Rare Variants Influence COPD Risk, Targeted Sequencing Study Finds

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NEW YORK (GenomeWeb) – A targeted sequencing study has homed in on rare variants that contribute to chronic obstructive pulmonary disease risk.

Although smoking is a main risk factor for COPD, genetic factors also contribute to lung function and disease risk. A team of UK researchers followed up on 26 loci previously linked to lung function in 300 people with COPD and 300 controls who'd been smokers. As they reported in *PLOS One* yesterday, their two-stage analysis linked rare variants to COPD.

"These findings can lead to an improved understanding of the molecular pathways involved in the development of COPD," the University of Leicester's Martin Tobin and his colleagues wrote in their paper.

Tobin's team used a pooled sequencing approach in which each pool contained DNA from 25 cases or 25 controls. The 300 cases all had COPD, as gauged through spirometry, while the 300 controls did not, though they were all smokers.

The researchers focused their sequencing effort on 26 loci previously linked to lung function, sequenced their cohort to 30X coverage per sample in these regions, and aligned their data against 1000 Genomes Project phase 1 data. Using three different calling algorithms — vipR, SNVer, and Syzygy — the researchers called between 39,211 SNPs and 62,506 SNPs. After quality control processing, they whittled that list down to 18,177 SNPs and 643 indels. In a single-variant analysis, they noted eight SNPs and three indels that met their significance threshold.

For the second part of their study, Tobin and his colleagues followed up on the top signals in 4,249 COPD cases and 11,916 smoking controls from the UK BiLEVE study. One variant — rs999741 in the HTR4 region — had a nominally significant P-value, though after conditioning it upon the nearby rs1985524 that has been previously reported, it was no longer significant.

Sentinel lung SNPs in four regions — MECOM, HHIP, SPATA9, and HTR4 — also reached significance in the first stage, though only HHIP and HTR4 were confirmed in the UK BiLEVE cohort. Both have previously been linked to COPD risk, the investigators noted.

Using two collapsing methods, the researchers aimed to boost their ability to identify associations with rare variants using sliding window-, gene-, and exon-based approaches. In this analysis, sliding windows within MECOM, a window upstream of HHIP, and TNXB were associated with disease.

The strongest signal in the second stage of their study was for a sliding window in an intronic region of MECOM that houses a DNase hypersensitivity site, the researchers noted. MECOM encodes transcripts that code for nuclear transcription factors, and variants in it have been linked to osteoporosis, renal function, and nasopharyngeal carcinoma in East Asians and to blood pressure and magnesium level in Europeans.

The sliding window upstream of HHIP, meanwhile, also includes a DNase hypersensitivity site and transcription factor binding sites. It does not, though, extend to a nearby region known to interact with the HHIP promoter and act as an enhancer.

While this study had small sample size, the researchers said that it provides evidence that rare variants contribute to COPD risk. "These findings will contribute to improve the knowledge of the biological mechanisms underlying the COPD and may lead to the development of new preventive and treatment strategies," they wrote.

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