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Correlation between Systemic Inflammatory Response and Quality of Life in Patients with Chronic Rhinosinusitis

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Abstract

Background: Local sinonasal inflammation resulting from altered T-cell immune signaling is a contributor to the pathogenesis of chronic rhinosinusitis (CRS). CRS patients experience negative impacts on quality of life (QOL) and suffer from comorbidities linked to systemic inflammation. However, systemic inflammatory profiling to evaluate the association between systemic inflammation and QOL in CRS has not been performed. Our objectives were to compare local and systemic inflammatory gene expression in patients with CRS to determine if systemic markers of inflammation associate with disease severity and disease-specific QOL.

Materials and Methods: A prospective observational study was conducted comparing sixteen patients with CRS to ten controls. Inflammatory gene expression in the anterior ethmoid tissues and peripheral blood of patients was measured using multiplex gene expression analysis and correlated to disease severity (computed tomography and nasal endoscopy) and disease-specific QOL (Sino-Nasal Outcomes Test-22 and Rhinosinusitis Disability Index) using linear regression analyses.

Results: Patients with CRS demonstrated significant increases in the expression of *ctla4* and *jak1* in sinonasal tissue and blood ($p < 0.05$), whereas the gene expression of *hla-dqa1*, *hla-dqb1*, and *dup4* was significantly decreased in patients with CRS compared to controls ($p < 0.05$). Soluble and local *ctla4* and *jak1* demonstrated a significant positive correlation with clinical markers of disease severity and disease-specific QOL ($p < 0.05$).

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Conclusions: Local and systemic gene expression involved in T-cell immune signaling was found to be significantly altered in the blood and sinonasal tissues of patients with CRS compared to controls and significantly correlated to disease severity and QOL in patients with CRS.

BACKGROUND

Chronic rhinosinusitis (CRS) is a multifactorial inflammatory disease that has been linked to a complex interplay of genetics, anatomy, acquired mucociliary dysfunction, and T-cell signaling dysregulation.^{1,2} Altered CD4+ T-cell signaling plays a critical role in the pathophysiology of CRS by creating an unbalanced T-cell response that results in the upregulation of inflammatory cytokines in the sinonasal tissues and ultimately contributes to a localized chronic inflammatory state.^{3,4} However, whether patients with CRS also experience perturbed levels of systemic inflammation that contributes to their disease pathophysiology and the impact this has on quality of life (QOL) remains unclear.

In addition to the common symptoms of sinusitis, such as nasal congestion/drainage, facial pain/pressure, and anosmia, patients with CRS also experience significantly worse QOL⁵ and are at greater risk of having comorbid inflammatory conditions.⁶ Inflammatory conditions previously associated with CRS include chronic obstructive pulmonary disease (COPD), bronchiectasis, rheumatoid arthritis (RA), and asthma.⁶ CRS patients are also more likely to suffer from depression, fatigue, anxiety, and sleep dysfunction,⁵⁻⁸ conditions that have been previously associated with elevated levels of systemic inflammatory markers.⁹ While the etiology of the association between CRS and other inflammatory conditions is currently unknown, we hypothesize that an altered systemic inflammatory response might largely contribute to disease severity and QOL in patients with CRS.

The objectives of this study were to determine whether there is evidence of systemic inflammation in patients with CRS compared to controls and to evaluate whether systemic inflammation is associated with CRS-specific disease severity and/or QOL. To address these objectives, the gene expression of local and systemic inflammatory molecules was compared between patients with a diagnosis of CRS without nasal polyps (CRSsNP) and control patients. Previous studies investigating inflammatory gene expression in patients with allergic rhinitis and systemic lupus erythematosus (SLE) have used the Nanostring nCounter system to identify differentially expressed inflammatory genes.^{10,11} We employed the Nanostring nCounter system technology, which allowed us to perform an exploratory analysis to compare the expression of over 500 inflammatory genes in the blood and sinonasal tissue and identify differentially expressed genes between CRS patients and controls. We hypothesized that patients with CRSsNP would exhibit differences in both systemic and local markers of inflammation compared to controls and that identified genes would associate to CRS-specific disease severity and QOL.

MATERIALS & METHODS

Subjects and Data Collection

Study participants were enrolled using informed consent procedures from the University of Utah Sinus and Skull Base Clinic and with approval from the University of Utah

Institutional Review Board (IRB #61810). Patients meeting inclusion criteria were adult patients with a diagnosis of CRSsNP according to the 2015 American Academy of Otolaryngology Adult Sinusitis Guideline.¹² Patients with a diagnosis of CRS with nasal polyps (CRSwNP) were excluded from the study in an attempt to create a more homogenous phenotype of CRS. Study questionnaires included the Sinonasal Outcomes Test (SNOT-22) and the Rhinosinusitis Disability Index (RSDI). All patients underwent a formal evaluation in the tertiary rhinology clinic at the University of Utah consisting of a full history, head and neck physical exam, review of computerized tomography scans (CT), and nasal endoscopy. Demographic information and medical/social history were obtained from each study participant, and those who failed to complete all study-related questionnaires during the initial enrollment meeting were excluded. Patients with RA, COPD, and SLE were excluded, as these diseases are known to have a systemic inflammatory component. Additionally, patients with multiple sclerosis (MS), cancer, cystic fibrosis (CF), fibromyalgia, and heart failure were also excluded given the high likelihood of comorbid chronic inflammation. Patients with a history of smoking and alcohol use were excluded due to concern that significant use of both substances contributes to an increase in systemic inflammation.^{13,14} All patients undergoing endoscopic sinus surgery (ESS) for CRSsNP had previously undergone appropriate medical management of their disease prior to proceeding with surgery.

Control subjects consisted of patients undergoing nasal surgery for indications other than chronic or recurrent acute sinusitis such as septoplasty. These patients were diagnosed with nasal obstruction secondary to septal deviation and/or turbinate hypertrophy and underwent a septoplasty and/or turbinate reduction. Patients with a history of cerebral spinal fluid leak undergoing endoscopic repair were also included. All control patients underwent a full history, head and neck physical exam, review of CT scans when appropriate, and nasal endoscopy. Demographic information and medical/social history were obtained and those who failed to complete all study-related questionnaires during the initial enrollment meeting were excluded. Patients with a history of RA, COPD, SLE, MS, cancer, CF, fibromyalgia, or heart failure were excluded as stated above. Patients with a history of smoking and alcohol use were also excluded.

Tissue Collection

Tissues were obtained from each study subject intraoperatively. For ESS and control patients, sinonasal tissues were taken from the anterior ethmoid (~4.0 mm²), flash frozen, and stored at -80°C until assayed. Blood samples were also collected intraoperatively; freshly drawn whole blood (0.5 mL) was placed into 1.0 mL of RNeasy lysis buffer (Applied Biosystems/Life Technologies Corp., Carlsbad, CA), flash frozen, and stored at -80°C until assayed.

mRNA Extraction

The frozen tissue specimens were transferred to a 2 mL homogenization tube containing 0.6 mL of lysis buffer and a 5 mm stainless steel bead. The tissue was immediately homogenized using a Qiagen Tissuelyser LT. RNA was isolated using the Qiagen AllPrep RNA miRNA Universal Kit (Cat #82204, Lot#154047946) on the QiaCube (Serial # 50772)

using the manufacturer's protocol. Each RNA sample was eluted with 60 µl RNaseFree water (54 µL remaining after quantification). RNA was quantified using NanoDrop 8000 and Qubit.

Gene Expression Analysis

Sinonasal and blood tissues were subjected to gene expression analyses using the nCounter System and Human Immunology v2 Panels consisting of 579 immune and inflammation-associated genes and 15 housekeeping genes (NanoString Technologies, Seattle, WA). Nucleic acid extraction, mRNA quantification, and gene expression profiling was performed by the Biorepository and Molecular Pathology Core and the Molecular Diagnostic Core at the Huntsman Cancer Institute (University of Utah, Salt Lake City, UT). Briefly, the samples were subjected to overnight hybridization reaction at 65°C, where 5 µL of total RNA samples were combined with 8 µL of nCounter Reporter probes in hybridization buffer and 2 µL nCounter capture probes for a total reaction volume of 15 µL. Post-hybridization the target genes were quantified with the nCounter Digital Analyzer and analyzed with the use of the nSolver platform. Fifteen housekeeping genes (*abcf1*, *alas1*, *eef1g*, *g6pd*, *gapdh*, *gusb*, *hprt1*, *oaz1*, *polr1b*, *polr2a*, *ppia*, *rpl19*, *sdha*, *tbp*, and *tubb*) were used for background subtraction and normalization of the raw mRNA transcript counts of all samples. After normalization, the ratio of difference in the means of the log-transformed normalized data to the square root of the sum of the variances of samples in the two groups was generated. A two-tailed t-test on the log-transformed normalized data was then performed assuming unequal variance. The data are reported as the mean ± the standard error of the mean gene transcript copy in each treatment group.

Research Instruments

CT and Endoscopy Scores—Patients received a high-resolution CT scan of the sinuses with 1-mm contiguous slices. The images were then evaluated by the enrolling physicians and given a score based on the Lund-Mackay scoring system.¹⁵ Final scores range from 0–24, with higher scores representing more severe disease. At enrollment, study patients also underwent an endoscopic sinonasal examination. The Lund-Kennedy scoring system was used to score the endoscopic exam, which ranges from 0–20, with higher scores corresponding to worse exams.¹⁶

Sinonasal Outcomes Test (SNOT-22)—The SNOT-22 is a validated measure of disease-specific QOL in patients with CRS that consists of 22 sinus-related symptoms and was given to all study subjects.¹⁷ Higher total scores (range 0–110) correspond to worse disease severity. The symptoms have been divided into five distinct subdomains including rhinologic, extra-nasal, ear/facial, psychological dysfunction, and sleep dysfunction. Scores are calculated and recorded for each of the subdomains.¹⁸

Rhinosinusitis Disability Index (RSDI)—The RSDI is a 30-item survey instrument comprised of 3 subdomains to assess the impacts of rhinosinusitis on a participants physical (score range: 0–44), functional (score range: 0–36), and emotional (score range: 0–40) status and was administered to all study subjects.¹⁹ Higher subdomain and total RSDI scores

(score range: 0–120) represent worse QOL and greater impact of rhinosinusitis symptoms on a patient's daily function.

Statistical Analyses

Patient data were collected using the previously described standardized research instruments. Primary outcomes used for comparison between the two groups consisted of patient demographics, sinonasal and blood mRNA transcript copy counts, and clinical measures of disease severity, including CT, nasal endoscopy, SNOT-22, and RSDI scores. All participants were assigned a unique study identifier to ensure confidentiality. Data were manually entered into an electronic database (Microsoft Access; Microsoft Corp., Redmond, WA) by a trained research coordinator. SPSS (IBM Corp., Armonk, NY, Version 25.0) statistical software was used for data analyses, and descriptive statistics were calculated to summarize patient characteristics, such as age, gender, and other health conditions. Linear regression analyses were performed, and Pearson correlation coefficients were used to identify associations between mRNA expression in blood and sinonasal tissues. To identify correlations between gene expression and clinical markers of disease severity, Pearson correlation coefficients were also calculated for mRNA transcript copy counts and clinical markers of disease severity (*i.e.*, Lund-McKay, nasal endoscopy, SNOT-22, and RSDI scores).

RESULTS

Demographics

A total of sixteen patients with CRSsNP and ten control patients were prospectively enrolled into this investigation. Cohort demographics and comorbidities are described in Table 1. Asthma was the only comorbidity with a significant difference between the two cohorts ($p=0.014$).

Gene expression comparisons between sinonasal and blood tissues

mRNA counts between the sinonasal and blood tissue were compared to identify genes that were significantly increased or decreased locally and systemically, respectively. Seven overlapping genes demonstrated statistically significant differences in mRNA transcript copy counts between controls and patients with CRSsNP both in the sinonasal and blood tissues. Two genes were significantly increased in patients with CRSsNP when compared to controls; soluble cytotoxic T-lymphocyte associated antigen 4 (*sctla4*) demonstrated significantly elevated counts of mRNA in the sinonasal (50.31 vs 19.78; $p=0.0006$) and blood (29.49 vs 17.17; $p=0.0297$) tissues. Janus kinase 1 (*jak1*) also demonstrated significantly elevated mRNA counts in CRSsNP patients in the sinuses (713.59 vs 385.87; $p=0.0033$) and the blood (731.78 vs 427.38; $p=0.0070$) (Figure 1).

Multiple genes were significantly downregulated in the blood and sinuses of patients with CRSsNP compared to controls. CRSsNP patients demonstrated significantly lower mRNA transcript copy counts of dual specific protein phosphatase 4 (*dusp4*) in sinonasal (244.14 vs 404.86; $p=0.0162$) and blood (12.81 vs 23.09; $p=0.0023$) tissues. Human leukocyte antigen-DQA1 (*hla-dqa1*) mRNA counts were also significantly decreased in CRSsNP patients

(sinuses: 64.61 vs 568.35; $p=0.0293$ and blood: 43.86 vs 498.15; $p=0.0293$). Similarly, *hla-dqb1* also demonstrated significant differences in gene expression in CRSsNP compared to controls locally (sinuses: 41.1 vs. 262.34; $p=0.0109$) and systemically (blood: 25.55 vs 257.48; $p=0.0004$) (Figure 2).

Correlations between local and systemic gene expression

Table 2 examines the correlations of genes expressed between sinonasal and blood tissues. The expression of each unique gene in the sinuses was correlated with that of the same gene expressed in the blood. Additionally, *sctla4* was positively correlated with *jak1*, which was also elevated in patients with CRSsNP compared to controls, and negatively correlated with genes found to be downregulated in patients with CRSsNP compared to controls. Similar trends were evident with *jak1* expression. The expression of *hla-dqa1* and *hla-dqb1* in the sinuses was positively correlated with the expression of those same genes in the blood. Notably, *dusp4* expression in the sinuses did not correlate with *dusp4* expression in the blood, nor did it correlate with any of the other genes studied in the blood.

Correlations between local and systemic gene expression and clinical markers of disease severity

Next, we compared the gene expression of local markers to the clinical measures of disease severity, including CT and nasal endoscopy scores as well as QOL questionnaires (Table 3). Sinonasal tissue expression of *sctla4* was positively correlated with CT ($r=0.606$; $p<0.05$) and SNOT-22 ($r=0.455$; $p<0.05$) scores, indicating that the significant increase in *sctla4* was correlated with a more severe phenotype of CRSsNP. Expression of *jak1* in sinonasal tissues also demonstrated a positive correlation with CT ($r=0.507$; $p<0.05$) and SNOT-22 ($r=0.535$; $p<0.05$) scores. There was no significant correlation between disease severity measures and genes that were downregulated in the tissues of patients with CRSsNP compared to controls.

Table 4 reports the correlations between gene expression in the blood and clinical measures of disease severity. *sctla4* demonstrated a positive correlation with SNOT-22 scores ($r=0.469$; $p<0.05$). *jak1* also exhibited a positive correlation with clinical markers of disease severity, including CT ($r=0.486$; $p<0.05$), nasal endoscopy ($r=0.577$; $p<0.05$), and SNOT-22 ($r=0.451$; $p<0.05$) scores. Alternatively, *hla-dqa1* and *hla-dqb1* demonstrated a negative correlation with SNOT-22 and RSDI scores, suggesting that a higher gene expression in the blood is correlated with lower (improved) scores on QOL questionnaires.

DISCUSSION

This investigation demonstrated for the first time a unique expression profile of corresponding local and systemic inflammatory genes in patients with CRSsNP. Specifically, we identified two genes that were significantly upregulated in the sinonasal and blood tissues of patients with CRSsNP (*sctla4* and *jak1*). The expression of these genes also correlated with objective and subjective CRS-specific disease severity measures. Alternatively, we identified several genes that were significantly downregulated locally and systemically (*hla-dqa1*, *hla-dqb1* and *dusp4*) among patients with CRSsNP compared to

controls. Taken together, these data suggest that in addition to the well-established local sinonasal inflammatory endotyping observed in CRS, there is a corresponding perturbed systemic inflammatory profile with a significant association to CRS-specific disease severity. Further exploration of these genes and their associated functions may help to provide insight into their contribution to both subjective and objective measures of disease severity among patients with CRSsNP.

Significantly upregulated genes in CRSsNP

sCTLA-4 (soluble cytotoxic T-lymphocyte-associated protein 4)—CTLA-4 is a cell surface receptor expressed only on activated T-cells and plays a negative regulatory role in the T-cell response through direct competition with CD28, a homologue that binds to CD80/86 on antigen presenting cells and results in a co-stimulatory response that drives T-cell activation. By directly competing with CD28, CTLA-4 essentially blocks the co-stimulatory response resulting in attenuation of inflammatory T-cell signaling.^{20,21} CTLA-4 production is induced by the activation of CD4+ T-cells, which are associated with chronic inflammatory and autoimmune diseases.²² Two distinct isoforms have been identified: the full-length isomer, a transmembrane protein found primarily on T-cells (CTLA-4), and the soluble monomeric protein that is secreted extracellularly (sCTLA-4). sCTLA-4 has been linked to immune cell dysregulation with elevated levels of blood sCTLA-4 reported in patients with thyroid disease, type one diabetes, systemic lupus erythematosus, myasthenia gravis, and celiac disease.^{23,24} Similarly, patients with lower airway inflammation have demonstrated elevated levels of blood sCTLA-4.²⁵ Herein, we found that *sctla4*, the gene responsible for the translation of sCTLA-4 present in the blood, was upregulated in the upper airway and blood of patients with a chronic T-cell inflammatory response compared to controls. *sctla4* mRNA levels were also correlated with worsening objective and subjective disease severity measures (Tables 3 and 4), demonstrating that increased expression of *sctla4* is associated with increased disease severity and worse QOL. Previous research has identified sCTLA-4 in the blood as a potential biomarker for inflammatory diseases, such as AIT, celiac disease, and prostatitis due to the positive correlation of sCTLA-4 in the blood with clinical markers of disease.^{23,24,26} Similarly, the correlation of *sctla4* with clinical measures of disease severity in CRSsNP make this gene an interesting potential biomarker for CRS.

JAK1 (janus kinase 1)—The observed upregulation of *jak1* in the sinuses is not surprising, as JAK1 is a cytoplasmic tyrosine kinase that is critical for intracellular signal transduction of inflammatory pathway signaling and inflammatory cytokines, including IFN- γ , IL-6, and IL-17, which are also implicated in CRSsNP.^{27,28,29} We found that *jak1* was significantly elevated in the sinuses and blood of patients with CRSsNP compared to controls by nearly two-fold. The expression of *jak1* was positively correlated to objective (Lund Mackay and Lund Kennedy scores) and subjective (SNOT-22 scores) measures in patients with CRSsNP. These results demonstrate that *jak1* expression is increased in patients with CRSsNP and that the level of expression is associated with CRS-specific disease severity. Additionally, JAK1 inhibitors have been shown to effectively treat immune/inflammatory diseases.^{27,30} Although we are unable to comment on the future implications

of this data, it seems prudent to assume that treatment paradigms aimed at the inhibition of the *jak1*-mediated pathways may improve patient outcomes.

Significantly downregulated genes in CRSsNP

HLA-DQA1 and B1 (human leukocyte antigen)—The presentation of antigens to immune cells provides an essential link between innate and adaptive immunity, through which the *hla*-associated genes play a crucial role.³¹ There are two unique types of HLA molecules. Class I HLA molecules (*i.e.*, HLA-A, -B, and -C) are ubiquitously expressed in the body with the role of presenting endogenous antigens and are crucial in discerning foreign antigens from self-antigens and thus limiting potential autoimmune responses. The other is class II HLA molecules (*i.e.*, HLA-DR, -DQ, and -DP) that are expressed on immune cells and present exogenous or foreign proteins to other immune cells.^{31,32} This latter process is key in developing immune responses to foreign antigens. Specifically, HLA-DQA1 and HLA-DQB1 combine to form a heterodimer that displays foreign peptides to T-cells and contributes to T-cell activation.³³ Unique single nucleotide polymorphisms that alter or disrupt this interaction have been associated with various autoimmune and inflammatory diseases.³⁴ Previous observations suggest that polymorphisms in HLA-DQ are linked to idiopathic bronchiectasis and CRS.^{35,36} In the current study, *hla-dqa1* and *hla-dqb1* demonstrated significantly lower levels of expression in both the sinuses and blood in patients with CRSsNP. Furthermore, *hla-dqa1* and *hla-dqb1* demonstrated a negative correlation to disease-specific QOL. Patients demonstrating increased expression of *hla-dqa1* and *hla-dqb1* in the blood had lower (improved) SNOT-22 and RSDI scores. While HLA polymorphisms can certainly affect protein function, polymorphisms can also affect expression and transcription of HLA molecules.^{31,32} Patients with CRSsNP demonstrate decreased expression of *hla-dqa1* and *b1* in both blood and sinonasal tissues. Further research evaluating the contribution of *hla-dqa1* and *hla-dqb1* expression to the pathogenesis of CRS and how these markers contribute to the inflammatory endotypes commonly associated with CRSsNP is needed.

DUSP4 (dual specific protein phosphatase 4)—DUSP4 is a mitogen-activated protein kinase phosphatase that dephosphorylates just another kinase (JNK) and p38, resulting in the inhibition of inflammatory cytokine production.³⁷ Overexpression of DUSP4 has been shown to suppress the production of inflammatory mediators and cytokines, including TNF- α and IL-6 which are both implicated in the Th1-mediated inflammatory response in CRSsNP.^{29,38} DUSP4 also has been shown to influence macrophage polarization by promoting alternatively activated macrophages.³⁸ Classically activated macrophages promote a strong Th1 response, resulting in proinflammatory signaling. In contrast, alternatively activated macrophages promote an anti-inflammatory state through increased endocytic clearance capacities, as well as reduced pro-inflammatory cytokine secretion.³⁹ Thus, DUSP4 decreases the secretion of pro-inflammatory cytokines and contributes to the inhibition of classically activated macrophages while enhancing the activity of alternatively activated macrophages, resulting in reduced inflammation.³⁸ It is possible that increased expression of DUSP4 acts as a protective mechanism against developing a persistent Th1 inflammatory response that contributes to sinonasal inflammation in CRS. Patients with CRSsNP demonstrated decreased gene expression of *dusp4* relative to controls which could

contribute to a persistent Th1 inflammatory response. Future research in this area is required to better determine the role of *dusp4* expression in the pathogenesis and endotypes of CRSsNP.

There are limitations of this study that require further discussion. Given the difficulty of obtaining human tissue for evaluation that adhere to the strict inclusion criteria, there is a relatively small sample size. However, the cohort size is ample based on the criteria for performing genome-wide association studies.⁴⁰ To our knowledge, this is the first study to examine the local and systemic inflammatory response in patients with CRSsNP and serves as a pilot investigation for future studies. Due to the small sample size, we were unable to control for all possible confounders contributing to systemic and local inflammation among patients. As a result, it is important to interpret this data with caution until further studies corroborate and build on our current findings. Second, CRS is a complex, multifactorial disease with various phenotypes and endotypes. In an effort to study a homogenous population of CRS patients, we excluded all CRSwNP patients from the study. Thus, our findings cannot be extended to this unique subset of patients with CRS. Third, a history of allergies was present in both the control group and the patients with CRSsNP. A significant proportion of control patients had a history of allergies. Many of these patients were undergoing septoplasty with inferior turbinate reduction, which is commonly performed on patients with allergic rhinitis. Unfortunately, eliminating control patients with allergic rhinitis would have significantly limited the number of control patients eligible for inclusion in the study. Allergy has been linked to chronic inflammation and elevated IgE levels that may play a role in the gene expression we observed. Although the difference in the prevalence of allergy between the CRSsNP group and controls was not statistically significant, it is possible that controls without a history of allergy may have exhibited even lower levels of inflammatory gene expression. Finally, patients with CRSsNP demonstrated a higher prevalence of asthma than controls. While this is a potential confounder, the proportion of patients with CRS and comorbid asthma is in line with previous research suggesting that 42% of CRS patients undergoing ESS also have asthma.⁴¹ As such, the prevalence of asthma in our cohort reflects the greater population of CRS patients. Recognizing these limitations, we are prospectively enrolling additional controls and patients with CRSsNP without a history of allergic rhinitis, allergy, and asthma to select for a more homogenous cohort with respect to possible inflammatory confounders and will perform similar analyses.

CONCLUSION

CRS is a chronic inflammatory disease of the nose and paranasal sinuses. Herein, we provide evidence that a systemic inflammatory component of the disease is also apparent and is associated with CRS-specific disease severity. These findings not only provide valuable information regarding the pathophysiology of CRSsNP, but also help to elucidate the relationship of CRSsNP with significant reported comorbidities such as sleep dysfunction and depression. Future research is required to determine how these uniquely identified markers contribute to the identified endotypes of CRSsNP, the clinical significance of these findings, and to further explore the possibility of using these findings to better guide treatment of patients with CRSsNP.

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Figure 1.

The gene expression of *sctla4* and *jak1* are significantly elevated in sinonasal and blood tissues of patients with CRSsNP compared to normal controls. The gene expression from each group were normalized to *abcf1*, *alas1*, *eef1g*, *g6pd*, *gapdh*, *gusb*, *hprt1*, *oaz1*, *polr1b*, *polr2a*, *ppia*, *rpl19*, *sdha*, *tbp*, *tubb* and plotted as the mean $\pm$ SEM of gene transcript copy in each treatment group. *sctla4* = soluble cytotoxic T-lymphocyte associated antigen; *jak1* = janus kinase 1. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

Figure 2.

The gene expression of *hla-dqa1*, *hla-dqb1*, and *dusp4* are significantly downregulated in the sinonasal and blood tissues of patients with CRSsNP compared to normal controls. The gene expression from each group were normalized to *abcf1*, *alas1*, *eef1g*, *g6pd*, *gapdh*, *gusb*, *hprt1*, *oaz1*, *polr1b*, *polr2a*, *ppia*, *rpl19*, *sdha*, *tbp*, *tubb*, and plotted as the mean $\pm$ SEM of gene transcript copy in each treatment group. *dusp4* = Dual specific protein phosphatase 4.

* $p < 0.05$; ** $p < 0.01$.

Table 1.

Demographics of patients with CRSsNP and normal controls

	Normal (n=10)		CRSsNP (n = 16)		
Sex	n	%	n	%	p-value
Female	3	30%	9	56%	0.191
Male	7	70%	7	44%	
Age	48		52		0.604
Race					
White	9	90%	16	100%	0.197
Other	1	10%	0	0%	
Diabetes	0	0%	2	13%	0.229
Asthma	0	0%	7	44%	0.014
Allergy	4	40%	10	62%	0.263
GERD	3	30%	3	20%	0.566
Headache disorder	1	10%	2	13%	0.846

CRSsNP = chronic rhinosinusitis without nasal polyposis; GERD = gastroesophageal reflux disease⁹⁹

Table 2.

Linear regression analyses with Pearson correlation coefficients comparing local and systemic gene expression in patients with CRSsNP and normal controls.

Tissue Expression	Blood Expression				
	<i>setla4</i>	<i>jak1</i>	<i>hla-dqa1</i>	<i>hla-dqb1</i>	<i>dusp4</i>
<i>setla4</i>	0.453 *	0.488 *	-0.390 *	-0.465 *	-0.441 *
<i>jak1</i>	0.765 **	0.670 **	-0.529 *	-0.593 *	-0.527 *
<i>hla-dqa1</i>	-0.106	-0.110	0.725 **	0.763 **	0.347
<i>hla-dqb1</i>	-0.131	-0.268	0.541 *	0.700 **	0.448 *
<i>dusp4</i>	-0.082	-0.117	0.360	0.179	0.090

*
($p < 0.05$,

**
 $p < 0.001$)

setla4= soluble cytotoxic T-lymphocyte-associated protein 4; *jak1*= janus kinase-1; *dusp4* = Dual specific protein phosphatase 4

Table 3.

Linear regression analyses with Pearson correlation coefficients comparing local gene expression in sinonasal tissue and clinical measures of disease severity in CRSsNP.

Tissue Expression	Clinical Measures of Disease Severity			
	CT	Endoscopy	SNOT-22	RSDI
<i>sctla4</i>	0.606 *	0.195	0.455 *	0.372
<i>jak1</i>	0.507 *	0.282	0.535 *	0.413
<i>hla-dqa1</i>	0.004	-0.080	-0.332	-0.396
<i>hla-dqb1</i>	-0.103	-0.204	-0.313	-0.438
<i>dusp4</i>	-0.377	-0.179	-0.146	-0.222

* ($p < 0.05$,

** ($p < 0.001$)

sctla4= soluble cytotoxic T-lymphocyte-associated protein 4; *jak1*= janus kinase-1; *dusp4* = Dual specific protein phosphatase 4

Table 4.

Linear regression analyses with Pearson correlation coefficients comparing the gene expression in blood and clinical measures of disease severity in CRSsNP.

Blood Expression	Clinical Measures of Disease Severity			
	CT	Endoscopy	SNOT-22	RSDI
<i>sctla4</i>	0.278	0.305	0.469 *	0.230
<i>jak1</i>	0.486 *	0.577 *	0.451 *	0.301
<i>hla-dqa1</i>	-0.332	-0.420	-0.479 *	-0.515 *
<i>hla-dqb1</i>	-0.325	-0.371	-0.555 *	-0.598 *
<i>dusp4</i>	-0.356	-0.018	-0.258	-0.333

*
($p < 0.05$,

**
 $p < 0.001$)

sctla4= soluble cytotoxic T-lymphocyte-associated protein 4; *jak1*= janus kinase-1; *dusp4* = Dual specific protein phosphatase 4