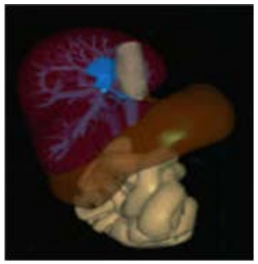
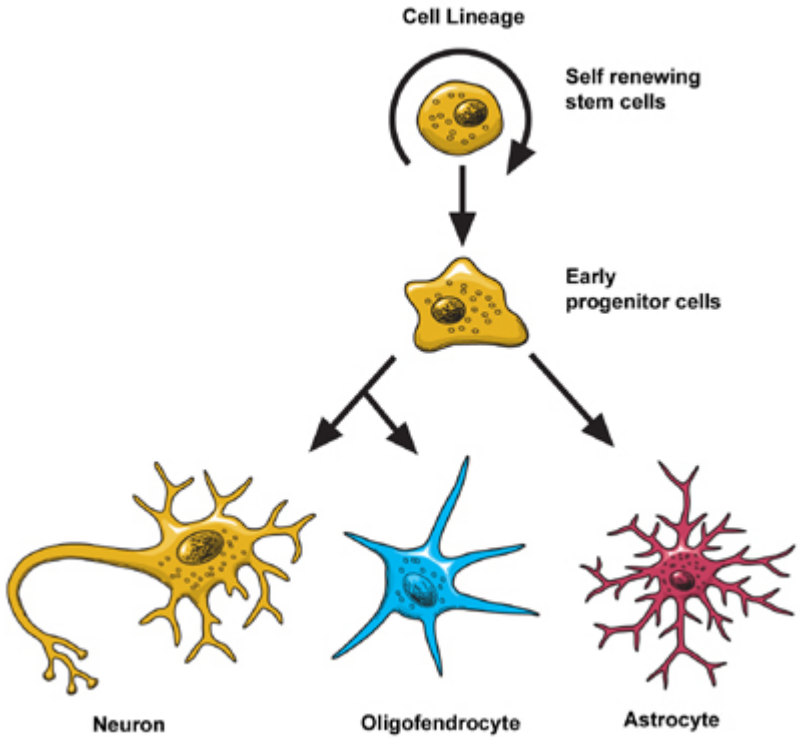
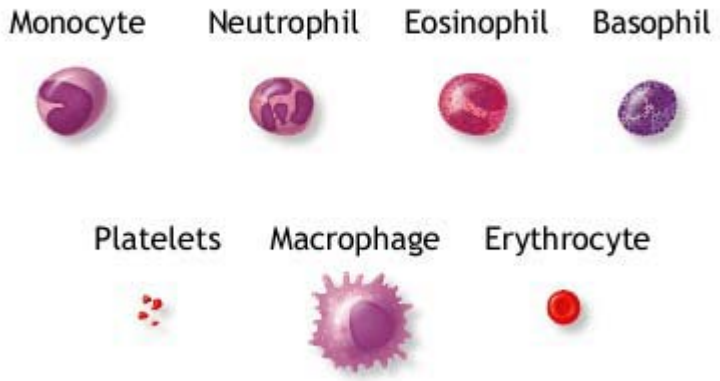
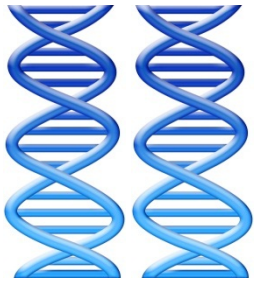
# Why are cells different from each other?

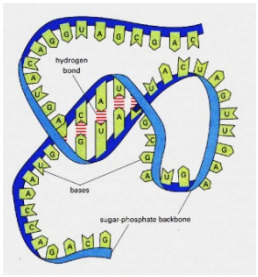



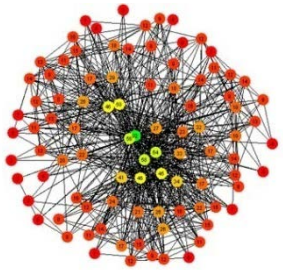



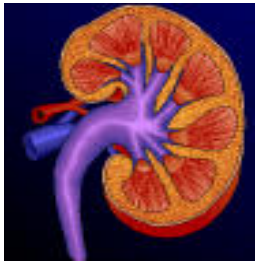



# Tissues are different from each other







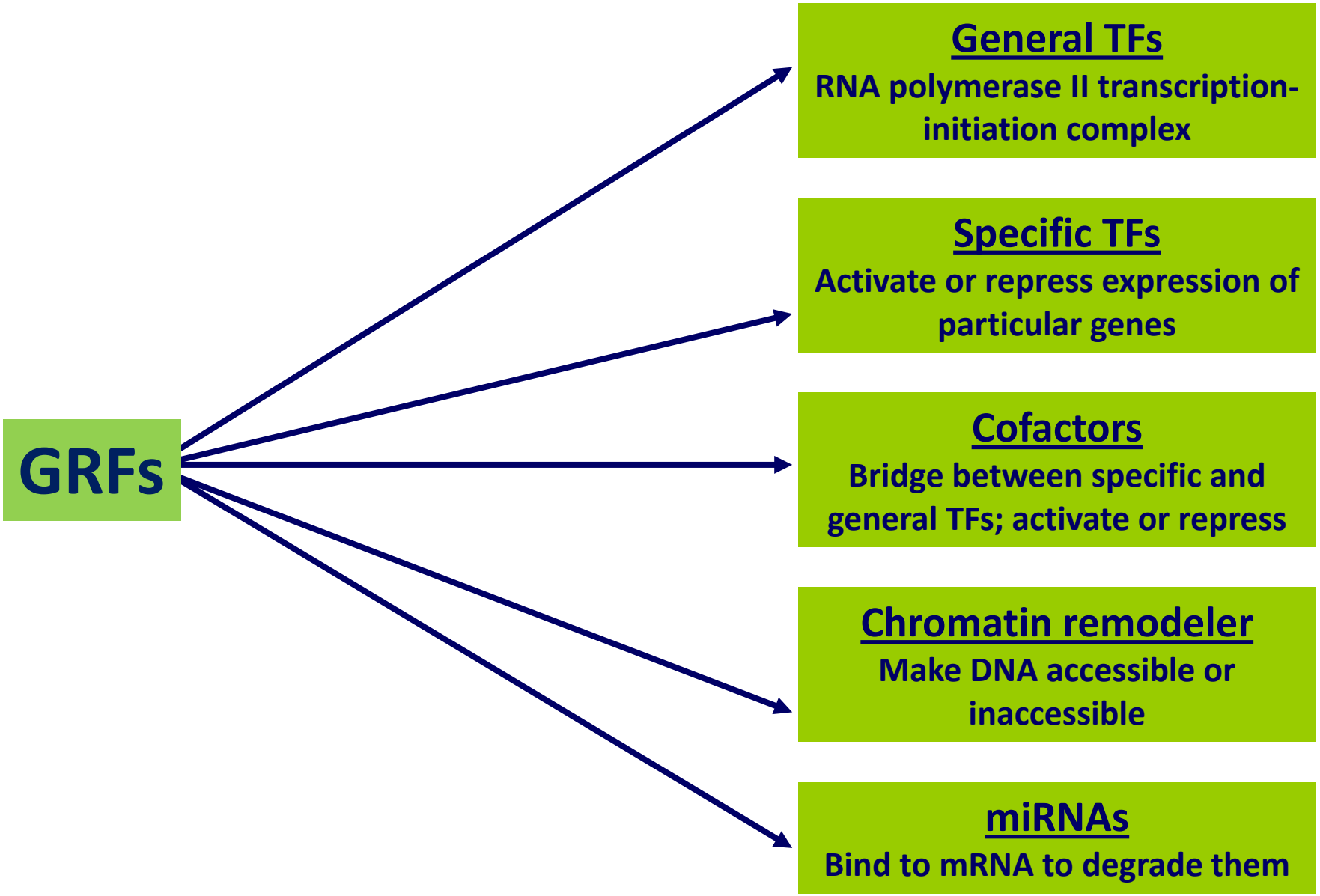
DNA → RNA → PROTEIN → PHENOTYPE

↓

**Gene regulatory factors (GRFs)**

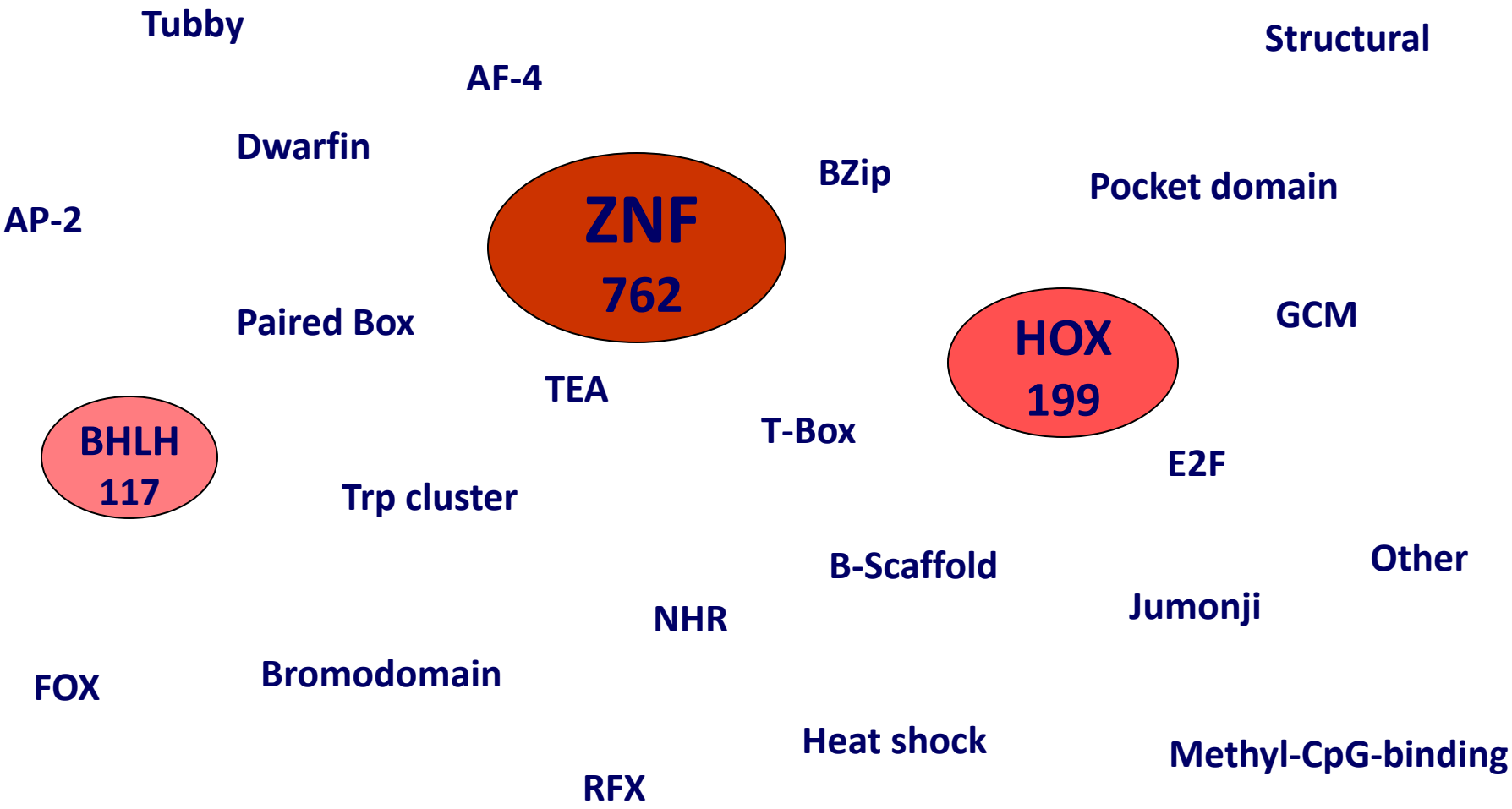
→ Differences in GRF genes

# Gene regulatory factors (GRFs)



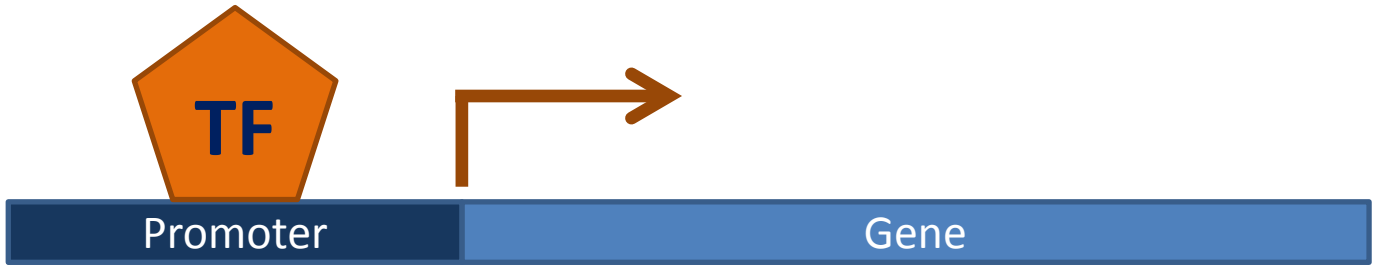
# Transcription factors (TFs)

**~ 1500 TFs in human genome**

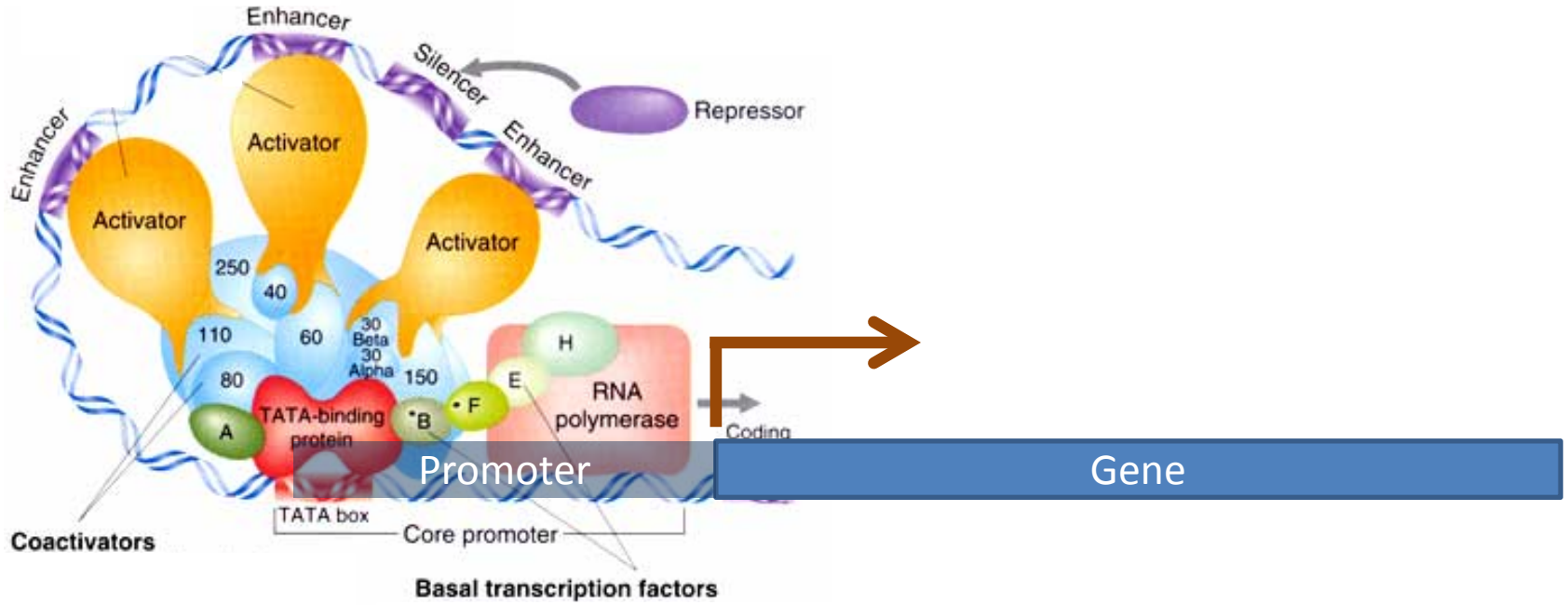



Modified after Messina et al., 2004

# TFs regulate expression of other genes

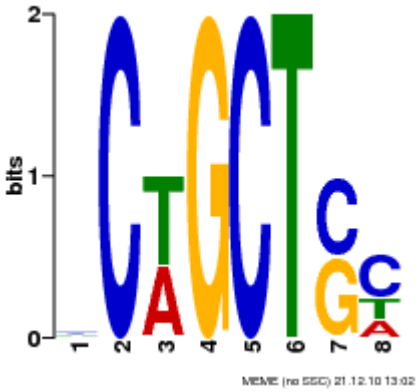


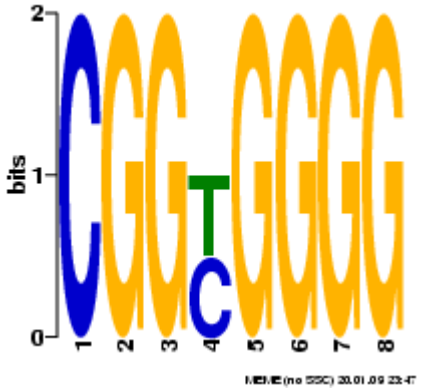
# TFs regulate expression of other genes

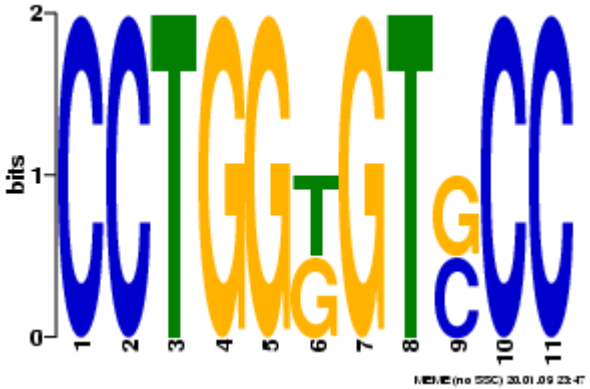


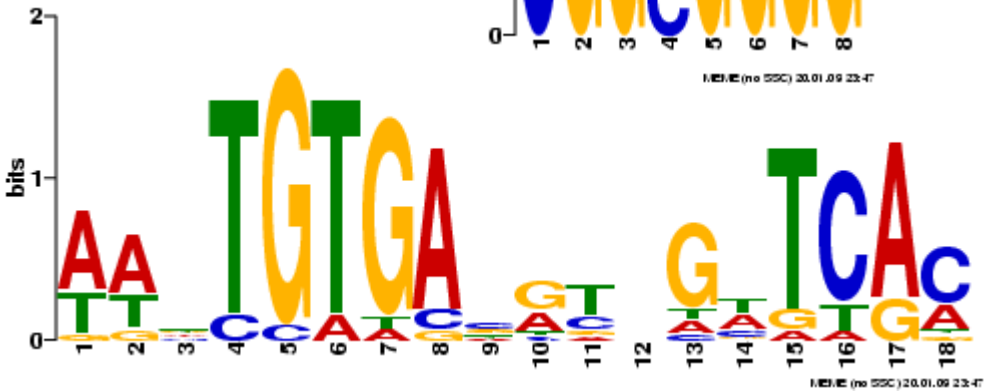

**Many TFs have to come together to start/stop transcription of a target**

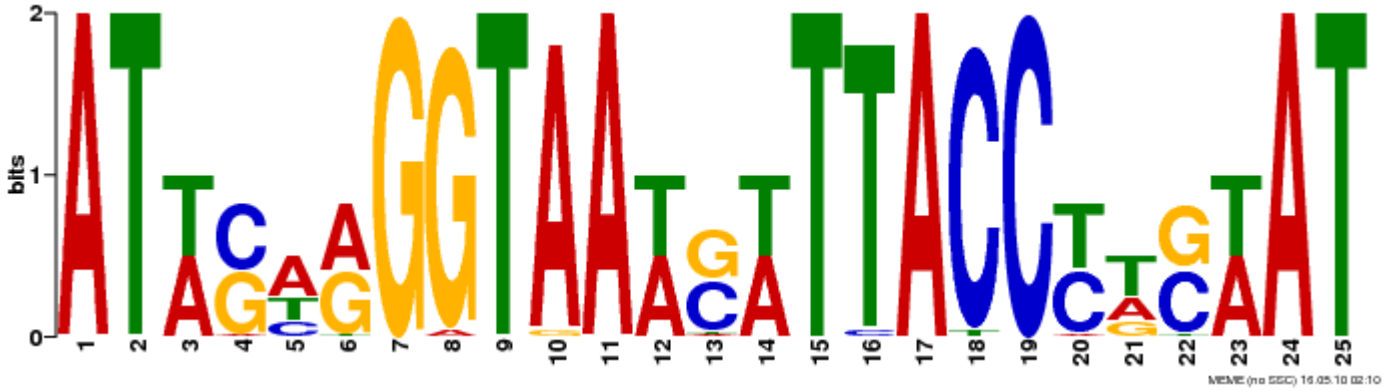
# TFs recognize specific sites/motifs in DNA



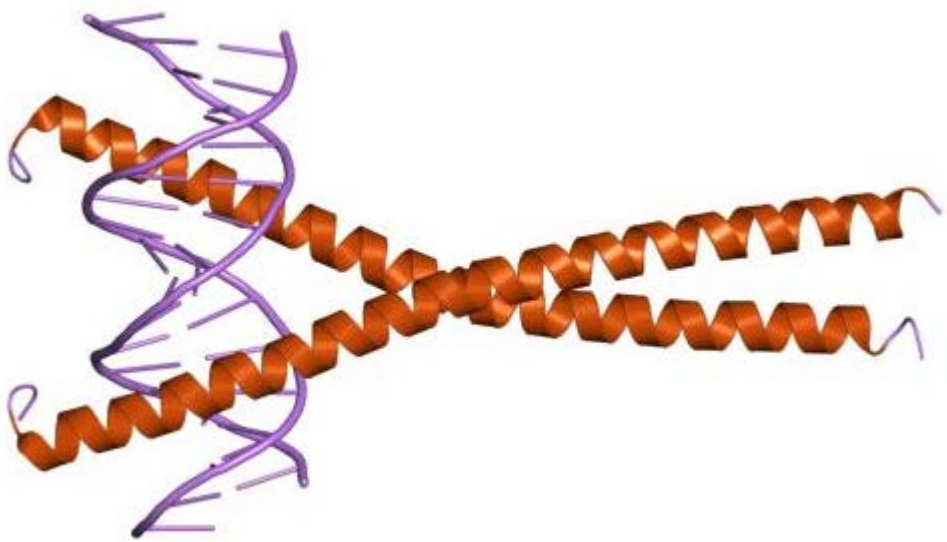



# Some TFs bind DNA as dimers

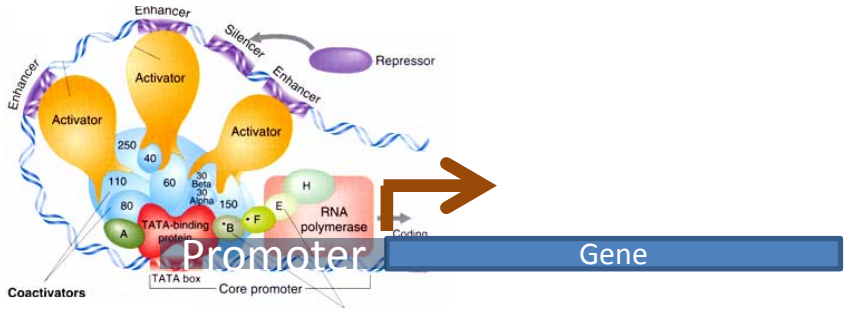
**Many TFs have to come together to start/stop transcription of a target**

bHLH: basic helix loop helix TFs
bZip: beta zipper TFs
NR: nuclear receptors

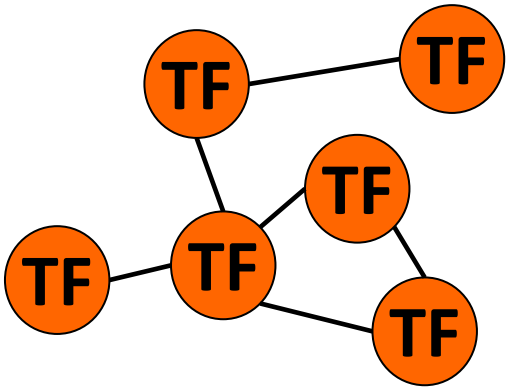


Homo-dimers or hetero-dimers → added complexity

# TFs network to regulate their targets



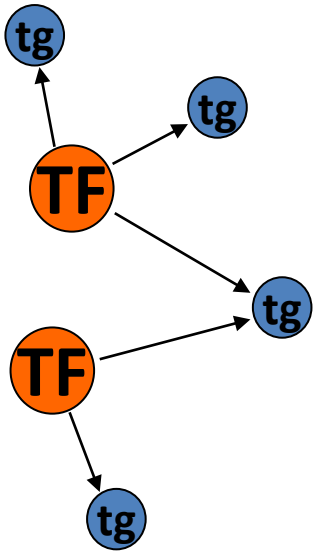

## TF-TF interaction network (PPI)




Nodes = Proteins
TFs

Links = relationship between the genes
interacting TFs
undirected

## Gene regulatory network (GRN)

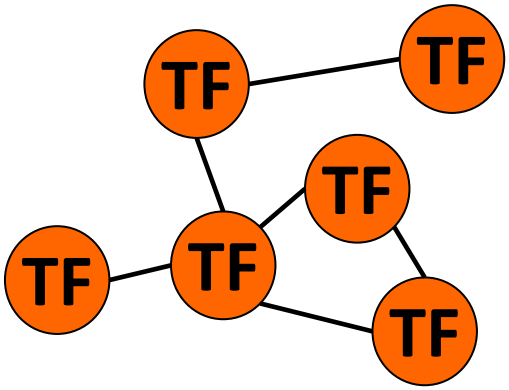



Nodes = genes/proteins
TFs, targets

Links = relationship between the genes
TF regulates target
directed, positive or negative

# Experiments to obtain networks

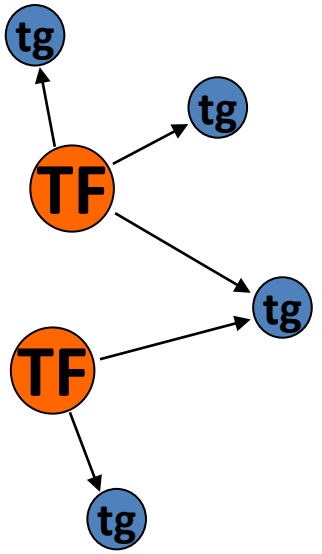
## TF-TF interaction network (PPI)




Nodes = Proteins
TFs

Links = relationship between the genes
interacting TFs
undirected

## Gene regulatory network (GRN)




Nodes = genes/proteins
TFs, targets

Links = relationship between the genes
TF regulates target
directed, positive or negative

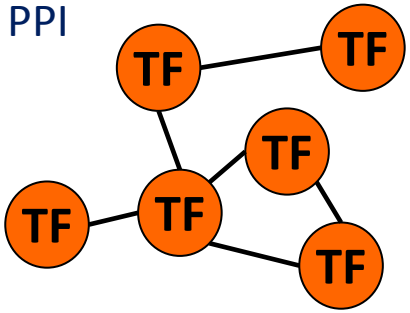
## Yeast-Two-Hybrid (Y2H)

## Chromatin immuno-precipitation (ChIP)-Seq

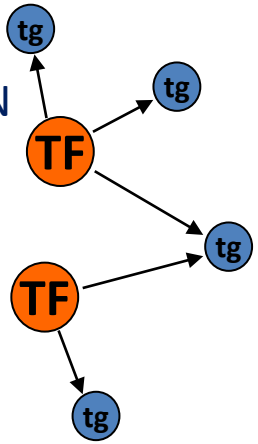

## Overexpression/knock-down of TFs, RNA-Seq

# Bioinformatics approach to obtain networks

PPI

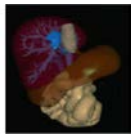



GRN

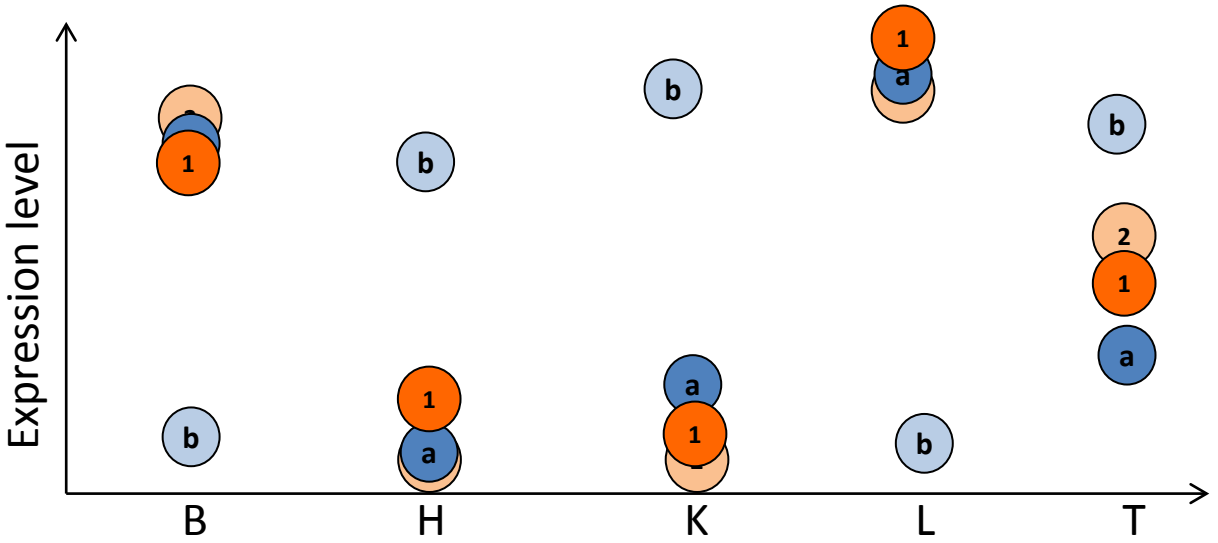


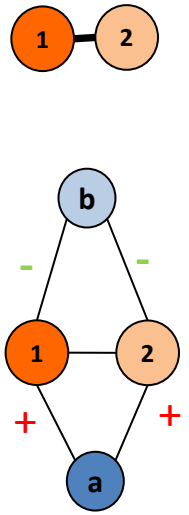

## Expression profiles



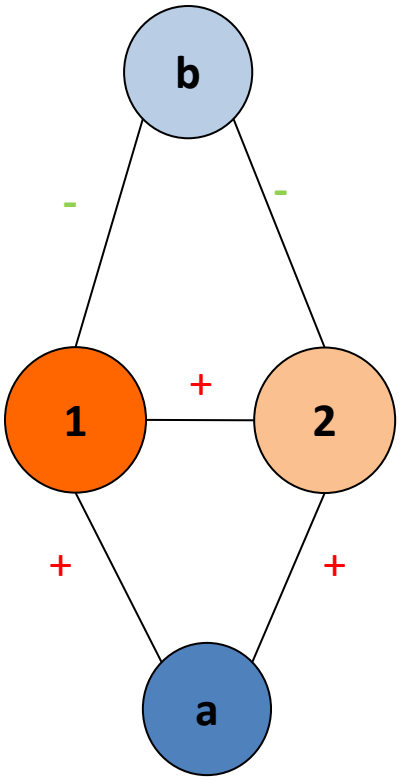

## Co-expression patterns




## → Co-expression network

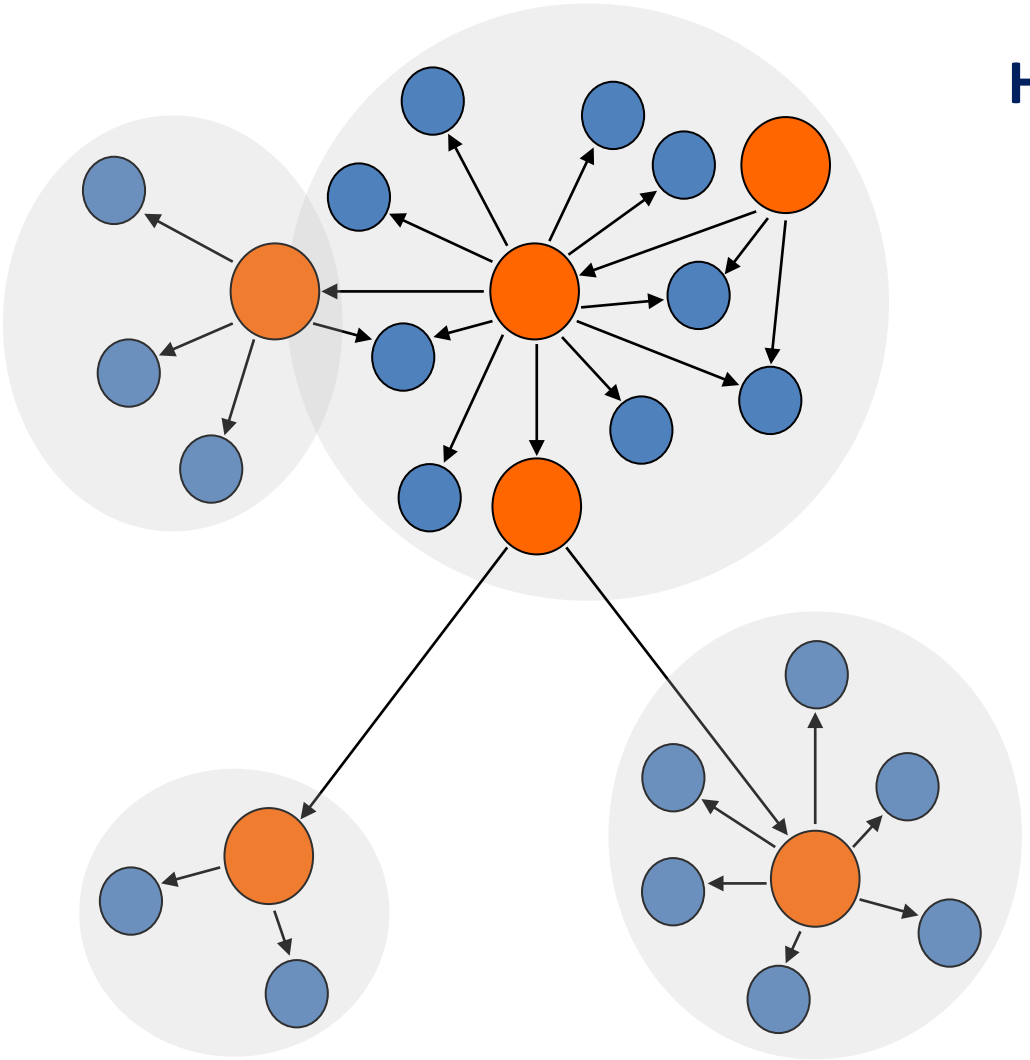
# Co-expression networks




**Nodes = genes/proteins**
**TFs and targets**

**Links = relationship between the genes**
**correlated in expression**
**positive or negative**
**undirected!**

# Features of GRNs and co-expression networks



**Hubs** ⟺ **peripheral nodes**

TFs — targets

## "Small world"

Get everywhere via a few nodes

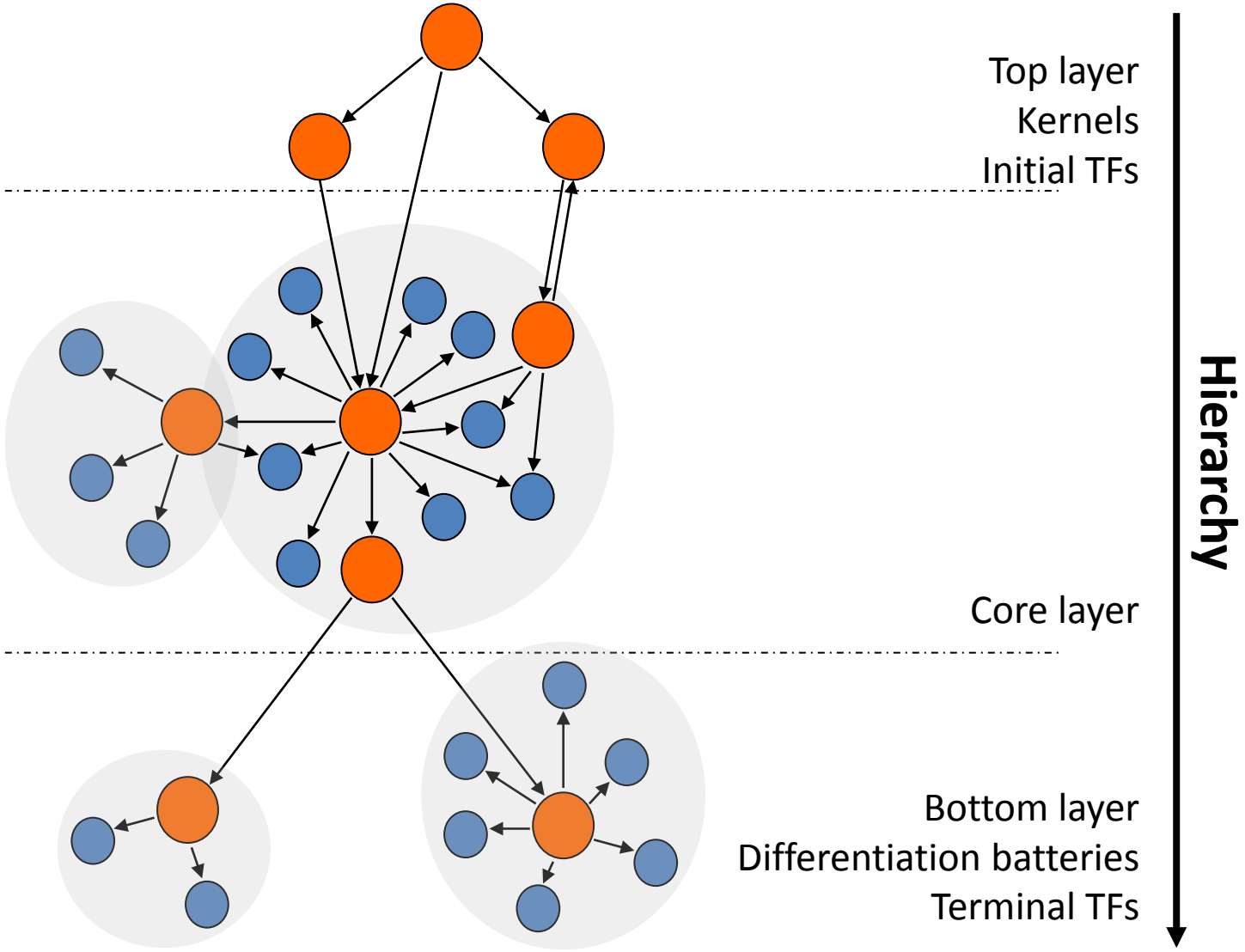
## Modular

Modules have different functions

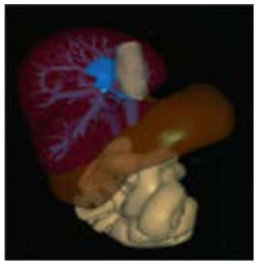
## Dynamic

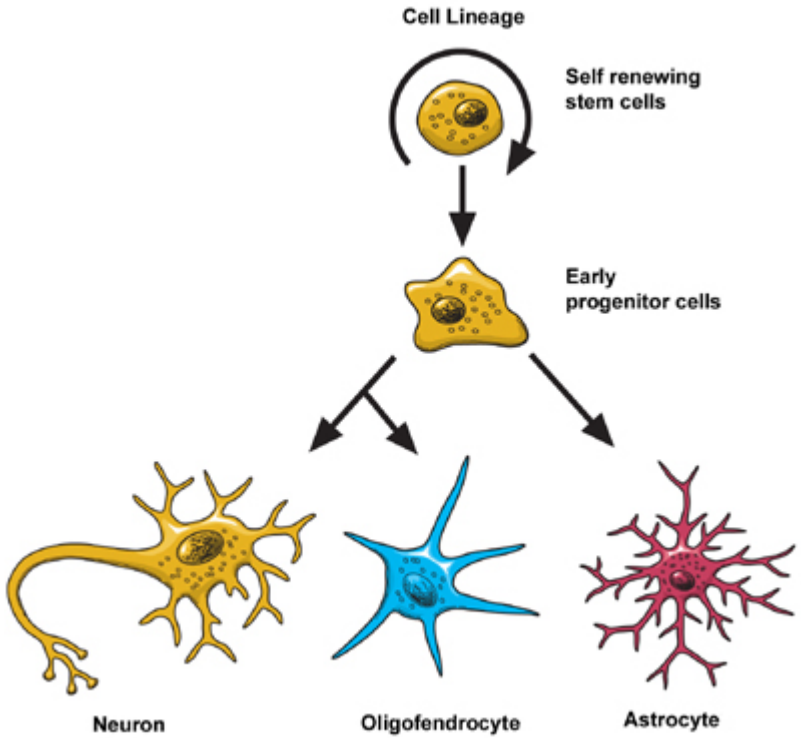
Change nodes and wires when environment changes

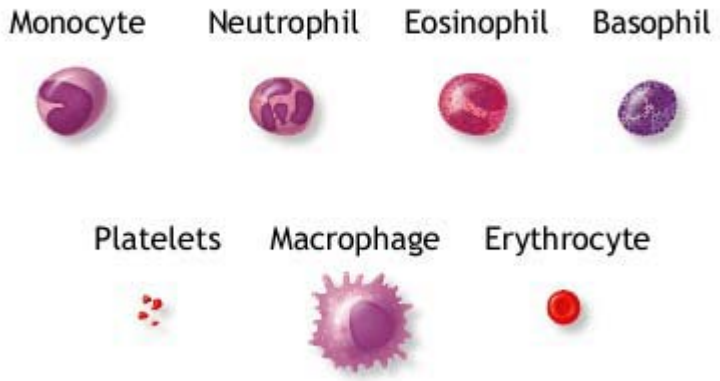
# GRNs are hierarchical



# Why are tissues different from each other?

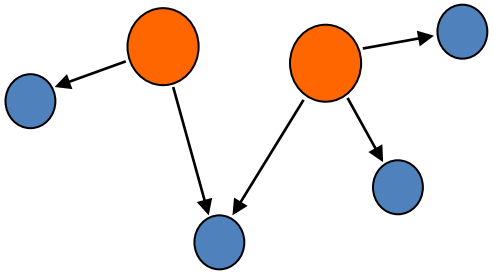



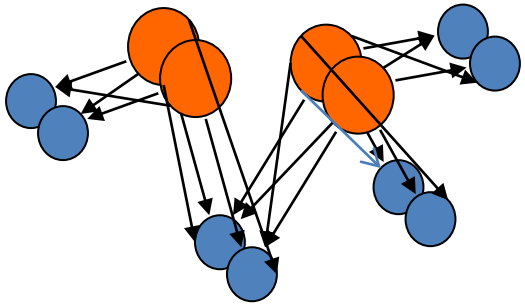
# Why do species look different?

# Evolution of networks

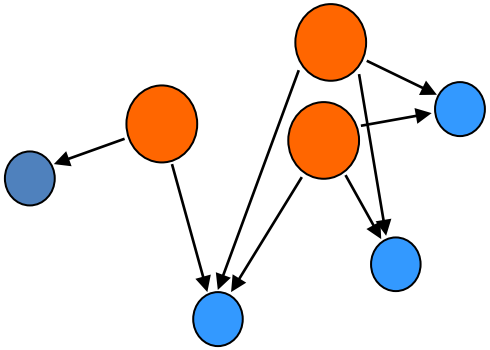
"Original network"



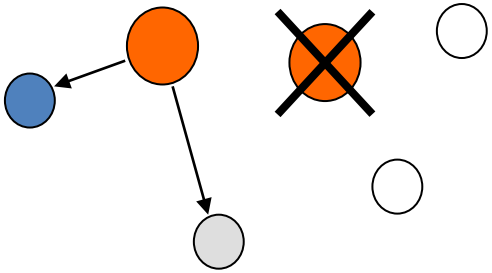
Whole genome duplication



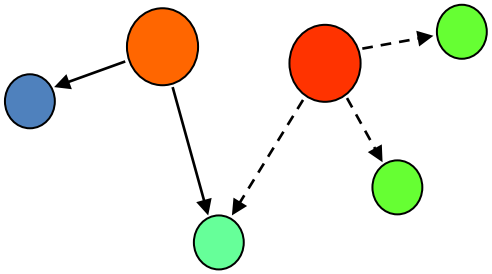
Node duplication



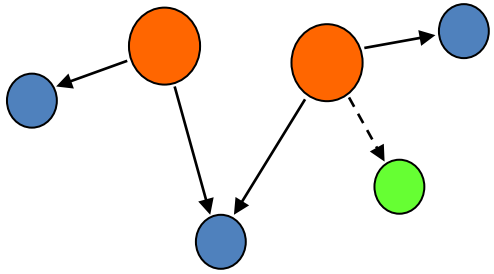
Node deletion



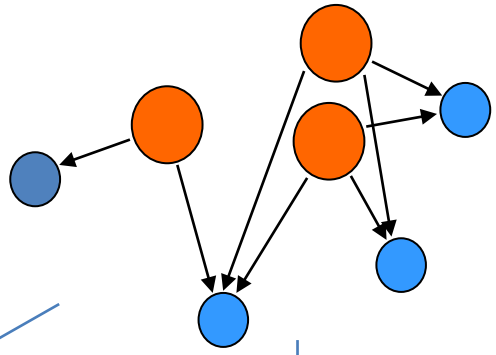
Sequence change in TF



Sequence change in binding site



# Divergence of duplicates



Pseudogenization

Sequence divergence:
New target genes

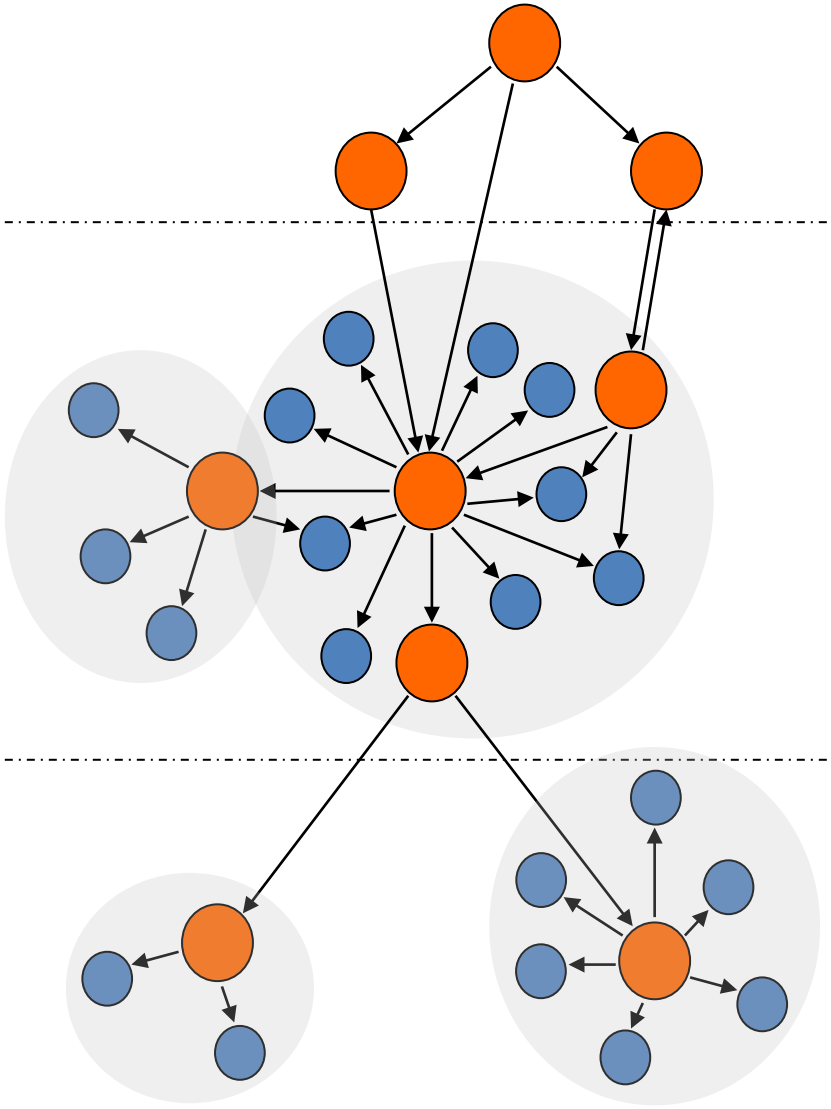
Expression divergence:
Function in other tissues
or time points

Very rapid, within a few million years!

One copy diverges: neo-functionalization

Both copies diverge: sub-functionalization

# Elements of networks change with different speed and consequences



Top layer
Kernels
Initial TFs

Core layer

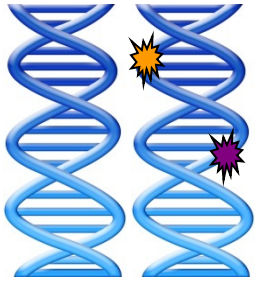
Bottom layer
Differentiation batteries
Terminal TFs

Hierarchy

**Big effect:**
Hubs
Initial TFs
Less frequent
Species differences,
Disease

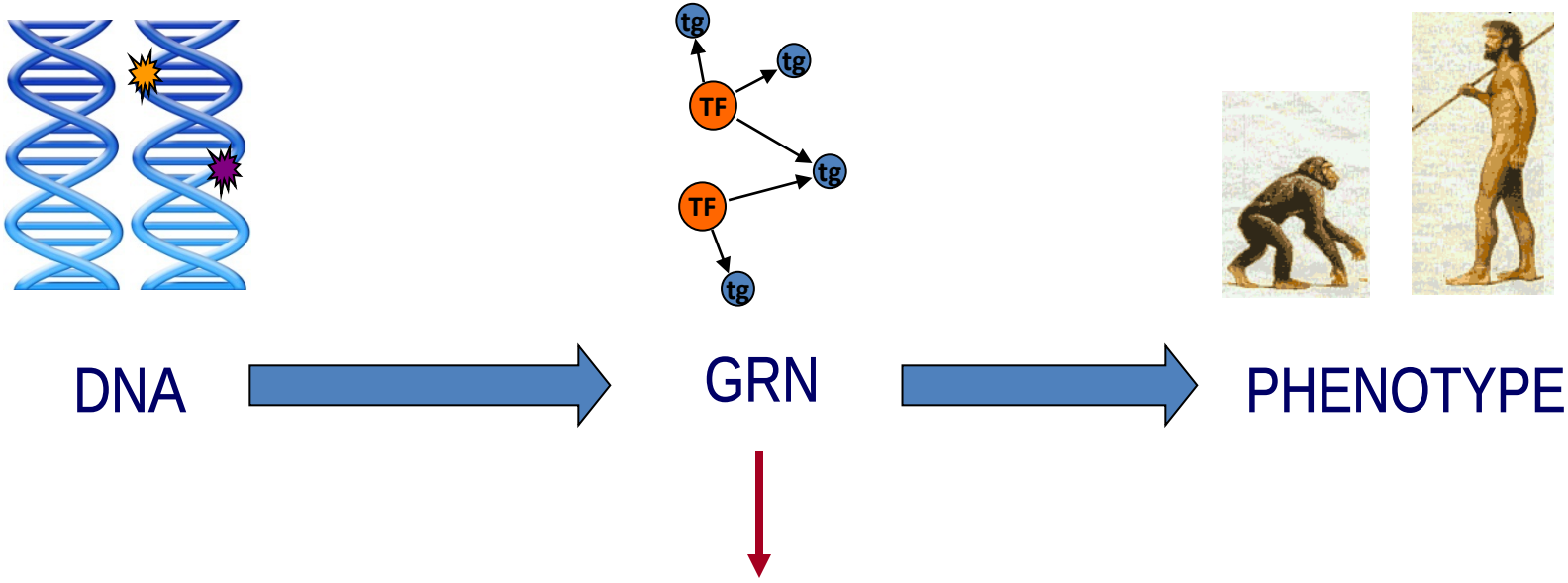
**Small effect:**
Peripheral nodes
Terminal TFs
More frequent
Cell differentiation

# Small sequence but big phenotypic differences



DNA → PHENOTYPE

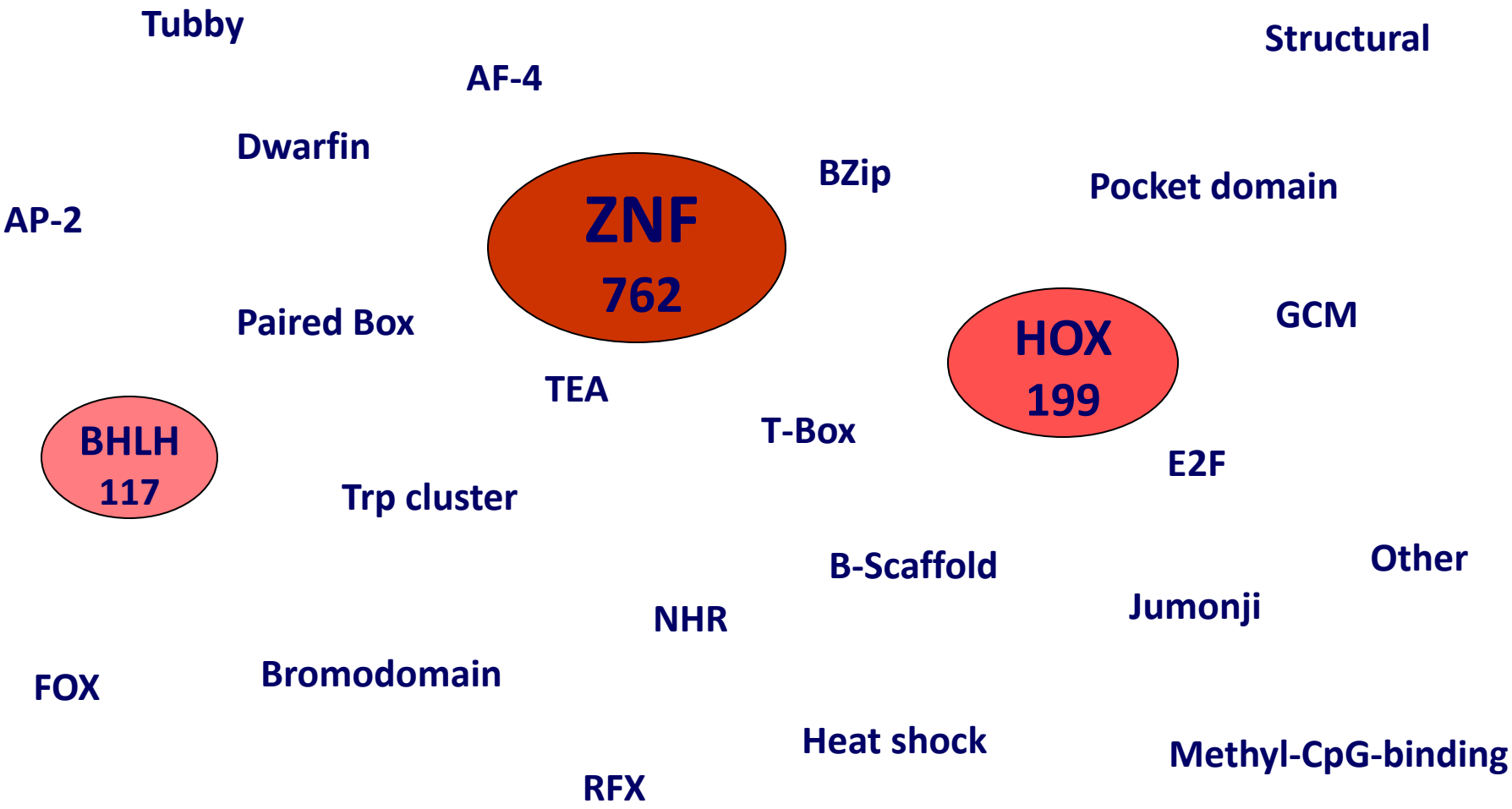
# Small sequence but big phenotypic differences




Differences in TFs?

# Transcription factors (TFs)

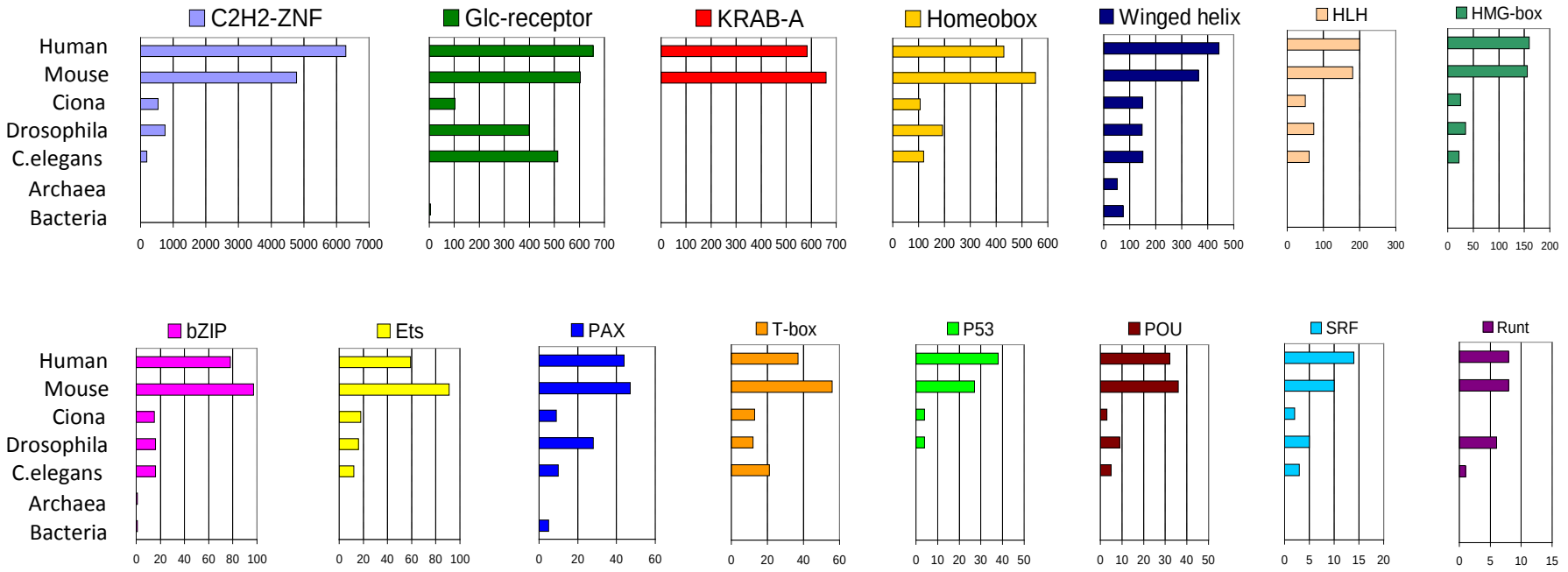
**~ 1500 TFs in human genome**




Modified after Messina et al., 2004

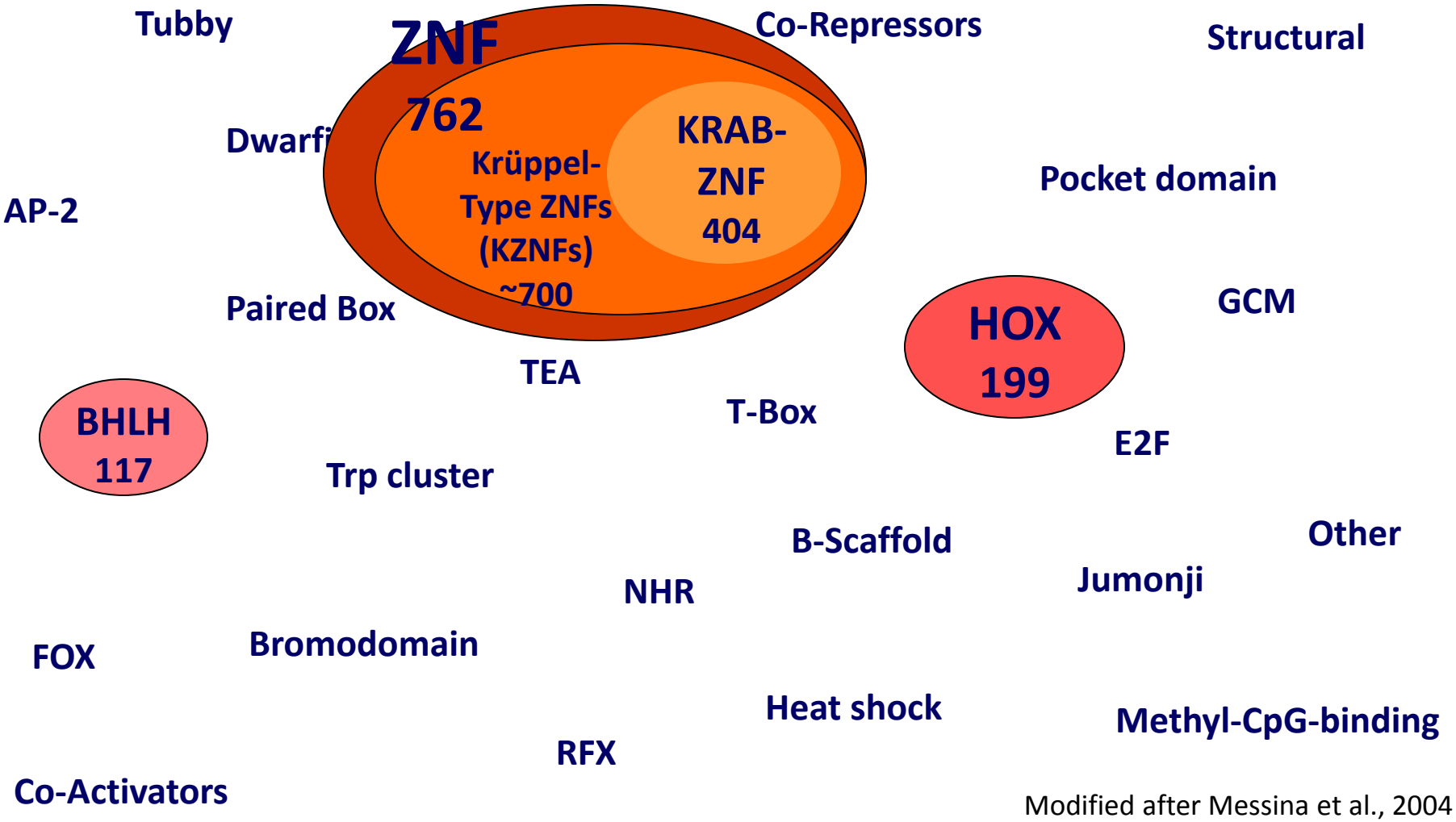
# Numbers of TFs are different between species

## # of TF domains:



# KRAB-ZNFs are biggest group of TFs

**~ 2000 TFs in human genome**

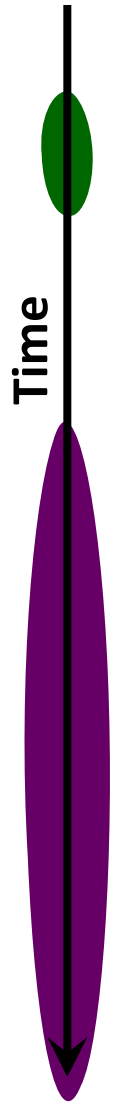


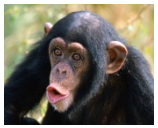
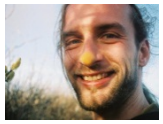

Modified after Messina et al., 2004

# Expansion of KRAB-ZNF genes

**KRAB joins zinc fingers**

**Rapid expansions of KRAB-ZNF genes**

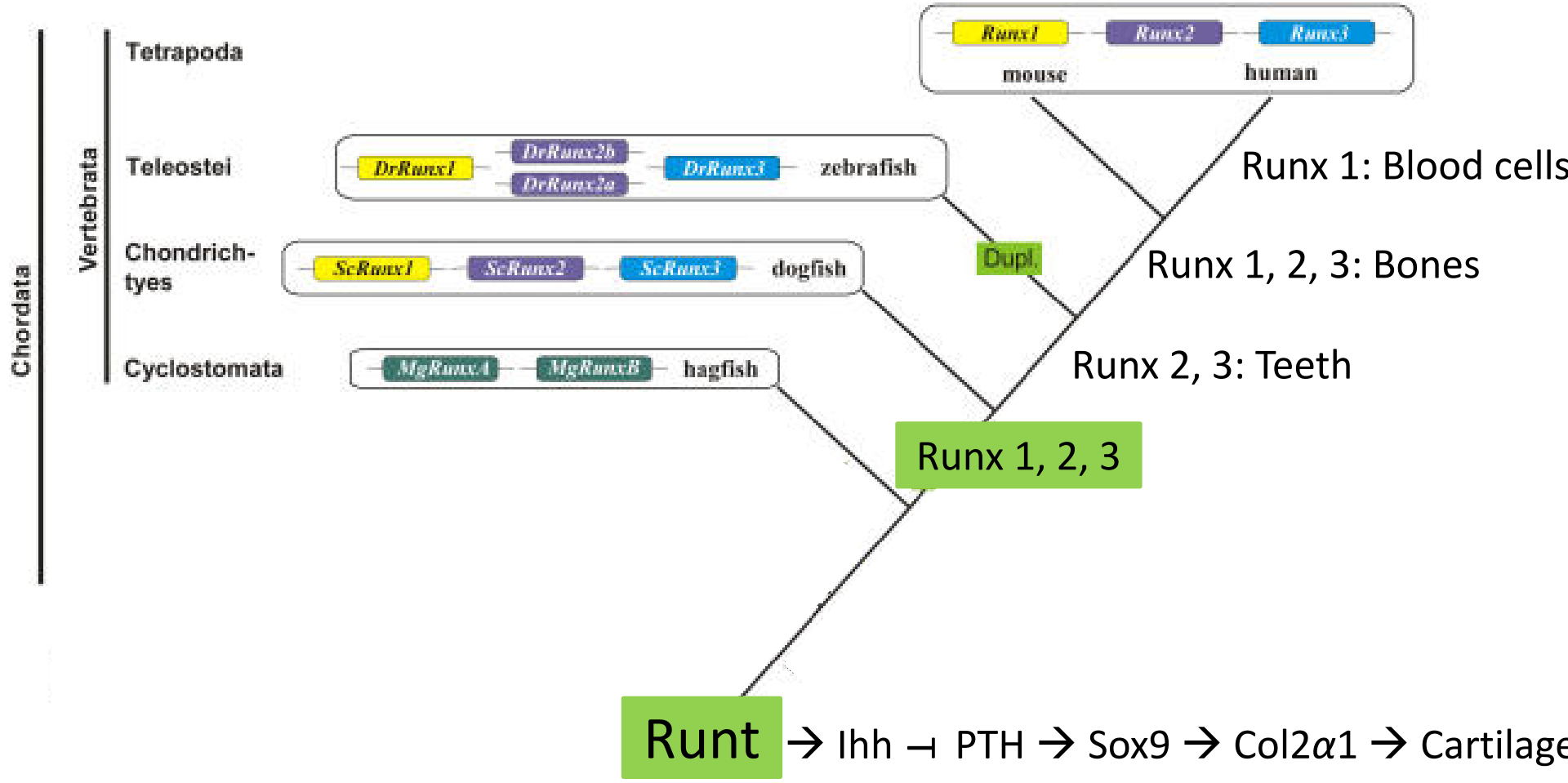



| | KRAB-ZNF genes | All Krüppel-type ZNF genes |
|---|---|---|
|  | 1 | ~700 |
|  | ? | ~700 |
|  | ~30 | ~600 |
|  | ~100 | ~800 |
|  | ~382 | ~680 |
|  | ~366 | ~655 |
|  | ~415 | ~730 |
|  | 423 | 768 |

Huntley et al. 2006

# Example: Neofunctionalization

**Duplications of transcription factor RUNT:**




**Sequence of Runx 1-3 very similar, but different expression patterns**

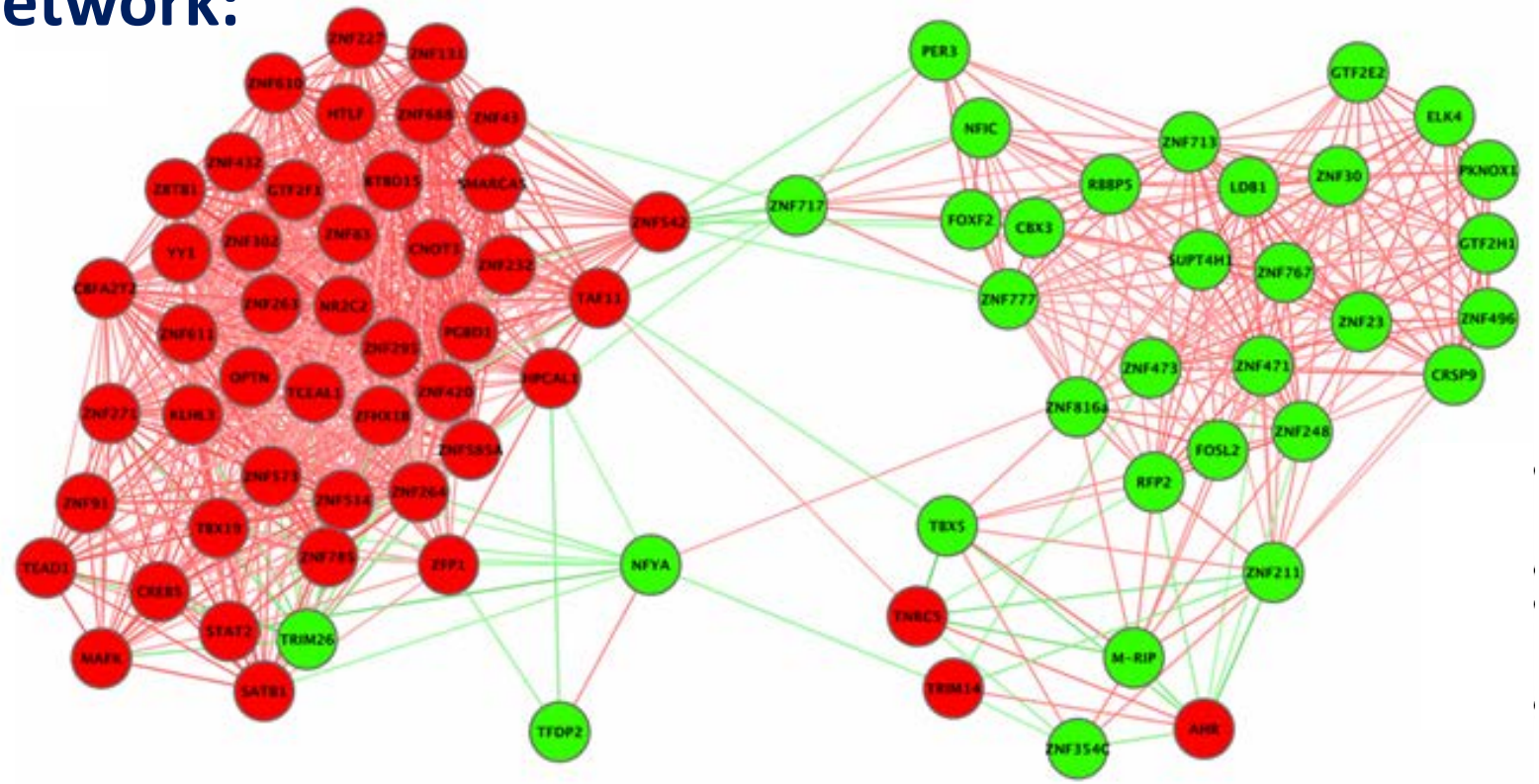
**Rewiring of GRN → evolution of new tissues**

# Example: Rewiring / gain of targets

Human

→ Co-expression network for all TFs → TFs with similar co-expression networks linked in wTO network

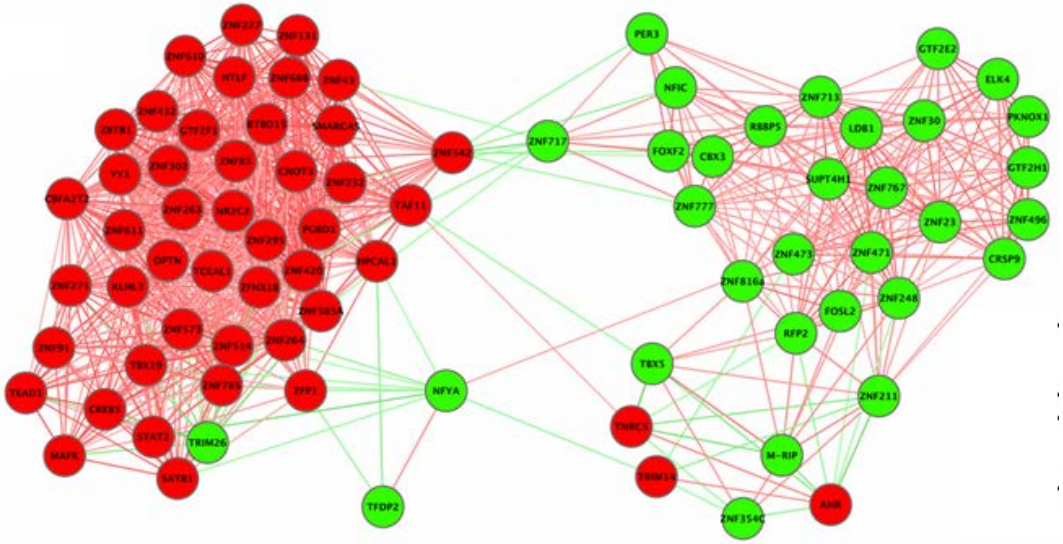
**wTO network:**

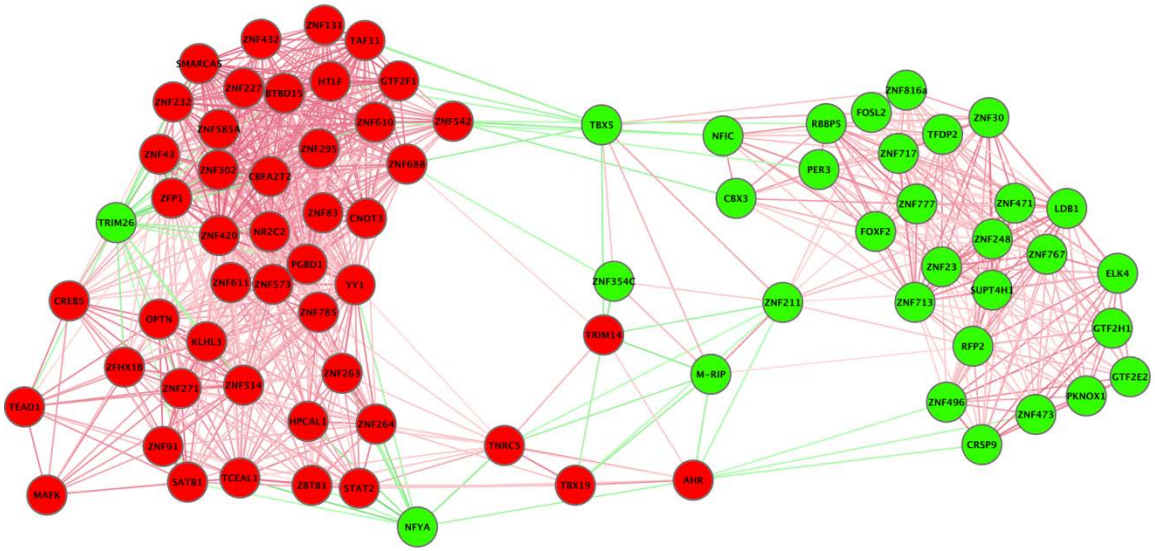


# Example: Rewiring / gain of targets

Human

Chimpanzee



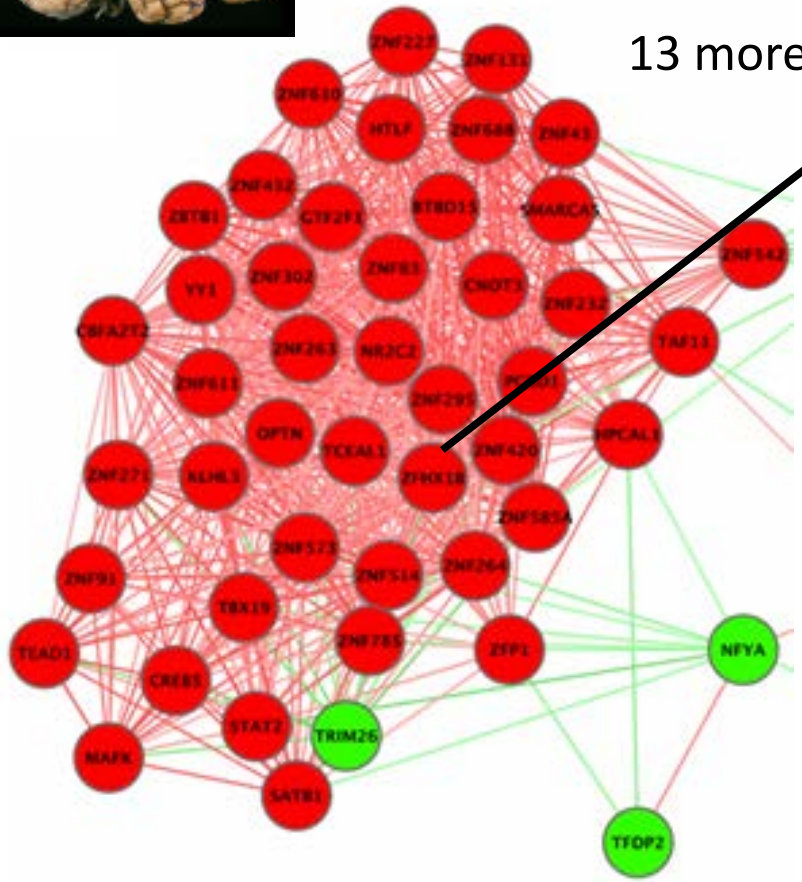
# Example: Rewiring / gain of targets

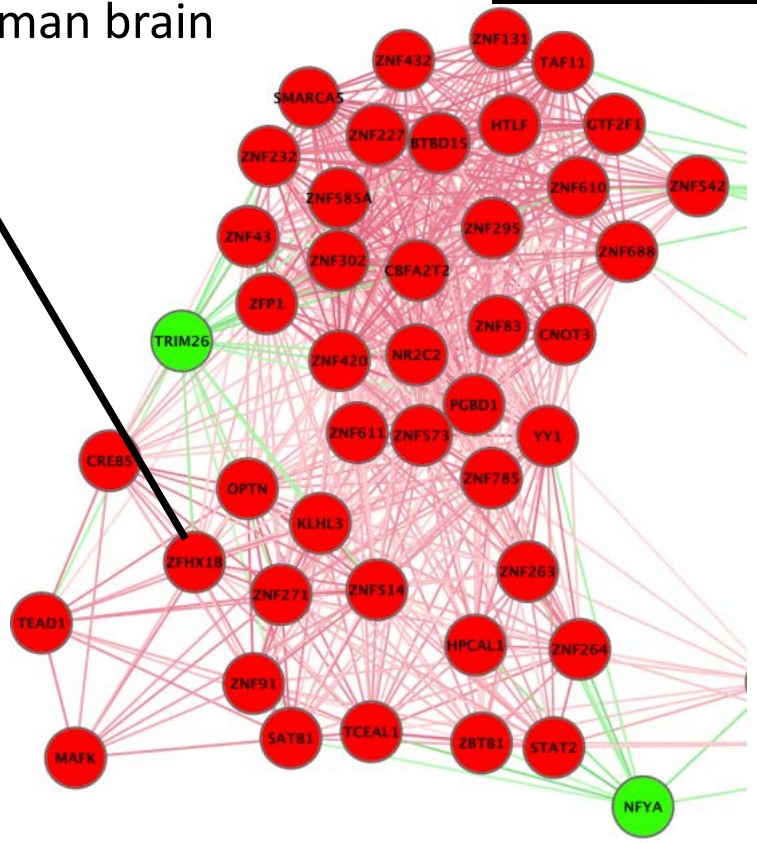
Human

Chimpanzee

ZFHX1B

13 more links in human brain




**Rewiring of ZFHX1B co-expression network**

**→ larger brain and higher cognitive abilities?**