Epigenomics for Precision Medicine

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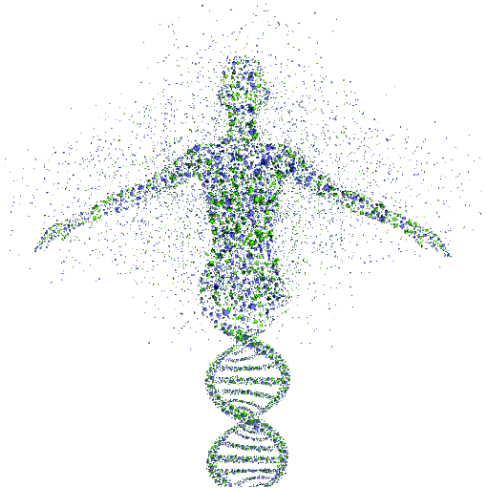
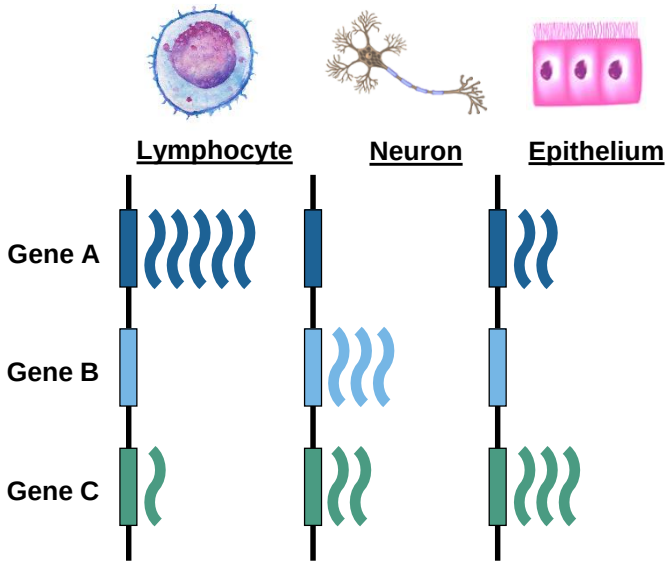
The big picture: regulation of gene expression

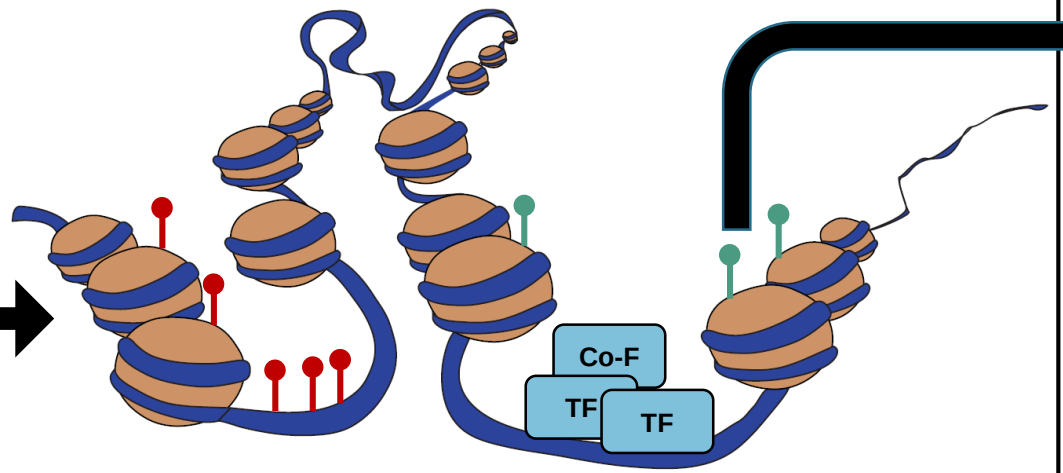


How does one genome sequence give rise to such a complex organism?

- One set of genes, but ***variable gene expression***

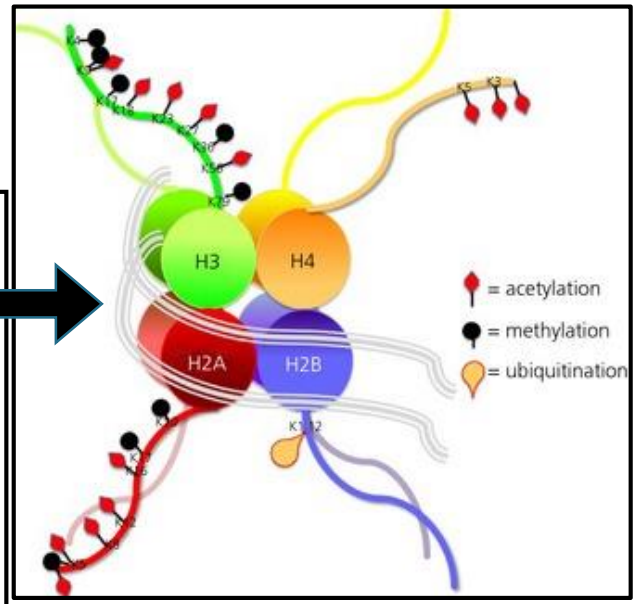


- DNA sequence is static, but DNA molecule is not → ***epigenomics!***

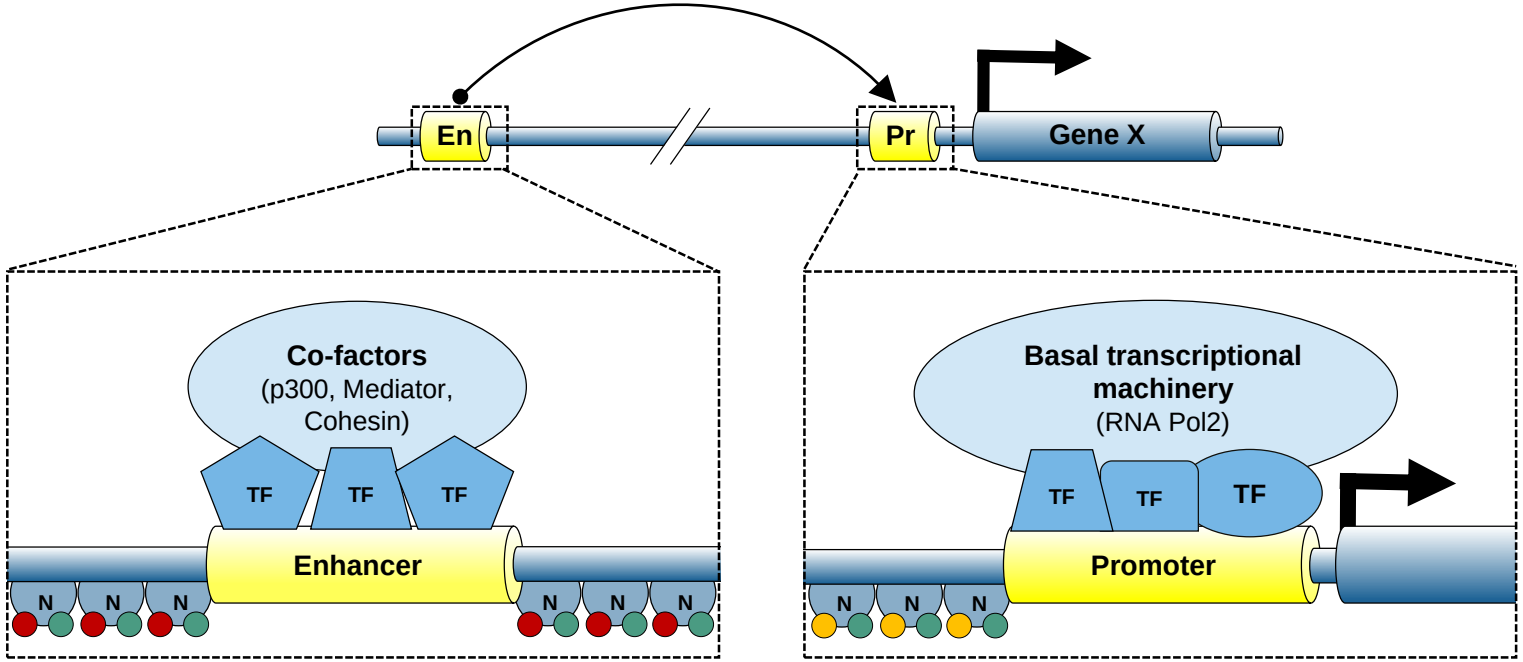


Key: acetylation methylation TF transcription factor or co-factor

Nucleosome



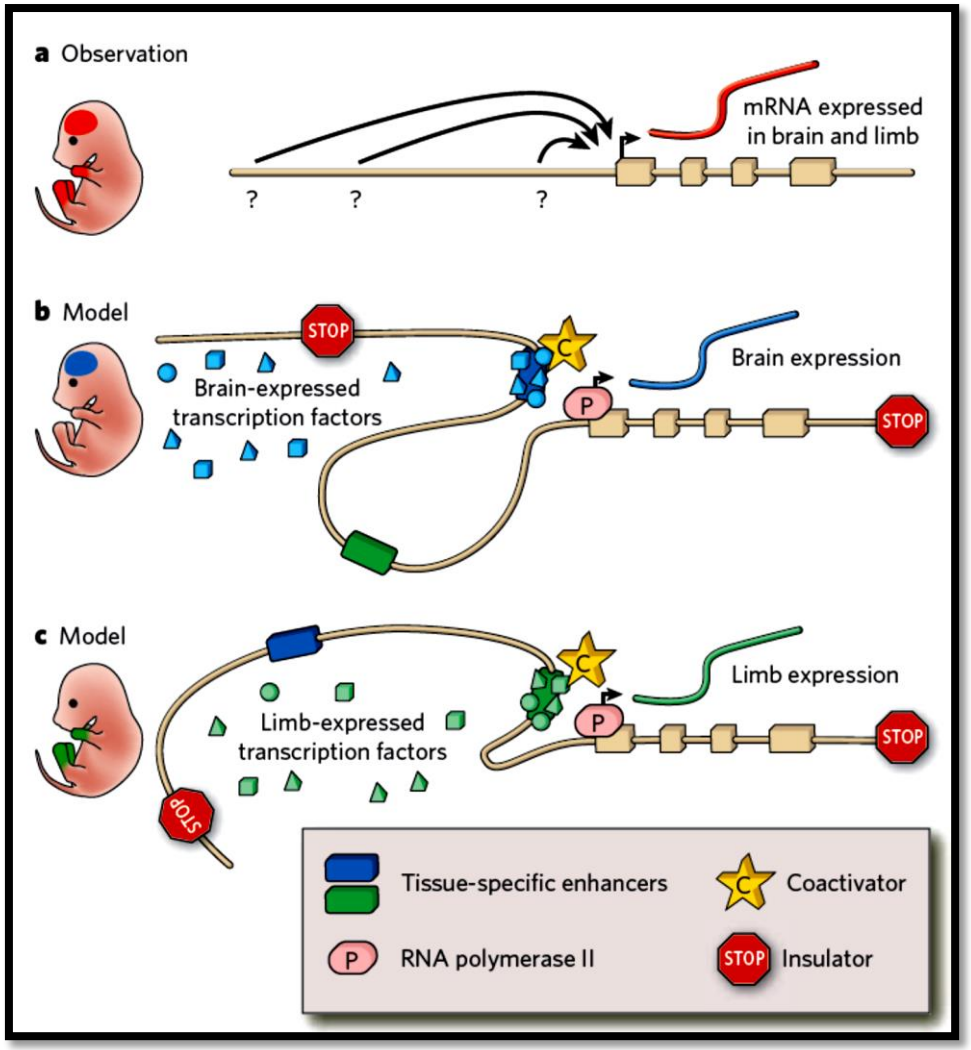
A working model for gene regulation



Key:

TF	**Transcription Factor**
N	**Nucleosome**
	Enhancer chromatin signature of H3K4me1 & H3K27ac
	Promoter chromatin signature of H3K4me3 & H3K27ac

Histone Modification Nomenclature:
H3 = Histone 3
K4 = Lysine 4
Me3 = tri-methylation

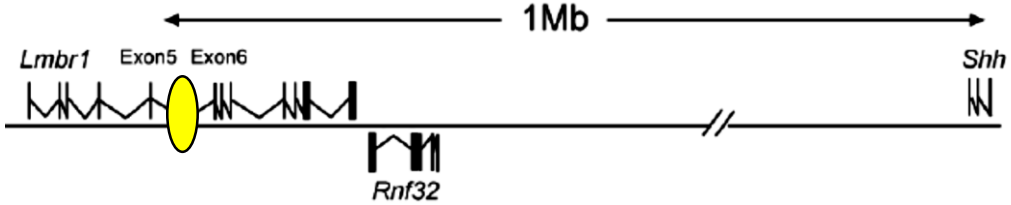


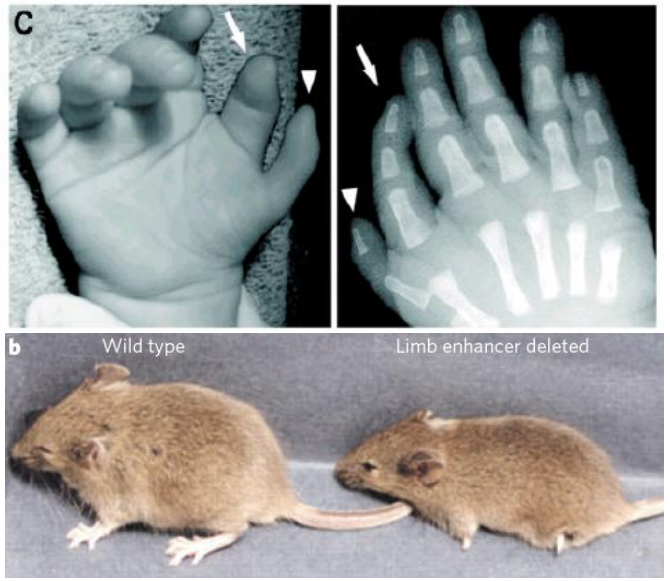
Visel et al., 2009. PMID: 19741700

Gene regulation & human disease

1) Isolated cases of highly penetrant mutations in regulatory sequence.

- Polydactyly [*SHH*] (Lettice et al., 2002; PMID: 12032320)
- β-thalassemia [*HBB*] (Driscoll et al., 1989; PMID: 2798417)
- Pierre robin sequence [*SOX9*] (Benko et al., 2009; PMID: 19234473)
- Pancreatic agenesis [*PTF1A*] (Weedon et al., 2014; PMID: 24212882)
- Congenital heart disease [*TBX5*] (Smemo et al., 2012; PMID: 22543974)
- Cancer [*TERT*] (Huang et al., 2013; PMID: 23348506)

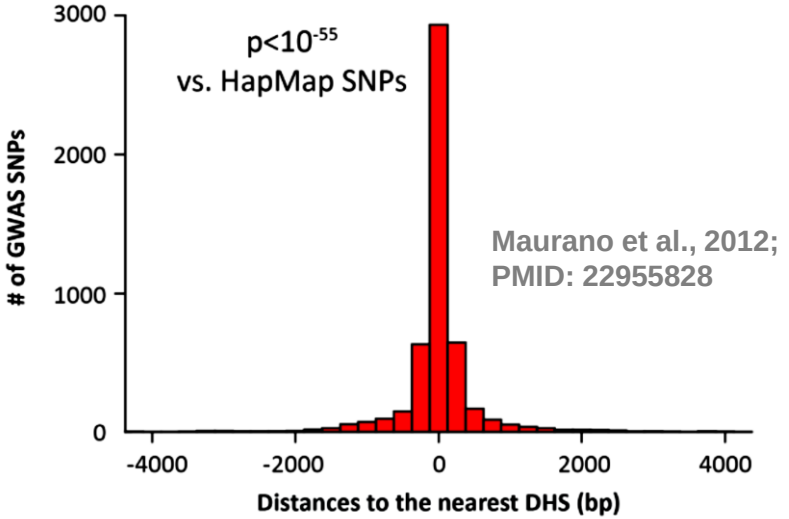




Lettice et al., 2003; PMID: 12837695
Sagai et al., 2005; PMID: 15677727

2) SNPs associated with disease by GWAS are enriched in regulatory sequence.

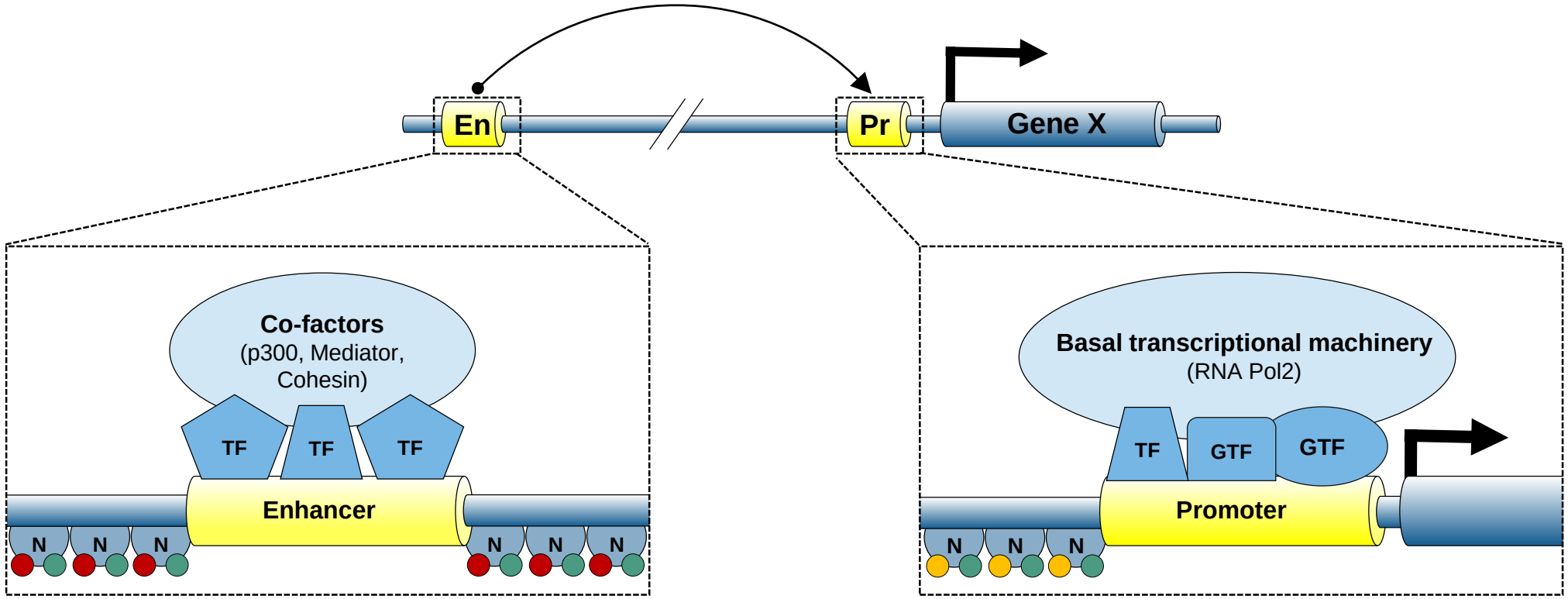
- Cleft lip [*IRF6*] (Rahimov et al., 2008; PMID: 18836445)
- Obesity/T2D [*IRX3*] (Smemo et al., 2014; PMID: 24646999)
- Hirschsprung's disease [*RET*] (Emison et al., 2005; PMID: 15829955)
- Long QT syndrome [*NOS1AP*] (Kapoor et al., 2014; PMID: 24857694)
- Pigmentation & melanoma [*IRF4*] (Praetorius et al., 2013; PMID: 24267888)



Maurano et al., 2012; PMID: 22955828

→ **For <u>precision medicine</u> we will need to better interpret regulatory (i.e non-coding) genetic variation. 98% of the human genome is non-coding!**

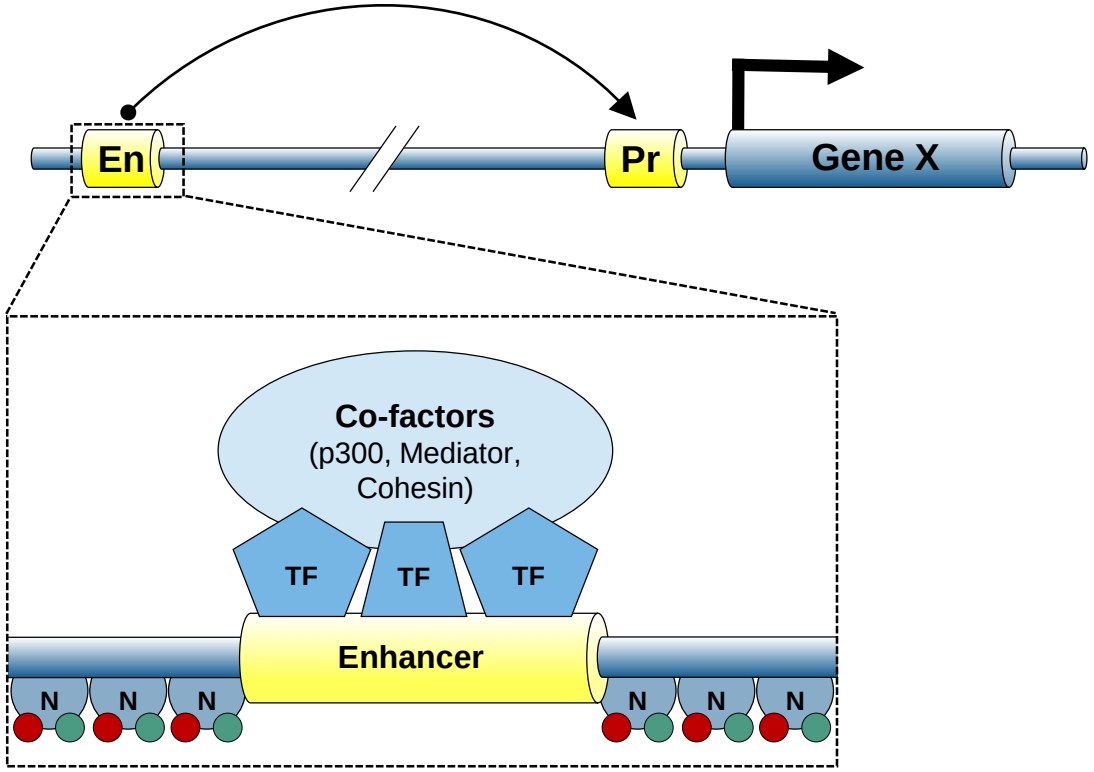
Epigenomic tools to interpret non-coding genome



Active ➡	• Nucleosome-free region of **"accessible" chromatin** • Adjacent nucleosomes enriched for **H3K4me1** & **H3K27ac**	• Nucleosome-free region of **"accessible" chromatin** • Adjacent nucleosomes enriched for **H3K4me3** & **H3K27ac**
Repressed ➡	• Little/no "accessible" chromatin • Nucleosomes may be enriched for **H3K27me3**	• Little/no "accessible" chromatin • Nucleosomes may be enriched for **H3K27me3**

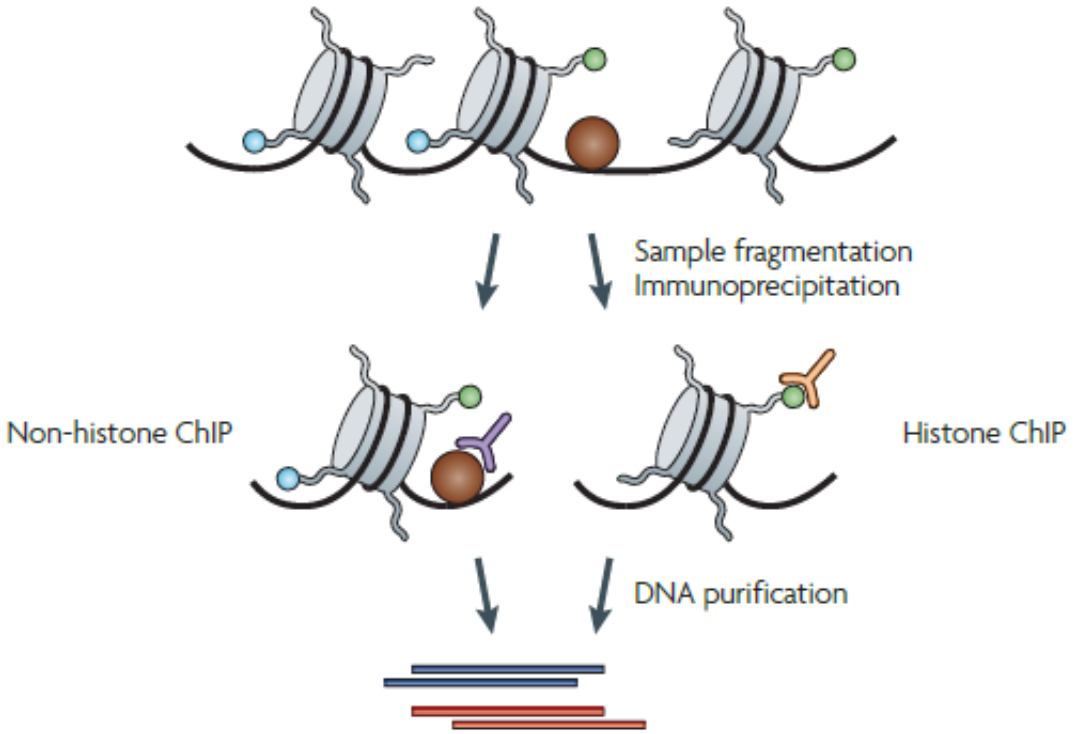
(also other states: silent, poised, bivalent)

Epigenomic tools to interpret non-coding genome



- Nucleosome-free region of **"accessible" chromatin**
- Adjacent nucleosomes enriched for **H3K4me1** & **H3K27ac**

Chromatin Immunoprecipitation Sequencing (ChIP-seq)



Sequencing

Adapted from Park, 2009; PMID: 19736561

Large-scale efforts to map epigenomes

ENCODE

"…to identify all functional elements in the human genome sequence."

- 2003-present
- Mouse has also been of ENCODE since 2007

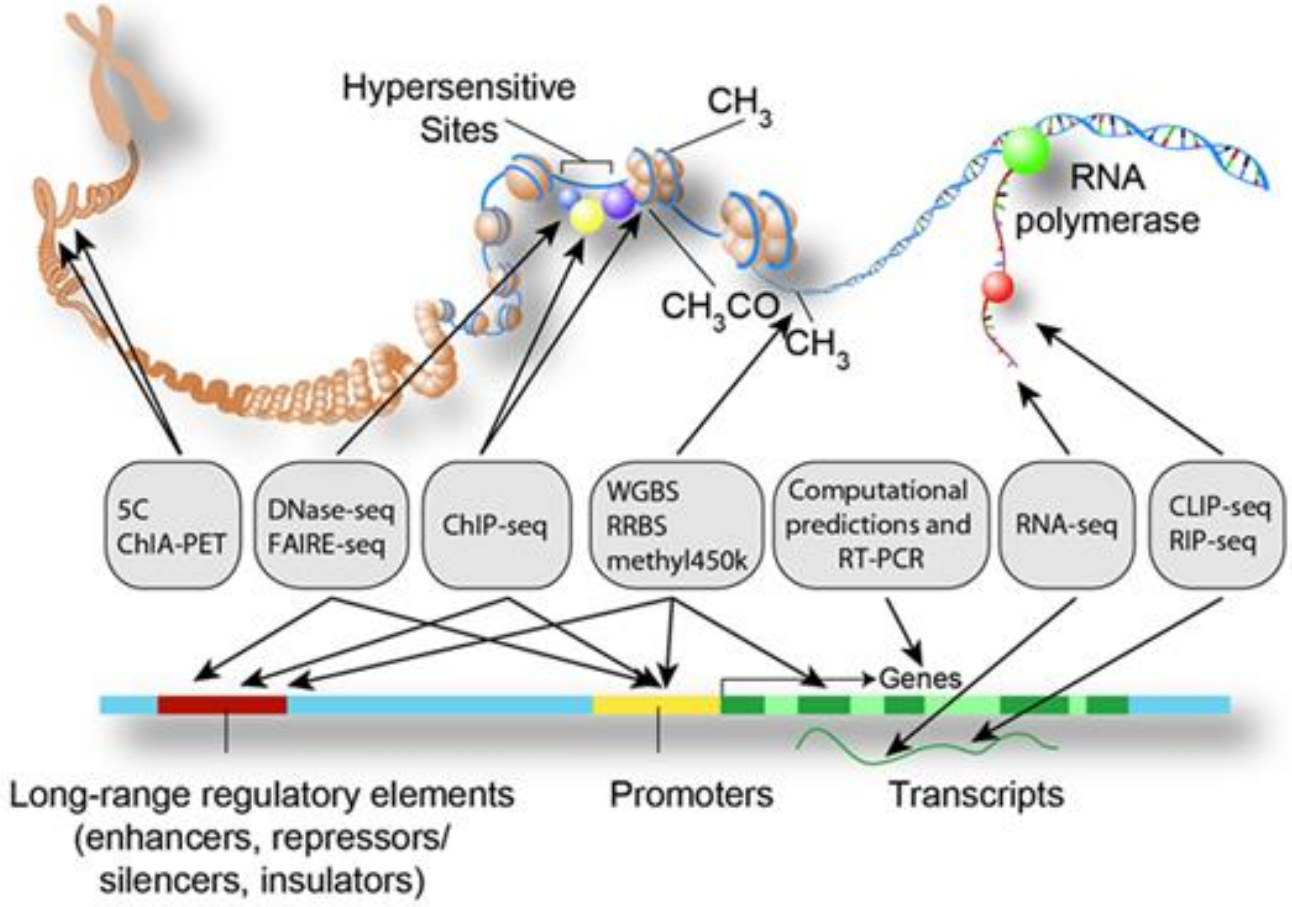
ROADMAP epigenomics PROJECT

"…goal of producing a public resource of human epigenomic data to catalyze basic biology and disease-oriented research"

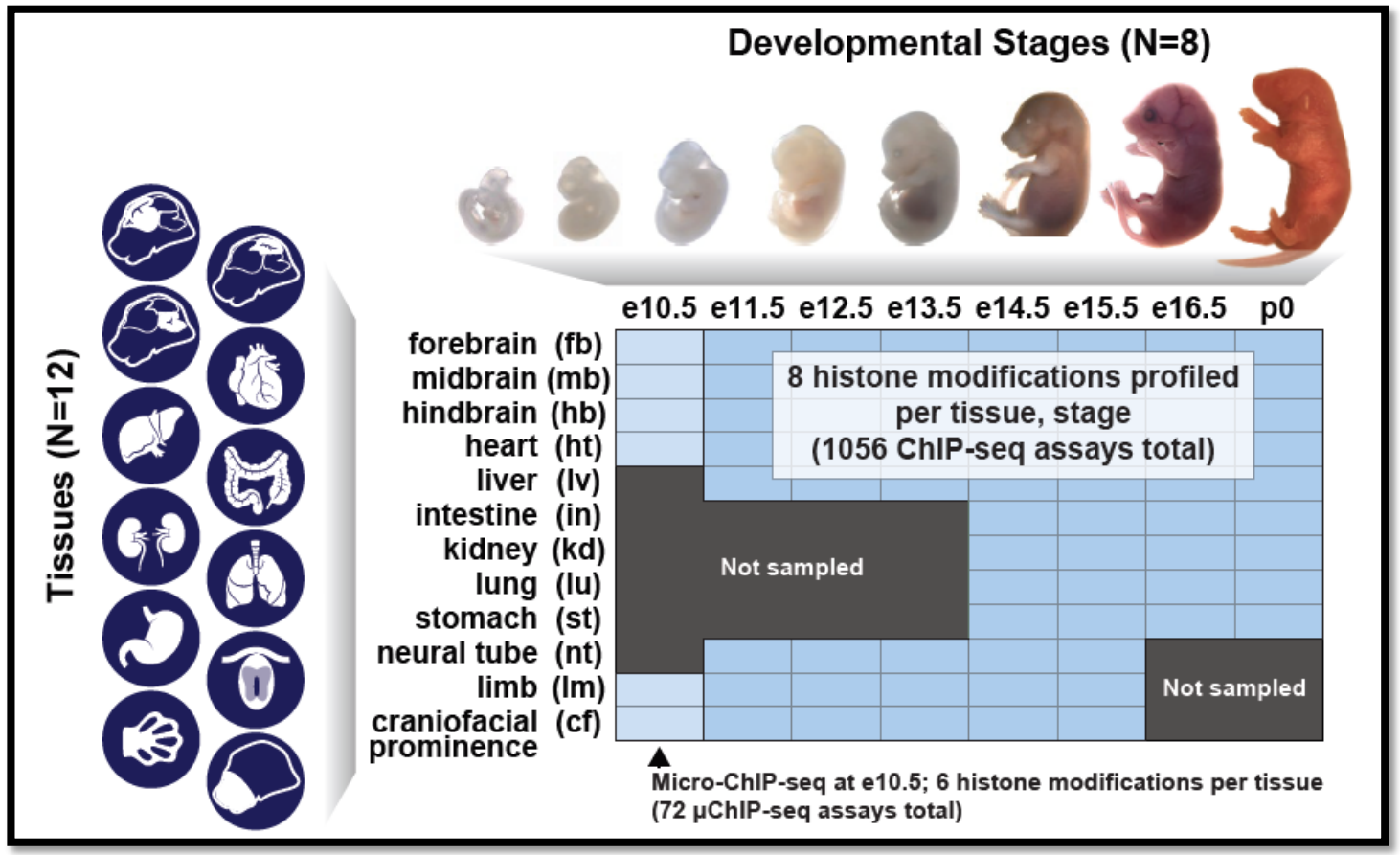
- 2008-2013

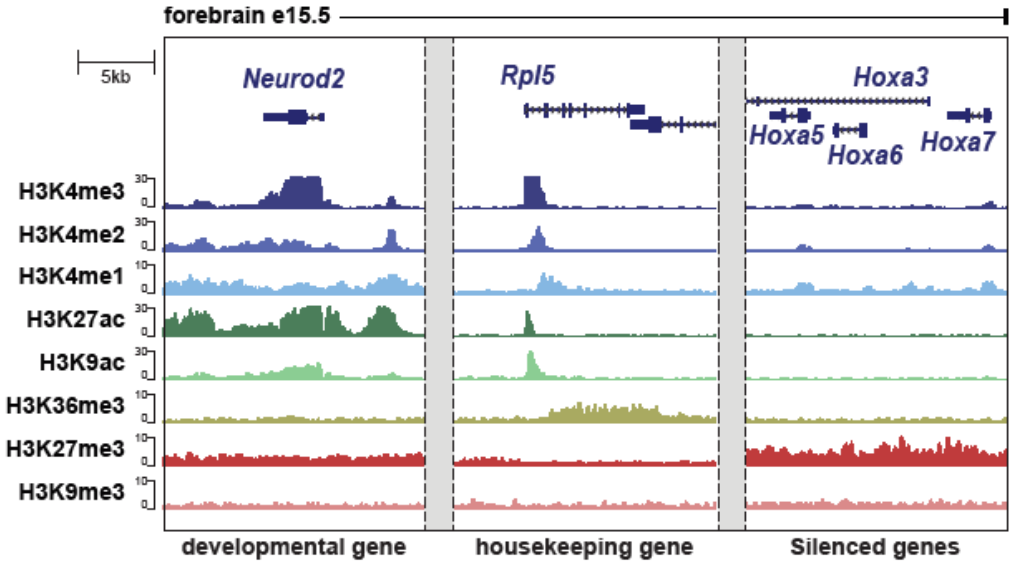
IHEC
International Human Epigenome Consortium

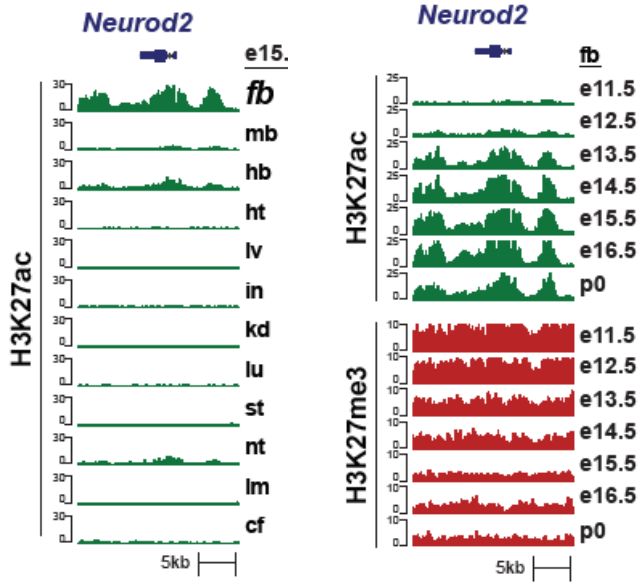
4D Nucleome



Systematic mapping of chromatin states during mouse development

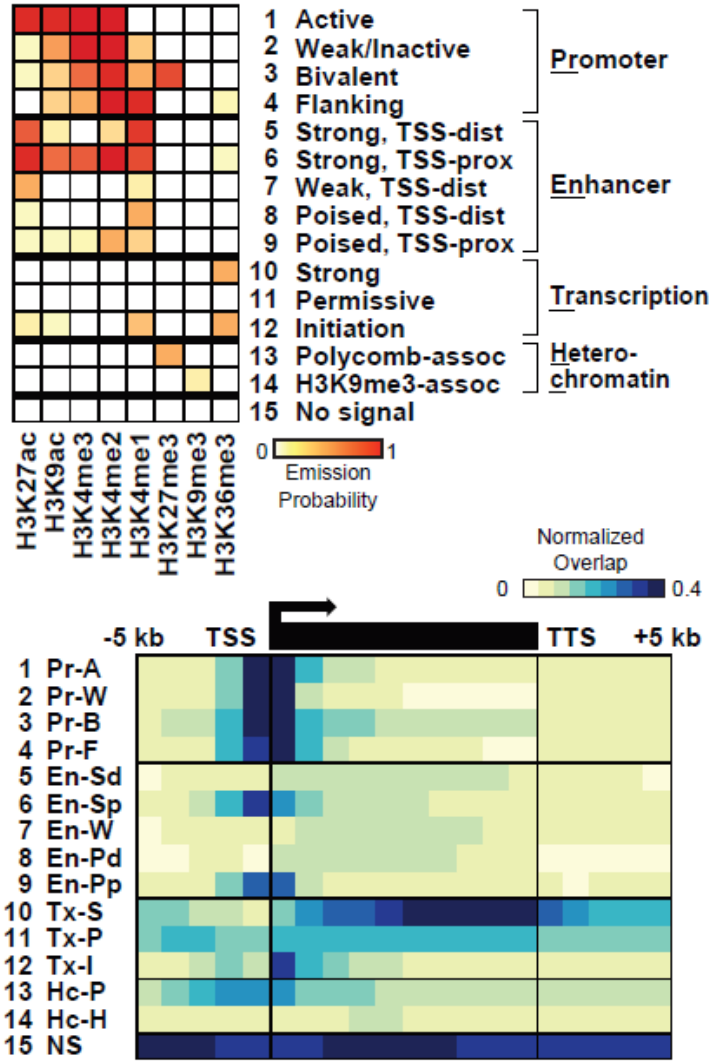


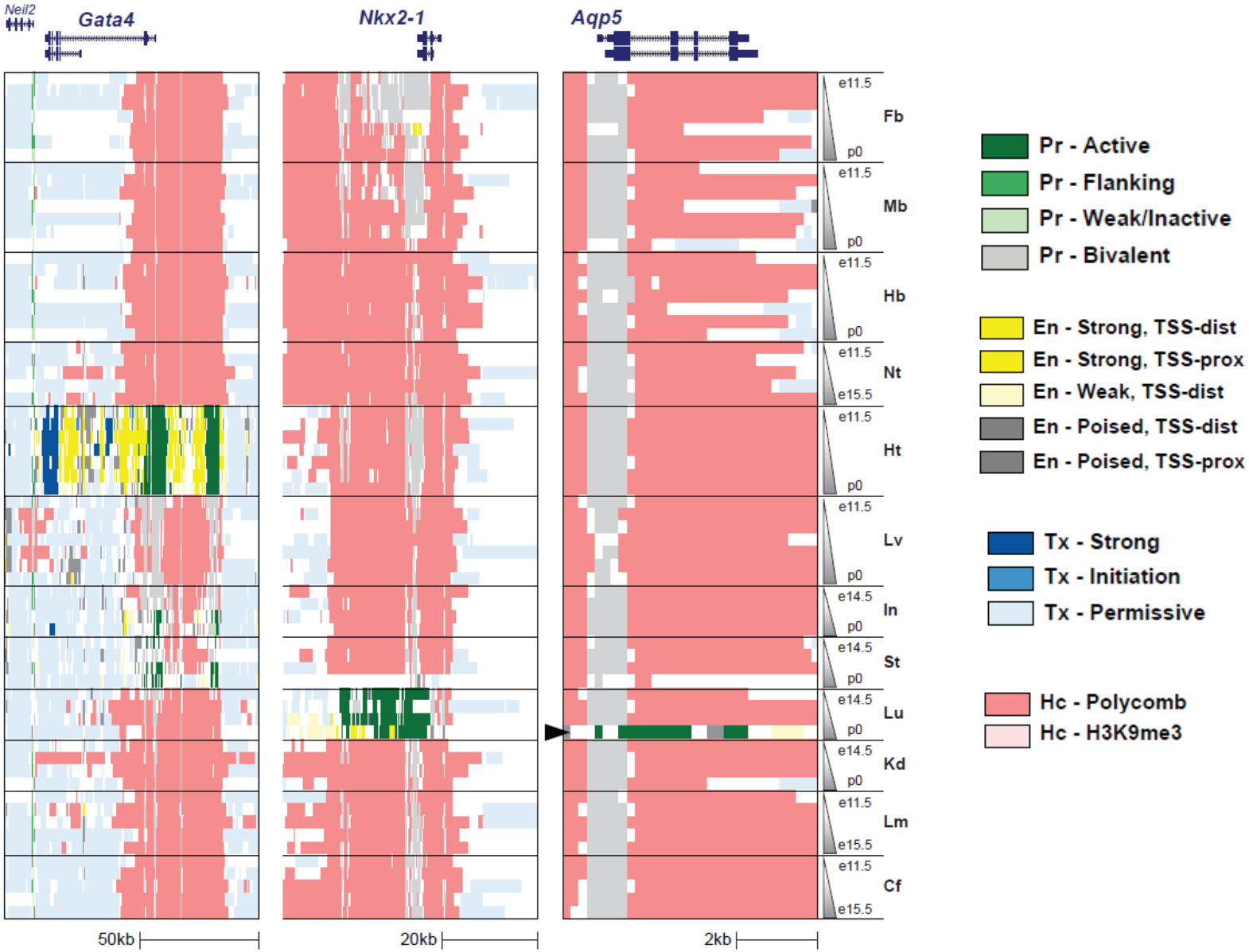




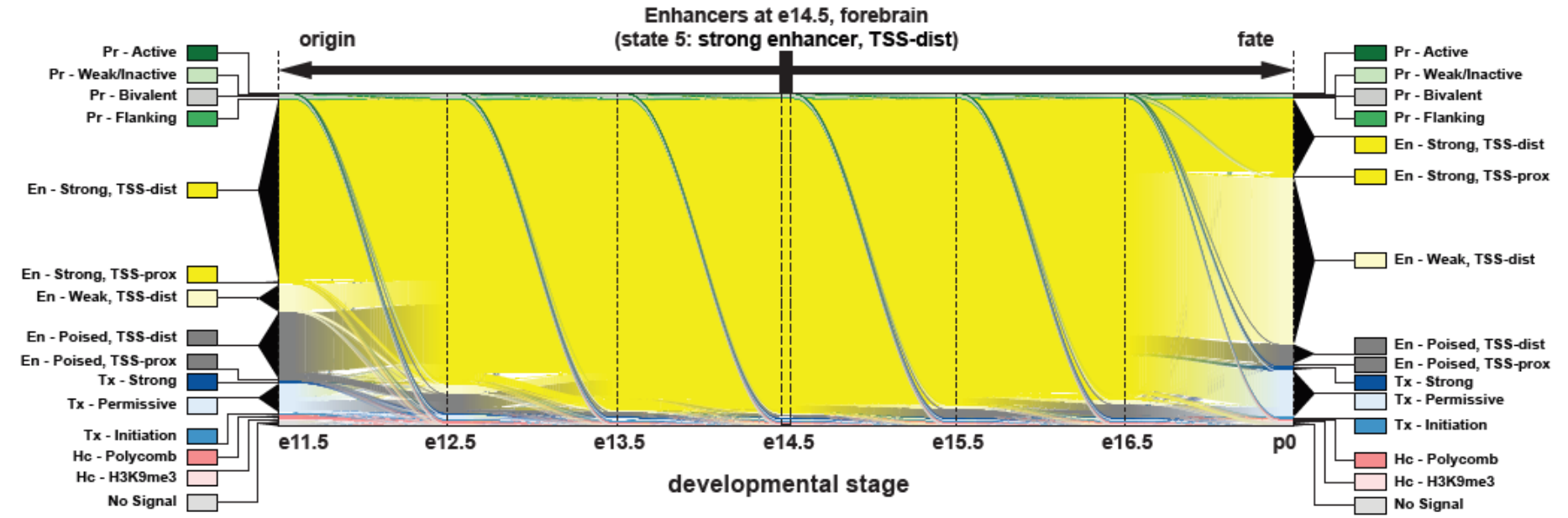
Integrating histone mods into chromatin states

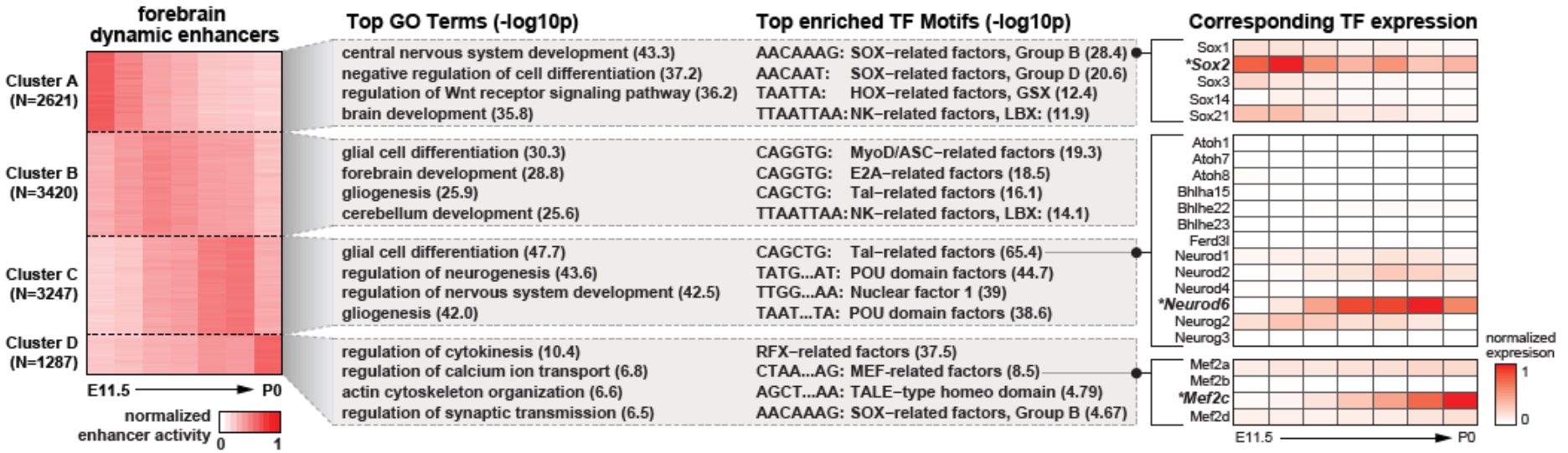
→ ChromHMM (Ernst and Kellis, 2012)



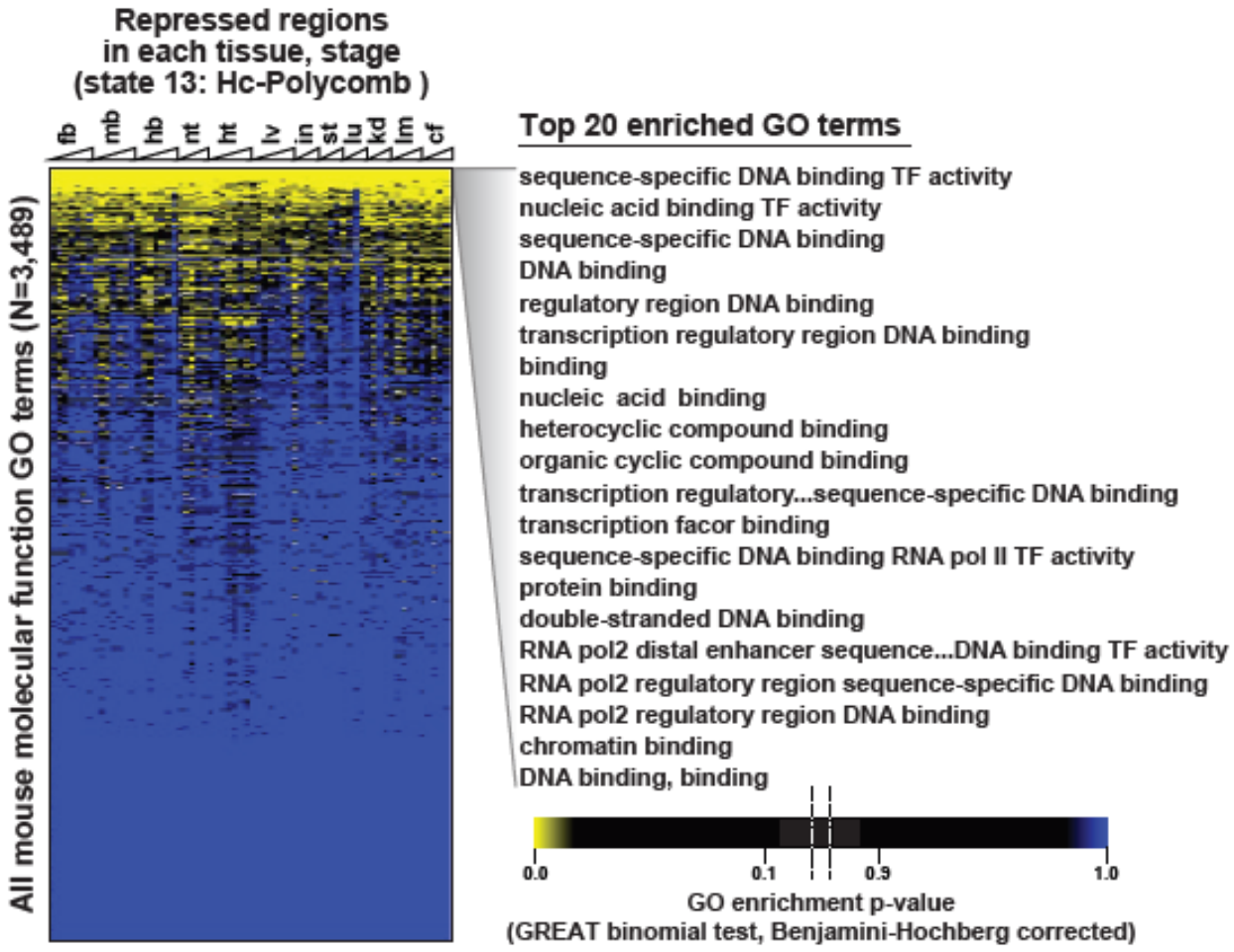


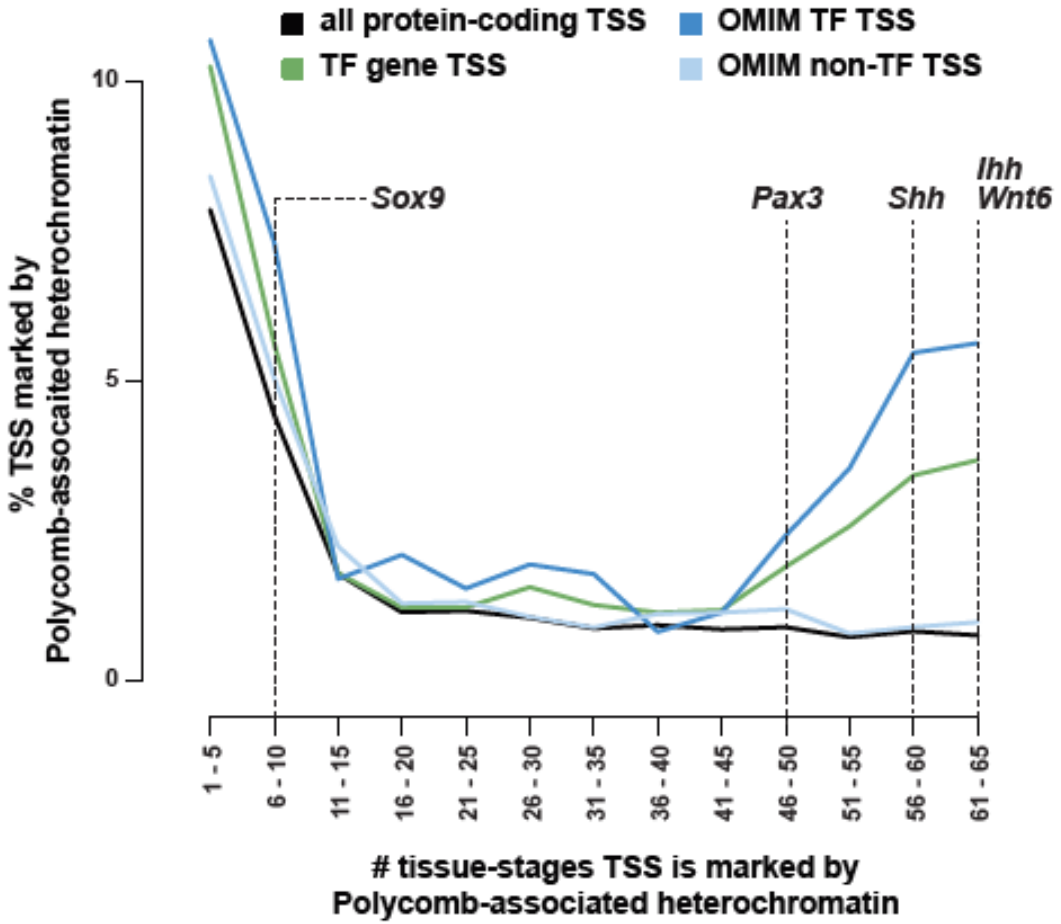
Dynamic Enhancers reveal developmental processes & regulators



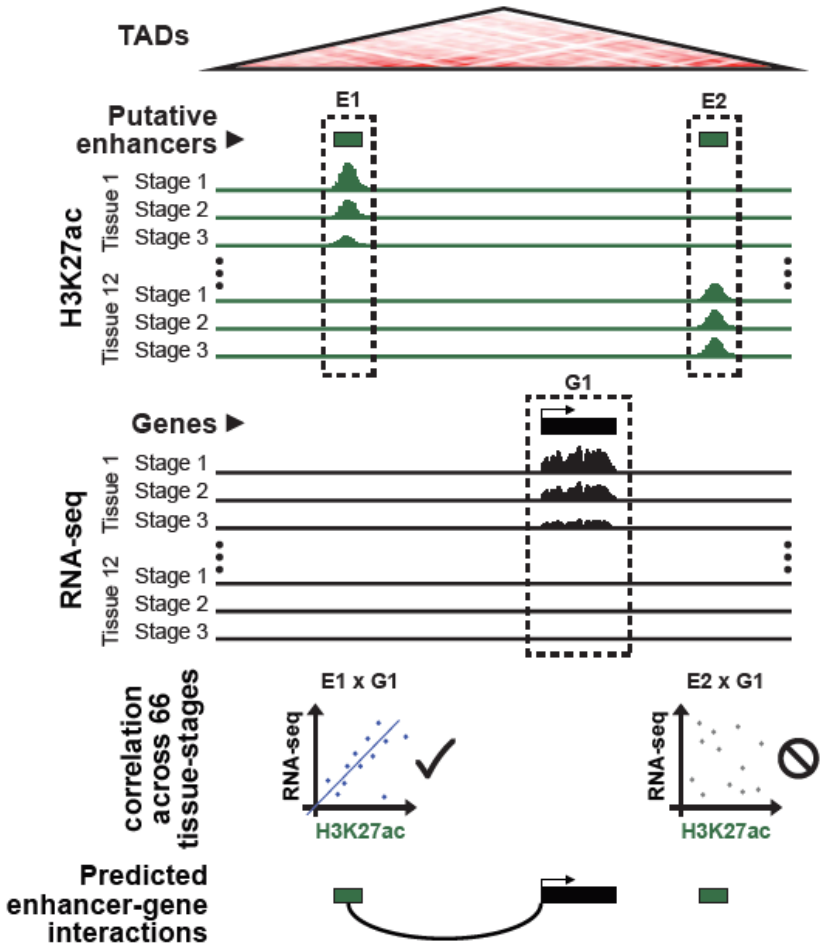


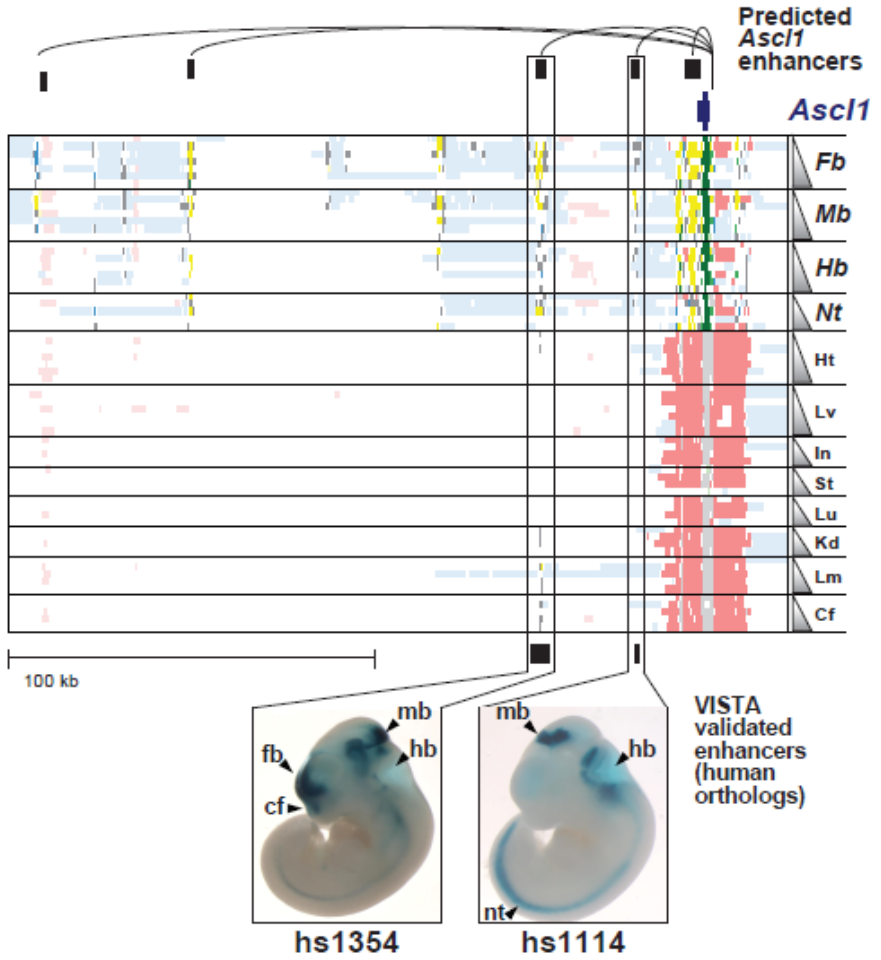
Polycomb-mediated repression targets TFs

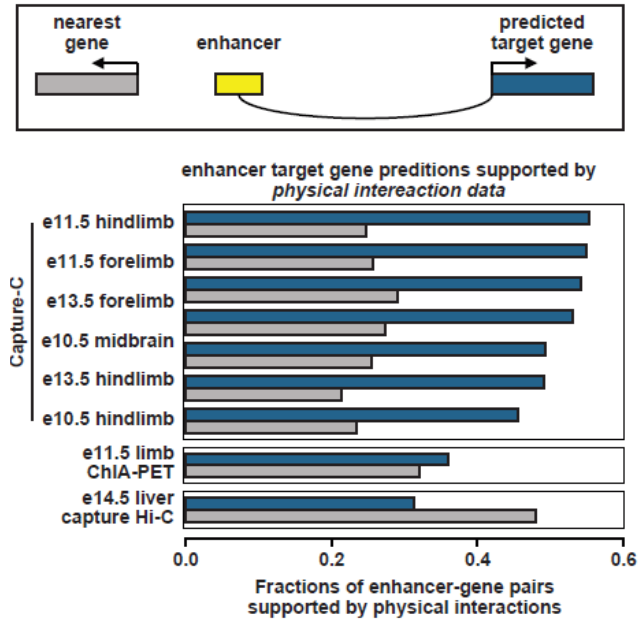




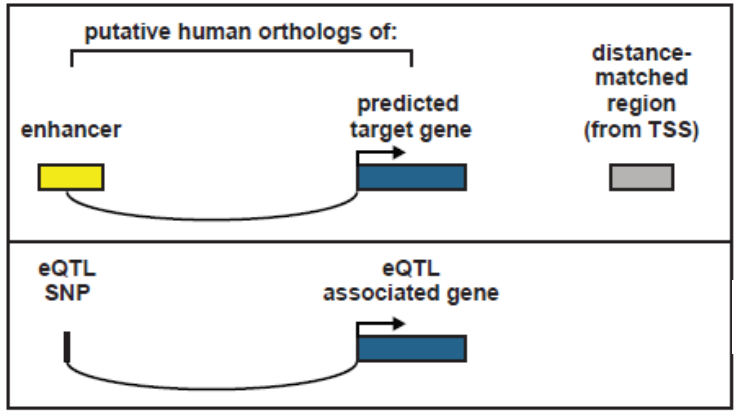
Connecting enhancers to target genes

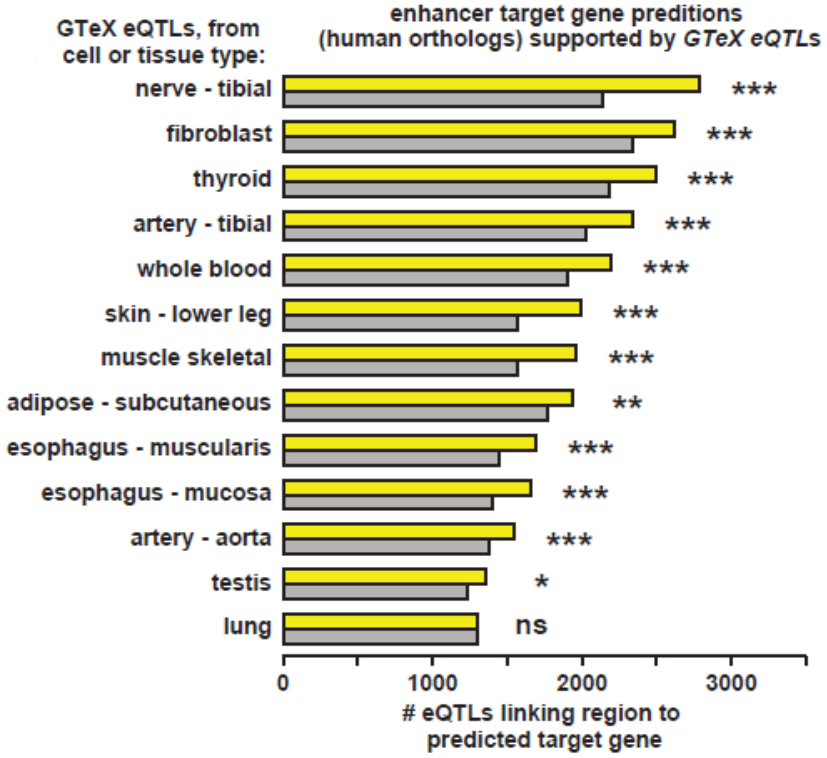


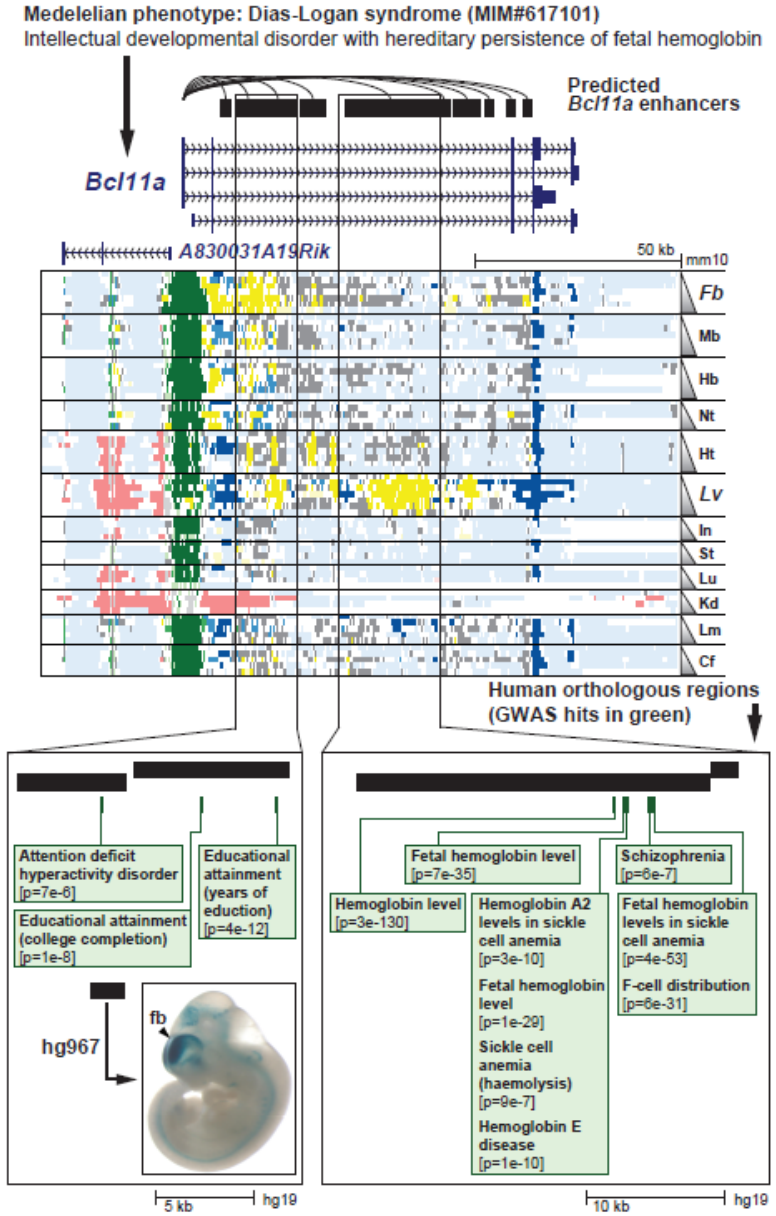




Insights into human disease etiology







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ENCODE

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