Interaction of genetic variants with secondhand smoke exposure in early life on time-to-asthma onset

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Asthma is a complex and heterogeneous disease that results from many genetic and environmental factors, in which age-of-onset plays an important role. Secondhand smoke exposure in early life (ETS) is a known risk factor for both childhood-onset and late-onset asthma. To identify genetic variants interacting with ETS exposure on asthma occurrence, we conducted a meta-analysis of five genome-wide interaction studies (GEWIS) of time-to-asthma onset (TAO) including both asthmatics and non-asthmatics (totaling 3,643 exposed (ETS⁺) and 5,275 non-exposed (ETS⁻) subjects of European ancestry) by using survival analysis techniques. Following a previous genome-wide analysis which examined the effect of individual SNPs in presence of interaction with ETS, the current study focused on the SNPxETS interaction test which allows detecting SNPs with a small (or no) marginal effect interacting with ETS. A pathway analysis based on the gene-set enrichment analysis (GSEA) approach, using the Gene Ontology (GO) database, was then applied to the GEWIS outcomes. We detected 33 SNPs belonging to 11 independent loci showing suggestive SNP×ETS interaction (P<10⁻⁵). The most significant interaction signals belonged to three loci: 13q21 (KLHL1, P=9.8×10⁻⁷), 16p13 (intergenic region, P=6.7×10⁻⁷) and 19q13 (ZNF761, P=10⁻⁶). Twelve GO categories were enriched in genes interacting with ETS on TAO (FDR≤5%); the most significant GOs (FDR<1%) were related to defense response to bacteria, oxidative stress and lipid metabolism. Further analysis investigating enrichment of loci interacting with ETS in cis-regulatory elements and co-localization with loci detected by epigenome-wide analysis of ETS in early life is underway.

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