A genome-wide association study of severe asthma exacerbations in Latino children and adolescents

Qi Yan1,16, Erick Forno1,16, Esther Herrera-Luis2,16, Maria Pino-Yanes2,3, Cancan Qi4,5, Raimon Rios6, Yueh-Ying Han6, Soyeon Kim7, Sam Oh7, Edna Acosta-Pérez8, Rong Zhang1, Donglei Hu7, Celeste Eng7, Scott Huntsman7, Lydiana Avila9, Nadia Boutaoui1, Michelle M. Cloutier10, Manuel E. Soto-Quiros9, Cheng-Jian Xu11,12, Scott T. Weiss13, Jessica Lasky-Su13, Megan R. Kiedrowski14, Camila Figueiredo6, Jennifer Bomberger14, Mauricio L. Barreto15, Gloria Canino8, Wei Chen1, Gerard H. Koppelman4,5, Esteban G. Burchard7,17 and Juan C. Celedón1,17

Affiliations: 1Division of Pediatric Pulmonary Medicine, University of Pittsburgh Medical Centre, Children’s Hospital of Pittsburgh, University of Pittsburgh, Pittsburgh, PA, USA. 2Genomics and Health Group, Dept of Biochemistry, Microbiology, Cell Biology and Genetics, Universidad de La Laguna, La Laguna, Spain. 3CIBER de Enfermedades Respiratorias, Instituto de Salud Carlos III, Madrid, Spain. 4Dept of Pediatric Pulmonology and Pediatric Allergy, Beatrix Children’s Hospital, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands. 5GRIAC Research Institute, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands. 6Instituto de Ciências da Saúde, Universidade Federal da Bahia, Salvador, Brazil. 7Dept of Medicine, University of California San Francisco, San Francisco, CA, USA. 8Behavioral Sciences Research Institute, University of Puerto Rico, San Juan, Puerto Rico. 9Dept of Pediatrics, Hospital Nacional de Niños, San José, Costa Rica. 10Dept of Pediatrics, University of Connecticut, Farmington, CT, USA. 11CiIM and TWINCORE, joint ventures between the Hannover Medical School and the Helmholtz Centre for Infection Research, Hannover, Germany. 12Dept of Internal Medicine and Radboud Center for Infectious Diseases, Radboud University Medical Center, Nijmegen, The Netherlands. 13Channing Division of Network Medicine, Brigham and Women’s Hospital, Harvard Medical School, Boston, MA, USA. 14Dept of Microbiology and Molecular Genetics, University of Pittsburgh, Pittsburgh, PA, USA. 15Instituto de Saúde Coletiva, Federal University of Bahia, Salvador, Brazil. 16Shared first authors. 17Shared senior authors.

Correspondence: Juan C. Celedón, Division of Pulmonary Medicine, UPMC Children’s Hospital of Pittsburgh, 4401 Penn Avenue, Pittsburgh, PA 15224, USA. E-mail: juan.celedon@chp.edu

ABSTRACT Severe asthma exacerbations are a major cause of school absences and healthcare costs in children, particularly those in high-risk racial/ethnic groups.

To identify susceptibility genes for severe asthma exacerbations in Latino children and adolescents, we conducted a meta-analysis of genome-wide association studies (GWAS) in 4010 Latino youth with asthma in four independent cohorts, including 1693 Puerto Ricans, 1019 Costa Ricans, 640 Mexicans, 256 Brazilians and 402 members of other Latino subgroups. We then conducted methylation quantitative trait locus, expression quantitative trait locus and expression quantitative trait methylation analyses to


This single-page version can be shared freely online.
assess whether the top single nucleotide polymorphism (SNP) in the meta-analysis is linked to DNA methylation and gene expression in nasal (airway) epithelium in separate cohorts of Puerto Rican and Dutch children and adolescents.

In the meta-analysis of GWAS, an SNP in *FLJ22447* (rs2253681) was significantly associated with 1.55 increased odds of severe asthma exacerbation (95% CI 1.34–1.79, \( p=6.3\times10^{-9} \)). This SNP was significantly associated with DNA methylation of a CpG site (cg25024579) at the *FLJ22447* locus, which was in turn associated with increased expression of *KCNJ2-AS1* in nasal airway epithelium from Puerto Rican children and adolescents (\( \beta=0.10, p=2.18\times10^{-7} \)).

SNP rs2253681 was significantly associated with both DNA methylation of a cis-CpG in *FLJ22447* and severe asthma exacerbations in Latino youth. This may be partly explained by changes in airway epithelial expression of a gene recently implicated in atopic asthma in Puerto Rican children and adolescents (*KCNJ2-AS1*).