Influence of gene-by-sex interaction on time-to-asthma onset: a large-scale genome-wide meta-analysis


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Background: 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.

Objective: Our goal was to identify genetic variants interacting with sex that influence time-to-asthma onset (TAO).

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**Methods:** We conducted a large-scale meta-analysis of nine genome-wide interaction studies (GEWIS) of TAO (totaling 7,104 men and 6,970 females of European ancestry) using survival analysis methods applied to pediatric and adult asthmatic and non-asthmatic subjects.

**Results:** 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 ($P_{\text{female}} = 9.1\times10^{-8}$ versus $P_{\text{male}} = 0.56$). The other two associations were male-specific: within SORCS2 intron 2 at 4q16 ($P_{\text{male}} = 1.3\times10^{-7}$ versus $P_{\text{female}} = 0.15$) and within DGKB intron 1 at 7p21 ($P_{\text{male}} = 3.9\times10^{-7}$ versus $P_{\text{female}} = 0.23$). Functional annotations indicated co-localization of these genetic variants with epigenetic marks and DNA regulatory elements in fibroblasts, lung or blood.

**Conclusion:** 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.