



Commentary

The BuMPy Road to COPD Gene Discovery

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Chronic obstructive pulmonary disease (COPD) is defined as irreversible airflow obstruction and is a major cause of morbidity and mortality worldwide. Exposure to cigarette smoke is the major environmental determinant of COPD but the pathophysiological response to smoke is highly variable demonstrating that other factors are involved. Epidemiological studies have clearly demonstrated that there is a genetic component to COPD. Targeted analysis of specific genes has identified several common sequence variants (polymorphisms) associated with COPD (Bossé, 2012). In addition, genome-wide analyses have identified polymorphisms that are implicated in the pathogenesis of COPD (Pillai et al., 2009) or associated with level of lung function in the general population (Artigas et al., 2015).

In this issue of *EBioMedicine*, Wang et al. investigated the bone morphogenetic protein receptor type 2 gene (*BMPR2*) as a potential genetic factor involved in the development of COPD (Wang et al., 2016). The authors selected *BMPR2* for study due to the anti-inflammatory role of this receptor in endothelial cells (Kim et al., 2013) and evidence that the expression of this gene is decreased by exposure to cigarette smoke (Llinas et al., 2011). *BMPR2* encodes a subunit of the receptor for several bone morphogenetic proteins (BMPs).

As their name suggests, BMPs are a family of growth factors that induce bone formation. However, BMPs have numerous other functions during development including roles in the generation of the neural crest, kidney, eye, ear and heart (Wu and Hill, 2009). BMPs also have functions unrelated to development such as iron metabolism (Parrow and Fleming, 2014) and glucose homeostasis (Qian et al., 2013). BMPs signal through a hetero-tetrameric receptor consisting of two type I receptors that enable signal transduction and two type II receptors that bind to the ligand. The *BMPR2* gene codes for a type II receptor for BMPs and mutations in this gene have been established as the main genetic cause of pulmonary arterial hypertension (Machado et al., 2015).

Wang and associates performed a genetic association study of *BMPR2* variants and COPD in a southern Chinese population (Wang et al., 2016). They investigated two polymorphisms in the 3' untranslated region of the *BMPR2* gene. The 3' untranslated region of an mRNA molecule is the sequence following the termination codon and plays an important role in the regulation of gene expression. Wang et al. found that the less frequent allele of both variants was associated with COPD and this association was particularly evident in non-smokers.

After demonstrating this novel association, the authors went on to explore the mechanistic basis of the finding (Wang et al., 2016). The genomic region containing the *BMPR2* variants was cloned into a vector molecule downstream of a reporter gene (a gene whose expression can be easily assayed in human cells). The clones were transfected into a cell line and the results showed that only one of the polymorphisms (rs6435156) altered the level of gene expression, suggesting that it was the causal variant for the association with COPD. Specifically, the T allele of rs6435156 (that was associated with COPD) resulted in lower gene expression, which is consistent with an anti-inflammatory role of *BMPR2* signaling.

The *in vitro* effect of rs6435156 on reporter gene function was supported by quantitative PCR and western blotting data in peripheral blood mononuclear cells from COPD patients. Wang et al. showed that there was a dose-dependent decrease in *BMPR2* mRNA and protein expression associated with the number of copies of the T allele (Wang et al., 2016). Furthermore, the effect of genotype on gene expression was stronger in the presence of cigarette smoke both *in vitro* and *in vivo*.

The rs6435156 polymorphism may affect gene expression levels *via* binding with a microRNA (miRNA). miRNA binding to mRNA results in transcript degradation or the inhibition of translation initiation. Wang et al. found that rs6435156 is located in a region that is predicted to bind a miRNA known as hsa-miR-20a. If the T allele of rs6435156 enhanced the binding of hsa-miR-20a it would be expected to result in decreased *BMPR2* expression levels. The authors showed that mimics of hsa-miR-20a did indeed result in decreased gene expression and this effect was only significant for the T allele of the variant (Wang et al., 2016).

This is an interesting study that includes a novel genetic epidemiological observation and convincing mechanistic data (Wang et al., 2016). The paper is a welcome addition to the literature as the genetic aspects of COPD have been underexplored in the Chinese population. However, a number of issues remain to be addressed. First, the association of these polymorphisms with COPD needs to be replicated in additional Chinese populations and examined in other racial groups. Given

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the likely importance of exposure to cigarette smoke it would be important to determine the genetic effect size in cases and controls with an equal smoking history. Second, there is an apparent contradiction between the epidemiological data showing the strongest association in non-smoking patients and the gene/protein expression data that demonstrate a larger genotype effect in the presence of cigarette smoke. Nevertheless, if these issues can be resolved the BMPs and their receptors may represent novel targets for therapeutic interventions in COPD patients.

Disclosure

The author declared no conflicts of interest.

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