

Shrine, Nick, Soler-Artigas, Maria, Portelli, Michael, Bennett, Neil D., Ntalla, Ioanna, Henry, Amanda, Billington, Charlotte K., Shaw, Dominic, Pogson, Zara E.K., Fogarty, Andrew, McKeever, Tricia, Jonker, Leon, Singapuri, Amisha, Heaney, Liam, Mansur, Adel, Chaudhuri, Rekha, Thomson, Neil, Holloway, John, Lockett, Gabrielle, Howarth, Peter, Djukanovic, Ratko, Hankinson, Jenny, Niven, Richard, Simpson, Angela, Chung, Kian, Sterk, Peter, Blakey, John, Adcock, Ian, Tobin, Martin, Hall, Ian, Brightling, Chris E., Wain, Louise and Sayers, Ian (2017) A genome wide association study of moderate-severe asthma in subjects from the United Kingdom. *European Respiratory Journal*, 50 (S61). PA1815.

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# **A Genome Wide Association Study of Moderate-Severe Asthma in subjects from the United Kingdom**

Nick Shrine, Maria Soler-Artigas, Michael Portelli, Neil Bennett, Ioanna Ntalla, Amanda Henry, Charlotte Billington, Dominic Shaw, Zara Pogson, Andrew Fogerty, Trish McKeever, Leon Jonker, Amisha Singapuri, Liam Heaney, Adel Mansur, Rekha Chaudhuri, Neil Thomson, John Holloway, Gabrielle Lockett, Peter Howarth, Ratko Djukanovic, Jenny Hankinson, Richard Niven, Angela Simpson, Kian Chung, Peter Sterk, John Blakey, Ian Adcock, Martin Tobin, Ian Hall, Chris Brightling, Louise Wain, Ian Sayers

European Respiratory Journal, 2017, vol. 50, issue suppl 61, DOI: 10.1183/1393003.congress-2017.PA1815. ERS International Congress 2017 abstracts.

## **Abstract**

**Rationale:** Genome wide association studies (GWAS) in asthma have been successful in identifying disease susceptibility genes, however to date these have focused on mild disease. The genetic risk factors for moderate-severe asthma remain unclear.

**Aim:** To identify common genetic variants affecting susceptibility to develop moderate-severe asthma.

**Methods:** We identified asthma cases and controls from UK Biobank and additional cases from the Genetics of Asthma Severity & Phenotypes (GASP) cohort. A genome-wide association study was undertaken in 5,135 European ancestry individuals with moderate-severe asthma based on British Thoracic Society criteria 3 or above and 25,675 controls free from lung disease, allergic rhinitis and atopic dermatitis. After imputation (UK10K + 1000 genomes Phase 3) and standard quality control measures, the association of 33,771,858 single nucleotide polymorphisms (SNPs) were tested. A logistic model of association of asthma status with imputed genotype dose was fitted using SNPTTEST adjusted for ancestry principal components.

**Results:** We identified 22 loci showing association ( $P < 5 \times 10^{-8}$ ) including novel signals in or near D2HGDH, STAT6, HLA-B, CD247, GATA3, PDCD1LG2, ZNF652, RPAP3, MUC5AC and BACH2. Previously described asthma loci where replicated including signals in or near HLA-DQB1, TSLP, IL1RL1/IL18R1, CLEC16A, GATA3, IL33, SMAD3, SLC22A5/IL13, C11orf30, ZBTB10, IKZF3-ORMDL3 and IKZF4.

**Conclusion:** The largest genome-wide association study of moderate-severe asthma to date was carried out and multiple novel loci were identified. These findings may provide new insight into the molecular mechanisms underlying this difficult to treat population.