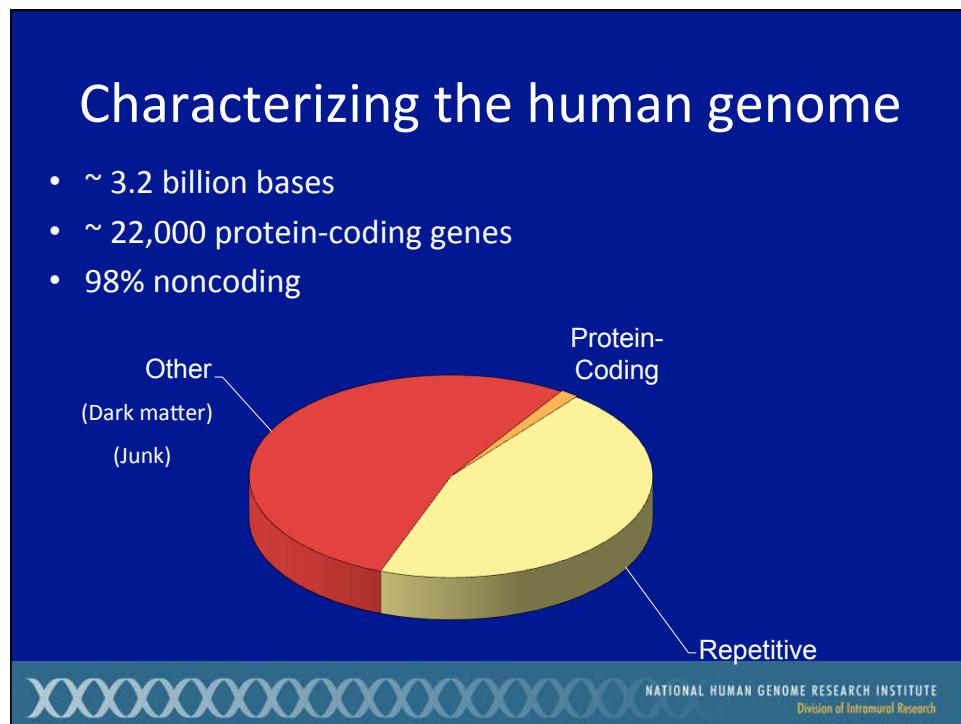
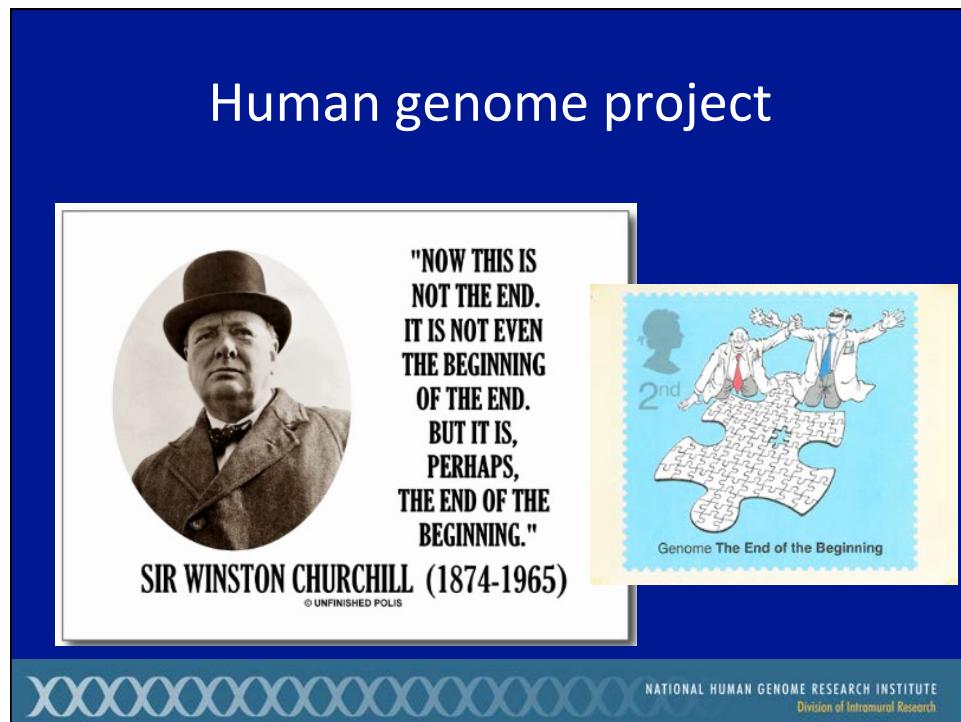
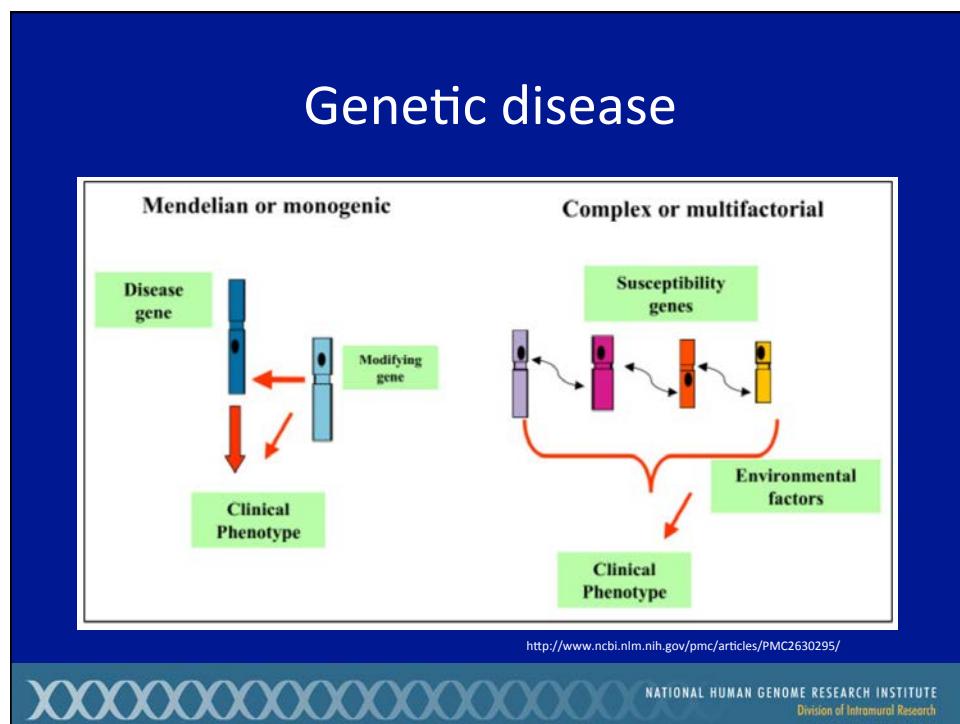
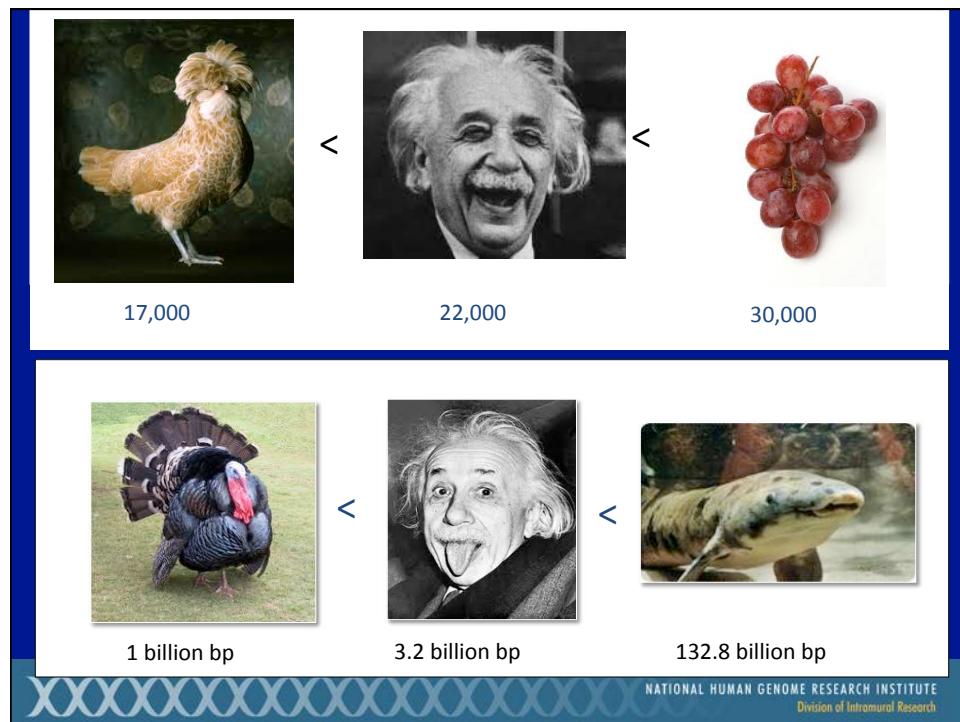
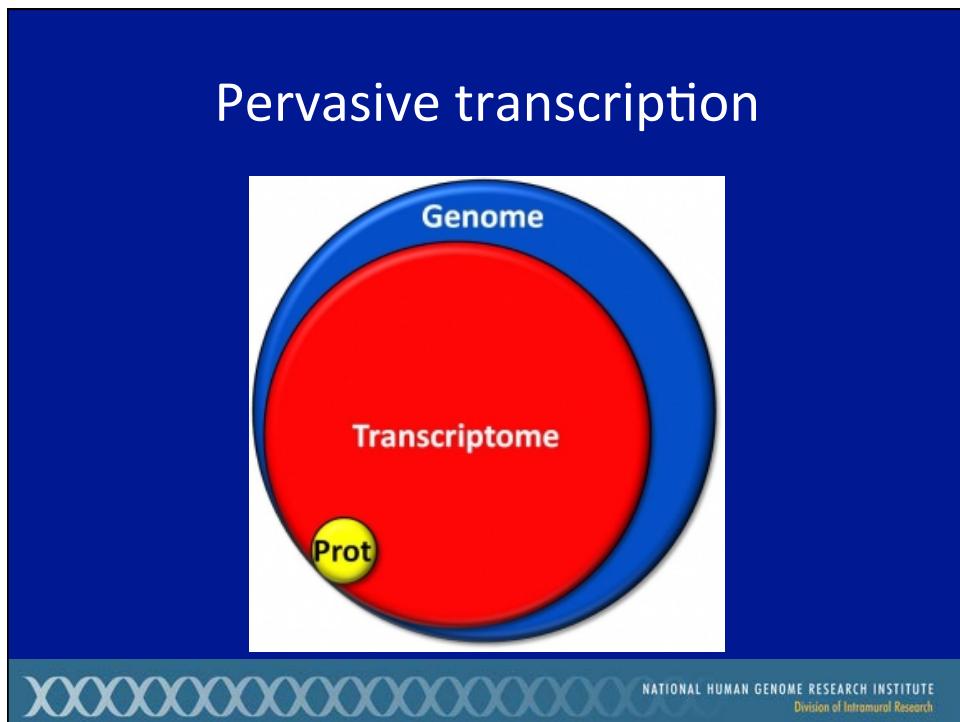


1.1. Genome composition









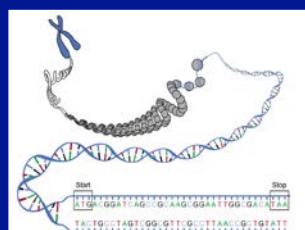
Envisioning the genome



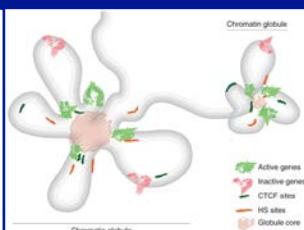
A. Linear sequence

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Envisioning the genome

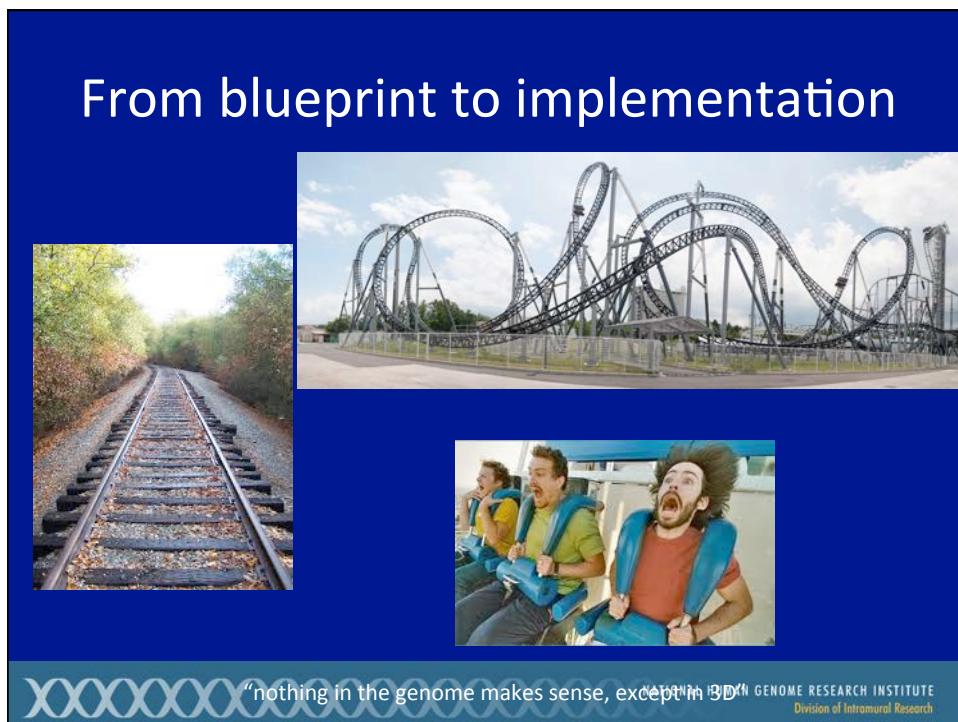
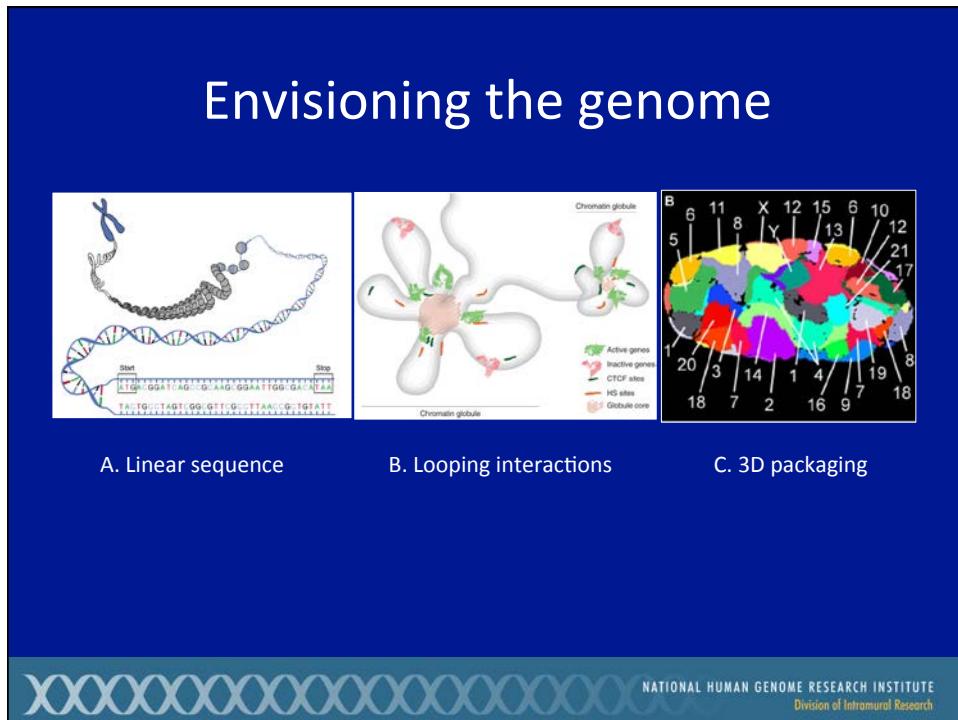


A. Linear sequence

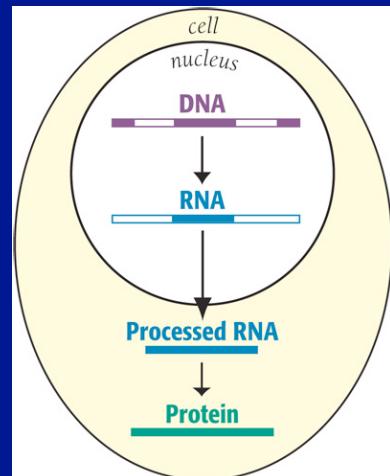


B. Looping interactions

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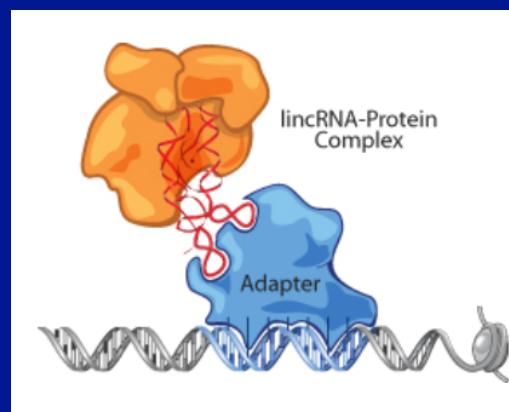


Central dogma - 1958



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Noncoding RNA



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1.2. Examining the linear sequence

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EVOLUTIONARY CLUES

Evolutionary Distance



Human



Chimpanzee



Horse



Rat

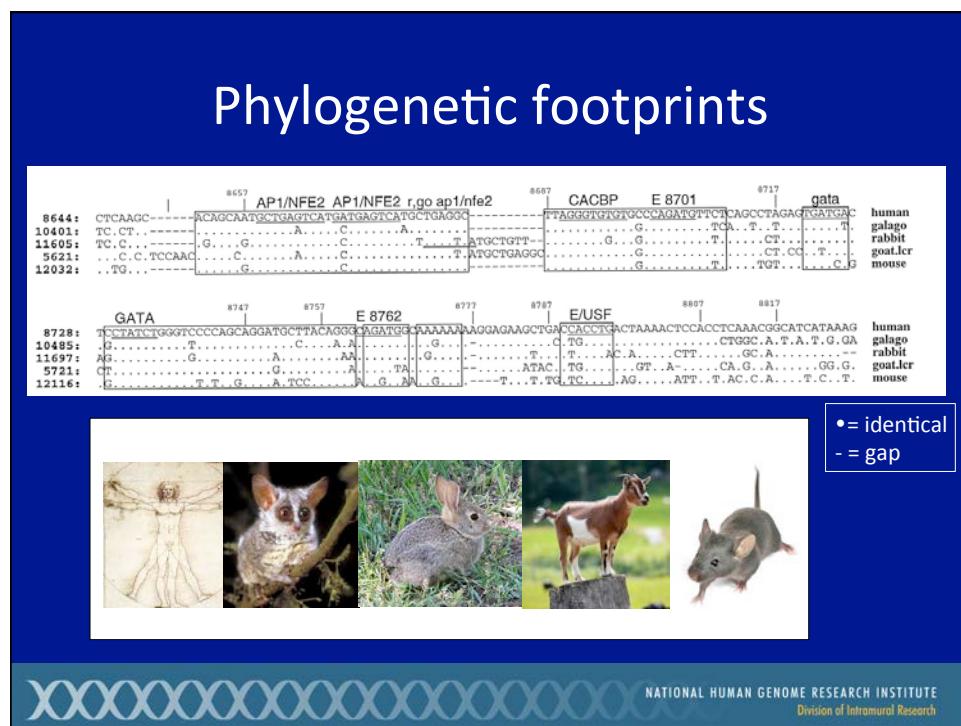
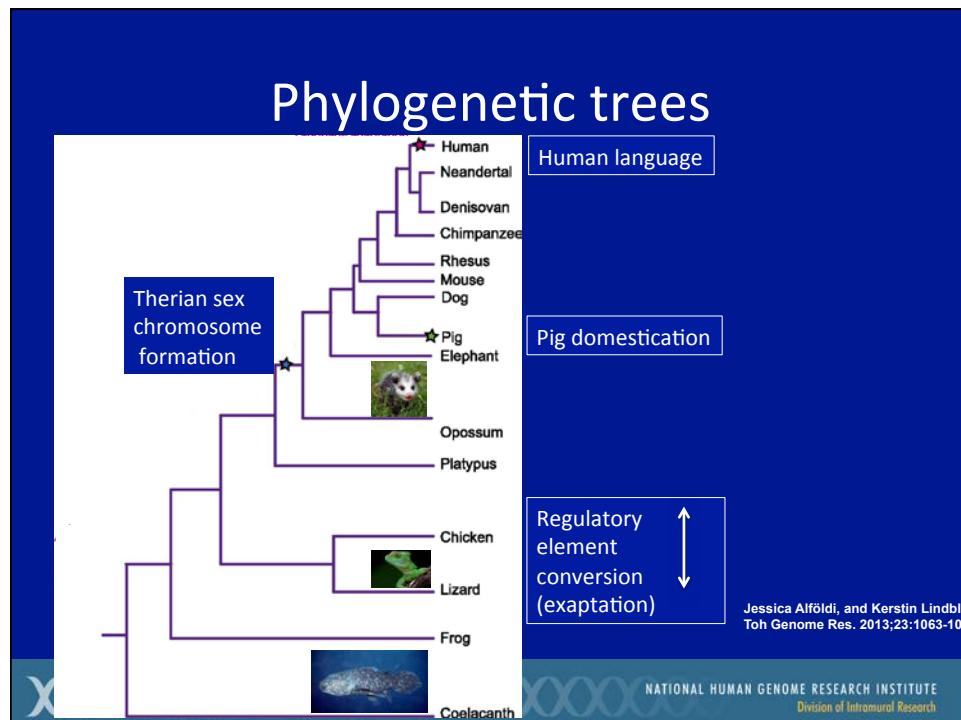


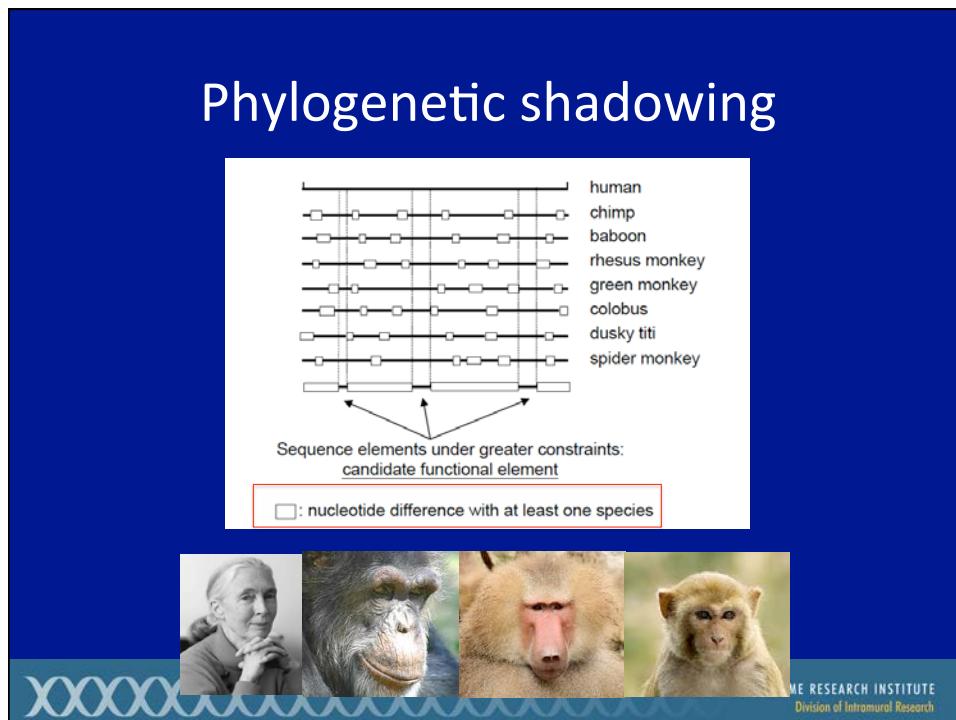
Platypus



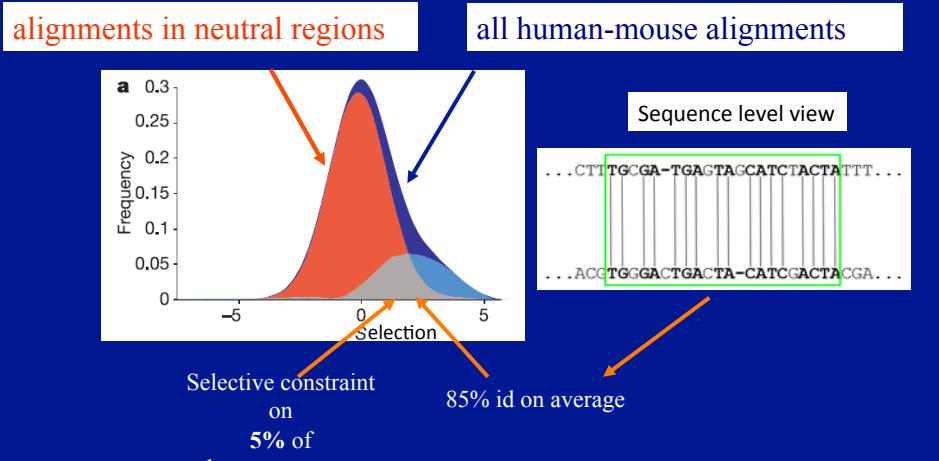
Pufferfish

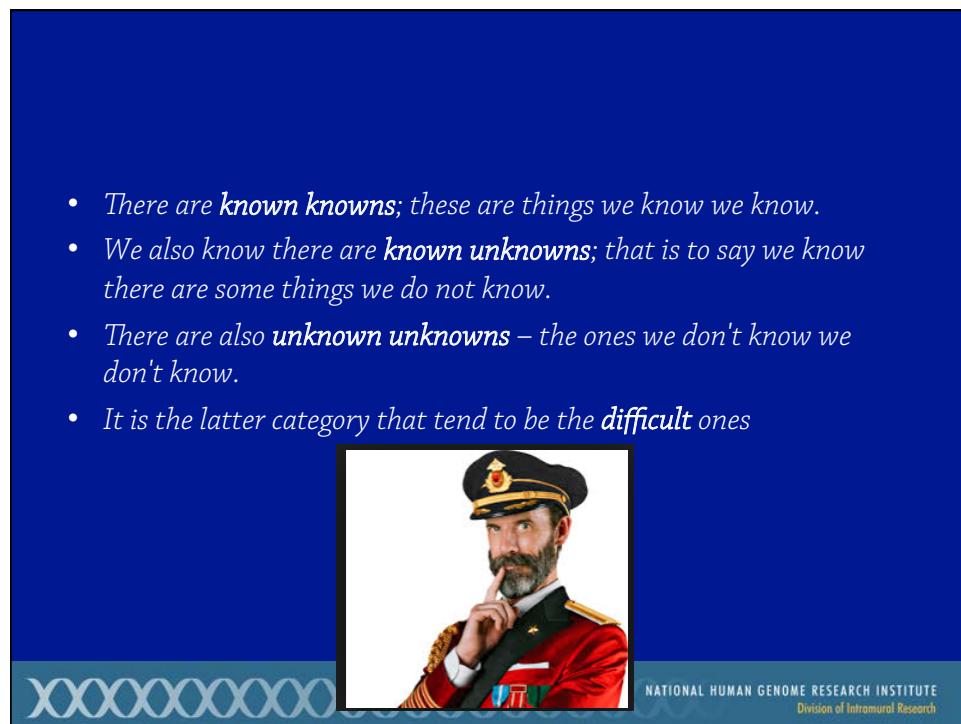
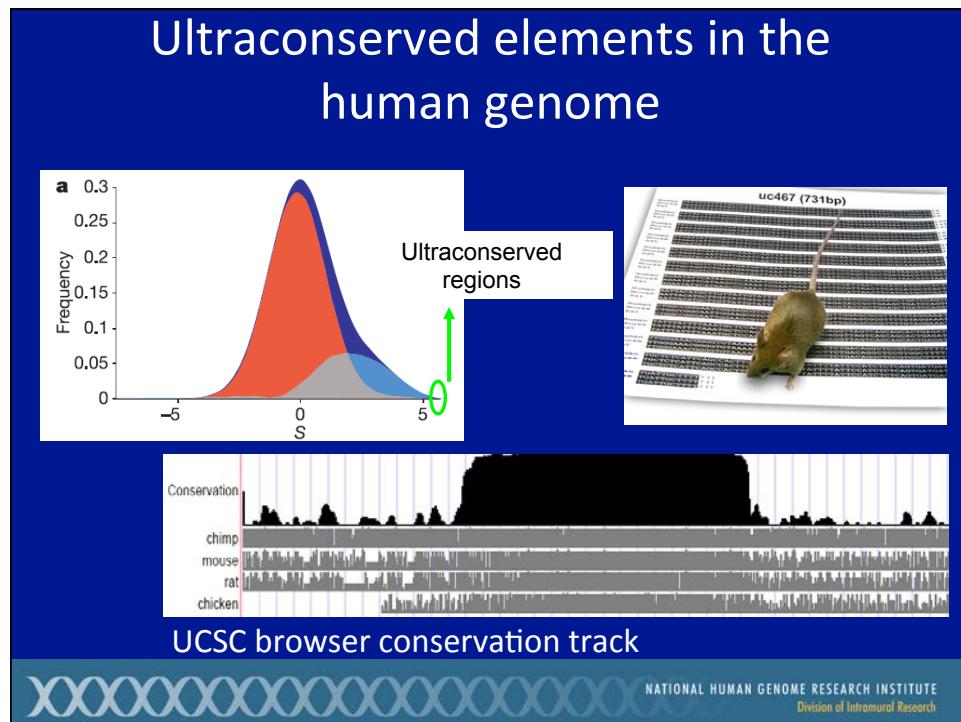
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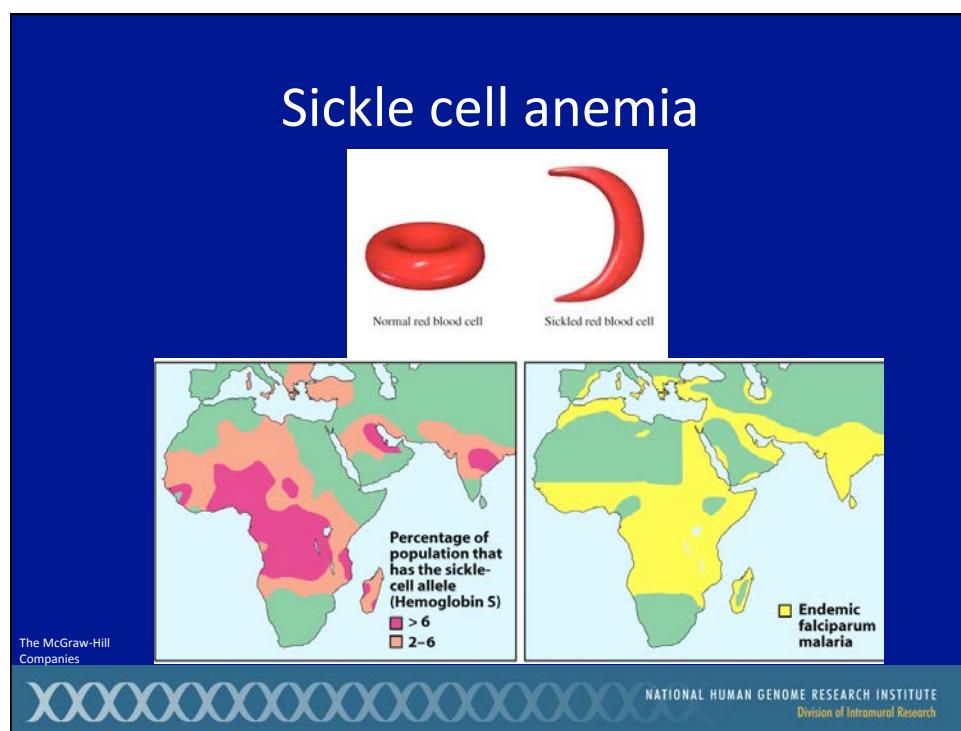
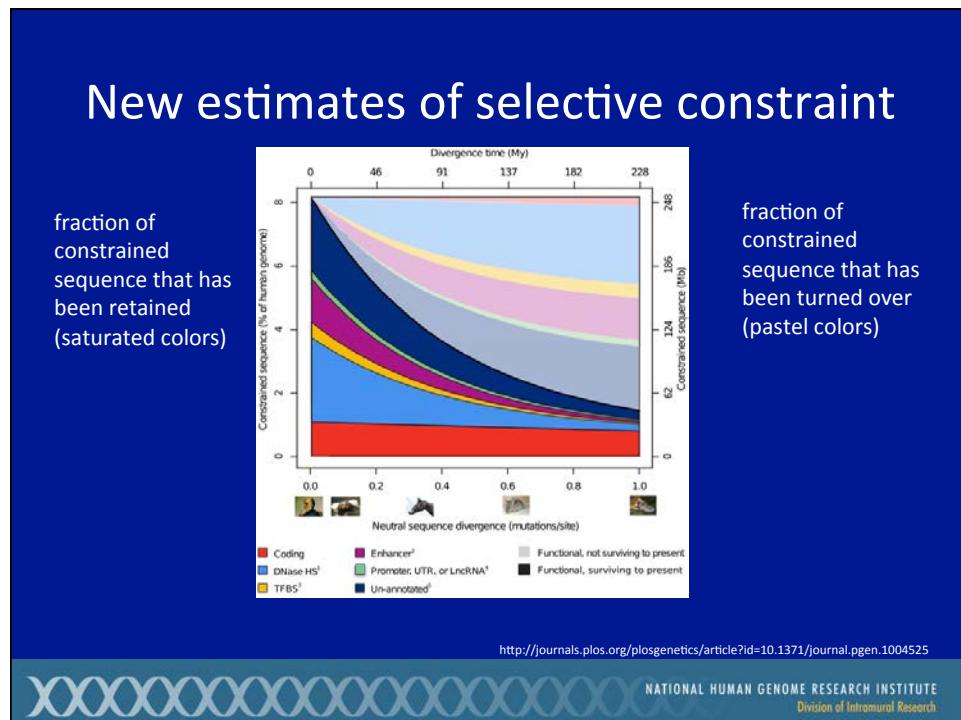


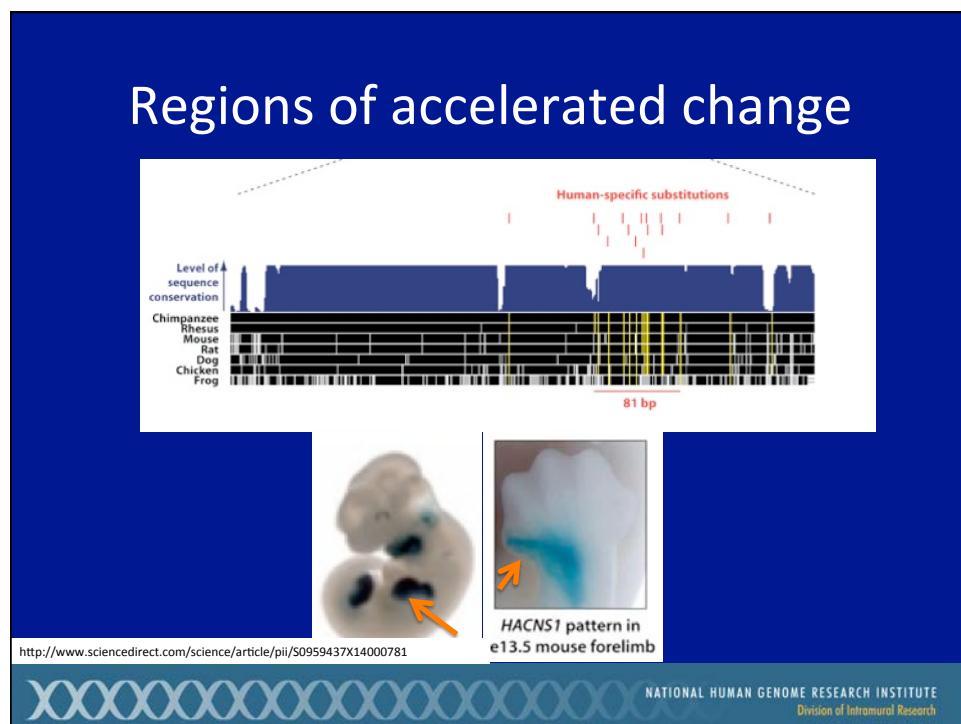
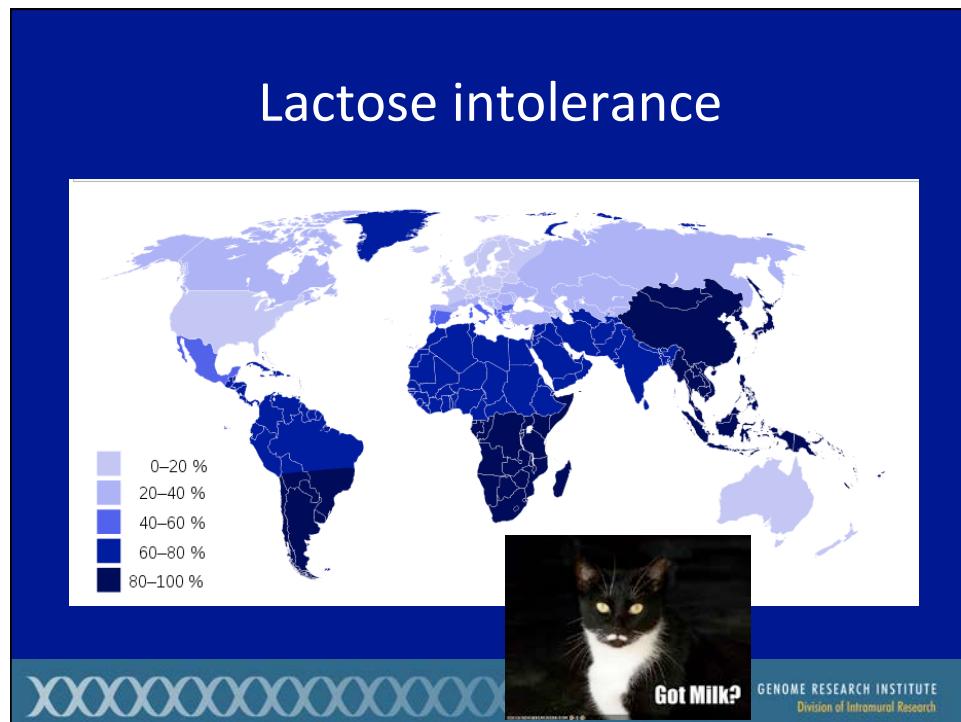


Conserved elements in the human genome









Regulatory variation

11 April 1975, Volume 188, Number 4184

SCIENCE



Evolution at Two Levels in Humans and Chimpanzees

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

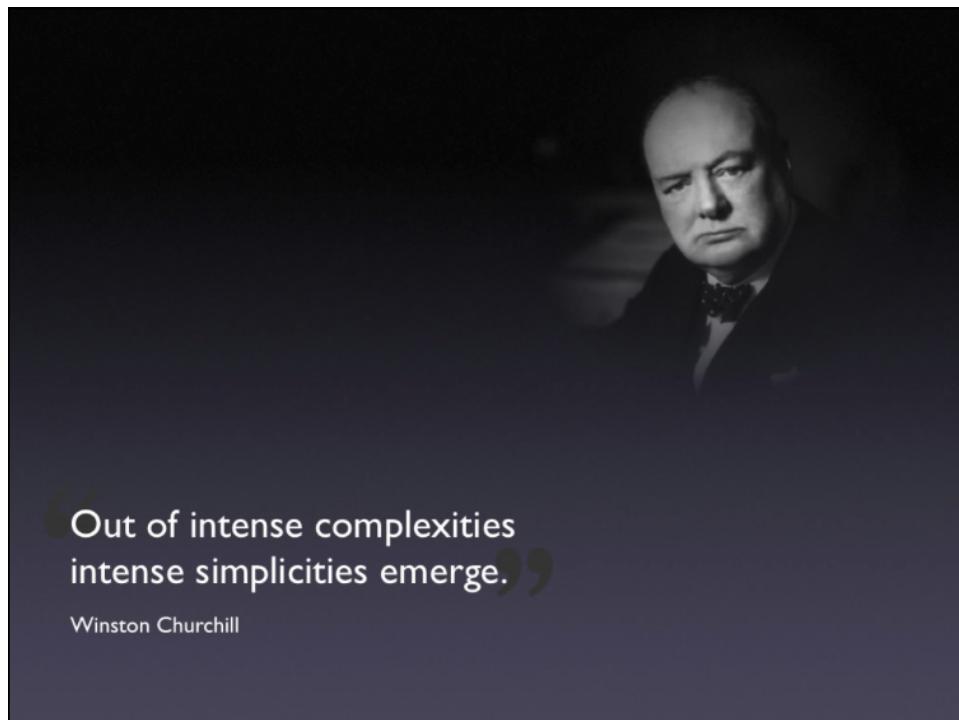
Mary-Claire King and A. C. Wilson

evidence concerning the molecular basis of evolution at the organismal level. We suggest that evolutionary changes in anatomy and way of life are more often based on changes in the mechanisms controlling the expression of genes than on sequence changes in proteins. We therefore propose that regulatory mutations account for the major biological differences between humans and chimpanzees.

Similarity of Human and Chimpanzee Genes

To compare human and chimpanzee genes, one compares either homologous proteins or nucleic acids. At the protein

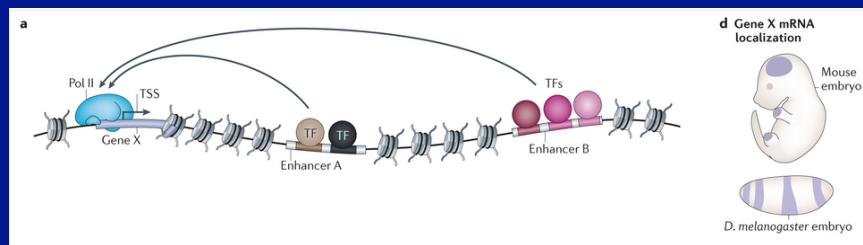
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2.1 Functional elements in linear sequence

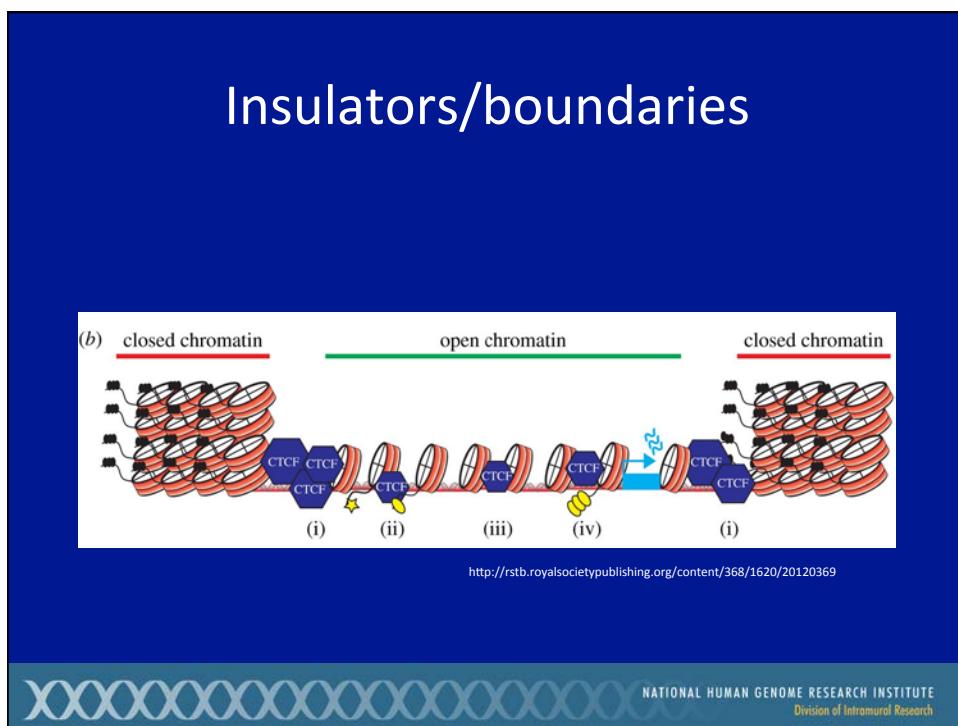
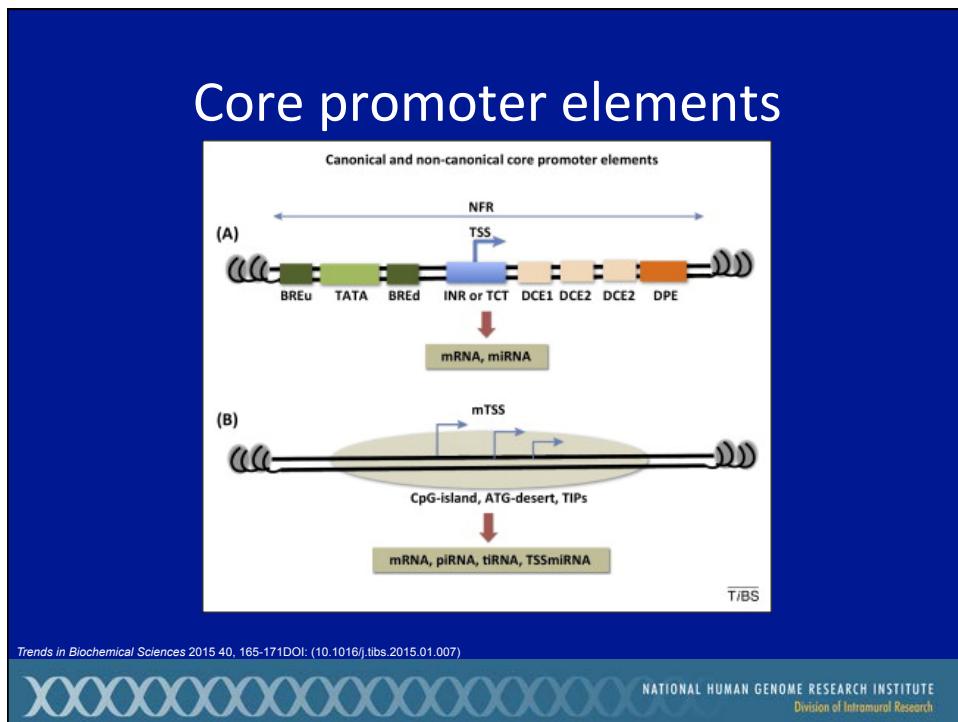
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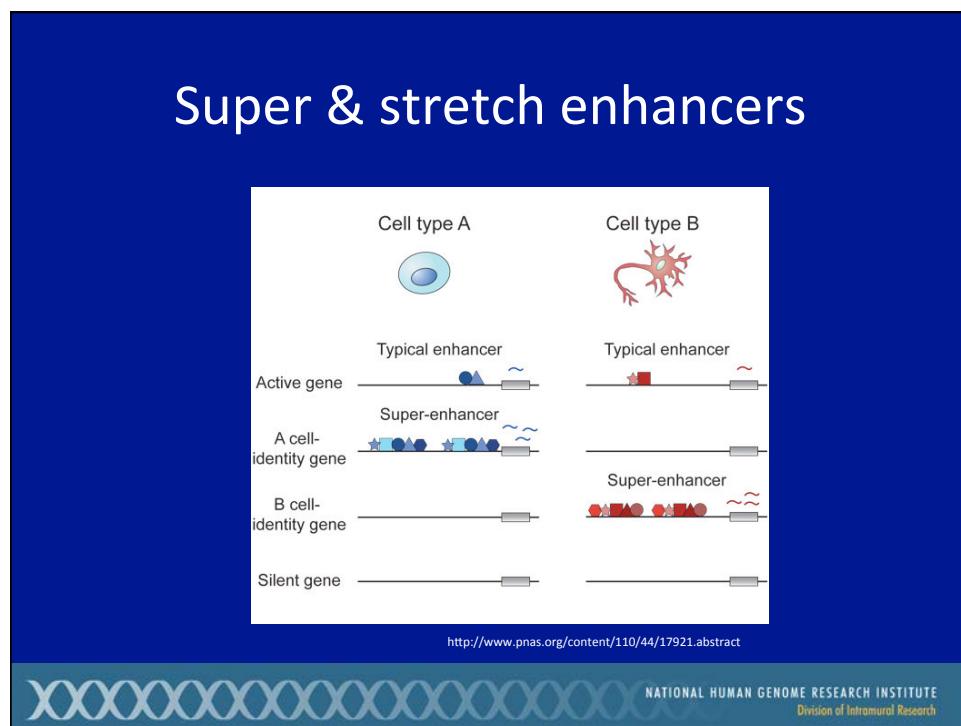
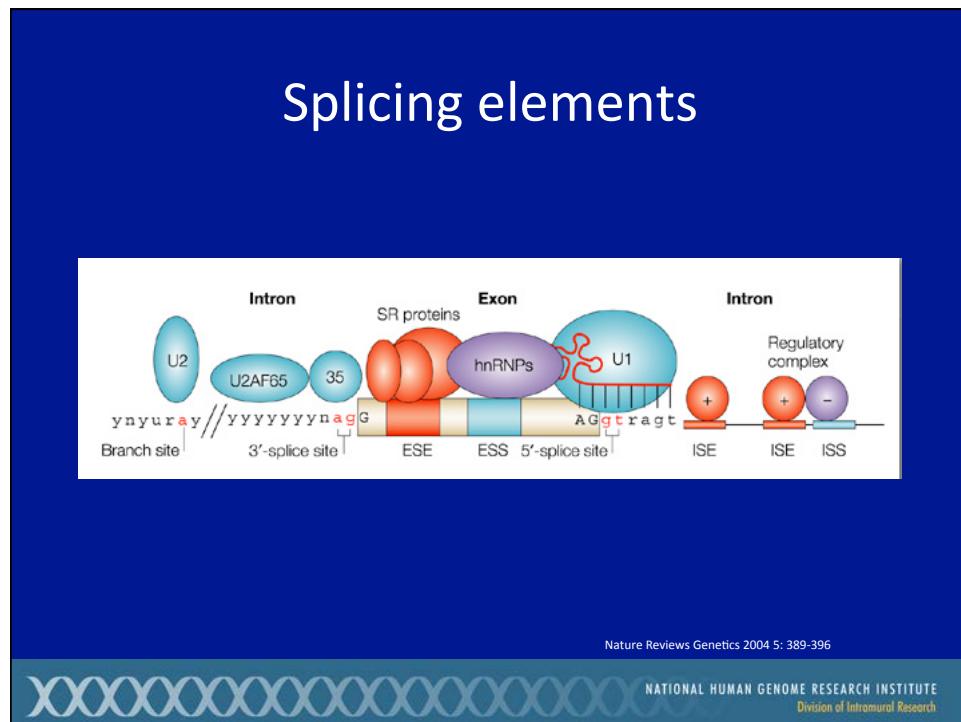
Enhancers

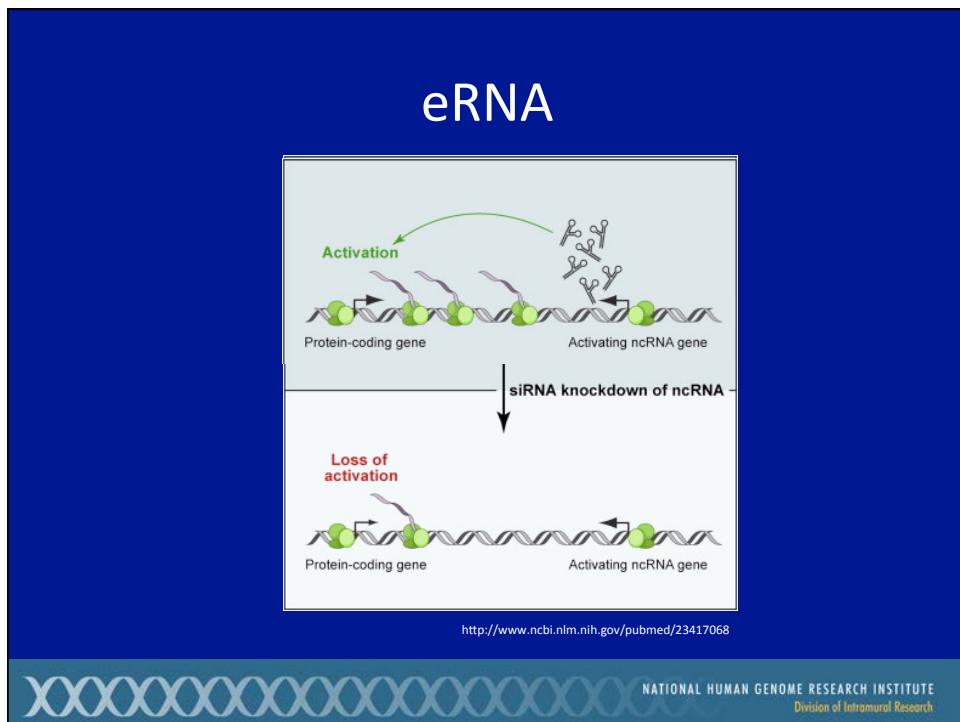


http://www.nature.com/nrg/journal/v15/n4/fig_tab/nrg3682_F1.html

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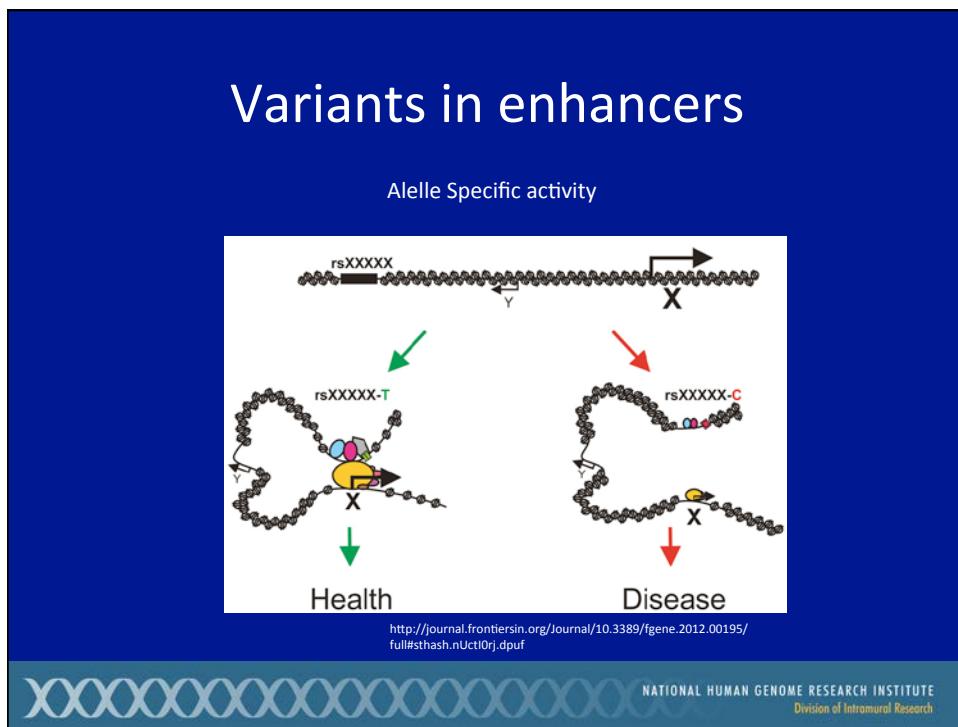
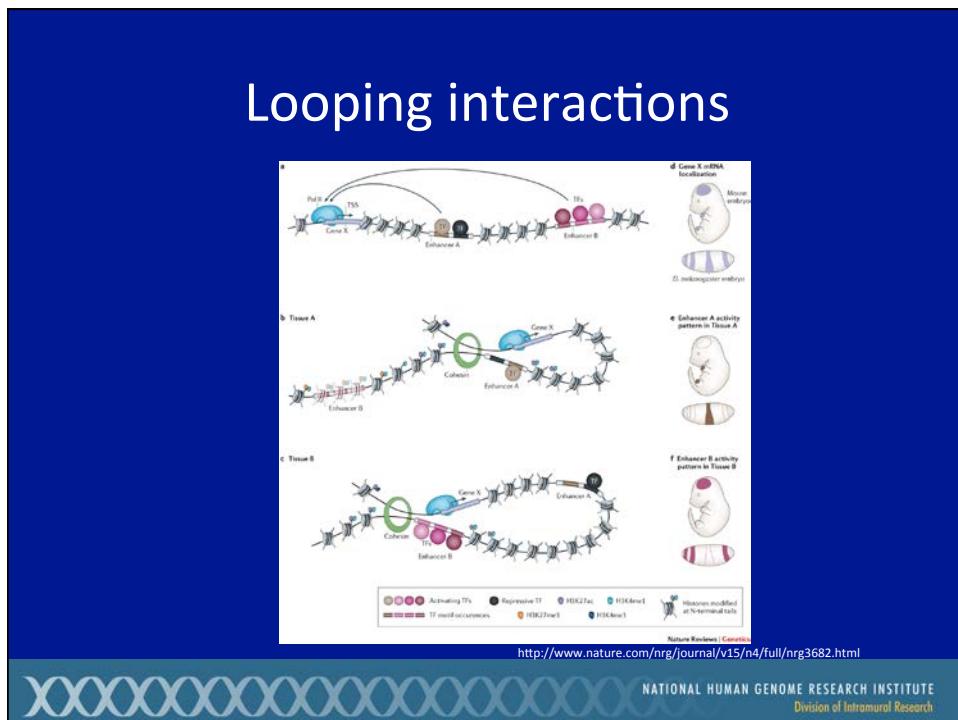


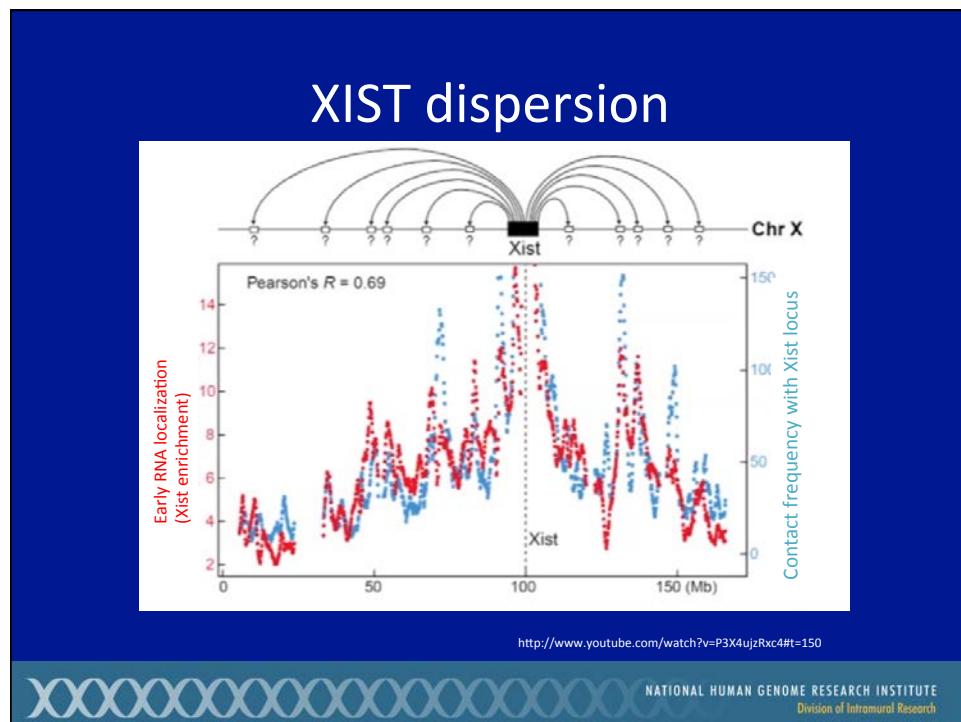




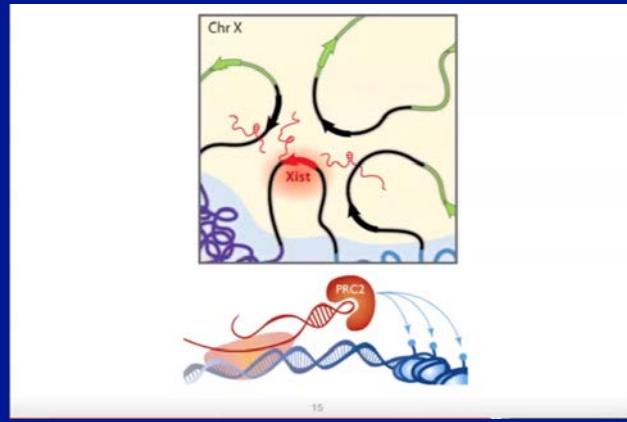
2.2. Looping interactions





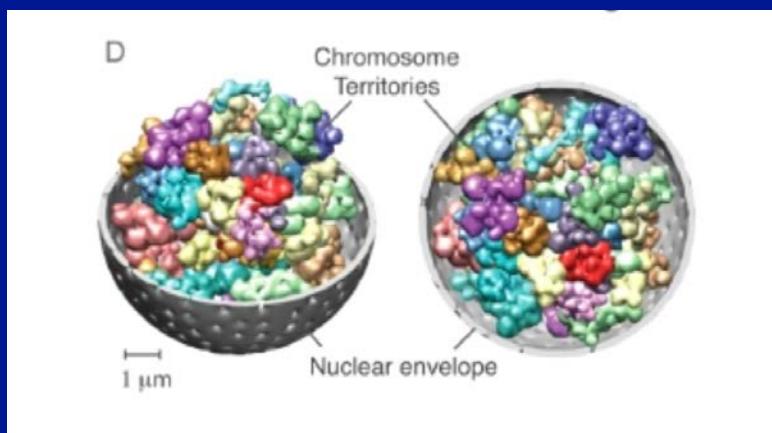


Regulatory architecture

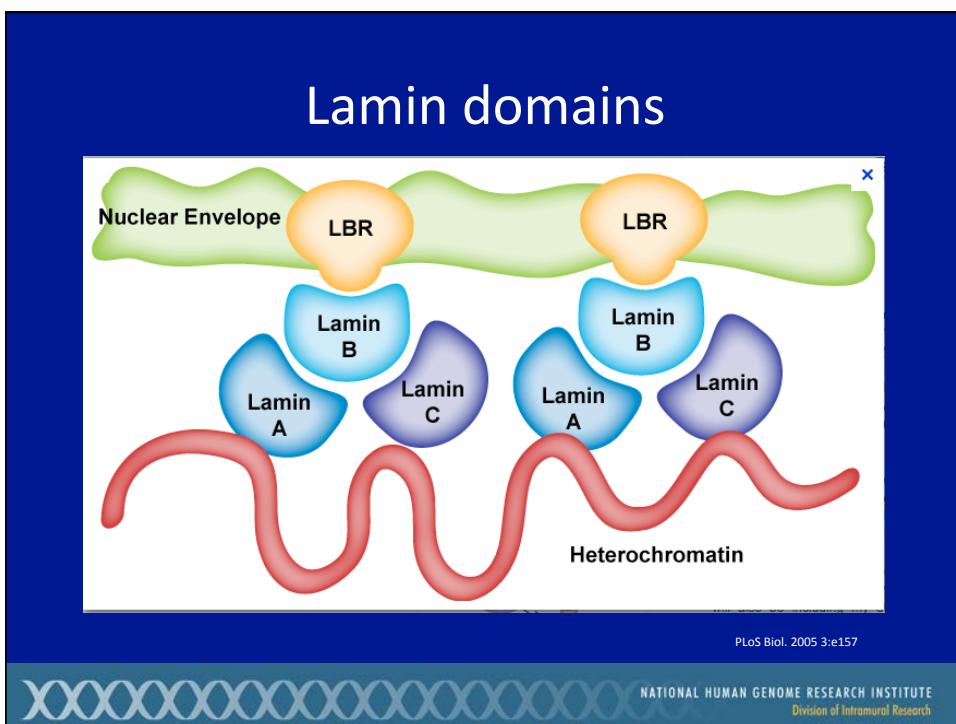
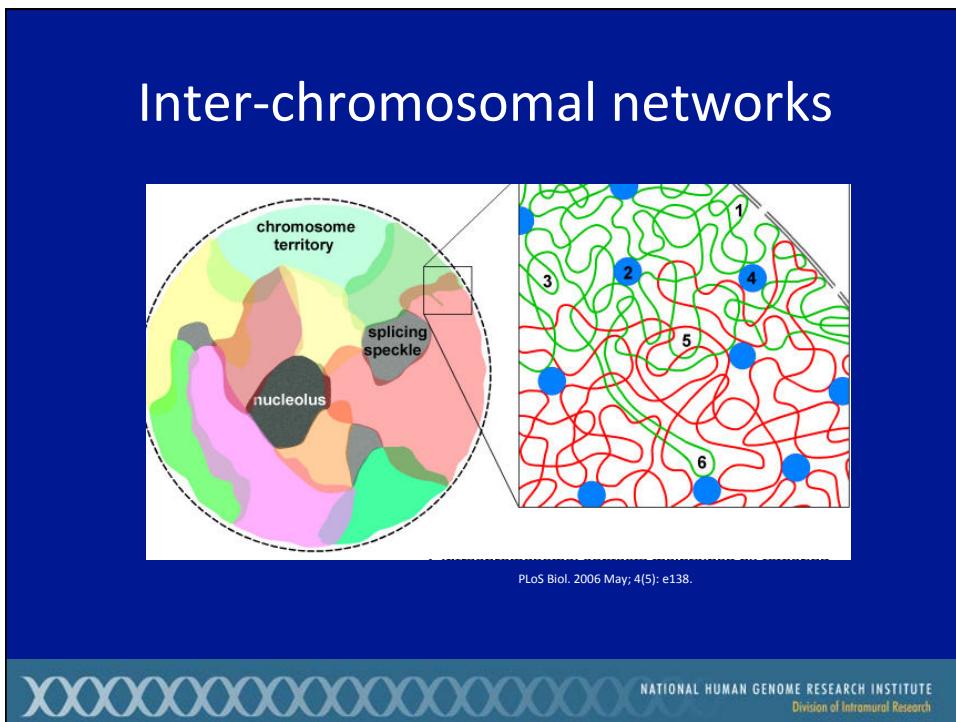


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2.3 3D packaging



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Progeria

Am J. Med Genet. 23:2603-24

http://www.pnas.org/content/109/41/16666

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Altered genome topology in cancer

a

LOCKs and LADs

Normal cell

b

Cancer cell

Heterochromatin (off)

Euchromatin (on)

RNA

lost

altered

RNA

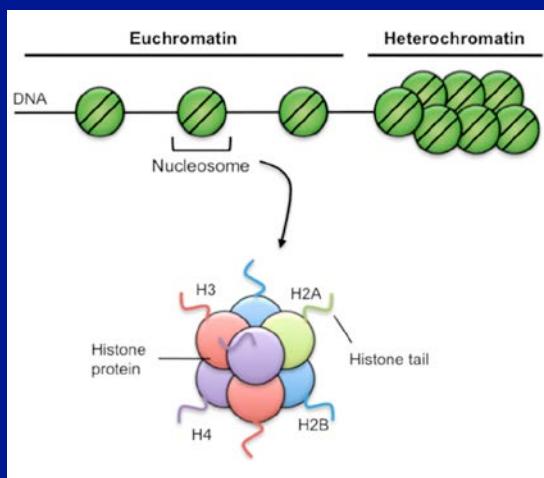
http://www.nature.com/nrc/journal/v13/n7/full/nrc3486.html

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3. Histone modifications

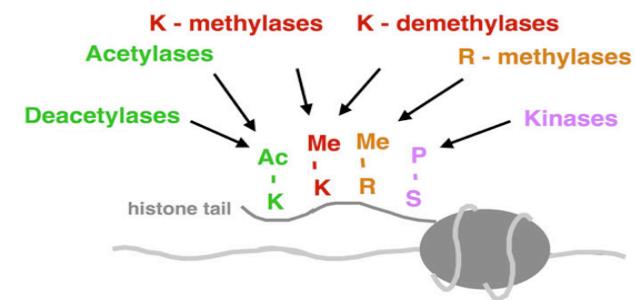
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Active and inactive chromatin



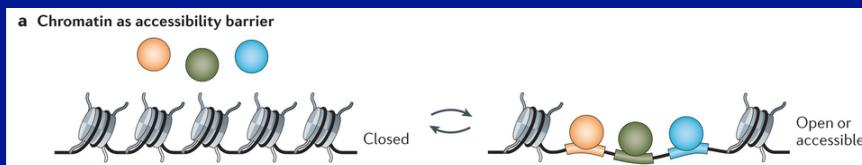
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Types of histone modifications



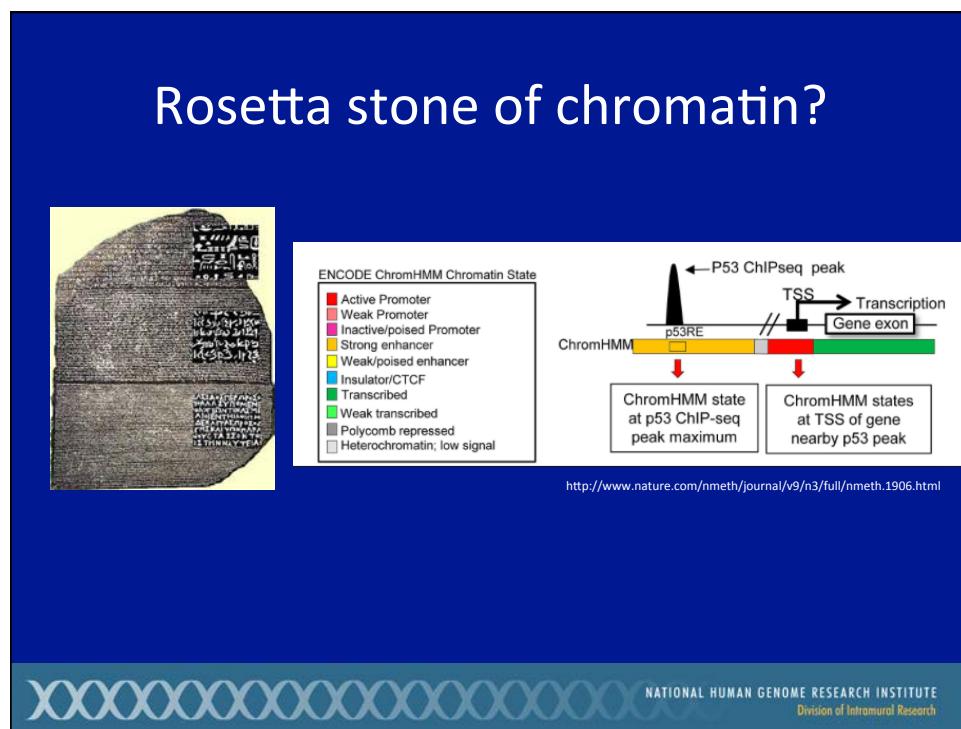
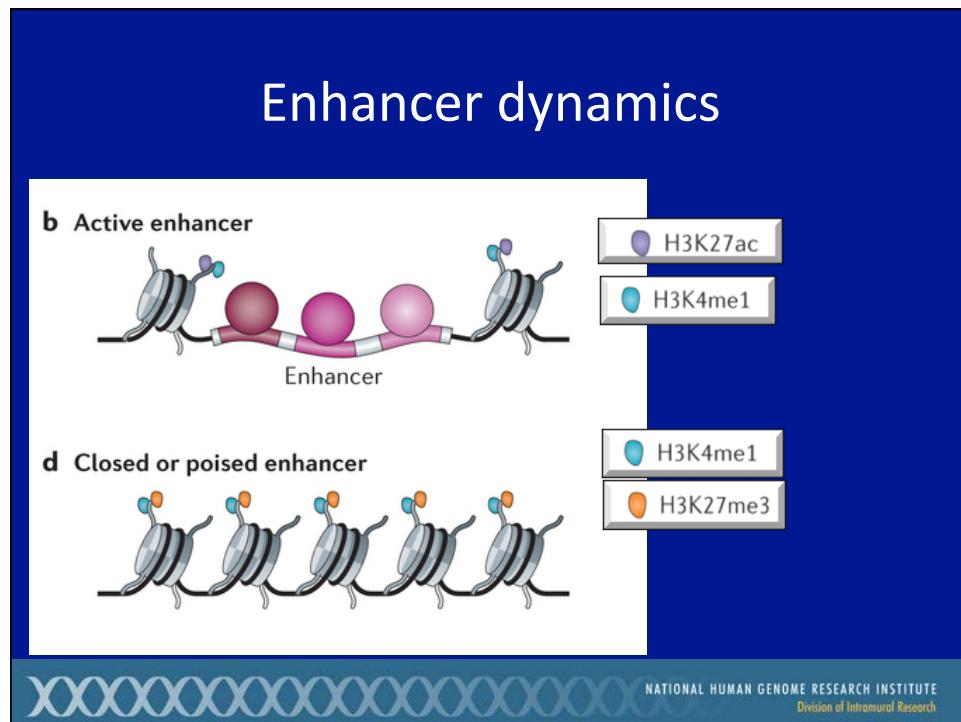
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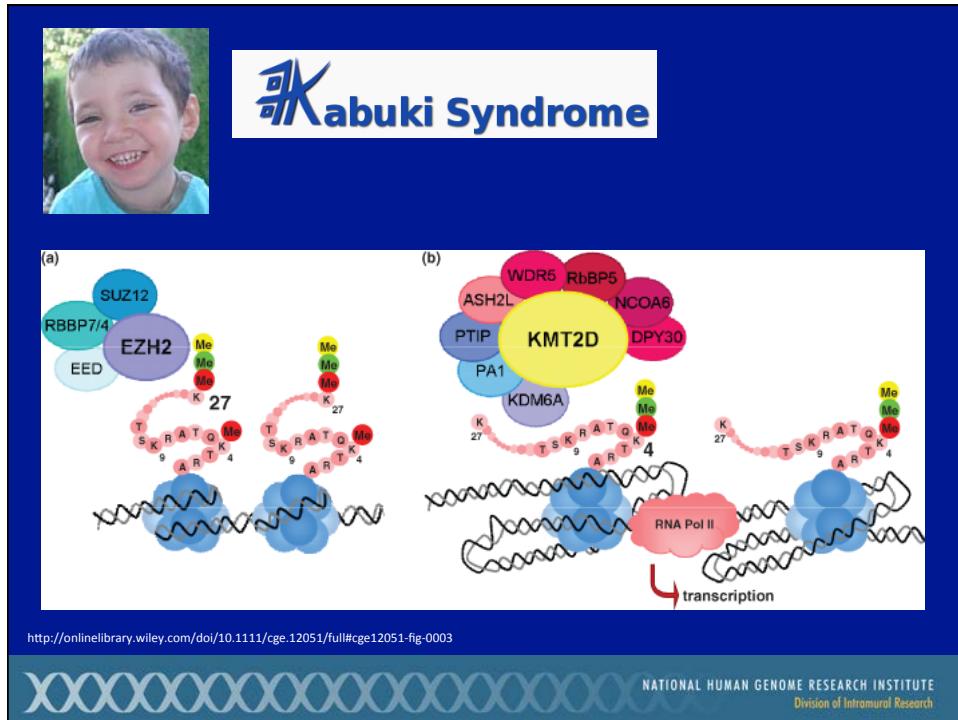
Chromatin as a regulator



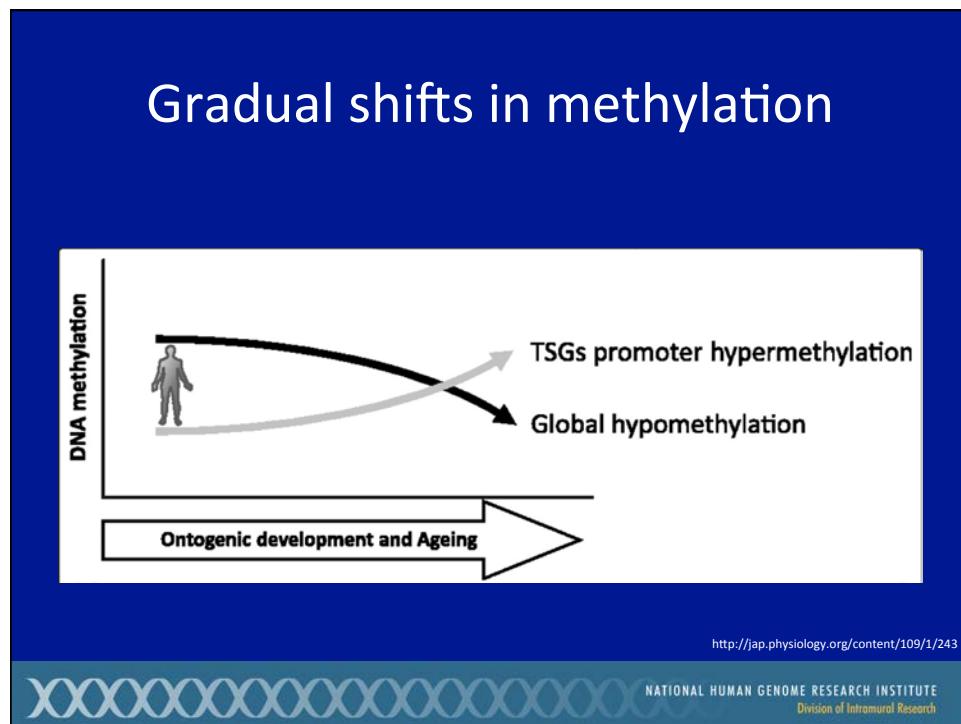
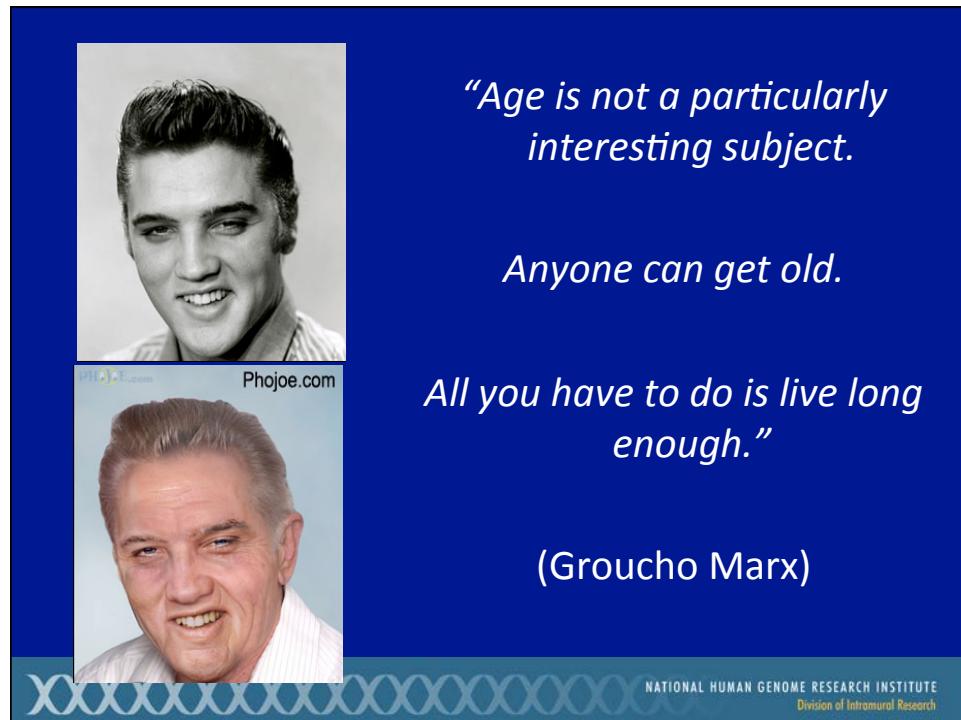
http://www.nature.com/nrg/journal/v15/n4/fig_tab/nrg3682_F2.html

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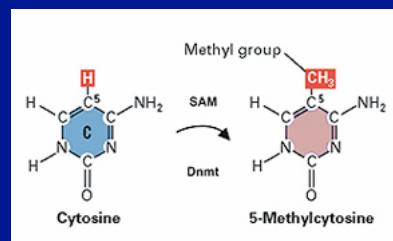




4. DNA methylation

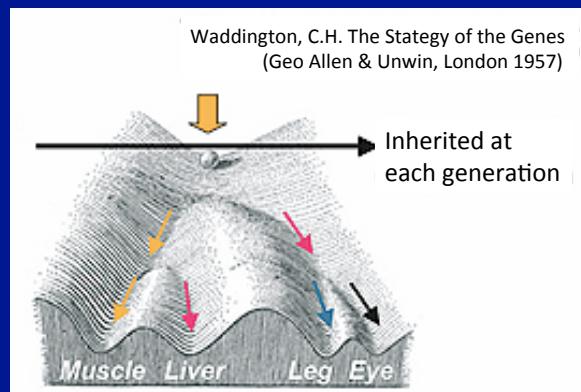


5-methyl cytosine

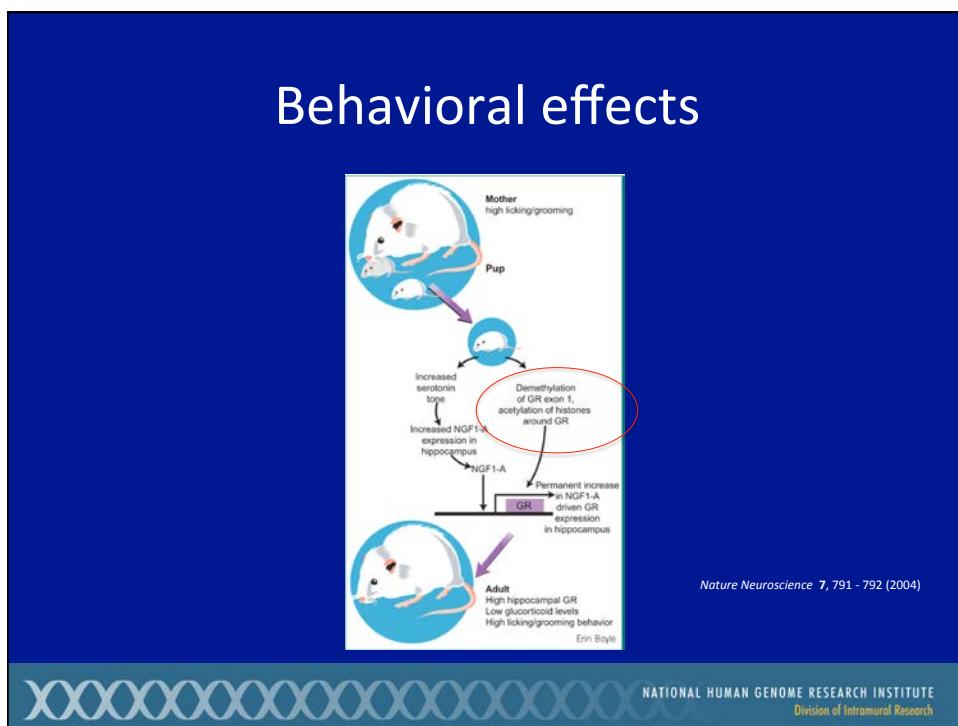
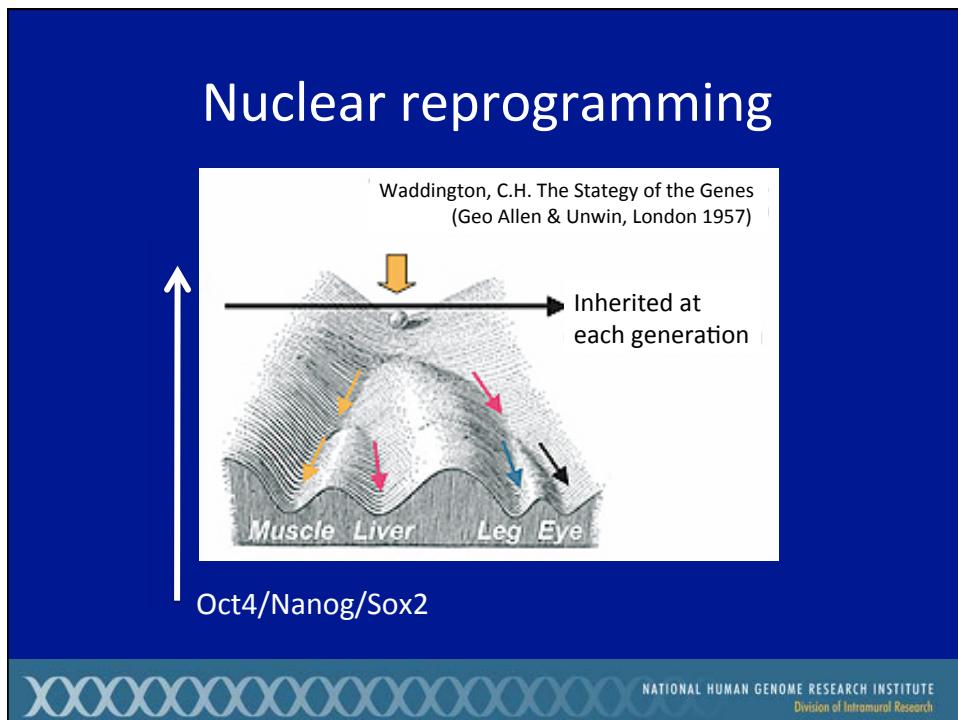


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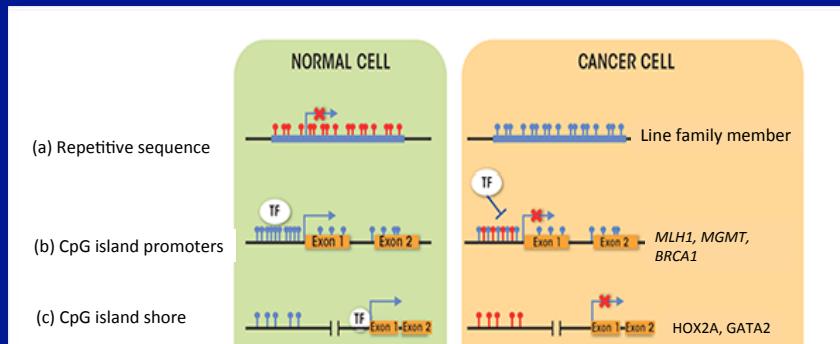
Waddington's epigenetic landscape



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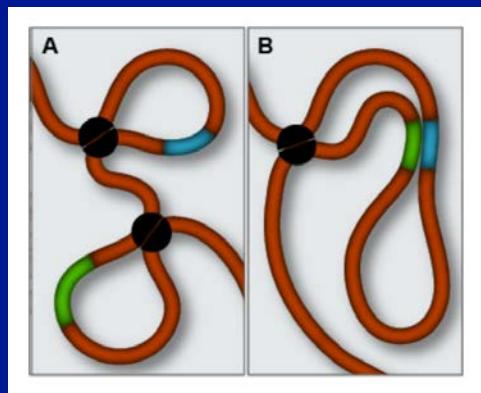
Methylation and cancer



Alcohol Research: Current Reviews, Volume 35, Issue Number 1

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Genome misfolding in cancer



PDGFRA and FIP1L1

normal

tumor

<https://www.broadinstitute.org/news/7706>

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5.1. Revisiting genome composition



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ENCODE

a surprisingly large amount of the human genome, 80.4%, is covered by at least one ENCODE-identified element

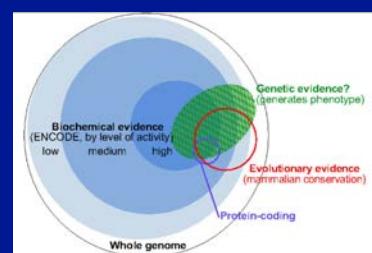
ARTICLE

An integrated encyclopedia of DNA elements in the human genome

The ENCODE Project Consortium*

The human genome encodes the blueprint of life, but the function of the vast majority of its nearly three billion bases is unknown. The Encyclopedia of DNA Elements (ENCODE) project has systematically mapped regions of transcription, transcription factor association, chromatin structure and histone modification. These data enabled us to assign biochemical functions for 80% of the genome, in particular outside of the well-studied protein-coding regions. Many discovered regulatory elements show strong evolutionary conservation and often act at long range to coordinate gene expression, providing new insights into the mechanisms of gene regulation. The newly identified elements also show a statistical correspondence to sequence variants linked to human disease, and can thereby guide interpretation of this variation. Overall, these results provide a framework for investigating the function of the remaining uncharacterized portion of our genome and genome, and is an expansive resource of functional annotations for biomedical research.

<http://www.nature.com/nature/journal/v489/n7414/full/nature11247.html>



<http://www.pnas.org/content/111/17/6131.abstract>

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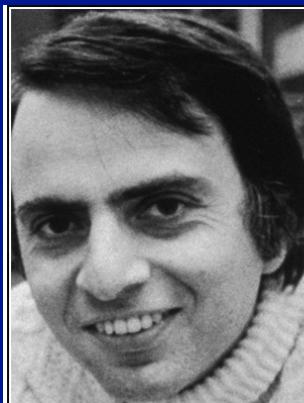
Tallying genomic features

Genomic element	Number	Source
Protein-coding genes	20330	GENCODE V17 (Feb2013, GRCh37) Ensembl 72
Long non-coding RNAs	13333	GENCODE V17
lncRNAs	6020	GENCODE V17
Pseudogenes	14154	GENCODE V17
Short non-coding RNAs	9078	GENCODE V17
miRNAs	3086	GENCODE V17
Promoters	70292	ENCODE [3]
Enhancers	399124	ENCODE [3]
TFBS (ChIP peaks)	636336	ENCODE [3]

lncRNAs, long intergenic non-coding RNAs; miRNAs, micro RNAs; TFBS, transcription factor binding sites.

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Defining function



The absence of evidence is not the evidence of absence.

— Carl Sagan —

AZ QUOTES

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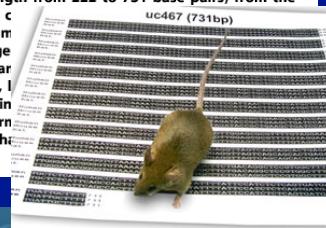
Deletion of promising regions

Deletion of Ultraconserved Elements Yields Viable Mice

Nadav Ahituv^{1,2*}, Yiwen Zhu¹, Axel Visel¹, Amy Holt¹, Veena Afzal¹, Len A. Pennacchio^{1,2}, Edward M. Rubin^{1,2*}

¹ Genomics Division, Lawrence Berkeley National Laboratory, Berkeley, California, United States of America, ² United States Department of Energy Joint Genome Institute, Walnut Creek, California, United States of America

Ultraconserved elements have been suggested to retain extended perfect sequence identity between the human, mouse, and rat genomes due to essential functional properties. To investigate the necessities of these elements *in vivo*, we removed four noncoding ultraconserved elements (ranging in length from 222 to 731 base pairs) from the mouse genome. To maximize the likelihood of observing a phenotype, we chose elements that are active in enhancers in a mouse transgenic assay and that are near genes that exhibit most of their activity in the mouse. When their expression is altered due to other genetic changes, these elements are often inactivated in the mouse and when their expression is altered due to other genetic changes, these elements are often inactivated in the mouse. The resulting lines of mice lacking these ultraconserved elements were viable and healthy, showing no abnormalities when assayed for a variety of phenotypes including growth, development, and behavior. In addition, more targeted screens, informed by the abnormalities observed in the investigated elements had been altered, also failed to reveal notable abnormalities. These results indicate that the ultraconserved elements do not necessarily reflect crucial functions required for viability.

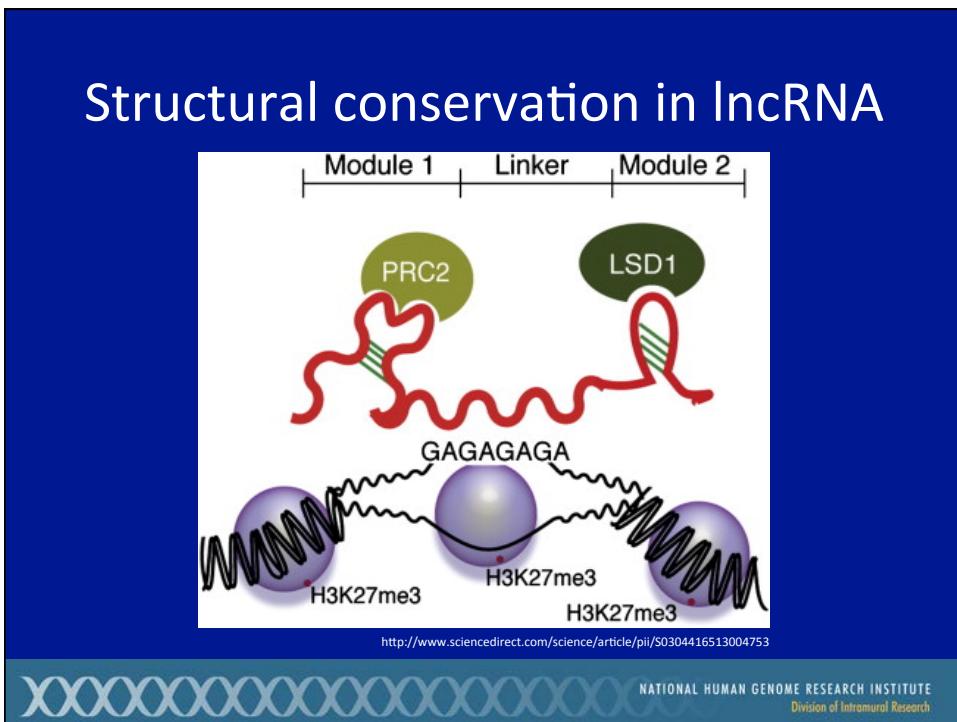


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Shadow enhancers (redundancy/resilience?)

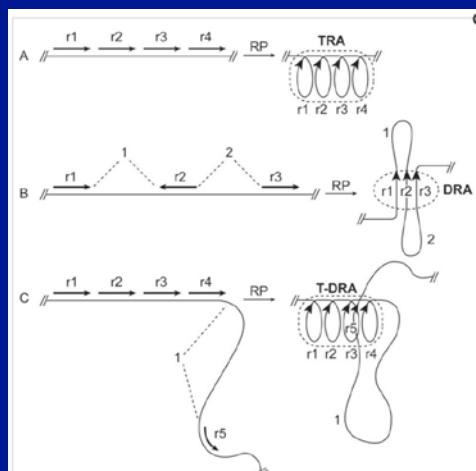


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5.2. Seemingly nonfunctional regions

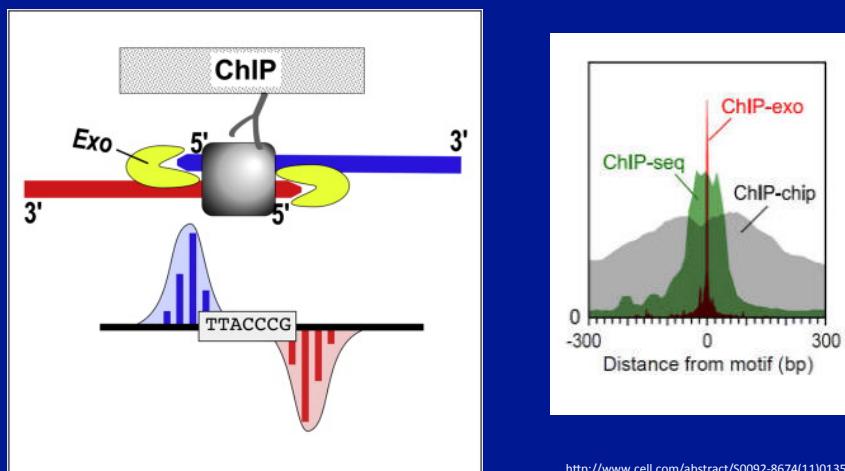
TE repeat pairing



<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3927610/figure/f1-genes-02-00502/>

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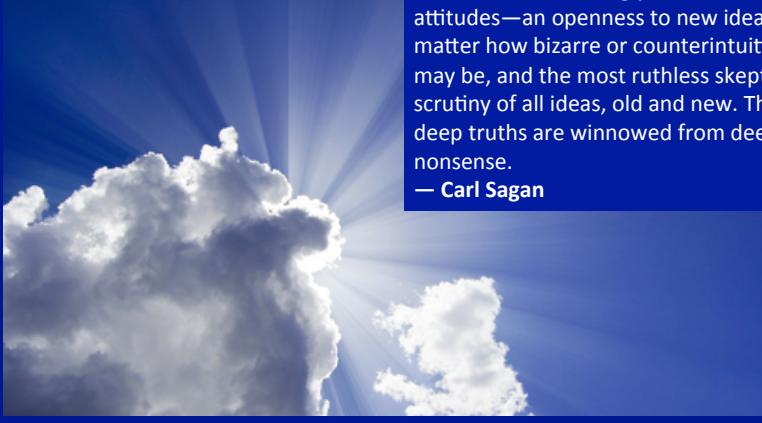
Wide-spread regulated RNA Pol II initiation



[http://www.cell.com/abstract/S0092-8674\(11\)01351-1](http://www.cell.com/abstract/S0092-8674(11)01351-1)

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Illuminating the dark matter



At the heart of science is an essential balance between two seemingly contradictory attitudes—an openness to new ideas, no matter how bizarre or counterintuitive they may be, and the most ruthless skeptical scrutiny of all ideas, old and new. This is how deep truths are winnowed from deep nonsense.

— Carl Sagan

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