A large-scale genome-wide meta-analysis of gene-by-sex interactions on time-to-asthma onset identified sex-specific risk loci

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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 eight independent loci showing SNP×Sex interaction at the 10⁻⁵ level. Among these loci, three were sex-specific TAO risk loci. The most significant association with TAO was female-specific in an intergenic region at 5q32 ($P_{\text{female}} = 9.1 \times 10^{-8}$ versus $P_{\text{male}} = 0.56$). The other two associations were male-specific: within SORCS2 intron 2 at 4q16 ($P_{\text{male}} = 1.3 \times 10^{-7}$ versus $P_{\text{female}} = 0.15$) and within DGKB intron 1 at 7p21 ($P_{\text{male}} = 3.9 \times 10^{-7}$ versus $P_{\text{female}} = 0.23$). The remaining five loci showed effects in opposite directions between males and females: 1p12 (within GDAP2, $P_{\text{male}} = 7.3 \times 10^{-4}$ versus $P_{\text{female}} = 4.6 \times 10^{-3}$), 2q32 (near NCKAP1, $P_{\text{male}} = 3.7 \times 10^{-3}$ versus $P_{\text{female}} = 3.7 \times 10^{-4}$), 3q26 (within NLGN1, $P_{\text{male}} = 7.3 \times 10^{-4}$ versus $P_{\text{female}} = 5.8 \times 10^{-5}$), 4p14 (in an intergenic region between PCDH7 and ARAP2, $P_{\text{male}} = 6.2 \times 10^{-3}$ versus $P_{\text{female}} = 4.9 \times 10^{-5}$) and 7q34 (within TBXASI, $P_{\text{male}} = 3.4 \times 10^{-4}$ versus $P_{\text{female}} = 4.9 \times 10^{-3}$).

None of these loci had been previously associated with asthma phenotypes. Functional annotations indicated colocalization of these genetic variants with 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. Most of the candidate genes in these loci are
involved in inflammatory process and immune cell regulation. Further replication of these findings are ongoing.