What is the evidence for genetics in chronic rhinosinusitis?

Frederick Yoo and Jeffrey D. Suh

Purpose of review
To perform analysis of evidence in current literature on the topic of genetics and chronic rhinosinusitis (CRS), with a particular focus on recent findings in the cystic fibrosis transmembrane regulator (CFTR), genes associated with primary ciliary dyskinesia, and taste receptor T2R38. Other genes that have been found to have association with CRS are also presented and discussed.

Recent findings
Recent studies in CFTR and CRS research have investigated possible CFTR-potentiators for treatment of refractory CRS. The T2R38 gene has been shown to be applicable in the clinical setting with a testable phenotype and may have a role in the prognosis and influencing management strategies of CRS patients. Many genes of the immune system have been studied, with genome-wide association studies and candidate-gene approaches identifying new associations that will need replication and further elucidation.

Summary
CRS is a multifactorial disease, with strong evidence of a genetic component in its pathophysiology for some cases. Currently, there are over 70 genes that have been genetically associated with CRS in the past 15 years. Future investigations into genetic causes and predispositions of CRS may allow for improved prognostication and development of disease-prevention strategies as well as novel therapeutic targets.

Keywords
chronic rhinosinusitis, cystic fibrosis transmembrane regulator, genetics, polymorphisms, TAS2R38

INTRODUCTION
Chronic rhinosinusitis (CRS) is a common ailment that affects approximately 13% of the US population and is responsible for over $8 billion in healthcare costs [1,2]. Its impact on the quality of life of patients suffering from this disease is significant, with studies showing that it is on par or worse than other chronic diseases such as congestive heart failure, chronic obstructive pulmonary disease, and back pain [3,4].

CRS is defined as sinonasal inflammation with symptoms of nasal discharge/postnasal drip, nasal congestion, sinus pain/pressure, and anosmia/hyposmia, lasting for at least 12 weeks. Although acute rhinosinusitis is largely considered to be secondary to bacterial infection, CRS is a multifactorial disorder that involves an interplay among environmental exposures, infectious causes, and genetic predisposition in its pathogenesis. CRS is often broken down into several classification systems, the most common separating out CRS with nasal polyps (CRSwNP) and CRS without nasal polyps (CRSsNP). In addition, there are histological classifications, including chronic inflammatory sinusitis with or without polyps and chronic eosinophilic sinusitis with or without polyps. Further complicating these classifications are the distinct clinical phenotypes associated with aspirin-exacerbated respiratory disease (AERD), allergic fungal rhinosinusitis, and systemic diseases such as cystic fibrosis (CF) and autoimmune disorders/vasculitides.

Genetic basis to CRS is strongly suggested in certain forms such as CRS associated with CF, as mutations in the CF transmembrane regulator (CFTR) gene impairing respiratory mucosal function have been shown to contribute to the development...
Nose and paranasal sinuses

KEY POINTS

- There is strong evidence for a genetic component in the pathophysiology of chronic rhinosinusitis and future genetic studies, whether in the form of genome-wide association studies or candidate gene studies, should be encouraged.
- Many genetic associations have been found with genes of the immune system in the last 15 years, but these relationships need to be further investigated as conclusions cannot be made on the basis of these studies alone.
- Recent developments into the CFTR gene and CRS have yielded new therapeutic targets, and investigations into CFTR potentiators as potential therapy in CRS patients have begun. In addition, the newly FDA-approved drug, ivacaftor (Vertex Pharmaceuticals, Boston, Massachusetts, USA), is a promising example of genetic studies in CFTR leading to targeted therapy.
- Research into the bitter taste receptor T2R38 is producing exciting results that may have broad implications into identifying patients at risk for CRS and prognostication in CRS patients undergoing surgery.

GWAS studies on the other hand are broad and hypothesis independent, allowing for identification of novel SNPs that differ in allelic frequency between cases and controls; however, they are expensive to undertake and require large numbers of patients [12].

Currently, a total of five GWAS studies investigating CRS have been published, with four coming from the same institution [13–17]. The first study performed in 2008 revealed a strong association of CRS with a locus on the 7q31.1–7q32.1 that is the location of the CFTR gene [13]. A subsequent study was able to identify approximately 600 SNPs from 445 genes that were potentially associated with CRS, but reported only their top 10 genes [14]. The other three studies have identified several other genes that may be implicated in the development of CRS, including the p73 gene, T2R genes (TAS2R38, TAS2R13, and TAS2R49), genes relating to the major histocompatibility complex 1, and 21 other genes involved in the immune response which were associated with Staphylococcus aureus colonization in CRS patients [15–17]. Though GWAS studies represent a powerful tool for identifying genes of interest, the clinical significance of these associations is difficult to define due to typically small sample sizes, the phenotypic heterogeneity of CRS and high potential for false positives; thus they require replication for confirmation and candidate gene approaches as follow-up studies [12,14].

Candidate gene approaches have utilized genotyping of cases versus controls and comparing the frequencies of SNPs in the genes of interest between these two groups. With this more targeted approach, they are able to investigate the presence of certain SNPs or alleles that may confer genetic susceptibility to CRS. Because of the varied phenotypes of CRS, most of these studies focus on a single subtype, most utilizing patients with CRSwNP as their cases [18*]. In these genetic studies, there is still difficulty determining causation, as SNPs can affect genes in different ways (altering gene regulation or altering protein function), or because of complex inheritance patterns that can lead to nonrandom inheritance along with confounding other genetic variations [12]. Also, the use of genetically modified murine models, such as ‘knock out’ mice, has also been employed to investigate the effect of certain immunological factors, which may play a role in the pathogenesis of CRS. The findings of these specific studies will be discussed in the following subsections.

INVESTIGATIONAL METHODS OF GENETICS IN CHRONIC RHINOSINUSITIS

Investigations into the genes associated with CRS are typically undertaken in two pathways: hypothesis driven, candidate gene approaches, and genome-wide association studies (GWAS). Candidate gene approaches are most often employed, but require a target gene that is already known or suspected to be involved in the pathogenesis of CRS, and comparing the allele frequencies of single nucleotide polymorphisms (SNPs) in CRS patients to control patients [12].

The objective of this review is to summarize the current literature and evidence in the role of genetics in CRS. Investigational methods into the study of genetics in CRS will be discussed, along with specific attention to the CFTR gene, genes associated with primary ciliary dyskinesia (PCD), and taste receptor (T2R) genes and their role in CRS, which have been subject to recent investigations. There will also be a brief overview of published studies of other immunological genes that have been associated with CRS.

THE CFTR GENE LOCUS AND CHRONIC RHINOSINUSITIS

CF is a disease caused by mutations in the CFTR gene, encoding for a chloride channel and
What is the evidence for genetics in chronic rhinosinusitis? Yoo and Suh

regulatory protein, and it is inherited in an autosomal recessive fashion. The disease is characterized by severe pulmonary disease and eventual development of CRS in nearly all patients, typically CRSwNP. The pathogenesis of CRS in CFTR dysfunction is thought to be related to decreased mucociliary clearance, abnormal sinonasal pH, decreased transport of thiocyanate that has antimicrobial and antioxidant properties, and local sinonasal hypoxia that may be implicated in biofilm formation [19–22]. In a genome-wide screen, the CFTR gene was noted to be associated with CRS with a locus identified at 7q31.1–7q32.1 [13]. The most common genetic mutation in North America is a deltaF508 variant, but over 2000 mutations of the CFTR have been associated with CF, with some exhibiting a milder phenotype [7∗]. Since the study in 2000 by Wang et al., which first identified an increased frequency of CFTR mutation in CRS patients, multiple studies have confirmed this finding, showing that populations with CRS have a greater chance of being CFTR mutation carriers [23–25]. Due to the prevalence of CFTR mutations in CRS patients, especially minor or mild/variable mutations, some have recommended CF genetic testing in patients with refractory CRS without classic pulmonary or gastrointestinal CF manifestations [26].

Recently, studies have investigated therapies targeting the CFTR-mediated chloride transport to improve mucociliary clearance in patients with CRS. One study serendipitously found that the use of low-concentration ethanol solution and another showed that chlorogenic acid both produced increased chloride transport and ciliary beat frequency in a dose-dependent manner [27∗,28∗]. In addition, resveratrol, a polyphenol, has shown promise as another potential CFTR targeting therapy, improving the function of CFTR in sinonasal mucosa after hypoxia-induced CFTR dysfunction [29∗]. A CFTR potentiator, ivacaftor, has recently been FDA approved for treatment of CF (targets the G551D-CFTR mutation), and a recent case report detailed the reversal of CRS symptoms and computed tomography findings after 10 months of treatment [30∗∗]. These recent publications highlight how genetic studies can lead to new therapeutic breakthroughs, especially in the case report for ivacaftor.

**PRIMARY CILIARY DYSKINESIA AND CHRONIC RHINOSINUSITIS**

PCD is a typically autosomal recessively inherited disease in which the structure and function of cilia are affected, leading to CRS, pulmonary disease, and chronic otitis media due to dysfunctional ciliary clearance, along with situs inversus and male infertility [31]. Diagnosis of this disease has typically relied on clinical features and diagnostic testing (imaging, nasal nitric oxide levels, ciliary beat frequency, and ciliary ultrastructural analysis on electron microscopy) [32∗]. The clinical diagnosis of PCD can be challenging due to variability in presentation, and ciliary ultrastructural analysis does not reveal obvious abnormalities in certain mutations such as DNAH11, HYDIN, CCDC164/DRC1, and CCDC65/DRC2 [32∗]. There is molecular genetic testing that can identify mutations in 32 PCD-associated genes, which has shown to improve diagnostic yield from 57% with ciliary ultrastructural analysis alone to 69% with both ciliary ultrastructural analysis and genetic analysis [33]. Whole exome sequencing performed on 20 previously genetically undiagnosed families allowed for molecular diagnosis in 11 of them, which shows the potential of genetic testing for diagnosis of this disease [32∗]. Recent mouse cell studies have successfully performed viral vector gene transfer to restore ciliary function, which could prove to be a potential therapeutic avenue in the future, but further studies are required [34].

**TASTE RECEPTORS AND CHRONIC RHINOSINUSITIS**

Recently, there has been investigation into the role of sinonasal sweet and bitter T2Rs and their role in innate immune response in CRS. Bitter T2Rs are found in human tongue, bronchial, and sinonasal epithelium, and when stimulated with bitter agonist phenylthiocarbamide, intracellular calcium levels increase, triggering the production of nitric oxide that increases mucociliary clearance and has bactericidal effects [35∗∗,36,37]. In addition, the T1R2/3 sweet taste receptors have been implicated in the regulation of the T2R-dependent calcium signaling [38]. Levels of nitric oxide in the nasal cavity have been linked to sinonasal health with reduced levels associated with sinusitis [39∗,40].

Specific SNPs inherited together in the **TAS2R38** gene at positions 49, 262, and 296 have been identified, which encode for specific amino acids at these positions, with the functional T2R38 containing proline, alanine, and valine (PAV variant), respectively, and the nonfunctional T2R38 containing alanine, valine, and isoleucine (AVI variant), respectively [41]. Patients who carry the PAV/PAV genotype are supertasters of the bitter agonist phenylthiocarbamide, with the PAV/AVI genotype intermediate tasters and the AVI/AVI genotype nontasters, and the PAV/PAV cells have been found to have a more robust nitric oxide production,
Nose and paranasal sinuses

mucociliary clearance, and bacterial killing compared with PAV/AVI and AVI/AVI cells [36]. The significance of a testable phenotype (supertasters versus nontasters) that correlates with the genotype is that it allows for easy testing in the clinical setting. A study investigating the taste sensitivity to phenylthiocarbamide and sinonasal symptoms in healthy patients found that supertasters reported fewer sinus infections and better sinonasal quality of life [42]. Multiple studies have shown that the distribution of PAV/PAV, PAV/AVI, and AVI/AVI genotypes differed significantly between CRS patients undergoing surgery and control patients [16,43,44]. In addition to the polymorphisms in T2R38, a GWAS study found missense variants in the TAS2R13 gene and two in the TAS2R49 gene, which were also significantly associated with CRS [16]. Further studies into the TAS2R38 gene have found significant associations between genotype and quality of life in deltaF508 CF patients, biofilm formation in CRSsNP patients, and postsurgical quality of life in CRSsNP patients at 6 months after sinus surgery [45*,46**,47**].

With these recent findings, utilizing the phenotype of patients as either supertasters or intermediate/nontasters, physicians may be able to better counsel patients regarding the outcomes of standard functional endoscopic sinus surgery or even modify their management approaches [47**]. Moreover, the TAS2R38 gene may represent a new therapeutic target, for which treatments can be developed to promote the T2R38-mediated innate immune response in patients with CRS [35**].

IMMUNOLOGICAL GENES ASSOCIATED WITH CHRONIC RHINOSINUSITIS

The immune system plays a significant role in the pathogenesis of CRS, and because of this, these genes have been a popular target for genetic studies. Table 1 summarizes a total of 73 genes that have been identified to have an association with CRS in previous genetic studies. Only 22 of these genetic associations have been replicated, which underscores the need for further investigations.

The human leukocyte antigen (HLA) system is a gene complex that encodes the major histocompatibility complex for antigen presentation. It is broken down into two groups, class I including HLA-A, HLA-B, and HLA-C, and class II that included HLA-DR, HLA-DQ, and HLA-DP, and these genes are highly variable with many different alleles. There are several HLA alleles that have been associated with CRS, mostly with polyps, in multiple studies, including HLA-A*74, HLA-A*24, HLA-B*54, HLA-B1*03, HLA-B1*08, HLA-B*07, HLA-B*57, HLA-Cw*04, HLA-Cw*12, HLA-DR7-DQA1*0201, HLA-DR7-DQB1*0202, HLA-DRB1*03, HLA-DRB1*08, HLA-DRB1*04, and HLA-DQB1*03 [48–53,55–57,112]. However, the majority of these associations have not been replicated, and their significance is largely unknown.

The innate immune system is the first line of defense and includes physical barriers such as the epithelium, the complement system, defensins, antimicrobial peptides, innate immune cells (mast cells, phagocytes, eosinophils, and natural killer cells), and pattern recognition receptors that recognize conserved microbial elements [i.e., Toll-like receptors (TLRs)]. Research has suggested the impairment of the innate immune system and failure to restore homeostasis contributes to chronic inflammation seen in CRS [113–115]. Antimicrobial factors such as lactoferrin, lysozyme, complement factors, defensins, surfactant proteins, cathelicidins, nitric oxide, and host-derived lipids have been found to have association with CRS, with differential expression of these molecules in CRS patients versus healthy controls, suggesting involvement of these innate immunity molecules in the pathogenesis of CRS [39*,114,116–123]. Multiple TLRs, including TLR-2, TLR-3, TLR-4, TLR-9, TLR-10, and their downstream signaling molecules (i.e., NF-kB) have been found to be differentially expressed in CRS tissue, compared with healthy controls [123–129]. Of these innate defense mechanisms, genetic associations have been found in the antimicrobial factors acyloxyacyl hydro-lase (which degrades bacterial lipopolysaccharides), nitric oxide synthase (produces nitric oxide improving mucociliary clearance and also has bactericidal effects), lactoferrin (an antimicrobial peptide), LAMA2 and LAMB1 (laminins that are extracellular proteins, components of the basement membrane), airway epithelial potassium ions KCNMA1 and KCNQ5 (which may have a role in mucociliary clear-ance akin to CFTR), and TLR-2 (recognizes conserved molecular patterns in gram positive bacteria and yeast), and its downstream signaling molecule IL-1 receptor-associated kinase 4 [14,67,79,82*,83,88,89,90*,91,96,97,100,107]. The associations for LAMA2, LAMB1, lactoferrin, KCNMA1, and KCNQ5 have not been replicated, and nonassociations have also been found for TLR2 in two other studies, bringing doubt into its association [96,130].

Other inflammatory response genes have also been associated with CRS, including genes for cytokines, enzymes involved in arachidonic acid metabolism, and prostaglandin receptors. Cyto- kine genes associated with CRS in previous genetic studies include TNF-alpha, TNF-beta, TNF-alpha-induced protein 3, IL-1 alpha, IL-1 beta, IL-1 receptor antagonist, IL-1 receptors, IL-4, IL-6, IL-10, IL-
What is the evidence for genetics in chronic rhinosinusitis? Yoo and Suh

Table 1. Genes that have been previously identified in genetic studies to have polymorphisms or alleles associated with chronic rhinosinusitis

<table>
<thead>
<tr>
<th>Gene Symbol</th>
<th>Gene Name</th>
<th>Function</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>CFTR</td>
<td>Cystic fibrosis transmembrane regulator</td>
<td>ABC transporter class ion channel</td>
<td>[13,23,25]</td>
</tr>
<tr>
<td>HLA-A</td>
<td>Human leukocyte antigen A locus</td>
<td>MHC class I receptor</td>
<td>[48,49]</td>
</tr>
<tr>
<td>HLA-B</td>
<td>Human leukocyte antigen B locus</td>
<td>MHC class I receptor</td>
<td>[50]</td>
</tr>
<tr>
<td>HLA-C</td>
<td>Human leukocyte antigen B locus</td>
<td>MHC class I receptor</td>
<td>[48]</td>
</tr>
<tr>
<td>HLA-DR</td>
<td>Human leukocyte antigen DR locus</td>
<td>MHC class II receptor</td>
<td>[48,51–55]</td>
</tr>
<tr>
<td>HLA-DQ</td>
<td>Human leukocyte antigen DQ locus</td>
<td>MHC class II receptor</td>
<td>[52,54,56,57]</td>
</tr>
<tr>
<td>CIITA</td>
<td>Human histocompatibility complex II transactivator</td>
<td>MHC class II receptor</td>
<td>[58]</td>
</tr>
<tr>
<td>TNFA</td>
<td>Tumor necrosis factor-alpha</td>
<td>Cytokine</td>
<td>[59–62]</td>
</tr>
<tr>
<td>TNFAIP3</td>
<td>Tumor necrosis factor-alpha induced protein 3</td>
<td>Downstream signaling in TNF-alpha, IL-1b, Toll-like receptors</td>
<td>[63]</td>
</tr>
<tr>
<td>TNFB</td>
<td>Tumor necrosis factor-beta</td>
<td>Cytokine</td>
<td>[64]</td>
</tr>
<tr>
<td>LTC4S</td>
<td>Leukotriene C4 synthase</td>
<td>Leukotriene C4 production</td>
<td>[65–67]</td>
</tr>
<tr>
<td>IL1A</td>
<td>Interleukin-1 alpha</td>
<td>Cytokine, production of inflammation</td>
<td>[59,68,69]</td>
</tr>
<tr>
<td>IL1B</td>
<td>Interleukin-1 beta</td>
<td>Cytokine, production of inflammation</td>
<td>[59,70]</td>
</tr>
<tr>
<td>IL1RN</td>
<td>Interleukin-1 receptor antagonist</td>
<td>Inhibits activity of IL-1</td>
<td>[71]</td>
</tr>
<tr>
<td>IL1R2</td>
<td>Interleukin-1 receptor type 2</td>
<td>Cytokine receptor</td>
<td>[72]</td>
</tr>
<tr>
<td>IL1RL1</td>
<td>Interleukin-1 receptor-like 1</td>
<td>Effector molecule of Th2 response</td>
<td>[73]</td>
</tr>
<tr>
<td>IL4</td>
<td>Interleukin-4</td>
<td>Cytokine, Th2 response</td>
<td>[74]</td>
</tr>
<tr>
<td>IL6</td>
<td>Interleukin-6</td>
<td>Cytokine, production of inflammation</td>
<td>[75,76]</td>
</tr>
<tr>
<td>IL10</td>
<td>Interleukin-10</td>
<td>Cytokine, anti-inflammatory</td>
<td>[77]</td>
</tr>
<tr>
<td>IL22RA1</td>
<td>Interleukin-22 receptor, alpha 1</td>
<td>Cytokine receptor, mediates innate immune response</td>
<td>[78,79]</td>
</tr>
<tr>
<td>IL33</td>
<td>Interleukin-33</td>
<td>Cytokine, production of Th2 cytokines</td>
<td>[80]</td>
</tr>
<tr>
<td>TGFB1</td>
<td>Transforming growth factor beta-1</td>
<td>Cytokine, controls proliferation, differentiation of many cell types</td>
<td>[79,81]</td>
</tr>
<tr>
<td>IRAK4</td>
<td>Interleukin-1 receptor-associated kinase 4</td>
<td>Downstream signaling of Toll-like receptors</td>
<td>[82*,83]</td>
</tr>
<tr>
<td>ADRB2</td>
<td>Beta2-adrenoceptor gene</td>
<td>Beta-adrenergic receptor</td>
<td>[84]</td>
</tr>
<tr>
<td>ALOX5</td>
<td>Arachidonate 5-lipoxygenase</td>
<td>Arachidonic acid metabolism, production of leukotrienes</td>
<td>[85]</td>
</tr>
<tr>
<td>ALOX5AP</td>
<td>Arachidonate 5-lipoxygenase activating protein</td>
<td>Activates arachidonate 5-lipoxygenase</td>
<td>[79,85]</td>
</tr>
<tr>
<td>ALOX15</td>
<td>Arachidonate 15-lipoxygenase</td>
<td>Arachidonic acid metabolism</td>
<td>[86]</td>
</tr>
<tr>
<td>CYSLTR1</td>
<td>Cysteinyl leukotriene receptor 1</td>
<td>Receptor for LTC4, LTD4, LTE4</td>
<td>[85]</td>
</tr>
<tr>
<td>COX2</td>
<td>Cyclooxygenase 2</td>
<td>Arachidonic acid metabolism, production of prostaglandins</td>
<td>[87]</td>
</tr>
<tr>
<td>NOS1</td>
<td>Nitric oxide synthase 1</td>
<td>Production of nitric oxide</td>
<td>[79,88]</td>
</tr>
<tr>
<td>NOS1AP</td>
<td>Nitric oxide synthase 1 associated protein</td>
<td>Adapter protein for nitric oxide synthase 1</td>
<td>[79]</td>
</tr>
<tr>
<td>NOS2A, INOS</td>
<td>Nitric oxide synthase 2, also known as inducible nitric oxide synthase</td>
<td>Production of nitric oxide</td>
<td>[67,89,90*]</td>
</tr>
<tr>
<td>LAMA2</td>
<td>Laminin, alpha 2</td>
<td>Extracellular protein, component of basement membrane</td>
<td>[14]</td>
</tr>
</tbody>
</table>
### Table 1 (Continued)

<table>
<thead>
<tr>
<th>Gene symbol</th>
<th>Gene name</th>
<th>Function</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAMB1</td>
<td>Laminin, beta 1</td>
<td>Extracellular protein, component of basement membrane</td>
<td>[14]</td>
</tr>
<tr>
<td>PARS2</td>
<td>Prolyl-tRNA synthetase 2, mitochondrial</td>
<td>Mitochondrial protein synthesis</td>
<td>[14,79]</td>
</tr>
<tr>
<td>NAV3</td>
<td>Neuron navigator 3</td>
<td>May regulate IL2 production, involved in neuron regeneration</td>
<td>[14]</td>
</tr>
<tr>
<td>CACNA11</td>
<td>Calcium channel, voltage-dependent, T type, alpha 11 subunit</td>
<td>Calcium channel protein</td>
<td>[14]</td>
</tr>
<tr>
<td>KIAA1456</td>
<td>Chromosome 8 open reading frame 79</td>
<td>Involved in mRNA function, tumor suppressor</td>
<td>[14]</td>
</tr>
<tr>
<td>MUSK</td>
<td>Muscle, skeletal, and receptor tyrosine kinase</td>
<td>Formation and maintenance of neuromuscular junction</td>
<td>[14]</td>
</tr>
<tr>
<td>TRIP12</td>
<td>Thyroid hormone receptor interactor 12</td>
<td>Regulation of DNA repair</td>
<td>[14]</td>
</tr>
<tr>
<td>AOAH</td>
<td>Acyloxyacyl hydrolase (neutrophil)</td>
<td>Degradation of bacterial lipopolysaccharides</td>
<td>[14,79,91]</td>
</tr>
<tr>
<td>MSRA</td>
<td>Methionine sulfoxide reductase A</td>
<td>Protein repair enzyme</td>
<td>[14]</td>
</tr>
<tr>
<td>INDO</td>
<td>Indoleamine 2,3-dioxygenase 1</td>
<td>Involved in peripheral immune tolerance</td>
<td>[72]</td>
</tr>
<tr>
<td>GSTT1</td>
<td>Glutathione-transferase theta 1</td>
<td>Detoxification enzyme</td>
<td>[92]</td>
</tr>
<tr>
<td>MMP-9</td>
<td>Matrix metalloproteinase-9</td>
<td>Degradation of extracellular matrix</td>
<td>[93,94]</td>
</tr>
<tr>
<td>SERPINA1</td>
<td>Serine protease inhibitor alpha-1 (alpha-1 antitrypsin)</td>
<td>Protease inhibitor, associated with chronic obstructive pulmonary disease</td>
<td>[95]</td>
</tr>
<tr>
<td>TLR2</td>
<td>Toll-like receptor 2</td>
<td>Pathogen-associated molecular pattern receptor, gram positive bacteria and yeast</td>
<td>[96,97]</td>
</tr>
<tr>
<td>TP73</td>
<td>Tumor protein p73</td>
<td>Tumor suppressor, cell cycle regulation</td>
<td>[15]</td>
</tr>
<tr>
<td>MET</td>
<td>Met proto-oncogene</td>
<td>Tyrosine kinase receptor, role in epithelial cell stimulation, and proliferation</td>
<td>[87,98]</td>
</tr>
<tr>
<td>UBE3C</td>
<td>Ubiquitin protein ligase E3C</td>
<td>Protein modification</td>
<td>[99]</td>
</tr>
<tr>
<td>LTF</td>
<td>Lactoferrin</td>
<td>Antimicrobial peptide</td>
<td>[100]</td>
</tr>
<tr>
<td>OSF-2</td>
<td>Osteoblast-specific factor-2</td>
<td>Regulator of fibrosis and collagen deposition</td>
<td>[100]</td>
</tr>
<tr>
<td>EMID2</td>
<td>Emilin/multimerin domain-containing protein 2</td>
<td>Component of extracellular matrix</td>
<td>[101]</td>
</tr>
<tr>
<td>DCBLD2</td>
<td>Human discoidin, CUB, and LCCL domain containing 2</td>
<td>Cell surface receptor, implicated in TH1/TH2 differentiation</td>
<td>[79,102]</td>
</tr>
<tr>
<td>RYBP</td>
<td>RING1 and YY1-binding protein</td>
<td>Regulator of transcription</td>
<td>[91]</td>
</tr>
<tr>
<td>CD14</td>
<td>Cluster of differentiation 14</td>
<td>Coreceptor of TLR4</td>
<td>[103]</td>
</tr>
<tr>
<td>PTGDR</td>
<td>Prostaglandin D2 receptor</td>
<td>Receptor for prostaglandin D2, involved in TH2 response</td>
<td>[67]</td>
</tr>
<tr>
<td>TSLP</td>
<td>Thymic stromal lymphopoietin</td>
<td>Cytokine involved in dendritic-mediated activation of Th2 response</td>
<td>[104]</td>
</tr>
<tr>
<td>TAS2R38</td>
<td>Taste receptor T2R38</td>
<td>Bitter taste receptor, role in innate immune response</td>
<td>[16,36,38,43,44,45*,46**,47**]</td>
</tr>
<tr>
<td>TAS2R13</td>
<td>Taste receptor T2R13</td>
<td>Bitter taste receptor</td>
<td>[16]</td>
</tr>
<tr>
<td>TAS2R49</td>
<td>Taste receptor T2R49</td>
<td>Bitter taste receptor</td>
<td>[16]</td>
</tr>
<tr>
<td>EBI3</td>
<td>Epstein–Barr virus induced gene 3</td>
<td>Downstream target of FOXP3</td>
<td>[105]</td>
</tr>
</tbody>
</table>
22 receptor, and IL-33 [59–64,68–80]. Arachidonic acid metabolism genes found to have associations with CRS include leukotriene C4 synthase, arachidonate 5-lipoxygenase, arachidonate 5-lipoxygenase–activating protein, arachidonate 15-lipoxygenase, cysteinyl leukotriene receptor 1, and cyclooxygenase-2 [65–67,79,85–87]. Some of these genes are associated with the Th2 response, including IL-4, IL-33, prostaglandin D2 receptor, and thymic stromal lymphopoietin, which may play a role in chronic eosinophilic rhinosinusitis and CRS associated with AERD [67,74,80,104]. There are also genes associated with autoimmune disease, such as indoleamine 2,3-dioxygenase 1 and cold-induced autoinflammatory syndrome 1, which have been associated with CRS in genetic studies [72,110].

**CONCLUSION**

There have been over 70 genes that have been identified to have genetic associations with CRS published in literature, but many of these genetic associations require further study. Some have suggested that genetic testing in CRS may be applicable for patients with severe refractory CRS, as they may be carrying CFTR mutation. As research into these genetic associations progress, improvements may be seen in disease prognostication and patient counseling, as well as the development of novel therapeutic targets and therapies, as has been seen in the case of CFTR gene and the bitter taste receptor T2R38.

**Acknowledgements**

None.

**Financial support and sponsorship**

None.

**Conflicts of interest**

There are no conflicts of interest.

**REFERENCES AND RECOMMENDED READING**

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Nose and paranasal sinuses

Review article that gives an overview of cystic fibrosis (CF) and sinusitis.
Large study of over 25 000 patients examining familial risk of chronic rhinosinusitis (CRS).
Good review article of all risk factors of CRS, with brief overview of genetics and CRS up to time of publication.
29. This study evaluates the effect of chlorogenic acid on upregulation of CFTR activity in terms of ion transport.
31. This study evaluates resveratrol as a potential therapeutic agent for CRS patients by reversal of acquired CFTR deficiency.
This case report is the first to describe reversal of CRS in a CF patient using the newly FDA-approved medication, ivacaftor, which targets the G551D CFTR mutation.
38. This study evaluates the use of whole exome sequencing as a potential diagnostic tool for patients with suspected primary ciliary dyskinesia without molecular diagnosis on current genetic testing methods.
What is the evidence for genetics in chronic rhinosinusitis? Yoo and Suh

Nose and paranasal sinuses


