The Origins and Evolution of Network Medicine and Impact on Health Care Globally

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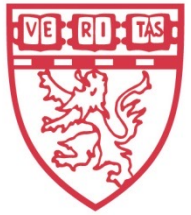
BRIGHAM AND WOMEN'S HOSPITAL



Edwin K. Silverman: Conflicts of Interest

- **1) Personal financial relationships with commercial interests relevant to medicine, within past 3 years:**
  - Grants: Bayer and Northpond Laboratories

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

  No relationships to disclose

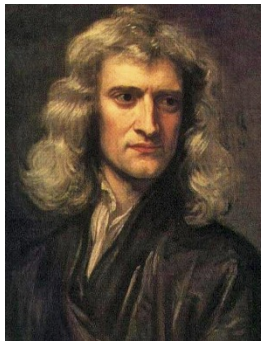
- **3) Personal relationships with tobacco industry entities within the past 3 years: No relationships to disclose**

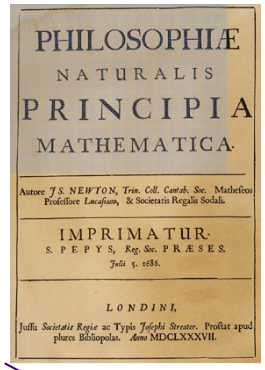
Danube Symposium Synopsis

- “Recently introduced Total-body PET systems offer a paradigm shift in medical sciences, providing a comprehensive assessment of the entire patient with their biological and clinical state, rather than just isolated diseases or organs.”

- Recently introduced Network Medicine approaches offer a paradigm shift in medical sciences, providing a comprehensive assessment of the entire patient with their biological and clinical state, rather than just isolated diseases or organs.

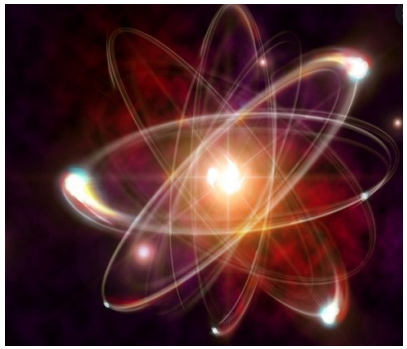
Recognition of Complexity in Physics





Newtonian Physics

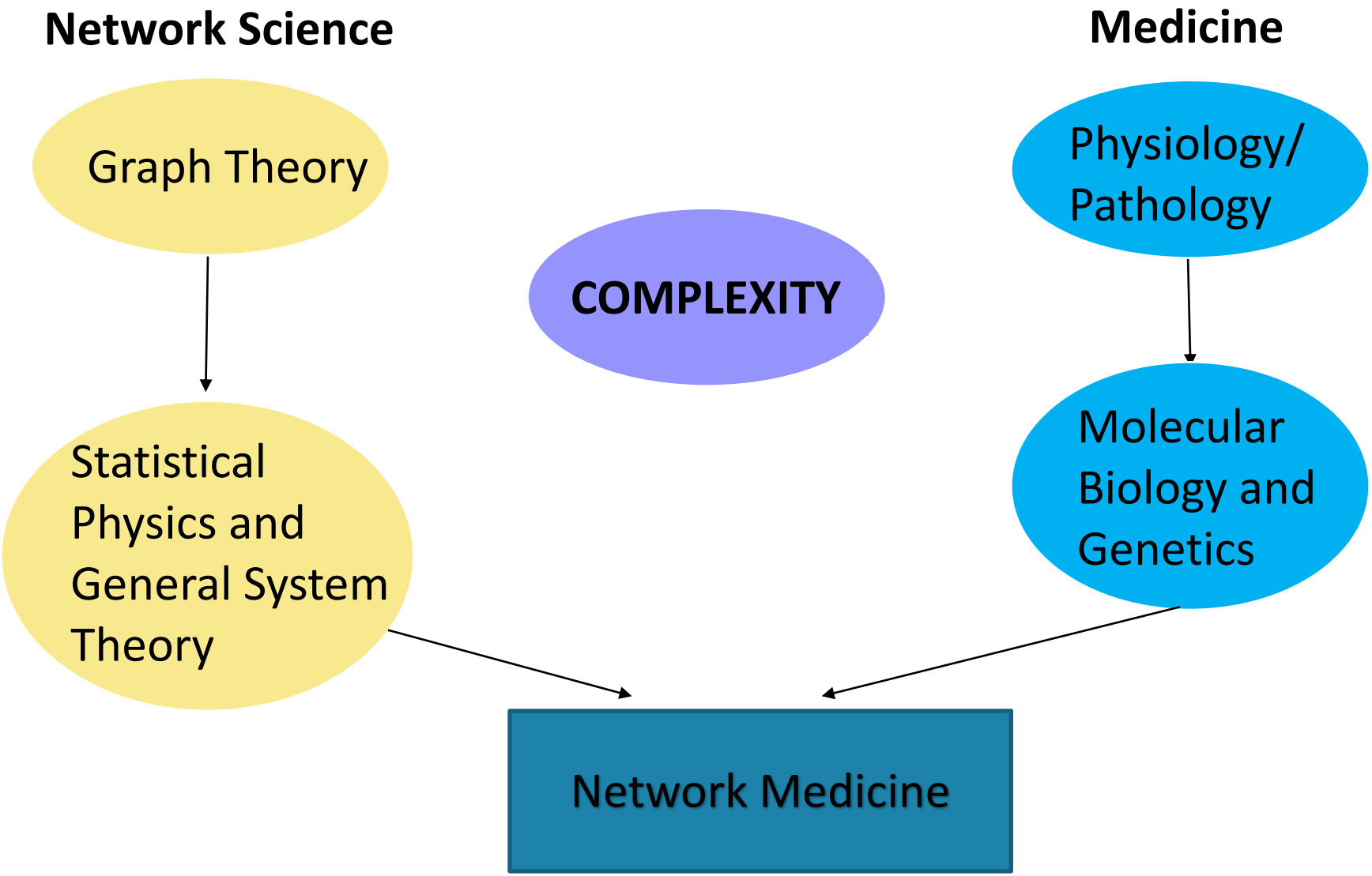
COMPLEXITY



Quantum Mechanics (Bohr, Planck, Einstein, Schrodinger, Heisenberg, etc.)

Chaos Theory ("Sensitive dependence on initial conditions"by Lorenz, Smale, Santa Fe Institute, etc.)

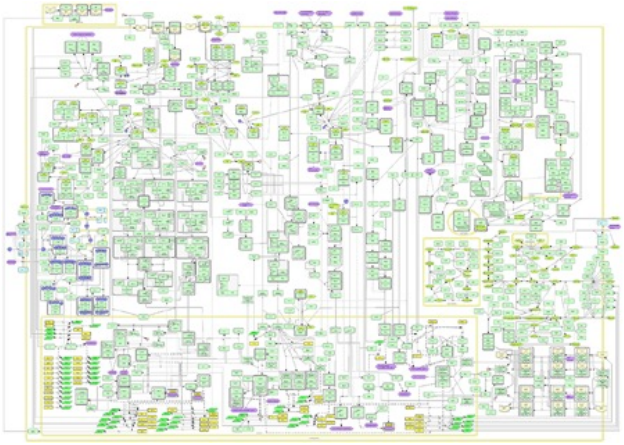
Overview of the History of Network Medicine



What Is a Network?

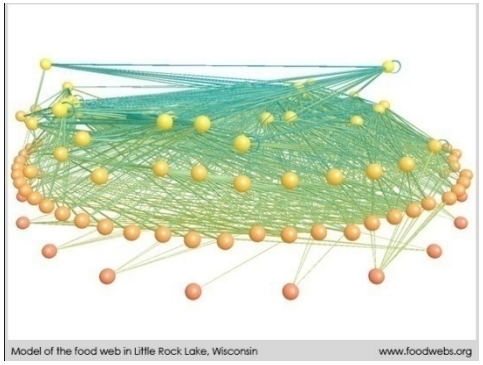
A collection of points (nodes) that are joined in pairs by lines (edges). A graphical approach to visualize and analyze relationships between variables of interest.

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



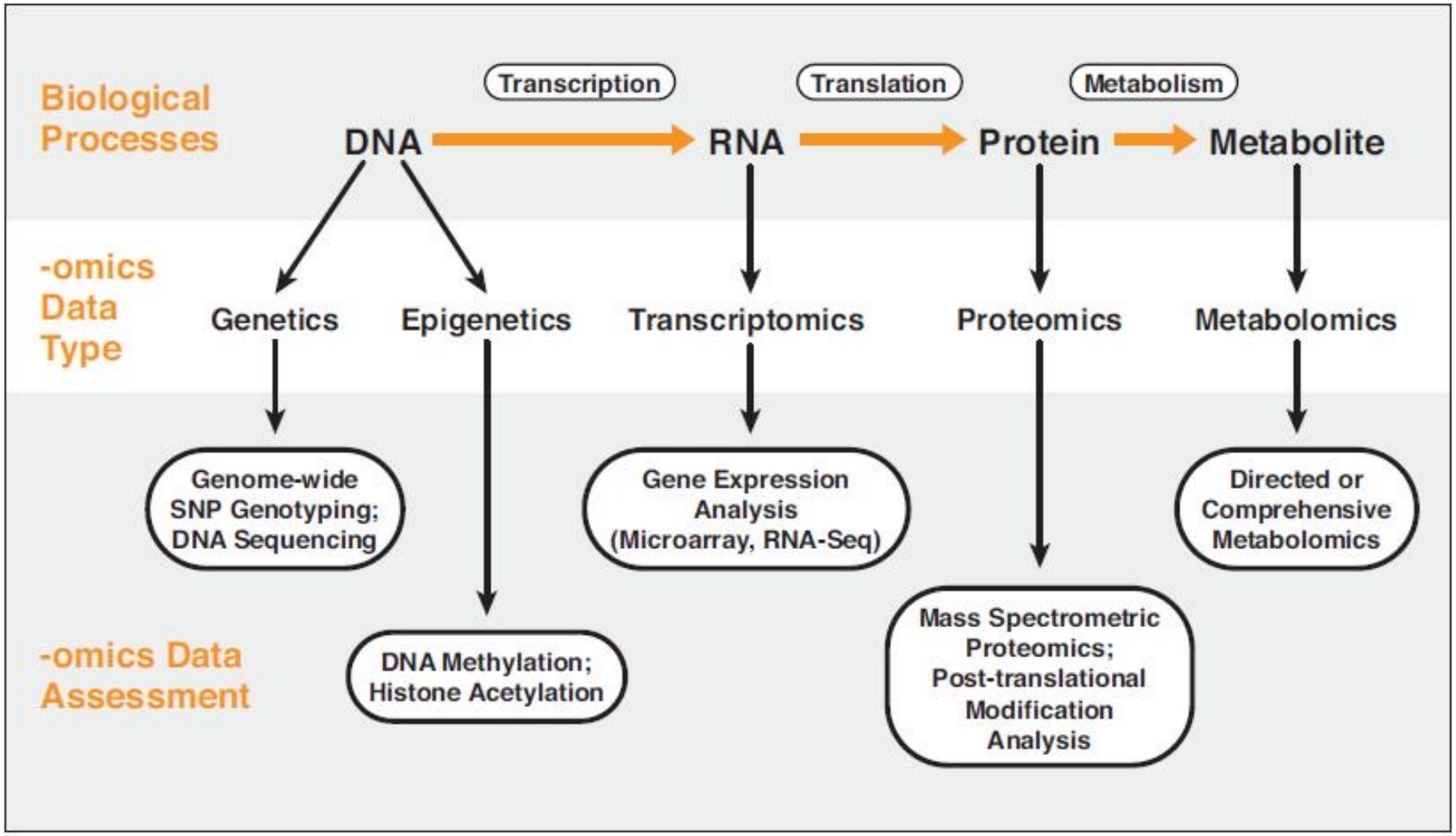
Biological Network

Social Network



Ecological Network

High Throughput Assessment of Multiple Biological Processes



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

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

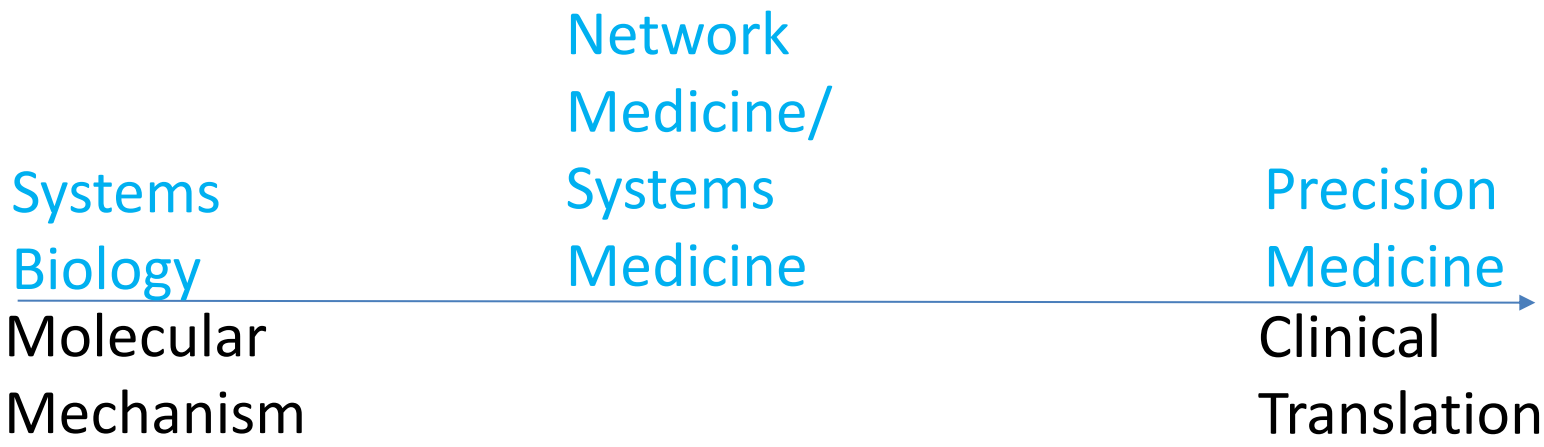
--Employs systems biology methods

Systems and Medicine: Terminology

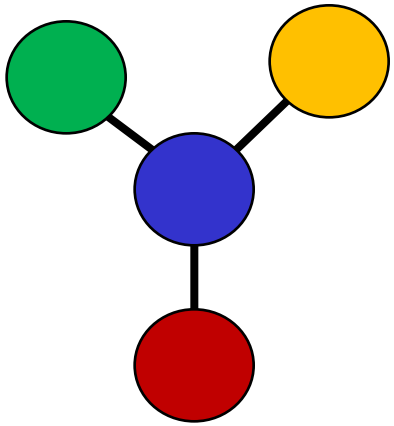
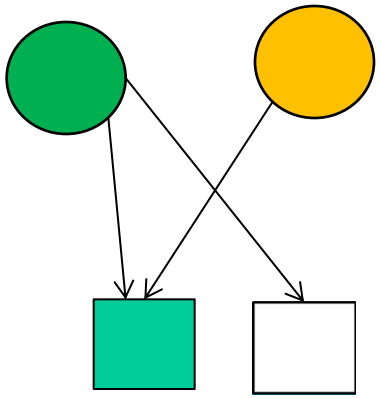
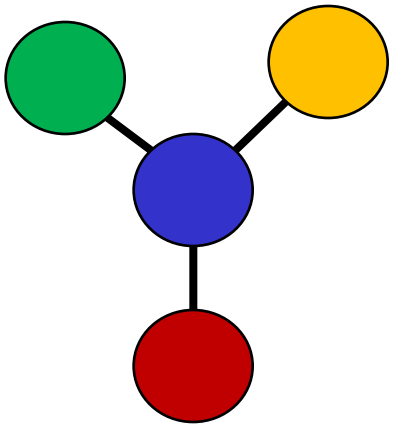
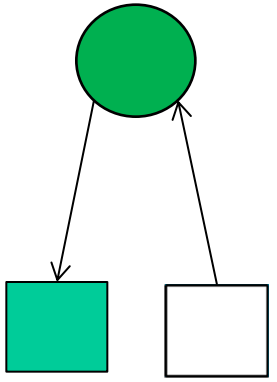
(Zanin/Schmidt, Network and Systems Medicine 2021)

- **Systems Biology:** Field of study focusing on complex interactions within biological systems, using a holistic approach. [See also Ron Germain: a scientific approach that combines the principles of engineering, mathematics, physics, and computer science with extensive experimental data to develop a quantitative as well as a deep conceptual understanding of biological phenomena, permitting prediction and accurate simulation of complex (emergent) biological behaviors.]
- **Systems Medicine:** Interdisciplinary field of study considers the human body as a system composed of interacting parts, with complex relationships on multiple levels that need to be understood based on a patient's genomics, behavior, and environment.
- **Precision Medicine:** Medical model using characterization of individual phenotypes and genotypes for tailoring the right therapeutic strategy for the right person at the right time, to determine disease predisposition, and to deliver timely and targeted prevention.

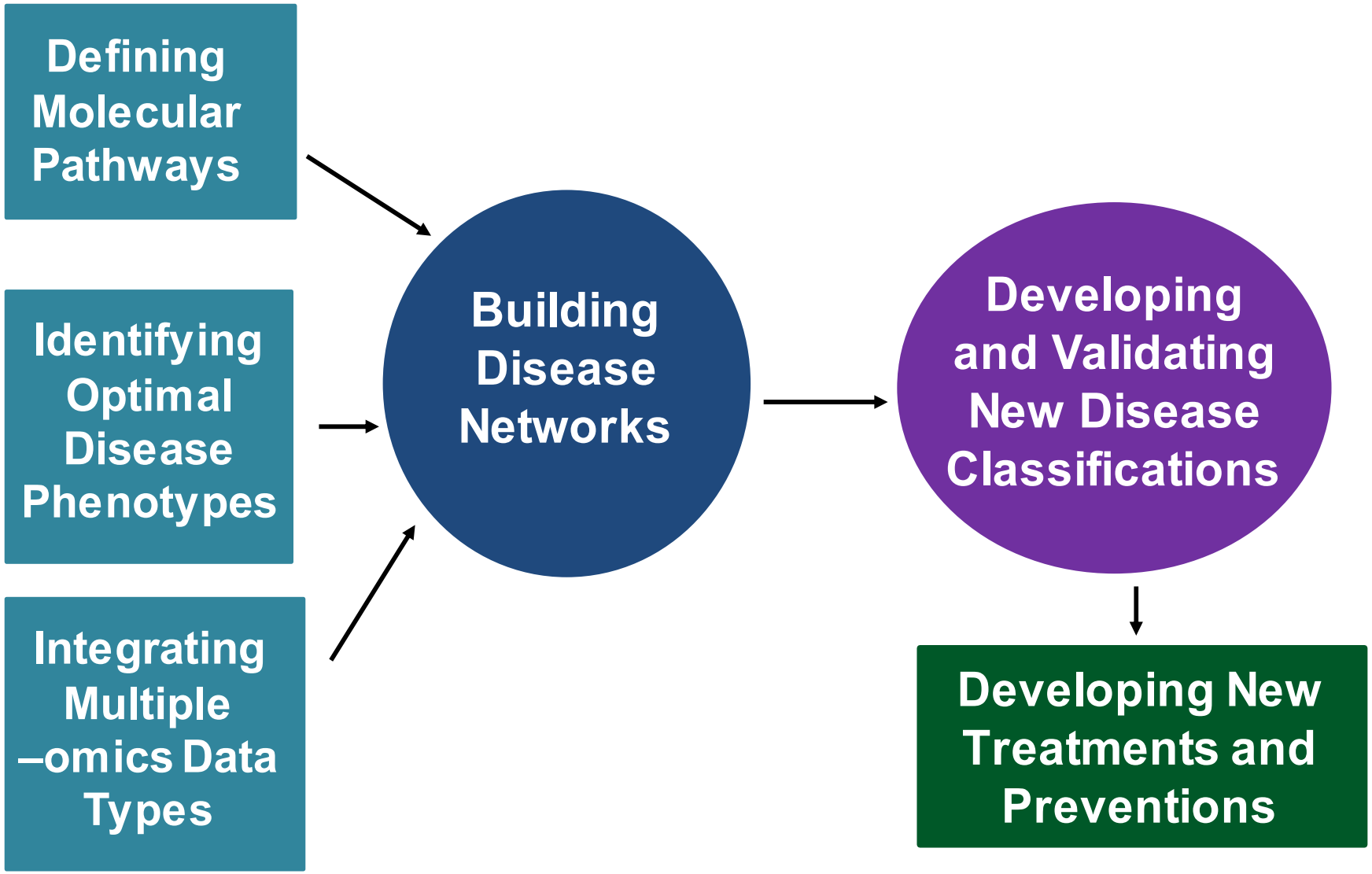
Systems, Networks, and Medicine: Relationships between Fields



Types of Networks Utilized in Network Medicine

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

Approaches to Complex Diseases in Channing Division of Network Medicine



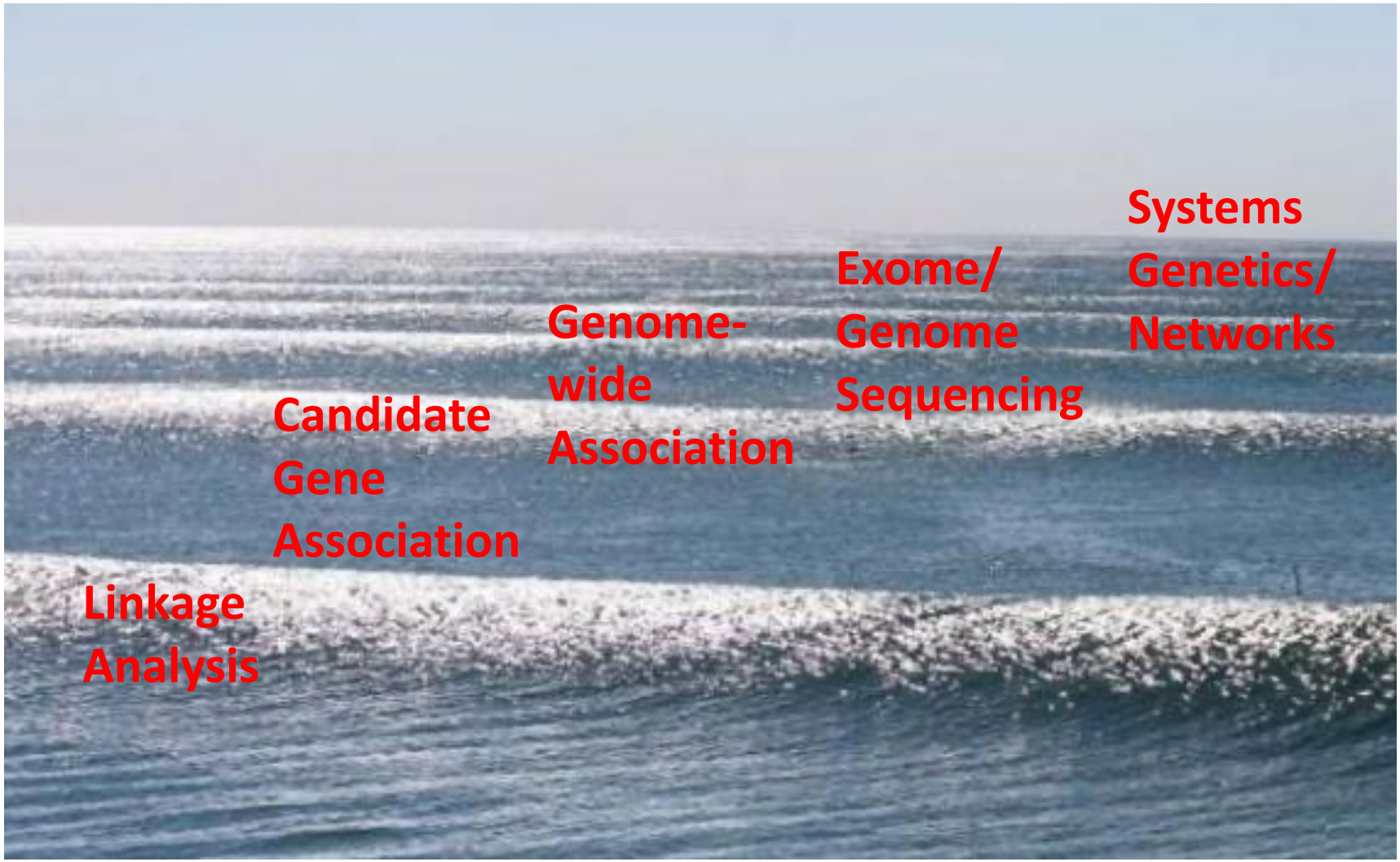
Principles of a Network Medicine Research Team:

1. Mix of network methodologists, data analysts, clinical experts, and molecular/cell biologists
2. Team is tailored to specific scientific question/project (size and members)
3. Mix of trainees, junior faculty, and senior faculty
4. Investigators can change roles throughout their careers

Network Medicine Alliance

- Includes 33 universities and institutions from around the world
- Founder: Joseph Loscalzo
  - Co-Founders: Albert-Laszlo Barabasi and Enrico Petrillo
- Goals: Promote interdisciplinary research in Network Medicine
- Website: https://www.network-medicine.org

Waves of Discovery in Complex Disease Genetics



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)

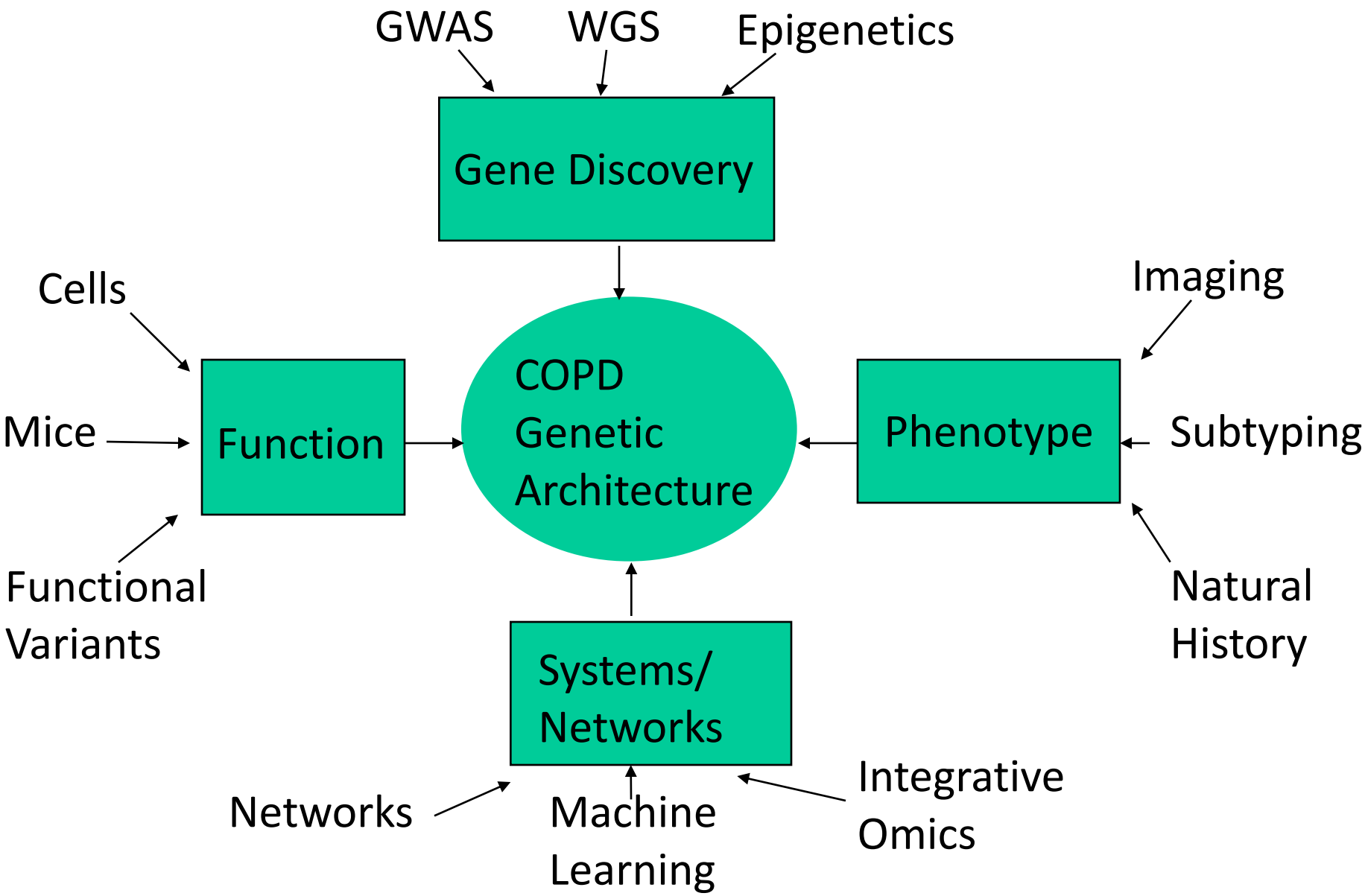
- **Reclassifying Complex Diseases:**
  - Based on etiology and disease pathophysiology

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

COPD: Background and Familial Aggregation

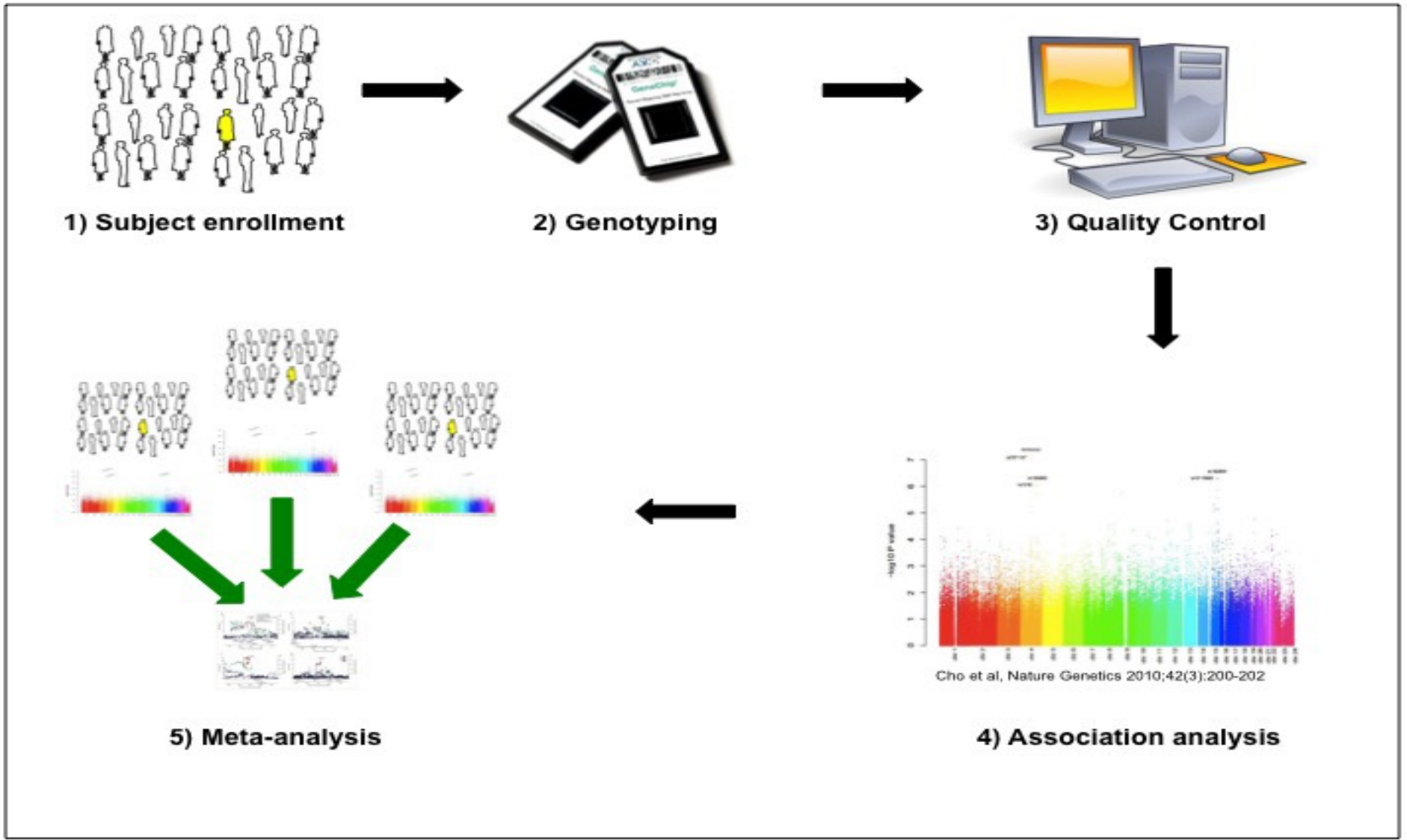
- Chronic airflow obstruction not fully reversible, as measured by lung function tests
- Fourth leading cause of death in the USA
- Abnormal but variable response to noxious particles/gases (e.g., cigarette smoking)
- Pathophysiology includes airway disease and lung parenchymal destruction (emphysema)
- Chronic lung inflammation in COPD can persist decades after smoking cessation
- COPD clusters in families, with quantitative genetic analysis demonstrating significant heritability for COPD of approximately 40%
- A small percentage of COPD patients inherit severe alpha-1 antitrypsin deficiency

COPD as a Model of Complex Disease



Approach for Genome-wide Association Studies

(Hardin, J COPDF 2014)



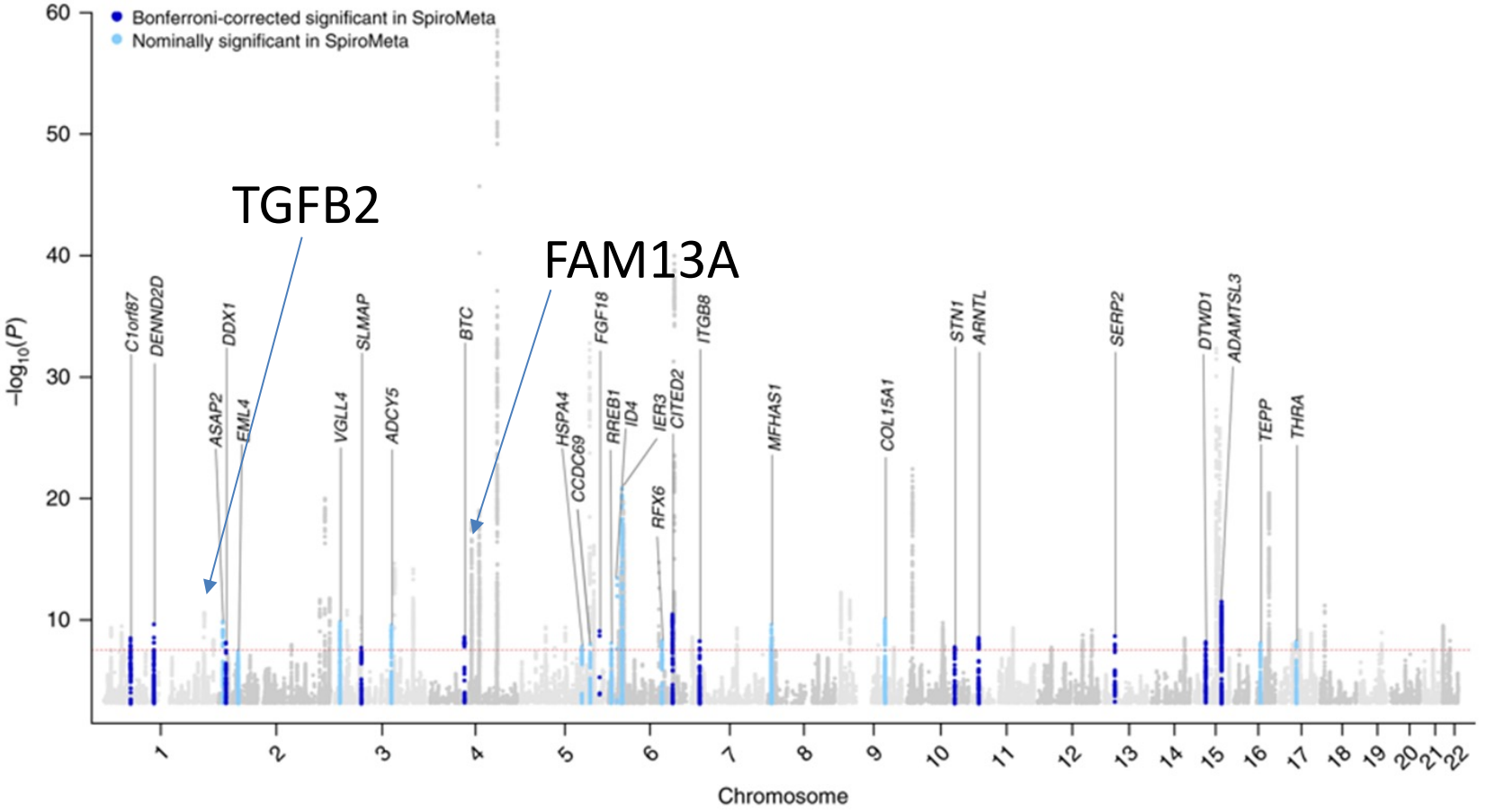
GWAS: Strengths and Weaknesses

- 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

International COPD Genetics Consortium COPD GWAS (Sakornsakolpat, Nat Genet, 2019)

- Included 35,735 COPD cases and 222,076 controls from 24 studies
- Identified 82 genome-wide significant ($P < 5x10^{-8}$) associations



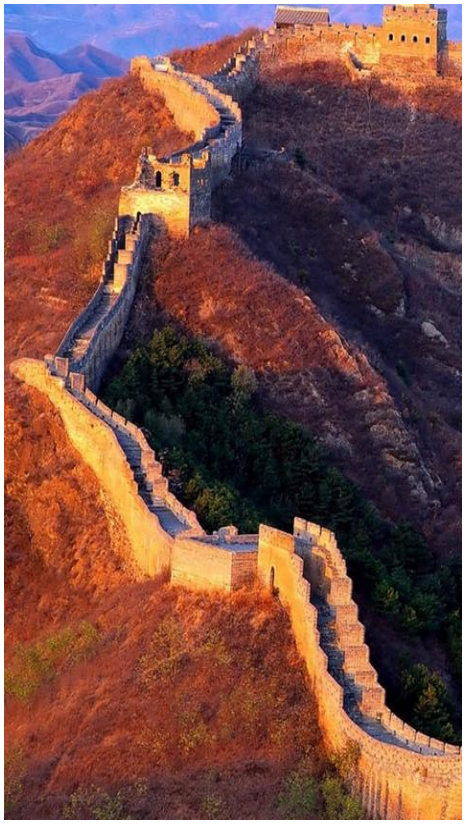
Moving from Gene Discovery to Gene Localization to Functional Validation

- **Discovery**
  - Genetic Association Analysis
  - Genotyping Panel or Whole Exome/Whole Genome Sequencing
- **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

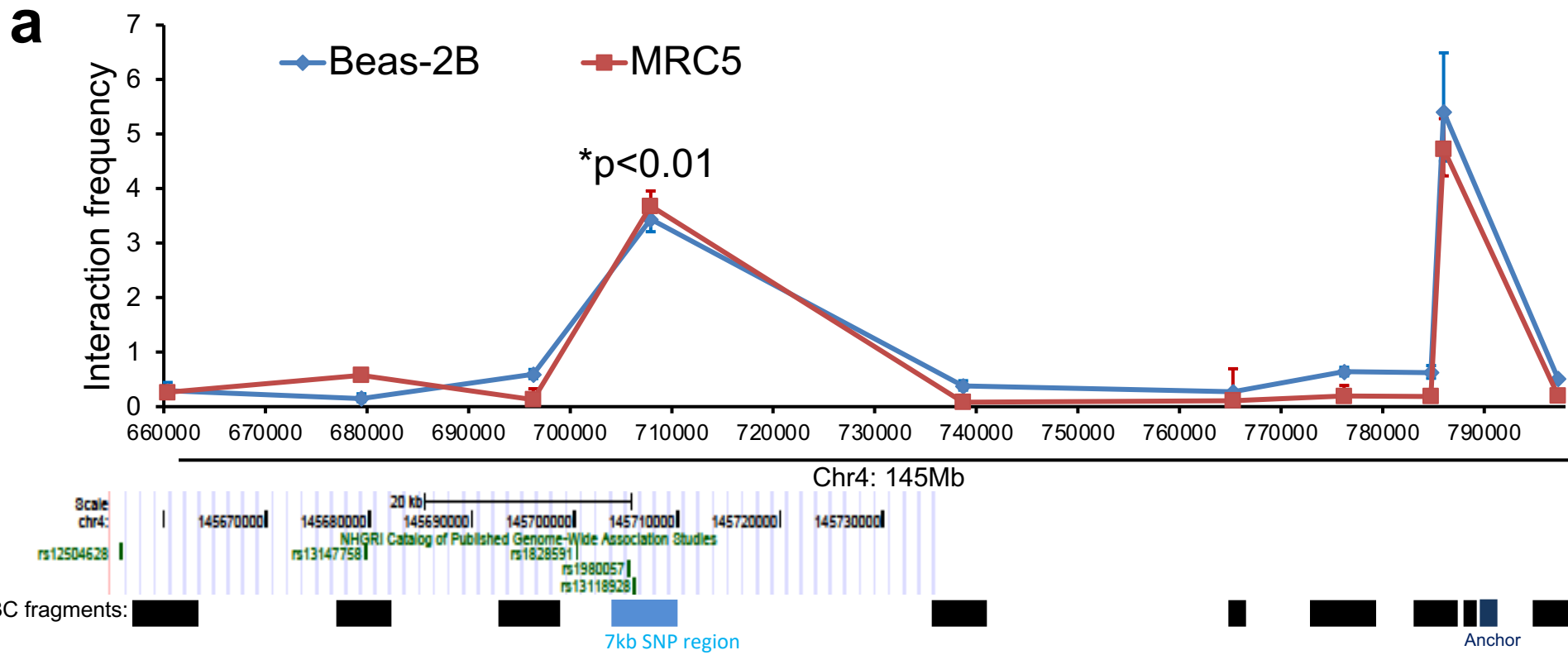


Cell/Molecular Biologists

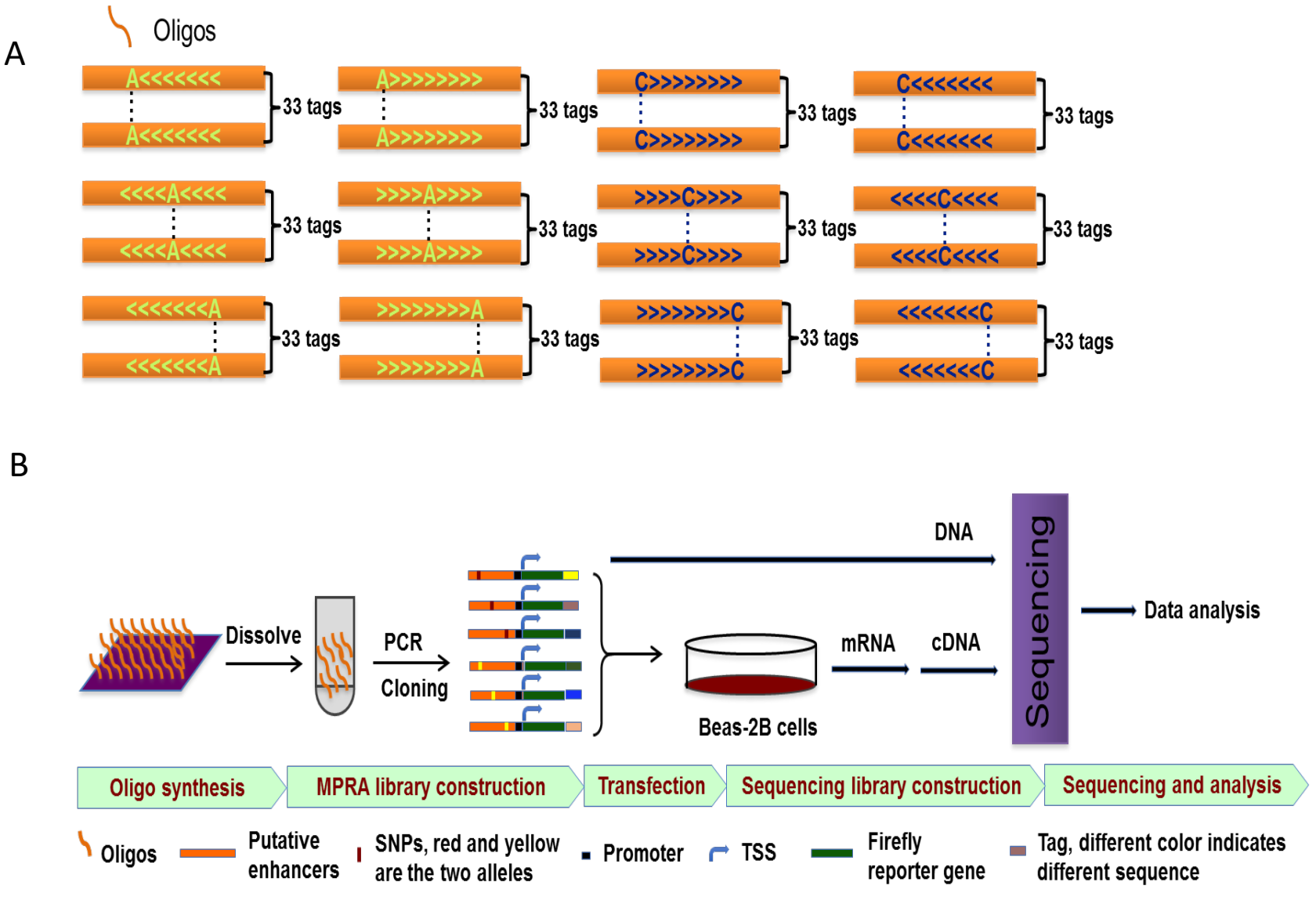
- No thanks, we have our own ideas of what to study
- We don't believe that what you found is important or useful

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

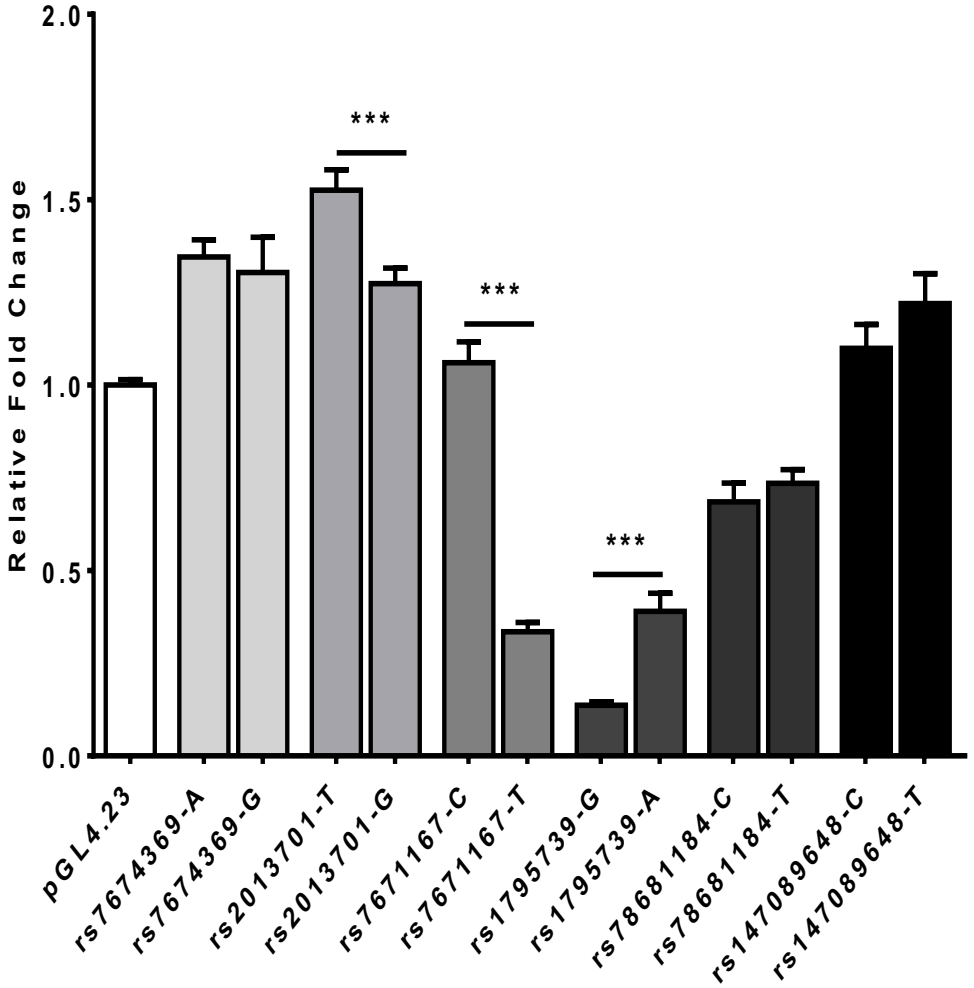
Chromosome conformation capture



Overview of MPRA Design for FAM13A GWAS SNPs
(Castaldi/Zhou, AJRCCM 2019)

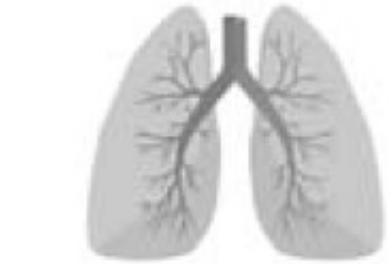


Reporter Assays Testing Allele-specific Enhancer Activity of FAM13A MPRA SNPs (P. Castaldi/X. Zhou, AJRCCM 2019)



- 606 SNPs were tested in MPRA; 45 SNPs showed evidence for allele-specific regulatory activity
- Selected six SNPs with consistent evidence in multiple experiments and strong GWAS associations
- Three variants had allele-specific activity in 16HBE validation reporter assays
- Chromatin conformation capture effects with FAM13A promoter were seen for rs2013701 and rs7671167
- Focused on rs2013701, which had increased FAM13A expression for risk allele

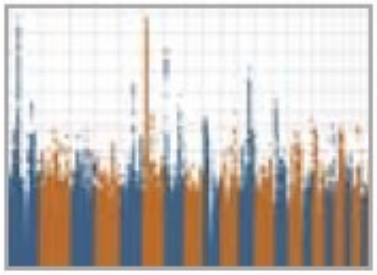
Using Chromatin Landscapes of Human Lung Cells to Predict Functional COPD GWAS Variants (Benway/Zhou, AJRCMB, 2021)



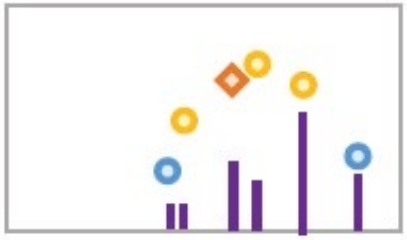
Isolate NHBE, SAEC, LF, AT-II, 16HBE cells

Culture in appropriate media/conditions

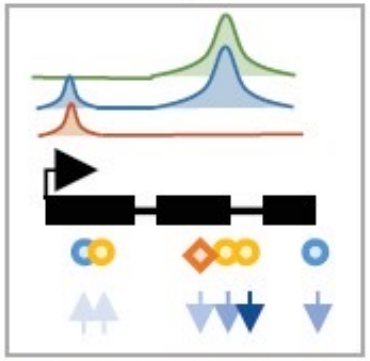
ATAC-Seq to assay open chromatin



COPD GWAS
[82 Loci, $P < 5 \times 10^{-8}$]
(Sakornsakolpat 2019)

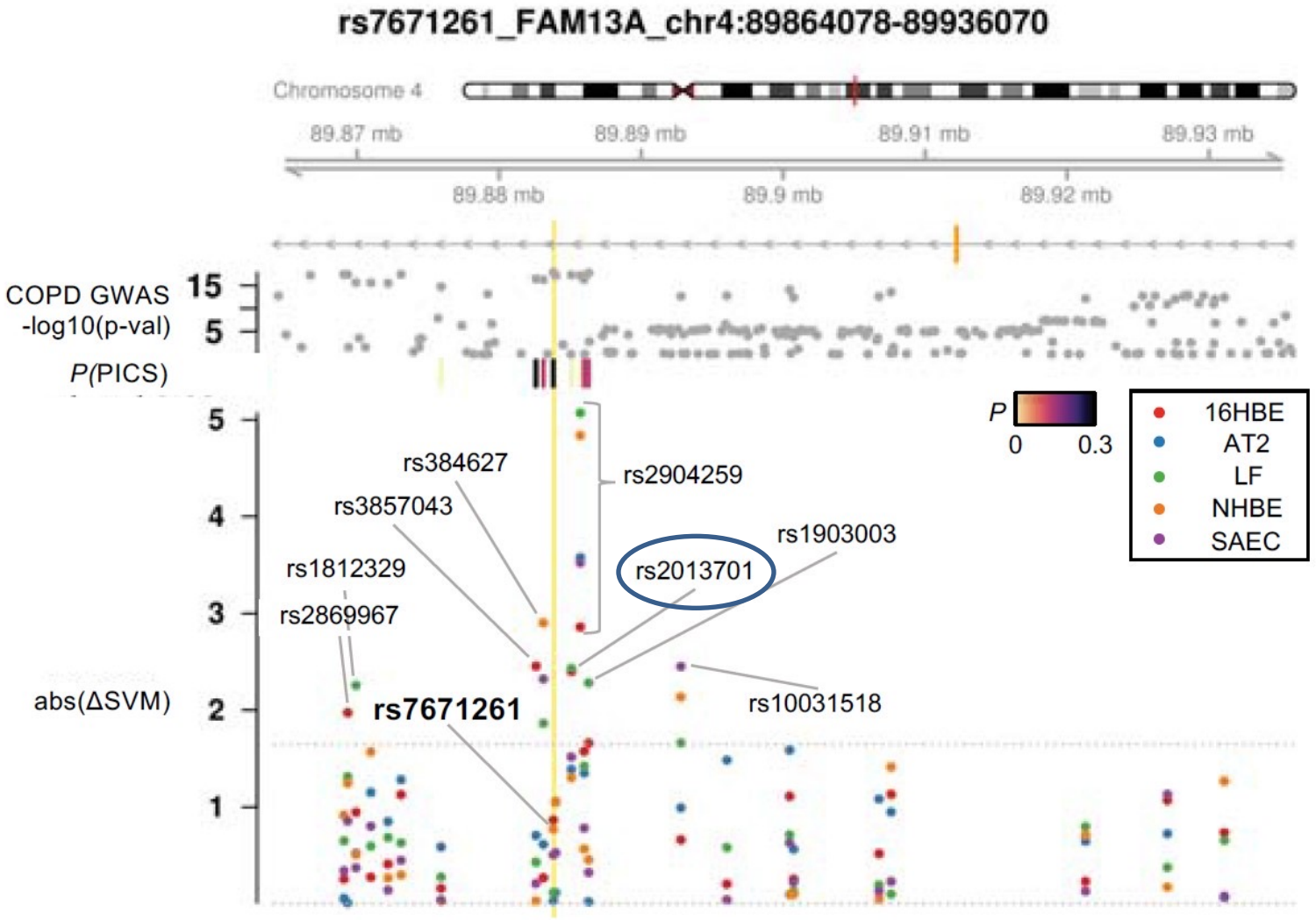


PICS fine-mapping of loci = ~7,300 variants



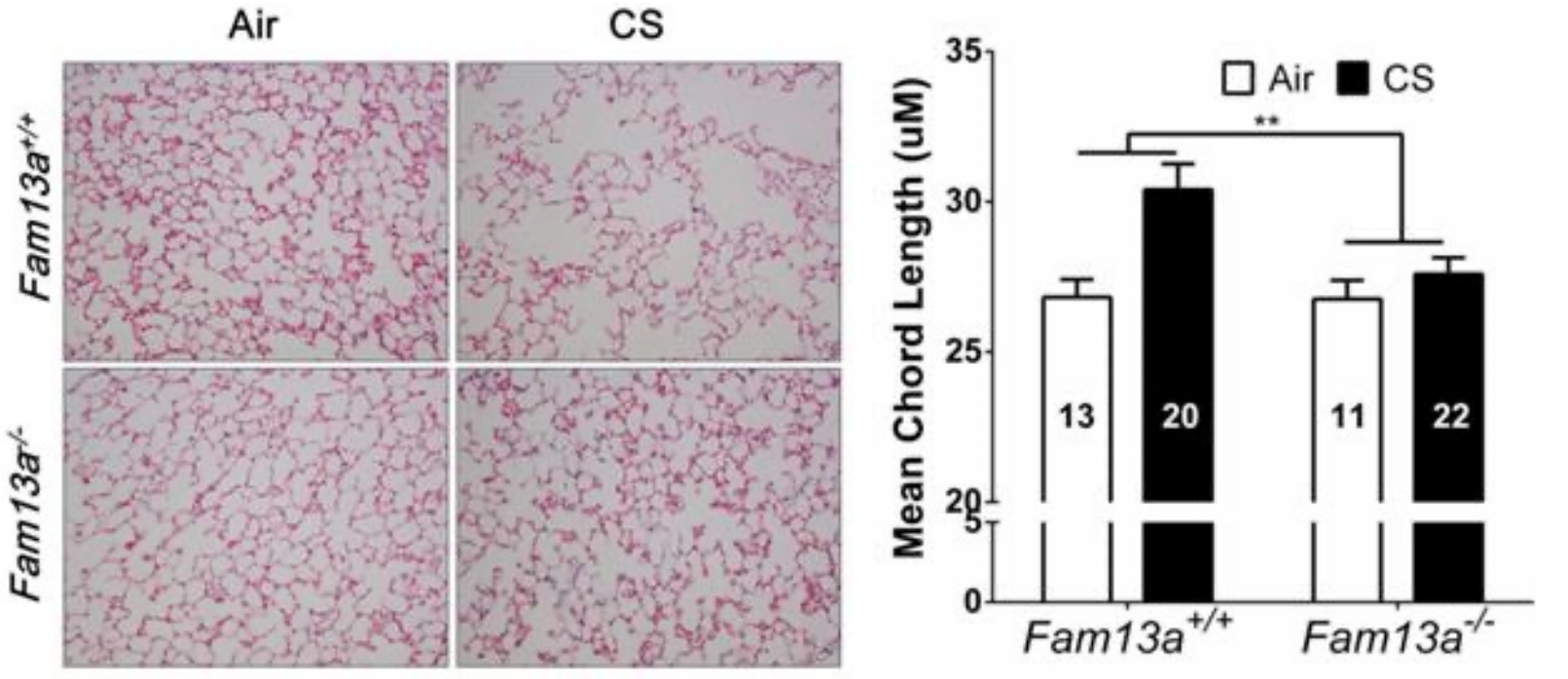
Predict variant effects (gkm-SVM + ΔSVM) = ~6,500 SNPs

Using Chromatin Landscapes of Human Lung Cells to Predict Functional COPD GWAS Variants (Benway/Zhou, AJRCMB, 2021)



Fam13a$^{-/-}$ Mice: Cigarette Smoke Effects

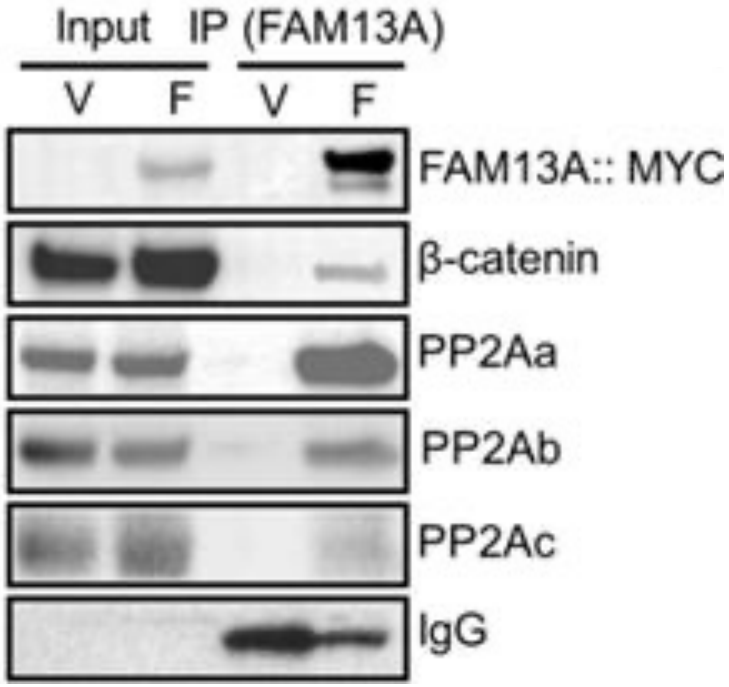
(Z. Jiang/X. Zhou, AJRCCM 2016)



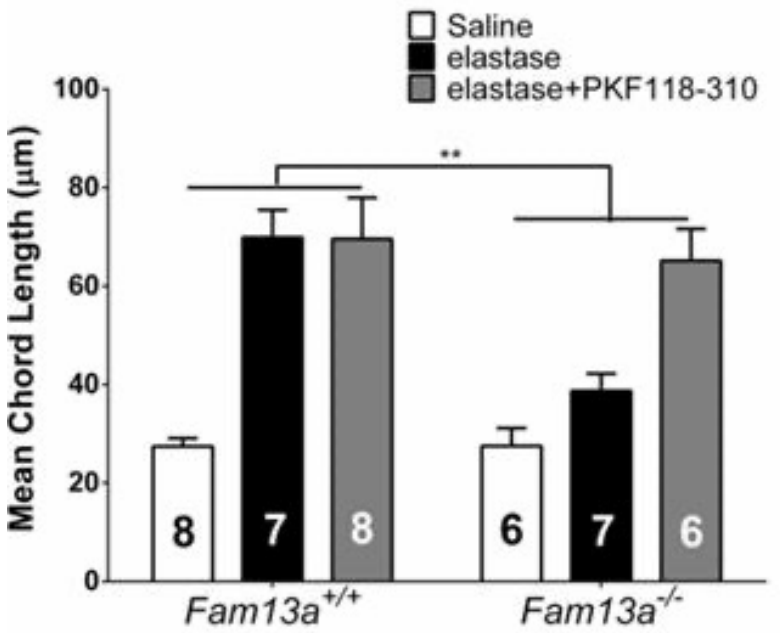
Note: Fam13a knockout is protected from emphysema development

FAM13A in *COPD*: Biological Mechanism

(Z. Jiang/X. Zhou, AJRCCM 2016)



Complex of FAM13A, PP2A, and Beta-catenin



Beta-catenin Inhibitor Reverses Fam13a KO Mouse Emphysema Protection

Identifying Key Genes in COPD GWAS Regions

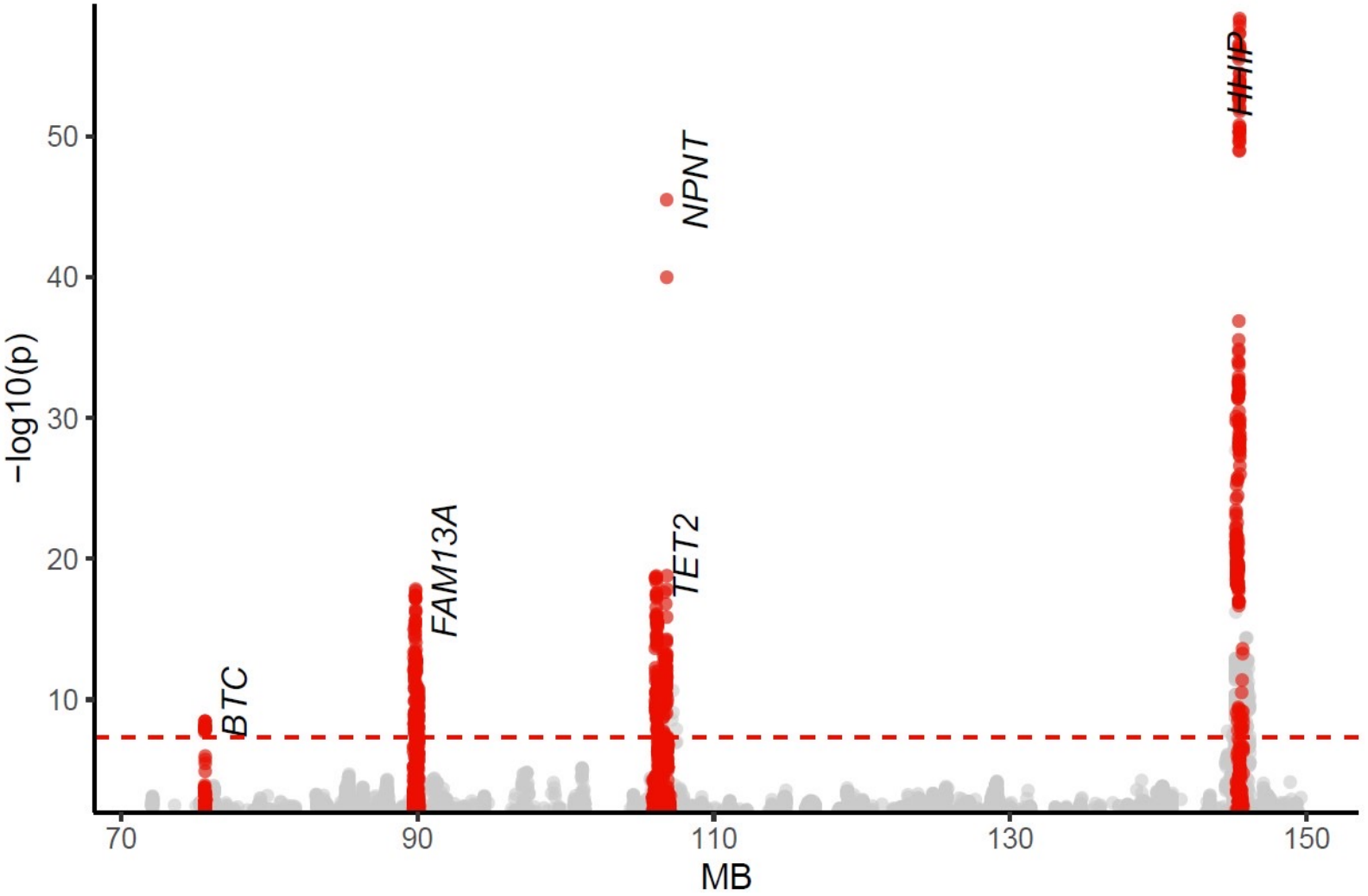
- Chromatin Interactions of Functional Variants with GWAS Genes (e.g., 3C): HHIP (Zhou, Hum Mol Genet 2012)
- Massively Parallel Reporter Assays to Find Functional Variants: FAM13A (Castaldi, AJRCCM 2019)
- Integration of chromatin landscapes with fine-mapped genetic variants using delta-SVM (Benway, AJRCMB 2021)
- Perturb-Seq approaches to combine CRISPR-interference with single cell RNA-seq (In progress by Malik/Cho/Zhou)
- Mouse Models of COPD GWAS Genes

Identifying Key Genes in COPD GWAS Regions

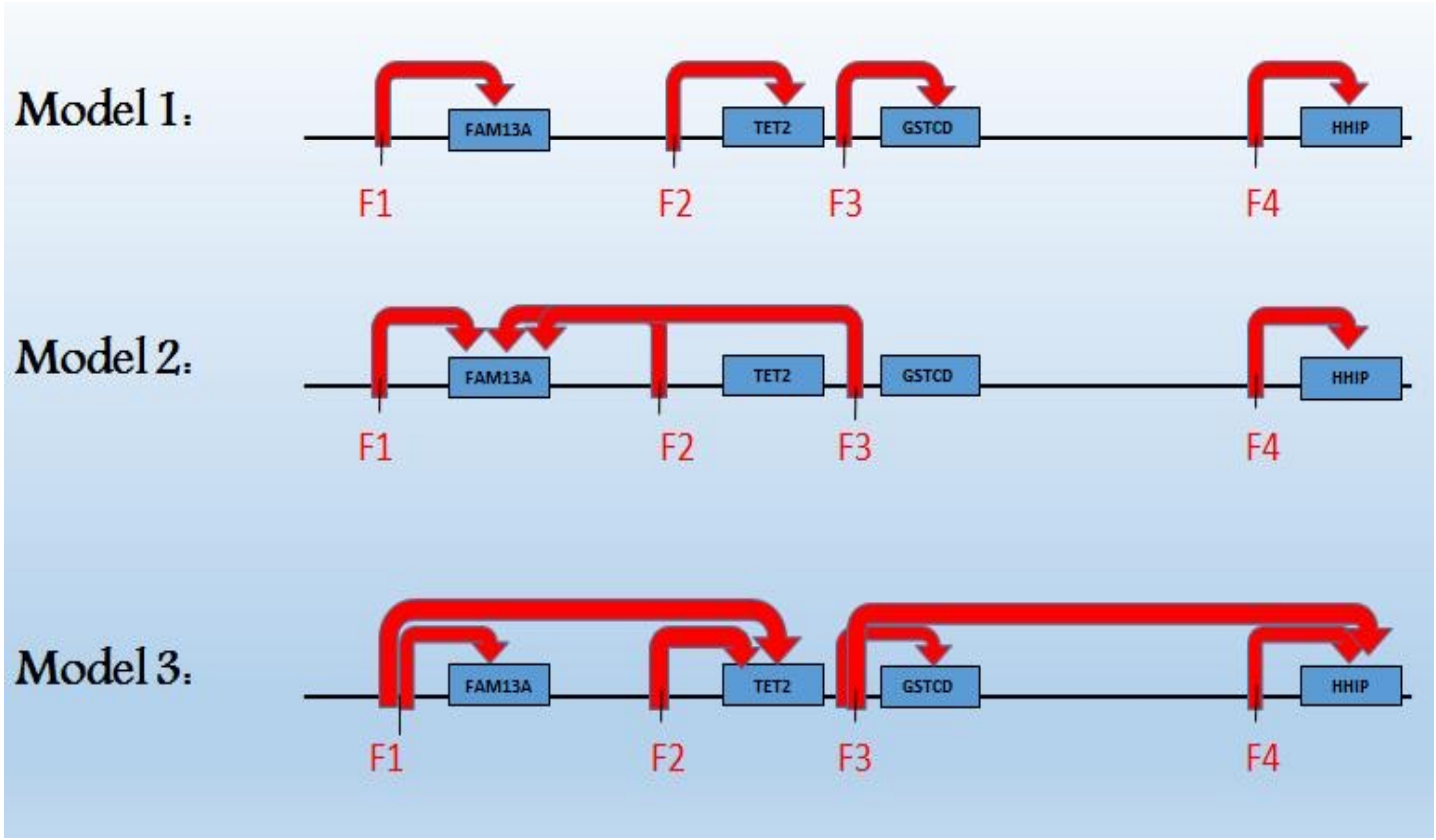
- What are high-confidence COPD susceptibility genes from GWAS based on genetic and functional evidence?
  - *HHIP, FAM13A, AGER, FBLN5, SFTPD, TET2, IREB2, MFAP2, DSP, FBXO38, NPNT, TGFB2, MMP12* (gene list and gene order is admittedly highly subjective)
  - Most COPD GWAS genes don't fit into pre-GWAS understanding of COPD pathogenesis
  - All COPD GWAS genetic variants are small effect size and likely work together in biological networks to influence disease risk

Cluster of COPD GWAS Signals on Chromosome 4q

(Sakornsakolpat, Nat Genet 2019)

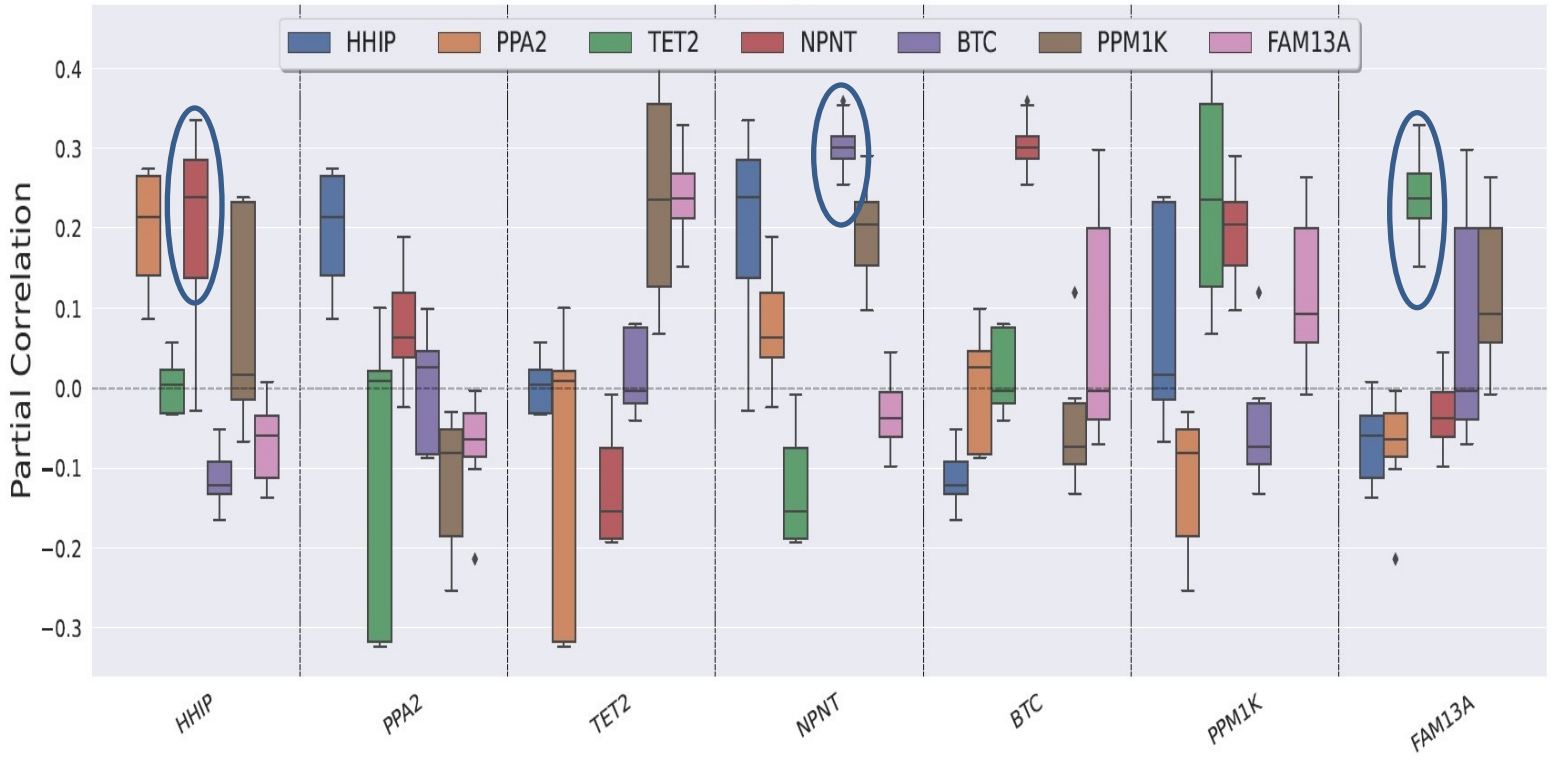


Potential Explanations for COPD GWAS Cluster on Chromosome 4q



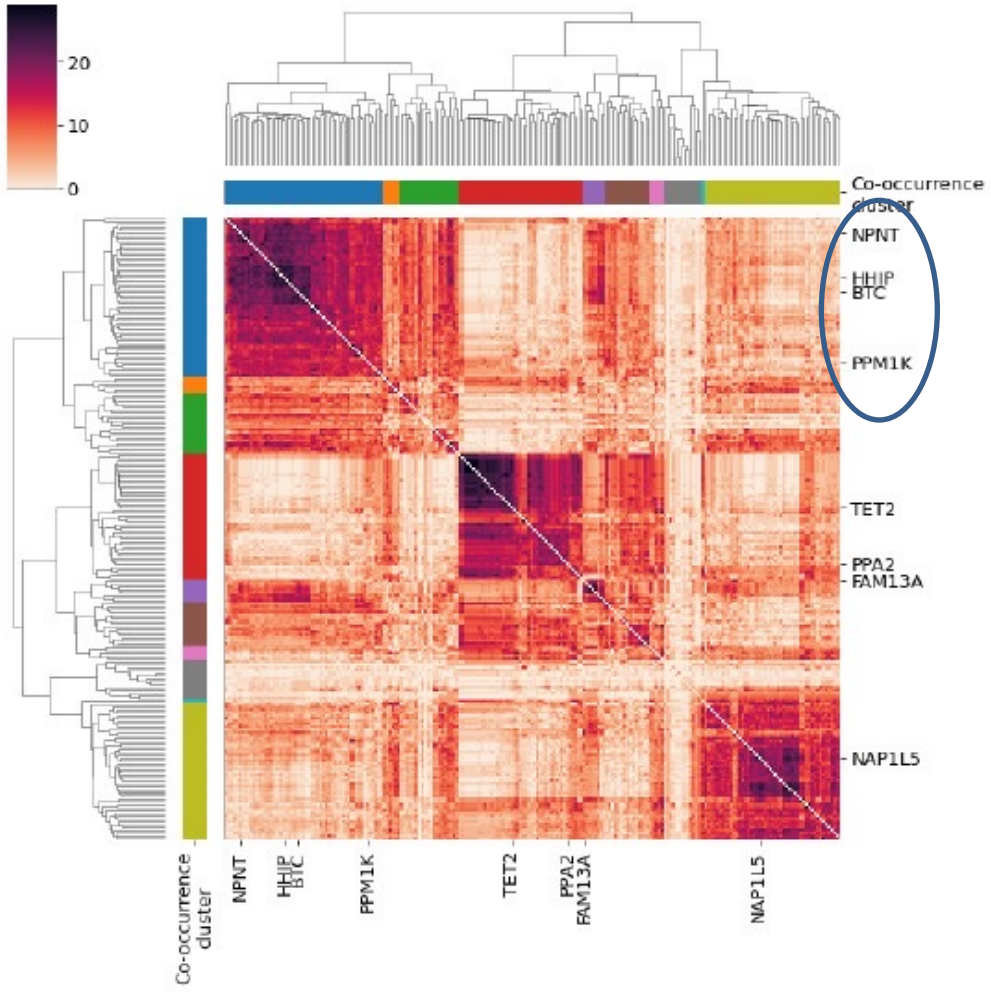
Partial Correlations between Gene Expression Levels of COPD Genes on Chromosome 4q Controlling for Protein-Protein Interactions

(Gentili, Submitted)



NPNT-HHIP, BTC-NPNT, and FAM13A-TET2 partial correlations were replicated in three independent lung tissue cohorts

Clustering of Partial Correlation Networks on Chromosome 4q (Gentili, Submitted)

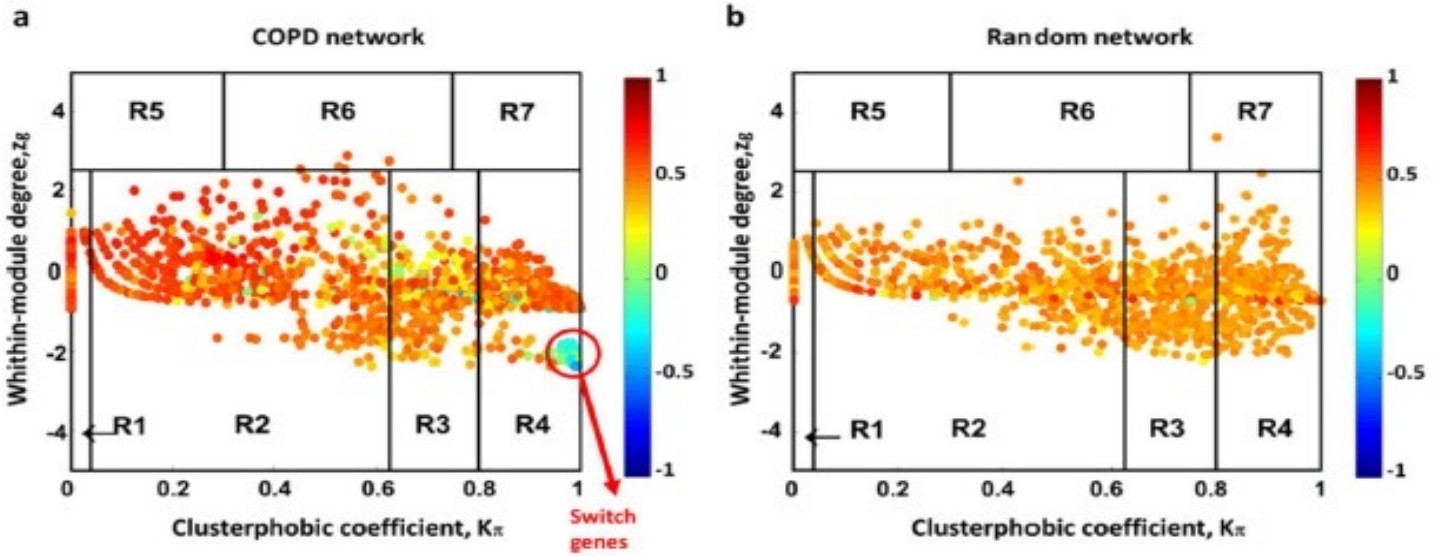


Clustering the co-expression network, four COPD genes (BTC, HHIP, NPNT, and PPM1K) appeared in the same network community

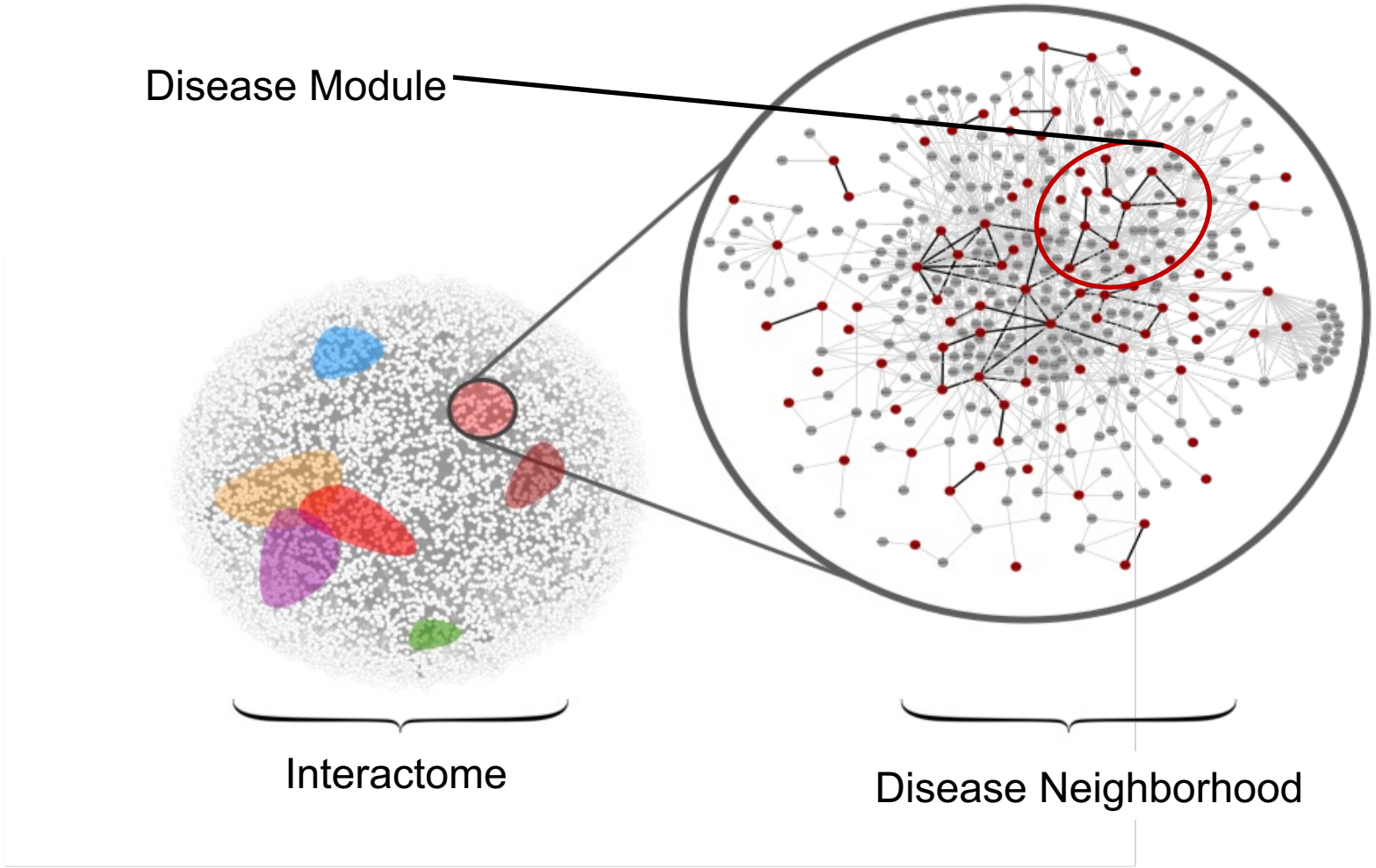
Integrated Transcriptomic Correlation Network Analysis of COPD

(Paci/Farina, Sci Rep 2020)

- SWItchMiner (SWIM) software was used to identify gene expression correlation network modules using lung tissue microarray data from 219 COPD and 108 controls for training and 111 COPD and 40 controls for testing
- SWIM exploited negative correlation in gene expression to identify 62 switch genes which may be drivers of complex disease
- SWIM identified three correlation network modules with 190, 1411, and 64 genes. For Module 1, CAVIN1 and AGER have highest module membership and are both down-regulated in COPD cases



Disease Modules, Disease Neighborhoods, and the Interactome



Leopold/Loscalzo, Circ Research 2018; 122:1302-1315

Mapping of COPD Seed Genes in the Interactome

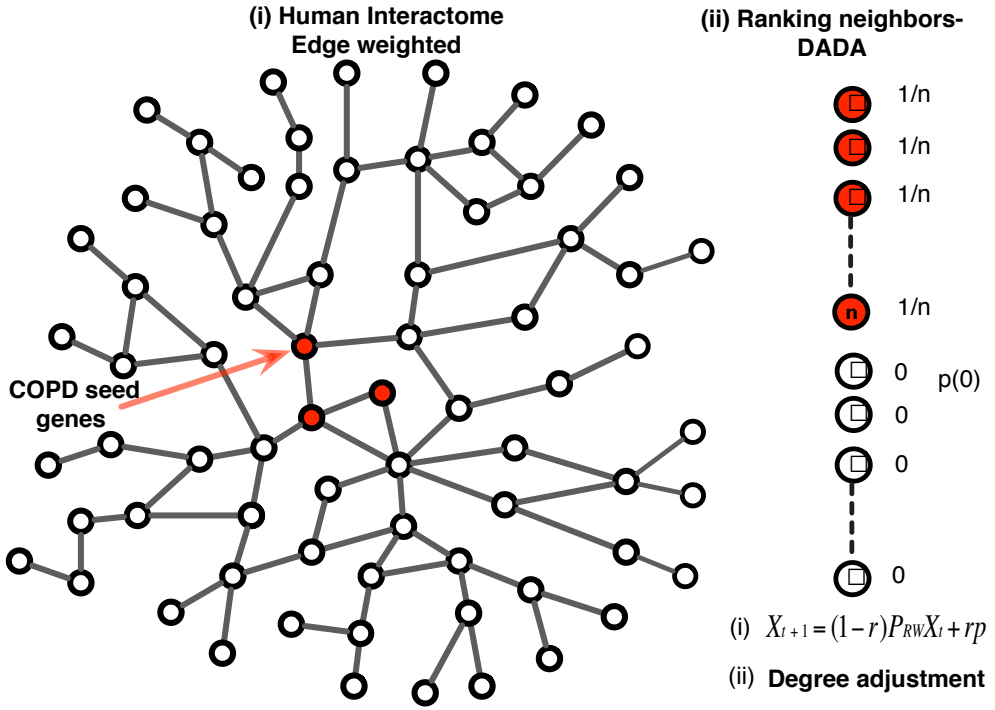
(Sharma, Sci Rep 2018)

COPD seed genes (n=11)

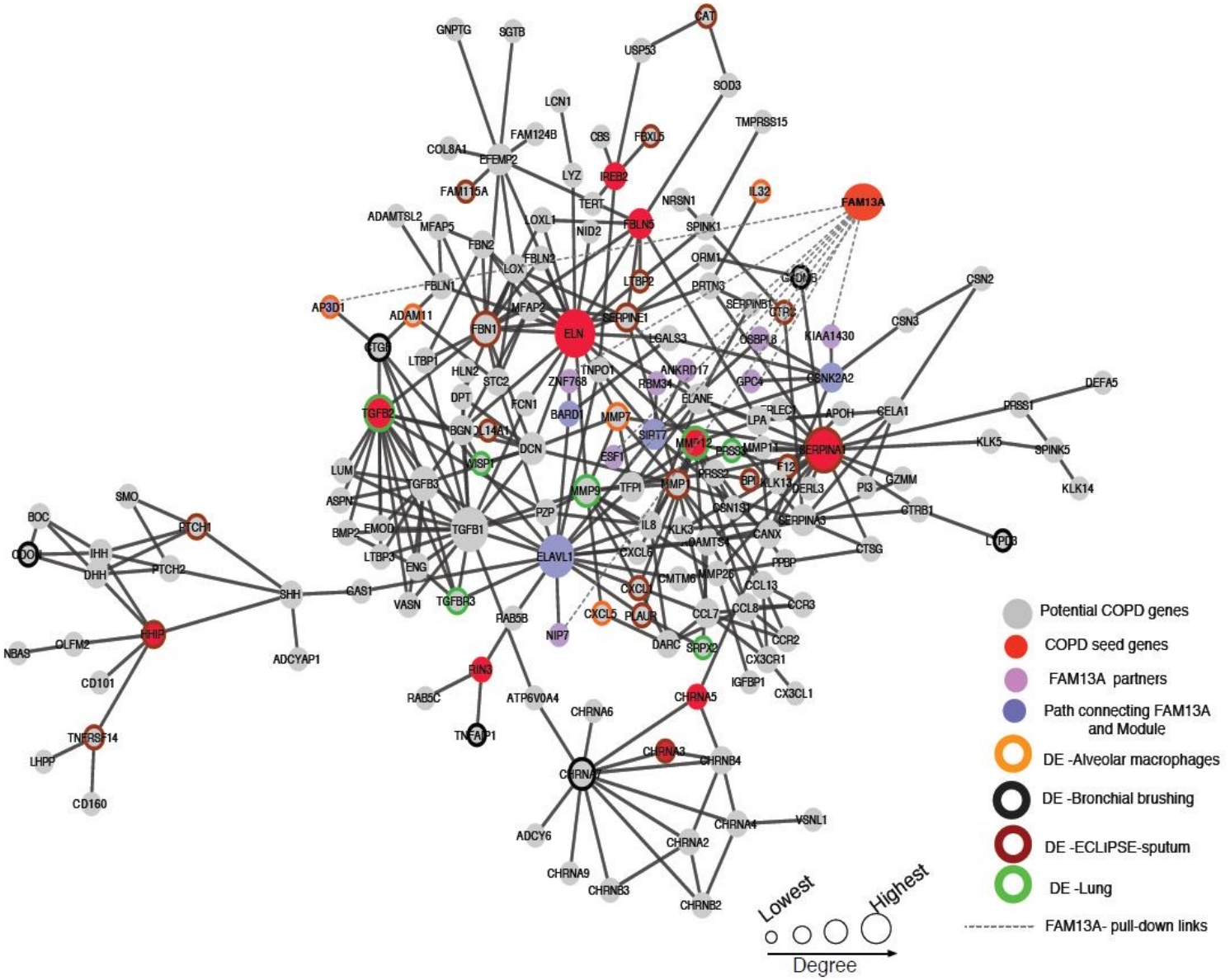
Mendelian Syndromes: SERPINA1, ELN, FBLN5

COPD GWAS: HHIP, FAM13A, IREB2, CHRNA3, CHRNA5, RIN3, TGFB2, MMP12

Network proximity calculations based on Random Walk–DADA method



COPD Disease Network Module: Expanded with FAM13A Interactors (Sharma, 2018)



COPD PPI Network Module: Shortest Paths between COPD GWAS Genes

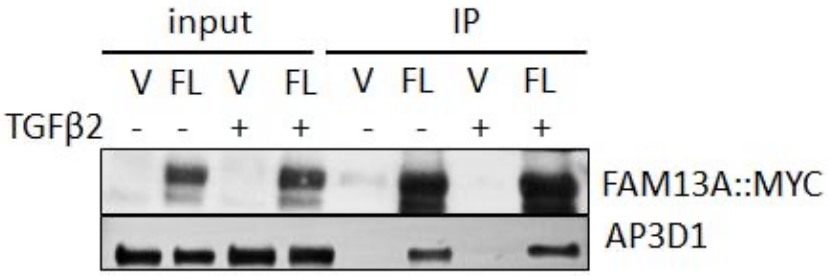
(Lu Gong/Xiaobo Zhou/Victor Hsu, AJRCMB 2021)

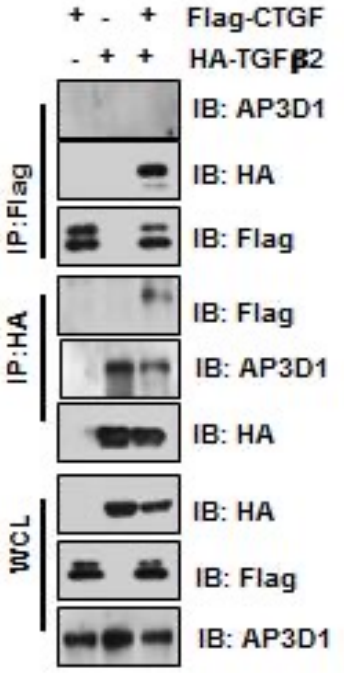
- Known components of the nicotinic acetylcholine receptor:
  - CHRNA5-CHRNA7-CHRNA3 and CHRNA5-CHRNB4-CHRNA3
- Known relationships of TGFBeta with the elastic fiber:
  - TGFB2-BGN-ELN-MMP12, TGFB2-DCN-ELN-MMP12, and TGFB2-FBN1-ELN-MMP12
- Potentially novel relationships between COPD GWAS genes:
  - FAM13A-AP3D1-CTGF-TGFB2
  - CHRNA5-CANX-LPA-MMP12

Technical Validation of FAM13A-AP3D1-CTGF-TGFB2 (Gong, AJRCMB 2021)

AP3D1 binds to TGFB2 but not CTGF

FAM13A binds to AP3D1

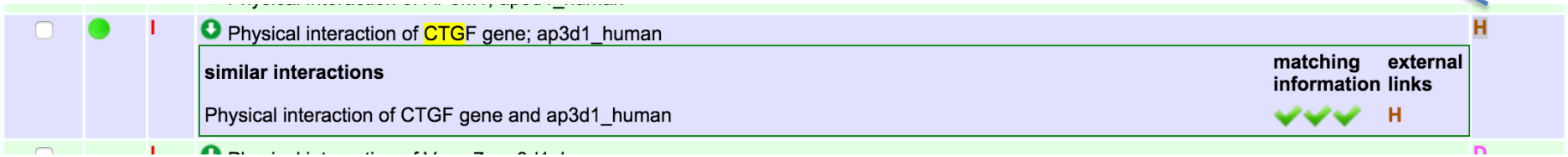




New Network Model: FAM13A-AP3D1-TGFB2-CTGF

AP3D1 – CTGF in consensuspathDB

HPRD dataset



AP3D1 – CTGF in consensuspathDB

ALTERNATE NAMES | DISEASES | PTMs & SUBSTRATES | SUMMARY | SEQUENCE | INTERACTIONS | EXTERNAL LINKS

Protein Interactions

PROTEIN INTERACTORS

Name of Interactor	Experiment Type	Type
ADP ribosylation factor 1	In Vivo ; In Vitro	Direct
ADP ribosylation factor 6	In Vivo ; In Vitro	Direct
Clathrin adaptor complex AP3, sigma 3B subunit	Yeast 2 Hybrid	Direct
Synaptobrevin like protein 1	In Vivo,In Vitro,Yeast 2 Hybrid	Direct
Vacuolar protein sorting 41	In Vitro ; In Vivo	Direct
~~Solute carrier family 30, member 3~~	~~In Vitro~~	~~Direct~~
Connective tissue growth factor	In Vitro	Direct
Clathrin adaptor complex AP3, sigma 3A subunit	In Vitro ; Yeast 2 Hybrid	Direct
Lysosome associated membrane protein 1 Adaptor related protein complex 3 mu 1 subunit	In Vitro	Complex
Adaptor related protein complex 2 alpha 1 subunit Adaptor related protein complex 1, gamma 1 subunit Phosphofurin acidic cluster sorting protein 1	In Vivo ; In Vitro	Complex
Clathrin adaptor complex AP3, sigma 3A subunit Centaurin gamma 2	In Vivo	Complex
Clathrin adaptor complex AP3, sigma 3B subunit Centaurin gamma 2	In Vivo	Complex

FEBS Lett. 2006 Feb 20;580(5):1376-82. Epub 2006 Jan 26.

CT domain of CCN2/CTGF directly interacts with fibronectin and enhances cell adhesion of chondrocytes through integrin alpha5beta1.

Hoshijima M[1], Hattori T, Inoue M, Araki D, Hanagata H, Miyauchi A, Takigawa M.

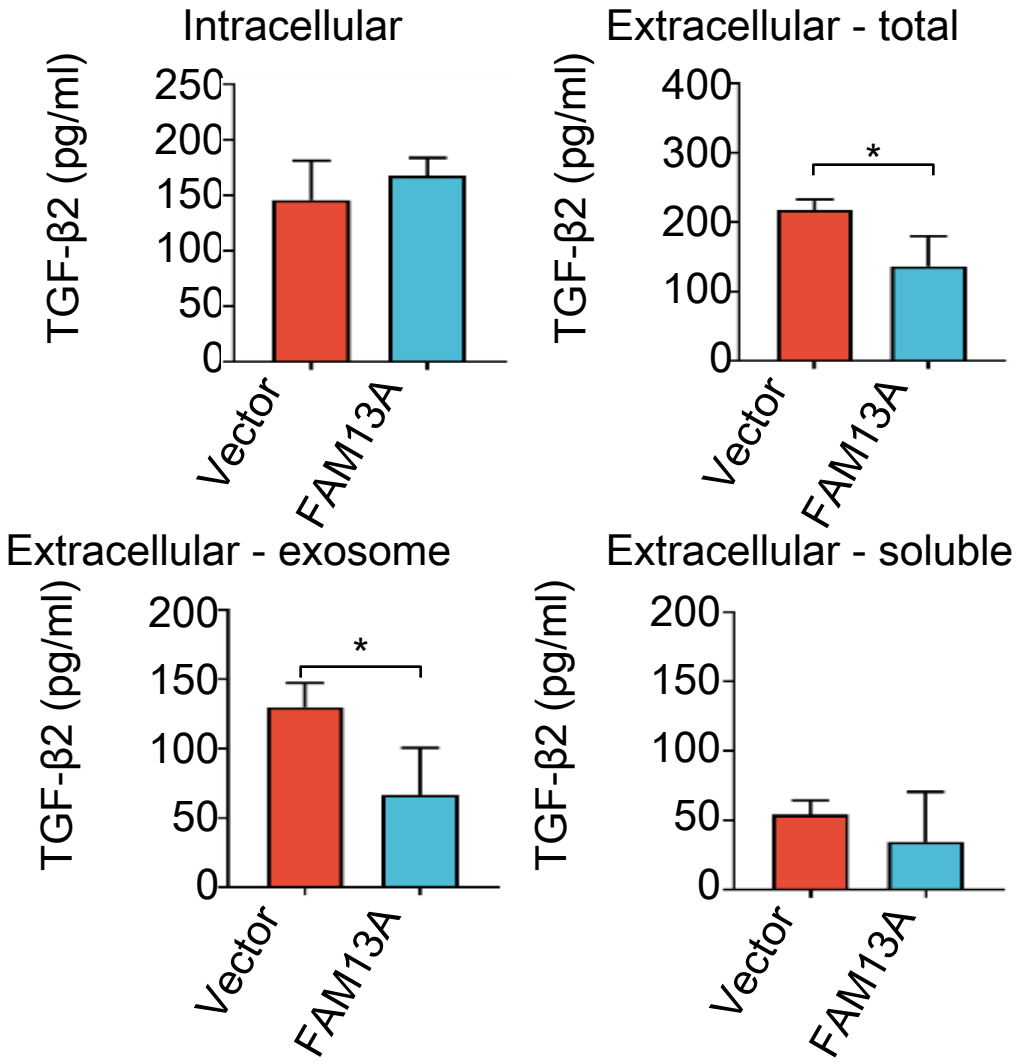
Author information

Abstract

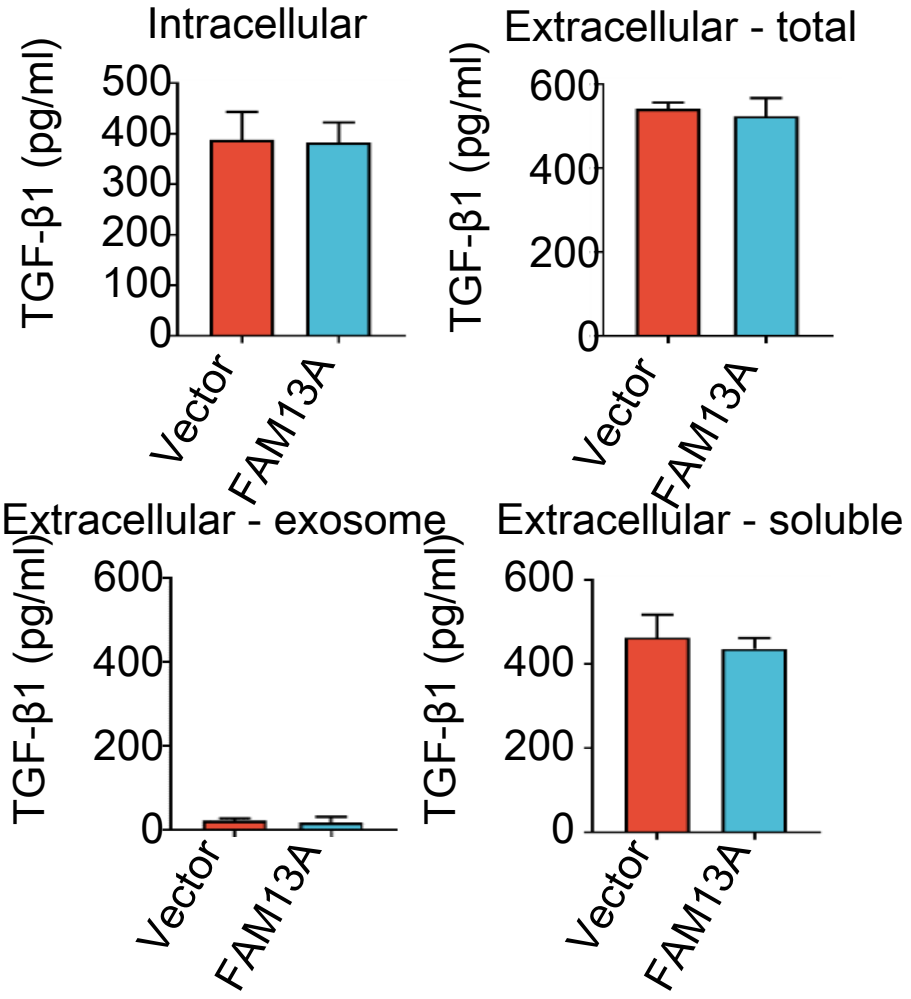
Searching for CCN family protein 2/connective tissue growth factor (CCN2/CTGF) interactive proteins by yeast-two-hybrid screening, we identified fibronectin 1 gene product as a major binding partner of CCN2/CTGF in the chondrosarcoma-derived chondrocytic cell line HCS-2/8. Only the CT domain of CCN2/CTGF bound directly to fibronectin (FN). CCN2/CTGF and its CT domain enhanced the adhesion of HCS-2/8 cells to FN in a dose-dependent manner. The CCN2/CTGF-enhancing effect on cell adhesion to FN was abolished by a blocking antibody against alpha5beta1 integrin (alpha5beta1), but not by one against anti-alphavbeta3 integrin. These findings suggest for the first time that CCN2/CTGF enhances chondrocyte adhesion to FN through direct interaction of its C-terminal CT domain with FN, and that alpha5beta1 is involved in this adhesion.

PMID: 16457822 DOI: 10.1016/j.febslet.2006.01.061

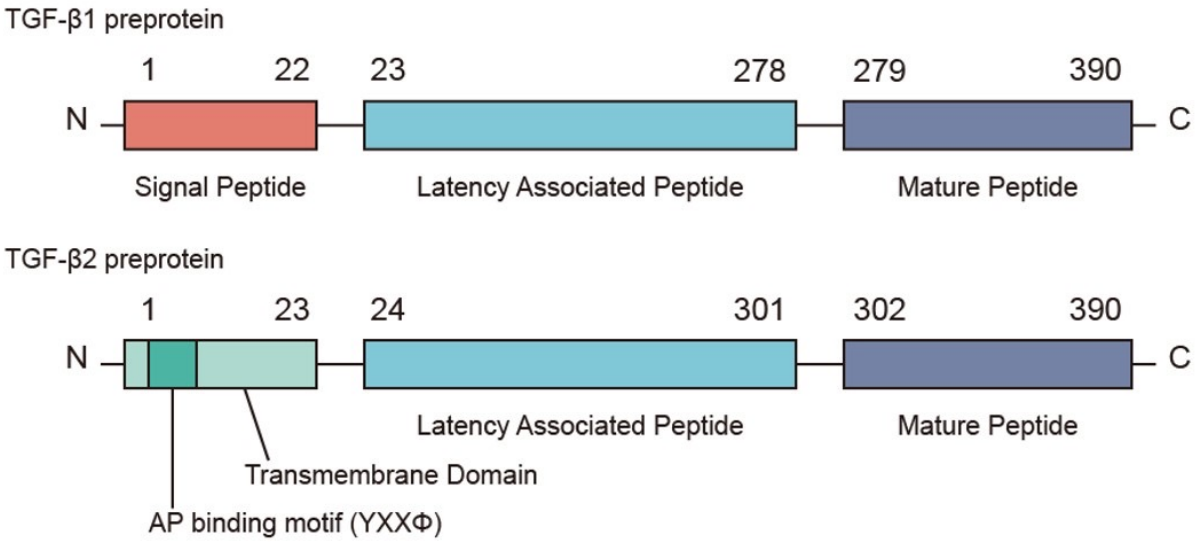
Functional Assessment of FAM13A-AP3D1-TGFB2 (Gong, AJRCMB 2021)

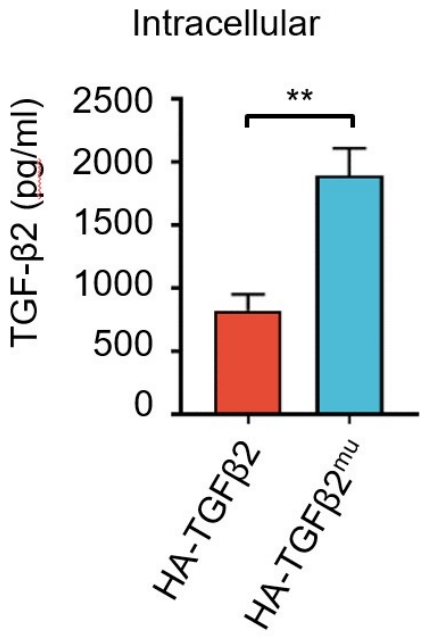


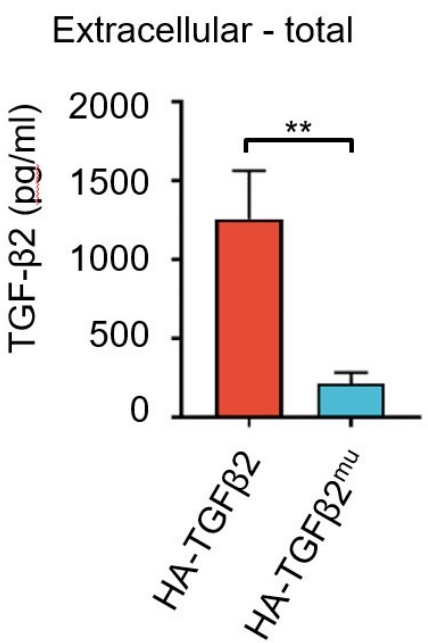
Functional Assessment of FAM13A-AP3D1-TGFB2 (Gong, AJRCMB 2021)



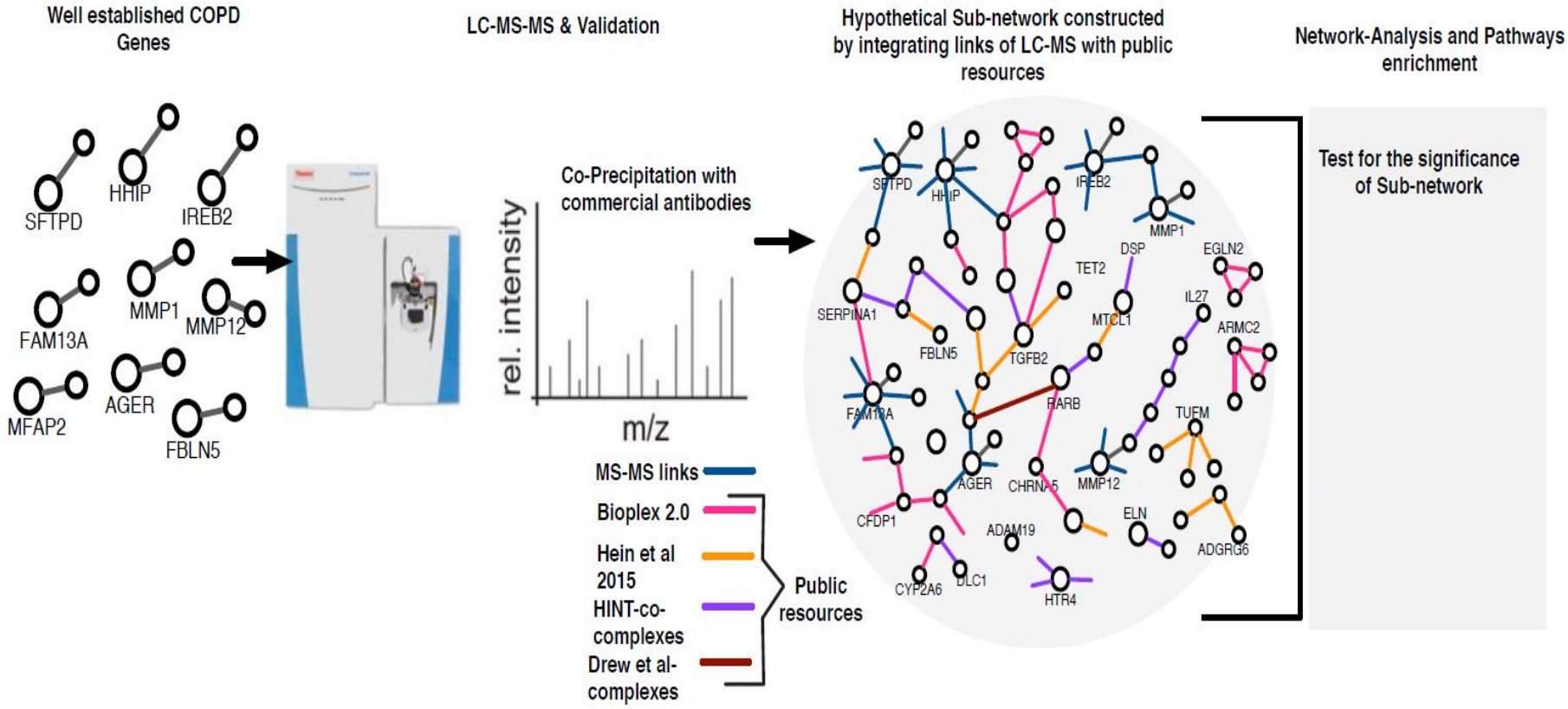
Functional Assessment of FAM13A-AP3D1-TGFB2 (Gong, AJRCMB 2021)







How Will We Build PPI Network Links between COPD GWAS Genes?

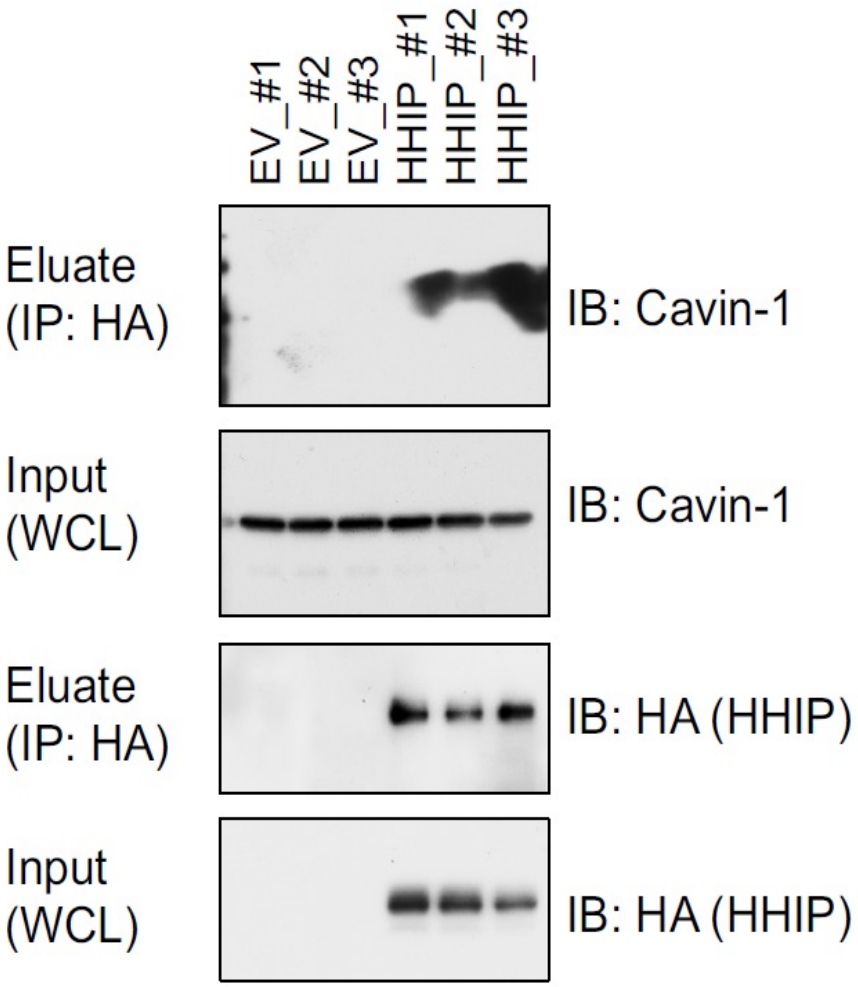


Protein Interactions of HHIP in IMR90 Cells

(Hiro Inuzuka and Zhonghui Xu)

- Used HHIP transfected into IMR90 (fibroblast) cells
- Pulled down HHIP and ran mass spectrometry analysis to identify detected proteins
- Analyzed data with SaintExpress software
- 78 proteins significantly different between HHIP vector and empty vector, including HHIP (as expected), multiple cytoskeletal components (e.g., TUBB4B, TUBA1C, ACTB), and CAVIN1

Validation of Cavin-1 as an HHIP interacting protein in IMR90 cells

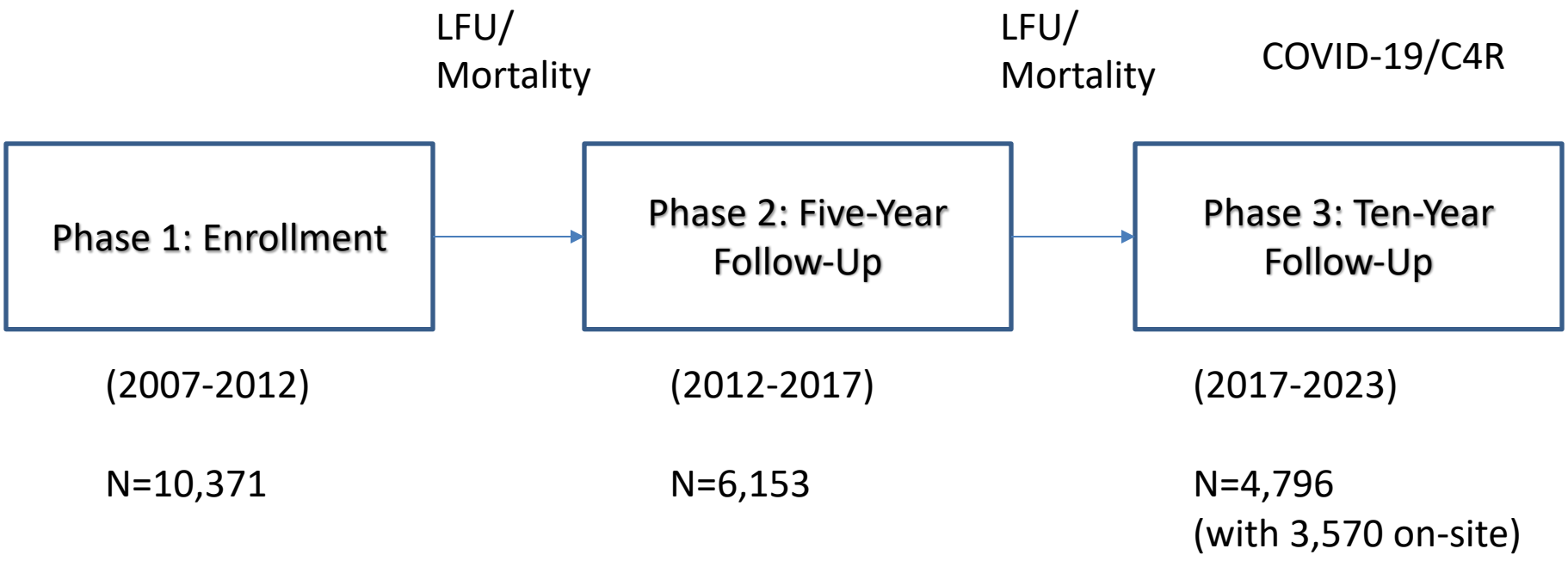


Co-precipitation assay performed by Hiroyuki Inuzuka and Wenyi Wei

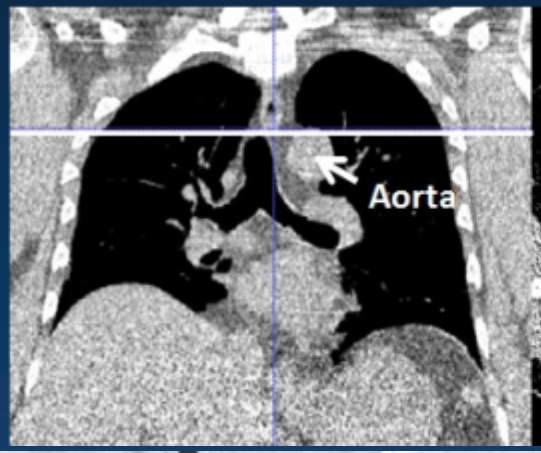
Experimental Protein-Protein Interactions: What Are We Learning?

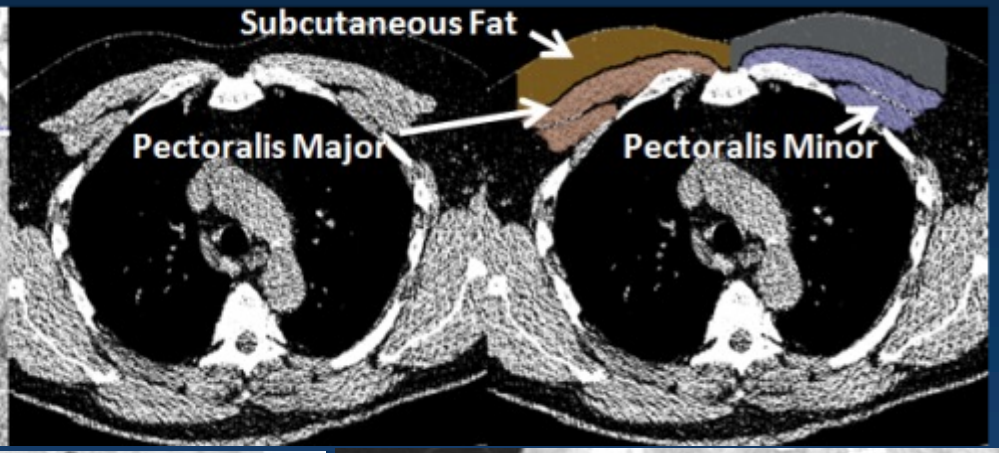
- There are substantial differences between cell types in protein-protein interactions for COPD GWAS gene products
- COPD GWAS gene products interact with many other proteins and likely have multiple biological functions beyond current knowledge
- Currently available public PPI databases miss most protein-protein interactions
- Relatively close connections between COPD GWAS genes can be identified using PPI network-based approaches

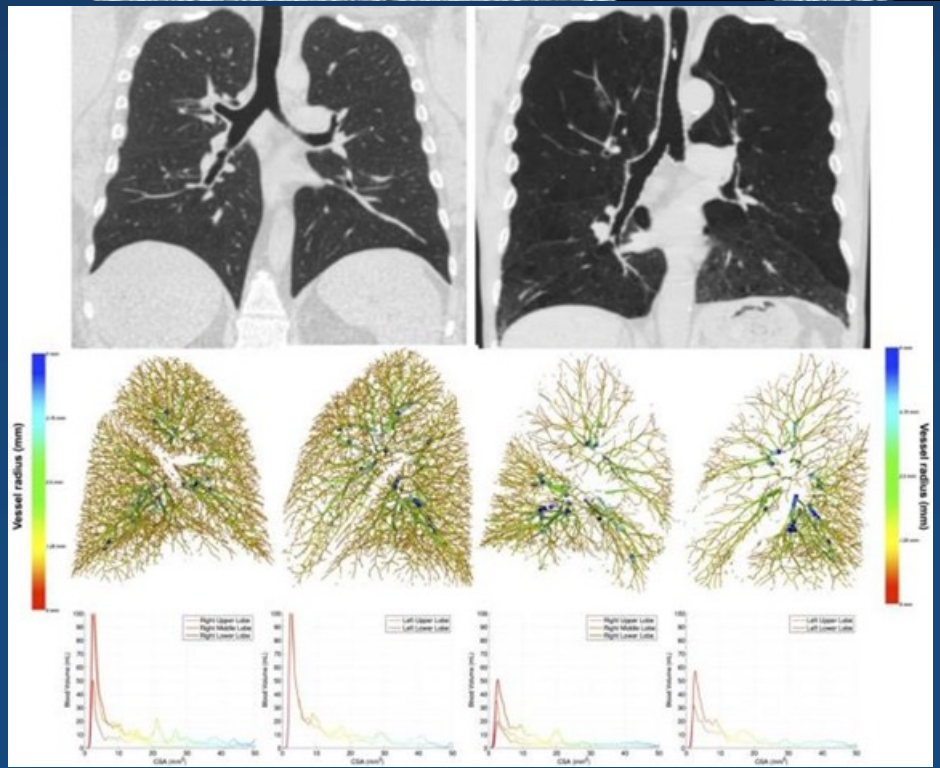
COPDGene Study Phases

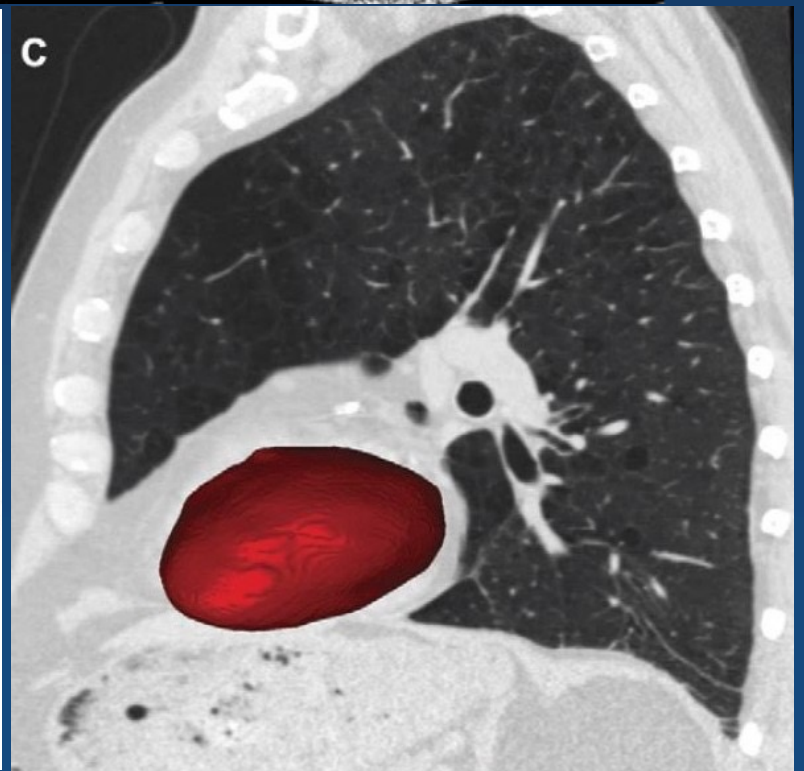


Measured Phenotypes on COPDGene Chest CT Scans (Washko/San Jose)



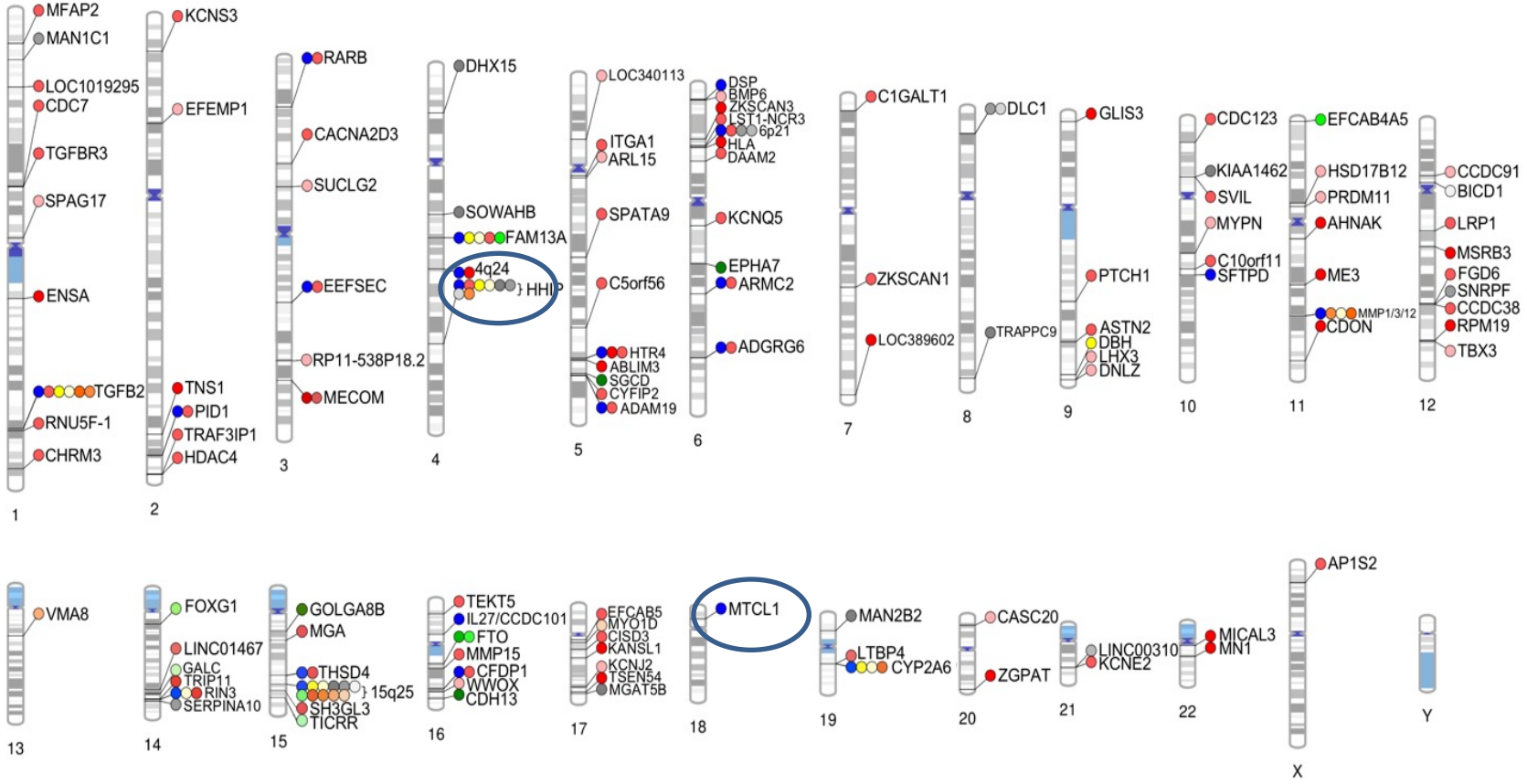






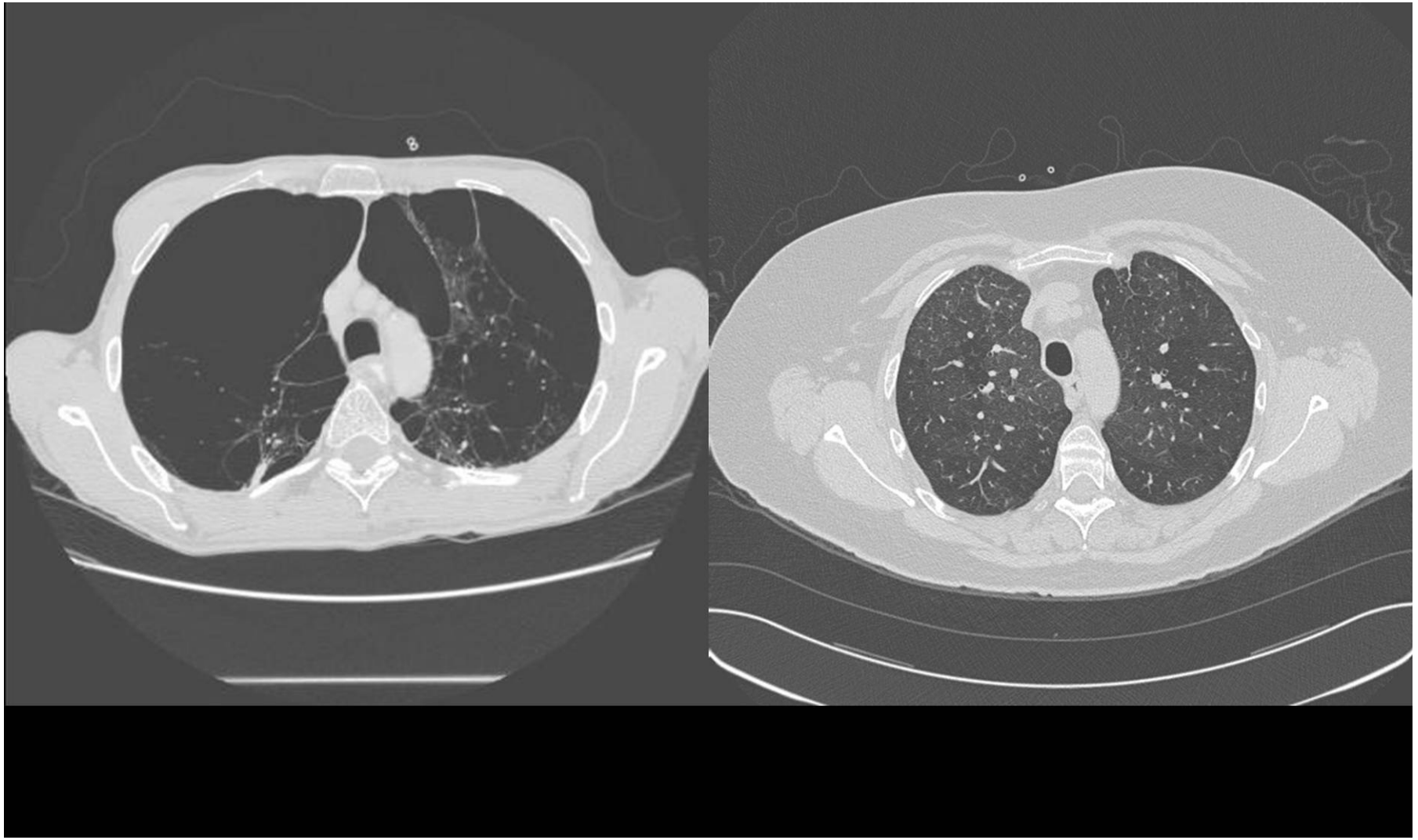
Genetic Associations for Different COPD-Related Phenotypes

(Ragland/Benway, AJRCCM, 2019)



Emphysema Predominant

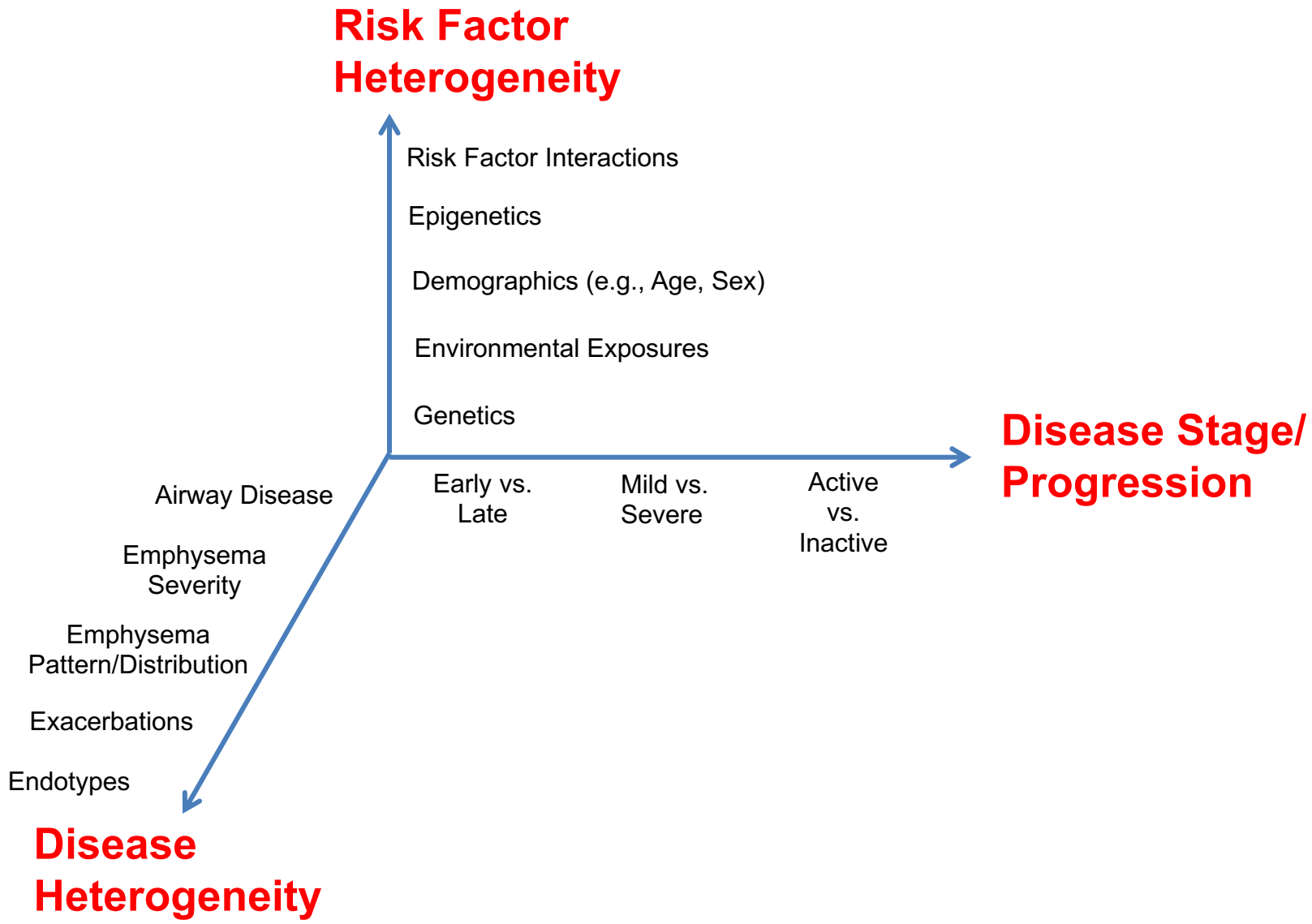
Airway Disease Predominant



Age 42, FEV_1 38%

Age 47, FEV_1 20%

Different Aspects of COPD Heterogeneity



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: Factor analysis
  - Defining disease trajectories: Bayesian nonparametric trajectory mixture modeling

Receiver-Operator Curve Analysis of Non-Emphysema-Predominant vs. Emphysema-Predominant Disease Prediction by Other Subtyping Variables (Castaldi/Silverman, Am J Epidemiol, 2023)

Subtyping Variables	Area Under Curve (Standard Error)	P-value for Subtype in Model
K-Means Cluster Categories	0.956 (0.948-0.964)	P<0.001
Disease Trajectory Categories	0.667 (0.641-0.694)	P<0.001
Factor Analysis (FA) Subtype Categories	0.922 (0.911-0.933)	P<0.001
GOLD Spirometry Categories	0.763 (0.748-0.779)	P<0.001
COPD 2019 Categories	0.651 (0.634-0.667)	P<0.001
FA Emphysema Axis Score	0.990 (0.987-0.993)	P<0.001
FA Airway Axis Score	0.518 (0.495-0.541)	N.S.

Subtype p-value is p-value for the independent variable subtype from logistic regression, or for categorical subtypes it is the minimum p-value across all subtype categories.

COPDGene Omics Data

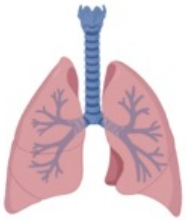
Omics Data Type	Phase 1 (Enrollment)	Phase 2 (Five-Year Follow-Up)	Phase 3 (Ten-Year Follow-Up)
Whole Genome Sequencing (Illumina)	9,921 completed	696 completed (without adequate Phase 1 DNA)	None planned
RNA-Seq (Illumina)	Not available	4,145 completed	1,520 funded but not yet completed 2,000 proposed to TOPMed
DNA Methylation (EPIC Array)	6,542 completed	5,598 completed	3,500 EPIC arrays proposed to TOPMed
Proteomics (SomaScan)	1,248 completed with 1.3K platform	6,017 completed with v4.0 platform	1,483 completed (v4.0) 2,000 proposed to TOPMed (v4.1)
Metabolomics (Metabolon)	1,183 completed	~6,000 recently completed	1,483 in progress 2,000 proposed to TOPMed

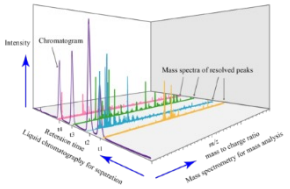
Rationale for Integrating Multiple Omics Data Types in Complex Disease

Challenge	Rationale
Measurement error	Reduce noise from a single Omics data type; accentuate correlated signal across multiple data types
Uncertain pathobiological mechanisms	Understand biological mechanisms for genetic variation
Single Omics data may not capture relevant signals	Different time scales are captured
Biological levels do not work in isolation	Interactions between biological levels can be found
Complex diseases do not act at a single biological level	Generate more accurate biological models of disease

Proteomics Analysis of Lung Tissue Samples

(Yu-Hang Zhang, Am J Physiol Lung 2021)





Trans-Proteomic Pipeline
Normalization (vsn)
Imputation (KNN)
Surrogate Variable Analysis
Linear Regression

100 COPD Cases
52 Controls

Clinically Indicated Thoracic Surgery

Liquid Chromatography-Mass Spectrometry/Mass Spectrometry

Bioinformatics Analysis

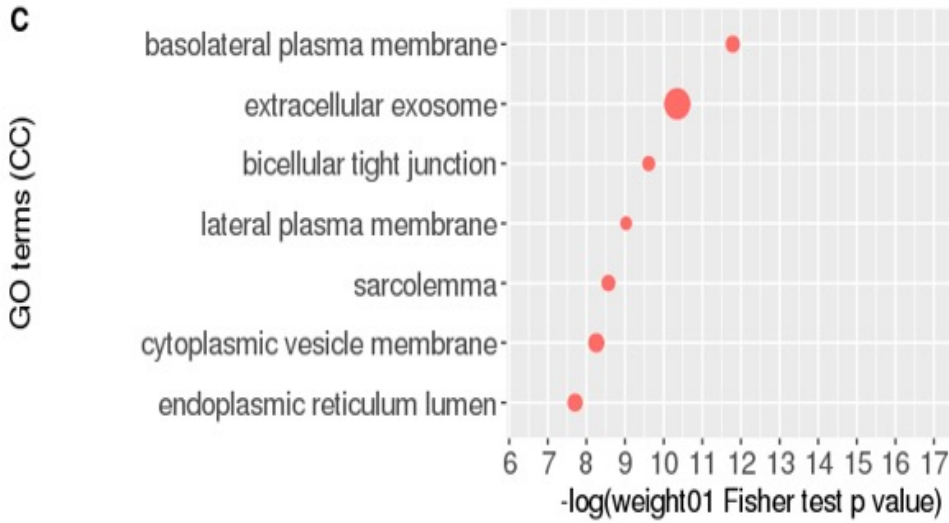
Proteomics Analysis of Lung Tissue Samples

(Yu-Hang Zhang, Am J Physiol Lung 2021)

AGRN
ANXA2
GPRC5A
PLLP
OCLN
LDHA
CAVIN1
IL33
EHD2
S100A10
EHD3
FTL
TENS3
SUSD2
DNAH5
ESAM
RASIP1
SRSF6
CAV1
AQP1
H3C1
SFTPB
LAMA4
FTH1
ARRB1

ANXA2
EHD2
EHD3
TNS3
ARRB1
S100A10
RASIP1
CAPG
DPYSL2
TGM2
MMP2

FGA
RAGE



COPD-associated Proteins (FDR < 0.05)

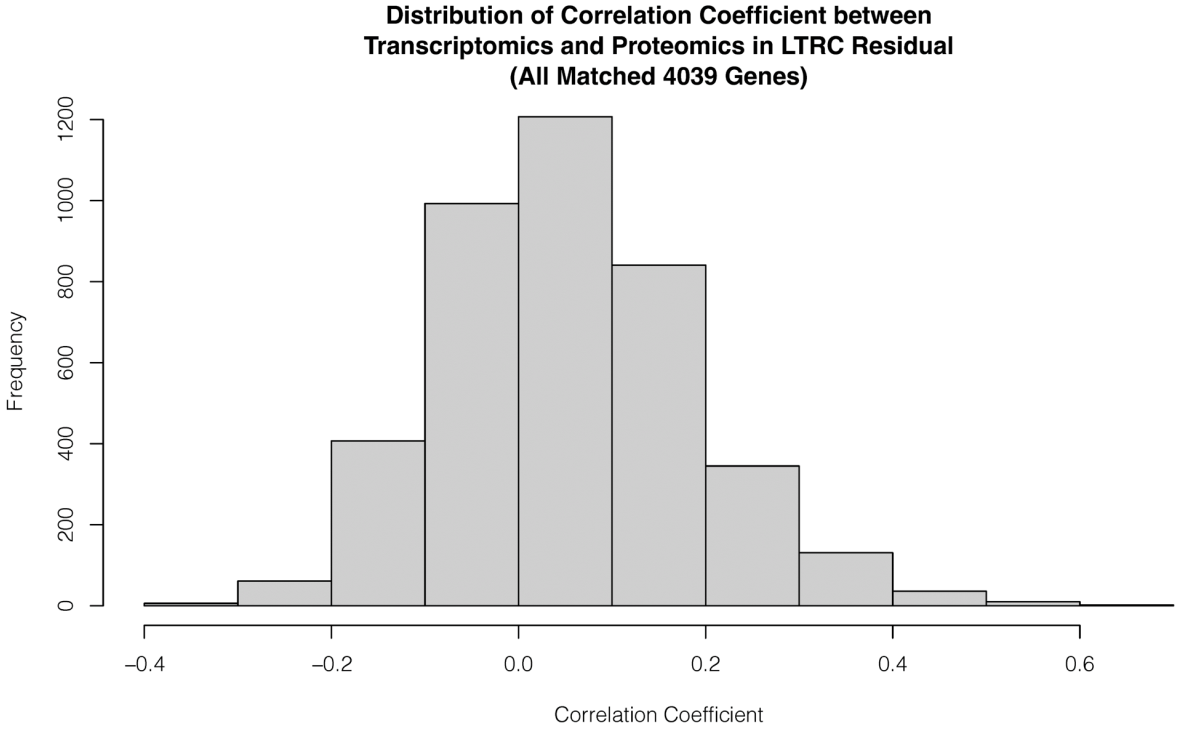
Overlap with Previous Lung Tissue Proteomics Studies (p<0.05)

Overlap with Previous Plasma Proteomics Studies (p<0.05)

Biological Processes for Top COPD-associated Proteins

How Similar Are Omics Data Types?
Lung Tissue Research Consortium (Zhang, AJRCMB 2023)

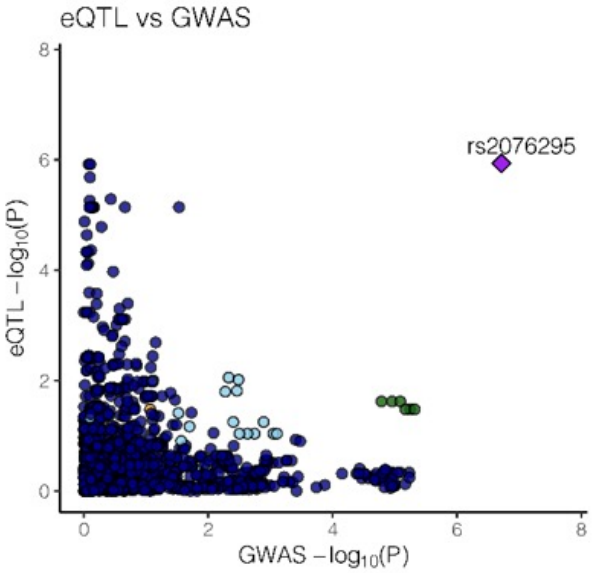
- 98 Lung Tissue Samples: 73 COPD and 25 Controls
- RNA-Seq by TOPMed
- Mass Spectrometry Proteomics on same lung tissue sample
- Compare residuals of RNA and protein for 4,039 matched genes after adjusting for COPD affection status, age, sex, and batch effects

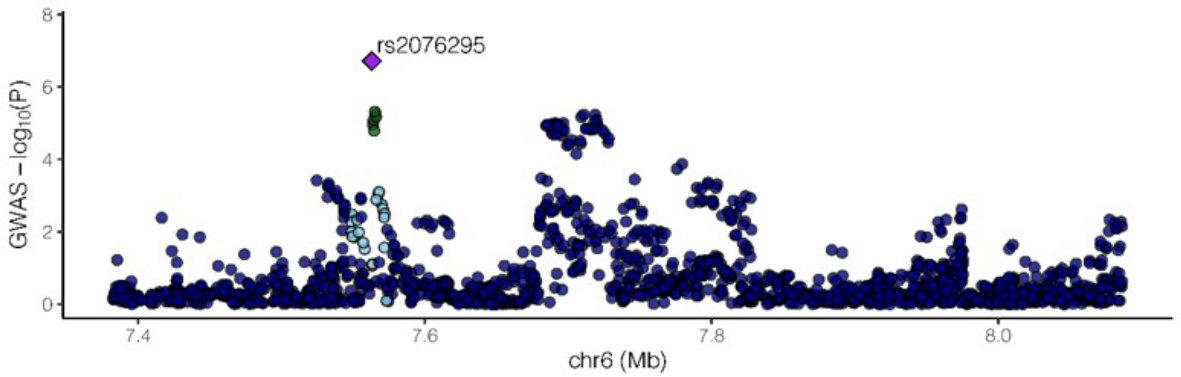


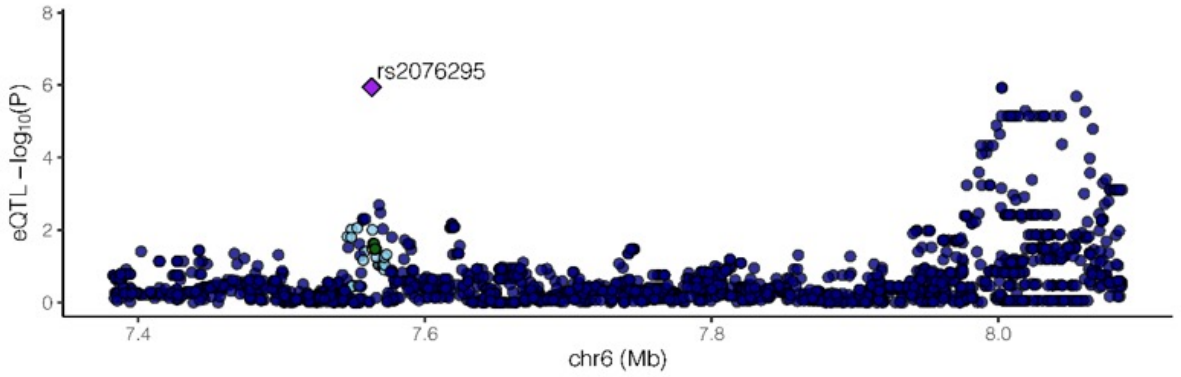
Median correlation coefficient is 0.054

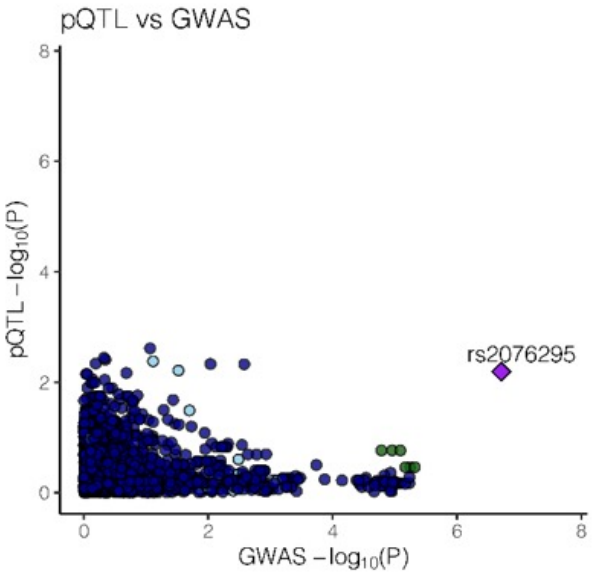
Colocalization of COPD GWAS and DSP Omics QTLs

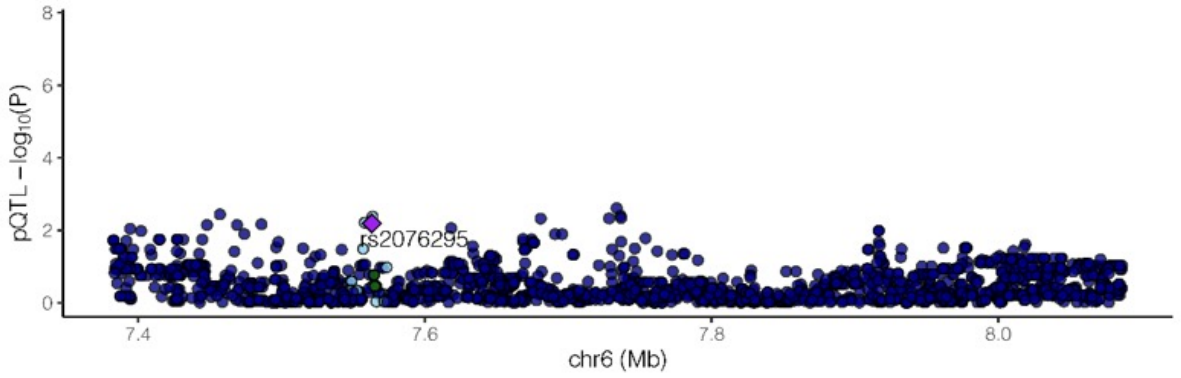
(Yu-Hang Zhang, Am J Resp Cell Mol Biol 2023)











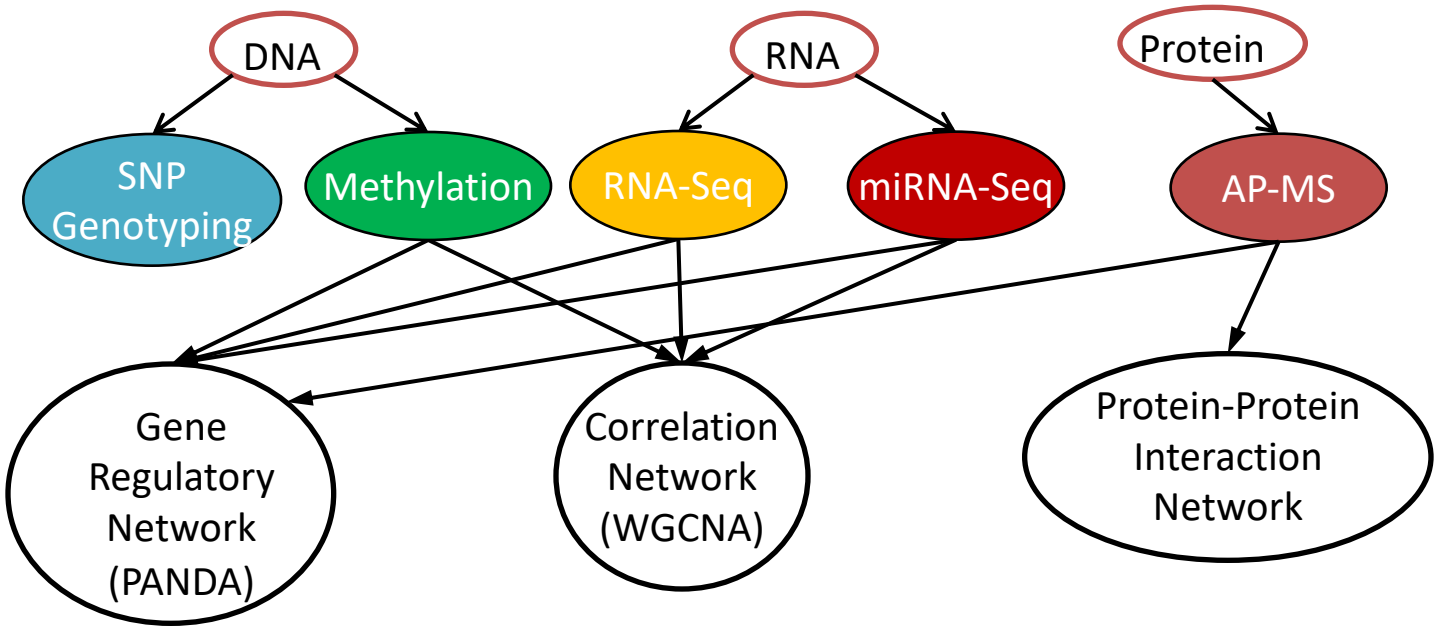
Evolution of Multiple Omics Research

	Approaches to Integrate Multiple Omics	Status
First Generation Multiple Omics Studies	--QTL studies linking genetics to Omics --Correlation network module preservation in WGCNA	--Well-established --Useful in selected applications
Second Generation Multiple Omics Studies	--Combine multiple Omics layers without prior biological knowledge (e.g., Similarity Network Fusion) --Create heterogeneous networks with different Omics data type nodes	--Methods exist, but utility of results is uncertain
Third Generation Multiple Omics Studies	--Combine multiple Omics leveraging prior biological knowledge in network models --Includes statistical framework for comparing networks --Includes functional validation	--Methods in development

Top-Down and Bottom-Up Approaches to Build Biological Networks

Example:
FAM13A-AP3D1-TGFB2

Top-Down Approach to Build Biological Networks



Understand Gene Regulation

Determine Biological Function

Define Disease Pathobiology

Bottom-Up Approach to Build Biological Networks

Find Functional Variants

Identify Key Gene(s) in GWAS Region

GWAS Region

Example:
FAM13A-CTNNB1

How Do We Know When We Have Learned Something Important About Complex Disease Pathogenesis?

- Challenging to move from population-level Omics data to new biological insights into complex diseases like COPD
- Approaches to build confidence and develop biological insights in genetics/Omics associations in complex diseases:
  - Replication in other populations
  - Orthogonal Information from different Omics data types and analytical approaches
  - Functional Validation in cell-based and animal model systems

Key Knowledge Gaps and Research Directions in Network Medicine

(Silverman et al., WIRES Systems Biology and Medicine 2020)

- Incompleteness of the Molecular Interactome
- Uncertainty about Key Genes in Genetic Association Loci
- Limited Application of Network Medicine to Human Samples and Diseases
- Gap between Systems Biology and Network Medicine
- Developing Analytical and Experimental Approaches for Network Validation
- Finding concordance/consistency in results based on different network methods and approaches
- Moving from Static to Dynamic Network Models

Collaborators

- *Functional Genetics of COPD:* Xiaobo Zhou, Augustine Choi, Suzanne Cloonan, Dawn DeMeo, Craig Hersh, Jarrett Morrow, John Quackenbush, Kimberly Glass, John Platig, Amitabh Sharma, Arda Halu, Yang-Yu Liu, Caroline Owen, Bart Celli, Miguel Divo, Zhiqiang Jiang, Taotao Lao, Raphael Bueno, Gerard Criner, Phuwanat Sakornsakolpat, Jeong Yun, Chris Benway, Feng Guo, Dandi Qiao, Lu Gong, Wenyi Wei, Victor Hsu
- *COPDGene:* James Crapo, Barry Make, John Hokanson, Elizabeth Regan, Russ Bowler, Carla Wilson, Terri Beaty, Michael Cho, Peter Castaldi, David Lynch, George Washko, Raul San Jose Estepar, James Ross, Merry-Lynn McDonald, Craig Hersh, Dawn DeMeo, Emily Wan, Brian Hobbs, Lystra Hayden, Adel El-Boueiz, Phuwanat Sakornsakolpat, Dandi Qiao, Wonji Kim, Matt Moll, Auyon Ghosh, and 21 Clinical Centers
- *COPD Proteomics:* Yu-Hang Zhang, Robert Moritz, Michael Cho, Peter Castaldi, Jarrett Morrow
- *COPD Networks:* Kimberly Glass, Amitabh Sharma, Michele Gentili, Arda Halu, Brian Hobbs, John Platig, Jarrett Morrow, David Deritei, Zhonghui Xu

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