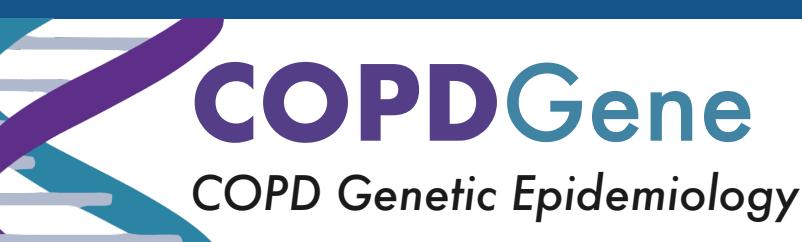
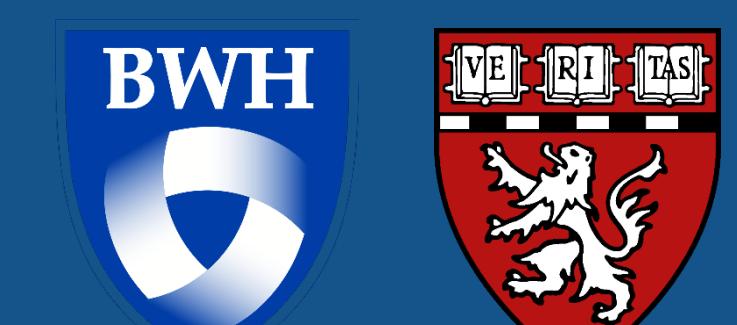


Genome-Wide Association Study of Parametric Response Mapping in the COPDGene Study Dissects Genetic Contributions to Emphysema and Functional Small Airway Disease



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RATIONALE

- Parametric response mapping (PRM) of paired lung computed tomography (CT) scans has improved assessment and characterization of chronic obstructive pulmonary disease (COPD), allowing for the quantification of two distinct components that contribute to airflow obstruction: emphysema and functional small airway disease (fSAD)^{1,2}.
- Previously, genome-wide association studies (GWAS) of quantitative imaging phenotypes have identified genetic variants associated with emphysema and gas trapping, several of which are also associated with COPD susceptibility and lung function levels^{3,4,5}.
- We hypothesized that the improved quantitative resolution of PRM would reveal novel genetic association signals distinct to each phenotypic component.

[1] Nat Med. 2012 Nov;18(11):1711-5.

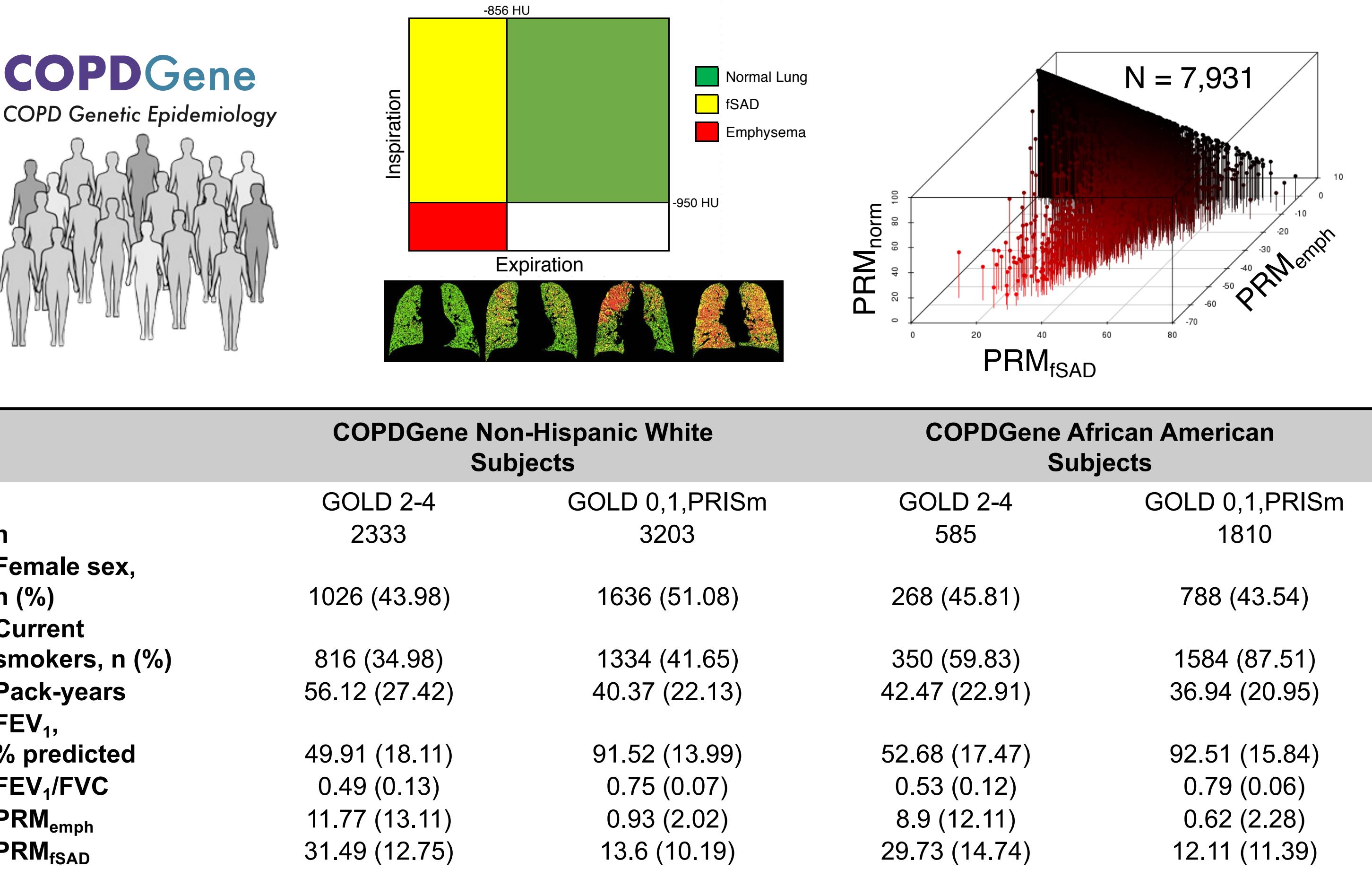
[2] Sci Rep. 2017 Jun 7;7(1):2999.

[3] Am J Respir Crit Care Med. 2015 Sep 1;192(5):559-69.

[4] Am J Respir Crit Care Med. 2014 Aug 15;190(4):399-409.

[5] Am J Respir Crit Care Med. 2017 Mar 15;195(6):757-771.

METHODS AND MATERIALS



We performed a GWAS of PRM percentage emphysema (PRM_{emph}) and PRM percentage fSAD (PRM_{fSAD}) in current and former cigarette smokers with and without COPD in the COPDGene study. Because PRM values are compositional by nature, we further performed a GWAS on isometric log ratio (ILR)-transformed PRM data to determine the single nucleotide polymorphisms (SNPs) specifically contributing to the individual phenotypic components and their relative ratios. Overall, 7,856 COPDGene participants were analyzed (5,499 non-Hispanic Whites [NHW] and 2,357 African-Americans [AA]). Association analyses were run separately for NHW and AA after controlling for age, gender, pack-years of smoking, current smoking status, and population stratification using principal components of genetic ancestry. To identify candidate causal genes we used S-PrediXcan to test the association between PRM phenotypes and genetic components of gene expression.

RESULTS & DISCUSSION

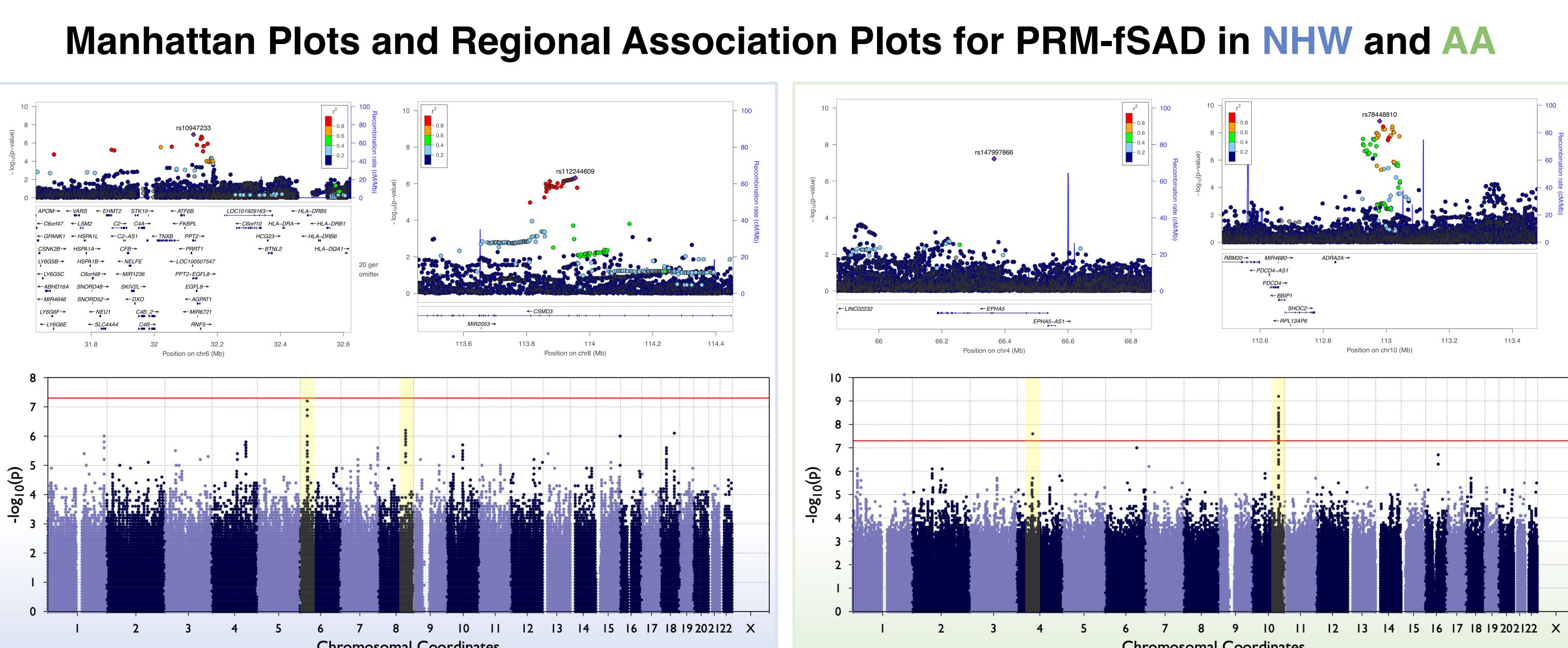
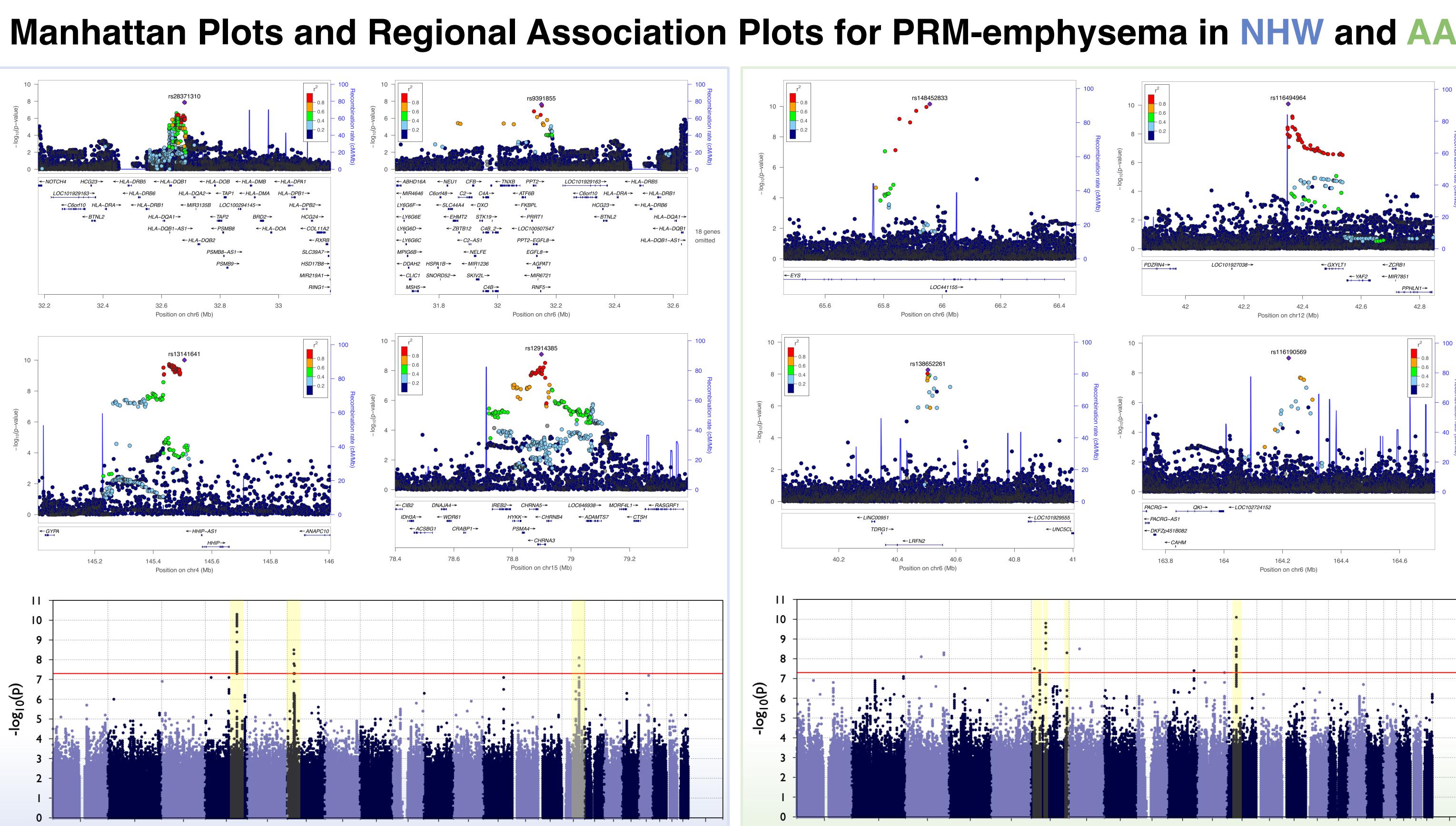
Genome-Wide Significant Associations for ILR-PRM-emphysema in NHW and AA

Marker Name (dbSNP)	Locus	Nearest Gene	Effect Allele C	Allele Frequency	Effect Size	P Value	Candidate causal genes (S-PrediXcan)
rs13141641	4q31.21	<i>HHIP</i>	T	40%	-0.19	1.00e-10	<i>GYPE</i> (8.3e-05), <i>FREM3</i> (6.7e-03), <i>HHIP</i> (1.7e-02), <i>OTUD4</i> (2.5e-02)
rs12914385	15q25.1	<i>CHRNA3</i>	T	41%	0.18	7.99E-10	<i>IРЕB2</i> (4.3e-06), <i>PSMA4</i> (1.0e-05), <i>RP11-160C18.2</i> (1.7e-05), <i>CHRNA3</i> (2.3e-05), <i>CHRNBA</i> (1.1e-04), <i>AC02728.1</i> (8.4e-04), <i>RP11-114H24.5</i> (5.5e-03), <i>MORF4L1</i> (8.8e-03), <i>ACSBG1</i> (1.2e-02), <i>CHRNA5</i> (2.0e-02), <i>RP11-160C18.4</i> (2.2e-02), <i>ADAMTS7</i> (4.4e-02)
rs28371310	6p21.32	<i>HLA-DQA2</i>	C	22%	-0.24	1.35E-08	<i>NOTCH4</i> (4.1e-04), <i>AGPAT1</i> (9.0e-04), <i>PPT2</i> (1.8e-03), <i>ATF6B</i> (6.1e-03), <i>HLA-DOB2</i> (6.4e-03), <i>HSPA1A</i> (6.7e-03), <i>C6orf25</i> (8.7e-03), <i>C4B</i> (1.1e-02), <i>BTNL2</i> (1.2e-02), <i>HLA-DRB9</i> (1.4e-02), <i>LY6G6C</i> (1.4e-02), <i>RPS7B</i> (1.8e-02), <i>CYP21A1P</i> (2.1e-02), <i>Xxbac-BPG254F23.7</i> (2.9e-02), <i>AGER</i> (2.9e-02), <i>C6orf48</i> (2.9e-02), <i>HNRNPA1P2</i> (3.3e-02), <i>CYP21A2</i> (3.4e-02), <i>HLA-DRB1</i> (3.4e-02), <i>TAP2</i> (3.5e-02), <i>NELFE</i> (3.8e-02), <i>DAXX</i> (4.2e-02), <i>DXO</i> (4.8e-02), <i>TNXA</i> (4.9e-02)
rs9391855	6p21.32	<i>RNF5</i>	T	4%	-0.40	2.37E-08	<i>NOTCH4</i> (4.1e-04), <i>AGPAT1</i> (9.0e-04), <i>PPT2</i> (1.8e-03), <i>ATF6B</i> (6.1e-03), <i>HLA-DOB2</i> (6.4e-03), <i>HSPA1A</i> (6.7e-03), <i>C6orf25</i> (8.7e-03), <i>NFKBIL1</i> (9.1e-03), <i>C4B</i> (1.1e-02), <i>BTNL2</i> (1.2e-02), <i>HLA-DRB9</i> (1.4e-02), <i>LY6G6C</i> (1.4e-02), <i>CYP21A1P</i> (2.1e-02), <i>Xxbac-BPG254F23.7</i> (2.9e-02), <i>AGER</i> (2.9e-02), <i>C6orf48</i> (2.9e-02), <i>HNRNPA1P2</i> (3.3e-02), <i>ABHD16A</i> (3.4e-02), <i>APOM</i> (3.4e-02), <i>CYP21A2</i> (3.4e-02), <i>HLA-DRB1</i> (3.4e-02), <i>TAP2</i> (3.5e-02), <i>Xxbac-BPG181B23.7</i> (3.6e-02), <i>NELFE</i> (3.8e-02), <i>LTA</i> (4.0e-02), <i>TNF</i> (4.3e-02), <i>DXO</i> (4.8e-02), <i>TNXA</i> (4.9e-02)
rs148452833	6q12	<i>EYS</i>	C	1%	-1.40	7.05E-11	NA
rs116494964	12q12	<i>GXYLT1</i>	T	1%	-1.44	8.12E-11	<i>PRICKLE1</i> (1.1e-02), <i>ZCRB1</i> (2.0e-02)
rs116190569	6q26	<i>QKI</i>	T	1%	-1.25	1.01E-09	NA
rs138652261	6p21.1	<i>LRFN2</i>	C	1%	-1.25	5.48E-09	NA
rs111730687	3p13	<i>GPR27</i>	T	1%	-1.67	1.02E-08	NA
rs140907604	3q26.31	<i>NLGN1</i>	A	1%	-2.00	1.60E-08	NA
rs185857173	2q37.1	<i>INPP5D</i>	C	1%	-1.93	1.65E-08	NA
rs117610895	7p12.2	<i>CDC14C</i>	C	1%	-2.15	2.39E-08	NA
rs75419265	8p23.1	<i>FDFT1</i>	T	1%	-1.28	4.32E-08	NA
rs111730687	3p13	<i>GPR27</i>	T	1%	-1.67	1.02E-08	NA

Top Genome-Wide Associations for ILR-PRM-fSAD in NHW and AA

Marker Name (dbSNP)	Locus	Nearest Gene	Effect Allele	Allele Frequency	Effect Size	P Value	Candidate causal genes (S-PrediXcan)
rs10947233	6p21.32	<i>PPT2</i>	T	4%	-0.17	1.16E-07	<i>NOTCH4</i> (2.8e-03), <i>C4B</i> (8.9e-03), <i>AGPAT1</i> (2.2e-02), <i>AGER</i> (2.3e-02), <i>LTB</i> (3.1e-02), <i>HSPA1A</i> (3.9e-02), <i>PPT2</i> (4.6e-02), <i>PSMB8</i> (4.7e-02), <i>Xxbac-BPG181B23.7</i> (4.8e-02), <i>NELFE</i> (4.9e-02)
rs112244609	8q23.3	<i>CSMD3</i>	T	5%	-0.15	4.77E-07	NA
rs185056867	16p13.3	<i>SLC9A3R2</i>	T	2%	0.22	1.08E-06	NA
rs1032297	4q31.21	<i>HHIP</i>	G	41%	-0.06	1.14E-06	<i>FREM3</i> (4.7e-02)
rs7629264	3q27.2	<i>VPS8</i>	A	42%	0.06	2.20E-06	NA
rs78448810	10q25.1	<i>ADRA2A</i>	T	5%	-0.29	1.44E-09	NA
rs147997866	4q13.1	<i>EPHA5</i>	A	1%	-0.76	6.00E-08	NA
rs118015239	16q12.2	<i>CHD9</i>	T	1%	-0.91	2.81E-07	NA
rs141357572	6q23.2	<i>EYA4</i>	A	1%	-0.64	3.48E-07	NA
rs186031302	2q14.3	<i>CNTNAP5</i>	C	1%	-0.78	8.77E-07	NA

- In NHW, three loci were found to be associated with PRM_{emph} (4q31 near *HHIP*, 6p21 near *AGER/RNF5/PBX2*, and 15q25 near *CHRNA5/CHRNA3/IРЕB2*). GWAS of the ILR-transformed PRM_{emph} phenotype confirmed association with these same three loci.
- In AA, no loci with MAF > 0.05 reached genome-wide significance for PRM_{emph}; rarer variants near *EYS*, *GXYLT1*, *QKI*, *LRFN2*, *GPR27*, *NLGN1*, *INPP5D*, *CDC14C*, and *FDFT1* were associated with ILR-PRM_{emph}.
- In NHW, no loci reached genome-wide significance for association with ILR-PRM_{fSAD}, although suggestive associations were found at the 6p21.32 locus (near *PPT2*) and 8q23.3 (near *CSMD3*).
- In AA, SNPs within the *ADRA2A* gene on chromosome 10 were associated with ILR-PRM_{fSAD}.



- Our GWAS study of PRM data for CT scans in the COPDGene study confirmed previous associations with emphysema at loci 4q31 (near *HHIP*), 6p21, and 15q25 (near *CHRNA3*). Further, for all three loci there is prior evidence of association with COPD and lung function. In genetic models, *Hhip* haploinsufficiency has been shown to sensitize mice to age-related emphysema.
- Additionally, we identified novel associations for fSAD, and emphysema in the AA population which may lead to insights about the distinct genetic and molecular etiologies of these two components which contribute to COPD.
- Replication of these findings, especially for the low frequency SNP associations, will be required.