Molecular Endotyping of Asthma: Precision Treatment Selection from Nasal Airway Transcriltomics

Transcriptomic Analysis of GSE152004 - 679 Nasal Epithelium Samples

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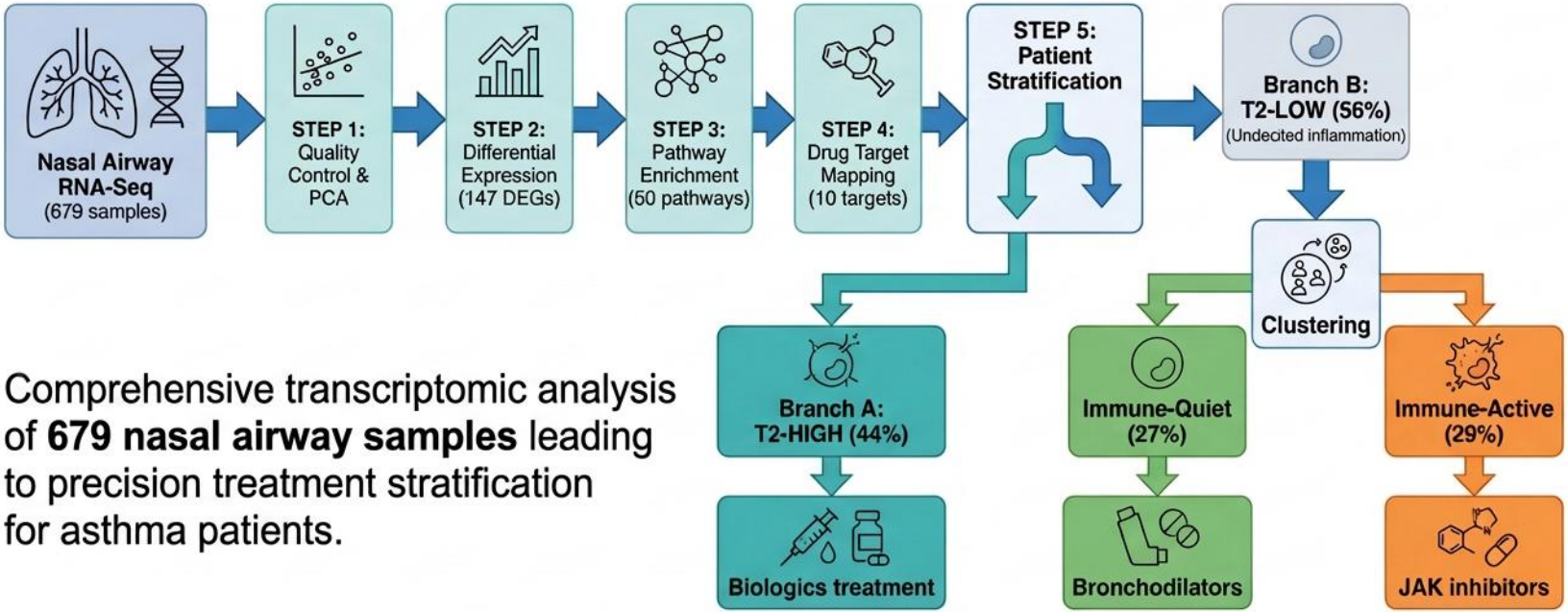
Study Overview: Graphical Abstract



Comprehensive transcriptomic analysis of **679 nasal airway samples** leading to precision treatment stratification for asthma patients.

(GEO: GSE152004)

Project Overview

1) Identify differentially expressed genes in asthma vs controls.

2) Validate findings against published literature.

3) Map FDA-approved drug targets.

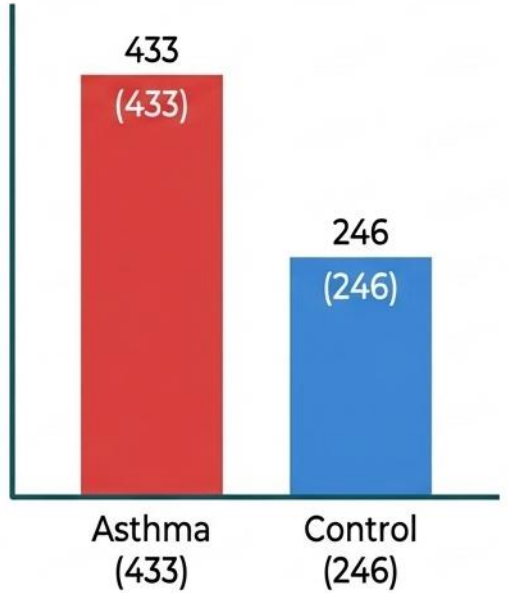
4) Stratify patients by pathway activation.

5) Define molecular endotypes for precision treatment.

(GEO: GSE152004)

Study Design & Dataset

- GEO Accession: GSE152004
- Nasal Airway Epithelium RNA-Seq
- Total Samples: 679 (433 Asthma, 246 Controls)
- Genes Profiled: 23,651 (after QC filtering)



Analytical Workflow

Raw Data
(HDF5)

Quality Control & Filtering

Differential Expression
(Mann-Whitney U, FDR correction)

Pathway Enrichment
(GO, KEGG, Reactome)

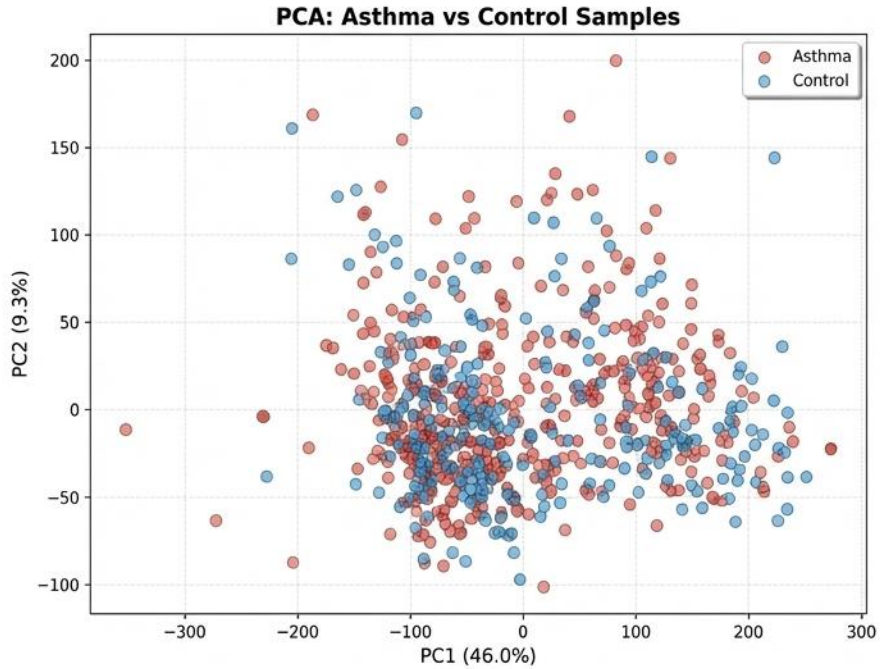
Drug Target Mapping

Patient Stratification
(T2-High vs T2-Low)

Endotype Clustering

(GEO: GSE152004)

Principal Component Analysis

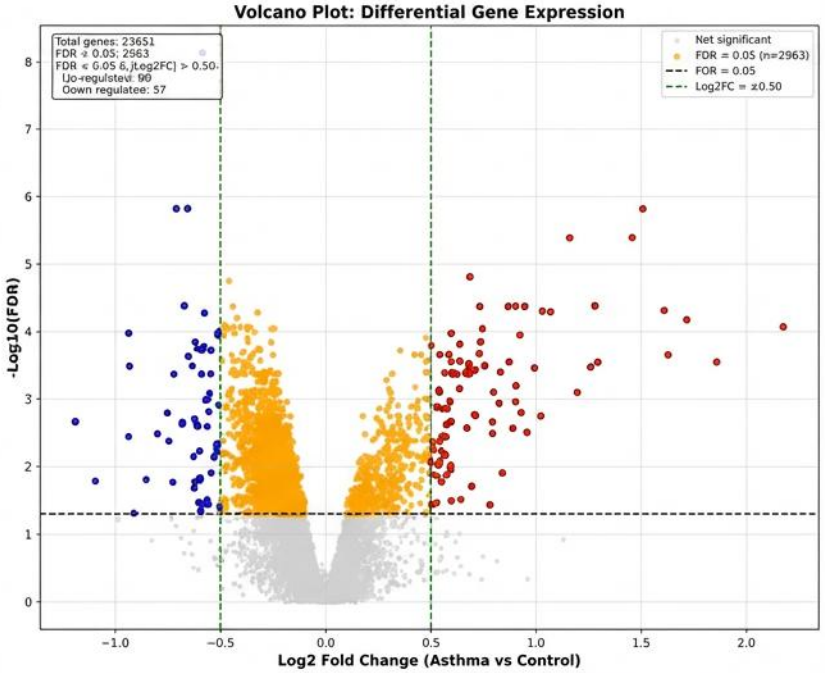


- PC1 captures 46.0% variance
- PC2 captures 9.3% variance
- Asthma (red) and Control (blue) samples show overlap but distinct trends
- Heterogeneity within asthma group suggests molecular subtypes

(GEO: GSE152004)

Differential Gene Expression Analysis

- Total genes tested: 23,651
- Significant genes (FDR < 0.05): 2,963
- After fold-change filtering (|Log2FC| > 0.5): 147 genes
- 90 UP-regulated (red) and 57 DOWN-regulated (blue) in asthma
- Top up-regulated genes: CST1, CLCA1, TPSAB1, CPA3 (mast cell markers)



(GEO: GSE152004)

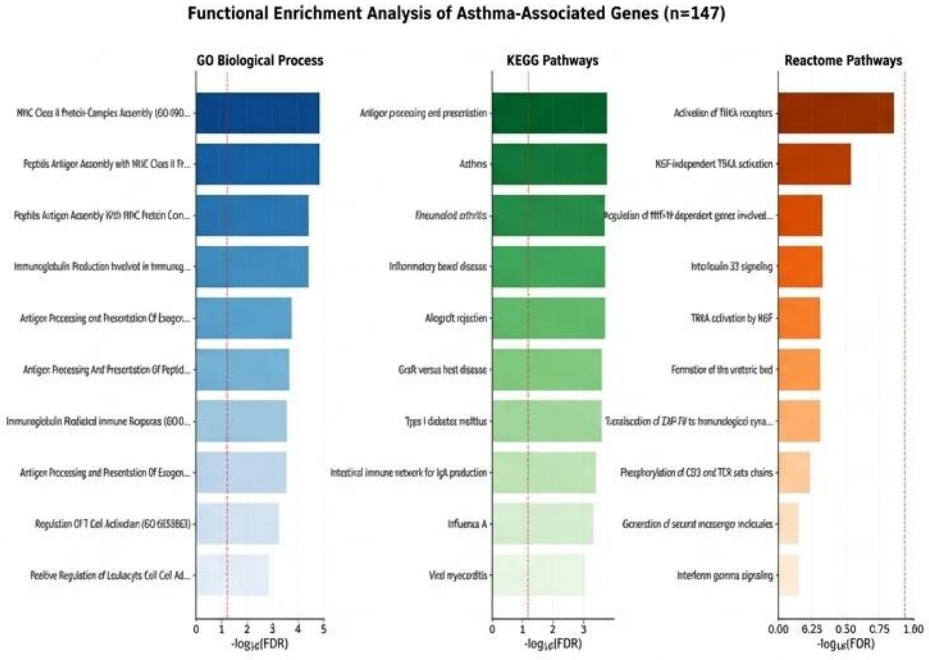
K-Dense

Top Differentially Expressed Genes

UP-REGULATED	DOWN-REGULATED
TPSAB1 (Log2FC=1.51) - Tryptase, mast cell marker	**B3GALT2** (Log2FC=-0.59)
CPA3 (Log2FC=1.46) - Carboxypeptidase A3, mast cell	**CX3CR1** (Log2FC=-0.66) - Chemokine receptor
CLCA1 (Log2FC=1.86) - Chloride channel	**IFNG** (Log2FC=-0.52) - Interferon gamma
CST1 (Log2FC=2.18) - Cystatin	**IL17A** (Log2FC=-0.60) - IL-17A
POSTN (Log2FC=0.99) - Periostin, T2 marker	

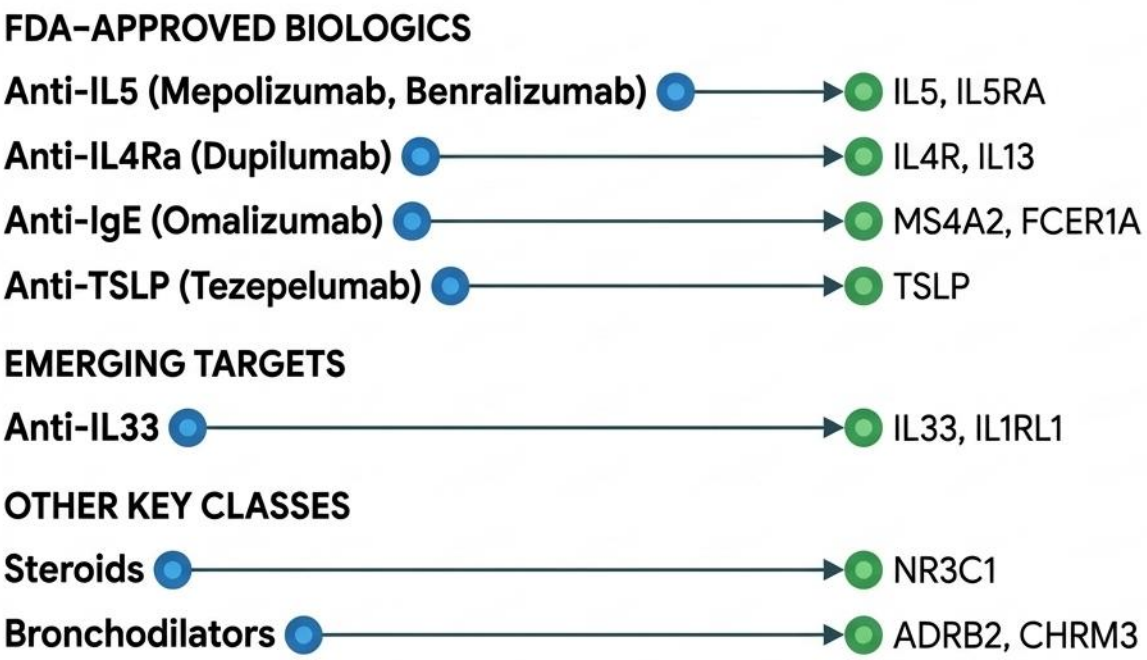
Key Insight: Mast cell markers dominate upregulated genes.

Pathway Enrichment Analysis



- 50 significantly enriched pathways identified (FDR<0.05)
- Top enriched pathways:
  - MHC Class II Assembly (FDR=1.44e-05)
  - Antigen Presentation (FDR=4.03e-05)
  - Immunoglobulin Production (FDR=4.08e-05)
- KEGG ASTHMA pathway directly enriched (FDR=1.55e-04) - validates methodology
- Databases used: GO Biological Process, KEGG, Reactome

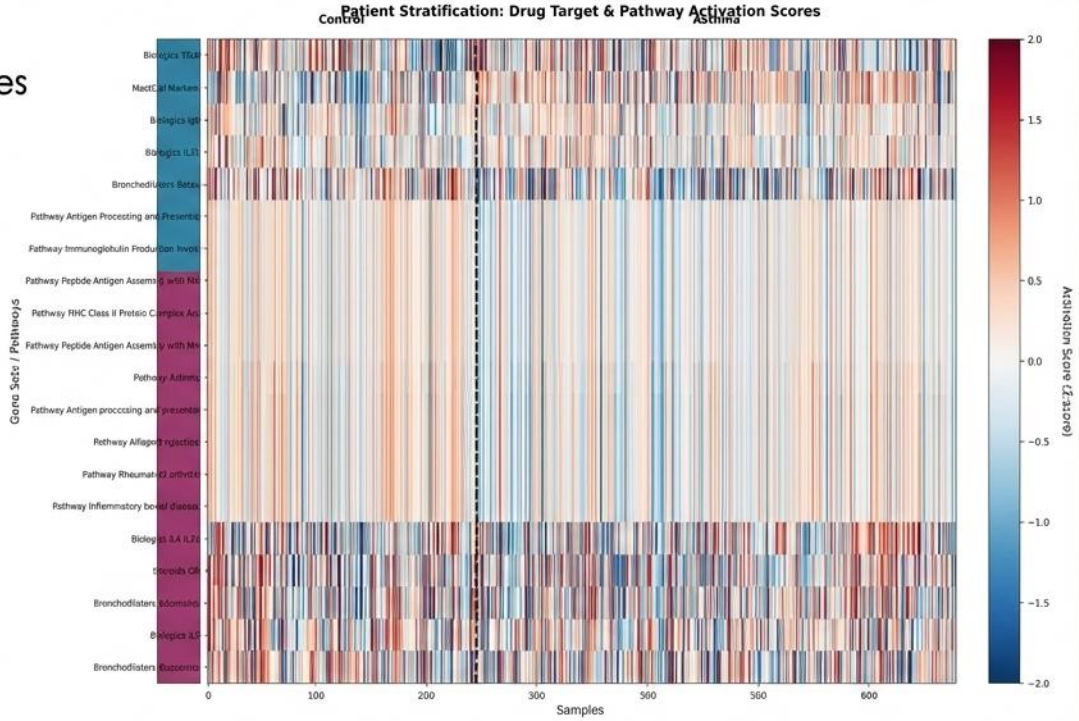
Drug Target Mapping



Patient Stratification by Pathway Activation

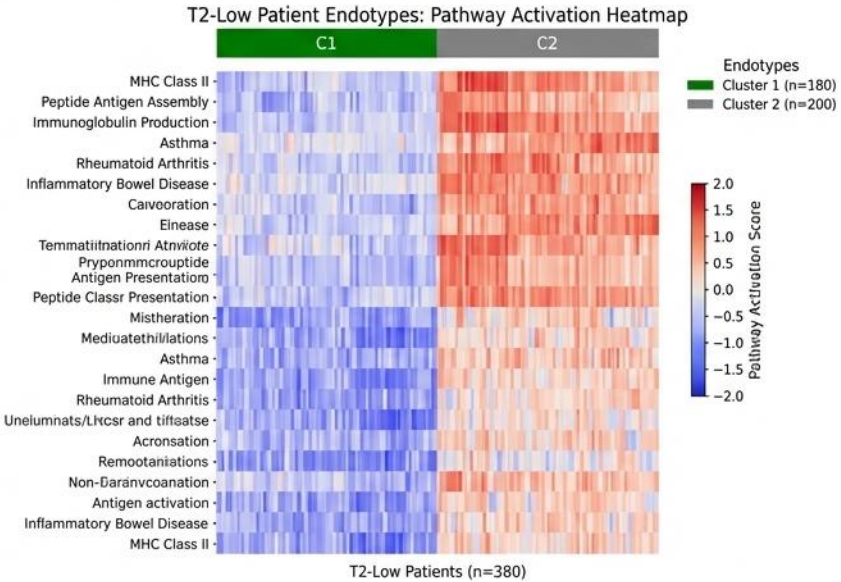
- **Analysis Approach:**
  - Calculated single-sample Z-scores for each drug target pathway.
  - Threshold: Control Mean + 2SD.
- **Results:**
  - **T2-HIGH** patients (drug targets activated): 53 (12.2%).
  - **T2-LOW candidates** (no drug targets activated): 380 (87.8%).

NOTE:
High **T2-low** percentage suggests:
1) Nasal tissue specificity,
2) Conservative threshold,
3) Molecular heterogeneity.



T2-Low Endotype Discovery

- **Methods:** K-means clustering on pathway activation scores for 380 T2-low patients. Optimal k=2 determined by silhouette analysis (score=0.5434).
- **Results:** Two DISTINCT ENDOTYPES.
  - **CLUSTER 1 - 'Immune-Quiet'** (180 patients, 47.4%): Low MHC Class II activation, minimal inflammation.
  - **CLUSTER 2 - 'Immune-Active'** (200 patients, 52.6%): High antigen presentation, elevated immune response.



ENDOTYPE CHARACTERIZATION

IMMUNE-QUIET (180 patients)

- **Biology:** Low MHC-II, minimal inflammation.
- **Mechanism:** Epithelial dysfunction, airway remodeling.
- **Key pathways:** Low antigen presentation.
- **Treatment focus:** Bronchodilators, epithelial repair.

IMMUNE-ACTIVE (200 patients)

- **Biology:** High MHC-II, non-T2 inflammation.
- **Mechanism:** Th1/Th17 driven, neutrophilic.
- **Key pathways:** High antigen presentation, cytokine signaling.
- **Treatment focus:** JAK inhibitors, anti-IL17.

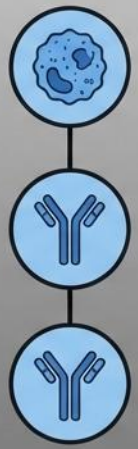
CLINICAL IMPLICATIONS: T2-HIGH PATIENTS

T2-High Group (299 patients, 44%)

MOLECULAR PROFILE

- Elevated IL-4, IL-5, IL-13 pathway activation
- High eosinophil-related gene expression

RECOMMENDED TREATMENT & MONITORING PATHWAY



Anti-IL-5 (Mepolizumab, Benralizumab)

Anti-IL-4Ra (Dupilumab)

Anti-IgE (Omalizumab)

EXPECTED OUTCOMES & MONITORING

- 50-70% reduction in exacerbations
- FEV1 improvement 100-200mL

MONITORING

- Blood eosinophils
- FeNO levels
- Serum IgE

CLINICAL IMPLICATIONS: T2-LOW PATIENTS

IMMUNE-ACTIVE (200 patients, 29%) | IMMUNE-QUIET (180 patients, 27%)

MOLECULAR PROFILE

- High MHC-II, non-T2 inflammation

EXPECTED OUTCOMES & MONITORING

- 30-50% exacerbation reduction

Sputum neutrophils, IL-17 levels

TREATMENT PATHWAY

High-dose ICS, JAK inhibitors (Tofacitinib)

Anti-IL-17A (Secukinumab), Macrolides

Macrolides

EXPECTED OUTCOMES & MONITORING

- LABA/LAMA bronchodilators, Low-dose ICS, Bronchial thermoplasty
- **Focus:** Airway mechanics, trigger avoidance

MONITORING

FEV1, peak flow, QoL scores

KEY CONCLUSIONS

SUMMARY OF FINDINGS & CLINICAL IMPLICATIONS

VALIDATED TRANSCRIPTOMIC SIGNATURE: 147 significant DEGs, mast cell markers dominate, KEGG Asthma pathway enriched.

THREE DISTINCT PATIENT GROUPS IDENTIFIED: T2-High (44%), T2-Low Immune-Active (29%), T2-Low Immune-Quiet (27%).

PRECISION TREATMENT FRAMEWORK:

- **T2-High** → Biologics (IL-5, IL-4Ra, IgE targeting)
- **Immune-Active** → JAK inhibitors, anti-IL-17
- **Immune-Quiet** → Bronchodilators, epithelial repair

CLINICAL IMPACT: Moves beyond trial-and-error to biology-driven treatment selection.

FUTURE DIRECTIONS & NEXT STEPS

VALIDATION

1) Validate 3-group stratification in independent cohorts.
2) Prospective clinical trials with stratified treatment.

BIOMARKER DEVELOPMENT

1) Develop minimal gene panels (qPCR-based).
2) Create rapid clinical assays for point-of-care testing.
3) Integrate with electronic health records.

CLINICAL IMPACT

1) Reduce trial-and-error in therapy selection.
2) Model cost-effectiveness vs. standard care.
3) Establish reimbursement pathways.

THANK YOU

Thank you for your attention.
Questions welcome.

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Date: December 2025
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Analysis pipeline available upon request.