Published in final edited form as:

Ann Allergy Asthma Immunol. 2019 February ; 122(2): 208–210. doi:10.1016/j.anai.2018.11.005.

Estrogen receptor-alpha (ESR1) polymorphism rs1999805 associates with asthma

Melissa H. Bloodworth^{1,*}, Mark Rusznak^{2,*}, Lisa Bastarache³, Janey Wang³, Dawn C. Newcomb^{1,2}

¹Department of Pathology, Microbiology, and Immunology, Vanderbilt University, Nashville, TN, USA

²Division of Allergy, Pulmonary and Critical Care Medicine, Department of Medicine, Vanderbilt University Medical Center, Nashville, TN, USA

³Department of Biomedical Informatics, Vanderbilt University, Nashville, TN, USA

Keywords

phenome-wide association study (PheWAS); asthma; estrogen receptor α

As adults, women have higher rates of asthma and allergic disease as well as increased asthma severity compared to men.¹ Pre or peri-menstrual worsening of asthma symptoms (PMA) were reported in 17% of women enrolled in the severe asthma research program, with 52% of these women with PMA having severe asthma.^{2, 3} Further, use of birth control medications or hormone replacement therapy during peri or post-menopause was also linked to worsening of asthma in some women.^{2, 4} Mouse models of asthma showed estrogen signaling through estrogen receptor-alpha (ER- α), and not ER- β , increased allergic airway inflammation, mucus production, and/or airway hyperresponsiveness.^{2, 4} Collectively, these findings suggest a critical role for ER- α signaling in asthma pathogenesis.

In this study, we sought to determine whether SNPs in ER- α (ESR1) or aromatase (CYP19A1), the enzyme that converts testosterone to estrogen, were associated with asthma or allergic disease phenotypes using a phenome-wide association study (PheWAS). PheWAS is a validated, reverse genetics technique that associates clinical phenotypes to genetic variants. PheWAS is able to determine if genetic polymorphisms are associated with clinical phenotypes using de-identified electronic health records (EHR).⁵ We studied ESR1 because of the importance of ER- α signaling in the pathogenesis of asthma. We also investigated CYP19A1 due to studies showing an increased risk of breast cancers and other diseases (see Table 1, bottom) with SNPs in CYP19A1 (see Table 1, bottom). While previous genome-wide association studies (GWAS) studies have not reported associations between asthma or lung function and SNPs in ESR1 or CYP19A1 in a population of both men and women,^{6, 7}

Address correspondence to: Dawn Newcomb, Ph.D., Division of Allergy, Pulmonary and Critical Care Medicine, Vanderbilt University School of Medicine, T-1218 MCN, VUMC, 1161 21st Ave South, Nashville, TN 37232-2650, USA, Telephone: 615-875-7782; fax: 615-343-7448, dawn.newcomb@vanderbilt.edu.

*These authors contributed equally to this work

Conflicts of interest: none

the stringent p-value thresholds for these GWAS studies likely missed associations. Therefore, we conducted a PheWAS on men and women (ages 18 years) using 14 SNPs in ESR1 or CYP19A1 that were previously associated with sex hormone related diseases in GWAS studies or identified in the original PheWAS catalog with genotyping information on 13,835 individuals (Table 1).⁵ In our PheWAS study, significant associations ($p < 0.05$) between the selected SNPs and ICD9 codes for wheezing, asthma, or allergic diseases were determined from Vanderbilt's BioVU databank with de-identified genotyping information on 36,400 subjects linked to the EHR. Genotyping was done on the Illumina HumanExome BeadChip platform, and a cutoff of 5,500 subjects with a respective SNP was needed to sufficiently power the PheWAS analysis.^{5, 8}

As shown in the top panel of Table 1, significant associations ($p < 0.05$) were identified for five SNPs with ICD9 codes for wheezing, asthma, or allergic diseases with a female predominance for all 5 SNPs. The bottom panel of Table 1 shows the two SNPs had no significant associations with asthma or allergic diseases and seven SNPs that had less than 5,500 subjects and were not analyzed. CYP19A1 SNP rs2305707 had an inverse association with allergic rhinitis ($OR = 0.90$, $p = 0.0101$). CYP19A1 SNP rs2899472 exhibited an inverse association with anaphylactic shock ($OR = 0.59$, $p = 0.0063$) and chronic sinusitis ($OR = 0.91$, $p = 0.0412$), and was associated with asthma exacerbations ($OR = 1.28$, $p = 0.0079$). ESR1 SNP rs543650 had an inverse association with wheezing ($OR = 0.86$, $p = 0.0471$). Further, ESR1 SNPs rs1999805 and rs2504063 associated with asthma ($OR = 1.07$, $p = 0.0434$) and chronic sinusitis ($OR = 1.08$, $p = 0.0452$), respectively. All the SNPs are located in the intronic region of the respective gene and the function of these SNPs is currently unknown.

We repeated the PheWAS in an independent cohort of 500,000 subjects in the UK BioBank using self-reported phenotype codes. Of the originally interrogated SNPs, ESR1 SNP rs1999805 was significantly associated with asthma ($p = 0.0365$) with 4,370 cases from 337,159 samples. Since this was self-reported data from questionnaires linked to genotyping data, we conducted a validation study on ESR1 SNP rs1999805 using the Vanderbilt BioVU MEGA Project. The MEGA cohort is a multi-ethnic consortium-built genotyping array with 53,000 subjects that are distinct from our original PheWAS on Illumina HumanExome BeadChip. ESR1 SNP rs1999805 again associated with asthma ($OR = 1.14$, $p = 0.0088$) in the MEGA cohort, demonstrating an association between ESR1 SNP rs1999805 and asthma in a third, independent study.

While a PheWAS offers an inexpensive, efficient insight into the association of disease phenotypes with genetic variants, the model has limitations. A selection bias exists, as genotyping information is available only from patients with blood drawn for laboratory testing. Further, ICD-9 billing codes utilize algorithms to assign code designations and may miss narrative, textual diagnoses in the EHR. This is particularly true in the case of asthma, where the diagnoses are difficult to confirm in the EHR because not every patient will have lung function or methacholine challenge tests performed. Further, patients in BioVU were not classified as intermittent, mild, moderate, or severe asthmatics and asthma medication use is unknown. The study also reports uncorrected P values. A Bonferroni correction may be used to reduce the likelihood of Type I statistical error. However, this study was performed as an exploratory analysis, and therefore, we excluded the use of multiple testing

corrections to reduce our Type II error rate.⁸ Combined, ESR1 SNP rs1999805 was associated with asthma in 3 independent, suggesting that this SNP may be important in asthma pathogenesis.

This is the first study to show that variants in ER- α signaling are associated with asthma in three separate cohorts. Understanding the role of the rs1999805 ESR1 variant in asthma pathogenesis bears important implications for all phases of women's lives, including puberty, child-bearing years, and menopause. Women with peri-menstrual worsening of asthma symptoms have decreased peak flow expiratory volumes and increased asthma symptoms just prior to menses compared to women without peri-menstrual worsening of asthma.^{2, 4} Previous studies have shown that estrogen signaling through ER- α is important in multiple lung cells types, including airway epithelial cells, smooth muscle, macrophages, and T cells. For example, increased ER- α signaling increased IL-4-induced expression of YM-1 and ARG1 in M2 macrophages, and mice lacking ER- α signaling (*esr1*^{-/-} mice) had decreased allergen-induced IgE serum production, eosinophil infiltration into the airways, bronchoalveolar lavage expression of type 2 cytokines (IL-13 and IL-5), and increased airway resistance.^{2, 4, 9, 10}

In conclusion, our findings from this exploratory study provide rationale for additional analysis of the implications of rs1999805 on ER- α signaling in asthma pathogenesis. The rs1999805 is present in a substantial portion of the US population with a minor allele frequency of 43.65%. Future studies using biologic samples from asthmatic women with or without the rs1999805 SNP will provide mechanistic insights on ER- α signaling in asthma pathogenesis.

Funding source:

R01 HL122554 (DCN), R21 AI 121420 (DCN), T32 GM07347 (Vanderbilt University MSTP), F30 AI118376 (MHB), ULTR000445 - Vanderbilt University CTSA

Abbreviations used:

EHR	electronic health record
ER-α	estrogen receptor alpha
GWAS	genome-wide association study
PheWAS	phenome-wide association study
SNPs	single nucleotide polymorphisms
OR	odds ratio
F	female

References

1. Zein JG & Erzurum SC. Asthma is Different in Women. *Curr Allergy Asthma Rep* 15 (2015). pp. 28. [PubMed: 26141573]

2. Fuseini H & Newcomb DC. Mechanisms Driving Gender Differences in Asthma. *Current Allergy and Asthma Reports* 17 (2017). pp. 19. [PubMed: 28332107]
3. Rao CK, Moore CG, Bleecker E et al. Characteristics of perimenstrual asthma and its relation to asthma severity and control: data from the Severe Asthma Research Program. *Chest* 143 (2013). pp. 984–992. [PubMed: 23632943]
4. Yung JA, Fuseini H & Newcomb DC. Hormones, sex, and asthma. *Ann Allergy Asthma Immunol* 120 (2018). pp. 488–494. [PubMed: 29410216]
5. Denny JC, Bastarache L, Ritchie MD et al. Systematic comparison of phenome-wide association study of electronic medical record data and genome-wide association study data. *Nat Biotechnol* 31 (2013). pp. 1102–1110. [PubMed: 24270849]
6. Moffatt MF, Gut IG, Demenais F et al. A large-scale, consortium-based genomewide association study of asthma. *N Engl J Med* 363 (2010). pp. 1211–1221. [PubMed: 20860503]
7. Soler Artigas M, Loth DW, Wain LV et al. Genome-wide association and large-scale follow up identifies 16 new loci influencing lung function. *Nat Genet* 43 (2011). pp. 1082–1090. [PubMed: 21946350]
8. Bloodworth MH, Rusznak M, Bastarache L et al. Association of ST2 polymorphisms with atopy, asthma, and leukemia. *J Allergy Clin Immunol* 142 (2018). pp. 991–993 e993. [PubMed: 29787780]
9. Keselman A, Fang X, White PB & Heller NM. Estrogen Signaling Contributes to Sex Differences in Macrophage Polarization during Asthma. *J Immunol* 199 (2017). pp. 1573–1583. [PubMed: 28760880]
10. Carey MA, Card JW, Bradbury JA et al. Spontaneous airway hyperresponsiveness in estrogen receptor-alpha-deficient mice. *Am.J.Respir.Crit Care Med* 175 (2007). pp. 126–135. [PubMed: 17095746]

Table 1.

Allergic phenotypes associated with polymorphisms in CYP19A and ESR1

Gene	SNP	PheWAS Code	MAF(%)	Cases	% F cases	Controls	OR	p value
CYP19A1	rs2305707	Allergic rhinitis (476)	14.66	2,819	62.5	20,679	0.90	0.0101
		Anaphylactic shock (946)	25.18	97		23,917	0.59	0.0063
	rs2899472	Chronic sinusitis (475)	25.18	1,371	66.2	20,679	0.91	0.0412
		Asthma exacerbation (495.2)	25.18	284		23,634	1.28	0.0079
ESR1	rs543650	Wheezing (512.1)	40.51	403	50.2	21,428	0.86	0.0471
	rs1999805	Asthma (495)	43.65	1,776	63.3	23,634	1.07	0.0434
	rs2504063	Chronic sinusitis (475)	42.34	1,371	56.1	20,679	1.08	0.0452
SNPs not sufficiently powered for PheWAS analysis (<5,500 patients) or no significant associations								
Gene	SNP	Disease that identified SNP	Reason not in PheWAS					
CYP19A1	rs10046	abnormal estradiol levels, breast cancer	<5,500 patients					
	rs4646	breast cancer treatment response	<5,500 patients					
	rs700158	hypertensive disorders of pregnancy	not significant					
	rs700519	breast cancer treatment response	not significant					
	rs936306	breast cancer	<5,500 patients					
	rs1870049	hypertensive disorders of pregnancy, menarche age, breast cancer	<5,500 patients					
ESR1	rs662516	esophagitis, acute upper respiratory infections	<5,500 patients					
	rs2234693	cardiovascular disease, myocardial infarction	<5,500 patients					
	rs9340799	cardiovascular disease, myocardial infarction	<5,500 patients					

abbreviations: F, female; OR, Odds Ratio; MAF, minor allele frequency; PheWAS, phenome-wide association study