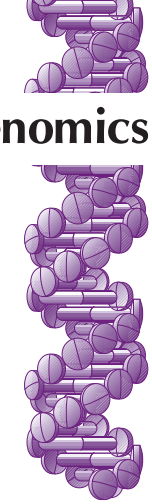
Special Report

For reprint orders, please contact: reprints@futuremedicine.com

Pharmacogenomics



Pharmacogenetics and the treatment of asthma

Heterogeneity defines both the natural history of asthma as well as patient's response to treatment. Pharmacogenomics contribute to understand the genetic basis of drug response and thus to define new therapeutic targets or molecular biomarkers to evaluate treatment effectiveness. This review is initially focused on different genes so far involved in the pharmacological response to asthma treatment. Specific considerations regarding allergic asthma, the pharmacogenetics aspects of polypharmacy and the application of pharmacogenomics in new drugs in asthma will also be addressed. Finally, future perspectives related to epigenetic regulatory elements and the potential impact of systems biology in pharmacogenetics of asthma will be considered.

First draft submitted: 30 January 2017; Accepted for publication: 7 May 2017; Published online: 4 August 2017

Keywords: allergy • asthma • personalized medicine • pharmacogenomics • phenotypes

María Isidoro-García*[1,2,3], Almudena Sánchez-Martín[2,4], Asunción García-Sánchez[2,5], Catalina Sanz[2,6], Belén García-Berrocal[1,2] & Ignacio Dávila[2,5,7]

[1]Department of Clinical Biochemistry, Pharmacogenetics Unit, University Hospital of Salamanca, Salamanca, Spain

[2]Institute for Biomedical Research of Salamanca (IBSAL), Allergy Department, Salamanca, Spain

[3]Department of Medicine, Faculty of Medicine, University of Salamanca, Salamanca, Spain

[4]Department of Pharmacy, Faculty of Medicine, University Hospital of Salamanca, Salamanca, Spain

[5]Department of Biomedical & Diagnostic Sciences, Faculty of Medicine, University of Salamanca, Spain

[6]Department of Microbiology & Genetics, Faculty of Biology, University of Salamanca, Salamanca, Spain

[7]Department of Allergy, Faculty of Medicine, University Hospital of Salamanca, Salmanaca, Spain

*Author for correspondence:
Tel.: +34 923 291 100; ext: 55209
misidoro@usal.es

Heterogeneity characterizes both the natural history of complex diseases as well as patient's response to treatment. The objective of personalized medicine (PM) is to understand the mechanisms underlying this variability in order to find the most adequate treatment for each individual patient. Asthma is a complex disease, caused by the interaction of multiple genetic and environmental factors [1,2]. There is increasing evidence of asthma heterogeneity based on molecular phenotyping, cluster analysis studies and biomarker studies. There are two major reasons that justify the pharmacogenetics research in asthma: there are interindividual differences in response to commonly used asthma medications and there is a subgroup of patients that does not respond to these drugs and, there is also a small subgroup who have shown an increased risk of rare, severe adverse events during long-acting β-agonists (LABA) treatment [3].

Phenotypes reflect the multifaceted interaction between genetic and environmental factors, resulting in different expressions of the disease [4]. In recent years, great efforts have been made to characterize phenotypes in asthma [5], using different omics and molecular phenotype techniques [6]. The phenotypic characterization of asthma has revealed different subgroups of patients who share common clinical-biological features, with the final goal of selecting the best treatment for each patient [7]. However, an appropriate phenotypic classification of patients does not seem sufficient to find the best treatment, therefore other factors such as the genetic background should be taken into account.

Pharmacogenomics contributes to understanding the genetic basis of therapy responsiveness and thus, to defining therapeutic targets or molecular markers; these could be used in the evaluation of the effectiveness of new drugs. Its main objective is to find genetic variations that could affect drug responsiveness, increasing efficacy and safety of treatments [8,9]. Currently, there are different methods for studying

Future Medicine part of fsg

70 McDonnell AM, Dang CH. Basic review of the cytochrome p450 system. *J. Adv. Pract. Oncol.* 4(4), 263–268 (2013).

71 Isidoro-García M, Sánchez-Martín A, García-Berrocal B, Román-Curto C. Primun non nocere, polypharmacy and pharmacogenetics. *Pharmacogenomics* 16(17), 1903–1905 (2015).

72 Isidoro-Garcia M, Sanchez-Martin A, Garcia-Berrocal B. impact of new technologies on pharmacogenomics. *Curr. Pharmacogenomics Pers. Med.* 14(2), 74–85 (2016).

73 Meyers DA, Bleecker ER, Holloway JW, Holgate ST. Asthma genetics and personalised medicine. *Lancet Respir. Med.* 2(5), 405–415 (2014).

74 Ortega VE, Meyers DA. Pharmacogenetics: implications of race and ethnicity on defining genetic profiles for personalized medicine. *J. Allergy Clin. Immunol.* 133(1), 16–26 (2014).

75 Tabatabaian F, Ledford DK, Casale TB. Biologic and new therapies in asthma. *Immunol. Allergy Clin. North Am.* 37(2), 329–343 (2017).

76 Pascual M, Roa S, García-Sánchez A *et al.* Genome-wide expression profiling of B lymphocytes reveals IL4R increase in allergic asthma. *J. Allergy Clin. Immunol.* 134(4), 972–975 (2014).

77 Slager RE, Otulana BA, Hawkins GA *et al.* IL-4 receptor polymorphisms predict reduction in asthma exacerbations during response to an anti-IL-4 receptor α antagonist. *J. Allergy Clin. Immunol.* 130(2), 516–522.e4 (2012).

78 Wenzel S, Ford L, Pearlman D *et al.* Dupilumab in persistent asthma with elevated eosinophil levels. *N. Engl. J. Med.* 368(26), 2455–2466 (2013).

79 Wenzel S, Castro M, Corren J *et al.* Dupilumab efficacy and safety in adults with uncontrolled persistent asthma despite use of medium-to-high-dose inhaled corticosteroids plus a long-acting β2 agonist: a randomised double-blind placebo-controlled pivotal Phase 2b dose-ranging trial. *Lancet Lond. Engl.* 388(10039), 31–44 (2016).

80 Isidoro-García M, Dávila-González I, Pascual de Pedro M, Sanz-Lozano C, Lorente-Toledano F. Interactions between genes and the environment. Epigenetics in allergy. *Allergol. Immunopathol. (Madr.).* 35(6), 254–258 (2007).

81 Pascual M, Suzuki M, Isidoro-Garcia M *et al.* Epigenetic changes in B lymphocytes associated with house dust mite allergic asthma. *Epigenetics* 6(9), 1131–1137 (2011).

82 Booton R, Lindsay MA. Emerging role of MicroRNAs and long noncoding RNAs in respiratory disease. *Chest* 146(1), 193–204 (2014).

83 Elbehidy RM, Youssef DM, El-Shal AS *et al.* MicroRNA-21 as a novel biomarker in diagnosis and response to therapy in asthmatic children. *Mol. Immunol.* 71, 107–114 (2016).

84 Dahlin A, Tantisira KG. Integrative systems biology approaches in asthma pharmacogenomics. *Pharmacogenomics* 13(12), 1387–1404 (2012).

85 Park H-W, Tantisira KG, Weiss ST. Pharmacogenomics in asthma therapy: where are we and where do we go? *Annu. Rev. Pharmacol. Toxicol.* 55, 129–147 (2015).

86 Bunyavanich S, Schadt EE. Systems biology of asthma and allergic diseases: a multiscale approach. *J. Allergy Clin. Immunol.* 135(1), 31–42 (2015).

87 Sanchez-Martín A, García-Sánchez A, Isidoro-García M. Review on pharmacogenetic and pharmacogenomics applied to the study of asthma. *Methods Mol. Biol.* 1434, 255–272 (2016).