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Title: Associations and interactions of genetic polymorphisms in innate immunity genes with early viral infections and susceptibility to asthma and asthma-related phenotypes

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Body: Background: The innate immune system is essential for host survival because it recognizes invading pathogens and mounts defensive responses. Objectives: Identify genetic associations of innate immunity genes and interactions with early viral infections (first 12 months of life) and asthma phenotypes in a high risk birth cohort Methods: Three Canadian family-based studies and one Australian population-based case control study (n=5565) were used to investigate associations of 321 single nucleotide polymorphisms (SNPs) in 26 innate immunity genes with: atopy, asthma, atopic asthma and airway hyper-responsiveness (AHR). Interactions between innate immunity genes and early viral exposure to three common viruses (parainfluenza, respiratory syncytial virus and picornavirus) were examined in the Canadian Asthma Primary Prevention Study using both family-based transmission disequilibrium test and case-control methods. Results: IL1R2 and TLR1 SNPs were associated with atopy after correction for multiple comparisons. There is significant evidence that SNP*virus interactions with these same SNPs modifies the risk for atopic asthma

and AHR in a high risk birth cohort. In addition, an NFKBIA SNP was associated with atopic asthma. All three viruses demonstrated a skew in the distribution of SNP*viral interactions (based on QQ plots) for AHR at 7 years of age. RSV was associated with an increased number of SNP*viral interactions for atopy and atopic asthma at 7 years of age. Conclusion: We have identified novel susceptibility genes for asthma and related traits and interactions between these genes and early life viral infections.