Genetic Advances in COPD: Insights from COPDGene

Margaret F. Ragland*[1], Christopher J. Benway*[2], Sharon M. Lutz[3], Russell P. Bowler[4], Julian Hecker[5], John E. Hokanson[6], James D. Crapo[4], Peter J. Castaldi[2], Dawn L. DeMeo[2,7], Craig P. Hersh[2,7], Brian D. Hobbs[2,7], Christoph Lange[5], Terri H. Beaty[8], Michael H. Cho[2,7], Edwin K. Silverman[2,7]

Online Supplement

Details Regarding the COPDGene Study Population:

The Genetic Epidemiology of COPD study (COPDGene) began enrollment in January 2008 with enrollment ending in July 2011. Five-year follow-up data collection was completed and 10-year follow-up is now underway. The study includes 10,198 individuals with inclusion criteria of age 45 to 80 years old and at least a 10 pack-year smoking history. Individuals who self-identified as non-Hispanic white or African American were enrolled. Subjects were recruited via advertisements at outpatient clinics, word of mouth communication, and outreach to community groups and churches at 21 clinical sites across the United States. Data collected includes detailed medical history, respiratory symptoms, exposure questionnaires, demographics, functional measures (six minute walk distance), lung function (spirometry before and after bronchodilator), and quantitative chest computed tomography (CT) scans (at both full inspiration to total lung capacity and relaxed exhalation to functional residual capacity). In order to include the full range of COPD subjects, individuals diagnosed with asthma in either the COPD or smoking control groups were included in the study. Further, potential participants were not excluded based on spirometric bronchodilator responsiveness. Exclusion criteria include pregnancy, history of other lung disease (pulmonary fibrosis, extensive bronchiectasis, cystic fibrosis), previous surgical excision of at least one lung lobe, metal in the chest, recent exacerbation of COPD treated with antibiotics or steroids, recent eye surgery, recent myocardial infarction, recent hospitalization for other reason, recent chest or abdominal surgery, inability to use albuterol, multiple self-described racial categories, history of chest radiation therapy, and first or second degree relative already enrolled in the study.

Table E1. Description of study populations described in this review

Study	Total Subjects	COPD Cases	Non-cases	Male	Female	Description
COPDGene, all subjects	10371	3786*	6585†	5524 (53%)	4847 (47%)	Enrolled 10,198 subjects of non-Hispanic white or African American ancestry, aged 45-80 years old, with a minimum of 10 pack-years of smoking and no other lung disease; 108 non-smoking controls and 65 subjects ineligible due to bronchiectasis or interstitial lung disease were also enrolled.
COPDGene, Non-Hispanic Whites	6933	2878*	4055†	3630 (52%)	3303 (48%)	
COPDGene, African Americans	3438	908*	2530†	1894 (55%)	1544 (45%)	
GenKOLS	1929	973‡	956¶	1051 (54%)	878 (46%)	Norwegian Genetics of Chronic Obstructive Lung Disease; subjects include Caucasians aged >40 years, current and former smokers with ≥ 2.5 pack-yrs of smoking history and no severe α1-antitrypsin deficiency.
NETT	389 (in COPD genetics studies)	389‡	-	250 (64%)	139 (36%)	The National Emphysema Treatment Trial; multicenter clinical trial to evaluate lung volume reduction surgery. Subjects had severe airflow obstruction and evidence of emphysema by CT and were all former-smokers.
NAS	472 (in COPD genetics studies)	-	472¶	472 (100%)	0 (0%)	Normative Aging Study; longitudinal study of healthy men established in 1963; smoking controls were of self-reported white ancestry and at least 10 pack-years of cigarette smoking with no evidence of airflow obstruction on most recent spirometry
ECLIPSE	2746	2164§	582‖	1411†† (65%)	750†† (35%)*	Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points; a large observational study of COPD patients and controls conducted at 46

						centres in 12 countries aimed at defining COPD phenotypes and identifying biomarkers and/or genetic parameters that help to predict disease progression
SPIROMICS	2877	1766[#]	1111**	1520 (53%)	1357 (47%)	Subpopulations and Intermediate Outcome Measures in COPD Study; smoking history ≥20 pack-years or <1 pack-year.
CHARGE (Studies included in lung function genetics publications described in this review)	37957	-	-	16593 (44%)	21364 (56%)	Cohorts for Heart and Aging Research in Genomic Epidemiology Consortium; includes 5 prospective cohort studies from the United States and Europe: the Age, Gene/Environment Susceptibility (AGES)—Reykjavik Study, the Atherosclerosis Risk in Communities (ARIC) Study, the Cardiovascular Health Study (CHS), the Framingham Heart Study (FHS), and the Rotterdam Study (RS).
SpiroMeta	20288	-	-	8600 (42%)	11688 (58%)	Included 14 studies of individuals of European ancestry; all individuals had measures of FEV1 and FVC and smoking status recorded.
MESA-SHARe	8224	313[‡] (not including Chinese)	1834[¶] (not including Chinese)	1147[††] (53%)	1000[††] (47%)	Multi-Ethnic Study of Atherosclerosis; combined participants of MESA Lung, MESA Family, and MESA Air Pollution Studies comprised of approximately 33% White, 31% African American, 26% Hispanic, and 9% Chinese individuals; a longitudinal study of subclinical cardiovascular disease
ICGC	63192	15256[‡]	47936[¶]	31162 (49%)	32030 (51%)	International COPD Genetics Consortium; combination of 26 cohorts. Cases were based on pre-bronchodilator evidence of moderate-to-severe airflow limitation by modified GOLD criteria and

						controls had normal spirometry.
BiLEVE	48943	9498‡	9748¶	9986 (52%)††	9260 (48%)††	UK Biobank Lung Exome Variant Evaluation consortium; subset of UK Biobank; COPD status defined by spirometry; includes both heavy and never-smokers.

* GOLD Status 2/3/4 with a post-bronchodilator forced expiratory volume in 1 s (FEV1) less than 80% of the predicted value and the ratio between FEV1 and forced vital capacity (FVC) less than 0.7

† GOLD Stage 1, PRISm (preserved FEV1/FVC but reduced FEV1) and smokers and non-smokers with normal spirometry

‡ FEV1 < 80% and FEV1 to FVC ratio of < 0.7

¶ FEV1 ≥ 80% and FEV1/FVC ≥ 0.7

§ Baseline post-bronchodilator FEV1 < 80% of the reference value and FEV1/FVC ≤ 0.7 and current or ex-smokers with a smoking history of ≥10 pack-years

|| Baseline post-bronchodilator FEV1 > 85% of the reference value and FEV1/FVC > 0.7; and current or ex-smokers with a smoking history ≥10 pack-years and non-smokers

Post-bronchodilator FEV1/FVC < 0.7; and current or ex-smokers with a smoking history of ≥20 pack-years

** Post-bronchodilator FEV1/FVC > 0.7 for current or ex-smokers with a smoking history of ≥ 20 pack-years and non-smokers (< 1 pack-year smoking) with pre-bronchodilator FEV1/FVC > 0.7

†† cases and non-cases only

Table E2. Summary of Genetic Findings in COPDGene African American subjects

Hobbs et al. 2017[19]	As part of this large, multi-cohort study of COPD status, a separate analysis including only African-ancestry subjects (including 910 cases and 1,566 controls from COPDGene) was performed. No unique genome-wide significant association signals were identified. Of the 22 lead variants from the combined meta-analysis across racial groups, the three most significant associations in this African-ancestry study were SNPs near *THSD4* ($p = 5.1 \times 10^{-5}$), *CHRNA5* ($p = 2.2 \times 10^{-3}$), and *ADGRG6* ($p = 5.3 \times 10^{-3}$).
Lutz et al. 2015[23]	In a GWAS for post-bronchodilator lung function, 3,260 COPDGene AA subjects were analyzed. The small number of genome-wide significant associations were all imputed SNPs, with low minor allele frequency (<5 %), and in a region with no other non-imputed SNPs. Of the significant results for FEV1/FVC in the meta-analysis, the three most significant associations in COPDGene AAs were near *CHRNA5* ($p = 3.14 \times 10^{-6}$), *CHRNA3* ($p = 6.02 \times 10^{-6}$), and *TGFB2* ($p = 5.24 \times 10^{-5}$).
Cho et al. 2015[27]	Meta-analysis of COPDGene NHW and AA subjects for emphysema and airway quantitative imaging phenotypes did not identify significant signals unique to AAs.
Castaldi et al. 2014[29]	GWAS of local histogram patterns analyzed 3,158 COPDGene AA subjects alone and as combined meta-analysis with NHWs. From the seven genome-wide significant loci in the meta-analysis, three

	exhibited narrower GWAS peaks in AAs (near *CHRNA5*, *CYP2A6*, and *VWA8*).
El-Boueiz et al. 2017[30]	Analyzed 2,955 COPDGene AA subjects as part of GWAS meta-analysis for emphysema distribution. Of the seven genome-wide significant loci for emphysema distribution in the meta-analysis, the most significant locus in COPDGene AAs was a variant near *TRAPPC9* associated with the upper-third/lower-third emphysema percentage ratio ($p = 4.98 \times 10^{-6}$).
McDonald et al. 2014[34]	Performed a GWAS of resting oxygen saturation of COPDGene AAs with COPD (n = 820). Reported five genome-wide significant associations: one variant near *FOXG1* ($p = 4.9 \times 10^{-8}$), two near *LINC00928* ($p = 4.8 \times 10^{-9}$, 2.2×10^{-8}) , and two near *TICRR* ($p = 2.5 \times 10^{-8}$, 4.6×10^{-8}).
Lee at al. 2014[37]	COPDGene AAs were incorporated in a GWAS meta-analysis for chronic bronchitis, leading to increasingly significant signals at *FAM13A*, *AGPDG1*, *CHRNA3*, and *EFCAB4A* loci.
Lee et al. 2015[39]	As part of a GWAS meta-analysis for pulmonary artery enlargement (PAE), 754 AA COPD cases and 1,749 AA control subjects were analyzed. Comparing COPD subjects with and without PAE, the meta-analysis identified significantly associated variants near *IREB2/AGPHD1* and *GALC*. Comparing COPD PAE subjects to smokers with normal spirometry, the most significant signal in the meta-analysis and COPDGene AAs only was near *CHRNA5* ($p_{overall} = 6.93 \times 10^{-10}$, $p_{AA} = 9.26 \times 10^{-5}$).
Hardin et al. 2016[46]	Identified genetic variants of bronchodilator response (BDR) in 811 COPDGene AA subjects. In African Americans, several variants in the genes *CDH13*, *SGCD* and *GOLGA8B* demonstrated genome-wide significance for their association with the response to β2-

	agonists. The associated SNPs were of low minor allele frequency (<5%). It was also reported that there was a small but significant difference between AAs and NHWs in the response to inhaled β2-agonists.
Begum et al. 2016[47]	Identified in COPDGene AAs a polymorphic CNV on chromosome 5q35.2 located between two genes (FAM153B and SIMK1, but also harboring several pseudo-genes) giving genome-wide significance in tests of association with total lung capacity as measured by chest CT scans.
Begum et al. 2016[48]	Identified a CNV component (a hemizygous deletion) on chromosome 3p26.1 associated with two quantitative phenotypes related to smoking behavior among African Americans.
Foreman et al. 2017[57]	Demonstrated that the heterozygous PiMZ genotype for alpha-1 antitrypsin in African Americans was associated with lower lung function, including FEV_1 percent predicted and FEV_1/FVC.

Table E3. Summary of Genome-wide Significant Associations with COPD-related Phenotypes

Study	Phenotype	Chr	rsID	Nearest Gene	Effect Allele	P value
Manichaikul et al. 2014[25]	Percent emphysema	12	rs7957346	SNRPF/CCDC38	C	2.20E-08
		6	rs10947233	PPT2	T	3.20E-08

	Upper-lower lobe emphysema ratio	19	rs10411619	MAN2B1	T	1.10E-09
		4	rs7698250	DHX15	T	1.80E-10
		17	rs7221059	MGATA5B	C	2.70E-08
Cho et al. 2015[27]	Percent emphysema at -950 HU	4	rs13141641	HHIP	T	1.70E-12
		15	rs55676755	CHRNA3	C	2.40E-09
		6	rs2070600	AGER	T	4.60E-09
		8	rs75200691	DLC1	T	9.70E-09
		14	rs45505795	SERPINA10	C	1.40E-08
	15th Percentile of Lung Density Histogram (Perc15)	8	rs74834049	DLC1	A	6.00E-10
		4	rs13141641	HHIP	T	8.40E-10
	Wall Area %	4	rs142200419	MIR2054	T	4.60E-09
	Square Root of Wall Area of 10 mm internal perimeter airways (Pi10)	6	rs2070600	AGER	T	3.50E-09
	Gas-trapping on expiratory CT at -856 HU	21	rs55706246	LINC00310	A	1.30E-08
Castaldi et al. 2014[29]	Local histogram: Normal	15	rs17486278	CHRNA5	A	8.30E-13

		4	rs138641402	HHIP	A	1.70E-09
		1	rs1690789	TGFB2	C	2.90E-08
		11	rs17368659	MMP12	G	1.10E-08
	Local histogram: moderate centrilobular emphysema	15	rs114205691	CHRNA3	C	3.10E-13
		19	rs56113850	CYP2A6	T	1.30E-09
		11	rs17368582	MMP12	G	2.70E+09
		1	rs1690789	TGFB2	C	7.90E-09
	Local histogram: severe centrilobular emphysema	15	rs9788721	AGPHD1	T	1.80E-13
		17	rs379123	MYO1D	T	1.50E-08
	Local histogram: panilobular emphysema	15	rs11852372	AGPHD1	A	1.50E-10
		13	rs9590614	VWA8	G	1.10E-08
El-Boueiz et al. 2017[30]	Upper – Lower Lobe Emphysema (Diff950)	15	rs138544659	CHRNA3/5	T	9.87E-15
		4	rs13141641	HHIP	T	1.76E-11
	(Upper Lobe Emphysema)/(Lower Lobe Emphysema (Ratio950)	4	rs13141641	HHIP	T	6.34E-18

		15	rs12914385	CHRNA3/5	T	1.72E-17
		4	rs2645694	SOWAHB	T	2.42E-08
		8	rs75755010	TRAPPC9	A	3.43E-08
		10	rs35374984	KIAA1462	A	3.83E-08
Halper-Stromberg et al. 2017[31]	Visual assessment of CT	15	rs2656072	IREB2	G	6.30E-09
	%LAA-950	15	rs2656072	IREB2	G	4.50E-08
McDonald et al. 2014[34]	Oxygen saturation	14	rs6576132	FOXG1	A	4.90E-08
		15	rs8038108	LINC00928	C	4.80E-09
		15	rs116033091	LINC00928	T	2.20E-08
		15	rs8025537	TICRR	C	2.50E-08
		15	rs147566087	TICRR	T	4.60E-08
Lee et al. 2014[37]	Chronic bronchitis	4	rs2869967	FAM13A	C	5.61E-10
		4	rs2045517	FAM13A	T	5.63E-10
		4	rs7671167	FAM13A	T	5.58E-09
		4	rs2904259	FAM13A	C	6.25E-09
		11	rs34391416	EFCAB4A	A	6.11E-10
		11	rs147862429	CHID1	T	2.90E-10
		11	rs13909846	CHID1	T	5.67E-09
		11	rs143705409	AP2A2	G	7.19E-10
		11	rs185786041	AP2A2	C	8.44E-10

		11	rs117455145	AP2A2	G	8.50E-10
Lee et al. 2015[39]	Pulmonary artery enlargement, COPD	15	rs7181486	IREB2	C	2.10E-08
		15	rs656219465	IREB2	G	2.12E-08
		15	rs17483929	IREB2	A	2.24E-08
		15	rs2009746	IREB2	G	2.25E-08
		15	rs72738718	IREB2	C	2.37E-08
		15	rs72736802	IREB2	T	2.72E-08
		14	rs7140285	GALC	T	3.75E-08
		15	rs8034191	AGPHD1	C	4.06E-08
		15	rs55983731	IREB2	T	4.39E-08
		15	rs17483686	IREB2	T	4.74E-08
		15	rs17483721	IREB2	C	4.90E-08
	Pulmonary artery enlargement, COPD vs. smokers w/ normal spirometry	15	rs17486278	CHRNA5	C	6.93E-10
Hancock et al. 2015[45]	Nicotine dependence	20	rs2273500	CHRNA4	C	8.00E-09
		20	rs6011779	CHRNA4	C	1.40E-08
		20	rs4809294	CHRNA4	A	3.80E-08
Hardin et al. 2016[46]	Bronchodilator responsiveness	6	rs17575208	EPHA7	A	8.92E-09

	as absolute volume of FEV1 (BDRABS)					
		16	rs115067260	CDH13	A	5.05E-09
		17	rs140948272	PITPNA	C	5.24E-09
	bronchodilator responsiveness as % of baseline FEV1 (BDRBASE)	5	rs10056066	SGCD	A	4.86E-08
	bronchodilator responsiveness as % of predicted FEV1 (BDRPRED)	16	rs114132812	CDH13	A	1.19E-08
		15	rs76677753	GOLGA8B	A	1.90E-08