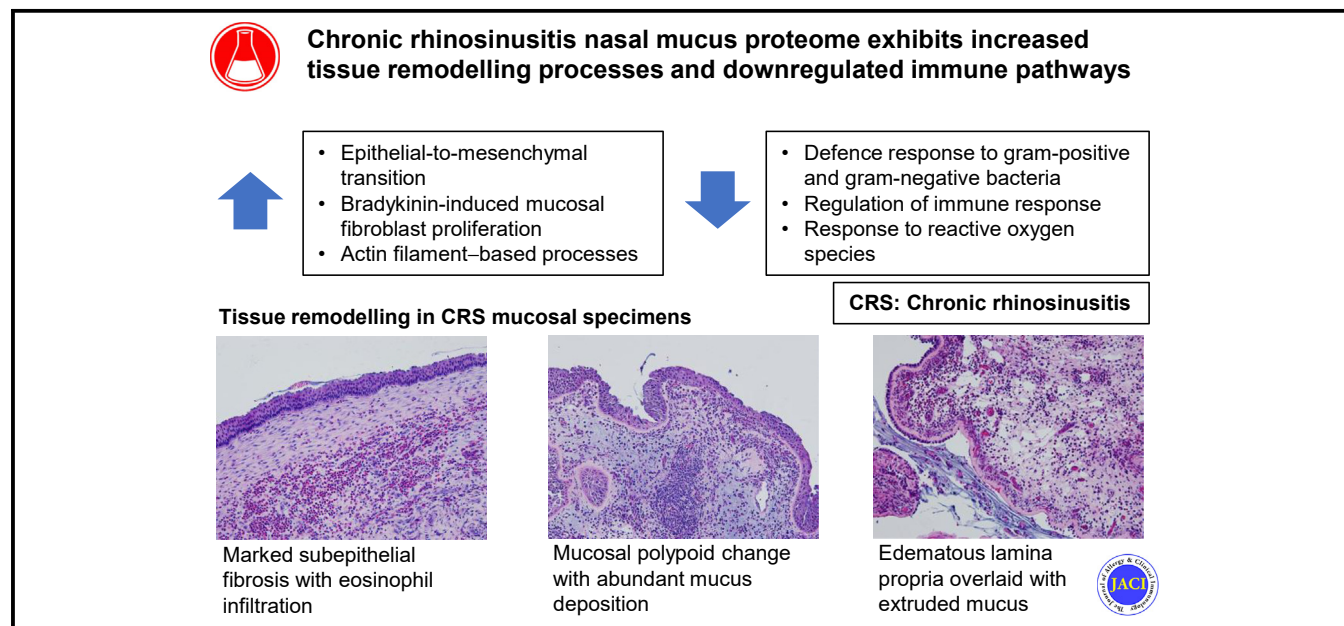


Proteomic analysis of nasal mucus samples of healthy patients and patients with chronic rhinosinusitis

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GRAPHICAL ABSTRACT



Background: Chronic rhinosinusitis (CRS) has a complex and multifactorial pathogenesis with a heterogeneous inflammatory profile. Proteomic analysis of nasal mucus may enable further understanding of protein abundances and biologic processes present in CRS and its endotypes compared with in healthy patients.

Objective: Our aim was to determine differences in the nasal mucus proteome of healthy patients and patients with CRS.

Methods: Nasal mucus was obtained from healthy patients, patients with CRS without nasal polyps (CRSsNP), and patients with CRS with nasal polyps (CRSwNP) before surgery. Gel electrophoresis was performed to fractionate the complex protein extracts before mass spectrometry analysis. Gene set

enrichment analysis was performed on differentially expressed proteins.

Results: A total of 33 patients were included in this study (12 healthy, 10 with CRSsNP, and 11 with CRSwNP). In all, 1142 proteins were identified in mucus samples from healthy patients, 761 in mucus samples from patients with CRSsNP, and 998 in mucus samples from patients with CRSwNP. Dysfunction in immunologic pathways, reduced cellular signaling, and increased cellular metabolism with associated tissue remodeling pathways were present in patients with CRS compared with in healthy patients.

Conclusion: Significant downregulation of mucosal immunity and antioxidant pathways with increased tissue modeling

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consultant for Tissium, Medtronic, and ENT Technologies. The rest of the authors declare that they have no relevant conflicts of interest.

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processes may account for the clinical manifestations of CRS. Ultimately, the differing proteome and biologic processes provide further insight into CRS pathogenesis and its endotypes. (J Allergy Clin Immunol 2020;■■■:■■■-■■■.)

Key words: Nasal mucus, proteomics, chronic rhinosinusitis, nasal polyps, endotypes, proteins

Chronic rhinosinusitis (CRS) endotypes and pathophysiology have evolved over time, with hypotheses suggesting the involvement of pathogen dysbiosis, immune dysregulation, and environmental factors.¹ Dysfunction of the epithelial barrier in patients with CRS has also been suggested as a key event in the disease process, although the precise mechanism by which this occurs remains unknown. Recent work in our department has demonstrated that locally produced mucus may have an important effect on the nasal epithelial barrier, with mucus from healthy patients shown to be associated with improved barrier integrity and mucociliary clearance, whereas mucus from patients with CRS was found to be associated with increased mucosal inflammation.² Elevated cytokine levels in mucus from patients with CRS have been identified and suggested as a novel endotyping tool.^{2,3} Furthermore, accumulation and aberrant activation of neutrophils with associated release of neutrophil serine proteases, such as elastase, cathepsin G, and proteinase 3, may contribute to the increased mucosal permeability.^{4,5} The different composition of mucus from healthy patients and mucus from patients with CRS and the regulation of inflammatory pathways may therefore contribute to the opposing effects on mucosal barrier function that have been observed.

Proteomic analysis of nasal mucus is capable of providing further insight into the physiologic and pathophysiologic pathways present in CRS. A systematic review of the literature conducted in our department identified 21 studies investigating the proteome of nasal mucus and mucosa from healthy patients and patients with CRS.⁶ Gene set enrichment analysis (GSEA) of the differentially expressed proteins identified increased immunologic, metabolic, and tissue remodeling pathways and processes present in patients with CRS compared with those in healthy patients. Notably, the most recent of these studies comparing the CRS and healthy proteome was published 8 years ago,⁷ and since then there have been considerable advances in the speed, resolution, and sensitivity of mass spectrometry (MS) equipment. The primary aim of this study was to provide an updated list of proteins and abundances in patients with CRS and healthy patients. Second, we sought to perform GSEA to determine differences in biologic processes that may account for disease processes in CRS and its endotypes.

METHODS

The Queen Elizabeth Hospital Human Research Ethics Committee, Adelaide, Australia (reference number HREC/15/TQEH/132) approved the collection of nasal mucus. Mucus samples from patients with CRS were collected from patients having endoscopic sinus surgery at the Department of Otorhinolaryngology Head and Neck Surgery of The Queen Elizabeth Hospital, Adelaide, Australia. Patient consent and mucus samples were obtained before surgery. Mucus samples from healthy patients were collected from patients who were undergoing endoscopic skull base surgery or septoplasty and had no clinical or radiologic evidence of sinus disease. Patient comorbidities and disease severity were documented

Abbreviations used

CRS: Chronic rhinosinusitis
CRSsNP: Chronic rhinosinusitis without nasal polyposis
CRSwNP: Chronic rhinosinusitis with nasal polyposis
emPAI: Exponentially Modified Protein Abundance Index
GO: Gene ontology
GSEA: Gene set enrichment analysis
MS: Mass spectrometry
ROS: Reactive oxygen species

preoperatively. Nasal mucosa tissue was obtained intraoperatively and reviewed by a pathologist. Patients who were younger than 18 years of age, pregnant, and undergoing systemic immunosuppression were excluded.

Histology

Mucosal specimens were collected, fixed in 10% neutral buffered formalin, and paraffin-embedded, after which 6- μ m sections were cut and stained with hematoxylin and eosin. The inflammatory infiltrate was assessed at the site of maximal infiltration, and the relative proportion and number per high power fields (40 $\times$ objective) of each inflammatory cell type were calculated.

Mucus collection and analysis

Mucus collection and extraction were performed as per a previously published technique with polyurethane foam without application of local anaesthesia.² Nasal mucus sample preparation and liquid chromatography–tandem MS analysis are described in detail in the [Methods section](#) of this article's Online Repository (available at www.jacionline.org). In summary, protein digests were separated by nanoliquid chromatography and analyzed with a quadrupole time-of-flight mass spectrometer. The identified proteins were matched with proteins in the Uniprot database by using MASCOT version 2.6 software (Matrix Science, London, United Kingdom).

Statistical analysis

Statistical analysis was conducted with R Core Team statistical software.⁸ The proteins identified were stratified on the basis of their presence in the mucus of either patients with CRS or healthy patients or in the mucus of both groups of patients. Protein abundance between groups was automatically calculated in terms of the Exponentially Modified Abundance Index (emPAI) by using the MASCOT software.⁹ The review by Dowle et al found emPAI values to be a reliable method of protein quantification.¹⁰ These MASCOT-derived emPAI values were converted to molar percentages by normalization against the sum of all emPAI values.^{9,11} Fold difference was calculated from the sum of molar percentages in all replicates by using the Student *t* test, with a 1.3-fold difference considered significant on the basis of the review by Dowle et al.^{10,11} GSEA was conducted on Enrichr (Ma'ayan Laboratory, New York, NY) on differentially expressed proteins across the 3 groups.^{12,13} Common gene sets from the differentially expressed proteins were grouped together to generate biologic process and pathways based on the Gene Ontology (GO) database. Only significant results (adjusted *P* value < .05 calculated by Enrichr) were included for further analysis.

RESULTS

A total of 33 patients were included in this study (12 healthy, 10 with CRSsNP, and 11 with CRSwNP) with a mean age of 46.2 years (SD 16.6 years). Patient demographics are summarized in [Table I](#). The nasal mucosal lamina propria of the patients with

TABLE I. Patient demographic characteristics

Characteristic	Healthy, no (%)	CRSsNP, no. (%)	CRSwNP, no. (%)	P value
Sex (M/F)	6/6	2/8	8/3	.054
Age (y), median (SD)	46.2 (19.1)	45.7 (16.4)	46.6 (15.4)	.963
Revision surgery	0 (0)	2 (20)	7 (64)	.002
Reformed smoker	1 (8)	1 (10)	1 (9)	.574
Active smoker	0 (0)	0 (0)	2 (18)	.062
Asthma	1 (8)	2 (20)	4 (36)	.258
GERD	1 (8)	2 (20)	1 (9)	.991
Diabetes mellitus	0 (0)	0 (0)	1 (9)	.357
Aspirin hypersensitivity	0 (0)	1 (10)	3 (27)	.131
Aeroallergen hypersensitivity	0 (0)	1 (10)	2 (18)	.315
Antibiotic hypersensitivity	0 (0)	1 (10)	0 (0)	.305
Mucus volume (μ L), median (SD)	235.8 (18.5)	213 (204.7)	290 (177.6)	.317
SNOT-22 score, median (SD)	—	58.6 (31.0)	55 (23.2)	.416
Lund-Mackay score, median (SD)	—	7.8 (2.6)	14.5 (5.2)	.0008
Lund-Kennedy score, median (SD)	—	5.6 (2.5)	9.8 (2.9)	.004
Inflammatory cell predominance	—	Eosinophilic 2 (20) Lymphocytic 1 (10) Lymphoplasmacytic 4 (40) Unknown 3 (30)	Eosinophilic 5 (45) Lymphocytic 2 (18) Lymphoplasmacytic 1 (9) Unknown 3 (27)	.589

F, Female; GERD, gastroesophageal reflux; M, male; SNOT-22, Sino-Nasal Outcome Test.

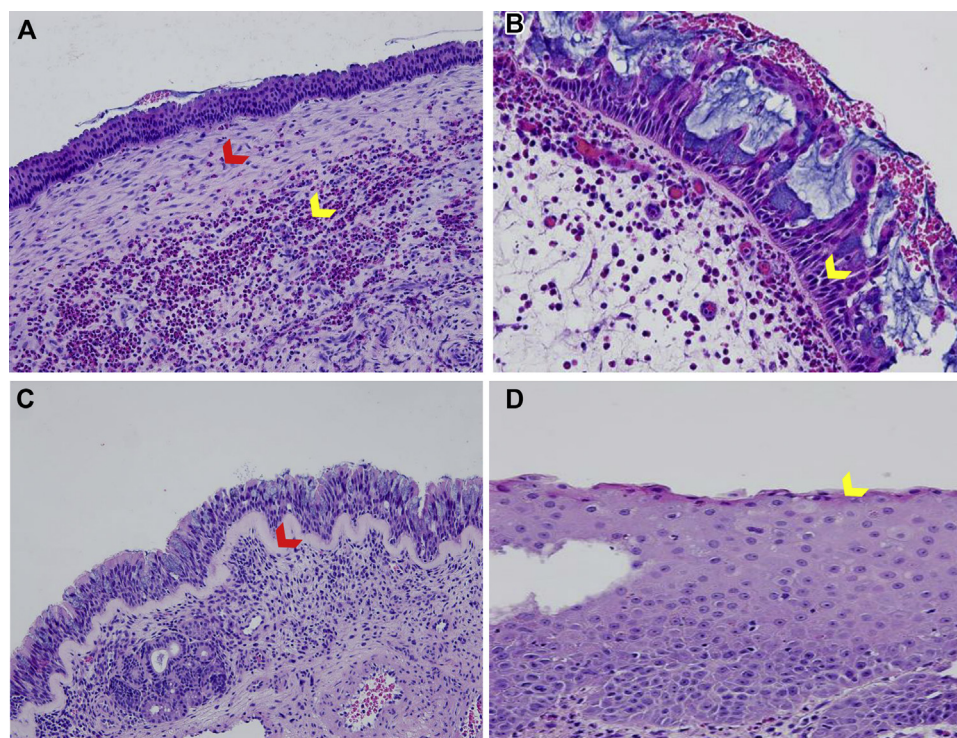


FIG 1. Histopathology of CRS mucosa demonstrating tissue remodeling. **A**, Marked subepithelial fibrosis (red arrow) with diffuse lamina propria eosinophil infiltration (yellow arrow) in CRSwNP. **B**, Respiratory epithelial and goblet cell hyperplasia (yellow arrow). **C**, Respiratory epithelial hyperplasia with marked basement membrane thickening (red arrow). **D**, Squamous metaplasia (yellow arrow) of hyperplastic respiratory epithelium in CRSwNP.

CRSwNP and those with CRSsNP showed increased eosinophil and lymphoplasmacytic infiltration, respectively. The eosinophil infiltration was diffusely distributed with occasional extension into the respiratory epithelium, whereas the infiltration of lymphocytes and plasma cells was either diffuse or perivascular (Fig 1). This was associated with tissue remodeling evidenced by respiratory epithelial hyperplasia, goblet cell hyperplasia,

basement membrane thickening, and occasional squamous metaplasia. Furthermore, the lamina propria demonstrated congestion and edema with seromucous gland hyperplasia with abundant mucus production (Fig 2).

A total of 1142 proteins were identified with at least 2 unique peptides across 12 mucus samples from healthy patients. In all, 761 and 998 proteins were identified with at least 2 unique

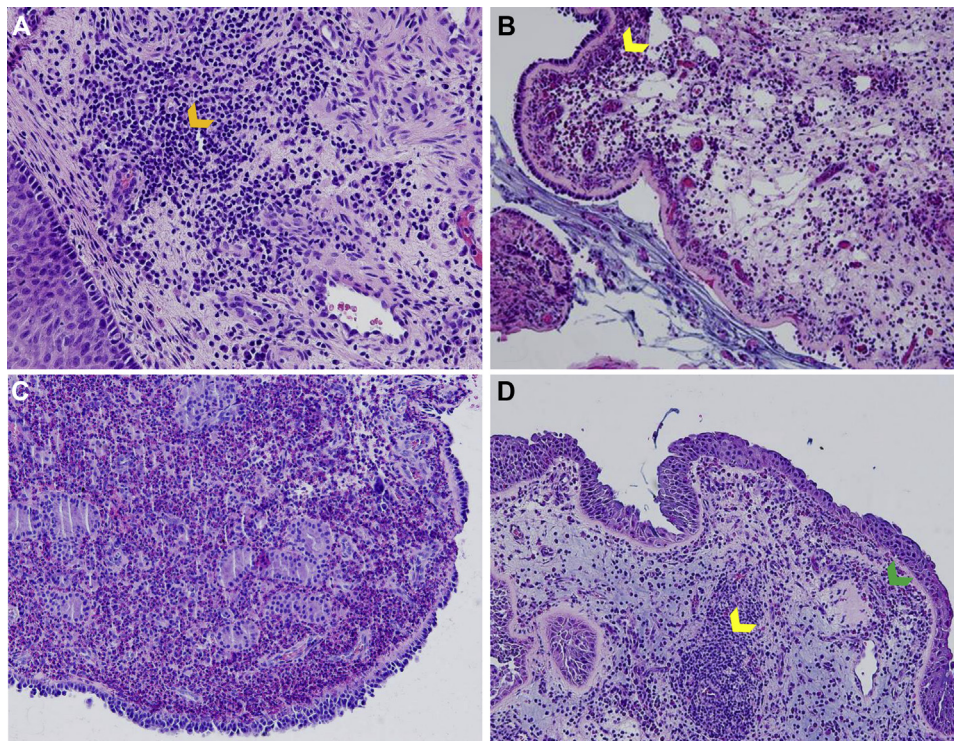


FIG 2. Histopathology of CRS mucosa demonstrating inflammatory cell infiltration. **A**, Marked lymphoplasmacytic infiltration (orange arrow) of the lamina propria in CRSsNP. **B**, Diffuse eosinophil infiltration (yellow arrow) of oedematous lamina propria overlaid with extruded mucus and necrotic debris in CRSwNP. **C**, Mucosal polyp with marked eosinophil infiltration. **D**, Mucosal polypoid change with perivascular lymphocytic cuffing (yellow arrow), eosinophil infiltration (green arrow), and abundant mucus deposition in CRSwNP.

TABLE II. Significantly different proteins between groups

Healthy vs CRSwNP						
AMBP	APOD	DMBT1	KNG1	KRT35	KRT6C	LDHA
PI3	PIGR	POTEE	RBP4	SERPINA4		
Healthy vs CRSsNP						
ACTB	ADH1C	ADH7	ALDOA	CAPG	CFL1	CSTB
GC	GOT1	HNRNPA1	IDH1	KPRP	KRT14	KRT16
MDH1	MUC5AC	POTEE	PSMA1	PSMB2	RNH1	RPSA
S100A7	S100P	SERPINB3	TPM3	TUBA1C	TXN	UGP2
YWHAE	YWHAQ					
CRSsNP vs CRSwNP						
AMBP	APOA4	ARPC2	CAPG	CAPZA2	CSTB	GC
HPX	HRG	IGLV1-51	IGLV3-19	KRT72	KRT9	LRG1
MDH1	MUC5AC	MYO5A	SCGB1D2	SERPINB3	TPM3	

peptides across mucus samples from 10 patients with CRSsNP and 11 with CRSwNP, respectively (see [Table E1](#) in this article's Online Repository at www.jacionline.org).

The healthy mucus proteome included 258 uniquely expressed proteins that were not present in diseased mucus (see [Table E2](#) in this article's Online Repository at www.jacionline.org). Pairwise analysis between mucus samples from healthy patients and samples from patients with CRSwNP identified 11 differentially expressed proteins ([Table II](#)). Pairwise

analysis between mucus from healthy patients and from patients with CRSsNP identified 30 differentially expressed proteins ([Table II](#)).

The CRS mucus proteome consisted of 268 uniquely expressed proteins, of which 97 were unique to CRSsNP mucus, 132 were unique to CRSwNP mucus, 39 were common to both types ([Table E2](#)). Pairwise analysis of mucus samples from patients with CRSwNP and from patients with CRSsNP identified 20 differentially expressed proteins ([Table II](#)).

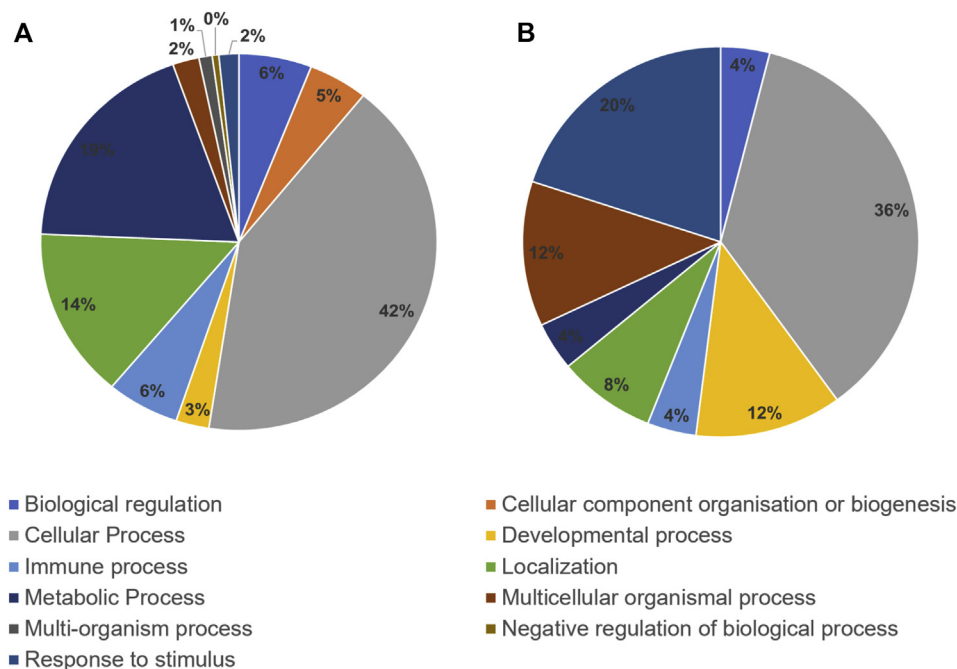


FIG 3. Downregulated biological processes in CRS versus healthy mucus. **(A)** CRSsNP versus healthy, **(B)** CRSwNP versus healthy. Percentage of all biological processes.

GSEA

GSEA was conducted on the differentially expressed proteins across mucus samples from healthy patients, patients with CRSsNP, and patients with CRSwNP (Table II). Biologic processes were identified on the basis of upregulation or downregulation of proteins and grouped according to the GO tree.

Downregulated biologic processes in mucus from patients with CRSsNP versus in mucus from healthy patients

A total of 186 significantly enriched biologic processes were stratified into 11 groups based on the GO tree (Fig 3). These were identified from 27 differentially expressed proteins between mucus samples from patients with CRSsNP and from healthy patients. Cellular (42%), metabolic (19%), and localization (14%) processes comprised 75% of all downregulated biologic processes in mucus from patients with CRSsNP compared with in mucus from healthy patients. Downregulated cellular processes included actin cytoskeletal organization (GO:0030042, GO:0007015, and GO:0008154); cell-cell signaling (GO:0060828 and GO:0060071); immune response surface receptor signaling (GO:0038093 and GO:0038095); cell cycle transition (GO:0010389 and GO:1901990); cell differentiation processes (GO:2000736); apoptosis (GO:1901030 and GO:1900739); cellular metabolic processes (GO:0006096, GO:0030091, GO:0070646, and GO:0046394); and response to stimulus (immune cell chemotaxis [GO:0090025 and GO:0010819], hydrogen peroxide-induced cell death [GO:1903205], and response to cytokines [GO:0033209 and GO:0070498]). The metabolic processes that were downregulated included ATP biosynthesis (GO:0006757), organic substance metabolic processes

(carbohydrate, protein, and DNA), and fat-soluble vitamin metabolism (GO:0006775). Localization processes downregulated in CRSsNP were associated with intracellular transport of proteins (GO:0046825, GO:0033158, and GO:0030705), transmembrane transport (GO:1901379), calcium transport (GO:1901019) and immune cell chemotaxis (mononuclear cell [GO:0071677], granulocyte [GO:0071624], and T-cell [GO:2000406]).

Downregulated biologic processes in mucus from patients with CRSwNP versus in mucus from healthy patients

In all, 26 significantly enriched biologic processes were stratified into 8 groups (Fig 3). These were identified from 4 differentially expressed proteins between mucus samples from patients with CRSwNP and mucus samples from healthy patients. Cellular process (36%), response to stimulus (20%), developmental process (12%), and multicellular organismal process (12%) made up 80% of all downregulated CRSwNP biologic processes. Downregulated cellular processes were composed of cell surface receptor signaling (GO:0002768, GO:0038093, and GO:0007173) and cellular metabolic processes involved in ATP generation (GO:0006757) and carboxylic acid metabolism (GO:0032787 and GO:0006090). The response to stimulus processes that were downregulated included detection (GO:0016045) and response to gram-positive (GO:0050830) and gram-negative bacteria (GO:0050829). The downregulated developmental processes included epithelial cell and tissue development (GO:0030855 and GO:0060429). Lastly, multicellular organismal processes were system processes involved in bitter taste perception (GO:0050913 and GO:0001580).

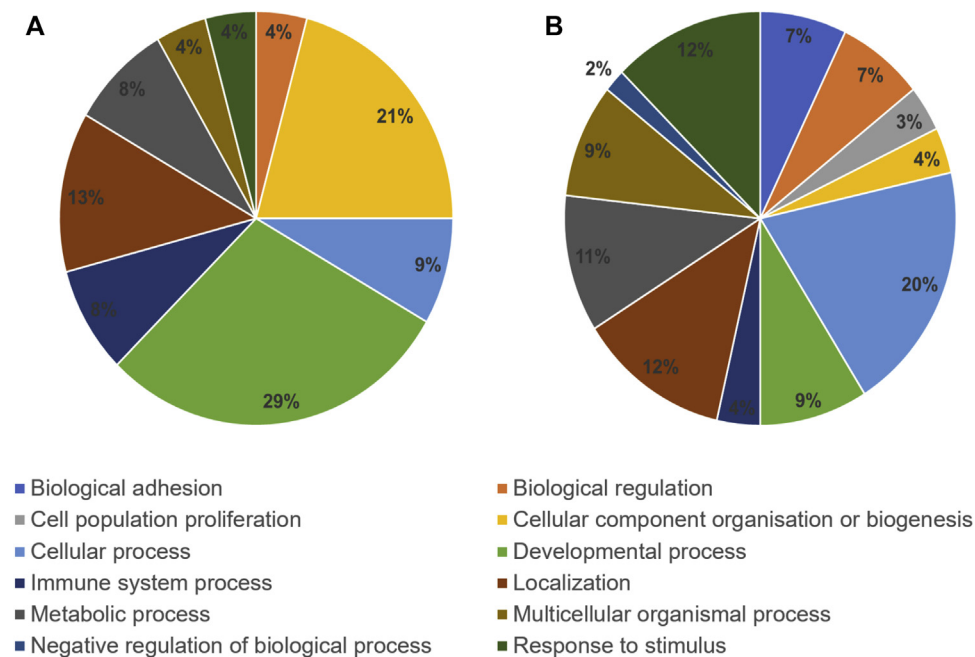


FIG 4. Upregulated biologic processes between CRS versus healthy mucus. **(A)** CRSsNP versus healthy, **(B)** CRSwNP versus healthy. Percentage of all biologic processes.

Upregulated biologic processes in mucus from patients with CRSsNP versus in mucus from healthy patients

In all, 24 significantly enriched biologic processes were stratified into 9 groups (Fig 4). These were identified from 3 differentially expressed proteins between mucus samples from patients with CRSsNP and mucus samples from healthy patients. Developmental processes (29%), cellular component organization or biogenesis (21%), and localization processes (13%) comprised 63% of all upregulated biologic processes in patients with CRSsNP. All upregulated developmental processes were associated with anatomic structure development, including epithelial barrier development (GO:0061436, GO:0008544, and GO:0060429) and differentiation (GO:0009913 and GO:0030216). Furthermore, cellular component organization or biogenesis processes were all associated with cell junction (GO:0007044 and GO:0031581) and cytoskeletal organization (GO:0007010, GO:0045110, and GO:0045109). Localization processes included negative regulation of cell motility (GO:2000146) and migration (GO:0030334 and GO:0030336).

Upregulated biologic processes in mucus from patients with CRSwNP versus in mucus from healthy patients

A total of 56 significantly enriched biologic processes were stratified into 12 groups (Fig 4). These were identified from differentially expressed proteins between mucus samples from patients with CRSwNP and mucus samples from healthy patients. Cellular processes (20%), response to stimulus (12%), and localization (12%) and metabolic processes (11%) comprised 55% of all upregulated CRSwNP biologic processes. Upregulated cellular processes included cell communication and signal transduction (GO:0010642, GO:0032873, GO:0046329, and

GO:0046328), protein metabolic processes (GO:0006464, GO:0032269, GO:0018149, and GO:0045861), exocytosis (GO:0045055), and platelet degranulation (GO:0002576). The downregulated response to stimulus processes included negative regulation of inflammatory response (GO:0050728), response to reactive oxygen species (ROS) (GO:0000302), response to axon injury (GO:0048678), regulation of blood coagulation (GO:0030193), and negative regulation of blood coagulation (GO:0030195). Localization processes included intracellular protein transport (GO:1900181, GO:0090317, GO:0042308, GO:0046823, and GO:0042306) and regulation of lymphocyte (GO:2000402) and T-cell migration (GO:2000404). Metabolic processes included carbohydrate (GO:0019318 and GO:0006006), lipid (GO:0045833), protein (GO:0030162), and heme (GO:0006787 and GO:0042167) metabolic processes.

Upregulated biologic processes in mucus from patients with CRSsNP versus in mucus from patients with CRSwNP

Nine significantly enriched biologic processes were stratified into 5 groups (Fig 5). They were identified from 2 differentially expressed proteins between mucus samples from patients with CRSsNP and patients with CRSwNP. Cellular processes (23%), developmental processes (22%), immune system processes (22%) and metabolic processes (22%) made up 89% of all upregulated biologic processes in CRSsNP compared with in CRSwNP. Cellular processes were those involved in intracellular signal transduction (GO:0048017 and GO:0048015). Developmental processes included structural development of the skin (GO:0043588) and epidermis (GO:0008544). Immune processes included activation of the innate immune response (GO:0002220) and lectin pathway (GO:0002223). Metabolic processes consisted of carbohydrate metabolism (GO:0006493 and GO:0016266).

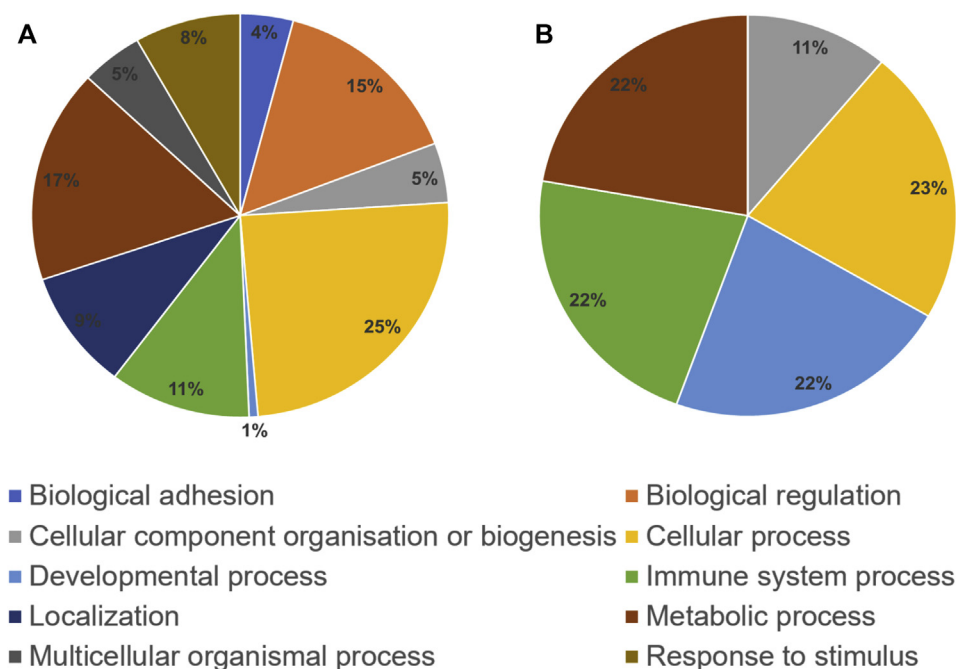


FIG 5. Upregulated biological processes between CRS phenotypes. (A) CRSsNP versus CRSwNP, (B) CRSwNP versus CRSsNP. Percentage of all biological processes.

Tissue remodeling pathways comprised 33% of upregulated pathways in CRSsNP, consisting of developmental processes (GO:0043588 and GO:0008544) and intermediate filament organization (GO:0045109).

Upregulated biologic processes in mucus from patients with CRSwNP versus in mucus from patients with CRSsNP

In all, 146 significantly enriched biologic processes were stratified into 5 groups (Fig 5). They were identified from 11 differentially expressed proteins between mucus samples from patients with CRSwNP and samples from patients with CRSsNP. Cellular processes (25%), metabolic processes (17%), and biologic regulation (15%) comprised 57% of upregulated pathways in patients with CRSwNP compared with in patients with CRSsNP. Cellular processes consisted of lipid (GO:0042304, GO:0006641, and GO:0010872) and protein metabolic processes (GO:0045861), actin filament-based processes (GO:0033275, GO:0030050, and GO:0034314), immune response regulation (GO:0038093, GO:0038095, and GO:0038094), and response to oxidative stress (GO:0071451). Metabolic processes included regulation of lipid (GO:0046890), protein (GO:0070613), and carbohydrate (GO:0006094) metabolism. Biologic regulation processes included regulation of lipid homeostasis (GO:0055088) and protease function (GO:0052547). Tissue remodeling pathways comprised 14% of upregulated pathways in CRSwNP, consisting of biologic adhesion processes (GO:0033629, GO:0033628, GO:0007159, GO:0001954, GO:0051894, and GO:0051893), cellular component organization processes (GO:1901890, GO:1903393, GO:0065003, GO:0120033, GO:0010592, GO:0010591, and GO:1902745), cellular processes (GO:0045010, GO:0033275, GO:0034314, and GO:0030050), localization processes (GO:0099515 and

GO:0099518) and positive regulation of epithelial-to-mesenchymal transition (GO:0010718).

DISCUSSION

The pathogenesis of CRS is complex and unclear, with no curative treatments currently available. The heterogeneous nature of this disease makes classification, prognostication, and management challenging for clinicians. The recent focus on CRS endotypes is an important step in understanding the various different inflammatory profiles present in patients with CRS and may ultimately allow individualized treatment protocols. Proteomic analysis of nasal mucus is capable of providing further insight into the upstream inflammatory processes that lead to the downstream clinical manifestations of CRS. This comprehensive study has utilized recent advances in MS technology to build on previous knowledge from studies comparing the healthy and CRS proteome that were conducted 8 years ago. In this study, we observed that CRS mucus demonstrated dysfunction in immunologic pathways, reduced cellular signaling, and increased cellular metabolism with associated tissue remodeling pathways. The dysregulation of these biologic processes in comparison with those in mucus from healthy patients may account for the clinical manifestations observed in CRS.

Tissue remodeling

Barrier dysfunction with increased paracellular permeability is a common feature in CRS. This study identified a greater proportion of biologic processes involved in cytoskeletal and barrier organization and assembly in mucus samples from patients with CRS than in mucus samples from healthy patients. Additionally, patients with CRSwNP appeared to have a greater number of upregulated tissue remodeling pathways than did patients with CRSsNP (20 vs 3). The upregulation of these

processes may have relevance in the context of epithelial-to-mesenchymal transition described as a result of inflammation and remodeling.¹⁴ Furthermore, positive regulation of the epithelial-to-mesenchymal transition (GO:0010718) biologic process was upregulated in CRSwNP compared with in CRSsNP, which may possibly contribute to polyp formation in these patients. This study found reduced expression of cofilin-1 in mucus from patients with CRSsNP compared with in mucus from healthy patients. The cofilin protein family and actin depolymerizing factor both regulate F-actin dynamics, which is essential in the stability and rearrangement of tight junctions and adherens junctions.^{15,16} Studies have suggested the importance of cofilin in establishing the paracellular barrier through tight junction and adherens junction reassembly.¹⁷ It has been proposed that loss of the cofilin proteins may lead to barrier dysfunction, resulting in increased exposure of submucosa to luminal bacteria with associated mucosal inflammation in murine models.¹⁷ The 40S ribosomal protein SA (RPSA) is expressed in the cell membrane, histones in the nucleus, and preribosome in the nucleolus.¹⁸ As a cell surface receptor for laminin, it plays a vital role in cell adhesion to the basement membrane and signal transduction pathways.^{18,19} The reduced expression of these proteins in nasal mucus may account for the barrier function observed in CRS. Together, these proteomic findings correlate with the mucosal histopathology findings of epithelial and goblet cell hyperplasia and increased basement membrane thickening.

This study demonstrated increased expression of kininogen-1 (KNG1) in mucus from patients with CRSwNP compared with in mucus from healthy patients. KNG1 is the precursor protein to high-molecular-weight kininogen, low-molecular-weight kininogen, and bradykinin. Physiologically, KNG1 is a vital constituent in the coagulation cascade and kallikrein-kinin system. Coagulation cascade dysfunction has been described in the pathogenesis of many inflammatory conditions.²⁰ The initiation of the coagulation cascade begins with the activation of factor XII with high-molecular-weight kininogen, which leads to the liberation of bradykinin.²¹ The binding of bradykinin B2 receptor induces neutrophil chemotaxis, vessel dilatation, and increased vascular permeability.^{22,23} Studies have demonstrated bradykinin-induced mucosal fibroblast proliferation in nasal and bronchial tissue, indicating a role in mucosal remodeling.^{24,25} These findings are demonstrated by the marked subepithelial fibrosis present in the CRSwNP histopathology samples. Deleted in brain malignant tumour (DBMT1) protein is a member of the scavenger receptor cysteine-rich superfamily. Elevated expression of DBMT1 in healthy respiratory epithelium has been described, with its deletion or inactivation leading to malignancy.^{26,27} DBMT1 has been demonstrated to be a regulator of nasal epithelial proliferation through apoptosis, where reduced levels of DBMT1 in nasal polyp tissue is associated with reduced apoptosis.²⁸ The findings from this study support these findings with a 2.5-increased fold change in the levels of DBMT1 in mucus from healthy patients compared with in the levels in mucus from patients with CRSwNP.

With the exception of KRT72, all of the keratins identified were overexpressed in mucus from patients with CRS compared with in mucus from healthy patients. KRT72 has a role in hair follicle formation and is likely a contaminant in the nasal mucus collection. Keratin presence in proteomic analysis is controversial owing to the potential for contamination. Despite this, the upregulation of keratin proteins in CRS mucus may represent

constant cytoskeletal reconstruction and remodeling secondary to chronic inflammation. This is further supported by the increased cellular remodeling and squamous metaplasia demonstrated in the CRS histology sections.

Mucociliary dysfunction

Mucociliary dysfunction is a feature present in chronic inflammatory diseases of the upper and lower airways. Effective mucociliary clearance is vital in maintaining a healthy environment in the nasal cavity through the clearance of invading pathogens. Thus, alterations in mucus composition that reflect dysfunction in cilia function may be related to the detrimental effects observed in CRS. The major constituents of mucus are mucins, encoded by MUC genes.²⁹ This study demonstrated elevated mucin 5AC (MUC5AC) expression in mucus from patients with CRS compared with in mucus from healthy patients. MUC5AC is expressed in mucus secreted from goblet cells located within the surface epithelium of the respiratory tract.³⁰ It is considered a major constituent of airway mucus that is vital in protecting the mucosa from inhaled invading pathogens and irritants, with consequent removal via the mucociliary system.³¹ Studies have found elevated expression of MUC5AC in the mucosal epithelium of patients with CRS with associated secretory cell hyperplasia and metaplasia compared with in the level of expression in healthy patients.^{30,32} IL-19, which has been identified in several inflammatory diseases with T_H2 immunologic responses, has been demonstrated to upregulate MUC5AC production through the STAT3 pathway.³³⁻³⁵ Tropomyosin alpha-3 chains (TPM3) bind to actin filaments stabilizing the cytoskeleton and have been found to be a key component in the proteome of cilia.³⁶ The reduced expression in mucus from patients with CRS found in this study may reflect poor cilia function compared with that in mucus from healthy patients. These changes present in mucus and cilia function may account for the reduced mucosal immunity and consequent barrier dysfunction observed in CRS.

Host immunity

Host immune system dysregulation is an important disease-modifying factor in CRS, contributing to disease severity and recalcitrance. Immune system processes encompassing signaling pathways and chemotaxis of granulocytes and lymphocytes were largely downregulated in the mucus from the groups of patients with CRSsNP and patients with CRSwNP compared with in mucus from the healthy group. Furthermore, defense response to gram-positive (GO:0050830) and gram-negative bacterial (GO:0050829) pathways were downregulated in mucus from patients with CRSwNP compared with in mucus from healthy patients. Bitter taste perception biologic processes were downregulated in patients with CRSwNP compared with in healthy patients. Studies have found the bitter taste receptor gene family, particularly T2R38, to be associated with activation of the local innate immune response through increased mucociliary clearance and bactericidal activity.^{37,38} Thus polymorphisms and reduced function in bitter taste receptors may play a role in sinonasal immunity in CRS.³⁹ The reduced expression of these pathways reflects the bacterial species commonly responsible for recurrent infections in patients with CRS.⁴⁰

Impairment in function of immune cells may account for the inadequate immune response against invading pathogens. Macrophage-capping protein (CAPG) is an actin-binding protein of the gelsolin/villin superfamily associated with cell motility.⁴¹ CAPG has exhibited its importance in host immunity through macrophage motility and facilitation of IgG complement phagocytosis.⁴² Thus, the reduced expression in CRSsNP mucus observed in this study may indicate impaired macrophage mediated inflammatory responses. Additionally, elafin (PI3), an endogenous protein expressed predominately in epithelial tissue, has the ability to inhibit neutrophil elastase and proteinase-3.⁴³ The upregulation of PI3 identified in inflamed sinus mucosa and nasal mucus from this study may account for reduced bacterial killing due to inactivated neutrophil serine proteases.⁴⁴

S100 proteins have a role as intracellular regulators and extracellular signaling proteins secreted to regulate activities of target cells. Intracellularly, they are capable of regulating cell proliferation, differentiation, apoptosis, inflammation, and calcium homeostasis. Extracellularly, the S100 proteins act via the activation of surface receptors, G-protein-coupled and scavenger receptors in the regulation of cell proliferation, differentiation, survival, inflammation, tissue repair, and antimicrobial activity.⁴⁵ S100A7 (psoriasin) is upregulated in inflammatory skin diseases induced by IL-17 and IL-22.⁴⁶ Additionally, it has antimicrobial responses through generation of ROS from neutrophils and binding to and reducing survival of *Escherichia coli*.^{47,48} The reduced expression of S100A7 in CRSsNP mucus may be associated with decreased mucosal immunity.

A range of proteins involved in immune function were found to be downregulated in patients with CRS compared with in healthy patients. Polymeric immunoglobulin receptor is a transmembrane protein expressed on the basolateral surface of ciliated epithelial cells in mucosal epithelium, assisting the transportation of IgA and IgM across the epithelial barrier to the mucosal surface in response to viral and bacterial infections.⁴⁹ There was a significant fold reduction of polymeric immunoglobulin receptor in mucus from both patients with CRSwNP and patients with CRSsNP compared with in mucus from healthy patients, indicating a reduced mucosal immunity present in patients with CRS compared with in healthy patients. Proteasome subunit beta type-2 (PSMB2) and proteasome subunit alpha type-1 (PSMA1) are essential subunits of the 20S proteasome complex, which in turn is a component of the immunoproteasome.⁵⁰ The immunoproteasome is capable of antigen presentation on MHC class I molecules. Deficiencies identified in mice have been associated with reduced CD8⁺ cell activation against hepatitis B and influenza virus infections.⁵¹⁻⁵³ Furthermore, its ability to influence T-cell polarization has been implicated in autoimmune diseases.⁵⁴ This study suggests that reduction in expression of proteasome subunits to be implicated in the heightened viral invasion in CRSsNP.⁵⁵ Increased levels of eosinophil cationic protein and eosinophil peroxidase were identified in mucus from patients with CRSwNP; although not statistically significant, this increase correlates well with the eosinophil inflammatory predominance in these patients.

Altered cellular metabolism

The regulation of cellular metabolic function is paramount to tissue homeostasis and survival. Mucus from patients with CRS appears to have reduced ATP metabolic pathways compared with

mucus from healthy patients. Conversely, carbohydrate and lipid metabolism pathways were upregulated in patients with CRS. These findings may be reflected in the increased metabolic demand required to combat the chronic inflammation and pathogen colonization. An increased level of glucose has been found in the airway fluid of patients with cystic fibrosis, as cells require constant glucose for cellular function and tissue integrity. The reduced ATP generation in patients with CRS may reflect the inability of these patients to keep up with the increased metabolic demand, leading to a buildup of ROS.

The balance in antioxidant pathways is vital in reducing cellular damage from ROS, the end result of cellular metabolism. The chronic inflammation associated with CRS places host cells at increased risk of oxidative damage and barrier dysfunction. Apolipoprotein A-IV (APOA4) has demonstrated roles in glucose homeostasis, antioxidant, and anti-inflammatory properties.⁵⁶⁻⁵⁸ In asthma, its immunomodulatory properties include improving bronchioalveolar epithelial integrity and reduction of mucin expression.⁵⁹ Elevated levels of APOA1 and APOA2 were found in patients with allergic rhinitis compared with the levels in healthy controls.⁶⁰ Increased expression may reflect the increased inflammation observed in CRSwNP compared with in CRSsNP. Alpha-1-microglobulin/bikunin precursor (AMB) belongs to the lipocalin superfamily of transport proteins and is suggested to play a role in regulation of inflammatory processes. Alpha-1 microglobulin (A1M), an acute-phase protein, is capable of inhibiting antigen-stimulated proliferation of lymphocytes and IL-2 secretion.⁶¹ Elevated levels of urinary A1M are associated with increased levels of the acute-phase proteins C-reactive protein and fibrinogen, indicating a role of A1M in the overall inflammatory status in patients.⁶² Elevated expression of A1M was found in mucus samples from patients with CRSwNP compared with in mucus from both patients with CRSsNP and healthy patients. Ribonuclease inhibitor (RHN1) resides within the cytosol, with its suggested biologic roles including protection from invading ribonucleases, regulation or termination of ribonuclease activity with known intracellular functions, and monitoring of the oxidative stress of the cell.⁶³ This study found 12-fold-reduced expression of RHN1 in patients with CRSsNP compared with in healthy patients, indicating a reduced protection against oxidative stressors.

Limitations

Complex protein mixtures, such as nasal mucus, require separation before MS analysis to improve protein visualization and identification. Gel electrophoresis is the most commonly used method for protein separation in mucus proteomic studies.⁶ The recovery of proteins from gel is poor for highly glycosylated and sialidated and sulphated proteins. Alternative non-gel-based separation methods include various chromatography techniques. Despite these limitations, we were able to identify a comprehensive catalog of proteins correlating well with previously published literature.⁶ Furthermore, minimal cytokines were identified by MS analysis within nasal mucus. Yoshikawa et al found MS to be insensitive for cytokines and growth factors on account of their small size and low abundance.⁶⁴ Multiplex assays of nasal mucus and mucosa are better alternatives for the detection and quantification of cytokines. The MS technique used in our study is validated and widely recognized as an effective method of shotgun proteomics. In contrast, Mueller et al used

ultracentrifugation to isolate exosomes for proteomic analysis via SOMAScan as a novel approach in nasal mucus proteomic research.^{65,66} SOMAScan is a novel and validated proteomic analysis method utilizing aptamers to affinity-purify proteins and the aptamers quantified using array technology. Our technique has the potential to identify more proteins present within the mucus samples, providing a more wholistic picture. SOMAScan has demonstrated itself to be an effective alternative to MS in proteomic analysis, especially when analyzing extracts with very high dynamic range, such as serum.⁶⁷

The shotgun proteomics and GSEA performed in this study has generated a vast array of biologic processes to aid in understanding and directing future research in the pathophysiology of CRS. The authors acknowledge that the statistical method used in this study may lead to detection of some false-positive proteins; however, we do not believe that this has significantly affected the downstream biologic analyses and conclusions. An omnibus test in the form of a 1-way ANOVA was performed to determine which proteins were differentially expressed across all 3 groups. A total of 20 significantly differentially expressed proteins (see Table E3 in this article's Online Repository at www.jacionline.org) were identified after controlling for false discovery rates; in contrast, 94 proteins were identified with the pairwise analysis. Subsequently, the reduced numbers of proteins led to a reduced number of unique biologic pathways identified on GSEA in the downstream analysis. Overall, both analyses demonstrated similar trends of increased tissue remodeling and immunologic pathways in mucus samples from patients with CRSsNP and patients with CRSwNP compared with in mucus samples from healthy patients. We believe that as an exploratory study, casting a wider net initially will aid in directing more focused studies and research in the future. Ultimately, these findings will direct further targeted analysis of prominent cellular pathways involved in this chronic inflammatory disease.

Conclusion

This study conducted shotgun proteomics on nasal mucus from healthy patients and patients with CRS, followed by GSEA of differentially expressed proteins to identify differences in biologic pathway regulation. The study identified significant down-regulation of mucosal immunity processes and antioxidant and metabolic pathways with associated tissue remodeling that may lead to the downstream manifestation in CRS. It is hoped that this study will guide further focused proteomic analysis and better understanding of different CRS endotypes.

Clinical implication: Identification of differences in immunologic pathways between healthy individuals and patients with chronic rhinosinusitis will aim to guide future research in the development of targeted immunotherapies.

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Supplementary Table 1. Protein list with emPAI value

Accession Number	Gene name	CRSsNP	CRSwNP	Healthy
A0A075B6I0	IGLV8-61	0.09	0.327273	0.3
A0A075B6I1	IGLV4-60	0	0.08	0
A0A075B6I9	IGLV7-46	0	0.083636	0.076667
A0A075B6K4	IGLV3-10	0.607	0.836364	0.888333
A0A075B6P5	IGKV2-28	0.176	0.16	0
A0A075B6R2	IGHV4-4	0.089	0.242727	0.148333
A0A075B6S2	IGKV2D-29	0.764	0.978182	0.9275
A0A0A0MS15	IGHV3-49	0.087	0	0
A0A0B4J1U7	IGHV6-1	0.084	0	0.07
A0A0B4J1V0	IGHV3-15	0.088	0.223636	0.073333
A0A0B4J1V1	IGHV3-21	0.089	0	0.074167
A0A0B4J1V2	IGHV2-26	0	0.078182	0
A0A0B4J1V6	IGHV3-73	0	0.080909	0
A0A0B4J1X5	IGHV3-74	0.586	0.598182	0.2075
A0A0B4J1Y8	IGLV9-49	0	0.08	0.22
A0A0B4J1Y9	IGHV3-72	0.086	0.14	0.071667
A0A0C4DH25	IGKV3D-20	1.52	1.331818	1.220833
A0A0C4DH38	IGHV5-51	0.09	0.163636	0
A0A0C4DH41	IGHV4-61	0.087	0.237273	0.145
A0A0C4DH68	IGKV2-24	0.783	0.790909	0.6525
A0AVT1	UBA6	0	0	0.005833
A0M8Q6	IGLC7	0	0.177273	0.1625
A2A2Z9	ANKRD18B	0	0	0.005833
A5PKW4	PSD	0	0	0.006667
A6NC98	CCDC88B	0	0.004545	0.004167
A6NCN2	KRT87P	0	1.461818	0
A6NE01	FAM186A	0	0	0.005
A6NHG4	DDTL	0	0.140909	0.128333
A6NMB1	SIGLEC16	0	0	0.028333
A6NMY6	ANXA2P2	0.079	0.057273	0.076667
A8MPP1	DDX11L8	0	0.008182	0
A8MTJ3	GNAT3	0.023	0.020909	0
A8MWD9	SNRPGP15	0	0	0.919167
B2RPK0	HMGB1P1	0	0.037273	0.034167
B5ME19	EIF3CL	0.022	0	0
B9A064	IGLL5	0.945	1.1	0.91
C9JRZ8	AKR1B15	0	0.070909	0.048333
E9PAV3	NACA	0	0.005455	0.015
O00148	DDX39A	0	0	0.049167
O00151	PDLIM1	0	0	0.0825
O00154	ACOT7	0	0.02	0
O00192	ARVCF	0.008	0	0
O00231	PSMD11	0	0.027273	0.025

O00232	PSMD12	0	0.015455	0.050833
O00299	CLIC1	0.546	1.264545	1.188333
O00303	EIF3F	0	0	0.020833
O00391	QSOX1	0.181	0.125455	0.1425
O00423	EML1	0	0.009091	0
O00483	NDUFA4	0.138	0	0
O00487	PSMD14	0.055	0.08	0.081667
O00560	SDCBP	0	0.027273	0
O00584	RNASET2	0	0	0.026667
O00602	FCN1	0	0.024545	0
O00750	PIK3C2B	0	0.004545	0
O00757	FBP2	0.052	0	0.020833
O00764	PDXK	0.054	0.168182	0.173333
O14578	CIT	0	0	0.003333
O14579	COPE	0	0.04	0.0225
O14618	CCS	0	0	0.044167
O14745	SLC9A3R1	0	0.021818	0.051667
O14791	APOL1	0.033	0.123636	0.113333
O14818	PSMA7	0.152	0.423636	0.455
O14933	UBE2L6	0	0.138182	0
O14950	MYL12B	0.184	0.173636	0.436667
O15020	SPTBN2	0	0.004545	0.004167
O15078	CEP290	0.003	0.002727	0.005833
O15119	TBX3	0.022	0	0
O15143	ARPC1B	0.036	0.051818	0.1025
O15144	ARPC2	0.107	0.707273	0.481667
O15145	ARPC3	0.166	0.399091	0.46
O15212	PFDN6	0	0	0.064167
O15217	GSTA4	0	0.057273	0.0525
O15305	PMM2	0	0.030909	0.028333
O15372	EIF3H	0	0.062727	0.093333
O15498	YKT6	0	0	0.0375
O15511	ARPC5	0.067	0.06	0.3
O43242	PSMD3	0	0.013636	0.0125
O43324	EEF1E1	0	0	0.043333
O43396	TXNL1	0	0.097273	0.119167
O43399	TPD52L2	0	0.082727	0.191667
O43447	PPIH	0	0.048182	0.118333
O43488	AKR7A2	0.023	0.033636	0.043333
O43490	PROM1	0.014	0	0
O43617	TRAPPC3	0	0	0.041667
O43633	CHMP2A	0	0.036364	0
O43681	ASNA1	0	0.034545	0.04
O43707	ACTN4	0.419	0.455455	0.556667
O43708	GSTZ1	0	0	0.034167
O43747	AP1G1	0	0.013636	0.0125

O43776	NARS	0	0	0.011667
O43790	KRT86	7.27	3.149091	0.455833
O43809	NUDT21	0	0	0.061667
O43866	CD5L	0	0.085455	0.1925
O60218	AKR1B10	0.173	0.68	0.628333
O60234	GMFG	0	0.213636	0.199167
O60256	PRPSAP2	0	0	0.019167
O60282	KIF5C	0.008	0	0.006667
O60437	PPL	0.018	0.02	0.078333
O60493	SNX3	0	0.216364	0.363333
O60547	GMDS	0.022	0	0.018333
O60610	DIAPH1	0	0	0.013333
O60635	TSPAN1	0	0.033636	0
O60664	PLIN3	0	0	0.085
O60701	UGDH	0	0.014545	0.026667
O60763	USO1	0.008	0.032727	0.013333
O60879	DIAPH2	0	0.006364	0
O60925	PFDN1	0	0.126364	0.2475
O75037	KIF21B	0.005	0	0
O75083	WDR1	0.042	0.089091	0.131667
O75116	ROCK2	0	0.007273	0
O75223	GGCT	0	0.261818	0.545833
O75347	TBCA	0.252	1.274545	1.534167
O75348	ATP6V1G1	0	0.073636	0.0675
O75367	H2AFY	0.038	0	0.091667
O75368	SH3BGRL	0	0.313636	0.543333
O75369	FLNB	0.008	0.046364	0.081667
O75376	NCOR1	0	0	0.0025
O75390	CS	0	0	0.015
O75420	GIGYF1	0.008	0	0
O75436	VPS26A	0	0.022727	0
O75534	CSDE1	0	0	0.008333
O75556	SCGB2A1	0.627	0.653636	0.9925
O75608	LYPLA1	0	0	0.0875
O75636	FCN3	0	0.094545	0
O75663	TIPRL	0	0	0.040833
O75821	EIF3G	0	0	0.021667
O75828	CBR3	0.072	0.159091	0.059167
O75832	PSMD10	0	0.036364	0.055
O75874	IDH1	0.119	0.359091	0.610833
O75882	ATRN	0	0.004545	0.0125
O75884	RBBP9	0	0	0.04
O75891	ALDH1L1	0	0.008182	0
O75964	ATP5MG	0.105	0	0
O76003	GLRX3	0	0.036364	0
O76009	KRT33A	2.411	2.53	0.2375

O76011	KRT34	0.844	0.982727	0.158333
O76013	KRT36	0	0.248182	0.0925
O76014	KRT37	0	0.050909	0
O76015	KRT38	0.165	0.215455	0
O76070	SNCG	0	0.139091	0.308333
O94760	DDAH1	0	0	0.025833
O94788	ALDH1A2	0	0.043636	0.026667
O94832	MYO1D	0.008	0	0
O94915	FRYL	0	0.002727	0
O94991	SLITRK5	0	0.007273	0
O95140	MFN2	0	0	0.008333
O95197	RTN3	0.008	0	0.006667
O95248	SBF1	0	0	0.003333
O95294	RASAL1	0	0.059091	0.041667
O95336	PGLS	0.035	0.134545	0.184167
O95433	AHSA1	0	0	0.02
O95445	APOM	0	0.085455	0.039167
O95568	METTL18	0	0	0.018333
O95678	KRT75	0	0.705455	0.335833
O95716	RAB3D	0.098	0	0.034167
O95777	LSM8	0	0.108182	0.484167
O95782	AP2A1	0.012	0	0
O95865	DDAH2	0	0	0.026667
O95968	SCGB1D1	0.467	1.083636	1.304167
O95969	SCGB1D2	0.492	1.579091	1.025
O95994	AGR2	0.521	0.719091	0.695
O96017	CHEK2	0	0.013636	0
P00326	ADH1C	0.678	1.296364	1.751667
P00338	LDHA	0.896	1.844545	2.024167
P00352	ALDH1A1	1.111	2.087273	1.863333
P00367	GLUD1	0.023	0	0.025833
P00390	GSR	0.032	0.073636	0.1425
P00403	MT-CO2	0.116	0	0.063333
P00441	SOD1	0.366	0.602727	0.6275
P00450	CP	0.441	0.637273	0.515833
P00491	PNP	0.148	0.197273	0.245833
P00492	HPRT1	0	0.120909	0.194167
P00505	GOT2	0.03	0.038182	0.086667
P00558	PGK1	0.713	1.827273	2.154167
P00568	AK1	0	0.070909	0.23
P00734	F2	0	0.040909	0
P00736	C1R	0	0	0.009167
P00738	HP	3.215	6.215455	4.023333
P00739	HPR	0	0.311818	0.249167
P00747	PLG	0.193	0.305455	0.264167
P00748	F12	0	0.047273	0.010833

P00751	CFB	0.321	0.535455	0.591667
P00915	CA1	0	0.463636	0.065833
P00918	CA2	0	0.079091	0.086667
P00966	ASS1	0.272	0.260909	0.444167
P01008	SERPINC1	0.94	1.961818	1.304167
P01009	SERPINA1	3.227	5.867273	3.404167
P01011	SERPINA3	1.416	1.615455	1.221667
P01019	AGT	0.044	0.153636	0.079167
P01023	A2M	1.041	1.588182	1.235833
P01024	C3	1.792	2.894545	2.455
P01031	C5	0.043	0.129091	0.140833
P01033	TIMP1	0.336	0.589091	0.318333
P01034	CST3	0.722	0.932727	0.965833
P01036	CST4	0.065	0.923636	0.503333
P01037	CST1	0	0.202727	0.093333
P01040	CSTA	3.444	4.446364	3.745833
P01042	KNG1	0.219	0.501818	0.285
P01591	JCHAIN	2.165	2.173636	2.281667
P01602	IGKV1-5	0	0	0.074167
P01619	IGKV3-20	1.344	1.255455	1.273333
P01700	IGLV1-47	0	0.170909	0.078333
P01701	IGLV1-51	0.282	0.838182	0.705
P01706	IGLV2-11	0.182	0.413636	0.303333
P01709	IGLV2-8	0.279	0.591818	0.5425
P01714	IGLV3-19	0.482	0.964545	0.803333
P01717	IGLV3-25	0.483	0.79	0.641667
P01718	IGLV3-27	0	0.086364	0
P01742	IGHV1-69	0	0.165455	0.075833
P01743	IGHV1-46	0	0	0.073333
P01764	IGHV3-23	0.455	0.165455	0.151667
P01768	IGHV3-30	0.158	0.43	0.656667
P01772	IGHV3-33	0.155	0.565455	0.39
P01780	IGHV3-7	1.35	1.836364	1.545
P01782	IGHV3-9	0	0.08	0
P01833	PIGR	1.483	1.348182	1.508333
P01834	IGKC	4.011	5.477273	4.303333
P01857	IGHG1	2.313	2.630909	2.534167
P01859	IGHG2	1.731	1.925455	1.789167
P01860	IGHG3	1.412	1.741818	1.706667
P01861	IGHG4	0.863	1.639091	1.323333
P01871	IGHM	1.361	1.617273	1.648333
P01876	IGHA1	2.334	2.312727	2.248333
P01877	IGHA2	1.061	0.973636	0.65
P01880	IGHD	0.022	0.031818	0.0675
P01903	HLA-DRA	0.034	0	0.028333
P01911	HLA-DRB1	0.032	0	0

P02042	HBD	0.586	3.620909	0.561667
P02100	HBE1	0	0.060909	0
P02533	KRT14	8.318	7.900909	6.414167
P02538	KRT6A	6.069	8.08	5.48
P02545	LMNA	0.139	0.287273	0.375833
P02585	TNNC2	0	0	0.048333
P02647	APOA1	4.781	10.50091	7.806667
P02649	APOE	0	0.621818	0.225833
P02652	APOA2	2.554	3.71	2.926667
P02654	APOC1	0	0.127273	0.233333
P02655	APOC2	0	0.192727	0
P02671	FGA	0.381	0.673636	0.460833
P02675	FGB	0.913	1.725455	1.218333
P02679	FGG	1.075	1.398182	1.2575
P02686	MBP	0	0	0.024167
P02743	APCS	0.358	0.828182	0.665833
P02746	C1QB	0.22	0.613636	0.4725
P02747	C1QC	0.216	0.459091	0.535833
P02748	C9	0.014	0.032727	0.041667
P02749	APOH	0	0.164545	0.090833
P02750	LRG1	0.128	0.376364	0.250833
P02751	FN1	0.157	0.277273	0.298333
P02753	RBP4	0	0.509091	0.154167
P02760	AMBP	0.137	0.618182	0.255833
P02763	ORM1	0.759	1.35	0.806667
P02765	AHSG	0.256	0.461818	0.323333
P02766	TTR	0.455	0.972727	0.605
P02768	ALB	20.552	31.58182	26.05583
P02774	GC	0.72	1.754545	1.391667
P02787	TF	2.305	4.663636	2.985
P02788	LTF	4.999	5.404545	5.6
P02790	HPX	0.501	1.087273	0.740833
P02792	FTL	0	0.242727	0.071667
P02794	FTH1	0.048	0.15	0.204167
P03950	ANG	0	0.058182	0
P03952	KLKB1	0	0.056364	0.025833
P03973	SLPI	3.904	4.673636	2.784167
P04003	C4BPA	0.081	0.085455	0.079167
P04004	VTN	0.043	0.092727	0.0425
P04040	CAT	0.1	0.253636	0.141667
P04062	GBA	0.015	0.013636	0
P04066	FUCA1	0	0	0.014167
P04075	ALDOA	1.102	1.905455	1.999167
P04080	CSTB	0.324	2.156364	2.430833
P04083	ANXA1	1.729	1.750909	2.063333
P04114	APOB	0.043	0.447273	0.379167

P04179	SOD2	0.106	0.22	0.168333
P04196	HRG	0.098	0.373636	0.2825
P04211	IGLV7-43	0	0.083636	0
P04217	A1BG	0.18	0.419091	0.284167
P04229	HLA-DRB1	0	0	0.026667
P04259	KRT6B	5.29	7.182727	3.918333
P04264	KRT1	9.717	10.15818	8.2425
P04279	SEMG1	0.038	0.045455	0.4725
P04406	GAPDH	0.906	1.684545	1.178333
P04632	CAPNS1	0.146	0.346364	0.339167
P04792	HSPB1	1.481	2.527273	2.619167
P04839	CYBB	0.047	0	0
P04899	GNAI2	0.036	0	0
P04908	HIST1H2AB	0.224	0	0
P04908	HIST1H2AE	0.224	0	0
P05023	ATP1A1	0.024	0	0.023333
P05089	ARG1	0.116	0.056364	0.036667
P05090	APOD	0.791	1.377273	0.766667
P05091	ALDH2	0	0	0.046667
P05107	ITGB2	0.081	0.009091	0
P05109	S100A8	8.793	9.561818	10.57
P05141	SLC25A5	0.449	0.026364	0.119167
P05154	SERPINA5	0	0.029091	0
P05155	SERPING1	0.48	0.865455	0.703333
P05156	CFI	0.026	0.092727	0.078333
P05161	ISG15	0	0.053636	0
P05164	MPO	0.541	0.550909	0.304167
P05198	EIF2S1	0	0.053636	0.120833
P05387	RPLP2	0	0.092727	0.17
P05388	RPLP0	0.063	0.098182	0.196667
P05452	CLEC3B	0	0.138182	0.314167
P05455	SSB	0	0.018182	0.025833
P05543	SERPINA7	0	0.126364	0.0625
P05546	SERPIND1	0.164	0.370909	0.266667
P05783	KRT18	0.276	0.448182	0.673333
P05787	KRT8	2.331	3.558182	3.674167
P05976	MYL1	0	0	0.066667
P06310	IGKV2-30	0	0.218182	0
P06312	IGKV4-1	0.17	0.375455	0.339167
P06396	GSN	0.428	0.510909	0.540833
P06576	ATP5F1B	0.193	0.022727	0.0925
P06681	C2	0	0.024545	0.026667
P06702	S100A9	10.566	16.26364	13.55917
P06703	S100A6	4.781	3.300909	3.218333
P06727	APOA4	0.861	3.69	2.383333
P06731	CEACAM5	0.048	0.038182	0.04

P06732	CKM	0	0.030909	0.028333
P06733	ENO1	1.67	2.472727	2.545833
P06737	PYGL	0.071	0.079091	0.041667
P06744	GPI	0.247	0.468182	0.469167
P06748	NPM1	0.029	0.184545	0.235
P06753	TPM3	0.286	0.781818	0.925833
P06899	HIST1H2BJ	0.71	0	0
P07099	EPHX1	0.099	0	0.0225
P07108	DBI	0	0.114545	0.105
P07195	LDHB	0.577	1.477273	1.386667
P07196	NEFL	0	0	0.0125
P07197	NEFM	0	0	0.0075
P07203	GPX1	0	0.040909	0.1675
P07205	PGK2	0	0.029091	0.0375
P07237	P4HB	0.181	0.180909	0.273333
P07305	H1FO	0	0	0.068333
P07339	CTSD	0.476	0.888182	0.799167
P07355	ANXA2	2.048	1.330909	1.484167
P07358	C8B	0.013	0	0.010833
P07360	C8G	0.12	0.35	0.515833
P07384	CAPN1	0.139	0.215455	0.289167
P07437	TUBB	0.154	0.512727	0.4275
P07476	IVL	0.028	0.06	0
P07477	PRSS1	0	0.032727	0
P07602	PSAP	0.063	0.177273	0.1925
P07686	HEXB	0	0.012727	0.03
P07711	CTSL	0	0	0.020833
P07737	PFN1	1.84	3.233636	3.3375
P07741	APRT	0.053	0.222727	0.419167
P07814	EPRS	0.013	0.009091	0.015
P07858	CTSB	0.063	0.134545	0.180833
P07864	LDHC	0	0	0.021667
P07900	HSP90AA1	0.288	0.525455	0.665
P07910	HNRNPC	0.028	0.151818	0.225
P07949	RET	0	0.006364	0
P07951	TPM2	0	0.042727	0.253333
P07954	FH	0	0.015455	0.014167
P07996	THBS1	0.068	0.019091	0.025833
P07998	RNASE1	0	0.159091	0.098333
P08133	ANXA6	0.095	0	0
P08174	CD55	0.022	0	0
P08185	SERPINA6	0	0.074545	0.016667
P08238	HSP90AB1	0.294	0.432727	0.580833
P08246	ELANE	0.277	0.371818	0.2925
P08263	GSTA1	0.727	1.159091	1.0525
P08311	CTSG	0.665	0.598182	0.335833

P08519	LPA	0	0.002727	0.004167
P08575	PTPRC	0.012	0	0
P08603	CFH	0.192	0.436364	0.4375
P08670	VIM	0.674	1.198182	1.413333
P08697	SERPINF2	0	0.063636	0.064167
P08708	RPS17	0	0	0.058333
P08727	KRT19	5.69	5.986364	6.576667
P08729	KRT7	0.881	1.653636	1.586667
P08754	GNAI3	0.023	0	0.019167
P08758	ANXA5	0.436	0.203636	0.2675
P08779	KRT16	8.365	9.622727	5.338333
P08865	RPSA	0.029	0.101818	0.196667
P08962	CD63	0	0.033636	0
P09012	SNRPA	0	0.028182	0.025833
P09104	ENO2	0	0.017273	0
P09210	GSTA2	0.749	0.913636	1.21
P09211	GSTP1	1.553	2.182727	1.895833
P09382	LGALS1	0	0.116364	0.121667
P09429	HMGB1	0	0	0.054167
P09455	RBP1	0	0.061818	0.155
P09467	FBP1	0.041	0.148182	0.229167
P09488	GSTM1	0	0.081818	0
P09496	CLTA	0	0.053636	0.06
P09497	CLTB	0	0	0.0325
P09525	ANXA4	0.186	0.023636	0.183333
P09619	PDGFRB	0	0	0.005833
P09651	HNRNPA1	0.111	0.366364	0.473333
P09668	CTSH	0	0	0.020833
P09669	COX6C	0.153	0	0
P09758	TACSTD2	0	0.023636	0
P09871	C1S	0	0.016364	0.038333
P09914	IFIT1	0	0.014545	0
P09960	LTA4H	0	0.025455	0.080833
P09972	ALDOC	0.072	0.128182	0.129167
P0C0L4	C4A	0.113	0.340909	0.209167
P0C0L5	C4B	0.234	0.293636	0.386667
P0C0L5	C4B_2	0.234	0.293636	0.386667
P0C0S5	H2AFZ	0.402	0.288182	0.474167
P0C7H8	KRTAP2-3	0.071	0.064545	0
P0C7P4	UQCRFS1P1	0.062	0	0.025833
P0CF74	IGLC6	0	0.095455	0.1625
P0CG38	POTEI	0.019	0	0
P0DMM9	SULT1A3	0	0	0.023333
P0DMR1	HNRNPCL4	0.03	0	0
P0DMV8	HSPA1A	0.333	0.599091	0.586667
P10153	RNASE2	0	0.085455	0

P10253	GAA	0	0	0.013333
P10412	HIST1H1E	0.094	0.041818	0.0775
P10599	TXN	1.786	3.400909	3.6175
P10620	MGST1	0.103	0	0
P10643	C7	0.019	0.020909	0.0425
P10809	HSPD1	0.075	0	0.055
P10909	CLU	0.556	0.994545	0.849167
P11021	HSPA5	0.103	0.070909	0.120833
P11055	MYH3	0	0	0.020833
P11142	HSPA8	0.422	0.691818	0.671667
P11171	EPB41	0	0	0.0075
P11215	ITGAM	0.074	0	0
P11216	PYGB	0.088	0.143636	0.245833
P11217	PYGM	0	0.027273	0
P11233	RALA	0	0	0.035
P11279	LAMP1	0.052	0	0
P11413	G6PD	0.143	0.270909	0.29
P11441	UBL4A	0	0	0.049167
P11586	MTHFD1	0	0.020909	0.019167
P11678	EPX	0.011	0.251818	0
P11684	SCGB1A1	0.396	0.111818	0.1025
P11766	ADH5	0.046	0.080909	0.104167
P11908	PRPS2	0	0.024545	0.045
P11940	PABPC1	0	0.039091	0.010833
P12035	KRT3	0	0.463636	0.2425
P12081	HARS	0	0	0.055
P12236	SLC25A6	0.306	0	0
P12273	PIP	4.619	4.093636	3.794167
P12277	CKB	0	0	0.139167
P12429	ANXA3	0.802	0.709091	0.365833
P12724	RNASE3	0.111	0.27	0.156667
P12814	ACTN1	0.191	0.213636	0.298333
P12830	CDH1	0.023	0.029091	0.0525
P12882	MYH1	0	0	0.029167
P12883	MYH7	0	0	0.025
P12955	PEPD	0	0.023636	0.021667
P12956	XRCC6	0	0.018182	0.044167
P13010	XRCC5	0.011	0.039091	0.1025
P13073	COX4I1	0.053	0	0
P13473	LAMP2	0.032	0	0
P13489	RNH1	0.018	0.098182	0.280833
P13498	CYBA	0.081	0	0
P13639	EEF2	0.297	0.544545	0.645833
P13645	KRT10	11.759	12.82091	8.380833
P13646	KRT13	2.673	2.192727	1.745
P13647	KRT5	6.863	8.63	5.883333

P13671	C6	0	0.058182	0.058333
P13693	TPT1	0.195	0.535455	0.970833
P13796	LCP1	0.361	0.459091	0.4375
P13797	PLS3	0.02	0.017273	0.050833
P13798	APEH	0	0.015455	0.039167
P13929	ENO3	0	0	0.035833
P14136	GFAP	0	0	0.015
P14174	MIF	0.092	0.400909	0.383333
P14222	PRF1	0	0.013636	0
P14314	PRKCSH	0.023	0	0.035
P14324	FDPS	0.019	0.044545	0.0475
P14406	COX7A2	0.138	0	0
P14550	AKR1A1	0.304	0.640909	0.881667
P14555	PLA2G2A	0	0	0.053333
P14618	PKM	0.916	1.665455	1.710833
P14625	HSP90B1	0.114	0.018182	0.060833
P14649	MYL6B	0	0.08	0
P14735	IDE	0.007	0.006364	0
P14780	MMP9	0.342	0.411818	0.3425
P14866	HNRNPL	0.014	0	0.011667
P14868	DARS	0	0.05	0.045833
P14902	IDO1	0	0.052727	0
P14923	JUP	0.703	0.689091	0.346667
P15104	GLUL	0.084	0.270909	0.360833
P15121	AKR1B1	0.026	0.149091	0.180833
P15144	ANPEP	0.037	0	0
P15153	RAC2	0.208	0.214545	0.266667
P15170	GSPT1	0	0	0.066667
P15259	PGAM2	0.068	0	0
P15311	EZR	0.514	0.559091	0.855
P15374	UCHL3	0	0.055455	0.105
P15531	NME1	0.58	1.743636	1.9675
P15559	NQO1	0.16	0.200909	0.271667
P15880	RPS2	0.08	0.139091	0.106667
P15924	DSP	0.424	0.380909	0.2325
P15941	MUC1	0.021	0.01	0.0175
P16050	ALOX15	0.073	0.191818	0.480833
P16070	CD44	0	0.01	0.009167
P16152	CBR1	0.331	0.831818	0.87
P16402	HIST1H1D	0.046	0.100909	0.0925
P16435	POR	0.012	0	0
P16949	STMN1	0	0.056364	0.273333
P17174	GOT1	0.031	0.259091	0.398333
P17213	BPI	0.026	0.030909	0.05
P17612	PRKACA	0	0	0.079167
P17655	CAPN2	0.022	0.053636	0.085833

P17844	DDX5	0	0	0.010833
P17858	PFKL	0	0	0.018333
P17900	GM2A	0	0.072727	0.266667
P17931	LGALS3	0.307	0.45	0.486667
P17980	PSMC3	0	0	0.034167
P17987	TCP1	0.03	0.029091	0.043333
P18077	RPL35A	0.169	0.084545	0.226667
P18085	ARF4	0.413	0.827273	0.899167
P18124	RPL7	0.132	0.07	0.109167
P18206	VCL	0.118	0.392727	0.453333
P18283	GPX2	0	0	0.076667
P18669	PGAM1	0	0.297273	0.299167
P19012	KRT15	0	0.184545	0.15
P19013	KRT4	1.532	0.965455	0.735833
P19338	NCL	0.032	0.08	0.098333
P19367	HK1	0.077	0	0.015
P19623	SRM	0	0	0.023333
P19652	ORM2	0.384	0.79	0.434167
P19823	ITIH2	0.215	0.515455	0.4725
P19827	ITIH1	0.141	0.349091	0.3225
P19878	NCF2	0	0	0.019167
P19957	PI3	0	0.496364	0.151667
P19971	TYMP	0.081	0.202727	0.189167
P20020	ATP2B1	0	0.005455	0
P20061	TCN1	0.339	0.290909	0.335833
P20160	AZU1	0.193	0.142727	0.06
P20290	BTF3	0	0	0.076667
P20292	ALOX5AP	0.099	0	0
P20340	RAB6A	0	0.063636	0.058333
P20591	MX1	0.012	0.043636	0.026667
P20618	PSMB1	0	0.382727	0.595
P20674	COX5A	0.064	0	0.053333
P20700	LMNB1	0.014	0.052727	0.0425
P20742	PZP	0.029	0.015455	0.019167
P20930	FLG	0.015	0.012727	0.005
P21281	ATP6V1B2	0	0.014545	0.020833
P21283	ATP6V1C1	0	0.019091	0.050833
P21291	CSRP1	0	0.043636	0.04
P21333	FLNA	0	0.01	0.051667
P21796	VDAC1	0.104	0	0.041667
P21860	ERBB3	0	0	0.005
P21926	CD9	0.038	0.069091	0.095
P21964	COMT	0.032	0.104545	0.165
P21980	TGM2	0.056	0.021818	0.071667
P22061	PCMT1	0	0.072727	0.1
P22079	LPO	0.095	0.030909	0.104167

P22102	GART	0	0	0.006667
P22234	PAICS	0	0	0.015833
P22307	SCP2	0	0	0.02
P22314	UBA1	0.068	0.157273	0.230833
P22352	GPX3	0.038	0.104545	0.1375
P22392	NME2	0.693	1.966364	1.798333
P22528	SPRR1B	0.242	0.77	0.504167
P22531	SPRR2E	0	0.891818	0
P22532	SPRR2D	0	0.891818	0
P22626	HNRNPA2B1	0.261	0.659091	0.685
P22695	UQCRC2	0.019	0	0
P22735	TGM1	0	0.013636	0
P22792	CPN2	0	0.034545	0
P22894	MMP8	0.037	0.093636	0.054167
P23141	CES1	0.014	0	0
P23142	FBLN1	0	0	0.061667
P23246	SFPQ	0.032	0.010909	0.059167
P23284	PPIB	0.126	0.262727	0.448333
P23381	WARS	0.066	0.256364	0.1
P23396	RPS3	0.396	0.598182	0.889167
P23490	LOR	0.037	0	0
P23526	AHCY	0.03	0.062727	0.223333
P23528	CFL1	0.684	1.96	2.5175
P24158	PRTN3	0.056	0.147273	0.046667
P24534	EEF1B2	0.04	0.036364	0.1
P24539	ATP5PB	0	0	0.028333
P24666	ACP1	0	0.051818	0.1425
P24821	TNC	0	0.008182	0.0175
P25311	AZGP1	1.903	2.602727	2.374167
P25398	RPS12	0	0.118182	0.231667
P25705	ATP5F1A	0.191	0	0.085
P25774	CTSS	0.025	0.118182	0.074167
P25786	PSMA1	0.134	0.546364	0.7825
P25787	PSMA2	0	0.081818	0.126667
P25788	PSMA3	0.055	0.292727	0.443333
P25789	PSMA4	0.129	0.339091	0.310833
P25815	S100P	0.929	1.719091	1.675
P26038	MSN	0.321	0.473636	0.726667
P26373	RPL13	0	0.060909	0
P26447	S100A4	0.87	2.142727	1.881667
P26583	HMGB2	0	0	0.056667
P26599	PTBP1	0	0.022727	0.013333
P26639	TARS	0	0.01	0.0375
P26640	VAR5	0	0.005455	0
P26641	EEF1G	0.058	0.184545	0.2025
P27105	STOM	0.281	0.135455	0

P27169	PON1	0.047	0.227273	0.1275
P27348	YWHAQ	0.498	1.114545	1.961667
P27361	MAPK3	0	0.019091	0.028333
P27482	CALML3	0.166	0.56	0.276667
P27487	DPP4	0.021	0.055455	0
P27695	APEX1	0	0.023636	0.043333
P27797	CALR	0	0	0.015833
P27824	CANX	0.013	0	0
P28062	PSMB8	0	0.146364	0.186667
P28065	PSMB9	0.177	0.278182	0.329167
P28066	PSMA5	0.242	0.606364	0.488333
P28070	PSMB4	0.087	0.185455	0.2075
P28072	PSMB6	0	0.129091	0.2475
P28074	PSMB5	0	0	0.156667
P28482	MAPK1	0	0	0.095
P28676	GCA	0.291	0.09	0
P28838	LAP3	0.104	0.313636	0.2425
P29034	S100A2	0.107	0.386364	0.605833
P29218	IMPA1	0	0.075455	0.095833
P29401	TKT	0.453	0.568182	0.605
P29508	SERPINB3	1.917	4.119091	3.794167
P29622	SERPINA4	0	0.143636	0.031667
P29692	EEF1D	0	0.152727	0.168333
P30041	PRDX6	0.83	1.884545	2.2375
P30043	BLVRB	0.046	0.323636	0.288333
P30044	PRDX5	0.86	1.619091	1.419167
P30048	PRDX3	0	0.031818	0.068333
P30049	ATP5F1D	0.061	0	0.050833
P30050	RPL12	0	0.053636	0.3475
P30084	ECHS1	0.049	0	0.04
P30085	CMPK1	0.075	0.269091	0.361667
P30086	PEBP1	0.312	0.705455	0.864167
P30101	PDIA3	0.095	0.092727	0.169167
P30153	PPP2R1A	0	0.026364	0.060833
P30520	ADSS	0	0	0.015
P30622	CLIP1	0	0.01	0
P30626	SRI	0.114	0.041818	0.131667
P30740	SERPINB1	0.662	1.623636	1.444167
P30838	ALDH3A1	0.858	1.607273	1.333333
P31025	LCN1	1.481	2.040909	3.17
P31146	CORO1A	0.05	0.154545	0.233333
P31151	S100A7	0.208	1.271818	1.149167
P31513	FMO3	0	0	0.0125
P31939	ATIC	0	0	0.025
P31944	CASP14	0.609	0.66	0.338333
P31946	YWHAB	1.447	2.58	2.198333

P31947	SFN	1.717	3.482727	2.689167
P31948	STIP1	0	0	0.018333
P31949	S100A11	2.182	3.415455	3.229167
P31997	CEACAM8	0.024	0	0
P32119	PRDX2	0.9	1.372727	1.6475
P32455	GBP1	0	0.025455	0.0375
P32969	RPL9	0	0.07	0.076667
P32969	RPL9P7	0	0.07	0.076667
P32969	RPL9P8	0	0.07	0.076667
P32969	RPL9P9	0	0.07	0.076667
P33176	KIF5B	0.017	0.010909	0.044167
P33764	S100A3	0.644	0	0
P34096	RNASE4	0.229	0.248182	0
P34932	HSPA4	0	0.035455	0.054167
P35080	PFN2	0	0.129091	0.1775
P35221	CTNNA1	0.029	0.011818	0.03
P35228	NOS2	0	0.009091	0
P35232	PHB	0.209	0	0.085
P35237	SERPINB6	0.034	0.04	0.150833
P35268	RPL22	0.206	0.254545	0.278333
P35321	SPRR1A	0	0.354545	0
P35527	KRT9	10.853	6.797273	6.4625
P35542	SAA4	0	0.067273	0
P35573	AGL	0	0.019091	0.045833
P35579	MYH9	0.255	0.183636	0.2525
P35580	MYH10	0	0.012727	0
P35606	COPB2	0.033	0.011818	0.025833
P35749	MYH11	0	0	0.011667
P35908	KRT2	8.948	9.930909	7.306667
P35916	FLT4	0	0	0.005
P35998	PSMC2	0	0.026364	0.034167
P36542	ATP5F1C	0.089	0	0.038333
P36543	ATP6V1E1	0	0.146364	0.341667
P36871	PGM1	0	0	0.060833
P36952	SERPINB5	0.217	0.388182	0.53
P36955	SERPINF1	0.172	0.36	0.3225
P36969	GPX4	0	0	0.061667
P36980	CFHR2	0	0.027273	0.025
P37802	TAGLN2	0.663	1.622727	1.714167
P37837	TALDO1	0.704	1.14	1.261667
P38159	RBMX	0	0.044545	0.094167
P38405	GNAL	0	0.019091	0
P38606	ATP6V1A	0.013	0.011818	0.034167
P38646	HSPA9	0.026	0	0
P39019	RPS19	0	0.060909	0.111667
P39023	RPL3	0	0	0.016667

P39687	ANP32A	0	0.05	0.250833
P40121	CAPG	0.063	0.42	0.498333
P40199	CEACAM6	0.04	0.022727	0
P40227	CCT6A	0	0.081818	0.1375
P40306	PSMB10	0.054	0.070909	0.18
P40394	ADH7	0.263	0.756364	1.211667
P40429	RPL13A	0	0.038182	0
P40616	ARL1	0	0.045455	0.07
P40692	MLH1	0.01	0	0
P40763	STAT3	0	0	0.008333
P40925	MDH1	0.282	1.052727	0.8725
P40926	MDH2	0.248	0.371818	0.468333
P41091	EIF2S3	0	0	0.0325
P41218	MNDA	0.044	0.058182	0.166667
P41250	GARS	0	0	0.013333
P41252	IARS	0.012	0.028182	0.02
P42025	ACTR1B	0	0.031818	0.018333
P42224	STAT1	0.026	0.08	0.071667
P42330	AKR1C3	0.121	0.480909	0.446667
P42574	CASP3	0.03	0.098182	0.09
P42704	LRPPRC	0.008	0	0.004167
P43487	RANBP1	0	0.039091	0.130833
P43490	NAMPT	0.062	0.126364	0.2225
P43652	AFM	0.129	0.479091	0.378333
P43686	PSMC4	0	0.017273	0.046667
P45880	VDAC2	0.03	0	0.04
P45974	USP5	0	0.017273	0.0075
P46100	ATRX	0	0.002727	0
P46779	RPL28	0.07	0	0
P46781	RPS9	0.22	0.183636	0.296667
P46782	RPS5	0	0.065455	0.088333
P46783	RPS10	0	0	0.045833
P46926	GNPDA1	0	0.080909	0.13
P46940	IQGAP1	0.053	0.055455	0.146667
P46976	GYG1	0	0.021818	0.061667
P47755	CAPZA2	0.029	0.158182	0.096667
P47756	CAPZB	0.061	0.246364	0.261667
P47897	QARS	0.01	0.024545	0.03
P47929	LGALS7	0.716	2.271818	1.035
P47929	LGALS7B	0.716	2.271818	1.035
P48047	ATP5PO	0	0	0.059167
P48059	LIMS1	0	0	0.02
P48444	ARCN1	0	0.064545	0.036667
P48506	GCLC	0	0	0.034167
P48556	PSMD8	0	0.033636	0.05
P48594	SERPINB4	0.423	0.950909	1.046667

P48595	SERPINB10	0	0.068182	0
P48637	GSS	0.045	0.083636	0.125833
P48643	CCT5	0	0	0.0125
P48668	KRT6C	1.148	5.942727	0.5125
P48735	IDH2	0.056	0.016364	0.023333
P48741	HSPA7	0	0.300909	0.175833
P49189	ALDH9A1	0.017	0.039091	0.120833
P49247	RPIA	0	0.025455	0.046667
P49327	FASN	0.011	0.096364	0.085833
P49368	CCT3	0.055	0.013636	0.083333
P49411	TUFM	0.019	0	0
P49419	ALDH7A1	0	0	0.0125
P49441	INPP1	0	0	0.0175
P49458	SRP9	0	0	0.295833
P49720	PSMB3	0	0.171818	0.425
P49721	PSMB2	0.044	0.283636	0.46
P49748	ACADVL	0.02	0	0
P49755	TMED10	0.04	0	0.054167
P49773	HINT1	0	0.295455	0.2025
P49788	RARRES1	0.075	0	0
P49913	CAMP	0.694	0.3	0.5175
P50135	HNMT	0	0.067273	0.060833
P50225	SULT1A1	0	0.065455	0.0375
P50395	GDI2	0.175	0.427273	0.376667
P50452	SERPINB8	0	0	0.085
P50453	SERPINB9	0	0	0.04
P50502	ST13	0	0	0.018333
P50583	NUDT2	0	0	0.155833
P50851	LRBA	0	0	0.003333
P50914	RPL14	0.043	0	0.071667
P50990	CCT8	0	0.081818	0.2525
P50991	CCT4	0	0.053636	0.138333
P50995	ANXA11	0	0	0.049167
P51148	RAB5C	0	0.093636	0.093333
P51149	RAB7A	0	0.284545	0.6525
P51571	SSR4	0.055	0	0
P51572	BCAP31	0.139	0	0.068333
P51580	TPMT	0	0.030909	0.028333
P51665	PSMD7	0	0.069091	0.041667
P51795	CLCN5	0	0.01	0
P51812	RPS6KA3	0	0	0.009167
P51858	HDGF	0	0.033636	0.061667
P51884	LUM	0	0.118182	0.06
P51991	HNRNPA3	0.048	0.055455	0.1275
P52209	PGD	0.397	0.617273	0.853333
P52272	HNRNPM	0	0.021818	0.018333

P52565	ARHGDIA	0.044	0.229091	0.385
P52566	ARHGDIB	0.404	0.815455	1.175833
P52740	ZNF132	0	0	0.0275
P52788	SMS	0	0	0.018333
P52790	HK3	0	0.011818	0.010833
P52895	AKR1C2	0.335	0.648182	0.630833
P52907	CAPZA1	0	0.041818	0.038333
P53004	BLVRA	0	0.078182	0.16
P53396	ACLY	0	0	0.005833
P53618	COPB1	0.017	0.028182	0.01
P53621	COPA	0.049	0.031818	0.059167
P53634	CTSC	0	0	0.014167
P53671	LIMK2	0	0	0.01
P53680	AP2S1	0	0.056364	0
P53990	IST1	0	0	0.019167
P53999	SUB1	0	0	0.064167
P54108	CRISP3	0.124	0.143636	0.103333
P54136	RARS	0	0	0.015
P54652	HSPA2	0	0.018182	0
P54727	RAD23B	0	0	0.018333
P54819	AK2	0	0	0.0725
P54920	NAPA	0	0	0.0375
P55058	PLTP	0.214	0.087273	0.188333
P55060	CSE1L	0	0.014545	0
P55072	VCP	0.188	0.289091	0.4225
P55210	CASP7	0	0.024545	0
P55259	GP2	0.023	0	0
P55263	ADK	0	0	0.038333
P55327	TPD52	0	0	0.034167
P55786	NPEPPS	0.056	0.063636	0.180833
P55854	SUMO3	0	0	0.085
P55884	EIF3B	0.02	0.009091	0.016667
P56192	MARS	0	0.008182	0
P56537	EIF6	0	0.192727	0.158333
P56715	RP1	0.004	0	0
P57735	RAB25	0	0.101818	0.163333
P58107	EPPK1	0.002	0.011818	0
P58499	FAM3B	0	0.033636	0
P59665	DEFA1	0.913	1.337273	0.9675
P59665	DEFA1B	0.913	1.337273	0.9675
P59827	BPIFB4	0.078	0	0
P59998	ARPC4	0.873	1.253636	1.0225
P60174	TPI1	1.066	1.905455	1.783333
P60228	EIF3E	0.017	0.024545	0.014167
P60660	MYL6	0.639	0.618182	0.841667
P60709	ACTB	2.013	3.377273	3.115

P60763	RAC3	0.116	0.042727	0.13
P60842	EIF4A1	0.146	0.230909	0.41
P60866	RPS20	0	0.077273	0.141667
P60900	PSMA6	0.127	0.501818	0.706667
P60903	S100A10	0.107	0	0.176667
P60953	CDC42	0.079	0.192727	0.3
P60981	DSTN	0.094	0.799091	1.3075
P60983	GMFB	0	0	0.090833
P61006	RAB8A	0.102	0.127273	0.141667
P61019	RAB2A	0.042	0.270909	0.443333
P61020	RAB5B	0	0.038182	0.035
P61026	RAB10	0.202	0.303636	0.55
P61081	UBE2M	0	0	0.04
P61086	UBE2K	0	0.067273	0.136667
P61088	UBE2N	0	0.212727	0.33
P61106	RAB14	0.111	0.125455	0.284167
P61158	ACTR3	0.049	0.173636	0.215833
P61160	ACTR2	0.111	0.134545	0.175
P61204	ARF3	0.663	0.874545	0.893333
P61224	RAP1B	0.129	0.073636	0.200833
P61247	RPS3A	0.032	0.12	0.105
P61289	PSME3	0	0.048182	0.0275
P61313	RPL15	0.041	0.037273	0
P61353	RPL27	0.07	0.062727	0
P61457	PCBD1	0	0	0.309167
P61586	RHOA	0.245	0.31	0.353333
P61604	HSPE1	0.564	0.19	0.466667
P61626	LYZ	5.965	7.35	8.369167
P61758	VBP1	0	0	0.036667
P61769	B2M	0.717	0.667273	0.8
P61803	DAD1	0.166	0	0
P61916	NPC2	0.064	0.373636	0.423333
P61923	COPZ1	0	0	0.0425
P61956	SUMO2	0	0.204545	0.373333
P61970	NUTF2	0	0.069091	0.126667
P61978	HNRNPK	0	0.077273	0.110833
P61981	YWHAG	0.506	1.059091	1.1875
P62081	RPS7	0	0.102727	0.170833
P62140	PPP1CB	0	0.035455	0.041667
P62195	PSMC5	0.02	0.040909	0.043333
P62241	RPS8	0.068	0.060909	0.09
P62244	RPS15A	0.13	0.270909	0.43
P62249	RPS16	0.252	0.318182	0.525833
P62258	YWHAE	1.345	2.894545	3.16
P62263	RPS14	0.066	0.06	0
P62269	RPS18	0.309	0.140909	0.485

P62277	RPS13	0.062	0.056364	0
P62280	RPS11	0.057	0.087273	0.1275
P62310	LSM3	0	0.090909	0.25
P62314	SNRPD1	0	0	0.143333
P62316	SNRPD2	0.083	0.075455	0.315833
P62318	SNRPD3	0.081	0.145455	0.2675
P62330	ARF6	0.051	0.046364	0.114167
P62333	PSMC6	0	0.041818	0.035
P62424	RPL7A	0	0.029091	0.026667
P62495	ETF1	0.019	0	0
P62701	RPS4X	0.106	0.068182	0.18
P62736	ACTA2	0.316	0.208182	0.291667
P62750	RPL23A	0.06	0	0.316667
P62753	RPS6	0.034	0.071818	0.028333
P62805	HIST1H4A	3.975	3.177273	3.034167
P62805	HIST1H4B	3.975	3.177273	3.034167
P62805	HIST1H4C	3.975	3.177273	3.034167
P62805	HIST1H4D	3.975	3.177273	3.034167
P62805	HIST1H4E	3.975	3.177273	3.034167
P62805	HIST1H4F	3.975	3.177273	3.034167
P62805	HIST1H4H	3.975	3.177273	3.034167
P62805	HIST1H4I	3.975	3.177273	3.034167
P62805	HIST1H4J	3.975	3.177273	3.034167
P62805	HIST1H4K	3.975	3.177273	3.034167
P62805	HIST1H4L	3.975	3.177273	3.034167
P62805	HIST2H4A	3.975	3.177273	3.034167
P62805	HIST2H4B	3.975	3.177273	3.034167
P62805	HIST4H4	3.975	3.177273	3.034167
P62820	RAB1A	0.2	0.235455	0.555833
P62826	RAN	0.041	0.224545	0.300833
P62829	RPL23	0.074	0	0.061667
P62851	RPS25	0.147	0.210909	0.433333
P62854	RPS26	0.154	0.139091	0
P62857	RPS28	0.36	0.162727	0.596667
P62873	GNB1	0	0.022727	0.020833
P62888	RPL30	0.089	0.080909	0.074167
P62906	RPL10A	0.04	0.059091	0.033333
P62913	RPL11	0.051	0.045455	0.153333
P62917	RPL8	0	0.031818	0.029167
P62937	PPIA	2.829	3.322727	3.206667
P62979	RPS27A	0.879	1.110909	1.184167
P62993	GRB2	0	0	0.053333
P63000	RAC1	0	0.144545	0.265
P63092	GNAS	0	0	0.016667
P63104	YWHAZ	2.363	3.983636	4.076667
P63165	SUMO1	0	0	0.085

P63167	DYNLL1	0	0.106364	0.2925
P63173	RPL38	0	0	0.275833
P63208	SKP1	0	0.05	0
P63220	RPS21	0.286	0.501818	0.579167
P63241	EIF5A	0.063	0.562727	0.825
P63244	RACK1	0.061	0.260909	0.135833
P67936	TPM4	0	0.225455	0.584167
P68032	ACTC1	0	0.771818	0
P68036	UBE2L3	0.059	0.23	0.376667
P68104	EEF1A1	0	0.136364	0
P68366	TUBA4A	0	0.118182	0.245
P68371	TUBB4B	0.387	0.55	0.758333
P68871	HBB	2.299	7.307273	3.955833
P69891	HBG1	0	0.372727	0
P69905	HBA1	0.948	6.190909	1.211667
P69905	HBA2	0.948	6.190909	1.211667
P78371	CCT2	0	0.084545	0.159167
P78385	KRT83	3.963	2.337273	0
P78386	KRT85	4.224	3.430909	0.189167
P78417	GSTO1	0.147	0.48	0.649167
P78527	PRKDC	0.003	0.012727	0.015
P80188	LCN2	1.936	2.679091	2.200833
P80303	NUCB2	0.121	0.130909	0.2075
P80511	S100A12	1.153	1.8	1.273333
P80748	IGLV3-21	0	0.083636	0
P81605	DCD	1.061	1.413636	0.970833
P83731	RPL24	0	0.053636	0
P84085	ARF5	0.26	0.366364	0.506667
P84095	RHOG	0	0	0.039167
P84098	RPL19	0.043	0.063636	0.035833
P84103	SRSF3	0.053	0	0.044167
P98088	MUC5AC	0.136	0.01	0.006667
P98160	HSPG2	0.002	0	0
P98161	PKD1	0	0	0.001667
P98171	ARHGAP4	0	0.007273	0
P99999	CYCS	0	0.906364	0.705
Q00325	SLC25A3	0.124	0	0.0425
Q00341	HDLBP	0.006	0	0
Q00610	CLTC	0.138	0.130909	0.19
Q00765	REEP5	0.047	0.042727	0.078333
Q00796	SORD	0.138	0.392727	0.516667
Q01082	SPTBN1	0.022	0.036364	0.073333
Q01105	SET	0.029	0.120909	0.138333
Q01469	FABP5	1.552	2.975455	3.026667
Q01518	CAP1	0.122	0.448182	0.554167
Q01546	KRT76	0.115	0.539091	0

Q01813	PFKP	0.01	0.05	0.0825
Q02383	SEMG2	0.021	0.019091	0.355833
Q02413	DSG1	0.193	0.208182	0.1
Q02817	MUC2	0.006	0	0
Q02818	NUCB1	0.017	0	0.0225
Q02878	RPL6	0	0.060909	0
Q03252	LMNB2	0	0	0.010833
Q03591	CFHR1	0	0.114545	0.156667
Q04637	EIF4G1	0	0.006364	0
Q04695	KRT17	4.437	5.154545	2.93
Q04760	GLO1	0	0.11	0.350833
Q04828	AKR1C1	0.424	0.920909	0.938333
Q04837	SSBP1	0.107	0	0
Q04917	YWHAH	0.224	0.522727	0.703333
Q05315	CLC	0	0.220909	0.054167
Q06033	ITIH3	0	0.008182	0
Q06210	GFPT1	0.022	0.021818	0.0575
Q06323	PSME1	0.694	1.754545	1.560833
Q06830	PRDX1	3.982	5.725455	6.193333
Q07020	RPL18	0	0	0.078333
Q07654	TFF3	0	0.258182	0
Q07960	ARHGAP1	0	0.025455	0.015
Q08188	TGM3	0.051	0.027273	0.03
Q08211	DHX9	0.027	0.024545	0.024167
Q08257	CRYZ	0	0	0.035833
Q08380	LGALS3BP	0.371	0.19	0.350833
Q08554	DSC1	0.077	0.048182	0.0375
Q09472	EP300	0	0.002727	0
Q09666	AHNAK	0.002	0.008182	0.028333
Q0VDD8	DNAH14	0	0.006364	0
Q10567	AP1B1	0.008	0.007273	0
Q10588	BST1	0	0.023636	0
Q12792	TWF1	0.023	0.067273	0.0625
Q12905	ILF2	0	0.030909	0.074167
Q12906	ILF3	0	0.022727	0.036667
Q12996	CSTF3	0.011	0.03	0.009167
Q13045	FLII	0	0	0.005
Q13126	MTAP	0	0.044545	0.081667
Q13162	PRDX4	0	0	0.0425
Q13200	PSMD2	0.018	0.036364	0.041667
Q13201	MMRN1	0	0	0.005
Q13228	SELENBP1	0.329	0.752727	0.8375
Q13231	CHIT1	0	0	0.0225
Q13263	TRIM28	0	0	0.008333
Q13347	EIF3I	0	0.023636	0
Q13363	CTBP1	0	0	0.015833

Q13367	AP3B2	0.007	0	0
Q13404	UBE2V1	0.112	0.43	0.47
Q13409	DYNC1I2	0	0	0.025833
Q13421	MSLN	0.197	0.216364	0.175
Q13510	ASAH1	0.168	0.420909	0.396667
Q13576	IQGAP2	0	0	0.008333
Q13618	CUL3	0	0	0.008333
Q13620	CUL4B	0	0	0.006667
Q13630	TSTA3	0.042	0.038182	0.126667
Q13740	ALCAM	0.014	0.06	0.040833
Q13797	ITGA9	0	0	0.006667
Q13813	SPTAN1	0.016	0.046364	0.091667
Q13835	PKP1	0.157	0.117273	0.078333
Q13838	DDX39B	0	0.060909	0.068333
Q13867	BLMH	0.027	0.015455	0
Q13885	TUBB2A	0	0.179091	0
Q13938	CAPS	0.842	1.612727	1.890833
Q14011	CIRBP	0.057	0.050909	0.14
Q14019	COTL1	0.252	0.946364	0.821667
Q14103	HNRNPD	0	0.1	0.1825
Q14116	IL18	0.045	0.067273	0.243333
Q14134	TRIM29	0	0.012727	0.011667
Q14152	EIF3A	0.032	0.020909	0.0325
Q14203	DCTN1	0.006	0.011818	0.01
Q14204	DYNC1H1	0.02	0.063636	0.120833
Q14210	LY6D	0	0.073636	0.0675
Q14232	EIF2B1	0	0.025455	0.0375
Q14240	EIF4A2	0	0.086364	0.025833
Q14315	FLNC	0	0.002727	0
Q14376	GALE	0.024	0.021818	0.04
Q14508	WFDC2	0.161	0.147273	0.135
Q14525	KRT33B	1.806	1.940909	0.2975
Q14532	KRT32	0.588	0.492727	0.041667
Q14533	KRT81	3.461	1.129091	0
Q14624	ITIH4	0.26	0.58	0.4325
Q14651	PLS1	0.013	0	0.039167
Q14686	NCOA6	0	0	0.003333
Q14697	GANAB	0.025	0.007273	0.006667
Q14739	LBR	0.02	0	0
Q14764	MVP	0.237	0.272727	0.339167
Q14847	LASP1	0.032	0	0.149167
Q14894	CRYM	0.156	0.502727	0.53
Q14914	PTGR1	0.042	0	0.065
Q14974	KPNB1	0.024	0.021818	0.0275
Q14CN4	KRT72	0.045	0.269091	0.115
Q15008	PSMD6	0	0.040909	0.016667

Q15019	SEPTIN2	0	0	0.065833
Q15046	KARS	0	0	0.010833
Q15063	POSTN	0	0.012727	0.06
Q15075	EEA1	0	0.012727	0.021667
Q15080	NCF4	0	0	0.031667
Q15102	PAFAH1B3	0	0.034545	0.031667
Q15149	PLEC	0.019	0.06	0.085
Q15181	PPA1	0.076	0.279091	0.410833
Q15185	PTGES3	0	0.084545	0.123333
Q15233	NONO	0	0	0.039167
Q15257	PTPA	0	0.046364	0.09
Q15323	KRT31	1.66	2.216364	0.389167
Q15365	PCBP1	0.025	0.144545	0.275
Q15366	PCBP2	0	0	0.045
Q15370	ELOB	0	0.299091	0.46
Q15382	RHEB	0.084	0.076364	0.414167
Q15393	SF3B3	0	0.005455	0.005
Q15517	CDSN	0.018	0	0
Q15631	TSN	0	0.144545	0.125
Q15691	MAPRE1	0	0	0.026667
Q15772	SPEG	0	0	0.005
Q15819	UBE2V2	0	0.102727	0.243333
Q15907	RAB11B	0.175	0.521818	0.456667
Q16181	SEPTIN7	0	0.016364	0.023333
Q16204	CCDC6	0	0	0.014167
Q16378	PRR4	0.073	0.066364	0.060833
Q16478	GRIK5	0	0	0.006667
Q16531	DDB1	0	0.031818	0.036667
Q16629	SRSF7	0.036	0	0
Q16698	DECR1	0.026	0	0.035
Q16719	KYNU	0.017	0	0.028333
Q16777	HIST2H2AC	0.227	0	0
Q16836	HADH	0	0	0.023333
Q16851	UGP2	0.025	0.196364	0.304167
Q16881	TXNRD1	0	0.029091	0.048333
Q16891	IMMT	0.011	0	0
Q2TAA8	TSNAXIP1	0.012	0	0
Q2VIQ3	KIF4B	0.006	0	0
Q2VIR3	EIF2S3B	0	0.016364	0
Q32MZ4	LRRFIP1	0	0.024545	0.0775
Q3SY84	KRT71	0	0.05	0
Q3V6T2	CCDC88A	0	0	0.003333
Q3ZCM7	TUBB8	0	0	0.015
Q4G0X9	CCDC40	0.014	0.019091	0.02
Q53GD3	SLC44A4	0	0.015455	0
Q53H82	LACTB2	0	0	0.024167

Q562R1	ACTBL2	0.082	0	0.125
Q58FG1	HSP90AA4P	0	0.027273	0
Q5CZC0	FSIP2	0	0	0.000833
Q5D862	FLG2	0.03	0.045455	0.025
Q5JW98	CALHM4	0.079	0	0
Q5JXB2	UBE2NL	0.062	0.112727	0.139167
Q5M775	SPECC1	0	0	0.005833
Q5QNW6	HIST2H2BF	1.663	1.001818	0.805
Q5SYB0	FRMPD1	0	0.004545	0
Q5T200	ZC3H13	0	0	0.003333
Q5T749	KPRP	0.013	0.108182	0.089167
Q5TCS8	AK9	0.004	0	0
Q5THR3	EFCAB6	0	0	0.004167
Q5TZA2	CROCC	0.012	0.014545	0.006667
Q5VTE0	EEF1A1P5	0.422	0.586364	0.681667
Q5VW32	BROX	0	0.018182	0
Q63HK5	TSHZ3	0	0	0.011667
Q63HN8	RNF213	0	0.001818	0
Q63HR2	TNS2	0.006	0	0.005
Q68DQ2	CRYBG3	0.003	0	0
Q6A162	KRT40	0	0.048182	0.024167
Q6A163	KRT39	0.182	0.037273	0
Q6BCY4	CYB5R2	0	0.027273	0.025
Q6DN03	HIST2H2BC	0.114	0	0
Q6EMB2	TTLL5	0.006	0	0
Q6GMV3	PTRHD1	0	0.062727	0.115
Q6IS14	EIF5AL1	0	0.057273	0
Q6KB66	KRT80	0.097	0.032727	0.045
Q6MZM0	HEPHL1	0.01	0	0
Q6P4A8	PLBD1	0	0.028182	0
Q6P5S2	LEG1	0.426	0.499091	0.580833
Q6PRD1	GPR179	0	0.002727	0
Q6S8J3	POTEE	0.051	0.088182	0.166667
Q6UWP8	SBSN	0.061	0.077273	0.031667
Q6UWW0	LCN15	0.341	0.477273	0.548333
Q6UX06	OLFM4	0	0	0.013333
Q6UXB2	CXCL17	0.16	0.072727	0.066667
Q6VAB6	KSR2	0	0.007273	0.006667
Q6VUC0	TFAP2E	0	0.018182	0.066667
Q6XQN6	NAPRT	0	0.021818	0.063333
Q6ZMW3	EML6	0	0	0.003333
Q6ZU15	SEPTIN14	0	0	0.015
Q6ZVX7	NCCRP1	0	0.101818	0.0675
Q6ZWH5	NEK10	0	0.006364	0
Q71DI3	HIST2H3A	0.638	0.612727	0.841667
Q71DI3	HIST2H3C	0.638	0.612727	0.841667

Q71DI3	HIST2H3D	0.638	0.612727	0.841667
Q71UM5	RPS27L	0.131	0	0.109167
Q7KZF4	SND1	0.013	0.008182	0.015
Q7L014	DDX46	0	0	0.011667
Q7L1Q6	BZW1	0	0.017273	0.066667
Q7L266	ASRGL1	0	0.143636	0.039167
Q7L576	CYFIP1	0.026	0.023636	0.015833
Q7L7X3	TAOK1	0	0	0.02
Q7L9L4	MOB1B	0	0.035455	0
Q7RTS7	KRT74	0.1	0.071818	0.139167
Q7Z2K8	GPRIN1	0	0.008182	0
Q7Z3E5	ARMC9	0.01	0	0
Q7Z3Y7	KRT28	0.064	0.116364	0.191667
Q7Z3Y8	KRT27	0.029	0.062727	0.033333
Q7Z406	MYH14	0.126	0.054545	0.065833
Q7Z4W1	DCXR	0	0.055455	0.101667
Q7Z5L0	VMO1	0.092	0.041818	0.076667
Q7Z6Z7	HUWE1	0	0	0.001667
Q7Z794	KRT77	0.152	0.63	0.5525
Q7Z7A1	CNTRL	0	0.002727	0
Q86SJ6	DSG4	0.016	0.014545	0
Q86UP2	KTN1	0	0.007273	0
Q86VD1	MORC1	0	0	0.006667
Q86VP6	CAND1	0.006	0.049091	0.044167
Q86WA8	LONP2	0.009	0	0
Q86WR0	CCDC25	0	0	0.033333
Q86WX3	RPS19BP1	0	0.063636	0
Q86X76	NIT1	0	0	0.021667
Q86XW9	NME9	0	0.022727	0
Q86Y46	KRT73	0.253	0.248182	0.099167
Q86YZ3	HRNR	0.075	0.061818	0.0425
Q8IUC1	KRTAP11-1	0.057	0.051818	0
Q8IV04	TBC1D10C	0	0.049091	0.015
Q8IVF6	ANKRD18A	0	0.007273	0.006667
Q8IVL1	NAV2	0	0	0.0025
Q8IWN7	RP1L1	0	0.002727	0
Q8IYW2	CFAP46	0	0	0.0025
Q8IZ83	ALDH16A1	0	0.009091	0
Q8IZP2	ST13P4	0	0	0.048333
Q8N1A0	KRT222	0	0	0.046667
Q8N1N4	KRT78	0.318	0.242727	0.085
Q8N335	GPD1L	0.024	0.083636	0.079167
Q8N3K9	CMYA5	0.004	0.007273	0.009167
Q8N4F0	BPIFB2	0.587	0.534545	0.498333
Q8N554	ZNF276	0	0.011818	0
Q8N8N7	PTGR2	0	0	0.02

Q8NAB2	KBTBD3	0	0	0.010833
Q8NBJ4	GOLM1	0.165	0.088182	0.06
Q8NE09	RGS22	0.006	0	0
Q8NEB7	ACRBP	0	0	0.03
Q8NFU3	TSTD1	0.093	0.084545	0.155
Q8TAX7	MUC7	0.134	0.130909	0.1
Q8TCA0	LRRC20	0	0.045455	0
Q8TD57	DNAH3	0.002	0.001818	0
Q8TDB8	SLC2A14	0.016	0	0
Q8TDL5	BPIFB1	2.128	1.296364	1.4725
Q8TDQ7	GNPDA2	0	0	0.040833
Q8TE77	SSH3	0	0	0.01
Q8TF66	LRRC15	0.021	0.04	0
Q8WUM4	PDCD6IP	0.064	0.068182	0.200833
Q8WVQ1	CANT1	0	0.019091	0.0175
Q8WVV4	POF1B	0.028	0.079091	0
Q8WVY7	UBLCP1	0	0	0.07
Q8WW52	FAM151A	0	0	0.011667
Q8WWA0	ITLN1	0.088	0.098182	0.073333
Q8WXG6	MADD	0.01	0	0
Q8WXG9	ADGRV1	0.001	0	0
Q8WXQ8	CPA5	0.019	0	0.015833
Q8WZ42	TTN	0	0.001818	0.000833
Q92499	DDX1	0	0	0.0225
Q92599	SEPTIN8	0	0	0.020833
Q92616	GCN1	0	0.003636	0.0025
Q92688	ANP32B	0.034	0.096364	0.203333
Q92734	TFG	0	0.019091	0.0175
Q92743	HTRA1	0.028	0	0.023333
Q92747	ARPC1A	0	0	0.018333
Q92764	KRT35	1.067	0.912727	0.038333
Q92817	EVPL	0.008	0.003636	0.01
Q92820	GGH	0	0.023636	0.021667
Q92841	DDX17	0	0	0.009167
Q92930	RAB8B	0	0	0.058333
Q92945	KHSRP	0	0.010909	0.02
Q93008	USP9X	0.003	0	0
Q969N2	PIGT	0	0.012727	0
Q96A72	MAGOHB	0	0.056364	0.155
Q96BQ1	FAM3D	0.04	0.085455	0
Q96BW5	PTER	0	0.034545	0.06
Q96BY7	ATG2B	0	0	0.003333
Q96C19	EFHD2	0.2	0.492727	0.643333
Q96CN7	ISOC1	0	0.042727	0.039167
Q96DA0	ZG16B	1.246	1.34	1.436667
Q96DB5	RMDN1	0	0.023636	0

Q96DR8	MUCL1	0	0.131818	0
Q96DT5	DNAH11	0	0.001818	0
Q96EN8	MOCOS	0	0.008182	0
Q96FC7	PHYHIPL	0	0.02	0
Q96FJ2	DYNLL2	0	0.109091	0.2975
Q96FQ6	S100A16	0.1	0.256364	0.386667
Q96FW1	OTUB1	0	0.136364	0.1775
Q96G03	PGM2	0	0.018182	0.033333
Q96GW7	BCAN	0	0	0.010833
Q96HN2	AHCYL2	0	0.011818	0.021667
Q96IU4	ABHD14B	0.045	0.122727	0.175
Q96JH7	VCPIP1	0.006	0.005455	0
Q96KP4	CNDP2	0.11	0.166364	0.410833
Q96KR1	ZFR	0.021	0.025455	0.033333
Q96LP2	FAM81B	0	0.016364	0
Q96NG3	TTC25	0.024	0.010909	0
Q96NL6	SCLT1	0.033	0.01	0.009167
Q96P63	SERPINB12	0.154	0.036364	0.0425
Q96PD5	PGLYRP2	0	0.012727	0
Q96PI1	SPRR4	0	0.13	0
Q96QA5	GSDMA	0	0.060909	0
Q96QK1	VPS35	0	0.029091	0.038333
Q96QZ7	MAGI1	0	0.004545	0
Q96T68	SETDB2	0	0	0.009167
Q96TA1	NIBAN2	0.022	0.031818	0.094167
Q99417	MYCBP	0	0.267273	0
Q99436	PSMB7	0.032	0.029091	0.08
Q99459	CDC5L	0	0.009091	0.008333
Q99460	PSMD1	0.017	0.02	0.028333
Q99471	PFDN5	0	0.055455	0.086667
Q99497	PARK7	0.702	1.503636	1.691667
Q99536	VAT1	0	0	0.0725
Q99570	PIK3R4	0	0	0.005
Q99578	RIT2	0.04	0	0
Q99584	S100A13	0	0.942727	0.694167
Q99598	TSNAX	0	0	0.024167
Q99623	PHB2	0.143	0	0.094167
Q99714	HSD17B10	0.059	0	0
Q99728	BARD1	0	0	0.008333
Q99741	CDC6	0	0.012727	0
Q99798	ACO2	0.016	0	0
Q99832	CCT7	0	0	0.085833
Q99873	PRMT1	0	0	0.029167
Q99933	BAG1	0	0	0.045
Q99935	OPRPN	0	0	0.03
Q9BPU6	DPYSL5	0.015	0	0.0125

Q9BPX5	ARPC5L	0	0	0.0525
Q9BQE3	TUBA1C	0.294	0.586364	0.684167
Q9BQE5	APOL2	0	0.036364	0
Q9BR76	CORO1B	0	0.015455	0.05
Q9BRA2	TXNDC17	0	0.071818	0.2475
Q9BRF8	CPPED1	0.053	0.100909	0.115833
Q9BS26	ERP44	0	0	0.015833
Q9BS40	LXN	0.038	0.103636	0.095
Q9BT78	COPS4	0	0	0.016667
Q9BUL8	PDCD10	0	0.06	0.161667
Q9BUT1	BDH2	0	0	0.098333
Q9BV20	MRI1	0	0	0.02
Q9BVA1	TUBB2B	0.018	0.073636	0.043333
Q9BVJ7	DUSP23	0	0.058182	0
Q9BVK6	TMED9	0.072	0	0
Q9BW30	TPPP3	0.199	0.590909	0.626667
Q9BWD1	ACAT2	0	0.031818	0.0475
Q9BXL6	CARD14	0	0	0.006667
Q9BXS5	AP1M1	0	0.017273	0.025
Q9BYE4	SPRR2G	0	0	0.1275
Q9BYP9	KRTAP9-9	0.055	0	0
Q9BYQ3	KRTAP9-3	0.053	0	0
Q9BYR4	KRTAP4-3	0.041	0.037273	0
Q9BYR8	KRTAP3-1	0.191	0.094545	0
Q9BZQ8	NIBAN1	0	0	0.015
Q9BZZ5	API5	0	0	0.0125
Q9C099	LRRCC1	0.007	0	0
Q9GIY3	HLA-DRB1	0.032	0	0
Q9GZZ8	LACRT	0	0.326364	0.233333
Q9H008	LHPP	0	0.03	0
Q9H0U4	RAB1B	0.442	0.774545	0.7425
Q9H299	SH3BGRL3	0.12	0.311818	0.56
Q9H2G2	SLK	0.006	0.005455	0.038333
Q9H2U2	PPA2	0	0	0.045833
Q9H3K6	BOLA2	0	0	0.100833
Q9H3K6	BOLA2B	0	0	0.100833
Q9H444	CHMP4B	0	0.059091	0.166667
Q9H4G4	GLIPR2	0.062	0	0
Q9H4M9	EHD1	0	0	0.019167
Q9H6K5	PRR36	0.007	0	0
Q9H6S0	YTHDC2	0	0.004545	0
Q9H892	TTC12	0	0	0.009167
Q9HAB8	PPCS	0	0.140909	0.211667
Q9HAU5	UPF2	0	0	0.005
Q9HAV0	GNB4	0	0	0.020833
Q9HB40	SCPEP1	0	0	0.07

Q9HB71	CACYBP	0	0	0.030833
Q9HBL7	PLGRKT	0.062	0	0
Q9HC38	GLOD4	0.043	0.37	0.344167
Q9HC84	MUC5B	0.135	0.014545	0.0275
Q9HCY8	S100A14	0.468	0.181818	0.303333
Q9HD89	RETN	0.098	0.089091	0.080833
Q9HDC9	APMAP	0.072	0	0
Q9NP55	BPIFA1	0.933	1.066364	1.066667
Q9NP58	ABCB6	0.009	0.024545	0.015
Q9NPJ3	ACOT13	0.073	0	0
Q9NQR4	NIT2	0	0.028182	0.041667
Q9NQW7	XPNPEP1	0	0	0.016667
Q9NR31	SAR1A	0	0.040909	0.075
Q9NR45	NANS	0.023	0.116364	0.326667
Q9NR48	ASH1L	0	0.005455	0
Q9NRW1	RAB6B	0	0	0.035833
Q9NRX2	MRPL17	0	0.047273	0
Q9NSB2	KRT84	0.057	0.060909	0.120833
Q9NSB4	KRT82	0.3	0.538182	0.046667
Q9NTK5	OLA1	0	0	0.055
Q9NU22	MDN1	0	0	0.000833
Q9NUQ9	FAM49B	0	0	0.081667
Q9NVH2	INTS7	0	0	0.006667
Q9NVJ2	ARL8B	0.047	0	0.039167
Q9NW64	RBM22	0	0	0.015833
Q9NY33	DPP3	0.011	0.032727	0.088333
Q9NYL9	TMOD3	0	0	0.030833
Q9NYU2	UGGT1	0.005	0	0
Q9NZD2	GLTP	0.069	0.202727	0.445833
Q9NZM1	MYOF	0.004	0	0
Q9NZT1	CALML5	0.497	0.933636	0.5375
Q9P0W8	SPATA7	0.026	0	0
Q9P1Z0	ZBTB4	0	0	0.006667
Q9P227	ARHGAP23	0.005	0.018182	0.004167
Q9P2D1	CHD7	0.005	0	0.0025
Q9P2E9	RRBP1	0.006	0.063636	0.0475
Q9P2M7	CGN	0	0	0.005
Q9P2R3	ANKFY1	0	0	0.005833
Q9P2T1	GMPR2	0.025	0.044545	0.0325
Q9UBC9	SPRR3	1.292	0.988182	1.405833
Q9UBQ0	VPS29	0	0.045455	0.083333
Q9UBR2	CTSZ	0	0	0.023333
Q9UBZ9	REV1	0	0.005455	0.005
Q9UDY2	TJP2	0	0	0.005833
Q9UFH2	DNAH17	0	0	0.001667
Q9UGM3	DMBT1	0.118	0.086364	0.134167

Q9UHB6	LIMA1	0	0	0.008333
Q9UHQ9	CYB5R1	0	0	0.023333
Q9UHV9	PFDN2	0	0.224545	0.239167
Q9UIV8	SERPINB13	0	0.06	0.103333
Q9UJ70	NAGK	0	0.022727	0.054167
Q9UJT2	TSKS	0	0	0.035
Q9UJT9	FBXL7	0	0	0.020833
Q9UKK3	PARP4	0	0	0.011667
Q9UKM9	RALY	0	0.042727	0.1375
Q9UKX2	MYH2	0	0	0.025
Q9UL25	RAB21	0	0.06	0.033333
Q9UL46	PSME2	0.354	0.564545	0.665
Q9ULA0	DNPEP	0	0.015455	0.030833
Q9ULZ3	PYCARD	0.047	0.177273	0.4675
Q9UM07	PADI4	0	0	0.015
Q9UM54	MYO6	0.015	0	0.0075
Q9UMN6	KMT2B	0	0.003636	0.0025
Q9UMS4	PRPF19	0	0	0.035
Q9UMY4	SNX12	0	0	0.173333
Q9UNM6	PSMD13	0.022	0.127273	0.301667
Q9UNX3	RPL26L1	0.062	0.056364	0
Q9UQ16	DNM3	0	0.008182	0
Q9UQ35	SRRM2	0.003	0.002727	0
Q9UQ80	PA2G4	0	0.055455	0.160833
Q9Y230	RUVBL2	0.018	0	0.0575
Q9Y250	LZTS1	0	0	0.010833
Q9Y262	EIF3L	0.021	0	0.010833
Q9Y265	RUVBL1	0	0.016364	0.056667
Q9Y266	NUDC	0	0	0.045833
Q9Y277	VDAC3	0.031	0	0
Q9Y2A7	NCKAP1	0.01	0	0.005833
Q9Y2H9	MAST1	0	0	0.004167
Q9Y2Q3	GSTK1	0.127	0.083636	0.1375
Q9Y2S2	CRYL1	0	0.023636	0
Q9Y376	CAB39	0.024	0.033636	0.05
Q9Y3C8	UFC1	0.053	0	0
Q9Y3D6	FIS1	0	0.057273	0
Q9Y3E7	CHMP3	0	0	0.033333
Q9Y3I0	RTCB	0	0	0.013333
Q9Y3U8	RPL36	0	0	0.079167
Q9Y3Z3	SAMHD1	0	0	0.065
Q9Y446	PKP3	0	0.014545	0
Q9Y490	TLN1	0.008	0.057273	0.066667
Q9Y4C4	MFHAS1	0	0.006364	0
Q9Y4G6	TLN2	0	0.01	0
Q9Y4I1	MYO5A	0.004	0.025455	0.02

Q9Y4L1	HYOU1	0.012	0	0
Q9Y566	SHANK1	0	0	0.003333
Q9Y5P6	GMPPB	0	0.020909	0.038333
Q9Y5W7	SNX14	0	0	0.013333
Q9Y5Z4	HEBP2	0.117	0.342727	0.240833
Q9Y623	MYH4	0.019	0	0.025
Q9Y678	COPG1	0	0.012727	0.0075
Q9Y6B6	SAR1B	0	0	0.0375
Q9Y6N5	SQOR	0.04	0	0
Q9Y6R7	FCGBP	0.053	0.08	0.058333
Q9Y6V0	PCLO	0	0.001818	0

CRSSNP: Chronic rhinosinusitis without nasal polyps, CRSwNP: Chronic rhinosinusitis with nasal polyps.

Supplementary Table 2. Unique proteins

Healthy Proteins						
ACLY	ACRBP	ADK	ADSS	AHSA1	AK2	ALDH2
ALDH7A1	ANKFY1	ANKRD18B	ANXA11	API5	ARPC1A	ARPC5L
ATG2B	ATIC	ATP5PB	ATP5PO	BAG1	BARD1	BCAN
BDH2	BOLA2	BOLA2B	BTF3	C1R	CACYBP	CALR
CARD14	CCDC25	CCDC6	CCDC88A	CCS	CCT5	CCT7
CFAP46	CGN	CHIT1	CHMP3	CIT	CKB	CLTB
COPS4	COPZ1	CRYZ	CS	CSDE1	CTBP1	CTSC
CTSH	CTSL	CTSZ	CUL3	CUL4B	CYB5R1	DDAH1
DDAH2	DDX1	DDX17	DDX39A	DDX46	DDX5	DIAPH1
DNAH17	DYNC1I2	EEF1E1	EFCAB6	EHD1	EIF2S3	EIF3F
EIF3G	EML6	ENO3	EPB41	ERBB3	ERP44	FAM151A
FAM186A	FAM49B	FBLN1	FBXL7	FLII	FLT4	FMO3
FSIP2	FUCA1	GAA	GARS	GART	GCLC	GFAP
GMFB	GNAS	GNB4	GNPDA2	GPX2	GPX4	GRB2
GRIK5	GSPT1	GSTZ1	H1FO	HADH	HARS	HLA-DRB1
HMGB1	HMGB2	HUWE1	IGHV1-46	IGKV1-5	INPP1	INTS7
IQGAP2	IST1	ITGA9	KARS	KBTBD3	KRT222	LACTB2
LDHC	LIMA1	LIMK2	LIMS1	LMNB2	LRBA	LYPLA1
LZTS1	MAPK1	MAPRE1	MAST1	MBP	MDN1	METTL18
MFN2	MMRN1	MORC1	MRI1	MYH1	MYH11	MYH2
MYH3	MYH7	MYL1	NAPA	NARS	NAV2	NCF2
NCF4	NCOA6	NCOR1	NEFL	NEFM	NIBAN1	NIT1
NONO	NUDC	NUDT2	NUDT21	OLA1	OLFM4	OPRPN
PADI4	PAICS	PARP4	PCBD1	PCBP2	PDGFRB	PDLIM1
PFDN6	PFKL	PGM1	PIK3R4	PKD1	PLA2G2A	PLIN3
PPA2	PRDX4	PRKACA	PRMT1	PRPF19	PRPSAP2	PSD
PSMB5	PSMC3	PTGR2	RAB6B	RAB8B	RAD23B	RALA
RARS	RBBP9	RBM22	RHOG	RNASET2	RPL18	RPL3
RPL36	RPL38	RPS10	RPS17	RPS6KA3	RTCB	SAMHD1
SAR1B	SBF1	SCP2	SCPEP1	SEPTIN14	SEPTIN2	SEPTIN8
SERPINB8	SERPINB9	SETDB2	SHANK1	SIGLEC16	SMS	SNRPD1
SNRPGP15	SNX12	SNX14	SPECC1	SPEG	SPRR2G	SRM
SRP9	SSH3	ST13	ST13P4	STAT3	STIP1	SUB1
SULT1A3	SUMO1	SUMO3	TAOK1	TIPRL	TJP2	TMOD3
TNNC2	TPD52	TRAPPC3	TRIM28	TSHZ3	TSKS	TSNAX
TTC12	TUBB8	UBA6	UBE2M	UBL4A	UBLCP1	UPF2
VAT1	VBP1	XPNPEP1	YKT6	ZBTB4	ZC3H13	ZNF132

CRSsNP Proteins						
ACADVL	ACO2	ACOT13	ADGRV1	AK9	ALOX5AP	ANPEP
ANXA6	AP2A1	AP3B2	APMAP	ARMC9	ARVCF	ATP5MG
BPIFB4	CALHM4	CANX	CD55	CDSN	CEACAM8	CES1
COX4I1	COX6C	COX7A2	CRYBG3	CYBA	CYBB	DAD1
EIF3CL	ETF1	GIGYF1	GLIPR2	GNAI2	GP2	HDLBP
HEPHL1	HIST1H2AB	HIST1H2AE	HIST1H2BJ	HIST2H2AC	HIST2H2BC	HLA-DRB1
HLA-DRB1	HNRNPCL4	HSD17B10	HSPA9	HSPG2	HYOU1	IGHV3-49
IMMT	ITGAM	KIF21B	KIF4B	KRTAP9-3	KRTAP9-9	LAMP1
LAMP2	LBR	LONP2	LOR	LRRCC1	MADD	MGST1
MLH1	MUC2	MYO1D	MYOF	NDUFA4	PGAM2	PLGRKT
POR	POTEI	PROM1	PRR36	PTPRC	RARRES1	RGS22
RIT2	RP1	RPL28	S100A3	SLC25A6	SLC2A14	SPATA7
SQOR	SRSF7	SSBP1	SSR4	TBX3	TMED9	TSNAXIP1
TTLL5	TUFM	UFC1	UGGT1	UQCRC2	USP9X	VDAC3

CRSwNP Proteins						
ACOT7	ACTC1	ALDH16A1	ALDH1L1	ANG	AP2S1	APOC2
APOL2	ARHGAP4	ASH1L	ATP2B1	ATRX	BROX	BST1
CASP7	CD63	CDC6	CHEK2	CHMP2A	CLCN5	CLIP1
CNTRL	CPN2	CRYL1	CSE1L	DDX11L8	DIAPH2	DNAH11
DNAH14	DNM3	DUSP23	EEF1A1	EIF2S3B	EIF3I	EIF4G1
EIF5AL1	EML1	ENO2	EP300	F2	FAM3B	FAM81B
FCN1	FCN3	FIS1	FLNC	FRMPD1	FRYL	GLRX3
GNAL	GPR179	GPRIN1	GSDMA	GSTM1	HBE1	HBG1
HSP90AA4P	HSPA2	IDO1	IFIT1	IGHV2-26	IGHV3-73	IGHV3-9
IGKV2-30	IGLV3-21	IGLV3-27	IGLV4-60	IGLV7-43	ISG15	ITIH3
KRT37	KRT71	KRT87P	KTN1	LHPP	LRRC20	MAGI1
MARS	MFHAS1	MOB1B	MOCOS	MRPL17	MUCL1	MYCBP
MYH10	MYL6B	NEK10	NME9	NOS2	PCLO	PGLYRP2
PHYHIPL	PIGT	PIK3C2B	PKP3	PLBD1	PRF1	PRSS1
PYGM	RET	RMDN1	RNASE2	RNF213	ROCK2	RP1L1
RPL13	RPL13A	RPL24	RPL6	RPS19BP1	SAA4	SDCBP
SERPINA5	SERPINB10	SKP1	SLC44A4	SLITRK5	SPRR1A	SPRR2D
SPRR2E	SPRR4	TACSTD2	TFF3	TGM1	TLN2	TSPAN1
TUBB2A	UBE2L6	VARS	VPS26A	YTHDC2	ZNF276	

CRSsNP: Chronic rhinosinusitis without nasal polyposis, CRSwNP: Chronic rhinosinusitis with nasal polyposis

Supplementary Table 3. Differentially expressed proteins across all groups detected via Omnibus test

ADH7	CAPG	CFL1	CSTB	GC
GOT1	IDH1	KNG1	KPRP	KRT72
MDH1	MUC5AC	MYO5A	PIGR	PSMA1
PSMB2	S100A7	TPM3	UGP2	YWHAE

Methods Supplement

Mucus Preparation

Mucus samples were mixed with 500 μ L of 1 $\times$ PBS and centrifuged as 12,000 g for 5 minutes. Supernatant was aspirated and mixed with 10 times volume of acetone (Chem-Supply, SA, Australia) and incubated at -20°C for one hour to allow for protein precipitation. Protein was collected following centrifugation at 10,000 rpm for 10 minutes and resolubilised in 35 μ L of 6 M urea (Univar, NSW, Australia) with 5 mM Dithiothreitol (DTT, Sigma-Aldrich, MO, USA). EZQ protein quantification kit (Bio-Rad, CA, USA) was employed to calculate the amount of protein required for a loading concentration of 20 μ g per well for gel electrophoresis.

Gel Electrophoresis

20 μ g of protein from mucus samples were mixed with 4x sample buffer consisting of DTT, Glycerol, SDS and Bromophenol blue as described previously.⁸ 40 μ L of sample was loaded into each well of the Mini-PROTEAN TGX 4-20% Stain-Free Gels (Bio-Rad, CA, USA). Electrophoresis was performed for 30 minutes at 200V. Gels were stained with Coomassie blue stain (Coomassie Brilliant Blue R-250) for visualisation and scanned with GelDoc™ EZ Imager (Bio-Rad, CA, USA). Gels were stored in fixative (20% methanol, 7.5% acetic acid) at room temperature prior to mass spectrometry.

Trypsin gel digest

Each lane of the SDS-PAGE gels, were cut into twelve equal sized gel pieces using sterile scalpels and transferred into 1.5 mL maximum recovery tubes (Axygen, CA, USA). Dissected gel pieces were de-stained with 50% methanol (Univar, Vic

Australia). This was followed by sequential reduction and alkylation with 100 mM DTT and 400 mM iodoacetamide (Bio-Rad, MO, USA) and dehydrated in acetonitrile (BDH Laboratory Supplies, Poole, UK). Gel pieces were rehydrated with 100 mM ammonium bicarbonate (Sigma-Aldrich, MO, USA) containing trypsin digest containing trypsin (Promega, WI, USA) and 1 mM calcium chloride (BDH Chemicals, Vic, Australia) for 12 hours. Supernatant was collected and transferred into mass spectrometry vials (Thermo Scientific, TN, USA).

ESI-Q-TOF Mass Spectrometry and Protein Identification

Tryptic digests were analysed with an Ekspert nano-LC 415 μ HPLC (Eksigent, CA, USA), coupled online to a quadrupole time-of-flight mass spectrometer (Sciex TripleTOF 5600⁺; ON, Canada). Samples were loaded onto a Protecol trap column, 3 μ 120 Å, C18, 10 mm x 300 μ m (Trajan Scientific P/N 2POL-03T30K) and desalted in water with 0.1% formic acid, 2% ACN (v/v) at a flow rate of 20 μ L/min for 5 minutes. Peptides were separated on a 15 cm x 75 μ m column packed with 5 μ m porous silica C18 beads (Nikkyo Technos, Tokyo, Japan) and electrosprayed from columns integrated spray emitter at 2kV. Mobile phases A and B were water with 0.1% formic acid (v/v) and ACN, 0.1% formic acid (v/v). Peptides were eluted at a constant flow rate of 500 nL/min, a binary gradient was ramped from 5% to 25% B within 6 minutes, increased to 40% B within 2 minutes, then further increased to 95% B within 2 minutes for washing. After 3 minutes the organic phase was returned to 5% ACN within 3 minutes and the column re-equilibrated for a further 10 minutes.

Full MS scans in the m/z 350-1500 mass range were acquired with a 100 ms transient time in positive ion mode. Following each MS scan, the 20 most intense multiply

charged ions were subjected to collision-induced dissociation and the MS2 spectra were acquired in high sensitivity mode with an accumulation time of 25 ms, with a mass range of m/z 50-1500. Only precursors with a charge state ≥ 2 and ≤ 5 were included and previously fragmented ions were dynamically excluded for 30 seconds after 3 occurrences. Rolling collision energy and dynamic accumulation were both enabled for all MS2 spectra acquired.

Database Search

Liquid chromatography-tandem mass spectrometry (LC-MS/MS) data was analysed by searching the Uniprot database (Downloaded 15 February 2017) with MASCOT v2.6 (Matrix Science, London, UK). Search parameters included: mass value (Monoisotopic), enzyme (Trypsin); maximum missed cleavage (2), fixed modifications (Carbamidomethyl); variable modifications (methionine oxidation and serine/threonine/tyrosine phosphorylation); peptide charge (2+, 3+, 4+), peptide tolerance (± 20 ppm); MS/MS tolerance (± 0.05 Da). Acceptance parameters were two or more unique peptides after automatic validation (False discovery rate 1%). Identified proteins were annotated from Uniprot, and emPAI scores were calculated from the MASCOT software v2.6 using the same search parameters.