Network Medicine Approaches to Chronic Obstructive Pulmonary Disease

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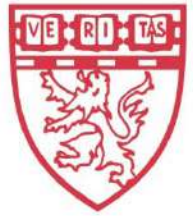
BRIGHAM AND WOMEN'S HOSPITAL



Edwin K. Silverman: Conflicts of Interest

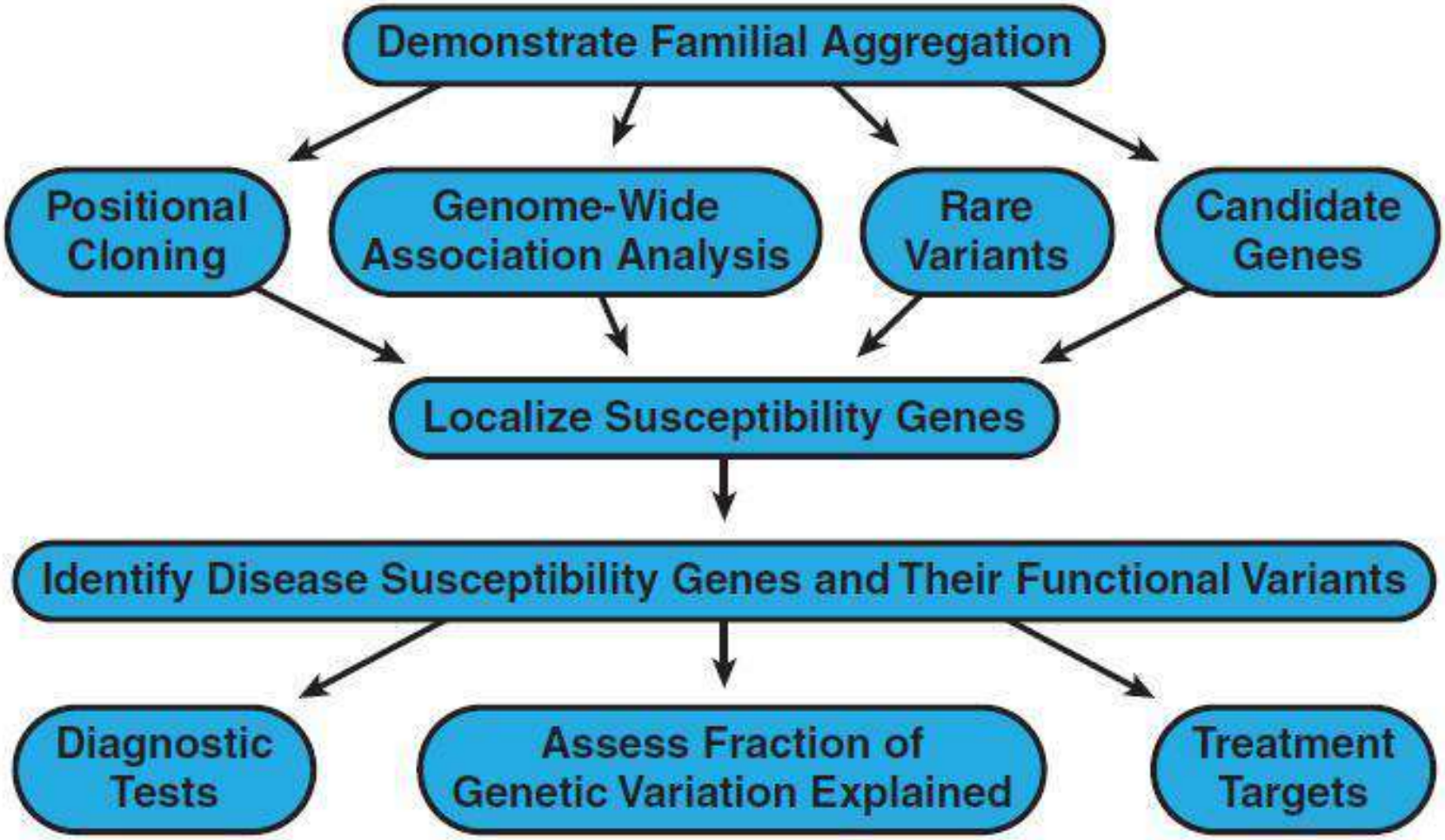
- **1) Personal financial relationships with commercial interests relevant to medicine, within past 3 years:**
  - Grants: GlaxoSmithKline
  - Lecture Fees (Honoraria): Novartis

- **2) Personal financial support from a non-commercial source relevant to medicine, within past 3 years:**

  No relationships to disclose

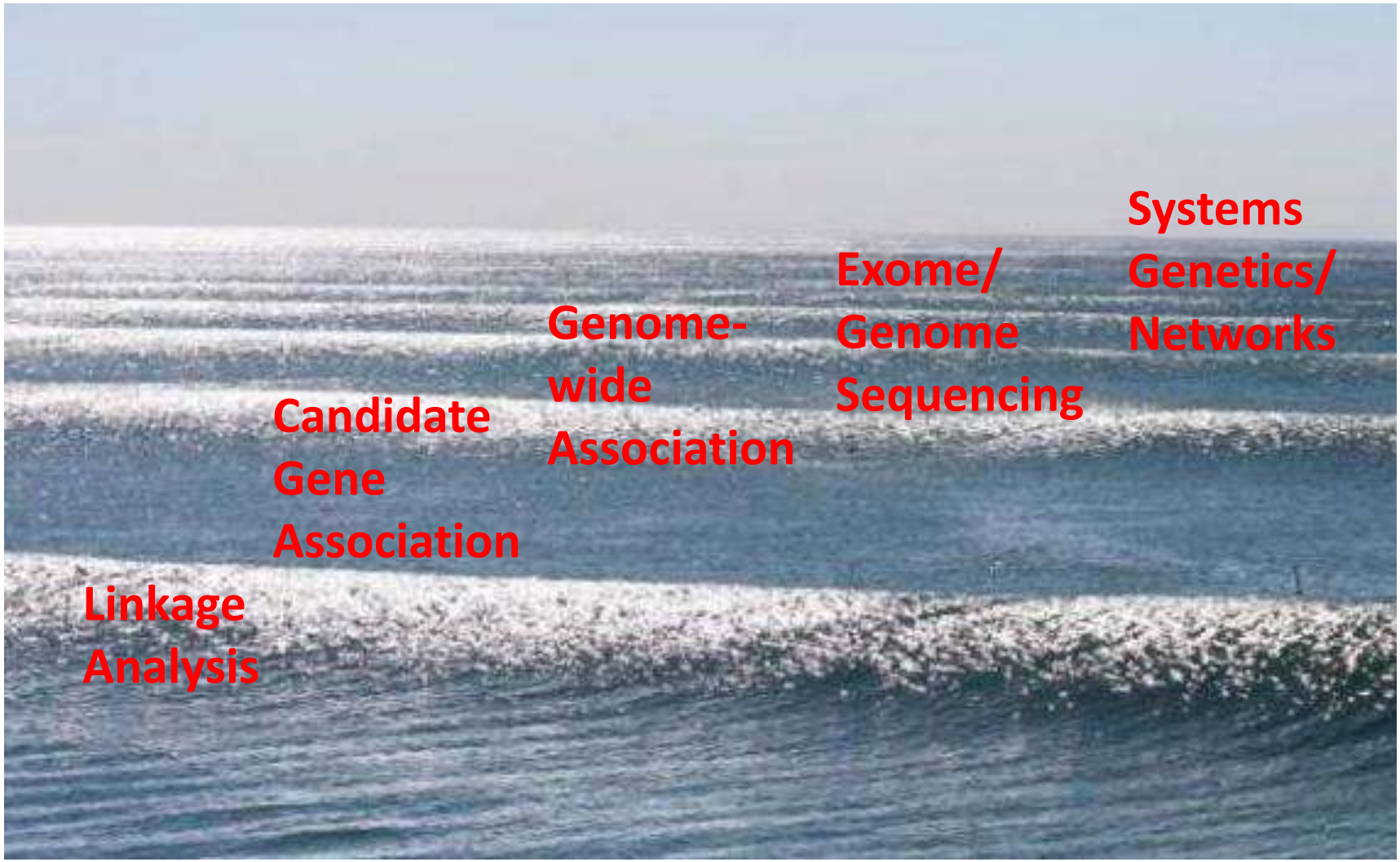
- **3) Personal relationships with tobacco industry entities within the past 3 years: No relationships to disclose**

Overview of Complex Disease Genetics



From Network Medicine: Complex Systems in Human Disease and Therapeutics, edited by Loscalzo/Barabasi/Silverman

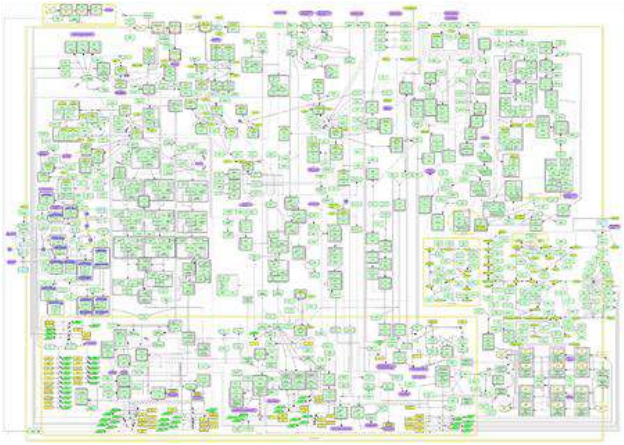
Waves of Discovery in Complex Disease Genetics



What Is a Network?

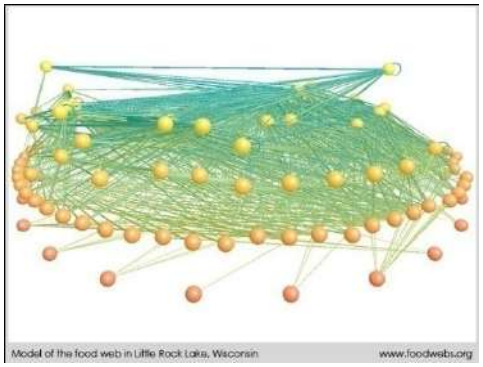
A collection of points (nodes) that are joined in pairs by lines (edges). A graphical approach to visualize and analyze relationships between variables of interest.

(Adapted from M. Newman, Networks: An Introduction, 2010)



Biological Network

Social Network



Ecological Network

What Is Network Medicine?

The study of cellular, disease, and social networks which aims to quantify the complex interlinked factors contributing to individual diseases.

(Adapted from Barabasi, NEJM 2007; 357:404)

Key components of Network Medicine:

--Holistic rather than reductionist approach

--Construction of molecular disease networks

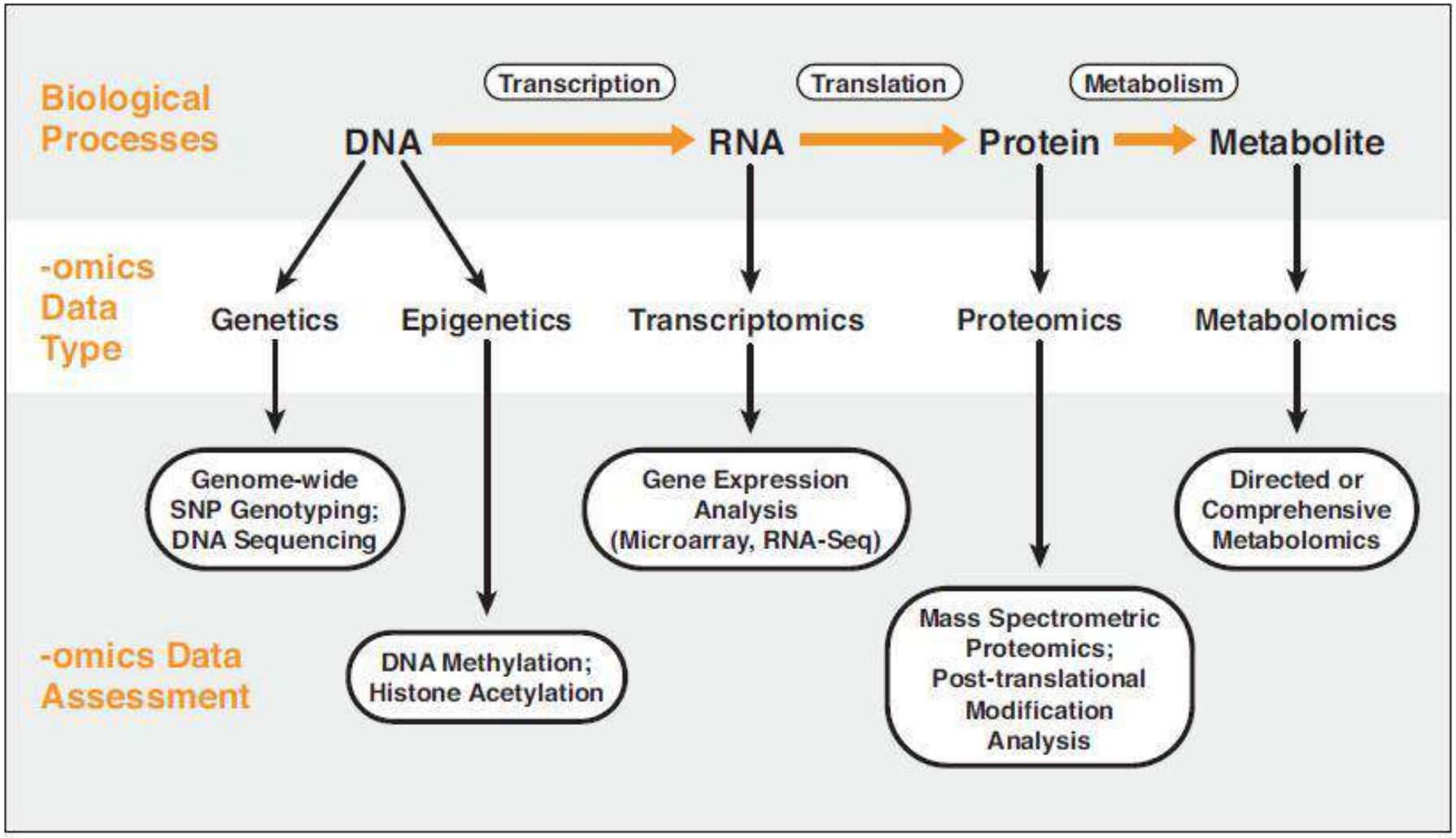
--Non-linear responses of complex systems

--Emergent properties from entire network

--Investigates responses of networks to various types of perturbation

--Employs systems biology methods

High Throughput Assessment of Multiple Biological Processes



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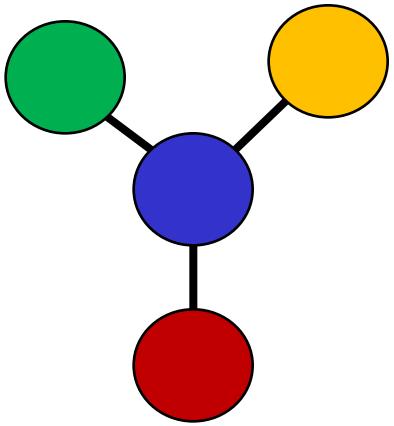
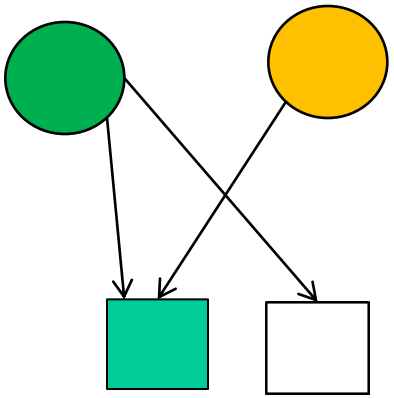
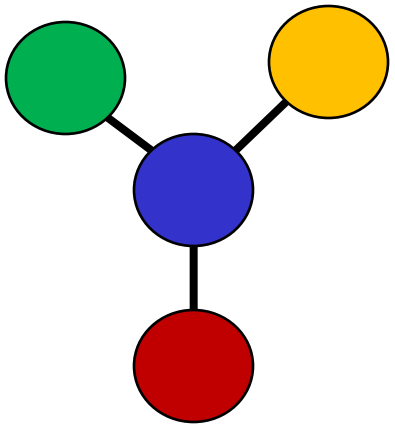
Types of Networks Utilized in Network Medicine

	Correlation Network	Gene Regulatory Network	Protein-Protein Interaction Network
			
Nodes:	Omics Data for a Gene	Transcription Factors (Circles) and Genes (Squares)	Protein
Edges:	Correlation between Omics Data	Gene Regulatory Relationship	Physical Interactions

Chronic Obstructive Pulmonary Disease: Definition

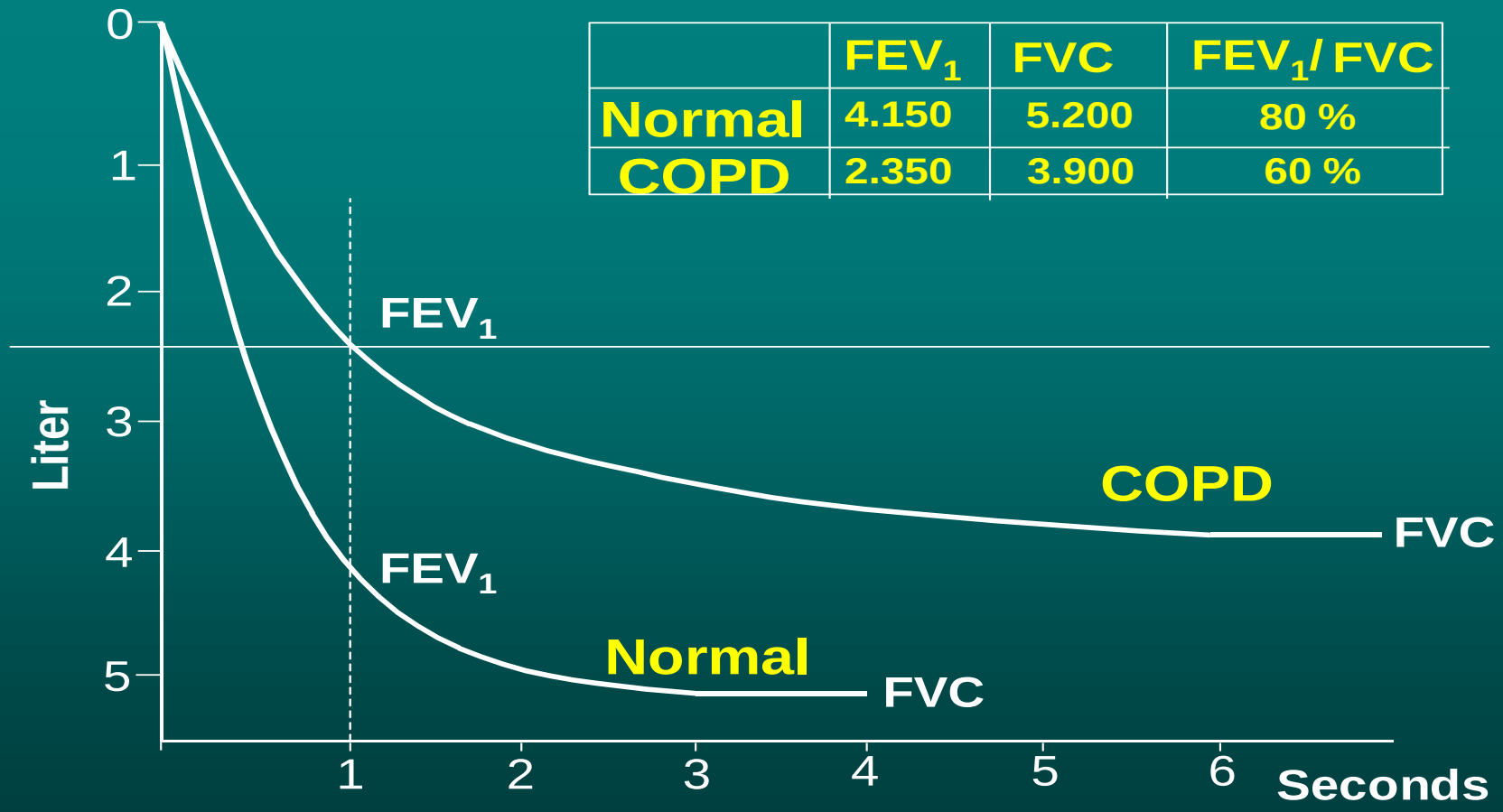
Chronic obstructive pulmonary disease (COPD) is a common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases (GOLD Project 2017).

- COPD includes:
  - Emphysema
  - Chronic Bronchitis
  - Small Airway Disease

- Disease Impact: Third Leading Cause of Death in the U.S.

Spirometry: Normal and COPD

	FEV_1	FVC	FEV_1/ FVC
Normal	4.150	5.200	80 %
COPD	2.350	3.900	60 %



Thanks to GOLD Project for Slide

Risk Factors for COPD

Exposures	Tobacco Smoke
	Cooking with Biomass Fuel
	Occupational Dusts and Chemicals
	Respiratory Infections (?)
Host Factors	Genes (e.g., AAT deficiency)
	Airway Hyperresponsiveness
	Reduced Lung Growth

Thanks to ACCP/Chest Foundation Task Force on
Women and Girls, Tobacco, and Lung Cancer for Slide

COPD: Evidence for Genetic Determinants

- Development of COPD in smokers is highly variable (Burrows 1977).
- Pulmonary function in the general population and COPD cluster in families (Lewitter 1984, Redline 1987, Larson 1970, Silverman 1998).
- Twin study of 22,422 Danish and 27,668 Swedish twin pairs estimated COPD heritability ~60% (Ingebrigtsen 2010).
- A small percentage of COPD patients inherit severe alpha-1 antitrypsin deficiency.

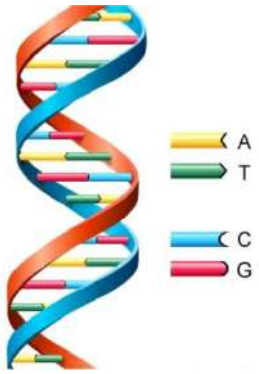
Potential Impact of Genetics on Complex Disease Diagnosis and Treatment

- **Learning about New Biological Pathways in Disease Pathogenesis:**
  - Nature's pertubations of human biological networks
  - Identifying targets for new drug development: 8% of FDA approved drugs vs. 2% of Phase 1 drugs have OMIM/GWAS support (Nelson, Nat Genet 2015; 47: 856)

- **Reclassifying Complex Diseases:**
  - Based on etiology and disease pathophysiology

- **Pharmacogenetics:**
  - Finding patients likely to have excellent treatment response
  - Avoiding treatment of individuals at high risk for adverse events

Components of a Genetic Association Study



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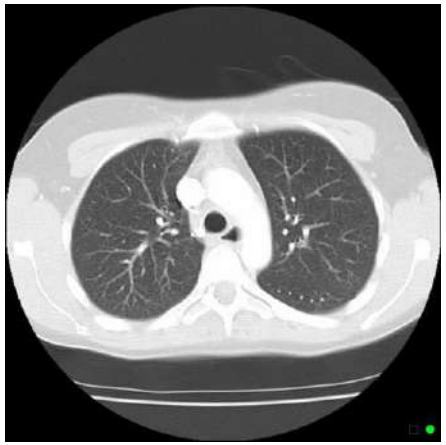


- Phenotype
- Study Population
- Genetic Variation Assessment
- Statistical Analysis Method

Phenotypes for Genetic Association Studies

- Phenotype: A measurable characteristic of an individual
- Quantitative or Categorical
  - Categorical Example: Presence vs. absence of COPD
  - Quantitative Example: Densitometric measurement of emphysema
- Technical variability may be important
  - Different imaging machines (brand, model)
  - Different imaging protocols (e.g., radiation dose)
  - Other center-specific effects (e.g., breathing instructions)
- Biological variability may be important
  - Impact of physical characteristics (e.g., BMI)
  - Impact of other subject factors (e.g., current smoking)

Study Populations for Genetic Association Studies

- Subjects Analyzed
  - Cases and Controls
  - Population Samples
  - Family Units
- Geography/Ethnicity
  - Isolated vs. Heterogeneous Populations
  - Challenges and Benefits of Racial Diversity

Genotypes for Genetic Association Studies

- Types of Genetic Variants
  - Single Nucleotide Polymorphism (SNP)
  - Insertion/Deletion
  - Copy Number Variants

- Approaches for Assessing Genotypes
  - Single variant assessment
  - Genome-wide genotyping arrays
  - Sequencing (whole exome or whole genome)

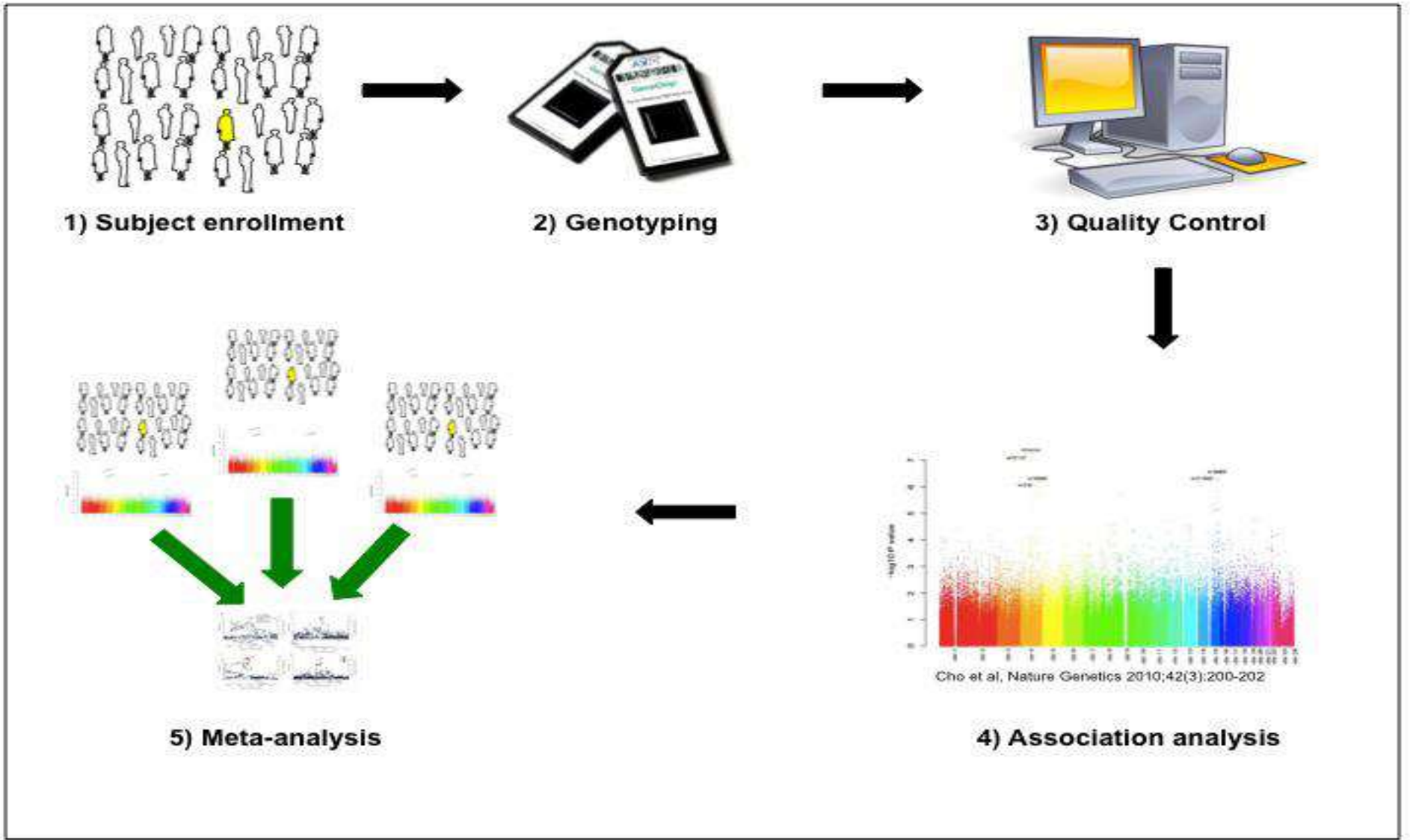
Statistical Analysis Methods for Genetic Association Studies

- Statistical Analysis with Regression
  - Logistic Regression (Categorical Phenotypes; e.g., Case-Control)
  - Multiple Linear Regression (Quantitative Phenotypes)
  - Differential Transmission to Affected subjects (Family Units)

- Key Issues in Statistical Analysis
  - Imputation of missing genotypes with standard reference panels
  - Quality control of genotype data (e.g., Hardy-Weinberg proportions in control subjects)
  - Covariate adjustment in regression analysis (e.g., Clinical Center, Scanner Model, BMI, Current smoking, Genetic Ancestry)
  - Multiple testing correction ($p<5 \times 10^{-8}$)
  - Correlation of nearby genetic variants (linkage disequilibrium)

Approach for Genome-wide Association Studies

(Hardin, J COPDF 2014)



GWAS: Strengths and Weaknesses

- Strengths
  - Multiple genome-wide significant results found in many complex diseases
  - GWAS associations have often been replicated by multiple studies
  - Genotyping and Analysis approaches are well-established

- Weaknesses
  - Functional variants identified in a small minority of loci
  - Odds ratios for identified GWAS loci are low
  - GWAS loci (at least in isolation) are not very useful for prediction
  - Much of the estimated heritability remains unexplained

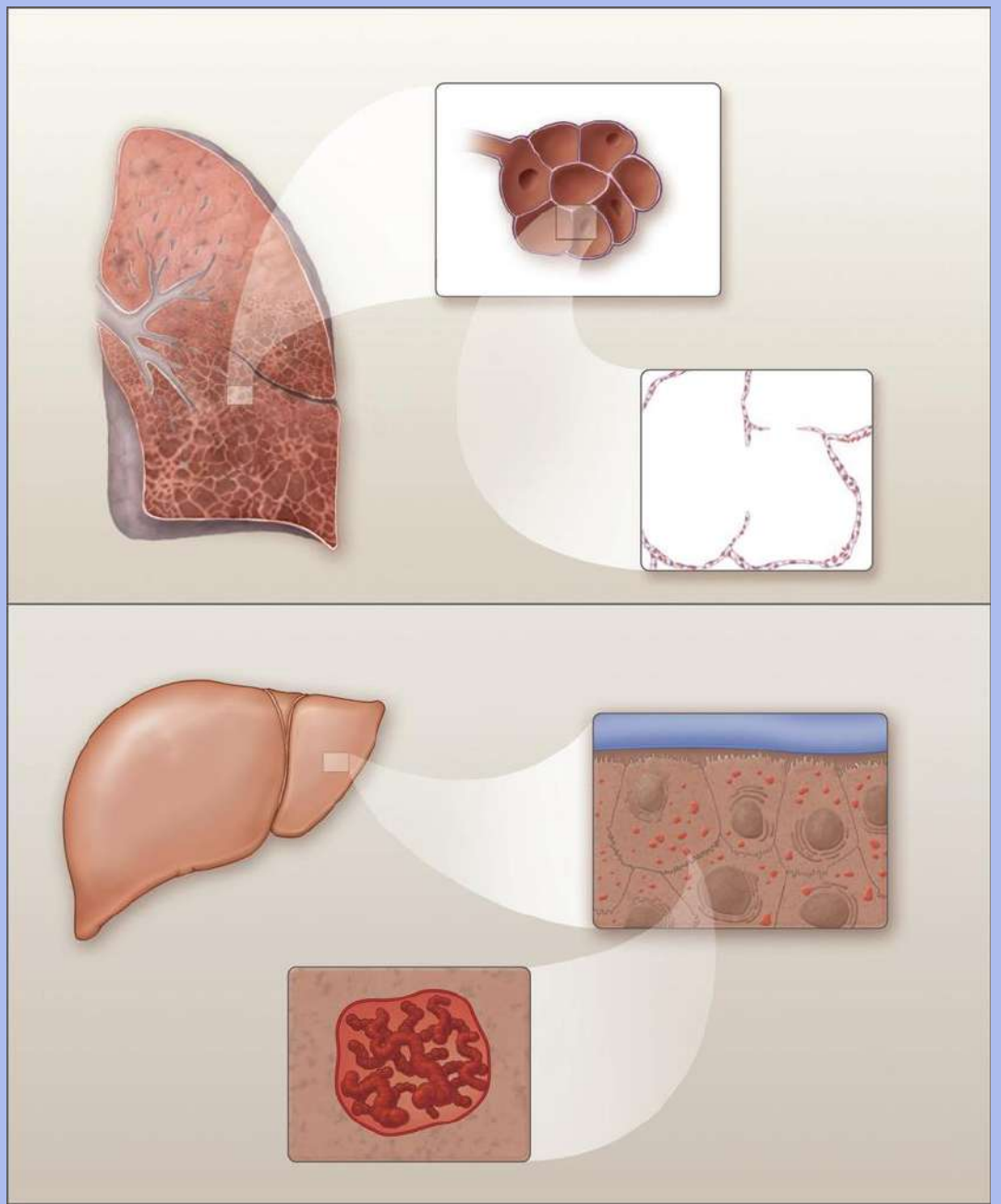
Alpha-1 Antitrypsin Deficiency

- AAT is the major plasma protease inhibitor of leukocyte elastase
- PI Z individuals have approximately 15% of normal plasma AAT levels
- Z mutation is functional
- Only ~1% of COPD patients in USA are PI Z

Alpha-1 Antitrypsin Deficiency: Pathophysiology

Lung Disease

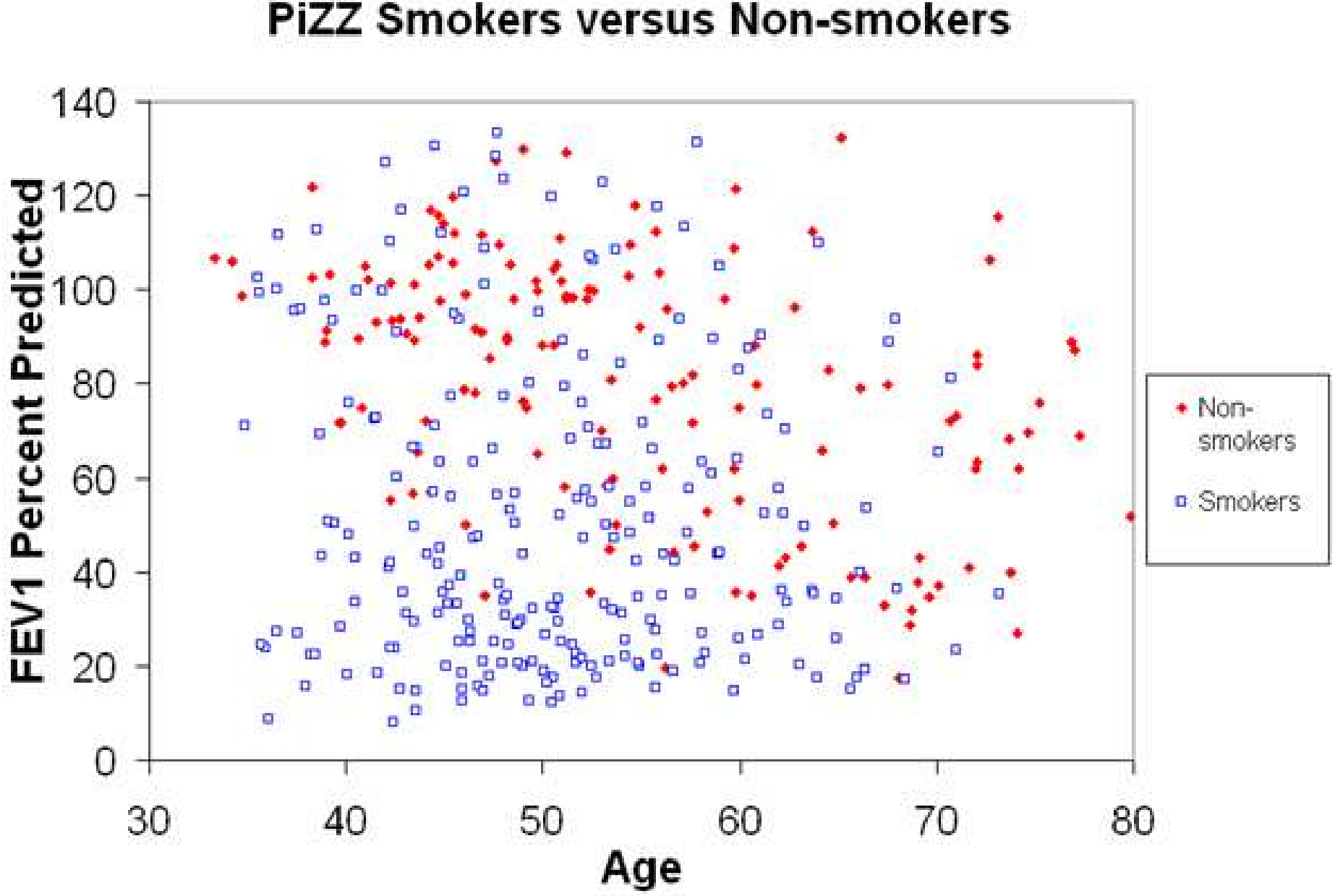
Liver Disease



From Silverman and Sandhaus, NEJM 2009

Variable Expression of Lung Disease in PI Z Individuals

- Only 3 of 5 initial PI Z subjects described by Laurell and Eriksson (1963) had lung disease
- Black and Kueppers (1978) demonstrated marked variability in pulmonary function and respiratory symptoms among PI Z nonsmokers
- Substantial variability in pulmonary function among PI Z subjects was found in relation to smoking status and ascertainment [Tobin (1983), Silverman (1989), Seersholm (1995)]


PiZZ Smokers versus Non-smokers
FEV1 Percent Predicted
140
120
100
80
60
40
20
0
30
40
50
60
70
80
Age
Non-smokers
Smokers

Are People with PI MZ at Increased Risk for Lung Disease?

(Hersh, Thorax 2004)

- Case-control studies suggest an increased risk for lung disease in PI MZ individuals
- General population surveys do not find reduced lung function in PI MZ individuals
- Unclear if PI MZ subjects are at increased risk for COPD

Populations for COPD Genetic Association Studies

Study	Study Design	Current Sample Size	Principal Investigator
Boston Early-Onset COPD Study (EOCOPD)	Extended pedigrees	~1200	Silverman
National Emphysema Treatment Trial Genetics Ancillary Study (NETT)	COPD Cases	~400	Silverman
Normative Aging Study (NAS)	Smoking Controls	~400	Litonjua
GenKOLS (Norway) COPD Study	Case-Control	~1600	Bakke
International COPD Genetics Network (ICGN)	Nuclear Families	~3000	Lomas/ Silverman
ECLIPSE	Case-Control	~2400	Multicenter
Genetic Epidemiology of COPD (COPDGene)	Case-Control	10,192	Crapo/ Silverman

PI MZ Subjects in the COPDGene Study (M. Foreman, Annals of ATS, 2017)

- COPDGene Study Population: 10,090 subjects with passing AAT Genotypes
  - Non-Hispanic Whites: 5909 PI M, 256 PI MZ
  - African Americans: 3289 PI M, 22 PI MZ

- Clinical and Imaging Phenotypes:
  - COPD Affection Status (post-BD FEV_1 < 80% pred, FEV_1/FVC < 0.7)
  - Quantitative post-bronchodilator spirometric phenotypes
  - CT emphysema (-950 HU, Insp) and Gas Trapping (-856 HU, Exp)

- Association Analysis:
  - Multiple linear regression, adjusting for age, gender, pack-years, and current smoking

PI MZ Subjects in the COPDGene Study

(M. Foreman, Annals of ATS, 2017)

Multivariable Models for PI MZ Genotype in 8,271 Non-Hispanic Whites (239 MZ) and African Americans (22 MZ)

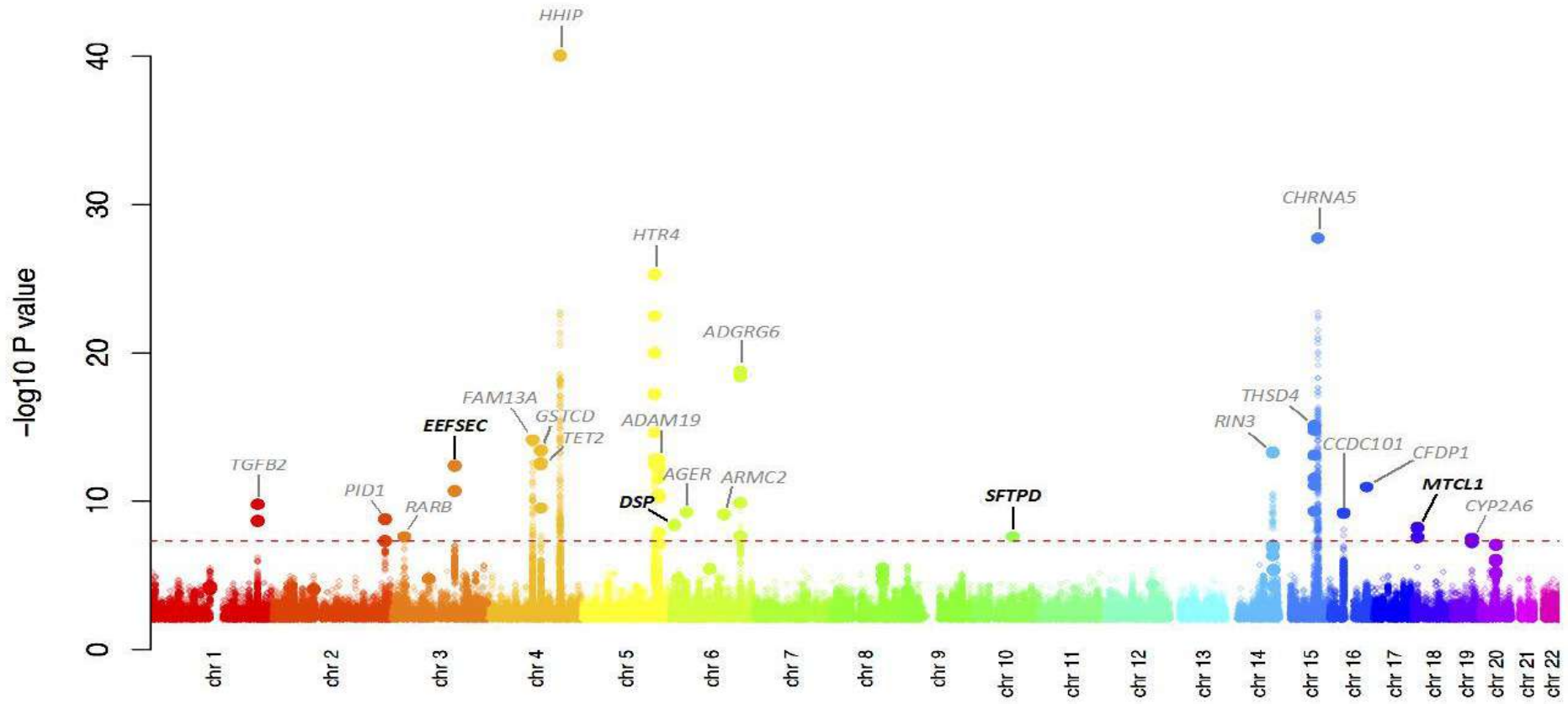
Outcome	Odds (CI) or Estimate (se) in NHW	PI MZ p-value in NHW	Odds (CI) or Estimate (se) in AA	PI MZ p-value in AA
COPD Affection Status	1.4 (1.05 – 1.9)	0.02	2.0 (0.8- 5.4)	0.2
Log (Emphysema)	0.3 (0.1)	0.001	0.5 (0.3)	0.08
Log (Gas Trapping)	0.13 (0.07)	0.05	0.3 (0.2)	0.3
FEV_1 (% pred)	-5.4 (1.7)	0.001	-13.0 (5.0)	0.01
FEV_1/FVC	-0.03 (0.01)	0.003	-0.10 (0.03)	0.02

International COPD Genetics Consortium COPD GWAS (Hobbs/Cho, Nat Genet 2017)

- **Phenotype:** Presence or Absence of COPD defined based on spirometry
- **Study Populations:** 15,256 COPD cases and 47,936 controls from 26 collaborating studies
- **Genotypes:** Multiple different genome-wide SNP panels with imputed genotypes using 1000 Genomes Project
- **Statistical Analysis:** Logistic regression with covariate adjustment separately in each study population, followed by meta-analysis across studies

International COPD Genetics Consortium COPD GWAS (Hobbs/Cho, Nat Genet 2017)

- Included discovery in 15,256 COPD cases and 47,936 controls from 26 studies with genotyping of select top results ($P < 5x10^{-6}$) in 9,498 COPD cases and 9,748 controls from UK-BiLEVE

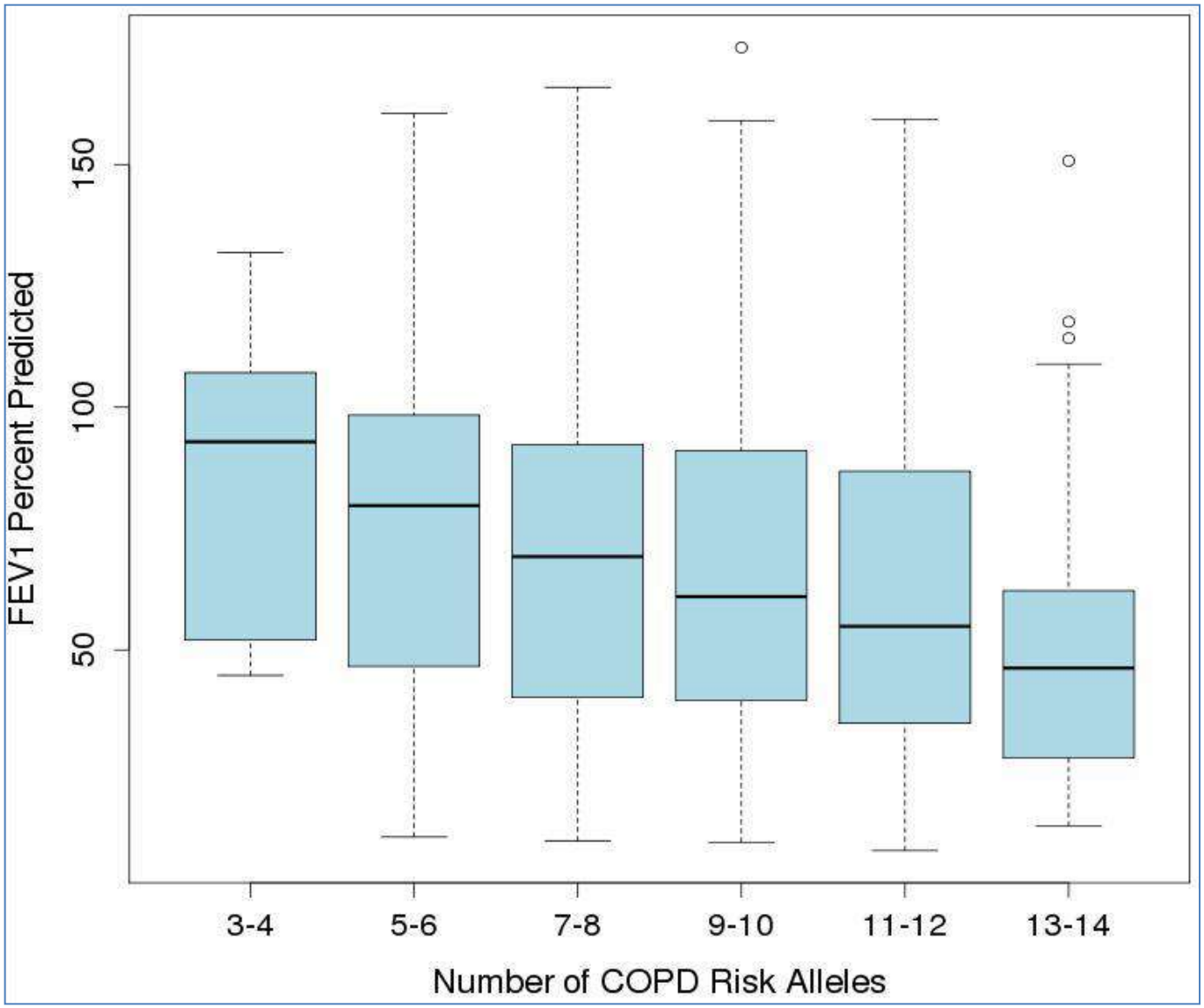


Replication of COPD GWAS Regions

Locus	First Author (Year)	SNP	Odds Ratio	P-value
HHIP	Van Durme (2010)	rs13118928	0.80	2×10^{-4}
HHIP	Zhou (2012)	rs13118928	0.68	2×10^{-3}
HHIP	Wain (2015)	rs1032296	0.88	7×10^{-7}
FAM13A	Young (2011)	rs7671167	0.79	0.01
FAM13A	Xie (2015)	rs7671167	0.53 (CC genotype)	8×10^{-8} (CC)
CHRNA3/5	Wilk (2012)	rs1051730	1.17	3×10^{-7}
CHRNA3/5	Hardin (2012)	rs8034191	1.89	7×10^{-7}
IREB2	Chappell (2011)	rs2568494	1.30	5×10^{-4}
MMP1/MMP12	Hunninghake (2012)	rs2276109	N/A	4×10^{-5}
	Arja (2014)	rs2276109	0.48	0.01
	Jackson (2016)	rs17368582	0.71	5x10-6

COPD Genetic Risk Scores Are Associated with Lung Function in the International COPD Genetics Network

(R. Busch, AJRCMB, 2017)



After adjustment for covariates, each additional risk allele predicted 1.9% (95% CI 1.2 to 2.5) decrease in FEV_1 (% predicted)

Moving from Gene Discovery to Gene Localization to Functional Validation

- **Discovery**
  - Genetic Association Analysis
- **Localization**
  - Fine Mapping
  - Long-range Genetic Interactions
  - Regions containing functional activity
- **Functional Validation**
  - Cell-based models
  - Animal models

Relationship of Genetics Research to Cell/Molecular Biology Studies

GWAS Associations

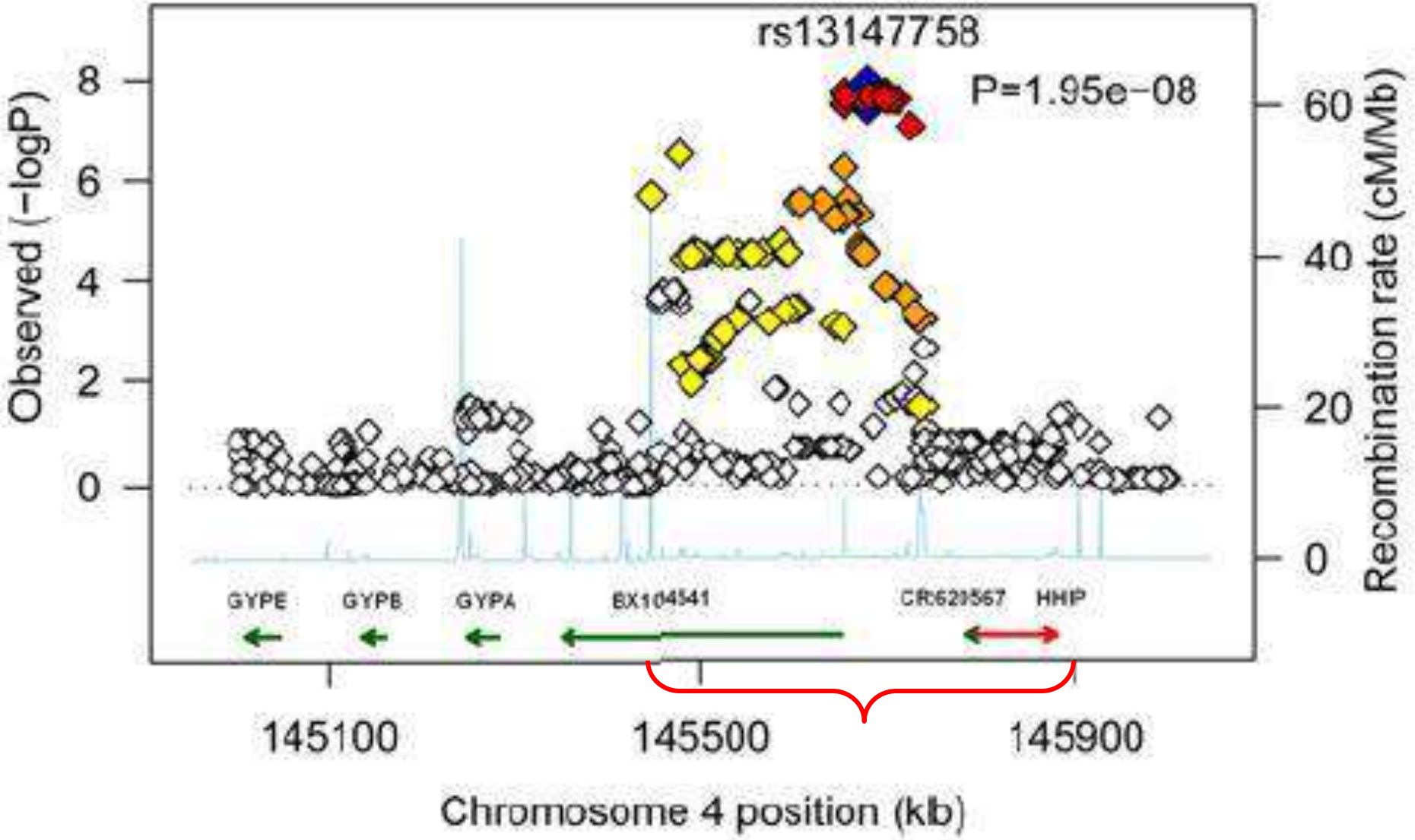
Genetics Researchers

Cell/Molecular Biologists

- No thanks, we have our own ideas of what to study
- We don't believe that what you found is important or useful

COPD GWAS Locus Near HHIP

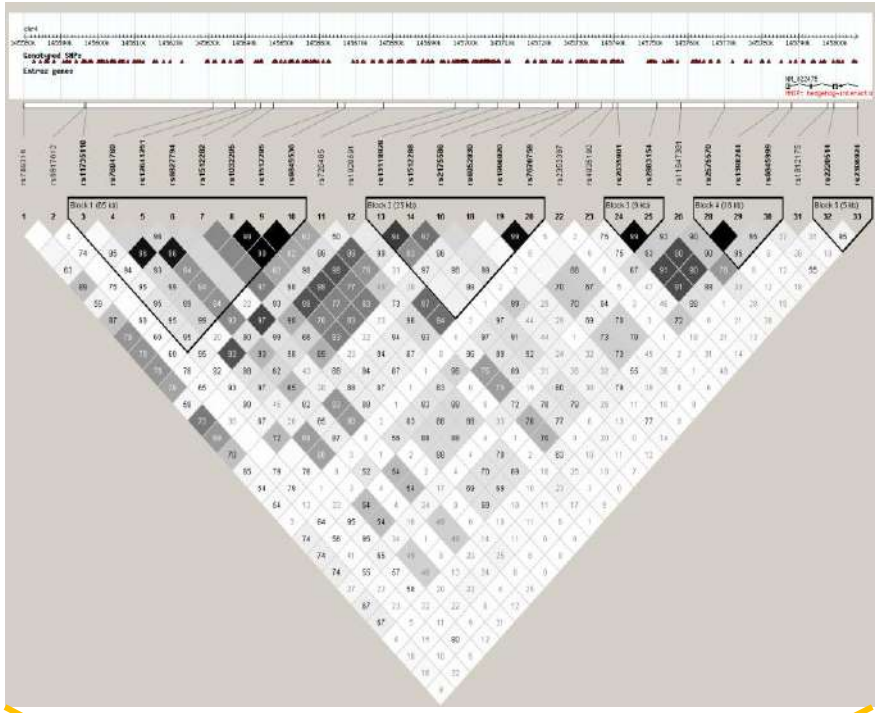
(Wilk, PLoS Genetics 2009)

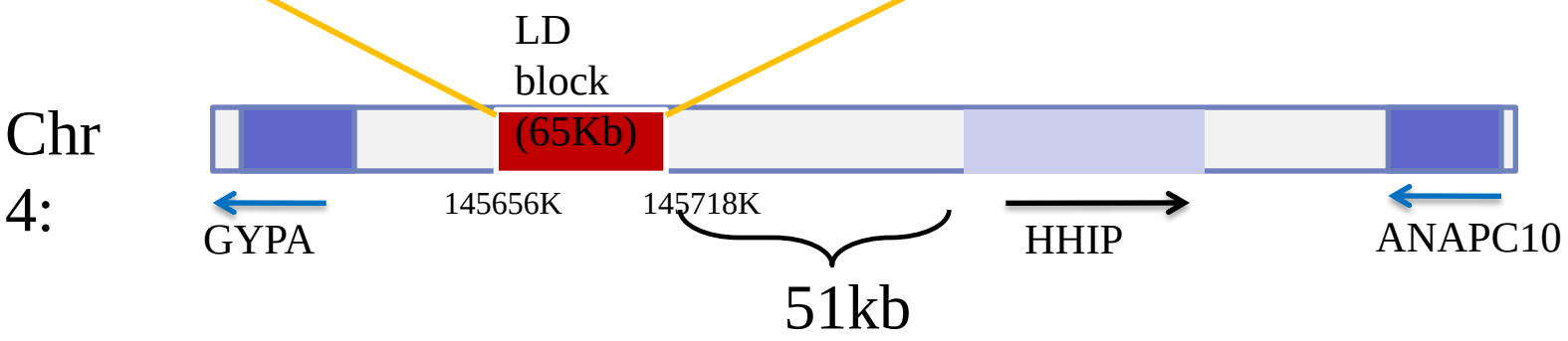


HHIP COPD GWAS Region: Where Are the Functional Variants?

- Within HHIP Gene: Could be long-range LD with untested/undetected variants
- In a Novel Gene within Association Region
- In a Novel Functional Element in Association Region
- **Long-range Regulation of HHIP**
- Long-range Regulation of Another Gene

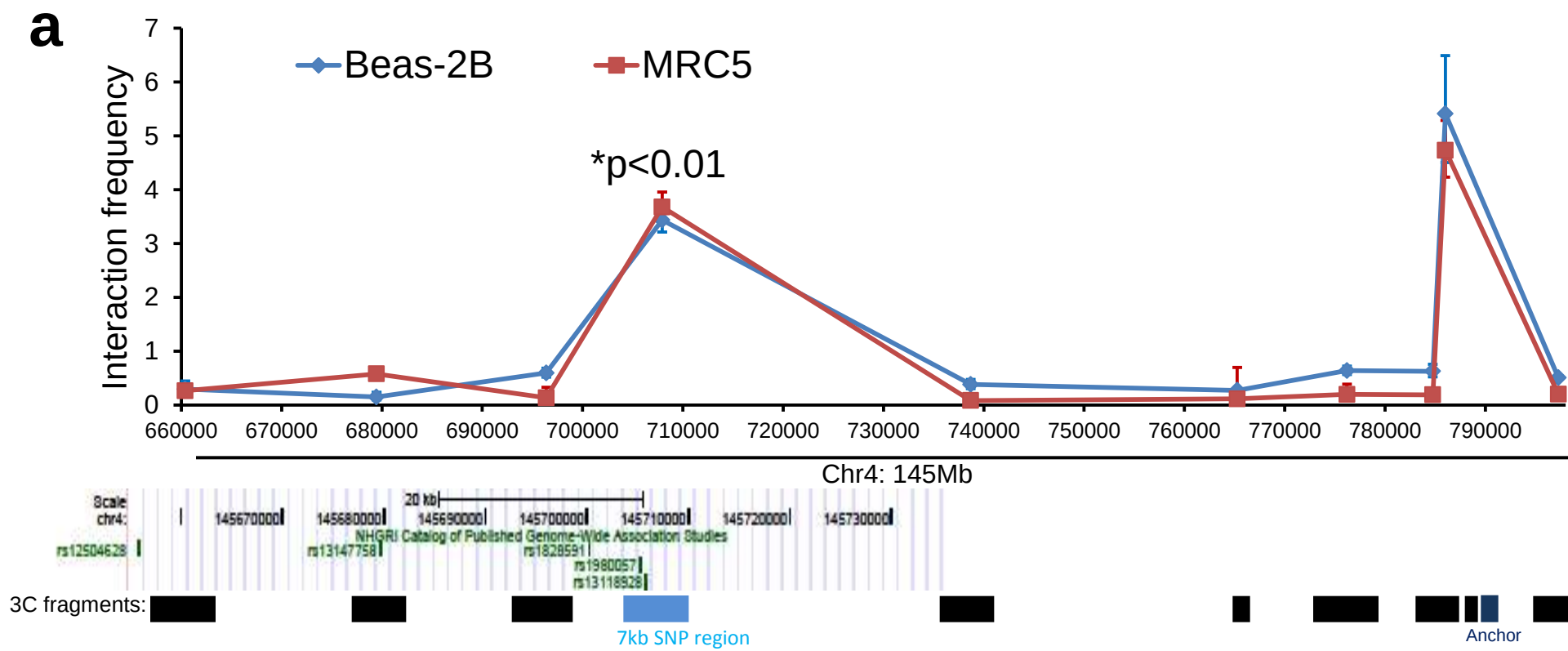
Linkage Disequilibrium (r^2) in HHIP Region





Long-range Interaction Detected Between COPD GWAS Region and HHIP Promoter (Zhou, Hum Mol Genet, 2012)

Chromosome conformation capture

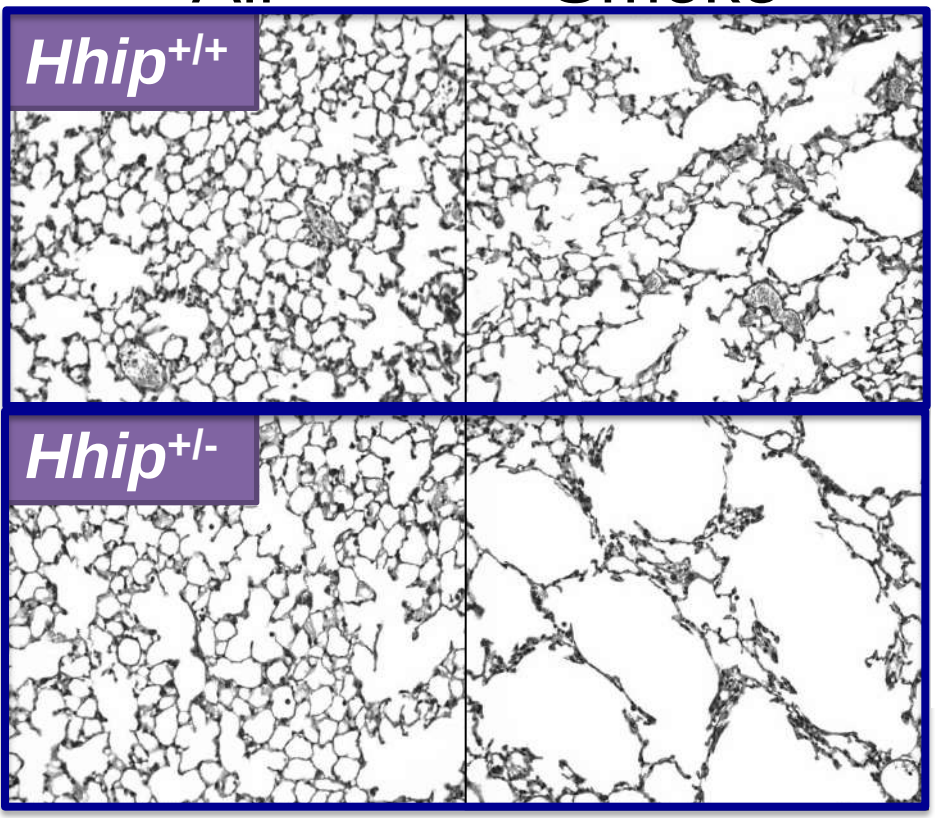


Hhip$^{+/-}$ Mice: Cigarette Smoke Effects

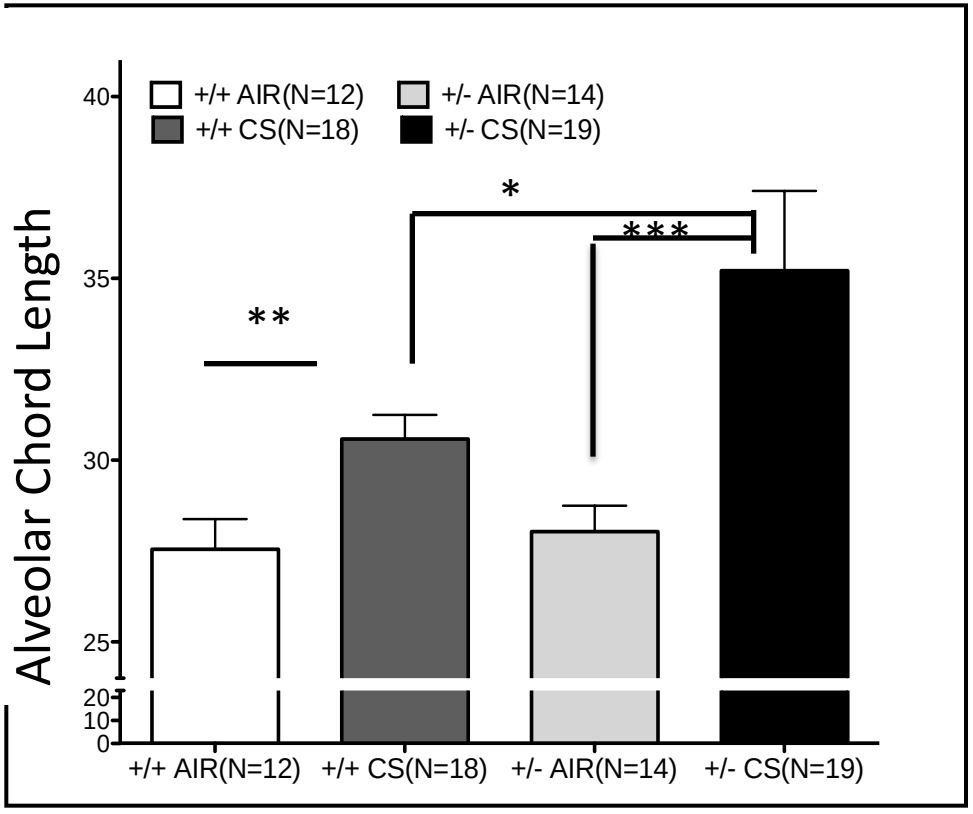
(T. Lao/X. Zhou, Genome Med 2015)

C57BL/6 ---Gill staining

Air Smoke



Mean Chord Length



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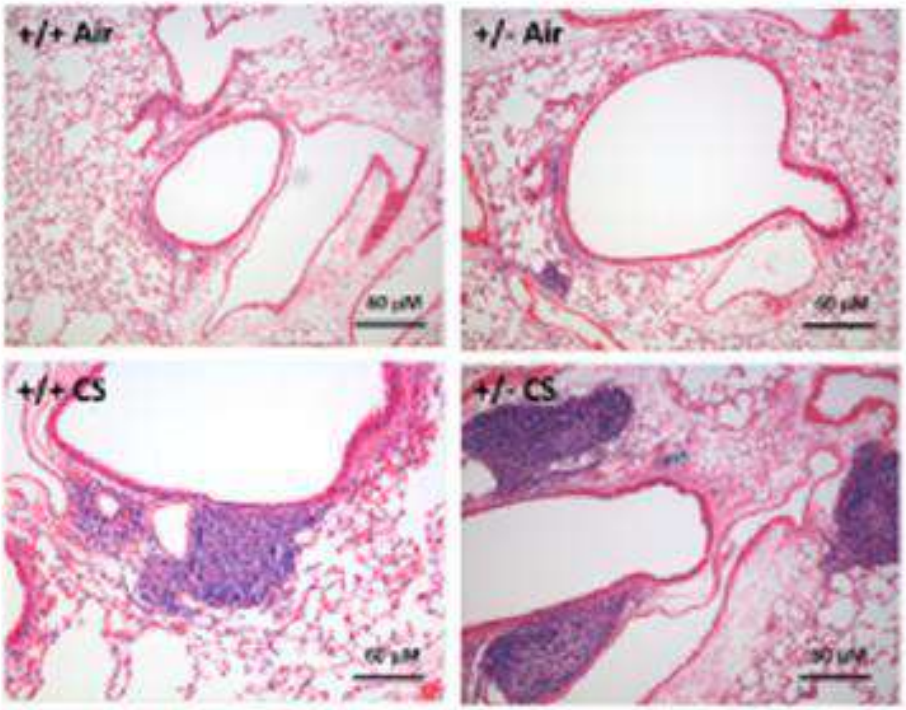
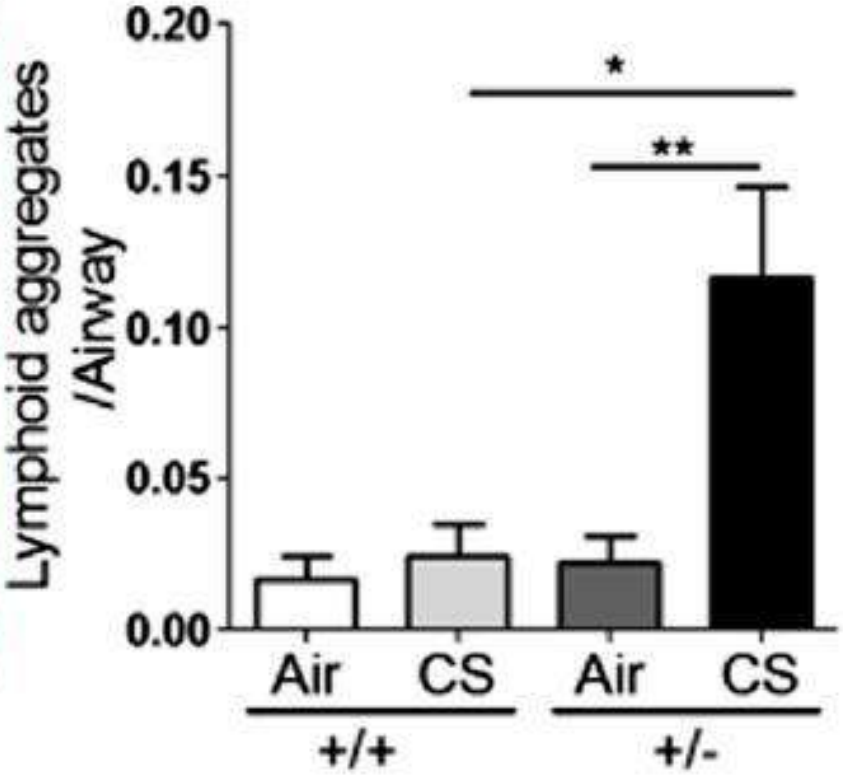
(T. Lao/X. Zhou, Genome Med 2015; 7: 12)

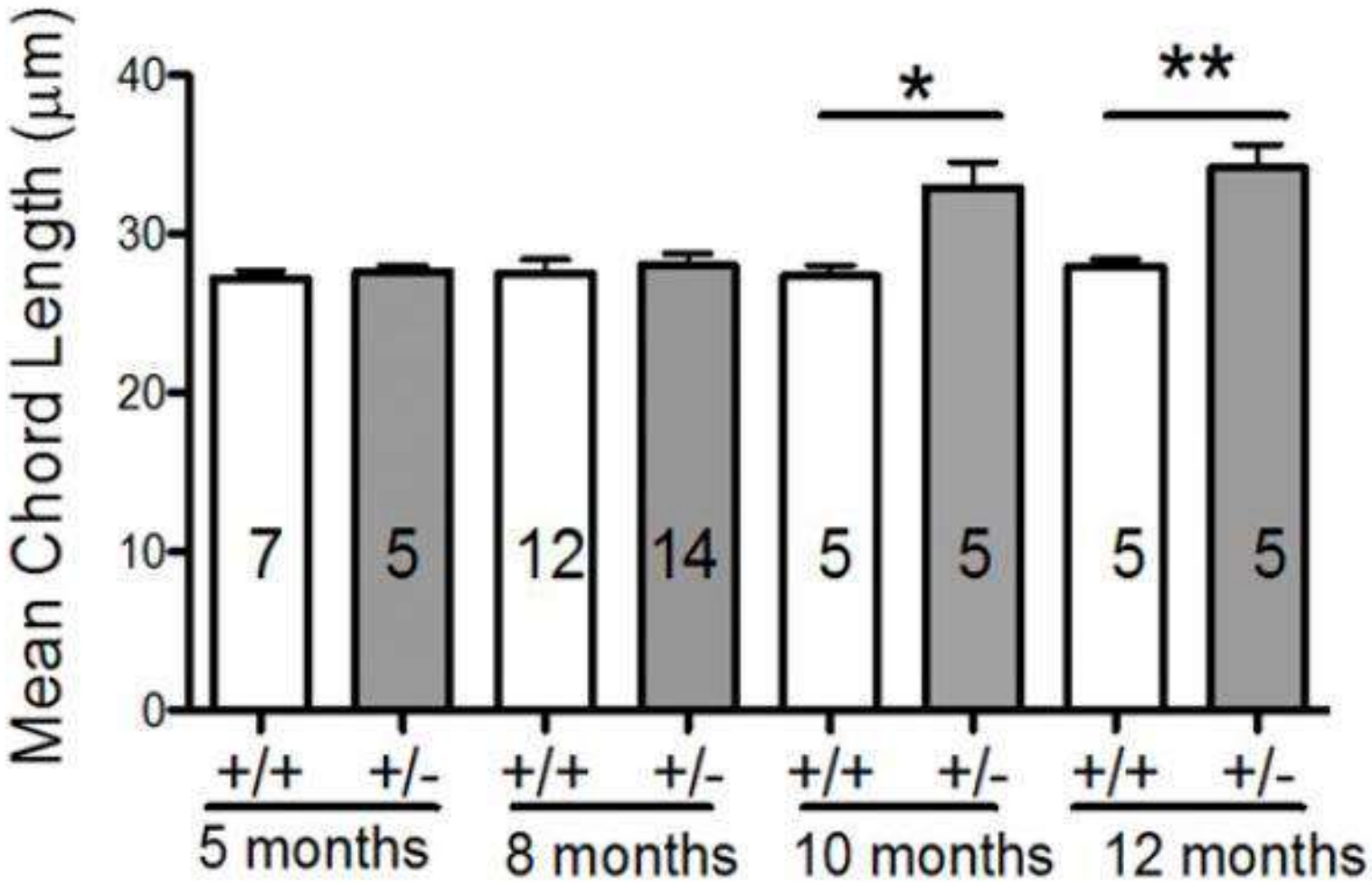




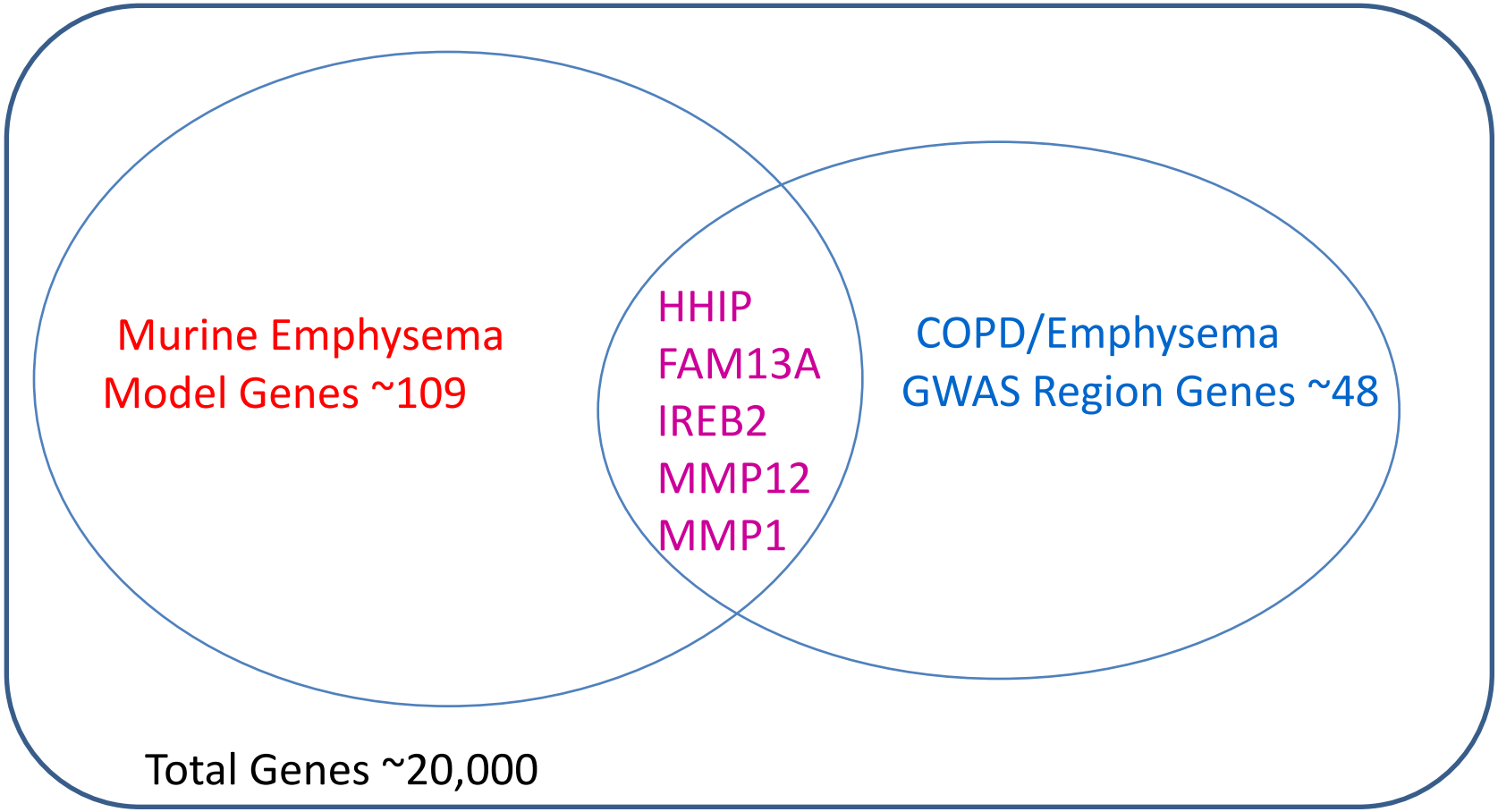
Note: 1) Lymphoid aggregates contain mainly CD8+ T cells and B cells
2) Differential gene expression highlighted lymphocyte activation

Aging-Related Emphysema in Hhip+/- Mice Without Smoke Exposure

(Lao, PNAS 2016)



Overlap of Murine Emphysema Model Genes and COPD GWAS Region Genes



Functional Validation of COPD GWAS Genes in Murine Models

Gene	Reference	Model	Phenotype	Postulated Biological Effect/Pathway
MMP1	D'Armiento (1992)	Transgenic	Increased Emphysema	Collagenase Activity
MMP12	Hautamaki (1997)	Knock-out	Decreased Emphysema	Metalloelastase Activity
HHIP	Lao (2015)	Heterozygous Knock-out	Increased Emphysema	Lymphocyte Activation
IREB2	Cloonan (2016)	Knock-out	Decreased Emphysema and Airway Disease	Mitochondrial Iron
FAM13A	Jiang (2016)	Knock-out	Decreased Emphysema	Wnt/Beta Catenin

Functional Genetics of COPD Lung Tissue Population

(Morrow/Hersh, Sci Rep 2017)

	COPD cases N=111	Control smokers N=40	P-value
Age	63.3 (± 6.6)	65.7 (± 9.0)	n.s.
Female sex	59 (53.2%)	25 (62.5%)	n.s.
Race African American White Other	 18 (16.2%) 90 (81.1%) 3 (2.7%)	 5 (12.5%) 34 (85.0%) 1 (2.5%)	n.s.
Pack-years of smoking	61.3 (± 26.3)	33.6 (± 21.0)	<0.0001
FEV_1 % predicted	26.5 (± 9.4)	98.7 (± 12.5)	<0.0001
FEV_1/FVC	0.32 (± 0.10)	0.79 (± 0.05)	<0.0001

No Differential Expression of COPD GWAS Genes in Lung Tissue (Morrow, Sci Rep 2017)

Rank	Gene	P Value	Adjusted P value
1680	MMP12	0.02	0.30
3277	HHIP	0.04	0.42
6372	AGER	0.11	0.59
6537	IREB2	0.12	0.60
8216	DLC1	0.16	0.66
8688	CHRNA5	0.18	0.67
13798	FAM13A	0.34	0.80
19429	CHRNA3	0.53	0.89
22640	RIN3	0.64	0.93
29796	TGFB2	0.89	0.98

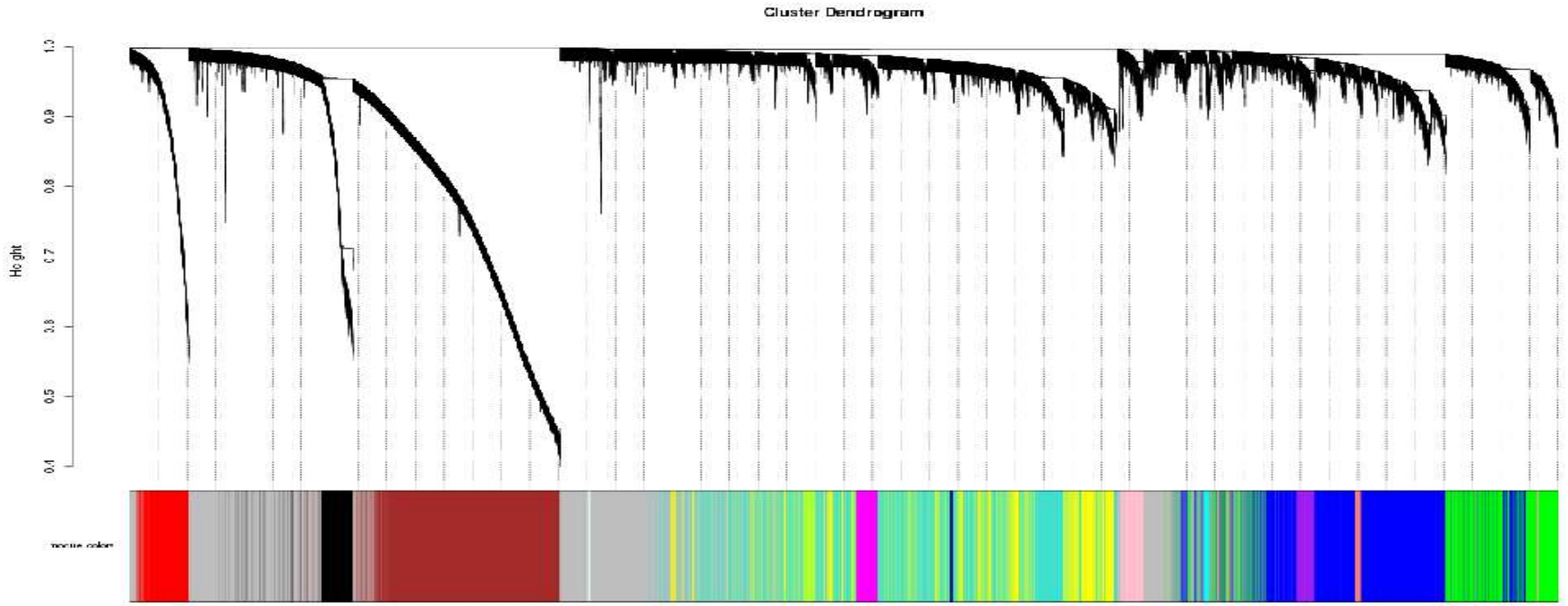
Note: Top differentially expressed gene was HMGB1, a known interactor with AGER

Are Interactors with COPD GWAS Genes More Likely To Be Differentially Expressed in Lung Tissue? (Morrow, Sci Rep 2017)

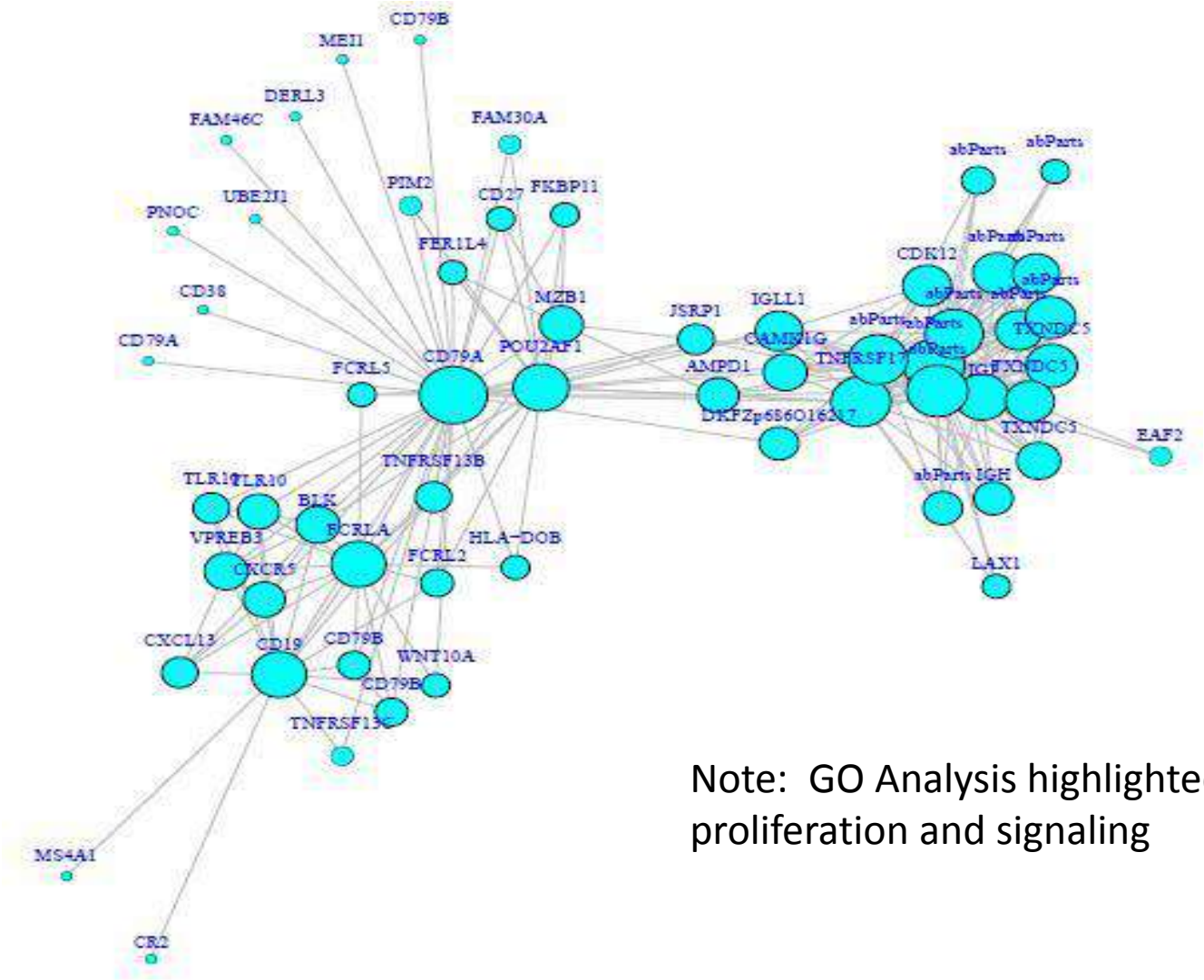
Experiment	Number of genes or proteins	Enrichment p-value for FEV_1 Genes	Enrichment p-value for COPD Genes
IREB2 RNA immunoprecipitation seq	4008	3.6×10^{-11}	2.4×10^{-5}
IREB2 trans-eQTLs at p<0.05	1612	1.4×10^{-10}	0.0002
HHIP Tandem affinity purification	216	1.8×10^{-6}	0.06
HHIP trans-eQTLs at p<0.05	1560	2.4×10^{-5}	0.09
Hhip$^{+/-}$ mouse 6 mo. smoking experiment, genotype x smoke interaction	492	2.7×10^{-6}	0.0001
FAM13A trans-eQTL at p<0.05	1753	$<1.0 \times 10^{-12}$	2.7×10^{-6}
FAM13A Tandem affinity purification	97	0.3	1

Weighted Gene Co-Expression Network Analysis in COPD vs. Control Lung Tissue (Morrow/Hersh, 2017)

- Methods:
  - WGCNA method analyzes correlation in gene expression; retains scale-free degree distribution of coexpression network
  - WGCNA produces a set of modules (labeled by color), each containing a set of unique genes



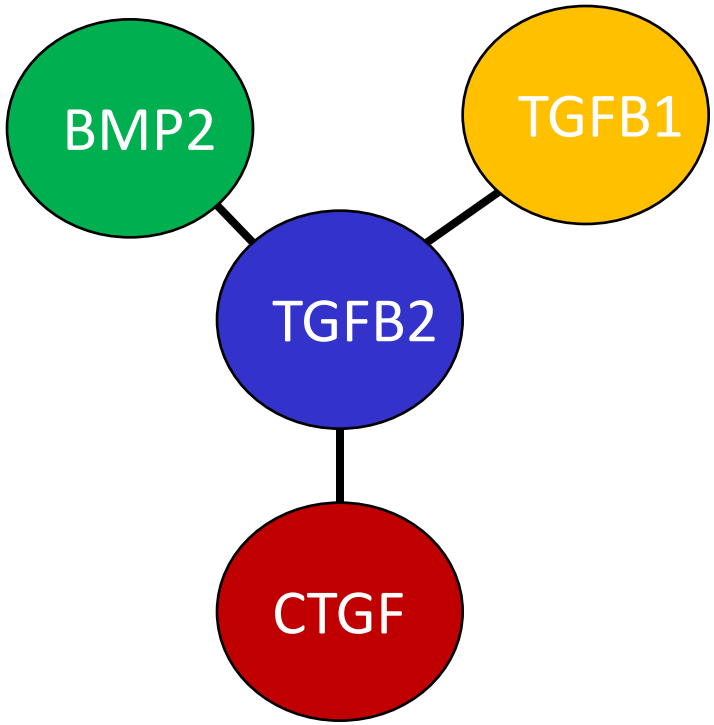
Cyan Module from WGCNA Analysis of Lung Tissue Population (Morrow/Hersh, 2017)



Note: GO Analysis highlighted B cell proliferation and signaling

Can We Leverage Protein-Protein Interactions To Understand How Genetic Determinants Influence COPD Pathogenesis?

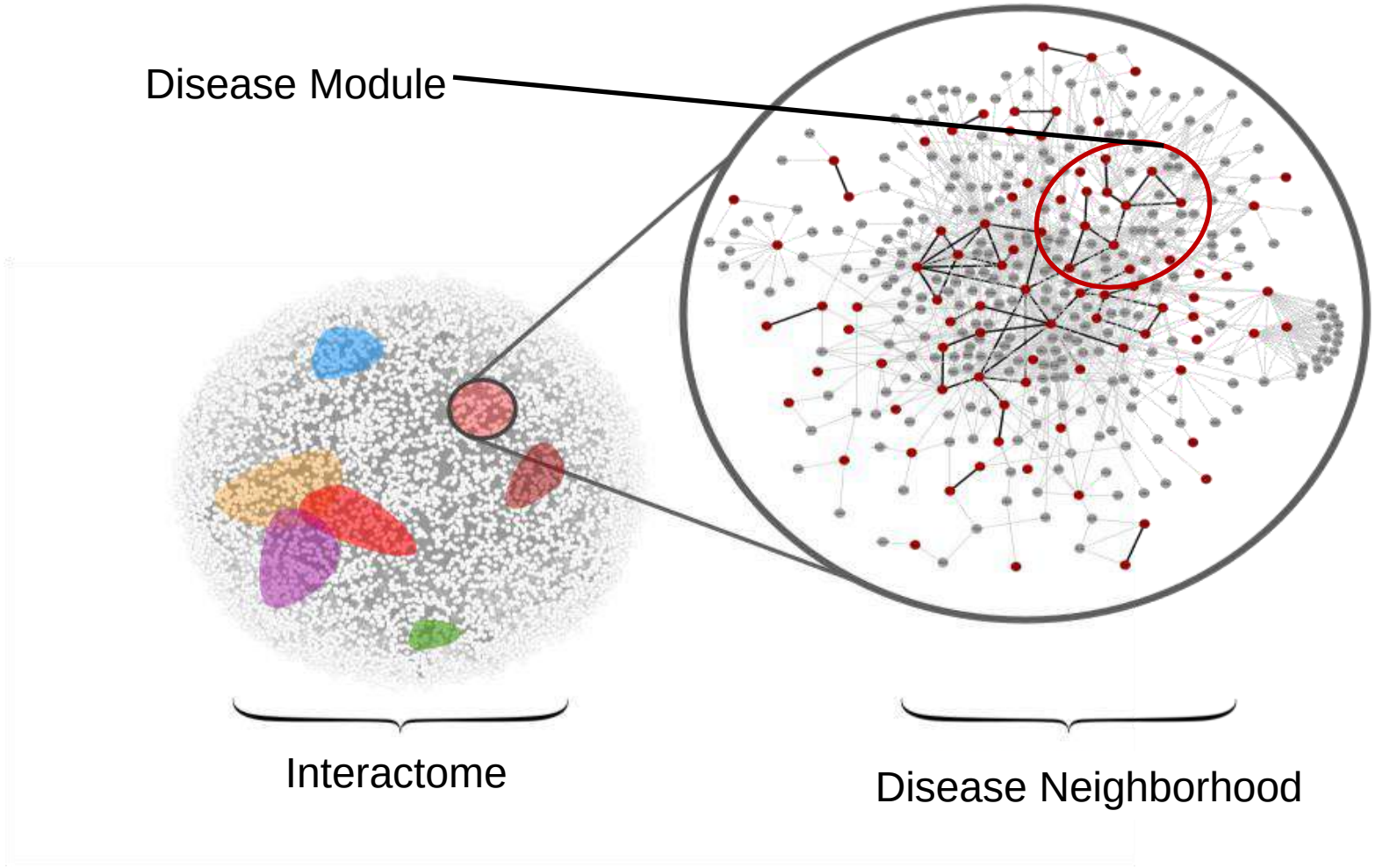
Protein-Protein Interaction Network



Nodes: Proteins

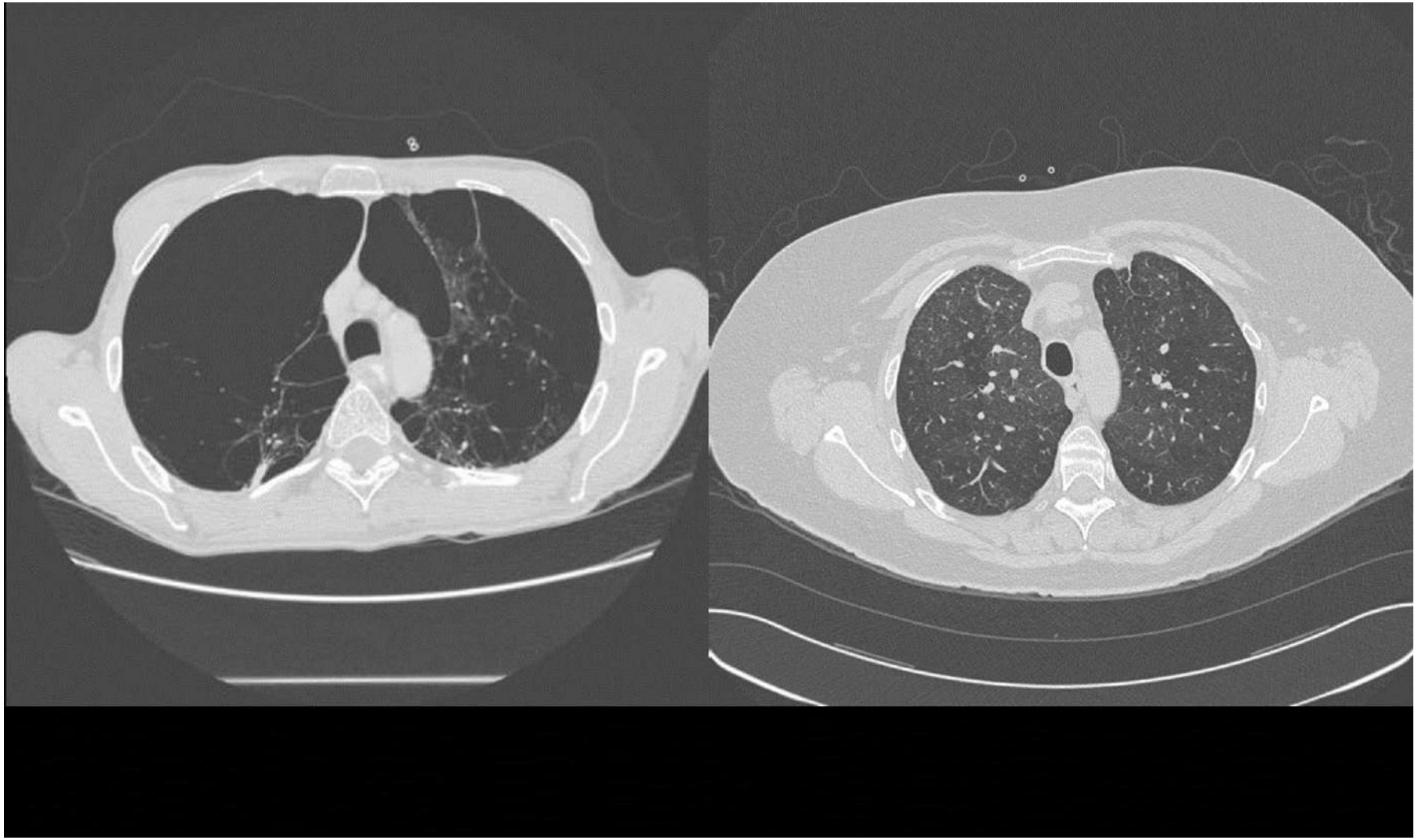
Edges: Physical interactions between proteins

Disease Modules, Disease Neighborhoods, and the Interactome



Emphysema Predominant

Airway Disease Predominant



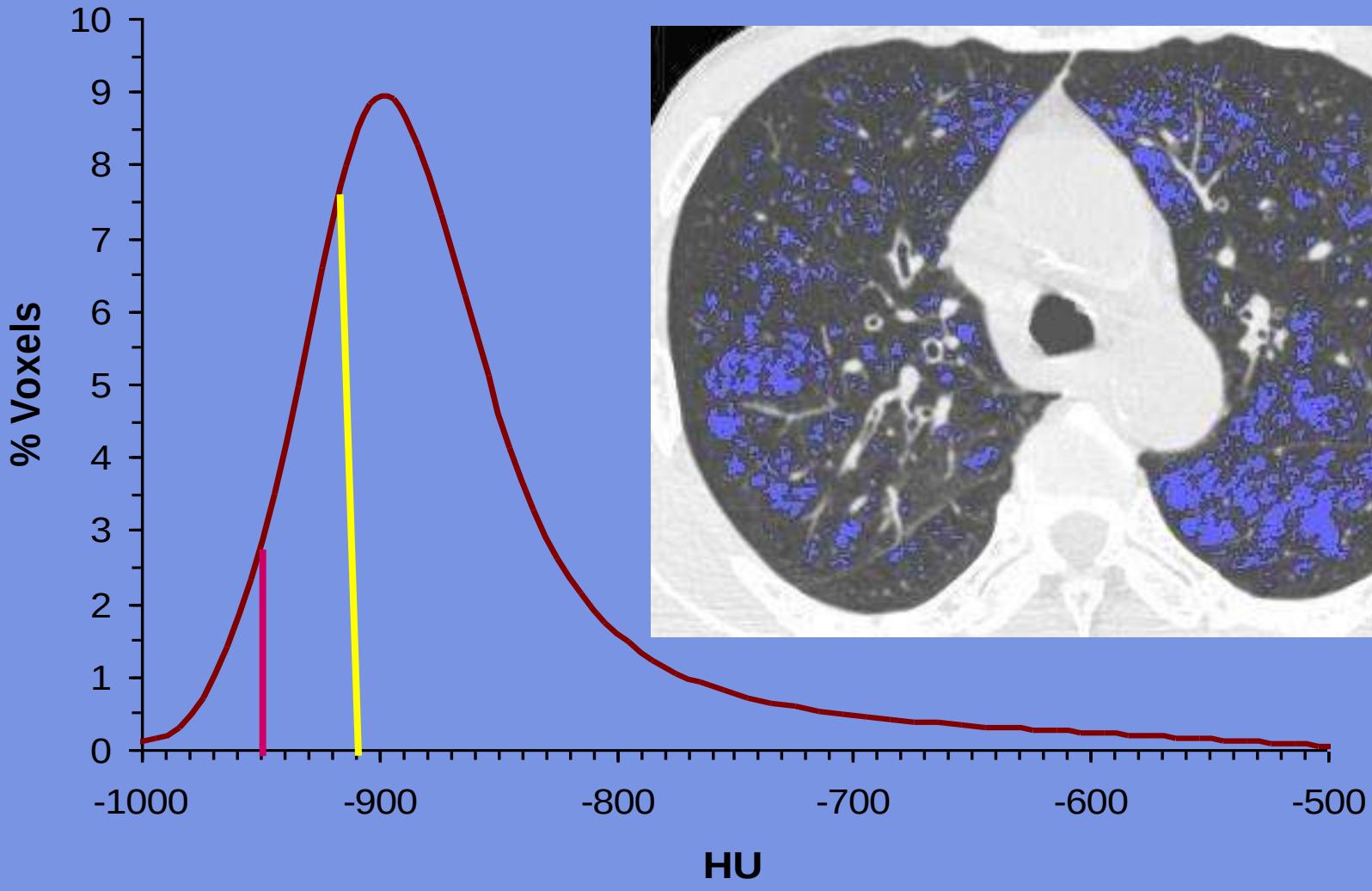
Age 42, FEV_1 38%

Age 47, FEV_1 20%

COPD Is Heterogeneous

- COPD Subtypes (Disease Processes)
  - Emphysema
  - Airway Disease
- COPD-Related Phenotypes (Disease Manifestations)
  - COPD Exacerbations
  - Cachexia
  - Functional Impairment
  - Co-morbid Diseases

Quantification of Emphysema



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

GWAS of Quantitative Imaging Phenotypes
(Cho, AJRCCM, 2015)

Phenotype	Chr	Marker Name	Closest Gene	Modified Random Effects P value
%LAA-950	4	rs13141641	HHIP	1.7×10^{-12}
	15	rs55676755	CHRNA3	2.4×10^{-9}
	6	rs2070600	AGER	4.6×10^{-9}
	8	rs75200691	DLC1	9.7×10^{-9}
	14	rs45505795	SERPINA10	1.4×10^{-8}
Wall Area %	4	rs142200419	MIR2054	4.6×10^{-9}
Gas Trapping	6	rs2070600	AGER	3.5×10^{-9}
	21	rs55706246	LINC00310	1.3×10^{-8}

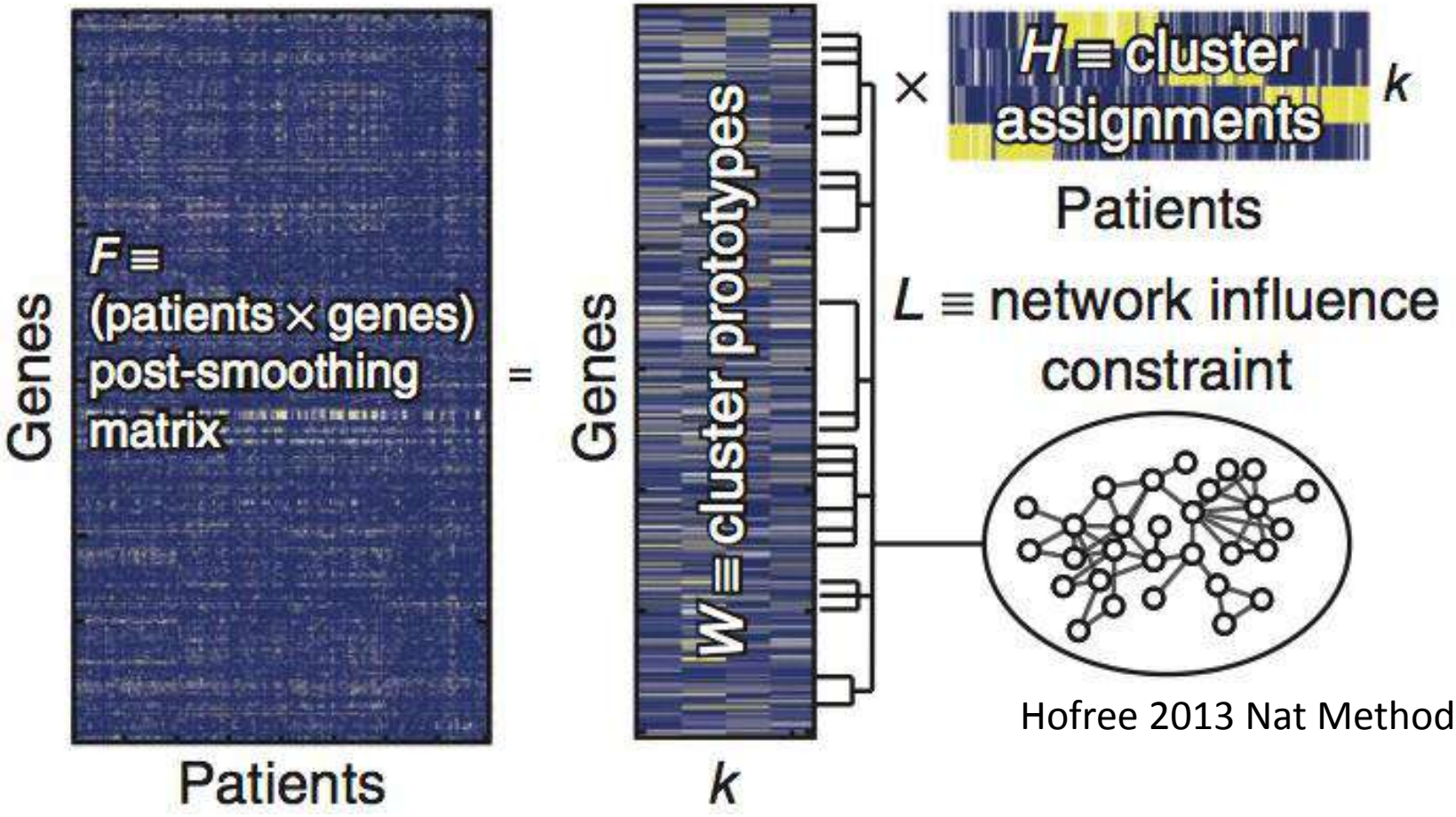
Meta-analysis of COPDGene, ECLIPSE, GenKOLS, and NETT

COPDGene Study
Approaches to Define COPD Subtypes

- Clinical Subtypes
  - Imaging-based expert classification
  - Epidemiologically-driven analysis of COPD-related phenotypes
- Machine Learning Approaches
  - Defining groups: Cluster analysis
  - Defining disease axes: Principal components analysis

Network-based stratification of tumor mutations

Matan Hofree[1], John P Shen[2], Hannah Carter[2], Andrew Gross[3] & Trey Ideker[1–3]



Hofree 2013 Nat Methods

Applying Network-Based Stratification to COPD

(Chang/Castaldi, Genomics 2016)

- Rationale
  - Gene expression array data is noisy
  - External information about groups of genes expected to act together could guide solutions
  - NBS merges data-driven pattern finding with protein interaction network data to arrive at more “biologically” informed subtypes
- Methods:
  - Peripheral blood gene expression microarrays
  - Primary analysis in ECLIPSE (n=229) with replication in COPDGene (n=135) COPD cases and smoking controls
  - Feature selection – 1,812 genes with expression levels associated with FEV_1, FEV_1/FVC, or CT emphysema

NBS Clinical Replication in COPDGene (Chang/Castaldi, Genomics 2016)

ECLIPSE

	C1	C2	C3	C4
N	29	89	93	18
FEV_1	49	67	82	87
FEV_1/FVC	0.43	0.53	0.63	0.69
Emphysema	20	13	6	6

COPDGene

C1	C2	C3	C4
19	50	61	5
49	67	72	87
0.48	0.59	0.63	0.70
10	5	2	1

Note: Clustering without network constraint was much less reproducible

Severe COPD Cases from Korea, Poland, and USA Have Substantial Differences in Respiratory Symptoms and Other Respiratory Illnesses

(Kim/Silverman, Int J COPD 2017)

- **Hypothesis:** Severe COPD patients in different geographic regions would have differences in respiratory symptoms, environmental exposures, and other respiratory illnesses
- **Methods:**
  - Study populations of severe COPD (FEV1 < 50% pred) from Poland (n=316), South Korea (n=173), and USA (n=339)
  - Subjects with interstitial lung disease, diffuse bronchiectasis, and lung parenchymal destruction by tuberculosis were excluded
  - Similar phenotyping with pre/post-bronchodilator spirometry and standardized questionnaire
  - Data Analysis: Univariate and Multivariate comparisons between study populations

Severe COPD Cases from Korea, Poland, and USA

(Kim/Silverman, Int J COPD 2017)

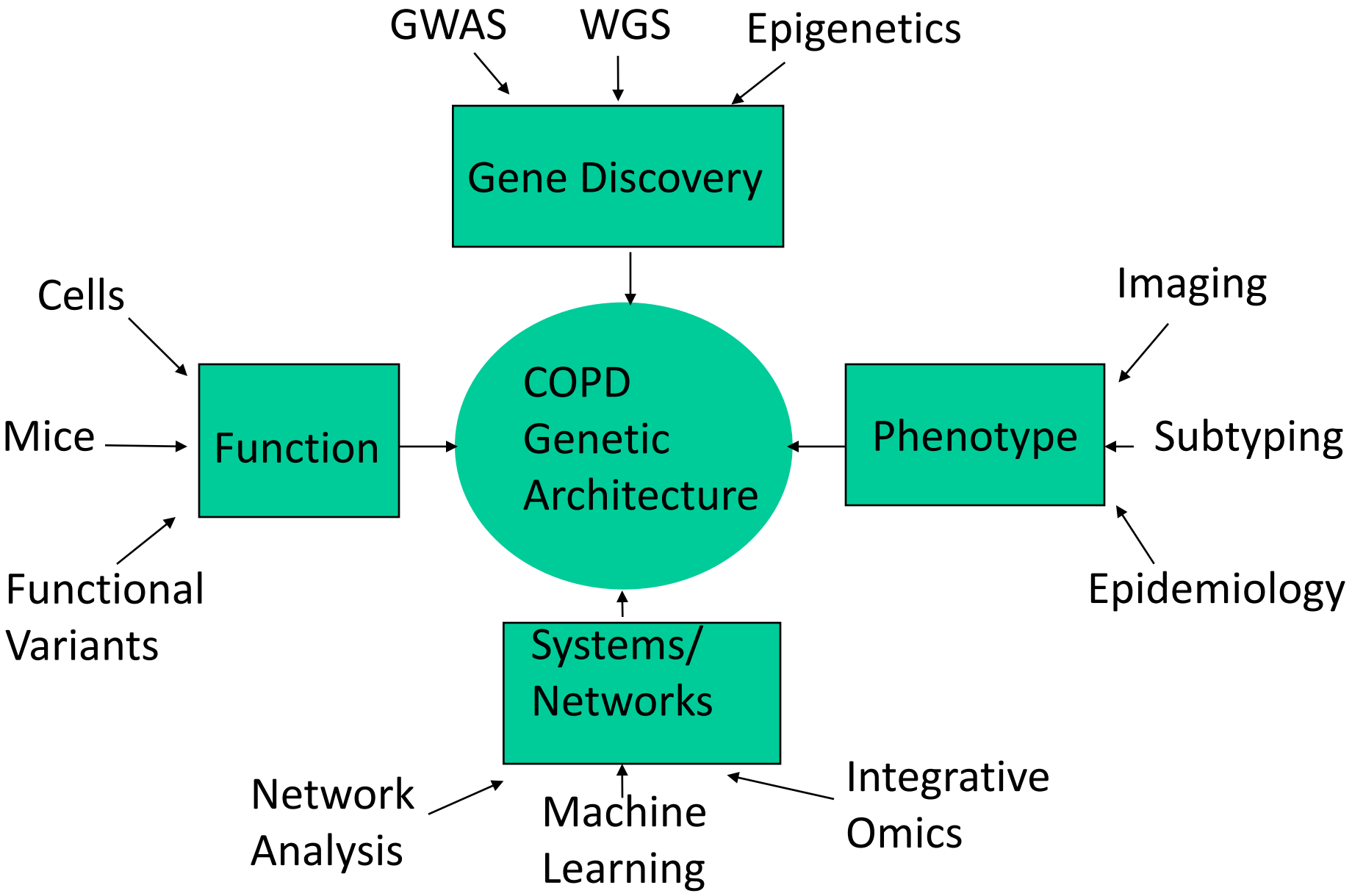
	POLAND (n=316)	KOREA (n=173)	USA (n=339)	p value
RESPIRATORY ILLNESSES				
History of Pneumonia	184 (58.2)	38 (22.0)	228 (67.3)	< 0.0001
History of Tuberculosis	34 (10.8)	67 (38.7)	1 (0.3)	< 0.0001
Physician-Diagnosed Asthma	5 (1.6)	76 (43.9)	108 (31.9)	< 0.0001
Lung Trouble Before Age 16	49 (15.5)	11 (6.4)	45 (13.3)	0.01

- Higher rates of chronic bronchitis in Poland, but more frequent attacks of wheezing and diagnosed asthma in USA and Korea
- Lower rates of pneumonia in Korea
- History of tuberculosis: Korea > Poland > USA (and different than controls in those countries)
- Differences in disease manifestations could relate to environmental exposures, treatment differences, diagnostic approaches and/or genetics

Significant Insights From COPD Genetic Studies

- Alpha-1 antitrypsin PI MZ genotype is a significant risk factor for COPD in smokers
- 24 genomic regions have been shown to contain genetic determinants that influence COPD and/or emphysema susceptibility by GWAS
- A functional genetic variant upstream from *HHIP* has been found in the COPD GWAS region on chromosome 4q31
- Several novel COPD susceptibility genes identified by GWAS have been supported by animal models of emphysema
- Functional studies of COPD GWAS genes are implicating key biological pathways in COPD pathogenesis
- Network-based analysis has the potential to provide insights into COPD pathobiology and heterogeneity

COPD as a Model of Complex Disease



Collaborators

- *ECLIPSE Genetics Study:* Michael Cho, DK Kim, Wayne Anderson, Sreekumar Pillai, Xiangyang Kong, David Lomas, ECLIPSE Steering/Scientific Committees
- *Norway Case-Control Study:* Per Bakke, Amund Gulsvik, Sreekumar Pillai, Craig Hersh, Dawn DeMeo, Michael Cho
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