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Determining The Contribution Of IL33 And IL1RL1 Polymorphisms To Clinical And Immunological Features Of Asthma

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Rationale: *IL33* (9p24.1) and the *IL33* receptor (*IL1RL1*, 2q12) have been reproducibly identified as asthma susceptibility genes. However, the variants driving genetic associations are not yet fully defined. Using a population based birth cohort of 1059 children (Manchester Asthma and Allergy Study-(MAAS)) and 2536 adults with asthma (Genetics of Asthma Severity and Phenotypes - (GASP)) cohort we aimed to define genetic variants associated with clinical and immunological features of asthma.

Methods: MAAS samples were genotyped using the Illumina 610 Quad array and imputed using 1000G reference panel. GASP samples were genotyped using two custom designed Affymetrix arrays (UK BiLEVE/UK Biobank array). Datasets were quality controlled for gender mismatches, outliers and relatedness. Data was generated for the *IL33/IL1RL1* regions consisting of the genes and surrounding regions (chr9:5715785–6757983 & chr2:102427961–103468497) on the following traits: asthma diagnosis (MAAS), atopy, FEV₁ (GASP) and FEV₁/FVC (MAAS and GASP) as well as total blood eosinophil counts and serum total IgE levels (GASP). Variables for blood eosinophils and total IgE were log10 transformed. Analysis was carried out in PLINK using linear or logistic regression modelling including appropriate covariates for each trait.

Results: In the MAAS cohort, we replicated the association of the *IL33* locus with asthma diagnosis, identifying potentially two independent novel signals in that locus (rs10975398; $P=1.70E-05$; $B=-1.519$; $MAF=0.32$ and rs2890697; $P=1.10E-04$; $B=-1.573$; $MAF=0.43$). This association survived a Bonferroni correction for multiple testing. Although not surviving correction, an association was also identified for atopy in the *IL1RL1* locus for MAAS ($P=1.08E-04$; $MAF=0.48$). In GASP we identified modest associations not in known LD with published loci (P -value range: $5.00E-02$ – $7.60E-04$) for FEV₁, FEV₁/FVC, atopy, blood eosinophils and total IgE in both the *IL33* and *IL1RL1* loci.

Multiple SNPs presented nominal association ($P<0.01$) with more than one trait such as atopy & total IgE, providing supporting evidence for association.

Conclusion: We replicated the association of *IL33* region SNPs with asthma diagnosis in MAAS, highlighting the role of this locus in childhood asthma. Although trait association signals did not survive correction for multiple testing, nominal association across multiple phenotypes in GASP provides suggestive evidence of the role of the *IL33/IL1RL1* genetic polymorphisms in determining clinical and immunological features of asthma.

*Drs Bennett, Hankinson and Portelli contributed equally to this study

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