Evolution of the genotype–phenotype relationship of human disease genes
Research Keywords

Network  Bioinformatics  Transcriptome
Evolution  Genetic diseases  Function
Computational biology  Membrane proteins
Proteome  Structure  Domain
Systems biology  Protein–protein interaction
Conformational change  Subcellular localization
Recent publications

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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.

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

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.

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

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

Diagram showing the increase in network connections and gene essentiality changes between yeast and mouse. The diagram illustrates the number of essential genes and network connections for different conditions in yeast and mouse.

- Yeast PPI network
  - Essential (E2E)
  - Nonessential (N2E)

- Mouse PPI network
  - Essential (E2E)
  - Nonessential (N2E)

Table showing network connections in yeast and mouse for different conditions:

<table>
<thead>
<tr>
<th>Condition</th>
<th>Network connections in yeast</th>
<th>Network connections in mouse</th>
<th>Increase of network connections</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>20</td>
<td>30</td>
<td>1 (ratio)</td>
</tr>
<tr>
<td>E2E</td>
<td>30 (p = 8.07x10^-6)</td>
<td>50 (p = 3.46x10^-7)</td>
<td>2 (ratio)</td>
</tr>
<tr>
<td>N2E</td>
<td>10 (p = 5.65x10^-3)</td>
<td>20 (p = 2.29x10^-5)</td>
<td>2 (ratio)</td>
</tr>
<tr>
<td>E2N</td>
<td>20 (p = 1.25x10^-28)</td>
<td>40 (p = 3.09x10^-24)</td>
<td>2 (ratio)</td>
</tr>
<tr>
<td>N2N</td>
<td>10</td>
<td>20</td>
<td>2 (ratio)</td>
</tr>
</tbody>
</table>
Comparison of network connections in various species

(a) Increase of network connections

(b) Increase of network connections comparison

Yeast - Worm: $p = 1.19 \times 10^{-5}$
Worm - Chicken: $p = 2.07 \times 10^{-3}$
Chicken - Mouse: $p = 1.81 \times 10^{-2}$
Network connections of \textit{Map2k1} in yeast, worm, chicken, and mouse
Protein complex membership and evolution of gene essentiality changes

(a) Fraction of genes newly involved in complexes (%)

- Control: 0 (p = 0.24)
- E2E: 5 (p = 3.55 \times 10^{-10})
- N2E: 10 (p = 0.21)
- E2N: 15 (p = 1.43 \times 10^{-6})
- N2N: 15 (p = 0.82)

(b) Evolutionary rate (dN/dS)

- Control: 0.05 (p = 5.67 \times 10^{-5})
- E2E: 0.05 (p = 2.79 \times 10^{-7})
- N2E: 0.05 (p = 0.82)
- E2N: 0.05 (p = 0.82)
- N2N: 0.05 (p = 0.82)
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.
controversy over the centrality-lethality rule

Centrality-lethality rule

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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.

[Diagram showing gene sets and network connections with R² values 0.55 and 0.97]
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.