PERSPECTIVE

How can genetics help?

Smoking and COPD have one of the strongest relationships in clinical epidemiology. But don't forget the genetics, says **Edwin K. Silverman**.

Many people who develop chronic obstructive pulmonary disease (COPD) blame themselves rather than the tobacco industry, which continues to promote cigarette smoking though the dangers are well-known. This disturbing 'blame and sham' attitude among patients is based on one of the most well-established associations in clinical epidemiology: the causal relationship between cigarette smoking and COPD. Exposure to cooking stove smoke from biomass fuels is also an important COPD risk factor in some parts of the world.

Although these environmental risk factors are strong, recent research suggests that genetics also plays a key role in COPD. Identifying genetic determinants and investigating their functions may lead to important progress in COPD pathobiology, diagnosis and treatment. It could also help patients understand that the disease is not their fault.

Genetics provided one of the first clues regarding COPD pathogenesis. A small percentage of patients inherit severe α1-antitrypsin deficiency (A1ATD), a well-characterized, rare syndrome that often includes COPD. The discovery of A1ATD nearly 50 years ago led to the protease–antiprotease hypothesis for COPD, which postulates that lung destruction results from an excess of protein-degrading enzymes relative to their enzyme inhibitors. This hypothesis remains important in current COPD pathobiology.

Not all smokers are equally likely to develop COPD. An underlying susceptibility appears to run in families. Indeed, familial studies of severe, early-onset COPD patients without A1ATD suggest other genetic risk factors. Smokers who are first-degree relatives of these subjects are about three times more likely to develop COPD than are smokers in general. Non-smokers who are first-degree relatives of these subjects are not at increased risk[1], suggesting that genetic factors may interact with smoking.

As with other complex diseases — those influenced by multiple genetic and environmental factors — many studies of candidate genes have failed to replicate. Yet subsequent genome-wide association studies (GWAS) have found four genomic regions associated with COPD that meet the stringent standard for statistical significance in genome-wide studies[2–5].

Two of these genomic regions, near the *HHIP* and *FAM13A* genes — the former a member of the developmentally essential hedgehog pathway, the latter a gene of unknown function — are also associated with variations in lung function levels in samples taken from the general population[5,6]. An association with lung function does not in and of itself prove susceptibility to COPD; genes that influence traits that vary among healthy people, such as height, are not always the same ones that influence pathological conditions, such as dwarfism. However, the associations of COPD to genomic regions near *HHIP* and *FAM13A* are convincing. They have been replicated in several studies, and a potential functional genetic variant that regulates *HHIP* gene expression has been found upstream from *HHIP*[7]. Further study of *HHIP* and *FAM13A* may identify new biological pathways involved in COPD.

The other two regions identified by GWAS, on chromosome 15 and chromosome 19, include many genes of interest, including several related to nicotine addiction. The chromosome 19q region has been associated with smoking behaviour; it is the location of the gene *CYP2A6*, involved in nicotine metabolism. Similarly, the chromosome 15q25 region, which contains genes for several components of the nicotinic acetylcholine receptor, has been convincingly related to smoking behaviour. The same region also contains the gene *IREB2*, which encodes an iron binding protein that has been potentially linked to COPD susceptibility.

The overwhelming association between COPD and smoking provides a unique opportunity to understand the relationships between environmental and genetic influences on risk of disease. In most complex diseases, environmental factors are either unknown or difficult to measure. Cigarette smoking behaviour, on the other hand, can be accurately quantified. Of course, genes and the environment are intertwined; genetic determinants of nicotine addiction may influence exposure to COPD's key environmental risk factor. Furthermore, the risk from smoking suggests that epigenetic factors may also influence COPD pathogenesis[8].

The next generation of genetic research on COPD will include studies of rare genetic variants assessed by sequencing or genotyping the variants in patients' exomes (the protein-coding portions of the genome) and ultimately by sequencing their entire genomes. Advances in computational biology and phenotype characterization based on imaging and clinical observation will also be needed in coordination with genetic studies to dissect the COPD syndrome into groups of patients with different subtypes — an initiative with both diagnostic and therapeutic implications. COPD is highly heterogeneous, with variable amounts of emphysema and airway disease. Integrating genetic studies with chest computed tomography (CT) scans has already identified the *BICD1* gene as a potential determinant of emphysema.

GENETICS COULD HELP PATIENTS REALIZE IT'S NOT THEIR FAULT

However, comprehensive understanding of the complex pathobiology of COPD will probably require the integration of multiple -omics data types (for example, proteomics, transcriptomics and metabolomics) with detailed phenotypic assessment, epigenetics, and genetic variants using systems biology and network science approaches.

Avoiding tobacco smoke will always be an essential public health message. But for millions already suffering, advances in genetics, pathophysiology and phenotyping may lead to new opportunities for specific diagnosis and personalized treatment of COPD. ■

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The author would like to acknowledge helpful discussions with Craig Hersh, Michael Cho, Dawn DeMeo, Scott Weiss and James Crapo. The author declares a conflict of interest go.nature.com/tah34c