Rare mutations do not explain 'missing heritability' in asthma

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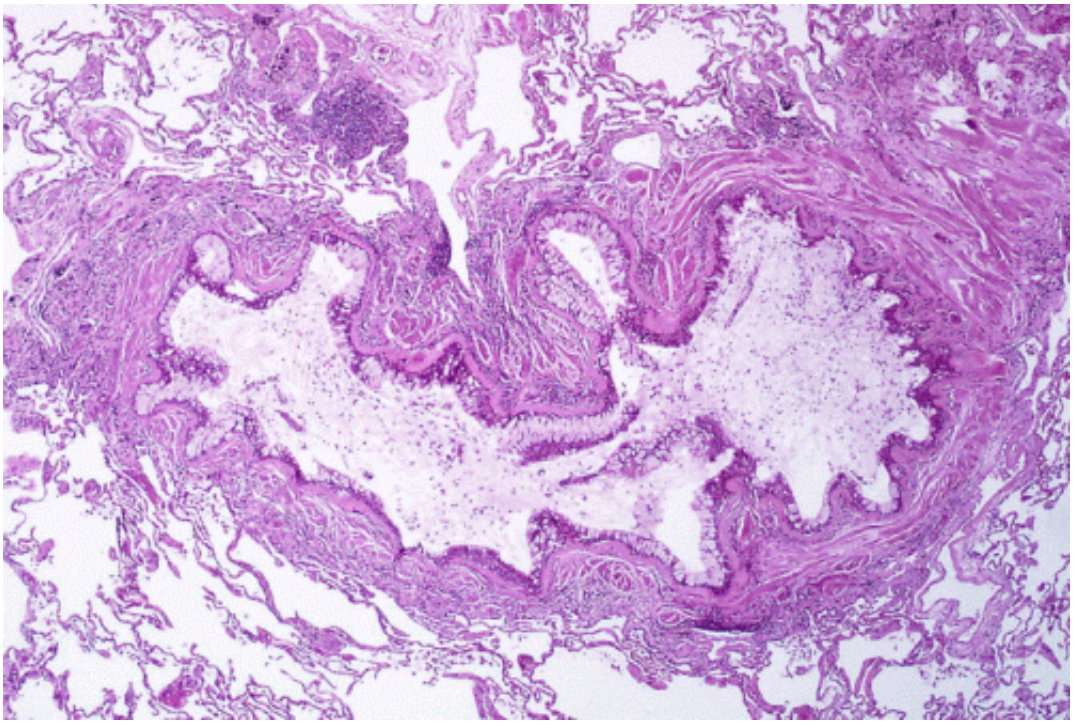

Obstruction of the lumen of a bronchiole by mucoid exudate, goblet cell metaplasia, and epithelial basement membrane thickening in a person with asthma. Credit: Yale Rosen/Wikipedia/CC BY-SA 2.0

Despite a strong suspected link between genetics and asthma, commonly found genetic mutations account for only a small part of the risk for developing the disease - a problem known as missing heritability.

Rare and low frequency genetic mutations have been thought to explain missing heritability, but it appears they are unlikely to play a major role, according to a new study led by scientists from the University of Chicago. Analyzing the coding regions of genomes of more than 11,000 individuals, they identified mutations in just three genes that were associated with asthma risk. Each was associated with risk in specific ethnicities. Their findings, published in *Nature Communications* on Jan. 16, suggest gaps in the current understanding of asthma genetics.

"Previous studies have likely overestimated the heritability of asthma," said study senior author Carole Ober, PhD, Blum-Riese Professor and chair of the Department of Human Genetics at the University of Chicago. "This could be because those estimates are based on correlations between family members that share environment as well as genes, which could inflate the heritability. Gene-environment interactions are not considered in these large scale association studies, and we know that these are particularly important in establishing individual risks for asthma."

Asthma affects more than 25 million adults and children of all ages and ethnicities in the US. Due to the widespread nature of the disease, most studies of its genetic underpinnings have focused on commonly occurring mutations, referred to as genetic variants. However, while numerous such variants have been identified, they are able to account for only a small proportion of the risk for inheriting or developing asthma. Rare mutations, found in less than five percent of the population, have been hypothesized to explain this disparity.

Graduate student Catherine Igartua led the analysis under the supervision of co-senior author Dan Nicolae, PhD, Professor in the Departments of Medicine, Statistics and Human Genetics. She evaluated nearly 33,000 rare or low frequency mutations in more than 11,000 individuals of a variety of ethnicities representing European, African and Latino

backgrounds. She analyzed mutations jointly across subjects, using a technique that allowed them to study mutations common in one ethnicity, but rare in others.

Only mutations in the genes GRASP, GSDMB and MTHFR showed a statistical link to asthma risk. Mutations in the first two genes were found primarily in Latino individuals, and mutations in the last gene in those with African ancestry. These genes, involved in protein scaffolding, apoptosis regulation and vitamin B9 metabolism respectively, have as yet unknown roles in asthma. The rarity and ethnic-specificity of these genes is insufficient to account for the widespread prevalence of asthma.

Although rare mutations might not contribute much to population asthma risk, these genes still have the potential to serve as targets for therapeutic development. Ober points to the discovery of rare mutations in the LDL receptor that eventually led to the development of statins to treat high cholesterol. She also notes that it is possible, but unlikely, that there are mutations with large effects on asthma risk outside of their screen as it looked at approximate 60 percent of mutations in coding regions of the genome.

"It was assumed that there would be rare mutations with larger effect sizes than the common variants we have been studying," Ober said. "Surprisingly, we found that low frequency mutations explain only a very small amount of asthma risk."

More information: "Ethnic-specific associations of rare and low-frequency DNA sequence variants with asthma," *Nature Communications*, 2015.