

# Network Analysis of Genome-Wide Association Studies for Chronic Obstructive Pulmonary Disease in the Context of Biological Pathways

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## Network Analysis of Genome-Wide Association Studies for Chronic Obstructive Pulmonary Disease in the Context of Biological Pathways

To the Editor:

Chronic obstructive pulmonary disease (COPD) is a common respiratory disease projected to be the third leading cause of death by 2020 (1). The main risk factor is tobacco smoking, but other

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environmental exposures may also contribute (1). Furthermore, host factors including genetic abnormalities, abnormal lung development, and accelerated aging increase susceptibility to COPD (1). However, the causal mechanisms remain poorly understood (2).

As a result of genome-wide association studies, many interesting genetic variations, including SNPs, have been discovered. However, the interpretation of these large amounts of data within the context of biological systems, disease processes, and unknown gene functions remains difficult. Considering genes in a biological context may aid in the elucidation of SNP function. Network analysis provides a way of deciphering the biological relationships among SNPs, genes, and pathways by providing a framework that allows for the integration, analysis, and display of these complex data (3).

We used data from a recent meta-analysis to identify and extract all genetic variants published in pooled and meta-analysis studies related COPD risk (Prospero CRD4201705; May 2018). We extracted the 181 significant genetic variants (regardless of linkage disequilibrium) mapped to 99 genes that included 176 SNPs with reference SNP cluster identifier (rs) and other variants such as multiple SNP combinations, insertions and deletions, or length polymorphisms.

Genes and variants were represented in a SNP–gene network using Cytoscape version 3.6. Second, the genes were used to retrieve the biological pathways from WikiPathways Human curated collection (10 July 2018). Genes present in one or more pathways were displayed in a Cytoscape gene–pathway network. The SNP–gene and gene–pathway networks were then consolidated by merging them. This yielded a SNP–gene–pathway network that was used as a basic reference for the biological interpretation of the connected elements. Finally, genes were classified according to their function and potential effect, using the variant effect predictor analysis in Ensembl (4).

Our analysis produced four different visualizations. In Table 1, an overview of the main characteristics of the networks is reported. In each network title, the digital object identifier to the Network Data Exchange visualization is provided and the main features of the networks and nodes codes are reported, all of which are fully downloadable and interactive.

The networks consist of 181 variant nodes, 99 gene nodes, and 315 pathway nodes, and 735 connections between them. Of the original set of 99 genes, 74 genes are present in pathways from the curated WikiPathways collection. The basic version, Gene–pathway network, highlights the three elements: SNPs, genes, and pathways in different colors.

The Functional gene map visualization presents functional classes in the network. Here we show 13 nonoverlapping functional classes: Addiction, Cellular interaction, Cellular metabolism, Cellular structure, Detoxification, Development, Homeostasis organismal, Inflammation, Lung function, Metabolism organismal, Regulation, Tissue remodeling, and Unknown. Interestingly, some of the gene functional classes are dispersed, whereas in others all are connected. Cellular metabolism (forest green) shows dispersion: 15 genes are not connected in the major central network, and 7 of the 15 do not present any pathway connections. Comparatively, all five genes related to Detoxification cluster in a specific area (refer to online visualization, pink-nodes). Similarly, all 15 genes involved in Inflammation are intensely connected to genes and other pathways and are grouped in the



contains 149 modifiers (or noncoding variants) and 19 moderate (or missense) and two low-impact (or synonymous) SNPs. Polyphen (5) and Sorting Intolerant From Tolerant (6) prediction scores, presented in the network table as attributes, were also consulted to elucidate the deleteriousness of the 19 missense variants. The Polyphen resulted in five probably damaging (rs141159367, rs1051740, rs10499052, rs146043252, and rs28929474) and two possibly damaging (rs1048943 and rs181206) SNPs. Sorting Intolerant from Tolerant indicated that only three (rs1051740, rs10499052, and rs146043252) of the seven SNPs identified by Polyphen are predicted to be deleterious. Because of this discrepancy, we considered the more extensive list. In Figure 1, a SNP-gene-pathway subnetwork is presented, highlighting only the connections related to the seven genes carrying the deleterious missense SNPs.

The variant effect predictor analysis showed that the vast majority of the SNPs associated with COPD are modifiers. Nineteen of the 181 variants were missense SNPs mutations. Of these, seven SNPs (rs10499052, rs28929474, rs181206, rs1048943, rs1051740, rs141159367, and rs146043252) showed alterations predicted to be deleterious in the associated proteins for SLC22A11 (solute carrier family 22 member 11), AK9 (adenylate kinase 9), SERPINA1 (serpin family A member 1), IL27, CYP1A1 (cytochrome P450 family 1 subfamily A member), EPHX1 (epoxide hydrolase 1), and TESMIN (testis-expressed metallothionein-like protein), respectively. Figure 1 displays the interactions of those seven genes with the missense SNPs and pathways. Interestingly, all but two of the deleterious alterations, located in AK9 and TESMIN, are in genes that are either directly or indirectly involved in inflammatory pathways. The AK9 gene mutation is involved in cellular metabolic processes and in extrapulmonary tissues (7), whereas TESMIN is involved in heavy metal ion binding and sequestering.

IL27 and SERPINA1 encode proteins directly involved in inflammation. The leucine to proline substitution caused by rs181206 (IL27) was predicted to be possibly damaging by Polyphen, indicating a strong change in protein structure. Proline is known to have an exceptional conformational rigidity, often causing structural changes. SERPINA1 mutations account for around 2% of all COPD cases (8); however, the PiMZ variant associated with this gene was only observed in crude estimates and disappeared after adjusting for smoking (9). Two deleterious SNPs, rs1048943 and rs1051740, associated with CYP1A1 and EPHX1, are involved in detoxification pathways and, under some circumstances, may be directly linked, as in benzo(a)pyrene-metabolism (WikiPathways identifier: WP696). ■

**Author disclosures** are available with the text of this letter at [www.atsjournals.org](http://www.atsjournals.org).

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## Resistance Heterogeneity and Small Airway Asthma Phenotype



To the Editor:

We read with interest the elegant modeling data of Foy and colleagues (1), who reported a 40% narrowing of small airways was associated with clinically relevant alterations in asthma control and quality of life. Such effects were commensurate with observed responses to biologics on the frequency-dependent heterogeneity of the resistance component of respiratory impedance measured by impulse oscillometry (IOS), where the mean pooled effect on resistance at 5 Hz (R5) – resistance at 20 Hz (R20) was  $-0.04$  (95% confidence interval [CI],  $-0.03$  to  $-0.05$ ) (kPa/L) · s.

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