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.)

Key words: *Genetics, genome, variation, chronic rhinosinusitis, nasal polyposis, single nucleotide polymorphism, polymorphism, candidate gene, linkage, genome wide association study, susceptibility, sinusitis*

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