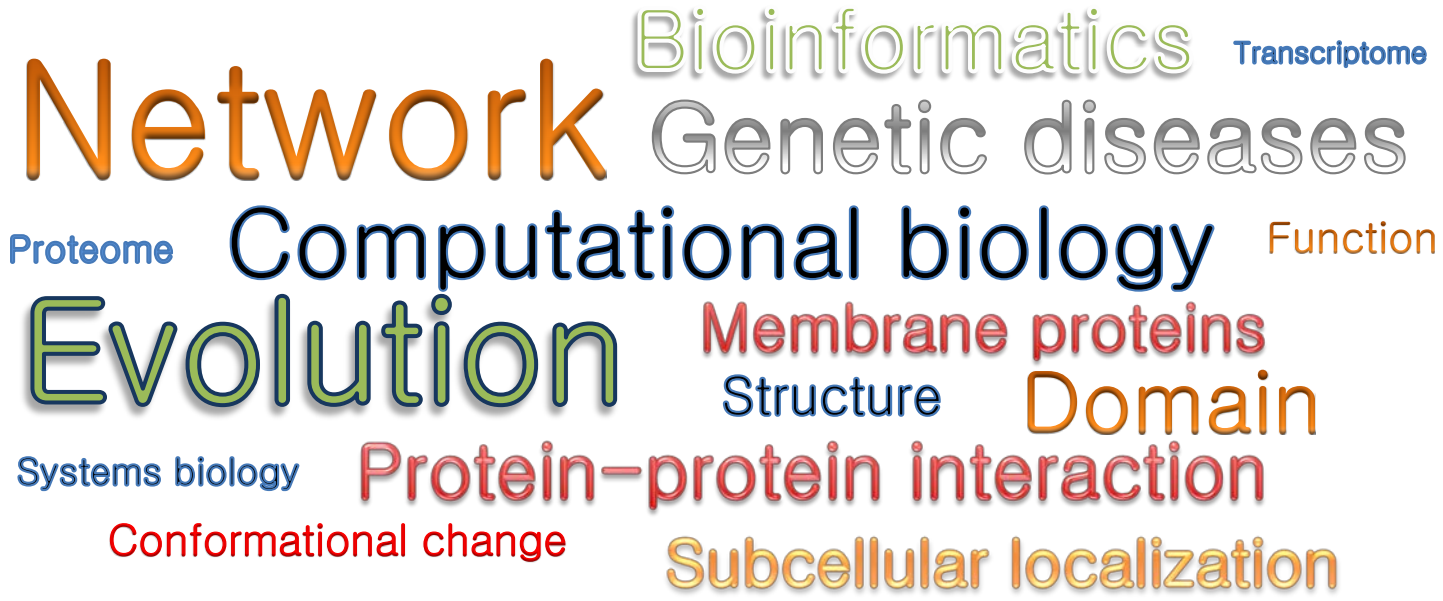
Evolution of the genotype-phenotype relationship of human disease genes

Sanguk Kim

POSTECH

Research Keywords



Recent publications

1. Genetic alterations in mesiodens as revealed by targeted NGS and **gene co-occurrence network** analysis. ***Oral Dis***. 2017 Apr 17.
2. **Network Modules of the Cross-Species** Genotype-Phenotype Map Reflect the Clinical Severity of Human Diseases. ***PLoS One***. 2015 Aug 24;10(8):e0136300
3. Metazoans evolved by taking domains from soluble proteins to expand **intercellular communication network**. ***Scientific Reports***. 2015 Apr 29;5:9576
4. Linear motif-mediated interactions have contributed to the evolution of **modularity in complex protein interaction networks**. ***PLoS Comput Biol. 2014*** Oct 9;10(10):e1003881.
5. **Feedback regulation** via AMPK and HIF-1 mediates ROS-dependent longevity in Caenorhabditis elegans. ***Proc Natl Acad Sci U S A***. 2014 Oct 21;111(42):E4458
6. Spatial and functional organization of **mitochondrial protein network**. ***Scientific Reports*** 2013 3:1403.
7. **Network rewiring** is an important mechanism of gene essentiality change. ***Scientific Reports*** 2012 2:900.
8. Rewiring of PDZ **domain-ligand interaction network** contributed to eukaryotic evolution. ***PLoS Genetics***. 2012 8(2):e1002510.
9. Evolutionary history of human disease genes reveals **phenotypic connections** and comorbidity among genetic diseases. ***Scientific Reports*** 2012 2:757.
10. **Network clustering** revealed the systemic alterations of mitochondrial protein expression. ***PLoS Comp. Biol***. 2011 7(6):e1002093.
11. Protein localization as a principal feature of the etiology and **comorbidity of genetic diseases**. ***Mol Sys Biol.*** 2011 7:494.
12. Molecular evolution of protein conformational changes revealed by a **network of evolutionarily coupled residues**. ***Mol Biol Evol***. 2011 28:2675.

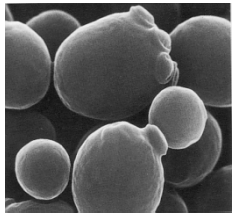
Structural Bioinformatics Laboratory
Pohang University of Science and Technology

Acknowledgement

SBI lab
JiHye Hwang
Inhae Kim
Sung gyu Han
Heetak Lee
Sangjin Han
Donghyo Kim

SBI Alumni
Dr. Jou-hyun Jeon
Dr. Jae-seong Yang
Dr. Solip Park
Dr. Yoonsup Choi
Dr. Jinho Kim
Dr. HyunJun Nam

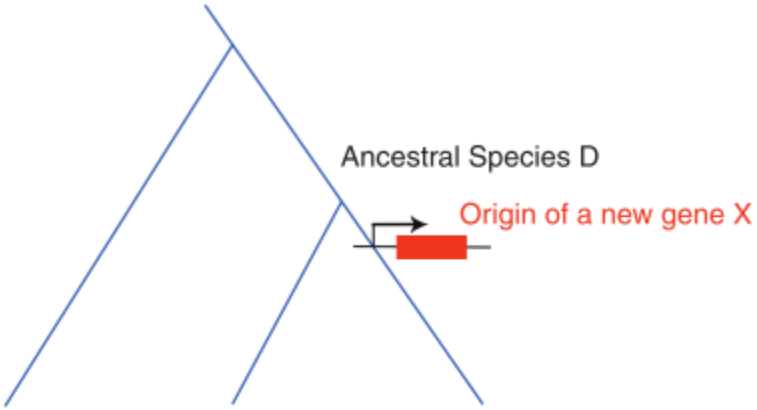
Increase of network complexity has a major impact on gene essentiality changes.



Mechanism of gene essentiality changes

Young genes quickly become essential by gaining new functions

But it is unclear how this event occur.



	Species A	Species B	Species C	Species C mutant	Species D
Genotype (Gene X activity)	No	No	Yes	No	No
Phenotype (Viability)	Viable	Viable	Viable	Lethal	Viable (infered)
Essentiality of the new gene X	Not essential	Not essential	Essential		Not essential

Chen et al., Science 2008

Gene essentiality often changes during evolution

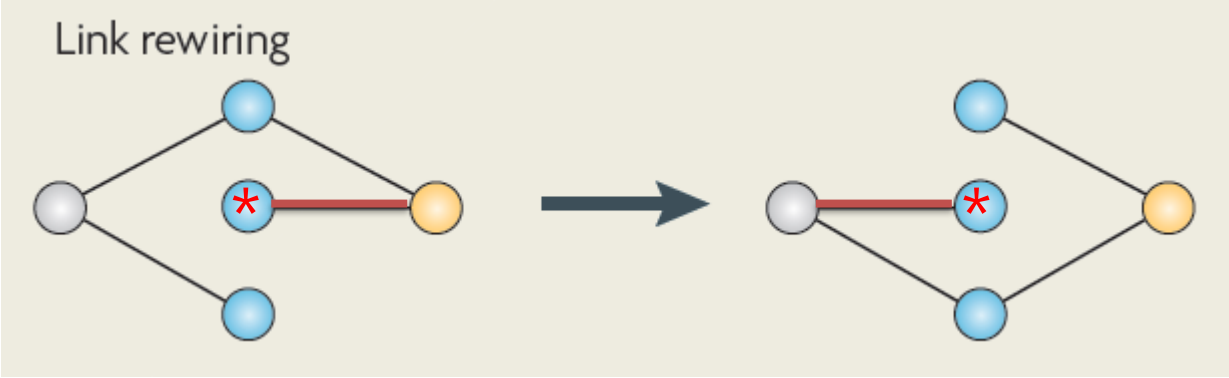
Map2k1 (nonessential in yeast but essential in mouse)

- *"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)*

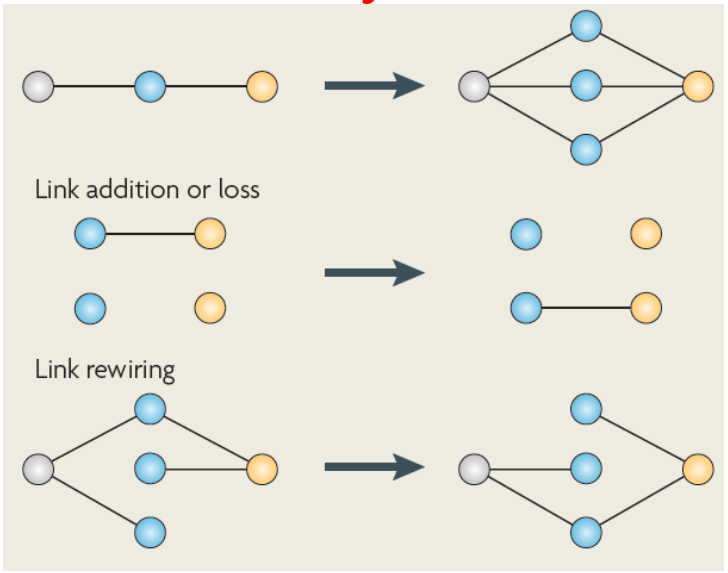
It is unclear how nonessential genes become essential in more complex organism

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.

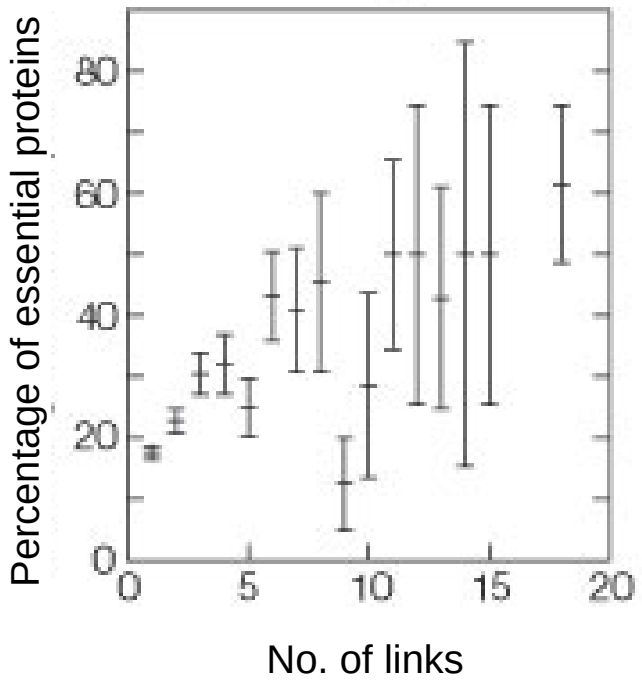


controversy over the centrality-lethality rule

Centrality-lethality rule

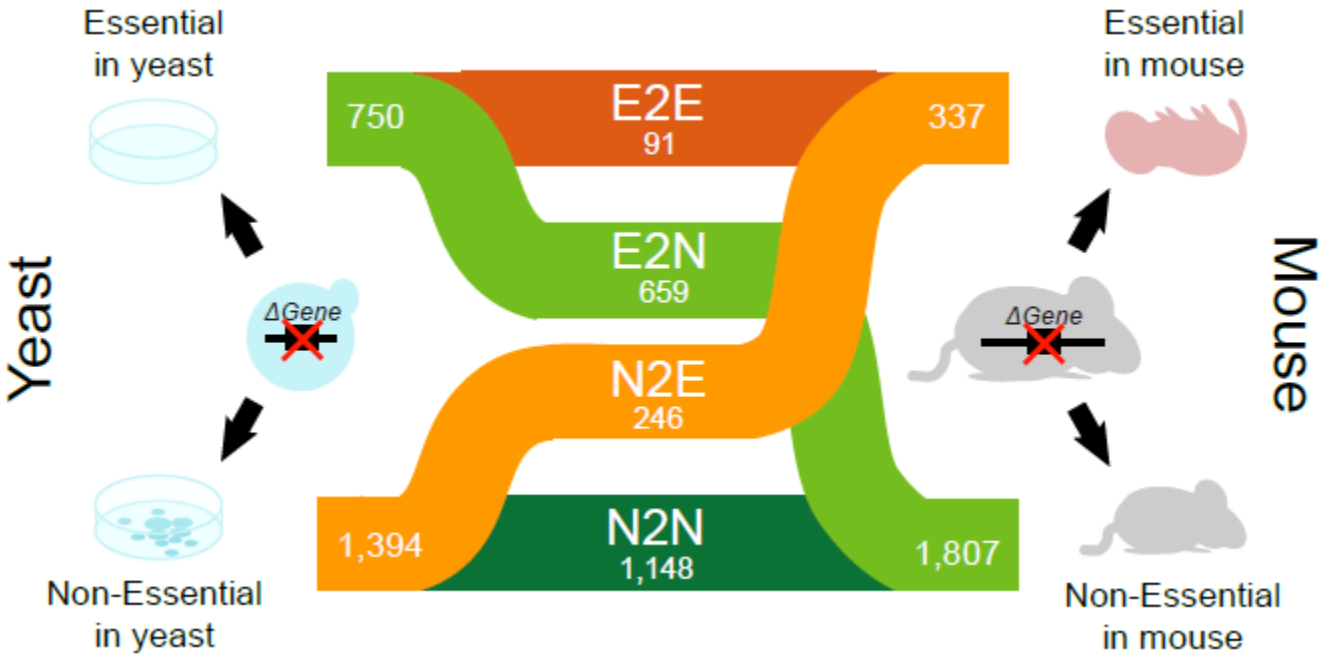
- The most highly connected proteins in the cell are the most important for its survival.
- But the weak correlation has been a problem.

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

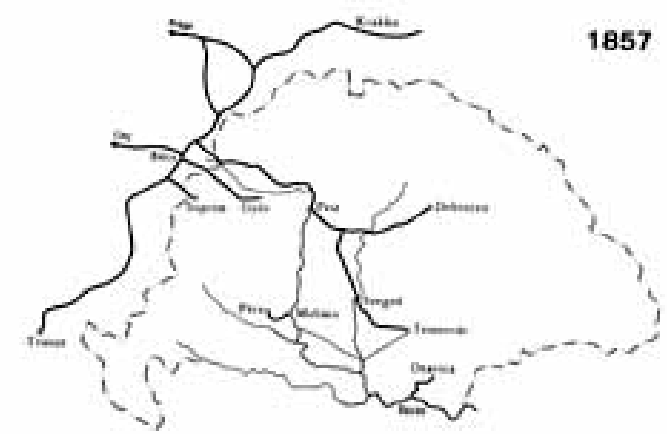


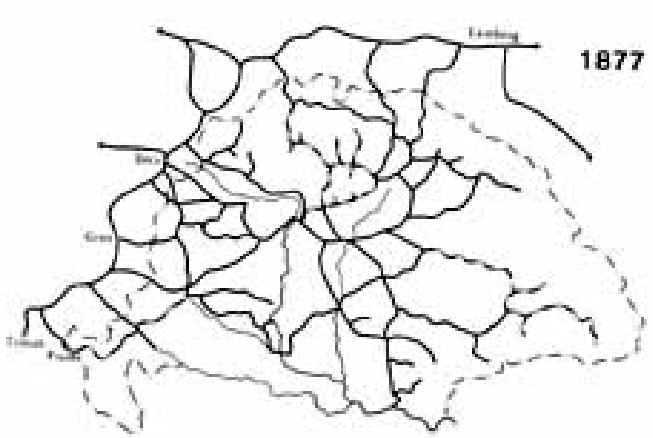
H. Jeong, S. P. Mason, A.-L. Barabási and Z. N. Oltvai
Nature 2001

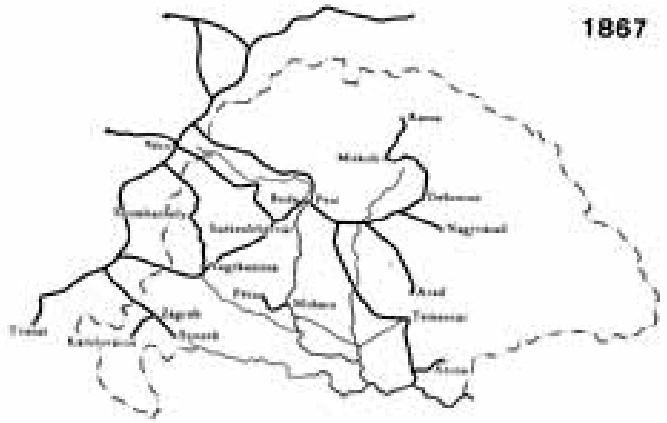
Genes essentiality changes between species

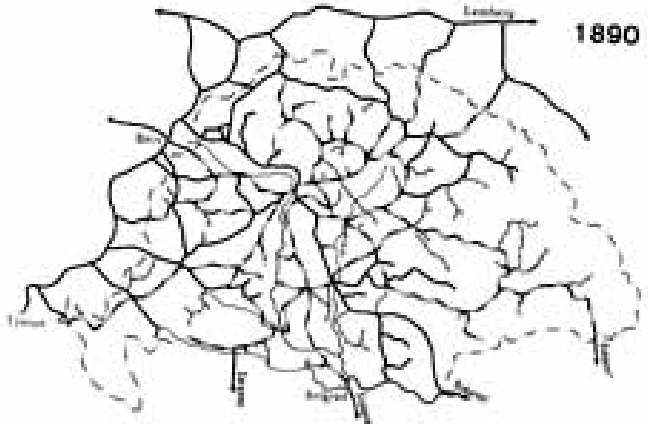


Network Evolution

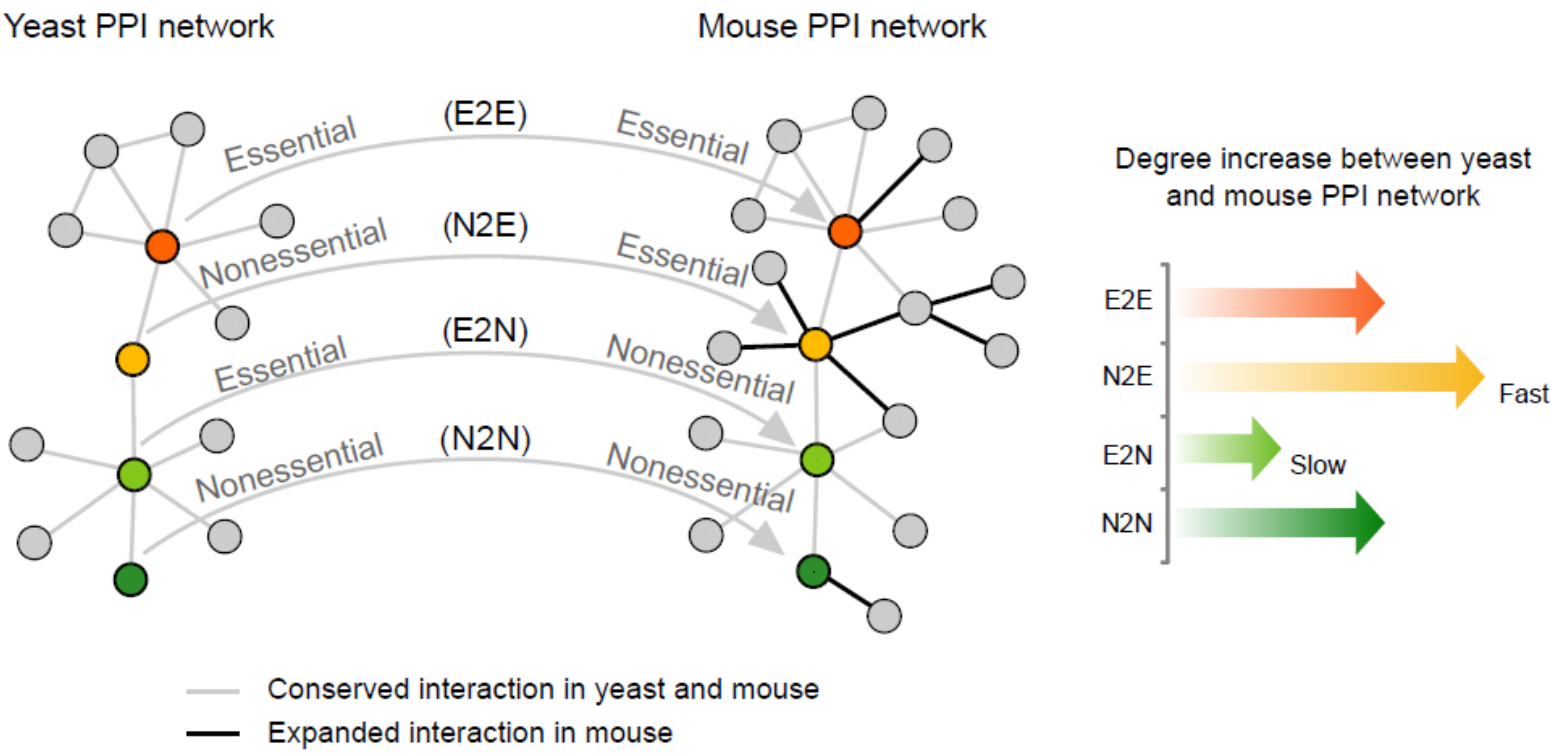




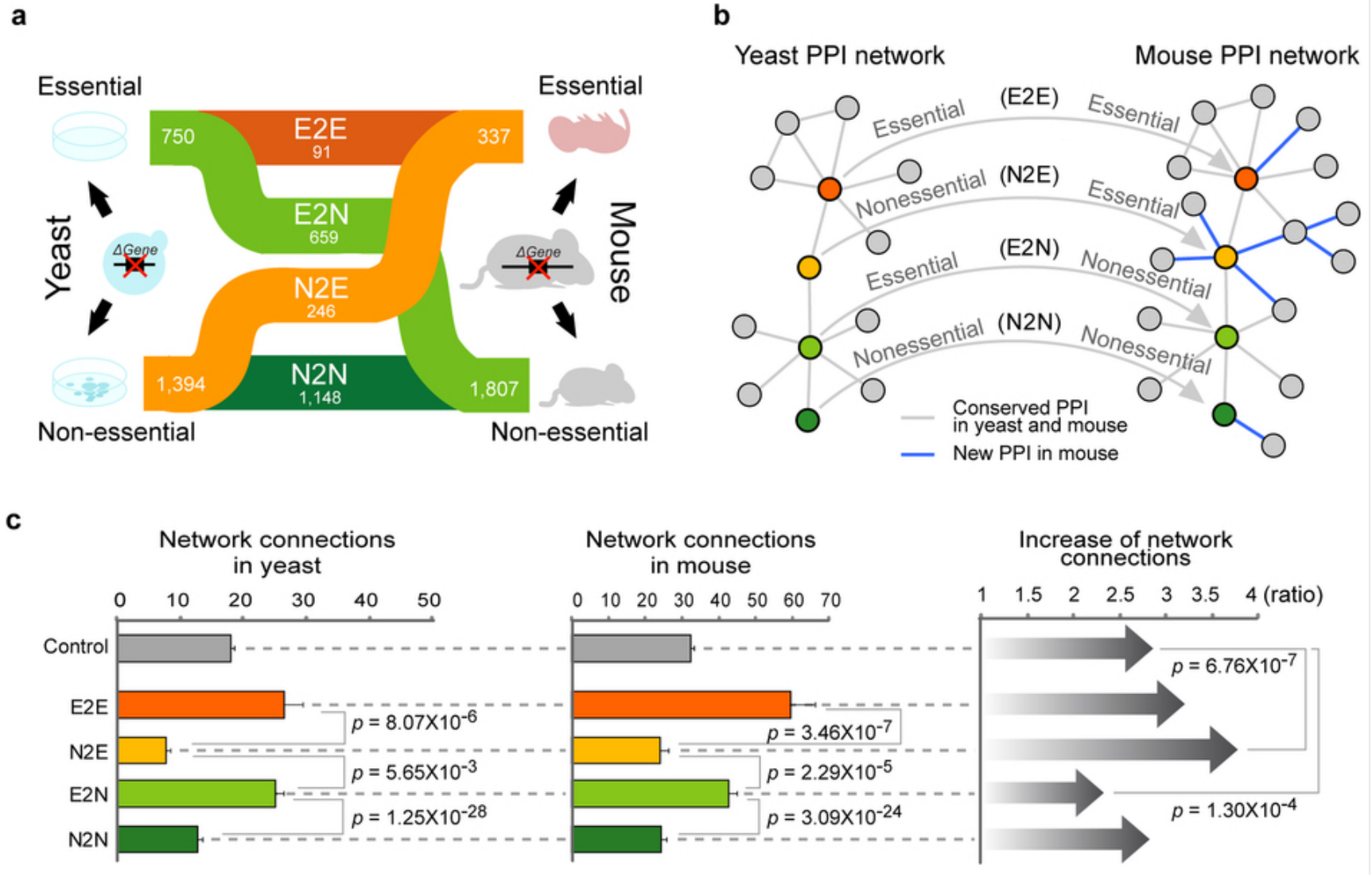




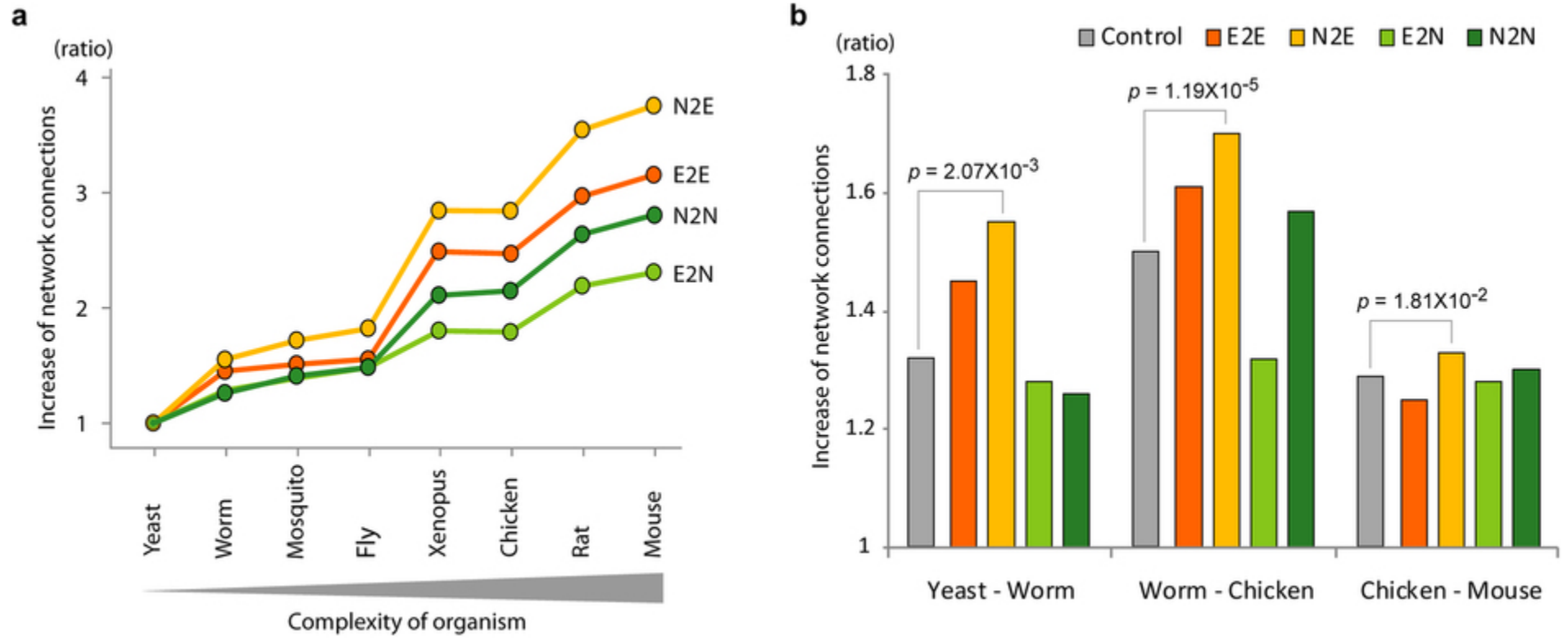
Increase of network degree is responsible for gene essentiality changes between yeast and mouse.



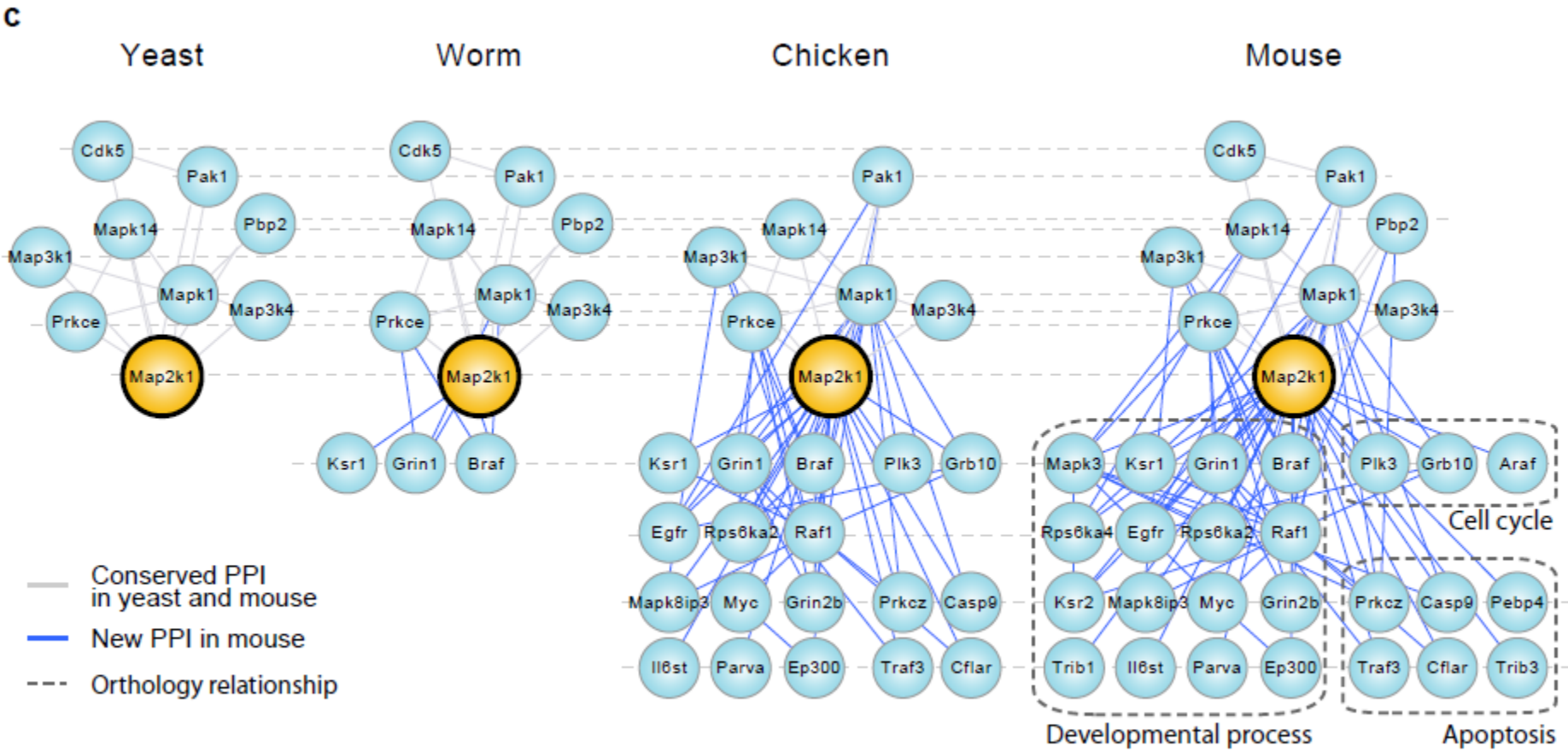
Increase in network connections and gene essentiality changes between yeast and mouse



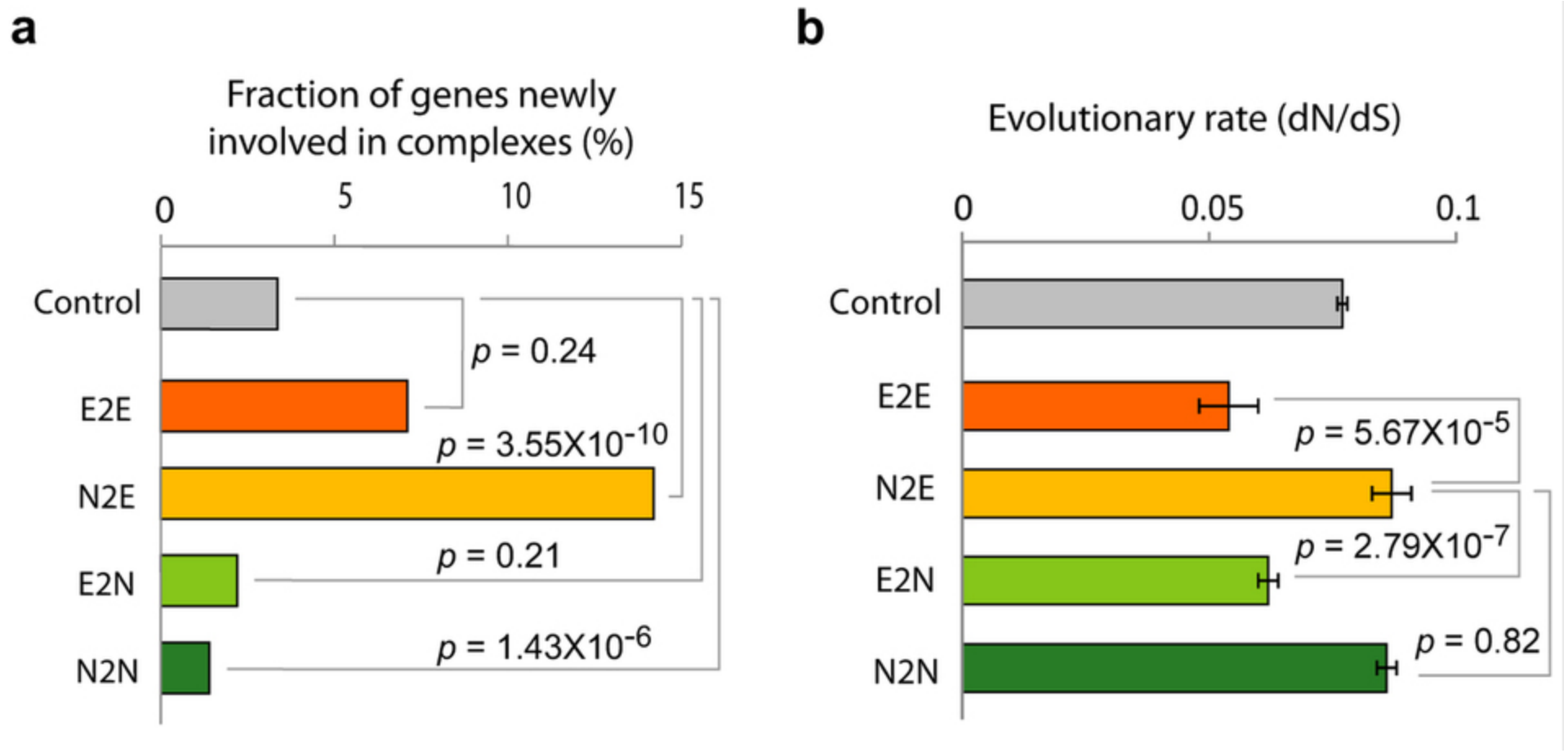
Comparison of network connections in various species



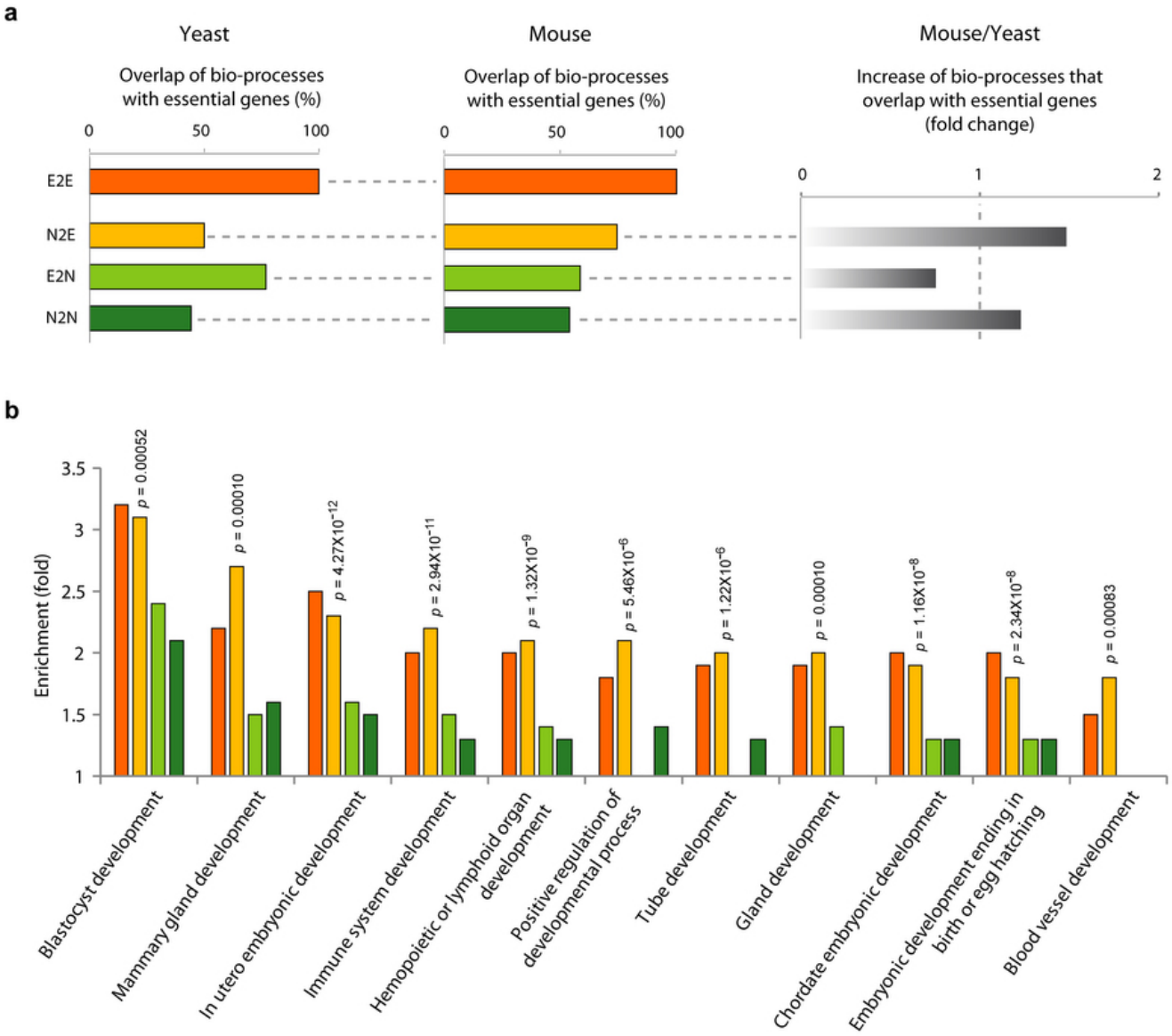
Network connections of *Map2k1* in yeast, worm, chicken, and mouse



Protein complex membership and evolution of gene essentiality changes

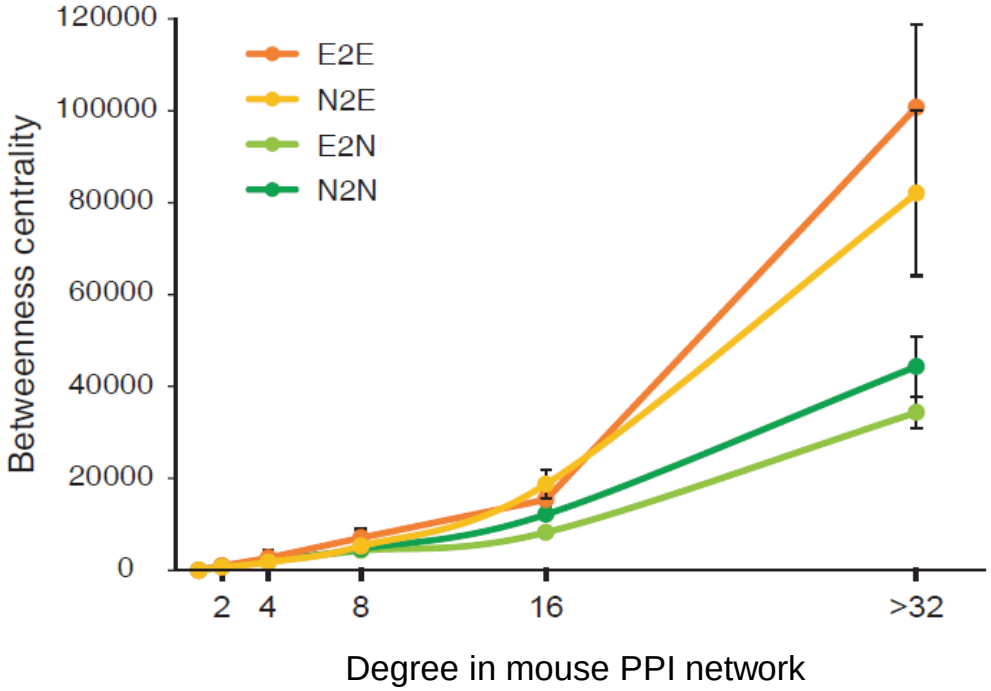


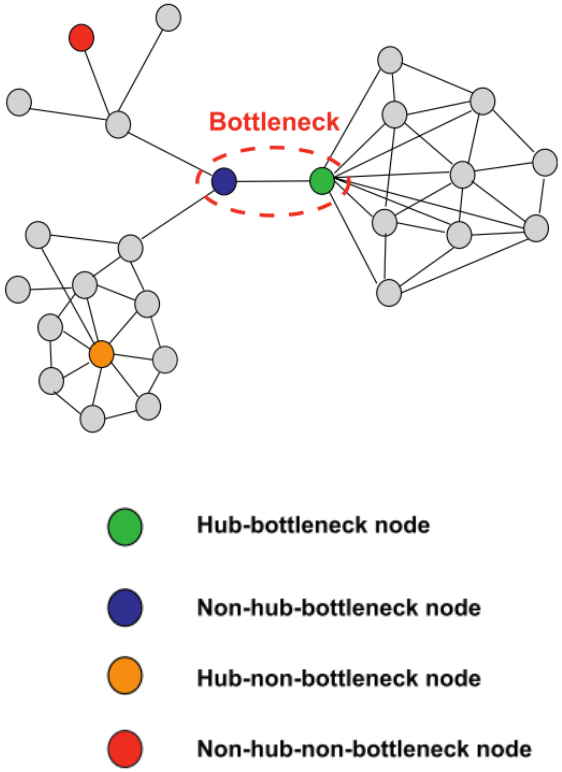
N2E genes integrated into vital pathways via interaction rewiring



Old genes became essential by participating into vital pathways.

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





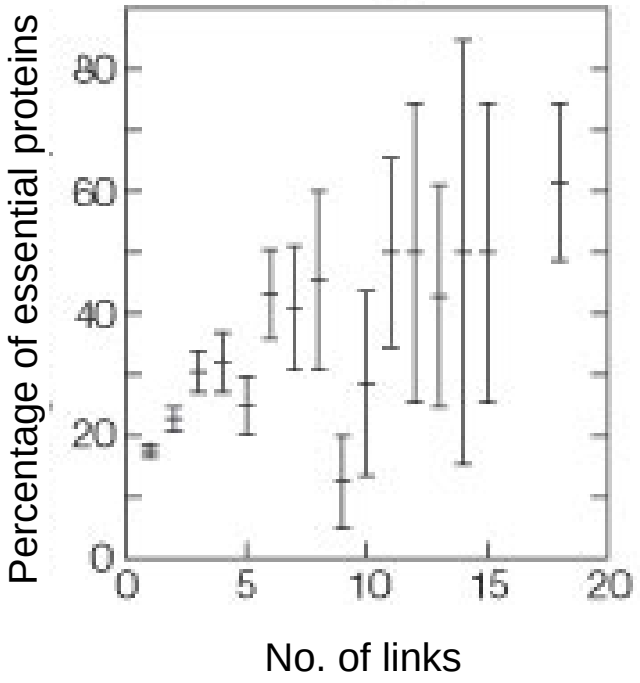
Haiyuan Yu, Mark Gerstein, Plos CB 2007

controversy over the centrality-lethality rule

Centrality-lethality rule

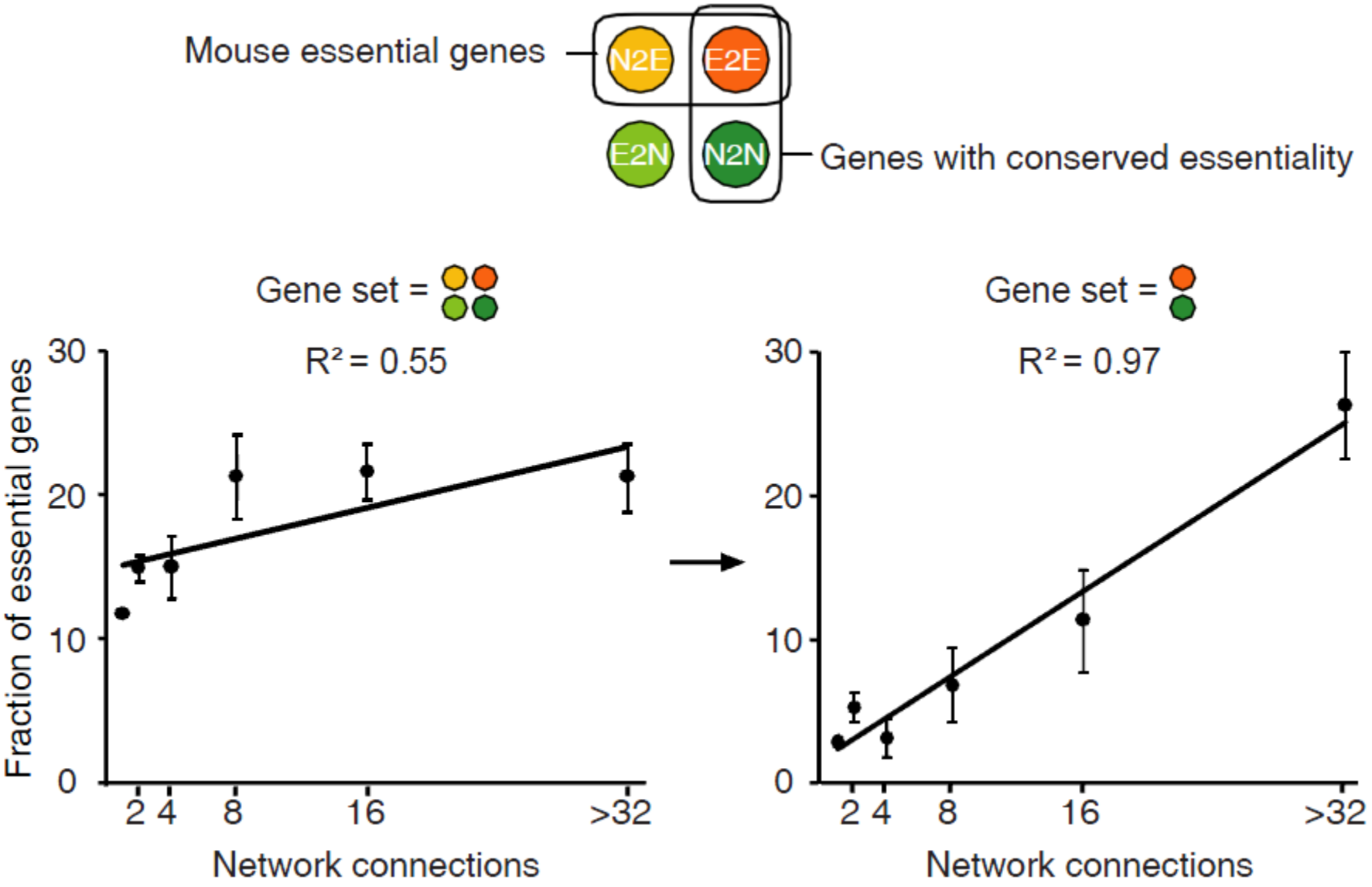
- The most highly connected proteins in the cell are the most important for its survival.
- But the weak correlation has been a problem.

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



Conclusions

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

2. Young genes quickly become essential by gaining new functions.

3. Essential genes integrated into vital pathways via interaction rewiring.