ENCODE

MMG 835, SPRING 2016
Eukaryotic Molecular Genetics

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ENCODE: Encyclopedia of DNA Elements

There is a lot of non-coding sequence (humans & other eukaryotes) - does it do anything?

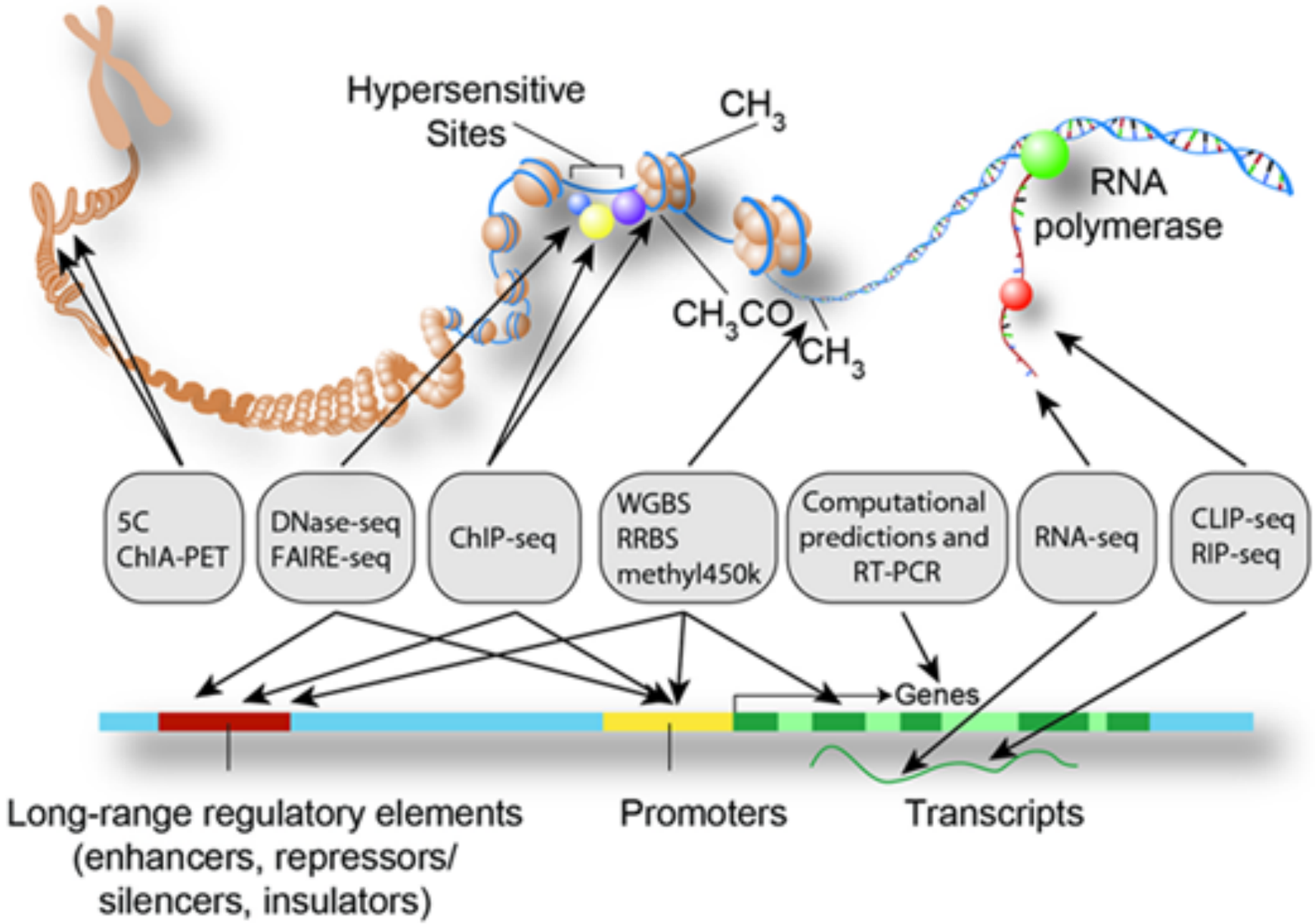
- Identify all functional elements in the genome
  - Freely available resources
    - gene regulation
    - gene basis of disease

ENCODE: Encyclopedia of DNA Elements

functional element is used to denote a discrete region of the genome that encodes a defined product (e.g., protein) or a reproducible biochemical signature, such as transcription or a specific chromatin structure.

The ENCODE Project Consortium PLoS Biol 9(4): e1001046 (2011).

ENCODE: Encyclopedia of DNA Elements



The ENCODE Project Consortium PLoS Biol 9(4): e1001046 (2011).

encodeproject.org

The National Human Genome Research Institute **m***od*el **o**rganism **ENC**yclopedia **O**f **D**NA **E**lements

modENCODE model organisms, C. elegans and D. melanogaster.

http://www.modencode.org

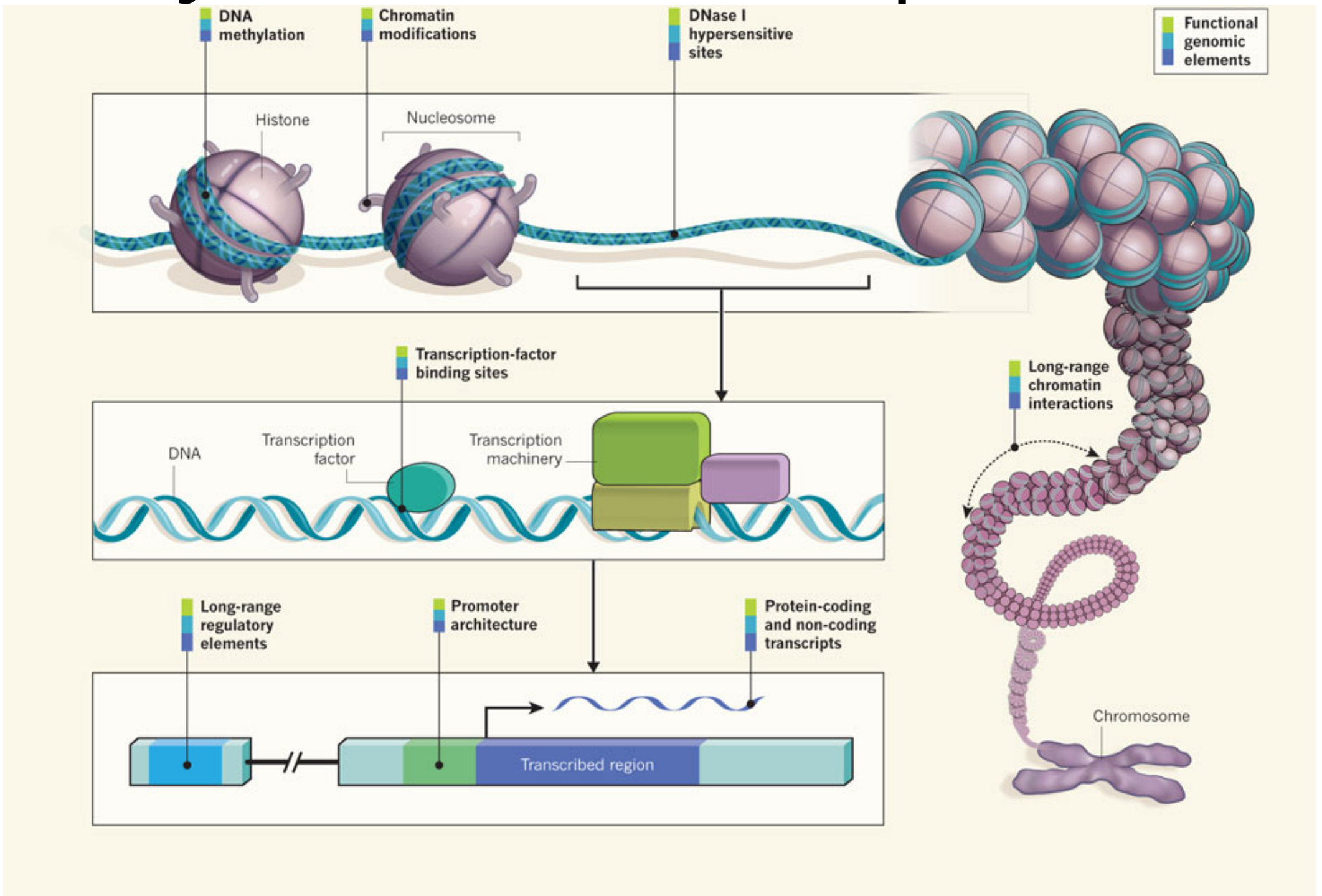
ENCODE: Encyclopedia of DNA Elements

Pilot phase

- 2003, National Human Genome Research Institute (NHGRI) introduction
- targeted 44 regions ~ 1% of human genome
- assembling a comprehensive encyclopedia of the functional elements in these regions showing their identity and precise location.

The ENCODE Project Consortium PLoS Biol 9(4): e1001046 (2011).
encodeproject.org

Beyond the Sequence



Ecker et al., *Nature* **489**, 52–55 (2012)

Beyond the Sequence

- Functional genomic elements that orchestrate the development and function of a human.
- Degree of DNA methylation
- Chemical modifications to histones
- Long-range chromatin interactions, (e.g. looping)
  - Alter the relative proximities of different chromosomal regions in 3 dimensions
  - Affect transcription.
- Binding activity of transcription-factor proteins
- Architecture (location & sequence) of gene-regulatory DNA elements
  - promoter region upstream of the point at which transcription of an RNA molecule begins
  - more distant (long-range) regulatory elements.

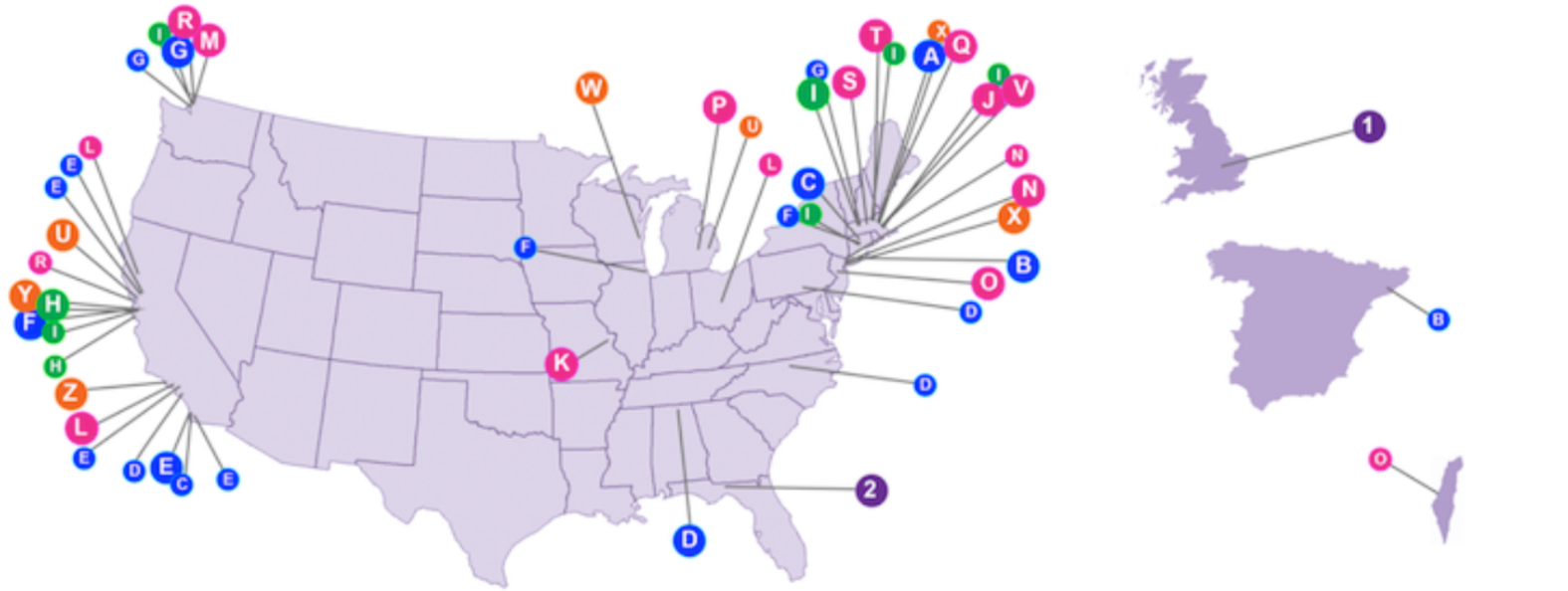
Ecker et al., *Nature* **489**, 52–55 (2012)

Beyond the Sequence

- Accessibility of the genome to the DNA-cleavage protein DNase I.
  - DNase I hypersensitive sites
    - indicate specific sequences at which the binding of transcription factors and transcription-machinery proteins has caused nucleosome displacement.
- Catalogues the sequences and quantities of RNA transcripts
  - non-coding regions
  - protein-coding regions.

Ecker et al., *Nature* **489**, 52–55 (2012)

ENCODE: Encyclopedia of DNA Elements



Production Groups

- **A** Broad Institute
- **B** Cold Spring Harbor; Centre for Genomic Regulation (CRG);
- **C** University of Connecticut Health Center; UCSD
- **D** HudsonAlpha; Pennsylvania State; UC Irvine; Duke; Caltech
- **E** UCSD; Salk Institute ; Joint Genome Institute; Lawrence Berkeley National Laboratory; UCSD
- **F** Stanford; University of Chicago; Yale
- **G** University of Washington; Fred Hutchinson Cancer Research Center; University of Massachusetts Medical School

Data Coordination Center

- **H** Stanford; UCSC

Data Analysis Center

- **I** University of Massachusetts Medical School; Yale; MIT; Stanford; Harvard; University of Washington

Technology Development Groups

- **J** MIT
- **K** Washington University, St. Louis
- **L** USC; Ohio State University; UC, Davis
- **M** University of Washington
- **N** Sloan-Kettering; Weill Cornell Medical College
- **O** Princeton; Weizmann
- **P** University of Michigan
- **Q** Broad Institute
- **R** University of Washington; UCSF
- **S** Advanced RNA Technologies, LLC
- **T** Harvard

Computational Analysis Groups

- **U** Berkeley; Wayne State University
- **V** MIT
- **W** University of Wisconsin
- **X** Sloan-Kettering; Broad Institute
- **Y** Stanford
- **Z** UCLA

Affiliated Groups

- **1** Wellcome Trust Sanger Institute
- **2** Florida State University

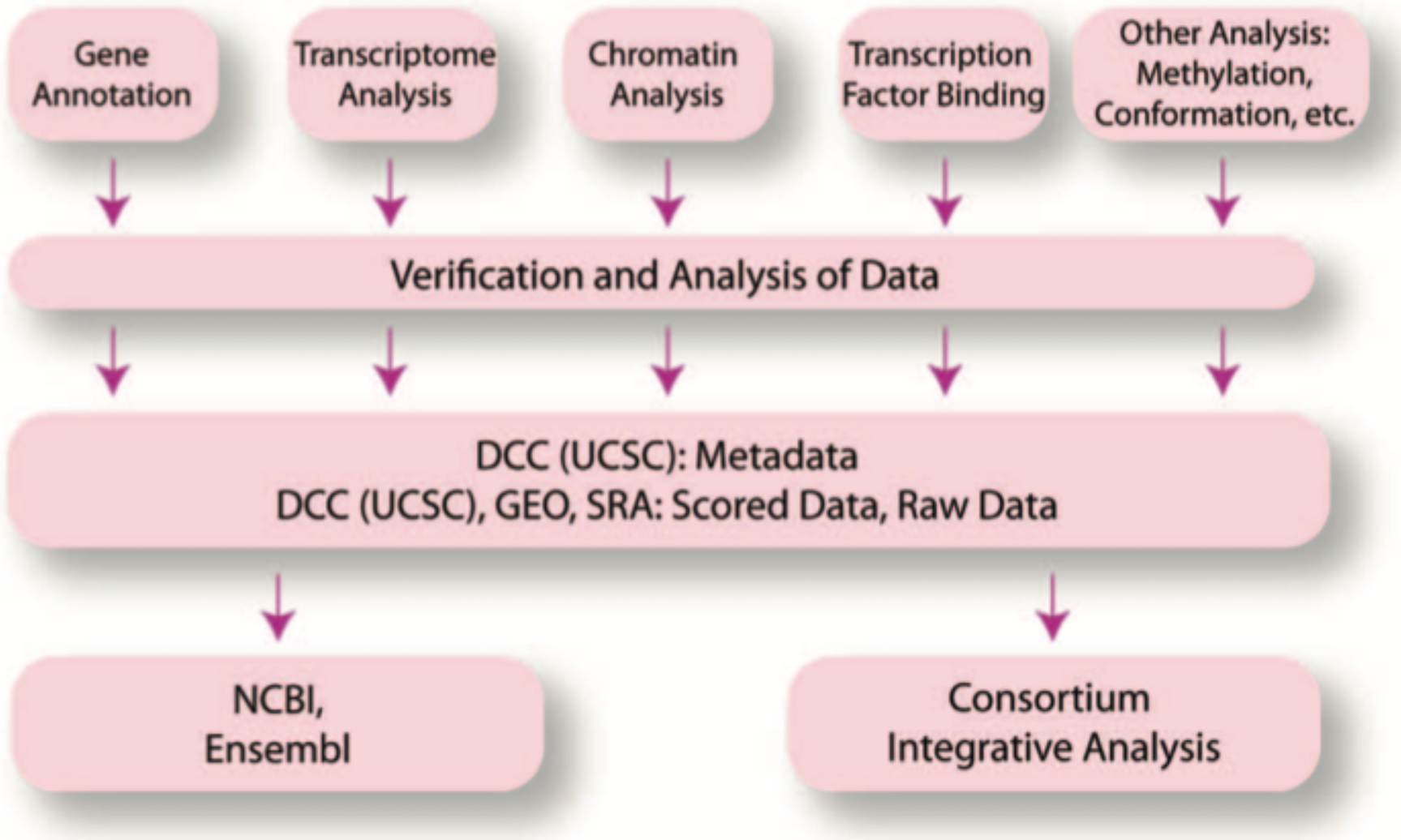
The ENCODE Project Consortium PLoS Biol 9(4): e1001046 (2011).

encodeproject.org

ENCODE: Encyclopedia of DNA Elements

Data Production

Data Storage & Access



The ENCODE Project Consortium PLoS Biol 9(4): e1001046 (2011).
encodeproject.org

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EXPERIMENTAL TARGETS

- **DNA methylation**: regions layered with chemical methyl groups, which regulate gene expression.
- **Open chromatin**: areas in which the DNA and proteins that make up chromatin are accessible to regulatory proteins.
- **RNA binding**: positions where regulatory proteins attach to RNA.
- **RNA sequences**: regions that are transcribed into RNA.
- **ChIP-seq**: technique that reveals where proteins bind to DNA.
- **Modified histones**: histone proteins, which package DNA into chromosomes, modified by chemical marks.
- **Transcription factors**: proteins that bind to DNA and regulate transcription.

Maher, Nature 489, p. 46 (2012).

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- **CELL LINES**
- **Tiers 1 and 2:** widely used cell lines prioritized.
  - Tier 1. Highest-priority. 3 widely studied cell lines:
    - K562 erythroleukaemia cells
    - GM12878, a B-lymphoblastoid cell line (also in1000 Genomes project)
    - H1 embryonic stem cell (H1 hESC) line.
  - Tier 2. The second-priority. Include
    - HeLa-S3 cervical carcinoma cells
    - HepG2 hepatoblastoma cells
    - Primary (non-transformed) human umbilical vein endothelial cells (HUVECs).
- **Tier 3:** all other ENCODE cell types.

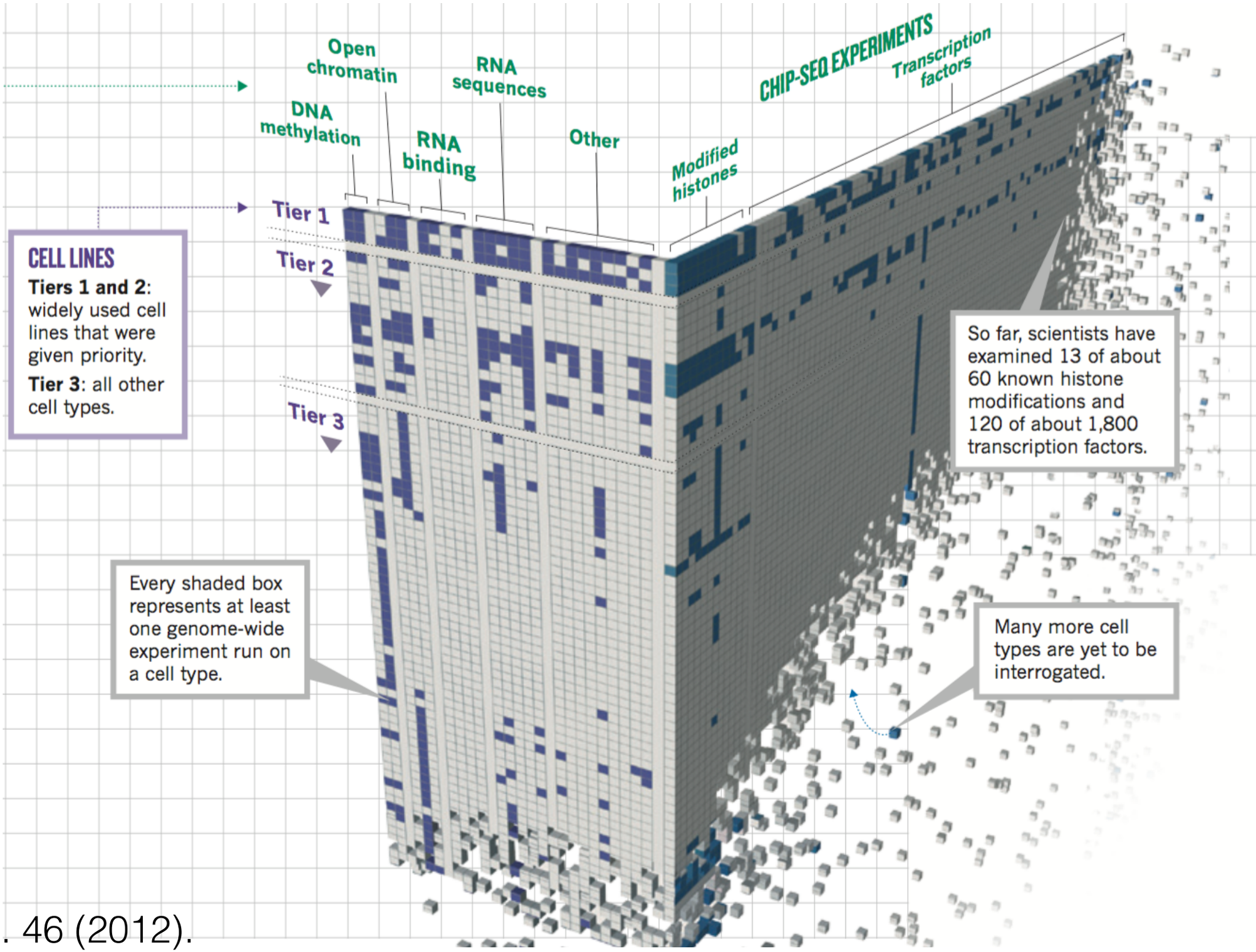
The ENCODE Project Consortium, Nature 489:57-74 (2012)

ENCODE

2012
Publication:

24 experiment types

> 150 cell lines



Maher, Nature 489, p. 46 (2012).

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- **RNA-seq.** Isolation of RNA sequences, often with different purification techniques to isolate different fractions of RNA followed by high-throughput sequencing.
- **CAGE.** Cap analysis gene expression.
  - Capture of the methylated cap at the 5’ end of RNA
  - High-throughput sequencing of a small tag adjacent to the 5’ methylated caps.
  - 5’ methylated caps are formed at the initiation of transcription, although other mechanisms also methylate 5’ ends of RNA.
- **RNA-PET.** RNA-paired end tag (PET).
  - Simultaneous capture of RNAs with both a 5’ methyl cap and a poly(A) tail, indicative of a full-length RNA.
  - High-throughput sequencing a short tag from each end.

The ENCODE Project Consortium, Nature 489:57-74 (2012)

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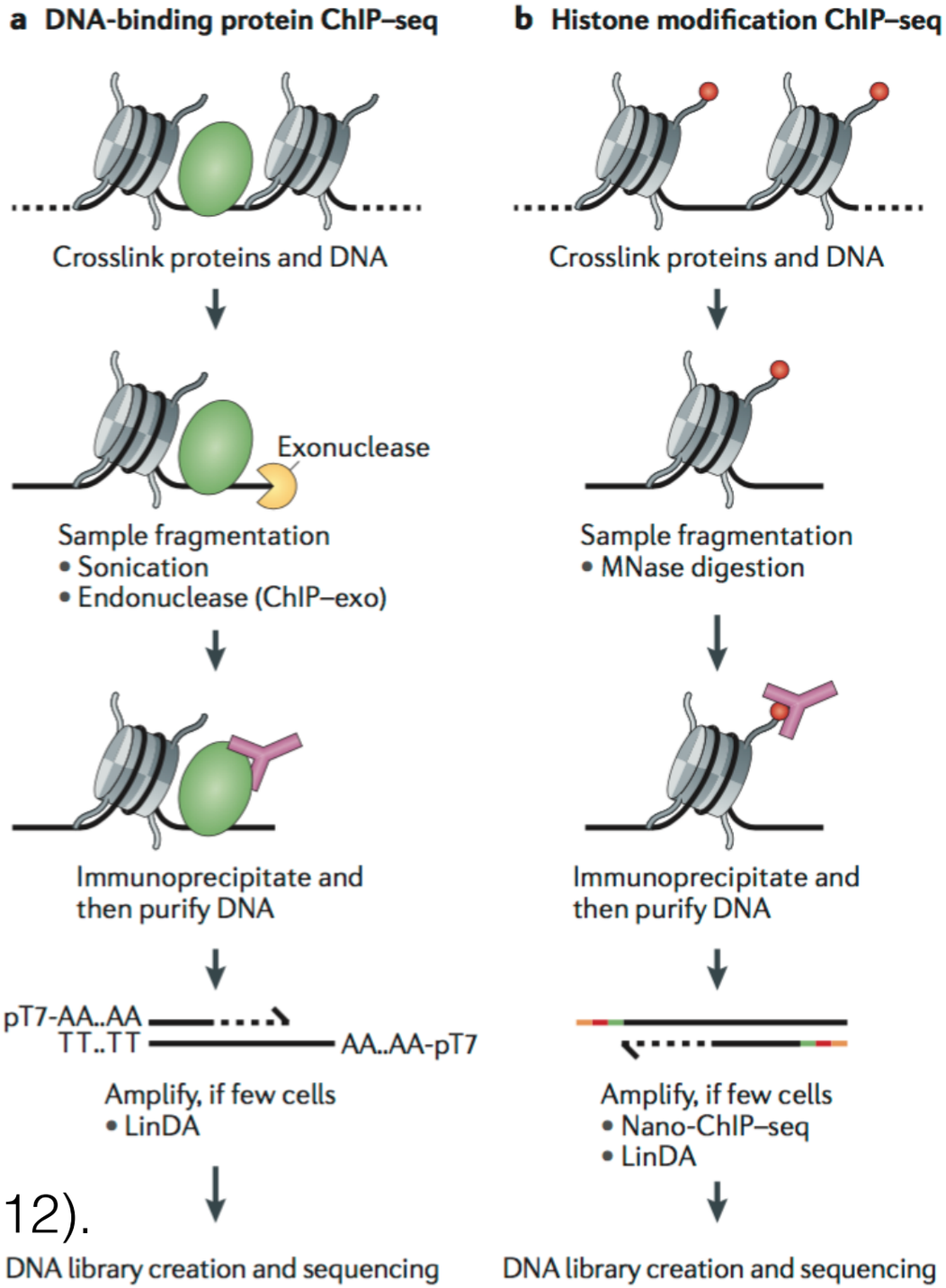
- **ChIP-seq.** Chromatin immunoprecipitation followed by sequencing.
  - Specific regions of crosslinked chromatin (genomic DNA in complex with its bound proteins) selected by antibody to a specific epitope.
  - High-throughput sequencing enriched sample to determine the regions in the genome most often bound by the protein to which the antibody was directed.
  - Most often used are antibodies to any chromatin-associated epitope, including
    - transcription factors
    - chromatin binding proteins
    - specific chemical modifications on histone proteins.



The ENCODE Project Consortium, Nature 489:57-74 (2012).
Furey, Nature Reviews Genetics 13, 840-852 (2012).

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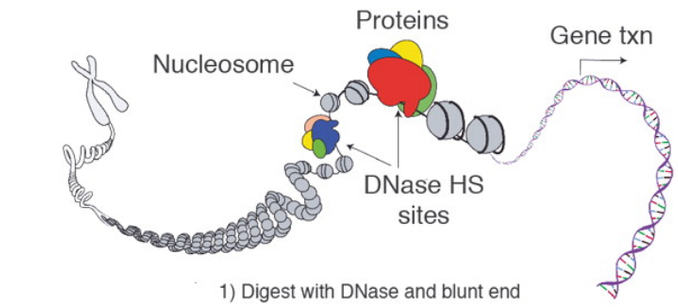
- **DNase-seq.** Adaption of established regulatory sequence assay to modern techniques.
  - The DNase I enzyme will preferentially cut live chromatin preparations at sites where nearby there are specific (non-histone) proteins.
  - Resulting cut points are then sequenced using high-throughput sequencing to determine those sites ‘hypersensitive’ to DNase I, corresponding to open chromatin.



The ENCODE Project Consortium, Nature 489:57-74 (2012).
Song, Lingyun & Crawford. Cold Spring Harbor protocols 2010.2 (2010): pdb.prot5384.

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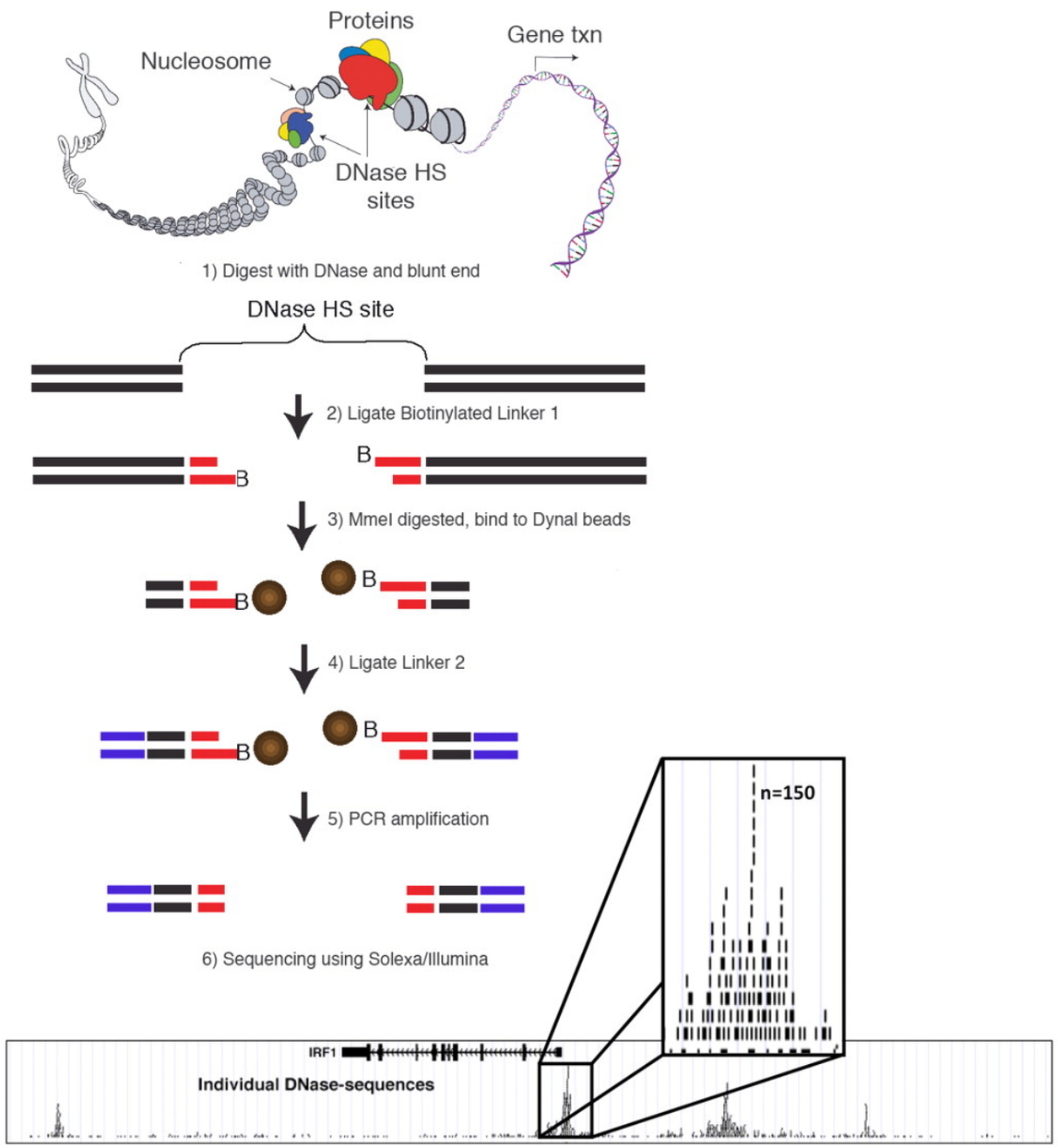
- **DNase-seq protocol**
  - nuclei are digested with DNase I.
  - digested DNA embedded in low-melt gel agarose plugs to reduce additional random shearing
  - DNA (while still in the plugs) is blunt-ended, extracted, & ligated to biotinylated linker 1 (red).
  - Excess linker removed by gel purification.
  - Biotinylated fragments digested with MmeI and captured by streptavidin-coated Dynal beads (brown balls).
  - Linker 2 (blue bars) ligated to the 2-base overhang generated by MmeI
  - Ditagged DNAs amplified by PCR and sequenced



Song, Lingyun & Crawford. Cold Spring Harbor protocols 2010.2 (2010): pdb.prot5384

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- **FAIRE-seq.** Formaldehyde assisted isolation of regulatory elements.
  - FAIRE isolates nucleosome-depleted genomic regions by exploiting the difference in crosslinking efficiency between nucleosomes (high) and sequence-specific regulatory factors (low).
  - FAIRE consists of crosslinking, phenol extraction, and sequencing the DNA fragments in the aqueous phase.
- **RRBS.** Reduced representation bisulphite sequencing.
  - Bisulphite treatment of DNA sequence converts unmethylated cytosines to uracil.
  - To focus the assay and save costs, specific restriction enzymes that cut around CpG dinucleotides can reduce the genome to a portion specifically enriched in CpGs.
  - Enriched sample is then sequenced to determine the methylation status of individual cytosines quantitatively.

The ENCODE Project Consortium, Nature 489:57-74 (2012).

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Summary of Transcription Factor Classes Analyzed

Acronym	Description	Factors analysed
ChromRem	ATP-dependent chromatin complexes	5
DNARep	DNA repair	3
HISase	Histone acetylation, deacetylation or methylation complexes	8
Other	Cyclin kinase associated with transcription	1
Pol2	Pol II subunit	1 (2 forms)
Pol3	Pol III-associated	6
TFNS	General Pol II-associated factor, not site-specific	8
TFSS	Pol II transcription factor with sequence-specific DNA binding	87

The ENCODE Project Consortium, Nature 489:57-74 (2012).

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Histone Modifications and Variants

Histone modification or variant	Signal characteristics	Putative functions
H2A.Z	Peak	Histone protein variant (H2A.Z) associated with regulatory elements with dynamic chromatin
H3K4me1	Peak/region	Mark of regulatory elements associated with enhancers and other distal elements, but also enriched downstream of transcription starts
H3K4me2	Peak	Mark of regulatory elements associated with promoters and enhancers
H3K4me3	Peak	Mark of regulatory elements primarily associated with promoters/transcription starts
H3K9ac	Peak	Mark of active regulatory elements with preference for promoters
H3K9me1	Region	Preference for the 5′ end of genes
H3K9me3	Peak/region	Repressive mark associated with constitutive heterochromatin and repetitive elements
H3K27ac	Peak	Mark of active regulatory elements; may distinguish active enhancers and promoters from their inactive counterparts
H3K27me3	Region	Repressive mark established by polycomb complex activity associated with repressive domains and silent developmental genes
H3K36me3	Region	Elongation mark associated with transcribed portions of genes, with preference for 3′ regions after intron 1
H3K79me2	Region	Transcription-associated mark, with preference for 5′ end of genes
H4K20me1	Region	Preference for 5′ end of genes

The ENCODE Project Consortium, Nature 489:57-74 (2012).

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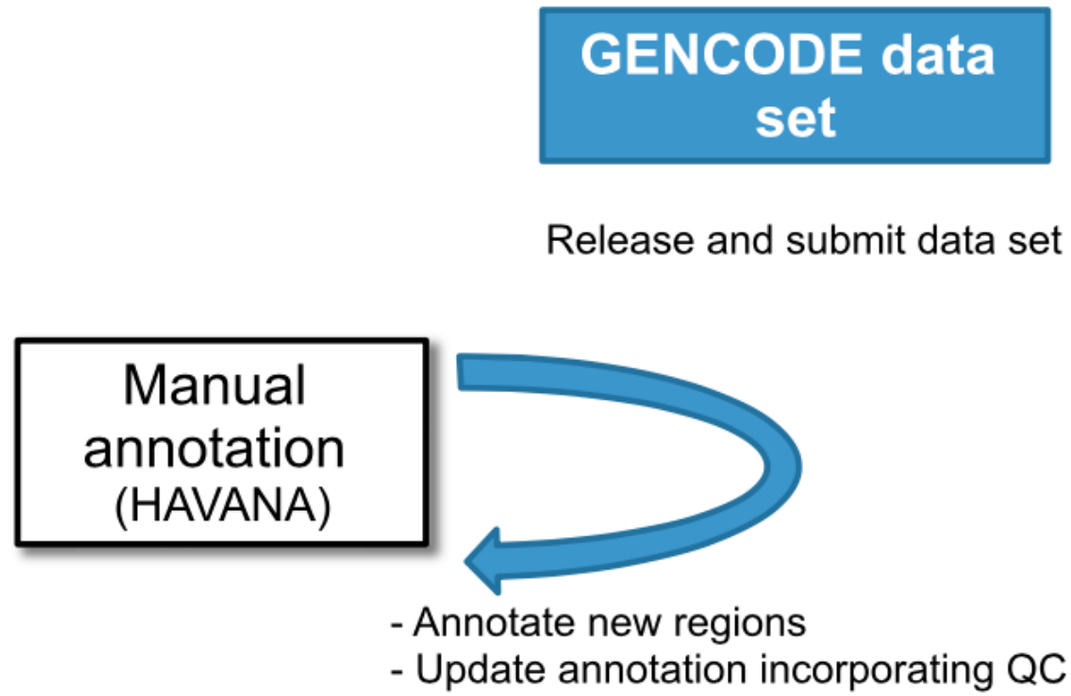
GENCODE: The reference human genome annotation for The ENCODE Project



Harrow et al., Genome Res. 22:1760-1774 (2012)

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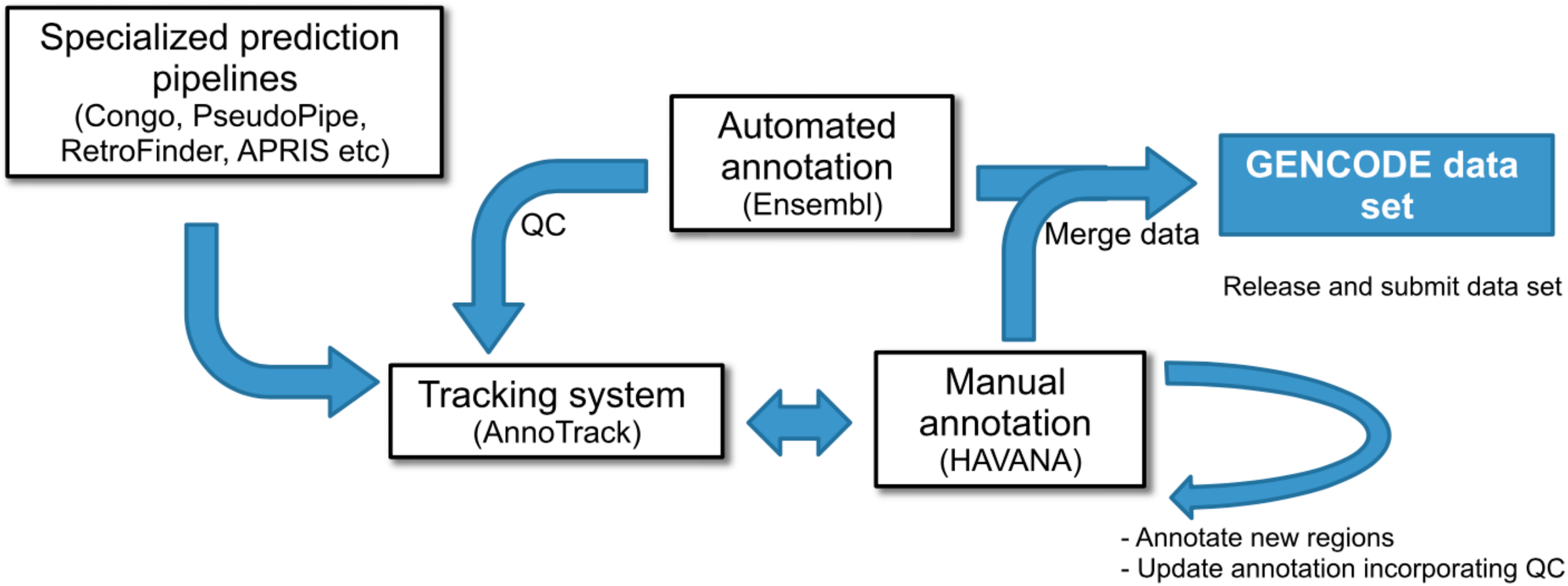

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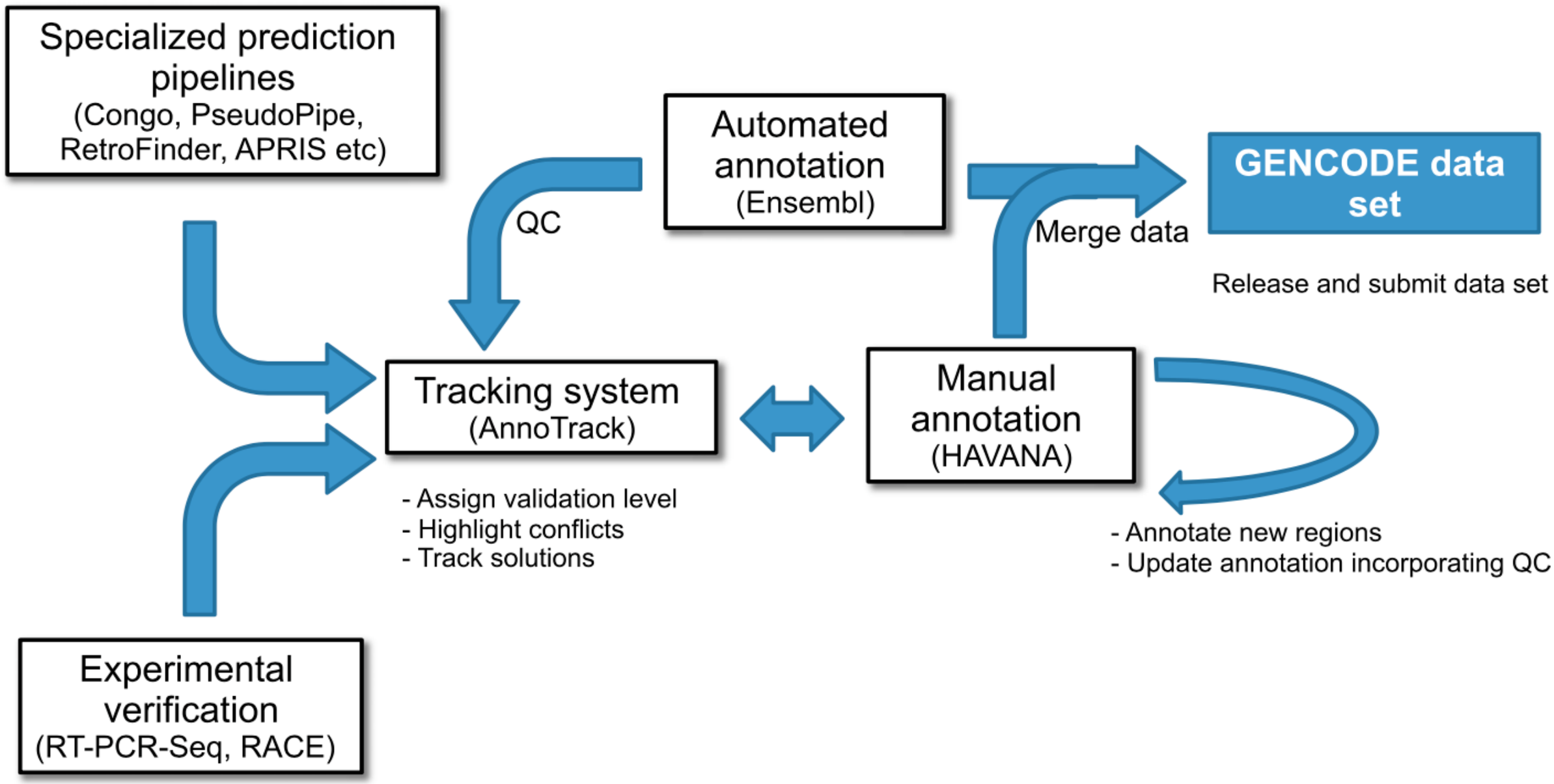

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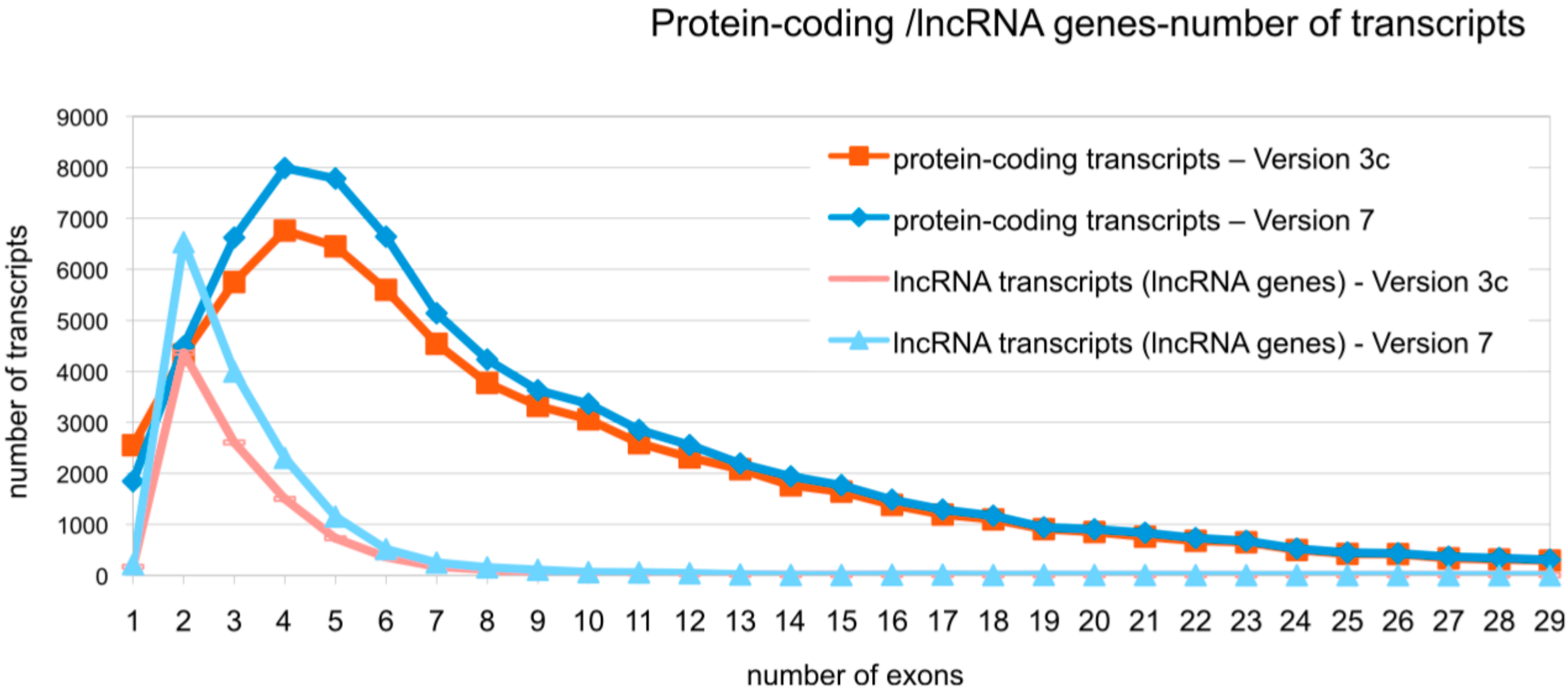

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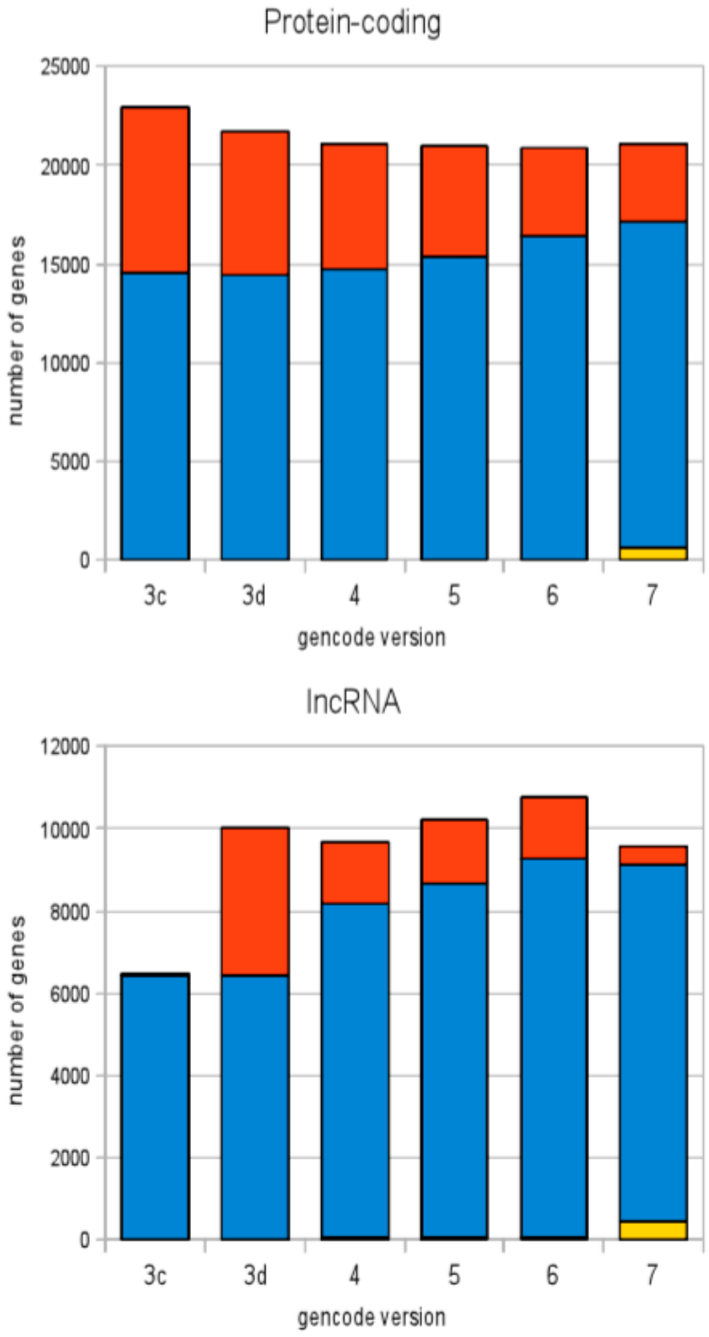


- **Level 3 (automatically annotated)**
- **Level 2 (manually annotated)**
- **Level 1 (validated)**

Harrow et al., Genome Res. 22:1760-1774 (2012)

ENCODE

Findings

- Large amount of human genome, 80.4%, is covered by at least one ENCODE-identified element
  - Different RNA types, covering 62% of the genome (although the majority is inside of introns or near genes).
  - Regions highly enriched for histone modifications (56.1%).
  - Excluding RNA elements and broad histone elements, 44.2% of the genome is covered.
    - Regions of open chromatin (15.2%)
    - Sites of transcription factor binding (8.1%)
      - with 19.4% covered by at least one DHS or transcription factor ChIP-seq peak across all cell lines.
  - 8.5% of bases are covered by either
    - a transcription-factor-binding-site motif (4.6%)
    - or a DHS footprint (5.7%).

The ENCODE Project Consortium, Nature 489:57-74 (2012).

ENCODE

Findings

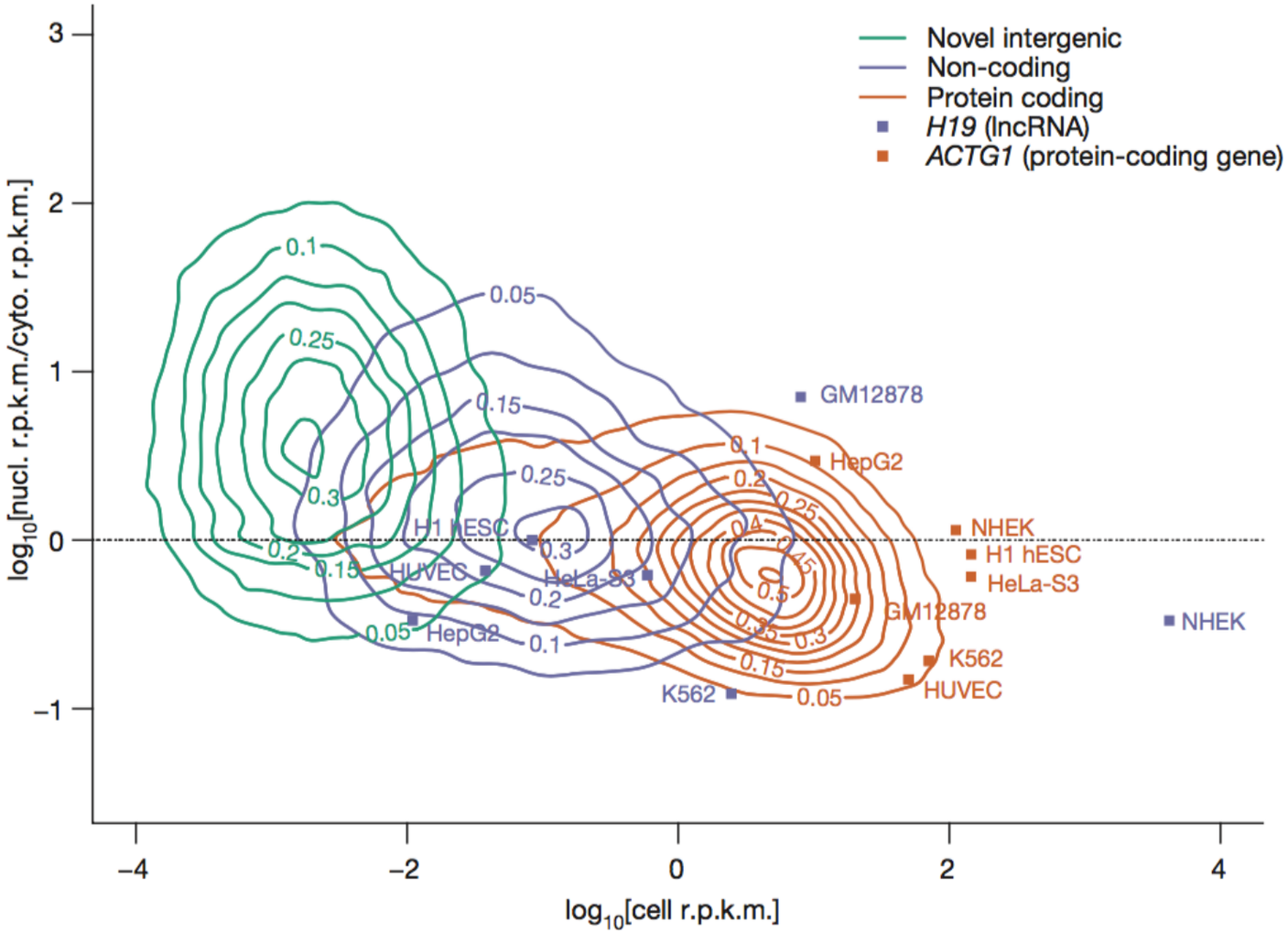
- ENCODE project did not assay all cell types, or all transcription factors.
- It sampled few specialized or developmentally restricted cell lineages.
- Are these proportions underestimates of the total amount of functional bases?

The ENCODE Project Consortium, Nature 489:57-74 (2012).

ENCODE

RNA

- 15 Cell lines
  - RNA-Seq, RNA-PET, CAGE
  - polyadenylated RNAs (polyA+)
  - non-polyadenylated RNAs (polyA-)
- Observed range of gene expression spans
  - 6 orders of magnitude for polyA + (10^{-2} -10^{4} reads per kilobase per million reads [r.p.k.m.])
  - 5 orders of magnitude (from 10^{-2} - 10^{3} r.p.k.m.) for polyA-

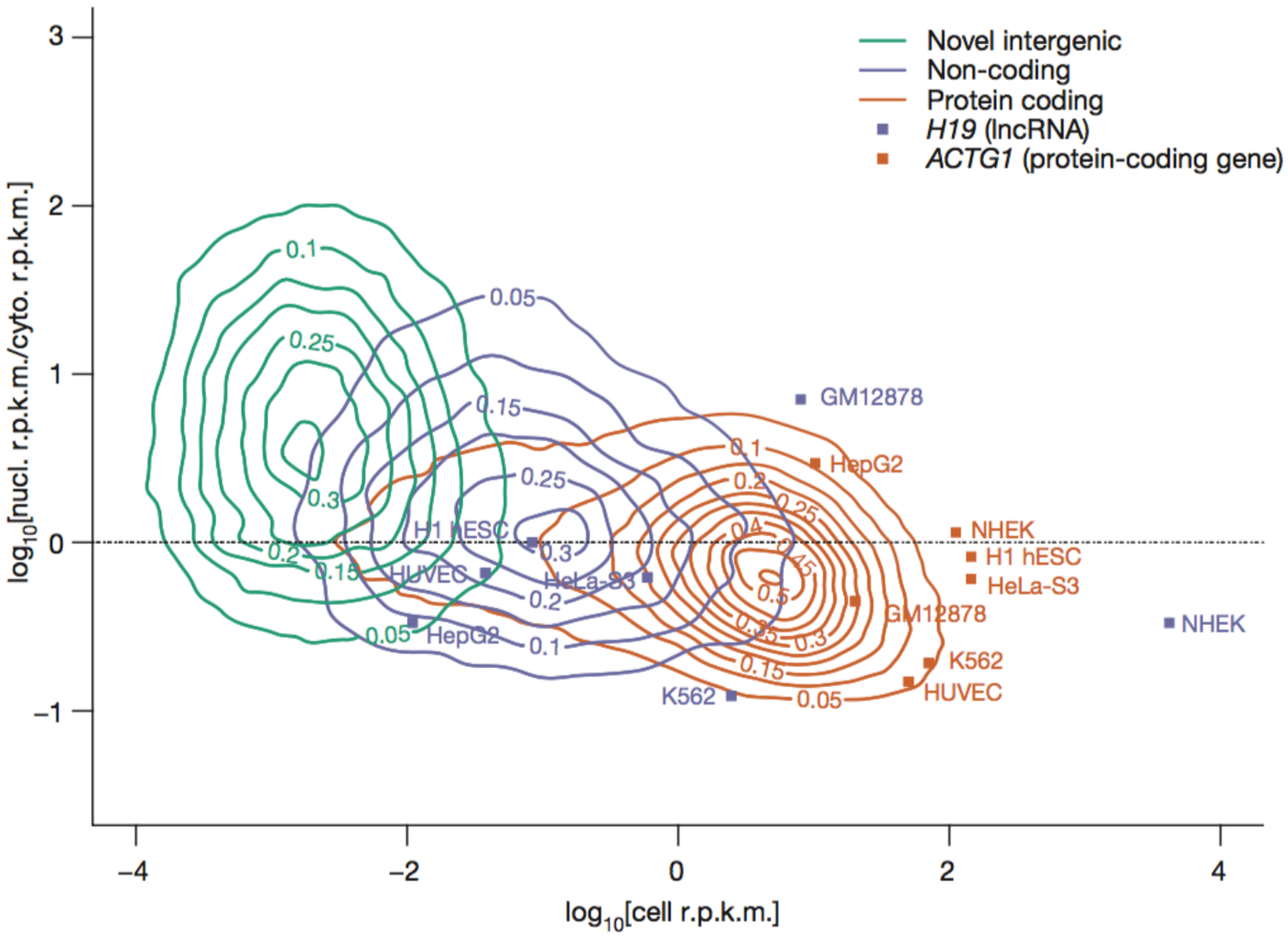


Djebali et al., Nature 489:101-108 (2012).
The ENCODE Project Consortium, Nature 489:57-74 (2012).

ENCODE

RNA

- Average Expression < 1 molecule/ cell (assuming 1-4 RPKM approximates to 1 molecule/ cell) for
  - ~ 25% of protein-coding RNAs (orange)
  - ~ 80% of lncRNAs (blue)
- Novel antisense and intergenic genes predicted in this study expression ranging from 10^{-4} to 10^{-1} r.p.k.m.



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The ENCODE Project Consortium, Nature 489:57-74 (2012).

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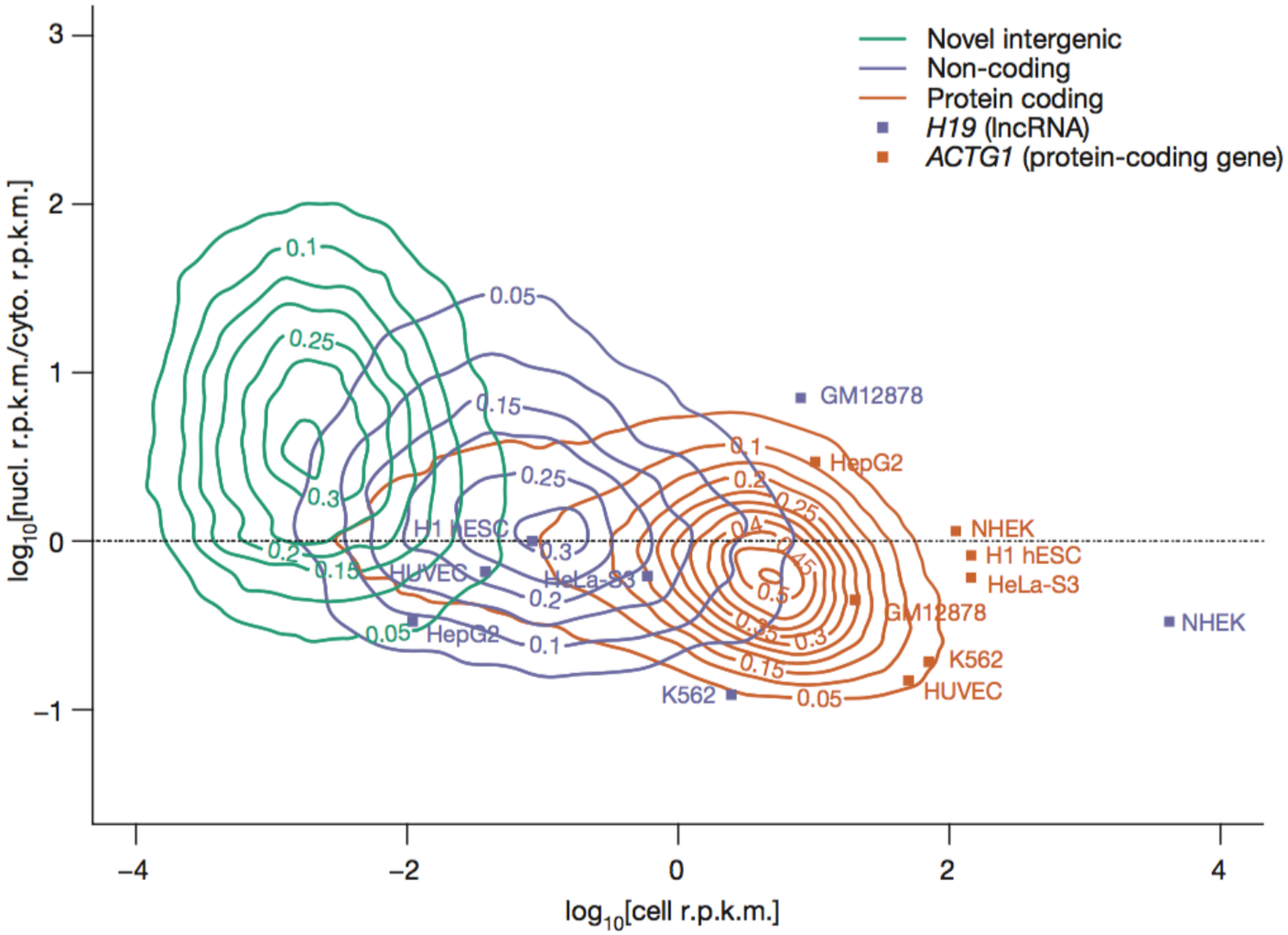
RNA

- Lower levels of gene expression in lncRNAs may be due to
  - consistent low RNA copy number in all cells within the population interrogated
  - restricted expression in only a subpopulation of cells.
- In some cell lines, individual lncRNAs can exhibit steady-state expression levels as high as those of protein-coding genes. E.g.:
  - protein-coding gene actin, gamma 1 (ACTG1)
  - non-coding gene, H19.



Djebali et al., Nature 489:101-108 (2012).
The ENCODE Project Consortium, Nature 489:57-74 (2012).

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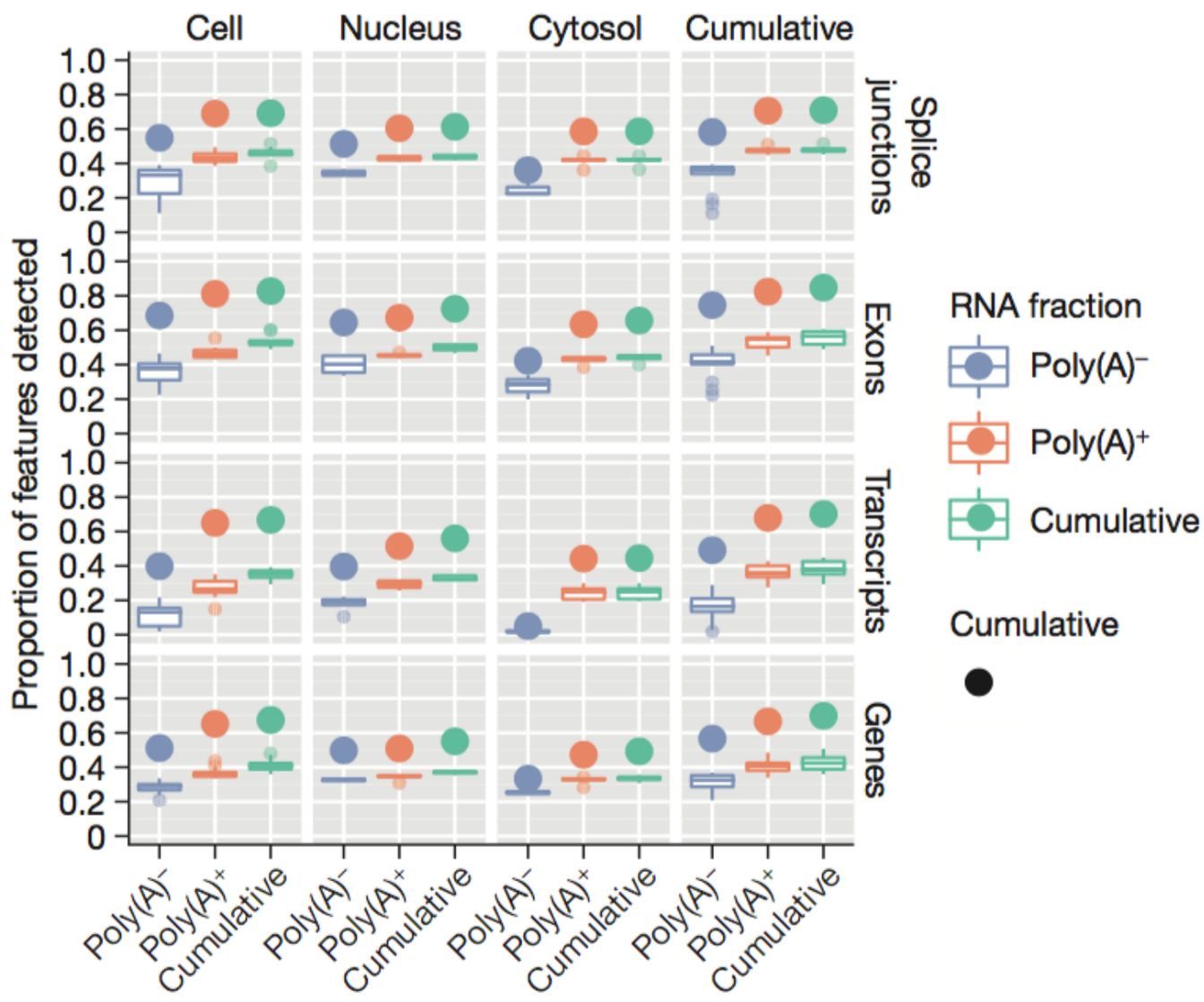
RNA

- Cumulatively detection of 70% of annotated splice junctions, transcripts & genes
- Detected approximately 85% of annotated exons with an average coverage by RNA-seq contigs of 96%.



Djebali et al., Nature 489:101-108 (2012).
The ENCODE Project Consortium, Nature 489:57-74 (2012).

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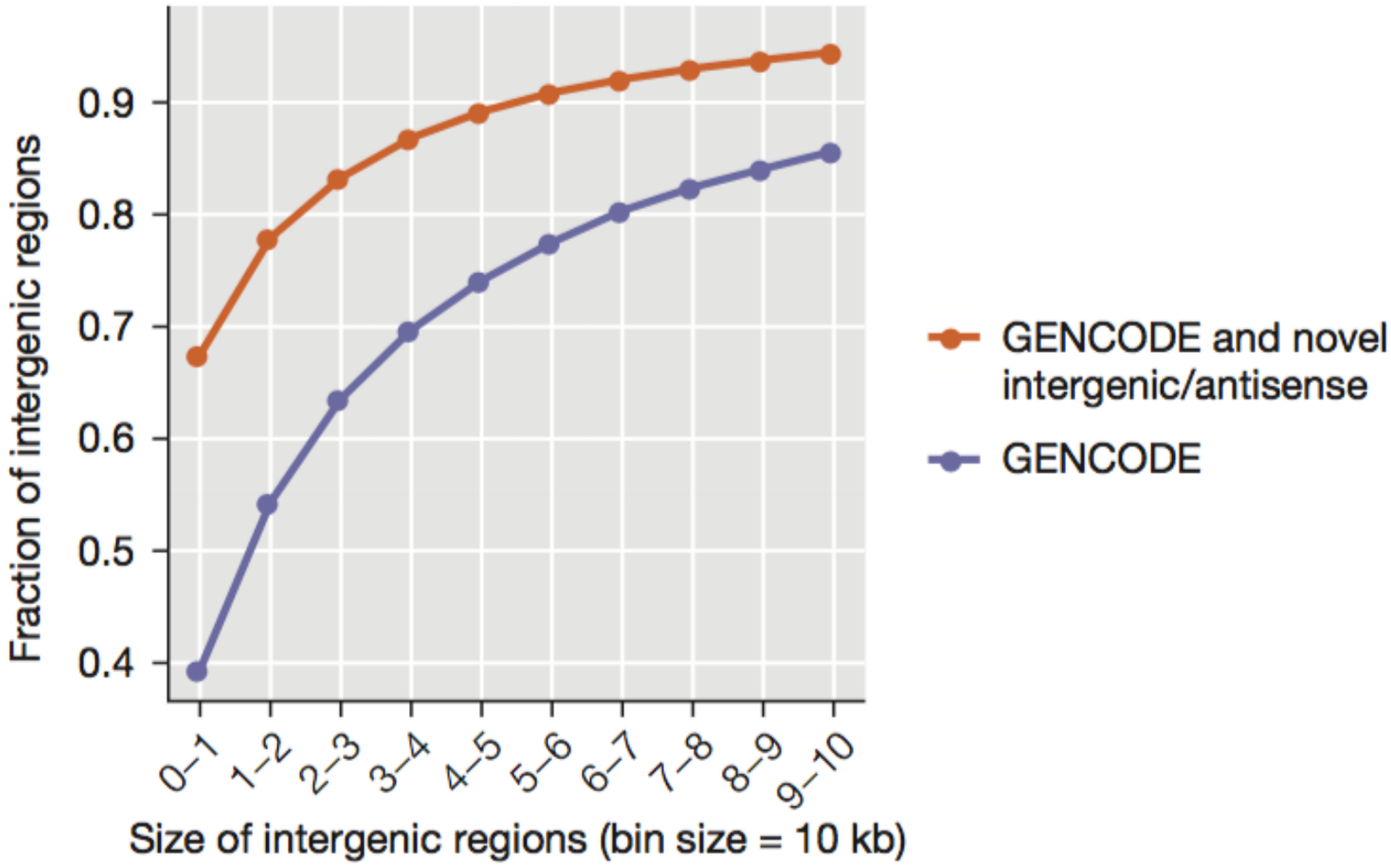
RNA

- Expansion of genic regions
  - discovery of new isoforms identification of novel intergenic transcripts
- Increase in the number of intergenic regions (from 32,481 to 60,250) due to
  - their fragmentation
  - a decrease in their lengths (from 14,170 bp to 3,949 bp median length).



Djebali et al., Nature 489:101-108 (2012).
The ENCODE Project Consortium, Nature 489:57-74 (2012).

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RNA

Increased overlap of genic regions.

- Determination of genic regions currently defined by
  - Cumulative lengths of the isoforms
  - Their genetic association to phenotypic characteristics.
- Continued reduction in the lengths of intergenic regions will lead to the overlap of most genes previously assumed to be distinct genetic loci.
- **Reconsideration of the definition of a gene.** Proposition:
  - The transcript as the basic atomic unit of inheritance.
  - Gene to denote a higher-order concept intended to capture all those transcripts (eventually divorced from their genomic locations) that contribute to a given phenotypic trait.

Djebali et al., Nature 489:101-108 (2012).
The ENCODE Project Consortium, Nature 489:57-74 (2012).

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7 combined Chromatin States across the Genome

Table 3 | Summary of the combined state types

Label	Description	Details*	Colour
CTCF	CTCF-enriched element	Sites of CTCF signal lacking histone modifications, often associated with open chromatin. Many probably have a function in insulator assays, but because of the multifunctional nature of CTCF, we are conservative in our description. Also enriched for the cohesin components RAD21 and SMC3; CTCF is known to recruit the cohesin complex.	Turquoise
E	Predicted enhancer	Regions of open chromatin associated with H3K4me1 signal. Enriched for other enhancer-associated marks, including transcription factors known to act at enhancers. In enhancer assays, many of these (>50%) function as enhancers. A more conservative alternative would be *cis*-regulatory regions. Enriched for sites for the proteins encoded by *EP300*, *FOS*, *FOSL1*, *GATA2*, *HDAC8*, *JUNB*, *JUND*, *NFE2*, *SMARCA4*, *SMARCB1*, *SIRT6* and *TAL1* genes in K562 cells. Have nuclear and whole-cell RNA signal, particularly poly(A)− fraction.	Orange
PF	Predicted promoter flanking region	Regions that generally surround TSS segments (see below).	Light red
R	Predicted repressed or low-activity region	This is a merged state that includes H3K27me3 polycomb-enriched regions, along with regions that are silent in terms of observed signal for the input assays to the segmentations (low or no signal). They may have other signals (for example, RNA, not in the segmentation input data). Enriched for sites for the proteins encoded by *REST* and some other factors (for example, proteins encoded by *BRF2*, *CEBPB*, *MAFK*, *TRIM28*, *ZNF274* and *SETDB1* genes in K562 cells).	Grey
TSS	Predicted promoter region including TSS	Found close to or overlapping GENCODE TSS sites. High precision/recall for TSSs. Enriched for H3K4me3. Sites of open chromatin. Enriched for transcription factors known to act close to promoters and polymerases Pol II and Pol III. Short RNAs are most enriched in these segments.	Bright red
T	Predicted transcribed region	Overlap gene bodies with H3K36me3 transcriptional elongation signal. Enriched for phosphorylated form of Pol II signal (elongating polymerase) and poly(A)$^+$ RNA, especially cytoplasmic.	Dark green
WE	Predicted weak enhancer or open chromatin *cis*-regulatory element	Similar to the E state, but weaker signals and weaker enrichments.	Yellow

* Where specific enrichments or overlaps are identified, these are derived from analysis in GM12878 and/or K562 cells where the data for comparison is richest. The colours indicated are used in Figs 5 and 7 and in display of these tracks from the ENCODE data hub.

The ENCODE Project Consortium, Nature 489:57-74 (2012).

ENCODE

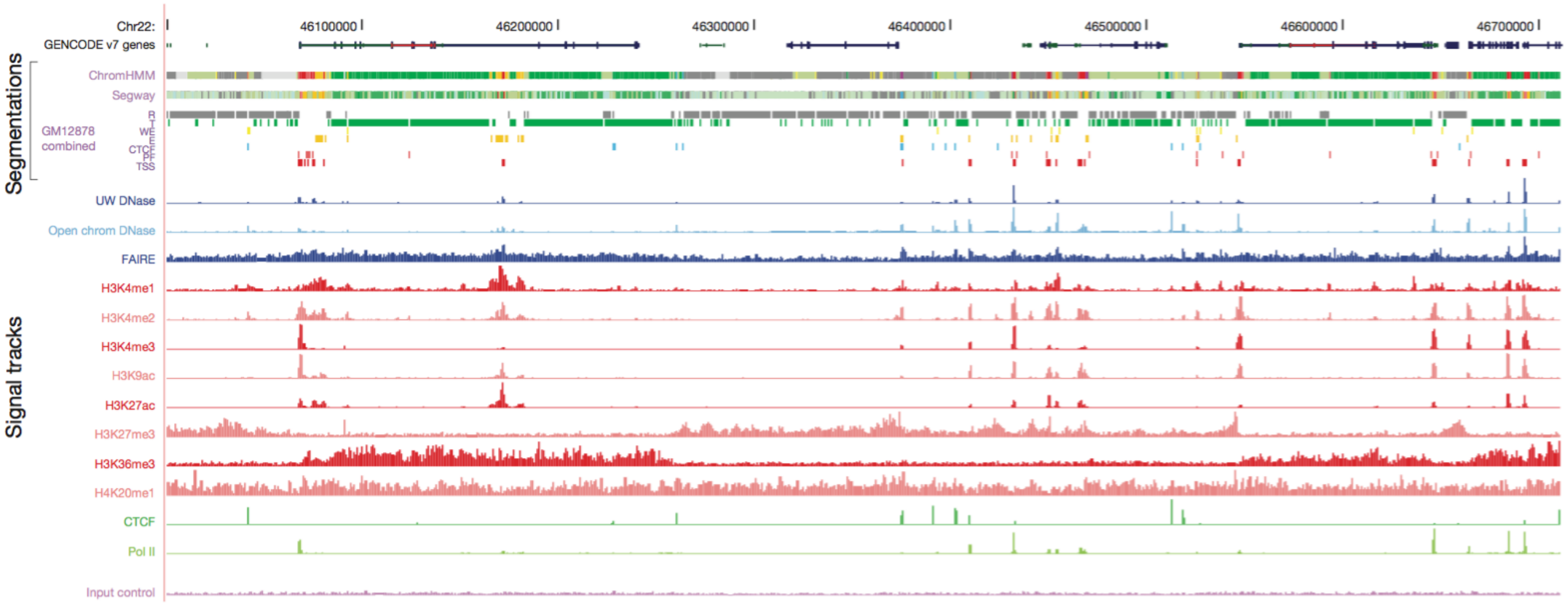
7 combined Chromatin States across the Genome

- Distinct core promoter region
  - TSS (Predicted promoter region containing TSS)
  - PF (Promoter flanking region)
- Active gene bodies
  - T, (Predicted transcribed region)
- 3 ‘active’ distal states.

  Two enhancer states. Occurrence in regions of open chromatin with high H3K4me1 differ in the levels of marks such as H3K27ac, (active vs inactive enhancers).
  - E (Predicted enhancers)
  - WE (Predicted weak enhancers)
  - CTCF-enriched region
    - High CTCF binding includes sequences that function as insulators in a transfect assay.
- R, repressed state (R) summarizes sequences split between different classes of actively repressed or inactive, quiescent chromatin.

The ENCODE Project Consortium, Nature 489:57-74 (2012).

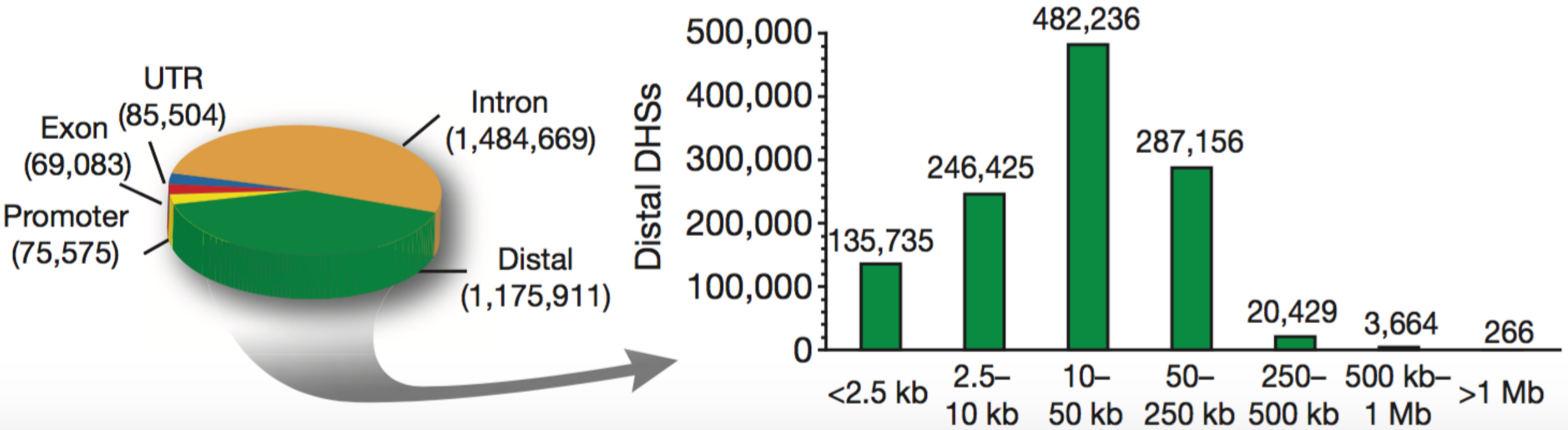
ENCODE



GM12878 cells example & compressed view of GENCODE annotations.

The ENCODE Project Consortium, Nature 489:57-74 (2012).

ENCODE



2,890,742 DHSs

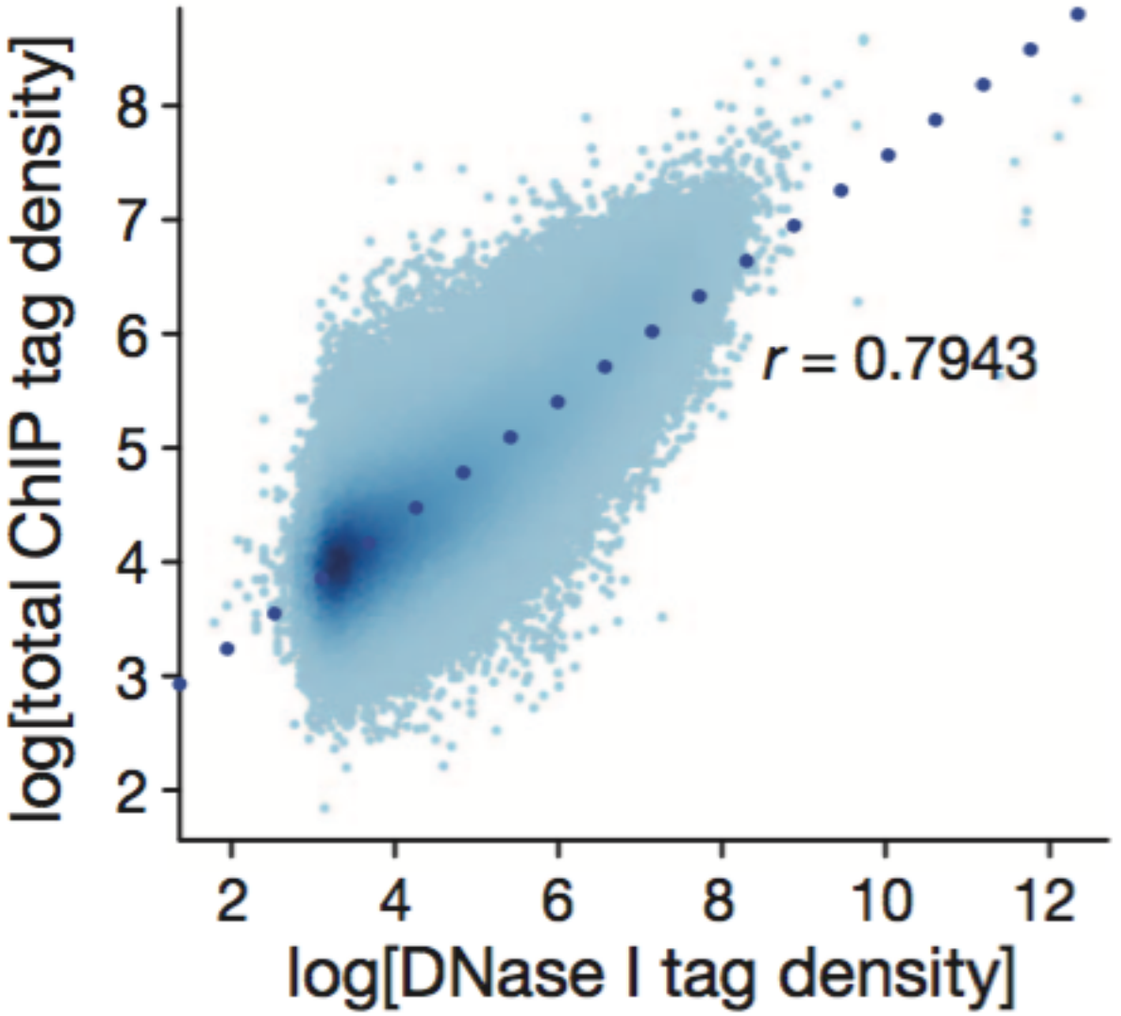
Promoter DHSs defined as the first DHS localizing within 1 kb upstream of a GENCODE TSS.

Distribution of intergenic DHSs relative to Gencode

Thurman et al., Nature 489:75-82 (2012).

ENCODE

- 42 transcription factors mapped by ENCODE ChIP-seq in K562 cells.
- Genome-wide correlation (r=0.7943) between ChIP-seq and DNase I tag densities (log10).



Thurman et al., Nature 489:75-82 (2012).

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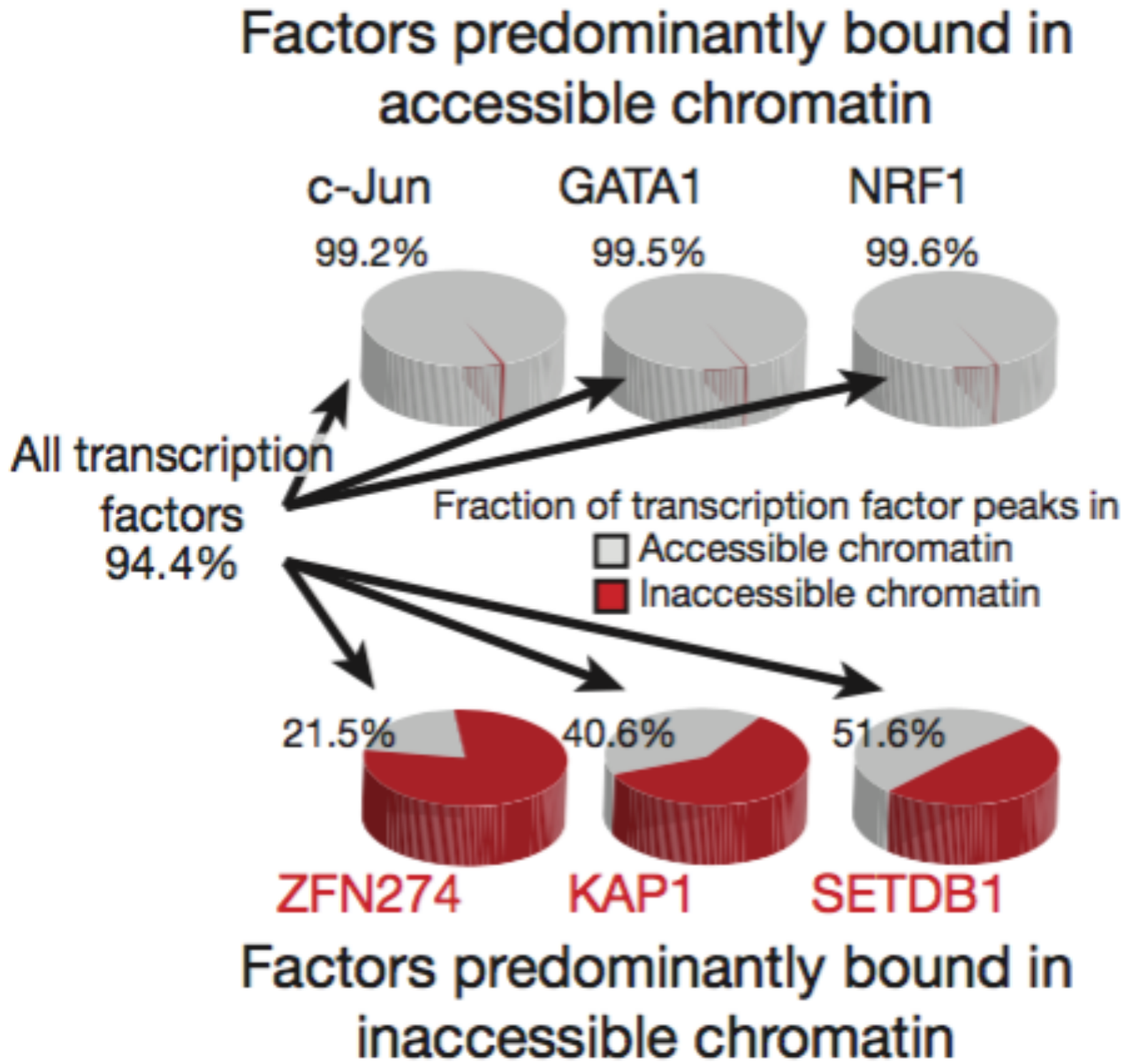
94.4% of combined 1,108,081 ChIP-seq peaks from all transcription factors assayed in K562 cells fall within accessible chromatin regions (grey).

[median factor 98.2% of its binding sites]

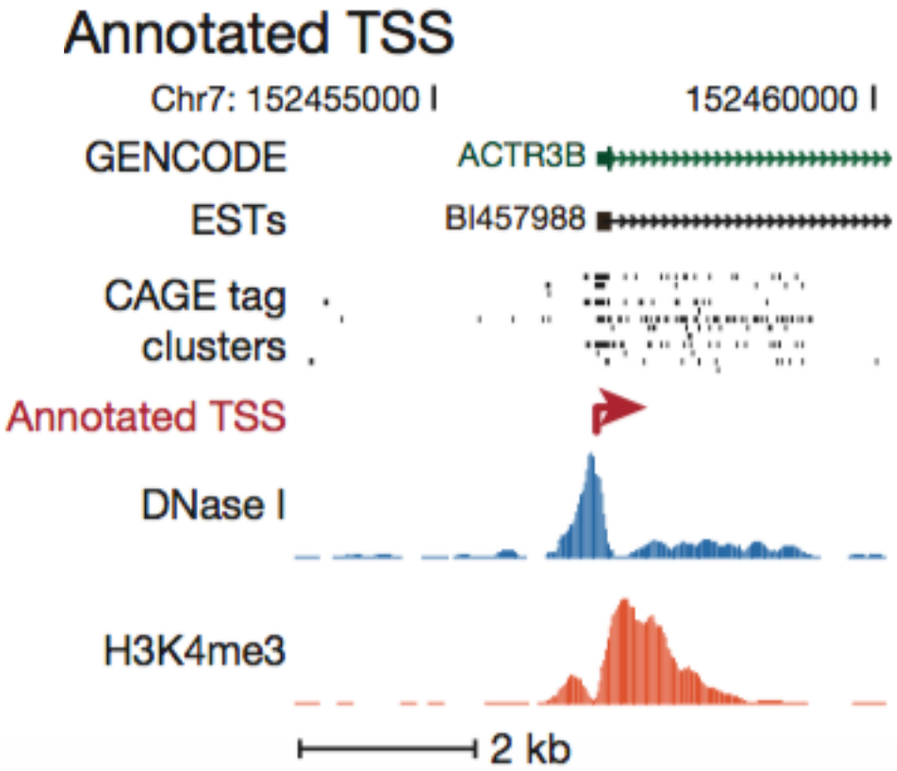


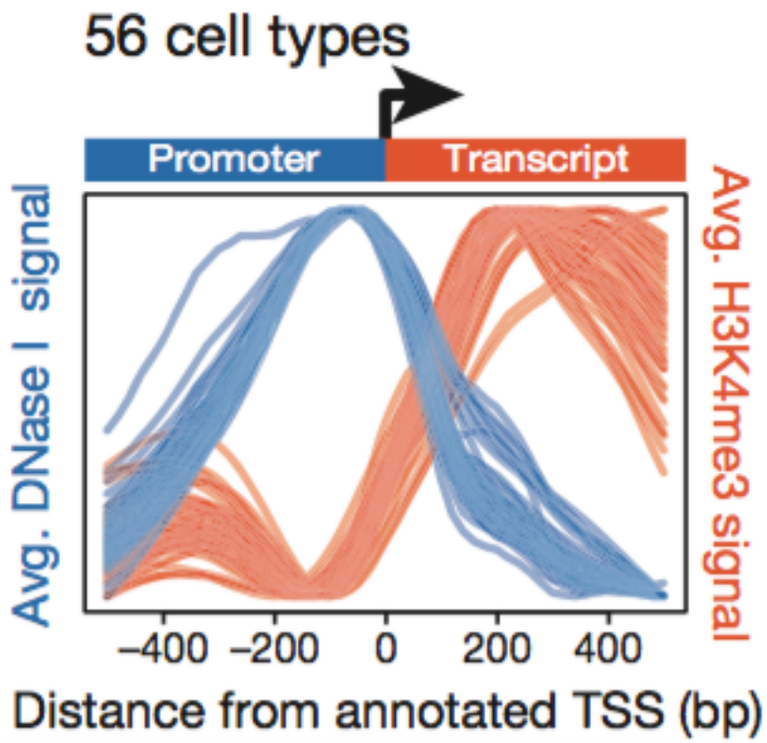
Small number of TF in this bottom paradigm, eg. known chromatin repressors, e.g. KRAB-associated factors

Thurman et al., Nature 489:75-82 (2012).

ENCODE

- ChIP-seq for H3K4me3 in 56 cell types using the same samples for DNaseI data
- Asymmetrical patterning
- Precise to the TSS
- Rigidly positioned nucleosome immediately downstream from the promoter DHS
- ~ Invariant across cell types





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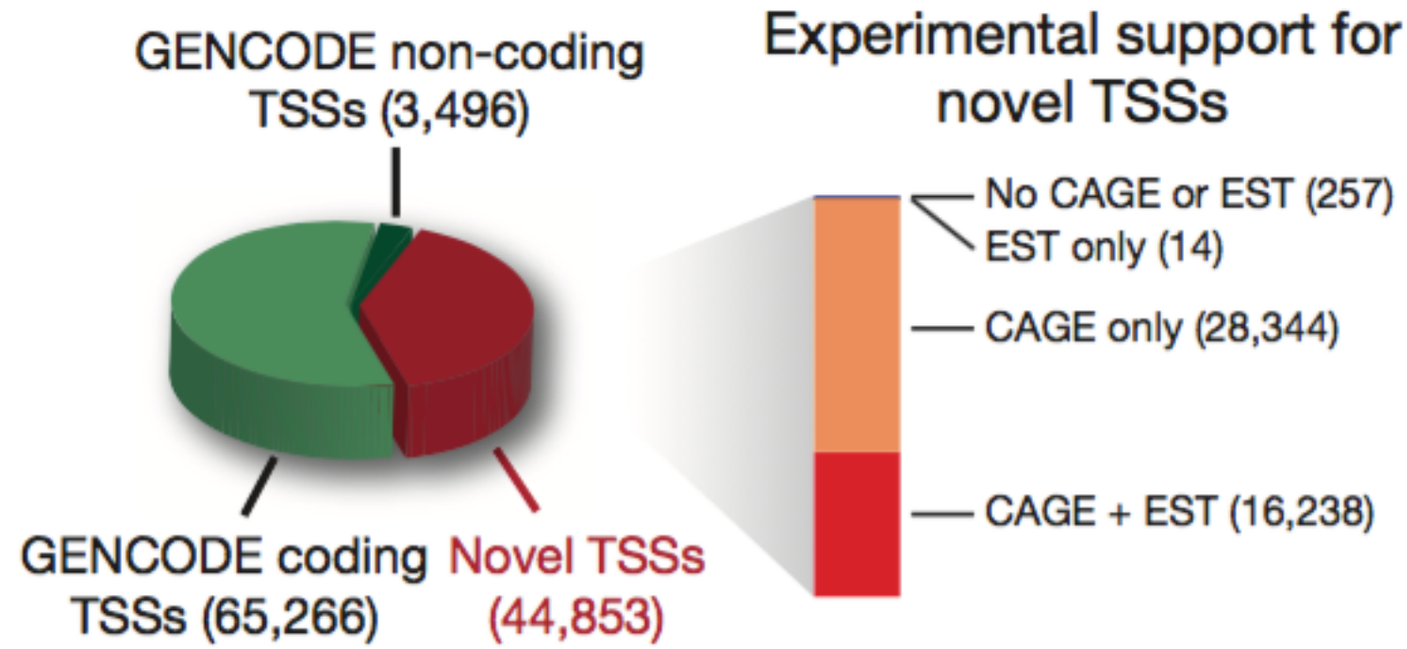
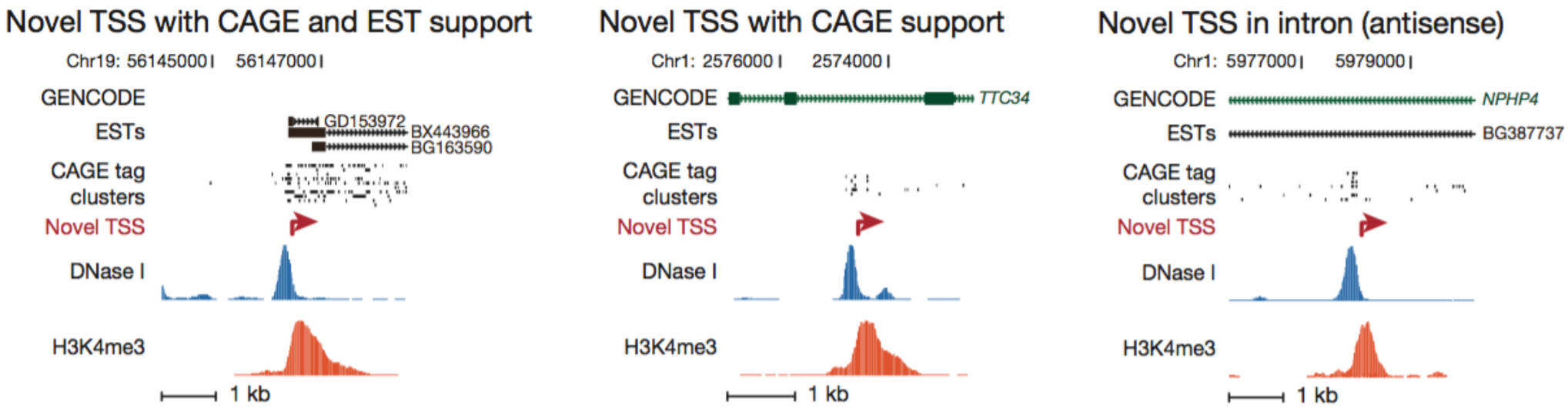


- Use pattern to predict and validate novel TSSs



Thurman et al., Nature 489:75-82 (2012).

ESTs, spliced expressed sequence tags

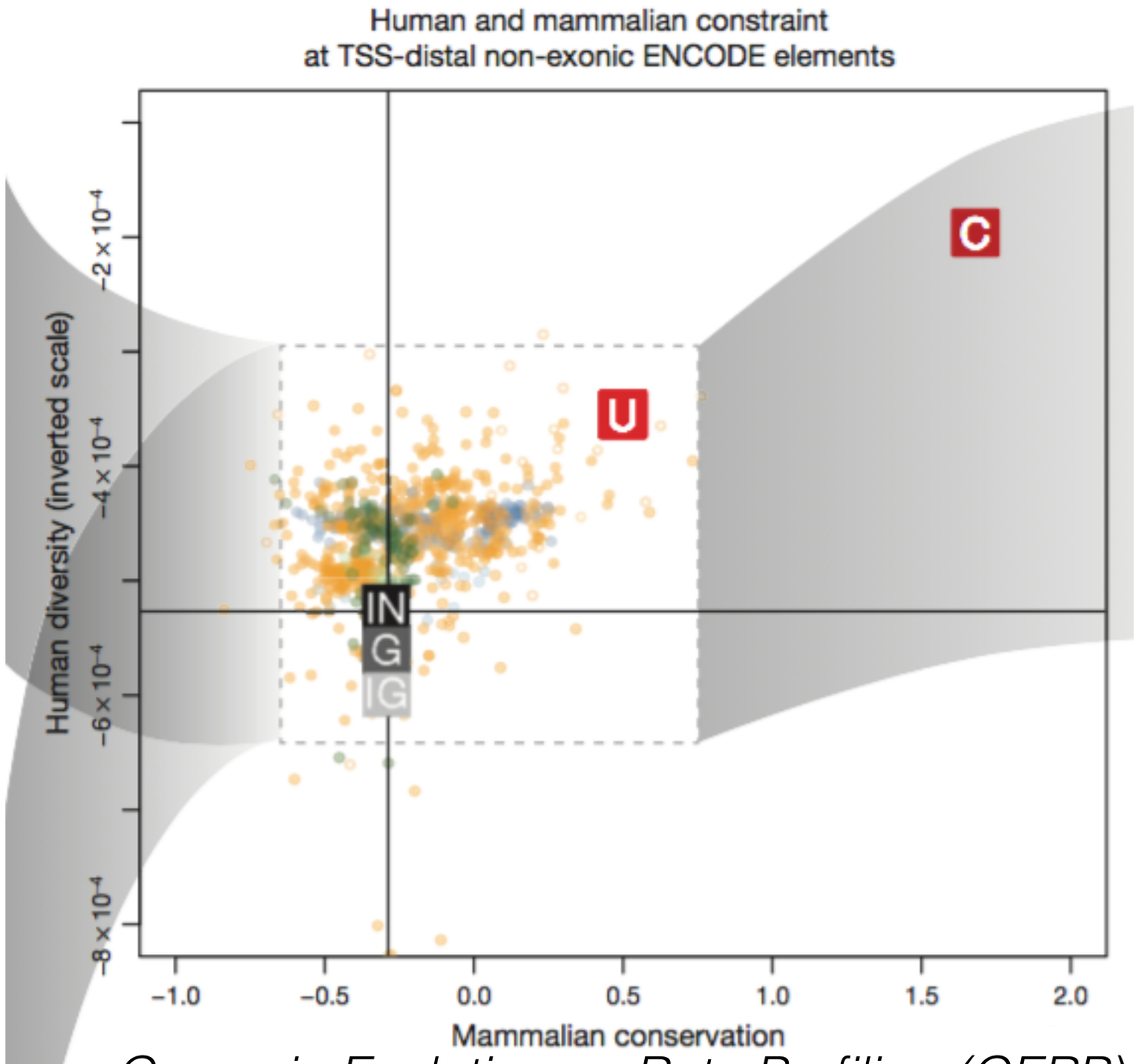
CAGE, cap analysis of gene expression

ENCODE

Conservation

Diversity, a measure of negative selection in the human population (mean expected heterozygosity, (inverted scale)

- Point: average for a single data set.
- Filled Square: Coding (C), UTR (U), genomic (G), intergenic (IG) & intronic (IN) average



24 mammals, Average Genomic Evolutionary Rate Profiling (GERP)

The ENCODE Project Consortium, Nature 489:57-74 (2012).

ENCODE

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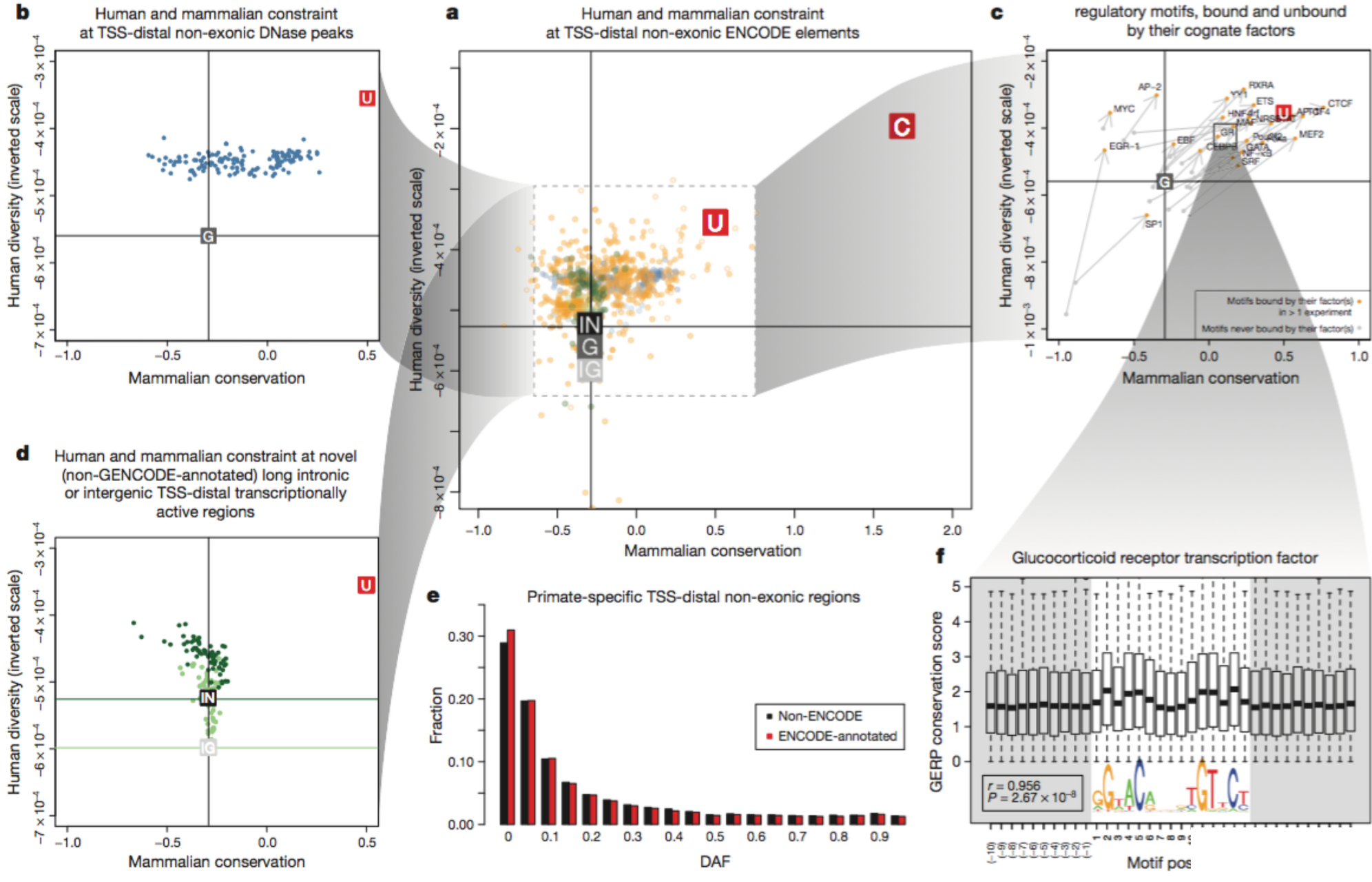
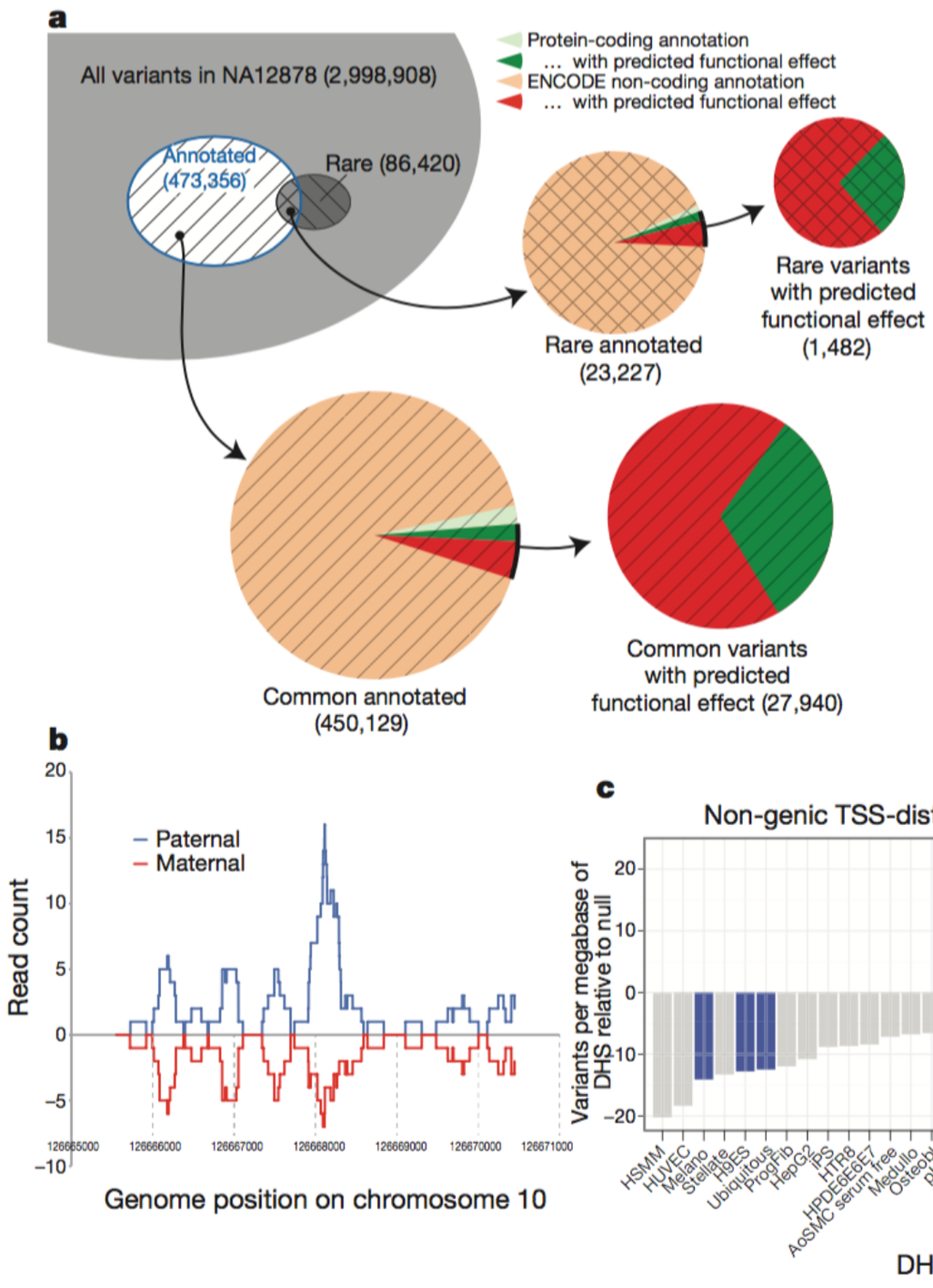


The ENCODE Project Consortium, Nature 489:57-74 (2012).

ENCODE

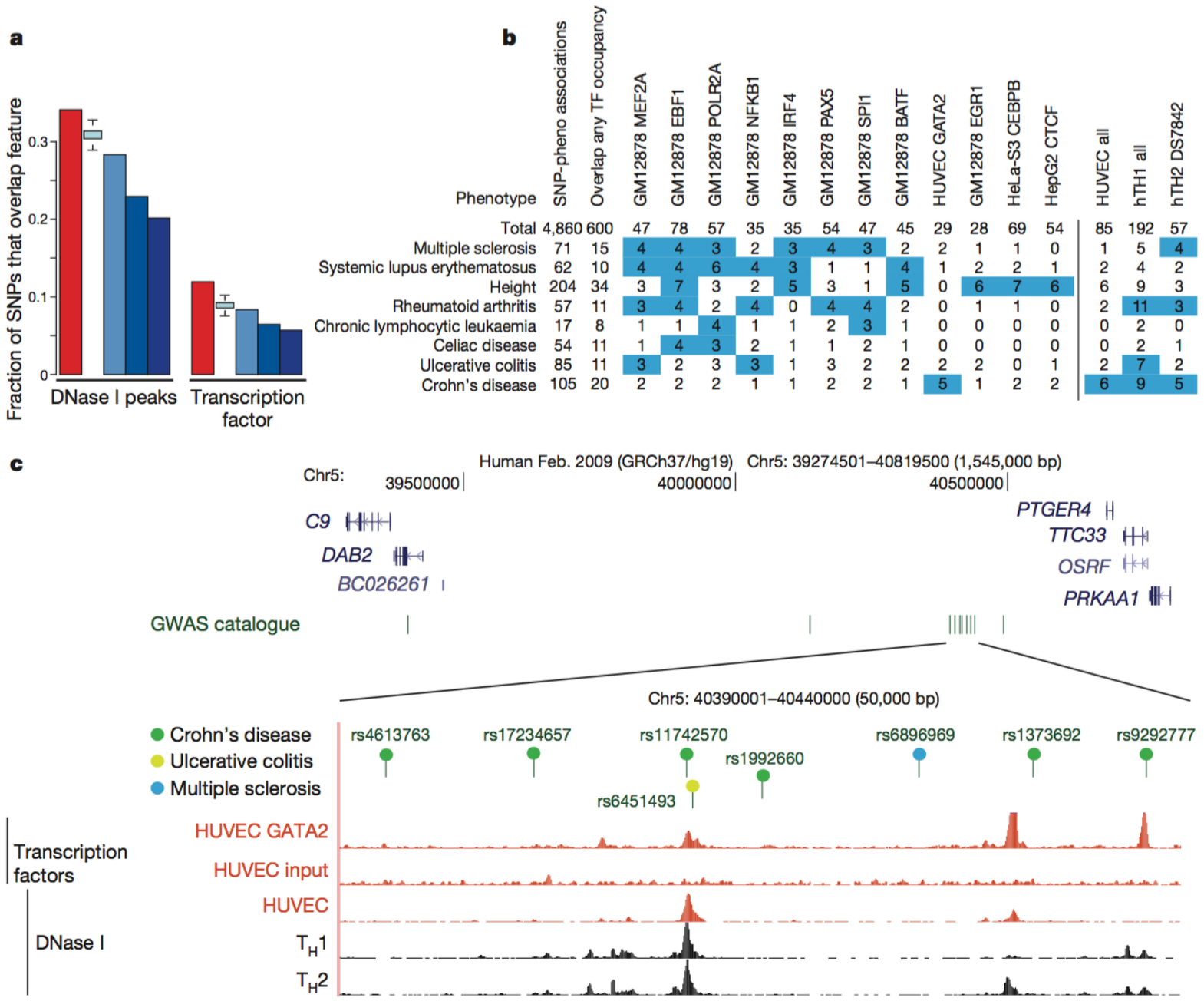
- Multiple Variants identified
- Individual basis considerations



The ENCODE Project Consortium, Nature 489:57-74 (2012).

ENCODE

- GWAS comparisons
- Disease associations



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ENCODE

Current Research

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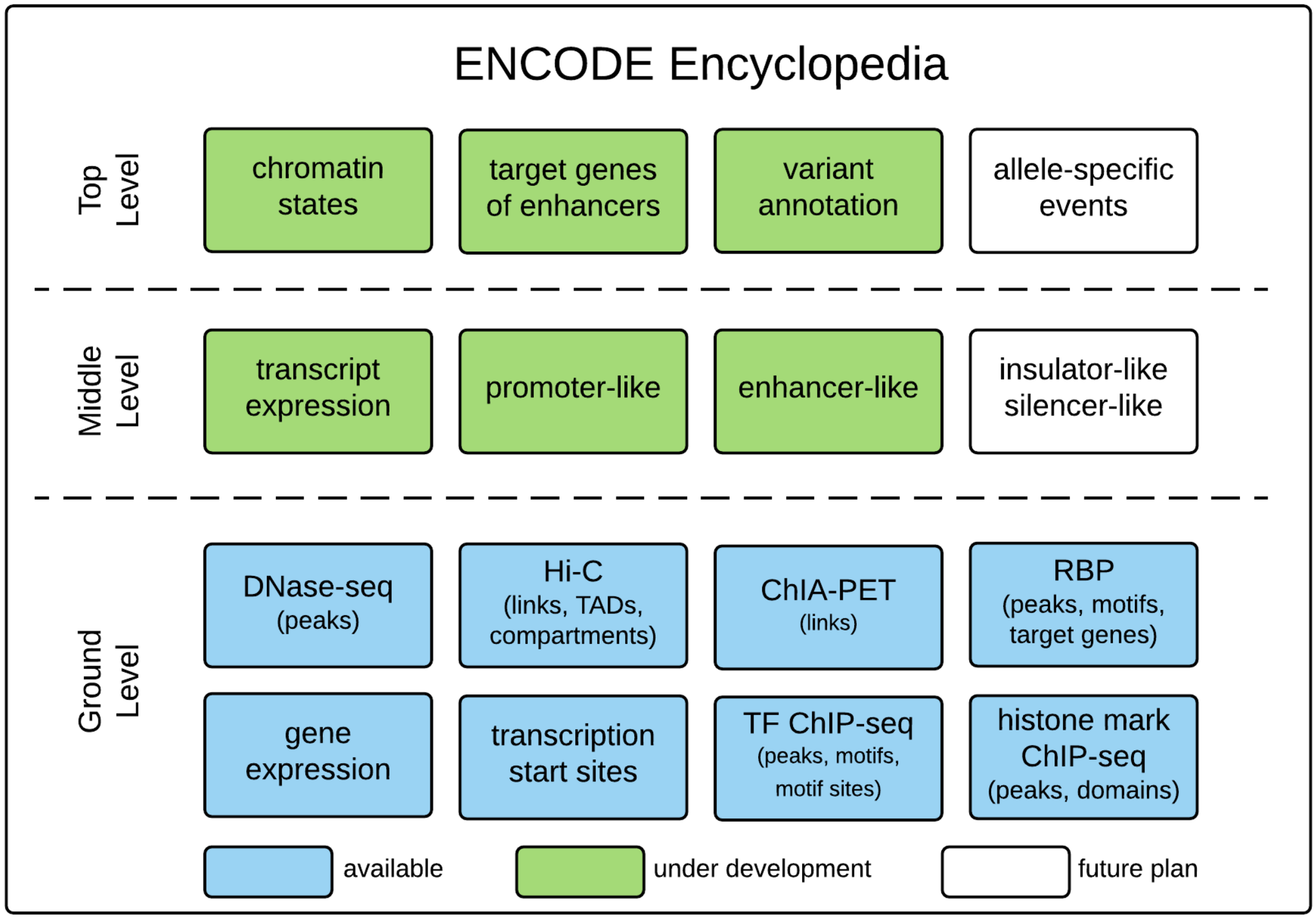
ENCODE



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ENCODE

Ground level annotations are typically derived directly from the experimental data.

Gene expression (RNA-seq)

The expression levels of genes annotated by GENCODE 19 in ~60 human cell types

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CTCF Motif from Factorbook

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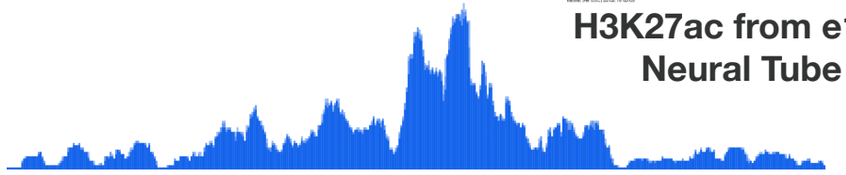
Peaks of a variety of histone marks computed from ~600 ChIP-seq experiments.



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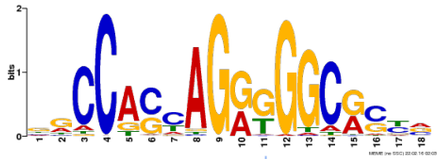

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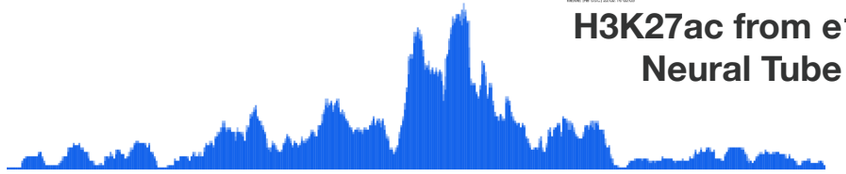
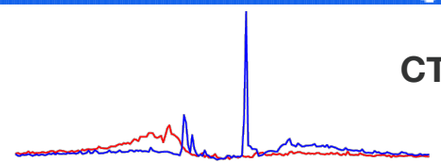


Open Chromatin (DNase-seq)

DNase I hypersensitive sites (also known as DNase-seq peaks) computed from ~300 human and mouse experiments.



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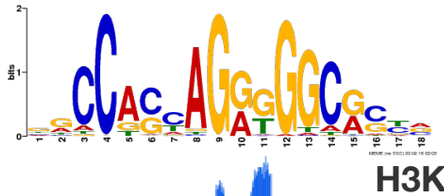

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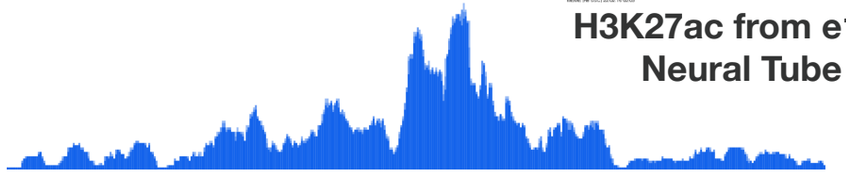

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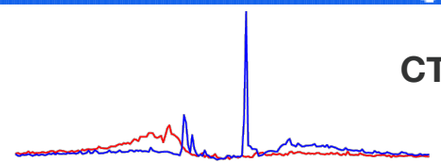

Topologically associating domains (TADs) and Compartments (Hi-C)

TADs and A and B compartments computed from 12 human cell lines.

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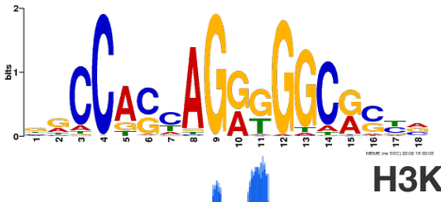

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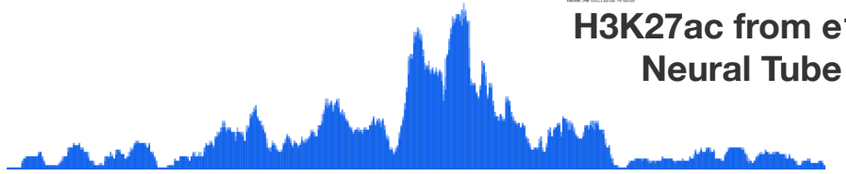

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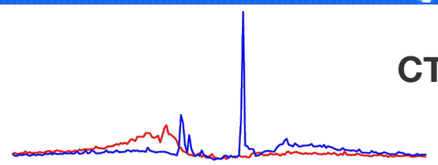

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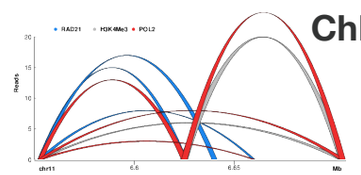
Promoter-enhancer links (ChIA-PET)

Links between promoters and distal regulatory elements such as enhancers computed from 8 ChIA-PET experiments.



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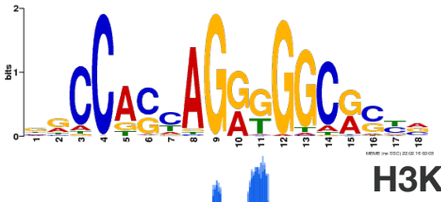

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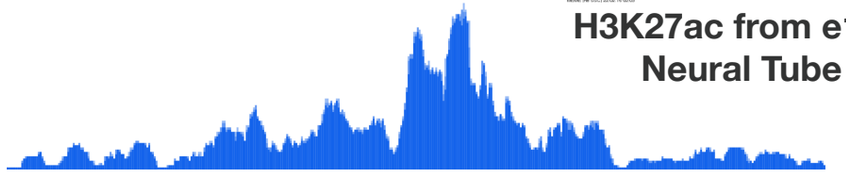

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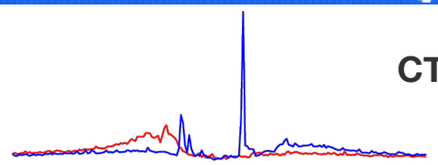

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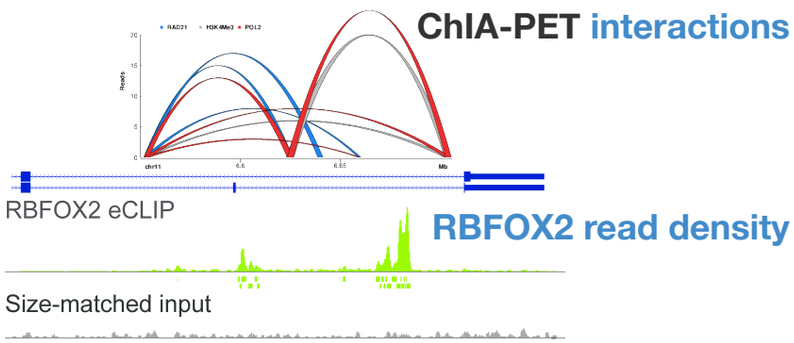

RNA Binding Protein Occupancy (eCLIP-seq)
Peaks computed from eCLIP-seq data in human cell lines K562 and HepG2 for a large number of RNA Binding Proteins (RBPs).

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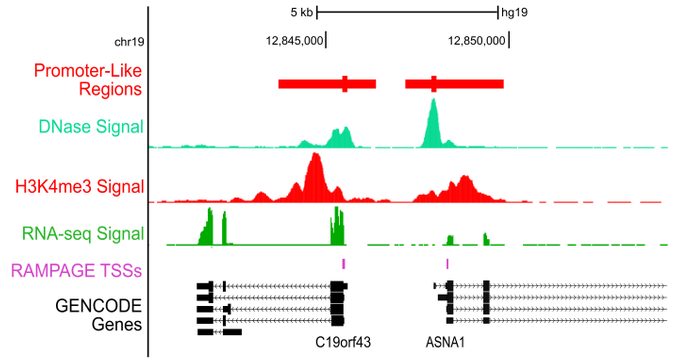
ENCODE

Middle level annotations integrate multiple types of experimental data and multiple ground level annotations.

Promoter-like regions

- DNase hypersensitivity and histone modification H3K4me3 are well-known indicators of active and poised promoters.
- Developed an unsupervised method that combines DNase and H3K4me3 signals in the same cell type to predict promoter-like genomic regions.



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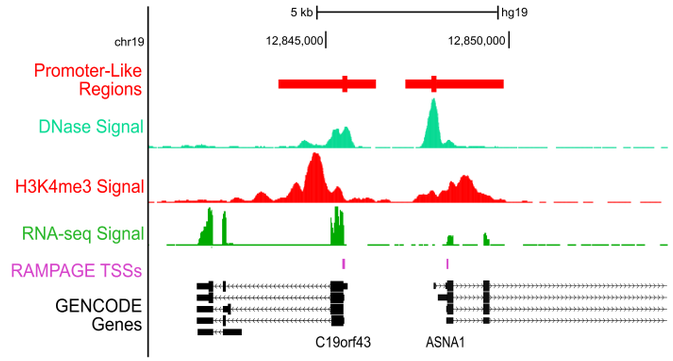
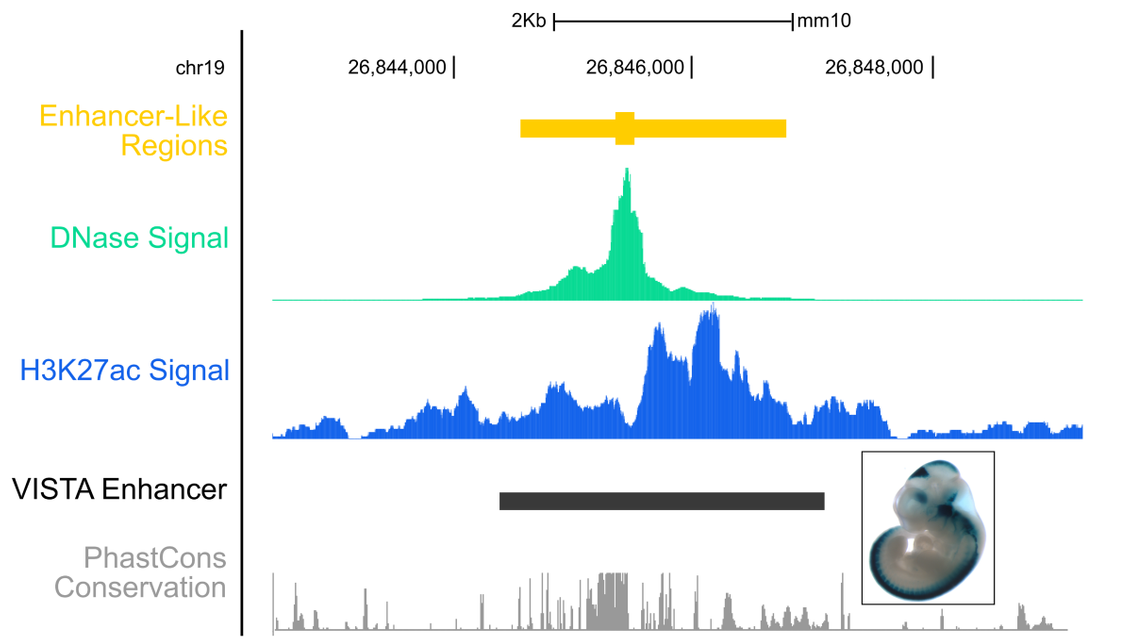


Enhancer-like regions

- DNase hypersensitivity and histone modification H3K27ac are well-known indicators of active enhancers.
- Developed an unsupervised method that combines DNase and H3K27ac signals in the same cell type to predict enhancer-like genomic regions.
- Applied method to 52 human cell types and 20 mouse cell types with both DNase and H3K27ac data generated by the ENCODE and Roadmap Epigenomic consortia.



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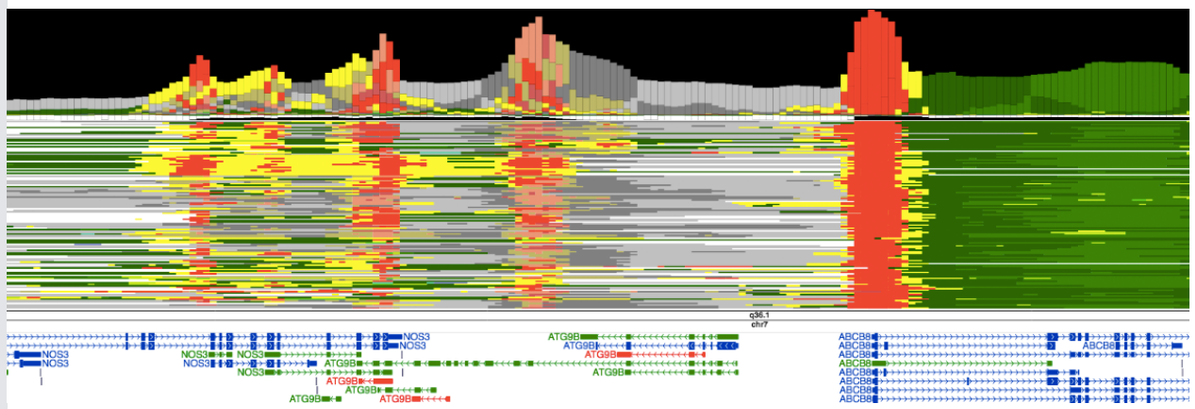
ENCODE

Top level annotations integrate a broad range of experimental data and ground and middle level annotations.

Chromatin states

- Semi-automated genomic annotation methods such as ChromHMM and Segway
  - Take as input a panel of epigenomic data (including histone mark ChIP-seq and DNase-seq) in a particular cell type
  - Use machine learning methods to simultaneously partition the genome into segments and assign chromatin states to these segments
  - States are assigned such that two segments with the same state exhibit similar epigenomic patterns.
  - The procedure is "semi-automated" because states are then manually compared with known biological information in order to designate each state as an enhancer-like, promoter-like, gene body, etc.



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