Published in final edited form as:

Pharmacogenet Genomics. 2018 November ; 28(11): 256–259. doi:10.1097/FPC.0000000000000355.

Leveraging Electronic Health Records to Assess the Role of ADRB2 SNPs in Predicting Exacerbation Frequency in Asthma Patients

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Abstract

Asthma is the leading chronic disease in children. Several studies have identified genetic biomarkers associated with susceptibility and severity in both adult and pediatric cases. In this study, we evaluated outcome in 400 African American and European American pediatric cases all of whom were regular users of inhaled corticosteroids. Patients were stratified by genotype using two single nucleotide polymorphisms (SNPs) in the beta-2 adrenergic receptor (*ADRB2*) gene – rs1042713 and rs1042714, previously associated with asthma outcome. These correspond to nonsynonymous SNPs at positions 16 [arginine to glycine (Arg16Gly); rs1042713] and 27 [glutamic acid to glutamine (Glu27Gln); rs1042714], which are relatively common (minor allele frequencies ~40–50%), and have been well characterized in asthma pharmacogenetics. We controlled for adherence to National Heart, Lung and Blood Institute (NHLBI) guidelines using deep mining of electronic health record (EHR) data to determine treatment course. We found no significant effect for rs1042713 (Arg16Gly), but did identify an effect for rs1042714, where participants homozygous for Gln27 had increased exacerbations while taking inhaled corticosteroids in comparison with those who were either heterozygous or homozygous for Glu27. This is consistent with previous studies and demonstrates for the first time that the Glu27 variant in the *ADRB2* gene is associated with increased frequencies of asthma exacerbations. Moreover, this study also lends an important proof-of-principle on how EHRs linked to genotype can be efficiently and systematically mined to delineate health outcomes.

Introduction

Asthma, a chronic disorder characterized by impaired respiratory function and/or airflow, is one of the most common disorders worldwide and the leading chronic disease in children. Currently, an estimated 14 million individuals, including ~11 million children, in the United States have been diagnosed with asthma in their lifetime, with prevalence increasing by ~1-2% each year(1).

Several genes have been validated as risk factors for asthma susceptibility and receptiveness controller therapies(2), including *ADRB2*, a 2015 bp-long intronless gene found on chromosome 5q31-32. *ADRB2* encodes the beta-2-adrenergic receptor (Beta2 AR), a type of G protein-coupled receptor that is highly expressed in bronchial smooth muscle cells. Risk/outcome-associated SNPs identified in the coding region of the *ADRB2* gene include Arg16Gly (rs1042713) and Gln27Glu (rs1042714), both of which occur in amino acids found near the protein's ligand binding site for epinephrine(2). *In-vivo* studies of *ADRB2* SNPs at rs1042713 and rs1042714 suggest that, in general, these variants are most likely not disease-causing but instead potentially indicate/predict responsiveness to agonists and antagonists(12).

In seeking to further delineate the impact of *ADRB2* variants on asthma outcome, we control for severity, guideline adherence, and BMI (long-associated with impaired outcome in terms of severity and susceptibility)(3, 4). Outcome is measured by asthma exacerbation frequency, adapting an approach by Basu et al.(5). Many treatment guidelines, including NHLBI's, specifically focus on reducing exacerbations as a treatment goal and measure of treatment efficacy(6), and a key component of reducing risk in the long term(7). We hypothesize that, controlling for other factors, patients with Arg16Gly and Gln27Glu polymorphisms experience differential outcome as measured by asthma exacerbation.

Methods

This study was undertaken with the Electronic Medical Records and Genomics (eMERGE) consortium. Patients were identified using a phenotyping algorithm that classified cases and severity based on ICD-9 codes, asthma controller therapy, structured queries, and natural language processing. This algorithm had a 96.1% success rate in correctly identifying cases and was validated in pediatric cohorts(8). Inclusion and exclusion criteria are reviewed briefly - see(8) and(9) for further details.

Recruitment

Participants were recruited at the Center for Applied Genomics (CAG) at The Children's Hospital of Philadelphia under a large-scale biobanking/recruitment project, *A Study of the Genetic Causes of Complex Pediatric Disorders*, (n>100,000). After being seen in either the ambulatory or patient setting, patients were invited to enroll in CAG's project. Our broad consent protocol includes DNA extraction, blood/sera, EHR access, and permission to perform genomic studies.

EHR Extraction

The EHR product, EpicCare® (Epic Systems, WI), includes reason for visit, diagnosis codes (ICD), growth measurements, medications, referrals, all laboratory results, radiology reports, surgical notes, discharge summaries, Emergency Department summaries, and specialist reports.

Genotyping

SNPs were directly genotyped on a variety of Illumina arrays (primarily HapMap and OMNI). Ancestry was determined by principal component analysis using Eigenstrat 3.0 on the genotyping data. Samples were separated into African Americans (AAs) and European Americans (EAs) based on principal components, and participants of mixed ancestry were excluded. For the rs1042713 SNP, participants were coded as '0', '1', or '2' indicating whether they respectively had zero, one, or two copies of the A allele. Similarly, for rs1042714, patients were coded as '0', '1', or '2' for the G allele.

Inclusion/Exclusion Criteria

Asthma cases were defined as children >4 and <18 years of age who received an ICD-9 asthma code (493.*) on at least two separate calendar days as well as documented prescription(s) for at least one asthma-related medication. Only asthmatics evaluated in Allergy or Pulmonology clinics were included.

Children were excluded if they had evidence of chronic lung disease defined by ICD-9 codes(8) and(9), or if not evaluated in a subspecialty clinic after 2007 (i.e. before NHLBI guidelines). If a body mass index >40 was recorded at any point, cases were excluded.

Guideline Adherence

We defined “meeting the NHLBI guidelines” as having all five of the following requirements: 1) documented asthma control test (ACT), 2) asthma care plan (ACP) in the EHR 3) bi-annual follow-up visits (determined using a threshold of 75% of visits being within 200 days of one another), 4) PFT data (NHLBI recommends PFTs at least once every two years; we used a lower threshold of simply having at least one set of documented PFT results which helped to account for younger children among whom PFT data would be limited), and 5) on at least one ICS medication(7). Prescriptions for asthma-related medications (i.e. Leukotriene agonists, ICS/LABA) in addition to ICS were noted and considered beyond the scope of the guidelines. Medication adherence was recorded but patient data was limited (available in <40% patients) and therefore not included. Patients whose treatment met all criteria were coded as “1” versus “0” where at least one criterion was missed.

Outcomes Measures

Only visits considered “asthma-related”, defined as having a diagnosis of asthma on the same day, were considered. Exacerbations were defined as a prescription for systemic steroids with an associated asthma (ICD-9 493.*) diagnosis on the same calendar day. Steroid prescriptions within 14 days of a previous prescription were considered the same exacerbation. Any exacerbation within the January 1, 2008 and June 1, 2016 timeframe was included.

Analysis Plan

Given an eligible cohort of 4661 patients that met algorithm criteria, we randomly selected 400 cases, in whom direct genotyping data was available (the remainder of whom will be

directly genotyped/analyzed as part of Phase 2 studies). Analyses were performed in two stages, comparing the effects of genotype on outcome in 1) AAs and EAs separately, and 2) AA and EA cohorts combined. Exacerbations were coded as present/absent contingent on whether the patient did/not experience an exacerbation in the previous 12 months. This approach is similar to Basu et al.(5) who used exacerbations/last 6-months as the primary outcome measure. Individuals with a z-score-adjusted BMI >95% were excluded from analyses.

Results

Guideline Adherence

Of 400 cases studied, 379 had an updated ACP, 224 had at least one completed ACT, 368 had PFT data, all 400 had a prescription for at least one ICS medication, and 243 had bi-annual follow-up visits. A total of 123 cases had been treated according to all 5 guidelines. Supplementary Table 1, Supplemental Digital Content 1, <http://links.lww.com/FPC/B326>, provides a breakdown of guideline adherence according to demographic factors.

For the most part, total guideline adherence was evenly distributed. Adherence of all the guidelines seemed to increase with more recent birth years, possibly because older patients had experienced contact with the hospitals before the release of the guidelines.

Exacerbation Frequency

With severity, compliance, and both genotypes as predictors in a binary logistic regression, we tested the hypothesis that the Arg16Gly and Glu27Gln genotypes were associated with exacerbations. No significant effect of genotype was observed for either ancestral group. However, in a combined meta-analysis, individuals homozygous for Gln27 were found to be disproportionately more likely to experience exacerbations *versus* those who were heterozygous ($\chi^2 = 6.45$, $P = 0.040$) or Glu27 homozygous ($\chi^2 = 6.16$, $P = 0.013$). We did not correct for multiple comparisons, noting that the direction-of-effect is the same for both comparisons. We did not observe a significant difference between patients who were heterozygous versus Glu27 homozygous ($\chi^2 = 0.738$, $P = 0.390$). We did not identify any significant differences for rs1042713 (Arg/Gly16).

Unsurprisingly, there was also a marked effect of severity ($\chi^2 = 10.02$, $P = 0.007$), with increased severity significantly and increasingly associated with a higher likelihood of experiencing an exacerbation. We also observed a marked effect for patient compliance, which was associated with reduced exacerbation frequency ($\chi^2 = 32.30$, $P < 0.001$).

Discussion

Both Arg16Gly and Gln27Glu have previously been linked to asthma outcome, including response to first-line bronchodilator therapy(2). Although we found no effect for the Arg16Gly allele, we did uncover an association with Gln27, where individuals were disproportionately more likely to experience *versus* those who were heterozygous ($P = 0.040$) or Glu27 homozygous ($P = 0.013$).

Given Beta2 AR's known role in bronchodilation, medications that influence bronchodilation may interact differently with the protein depending on the SNP. Mutations at or near the active site could impact the efficacy of beta-agonist medication. As ICS medications work to reduce the inflammation that can affect bronchodilation, these mutations could also impact the efficacy of ICS. Already, several studies have shown that varying the use of beta-agonists treatments like albuterol with polymorphic patients has brought about poorer results in airway function improvement, with patients with polymorphisms at codons 16 or 27 largely seeing no improvement in peak flow as compared to patients without these SNPs(10). Furthermore, a study in COPD patients found that patients treated with ICS did not respond as well to long-acting beta-agonist treatment—patients with rs1042713 had exacerbations sooner with ICS compared to without. Acknowledging the caveat of a limited sample size—and by association relatively modest power—these support the suggestion that *ADRB2* SNPs affect the efficacy and interaction of common asthma medications. These findings underscore the potential relevance of incorporating patients' genotypic information into their asthma treatment plans, where medical teams can leverage genotype information to develop individualized treatment plans.

That our results do not show an association between the Arg16Gly SNP and asthma exacerbations is surprising given that many studies have supported an association between the two and the Arg16Gly allele is in linkage with Gln27. However, the effect of these SNPs on asthma outcome has been seen to greatly vary by race, with many Asian populations exhibiting an association between Arg16Gly and asthma susceptibility. In comparison, Gln27 has not been the focus of many studies.

In parallel, this study also illustrates how EHR data linked to genotypes can systematically be used to delineate health outcomes for disease populations. By showing associations between genotype and response to inhaled corticosteroid treatment as reflected in frequency of asthma exacerbations for asthma, we outline a model whereby systematic data-mining of biobanked samples, which are coupled to EHRs can be used to identify genotype-health outcome associations and inform treatment (for appropriately-consented participants). This demonstrates a success for data-mining of de-identified EHR data, and the utility of unbiased large-scale recruitment and biobanking in informing pharmacogenomic effects for common diseases.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements:

The authors thank all patients and control subjects for their participation in the study. They also thank the Electronic Medical Records and Genomics network for their support.

Funding:

The study was funded by the National Human Genome Research Institute through the following grants: U01HG8684 and U01HG006830. Additional funding was supplied by the CHOP Endowed Chair in Genomic Research (Hakonarson).

References

1. CDC Center for Disease Control and Prevention. Asthma facts: CDC's National Asthma Control Program Grantees. Atlanta, GA: Department of Health and Human; 2013.
2. de Paiva AC, Marson FA, Ribeiro JD, Bertuzzo CS. Asthma: Gln27Glu and Arg16Gly polymorphisms of the beta2-adrenergic receptor gene as risk factors. *Allergy Asthma Clin Immunol* 2014; 10:8. [PubMed: 24499171]
3. Litonjua AA, Gong L, Duan QL, Shin J, Moore MJ, Weiss ST, et al. Very important pharmacogene summary ADRB2. *Pharmacogenet Genomics* 2010; 20:64–69. [PubMed: 19927042]
4. Taylor B, Mannino D, Brown C, Crocker D, Twum-Baah N, Holguin F. Body mass index and asthma severity in the National Asthma Survey. *Thorax* 2008; 63:14–20. [PubMed: 18156567]
5. Hjellvik V, Tverdal A, Furu K. Body mass index as predictor for asthma: a cohort study of 118 723 males and females. *Eur Respir J* 2010; 35:1235–1242. [PubMed: 20075044]
6. Basu K, Palmer CN, Tavendale R, Lipworth BJ, Mukhopadhyay S. Adrenergic beta(2)-receptor genotype predisposes to exacerbations in steroid-treated asthmatic patients taking frequent albuterol or salmeterol. *J Allergy Clin Immunol* 2009; 124:1188.e3–1194.e3. [PubMed: 19800676]
7. Shen J, Johnston M, Hays RD. Asthma outcome measures. *Expert Rev Pharmacoecon Outcomes Res* 2011; 11:447–453. [PubMed: 21831026]
8. National Asthma Education and Prevention Program. Expert Panel Report 3 (EPR-3): guidelines for the diagnosis and management of asthma-summary report 2007. *J Allergy Clin Immunol* 2007; 120 (Suppl):S94–S138. [PubMed: 17983880]
9. Almoguera B, Vazquez L, Mentch F, Connolly J, Pacheco JA, Sundaresan AS, et al. Identification of four novel loci in asthma in European American and African American Populations. *Am J Respir Crit Care Med* 2017; 195:456–463. [PubMed: 27611488]
10. Hysinger EB, Roizen JD, Mentch FD, Vazquez L, Connolly JJ, Bradfield JP, et al. Mendelian randomization analysis demonstrates that low vitamin D is unlikely causative for pediatric asthma. *J Allergy Clin Immunol* 2016; 138:1747.e4–1749.e4. [PubMed: 27554823]
11. Price AL, Patterson NJ, Plenge RM, Weinblatt ME, Shadick NA, Reich D. Principal components analysis corrects for stratification in genome-wide association studies. *Nat Genet*, 382006. 904–909. [PubMed: 16862161]
12. Patterson N, Price AL, Reich D. Population structure and eigenanalysis. *PLoS Genet* 2006; 2:e190. [PubMed: 17194218]
13. Israel E, Drazen JM, Liggett SB, Boushey HA, Cherniack RM, Chinchilli VM, et al. The effect of polymorphisms of the beta(2)-adrenergic receptor on the response to regular use of albuterol in asthma. *Am J Respir Crit Care Med* 2000; 162:75–80. [PubMed: 10903223]
14. Rabe KF, Fabbri LM, Israel E, Kögler H, Riemann K, Schmidt H, et al. Effect of ADRB2 polymorphisms on the efficacy of salmeterol and tiotropium in preventing COPD exacerbations: a prespecified substudy of the POETCOPD trial. *Lancet Respir Med* 2014; 2:44–53. [PubMed: 24461901]
15. Carroll CL, Sala KA, Zucker AR, Schramm CM. β 2-Adrenergic receptor haplotype linked to intubation and mechanical ventilation in children with asthma. *J Asthma* 2014; 49:563–568.
16. Birbian N, Singh J, Jindal SK, Singla N. Association of β 2-adrenergic receptor polymorphisms with asthma in a North Indian population. *Lung* 2012; 190:497–504. [PubMed: 22821646]
17. Gao JM, Lin YG, Qui CC, Liu YW, Ma Y, Liu Y. Beta2-adrenergic receptor gene polymorphism in Chinese Northern asthmatics. *Chin Med Sci J* 2004; 19:164–169. [PubMed: 15506640]
18. Chiang CH, Lin MW, Chung MY, Yang UC. The association between the IL-4, ADR β 2 and ADAM 33 gene polymorphisms and asthma in the Taiwanese population. *Chin Med Sci J* 2012; 75:635–643.
19. Xie H, Cheng Y, Huo Y, Huang G, Su J. Association between β 2-adrenoceptor gene polymorphisms and asthma risk: an updated meta-analysis. *PLoS ONE* 2014; 9:e101861. [PubMed: 24992184]

Table 1.
Genotypic Breakdown of African American and European American patients.

	Rs1042713			Rs1042714		
	GG*	AG*	AA*	CC*	CG*	GG*
All	122	202	76	200	167	33
African American	57	108	46	147	62	2
European American	65	94	30	53	105	31

Table 2.
Breakdown of Guideline Adherence.

ICS medication was adhered to by all included participants (n=373), as this was an inclusionary criterion. This was followed by asthma care plan (355), pulmonary function testing (338), regular visits (225), and asthma control tests (197). Average birth year for the included participants was 2000.5 and average birth year range was 1996-2001.

Demographics			ACP	ACT	PFT	ICS	Visits	All
Birth Year	2002-2008	170	165	101	149	170	124	71
	1996-2001	153	146	85	143	153	79	46
	1989-1995	50	44	11	46	50	22	6
Sex*	Female	141	136	79	129	141	72	42
	Male	230	217	116	207	230	152	80
Ancestry	African American	166	165	127	157	166	100	80
	European American	207	190	70	181	207	125	43
BMI Percentile	0-25%	45	42	18	37	45	28	12
	25-50%	62	56	27	56	62	43	16
	50-75%	87	83	50	81	87	58	36
	75-100%	179	174	102	164	179	96	59
Atopy	Yes	354	336	186	321	354	211	114
	No	19	19	11	17	19	14	9
Total		373	355	197	338	373	225	123

ACT = documented asthma control test; ACP = asthma care plan; PFT = pulmonary function test; ICS = inhaled corticosteroids.

* Two patients had conflicting identities in Epic vs. survey data and were not included in sex totals.

Table 3.
Exacerbation Frequency by Genotype.

Overall effect of the Gln/Glu27 genotype on asthma exacerbations at a mean frequency of every 6 months or more. There was no difference for individuals of African American or European American Ancestry when analyzed separately, but the difference did reach significance when meta-analyzed

	N	Proportion with exacerbations
Gln/Gln27	181	35.9%
Gln/Glu27	158	22.2%
Glu/Glu27	34	14.7%