brief section on Hox cluster miRNA regulation
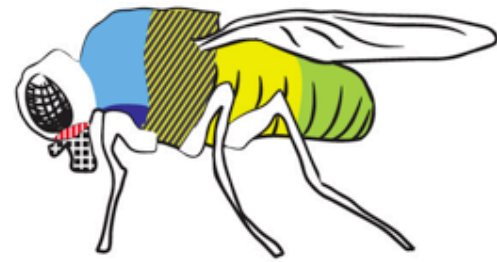
Stam DNase Papers

Circuitry and Dynamics of Human Transcription Factor Regulatory Networks

An expansive human regulatory lexicon
encoded in transcription factor footprints

The accessible chromatin landscape of the human genome

Roger Alexander

Gerstein lab journal club

10 October 2012

Fruit fly larva

Fruit fly hox genes

Human *Hoxa*
Human *Hoxb*
Human *Hoxc*
Human *Hoxd*

Human embryo

from Neil Shubin's
Your Inner Fish
A Journey into the 3.5-Billion-Year History of the Human Body

A **Urhox gene** — 1 gene

B Unequal crossover

C 2 genes

Divergence

D l

3 genes

E r

4 genes

F l

5 genes
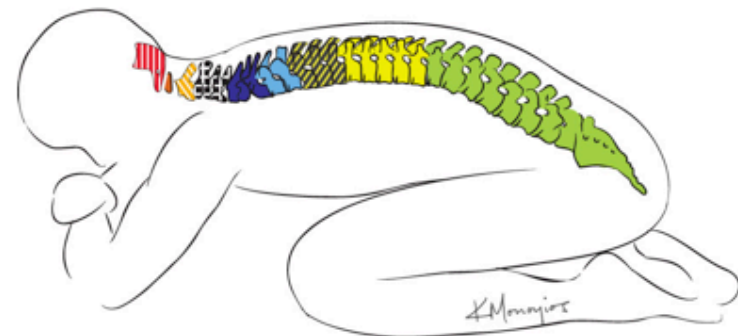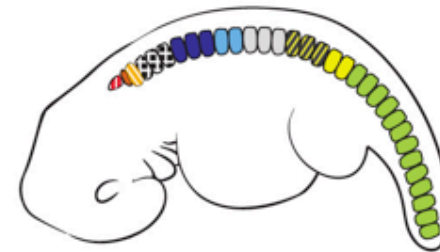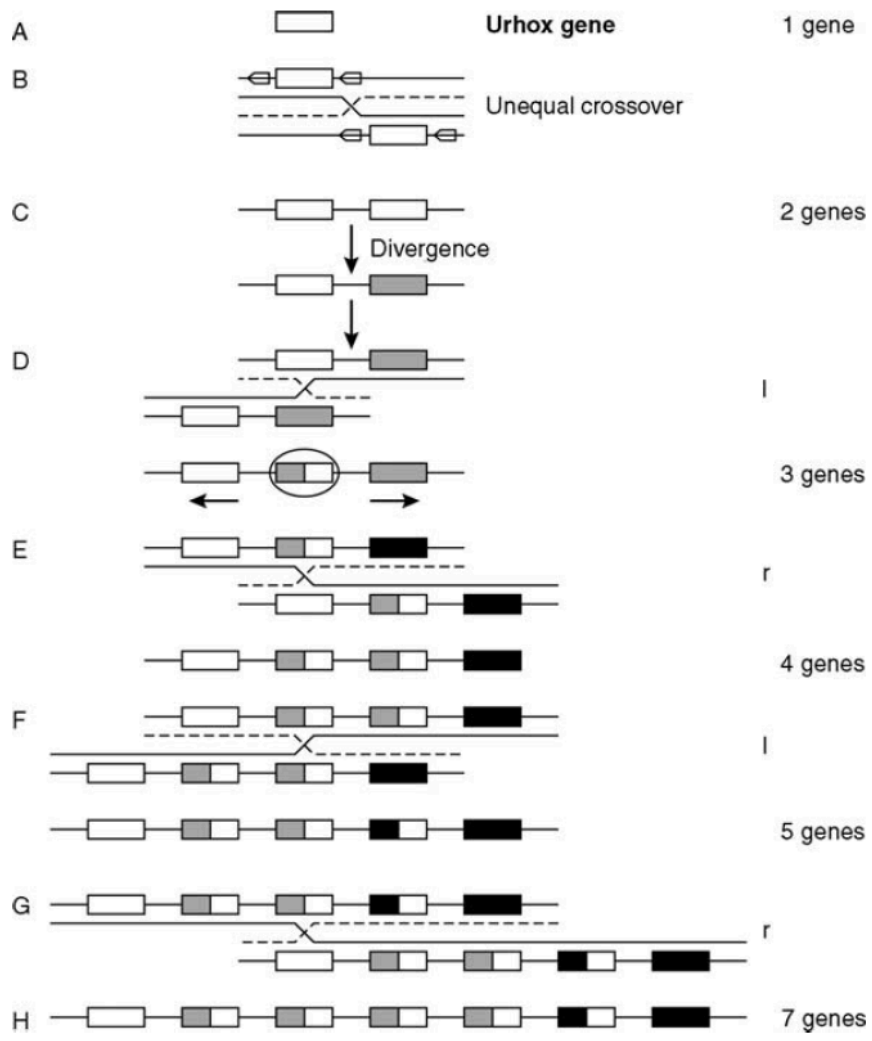
G r

H 7 genes

Fruit fly larva

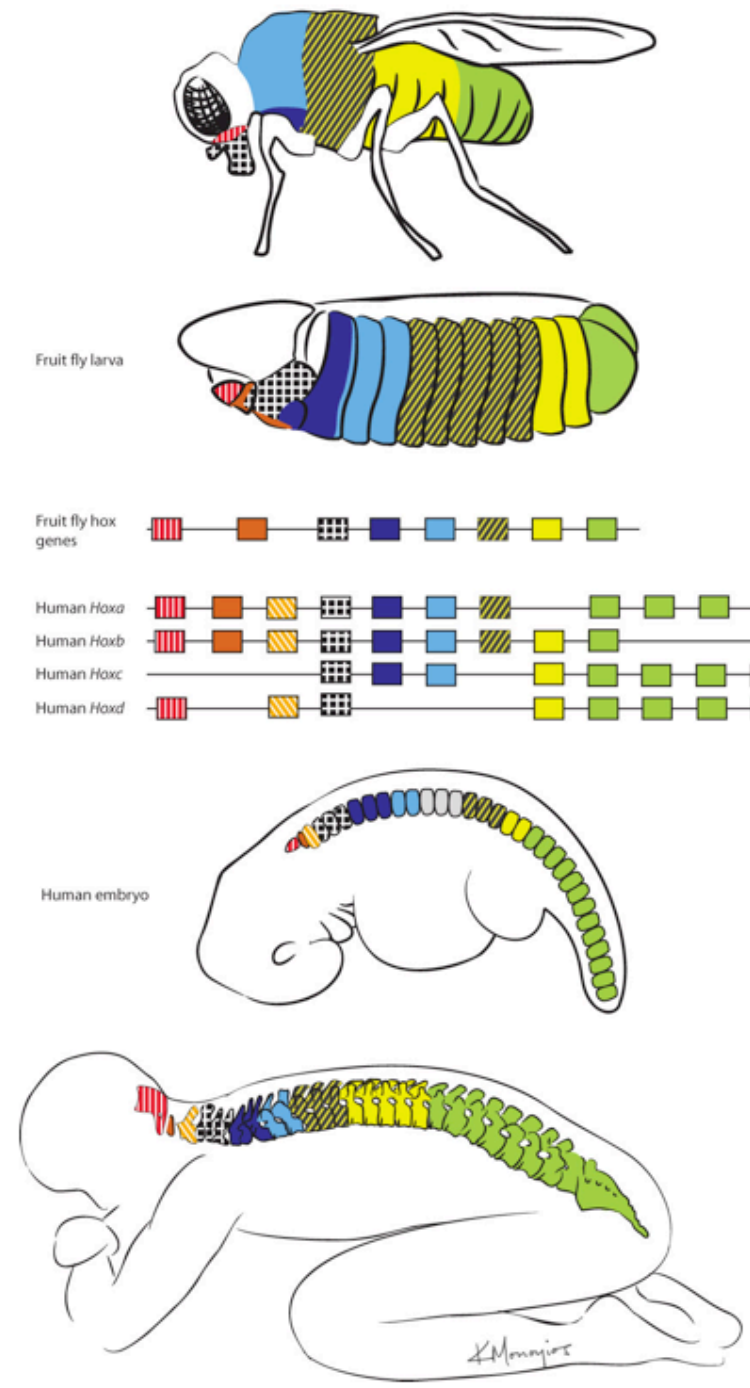Fruit fly hox genes

Human Hoxa
Human Hoxb
Human Hoxc
Human Hoxd

Human embryo

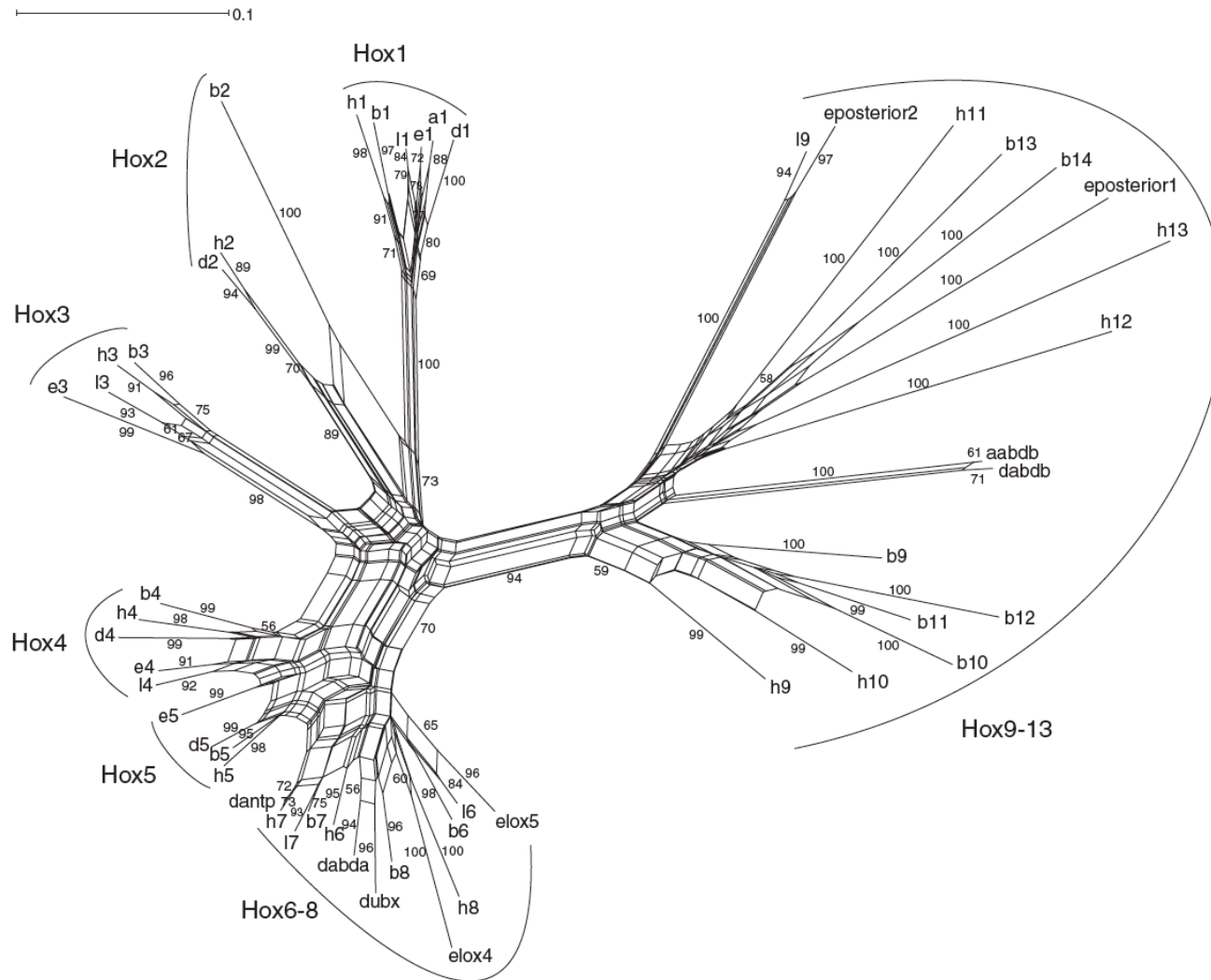Evolution of the Hox Gene Complex from an
Evolutionary Ground State.
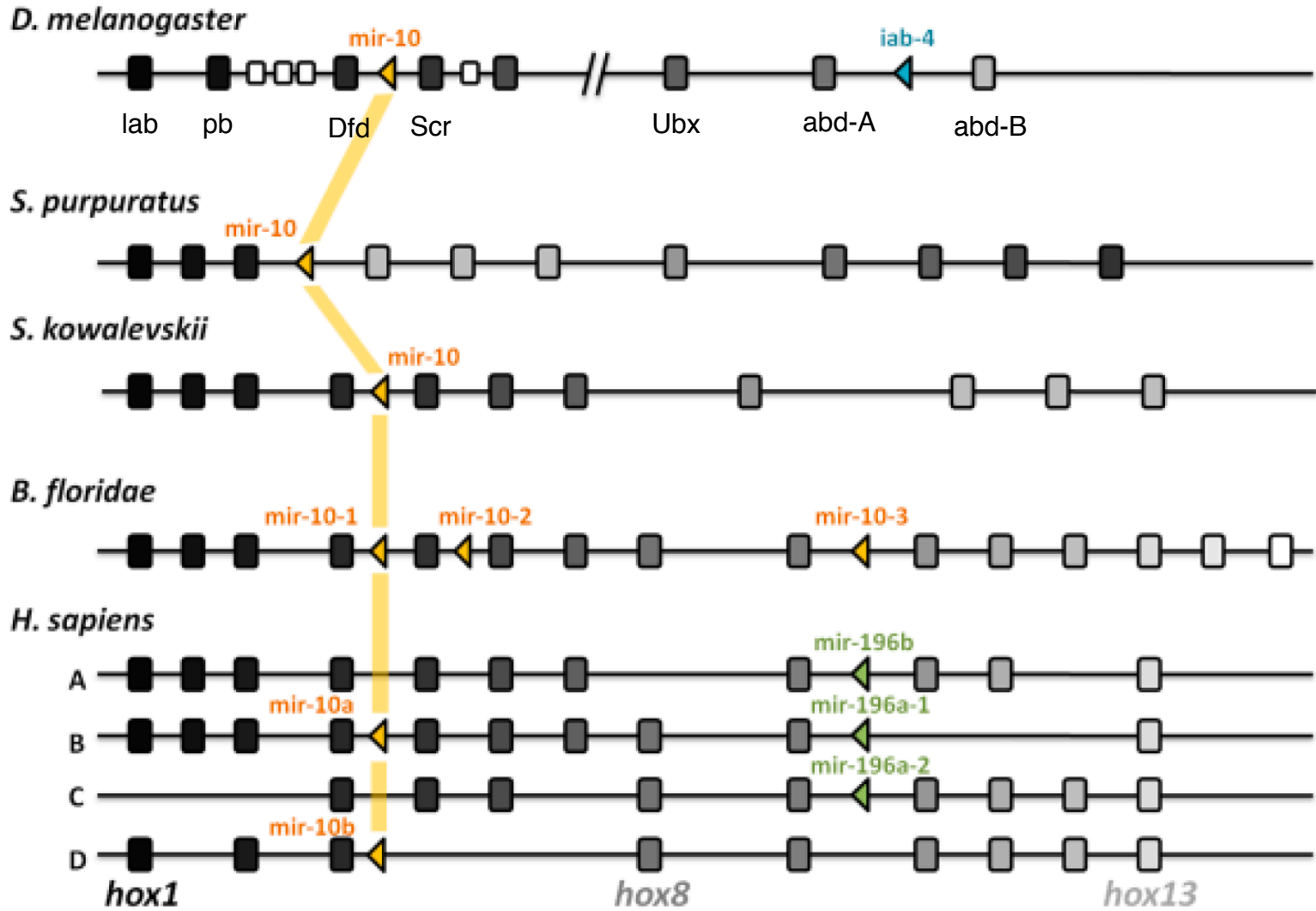*Curr. Top. Devel. Biol.* (2009) 88: 35
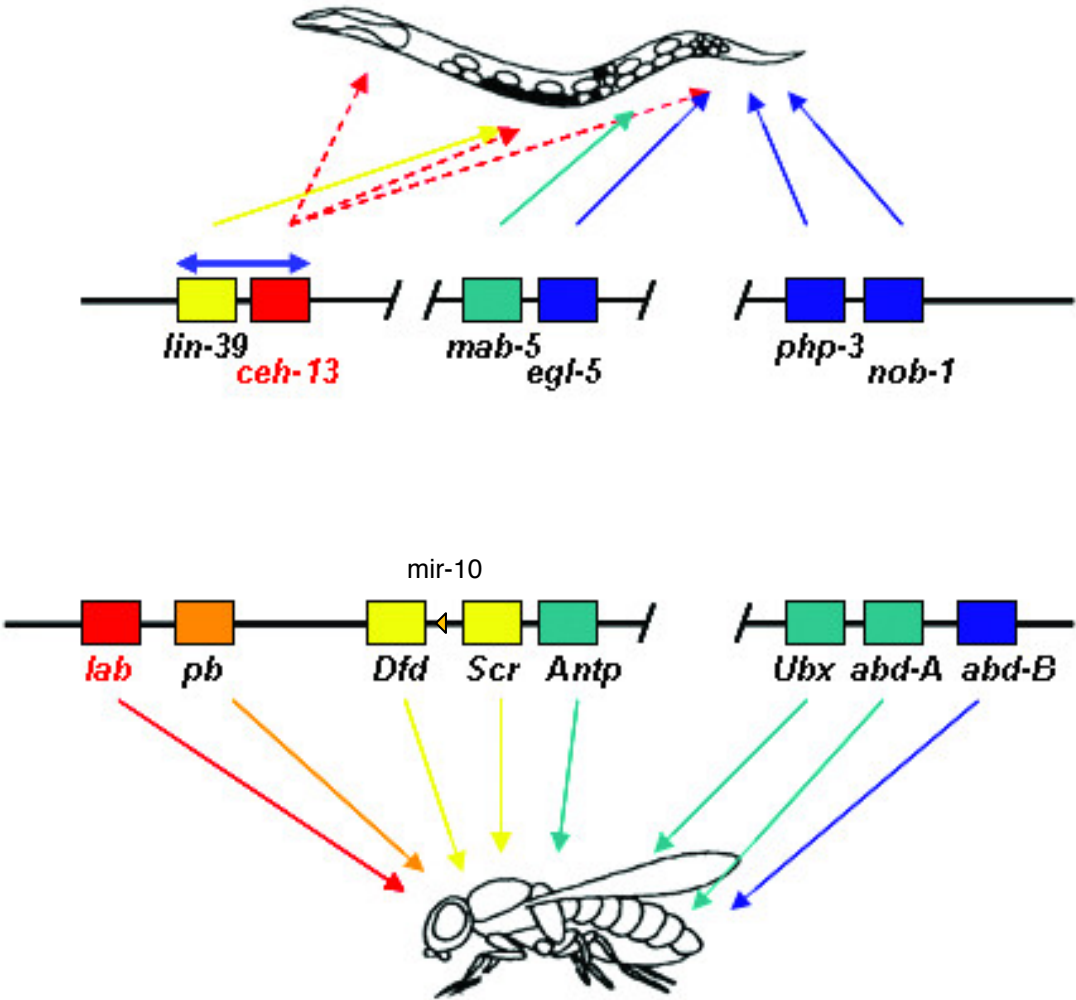
Evolution of HOX gene clusters

Evolution of the Hox Gene Complex from an Evolutionary Ground State.
Curr. Top. Devel. Biol. (2009) 88: 35

Evolution of HOX gene clusters:
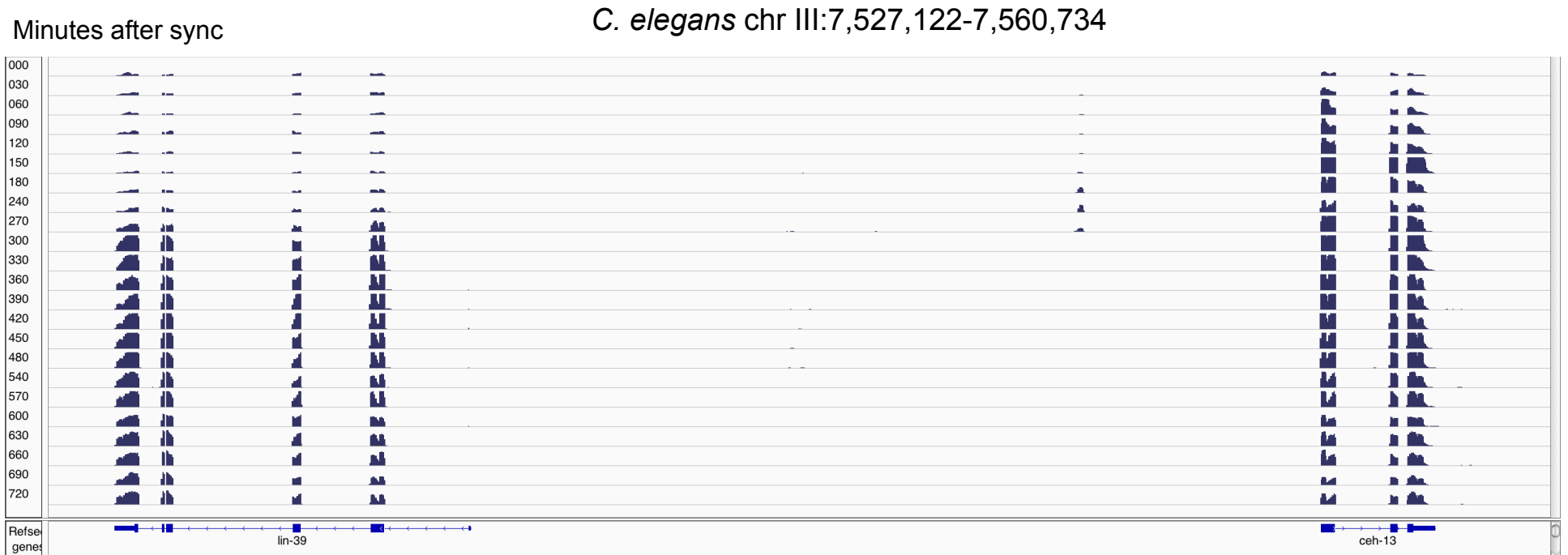# Regulation by Homologous and Analogous miRNAs

microRNA complements in deuterostomes: origin and evolution of microRNAs.
Evol. Devel. (2011) 13: 15
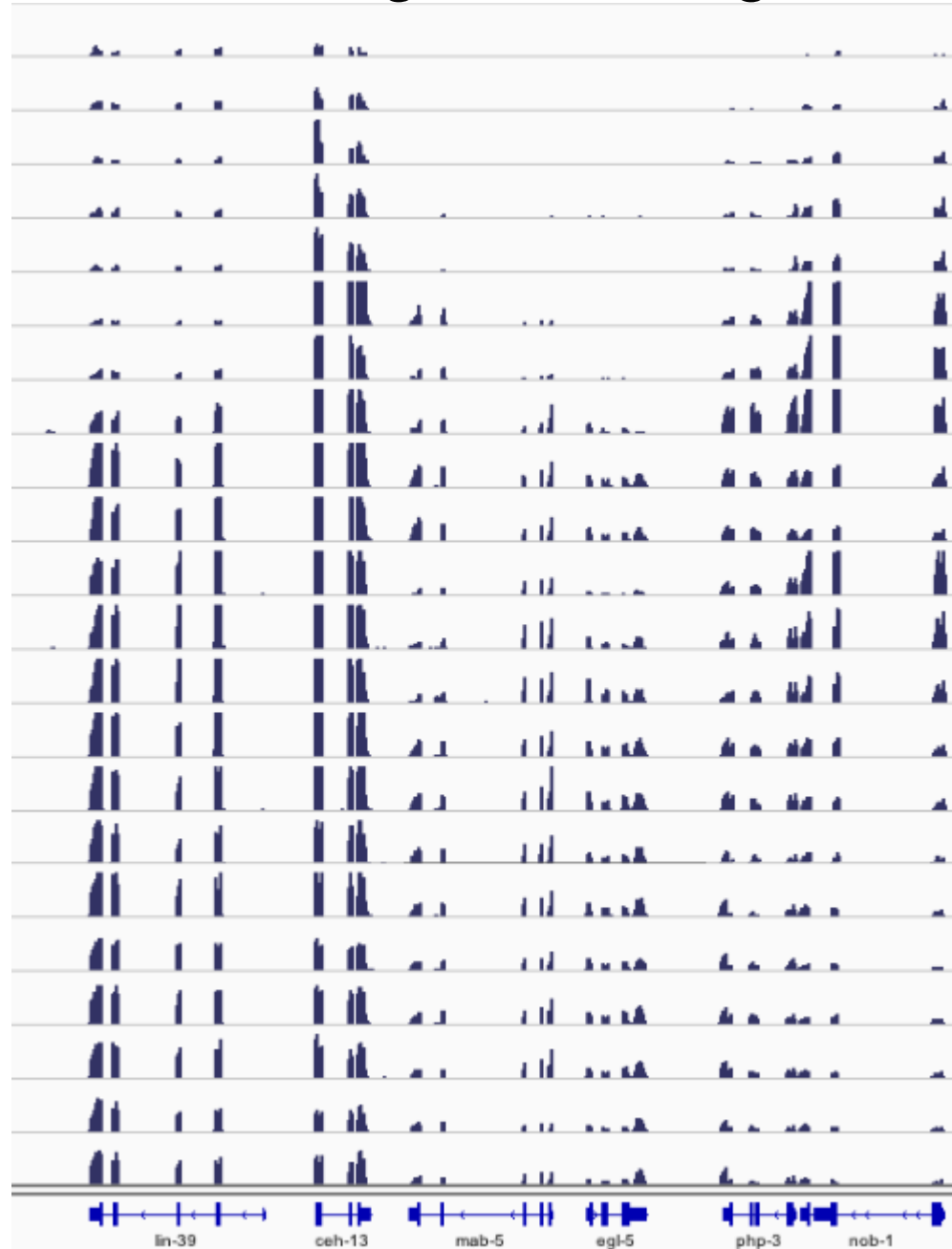
Evolution of HOX gene clusters

BMC Devel. Biol. (2010) 10: 78

Expression in *C. elegans* HOX gene cluster

Early Embryo in strain N2

Minutes after sync

C. elegans chr III:7,527,122-7,560,734

with He Zhu

Expression in *C. elegans* HOX gene cluster

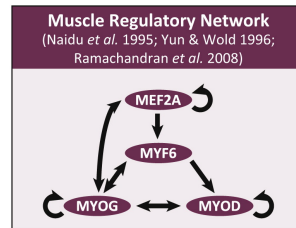Early Embryo in strain N2

lin-39   ceh-13   mab-5   egl-5   php-3   nob-1

with He Zhu

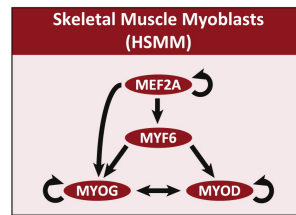# Circuitry and Dynamics of Human Transcription Factor Regulatory Networks

A

1) Use DNaseI footprints to determine occupied binding elements within promoter proximal regions of TF genes (+/-5kb of TSS)

2) Identify other TFs targeted by TF in (1)

3) Generate network

4) Repeat in 41 cell-types using all 475 TFs with recognition motifs

B Muscle Regulatory Network
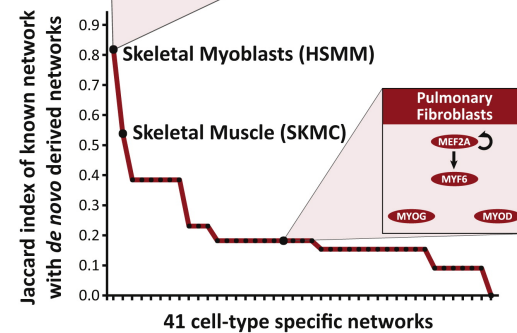(Naidu *et al.* 1995; Yun & Wold 1996; Ramachandran *et al.* 2008)

Skeletal Muscle Myoblasts (HSMM)
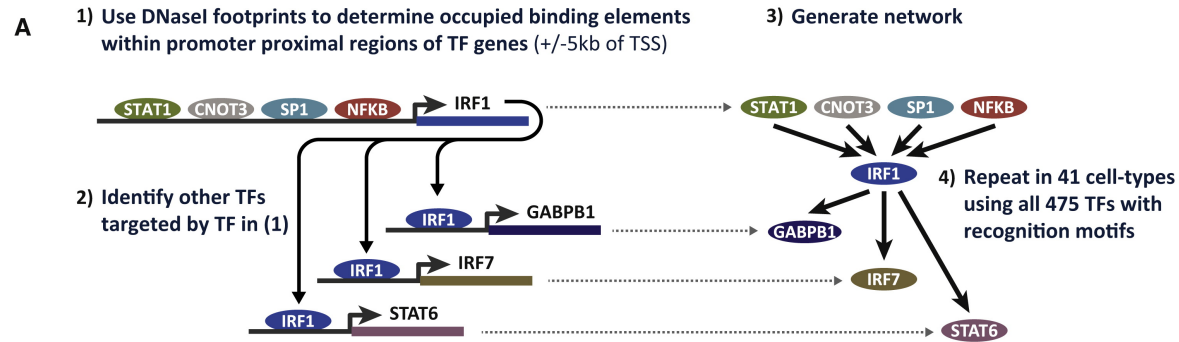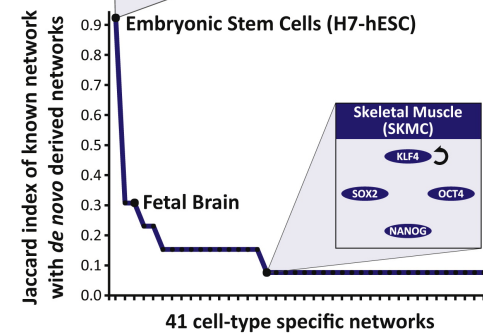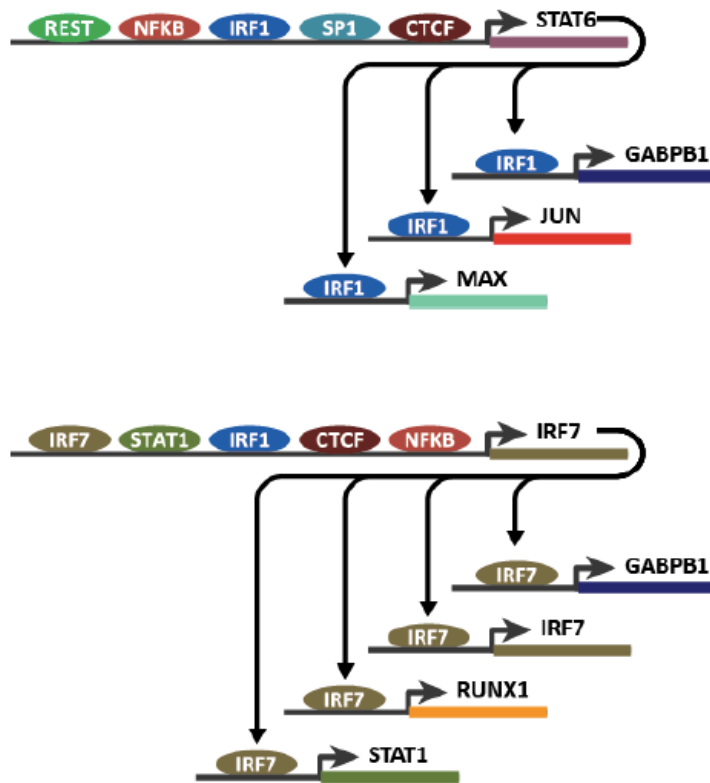
Well-described Networks

De novo derived Networks

C Mouse Embryonic Stem Cells
(Kim *et al.* 2008)

Human Embryonic Stem Cells (H7-hESC)

D Jaccard index of known network with *de novo* derived networks

Skeletal Myoblasts (HSMM)

Skeletal Muscle (SKMC)

Pulmonary Fibroblasts

41 cell-type specific networks

E Jaccard index of known network with *de novo* derived networks

Embryonic Stem Cells (H7-hESC)

Fetal Brain

Skeletal Muscle (SKMC)

41 cell-type specific networks

Cell-type- and Tissue-specific Regulatory Networks from DNase Data

Delineating the circuitry of human TFs

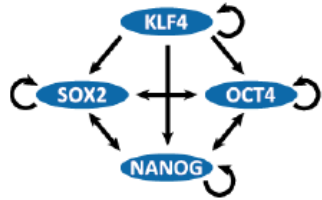Repeat for all 475 TF genes with annotated recognition sequences

then

Repeat for 41 different cell types

10

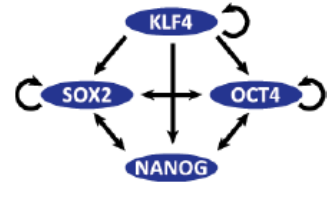# Cell-type- and Tissue-specific Regulatory Networks from DNase Data

De novo-derived networks accurately recapitulate known TF-to-TF network relationships
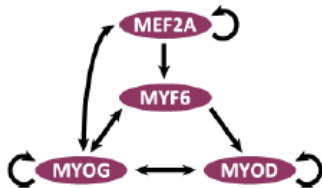
Figure 1
Cell (2012) 150: 1274

Circuitry and Dynamics of Human Transcription Factor Regulatory Networks

A Number of cell-types that a transcriptional regulatory interaction was observed in

B Transcriptional Network Overlap

C Edge vs. Footprint overlap for H7-hESC, HSMM and HRCEpiC

D Network of edges unique to Skeletal Myoblasts (HSMM)

E Network of edges unique to Renal Cortical Epithelium (HRCEpiC)

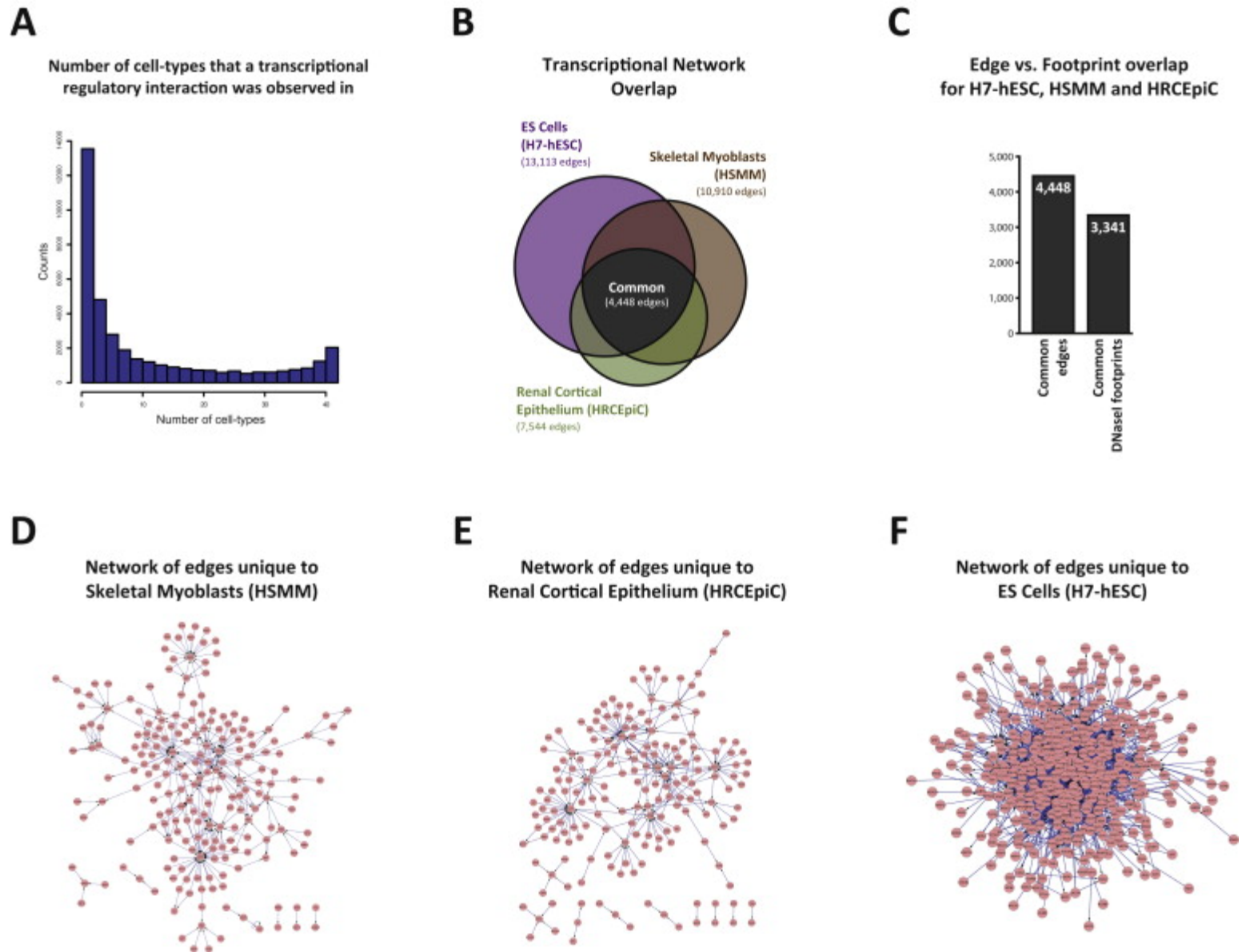**F** Network of edges unique to ES Cells (H7-hESC)

Figure S1
Cell (2012) 150: 1274

Circuitry and Dynamics of Human Transcription Factor Regulatory Networks

Figure 2
Cell (2012) 150: 1274

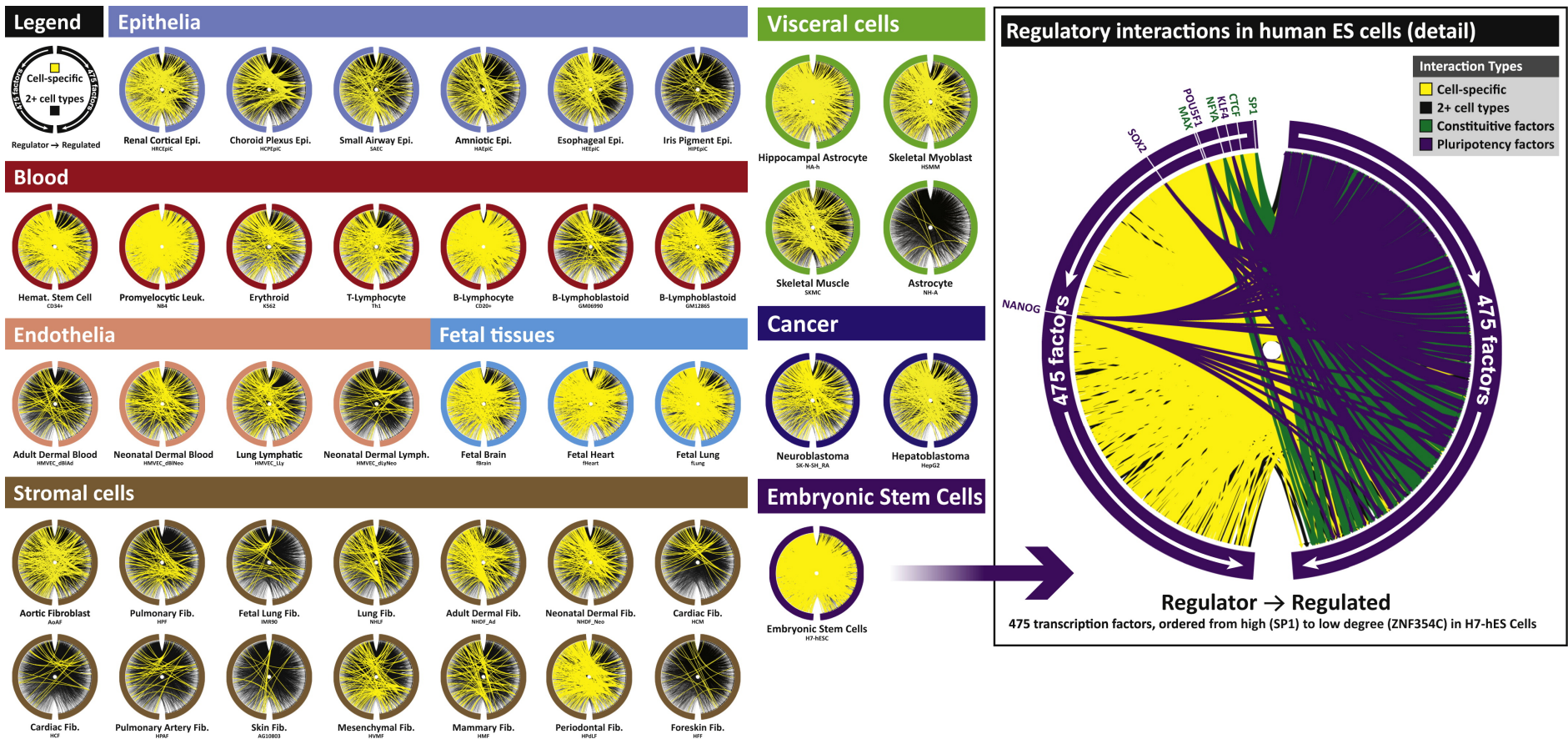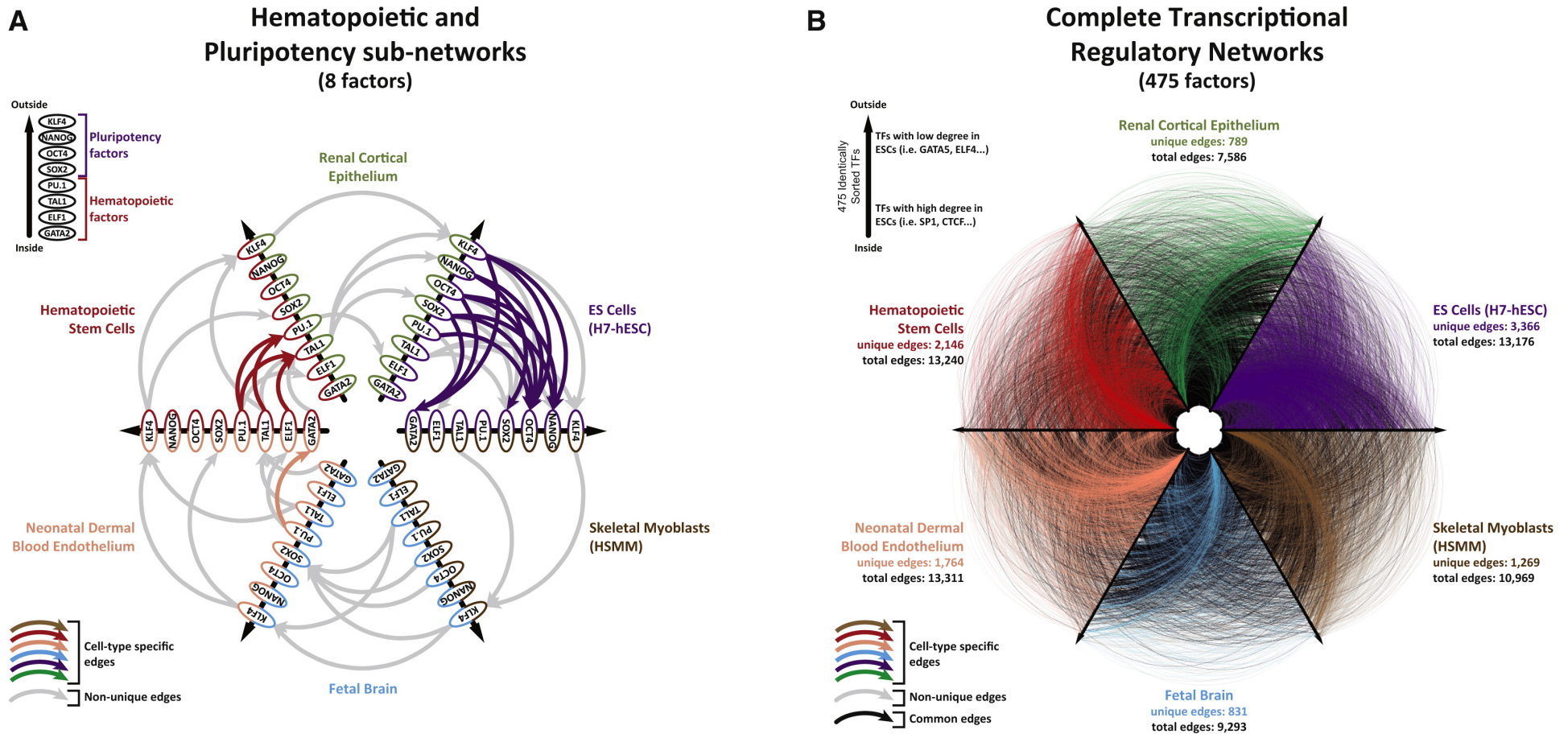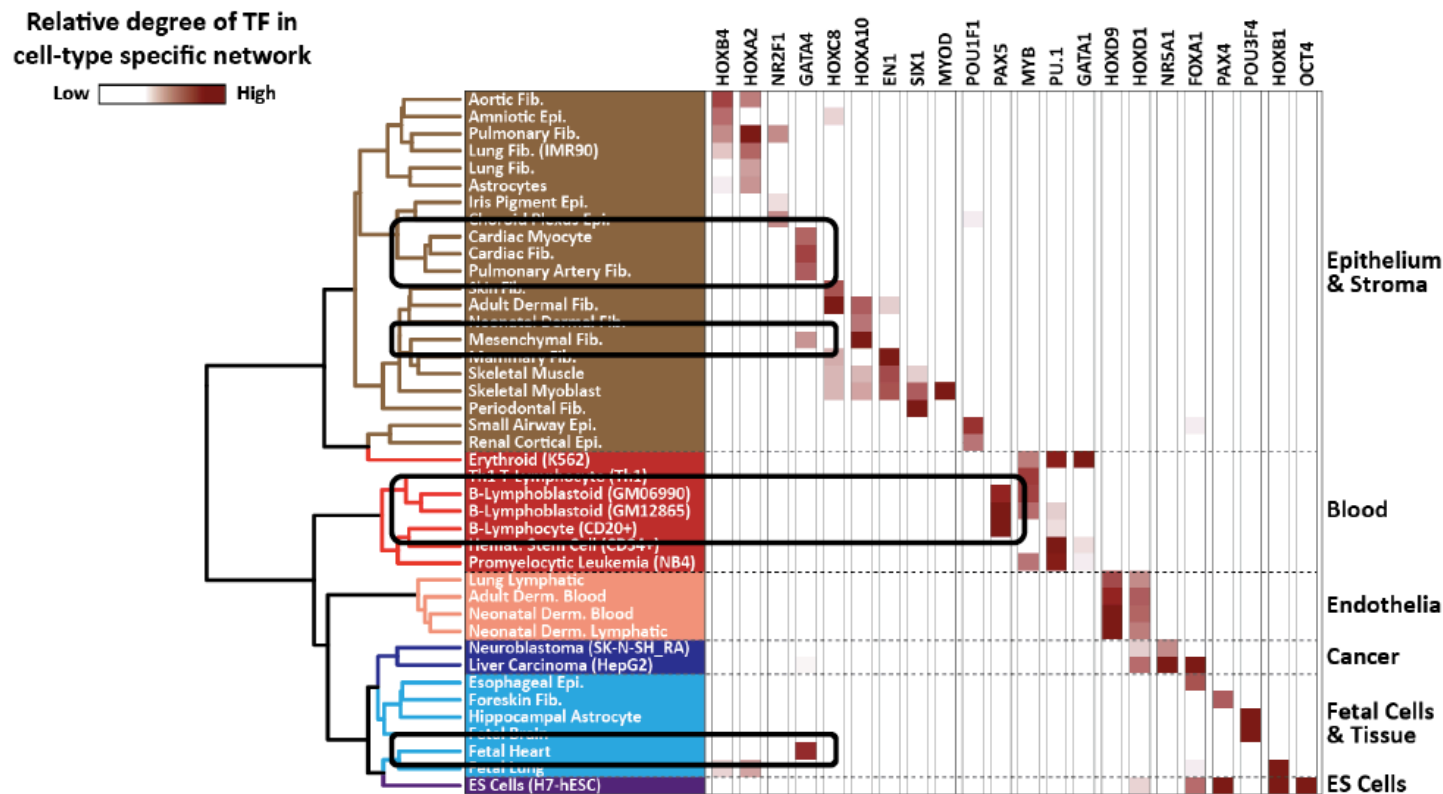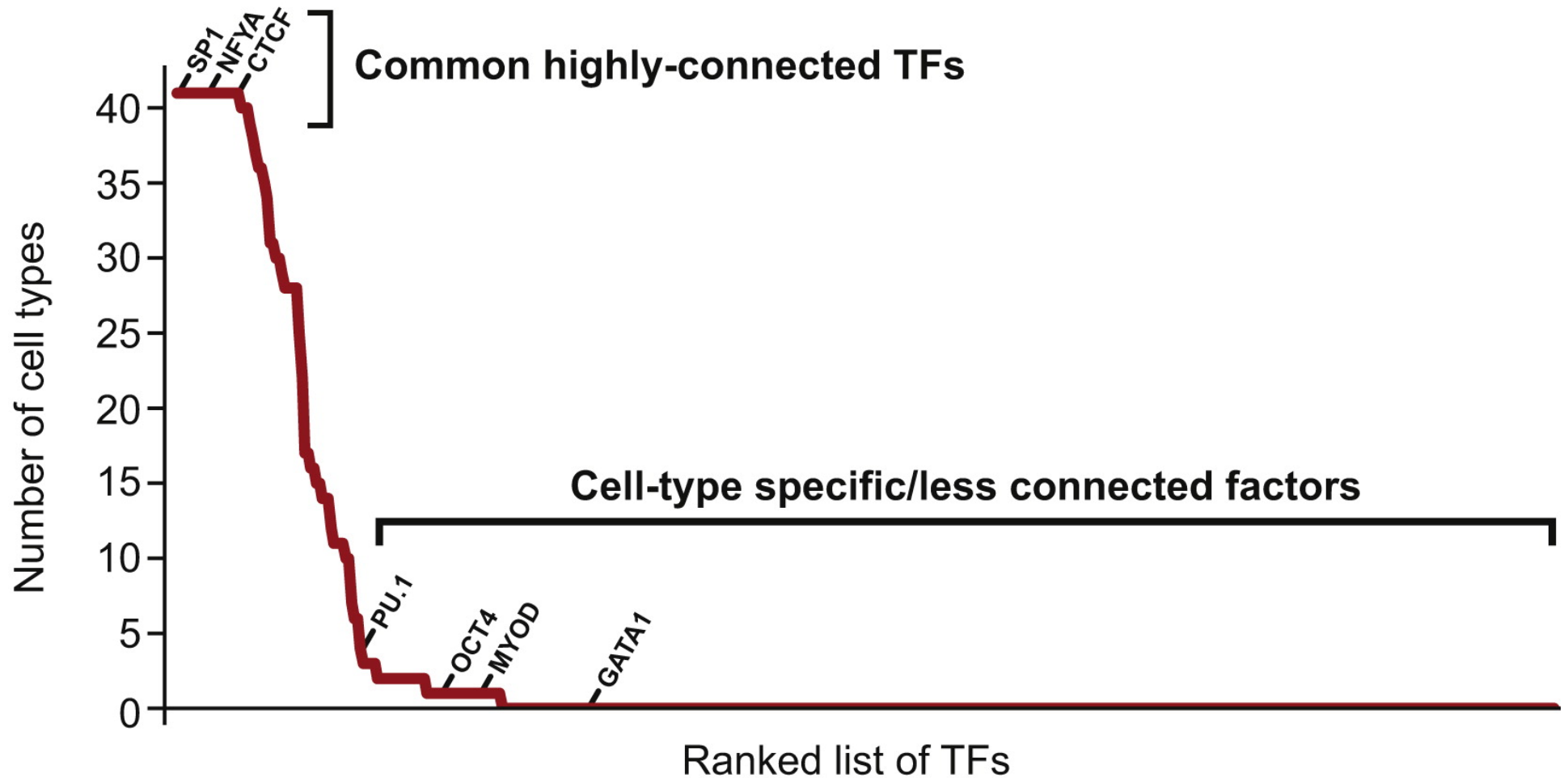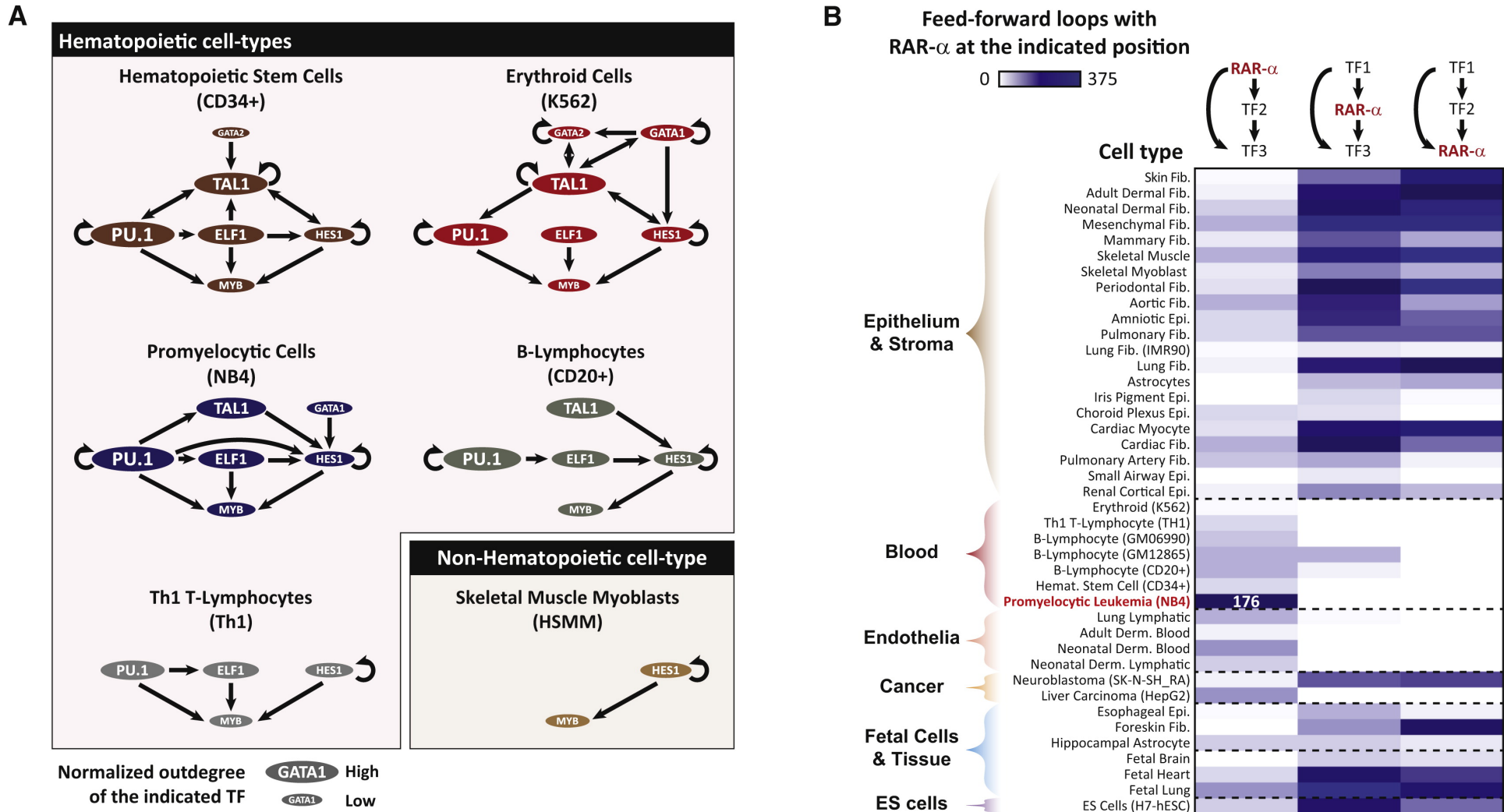# Circuitry and Dynamics of Human Transcription Factor Regulatory Networks

A — Hematopoietic and Pluripotency sub-networks (8 factors)

B — Complete Transcriptional Regulatory Networks (475 factors)

Figure 3
Cell (2012) 150: 1274

Cell-type- and Tissue-specific
Regulatory Networks from DNase Data

Functionally related cell types share similar core transcriptional regulatory networks

Cluster cell types ➡ Identify which cell types are governed by similar TFs

Figure 4
Cell (2012) 150: 1274

Number of cell types in which a given factor is among the top 10% of highest degree nodes

Figure S2
Cell (2012) 150: 1274

Circuitry and Dynamics of Human Transcription Factor Regulatory Networks

Figure 5
Cell (2012) 150: 1274

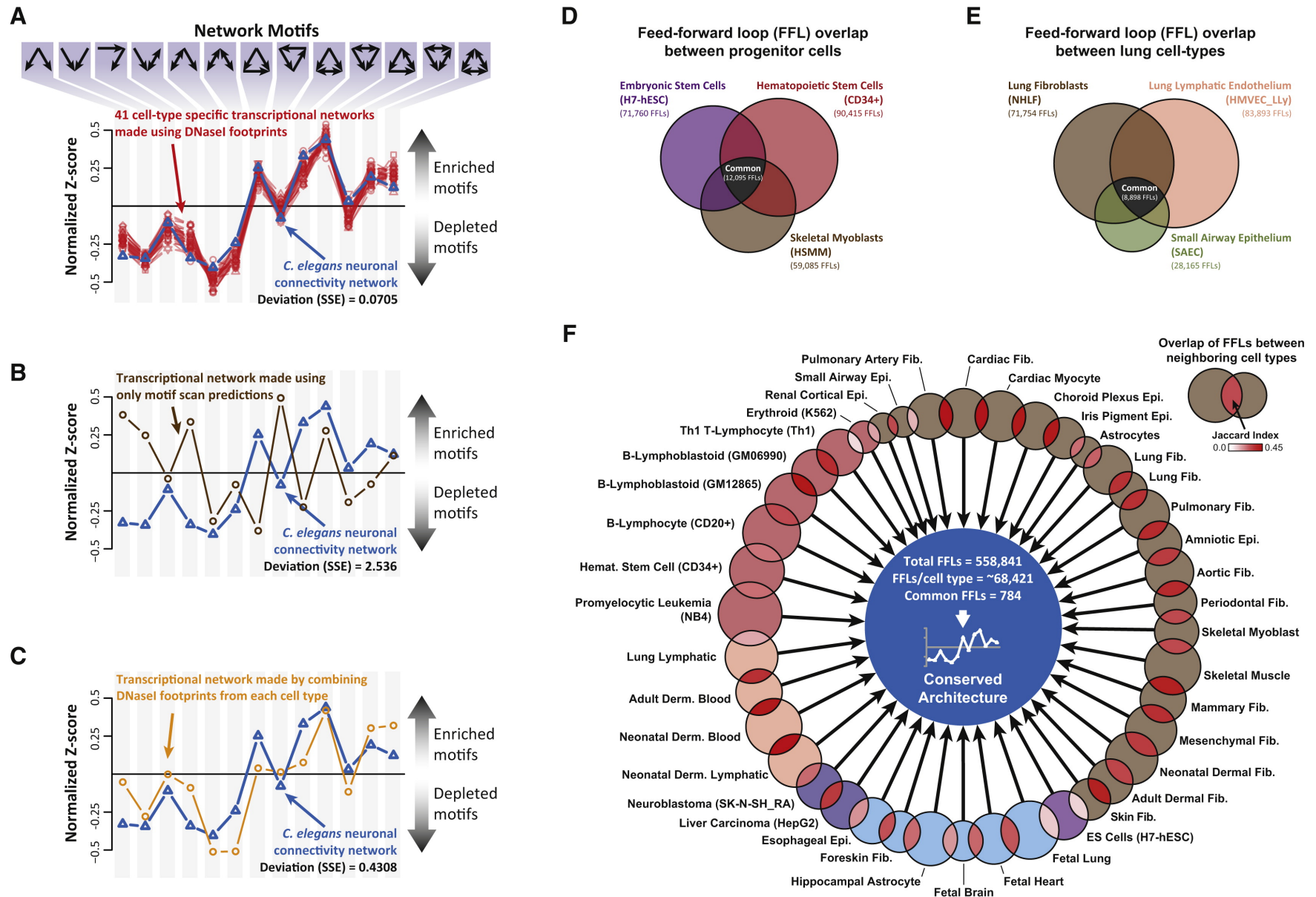# Circuitry and Dynamics of Human Transcription Factor Regulatory Networks

Figure 6
Cell (2012) 150: 1274

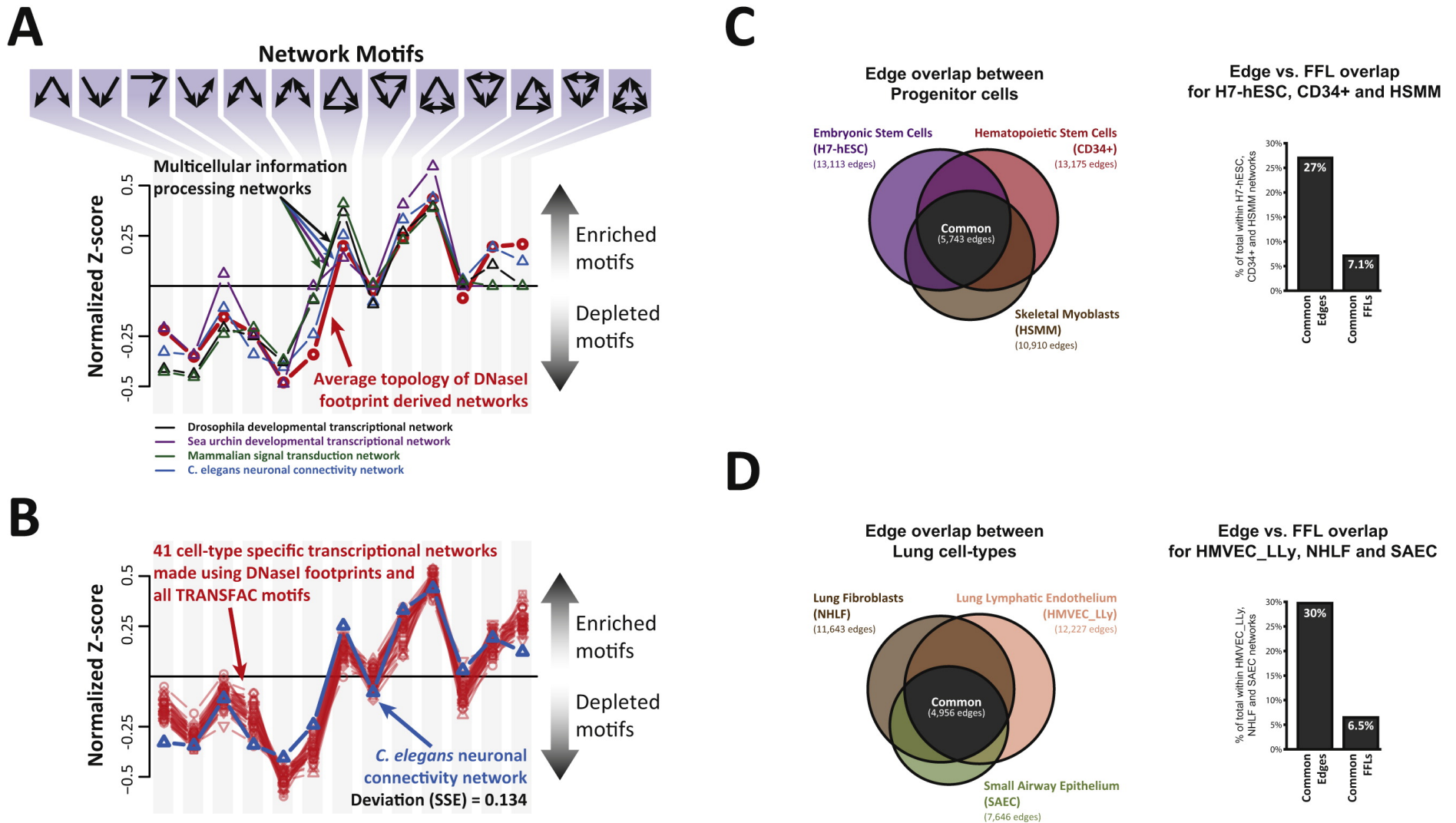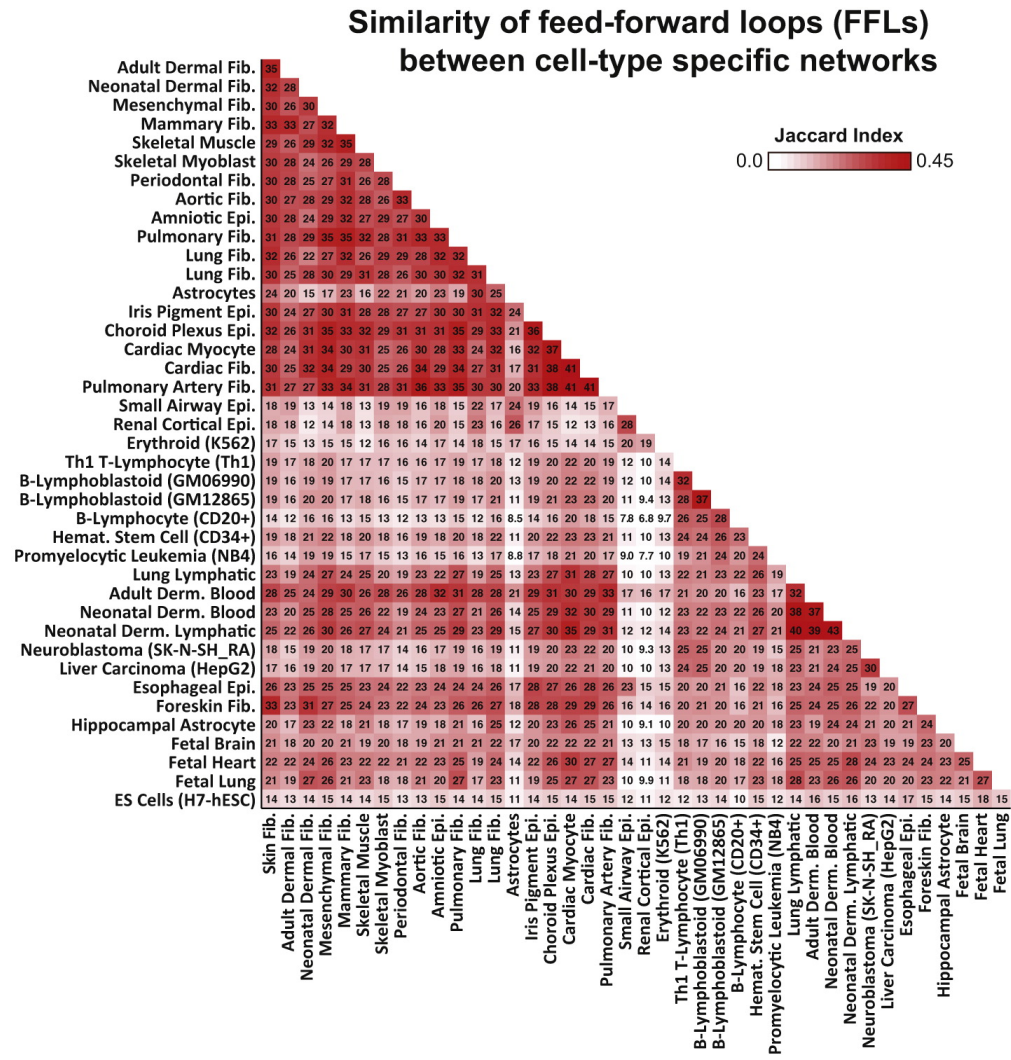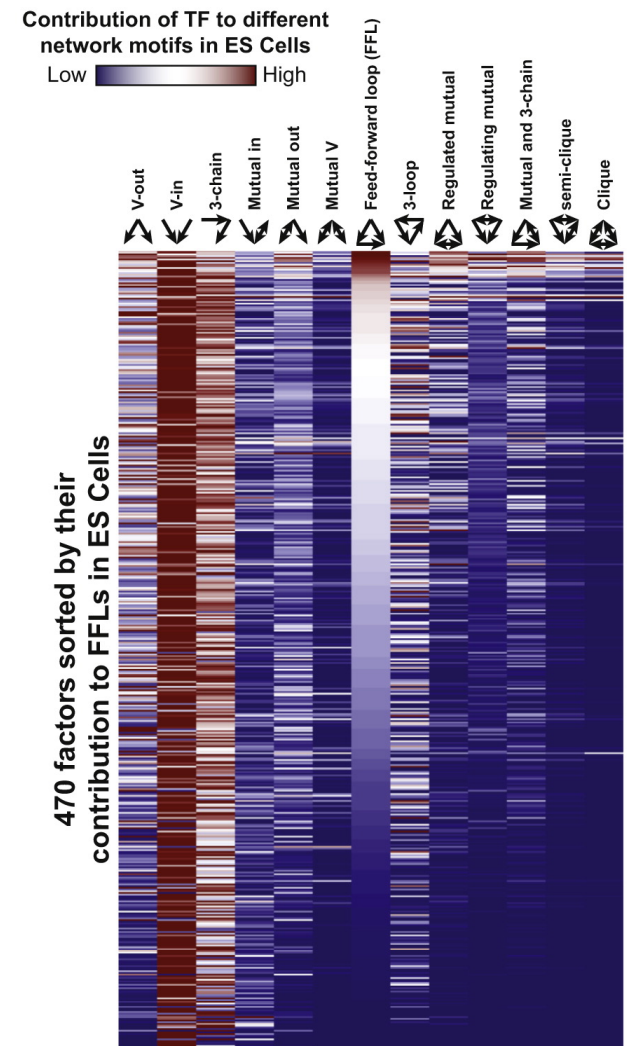# Circuitry and Dynamics of Human Transcription Factor Regulatory Networks

Figure S3
Cell (2012) 150: 1274

Circuitry and Dynamics of Human Transcription Factor Regulatory Networks

E

Similarity of feed-forward loops (FFLs) between cell-type specific networks

F

Contribution of TF to different network motifs in ES Cells

Figure S3
Cell (2012) 150: 1274

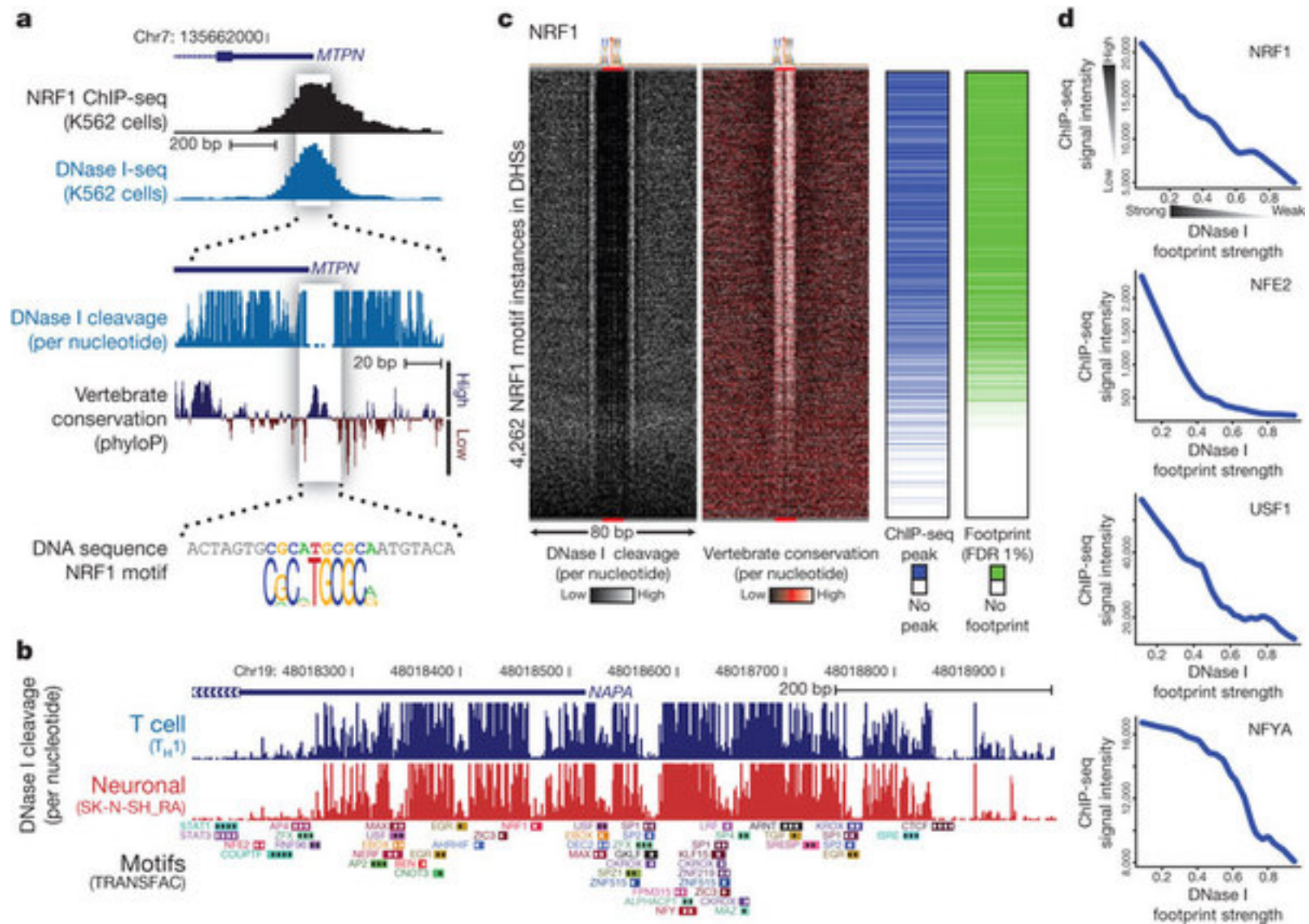# An expansive human regulatory lexicon encoded in transcription factor footprints

Figure 1
Nature (2012) 489: 83

21

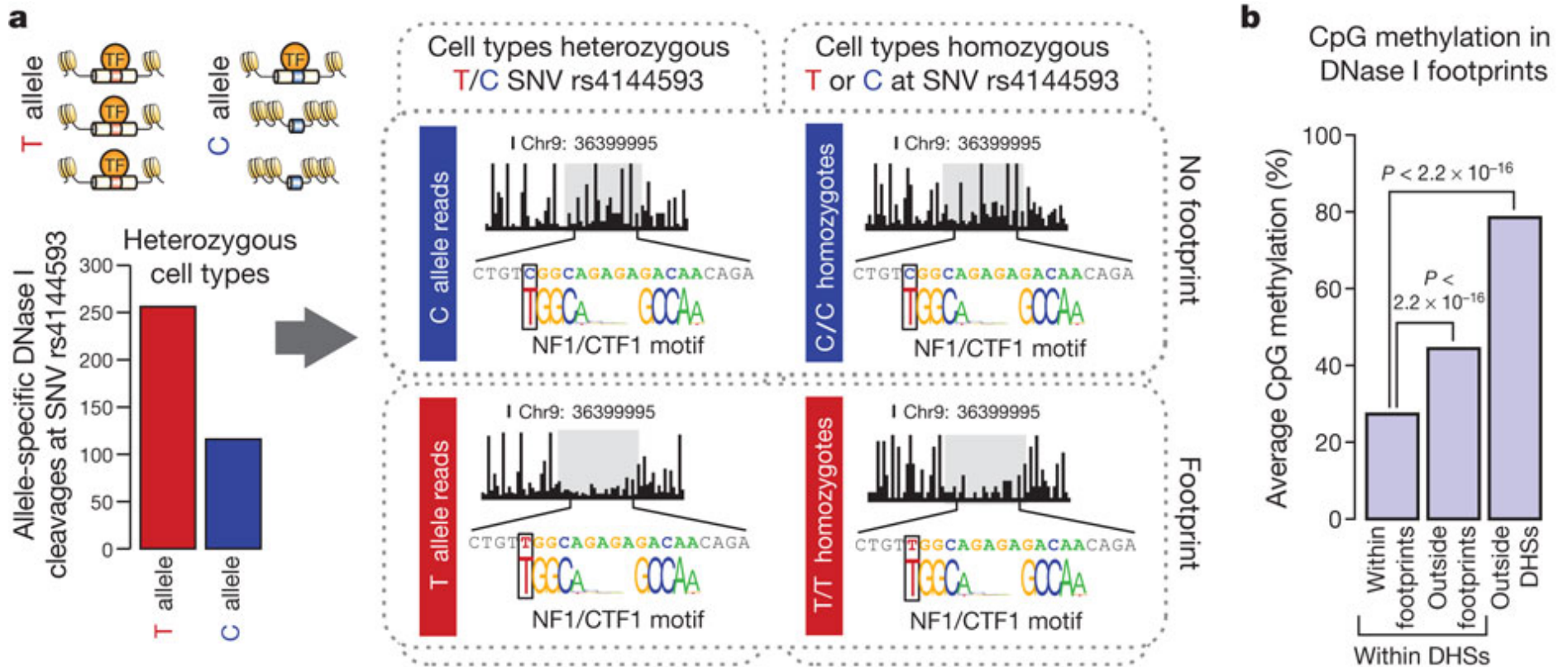# An expansive human regulatory lexicon encoded in transcription factor footprints

Figure 2
Nature (2012) 489: 83

22

An expansive human regulatory lexicon encoded in transcription factor footprints

Figure 3
Nature (2012) 489: 83

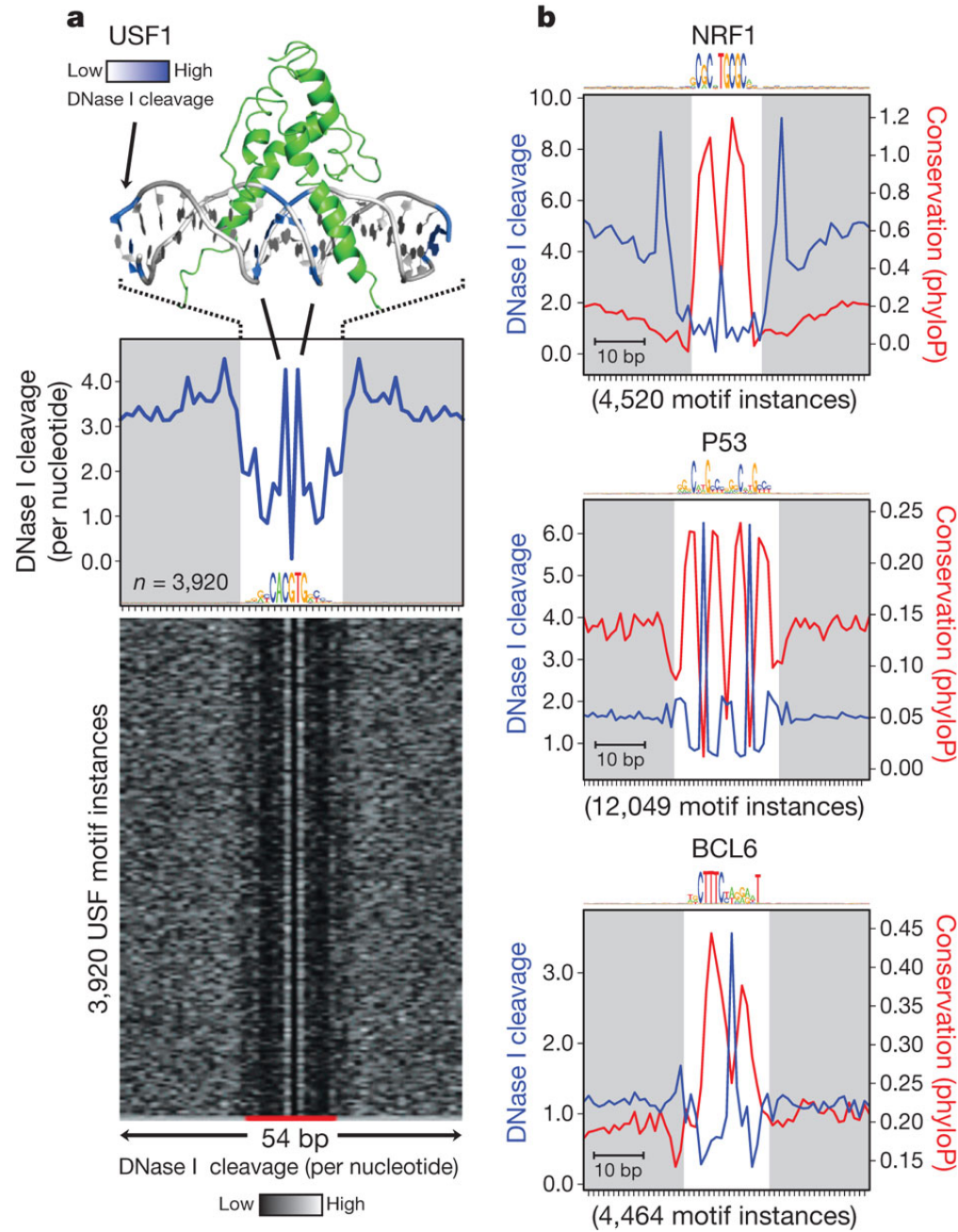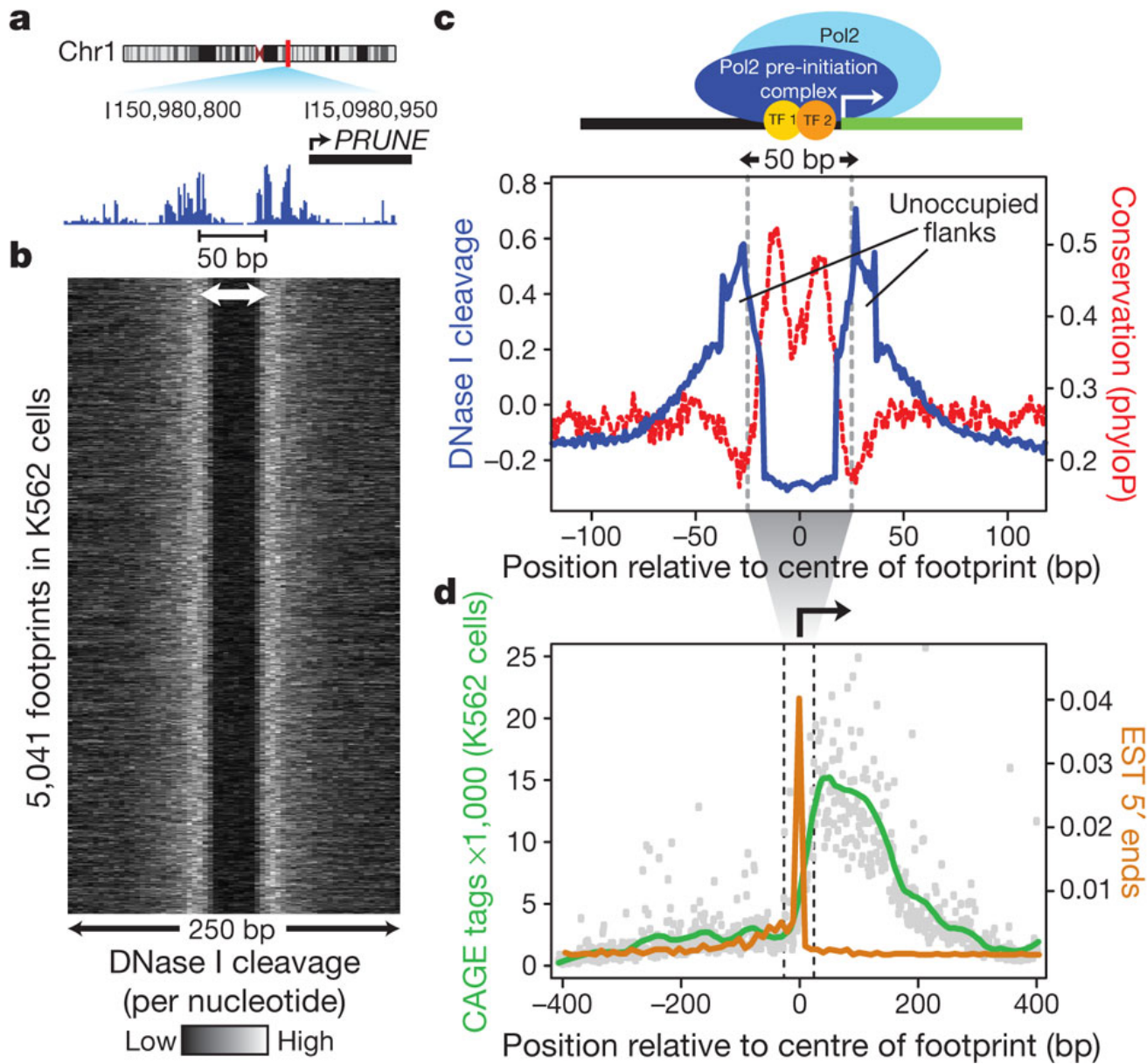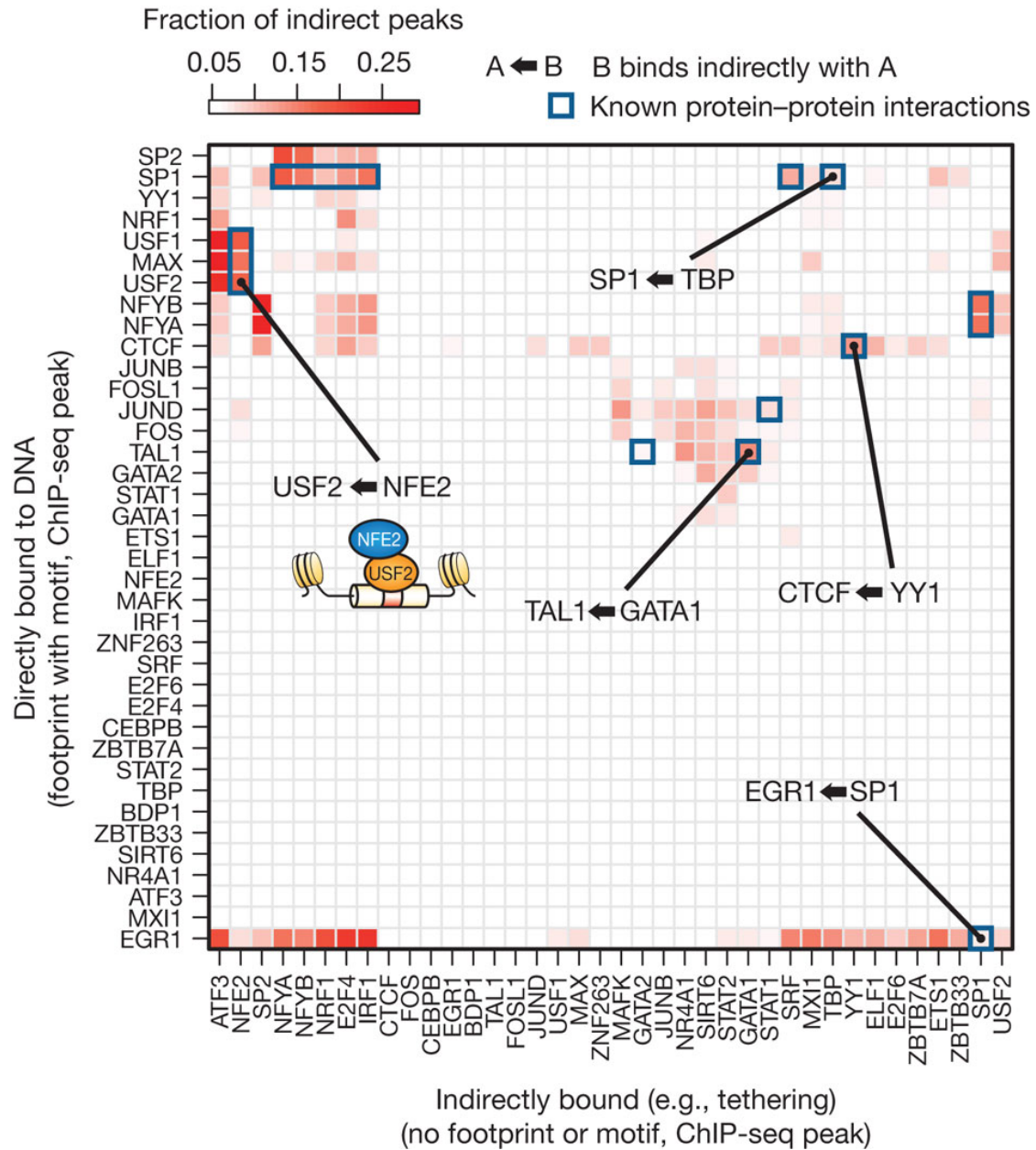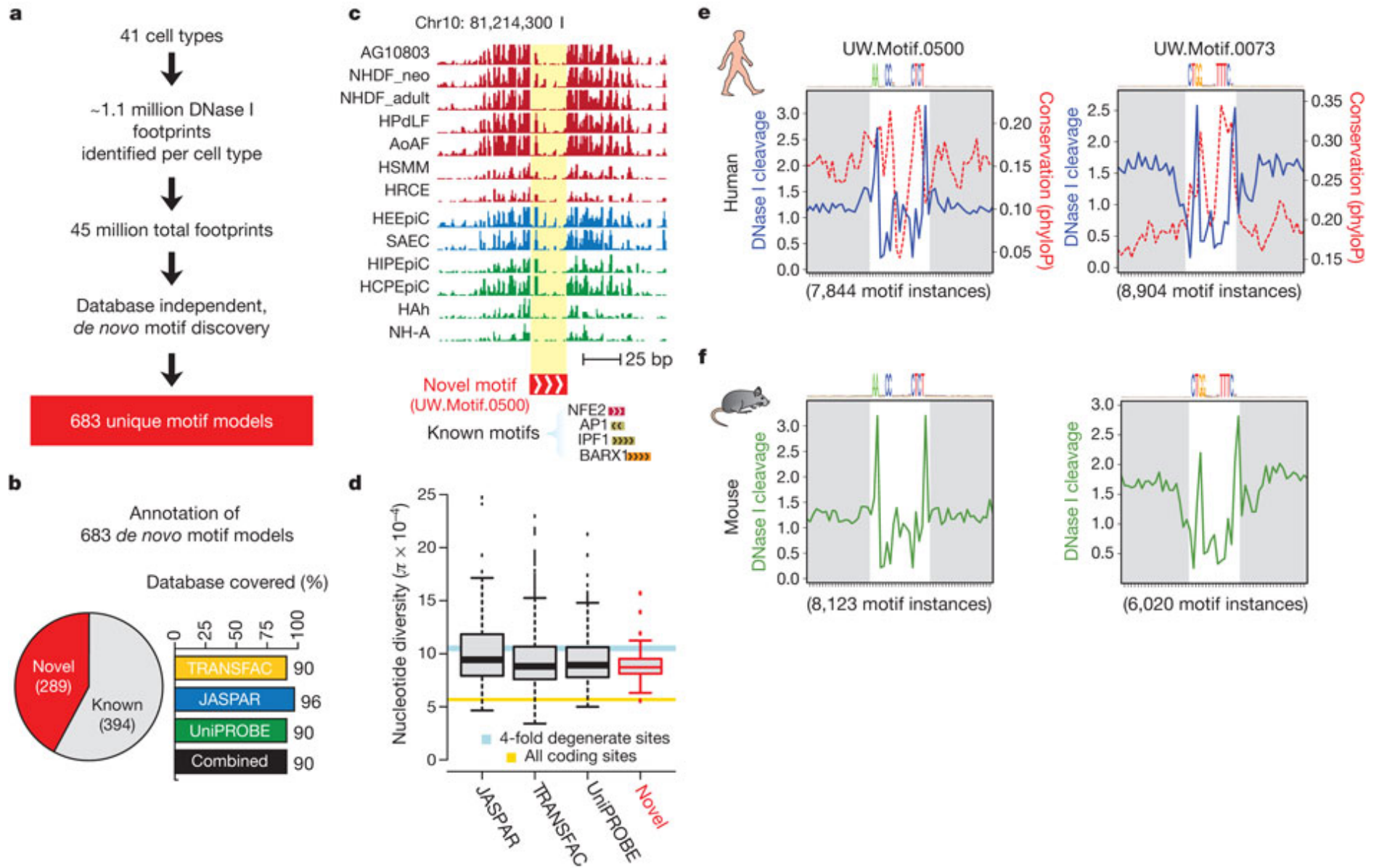# An expansive human regulatory lexicon encoded in transcription factor footprints

Figure 4
Nature (2012) 489: 83

An expansive human regulatory lexicon encoded in transcription factor footprints

Figure 5
Nature (2012) 489: 83

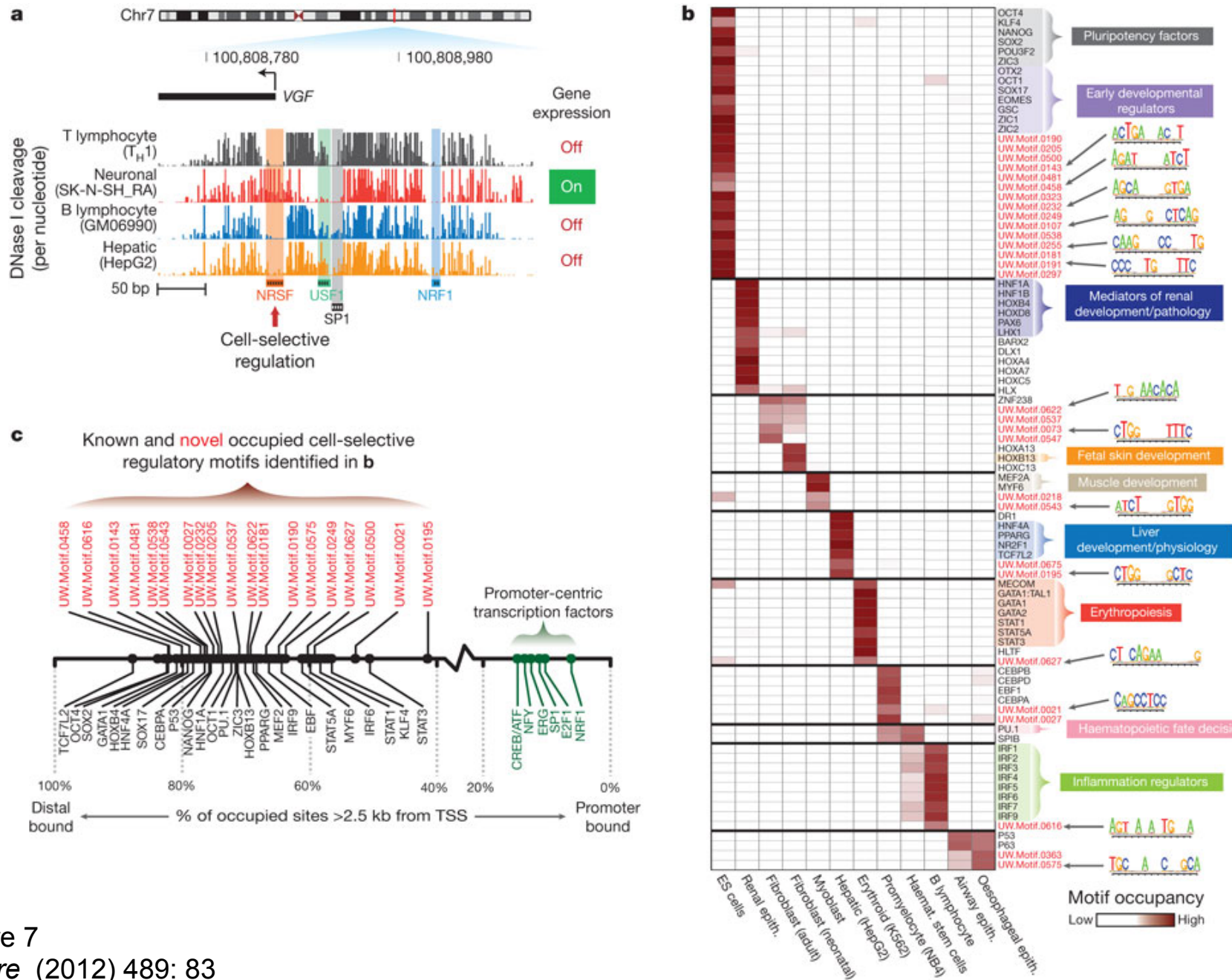# An expansive human regulatory lexicon encoded in transcription factor footprints

Figure 6
Nature (2012) 489: 83

26

An expansive human regulatory lexicon encoded in transcription factor footprints

Figure 7
Nature (2012) 489: 83

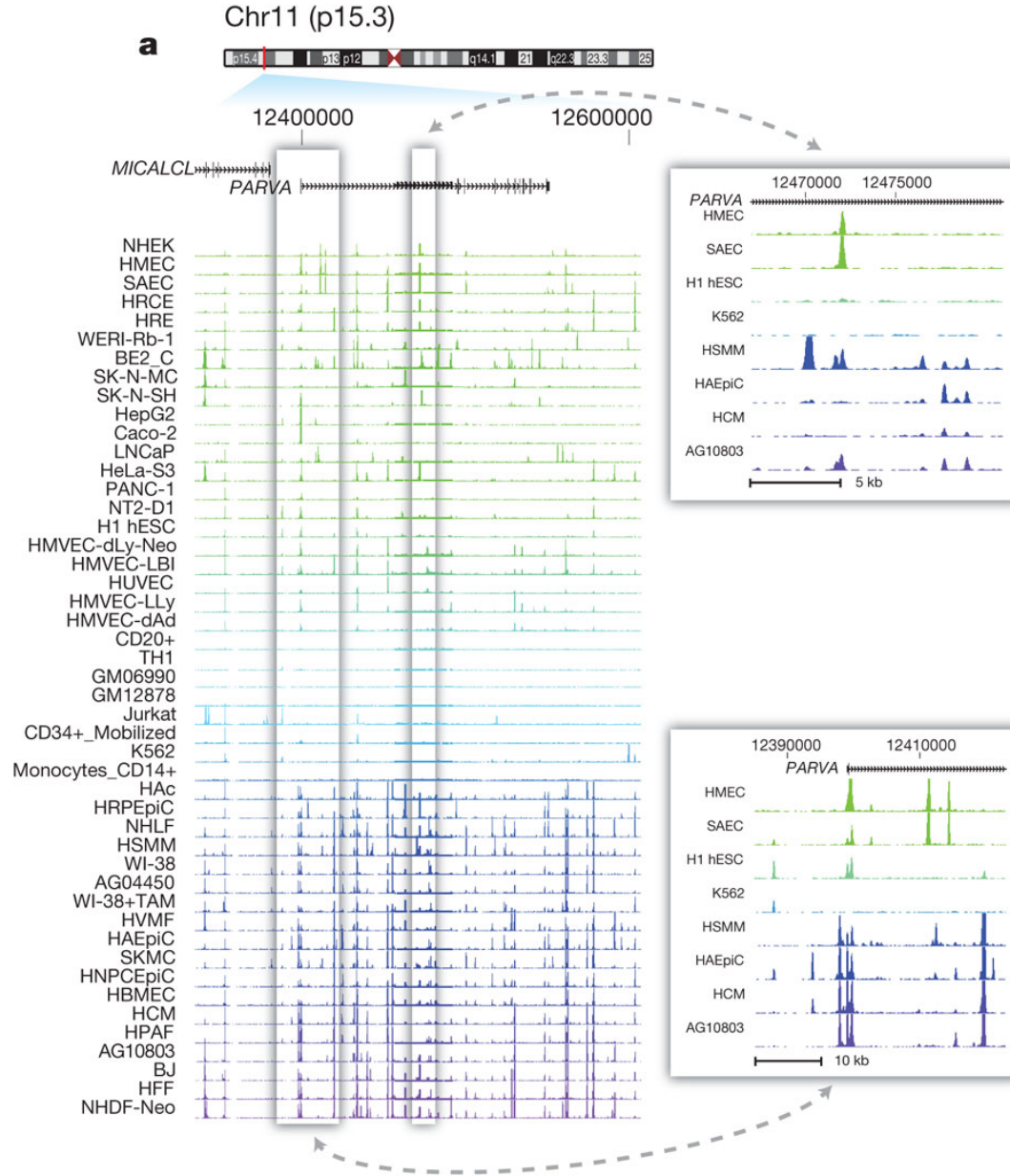# The accessible chromatin landscape of the human genome

Figure 1
Nature (2012) 489: 75

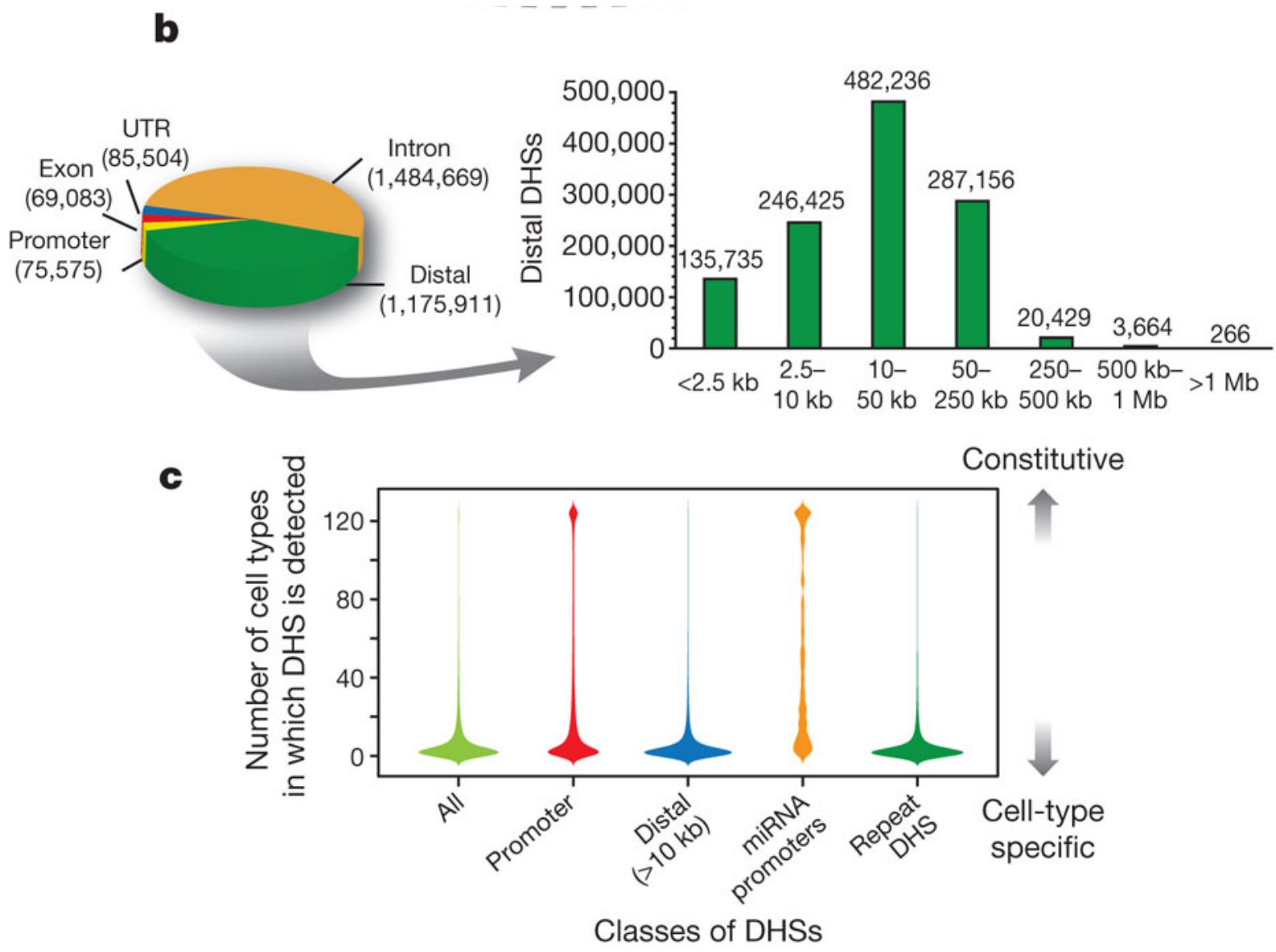# The accessible chromatin landscape of the human genome
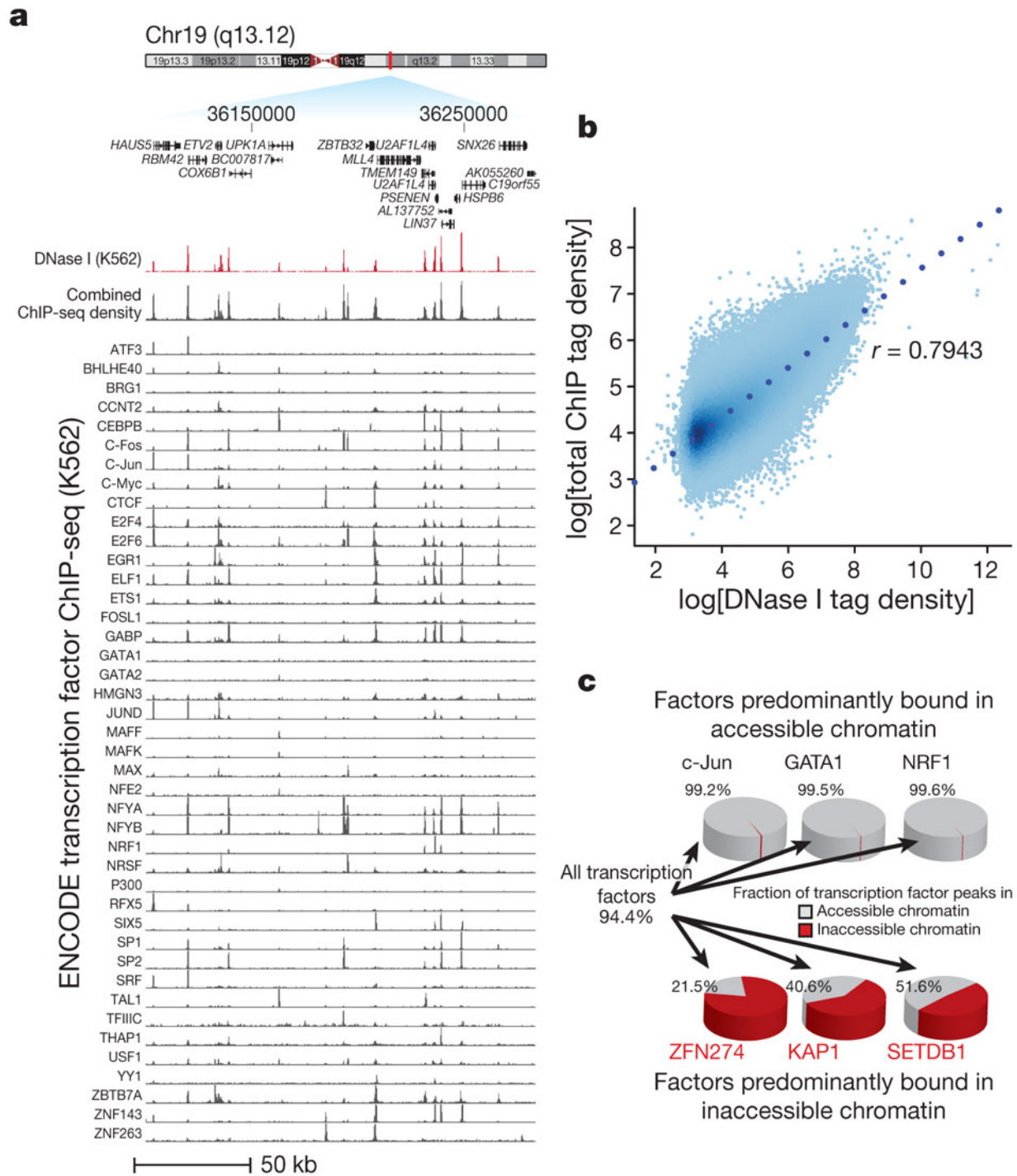

Figure 1
Nature (2012) 489: 75

Figure 2
Nature (2012) 489: 75

30

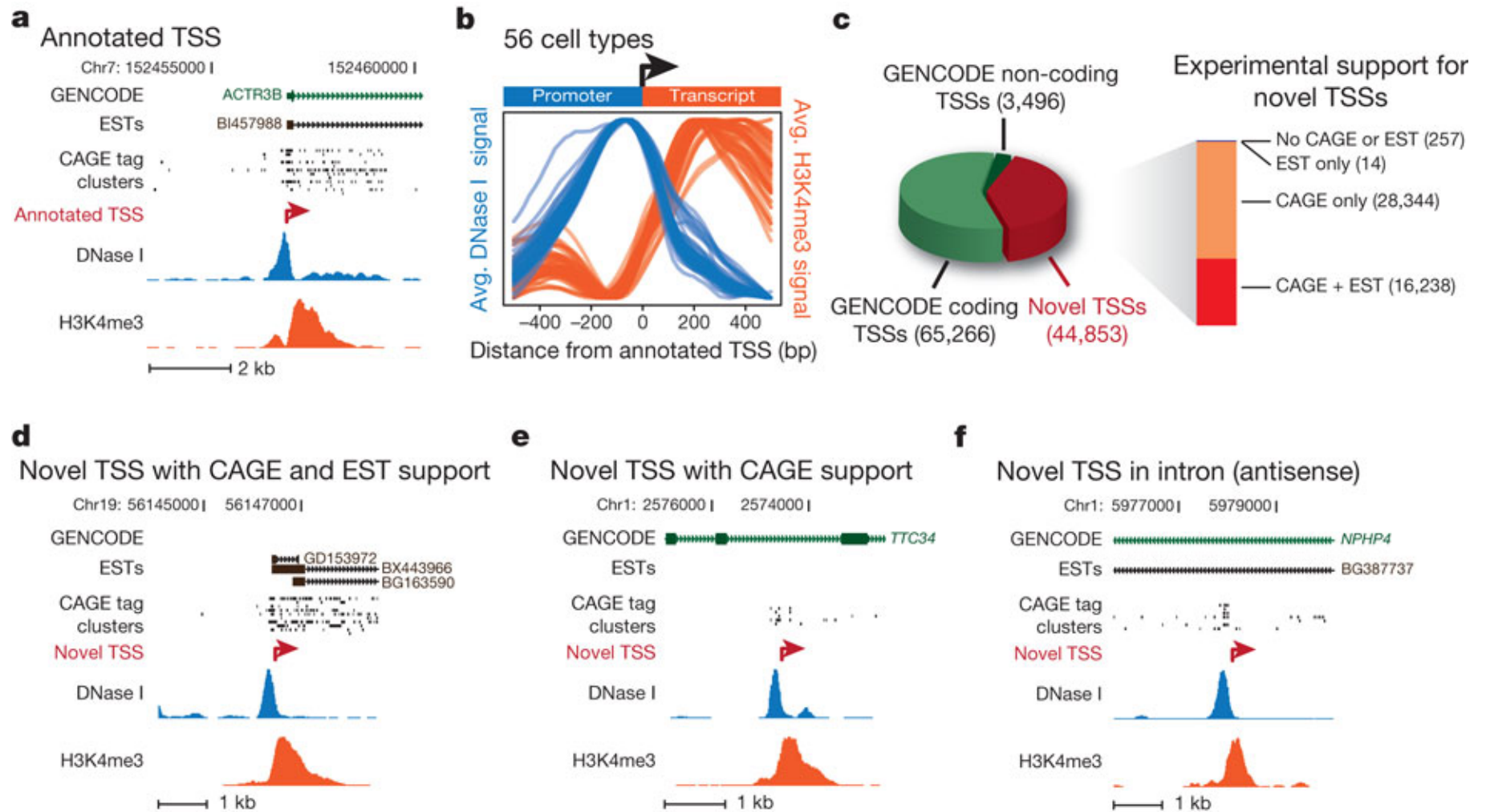# The accessible chromatin landscape of the human genome

Figure 3
Nature (2012) 489: 75
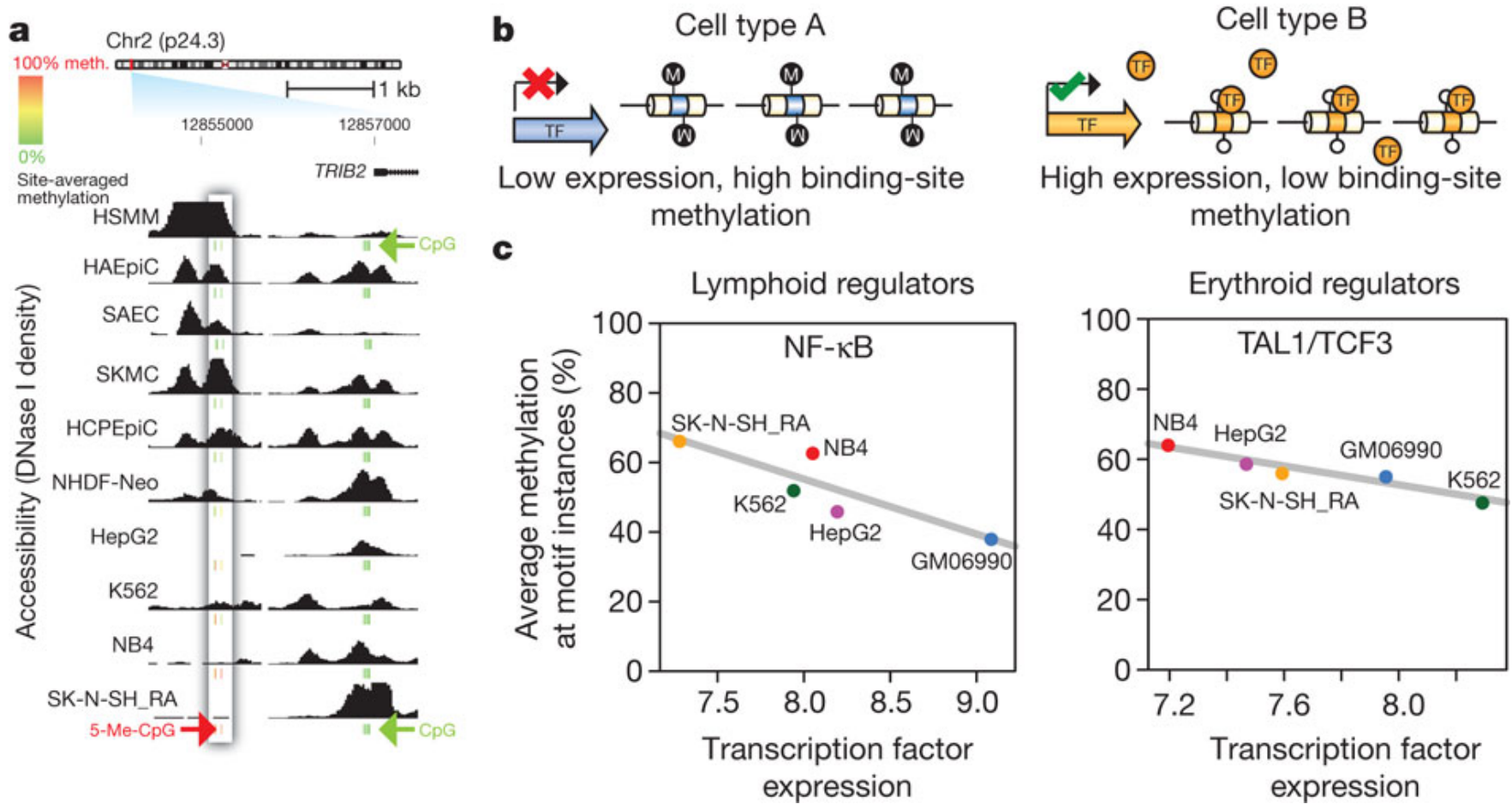
The accessible chromatin landscape of the human genome

Figure 4
Nature (2012) 489: 75

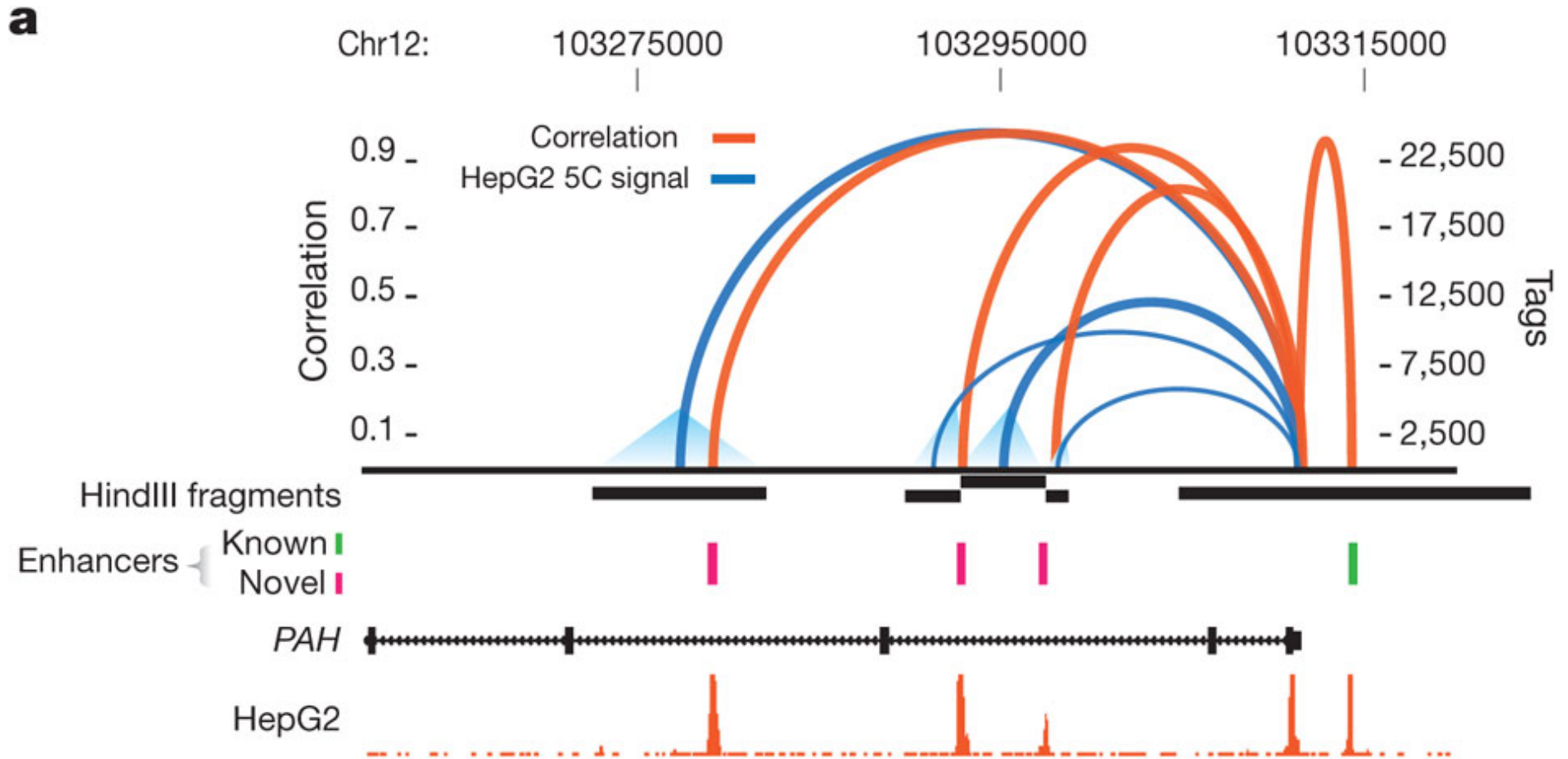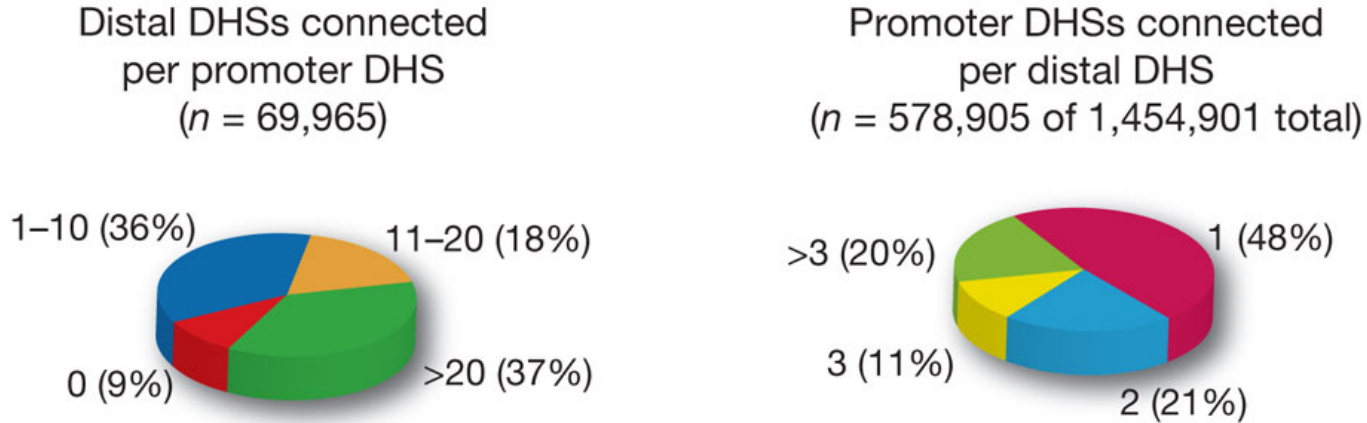# The accessible chromatin landscape of the human genome

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Nature (2012) 489: 75

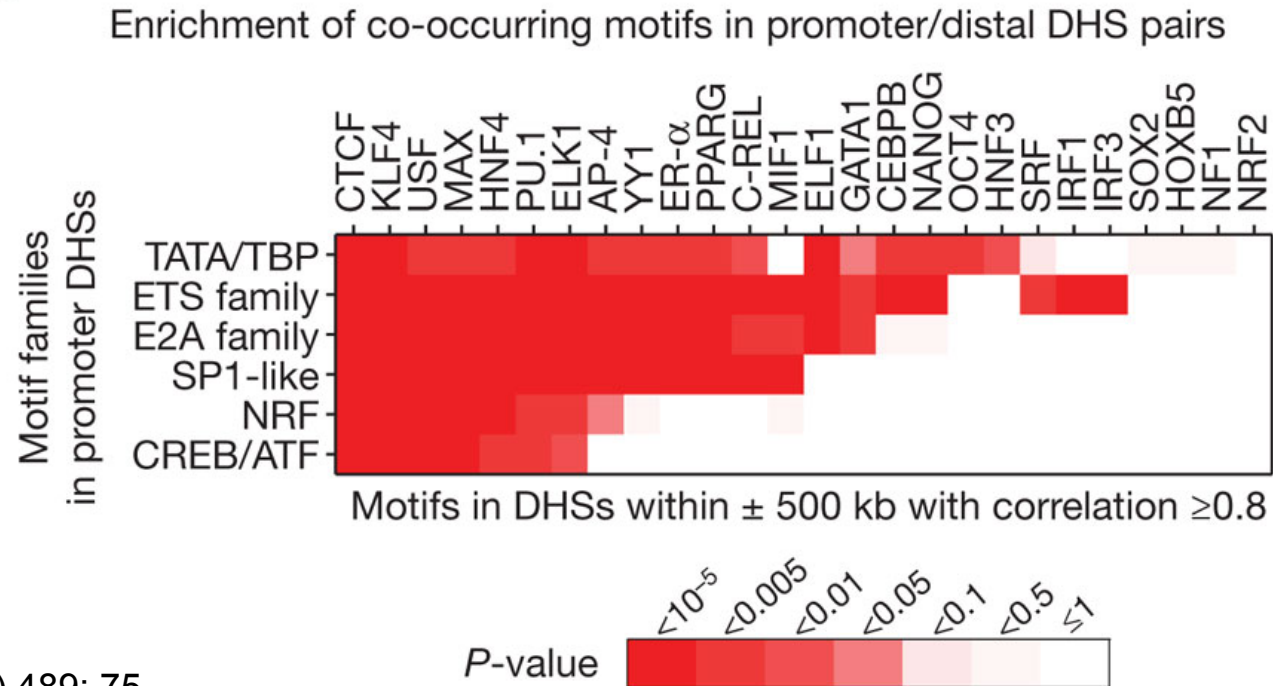# The accessible chromatin landscape of the human genome

Figure 5
Nature (2012) 489: 75

The accessible chromatin landscape of the human genome

Figure 6
Nature (2012) 489: 75

The accessible chromatin landscape of the human genome
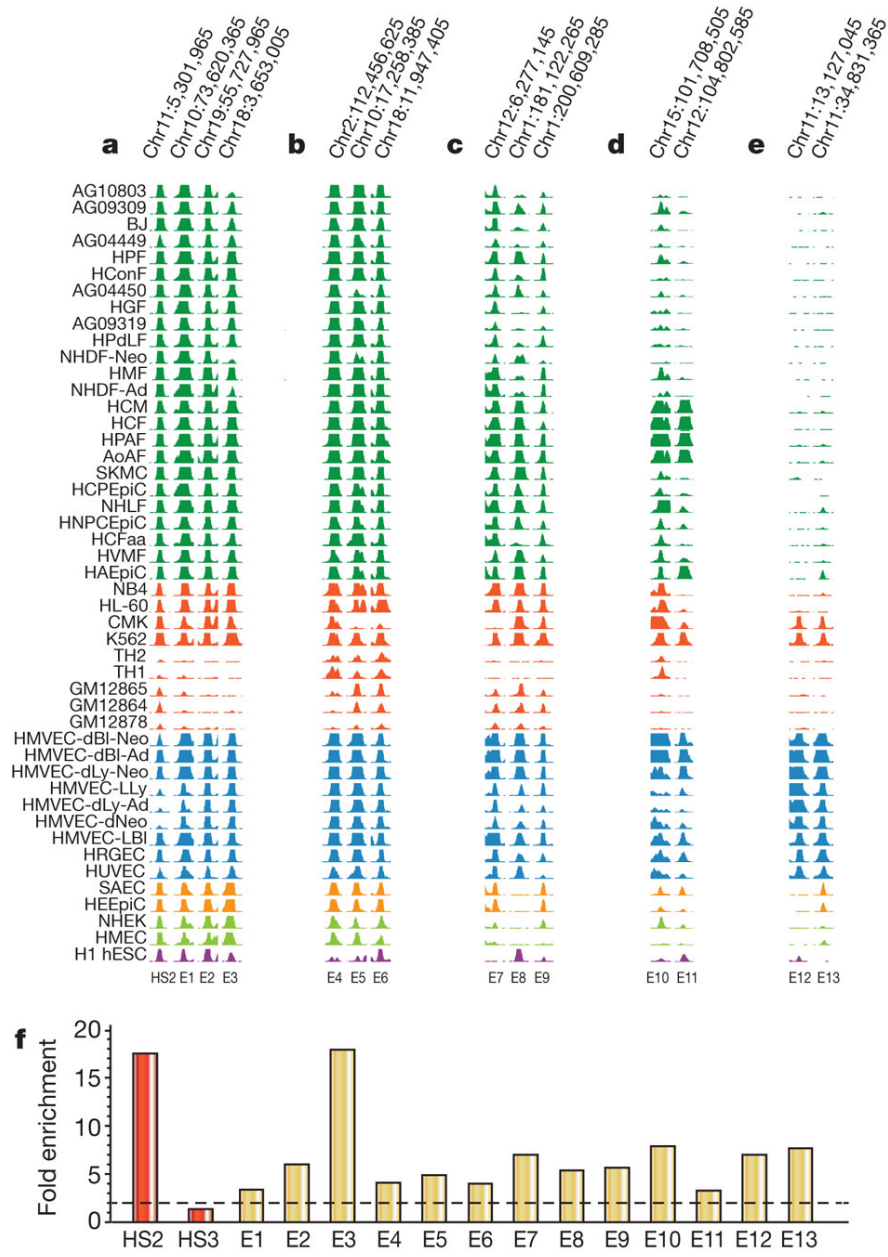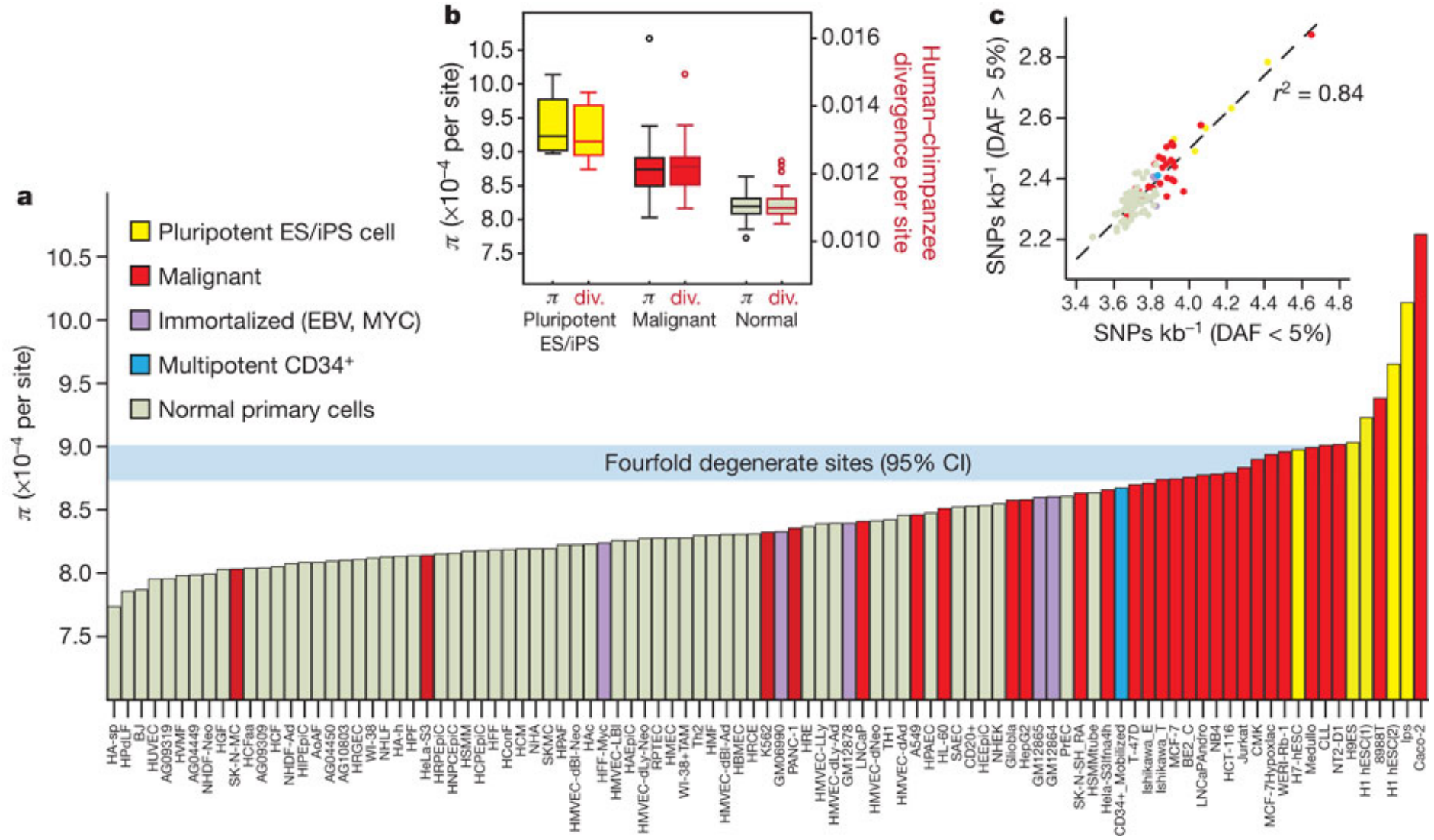

Figure 7
Nature (2012) 489: 75

END