Genetics of chronic rhinosinusitis: State of the field and directions forward

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The cause of chronic rhinosinusitis (CRS) remains unclear. Study of the genetic susceptibility to CRS might 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 (ie, 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 (eg, 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. (J Allergy Clin Immunol 2013;131:977-93.)

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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 (eg, nasal congestion or discharge) of at least 12 weeks' duration and objective confirmation of sinonasal disease (by means of 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 those with heart failure or back pain in some domains.[6] The availability of effective therapies for CRS is limited, especially in the most severe cases, and understanding the cause might be the best way to develop effective therapeutic strategies.[7]

CRS has been under active investigation for the past 25 years, but intense debate continues regarding the cause 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 (Fig 1).[8,9] One manifestation of this ongoing controversy is the existence of several proposed approaches to dividing CRS into subphenotypes, or endotypes, which might reflect distinct pathogenetic mechanisms or therapeutic responsiveness. CRS is frequently classified as chronic rhinosinusitis with nasal polyposis (CRSwNP) or chronic rhinosinusitis without nasal polyposis (CRSsNP) by many clinicians and researchers.[1,2] Some studies have suggested a T_H2 inflammatory profile (eg, increased levels of eosinophils, IL-5, and IL-13 in sinonasal tissue) might be more characteristic of CRSwNP than CRSsNP.[8,10,11] However, sinonasal T_H2 inflammation has not been identified in all patients with CRSwNP, and there is evidence of T_H1 and T_H2 overlap in both groups.[12] Another suggested approach to subdividing CRS relies on histologic classification: CRS can be categorized as chronic hyperplastic eosinophilic sinusitis (CHES, which is defined as increased sinonasal tissue eosinophilia or immunohistochemical staining for activated eosinophilic cationic protein) or chronic inflammatory sinusitis (CIS, which is defined as CRS without evidence for CHES).[13] By using this method, nasal polyposis can be associated with either CHES or CIS. Beyond these general classification systems, distinct subphenotypes of CRS might exist that span or supersede these categories, such as aspirin-exacerbated respiratory disease (AERD) and allergic fungal rhinosinusitis.[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]

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Abbreviations used

AERD: Aspirin-exacerbated respiratory disease
AF: Allele frequency
AIA: Aspirin-intolerant asthma
aka: Also known as
AOAH: Acyloxyacyl hydrolase gene
ATA: Aspirin-tolerant asthma
CF: Cystic fibrosis
CFTR: Cystic fibrosis transmembrane conductance regulator
CHES: Chronic hyperplastic eosinophilic sinusitis
CIS: Chronic inflammatory sinusitis
CRS: Chronic rhinosinusitis
CRSsNP: Chronic rhinosinusitis without nasal polyposis
CRSwNP: Chronic rhinosinusitis with nasal polyposis
CT: Computed tomography
eQTL: Expression quantitative trait locus
GST: Glutathione-S-transferase
GWAS: Genome-wide association study
IL1A: IL-1α gene
IL1B: IL-1β gene
IL1RL1: IL-1 receptor–like 1
IRAK4: IL-1 receptor–associated kinase 4
LD: Linkage disequilibrium
LTC4S: Leukotriene C_4 synthase gene
MET: Met proto-oncogene
MMP: Matrix metalloproteinase
NOS: Nitric oxide synthase
OR: Odds ratio
PAI-1: Plasminogen activator inhibitor 1
pGWAS: Pooling-based genome-wide association study
RARS: Recurrent acute rhinosinusitis
RYBP: Ring1 and YY1 binding protein
SNP: Single nucleotide polymorphism
TLR: Toll-like receptor
TP73: Tumor protein p73 gene

the most appropriate method for cataloguing CRS remains a matter of debate, as does the cause 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 efforts,[15-17] 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. Although more recent studies have attempted to search for genes related to sinus disease by use of DNA microarrays[14,18-20] and protein expression analyses,[20-22] we still lack a clear understanding of the underlying molecular pathology. A fundamental problem is that 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 can affect the development of CRS from its onset. Along with our inability to predict which patients will have 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 cause of many chronic relapsing and remitting diseases.[23] Study of the genetic susceptibility to CRS might be a valuable path toward understanding the development of this burdensome disorder. Advantages of this strategy include the following: (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 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 disease[24]; whole-genome sequencing, which collects complete genetic information and therefore can detect rare genetic variants associated with disease[24]; exome sequencing, in which only the coding portions of genes (exons) are sequenced[24]; RNA sequencing, which explores how variation in RNA transcripts might correlate with disease[25]; epigenomics, the study of how disease can be associated with biochemical modifications of DNA that affect gene regulation (eg, DNA methylation or histone acetylation)[26]; proteomics, the large-scale analysis of the structure and function of proteins in cells or tissues[22]; and metabolomics, the global analysis of small metabolites involved in cellular processes that might 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 used 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 had 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 dyskinesia,[37] as well as monogenic diseases, such as cystic fibrosis (CF), which is caused by a deficiency in epithelial chloride transport caused by mutations in the cystic fibrosis transmembrane conductance regulator gene (*CFTR*) gene.[38] Lastly, the inflammatory features of CRS have similarities to those seen in patients with allergic rhinitis and asthma, 2 complex diseases with well-established genetic components[24,39] and strong clinical associations with

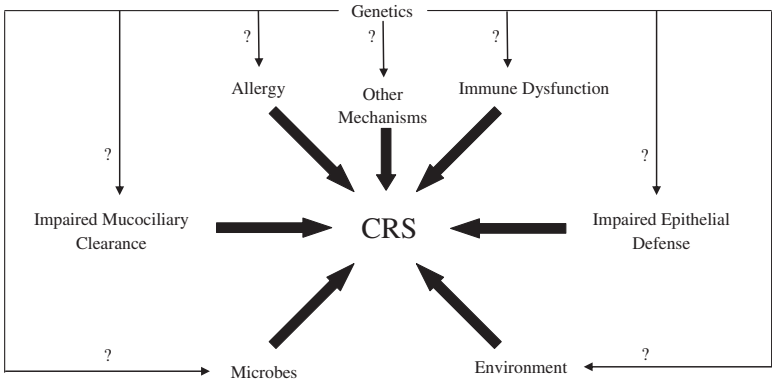

FIG 1. Identified factors that might contribute to the development of CRS. Genetic variation can contribute to the pathogenesis of CRS by influencing some or all of the various mechanisms illustrated above.

CRS.[1,3] Indeed, studies have demonstrated common molecular and cellular aspects of these disorders, leading to the unified airway concept, which postulates that the common clinical manifestations of CRS, allergic rhinitis, and asthma suggest a shared cause.[40]

GENETICS OF CRS: CURRENT STATE OF THE FIELD AND LIMITATIONS OF 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 those without CRS (control subjects). 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 disease 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 patients with CRS. One linkage analysis has been conducted, although the small sample size limited its utility.[41] Although GWASs have provided useful information for a host of diseases, including related conditions, such as asthma (reviewed in Ober and Yao[24]), there are only 2 such studies of CRS.[28,42] There are several reasons for the paucity of GWASs 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 GWASs for producing a smaller direct effect on clinical medicine than was initially anticipated or promoted,[43] GWASs 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, immunologic, 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 (eg, AERD and allergic fungal rhinosinusitis). Classification systems for CT scan findings are crude at best, and most studies do not mention issues, such as minimal abnormalities (eg, mucous retention cysts), that are likely inconsequential. Similar problems plague methods of classifying endoscopic findings in patients with CRS, histologic results, and even clinical comorbidities (atopy by report, skin test, or serum test; asthma by self-report, doctor's diagnosis, or pulmonary function testing). Because variants can be associated with subsets of the disease, a more complete evaluation might be necessary for identification of a true genetic signal; conversely, lack of information might dilute such a signal. For example, because CRSwNP and CRSsNP might be distinct in their genetic susceptibility,[2,8,56] combining these groups could obscure genetic associations. Furthermore, subphenotypes of CRS (eg, CRS associated with asthma or CRS associated with AERD) might be pathogenetically unique and thus yield a genetic signature distinct from that of CRS without these comorbidities. Even before categorizing CRS into subphenotypes, inadequate inclusion criteria for the primary diagnosis of CRS in a research study (eg, lack of endoscopy or adequate imaging[57-59]) or insufficient scrutiny of ambiguous radiographic findings (eg, inclusion cysts on sinus CT) can result in incorrect assignment of cases and control subjects.

Additionally, there is real concern for the presence of undiagnosed CRS among control subjects (because of difficulties in phenotyping control subjects with endoscopy and CT imaging). Incorrect or inadequate phenotyping of patients with CRS and control subjects diminish study power, but this can be overcome by increasing the sample size of cases, control subjects, or both. However, no large genetic studies of CRS have been performed to date. Because the cause 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 patients with 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 might account for the association. An SNP can directly cause disease by altering gene regulation or by changing protein function. Alternatively, the identified SNP might be in linkage disequilibrium (LD) with the actual causal variant (ie, the identified genotyped SNP could be some distance away from the actual causal [ungenotyped] SNP, but because these 2 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 might also be due to allele frequencies caused by unknown or undetected differences between the ancestry proportions of the case and control groups (ie, population structure) and therefore unrelated to CRS disease. This must be considered if patients with CRS and control subjects are not adequately matched for ancestry (eg, by assessing polymorphisms that are known to differ in allele frequency [AF] between populations).[60] The associated SNP might be an expression quantitative trait locus (eQTL) for a gene elsewhere in the genome (ie, 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 could be falsely positive because of a type 1 statistical error, which is a common risk inherent in genetic studies if methodological safeguards (eg, 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 I. A comprehensive list of studies and their major findings (statistically significant or negative studies) is provided in Table E1 in this article's Online Repository at www.jacionline.org.

CRS and the *CFTR* locus

The vast majority of patients with CF 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 is the ΔF508 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 patients with CF suggests *CFTR* might contribute to the pathogenesis of CRS, and this relationship might 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 patients with CF 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 patients with CRS were more likely to be *CFTR* carriers compared with control subjects (7% vs 2%). Use of objective measures to confirm CRS (ie, nasal endoscopy or sinus CT) was a strength of this study. The most frequent mutations identified in this study were the ΔF508 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 patients with CRS and control subjects 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 (ie, parents of children with known CF).[44] Studies of populations outside the United States have reported similar associations.[66,67] Additionally, results from a linkage study (reviewed in our discussion of linkage analyses and GWASs) 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 might reveal the prevalence of *CFTR* mutations in patients with 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 patients with CRS with comorbid asthma (42% [16/38 patients]) and even higher in their very small sample of patients with CRSwNP (66% [4/6 patients with CRSwNP patients in the study]).[68] The authors estimated they would have missed 75% of *CFTR* mutation carriers (ie, 30/41 patients) if they had used only genetic screening for the 23 most common *CFTR* mutations for patients with CF 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 might prove worthwhile.

Several mechanisms have been proposed to explain how CFTR dysfunction affects sinonasal disease in patients with CF, and these also might apply to *CFTR* mutations associated with CRS without other features of CF. First, decreased mucociliary clearance has been observed in the sinonasal epithelium in patients with CF, which might predispose to recurrent infection and chronic inflammation.[38] Susceptibility to recurrent sinusitis in patients with CF could also be due to other alterations in host defense associated with CFTR dysfunction, including abnormal sinonasal pH[69] and decreased transport of thiocyanate (which functions both as an antioxidant and as an antimicrobial) into the airways of patients with CF.[70] Moreover, the hyperviscous mucus layer of patients with CF contains an abnormally low oxygen tension (attributed to increased oxygen use by epithelial cells), and this local hypoxia has been associated with biofilm formation and bacterial proliferation, features that have been implicated in

TABLE I. Genes significantly associated with CRS in 1 or more studies

Gene	Chromosome location	Variation surveyed	Phenotype	OR	*P* value	AF (cases; control subjects)	Reference
Genes involved in chloride ion transport							
CFTR	7q31	Multiple SNPs	CRSsNP	NA	.0023	NA	41
		Multiple SNPs	CRS*	NA	.04	0.07; 0.02	64
		Multiple SNPs	CRS*	3.5	<.05	0.12; 0.04	65
		M470V	CRSwNP (eosinophilic)	NA	.316	0.69; 0.48	161
		Multiple SNPs	CRS*	NA	NA	0.36; 0.14	44
		Multiple SNPs	CRSwNP	NA	>.05	0.05; 0.05	66
		G551D	CRSwNP with AIA	NA	NA	NA	67
		591del18	Recurrent CRSwNP	NA	NA	NA	162
		Multiple SNPs	CRSwNP and CRSsNP	NA	NA	Varied, see reference	68
Genes encoding human leukocyte antigens							
HLA-A	6p21	Multiple SNPs	CRSwNP	71.3 for HLA-A*74	<.03	0.03; 0	80
		Multiple SNPs	CRS ("intractable")	NA	NS	Varied, see reference	57
		HLA-A*24	CRSwNP with AIA	NA	<.05	0.278; 0.125	46
		Multiple SNPs	CRSwNP	NA	>.05	Varied, see reference	46
		Multiple SNPs	CRSwNP	NA	NS	Varied, see reference	163
		Haplotype A1/B8	CRSwNP with asthma	NA	NA	NA	81
		HLA-A*1	CRSwNP with "seronegative inflammatory rheumatism"	NA	NA	0.6; no control subjects in the study	164
HLA-B	6p21	Multiple SNPs	CRS ("intractable")	3.23 for HLA-B54	<.037	0.293; 0.114	57
		Multiple SNPs	CRSwNP	NA	<.05	Varied, see reference	46
		Multiple SNPs	CRSwNP	NA	NA	Varied, see reference	163
		Multiple SNPs	CRSwNP with "seronegative inflammatory rheumatism"	NA	NA	0.6; no control subjects	164
HLA-C	6p21	Multiple SNPs	CRSwNP	NA	<.05	Varied, see reference	46
		HLA-Cw*12	CRSwNP with AIA	NA	<.05	0.167; 0	46
		Multiple SNPs	CRS ("intractable")	NA	NS	Varied, see reference	57
HLA-DR	6p21	Multiple SNPs	CRSwNP in ATA	Varied, see reference	.005-.007	Varied, see reference	165
		Multiple SNPs	CRSwNP	Varied, see reference	.009-.03	Varied, see reference	45
		HLA-DR*16	CRSwNP	8.9	.03	0.05; 0.0062	82
		HLA-DRB1*04	CRSwNP with AIA	NA	<.05	0.444; 0.234	46
		HLA-DR*7	CRSwNP	2.55	<.05	NA	84
		Multiple SNPs	CRS ("intractable")	NA	NS	Varied, see reference	57
HLA-DQ	6p21	HLA-DQB1*03	CRSwNP	4.25	<.001	0.5; 0.19‖	166
		HLA-DQB1*03	AFRS	8.22	<.001	0.66; 0.19‖	166
		Multiple SNPs	CRSwNP	Varied, see reference	.001-.04	Varied, see reference	82
		HLA-DQA1*0201	CRSwNP	6.79	.0027	0.0968; 0.0166	83
		Multiple SNPs	CRSwNP	Varied, see reference	<.05	Varied, see reference	84
		Multiple SNPs	CRSwNP	NA	>.05	Varied, see reference	46
		Multiple SNPs	CRS ("intractable")	NA	NS	Varied, see reference	57
Genes involved in innate immunity							
CD14	5q31	rs2569190	CRSwNP	1.88	.04	0.44; 0.37	96
		rs2569190	CRSwNP	NA	>.05	NA	95
IRAK4	12q12	Multiple SNPs	CRS ("severe"†)	NA	>.05	NA	97
		Multiple SNPs	CRSsNP	Varied, see reference	NS	Varied, see reference	98
		Multiple SNPs	CRSwNP	Varied, see reference	NS	Varied, see reference	98
LTF	3p21	140 A / G	CRSwNP	4.27	<.001	0.38; 0.12	103
MET	7q31	Haplotype‡	CRS ("severe"§)	Varied, see reference	.018	0.349; 0.264	93
		−14 C > G	CRSwNP	5.52	<.001	0.34; 0.08	102
NOS1	12q24	Multiple SNPs	CRS ("severe"§)	Varied, see reference	.0023-.0129	Varied, see reference	99
NOS1AP	1q23	rs4657164	CRS ("severe"§)	1.67	.0178	0.195; 0.128	99
NOS2A	17q11-q12	Promoter VNTR	CRSwNP	14.39	.001	NA	47
		Promoter VNTR	CRSwNP with asthma	0.36	.018	0.06; 0.02	101
		Promoter VNTR	CRSwNP with AIA	0.25	.005	0.08; 0.023	101

(Continued)

TABLE I. *(Continued)*

Gene	Chromosome location	Variation surveyed	Phenotype	OR	*P* value	AF (cases; control subjects)	Reference
SERPINA1	14q32	rs1243168	CRS ("severe"†)	6 for genotype TT	.0211	0.19 for entire cohort	92
TLR2	4q32	Multiple SNPs	CRS*	Varied, see reference	.008-.022	Varied, see reference	49
		rs5743708	CRSwNP	NA	>.05	0.07; 0.12	48
Genes involved in T_H2 inflammation							
IL1RL1	2q12	Multiple SNPs	CRS ("severe"§)	Varied, see reference	.008-.04	Varied, see reference	116
		rs13431828	CRSwNP	0.92	.3887	0.10; 0.11	98
		rs13431828	CRSsNP	0.64	.04464	0.07; 0.11	98
		rs1420101	CRSwNP	1.14	.386	0.43; 0.398	114
IL4	5q31	rs2243250	CRSwNP	0.529 (for TT genotype compared with CC genotype)	.028	0.29; 0.15	109
		rs2243250	CRSsNP	NA	.378	0.20; 0.15	109
		−33 T > C	CRSwNP	1.818	.0236	NA	111
IL13	5q31	Multiple SNPs	CRS with AIA	Varied, see reference	<.001-.012	Varied, see reference	58
IL33	9p24	rs3939286	CRSwNP	1.6	.0041	0.307; 0.216	114
Other genes involved in inflammation							
IDO1	8p12-p11	rs7820268	CRSwNP with AIA	0.58	.011	0.101; 0.163	120
IL1A	2q14	rs17561	CRSwNP	2.743	<.001	0.44; 0.18	126
		rs17561	CRSwNP in asthmatic patients	2.73 for GG genotype	.005	0.20; 0.34	134
		Multiple SNPs	CRS ("severe"§)	Varied, see reference	.003-.02	Varied, see reference	131
		Multiple SNPs	CRSwNP	NA	>.05	NA	95
IL1B	2q14	rs16944	CRSwNP	0.9 for CC genotype	.01	0.38; 0.46	126
		rs16944	CRS ("severe"§)	NA	>.05	0.33 for entire cohort	131
		Multiple SNPs	CRSwNP	NA	>.05	NA	95
		rs16944	CRSwNP in asthmatic patients	NA	.606	0.40; 0.368	134
		Multiple SNPs	CRS ("recalcitrant"§)	NA	.29-.69	Varied, see reference	51
		−31 T > C	CRS*	1.639 for CC genotype	<.05	NA	135
IL1R2	2q12	rs11688145	CRSwNP with AIA	0.66	.0024	0.244; 0.330	120
IL1RN	2q14	VNTR in Intron 2	CRS ("recalcitrant"§)	3.39 for 2 or 4 repeats	<.05	0.17; 0.06	51
IL6	7p21	rs1800796	CRS*	1.932	<.05	0.163; 0.236	121
		rs13447445	CRSwNP	NA	>.05	NA	95
IL22RA1	1p36	Multiple SNPs	CRS ("severe"‖)	1.716-1.977	.0006-.0014	Varied, see reference	119
LTA	6p21	TNFB*2 allele	CRS ("intractable")	NA	<.05	0.74; 0.56	50
TNF	6p21	Multiple SNPs	CRSwNP	Varied, see reference	<.001-.87	Varied, see reference	95
		rs1800629	CRSwNP	1.86	.01	0.19; 0.12	126
		rs1800629	CRSwNP	3.68	.016	0.186; 0.063	127
		rs1800629	CRS*	NA	>.05	0.08; 0.11	50
		Multiple SNPs	CRSwNP	NA	>.05	Varied, see reference	83
		Multiple SNPs	CRS ("severe"‖)	Varied, see reference	>.05	Varied, see reference	131
TNFAIP3	6q23	Multiple SNPs	CRS ("severe"†)	Varied, see reference	<.05	Varied, see reference	118
Genes involved in tissue remodeling							
MMP9	20q11-q13	rs3918242	CRSwNP with AIA	NA	.014	0.19; 0.08	145
		Multiple SNPs	CRSwNP	Varied, see reference	.011-.034	Varied, see reference	144
		rs3918242	CRSwNP	NA	>.05	0.05; 0.08	145
POSTN	13q13	−33 C > G	CRSwNP	4.56	<.001	0.44; 0.14	103
TGFB1	19q13	rs1800469	CRSsNP with AIA	NA	.012	NA	59
		rs11466315	CRSwNP	NA	>.05	NA	95
		rs1800469	CRSwNP	NA	>.05	NA	59
Genes involved in arachidonic acid metabolism							
LTC4S	5q35	rs730012	CHES	1.6	.04	0.31; 0.19	13
		rs730012	CIS	NA	>.05	0.27; 0.19	13
		rs730012	CRSwNP with atopy	0.61	.033	0.66; 0.76	101
		Multiple SNPs	CRS ("severe"†)	NA	NS	Varied, see reference	150
PTGDR	14q22	Diplotype**	CRSwNP	2.44	.043	0.08; 0.04	101
		Diplotype**	CRSwNP with asthma	3.17	.013	0.10; 0.04	101
		Diplotype**	CRSwNP with AIA	3.16	.041	0.12; 0.04	101
PTGS2	1q25	−765 C > G	CRSwNP	6.05	<.001	0.41; 0.1	102

(Continued)

TABLE I. *(Continued)*

Gene	Chromosome location	Variation surveyed	Phenotype	OR	*P* value	AF (cases; control subjects)	Reference
Other genes significantly associated with CRS							
ADRB2	5q31-q32	Arg16Gly	CRSwNP	NA	.0386	NA	152
AOAH	7p14-p12	rs4504543	CRSsNP	0.03	8.11×10^{-11}	0.07; 0.21	91
		rs4504543	CRS ("severe"†)	0.52	.000266	0.26; 0.4	28
		rs4504543	CRSsNP	0.96	.6371	0.20; 0.21	91
CACNA1I	22q13	rs3788568	CRS ("severe"†)	0.52	.000118	0.31; 0.47	28
DCBLD2	3p12-q11	rs828618	CRSwNP with asthma	0.66	.05¶	0.383; 0.443	167
EMID2	7q22	EMID2_BL1_ht2#	CRSwNP with asthma	0.54	.03	0.18; 0.29	168
GSTT1	22q11	Homozygous deletion ("null")	CRSwNP	2.03	<.05	0.28; 0.15	54
		Homozygous deletion ("null")	CRSwNP	1.65	.112	0.337; 0.235	52
		Homozygous deletion ("null")	CRSwNP	NA	.666	0.40; 0.323	151
		Homozygous deletion ("null")	CRSsNP	NA	.666	0.277; 0.323	151
KIAA1456	8p22	rs11779957	CRS ("severe"†)	2.12	.000184	0.31; 0.17	28
LAMA2	6q22-q23	rs2571584	CRS ("severe"†)	0.43	.000006	0.20; 0.37	28
LAMB1	7q22	rs4727695	CRS ("severe"†)	0.35	.000085	0.06; 0.16	28
MSRA	8p23	rs7001821	CRS ("severe"†)	1.88	.000296	0.44; 0.3	28
MUSK	9q31-q32	rs10817091	CRS ("severe"†)	0.54	.000218	0.37; 0.52	28
NAV3	12q14	rs1726427	CRS ("severe"†)	2.03	.000067	0.38; 0.23	28
PARS2	1p32	rs2873551	CRS ("severe"†)	0.49	.000026	0.34; 0.51	28
PTGS2	1q25	−765 C > G	CRSwNP	6.05	<.001	0.41; 0.1	102
RYBP	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
TP73	1p36	rs3765731	CRS ("severe"†)	0.6533	NA	NA	42
TRIP12	2q36	rs1035833	CRS ("severe"†)	0.51	.00023	0.21; 0.34	28

AFRS, Allergic fungal rhinosinusitis; *NA*, not applicable; *NS*, not significant; *VNTR*, variable number tandem repeats.
*CRS phenotype (eg, presence or absence of nasal polyposis) not otherwise specified.
†Seventy-five percent with CRSwNP, 13% with CRSsNP, and 12% with recurrent acute sinusitis.
‡The study investigators constructed a haplotype for *MET* using polymorphisms rs38850, rs38855, and rs38857.
§Sixty-nine percent with CRSwNP and 31% with CRSsNP.
‖Seventy-five percent with CRSwNP and 25% with CRSsNP.
¶$P_{uncorrected} = .006$, $P_{corrected} = .05$.
#The study investigators constructed the haplotype EMID2_B*L1_ht2* using polymorphisms found to be nominally significant in this study (ie, 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).

patients with CRS.[71] Insights from the lower airway in patients with CF suggest additional hypotheses for the origin of *CFTR* mutation–induced sinonasal inflammation; for example, increased levels of IL-8, Toll-like receptor (TLR) 2 activity, or both might 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 might underlie sinus disease, further investigation of the importance of *CFTR* in patients with CRS is warranted. Exploring this relationship is not without challenges, including the following: the large number of mutations to be studied given the size of this gene, the possibility that only rare *CFTR* variants can cause CRS, and the interethnic variation in allele frequencies of *CFTR* mutations.[75-78]

CRS and *HLA* genes

Presentation of antigen is an important link between innate and adaptive immunity, and the *HLA* genes play a critical role in antigen presentation. The 3 major HLA class I molecules (HLA-A, HLA-B, and HLA-C) are nearly ubiquitously expressed in the body and primarily present "endogenous" antigens (ie, antigenic peptides derived from proteins synthesized within the cell); the 3 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 (eg, insulin-dependent diabetes mellitus and ankylosing spondylitis),[23] but the relationship between patients with 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 because of the significant immunodysregulation that is characteristic of patients with CRS.

Several groups have examined variation in *HLA* in patients with 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*, and *HLA-A1/B8* haplotypes).[45,46,57,80-84] However, there remains no consensus because 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 2 populations: a case series of 29 patients with CRSwNP from the United Kingdom by Moloney and Oliver[81] and an Austrian case-control study of 89 patients with CRSwNP and 1070 control subjects by Luxenberger et al.[80] Neither study found *HLA-A1/B8* to be associated with CRSwNP itself.[80,81] However, the United Kingdom study found *HLA-A1/B8* was present in 3 of their 4 patients with CRSwNP 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 patients with CRSwNP and 99 control subjects, Ramirez-Anguiano et al[45] found the *HLA-DRB1*04* allele was significantly associated with CRSwNP (odds ratio [OR], 2.2; 95% CI, 1.2-4.2; $P = .009$). However, a Turkish study of 66 patients with CRSwNP and 100 control subjects by Keles et al[46] did not find *HLA-DRB1*04* to be more frequent in patients with CRSwNP compared with control subjects (AF in patients with CRSwNP, 23.4%; AF in control subjects, 23.4%; $P > .05$). The Turkish study did find that *HLA-DRB1*04* was more frequent in patients with CRSwNP with associated asthma or with AERD (AF in patients with CRSwNP with asthma, 32.4%; AF in patients with CRSwNP with AERD, 44.4%; AF in control subjects, 23.4%; $P < .05$ for both comparisons).[46] Of note, none of the patients with CRSwNP in the study of Mexican Mestizos had AERD, and only 4 (12%) patients had asthma.[45] These differences suggest *HLA-DRB1*04* might be associated with distinct CRS phenotypes (eg, 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 (eg, the epithelial barrier and mucociliary clearance of pathogens), antimicrobial molecules (eg, complement, defensins, and pentraxins), hematopoietic cells (eg, 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 might underlie the pathogenesis of CRS.[86-89] For example, studies have shown decreased levels of the antimicrobial S100 proteins in sinonasal tissue from patients with CRS compared with 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)* might influence the ability of upper respiratory tract cells to combat infection.[90] Thus innate immunity genes appear to be worthy candidates for studies of genetic variation in patients with 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 unproved: assessment of possible LD and eQTL is inconsistent in these studies,[91-93] and, to our knowledge, functional assessments of implicated SNPs have not yet been reported.

A candidate gene study from Germany (68 patients with CRSwNP and 51 control subjects) 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 patients with CRSwNP and 153 control subjects) found no association between CRSwNP and the TLR4 coreceptor CD14 ($P > .05$), but a more recent study from Iran (106 patients with CRSwNP and 87 control subjects) 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 patients with CRS (75% with CRSwNP, 13% with CRSsNP, and 12% with recurrent acute rhinosinusitis [RARS]) and 200 control subjects and found no association with genetic variation in the TLR4 signaling molecule MyD88 or IL-1 receptor–associated kinase 4 gene (*IRAK4*), which mediate downstream signaling of multiple TLRs. 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 might have been diluted by phenotype heterogeneity in this study, although limited power for subgroup analysis might 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 could represent a reasonable and practical approach to finding genetic variation involved.

In a larger more recent study of Chinese patients (324 patients with CRSwNP, 341 patients with CRSsNP, and 326 control subjects), 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 patients with CRSwNP and patients with 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 patients with CRS based on 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% with CRSwNP and 25% with CRSsNP) and 196 control subjects 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 patients with CRSwNP and 98 control subjects) that examined the relationship between CRSwNP and variable number tandem repeats 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 with control subjects.[47] Results from a more recent Spanish study supported a relationship between *NOS2A* variable number tandem repeats and certain subphenotypes of CRSwNP: 15 or more CCTTT repeats were associated with patients with CRSwNP with asthma (n = 144, P = .034 compared with 245 control subjects), as well as patients with CRSwNP with aspirin-intolerant asthma (AIA; n = 75, P = .005 vs control subjects).[101]

In addition to identifying associations between CRS, *IRAK4*, and NOS family members, Castano et al[93] have used candidate gene studies of their Quebecois sample to demonstrate significant relationships between CRS and the met proto-oncogene *(MET)* locus (also known as [aka] hepatocyte growth factor receptor, which is thought to be involved in epithelial cell proliferation[1,93]) and serpin peptidase inhibitor, clade A (α-1 antiproteinase, antitrypsin), member 1 *(SERPINA1)*,[92] the molecule that underlies α-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 genome-wide association studies (pGWASs) have implicated additional genetic variation in innate immunity in the pathogenesis of CRS.[28,42] These findings are reviewed in our discussion of GWASs and linkage studies.

CRS and genes involved in T_H2 inflammation

Evidence supports a T_H2 inflammatory profile for CRSwNP, including increased T_H2 cytokine levels (eg, IL-5 and IL-13) and eosinophil numbers in sinonasal tissue from patients with CRSwNP.[8,10,11] Furthermore, studies have linked genetic variants in genes encoding T_H2 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 might be more associated with T_H2 inflammation than CRSsNP[8,10,11]) and genetic variation in T_H2 inflammatory mediators might provide insights into the cause of CRS. Although single studies have not identified significant associations between genetic variation in the T_H2-associated chemokines CCL2 (aka monocyte chemoattractant protein 1)[95] and CCL11 (aka eotaxin),[108] other research efforts have yielded promising leads linking CRS to variation in T_H2-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 with CRSwNP and 45 with CRSsNP) and 70 control subjects 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 with CC genotype, 0.529; 95% CI, 0.307-0.912; P = .028). The authors acknowledged their finding contrasted with those of prior reports of increased functional IL-4 expression associated with the T allele (because of enhanced binding of the transcription factor nuclear factor of activated T cells 1).[109] The question of how the T allele at rs2243250 might reduce the risk of CRSwNP while increasing IL-4 expression remains unresolved. This investigator group subsequently reported the T allele might be associated with lower expression of 5-lipoxygenase in nasal polyp tissue.[110] Both of these studies await successful replication. A recent Chinese study did not 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 1 study has examined genetic variation in *IL13* in patients with CRS. In a Korean study of 162 patients with AIA, 111 of whom received a diagnosis of 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 patients with AIA demonstrated that SNPs in the *IL13* promoter (rs1881457 and rs1800925) were significantly associated with CRS (P = .012 and P = .001, respectively). 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 causes for the positive associations identified in this study (other than causality) was not explored. Also, this study evaluated atopy by using aeroallergen skin prick testing, but the analysis did not specify whether the significant association between *IL13* and CRS in patients with AIA 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 T_H2 cells.[112] To our knowledge, no study has replicated this association between *IL13* and CRS.

IL-33 is another cytokine known to induce T_H2 immune polarization,[24] and genetic variation in *IL33* has been implicated in patients with allergic disease, including a well-replicated association with asthma.[24] *IL33* mRNA has been reported to be increased in epithelial cells from patients with CRSwNP.[113] To date, only 1 genetic study of *IL33* and CRS has been reported. In a well-phenotyped study of more than 700 Belgian patients (284 patients with CRSwNP and 427 control subjects) 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 might 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 IL-1 receptor–like 1 (IL1RL1; aka 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 an SNP (rs13431828) to be associated with CRS in a Quebecois population,[116] but these investigators did not find a significant association in a subsequent study involving Chinese patients.[91] A Belgian study did not detect an association between another *IL1RL1* SNP (rs1420101) and CRSwNP.[114] These disparate results might reflect AF differences among populations, gene-environment interactions that are distinct, or simply a spurious association.[91]

CRS and other proinflammatory genes

Although prior studies have suggested T_H2 immune deviation might be more characteristic of CRSwNP than CRSsNP,[8,10,11] both T_H1 and T_H2 inflammatory features are found in patients with CRSwNP and patients with CRSsNP.[12,117] Thus studies of the genetics of CRS have extended beyond T_H2-associated molecules to include other mediators of inflammation and associated processes (eg, cell adhesion and communication). Results from these investigations have been mixed, yielding little improvement in our understanding of the underlying biology of CRS. Significant associations have been reported between CRS and variants in lymphotoxin α (*LTA*; aka TNF-β, a lymphokine also involved in lymphangiogenesis)[50]; TNF-α–induced protein 3 (*TNF-AIP3*; aka *A20*, which modulates nuclear factor κB transcription factor activation)[118]; IL-22 receptor α1 (*IL22RA1*; involved in production of acute-phase reactants and antimicrobial peptides)[119]; indoleamine 2,3-dioxygenase (*IDO1*; associated with immune tolerance)[120]; and 2 inhibitory receptors of IL-1 (IL-1 receptor antagonist [*IL1RN*] and IL-1 receptor, type II [*IL1R2*]).[51,120] To our knowledge, replication of these findings has not yet been reported. One Chinese study of 123 patients with CRS (subphenotype unspecified) and 239 control subjects identified an association between CRS and genetic variation in IL-6,[121] which supports prior clinical experiments implicating IL-6 in patients with CRSwNP[122]; a prior US study found no association between CRSwNP and *IL6*,[95] and therefore the results of the Chinese study await replication. Individual studies have not shown 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, aka 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.

An 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 might 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 patients with CRSwNP (evaluated by means of CT, also with nasal polyps visible to "the unaided eye") and 153 control subjects 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 patients with CRSwNP and 95 control subjects) 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, 1.4-7.1; $P = .004$) but found no significant relationship between patients with 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 increased TNF production.[128-130] Studies of Quebecois (n = 206 patients with CRS and 196 control subjects)[131] and Japanese (n = 38 patients with CRS and 35 control subjects)[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 (ie, they are eQTLs).

The SNP rs17561 in the coding region of the IL-1α gene *(IL1A)* has been linked to autoimmunity[132] 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 patients with CRS compared with control subjects (OR, 1.48; 95% CI, 1.06-2.05; $P = .02$). Similarly, a Turkish study of 82 patients with CRSwNP and 106 control subjects reported a trend for the TT genotype to be more prevalent among patients with CRSwNP compared with control subjects (OR, 5.8; 95% CI, 3.1-11.0; $P = .05$).[126] However, a Finnish study of 35 asthmatic patients with CRSwNP and 210 asthmatic patients 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 to be associated with CRSwNP; the GG genotype was identified in 68.6% of asthmatic patients with CRSwNP compared with 40.4% of asthmatic patients 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-1α, differential levels of IL-1α expression have yet to be associated with this SNP. Studies of polymorphisms in the IL-1β gene *(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 TGF-β levels appear to be higher in patients with CRSsNP and lower in patients with CRSwNP compared with those in control subjects.[8,136-138] Levels of matrix

metalloproteinases (MMPs; which act on extracellular matrix components) and tissue inhibitor of matrix metalloproteinases also differ in sinonasal tissue from patients with CRSwNP and patients with CRSsNP compared with those in control tissue.[8,138,139] Additionally, fibrinolytic components, such as plasminogen activator inhibitor 1 (PAI-1) and tissue plasminogen activator, are known to mediate remodeling and fibrosis,[140-142] and they have been implicated in diseases such as asthma and CRS.[143]

On the basis of these data, these molecules appear as attractive targets for study of genetic variation in patients with CRS. However, conclusions from this body of literature remain elusive because of heterogeneity of phenotype, sparse replication of positive findings, unclear functional relevance of implicated SNPs, and limited power because of small sample size. MMP9 protein levels are reported to be abnormal in sinonasal tissue,[139] and 2 candidate gene studies have implicated *MMP9* in CRS pathogenesis.[144,145] A Taiwanese study of 203 patients with CRSwNP (characterized by history, CT, and endoscopy) and 730 control subjects by Wang et al[44] 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 patients with CRSwNP and 115 control subjects found this SNP was associated with CRSwNP only among their AIA subgroup (n = 13; $P = .014$; OR, not specified)[145]; the proportion of patients with AIA in the Taiwanese study was not specified.[144] This ambiguity highlights the importance of rigorous phenotyping in study design, even within a population of patients with well-characterized CRSwNP.

Additionally, 2 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 patients with AIA (including 72 patients with CRSwNP and 59 patients with CRSsNP), 324 patients with ATA (including 10 patients with CRSwNP and 179 patients with CRSsNP), and 456 control subjects. Confirmation of CRS was limited to rhinoscopy and paranasal sinus radiography. In a secondary analysis of the AIA subgroup, CRSsNP was more frequent among patients with the CT or TT genotypes at rs11466315 compared with those with the CC genotype (87.1% vs 68.2%, $P = .012$).[59] Although other studies have identified increased local TGF-β expression in the sinonasal tissue of patients with CRSsNP,[8,136-138] this study found the implicated CT and TT genotypes of rs11466315 to be associated with lower serum levels of TGF-β in this study (TGF-β levels 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 patients with ATA or between *TGFB1* and CRSwNP.[59] Similarly, Bernstein et al[95] found no association between rs11466315 and CRSwNP in their study of 179 patients with CRSwNP and 153 control subjects.

Despite studies of sinonasal tissue suggesting a role for other tissue-remodeling components in the development of CRS, including MMP2, tissue plasminogen activator, and PAI-1,[138,139,141,142] studies of *MMP2* and *SERPINE1* (aka *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 patients with CRSwNP and 136 control subjects, 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 might have been underpowered (n = 51 patients with CHES, n = 16 patients with CIS, and n = 66 control subjects), perhaps explaining why a subset analysis of patients with CRSwNP and patients with CRSsNP was not performed.[13]

CRS and genes involved in arachidonic acid metabolism

Arachidonic acid metabolism is disrupted in patients with AERD (aka 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 patients with 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 patients with CHES and patients with CIS in the United States reported the minor allele C in a leukotriene C_4 synthase gene *(LTC4S)* promoter SNP (rs730012) as more frequent in patients with CHES than in control subjects (AF for C allele in patients with CHES, 0.31; AD for C allele in control subjects, 0.19; $P = .04$).[13] The frequency of nasal polyposis among patients in this study was not specified, nor was the frequency of nasal polyposis 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 control subjects (0.19, $P > .05$).[13] A Spanish study found the C allele at this SNP was significantly more common among atopic patients with CRSwNP compared with control subjects (patients with atopic CRSwNP, n = 74, C allele AF = 0.34; control subjects, n = 245, AF = 0.24; $P = .033$ for comparison).[101] In contrast, Al Shemari et al[150] did not replicate the association between *LTC4S* and CRS in Quebecois patients (75% with CRSwNP, 25% with CRSsNP, and 12% with 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 patients with CRSwNP and 245 control subjects) support the 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 D_2 receptor *(PTGDR)*, which was significantly associated with CRSwNP and AERD (see Table I).[101] Another recent publication reported an association between the

gene encoding COX-2 *(PTGS2)* and CRSwNP (−765G/C: OR, 6.05; 95% CI, 4.15-8.83; $P < .001$) among 195 patients with CRSwNP and 200 matched control subjects.[102]

Other candidate gene studies in patients with CRS

An assortment of other molecules has been examined in genetic studies of patients with CRS, but as with the work discussed thus 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 patients with CRSwNP and 167 control subjects (OR, 2.03; 95% CI, 1.03-4.011; $P < .05$)[54]; other studies using another Turkish sample (98 patients with CRSwNP and 102 control subjects) and a German population (69 patients with CRSwNP, 49 patients with CRSsNP, and 52 control subjects) did not find a significant association with variation in this gene.[52,151] None of these studies detected an association in patients with CRSwNP or patients with CRSsNP with genetic variation in genes coding for other enzymes in this pathway (glutathione S-transferase M1 *[GSTM1]* and 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 adrenergic β_2-receptor gene *(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 with CRSwNP, 332 with CRSsNP, and 315 control subjects) has identified an association between CRSwNP, CRSsNP, and Ring1 and YY1 binding protein (*RYBP*; patients with CRSwNP: OR, 2.76, $P = 3.24 \times 10^{-6}$; patients with 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 mediators[91]; its direct effect on CRS pathogenesis remains unclear. All these results, although intriguing, require replication.

INSIGHTS FROM GENOME-WIDE APPROACHES: LINKAGE STUDIES AND GWASs

Whereas the majority of studies regarding genetic susceptibility in patients with CRS have used candidate gene approaches, 2 groups have used genome-wide study designs (ie, linkage analysis and pooling-based GWAS [pGWAS]) to answer this question.[28,41,42] By using a hypothesis-independent approach, these studies have provided additional support for genes previously suspected in patients with CRS (eg, *CFTR*) and also identified numerous genes heretofore unexplored in patients with 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 because of the challenges of extensive variation within the *CFTR* gene, as well as the large number of other candidate loci in this region.[41]

Two pGWASs of patients with CRS have been published.[28,42] Unlike traditional GWASs, 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 control subjects from Quebec. This study identified novel associations between CRS and variation in genes involved in basement membrane formation: laminin, α2 (*LAMA2*); laminin, β1 (*LAMB1*); and the acyloxyacyl hydrolase gene (*AOAH*).[28] The *AOAH* gene is particularly interesting because it contributes to host defense against bacterial LPS 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]

In addition to *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 patients with CRS (CRSwNP and CRSsNP combined) and 196 control subjects and found an association between CRS and variation in the epithelial tumor protein p73 gene (*TP73*).[42] In particular, AA homozygotes at the *TP73* SNP rs3765731 had a 7-fold lower risk of CRS compared with GG homozygotes (OR, 0.14).[42] A possible role for *TP73* in patients with 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 patients with 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 using gene sequencing of *CFTR* (and examining populations of other ancestries) might yield additional insights, although the large amount of variation in this gene might prove a challenge to such studies. It is also possible that many rare variants in *CTFR* are involved, in which case a gene-based approach that analyzes all variation within 1 gene might 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, and

therefore the genes examined cannot be excluded as candidates for involvement in CRS. Studies that reported positive associations often had limited phenotyping (eg, the unclear importance of AERD in the association between CRS and *HLA-DRB1*04*[45,46]) or included a heterogeneous phenotype (eg, CRSwNP, CRSsNP, and RARS combined[150]). In some sense this could be an advantage because the 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, and therefore 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 (eg, *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 (eg, tobacco smoke and particulate air pollutants) might be relevant in patients with CRS, but these relationships remain largely unknown.[1] Several studies have examined the role of tobacco smoke in patients with CRS: for example, CRS might be more prevalent among tobacco smokers, and postoperative outcomes for smokers undergoing sinus surgery could be worse than for nonsmokers.[1] This relationship might 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 genetic studies that account for potential gene-environment interactions in patients with CRS might 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 patients with disease and control subjects 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 (eg, nasal polyposis) and other potential comorbid conditions (eg, asthma, atopy, and AERD) that might suggest distinct pathogenic mechanisms are 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. Because of the myriad of environmental and other nongenetic influences that likely affect disease expression, approaches that take advantage of cell culture–based intermediate phenotypes for disease might 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 GWASs to study CRS. GWASs have proved useful for understanding complex disease traits and have produced a number of novel insights into disease biology (eg, regarding the potential importance of ORM1-like 3 *[ORMDL3]* in asthmatic patients[24]). GWASs 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 GWASs 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 (eg, epigenomics, exome and whole-genome sequencing, and transcriptomics) and that are now feasible in terms of time, analysis, and cost, alternative strategies that supplant GWASs can be used for identification of genes involved in CRS biology. Epigenomics, the systematic study of epigenetic changes (eg, DNA methylation and histone modification), can generate new discoveries regarding how gene dysregulation can affect patients with CRS, but investigators are only beginning to use this methodology to study CRS.[159,160] Whole-genome sequencing studies of small kindreds could be performed by identifying families with multiple 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 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 with 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, although with caveats in the available data. Studies suggest that 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 might 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 could 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 (eg, exome sequencing, whole-genome sequencing, or epigenomics) will set the stage for great progress in understanding CRS in the near future.

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TABLE E1. Catalogue of genetic studies of CRS (genes are ordered alphabetically)

Gene	Chromosome location	Variation surveyed	Phenotype	OR	*P* value	AF (cases; control subjects)	Reference
ADRB2	5q31-q32	Arg16Gly	CRSwNP	NA	.0386	NA	152
ALOX5	10q11	Multiple SNPs	CRS ("severe"*)	NA	NS	Varied, see reference	150
ALOX5AP	13q12	Multiple SNPs	CRS ("severe"*)	NA	NS	Varied, see reference	150
AOAH	7p14-p12	rs4504543	CRSsNP	0.03	8.11×10^{-11}	0.07; 0.21	91
		rs4504543	CRS ("severe"*)	0.52	.000266	0.26; 0.4	28
		rs4504543	CRSwNP	0.96	.6371	0.20; 0.21	91
CACNA1I	22q13	rs3788568	CRS ("severe"*)	0.52	.000118	0.31; 0.47	28
CCL2	17q11-q12	rs3917882	CRSwNP	NA	>.05	NA	95
CCL5	17q11-q12	rs2107538	CRSwNP	NA	>.05	NA	95
CCL11	17q21	Multiple SNPs	CRSwNP	NA	>.05	Varied, see reference	E1
CD14	5q31	rs2569190	CRSwNP	1.88	.04	0.44; 0.37	96
		rs2569190	CRSwNP	NA	>.05	NA	95
CFTR	7q31	Multiple SNPs	CRSsNP	NA	.0023	NA	41
		Multiple SNPs	CRS†	NA	.04	0.07; 0.02	64
		Multiple SNPs	CRS†	3.5	<.05	0.12; 0.04	65
		M470V	CRSwNP (eosinophilic)	NA	.316	0.69; 0.48	161
		Multiple SNPs	CRS†	NA	NA	0.36; 0.14	44
		Multiple SNPs	CRSwNP	NA	>.05	0.05; 0.05	66
		G551D	CRSwNP with AIA	NA	NA	NA	67
		591del18	Recurrent CRSwNP	NA	NA	NA	162
		Multiple SNPs	CRSwNP and CRSsNP	NA	NA	Varied, see reference	68
CYSLTR1	Xq13-q21	Multiple SNPs	CRS ("severe"*)	NA	NS	Varied, see reference	150
		rs320995	CRSwNP	NA	NS	0.24; 0.29	101
CYSLTR2	13q14	Multiple SNPs	CRS ("severe"*)	NA	NS	Varied, see reference	150
DCBLD2	3q12	rs828618	CRSwNP with asthma	0.66	.05‡	0.383; 0.443	167
EMID2	7q22	EMID2_BL1_ht2§	CRSwNP with asthma	0.54	.03	0.18; 0.29	168
GATA2	3q21	rs4431128	CRSwNP	0.82	.33	0.15; 0.176	114
GFRA2	8p21	rs748065	CRSwNP	0.79	.132	0.677; 0.726	114
GJB2	13q11-q12	Gene sequenced	CRSsNP or RARS	NA	NA	0.053 in cases (no control subjects in study)	E2
GJB6	13q12	Gene sequenced	CRSsNP or RARS	NA	NA	0 (no mutations detected)	E2
GSTM1	1p13	Homozygous deletion ("null")	CRSwNP	0.95	>.05	0.40; 0.449	54
		Homozygous deletion ("null")	CRSwNP	0.92	.754	0.439; 0.461	52
		Homozygous deletion ("null")	CRSwNP	N/A	.855	0.425; 0.288	151
		Homozygous deletion ("null")	CRSsNP	NA	.855	0.288; 0.288	151
GSTP1	11q13	Ile105Val	CRSwNP	1.61	>.05	0.493; 0.353	54
		Ile105Val	CRSwNP	NA	.328	0.452; 0.29	151
		Ile105Val	CRSsNP	NA		0.258; 0.29	151
GSTT1	22q11	Homozygous deletion ("null")	CRSwNP	2.03	<.05	0.28; 0.15	54
		Homozygous deletion ("null")	CRSwNP	1.65	.112	0.337; 0.235	52
		Homozygous deletion ("null")	CRSwNP	NA	.666	0.40; 0.323	151
		Homozygous deletion ("null")	CRSsNP	NA	.666	0.277; 0.323	151
HLA-A	6p21	Multiple SNPs	CRSwNP	71.3 for HLA-A*74	<.03	0.03; 0	80
		Multiple SNPs	CRS ("intractable")	NA	NS	Varied, see reference	57
		HLA-A*24	CRSwNP with AIA	NA	<.05	0.278; 0.125	46
		Multiple SNPs	CRSwNP	NA	>.05	Varied, see reference	46
		Multiple SNPs	CRSwNP	NA	NS	Varied, see reference	163
		Haplotype A1/B8	CRSwNP with asthma	NA	NA	NA	81

(Continued)

TABLE E1. *(Continued)*

Gene	Chromosome location	Variation surveyed	Phenotype	OR	*P* value	AF (cases; control subjects)	Reference
		HLA-A*1	CRSwNP with "seronegative inflammatory rheumatism"	NA	NA	0.6; no control subjects in the study	164
HLA-B	6p21	Multiple SNPs	CRS ("intractable")	3.23 for HLA-B54	<.037	0.293; 0.114	57
		Multiple SNPs	CRSwNP	NA	<.05	Varied, see reference	46
		Multiple SNPs	CRSwNP	NA	NA	Varied, see reference	163
		Multiple SNPs	CRSwNP with "seronegative inflammatory rheumatism"	NA	NA	0.6; no control subjects	164
HLA-C	6p21	Multiple SNPs	CRSwNP	NA	<.05	Varied, see reference	46
		HLA-Cw*12	CRSwNP with AIA	NA	<.05	0.167; 0	46
		Multiple SNPs	CRS ("intractable")	NA	NS	Varied, see reference	57
HLA-DR	6p21	Multiple SNPs	CRSwNP in ATA	Varied, see reference	.005-.007	Varied, see reference	165
		Multiple SNPs	CRSwNP	Varied, see reference	.009-.03	Varied, see reference	45
		HLA-DR*16	CRSwNP	8.9	.03	0.05; 0.0062	82
		HLA-DRB1*04	CRSwNP with AIA	NA	<.05	0.444; 0.234	46
		HLA-DR*7	CRSwNP	2.55	<.05	NA	84
		Multiple SNPs	CRS ("intractable")	NA	NS	Varied, see reference	57
HLA-DQ	6p21	HLA-DQB1*03	CRSwNP	4.25	<.001	0.5; 0.19‖	166
		HLA-DQB1*03	AFRS	8.22	<.001	0.66; 0.19‖	166
		Multiple SNPs	CRSwNP	Varied, see reference	.001-.04	Varied, see reference	82
		HLA-DQA1*0201	CRSwNP	6.79	.0027	0.0968; 0.0166	83
		Multiple SNPs	CRSwNP	Varied, see reference	<.05	Varied, see reference	84
		Multiple SNPs	CRSwNP	NA	>.05	Varied, see reference	46
		Multiple SNPs	CRS ("intractable")	NA	NS	Varied, see reference	57
IDO1	8p12-p11	rs7820268	CRSwNP with AIA	0.58	.011	0.101; 0.163	120
IFNG	12q14	rs2430561	CRSwNP	NA	>.05	NA	95
IKZF2	2q34	rs12619285	CRSwNP	0.95	.745	0.293; 0.304	114
IL1A	2q14	rs17561	CRSwNP	2.743	<.001	0.44; 0.18	126
		rs17561	CRSwNP in asthmatic patients	2.73 for GG genotype	.005	0.20; 0.34	134
		Multiple SNPs	CRS ("severe"¶)	Varied, see reference	.003-.02	Varied, see reference	131
		Multiple SNPs	CRSwNP	NA	>.05	NA	95
IL1B	2q14	rs16944	CRSwNP	0.9 for CC genotype	.01	0.38; 0.46	126
		rs16944	CRS ("severe"¶)	NA	>.05	0.33 for entire cohort	131
		Multiple SNPs	CRSwNP	NA	>.05	NA	95
		rs16944	CRSwNP in asthmatic patients	NA	.606	0.40; 0.368	134
		Multiple SNPs	CRS ("recalcitrant"#)	NA	.29-.69	Varied, see reference	51
		−31 T > C	CRS†	1.639 for CC genotype	<.05	NA	135
IL1R2	2q12	rs11688145	CRSwNP with AIA	0.66	.0024	0.244; 0.330	120
IL1RL1	2q12	Multiple SNPs	CRS ("severe"¶)	Varied, see reference	.008-.04	Varied, see reference	116
		rs13431828	CRSwNP	0.92	.3887	0.10; 0.11	98
		rs13431828	CRSsNP	0.64	.04464	0.07; 0.11	98
		rs1420101	CRSwNP	1.14	.386	0.43; 0.398	114
IL1RN	2q14	VNTR in Intron 2	CRS ("recalcitrant"#)	3.39 for 2 or 4 repeats	<.05	0.17; 0.06	51
IL4	5q31	rs2243250	CRSwNP	0.529 (for TT genotype compared with CC genotype)	.028	0.29; 0.15	109
		rs2243250	CRSsNP	NA	.378	0.20; 0.15	109
		−33 T > C	CRSwNP	1.818	.0236	NA	111
IL5	5q31	rs4143832	CRSwNP	0.87	.439	0.80; 0.822	114
IL6	7p21	rs1800796	CRS†	1.932	<.05	0.163; 0.236	121
		rs13447445	CRSwNP	NA	>.05	NA	95
IL10	1q31-q32	Multiple SNPs	CRSwNP	NA	>.05	NA	95
		rs1800896	CRS†	NA	>.05	NA	111
IL13	5q31	Multiple SNPs	CRS with AIA	Varied, see reference	<.001-.012	Varied, see reference	58
		Multiple SNPs	CRS with ATA	NA	NS	Varied, see reference	58

(Continued)

TABLE E1. *(Continued)*

Gene	Chromosome location	Variation surveyed	Phenotype	OR	*P* value	AF (cases; control subjects)	Reference
IL22RA1	1p36	Multiple SNPs	CRS ("severe"¶)	1.716-1.977	.0006-.0014	Varied, see reference	119
IL33	9p24	rs3939286	CRSwNP	1.6	.0041	0.307; 0.216	114
IRAK4	12q12	Multiple SNPs	CRS ("severe"*)	NA	>.05	NA	97
		Multiple SNPs	CRSsNP	Varied, see reference	NS	Varied, see reference	98
		Multiple SNPs	CRSwNP	Varied, see reference	NS	Varied, see reference	98
KIAA1456	8p22	rs11779957	CRS ("severe"*)	2.12	.000184	0.31; 0.17	28
LAMA2	6q22-q23	rs2571584	CRS ("severe"*)	0.43	.000006	0.20; 0.37	28
LAMB1	7q22	rs4727695	CRS ("severe"*)	0.35	.000085	0.06; 0.16	28
LTA	6p21	TNFB*2 allele	CRS ("intractable")	NA	<.05	0.74; 0.56	50
LTC4S	5q35	rs730012	CHES	NA	.04	0.31; 0.19	13
		rs730012	CIS	NA	>.05	0.27; 0.19	13
		rs730012	CRSwNP with atopy	0.61	.033	0.66; 0.76	101
		Multiple SNPs	CRS ("severe"*)	NA	NS	Varied, see reference	150
LTF	3p21	140 A/G	CRSwNP	4.27	<.001	0.38; 0.12	103
MET	7q31	Haplotype**	CRS ("severe"¶)	Varied, see reference	.018	0.349; 0.264	93
		−14 C > G	CRSwNP	5.52	<.001	0.34; 0.08	102
MHC	6p21	rs2269426	CRSwNP	0.92	.588	0.347; 0.366	114
MMP2	16q13-q21	Multiple SNPs	CRSwNP	Varied, see reference	>.05	Varied, see reference	E3
MMP9	20q11-q13	rs3918242	CRSwNP with AIA	NA	.014	0.19; 0.08	145
		Multiple SNPs	CRSwNP	Varied, see reference	.011-.034	Varied, see reference	144
		rs3918242	CRSwNP	NA	>.05	0.05; 0.08	145
MSRA	8p23	rs7001821	CRS ("severe"*)	1.88	.000296	0.44; 0.30	28
MYD88	3p22	Multiple SNPs	CRS ("severe"*)	NA	>.05	NA	97
MUSK	9q31-q32	rs10817091	CRS ("severe"*)	0.54	.000218	0.37; 0.52	28
MYB	6q22-q23	rs9494145	CRSwNP	1.21	.276	0.793; 0.754	114
NAV3	12q14	rs1726427	CRS ("severe"*)	2.08	.000067	0.38; 0.23	28
NOS1	12q24	Multiple SNPs	CRS ("severe"¶)	Varied, see reference	.0023-.0129	Varied, see reference	99
NOS1AP	1q23	Multiple SNPs	CRS ("severe"¶)	Varied, see reference	.0178-.8051	Varied, see reference	99
NOS2A	17q11-q12	Promoter VNTR	CRSwNP	14.39	.001	NA	47
		Promoter VNTR	CRSwNP with asthma	0.36	.018	0.06; 0.02	101
		Promoter VNTR	CRSwNP with AIA	0.25	.005	0.08; 0.023	101
PARS2	1p32	rs2873551	CRS ("severe"*)	0.49	.000026	0.34; 0.51	28
POSTN	13q13	−33 C > G	CRSwNP	4.56	<.001	0.44; 0.14	103
PTGDR	14q22	Diplotype††	CRSwNP	2.44	.043	0.08; 0.04	101
		Diplotype††	CRSwNP with asthma	3.17	.013	0.10; 0.04	101
		Diplotype††	CRSwNP with AIA	3.16	.041	0.12; 0.04	101
PTGS2	1q25	−765 C > G	CRSwNP	6.05	<.001	0.41; 0.1	102
SCGB1A1	11q12	rs3741240	CRSwNP	NA	.386	0.394 for entire cohort	123
		rs3741240	CRSsNP	NA	.233	0.394 for entire cohort	123
SERPINA1	14q32	Multiple SNPs	CRS ("severe"*)	Varied, see reference	.0211	Varied, see reference	92
SERPINE1	7q21-q22	rs1799762	CIS	NA	>.05	0.53; 0.45	13
		rs1799762	CHES	NA	>.05	0.44; 0.45	13
SH2B3	12q24	rs3184504	CRSwNP	0.94	.666	0.513; 0.530	114
RYBP	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
TGFB1	19q13	rs1800469	CRSsNP with AIA	NA	.012	NA	59
		rs11466315	CRSwNP	NA	>.05	NA	95
		rs1800469	CRSwNP	NA	>.05	NA	59
TLR2	4q32	Multiple SNPs	CRS†	Varied, see reference	.008-.022	Varied, see reference	49
		rs5743708	CRSwNP	NA	>.05	0.07; 0.12	48
TNF	6p21	Multiple SNPs	CRSwNP	Varied, see reference	<.001-.87	Varied, see reference	95
		rs1800629	CRSwNP	1.86	.01	0.19; 0.12	126
		rs1800629	CRSwNP	3.68	.016	0.186; 0.063	127
		rs1800629	CRS†	NA	>.05	0.08; 0.11	50
		Multiple SNPs	CRSwNP	NA	>.05	Varied, see reference	83
		Multiple SNPs	CRS ("severe"¶)	Varied, see reference	>.05	Varied, see reference	131
TNFAIP3	6q23	Multiple SNPs	CRS ("severe"*)	Varied, see reference	<.05	Varied, see reference	118
TNFAIP6	2q23	Multiple SNPs	CRS ("severe"*)	Varied, see reference	>.05	Varied, see reference	118
TP73	1p36	rs3765731	CRS ("severe"*)	0.6533	NA	NA	42

(Continued)

TABLE E1. *(Continued)*

Gene	Chromosome location	Variation surveyed	Phenotype	OR	*P* value	AF (cases; control subjects)	Reference
TRAF6	11p12	Multiple SNPs	CRS ("severe"*)	NA	>.05	NA	97
TRIP12	2q36	rs1035833	CRS ("severe"*)	0.51	.00023	0.21; 0.34	28
WDR36	5q22	rs2416257	CRSwNP	1.32	.171	0.867; 0.828	114

AFRS, Allergic fungal rhinosinusitis; *NA*, not applicable; *NS*, not significant; *VNTR*, variable number tandem repeats.

*Seventy-five percent with CRSwNP, 13% with CRSsNP, and 12% with RARS.

†CRS phenotype (eg, presence or absence of nasal polyposis) not otherwise specified.

‡$P_{uncorrected} = .006$, $P_{corrected} = .05$.

§The study investigators constructed the haplotype EMID2_B*L1_ht2 by* using polymorphisms found to be nominally significant in this study (ie, *rs6945102*, *rs4729697*, *rs221*, and *rs10435333)*.

‖AF for control group was estimated from prior literature.

¶Seventy-five percent with CRSwNP and 25% with CRSsNP.

#Sixty-nine percent with CRSwNP and 31% with CRSsNP.

**The study investigators constructed a haplotype for *MET* using polymorphisms rs38850, rs38855, and rs38857.[E4]

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