Introduction

Prologue. Asthma influences 25.7 million persons in the United States, including 7 million Youngsters [1]. In spite of the fact that asthmatic patients share similar clinical symptoms, those infection may be heterogeneous [2]. This heterogeneity contributes of the challenge clinched alongside both considering and treating asthma. Almost two thirds about asthmatic Youngsters reported minimum 1 assault in the previous year [3]. Highlighting those suboptimal administration of adolescence asthma [4]. The recurrence of absent or incomplete viability On asthma medication need been evaluated to make 40% should 70% [5]. Currently, systemic corticosteroid medicine will be acknowledged the most viable solution for control from claiming incessant asthma andrescue of intense worsening. Transcriptional profiling of individual group reactions is a fundamental and basic next step with exceptional comprehend this individual variety and identify biomarkers from claiming systemic corticosteroid medicine reaction. This approach need been utilized effectively on arrange sub phenotypes of asthma, including medication reaction phenotypes [6-9]. Past investigations have regularly utilized specimens requiring bronchoscopy or induced sputum collection, which is not constantly attainable in clinical practice, particularly previously, know youngsters with a intense asthma exacerbation (AAE). In the available examine we utilized genome-wide expression profiling of nasal epithelial phones with distinguish genes with transient outflow designs (before Also following treatment) that reliably What's more dependably discriminated the middle of systemic corticosteroid medication reaction gatherings Around kids hospitalized for asthma exacerbations. Nasal epithelial phones can be promptly sampled securely Throughout a asthma attack [10]. What's more reflect transformations watched in the bronchial aviation routes for asthmatic know Youngsters [11], we distinguished Also replicated genes perioestin, SerpinB2 Also CLCA1, the mrna statement for which consistently discriminated the middle of great Also poor responders to systemic corticosteroid medicine.

Subject of Periostin, SerpinB2 and CLCA1 Gene Expression as Potential Predictors of Corticosteroid Therapy Response in Childhood Asthma

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Abstract

Currently, systemic corticosteroid treatment is considered the most effective medication for control of chronic asthma and rescue of acute exacerbation. Children can have poorly controlled asthma for numerous reasons. It is important to identify the underlying causes that contribute to poorly controlled asthma in each patient so that management strategies can be personalized to achieve the best outcomes. We have identified a biological basis for poor corticosteroid treatment response that can be used to distinguish a subgroup of children with asthma who respond poorly to treatment. Nasal periostin, SerpinB2 and CLCA1 gene expression might be a clinically useful biomarker to identify a subset of children with difficult-to-treat asthma with a biologic cause for poor corticosteroid response. Targeting periostin, SerpinB2 and CLCA1 pathways in this subset might be a useful therapeutic strategy to enhance corticosteroid response.

1. Methods

2.1 Subjects

Then afterward regulate Audit table approval, Youngsters provided for a analysis of asthma In those period for 5 on 18 a considerable length of time who introduced of the Benha college healing facility crisis Branch (ED) for a AAE were recruited. Of the 40 subjects consented, 21 were hospitalized for asthma exacerbation. Also 15 required genome-wide mrna outflow information to both run through focuses. These 15 patients were utilized Similarly as a disclosure accomplice will test those affiliation the middle of gene interpretation and systemic corticosteroid medication reaction. An answer companion from claiming 25 know youngsters hospitalized to asthma were recruited to further accept the discoveries from those finding accomplice.

Subjects Gave demographic, environmental, asthma trigger. Furthermore personage Furthermore crew unfavorable susceptibility Also asthma history information. Parental report card about current breathed in corticosteroid (ICS) controller prescription (eg, mometasone, fluticasone, beclomethasone dipropionate, fluticasone/salmeterol, mometasone/formoterol and budesonide/formoterol) might have been Additionally gathered. Will evaluate benchmark asthma manifestation seriousness Furthermore control. An respiratory side effect score might have been ascertained (based once recurrence of wheeze, cough, shortness of breath, and midsection tightness) [12] and the age-specific asthma control test score might have been gathered. [13].

2.2 Treatment protocol and treatment response definitions

Enrolled patients were treated according to the CCHMC evidence-based treatment protocol for inpatient asthma exacerbations [14-16]. The admitting physician determined the initial interval of albuterol treatments, which were subsequently spaced based on physician or respiratory therapist assessments. Patients received 2 mg/kg/d prednisone while hospitalized, and ICSs were continued through a mouthpiece. Length of stay (LOS) was calculated as the number of hours from the
time the admission decision was made to the time the subject met clinical discharge criteria. Good responders were defined as those with an LOS of 24 hours or less, and poor responders were defined as those with an LOS of greater than 24 hours.

2.3 Nasal epithelial cell sample collection and processing

Nasal epithelial samples were collected at 2 time points from each subject (1) in the ED (S0) and (2) on the inpatient floor 18 to 24 hours after receiving corticosteroids in the ED (S1). Nasal samples collected contained more than 90% epithelial cells.[10] Expression profiles were generated on the Affymetrix Human Gene 1.0 ST platform. Quantitative real-time PCR (qRT-PCR) was used to validate and replicate candidate genes.

3. Statistical analysis

3.1 Detection of differentially expressed genes in the discovery set

To identify candidate genes, we performed sequential filtering to balance concerns of type I and II errors. First, we sought to identify genes reliably expressed in nasal cells (raw signal >100 in at least 2 samples). Next, we sought to identify genes responsive to treatment (S1/S0 > 1.5 or S1/S0 < 0.66; S1/S0 is defined as gene expression at S1 relative to that at S0). Then we identified genes with significant differences in S1/S0 ratio between the good and poor responder groups.

A P value threshold of .05 was used because independent replication samples and complementary biologic studies minimize the risk of false-positive discovery to minimize the risk of missing true associations. We then identified those genes with a high rate of prediction accuracy (>0.80) through linear discriminant analysis. To validate these results, we performed qRT-PCR.

3.2 Microarray data analysis

Microarray cell image files were analyzed with Gene Spring GX software. Probe-level measurements were subject to initial background correction and normalization by using GC-robust multi-array average. Transcript levels were normalized per chip to the 50th percentile array average. Transcript level measurements were compared between the good and poor responders, and no difference in age between the good and poor responders. There were no differences in individual parent-reported asthma triggers (datanot shown), mean baseline respiratory symptom frequencies, asthma control scores, or proportions of patients presenting to the ED while receiving a controller medicine between the discovery and replication cohorts Table (1). By design, the discovery and replication cohorts were similar with respect to month admitted, S0 time, and S1 time Table (1). Demographics and clinical features were also compared between the good and poor responders, and no differences were detected Table (2).

In the discovery phase we used t tests (with log transformation) to identify genes between good and poor responders.

Linear discriminant analysis [17] was applied to identify genes that best discriminated between good and poor responders. For replication, we first examined whether there were differences between the discovery and replication cohorts that might introduce bias. Time of admission was significantly different between the discovery and replication cohorts. Thus we matched our replication cohort to the discovery cohort based on month and S0 and S1 times by using propensity scores [18]. Importantly, gene expression profiles were not considered in the matching process. After matching, we performed t tests comparing the quantitative PCR results from good and poor responders. A linear regression model was fitted to examine the association between the Periostin, SerpinB2 and CLCA1 mRNA expression change (S1/S0) and the continuous length of hospital stay (in hours) in the combined discovery and replication cohorts.

4. Results

4.1 Subjects

The discovery and replication cohorts were primarily male Table (1). The discovery cohort was older than the replication cohort, but within each cohort, there was no difference in age between the good and poor responders. There were no differences in individual parent-reported asthma triggers (datanot shown), mean baseline respiratory symptom frequencies, asthma control scores, or proportions of patients presenting to the ED while receiving a controller medicine between the discovery and replication cohorts Table (1). By design, the discovery and replication cohorts were similar with respect to month admitted, S0 time, and S1 time Table (1). Demographics and clinical features were also compared between the good and poor responders, and no differences were detected Table (2).

The baseline average respiratory symptom score represents the average number of times per week the patient had coughing, wheezing, shortness of breath, or chest tightness, pain, or both. A score was assigned for each of the 4 symptoms, and then an average was taken. A higher score represents higher symptom frequency. The values of the scores for each symptom are as follows: 0, never; 1, less than 1 time per week; 2, 1 to 2 times per week; 3, 3 to 5 times per week; and 4, 6 to 7 times per week.

Table (1) Description of the discovery, and replication cohort

<table>
<thead>
<tr>
<th>Discovery cohort (n= 15)</th>
<th>Replication cohort (n= 25)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y), mean (SD)</td>
<td>13.4 (3.8)</td>
<td>8.1 (2.8)</td>
</tr>
<tr>
<td>Age range (y)</td>
<td>7.4-18.0</td>
<td>5.0-15.1</td>
</tr>
<tr>
<td>Male sex (%)</td>
<td>73.3</td>
<td>64.0</td>
</tr>
<tr>
<td>Admission month, range</td>
<td>April-December</td>
<td>March-November</td>
</tr>
<tr>
<td>S0 sample time (24 h)</td>
<td>9.3-20.8</td>
<td>10.0-21.4</td>
</tr>
<tr>
<td>S1 sample time (24 h)</td>
<td>8.1-16.7</td>
<td>8.5-17.3</td>
</tr>
<tr>
<td>ACT score (SD)</td>
<td>16.0 (2.5)</td>
<td>16.0 (4.4)</td>
</tr>
</tbody>
</table>

4.2 Identification of genes differentially expressed between good and poor responder groups in the discovery cohort

We used a multistep filtering process to identify genes. Starting with more than 20,000 genes, we identified 8 genes that were nominally significant (P < .05) and had a prediction accuracy of 0.80 or greater. Of these 8 genes, qRT-PCR expression of superoxide dismutase 2 (SOD2), tyrosine protein kinase (HCK), serglycin (SRGN), Periostin, SerpinB2 and CLCA1 was significantly induced at S0 compared with that seen in the poor responder group. CD300A was not detectable in most samples, and reliable results could not be achieved for lymphocyte cytotoxic protein 2 (LCP2), formyl peptide receptor 1 (FPR1), and low-affinity immunoglobulin g Fc region receptor III-A (FCGR3A) because of low copy numbers.

4.3 Periostin, SerpinB2 and CLCA1 mRNA expression change predicts corticosteroid treatment response in the replication cohort

To substantiate our findings, we recruited an independent prospective cohort to serve as a replication. High baseline mRNA expression of Periostin, SerpinB2 and CLCA1 occur in the good responder group compared with that seen in the poor responder group, replicating our findings from the discovery cohort. Expression of SOD2, HCK, and SRGN was not significantly different between the treatment response groups (data not shown).

To evaluate whether the observed Periostin, SerpinB2 and CLCA1 mRNA expression change was attributable to a baseline difference in Periostin, SerpinB2 and CLCA1 mRNA expression at 0, we compared Periostin, SerpinB2 and CLCA1 expression at S0 in all patients; no significant difference was detected. To test whether the baseline ICS exposure was a confounding factor for the corticosteroid treatment response, we compared the proportion of subjects who presented to the ED while receiving ICS between the good and poor responders; no significant difference was detected Table (2).

5. Discussion

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References


