Network Biology and Evolution of Human Genetic Diseases

Sanguk Kim

POSTECH

Outline

- Introduction of Network Biology and Medicine

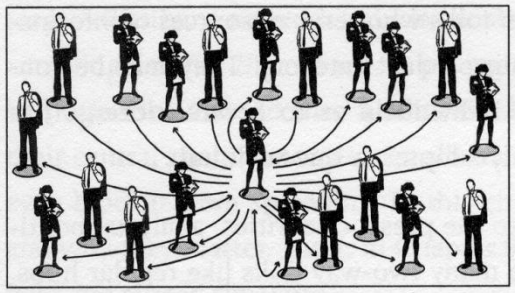
- Network Distance & Localization -> Disease Comorbidity ***Nature Mol Sys Biol.* 2011**
  Human disease evolution ***Nature Scientific Reports 2012***
  Mitochondrial protein network ***Nature Scientific Reports 2013***

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

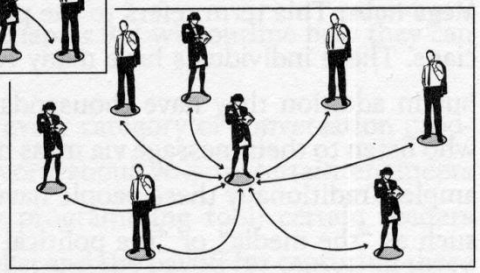
- Network Rewiring and Evolution -> Gene essentiality changes ***Nature Scientific Reports 2012***
  Neuronal Disease ***PLoS Genetics* 2012**

1. Spatial and functional organization of mitochondrial protein network. ***Nature Scientific Reports 2013*** 3:1403.
2. Network rewiring is an important mechanism of gene essentiality change. ***Nature 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. ***Nature 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

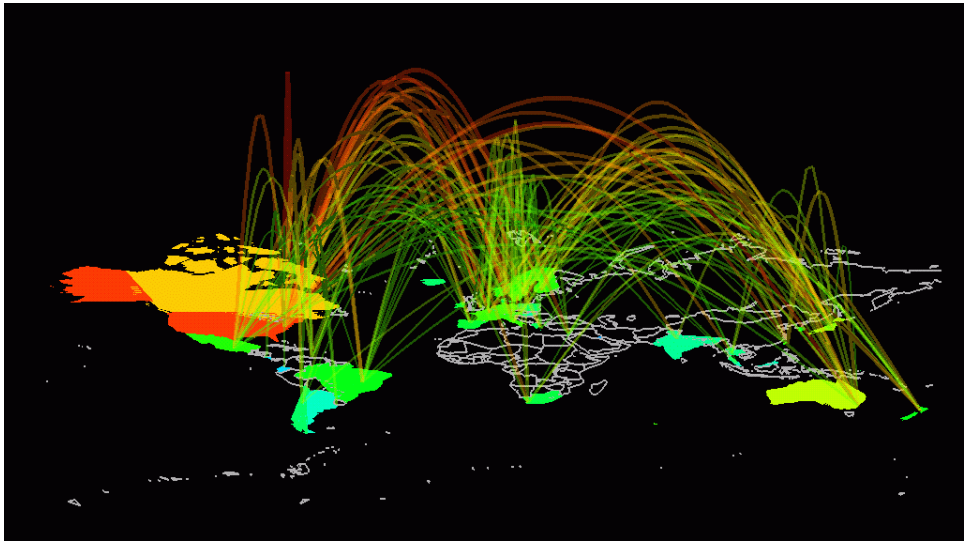


Mega-Hub. An MTV veejay spreads the word to thousands or millions of people through one-way links.

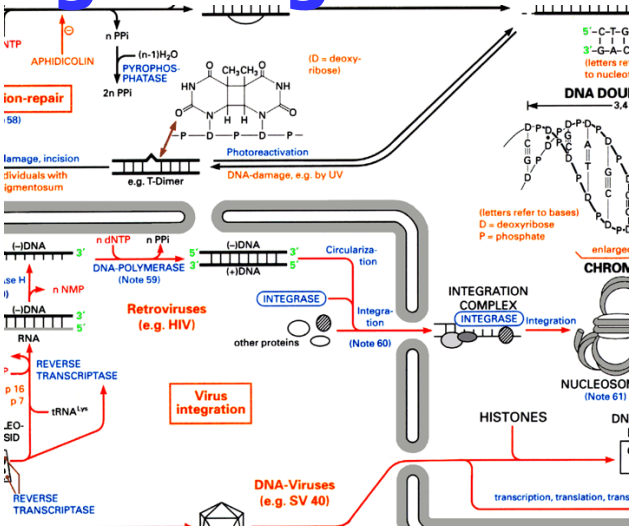


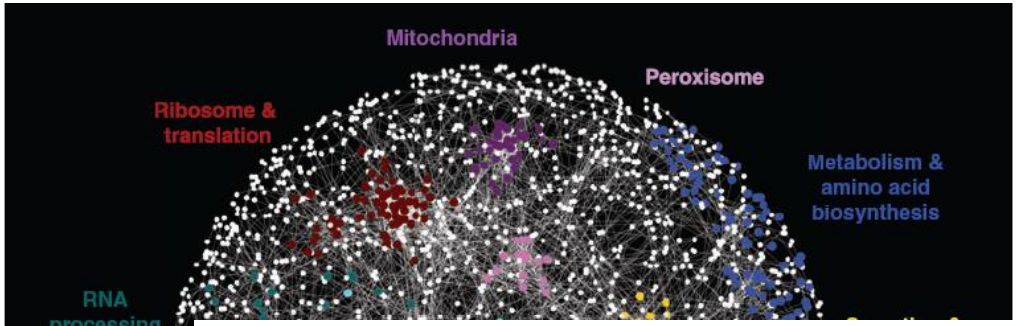
Hub. This undergraduate has spread the word to seven other people through two-way links.

Internet

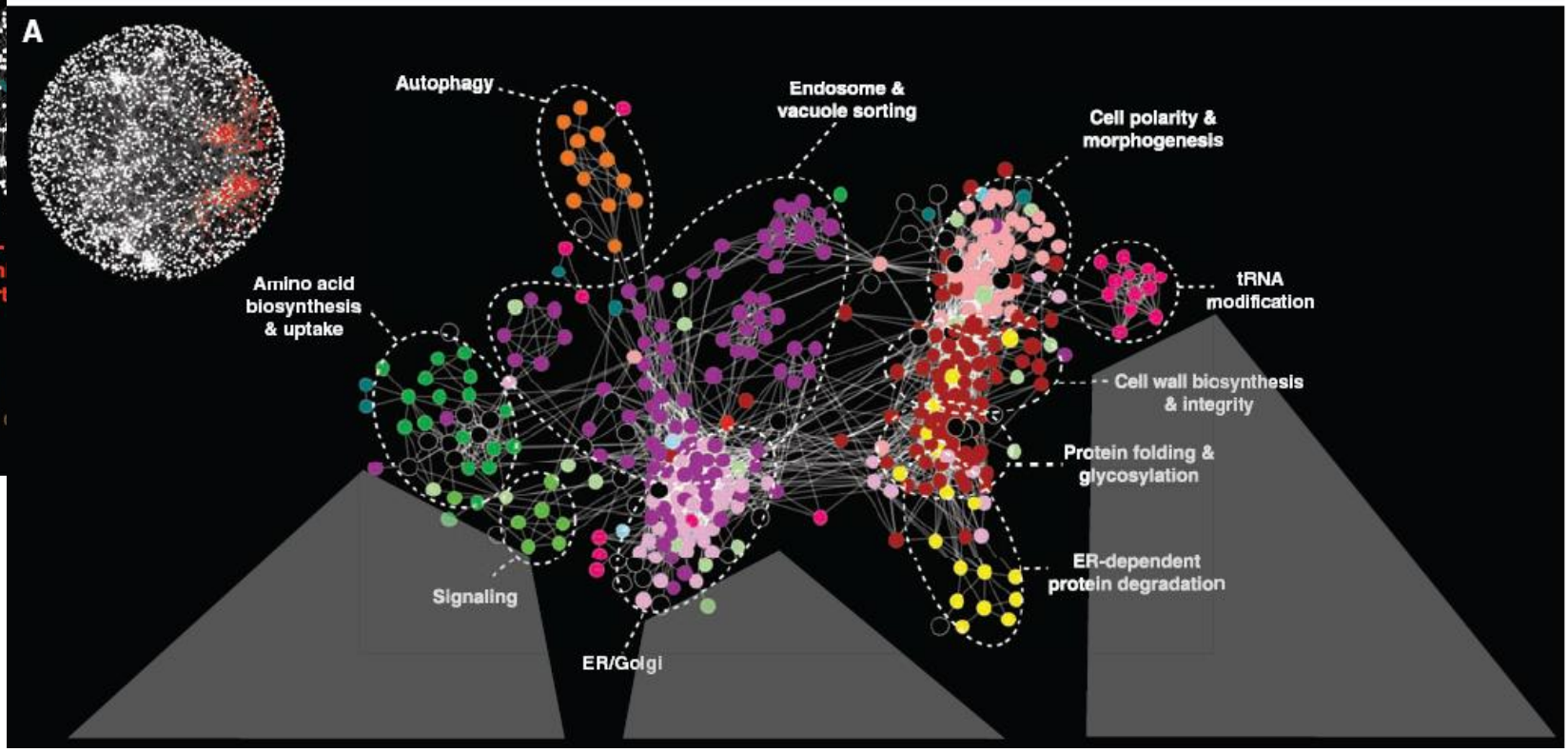


Biological signaling network





Biological Network

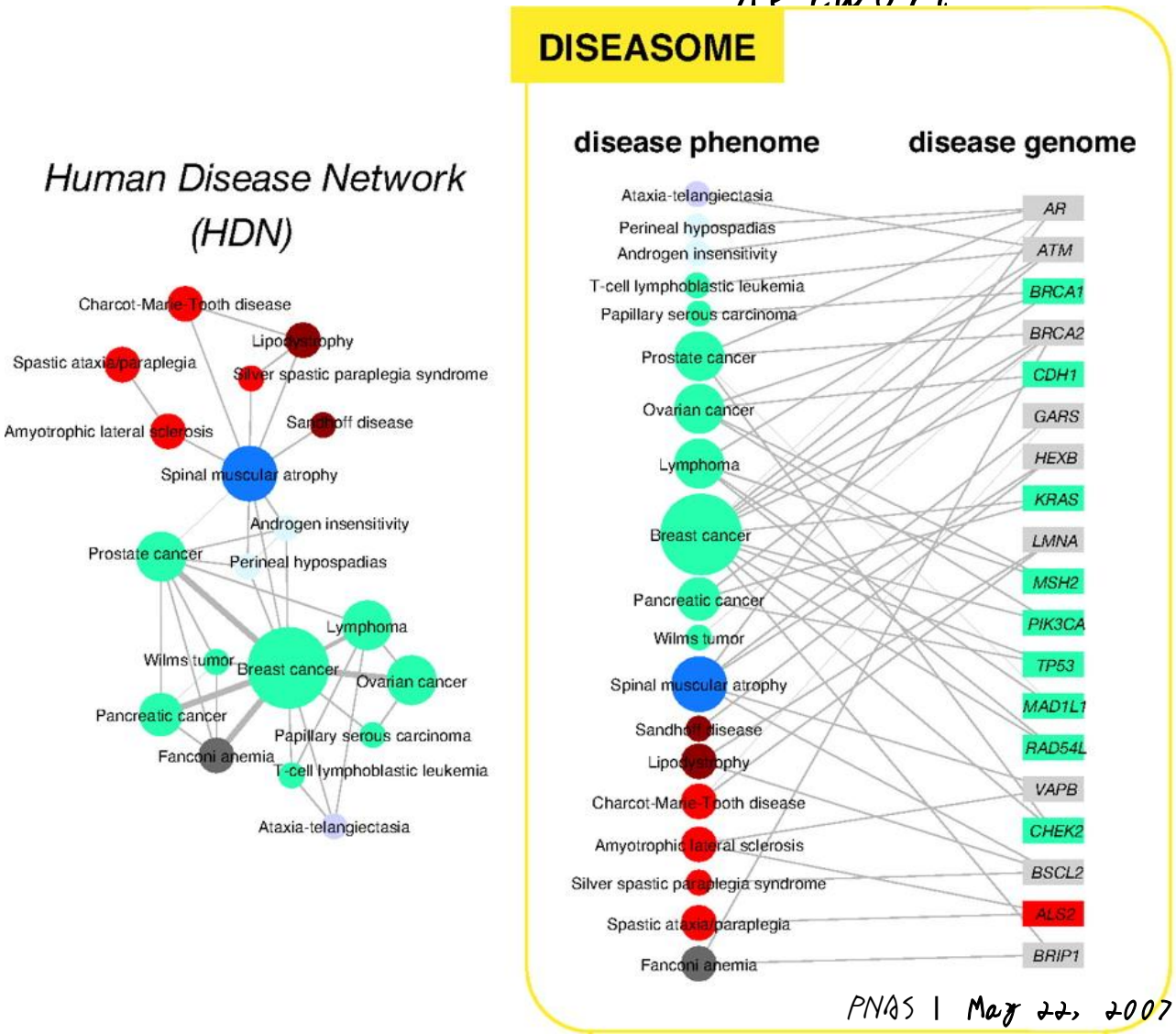


Disease pleiotropy and network modularity

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

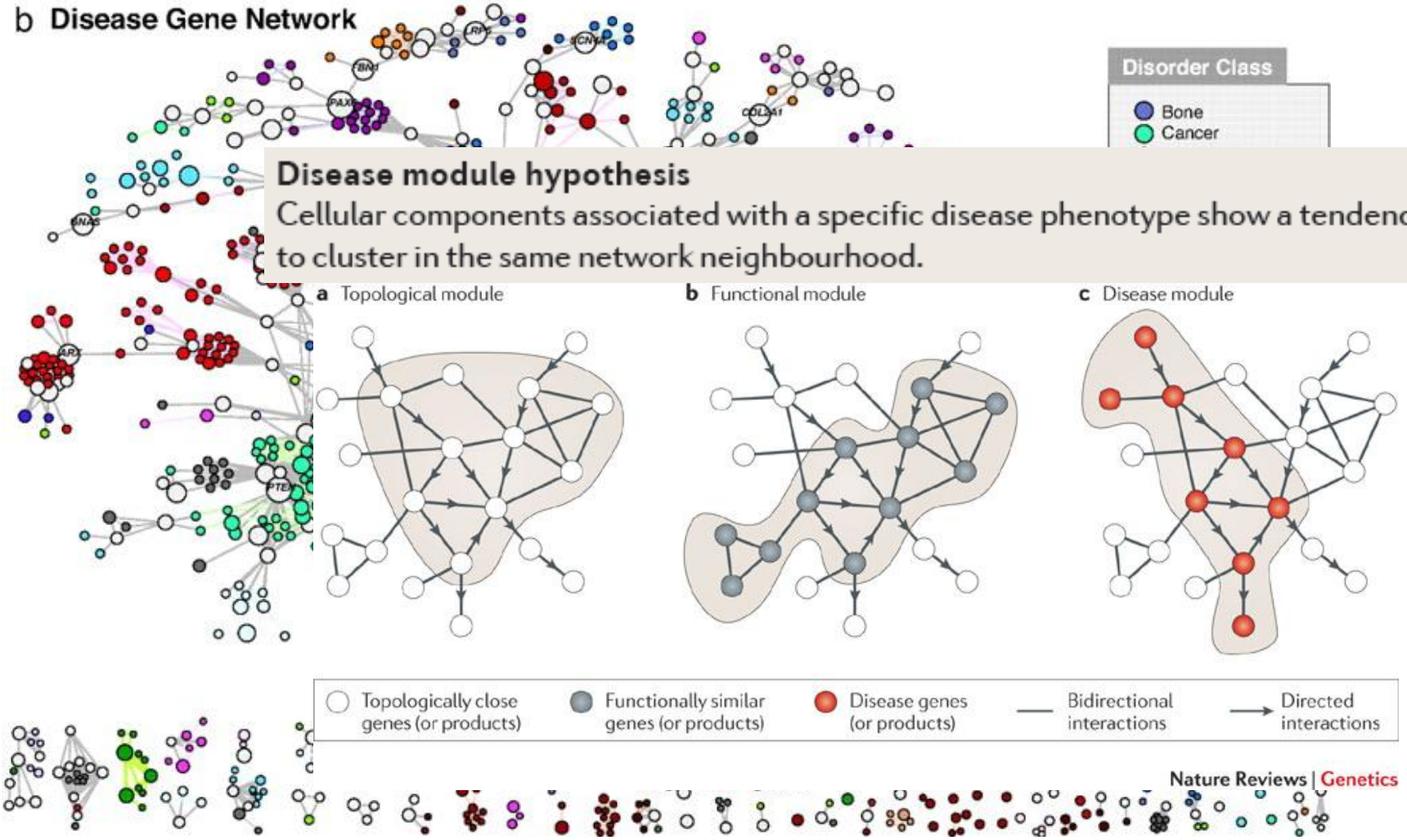
The human disease network

Construction of the diseasome bipartite network

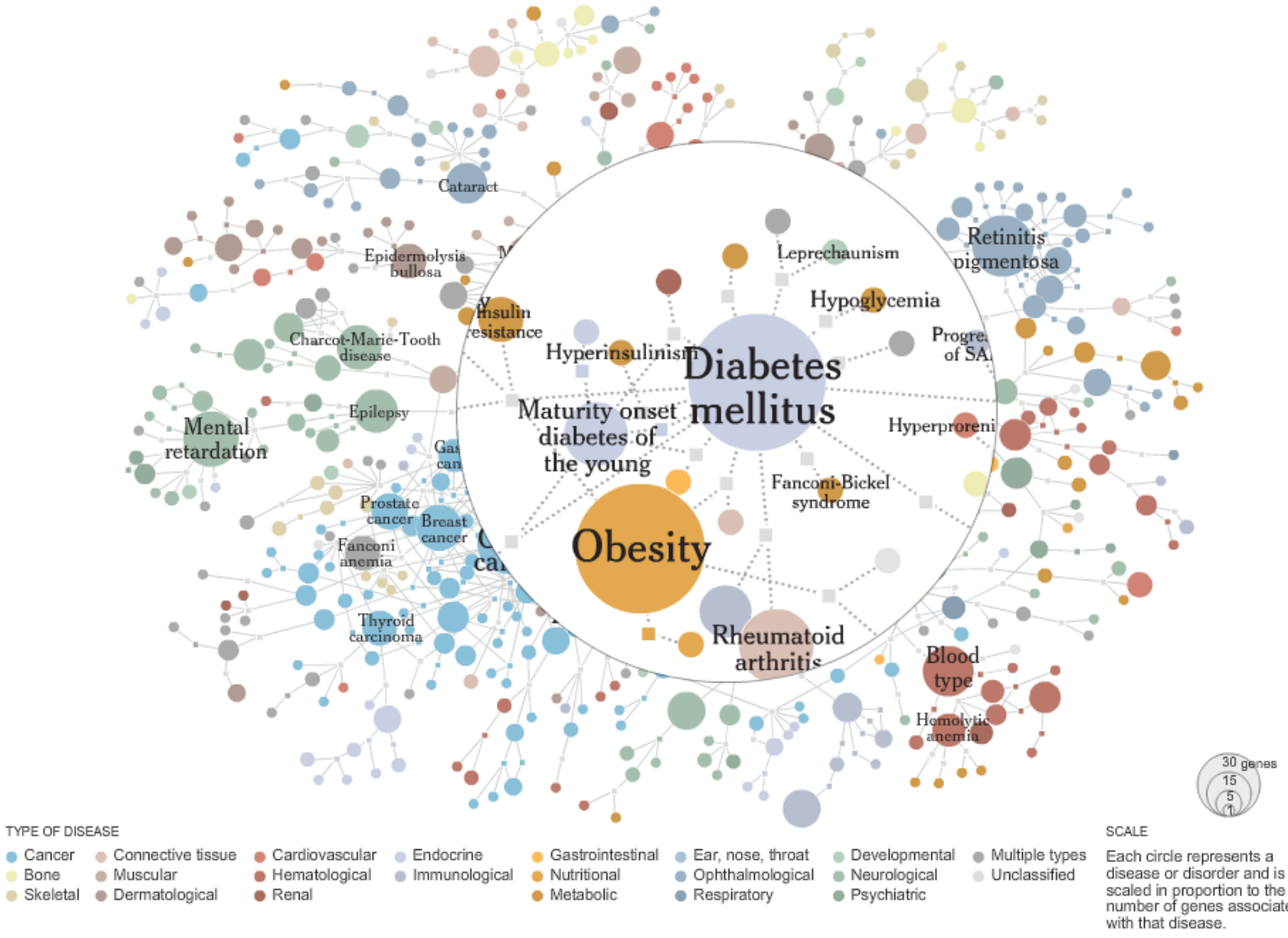


PNAS | May 22, 2007 | vol. 104 | no. 21 | 8685-8690

Disease Gene Network



Example: Diabetes in the Human disease network



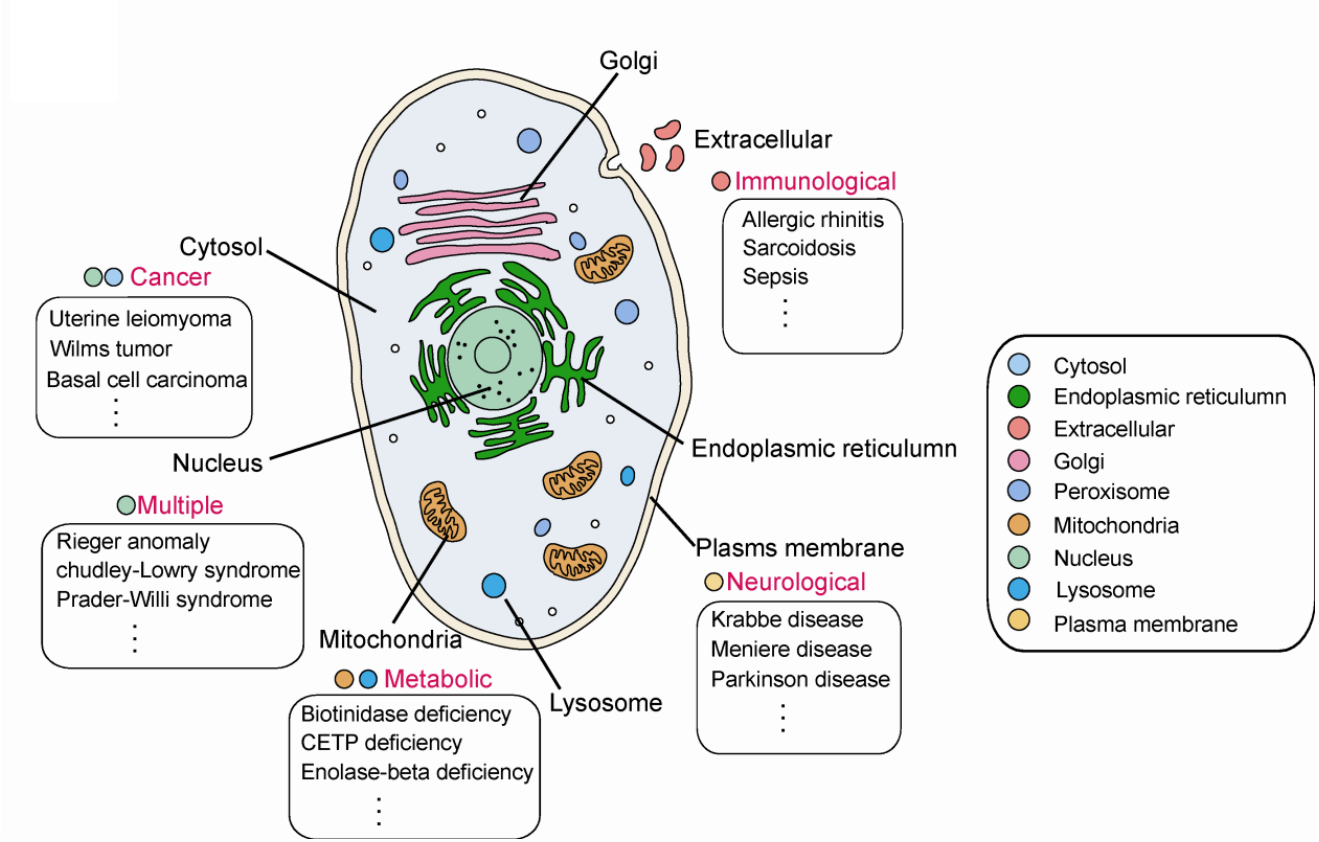
Outline

- Introduction of Network Biology and Medicine
- Network Distance & Localization -> Disease Comorbidity ***Nature Mol Sys Biol.* 2011**
  Human disease evolution ***Nature Scientific Reports 2012***
  Mitochondrial protein network ***Nature Scientific Reports 2013***
- Network Clustering -> Cancer ***PLoS Comp. Biol.* 2011**
- Network Rewiring and Evolution -> Gene essentiality changes ***Nature Scientific Reports 2012***
  Neuronal Disease ***PLoS Genetics* 2012**

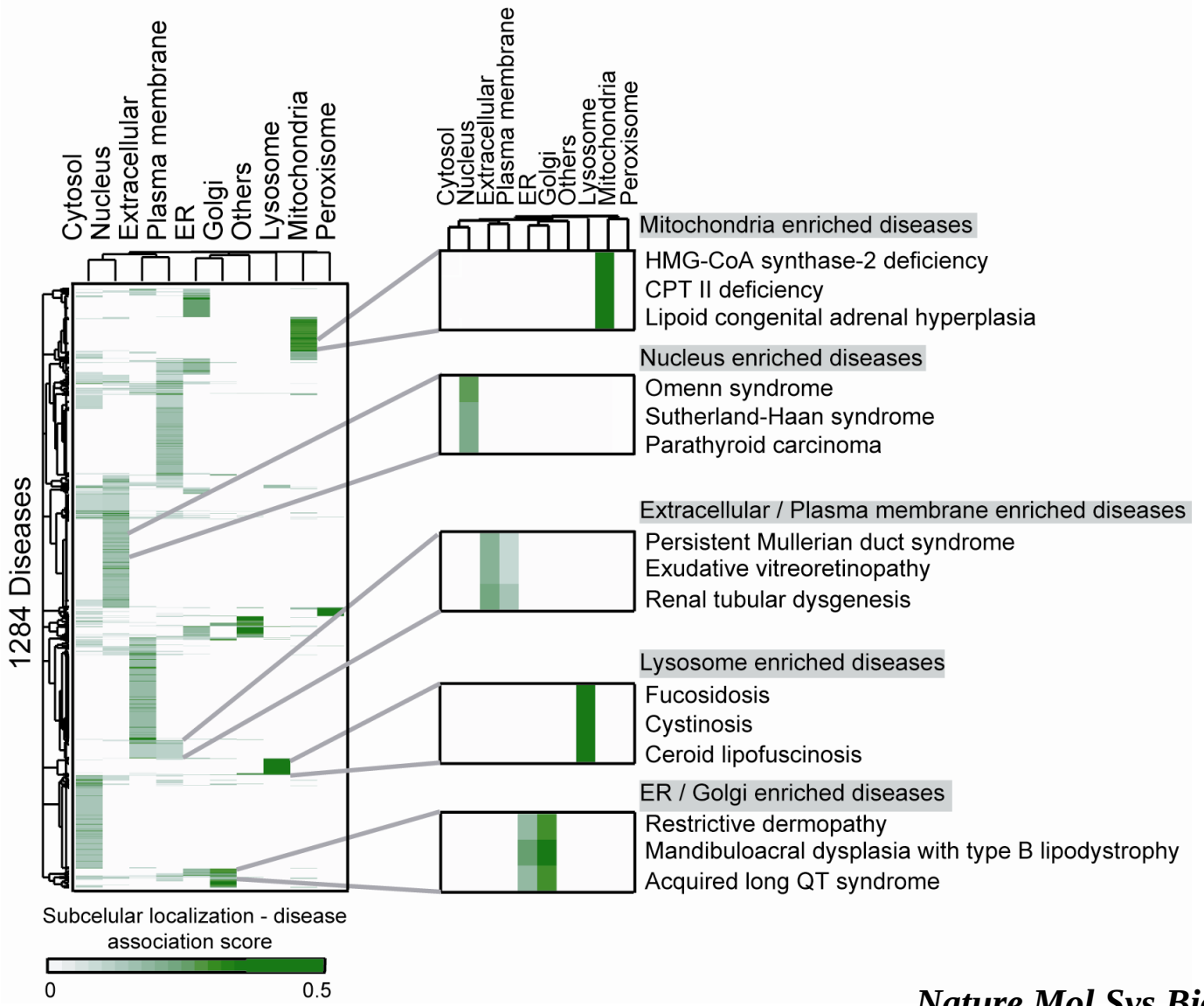
1. Spatial and functional organization of mitochondrial protein network. ***Nature Scientific Reports 2013*** 3:1403.
2. Network rewiring is an important mechanism of gene essentiality change. ***Nature Scientific Reports 2012*** 2:900.
3. Rewiring of PDZ domain-ligand interaction network contributed to eukaryotic evolution. ***PLoS Genetics*. 2012** 8(2):e1002510.
4. Evolutionary history of human disease genes reveals phenotypic connections and comorbidity among genetic diseases. ***Nature 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.

Protein localization as a principal feature of the etiology and comorbidity of genetic diseases

Protein subcellular localization and Human diseases

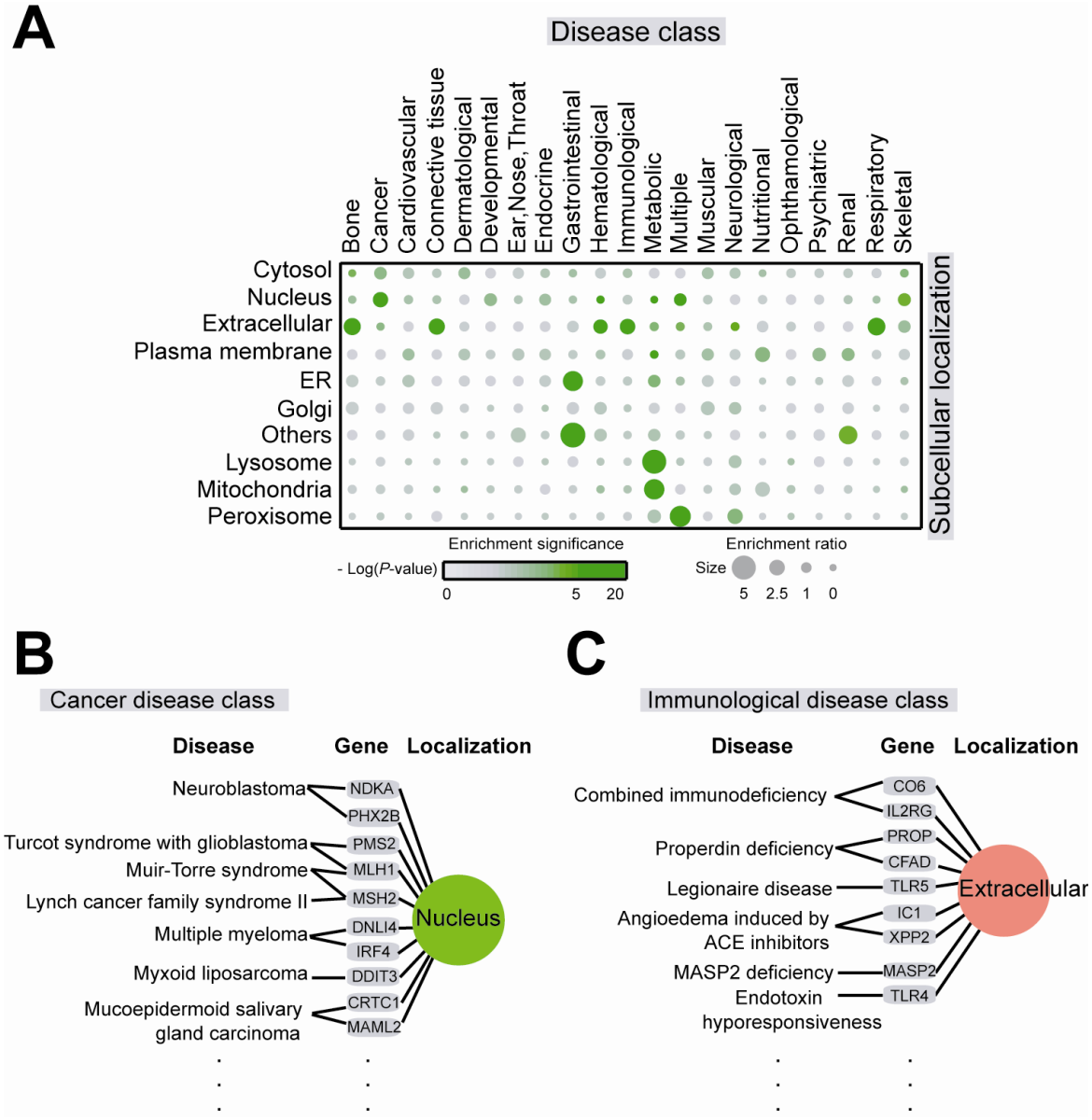


Relationships between disease-associated proteins and their subcellular localizations



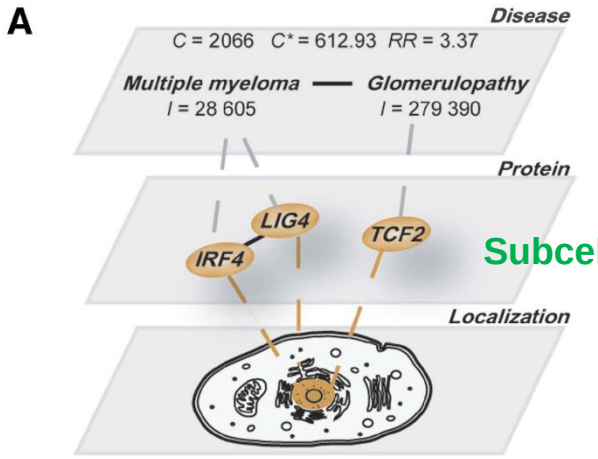
Nature Mol Sys Biol. 2011

Correlation between disease classes and subcellular localizations

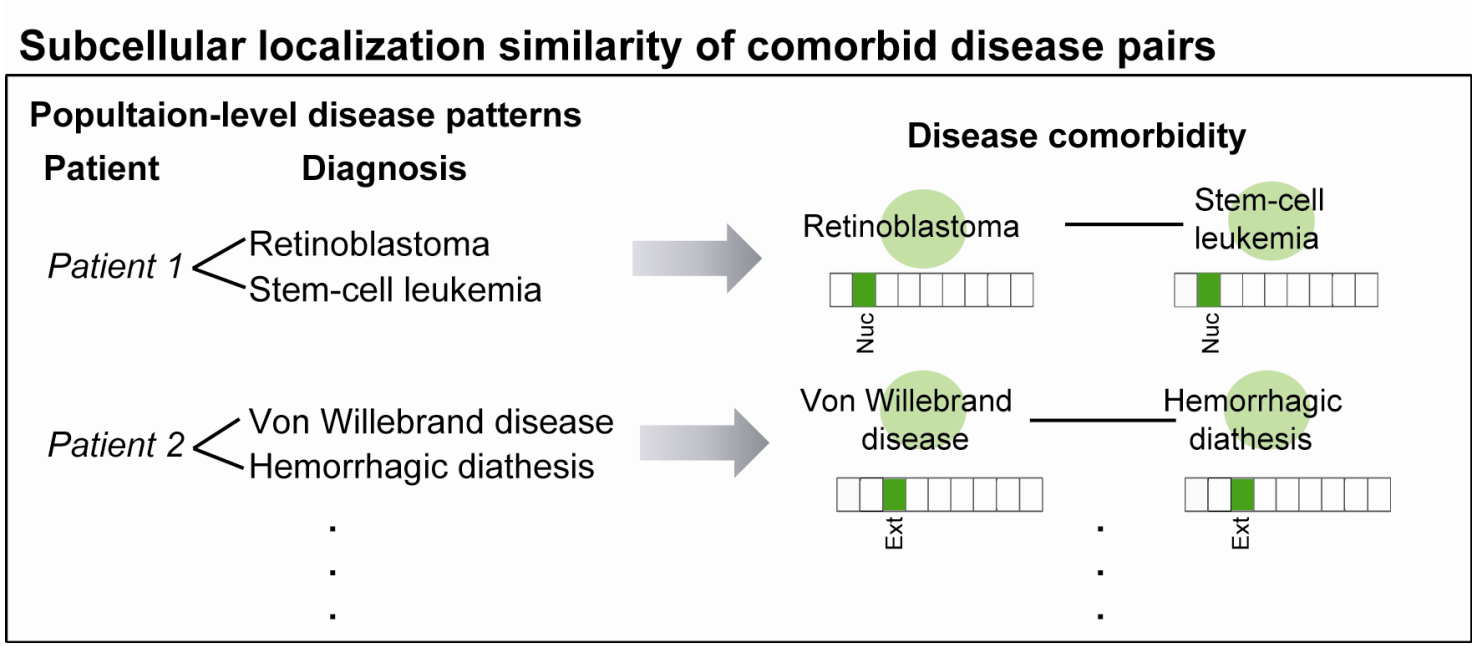


Nature Mol Sys Biol. 2011

The implication of subcellular localization for disease comorbidity

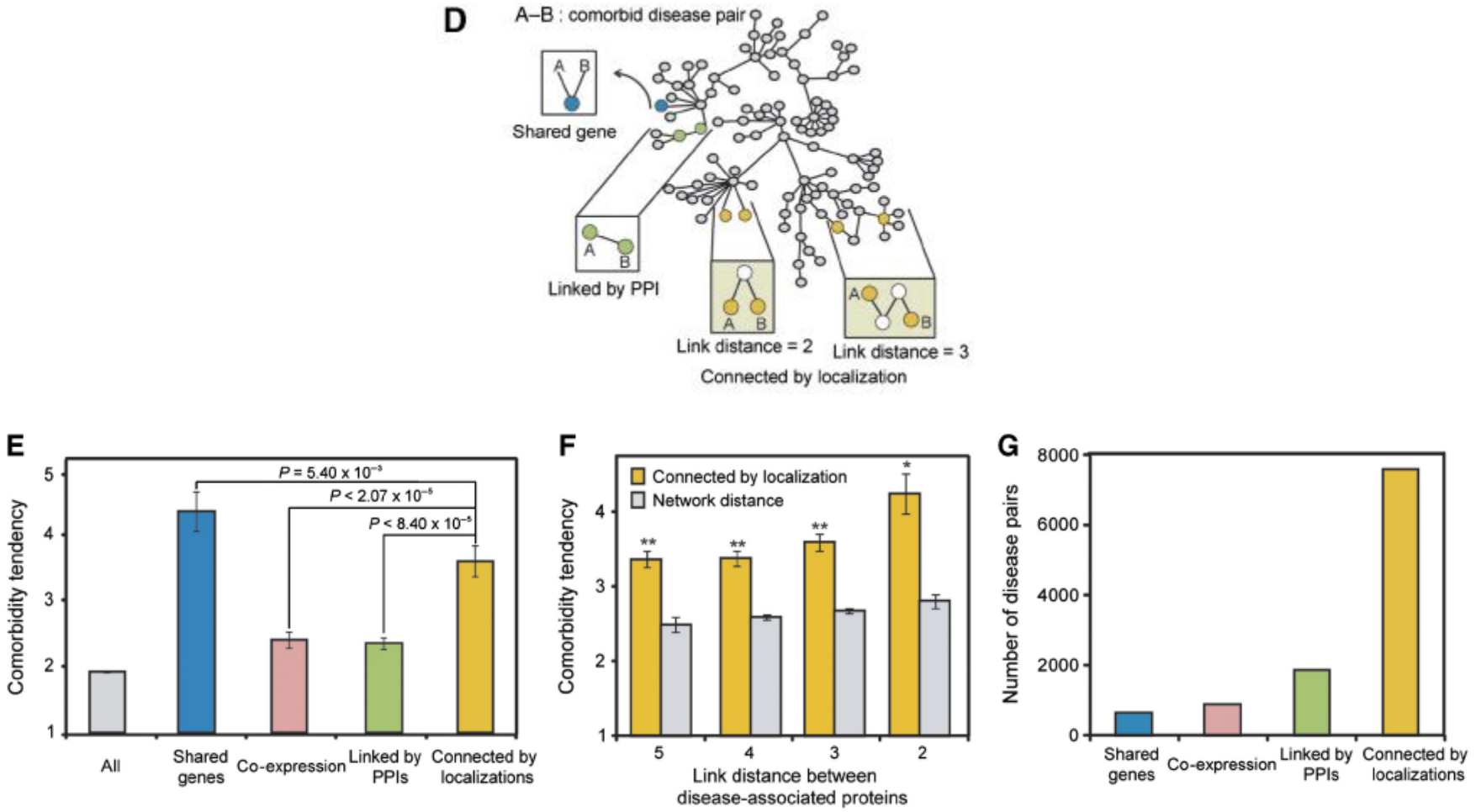


Subcellular localization similarity of human diseases



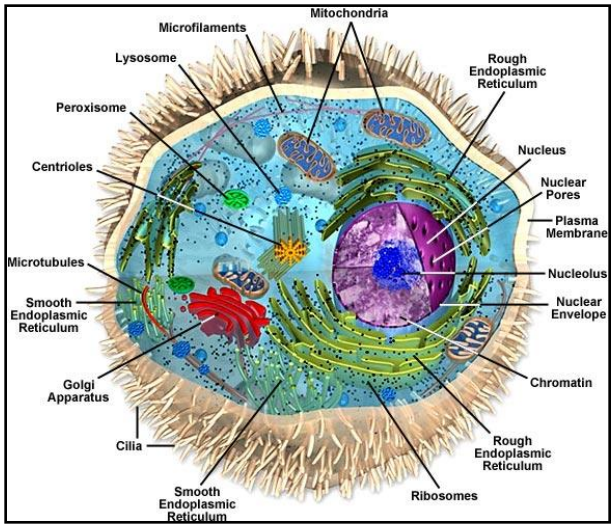
Nature Mol Sys Biol. 2011

The implication of subcellular localization for disease comorbidity



Nature Mol Sys Biol. 2011

Disease gene finding through subcellular localization

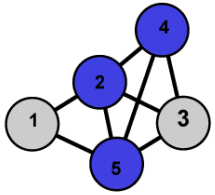


Construction of functional interaction networks through consensus localization predictions of the human proteome.

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

A

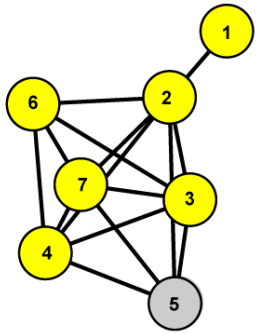
Localization: Plasma membrane
Disease: Basal cell carcinoma



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

B

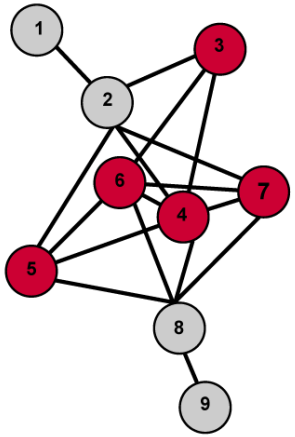
Localization: Cytosol
Disease: Deafness, autosomal dominant



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

•Introduction of Network Biology and Medicine

•Network Distance & Localization -> Disease Comorbidity ***Nature Mol Sys Biol.* 2011**

Human disease evolution ***Nature Scientific Reports 2012***

Mitochondrial protein network ***Nature Scientific Reports 2013***

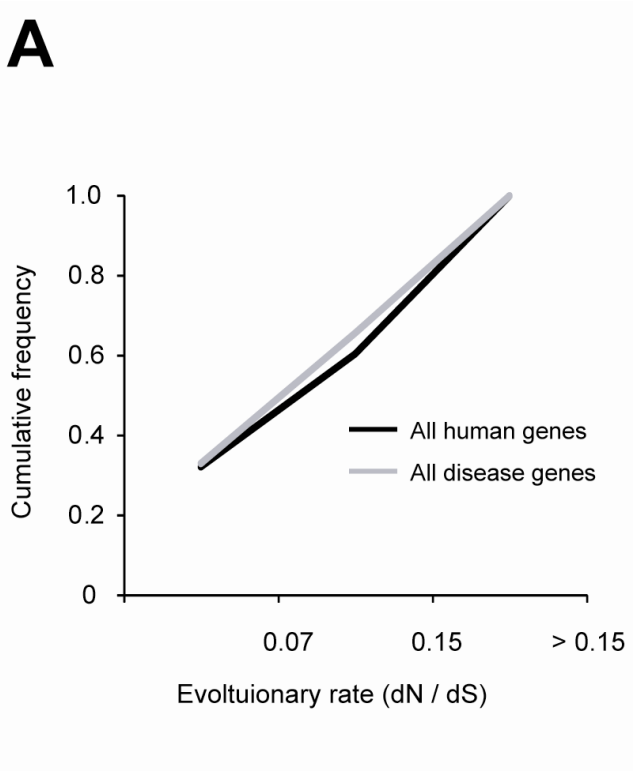
•Network Clustering -> Cancer ***PLoS Comp. Biol.* 2011**

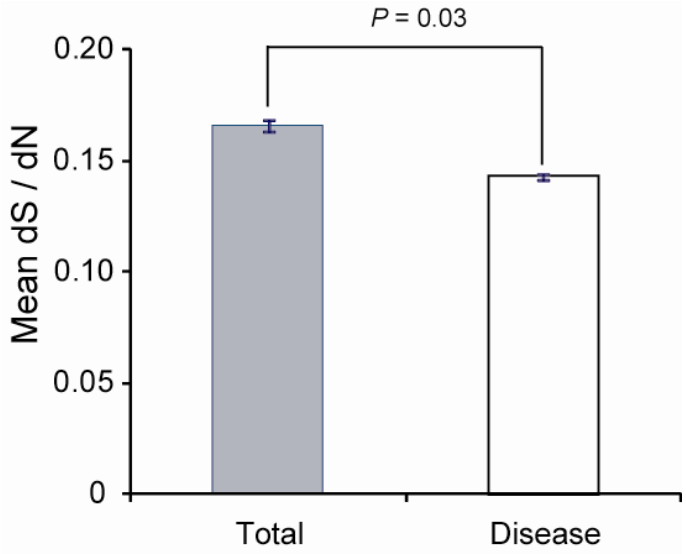
•Network Rewiring and Evolution -> Gene essentiality changes ***Nature Scientific Reports 2012***

Neuronal Disease ***PLoS Genetics* 2012**

1. Spatial and functional organization of mitochondrial protein network. ***Nature Scientific Reports 2013*** 3:1403.
2. Network rewiring is an important mechanism of gene essentiality change. ***Nature 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. ***Nature 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.

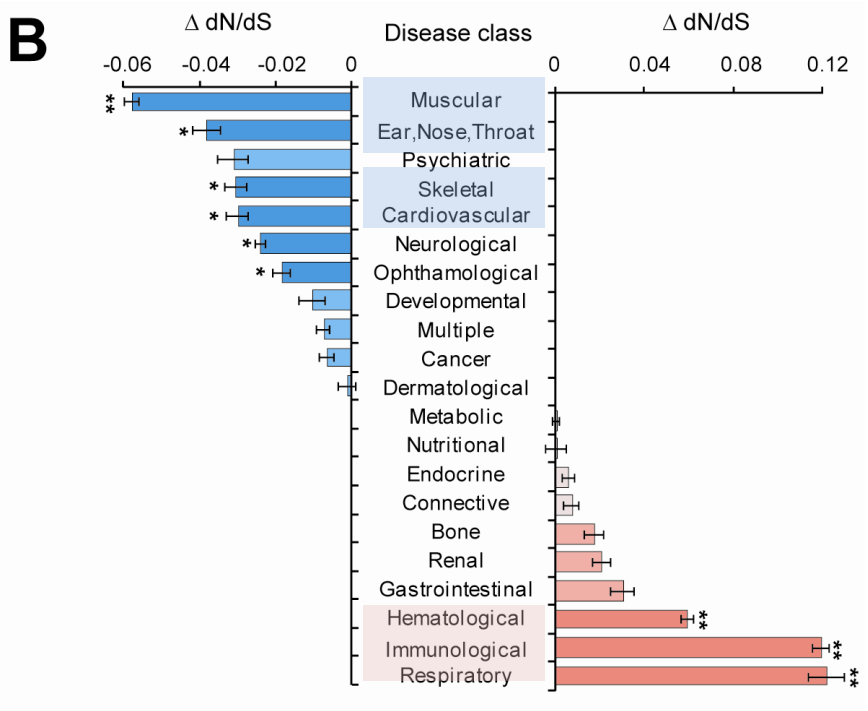
Human disease genes; fast or slow evolving ?





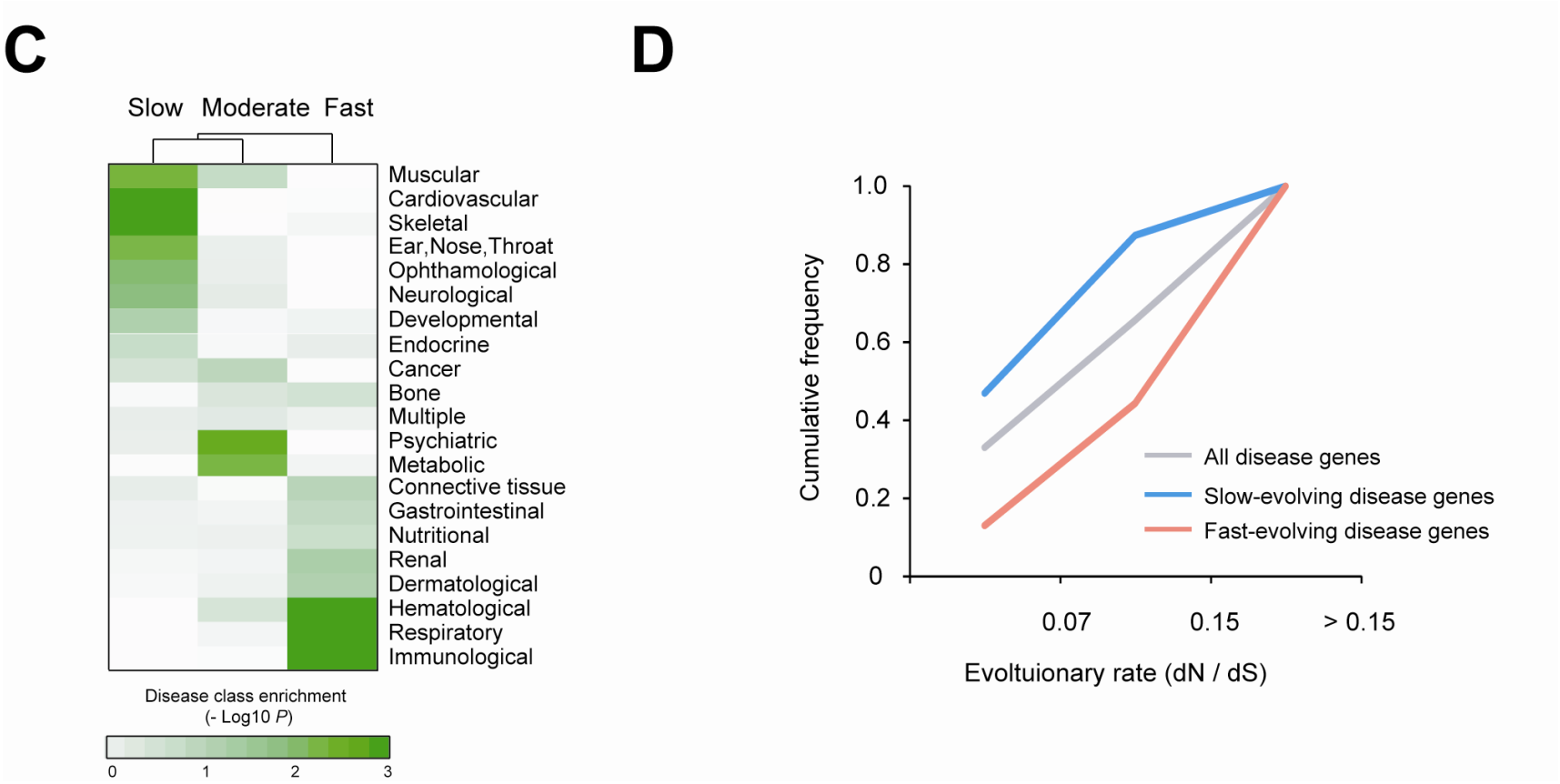
Suppl. Figure

Human disease genes have diverse evolutionary rates

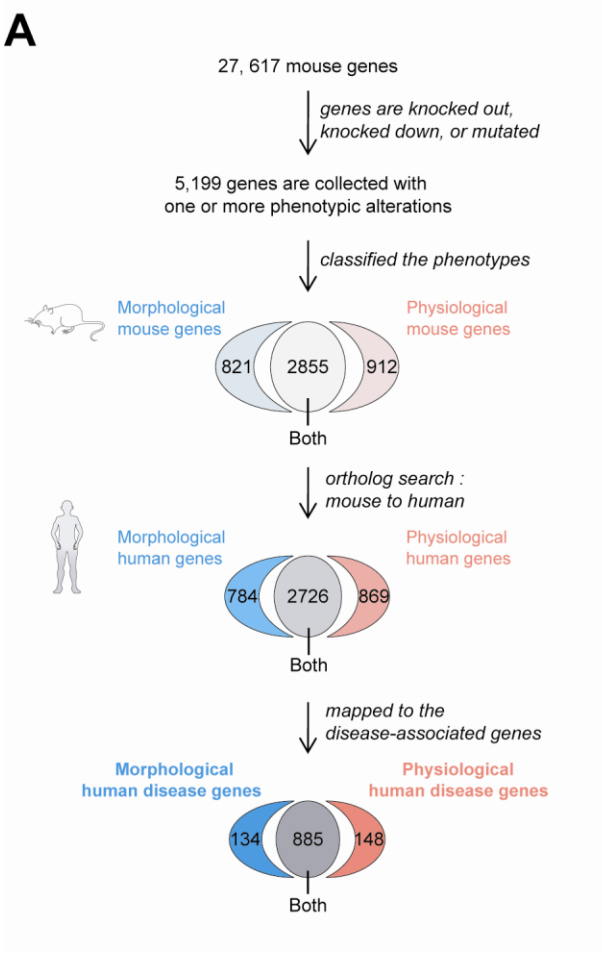


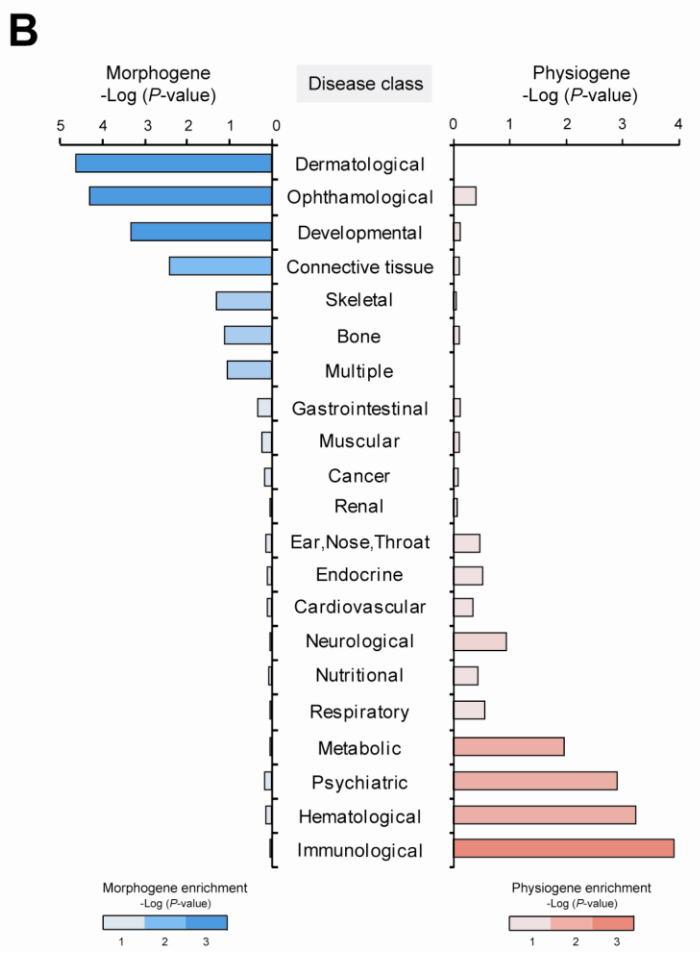
Phenotypically similar disease classes share similar evolutionary history

Human disease genes have diverse evolutionary rates



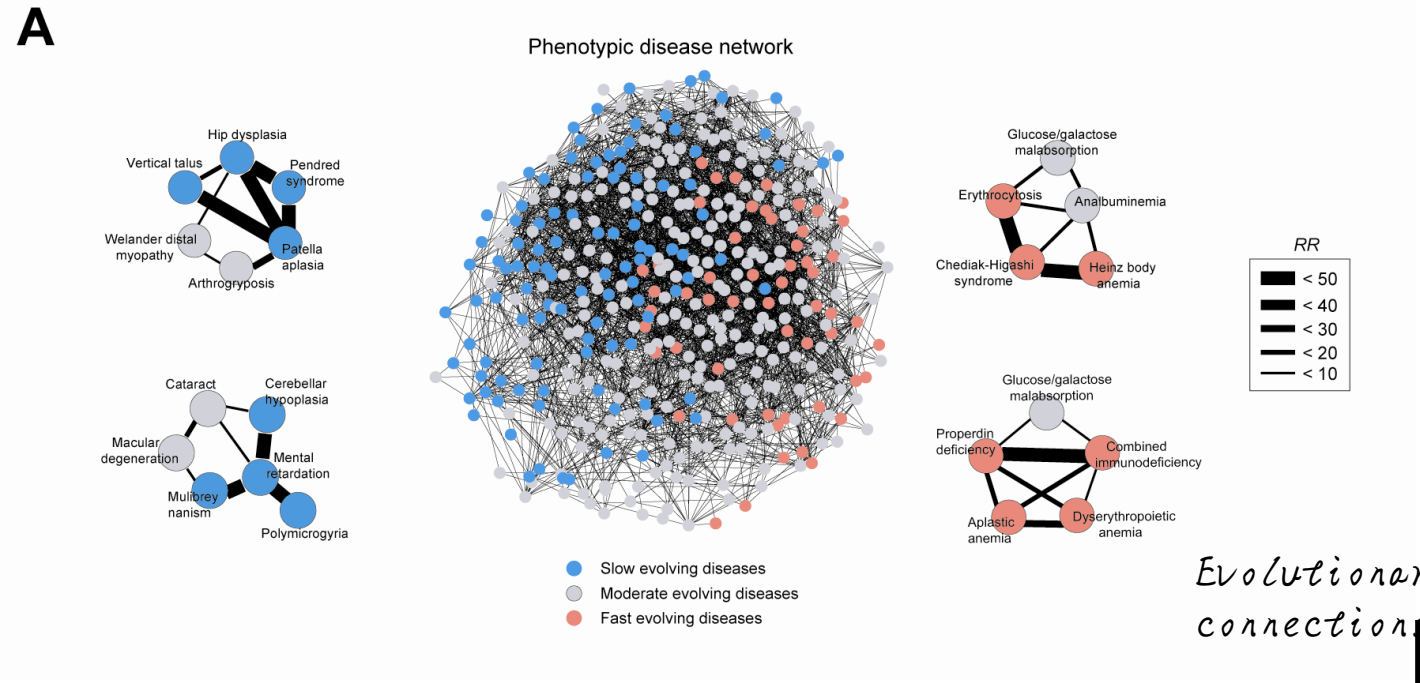
Morphogenes and physiogenes enriched dibberently In various disease classes





Evolution connect genotype to phenotype

Molecular connections in the comorbid disease pairs



Evolutionary connections

Molecular connections

Phenotypic connections : comorbidity

•Introduction of Network Biology and Medicine

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

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

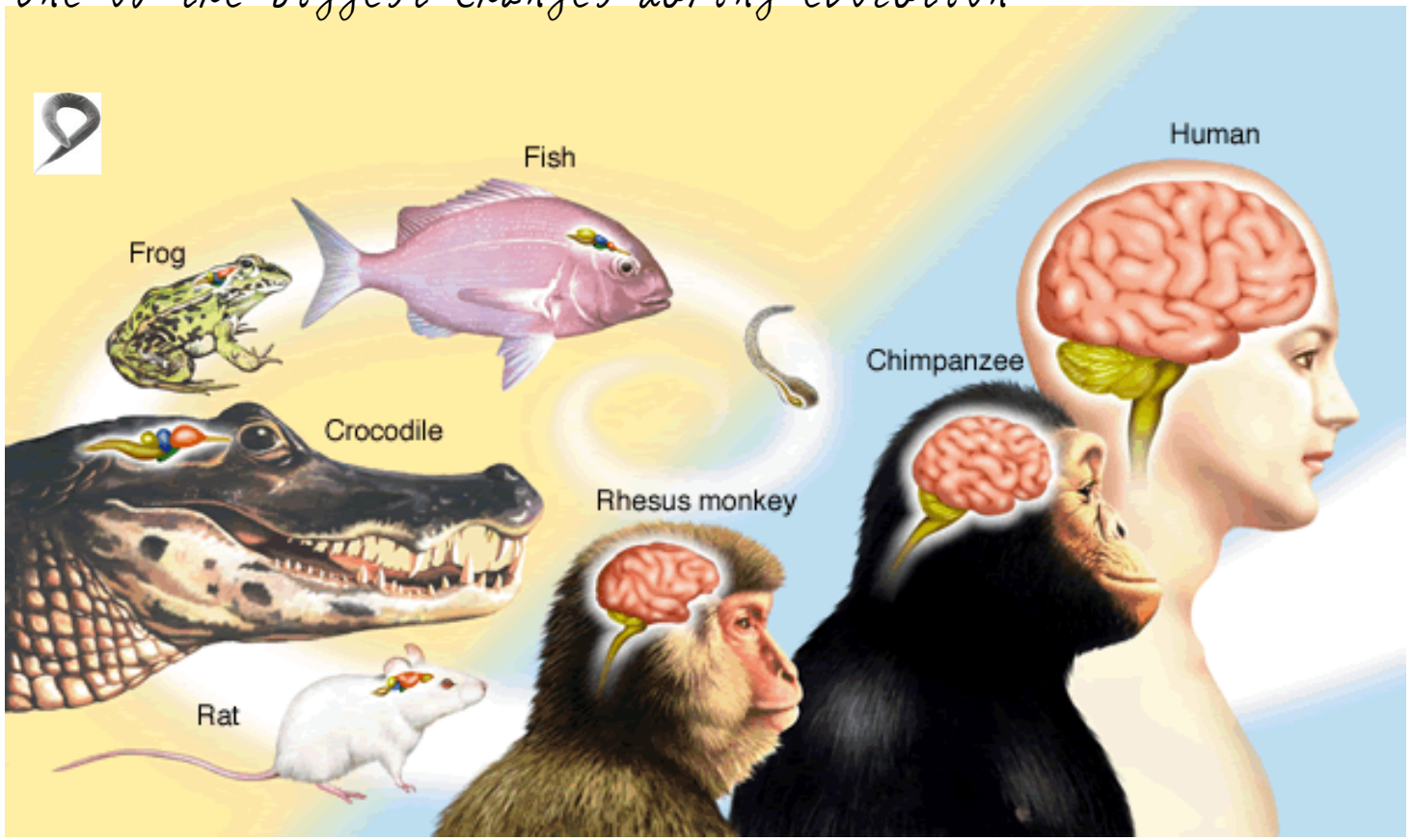
•Network Rewiring and Evolution -> Gene essentiality changes ***Nature Scientific Reports 2012***
Neuronal Disease ***PLoS Genetics* 2012**

1. Spatial and functional organization of mitochondrial protein network. ***Nature Scientific Reports 2013*** 3:1403.
2. Network rewiring is an important mechanism of gene essentiality change. ***Nature 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. ***Nature 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.

Rewiring of PDZ domain-ligand interaction network contributed to eukaryotic evolution

Evolution of brain

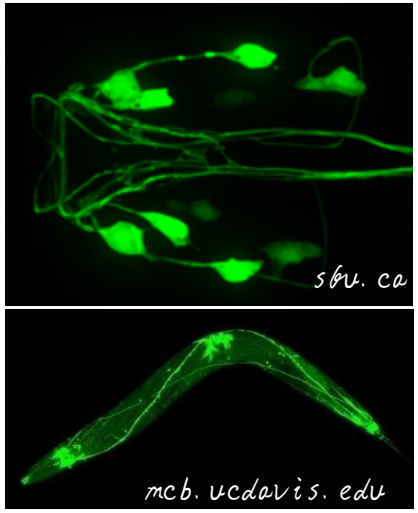
One of the biggest changes during evolution

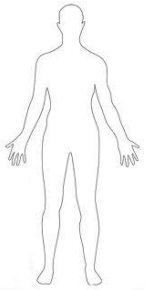


http://www.brain.riken.jp

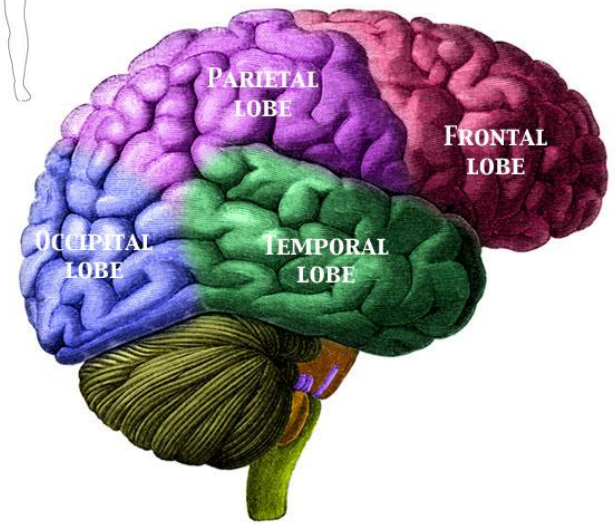
Increase of synaptic diversity (number of brain regions)

C. elegans brain





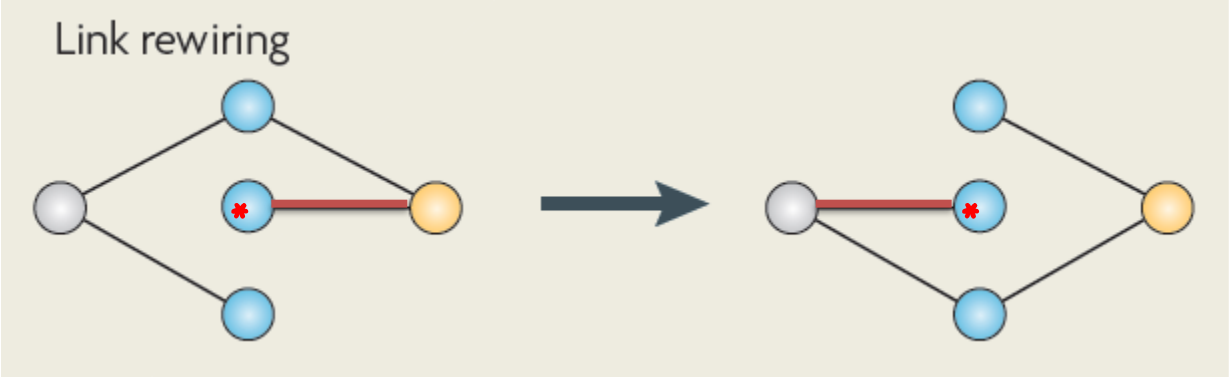
Human brain



lilachrysikou.wordpress.com

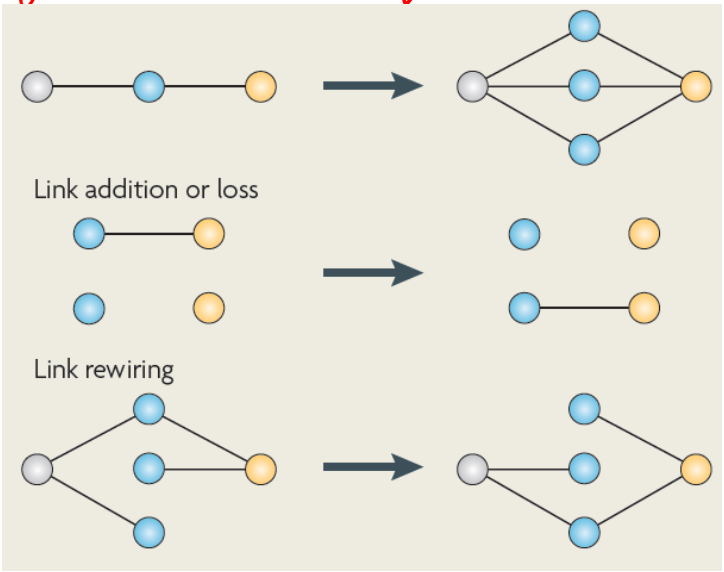
What is the molecular level explanation of neuronal development?

Rewiring of interactions



T. Yamada and P. Bork, Nat. Rev. Mol. Cell biol. 2009

Interaction rewiring can reconfigure molecular systems without a gain or loss of gene.

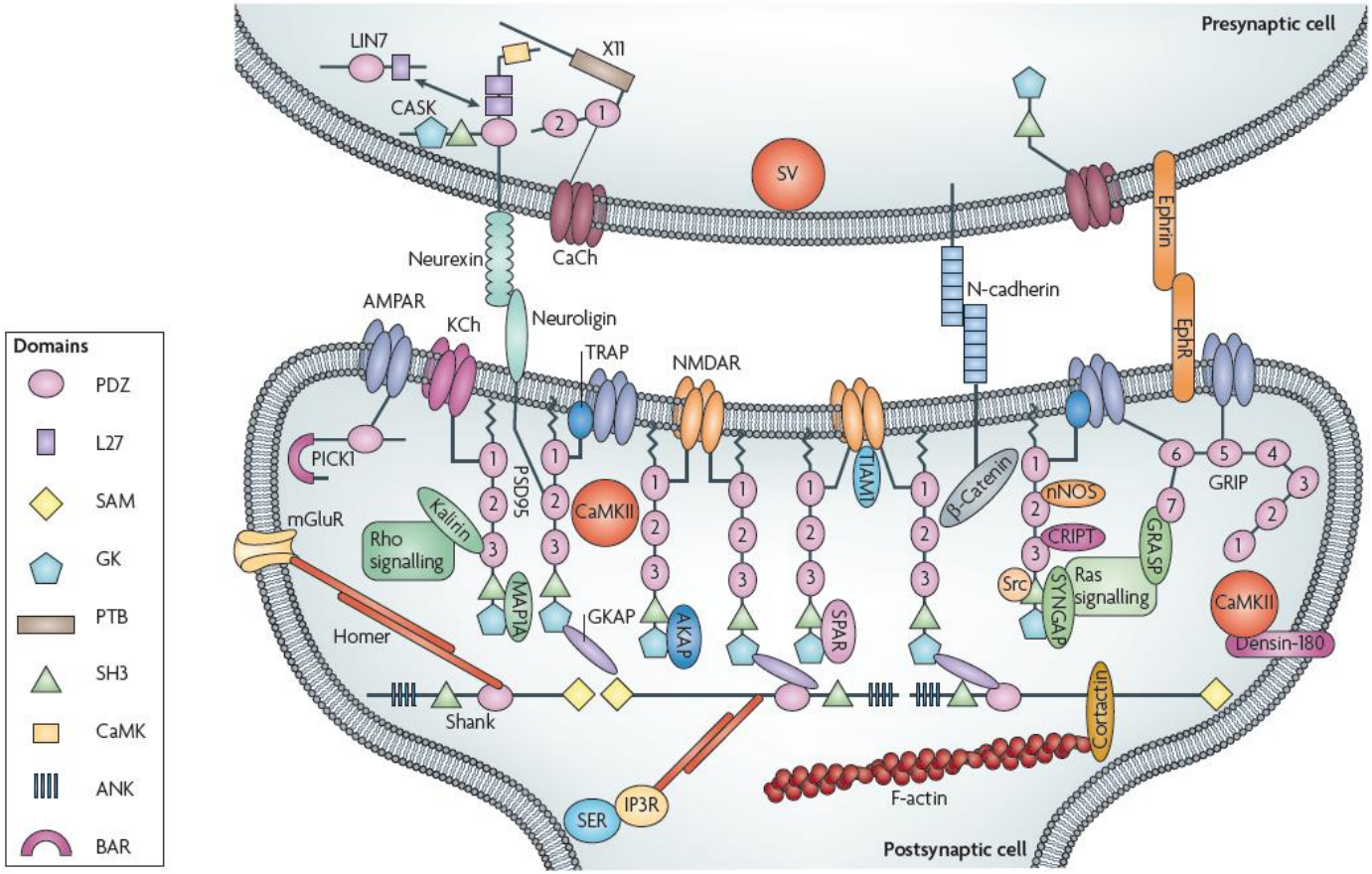


PDZ protein interactions play important roles in the postsynaptic density (PSD)

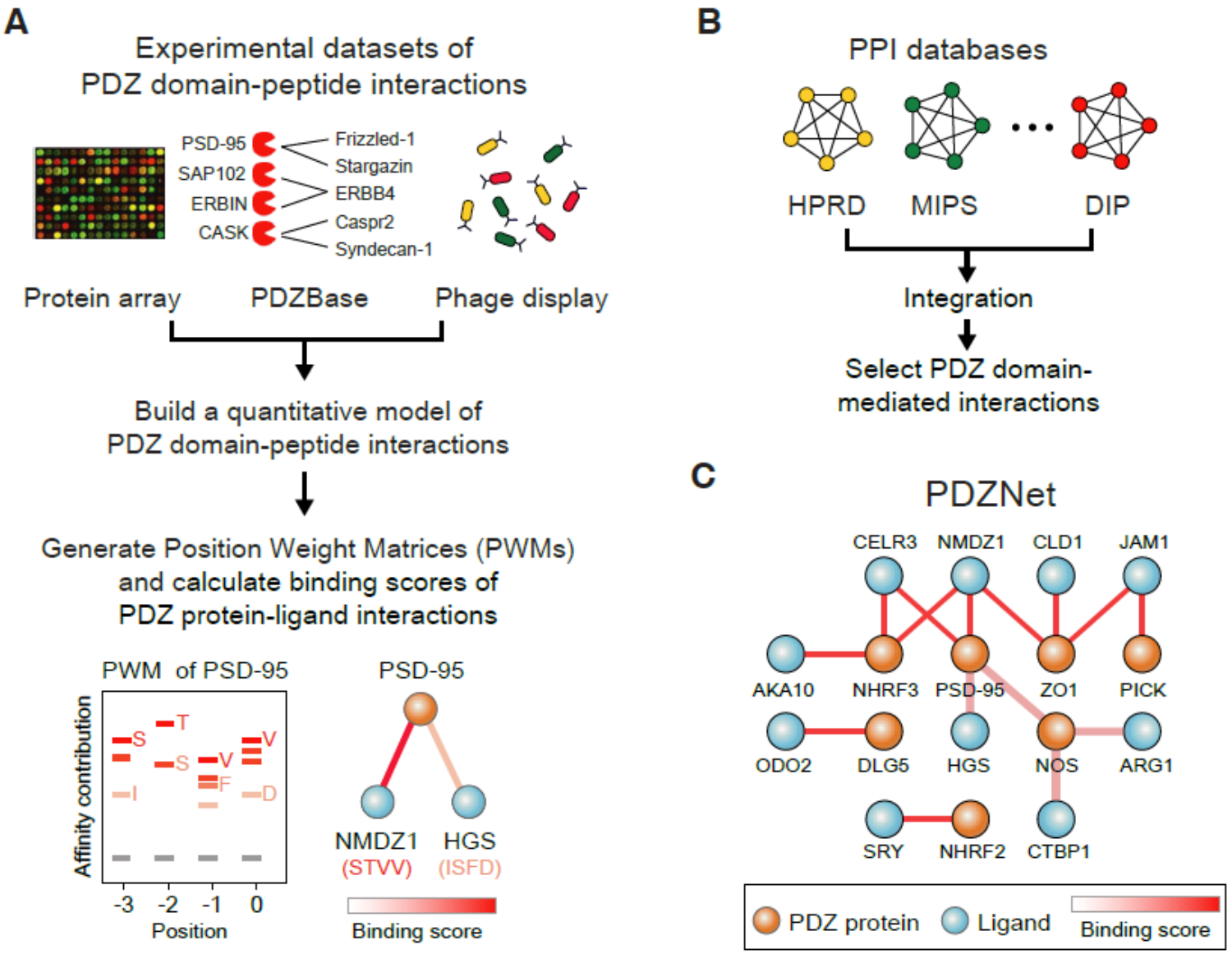
Organization and dynamics of PDZ-domain-related supramodules in the postsynaptic density

Wei Feng and Mingjie Zhang

NATURE REVIEWS | NEUROSCIENCE | FEBRUARY 2009

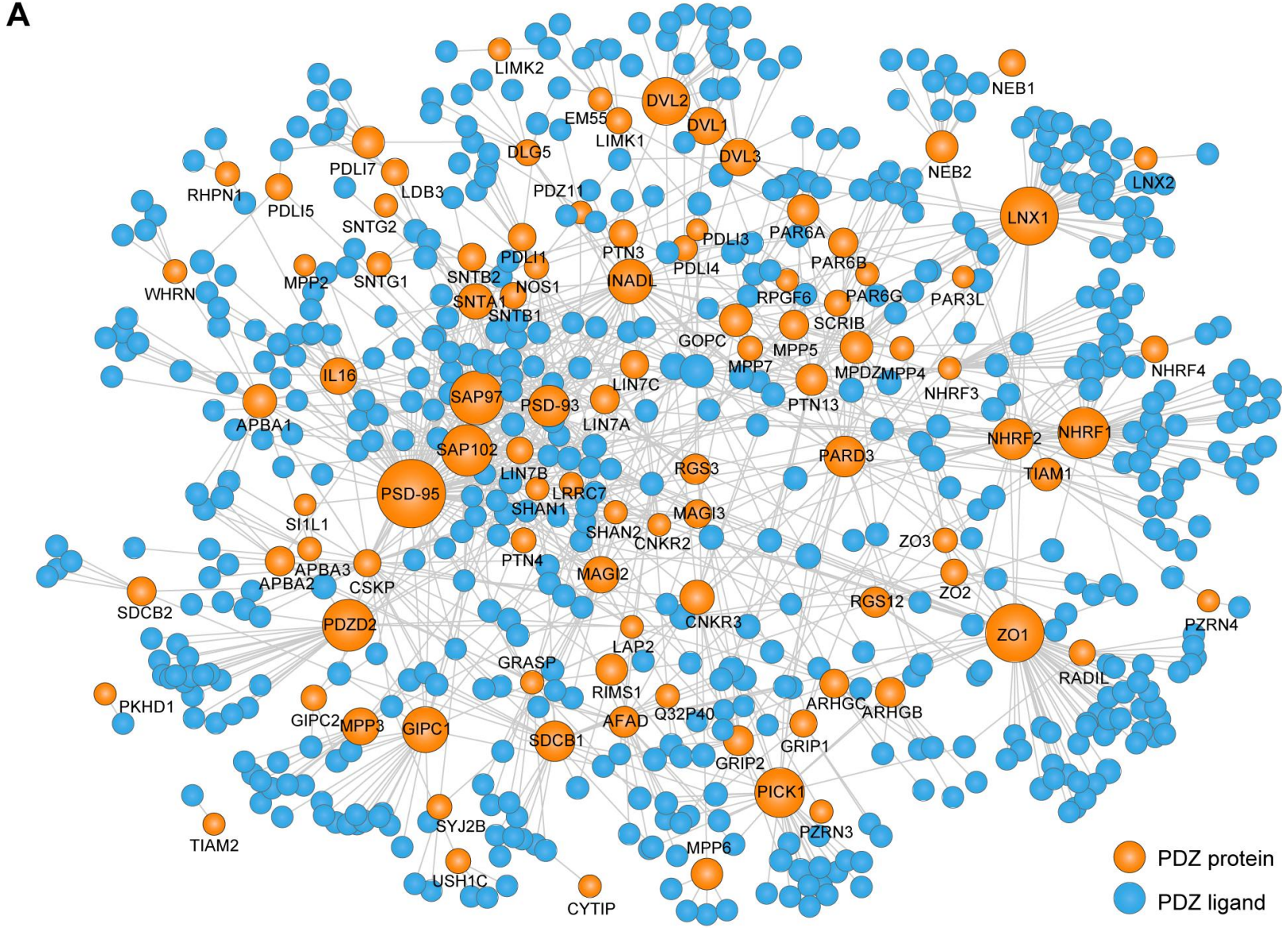


Construction of human PDZ domain-ligand interaction network (PDZNet)



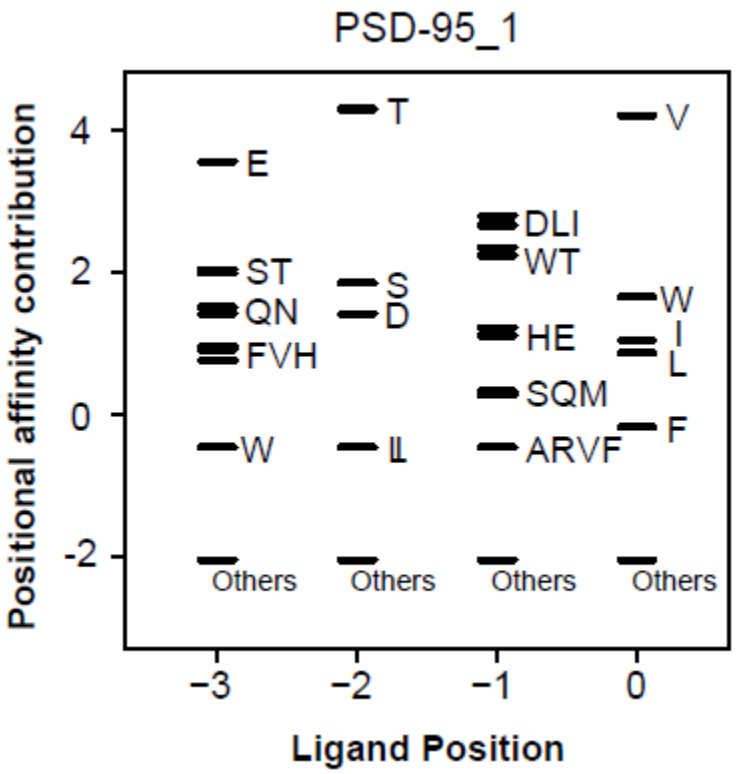
PLoS Genetics 2012

Human PDZNet



PLoS Genetics 2012

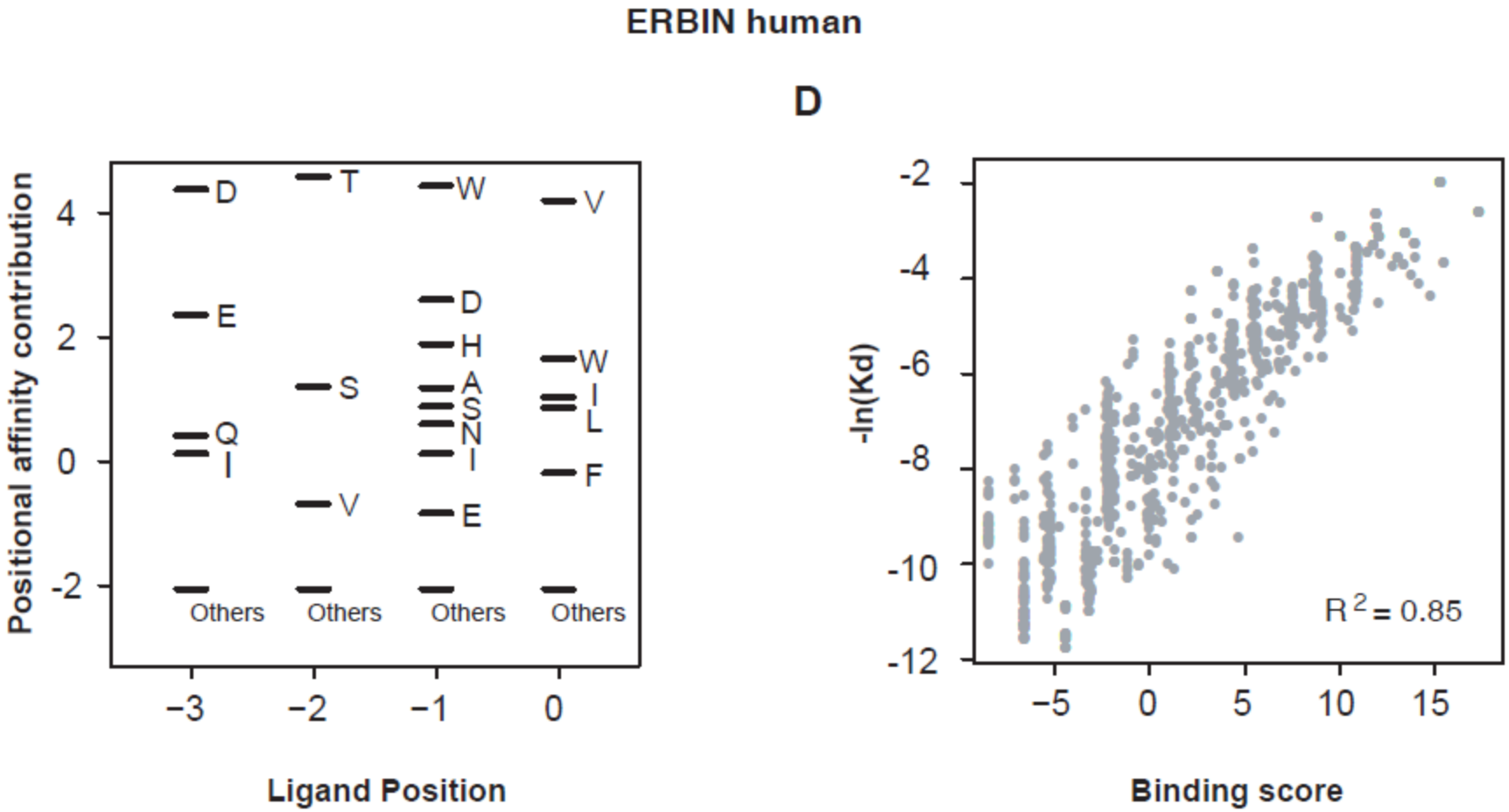
PWM can identify the known binders of PDZ domains



Species	Ligand	C-terminal	Percentile rank (%)	Binding score
Human	PMCA4b	ETSV	99.86	13.05
	PMCA2b	ETSL	99.26	9.49
Mouse	Frizzled-4	ETVV	99.96	13.80
	Frizzled-1	ETTV	99.93	13.49
	Frizzled-2	ETTV	99.93	13.49
	Frizzled-7	ETAV	99.87	13.19
	Sema4c	ESSV	99.59	10.61
	BAI1	QTEV	99.56	10.52
	Stargazin	TTPV	99.36	9.77
Rat	Kv1.4	ETDV	99.98	14.72
	ERBB4	NTVV	99.76	12.67
	NMDAR2A	ESDV	99.72	12.28
	NMDAR2B	ESDV	99.72	12.28
	SynGAP	QTRV	99.19	9.79
	PKC-A	QSAV	98.64	8.99
	Sec8	ITTV	98.12	7.93
	GluR6	ETMA	96.19	6.00

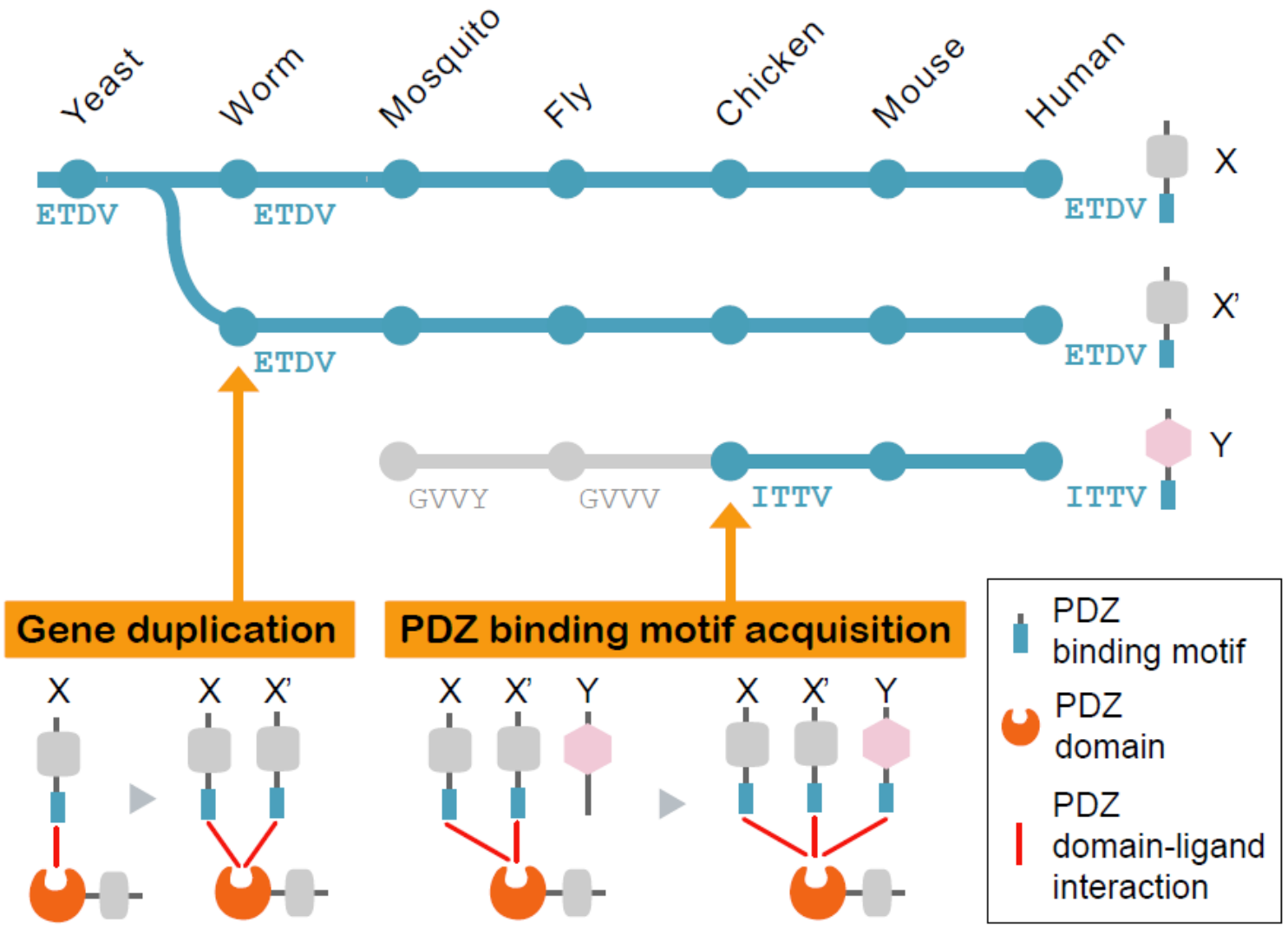
***PLoS Genetics* 2012**

Binding scores correlate well with experimental affinities



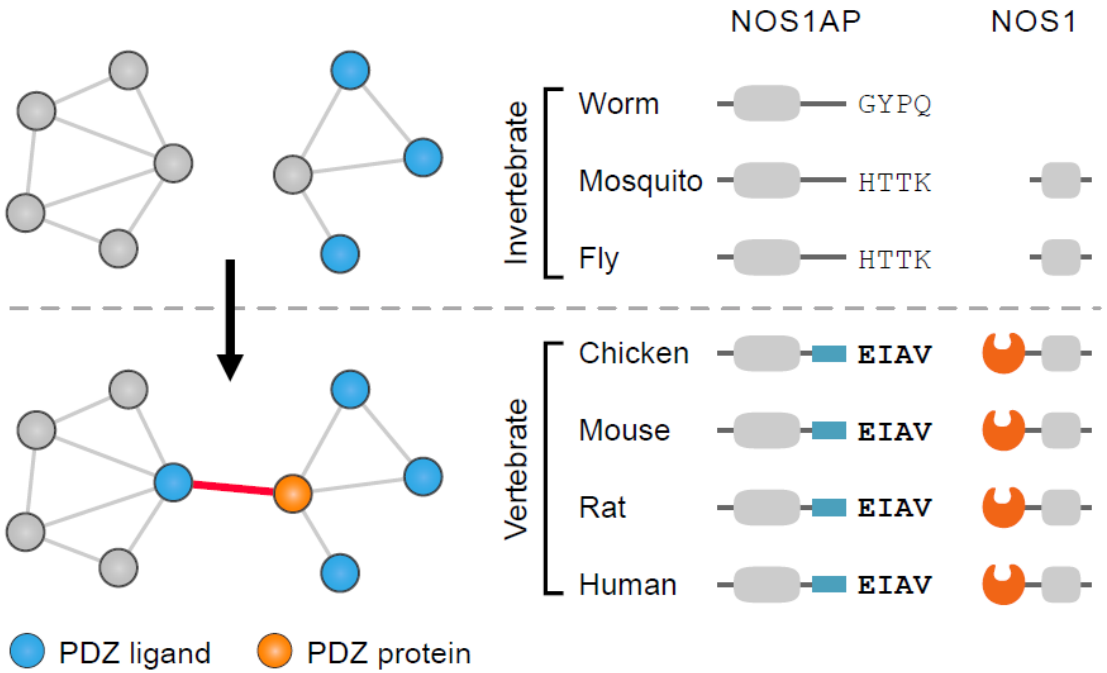
PLoS Genetics 2012

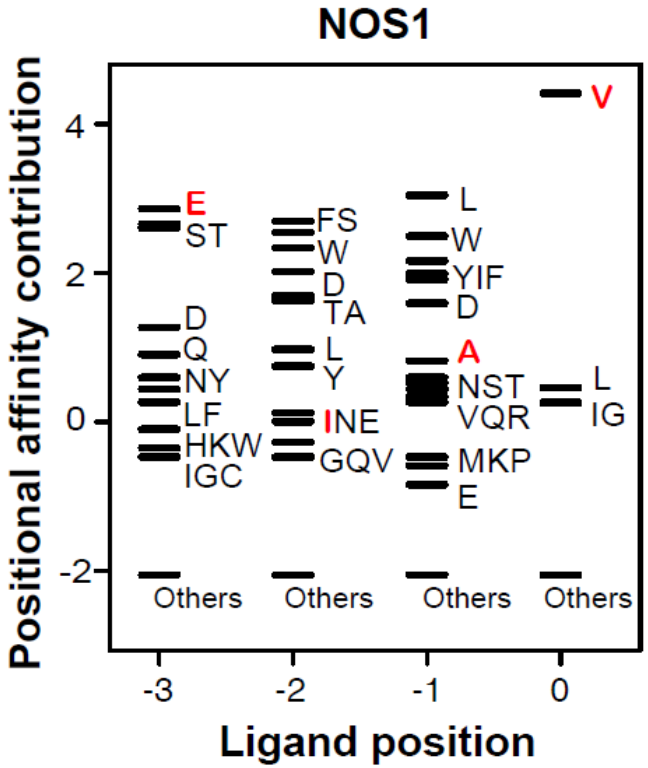
Two evolutionary models describe the expansion of PDZ domain-ligand interactions



PLoS Genetics 2012

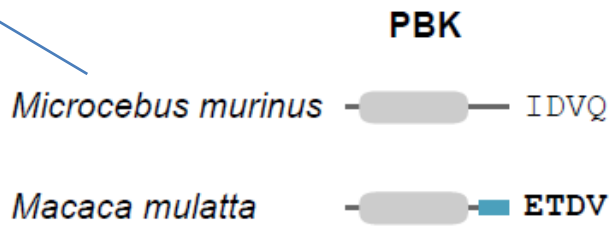
Examples of a PDZ domain-ligand interaction created by sequence mutations

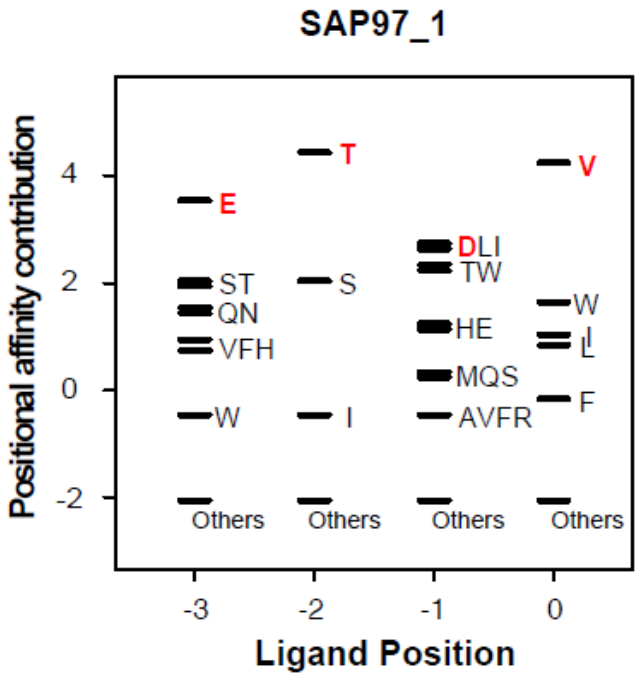


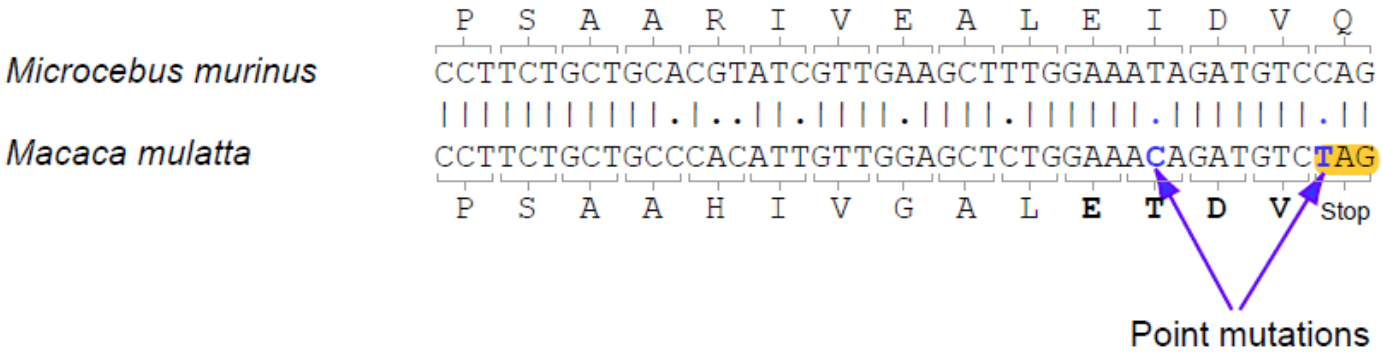


PLoS Genetics 2012

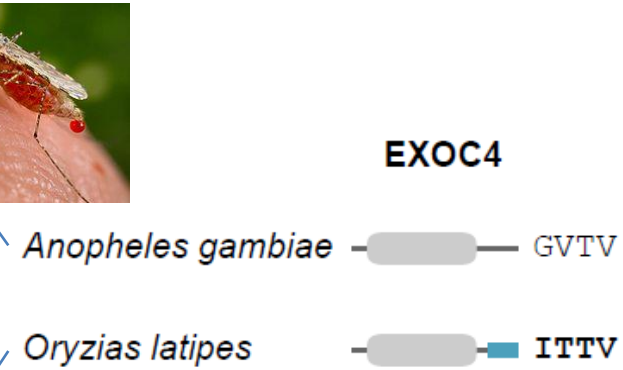
A point mutation generated a PDZ-binding motif in the C-terminal amino acids of the Macaca mulatta PBK protein.

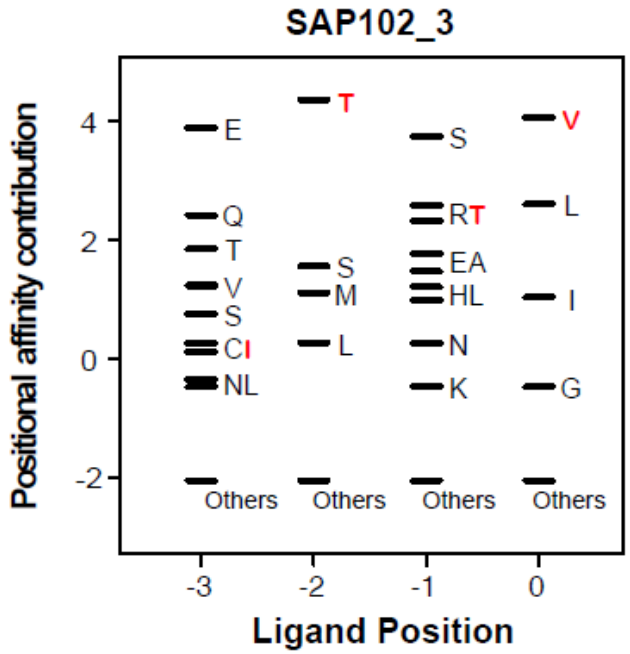


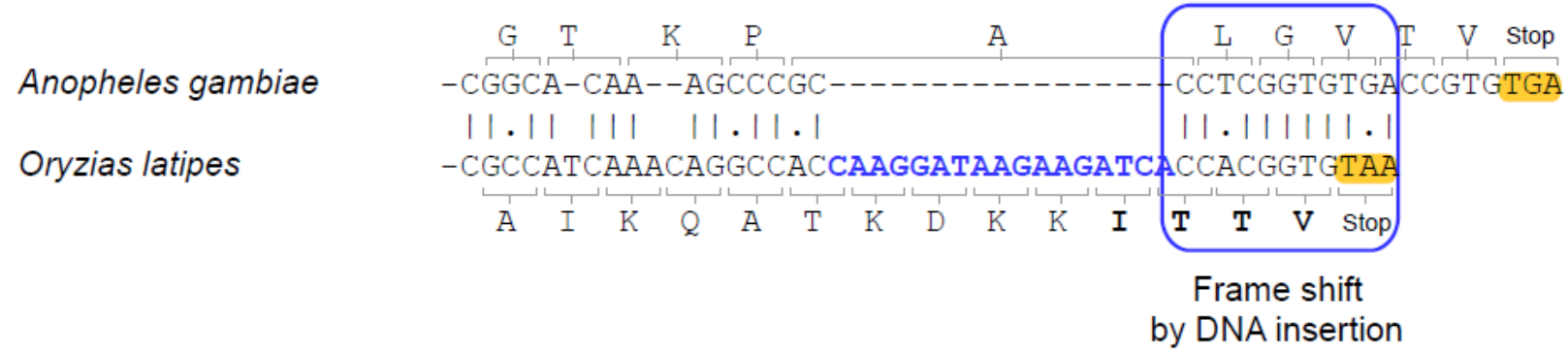




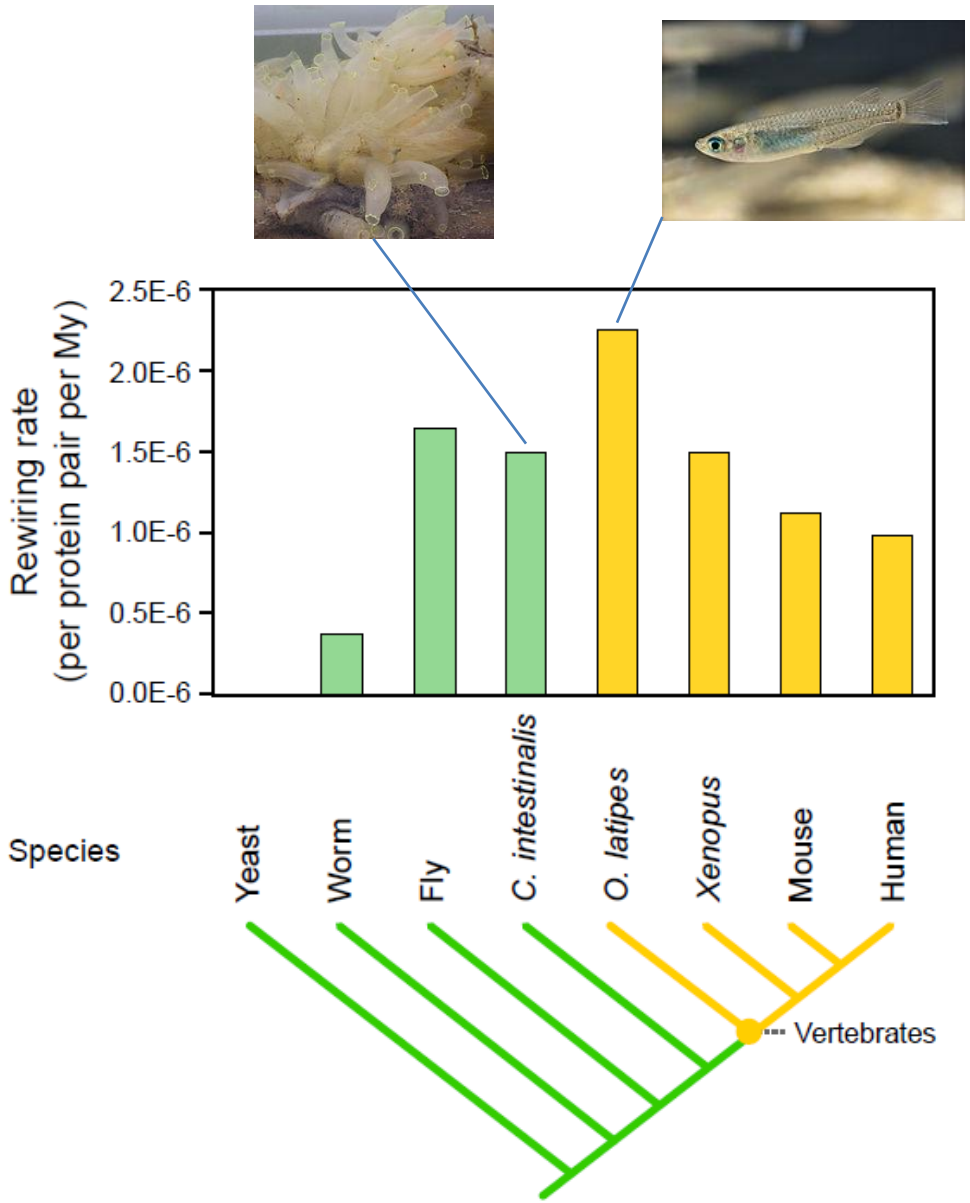
A DNA segment insertion generated a PDZ-binding motif in the C-terminal amino acids of the Oryzias latipes EXOC4 protein.







Rewiring of PDZ domain-ligand interactions plays an important role in the evolution of nervous systems in vertebrates.



***PLoS Genetics* 2012**

•Introduction of Network Biology and Medicine

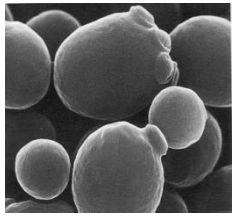
•Network Distance & Localization -> Disease Comorbidity ***Nature Mol Sys Biol.* 2011**
Human disease evolution ***Nature Scientific Reports 2012***
Mitochondrial protein network ***Nature Scientific Reports 2013***

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

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

1. Spatial and functional organization of mitochondrial protein network. ***Nature Scientific Reports 2013*** 3:1403.
2. Network rewiring is an important mechanism of gene essentiality change. ***Nature 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. ***Nature 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.

Increase of network complexity has a major impact on gene essentiality changes.



Mechanism of gene essentiality

Complex relationship between genotype and phenotype

Gene essentiality often changes during evolution

Map2k1 (nonessential in yeast but essential in mouse)

- "Map2k1-/- embryos die at mid-gestation from abnormal development and hypovascularization of the placenta." (Vickram Bissonauth, et al. Development 2006)

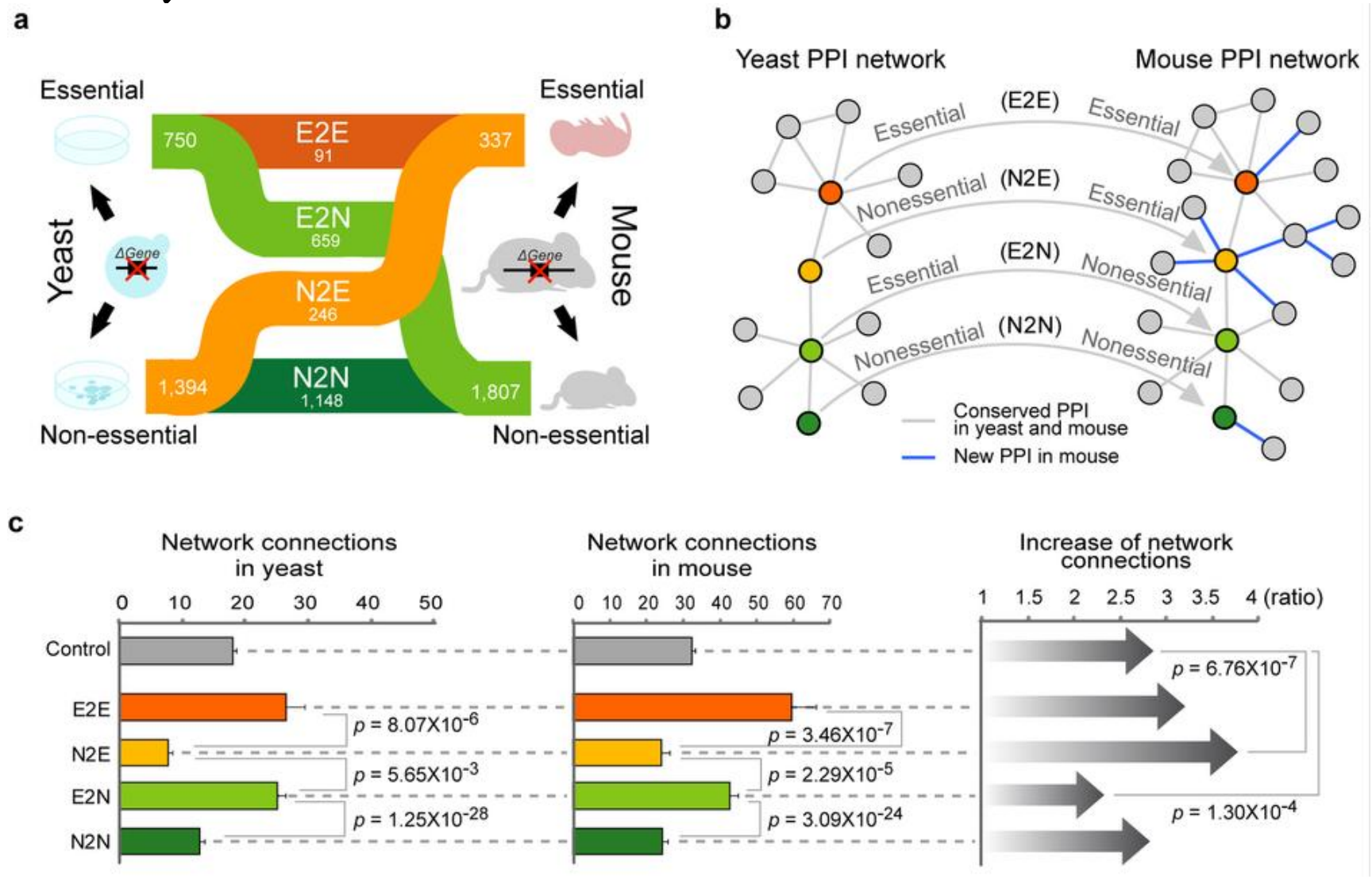
- "In the mouse, loss of Map2k1 function causes embryonic lethality." (Valérie Nadeau, et al. Development 2009)

Ada (nonessential in yeast but essential in mouse)

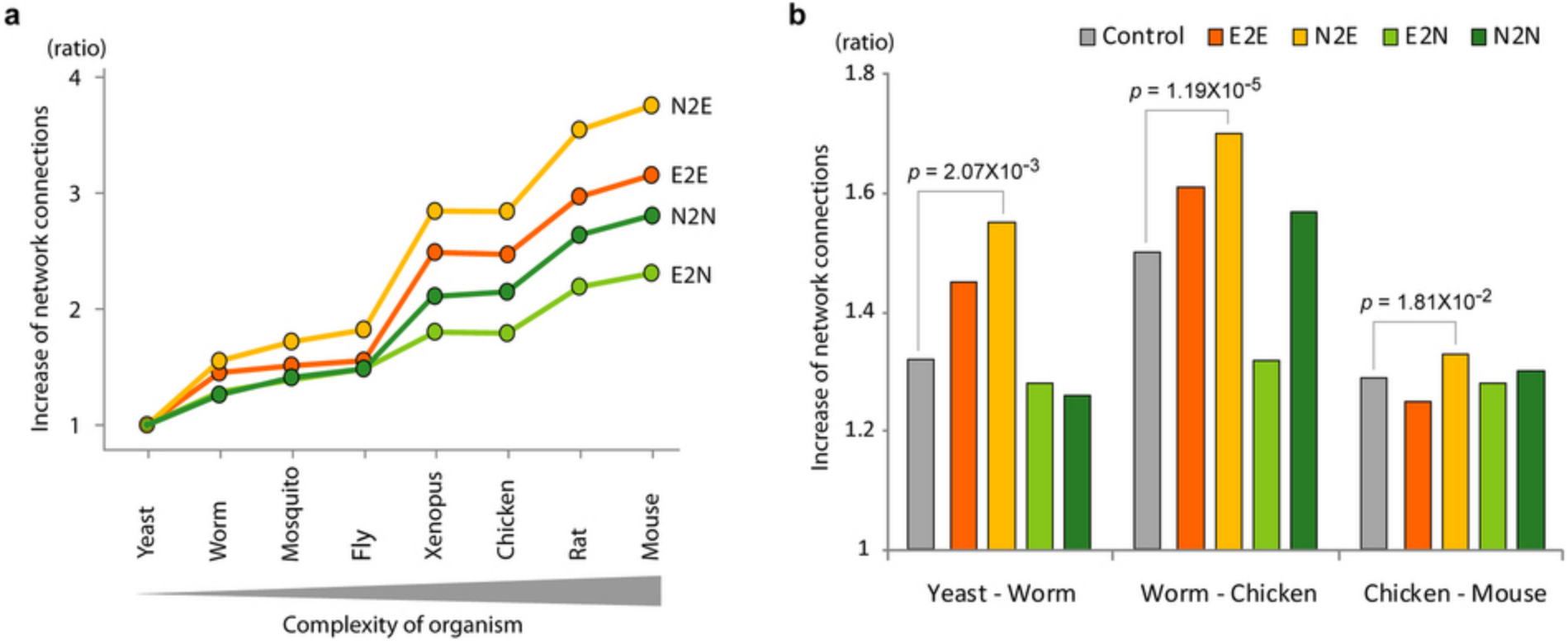
- "Adenosine deaminase deficient (Ada) mice die perinatally." (Alexandra A. J. Migchielsen, et al. Nat. Genetics 1995)

It is unclear how nonessential genes become essential in more complex organisms

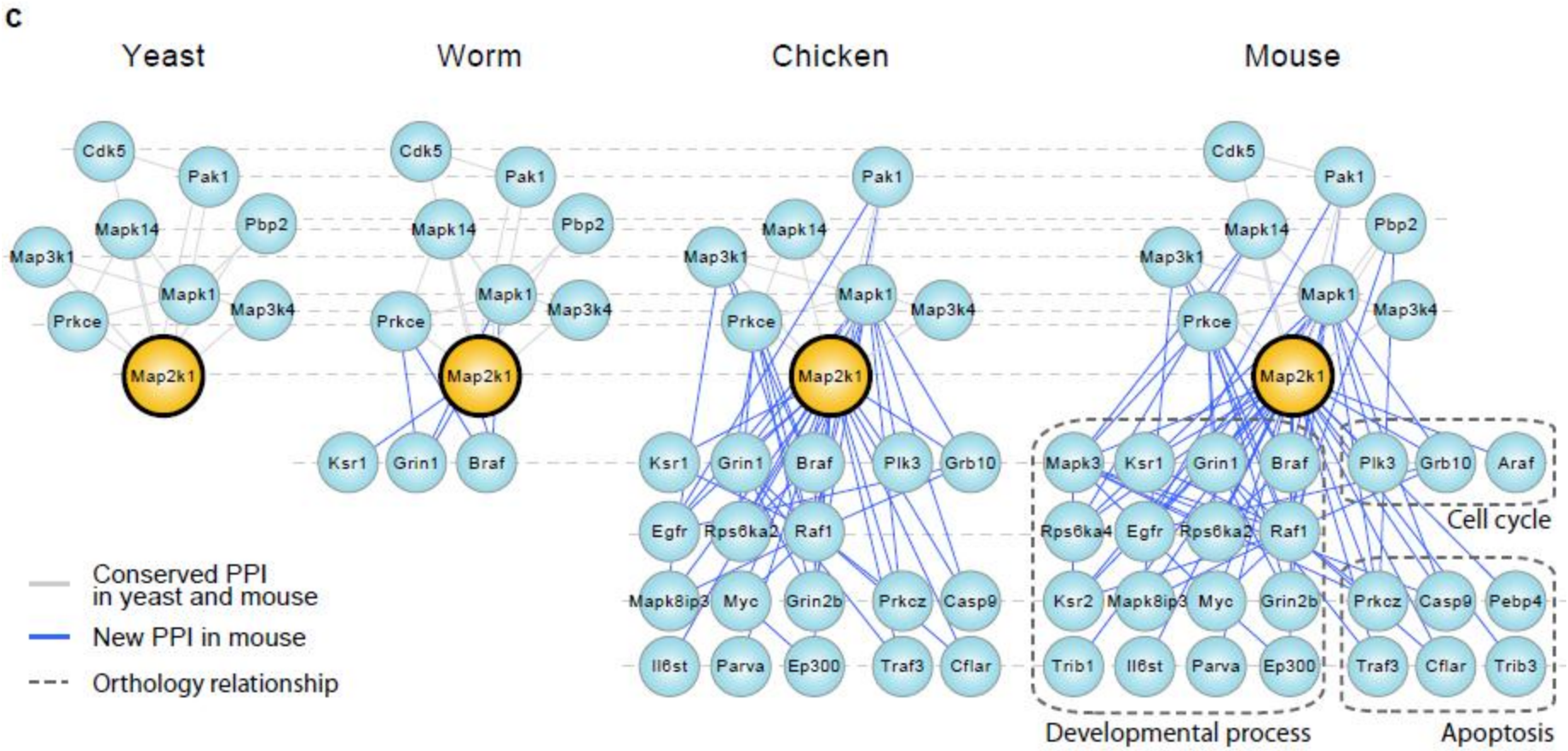
Increase in network connections and gene essentiality changes between yeast and mouse



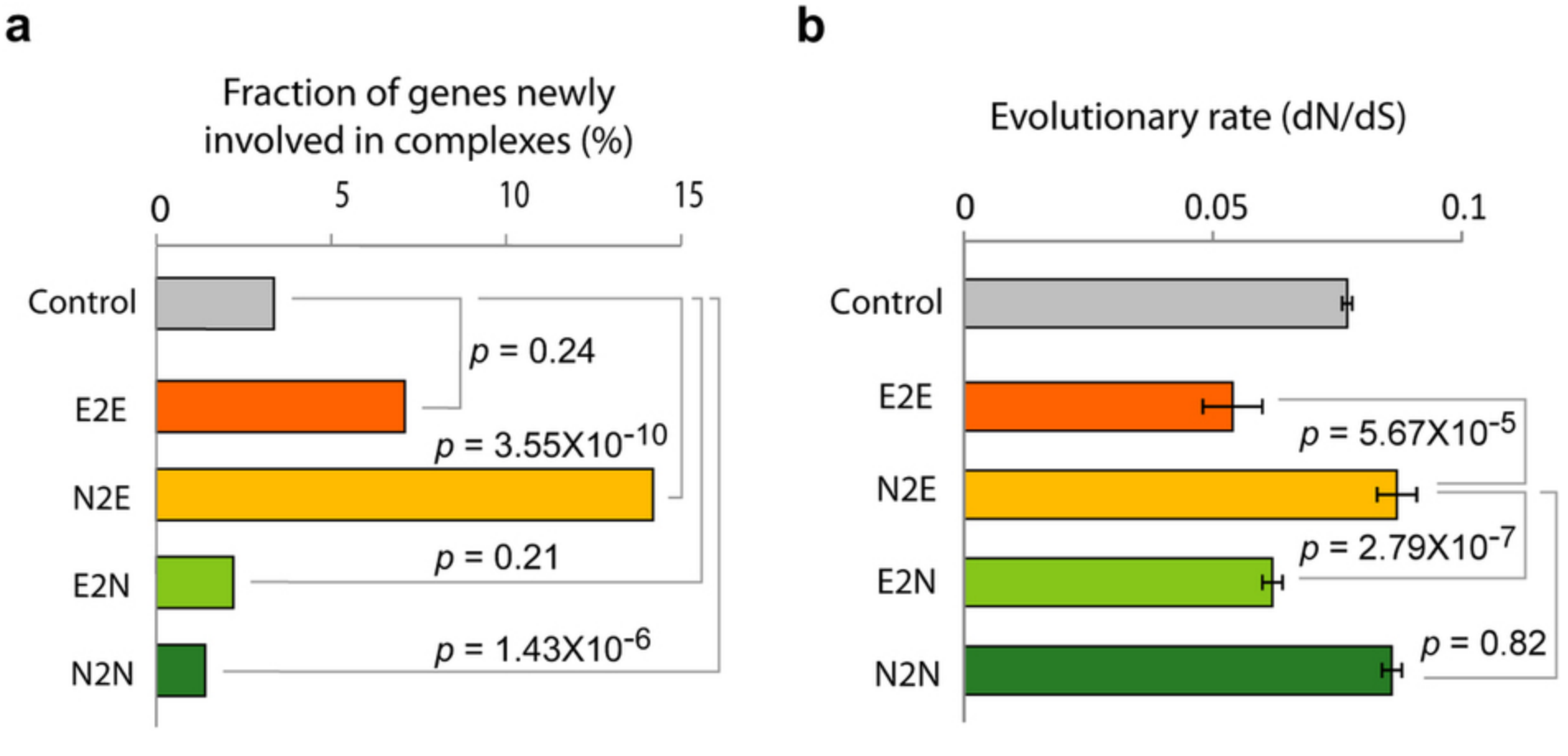
Comparison of network connections in various species



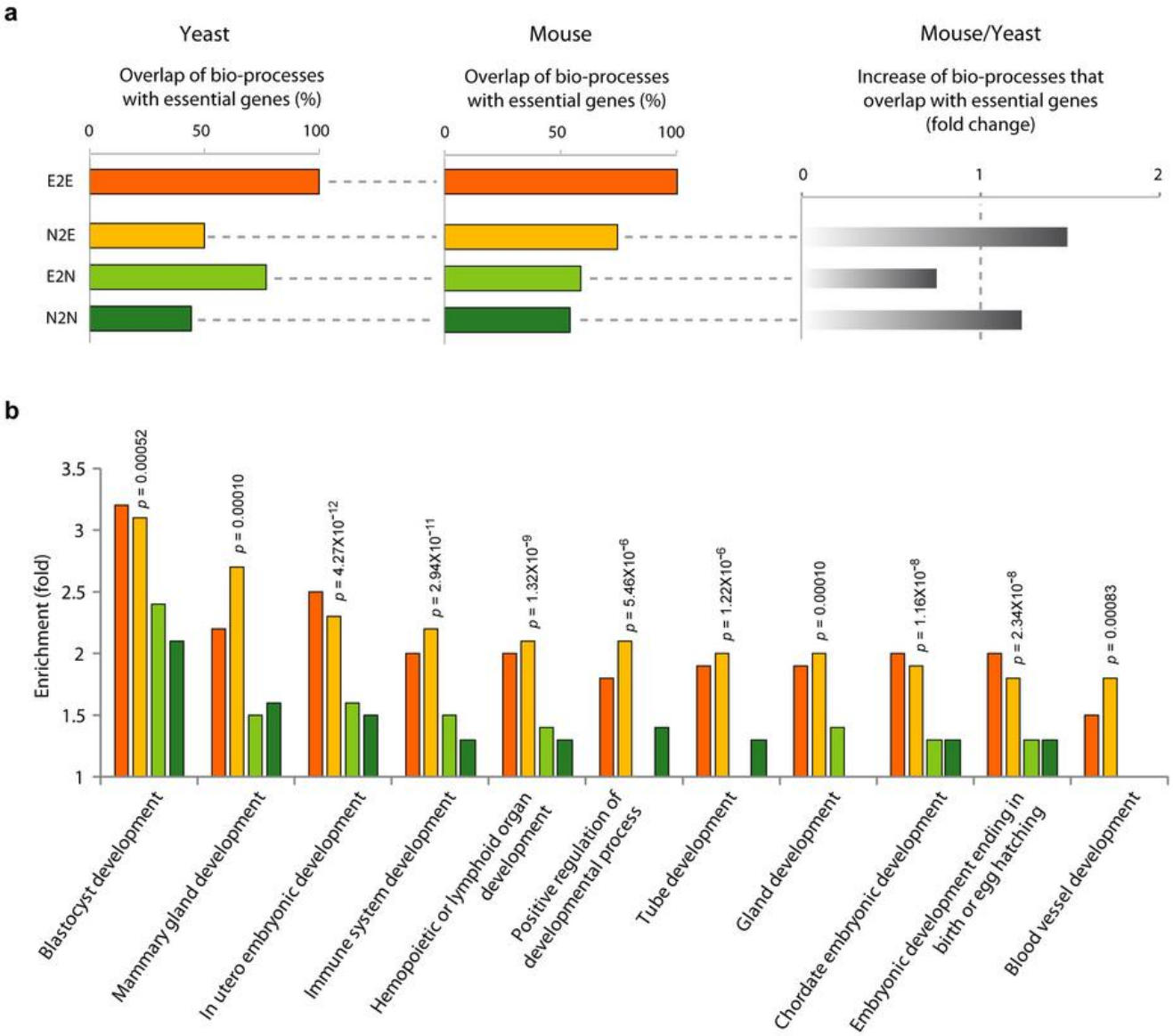
Network connections of Map2k1 in yeast, worm, chicken, and mouse



Protein complex membership and evolution of gene essentiality changes

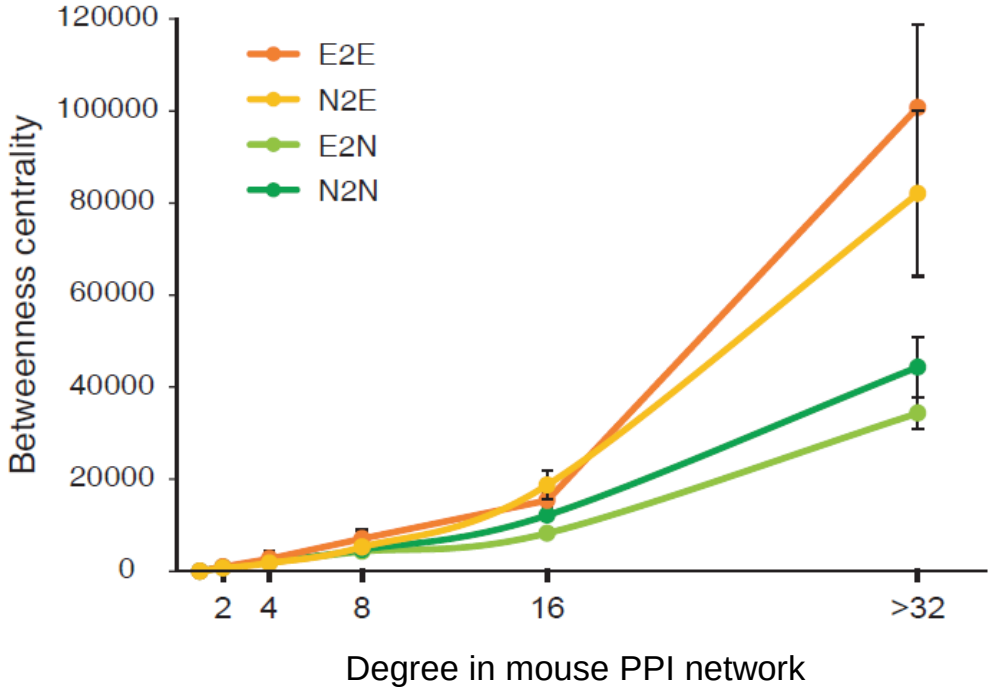


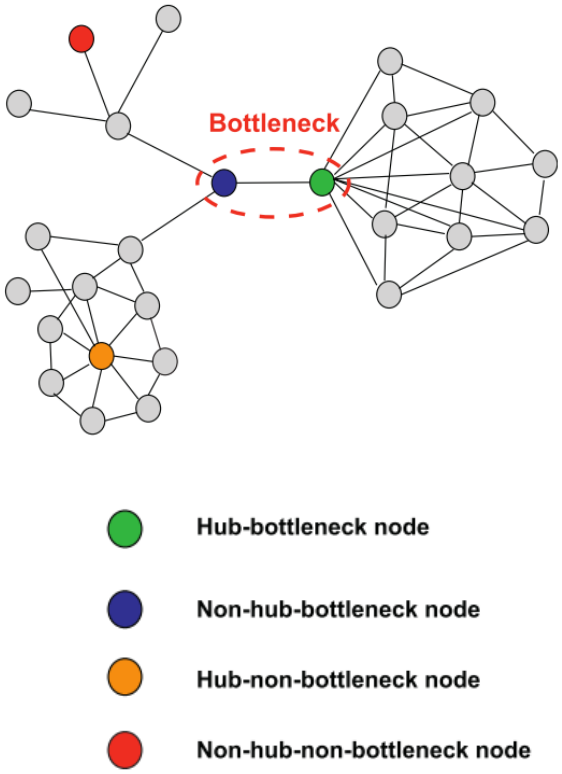
N2E genes integrated into vital pathways via interaction rewiring



Old genes became essential by participating into vital pathways.

N2E genes often bridge functional modules and control information flow in the PPI network.





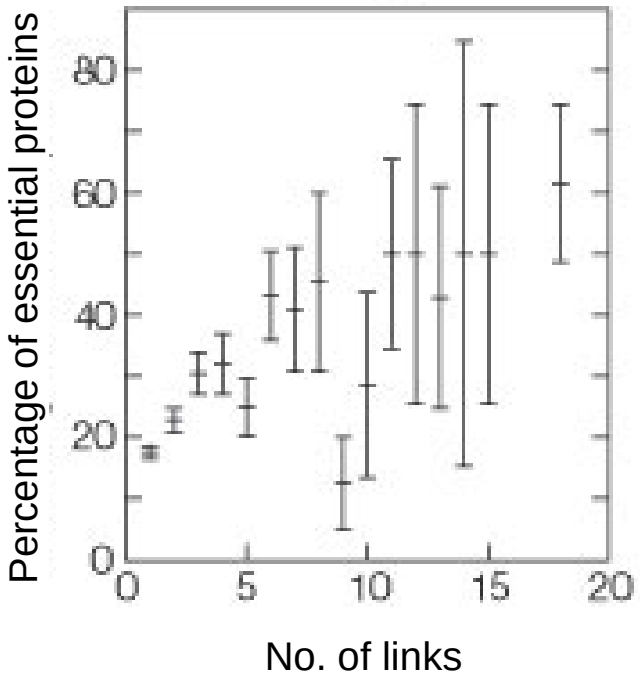
Haiyuan Yu, Mark Gerstein, Plos CB 200

controversy over the centrality-lethality rule

Centrality-lethality rule

- The most highly connected proteins in the cell are the most important for its survival.
- But the weak correlation has been a problem.

red, lethal; green, non-lethal;
orange, slow growth; yellow, unknown



H. Jeong, S. P. Mason, A.-L. Barabási and Z. N. Oltvai
Nature 2001

The C-L rule dramatically improved for the genes keeping their essentiality both in yeast and mouse