Epithelial 15-lipoxygenase as a convergent node of arachidonic acid dysregulation in chronic rhinosinusitis with nasal polyps: integrated genetic, metabolomic and single-cell evidence

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Chronic rhinosinusitis with nasal polyps (CRSwNP) is a common type 2 inflammatory disease of the upper airway. Dupilumab, an antibody against the interleukin-4 receptor α (IL-4Rα), shrinks polyps and relieves symptoms [1], yet part of the epithelial disease program persists during treatment [2]. Arachidonic acid metabolism is closely tied to type 2 airway inflammation, and most attention has gone to cysteinyl leukotrienes and prostaglandin D2 [3]. 15-Lipoxygenase (ALOX15) is a different lead. A loss-of-function variant in ALOX15 lowers the risk of nasal polyps by about two-thirds [4], and ALOX15 products are increased in eosinophilic polyps [5]. Whether common variants that regulate ALOX15 expression also influence disease, whether its products rise in the nose, which cells carry it and how far IL-4Rα blockade reverses it have not been established. We addressed these questions by following the pathway through genetics, nasal secretion metabolomics, tissue and single-cell transcriptomics and data from a dupilumab trial.

Methods. Datasets and accession numbers are listed in Supplementary Table SI, and full methods are given in the Supplementary Methods. Genetic analyses used the genome-wide association study (GWAS) of 1400 plasma metabolites in 8299 individuals of European ancestry [6] as exposure and the FinnGen–UK Biobank CRSwNP GWAS (9626 cases, 685,602 controls) [7] as outcome. Ninety-five nasal secretion metabolites with instruments were screened by Mendelian randomization (MR). The four leading long-chain polyunsaturated fatty acids (PUFAs) were re-analyzed with genome-wide instruments, supplemented by MR-Egger, weighted median, MR-PRESSO and leave-one-out analyses, and tested for colocalization at the FADS locus. Summary-data-based MR (SMR) with the heterogeneity in dependent instruments (HEIDI) test was run for 48 arachidonic acid pathway genes using GTEx v8 cis-expression quantitative trait loci (eQTLs), with asthma from the same GWAS as a comparison outcome.

Nasal secretion mass spectra from 28 patients described by the source study as having type 2 chronic rhinosinusitis with nasal polyps on postoperative pathology and 12 controls (MetaboLights MTBLS13192) were re-quantified. Medication use, including corticosteroid type, timing and washout, was unreported. Lipoxygenase isomers were assigned from diagnostic tandem mass spectrometry (MS2) fragments (Metabolomics

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Standards Initiative level 2). The 15- to 12-hydroxyeicosatetraenoic acid (15-HETE/12-HETE) ratio was a relative lipid-product measure reducing common dilution effects, not a direct enzyme activity assay. Diagnostic fragments required ≥ 5% of the base peak and ≥ 3 MS2 spectra per retention-time bin. Fixed-window MS1 peak areas > 0 defined detection, without additional signal-to-noise or detection-limit thresholds. Groups were compared by two-sided Mann–Whitney *U* tests with Benjamini–Hochberg correction across 4890 global features or six targeted products. Global features detected in ≥ 80% of each group were retained; after $\log_2$ transformation, missing values were replaced by each feature's minimum observed value. All six targeted products had positive areas in all 40 samples, requiring no imputation. All ratios were finite and positive, without missing values or zero denominators. The ratio used the same two-sided test; its *p*-value was unadjusted and excluded from BH correction.

Tissue expression was analyzed in three polyp cohorts (GSE136825, GSE179265, GSE36830). Cellular localization used 36,991 flow-sorted cells from 19 polyps (GSE196169) [8] and 92,446 unsorted cells from 15 polyps (GSE276503) [9]. Eosinophils and epithelial cells were compared at matched sequencing depth in childhood asthma nasal lavage (GSE299751). Treatment effects used paired baseline and week-24 SINUS-52 nasal brushings (NCT02898454; 47 dupilumab, 19 placebo; GSE267331) [2]. For 356 expected disease-signature genes, restoration was the placebo-corrected change signed against the disease effect; equivalence tests assessed absence of restoration. Multiple testing used the Benjamini–Hochberg false discovery rate (FDR), reported as FDR or *q*.

Results. Eleven of the 95 screened metabolites reached FDR < 0.05. The top seven were all long-chain PUFAs, and each had its lead variant in the FADS1/FADS2 region (Supplementary Figure S10). Re-estimated with genome-wide instruments, arachidonate, adrenate and eicosapentaenoate were associated with CRSwNP (inverse-variance weighted OR = 1.14–1.20). MR-PRESSO, however, flagged the FADS lead variants as outliers. Once they were removed, none of the estimates reached statistical significance (OR = 1.03–1.11, all $p \geq 0.064$), and no upper confidence limit exceeded 1.26 (Supplementary Figure S2, Supplementary Table SII). What these fatty acids share with CRSwNP is the locus itself: colocalization gave posterior probabilities of 0.92–0.96 for a common causal variant at FADS, against 0.015 for linoleate, and the signal colocalized with FADS1 expression (Figure 1 A). Apart from FADS1, ALOX15 was the only one of the 48 pathway genes to pass Bonferroni correction and the HEIDI test. Higher genetically predicted ALOX15 expression went with higher CRSwNP risk (SMR OR = 1.60, 95% CI: 1.33–1.91, $p = 4.1 \times 10^{-7}$), whereas no association was detected for asthma (OR = 0.96, $p = 0.11$) (Figure 1 B). The lead eQTL variant was not linked to the known protective loss-of-function variant ($r^2 = 0.003$).

Nasal secretions from patients contained more 15-lipoxygenase products of all three substrates: 15-HETE from arachidonic acid (+1.63 $\log_2$, $q = 0.013$), 17-hydroxydocosahexaenoic acid (17-HDHA) from docosahexaenoic acid (+2.37, $q = 0.0014$) and 15-hydroxyeicosapentaenoic acid (15-HEPE) from eicosapentaenoic acid (+1.59, $q = 0.0014$). 12-HETE, the 12-lipoxygenase product of arachidonic acid, went down (–0.72, $q = 0.013$) (Figure 1 C). Within each sample, the 15-HETE/12-HETE ratio had a median of 0.86 in controls and 4.02 in patients (unadjusted $p = 1.2 \times 10^{-5}$) (Figure 1 D, Supplementary Figure S3). Adrenic acid (+3.67 $\log_2$, $q = 6.1 \times 10^{-4}$) and docosapentaenoic acid (+2.92, $q = 4.8 \times 10^{-4}$) were raised as well (Supplementary Table SIII).

In GSE136825, polyps expressed more ALOX15 (+1.30 $\log_2$, FDR 2.8×10^{-3}) and ALOX5 and less CYP2J2 than control mucosa, and the two other cohorts showed the same directions (Supplementary Figures S4 and S14). Single-cell data showed epithelial enrichment of ALOX15 transcripts (Figure 1 E). Between 72.7% and 82.8% of basal, secretory and ciliated cells expressed it, and in all 16 samples with at least 20 epithelial cells the epithelium had the highest expression. ALOX5 and HPGDS, by contrast, were mast-cell enzymes, and TBXAS1 a myeloid one (Supplementary Figure S5, Supplementary Table SV). The unsorted polyps gave the same answer. There the epithelium ranked first in all 15 samples and accounted for 94.2% of the ALOX15 expression signal among captured cells (Figure 1 E), while 5.8% of macrophages expressed the gene. In nasal lavage, where eosinophils were also captured, ALOX15 was detected at matched sequencing depth in 47.3% of epithelial cells and 14.3% of eosinophils (Supplementary Figure S6).

In the SINUS-52 brushings, 20 of the 356 signature genes returned toward control levels with dupilumab (FDR < 0.05), most of them type 2 epithelial markers. For 187 genes the change was formally equivalent to no restoration, and the median restoration was 6.6% of the disease effect (Figure 1 F, Supplementary Figure S8). ALOX15, the enzyme singled out by the genetic analysis, was the only key pathway enzyme above the expression threshold in brushings. Tested on its own, it recovered by 0.62 $\log_2$ (95% CI: 0.11–1.14), which is 48% of its disease effect ($p = 0.019$) (Supplementary Table SVI).

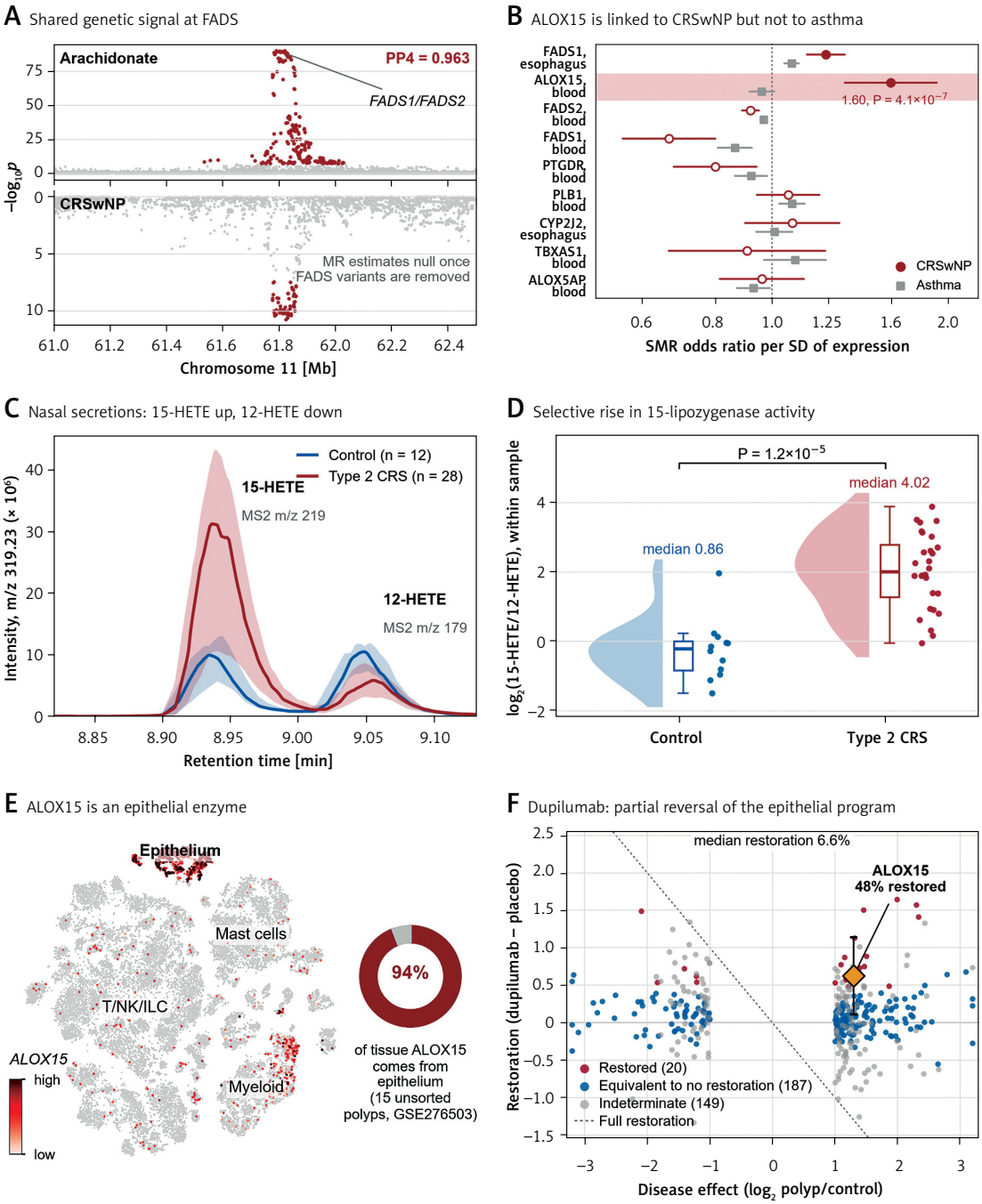

Figure 1. Epithelial ALOX15 in chronic rhinosinusitis with nasal polyps (CRSwNP). **A** – Association of variants on chromosome 11 with plasma arachidonate (top) and CRSwNP (bottom, inverted); red, genome-wide significant variants at FADS1/FADS2; PP4, posterior probability of a shared causal variant; MR, Mendelian randomization. **B** – Gene-level summary-data-based Mendelian randomization: odds ratios (95% CI) per SD of genetically predicted expression for CRSwNP (circles; filled, passing Bonferroni correction and the HEIDI test) and asthma (squares). **C** – Extracted ion chromatogram of HETE isomers (m/z 319.23) in nasal secretions; lines, group medians; shading, interquartile range; peaks assigned from diagnostic tandem mass spectrometry (MS2) fragments. **D** – Within-sample 15-HETE/12-HETE ratio in controls and patients with type 2 chronic rhinosinusitis (CRS) with nasal polyps, as described in the source study (Mann–Whitney *U* test; unadjusted *p*-value). **E** – ALOX15 expression across 36,991 polyp cells (t-distributed stochastic neighbor embedding, t-SNE; GSE196169); ring, share of the captured-cell ALOX15 expression signal contributed by epithelium in 15 unsorted polyps (GSE276503). **F** – Disease effect and placebo-corrected restoration after dupilumab for 356 signature genes in SINUS-52 nasal brushings (GSE267331); diamond, ALOX15 with 95% CI

Discussion. These analyses provided convergent evidence supporting ALOX15 involvement. Loss of ALOX15 function protects against nasal polyps [4]; higher genetically predicted whole-blood ALOX15 expression was associated with higher risk. These associations do not establish that increased epithelial ALOX15 expression causes CRSwNP. No asthma association was detected, despite its genetic correlation with polyps [7]; the relevant tissue and mechanism remain unresolved. Nasal products of three substrates rose while 12-HETE fell, suggesting altered relative lipid-product formation or handling rather than directly measuring epithelial ALOX15 activity. This agrees with increased 15-HETE in eosinophilic polyps [5]. As in asthma [10], estimates were sensitive to FADS. Available genetic analyses provide no robust evidence for a causal effect of measured circulating fatty acids on CRSwNP. Recent MR studies also investigated circulating fatty acids in pneumonia and metabolite-mediated relationships between inflammatory cytokines and acute respiratory distress syndrome [11, 12].

Epithelial cells contributed most of the captured ALOX15 transcript signal. ALOX15+ macrophages reported previously [13, 14], contributed less in our data. Macrophage ALOX15 can recruit eosinophils through CCL13 [14], while epithelial transcript enrichment suggests another potential lipid-product/lipid source, without establishing its enzymatic contribution. ALOX15 is induced by IL-4/IL-13 through STAT6 [15], and its expression decreased during dupilumab treatment. The remaining epithelial signature changed less (median restoration 6.6%). Brushings exclude mast cells, myeloid cells and subepithelial macrophages; responses in those compartments require treated-patient biopsies.

The data came from different cohorts, with level 2 metabolite identification. The small secretion cohort (28 patients, 12 controls) limits assessment of confounding, clinical heterogeneity and reproducibility. Unreported medication use leaves corticosteroid and other treatment confounding unassessed. Transcript and lipid measurements do not establish epithelial ALOX15 protein abundance or activity. Lower eosinophil transcript detection does not exclude substantial functional contributions depending on per-cell protein expression or enzyme activity. ALOX15 protein and products should be measured in polyps before and after biologic therapy, and inhibition test. These findings prioritize ALOX15 for functional investigation; therapeutic benefit remains unestablished.

Data availability

All data are publicly available from the GWAS Catalog (GCST90652531, GCST90652530, GCST90199621–GCST90201020), GTEx v8, MetaboLights (MTBLS13192) and the Gene Expression Omnibus (GSE136825, GSE179265, GSE36830, GSE198950, GSE196169, GSE276503, GSE299751 and GSE267331).

Supplementary material: Supplementary Methods, Supplementary Figures S1–S18 and Supplementary Tables SI–SXVIII.

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Ethical approval

Not applicable. Only publicly available, de-identified data from studies with ethical approval were analyzed; no new human data or samples were collected.

Conflict of interest

The author declares no conflict of interest.

References

1. Bachert C, Han JK, Desrosiers M, et al. Efficacy and safety of dupilumab in patients with severe chronic rhinosinusitis with nasal polyps (LIBERTY NP SINUS-24 and LIBERTY NP SINUS-52): results from two multicentre, randomised, double-blind, placebo-controlled, parallel-group phase 3 trials. Lancet 2019; 394: 1638-50.
2. Gayvert K, Desrosiers M, Laidlaw TM, et al. Nasal brushing molecular endotyping distinguishes patients with chronic rhinosinusitis with nasal polyps with better response to dupilumab. J Allergy Clin Immunol 2024; 154: 619-30.
3. Laidlaw TM, Boyce JA. Updates on immune mechanisms in aspirin-exacerbated respiratory disease. J Allergy Clin Immunol 2023; 151: 301-9.
4. Kristjansson RP, Benonisdottir S, Davidsson OB, et al. A loss-of-function variant in ALOX15 protects against nasal polyps and chronic rhinosinusitis. Nat Genet 2019; 51: 267-76.
5. Sakashita M, Kidoguchi M, Imoto Y, et al. ALOX15-driven ω-6 fatty acid metabolism promotes type 2 inflammation in eosinophilic chronic rhinosinusitis with nasal polyps. J Allergy Clin Immunol Glob 2026; 5: 100759.
6. Chen Y, Lu T, Pettersson-Kymmer U, et al. Genomic atlas of the plasma metabolome prioritizes metabolites implicated in human diseases. Nat Genet 2023; 55: 44-53.
7. Saarentaus EC, Fischer-Rasmussen K, Sliz E, et al. 131 genetic loci highlight immunological pathways and tissues in nasal polyposis and asthma. Nat Commun 2025; 16: 9879.
8. Bangert C, Villazala-Merino S, Fahrenberger M, et al. Comprehensive analysis of nasal polyps reveals a more pronounced type 2 transcriptomic profile of epithelial cells and mast cells in aspirin-exacerbated respiratory disease. Front Immunol 2022; 13: 850494.
9. Xie X, Wang P, Jin M, et al. IL-1β-induced epithelial cell and fibroblast transdifferentiation promotes neutrophil recruitment in chronic rhinosinusitis with nasal polyps. Nat Commun 2024; 15: 9101.
10. Huang T, Long Y, Ou Y, Li J, Huang Y, Gao J. Association between circulating fatty acid metabolites and asthma

risk: a two-sample bidirectional Mendelian randomization study. BMC Med Genomics 2023; 16: 112.
11. Chen X, Wu X, Mao P, et al. Causal analysis of plasma fatty acids and pneumonia: identifying diagnostic biomarkers through transcriptome-wide association study. Arch Med Sci 2025; doi: 10.5114/aoms/208380.
12. Fu F, Lin Z. The plasma metabolite-mediated relationship between inflammatory cytokines and acute respiratory distress syndrome. Arch Med Sci 2026; 22: 1130-40.
13. Liu C, Wang K, Liu W, Zhang J, Fan Y, Sun Y. ALOX15+ M2 macrophages contribute to epithelial remodeling in eosinophilic chronic rhinosinusitis with nasal polyps. J Allergy Clin Immunol 2024; 154: 592-608.
14. Cui Y, Liu C, Wang K, et al. Subepithelial ALOX15+ macrophage niches orchestrate eosinophil recruitment in chronic rhinosinusitis with nasal polyps via the ALOX15-ERK-CCL13 axis. Rhinology 2026; 64: 691-703.
15. Conrad DJ, Lu M. Regulation of human 12/15-lipoxygenase by Stat6-dependent transcription. Am J Respir Cell Mol Biol 2000; 22: 226-34.