Pediatric Pulmonology

ORIGINAL ARTICLE

Violence-Related Distress, Nasal Epithelial Gene Expression, and T17-High Asthma in Youth

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Received: 25 October 2025 | **Revised:** 29 December 2025 | **Accepted:** 22 January 2026

Funding: National Heart, Lung, and Blood Institute, Grant/Award Numbers: HL117191, HL119952, HL168539

Keywords: asthma endotypes | children | distress | violence

ABSTRACT

Background: Little is known about the mechanisms underlying the link between violence-related distress and asthma, particularly for asthma endotypes.

Methods: Cross-sectional analysis of violence-related distress in the previous 6 months (assessed using the Checklist of Children's Distress Symptoms [CCDS] scale) and nasal epithelial gene expression in 3 studies of youth with asthma aged 8–20 years: Stress and Treatment Response in Puerto Rican and African American Children with Asthma (STAR, $n = 128$), Epigenetic Variation and Childhood Asthma in Puerto Ricans (EVA-PR, $n = 228$), and Vitamin D Kids Asthma (VDKA, $n = 47$). We then tested for the association between expression of CCDS-related genes and nasal epithelial transcriptomic profiles corresponding to T2-high and T17-high asthma endotypes.

Results: In a meta-analysis of the CCDS score in the three cohorts, we identified 12 differentially expressed genes (DEGs) with false discovery rate-adjusted p value (FDR-P) < 0.05 and the same direction of association as in the discovery cohort (EVA-PR) in at least one replication cohort. Of these 12 DEGs, 9 (*S100A7A, CCL2, CCL8, CXCL9-11, COL15A1, CD300E*, and *LILRB1*) were upregulated and significantly associated with T17-high asthma in a meta-analysis of the three cohorts. Two genes belong to the CC Motif Chemokine Ligand family (*CCL2, CCL8*) and 3 belong to the CXC Motif Chemokine Ligand family (*CXCL9, CXCL10*, and *CXCL11*).

Conclusion: Nine novel genes were associated with violence-related distress and T17-high asthma in three cohorts of predominantly minoritized youth with asthma. Our findings may help uncover biologic processes underlying the violence-asthma link and could represent novel therapeutic targets for T17-high asthma.

1 | Introduction

Asthma is the most common chronic respiratory disease among children worldwide [1]. Puerto Ricans are disproportionately affected by childhood asthma [2, 3], likely due to multiple factors, including exposure to violence and related distress [4, 5]

Asthma is not a single condition but a heterogeneous syndrome comprising distinct phenotypes, each defined by clinical traits

(e.g., atopic asthma: asthma with atopy [sensitization to ≥ 1 aero-allergen]) [1, 6]. Such phenotypes are easily identifiable in clinical practice but are not well correlated with causal mechanisms [6]. Over the last two decades, studies of gene expression in bronchial epithelial samples from affected adults have defined underlying mechanisms or endotypes of asthma [7–9], which ultimately led to the development of targeted treatments for severe forms of one endotype: T-helper 2 (T2)-high asthma [6]. Indeed, severe T2-high asthma can now be treated with various monoclonal antibodies, with specific treatment chosen according to levels of biomarkers of T2 immune responses in blood and exhaled breath [6].

Studying endotypes other than T2-high asthma (collectively referred to as "T2-low asthma") has been challenging because such endotypes cannot be accurately identified without analyzing samples obtained during a bronchoscopy (an invasive test requiring sedation). Leveraging the knowledge that gene expression in nasal (airway) epithelial is well correlated with that in bronchial (airway) epithelium, we recently showed that distinct nasal epithelial transcriptomic profiles identified T2-high, T17-high, and T2-low/T17-low asthma endotypes in three independent cohorts, including predominantly Puerto Rican and African American youths [10].

Previous work from our group and others suggests a potential link between violence-related distress and biomarkers or traits partly correlated with T2-high (e.g., high total IgE, blood eosinophilia) and T17-high (e.g., corticosteroid resistance, blood neutrophilia) asthma endotypes [5, 11–15]. Building on this work and leveraging our novel non-invasive approach to asthma endotyping, we recently demonstrated that exposure to violence and related distress were associated with T2-high and T17-high asthma in a cross-sectional study of Puerto Rican youths aged 9 to 20 years [16].

Based on our prior findings, we hypothesized that expression of genes altered by violence-related distress would be linked to T2-high and T17-high asthma in children and adolescents at high risk for asthma morbidity. We tested this hypothesis by first conducting a differential expression (DE) analysis for violence-related distress using RNA from nasal epithelial samples in a cohort of Puerto Rican youth and in two ethnically diverse cohorts and then assessing whether genes differentially expressed for violence-related distress are also associated with T2-high or T17-high asthma in these three cohorts.

2 | Methods

2.1 | Discovery Cohort

The Epigenetic Variation and Childhood Asthma in Puerto Ricans study (EVA-PR) is a case-control study of asthma in Puerto Rican youth aged 9–20 years. Subject recruitment and study procedures for EVA-PR were previously described [17]. In brief, subjects were recruited in the metropolitan area of San Juan and Caguas (Puerto Rico) from February 2014 to May 2017, using multistage probabilistic sampling. All participants had to have four Puerto Rican grandparents, were never smokers or former smokers with <5 pack-years of smoking, and had no chronic diseases other than asthma. Cases had physician-diagnosed asthma and wheeze in the prior year, and control subjects had neither physician-diagnosed asthma nor wheeze in the prior year. The study protocol included administration of questionnaires and collection of nasal samples. All participants had not received systemic (intravenous, intramuscular, or oral) corticosteroids and had no self-reported upper respiratory illnesses in the 4 weeks before nasal sampling. All participants completed the validated Checklist of Children's Distress Symptoms (CCDS) questionnaire, a 28-item validated scale that assesses distress symptoms as a result of exposure to violence in the previous 6 months [18–21]. An overall score is obtained by summing the scores for all questions, and then dividing by the number of questions so that the final CCDS score ranges between 1 and 5. The study was approved by the institutional review boards (IRBs) of the University of Puerto Rico (Protocol #0160713) and the University of Pittsburgh (Protocol #20050135). Written parental consent and child assent were obtained for participants under 18 years old, and written consent was obtained from participants 18 years and older.

Nasal epithelial samples were collected from the inferior turbinate of study participants, as previously described [17]. Prior to RNA extraction, CD326(+) nasal epithelial cells were extracted in a subset of samples to account for potential effects of distinct cell types. RNA-Seq was then conducted at the Genomics Core of the University of Pittsburgh, with library preparation done using TruSeq Stranded Total RNA Library Prep Kit with Ribo-Zero Gold High Throughput kit, which removes both cytoplasmic and mitochondrial ribosomal RNA (rRNA) (Illumina, San Diego, CA), according to the manufacturer's protocol [17, 22]. Libraries were run on the Illumina NextSeq. 500 platform, with paired-end 75 cycles and with 80 million reads per sample. Whole-genome genotyping was conducted in DNA from blood samples using the Illumina HumanOmni2.5 BeadChip platform, as previously described [23]. Imputation of non-genotyped single-nucleotide polymorphisms (SNPs) was performed with the Imputation Server [24], using the Haplotype Reference Consortium r1.1 2016 as the reference panel [25].

2.2 | Replication Cohorts

2.2.1 | Vitamin D Kids Asthma Study (VDKA)

As previously reported, VDKA was a 48-week randomized, double-blinded, placebo-controlled clinical trial of vitamin D_3 supplementation (4000 IU/day) to prevent severe asthma exacerbations in children ages 6–16 years [26]. Children with mild persistent asthma, ≥ 1 severe asthma exacerbation in the previous year, and a serum vitamin D < 30 ng/mL were recruited from seven US sites, including the University of Pittsburgh. Of the 115 children randomized at the Pittsburgh site, 52 participated in an ancillary study of nasal epithelial gene expression, providing nasal samples after 4 weeks of treatment with low dose inhaled fluticasone (88 mcg twice a day for children < 12 years old and 110 mcg twice a day for children ≥ 12 years old) and completed the CCDS questionnaire (as they were 9 years and older) at the exit visit. As in EVA-PR, all participants had not received systemic corticosteroids or self-reported an upper respiratory illness in the 4 weeks prior to nasal sampling. The study was approved by the IRBs of all participating institutions, and the RNA-Seq ancillary study was approved by the IRB of the University of Pittsburgh (Protocol #12020541). Written parental consent and assent were obtained

from all participants. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

2.2.2 | *Stress and Treatment Response in Puerto Rican and African American Children with Asthma*

Subject recruitment and study design for the Stress and Treatment Response in Puerto Rican and African American Children with Asthma study (STAR) were previously described [10]. In brief, STAR was a study of response to inhaled corticosteroids (ICS) in youth recruited at the University of Puerto Rico Medical Center and UPMC Children's Hospital of Pittsburgh from June 2018 to May 2022. Eligible participants were youth ages 8–20 years who were steroid naïve (no treatment with ICS, nasal steroids, or systemic corticosteroids for at least 4 weeks) and never smokers or former smokers with <5 pack-years, and who had physician-diagnosed mild to moderate persistent asthma and at least three grandparents who were Puerto Rican (in Puerto Rico) or African American (in Pittsburgh). At the baseline visit, all participants completed the CCDS questionnaire and had RNA sequenced in nasal epithelial samples collected as in EVA-PR. The study was approved by the IRBs of the University of Puerto Rico (Protocol #0160217) and the University of Pittsburgh (Protocol #20020036). Written parental consent and assent were obtained from participants < 18 years old, and consent was obtained from participants ≥ 18 years old.

2.3 | RNA Sequencing and Data Preprocessing

In EVA-PR, VDKA, and STAR, RNA-Seq quality control was conducted using FastQC [28] and summarized by MultiQC. 3′ adapters and bad-quality reads were trimmed with Trim Galore! [27] and Cutadapt [28]. Using the STAR RNA-seq aligner [29], trimmed reads were aligned to the latest human reference genome at the time of the studies (hg19 for EVA-PR and hg38 for VDKA and STAR) and annotated using RSEM [30]. Samples with poor overall quality and low alignment rate were excluded from the analysis. After QC, genes with low expression (mean count < 2), low variation (standard deviation of count < 0.1), and sex chromosome genes were removed from downstream analyses. After preprocessing and filtering, a total of 17,724, 18,487, and 16,068 genes were retained for the analyses in EVA-PR, VDKA, and STAR, respectively.

In all cohorts, viral abundance was also quantified in nasal RNA-Seq data using the nf-core tax-profiler pipeline, with taxonomic annotation and read quantification carried out by Kraken2 [31] against the Maxikraken2_1903_140GB database (March 2019). Viral abundance profiles were subsequently transformed using a centered log-ratio (CLR) approach to account for compositionality.

2.4 | Statistical Analysis

The DE analysis of CCDS in nasal epithelial samples from subjects in our discovery cohort (EVA-PR) was conducted using a multivariable negative binomial regression framework employing the DESeq. 2 package in R 4.1.1., with correction for multiple testing using the Benjamini-Hochberg false discovery rate (FDR) method. This multivariable analysis was adjusted for age, sex, household income (< vs. ≥ US $15,000/year, the median income in Puerto Rico at the time of the study), cell sorting protocol, asthma status (case vs. control), and the top five principal components (PCs) derived from genome-wide genotypic data (to control for potential population stratification, as previously described) [23].

We attempted to replicate our findings in EVA-PR in VDKA and STAR. As in EVA-PR, replication analyses were conducted using a multivariable negative binomial regression approach. The model in STAR was adjusted for age, sex, household income (< vs. ≥ US $30,000 in Pittsburgh, PA or < vs. ≥ US $15,000 in San Juan, PR), cell sorting protocol and study site (San Juan or Pittsburgh). In VDKA, the model was adjusted for age, sex, race, vitamin D level, household income (< vs. ≥ US $30,000) and cell sorting protocol. A meta-analysis of the three study cohorts was then conducted using inverse variance-weighted average methods. Genes that had the same direction of association as in EVA-PR in at least one replication cohort, as well as an FDR-P < 0.05 in the meta-analysis of the three cohorts, were considered differentially expressed genes (DEGs). Based on genes with raw $p < 0.01$ from the DE of the CCDS score in the meta-analysis, we performed a canonical pathway enrichment analysis using IPA [32] and identified enriched pathways at FDR-P < 0.05.

Next, we investigated whether DEGs associated with violence-related distress also showed associations with T17-high or T2-high asthma. As previously described [10], K-means clustering analysis was performed across all asthma samples in each study, based on expression of selected T2 (*POSTN*, *CLCA1*, and *SERPINB2)* and T17 (*CXCL1*, *CXCL2*, *CXCL3*, *CSF3*, and *IL8*) signature genes. These three clusters were annotated according to the T2 panel 3-gene mean (3GM) and T17 panel 5-gene mean (5GM) into $T2^{HIGH}/T17^{LOW}$, $T17^{HIGH}/T2^{LOW}$, and $T2^{LOW}/T17^{LOW}$ profiles, corresponding to three endotypes (T2-high, T17-high, and T2-low/T17-low, respectively). We previously showed consistent results using 5 alternative clustering approaches [10].

We then compared: (1) participants with T2-high asthma to all others (i.e., those with T17-high or T2-low/T17-low asthma), and (2) participants with T17-high asthma to all others (i.e., those with T2-high or T2-low/T17-low asthma) using logistic regression in EVA-PR. To replicate our findings, we conducted a similar logistic regression analysis in VDKA and STAR. All models were adjusted for age, sex, cell sorting protocol, and annual household income. Models in EVA-PR were additionally adjusted for the top five PCs, those in VDKA were additionally adjusted for vitamin D level, and those in STAR were additionally adjusted for study site. Inverse variance-weighted average fixed-effect methods were then used for the meta-analysis in the three cohorts. Genes were considered significant if they had $p < 0.0042$ (0.05/12 genes tested) in the meta-analysis with the same direction of association as in EVA-PR in at least one cohort.

We also performed association analyses to evaluate the relationships between selected DEGs, viral abundance, and lung function measures. Lung function measures included pre-

bronchodilator and post-bronchodilator forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC), and the FEV_1/FVC ratio. Associations between gene expression, viral abundance, and lung function outcomes were estimated within each cohort (EVA-PR, VDKA, and STAR) and combined using meta-analysis to obtain pooled effect estimates.

3 | Results

3.1 | Characteristics of the Discovery and Replication Cohorts

The main characteristics of participants in EVA-PR and the replication cohorts (VDKA and STAR) are shown in Table 1, according to their asthma status. Cases (participants with asthma) were more likely to be male than controls in EVA-PR, and participants in VDKA were younger than those in EVA-PR or STAR. The mean CCDS score ranged from approximately 2 to 2.4 points across all three cohorts, with similar score distributions (Supporting Information S1: E-Figure 1).

3.2 | DE Analysis of CCDS Score

In the DE meta-analysis, we identified 12 DEGs with FDR-adjusted $p < 0.05$ and the same direction of association as in EVA-PR in at least one replication cohort. Of these 12 DEGs, 2 were downregulated and 10 were upregulated as the CCDS score increased (Table 2 and Figure 1). Of the 12 DEGs, 2 belong to the CC Motif Chemokine Ligand family (*CCL2, CCL8*) and 3 belong to the CXC Motif Chemokine Ligand family (*CXCL9, CXCL10, CXCL11*). The two gene families encode chemokines that participate in immune cell recruitment and activation during inflammation, thereby exerting a key influence on the modulation of immune and inflammatory reactions.

3.3 | Association of DEGs With T2-High or T17-High Asthma

Supporting Information S1: E-Table 1 shows the main characteristics of participants in the EVA-PR, VDKA and STAR, by asthma endotype status. As previously shown [10], youths with T2-high asthma exhibited significantly greater IgE levels, blood eosinophil counts, and FeNO values compared with other endotypes, consistent with canonical features of type 2 inflammation.

We next tested for the association between the 12 DEGs for violence-related distress and T17-high or T2-high asthma across the EVA-PR, VDKA, and STAR cohorts. Our analysis revealed that 9 of the DEGs for violence-related distress (*S100A7A, CCL2, CCL8, CXCL9-11, COL15A1, CD300E*, and *LILRB1*) were significantly associated with T17-high asthma in the meta-analysis of the three cohorts (Table 3). Notably, increased expression of these 9 genes was positively associated with T17-high asthma (Supporting Information S1: E-Figure 2A). In the association analysis of T2-high asthma, five genes were identified as differentially expressed: *S100A7A*, *CXCL9*, *CXCL10*, *CXCL11*, and *PDGFRA* (Supporting Information S1: Table E2). Upregulation of these genes was found to be negatively associated with T2-high asthma (Supporting Information S1: E-Figure 2B). This opposing association between the two analysis aligns with the inherent inverse relationship between T2-high and T17-high asthma endotypes.

3.4 | DEGs, Lung Function, and Viral Abundance

We next examined associations between the 12 DEGs for violence-related distress and lung function measures across the EVA-PR, VDKA, and STAR cohorts. In this meta-analysis, *S100A7A* and *COL15A1* were significantly associated with post-

TABLE 1 | Characteristics of study participants in the discovery and replication cohorts.

	Asthma			
	EVA-PR		VDKA	STAR
Variable[a]	Yes ($N = 228$)	No ($N = 240$)	Asthma ($N = 47$)	Asthma ($N = 128$)
Age	15.4 (2.8)	15.7 (3.0)	11.3 (2.1)	13.9 (2.8)
CCDS score	2.03 (0.61)	1.94 (0.66)	2.22 (0.88)	2.41 (0.70)
Household income[b]				
At/above the median	94 (41.2%)	112 (46.7%)	31 (66.0%)	71 (55.5%)
Below the median	134 (58.8%)	128 (53.3%)	16 (34.0%)	57 (44.5%)
Sex*				
Female	100 (43.9%)	132 (55.0%)	16 (34.0%)	68 (53.1%)
Male	128 (56.1%)	108 (45.0%)	31 (66.0%)	60 (46.9%)
Race/ethnicity				
Black or African American	—	—	23 (48.9%)	88 (68.8%)
Puerto Rican	228 (100%)	240 (100%)	—	40 (31.2%)
White	—	—	14 (29.8%)	—
Other/Unknown	—	—	10 (21.3%)	—

Abbreviations: CCDS, Checklist of Children's Distress Symptoms scale; EVA-PR, Epigenetic Variation and Childhood Asthma in Puerto Ricans study; STAR, Stress and Treatment Response in Puerto Rican and African American children with Asthma; VDKA, Vitamin D Kids Asthma study.
[a]Values are presented as number (%) or mean (standard deviation).
[b]Median household income: $15,000/year for EVA-PR and the Puerto Rico site of STAR, and $30,000/year for VDKA and the Pittsburgh site of STAR.
*$p < 0.05$ for the comparison of cases and controls in EVA-PR.

TABLE 2 | Differential expression meta-analysis results for violence-related distress in EVA-PR and in the replication cohorts (VDKA and STAR).

			EVA-PR			VDKA		STAR		Meta analysis		
Gene	**Chromosome**	**Description**	**lg2FC**	**Raw *p* value**	**FDR**	**lg2FC**	**Raw *p* value**	**lg2FC**	**Raw *p* value**	**Effect**	**Raw *p* value**	**FDR**
S100A7A[a]	1	S100 calcium-binding protein A7A	1.841	2.36E-11	**1.39E-07**	0.231	5.66E-01	0.275	5.17E-01	1.093	4.93E-08	4.47E-04
JCHAIN	4	Joining chain of multimeric IgA and IgM	1.058	5.11E-12	**4.53E-08**	−0.331	3.75E-01	−0.002	9.95E-01	0.679	7.54E-08	4.47E-04
CCL8[a]	17	C-C motif chemokine ligand 8	1.773	2.41E-08	**1.07E-04**	−0.343	8.56E-01	0.432	6.44E-01	1.585	9.54E-08	4.47E-04
CCL2[a]	17	C-C motif chemokine ligand 2	0.951	2.81E-07	**7.11E-04**	0.625	1.50E-01	0.444	3.00E-01	0.838	1.17E-07	4.47E-04
FLG2[a]	1	Filaggrin 2	−1.159	1.56E-07	**5.16E-04**	−0.721	8.23E-02	−0.254	4.71E-01	-0.873	3.15E-07	9.62E-04
CXCL11[a]	4	C-X-C motif chemokine ligand 11	1.066	1.75E-07	**5.16E-04**	0.514	7.81E-01	0.119	7.53E-01	0.849	2.03E-06	5.17E-03
CXCL10[a]	4	C-X-C motif chemokine ligand 10	0.781	1.25E-05	**1.84E-02**	1.110	**9.70E-03**	0.165	5.95E-01	0.682	2.78E-06	5.70E-03
CXCL9[a]	4	C-X-C motif chemokine ligand 9	0.696	6.32E-06	**1.12E-02**	0.575	7.19E-01	0.397	1.31E-01	0.619	2.98E-06	5.70E-03
COL15A1[a]	9	collagen type XV alpha 1 chain	0.786	1.71E-06	**3.80E-03**	0.251	5.90E-01	0.166	7.14E-01	0.668	5.18E-06	8.80E-03
FAM25A[a]	10	Family with sequence similarity 25 member A	−0.756	4.68E-04	3.95E-01	−0.509	1.43E-01	−0.604	**4.32E-02**	−0.664	2.16E-05	3.29E-02
CD300E[a]	17	CD300e molecule	0.938	2.50E-05	**3.41E-02**	1.528	**1.39E-02**	−0.181	6.98E-01	0.806	2.48E-05	3.44E-02
PDGFRA[a]	4	Platelet-derived growth factor receptor alpha	0.167	1.80E-02	1.00E + 00	0.529	**9.93E-04**	0.353	**1.83E-02**	0.246	3.46E-05	4.41E-02
LILRB1[a]	19	Leukocyte immunoglobulin like receptor B1	0.454	5.01E-05	**5.22E-02**	0.506	1.33E-01	0.062	8.21E-01	0.407	3.96E-05	4.66E-02

Abbreviations: EVA-PR, Epigenetic Variation and Childhood Asthma in Puerto Ricans study; STAR, Stress and Treatment Response in Puerto Rican and African American children with asthma; VDKA, Vitamin D Kids Asthma study.
[a]Genes with FDR < 0.05 in meta-analysis, and have the same effect direction as EVA-PR in at least one replication cohort.

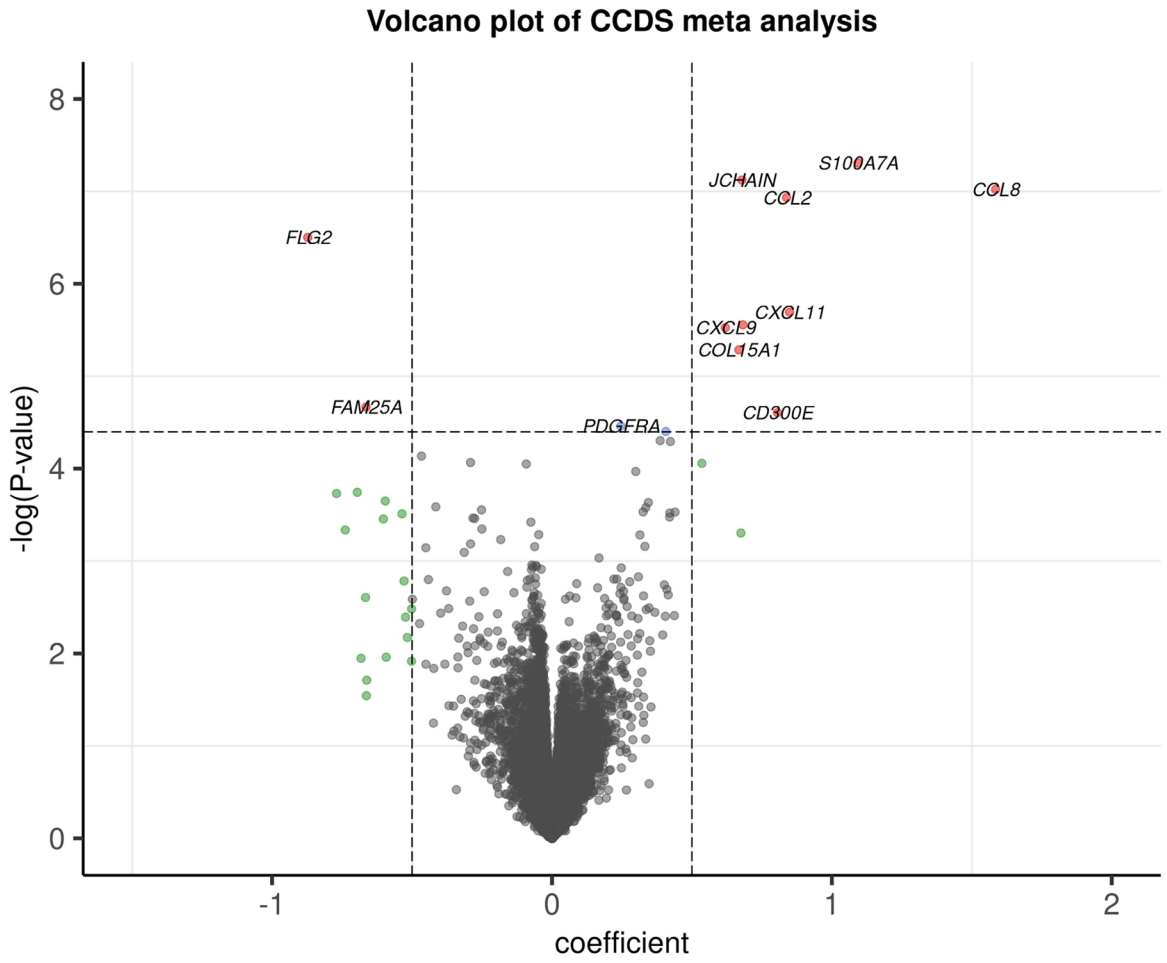

FIGURE 1 | Volcano plot of differential expression meta-analysis of CCDS. Volcano plot showing the log2 fold change) and –log10 (FDR-adjusted *p* value) of all the genes in meta-analysis of the three cohorts. DEGs above the dashed line and outside the two vertical dashed line had FDR-adjusted *p*-value < 0.05 and | log2(fold change) | > 0.5, which were colored in red. CCDS, Checklist of Children's Distress Symptoms scale. [Color figure can be viewed at wileyonlinelibrary.com]

bronchodilator FEV_1/FVC (Supporting Information S1: E-Table 3). Notably, higher expression of these genes was generally linked to lower FEV_1 and FEV_1/FVC, consistent with airflow obstruction. We further assessed the relation between DEGs by violence-related distress and viral abundance derived from nasal RNA-Seq data. The meta-analysis of all cohorts identified four genes—*CCL2*, *CCL8*, *CD300E*, and *LILRB1*—significantly associated with higher viral abundance (Figure 2).

3.5 | Pathway Analysis

We selected 249 genes with $p < 0.01$ in the meta-analysis of DE by CCDS for subsequent analysis using Ingenuity Pathway Analysis (IPA). Among these genes, we identified 44 significantly enriched pathways (Supporting Information S1: E-Table 4) with FDR-$p < 0.05$. Of these, 18 pathways were found to be activated (Figure 3A), including Pathogen-Induced Cytokine Storm Signaling Pathway, Interferon gamma signaling, and IL-17A Signaling in Fibroblasts. Conversely, 16 pathways were observed to be inhibited (Figure 3B), such as those related to Eukaryotic Translation and EIF2 Signaling.

4 | Discussion

Few human studies, mostly focusing on genetics and epigenetics, have explored omics mechanisms for the association between violence-related distress and asthma [16, 21, 33, 34]. To our knowledge, this is the first to study to examine if violence-related distress is associated with differential nasal (airway) epithelial gene expression in youth with asthma, and to test if these DEGs are associated with specific asthma endotypes. Identifying whether violence-related distress is associated with specific asthma endotypes could help develop better approaches to the prevention and management of childhood asthma in populations at risk [4, 16, 35].

In a transcriptome-wide association analysis using RNA from nasal (airway) epithelial samples from participants in 3 cohorts, including predominantly Puerto Rican and African American children and adolescents, 12 genes were differentially expressed by violence-related distress. Further, increased nasal epithelial expression of 9 of these 12 genes (*S100A7A*, *CCL2*, *CCL8*, *CXCL9-11*, *COL15A1*, *CD300E*, and *LILRB1*) was associated with T17-high asthma. Although T17-high asthma was recently shown to be common in minoritized youth with asthma [10], relatively little is known about this endotype, for which we lack targeted therapies [36].

TABLE 3 | Results of the analysis of association between top differentially expressed genes by violence-related distress and T17 high asthma.

			EVAPR		VDKA		STAR		Meta analysis	
Gene	**Chromosome**	**Description**	**log OR**	**Raw p value**	**log OR**	**Raw p value**	**log OR**	**Raw p value**	**Effect**	**Raw p value**
*S100A7A**	1	S100 calcium-binding protein A7A	0.560	3.62E-05	0.566	1.63E-01	0.820	1.60E-04	0.628	1.39E-08
*CCL8**	17	C-C Motif Chemokine Ligand 8	0.510	2.01E-04	0.736	1.08E-01	0.485	6.55E-02	0.520	9.76E-06
*CCL2**	1	C-C motif chemokine ligand 2	0.386	1.90E-05	0.219	4.07E-01	0.131	1.98E-01	0.270	3.60E-05
FLG2	4	filaggrin 2	−0.292	6.76E-02	0.152	8.81E-01	-0.695	9.35E-02	−0.333	2.37E-02
*CXCL11**	4	C-X-C motif chemokine ligand 11	0.297	2.11E-05	0.299	8.20E-02	0.304	1.86E-03	0.299	2.88E-08
*CXCL10**	4	C-X-C motif chemokine ligand 10	0.340	3.19E-06	0.269	1.39E-01	0.281	4.26E-03	0.314	1.74E-08
*CXCL9**	9	C-X-C motif chemokine ligand 9	0.337	2.47E-05	0.246	2.03E-01	0.324	7.03E-03	0.324	2.66E-07
*COL15A1**	10	Collagen type XV alpha 1 chain	0.535	2.32E-03	−1.136	3.63E-01	0.425	3.68E-01	0.493	2.50E-03
FAM25A	4	Family with sequence similarity 25 member A	0.037	4.42E-01	0.008	9.59E-01	-0.095	2.94E-01	0.008	8.50E-01
*CD300E**	17	CD300e molecule	0.831	1.57E-08	1.017	5.75E-02	0.404	1.81E-02	0.665	1.11E-09
PDGFRA	4	Platelet-derived growth factor receptor alpha	0.147	4.95E-01	1.196	2.74E-01	0.890	2.56E-03	0.426	1.33E-02
*LILRB1**	19	Leukocyte immunoglobulin like receptor B1	0.848	1.83E-06	0.754	5.69E-02	0.626	2.24E-03	0.753	3.19E-09

Abbreviations: EVA-PR, Epigenetic Variation and Childhood Asthma in Puerto Ricans study; STAR, Stress and Treatment Response in Puerto Rican and African American children with asthma; VDKA, Vitamin D Kids Asthma study.
*Genes with p value < 0.0042 (0.05/12) in meta-analysis.

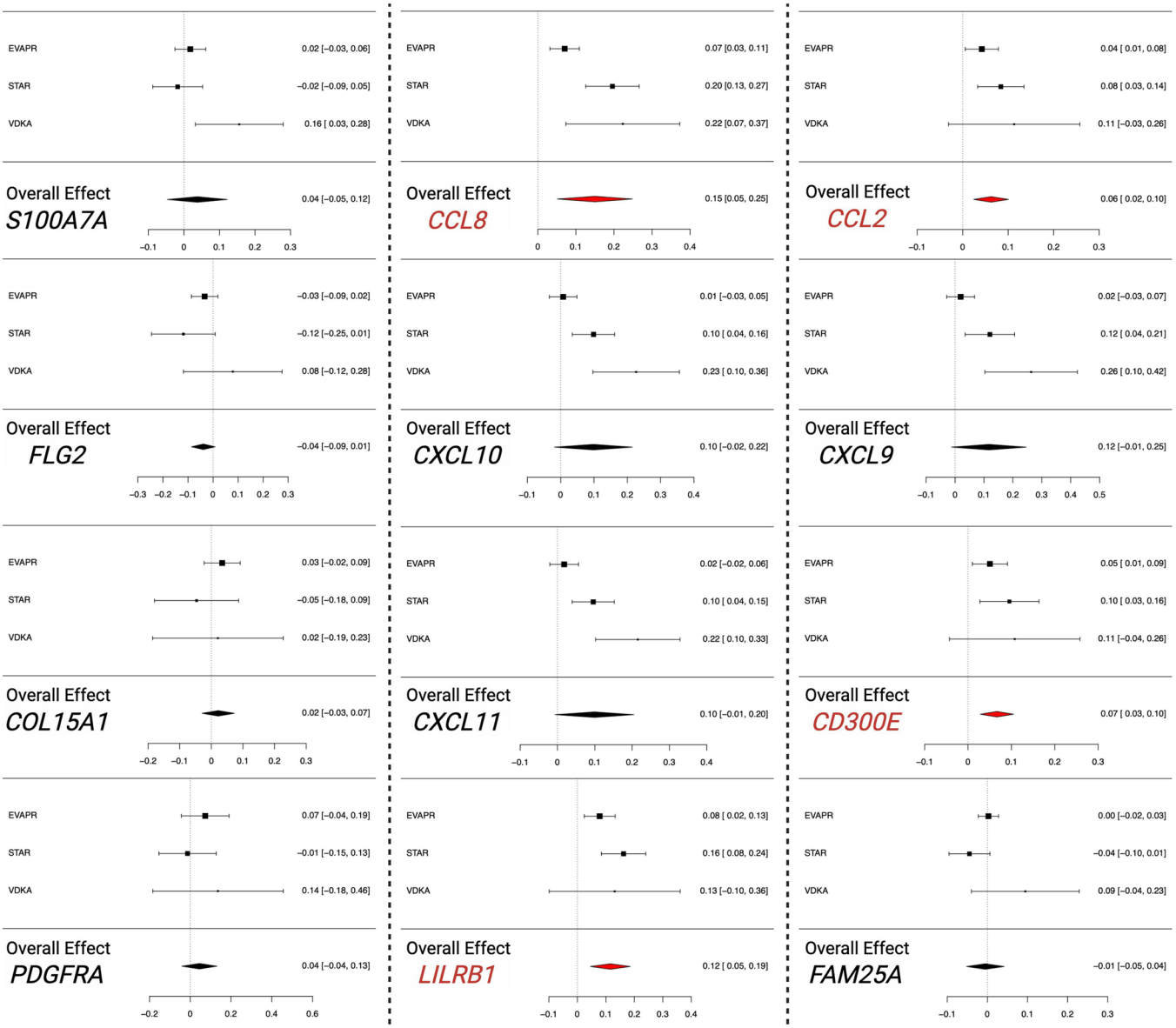

FIGURE 2 | Meta-analysis of Viral Abundance–Associated Genes Across EVA-PR, VDKA, and STAR Cohorts. Forest plots show cohort-specific and overall meta-analysis effect estimates for genes associated with viral abundance. Each panel displays the effect sizes (squares) with 95% confidence intervals across EVA-PR, STAR, and VDKA cohorts, along with pooled meta-analysis estimates (diamonds). Genes with significant overall effects are highlighted in red. The x-axis indicates the direction and magnitude of the associations, where positive values correspond to increased gene expression with higher viral abundance. [Color figure can be viewed at wileyonlinelibrary.com]

While we cannot determine causality in this cross-sectional study, current evidence suggests that violence-related distress may plausibly affect the pathogenesis of T17-high asthma by altering airway epithelial gene expression through neuro-immune and neuro-hormonal mechanisms (Figure 4). This is supported by our recent findings in a study of Puerto Rican youths [16] and reported associations between such distress or other types of chronic stress and T17-related traits such as blood neutrophilia [14, 15, 37] and corticosteroid resistance [5, 38]. Further, mouse models have demonstrated that chronic stress increases noradrenaline, which interacts with beta-3-adrenergic receptors to signal bone marrow cells to decrease CXCL12 levels, thereby increasing hematopoietic stem cell proliferation and increasing neutrophil production [15]. Moreover and consistent with our current findings for enrichment of interferon-gamma signaling and IL17-A signaling pathways, a murine model showed that psychologic stress exacerbates inflammatory responses via overactivation of the IL-23/T17 axis [39] and a study of 28 adults with asthma showed that chronic stress was associated with enhanced IL17A mRNA expression in blood in response to acute stress and whole-lung allergen challenge [40].

Studies of circulating chemokines have implicated *CCL2* in post-traumatic stress disorder (PTSD) [41, 42] and depression [43]. Further, *CCL2* has been associated with T17 immune responses, and blocking the CCL2/CCR2 axis has been shown to impede T-helper 17 cell migration in murine models [44]. Previous studies have demonstrated that *CCL8* expression increases in the setting of chronic stress [45] and in the presence of IL-17A [46]. In the current study, both *CCL2* and *CCL8* were also significantly associated with higher viral abundance,

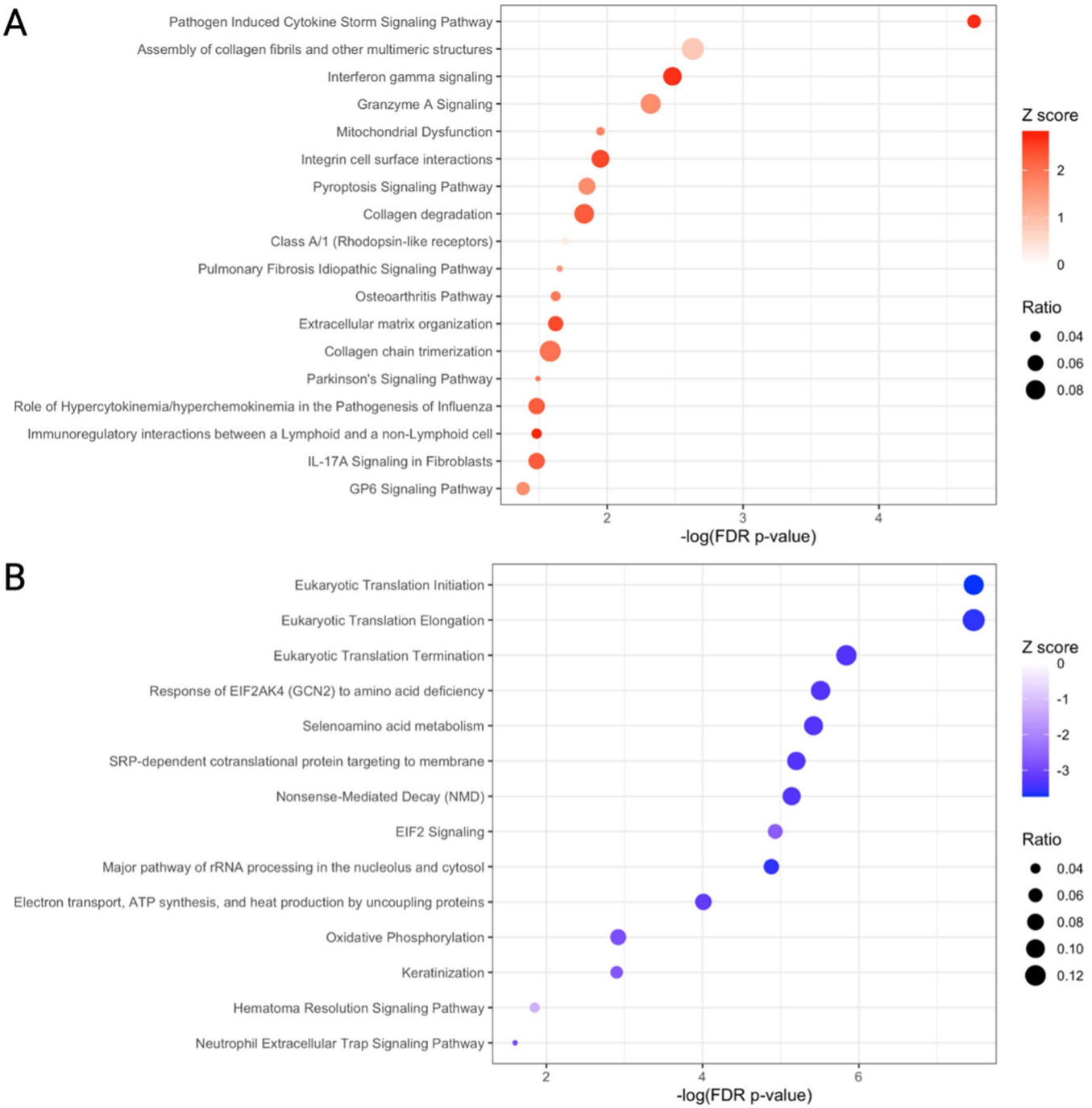

FIGURE 3 | Ingenuity Canonical Pathways enriched in CCDS DE meta-analysis. The plot represents canonical pathways enriched by DEGs identified from CCDS DE meta-analysis. The x-axis represents the -log (FDR p-value), indicating the significance of each pathway. The y-axis lists the pathways in order of significance. The size of the dots indicates the ratio. The color gradient represents the z-score, with white indicating a z-score of 0, red indicating higher positive z-scores, and blue indicating higher negative z-scores. (A) is the activated pathways with positive enrichment z-scores. (B) is the inhibited pathways with a negative enrichment z-score. [Color figure can be viewed at wileyonlinelibrary.com]

suggesting that these chemokines may not only mediate the link between violence-related distress and T17-high asthma, but could also contribute to increased susceptibility to viral colonization or persistence in the airways. Further, immune-modulating genes *CD300E* and *LILRB1* were upregulated in T17-high asthma, suggesting that chronic psychosocial stress may be associated with altered innate or adaptive immune responses. Together, these findings suggest that these chemokines and immune regulatory genes play a dual role in bridging chronic stress, dysregulation of immune responses to viruses, and T17-driven asthma pathogenesis.

Beyond chemokines, we also found that *COL15A1* (Collagen Type XV Alpha 1 Chain) and *S100A7A* (S100 calcium-binding protein A7A) were significantly associated with lower post-bronchodilator FEV_1/FVC ratio, suggesting that stress-induced dysregulation of these epithelial genes may contribute to impaired lung function in youth with asthma. Further, *COL15A1*'s association with lower post-BD FEV1/FVC ratio

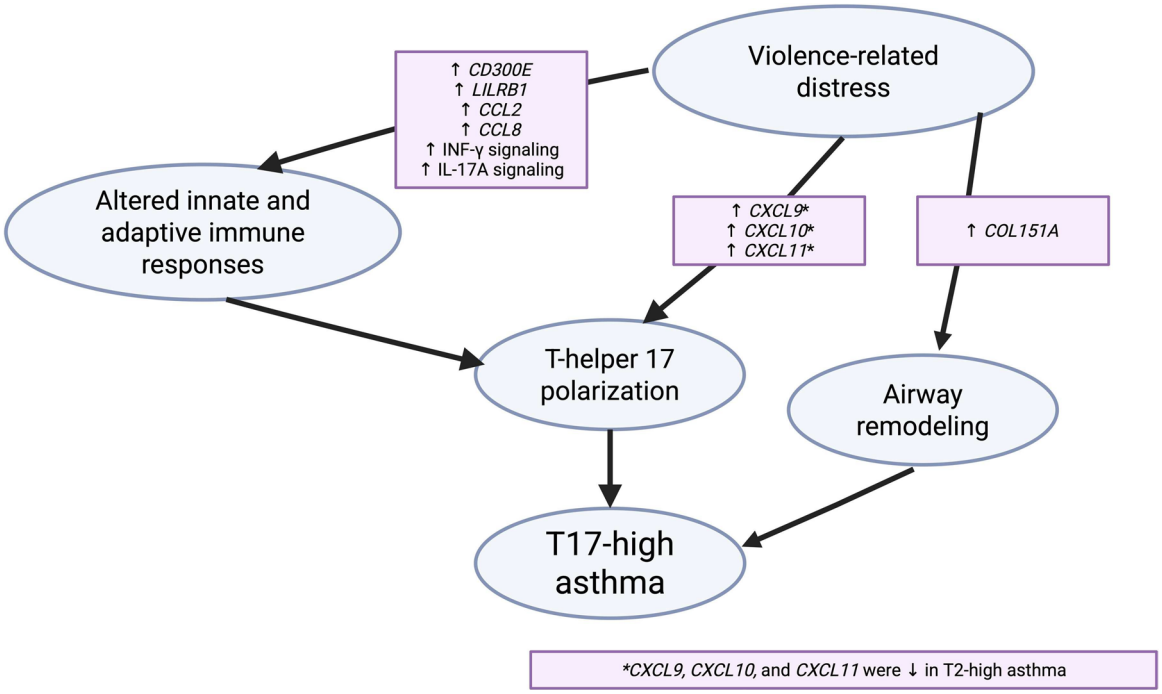

FIGURE 4 | Schematic diagram of the proposed link between violence-related distress, T17 pathway activation, and T17-high asthma. [Color figure can be viewed at wileyonlinelibrary.com]

raises the possibility that extracellular matrix remodeling may contribute to stress-related airway changes and the observed decreased ICS response among individuals with T2-low asthma.

Upregulated expression of *CXCL9*, *CXCL10*, and *CXCL11* was associated with violence-related distress and T17-high asthma, while their downregulated expression was associated with T2-high asthma. These chemokines regulate T-helper 1 cell differentiation [47] but have also been shown to be associated with T-helper 17 cell differentiation [47–49]. Expression of *S100A7A* and *PDGFRA* (platelet-derived growth factor receptor alpha) was also downregulated in T2-high asthma. *PDGFRA* encodes a tyrosine protein kinase that influences cell migration and chemotaxis, and variants in this gene were recently associated with aspirin-exacerbated respiratory disease [50]. Moreover, an *FIP1L1-PDGFRA* fusion gene has been linked with progressive eosinophilia in a patient with asthma and rhinitis, as well as with eosinophilic atypia in a patient with asthma and myeloid/lymphoid neoplasm [51, 52].

This is a cross-sectional study, and thus our findings need replication in longitudinal studies to determine temporal relationships and stability of endotypes over time. Moreover, prospective studies should help differentiate any potential effects of short- to median-term violence-related distress (as assessed by the CCDS) on airway epithelial gene expression from those of long-term distress, while also assessing causality through experimental validation and proteomic analyses.

We acknowledge additional study limitations. First, not all genes that were significant in the meta-analysis were significant in all 3 individual studies, likely due to the smaller sample size of VDKA and STAR and/or differences in social determinants of health and geographic location across studies. Second, confounding is possible in any observational study. We controlled for age, sex, and household income (a proxy for socioeconomic status), but lack data on other potential confounders such as comorbid mental health conditions and outdoor pollutants. Moreover, we did not control for asthma severity or medication use, though all individuals in STAR had mild to moderate persistent asthma and were steroid naïve, while all individuals in VDKA had mild persistent asthma and were receiving low-dose ICS at the time of nasal epithelial sampling. Third, only VDKA included non-Hispanic white participants, and it is possible that our findings in Puerto Ricans and African Americans may not be generalizable to youths in other ethnic groups (e.g., American Indians and Alaska Natives) or other low-income urban populations.

In summary, we have identified nine novel genes, including five chemokines, associated with both violence-related distress and T17-high asthma in youth with asthma. If replicated in other studies, these genes may help uncover the underlying biological processes that drive the association between chronic stress and T17-high asthma.

Author Contributions

Molin Yue: formal analysis, investigation, writing – original draft, writing – review and editing. **Kristina Gaietto:** formal analysis, writing – review and editing. **Zhongli Xu:** software, writing – review and editing. **Yueh-Ying Han:** data curation, writing – review and editing. **Erick Forno:** project administration, writing – review and editing. **Franziska Rosser:** project administration, writing – review and editing. **Xueping Zhou:** software, writing – review and editing. **Ligia Chavez:** project administration, writing – review and editing. **Gregory E. Miller:** investigation, writing – review and editing. **Simon Goldberg:** investigation, writing – review and editing. **Melissa Rosenkranz:** investigation, writing – review and editing. **Wei Chen:** formal analysis, writing – review and editing. **Juan C. Celedón:** supervision, conceptualization, funding acquisition, formal analysis, investigation, writing – review and editing.

Acknowledgments

This study was supported by the US National Institutes of Health (NIH, grants HL117191 and HL119952). The project was also supported by the Pediatric Clinical and Translational Research Center (PCTRC) at the University of Pittsburgh Medical Center Children's Hospital of Pittsburgh through NIH grant UL1TR001857. F.R.'s contribution was supported by NIH grant HL159333. The sponsors had no role in the design or implementation of the study, or the drafting and submission of the manuscript.

Conflicts of Interest

Dr. Celedón received nonfinancial support from Merck during the conduct of the Stress and Treatment Response in Puerto Rican and African American Children with Asthma (STAR) study and from Pharmavite and GSK during the conduct of the Vitamin D Kids Asthma (VKDA) study. The other authors declare no conflicts of interest.

Data Availability Statement

Deidentified RNA-Seq data for STAR and VDKA are available in dbGap (accession number for STAR: phs004052.v1.p1and accession number for VDKA: phs004051.v1.p1). We have no permission to share genetic data for EVA-PR.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.
E-Figure 1: Distribution of CCDS (Checklist of Children's Distress Symptom) scale in all studies. **E-Figure 2:** Heatmap of Gene Expression Across Study Cohorts and T17 Profiles. **E-Table 1:** Clinical and Biomarker Characteristics Across Asthma Endotypes in the EVA-PR, VDKA, and STAR Cohorts. **E-Table 2:** Analysis of top signals in CCDS analysis and T2-high asthma. **E-Table 3:** Meta-analysis of Selected Gene Expression Associations with Lung Function Across EVA-PR, VDKA, and STAR Cohorts. **E-Table 4:** Top functional Ingenuity pathways enriched by the top DEGs in the TWAS of CCDS.