Genetic correlation of Chronic Obstructive Pulmonary Disease and non-pulmonary comorbidity

Ivana Nedeljković, Maaike de Vries, Judith M. Vonk, Lies Lahousse, Bruno H.C. Stricker, Guy G. Brusselle, Najaf Amin, Marike Boezen, Cornelia M. van Duijn.

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ABSTRACT

COPD is a complex disease which co-occurs with a range of pulmonary and systemic pathologies. The co-occurrence may be explained by common determinants or a joint pathogenesis that may in part be driven by genetic factors. We explored the genetic overlap between COPD and comorbid conditions. For this study, genome wide association study (GWAS) summary statistics for COPD were obtained from the International COPD Genetics Consortium (ICGC). Linkage Disequilibrium (LD) regression was used to determine the genetic correlation of COPD with phenotypes for which GWAS summary statistics data are publicly available at the LD Hub database on 16th February 2019 (http://ldsc.broadinstitute.org/ldhub/).

As expected, we find marginal significant evidence for genetic correlation of COPD with a variety of comorbidities including cardio-metabolic traits (acute myocardial infarction, coronary artery disease, angina pectoris, hypertension, diabetes, chronic kidney disease). The strongest association were seen for diabetes based on significance and essential hypertension in terms of strength of correlation. An unexpected but intriguing finding is the correlation of COPD with family history of depression in siblings (most significant finding) and attention deficit hyperactivity disorder (strongest correlation). Finally, we find marginal evidence for significance of genetic correlation of COPD to female reproductive traits, autoimmune diseases of the bowel and aging disorders such as cataract.

This study pinpoints diseases that are genetically correlated with COPD and highlights the significance of studying comorbidities of COPD.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a common cause of morbidity and mortality worldwide, characterized by persistent and progressive limitation in lung function.[1,2] COPD often co-occurs with other pulmonary pathology. Co-occurrence may be explained by a shared pathogenesis which is part of the COPD pathology spectrum or a consequence of COPD.[3] The disorders associated with COPD include a range of pulmonary pathologies such as asthma, pneumonia, pulmonary hypertension, pulmonary embolism, obstructive sleep apnoea, idiopathic pulmonary fibrosis and lung cancer. However, COPD is also a systemic disorder that is associated with non-pulmonary comorbid diseases.[4,5] These involve cardio-metabolic pathology, loss of bone mass density, depression, among many others.[6]

Both the pulmonary and non-pulmonary comorbidities may in part be explained by common factors such as smoking, sedentary behavior, lcohol, diet, ageing and polypharmacy or by shared pathophysiological mechanisms such as the systemic inflammation.[4,6] There is evidence for genetic correlation between COPD and asthma.[7] Although only one of the COPD loci identified to date was also genome wide significantly implicated in asthma,[7,8] an integrative genomic approach called Linkage Disequilibrium (LD) regression brought to surface a strong and significant genetic correlation between COPD, asthma and lung function parameters.[7] In addition, there was also a significant evidence for genetic correlation with height and smoking.[7] To our knowledge, up until now, only these specific traits were tested using a "candidate-disease" approach based on prior knowledge of COPD comorbidity.

The aim of the present analyses was to explore the genetic overlap between COPD and other diseases using LD regression and the wealth of GWAS data available for data mining.

METHODS

For this study, GWAS results for COPD were obtained from the largest study performed to date by Hobbs et al.[7] This study was conducted by the International COPD Genetics Consortium (ICGC), in which 22 studies with GWAS and COPD data (case-control or population based) were included. For the COPD GWAS, the consortium performed a genetic association analyses in 15,256 cases and 47,936 controls. To benchmark the finding the consortium replicated top results ($P < 5\times10^{-6}$) in 9,498 cases and 9,748 controls. In the combined meta-analysis, 22 loci were associated to

COPD at genome-wide significance. All SNPs, independent of the significance, are included in the genetic correlation analysis of the present study.

LD regression exploits data of the GWAS, available in the public domain. For many different comorbidities, summary-level GWAS results are publicly available at LD Hub for LD regression.[9] We evaluated the genetic correlations of COPD with the 126 diseases on LD Hub (access date: 16th February 2019). For a given pair of traits, LD score regression estimates the expected population correlation between the best possible linear SNP-based predictor for each trait. The analysis is restricted to common SNPs. As pulmonary comorbidities are already investigated and shown to have genetic overlap with COPD, we were interested in extra-pulmonary comorbid conditions. As we focus on the question whether there is a genetic overlap between COPD and extra-pulmonary disorders, we focus on disorders and other determinants that are positively correlated to COPD.

RESULTS

Our LD score regression showed marginal significant positive correlations of COPD and 20 different traits. All significant (P<0.05) extra-pulmonary correlations are presented in **Table 1.** These and other diseases tested in the analysis are presented in **Supplementary table 1**, which also shows confirmation of the already established genetic overlap with pulmonary comorbidities**.** The most statistically significant genetic correlation of COPD was found for depression of a sibling (r_g=0.29; P=0.0007) while attention deficit hyperactivity disorder (ADHD) showed a remarkably strong correlation (r_g=0.51; P=0.0031). Further among neuro-psychiatric diseases, we found evidence for correlation of COPD and schizophrenia (r_g=0.09; P=0.049).

Various cardio-metabolic diseases were found to be genetically correlated to COPD. The strongest association in terms of significance is seen for diabetes diagnosed by doctor (r_g=0.17; P=0.002). Also diabetes of a sibling and mother (r_g=0.16; P=0.02 and r_g=0.17; P=0.02, respectively) is found to be positively correlated as well as high blood pressure diagnosed by doctor and essential hypertension (r_g=0.11; P=0.01 and r_g=0.36; P=0.04, respectively). We also see marginal evidence for genetic correlation with acute myocardial infarction (AMI, r_g=0.21; P=0.02), syncope and collapse (r_g=0.23; P=0.03), angina pectoris (r_g=0.15; P=0.03) and heart attack diagnosed by doctor (r_g=0.14; P=0.05). Finally, in this paper, we show significant genetic correlation to coronary artery disease (CAD, r_g=0.11; P=0.05) which was reported earlier, but was not significant.[7] We further found evidence for correlation to typical aging disorders including, senile cataract (r_g=0.32; P=0.03), and chronic kidney disease (r_g=0.26; P=0.03), which is strongly associated to hypertension and cardiovascular disease.

Table 1. Significant (P<0.05) genetic correlation results of COPD with comorbidities

Comorbidity	Study PMID	Ethnicity	r_g	SE	h^2	P
Illnesses of siblings: Severe depression	UKBB	European	0.289	0.085	0.014	**0.0007**
Diabetes diagnosed by doctor	UKBB	European	0.171	0.056	0.043	**0.0021**
Attention deficit hyperactivity disorder	27663945	European	0.510	0.173	0.075	**0.0031**
Inflammatory Bowel Disease	26192919	European	0.137	0.055	0.321	**0.013**
High blood pressure diagnosed by doctor	UKBB	European	0.105	0.043	0.116	**0.014**
Crohns disease	26192919	European	0.133	0.056	0.493	**0.018**
Diagnoses - main ICD10: I21 Acute myocardial infarction	UKBB	European	0.207	0.089	0.010	**0.020**
Illnesses of siblings: Diabetes	UKBB	European	0.162	0.071	0.021	**0.022**
Illnesses of mother: Diabetes	UKBB	European	0.165	0.072	0.019	**0.022**
Diagnoses - main ICD10: H25 Senile cataract	UKBB	European	0.317	0.141	0.004	**0.025**
Chronic Kidney Disease	26831199	Mixed	0.255	0.114	0.019	**0.025**
Diagnoses - main ICD10: R55 Syncope and collapse	UKBB	European	0.230	0.108	0.006	**0.033**
Angina pectoris diagnosed by doctor	UKBB	European	0.153	0.072	0.022	**0.034**
Diagnoses - main ICD10: N92 Excessive frequent and irregular menstruation	UKBB	European	0.227	0.107	0.008	**0.035**
Diagnoses - main ICD10: N81 Female genital prolapse	UKBB	European	0.248	0.121	0.006	**0.041**
Diagnoses - main ICD10: I10 Essential (primary) hypertension	UKBB	European	0.361	0.179	0.003	**0.044**
Coronary artery disease	26343387	Mixed	0.110	0.056	0.079	**0.047**
Heart attack diagnosed by doctor	UKBB	European	0.144	0.072	0.019	**0.047**
Schizophrenia	25056061	Mixed	0.091	0.046	0.458	**0.049**
Illnesses of mother: Breast cancer	UKBB	European	0.177	0.090	0.010	**0.050**

Study PMID: PubMed ID for a given GWAS used in the analysis; UKBB: United Kingdom BioBank - unpublished GWAS results; r_g: genetic correlation coefficient; SE: standard error of r_g; h^2: SNP heritability; P: P-value.

Among the other diseases found to show marginal genetic correlation with COPD were inflammatory bowel disease (r_g=0.14; P=0.01), Crohn's disease (r_g=0.13; P=0.02), and female reproductive conditions including excessive frequent and irregular menstruation and genital prolapse (r_g=0.23; P=0.04 and r_g=0.25; P=0.04, respectively). Finally, we found that a breast cancer of mother was genetically correlated to COPD (r_g=0.18; P=0.05).

DISCUSSION

In this study focussing on the question whether there is a genetic overlap between COPD and extra pulmonary disorders, we find marginally significant evidence for genetic correlation of COPD with psychiatric, cardiovascular, inflammatory disorders of the bowel, age-related disorders such as cataract and female reproductive system disorders. Of note is that for three disorders (diabetes, severe depression and breast cancer) we find evidence for genetic correlation of COPD with family history rather than the co-occurrence of the disease in an individual.

COPD is genetically correlated to wide range of cardiovascular disorders (AMI, CAD and angina pectoris) and their risk factors (hypertension, diabetes, chronic kidney disease). The genetic correlation of COPD to cardiovascular disease is expected based on the findings that COPD and cardiovascular comorbidities may have common pathogenic mechanisms and that cardiovascular mortality accounts for 20-30% of deaths in COPD.[10,11]

Lung function has been found to be a better predictor of cardiovascular mortality than cholesterol.[12] Yet, previous study failed to show significant genetic overlap of COPD with cardiovascular disease.[7] Using larger genome wide association studies, we confirm the genetic overlap with cardiovascular disease and its risk factors. Of note is that diabetes shows the strongest genetic correlation in term of statistical significance. Not only diabetes of the person but also the family history of diabetes in siblings and the mother are found to be genetically correlated to COPD. Such correlations with family history strongly suggests a joint genetic aetiology. Although not the most significantly correlated, the strongest genetic correlation with COPD and cardiovascular pathology is seen for essential hypertension.

COPD is more strongly genetically correlated to neuropsychiatric pathology than to cardiovascular pathology, both in terms of statistical significance (family history of depression in a sibling) and strength of correlation (ADHD). These findings are both puzzling and intriguing, in particular for ADHD, which is not only the third most significantly associated disorder but shows an extremely strong association to COPD, a disorders with a typically late onset and a strong link to smoking. It is tempting to speculate that, as both disorders show a strong association to smoking, ADHD is also significantly genetically correlated to lung cancer. However, ADHD is also genetically correlated to diabetes and related traits, which may be another logical pathway.

The strong genetic correlation between COPD and family history of depression in a sibling is of interest since the prevalence of depression in COPD is high.[13,14] Also it has been suggested that relationship between depression and COPD is likely to

be bidirectional, in that COPD may increase the risk of depression and vice versa, depression may increase the risk of COPD.[15] However, we found no significant genetic overlap between depression and COPD in the same person which is difficult to explain. This is why we further tested the correlation of COPD and major depressive disorder using results of the largest to date GWAS on depression[17] and showed borderline significant correlation (r_g=0.25, P=0.058). This can mean that increasing sample sizes further we can reach enough power to detect true risk variants which play a role in the overlapping pathways. However, at this point we cannot exclude a false positive finding. The same holds for the genetic correlation of COPD to schizophrenia, which is a disease associated with many loci in the genome, which may generate false positive findings.

There are two other disorders for which we also only find a positive family history is genetically associated to COPD: diabetes and breast cancer in the mother. The genetic overlap with diabetes is very consistent for the person her/himself and the family history. For breast cancer the same problem occurs as with depression: no genetic correlation is found with the disease itself. These finding should be followed up in the near future. Finally, to our knowledge, we found for the first time evidence for a genetic correlation between COPD and cataract and inflammatory gastrointestinal disorders. Also this finding raise interesting hypothesis: the genetic correlation of COPD and cataract may be related to diabetes while the genetic correlation of COPD and inflammatory gastrointestinal disorders may be explained by common immune pathways.

Although we both confirmed long expected genetic correlations with cardiovascular disease and found new intriguing ones, this study is by no means an endpoint. Our finding provide new leads into the comorbidity research. There may be various explanations for the genetic correlation including the genetic localization on the same chromosome, pleiotropy, i.e., the protein encoded by a gene has a biological function in the lung but also in other tissues, shared pathogenesis which may be partial, and/or that one trait is in the causal pathway of the other.

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