ITGAM and FCGR3B contribute to recurrent and limited CRSwNP in children through phagosome pathway

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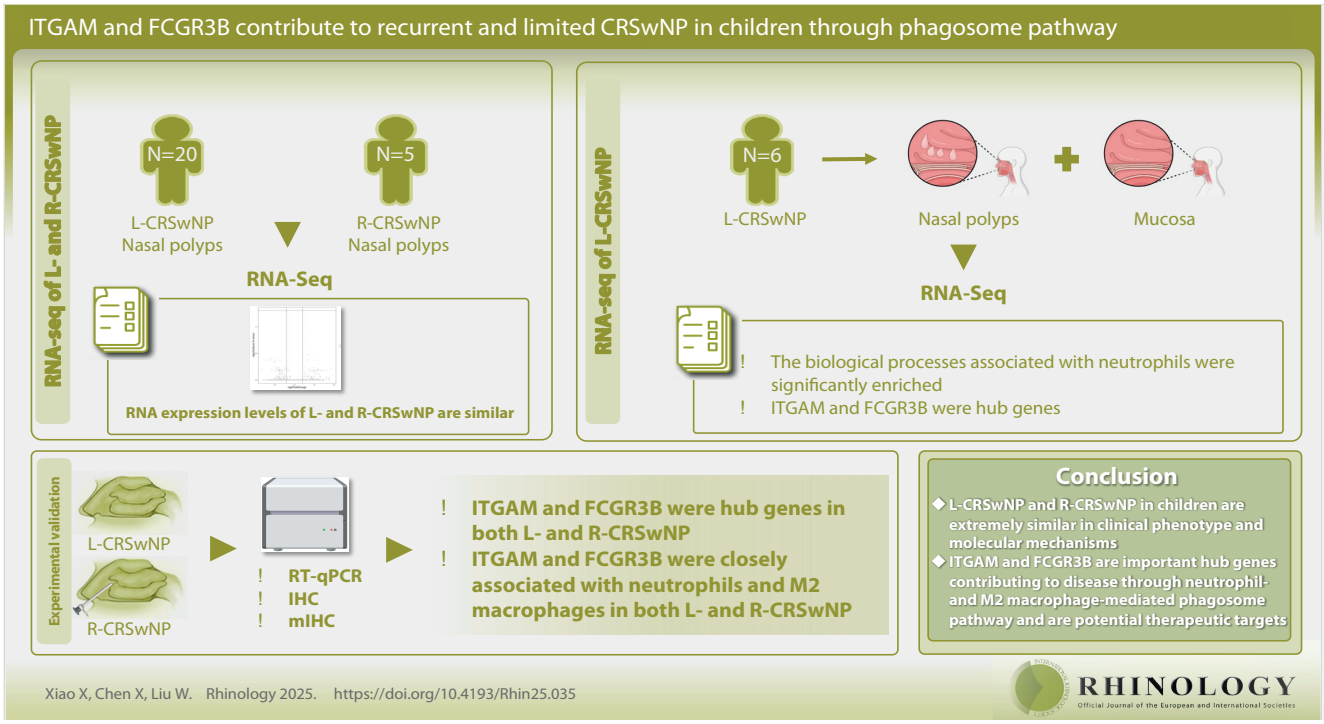
Rhinology 63: 6, 0 - 0, 2025

https://doi.org/10.4193/Rhin25.035



Abstract

Background: Chronic rhinosinusitis with nasal polyps (CRSwNP) is more common in children with limited CRSwNP (L-CRSwNP). L-CRSwNP shares similar clinical phenotypes with recurrent CRSwNP (R-CRSwNP). This study aimed to explore the molecular mechanisms of L- and R-CRSwNP in children.

Methodology: Compared clinical characteristics and RNA sequencing data of 20 L-CRSwNP and 5 R-CRSwNP in children. Paired analyzed RNA sequencing data of 6 children with L-CRSwNP polyps and mucosal tissue samples. Conducted GO and KEGG enrichment analyses. Identified hub genes through protein-protein interaction networks (PPI). Validated hub genes in L- and R-CRSwNP using real-time quantitative PCR (RT-qPCR), immunohistochemistry (IHC), and multiplex immunohistochemistry (mIHC).

Results: RNA-seq analysis of L- and R-CRSwNP polyp showed no differentially expressed genes (DEGs). RNA-seq paired analysis of L-CRSwNP identified 1419 DEGs. GO enrichment analysis showed significant enrichment for biological processes associated with neutrophils. ITGAM and FCGR3B were identified as hub genes by PPI analysis. RT-qPCR and IHC results suggested the expression levels of ITGAM and FCGR3B were significantly increased in L- and R-CRSwNP. mIHC results suggested ITGAM and FCGR3B were closely associated with neutrophils and M2 macrophages in L- and R-CRSwNP.

Conclusions: L- and R-CRSwNP in children exhibit similar clinical phenotypes and molecular mechanisms. ITGAM and FCGR3B are hub genes contributing to disease through neutrophil- and M2 macrophage-mediated phagosome pathway.

Key words: ITGAM, FCGR3B, phagosome, children, limited CRSwNP, recurrence

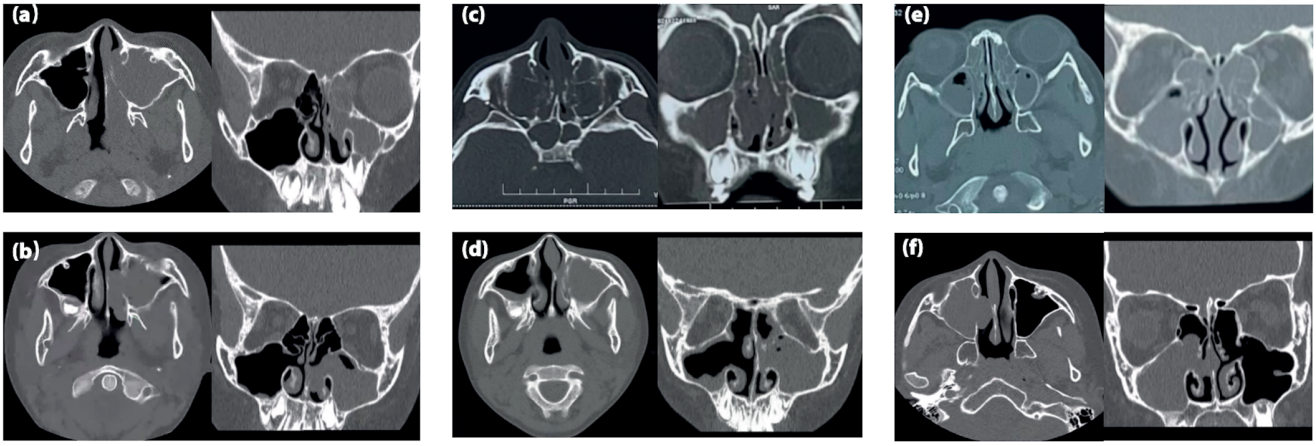


Figure 1. Preoperative images of R-CRSwNP children at first surgery and recurrent surgery. (a) Patient 1: First surgical preoperative sinus CT on August 25, 2021; (b) Patient 1: Recurrent surgical preoperative sinus CT on July 12, 2022; (c) Patient 2: First surgical preoperative sinus CT on October 24, 2021; (d) Patient 2: Recurrent surgical preoperative sinus CT on July 25, 2022; (e) Patient 3: First surgical preoperative sinus CT on December 28, 2021; (f) Patient 3: Recurrent surgical preoperative sinus CT on October 18, 2022.

Introduction

Chronic rhinosinusitis (CRS) is a highly heterogeneous disease associated with chronic inflammation of the nasal mucosa, with a prevalence of 3-6%, based on a combination of symptoms and endoscopy or CT scanning [1-3]. CRS has a prevalence of 4% in children [4], with the highest incidence rate from 7-10 years of age [5]. Common symptoms of CRS in children include persistent or intermittent nasal congestion, mucus, or mucopurulent nasal discharge. Some children may also experience sleep disorders, secretory otitis media, etc. [6]. Severe CRS has an impact on children's quality of life and generalized development [7, 8] and imposes a heavy economic burden on families and society [9].

CRS can be categorized into chronic rhinosinusitis with nasal polyps (CRSwNP) and chronic rhinosinusitis without nasal polyps (CRSsNP) based on phenotype. CRSwNP is further categorized in EPOS 2020 according to anatomical distribution into limited CRSwNP (L-CRSwNP) with unilateral lesions and diffuse CRSwNP (D-CRSwNP) with bilateral lesions [10]. Surgery is required for CRSwNP children who failed conservative treatment. However, the recurrence rate of CRSwNP is still as high as 10-35% after functional endoscopic sinus surgery (FESS) [11, 12].

Antrochoanal polyp (ACP) is a special type of L-CRSwNP in which the polyp originates from the maxillary sinus, and the inflammation involves only one side of the maxillary sinus. ACP accounts for a large percentage of L-CRSwNP cases in children [13]. In some children, nasal polyps originating from the maxillary sinus block drainage channels such as the middle meatus, leading to obstructive inflammation of the ipsilateral ethmoid sinus, frontal sinus, and sphenoid sinus. Therefore, for nasal polyps in children, it may make more sense to categorize them based on anatomical range. Furthermore, summarizing the clinical data from our center, we found an interesting phenomenon: for CRSwNP patients, regardless of being D-CRSwNP or L-CRSwNP before the first surgery, their recurrence mostly presented as a single polyp with a unilateral maxillary sinus origin (Figure 1). Accordingly, we hypothesized that the recurrence mechanism of CRSwNP in children may be like the pathogenesis of L-CRSwNP. Based on this hypothesis, this study aims to explore the molecular mechanisms of the CRSwNP recurrence and L-CRSwNP development in children.

Materials and methods

Subjects of study and experimental design

91 children with CRSwNP who attended the Hospital from 2018 to 2024 were included in this study. Inclusion criteria: children who met the diagnostic criteria of EPOS 2020 [10] for pediatric L-CRSwNP and underwent FESS surgery and children who recurred within 1 year after postoperative follow-up in the outpatient clinic and medication. Regular postoperative outpatient follow-up was performed: all enrolled children were on standardized medication (nasal glucocorticoids and saline; mucolytics were added in some children according to the change in their condition; allergic children were treated with environmental control, anti-allergy, and isolation of allergens) in the outpatient clinic. Exclusion criteria: children with primary ciliary dyskinesia, cystic fibrosis, fungal sinusitis, autoimmune diseases, and sinus tumors; patients who had been on antibiotics or topical/systemic steroids for 4 weeks before surgery. Polyps and paired mucosal tissue samples of L-CRSwNP and polyp tissue samples of R-CRSwNP were collected for experiment and data analysis (Figure 2).

The study was approved by the Ethics Committee of the Hospital, and informed consent was obtained from all subjects and their parents/guardians, with the consent form signed by at least one parent/guardian ([2022]-E-035-Y).

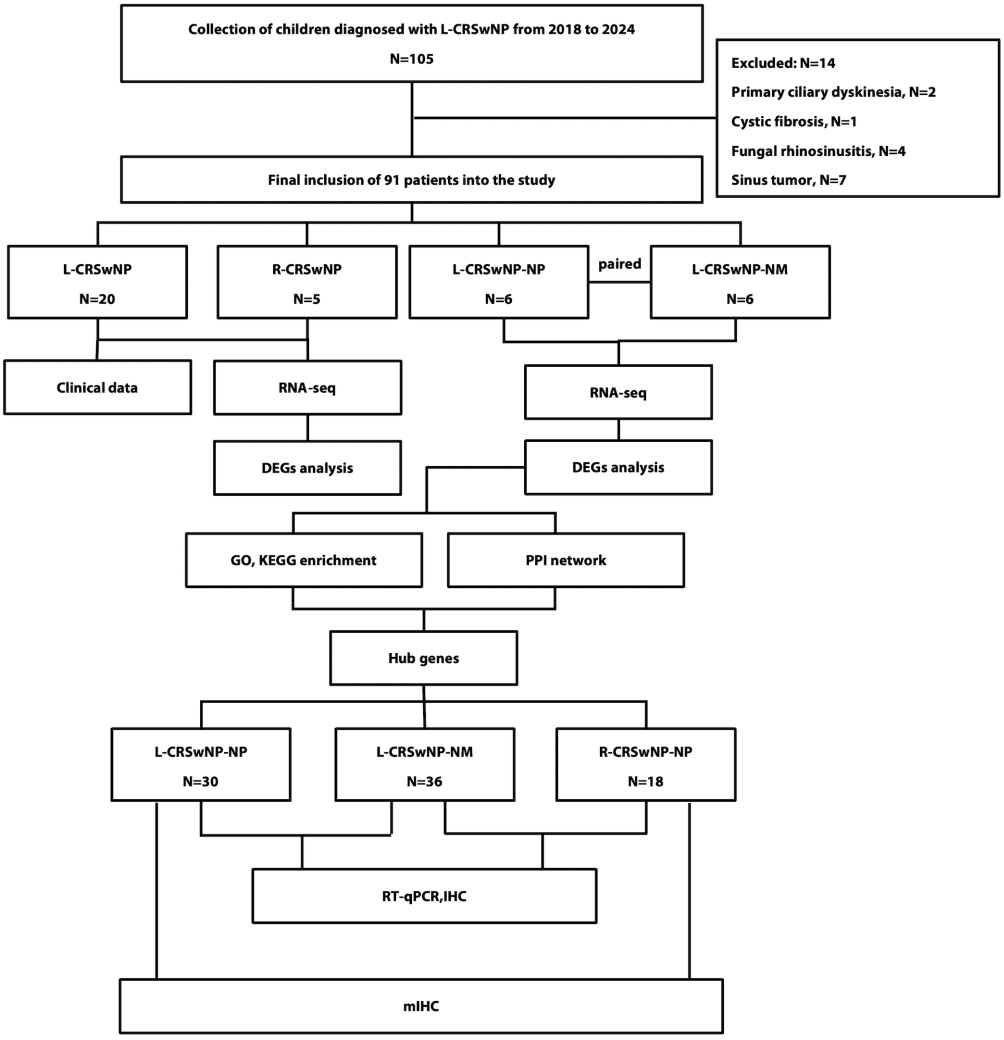


Figure 2. Research flow chart. L-CRSwNP: limited chronic rhinosinusitis with nasal polyps; R-CRSwNP: recurrent chronic rhinosinusitis with nasal polyps; NP: nasal polyps; NM: mucosa; N: number of people; RNA-seq: RNA sequencing; DEGs: differentially expressed genes; IHC: immunohistochemistry; mIHC: multiplex immunohistochemical; PPI: protein-protein interaction.

RNA sequencing and analysis

Total RNA was extracted from tissue for quality control and library construction. All samples were sequenced in the HiSeq 6000 platform (Illumina, San Diego, CA, USA). Raw reads obtained from sequencing were processed to obtain high-quality (clean) reads. Gene expression levels were quantified as fragments per kilobase of exon model per million mapped fragments (FPKM). The datasets generated during the current study are available in the GEO repository. The principal component analysis (PCA) results of genes were extracted and visualized using the ANNUOYUN platform (solargenomics.com). Significantly differentially expressed genes (DEGs) were obtained by differential expression analysis using DESeq2 (RRID: SCR_015687). R software (version 3.6.3; RRID: SCR_001905) was used to perform Gene Ontology (GO), Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis, and to visualize the results. Protein-protein Interaction (PPI) networks were constructed using the STRING database (http://string-db.org/;rid: SCR_005223). DEGs were analyzed using the cytoHubba plug-in (RRID: SCR_003032) in Cytoscape software (version 3.8.2; RRID: SCR_017677). The top 10 hub genes were screened using the MNC algorithm.

Real-Time quantitative Polymerase Chain Reaction (RT-qPCR)

RNA was extracted from tissues using Trizol reagent (R011-100, Genebetter). The quality of total RNA was assessed using NanoDrop 2000 (Thermo Fisher Scientific, Waltham, MA, USA). Single-stranded cDNA was synthesized by reverse transcription. RT-qPCR was performed using SYBR Green Mix (2X) (US Everbright® INC, USA) to assess gene expression levels (Table S1). Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) was

Table 1. Summary of clinical characteristics of R-CRSwNP and L-CRSwNP.

	L-CRSwNP (n=20)	R-CRSwNP (n=5)	P value
Sex, male	16 (80%)	5 (100%)	0.5494a
Age (years)	9.50±2.79	10.15±1.90	0.6271b
Medical history (months)	23.5 (7.5-36)	36 (24-60)	0.1649c
Allergy, n	14 (70%)	4 (80%)	>0.9999a
Asthma, n	6 (31.58%), n=19	1 (20%)	>0.9999a
Lund-Mackay score	7±3.03	5.4±2.30	0.2434b
Serum IgE (IU/ml)	48.8 (25.6-106.45), n=19	13.9 (12.1-16.3)	**0.0439c***
Blood Test			
Eos in blood (%)	2.86±1.66	4.86±5.35	0.4519d
Lymphocytes in blood (%)	43.3±7.91	40.64±10.93	0.523b
Neu in blood (%)	48.95 (37.75-50.9)	44.8 (38.6-57)	0.7671c
Detection of Exhaled Nitric Oxide			
$FeNO_{50}$	16 (12-36), n=17	15 (12-15.5), n=3	0.6026c
$FnNO_{10}$	417 (259.25-529.25), n=16	321 (318-334), n=3	0.4138c
Family history	6 (33.33%) n=18	0	0.2725a
Passive smoking	2 (0-8) n=16	0 (0-10)	0.7475c
disease severity			
Lund-Mackay scoring	7±3.03	5.4±2.30	0.2434b
Lund-Kennedy scoring	8 (6-8) n=19	6 (5-8) n=3	0.1273c

Data are expressed using mean ± standard deviation or median (interquartile spacing). a. Fisher's Exact Test; b. Independent Samples t-Test; c. Mann-Whitney U Test; d. Welch's t-Test.

used as a housekeeping gene for normalization. Relative gene expression was calculated using the $2^{-\Delta\Delta CT}$ method [14].

Immunohistochemistry (IHC)

Three-micron-thick sections were obtained from blocks of nasal polyps and nasal mucosa. Dewaxed in xylene and rehydrated in graded ethanol. Slides were incubated with anti-ITGAM (1:3000 dilution, ab133357, Abcam), anti-IL8 (1:1000 dilution, ab106350, Abcam), anti-FN1 (1:2000 dilution, ab268020, Abcam), anti-IFNG (1:200 dilution, ab268020, Abcam), anti-ITGAX (1:500 dilution, ab52632, Abcam), anti-EGF (1:400 dilution, ab9695, Abcam), or anti-FCGR3B (1:100 dilution, ATP176, AtaGenix, Wuhan, China) for 1 hour at 37°C. DAB (3'-3-diaminobenzidine tetrahydrochloride, Zhongshan Jinqiao Biotechnology, Beijing, China) was used as the chromogen, followed by Harris hematoxylin counterstain. Slides were analyzed under a light microscope (SopTop EX30 biological microscope, China). 5 images were taken for each slide (AJ-VERT imaging system, Germany) at a high-power (40×objective) field. AOD was calculated independently for each image for IHC analysis (Image Pro Plus 32 analysis system, USA).

Multiplex immunohistochemistry (mIHC)

Paraffin-embedded sections were dewaxed and hydrated. Perform blocking after antigen retrieval. Slides were incubated with anti-CD15 (1:50 dilution, Abcam, ab135377), anti-CD206 (1:300 dilution, CST, #24595S), CD16b (1:300 dilution, AtaGenx, ATP176), CD11b (1:1000 dilution, Abcam, ab133357), or CD86 (1:1000 dilution, CST, #91882) at room temperature for 1.5 hours. Sections were incubated with secondary antibodies. After counterstaining the cell nuclei with DAPI, the tissue autofluorescence was quenched, and the slides were mounted. Slides were analyzed using the PhenoImager Fusion imaging system (AKOYA, USA), and the appropriate images were taken at high power (20×objective) using the Phenochart (Akoya, USA).

Statistical analysis

Data were analyzed using GraphPad Prism9 (Version 9.3.1) software. Continuous variables were tested for normal distribution with the Shapiro-Wilk test. Normal distribution measures are shown as mean±standard deviation (mean±SD), while non-normally distributed measures are shown as median (interquartile spacing). Comparisons between the two groups were conducted using an independent samples t-test (two-tailed), the nonparametric Mann-Whitney U test, or the Welch t-test. The results were considered significant at $P<0.05$.

Results

Clinical characteristics and RNA-seq of R-CRSwNP and L-CRSwNP

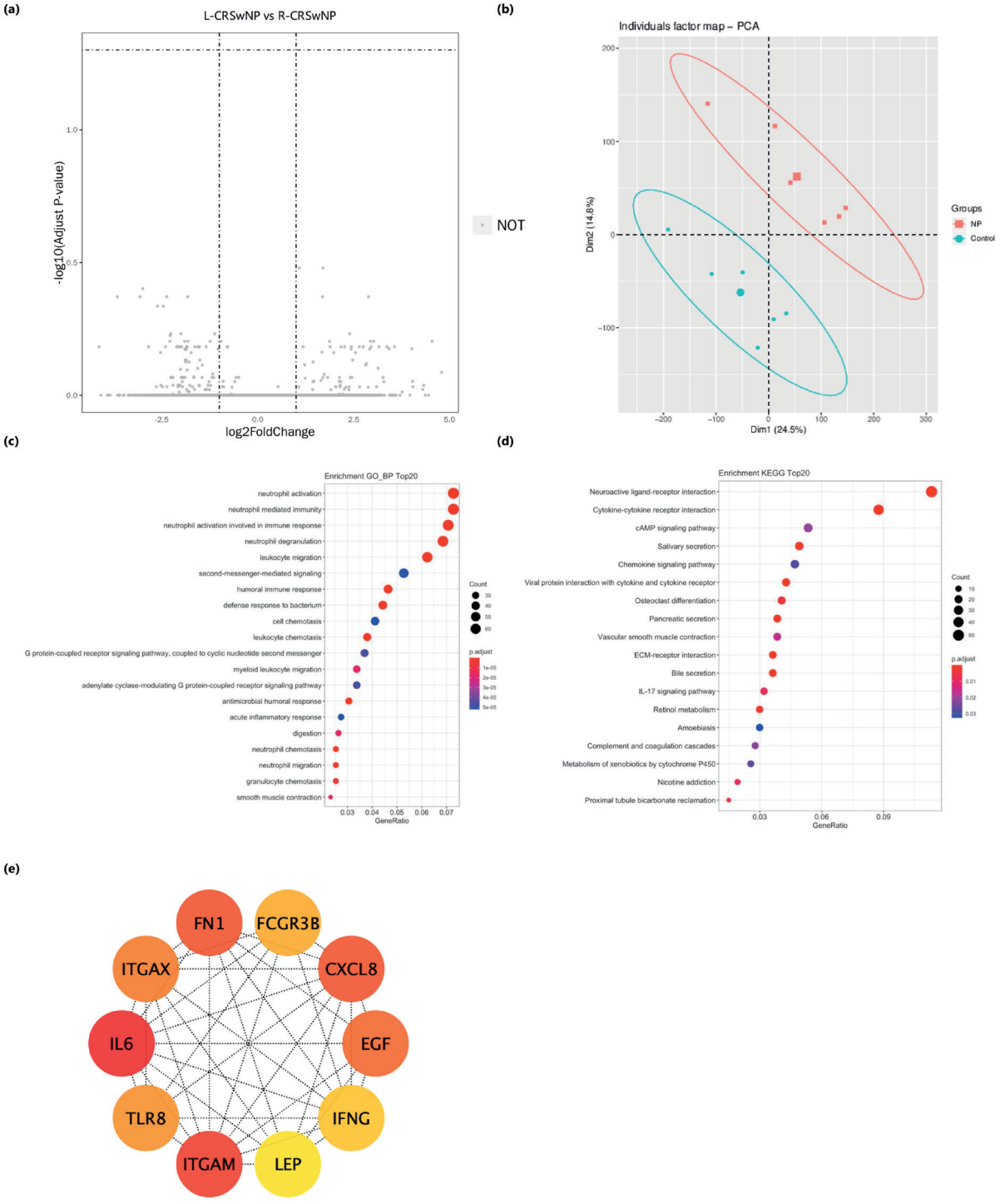


Figure 3. Bioinformatics Analysis Results of RNA sequencing. (a) No significantly differentially expressed genes between L-CRSwNP and R-CRSwNP; (b) Principal component analysis of genes in L-CRSwNP polyps and paired mucosa: polyps were remarkably segregated from mucosal tissue; (c) Bubble chart showing the TOP20 items that were significantly enriched in the biological processes of L-CRSwNP polyps and paired mucosa; (d) Bubble chart showing the KEGG pathway significantly enriched in L-CRSwNP polyps and paired mucosa; (e) hub genes screened from RNA-seq data of polyps and paired mucosa of L-CRSwNP.

Clinical characteristics of R-CRSwNP

Comparing the clinical characteristics of R-CRSwNP and L-CRSwNP children, there were no significant differences in the clinical indicators, except that serum IgE was significantly higher in the L-CRSwNP group compared with the R-CRSwNP group ($P<0.05$) (Table 1).

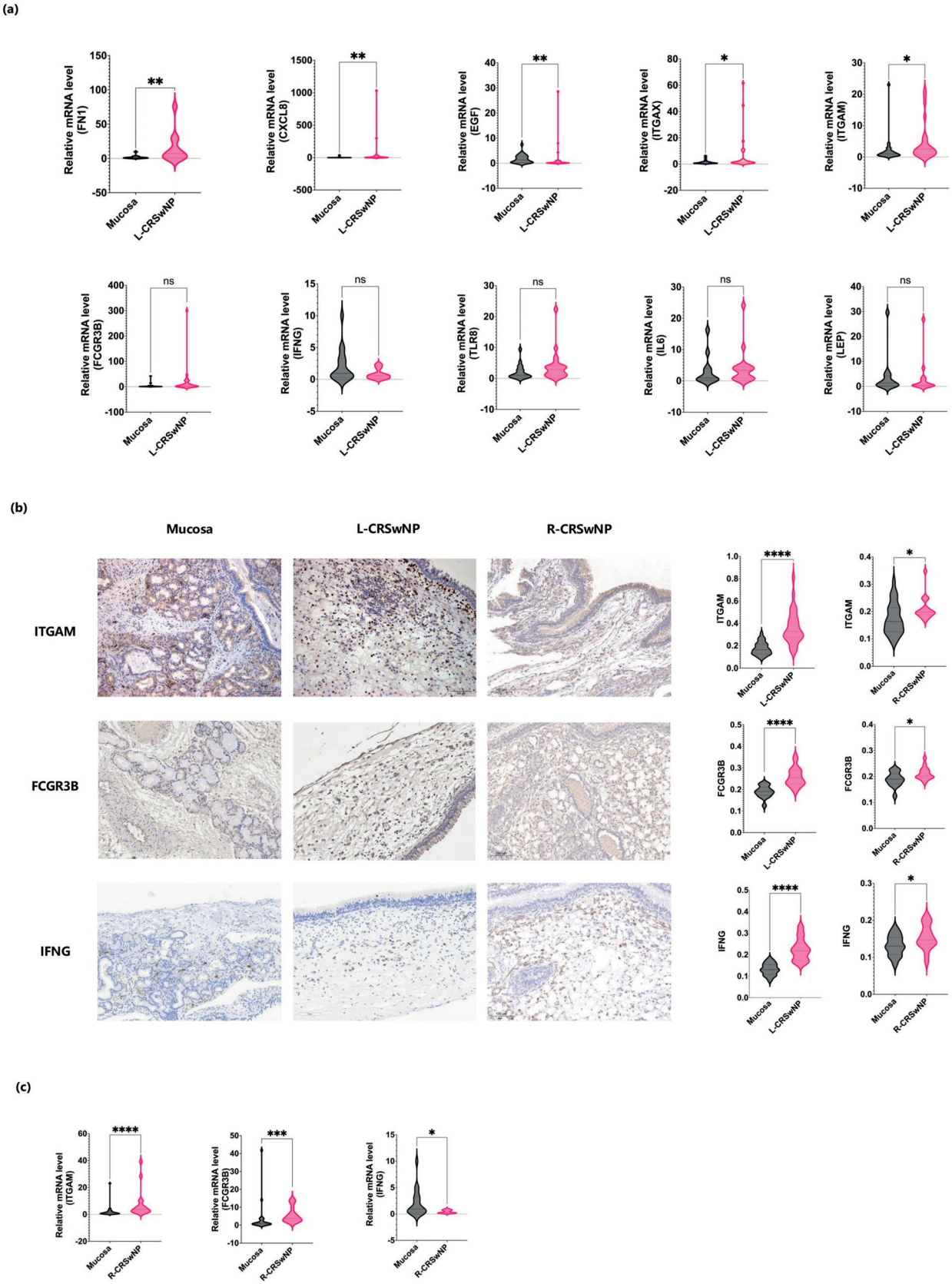


Figure 4. RT-qPCR and Immunohistochemistry Results of Hub Genes in L-CRSwNP and R-CRSwNP. (a) RT-qPCR results of hub genes in L-CRSwNP; (b) Immunohistochemistry results of ITGAM, FCGR3B, IFNG in L-CRSwNP and R-CRSwNP; (c) RT-qPCR results of ITGAM, FCGR3B, IFNG in R-CRSwNP. *P<0.05, **P<0.01, ***P<0.001, ****P<0.0001.

RNA-seq of R-CRSwNP and L-CRSwNP

There were no significantly DEGs between the L-CRSwNP group and the R-CRSwNP group (|log2 fold-change|≥2, P.adj<0.05) (Figure 3a), which implies that the clinical phenotype and RNA expression levels of L-CRSwNP and R-CRSwNP are quite similar.

RNA-seq of L-CRSwNP

Another 6 polyps and mucosal tissue samples from L-CRSwNP were selected for RNA-seq and paired analysis. PCA analysis showed the remarkable separation of polyps and mucosal tissue (Figure 3b). A total of 1419 DEGs were screened between polyps and mucosal tissue, of which 604 were up-regulated genes and 815 down-regulated genes. Figure 3c-d shows the results of GO and KEGG enrichment analyses of DEGs. Biological processes are mainly associated with neutrophils: the top five biological processes are neutrophil activation, neutrophil mediated immunity, neutrophil activation involved in immune response, neutrophil degranulation and leukocyte migration. 18 pathways were screened by KEGG enrichment analysis: Neuroactive ligand-receptor interaction, cytokine-cytokine receptor interaction, CAMP signaling pathway, IL-17 signaling pathway, etc. We constructed a PPI network of DEGs and found that interleukin 6 (IL6), integrin subunit alpha M (ITGAM), C-X-C motif chemokine ligand 8 (CXCL8), fibronectin 1 (FN1), epidermal growth factor (EGF), integrin subunit alpha X (ITGAX), toll-like receptor 8 (TLR8), Fc gamma receptor IIIb (FCGR3B), interferon-gamma (IFNG), and leptin (LEP) interact more closely (hub genes) (Figure 3e).

RNA and protein expression of the hub genes

RT-qPCR was performed using another 27 polyps and 29 uncinate process mucosa with L-CRSwNP to verify the expression of the above 10 hub genes at the RNA level. Compared to the mucosa, the expression levels of FN1 (P<0.001), CXCL8 (P<0.01), EGF (P<0.01), ITGAX (P<0.05) and ITGAM (P<0.05) were significantly increased, the expression level of FCGR3B was considerably increased and the expression level of IFNG was considerably decreased in polyps (Figure 4a). Therefore, we used IHC to examine these seven genes.

IHC was performed on 30 polyps and 36 uncinate process mucosa with L-CRSwNP. The expression of ITGAM, IFNG, and FCGR3B was significantly increased in polyps compared to mucosa (P<0.0001) (Figure 4b). Similarly, RT-qPCR and IHC of 18 R-CRSwNP showed that both RNA and protein expression of ITGAM and FCGR3B were significantly increased in R-CRSwNP (P<0.05) (Figure 4b-c).

mIHC of ITGAM and FCGR3B in L-CRSwNP and R-CRSwNP

We used mIHC to localize ITGAM and FCGR3B in polyp tissue. The results showed that ITGAM and FCGR3B were closely associated with neutrophils (CD15+), M1 macrophages (CD86+), and M2 macrophages (CD206+) (Figure 5a-b). Whether in ITGAM+FCGR3B+ double-positive cells or ITGAM+/FCGR3B+ single-positive cells, the percentage of neutrophils was the highest, and the percentage of M2 macrophages was higher than that of M1 macrophages (Figure 5c).

Discussion

Summarizing the clinical phenotypes of children who were admitted for surgery for CRSwNP in our center from 2021 to 2024, L-CRSwNP accounted for up to 65.31% and R-CRSwNP accounted for 14.29%. Although many studies of adult CRSwNP suggest that CRSwNP patients with allergies have a more severe clinical presentation and a higher risk of recurrence, our results show that children with R-CRSwNP have lower serum IgE levels, which is consistent with the study by Schramm et al. [15]. This reaffirms the fact that CRSwNP in children and adults has a different pathogenesis. More than that, comparing the RNA-seq results of R-CRSwNP and L-CRSwNP showed no DEGs. This suggests that R-CRSwNP and L-CRSwNP are very similar to each other from clinical phenotype to molecular mechanism.

Through the RNA-seq results of L-CRSwNP polyps and paired mucosas, we noted that neutrophil-related biological processes were significantly enriched and that ITGAM and FCGR3B were important hub genes involved in the phagosome pathway. Phagocytosis is the process of cellular uptake of larger particles and is a core mechanism for tissue remodeling, inflammation, and resistance to infectious agents. The basic process involves the binding of particles to the cell surface, the formation of endocytic vesicles called phagosomes, the maturation of the phagosomes into phagolysosomes, and finally digestion within the phagolysosomes [16]. Phagocytes (mononuclear phagocyte system and neutrophils) have many receptors on their surface to constantly sense and edit the extracellular environment [17]. Phagosomes are formed when specific receptors on the surface of phagocytes recognize ligands on the surface of particles. These receptors can interact with target cells either directly through the structural determinants on the surface of the targets (non-opsonic phagocytosis) or indirectly by recognizing host-provided opsonic (opsonin-dependent phagocytosis). Among the most characterized opsonin receptors are the various receptors for the Fc portion of IgG (FcγR) and complement receptor 3 (CR3), which binds complement protein 3bi [16]. FcγR binds to the Fc portion of IgG [18] or IgA [19] antibodies and includes three types, FcγR I, FcγR II, and FcγR III, with constitutive activity in phagocytes. Complement receptors bind to activated complement components on particles [20], with CR3 being the most potent phagocytic receptor, formed by the αMβ2 integrin coupled to the integrin α M encoded by ITGAM and integrin β2 encoded by ITGB2 [21, 22]. CR3 binds but does not internalise particles in the absence of additional stimuli [23]. The proteins encoded by the hub genes FCGR3B and ITGAM that we validated are

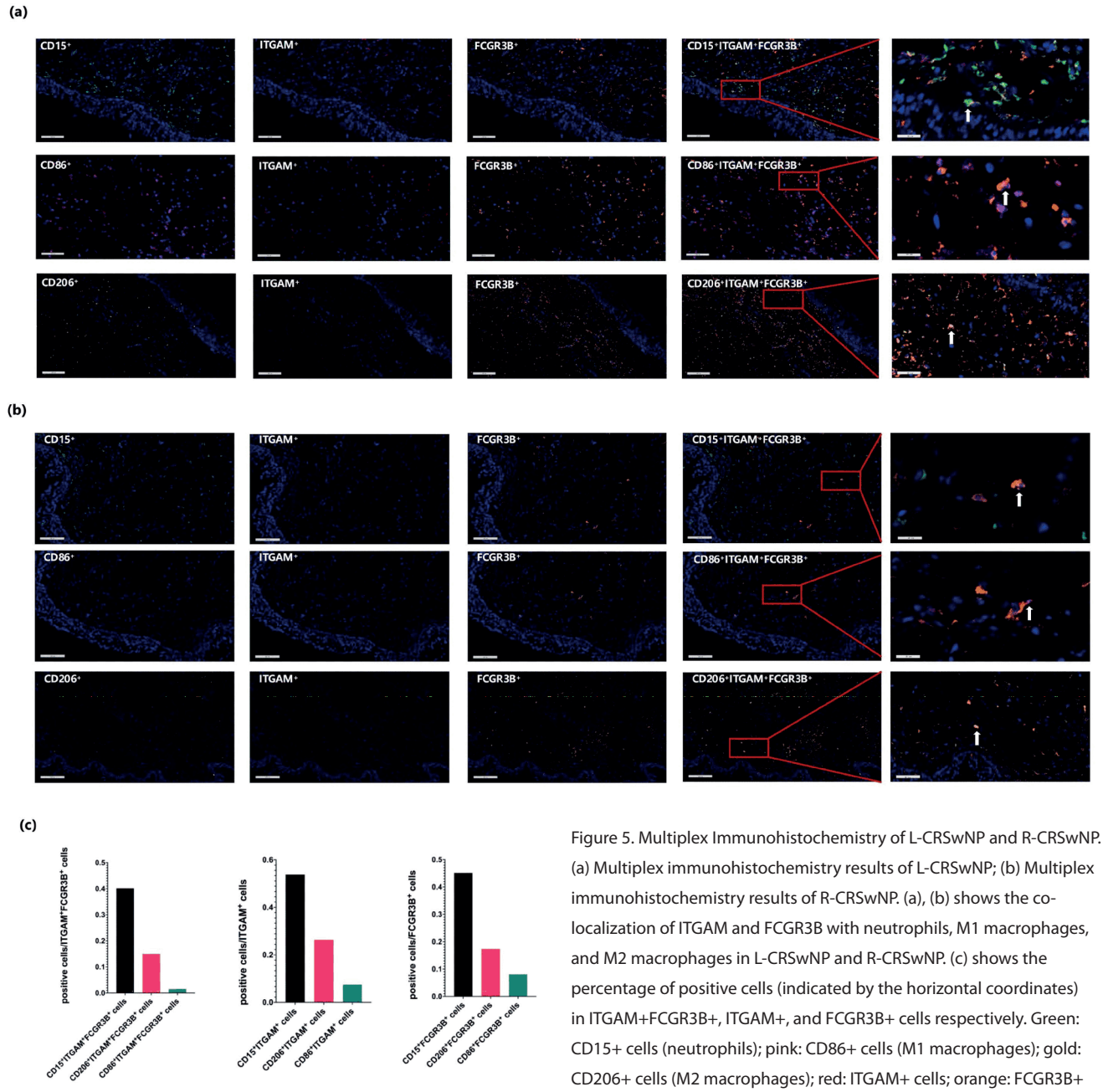


Figure 5. Multiplex Immunohistochemistry of L-CRSwNP and R-CRSwNP. (a) Multiplex immunohistochemistry results of L-CRSwNP; (b) Multiplex immunohistochemistry results of R-CRSwNP. (a), (b) shows the co-localization of ITGAM and FCGR3B with neutrophils, M1 macrophages, and M2 macrophages in L-CRSwNP and R-CRSwNP. (c) shows the percentage of positive cells (indicated by the horizontal coordinates) in ITGAM+FCGR3B+, ITGAM+, and FCGR3B+ cells respectively. Green: CD15+ cells (neutrophils); pink: CD86+ cells (M1 macrophages); gold: CD206+ cells (M2 macrophages); red: ITGAM+ cells; orange: FCGR3B+ cells. White arrows mark co-localized cells.

important components of FcγR and CR3, respectively. FcγR and CR3 cooperate as phagocytic receptors, which in turn effectively recognize particles and initiate phagocytosis. For example, in macrophages, CR3 initiates a different type of phagocytosis than that mediated by the antibody FCGR receptor. Similarly, there is cooperation between FCGR3B and CR3 in neutrophils [24, 25]. Neutrophil and macrophage phagosome formation is generally similar, but there is some cellular specificity. For example, in macrophages, antibody-dependent phagocytosis involves the signaling molecules Syk, PI3K, PKC, and ERK, but is not dependent on increased cytosolic calcium concentration [26, 27]. And neutrophils need calcium for fusion (28). In addition, in neutrophils, pathogens can bind to FcγR or complement receptors (e.g., CR3) to initiate phagocytosis using immune receptor signaling pathways, while CR3 can also conduct an independent integrin signaling pathway [29].

Therefore, we looked for the association of ITGAM and FCGR3B expression with neutrophils and phagocytes in R-CRSwNP and L-CRSwNP. We discovered that ITGAM and FCGR3B had the highest proportion of neutrophils and were strongly linked to M2 macrophages, indicating their involvement in children's R-CRSwNP and L-CRSwNP. Macrophages are classified as either classically activated macrophages (M1) or selectively activated macrophages (M2), depending on their phenotype and func-

tion. M1 macrophages promote inflammation and accelerate extracellular matrix degradation and apoptosis [30, 31]. M2 macrophages assist in tissue remodeling, promote angiogenesis, and have anti-inflammatory effects [32]. This supports our finding that M2 macrophages exhibit a stronger correlation with ITGAM and FCGR3B. By promoting angiogenesis and tissue remodeling, ITGAM and FCGR3B may contribute to the formation and recurrence of polyps. Therefore, through neutrophil and macrophage phagocytosis, ITGAM and FCGR3B may both independently and collectively affect the formation of L-CRSwNP, as well as the recurrence of CRSwNP in children. The identification of ITGAM and FCGR3B provides a new direction for the optimization of clinical diagnosis and treatment procedures. First, the hub genes we identified demonstrate potential association with disease recurrence. Following further validation, these genes may serve as key biomarkers through rapid diagnostic kits for early high-risk detection. Second, these findings could enable a shift from empirical treatment to targeted therapies specifically for R-CRS and L-CRSwNP.

This study has two main limitations that should be acknowledged: First, the primary limitation is the relatively small sample size, attributable to two constraining factors: the single-center study design with fewer children suffering recurrence, and budgetary constraints that limited additional basic experiments. While our RNA-seq analysis suggests similarities between R-CRSwNP and L-CRSwNP, the limited sample size may affect the generalizability of the finding. In future studies, we plan to include more samples to further explore the relationship between R-CRSwNP and L-CRSwNP and perform proteomic analyses to validate findings at the protein level. Second, although we identified ITGAM and FCGR3B as hub genes through RNA-seq, RT-qPCR, IHC and mIHC, their specific mechanistic roles in disease pathogenesis require further validation through well-controlled in vitro and in vivo functional studies.

Conclusion

L-CRSwNP and R-CRSwNP are very similar in clinical phenotype and molecular mechanism. ITGAM and FCGR3B are important hub genes that contribute to the disease through neutrophil and M2 macrophage-mediated phagosome and are their potential therapeutic targets.

Acknowledgements

We appreciate Mr. Kyle Pfeifer for his help and support in this study.

Authorship contribution

YH, WG and PW are responsible for final approval of the article before submission. XX, XC and WL are responsible for drafts and visions during the writing process. NZ, CJ, JW, JC, JZ, XY, XK, TW are responsible for analysis and interpretation of data. LT, XY, WZ and CL are responsible for acquisition of data and collection of samples.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Funding

This work was supported by the Capital's Funds for Health Improvement and Research [2024-2-2098]; the Beijing Natural Science Foundation [7242052]; the Training Fund for Open Projects at Clinical Institutes and Departments of Capital Medical University [CCMU2023ZKYXY001]; the Respiratory Research Project of National Clinical Research Center for Respiratory Diseases [HXZX-202109]; the Beijing Natural Science Foundation-Haidian Original Innovation Joint Fund [L232034]; the Special Projects for Organized Scientific Research at Chinese Institutes for Medical Research [CX23YZ10]; Beijing Municipal Science & Technology Commission Proof of Concept Center [No. 2024030119] and the Capital's Funds for Health Improvement and Research [2024-1-2093].

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Rhinology 63: 6, 0 - 0, 2025
https://doi.org/10.4193/Rhin25.035

Received for publication:
January 14, 2025
Accepted: June 4, 2025

Associate Editor:
Sanna Toppila-Salmi

# contributed equally to this work. Author order was determined.

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This manuscript contains online supplementary material

SUPPLEMENTARY MATERIAL

Primer	Sequence
ITGAM-F	TTCAGGGATCCAGGGTGGT
ITGAM-R	GTAGTCGCACTGGTAGAGGC
IFNG-F	GAGTGTGGAGACCATCAAGGA
IFNG-R	TGGACATTCAAGTCAGTTACCGAA
FCGR3B-F	AACTGCTCTGCTACTTCTAGTTTCA
FCGR3B-R	ATTGAGGCTCCAGGAACACC
CXCL8-F	GCTCTGTGTGAAGGTGCAGT
CXCL8-R	ATTTCTGTGTTGGCGCAGTG
EGF-F	AGGACTGATTTGCCCTGACTC
EGF-R	CATCATGGAGGCAGTACCCA
LEP-F	CATTTCACACACGCAGTCAGT
LEP-R	CTGGAAGGCATACTGGTGAGG
TLR8-F	CCAAGCTCCCTACGCAAACT
TLR8-R	TGAAGCACCTCGGACAGTTC
IL6-F	AACTCCTTCTCCACAAGCG
IL6-R	GCGGCTACATCTTTGGAATCT
ITGAX-F	CGGTACTGTACAAAGTTGGCT
ITGAX-R	ATTTCTCACTGGGCGGGC
FN1-F	CGGTGGCTGTCAGTCAAAG
FN1-R	AAACCTCGGCTTCCTCCATAA
β-actin-F	CCTGGCACCCAGCACAAT
β-actin-R	GGGCCGGACTCGTCATAC

Table S1. Primers for RT-qPCR.