



Combining bioinformatics and machine learning to identify common mechanisms and biomarkers of childhood asthma and obesity

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Background: Childhood asthma (CA), a chronic inflammatory disorder of the airways, and childhood obesity (CO), characterized by low-grade systemic inflammation, frequently coexist. This study seeks to elucidate shared biological mechanisms underlying CA and CO and to identify potential biomarkers via comprehensive bioinformatics analyses of public datasets.

Methods: CA and CO gene expression datasets were retrieved from the Gene Expression Omnibus (GEO). Differentially expressed genes (DEGs) common to both conditions were identified, with hub genes (HGs) screened via four machine learning (ML) algorithms. The diagnostic performance of candidate HGs was evaluated utilizing receiver operating characteristic (ROC) curve analysis. Functional characterization was conducted utilizing Gene Ontology (GO), Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis, and single-gene gene set enrichment analysis (GSEA). In addition, competitive endogenous RNA (ceRNA) networks were constructed to further explore regulatory relationships and shared pathogenic mechanisms.

Results: There were 25 key genes closely linked to CA and CO identified. Enrichment analyses indicated the main involvement of these genes in immune and inflammatory responses, as well as extracellular matrix organization and tissue remodeling. ML analyses ultimately identified *NTRK2* and *RGS1* as HGs, which demonstrated favorable diagnostic performance in ROC analyses. Furthermore, a ceRNA regulatory network comprising 104 long noncoding RNAs (lncRNAs), 80 microRNAs (miRNAs), and the two HGs was constructed.

Conclusions: This study identified *NTRK2* and *RGS1* as key HGs shared between CA and CO, presenting fresh insights into their common pathogenic mechanisms. These findings possibly contribute to developing improved diagnostic biomarkers and targeted therapeutic strategies for CA comorbid with obesity.

Keywords: Childhood asthma (CA); childhood obesity (CO); bioinformatics; machine learning (ML)

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Introduction

Obesity and asthma constitute two major global health challenges in the pediatric population, with their steadily increasing prevalence imposing substantial economic and societal burdens worldwide (1). Accumulating evidence indicates that children with obesity are at a significantly elevated asthma risk. Moreover, among children with established asthma, coexisting obesity is linked to greater disease severity, poorer symptom control, increased frequency of exacerbations, and an overall reduction in asthma-related quality of life (2).

Extensive epidemiological data have demonstrated a strong relation of obesity, or excessive early-life weight gain, to childhood asthma (CA) development (3–5). Multiple longitudinal studies have consistently shown that obesity often precedes the onset of asthma. For instance, a large-scale cohort analysis from the Taiwan Children Health Study identified obesity as the strongest risk factor for incident asthma, with a hazard ratio (HR) of 1.28 [95% confidence interval (CI): 1.05–1.56] (6). These findings are further supported by a meta-analysis of prospective studies revealing a clear dose-response relationship, whereby children with obesity exhibited nearly a twofold increased risk of developing asthma [odds ratio (OR) =1.9] (7). Notably, the interaction between asthma and obesity possibly originates even before birth. Maternal obesity and excessive

gestational weight gain are independently linked to a 15–30% elevated asthma risk in offspring (8,9). Intriguingly, emerging evidence suggests that this relation is possibly bidirectional. A recent longitudinal study demonstrated that children with asthma displayed a notably greater likelihood of obesity during a 10-year follow-up, indicating that asthma itself possibly predisposes individuals to subsequent weight gain (10).

The relation of asthma to obesity extends beyond simple coexistence. Although bidirectional pathophysiological interactions have been proposed, the underlying causal mechanisms remain incompletely understood (1). Proposed mechanisms involve common genetic predisposition, factors linked to diet and nutrition, changes in the gut microbiota, persistent body-wide inflammation, impaired metabolic processes, and structural as well as functional modifications in the lungs related to obesity (1,2). Therefore, elucidating the shared molecular and genetic mechanisms underlying the comorbidity of CA and childhood obesity (CO) is of substantial clinical importance, with the potential to identify novel therapeutic targets and improve disease management.

As bioinformatics advances, large public genomic datasets have become increasingly accessible, enabling the systematic exploration of disease pathogenesis and inter-disease relationships. Machine learning (ML), a key component of artificial intelligence widely utilized in bioinformatics research, is an emerging, powerful biomarker discovery and disease classification tool. This study aims to identify common hub genes (HGs) and pathways linking CA and CO through integrated bioinformatics analyses, thereby elucidating shared molecular mechanisms and offering novel insights into their comorbidity. We present this article in accordance with the TRIPOD reporting checklist (available at <https://tp.amegroups.com/article/view/10.21037/tp-2026-1-0108/rc>).

Methods

Data collection and processing

Gene expression profiling datasets came from the GEO (<http://www.ncbi.nlm.nih.gov/geo>). Specifically, GSE152004 (441 asthmatic and 254 healthy samples) and GSE65204 (36 asthmatic and 33 healthy samples) were used for CA, while GSE205668 (26 obese and 35 healthy samples) and GSE88837 (15 obese and 15 healthy samples) were used for CO. Among these, GSE152004 and GSE205668 were designated as training datasets to identify

Highlight box

Key findings

- This study identified *NTRK2* and *RGS1* as hub genes (HGs) for childhood asthma and obesity through integrated bioinformatics and machine-learning analyses.

What is known and what is new?

- Existing evidence indicates a significant association and bidirectional interaction between childhood obesity and asthma, but their shared molecular mechanisms and diagnostic biomarkers remain unclear.
- This study is new in employing integrated bioinformatics and machine learning to identify *NTRK2* and *RGS1* as shared HGs and constructing a comprehensive competitive endogenous RNA regulatory network (104 lncRNAs, 80 miRNAs) for these conditions.

What is the implication, and what should change now?

- These findings imply that *NTRK2* and *RGS1* could serve as biomarkers for comorbid asthma and obesity, suggesting that future research should focus on validating these targets for diagnosis and therapy.

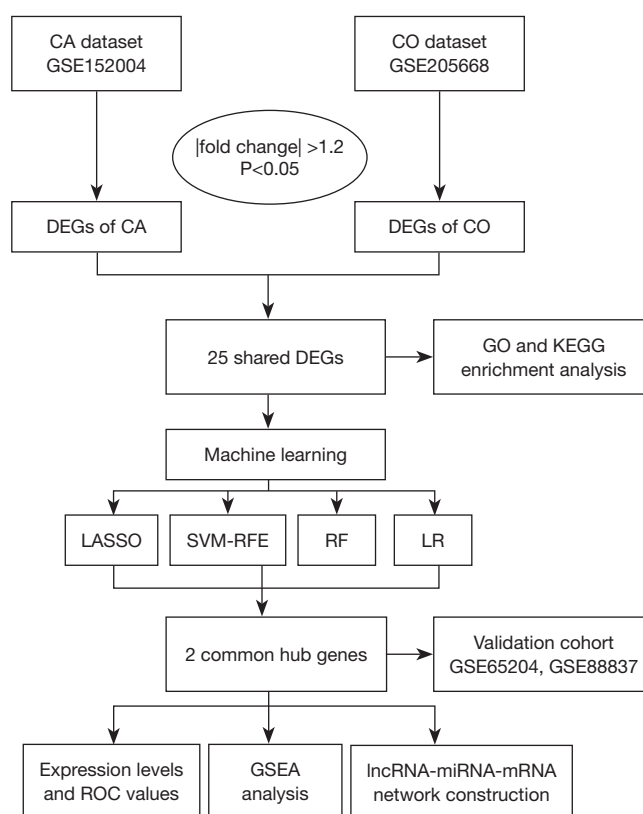


Figure 1 Study flowchart. CA, childhood asthma; CO, childhood obesity; DEGs, differentially expressed genes; GO, Gene Ontology; GSE, gene expression omnibus series; GSEA, gene set enrichment analysis; KEGG, Kyoto Encyclopedia of Genes and Genomes; LASSO, least absolute shrinkage and selection operator; LR, logistic regression; lncRNAs, long noncoding RNAs; mRNA, messenger RNA; miRNAs, microRNAs; RF, random forest; ROC, receiver operating characteristic; SVM-RFE, support vector machine recursive feature elimination.

genes commonly related to CA and CO. GSE65204 and GSE88837 served as independent external validation datasets to confirm gene expression patterns and evaluate the diagnostic performance of candidate genes. Differential expression analysis (DEA) was conducted on the training datasets to identify differentially expressed genes (DEGs) in CA and CO, respectively. Subsequently, ML algorithms, including least absolute shrinkage and selection operator (LASSO) regression, support vector machine-recursive feature elimination (SVM-RFE), logistic regression (LR), and random forest (RF), were applied to screen shared HG from the intersecting DEGs. The diagnostic performance of the identified HGs was further validated using external validation datasets. Subsequent analyses comprised single-gene gene set enrichment analysis (GSEA) and competitive endogenous RNA (ceRNA) network analysis. The overall study design is illustrated in *Figure 1*. The study was conducted in accordance with the Declaration of Helsinki

and its subsequent amendments.

DEG identification

DEGs across disease and control cohorts in the CA dataset (GSE152004) and the CO dataset (GSE205668) were identified utilizing limma in R. Adjusted $P < 0.05$ and $|\text{fold change}| > 1.2$ suggested statistically significant DEGs. DEG distributions and expression patterns were visualized via volcano plots and hierarchical clustering heatmaps generated through ggplot2 and pheatmap. The ggvnn package was applied to identify and illustrate genes exhibiting consistent expression trends across CA and CO datasets.

Functional enrichment analysis

Functional annotation of DEGs was carried out utilizing

Gene Ontology (GO) enrichment analysis, involving biological process (BP), cellular component (CC), and molecular function (MF), and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis via clusterProfiler in R. $P < 0.05$ denotes significance. Enrichment results were visualized via ggplot2 and enrichplot.

ML-based HGs

LASSO regression, SVM-RFE, RF, and LR were leveraged to identify possible biomarkers. The penalty parameter λ for LASSO was determined using 5-fold cross-validation. SVM-RFE employed a radial basis function (RBF) kernel and conducted RFE with 5-fold cross-validation, iteratively removing the feature with the smallest contribution to classification and ultimately selecting the feature subset that minimized the cross-validation error. The RF model was constructed with 1,000 decision trees. The number of candidate variables at each node was set to the default value (the floor of the square root of the total number of variables). Feature importance was evaluated based on the mean decrease in the Gini index, and features with an importance score greater than 0.5 were retained. LR analysis was conducted through univariate LR models, in which each gene was individually evaluated utilizing a binomial family to estimate ORs and 95% CI; genes with $P < 0.05$ were considered statistically significant. Genes identified by all four algorithms were defined as candidate biomarkers, and those shared between CA and CO were designated as HGs.

HG validation and assessment

The identified candidate HGs were validated in the training and external validation datasets for CO and CA. Differences in gene expression across disease and control groups were examined, and $P < 0.05$ suggested significantly DEGs. Candidate genes exhibiting consistent and statistically significant expression differences across datasets were ultimately defined as HGs. Boxplots were generated to visualize expression distributions. Subsequently, the diagnostic performance of HGs in the training and validation cohorts was examined through receiver operating characteristic (ROC) curves via pROC in R. The predictive accuracy of every HG was quantified using the area under the curve (AUC).

Single-gene GSEA

Single-gene GSEA was carried out utilizing a correlation-based approach. Pearson correlation coefficients were calculated across expression levels of every gene and those of the HG to generate a ranked gene list. The GSEA algorithm was then applied to the Kyoto Encyclopedia of KEGG pathway database and GO functional gene sets to identify biological pathways and functional modules significantly linked to HG expression patterns.

lncRNA-miRNA-messenger RNA (mRNA) network

ceRNAs act as molecular sponges that competitively bind shared microRNAs (miRNAs), thereby regulating gene expression. A ceRNA regulatory network encompasses interactions among mRNAs, miRNAs, and long noncoding RNAs (lncRNAs). To construct the ceRNA network, miRNAs targeting the HGs were predicted utilizing miRTarBase (<https://miRTarBase.cuhk.edu.cn/>), miRWalk (<http://mirwalk.umm.uni-heidelberg.de/>), and TargetScan (https://www.targetscan.org/vert_80/). Subsequently, lncRNAs potentially interacting with these miRNAs were identified using StarBase (<https://starbase.sysu.edu.cn/>). All predicted interactions were integrated and visualized via Cytoscape 3.10.4 for lncRNA-miRNA-mRNA regulatory network construction.

Statistical analysis

R software version 4.5.0 was used to perform statistical analyses. Differences between the two groups were compared by the Wilcoxon rank-sum test. $P < 0.05$ was regarded as statistically significant.

Results

DEG identification

DEA of the CA cohort (GSE152004) identified 251 DEGs with significant transcriptional alterations, including 81 upregulated and 170 downregulated genes (*Figure 2A*). In GSE205668, 8,576 DEGs were found. 8,353 were upregulated, and 223 were downregulated (*Figure 2B*). Venn diagram analysis revealed 25 DEGs shared between CA and CO (*Figure 2C,2D*), of which 24 were upregulated, and one was downregulated in conditions.

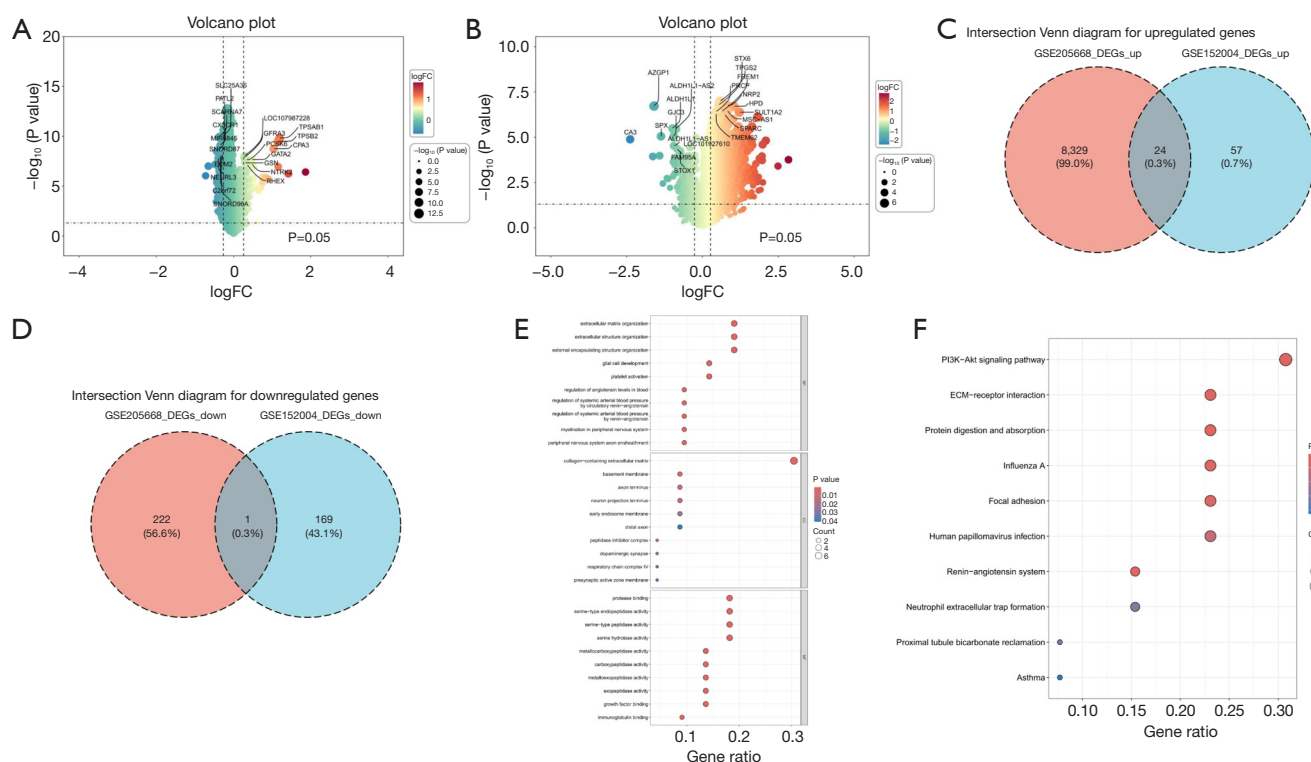


Figure 2 DEG identification in CA (GSE152004) and CO (GSE205668). (A,B) Volcano plots of all DEGs in GSE152004 and GSE205668. (C,D) Venn diagram identifying co-upregulated and co-downregulated DEGs. (E,F) The enrichment analysis results of the GO and KEGG pathways. BP, biological process; CA, childhood asthma; CC, cellular component; CO, childhood obesity; FC, fold change; GO, Gene Ontology; GSE, gene expression omnibus series; KEGG, Kyoto Encyclopedia of Genes and Genomes; MF, molecular function.

Enrichment analysis

To elucidate shared biological mechanisms between CA and CO, GO BP, and KEGG pathway enrichment analyses were performed on the common DEGs. GO enrichment analysis demonstrated that these genes were predominantly involved in extracellular matrix organization, glial cell development, and platelet activation within the BP category; collagen-containing extracellular matrix, basement membrane, and axon terminus within the CC category; protease binding, serine-type endopeptidase activity, and serine-type peptidase activity in the MF category (Figure 2E). KEGG pathway enrichment analysis revealed the main enrichment of shared DEGs in the PI3K-Akt signaling pathway, extracellular matrix-receptor interaction, protein digestion and absorption, the renin-angiotensin system, as well as neutrophil extracellular trap (NET) formation (Figure 2F).

HGs identified via ML

In GSE152004, 24 genes were selected via SVM-RFE (Figure 3A). LASSO regression identified six genes corresponding to the minimum binomial deviance (Figure 3B). After RF and LR analyses, 25 genes were ultimately selected (Figure 3C-3E). Intersection of the results derived from these four ML algorithms yielded six overlapping genes, *RGS1*, *NTRK2*, *CPXM2*, *TPSAB1*, *CHAD*, and *SNORA105A*, which were considered candidate biomarkers for CA (Figure 3F). In the CO dataset (GSE205668), SVM-RFE and RF analyses identified 487 genes (Figure 3G-3I). LASSO regression further screened eight genes (Figure 3J), while LR analysis selected 484 genes (Figure 3K). The intersection of these four methods resulted in six overlapping genes, *RGS1*, *TPSD1*, *CSTA*, *NTRK2*, *SLC9A3*, and *PXDN*, as candidate biomarkers for CO (Figure 3L). By overlapping the candidate genes identified across CA and CO datasets, two common diagnostic markers, *RGS1* and *NTRK2*, were ultimately identified as shared HGs.

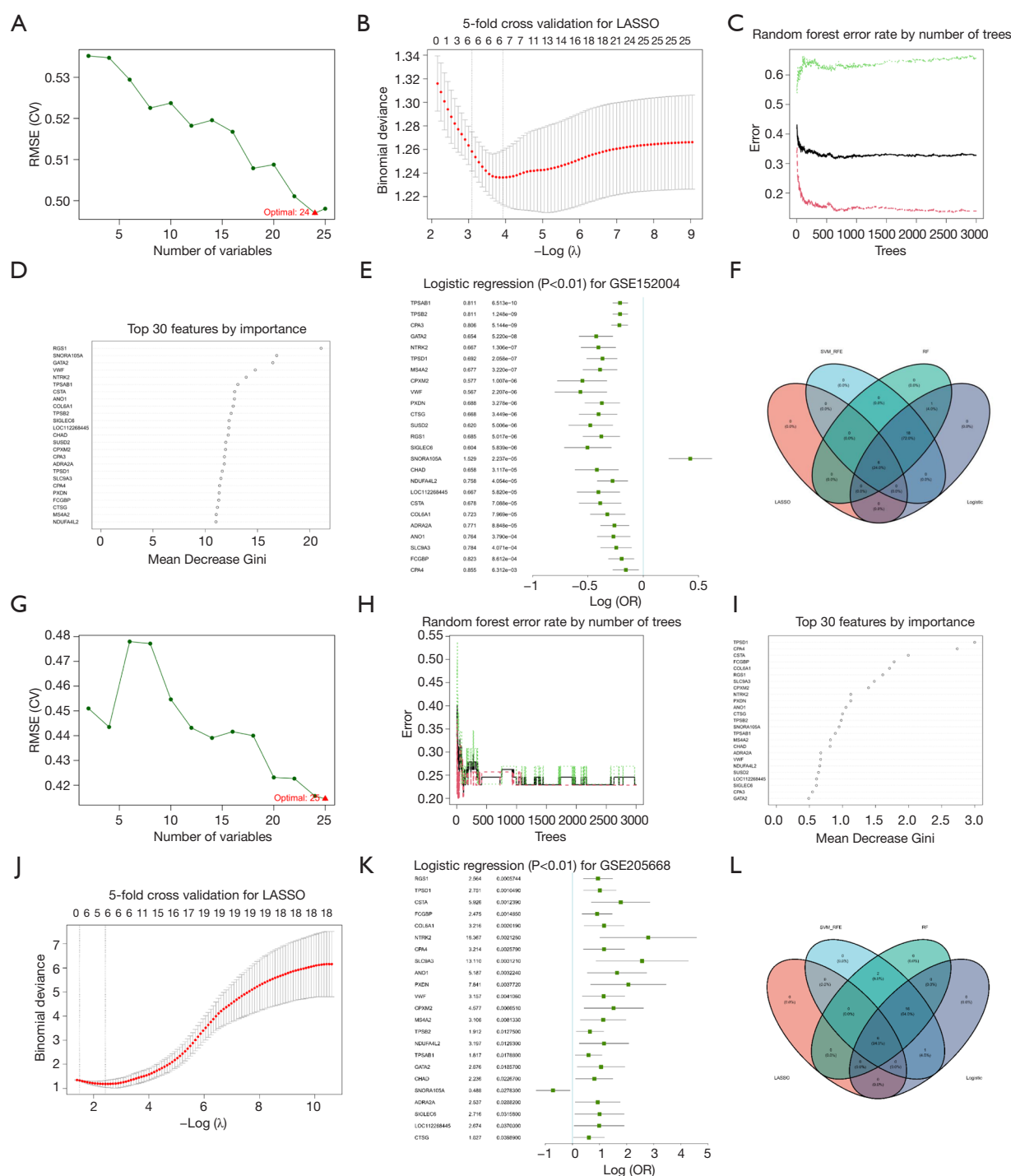


Figure 3 ML in screening HGs. (A-E) Results of SVM-RFE, LASSO, RF, and LR for CA. (F) Venn diagram presenting the six genes identified within CA. (G-K) Results of SVM-RFE, LASSO, RF, and LR for CO. (L) Venn diagram presenting the six genes identified within CO. CA, childhood asthma; CO, childhood obesity; CV, coefficient of variation; GSE, gene expression omnibus series; HGs, hub genes; LASSO, least absolute shrinkage and selection operator; LR, logistic regression; RF, random forest; RMSE, root mean square error; SVM-RFE, support vector machine recursive feature elimination.

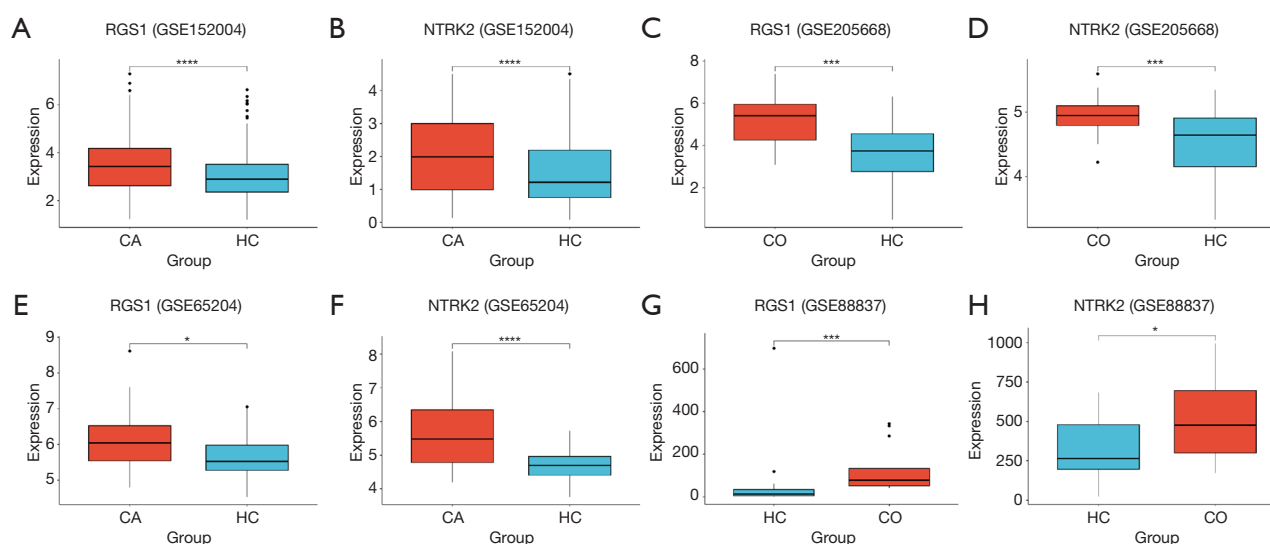


Figure 4 Validation of HG expression levels in training and validation sets. The red box represents the disease cohort, and the blue represents the control cohort. *, $P<0.05$; ***, $P<0.001$; ****, $P<0.0001$. (A-D) Expression of two HGs in CA-GSE152004 and CO-GSE205668; (E-H) expression of two HGs in CA-GSE65204 and CO-GSE88837. CA, childhood asthma; CO, childhood obesity; GSE, gene expression omnibus series; HC, healthy control; HGs, hub genes.

HG validation and predictive accuracy assessment

Expression validation demonstrated that *RGS1* and *NTRK2* were significantly upregulated in disease groups compared with control groups in training and validation datasets ($P<0.05$; Figure 4). These findings supported the robustness of the identified HGs. ROC curve analyses were subsequently performed to evaluate the diagnostic performance of *RGS1* and *NTRK2*. In GSE152004, the AUCs for *RGS1* and *NTRK2* were 0.616 and 0.621. In GSE205668, the corresponding AUCs were 0.780 and 0.763 (Figure 5A-5D). In the CA validation dataset (GSE65204), the AUCs for *RGS1* and *NTRK2* were 0.657 and 0.777, while in the CO validation dataset (GSE88837), the AUCs reached 0.867 and 0.729 (Figure 5E-5H), indicating favorable diagnostic performance across independent cohorts.

Single-gene GSEA of HGs

Single-gene GSEA was performed to explore the functional roles of *RGS1* and *NTRK2* (Figure S1). GO enrichment analysis revealed the significant link of *RGS1* to ciliary structure and immune response-related processes, whereas *NTRK2* was predominantly linked to RNA splicing and ribosome biogenesis in the CA cohort (Figure S1A,S1B). In

the CO group, *RGS1* was mainly enriched in mitochondrial respiratory chain and ribosomal structure-related processes, while *NTRK2* was linked to membrane trafficking and vesicular transport (Figure S1E,S1F). KEGG pathway analysis further demonstrated that, in the CA group, *RGS1* was significantly enriched in immune and inflammatory signaling pathways, including TNF signaling and NF- κ B signaling pathways, as well as cytokine-cytokine receptor interaction, whereas *NTRK2* was primarily linked to the spliceosome, proteasome, and T cell differentiation-related pathways (Figure S1C,S1D). In the CO group, *RGS1* was enriched in immune-related pathways like B cell receptor signaling and lysosomal pathways, while *NTRK2* was mainly linked to proteasome, autophagy, and endocytosis pathways (Figure S1G,S1H).

Construction of the lncRNA-miRNA-mRNA

Target miRNAs of *NTRK2* and *RGS1* were predicted utilizing TargetScan, miRTarBase, and miRWalk, yielding 80 miRNAs after integration. Subsequently, lncRNAs potentially interacting with these miRNAs were predicted utilizing StarBase. After removal of duplicate entries and application of stringent filtering criteria, 104 high-confidence lncRNAs were retained. A ceRNA network was constructed utilizing Cytoscape, comprising 104 lncRNAs, 80 miRNAs,

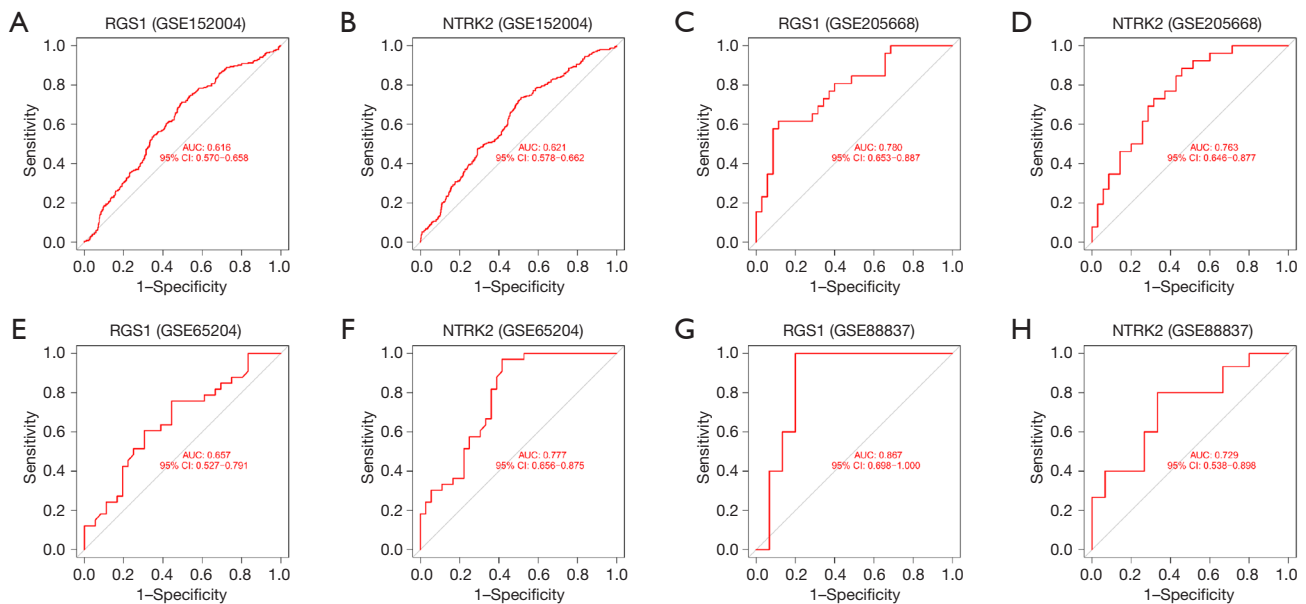


Figure 5 The ROC curves of the HG in the training (A-D) and validation (E-H) sets. AUC, area under the curve; CI, confidence interval; GSE, gene expression omnibus series; HGs, hub genes; ROC, receiver operating characteristic.

and the two HGs (*NTRK2* and *RGS1*) (Figure 6A). To identify key regulatory components within the network, degree-based topological analysis was performed. As illustrated in Figure 6B, the top 30 ceRNAs were identified, among which hsa-miR-23a-3p, hsa-miR-760, and hsa-miR-149-5p interacted with *NTRK2* and *RGS1*, suggesting their potential central roles in the regulatory network.

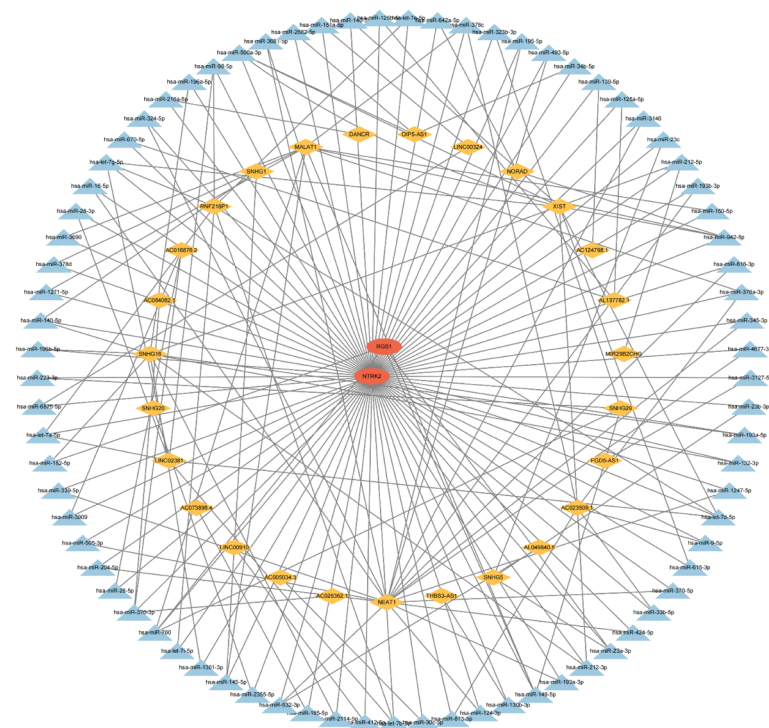
Discussion

CA and CO are highly prevalent conditions that exert profound and lasting effects on patient health and quality of life. Although the association between these two disorders has been well established (11), the underlying genetic and molecular interactions remain unclear. The present study represents the first integrative analysis of gene expression datasets from CA and CO aimed at identifying shared biological mechanisms and key biomarkers implicated in the disease development.

This study initially identified 25 overlapping DEGs shared between CA and CO. Functional enrichment analyses utilizing GO and KEGG databases provided insights into the potential biological mechanisms underlying their comorbidity. GO enrichment analysis revealed significant involvement in BPs like extracellular matrix and structural organization, regulation of blood

pressure and angiotensin signaling, peripheral nervous system myelination, and platelet activation. Enriched CCs included collagen-containing extracellular matrix, basement membrane, axon terminus, neuron projection terminus, early endosome membrane, and distal axon. With respect to MF, the identified genes were primarily linked to serine-type endopeptidase, serine-type peptidase and hydrolase, metallopeptidase activities, and growth factor binding. KEGG pathway analysis further demonstrated significant enrichment in the PI3K/Akt signaling pathway, extracellular matrix-receptor interaction, renin-angiotensin system, NET formation, and focal adhesion pathways. Among these, the PI3K/Akt signaling pathway emerged as a particularly relevant shared mechanism. This pathway is central in regulating vital cellular processes like proliferation, differentiation, and apoptosis (12,13). In metabolic disorders such as obesity and diabetes, insulin activates multiple downstream signaling cascades to regulate lipid and glucose metabolism, with PI3K/Akt serving as the principal insulin-mediated pathway. Under physiological conditions, insulin-induced activation of PI3K/Akt maintains metabolic homeostasis; however, chronic energy excess and elevated free fatty acid levels disrupt this pathway, leading to insulin resistance and promoting obesity and type 2 diabetes (14,15). Notably, the PI3K/Akt pathway has also been identified as a critical therapeutic

A



B

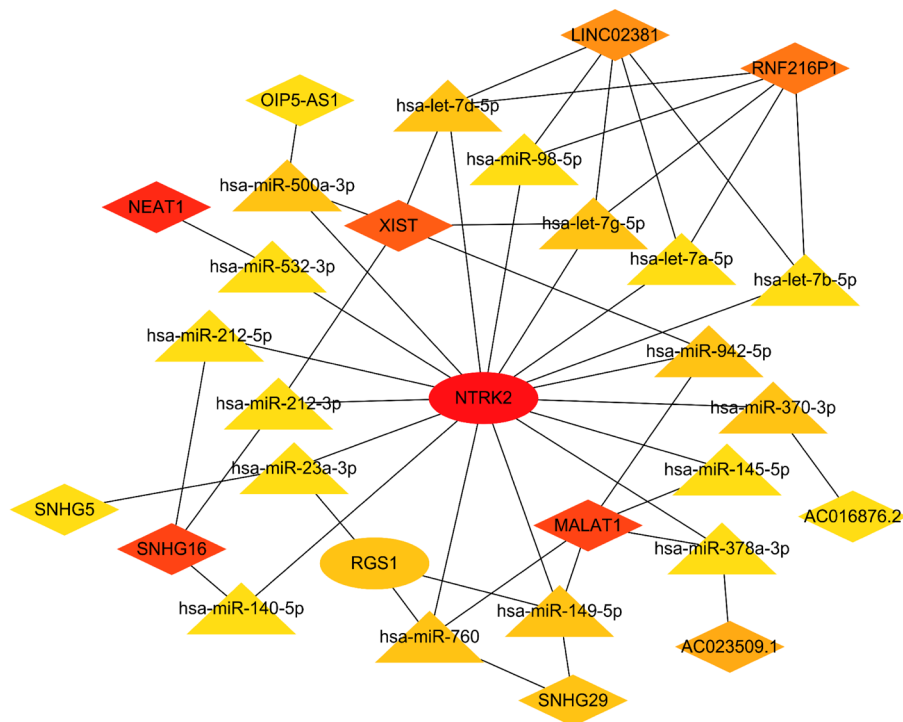


Figure 6 lncRNA-miRNA-mRNA network construction. (A) The lncRNA-miRNA-mRNA network. Diamonds, triangles, and ellipses represent lncRNAs, miRNAs, and mRNAs. (B) The top 30 ranked ceRNAs. ceRNA, competitive endogenous RNA; lncRNAs, long noncoding RNAs; mRNA, messenger RNA; miRNAs, microRNAs.

target in asthma, where its inhibition alleviates airway inflammation and subsequently reduces airway remodeling and hyperresponsiveness (16). These findings suggest that modulation of the PI3K/Akt signaling pathway possibly represents a promising therapeutic strategy for obesity-associated asthma. Subsequently, four ML algorithms were applied to identify shared HGs, ultimately revealing *NTRK2* and *RGS1* as key biomarkers significantly linked to CA and CO. genes were consistently upregulated in disease groups across training and validation datasets and demonstrated favorable diagnostic performance, underscoring their potential clinical relevance.

NTRK2, also known as TrkB, is the high-affinity receptor for brain-derived neurotrophic factor (BDNF) and is critical in activity-dependent neuronal plasticity (17). Human genetic studies have linked mutations in *NTRK2* to hyperphagia and severe obesity. For example, individuals carrying a heterozygous missense mutation (Y722C) in *NTRK2* exhibit marked hyperphagia and early-onset obesity (18). Consistently, TrkB hypomorphic mice expressing approximately 25% of normal TrkB levels display pronounced obesity, hyperphagia, and hyperdipsia (19). Furthermore, peripheral administration of NT-4, a TrkB agonist, has been shown to suppress appetite and reduce body weight in a dose-dependent manner across multiple murine obesity models (20). These findings appear to contrast with our observation of significantly elevated *NTRK2* expression in disease cohorts. Several plausible explanations possibly account for this discrepancy. First, it was proposed that the elevated *NTRK2* expression observed in the present study may reflect a compensatory upregulation in peripheral blood under chronic inflammatory conditions associated with the comorbidity of asthma and obesity. BDNF and its receptor TrkB are well-established mediators of nervous system development, neuroplasticity, and cognitive function (21). Emerging evidence further indicates that the BDN-TrkB signaling pathway is closely involved in inflammation and oxidative stress (22), exerting protective effects through activation of downstream survival pathways such as PI3K/Akt, thereby enhancing cellular resistance to oxidative stress (23). Accordingly, under chronic inflammatory conditions, upregulation of *NTRK2* may represent an adaptive mechanism aimed at augmenting the anti-inflammatory and reparative functions of BDNF signaling in response to sustained inflammatory insults. However, this compensatory response may be insufficient to fully reverse the established inflammatory state, reflecting a “compensatory yet inadequate” adaptive process. Second, tissue-specific

differences likely contribute to these divergent findings. The present analysis was based on peripheral blood samples, whereas prior studies implicating *NTRK2* in obesity have predominantly focused on adipose tissue or hypothalamic regulation of appetite. Third, experimental models such as gene knockouts often represent congenital loss-of-function states, whereas our data reflect chronic, established disease conditions in humans. Importantly, *NTRK2* has also been implicated in asthma pathophysiology. Increased cholinergic innervation has been observed in asthmatic airway biopsies, accompanied by elevated *NTRK2* expression in human lung tissue, suggesting that TrkB-mediated cholinergic neuroplasticity may contribute to developing airway hyperresponsiveness and inflammation (24). Therefore, the BDNF-TrkB signaling axis is a promising therapeutic target in asthma.

RGS1, a prominent member of the RGS family, is predominantly expressed in hematopoietic cells, including T and B lymphocytes, natural killer and dendritic cells, as well as monocytes (25–27). Recent research on *RGS1* has primarily focused on its role in tumor progression and renal interstitial fibrosis (28–30). Notably, previous studies have demonstrated consistent upregulation of *RGS1* in high-fat diet-induced obesity models (31) and insulin resistance-associated atherosclerosis models (32), although its precise mechanistic role remains to be fully elucidated. These findings are concordant with our results. In a lipopolysaccharide (LPS)-induced mouse model of spinal cord injury, *RGS1* was markedly upregulated and promoted the expression of inflammatory mediators via activation of the NF- κ B and p38 MAPK signaling pathways (33). In a rat model of arthritis, silencing *RGS1* inhibited the TLR signaling pathway and reduced the levels of TNF- α , IL-1 β , and IL-17, thereby attenuating the inflammatory response (34). These findings suggest that *RGS1*, as an immune regulatory molecule, modulates immune function through the regulation of key immune-related signaling pathways. Accordingly, increased expression of *RGS1* in peripheral blood may reflect a negative feedback regulatory response to aberrant immune activation in the context of asthma-obesity comorbidity. With respect to metabolic pathways, downregulation of *RGS2* has been shown to enhance insulin signaling and promote glucose and fatty acid oxidation (35). Moreover, elevated baseline *RGS1* expression has been linked to a dual super-response to mepolizumab therapy in patients with severe asthma and chronic rhinosinusitis with nasal polyps (36), further supporting its relevance in immune-mediated airway disease.

miRNAs mainly regulate gene expression at the post-transcriptional level, whereas lncRNAs exert broader regulatory effects across epigenetic, transcriptional, and post-transcriptional layers, collectively playing critical roles in disease pathogenesis. An lncRNA-miRNA-mRNA ceRNA regulatory network was developed on the two identified HGs. Within this network, hsa-miR-23a-3p, hsa-miR-760, and hsa-miR-149-5p were identified as common regulators of *NTRK2* and *RGS1*. Notably, hsa-miR-23a-3p has been proposed as a potential molecular marker for identifying obese children and individuals at increased risk of metabolic syndrome (37). Hsa-miR-760 is downregulated in multiple malignancies and is a possible prognostic biomarker in cancer (38); for instance, miR-760 suppresses colorectal cancer progression by targeting the BATF3/AP-1/cyclin D1 signaling axis, and reduced miR-760 expression is linked to poor clinical outcomes (39). Additionally, miR-149-5p has been shown to inhibit prostate cancer progression by targeting *RGS17* (40). To date, however, no studies have directly linked hsa-miR-760 or hsa-miR-149-5p to the pathogenesis of CA or CO, highlighting the need for further experimental validation.

As detectable gene markers in peripheral blood, *RGS1* and *NTRK2* offer the advantages of minimal invasiveness and ease of acquisition, demonstrating considerable potential for clinical application. In terms of diagnosis, rather than relying on a single biomarker, *RGS1* and *NTRK2* may be incorporated into a multi-gene diagnostic panel alongside body mass index (BMI), lung function parameters, and inflammatory markers (such as IgE, eosinophil counts, IL-6, and TNF- α) to construct a composite diagnostic model. Such an approach may facilitate the early identification of children at high risk for asthma-obesity comorbidity, thereby enabling precise stratification and individualized intervention. From a therapeutic perspective, *RGS1* participates in inflammatory responses through regulation of the NF- κ B, MAPK, and TLR signaling pathways, while the BDNF-TrkB signaling pathway also plays a pivotal role in inflammation and oxidative stress. Targeting these pathways with small-molecule inhibitors or agonists may therefore represent a promising strategy for the treatment of this comorbidity.

Future research should prioritize several key directions. First, the expression levels of *RGS1* and *NTRK2*, as well as their associations with disease severity and treatment response, should be validated in larger, multicenter clinical cohorts. Second, integration of gene expression data with multidimensional phenotypic parameters, including BMI,

lung function, and inflammatory markers, is warranted to better delineate the clinical utility of these genes in disease subtyping. Finally, both *in vitro* and *in vivo* studies are required to elucidate the precise molecular mechanisms by which *RGS1* and *NTRK2* regulate inflammation and metabolism, thereby providing a theoretical foundation for targeted interventions and promoting the translation of these biomarkers into clinical practice.

Limitations

However, our study had limitations. First, the sample sizes of the training datasets, particularly for obesity, were relatively small, and dataset heterogeneity may have introduced potential biases. Second, although the diagnostic performance of the HGs reached statistical significance, the AUC values were only moderate, especially in the asthma validation dataset (GSE65204), thus warranting further validation in larger and more diverse cohorts. Third, the findings were primarily derived from bioinformatics analyses and lack experimental validation.

Conclusions

This study identified two shared HGs, *NTRK2* and *RGS1*, linked to CA and CO. Elucidation of the common molecular mechanisms linking these conditions deepens our understanding of their comorbidity and lays a theoretical groundwork for developing cross-disease precision diagnostic tools and targeted therapeutic strategies, with the ultimate goal of improving clinical outcomes in affected pediatric populations.

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None.

Footnote

Reporting Checklist: The authors have completed the TRIPOD reporting checklist. Available at <https://tp.amegroups.com/article/view/10.21037/tp-2026-1-0108/rc>

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki and its subsequent amendments.

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