J Korean Med Sci. 2024 Nov 4;39(42):e275
https://doi.org/10.3346/jkms.2024.39.e275
eISSN 1598-6357·pISSN 1011-8934

JKMS

Original Article
Respiratory Diseases & Critical Care Medicine

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Genome-Wide Association Analysis of Rapid Decline in Lung Function: Analysis From the Korean Genome and Epidemiology Study

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OPEN ACCESS

Received: May 11, 2024
Accepted: Jul 30, 2024
Published online: Aug 26, 2024

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ABSTRACT

Background: A rapid decline in forced expiratory volume in 1 second (FEV1) is considered an important phenotype of the development of chronic obstructive pulmonary disease (COPD). However, the associations between specific genetic variants (single-nucleotide polymorphisms; SNPs) and this phenotype remain uncertain.
Methods: We enrolled 6,516 individuals from the Korean Genome and Epidemiology Study (KoGES). A rapid decline in FEV1 was defined as an annual decrease of FEV1 ≥ 60 mL/year. A multivariable logistic regression model was used to assess the associations between SNP variants and the rapid decline in FEV1. Considering the significant impact of smoking on lung function, a subgroup analysis based on smoking history was also conducted.
Results: A genome-wide association analysis of the rapid decline in FEV1 identified 15 association signals ($P < 5.0 \times 10^{-8}$). Among the 15 nucleotide variants, rs9833533 and rs1496255 have been previously reported to be associated with lung function development. In the subgroup analysis, rs16951883 (adjusted odds ratio [aOR], 3.24; $P = 5.87 \times 10^{-8}$) was the most significant SNP associated with rapid decline in FEV1 among never smokers, followed by rs41476549, rs16840064, and rs1350110. Conversely, among ever smokers, rs10959478 (aOR, 4.74; $P = 8.27 \times 10^{-7}$) showed the highest significance, followed by rs6805861, rs9833533, and rs16906215.
Conclusion: We identified 15 nucleotide variants linked to a rapid decline in FEV1, including two SNPs previously reported to be associated with lung function development. Additional SNPs, which were associated with COPD, may be found using novel phenotypes.

Keywords: Pulmonary Disease; Chronic Obstructive; Respiratory Function Tests; Spirometry; Genetic Techniques; Genome-Wide Association Study; KoGES

Disclosure
The authors have no potential conflicts of interest to disclose.

Data Availability Statement
The datasets analyzed during the study are not publicly available due to personal data protection. However, they can be obtained from the corresponding author upon reasonable request.

Author Contributions
Conceptualization: Choi JY. Formal analysis: Kim SH. Supervision: Choi JY. Validation: Choi JY. Writing - original draft: Kim SH. Writing - review & editing: Lee H, Jo YS, Yoo J.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a prevalent chronic respiratory disease that burdens affected individuals and societies worldwide.[1] COPD is often diagnosed late, necessitating the identification of novel phenotypes for early detection and intervention.[2] Recent COPD guidelines recommend investigating early detection methods of COPD by introducing new categories, such as pre-COPD, COPD in young people, and early COPD.[3] To achieve this, novel phenotypes are needed beyond the traditional study outcomes based on forced expiratory volume in 1 second (FEV1)/forced vital capacity (FVC) ratio. One proposed phenotype is a rapid decline in lung function, as often defined by the annual decline in FEV1.[4] This phenotype may have significant clinical impact, as individuals with a rapid decline in FEV1 are at increased risks for cardiovascular disease (CVD), lung cancer, and mortality.[5-7]

The impact of genetic risk factors for COPD has been well-established, with alpha-1 antitrypsin deficiency being the most well-known example.[8] Since COPD often develops through the interaction of environmental and genetic factors, no other definitive genetic deficiency has been identified. However, several studies have shown that various genetic factors are associated with the risk of COPD development and specific COPD characteristics.[9] One promising approach for identifying these genetic factors is genome-wide association analysis.[10] Previous genome-wide association studies (GWAS) identified associations between several loci and lung function, including between chromosome 4 and FEV1/FVC.[11]

As far as we know, no study has investigated single-nucleotide polymorphisms (SNPs) specifically associated with a rapid decline in FEV1. Considering clinical significance of rapid decline in FEV1, it would be very informative to investigate which SNPs were associated with this phenotype. Therefore, this study aimed to investigate novel SNP loci associated with a rapid decline in FEV1.

METHODS

Study population

We analyzed a regional cohort from the Korean Genome and Epidemiology Study (KoGES), comprising participants aged 40–69 years in the Ansan (urban) and Ansung (rural) areas, which was estabilised to identify factors affecting chronic diseases. Initial measurements were conducted from May 2001 to February 2003, followed by six biennial lung function assessments. This identified 1,589,725 SNP variants from 8,840 subjects. Further details on GWAS using Ansan-Ansung cohort have been described previously.[12]

From 10,030 individuals, we excluded 247 without baseline lung function measurements and 2,457 who had fewer than two additional lung function measurements. We further excluded 810 individuals without GWAS data. As a result, 6,516 individuals were included in the final analysis.

Phenotype: rapid decline in FEV1

A rapid decline in FEV1 was defined as an annual decrease of FEV1 ≥ 60 mL/year.[13] The annual FEV1 decrease rate was assessed using least-square linear regression analysis of years and FEV1.[4] Lung function was measured using a spirometer (VMAX2130; SensorMedics, Yorba

https://doi.org/10.3346/jkms.2024.39.e275

Linda, CA, USA). All measurements were pre-bronchodilator values, and trained technicians tested the participants three times; the highest value was recorded in accordance with the American Thoracic Society/European Respiratory Society guidelines.[14]

Covariates

Hypertension was defined as a systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, or having physician-diagnosed hypertension. Diabetes mellitus was defined as a fasting plasma glucose level ≥ 126 mg/dL, hemoglobin A1c ≥ 6.5, or having physician-diagnosed diabetes mellitus. Respiratory symptoms, including persistent cough within 3 months, phlegm accompanied by cough for > 3 months during a year, and dyspnea when walking on flat ground, were assessed using a self-report questionnaire. CVDs comprised myocardial infarction, coronary diseases, and congestive heart failure. A history of pulmonary tuberculosis (TB) was identified on the basis of chest X-rays. Asthma, myocardial infarction, coronary diseases, and congestive heart failure were assessed using a self-report questionnaire. The KoGES Baseline Core Questionnaire and additional information have been described previously.[15]

Statistical analysis

Data are expressed as mean ± standard deviation or median with interquartile range (IQR) for continuous variables, and as number with percentage for categorical variables as appropriate. The *t*-test or Mann–Whitney *U* test was used for continuous variables, while the χ^2 or Fisher's exact test was used for categorical variables to compare between individuals with and without a rapid decline in FEV1, as appropriate.

For quality control, we removed SNPs that had a "genotype call ratio" > 0.05, a minor allele frequency < 0.01, and a *P* value for Hardy–Weinberg equilibrium ≤ 10^{-5}. A multivariable logistic regression model was used to assess the associations between SNP variants and the rapid decline in FEV1. The model was adjusted for age, sex, body mass index (BMI), smoking status, baseline FEV1, respiratory symptoms, and comorbidities (history of TB, asthma, CVD, hypertension, and diabetes). Considering the significant impact of smoking on lung function and the development of chronic lung diseases, we conducted a subgroup analysis based on smoking history. The threshold for genome-wide significance was $P < 5.0 \times 10^{-8}$. We adjusted the subgroup analysis threshold as possible significance ($P < 1.0 \times 10^{-5}$), considering the smaller sample size, and only SNPs that satisfied genome-wide significance in the combined analysis were considered significant. All analyses were performed using PLINK (ver. 1.9) and R software (ver. 4.3.2; R Development Core Team, Vienna, Austria).

Ethics statement

Ethical approval was obtained from the Institutional Review Board (IRB) of Incheon St. Mary's Hospital (No. OC23ZISI0033). Written informed consent was obtained when genetic analysis data from KoGES was first collected. However, as this study used anonymized data that had already been completed, the requirement for obtaining additional informed consent was waived.

RESULTS

Baseline characteristics of the study participants

Table 1 summarizes the baseline characteristics of the study participants. Among all 6,516 individuals, the mean age was 51.5 years, with 51.3% being women. During median 11.6 years of follow-up (IQR, 9.8–11.8 years), 1,062 (16.3%) had a rapid decline in FEV1.

https://doi.org/10.3346/jkms.2024.39.e275

Table 1. Baseline characteristics of the study population

Characteristics	Total population (N = 6,516)	Individuals without a rapid decline in FEV1 (n = 5,454)	Individuals with a rapid decline in FEV1 (n = 1,062)	*P* value
Age, yr	51.5 ± 8.5	51.2 ± 8.4	53.2 ± 8.9	< 0.001
Sex, male	3,174 (48.7)	2,385 (43.7)	789 (74.3)	< 0.001
BMI, kg/m^2 (n = 6,477)	24.7 ± 3.0	24.8 ± 3.0	24.1 ± 3.0	< 0.001
Ever smoker (n = 6,450)	2,654 (41.1)	1,984 (36.8)	670 (63.5)	< 0.001
Respiratory symptoms (n = 6,380)	620 (9.7)	498 (9.3)	122 (11.9)	0.013
Comorbidities				
Hypertension (n = 6,506)	1,991 (30.6)	1,640 (9.7)	351 (33.1)	0.063
Diabetes mellitus (n = 6,500)	754 (11.6)	619 (11.4)	135 (12.7)	0.226
Cardiovascular disease (n = 6,512)	107 (1.6)	88 (1.6)	19 (1.8)	0.782
Asthma (n = 6,512)	128 (2.0)	111 (2.0)	17 (1.6)	0.415
A history of pulmonary tuberculosis (n = 6,507)	639 (9.8)	528 (9.7)	111 (10.5)	0.477
Cancer (n = 6,513)	88 (1.4)	79 (1.4)	9 (0.8)	0.159
Lung function				
FVC, L	3.6 (3.0–4.3)	3.5 (3.0–4.2)	4.3 (3.6–4.8)	< 0.001
FVC, %pred	105 (96–114)	104 (95–113)	110 (101–119)	< 0.001
FEV1, L	2.9 (2.4–3.4)	2.8 (2.4–3.3)	3.3 (2.8–3.8)	< 0.001
FEV1, %pred	112 (102–123)	111 (101–122)	117 (106–128)	< 0.001
FEV1/FVC, %	81 (76–85)	81 (77–85)	80 (74–84)	< 0.001

Data are expressed as mean ± standard deviation or median (interquartile range) for continuous variables, and as number (%) for categorical variables.
BMI = body mass index, FVC = forced vital capacity, FEV1 = forced expiratory volume in 1 second.

Individuals with a rapid decline in FEV1 were older (53.2 ± 8.9 vs. 51.2 ± 8.4 years, $P < 0.001$), more likely to be men (74.3% vs. 43.7%, $P < 0.001$), and had a lower BMI (24.1 ± 3.0 vs. 24.8 ± 3.0 kg/m^2, $P < 0.001$) than those without a rapid decline in FEV1. Moreover, the proportion of ever smokers (63.5% vs. 36.8%, $P < 0.001$) and the rate of respiratory symptoms (11.9% vs. 9.3%, $P < 0.001$) were higher in individuals with a rapid decline in FEV1 than in those without a rapid decline in FEV1. Regarding baseline lung function, FVC (4.3 [IQR, 3.6–4.8] vs. 3.5 [IQR, 3.0–4.2] L, $P < 0.001$) and FEV1 (3.3 [IQR, 2.8–3.8] vs. 2.8 [IQR, 2.4–3.3] L, $P < 0.001$) were higher in individuals with a rapid decline in FEV1, while FEV1/FVC (80% [74–84%] vs. 81% [77–85%], $P < 0.001$) was lower compared to individuals without a rapid decline in FEV1. There were no differences in comorbidities between individuals with and without a rapid decline in FEV1 ($P > 0.05$ for all).

Genome-wide association analysis results for the rapid decline in FEV1

Genome-wide association analysis of the rapid decline in FEV1 identified 15 associated signals ($P < 5.0 \times 10^{-8}$) (**Table 2**). As shown in **Fig. 1**, the SNP that had the most significant association with a rapid decline in FEV1 was rs41476549 (adjusted odds ratio [aOR], 2.43; $P = 4.35 \times 10^{-11}$). Of the 15 SNPs, rs9833533 (aOR, 2.30; $P = 4.91 \times 10^{-9}$) and rs1496255 (aOR, 2.43; $P = 8.93 \times 10^{-9}$) were previously reported to be associated with lung function, maximum voluntary ventilation (MVV) and MVV along with FVC and FEV1, respectively.[12] Of the remaining SNPs, rs17248901 (aOR, 2.15; $P = 1.73 \times 10^{-8}$) and rs16951883 (aOR, 2.79; $P = 6.05 \times 10^{-10}$) had been identified previously and are linked to subscapular skinfold thickness.[16] The other SNPs were not reported previously.

In the subgroup analysis, rs16951883 (aOR, 3.24; $P = 5.87 \times 10^{-8}$) was the most significant SNP associated with rapid decline in FEV1 among never smokers, followed by rs41476549, rs16840064, and rs1350110. Conversely, among ever smokers, rs10959478 (aOR, 4.74; $P = 8.27 \times 10^{-7}$) showed the highest significance, followed by rs6805861, rs9833533, and rs16906215.

https://doi.org/10.3346/jkms.2024.39.e275

Table 2. Identified SNPs from the GWAS analysis

Rank	SNP	CHR	BP	Risk allele	No.	aOR	*P*	Reported gene and trait
1	rs41476549	11	90617150	C	5,966	2.43	4.35×10^{-11}	No results found
2	rs6805861	3	440476	T	5,985	2.45	1.01×10^{-10}	No results found
3	rs16906215	9	119586079	G	6,137	2.51	5.24×10^{-10}	No results found
4	rs16951883	16	10226280	C	5,982	2.79	6.05×10^{-10}	ATF7IP2, RN7SL493P: Subscapular skinfold thickness[12]
5	rs16840064	2	138479321	A	5,997	2.40	1.09×10^{-9}	No results found
6	rs1481797	8	72168704	C	5,945	2.15	4.24×10^{-9}	No results found
7	rs9833533	3	60543293	A	6,079	2.30	4.91×10^{-9}	FHIT: Lung function (maximal voluntary ventilation)[8]
8	rs1496255	4	121823884	G	6,058	2.43	8.93×10^{-9}	PRDM5, MAD2L1-DT: Lung function (maximal voluntary ventilation), Lung function (forced expiratory volume in 1 second), Lung function (forced vital capacity)[8]
9	rs798912	7	120695721	C	6,120	2.53	1.26×10^{-8}	No results found
10	rs17248901	3	36622465	C	6,043	2.15	1.73×10^{-8}	NBPF21P, STAC: Subscapular skinfold thickness[12]
11	rs17071575	3	64788208	A	6,037	2.05	1.93×10^{-8}	No results found
12	rs17109716	14	79206598	A	6,093	2.10	3.52×10^{-8}	No results found
13	rs17145229	11	82862073	C	6,029	2.30	3.82×10^{-8}	No results found
14	rs10959478	9	11032142	C	6,153	3.07	4.52×10^{-8}	No results found
15	rs1350110	2	184836188	A	6,114	2.24	4.73×10^{-8}	No results found
Never smoker								
1	rs16951883	16	10226280	C	3,517	3.24	5.87×10^{-8}	ATF7IP2, RN7SL493P: Subscapular skinfold thickness[12]
2	rs41476549	11	90617150	C	3,500	2.58	3.99×10^{-7}	No results found
3	rs16840064	2	138479321	A	3,532	2.60	2.10×10^{-6}	No results found
4	rs1350110	2	184836188	A	3,604	2.54	2.14×10^{-6}	No results found
Ever smoker								
1	rs10959478	9	11032142	C	2,527	4.74	8.27×10^{-7}	No results found
2	rs6805861	3	440476	T	2,462	2.55	1.60×10^{-6}	No results found
3	rs9833533	3	60543293	A	2,488	2.66	1.77×10^{-6}	FHIT: Lung function (maximal voluntary ventilation)[8]
4	rs16906215	9	119586079	G	2,526	2.73	2.83×10^{-6}	No results found

Smoking was excluded in the adjusted for the subgroup analysis.
SNP = single-nucleotide polymorphism, GWAS = genome-wide association study, CHR = chromosome, BP = base pair, aOR = adjusted odds ratio.

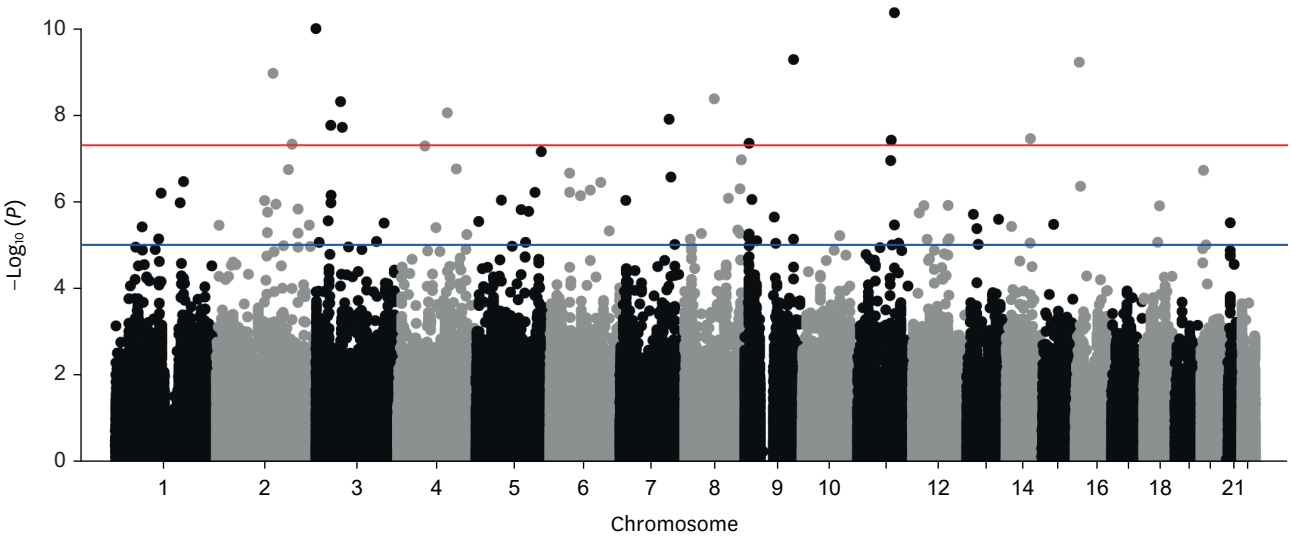

Fig. 1. Manhattan plots of the genome-wide association analysis of rapid decline in FEV1.
The blue and red horizontal lines indicate possible significance (1×10^{-5}) and the genome-wide threshold (5×10^{-8}), respectively.
FEV1 = forced expiratory volume in 1 second.

DISCUSSION

In this long-term large-scale GWAS, we found 15 SNPs that were associated with a rapid decline in FEV1 after adjusting for various possible confounders. Two of these SNPs had been reported to associated with lung function previously.[12] Of remained 13 SNPs, 11 were newly

https://doi.org/10.3346/jkms.2024.39.e275

identified in our study and rs41476549 had the most significant association with a rapid decline in FEV1. Besides, there was a distinguishable difference in associated SNPs between never smokers and ever smokers.

Many GWAS have examined lung function, and several SNPs and genes have been reported.[11,17] However, the concept of COPD was recently changed to emphasize early recognition thereof.[18] Several etiotypes and phenotypes have been proposed, but GWAS of these traits have been limited.[19] Investigation of genetic predisposition could have an important role in the early recognition of COPD. Hence, it may be time to refocus on genetic research on COPD.

Although rapid lung function decline has been suggested as one of the trajectories leading to COPD, the role of rapid FEV1 decline as a distinct COPD phenotype has not been firmly established.[3] In our study, individuals with rapid FEV1 decline exhibited features similar to those with COPD, such as older age, a predominance of males and ever smokers, and more frequent respiratory symptoms, despite preserved lung function.[1] In this context, rapid FEV1 decline may be a useful marker for identifying individuals prone to developing COPD.

In line with a previous study that evaluated the correlations between SNPs and lung function development, our findings suggest that individuals with the rs1496255 and rs9833533 nucleotide variants may be more likely to have a rapid decline in FEV1.[12] These results indicate that certain polymorphisms may affect both the development and decline of lung function. Consequently, the risk of rapid lung function decline in individuals with specific developmental trajectories should be considered. We identified 15 important SNPs, most of which are newly discovered. This means additional genetic factors may be uncovered by defining novel phenotypes. Therefore, future studies focusing on other phenotypes that predispose individuals to the development of COPD are warranted.

To understand the underlying mechanisms by which SNP variations contribute to rapid decline in FEV1, it is necessary to identify the specific pathophysiological processes involved. Some of the SNPs identified in this study were also associated with other lung functions, suggesting the possibility of genetic pleiotropy.[9] Rapid decline in FEV1 may represent an intermediate phenotype that leads to airflow limitation. However, given that this is a population-based observational study, future research is needed to clarify the exact mechanisms.

Considering subgroup analysis based on smoking history, it may be possible to identify individuals susceptible to certain risk factors for rapid lung function decline. SNPs identified in ever smokers may be used to investigate those susceptible to smoking or gene-by-smoking interaction. For example, the study of rs2829474, which is associated with complications related to alpha-1 antitrypsin deficiency, revealed a strong interaction with smoking.[20] Similarly, rs10959478, which showed the most significant association with rapid FEV1 decline among ever smokers, may also interact with smoking. If this SNP variation can be replicated in other datasets, further investigation should focus on whether interventions, such as smoking cessation, can mitigate the risk of rapid FEV1 decline in individuals with this SNP variation.

We should acknowledge the limitations of this study. First, our analysis did not include some potential confounders, such as a history of childhood infection, the lung microbiome, or current use of respiratory medicine.[21] Second, there was uncertainty about the threshold for rapid decline in lung function, as we used decrease in FEV1 ≥ 60 mL/year based on an earlier

definition, which is approximately twice the normal decline seen in the general population.[13] Nevertheless, several studies have shown that this cut-off value is clinically relevant across various age groups.[6,22] Third, this study examined only an Asian population. Therefore, our results should be generalized cautiously. Fourth, as there has been no external validation; additional research is needed to confirm the reproducibility of our results.

In conclusion, we identified 15 nucleotide variants linked to a rapid decline in FEV1, including rs1496255 and rs9833533, which have been previously reported to be associated with lung function development. Additional SNPs, which were associated with the risk of COPD, may be found using novel phenotypes.

ACKNOWLEDGMENTS

This study was conducted with bioresources from National Biobank of Korea, The Korea Disease Control and Prevention Agency, Republic of Korea (KBN-2023-005).

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