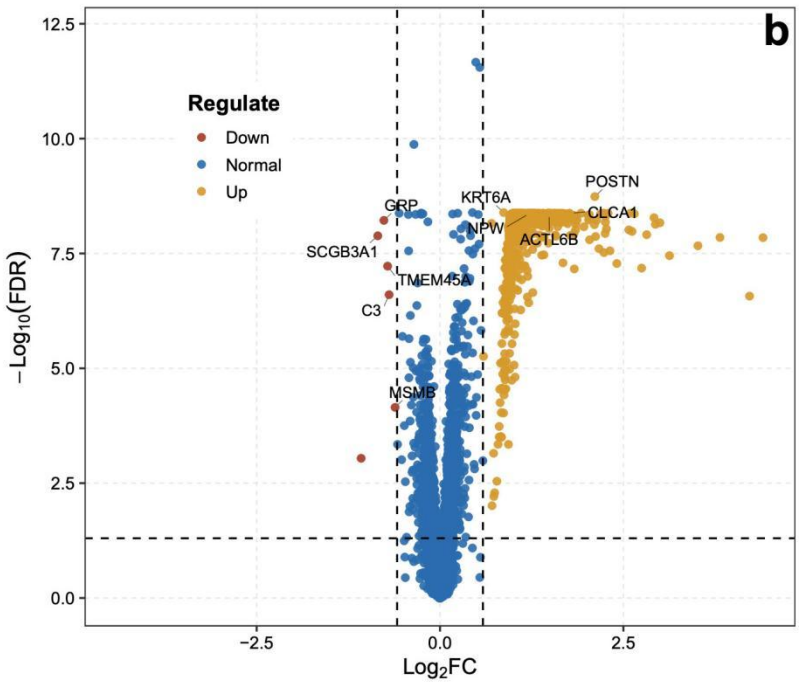
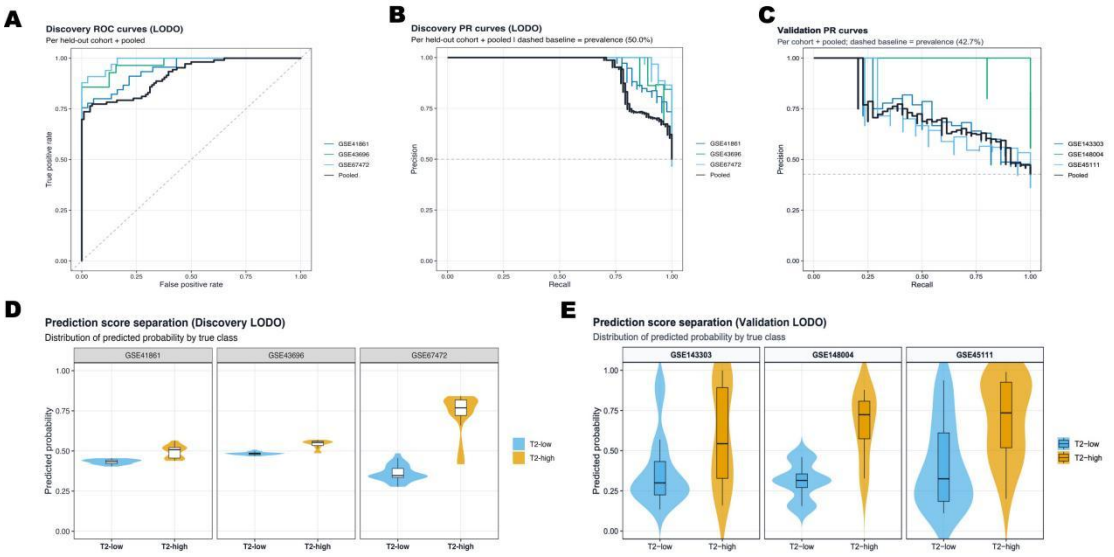
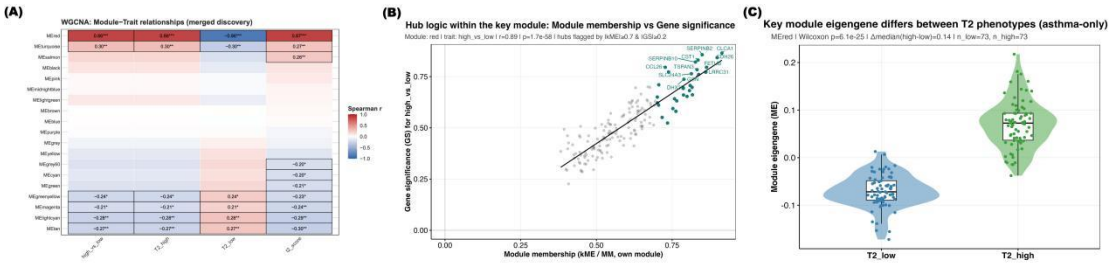


S1 Fig. Volcano plots of differential expression in the validation cohorts (asthma vs control).

Each point represents a gene, with log2 fold change on the x-axis and −log10(FDR) on the y-axis. Significantly upregulated genes are shown in yellow, downregulated genes in red, and non-significant genes in blue. Dashed lines indicate the thresholds used to define differential expression (FDR < 0.05, corresponding to −log10[FDR] = 1.30, and |log2FC| > 0.585). Selected genes are annotated, including upregulated markers (e.g., POSTN, CLCA1, and ACTL6B) and downregulated markers (e.g., SCGB3A1, C3, and GRP)

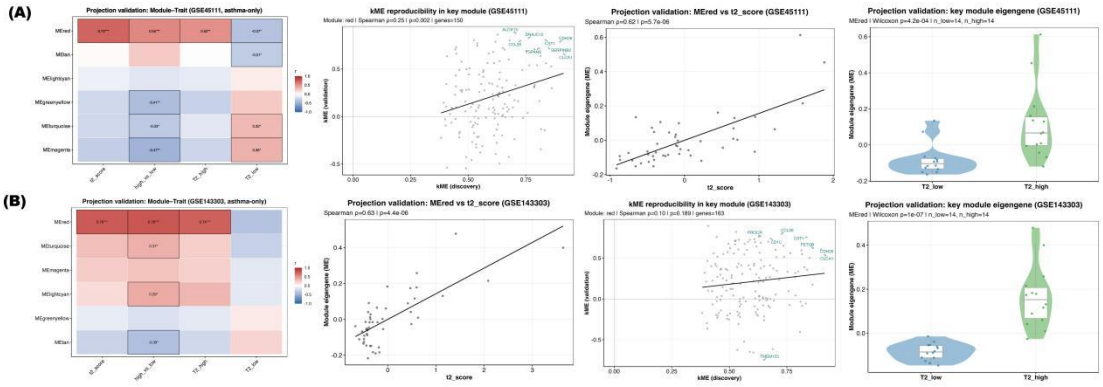


S2 Fig. Detailed ROC and precision–recall curves and predicted-probability separation for the leakage-controlled elastic-net baseline model.
(A) Discovery LODO ROC curves for T2-high versus T2-low classification, shown for each held-out cohort (GSE41861, GSE43696, and GSE67472) and the pooled curve; the diagonal line indicates no-discrimination performance. (B) Discovery LODO precision–recall curves for each held-out cohort and the pooled curve; the dashed horizontal line denotes the precision–recall baseline equal to the positive-class prevalence (30.0%). (C) External-validation precision–recall curves shown for each cohort (GSE143303, GSE148004, and GSE45111) and the pooled curve; the dashed baseline denotes the positive-class prevalence (42.7%). (D) Separation of predicted probabilities by true class in discovery LODO, shown for each held-out cohort as violin plots with embedded boxplots (median and IQR) for T2-low (blue) and T2-high (orange). (E) Predicted-probability separation by true class in the validation cohorts, shown per cohort using the same visualisation and class colours.



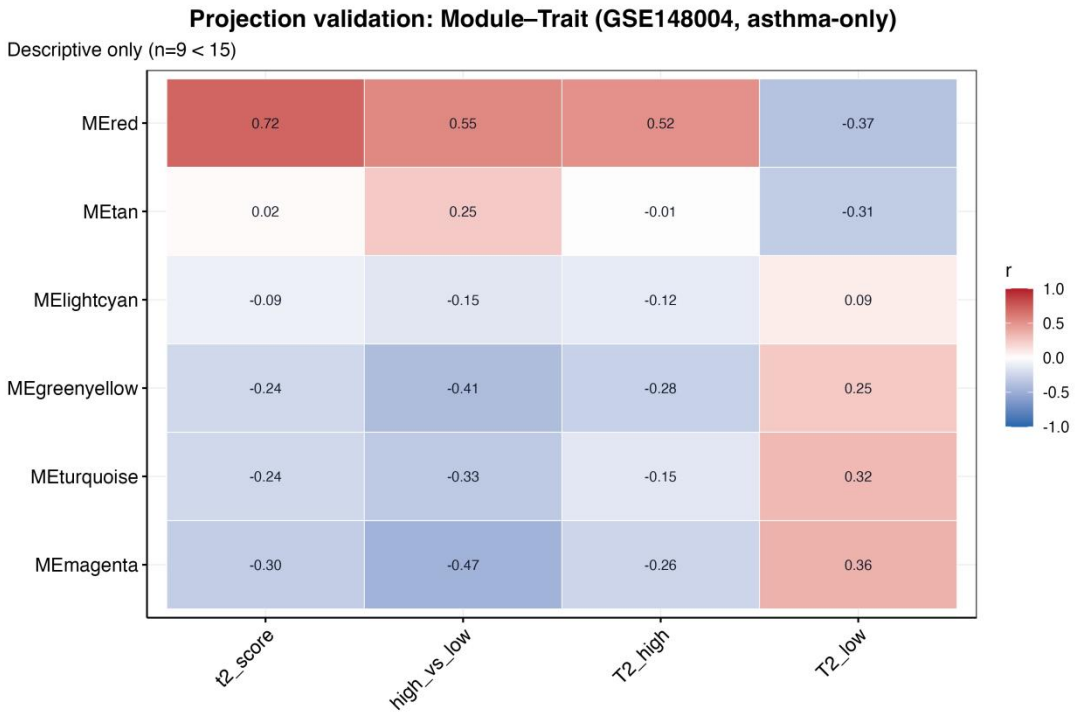
S3 Fig. WGCNA in the discovery set identifies a T2-associated co-expression module.

Weighted gene co-expression network analysis (WGCNA) was performed on the merged discovery data. (A) Module–trait relationship heatmap showing Spearman correlations (ρ) between module eigengenes (rows) and traits (columns); numbers indicate ρ with corresponding P values, and colour intensity reflects effect size. (B) Hub-gene analysis within the red module (MEred), plotting module membership (kME) against gene significance for T2 status (T2-low vs T2-high); each point represents a gene, and labelled genes denote top hub or feature genes (fitted line shown). (C) Distribution of the MEred eigengene in T2-low and T2-high asthma samples, shown as violin plots with embedded boxplots (median and IQR) and overlaid individual samples; group differences were tested using a Wilcoxon rank-sum test, with statistics shown in-panel.



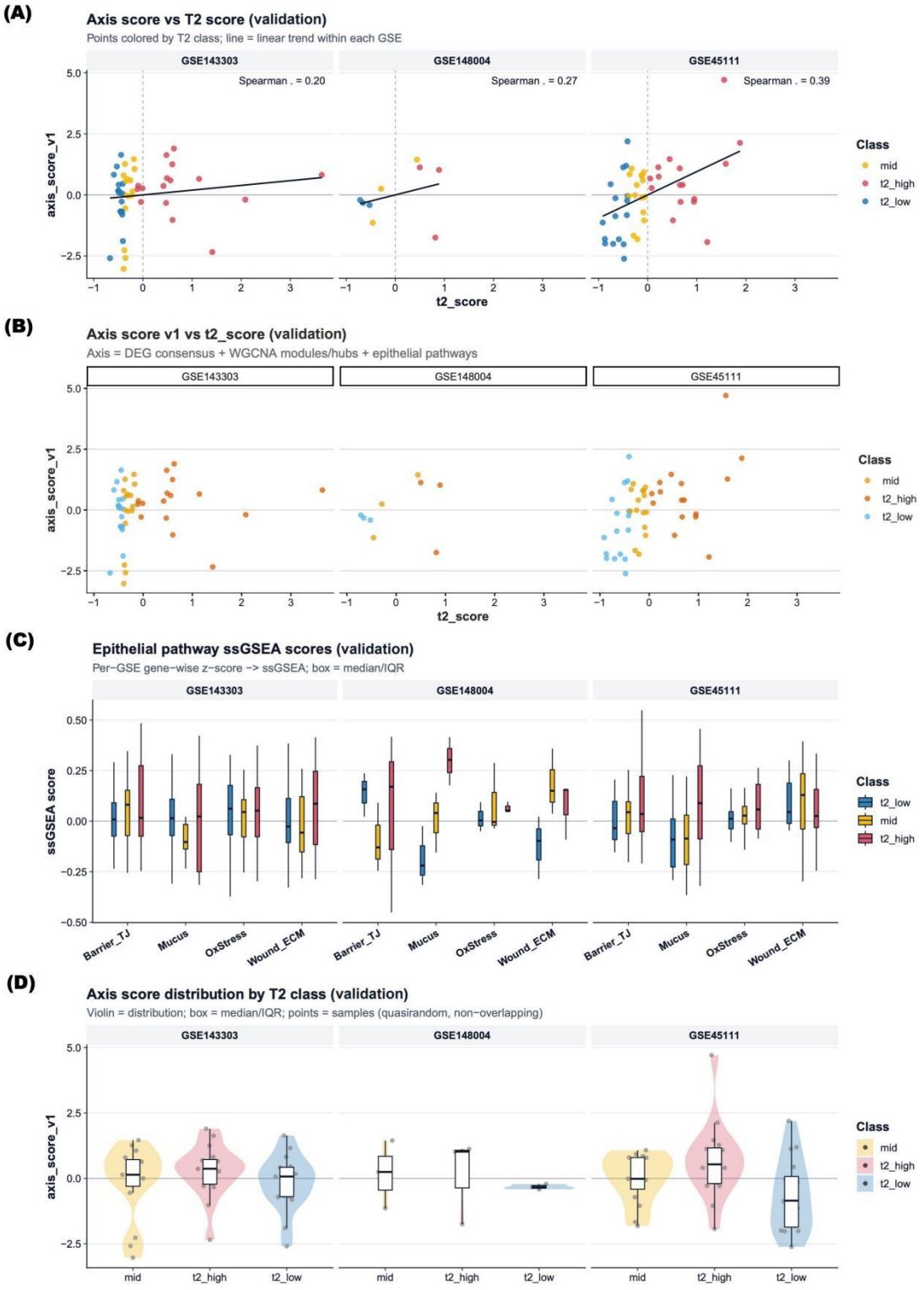
S4 Fig. Projection validation of the discovery WGCNA red module (MEred) in independent validation cohorts.

Discovery-derived co-expression modules were projected into independent validation cohorts (asthma-only) to assess preservation of T2-associated structure. (A) GSE45111 and (B) GSE143303. For each cohort, the left panel shows the projected module–trait relationship heatmap, with Spearman correlations (ρ) and corresponding P values shown in-panel. The middle-left panel evaluates kME reproducibility for MEred by plotting gene-wise module membership in the discovery set (kME_discovery) against projected module membership in the validation cohort (kME_projection), with Spearman's ρ and P values shown in-panel and top hub genes annotated. The middle-right panel shows the association between the projected MEred eigengene and the T2 score, with Spearman's ρ and P values shown in-panel. The right panel shows the distribution of the projected MEred eigengene across T2-low and T2-high groups, shown as violin plots with embedded boxplots and overlaid samples; group differences were assessed using a Wilcoxon rank-sum test, with statistics shown in-panel.



S5 Fig. Projection validation of discovery WGCNA module–trait relationships in GSE148004 (asthma-only; descriptive).

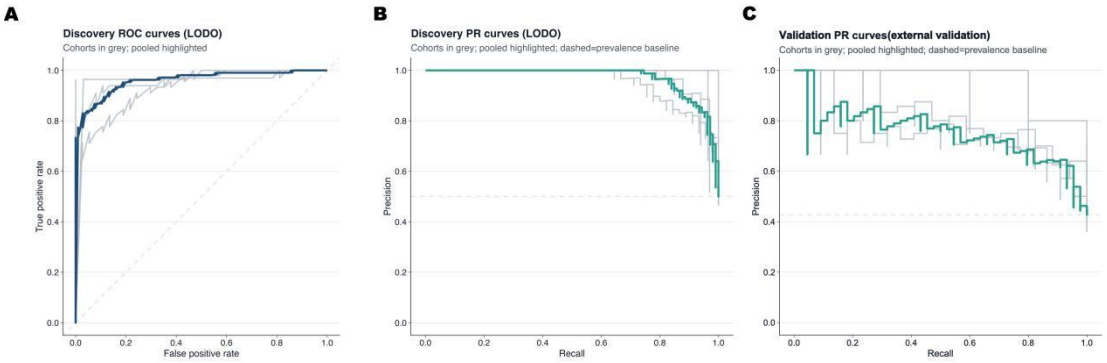
Discovery-derived WGCNA modules were projected into the independent validation cohort GSE148004. The heatmap shows Spearman correlations (ρ) between projected module eigengenes (rows, including MEred) and T2-related traits (columns: the T2 score, T2-high vs T2-low, T2-high, and T2-low); numbers indicate correlation coefficients, and colour intensity reflects effect size. Owing to the small asthma-only sample size (n = 9) and insufficient gene coverage for the projected MEred module, these results are descriptive only, and downstream hub-gene and eigengene analyses were not performed.



S6 Fig. Validation-set behaviour of the T2-associated epithelial axis and related epithelial programmes.

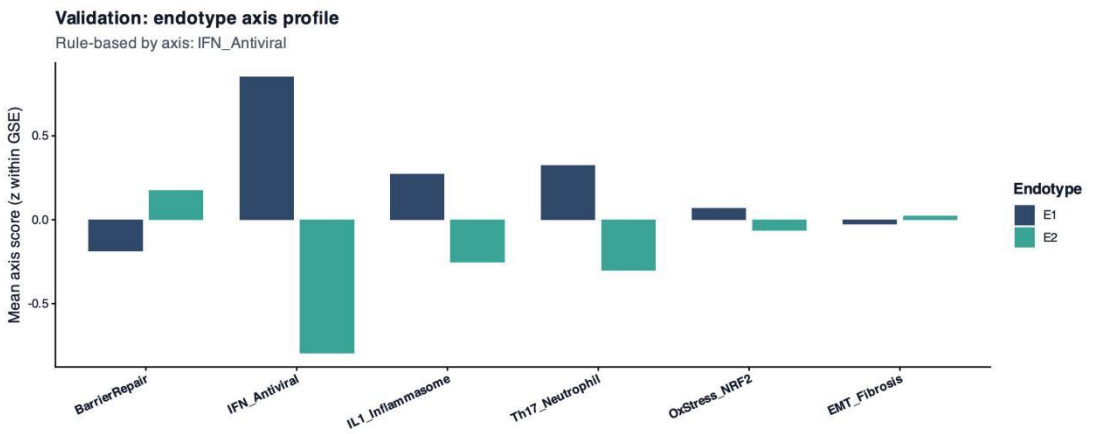
Analyses were performed in the independent validation cohorts (GSE143303, GSE148004, and GSE45111), with samples coloured by T2 class (T2-low, T2-mid, and T2-high). (A) Within-cohort association between the T2 epithelial axis score and

the T2 score in each validation cohort, with Spearman's ρ shown in-panel; the black line denotes the within-cohort linear trend. (B) Scatter plots of the T2 epithelial axis score versus the T2 score shown by cohort; the axis was derived from DEG consensus, WGCNA modules and hubs, and epithelial pathway evidence. (C) Epithelial pathway activity in the validation cohorts, shown as ssGSEA scores computed from per-GSE gene-wise Z-scores for Barrier_TJ, Mucus, OxStress, and Wound_ECM, stratified by T2 class (boxplots show median and IQR). (D) Distribution of the T2 epithelial axis score across T2 classes in each validation cohort, shown as violin plots with embedded boxplots (median and IQR) and overlaid individual samples.



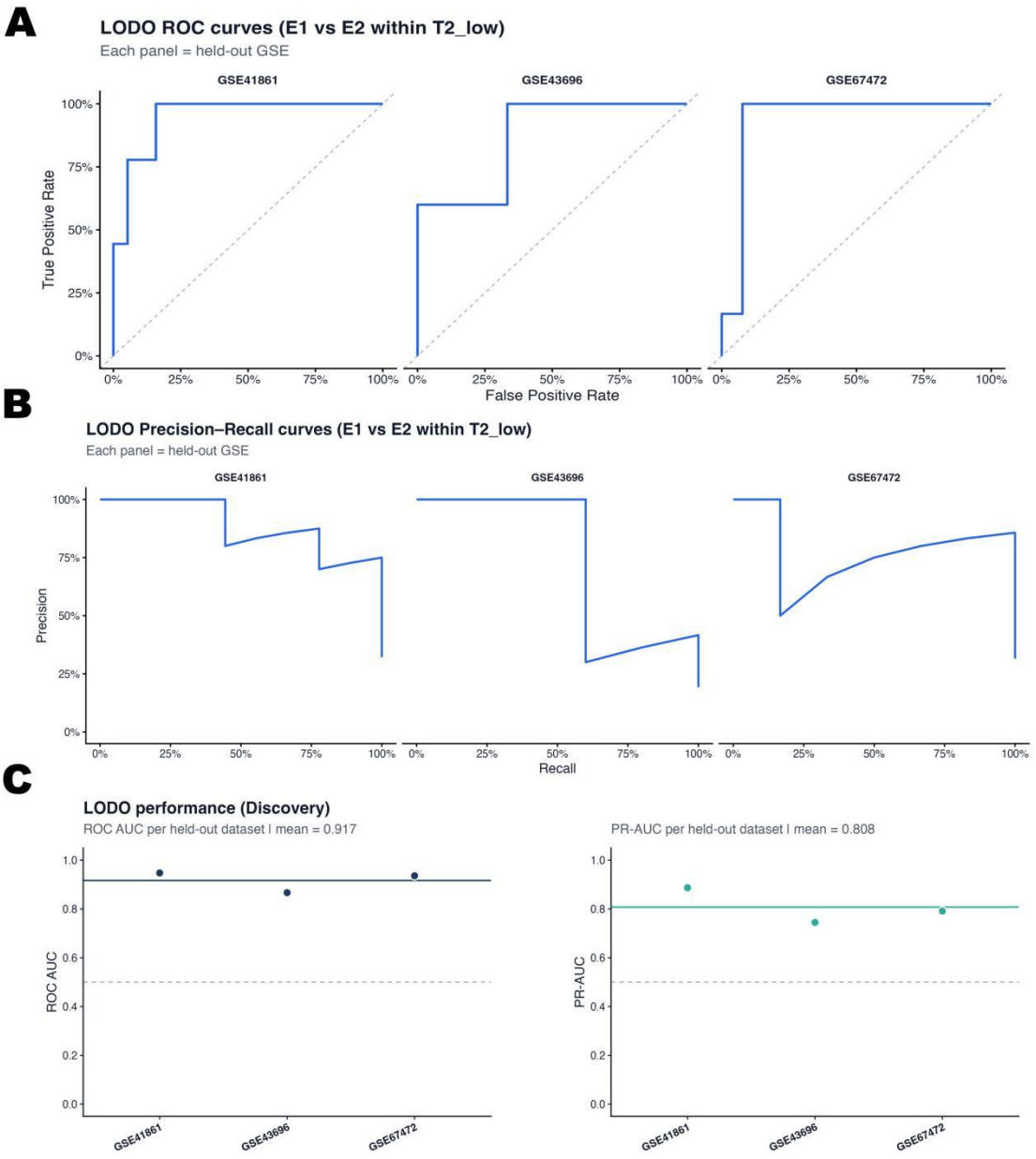
S7 Fig. Detailed discrimination curves for the leakage-controlled elastic-net baseline model for T2-high versus T2-low classification.

(A) Discovery leave-one-dataset-out (LODO) receiver operating characteristic (ROC) curves, shown for each held-out discovery cohort, with the pooled curve highlighted; the diagonal dashed line indicates no-discrimination performance. (B) Discovery LODO precision–recall curves, shown for each held-out discovery cohort, with the pooled curve highlighted; the dashed horizontal line indicates the prevalence-based baseline. (C) External-validation precision–recall curves in the independent validation cohorts, shown for each cohort with the pooled curve highlighted; the dashed horizontal line indicates the prevalence-based baseline.



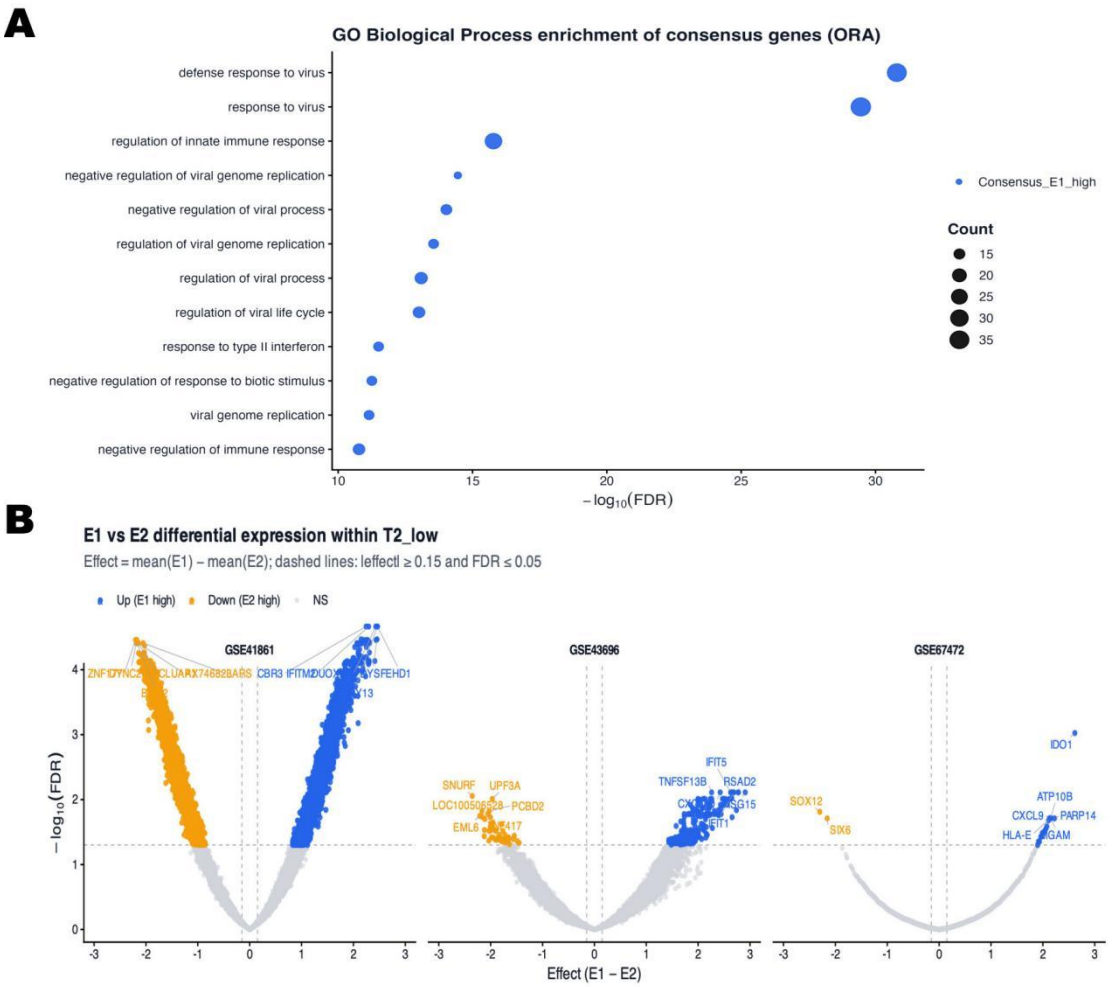
S8 Fig. Validation endotype axis profile for E1 and E2 in the independent validation cohorts.

Bars show the mean zWithinGSE-standardised scores for the six non-T2 axes in E1 and E2 across the validation cohorts. Rule-based endotype assignment was defined using the IFN_Antiviral axis. Relative to E2, E1 shows higher mean scores for IFN_Antiviral, IL1_Inflammasome, Th17/Neutrophil, and OxStress_NRF2, together with opposite trends for BarrierRepair and EMT/Fibrosis.



S9 Fig. Discovery LODO performance of the minimal E1/E2 classifier within T2-low asthma.

(A) Leave-one-dataset-out (LODO) ROC curves for classification of E1 versus E2 within T2-low samples, shown separately for each held-out discovery cohort. The diagonal dashed line indicates no-discrimination performance. (B) LODO precision–recall curves for E1 versus E2 within T2-low samples, shown separately for each held-out discovery cohort. (C) Per-cohort performance summary in the discovery set, showing ROC AUC and PR-AUC for each held-out discovery cohort. Solid horizontal lines indicate the mean across held-out cohorts, and dashed horizontal lines indicate the reference level.



S10 Fig. Functional enrichment and cohort-level differential-expression patterns for E1 versus E2 within T2-low asthma.

(A) Gene Ontology Biological Process over-representation analysis of consensus E1-high genes. Terms are ranked by enrichment significance; bubble size indicates gene count, and the x-axis shows −log10(FDR). (B) Cohort-specific differential-expression volcano plots for E1 versus E2 within T2-low samples in the discovery cohorts (GSE41861, GSE43696, and GSE67472). Effect size was defined as mean(E1) − mean(E2). Dashed lines indicate the prespecified thresholds for effect size and significance ($|\text{effect}| \geq 0.15$ and $\text{FDR} \leq 0.05$). Blue points indicate genes upregulated in E1 (E1-high), orange points indicate genes upregulated in E2 (E2-high), and grey points indicate non-significant genes. Selected genes are annotated.