64:746–53. [PubMed: 19254290]
95. Bernstein JM, Anon JB, Rontal M, Conroy J, Wang C, Sucheston L. Genetic polymorphisms in chronic hyperplastic sinusitis with nasal polyposis. *Laryngoscope*. 2009; 119:1258–64. [PubMed: 19405090]
96. Yazdani N, Amoli MM, Naraghi M, Mersaghian A, Firouzi F, Sayyahpour F, et al. Association between the functional polymorphism C-159T in the CD14 promoter gene and nasal polyposis: potential role in asthma. *J Investig Allergol Clin Immunol*. 2012; 22:406–11.
97. Tewfik MA, Bosse Y, Hudson TJ, Desrosiers M, Vallee-Smejda S. TLR Signalling Gene Polymorphisms in Chronic Rhinosinusitis. *Otolaryngol Head Neck Surg*. 2007; 137:1. [PubMed: 17599556]
98. Zhang Y, Desrosiers M, Mfuna-Endam L, Filali-Mouhim A, Zhang L. Demonstration Of A Common Genetic Basis To CRS In Chinese And Caucasian Populations. *J Allergy Clin Immunol*. 2011:127.
99. Zhang Y, Endam LM, Filali-Mouhim A, Bosse Y, Castano R, Desrosiers M. Polymorphisms in the nitric oxide synthase 1 gene are associated with severe chronic rhinosinusitis. *Am J Rhinol Allergy*. 2011; 25:e49–54. [PubMed: 21679499]
100. Yamamoto M, Tochino Y, Chibana K, Trudeau JB, Holguin F, Wenzel SE. Nitric oxide and related enzymes in asthma: relation to severity, enzyme function and inflammation. *Clin Exp Allergy*. 2011
101. Benito Pescador D, Isidoro-Garcia M, Garcia-Solaesa V, Pascual de Pedro M, Sanz C, Hernandez-Hernandez L, et al. Genetic association study in nasal polyposis. *J Investig Allergol Clin Immunol*. 2012; 22:331–40.
102. Sitarek P, Zielinska-Blizniewska H, Dziki L, Milonski J, Przybylowska K, Mucha B, et al. Association of the -14C/G MET and the -765G/C COX-2 Gene Polymorphisms with the Risk of Chronic Rhinosinusitis with Nasal Polyps in a Polish Population. *DNA Cell Biol*. 2012
103. Zielinska-Blizniewska H, Sitarek P, Milonski J, Dziki L, Przybylowska K, Olszewski J, et al. Association of the -33C/G OSF-2 and the 140A/G LF gene polymorphisms with the risk of chronic rhinosinusitis with nasal polyps in a Polish population. *Mol Biol Rep*. 2012; 39:5449–57. [PubMed: 22173721]
104. Walley AJ, Cookson WO. Investigation of an interleukin-4 promoter polymorphism for associations with asthma and atopy. *J Med Genet*. 1996; 33:689–92. [PubMed: 8863163]
105. Noguchi E, Shibasaki M, Arinami T, Takeda K, Yokouchi Y, Kawashima T, et al. Association of asthma and the interleukin-4 promoter gene in Japanese. *Clin Exp Allergy*. 1998; 28:449–53. [PubMed: 9641571]
106. Hunninghake GM, Soto-Quiros ME, Avila L, Su J, Murphy A, Demeo DL, et al. Polymorphisms in IL13, total IgE, eosinophilia, and asthma exacerbations in childhood. *J Allergy Clin Immunol*. 2007; 120:84–90. [PubMed: 17561245]
107. Beghe B, Hall IP, Parker SG, Moffatt MF, Wardlaw A, Connolly MJ, et al. Polymorphisms in IL13 pathway genes in asthma and chronic obstructive pulmonary disease. *Allergy*. 2010; 65:474–81. [PubMed: 19796199]
108. Ekinci S, Erbek SS, Yurtcu E, Sahin FI. Lack of association between eotaxin-1 gene polymorphisms and nasal polyposis. *Otolaryngol Head Neck Surg*. 2011; 145:1036–9. [PubMed: 21825098]

109. Yea SS, Yang YI, Park SK, Jang WH, Lee SS, Seog DH, et al. Interleukin-4 C-590T polymorphism is associated with protection against nasal polyps in a Korean population. *Am J Rhinol.* 2006; 20:550–3. [PubMed: 17063753]
110. Park SK, Heo KW, Jung H, Yea SS, Yang YI. Expression of cyclooxygenase-2 and 5-lipoxygenase in nasal polyps associated with interleukin-4 promoter polymorphism -590. *Otolaryngol Head Neck Surg.* 2006; 135:928–32. [PubMed: 17141086]
111. Zhang ML, Ni PH, Cai CP, Chen NJ, Wang SL. [Association of susceptibility to chronic rhinosinusitis with genetic polymorphisms of IL-4 and IL-10]. *Zhonghua Er Bi Yan Hou Tou Jing Wai Ke Za Zhi.* 2012; 47:212–7. [PubMed: 22805022]
112. Vercelli D. Discovering susceptibility genes for asthma and allergy. *Nat Rev Immunol.* 2008; 8:169–82. [PubMed: 18301422]
113. Reh DD, Wang Y, Ramanathan M Jr, Lane AP. Treatment-recalcitrant chronic rhinosinusitis with polyps is associated with altered epithelial cell expression of interleukin-33. *Am J Rhinol Allergy.* 2010; 24:105–9. [PubMed: 20338108]
114. Buysschaert ID, Grulois V, Eloy P, Jorissen M, Rombaux P, Bertrand B, et al. Genetic evidence for a role of IL33 in nasal polyposis. *Allergy.* 2010; 65:616–22. [PubMed: 19860791]
115. Plager DA, Kahl JC, Asmann YW, Nilson AE, Pallanch JF, Friedman O, et al. Gene transcription changes in asthmatic chronic rhinosinusitis with nasal polyps and comparison to those in atopic dermatitis. *PLoS One.* 2010; 5:e11450. [PubMed: 20625511]
116. Castano R, Bosse Y, Endam LM, Desrosiers M. Evidence of association of interleukin-1 receptor-like 1 gene polymorphisms with chronic rhinosinusitis. *Am J Rhinol Allergy.* 2009; 23:377–84. [PubMed: 19671251]
117. Schleimer RP, Kato A, Peters A, Conley D, Kim J, Liu MC, et al. Epithelium, inflammation, and immunity in the upper airways of humans: studies in chronic rhinosinusitis. *Proc Am Thorac Soc.* 2009; 6:288–94. [PubMed: 19387032]
118. Cormier C, Bosse Y, Mfuna L, Hudson TJ, Desrosiers M. Polymorphisms in the tumour necrosis factor alpha-induced protein 3 (TNFAIP3) gene are associated with chronic rhinosinusitis. *J Otolaryngol Head Neck Surg.* 2009; 38:133–41. [PubMed: 19344623]
119. Endam LM, Bosse Y, Filali-Mouhim A, Cormier C, Boisvert P, Boulet LP, et al. Polymorphisms in the interleukin-22 receptor alpha-1 gene are associated with severe chronic rhinosinusitis. *Otolaryngol Head Neck Surg.* 2009; 140:741–7. [PubMed: 19393422]
120. Sekigawa T, Tajima A, Hasegawa T, Hasegawa Y, Inoue H, Sano Y, et al. Gene-expression profiles in human nasal polyp tissues and identification of genetic susceptibility in aspirin-intolerant asthma. *Clin Exp Allergy.* 2009; 39:972–81. [PubMed: 19489917]
121. Zhang M, Ni P, Cai C, Chen N, Wang S. [The association between genetic polymorphisms of IL-6 and the susceptibility of chronic rhinosinusitis]. *Lin Chung Er Bi Yan Hou Tou Jing Wai Ke Za Zhi.* 2012; 26:197–200. 4. [PubMed: 22667128]
122. Peters AT, Kato A, Zhang N, Conley DB, Suh L, Tancowny B, et al. Evidence for altered activity of the IL-6 pathway in chronic rhinosinusitis with nasal polyps. *J Allergy Clin Immunol.* 2010; 125:397–403. e10. [PubMed: 20159251]
123. Zhang F, Xiong ZG, Cao PP, You XJ, Gao QX, Cui YH, et al. Lack of association of Clara cell 10-kDa protein gene variant with chronic rhinosinusitis in a Chinese Han population. *Am J Rhinol.* 2008; 22:376–80. [PubMed: 18702901]
124. Pasaje CF, Bae JS, Park BL, Cheong HS, Jang AS, Uh ST, et al. Lack of association between CD58 genetic variations and aspirin-exacerbated respiratory disease in a Korean population. *J Asthma.* 2011; 48:539–45. [PubMed: 21726122]
125. Qidwai T, Khan F. Tumour necrosis factor gene polymorphism and disease prevalence. *Scand J Immunol.* 2011; 74:522–47. [PubMed: 21790707]
126. Erbek SS, Yurtcu E, Erbek S, Atac FB, Sahin FI, Cakmak O. Proinflammatory cytokine single nucleotide polymorphisms in nasal polyposis. *Arch Otolaryngol Head Neck Surg.* 2007; 133:705–9. [PubMed: 17638785]
127. Batikhan H, Gokcan MK, Beder E, Akar N, Ozturk A, Gerceker M. Association of the tumor necrosis factor-alpha -308 G/A polymorphism with nasal polyposis. *Eur Arch Otorhinolaryngol.* 2010; 267:903–8. [PubMed: 20012441]

128. Allen RD. Polymorphism of the human TNF-alpha promoter--random variation or functional diversity? *Mol Immunol.* 1999; 36:1017–27. [PubMed: 10698305]
129. Kroeger KM, Carville KS, Abraham LJ. The -308 tumor necrosis factor-alpha promoter polymorphism effects transcription. *Mol Immunol.* 1997; 34:391–9. [PubMed: 9293772]
130. Wilson AG, Symons JA, McDowell TL, McDevitt HO, Duff GW. Effects of a polymorphism in the human tumor necrosis factor alpha promoter on transcriptional activation. *Proc Natl Acad Sci U S A.* 1997; 94:3195–9. [PubMed: 9096369]
131. Mfuno Endam L, Cormier C, Bosse Y, Filali-Mouhim A, Desrosiers M. Association of IL1A, IL1B, and TNF gene polymorphisms with chronic rhinosinusitis with and without nasal polyposis: A replication study. *Arch Otolaryngol Head Neck Surg.* 2010; 136:187–92. [PubMed: 20157068]
132. Harrison P, Pointon JJ, Chapman K, Roddam A, Wordsworth BP. Interleukin-1 promoter region polymorphism role in rheumatoid arthritis: a meta-analysis of IL-1B-511A/G variant reveals association with rheumatoid arthritis. *Rheumatology (Oxford).* 2008; 47:1768–70. [PubMed: 18838388]
133. Karjalainen J, Hulkkonen J, Pessi T, Huhtala H, Nieminen MM, Aromaa A, et al. The IL1A genotype associates with atopy in nonasthmatic adults. *J Allergy Clin Immunol.* 2002; 110:429–34. [PubMed: 12209090]
134. Karjalainen J, Joki-Erkila VP, Hulkkonen J, Pessi T, Nieminen MM, Aromaa A, et al. The IL1A genotype is associated with nasal polyposis in asthmatic adults. *Allergy.* 2003; 58:393–6. [PubMed: 12752325]
135. Chen N, Ni P, Cai C, Wang S. [Association of IL-1beta gene -31T/C polymorphism with chronic rhinosinusitis]. *Lin Chung Er Bi Yan Hou Tou Jing Wai Ke Za Zhi.* 2011; 25:197–200. [PubMed: 21604462]
136. Van Bruaene N, Derycke L, Perez-Novo CA, Gevaert P, Holtappels G, De Ruyck N, et al. TGF-beta signaling and collagen deposition in chronic rhinosinusitis. *J Allergy Clin Immunol.* 2009; 124:253–9. 9, e1–2. [PubMed: 19500825]
137. Van Bruaene N, Novo CP, Van Crombruggen K, Deruyck N, Holtappels G, Van Cauwenberge P, et al. Inflammation and remodelling patterns in early stage chronic rhinosinusitis. *Clin Exp Allergy.* 2011
138. Li X, Meng J, Qiao X, Liu Y, Liu F, Zhang N, et al. Expression of TGF, matrix metalloproteinases, and tissue inhibitors in Chinese chronic rhinosinusitis. *J Allergy Clin Immunol.* 2010; 125:1061–8. [PubMed: 20392482]
139. Watelet JB, Bachert C, Claeys C, Van Cauwenberge P. Matrix metalloproteinases MMP-7, MMP-9 and their tissue inhibitor TIMP-1: expression in chronic sinusitis vs nasal polyposis. *Allergy.* 2004; 59:54–60. [PubMed: 14674934]
140. Ghosh AK, Vaughan DE. PAI-1 in tissue fibrosis. *J Cell Physiol.* 2012; 227:493–507. [PubMed: 21465481]
141. Takabayashi T, Kato A, Peters AT, Hulse KE, Suh LA, Carter R, et al. Excessive Fibrin Deposition in Nasal Polyps Caused by Fibrinolytic Impairment through Reduction of t-PA Expression. *Am J Respir Crit Care Med.* 2012
142. Sejima T, Holtappels G, Bachert C. The expression of fibrinolytic components in chronic paranasal sinus disease. *Am J Rhinol Allergy.* 2011; 25:1–6. [PubMed: 21711960]
143. Lee SH, Eren M, Vaughan DE, Schleimer RP, Cho S. A PAI-1 inhibitor reduces airway remodeling in a murine model of chronic asthma. *Am J Respir Cell Mol Biol.* 2012
144. Wang LF, Chien CY, Tai CF, Kuo WR, Hsi E, Juo SH. Matrix metalloproteinase-9 gene polymorphisms in nasal polyposis. *BMC Med Genet.* 2010; 11:85. [PubMed: 20529372]
145. Erbek SS, Yurtcu E, Erbek S, Sahin FI. Matrix metalloproteinase-9 promoter gene polymorphism (-1562C>T) in nasal polyposis. *Am J Rhinol Allergy.* 2009; 23:568–70. [PubMed: 19958602]
146. Settiple GA. Epidemiology of nasal polyps. *Allergy Asthma Proc.* 1996; 17:231–6. [PubMed: 8922141]
147. Dykewicz MS, Hamilos DL. Rhinitis and sinusitis. *J Allergy Clin Immunol.* 2010; 125:S103–15. [PubMed: 20176255]

148. Perez-Novo CA, Watelet JB, Claeys C, Van Cauwenberge P, Bachert C. Prostaglandin, leukotriene, and lipoxin balance in chronic rhinosinusitis with and without nasal polyposis. *J Allergy Clin Immunol.* 2005; 115:1189–96. [PubMed: 15940133]
149. Gosepath J, Brieger J, Mann WJ. New immunohistologic findings on the differential role of cyclooxygenase 1 and cyclooxygenase 2 in nasal polyposis. *Am J Rhinol.* 2005; 19:111–6. [PubMed: 15921208]
150. Al-Shemari H, Bosse Y, Hudson TJ, Cabaluna M, Duval M, Lemire M, et al. Influence of leukotriene gene polymorphisms on chronic rhinosinusitis. *BMC Med Genet.* 2008; 9:21. [PubMed: 18366797]
151. Fruth K, Best N, Amro M, Ingel K, Gosepath J, Mann WJ, et al. No evidence for a correlation of glutathione S-transferase polymorphisms and chronic rhinosinusitis. *Rhinology.* 2011; 49:180–4. [PubMed: 21743873]
152. Bussu F, Tiziano FD, Giorgio A, Pinto AM, De Corso E, Angelozzi C, et al. Arg16gly polymorphism of the beta2-adrenoceptor gene (ADRBeta2) as a susceptibility factor for nasal polyposis. *Am J Rhinol.* 2007; 21:378–82. [PubMed: 17621827]
153. Kohyama K, Abe S, Kodaira K, Yukawa T, Hozawa S, Morioka J, et al. Arg16Gly beta2-Adrenergic Receptor Gene Polymorphism in Japanese Patients with Aspirin-Exacerbated Respiratory Disease. *Int Arch Allergy Immunol.* 2011; 156:405–11. [PubMed: 21829036]
154. Basu K, Palmer CN, Tavendale R, Lipworth BJ, Mukhopadhyay S. Adrenergic beta(2)-receptor genotype predisposes to exacerbations in steroid-treated asthmatic patients taking frequent albuterol or salmeterol. *J Allergy Clin Immunol.* 2009; 124:1188–94. e3. [PubMed: 19800676]
155. Choudhry S, Ung N, Avila PC, Ziv E, Nazario S, Casal J, et al. Pharmacogenetic differences in response to albuterol between Puerto Ricans and Mexicans with asthma. *Am J Respir Crit Care Med.* 2005; 171:563–70. [PubMed: 15557128]
156. Ojogun N, Kuang TY, Shao B, Greaves DR, Munford RS, Varley AW. Overproduction of acyloxyacyl hydrolase by macrophages and dendritic cells prevents prolonged reactions to bacterial lipopolysaccharide in vivo. *J Infect Dis.* 2009; 200:1685–93. [PubMed: 19860560]
157. Barnes KC, Grant A, Gao P, Baltadjieva D, Berg T, Chi P, et al. Polymorphisms in the novel gene acyloxyacyl hydroxylase (AOAH) are associated with asthma and associated phenotypes. *J Allergy Clin Immunol.* 2006; 118:70–7. [PubMed: 16815140]
158. Li CW, Shi L, Zhang KK, Li TY, Lin ZB, Lim MK, et al. Role of p63/p73 in epithelial remodeling and their response to steroid treatment in nasal polyposis. *J Allergy Clin Immunol.* 2011; 127:765–72. e1–2. [PubMed: 21269671]
159. Cho JS, Moon YM, Park IH, Um JY, Moon JH, Park SJ, et al. Epigenetic regulation of myofibroblast differentiation and extracellular matrix production in nasal polyp-derived fibroblasts. *Clin Exp Allergy.* 2012
160. Seiberling KA, Church CA, Herring JL, Sowers LC. Epigenetics of chronic rhinosinusitis and the role of the eosinophil. *Int Forum Allergy Rhinol.* 2012; 2:80–4. [PubMed: 22311846]
161. Bucholtz GA, Ejercito VS, Burmester JK. The cystic fibrosis conductance regulator gene exon sequence is normal in a patient with edematous eosinophilic nasal polyps. *Am J Rhinol.* 1999; 13:221–3. [PubMed: 10392242]
162. Varon R, Magdorf K, Staab D, Wahn HU, Krawczak M, Sperling K, et al. Recurrent nasal polyps as a monosymptomatic form of cystic fibrosis associated with a novel in-frame deletion (591del18) in the CFTR gene. *Hum Mol Genet.* 1995; 4:1463–4. [PubMed: 7581390]
163. Jacobs RL, Freda AJ, Culver WG. Primary nasal polyposis. *Ann Allergy.* 1983; 51:500–5. [PubMed: 6638613]
164. Laroche M, Ginesty E, Serrano E, Cantagrel A, Bon E, Moulinier L, et al. Inflammatory rheumatism and nasal polyposis. *Clin Rheumatol.* 1997; 16:207–11. [PubMed: 9093805]
165. Kim JH, Park BL, Cheong HS, Pasaje CF, Bae JS, Park JS, et al. HLA-DRA polymorphisms associated with risk of nasal polyposis in asthmatic patients. *Am J Rhinol Allergy.* 2012; 26:12–7. [PubMed: 22391069]
166. Schubert MS, Hutcheson PS, Graff RJ, Santiago L, Slavin RG. HLA-DQB1 *03 in allergic fungal sinusitis and other chronic hypertrophic rhinosinusitis disorders. *J Allergy Clin Immunol.* 2004; 114:1376–83. [PubMed: 15577839]

Figure 1. Identified Factors that May Contribute to the Development of Chronic Rhinosinusitis
Genetic variation may contribute to the pathogenesis of chronic rhinosinusitis by influencing some or all of the various mechanisms illustrated above.

Table 1

Genes Significantly Associated with Chronic Rhinosinusitis (CRS) in One or More Studies.

<i>Gene</i>	Chromosome location	Variation surveyed	Phenotype	Odds ratio	<i>P</i> value	Allele frequency (cases; controls)	Reference number
gGene Involved in Chloride Ion Transport <i>CFTR</i>	7q31	Multiple SNPs	CRSsNP	N/A	0.0023	N/A	41
		Multiple SNPs	CRS [*]	N/A	0.04	0.07; 0.02	64
		Multiple SNPs	CRS [*]	3.5	<0.05	0.12; 0.04	65
		M470V	CRSwNP (eosinophilic)	N/A	0.316	0.69; 0.48	161
		Multiple SNPs	CRS [*]	N/A	N/A	0.36; 0.14	44
		Multiple SNPs	CRSwNP	N/A	>0.05	0.05; 0.05	66
		G551D	CRSwNP with AIA	N/A	N/A	N/A	67
		591del18	Recurrent CRSwNP	N/A	N/A	N/A	162
		Multiple SNPs	CRSwNP and CRSsNP	N/A	N/A	Varied - see ref	68
Genes Encoding Human Leukocyte Antigens							
<i>HLA-A</i>	6p21	Multiple SNPs	CRSwNP	71.3 for HLA-A [*] 74	<0.03	0.03; 0	80
		Multiple SNPs	CRS (“intractable”)	N/A	NS	Varied - see ref	57
		HLA-A [*] 24	CRSwNP with AIA	N/A	<0.05	0.278; 0.125	46
		Multiple SNPs	CRSwNP	N/A	>0.05	Varied - see ref	46
		Multiple SNPs	CRSwNP	N/A	NS	Varied - see ref	163
		Haplotype A1/B8	CRSwNP with asthma	N/A	N/A	N/A	81
		HLA-A [*] 1	CRSwNP with “seronegative inflammatory rheumatism”	N/A	N/A	0.6; no controls in the study	164
<i>HLA-B</i>	6p21	Multiple SNPs	CRS (“intractable”)	3.23 for HLA-B54	<0.037	0.293; 0.114	57
		Multiple SNPs	CRSwNP	N/A	<0.05	Varied - see ref	46
		Multiple SNPs	CRSwNP	N/A	N/A	Varied - see ref	163
		Multiple SNPs	CRSwNP with “seronegative inflammatory rheumatism”	N/A	N/A	0.6; no controls	164
<i>HLA-C</i>	6p21	Multiple SNPs	CRSwNP	N/A	<0.05	Varied - see ref	46
		HLA-Cw [*] 12	CRSwNP with AIA	N/A	<0.05	0.167; 0	46
		Multiple SNPs	CRS (“intractable”)	N/A	NS	Varied - see ref	57
<i>HLA-DR</i>	6p21	Multiple SNPs	CRSwNP in ATA	Varied - see ref	0.005-0.007	Varied - see ref	165
		Multiple SNPs	CRSwNP	Varied - see ref	0.009-0.03	Varied - see ref	45
		HLA-DR [*] 16	CRSwNP	8.9	0.03	0.05;0.0062	82

<i>Gene</i>	Chromosome location	Variation surveyed	Phenotype	Odds ratio	<i>P</i> value	Allele frequency (cases; controls)	Reference number
<i>HLA-DQ</i>	6p21	HLA-DRB1 *04	CRSwNP with AIA	N/A	<0.05	0.444; 0.234	46
		HLA-DR *7	CRSwNP	2.55	<0.05	N/A	84
		Multiple SNPs	CRS (“intractable”)	N/A	NS	Varied - see ref	57
		HLA-DQB1 *03	CRSwNP	4.25	<0.001	0.5; 0.19 ^{//}	166
		HLA-DQB1 *03	AFS	8.22	<0.001	0.66; 0.19 ^{//}	166
		Multiple SNPs	CRSwNP	Varied - see ref	0.001-0.04	Varied - see ref	82
		HLA-DQA1 *0201	CRSwNP	6.79	0.0027	0.0968; 0.0166	83
		Multiple SNPs	CRSwNP	Varied - see ref	<0.05	Varied - see ref	84
		Multiple SNPs	CRSwNP	N/A	>0.05	Varied - see ref	46
		Multiple SNPs	CRS (“intractable”)	N/A	NS	Varied - see ref	57
		Genes Involved in Innate Immunity					
<i>CD14</i>	5q31	rs2569190	CRSwNP	1.88	0.04	0.44; 0.37	96
<i>IRAK4</i>	12q12	rs2569190	CRSwNP	N/A	>0.05	N/A	95
		Multiple SNPs	CRS (“severe” [†])	N/A	>0.05	N/A	97
		Multiple SNPs	CRSsNP	Varied - see ref	NS	Varied - see ref	98
		Multiple SNPs	CRSwNP	Varied - see ref	NS	Varied - see ref	98
<i>LTF</i>	3p21	140 A / G	CRSwNP	4.27	<0.001	0.38; 0.12	103
<i>MET</i>	7q31	Haplotype [‡]	CRS (“severe” [§])	Varied - see ref	0.018	0.349; 0.264	93
		−14 C > G	CRSwNP	5.52	<0.001	0.34; 0.08	102
<i>NOS1</i>	12q24	Multiple SNPs	CRS (“severe” [§])	Varied - see ref	0.0023-0.0129	Varied - see ref	99
<i>NOS1AP</i>	1q23	rs4657164	CRS (“severe” [§])	1.67	0.0178	0.195; 0.128	99
<i>NOS2A</i>	17q11-q12	Promoter VNTR	CRSwNP	14.39	0.001	N/A	47
		Promoter VNTR	CRSwNP with asthma	0.36	0.018	0.06; 0.02	101
		Promoter VNTR	CRSwNP with AIA	0.25	0.005	0.08; 0.023	101
<i>SERPINA1</i>	14q32	rs1243168	CRS (“severe” [†])	6 for genotype TT	0.0211	0.19 for entire cohort	92
<i>TLR2</i>	4q32	Multiple SNPs	CRS [*]	Varied - see ref	0.008-0.022	Varied - see ref	49
		rs5743708	CRSwNP	N/A	>0.05	0.07; 0.12	48
Genes Involved in T helper 2 (Th2) Inflammation							
<i>IL1RL1</i>	2q12	Multiple SNPs	CRS (“severe” [§])	Varied - see ref	0.008-0.04	Varied - see ref	116
		rs13431828	CRSwNP	0.92	0.3887	0.10; 0.11	98
		rs13431828	CRSsNP	0.64	0.04464	0.07; 0.11	98
		rs1420101	CRSwNP	1.14	0.386	0.43; 0.398	114
<i>IL4</i>	5q31	rs2243250	CRSwNP	0.529 (for TT genotype compared to CC genotype)	0.028	0.29; 0.15	109
		rs2243250	CRSsNP	N/A	0.378	0.20; 0.15	109

<i>Gene</i>	Chromosome location	Variation surveyed	Phenotype	Odds ratio	<i>P</i> value	Allele frequency (cases; controls)	Reference number
		−33 T > C	CRSwNP	1.818	0.0236	N/A	111
<i>IL13</i>	5q31	Multiple SNPs	CRS with AIA	Varied - see ref	<0.001-0.012	Varied - see ref	58
<i>IL33</i>	9p24	rs3939286	CRSwNP	1.6	0.0041	0.307; 0.216	114
Other Genes Involved Inflammation							
<i>IDO1</i>	8p12-p11	rs7820268	CRSwNP with AIA	0.58	0.011	0.101; 0.163	120
<i>IL1A</i>	2q14	rs17561	CRSwNP	2.743	<0.001	0.44; 0.18	126
		rs17561	CRSwNP in asthmatics	2.73 for GG genotype	0.005	0.20; 0.34	134
		Multiple SNPs	CRS (“severe” [§])	Varied - see ref	0.003-0.02	Varied - see ref	131
		Multiple SNPs	CRSwNP	N/A	>0.05	N/A	95
<i>IL1B</i>	2q14	rs16944	CRSwNP	0.9 for CC genotype	0.01	0.38; 0.46	126
		rs16944	CRS (“severe” [§])	N/A	>0.05	0.33 for entire cohort	131
		Multiple SNPs	CRSwNP	N/A	>0.05	N/A	95
		rs16944	CRSwNP in asthmatics	N/A	0.606	0.40; 0.368	134
		Multiple SNPs	CRS (“recalcitrant” [§])	N/A	0.29-0.69	Varied - see ref	51
		−31 T > C	CRS *	1.639 for CC genotype	<0.05	N/A	135
<i>IL1R2</i>	2q12	rs11688145	CRSwNP with AIA	0.66	0.0024	0.244; 0.330	120
<i>IL1RN</i>	2q14	VNTR in Intron 2	CRS (“recalcitrant” [§])	3.39 for 2 or 4 repeats	<0.05	0.17; 0.06	51
<i>IL6</i>	7p21	rs1800796	CRS *	1.932	<0.05	0.163; 0.236	121
		rs13447445	CRSwNP	N/A	>0.05	N/A	95
<i>IL22RA1</i>	1p36	Multiple SNPs	CRS (“severe” [¶])	1.716-1.977	0.0006-0.0014	Varied - see ref	119
<i>LTA</i>	6p21	TNFB * ₂ allele	CRS (“intractable”)	N/A	<0.05	0.74; 0.56	50
<i>TNF</i>	6p21	Multiple SNPs	CRSwNP	Varied - see ref	<0.001-0.87	Varied - see ref	95
		rs1800629	CRSwNP	1.86	0.01	0.19; 0.12	126
		rs1800629	CRSwNP	3.68	0.016	0.186; 0.063	127
		rs1800629	CRS *	N/A	>0.05	0.08; 0.11	50
		Multiple SNPs	CRSwNP	N/A	>0.05	Varied - see ref	83
		Multiple SNPs	CRS (“severe” [¶])	Varied - see ref	>0.05	Varied - see ref	131
<i>TNFAIP3</i>	6q23	Multiple SNPs	CRS (“severe” [‡])	Varied - see ref	<0.05	Varied - see ref	118
Genes Involved in Tissue Remodeling							
<i>MMP9</i>	20q11-q13	rs3918242	CRSwNP with AIA	N/A	0.014	0.19; 0.08	145
		Multiple SNPs	CRSwNP	Varied - see ref	0.011-0.034	Varied - see ref	144
		rs3918242	CRSwNP	N/A	>0.05	0.05; 0.08	145
<i>POSTN</i>	13q13	−33 C > G	CRSwNP	4.56	<0.001	0.44; 0.14	103
<i>TGFB1</i>	19q13	rs1800469	CRSsNP with AIA	N/A	0.012	N/A	59

<i>Gene</i>	Chromosome location	Variation surveyed	Phenotype	Odds ratio	<i>P</i> value	Allele frequency (cases; controls)	Reference number
		rs11466315	CRSwNP	N/A	>0.05	N/A	95
		rs1800469	CRSwNP	N/A	>0.05	N/A	59
Gene Involved in Arachidonic Acid Metabolism							
<i>LTC4S</i>	5q35	rs730012	CHES	1.6	0.04	0.31; 0.19	13
		rs730012	CIS	N/A	>0.05	0.27; 0.19	13
		rs730012	CRSwNP with atopy	0.61	0.033	0.66; 0.76	101
		Multiple SNPs	CRS("severe" $\ddagger$)	N/A	NS	Varied - see ref	150
<i>PTGDR</i>	14q22	Diplo type $\ddagger\ddagger$	CRSwNP	2.44	0.043	0.08; 0.04	101
		Diplo type $\ddagger\ddagger$	CRSwNP with asthma	3.17	0.013	0.10; 0.04	101
		Diplo type $\ddagger\ddagger$	CRSwNP with AIA	3.16	0.041	0.12; 0.04	101
<i>PTGS2</i>	1q25	-765 C > G	CRSwNP	6.05	<0.001	0.41; 0.1	102
Other Genes Significantly Associated with CRS							
<i>ADRB2</i>	5q31-q32	Arg16Gly	CRSwNP	N/A	0.0386	N/A	152
<i>AOAH</i>	7p14-p12	rs4504543	CRSsNP	0.03	8.11×10^{-11}	0.07; 0.21	91
		rs4504543	CRS ("severe" $\ddagger$)	0.52	0.000266	0.26; 0.4	28
		rs4504543	CRSsNP	0.96	0.6371	0.20; 0.21	91
<i>CACNAII</i>	22q13	rs3788568	CRS ("severe" $\ddagger$)	0.52	0.000118	0.31; 0.47	28
<i>DCBLD2</i>	3p12-q11	rs828618	CRSwNP with asthma	0.66	0.05 ∇	0.383; 0.443	167
<i>EMID2</i>	7q22	EMID2_BLI1_ht 2 ^{**}	CRSwNP with asthma	0.54	0.03	0.18; 0.29	168
<i>GSTT1</i>	22q11	homozygous deletion ("null")	CRSwNP	2.03	<0.05	0.28; 0.15	54
		homozygous deletion ("null")	CRSwNP	1.65	0.112	0.337; 0.235	52
		homozygous deletion ("null")	CRSwNP	N/A	0.666	0.40; 0.323	151
		homozygous deletion ("null")	CRSsNP	N/A	0.666	0.277; 0.323	151
<i>KIAA1456</i>	8p22	rs11779957	CRS ("severe" $\ddagger$)	2.12	0.000184	0.31;	0.17 28
<i>LAMA2</i>	6q22-q23	rs2571584	CRS ("severe" $\ddagger$)	0.43	0.000006	0.20; 0.37	28
<i>LAMB1</i>	7q22	rs4727695	CRS ("severe" $\ddagger$)	0.35	0.000085	0.06; 0.16	28
<i>MSRA</i>	8p23	rs7001821	CRS ("severe" $\ddagger$)	1.88	0.000296	0.44; 0.3	28
<i>MUSK</i>	9q31-9q32	rs10817091	CRS ("severe" $\ddagger$)	0.54	0.000218	0.37; 0.52	28
<i>NAV3</i>	12q14	rs1726427	CRS ("severe" $\ddagger$)	2.03	0.000067	0.38; 0.23	28
<i>PARS2</i>	1p32	rs2873551	CRS ("severe" $\ddagger$)	0.49	0.000026	0.34; 0.51	28

Gene	Chromosome location	Variation surveyed	Phenotype	Odds ratio	P value	Allele frequency (cases; controls)	Reference number
<i>PTGS2</i>	1q25	-765 C > G	CRSwNP	6.05	<0.001	0.41; 0.1	102
<i>RYBP</i>	3p13	rs4532099	CRSwNP	2.76	3.24×10^{-6}	0.15; 0.06	91
		rs4532099	CRSsNP	2.45	4.12×10^{-5}	0.13; 0.06	91
<i>TP73</i>	1p36	rs3765731	CRS ("severe" [†])	0.6533	N/A	N/A	42
<i>TRIP12</i>	2q36	rs1035833	CRS ("severe" [†])	0.51	0.000230	0.21; 0.34	28

Abbreviations AFS=allergic fungal sinusitis; AIA=aspirin-intolerant asthma; ATA=aspirin-tolerant asthma; CHES=chronic hyperplastic eosinophilic sinusitis; CIS=chronic inflammatory sinusitis (without eosinophilic infiltrate); CRS=chronic rhinosinusitis; CRSsNP=chronic rhinosinusitis without nasal polyps; CRSwNP=chronic rhinosinusitis with nasal polyps; N/A=not applicable; NS=not significant; ref=reference; SNP=single nucleotide polymorphism; VNTR=variable number tandem repeats

* CRS phenotype (e.g., presence or absence of nasal polyposis) not otherwise specified

[†] 75% CRSwNP, 13% CRSsNP, 12% recurrent acute sinusitis

[‡] The study investigators constructed a haplotype for *MET* using polymorphisms rs38850, rs38855, and rs38857.

[§] 69% CRSwNP, 31% CRSsNP

^{||} 75% CRSwNP, 25% CRSsNP

[¶] $P_{\text{uncorrected}} = 0.006$, $P_{\text{corrected}} = 0.05$

^{***} The study investigators constructed the haplotype EMID2_*BLI*_ht2 using polymorphisms found to be nominally significant in this study (i.e., rs6945102, rs4729697, rs221, and rs10435333).

^{††} The study investigators constructed a diplotype for *PTGDR* using polymorphisms -613C>T, rs8004654, rs803010, and rs11157907 (namely, diplotype CCCT/CCCC).