Introduction to Systems Biology
Class 03

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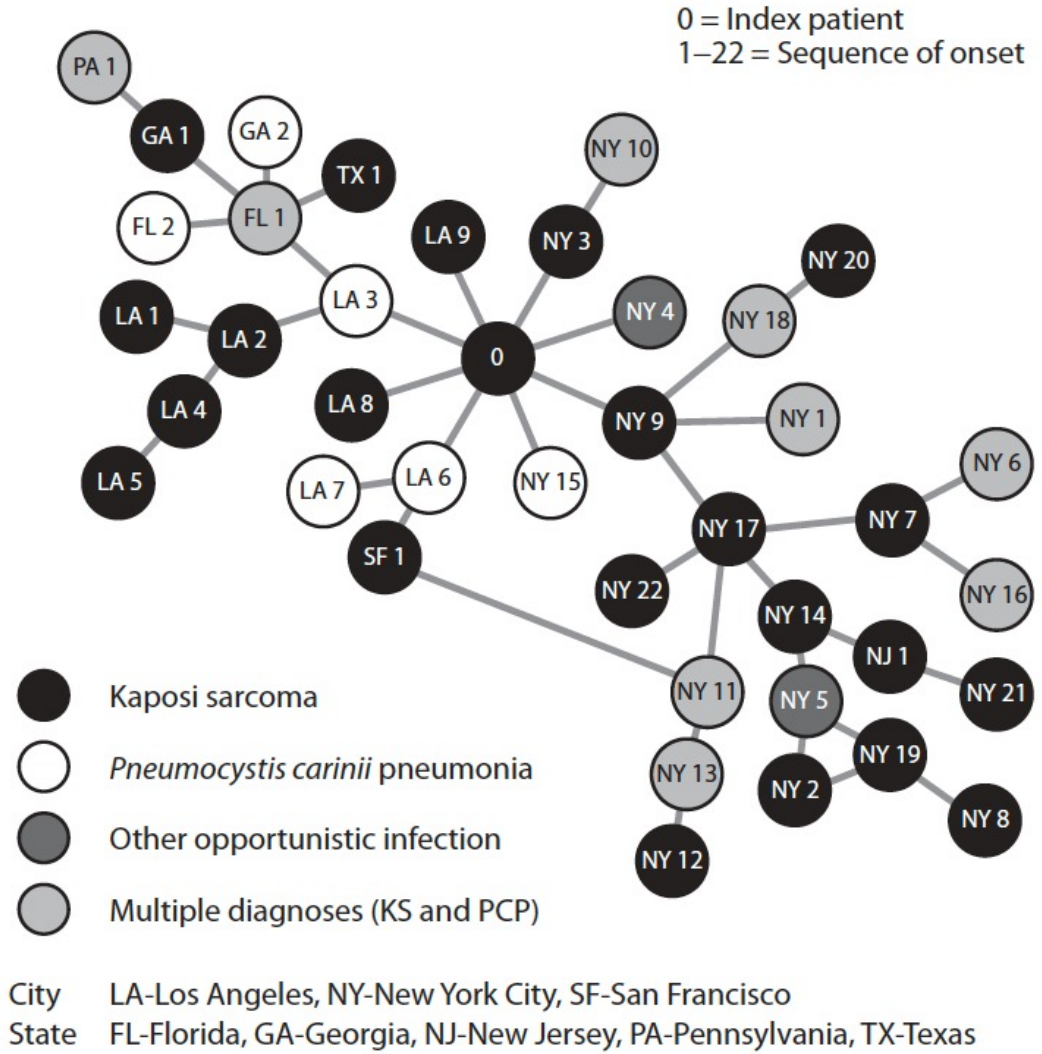
Network medicine

1. Social networks in human disease
2. Complex disease genetics
3. Transcriptomics network
4. Post-translational modifications of the proteome
5. Epigenetics and network medicine
6. Metabolomics
7. Integrative approaches

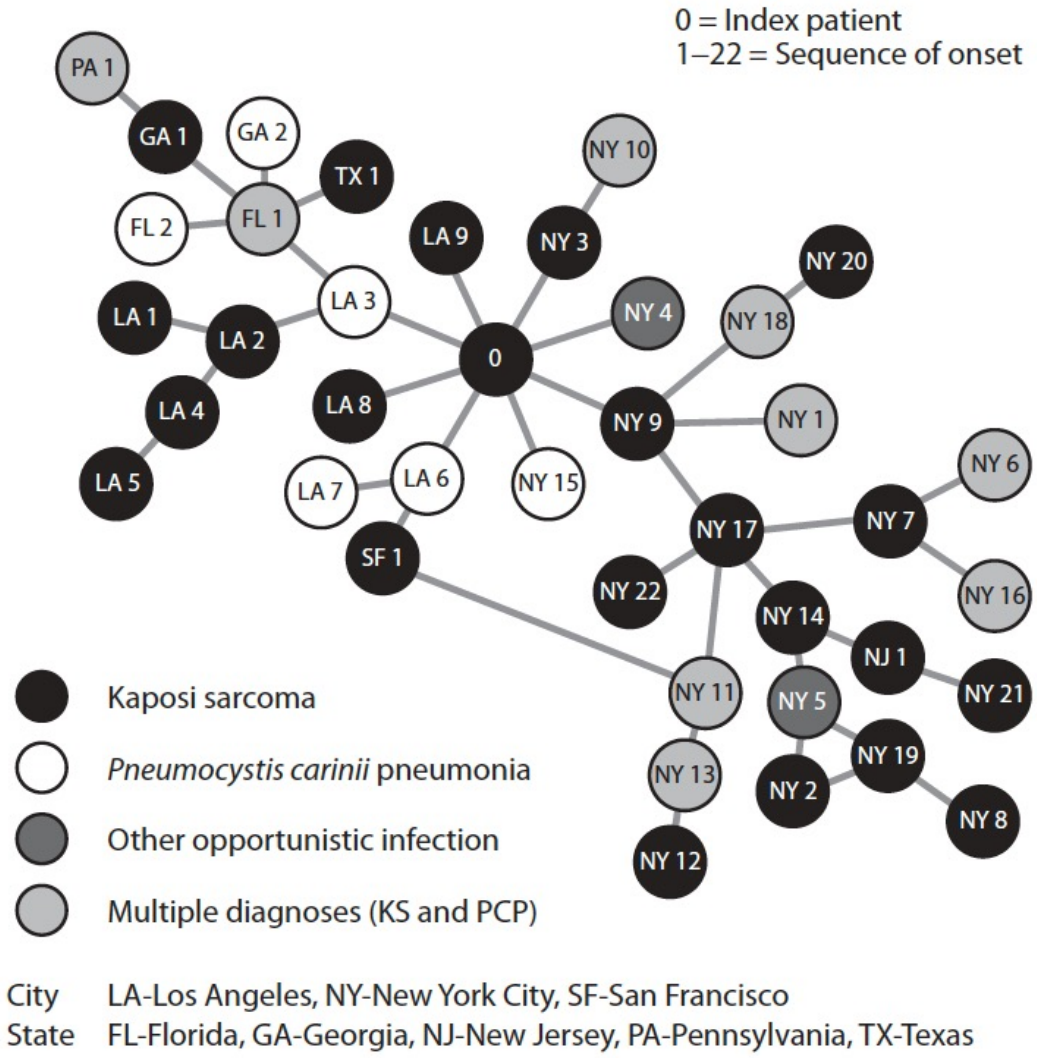
"Network Medicine: Complex Systems in Human Disease and Therapeutics."
Book edited by Loscalzo, Barabási and Silverman, 2017.

Social Networks in Disease



Luke and Stamatakis. Annual review of public health, 2012

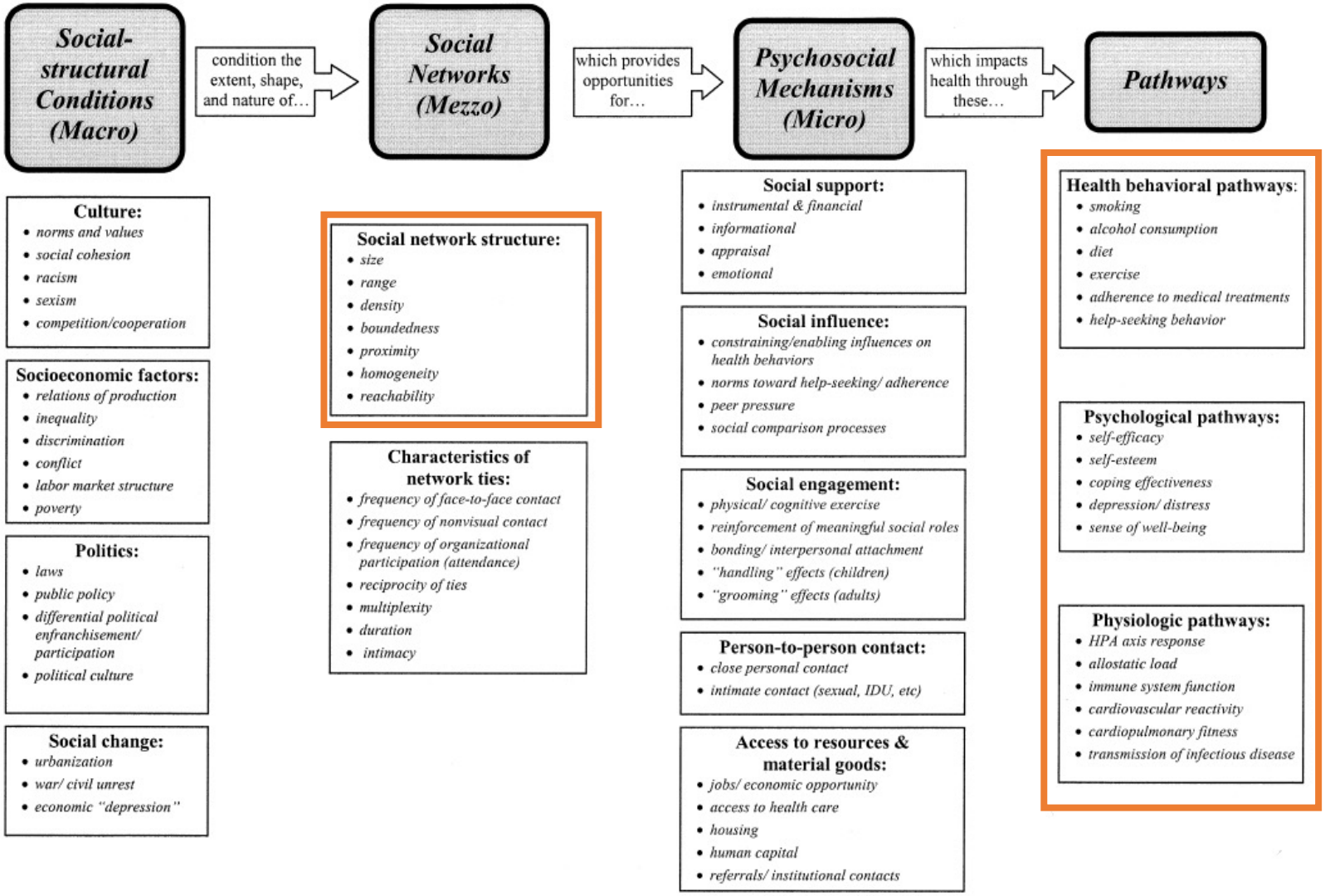
Social Networks in Disease



Characteristic	Interpretation
Input	Interview metadata
Nodes	Individuals with HIV-AIDS
Edges	Sexual partner
Topology	Scale-free

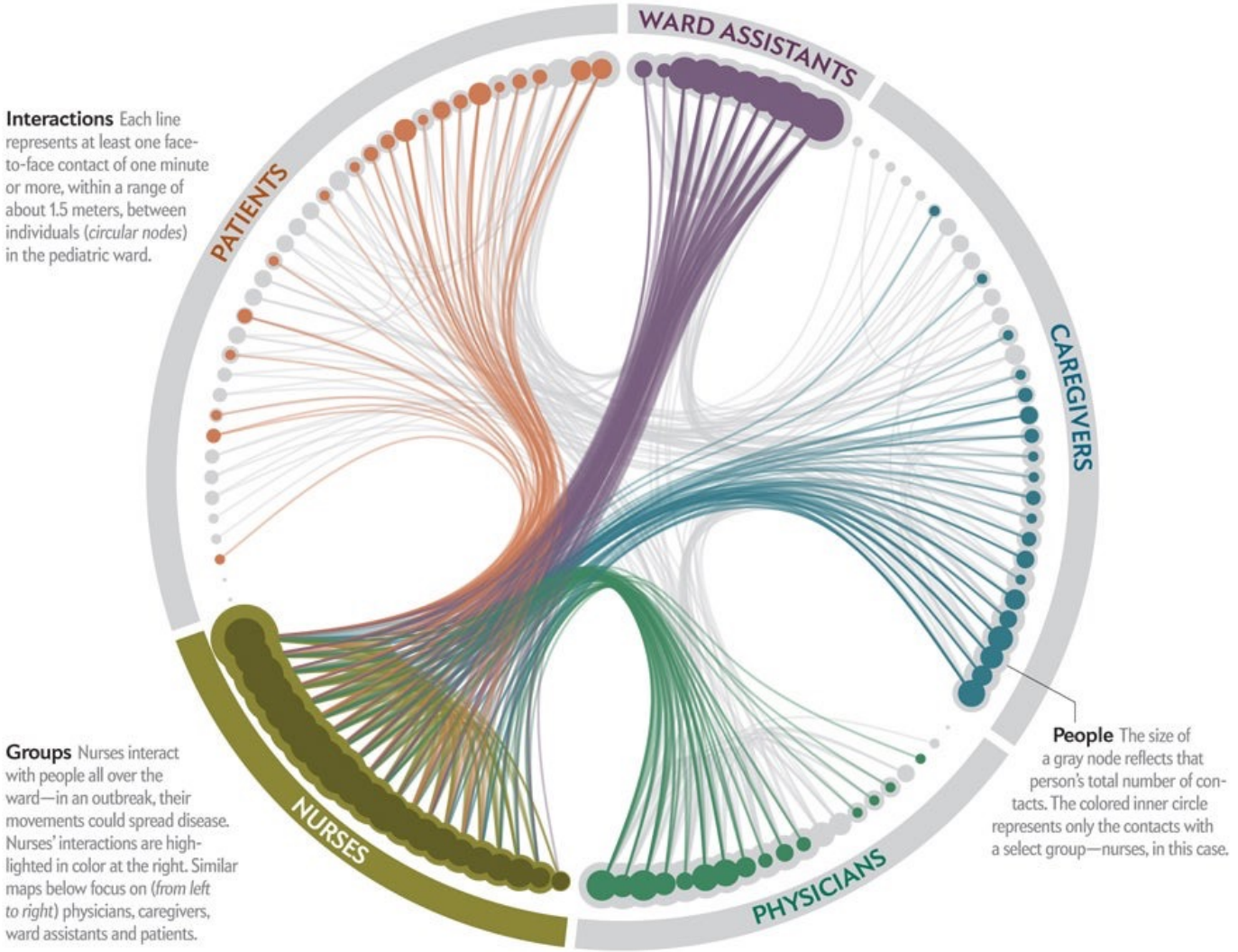
Luke and Stamatakis. Annual review of public health, 2012

Social Networks in Disease



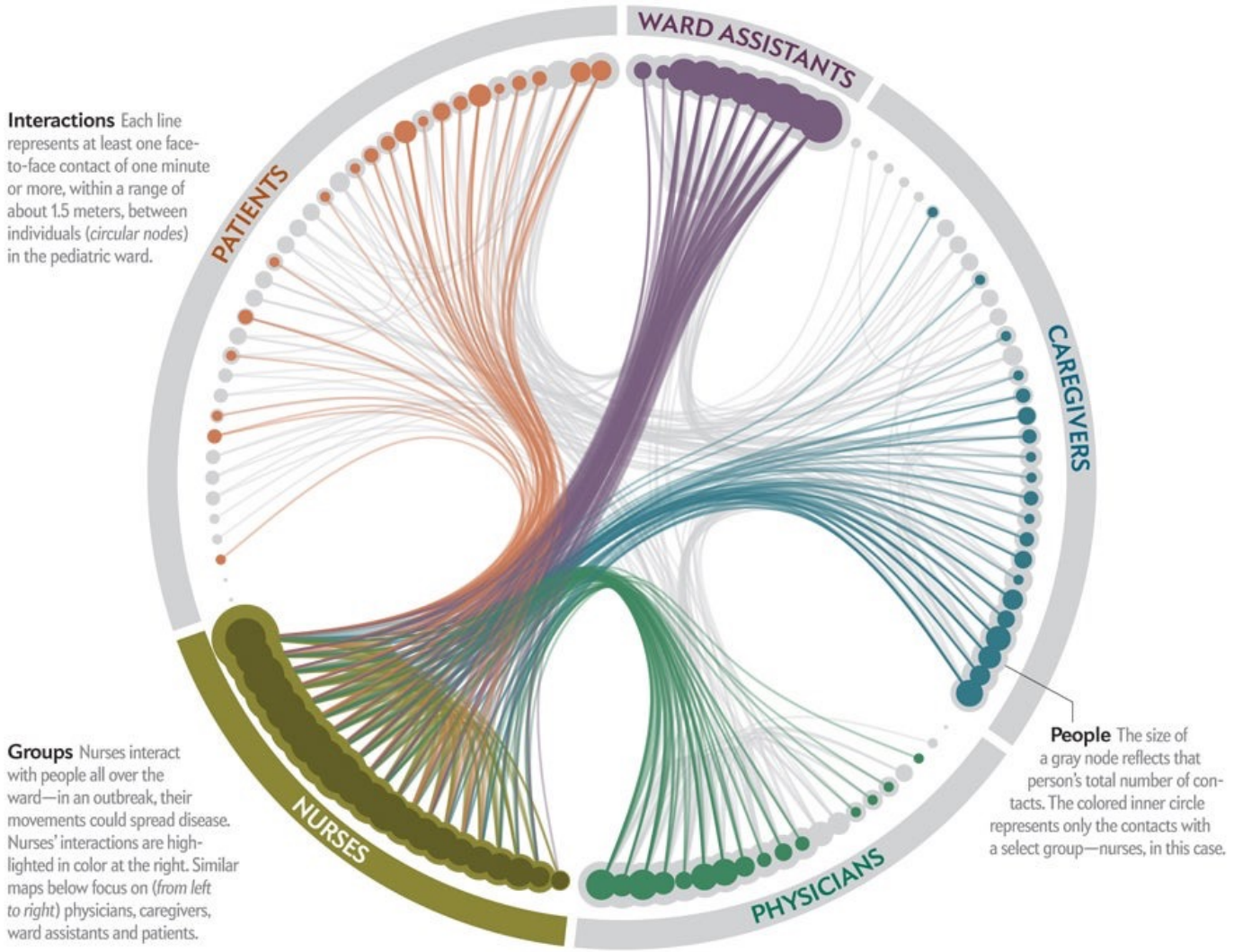
Berkman et al. Social Science & Medicine, 2000.

Social Networks in Disease



https://www.scientificamerican.com/article/rfid-tags-track-possible-outbreak-pathways-in-hospital/

Social Networks in Disease



Characteristic	Interpretation
Input	Metadata from a pediatric hospital
Nodes	Professionals in a hospital
Edges	Each least one face-to-face contact of > 1 min
Topology	Scale-free

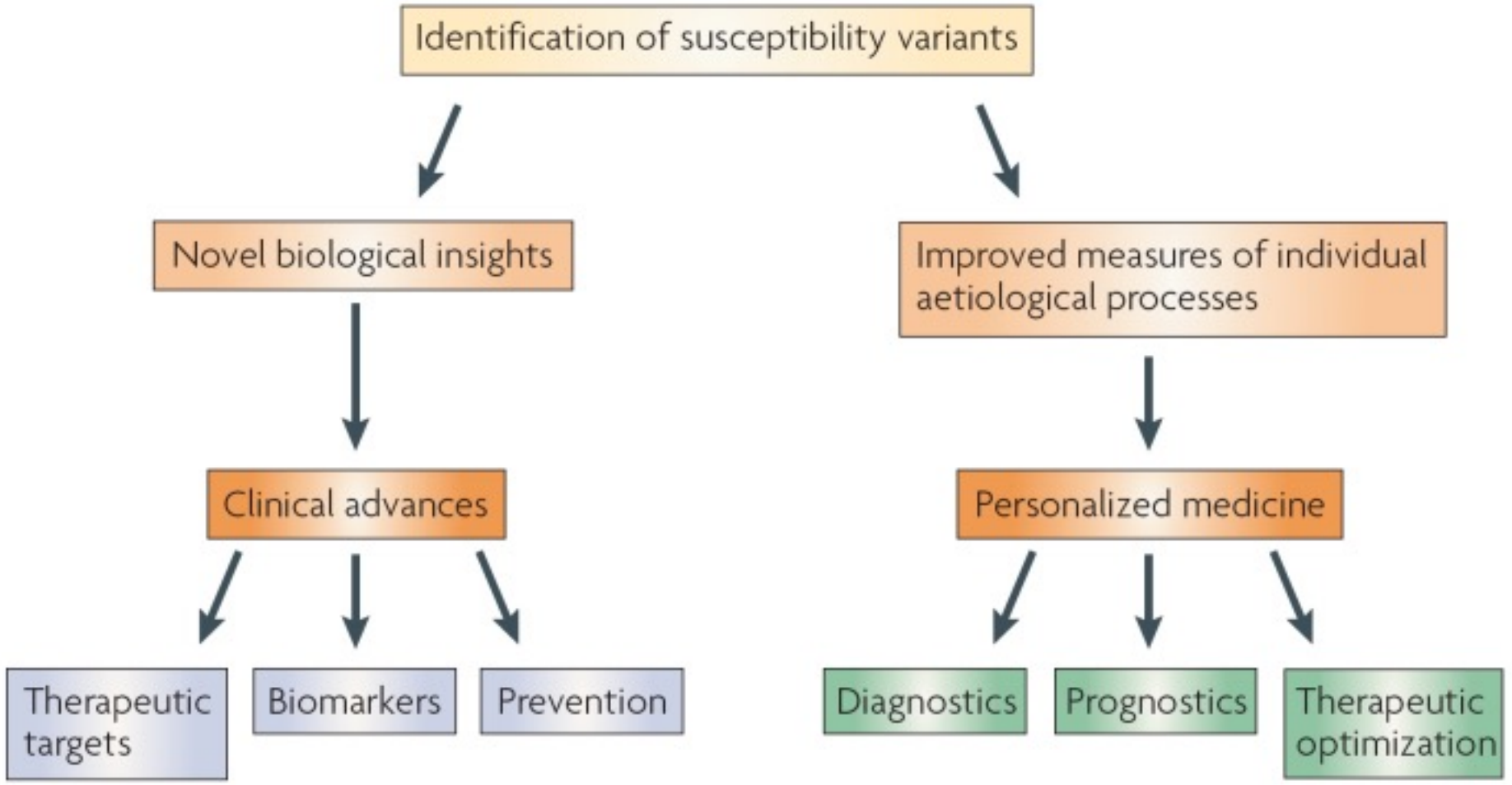
https://www.scientificamerican.com/article/rfid-tags-track-possible-outbreak-pathways-in-hospital/

Complex disease genetics

- Definition of complex disease:
  - Caused by a combination of genetic, environmental, and lifestyle factors
  - Majority of diseases fall into this category, including several congenital defects and adult-onset diseases
  - Examples includes Alzheimer's disease, asthma, Parkinson's disease, multiple sclerosis, autoimmune diseases…

Craig, J. (2008) Complex diseases: Research and applications. Nature Education.

GWAS Help Unravel Complex Traits



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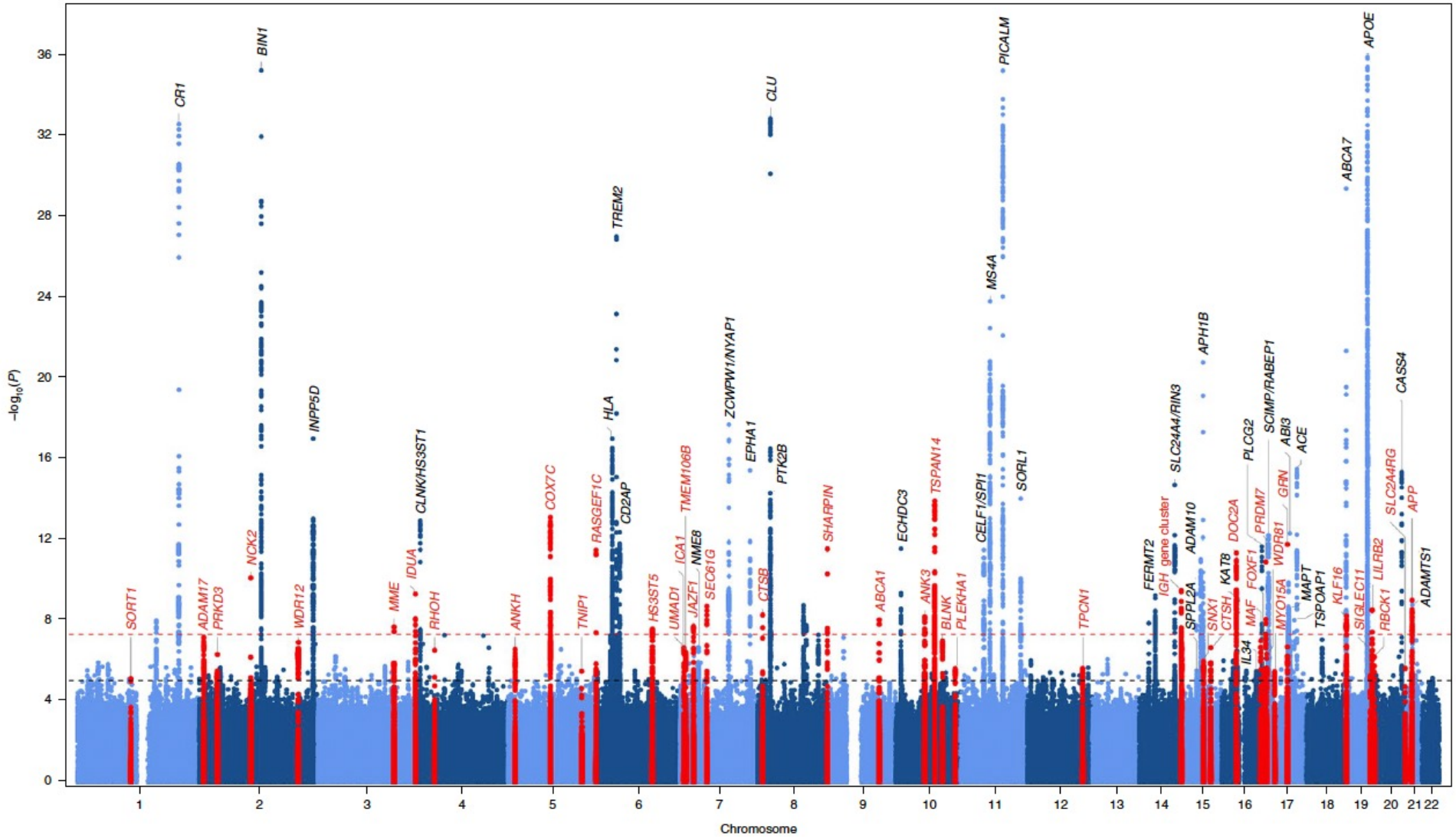
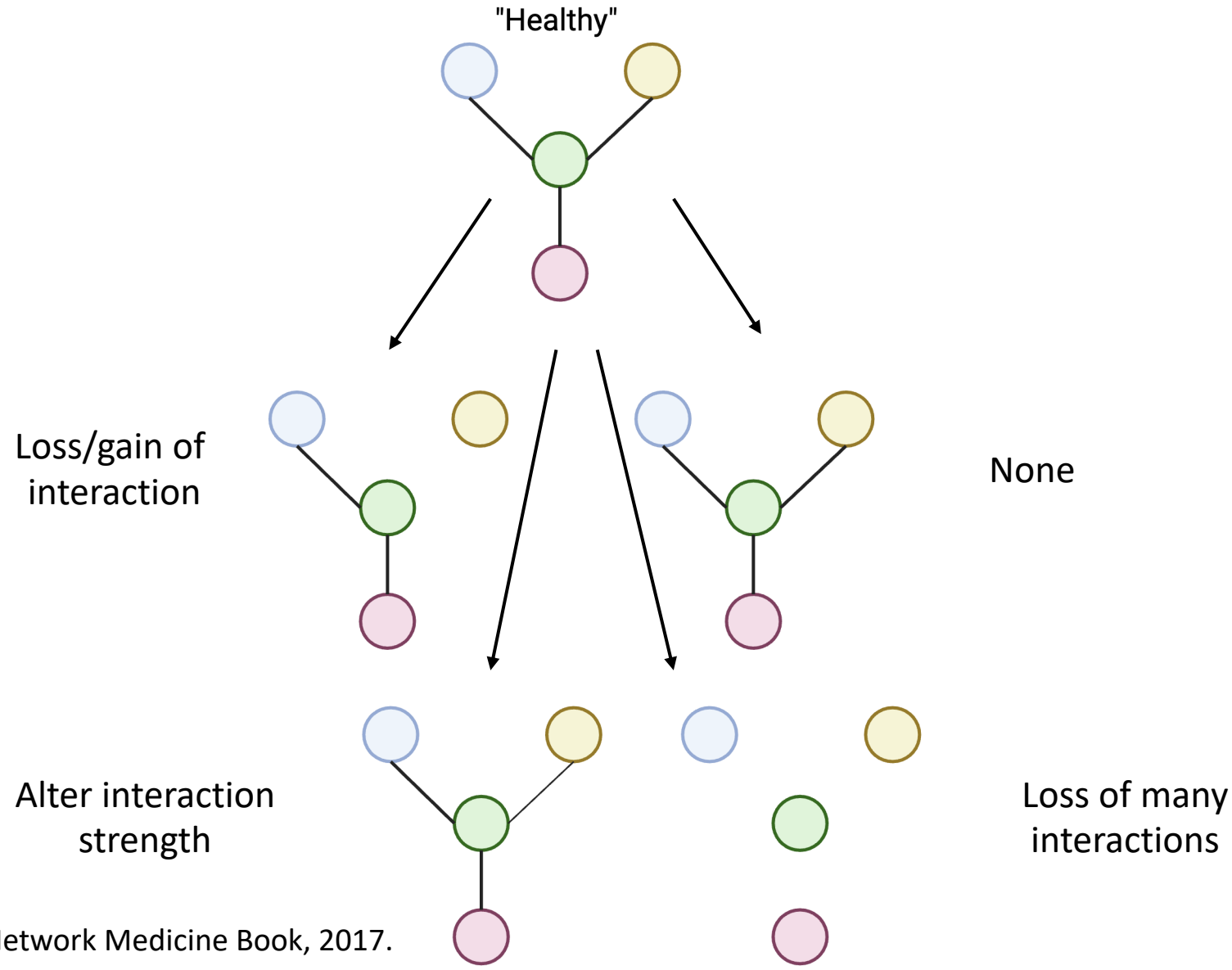
Complex disease genetics



Bellenguez et al. Nat Genetics, 2022

111,326 AD cases and 677,663 controls
75 risk loci, of which 42 were new at the time of analysis

Complex disease genetics

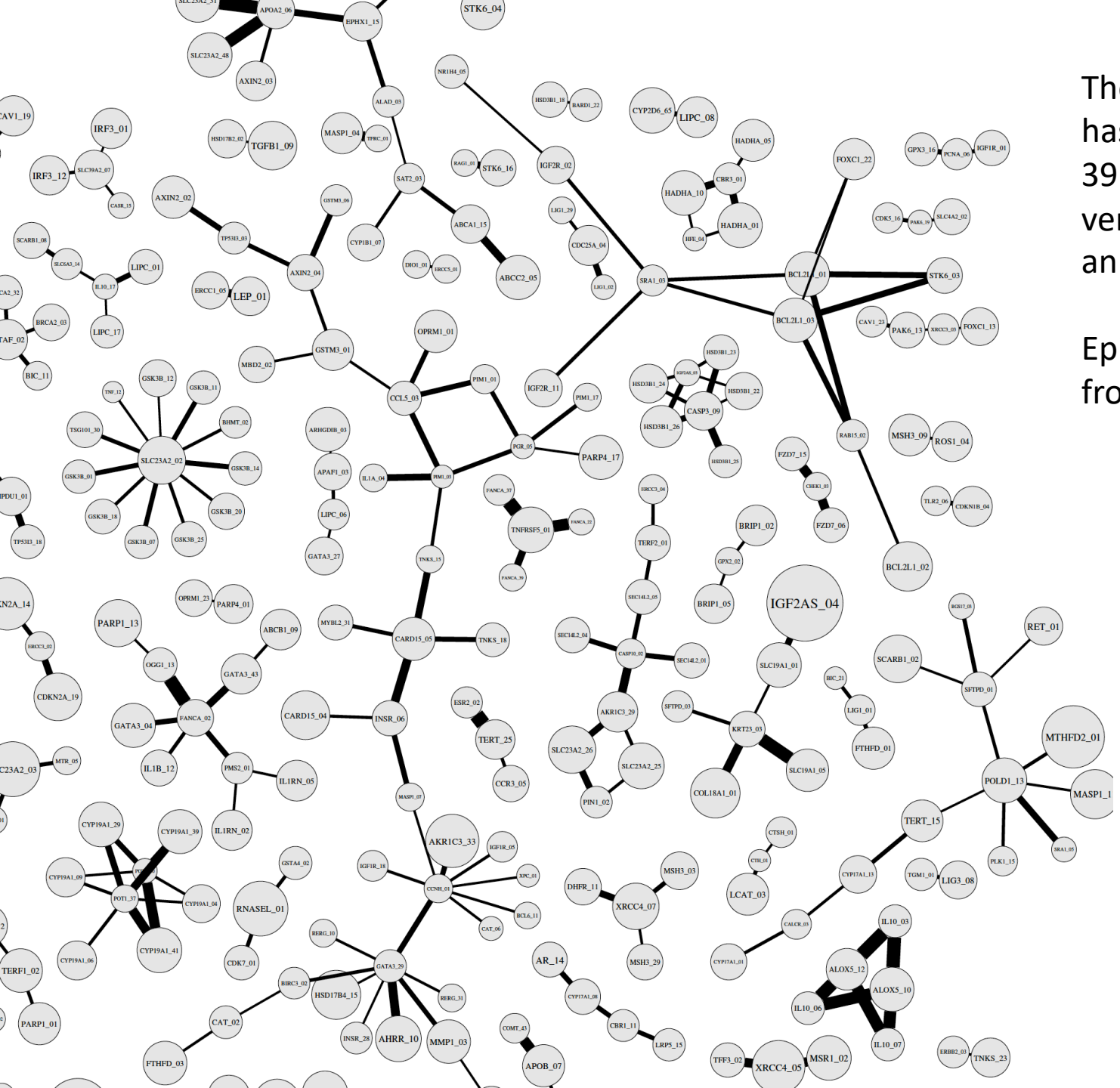


Loscalzo, Barabási, Silverman. Network Medicine Book, 2017.
Figure created with Biorender.

Complex disease genetics

Etiology	Rational
Common genetic variants	Common variants are likely to be found in GWAS with larger sample sizes.
Rare genetics variants	Resequencing studies could identify rare genetic determinants.
Interactions	Gene-gene and gene-environment interactions are likely important.
Inaccurate heritability estimates	Heritability estimates are usually generated under assumptions of no gene-gene or gene-environment interactions.
Phenotypic heterogeneity	Most complex diseases are likely to be syndromes with multiple disease subtypes.

Loscalzo, Barabási, Silverman. Network Medicine Book, 2017.



There are 319 vertices and 255 edges. The network has 79 connected components and the largest one has 39 vertices. The width of an edge and the size of a vertex are in proportion to their weights. The length of an edge is for layout purposes only.

Epistesis network created with a panel of 1422 SNPs from patients with bladder cancer.

Integration of genetic variants with single Omics approach

Hu et al, BMC Bioinformatics, 2011.

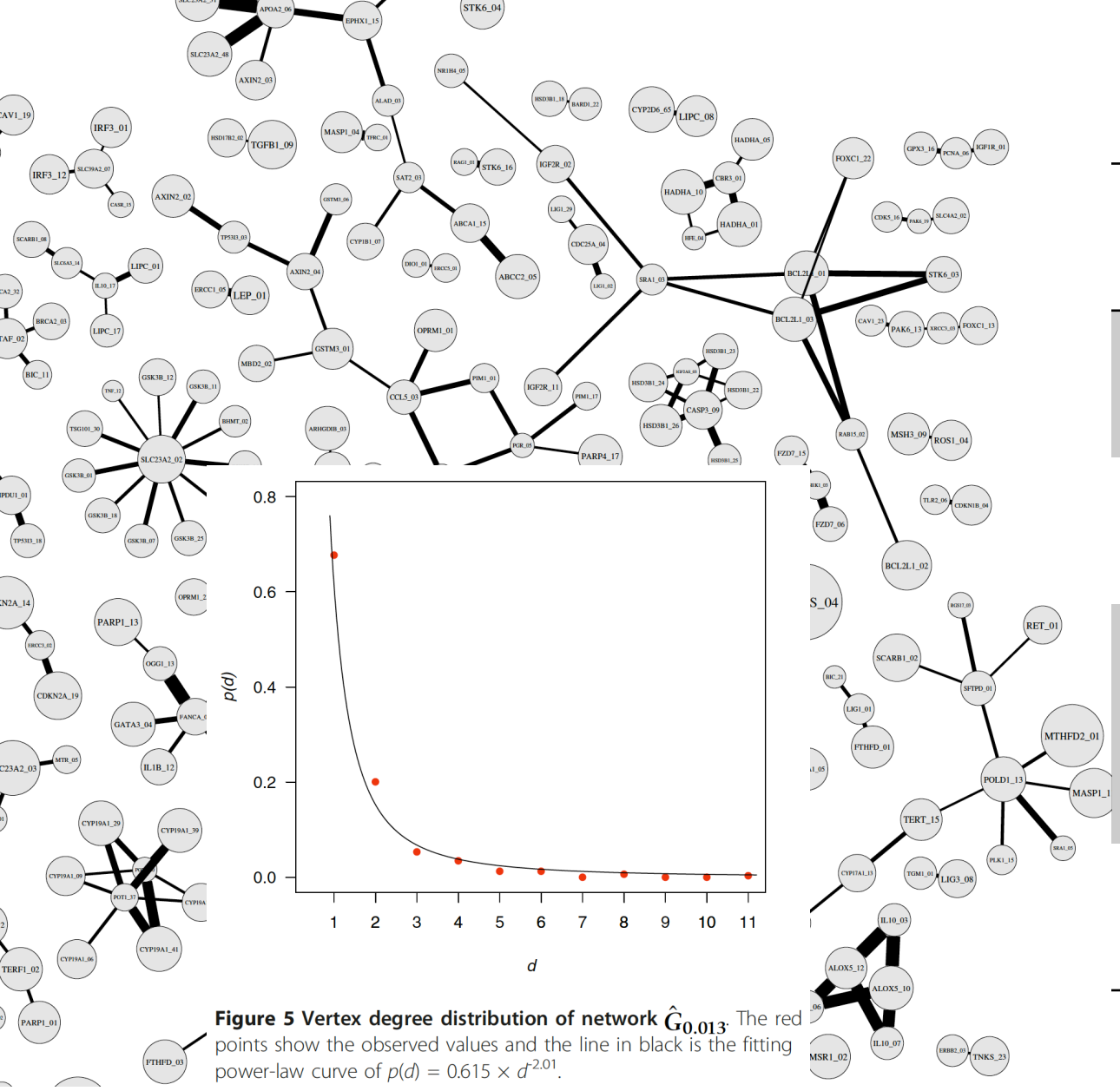
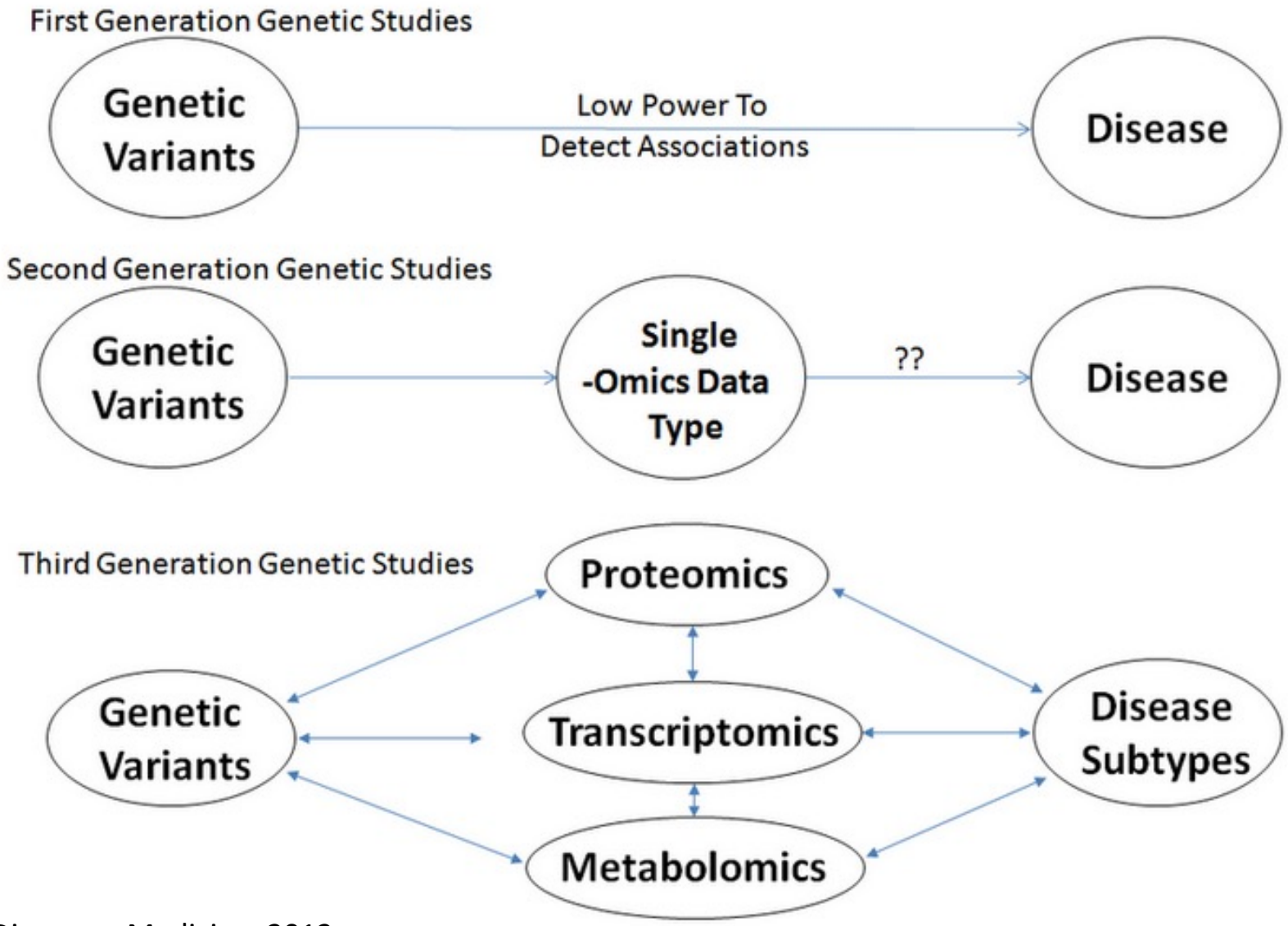


Figure 5 Vertex degree distribution of network $\hat{G}_{0.013}$. The red points show the observed values and the line in black is the fitting power-law curve of $p(d) = 0.615 \times d^{-2.01}$.

Characteristic	Interpretation
Input	SNP panel of 1422 variants Bladder cancer patients
Nodes	Genes
Edges	Built incrementally adding edges between SNPs if the strength of their pairwise interactions was greater than a given threshold
Topology	Scale-free

Hu et al, BMC Bioinformatics, 2011.

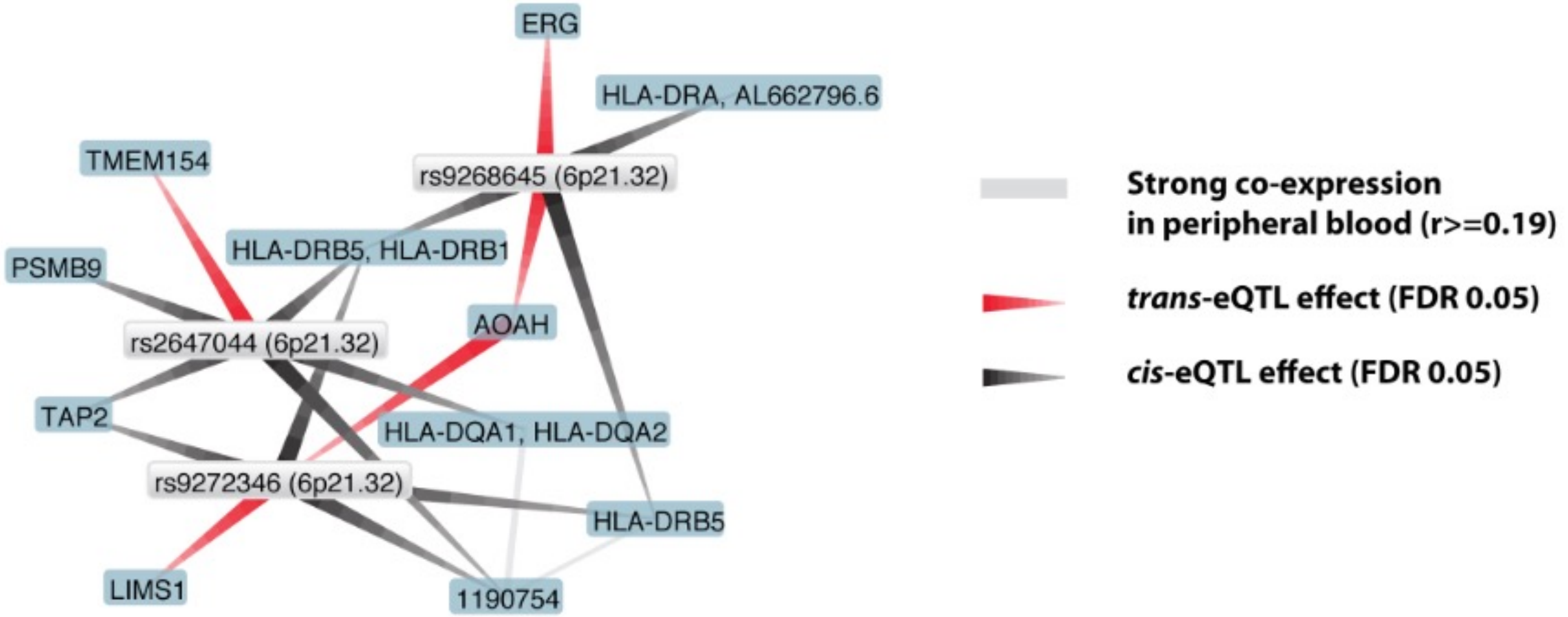
Complex disease genetics



Silverman and Loscalzo. Discovery Medicine, 2012.

Complex disease genetics

Network constructed from eQTL SNPs in type I Diabetes

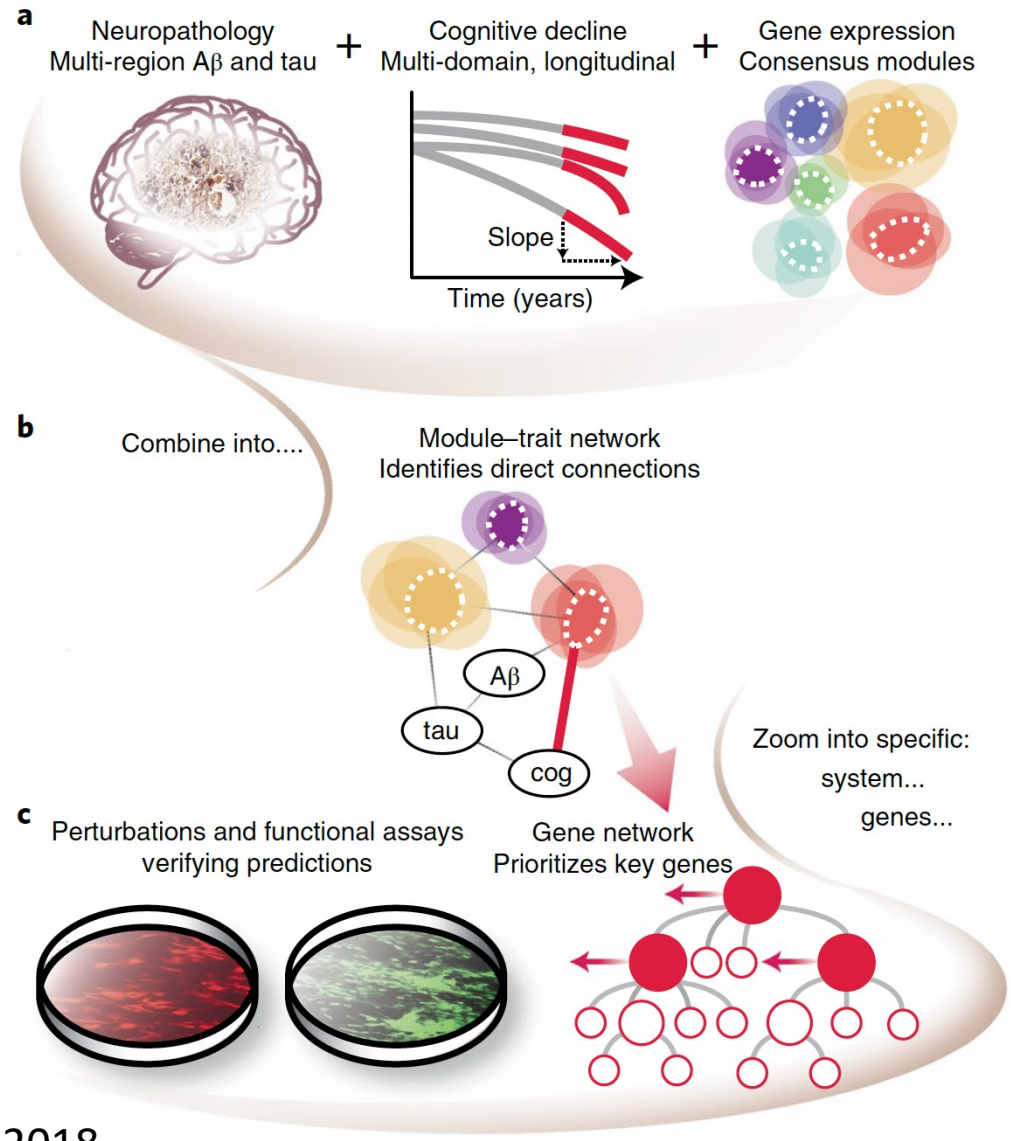


Fehrmann et al. Plos Genetics, 2011.

Transcriptomics network

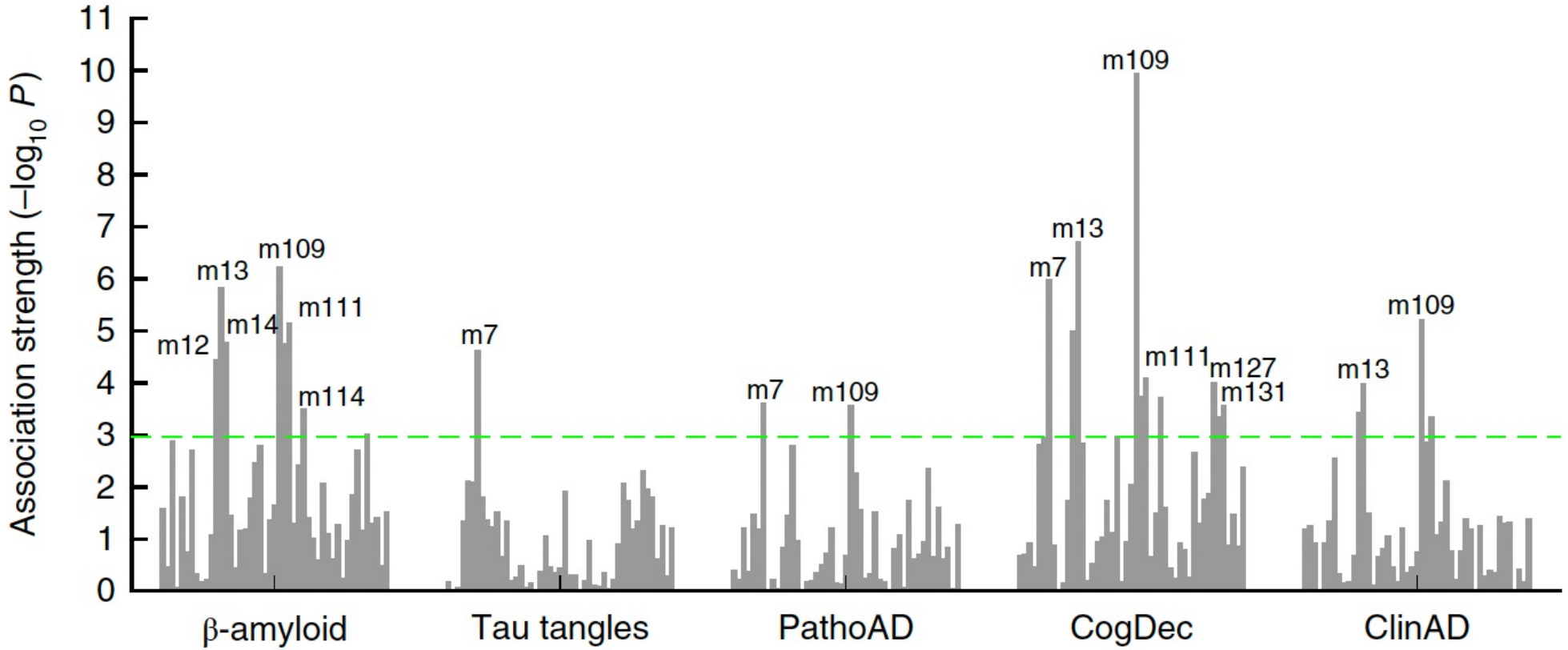
- Defined as the collection of all RNA molecules in the cell, including messenger RNA (mRNA)
- The abundance level of these molecules are commonly referred to as “gene expression”
- The reads are aligned to a reference genome **->** counts are quantified by sample **->** Joined in a matrix **->** Normalizad and adjusted **=** How much a gene is expressed in a sample?

Transcriptomics network



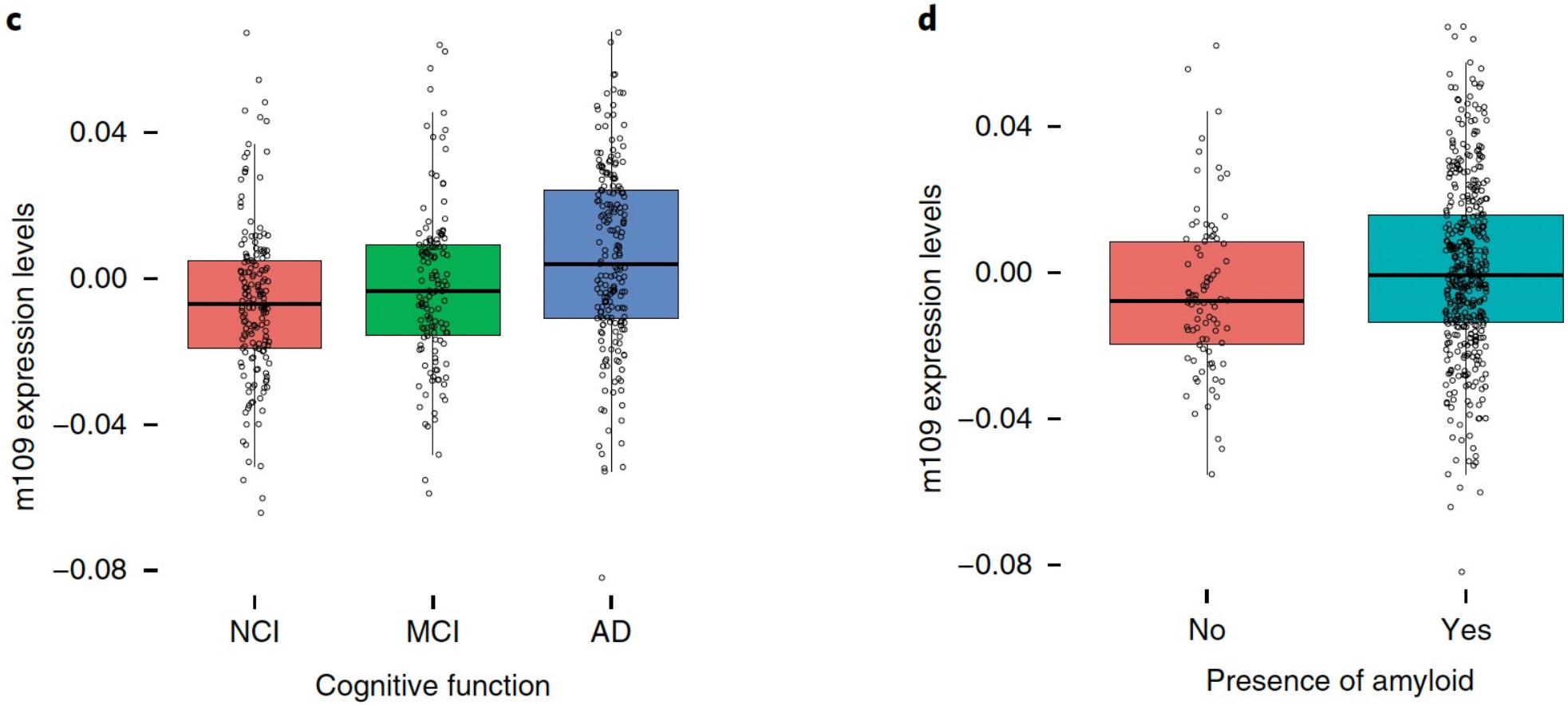
Mostafavi, Gaiteri et al. Nat Genetics, 2018.

Transcriptomics network



Mostafavi, Gaiteri et al. Nat Genetics, 2018.

Transcriptomics network

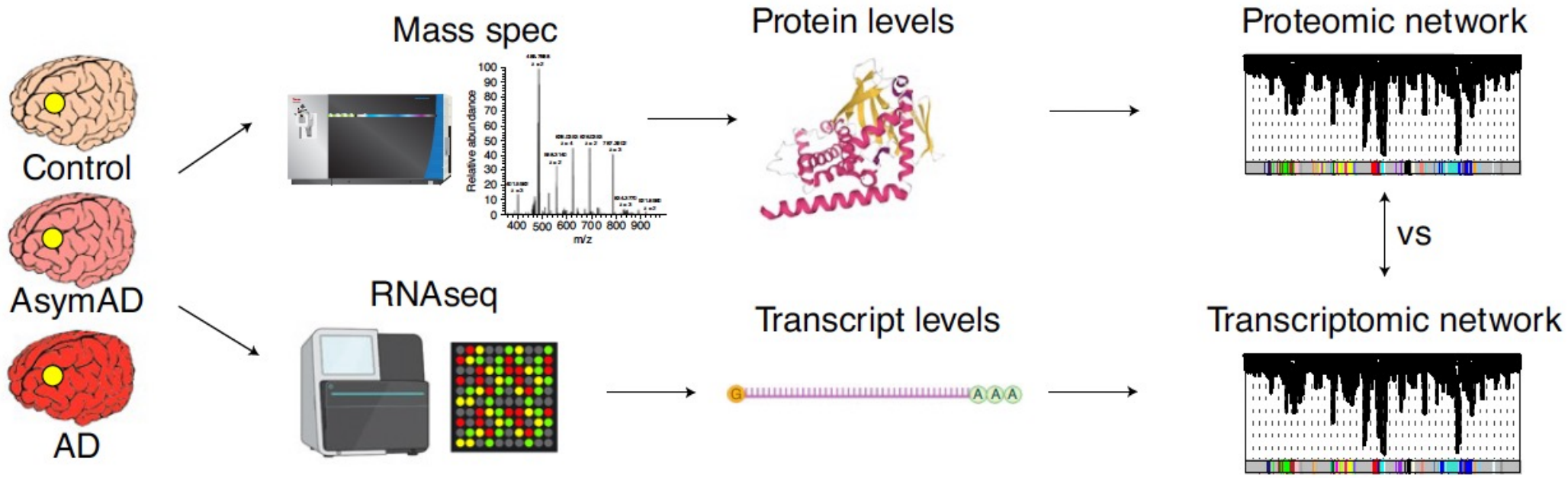


Mostafavi, Gaiteri et al. Nat Genetics, 2018.

Post-translational modifications of the proteome

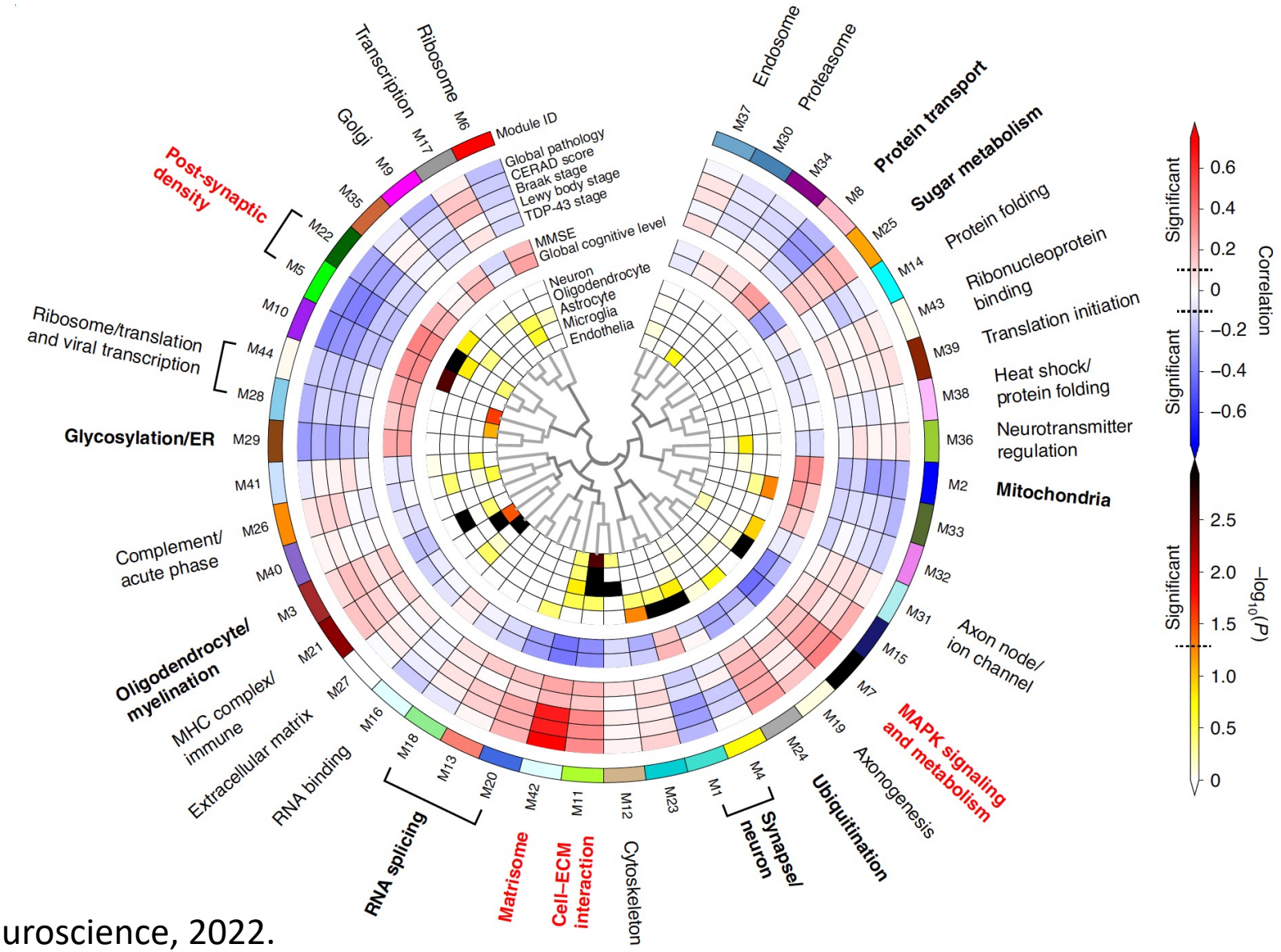
- Johnson et al. Nat Neuroscience, 2022 analyzed the proteome from ROSMAP
- They used WGCNA to create co-expression networks
- 8,619 proteins measured with TMT
- 516 individuals for the RNASeq

Post-translational modifications of the proteome



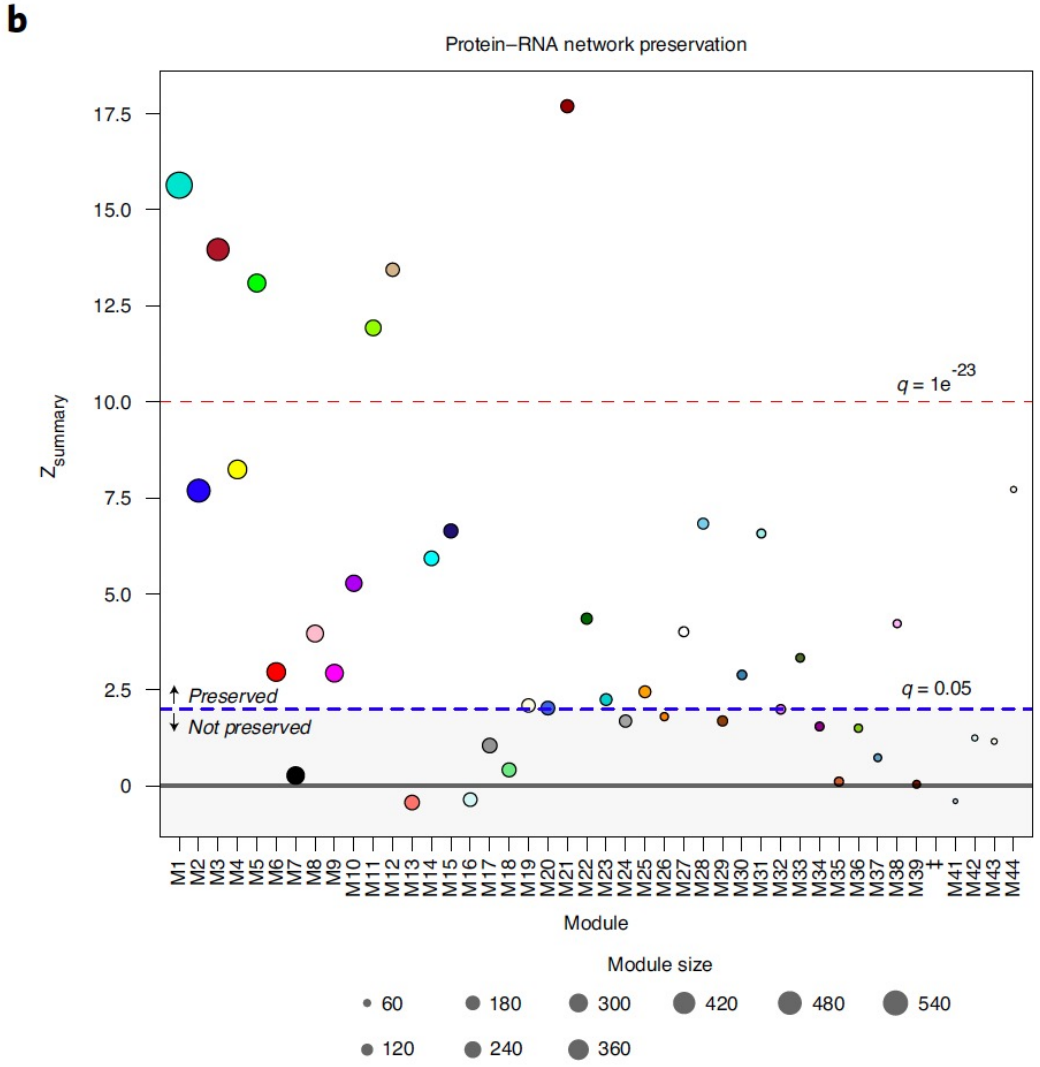
Johnson et al. Nat Neuroscience, 2022.

Post-translational modifications of the proteome



Johnson et al. Nat Neuroscience, 2022.

Post-translational modifications of the proteome



Protein modules not Preserved in RNA network		Correlation Path	Cog
M7	MAPK/metabolism	0.37	–0.42
M13	RNA splicing	0.03	–0.10
M16	RNA binding	–0.15	0.07
M17	transcription	0.05	–0.04
M18	RNA splicing	–0.07	–0.03
M24	**Ubiquitination**	**0.28**	**–0.25**
M26	Complement/acute phase	0.07	–0.01
M29	**Glycosylation/ER**	**–0.29**	**0.27**
M32	Ambiguous	–0.13	0.18
M34	Ambiguous	–0.07	0.07
M35	Ambiguous	–0.06	0.05
M36	Neurotransmitter regulation	0.07	–0.09
M37	Endosome	–0.02	–0.06
M39	Translation initiation	0.09	–0.06
M40	Ambiguous	0.03	–0.10
M41	Ambiguous	–0.06	–0.08
M42	Matrisome	0.75	–0.40
M43	Ribonucleoprotein binding	0.04	–0.08

Johnson et al. Nat Neuroscience, 2022.

Tasks

- Q1: What is one example of a network without Omics data?
- Q2: Besides network, what other data analysis can be done in the context of System's Biology?

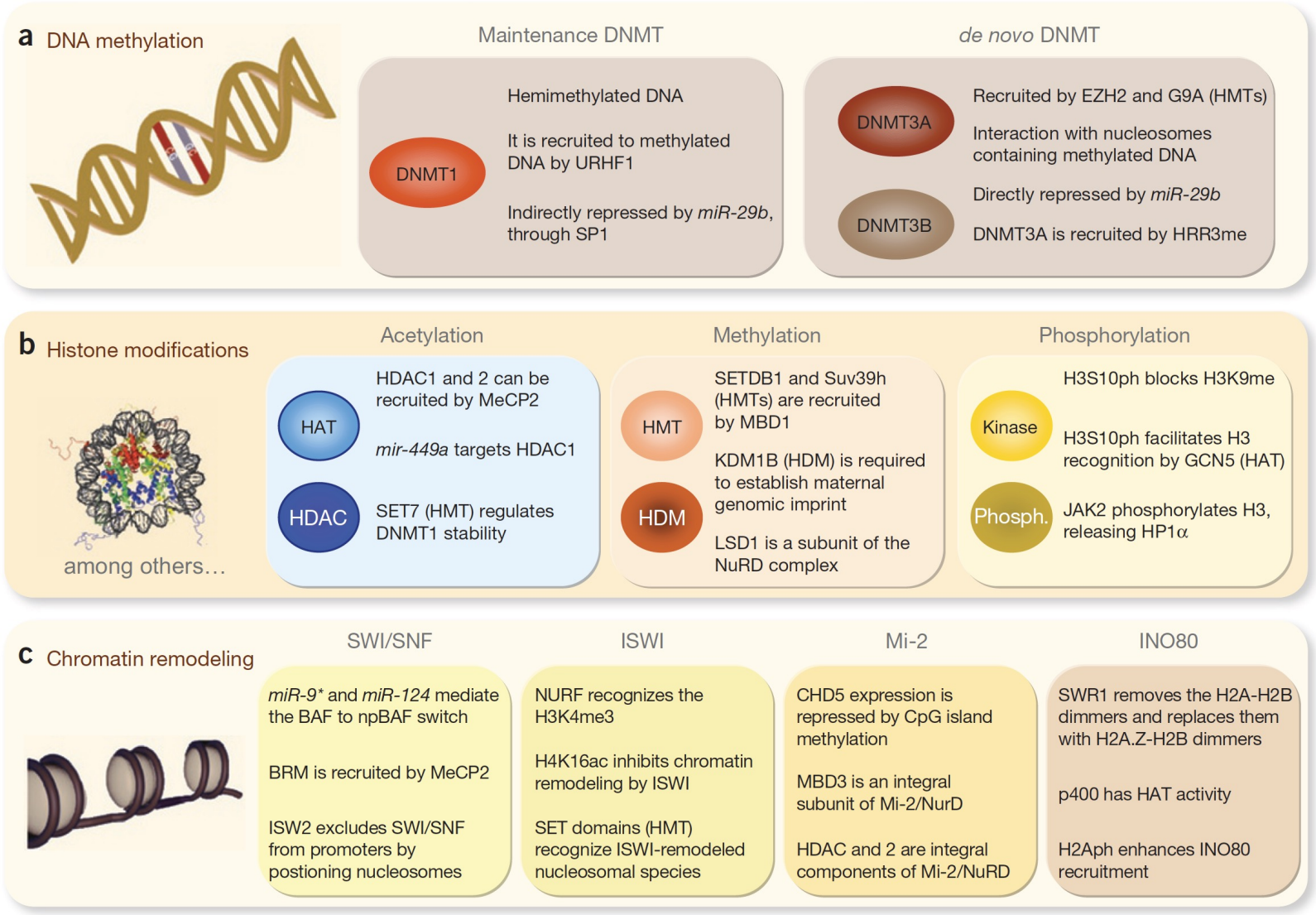
Epigenetics and network medicine

- Epigenetic marks include (not limited to):
  - Noncoding RNAs
  - Histone modifications
  - DNA methylation

- The complexity of methylation and demethylation events, and the interplay between the different epigenetic marks, supports the relevance of placing these observations in a network context.

Book edited by Loscalzo, Barabási and Silverman, Network Medicine 2017.

Epigenetics and network medicine



Portela & Esteller. Epigenetic modifications and human disease. Nat Biotech, 2010.

Epigenetics and network medicine

Table 1 Epigenetic modifications in human diseases

Aberrant epigenetic mark	Alteration	Consequences	Examples of genes affected and/or resulting disease
Cancer			
DNA methylation	CpG island hypermethylation	Transcription repression	*MLH1* (colon, endometrium, stomach[11]), *BRCA1* (breast, ovary[11]), *MGMT* (several tumor types[11]), *p16^{INK4a}* (colon[11])
	CpG island hypomethylation	Transcription activation	*MASPIN* (pancreas[92]), *S100P* (pancreas[92]), *SNCG* (breast and ovary[92]), *MAGE* (melanomas[92])
	CpG island shore hypermethylation	Transcription repression	*HOXA2* (colon[20]), *GATA2* (colon[20])
	Repetitive sequences hypomethylation	Transposition, recombination genomic instability	*L1* (ref. 11), *IAP*[11], *Sat2* (ref. 107)
Histone modification	Loss of H3 and H4 acetylation	Transcription repression	*p21^{WAF1}* (also known as *CDKN1A*)[11]
	Loss of H3K4me3	Transcription repression	*HOX* genes
	Loss of H4K20me3	Loss of heterochromatic structure	*Sat2*, *D4Z4* (ref. 107)
	Gain of H3K9me and H3K27me3	Transcription repression	*CDKN2A, RASSF1* (refs. 115–116)
Nucleosome positioning	Silencing and/or mutation of remodeler subunits	Diverse, leading to oncogenic transformation	*BRG1, CHD5* (refs. 127–131)
	Aberrant recruitment of remodelers	Transcription repression	*PLM-RARa*[103] recruits NuRD
	Histone variants replacement	Diverse (promotion cell cycle/destabilization of chromosomal boundaries)	H2A.Z overexpression/loss

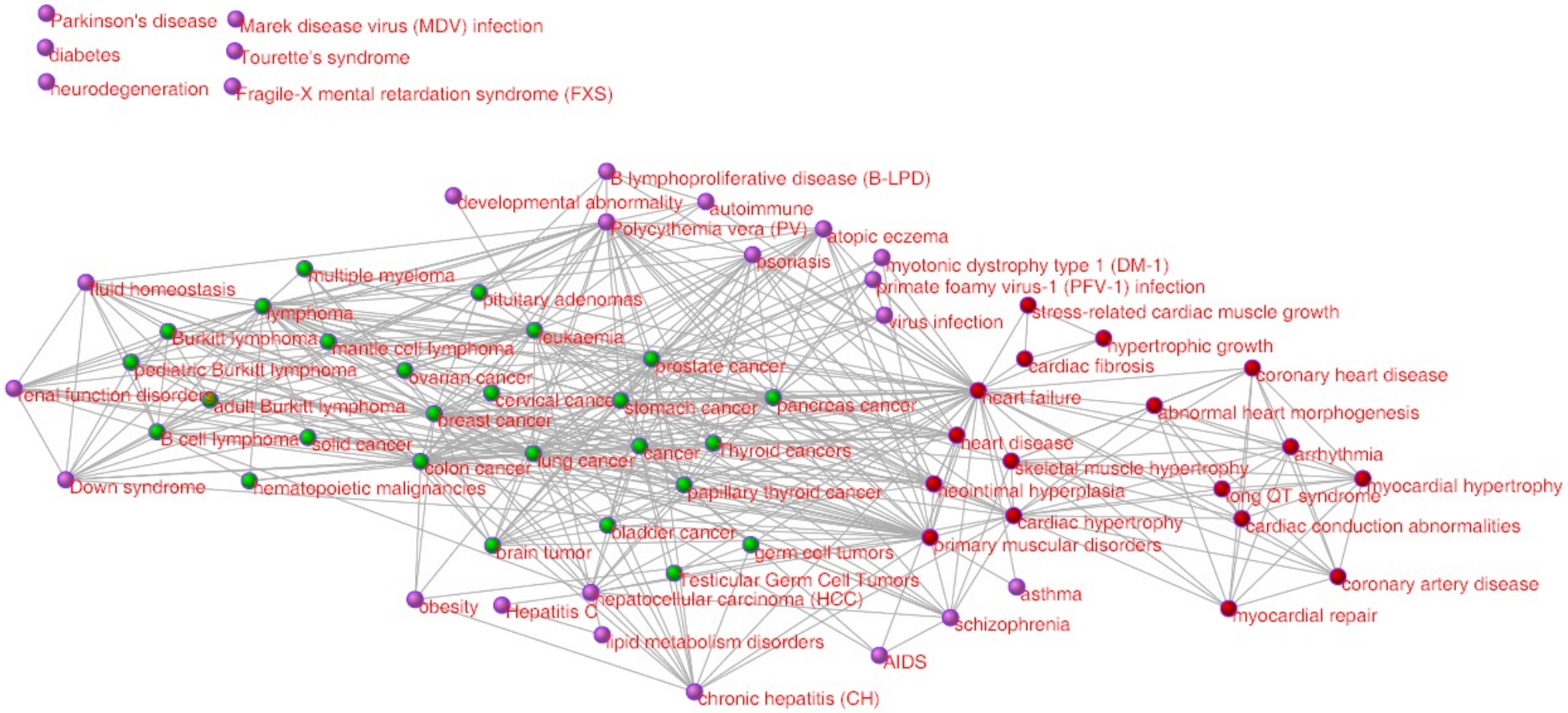
Portela & Esteller. Epigenetic modifications and human disease. Nat Biotech, 2010.

Epigenetics and network medicine

Neurological disorders			
DNA methylation	CpG island hypermethylation	Transcription repression	Alzheimer's disease (*NEP*)[135]
	CpG island hypomethylation	Transcription activation	Multiple sclerosis (*PADI2*)[135]
	Repetitive sequences aberrant methylation	Transposition, recombination genomic instability	ATRX syndrome (subtelomeric repeats)[135,143]
Histone modification	Aberrant acetylation	Diverse	Parkinson's and Huntington's diseases[135]
	Aberrant methylation	Diverse	Huntington's disease and Friedreich's ataxia[135]
	Aberrant phosphorylation	Diverse	Alzheimer's disease[135]
Nucleosome positioning	Misposition in trinucleotide repeats	Creation of a 'closed' chromatin domain	Congenital myotonic dystrophy[151]
Autoimmune diseases			
DNA methylation	CpG island hypermethylation	Transcription repression	Rheumatoid arthritis (*DR3*)[154,155]
	CpG island hypomethylation	Transcription activation	SLE (*PRF1*, *CD70*, *CD154*, *AIM2*)[6]
	Repetitive sequences aberrant methylation	Transposition, recombination genomic instability	ICF (*Sat2*, *Sat3*), rheumatoid arthritis (*L1*)[152,155]
Histone modification	Aberrant acetylation	Diverse	SLE (*CD154*, *IL10*, IFN-γ)[6]
	Aberrant methylation	Diverse	Diabetes type 1 (*CLTA4*, *IL6*)[159]
	Aberrant phosphorylation	Diverse	SLE (NF-κB targets)
Nucleosome positioning	SNPs in the 17q12-q21 region	Allele-specific differences in nucleosome distribution	Diabetes type 1 (*CLTA4*, *IL6*)
	Histone variants replacement	Interferes with proper remodeling	Rheumatoid arthritis (histone variant macroH2A at NF-κB targets)[157]

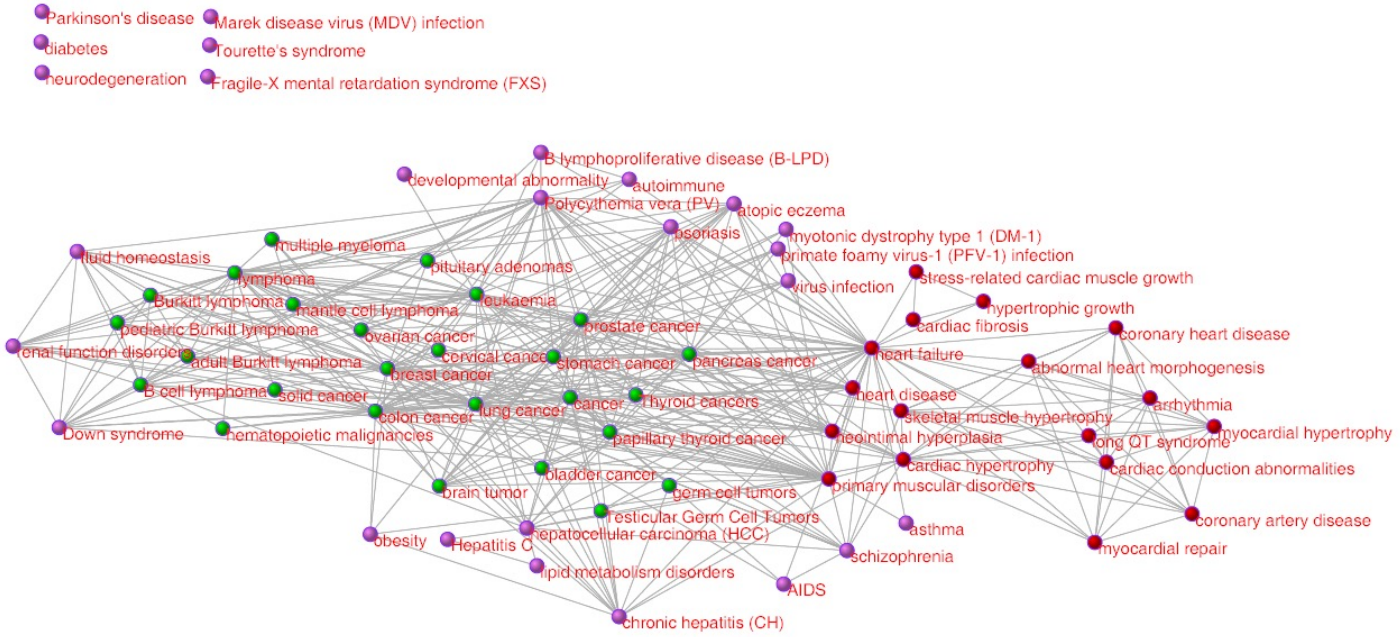
Portela & Esteller. Epigenetic modifications and human disease. Nat Biotech, 2010.

Epigenetics and network medicine



Lu et al. Plos One, 2008.

Epigenetics and network medicine

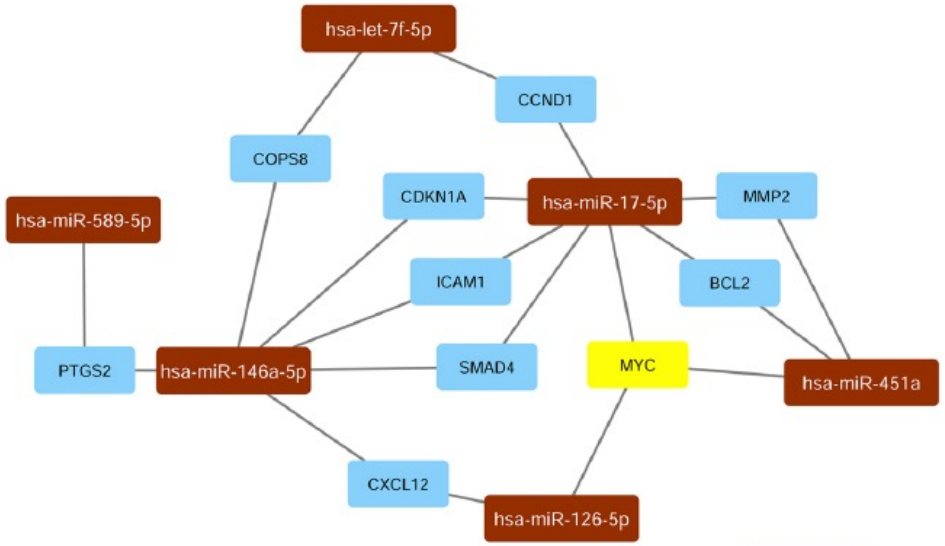


Characteristic	Interpretation
Input	Expression profile of 345 miRNAs in 40 tissues SNPs from public database to classify miRNAs in conserved or not across the diseases
Nodes	Complex diseases
Edges	Assign an edge to two diseases if they were associated with one common miRNA
Topology	Scale-free

Lu et al. Plos One, 2008.

Epigenetics and network medicine

hsa-let-7f-5p: **2** shared interactions
hsa-miR-126-5p: **2** shared interactions
hsa-miR-146a-5p: **6** shared interactions
hsa-miR-17-5p: **7** shared interactions
hsa-miR-451a: **3** shared interactions
hsa-miR-486-5p: **0** shared interactions (Excluded from network)
hsa-miR-589-5p: **1** shared interactions
hsa-miR-941: **0** shared interactions (Excluded from network)



More than 2 interactions: nodes coloured **Yellow**
2 interactions: nodes coloured **Blue**

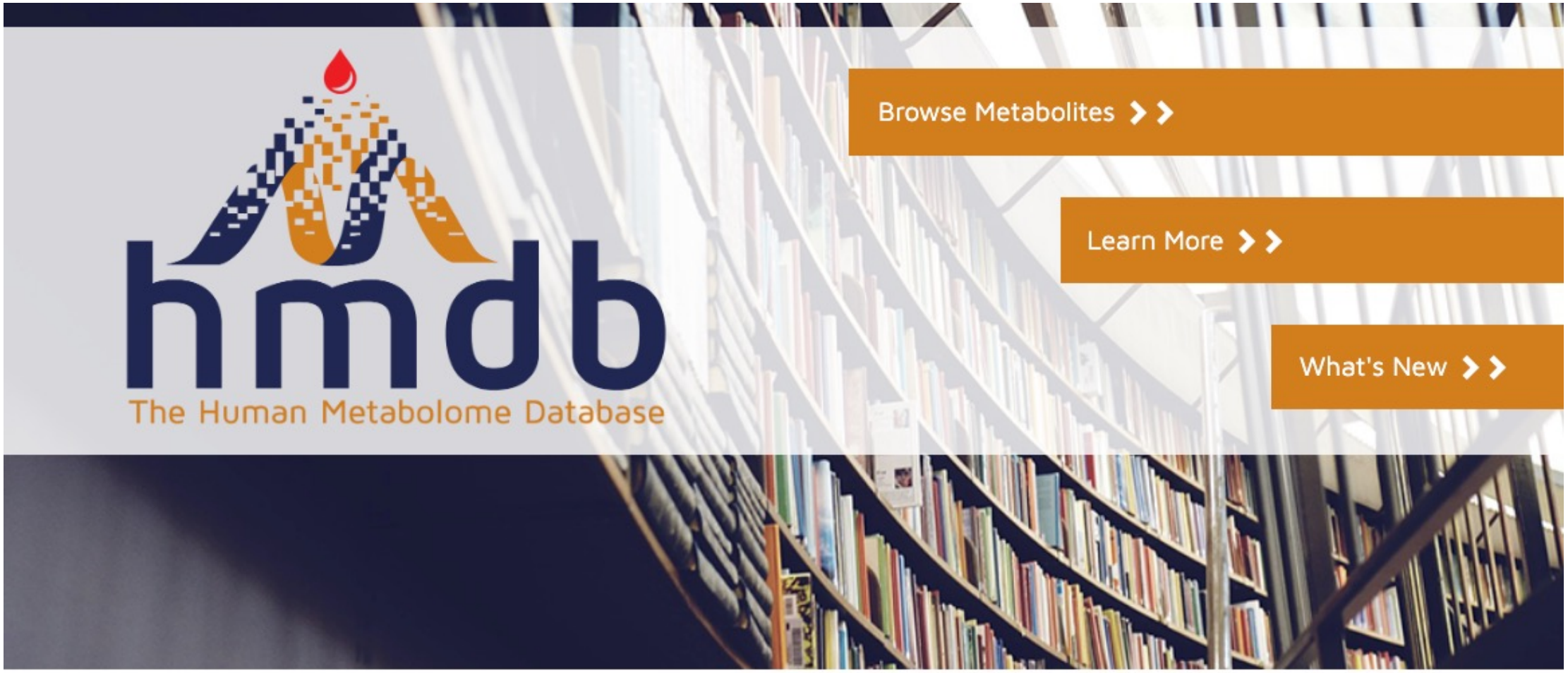
Lopes et al. Scientific Reports, 2018.

Metabolomics

- The molecules include carbohydrates, sugar, fatty acids, lipids, nucleotides, amino acids and short peptide chains.
- The total number of metabolites remains unknown and varies by specie.
- Challenges in measurement includes:
  - Differences in physical compounds
  - Analytical tools as nuclear magnetic resonance (NMR) and mass spectrometry (MS) have a linear dynamic range but the molecule concentration will exceed this
  - Differences in chemical stability

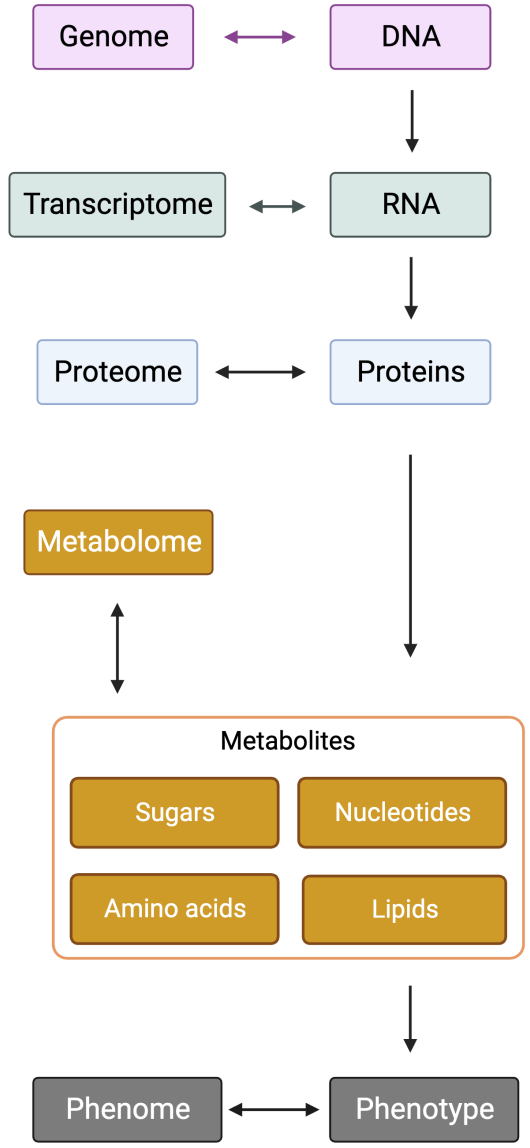
Book edited by Loscalzo, Barabási and Silverman, Network Medicine 2017.

Metabolomics



https://hmdb.ca/

Metabolomics



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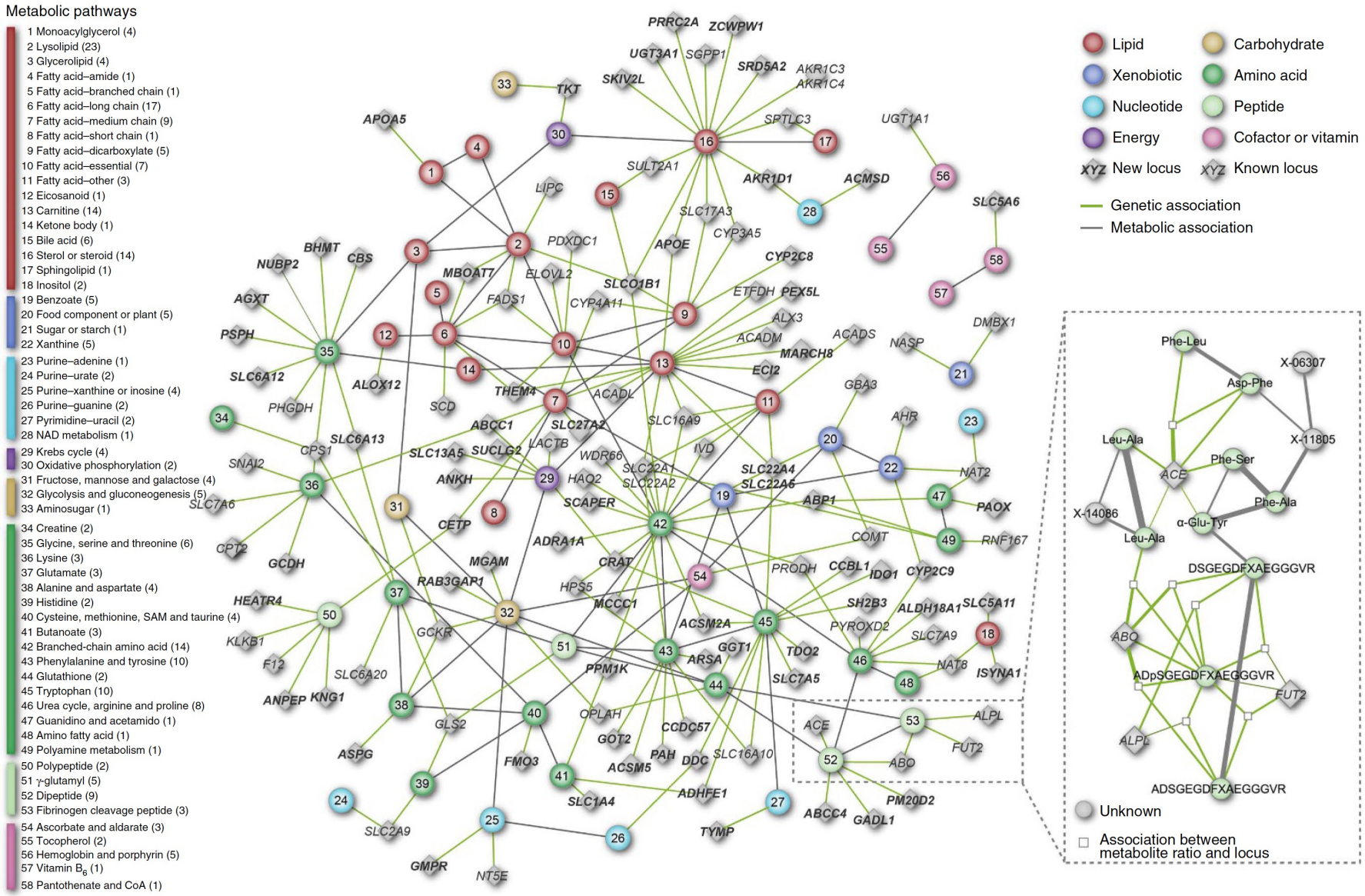
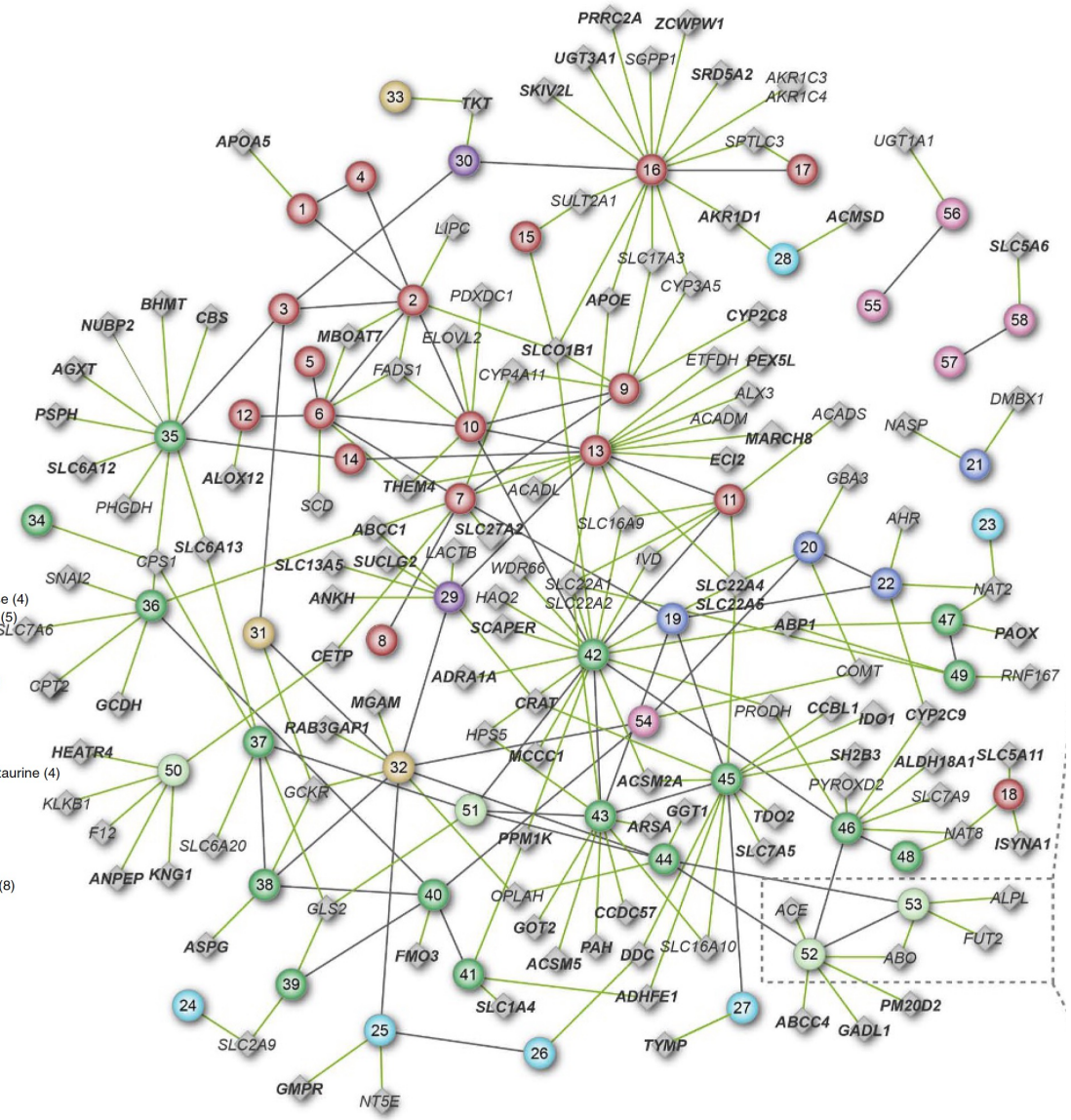
Metabolomics



Shin et al. Nat Genetics, 2013.

Metabolomics



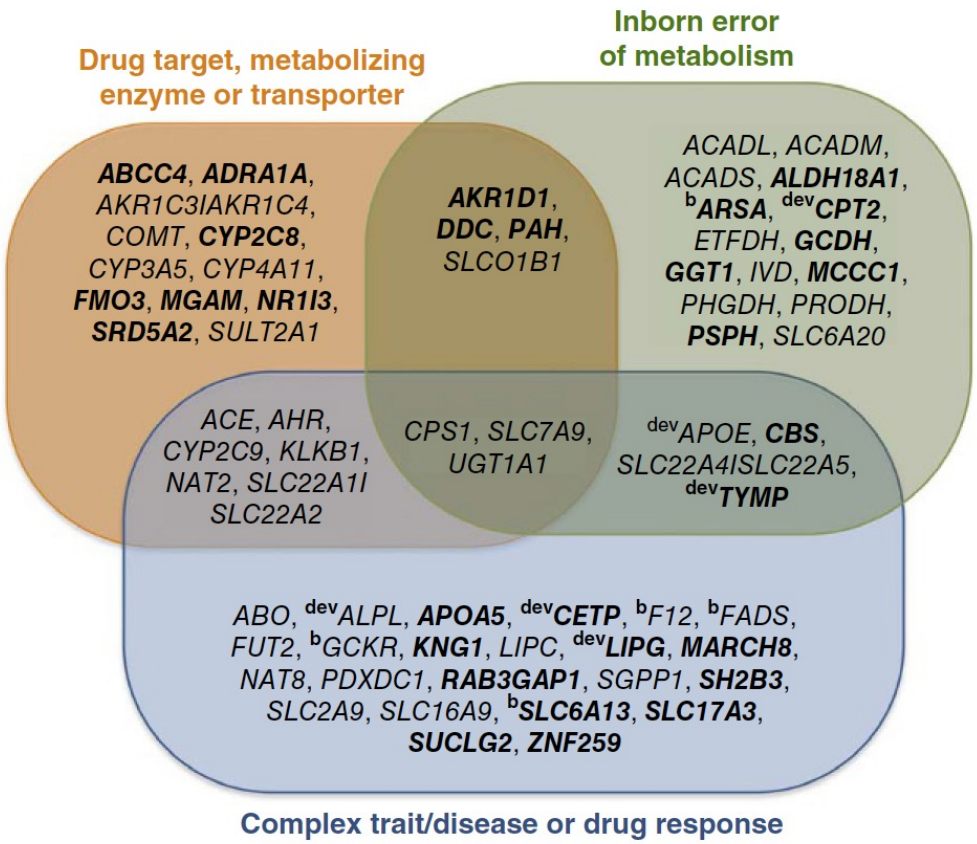
Shin et al. Nat Genetics, 2013.

Characteristic	Interpretation
Input	Combined genetic associations with metabolite concentrations
Nodes	Circular = set of metabolites belonging to the same pathway Diamond = Genetic locus
Edges	Gaussian graphical model (GGN) results. At least one connection in the underlying metabolite network between two metabolites
Topology	Scale-free

Numbers associated with each pathway name indicate the number of metabolites contained within each pathway node.

Metabolomics

Medical and pharmacological relevance of metabolomic associations



Enzyme
bABP1, ACMSD, ACSM2A, ACSM5, bADHFE1, AGXT, bALOX12, ANPEP, ASPG, bBHMT, bCCBL1, CRAT, ECI2, ELOVL2, GADL1, GBA3, GLS2, GMPR, GOT2, bHAO2, bIDO1, ISYNA1, bNT5E, OPLAH, PAOX, PPM1K, RNF167, devSCD, SKIV2L, SPTLC3, bTDO2, THEM4, devTKT, UGT3A1

Transporter
devABCC1, ANKH, bOSTalpha, SLC5A6, devSLC7A5, SLC13A5, SLC16A10, bSLC1A4, bSLC27A2, bSLC5A11, bSLC6A12, SLC7A6

Growth factor
ANGPTL3

Ion channel
PEX5L

Transcriptional regulator
ALX3, DMBX1, SNAI2

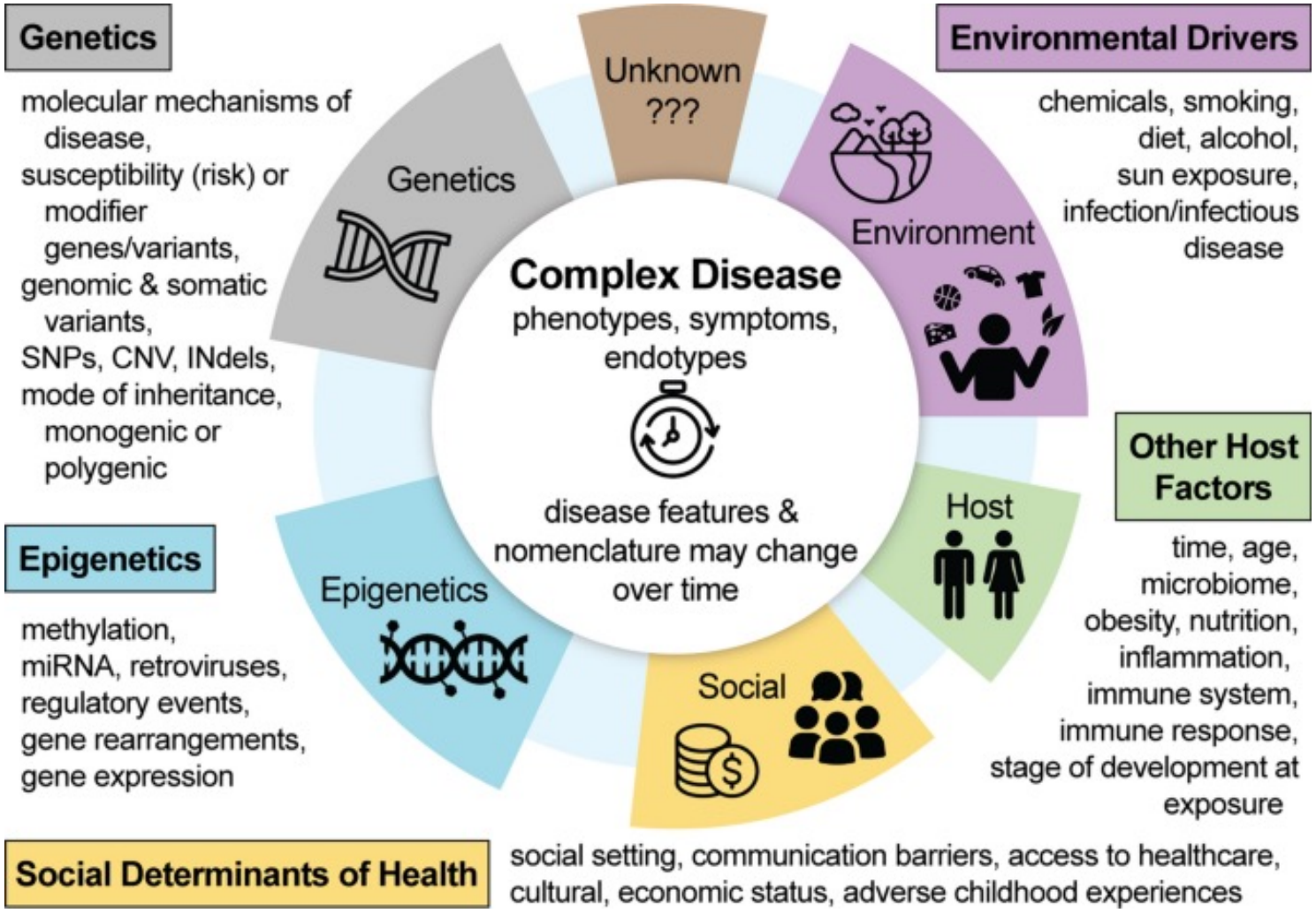
Other
CCDC57, DIP2C, HEATR4, HPS5, bLACTB, MBOAT7, NASP, NUBP2, PM20D2, PRRC2A, PYROXD2, SCAPER, WDR66, ZCWPW1

Shin et al. Nat Genetics, 2013.

Tasks

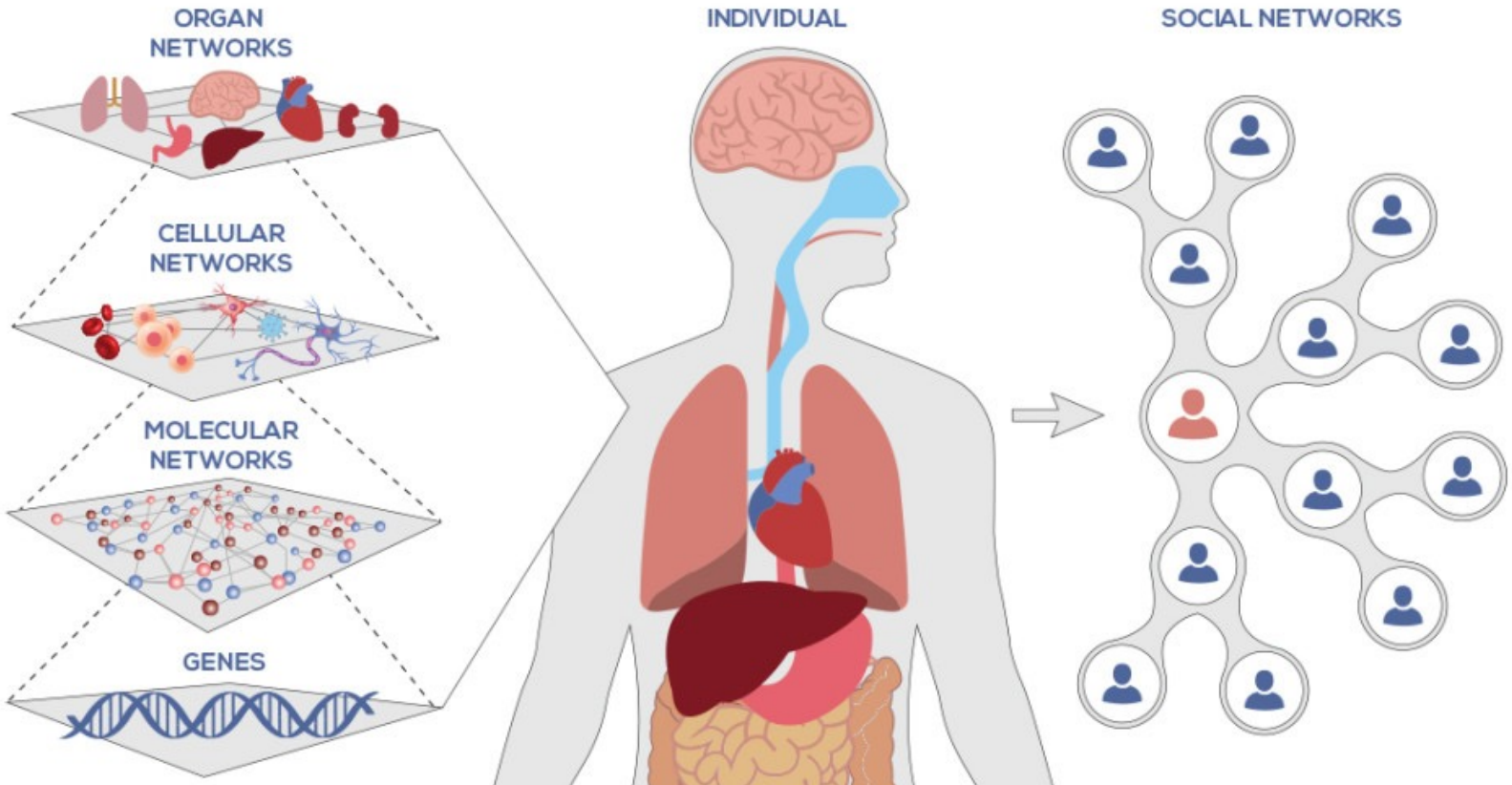
- Q1: List the networks we talked about today.
- Q2: Why network is widely used in Systems Biology?

Modeling the enigma of complex disease etiology



Schriml et al. Journal of Translational Medicine, 2023.

Network of networks



https://isbscience.org/about/what-is-systems-biology/

Thank you!

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