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# **The HHIP gene: from a candidate to an established participant in COPD susceptibility**

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Reconciling genome-wide association studies (GWAS) findings with the science of genetic is a mandatory step before translating a discovery into an opportunity. Hedgehog Interacting Protein (HHIP) was recurrently found as a candidate for carrying this kind of hopes. The paradox resides in the apparent lack of biological relevance of the intergenic single nucleotide polymorphisms (SNPs) despite being recurrently identified as one key polymorphic locus associated with chronic obstructive pulmonary disease (COPD), including largest GWAS meta-analysis conducted so far.<sup>1</sup> Better identification of lung function trajectories allowed to consider developmental pathways—where Hedgehog pathway is a confirmed player—reinforced the conviction throughout the community that HHIP deserved worthy investigations: COPD takes roots during lung development when fractal branching of the airways still occurs.<sup>2</sup> This process starts very early in utero but terminates around age 4. Whether Hedgehog pathway is reactivated during airway reparation later in life is highly likely,<sup>3</sup> even though many findings from mice may not necessarily translate into humans.<sup>4</sup>

Moreover, the SNPs identified to date were found mostly outside the coding regions of the HHIP gene located in 4q31, in a region called “COPD locus”.<sup>5</sup> Interests rise when KO mice were found with hypoplastic airways and lungs<sup>6</sup>—a model lethal at birth, in contrast with haploinsufficiency where airways and lungs kept normal appearance in a healthy environment.<sup>7</sup> The need for understanding whether solid evidence could associate HHIP SNPs with increased environmental susceptibility—as a basis for COPD development became obvious.

In this issue of the journal, a multidisciplinary international team combined sophisticated techniques to provide evidence that a distal enhancer for HHIP is involved in maintaining chromatin structure—that may act as an insulator—and could be seen as an epigenetic regulation of airway homeostasis.<sup>8</sup> Taking advantage of CRISPR-Cas9 genome editing and multi-omics techniques including among others single nuclei ATACseq, single cell RNAseq, Chromatin conformation capture assay (3C) but also siRNA and pharmacological modulation in multiple cell sources including human healthy and COPD lungs and induced pluripotent stem cells, Guo and colleagues, have established robustly a key distal enhancer specifically in human lung cells. This “T2” enhancer, highly conserved in humans compared to mice and located between the “COPD locus” and the HHIP promoter, was strongly involved in modulating HHIP expression, translated at the protein level. The experimentally induced loss of HHIP expression, normally mediated by the T2 enhancer, led to enhanced Epithelial–Mesenchymal Transition in a TGFbeta dependant manner through its intracellular effector SMAD-3 binding.

This negative feedback loop would be applied in a wound-healing condition, which highly frequently occurs in COPD airways. TGF-beta and HHIP cross links, independently from the Hedgehog pathway activation either canonical or non-canonical, and it appears as a promising avenue for future exploration. Numerous questions remain unanswered.

1 Many SNPs around the HHIP gene have been reported as potential candidates and further work is essential to address them all clearly.

2 Identifying in the COPD population whether these SNPs are really overrepresented and to which extent they can be associated with different characteristics of the disease (e.g. lung function trajectory and age at onset, emphysema, susceptibility to virally triggered exacerbation, etc)

3 Whether some cells are more specifically vehiculating this loss of regulation. Since impaired lung growth starts in the airways and because small airway disease precedes emphysema, Respiratory Airway Secretary Cells as basal and club cells appear as appropriate ontogenic candidates to carry this COPD susceptibility more than alveolar type 2 cells. Nevertheless, this requires dedicated work given the highly controversial literature currently reported in this area.

4 Finally, translating these findings into opportunities. Beyond identifying people susceptible to develop COPD early, the ultimate goal would be to assess whether the restoration of physiological regulation of HHIP expression—that might be achievable pharmacologically or by gene editing—will protect from COPD.

## Contributors

Zakaria Lahmar reviewed the draft and extensively searched literature; Anne Bergougnoux assessed evidence and reviewed the draft; Arnaud Bourdin wrote the first draft of the manuscript. All the authors read and approve the manuscript.

## Declaration of interests

Bourdin A: GSK—non-financial support during the conduct of the study; Acceleron Pharma, Actelion, Galapagos, Merck Sharp & Dohme, NuVaira, Pulmonx, United Therapeutics, Vertex Pharmaceuticals— other; Boehringer Ingelheim—grants, personal fees; AstraZeneca, Chiesi, GSK, Regeneron Pharmaceuticals Inc., Sanofi—personal fees. Bergougnoux A: no conflict of interest. Lahmar Z: no conflict of interest.

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