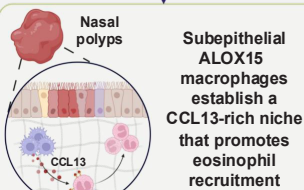
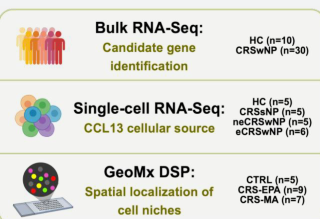


Subepithelial ALOX15⁺ macrophage niches orchestrate eosinophil recruitment in chronic rhinosinusitis with nasal polyps via the ALOX15-ERK-CCL13 axis

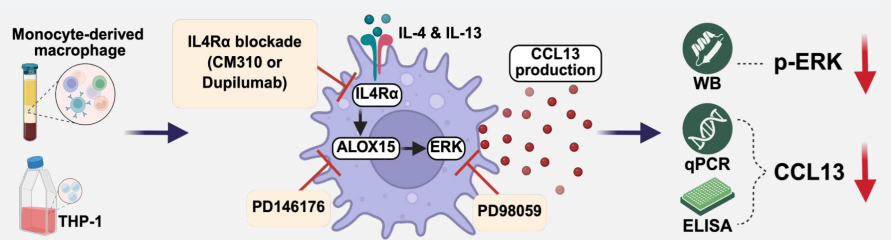
Yueming Cui^{1,2,3,4}, Chang Liu³, Kanghua Wang³, Wenqin Liu², Weiping Wen^{1,2,3,4,*}, Jianbo Shi^{2,*}, and Yueqi Sun^{1,3,4,*} *Rhinology* 64: 5, 0 - 0, 2026
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Subepithelial ALOX15⁺ macrophage niches orchestrate eosinophil recruitment in chronic rhinosinusitis with nasal polyps via the ALOX15-ERK-CCL13 axis

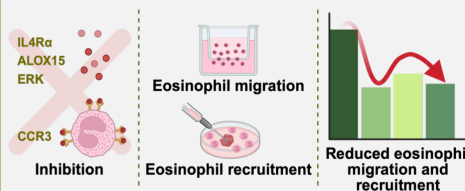
1. Integrated transcriptomic profiling



2. IL-4/IL-13 activate the macrophage ALOX15-ERK-CCL13 axis



3. Functional migration assays



CONCLUSION

- Subepithelial ALOX15 macrophage niches promote eosinophil recruitment in eCRSwNP
- The IL-4Ra-ALOX15-ERK-CCL13 axis represents a potential therapeutic target for eCRSwNP

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Abstract

Background: Eosinophilic chronic rhinosinusitis with nasal polyps (eCRSwNP) is characterized by intense type 2 inflammation and high recurrence rate. The precise spatial determinants and cellular mechanisms sustaining tissue eosinophilia within the polyp microenvironment remain unknown. This study aimed to identify the spatially cellular niches driving eosinophil recruitment and evaluate the therapeutic efficacy of targeting specific macrophage-driven pathogenic loops in eCRSwNP.

Methodology: Transcriptomic profiles were analyzed using bulk RNA-sequencing of nasal polyp tissues from CRSwNP patients (n = 30, stratified by eosinophilic severity) and healthy controls (HC, n = 10). Spatial transcriptomics (GeoMx DSP) and single-cell RNA sequencing analyses were utilized to map macrophage niches. Mechanistic findings were validated ex vivo and in vitro using human sinonasal explant models and migration assays, incorporating an independent cohort of healthy controls (n = 12).

Results: Bulk transcriptomics of nasal polyps stratified across a gradient of tissue eosinophil density identified ALOX15 and CCL13 as top candidates positively correlating with tissue eosinophilia. Spatial transcriptomics revealed that subepithelial ALOX15⁺ macrophages served as the primary source of CCL13, and the localized CCL13 expression significantly correlated with eosinophil density in epithelial areas. Mechanistically, IL-4/IL-13 induces ALOX15-ERK-CCL13 axis in macrophages. Functional explant assays confirmed that ALOX15⁺ macrophages drive eosinophil recruitment via CCR3. IL-4Ra blockade with Dupilumab or Stapokibart abrogated the pathogenic ALOX15-CCL13 loop and attenuated eosinophil chemotaxis.

Conclusions: Our findings identify the subepithelial ALOX15⁺ macrophage niche as a pivotal spatial determinant of eosinophilia in eCRSwNP. Targeting this specialized immune hub with emerging biologics offers a promising precision therapeutic strategy.

Key words: 15-lipoxygenase-1, eosinophil, macrophage, nasal polyps, rhinosinusitis

Introduction

Chronic rhinosinusitis with nasal polyps (CRSwNP) is a multifaceted inflammatory condition of the sinonasal mucosa characterized by persistent dysfunction and tissue remodeling⁽¹⁻³⁾. Within this clinical spectrum, eosinophilic CRSwNP (eCRSwNP) represents a distinct endotype defined by intense Type 2 (T2) inflammation, a high prevalence of comorbidities such as asthma, and a marked reliance on corticosteroid therapy, alongside a high propensity for postoperative recurrence^(1, 4, 5). Despite the clinical success of biological therapies, the cellular mechanisms governing the localized sequestration of eosinophils within polyp tissue remain poorly characterized, necessitating a deeper exploration of the tissue microenvironment.

The recruitment of eosinophils is traditionally viewed through an epithelium-centric lens, focusing on epithelial alarmins⁽⁶⁻⁸⁾ and epithelial-derived chemokines such as CCL26^(9, 10). However, emerging evidence suggests that the subepithelial niche acts as a critical immunological hub, where specialized immune cell populations sustain chronic tissue eosinophilia⁽¹¹⁻¹⁴⁾. Macrophages, particularly those polarized by IL-4 and IL-13, are known orchestrators of T2 responses⁽¹⁵⁾. While ALOX15 has been identified as a metabolic hallmark of T2-high airway disease⁽¹⁶⁾, its functional significance within specific subepithelial macrophage sub-populations, and how these cells spatially coordinate with eosinophil niches, remains a significant research gap.

In this study, we hypothesized that IL-4/IL-13 stimulation induces a specific ALOX15⁺ macrophage phenotype in the subepithelial region, which subsequently drives local eosinophil recruitment via the ERK-mediated production of CCL13. To investigate this, we utilized a multi-omic approach, integrating bulk RNA-sequencing and single-cell analysis with GeoMx Digital Spatial Profiling (DSP) to map these interactions within their native histological architecture. Beyond mechanistic discovery, we sought to address the translational potential of the ALOX15-CCL13 axis. While IL-4Ra blockade has revolutionized the treatment of T2-high CRSwNP, its direct impact on macrophage-driven chemoattractant niches remains poorly defined. Here, we employed a human sinonasal explant model to demonstrate that ALOX15⁺ macrophages are functional drivers of eosinophil recruitment and activation in the nasal mucosa. Furthermore, by utilizing an in vitro human monocyte-derived macrophage model, we evaluated the therapeutic efficacy of IL-4Ra blockade. We demonstrate that treatment with either Dupilumab⁽¹⁷⁾ or the emerging IL-4Ra antagonist Stapokibart (CM310)⁽¹⁸⁾ effectively disrupts the ALOX15-CCL13 pathogenic loop, significantly attenuating subsequent eosinophil chemotaxis. Our findings identify the subepithelial ALOX15⁺ macrophage niche as a pivotal spatial determinant of tissue eosinophilia and provide a strong mechanistic rationale for targeting this axis with current and next-generation biological therapies.

Materials and methods

Subjects and sample collection

This study enrolled adult patients (aged 18-65 years) undergoing endoscopic sinus surgery for CRSwNP at the Seventh Affiliated Hospital of Sun Yat-sen University. The study protocol was approved by the Institutional Ethics Committee, and written informed consent was obtained from all participants. CRSwNP was diagnosed according to EPOS 2020 guidelines⁽¹⁾. To minimize confounding effects on the transcriptomic and cellular profiles, strict exclusion criteria were applied. We excluded patients with acute asthma exacerbation or upper respiratory tract infection within four weeks preoperatively, fungal rhinosinusitis, immunodeficiency, or systemic vasculitis. Furthermore, patients with any prior history of biological therapies, or those who had received systemic corticosteroids within three months, or intranasal corticosteroids/antileukotrienes within two weeks prior to surgery were strictly excluded.

Nasal polyp tissues were obtained from CRSwNP patients during surgery. For bulk RNA sequencing, a cohort of 30 CRSwNP patients was selected and stratified based on a gradient of tissue eosinophilia to capture the spectrum of type 2 inflammation. Transcriptomic data for healthy controls (n = 10) were retrieved from a public database⁽¹⁹⁾. For histological and functional assays (explant cultures and migration assays), control middle turbinate mucosa was collected from separate participants (n = 12) undergoing septoplasty for nasal septal deviation, excluding those with rhinitis or sinusitis.

Allergic rhinitis (AR) and asthma were diagnosed according to the ARIA (2016 revision)⁽²⁰⁾ and the current Global Initiative for Asthma (GINA) guidelines⁽²¹⁾, respectively. Patients with NSAID-exacerbated respiratory disease (N-ERD) were not present in our enrolled cohort, thereby excluding the confounding effects of this severe phenotype.

Detailed demographic and clinical characteristics, including smoking status, are summarized in Table S1.

Experimental procedures

Detailed protocols for all experimental procedures are available in the Supporting Information (Appendix S1). Briefly:

Tissue analysis: Histopathologic evaluation, immunofluorescence staining, bulk RNA-sequencing, and single-cell RNA-sequencing re-analysis were performed as previously described⁽²²⁻²⁵⁾. Spatial transcriptomic profiling was conducted using the NanoString GeoMx DSP platform as per our previous protocol⁽²⁵⁾.

Cell culture and isolation: THP-1 cells (Procell) and human monocyte-derived macrophages were cultured and polarized into M0 and M2 phenotypes⁽²⁵⁻²⁸⁾. The human eosinophilic cell line EOL-1 (FuHeng) was transfected with a GFP-encoding plasmid (Taitool Bioscience) for visualization. Primary peripheral

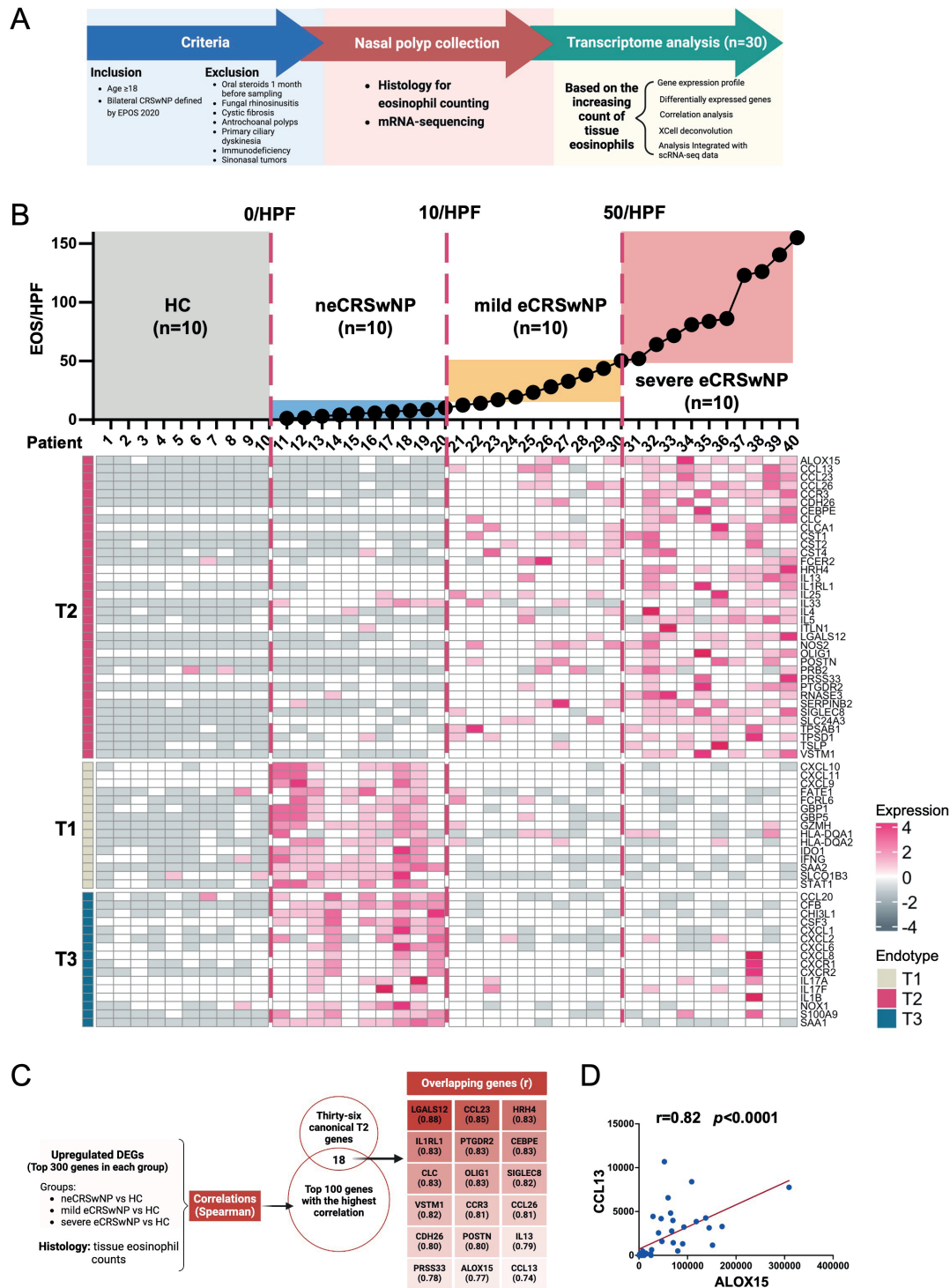


Figure 1. Transcriptomics-based screening of molecular signatures associated with eosinophils in CRSwNP. A. study workflow. B. Transcriptome expression and tissue eosinophil counts for healthy controls (HC, numbered 1-10, tissue eosinophils count were not done) and individual CRSwNP patients (numbered 11-40 by increasing tissue eosinophilia, upper panel) are shown, with dashed lines indicating thresholds (0 eosinophils/HPF, 10 eosinophils/HPF and 50 eosinophils/HPF). The heatmap (red: upregulated, gray: downregulated) displays 36, 15, and 16 DEGs associated with T2, T1, and T3 biomarkers, respectively (lower panel). Columns represent individual subjects (four groups: HC, neCRSwNP, mild eCRSwNP, and severe eCRSwNP, n=10 for each group) matched vertically to upper panel. C. Identification of key T2 biomarkers associated with tissue eosinophils in CRSwNP. Upregulated DEGs were selected from the top 300 genes in each comparison group: neCRSwNP (n = 10) vs. HC (n = 10), mild eCRSwNP (n = 10) vs. HC (n = 10), and severe eCRSwNP (n = 10) vs. HC (n = 10). Spearman correlation analysis with tissue eosinophil counts identified overlapping genes between the 36 canonical T2 genes and the top 100 genes with the strongest correlation to eosinophil counts. Eighteen genes were found to overlap, with their correlation coefficients (r) shown in the right panel. D. Correlation between CCL13 and ALOX15 expression levels based on bulk RNA-sequencing data from 30 patients with CRSwNP and 10 healthy controls (n = 40).

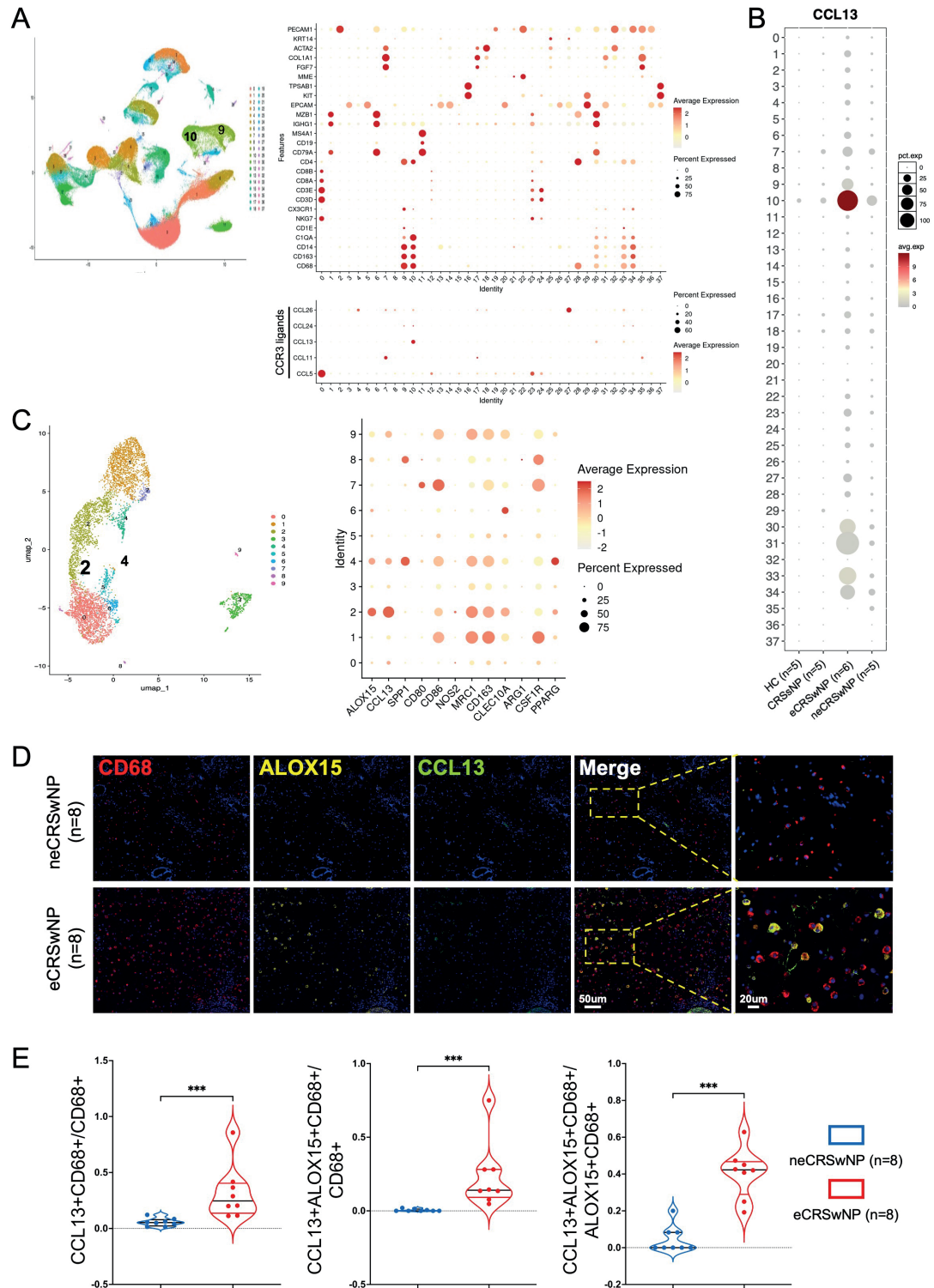


Figure 2. ALOX15⁺ macrophages are the main cells producing CCL13 in eCRSwNP. A. UMAP visualizing cell populations identified through unsupervised cluster analysis of human nasal mucosal and polyp tissues from 16 individuals (5 healthy controls, 5 patients with neCRSwNP and 6 patients with eCRSwNP). Bubble heatmap displaying expression of marker genes, as well as CCR3 ligands, across all cellular clusters. B. Bubble heatmap illustrating CCL13 expression across all cellular clusters, comparing its distribution and expression levels among healthy controls (HC, n = 5), CRSwNP (n = 5), neCRSwNP (n = 5), and eCRSwNP (n = 6) groups. C. UMAP showing ten subpopulations of macrophages through unsupervised cluster analysis. Bubble heatmap showing the distributions of ALOX15, CCL13 and other functional markers among macrophage subpopulations. D. Representative photomicrographs showing immunofluorescence staining of CCL13 (green) on ALOX15⁺ macrophages in neCRSwNP and eCRSwNP. ALOX15⁺ macrophages are identified by the colocalization of CD68 (red) and ALOX15 (yellow). E. Quantification of CCL13⁺CD68⁺ cells and CCL13⁺ALOX15⁺CD68⁺ cells within total CD68⁺ cells, and CCL13⁺ALOX15⁺CD68⁺ cells within ALOX15⁺CD68⁺ cells, in neCRSwNP (n = 8) and eCRSwNP (n = 8) as detected by immunofluorescence staining. **** p < 0.0001.

blood eosinophils were isolated using the Eosinophil Isolation Kit (Miltenyi Biotec).

Functional assays: Eosinophil recruitment was assessed using a human sinonasal explant model⁽²⁹⁻³⁴⁾ and Transwell migration assays^(31, 33, 35, 36).

Molecular assays: Gene and protein expression levels were quantified using real-time PCR, ELISA, and Western blot analysis as previously described^(9, 25).

Statistical analysis

Statistical analyses were performed using SPSS version 26.0 (IBM Corp., Armonk, NY, USA). Data distribution was assessed for normality. Continuous variables are presented as medians with interquartile ranges (IQR) or means $\pm$ standard deviations (SD), as appropriate. Differences between two groups were analyzed using the Student's t-test or Mann-Whitney U test. Multigroup comparisons were performed using ANOVA or the Kruskal-Wallis test, followed by post hoc corrections (Bonferroni or Dunn's test). Correlations were evaluated using Spearman's rank correlation coefficient. A P-value < 0.05 was considered statistically significant.

Results

Transcriptomic profiling identifies ALOX15 and CCL13 as key correlates of eosinophil infiltration

To elucidate gene expression patterns associated with eosinophil infiltration severity in CRSwNP, we performed bulk RNA-seq analysis on nasal polyp tissues categorized based on increasing eosinophil counts. Thirty CRSwNP patients were selected, representing a gradient of tissue eosinophilia (Figure 1A-B). According to previously established criteria for eosinophilic CRSwNP (eCRSwNP)⁽⁴⁾, we stratified patients into three groups using eosinophil count thresholds of 10 eosinophils/HPF and 50 eosinophils/HPF: non-eCRSwNP (neCRSwNP), mild eCRSwNP, and severe eCRSwNP (Figure 1B). Clinical and histopathological details of the subjects are summarized in Tables S1 and S2. Differential expression analysis revealed distinct yet overlapping molecular landscapes. While a core set of upregulated genes was shared across all subgroups, unique signatures distinguished each phenotype (Figure S1A-B; Tables S3-S5). Notably, the expression of canonical T2 markers, including IL-4, IL-13, POSTN, ALOX15, and CCL13, exhibited a progressive increase paralleling eosinophil count, peaking in the severe eCRSwNP group. In contrast, neCRSwNP tissues were characterized by elevated T1/T3-related signatures (Figure 1B). To identify potential molecular drivers, we correlated global gene expression with tissue eosinophil levels. Among the top 100 genes showing the strongest positive correlations, 18 were established T2 biomarkers, including SIGLEC8, CCR3, POSTN, and

notably, ALOX15 and CCL13 (Figure 1C, S1C). These two genes emerged as the top candidates for further investigation, supported by a robust positive correlation between their expression levels ($r = 0.82$, Figure 1D), suggesting a potential functional synergy in driving eosinophilic inflammation.

Importantly, as detailed in Table S1, the prevalence of comorbid asthma and allergic rhinitis, as well as macroscopic severity metrics including Lund-Mackay CT scores and Lund-Kennedy endoscopic scores, did not significantly differ among the three groups. Notably, while the total SNOT-22 scores were comparable, both mild and severe eCRSwNP patients exhibited significantly higher scores for decreased sense of smell/taste compared to the neCRSwNP groups. These findings indicate that the ALOX15/CCL13 gradient is a specific molecular feature of tissue eosinophilia that manifests clinically as impaired olfaction, independent of the total macroscopic polyp burden or systemic comorbidities.

ALOX15⁺ macrophages, but not total M2 macrophages, correlate with eosinophil infiltration severity

Immune cell deconvolution (xCell) indicated that while eCRSwNP tissues exhibited a general shift toward M2 polarization compared to neCRSwNP, total M2 scores did not significantly differ between mild and severe disease states (Figure S2A). This suggested that broad M2 classification is insufficient to explain the gradient of eosinophilia. We therefore investigated the specific ALOX15⁺ subset. Immunofluorescence quantification ($n = 37$) confirmed that total M2 macrophages (CD68⁺CD163⁺) failed to correlate with tissue eosinophilia. In contrast, ALOX15⁺ macrophages (defined as CD68⁺ALOX15⁺ or CD68⁺CD163⁺ALOX15⁺) exhibited a significant positive correlation with eosinophil counts ($r = 0.4015$ or 0.39 ; Figure S2B-C). These findings establish ALOX15 expression as a specific marker for the pathogenic macrophage phenotype linked to eosinophil sequestration.

ALOX15⁺ macrophages are a major source of CCL13 in eCRSwNP

To determine the cellular sources of CCR3 ligands (CCL13, CCL26, CCL24, CCL11, and CCL5) in CRSwNP, we reanalyzed previously published single-cell RNA-seq data from CRS samples⁽³⁷⁾. As shown in Figure 2A-B, CCL13 expression was predominantly identified in cluster 10, characterized by CD68⁺CD163⁺ macrophages in eCRSwNP. In contrast, CCL26 expression was mainly detected in cluster 27 (EPCAM⁺ epithelial cells), CCL11 expression in cluster 7 (COL1A1⁺ stromal cells), and CCL5 expression primarily in cluster 0 (CD3E⁺ T cells). Considering previous evidence of prominent ALOX15 expression in macrophages from eCRSwNP patients (25), we further assessed whether ALOX15⁺ macrophages specifically produced CCL13. Macrophages were subdivided into 10 distinct subclusters through unsupervised clustering analysis (Figure 2C). Notably, subcluster

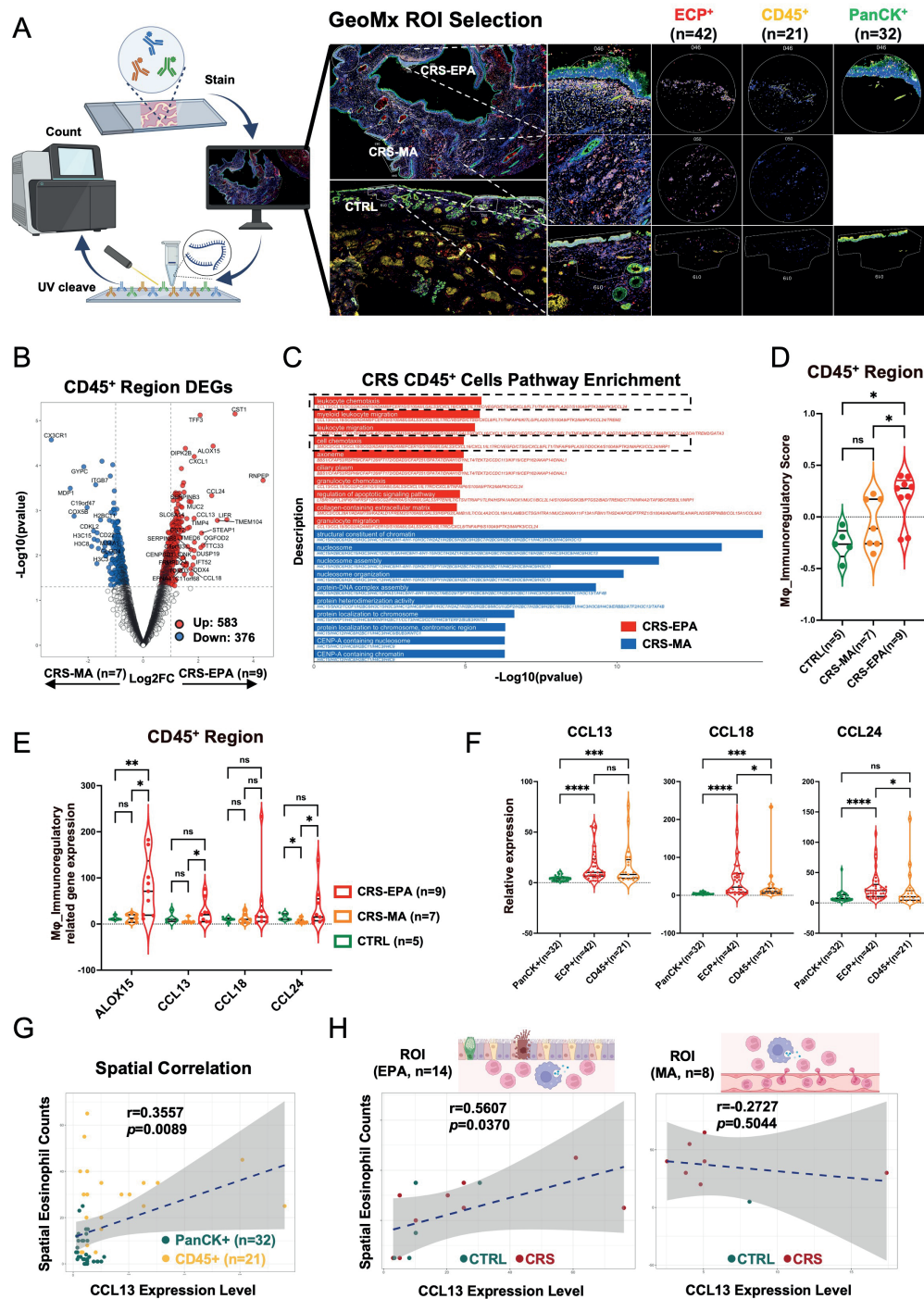


Figure 3. Spatial transcriptomics reveals a subepithelial ALOX15⁺ macrophage niche associated with CCL13-mediated eosinophil recruitment. A. Schematic of the GeoMx Digital Spatial Profiling (DSP) workflow and region of interest (ROI) selection strategy. ROIs were selected and segmented from CRS-EPA, CRS-MA, and CTRL tissues based on fluorescent morphology markers: PanCK⁺ (epithelial cells), CD45⁺ (immune cell infiltrates), and ECP⁺ (eosinophil-rich clusters). B. Volcano plot displaying differentially expressed genes (DEGs) in CD45⁺ immune-rich regions between CRS-EPA (n = 9) and CRS-MA (n = 7). Red and blue dots represent significantly up-regulated (583 genes) and down-regulated (376 genes) transcripts in CRS-EPA, respectively. C. Gene Ontology (GO) enrichment analysis of up-regulated (red) and down-regulated (blue) pathways in CD45⁺ regions of CRS-EPA versus CRS-MA. D. Comparison of the macrophage (Mφ) immunoregulatory score in CD45⁺ regions across CTRL (n = 5), CRS-MA (n = 7), and CRS-EPA (n = 9) groups. E. Relative expression of key macrophage-associated genes (ALOX15, CCL13, CCL18, and CCL24) in CD45⁺ regions across the three groups. F. Relative expression levels of CCL13, CCL18, and CCL24 across different spatial compartments, including PanCK⁺ epithelium (n = 32), ECP⁺ areas (n = 42), and CD45⁺ immune niches (n = 21). G. Spatial correlation analysis between CCL13 expression levels and local eosinophil counts across all analyzed ROIs (PanCK⁺, n = 32; CD45⁺, n = 21). H. ROI-specific spatial correlation analysis showing a significant association between CCL13 and eosinophil infiltration within EPA regions (left panel, n = 14, $r=0.5607$, $p=0.0370$), which is absent in MA regions (right panel, n = 8, $r=-0.2727$, $p=0.5044$). Statistical significance was determined by one-way ANOVA or Pearson's correlation; * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$; ns, not significant.

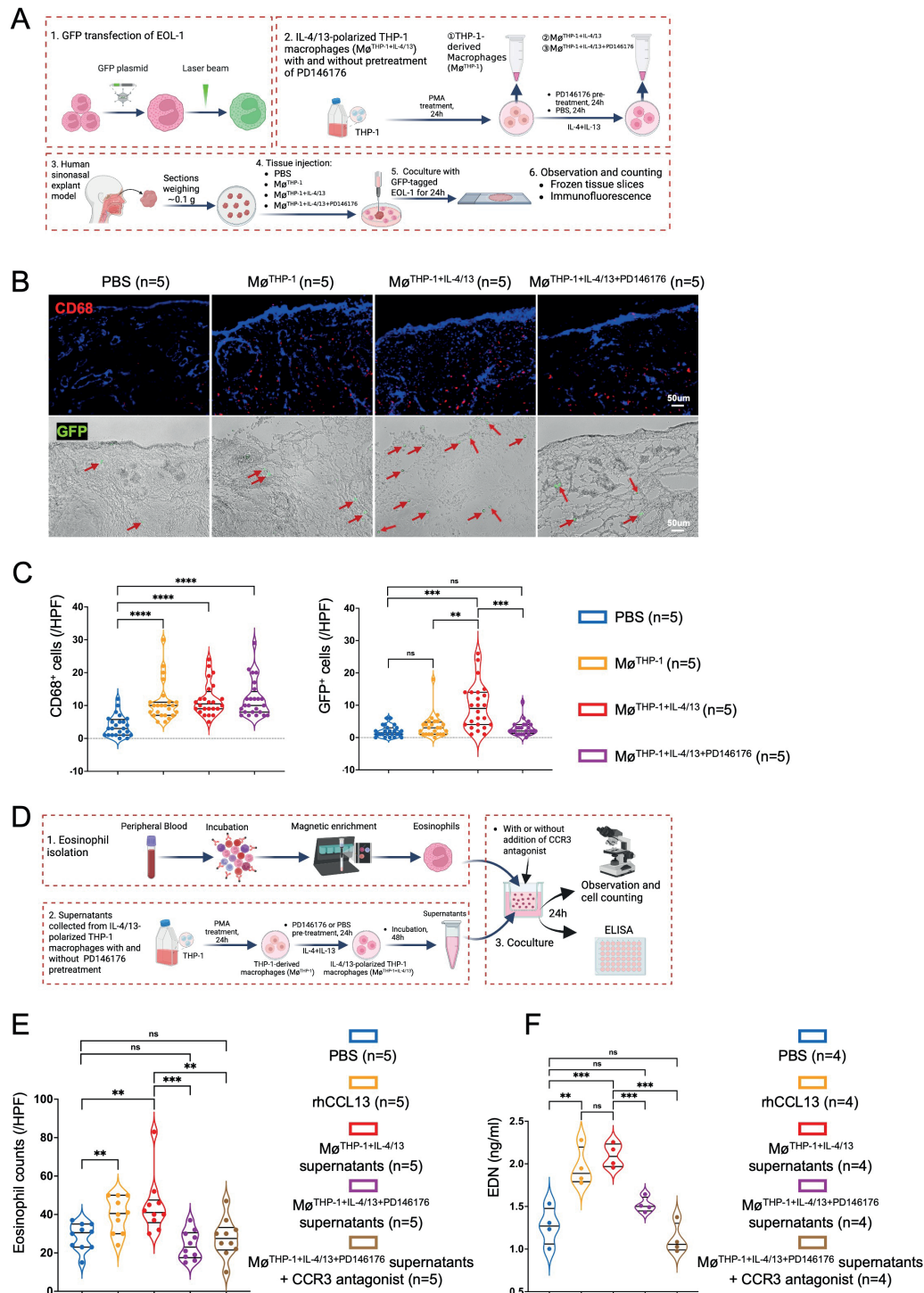


Figure 4. ALOX15⁺ macrophages promote eosinophil recruitment and activation through the CCL13/CCR3 axis. A. Schematic illustration of the experimental design using a human sinonasal explant model. EOL-1 cells were transfected with GFP to track recruitment. THP-1 derived macrophages (M ϕ ^{THP-1}) were polarized with IL-4/IL-13 (M ϕ ^{THP-1}+IL-4/IL-13) to induce an ALOX15⁺ phenotype, with or without pretreatment with the ALOX15 inhibitor PD146176. Schemes were created with BioRender. B. Representative immunofluorescence and bright-field images of nasal mucosal sections. CD68⁺ macrophages are shown in red, and recruited GFP⁺ EOL-1 cells are indicated by red arrows. Scale bar = 50 μ m. C. Quantification of CD68⁺ macrophages and recruited GFP⁺ cells per high-power field (HPF) in the sinonasal explants across different treatment conditions (n = 5). D. Schematic overview of the eosinophil isolation and transwell migration assay. Primary eosinophils isolated from peripheral blood were cocultured with recombinant human CCL13 (rhCCL13) or supernatants from polarized M ϕ ^{THP-1}, in the presence or absence of PD146176 or a CCR3 antagonist. E. Quantification of eosinophil migration in the transwell system, presented as eosinophil counts per HPF (n = 5). F. Concentrations of eosinophil-derived neurotoxin (EDN) in the bottom chamber supernatants measured by ELISA (n = 4) to assess eosinophil activation. Data are presented as mean $\pm$ SEM. Statistical significance was determined by one-way ANOVA; ns, not significant, ** p < 0.01, *** p < 0.001, **** p < 0.0001.

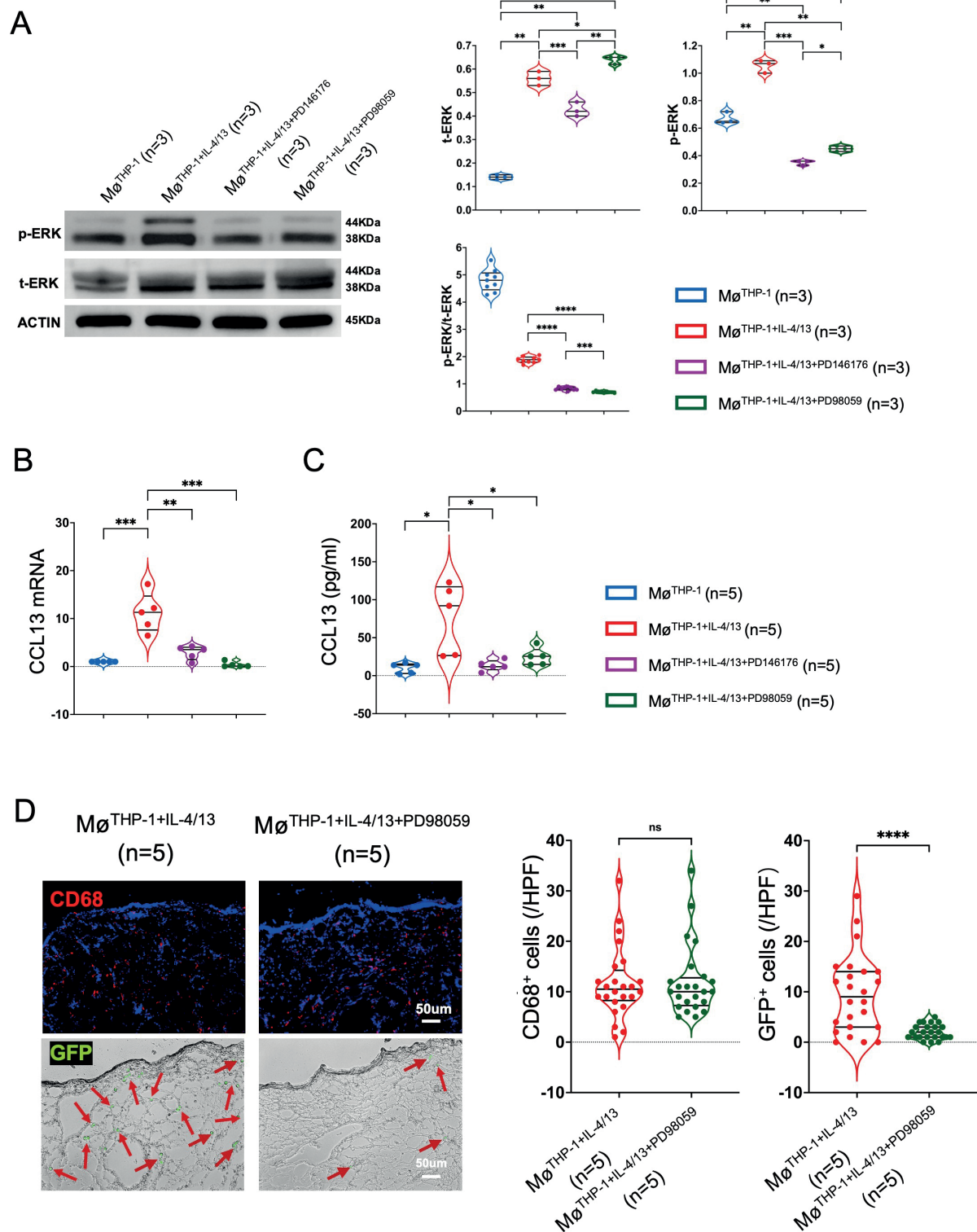


Figure 5. ALOX15-driven ERK activation regulates CCL13 production and eosinophil recruitment by IL-4/IL-13-polarized macrophages. A. Western blot analysis showing ERK expression in $M\phi^{THP-1}$, and $M\phi^{THP-1+IL-4/13}$, with or without pretreatment with PD146176 or PD98059. Phosphorylated ERK (p-ERK) levels were significantly higher in $M\phi^{THP-1+IL-4/13}$ compared to $M\phi^{THP-1}$ and were reduced by either PD146176 or PD98059. Quantification of relative p-ERK levels was shown (right panel) ($n = 3$). B. Real-time PCR analysis of CCL13 mRNA expression in macrophages ($n = 5$). C. ELISA analysis of CCL13 protein levels in the culture supernatants ($n = 5$). D. Immunofluorescence and histological analysis of sinonasal tissues injected with untreated $M\phi^{THP-1+IL-4/13}$ or PD98059-pretreated $M\phi^{THP-1+IL-4/13}$. Quantification of CD68⁺ and GFP⁺ cells per high-power field (HPF) is shown ($n = 5$). ns, not significant; * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$.

2 and 4 demonstrated significant co-expression of both ALOX15 and CCL13, suggesting that ALOX15⁺ macrophages are the principal producers of CCL13 (Figure 2C). Immunofluorescence staining validated these findings, illustrating that CCL13⁺ cells largely co-localized with CD68⁺ ALOX15⁺ macrophages (Figure 2D). The baseline distribution of ALOX15⁺ macrophages in healthy control nasal mucosa has been previously characterized and published by our group ⁽²⁵⁾, establishing their specific enrichment in eCRSwNP. Quantitative analysis confirmed significantly higher proportions of CCL13⁺CD68⁺ macrophages, CCL13⁺ ALOX15⁺CD68⁺ macrophages within total CD68⁺ cells, and CCL13⁺ ALOX15⁺CD68⁺ macrophages within ALOX15⁺CD68⁺ cells in eCRSwNP compared to neCRSwNP (Figure 3E). Collectively, these data indicate that ALOX15⁺ macrophages represent the major cellular source of CCL13 in eCRSwNP.

Spatial transcriptomics reveals a subepithelial ALOX15⁺ macrophage niche linked to CCL13-mediated eosinophil recruitment

To map the in situ immune architecture, we performed GeoMx DSP on tissue sections segmented into epithelial (PanCK⁺), immune-rich (CD45⁺), and eosinophil-rich (ECP⁺) regions of interest (ROIs) (Figure 3A). Comparison of CD45⁺ compartments revealed profound transcriptional heterogeneity: the immune microenvironment of the epithelial area (CRS-EPA) was distinct from the mesenchymal area (CRS-MA), characterized by the upregulation of 583 genes including ALOX15, CCL13, CCL18, and CLC (Figure 3B). Gene Ontology (GO) analysis confirmed that these signatures were predominantly enriched for leukocyte migration and granulocyte chemotaxis, whereas CRS-MA regions favored chromatin organization pathways (Figure 3C).

Consistent with this myeloid-centric profile, macrophage immunoregulatory scores were significantly elevated in the CD45⁺ regions of CRS-EPA compared to both healthy controls and CRS-MA (Figure 3D). This was accompanied by marked overexpression of macrophage-associated markers (ALOX15, CCL13, CCL18, and CCL24) specifically within these subepithelial immune hotspots (Figure 3E).

Crucially, we leveraged spatial co-localization analysis to pinpoint the functional source of eosinophil recruitment. While CCL13, CCL18, and CCL24 were all enriched in CD45⁺ and ECP⁺ niches rather than the epithelium (Figure 3F), only CCL13 expression exhibited a significant positive spatial correlation with local eosinophil density (Figure 3G). This correlation was robustly maintained within the EPA ($r = 0.5607$, $p = 0.037$) but was notably absent in the MA (Figure 3H), indicating a spatially restricted mechanism. In contrast, neither CCL18 nor CCL24 showed significant spatial association with eosinophils despite their global upregulation (Figure S3). These in situ data define a specialized subepithelial niche where ALOX15⁺ macrophages

create a high-CCL13 microenvironment essential for localized eosinophil sequestration.

ALOX15⁺ macrophages drive eosinophil recruitment via the CCL13-CCR3 axis

To validate the functional role of ALOX15⁺ macrophages, we utilized a modified human sinonasal explant model. Tissues injected with IL-4/IL-13-polarized macrophages (M ϕ ^{THP-1+IL-4/13}) triggered a robust infiltration of GFP-tagged EOL-1 eosinophils (Figure 4A-C). To confirm that CCL13 is the sufficient mediator of this process, we treated explants directly with recombinant human CCL13 (rhCCL13). Indeed, rhCCL13 treatment alone recapitulated the profound eosinophil infiltration and activation observed with polarized macrophages (confirmed by MBP staining and GFP quantification; Figure S5). Conversely, pretreatment of macrophages with the ALOX15 inhibitor PD146176 significantly abrogated this recruitment, reducing eosinophil counts to baseline levels (Figure 4B-C).

To mechanistically confirm the signaling pathway, we performed transwell assays using primary human eosinophils. Supernatants from M ϕ ^{THP-1+IL-4/13} induced eosinophil migration and EDN release at levels comparable to rhCCL13. Notably, this chemotactic effect was effectively blocked by either inhibiting ALOX15 production (PD146176) or by treating eosinophils with a CCR3 antagonist (Figure 4D-F). These findings were consistently observed in EOL-1 cells (Figure S4), collectively confirming that ALOX15⁺ macrophages orchestrate eosinophil recruitment through a specific CCL13-CCR3 signaling loop.

ALOX15-dependent ERK signaling governs CCL13 production and eosinophil recruitment

To dissect the intracellular signaling linking ALOX15 to CCL13 production, we first ruled out the NF- κ B pathway, as the inhibitor BAY 11-7082 failed to suppress CCL13 expression (Figure S6). We therefore focused on ERK signaling, a known downstream target of ALOX15. Western blot analysis confirmed that IL-4/IL-13 stimulation induced robust ERK phosphorylation in macrophages. Crucially, this activation was significantly abrogated by either the ALOX15 inhibitor (PD146176) or the ERK inhibitor (PD98059), demonstrating that ERK phosphorylation is ALOX15-dependent (Figure 5A). This signaling axis proved essential for chemokine synthesis: blockade of either ALOX15 or ERK marked suppressed CCL13 levels at both the transcriptional and protein secretion levels (Figure 5B-C). Functionally, in the sinonasal explant model, macrophages pretreated with the ERK inhibitor recruited significantly fewer GFP⁺ eosinophils compared to untreated controls, despite comparable macrophage retention (Figure 5D). Collectively, these data delineate a critical ALOX15-ERK-CCL13 axis governing macrophage-driven eosinophil sequestration.

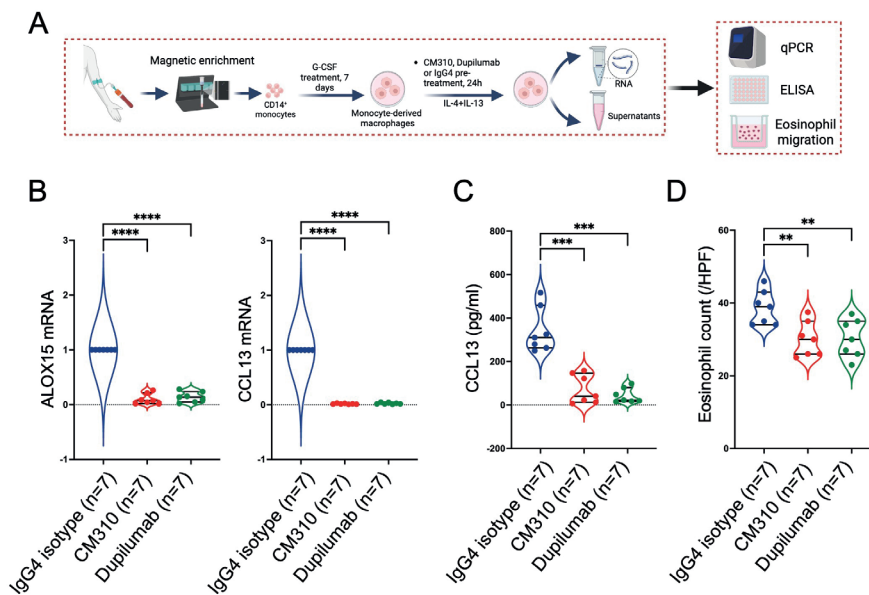


Figure 6. IL-4Ra blockade by Dupilumab or Staphokibart (CM310) prevents IL-4/IL-13-induced macrophage ALOX15 and CCL13 expression and subsequent eosinophil chemotaxis. A. Schematic representation of the experimental workflow. CD14⁺ monocytes were isolated from peripheral blood mononuclear cells (PBMCs) and differentiated into monocyte-derived macrophages using M-CSF for 7 days. Macrophages were pre-treated with CM310, Dupilumab, or an IgG4 isotype control for 24 hours, followed by stimulation with IL-4 and IL-13. B. Relative mRNA expression levels of ALOX15 and CCL13 in macrophages determined by qPCR (n = 7). C. CCL13 protein concentrations in the culture supernatants measured by ELISA (n = 7). D. Eosinophil migration counts per high-power field (HPF) in response to macrophage-derived supernatants, assessed using a transwell chemotaxis assay (n = 7). Data are presented as means $\pm$ SEM from at least three independent experiments. Statistical significance was determined by one-way ANOVA. ** p < 0.01, *** p < 0.001, **** p < 0.0001.

IL-4Ra blockade abrogates the ALOX15-CCL13 axis and attenuates eosinophil recruitment

Given that the ALOX15-CCL13 axis is driven by T2 cytokines, we hypothesized that upstream IL-4Ra blockade could disrupt this pathogenic loop. To validate this, human monocyte-derived macrophages were stimulated with IL-4/IL-13 in the presence of Dupilumab or Staphokibart (CM310). Both biologics significantly abrogated the induction of ALOX15 and CCL13 at both the mRNA and protein levels compared to IgG4 isotype controls, demonstrating comparable inhibitory efficacy (Figure 6A-C). Functionally, this molecular suppression translated into reduced chemotactic potential: supernatants from macrophages treated with either inhibitor induced significantly less eosinophil migration than controls (Figure 6D). These findings provide translational evidence that targeting IL-4Ra effectively collapses the macrophage-driven ALOX15-CCL13 niche, thereby preventing eosinophil sequestration.

Discussion

In this study, we provide a comprehensive characterization of the spatially resolved molecular landscape governing eosinophil recruitment in eCRSwNP. By integrating bulk, single-cell, and spatial transcriptomics, we identified the ALOX15-CCL13 axis as a central molecular determinant of tissue eosinophilia severity.

A key finding of our research is the identification of a unique subepithelial niche where ALOX15⁺ macrophages serve as the primary cellular source of CCL13. We demonstrate that this spatially restricted interaction creates a high-CCL13 microenvironment that is specifically linked to localized eosinophil sequestration in epithelial areas, a correlation that was notably absent in non-eosinophilic regions. Mechanistically, our functional assays using sinonasal explants and primary eosinophils confirmed that ALOX15⁺ macrophages drive eosinophil recruitment and activation through an ERK-dependent CCL13-CCR3 signaling pathway. Finally, we provide translational evidence that IL-4Ra blockade with either Dupilumab or Staphokibart (CM310) effectively suppresses this pathogenic loop. Collectively, these findings advance our understanding of the spatial immunology of nasal polyps and position the subepithelial ALOX15⁺ macrophage niche as a high-value therapeutic target.

A significant portion of existing literature on T2-high airway inflammation emphasizes the airway epithelium as the primary source of eosinophil-recruiting chemokines and cytokines^(9, 33, 38). However, our findings suggest a necessary refinement of this epithelium-centric paradigm in the context of eCRSwNP architecture. By leveraging single-cell RNA sequencing and spatially resolved transcriptomics, we observed that CCL13 is predominantly localized within subepithelial CD45⁺ immune niches and

ECP⁺ eosinophil-rich clusters rather than the PanCK⁺ epithelium. This shift in cellular focus identifies ALOX15⁺ macrophages as the principal orchestrators of the local chemokine gradient within the polyp microenvironment. Furthermore, our data refine the conventional M1/M2 macrophage dichotomy often used to describe T2 inflammation. While total M2 macrophage scores estimated by xCell increased in eosinophilic polyps, they failed to correlate significantly with the actual density of tissue eosinophil infiltration. In contrast, the specific subset of ALOX15⁺ macrophages demonstrated a significant correlation with eosinophil sequestration. This distinction underscores that the functional acquisition of an ALOX15⁺ phenotype is a more pathologically relevant determinant of disease severity than broad, lineage-based macrophage classification. The implementation of GeoMx DSP in this study provides high-resolution insights into the spatial organization of the sinonasal microenvironment, significantly extending the findings of recent single-cell transcriptomic analyses⁽³⁷⁾. By segmenting tissue compartments into PanCK⁺ epithelial and CD45⁺ immune-rich regions, we identified a distinct subepithelial niche that serves as a critical immunological hub in eCRSwNP. Our discovery of ALOX15⁺ macrophages as the central component of this niche builds upon our recent evidence characterizing these cells as drivers of epithelial remodeling via CCL13 secretion⁽²⁵⁾. However, the current study reveals a more direct role for these cells in orchestrating the inflammatory architecture of the polyp⁽¹³⁾. While broad transcriptomic screening and previous spatial studies have mapped the global upregulation of Type 2 chemokines^(13,37), our spatially resolved analysis demonstrates that the architectural context is the primary determinant of eosinophil sequestration. Crucially, although CCL13, CCL18, and CCL24 were all globally elevated in the CD45⁺ regions of CRS-EPA, only CCL13 levels exhibited a significant and specific spatial correlation with local eosinophil density (Figure 3G-H). In contrast, neither CCL18 nor CCL24 showed a significant spatial association with eosinophils despite their significant overall expression (Figure S3), highlighting the specialized functional requirement of a CCL13-rich microenvironment for local eosinophil accumulation. These findings align with emerging concepts of specialized "chemokine niches" in chronic inflammatory diseases and confirm that ALOX15⁺ macrophages in the subepithelial region create a spatially restricted determinant of tissue eosinophilia that is distinct from traditional epithelium-derived signals. Characterization of the ALOX15-ERK-CCL13 axis provides a definitive mechanistic link between subepithelial ALOX15⁺ macrophages and eosinophil accumulation. We found that ALOX15 inhibition significantly abrogates ERK phosphorylation and subsequent CCL13 production, extending our previous work on epithelial remodeling to identify this axis as a potent driver of local eosinophil sequestration. While ERK-mediated chemokine induction is well-established in epithelial cells (e.g., CCL26)⁽⁹⁾,

our study shifts the focus to ALOX15-driven ERK signaling in macrophages as a critical source of CCL13. Functional validation using CCR3 antagonists and sinonasal explants further confirmed that macrophage-derived CCL13 facilitates eosinophil recruitment and activation via the CCR3 receptor. Notably, the unique spatial correlation of CCL13 with eosinophils, which was absent for other CCR3 ligands like CCL18 and CCL24, establishes this subepithelial axis as a specific, spatially restricted determinant of eosinophilic inflammation in eCRSwNP.

While we established the functional role of the macrophage-driven axis using a CCR3 antagonist, it is important to note that CCR3 serves as a receptor for multiple chemokines, including CCL11, CCL13, CCL24, and CCL26⁽³⁹⁾. Ideally, specific neutralization of CCL13 would definitively confirm its necessity. However, our integrated multi-omic analysis provides compelling evidence identifying CCL13 as the primary functional ligand in this specific subepithelial niche. First, our direct tissue injection of recombinant human CCL13 (rhCCL13) fully recapitulated the eosinophil recruitment phenotype (Figure S5), establishing the sufficiency of this chemokine. Second, regarding necessity, our spatial transcriptomic profiling revealed a high degree of specificity: localized expression of CCL13, but not CCL18 or CCL24, significantly correlated with eosinophil density within the subepithelial immune hotspots (Figure 3G-H and Figure S3). Furthermore, scRNA-seq analysis indicated that CCL13 is the predominant CCR3 ligand produced by ALOX15⁺ macrophages, whereas CCL26 is primarily epithelial-derived. Collectively, these data strongly suggest that the abrogation of eosinophil migration by CCR3 blockade in our macrophage co-culture models is attributable to the interruption of CCL13 signaling, identifying it as the critical spatial determinant of eosinophil sequestration in eCRSwNP.

Our findings provide a compelling mechanistic rationale for the clinical efficacy of targeting the IL-4Ra signaling axis in eCRSwNP. We demonstrate that IL-4Ra blockade, using either Dupilumab⁽¹⁷⁾ or the emerging antagonist Stapokibart (CM310)⁽¹⁸⁾, significantly abrogates the IL-4/IL-13-induced upregulation of ALOX15 and CCL13 in human macrophages. Importantly, this molecular inhibition translates into a marked reduction in functional eosinophil chemotaxis, indicating that these biological agents effectively disrupt the macrophage-driven pathogenic loop within the subepithelial niche. The comparable potency of CM310 to Dupilumab in suppressing this signaling axis highlights its potential as a promising therapeutic option for managing T2-high airway inflammation. By specifically deactivating the spatially restricted ALOX15-CCL13 axis, these therapies offer a targeted approach to resolving chronic tissue eosinophilia that extends beyond broad immunosuppression, reinforcing the importance of precision intervention in eCRSwNP.

Despite the novel insights provided by this study, several limitations should be acknowledged. First, while our mechanistic

assays primarily utilized THP-1 derived macrophages and an ex vivo human sinonasal explant model, these findings were corroborated by experiments using primary human monocyte-derived macrophages and validated with in situ spatial transcriptomic data. Second, although we confirmed the necessity of the receptor-ligand interaction using a CCR3 antagonist, the lack of commercially available neutralizing antibodies for human CCL13 with validated blocking efficacy prevented direct ligand neutralization. However, by integrating spatial transcriptomics, which identified CCL13 as the predominant ligand in the ALOX15⁺ niche, with functional assays using recombinant CCL13, we provided converging evidence for the specificity of this axis. Third, a significant technical challenge in the in vivo validation of our findings is the absence of a direct functional ortholog for CCL13 in rodents, which precludes the use of standard murine models of allergic inflammation. To circumvent this, we employed a modified human sinonasal explant model that preserves the native human tissue architecture and cellular diversity. Fourth, while a higher proportion of current smokers was present in the severe eCRSwNP cohort, our in vitro data establish that the ALOX15-CCL13 axis is strictly dependent on canonical Type 2 cytokines (IL-4/IL-13), minimizing the likelihood of smoking-induced confounding. Future research utilizing humanized mouse models^(40, 41) or advanced microfluidic "organ-on-a-chip" technologies^(42, 43) may offer more complex platforms to evaluate the long-term systemic and local effects of the ALOX15-CCL13-eosinophil axis.

Conclusion

Our study identifies the subepithelial ALOX15⁺ macrophage

niche as a pivotal spatial determinant of eosinophil recruitment and activation in eCRSwNP. By demonstrating that the ALOX15-ERK-CCL13 signaling axis is effectively targeted by IL-4Ra blockade with agents like Stapokibart (CM310), we provide a strong mechanistic rationale for precision therapeutic strategies in T2-high airway inflammation.

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Author contributions

YC, CL, KW and WL participated in tissue sample collection and performed RNA-Seq experiments and histology and immunostaining. YC performed cell experiments. YC, CL, WL and YS analyzed data. YC, JS, WW, and YS participated in data discussions and study design. YC and YS prepared the manuscript.

Conflict of interest

All authors declare no financial or commercial conflicts of interest.

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SUPPLEMENTARY MATERIAL

Materials and Methods**Subjects and sample collection**

Adult patients (aged 18–65 years) undergoing endoscopic sinus surgery for CRSwNP at the Seventh Affiliated Hospital of Sun Yat-sen University were enrolled. The study protocol was approved by the Institutional Ethics Committee, and written informed consent was obtained from all participants. CRSwNP was diagnosed according to the European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS) 2020 guidelines⁽¹⁾. Exclusion criteria included acute asthma exacerbation or upper respiratory tract infection within four weeks preoperatively, and comorbid conditions such as antrochoanal polyps, cystic fibrosis, primary ciliary dyskinesia, fungal sinusitis, immunodeficiency, or systemic vasculitis. Patients receiving immunotherapy, oral glucocorticoids within three months, or intranasal glucocorticoids/antileukotrienes within two weeks prior to surgery were also excluded. Nasal polyp tissues were obtained from CRSwNP patients during surgery. For bulk RNA sequencing, a cohort of 30 CRSwNP patients was selected and stratified based on a gradient of tissue eosinophilia to capture the spectrum of type 2 inflammation. Transcriptomic data for healthy controls (n=10) were retrieved from a public database⁽²⁾. For histological and functional assays (explant cultures and migration assays), control middle turbinate mucosa was collected from separate participants (n=12) undergoing septoplasty for nasal septal deviation, excluding those with rhinitis or sinusitis. Demographic data are detailed in Table S1.

Clinical assessment

At baseline, atopic status was determined by specific IgE assays (HOB Biotech Group, Suzhou, China) for common local inhalant allergens; a concentration >0.35 IU/mL was defined as positive. Allergic rhinitis (AR) and asthma were diagnosed according to the ARIA guidelines (2016 revision)⁽³⁾ and the current Global Initiative for Asthma (GINA) guidelines⁽⁴⁾, respectively. Peripheral blood eosinophil counts were quantified via complete blood count (CBC) prior to surgery. Disease severity was evaluated using the modified Lund-Kennedy (L-K) endoscopic score (range: 0–12)⁽⁵⁾ and the Lund-Mackay (L-M) CT score (range: 0–24)⁽⁶⁾. Subjective symptom burden was assessed using the 22-item Sinonasal Outcome Test (SNOT-22), with each item scored from 0 to 5⁽⁷⁾.

Histopathologic evaluation

Surgically resected nasal polyp tissues were fixed in 10% neutral buffered formalin, embedded in paraffin, and sectioned at 4 µm thickness. Sections were stained with hematoxylin and eosin

(H&E). For quantitative analysis, five high-power fields (HPF, ×400) exhibiting the densest cellular infiltration within the subepithelial layer were selected. Histopathological parameters were evaluated as previously described⁽⁸⁾, including goblet cell hyperplasia, squamous metaplasia, basement membrane thickening, subepithelial edema, fibrosis, and inflammatory cell counts. Eosinophil counts were quantified as the absolute number per HPF. Epithelial hyperplasia was assessed by measuring the vertical thickness of the epithelium (averaged from five random points per HPF) at 200× magnification.

Bulk RNA sequencing analysis

Total RNA was extracted from fresh nasal polyp tissues using TRIzol reagent (Invitrogen, Carlsbad, CA, USA) and integrity was verified using the Agilent 2100 Bioanalyzer (Agilent Technologies, Santa Clara, CA, USA). Libraries were sequenced on the Illumina NovaSeq 6000 platform. Raw reads were quality-filtered using FastQC and aligned to the human reference genome (GRCh38/HG38) using HISAT2. Differential expression analysis was performed using the DESeq2 R package (v1.42.0), with significance defined as an adjusted $p < 0.05$ and $|\log_2(\text{fold change})| \geq 0.585$. To estimate the cellular composition of the tumor microenvironment, immune cell deconvolution was performed using the xCell algorithm (<https://xcell.ucsf.edu/>), which infers the relative abundance of immune cell types based on gene signature enrichment.

Immunofluorescent staining

Multiplex immunofluorescence was performed using a tyramide signal amplification (TSA) strategy as previously described⁽⁹⁾. Briefly, paraffin-embedded sections were deparaffinized, and antigen retrieval was performed in citrate buffer (pH 6.0) via microwave heating. The staining involved three sequential rounds of labeling. In each round, sections were incubated with a primary antibody overnight at 4°C, followed by a corresponding HRP-conjugated secondary antibody (50 min, RT) and a specific TSA-fluorophore substrate (10 min, RT). Between rounds, antibody stripping was achieved by microwave heating in citrate buffer.

The following primary antibodies were used: anti-CD68 (1:400, Servicebio, Wuhan, China), anti-CD163 (1:400, Servicebio, Wuhan, China), anti-ALOX15 (1:400, Abcam, Cambridge, UK), and anti-CCL13 (1:200, Santa Cruz Biotechnology, Dallas, TX, USA). For single-plex staining, anti-MBP (1:200, OriGene, Rockville, MD, USA) was used. Nuclei were counterstained with DAPI. Images were acquired using an automatic slide scanner (Pannoramic MIDI, 3DHISTECH). Quantitative analysis was performed on five

randomly selected high-power fields (HPF, $\times 400$) representing the densest inflammatory regions.

Single-cell RNA-sequencing analysis

We re-analyzed a previously published scRNA-seq dataset of CRSwNP samples⁽¹⁰⁾, specifically focusing on the macrophage compartment. Quality control, data normalization, and dimensionality reduction (UMAP) were performed as described in our prior work⁽⁹⁾. Cell clustering was conducted using the Seurat R package (v4.0). Macrophage subclusters, defined by robust CD68 and CD163 expression, were isolated and re-clustered. This yielded 12 distinct subgroups, which were annotated based on canonical lineage markers. Statistical analyses were conducted using R (version 4.2.0), and graphical plots were generated using Scanpy (Python), ggplot2 (v3.4.0), or custom scripts.

Spatial transcriptomics profiling and analysis

Spatial transcriptomic profiling was performed using the NanoString GeoMx[®] Digital Spatial Profiler (NanoString Technologies, Seattle, WA, USA) as previously described⁽⁹⁾. Tissue microarrays (TMAs) were constructed using nasal polyp tissues from eCRSwNP patients (n=5) and control subjects (n=3). Slides were prepared according to the GeoMx[®] DSP Manual (MAN-10087-04). Following deparaffinization and antigen retrieval, slides were hybridized with the Whole Transcriptome Atlas (WTA) probe mix, which targets >18,000 human protein-coding genes conjugated to photocleavable oligonucleotide barcodes. To guide the selection of regions of interest (ROIs), slides were stained with fluorescent morphology markers: anti-CD45 (Cat# ab30470, Abcam) for immune cells, anti-PanCK (Cat# ab7753, Abcam) for epithelium, anti-ECP (Cat# 55338-1-AP, Proteintech) for eosinophils, and DAPI (Cat# D1306, ThermoFisher) for nuclei. To quantitatively define the subepithelial niche prior to ROI selection, distance-to-basal lamina analysis was performed on multiplex immunofluorescence images. The basal lamina was demarcated based on PanCK staining, and the subepithelial niche was morphometrically defined as the stromal region within 200 μ m of this interface. This definition strictly guided the segmentation of ROIs for GeoMx DSP, ensuring that the CRS-EPA ROIs accurately captured this specific microenvironment. Based on immunofluorescent visualization, specific ROIs were segmented into epithelial (PanCK⁺) and immune-enriched (CD45⁺) compartments. UV light was projected onto the selected areas to photocleave the oligonucleotide barcodes from the hybridized RNA probes. The released barcodes were micro-aspirated, indexed, and amplified via PCR. Libraries were purified and sequenced on the Illumina NovaSeq 6000 system. Raw counts were processed, quality-controlled, and normalized (Q3 normalization) using the GeoMx DSP Analysis Suite. To characterize transcriptional heterogeneity within the CD45⁺ compartment, differential expression analysis between the epithelial

area (EPA) and mesenchymal area (MA) was performed using a linear mixed model (LMM) or the edgeR R package (v4.0.5). Differentially expressed genes (DEGs) were identified based on a p-value < 0.05 and $|\log_2(\text{fold change})| \geq 0.585$. Functional enrichment analysis was conducted using the clusterProfiler package (v4.10.1). Gene Ontology (GO) terms with a Benjamini-Hochberg (BH) adjusted p-value < 0.05 were considered significantly enriched.

To assess the functional phenotype of macrophages within spatial niches, we curated a "Macrophage Immunoregulatory" gene signature based on previous studies⁽⁹⁻¹¹⁾ (gene list provided in Table S7). Region-specific enrichment scores for this signature were calculated using the Gene Set Variation Analysis (GSVA) algorithm (R package v1.50.0), allowing for the quantification of pathway activity in each spatially resolved ROI.

Isolation and differentiation of human monocyte-derived macrophages

Peripheral blood mononuclear cells (PBMCs) were isolated from fresh human peripheral blood mixed 1:1 with HBSS via density gradient centrifugation using Lymphocyte Separation Medium (MP Biomedicals). Following erythrocyte lysis (Invitrogen), CD14⁺ monocytes were purified using anti-human CD14 MicroBeads and LS columns (Milenyi Biotec) according to the manufacturer's protocol. The purity of the isolated CD14⁺ fraction was confirmed prior to seeding. Monocytes were plated at a density of 5×10^5 cells/well in 12-well plates and cultured in RPMI-1640 supplemented with 10% FBS, 1% penicillin-streptomycin, and 50 ng/mL recombinant human M-CSF (Proteintech) for 7 days to promote differentiation into resting macrophages (M0).

THP-1 cell culture and differentiation

The human monocytic cell line THP-1 (Procell, China) was maintained in complete RPMI-1640 medium at 37°C with 5% CO₂. Differentiation into M0 macrophages (M0^{THP-1}) was induced by incubation with phorbol 12-myristate 13-acetate (PMA) for 24 hours. Adherent cells were washed with PBS to remove non-adherent cells before subsequent polarization or treatment.

Macrophage polarization and pharmacological intervention

To induce type 2 polarization, both human monocyte-derived macrophages (HMDMs) and M0^{THP-1} were stimulated with recombinant human IL-4 (20 ng/mL) and IL-13 (20 ng/mL) (Proteintech) for 24 hours⁽¹²⁻¹⁴⁾. For mechanistic studies involving pharmacological inhibitors or neutralizing antibodies, a sequential treatment protocol was employed: HMDMs (IL-4R α blockade): Matured HMDMs were pretreated with the IL-4R α -targeting antibodies Stapokibart (CM310) (100 nM, AmBeed) or Dupilumab (100 nM, AmBeed), or an isotype control Human IgG4 (100 nM, Sino Biological), for 24 hours prior to cytokine stimulation (15,16). THP-1 (Signal Transduction Inhibition): M0^{THP-1}

cells were pretreated with the ALOX15 inhibitor PD146176 (10 μ M, Sigma) or the ERK inhibitor PD98059 (20 μ M, AmBeed) for 24 hours before cytokine addition. Following the inhibitor pretreatment (24 h) and subsequent cytokine stimulation (24 h), the culture medium was aspirated. Cells were washed with PBS and replenished with fresh cytokine-free RPMI-1640 medium. Conditioned supernatants were collected after an additional 48 hours of culture, centrifuged at $1,000 \times g$ for 10 minutes to remove debris, and stored at -80°C for ELISA quantification of CCL13 and eosinophil migration assays. Simultaneously, cells were harvested using Accutase (Gibco) for protein analysis or lysed directly for RNA extraction and qRT-PCR.

Lentiviral transduction of EOL-1 cells

The human eosinophilic leukemia cell line EOL-1 (FuHeng Biology, Shanghai, China) was maintained in RPMI-1640 medium supplemented with 10% FBS and 1% penicillin/streptomycin. To enable fluorescent tracking, EOL-1 cells were transduced with GFP-encoding lentiviral particles (Vector: VSVG-L7066-R; Titer: 1×10^8 TU/mL; Taitool Bioscience, Shanghai, China). Briefly, cells were seeded in 24-well plates at a density of 5×10^5 cells/mL and incubated with the viral suspension in the presence of polybrene (5 μ g/mL) to enhance infection efficiency. Transduction efficiency was monitored via fluorescence microscopy after 24–48 hours. Cultures exhibiting $>80\%$ GFP positivity and robust viability were expanded for downstream assays.

Isolation of primary human eosinophils

Peripheral blood eosinophils were isolated from fresh whole blood using the Eosinophil Isolation Kit (Miltenyi Biotec, San Diego, CA, USA) via a negative selection strategy. Briefly, granulocytes were enriched by density gradient centrifugation using Lymphocyte Separation Medium (MP Biomedicals). The granulocyte/RBC pellet was collected, and erythrocytes were sedimented using 3% dextran followed by hypotonic lysis (Invitrogen). The remaining granulocytes were incubated with a Biotin-Antibody Cocktail targeting non-eosinophils, followed by Anti-Biotin MicroBeads. Eosinophils were purified by passing the cell suspension through magnetic columns to deplete magnetically labeled non-eosinophils. The high-purity eosinophils in the flow-through were collected and resuspended in complete RPMI-1640 medium for immediate use.

Ex vivo eosinophil recruitment assay (human sinonasal explant model)

A human sinonasal explant model was established to evaluate tissue-specific eosinophil recruitment^(17–22). Middle turbinate mucosa was obtained from healthy controls, washed with PBS containing antibiotics and amphotericin B, and dissected into standardized fragments (approx. 0.1 g). To assess macrophage-

driven recruitment, tissue fragments were micro-injected with 10 μ l of either rhCCL13 (10 μ g/mL) or concentrated suspensions (5×10^6 cells/mL) of macrophages ($\text{M}\phi^{\text{THP-1}}$) subjected to different polarization or inhibitor treatments (IL-4/IL-13, PD146176, or PD98059). The injected tissues were submerged in culture medium containing GFP-tagged EOL-1 cells (1×10^5 cells/well) and co-cultured for 24 hours.

Following incubation, tissues were harvested, embedded in OCT compound, and cryosectioned at 4 μ m. Eosinophil infiltration was quantified by counting GFP-positive cells within the tissue stroma using fluorescence microscopy (Excitation: 490 nm; Emission: 525 nm). Data were analyzed from the five densest regions per section at 400 $\times$ magnification.

Transwell migration assay

Chemotaxis assays were performed using 24-well Transwell chambers with 8- μ m pore size inserts (BD Biosciences) (20,21,23,24). EOL-1 cells or primary eosinophils (1×10^5 cells in 200 μ l) were seeded into the upper chamber. The lower chamber was filled with 500 μ l of RPMI-1640 containing potential chemoattractants: rhCCL13 (100 ng/mL) or cell-free supernatants from polarized/treated macrophages. For receptor blocking experiments, a CCR3 antagonist (100 μ M, AmBeed) was added to the upper chamber. After 24 hours of incubation at 37°C , migrated cells in the lower chamber were collected and counted. Additionally, Eosinophil-Derived Neurotoxin (EDN) levels in the lower chamber supernatant were quantified by ELISA as a marker of eosinophil activation.

RNA extraction and quantitative real-time PCR

Total RNA was extracted from cultured macrophages using the Total RNA Extraction Kit (Fastgene, Shanghai, China). RNA concentration and purity were verified using a NanoDrop 2000 spectrophotometer (Thermo Fisher Scientific). Complementary DNA (cDNA) was synthesized from 500 ng of total RNA using the PrimeScript™ RT Master Mix (Takara, Japan). qRT-PCR was performed on a Roche LightCycler 480 system (Roche, Basel, Switzerland) using SYBR Premix Ex Taq (Takara). The reaction mixture contained cDNA equivalent to 10 ng of total RNA. Relative gene expression was calculated using the $\Delta\Delta\text{CT}$ method, normalized to the housekeeping gene 18S rRNA. Primer sequences are listed in Table S6.

Enzyme-Linked Immunosorbent Assay (ELISA)

The concentrations of secreted EDN and CCL13 in cell-free culture supernatants were quantified using commercial ELISA kits (EDN: Cloud-Clone Corp, TX, USA; CCL13: Boster, Wuhan, China) according to the manufacturers' instructions. The lower limits of detection were 0.312 ng/mL for EDN and 7.8 pg/mL for CCL13. Absorbance was measured at 450 nm using a microplate reader.

Western blot analysis

Cells were harvested and lysed in RIPA buffer (Servicebio, Wuhan, China) supplemented with both protease and phosphatase inhibitor cocktails to preserve protein phosphorylation. Protein concentration was quantified using a BCA Assay Kit (Servicebio). Denatured protein samples (30 µg) were resolved by 4-12% SDS-PAGE and transferred onto PVDF membranes (Servicebio) using a wet transfer system (300 mA, 30 min). Membranes were blocked with 5% non-fat dry milk for 30 min at room temperature and incubated overnight at 4°C with primary antibodies against p-ERK (1:1000, Abcam), t-ERK (1:1000, Proteintech), and β-actin (1:2000, Servicebio). After incubation with HRP-conjugated secondary antibodies, protein bands were visualized via an enhanced chemiluminescence (ECL) system and analyzed using AIWBwell™ software.

Statistical analysis

Statistical analyses were performed using SPSS version 26.0 (IBM Corp., Armonk, NY, USA). The normality of data distribution was assessed using the Shapiro-Wilk test. Continuous variables are presented as mean ± standard deviation (SD) for normally distributed data or median with interquartile range (IQR) for non-normally distributed data. Comparisons between two groups were determined by the Student's t-test or the Mann-Whitney U test. For comparisons involving three or more groups, one-way analysis of variance (ANOVA) with Bonferroni post hoc test or the Kruskal-Wallis test followed by Dunn's post hoc test was utilized. Correlations were evaluated using Spearman's rank correlation coefficient. A P-value < 0.05 was considered statistically significant.

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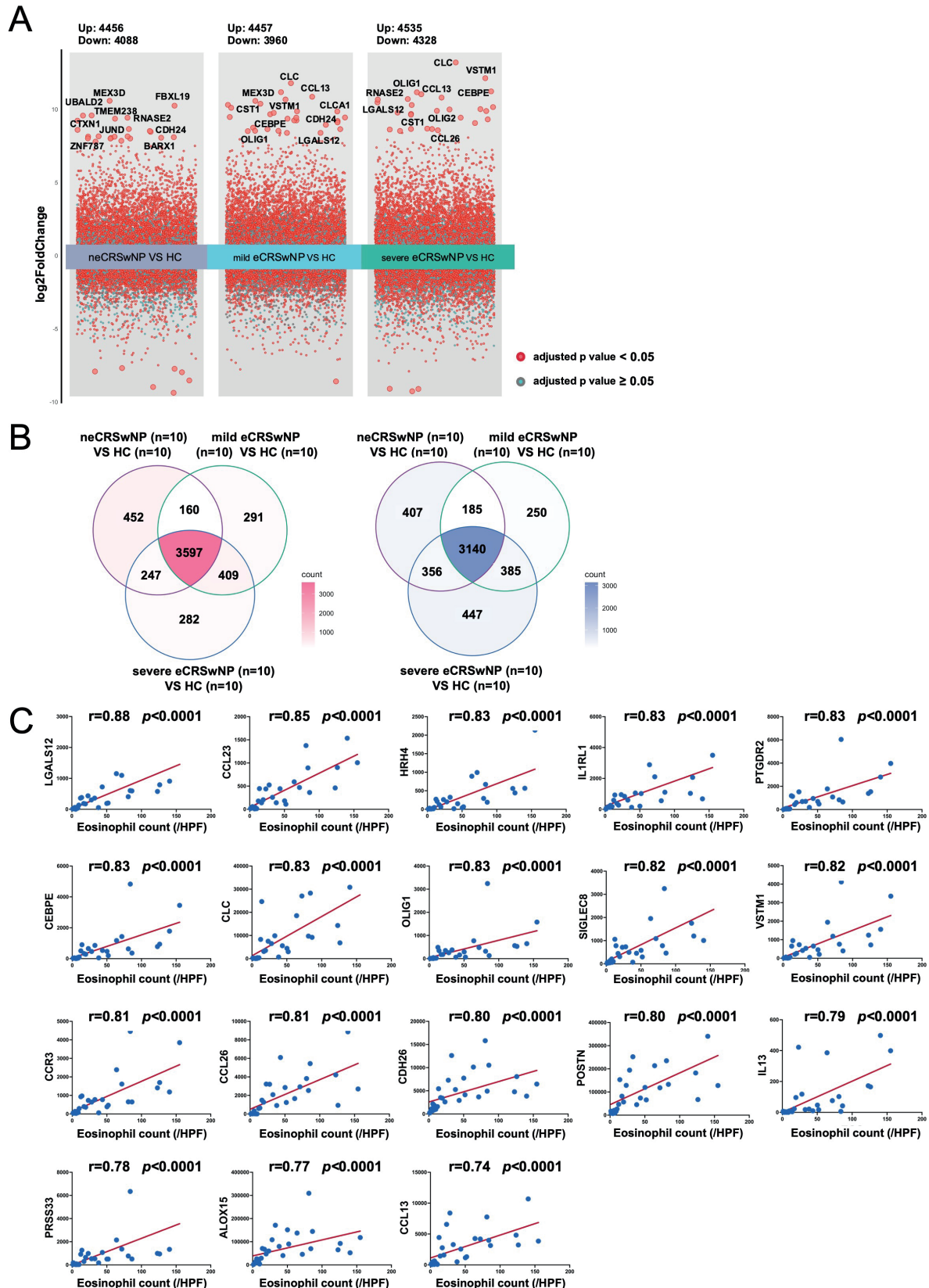


Figure S1. Transcriptomic analysis of CRSwNP stratified by different degree of eosinophil infiltration. A. The volcano plots display DEGs in neCRSwNP (n = 10), mild eCRSwNP (n = 10), and severe eCRSwNP (n = 10) compared to healthy controls (n = 10). B. The Venn diagrams show the numbers of overlapping and unique upregulated (left panel) and downregulated (right panel) DEGs across the three groups compared to healthy controls. C. Scatter plots show the correlation between tissue eosinophil counts and the expression of 18 DEGs that overlap with the 36 canonical T2 biomarker genes in CRSwNP (n = 30).

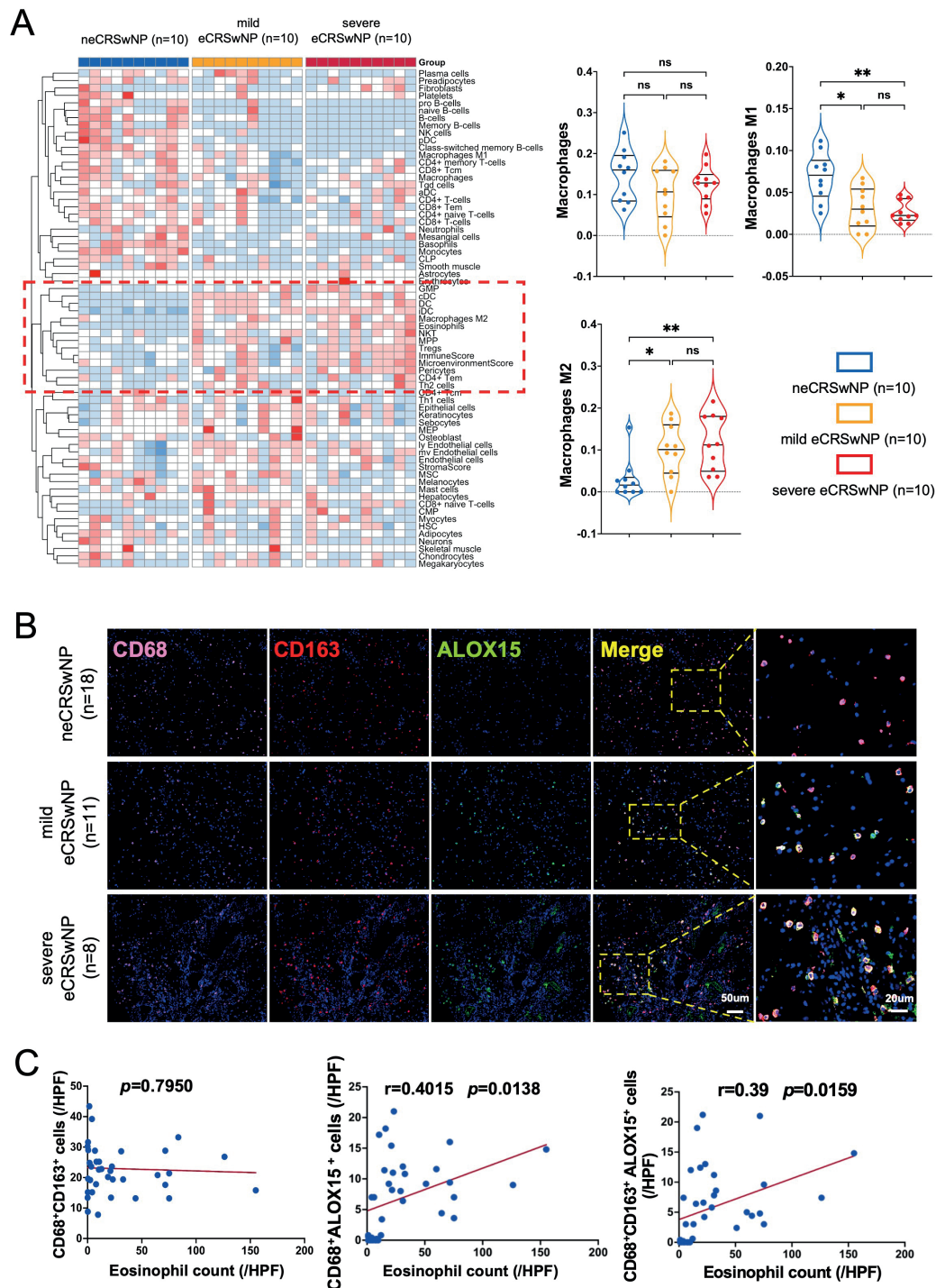
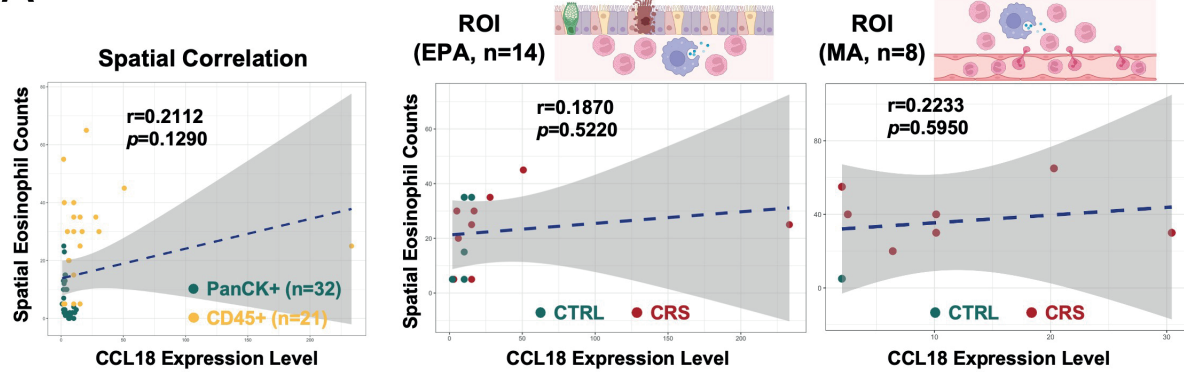


Figure S2. Cellular composition analysis reveals enrichment of ALOX15+ macrophages in severe eCRSwNP. A. Heatmap displaying the relative abundance of cell types inferred from bulk tissue transcriptomic profiling using the xCell tool across groups of neCRSwNP (n = 10), mild eCRSwNP (n = 10), and severe eCRSwNP (n = 10). Samples are grouped on the x-axis based on the degree of tissue eosinophil infiltration (neCRSwNP: <10/HPF; mild: 10–50/HPF; severe: >50/HPF), and cell types are hierarchically clustered on the y-axis. The red dashed box highlights the enrichment cluster containing eosinophils and macrophages. Violin plots to the right quantify the relative abundance scores of total macrophages, M1 macrophages, and M2 macrophages across the three groups. B. Representative immunofluorescence images showing macrophage phenotypes in nasal polyp tissues. Sections were co-stained for pan-macrophage marker CD68 (magenta), M2 marker CD163 (red), and ALOX15 (green). Nuclei were counterstained with DAPI (blue). Yellow dashed boxes indicate regions shown at higher magnification in the rightmost panels. Colocalization of CD68, CD163, and ALOX15 indicates ALOX15+ M2 macrophages. Scale bars: 50 μ m (main images) and 20 μ m (insets). C. Correlation analyses between tissue eosinophil counts (/HPF) and the quantified numbers of CD68+CD163+ (left panel), CD68+ALOX15+ (middle panel), and CD68+CD163+ALOX15+ triple-positive cells (right panel) per HPF (n = 37 total samples). Data in violin plots are presented as mean $\pm$ SEM. Statistical significance was determined by one-way ANOVA (for A) or correlation analysis (for C). The correlation coefficient (r) and p-value are indicated in the scatter plots. ns, not significant, *p < 0.05, **p < 0.01.

A



B

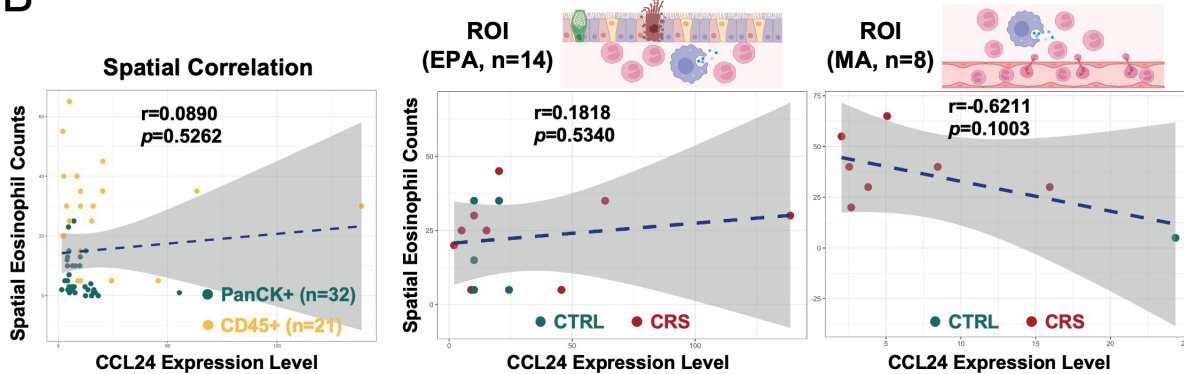


Figure S3. Spatial correlation analysis of CCL18 and CCL24 expression with local eosinophil counts. A. Spatial correlation between CCL18 expression levels and local eosinophil counts. Left: correlation across all ROIs ($n = 53$); Middle and Right: correlation within specific sub-compartments (EPA, $n = 14$; MA, $n = 8$). No significant correlation was observed ($p > 0.05$). B. Spatial correlation between CCL24 expression levels and local eosinophil counts. Scatter plots indicate that local CCL24 expression does not significantly correlate with the spatial density of eosinophils in either EPA or MA regions. Data are presented as Pearson's correlation coefficients (r) and corresponding p -values.

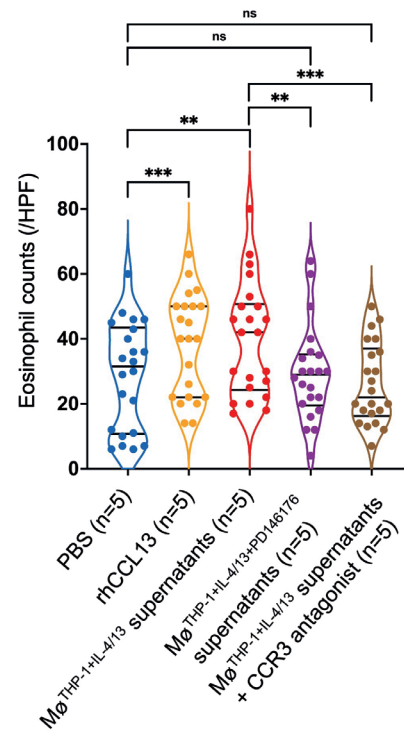


Figure S4. ALOX15+ macrophages induce Eol-1 migration through CCR3 signaling. Eol-1 cells were cocultured in a transwell system with supernatants derived from MøTHP-1+IL-4/13, with and without PD146176 pretreatment, and in the presence or absence of CCR3 antagonist. Quantification of Eol-1 migration across conditions, presented as eosinophil counts per high-power field (HPF) (n = 5). ns, not significant. **p < 0.01, ***p < 0.001.

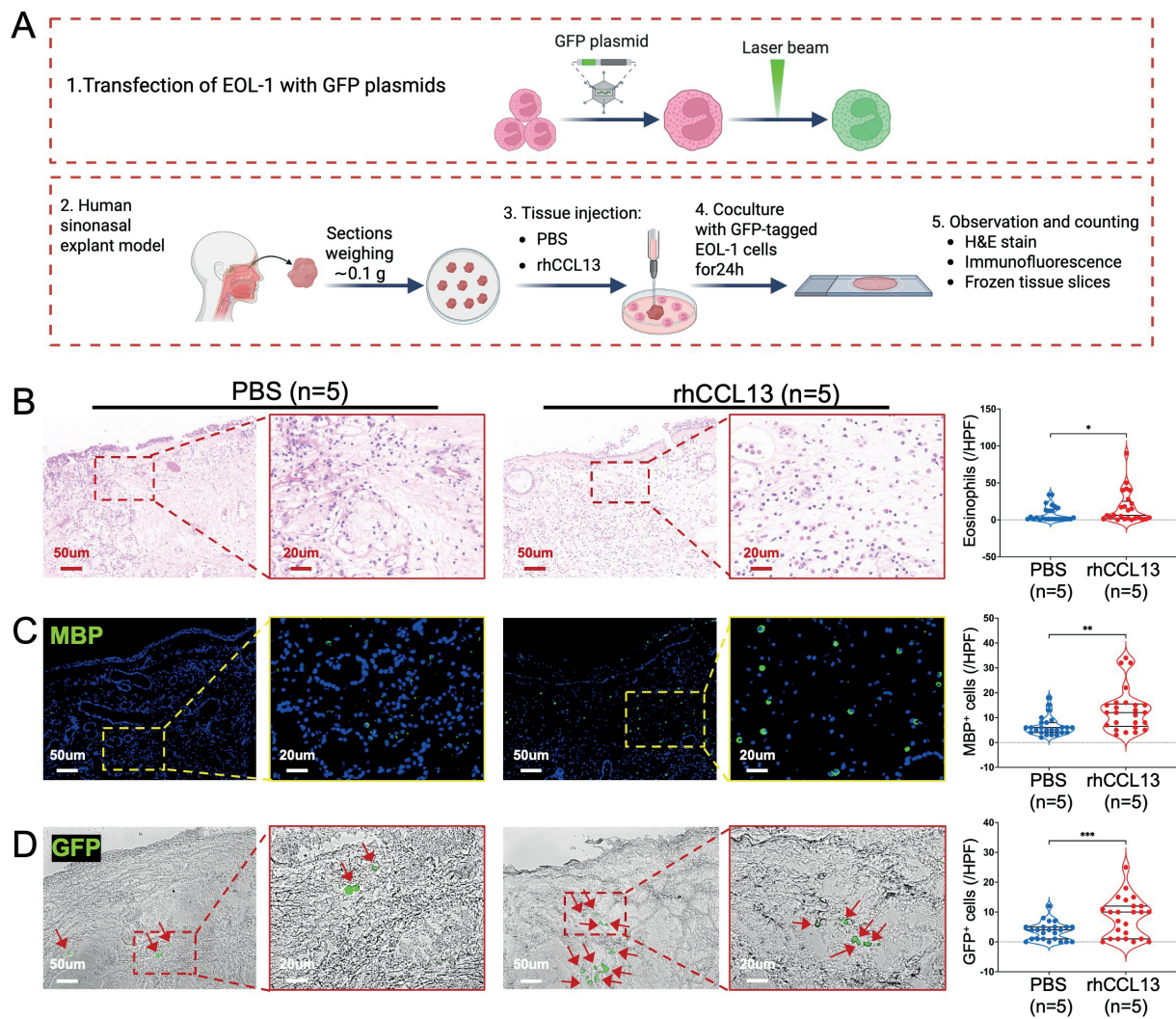


Figure S5. CCL13 induces eosinophil migration into nasal mucosa. A. Schematic diagram illustrating the experimental model used for eosinophil recruitment into nasal mucosal tissues. EOL-1 cells were transfected with GFP plasmids and cocultured with sinus mucosal tissue after tissue injection with PBS or recombinant human CCL13 (rhCCL13). Scheme was created in BioRender. B-D. Representative images of nasal mucosa stained with H&E (B), immunofluorescence for major basic protein (MBP) (C), and GFP fluorescence (D) to visualize EOL-1 cells. Quantitative analysis for each staining method is shown on the right (n = 5). Red arrows indicate GFP-positive EOL-1 cells in panel D.

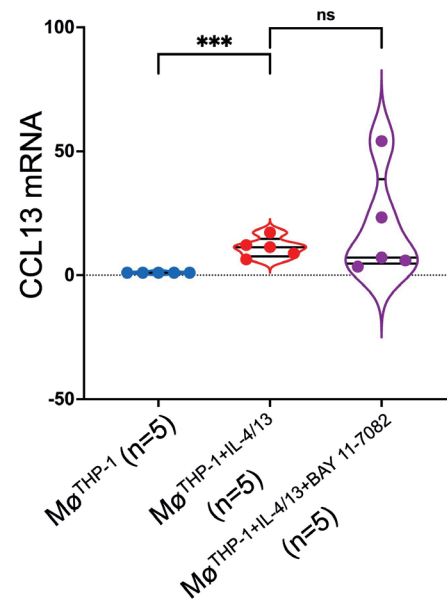


Figure S6. CCL13 mRNA expression in Mø^{THP-1} and Mø^{THP-1}+IL-4/13, with or without pretreatment using the NF-κB inhibitor BAY 11-7082. n = 5. ns, not significant. ***p < 0.001.

Table S1. Characteristics of CRSwNP subjects used for bulk RNA-Seq analysis.

	neCRSwNP	Mild eCRSwNP	Severe eCRSwNP	P
Subject, n	10	10	10	
Male, n (%)	7(70.0%)	6(60.0%)	6(60.0%)	0.639, 0.639, 1.000
Age, mean (SD)	40.2(22.6)	37.4(6.4)	36.3(10.3)	0.770, 0.853, 0.631
Current smoker, n (%)	2(20.0%)	0(0%)	4(40.0%)	0.136, 0.329, 0.025
Allergic rhinitis, n (%)	2(20.0%)	4(40.0%)	6(60.0%)	0.329, 0.068, 0.371
Asthma, n (%)	2(20.0%)	2(20.0%)	3(30.0%)	1.000, 0.606, 0.606
N-ERD, n (%)	0(0%)	0(0%)	0(0%)	-
Prior sinus surgery, n (%)	0(0%)	2(20.0%)	2(20.0%)	0.136, 0.136, 1.000
Pre-operative L-K endoscopic score, median (IQR)	9.5(2.5)	8.0(3.8)	10.0(4.8)	0.448, 0.579, 0.436
Pre-operative L-M CT score, median (IQR)	17.0(10.5)	16.5(4.5)	19.0(9.3)	0.796, 0.393, 0.315
Pre-operative SNOT-22, median (IQR)	23.0(26.8)	32.0(33.5)	41.0(26.3)	0.370, 0.237, 0.780
Decreased sense of smell/taste item of SNOT-22 (IQR)	1.0(2.0)	5.0(2.25)	4.0(1.5)	0.000, 0.003, 0.999
Blood eosinophil count, median (IQR) ($\times 10^9/L$)	0.15(0.23)	0.47(0.33)	0.37(0.45)	0.001, 0.005, 0.853
Blood eosinophil percentage, median (IQR) (%)	2.3(2.73)	7.7(2.60)	5.65(6.18)	0.000, 0.002, 0.280

The last column shows the p-values for comparisons between mild eCRSwNP vs. neCRSwNP, severe eCRSwNP vs. neCRSwNP, and severe eCRSwNP vs. mild eCRSwNP, respectively. Pairwise comparisons were performed using the Mann-Whitney U test with Bonferroni correction. Results in boldface indicate a p value of less than 0.05. EOS, eosinophil; SD, standard deviation; IQR, interquartile range; N-ERD, NSAID-exacerbated respiratory disease; L-K, Lund Kennedy; L-M, Lund Mackay; CT, computed tomography; SNOT-22, Sino-nasal Outcome Test-22.

Table S2. Histopathological analysis of CRSwNP used for bulk RNA-Seq analysis.

	neCRSwNP	Mild eCRSwNP	Severe eCRSwNP	P
Subject, n (%)	10	10	10	
Epithelial hyperplasia, median (IQR) (μm)	148.8(95.9)	92.7(95.4)	88.0(97.9)	0.101, 0.129, 0.943
Goblet cell hyperplasia, median (IQR)/(HPF)	0(0.5)	16(44.0)	28.0(33.5)	0.055, 0.005 , 0.343
Squamous metaplasia, median (IQR)	0(0.0)	0(0.2)	0(0.9)	0.601, 0.440, 0.639
Basement membrane thickening, median (IQR)	1.0(0.4)	1.7(1.7)	1.7(0.8)	0.089, 0.009 , 0.912
Total number of inflammatory cells, median (IQR) (/HPF)	96.7(93.3)	84.4(61.9)	134.5(94.9)	0.631, 0.143, 0.043
Subepithelial edema, median (IQR)	3.0(0.4)	2.9(0.8)	3.0(0.1)	0.684, 0.579, 0.315
Gland number, median (IQR) (/HPF)	5.3(4.2)	5.4(6.1)	1.9(5.3)	0.853, 0.063, 0.123
Fibrosis, median (IQR)	1.4(0.7)	1.7(1.1)	1.2(0.4)	0.684, 0.280, 0.247

The last column shows the p-values for comparisons between mild eCRSwNP vs. neCRSwNP, severe eCRSwNP vs. neCRSwNP, and severe eCRSwNP vs. mild eCRSwNP, respectively. Pairwise comparisons were performed using the Mann-Whitney U test with Bonferroni correction. Results in boldface indicate a p value of less than 0.05. EOS, eosinophil; SD, standard deviation; IQR, interquartile range; HPF, high power field.

Table S3. Top300 upregulated and downregulated DEGs in neCRSwNP versus healthy controls.

gene	log2FoldChange	padj	group	gene	log2FoldChange	padj	group
MEX3D	9.904683861	2.89E-44	up	PRSS48	-8.778012516	1.44E-23	down
FBXL19	9.59480498	3.30E-44	up	GPR22	-8.408528798	9.88E-31	down
UBALD2	8.970541824	4.50E-62	up	TYR	-7.986665867	2.66E-07	down
TMEM238	8.961559706	4.82E-22	up	SMIM18	-7.462616855	9.49E-29	down
CTXN1	8.82607193	1.59E-30	up	RPA4	-7.412126421	2.07E-06	down
ZNF787	8.763287804	1.55E-54	up	POU5F2	-7.242279257	4.57E-44	down
JUND	8.636943283	1.30E-67	up	RNF113B	-7.195948858	1.30E-09	down
RNASE2	8.10158902	1.78E-22	up	ANKRD62	-7.011692699	0.000126191	down
BARX1	8.045689875	3.80E-20	up	PSG11	-6.827349777	0.011534039	down
CITED4	7.976261348	2.02E-32	up	HIST1H4C	-6.656872941	2.79E-14	down
CDH24	7.921068126	8.31E-34	up	PRR4	-6.591133373	6.18E-13	down
ZBTB12	7.633779263	3.02E-28	up	PSG1	-6.546786899	0.001535632	down
MEPCE	7.628361037	2.94E-39	up	OR51I1	-6.353333109	3.85E-05	down
BRSK1	7.61681376	1.26E-27	up	OR1Q1	-6.282794595	0.000233811	down
NXPH4	7.609312241	5.00E-20	up	CRISP3	-6.282271183	7.59E-10	down
IER5L	7.577643286	3.84E-33	up	MYH2	-6.236939544	0.026412179	down
SHANK1	7.544833271	1.32E-22	up	BLID	-6.233116557	0.000342185	down
CARMIL2	7.537014081	3.38E-45	up	PSG7	-6.093650212	0.034490542	down
TMEM158	7.503704632	1.93E-18	up	HIST2H4A	-6.089045751	3.97E-12	down
ADRA2C	7.494895791	2.90E-25	up	UBQLN3	-5.949101968	0.004485719	down
FOXO6	7.492982356	4.14E-24	up	OR51I2	-5.763469549	0.019370284	down
CHMP4B	7.346307221	5.32E-275	up	CPHXL	-5.60566153	0.002473186	down
ZNF579	7.295486377	1.49E-48	up	SEZ6	-5.561063009	4.16E-15	down
NACC1	7.18020029	5.60E-81	up	AC008764.1	-5.519104099	2.56E-05	down
NRGN	7.176076066	1.31E-21	up	DDI1	-5.431862442	0.008177372	down
VPS37D	7.028771346	2.07E-21	up	EPB42	-5.419516655	0.005376604	down
ZFPM1	7.022380122	3.60E-34	up	HSD17B13	-5.350915633	1.62E-14	down
STX16-NPEPL1	7.021902426	9.30E-18	up	TAS2R30	-5.31817953	3.18E-05	down
H1FX	7.013888106	1.63E-71	up	TSPYL6	-5.277211883	0.015923457	down
PLPPR3	7.013435763	5.94E-25	up	S100G	-5.272885523	6.28E-05	down
FZD8	7.002141868	9.94E-53	up	NTS	-5.2607169	8.74E-14	down
CBARP	6.97070394	1.55E-15	up	SLC26A9	-5.254977267	0.000249778	down
PRR36	6.934377645	3.69E-21	up	SUMO4	-5.244201785	1.77E-17	down
EHBP1L1	6.928022137	2.21E-141	up	SARNP	-5.235684349	3.88E-20	down
UTS2R	6.885471565	3.73E-15	up	AP001267.5	-5.195297311	0.000836296	down
ALYREF	6.838664989	2.97E-51	up	C6orf58	-5.191008915	3.13E-07	down
SHISA8	6.808964083	3.07E-16	up	MUC21	-5.169273719	5.00E-06	down
ZBTB7A	6.770433189	3.34E-129	up	AGRP	-5.154539432	0.003230022	down
SCX	6.694558382	3.25E-18	up	GPR101	-5.150396164	0.048461491	down
KCNC3	6.687850799	6.47E-34	up	LRRC19	-5.117200662	2.97E-16	down
ANO8	6.686064107	7.64E-51	up	AADACL2	-5.113910576	1.69E-11	down
BICRA	6.685196784	6.09E-59	up	SERPIND1	-5.091587746	4.31E-13	down
C11orf96	6.684479164	2.56E-21	up	LYG2	-5.085861838	1.37E-14	down
FOXD1	6.64077691	5.69E-10	up	ZBTB20	-5.057133728	5.67E-54	down
MT-ND3	6.629792654	5.26E-93	up	OR10A2	-5.03510767	3.07E-09	down

gene	log2FoldChange	padj	group	gene	log2FoldChange	padj	group
CEBPB	6.588238089	8.20E-38	up	FAM156B	-5.011868346	1.83E-17	down
SOX18	6.508033521	5.69E-22	up	OR5P3	-4.987899386	0.007021422	down
PTMS	6.499407192	5.78E-150	up	PRB2	-4.986444213	2.34E-05	down
WAS	6.495106492	2.12E-80	up	ANKRD20A1	-4.859382232	2.12E-07	down
CDH22	6.482723843	1.30E-14	up	PSG6	-4.856863874	0.005326032	down
ECEL1	6.451299841	4.69E-13	up	CBLN2	-4.85659835	0.019694673	down
MYPOP	6.436507689	1.24E-39	up	ABRA	-4.802989663	7.00E-08	down
NYAP1	6.425820735	2.87E-18	up	C12orf40	-4.78336905	0.000113843	down
FAM171A2	6.370330659	1.52E-12	up	SYNPR	-4.776217822	0.000737504	down
PRR12	6.355634192	1.84E-51	up	SHOX	-4.769319748	0.029514092	down
CLEC4D	6.348505527	2.35E-13	up	SPINK4	-4.76169911	0.004640645	down
LRFN1	6.347963514	1.92E-17	up	RHOXF2	-4.759531356	0.003054812	down
TGFB1	6.330665514	9.35E-38	up	CA1	-4.745455469	1.81E-09	down
HCN2	6.321552726	3.62E-15	up	SMIM2	-4.722319663	0.004116527	down
GAL3ST2	6.253497977	5.03E-17	up	RAB40AL	-4.72205947	0.000104573	down
TMEM240	6.243645102	4.14E-15	up	SPDYE16	-4.715695841	1.44E-24	down
GRIN2D	6.242576935	6.58E-17	up	PRB4	-4.714682438	0.000842763	down
UCN3	6.235575794	1.29E-19	up	OR2A4	-4.668592049	2.45E-08	down
SUCNR1	6.18415331	8.49E-12	up	CCDC54	-4.637934818	0.046689366	down
CDC42EP5	6.14665535	4.56E-42	up	TMPRSS11F	-4.63661798	0.024335041	down
SEMA6B	6.137243861	2.37E-32	up	BTBD18	-4.628387929	5.65E-12	down
SPI1	6.12531423	7.98E-73	up	KRT4	-4.61156903	4.99E-07	down
LCNL1	6.120411268	6.52E-09	up	TCP11X1	-4.577011758	0.002347317	down
ZNF775	6.108832771	9.02E-19	up	PRB3	-4.569006912	0.000153735	down
COL18A1	6.090282974	3.40E-105	up	ELOA2	-4.539544773	0.006696235	down
SEPT5-GP1BB	6.019234233	1.63E-13	up	NANOGP8	-4.532898956	1.08E-16	down
RCOR2	5.973824125	8.08E-16	up	RAMACL	-4.498775471	4.62E-27	down
NLRP6	5.970931598	4.51E-13	up	CAPNS2	-4.496983847	1.03E-08	down
CHCHD10	5.958321885	2.70E-61	up	OR2D2	-4.480670915	0.043674237	down
SBNO2	5.956113739	4.67E-39	up	C9	-4.450348892	2.08E-06	down
ZIC2	5.94199218	3.37E-08	up	GRIN2B	-4.440957013	0.001883907	down
CCL13	5.903333305	4.32E-15	up	PRH2	-4.40145844	4.26E-11	down
ZNF865	5.889855376	7.29E-22	up	INSYN2	-4.400957003	1.35E-32	down
LMTK3	5.856590124	1.01E-10	up	AC104389.4	-4.395575236	3.00E-13	down
PPP1R14B	5.832022777	1.39E-52	up	AC104472.3	-4.392857512	0.003943972	down
DBH	5.824708238	8.88E-14	up	GNAT2	-4.389556204	2.27E-33	down
NXPH2	5.799459873	2.16E-05	up	CIDEC	-4.351272879	0.003054812	down
PPP1R9B	5.797283218	1.41E-86	up	C1orf105	-4.349709059	0.027919124	down
PRPF19	5.766630694	2.18E-64	up	MEP1B	-4.336296475	0.003978731	down
PPDPF	5.760768617	2.95E-108	up	CYP26A1	-4.305707151	2.62E-08	down
GJD3	5.760360064	8.75E-26	up	SYCP3	-4.272423733	4.62E-16	down
PPP1R37	5.732807294	4.04E-94	up	PPBP	-4.270646753	0.000203572	down
PRRX2	5.685376728	3.03E-21	up	CRISP2	-4.262991596	2.41E-21	down
ESPNL	5.674385045	2.00E-07	up	CBY3	-4.257985607	2.26E-07	down
SH2B2	5.670760199	8.47E-30	up	PRR26	-4.23782466	1.29E-23	down
CLC	5.653891876	3.31E-14	up	AC025287.4	-4.23631888	3.70E-05	down
C1QL1	5.653739149	8.46E-14	up	SMIM34A	-4.219797323	0.004428309	down

gene	log2FoldChange	padj	group	gene	log2FoldChange	padj	group
AC009690.1	5.652910297	1.86E-08	up	PSG8	-4.215218182	0.015452415	down
ELFN2	5.629466689	4.60E-08	up	PRB1	-4.206650349	0.000828027	down
CUX2	5.628369233	6.86E-11	up	APOBEC2	-4.19203069	7.76E-14	down
SPINDOC	5.627487802	1.08E-54	up	OR52H1	-4.187067657	0.0352617	down
FOXP3	5.623303717	1.12E-27	up	HMGCS2	-4.174955248	7.49E-06	down
FIGNL2	5.619447744	2.06E-12	up	STXBP5L	-4.164052192	1.64E-06	down
CDKN1C	5.585246671	1.02E-29	up	HIST2H4B	-4.145345839	1.12E-05	down
DRD4	5.550749702	9.08E-10	up	CCDC179	-4.141167623	0.021880036	down
UBE2M	5.546413432	8.77E-82	up	PRH1	-4.124587466	3.22E-35	down
LCN10	5.540794325	5.93E-12	up	C1QTNF3-AMACR	-4.107567323	0.000942008	down
DBX1	5.530012385	0.000499837	up	SLC26A5	-4.096193473	1.02E-09	down
TOR4A	5.522786396	1.03E-30	up	LHFPL4	-4.091348136	5.22E-13	down
HOXB4	5.514083613	7.22E-14	up	NXF2	-4.06876113	0.011895775	down
CLDND2	5.506831329	3.46E-12	up	PLET1	-4.039756937	8.25E-05	down
EMILIN1	5.497231697	1.79E-35	up	SPATA21	-4.029848229	0.000752024	down
WNT2	5.495894627	0.000264228	up	CPB2	-3.94025483	0.008049411	down
NOTUM	5.488499501	1.52E-09	up	DACH2	-3.925267626	0.000968406	down
KLF13	5.460902543	7.16E-63	up	AC098650.1	-3.921643098	0.013978334	down
CXCL9	5.460709145	3.22E-14	up	NRAP	-3.912729209	0.000423962	down
SECTM1	5.453548773	1.01E-36	up	RNF133	-3.909449917	0.001665687	down
LGALS12	5.451053833	6.00E-08	up	OR2AE1	-3.897132413	0.004216468	down
KLF2	5.449395694	3.06E-64	up	TXNDC8	-3.896593375	1.38E-06	down
CHRD2	5.433244874	1.55E-05	up	CDRT4	-3.889048362	3.57E-09	down
APOBR	5.429541847	1.85E-25	up	FGF16	-3.87189558	0.000266949	down
RETN	5.428320273	1.50E-06	up	MUSK	-3.862112917	1.47E-07	down
FOXL2	5.424837187	2.06E-07	up	CA6	-3.854459941	0.00393742	down
AMH	5.422935576	1.55E-09	up	AC136428.1	-3.839115498	0.029501331	down
NUDT3	5.417645615	6.88E-27	up	C9orf131	-3.836285937	0.024406333	down
C8orf82	5.415932273	9.59E-73	up	QRFR	-3.812523711	3.70E-05	down
SKI	5.414687295	4.10E-60	up	CCDC196	-3.799966607	6.29E-05	down
C2CD4B	5.392561644	3.35E-15	up	AL117339.5	-3.771806251	9.06E-17	down
CEBPD	5.354588633	1.42E-23	up	SPDYE3	-3.766213513	2.91E-11	down
HOXC4	5.349357113	4.87E-13	up	REG4	-3.766067759	0.007135315	down
RPL28	5.347872039	1.97E-142	up	FEZF1	-3.764868426	1.05E-05	down
TBX1	5.334345318	7.83E-59	up	ANKRD7	-3.742851907	9.41E-06	down
TWIST1	5.330656372	1.16E-27	up	AC023055.1	-3.732329921	0.009401285	down
SEMA3F	5.314172641	1.15E-32	up	RNASE7	-3.701745401	1.50E-06	down
APOE	5.311914858	2.44E-38	up	RNASE8	-3.669170112	0.000964463	down
CBLN1	5.28890728	1.07E-12	up	NDUFV2	-3.647501085	7.57E-23	down
INSRR	5.270105616	7.66E-12	up	STPG2	-3.645969355	3.11E-10	down
SCAF1	5.265524111	8.79E-129	up	SMIM32	-3.623486398	0.021838125	down
TBX4	5.26468294	3.12E-08	up	PIK3C2G	-3.616041373	8.22E-06	down
CCL11	5.259860426	5.82E-16	up	UPK1B	-3.602458711	2.66E-07	down
SLC9A3	5.252938332	2.26E-22	up	C17orf78	-3.60171024	0.015453419	down
GPA33	5.252469342	1.99E-09	up	KCNV2	-3.582620346	0.000289824	down
AC068987.5	5.236884589	2.02E-08	up	CA2	-3.578073499	2.81E-08	down

gene	log2FoldChange	padj	group	gene	log2FoldChange	padj	group
SERPINA3	5.227719326	5.57E-09	up	C10orf90	-3.576692413	4.40E-05	down
SPRR2A	5.221641541	6.11E-05	up	FGF12	-3.556906759	6.34E-14	down
ABHD17A	5.21705757	7.51E-60	up	LRRTM3	-3.518310258	7.41E-05	down
NTNG2	5.202813736	1.29E-12	up	SPATA12	-3.505801937	9.65E-08	down
HES4	5.183856198	8.79E-16	up	LRTM1	-3.50179687	0.038280194	down
SEMA7A	5.180734552	7.25E-15	up	AC001226.2	-3.491048173	5.50E-15	down
LKAAEAR1	5.177913331	1.45E-07	up	ACSM6	-3.480187713	2.85E-06	down
IQCJ-SCHIP1	5.166483099	1.34E-11	up	HIST1H1E	-3.445696317	0.005577872	down
TPBGL	5.157799521	8.73E-10	up	PSG3	-3.400079559	0.007930356	down
COL22A1	5.15311916	1.17E-11	up	PON3	-3.393367515	4.99E-16	down
NRARP	5.151060523	1.19E-28	up	AMY1B	-3.376131049	1.30E-07	down
SNRNP70	5.150843427	3.94E-99	up	FOXN1	-3.365288381	6.05E-07	down
RPH3A	5.149569215	9.65E-08	up	SLC4A9	-3.364764409	0.011365251	down
VSTM1	5.143534923	1.90E-07	up	PRSS41	-3.349462455	0.028044249	down
ESPN	5.118764439	2.12E-28	up	ITLN1	-3.346812444	0.000825154	down
HAMP	5.109925073	9.27E-09	up	SPDYE1	-3.343081389	6.98E-17	down
MARCO	5.087092232	7.83E-07	up	TAS2R31	-3.339040467	3.33E-05	down
ZNF503	5.085099831	4.76E-55	up	SPDYE2	-3.331532759	5.22E-17	down
GRASP	5.082698969	2.08E-26	up	GSTA2	-3.322931241	1.10E-05	down
SAA1	5.078276901	8.36E-53	up	PAH	-3.321540643	0.010017939	down
GPIHBP1	5.073527324	7.85E-22	up	SCGN	-3.315892825	0.03747105	down
MAPKAPK2	5.066179942	2.11E-91	up	LRRTM2	-3.306149641	3.73E-19	down
CEBPE	5.045632773	1.85E-07	up	NKX3-1	-3.299171162	1.01E-10	down
DUSP9	5.043659596	7.79E-09	up	BOLL	-3.295974684	0.005522845	down
ADRA2A	5.04261442	7.90E-37	up	ANKRD36B	-3.29220834	1.50E-27	down
PPIAL4A	5.030663563	5.29E-06	up	KCTD4	-3.291950005	7.49E-06	down
ADGRB1	5.025148041	2.96E-12	up	HP	-3.290524765	5.16E-05	down
SRXN1	5.024242157	3.38E-10	up	SLC25A48	-3.281840653	2.92E-06	down
FZD2	5.016439187	7.33E-12	up	SEMG2	-3.278102657	0.000617129	down
HDGFL2	5.011974766	1.93E-102	up	BPIFB3	-3.259860161	0.004648403	down
RASSF10	5.010472266	1.78E-13	up	CALCB	-3.258832635	0.019898512	down
TCF15	5.002853651	4.27E-08	up	SPDYE5	-3.258052096	3.41E-30	down
SCARF2	4.996015986	1.80E-23	up	FXVD2	-3.22855449	0.000271375	down
CTU1	4.991691142	7.58E-22	up	CEACAM8	-3.200347205	0.010727435	down
SH3BP1	4.99056521	1.25E-41	up	CLEC19A	-3.197545891	0.000518186	down
APOBEC3H	4.981920369	1.39E-12	up	RHCE	-3.186705244	3.00E-05	down
GRIK5	4.976693866	3.86E-23	up	ADGRF2	-3.176733351	0.000805819	down
ICAM5	4.971185026	4.08E-11	up	MUC7	-3.175097731	0.000803487	down
KCNK13	4.966813719	3.90E-09	up	NKAIN1	-3.161895014	0.017545038	down
C5orf38	4.966445226	1.68E-11	up	INSL6	-3.160518462	1.26E-10	down
SLC26A4	4.954413518	3.64E-18	up	SLC6A11	-3.145737481	0.03106523	down
SCRIB	4.95031984	2.01E-28	up	PCDHGA8	-3.144100949	6.81E-06	down
IRX5	4.939196001	4.54E-14	up	EIF3CL	-3.136859412	1.52E-13	down
RNF208	4.936321929	3.87E-22	up	ZNF573	-3.131435887	1.70E-13	down
FOXQ1	4.903081272	8.65E-38	up	SPICE1	-3.124562972	2.95E-26	down
CACNG6	4.90195642	1.10E-13	up	GLYATL1	-3.102718179	9.04E-05	down
CCDC188	4.901242745	2.62E-14	up	LEFTY1	-3.099857761	0.002783061	down

gene	log2FoldChange	padj	group	gene	log2FoldChange	padj	group
KISS1R	4.893162994	5.91E-06	up	SLC3A1	-3.099614915	2.46E-05	down
C4B	4.888448846	5.27E-21	up	CYP4B1	-3.098134452	1.04E-06	down
DUSP8	4.878402381	4.37E-23	up	TM4SF20	-3.093608136	0.0490125	down
PROK2	4.86940141	2.55E-09	up	FCAMR	-3.093244443	0.009713049	down
CTS2	4.867158066	2.05E-42	up	ZNF460	-3.081087333	2.96E-10	down
CPLX1	4.86245893	1.74E-22	up	PRG2	-3.066030407	0.022412262	down
RPL39	4.854471753	7.72E-63	up	C9orf153	-3.060825206	0.004815293	down
MEFV	4.846201416	1.27E-08	up	NANOG	-3.058500131	0.008221339	down
NRXN2	4.845517711	2.92E-14	up	DYNC111	-3.057445995	2.35E-10	down
RPS28	4.840481965	5.98E-114	up	NOL4	-3.043633192	0.046890567	down
ADGRA2	4.832983144	9.20E-40	up	TEX54	-2.999896651	0.001682388	down
LSM14B	4.819041005	8.45E-148	up	REC114	-2.988811835	0.049900854	down
ASCL3	4.818620568	2.70E-11	up	SLCO1A2	-2.987603735	2.70E-05	down
NLGN2	4.817678301	7.85E-37	up	C6orf10	-2.979143943	0.011469885	down
CFHR1	4.815632141	3.91E-21	up	1-Dec	-2.97194732	0.001999321	down
SPRN	4.809993193	3.78E-08	up	CALML5	-2.967976902	0.00187403	down
SYNGAP1	4.80670914	1.37E-43	up	NLRP2B	-2.96181611	0.02760634	down
PBX2	4.801720781	1.55E-131	up	TCN1	-2.960197564	1.73E-05	down
NCR1	4.797047498	5.77E-10	up	FAM218A	-2.947063094	1.68E-13	down
4-Mar	4.79143267	3.63E-08	up	EDDM13	-2.946373331	2.04E-17	down
RPS21	4.779279686	2.08E-55	up	POLR2J2	-2.942447594	1.01E-11	down
HPCAL4	4.772830157	1.21E-08	up	IGSF11	-2.929623181	2.99E-05	down
RTN4RL1	4.755882026	1.59E-19	up	PON1	-2.92616333	0.034112364	down
RPLP2	4.755481074	2.03E-75	up	AADAC	-2.924649053	0.00606737	down
ZNF598	4.748961891	6.94E-52	up	HHLA2	-2.914430756	0.003158146	down
BCL9L	4.744525867	2.19E-51	up	ADH1B	-2.913581674	2.70E-05	down
GMNC	4.743778762	4.34E-06	up	CHRM1	-2.913012779	0.000156447	down
ZNF628	4.731314275	2.02E-30	up	CIDEA	-2.903799377	0.048496598	down
RTP5	4.729589385	1.62E-08	up	SEC14L3	-2.899935473	0.000260493	down
CLEC3B	4.72714729	5.29E-13	up	ANKRD36C	-2.88502676	1.10E-19	down
TMEM150B	4.716119217	3.38E-10	up	LRRN4	-2.882640519	0.000757637	down
LINGO3	4.70040169	1.75E-11	up	SUN3	-2.880899628	0.048295392	down
TGFBR3L	4.687069907	5.87E-11	up	TMEFF2	-2.861076011	0.006473175	down
VWA1	4.664301507	8.90E-38	up	ANGPTL5	-2.859593009	0.000339156	down
WNT6	4.662123249	6.09E-11	up	PRRG3	-2.853342283	1.29E-09	down
OGFR	4.656763934	3.57E-64	up	GUCY2C	-2.841839774	8.39E-13	down
GAL3ST1	4.656065762	1.48E-07	up	SLC10A1	-2.839601696	2.52E-05	down
FAM181B	4.653487355	9.12E-23	up	POPDC3	-2.828304398	0.04885141	down
TBX2	4.650542899	9.92E-26	up	GNMT	-2.824466767	3.24E-10	down
IGDCC3	4.6436175	1.34E-05	up	C1QTNF9B	-2.820295458	0.010726342	down
FGF11	4.642229047	3.88E-10	up	OVOL1	-2.819948311	3.27E-08	down
KLHDC7B	4.638635369	1.42E-17	up	PRSS37	-2.818876379	0.026309205	down
PRKCG	4.620938326	1.19E-05	up	AC007325.4	-2.814849745	4.30E-07	down
CYBA	4.620298286	2.42E-47	up	GLRB	-2.804868189	1.11E-12	down
PPP1R12C	4.616454652	1.82E-155	up	PCOLCE2	-2.799650764	0.001593575	down
APOC1	4.614125515	2.02E-10	up	PARD6B	-2.788683528	2.00E-28	down
GIPC3	4.612460915	1.84E-13	up	PLA2G4F	-2.788252093	0.000952171	down

gene	log2FoldChange	padj	group	gene	log2FoldChange	padj	group
MAP7D1	4.60978969	1.21E-89	up	SCRG1	-2.776526855	1.32E-05	down
EMX2	4.605538588	1.94E-05	up	ZNF565	-2.77540142	1.15E-41	down
ADAMTS10	4.60236184	1.54E-21	up	MEIS1	-2.772980576	6.70E-21	down
CSPG5	4.595801993	1.60E-08	up	MAG	-2.771901349	0.012496353	down
MIDN	4.594260392	4.65E-54	up	OVOL3	-2.76627551	0.028687882	down
SLC17A7	4.590974649	1.57E-05	up	GNRHR	-2.761588023	6.77E-08	down
C22orf42	4.580926707	0.001698905	up	AL031708.1	-2.758705441	2.41E-09	down
MBD6	4.574891148	1.61E-25	up	MOGAT1	-2.751687817	0.041337513	down
SAA2	4.572345478	1.82E-21	up	FREM3	-2.751215107	0.000785955	down
OLIG1	4.567468016	7.90E-06	up	UNC80	-2.746613453	0.000828105	down
SOCS1	4.561527573	2.92E-15	up	GPC3	-2.735641536	6.95E-13	down
LCN8	4.560156288	0.000481266	up	TGM5	-2.73507894	0.000619253	down
BASP1	4.554849123	5.85E-24	up	LRRC14B	-2.733952916	0.042708581	down
SLC2A4RG	4.551760406	1.12E-46	up	TET1	-2.7296785	8.80E-16	down
TMSB10	4.551061881	1.83E-41	up	ANKUB1	-2.725375742	3.22E-05	down
C4A	4.550126019	1.74E-16	up	HTR2A	-2.720033633	0.04055184	down
CACNA1H	4.541269916	6.41E-30	up	AGMO	-2.713281257	0.025093387	down
GLT1D1	4.538506425	6.87E-10	up	CFAP206	-2.697391965	0.002576333	down
MAP3K10	4.52560889	1.75E-41	up	ADH6	-2.692061135	6.13E-05	down
IRF2BPL	4.525088302	8.57E-92	up	MCOLN3	-2.691053317	1.30E-07	down
CIB2	4.521672938	1.19E-26	up	HERC3	-2.689075101	4.93E-06	down
ASPDH	4.520890594	2.80E-07	up	BCL11A	-2.675529405	3.43E-31	down
ZNF653	4.514298079	9.11E-18	up	ABCG8	-2.665366033	0.005333001	down
CYSLTR2	4.512503076	2.25E-06	up	AC092718.8	-2.657171466	0.020798147	down
LYL1	4.510640084	7.32E-13	up	ST3GAL3	-2.643010909	3.61E-13	down
ZNF777	4.501412205	6.71E-17	up	LDHB	-2.633581312	1.42E-15	down
FSTL5	4.497575034	0.019772153	up	CPA6	-2.625150306	0.030417646	down
NAT8L	4.496221278	1.94E-07	up	EPHX4	-2.621634513	7.23E-07	down
BCL3	4.491056373	2.03E-29	up	ANKRD36	-2.617065193	7.14E-22	down
INAFM1	4.489121377	1.33E-33	up	KLB	-2.615861533	0.000629121	down
SAMD14	4.486919605	8.28E-18	up	TTC9B	-2.615845837	0.002213599	down
FCAR	4.48661488	1.09E-07	up	ARG1	-2.610253831	4.79E-05	down
MT2A	4.477923756	4.38E-18	up	PRSS8	-2.608888031	2.30E-12	down
ZSWIM9	4.475824507	1.47E-32	up	IL13RA2	-2.60621863	2.68E-05	down
MZT2B	4.475049424	1.51E-35	up	NFIA	-2.602082607	3.33E-39	down
FBRSL1	4.471355531	1.05E-62	up	GATM	-2.597155823	1.87E-09	down
FAM43B	4.468130418	8.69E-06	up	TIMP4	-2.592637865	6.92E-06	down
AC136616.1	4.467599111	0.001232055	up	GRB14	-2.588688242	0.001576184	down
CALN1	4.460643084	2.50E-05	up	AP000275.2	-2.588609424	2.58E-12	down
GPRC6A	4.456771587	3.50E-05	up	C2orf91	-2.587666992	0.028848484	down
MT1G	4.45497073	3.92E-15	up	HDHD2	-2.583977176	1.04E-21	down
NES	4.446755196	4.52E-38	up	DPT	-2.58291355	0.000121179	down
FAM83H	4.416162762	8.11E-46	up	CYP2A6	-2.578549974	0.000109739	down
HIC1	4.408287973	3.14E-55	up	TOB1	-2.577230113	2.27E-14	down
SAMD11	4.397194527	1.75E-18	up	FAM171B	-2.576505734	2.15E-14	down
GNAO1	4.396498824	7.27E-24	up	POLDIP3	-2.576438871	0.001425984	down
STK11	4.388670642	1.23E-23	up	RNF128	-2.563731701	9.07E-06	down

gene	log2FoldChange	padj	group	gene	log2FoldChange	padj	group
RPL27	4.374323988	9.27E-75	up	FOLH1	-2.551745013	1.87E-05	down
PAEP	4.366471566	0.014658848	up	AC010542.3	-2.550732952	0.025052966	down
ZNF414	4.363855434	4.53E-44	up	CREG2	-2.550114825	0.006084725	down
NPY	4.361740667	0.001995095	up	DEGS2	-2.548479298	1.58E-08	down
TRIR	4.349559856	3.17E-64	up	NELL2	-2.543898709	4.36E-06	down
ARHGAP23	4.348105013	2.52E-50	up	NDRG2	-2.540139826	2.98E-11	down
GSC	4.342101922	4.03E-08	up	MYBPC1	-2.537206173	0.013279113	down
MGAT5B	4.341314745	2.20E-08	up	SOSTDC1	-2.533672714	8.38E-15	down
SETD1A	4.33036426	2.14E-86	up	ACOT11	-2.521680496	5.72E-11	down
TMEM121B	4.325503669	7.19E-09	up	GPAT2	-2.520130961	1.37E-06	down
EID2	4.323316882	6.89E-28	up	PIP	-2.517688494	0.012830937	down
SCG2	4.320770251	6.87E-12	up	FBXO15	-2.512120017	0.008005002	down
PALM	4.318715156	7.10E-22	up	ZNF286A	-2.511481394	1.26E-26	down
CATSPER1	4.31563352	1.50E-06	up	FAM156A	-2.505759829	7.80E-09	down
PLCB3	4.314702821	2.09E-74	up	PRSS35	-2.504614177	0.000469272	down
RNASE3	4.314443968	0.001163555	up	BTNL3	-2.500130719	0.023436876	down
IHH	4.307458265	0.001649	up	ZNF410	-2.498757104	2.21E-14	down
RPL38	4.303582944	1.35E-67	up	PTH2R	-2.490443813	0.000315182	down
LAMP1	4.295714876	1.88E-36	up	SLC22A16	-2.490214056	0.010381699	down
U2AF2	4.295433653	1.07E-72	up	CAPN9	-2.489892174	2.01E-06	down
KLF16	4.292748132	9.06E-32	up	ART3	-2.488061108	0.004457918	down

Table S4. Top300 upregulated and downregulated DEGs in mild eCRSwNP versus healthy controls.

gene	log2FoldChange	padj	group	gene	log2FoldChange	padj	group
CLC	11.03710851	7.78E-56	up	PRSS48	-8.049455153	5.32E-20	down
TMEM238	10.46151902	1.96E-43	up	POU5F2	-7.690084741	9.95E-54	down
MEX3D	10.16494496	6.90E-50	up	OR1Q1	-7.2802643	0.000149588	down
FBXL19	9.993070301	3.26E-48	up	TYR	-7.260532	1.18E-06	down
CCL13	9.898806517	2.76E-44	up	RNF113B	-7.043228367	3.44E-09	down
VSTM1	9.718011199	1.29E-33	up	GPR22	-6.984099834	8.51E-20	down
SHISA8	9.64657326	4.90E-39	up	SMIM18	-6.895738106	1.08E-26	down
UBALD2	9.459533322	4.86E-75	up	ANKRD62	-6.857829587	0.000170624	down
CTXN1	9.237150367	4.31E-22	up	PSG11	-6.680422493	0.012437449	down
CST1	9.226838489	7.68E-23	up	BLID	-6.655356744	0.000398497	down
ZNF787	9.134603983	9.46E-59	up	HIST1H4C	-6.613756043	1.89E-19	down
ADRA2C	9.046731026	1.33E-39	up	UBQLN3	-6.373875247	0.005524939	down
CEBPE	8.86828299	5.96E-29	up	RAB40AL	-6.299165718	5.59E-07	down
SUCNR1	8.839034629	1.10E-29	up	ELOA2	-6.278775455	0.007231944	down
OLIG1	8.831453532	1.82E-31	up	PRR4	-6.210395903	2.27E-14	down
JUND	8.764239169	2.85E-98	up	LRTM1	-6.147056949	0.007511736	down
CITED4	8.655702962	1.44E-45	up	BRINP3	-6.14673984	0.000512555	down
CDH24	8.654347017	2.30E-37	up	ZBTB20	-6.116706915	2.36E-113	down
CLCA1	8.617770255	1.87E-15	up	TAS2R30	-6.053876895	2.11E-06	down
LGALS12	8.523037953	8.01E-27	up	CPB2	-6.043604826	0.001577781	down
UTS2R	8.367318873	2.91E-19	up	CCDC196	-6.009225872	4.97E-09	down
BARX1	8.186844699	5.72E-32	up	FEZF1	-5.974668848	2.04E-09	down
BRSK1	8.09481767	1.04E-30	up	PLET1	-5.964638438	6.16E-09	down
FOXO6	8.091448688	1.49E-27	up	PSG7	-5.945237292	0.03760091	down
NXPH4	7.986352804	3.54E-19	up	TSPYL6	-5.704822865	0.019548153	down
COL6A5	7.986089244	6.39E-12	up	PBOV1	-5.689120843	0.049717169	down
NRGN	7.967278107	1.18E-27	up	OR51I1	-5.622785419	0.000151575	down
ZNF579	7.856159865	1.25E-54	up	OR51I2	-5.613950051	0.023143186	down
VPS37D	7.853916204	2.09E-25	up	INSYN2	-5.608714954	8.68E-56	down
PLPPR3	7.835640152	4.13E-14	up	TCP11X1	-5.5953719	0.000969039	down
ZBTB12	7.828207148	4.90E-29	up	BOLL	-5.547997732	0.000198971	down
CARMIL2	7.778580194	5.46E-31	up	ABRA	-5.543204752	2.68E-09	down
MEPCE	7.734979828	4.47E-41	up	OR10A2	-5.525528589	9.94E-09	down
H1FX	7.703115055	3.72E-111	up	HIST2H4A	-5.487246431	1.88E-11	down
SHANK1	7.698626506	1.53E-25	up	OR5P3	-5.413506834	0.008463593	down
OLIG2	7.675890095	1.16E-19	up	SERPIND1	-5.40659506	1.83E-14	down
IER5L	7.598748461	4.54E-39	up	BTBD18	-5.351997474	1.34E-11	down
CCL26	7.563987548	2.83E-23	up	C6orf10	-5.351444713	0.000242973	down
ZFPM1	7.549692064	9.23E-46	up	SUMO4	-5.296437442	1.24E-13	down
PRR36	7.542645737	2.91E-21	up	SEZ6	-5.264775497	2.02E-12	down
NACC1	7.444020303	1.77E-104	up	C12orf40	-5.23556948	5.99E-05	down
CHMP4B	7.433040083	2.07E-208	up	CPHXL	-5.162257601	0.002645987	down
CDC42EP5	7.420858615	5.12E-75	up	CCDC179	-5.156816842	0.017586266	down
TMEM158	7.419412678	6.25E-31	up	SLC26A9	-5.13794267	0.000237912	down
CBARP	7.412736775	9.43E-23	up	S100G	-5.123018589	0.000136898	down

gene	log2FoldChange	padj	group	gene	log2FoldChange	padj	group
MARCO	7.330543349	5.34E-08	up	AC008764.1	-5.079701467	5.37E-05	down
SOX18	7.314017851	1.22E-39	up	AP001267.5	-5.047385611	0.001486097	down
TRPM5	7.310731885	4.17E-14	up	NXF2	-4.989217837	0.003001116	down
RNASE2	7.252065103	1.15E-16	up	LHFPL4	-4.978765904	1.25E-17	down
FAM171A2	7.210219271	1.47E-20	up	SARNP	-4.93409299	3.42E-14	down
STX16-NPEPL1	7.18956729	1.22E-16	up	STXBP5L	-4.901376861	4.22E-06	down
ALYREF	7.180403934	1.56E-59	up	C3orf30	-4.828886256	0.007354465	down
CDH22	7.062838114	3.32E-21	up	DNAJB7	-4.809638705	0.000199485	down
EHBP1L1	7.059052189	1.85E-91	up	AC104389.4	-4.797647679	1.05E-16	down
ANO8	7.054191003	1.43E-51	up	SPDYE3	-4.786189046	5.81E-17	down
NYAP1	7.049682215	4.19E-21	up	CALR3	-4.783081201	0.014625125	down
SCX	7.044507064	2.75E-18	up	PSG1	-4.751634447	0.037105212	down
BICRA	6.999156367	1.32E-50	up	SLC26A5	-4.741692069	5.20E-14	down
TMEM240	6.944012429	2.95E-21	up	SPATA21	-4.713451642	5.85E-05	down
CCL18	6.891458949	1.47E-09	up	PSG6	-4.706577605	0.007527333	down
MT-ND3	6.880173038	3.42E-102	up	DDI1	-4.704809734	0.012767913	down
PTMS	6.859862938	3.32E-218	up	AC091167.6	-4.664756853	0.033679603	down
ZBTB7A	6.838645379	1.90E-130	up	SYCP3	-4.631315172	5.20E-21	down
ZNF775	6.821019352	2.28E-29	up	AC098650.1	-4.63111307	0.006578536	down
TCF15	6.737492313	2.85E-19	up	AL117339.5	-4.618053906	1.78E-25	down
LCN10	6.73319254	3.12E-16	up	OR52H1	-4.614808159	0.036583935	down
MYPOP	6.728755908	3.70E-42	up	HIST2H4B	-4.606441676	2.30E-08	down
COL18A1	6.673599009	1.15E-103	up	AADACL2	-4.584957234	3.93E-08	down
DRD4	6.663034105	8.74E-14	up	SPINK4	-4.580957389	0.002900542	down
CHCHD10	6.659963655	2.71E-89	up	GNAT2	-4.575709615	1.86E-17	down
SEPT5-GP1BB	6.657014611	3.11E-14	up	AC025287.4	-4.566086663	0.000218961	down
TGFB1	6.643547398	5.71E-41	up	SPDYE16	-4.565521201	1.21E-18	down
KCNC3	6.637389323	1.82E-26	up	RPA4	-4.563166498	0.000360725	down
FIGNL2	6.623164849	8.93E-20	up	AC104472.3	-4.535999694	0.006923099	down
LRFN1	6.596381329	1.37E-19	up	ANKRD36C	-4.524956321	4.74E-52	down
SEMA6B	6.591666294	8.10E-52	up	C1orf105	-4.491882781	0.022304725	down
CEBPB	6.589725017	5.53E-46	up	KCNJ18	-4.402237255	0.001348171	down
UGT2B11	6.585778514	4.03E-10	up	C9	-4.331615237	5.16E-06	down
FOXL2	6.578662707	8.65E-10	up	HTR2A	-4.31464899	0.001744298	down
PRR12	6.571239068	3.34E-50	up	INSL6	-4.243287836	7.95E-11	down
WAS	6.570884353	2.37E-45	up	ANKRD7	-4.239049062	5.66E-06	down
FOXD1	6.553978865	2.00E-13	up	MYOCOS	-4.237875779	0.037899035	down
GRIN2D	6.544139278	4.88E-18	up	RAMACL	-4.232535829	4.04E-41	down
AC009690.1	6.528575428	2.32E-15	up	PRR26	-4.208755422	1.87E-19	down
RETN	6.52577912	2.24E-08	up	CCDC54	-4.194290304	0.047502398	down
ECEL1	6.441950935	6.37E-21	up	LYG2	-4.180976863	7.79E-19	down
PPDPF	6.43212799	1.46E-138	up	MUSK	-4.172904308	5.50E-10	down
CHAT	6.410138915	2.77E-07	up	AC023055.1	-4.157527252	0.015375365	down
SEMA7A	6.404752554	7.38E-23	up	PSG8	-4.125459024	0.008929983	down
GPIHBP1	6.387719805	5.77E-42	up	AC001226.2	-4.110768868	5.17E-16	down
RCOR2	6.367319203	8.05E-17	up	MEP1B	-4.101158402	0.013785656	down
ZNF865	6.354290362	9.85E-26	up	TXNDC8	-4.063869387	1.86E-05	down

gene	log2FoldChange	padj	group	gene	log2FoldChange	padj	group
PPP1R37	6.352269174	7.61E-99	up	RNF133	-4.059505968	0.000313204	down
SPI1	6.323027558	1.43E-69	up	NLRP2B	-4.039596417	0.007746202	down
C11orf96	6.302497427	3.67E-27	up	SERPINA6	-4.03856553	0.012061434	down
KLF2	6.284362718	5.59E-84	up	GSTA2	-4.032166365	8.63E-08	down
AMH	6.260682136	1.63E-06	up	SPATA12	-3.980143081	1.15E-10	down
HCN2	6.257286486	1.35E-14	up	PIK3C2G	-3.951650768	1.98E-05	down
PPP1R14B	6.237378816	8.99E-90	up	EIF3CL	-3.945971058	6.31E-39	down
GAL3ST2	6.231319915	4.18E-15	up	STPG2	-3.925035758	3.85E-07	down
NTNG2	6.195623295	1.33E-19	up	NANOGP8	-3.917580997	4.46E-11	down
APOE	6.183593753	6.39E-70	up	SCGN	-3.893137511	0.007974403	down
ESPNL	6.181079531	1.27E-14	up	PRH1	-3.877737573	2.52E-36	down
SLC9A3	6.147412734	3.81E-31	up	CA6	-3.877731083	0.002021936	down
FZD8	6.117590036	4.18E-36	up	ANKRD36B	-3.858207985	1.13E-29	down
PPP1R9B	6.089672545	1.07E-76	up	LRRC19	-3.856475287	3.32E-12	down
SH2B2	6.074426628	8.05E-31	up	PSG4	-3.825692445	0.040948778	down
HRH4	6.073175274	3.33E-15	up	CCDC144A	-3.751069239	0.02790891	down
CCL24	6.070915377	1.67E-18	up	APOBEC2	-3.741921043	1.17E-16	down
HES4	6.069403838	1.61E-20	up	HRNR	-3.740978027	5.65E-06	down
APOBR	6.041426875	3.79E-30	up	ZNF460	-3.691721516	8.46E-14	down
HTR3C	6.012416981	1.14E-08	up	SLC3A1	-3.656648027	0.000146651	down
C8orf82	6.004374633	7.94E-115	up	NDUFV2	-3.652627239	7.37E-20	down
CBLN1	5.979514422	1.78E-10	up	CDRT4	-3.612644001	3.08E-05	down
PRPF19	5.963665548	5.50E-60	up	CA1	-3.609695613	6.78E-05	down
TBX1	5.933291227	3.51E-60	up	ANKRD20A1	-3.608143454	3.71E-06	down
TOR4A	5.926826987	3.52E-43	up	ZNF573	-3.600398646	3.31E-16	down
TBX4	5.919971368	8.44E-12	up	CAPNS2	-3.590756921	2.49E-05	down
GRASP	5.890844472	1.32E-36	up	GABRA2	-3.550777714	0.001591582	down
CLDND2	5.889200137	3.67E-10	up	B3GALT1	-3.546060801	4.61E-06	down
ICAM5	5.877125	5.83E-16	up	GUCY2F	-3.543943764	0.020637254	down
SPINDOC	5.874412859	1.30E-52	up	TRPA1	-3.531875885	3.84E-05	down
C5orf38	5.87362537	4.81E-17	up	SLC5A5	-3.506364124	0.040227585	down
RNF208	5.851537795	7.25E-38	up	ODAPH	-3.487864572	0.023387855	down
CPLX1	5.851105522	2.70E-23	up	MOGAT1	-3.481225139	0.024622556	down
EEF1A2	5.845344754	1.23E-11	up	CRISP3	-3.468143156	0.00401293	down
NUDT3	5.837299318	4.73E-45	up	AC108941.2	-3.454844205	0.005867842	down
HBA1	5.828922709	1.16E-13	up	CBY3	-3.429990588	1.81E-06	down
UBE2M	5.824504871	7.73E-74	up	SPDYE1	-3.408895629	4.90E-17	down
ABHD17A	5.807096074	8.60E-85	up	SPDYE5	-3.404228061	8.88E-25	down
ADGRB1	5.780949295	9.99E-16	up	TEX38	-3.385784832	0.012129209	down
KLF13	5.74885889	7.20E-65	up	SLC35G6	-3.375515685	0.012115063	down
CTU1	5.746831673	6.65E-42	up	KCTD4	-3.364260959	0.000379641	down
CCDC188	5.741833829	1.04E-15	up	ADGRF2	-3.35338299	0.003392627	down
SNRNP70	5.739795983	3.60E-88	up	FAM156B	-3.349783922	8.07E-08	down
HOXB4	5.719988376	8.74E-11	up	CERS3	-3.344449105	2.54E-06	down
CYSLTR2	5.710373227	3.38E-09	up	DGAT2L6	-3.337160976	0.01750255	down
HS3ST4	5.708474939	3.65E-14	up	QRFR	-3.327479675	0.00988799	down
ESPN	5.674424657	4.14E-32	up	AC013470.2	-3.324076031	0.000548144	down
SCAF1	5.67146974	6.78E-141	up	SPDYE2	-3.319705081	6.54E-17	down

gene	log2FoldChange	padj	group	gene	log2FoldChange	padj	group
NLRP6	5.669948541	2.86E-13	up	SPICE1	-3.314971315	1.18E-24	down
PRRX2	5.658725731	3.11E-41	up	IL1A	-3.308100834	0.028336907	down
SBNO2	5.64989741	1.97E-36	up	PRH2	-3.303639394	1.10E-09	down
SOC51	5.645329689	7.56E-41	up	FREM3	-3.300431444	0.000700399	down
CEBPD	5.631896951	7.53E-31	up	AL031708.1	-3.293081869	6.44E-07	down
HAMP	5.618494087	5.50E-10	up	ARHGAP8	-3.280345676	8.21E-06	down
TWIST1	5.592643754	3.86E-38	up	ODF3	-3.275854175	0.037983016	down
GNG13	5.592238252	1.67E-06	up	1-Dec	-3.263166767	0.000122656	down
LINGO3	5.57662434	4.54E-15	up	C10orf90	-3.262661526	2.58E-05	down
SKI	5.572188703	9.14E-60	up	GRIN2B	-3.258649619	0.00479405	down
AC068987.5	5.570242927	7.15E-11	up	ACSM6	-3.255898992	0.002900542	down
UCN3	5.569878668	1.85E-12	up	IL23R	-3.235787858	0.010259222	down
EMILIN1	5.568562389	1.12E-39	up	FGF16	-3.234103992	0.002891941	down
DBH	5.567270982	5.21E-11	up	PRSS37	-3.213916584	0.008410308	down
LKAAEAR1	5.563203459	4.49E-07	up	AC010542.3	-3.211766103	0.007200251	down
TBX2	5.554267465	1.03E-36	up	PPBP	-3.204543799	0.010137042	down
IQCJ-SCHIP1	5.521605578	2.06E-14	up	OR2AE1	-3.187912807	0.02470448	down
C1QL1	5.520377574	2.24E-09	up	GNRHR	-3.184259185	3.57E-09	down
FOXP3	5.518828138	2.52E-14	up	KRT12	-3.177751085	0.001274659	down
RPL28	5.51561283	1.57E-140	up	CLEC19A	-3.172518093	0.000363293	down
SEMA3F	5.507027515	9.02E-35	up	GBP7	-3.171366294	0.003619285	down
SRXN1	5.479344786	8.10E-14	up	C1QTNF9B	-3.16021585	0.006281323	down
HBD	5.46182817	2.23E-09	up	ART3	-3.158227992	0.002401364	down
MT3	5.420009132	5.86E-11	up	SCRG1	-3.158087963	5.73E-08	down
CDKN1C	5.415970798	2.99E-42	up	LUZP2	-3.156026122	2.65E-05	down
SCARF2	5.414814565	3.90E-36	up	PCDHGA8	-3.143548635	3.80E-07	down
FAM43B	5.409003113	1.73E-08	up	SLCO1B3	-3.139612335	0.000100134	down
SCRIB	5.407187525	3.81E-34	up	CDH10	-3.1339719	0.034134373	down
NOTUM	5.403906025	1.00E-08	up	GRM5	-3.108274056	0.019029799	down
GAL3ST1	5.399311337	3.10E-11	up	REC114	-3.101276376	0.023456802	down
ZNF503	5.350586267	2.75E-73	up	BAAT	-3.086016286	0.030678745	down
RPS21	5.348863381	5.61E-91	up	ANKRD36	-3.08338994	5.67E-22	down
LYL1	5.343542227	6.57E-20	up	KCNV2	-3.083156951	9.50E-05	down
RTN4RL1	5.340499896	6.14E-24	up	C9orf153	-3.078395452	0.0022707	down
GJD3	5.339949235	1.44E-24	up	AGRP	-3.070150289	0.021312423	down
RPS28	5.3358358	8.59E-143	up	C17orf78	-3.065247809	0.010565967	down
CTSZ	5.329381339	4.60E-47	up	CRISP2	-3.060039167	2.03E-05	down
APOC1	5.324783205	2.17E-19	up	C9orf131	-3.057995573	0.018927178	down
PTGDR2	5.324372985	1.73E-15	up	FGF5	-3.055422923	0.03805045	down
TPBGL	5.31786565	4.59E-10	up	SYT14	-3.0450072	0.008282559	down
ADGRE1	5.310962225	1.12E-12	up	GLYATL1	-3.030907076	0.003134485	down
SPRR2A	5.300235676	0.000472276	up	NKX3-1	-3.013813566	1.86E-06	down
HDGFL2	5.297596762	3.92E-77	up	LRRTM3	-3.007179294	0.000898174	down
DUSP9	5.285968504	7.84E-10	up	NELL2	-3.006194651	1.22E-07	down
NAT8L	5.285112535	6.17E-12	up	PARD6B	-2.981338307	5.48E-31	down
INAFM1	5.274678506	2.61E-52	up	C2orf91	-2.974949517	0.026263666	down
MAPKAPK2	5.25809576	2.17E-79	up	KCNJ13	-2.965889601	3.41E-10	down

gene	log2FoldChange	padj	group	gene	log2FoldChange	padj	group
ARTN	5.252182133	3.63E-14	up	ZNF565	-2.962143209	4.83E-52	down
SECTM1	5.236612033	1.66E-41	up	TAS2R31	-2.96115999	6.16E-06	down
WNT6	5.235281905	3.51E-18	up	TRPC5	-2.958151546	0.036337515	down
CACNG6	5.2348227	1.48E-16	up	BTNL3	-2.954351254	0.008131257	down
GIPC3	5.233666986	1.47E-15	up	AP000275.2	-2.948184136	1.14E-15	down
ADAMTS10	5.229633218	1.38E-24	up	LRRC9	-2.934453093	0.024933363	down
FOXQ1	5.224754364	2.55E-38	up	GUCY2C	-2.934417882	5.82E-12	down
INSRR	5.216084319	1.45E-11	up	ANKUB1	-2.921466265	0.000202869	down
PLCB2	5.205258478	8.10E-32	up	ZNF98	-2.92143698	0.009753619	down
CUX2	5.202592698	5.72E-09	up	CYP24A1	-2.915974687	0.000121969	down
NRARP	5.198234255	2.01E-34	up	FAM218A	-2.906306794	4.13E-10	down
KLF15	5.194465892	2.32E-17	up	PRSS35	-2.902145709	3.80E-05	down
TEX15	5.189099512	2.49E-08	up	HMGCS2	-2.900448848	0.000413	down
MAP3K10	5.18195064	1.87E-75	up	DIO2	-2.899915402	1.60E-08	down
RPLP2	5.174929589	3.82E-102	up	PRR27	-2.896987541	0.016874501	down
SOX17	5.168535698	9.95E-19	up	ARSH	-2.895957587	0.000763935	down
SH3BP1	5.154686692	5.55E-36	up	SLC10A1	-2.895639962	1.22E-05	down
ZNF628	5.153714055	2.79E-49	up	SHISA2	-2.89346855	2.13E-11	down
PPP1R12C	5.146698731	4.38E-176	up	SVOP	-2.892510841	0.014286961	down
SH2D6	5.139829037	3.30E-07	up	C9orf84	-2.889463166	8.55E-13	down
FBRSL1	5.137909019	2.03E-81	up	GSTA3	-2.882195978	0.000682337	down
MZT2B	5.134244536	6.81E-63	up	PLA2G4F	-2.879374496	0.000453624	down
SLC2A4RG	5.113292543	5.57E-82	up	BCL11A	-2.877489635	1.44E-28	down
VWA1	5.101040959	1.93E-51	up	FRMPD2	-2.868772945	0.000960399	down
HK3	5.099600079	2.63E-12	up	AP002495.1	-2.852758516	3.83E-16	down
RTP5	5.089173599	3.30E-07	up	MROH9	-2.848876499	0.000637993	down
TMEM150B	5.0859961	2.33E-11	up	NKAIN1	-2.842222968	0.033338188	down
COL6A2	5.085016572	3.38E-69	up	PSG3	-2.8376417	0.034038877	down
C6orf222	5.060655709	1.60E-07	up	HERC3	-2.832495467	6.09E-06	down
RPL39	5.045322743	1.27E-65	up	EDDM13	-2.825683294	1.15E-17	down
LCNL1	5.041737132	1.32E-05	up	MAGED4	-2.822546652	1.69E-06	down
GRIK5	5.038810468	5.25E-33	up	TIMP4	-2.820839289	8.88E-05	down
KISS1	5.035988742	6.60E-06	up	CIDEC	-2.817738951	0.020806942	down
TXNDC5	5.031317287	1.15E-34	up	PRRG3	-2.812845345	1.44E-07	down
B4GALNT4	5.024760756	2.40E-16	up	CCDC38	-2.811348826	0.008463314	down
ADGRG3	5.021672961	4.20E-13	up	REN	-2.810503559	0.002243853	down
PRKCG	5.019578696	2.52E-05	up	C6orf163	-2.809021582	3.02E-13	down
CIB2	5.018420626	7.81E-26	up	ANGPTL7	-2.804609108	0.017864572	down
ZNF598	5.017481674	5.55E-56	up	LRRTM2	-2.796719591	8.11E-19	down
CHRD12	5.017352913	2.49E-07	up	AMY1B	-2.785637395	0.000318072	down
LSM14B	5.003675468	2.33E-120	up	FAM171B	-2.778680337	4.06E-14	down
SHANK3	4.993637427	6.23E-35	up	PON1	-2.776849117	0.044244722	down
ISLR2	4.96951944	4.87E-11	up	MALRD1	-2.776086611	0.003967515	down
CACNA1H	4.96826147	2.01E-33	up	BBOX1	-2.759598076	2.39E-07	down
ZNF414	4.966198008	2.01E-58	up	POLR2J2	-2.757487672	3.94E-13	down
FAM181B	4.963302758	1.47E-23	up	LDHAL6B	-2.756893157	0.02247569	down
IRX5	4.961270464	4.70E-13	up	CORIN	-2.756816803	6.85E-06	down

gene	log2FoldChange	padj	group	gene	log2FoldChange	padj	group
STK11	4.957279902	1.17E-30	up	GPR18	-2.755996076	1.08E-07	down
DPYSL5	4.956610884	7.55E-07	up	PRB3	-2.755200665	0.01042249	down
PBX2	4.953368595	2.76E-114	up	GRK7	-2.748505943	0.024304009	down
ADRA2A	4.948899018	2.18E-39	up	GSTO2	-2.747430698	7.09E-12	down
KCNK13	4.928583834	6.55E-10	up	EPHX3	-2.739121741	3.95E-06	down
MAFA	4.925083488	1.00E-07	up	ARG1	-2.738705396	3.81E-05	down
SEMA6C	4.923765485	9.03E-20	up	DYNC1I1	-2.72998797	7.30E-09	down
MGAT5B	4.908498983	1.91E-11	up	TEX54	-2.721209999	0.000166908	down
NLGN2	4.907159283	3.22E-32	up	RGPD6	-2.719774963	1.24E-08	down
HMX3	4.904326297	3.73E-06	up	GLRB	-2.714871915	3.79E-07	down
LMNTD2	4.888634413	4.41E-13	up	TET1	-2.713458091	1.98E-12	down
SPRR1B	4.863594155	7.44E-05	up	FGF12	-2.71201816	6.22E-09	down
LST1	4.863203277	1.32E-23	up	FIBIN	-2.710645496	1.76E-05	down
SLN	4.859722996	2.63E-07	up	NFIA	-2.710625804	3.55E-38	down
SLC17A7	4.849133278	4.19E-08	up	DUXB	-2.707153978	0.006090923	down
ANKRD63	4.845925258	7.95E-07	up	MAP3K15	-2.701150082	0.018742086	down
C4orf48	4.845744141	1.06E-22	up	IGSF11	-2.698192866	3.49E-05	down
MBD6	4.841217604	9.69E-26	up	CYP2F1	-2.660870091	8.31E-05	down
OGFR	4.834862867	1.50E-62	up	ANGPTL5	-2.65915574	0.007423222	down
SPRN	4.828754946	1.93E-09	up	CFAP206	-2.658221085	0.016720029	down
ZNF653	4.815884409	7.02E-18	up	FAM156A	-2.647507054	2.29E-09	down
ZSWIM9	4.807583331	2.59E-33	up	PENK	-2.647352492	0.002490609	down
POSTN	4.805464896	2.62E-20	up	FBXO39	-2.646798266	2.15E-06	down
SYNGAP1	4.803991639	1.19E-37	up	THRSP	-2.6328121	0.015462733	down
NRROS	4.802806293	1.69E-39	up	CALCB	-2.629712535	0.045518555	down
ZNF777	4.791969783	5.14E-19	up	MEIS1	-2.618257878	2.82E-19	down
NTN3	4.790610631	1.98E-08	up	GPR182	-2.618104857	0.03529529	down
FZD2	4.790319239	1.67E-10	up	TOB1	-2.615542555	1.43E-13	down
IRX1	4.788788896	4.95E-07	up	ZNF286A	-2.615088907	1.15E-24	down
IGDCC3	4.788311905	2.25E-05	up	ODF3L1	-2.611530116	0.011871551	down
ADGRA2	4.787411759	2.64E-48	up	CA2	-2.610802179	0.000261079	down
BCL9L	4.786150668	2.08E-49	up	TGM5	-2.609483349	0.000856539	down
CYBA	4.769345654	2.82E-49	up	ASTL	-2.607905452	0.00707612	down
RNF225	4.763470947	4.51E-09	up	SEC14L3	-2.601487662	0.001673122	down
NES	4.762168504	1.11E-44	up	RNASE7	-2.599696543	0.001010329	down
CARD9	4.757890881	2.87E-09	up	PAH	-2.589381871	0.041768069	down
COL5A3	4.752720698	1.92E-30	up	FOXP1	-2.587565276	8.10E-36	down
ZNF316	4.745734424	1.01E-79	up	VNN3	-2.575192911	8.55E-05	down
ELFN2	4.741696199	2.26E-05	up	CHRNA9	-2.574377879	0.007762345	down
HES5	4.737055979	2.53E-05	up	AKR1B15	-2.567722435	0.027011738	down
NRXN2	4.736541674	1.45E-12	up	HNF1B	-2.567658223	0.004405968	down
RASGRP4	4.732710333	1.12E-25	up	C16orf46	-2.56595243	0.046844781	down
WNT9B	4.727998397	2.20E-09	up	PON3	-2.565120566	1.12E-09	down
GMNC	4.719244221	2.10E-05	up	FXDY2	-2.557629037	0.003761319	down
DUSP8	4.712995269	1.80E-21	up	CELA2B	-2.556182291	0.002568731	down
C2CD4B	4.70382711	1.68E-12	up	ANKRD18B	-2.554701855	0.000112958	down
ASCL2	4.701805	8.83E-20	up	OVOL1	-2.554419648	3.06E-06	down

Corrected Proof

Macrophages in nasal polyps

gene	log2FoldChange	padj	group	gene	log2FoldChange	padj	group
PRSS57	4.698834777	0.000480613	up	MKRN3	-2.554235886	4.45E-10	down
ANKRD24	4.69636792	3.64E-14	up	GDF3	-2.553526475	0.022358727	down
FAM83H	4.695672636	8.67E-56	up	HARBI1	-2.550998862	1.88E-45	down
RAET1L	4.695460422	0.000483296	up	BPIFB3	-2.548488505	0.025078387	down
LAIR2	4.694157843	5.39E-07	up	XKR9	-2.544886368	0.022206703	down
INO80E	4.681201868	1.42E-52	up	KIAA1210	-2.539095238	0.002209794	down
HOXC4	4.680419954	4.54E-07	up	PMP2	-2.53760837	0.03413236	down
KISS1R	4.671210317	4.94E-05	up	CACNA1E	-2.536552304	0.007691448	down
HIC1	4.667715432	1.33E-57	up	C11orf65	-2.536170315	3.16E-12	down
MAP7D1	4.665163651	6.08E-80	up	LRRN4	-2.528782349	0.01417019	down
FGF11	4.651189607	2.59E-09	up	CXCL6	-2.524737301	0.000771229	down
LMTK3	4.646718152	0.001511733	up	BRINP2	-2.518806267	0.00401293	down
HSD17B1	4.64577457	1.63E-08	up	NR1H4	-2.516979781	0.005754692	down
RPL27	4.641295905	8.89E-88	up	RHCE	-2.516337755	0.000828838	down
SOX1	4.63858801	0.004855501	up	ACTC1	-2.513070814	0.03206122	down
SAG	4.634893275	7.69E-09	up	XKR4	-2.505273957	0.003647828	down
PLCB3	4.6287606	1.47E-68	up	CYP2C18	-2.502737766	0.000511706	down
TRIR	4.619986619	9.09E-74	up	KCTD14	-2.502029772	6.29E-09	down
COL6A1	4.602271244	1.93E-64	up	LRAT	-2.49334743	1.04E-05	down

Table S5. Top300 upregulated and downregulated DEGs in severe eCRSwNP versus healthy controls.

gene	log2FoldChange	padj	group	gene	log2FoldChange	padj	group
CLC	12.36171915	7.65E-74	up	PRSS48	-8.679800999	6.82E-23	down
VSTM1	11.35481113	1.52E-40	up	BRINP3	-8.530424256	0.006492766	down
CEBPE	10.51053549	2.17E-32	up	GPR22	-8.518958683	1.80E-29	down
OLIG1	10.45377675	1.05E-29	up	TYR	-7.884621197	4.32E-07	down
CCL13	10.32714533	2.90E-66	up	RNF113B	-7.679344834	3.84E-10	down
RNASE2	10.11120529	1.06E-28	up	SMIM18	-7.568935962	7.77E-27	down
LGALS12	10.02072727	4.72E-35	up	POU5F2	-7.545897042	1.95E-42	down
MEX3D	9.989309642	6.59E-45	up	PRR4	-7.400470377	1.15E-18	down
FBXL19	9.806071078	9.41E-47	up	PLET1	-6.886780249	1.22E-10	down
SUCNR1	9.638723993	2.14E-37	up	OR1Q1	-6.764718998	0.000190971	down
OLIG2	9.505556803	2.36E-22	up	PSG11	-6.728578806	0.013309525	down
CLCA1	9.374204629	7.88E-13	up	BLID	-6.710057857	0.000393009	down
TMEM238	9.353365768	3.71E-25	up	BPIFB6	-6.680226565	0.000172549	down
UBALD2	9.264812059	4.46E-69	up	PSG8	-6.616990825	0.004897654	down
CST1	9.253237762	5.42E-20	up	KCTD4	-6.515823147	3.65E-11	down
SHISA8	9.152688323	3.80E-30	up	OR51I1	-6.256466505	6.04E-05	down
ADRA2C	9.068257339	1.10E-32	up	LRTM1	-6.199612964	0.007636798	down
ZNF787	9.017613668	4.91E-57	up	CRISP3	-6.0681114	3.96E-06	down
JUND	8.829854431	3.69E-75	up	PSG3	-6.02278792	0.00068758	down
UGT2B11	8.719377692	2.33E-21	up	AC008764.1	-5.9965727	1.80E-05	down
CDH24	8.482679643	1.12E-39	up	SEZ6	-5.987222833	9.27E-14	down
HRH4	8.128115211	4.66E-25	up	HIST1H4C	-5.97757965	5.52E-11	down
CCL26	8.103365053	2.63E-28	up	TXNDC8	-5.972377556	3.51E-10	down
COL6A5	8.099450307	6.71E-21	up	ZBTB20	-5.929787012	1.51E-85	down
BARX1	8.068827932	7.53E-22	up	ACSM6	-5.923434994	2.70E-09	down
BRSK1	8.025390819	1.17E-30	up	SLCO6A1	-5.883238283	0.045023041	down
CCL18	7.980856621	6.97E-14	up	S100G	-5.757290478	4.56E-05	down
FOXO6	7.932478543	1.73E-27	up	PSG7	-5.708276694	0.024123626	down
CBARP	7.85407809	2.74E-23	up	MUSK	-5.673091973	1.47E-09	down
CDH22	7.762384131	1.71E-21	up	OR51I2	-5.667500245	0.023006097	down
CTXN1	7.747373316	4.59E-17	up	TCP11X1	-5.656660235	0.002671573	down
NXPH4	7.734111304	1.99E-23	up	PSG6	-5.634067527	0.007518919	down
SHANK1	7.706717281	7.45E-27	up	SPINK4	-5.629667166	0.000462802	down
TMEM158	7.665387958	1.63E-28	up	NXF2	-5.624780535	0.00184235	down
IER5L	7.657533504	1.85E-35	up	CA1	-5.595390687	6.01E-13	down
CITED4	7.619055956	7.17E-36	up	TMPRSS11F	-5.526443392	0.01238605	down
NRGN	7.553619845	9.59E-26	up	ABRA	-5.498350555	8.49E-05	down
ZFPM1	7.553499298	7.81E-37	up	ELOA2	-5.479053986	0.005078286	down
ZBTB12	7.52464325	1.42E-27	up	CRISP2	-5.465671687	8.80E-17	down
MEPCE	7.518446969	1.69E-38	up	PRB3	-5.439418025	1.17E-05	down
CARMIL2	7.507301315	2.56E-30	up	FEZF1	-5.381290712	7.91E-07	down
ZNF579	7.475169686	2.95E-51	up	DDI1	-5.341487905	0.010408901	down
SEMA7A	7.462033254	2.28E-24	up	PSG1	-5.338657619	0.007481731	down
NACC1	7.404088565	7.69E-84	up	EPB42	-5.31940996	0.006724835	down
CHMP4B	7.367715958	1.48E-232	up	GLYATL1	-5.298137856	5.94E-10	down

gene	log2FoldChange	padj	group	gene	log2FoldChange	padj	group
STX16-NPEPL1	7.257577144	8.97E-16	up	SMIM34A	-5.278717685	0.002050705	down
WAS	7.251456651	4.96E-45	up	CPB2	-5.248105285	0.00203113	down
VPS37D	7.245591436	2.77E-22	up	SCGN	-5.247421681	0.001431485	down
UTS2R	7.227955657	9.56E-16	up	CCDC179	-5.214481615	0.016679025	down
H1FX	7.225826516	1.32E-74	up	LRRC19	-5.197000211	7.79E-24	down
APOBR	7.20437173	4.48E-30	up	SUMO4	-5.150815561	8.07E-22	down
SOX18	7.143990051	6.54E-28	up	RNASE8	-5.131912018	4.71E-05	down
TRPM5	7.103769857	4.81E-12	up	OR10A2	-5.12761594	2.86E-08	down
NTNG2	7.090602932	2.96E-16	up	INSYN2	-5.109677856	2.38E-55	down
SPI1	7.042627858	9.66E-57	up	AP001267.5	-5.102394891	0.00126938	down
CDC42EP5	7.02442055	2.23E-44	up	GRIN2B	-5.087298587	0.00092175	down
ECEL1	7.011950726	3.91E-18	up	SARNP	-5.073216398	5.11E-23	down
ALYREF	6.980082601	1.09E-51	up	RPA4	-5.071427481	5.21E-05	down
BICRA	6.972023266	1.58E-51	up	SYCP3	-5.027930161	3.24E-28	down
EHBP1L1	6.92784858	2.62E-110	up	GNAT2	-5.024592584	2.46E-31	down
ADGRE1	6.920427043	6.53E-23	up	BOLL	-5.022245378	0.000462393	down
SEPT5-GP1BB	6.918521573	2.19E-15	up	BTBD18	-5.016980855	2.45E-11	down
SEMA6B	6.862129492	1.18E-44	up	HIST2H4A	-5.015539614	3.68E-07	down
TGFB1	6.83691515	8.22E-41	up	MRGPRX3	-5.004910511	0.007938022	down
FAM171A2	6.827092799	5.81E-19	up	QRFPR	-5.001308184	4.31E-05	down
MT-ND3	6.820557474	2.61E-98	up	CPHXL	-4.931554021	0.004882557	down
ZBTB7A	6.797515697	1.29E-108	up	FREM3	-4.923649938	1.29E-06	down
ANO8	6.786656194	4.76E-49	up	C12orf40	-4.916054293	8.59E-06	down
PTMS	6.768594695	4.13E-247	up	OR5P3	-4.897602396	0.00904765	down
LRFN1	6.761567916	5.06E-18	up	SLC26A9	-4.850186772	0.000625588	down
KCNC3	6.759561578	1.34E-29	up	RNF133	-4.848869752	0.000398148	down
TMEM240	6.757334128	3.72E-19	up	METTL21C	-4.821309359	0.034839192	down
HCN2	6.70161737	1.07E-13	up	TAS2R30	-4.801956128	6.08E-05	down
CEBPB	6.666446227	1.15E-40	up	C9	-4.72825163	2.77E-07	down
SAG	6.652018983	7.04E-14	up	AC091167.6	-4.719877442	0.031903302	down
PTGDR2	6.642455111	1.56E-19	up	PPBP	-4.719725713	0.000690634	down
MYPOP	6.627508181	2.26E-36	up	HMGCS2	-4.717668708	5.04E-10	down
COL18A1	6.617626823	7.77E-109	up	KRT12	-4.706946852	0.001449167	down
NYAP1	6.578873837	3.89E-17	up	ANKRD36C	-4.704920058	7.51E-57	down
ZNF775	6.575019929	4.95E-22	up	UBQLN3	-4.704710791	0.04096925	down
CCL24	6.553131166	8.02E-21	up	NKX3-1	-4.667023695	4.87E-25	down
TCF15	6.497073038	2.49E-12	up	OR52H1	-4.666814788	0.035747815	down
PRR12	6.470880013	1.00E-48	up	SPDYE3	-4.663204769	8.28E-16	down
TBX4	6.458696393	1.22E-14	up	CCDC196	-4.649199354	2.98E-07	down
LINGO3	6.444429114	2.32E-14	up	ANKRD20A1	-4.640387401	5.55E-09	down
HK3	6.430933395	8.20E-17	up	TSPYL6	-4.601971031	0.02357413	down
KLF2	6.420460071	3.30E-74	up	AC010547.4	-4.575353912	0.004963894	down
GRIN2D	6.414787193	3.47E-17	up	AC104389.4	-4.57229406	5.00E-11	down
LMTK3	6.407200138	1.02E-13	up	OR2A5	-4.568444765	0.030110224	down
ADGRG3	6.371867837	2.31E-19	up	PAH	-4.545528899	0.012270483	down
PRR36	6.314249796	5.34E-16	up	SPDYE16	-4.538938926	2.92E-16	down
CACNG6	6.305214808	2.18E-20	up	AADACL2	-4.528813285	2.70E-09	down

gene	log2FoldChange	padj	group	gene	log2FoldChange	padj	group
CYSLTR2	6.29818047	7.60E-12	up	SMIM32	-4.522950769	0.029181222	down
C11orf96	6.269950483	1.34E-20	up	CBY3	-4.515671026	2.37E-08	down
CHCHD10	6.264807048	1.70E-65	up	FGF5	-4.515602185	0.007571263	down
HAMP	6.246480595	8.55E-13	up	FGF16	-4.511997868	3.58E-05	down
SOCS1	6.245032879	2.09E-29	up	CDRT4	-4.500144538	5.69E-09	down
ICAM5	6.239381992	1.55E-18	up	FAM156B	-4.479560646	1.17E-22	down
ZNF865	6.237742197	1.98E-23	up	LHFPL4	-4.474837704	4.59E-09	down
PPP1R9B	6.230926499	1.22E-66	up	LYG2	-4.44243857	2.53E-42	down
IQCJ-SCHIP1	6.226487906	6.14E-17	up	HTR2A	-4.404523977	0.010762975	down
RNASE3	6.224579302	8.22E-09	up	RHOXF2	-4.371979034	0.008892254	down
AC009690.1	6.21579352	2.64E-11	up	CA6	-4.371466879	0.000137643	down
FIGNL2	6.205899281	2.20E-15	up	ANKRD7	-4.350204911	4.03E-05	down
TOR4A	6.141383836	3.06E-35	up	SMIM2	-4.3399191	0.026022622	down
SPINDOC	6.137851562	2.63E-61	up	AL117339.5	-4.323912187	6.67E-27	down
PLCB2	6.129678327	6.40E-35	up	REG4	-4.31904667	0.000654581	down
MMP25	6.091028385	1.87E-26	up	CTAGE1	-4.305826552	0.036483559	down
AMH	6.07879335	1.72E-10	up	AC104472.3	-4.298744655	0.005477326	down
PLPPR3	6.071987859	5.37E-10	up	STXBP5L	-4.295051897	7.98E-06	down
RCOR2	6.070944989	3.10E-14	up	ANGPTL7	-4.292629058	0.000679715	down
LCN10	6.066967919	7.87E-13	up	B3GALT1	-4.291835392	2.54E-08	down
PPP1R14B	6.04242857	1.60E-56	up	DACH2	-4.288540369	0.000180763	down
SLC9A3	6.034850148	7.56E-36	up	HNF4A	-4.246906822	0.034380575	down
GPIHBP1	6.032195063	2.02E-30	up	RNASE7	-4.239920516	6.59E-06	down
SCX	6.009028879	3.11E-14	up	AC010542.3	-4.224170042	0.001997071	down
CBLN1	6.007148519	4.86E-05	up	CCDC175	-4.219069088	2.23E-07	down
GAL3ST2	5.986439023	1.35E-13	up	SLC5A5	-4.205325993	0.008907865	down
PPP1R37	5.975593443	3.99E-112	up	C10orf90	-4.205121236	1.46E-07	down
FZD8	5.937745189	4.28E-29	up	OPRK1	-4.204913141	0.048207474	down
KLF13	5.933024071	9.26E-59	up	GABRA2	-4.201949657	0.000407328	down
MARCO	5.929583616	9.80E-05	up	PRR27	-4.200237966	0.000333546	down
LST1	5.912653858	1.03E-28	up	TEDDM1	-4.192828349	0.020927152	down
RAB44	5.906223431	2.77E-15	up	PRH2	-4.16602257	7.65E-11	down
LYL1	5.903707102	3.58E-18	up	NANOGP8	-4.160089819	7.76E-14	down
NUDT3	5.902879344	6.23E-29	up	MYBPC1	-4.158800088	1.45E-05	down
CACNG8	5.902767312	2.01E-10	up	KCNJ18	-4.149082319	0.003781478	down
PRRX2	5.895245846	5.54E-27	up	SLC3A1	-4.114082593	6.87E-06	down
CCL23	5.893462568	2.07E-20	up	C9orf131	-4.109021148	0.005776316	down
PRPF19	5.882778404	1.39E-64	up	SERPIND1	-4.105549799	1.33E-09	down
SH2B2	5.868529551	3.84E-28	up	GSTA2	-4.097166588	4.74E-06	down
PPDPF	5.855697012	5.48E-186	up	MEP1B	-4.0963019	0.003342294	down
RBP4	5.852057881	4.99E-09	up	SPINK1	-4.090191917	0.046933419	down
SBNO2	5.821411016	1.89E-37	up	PRR26	-4.085130115	1.65E-18	down
SRXN1	5.810203009	1.02E-12	up	LUZP2	-4.082370965	1.45E-07	down
C1QL1	5.790096935	1.61E-12	up	TM4SF4	-4.071860544	0.018182871	down
APOE	5.751072754	1.14E-53	up	PRH1	-4.059046223	6.09E-36	down
CCR3	5.745019633	8.43E-15	up	C9orf153	-4.040130325	0.004199699	down
HTR3C	5.73577801	1.16E-06	up	RAMACL	-4.029833713	6.65E-43	down

gene	log2FoldChange	padj	group	gene	log2FoldChange	padj	group
SEMA3F	5.710649831	5.13E-38	up	C1QTNF9B	-4.028780081	0.001452785	down
RASGRP4	5.704924653	2.24E-26	up	SLC26A5	-4.018220443	4.12E-14	down
RPL28	5.674548795	2.82E-149	up	EPPIN-WFDC6	-4.010161586	0.000782333	down
C8orf82	5.669024689	4.07E-101	up	SYT14	-3.999107305	0.000415261	down
SH3BP1	5.66882046	2.08E-35	up	PON1	-3.997137946	0.037646116	down
CEBPD	5.656264865	1.12E-26	up	BPIFB3	-3.988331557	0.003132613	down
UBE2M	5.644836231	2.75E-78	up	PMP2	-3.976824486	0.000638233	down
SKI	5.643465155	1.22E-62	up	ACTC1	-3.968126537	0.001981122	down
HS3ST4	5.638172907	1.44E-12	up	XKR4	-3.964485708	7.28E-07	down
GRASP	5.636217361	7.51E-32	up	MFAP5	-3.958659378	4.61E-06	down
NOTUM	5.615431956	5.10E-12	up	CIDECD	-3.946157541	0.0147057	down
NLRP12	5.602378098	1.11E-09	up	CDH19	-3.942549865	1.64E-05	down
ABHD17A	5.592052154	3.07E-62	up	BPIFB2	-3.942190735	0.001352756	down
FOXD1	5.574167934	3.71E-10	up	PLA2G2A	-3.93556419	0.00018172	down
FOXL2	5.555255664	2.77E-07	up	RGPD6	-3.88400766	1.19E-08	down
ESPNL	5.548668496	1.92E-10	up	AC013470.2	-3.880613819	2.49E-05	down
FFAR2	5.548070204	1.10E-07	up	HP	-3.874283493	0.000375049	down
HES4	5.543673435	2.36E-17	up	AGBL1	-3.869899205	0.019217861	down
TBX2	5.53951692	3.11E-35	up	ART3	-3.868165849	2.23E-05	down
EMILIN1	5.51393361	7.13E-39	up	SPATA12	-3.865910123	9.87E-07	down
CHAT	5.512272888	3.64E-05	up	AC001226.2	-3.84142436	1.38E-13	down
CTS2	5.500512595	3.83E-50	up	INSL6	-3.831986067	5.23E-10	down
GPR42	5.483919506	4.37E-07	up	CALCB	-3.820912827	0.010948191	down
ADGRB1	5.476883233	4.14E-12	up	REN	-3.8196627	0.000179706	down
GJD3	5.468054292	3.56E-28	up	ADGRF2	-3.801231875	5.09E-05	down
PADI4	5.457376803	1.17E-10	up	ANKUB1	-3.800591028	6.83E-07	down
CTU1	5.447170316	1.09E-25	up	DUXB	-3.77378491	0.000630765	down
TEX15	5.446508655	1.85E-09	up	FIBIN	-3.773018161	7.75E-09	down
NLRP6	5.445554048	1.56E-10	up	C19orf67	-3.77067708	1.05E-06	down
POSTN	5.44150051	1.80E-25	up	GRM5	-3.750717944	0.004968051	down
ANKRD63	5.432530499	1.72E-09	up	ANKRD36B	-3.742671306	1.50E-39	down
TWIST1	5.423346265	1.67E-33	up	MLIP	-3.740421329	0.000249312	down
SIGLEC8	5.405876386	8.12E-15	up	MROH9	-3.725210072	1.44E-06	down
SLN	5.375556239	8.45E-09	up	LDHAL6B	-3.724514994	0.028021884	down
GRIK5	5.375441901	3.44E-24	up	LRRC9	-3.717918899	0.001339985	down
TBX1	5.367873559	6.42E-74	up	RAB40AL	-3.699887865	0.00266539	down
MS4A6E	5.355636924	1.02E-06	up	KCNV2	-3.694760075	8.19E-05	down
DBH	5.35028158	1.03E-10	up	DGAT2L6	-3.691380979	0.027879916	down
SCAF1	5.349132508	3.12E-148	up	ASB11	-3.690165273	0.016237269	down
NRARP	5.339511273	2.71E-40	up	PRSS37	-3.682710661	0.010147297	down
SNRNP70	5.329942597	8.82E-87	up	CHRM1	-3.67347404	2.13E-06	down
DRD4	5.327982743	8.29E-11	up	ARHGAP8	-3.649600114	3.67E-06	down
TIMD4	5.324131631	4.74E-07	up	CA2	-3.648588928	3.96E-07	down
WNT6	5.294778395	2.01E-17	up	GLRB	-3.635262235	4.42E-09	down
FOXP3	5.286893294	1.77E-19	up	GBP7	-3.62051603	0.003977565	down
NRROS	5.279496886	1.45E-39	up	SPDYE5	-3.602770424	4.41E-46	down
GDNF	5.253109082	3.46E-14	up	SVOP	-3.600487104	0.015606133	down

gene	log2FoldChange	padj	group	gene	log2FoldChange	padj	group
AC068987.5	5.24471446	8.94E-08	up	PRRG3	-3.596524879	1.11E-14	down
CPLX1	5.23900744	4.30E-23	up	FRMPD2	-3.589501819	0.000245775	down
CDKN1C	5.217698033	1.80E-34	up	SPATA21	-3.584949859	0.004259028	down
IL1RL1	5.214265458	1.02E-06	up	PRB4	-3.581609348	0.000546434	down
CCL11	5.213681844	4.02E-15	up	FBXO15	-3.563185992	0.000602001	down
GIPC3	5.211457606	4.21E-16	up	SPICE1	-3.558855682	1.09E-30	down
SECTM1	5.209135511	1.36E-35	up	APOBEC2	-3.555135115	1.50E-10	down
HCN1	5.201011018	1.61E-05	up	LRRTM3	-3.519172748	0.001274232	down
MAPKAPK2	5.190471505	2.52E-86	up	FYB2	-3.510230429	4.12E-09	down
SLC17A7	5.186806389	1.25E-09	up	AC025287.4	-3.504596612	0.002708808	down
GNG13	5.177640221	2.20E-05	up	TIMP4	-3.49462655	8.49E-08	down
SCARF2	5.174750084	3.23E-28	up	GSTO2	-3.494184972	1.01E-17	down
HOXB4	5.164650674	1.89E-11	up	TMEM270	-3.4862396	0.001352523	down
DUSP9	5.160271928	1.27E-09	up	SEMA3E	-3.478135609	3.33E-10	down
SCRIB	5.159811645	3.84E-32	up	AL031708.1	-3.47479633	3.69E-10	down
NAT8L	5.148060572	4.35E-08	up	MUC7	-3.459518412	0.002443509	down
HPCAL4	5.144570818	2.45E-09	up	CORIN	-3.455004529	6.17E-08	down
GFI1B	5.139569567	5.62E-11	up	PRG2	-3.452635593	0.048071479	down
ADRA2A	5.136281666	5.20E-45	up	ARSH	-3.451381123	6.60E-05	down
PRSS33	5.130460834	3.14E-13	up	GUCY2C	-3.449582083	2.86E-10	down
CCDC188	5.129335383	8.97E-14	up	TSPAN19	-3.438969123	0.001405531	down
PBX2	5.121635446	3.01E-94	up	MOGAT1	-3.438943475	0.04917738	down
RPL39	5.113276241	3.55E-70	up	CDH10	-3.438133652	0.024361334	down
LFNG	5.0979161	6.03E-37	up	ANKRD62	-3.43779657	0.015355785	down
HDGFL2	5.089401388	5.96E-97	up	NEURL3	-3.436759252	3.10E-17	down
SOX17	5.074800193	1.43E-15	up	NELL2	-3.428335029	4.46E-10	down
COL6A2	5.074064865	7.05E-89	up	AMY1B	-3.422216413	8.30E-06	down
ZNF503	5.07033174	2.85E-63	up	TAS2R31	-3.422032309	6.56E-08	down
OR7D2	5.063113068	0.0007908	up	PIK3C2G	-3.41449306	0.000690049	down
FZD2	5.06151051	1.93E-11	up	CHRNA9	-3.398899062	0.005014661	down
FAM43B	5.048550307	2.11E-09	up	CHRM3	-3.390120294	1.34E-06	down
KCNK13	5.045251364	6.85E-10	up	GJB7	-3.385015324	9.70E-05	down
C2CD4B	5.034427652	1.60E-14	up	HIST2H4B	-3.377589254	0.000140062	down
ZNF628	5.029554455	1.06E-45	up	SCRG1	-3.376590068	1.48E-08	down
IGDCC3	5.02603365	2.26E-08	up	SLCO1B1	-3.36205121	0.033580855	down
CLDND2	5.025716944	2.79E-08	up	FAM237B	-3.339296598	0.000869934	down
FGF11	5.022792012	1.08E-11	up	WFDC6	-3.331784653	0.002618408	down
LSM14B	4.998159682	5.60E-117	up	OR2A4	-3.316374713	0.001828076	down
B4GALNT4	4.992775735	1.95E-20	up	ZNF573	-3.315157921	1.39E-15	down
ESPN	4.992080931	3.25E-29	up	CWH43	-3.315156096	0.015490961	down
RPS21	4.989616089	3.81E-66	up	STPG2	-3.307468028	7.35E-08	down
EMX2	4.983242637	5.14E-06	up	SLC10A1	-3.301125439	3.08E-08	down
RPS28	4.979733098	2.23E-135	up	WNT8B	-3.294482441	0.018984527	down
RNF208	4.974836903	1.31E-29	up	C2orf91	-3.289331312	0.012757819	down
FBRSL1	4.971553194	4.10E-61	up	SLC4A9	-3.289089357	0.006057975	down
APOC1	4.971213599	4.10E-16	up	DIO2	-3.28338225	7.43E-09	down
PPP1R12C	4.970426447	8.17E-152	up	BEST4	-3.276899178	0.00013528	down

gene	log2FoldChange	padj	group	gene	log2FoldChange	padj	group
TMEM150B	4.944270964	1.44E-10	up	POLDIP3	-3.270913135	0.000177686	down
ADAMTS10	4.942295228	9.05E-23	up	NDUFV2	-3.262560664	7.98E-21	down
MAFA	4.923957407	3.30E-05	up	CLEC19A	-3.258203452	0.000153446	down
NTRK1	4.918153455	7.44E-30	up	KLB	-3.250959061	8.04E-06	down
LKAAEAR1	4.917922927	5.16E-05	up	NKAIN1	-3.249810489	0.0329518	down
RPLP2	4.91623256	1.34E-89	up	LPO	-3.247599193	0.00375526	down
CREB3L3	4.909139305	3.15E-05	up	FCAMR	-3.239629243	0.023225408	down
TMEM132E	4.905914524	5.04E-12	up	ZNF474	-3.236037734	0.000164994	down
PPIAL4A	4.905815529	0.00186742	up	BEST3	-3.225649919	0.011077654	down
EEF1A2	4.903529336	3.57E-08	up	TEX38	-3.225317019	0.009171112	down
SPRN	4.888940765	5.19E-10	up	CFAP206	-3.221196081	0.003421259	down
METRNL	4.88541126	3.42E-44	up	FXD2	-3.210375167	0.000593999	down
MUC6	4.874911158	1.86E-07	up	LRR74B	-3.20712762	0.003031777	down
TPBGL	4.873401694	1.24E-09	up	FAM156A	-3.207077506	6.67E-15	down
NLGN2	4.869145611	2.16E-36	up	HNF1B	-3.205331778	0.00266539	down
ZNF598	4.868263065	7.64E-56	up	ZBP1	-3.202774109	0.037765691	down
ITGAM	4.859614146	7.17E-15	up	GNMT	-3.193661004	3.65E-11	down
CYBA	4.859375888	1.93E-41	up	TRPA1	-3.190748491	2.33E-05	down
C6orf222	4.856770167	0.00035186	up	FOLH1	-3.190585357	7.45E-07	down
CARD9	4.850666757	1.07E-08	up	IL23R	-3.18933294	0.014373514	down
ARHGAP23	4.845866991	2.22E-51	up	AP000275.2	-3.174390164	4.62E-16	down
RNF225	4.842671978	2.96E-07	up	LRAT	-3.166878536	5.47E-05	down
GPR27	4.842254758	1.86E-12	up	PIP	-3.162463964	0.008188001	down
MAP3K10	4.840983318	3.52E-54	up	ACADL	-3.161181212	5.56E-09	down
SLC2A4RG	4.84080506	8.46E-67	up	GDF3	-3.160778021	0.014930133	down
SPRR2A	4.838434806	0.002931278	up	PON3	-3.159850229	5.24E-13	down
FFAR3	4.812279734	2.65E-06	up	NRG3	-3.139031449	0.013536954	down
CIB2	4.810708176	1.03E-26	up	C6orf10	-3.134655615	0.011546804	down
CACNA1H	4.809926645	3.76E-35	up	SRRM4	-3.132438685	0.030115946	down
INSRR	4.806962908	2.16E-11	up	FGF12	-3.127200146	6.77E-10	down
GCKR	4.806769757	1.94E-07	up	PPP1R36	-3.122112278	1.70E-08	down
MBD6	4.805289081	1.22E-25	up	DCDC2B	-3.11593892	0.00011632	down
RTN4RL1	4.80170855	1.00E-16	up	SUN3	-3.109559818	0.049798721	down
CUX2	4.795813036	1.08E-05	up	SEC14L3	-3.106909907	0.000253971	down
C5orf38	4.793852113	4.55E-09	up	BCL11A	-3.106832202	3.67E-37	down
ADORA3	4.777208247	1.82E-10	up	UGT2B7	-3.106052761	0.00104438	down
KRT72	4.771859333	6.26E-07	up	ESRRG	-3.10014578	6.14E-16	down
MZT2B	4.769123399	7.31E-40	up	PARD6B	-3.089064474	4.74E-29	down
VWA1	4.765141024	8.70E-40	up	FAM171B	-3.083251905	4.48E-16	down
INAFM1	4.76384131	4.75E-47	up	ZNF460	-3.077711436	8.32E-11	down
KCNJ6	4.748974583	1.03E-05	up	WIF1	-3.075363033	0.005404993	down
MAP7D1	4.742308054	7.93E-83	up	PLP1	-3.070688309	1.05E-07	down
MS4A3	4.741896893	1.80E-07	up	CYP3A43	-3.066730619	0.006320375	down
LIPN	4.741323542	2.84E-08	up	DNAJB7	-3.064611855	0.002183895	down
NRXN2	4.740832143	7.59E-14	up	C9orf84	-3.059508486	3.51E-15	down
SH2D6	4.730886448	1.14E-05	up	ASTL	-3.056526584	0.002211876	down
ARTN	4.72940651	1.79E-17	up	BBOX1	-3.055905444	5.33E-11	down

gene	log2FoldChange	padj	group	gene	log2FoldChange	padj	group
STK11	4.720991788	8.09E-27	up	MEIS1	-3.05133994	2.56E-24	down
NKX3-2	4.716740139	0.000995347	up	NRXN1	-3.04350765	0.003382548	down
NTN3	4.713144097	1.26E-06	up	MAGED4	-3.043330128	1.94E-07	down
PANX2	4.70962757	4.45E-16	up	OVOL1	-3.042064385	5.85E-08	down
FJX1	4.703439663	8.79E-11	up	AP001931.1	-3.041716861	3.74E-06	down
FOXQ1	4.697601517	1.74E-31	up	KCNRG	-3.037576617	0.000118716	down
CRABP1	4.692381823	8.97E-20	up	DCAF12L2	-3.032629945	0.02387619	down
SERPINA3	4.688415281	2.24E-05	up	CYP2F1	-3.03110454	3.16E-06	down
HOXC4	4.686309343	2.89E-05	up	LYZ	-3.030484351	0.001362379	down
CD209	4.673949337	5.75E-13	up	SLC22A3	-3.026168539	3.04E-06	down
AC136616.1	4.669958812	0.000298537	up	SPDYE1	-3.024893556	1.06E-13	down
BCL9L	4.665073104	1.40E-47	up	IGSF11	-3.015409818	2.65E-05	down
DPPA4	4.662417881	4.08E-05	up	TUBA4B	-3.010470829	0.003974857	down
COL5A3	4.660834491	6.31E-40	up	SLC13A2	-3.010191624	1.69E-07	down
CACNA1I	4.653183344	3.76E-10	up	FAM218A	-3.00935089	1.22E-11	down
FAM83H	4.643751452	9.82E-40	up	CYP4A11	-3.009053927	1.94E-06	down
UCN3	4.641643293	3.54E-08	up	GRIA2	-3.006187362	0.000976969	down
NES	4.638009908	1.07E-45	up	PIGR	-3.005615388	3.89E-07	down
COL6A1	4.63663769	3.50E-87	up	SHISA2	-3.001058071	3.03E-11	down
RPL27	4.63396629	2.17E-86	up	C6orf118	-2.99210507	0.003099234	down

Table S6. Primers used for RT-PCR analysis.

Primer	Forward Sequence	Reverse Sequence
ALOX15	TGGAAGGACGGGTTAATTCTGA	GCGAAACCTCAAAGTCAACTCT
CCL13	CTCAACGTCCCATCTACTTGC	TCTTCAGGGTGTGAGCTTTCC
18S	GGAGTATGGTTGCAAAGCTGA	ATCTGTCAATCCTGTCCGTGT

Table S7. Genesets used in Mφ_Immunoregulatory scores analysis.

CD68	ALOX15	CTSB	MMP9	CCL13	TGF-B1	VEGFA	WNT7B	IL1RN
CD163	CST1	CTSC	MMP14	CCL18	TGF-B2	VEGFB	VIM	IL1R2
CD274	FN1	CTSD	MMP19	CCL20	TGF-B3	VEGFC	ARG2	IL10
MRC1	CTSA	CTSZ	POSTN	CCL24	EGR1	VEGFD	CSF1R	IL4R