[BIOINFO 2025]

Transcriptome- and Proteome-wide Association Studies to Identify Potential Causal Mechanisms of Asthma

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Asthma is one of the most representative chronic inflammatory diseases of the respiratory tract, characterized by inflammation and narrowing of the airways. Millions of people worldwide suffer from asthma, with approximately 420,000 deaths reported annually from the disease itself or its complications. Despite the strong genetic background of asthma, previous studies have only attempted to find genetic associations, and the underlying causal mechanisms are still not fully revealed. To address this unmet need, we re-prioritized candidate genes for asthma through a transcriptome-wide association study (TWAS) and a proteome-wide association study (PWAS). This was achieved by incorporating genome-wide association statistics with molecular quantitative trait loci (molQTL) panels for blood tissue at both the transcriptome and proteome levels. We then validated 111 genes from TWAS and 18 genes from PWAS through colocalization analysis, identifying 47 and 11 genes at the transcriptome and proteome levels, respectively. Interestingly, Toll-like receptor 1 (TLR1) was significantly associated in both TWAS and PWAS, but with the opposite directionality. Its causality was further validated with Mendelian randomization tests. We then analyzed the biological validity by propagating the gene-wise weights across a multi-layered network representing the transcriptome and proteome level spaces, identifying an enriched functional cluster at an integrative level. This is the first study to simultaneously test the effects of genetic variants of asthma at the multi-omics level. We believe that our results are highly valuable for unraveling the causal mechanisms of asthma genetics.