Genetic and Immune Dysregulation in Chronic Rhinosinusitis

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KEYWORDS

- Chronic rhinosinusitis • Chronic rhinosinusitis with nasal polyps
- Chronic rhinosinusitis without nasal polyps • Genetics
- Single-nucleotide polymorphisms • Immune dysregulation
- Primary immunodeficiency

KEY POINTS

- Local defects in innate and adaptive immunity have been implicated in the pathogenesis of refractory chronic rhinosinusitis (CRS).
- A genetic basis in CRS is suggested by an association with well-defined heritable disorders as well as limited evidence of a familial inheritance pattern.
- More than 445 single-nucleotide polymorphisms have been associated with CRS, although these largely have not been replicated.
- Systemic immune dysregulation in refractory CRS may be demonstrated with laboratory testing of humoral and cell-mediated immunity.

INTRODUCTION

Chronic rhinosinusitis (CRS) is defined in adults as persistent symptoms of sinonasal inflammation for 12 or more weeks with confirmatory objective findings on nasal endoscopy or computed tomography (CT).[1,2] CRS is a multifactorial disease with proposed etiopathologies including occupational/environmental exposures, infection, immune dysfunction, and genetic predisposition. As understanding of the disease evolves, clinical phenotypes have emerged that allow subclassification within the entity once identified solely as CRS. The presence or absence of polyps is used as a primary distinction because of easily recognizable clinical features and underlying inflammatory profiles. CRS with nasal polyps (CRSwNP) is characterized by T helper (Th)-2 polarization, with eosinophilia, increased levels of interleukin-4 (IL-4), IL-5, and IL-13, as well as high local production of immunoglobulin E (IgE). CRS without nasal

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polyps (CRSsNP) demonstrates a mixed cytokine profile that lacks Th2 polarization. High levels of interferon-γ (IFN-γ) and transforming growth factor-β have been reported in CRSsNP,[3] but the consistency of this feature continues to be under investigation.[4–6] Although Th2 polarization clearly characterizes CRSwNP in Western countries, evidence suggests that Th2 skewing may be absent in CRSwNP patients in China. This difference may be disappearing as the region undergoes modernization.[7] A third distinct phenotype of CRS is aspirin-exacerbated respiratory disease (AERD), which is fully discussed elsewhere in this issue.

Clinically, otolaryngologists encounter refractory forms of rhinosinusitis within each phenotype. No consensus statement defining recalcitrant CRS exists; however, broadly speaking, CRS is considered refractory when it responds poorly to medical and surgical therapy. Multiple theories and possible pathophysiologic mechanisms have been proposed to explain recalcitrance in CRS. In this review, the authors focus specifically on the contribution of genetics and immunologic dysregulation.

At the most basic level, support for an underlying genetic contribution to CRS stems from observations of familial inheritance patterns.[8–10] Most of these observations were made in patients with nasal polyps, and, therefore, conclusions about the familial inheritance pattern of CRSsNP cannot be drawn. In patients with nasal polyps, a heritability of 14% to 42% has been described.[9,10] Cohen and colleagues[10] subclassified CRSwNP patients into 3 groups: isolated polyps, polyps with asthma, and AERD. Interestingly, they found that AERD had the highest heritability (42%) followed by asthma and polyps (30%) and isolated polyps (15%). In addition, they demonstrated a correlation with the number of family members (frequency) with nasal polyposis and the severity of disease showing that severity is proportional to the penetrance of an underlying genetic component.

As a caveat, growing evidence suggests that multiple endotypes of CRS, yet to be fully elucidated, may be present beyond the CRSsNP/CRSwNP/AERD classification scheme. Recognition that CRS remains a complex and incompletely defined disease has important consequences for weighing the validity of genetic and immunologic studies. Without precise definitions of CRS subtypes, meaningful interpretation of research findings is difficult, particularly when detailed clinical information, including raw laboratory and radiographic findings, is not available. At present, differences among CRS subtypes are likely obscured by classifications based on an incomplete understanding, and current scoring systems used for clinical research do not capture CRS features with sufficient granularity. Because of the variety within CRS, more meticulous gathering of patient data with subclassification will almost certainly be necessary to detect true genetic and immunologic contributors. Even if precise categorization were possible, CRS fluctuates in severity and characteristics over time and can develop later in life, so flawed subtype assignments are possible, particularly in genetic studies. All of these challenges must be appreciated, and the existing CRS literature should be evaluated through this lens.

Innate Immunity and Epithelial Barrier Dysfunction in Chronic Rhinosinusitis

Among the mechanisms proposed to contribute to CRS pathogenesis and recalcitrance, many involve abnormalities of local mucosal immune defense. Sinonasal innate immune function begins with the physical epithelial barrier, mucus production, and mucociliary clearance, extending to involve secreted antimicrobial factors and phagocytic hematopoietic cells that combat infection in the airway lumen.[11] Multiple inflammatory mediators produced by epithelial cells and other nonlymphocytic cell populations interact with the adaptive immune system to drive antigen-specific antibody production. Although lymphocytes had long been assumed to be the principal