β2 adrenergic receptor polymorphisms and COPD exacerbations: a complicated story

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Genomics has significantly improved our understanding of chronic obstructive pulmonary disease (COPD) over the past decade. Genome-wide association studies have identified a number of genetic variants associated with lung function and susceptibility to COPD,[1 2] and have helped explain why only some smokers develop COPD and why never-smokers can also be affected by the disease. Once COPD is diagnosed, reducing the burden of respiratory exacerbations is a clinical priority because these events are associated with accelerated lung function decline[3] and increased mortality.[4] However, not all patients with COPD experience exacerbations.[5 6] Therefore, identifying individuals at increased risk of exacerbations may help target management and improve outcomes. Beyond the susceptibility to COPD, genomics may also help inform the morbidity of COPD. A previously reported twin study suggests that more than 60% of the risk of severe COPD exacerbations can be attributed to genetic factors.[7] Among those, genetic polymorphisms of the β2 adrenergic receptor have been of particular interest.[8 9]

Using data from individuals with COPD in the Copenhagen General Population Study (n=5262) and the Copenhagen City Heart Study (n=923), Ingebrigtsen *et al* tested the association of β2 adrenergic receptor polymorphisms Gly16Arg (rs1042713, c.46G>A) and Gln27Glu (rs1042714, c.79C>G) with incident risk of COPD exacerbations requiring hospitalisation.[10] In the Copenhagen General Population Study, compared with 16Gly homozygotes, 16Gly/Arg heterozygotes (HR 1.62, 95% CI 1.30 to 2.03, p=0.00002) and 16Arg homozygotes (HR 1.41, 95% CI 1.04 to 1.91, p=0.03) were more likely to experience severe COPD exacerbations. In addition, compared with 27Glu homozygotes, 27Gln/Glu heterozygotes (HR 1.35, 95% CI 1.03 to 1.76, p=0.03) and 27Gln homozygotes (HR 1.49, 95% CI 1.12 to 1.98, p=0.006) also had higher hazards of severe exacerbations. Similar trends were observed in the Copenhagen City Heart Study, with the exception of 16Arg homozygotes and 16Gly homozygotes who had a comparable exacerbation risk. The associations found in the Copenhagen General Population Study persisted after adjusting for forced expiratory volume in one second % predicted and after excluding individuals on any inhaled medications. There were no interactions between any of the polymorphisms and long-acting β2 agonist use. Additionally, the authors conducted subgroup analyses to further explore the observed associations. Of the 3601 27Gln/Glu heterozygotes and 27Glu homozygotes in the Copenhagen General Population Study, only one individual was a 16Arg homozygote, thereby demonstrating that these polymorphisms are in linkage disequilibrium. In the subgroup of 27Gln homozygotes only, the 16Gly/Arg heterozygote and 16Arg homozygote states remained strongly associated with exacerbation risk. In the subgroup of 16Gly homozygotes only, the 27Gln/Glu heterozygote and 27Gln homozygote states were not associated with exacerbations. Therefore, these subgroup analyses point to a potentially influential genetic effect of the 16Arg allele specifically.

Taken together, these findings suggest that β2 adrenergic receptor genotypes may affect the risk of severe respiratory exacerbations in individuals with COPD, especially the 16Arg allele of the rs1042713 polymorphism. One possible mechanism behind this association is downregulation of β2 adrenergic receptors in the airways of 16Arg carriers after administration of short-acting β2 agonists during an exacerbation.[11] This downregulation may in turn predispose these patients to experience decreased response to treatment and to subsequently have a higher likelihood of requiring hospitalisation. Strengths of this analysis include the large size of the Copenhagen General Population Study cohort, the validated outcome measure based on national Danish Patient Registry data and the conduction of multiple sensitivity and subgroup analyses. Furthermore, the findings of this study could potentially impact a large number of individuals with COPD given the high prevalence of the studied β2 adrenergic receptor polymorphisms. For comparison, while it is estimated that fewer than 10% of COPD patients carry the Pi*Z allele variant in the SERPINA1 gene associated with alpha-1 anti-trypsin deficiency,[12] more than 60% are carriers of the 16Arg allele in rs1042713.[8–10]

However, despite the strengths of this study, the nature and magnitude of the association between β2 adrenergic receptor polymorphisms and COPD exacerbations remain uncertain. Results of the Gly16Arg polymorphism of the Copenhagen General Population Study were not replicated in the Copenhagen City Heart Study. Although the latter cohort was smaller than the former, it still included more than 900 participants and the magnitude and width of effect sizes for 16Arg homozygotes compared with 16Gly homozygotes is not particularly convincing (HR 1.02, 95% CI 0.67 to 1.55, p=0.92). Furthermore, in another analysis by Bleecker *et al* that included more than 2800 COPD patients enrolled in two clinical trials, there were no differences in the rate of moderate/severe exacerbations for Gly16Arg polymorphism variations in any of the studied arms (combined budesonide/formoterol, budesonide only, formoterol only and placebo).[8] In contrast, in a prespecified substudy of 5125 participants enrolled in the POET (Prevention of Exacerbations with Tiotropium)-COPD trial, Rabe *et al* found that 16Arg homozygotes had better moderate/severe exacerbation outcomes when on salmeterol, but not tiotropium.[9] The Gln27Glu polymorphism was not associated with exacerbation risk in this study. Therefore, the results of the studies by Bleecker *et al* and Rabe *et al* do not concur with those of Ingebrigtsen *et al*. However, the Bleecker and Rabe analyses had a substantially lower proportion of female participants, enrolled subjects with more severe airflow obstruction and were derived from clinical trials, not population-based studies.

These conflicting results should not discourage further investigation of the association between β2 adrenergic receptor polymorphisms and COPD exacerbations. In fact, they beg for elucidation of many important unanswered questions: is there a defined subgroup of individuals with COPD in which these polymorphisms are reliable prognostic markers? Why is homozygosity for 16Arg a risk factor for exacerbations in some studies, but

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a protective one in others? Should these polymorphisms be incorporated within a genetic risk score to further improve their discriminative ability? Because their association with exacerbations may be modulated by type of inhaler treatment, can they be leveraged to guide pharmacogenetic studies in COPD? Answers to these questions have the potential to advance precision medicine in COPD. For the time being, however, the clinical value of these polymorphisms remains unknown. Should patients with the 16Arg allele, for instance, receive short-acting muscarinic antagonists rather than short-acting β2 agonists during exacerbations? Further, such testing is conceivably costly and typically requires a blood draw. Therefore, it is important to determine the incremental gain it provides to existing exacerbation risk models that include lung function and history of prior exacerbations.[5 13]

The contributions of genomics to our knowledge of COPD exacerbation risk are still largely unexplored. Genetic polymorphisms beyond those associated with β2 adrenergic receptors and alpha-1 anti-trypsin deficiency may be informative and deserve further study. Given the high morbidity and mortality of COPD exacerbations and their significant variability both within and between individuals, leveraging the potential of genomics to better understand the susceptibility to these events is warranted.

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