ORIGINAL ARTICLE
COPD

SHAREABLE PDF

The pharmacogenomics of inhaled corticosteroids and lung function decline in COPD

Ma'en Obeidat[1], Alen Faiz[2], Xuan Li[1], Maarten van den Berge[2], Nadia N. Hansel[3], Philippe Joubert[4], Ke Hao[5], Corry-Anke Brandsma[2], Nicholas Rafaels[6], Rasika Mathias[7], Ingo Ruczinski[8], Terri H. Beaty[9], Kathleen C. Barnes[6], S.F. Paul Man[1], Peter D. Paré[1] and Don D. Sin[1]

Affiliations: [1]The University of British Columbia Center for Heart Lung Innovation, St Paul's Hospital Vancouver, BC, Canada. [2]University of Groningen, University Medical Center Groningen, Dept of Pulmonology, GRIAC research institute, Groningen, The Netherlands. [3]Pulmonary and Critical Care Medicine, School of Medicine, Johns Hopkins University, Baltimore, MD, USA. [4]Institut Universitaire de Cardiologie et de Pneumologie de Québec, Laval University, Québec, QC, Canada. [5]Dept of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai, New York, NY, USA. [6]Division of Biomedical Informatics and Personalized Medicine, Dept of Medicine, University of Colorado School of Medicine, Aurora, CO, USA. [7]Division of Genetic Epidemiology, School of Medicine, Johns Hopkins University, Baltimore, MD, USA. [8]Dept of Biostatistics, Bloomberg School of Public Health, Johns Hopkins University, Baltimore, MD, USA. [9]Dept of Epidemiology, Bloomberg School of Public Health, Johns Hopkins University, Baltimore, MD, USA.

Correspondence: Ma'en Obeidat, UBC Centre for Heart Lung Innovation, St Paul's Hospital, 1081 Burrard Street, Vancouver, BC V6Z 1Y6, Canada. E-mail: maen.obeidat@hli.ubc.ca

@ERSpublications
Genetic variants are associated with the effect of inhaled corticosteroids on long-term lung function decline in COPD patients. These variants may provide new insight on the potential biology of steroid responsiveness in COPD. http://bit.ly/2Ua7n9F

Cite this article as: Obeidat M, Faiz A, Li X, *et al*. The pharmacogenomics of inhaled corticosteroids and lung function decline in COPD. *Eur Respir J* 2019; 54: 1900521 [https://doi.org/10.1183/13993003.00521-2019].

ABSTRACT Inhaled corticosteroids (ICS) are widely prescribed for patients with chronic obstructive pulmonary disease (COPD), yet have variable outcomes and adverse reactions, which may be genetically determined. The primary aim of the study was to identify the genetic determinants for forced expiratory volume in 1 s (FEV_1) changes related to ICS therapy.

In the Lung Health Study (LHS)-2, 1116 COPD patients were randomised to the ICS triamcinolone acetonide (n=559) or placebo (n=557) with spirometry performed every 6 months for 3 years. We performed a pharmacogenomic genome-wide association study for the genotype-by-ICS treatment effect on 3 years of FEV_1 changes (estimated as slope) in 802 genotyped LHS-2 participants. Replication was performed in 199 COPD patients randomised to the ICS, fluticasone or placebo.

A total of five loci showed genotype-by-ICS interaction at $p<5\times10^{-6}$; of these, single nucleotide polymorphism (SNP) rs111720447 on chromosome 7 was replicated (discovery $p=4.8\times10^{-6}$, replication $p=5.9\times10^{-5}$) with the same direction of interaction effect. ENCODE (Encyclopedia of DNA Elements) data revealed that in glucocorticoid-treated (dexamethasone) A549 alveolar cell line, glucocorticoid receptor binding sites were located near SNP rs111720447. In stratified analyses of LHS-2, genotype at SNP rs111720447 was significantly associated with rate of FEV_1 decline in patients taking ICS (C allele β 56.36 mL·year^{-1}, 95% CI 29.96–82.76 mL·year^{-1}) and in patients who were assigned to placebo,

although the relationship was weaker and in the opposite direction to that in the ICS group (C allele β −27.57 mL·year^{-1}, 95% CI −53.27– −1.87 mL·year^{-1}).

The study uncovered genetic factors associated with FEV1 changes related to ICS in COPD patients, which may provide new insight on the potential biology of steroid responsiveness in COPD.