Genome-Wide Association Analysis of Body Mass in Chronic Obstructive Pulmonary Disease

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Cachexia, whether assessed by body mass index (BMI) or fat-free mass index (FFMI), affects a significant proportion of patients with chronic obstructive pulmonary disease (COPD), and is an independent risk factor for increased mortality, increased emphysema, and more severe airflow obstruction. The variable development of cachexia among patients with COPD suggests a role for genetic susceptibility. The objective of the present study was to determine genetic susceptibility loci involved in the development of low BMI and FFMI in subjects with COPD. A genome-wide association study (GWAS) of BMI was conducted in three independent cohorts of European descent with Global Initiative for Chronic Obstructive Lung Disease stage II or higher COPD: Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-Points (ECLIPSE; n = 1,734); Norway-Bergen cohort (n = 851); and a subset of subjects from the National Emphysema Treatment Trial (NETT; n = 365). A genome-wide association of FFMI was conducted in two of the cohorts (ECLIPSE and Norway). In the combined analyses, a significant association was found between rs8050136, located in the first intron of the fat mass and obesity–associated (*FTO*) gene, and BMI ($P = 4.97 \times 10^{-7}$) and FFMI ($P = 1.19 \times 10^{-7}$). We replicated the association in a fourth, independent cohort consisting of 502 subjects with COPD from COPDGene ($P = 6 \times 10^{-3}$). Within the largest contributing cohort of our analysis, lung function, as assessed by forced expiratory volume at 1 second, varied significantly by *FTO* genotype. Our analysis suggests a potential role for the *FTO* locus in the determination of anthropomorphic measures associated with COPD.

Keywords: chronic obstructive pulmonary disease genetics; chronic obstructive pulmonary disease epidemiology; chronic obstructive pulmonary disease metabolism; genome-wide association study

The heterogeneity of chronic obstructive pulmonary disease (COPD) is illustrated by the observation that a substantial subset of patients develop cachexia, whereas others do not. The reported prevalence of cachexia in COPD has varied due to differing metrics and thresholds used to define the condition. Low body mass index (BMI) is a widely available metric which has been shown to be an independent risk factor for increased mortality (1–3) and is associated with the presence of higher GOLD (Global Initiative for Chronic Obstructive Lung Disease) stage (4) and increased emphysema (5, 6) in individuals with COPD. The prevalence of low BMI, which has been variably defined as BMI less than 18.5–21, is estimated to include approximately 10% of the COPD population (2, 7), with even higher rates in severe to very severe COPD (GOLD stages III–IV).

Clinical concern regarding disproportionate muscle wasting among patients with COPD has encouraged an increasing number of researchers to include assessments of lean body mass. Because of the relative ease of implementation, bioimpedance measurements, with subsequent calculation of fat-free mass (FFM) or FFM index (FFMI) have become increasingly popular. Although variation also exists regarding the threshold used to define low FFMI, the prevalence of low FFMI in COPD is estimated to be between 20–50% in most studies (4, 8–10). In subjects with COPD, low FFMI has been associated with increased mortality (8, 11), more advanced GOLD stage (11), and reduced peripheral muscle strength and exercise capacity (10, 12, 13).

Heterogeneity in the development of cachexia in subjects with COPD suggests the interplay of exogenous (environmental) and endogenous (genetic) factors. Theoretical mechanisms proposed to explain the development of low body and muscle mass in some subjects with COPD include altered energy balance, increased inflammation, and disuse atrophy (14). Genetic susceptibility toward the development of low body weight has been investigated with regard to polymorphisms in candidate genes, such as TNF-α (*TNF*), IL-1β (*IL1B*) and IL-6 (*IL6*) (15), secretory phospholipase A2 (*PLA2G2D*) (16), and the bradykinin receptor (*BDKRB2*) (17). To further investigate the role of common genetic variants on body mass in COPD, we conducted a genome-wide association analysis in three independent COPD cohorts, with replication in a fourth cohort.

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MATERIALS AND METHODS

Study Populations, Phenotypes, and Data Collection

Data from three independent cohorts of subjects with COPD were used in the primary analysis, with replication in a fourth independent cohort. The protocol was approved by all relevant institutional review boards, and informed consent was obtained from all participants.

The first cohort consisted of 1,887 white subjects with COPD from the Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-Points (ECLIPSE) Trial (ClinicalTrials.gov identifier, NCT00292552; GlaxoSmithKline study code SCO104960). Details regarding the ECLIPSE study have been published previously (11). Subjects were between 40 and 75 years of age, had a baseline forced expiratory volume at 1 second (FEV_1)/forced vital capacity (FVC) ratio 0.7 or less, post-bronchodilator FEV_1 of less than 80% predicted, and 10 pack-years or more of smoking. BMI, bioimpedance measurements, and low-dose volumetric chest computed tomography (CT) were assessed at the first study visit.

A second cohort consisted of 933 individuals with COPD from Bergen, Norway—the details regarding this cohort have been published previously (18, 19). Cases had post-bronchodilator FEV_1/FVC of less than 0.7, FEV_1 less than 80% predicted, and 2.5 pack-years or more of smoking. BMI and bioimpedance measurements were obtained using a protocol identical to that employed for the ECLIPSE cohort. A subset of Norway subjects underwent high-resolution chest CT scanning ($n = 427$).

The third cohort consisted of a subset of 385 self-reported white subjects from the National Emphysema Treatment Trial (NETT) enrolled in the NETT Genetics Ancillary Study. Details regarding the study and cohort have been published previously (20, 21). All subjects had a post-bronchodilator FEV_1 of 45% predicted or less, with evidence of bilateral emphysema on chest CT.

The replication population consisted of 502 non-Hispanic, white individuals with COPD enrolled in COPDGene (www.copdgene.org). Subjects were between 45 and 80 years old, had a post-bronchodilator FEV_1/FVC ratio less than 0.7, an FEV_1 less than 80% predicted, and 10 pack-years or more of smoking. BMI and chest CT scan images were obtained at enrollment.

Genotyping

Details regarding the genotyping platforms, quality control, and data cleaning measures for each cohort have been described previously (22), and are summarized in the online supplement. Genome-wide single nucleotide polymorphism (SNP) genotype data were obtained using the Illumina platform (Illumina, Inc., San Diego, CA) in the three primary cohorts (ECLIPSE, Norway, and NETT). Genotyping of SNP rs8050136 in the replication cohort (COPDGene) was performed using the Taqman assay (Applied Biosystems, Carlsbad, CA).

Population Stratification and Association Analysis

Principal components were generated and used to adjust for population stratification in each cohort (22); details are outlined in the online supplement. Genome-wide association analyses were performed in PLINK (23) (v1.06). Linear regression with either BMI or FFMI as the continuous dependent variable was used. SNPs were tested for association under an additive model, with the final model in each cohort adjusted for significant principal components and sex. For the meta-analysis, we generated a Liptak combined two-sided *P* value using Z scores weighted on sample size (24, 25); a *P* value of 5×10^{-7} or less was considered significant.

Association testing in the replication cohort (COPDGene) was performed under an additive model using BMI as a continuous dependent variable with adjustment for sex. A one-sided *P* value less than 0.05 was considered significant.

RESULTS

Baseline characteristics of the subjects in each cohort are presented in Table 1. Subjects in NETT had the most severe airflow obstruction and highest number of pack-years. The relatively modest estimate of emphysema in this cohort compared with the other studies may be due to differences in CT scanning protocols. The restricted range of BMI in NETT subjects is due to exclusion of subjects with extreme BMIs at enrollment (21). Differences observed by sex within each cohort are illustrated in Table E2 in the online supplement. BMI and FFMI were significantly lower in females.

Because of baseline differences in age, pack-years of smoking, CT scanning protocols, and cohort entry criteria, we elected to conduct our initial analyses within each cohort separately. The most significant associations from genome-wide analysis of the individual cohorts are summarized in Table E3 in the online supplement—none of the associations reached genome-wide significance ($P \leq 5 \times 10^{-7}$). Genomic inflation factors of each of the primary genome-wide analyses, after adjustment for genetic ancestry with principal components, were 1.00, and suggest minimal residual population stratification. The most significant associations obtained after combining the *P* values of all the cohorts are summarized in Table 2; the inflation factor of the combined analysis was likewise minimal, at 1.00 (Figure 1). The most significant associations from our combined analysis included four SNPs located in the first intron of the fat mass and obesity–associated (*FTO*) gene, with the most highly associated SNP (rs8050136) reaching genome-wide significance ($P = 4.97 \times 10^{-7}$). Within the standard reference population for subjects of European descent, the HapMap CEU population, the most significantly associated SNPs from our analysis are all in strong linkage disequilibrium ($R^2 \geq 0.8$) with each other and with rs9939609, a well characterized intronic SNP in the literature on *FTO* (Figure E1).

The results of the combined genome-wide association analysis with FFMI are summarized in Table 3. The inflation factors of the individual analyses were minimal at 1.01; the combined analysis inflation factor was again minimal at 1.01. The same four SNPs in the first intron of *FTO* were the most highly associated. Despite a smaller sample size in this analysis, a lower *P* value was obtained, which may be due decreased heterogeneity or increased specificity of the phenotype.

TABLE 1. BASELINE CHARACTERISTICS OF SUBJECTS

	ECLIPSE	Norway	NETT	COPDGene
n	1,734	851	365	502
Male (%)	66.9	60.1	64.9	49.6
Age	63.7 (7.1)	65.5 (10.1)	67.5 (5.8)	64.8 (8.1)
FEV_1 % predicted*	47.7 (15.7)	50.7 (17.5)	28 (7.4)	48.8 (18.4)
FVC % predicted*	85.7 (20.1)	78.6 (16.5)	69.1 (15.8)	76.1 (16.9)
FEV_1/FVC*	0.45 (0.12)	0.51 (0.13)	0.32 (0.06)	0.48 (0.13)
Pack-years	50.4 (27.4)	32.0 (18.6)	66.1 (30.9)	54.7 (26.7)
Body mass index	26.7 (5.6)	25.3 (5)	25.0 (3.5)	28.1 (6.3)
Cachectic, %†	13.2	19.3	14.5	11.4
Fat-free mass index	17.3 (2.7)	16.8 (2.3)	N/A	N/A
Emphysema at −950 HU, %	18.4 (12.1)	11.5 (11.8) §	16.8 (10.8)	15.7 (13.4)
Hypertension, %‡	33.1	35.6	26.9 ‖	48.2
Diabetes type 2, %‡	9.8	5.4	0.6 ‖	10

Definition of abbreviations: COPDGene, The Genetic Epidemiology of Chronic Obstructive Pulmonary Disease Study; ECLIPSE, Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-Points; FEV_1, forced expiratory volume at 1 second; FVC, forced vital capacity; NETT, National Emphysema Treatment Trial.

Data are presented as mean (SD) values, unless otherwise noted.

* Post-bronchodilator values.

† Cachexia defined as BMI <21.

‡ Data are based on self-reported history of hypertension and diabetes.

§ $n = 418$ (CT performed on subset of subjects).

‖ Data are based upon examiner review of use of antihypertensive medications and insulin use.

TABLE 2. COMBINED GENOME WIDE ASSOCIATION RESULTS FOR BODY MASS INDEX ANALYSIS

Rank	SNP	Minor Allele	Minor Allele Frequency	*P* Value in Individual Cohorts			Combined *P* Value	Type	Closest Gene
				ECLIPSE	Norway	NETT			
1	rs8050136	A	0.39–0.42	1.96×10^{-5}	1.9×10^{-3}	6.6×10^{-1}	4.97×10^{-7}	Intronic	*FTO*
2	rs743741	C	0.13–0.14	9.58×10^{-5}	7.3×10^{-3}	1.4×10^{-1}	1.16×10^{-6}	Intronic	*SYN3*
3	rs3751812	T	0.39–0.42	4.42×10^{-5}	1.9×10^{-3}	6.3×10^{-1}	1.21×10^{-6}	Intronic	*FTO*
4	rs743742	A	0.16–0.17	1×10^{-4}	4.7×10^{-2}	1.9×10^{-2}	3.41×10^{-6}	Intronic	*SYN3*
5	rs9930333	G	0.42–0.44	8.71×10^{-5}	4.2×10^{-3}	6.1×10^{-1}	4.17×10^{-6}	Intronic	*FTO*
6	rs9941349	T	0.41–0.43	1×10^{-4}	2.8×10^{-3}	6.6×10^{-1}	4.39×10^{-6}	Intronic	*FTO*
7	rs3817193	T	0.15–0.16	1.21×10^{-5}	2×10^{-1}	7.6×10^{-1}	7.46×10^{-6}	Intronic	*ZSCAN2*
8	rs2358944	G	0.13–0.14	5×10^{-4}	2.7×10^{-3}	9.1×10^{-1}	1.29×10^{-5}	Intergenic	*RPSAP52*
9	rs10860821	A	0.29	9.64×10^{-5}	3.9×10^{-1}	4.6×10^{-3}	1.40×10^{-5}	Downstream	AC084398.4
10	rs289698	C	0.05–0.06	2×10^{-4}	5×10^{-2}	2.8×10^{-1}	1.66×10^{-5}	Intronic	*GALNAC3*

Definition of abbreviations: ECLIPSE, Evaluation of Chronic Obstructive Pulmonary Disease Longitudinally to Identify Predictive Surrogate End-Points; NETT, National Emphysema Treatment Trial; SNP, single nucleotide polymorphism.

Models in each cohort employed body mass index as a continuous dependent variable. All models were adjusted for sex and significant principal components.

The mean values of BMI, FFMI, post-bronchodilator FEV_1 % predicted, FVC % predicted, FEV_1/FVC, and percent emphysema at −950 Hounsfield units by rs8050136 genotype in the ECLIPSE cohort are illustrated in Table 4. The minor allele was associated with a significantly higher BMI, FFMI, FEV_1 % predicted, and FEV_1/FVC, as well as less total emphysema. There were no significant differences in FVC percent predicted by *FTO* genotype. Similar results were obtained for the other three *FTO* SNPs (data not shown). SNPs within genes previously reported to be associated with COPD-related cachexia in the literature, such as *TNF*, *IL1B*, and *IL6*, did not demonstrate genome-wide significant associations in our analysis, but did have trends toward association (Table E4). In addition, in linear regression models with BMI, FFMI, lung function, and emphysema as dependent variables, no significant SNP by smoking (pack-years) interactions were noted under a multiplicative model for the most highly associated SNP from our analyses.

The most significantly associated SNP from our combined analyses, rs8050136, was genotyped in subjects from COPDGene with GOLD stage II or higher disease. Using linear regression, with BMI as a continuous dependent variable and adjusting for sex, the one-sided *P* value for association reached significance at 6.0×10^{-3}. The direction of effect was consistent with that observed in our preceding combined genome-wide association analysis. The Liptak combined *P* value for rs8050136 for all four cohorts was 4.14×10^{-8}. In unadjusted ANOVA of the COPDGene cohort, the minor allele again demonstrated a trend toward higher BMI and FEV_1 % predicted, and less emphysema (data not shown). Although none of these trends were statistically significant, this may be due to decreased power related to the relatively smaller sample size when compared with the ECLIPSE cohort.

DISCUSSION

The *FTO* gene was first identified as a susceptibility locus for adult and childhood obesity in a genome-wide association study of type 2 diabetes mellitus in 2007 (26). Within populations of European ancestry, several SNPs within a single linkage disequilibrium (LD) block located in the first intron have consistently been associated with BMI (27–31). Despite significantly different allele frequencies and LD structure in this region among non-European populations (31), replication of SNPs originally identified in white populations has been demonstrated in American Hispanic (31–33), black (32, 34), and Chinese (35) populations.

The minor allele of the most frequently associated SNP in *FTO*, rs9939609, confers an approximately 20–30% increased risk per allele for being overweight or obese (26, 36). Similar estimates have been obtained for the minor alleles of other SNPs within this LD block (27, 28), including rs8050136 (33, 34). The LD structure of this region, although beneficial in reducing the number of tagging SNPs needed for association discovery, has proven challenging with regard to identification of a putative causal variant. Despite exhaustive searches for functional variants in the region, none have been definitively identified (26, 27). Speculation regarding possible roles for transcription factor binding, splice site variation, or long-range control mediated by these intronic variants exists. Provocatively, rs8050136, the most significantly associated SNP in our analysis, is located within a putative transcription factor–binding domain for cut-like homeobox 1 (*CUX1*). Preferential binding of the "A" allele by *CUX1* has been demonstrated in human fibroblast cultures, with small interfering RNA (siRNA) knockdown experiments demonstrating a reduction of *FTO* transcription in the absence of *CUX1* (37).

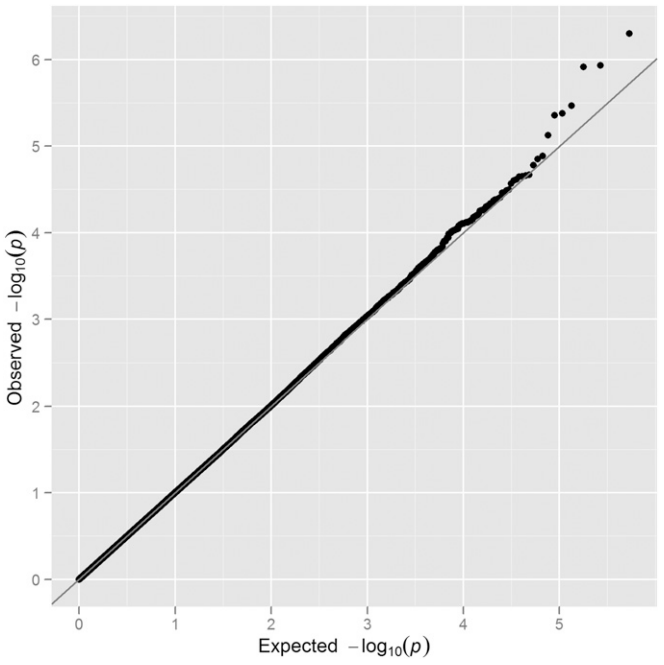

Figure 1. Quantile–quantile (Q-Q) plot of expected versus actual *P* values in combined analysis for body mass index.

TABLE 3. COMBINED GENOME-WIDE ASSOCIATION RESULTS FOR FAT-FREE MASS INDEX ANALYSIS

		Individual Cohort *P* Values				
Rank	SNP	ECLIPSE	Norway	Combined *P* Value	Type	Closest Gene
1	rs8050136	1.93×10^{-5}	8×10^{-4}	1.19×10^{-7}	Intronic	*FTO*
2	rs3751812	2.69×10^{-5}	8×10^{-4}	1.73×10^{-7}	Intronic	*FTO*
3	rs9941349	4.15×10^{-5}	1.4×10^{-3}	4.21×10^{-7}	Intronic	*FTO*
4	rs9930333	5.77×10^{-5}	2.3×10^{-3}	8.20×10^{-7}	Intronic	*FTO*
5	rs17060242	7.51×10^{-5}	8.1×10^{-3}	2.53×10^{-6}	Intergenic	RP11-285B24.1
6	rs10852521	6.84×10^{-5}	2.53×10^{-2}	5.27×10^{-6}	Intronic	*FTO*
7	rs3817193	4.34×10^{-6}	3.97×10^{-1}	5.99×10^{-6}	Intronic	*ZSCAN2*
8	rs1443936	1×10^{-4}	1.94×10^{-2}	6.52×10^{-6}	Intergenic	AC138057.1
9	rs4456263	1.23×10^{-5}	2.25×10^{-1}	7.47×10^{-6}	Intronic	*NTM, OPCML*
10	rs12686399	1.66×10^{-5}	2.12×10^{-1}	9.24×10^{-6}	Intergenic	RP11-373A6

Definition of abbreviations: ECLIPSE, Evaluation of Chronic Obstructive Pulmonary Disease Longitudinally to Identify Predictive Surrogate End-Points; SNP, single nucleotide polymorphism.

Models used fat-free mass index as a continuous dependent variable. All models were adjusted for sex and significant principal components. SNP rs10867970 was ranked sixth ($P = 5.24 \times 10^{-6}$), but was only present in the Norway cohort.

The association between *FTO* variants and obesity-related complex diseases, such as diabetes, hyperlipidemia, and hypertension, appear to be mediated largely, if not entirely, through the effect of *FTO* on BMI (26, 29, 32, 33, 36). However, a longitudinal study of Danish men demonstrated increased all-cause mortality associated with the minor allele of rs9939609 *independent* of BMI (38), thus suggesting that *FTO* may exert its effects in ways that are incompletely assessed by current disease-defining measures. Although the minor allele of *FTO* may confer increased mortality risk to the general population, the opposite effect may be true in certain disease states such as COPD. The body mass index, airway obstruction, dyspnea, and exercise capacity (BODE) index has identified a BMI of less than 21 as a risk factor for increased mortality among patients with COPD (1). Within ECLIPSE, the minor allele frequency of rs8050136 in this low-BMI subgroup was significantly lower ($P = 1.5 \times 10^{-3}$) than that of the general COPD population (Figure 2). The concept that polymorphisms conferring differential effects may be beneficial under certain circumstances and detrimental under alternate circumstances likely applies to *FTO*. Clinical observations have been made that certain malignancies are associated with either high or low BMI—examples include renal cell carcinoma and lung cancer, respectively. The *FTO* risk allele for obesity was found to confer increased risk for renal malignancies, but was found to be protective against primary lung malignancies (39).

Although *FTO* genotype does not appear to affect birth weight, genotype effects are evident by childhood (26, 27), with continued strong evidence of association into early adulthood and mid-life (28, 31) and possible attenuation in senescence (36). The association between *FTO* genotype and lung function noted in our cohorts has not been previously described, although the individual associations of low body mass with low lung function and low body mass with *FTO* genotype are not surprising. Whether *FTO* genotype impacts lung function and the response to smoking directly, as opposed to acting through BMI, will need to be explored through other avenues, such as functional studies or causal modeling analyses. Interestingly, in a *post hoc* analysis of the ECLIPSE cohort, rs8050136 genotype was a significant predictor of post-bronchodilator FEV_1 % predicted under an additive model, even after correcting for age, sex, pack-years of smoking, and BMI.

The function of the *FTO* gene itself remains incompletely characterized. The gene spans over 227 kb, is comprised of nine exons, and is highly conserved among vertebrates and marine algae (40, 41). The gene product has been characterized as a 2-oxoglutarate–dependent nucleic acid demethylase which almost exclusively catalyzes the demethylation of 3-methylthymine on single stranded DNA and 3-methyluracil on RNA transcripts (42, 43). Gene ontology analyses suggest a possible role in environmental sensing with a subsequent nuclear site of action (44). Interestingly, the 2-oxoglutarate–dependent family of enzymes includes hypoxia-inducible factor-1α hydroxylases (*HIF1A*), a widely expressed enzyme that serves as an oxygen sensor. *FTO* activity also appears responsive to ambient oxygen levels, and demonstrates reduced activity in hypoxemic environments (42).

The mechanism by which the *FTO* gene product impacts body mass likewise remains unclear. *FTO* is expressed ubiquitously in adult and fetal tissues, including the lung, of both mice and humans (26, 27, 45). Rare exonic mutations resulting in qualitative and quantitative changes in *FTO* have been reported. Severe malformations and early death were described in a large consanguineous pedigree where an R316Q missense mutation in *FTO* was identified (46). Interestingly, fibroblast cultures from individuals homozygous for the mutation suggested a possible early senescence phenotype (46), a process which may be relevant in COPD.

Although qualitative changes in the *FTO* gene product have been demonstrated to have striking phenotypic effects, murine strains lacking *Fto* entirely are viable, and are born at a normal weight (45). Homozygous *Fto* knockout mice are morphologically normal but demonstrate decreased weight gain shortly after birth, and achieve an overall smaller adult size. Furthermore, *Fto* knockout mice exhibit relative hyperphagia, decreased spontaneous physical activity, increased energy expenditure, and relative resistance to the effects of an obesogenic diet. To date, however,

TABLE 4. MEAN BODY MASS INDEX, FEV_1, FVC, FEV_1/FVC, AND EMPHYSEMA BY rs8050136 GENOTYPE IN ECLIPSE

	Genotype			ANOVA
	C/C	C/A	A/A	*P* Value
n	638	828	268	—
Body mass index	26	27	27.5	0.0001
Fat-free mass index	17	17.4	17.7	0.0002
FEV_1 % predicted*	46.2	48.5	48.6	0.0111
FVC % predicted*	85.3	86.1	85.7	0.7027
FEV_1/FVC, %*	0.43	0.45	0.45	0.0069
Emphysema at −950 HU, %	19.8	17.8	16.8	0.0021

Definition of abbreviations: ECLIPSE, Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints; FEV_1, forced expiratory volume at 1 second; FVC, forced vital capacity.

* Post-bronchodilator values.

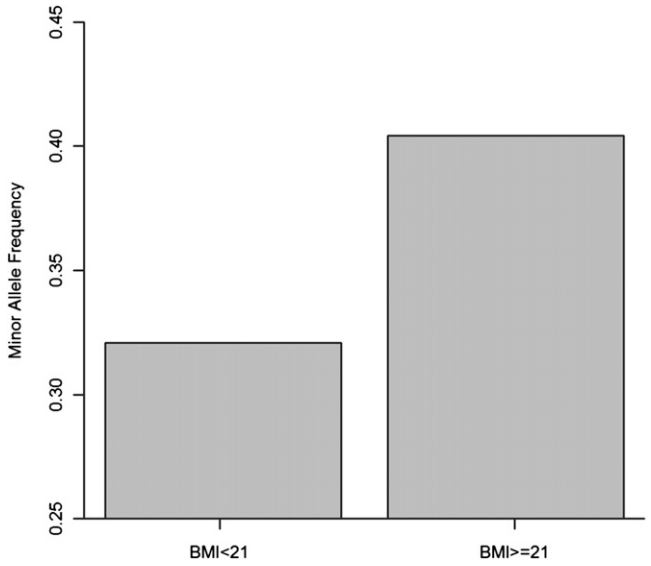

Figure 2. Minor allele frequency of rs8050136 in Evaluation of Chronic Obstructive Pulmonary Disease (COPD) Longitudinally to Identify Predictive Surrogate End-Points (ECLIPSE) population based on the presence or absence of low body mass index (BMI $<$ 21) in ECLIPSE ($P = 1.5 \times 10^{-3}$).

Fto knockout mice have not been systematically assessed for pulmonary phenotypes or effects.

We demonstrate that a locus implicated as a determinant of basal metabolism is associated with BMI and FFMI in subjects with COPD. Our analysis represents the first report of this association in a study population unselected for traditional "metabolic diseases," such as diabetes or obesity. Consistent with previous genome-wide association studies, the most highly associated locus was entirely distinct from the loci previously explored in candidate gene studies, such as inflammatory biomarkers or cytokines. Given that the mean BMI in our populations was in the overweight range, concern regarding the relevance to the development of cachexia may exist. However, given the continuous distribution of body and muscle mass composition in subjects with COPD, we believe that the association with *FTO* described in our study remains relevant to the discussion of cachexia and anthropomorphic features in COPD. Beyond the systemic effects, the relationship between the *FTO* locus and lung function implicated in our analyses may represent an area of interest for future studies.

We acknowledge several limitations to our study. The association demonstrated with *FTO*, although biologically plausible, fails to meet the strict genome-wide statistical significance threshold proposed by some investigators (47). Second, no clear functional variant associated or attributable to the most highly associated SNPs in our analyses has been identified. Finally, as mentioned previously here, the limited number of truly cachectic subjects in each of our cohorts limits our ability to extrapolate our results to the clinically observed phenomenon of COPD-related cachexia. Nonetheless, we contend that the association of *FTO* SNPs with BMI and FFMI in subjects with COPD could provide important clues to the mechanisms of cachexia that develops in a subset of subjects with COPD.

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