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


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 SNPTEST adjusted for ancestry principal components.

Results: We identified 22 loci showing association (P < 5 × 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 where identified. These findings may provide new insight into the molecular mechanisms underlying this difficult to treat population.