Investigation of genome-wide gene-by-sex interactions on time-to-asthma onset

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Abstract

Asthma is a complex disease with sex-specific differences in prevalence, clinical and biological features. Asthma is more prevalent in males during childhood, while it becomes more frequent in females in adolescence and adulthood. The mechanisms behind these sex-specific differences are not well understood and may involve hormonal changes together with differential genetic predisposition. To identify genetic variants interacting with sex that influence time-to-asthma onset (TAO), we conducted a large-scale meta-analysis of nine gene-environment-wide interaction studies (GEWIS) of TAO (totaling 7,104 men and 6,970 females of European ancestry) by using survival techniques applied to pediatric and adult asthmatic and non-asthmatic subjects. We detected three independent loci showing SNP×Sex interaction at the 10⁻⁵ level. The most significant association with TAO was female-specific in an intergenic region at 5q32 ($P_{\text{female}} = 9.1 \times 10^{-8}$ versus $P_{\text{male}} = 0.56$ for rs6872558). The other two associations were male-specific: within SORCS2 intron 2 at 4q16 ($P_{\text{male}} = 1.3 \times 10^{-7}$ versus $P_{\text{female}} = 0.15$ for rs10005462) and within DGKB intron 1 at 7p21 ($P_{\text{male}} = 3.9 \times 10^{-7}$ versus $P_{\text{female}} = 0.23$ for rs2189717). None of these loci had been previously associated with asthma phenotypes. Functional annotations indicated co-localization of these genetic variants with epigenetic marks and DNA regulatory elements in fibroblasts, lung or blood. By testing gene-by-sex interactions, we identified novel loci influencing asthma risk in a sex-specific manner. Candidate genes in these loci are involved in inflammatory process and immune cell regulation. Further replication of these findings are ongoing.