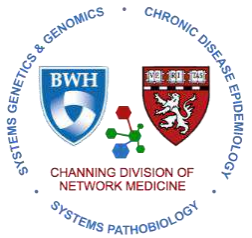
Mahidol University
Faculty of Medicine
Siriraj Hospital

COPDGene®
COPD Genetic Epidemiology



Genetics and Integrative Approaches in Chronic Obstructive Pulmonary Disease

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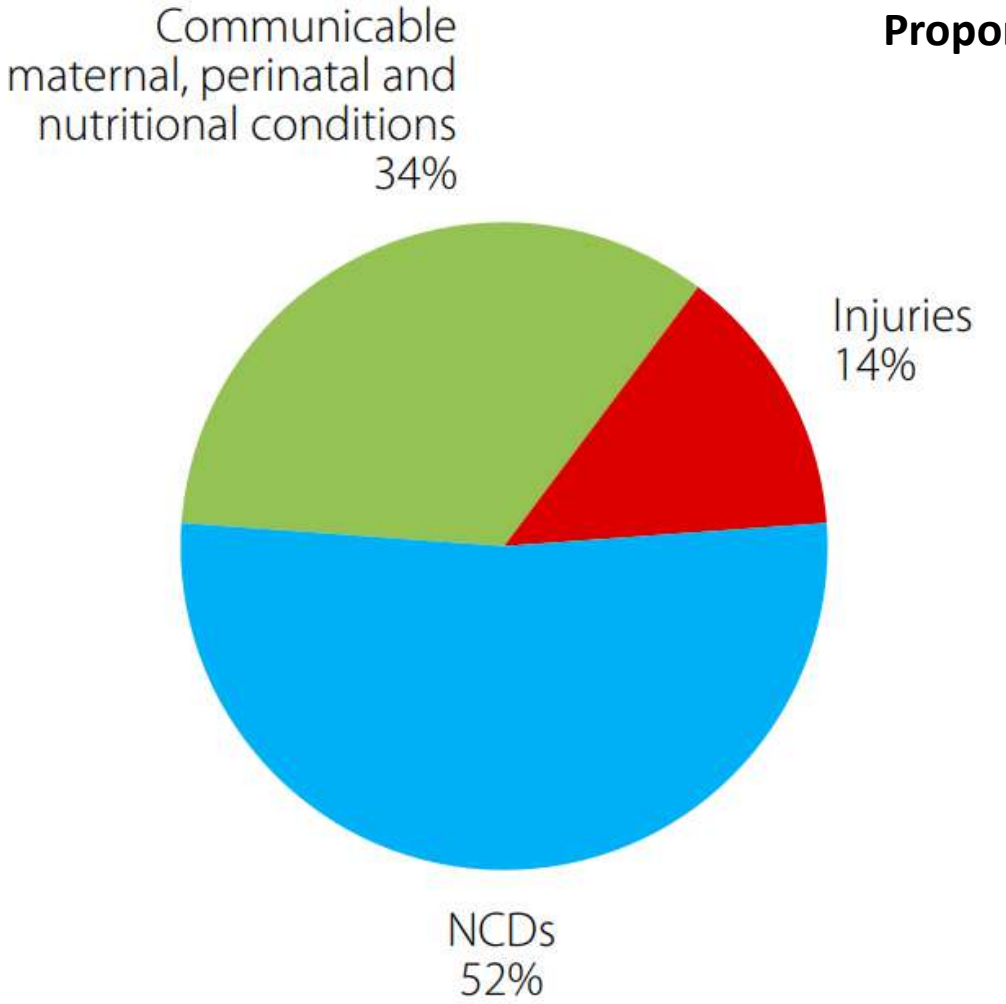
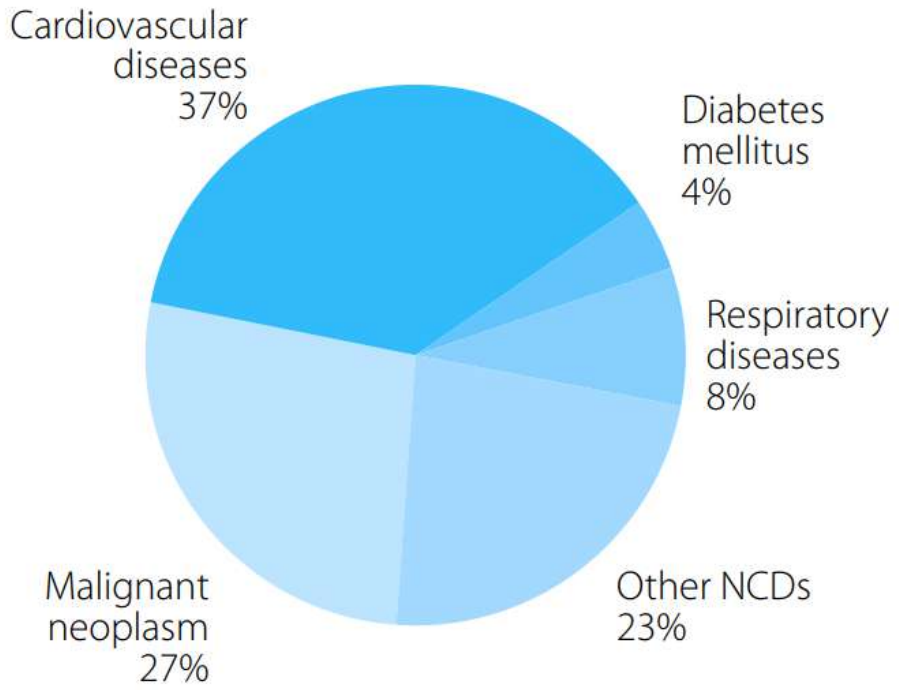
Faculty of Medicine Siriraj Hospital, Mahidol University

Channing Division of Network Medicine, Brigham and Women's Hospital

Introduction

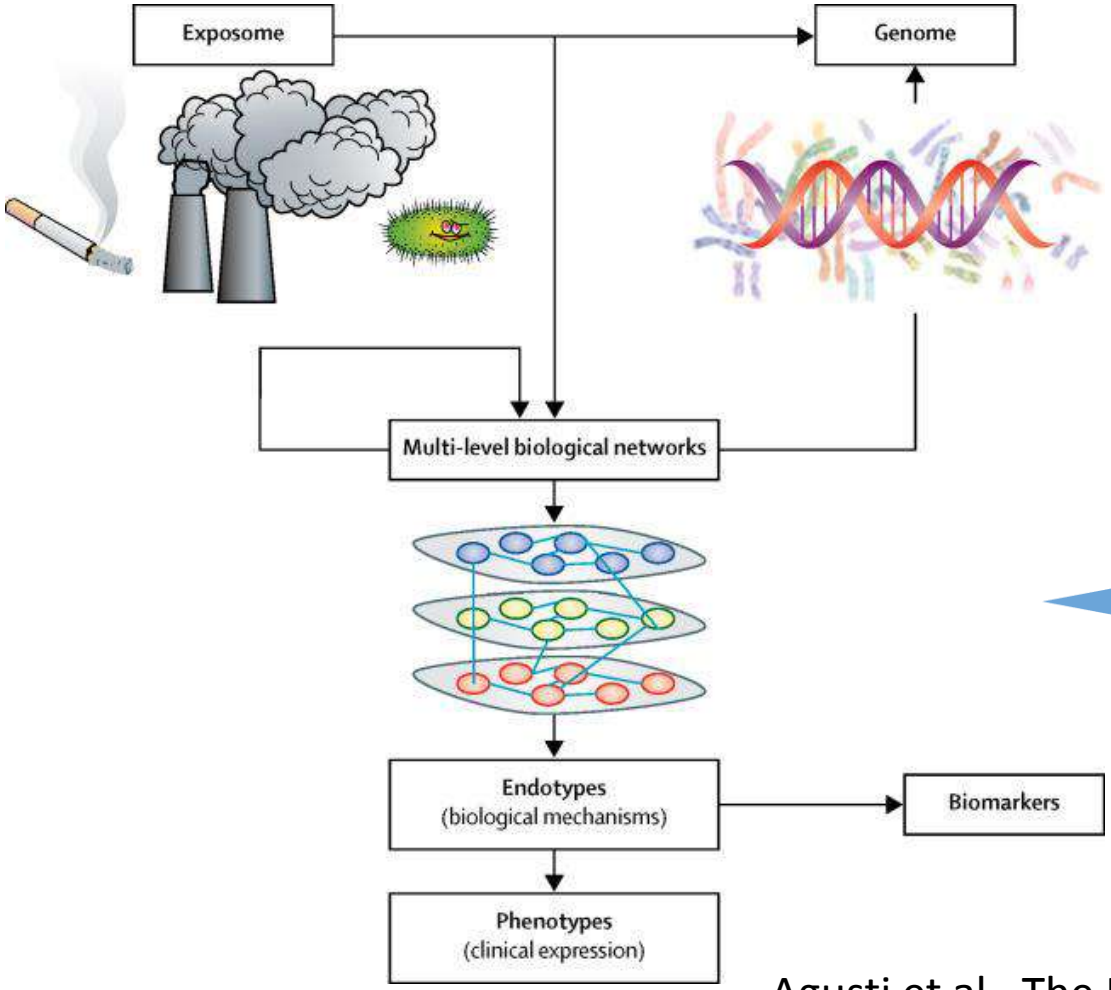
Proportion of global deaths under the age 70 years, by cause of death, comparable estimates, 2012

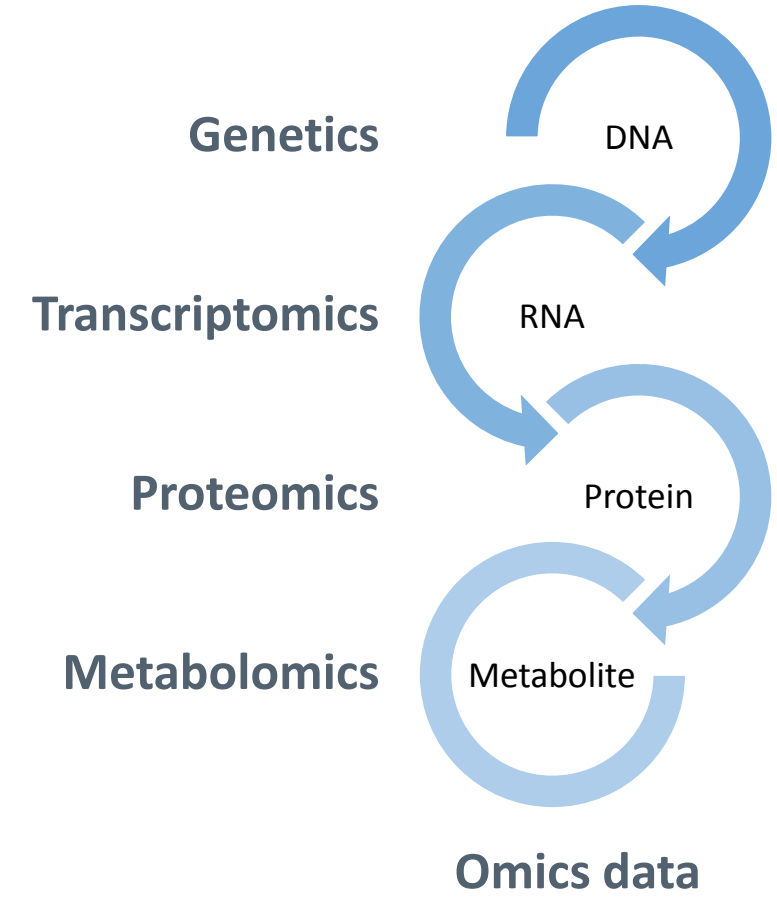




World Health Organization, 2014

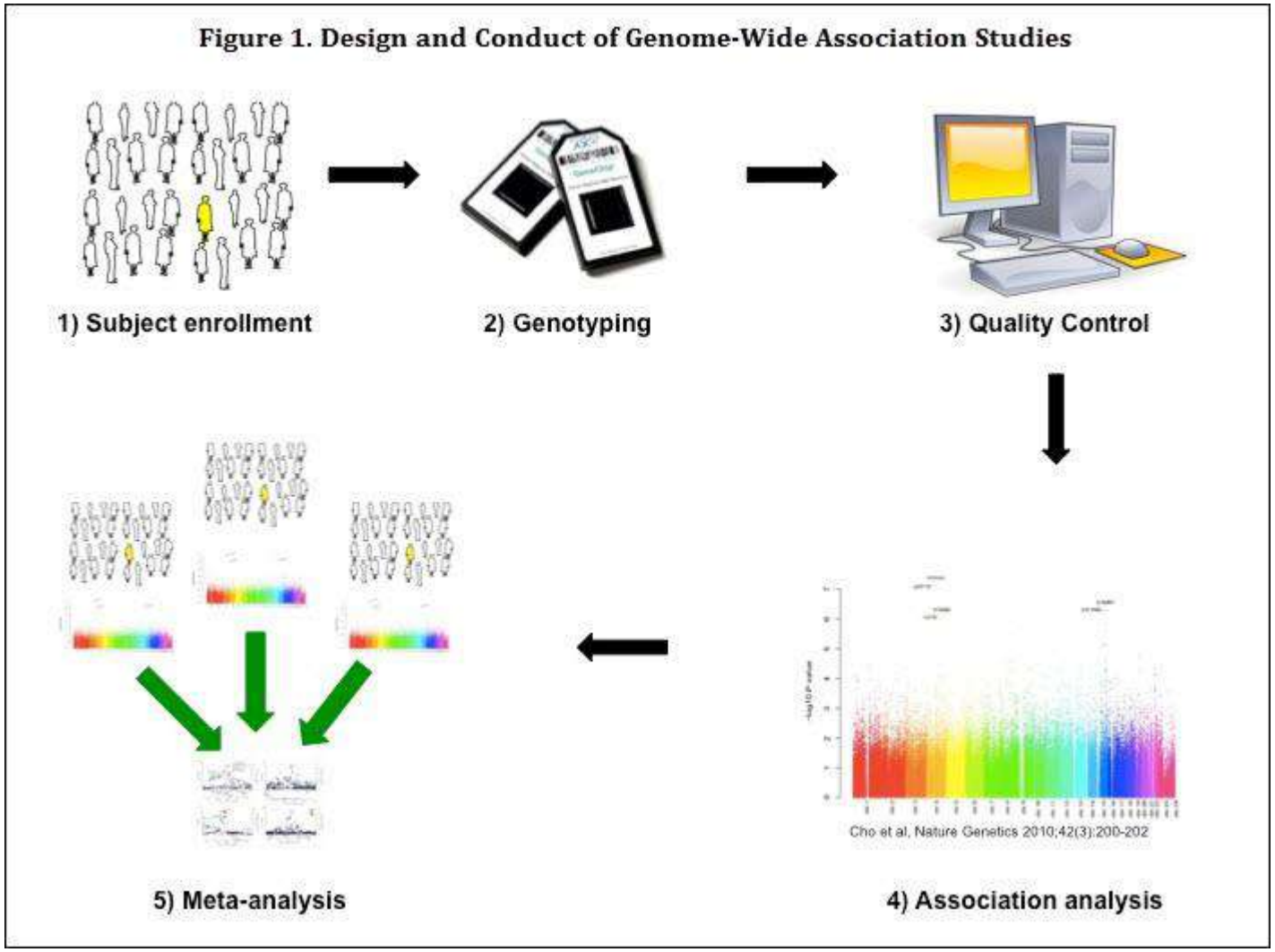
Associations between genes, environment, endotypes, biomarkers, and phenotypes





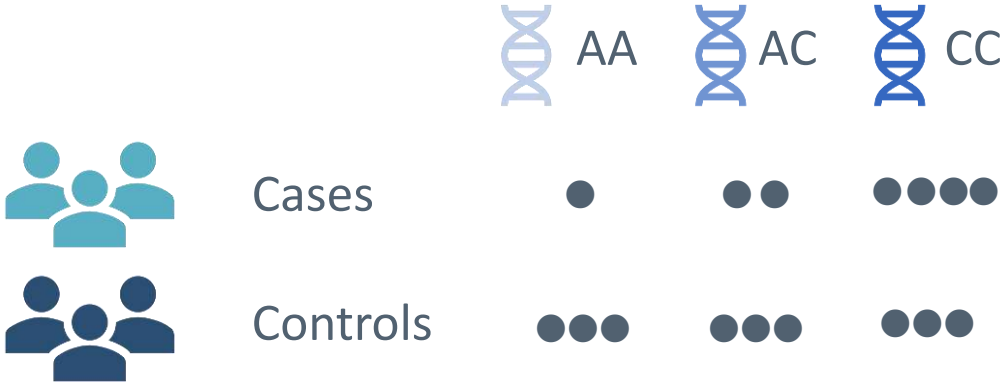
Agusti et al., The Lancet, 2017.

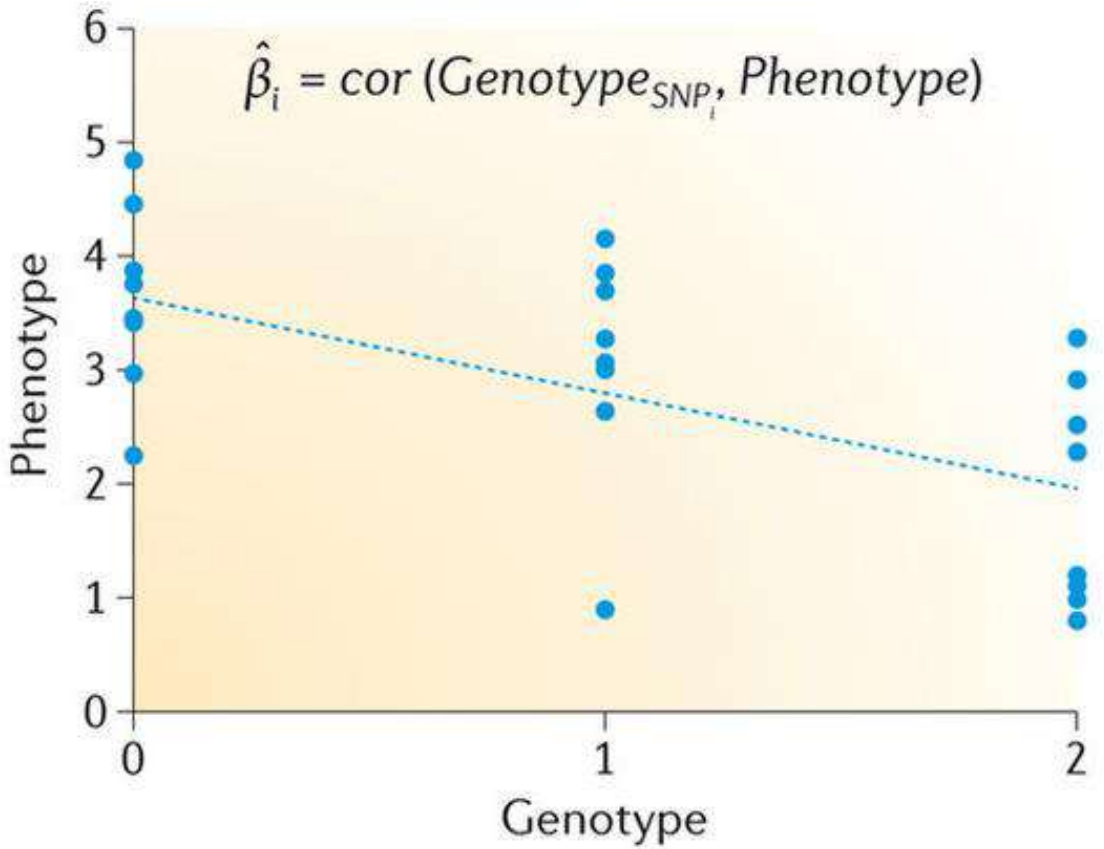
Genome-wide association studies



Hardin and Silverman, Journal of COPD Foundation, 2014

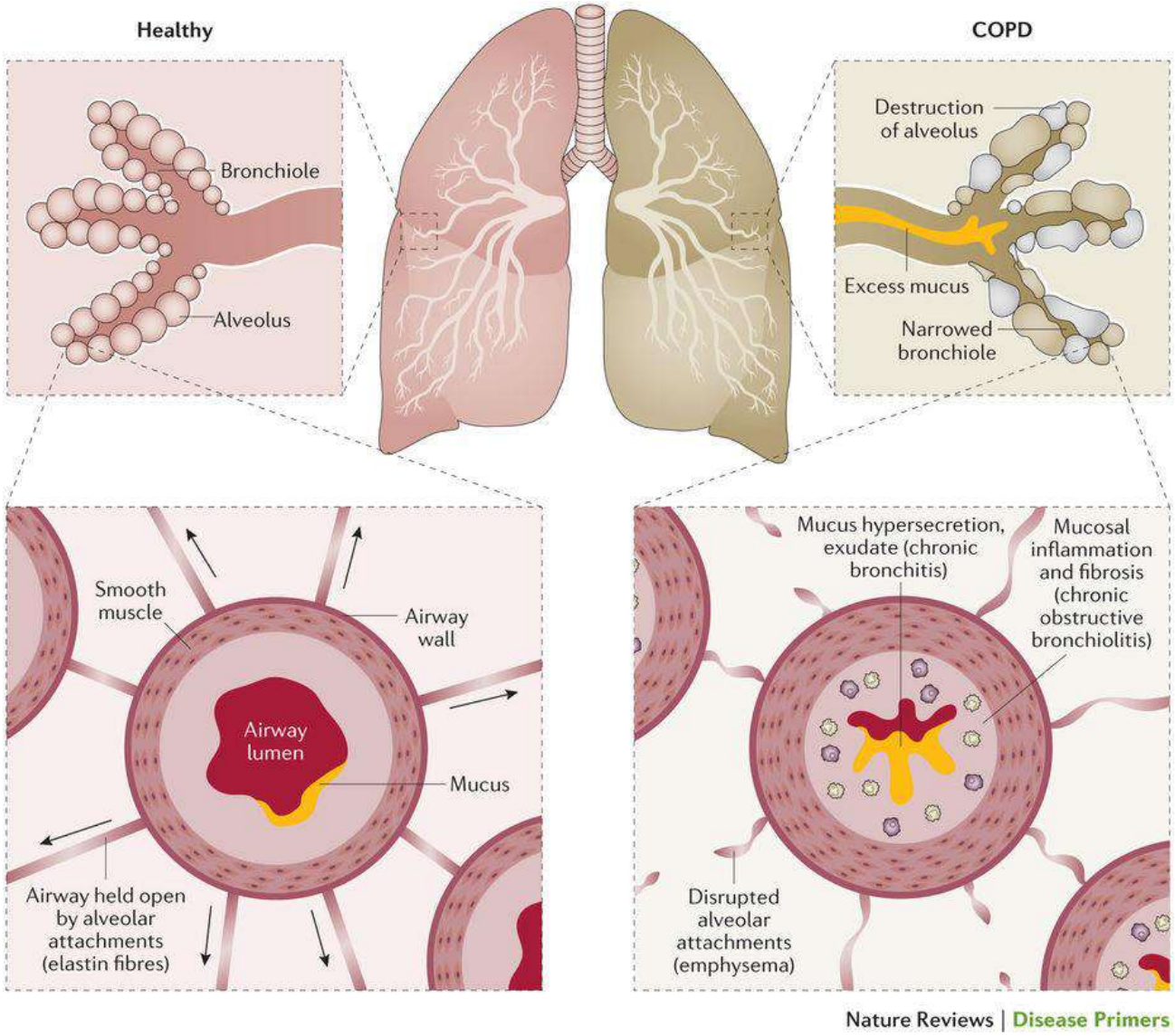
Genome-wide association studies





Pasaniuc and Price, Nature Review Genetics, 2017

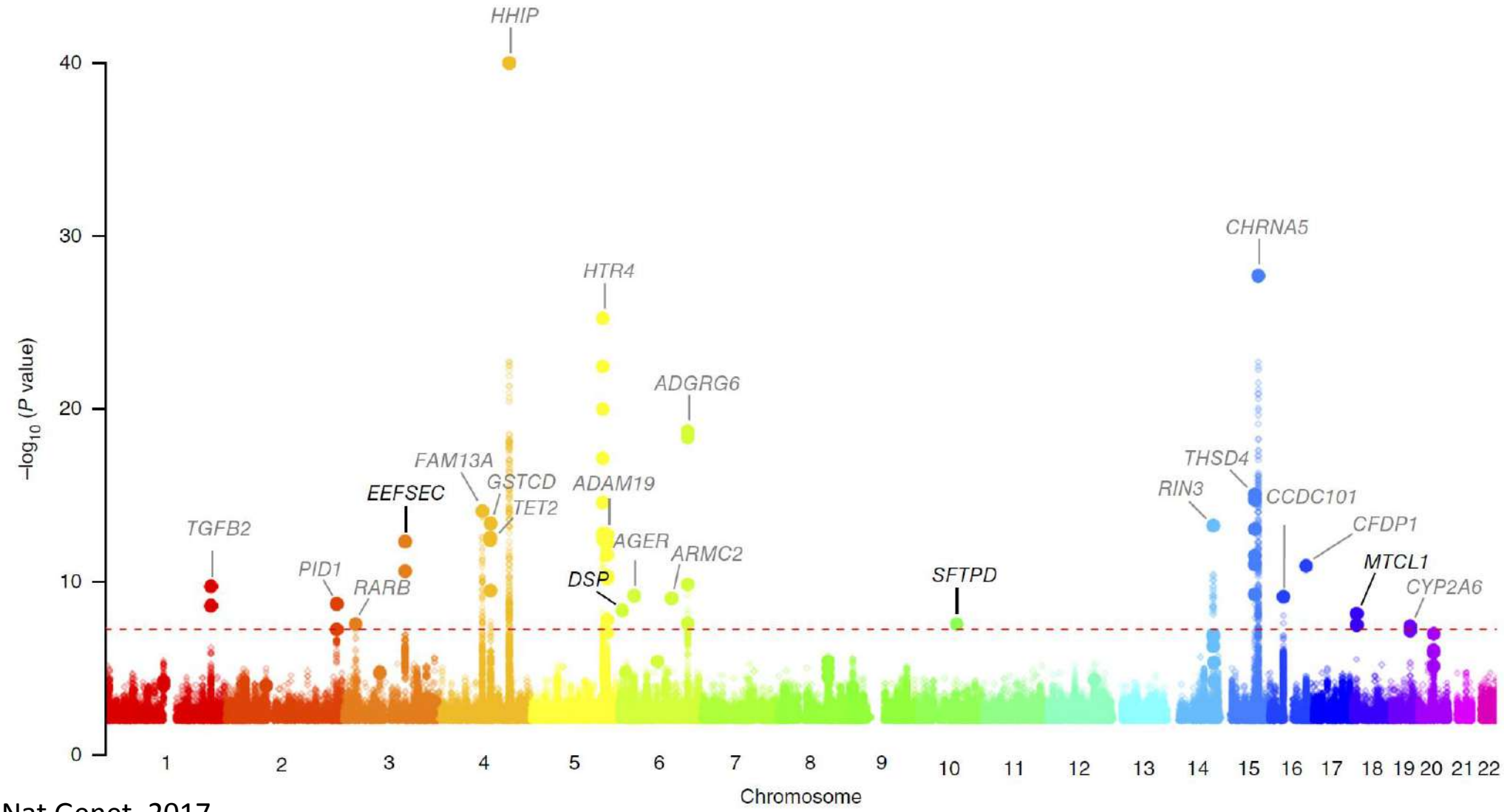
Chronic Obstructive Pulmonary Disease



- **Inflammation, fibrosis, and destruction of small airways**
  -> narrowed airways
- **disruption of alveolar attachments**
  -> emphysema
- **mucus and inflammatory exudate**
  -> luminal occlusion

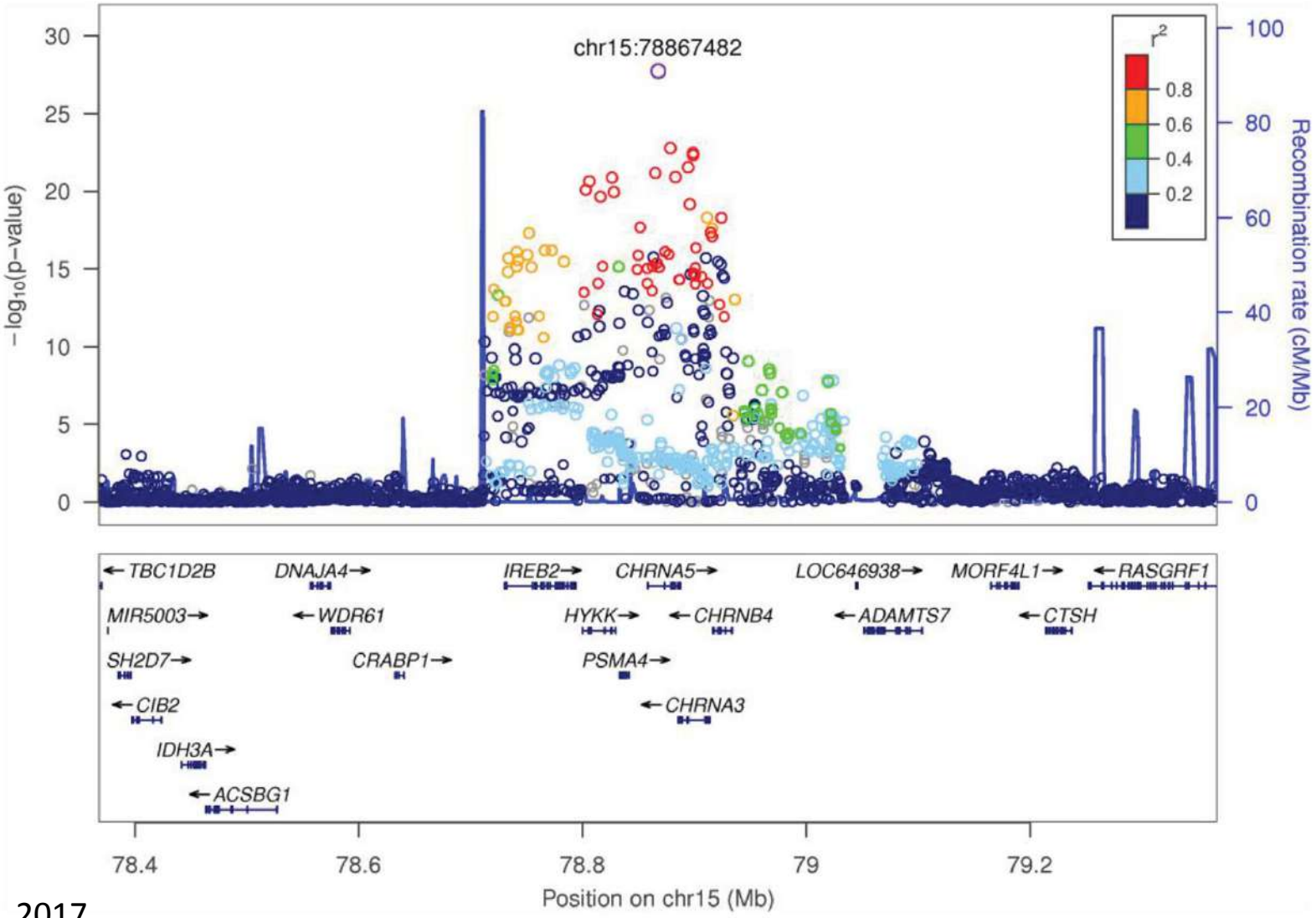
Barnes et al., Nature Reviews Disease Primers, 2015

Recent GWAS and meta-analysis of COPD



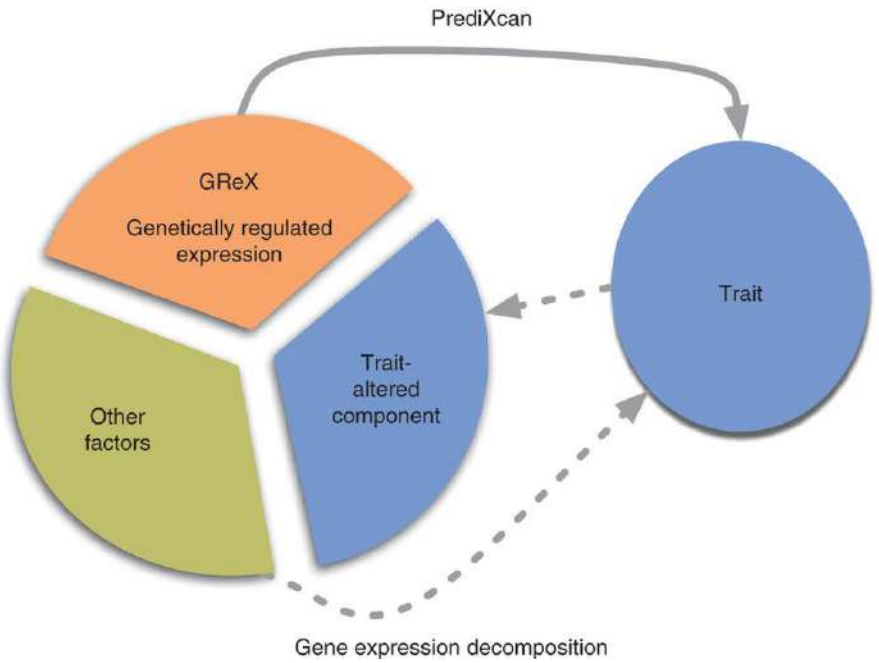
Hobbs, et al. Nat Genet, 2017.

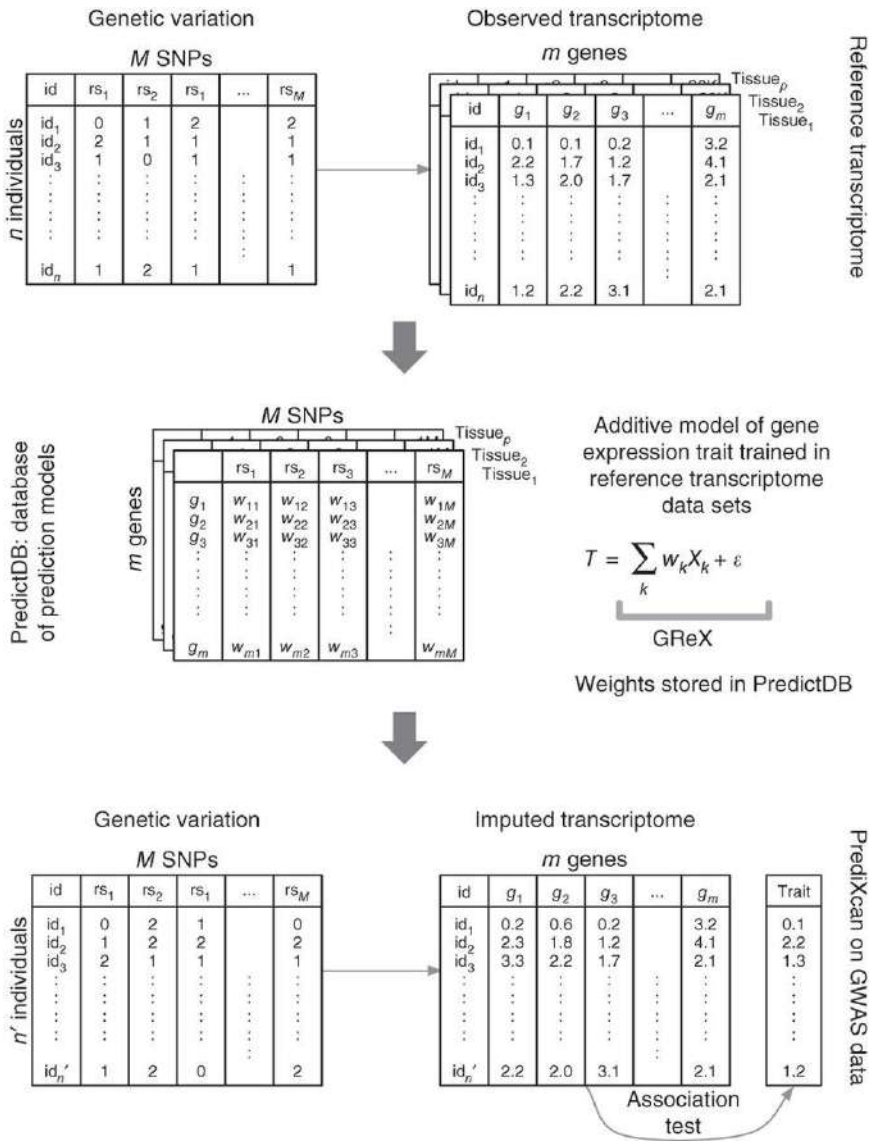
Regional association plot (chr15q25.1 locus)



Hobbs, et al. Nat Genet, 2017.

TWAS Machinery





Gamazon, et al. Nat Genet, 2015.

Our GWAS and Transcriptome DBs

GWASs from COPDGene + ECLIPSE + NETT/NAS + GenKOLS

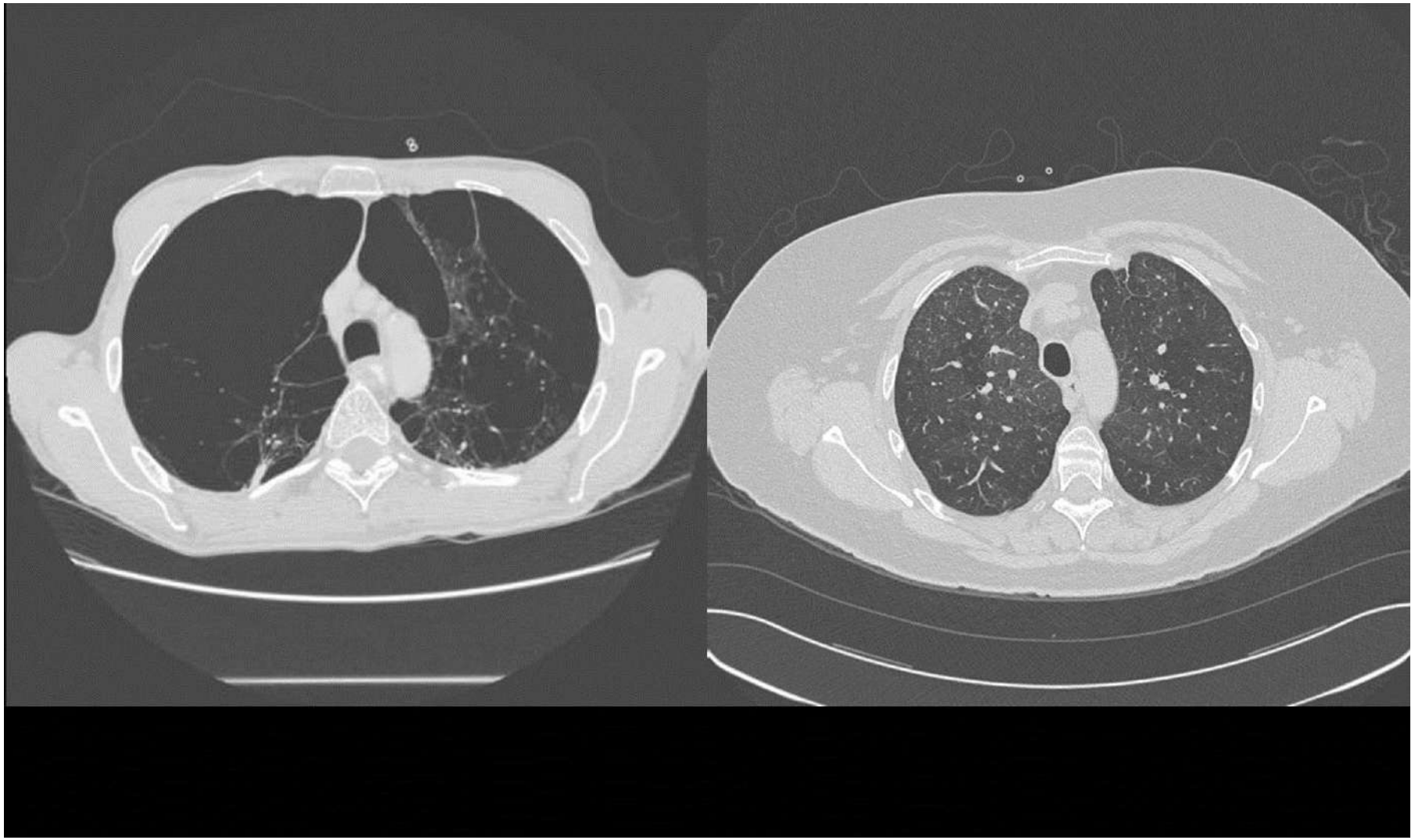
- **Severe COPD** (3,497 cases and 5,704 controls)
- **Quantitative emphysema** (12,031 individuals)
  - %LAA-950 ↑ with more emphysema
  - Perc15 ↓ with more emphysema

Expression data (eQTL and prediction models)

- **Discovery**
  - DGN-Blood
  - GTEx-Lung
- **Validation**
  - GTEx-Blood
  - Lung-eQTL Consortium

Cho, et al. Lancet Resp Med, 2014
Cho, et al. AJRCCM, 2015

CT Scans of Two Boston EOCOPD Study Probands (Craig Hersh)

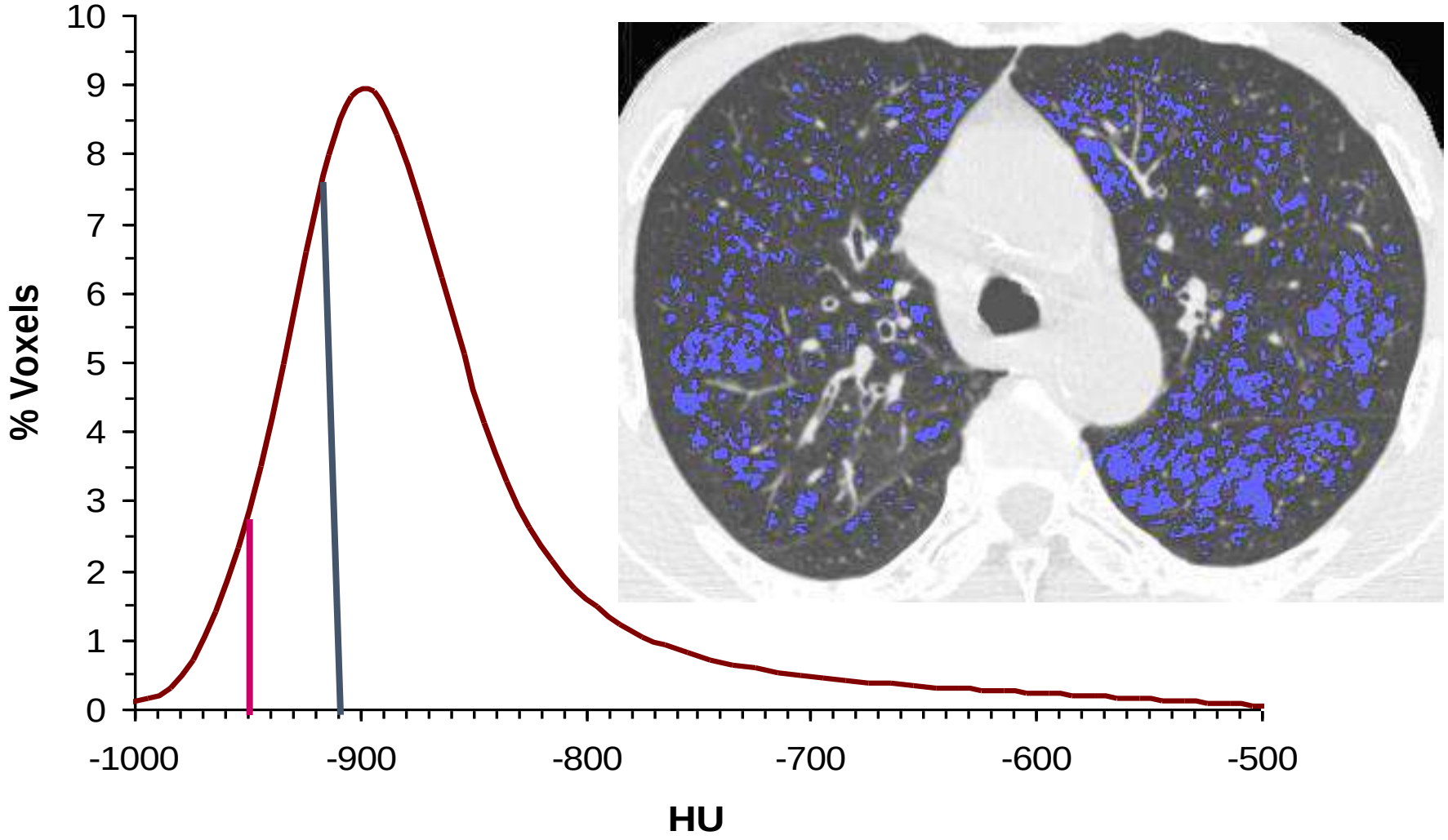


Age 42, FEV1 38%

Age 47, FEV1 20%

Courtesy of Dr. Edwin Silverman

Quantification of Emphysema



Hayhurst Lancet 1984, Müller Chest 1988, Gould ARRD 1988, Gevenois AJRCCM 1995, Coxson AJRCCM 1999; Slide from H. Coxson

Courtesy of Dr. Edwin Silverman

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Cho, et al. Lancet Resp Med, 2014
Cho, et al. AJRCCM, 2015

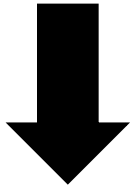
Severe COPD
(3,497 cases and
5,704 controls)

COPDGene
ECLIPSE
NETT/NAS
GenKOLS (Norway)

Quantitative emphysema
%LAA-950 and Perc15
(12,031 individuals)

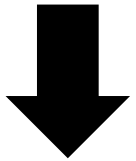
Summary Statistics from GWASs

Transcriptome References for **Discovery**



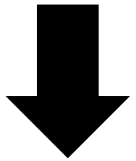
DGN-Blood
GTEx-Lung

Validation using independent references



GTEx-Blood
Lung-eQTL Consortium

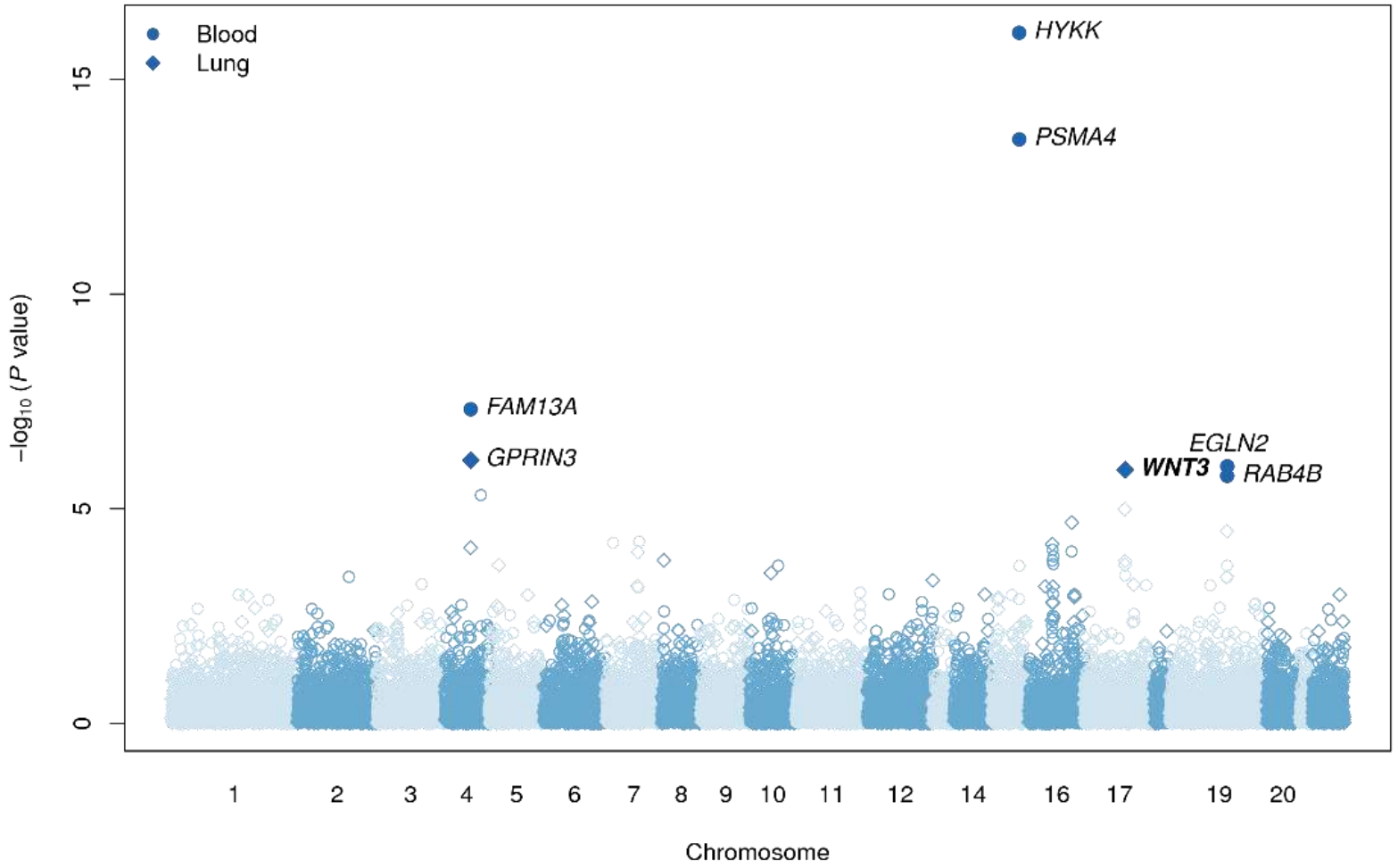
Test for **Colocalization**



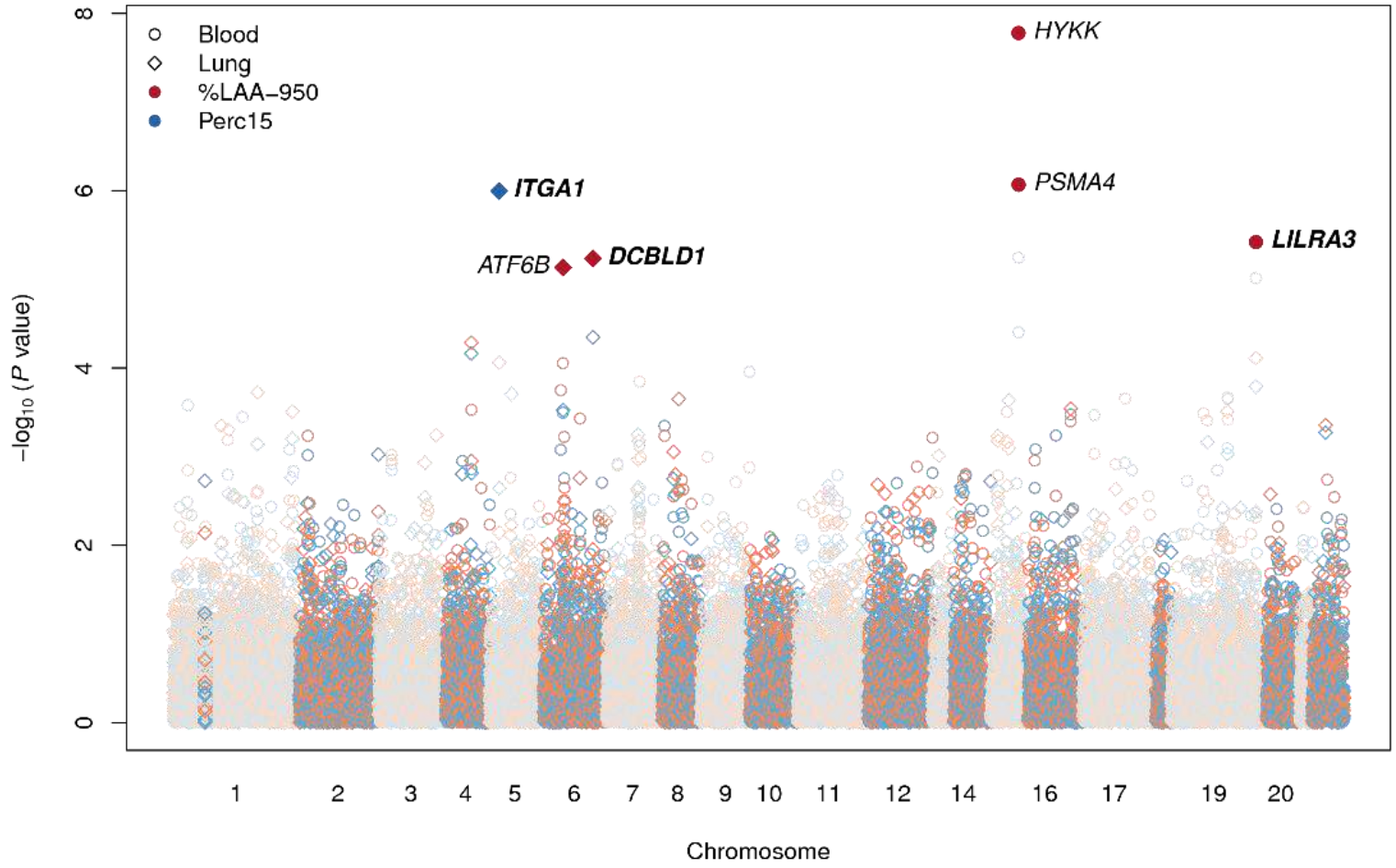
GTEx-Blood
GTEx-Lung
Lung-eQTL Consortium

Transcriptome-Disease Associations

TWAS Findings in Severe COPD



TWAS Findings in Quantitative Emphysema



Validation with Independent expression DBs

Genetic Loci	Phenotype	Gene	Tissue	Discovery		Validation	
				Z score	P value	Z score	P value
6q22	%LAA-950	*DCBLD1*	Lung	4.53	5.80E-06	3.81	1.40E-04
15q25	Severe COPD	*PSMA4*	Blood	7.62	2.50E-14	7.57	3.80E-14
15q25	%LAA-950	*PSMA4*	Blood	4.92	8.50E-07	5.10	3.40E-07
17q21	Severe COPD	*WNT3*	Lung	4.85	1.20E-06	4.60	4.30E-06
19q13	Severe COPD	*EGLN2*	Blood	4.89	1.00E-06	4.35	1.30E-05
19q13	Severe COPD	*RAB4B*	Blood	-4.78	1.70E-06	-3.82	1.30E-04
19q13	%LAA-950	*LILRA3*	Blood	-4.62	3.80E-06	-4.13	3.60E-05

Co-localization

Locus	Phenotype	Gene	Tissue	Colocalized variant	Colocalization Probability
6q22	%LAA-950	*DCBLD1*	Lung	rs34882116	0.13
15q25	Severe COPD	*PSMA4*	Blood	rs56077333	0.46
15q25	%LAA-950	*PSMA4*	Blood	rs56077333	0.14
17q21	Severe COPD	*WNT3*	Lung	rs199520	0.21
19q13	Severe COPD	*EGLN2*	Blood	rs35755165	0.12
19q13	%LAA-950	*LILRA3*	Blood	rs103294	0.99

Hormozdiari, et al. AJHG, 2016

Biological relevance

Gene	Evidence
WNT3	• the Wnt-beta-catenin-TCF signaling pathway • tetra-amelia syndrome • down-regulated in smokers compared with nonsmokers (small airway epithelium) • in strong LD with GWAS loci for FEV_1, FVC, interstitial lung disease, and idiopathic pulmonary fibrosis
LILRA3	• encoding a soluble leukocyte immunoglobulin like receptor for MHC class I • in modest LD with variants suggestively associated with FEV_1/FVC
DCBLD1	• an integral component of cell membranes and binds to oligosaccharides • in LD with variants associated with lung cancer

Pathway enrichment analyses

Phenotype	Tissue	Functional category	P value
Severe COPD	Lung	collagen binding involved in cell-matrix adhesion	2.70E-03
Severe COPD	Lung	proteasome core complex	2.80E-02
Severe COPD	Lung	translation factor activity, RNA binding	3.70E-02
%LAA-950	Blood	MHC class II protein complex	5.20E-05
%LAA-950	Blood	PD-1 signaling	6.30E-04
%LAA-950	Blood	Downstream TCR signaling	8.00E-04
%LAA-950	Blood	Asthma	4.80E-03
%LAA-950	Blood	T cell receptor signaling pathway	6.60E-03
Perc15	Lung	negative regulation of ERBB signaling pathway	4.50E-02

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- Channing Division of Network Medicine
  - Edwin Silverman
  - Michael Cho
  - Jarrett Morrow, Peter Castaldi, and Craig Hersh
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  - Nitipatana Chierakul
  - Bhoom Suktitipat, Surakameth Mahasirimongkol, Wanna Thongnoppakhun, and Ratchadaporn Chanayat
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