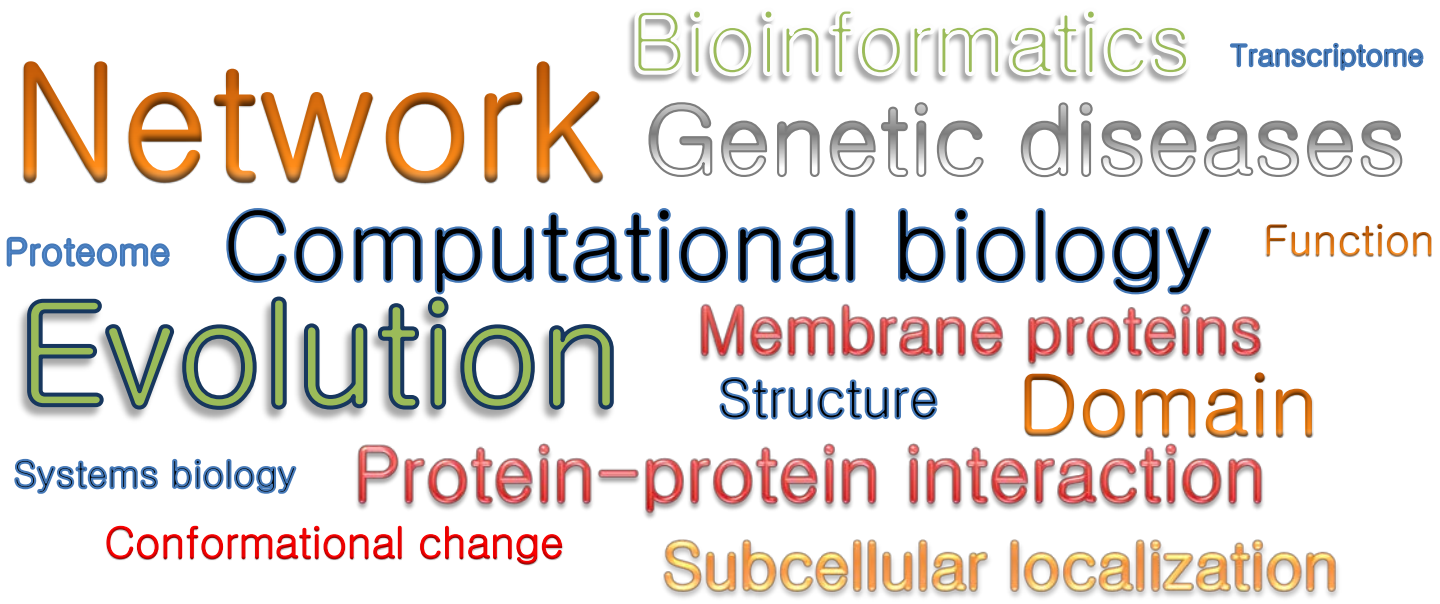
human disease network analysis reveals the clinical severity of genetic disorders

POSTECH
생명과학과 김상욱

Research Keywords



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Acknowledgement

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Bui Phuong Thao
Heetak Lee
Sangjin Han
Jinsuk Hong

Network Biology and Medicine

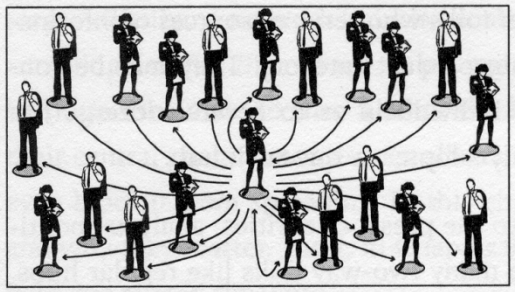
- Network Distance & Localization -> Disease Comorbidity ***Nature Mol Sys Biol.*** **2011**
  Human disease evolution ***Scientific Reports 2012***
  Mitochondrial protein network ***Scientific Reports 2013***

- Network Clustering -> Cancer ***PLoS Comp. Biol.*** **2011**

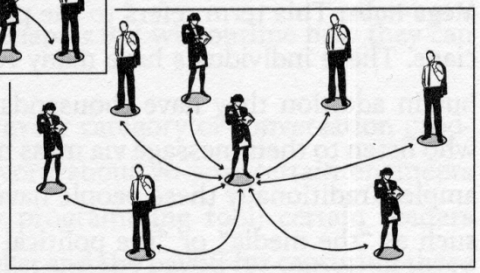
- Network Rewiring and Evolution -> Gene essentiality changes ***Scientific Reports 2012***
  Neuronal Disease ***PLoS Genetics*** **2012**

1. Spatial and functional organization of mitochondrial protein network. ***Scientific Reports 2013*** 3:1403.
2. Network rewiring is an important mechanism of gene essentiality change. ***Scientific Reports 2012*** 2:900.
3. Rewiring of PDZ domain-ligand interaction network contributed to eukaryotic evolution. ***PLoS Genetics*****. 2012** 8(2):e1002510.
4. Evolutionary history of human disease genes reveals phenotypic connections and comorbidity among genetic diseases. ***Scientific Reports 2012*** 2:757.
5. A multifunctional core-shell nanoparticle for dendritic cell-based cancer immunotherapy ***Nature Nanotechnology*** **2011** 6(10):675-682.
6. Network clustering revealed the systemic alterations of mitochondrial protein expression" ***PLoS Comp. Biol.*** **2011** 7(6):e1002093.
7. Protein localization as a principal feature of the etiology and comorbidity of genetic diseases ***Nature Mol Sys Biol.*** **2011** 7:494.

Society

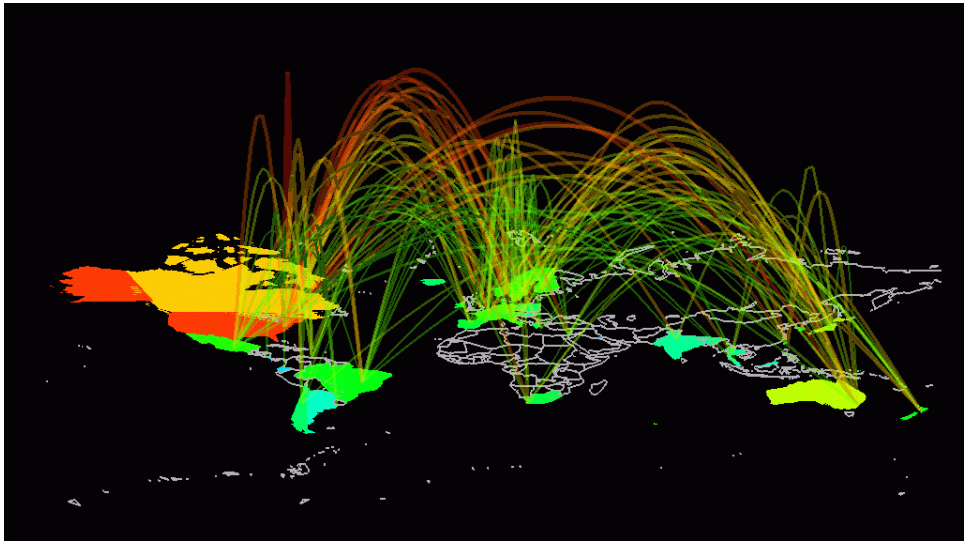


Mega-Hub. An MTV veejay spreads the word to thousands or millions of people through one-way links.

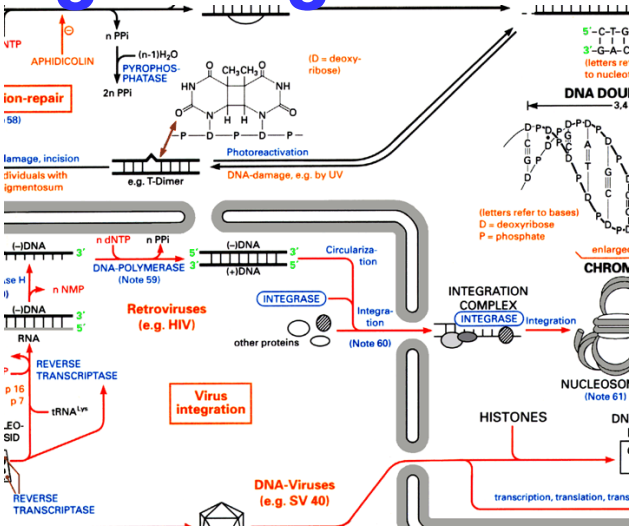


Hub. This undergraduate has spread the word to seven other people through two-way links.

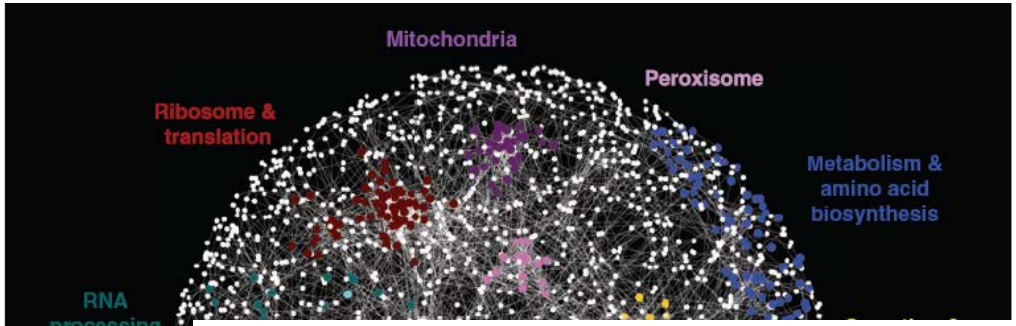
Internet

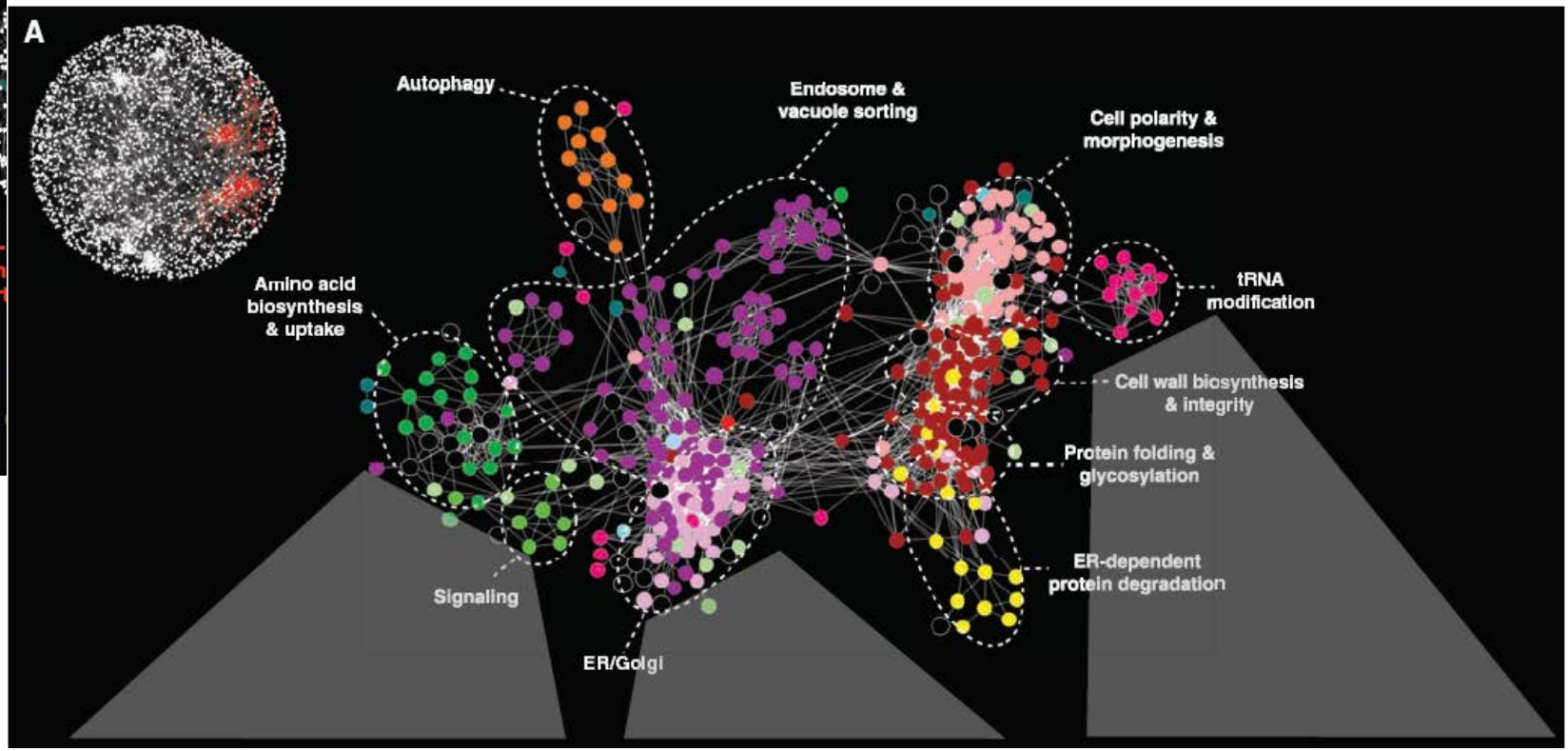


Biological signaling network



Biological Network

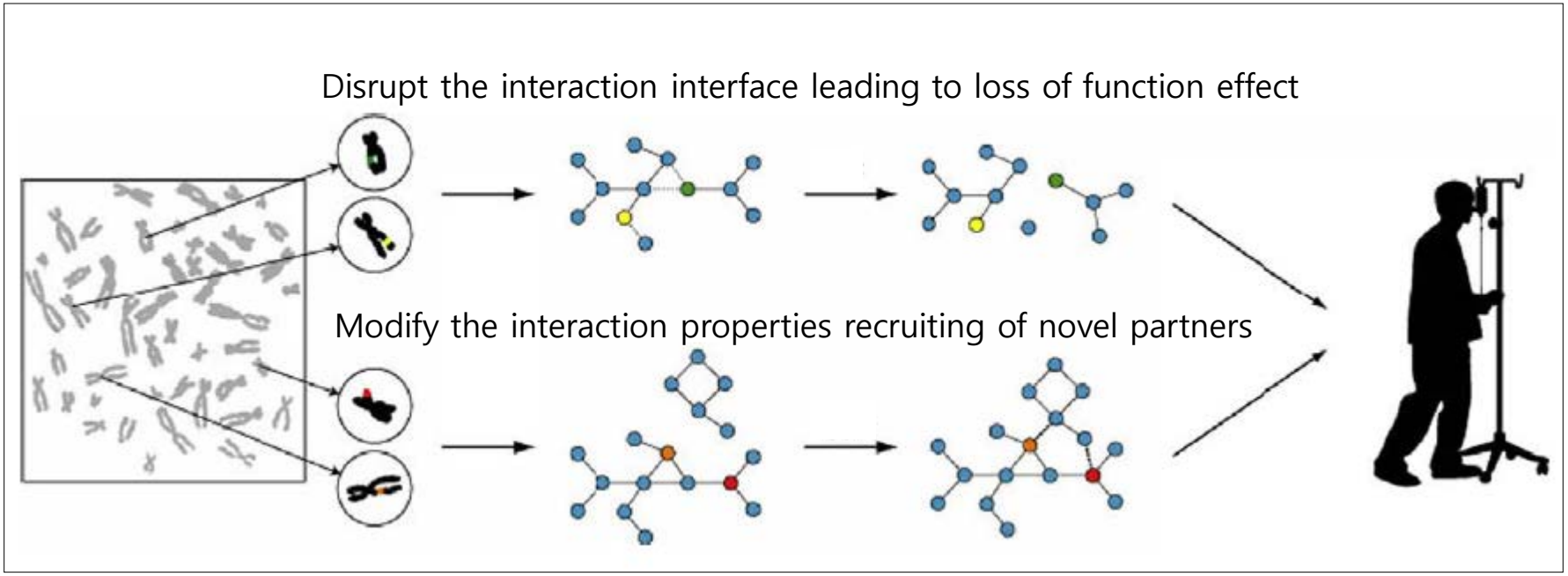




Disease pleiotropy and network modularity

Costanzo et al. The Genetic Landscape of a Cell. Science (2010) vol. 327 (5964) pp. 425
http://www.sciencemag.org/cgi/content/full/327/5964/425

Disease mechanism in the protein interaction network

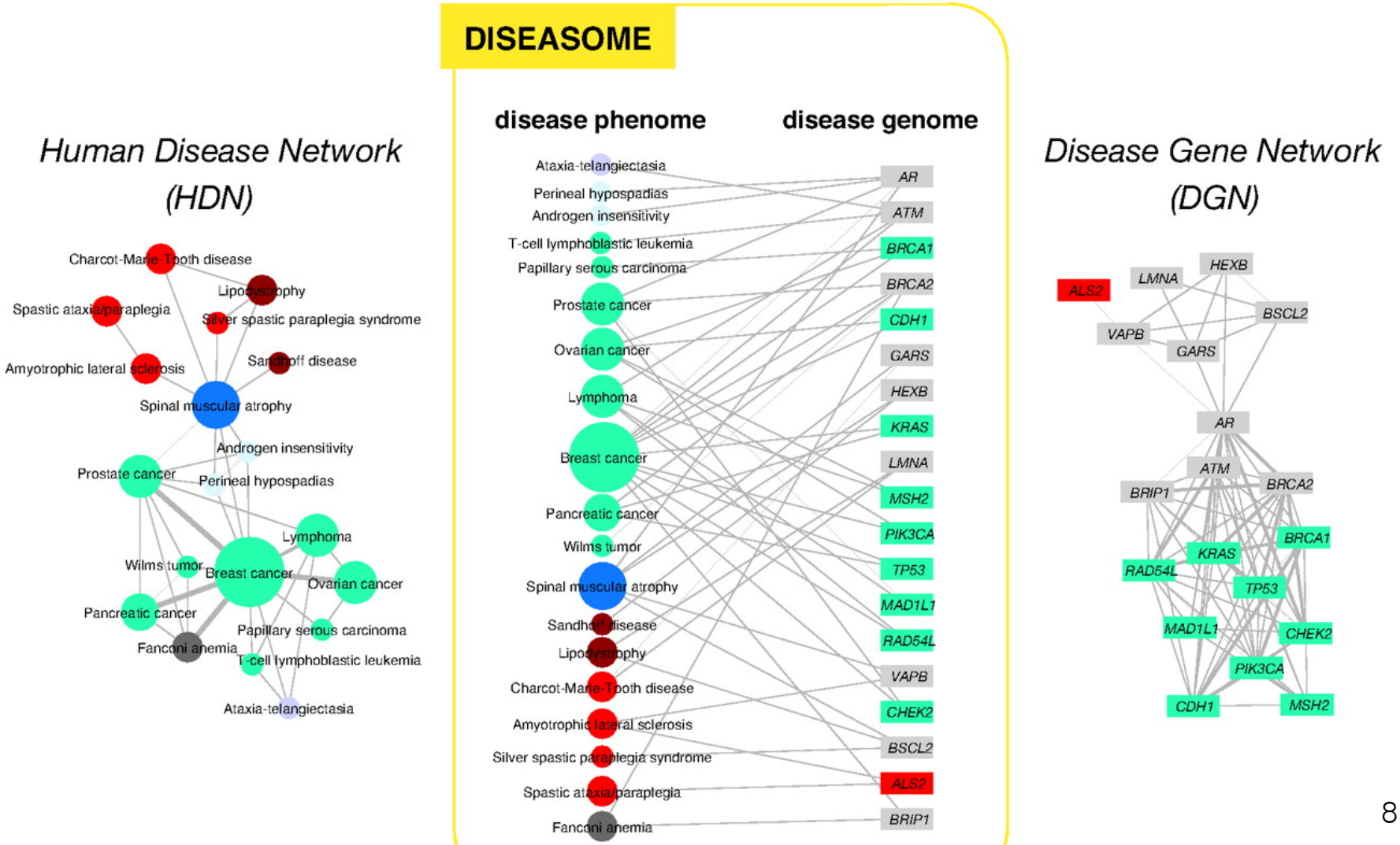


Major issues of Network Medicine

Medical language system, Biomedical vocabularies, Clinical repository
Disease classification, Disease gene mapping, Network medicine, Autonomic diagnosis

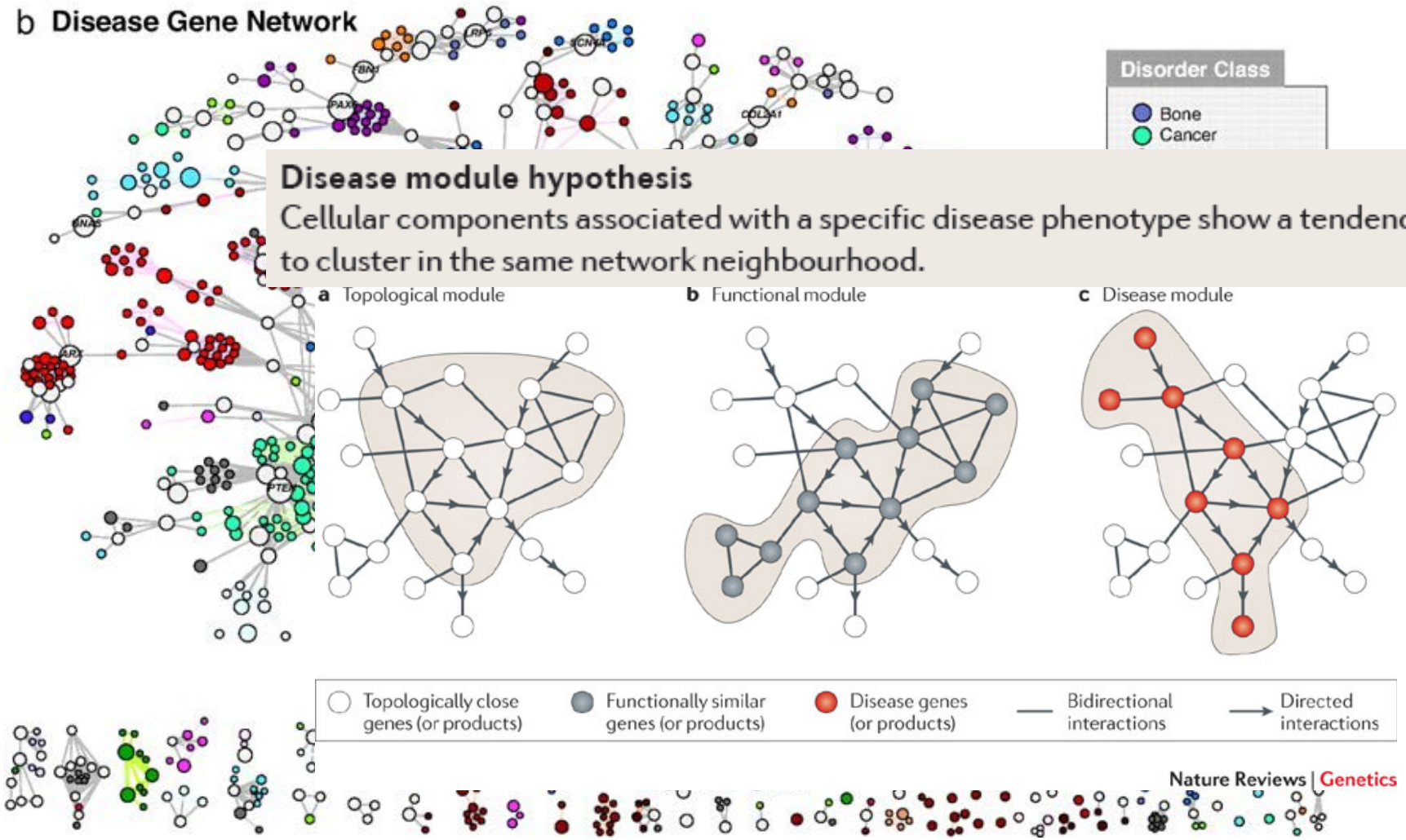
The human disease network

Construction of the diseasome bipartite network

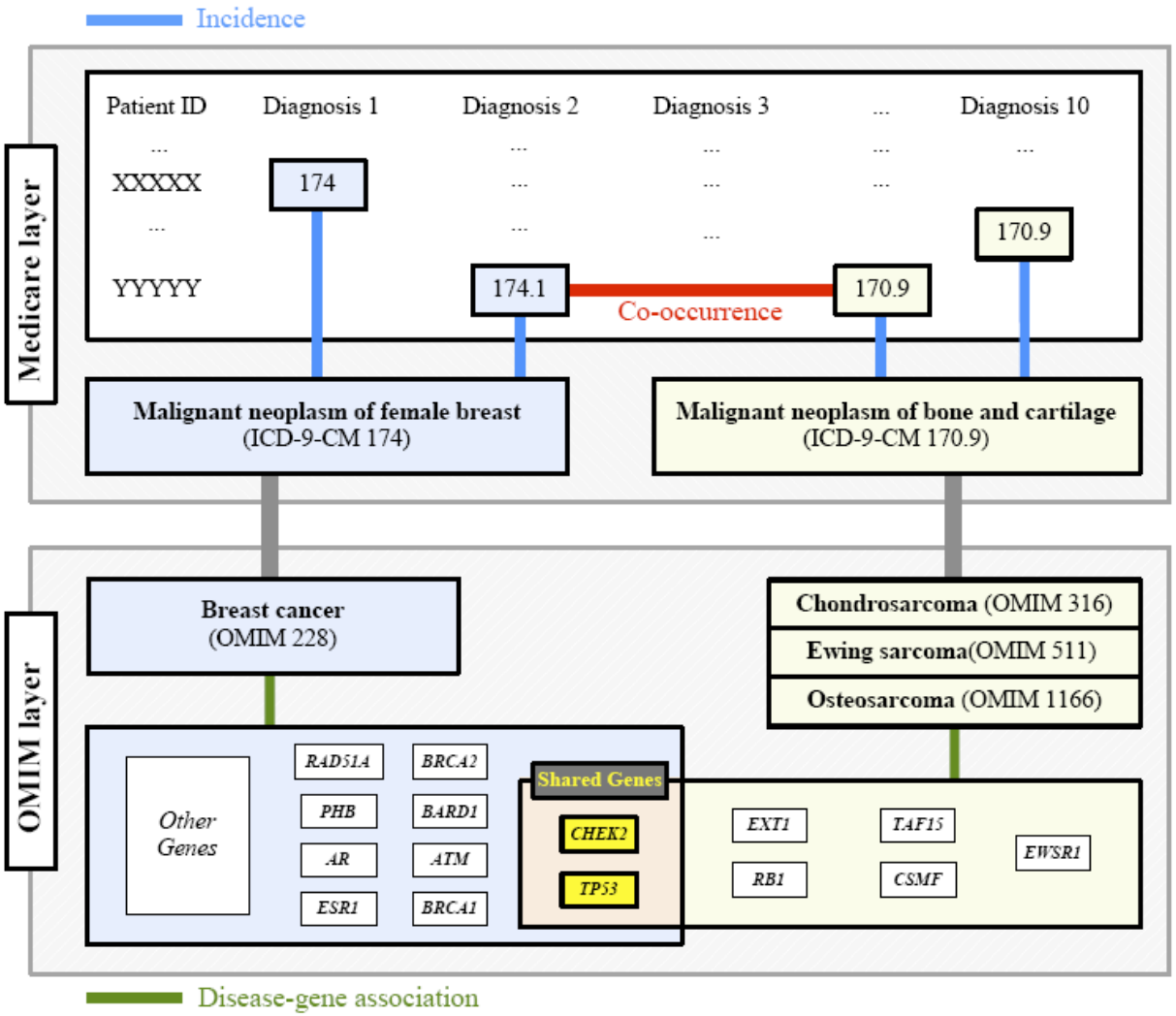


PNAS | May 22, 2007 | vol. 104 | no. 21 | 8685–8690

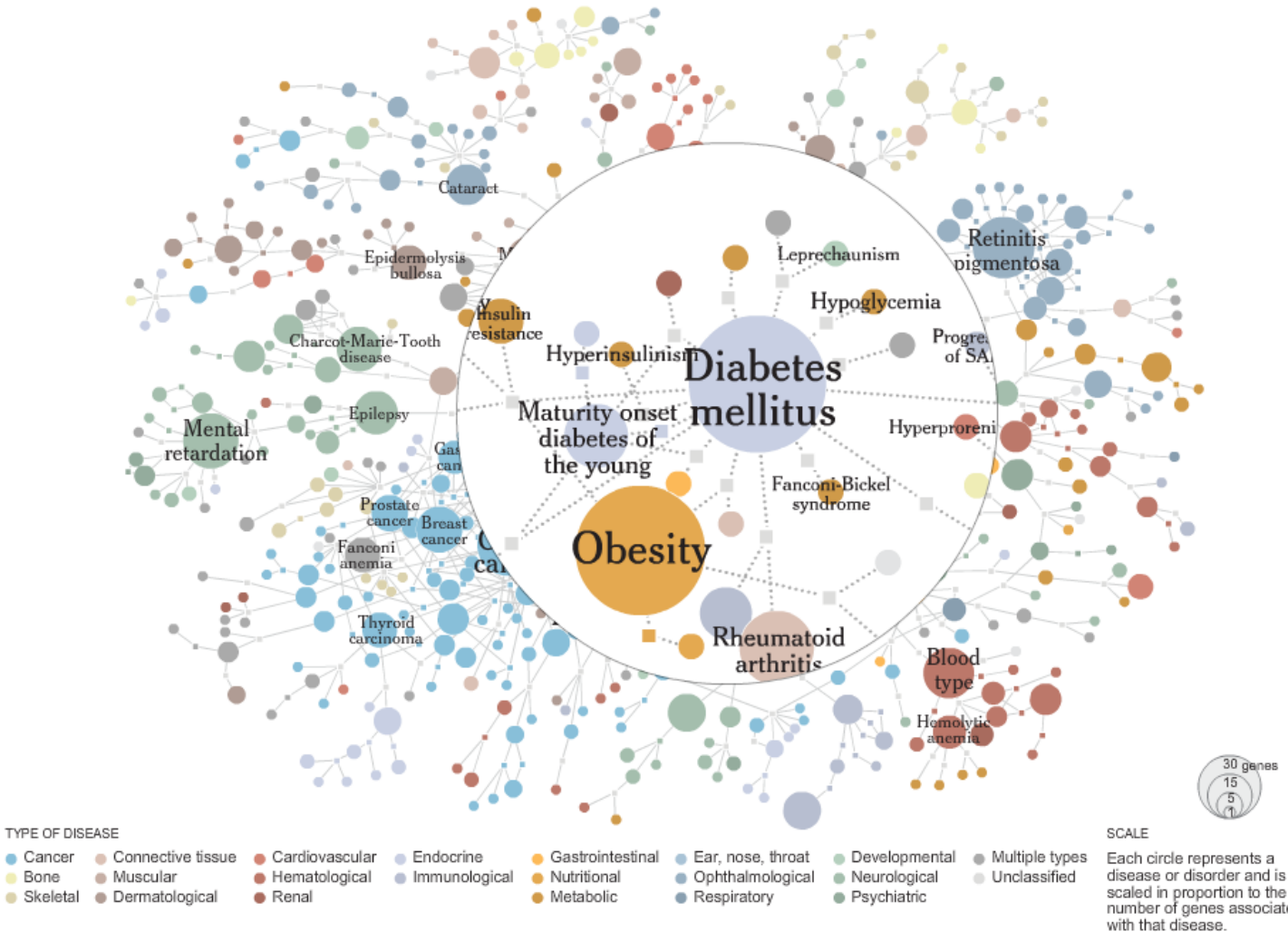
Disease Gene Network



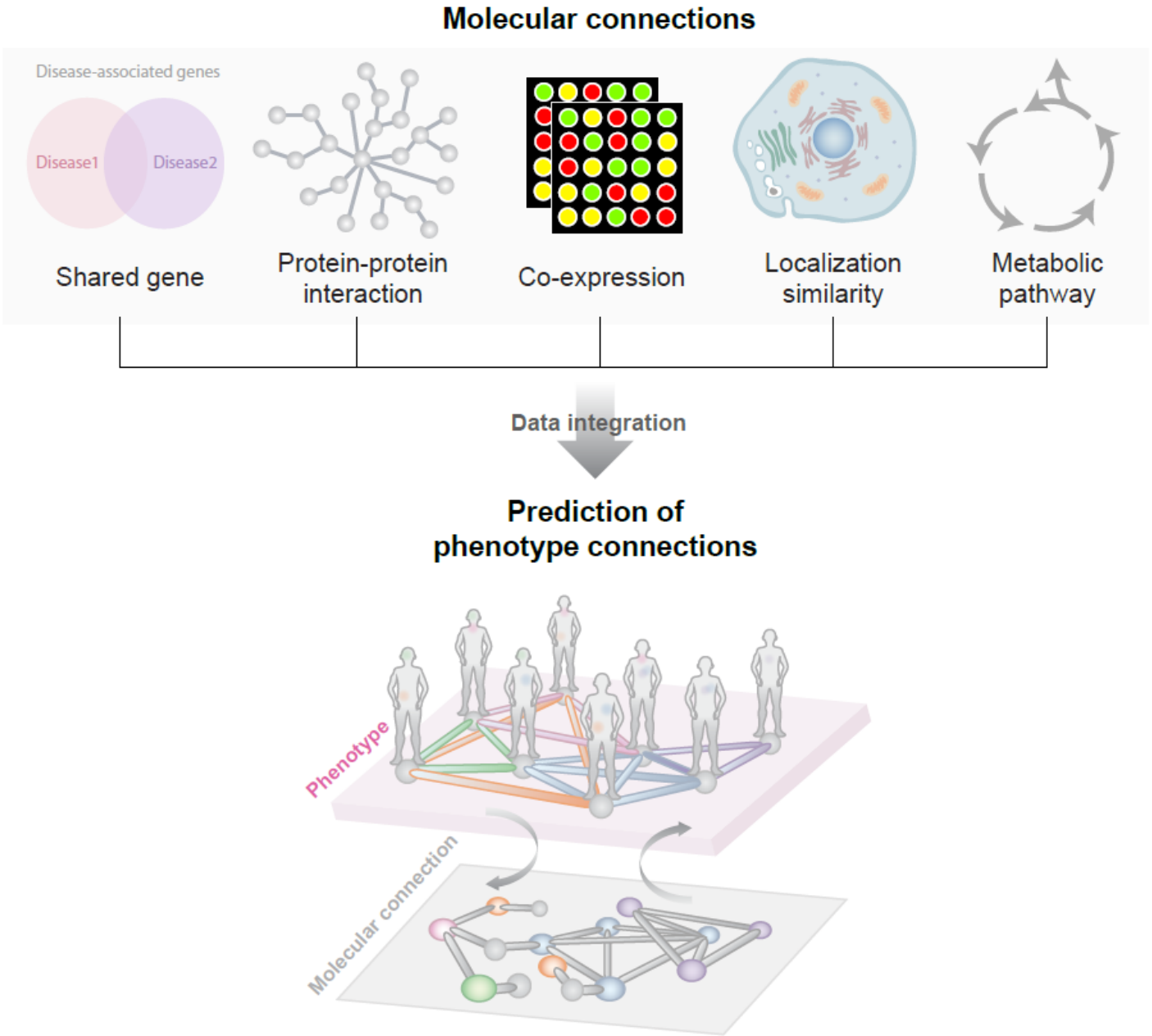
Procedures to connect comorbidity and genetic associations



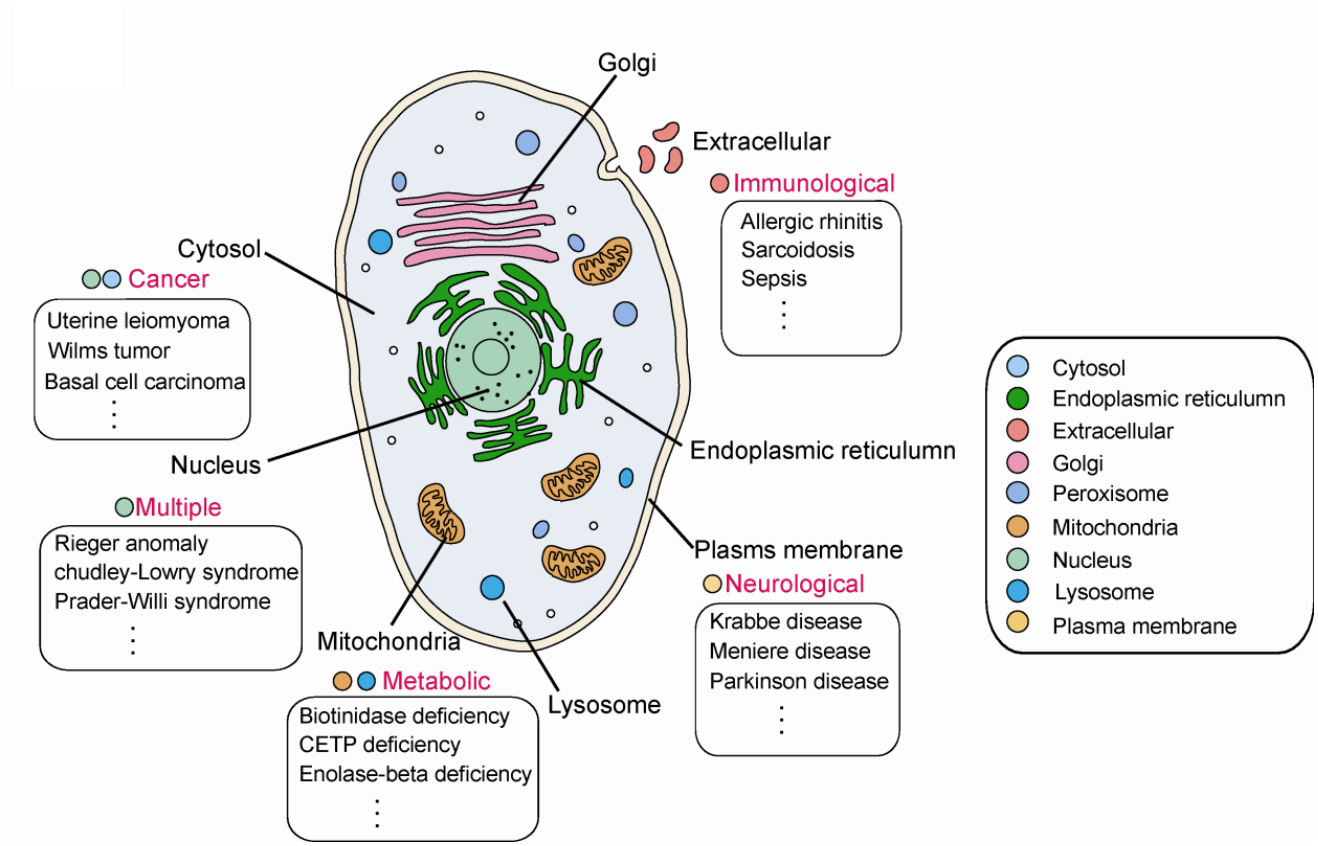
Example: Diabetes in the Human disease network



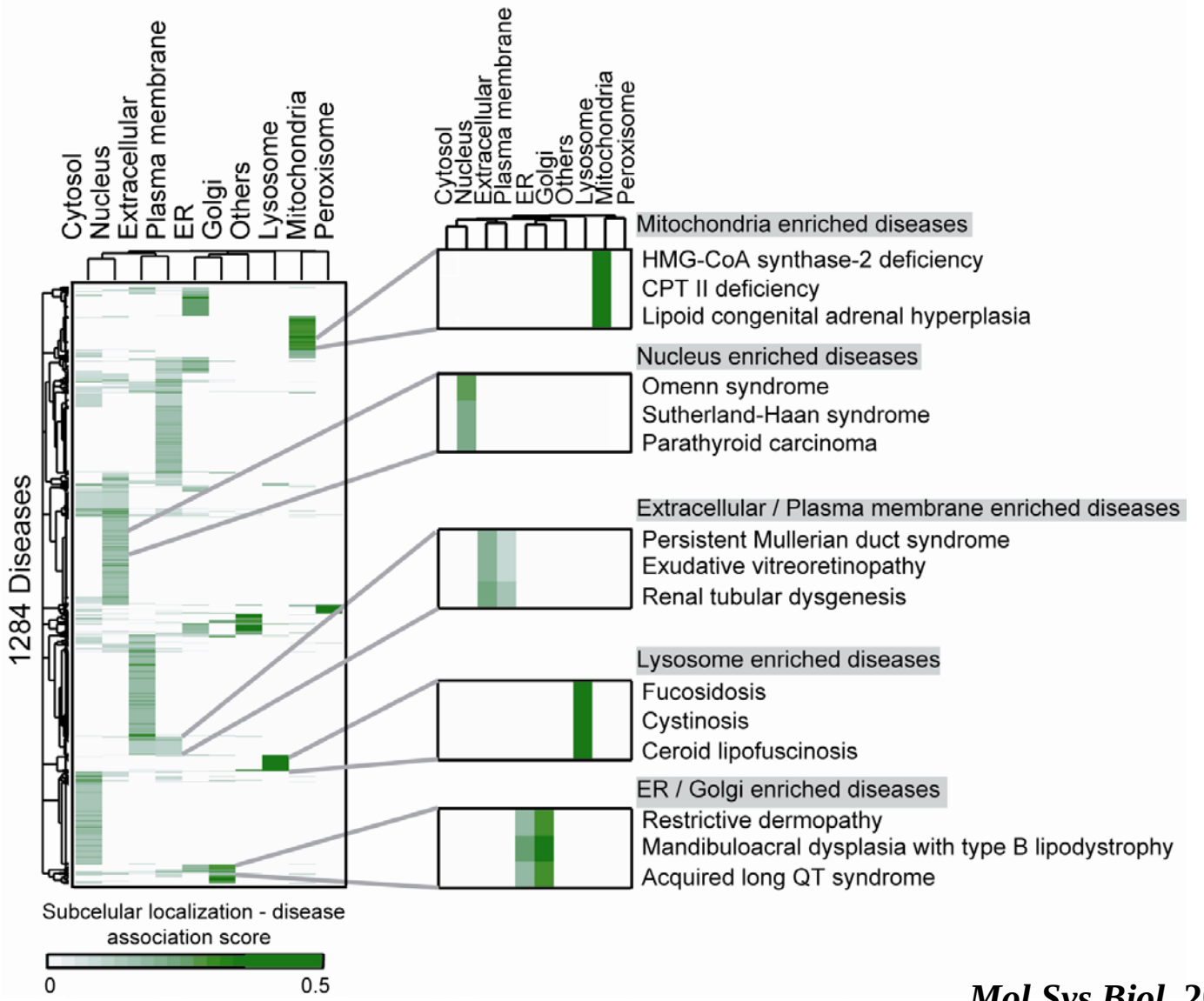
Integrative approach to predict phenotype connections



Protein subcellular localization and Human diseases

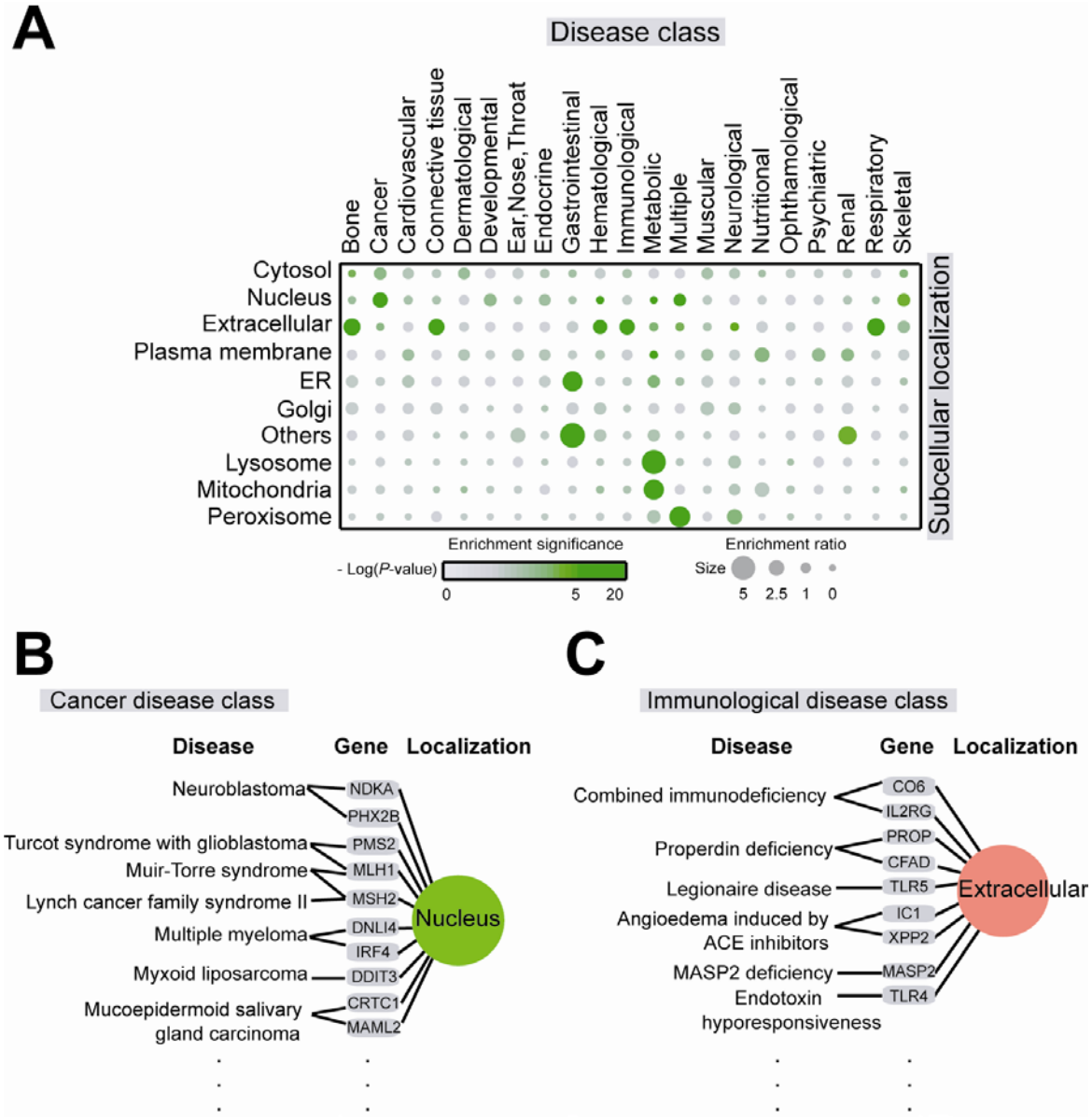


Relationships between disease-associated proteins and their subcellular localizations



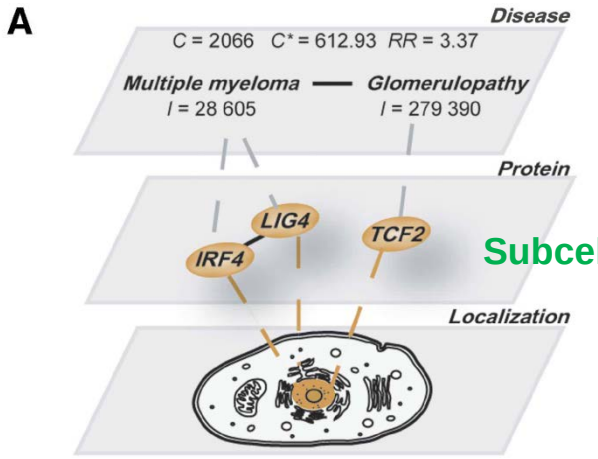
Mol Sys Biol. **2011** 7:494.

Correlation between disease classes and subcellular localizations

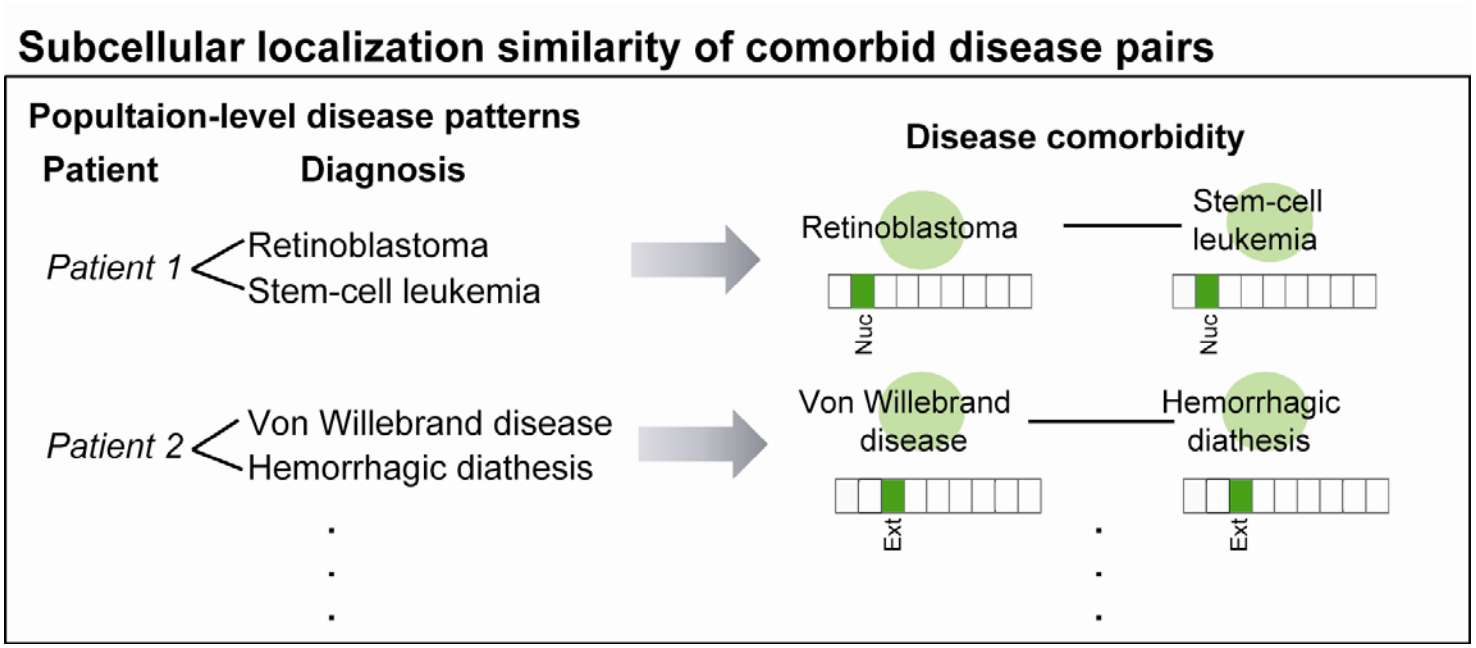


Mol Sys Biol. **2011** 7:494.

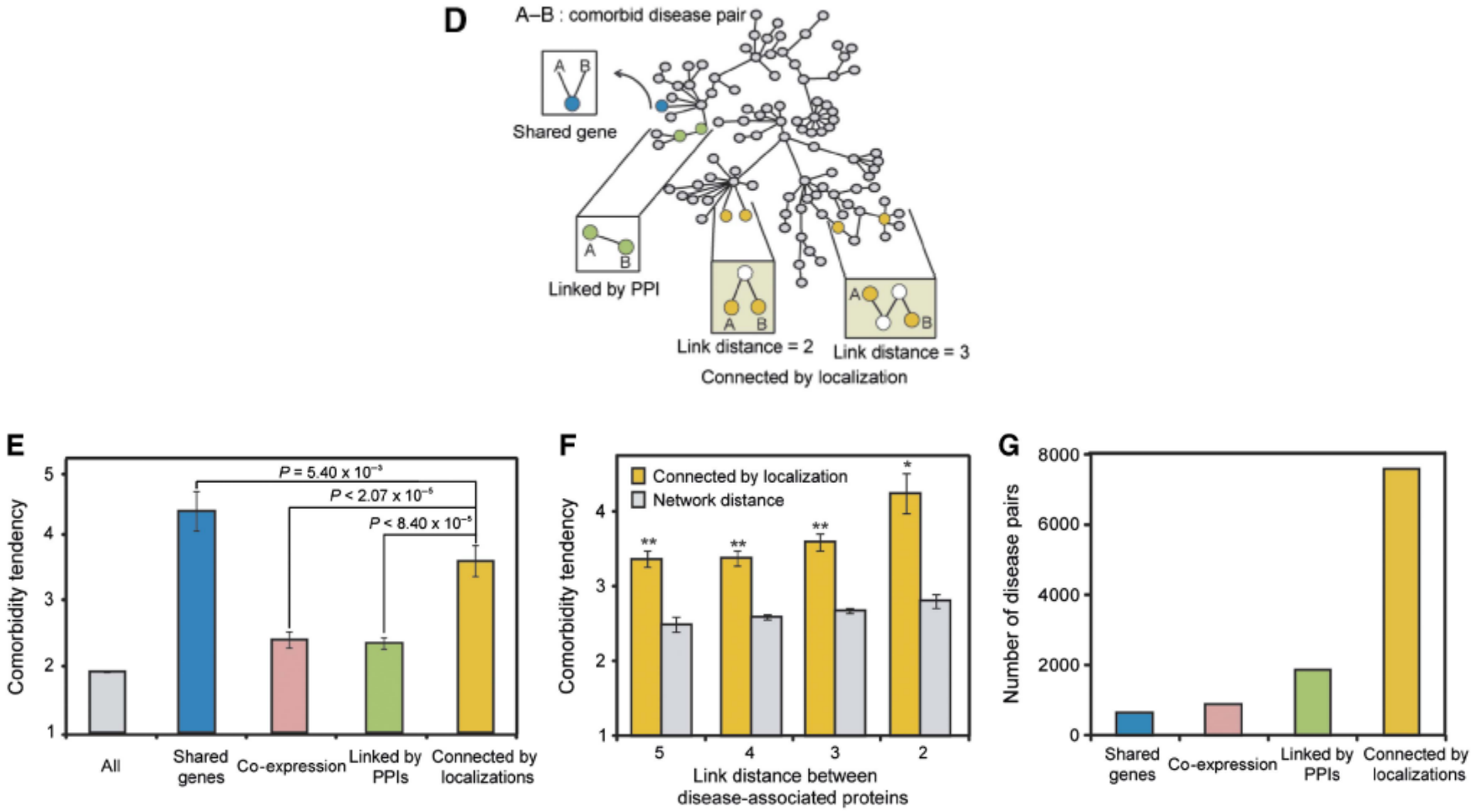
The implication of subcellular localization for disease comorbidity



Subcellular localization similarity of human diseases

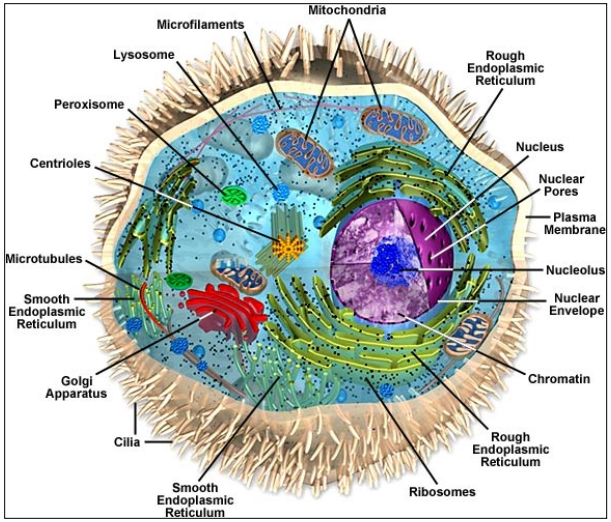


The implication of subcellular localization for disease comorbidity



Mol Sys Biol. **2011** 7:494.

Subcellular localization and human diseases

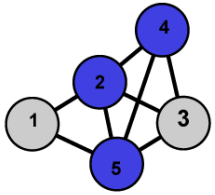


Construction of functional interaction networks through consensus localization predictions of the human proteome.

Park et .al..J. Proteome Res., **2009**, *8* (7), pp 3367–3376

A

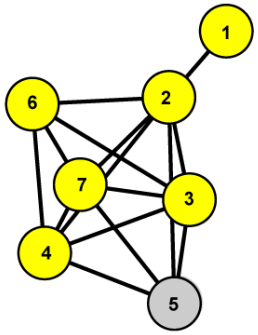
Localization: Plasma membrane
Disease: Basal cell carcinoma



1: GP107_Human
2: PTC1_Human
3: HHIP_Human
4: SMO_Human
5: PTC2_Human

B

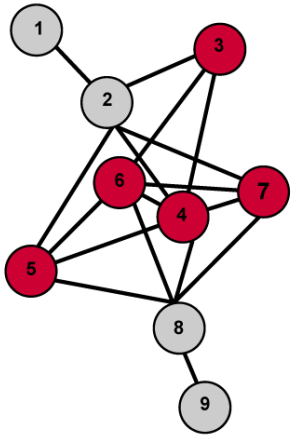
Localization: Cytosol
Disease: Deafness, autosomal dominant



1: MYO3A_Human (Con)
2: WHRN_Human
3: MYO15_Human
4: OMP_Human
5: MYO6_Human
6: MYO7A_Human
7: USH1C_Human (Con)

C

Localization: Nucleus
Disease: Mental retardation



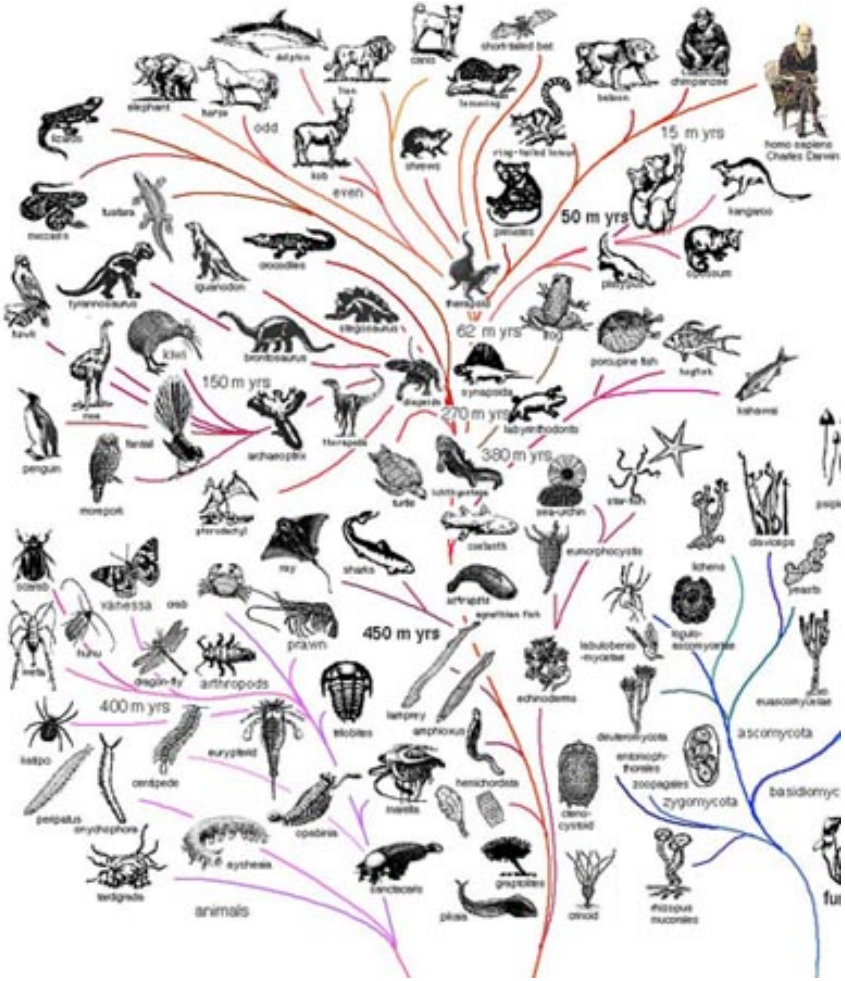
1: VEX2_Human (Con)
2: ARX_Human
3: ZNF81_Human
4: JADIC_Human
5: AFF2_Human (Con)
6: OPHN1_Human
7: ZNF41_Human (Con)
8: ACSL4_Human
9: TMEM9_Human

> Protein localization information facilitates the identification of disease associated genes

Evolutionary history of human disease genes reveals phenotypic connections and comorbidity among genetic diseases

A philosophical question?

Evolution of human diseases

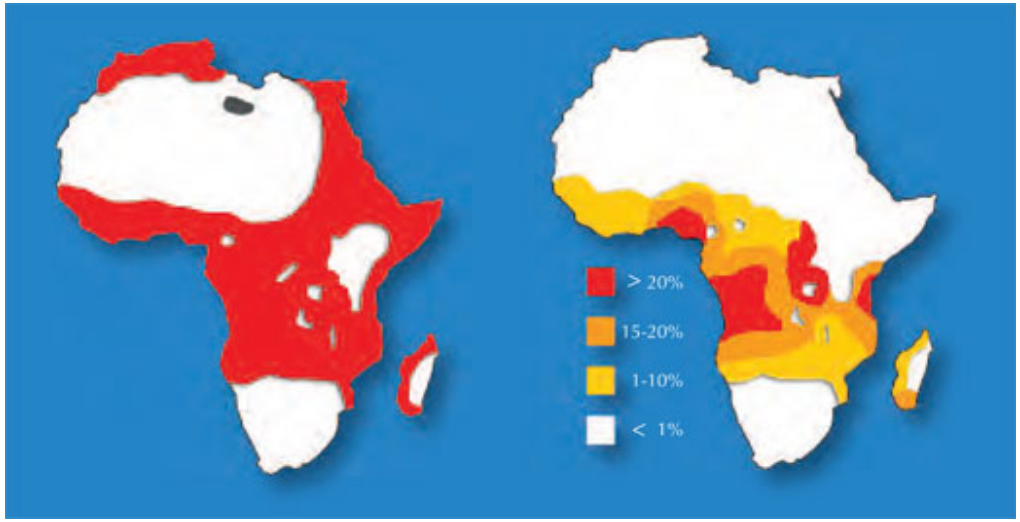


gain or loss of function ?

Evolution of anatomy and physiology

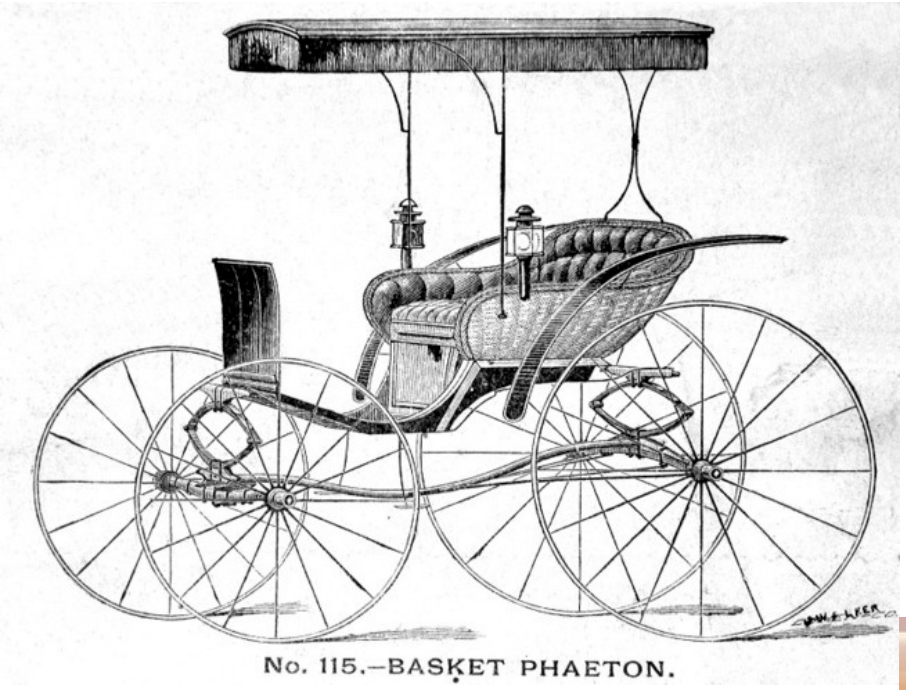
Disease and evolution

Why do we need diseases?



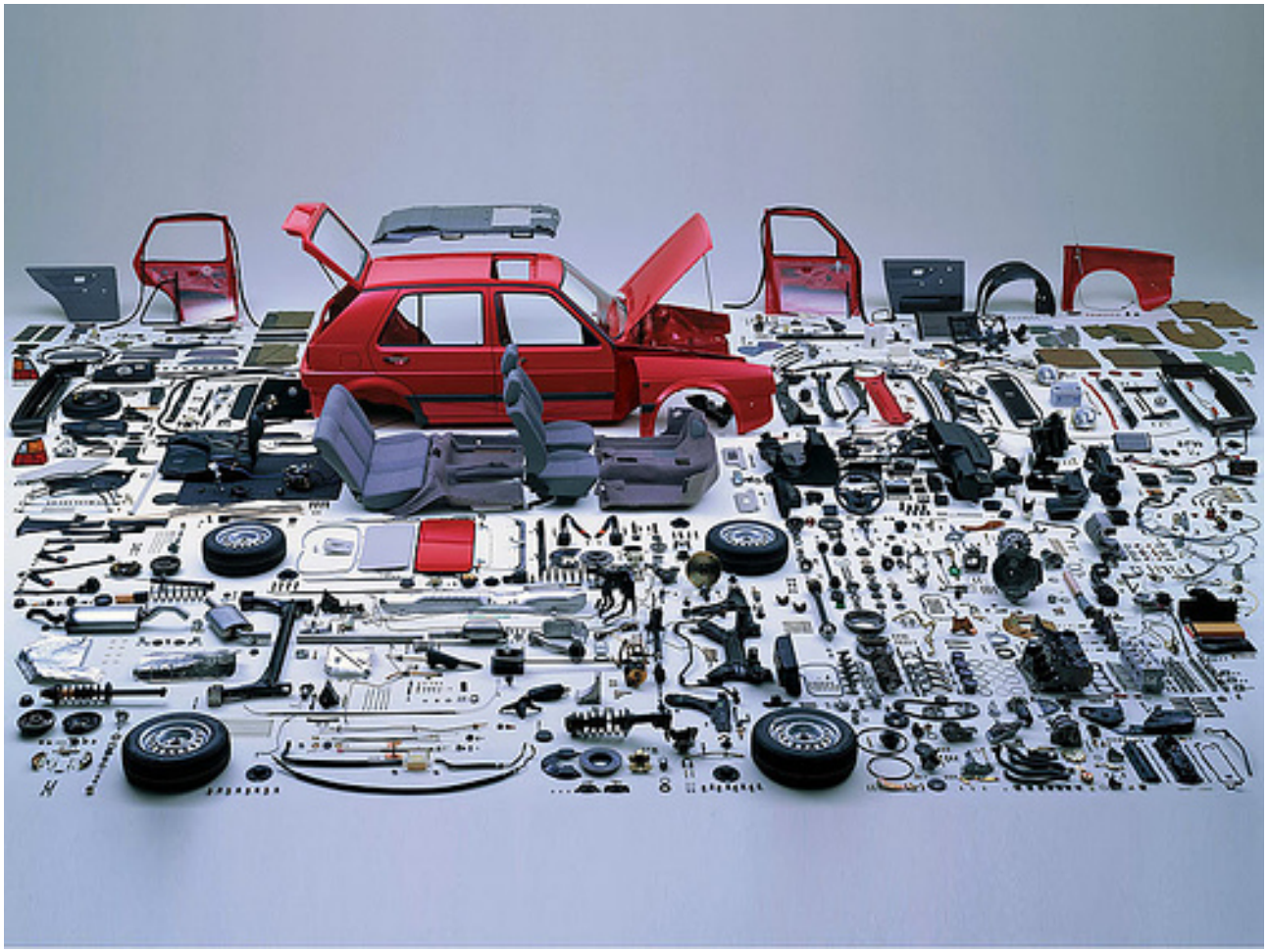
Comparison of the distribution of malaria (left) and sickle-cell anaemia (right) in Africa

Evolution of automobiles

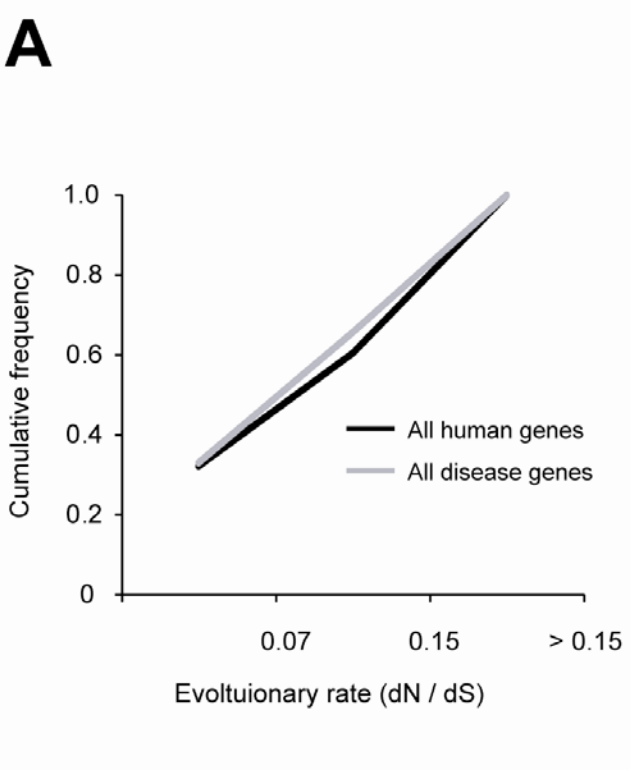


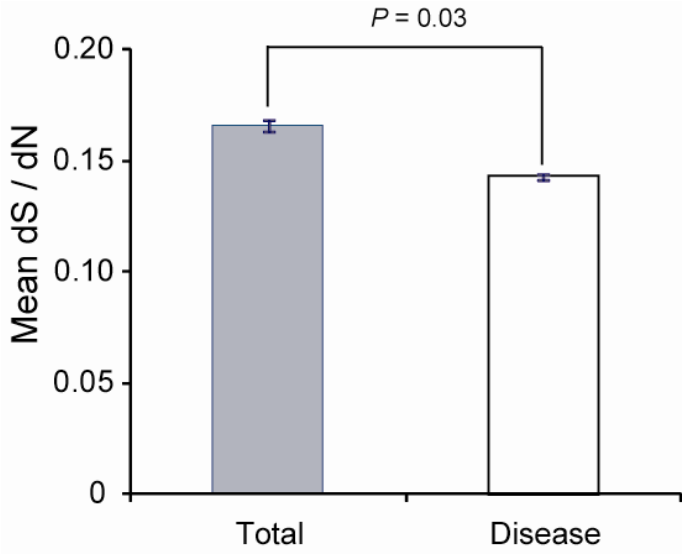
No. 115.—BASKET PHAETON.

Conserved (common) or evolving (species specific) parts ?



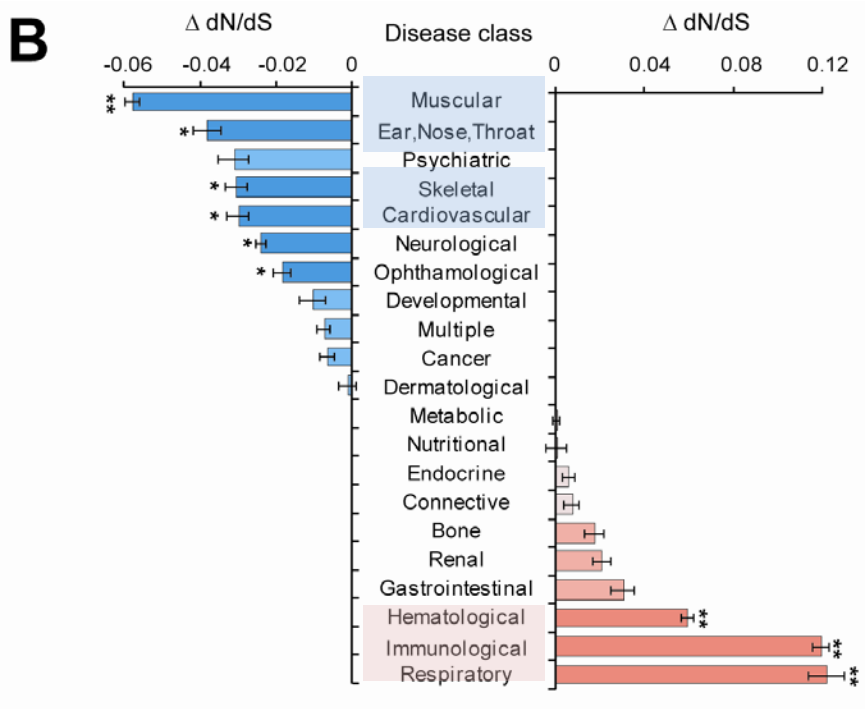
Human disease genes; fast or slow evolving ?





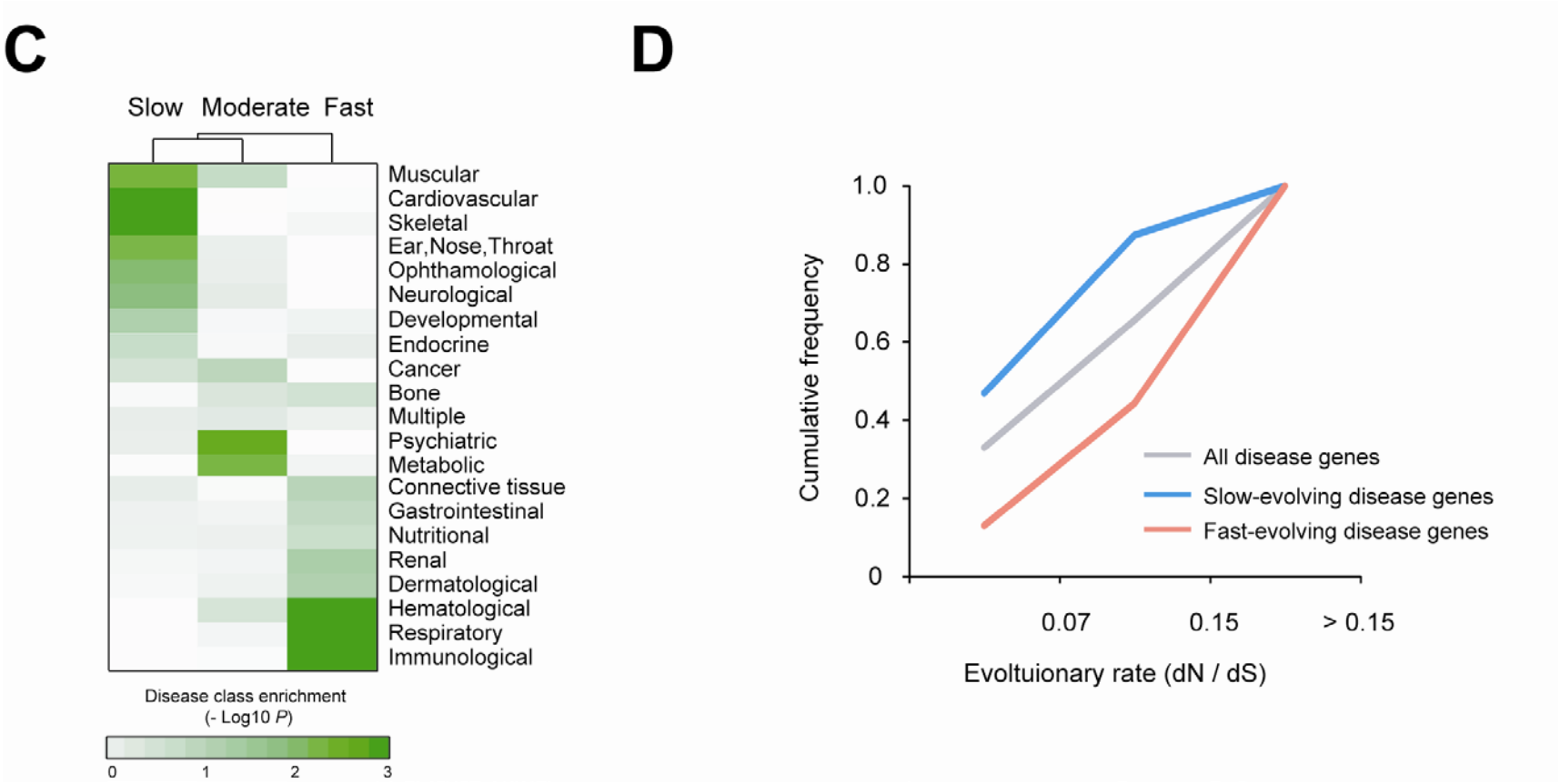
Suppl. Figure

Human disease genes have diverse evolutionary rates

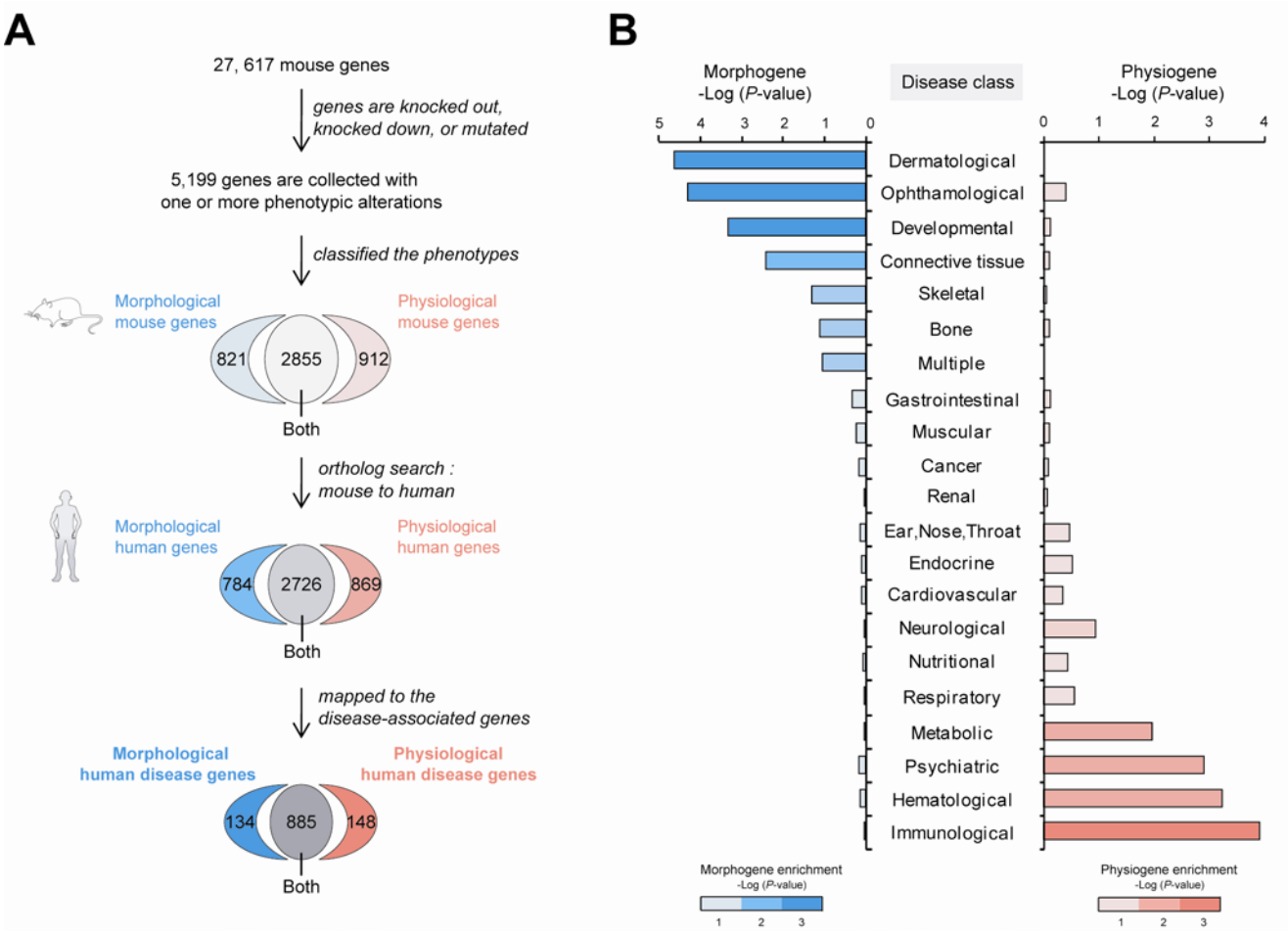


Phenotypically similar disease classes share similar evolutionary history

Human disease genes have diverse evolutionary rates

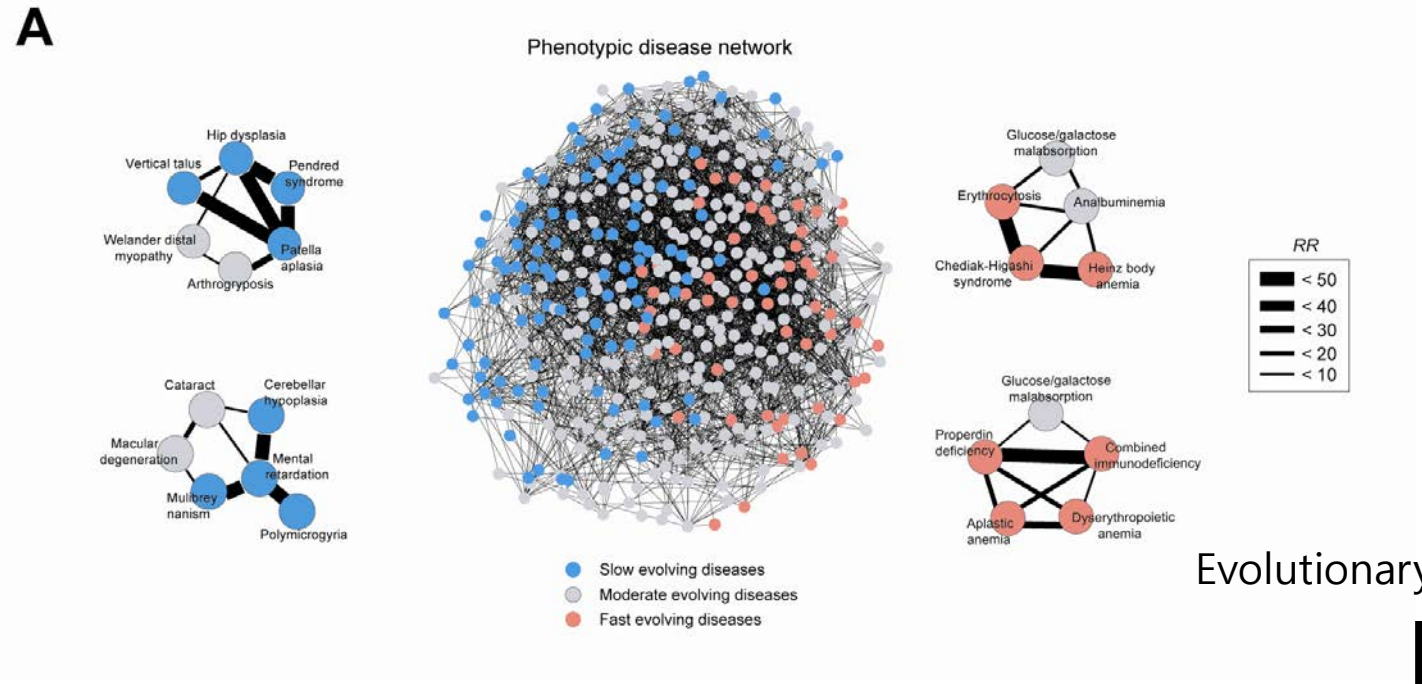


Morphogenes and physiogenes enriched differently In various disease classes



Evolution connect genotype to phenotype

Molecular connections in the comorbid disease pairs



Evolutionary connections

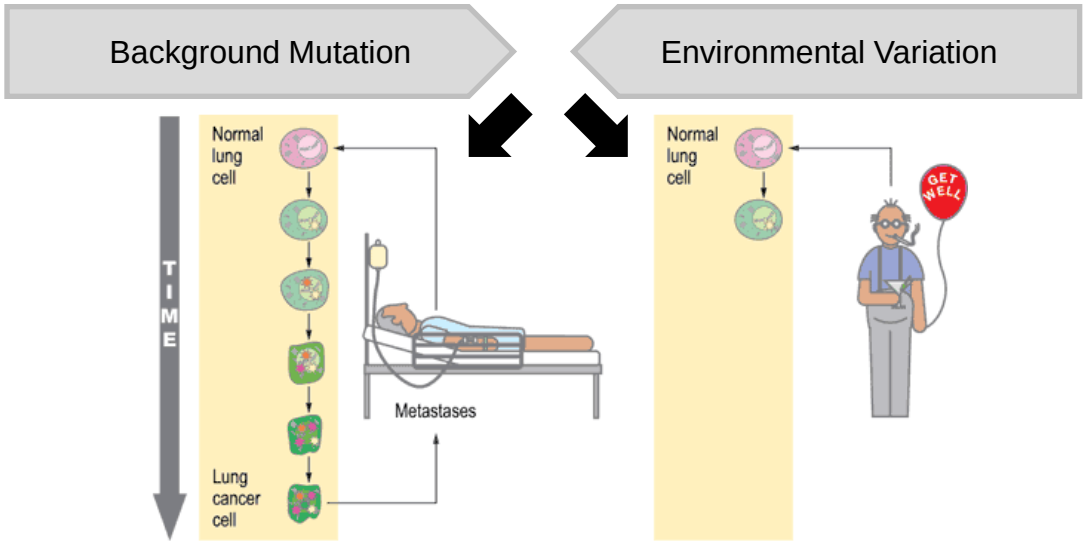
↓

Molecular connections

↓

Phenotypic connections
: *comorbidity*

- **It is hard to relate mutations with disease due to various genetic backgrounds and environmental factors**

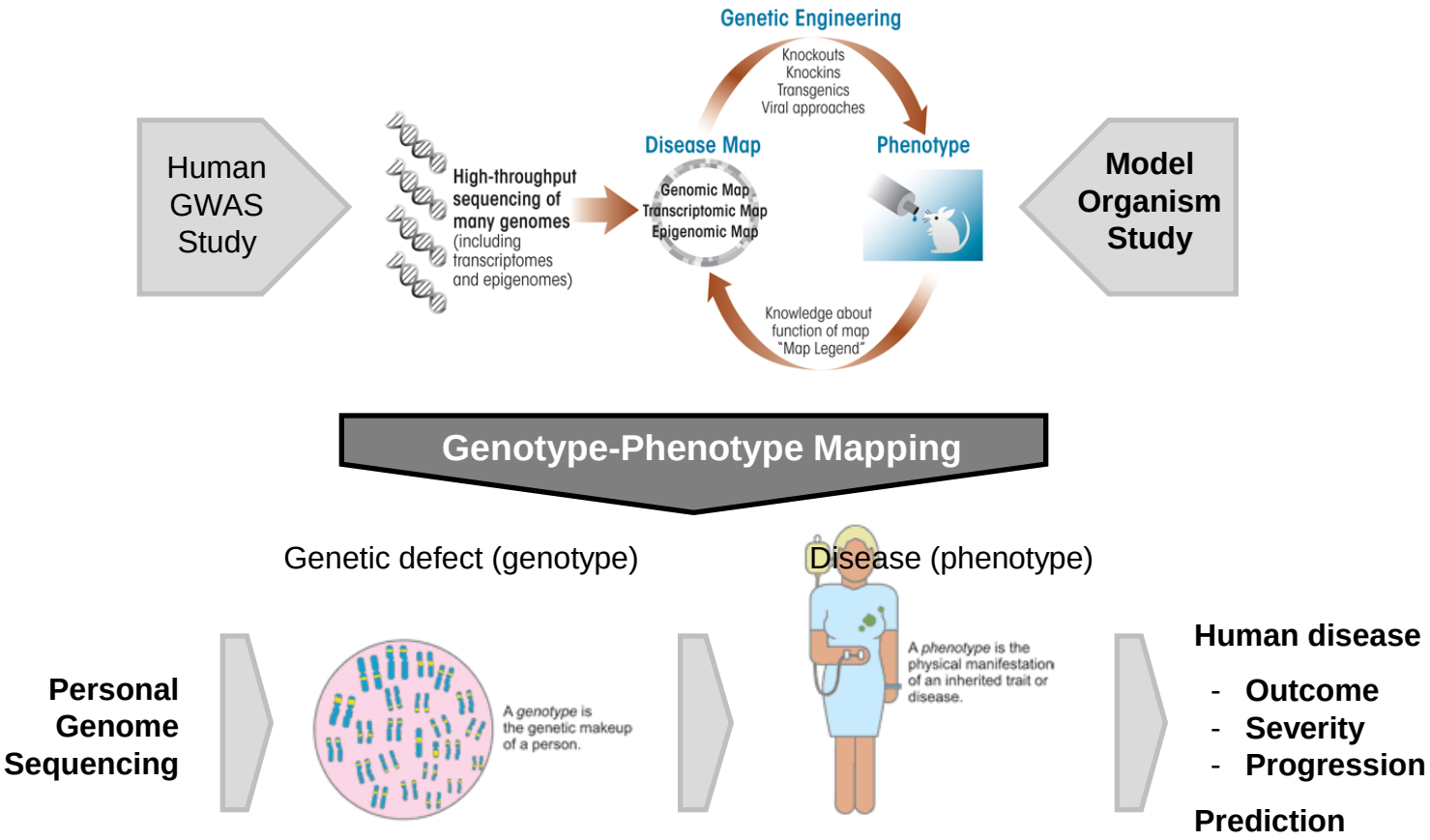


Cancer Phenotype
(Malignant cancer)

Health Phenotype
(sometimes benign tumor)

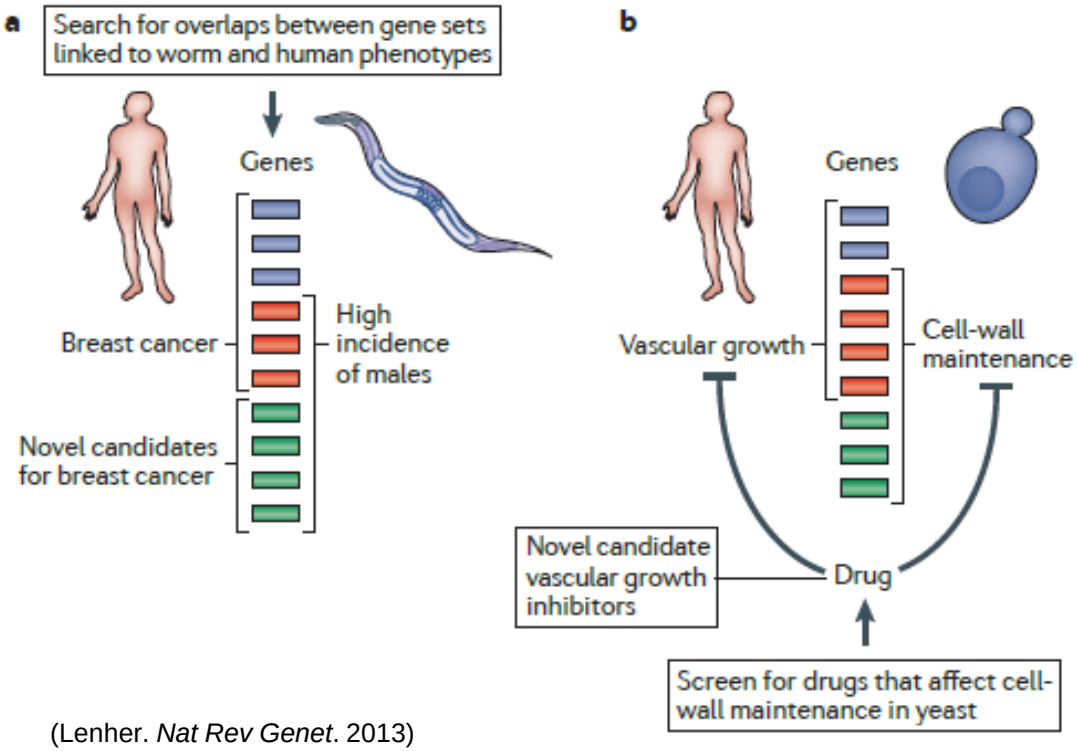
Building genotype-phenotype map from model organism is important for human disease prognosis.

- Disease-associated genes found by GWAS have low heritability and small effect for clinical use (Human disease outcome, severity, and progression prediction).
- Experiments on model organisms offers opportunity to evaluate the phenotypic effect of disease-causing mutations



(Modified from Matthew et al. *Alcohol Research: Curr Reviews*. 2011)

Model organism genotype-phenotype maps have relevance to human disease.

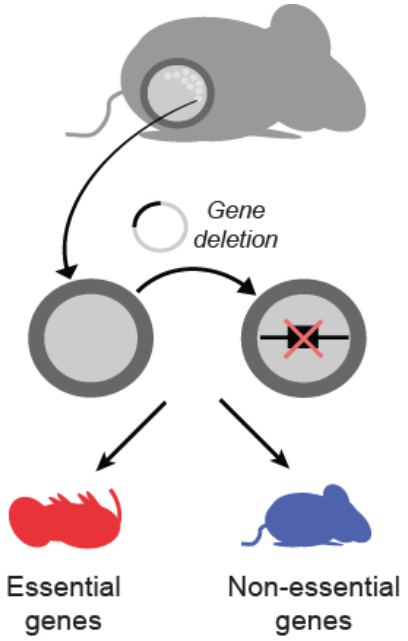


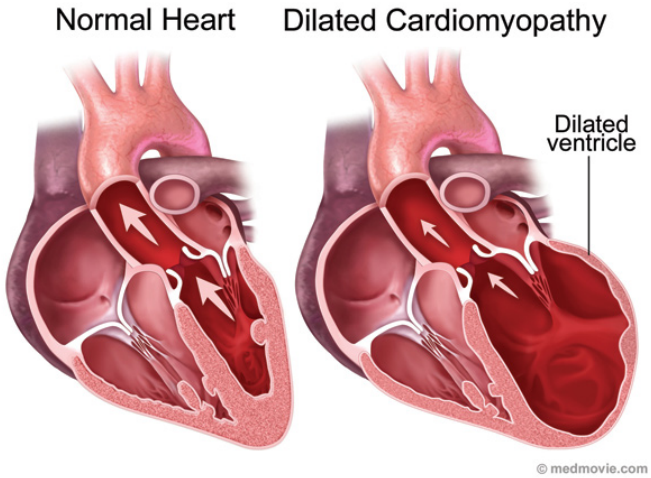
(Lenher. *Nat Rev Genet*. 2013)

Relationship between gene essentiality and disease-association is under debate.

Essential genes are associated with human diseases.

- Essential genes are required for survival and contribute to fitness of model organism.
- Perturbations of essential genes cause discernible phenotypic symptoms as human disease phenotypes.

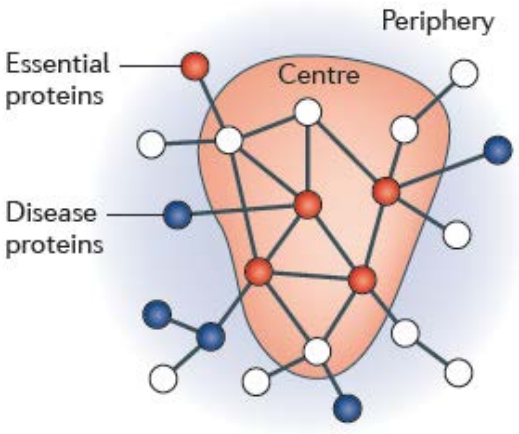




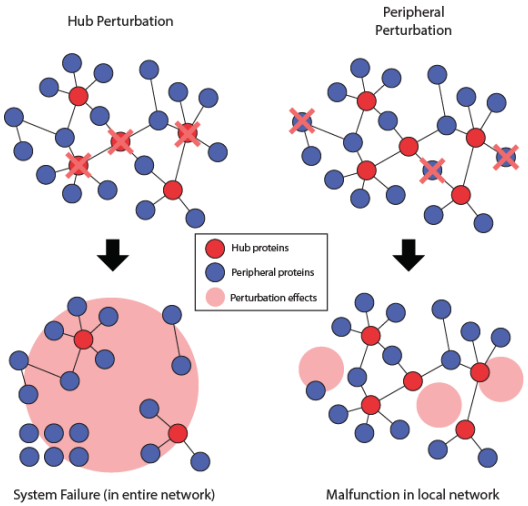
- In mouse, knock-out of ACTC-1 makes mouse lethal with heart development failure.
- In human, mutations in ACTC-1 are found in cardiomyopathy patients.

However, many non-essential genes are also related with human diseases.

Perturbation of		Effects	Network
Disease genes	Individuals can tolerate disease-causing mutations longer, often past their reproductive age.	Malfunction (Disease)	**Periphery**
Essential genes	Functional perturbation of essential genes leads to abortion in the embryonic stages.	System Failure (Death)	**Hub**



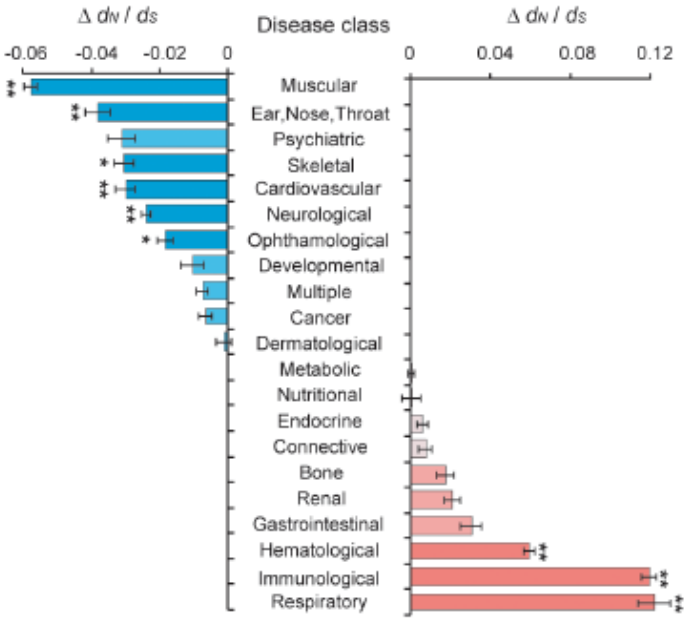
(Barabasi et al. *Nat Genet Rev*. 2011)



Death Disease

Genotype and phenotypes of human diseases are diverse.

- Diseases are caused by mutation of conserved gene effecting loss of function in organism.
- Some disease phenotypes are beneficial for survival and reproduction of organisms.



(Park et al. *Scientific Reports*. 2012)

Genotype-phenotype relationship of human disease are diverse.

Apply

Interpretation of human disease from genotype-phenotype map of model organism

Investigation of association between essential genes and human disease genes

OMIM®
Online Mendelian Inheritance in Man®

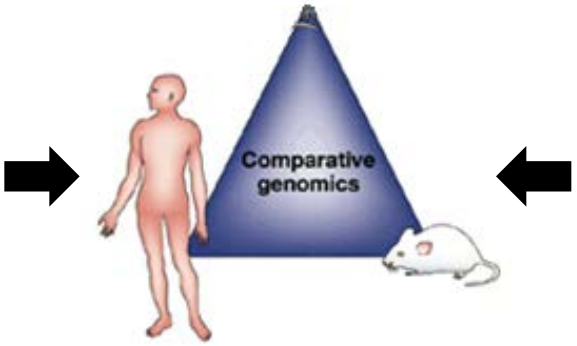
Human genes and genetic disease phenotypes

↓

Human disease genome

1,954 disease genes

Comparative genomics
orthologue mapping based on sequence homology (inparanoid) and gene annotation (ensemble)



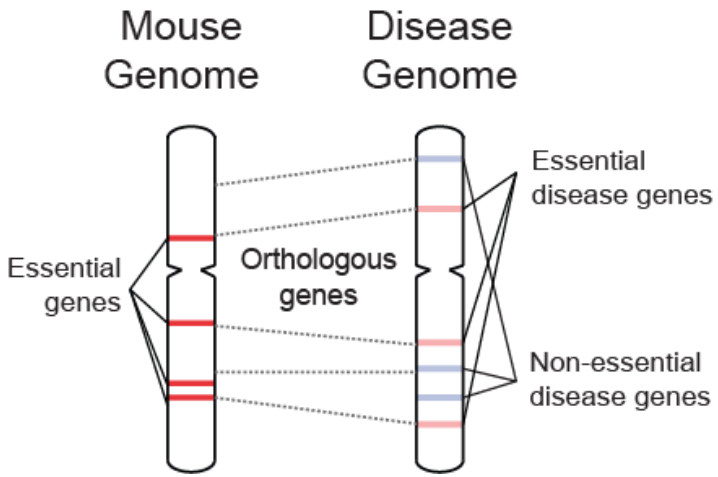
MGI

Model organism
Genotype-phenotype mapping

↓

Mouse essential genome

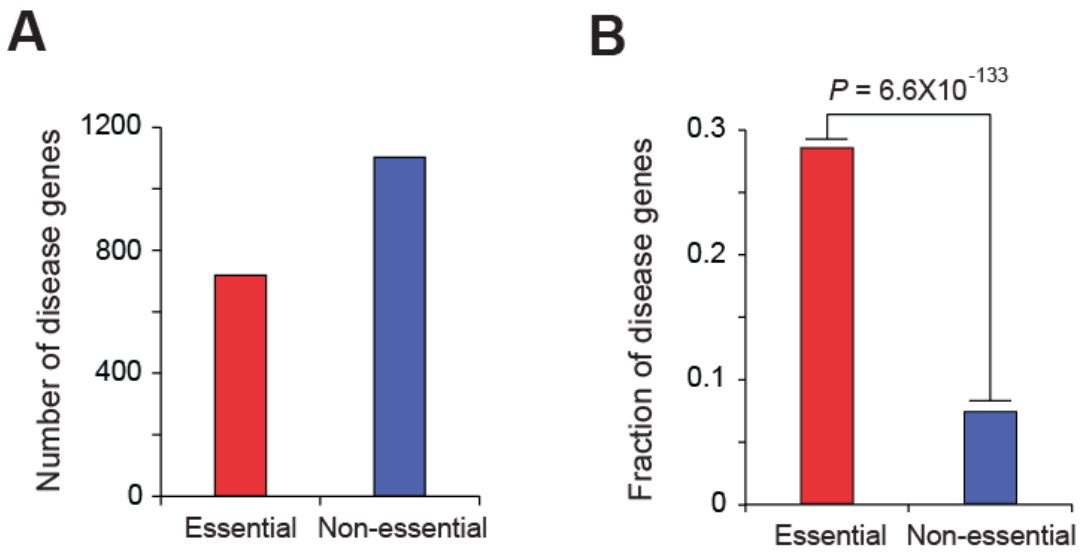
2,726 essential genes



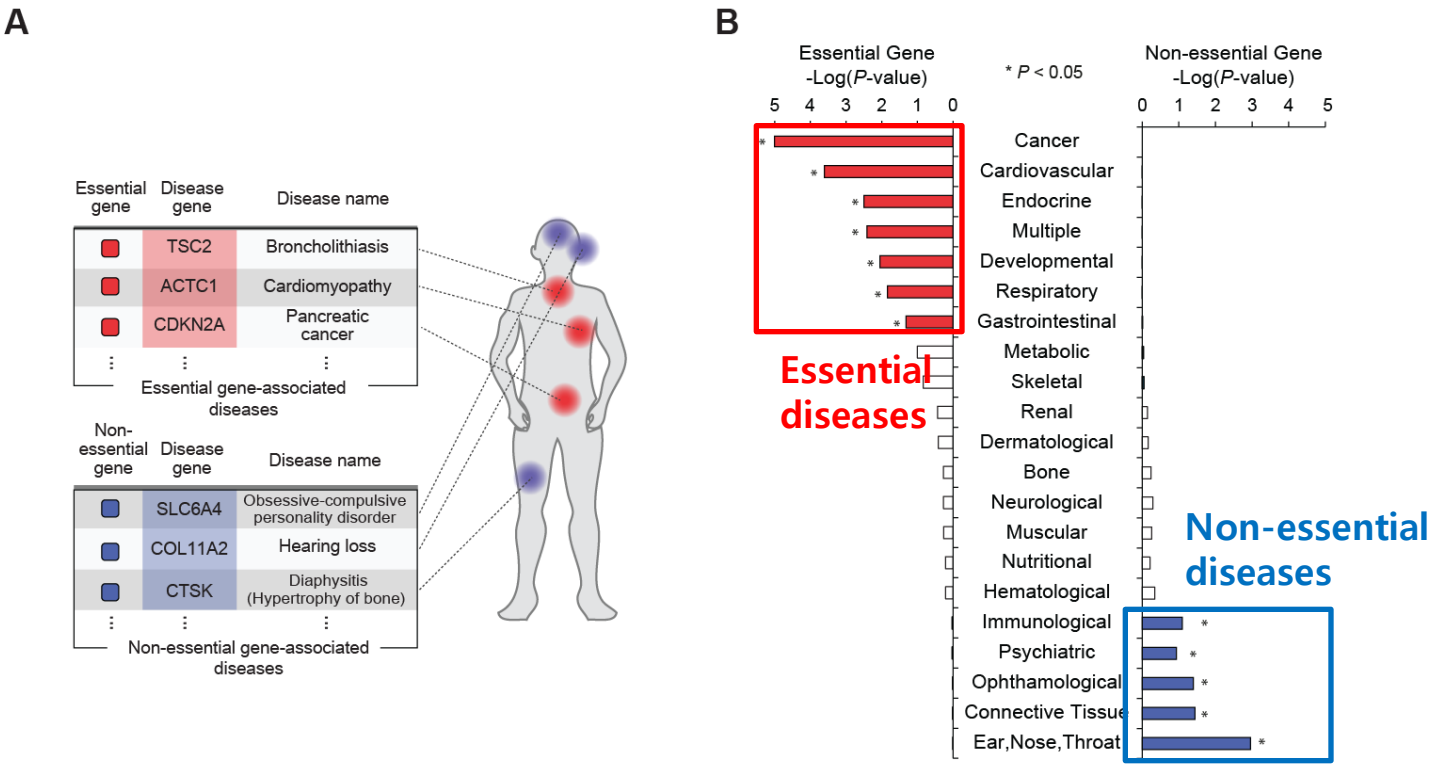
Mouse model organism
high sequence homology with human
well-annotated mutant phenotypes

Criteria of defining essential genes
Embryonic lethality
Prenatal lethality
Survival postnatal lethality
Abnormal reproductive system morphology or physiology
Premature death or induced morbidity
Mutant life span < 50 days

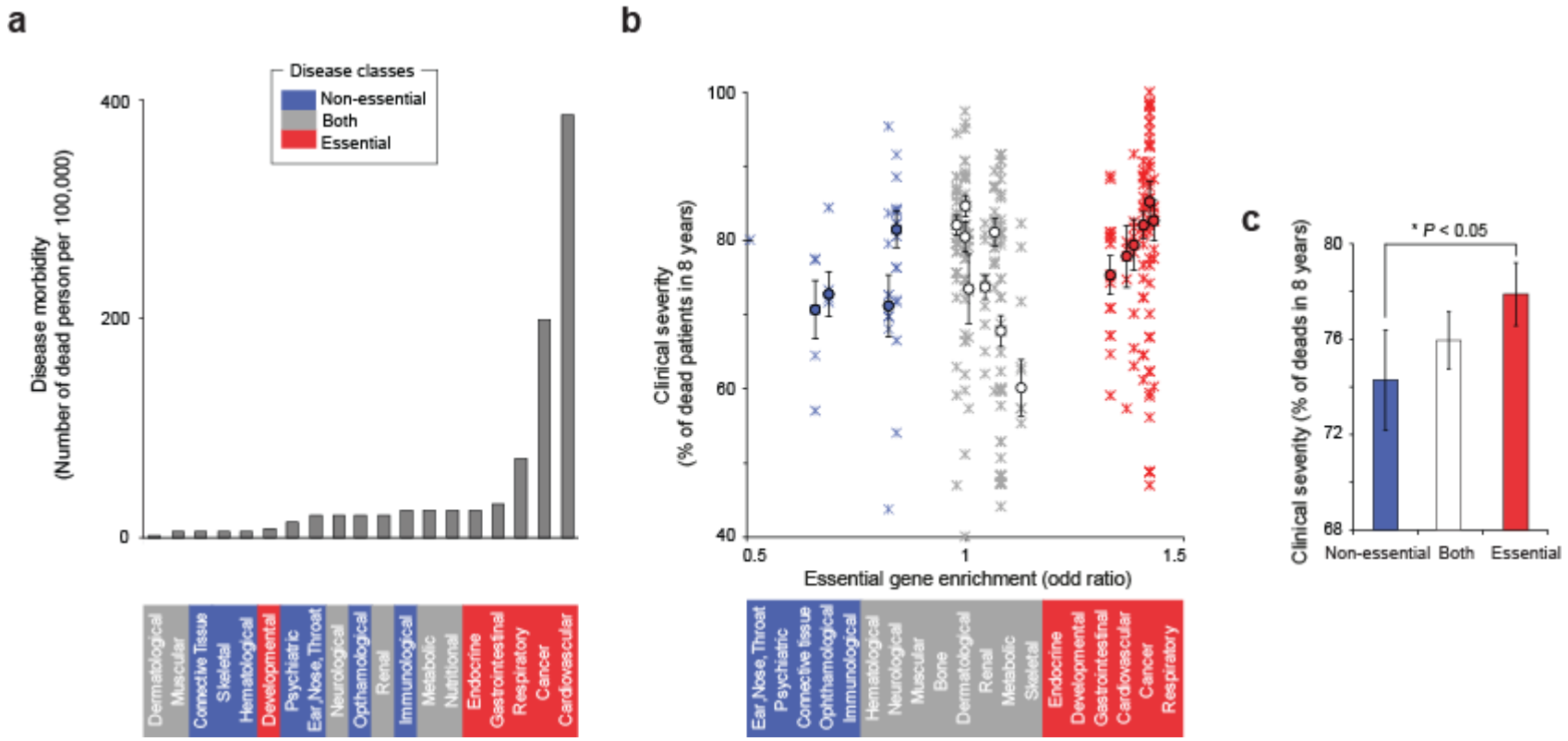
Gene Essentiality and Human disease-association



Human diseases associated with essential or non-essential genes are different.

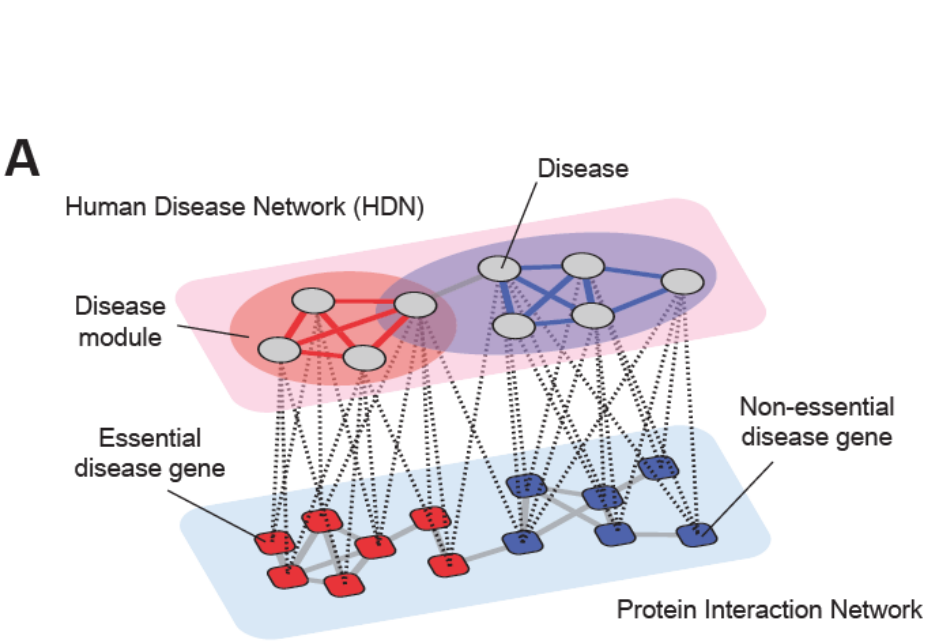


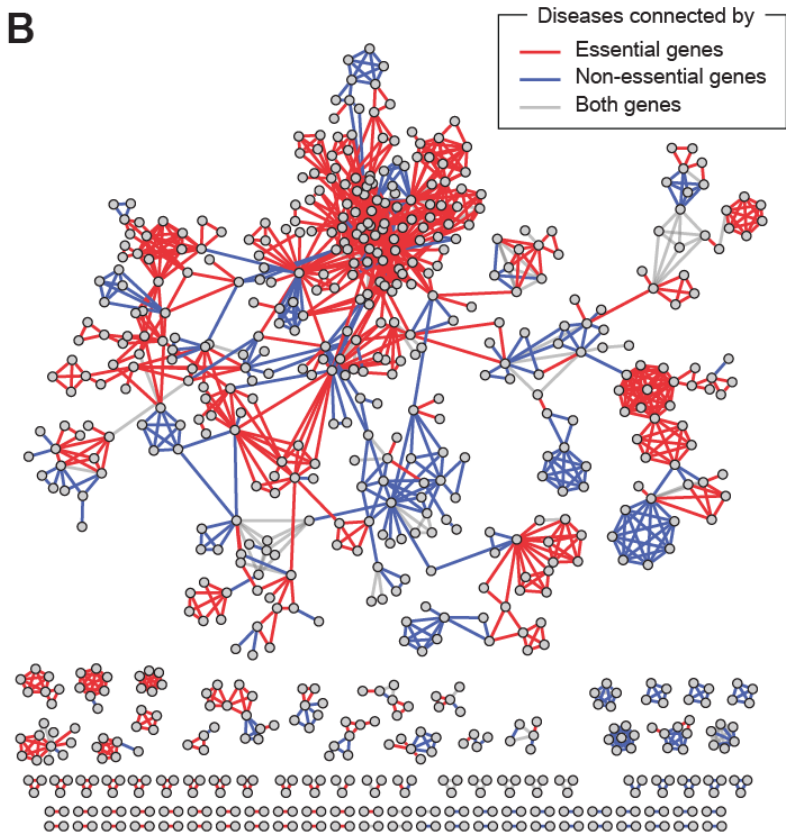
Essential diseases are more clinically severe than non-essential diseases in human population study.



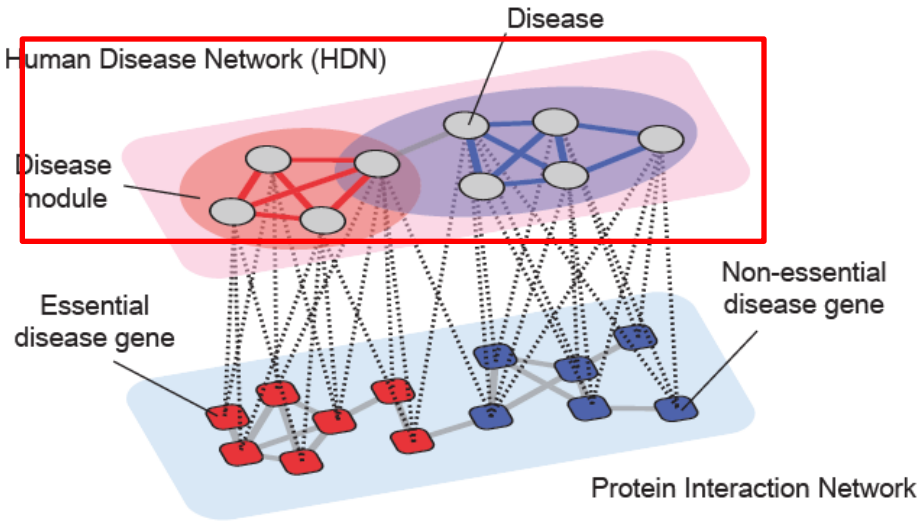
- We investigated disease progression (death or viable) of specific diseases patients from medicare patients population data (13,039,018).
- Essential disease classes have higher fraction of dead patients in 8 years than non-essential disease classes.
- Top 5 of disease classifications causes death in US are overlapped with essential diseases.

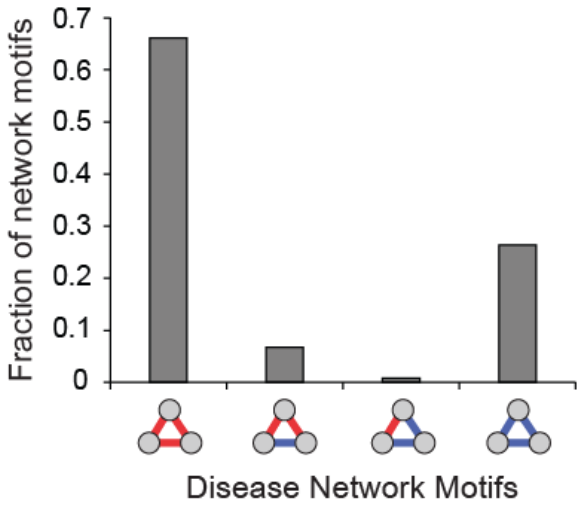
Association between gene essentiality and disease classes is originated from disease module connected by essential or non-essential genes in HDN.





- Goh et al. found that diseases in same major class are clustered in Human Disease Network (HDN).
- Diseases connected by essential or non-essential genes have strong modularity in HDN.

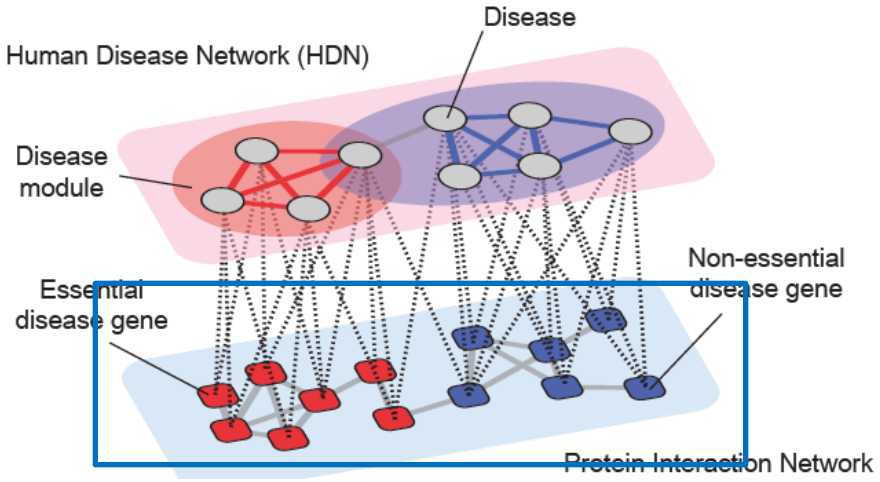


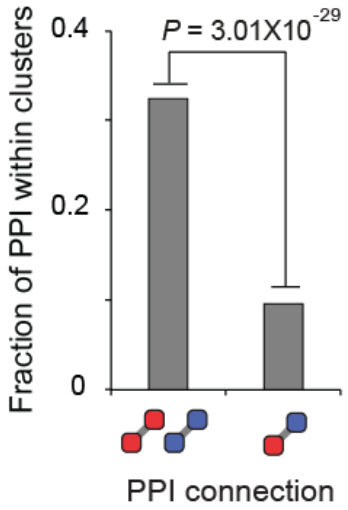


- Complete disease network motif composed by 3 diseases is basic component of disease modules.
- 90% of disease network motif found from HDN are connected by all essential or non-essential genes.

Clustering of essential or non-essential gene

in protein interaction network is related with diseases modules in HDN.



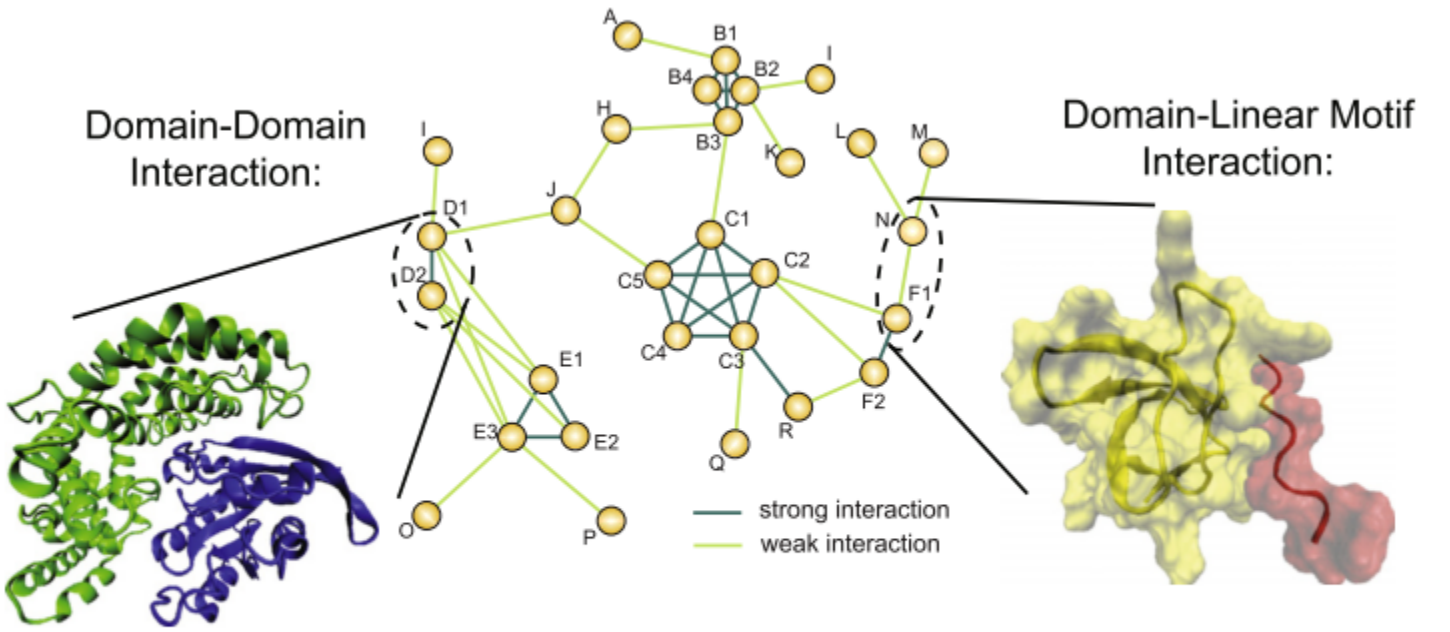


- Protein interaction composed by all essential or non-essential genes tend to connect within module in protein interaction network.
- Modularity of human diseases is closely related with protein interaction network (PIN).

Unpublished work

Domain-Linear Motif Interactions Shape the Modular Architecture of Human Protein-protein Interaction Network During Evolution

Two types of PPI: DDI and DLI



- Domain length from 25 - 500 AA
- Affinities: K_D nM to pM
- Rather stable interactions
- Examples: BTB(POZ), Ras-GAP, CARD

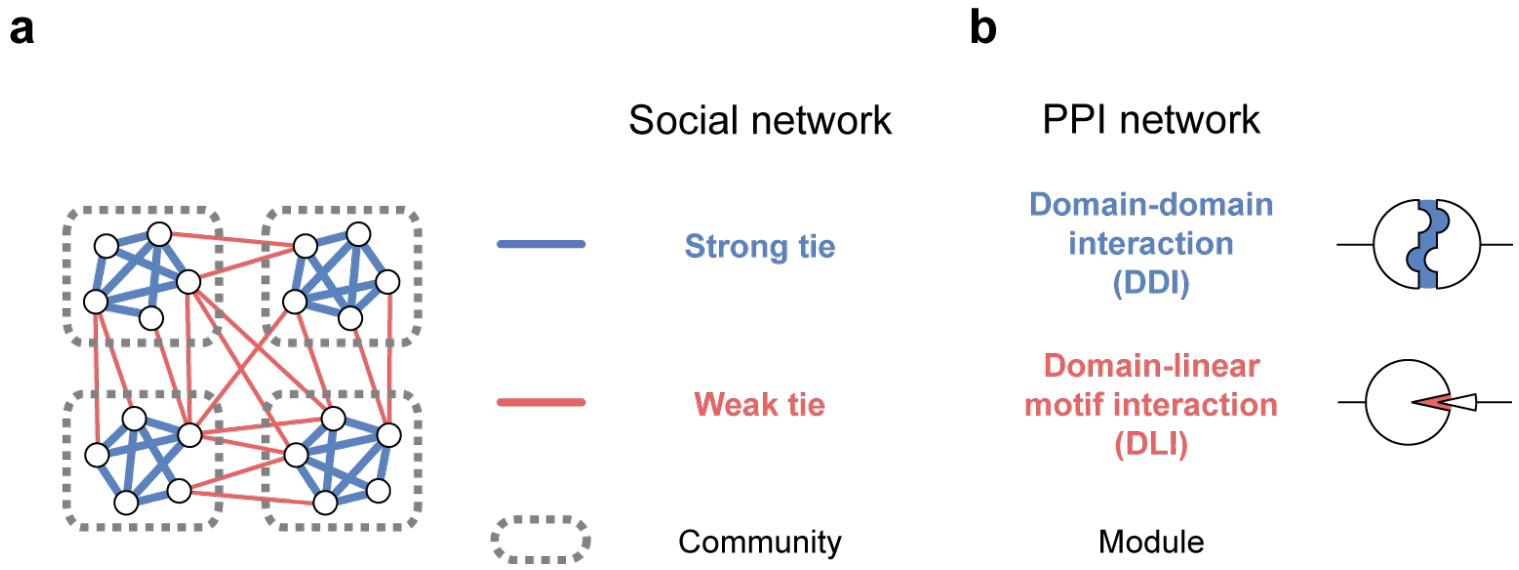
Strong and obligate

- Motif length from 3 - 10 AA
- Affinities: K_D ~ μM
- Rather transient interactions
- Examples: Sh3/PxxP, EVH1/FPPPP

Weak and transient

FEBS Lett. 2008 Apr 9;582(8):1220-4.

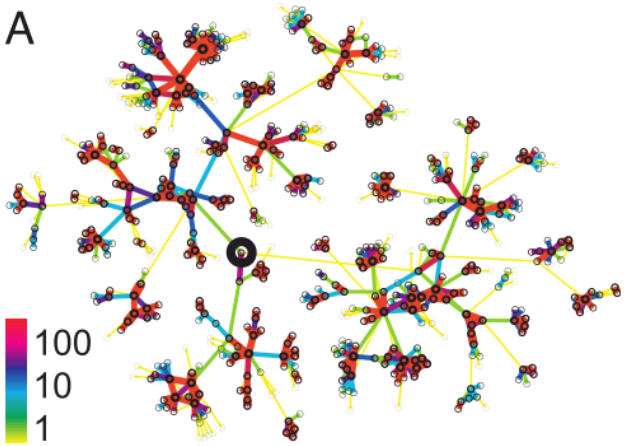
Hypothesis; Interaction strength is related with modular architecture



DDIs and DLIs have distinct roles for the modular architecture of PPI networks and its evolution.

The strength of weak ties

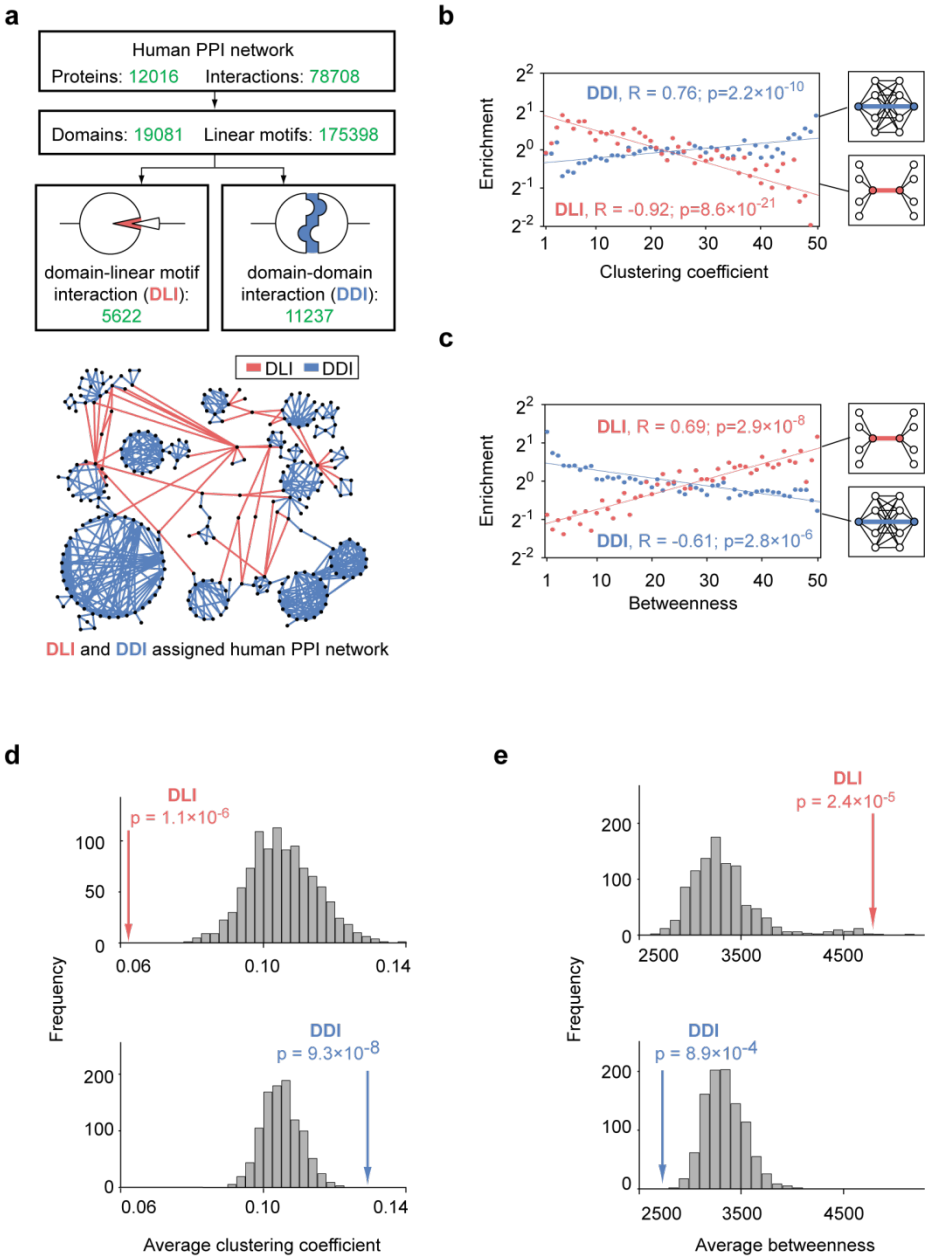
Mobile call graph with call duration



Proc Natl Acad Sci U S A. 2007 May 1;104(18):7332–6.

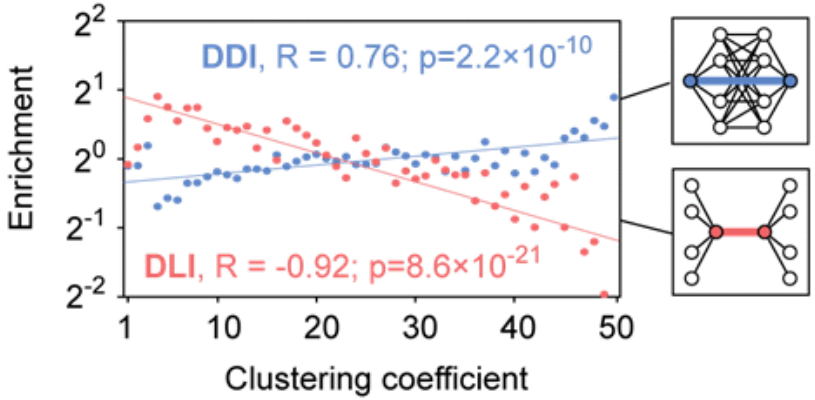
Weak interactions connect between modules, whereas strong interactions cluster nodes within modules.

DLIs and DDIs have different topological roles in the PPI network

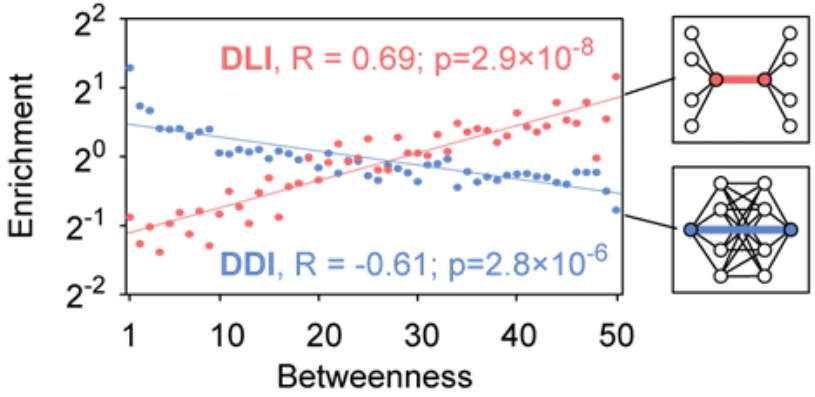


DDIs are enriched in within modular interactions and DLIs are enriched in between modular interactions in the PPI network

b



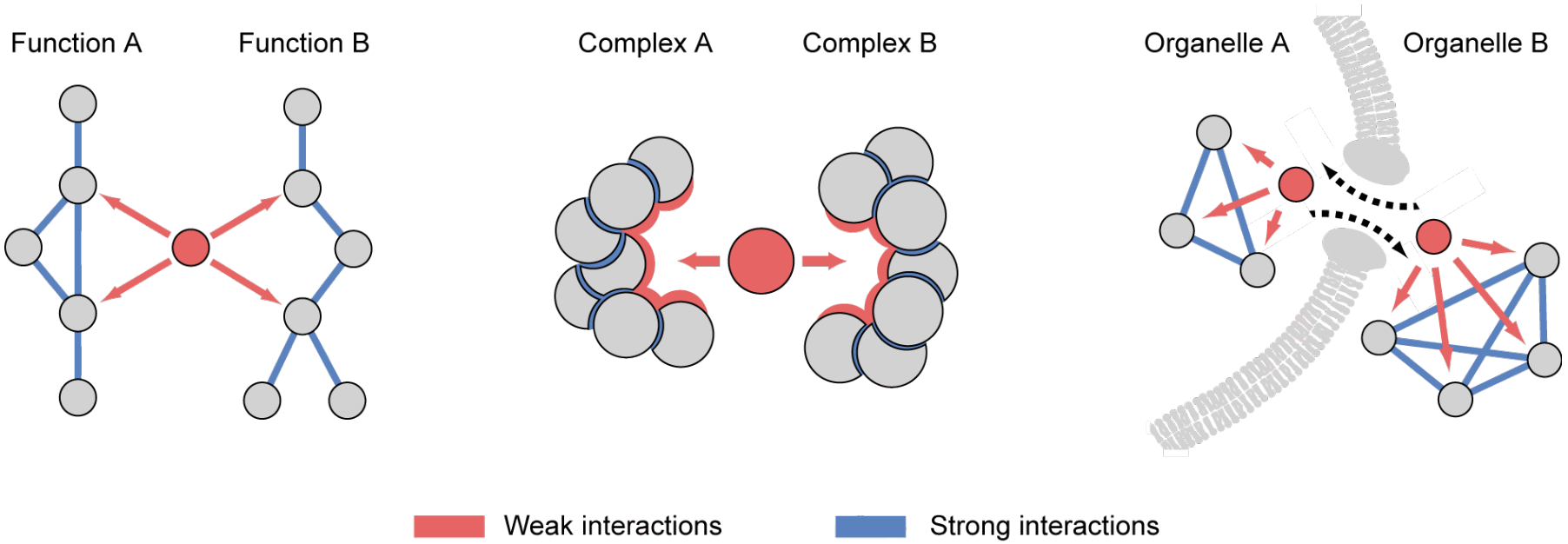
c



DDIs – cluster proteins

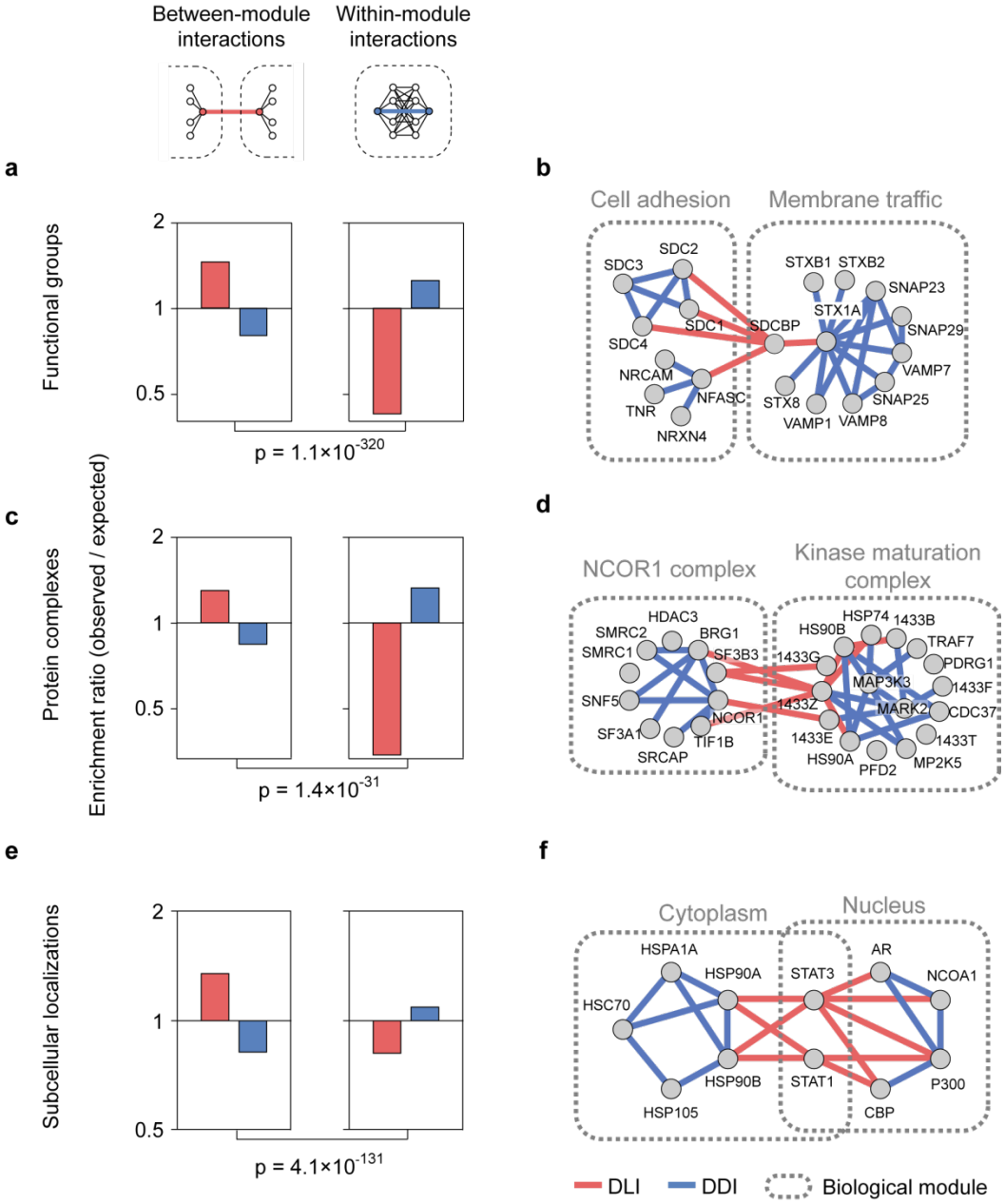
DLIs – connect different topological clusters

Weak (transient) interactions have important roles in biological network

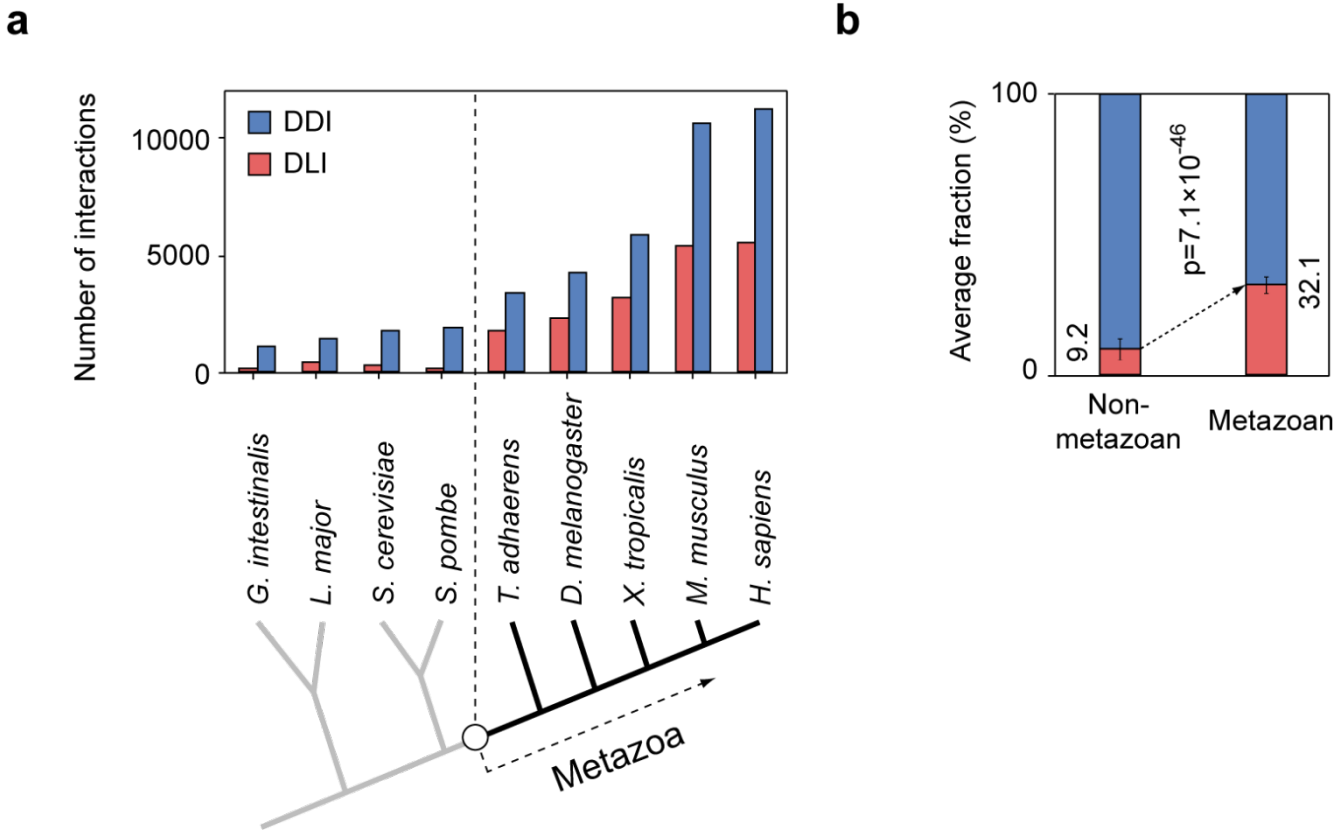


Weak interactions are physically more suitable for transient interactions between biological modules, including functional groups, protein complexes, and subcellular localizations.

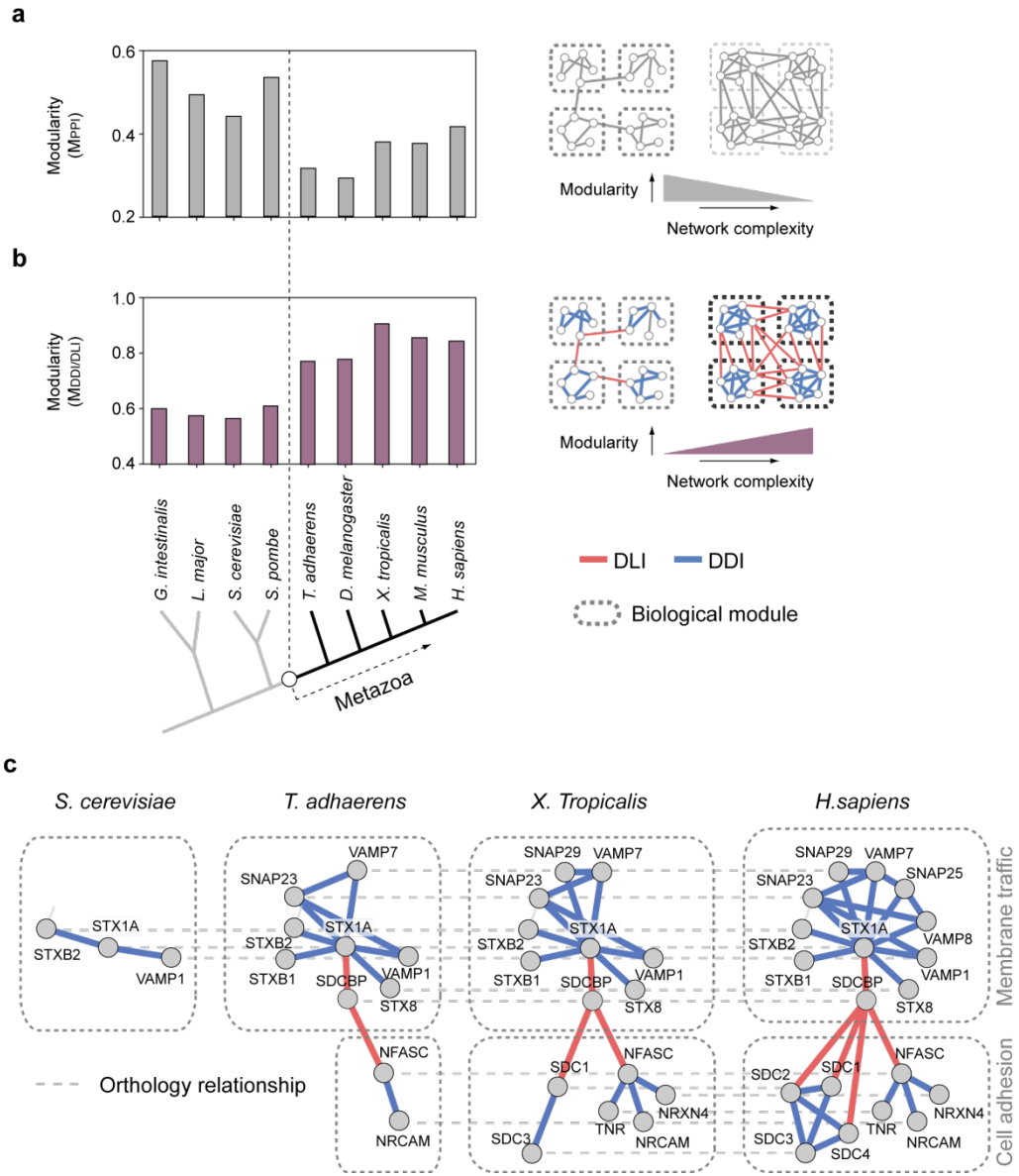
DDIs are enriched in within modular interactions and DLIs are enriched in between modular interactions in the PPI network



Transient interactions have increased during the course of metazoan species evolution



Transient interactions improved the modularity of PPI networks



Refinement of module detection by using DLI and DDI information