**17q21 gene variance and the risk of exacerbations in asthmatic children treated with inhaled corticosteroids: a meta-analysis in the PiCA consortium**

Farzan N 1,2, Vijverberg SJ1,2, Burchard EG3, Canino G4, Celedón JC5, Cloutier MM6, Forno E5, Hawcutt DB7,8, Kabesch M9,10, Karimi L11, Melén E12,13, Mukhopadhyay S14,15, Nilsson S12,13, Palmer CN15, Pino-Yanes M16,17, Pirmohamed M18, Potočnik U19,20, Raaijmakers JA1, Repnik K19,20, Schieck M9,10, Smyth RL21, Soares P14, Tantisira KG22,23, Turner S24, Verhamme KM11, Maitland-van der Zee AH1,2

*1Division of Pharmacoepidemiology and Clinical Pharmacology, Faculty of Science, Utrecht University, Utrecht, Netherlands, 2**Department of Respiratory Medicine, Academic Medical Center (AMC). University of Amsterdam, Amsterdam, theNetherlands, 3Departments of Medicine, Bioengineering and Therapeutic Sciences University of California, San Francisco, USA, 4Behavioral Sciences institute, University of Puerto Rico, Medical Sciences Campus, San Juan, Puerto Rico, 5Division of Pulmonary Medicine, Allergy, and Immunology, Children’s Hospital of Pittsburgh of the University of Pittsburgh Medical Center, University of Pittsburgh, Pittsburgh, Pennsylvania, 6University of Connecticut Health Center, Asthma Center, Connecticut Children's Medical Center, Connecticut, United States of America,* *7Department of Women's and Children's Health, University of Liverpool, Liverpool, UK, 8Alder Hey Children's Hospital, Liverpool, UK, 9Dept. of Pediatric Pneumology and Allergy, University Children's Hospital Regensburg (KUNO), Regensburg, Germany, 10Dept. of Pediatric Pneumology, Allergy and Neonatology, Hannover Medical School, Hannover, Germany.* *Member of the German Lung Research Center (DZL),11Dept. of Medical Informatics, Erasmus University Medical Center, Rotterdam, the Netherlands. 12Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden, 13Centre of Occupational and Environmental Medicine, Stockholm County Council, Stockholm, Sweden, 14Academic Department of Paediatrics, Brighton and Sussex Medical School, Royal Alexandra Children's Hospital, Brighton, United Kingdom, 15Population Pharmacogenetics Group, Biomedical Research Institute, Ninewells Hospital and Medical School, University of Dundee, Dundee, United Kingdom, 16CIBER de Enfermedades Respiratorias, Instituto de Salud Carlos III, Madrid, Spain, 17Research Unit, Hospital Universitario N.S. de Candelaria, Santa Cruz de Tenerife, Spain*, *18Department of Molecular and Clinical Pharmacology, Institute of Translational Medicine, University of Liverpool, Liverpool, United Kingdom, 19Centre for Human Molecular Genetics and Pharmacogenomics, Faculty of Medicine, University of Maribor, Maribor, Slovenia, 20Faculty for Chemistry and Chemical Engineering, University of Maribor, Maribor, Slovenia, 21Institute of Child Health, University College London, London, United Kingdom, 22The Channing Division of Network Medicine, Dept. of Medicine, Brigham and Women’s hospital and Harvard Medical School, Boston, United States of America, 23Division of Pulmonary and Critical Care Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, United States of America, 24Child Health, University of Aberdeen, Aberdeen, United Kingdom.*

**Abstract**

Background:17q21 gene variants are the strongest known genetic determinants for early onset childhood asthma, but have also been associated with uncontrolled asthma despite asthma treatment.

Aim: To assess the association between a variant in the 17q21 locus (rs7216389) and asthma exacerbations despite the use of inhaled corticosteroids (ICS) in asthmatic children and young adults.

Methods: We meta-analyzed the association between the 17q21 locus (rs7216389) and exacerbations in 4,156 children and young adults with reported ICS use in twelve studies participating in the global Pharmacogenomics of Childhood Asthma (PiCA) consortium. The following studies were included: BAMSE (n=122, Sweden), BREATHE (n=806, Scotland, UK), CAMP (n=172, USA), eSTATE (n=102, the Netherlands), GALA II (n=745, USA), HPR (n=123, USA), MAGICS (n=155, Germany), PACMAN (n= 530, the Netherlands), PAGES (n=354, Scotland, UK), PASS (n=390, UK), SAGE II (n=468, USA) and SLOVENIA (n=199, Slovenia). Two outcome measures were studied: hospitalization/emergency room (ER) visits (available in 12 studies, n= 4,156 patients) and oral corticosteroid (OCS) use (available in 9 studies, n=3,512 patients) in the last 6 or 12 months of the study or first year of the trial. Meta-analyses with random effects were performed using an additive genetic model adjusted for age, gender and British Thoracic Society (BTS) treatment steps.

Results: The variant in the 17q21 locus was statistically significantly associated with an increased risk of OCS use (OR per increase in variant allele= 1.19, 95%CI: 1.02-1.39, p=0.03) (fig 1). The SNP was not statistically significantly associated hospitalization / ER visits, even though the summary effect estimate pointed in the same direction (OR per increase in variant allele= 1.17, 95%CI: 0.96- 1.42).

Conclusion: The findings suggest that variation in the 17q21 locus contributes to a higher risk of exacerbations despite the use of ICS in children and young adults.

|  |
| --- |
| final_OCS_analysis |
| Figure 1. Forest Plot of rs7216389 for OCS use in all studies. Odds Ratios (OR) and corresponding 95% Confidence Intervals (95% CI) for individuals with rs7216389, controlling for age, sex and BTS treatment step.  |