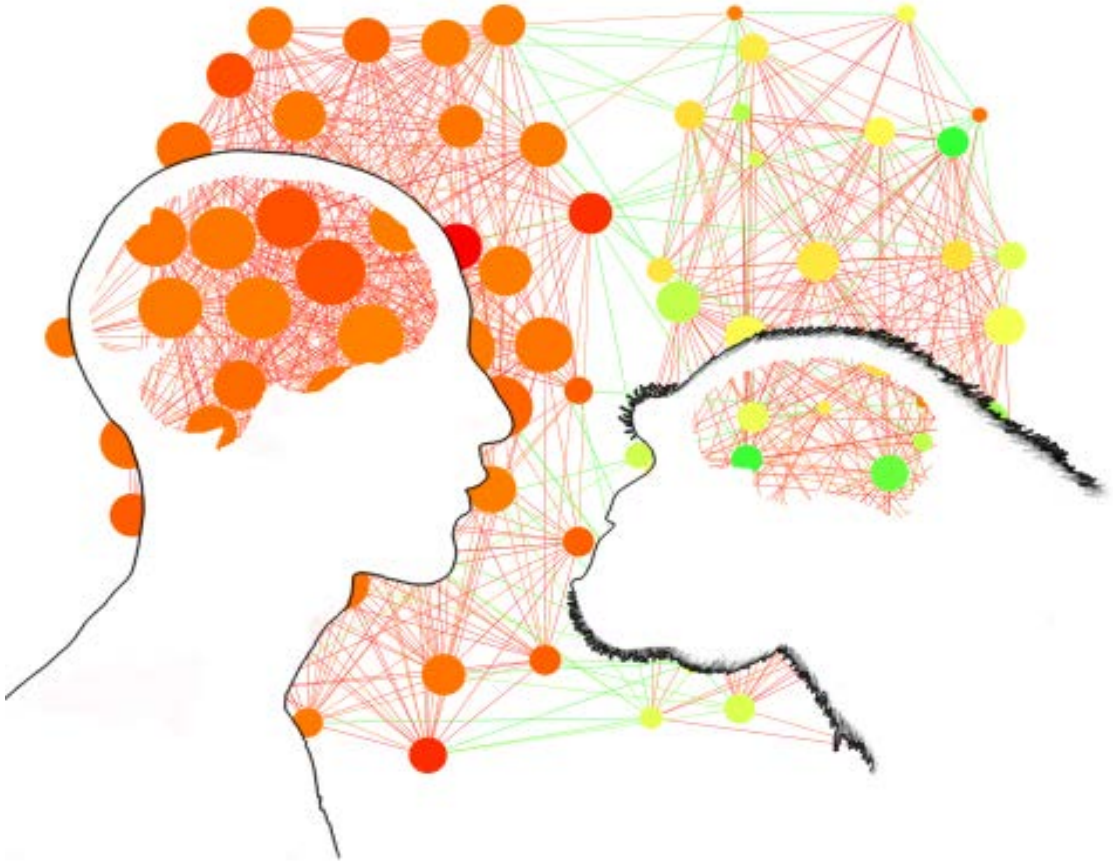
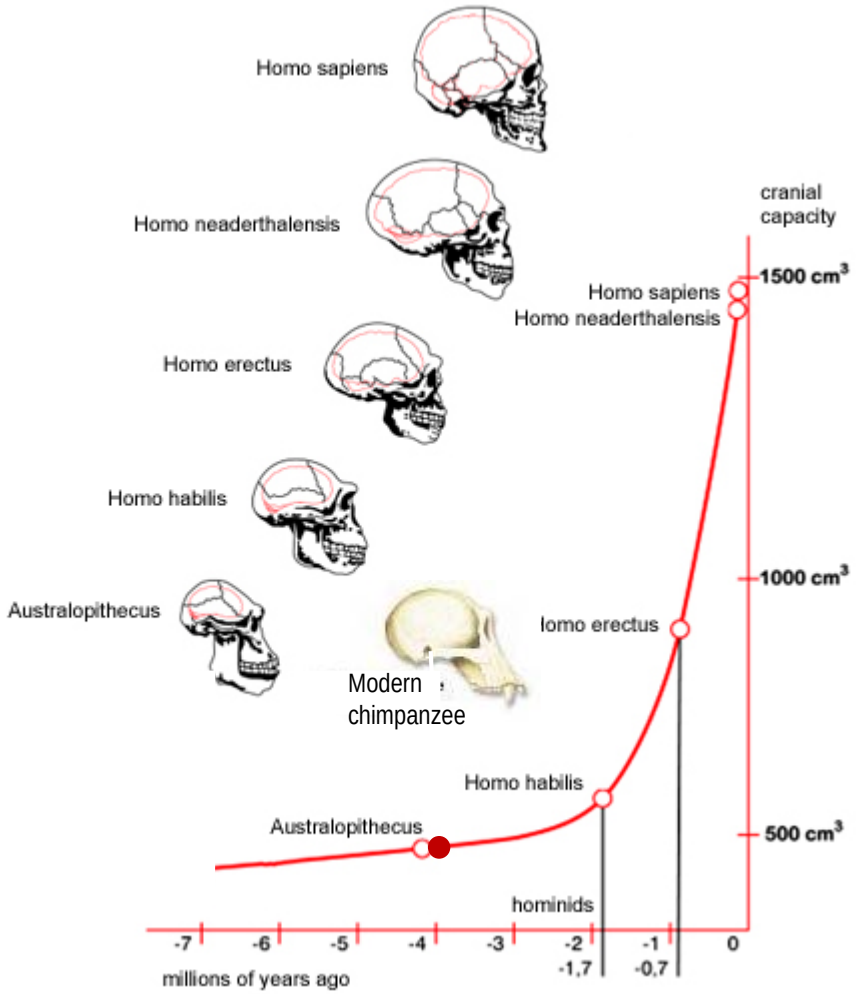
Molecular evolution of primate brains



Katja Nowick
Human Biology and Primate Evolution group

Freie Universität Berlin

Changes in Brain Size, Cognition, and Behavior

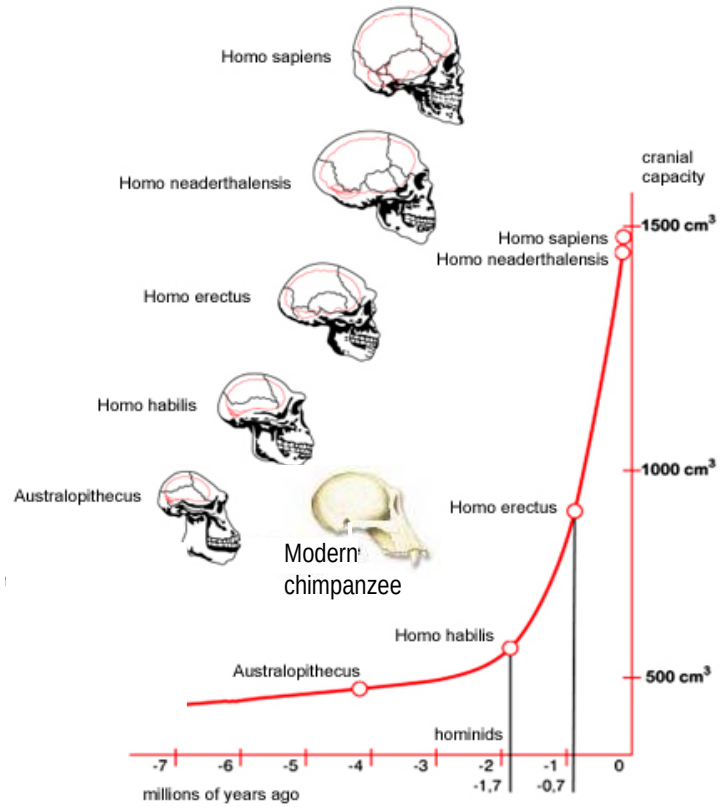


Human specific set of cognitive abilities:

- More complex communication (spoken language, abstract symbols and grammar)
- Acquire new knowledge more quickly (e.g. by learning from others)
- Maintain knowledge over generations
- Shape environment according to our needs
- Stronger pro-sociality and cooperativity

Molecular basis for these phenotypes largely unknown

Changes in Brain Size, Cognition, and Behavior



Human specific set of cognitive abilities:

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- Shape environment according to our needs
- Stronger pro-sociality and cooperativity

Very likely, many genes responsible for these traits → "complex traits"

How can we find the responsible genes?
Candidates can come from biomedical research

Complex diseases, e.g. Schizophrenia

Monozygotic twins: if one has schizophrenia, then the probability, that the other twin also gets schizophrenia is 40%
→ Genetic component, but it cannot only be one responsible gene

Motor might not function, because

- crank
- gears
- piston
- gasket
- spark plugs
- …

Are broken

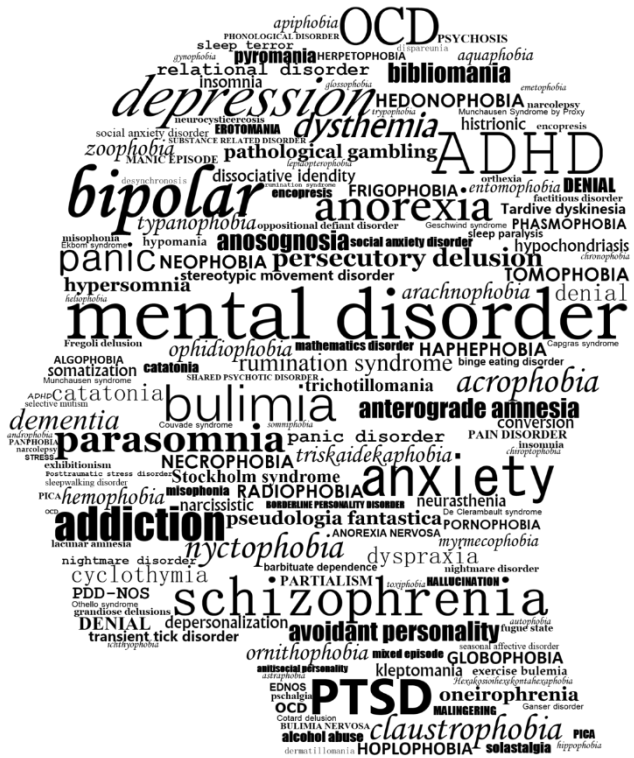
Motor not completely broken but stutters and wheezes

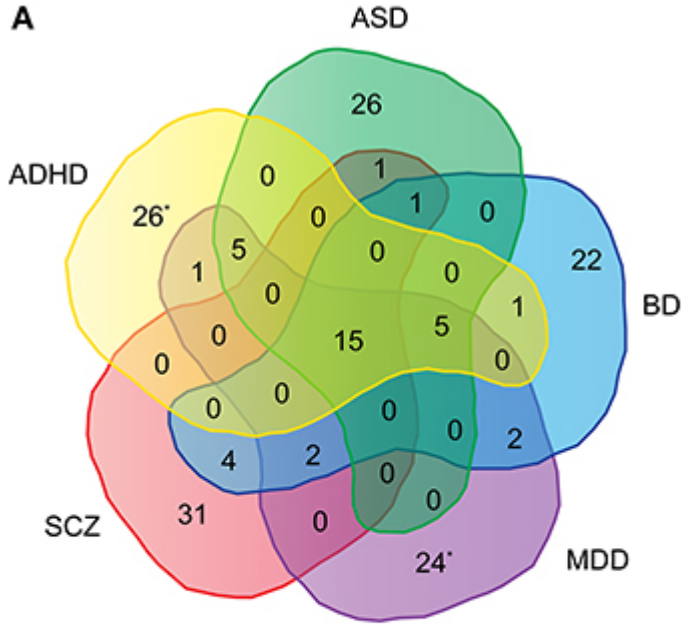
And the problem is more extreme in Winter

Schizophrenia can be caused by different mutations
One mutation alone often doesn't cause the disease, but a combination of mutations does
e.g. hyperactive dopaminergic neurons, fewer GABAergic neurons …
Possible environmental triggers: Birth in Winter, living in a city, cannabis, infections …

Even though monozygotic twins carry the same mutations, the environment determines if the individual develops the disease or not

Cognitive diseases





B

Genes shared among	N genes
6 disorders	0
5 disorders	15
At least 4 disorders	20
At least 3 disorders	28
At least 2 disorders	39

Lotan et al. (2014) Frontiers Neuroscience

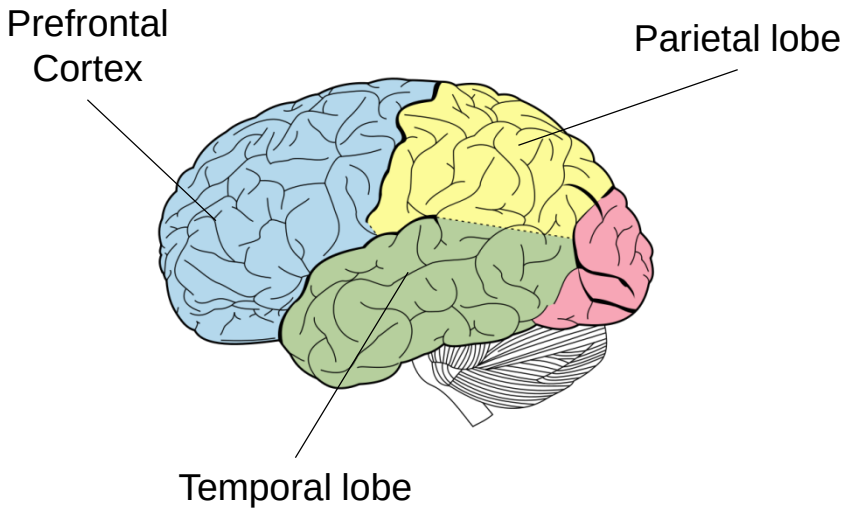
Many similar disorders

Hundreds of associated mutations already identified

One and the same mutation can be involved in several diseases

Many cognitive disorders seem to be human specific

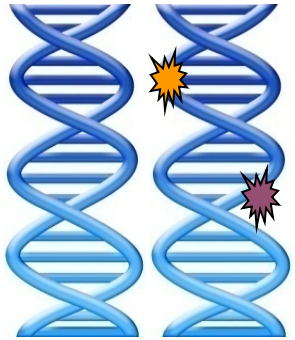
e.g. Alzheimer's disease:



- Complete Alzheimer pathology has never been observed in non-human primates
- Evolutionary young brain regions show disease phenotype first (prefrontal cortex, parietal lobe)

Do the same molecular changes that gave rise to the evolution of uniquely human cognitive abilities also render the human brain vulnerable to cognitive and mental disorders?

Small Sequence but Big Phenotypic Differences



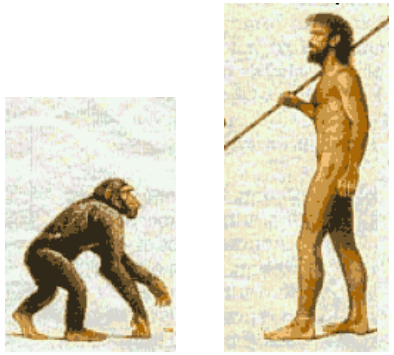
Genome

3-4%

Evolution at Two Levels in Humans and Chimpanzees

Their macromolecules are so alike that regulatory mutations may account for their biological differences.

Mary-Claire King and A. C. Wilson

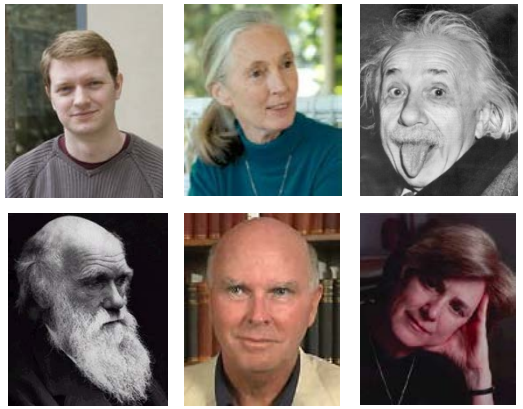


Phenome

Gene expression differences

How much expression differences do we have?

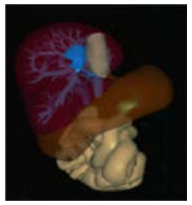
6 humans



5 chimpanzees

Brain (Prefrontal Cortex (PFC))

Liver



Kidney

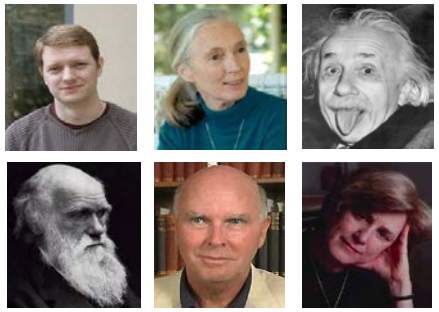
Heart

Testis

Khaitovich et al. 2005

How much expression differences do we have?

6 humans



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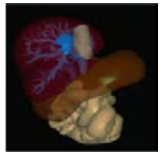


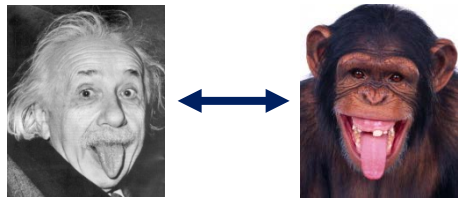
Kidney

Heart

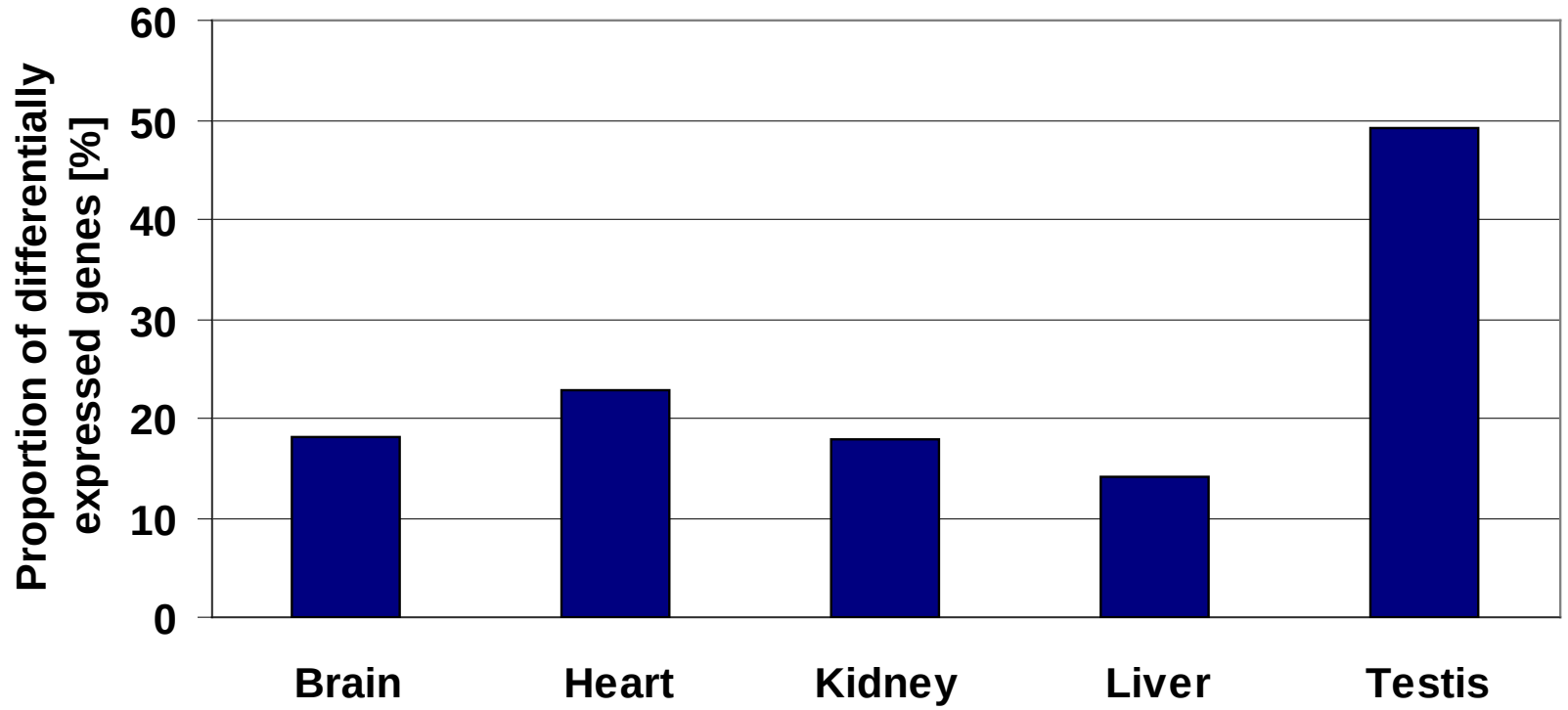
Testis

- **Guess, what percentage of genes is differentially expressed**
- **Guess, which tissue has the most expression changes**

How much expression differences do we have?



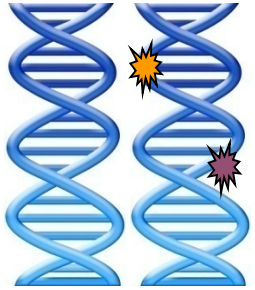
T-test,
adjusted p<0.05,
Fold Change >1.2

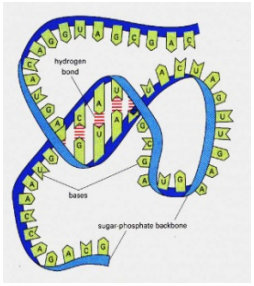


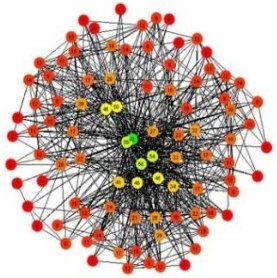
Between 15 and 50% of the expressed genes are differentially expressed

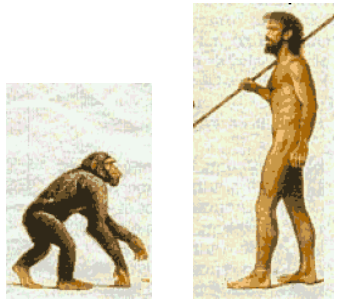
Khaitovich et al. 2005
Nowick et al. 2009

Which changes drive the expression differences?









Genome → Transcriptome → Proteome → Phenome

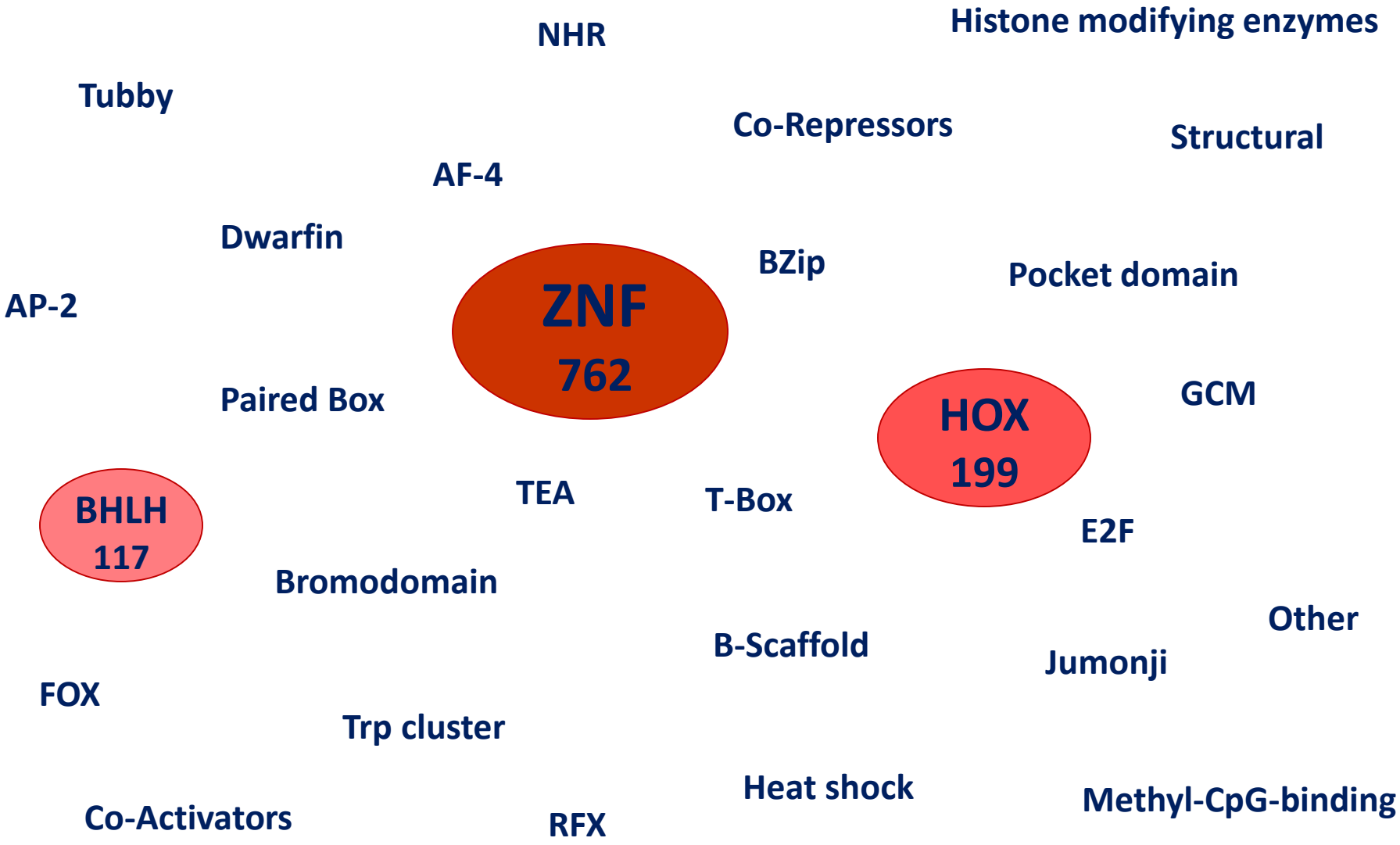
3-4% 15-50%

Gene regulatory factors (GRFs) are important

- Transcription factors (TFs)
- Histone modifying enzymes
- Non-coding RNAs (ncRNAs)

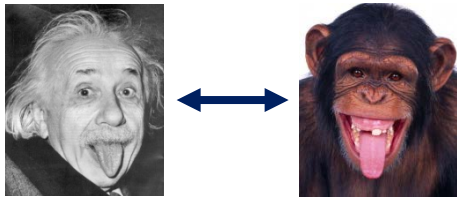
Transcription Factor Families

3315 TFs in human genome



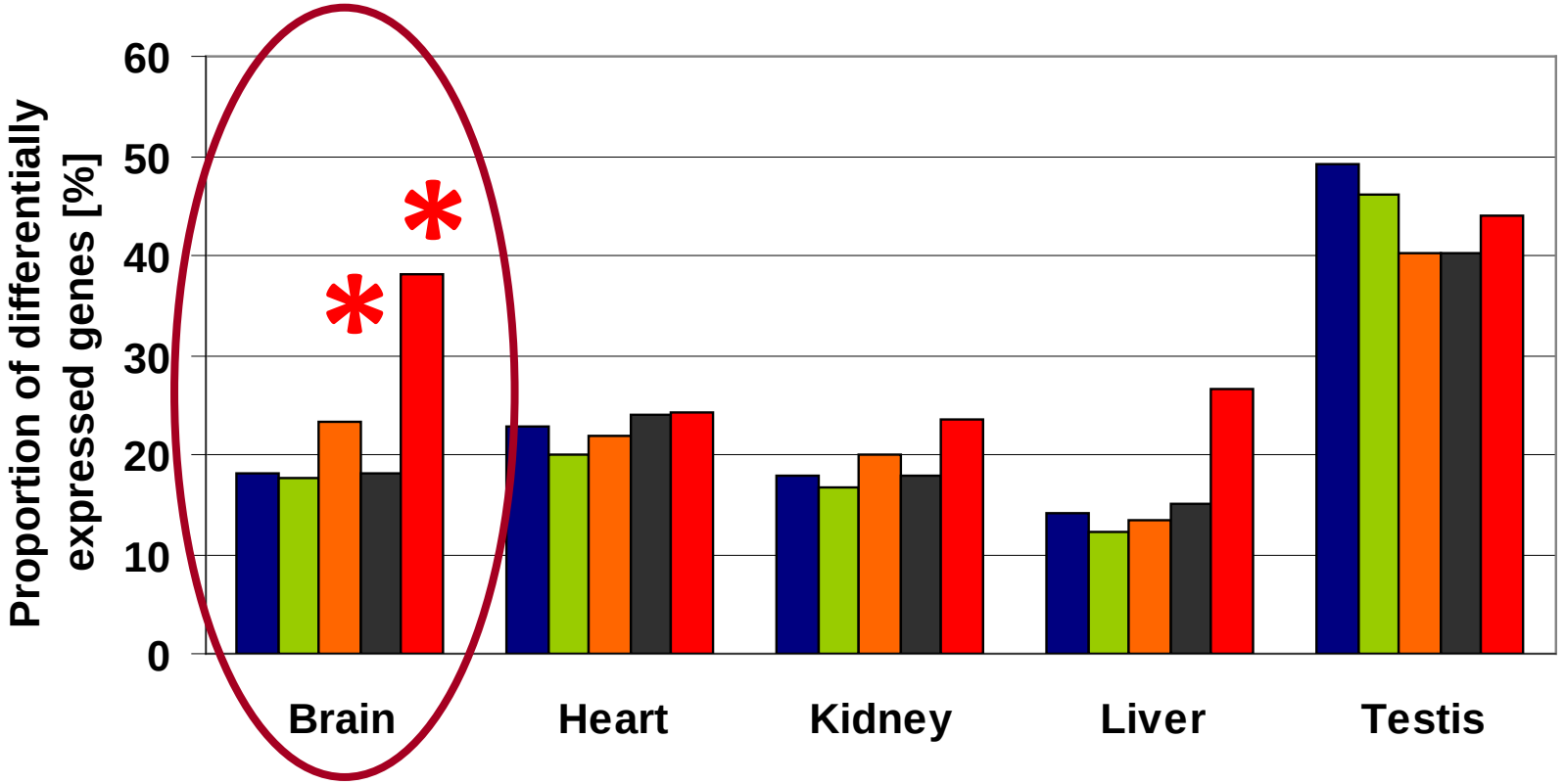
Perdomo Sabogal et al.; 2019

Differentially expressed TFs



All genes
All TFs
All KRAB-ZNFs
Conserved KRAB-ZNFs
Primate-spec. KRAB-ZNFs

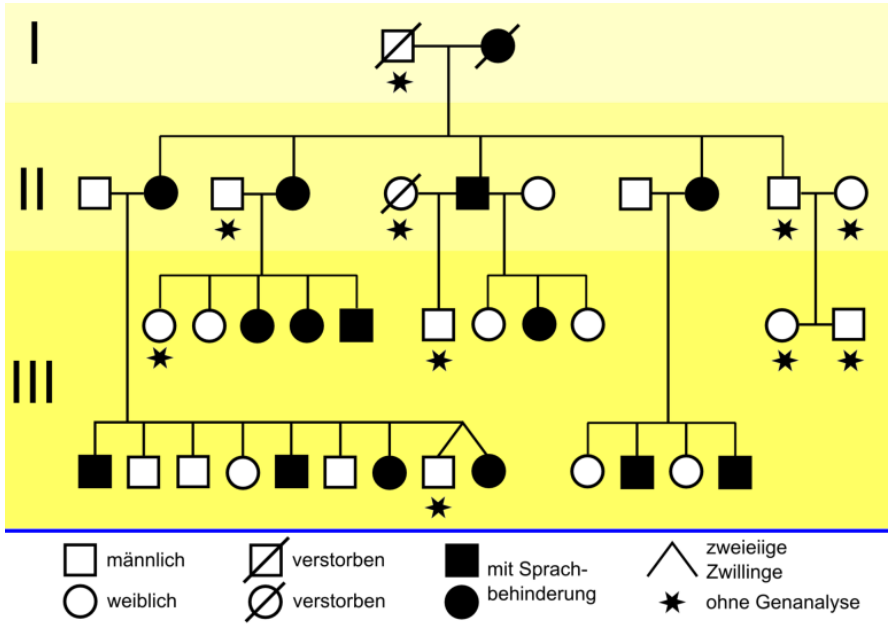
T-test,
adjusted p<0.05,
Fold Change >1.2



→ Recently evolved KRAB-ZNFs are enriched among brain changed genes

Evolution of language: FOXP2

- In 1990s: Investigation of a family in London (“KE family”) with several family members with speech problems
- Verbal developmental dyspraxia: mainly probems with articulation
- → Mutation in the gene FOXP2 associated with speech problems



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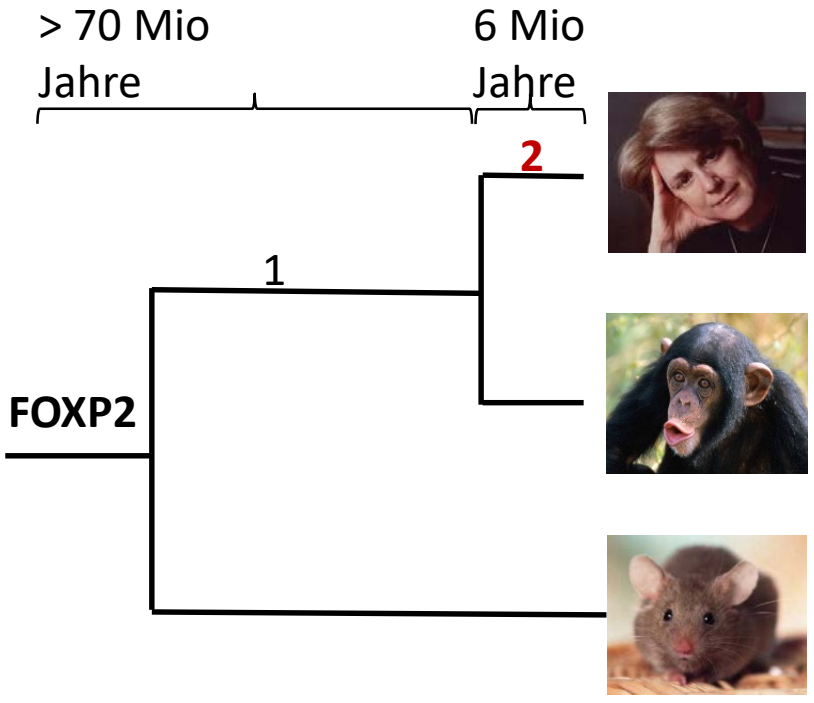

→ FOXP2 differences probably involved in evolution of language

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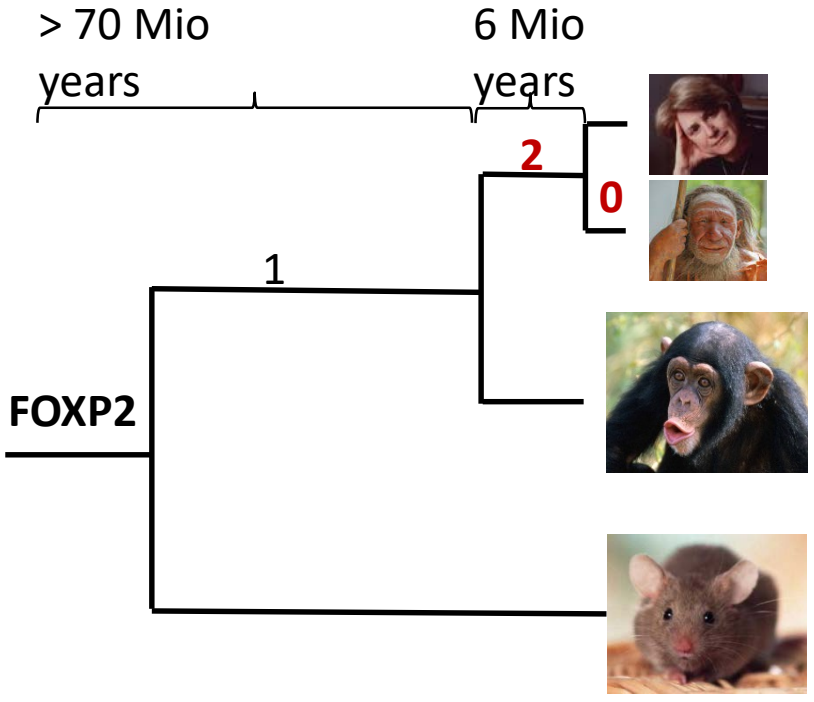


→ FOXP2 differences probably involved in evolution of language

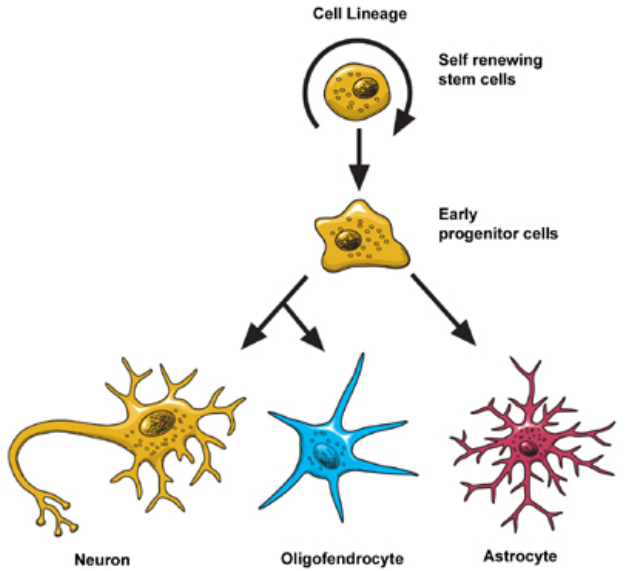
→ Neanderthals could probably talk

TFs in the nervous system

Involved in

- Brain development
- Neuronal differentiation
- Learning and memory

…



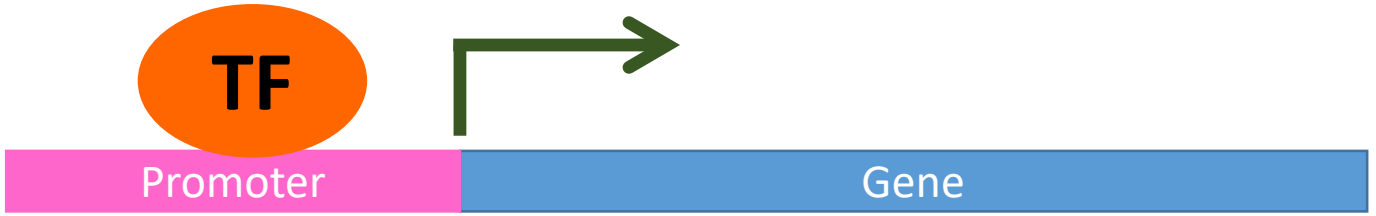
TFs are enriched among genes associated with

- Intellectual Disability
- Autism Spectrum Disorder
- And other cognitive disorders

Berto et al. 2016

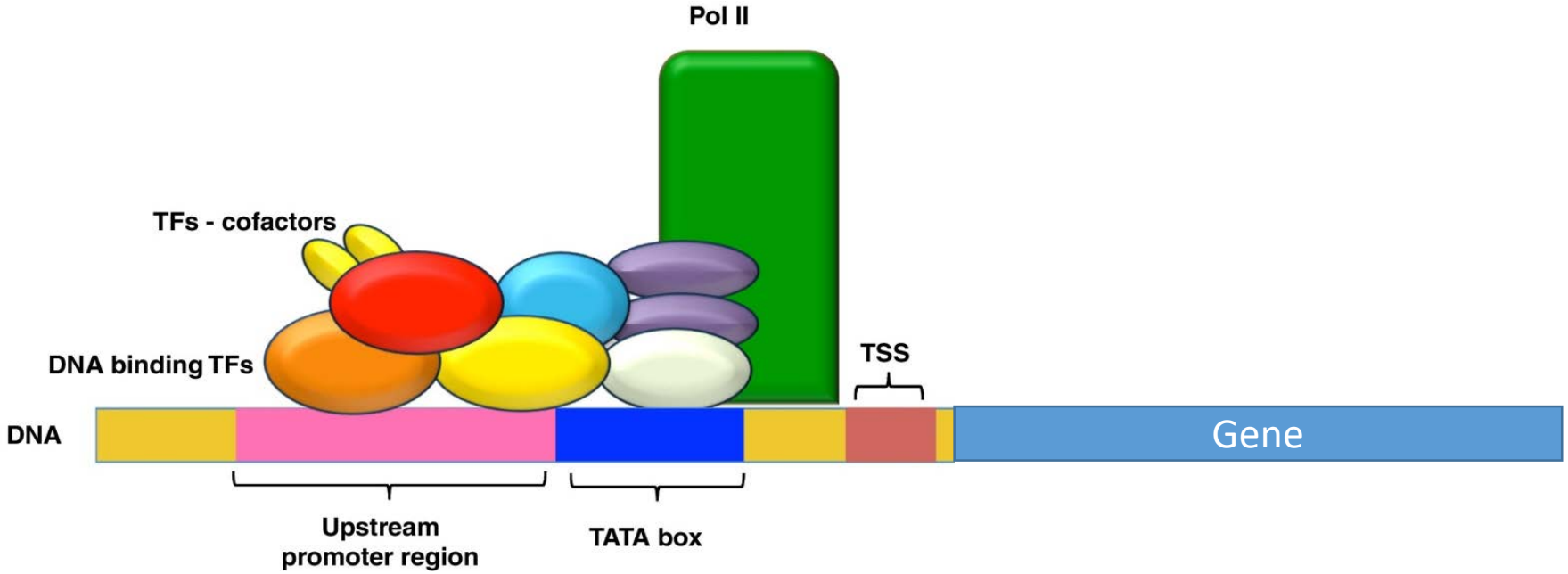
TFs regulate expression of other genes

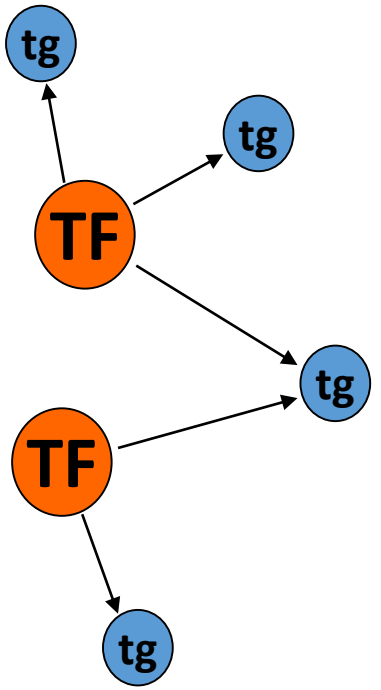
Transcription factors bind to DNA to regulate their target genes



TFs regulate expression of other genes

Transcription factors bind to DNA to regulate their target genes
And co-factors bind to transcription factors



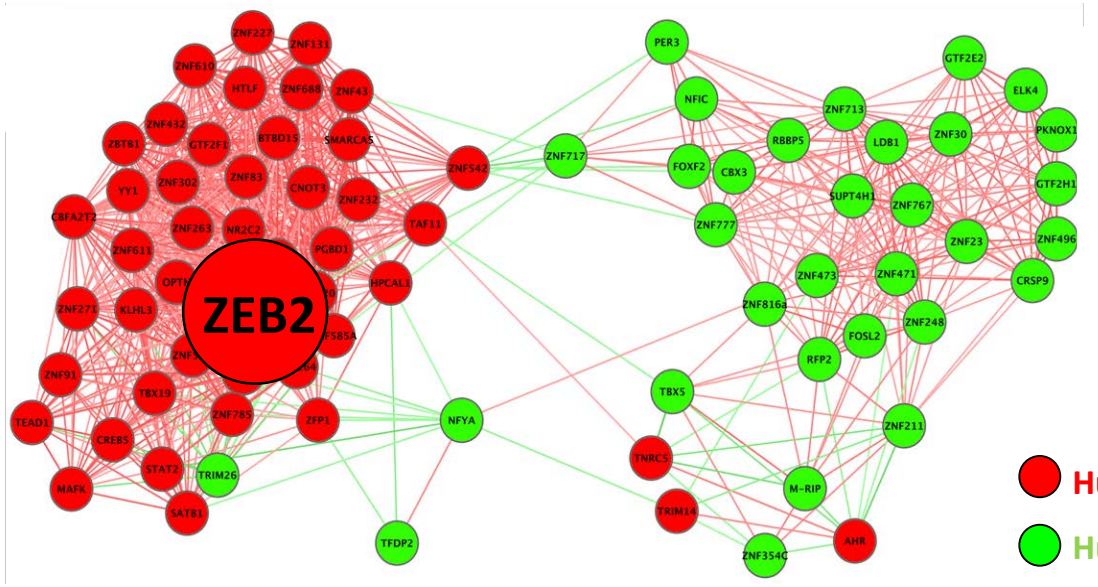


Many TFs have to come together to start/stop transcription of a target → form networks

A TF network that changed in brain

Network built from TFs and their correlated genes
with changed expression in the PFC

Correlations were calculated using data from 5 tissues



Nowick et al., PNAS, 2009

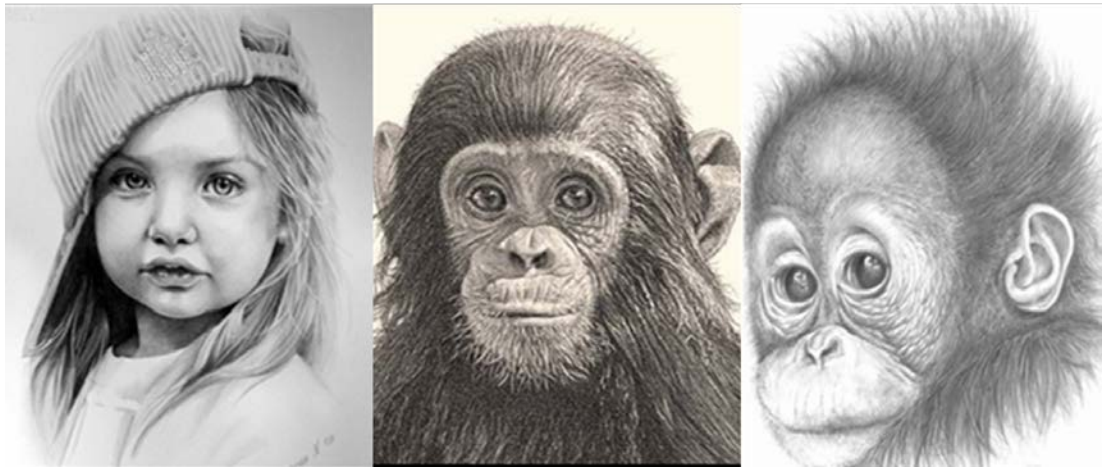
Functions of ZEB2

- More highly expressed in human PFC
- Significantly more links in human PFC than chimpanzee PFC network
  → indicates significant differences in target genes between the two species

- Development of the nervous system
- Differentiation of neuronal progenitors
- Mutations → Mowat-Wilson syndrome: microcephaly, intellectual disability

→ What are the target genes of ZEB2 in different great apes?
→ Are functional changes in ZEB2 related to morphological and functional changes of the human brain?

Comparative functional analysis of ZEB2



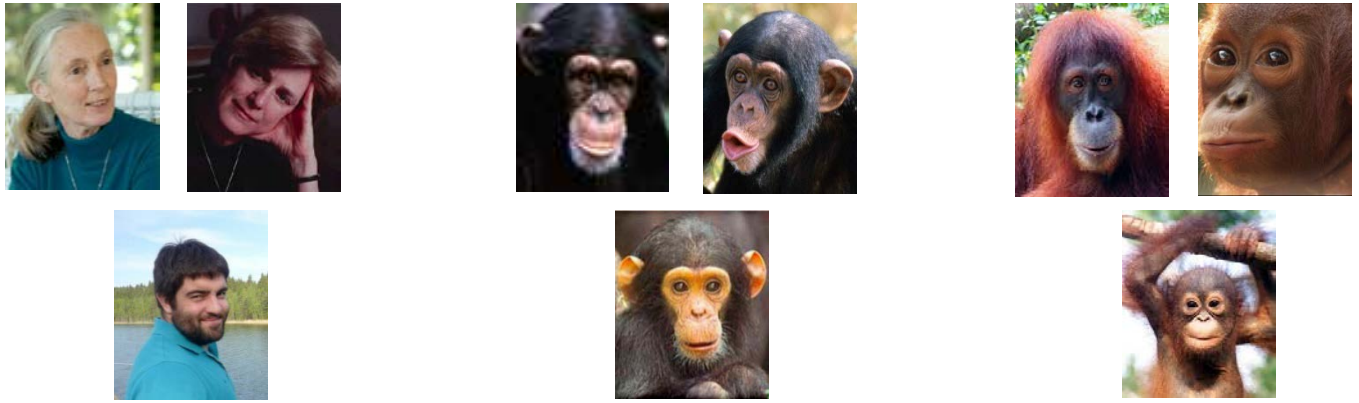
Human cell lines

Chimpanzee cell lines

Orang-utan cell lines

Comparative functional analysis of ZEB2

Three B-lymphoblastoid, one fibroblast cell lines per species

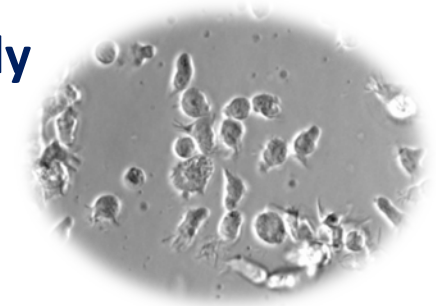


Chromatin immunoprecipitation with ZEB2 antibody

→ ChIP-Seq (50 bp Illumina reads)

Knock-down of ZEB2 with two specific siRNAs

→ RNA-Seq (2 x 100 bp Illumina reads)



Comparative functional analysis of ZEB2

What are target genes of ZEB2?

Do target genes differ between species?

In which regulatory networks is ZEB2 involved in?

Have these networks changed during evolution?

Which role did ZEB2 play during brain evolution?

Acknowledgements

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Thank you for your attention ☺

Any questions?