A functional selection model explains evolutionary robustness despite plasticity in regulatory networks

调控网络进化稳健性的功能选择模型

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Background

- Evolutionary rewiring of regulatory networks is an important source of diversity among species and it is often driven by the gain or loss of cis-regulatory elements in gene promoters bound by sequence-specific transcription factors or chromatin remodelers.
- Previous evidence suggested substantial divergence of regulatory networks across species.
- Systematically assessing the extent of this plasticity and its functional implications has been challenging due to limited experimental data and the noisy nature of computational predictions.

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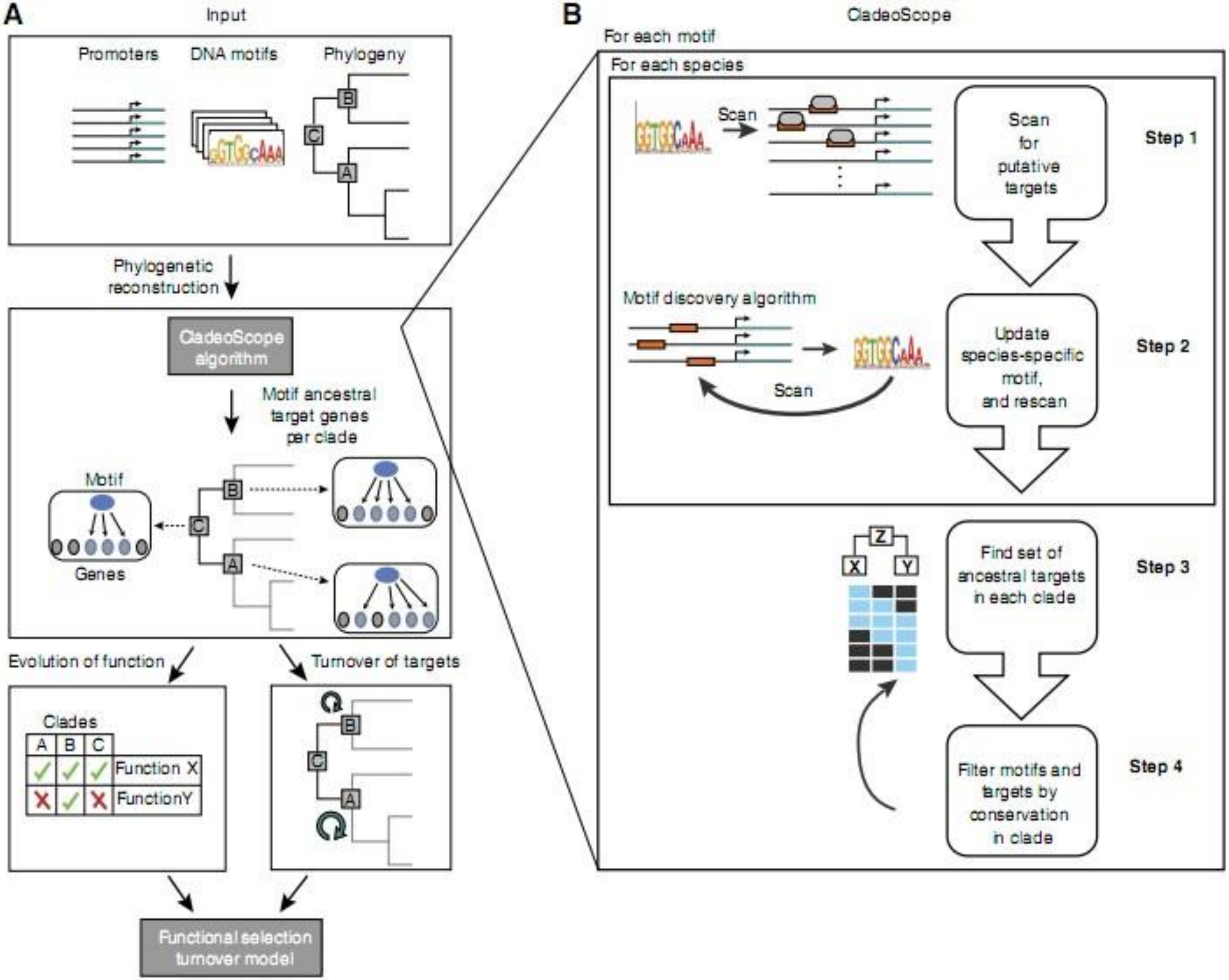
The model



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The model

a computational framework

- CladeoScope--- reconstructing cis-regulatory networks and their evolution across a phylogeny of species.
- two assumptions：

1.The binding specificities of transcription factors, represented as DNA motifs, are largely conserved.

2.The motif targets are conserved across several related species within a monophyletic clade provide a reliable and conservative estimate for the targets in the ancestor of the clade.

- four steps：1.Initialization 2.Species-Specific Motifs 3.Network Refinement 4.Filtration

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The model

A functional selection turnover model

- Two models:

(1) a ‘neutral’ turnover model, where targets are gained and lost at the same rates .

(2) a ‘module-specific’ turnover model, where turnover rates—both gain and loss—are different for targets .

Functional selective pressure acts differentially to conserve motif-target relations within the same biological process.

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Results

Systematic reconstruction of the regulatory history of 23 Ascomycota species.

We applied CladeoScope to 88 DNA motifs associated with known transcription factors or groups of paralogous factors across 23 Ascomycota species.

- 1.CladeoScope is robust to noise in target prediction and to different parameters.
- 2.Regulatory motifs are detectable across large evolutionary distances.

In most cases (73%), detectable motifs and factors are co-conserved.

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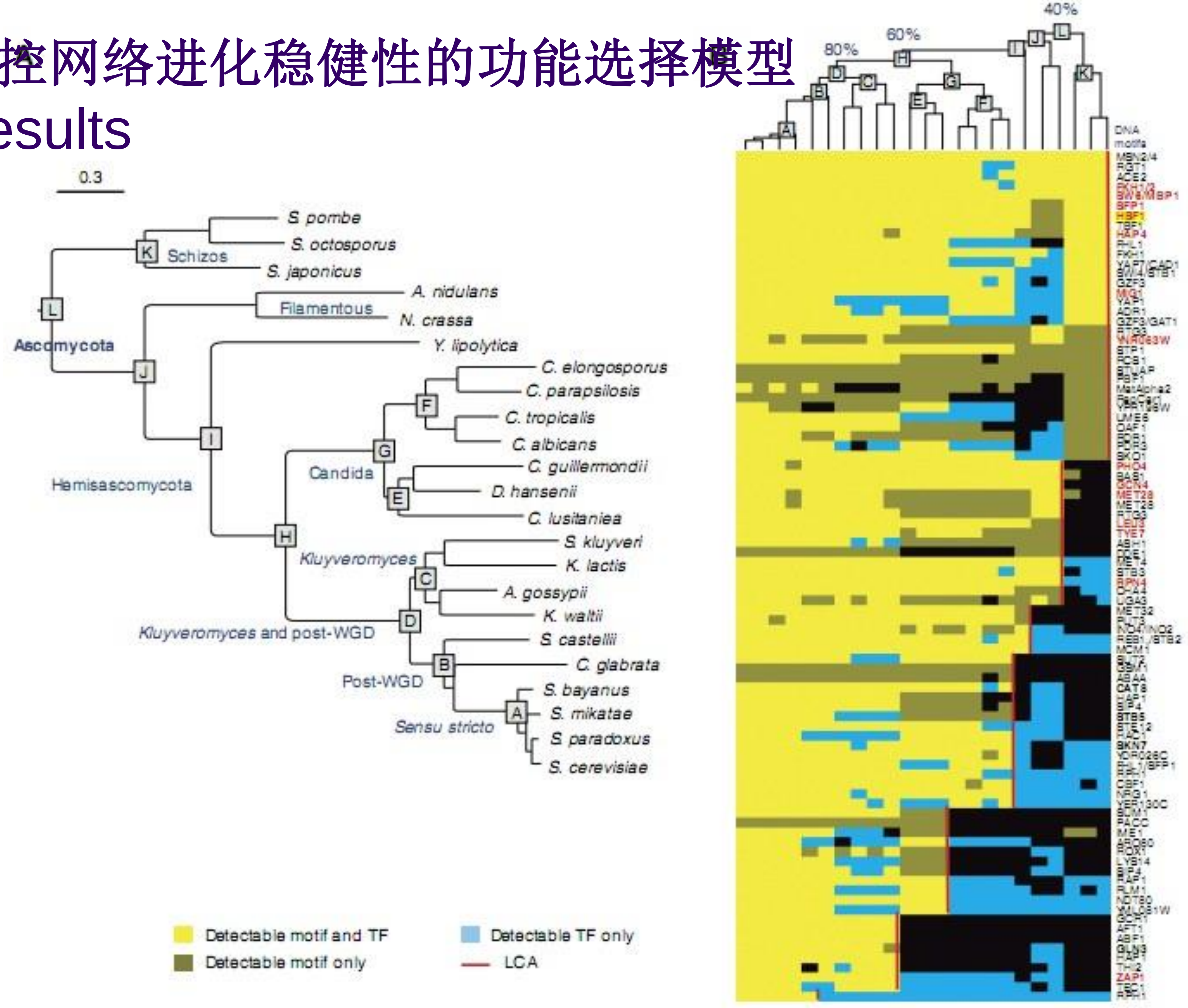

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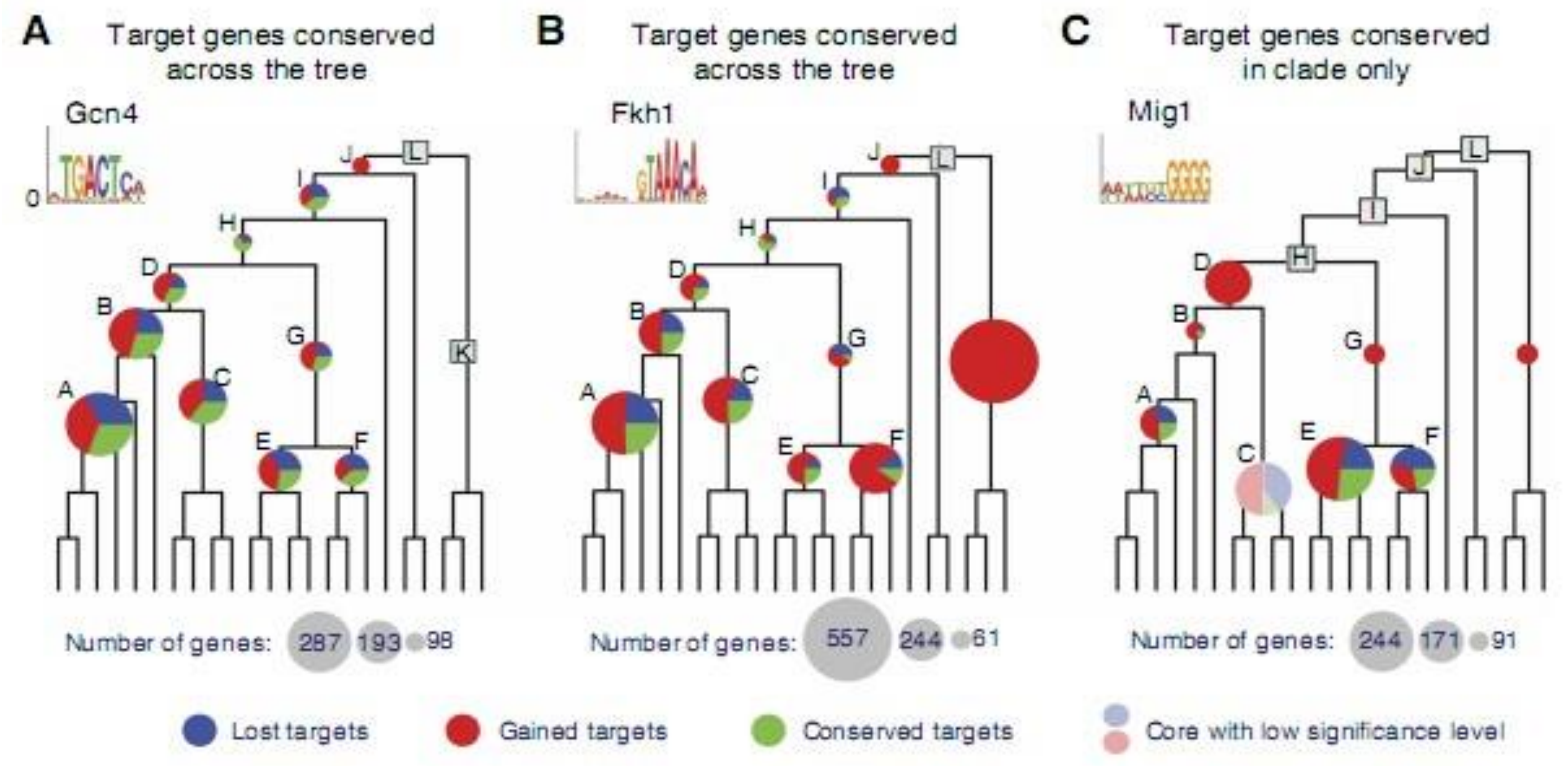
- 3.Rapid target turnover for conserved motifs during evolution.



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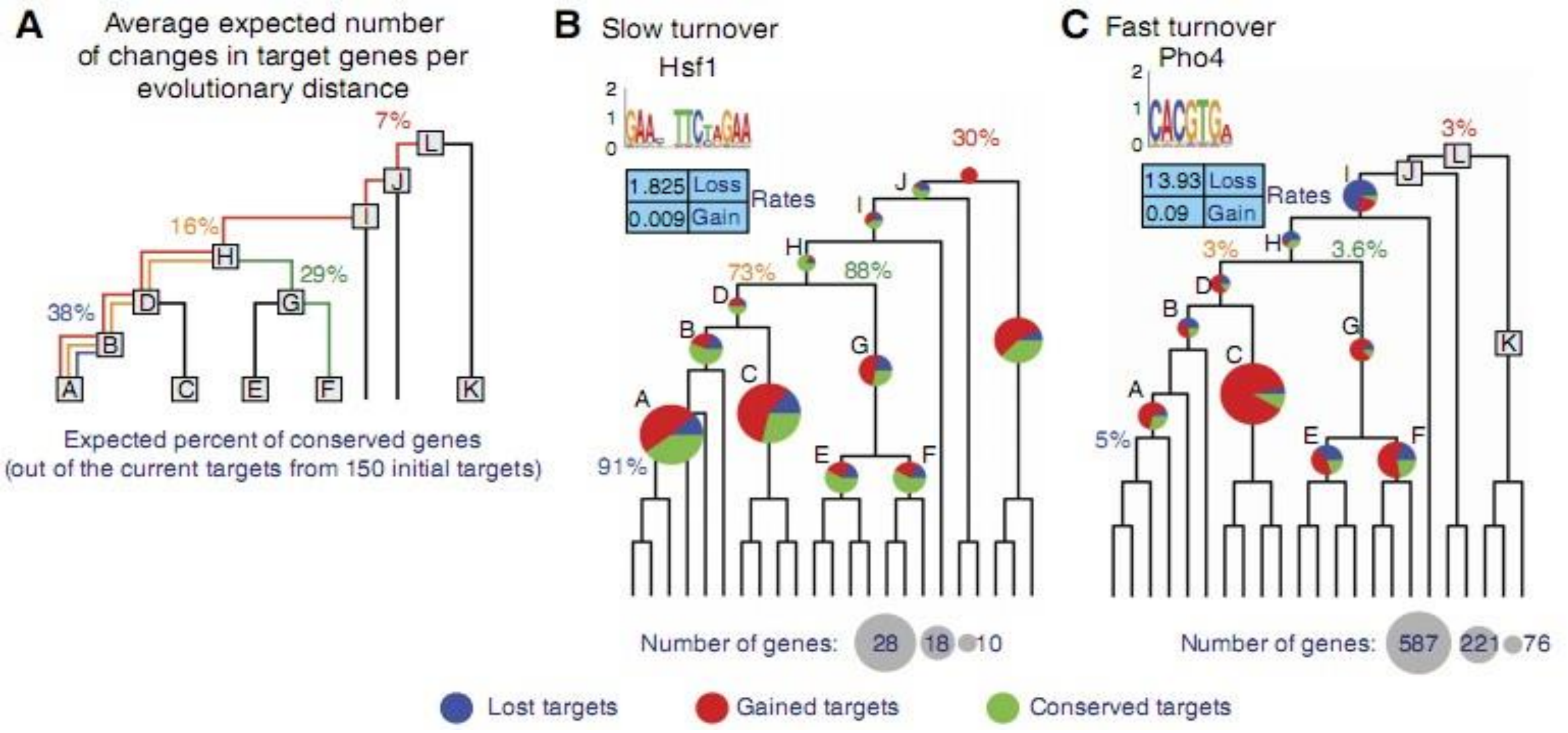

Gain and loss rates of motif targets. (A) The number shown is the fraction of extant targets expected to be derived from an ancestral target.(B, C) Turnover rates for motifs with high turnover rates (Hsf1; B) and low turnover rates (Pho4)

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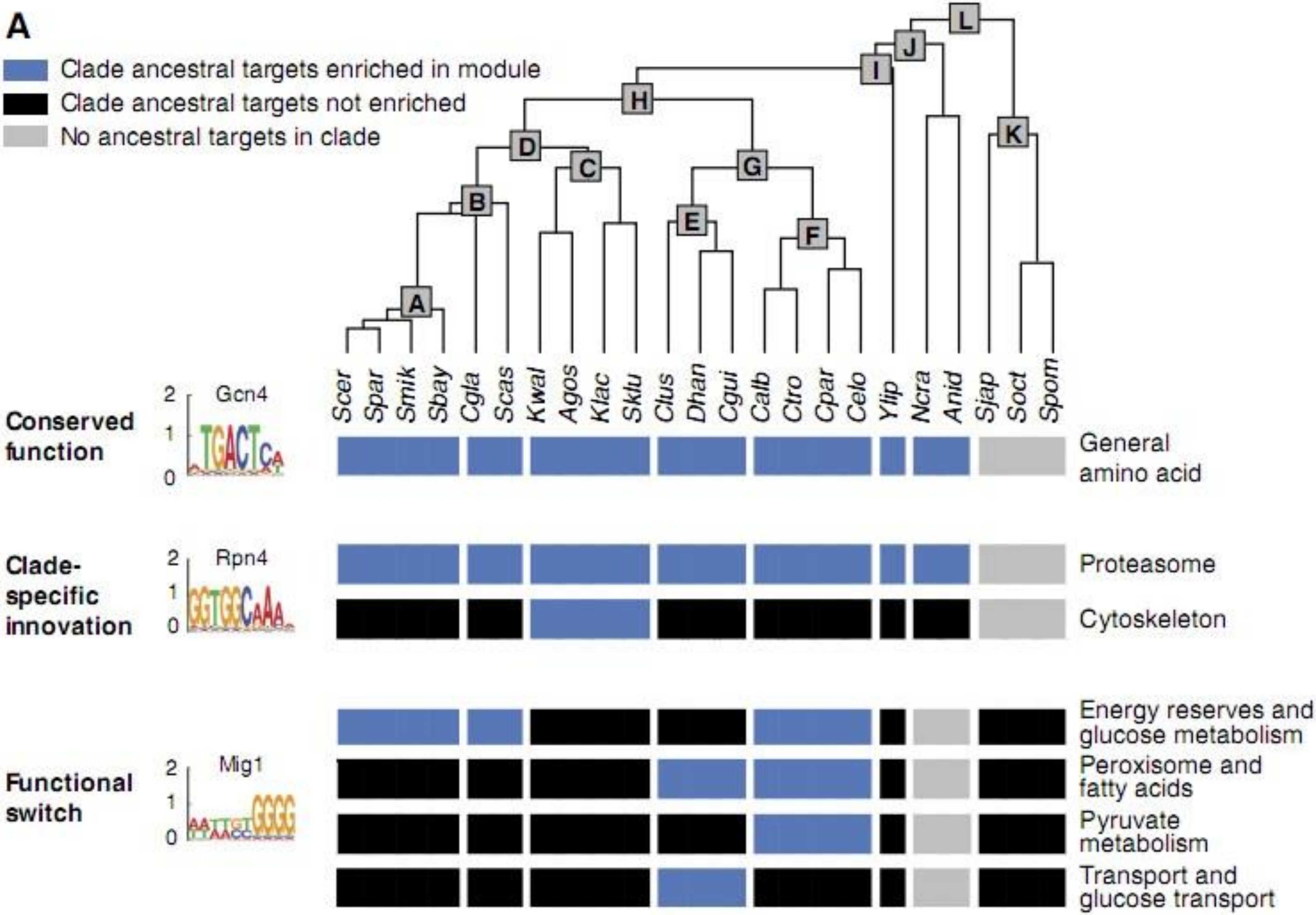
To assess the functional implications of target turnover, we next associated each motif in each clade with a regulatory function.

- Functional expansion: a motif gains a new function in a specific clade in addition to maintaining its ancestral function.
- Functional switch :losing one function while gaining another.


A
Clade ancestral targets enriched in module
Clade ancestral targets not enriched
No ancestral targets in clade
L
J
I
H
K
D
C
G
B
E
F
A
Scer
Spar
Smik
Sbay
Cgla
Scas
Kwal
Agos
Klac
Sklu
Clus
Dhan
Cgui
Calb
Ctro
Cpar
Celo
Ylip
Ncra
Anid
Sjap
Soct
Spom
Conserved function
Gcn4
2
1
0
General amino acid
Clade-specific innovation
Rpn4
2
1
0
Proteasome
Cytoskeleton
Functional switch
Mig1
2
1
0
Energy reserves and glucose metabolism
Peroxisome and fatty acids
Pyruvate metabolism
Transport and glucose transport

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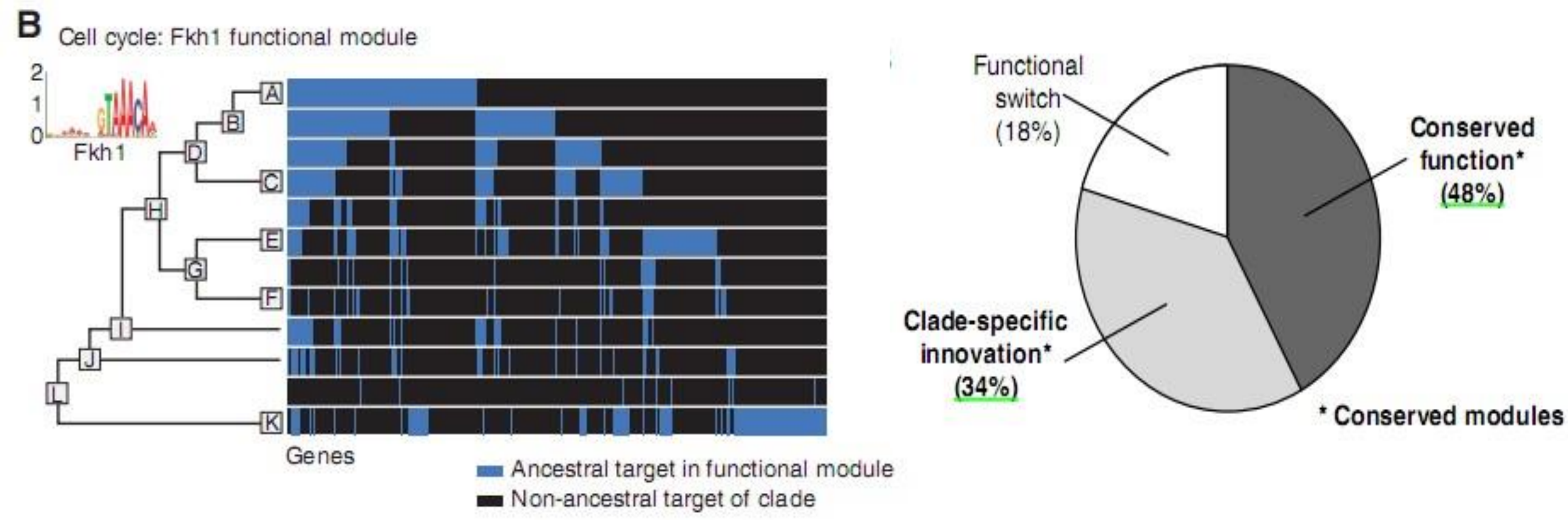
Results

- 4.Conservation of regulatory function despite high turnover rate of targets.



Although the motif might gain or lose an association to functional modules during evolution, 82% of all the motifs have at least one conserved function across all clades.

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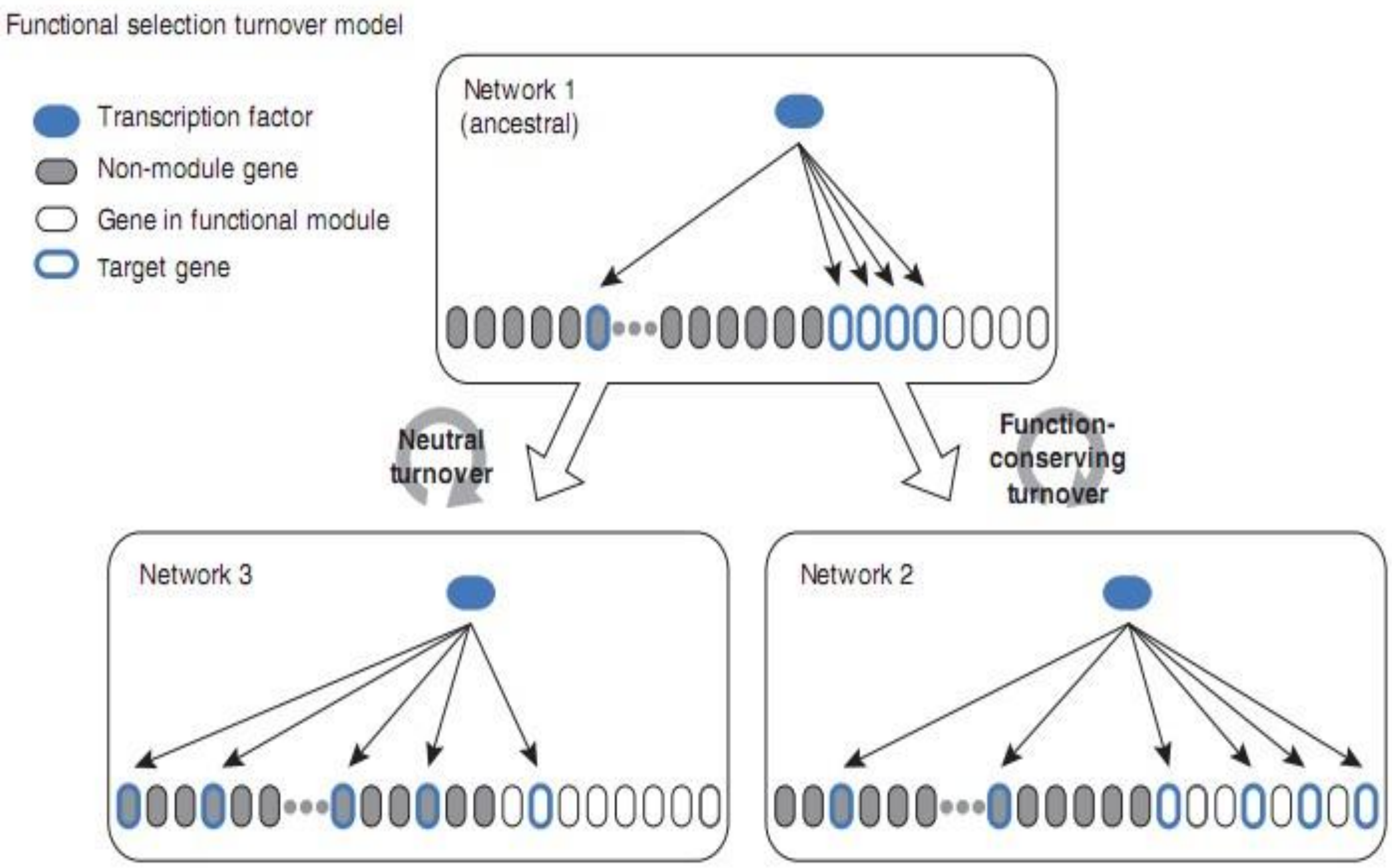
Results

The observed conservation of regulatory function despite high target turnover suggests that the global functional role sassociated with a regulatory motif are under stronger selection than the individual regulatory interactions. To formalize this notion we propose the Functional Selection Turnover Model.



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Results

- 5.In nearly all cases , target turnover is significantly constrained by the genes’ function.

- To examine the generality of our results, we tested whether they hold at the level of individual species as well as clades.
- Overall, this analysis demonstrates the generality of our findings at different evolutionary distances, measurement methods ,phylogenetic resolution and group .

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1. we systematically identified cis-regulatory interactions for 88 known regulatory DNA motifs across the 23 species. We exploited this resource to study the regulatory history of specific transcription factors and to reach general principles of regulatory evolution. In addition, this constitutes a rich public resource.

2.The seemingly contradictory trends of a broad conservation of the functions, and the pervasive gain and loss of the motif in individual targets within the module are reconciled by our proposed Functional Selection Turnover Model.

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3.There are several potential explanations for the observed conservation of regulatory function despite high target turnover.

First, determination of transcription factor targets based on cis-regulatory elements is challenging and noisy. To exclude this option, we compared evolutionary conserved target genes at the clade level instead of target genes for individual species.

Second, the transcription factor may target additional genes in some species, thus expanding the scope of functions it regulates.

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4.Functional selection forces are more permissive than has been previously assumed.

5.Although turnover within a module may not affect the overall regulatory role of a factor, it may allow for more subtle fine-tuning of gene regulation, facilitating adaptation while controlling against dramatic changes in phenotype.

Thank you!