Fine mapping of lung function association in the MHC region by haplotype imputation reveals an amino acid change underlying SNP associations

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We performed a Genome-wide association study (GWAS) of lung function quantitative traits forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC) and their ratio (FEV_1/FVC) in 48,493 samples of European Ancestry (UK BiLEVE study) which, in addition to confirming 4 previously identified lung function signals in the major histocompatibility complex (MHC) on chromosome 6, identified 2 new secondary independent signals.

In order to fine map the MHC GWAS signals, we used a published reference panel to impute HLA classical alleles and amino acid changes and tested their association with lung function traits. The new second most significant signal across the MHC region for both FEV_1 ($P=5.7\times10^{-13}$) and FEV_1/FVC ($P=1.2\times10^{-20}$) was an association with *HLA-DQB1* amino acid 57 Alanine present/absent (Alanine frequency=36.6%). After conditioning on the amino acid variant, 1 of 2 genome-wide significant ($P<5\times10^{-8}$) GWAS signals for FEV_1 and 5 of 6 for FEV_1/FVC were strongly attenuated (minimum $P=2.1\times10^{-5}$). Stepwise conditional analyses showed that the majority of the MHC lung function association signal could be explained by just the lead independent GWAS SNP and the amino acid change for both traits.

Using haplotype imputation allowed us to build upon lung function GWAS discovery to pinpoint a potential causal variant in the MHC (*HLA-DQB1* amino acid change 57, previously linked to type 1 diabetes risk) that explains a substantial proportion of the variance previously attributed to GWAS SNPs in this region.