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REVIEW

PEDIATRIC PULMONOLOGY WILEY

Integrating genomics as clinical biomarkers in pediatric pulmonology

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Abstract

Respiratory diseases often result from complex interactions between an individual's genetic predisposition and their exposure to various environmental and other risk factors. Here we will briefly review how various types of "omics", particularly epigenomics and transcriptomics, hold promise for translation into clinical biomarkers in pediatric pulmonary medicine, using asthma and cystic fibrosis as examples.

KEYWORDS
asthma, cystic fibrosis, genomics, transcriptomics

Childhood respiratory diseases often result from complex interactions between an individual's genetic predisposition and their exposure to various environmental and other factors. For instance, asthma has a significant hereditary component, and hundreds of single nucleotide polymorphisms (SNPs) have been associated with childhood- or adult-onset asthma.[1] Yet, altogether, genetic variants explain only a small proportion of asthma heritability, clinical characteristics, or severity. Cystic fibrosis (CF) is a monogenic disease caused by mutations in the *CFTR* gene, yet there is significant phenotypic variability even among individuals who share the same mutations. Over the past decade, there has been increasing interest in studying epigenetic regulation and gene expression to further our understanding of disease pathogenesis. Gene regulation and expression change over time, with age, in response to environmental and other exposures, and likely also in response to pharmacological treatment and other interventions. As such, epigenetic and transcriptomic studies are uniquely positioned to study dynamic disease pathobiology, particularly in pediatrics.

Asthma has a significant hereditary component, with various studies reporting h_0 as high as ~90%. Yet, despite studies over the past two decades reporting hundreds of SNPs associated with asthma, overall heritability remains largely unexplained, individual disease SNP-based classification is suboptimal, and most asthma SNPs fall in intergenic regions or lack clear mechanistic roles. More recently, epigenetic and transcriptomic approaches have improved our ability to classify disease—showing potential for eventual translation into diagnostic biomarkers. We examined DNA methylation profiles in nasal epithelium and constructed "epigenetic risk scores" that accurately classified atopic asthma (vs. healthy controls) with ~82%–88% accuracy in a discovery cohort of Puerto Rican youth, a replication cohort predominantly composed of African American children in the United States and a European birth cohort.[2] Using nasal transcriptomics, we demonstrated similar ability to identify atopic asthma: we constructed "transcriptomic risk scores" (TRS) for asthma with areas under the curve ~0.89–0.92 and positive predictive value ~0.88–0.93 that replicated in independent data sets.[3] Lemmonier et al. reported a clear "dose–response" relationship between the expression level of certain genes and the number of individual atopic diseases (atopic dermatitis, allergic rhinitis, and/or atopic asthma), as further proof-of-concept that gene expression levels could serve as diagnostic biomarkers.[4]

Transcriptomics could also serve as severity and prognostic biomarkers. In a prospective cohort of 66 children with persistent asthma participating in a clinical trial of vitamin D supplementation, we were able to create TRS that significantly associated with time to the next severe asthma exacerbation.[5] Children in the high-risk TRS group had ~5-fold higher rate of severe exacerbations than those in the low-risk group. After 3 months of follow-up, none of the low-risk

subjects had had a hospitalization or emergency department visit for asthma, compared with ~25% of the high-risk group; after 48 weeks, corresponding proportions were 21% versus 73%. If these findings are replicated and extended to other populations and outcomes, "omics" could play a role in clinical decision-making in the not-too-distant future.

Finally, "omics" could also serve as important biomarkers to predict treatment response. *CFTR* modulators, in particular elexacaftor/tezacaftor/ivacaftor (ETI), have made an extraordinary impact in the lives of persons with CF (pwCF). Yet, not everyone responds equally to these medications. Transcriptomic profiles in nasal respiratory epithelium and blood markedly change in response to modulators.[6] Using gene expression profiles from nasal epithelium collected before ETI initiation, we were able to build TRS that predicted subsequent ETI response in FEV_1, year-best FEV_1, and BMI with ~85% accuracy.[7] After adjusting for age, sex, baseline FEV_1, F508del zygosity (homozygous vs. heterozygous), previous use of other CFTR modulators, and other processing/batch covariates, we were able to identify pwCF who went on to have FEV_1 improvements of ≥5% (compared to those whose FEV_1 improved <5% or declined) with over 97% accuracy.[7]

These examples show the significant potential for "omics" approaches not just to further our knowledge of disease pathobiology, but also to serve as biomarkers that could soon have diagnostic, prognostic, and therapeutic utility in clinical care. Single-cell, single-nucleus, and spatial RNA-sequencing and other similar approaches may lead to even further progress, although currently these technologies are still too involved and expensive to consider clinical applications.

AUTHOR CONTRIBUTIONS

Erick Forno: Conceptualization; writing—original draft; writing—review and editing.

CONFLICT OF INTEREST STATEMENT

The author declares no conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no data sets were generated or analyzed during the current study.

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