

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). ■

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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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To further put these changes into clinical context, we previously measured IOS in response to propranolol-induced bronchoconstriction in patients with asthma where there was a 0.05 (kPa/L) · s increase in R5 – R20 corresponding to a 104.1% (95% CI, 22.6 to 185.6%) change, along with a subsequent bronchodilator response to salbutamol of –0.17 (kPa/L) · s and –115.6% (95% CI, –55.6% to –175.7%), respectively (2). Moreover, in a health informatics evaluation of 302 patients with asthma, there was a 45% increased risk for worse control in relation to oral corticosteroid use, and 47% in relation to inhaled albuterol use measured during a 2-year period when comparing cohorts of patients with asthma, using a cutoff value for R5 – R20 of less than or greater than 0.07 (kPa/L) · s (3).

Hence, the small airway asthma phenotype reflected by abnormal R5 – R20 is associated with poorer control. We believe the findings of Foy and colleagues (1) are important in further validating the use of IOS in determining effects of treatments on small airways of patients with asthma. ■

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Reply to Lipworth and Kuo

From the Author:

I thank Prof. Lipworth and Dr. Kuo for their comments on our manuscript (1). Our attempt is the first of its kind to link patient-based computational models of the small airways with patient outcome measures. In line with the comments made by Prof. Lipworth with respect to resistance at 5 Hz (R5) – resistance at 20 Hz (R20) and asthma risk in cross-sectional studies, I and others recently reported the

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results of the ATLANTIS (Assessment of Small Airways Involvement in Asthma) study, a large multinational study evaluating the association of small airway disease with adult asthma outcomes (2).

ATLANTIS clearly identified that the oscillometry measure R5 – R20 was one of the strongest predictors of both asthma control and prior asthma exacerbations among all the potential small airway indices.

The combination of our findings (1) with the ATLANTIS study results (2) should now enable investigators to test interventions that target the small airways, with R5 – R20 as an outcome measure. ■

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Not All Home-based Exercise Programs Are Home-based Pulmonary Rehabilitation Programs

To the Editor:

I read with great interest the article by Bhatt and colleagues entitled, “Video Telehealth Pulmonary Rehabilitation Intervention in Chronic Obstructive Pulmonary Disease Reduces 30-Day Readmissions” (1).

The authors delivered pulmonary rehabilitation (PR), using two-way live videoconferencing on a smartphone to 80 patients after hospitalization for a chronic obstructive pulmonary disease (COPD) acute exacerbation (AE), and compared them with 160 matched patients. They report 30-day readmission rates, either all-cause or for COPD AE, in the patients who participated in video PR that are approximately three times lower than in the comparison group.

This study highlights the question of whether issues of access and adherence to conventional in-center PR can be safely addressed by using technology to bring a program directly to patients in their

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